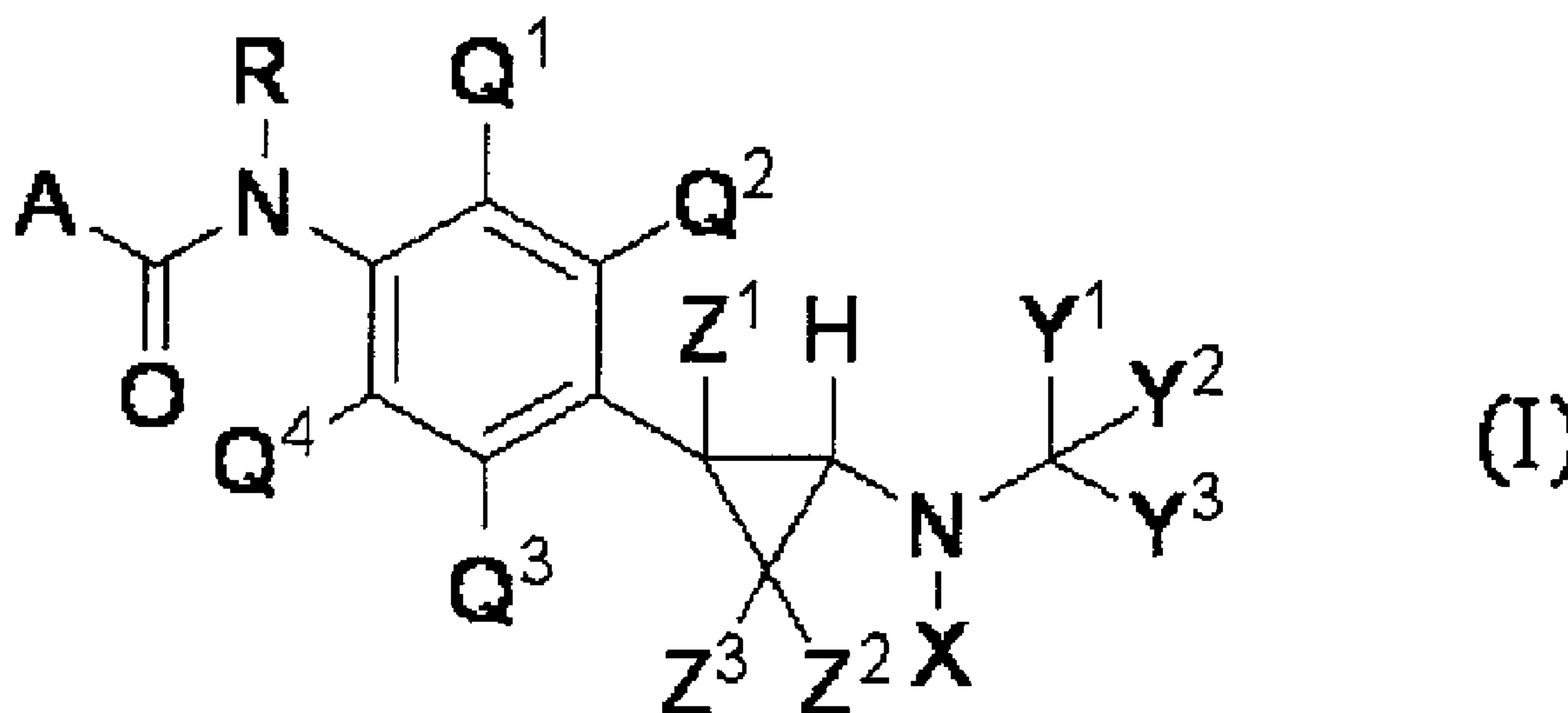




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...

(54) Titre : COMPOSES DE CYCLOPROPANAMINE
(54) Title: CYCLOPROPANAMINE COMPOUND



(57) Abrégé/Abstract:

The present invention provides a compound which has an inhibitory activity on lysine-specific demethylase 1 and is useful as a medicinal agent such as a prophylactic or therapeutic agent for cancer and central nervous system diseases. The present invention



(51) Cl.Int./Int.Cl. (suite/continued) *A61K 31/426* (2006.01), *A61K 31/428* (2006.01), *A61K 31/429* (2006.01), *A61K 31/433* (2006.01), *A61K 31/4406* (2006.01), *A61K 31/4409* (2006.01), *A61K 31/4453* (2006.01), *A61K 31/4468* (2006.01), *A61K 31/451* (2006.01), *A61K 31/495* (2006.01), *A61K 31/55* (2006.01), *A61P 35/00* (2006.01), *A61P 35/02* (2006.01), *C07C 235/56* (2006.01), *C07C 237/40* (2006.01), *C07C 271/22* (2006.01), *C07D 207/06* (2006.01), *C07D 207/337* (2006.01), *C07D 209/08* (2006.01), *C07D 209/42* (2006.01), *C07D 209/46* (2006.01), *C07D 209/48* (2006.01), *C07D 211/56* (2006.01), *C07D 211/58* (2006.01), *C07D 211/76* (2006.01), *C07D 213/04* (2006.01), *C07D 213/38* (2006.01), *C07D 213/56* (2006.01), *C07D 223/16* (2006.01), *C07D 231/14* (2006.01), *C07D 231/20* (2006.01), *C07D 231/22* (2006.01), *C07D 231/56* (2006.01), *C07D 233/61* (2006.01), *C07D 233/64* (2006.01), *C07D 239/36* (2006.01), *C07D 261/08* (2006.01), *C07D 261/10* (2006.01), *C07D 263/32* (2006.01), *C07D 263/34* (2006.01), *C07D 277/20* (2006.01), *C07D 277/28* (2006.01), *C07D 277/30* (2006.01), *C07D 277/62* (2006.01), *C07D 285/06* (2006.01), *C07D 295/14* (2006.01), *C07D 309/14* (2006.01), *C07D 317/58* (2006.01), *C07D 333/20* (2006.01), *C07D 405/04* (2006.01), *C07D 409/04* (2006.01), *C07D 471/04* (2006.01), *C07D 495/04* (2006.01), *C07D 513/04* (2006.01)

(72) Inventeurs(suite)/Inventors(continued): CARY, DOUGLAS ROBERT, JP; TOMITA, DAISUKE, JP; IMAMURA, SHINICHI, JP; TSUCHIDA, KEN, JP; MATSUDA, SATORU, JP; HARA, RYUJIRO, JP

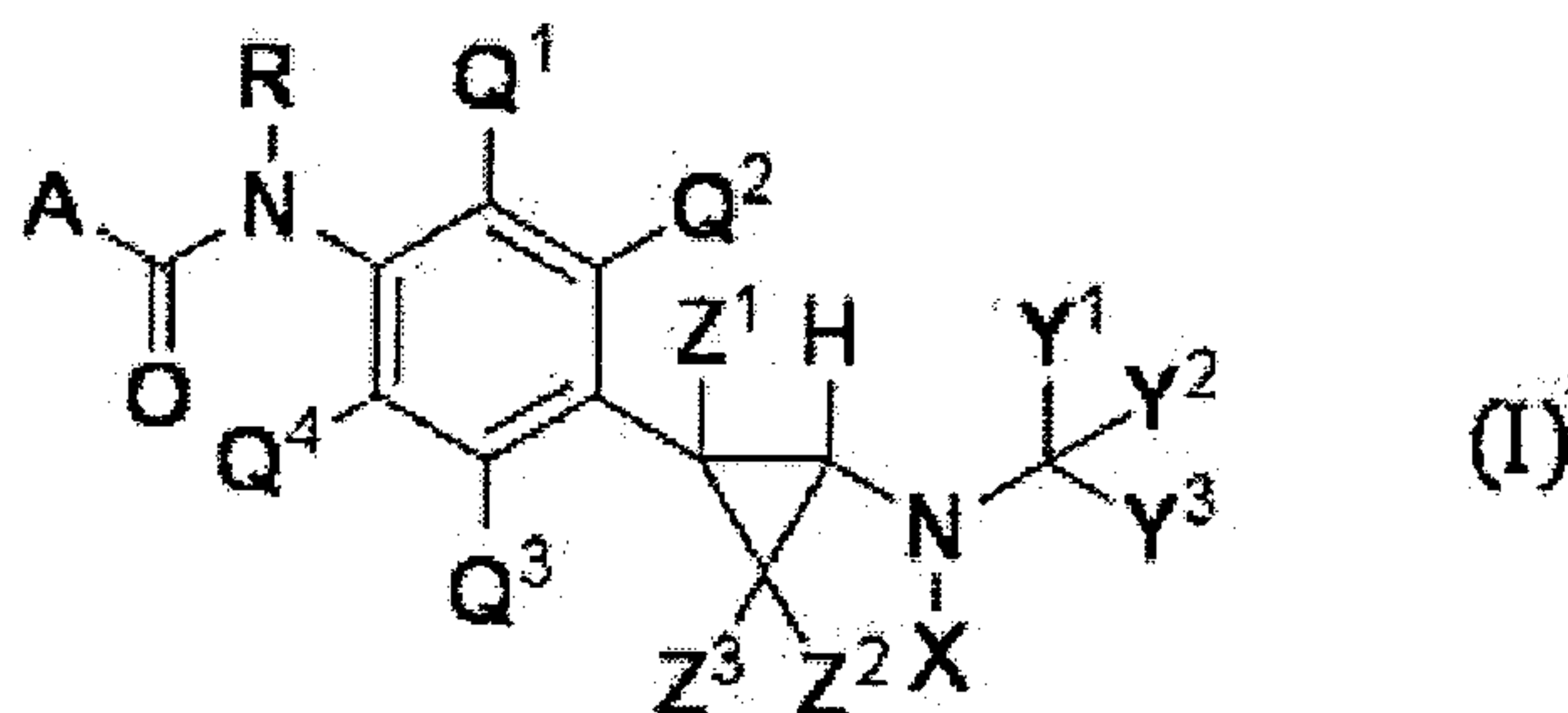
(74) Agent: FETHERSTONHAUGH & CO.

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

relates to a compound represented by formula (I) [wherein A represents a hydrocarbon or heterocyclic ring group which may have a substituent; R represents H or a hydrocarbon or heterocyclic ring group which may have a substituent; A and R may be bound together to form a ring which may have a substituent; Q¹, Q², Q³ and Q⁴ independently represent a hydrogen atom or a substituent; Q¹ and Q² or Q³ and Q⁴ may be bound together to form a ring which may have a substituent; X represents H or a linear hydrocarbon or saturated cyclic group which may have a substituent; Y¹, Y² and Y³ independently represent H or a hydrocarbon or heterocyclic ring group which may have a substituent; X and Y¹ or Y¹ and Y² may be bound together to form a ring which may have a substituent; and Z¹, Z² and Z³ independently represent H or a substituent] or a salt thereof.

ABSTRACT

The present invention provides a compound having a lysine-specific demethylase 1 inhibitory action, and useful as
 5 a medicament such as a prophylactic or therapeutic agent for cancer, and central nervous system diseases, and the like. The present invention relates to a compound represented by the formula



10 wherein A is a hydrocarbon group or heterocyclic group optionally having substituent(s); R is H, a hydrocarbon group or heterocyclic group optionally having substituent(s); A and R are optionally bonded to each other to form a ring optionally having substituent(s); Q¹, Q², Q³ and Q⁴ are each a hydrogen
 15 atom or a substituent; Q¹ and Q², and Q³ and Q⁴, are each optionally bonded to each other to form a ring optionally having substituent(s); X is H, an acyclic hydrocarbon group or saturated cyclic group optionally having substituent(s); Y¹, Y² and Y³ are each H, a hydrocarbon group or heterocyclic group
 20 optionally having substituent(s); X and Y¹, and Y¹ and Y², are each optionally bonded to each other to form a ring optionally having substituent(s); and Z¹, Z² and Z³ are each H or a substituent, or a salt thereof.

DESCRIPTION

Title of the Invention: CYCLOPROPANEAMINE COMPOUND

Technical Field

[0001]

5 The present invention relates to a cyclopropanamine compound having a lysine specific demethylase 1 (sometimes abbreviated as LSD1 in the present specification) inhibitory action and useful as a medicament such as a prophylactic or therapeutic agent for cancer, schizophrenia, Alzheimer's
10 disease, Parkinson's disease and Huntington's chorea, and the like.

[0002]

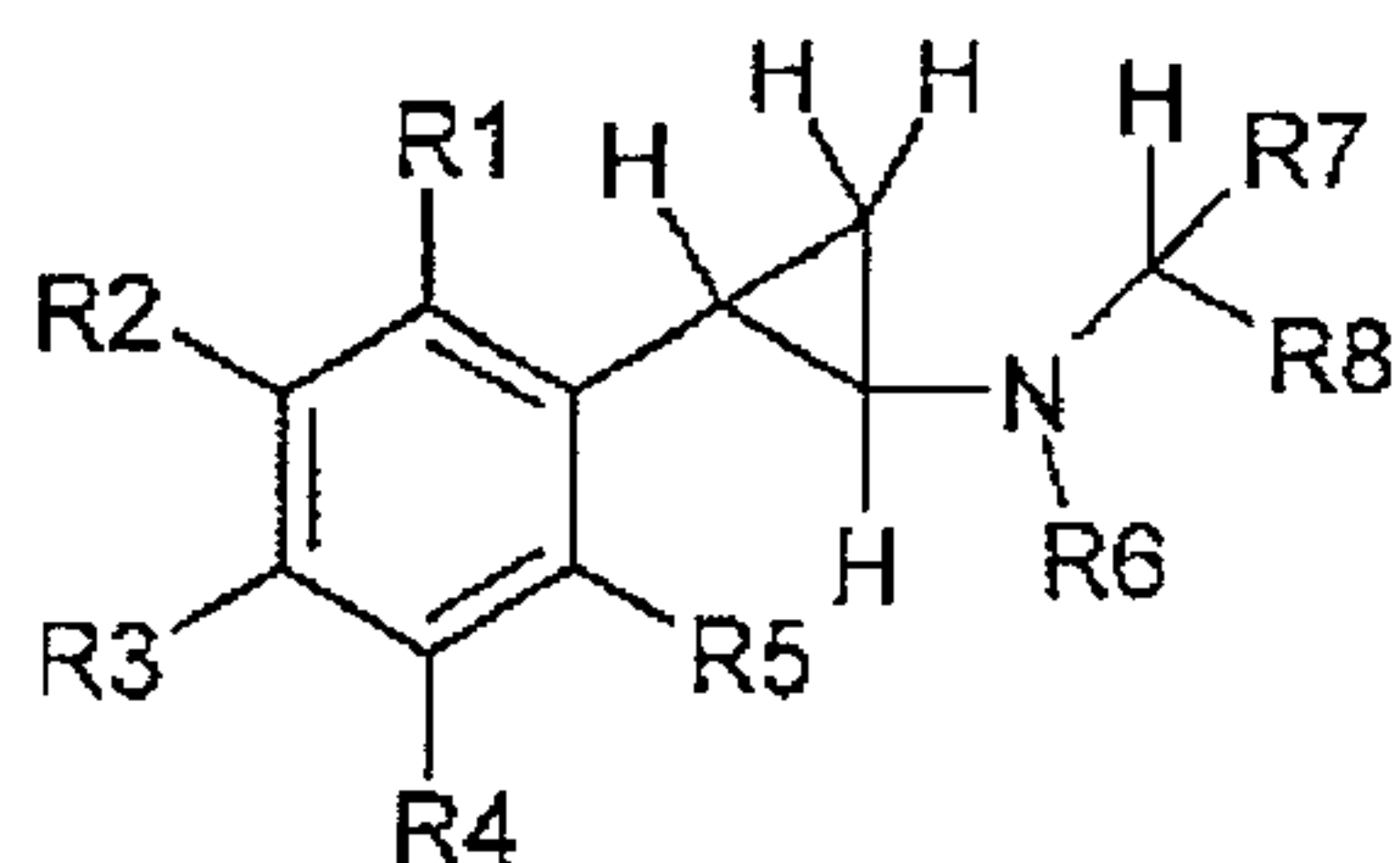
(Background of the Invention)

LSD1 is a demethylation enzyme of histone, catalyzes a
15 demethylation reaction of a monomethylated product and a dimethylated product of the 4th lysine residue of histone H3 (H3K4me1/2), and forms formaldehyde as a by-product. In addition, LSD1 forms a complex with flavin adenine dinucleotide (FAD) which is a kind of coenzyme, and FAD promotes oxidation
20 of lysine residue by enzymes as a redox mediator.

[0003]

WO 2010/084160 (patent document 1) discloses a compound of the following formula or a pharmaceutically acceptable salt thereof as an LSD1 inhibitor:

25 [0004]



FORMULA I

[0005]

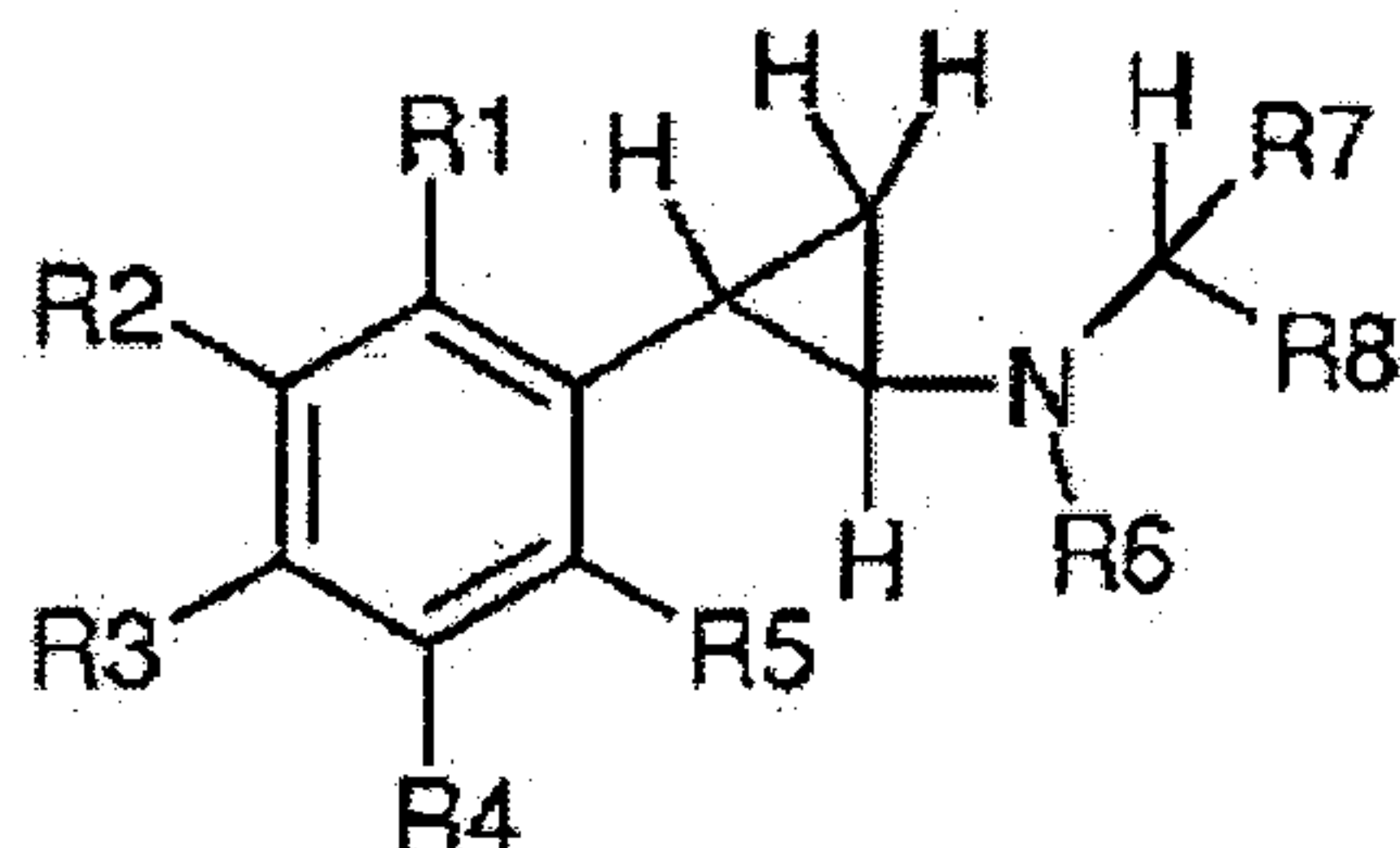
wherein R1-R5 are H, halo and the like; R6 is H or alkyl; R7 is H, alkyl or cycloalkyl; R8 is -L-heterocyclyl or -L-aryl
30 wherein L is $-(CH_2)_n-(CH_2)_n-$, $-(CH_2)_nNH(CH_2)_n-$, $-(CH_2)_nO(CH_2)_n-$ or

$-(CH_2)_nS(CH_2)_n-$, and n is 0, 1, 2 or 3.

[0006]

WO 2010/043721 (patent document 2) discloses a compound of the following formula or a pharmaceutically acceptable salt thereof as an LSD1 inhibitor:

[0007]



FORMULA I

[0008]

wherein R1-R5 are H, halo and the like; R6 is H or alkyl; R7 is H, alkyl or cycloalkyl; R8 is $-C(=O)NR_xR_y$ or $-C(=O)R_z$ wherein Rx and Ry are each independently H, alkyl and the like, and Rz is H, alkoxy and the like.

[0009]

WO 2011/035941 (patent document 3) discloses a compound of the following formula or a pharmaceutically acceptable salt thereof as an LSD1 inhibitor:

[0010]

$(A')_x-(A)-(B)-(Z)-(L)-(D)$

I

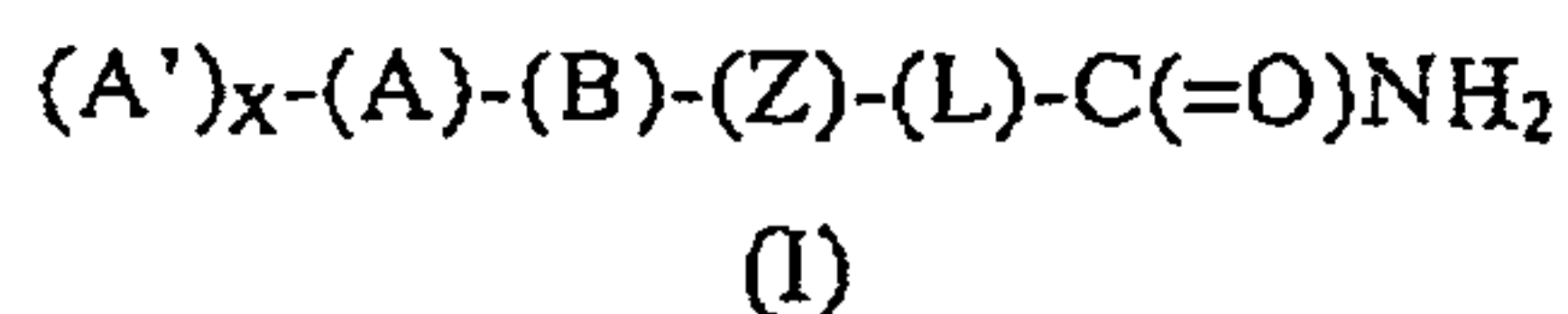
[0011]

wherein (A') is aryl, arylalkoxy, heterocyclyl and the like; (A) is heteroaryl or aryl; X is 0, 1, 2 or 3; (B) is a cyclopropyl ring; (Z) is $-NH-$; (L) is $-CH_2CH_2-$ and the like; (D) is $-N(-R_1)-R_2$, $-O-R_3$ or $-S-R_3$ wherein R1 and R2 are each independently H, alkyl and the like; and R3 is H, alkyl and the like.

[0012]

WO 2011/042217 (patent document 4) discloses a compound of the following formula or a pharmaceutically acceptable salt thereof as an LSD1 inhibitor:

[0013]



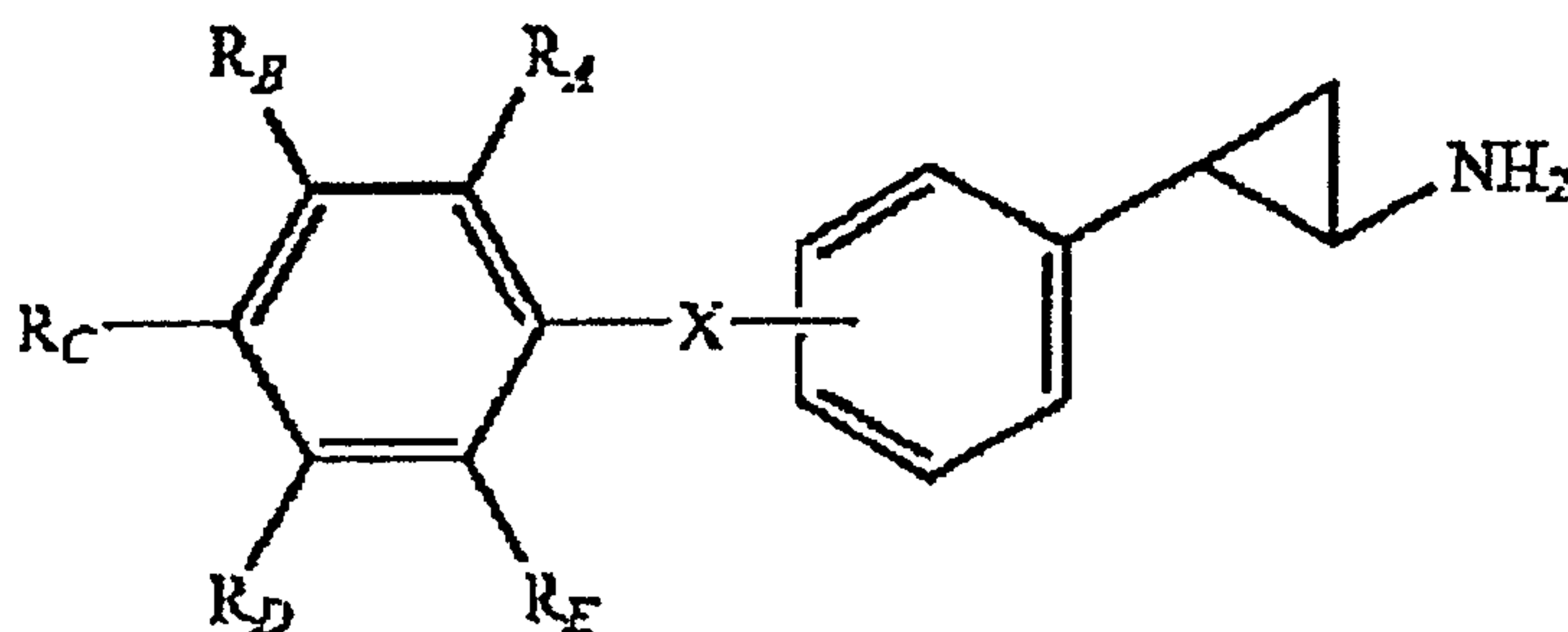
[0014]

wherein (A') is aryl, arylalkoxy, arylalkyl, heterocyclyl and
 5 the like; (A) is heteroaryl or aryl; X is 0, 1, 2 or 3; (B) is
 a cyclopropyl ring; (Z) is -NH-; (L) is $-(CH_2)_mCR_1R_2-$ wherein m
 is 0, 1, 2, 3, 4, 5 or 6; and R1 and R2 are each independently
 H or C1-6 alkyl.

[0015]

10 US2010/0324147 (patent document 5) discloses a compound
 of the following formula or a salt thereof as an LSD1
 inhibitor:

[0016]



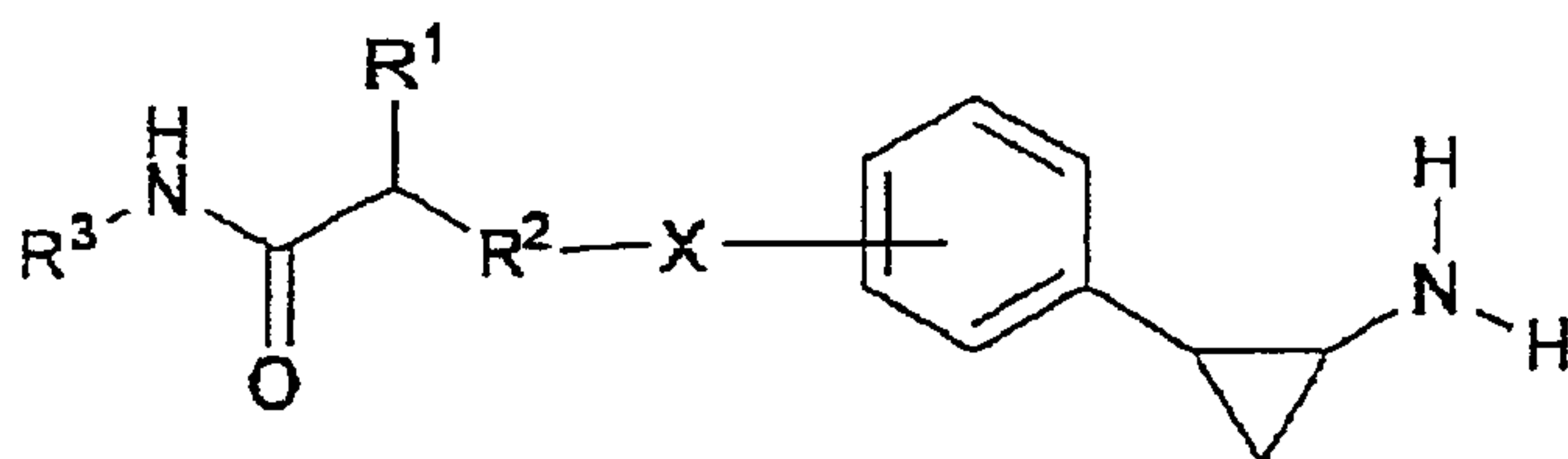
15 [0017]

wherein X is a bond, O, S or NH; and R_A, R_B, R_C, R_D and R_E are
 each independently H, C1-7 alkyl and the like.

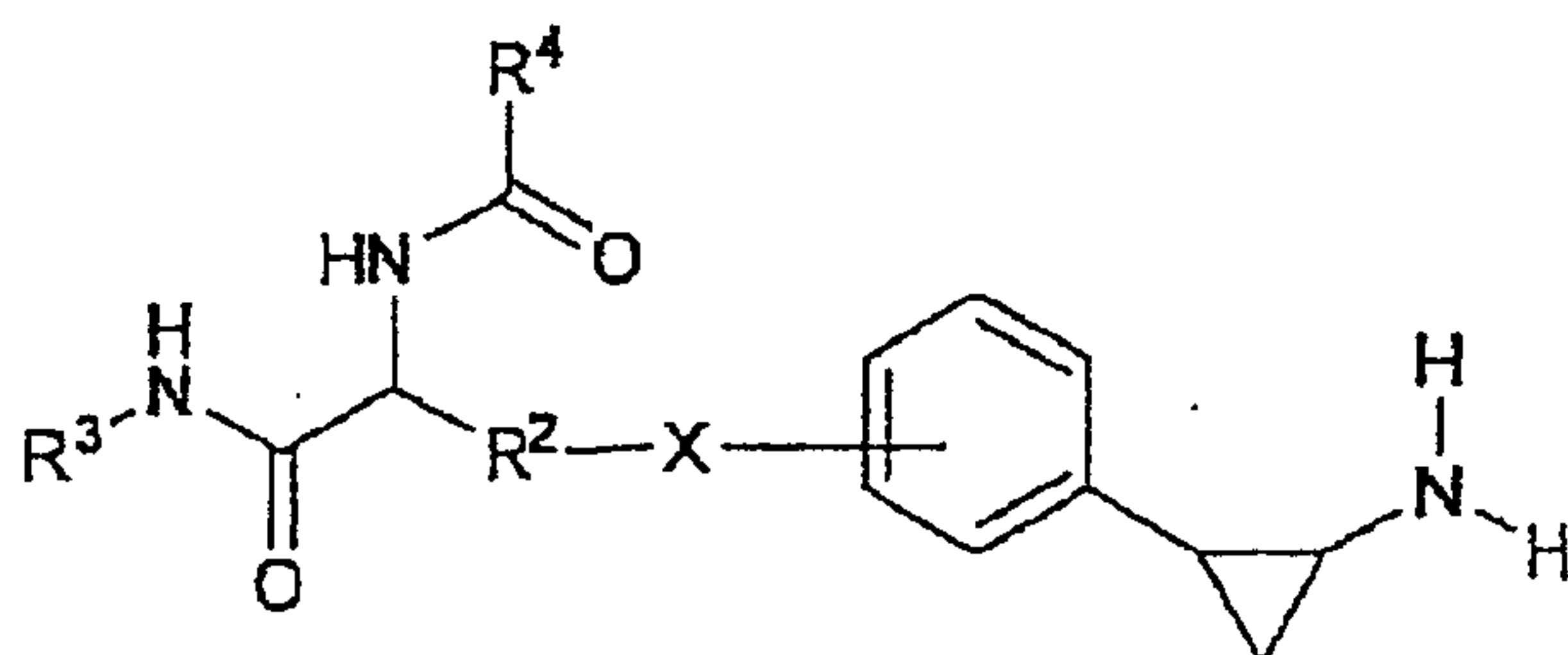
[0018]

WO 2010/143582 (patent document 6) discloses a compound
 20 of the following formula or a pharmaceutically acceptable salt
 thereof as an LSD1 inhibitor:

[0019]



(I)



(II)

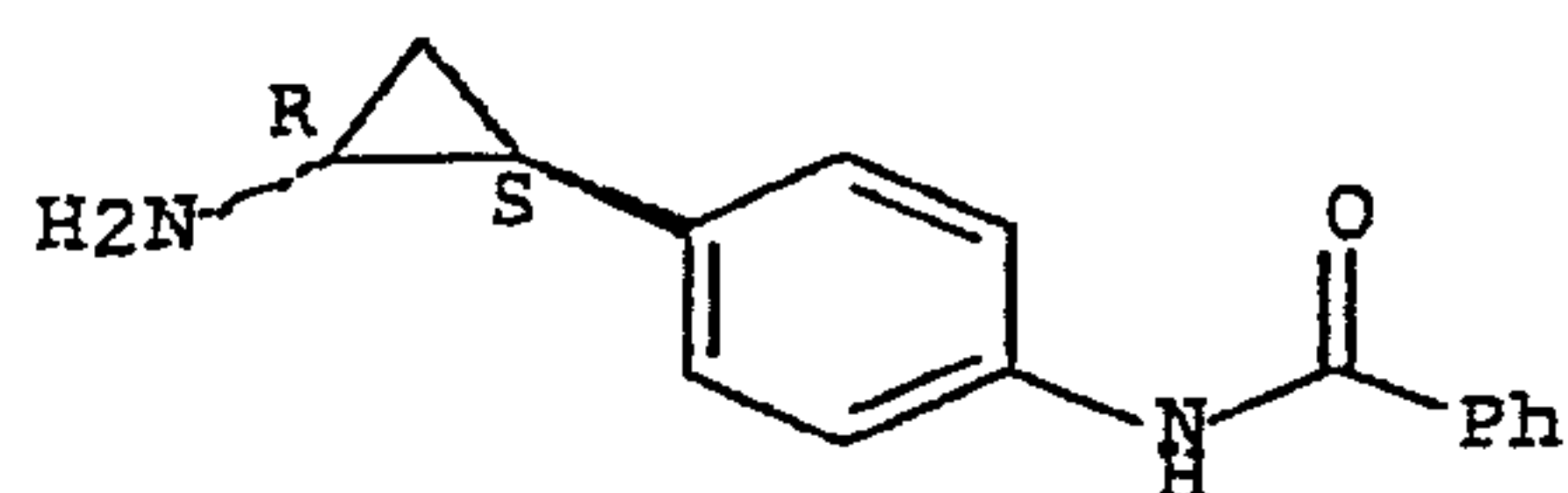
[0020]

wherein R¹ is H, an alkyl group optionally having a substituent attached thereto and the like; R² is an alkylene group
 5 optionally having a substituent attached thereto; R³ is an alkyl group optionally having a substituent attached thereto, a phenyl group optionally having a substituent attached thereto and the like; R⁴ is an alkyl group optionally having a substituent attached thereto, a phenyl group optionally having
 10 a substituent attached thereto and the like; and X is O, NH₂, NHCO, CONH, S or CH₂.

[0021]

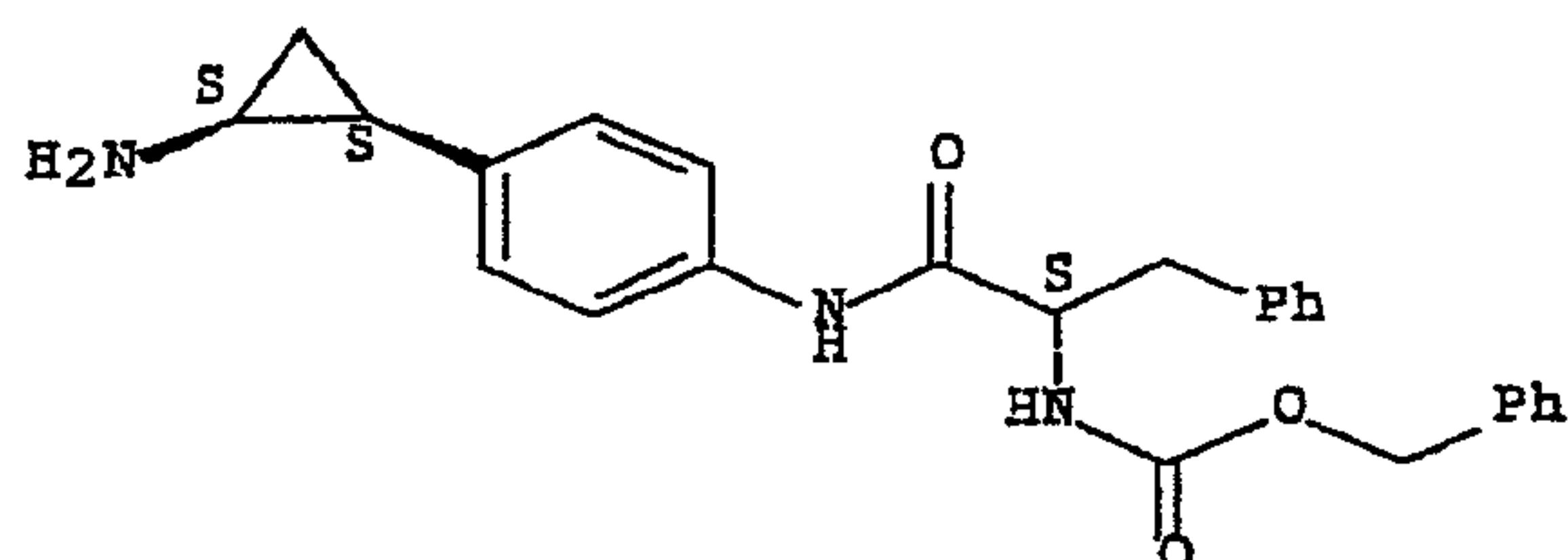
J. Am. Chem. Soc. 2010, 132, 6827-6833 (non-patent document 1) discloses compounds of the following formulas as an
 15 LSD 1/2 inhibitor:

[0022]

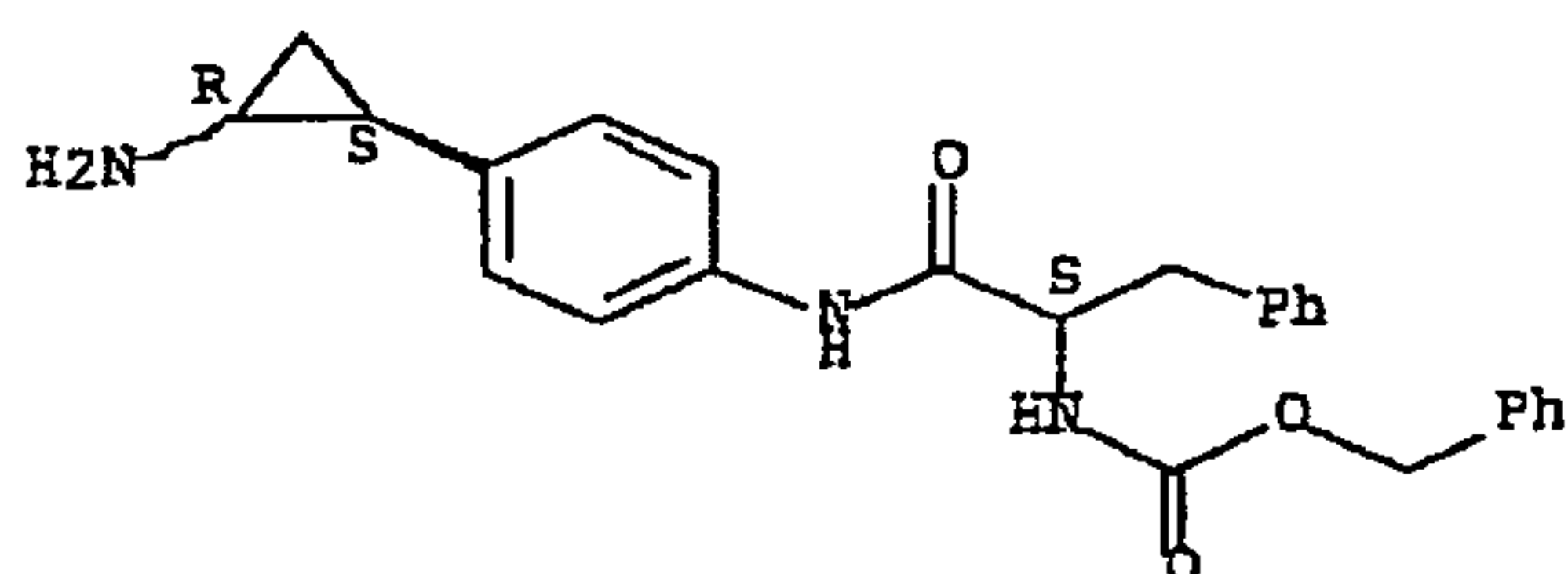


● HCl

(13b)



(15e)



● HCl

(14e)

[0023]

The Journal of Neuroscience, October 17, 2007, 27(42):
11254-11262 (non-patent document 2) discloses that a decrease
5 in histone H3K4 methylation and a decrease in Gad1 mRNA
expression are observed in the brain of schizophrenia patients.

Document List

patent documents

[0024]

- 10 patent document 1: WO2010/084160
patent document 2: WO2010/043721
patent document 3: WO2011/035941
patent document 4: WO2011/042217
patent document 5: US2010/0324147
15 patent document 6: WO2010/143582

non-patent documents

[0025]

- non-patent document 1: J. Am. Chem. Soc. 2010, 132, 6827-6833
non-patent document 2: The Journal of Neuroscience, October 17,

2007, 27(42):11254-11262

Summary of the Invention

Problems to be Solved by the Invention

[0026]

5 An object of the present invention is to provide a cyclopropanamine compound having a superior LSD1 inhibitory action and high LSD1 selectivity, and useful as a medicament such as a prophylactic or therapeutic agent for cancer, schizophrenia, Alzheimer's disease, Parkinson's disease and
10 Huntington's chorea.

Means of Solving the Problems

[0027]

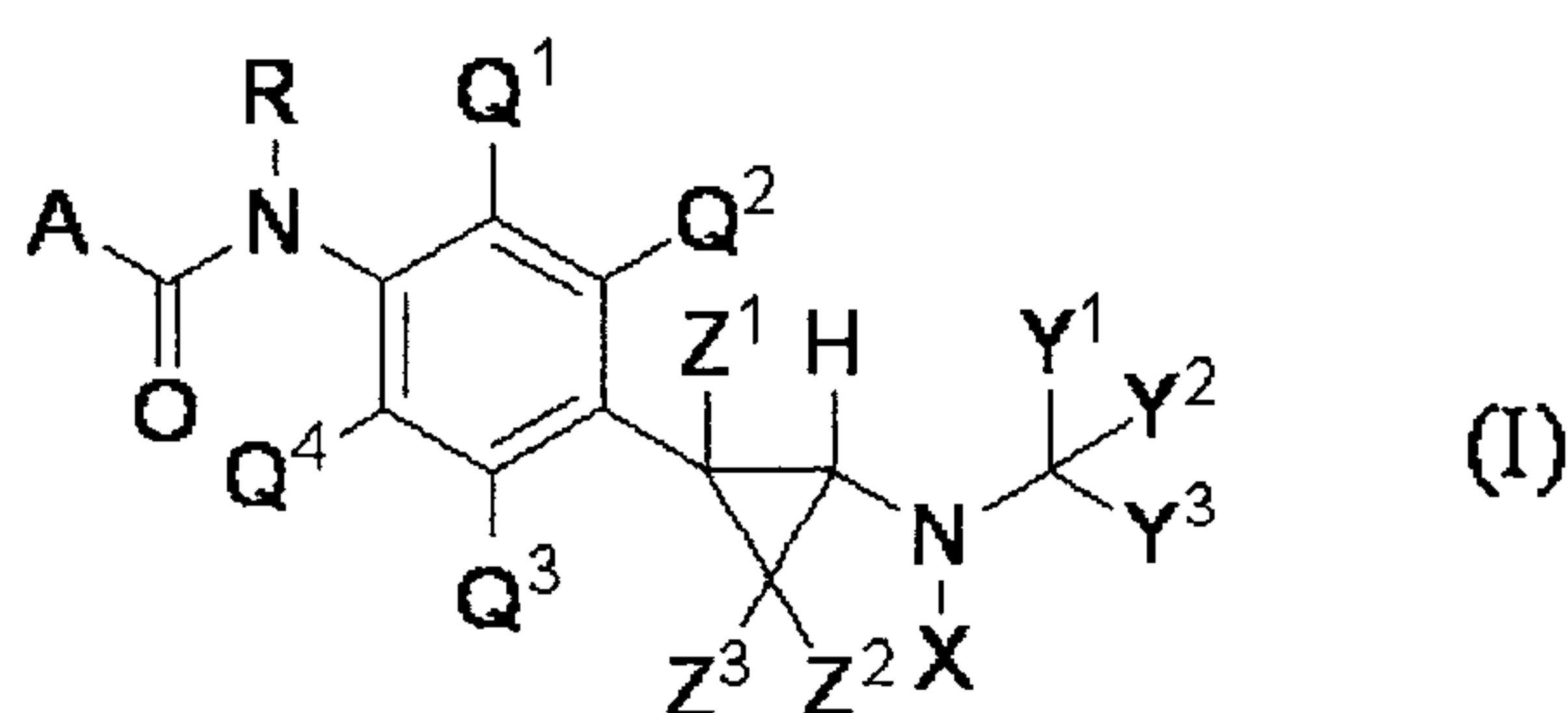
The present inventors have conducted intensive studies in an attempt to solve the aforementioned problems and found that
15 a compound represented by the following formula (I) has a superior LSD1 inhibitory action and high LSD1 selectivity, which resulted in the completion of the present invention.

[0028]

Accordingly, the present invention relates to the
20 following.

[1] A compound represented by the formula

[0029]



[0030]

25 wherein A is a hydrocarbon group optionally having substituent(s), or a heterocyclic group optionally having substituent(s);

R is a hydrogen atom, a hydrocarbon group optionally having substituent(s), or a heterocyclic group optionally having
30 substituent(s); or

A and R are optionally bonded to each other to form a ring

optionally having substituent(s);

Q^1 , Q^2 , Q^3 and Q^4 are each independently a hydrogen atom or a substituent; Q^1 and Q^2 , and Q^3 and Q^4 , are each optionally bonded to each other to form a ring optionally having

5 substituent(s);

X is a hydrogen atom, an acyclic hydrocarbon group optionally having substituent(s), or a saturated cyclic group optionally having substituent(s);

Y^1 , Y^2 and Y^3 are each independently a hydrogen atom, a
10 hydrocarbon group optionally having substituent(s), or a heterocyclic group optionally having substituent(s);

X and Y^1 , and Y^1 and Y^2 , are each optionally bonded to each other to form a ring optionally having substituent(s); and

Z^1 , Z^2 and Z^3 are each independently a hydrogen atom or a
15 substituent,

or a salt thereof (hereinafter sometimes to be abbreviated as compound (I)).

[0031]

[2] The compound of [1], wherein

20 A is

(1) a C_{3-8} cycloalkyl group optionally having substituent(s),

(2) a C_{6-14} aryl group optionally having substituent(s),

(3) a C_{6-14} aryl C_{1-6} alkyl group optionally having substituent(s),

25 (4) a C_{6-14} aryl C_{1-6} alkyl C_{6-14} aryl group optionally having substituent(s),

(5) a 4- to 11-membered heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 3 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom,
30 and optionally having substituent(s), or

(6) a C_{10-14} cyclic hydrocarbon group optionally having substituent(s);

R is a hydrogen atom or a C_{1-6} alkyl group optionally having substituent(s); or

35 A and R are optionally bonded to each other to form a 4- to 10-

membered heterocycle optionally having substituent(s), or a salt thereof.

[0032]

[2A] The compound of [1] or [2], wherein

5 A is

(1) a C₆₋₁₄ aryl group optionally having 1 to 3 substituents selected from

(a) a halogen atom,

(b) a C₁₋₆ alkyl group optionally having 1 to 5 halogen
10 atoms,

(c) a C₆₋₁₄ aryloxy group,

(d) a C₆₋₁₄ aryl C₁₋₆ alkyloxy group,

(e) a C₆₋₁₄ aryl-carbonylamino group,

(f) a C₆₋₁₄ aryl C₁₋₆ alkylamino group,

15 (g) a 4- to 7-membered heterocyclic group containing,
as a ring-constituting atom besides carbon atom, 1 to 4 hetero
atoms selected from a nitrogen atom, a sulfur atom and an
oxygen atom, and optionally having an oxo group and optionally
having 1 or 2 C₁₋₆ alkyl groups, and

20 (h) a C₁₋₆ alkyl group optionally having a 5-membered
heterocyclic group containing, as a ring-constituting atom
besides carbon atom, 2 or 3 nitrogen atoms,

(2) a C₆₋₁₄ aryl C₁₋₆ alkyl group optionally having a C₆₋₁₄ aryl
C₁₋₆ alkyloxy-carbonylamino group,

25 (3) a C₆₋₁₄ aryl C₁₋₆ alkyl C₆₋₁₄ aryl group,

(4) a C₃₋₈ cycloalkyl group,

(5) a 5-membered heterocyclic group containing, as a ring-
constituting atom besides carbon atom, 1 to 3 hetero atoms
selected from a nitrogen atom, a sulfur atom and an oxygen atom,
30 and optionally having 1 to 3 substituents selected from 1 or 2
C₁₋₆ alkyl groups optionally having 1 to 5 halogen atoms and a
phenyl group,

(6) a C₁₀₋₁₄ cyclic hydrocarbon group, or

(7) a 9- to 11-membered heterocyclic group containing, as a
35 ring-constituting atom besides carbon atom, 1 to 3 hetero atoms

selected from a nitrogen atom, a sulfur atom and an oxygen atom,
and optionally having 1 to 3 substituents selected from a C₁₋₆
alkyl-carbonyl group, a furyl group and a thienyl group;

R is a hydrogen atom or a C₁₋₆ alkyl group optionally having
5 substituent(s); or

A and R are optionally bonded to each other to form a 4- to 10-
membered heterocycle having 1 or 2 oxo groups,
or a salt thereof.

[0033]

10 [2B] The compound of [1], [2] or [2A], wherein
A is

a phenyl-C₁₋₆ alkyl group,
a C₃₋₆ cycloalkyl group,
a tetrahydronaphthyl group,

15 a phenyl group,

a biphenyl group,
a furyl group,
a thienyl group,
an oxazolyl group,

20 an isoxazolyl group,

a thiazolyl group,
a pyrazolyl group,
an indazolyl group,
a benzofuryl group,

25 a benzimidazolyl group,

a benzothiazolyl group,
an indolyl group, or

a tetrahydrobenzazepinyl group, each of which optionally has
substituent(s);

30 R is a hydrogen atom or a C₁₋₆ alkyl group; or

A and R are optionally bonded to each other to form a
dihydroisoindole ring having 1 or 2 oxo groups,
or a salt thereof.

[0034]

35 [2C] The compound of [1], [2], [2A] or [2B], wherein

A is

a phenyl-C₁₋₆ alkyl group,

a C₃₋₆ cycloalkyl group,

a tetrahydronaphthyl group,

5 a phenyl group,

a biphenyl group,

a furyl group,

a thienyl group,

an oxazolyl group,

10 an isoxazolyl group,

a thiazolyl group,

a pyrazolyl group,

an indazolyl group,

a benzofuryl group,

15 a benzimidazolyl group,

a benzothiazolyl group,

an indolyl group, or

a tetrahydrobenzazepinyl group, each of which optionally has 1 to 3 substituents selected from

20 (1) a halogen atom,

(2) a C₁₋₆ alkyl group optionally having 1 to 3 substituents selected from a halogen atom, a phenyl group, an imidazolyl group and a triazolyl group,

(3) a C₁₋₆ alkoxy group optionally having 1 to 3 substituents
25 selected from a halogen atom and a phenyl group,

(4) a C₁₋₆ alkyl-carbonyl group,

(5) a di-C₁₋₆ alkylamino group,

(6) a C₁₋₆ alkylsulfonyl group,

(7) a sulfamoyl group,

30 (8) a C₁₋₆ alkylsulfonylamino group,

(9) an oxo group,

(10) a C₃₋₆ cycloalkyl group,

(11) a phenyl group optionally having 1 to 3 substituents selected from a halogen atom and a C₁₋₆ alkyl group,

35 (12) a phenoxy group,

- (13) a phenylcarbonylamino group,
- (14) a benzyloxycarbonylamino group,
- (15) a benzoyl group,
- (16) a benzylamino group,
- 5 (17) a pyrazolyl group,
- (18) a dihydropyrazolyl group optionally having 1 to 3 substituents selected from a C₁₋₆ alkyl group and an oxo group,
- (19) an oxazolyl group,
- (20) a thiazolyl group having 1 or 2 C₁₋₆ alkyl groups,
- 10 (21) a tetrazolyl group,
- (22) a pyrrolyl group,
- (23) a piperazinyll group having 1 to 3 C₁₋₆ alkyl groups,
- (24) an imidazolyl group,
- (25) a pyridyl group,
- 15 (26) a pyrimidinyl group,
- (27) a piperidyl group optionally having one oxo group,
- (28) a thienyl group,
- (29) a furyl group, and
- (30) a thiadiazolyl group;
- 20 R is a hydrogen atom or a C₁₋₆ alkyl group; or
- A and R are optionally bonded to each other to form a dihydroisoindole ring having 1 or 2 oxo groups,
- or a salt thereof.

[0035]

- 25 [2D] The compound of [1], [2], [2A], [2B] or [2C], wherein A is
- a phenyl-C₁₋₆ alkyl group,
- a phenyl group,
- a biphenylyl group or
- 30 a pyrazolyl group, each of which optionally has 1 to 3 substituents selected from
- (1) a halogen atom,
- (2) a C₁₋₆ alkyl group optionally having 1 to 3 substituents selected from a halogen atom and a phenyl group,
- 35 (3) a phenylcarbonylamino group,

(4) a benzyloxycarbonylamino group, and

(5) a piperidyl group optionally having one oxo group;

R is a hydrogen atom; or

A and R are optionally bonded to each other to form a
 5 dihydroisoindole ring having 1 or 2 oxo groups,
 or a salt thereof.

[0036]

[2E] The compound of [1], [2], [2A], [2B], [2C] or [2D],
 wherein

10 R is a hydrogen atom or a C₁₋₆ alkyl group, or a salt thereof.

[0037]

[3] The compound of [1], [2], [2A], [2B], [2C], [2D] or [2E],
 wherein

Q¹ is a hydrogen atom or a C₁₋₆ alkyl group, and

15 Q², Q³ and Q⁴ are each a hydrogen atom,
 or a salt thereof.

[0038]

[3A] The compound of [1], [2], [2A], [2B], [2C], [2D], [2E] or
 [3], wherein

20 Q¹, Q², Q³ and Q⁴ are each a hydrogen atom,
 or a salt thereof.

[0039]

[4] The compound of [1], [2], [2A], [2B], [2C], [2D], [2E], [3]
 or [3A], wherein

25 X is a hydrogen atom or an optionally substituted C₁₋₆ alkyl
 group;

Y¹, Y² and Y³ are each independently

(1) a hydrogen atom,

(2) a C₁₋₂₀ alkyl group optionally having substituent(s),

30 (3) a C₃₋₈ cycloalkyl group optionally having substituent(s),

(4) a C₆₋₁₄ aryl group optionally having substituent(s),

(5) a C₆₋₁₄ aryl C₁₋₆ alkyl group optionally having
 substituent(s),

(6) a 5- to 7-membered monocyclic aromatic heterocyclic group
 35 containing, as a ring-constituting atom besides carbon atom, 1

to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, and optionally having substituent(s), or
 (7) a bicyclic or tricyclic aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1
 5 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, and optionally having substituent(s);
 X and Y¹ are optionally bonded to each other to form, together with the adjacent nitrogen atom and carbon atom,
 a 5- to 7-membered monocyclic nitrogen-containing nonaromatic
 10 heterocycle containing, as a ring-constituting atom besides carbon atom, one nitrogen atom, and optionally further containing one hetero atom selected from a nitrogen atom, a sulfur atom and an oxygen atom, and optionally having substituent(s);
 15 Y¹ and Y² are optionally bonded to each other to form, together with the adjacent carbon atom,
 (1) a 5- to 7-membered monocyclic nonaromatic heterocycle containing, as a ring-constituting atom besides carbon atom, one or two hetero atoms selected from a nitrogen atom, a sulfur
 20 atom and an oxygen atom, and optionally having substituent(s), or
 (2) a 7- to 10-membered bridged heterocycle containing, as a ring-constituting atom besides carbon atom, one or two hetero atoms selected from a nitrogen atom, a sulfur atom and an
 25 oxygen atom, and optionally having substituent(s),
 or a salt thereof.

[0040]

[4A] The compound of [1], [2], [2A], [2B], [2C], [2D], [2E], [3], [3A] or [4], wherein

30 X is a hydrogen atom or an optionally substituted C₁₋₆ alkyl group;

Y¹, Y² and Y³ are each independently

(1) a hydrogen atom,

(2) a C₁₋₂₀ alkyl group optionally having 1 to 3 substituents
 35 selected from

- (a) an amino group,
 - (b) a C₁₋₆ alkoxy group,
 - (c) a C₆₋₁₄ aryloxy group, and
 - (d) a C₆₋₁₄ aryl C₁₋₆ alkyloxy group,
- 5 (3) a C₃₋₈ cycloalkyl group,
- (4) a C₆₋₁₄ aryl group optionally having 1 to 3 substituents selected from
- (a) a halogen atom,
 - (b) a C₁₋₆ alkoxy group,
 - 10 (c) a C₁₋₃ alkylenedioxy group, and
 - (d) a di-C₁₋₆ alkylamino group,
- (5) a C₆₋₁₄ aryl C₁₋₆ alkyl group,
- (6) a 5- to 7-membered monocyclic aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1
- 15 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, and optionally having substituent(s), or
- (7) a bicyclic or tricyclic aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1
- 20 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, and optionally having substituent(s);
- X and Y¹ are optionally bonded to each other to form, together with the adjacent nitrogen atom and carbon atom,
- an optionally substituted 5- to 7-membered monocyclic nitrogen-containing nonaromatic heterocycle containing, as a ring-
- 25 constituting atom besides carbon atom, one nitrogen atom and optionally further containing one hetero atom selected from a nitrogen atom, a sulfur atom and an oxygen atom; and
- Y¹ and Y² are optionally bonded to each other to form, together with the adjacent carbon atom,
- 30 (1) a C₃₋₈ cycloalkane ring optionally having substituent(s),
- (2) a 2,3-dihydroindene ring,
- (3) a fluorene ring,
- (4) a 5- to 7-membered monocyclic nonaromatic heterocycle containing, as a ring-constituting atom besides carbon atom,
- 35 one or two hetero atoms selected from a nitrogen atom, a sulfur

atom and an oxygen atom, and optionally having 1 to 3 substituents selected from

- (a) a C₁₋₆ alkyl group optionally having substituent(s),
- (b) a C₆₋₁₄ aryl C₁₋₆ alkyl group,
- 5 (c) a C₂₋₆ alkenyloxy-carbonyl group,
- (d) a C₃₋₈ cycloalkyl group, and
- (e) a C₆₋₁₄ aryl group, or

(5) a 7- to 10-membered bridged heterocycle containing, as a ring-constituting atom besides carbon atom, one or two hetero
10 atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, and optionally having substituent(s), or a salt thereof.

[0041]

[4B] The compound of [1], [2], [2A], [2B], [2C], [2D], [2E],
15 [3], [3A], [4] or [4A], wherein

X is a hydrogen atom or a C₁₋₆ alkyl group optionally substituted by one C₃₋₆ cycloalkyl group;

Y¹, Y² and Y³ are each independently

- (1) a hydrogen atom,
- 20 (2) a C₁₋₂₀ alkyl group optionally having 1 to 3 substituents selected from an amino group, a C₁₋₆ alkoxy group, a phenyl group, a phenyloxy group and a benzyloxy group,
- (3) a C₃₋₈ cycloalkyl group,
- (4) a phenyl group optionally having 1 to 3 substituents
25 selected from a halogen atom, a C₁₋₆ alkoxy group, a C₁₋₃ alkylenedioxy group and a di-C₁₋₆ alkylamino group,
- (5) a pyridyl group optionally having 1 to 3 C₁₋₆ alkoxy groups,
- (6) a naphthyl group,
- (7) a biphenyl group,
- 30 (8) a thienyl group,
- (9) an imidazolyl group,
- (10) a thiazolyl group,
- (11) a piperidyl group optionally having 1 to 3 C₁₋₆ alkyl groups,
- 35 (12) an imidazopyridyl group,

- (13) an imidazothiazolyl group,
- (14) a thienopyridyl group, or
- (15) a 1,8-naphthyridinyl group;

Y^1 and Y^2 are optionally bonded to each other to form, together
 5 with the adjacent carbon atom,

- a C₃₋₈ cycloalkane ring,
- a pyrrolidine ring,
- a piperidine ring,
- a tetrahydropyran ring,
- 10 a 2,3-dihydroindene ring,
- a fluorene ring,
- a 8-azabicyclo[3.2.1]octane ring, or
- a tetrahydrothiopyran ring, each of which optionally has 1 to 3
 substituents selected from

- 15 (1) a halogen atom,
- (2) a C₁₋₆ alkyl group optionally having 1 to 3 substituents
 selected from a halogen atom and a phenyl group,
- (3) a C₃₋₆ cycloalkyl group,
- (4) an oxo group,
- 20 (5) a phenyl group,
- (6) a C₂₋₆ alkenyloxy-carbonyl group, and
- (7) a C₁₋₆ alkyl-carbonyl group; and

X and Y^1 are optionally bonded to each other to form a
 pyrrolidine ring together with the adjacent nitrogen atom and
 25 carbon atom,
 or a salt thereof.

[0042]

[5] The compound of [1], [2], [2A], [2B], [2C], [2D], [2E], [3],
 [3A], [4], [4A] or [4B], wherein
 30 Z^1 , Z^2 and Z^3 are each a hydrogen atom, or a salt thereof.

[0043]

[6] The compound of [1], [2], [2A], [2B], [2C], [2D], [2E], [3],
 [3A], [4], [4A], [4B] or [5], wherein

A is

35 a phenyl-C₁₋₆ alkyl group,

- a C₃₋₆ cycloalkyl group,
a tetrahydronaphthyl group,
a phenyl group,
a biphenyl group,
5 a furyl group,
a thienyl group,
an oxazolyl group,
an isoxazolyl group,
a thiazolyl group,
10 a pyrazolyl group,
an indazolyl group,
a benzofuryl group,
a benzimidazolyl group,
a benzothiazolyl group,
15 an indolyl group, or
a tetrahydrobenzazepinyl group, each of which optionally has 1
to 3 substituents selected from
(1) a halogen atom,
(2) a C₁₋₆ alkyl group optionally having 1 to 3 substituents
20 selected from a halogen atom, a phenyl group, an imidazolyl
group and a triazolyl group,
(3) a C₁₋₆ alkoxy group optionally having 1 to 3 substituents
selected from a halogen atom and a phenyl group,
(4) a C₁₋₆ alkyl-carbonyl group,
25 (5) a di-C₁₋₆ alkylamino group,
(6) a C₁₋₆ alkylsulfonyl group,
(7) a sulfamoyl group,
(8) a C₁₋₆ alkylsulfonylamino group,
(9) an oxo group,
30 (10) a C₃₋₆ cycloalkyl group,
(11) a phenyl group optionally having 1 to 3 substituents
selected from a halogen atom and a C₁₋₆ alkyl group,
(12) a phenoxy group,
(13) a phenylcarbonylamino group,
35 (14) a benzyloxycarbonylamino group,

- (15) a benzoyl group,
- (16) a benzylamino group,
- (17) a pyrazolyl group,
- (18) a dihydropyrazolyl group optionally having 1 to 3
- 5 substituents selected from a C₁₋₆ alkyl group and an oxo group,
- (19) an oxazolyl group,
- (20) a thiazolyl group having 1 or 2 C₁₋₆ alkyl groups,
- (21) a tetrazolyl group,
- (22) a pyrrolyl group,
- 10 (23) a piperazinyl group having 1 to 3 C₁₋₆ alkyl groups,
- (24) an imidazolyl group,
- (25) a pyridyl group,
- (26) a pyrimidinyl group,
- (27) a piperidyl group optionally having one oxo group,
- 15 (28) a thienyl group,
- (29) a furyl group, and
- (30) a thiadiazolyl group;

R is a hydrogen atom or a C₁₋₆ alkyl group; or

A and R are optionally bonded to each other to form a

20 dihydroisoindole ring having 1 or 2 oxo groups;

Q¹ is a hydrogen atom or a C₁₋₆ alkyl group;

Q², Q³ and Q⁴ are each a hydrogen atom;

X is a hydrogen atom or a C₁₋₆ alkyl group optionally

substituted by one C₃₋₆ cycloalkyl group;

25 Y¹, Y² and Y³ are each independently

- (1) a hydrogen atom,
- (2) a C₁₋₂₀ alkyl group optionally having 1 to 3 substituents
- selected from an amino group, a C₁₋₆ alkoxy group, a phenyl
- group, a phenyloxy group and a benzyloxy group,
- 30 (3) a C₃₋₈ cycloalkyl group,
- (4) a phenyl group optionally having 1 to 3 substituents
- selected from a halogen atom, a C₁₋₆ alkoxy group, a C₁₋₃
- alkylenedioxy group and a di-C₁₋₆ alkylamino group,
- (5) a pyridyl group optionally having 1 to 3 C₁₋₆ alkoxy groups,
- 35 (6) a naphthyl group,

- (7) a biphenylyl group,
 - (8) a thienyl group,
 - (9) an imidazolyl group,
 - (10) a thiazolyl group,
 - 5 (11) a piperidyl group optionally having 1 to 3 C₁₋₆ alkyl groups,
 - (12) an imidazopyridyl group,
 - (13) an imidazothiazolyl group,
 - (14) a thienopyridyl group, or
 - 10 (15) a 1,8-naphthyridinyl group;
- Y¹ and Y² are optionally bonded to each other to form, together with the adjacent carbon atom,
- a C₃₋₈ cycloalkane ring,
 - a pyrrolidine ring,
 - 15 a piperidine ring,
 - a tetrahydropyran ring,
 - a 2,3-dihydroindene ring,
 - a fluorene ring,
 - a 8-azabicyclo[3.2.1]octane ring, or
 - 20 a tetrahydrothiopyran ring, each of which optionally has 1 to 3 substituents selected from
- (1) a halogen atom,
 - (2) a C₁₋₆ alkyl group optionally having 1 to 3 substituents selected from a halogen atom and a phenyl group,
 - 25 (3) a C₃₋₆ cycloalkyl group,
 - (4) an oxo group,
 - (5) a phenyl group,
 - (6) a C₂₋₆ alkenyloxy-carbonyl group, and
 - (7) a C₁₋₆ alkyl-carbonyl group;
- 30 X and Y¹ are optionally bonded to each other to form a pyrrolidine ring, together with the adjacent nitrogen atom and carbon atom; and
- Z¹, Z² and Z³ are each a hydrogen atom, or a salt thereof.

35 [0044]

[6A] The compound of [1], [2], [2A], [2B], [2C], [2D], [2E], [3], [3A], [4], [4A], [4B], [5] or [6], wherein

A is

a phenyl-C₁₋₆ alkyl group,

5 a phenyl group,

a biphenyl group, or

a pyrazolyl group, each of which optionally has 1 to 3 substituents selected from

(1) a halogen atom,

10 (2) a C₁₋₆ alkyl group optionally having 1 to 3 substituents selected from a halogen atom and a phenyl group,

(3) a phenylcarbonylamino group,

(4) a benzyloxycarbonylamino group, and

(5) a piperidyl group optionally having one oxo group;

15 R is a hydrogen atom; or

A and R are optionally bonded to each other to form a dihydroisoindole ring having 1 or 2 oxo groups;

Q¹ is a hydrogen atom or a C₁₋₆ alkyl group;

Q², Q³ and Q⁴ are each a hydrogen atom;

20 X is a hydrogen atom;

Y¹, Y² and Y³ are each independently

(1) a hydrogen atom,

(2) a C₁₋₂₀ alkyl group,

(3) a C₃₋₈ cycloalkyl group, or

25 (4) a phenyl group optionally having 1 to 3 C₁₋₆ alkoxy groups;

Y¹ and Y² are optionally bonded to each other to form, together with the adjacent carbon atom,

piperidine ring optionally having 1 to 3 C₁₋₆ alkyl groups;

X and Y¹ are optionally bonded to each other to form a

30 pyrrolidine ring together with the adjacent nitrogen atom and carbon atom; and

Z¹, Z² and Z³ are each a hydrogen atom,

or a salt thereof.

[0045]

35 [7] The compound of [1], [2], [2A], [2B], [2C], [2D], [2E], [3],

[3A], [4], [4A], [4B], [5], [6] or [6A], wherein

A is

a phenyl group optionally having 1 to 3 C₁₋₆ alkyl groups substituted by 1 to 3 halogen atoms,

5 a biphenyl group, or

a pyrazolyl group;

R is a hydrogen atom; or

A and R are optionally bonded to each other to form a dihydroisoindole ring having 1 or 2 oxo groups;

10 Q¹ is a hydrogen atom or a C₁₋₆ alkyl group;

Q², Q³ and Q⁴ are each a hydrogen atom;

X is a hydrogen atom;

Y¹, Y² and Y³ are each independently a hydrogen atom or a C₃₋₈ cycloalkyl group;

15 Y¹ and Y² are optionally bonded to each other to form, together with the adjacent carbon atom,

a piperidine ring optionally having 1 to 3 C₁₋₆ alkyl groups;

and

Z¹, Z² and Z³ are each a hydrogen atom,

20 or a salt thereof.

[0046]

[7A] N-(4-{trans-2-

[(cyclopropylmethyl)amino]cyclopropyl}phenyl)biphenyl-4-carboxamide,

25 N-(4-{trans-2-[(1-methylpiperidin-4-yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide,

N-(4-{(1R,2S)-2-[(1-methylpiperidin-4-yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide,

N-(4-{(1S,2R)-2-[(1-methylpiperidin-4-

30 yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide or

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-1H-pyrazole-4-carboxamide,

or a salt thereof.

[0047]

35 [8] N-(4-{trans-2-

[(cyclopropylmethyl)amino]cyclopropyl}phenyl)biphenyl-4-carboxamide or a salt thereof.

[0048]

[8A] The compound of [8], wherein N-(4-{trans-2-

5 [(cyclopropylmethyl)amino]cyclopropyl}phenyl)biphenyl-4-carboxamide is

N-(4-{(1R,2S)-2-

[(cyclopropylmethyl)amino]cyclopropyl}phenyl)biphenyl-4-carboxamide, or

10 N-(4-{(1S,2R)-2-

[(cyclopropylmethyl)amino]cyclopropyl}phenyl)biphenyl-4-carboxamide,

or a salt thereof.

[0049]

15 [9] N-(4-{trans-2-[(1-methylpiperidin-4-yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide or a salt thereof.

[0050]

[9A] The compound of [9], wherein N-(4-{trans-2-[(1-

20 methylpiperidin-4-yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide is

N-(4-{(1R,2S)-2-[(1-methylpiperidin-4-

yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide, or

N-(4-{(1S,2R)-2-[(1-methylpiperidin-4-

25 yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide, or a salt thereof.

[0051]

[10] N-(4-{trans-2-

[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-1H-pyrazole-4-

30 carboxamide or a salt thereof.

[0052]

[11] A medicament containing the compound of [1] or a salt thereof.

[0053]

35 [12] The medicament of [11], which is a prophylactic or

therapeutic agent for cancer.

[0054]

[13] The medicament of [11], which is an LSD1 inhibitor.

[0055]

5 [14] The medicament of [11], which is a prophylactic or therapeutic agent for schizophrenia, Alzheimer's disease, Parkinson's disease or Huntington's chorea.

[0056]

[15] A method for the prophylaxis or treatment of schizophrenia,
10 Alzheimer's disease, Parkinson's disease or Huntington's chorea, comprising administering an effective amount of the compound of [1] or a salt thereof to a mammal.

[0057]

[15A] A method for the prophylaxis or treatment of cancer,
15 comprising administering an effective amount of the compound of [1] or a salt thereof to a mammal.

[0058]

[16] Use of the compound of [1] or a salt thereof for the production of a prophylactic or therapeutic agent for
20 schizophrenia, Alzheimer's disease, Parkinson's disease or Huntington's chorea.

[0059]

[16A] Use of the compound of [1] or a salt thereof for the production of a prophylactic or therapeutic agent for cancer.

25 [0060]

[17] The compound of [1] or a salt thereof for use in the prophylaxis or treatment of schizophrenia, Alzheimer's disease, Parkinson's disease or Huntington's chorea.

[0061]

30 [17A] The compound of [1] or a salt thereof for use in the prophylaxis or treatment of cancer.

[0062]

[18] A method of inhibiting LSD1, comprising administering an effective amount of the compound of [1] or a salt thereof to a
35 mammal.

[0063]

[18A] A prophylactic or therapeutic agent for schizophrenia, Alzheimer's disease, Parkinson's disease or Huntington's chorea, comprising the compound of [1] or a salt thereof.

5 [0064]

[18B] A prophylactic or therapeutic agent for cancer, comprising the compound of [1] or a salt thereof.

[0065]

[18C] Use of the compound of [1] or a salt thereof for the
10 production of an LSD1 inhibitor.

[0066]

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

Examples of the "substituent" for Q^1 , Q^2 , Q^3 , Q^4 , Z^1 , Z^2 or
15 Z^3 include a halogen atom, a cyano group, a nitro group, a hydrocarbon group optionally having substituent(s), a heterocyclic group optionally having substituent(s), an acyl group optionally having substituent(s), an amino group optionally having substituent(s), a carbamoyl group optionally
20 having substituent(s), a sulfamoyl group optionally having substituent(s), a hydroxy group optionally having a substituent, a sulfanyl (SH) group optionally having a substituent and the like.

[0067]

25 Examples of the "halogen atom" include fluorine, chlorine, bromine and iodine.

[0068]

Examples of the "hydrocarbon group" in the "hydrocarbon group optionally having substituent(s)" for A, R, Y^1 , Y^2 or Y^3 ,
30 and in the "hydrocarbon group optionally having substituent(s)" exemplified as the substituent for Q^1 , Q^2 , Q^3 , Q^4 , Z^1 , Z^2 or Z^3 include

(1) a C_{1-20} alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl,
35 octyl, nonyl, decyl, undecyl, dodecyl), preferably, a C_{1-6} alkyl

group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl),

(2) a C₂₋₆ alkenyl group (e.g., vinyl, allyl, isopropenyl, 2-butenyl),

5 (3) a C₂₋₆ alkynyl group (e.g., ethynyl, propargyl, 2-butyne),

(4) a C₃₋₈ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl),

(5) a C₃₋₈ cycloalkenyl group (e.g., cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl),

10 (6) a C₆₋₁₄ aryl group (e.g., phenyl, 1-naphthyl, 2-naphthyl, 2-anthryl, biphenyl),

(7) a C₆₋₁₄ aryl C₁₋₆ alkyl group (e.g., benzyl, phenethyl, diphenylmethyl, triphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-

15 phenylbutyl, 5-phenylpentyl),

(8) a C₆₋₁₄ aryl C₁₋₆ alkyl C₆₋₁₄ aryl group (e.g., benzylphenyl, phenethylphenyl), and

(9) a C₁₀₋₁₄ cyclic hydrocarbon group (e.g., tetrahydronaphthyl).
[0069]

20 Examples of the substituent of the aforementioned "hydrocarbon group optionally having substituent(s)" include substituents selected from the following substituent group A and the like.

[Substituent group A]

25 (1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine),

(2) a nitro group,

(3) a cyano group,

(4) a hydroxy group,

(5) an optionally halogenated C₁₋₆ alkoxy group,

30 (6) an optionally halogenated C₁₋₆ alkylthio group,

(7) a C₆₋₁₄ aryloxy group (e.g., phenoxy, naphthoxy),

(8) a C₆₋₁₄ aryl C₁₋₆ alkyloxy group (e.g., benzyloxy),

(9) a 5- to 7-membered heterocyclyloxy group,

(10) an amino group,

35 (11) a mono- or di-C₁₋₆ alkylamino group (e.g., methylamino,

- ethylamino, propylamino, isopropylamino, butylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, N-ethyl-N-methylamino),
- (12) a 4- to 7-membered (preferably, 5- to 7-membered) heterocyclic group optionally having substituent(s),
- (13) a formyl group,
- (14) a carboxy group,
- (15) a carbamoyl group,
- (16) a thiocarbamoyl group,
- (17) an optionally halogenated C₁₋₆ alkyl-carbonyl group,
- (18) a C₁₋₆ alkoxy-carbonyl group,
- (19) a C₆₋₁₄ aryl-carbonyl group (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl),
- (20) a heterocyclylcarbonyl group optionally having substituent(s),
- (21) a C₆₋₁₄ aryloxy-carbonyl group (e.g., phenyloxycarbonyl, 1-naphthyloxycarbonyl, 2-naphthyloxycarbonyl),
- (22) a C₆₋₁₄ aryl C₁₋₆ alkyloxy-carbonyl group (e.g., benzyloxycarbonyl, phenethyloxycarbonyl),
- (23) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, N-ethyl-N-methylcarbamoyl),
- (24) a carbamoyl-C₁₋₆ alkyl-carbamoyl group (e.g., carbamoylmethylcarbamoyl, carbamoylethylcarbamoyl),
- (25) a C₆₋₁₄ aryl-carbamoyl group (e.g., phenylcarbamoyl),
- (26) a heterocyclylcarbamoyl group optionally having substituent(s),
- (27) an optionally halogenated C₁₋₆ alkylsulfonyl group,
- (28) a C₆₋₁₄ arylsulfonyl group (e.g., phenylsulfonyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl),
- (29) a formylamino group,
- (30) an optionally halogenated C₁₋₆ alkyl-carbonylamino group,
- (31) a C₆₋₁₄ aryl C₁₋₆ alkylamino group (e.g., benzylamino),
- (32) a C₆₋₁₄ aryl-carbonylamino group (e.g., phenylcarbonylamino, naphthylcarbonylamino),

- (33) a C₁₋₆ alkoxy-carbonylamino group (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, tert-butoxycarbonylamino),
- (34) a C₆₋₁₄ aryl C₁₋₆ alkyloxy-carbonylamino group (e.g., benzyloxycarbonylamino),
- (35) a C₁₋₆ alkylsulfonylamino group (e.g., methylsulfonylamino, ethylsulfonylamino),
- (36) a C₁₋₆ alkyl-carbonyloxy group (e.g., acetoxy, propanoyloxy),
- (37) a C₆₋₁₄ aryl-carbonyloxy group (e.g., benzoyloxy, 1-naphthoyloxy, 2-naphthoyloxy),
- (38) a C₁₋₆ alkoxy-carbonyloxy group (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy),
- (39) a mono- or di-C₁₋₆ alkyl-carbamoyloxy group (e.g., methylcarbamoyloxy, ethylcarbamoyloxy, dimethylcarbamoyloxy, diethylcarbamoyloxy),
- (40) a C₆₋₁₄ aryl-carbamoyloxy group (e.g., phenylcarbamoyloxy, naphthylcarbamoyloxy),
- (41) a 5- or 6-membered heterocyclylcarbonyloxy group (e.g., nicotinoyloxy),
- (42) a sulfamoyl group,
- (43) an oxo group,
- (44) a C₃₋₆ cycloalkyl group, and
- (45) a phenyl group optionally having 1 to 3 substituents selected from a halogen atom and a C₁₋₆ alkyl group.

The number of the substituents is, for example, 1 to 5, preferably 1 to 3. When the number of the substituents is two or more, the respective substituents may be the same or different.

[0070]

When the "hydrocarbon group" of the aforementioned "hydrocarbon group optionally having substituent(s)" is a C₃₋₈ cycloalkyl group, a C₃₋₈ cycloalkenyl group, a C₆₋₁₄ aryl group, a C₆₋₁₄ aryl C₁₋₆ alkyl group or a C₆₋₁₄ aryl C₁₋₆ alkyl C₆₋₁₄ aryl group, examples of the substituent of the "hydrocarbon group

optionally having substituent(s)" include a substituent selected from

- (1) the aforementioned substituent group A,
- (2) a C₁₋₃ alkylenedioxy group (e.g., methylenedioxy, ethylenedioxy),
- (3) a C₁₋₆ alkyl group optionally having 1 to 5 halogen atoms, and
- (4) a C₁₋₆ alkyl group optionally having a 5-membered heterocyclic group (e.g., imidazolyl, triazolyl) containing 2 or 3 nitrogen atoms as a ring-constituting atom besides carbon atom, and the like.

The number of the substituents is, for example, 1 to 5, preferably 1 to 3. When the number of the substituents is two or more, the respective substituents may be the same or different.

[0071]

Examples of the aforementioned "optionally halogenated C₁₋₆ alkoxy group" include a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy, propoxy, butoxy, pentyloxy) optionally having 1 to 5, preferably 1 to 3, halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and the like. Specific examples include methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy and the like.

[0072]

Examples of the aforementioned "optionally halogenated C₁₋₆ alkylthio group" include a C₁₋₆ alkylthio group (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio) optionally having 1 to 5, preferably 1 to 3, halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and the like. Specific examples include methylthio, difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio,

pentylthio, hexylthio and the like.

[0073]

Examples of the "4- to 7-membered heterocyclic group" of the aforementioned "4- to 7-membered heterocyclic group optionally having substituent(s)" include a 4- to 7-membered (preferably, 5- to 7-membered) heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom and the like. Preferable examples of the 4- to 7-membered heterocyclic group include a 4- to 7-membered (preferably, 5- to 7-membered) nonaromatic heterocyclic group such as pyrrolidinyl (e.g., 1-, 2- or 3-pyrrolidinyl); imidazolidinyl (e.g., 1-, 2-, 4- or 5-imidazolidinyl); imidazolinyl (e.g., 2- or 4-imidazolinyl); pyrazolidinyl (e.g., 2-, 3- or 4-pyrazolidinyl); piperidinyl (e.g., 1-, 2-, 3- or 4-piperidinyl); piperazinyl (e.g., 1- or 2-piperazinyl); tetrahydropyranyl; morpholinyl; thiomorpholinyl; dihydropyrazolyl and the like; and a 5- to 7-membered aromatic heterocyclic group such as thienyl (e.g., 2- or 3-thienyl); furyl (e.g., 2- or 3-furyl); pyrrolyl (e.g., 1-, 2- or 3-pyrrolyl); imidazolyl (e.g., 1-, 2- or 4-imidazolyl); thiazolyl (e.g., 2-, 4- or 5-thiazolyl); oxazolyl (e.g., 2-, 4- or 5-oxazolyl); isothiazolyl (e.g., 3-isothiazolyl); isoxazolyl (e.g., 3-isoxazolyl); pyridyl (e.g., 2-, 3- or 4-pyridyl); pyrazolyl (e.g., 1-, 3- or 4-pyrazolyl); pyrazinyl (e.g., 2-pyrazinyl); pyrimidinyl (e.g., 2-, 4- or 5-pyrimidinyl); pyridazinyl (e.g., 3- or 4-pyridazinyl); oxadiazolyl (e.g., 1,2,4-oxadiazol-5-yl; 1,2,4-oxadiazol-3-yl); thiadiazolyl (e.g., 1,2,4-thiadiazol-5-yl; 1,2,4-thiadiazol-3-yl); triazolyl (e.g., 1,2,3-triazol-1-yl; 1,2,3-triazol-4-yl; 1,2,4-triazol-1-yl; 1,2,4-triazol-3-yl); tetrazolyl (e.g., 1- or 5-tetrazolyl); pyranyl (e.g., 2-, 3- or 4-pyranyl) and the like.

[0074]

Examples of the aforementioned "optionally halogenated

C₁₋₆ alkyl-carbonyl group" include a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, propanoyl, butanoyl, pentanoyl, hexanoyl) optionally having 1 to 5, preferably 1 to 3, halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and the like.

5 Specific examples include acetyl, monochloroacetyl, trifluoroacetyl, trichloroacetyl, propanoyl, butanoyl, pentanoyl, hexanoyl and the like.

[0075]

Examples of the aforementioned "C₁₋₆ alkoxy-carbonyl group" include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl and the like.

[0076]

Examples of the "heterocyclylcarbonyl group" of the aforementioned "heterocyclylcarbonyl group optionally having
15 substituent(s)" include nicotinoyl, isonicotinoyl, thenoyl (e.g., 2-thenoyl, 3-thenoyl), furoyl (e.g., 2-furoyl, 3-furoyl), morpholinocarbonyl, piperidinocarbonyl, pyrrolidin-1-ylcarbonyl, indolylcarbonyl and the like.

[0077]

20 Examples of the "heterocyclylcarbamoyl group" of the aforementioned "heterocyclylcarbamoyl group optionally having substituent(s)" include morpholinocarbamoyl, piperidinocarbamoyl, pyridylcarbamoyl (e.g., 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl), thienylcarbamoyl (e.g.,
25 2-thienylcarbamoyl, 3-thienylcarbamoyl), indolylcarbamoyl and the like.

[0078]

Examples of the aforementioned "optionally halogenated C₁₋₆ alkylsulfonyl group" include a C₁₋₆ alkylsulfonyl group
30 (e.g., methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, sec-butylsulfonyl, tert-butylsulfonyl) optionally having 1 to 5, preferably 1 to 3, halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and the like. Specific examples include methylsulfonyl,
35 difluoromethylsulfonyl, trifluoromethylsulfonyl, ethylsulfonyl,

propylsulfonyl, isopropylsulfonyl, butylsulfonyl, 4,4,4-trifluorobutylsulfonyl, pentylsulfonyl, hexylsulfonyl and the like.

[0079]

5 Examples of the aforementioned "optionally halogenated C₁₋₆ alkyl-carbonylamino group" include a C₁₋₆ alkyl-carbonylamino group (e.g., acetylamino, propanoylamino, butanoylamino) optionally having 1 to 5, preferably 1 to 3, halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and
10 the like. Specific examples include acetylamino, trifluoroacetylamino, propanoylamino, butanoylamino and the like.

[0080]

 Examples of the substituent of the aforementioned "5- to
15 7-membered heterocyclic group optionally having substituent(s)", "heterocyclylcarbonyl group optionally having substituent(s)" and "heterocyclylcarbamoyl group optionally having substituent(s)" include a substituent selected from the following substituent group B and the like.

20 [Substituent group B]

- (1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine),
- (2) a C₁₋₃ alkylenedioxy group (e.g., methylenedioxy, ethylenedioxy),
- (3) a nitro group,
- 25 (4) a cyano group,
- (5) an oxo group,
- (6) an optionally halogenated C₁₋₆ alkyl group,
- (7) a carbamoyl-C₁₋₆ alkyl group (e.g., carbamoylmethyl),
- (8) an optionally halogenated C₃₋₆ cycloalkyl group,
- 30 (9) a C₆₋₁₄ aryl group (e.g., phenyl, naphthyl),
- (10) a C₆₋₁₄ aryl C₁₋₆ alkyl group (e.g., benzyl, phenethyl),
- (11) an optionally halogenated C₁₋₆ alkoxy group,
- (12) an optionally halogenated C₁₋₆ alkylthio group,
- (13) a hydroxy group,
- 35 (14) an amino group,

- (15) a mono- or di-C₁₋₆ alkylamino group (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, N-ethyl-N-methylamino),
- 5 (16) a formyl group,
- (17) a carboxy group,
- (18) a carbamoyl group,
- (19) a thiocarbamoyl group,
- (20) an optionally halogenated C₁₋₆ alkyl-carbonyl group,
- 10 (21) a C₁₋₆ alkoxy-carbonyl group,
- (22) a C₂₋₆ alkenyloxy-carbonyl group (e.g., allyloxycarbonyl),
- (23) a C₆₋₁₄ aryl-carbonyl group (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl),
- (24) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g.,
- 15 methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, N-ethyl-N-methylcarbamoyl),
- (25) a mono- or di-C₆₋₁₄ aryl C₁₋₆ alkyl-carbamoyl group (e.g., benzylcarbamoyl),
- (26) an optionally halogenated C₁₋₆ alkylsulfonyl group,
- 20 (27) a C₆₋₁₄ arylsulfonyl group (e.g., phenylsulfonyl),
- (28) a sulfamoyl group,
- (29) a mono- or di-C₁₋₆ alkyl-sulfamoyl group (e.g., methylsulfamoyl, ethylsulfamoyl, dimethylsulfamoyl, diethylsulfamoyl, N-ethyl-N-methylsulfamoyl),
- 25 (30) a formylamino group,
- (31) an optionally halogenated C₁₋₆ alkyl-carbonylamino group,
- (32) a C₁₋₆ alkoxy-carbonylamino group (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino),
- 30 (33) a C₁₋₆ alkylsulfonylamino group (e.g., methylsulfonylamino, ethylsulfonylamino),
- (34) a C₁₋₆ alkyl-carbonyloxy group (e.g., acetoxy, propanoyloxy),
- (35) a C₁₋₆ alkoxy-carbonyloxy group (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy),
- 35

- (36) a 5- or 6-membered aromatic heterocyclic group (e.g., tetrazolyl, thiazolyl, oxazolyl, furyl, thienyl, pyrazolyl, pyrrolyl, imidazolyl, pyridyl, pyrimidinyl, thiadiazolyl) optionally having 1 to 3 C₁₋₆ alkyl groups,
- 5 (37) a dihydropyrazolyl group optionally having 1 to 3 substituents selected from a C₁₋₆ alkyl group and an oxo group,
- (38) a piperazinyl group having 1 to 3 C₁₋₆ alkyl groups,
- (39) a piperidyl group optionally having one oxo group,
- (40) a C₁₋₆ alkyl group optionally having 1 to 3 substituents
- 10 selected from a halogen atom, a phenyl group, an imidazolyl group and a triazolyl group,
- (41) a C₁₋₆ alkoxy group optionally having 1 to 3 substituents selected from a halogen atom and a phenyl group,
- (42) a C₁₋₆ alkylsulfonylamino group,
- 15 (43) a phenyl group optionally having 1 to 3 substituents selected from a halogen atom and a C₁₋₆ alkyl group,
- (44) a phenoxy group,
- (45) a phenylcarbonylamino group,
- (46) a benzyloxycarbonylamino group, and
- 20 (47) a benzylamino group.

The number of the substituents is, for example, 1 to 3. When the number of the substituents is two or more, the respective substituents may be the same or different.

[0081]

- 25 Examples of the aforementioned "optionally halogenated C₁₋₆ alkyl group" include a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl) optionally having 1 to 5, preferably 1 to 3, halogen atoms (e.g., fluorine, chlorine, bromine, iodine).
- 30 Specific examples include methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl,
- 35 hexyl, 6,6,6-trifluorohexyl and the like.

[0082]

Examples of the aforementioned "optionally halogenated C₃₋₆ cycloalkyl group" include a C₃₋₆ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) optionally
 5 having 1 to 5, preferably 1 to 3, halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and the like. Specific examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4,4-dichlorocyclohexyl, 2,2,3,3-tetrafluorocyclopentyl, 4-chlorocyclohexyl and the like.

10 [0083]

Examples of each of the aforementioned "optionally halogenated C₁₋₆ alkoxy group", "optionally halogenated C₁₋₆ alkylthio group", "optionally halogenated C₁₋₆ alkyl-carbonyl group", "C₁₋₆ alkoxy-carbonyl group", "optionally halogenated
 15 C₁₋₆ alkylsulfonyl group" and "optionally halogenated C₁₋₆ alkyl-carbonylamino group" include those exemplified as the "substituent" of the aforementioned "hydrocarbon group optionally having substituent(s)".

[0084]

20 Examples of the "heterocyclic group" of the "heterocyclic group optionally having substituent(s)" for A, R, Y¹, Y² or Y³, and the "heterocyclic group optionally having substituent(s)" exemplified as the substituent for Q¹, Q², Q³, Q⁴, Z¹, Z² or Z³ include (i) an aromatic heterocyclic group, (ii) a nonaromatic
 25 heterocyclic group and (iii) a 7- to 10-membered bridged heterocyclic group, each of which contains, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

[0085]

30 Here, examples of the "aromatic heterocyclic group" include a 4- to 14-membered (preferably 4- to 10-membered) aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, and the like.
 35 Preferable examples of the "aromatic heterocyclic group"

include a monocyclic aromatic heterocyclic group such as thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl,
 5 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, triazolyl, tetrazolyl, furazanyl, pyranyl and the like;

a fused polycyclic (preferably bicyclic or tricyclic) aromatic heterocyclic group such as benzothiophenyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzisothiazolyl,
 10 naphtho[2,3-b]thiophenyl, phenoxathiinyl, indolyl, isoindolyl, 1H-indazolyl, purinyl, 4H-quinoliziny, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl (e.g., 1,8-naphthyridinyl), quinoxalinyl, quinazolinyl, cinnolinyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, phenazinyl,
 15 phenothiazinyl, phenoxazinyl, phthalimido, imidazopyridyl, imidazothiazolyl, thienopyridyl etc., and the like.

[0086]

Examples of the "nonaromatic heterocyclic group" include a 4- to 14-membered (preferably 4- to 10-membered) nonaromatic
 20 heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom and the like. Preferable examples of the "nonaromatic heterocyclic group" include a monocyclic nonaromatic heterocyclic group such as
 25 azetidiny, tetrahydrothiophenyl, tetrahydrofuranyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, oxazolinyl, oxazolidinyl, pyrazolinyl, pyrazolidinyl, thiazolinyl, thiazolidinyl, tetrahydrothiazolyl, tetrahydroisothiazolyl, tetrahydrooxazolyl, tetrahydroisoxazolyl, piperidinyl,
 30 piperazinyl, tetrahydropyridinyl, dihydropyridinyl, tetrahydropyrimidinyl, tetrahydropyridazinyl, tetrahydropyranyl, azepanyl, morpholinyl, thiomorpholinyl, diazepanyl, azepinyl, azocanyl, diazocanyl and the like;

a fused polycyclic (preferably bicyclic or tricyclic)
 35 nonaromatic heterocyclic group such as dihydrobenzofuranyl,

dihydrobenzimidazolyl, dihydrobenzoxazolyl,
 dihydrobenzothiazolyl, dihydrobenzisothiazolyl,
 dihydronaphtho[2,3-b]thiophenyl, tetrahydroisoquinolyl,
 tetrahydroquinolyl, indolinyl, isoindolinyl,
 5 tetrahydrothieno[2,3-c]pyridinyl, tetrahydrobenzazepinyl,
 tetrahydroquinoxalinyl, tetrahydrophenanthridinyl,
 hexahydrophenothiazinyl, hexahydrophenoxazinyl,
 tetrahydrophthalazinyl, tetrahydronaphthyridinyl,
 tetrahydroquinazolinyl, tetrahydrocinnolinyl,
 10 tetrahydrocarbazolyl, tetrahydro- β -carbolinyl,
 tetrahydroacridinyl, tetrahydrophenazinyl,
 tetrahydrothioxanthenyl, octahydroisoquinolyl and the like.
 [0087]

Preferable examples of the "7- to 10-membered bridged
 15 heterocyclic group" include quinuclidinyl, 7-
 azabicyclo[2.2.1]heptanyl and the like.
 [0088]

Examples of the substituent of the "heterocyclic group
 optionally having substituent(s)" include substituents selected
 20 from the aforementioned substituent group B and the like.

The number of the substituents is, for example, 1 to 3.
 When the number of the substituents is two or more, the
 respective substituents may be the same or different.
 [0089]

25 Examples of the acyl group of the "acyl group optionally
 having substituent(s)" exemplified as the substituent for Q^1 ,
 Q^2 , Q^3 , Q^4 , Z^1 , Z^2 or Z^3 include $-COR^{1A}$, $-CO-OR^{1A}$, $-SO_2R^{1A}$, $-SOR^{1A}$,
 $-PO(OR^{1A})(OR^{2A})$ wherein R^{1A} and R^{2A} are each independently a
 hydrogen atom, a hydrocarbon group or a heterocyclic group, and
 30 the like.
 [0090]

Examples of the "hydrocarbon group" for R^{1A} or R^{2A} include
 the "hydrocarbon groups" exemplified for the "hydrocarbon group
 optionally having substituent(s)" exemplified as the
 35 substituent for Q^1 , Q^2 , Q^3 , Q^4 , Z^1 , Z^2 or Z^3 . The hydrocarbon

group is preferably a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₈ cycloalkyl group, a C₃₋₈ cycloalkenyl group, a C₆₋₁₄ aryl group, a C₆₋₁₄ aryl C₁₋₆ alkyl group and the like.

[0091]

5 Examples of the "heterocyclic group" for R^{1A} or R^{2A} include the "heterocyclic groups" exemplified for the "heterocyclic group optionally having substituent(s)" exemplified as the substituent for Q¹, Q², Q³, Q⁴, Z¹, Z² or Z³. The heterocyclic group is preferably thiazolyl, oxazolyl, 10 isothiazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrazinyl, benzoxazolyl, benzothiazolyl, quinolyl, isoquinolyl, pyrrolidinyl, piperidinyl, piperazinyl and the like.

[0092]

The acyl group optionally has 1 to 3 substituents at 15 substitutable position(s). Examples of such substituent include an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, ethyl); an optionally halogenated C₁₋₆ alkoxy group (e.g., methoxy, ethoxy); a halogen atom (e.g., fluorine, chlorine, bromine, iodine); a nitro group; a hydroxy group; an amino 20 group (e.g., methylamino, dimethylamino) optionally mono- or di-substituted by a C₁₋₆ alkyl group (e.g., methyl, ethyl); a C₁₋₆ alkoxy-carbonylamino group (e.g., tert-butoxycarbonylamino) and the like.

[0093]

25 Preferable examples of the acyl group include a formyl group, a carboxyl group, a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl), a C₂₋₆ alkenyl-carbonyl group (e.g., crotonoyl), a C₃₋₈ cycloalkyl-carbonyl group (e.g., 30 cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl), a C₃₋₈ cycloalkenyl-carbonyl group (e.g., 2-cyclohexenecarbonyl), a C₆₋₁₄ aryl-carbonyl group (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl), a C₆₋₁₄ aryl C₁₋₆ alkyl-carbonyl group (e.g., benzylcarbonyl, phenethylcarbonyl), an 35 aromatic heterocyclylcarbonyl group (e.g., nicotinoyl,

isonicotinoyl), a nonaromatic heterocyclylcarbonyl group (e.g., pyrrolidinylcarbonyl, piperidinylcarbonyl), a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl), a C₆₋₁₄ aryloxy-carbonyl group (e.g., phenyloxycarbonyl, naphthyloxycarbonyl), a C₆₋₁₄ aryl C₁₋₆ alkyloxy-carbonyl group (e.g., benzyloxycarbonyl, phenethyloxycarbonyl), a C₁₋₆ alkylsulfinyl group (e.g., methylsulfinyl, ethylsulfinyl), a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl), a C₆₋₁₄ arylsulfonyl group (e.g., phenylsulfonyl), a phosphono group, a mono- or di-C₁₋₆ alkylphosphono group (e.g., dimethylphosphono, diethylphosphono, diisopropylphosphono, dibutylphosphono) and the like.

[0094]

Examples of the "amino group optionally having substituent(s)", "carbamoyl group optionally having substituent(s)" and "sulfamoyl group optionally having substituent(s)" exemplified as the substituent for Q¹, Q², Q³, Q⁴, Z¹, Z² or Z³ include an amino group, a carbamoyl group and a sulfamoyl group, each of which optionally has 1 or 2 substituents selected from

(1) the "hydrocarbon group optionally having substituent(s)", "acyl group optionally having substituent(s)" and "heterocyclic group optionally having substituent(s)", each exemplified as the substituent for Q¹, Q², Q³, Q⁴, Z¹, Z² or Z³; and

(2) a carbamoyl group optionally having 1 or 2 substituents selected from a C₁₋₆ alkyl group (e.g., methyl, ethyl), a C₃₋₈ cycloalkyl group (e.g., cyclopropyl, cyclohexyl), a C₆₋₁₄ aryl group (e.g., phenyl) and a C₆₋₁₄ aryl C₁₋₆ alkyl group (e.g., benzyl). When the nitrogen atom constituting the amino group, carbamoyl group and sulfamoyl group is substituted by two substituents, the substituents may form, together with the adjacent nitrogen atom, a nitrogen-containing heterocycle. Examples of the "nitrogen-containing heterocycle" include a 5- to 7-membered nitrogen-containing heterocycle containing one

nitrogen atom as a ring-constituting atom besides carbon atom, and optionally further containing 1 or 2 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

Preferable examples of the nitrogen-containing heterocycle
 5 include pyrrolidine, imidazolidine, pyrazolidine, piperidine, piperazine, morpholine, thiomorpholine and the like.

[0095]

The "amino group optionally having substituent(s)", "carbamoyl group optionally having substituent(s)" and
 10 "sulfamoyl group optionally having substituent(s)" are preferably an amino group, a carbamoyl group and a sulfamoyl group, respectively, each of which optionally has "1 or 2 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₈ cycloalkyl group, a C₆₋₁₄ aryl group, a C₆₋₁₄ aryl
 15 C₁₋₆ alkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₆₋₁₄ aryl C₁₋₆ alkyl-carbonyl group, an aromatic heterocyclylcarbonyl group, a nonaromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, an aromatic heterocyclic group, a carbamoyl group, a mono- or di-
 20 C₁₋₆ alkyl-carbamoyl group and a mono- or di-C₆₋₁₄ aryl C₁₋₆ alkyl-carbamoyl group, each of which optionally has 1 to 3 substituents selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine), an optionally halogenated C₁₋₆ alkoxy group, a hydroxy group, a nitro group, an amino group
 25 and a carbamoyl group".

[0096]

Preferable examples of the amino group optionally having substituent(s) include an amino group, a mono- or di-C₁₋₆ alkylamino group (e.g., methylamino, dimethylamino, ethylamino,
 30 diethylamino, propylamino, dibutylamino), a mono- or di-C₂₋₆ alkenylamino group (e.g., diallylamino), a mono- or di-C₃₋₈ cycloalkylamino group (e.g., cyclopropylamino, cyclohexylamino), a mono- or di-C₆₋₁₄ arylamino group (e.g., phenylamino), a mono- or di-C₆₋₁₄ aryl C₁₋₆ alkylamino group (e.g., benzylamino,
 35 dibenzylamino), a mono- or di-(optionally halogenated C₁₋₆

alkyl)-carbonylamino group (e.g., acetylamino, propionylamino),
 a mono- or di-C₆₋₁₄ aryl-carbonylamino group (e.g.,
 benzoylamino), a mono- or di-C₆₋₁₄ aryl C₁₋₆ alkyl-carbonylamino
 group (e.g., benzylcarbonylamino), a mono- or di-aromatic
 5 heterocyclylcarbonylamino group (e.g., nicotinoylamino,
 isonicotinoylamino), a mono- or di-nonaromatic
 heterocyclylcarbonylamino group (e.g.,
 piperidinylcarbonylamino), a mono- or di-C₁₋₆ alkoxy-
 carbonylamino group (e.g., tert-butoxycarbonylamino), an
 10 aromatic heterocyclylamino group (e.g., pyridylamino), a
 carbamoylamino group, a (mono- or di-C₁₋₆ alkyl-carbamoyl)amino
 group (e.g., methylcarbamoylamino), a (mono- or di-C₆₋₁₄ aryl C₁₋₆
 alkyl-carbamoyl)amino group (e.g., benzylcarbamoylamino) and
 the like.

15 [0097]

Preferable examples of the carbamoyl group optionally
 having substituent(s) include a carbamoyl group, a mono- or di-
 C₁₋₆ alkyl-carbamoyl group (e.g., methylcarbamoyl,
 ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, N-ethyl-N-
 20 methylcarbamoyl), a mono- or di-C₂₋₆ alkenyl-carbamoyl group
 (e.g., diallylcarbamoyl), a mono- or di-C₃₋₈ cycloalkyl-
 carbamoyl group (e.g., cyclopropylcarbamoyl,
 cyclohexylcarbamoyl), a mono- or di-C₆₋₁₄ aryl-carbamoyl group
 (e.g., phenylcarbamoyl), a mono- or di-C₆₋₁₄ aryl C₁₋₆ alkyl-
 25 carbamoyl group (e.g., benzylcarbamoyl, phenethylcarbamoyl), a
 mono- or di-C₁₋₆ alkyl-carbonyl-carbamoyl group (e.g.,
 acetylcarbamoyl, propionylcarbamoyl), a mono- or di-C₆₋₁₄ aryl-
 carbonyl-carbamoyl group (e.g., benzoylcarbamoyl), an aromatic
 heterocyclylcarbamoyl group (e.g., pyridylcarbamoyl), and a
 30 nitrogen-containing heterocyclylcarbonyl group (e.g.,
 morpholinocarbonyl).

[0098]

Preferable examples of the sulfamoyl group optionally
 having substituent(s) include a sulfamoyl group, a mono- or di-
 35 C₁₋₆ alkyl-sulfamoyl group (e.g., methylsulfamoyl,

ethylsulfamoyl, dimethylsulfamoyl, diethylsulfamoyl, N-ethyl-N-methylsulfamoyl), a mono- or di-C₂₋₆ alkenyl-sulfamoyl group (e.g., diallylsulfamoyl), a mono- or di-C₃₋₈ cycloalkyl-sulfamoyl group (e.g., cyclopropylsulfamoyl, cyclohexylsulfamoyl), a mono- or di-C₆₋₁₄ aryl-sulfamoyl group (e.g., phenylsulfamoyl), a mono- or di-C₆₋₁₄ aryl C₁₋₆ alkyl-sulfamoyl group (e.g., benzylsulfamoyl, phenethylsulfamoyl), a mono- or di-C₁₋₆ alkyl-carbonyl-sulfamoyl group (e.g., acetylsulfamoyl, propionylsulfamoyl), a mono- or di-C₆₋₁₄ aryl-carbonyl-sulfamoyl group (e.g., benzoylsulfamoyl), an aromatic heterocyclylsulfamoyl group (e.g., pyridylsulfamoyl) and the like.

[0099]

Examples of the "hydroxy group optionally having a substituent" and "sulfanyl group optionally having a substituent" exemplified as the substituent for Q¹, Q², Q³, Q⁴, Z¹, Z² or Z³ include a hydroxy group and a sulfanyl group, each optionally having a substituent selected from the "hydrocarbon group optionally having substituent(s)", "acyl group optionally having substituent(s)" and "heterocyclic group optionally having substituent(s)" each exemplified as the substituent for Q¹, Q², Q³, Q⁴, Z¹, Z² or Z³.

[0100]

The "hydroxy group optionally having substituent(s)" and "sulfanyl group optionally having substituent(s)" are preferably a hydroxy group and a sulfanyl group, each optionally having the "substituent selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₈ cycloalkyl group, a C₆₋₁₄ aryl group, a C₆₋₁₄ aryl C₁₋₆ alkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group and an aromatic heterocyclic group, each of which optionally has 1 to 3 substituents selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine), an optionally halogenated C₁₋₆ alkoxy group, a hydroxy group, a nitro group, an amino group and a carbamoyl group".

[0101]

Preferable examples of the hydroxy group optionally having substituent(s) include a hydroxy group, a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy), a C₂₋₆ alkenyloxy group (e.g., allyloxy, 2-butenyloxy, 2-pentenylloxy, 3-hexenyloxy), a C₃₋₈ cycloalkyloxy group (e.g., cyclohexyloxy), a C₆₋₁₄ aryloxy group (e.g., phenoxy, naphthyloxy), a C₆₋₁₄ aryl C₁₋₆ alkyloxy group (e.g., benzyloxy, phenethyloxy), a C₁₋₆ alkyl-carbonyloxy group (e.g., acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, pivaloyloxy), a C₆₋₁₄ aryl-carbonyloxy group (e.g., benzoyloxy), an aromatic heterocyclyloxy group (e.g., pyridyloxy) and the like.

[0102]

Preferable examples of the sulfanyl group optionally having substituent(s) include a sulfanyl group, a C₁₋₆ alkylthio group (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio), a C₂₋₆ alkenylthio group (e.g., allylthio, 2-butenylthio, 2-pentenylthio, 3-hexenylthio), a C₃₋₈ cycloalkylthio group (e.g., cyclohexylthio), a C₆₋₁₄ arylthio group (e.g., phenylthio, naphthylthio), a C₆₋₁₄ aryl C₁₋₆ alkylthio group (e.g., benzylthio, phenethylthio), a C₁₋₆ alkyl-carbonylthio group (e.g., acetylthio, propionylthio, butyrylthio, isobutyrylthio, pivaloylthio), a C₆₋₁₄ aryl-carbonylthio group (e.g., benzoylthio), an aromatic heterocyclylthio group (e.g., pyridylthio) and the like.

[0103]

Examples of the "hydrocarbon group" of the "acyclic hydrocarbon group optionally having substituent(s)" for X include

- (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl),
- (2) a C₂₋₆ alkenyl group (e.g., vinyl, allyl, isopropenyl, 2-

butenyl),

(3) a C₂₋₆ alkynyl group (e.g., ethynyl, propargyl, 2-butyne) and the like.

Examples of the substituent of the "acyclic hydrocarbon group optionally having substituent(s)" for X include the substituents selected from the aforementioned substituent group A and the like.

The number of the substituents is, for example, 1 to 5, preferably 1 to 3. When the number of the substituents is two or more, the respective substituents may be the same or different.

[0104]

Examples of the "saturated cyclic group" of the "saturated cyclic group optionally having substituent(s)" for X include

(1) a C₃₋₈ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl),
 (2) a 4- to 14-membered (preferably 4- to 8-membered, more preferably 5- or 6-membered) saturated heterocyclic group (e.g., azetidiny, tetrahydrothiophenyl, tetrahydrofuranyl, pyrrolidinyl, imidazolidinyl, oxazolidinyl, pyrazolidinyl, thiazolidinyl, oxazolidinyl, isothiazolidinyl, isoxazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, azepanyl, diazepanyl, oxazepanyl, thiazepanyl, azocanyl, diazocanyl) containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, and the like.

Examples of the substituent of the "saturated cyclic group optionally having substituent(s)" for X include the substituents selected from the aforementioned substituent group B and the like.

The number of the substituents is, for example, 1 to 3. When the number of the substituents is two or more, the respective substituents may be the same or different.

[0105]

Examples of the "ring" of the "ring optionally having substituent(s)" optionally formed by A and R, bonded to each other, together with the adjacent carbonyl and nitrogen atom include a 5- to 7-membered monocyclic nitrogen-containing
 5 nonaromatic heterocycle (e.g., 2-oxopyrrolidine, 2-oxopiperidine, 2-oxopiperazine, 3-oxomorpholine, 3-oxothiomorpholine), and a 4- to 10-membered heterocycle (e.g., dihydroisoindole), each containing one nitrogen atom as a ring-constituting atom besides carbon atom, and optionally further
 10 containing one hetero atom selected from a nitrogen atom, a sulfur atom and an oxygen atom, and having 1 or 2 oxo groups, and the like.

Examples of the substituent of the "ring optionally having substituent(s)" optionally formed by A and R bonded to
 15 each other include the substituents selected from the aforementioned substituent group B and the like.

The number of the substituents is, for example, 1 to 3. When the number of the substituents is two or more, the respective substituents may be the same or different.

20 [0106]

Examples of the "ring" of the "ring optionally having substituent(s)" optionally formed by Q^1 and Q^2 , and Q^3 and Q^4 , each bonded to each other, together with the adjacent carbon atoms include a 5- or 6-membered aromatic ring or nonaromatic
 25 ring each optionally containing, as a ring-constituting atom besides carbon atom, 1 to 3 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom and the like. Examples of the "aromatic ring" include benzene, thiophene, furan, pyrrole, pyrazole, imidazole, thiazole, oxazole,
 30 isothiazole, isoxazole, oxadiazole, thiadiazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, pyran and the like. Examples of the "nonaromatic ring" include cyclopentene, cyclohexene, cyclohexadiene, dihydrothiophene, dihydrofuran, pyrroline, pyrazoline, imidazoline, thiazoline, oxazoline,
 35 isothiazoline, isoxazoline, tetrahydropyridine, dihydropyridine,

tetrahydropyrazine, dihydropyrazine, tetrahydropyrimidine, dihydropyrimidine, tetrahydropyridazine, dihydropyridazine, dihydropyran and the like.

Examples of the substituent of the "ring optionally having substituent(s)" optionally formed by Q^1 and Q^2 , and Q^3 and Q^4 , each bonded to each other, include the substituents selected from the aforementioned substituent group B and the like.

The number of the substituents is, for example, 1 to 3.
 10 When the number of the substituents is two or more, the respective substituents may be the same or different.
 [0107]

Examples of the "ring" of the "ring optionally having substituent(s)" optionally formed by X and Y^1 , bonded to each other, together with the adjacent nitrogen atom and carbon atom include a 5- to 7-membered nitrogen-containing nonaromatic heterocycle containing one nitrogen atom as a ring-constituting atom besides carbon atom, and optionally further containing one hetero atom selected from a nitrogen atom, a sulfur atom and an oxygen atom and the like. Examples of the "nitrogen-containing nonaromatic ring" include pyrrolidine, pyrroline, pyrazoline, imidazoline, thiazolidine, oxazolidine, isothiazolidine, isoxazolidine, thiazoline, oxazoline, isothiazoline, isoxazoline, piperidine, piperazine, morpholine, thiomorpholine, azepane, diazepane, oxazepane, thiazepane and the like.

Examples of the substituent of the "ring optionally having substituent(s)" optionally formed by X and Y^1 bonded to each other include the substituents selected from the aforementioned substituent group B and the like.

30 The number of the substituents is, for example, 1 to 3.
 When the number of the substituents is two or more, the respective substituents may be the same or different.
 [0108]

Examples of the "ring" of the "ring optionally having substituent(s)" optionally formed by Y^1 and Y^2 , bonded to each

other, together with the adjacent carbon atom include
 (1) a C₃₋₈ cycloalkane ring (e.g., cyclopropane, cyclobutane,
 cyclopentane, cyclohexane, cycloheptane, cyclooctane),
 (2) a 2,3-dihydroindene ring,

5 (3) a fluorene ring,

(4) a 4- to 14-membered (preferably 4- to 10-membered)
 nonaromatic heterocycle containing, as a ring-constituting atom
 besides carbon atom, 1 to 4 hetero atoms selected from a
 nitrogen atom, a sulfur atom and an oxygen atom and the like.

10 Preferable examples of the "nonaromatic heterocycle"
 include a monocyclic nonaromatic heterocycle such as azetidine,
 tetrahydrothiophene, tetrahydrofuran, pyrroline, pyrrolidine,
 imidazoline, imidazolidine, oxazoline, oxazolidine, pyrazoline,
 pyrazolidine, thiazoline, thiazolidine, tetrahydrothiazoline,
 15 tetrahydroisothiazoline, tetrahydrooxazoline,
 tetrahydroisoxazoline, piperidine, piperazine,
 tetrahydropyridine, dihydropyridine, tetrahydropyrimidine,
 tetrahydropyridazine, tetrahydropyran, azepane, morpholine,
 thiomorpholine, diazepane, azepine, azocane, diazocane,
 20 tetrahydrothiopyran and the like;

a fused polycyclic (preferably bicyclic or tricyclic)
 nonaromatic heterocycle such as dihydrobenzofuran,
 dihydrobenzimidazole, dihydrobenzoxazole, dihydrobenzothiazole,
 dihydrobenzisothiazole, dihydronaphtho[2,3-b]thiophene,
 25 tetrahydroisoquinoline, tetrahydroquinoline, indoline,
 isoindoline, tetrahydrothieno[2,3-c]pyridine,
 tetrahydrobenzazepine, tetrahydroquinoxaline,
 tetrahydrophenanthridine, hexahydrophenothiazine,
 hexahydrophenoxazine, tetrahydrophthalazine,
 30 tetrahydronaphththyridine, tetrahydroquinazoline,
 tetrahydrocinnoline, tetrahydrocarbazole, tetrahydro- β -
 carboline, tetrahydroacridine, tetrahydrophenazine,
 tetrahydrothioxanthene, octahydroisoquinoline, 8-
 azabicyclo[3.2.1]octane and the like.

35 Examples of the substituent of the "ring optionally

having substituent(s)" optionally formed by Y^1 and Y^2 bonded to each other include the substituents selected from the aforementioned substituent group B and the like.

The number of the substituents is, for example, 1 to 3.

5 When the number of the substituents is two or more, the respective substituents may be the same or different.

[0109]

Preferably, Q^1 is a hydrogen atom or a C_{1-6} alkyl group, and Q^2 , Q^3 and Q^4 are each a hydrogen atom.

10 Q^1 , Q^2 , Q^3 and Q^4 are each more preferably a hydrogen atom.

[0110]

Z^1 , Z^2 and Z^3 are each preferably a hydrogen atom.

[0111]

A is preferably a hydrocarbon group optionally having
15 substituent(s), more preferably,

(1) a C_{6-14} aryl group (e.g., phenyl, biphenyl) optionally having 1 to 3 substituents selected from

(a) a halogen atom,

(b) a C_{1-6} alkyl group optionally having 1 to 5 halogen
20 atoms,

(c) a C_{6-14} aryloxy group,

(d) a C_{6-14} aryl C_{1-6} alkyloxy group,

(e) a C_{6-14} aryl-carbonylamino group,

(f) a C_{6-14} aryl C_{1-6} alkylamino group, and

25 (g) a 5- to 7-membered nonaromatic heterocyclic group (e.g., piperidyl) containing, as a ring-constituting atom besides carbon atom, one or two hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, and optionally having an oxo group,

30 (2) a C_{6-14} aryl C_{1-6} alkyl group optionally having a C_{6-14} aryl C_{1-6} alkyloxy-carbonylamino group, or

(3) a C_{6-14} aryl C_{1-6} alkyl C_{6-14} aryl group.

[0112]

R is preferably a hydrogen atom or a C_{1-6} alkyl group,
35 more preferably, a hydrogen atom.

[0113]

X is preferably a hydrogen atom or a C₁₋₆ alkyl group optionally substituted by one C₃₋₆ cycloalkyl group, more preferably, a hydrogen atom or a C₁₋₆ alkyl group, further
5 preferably, a hydrogen atom.

[0114]

Preferably, Y¹, Y² and Y³ are each independently

- (1) a hydrogen atom,
- (2) a C₁₋₂₀ alkyl group optionally having 1 to 3 substituents
10 selected from an amino group, a C₁₋₆ alkoxy group, a phenyl group, a phenyloxy group and a benzyloxy group,
- (3) a C₃₋₈ cycloalkyl group,
- (4) a phenyl group optionally having 1 to 3 substituents selected from a halogen atom, a C₁₋₆ alkoxy group, a C₁₋₃
15 alkylenedioxy group and a di-C₁₋₆ alkylamino group,
- (5) a pyridyl group optionally having 1 to 3 C₁₋₆ alkoxy groups,
- (6) a naphthyl group,
- (7) a biphenylyl group,
- (8) a thienyl group,
- 20 (9) an imidazolyl group,
- (10) a thiazolyl group,
- (11) a piperidyl group optionally having 1 to 3 C₁₋₆ alkyl groups,
- (12) an imidazopyridyl group,
- 25 (13) an imidazothiazolyl group,
- (14) a thienopyridyl group, or
- (15) an 1,8-naphthyridinyl group.

[0115]

In another preferable embodiment, Y¹, Y² and Y³ are each
30 independently

- (1) a hydrogen atom,
- (2) a C₁₋₂₀ alkyl group optionally having 1 to 3 substituents selected from
 - (a) an amino group,
 - 35 (b) a C₁₋₆ alkoxy group,

- (c) a C₆₋₁₄ aryloxy group, and
- (d) a C₆₋₁₄ aryl C₁₋₆ alkyloxy group,
- (3) a C₃₋₈ cycloalkyl group,
- (4) a C₆₋₁₄ aryl group (e.g., phenyl, naphthyl, biphenyl)
- 5 optionally having 1 to 3 substituents selected from
 - (a) a halogen atom,
 - (b) a C₁₋₆ alkoxy group, and
 - (c) a C₁₋₃ alkylenedioxy group,
- (5) a C₆₋₁₄ aryl C₁₋₆ alkyl group, or
- 10 (6) a 5- to 7-membered monocyclic aromatic heterocyclic group (e.g., pyridyl, thienyl) containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, and optionally having 1 to 3 C₁₋₆ alkoxy groups.

15 [0116]

An embodiment wherein X and Y¹ are bonded to each other to form, together with the adjacent nitrogen atom and carbon atom, a 5- to 7-membered monocyclic nitrogen-containing nonaromatic heterocycle (e.g., pyrrolidine) containing one
 20 nitrogen atom as a ring-constituting atom besides carbon atom, and optionally further containing one hetero atom selected from a nitrogen atom, a sulfur atom and an oxygen atom is also preferable.

[0117]

25 When X and Y¹ are bonded to each other to form, together with the adjacent nitrogen atom and carbon atom, a ring optionally having substituent(s), Y² and Y³ are each preferably a hydrogen atom.

[0118]

30 An embodiment wherein Y¹ and Y² are bonded to each other to form, together with the adjacent carbon atom,
 a C₃₋₈ cycloalkane ring,
 a pyrrolidine ring,
 a piperidine ring,
 35 a tetrahydropyran ring,

a 2,3-dihydroindene ring,
 a fluorene ring,
 a 8-azabicyclo[3.2.1]octane ring, or
 a tetrahydrothiopyran ring, each of which optionally has 1 to 3
 5 substituents selected from

- (1) a halogen atom,
 - (2) a C₁₋₆ alkyl group optionally having 1 to 3 substituents
 selected from a halogen atom and a phenyl group,
 - (3) a C₃₋₆ cycloalkyl group,
 - 10 (4) an oxo group,
 - (5) a phenyl group,
 - (6) a C₂₋₆ alkenyloxy-carbonyl group, and
 - (7) a C₁₋₆ alkyl-carbonyl group,
- is also preferable.

15 [0119]

An embodiment wherein Y¹ and Y² are bonded to each other
 to form, together with the adjacent carbon atom,
 (1) C₃₋₈ cycloalkane (e.g., cycloheptane, cyclooctane),
 (2) 2,3-dihydroindene,
 20 (3) fluorene, or
 (4) a 5- to 7-membered monocyclic nonaromatic heterocycle (e.g.,
 piperidine) containing, as a ring-constituting atom besides
 carbon atom, one or two hetero atoms selected from a nitrogen
 atom, a sulfur atom and an oxygen atom, and optionally having 1
 25 to 3 substituents selected from

- (a) a C₁₋₆ alkyl group,
- (b) a C₆₋₁₄ aryl C₁₋₆ alkyl group, and
- (c) a C₂₋₆ alkenyloxy-carbonyl group,

is also preferable.

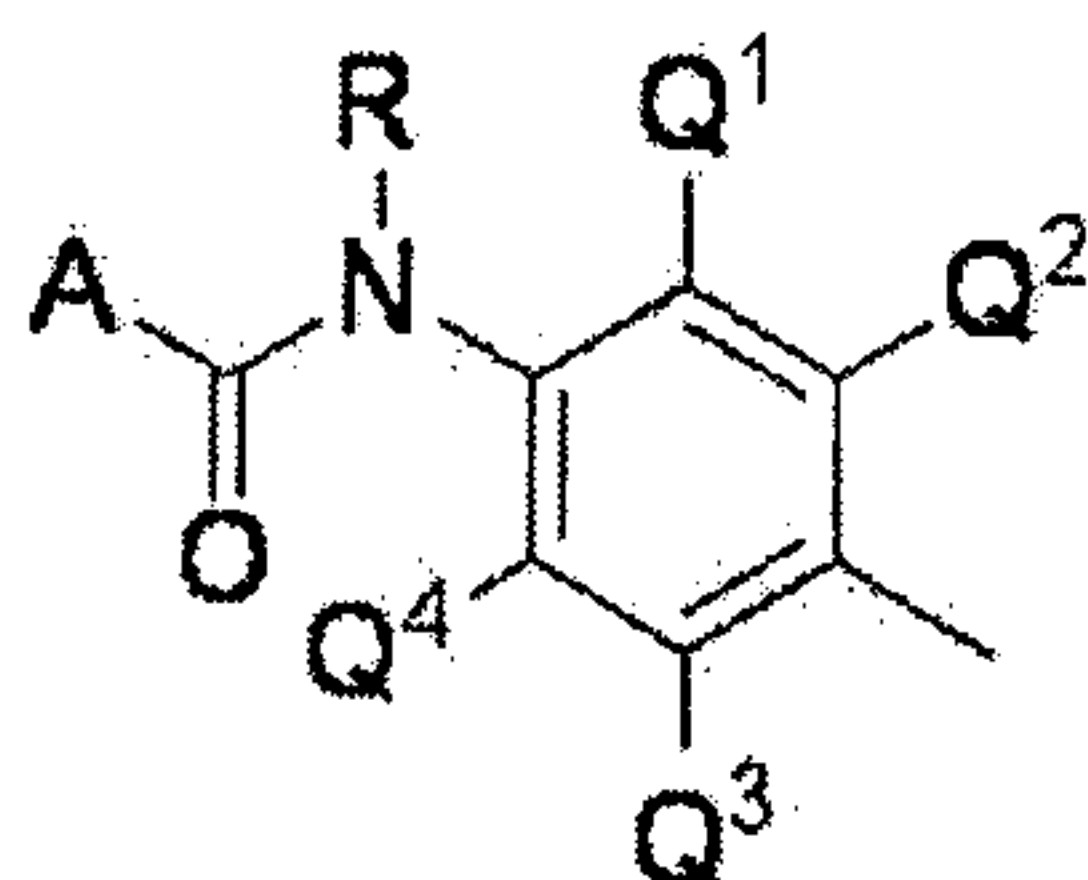
30 [0120]

When Y¹ and Y² are optionally bonded to each other to
 form, together with the adjacent carbon atom, a ring optionally
 having substituent(s), X and Y³ are each preferably a hydrogen
 atom.

35 [0121]

In the formula (I), the configuration of a substituent represented by the formula

[0122]



5 [0123]

and a substituent represented by the formula $-N(X)-C(Y^1)(Y^2)(Y^3)$ on a cyclopropane ring is preferably a trans form rather than a cis form.

[0124]

10 Specific preferable examples of compound (I) include the following compound.

[Compound A]

Compound (I) wherein

A is

15 (1) a C_{6-14} aryl group (e.g., phenyl, biphenyl) optionally having 1 to 3 substituents selected from

(a) a halogen atom,

(b) a C_{1-6} alkyl group optionally having 1 to 5 halogen atoms,

20 (c) a C_{6-14} aryloxy group,

(d) a C_{6-14} aryl C_{1-6} alkyloxy group,

(e) a C_{6-14} aryl-carbonylamino group,

(f) a C_{6-14} aryl C_{1-6} alkylamino group, and

(g) a 5- to 7-membered nonaromatic heterocyclic group

25 (e.g., piperidinyl) containing, as a ring-constituting atom besides carbon atom, one or two hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, and optionally having an oxo group,

(2) a C_{6-14} aryl C_{1-6} alkyl group optionally having a C_{6-14} aryl
30 C_{1-6} alkyloxy-carbonylamino group, or

(3) a C_{6-14} aryl C_{1-6} alkyl C_{6-14} aryl group;

R is a hydrogen atom;

Q^1 , Q^2 , Q^3 and Q^4 are each a hydrogen atom;

X is a hydrogen atom or a C_{1-6} alkyl group;

Y^1 , Y^2 and Y^3 are each independently

(1) a hydrogen atom,

5 (2) a C_{1-20} alkyl group optionally having 1 to 3 substituents selected from

(a) an amino group,

(b) a C_{1-6} alkoxy group,

(c) a C_{6-14} aryloxy group, and

10 (d) a C_{6-14} aryl C_{1-6} alkyloxy group,

(3) a C_{3-8} cycloalkyl group,

(4) a C_{6-14} aryl group (e.g., phenyl, naphthyl, biphenyl)

optionally having 1 to 3 substituents selected from

(a) a halogen atom,

15 (b) a C_{1-6} alkoxy group, and

(c) a C_{1-3} alkylenedioxy group,

(5) a C_{6-14} aryl C_{1-6} alkyl group, or

(6) a 5- to 7-membered monocyclic aromatic heterocyclic group

(e.g., pyridyl, thienyl) containing, as a ring-constituting

20 atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, and optionally having 1 to 3 C_{1-6} alkoxy groups;

X and Y^1 are optionally bonded to each other to form, together with the adjacent nitrogen atom and carbon atom, a 5- to 7-

25 membered monocyclic nitrogen-containing nonaromatic heterocycle

(e.g., pyrrolidine) containing one nitrogen atom as a ring-

constituting atom besides carbon atom, and optionally further

containing one hetero atom selected from a nitrogen atom, a sulfur atom and an oxygen atom;

30 Y^1 and Y^2 are optionally bonded to each other to form, together with the adjacent carbon atom,

(1) C_{3-8} cycloalkane (e.g., cycloheptane, cyclooctane),

(2) 2,3-dihydroindene,

(3) fluorene, or

35 (4) a 5- to 7-membered monocyclic nonaromatic heterocycle (e.g.,

piperidine) containing, as a ring-constituting atom besides carbon atom, one or two hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, and optionally having 1 to 3 substituents selected from

- 5 (a) a C₁₋₆ alkyl group,
 (b) a C₆₋₁₄ aryl C₁₋₆ alkyl group, and
 (c) a C₂₋₆ alkenyloxy-carbonyl group; and
Z¹, Z² and Z³ are each a hydrogen atom.

[0125]

10 The salt of compound (I) is preferably a pharmacologically acceptable salt. Examples of such salt include salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

15 Preferable examples of salts with inorganic bases include alkali metal salts such as sodium salts, potassium salts and the like; alkali earth metal salts such as calcium salts, magnesium salts and the like; aluminum salts; and ammonium salts.

20 Preferable examples of salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine and the like.

 Preferable examples of salts with inorganic acids include
25 salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like.

 Preferable examples of salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric
30 acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

 Preferable examples of salts with basic amino acids include salts with arginine, lysine, ornithine and the like.

 Preferable examples of salts with acidic amino acids
35 include salts with aspartic acid, glutamic acid and the like.

The salt of compound (I) is preferably a salt with an inorganic acid (preferably, hydrochloric acid) or an organic acid (preferably, trifluoroacetic acid).

[0126]

5 Compound (I) may also be used as a prodrug. A prodrug of compound (I) means a compound which is converted to compound (I) due to a reaction due to an enzyme, gastric acid, etc. under the physiological condition in the living body, that is, a compound which is converted to compound (I) with oxidation,
 10 reduction, hydrolysis, and the like according to an enzyme; a compound which is converted to compound (I) by hydrolysis etc. due to gastric acid, and the like. A prodrug for compound (I) may be a compound obtained by subjecting an amino group in compound (I) to an acylation, alkylation or phosphorylation
 15 (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-
 20 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,
 25 fumarylation, alanylation and dimethylaminomethylcarbonylation); a compound obtained by subjecting a carboxyl group in compound (I) to an esterification or amidation (e.g., a compound obtained by subjecting a carboxyl group in compound (I) to an ethyl
 30 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
 35 esterification and methylamidation) and the like. Any of these

compounds can be produced from compound (I) by a method known per se.

[0127]

The prodrug of compound (I) may be a compound that
5 converts to compound (I) under physiological conditions as described in Development of Pharmaceutical Products, vol. 7, Molecular Design, 163-198, Hirokawa Shoten (1990).

Compound (I) may be labeled with an isotope (e.g., ^2H , ^3H , ^{14}C , ^{35}S , ^{125}I , ^{11}C , ^{18}F) and the like.

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

Compound (I) may be an anhydrate or a hydrate. Compound
15 (I) may be a solvate or a non-solvate. Furthermore, compound (I) may be a deuterated compound.

Compound (I) may be a crystal, and both a single crystal and crystal mixtures are encompassed in compound (I). Crystals can be produced by crystallization according to crystallization
20 methods known per se.

In addition, compound (I) may be a pharmaceutically acceptable cocrystal or cocrystal salt. Here, the cocrystal or cocrystal salt means a crystalline substance consisting of two or more particular substances which are solids at room
25 temperature, each having different physical properties (e.g., structure, melting point, heat of melting, hygroscopicity, and stability). The cocrystal and cocrystal salt can be produced by cocrystallization method known per se.

When compound (I) includes isomers such as optical
30 isomers, stereoisomers, regioisomers, rotational isomers, geometrical isomers, and the like, one of the isomers and mixture are also encompassed in compound (I).

[0128]

Compound (I) or a prodrug thereof (hereinafter sometimes
35 to be simply abbreviated as the compound of the present

invention) has low toxicity (e.g., acute toxicity, chronic toxicity, genetic toxicity, reproductive toxicity, cardiotoxicity, carcinogenicity), and can be used as it is or in the form of a pharmaceutical composition (in the present specification, sometimes to be abbreviated as "medicament of the present invention") after mixing with a pharmacologically acceptable carrier etc. to mammals (e.g., human, mouse, rat, rabbit, dog, cat, bovine, horse, swine, monkey) as an agent for the prophylaxis or treatment of various diseases mentioned below.

[0129]

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

[0130]

Preferable examples of the vehicles are as follows: lactose, sucrose, D-mannitol, D-sorbitol, starch, α -starch, dextrin, crystalline cellulose, low-substituted hydroxypropyl cellulose, sodium carboxymethylcellulose, gum Arabic, pullulan, light anhydrous silicic acid, synthetic aluminum silicate, and magnesium metasilicic aluminate.

[0131]

Preferable examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica, and the like.

[0132]

Preferable examples of the binders are as follows: α -starch, sucrose, gelatin, gum Arabic, methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose,

crystalline cellulose, sucrose, D-mannitol, trehalose, dextrin, pullulan, hydroxypropylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone.

[0133]

5 Preferable examples of the disintegrants are as follows: lactose, sucrose, starch, carboxymethylcellulose, calcium carboxymethylcellulose, croscarmellose sodium, sodium carboxymethyl starch, light anhydrous silicic acid, and low-substituted hydroxypropylcellulose.

10 [0134]

Preferable examples of the solvents are as follows: water for injection, physiological saline, Linger solution, alcohol, propylene glycol, polyethylene glycol, sesame oil, corn oil, olive oil, and cottonseed oil.

15 [0135]

Preferable examples of the solubilizing agents are as follows: polyethylene glycol, propylene glycol, D-mannitol, trehalose, benzyl benzoate, ethanol, tris-aminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, 20 sodium salicylate, and sodium acetate.

[0136]

Preferable examples of the suspending agent include surfactants such as stearyl triethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium 25 chloride, benzetonium chloride, glycerin monostearate and the like; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and the like; polysorbates, and 30 polyoxyethylene hydrogenated castor oil.

[0137]

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

[0138]

35 Preferable examples of the buffering agent include buffer

solutions such as phosphates, acetates, carbonates, and citrates.

[0139]

Preferable examples of the soothing agent include benzyl
5 alcohol.

[0140]

Preferable examples of the preservative include p-hydroxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, and sorbic acid.

10 [0141]

Preferable examples of antioxidants include sulfites and ascorbates.

[0142]

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

20 [0143]

Preferable examples of the sweeteners include sodium saccharin, dipotassium glycyrrhizinate, aspartame and stevia.

[0144]

Examples of the dosage form of the medicament of the
25 present invention include oral preparations such as tablet (including sublingual tablet, orally disintegrating tablet), capsule (including soft capsule, microcapsule), granule, powder, troche, syrup, emulsion, suspension and the like; and parenteral agents such as injection (e.g., subcutaneous
30 injection, intravenous injection, intramuscular injection, intraperitoneal injection, drip infusion), external preparation (e.g., dermal preparation, ointment), suppository (e.g., rectal suppository, vaginal suppository), pellet, nasal preparation, pulmonary preparation (inhalant), eye drop and the like, which
35 can be respectively safely administered orally or parenterally.

[0145]

These preparations may be a release control preparation (e.g., sustained-release microcapsule) such as an immediate-release preparation, a sustained-release preparation and the
5 like.

[0146]

The medicament of the present invention can be manufactured by the common methods in the field of formulation technology, for example, methods listed in the Japanese
10 Pharmacopoeia, and the like.

[0147]

The content of the compound of the present invention in the medicament of the present invention varies based on the dosage forms, dosages of the compound of the present invention,
15 and the like. For example, it is approximately about 0.1 to 100 wt%.

[0148]

The compound of the present invention has a superior LSD1 inhibitory action and can be used as a prophylactic or
20 therapeutic agent for various diseases in mammals (e.g., human, mouse, rat, rabbit, dog, cat, bovine, horse, swine, monkey). Moreover, since the compound of the present invention shows low monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B) inhibitory activity and high LSD1 selectivity, it causes fewer
25 side effects.

[0149]

In addition, the compound of the present invention is expected to show, after transfer into the brain, suppression of a decrease in histone H3K4 methylation and suppression of a
30 decrease in Gad1 mRNA expression, which are derived from the inhibition of LSD1. As a result, it is also useful as a medicament based on superior actions of nerve activation, enhancement of neural plasticity, promotion of neurogenesis, and promotion of BDNF production.

35 [0150]

The compound of the present invention can be used as a prophylactic or therapeutic agent for cancer. Examples of the cancer include breast cancer, prostate cancer, pancreatic cancer, gastric cancer, lung cancer, colon cancer, rectal cancer, esophagus cancer, duodenal cancer, tongue cancer, pharyngeal cancer, brain tumor, neurinoma, non-small cell lung cancer, small cell lung cancer, liver cancer, kidney cancer, bile duct cancer, uterine body cancer, cervical cancer, ovarian cancer, urinary bladder cancer, skin cancer, hemangioma, malignant lymphoma, malignant melanoma, thyroid cancer, bone tumor, vascular fibroma, retinoblastoma, penile cancer, pediatric solid cancer, Kaposi's sarcoma, Kaposi's sarcoma derived from AIDS, maxillary tumor, fibrous histiocytoma, leiomyosarcoma, rhabdomyosarcoma, and leukemia. Among these, the compound can be preferably used for prostate cancer, leukemia, and malignant lymphoma.

[0151]

It is known that the level of H3K4me2, which is a substrate of LSD1, and memory improvement are correlated (Nature 2007, Vol. 447, page 175), and the compound of the present invention having a superior LSD1 inhibitory action can also be used as a prophylactic or therapeutic agent for neurodegenerative diseases.

[0152]

The compound of the present invention can be used as a prophylactic or therapeutic agent for central nervous system diseases. It is useful as a prophylactic or therapeutic agent for diseases such as

(1) psychiatric diseases [e.g., depression, major depression, bipolar depression, dysthymic disorder, emotional disorder (seasonal affective disorder and the like), recurrent depression, postpartum depression, stress disorder, depression symptom, mania, anxiety, generalized anxiety disorder, anxiety syndrome, panic disorder, phobia, social phobia, social anxiety disorder, obsessive disorder, post-traumatic stress syndrome,

- post-traumatic stress disorder, Tourette syndrome, autism, fragile X syndrome, Rett syndrome, adjustment disorder, bipolar disorder, neurosis, schizophrenia, chronic fatigue syndrome, anxiety neurosis, compulsive neurosis, panic disorder, epilepsy,
- 5 anxiety symptom, anxious mental state, emotional abnormality, cyclothymia, nervous erethism, faint, addiction, low sex drive, attention deficit hyperactivity disorder (ADHD), psychotic major depression, refractory major depression, treatment-resistant depression],
- 10 (2) neurodegenerative diseases [e.g., Alzheimer's disease, Alzheimer-type senile dementia, Parkinson's disease, Huntington's chorea, multi-infarct dementia, frontotemporal dementia, frontotemporal dementia with Parkinsonism, progressive supranuclear palsy, Pick's syndrome, Niemann-Pick
- 15 syndrome, corticobasal degeneration, Down's disease, vascular dementia, postencephalitic parkinsonism, dementia with Lewy body, HIV dementia, amyotrophic lateral sclerosis (ALS), motor neurogenesis disease (MND), Creutzfeldt-Jakob disease or prion disease, cerebral palsy, progressive supranuclear palsy,
- 20 multiple sclerosis],
- (3) age-related cognition and memory disorders [e.g., age-related memory disorders, senile dementia]
- (4) sleep disorders [e.g., intrinsic sleep disorders (e.g., psychophysiological insomnia and the like), extrinsic sleep
- 25 disorder, circadian rhythm disorders (e.g., time zone change syndrome (jet lag), shift work sleep disorder, irregular sleep-wake pattern, delayed sleep phase syndrome, advanced sleep phase syndrome, non-24-hour sleep-wake and the like), parasomnia, sleep disorders associated with internal medical or
- 30 psychiatric disorder (e.g., chronic obstructive pulmonary disease, Alzheimer's disease, Parkinson's disease, cerebrovascular dementia, schizophrenia, depression, anxiety neurosis), stress insomnia, insomnia, insomniac neurosis, sleep apnea syndrome],
- 35 (5) respiratory depression caused by anesthetics, traumatic

disease, or neurodegenerative disease and the like,
(6) traumatic brain injury, cerebral apoplexy, neurotic
anorexia, eating disorder, anorexia nervosa, hyperorexia, other
eating disorder, alcohol dependence, alcohol abuse, alcoholic
5 amnesia, alcohol paranoia, alcohol preference, alcohol
withdrawal, alcoholic insanity, alcohol intoxication, alcoholic
jealousy, alcoholic mania, alcohol-dependent psychiatric
disorder, alcoholic insanity, pharmacophilia, pharmacophobia,
pharmacomania, drug withdrawal, migraine, stress headache,
10 catatonic headache, diabetic neuropathy, obesity, diabetes,
muscular spasm, Meniere's disease, autonomic ataxia, alopecia,
glaucoma, hearing loss, hypertension, cardiac disease,
tachycardia, congestive cardiac failure, hyperventilation,
bronchial asthma, apnea, sudden infant death syndrome,
15 inflammatory disease, allergic disease, impotence, climacteric
disorder, infertility, cancer, immunodeficiency syndrome caused
by HIV infection, immunodeficiency syndrome caused by stress,
cerebrospinal meningitis, acromegaly, incontinence, metabolic
syndrome, osteoporosis, peptic ulcer, irritable bowel syndrome,
20 inflammatory bowel disease, ulcerative colitis, Crohn's disease,
stress gastrointestinal disorder, stress vomiting, stress ulcer,
diarrhea, constipation, postoperative ileus, and the like.
[0153]

The compound of the present invention is particularly
25 useful as a prophylactic or therapeutic agent for diseases such
as schizophrenia, Alzheimer's disease, Parkinson's disease,
Huntington's chorea and the like.
[0154]

Since the compound of the present invention has a
30 superior LSD1 inhibitory activity and action, it is expected to
show a superior treatment effect for the above-mentioned
diseases.
[0155]

The dosage of the compound of the present invention
35 varies depending on the administration subjects, administration

routes, target diseases, symptoms, and the like. For example, for oral administration to adult patients with cancer, generally a single dose is about 0.01 to 100 mg/kg body weight, preferably 0.1 to 50 mg/kg body weight, further preferably 0.5
5 to 20 mg/kg body weight, and this dosage is preferably administered 1 to 3 times daily.

[0156]

The compound of the present invention can be used in combination with a medicament such as chemotherapeutic agent,
10 immunotherapeutic agent, medicament inhibiting actions of cell growth factor and receptor thereof (hereinafter to be abbreviated as a concomitant drug).

By combining the compound of the present invention and a concomitant drug, a superior effect such as
15 (1) the dose can be reduced as compared to single administration of the compound of the present invention or a concomitant drug,
(2) the drug to be combined with the compound of the present invention can be selected according to the condition of
20 patients (mild case, severe case and the like),
(3) the period of treatment can be set longer by selecting a concomitant drug having different action and mechanism from the compound of the present invention,
(4) a sustained treatment effect can be designed by selecting a
25 concomitant drug having different action and mechanism from the compound of the present invention,
(5) a synergistic effect can be afforded by a combined use of the compound of the present invention and a concomitant drug, and the like, can be achieved.

30 [0157]

Hereinafter the compound of the present invention and a concomitant drug used in combination are referred to as the "combination agent of the present invention".

When using the combination agent of the present invention,
35 the administration time of the compound of the present

invention and the concomitant drug is not restricted, and the compound of the present invention or a pharmaceutical composition thereof and the concomitant drug or a pharmaceutical composition thereof can be administered to an administration subject simultaneously, or may be administered at different times. The dosage of the concomitant drug may be determined according to the dose clinically used, and can be appropriately selected depending on an administration subject, administration route, disease, combination and the like.

10 The administration mode of the combination agent of the present invention 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 methods:

15 (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

20 preparations of the compound of the present invention and the concomitant drug, which have 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., 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 employed in clinical situations.

The mixing ratio of the compound of the present invention and a concomitant drug can be appropriately determined depending on the administration subject, administration route, target disease, symptom, combination and the like.

5 For example, the content of the compound of the present invention in the combination agent of the present invention differs depending on the form of a preparation, and usually from about 0.01 to about 100 wt%, preferably from about 0.1 to about 50 wt%, further preferably from about 0.5 to about 20 wt%,
10 based on the preparation.

The content of the concomitant drug in the combination agent of the present invention differs depending on the form of a preparation, and usually from about 0.01 to about 100 wt%, preferably from about 0.1 to about 50 wt%, further preferably
15 from about 0.5 to about 20 wt%, based on the preparation.

The content of additives such as a carrier and the like in the combination agent of the present invention differs depending on the form of a preparation, and usually from about 1 to about 99.99 wt%, preferably from about 10 to about 90 wt%,
20 based on the preparation.

When the compound of the present invention and a concomitant drug are separately formulated into preparations, the contents thereof are similar to the above.

[0158]

25 Examples of the chemotherapeutic agent include alkylating agents (e.g., nitrogen mustard, nitrogen mustard-N-oxide hydrochloride, chlorambutyl, cyclophosphamide, ifosfamide, thiotepa, carboquone, improsulfan tosylate, busulfan, nimustine hydrochloride, mitobronitol, melphalan, dacarbazine,
30 ranimustine, estramustine phosphate sodium, triethylenemelamine, carmustine, lomustine, streptozocin, pipobroman, etoglucid, carboplatin, cisplatin, miboplatin, nedaplatin, oxaliplatin, altretamine, ambamustine, dibrospidium hydrochloride, fotemustine, prednimustine, pumitepa, ribomustin, temozolomide,
35 treosulphan, trophosphamide, zinostatin stimalamer, adozelesin,

cystemustine, bizelesin), metabolic antagonists (e.g., mercaptopurine, 6-mercaptopurine riboside, thioinosine, methotrexate, pemetrexed, enocitabine, cytarabine, cytarabine ocfosfate, ancitabine hydrochloride, 5-FU drug (e.g.,
5 fluorouracil, tegafur, UFT, doxifluridine, carmofur, gallocitabine, emitefur, capecitabine), aminopterin, nelzarabine, leucovorin calcium, tabloid, butocine, folinate calcium, levofolinate calcium, cladribine, emitefur, fludarabine, gemcitabine, hydroxycarbamide, pentostatin,
10 piritrexim, idoxuridine, mitoguazone, thiazophrine, ambamustine, bendamustine), antitumor antibiotics (e.g., actinomycin D, actinomycin C, mitomycin C, chromomycin A3, bleomycin hydrochloride, bleomycin sulfate, peplomycin sulfate, daunorubicin hydrochloride, doxorubicin hydrochloride,
15 aclarubicin hydrochloride, pirarubicin hydrochloride, epirubicin hydrochloride, neocarzinostatin, mithramycin, sarcomycin, carzinophilin, mitotane, zorubicin hydrochloride, mitoxantrone hydrochloride, idarubicin hydrochloride) and plant-derived antitumor agents (e.g., etoposide, etoposide
20 phosphate, vinblastine sulfate, vincristine sulfate, vindesine sulfate, teniposide, paclitaxel, docetaxel, vinorelbine).
[0159]

Examples of the immunotherapeutic agent include picibanil, krestin, schizophyllan, lentinan, ubenimex, interferon,
25 interleukin, macrophage colony stimulating factor, granulocyte colony stimulating factor, erythropoietin, lymphotoxin, BCG vaccine, corynebacterium parvum, levamisole, polysaccharide K, procodazole and anti-CTLA4 antibody.
[0160]

30 Examples of the "medicament inhibiting actions of cell growth factor and receptor thereof" include anti-VEGF antibody (e.g., Bevacizumab), anti-HER2 antibody (e.g., Trastuzumab, Pertuzumab), anti-EGFR antibody (e.g., Cetuximab, Panitumumab, Matuzumab, Nimotuzumab), anti-VEGFR antibody, anti-HGF antibody,
35 Imatinib mesylate, Erlotinib, Gefitinib, Sorafenib, Sunitinib,

Dasatinib, Lapatinib, Vatalanib, 4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-7-[3-(1-pyrrolidinyl)propoxy]quinazoline (AZD-2171), Lestaurtinib, Pazopanib, Canertinib, Tandutinib, 3-(4-bromo-2,6-difluorobenzyloxy)-5-[3-[4-(1-pyrrolidinyl)butyl]ureido]isothiazole-4-carboxamide (CP-547632), Axitinib, N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(pyridin-4-ylmethylamino)pyridine-3-carboxamide (AMG-706), Nilotinib, 6-[4-(4-ethylpiperazin-1-ylmethyl)phenyl]-N-[1(R)-phenylethyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (AEE-788), Vandetanib, Temsirolimus, Everolimus, Enzastaurin, N-[4-[4-(4-methylpiperazin-1-yl)-6-(3-methyl-1H-pyrazol-5-ylamino)pyrimidin-2-ylsulfanyl]phenyl]cyclopropanecarboxamide (VX-680), 2-[N-[3-[4-[5-[N-(3-fluorophenyl) carbamoylmethyl]-1H-pyrazol-3-ylamino]quinazolin-7-yloxy]propyl]-N-ethylamino]ethyl phosphate (AZD-1152), 4-[9-chloro-7-(2,6-difluorophenyl)-5H-primido[5,4-d][2]benzazepin-2-ylamino]benzoic acid (MLN-8054), N-[2-methoxy-5-[(E)-2-(2,4,6-trimethoxyphenyl)vinylsulfonylmethyl]phenyl]glycine sodium salt (ON-1910Na), 4-[8-cyclopentyl-7(R)-ethyl-5-methyl-6-oxo-5,6,7,8-tetrahydropteridin-2-ylamino]-3-methoxy-N-(1-methylpiperidin-4-yl)benzamide (BI-2536), 5-(4-bromo-2-chlorophenylamino)-4-fluoro-1-methyl-1H-benzimidazole-6-carbohydroxamic acid 2-hydroxyethyl ester (AZD-6244), N-[2(R),3-dihydroxypropoxy]-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzamide (PD-0325901) and everolimus (RAD001). [0161]

Examples of the concomitant drug for the central nervous system diseases include the following.

benzodiazepine (chlordiazepoxide, diazepam, potassium clorazepate, lorazepam, clonazepam, alprazolam etc.), L-type calcium channel inhibitor (pregabalin etc.), tricyclic or tetracyclic antidepressant (imipramine hydrochloride, amitriptyline hydrochloride, desipramine hydrochloride, clomipramine hydrochloride etc.), selective serotonin reuptake inhibitor (fluvoxamine maleate, fluoxetine hydrochloride,

citalopram hydrobromide, sertraline hydrochloride, paroxetine
 hydrochloride, escitalopram oxalate etc.), serotonin-
 noradrenaline reuptake inhibitor (venlafaxine hydrochloride,
 duloxetine hydrochloride, desvenlafaxine hydrochloride etc.),
 5 noradrenaline reuptake inhibitor (reboxetine mesylate etc.),
 mirtazapine, trazodone hydrochloride, nefazodone hydrochloride,
 bupropion hydrochloride, setiptiline maleate, 5-HT_{1A} agonist,
 (buspirone hydrochloride, tandospirone citrate, osemozotan
 hydrochloride etc.), 5-HT₃ antagonist (cyamemazine etc.), non-
 10 cardioselective β blocker (propranolol hydrochloride,
 oxprenolol hydrochloride etc.), histamine H₁ antagonist
 (hydroxyzine hydrochloride etc.), therapeutic drug for
 schizophrenia (chlorpromazine, haloperidol, sulpiride,
 clozapine, trifluoperazine hydrochloride, fluphenazine
 15 hydrochloride, olanzapine, quetiapine fumarate, risperidone,
 aripiprazole etc.), CRF antagonist, other antianxiety drug
 (meprobamate etc.), tachykinin antagonist (MK-869, saredutant
 etc.), medicament that acts on metabotropic glutamate receptor,
 CCK antagonist, β 3 adrenaline antagonist (amibegron
 20 hydrochloride etc.), GAT-1 inhibitor (tiagabine hydrochloride
 etc.), N-type calcium channel inhibitor, carbonic anhydrase II
 inhibitor, NMDA glycine site agonist, NMDA antagonist
 (memantine etc.), peripheral benzodiazepine receptor agonist,
 vasopressin antagonist, vasopressin V1b antagonist, vasopressin
 25 V1a antagonist, phosphodiesterase inhibitor, opioid antagonist,
 opioid agonist, uridine, nicotinic acid receptor agonist,
 thyroid hormone (T3, T4), TSH, TRH, MAO inhibitor (phenelzine
 sulfate, tranylcypromine sulfate, moclobemide etc.), 5-HT_{2A}
 antagonist, 5-HT_{2A} inverse agonist, COMT inhibitor (entacapone
 30 etc.), therapeutic drug for bipolar disorder (lithium carbonate,
 sodium valproate, lamotrigine, riluzole, felbamate etc.),
 cannabinoid CB1 antagonist (rimonabant etc.), FAAH inhibitor,
 sodium channel inhibitor, anti-ADHD drug (methylphenidate
 hydrochloride, methamphetamine hydrochloride etc.), therapeutic
 35 drug for alcoholism, therapeutic drug for autisma, therapeutic

drug for chronic fatigue syndrome, therapeutic drug for spasm,
 therapeutic drug for fibromyalgia syndrome, therapeutic drug
 for headache, therapeutic drug for insomnia (etizolam,
 zopiclone, triazolam, zolpidem, ramelteon, indiplon etc.),
 5 therapeutic drug for quitting smoking, therapeutic drug for
 myasthenia gravis, therapeutic drug for cerebral infarction,
 therapeutic drug for mania, therapeutic drug for hypersomnia,
 therapeutic drug for pain, therapeutic drug for dysthymia,
 therapeutic drug for autonomic ataxia, therapeutic drug for
 10 male and female sexual dysfunction, therapeutic drug for
 migraine, therapeutic drug for pathological gambler,
 therapeutic drug for restless legs syndrome, therapeutic drug
 for substance addiction, therapeutic drug for alcohol-related
 syndrome, therapeutic drug for irritable bowel syndrome,
 15 therapeutic drug for Alzheimer's disease (donepezil,
 galanthamine, memantine etc.), therapeutic drug for Parkinson's
 disease, therapeutic drug for ALS (riluzole etc., neurotrophic
 factor etc.), therapeutic drug for lipid abnormality such as
 cholesterol-lowering drug (statin series (pravastatin sodium,
 20 atrovastatin, simvastatin, rosuvastatin etc.), fibrate
 (clofibrate etc.), squalene synthetase inhibitor), therapeutic
 drug for abnormal behavior or suppressant of dromomania due to
 dementia (sedatives, antianxiety drug etc.), apoptosis
 inhibitor, antiobesity drug, therapeutic drug for diabetes,
 25 therapeutic drug for hypertension, therapeutic drug for
 hypotension, therapeutic drug for rheumatism (DMARD), anti-
 cancer agent, therapeutic drug for parathyroid (PTH), calcium
 receptor antagonist, sex hormone or a derivative thereof
 (progesterone, estradiol, estradiol benzoate etc.), neuronal
 30 differentiation promoter, nerve regeneration promoter, non-
 steroidal anti-inflammatory drug (meloxicam, tenoxicam,
 indomethacin, ibuprofen, celecoxib, rofecoxib, aspirin,
 indomethacin etc.), steroid (dexamethasone, cortisone acetate
 etc.), anti-cytokine drug (TNF inhibitor, MAP kinase inhibitor
 35 etc.), antibody medicament, nucleic acid or nucleic acid

derivative, aptamer drug, and the like.

[0162]

The above-mentioned concomitant drug may be used in a combination of two or more kinds at an appropriate ratio.

5 When the compound of the present invention is used in combination with a concomitant drug, the respective dosages can be reduced within a safe range in consideration of the opposite effects of the respective drugs. As a result, the opposite effect caused by these agents can be prevented safely.

10 The compound of the present invention can also be used in combination with a non-medication therapy. Specific examples of the non-medication therapy include (1) operation; (2) hypertensive chemical therapy using angiotensin II and the like; (3) gene therapy; (4) hyperthermic therapy; (5)
15 cryotherapy; (6) laser ablation method; (7) radiation therapy; and (8) immunotherapy.

[0163]

The production method of compound (I) of the present invention is explained in the following.

20 Compound (I) of the present invention can be produced, for example, according to the method shown in the following reaction scheme or a method analogous thereto and the like.

The compounds in the schemes may form a salt, and examples of such salt include those similar to the
25 aforementioned salts of compound (I).

While the compounds obtained in each step can be directly used for the next reaction in the form of a reaction mixture or as a crude product, they can be isolated and purified from a reaction mixture according to a conventionally known method
30 such as concentration, extraction, recrystallization, distillation, chromatography and the like.

In addition, the compound obtained in each step may be used after optical resolution by a known means such as chiral column chromatography, optical fractional crystallization,
35 diastereomer derivatization and the like.

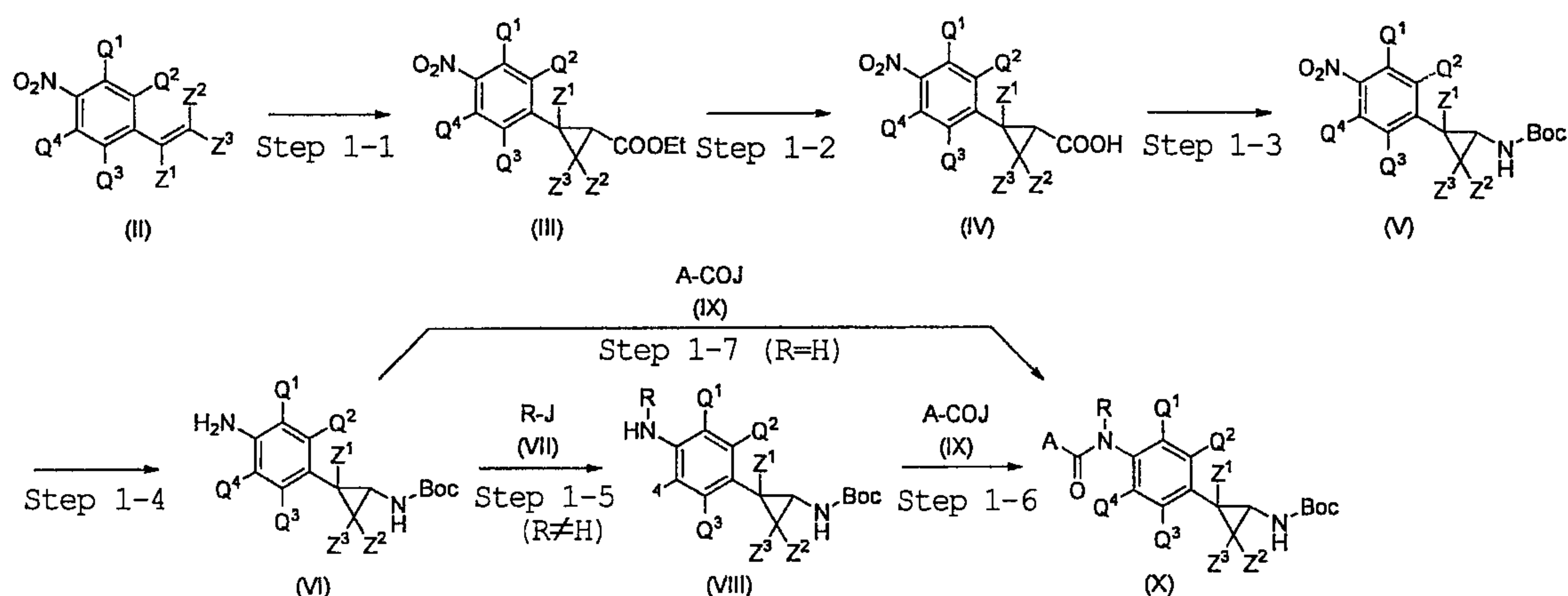
The outline of each reaction scheme is shown below, wherein each symbol in the compounds is as defined above.

[0164]

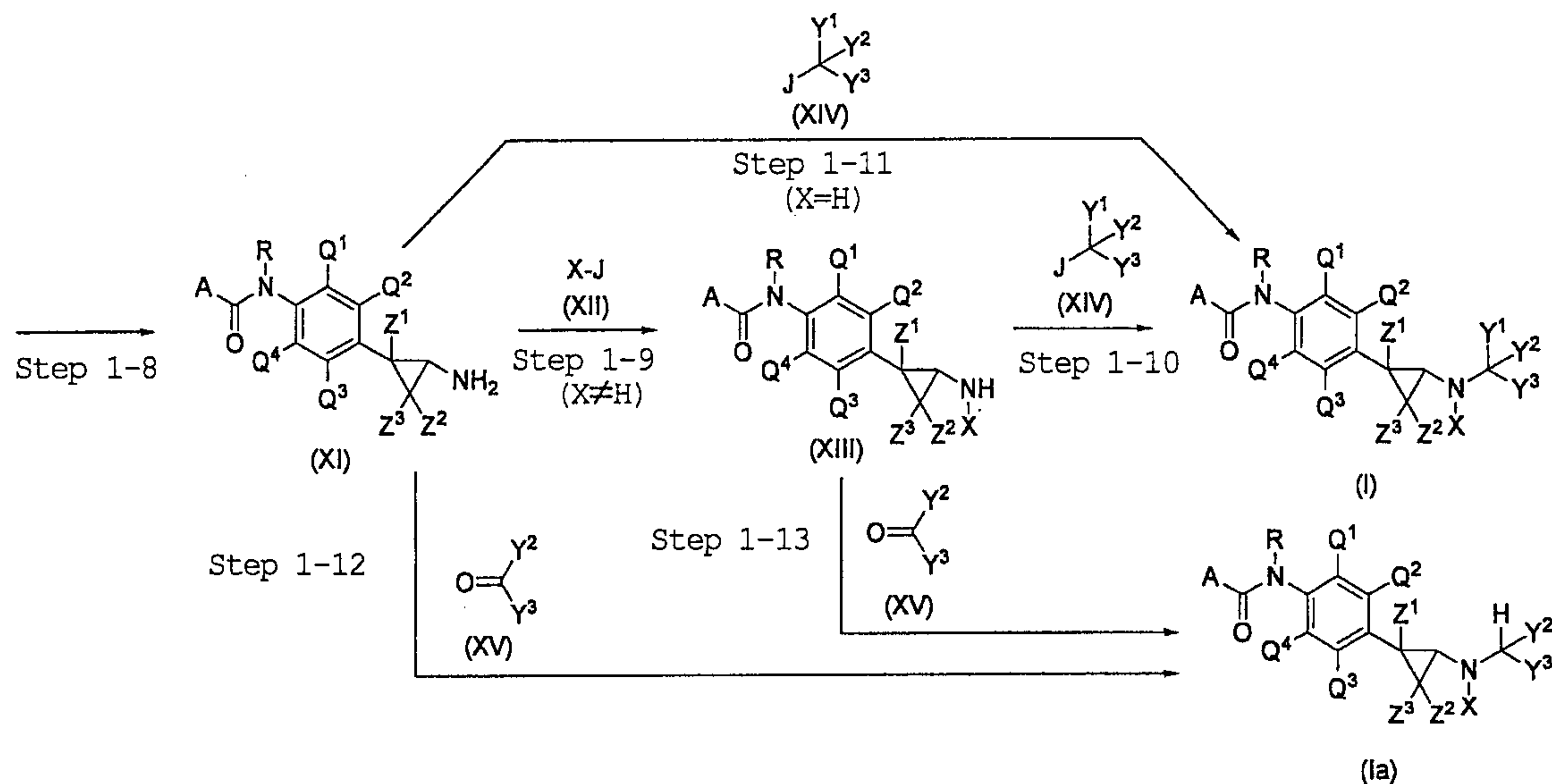
[Production method 1]

- 5 Compound (I) can be produced by the following production method or a method analogous thereto.

[0165]



[0166]



10

[0167]

wherein each symbol is as defined above, and J is a halogen atom (e.g., F, Cl, Br, I), p-toluenesulfonyloxy (OTs), methanesulfonyloxy (OMs) or OH.

15 [0168]

[Step 1-1]

In this Step, compound (II) is reacted with ethyl diazoacetate in the presence of a metal catalyst to produce

compound (III).

The starting material compound (II) may be a commercially available product, or can be produced by a method known per se [for example, the method described in Synlett 2002, 1137; 5 Journal of Organic Chemistry 2003, 68, 6354; Bioorganic and Medicinal Chemistry 2008, 16, 5452 and the like] or a method analogous thereto.

This reaction is generally performed in an inert solvent.

The amount of ethyl diazoacetate to be used is generally 10 1 - 10 molar equivalents relative to compound (II).

Examples of the inert solvent include chloroform, dichloromethane, 1,2-dichloroethane, carbon tetrachloride, tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, 1,4-dioxane, toluene, benzene, chlorobenzene, cyclohexane, N,N- 15 dimethylformamide, N,N-dimethylacetamide, acetonitrile and the like. Two or more kinds of these solvents may be used in an appropriate ratio.

Examples of the metal catalyst include copper(I) chloride, copper(II) acetylacetonate, copper(II) 20 trifluoromethanesulfonate, copper(II) sulfate, palladium(II) acetate, palladium(II) chloride, dirhodium(II) tetraacetate, and the like. Two or more kinds of these metal catalysts may be used in an appropriate ratio.

The amount of the metal catalyst to be used is generally 25 0.01 - 1 molar equivalent, preferably 0.1 - 0.5 molar equivalent, relative to compound (II).

The reaction temperature is generally about 0 - 150°C.

While the reaction time is not particularly limited, it is generally 0.1 - 100 hr, preferably 0.5 - 72 hr.

30 [0169]

[Step 1-2]

In this Step, compound (IV) is produced by subjecting compound (III) to hydrolysis.

This reaction is generally performed in the presence of a 35 base, in water or a water-containing solvent.

Examples of the base include sodium ethoxide, sodium methoxide, sodium hydroxide, lithium hydroxide, potassium hydroxide, barium hydroxide, sodium hydroperoxide and the like.

The amount of the base to be used is generally 1 - 1000
5 molar equivalents relative to compound (III).

Examples of the solvent to be used as the water-containing solvent include tetrahydrofuran, methanol, ethanol, isopropanol, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethyl sulfoxide, acetone
10 and the like. Two or more kinds of these solvents may be used in an appropriate ratio.

The reaction temperature is generally about 0 - 100°C.

While the reaction time is not particularly limited, it is generally 0.1 - 100 hr, preferably 0.5 - 72 hr.

15 [0170]

[Step 1-3]

In this Step, compound (IV) is reacted with diphenylphosphoryl azide and tert-butyl alcohol to produce compound (V).

20 This reaction is generally performed in the presence of a base in an inert solvent or an excess amount of tert-butyl alcohol.

Examples of the base include triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene,
25 potassium carbonate, cesium carbonate, potassium tert-butoxide and the like. Among these, triethylamine and diisopropylethylamine are preferable.

The amount of the base to be used is generally 1 - 10 molar equivalents relative to compound (IV).

30 Examples of the inert solvent include toluene, benzene, xylene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile and the like. Two or more kinds of these solvents may be used in an appropriate ratio.

The reaction temperature is generally about 0 - 150°C.

35 While the reaction time is not particularly limited, it

is generally 0.1 - 100 hr, preferably 0.5 - 72 hr.

[0171]

[Step 1-4]

In this Step, compound (V) is subjected to a reduction
5 reaction to produce compound (VI).

This reaction is generally performed in the presence of a metal reagent in a water-containing solvent.

Examples of the metal reagent include iron, zinc, nickel, tin, tin(II) chloride and the like.

10 The amount of the metal reagent to be used is generally 1 - 1000 molar equivalents relative to compound (V).

The progress of this reaction can be accelerated by adding an additive such as calcium chloride, ammonium chloride, sodium acetate, acetic acid, hydrochloric acid, hydrazine and
15 the like to the reaction system. The amount of such additive to be used is generally not less than 1 molar equivalent relative to compound (V).

Examples of the solvent to be used as a water-containing solvent include methanol, ethanol, isopropanol, tetrahydrofuran,
20 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile and the like. Two or more kinds of these solvents may be used in an appropriate ratio.

The reaction temperature is generally about 0 - 100°C.

While the reaction time is not particularly limited, it
25 is generally 0.1 - 100 hr, preferably 0.5 - 72 hr.

[0172]

[Step 1-5]

In this Step, compound (VI) is reacted with compound (VII) under basic conditions to produce compound (VIII) ($R \neq H$).

30 Compound (VII) may be a commercially available product, or can be produced by a method known per se [for example, the method described in "Advanced Organic Chemistry, 4th Ed." (by Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (by Richard C. Larock) and the like] or a method analogous
35 thereto.

The amount of compound (VII) to be used is generally 0.1 - 10 molar equivalents relative to compound (VI).

This reaction is generally performed in the presence of a base in an inert solvent.

5 Examples of the base include triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, potassium carbonate, sodium carbonate, cesium carbonate, potassium tert-butoxide, sodium hydroxide and the like. Among these, triethylamine, diisopropylethylamine and potassium
10 carbonate are preferable.

The amount of such base to be used is generally not less than 1 molar equivalent relative to compound (VI).

Examples of the inert solvent include tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide,
15 acetonitrile, dimethyl sulfoxide, acetone, methylene chloride and the like. Two or more kinds of these solvents may be used in an appropriate ratio.

The reaction temperature is generally about 0 - 150°C.

While the reaction time is not particularly limited, it
20 is generally 0.1 - 100 hr, preferably 0.5 - 72 hr.

[0173]

[Step 1-6]

In this Step, compound (VIII) is reacted with compound (IX) to produce compound (X).

25 Compound (IX) may be a commercially available product, or can be produced by a method known per se [for example, the method described in "Advanced Organic Chemistry, 4th Ed." (by Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (by Richard C. Larock) and the like] or a method analogous
30 thereto.

The amount of compound (IX) to be used is generally 0.1 - 10 molar equivalents relative to compound (VIII).

This reaction is generally performed in the presence of a base in an inert solvent.

35 Examples of the base include triethylamine,

diisopropylethylamine, pyridine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene, potassium carbonate, sodium carbonate, cesium carbonate, potassium tert-butoxide, sodium hydroxide and the like. Among these, triethylamine and
5 diisopropylethylamine are preferable.

The amount of the base to be used is generally not less than 1 molar equivalent relative to compound (VIII).

Examples of the inert solvent include tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, 1,4-dioxane, toluene,
10 benzene, xylene, N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, ethyl acetate, methylene chloride and the like can be mentioned. Two or more kinds of these solvents may be used in an appropriate ratio.

When a carboxylic acid is used as compound (IX), the
15 reaction can be accelerated by adding a condensing agent in the reaction system.

Examples of the condensing agent include 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate,
20 diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the
25 like.

The amount of the condensing agent to be used is generally 1 - 10 molar equivalents relative to compound (VIII).

In this reaction, a suitable condensation accelerator (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide, N,N-
30 dimethyl-4-aminopyridine etc.) can be used as necessary.

The amount of the condensation accelerator to be used is generally 0.1 - 10 molar equivalents relative to compound (VIII).

The reaction temperature is generally about 0 - 150°C.

35 While the reaction time is not particularly limited, it

is generally 0.1 - 100 hr, preferably 0.5 - 72 hr.

[0174]

[Step 1-7]

In this Step, compound (VI) is reacted with compound (IX)
5 to produce compound (X) (R=H).

This reaction can be carried out in the same manner as in
the aforementioned Step 1-6.

[0175]

[Step 1-8]

10 In this Step, compound (X) is subjected to a reaction for
removal of a tert-butoxycarbonyl group to produce compound (XI).

This reaction is generally performed in the presence of
an acid in an inert solvent or an excess amount of an acid.

Examples of the acid include trifluoroacetic acid,
15 hydrochloric acid, hydrobromic acid, sulfuric acid,
hydrofluoric acid and the like. Among these, hydrochloric acid
and trifluoroacetic acid are preferable.

The amount of the acid to be used is generally 1 - 1000
molar equivalents relative to compound (X).

20 Examples of the inert solvent include methanol, ethanol,
isopropanol, water, methylene chloride, toluene, benzene,
xylene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide,
N,N-dimethylacetamide, acetonitrile and the like. Two or more
kinds of these solvents may be used in an appropriate ratio.

25 The reaction temperature is generally about 0 - 150°C.

While the reaction time is not particularly limited, it
is generally 0.1 - 100 hr, preferably 0.5 - 72 hr.

[0176]

[Step 1-9]

30 In this Step, compound (XI) is reacted with compound
(XII) under basic conditions to produce compound (XIII) (X≠H).

Compound (XII) may be a commercially available product,
or can be produced by a method known per se [for example, the
method described in "Advanced Organic Chemistry, 4th Ed." (by
35 Jerry March), "Comprehensive Organic Transformations, 2nd Ed."

(by Richard C. Larock) and the like] or a method analogous thereto.

The amount of compound (XII) to be used is generally 0.1 - 10 molar equivalents relative to compound (XI).

5 This reaction is generally performed in the presence of a base in an inert solvent.

Examples of the base include triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, potassium carbonate, sodium carbonate, cesium carbonate,
10 potassium tert-butoxide, sodium hydroxide and the like. Among these, triethylamine, diisopropylethylamine and potassium carbonate are preferable.

The amount of the base to be used is generally not less than 1 molar equivalent relative to compound (XI).

15 Examples of the inert solvent include tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethyl sulfoxide, acetone, methylene chloride and the like. Two or more kinds of these solvents may be used in an appropriate ratio.

20 The reaction temperature is generally about 0 - 150°C.

While the reaction time is not particularly limited, it is generally 0.1 - 100 hr, preferably 0.5 - 72 hr.

[0177]

[Step 1-10]

25 In this Step, compound (XIII) is reacted with compound (XIV) under basic conditions to produce compound (I).

Compound (XIV) may be a commercially available product, or can be produced by a method known per se [for example, the method described in "Advanced Organic Chemistry, 4th Ed." (by
30 Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (by Richard C. Larock) and the like] or a method analogous thereto.

The amount of compound (XIV) to be used is generally 0.1 - 10 molar equivalents relative to compound (XIII).

35 This reaction is generally performed in the presence of a

base in an inert solvent.

Examples of the base include triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, potassium carbonate, sodium carbonate, cesium carbonate, 5 potassium tert-butoxide, sodium hydroxide and the like. Among these, triethylamine, diisopropylethylamine and potassium carbonate are preferable.

The amount of the base to be used is generally not less than 1 molar equivalent relative to compound (XIII).

10 Examples of the inert solvent include tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethyl sulfoxide, acetone, methylene chloride and the like. Two or more kinds of these solvents may be used in an appropriate ratio.

15 The reaction temperature is generally about 0 - 150°C.

While the reaction time is not particularly limited, it is generally 0.1 - 100 hr, preferably 0.5 - 72 hr.

Compound (I) can also be produced by one step from compound (XI) without via compound (XIII).

20 [0178]

[Step 1-11]

In this Step, compound (XI) is reacted with compound (XIV) under basic conditions to produce compound (I) (X=H).

This reaction can be carried out in the same manner as in 25 the aforementioned Step 1-10.

[0179]

[Step 1-12]

In this Step, compound (XI) is reacted with compound (XV) in the presence of a reducing agent to produce compound (Ia).

30 Compound (Ia) is compound (I) wherein $Y^1=H$. Compound (Ia) is encompassed in compound (I).

Compound (XV) may be a commercially available product, or can be produced by a method known per se [for example, the method described in "Advanced Organic Chemistry, 4th Ed." (by 35 Jerry March), "Comprehensive Organic Transformations, 2nd Ed."]

(by Richard C. Larock) and the like] or a method analogous thereto.

The amount of compound (XV) to be used is generally 0.1 - 10 molar equivalents relative to compound (XI).

5 This reaction is generally performed in the presence of a reducing agent in an inert solvent.

Examples of the reducing agent include sodium triacetoxyborohydride, sodium cyanoborohydride, sodium borohydride, 2-picoline borane complex and the like.

10 The amount of the reducing agent to be used is generally 1 - 10 molar equivalents relative to compound (XI).

Examples of the inert solvent include tetrahydrofuran, methanol, ethanol, isopropanol, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile,
15 methylene chloride, acetic acid, water and the like. Two or more kinds of these solvents may be used in an appropriate ratio.

The reaction temperature is generally about 0 - 150°C.

While the reaction time is not particularly limited, it
20 is generally 0.1 - 100 hr, preferably 0.5 - 72 hr.

Compound (XI) is reacted in advance with compound (XV) in the presence of a dehydrating agent (titanium(IV) isopropoxide, sodium hydrogen carbonate, sodium sulfate, magnesium sulfate, molecular sieve etc.) to produce enamine, which is reacted with
25 a reducing agent to produce the object compound (Ia).

[0180]

[Step 1-13]

In this Step, compound (XIII) is reacted with compound (XV) in the presence of a reducing agent to produce compound
30 (Ia).

This reaction can be carried out in the same manner as in the aforementioned Step 1-12.

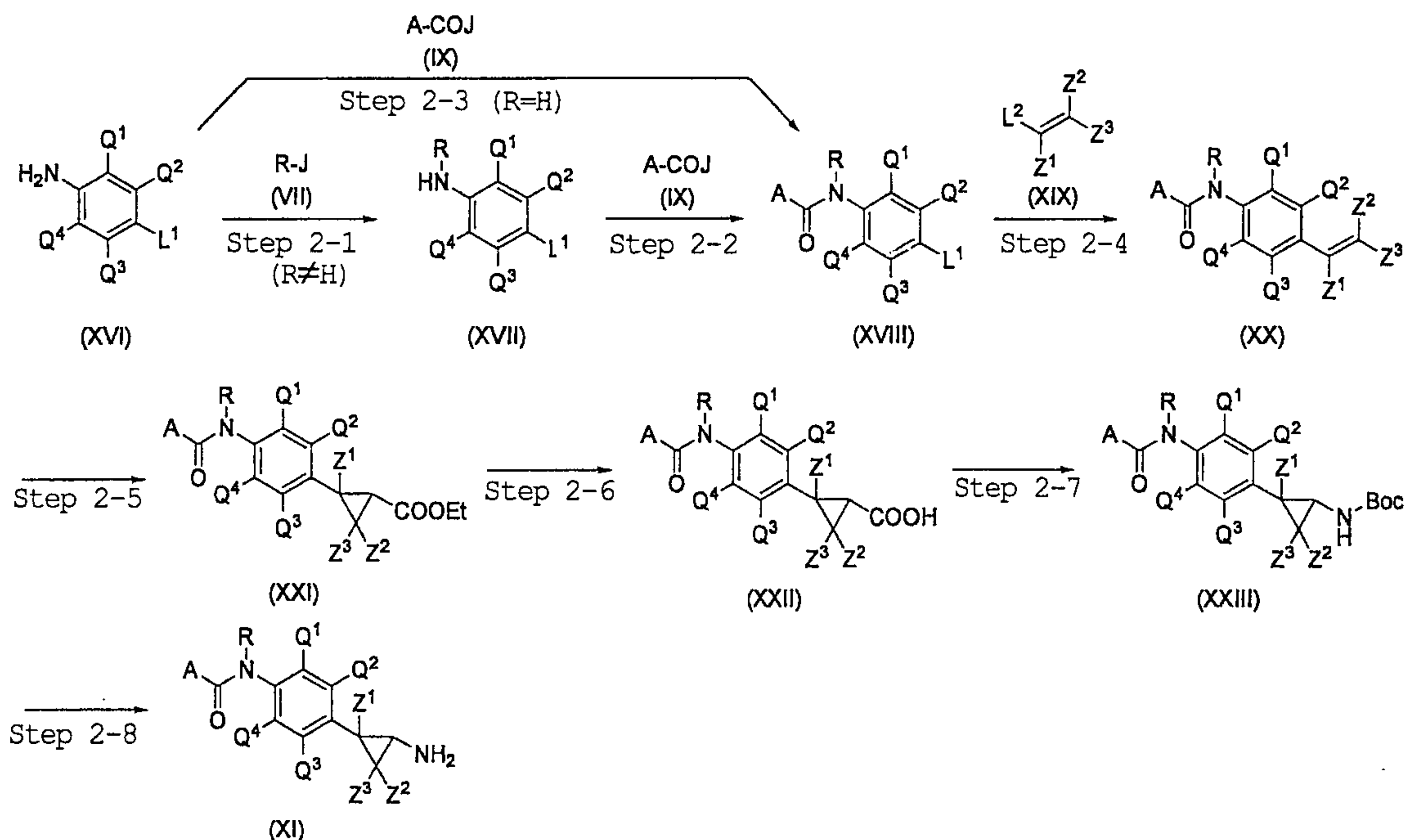
Compound (Ia) can also be produced by one step from compound (XI) without via compound (XIII).

35 [0181]

[Production method 2]

Compound (XI) can also be produced by the following production method or a method analogous thereto.

[0182]



5

[0183]

wherein each symbol is as defined above, J is a halogen atom (e.g., F, Cl, Br, I), OTs, OMs or OH, and L¹ and L² are each independently H, Cl, Br, I, trifluoromethanesulfonyloxy (OTf),
 10 B(OH)₂, BF₃K, B(-OCMe₂CMe₂O-) or a 9-BBN group.

[0184]

[Step 2-1]

In this Step, compound (XVI) is reacted with compound (VII) under basic conditions to produce compound (XVII) (R ≠ H).

15 This reaction can be carried out in the same manner as in the aforementioned Step 1-5.

[0185]

[Step 2-2]

In this Step, compound (XVII) is reacted with compound (IX) to produce compound (XVIII).
 20

This reaction can be carried out in the same manner as in the aforementioned Step 1-6.

[0186]

[Step 2-3]

In this Step, compound (XVI) is reacted with compound (IX) to produce compound (XVIII) (R=H).

This reaction can be carried out in the same manner as in
5 the aforementioned Step 1-6.

[0187]

[Step 2-4]

In this Step, compound (XVIII) is coupled with vinyl
compound (XIX) in the presence of a metal catalyst to produce
10 compound (XX).

Vinyl compound (XIX) may be a commercially available
product, or can be produced by a method known per se [for
example, the method described in Synlett 2002, 1137; Journal of
Organic Chemistry 2003, 68, 6354; Bioorganic and Medicinal
15 Chemistry 2008, 16, 5452 and the like] or a method analogous
thereto.

This reaction is generally performed in an inert solvent.

This reaction is performed under microwave irradiation
where necessary.

20 The amount of compound (XIX) to be used is generally 0.1
- 10 molar equivalents relative to compound (XVIII).

Examples of the inert solvent include water, methanol,
ethanol, chloroform, dichloromethane, 1,2-dichloroethane,
carbon tetrachloride, tetrahydrofuran, diethyl ether, 1,2-
25 dimethoxyethane, 1,4-dioxane, toluene, xylene, benzene,
chlorobenzene, N,N-dimethylformamide, N,N-dimethylacetamide, 1-
methylpiperidone, acetonitrile, dimethyl sulfoxide and the like.
Two or more kinds of these solvents may be used in an
appropriately ratio.

30 Examples of the metal catalyst include palladium(II)
acetate, palladium(II) chloride,
tris(dibenzylideneacetone)dipalladium(0),
bis(acetylacetonato)palladium(II), nickel(II) chloride,
copper(I) chloride, copper(I) acetate and the like. Two or
35 more kinds of these metal catalysts may be used in an

appropriately ratio.

The amount of the metal catalyst to be used is generally 0.001 - 1 molar equivalent, preferably 0.01 - 0.5 molar equivalent, relative to compound (XVIII).

5 The reaction can be accelerated by adding an appropriate ligand to the metal catalyst.

Examples of the ligand include triphenylphosphine, tri(o-tolyl)phosphine, tri(tert-butyl)phosphine, 1,1'-bis(diphenylphosphino)ferrocene, 2,2'-bis(diphenylphosphino)-
10 1,1'-binaphthyl and the like. A complex of the ligand with the aforementioned metal catalyst may be prepared in advance and used, or a commercially available complex already prepared may also be used.

The amount of the ligand to be used is generally 0.001 -
15 2 molar equivalents, preferably 0.01 - 1 molar equivalent, relative to compound (XVIII).

The reaction temperature is generally about 0 - 200°C.

While the reaction time is not particularly limited, it is generally 0.01 - 100 hr, preferably 0.1 - 72 hr.

20 [0188]

[Step 2-5]

In this Step, compound (XX) is reacted with ethyl diazoacetate in the presence of a metal catalyst to produce compound (XXI).

25 This reaction can be carried out in the same manner as in the aforementioned Step 1-1.

[0189]

[Step 2-6]

In this Step, compound (XXI) is subjected to hydrolysis
30 to produce compound (XXII).

This reaction can be carried out in the same manner as in the aforementioned Step 1-2.

[0190]

[Step 2-7]

35 In this Step, compound (XXII) is reacted with

diphenylphosphoryl azide and tert-butyl alcohol to produce compound (XXIII).

This reaction can be carried out in the same manner as in the aforementioned Step 1-3.

5 [0191]

[Step 2-8]

In this Step, compound (XXIII) is subjected to a reaction for removal of a tert-butoxycarbonyl group to produce compound (XI).

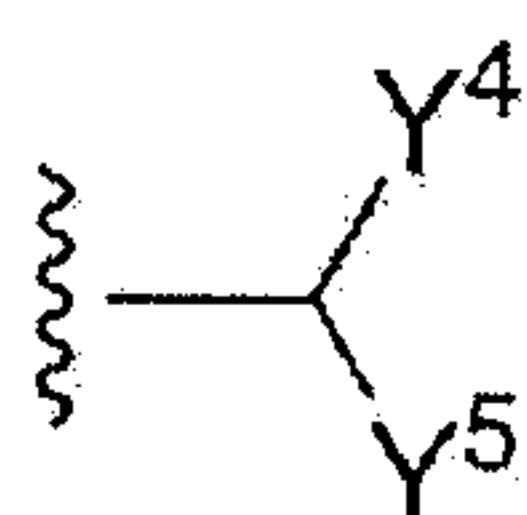
10 This reaction can be carried out in the same manner as in the aforementioned Step 1-8.

[0192]

[Production method 3]

Compound (Ic) which is compound (I) wherein X is a group
15 represented by

[0193]

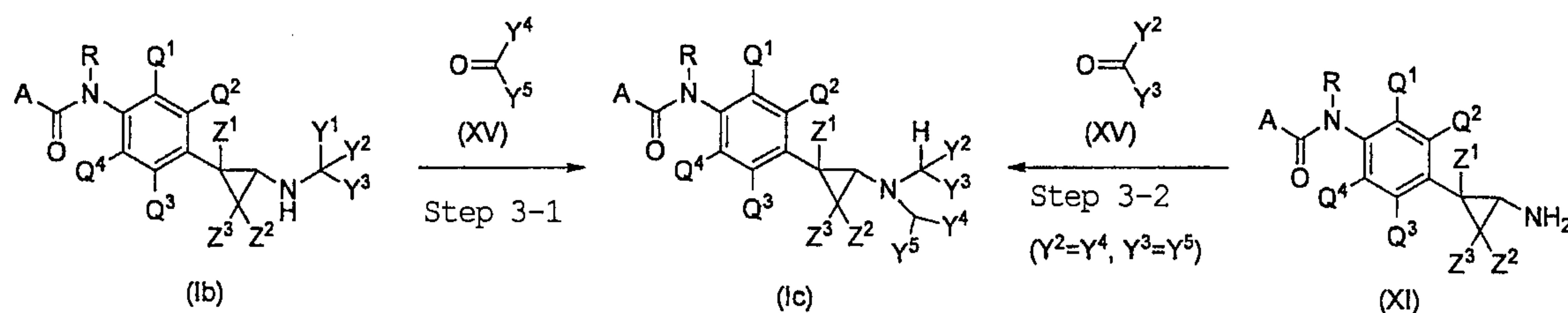


Xa

[0194]

wherein Y⁴ and Y⁵ are each independently a hydrogen atom, a
20 hydrocarbon group optionally having substituent(s), or a heterocyclic group optionally having substituent(s), and Y⁴ and Y⁵ are optionally bonded to each other to form a ring optionally having substituent(s),
can be produced by the following production method or a method
25 analogous thereto. Compound (Ib) is compound (I) wherein X=H. Compounds (Ib) and (Ic) are encompassed in compound (I).

[0195]



[0196]

wherein each symbol is as defined above, and J is a halogen atom (e.g., F, Cl, Br, I), OTs, OMs or OH.

[0197]

5 [Step 3-1]

In this Step, compound (Ib) is reacted with compound (XV) in the presence of a reducing agent to produce compound (Ic).

Compound (XV) may be a commercially available product, or can be produced by a method known per se [for example, the
10 method described in "Advanced Organic Chemistry, 4th Ed." (by Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (by Richard C. Larock) and the like] or a method analogous thereto.

This reaction can be carried out in the same manner as in
15 the aforementioned Step 1-12.

[0198]

[Step 3-2]

In this Step, compound (XI) is reacted with compound (XV) in the presence of a reducing agent to produce compound (Ic).

20 Compound (XV) may be a commercially available product, or can be produced by a method known per se [for example, the method described in "Advanced Organic Chemistry, 4th Ed." (by Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (by Richard C. Larock) and the like] or a method analogous
25 thereto.

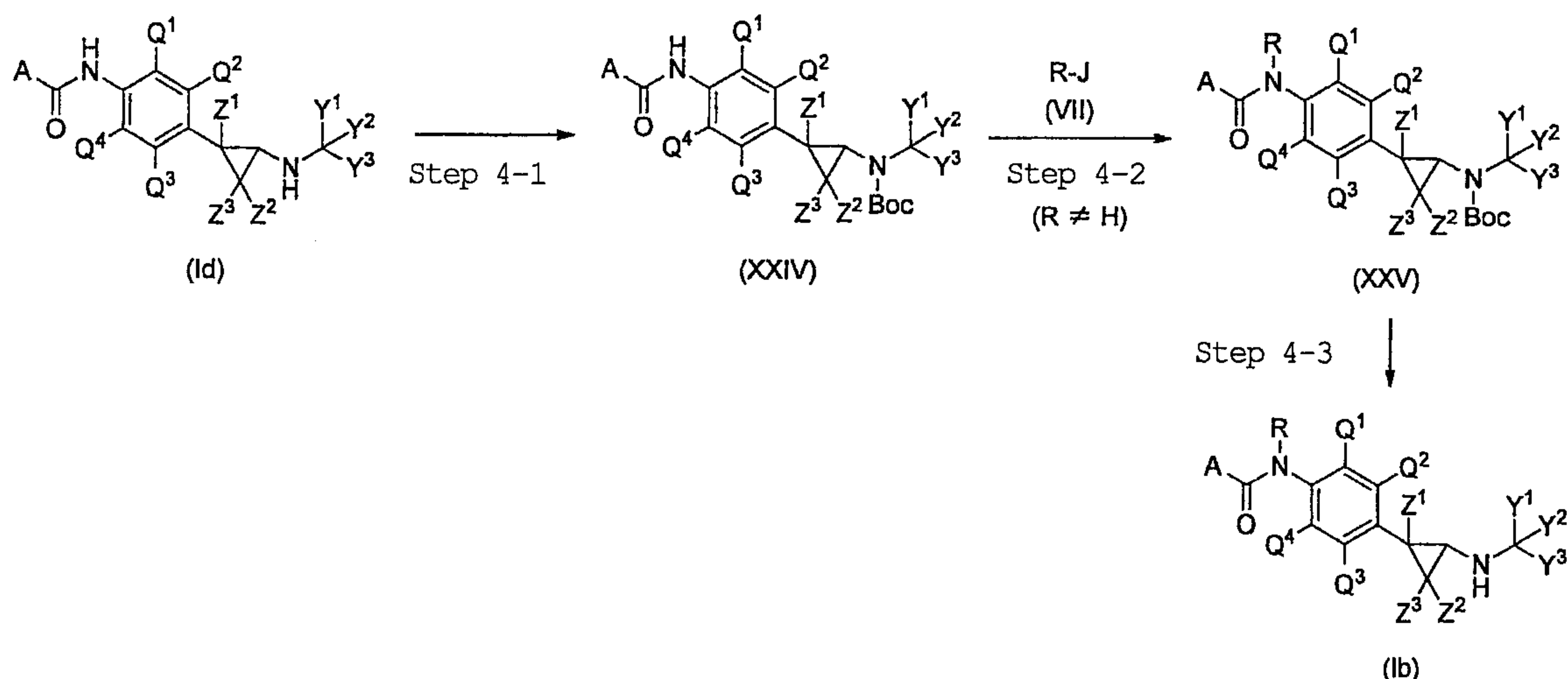
This reaction can be carried out in the same manner as in the aforementioned Step 1-12.

[0199]

[Production method 4]

30 Compound (Ib) which is compound (I) wherein X=H can also be produced by the following production method or a method analogous thereto. Compound (Id) is compound (I) wherein R=H, X=H. Compounds (Ib) and (Id) are encompassed in compound (I).

[0200]



[0201]

wherein each symbol is as defined above, and J is a halogen atom (e.g., F, Cl, Br, I), OTs, OMs or OH.

5 [0202]

[Step 4-1]

In this Step, compound (Id) is reacted with di-tert-butyl dicarbonate under basic conditions to produce compound (XXIV).

The amount of the di-tert-butyl dicarbonate to be used is
10 generally 0.1 - 10 molar equivalents relative to compound (Id).

This reaction is generally performed in the presence of a base in an inert solvent.

Examples of the base include triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene,
15 potassium carbonate, sodium carbonate, cesium carbonate, potassium tert-butoxide, sodium hydroxide and the like. Among these, triethylamine, diisopropylethylamine and sodium hydroxide are preferable.

The amount of the base to be used is generally not less
20 than 1 molar equivalent relative to compound (Id).

Examples of the inert solvent include tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethyl sulfoxide, acetone, methylene chloride, water and the like. Two or more kinds of these solvents may be
25 used in an appropriate ratio.

The reaction temperature is generally about 0 - 100°C.

While the reaction time is not particularly limited, it is generally 0.1 - 100 hr, preferably 0.5 - 72 hr.

[0203]

5 [Step 4-2]

In this Step, compound (XXIV) is reacted with compound (VII) under basic conditions to produce compound (XXV) ($R \neq H$).

This reaction can be carried out in the same manner as in the aforementioned Step 1-5.

10 [0204]

[Step 4-3]

In this Step, compound (XXV) is subjected to a reaction for removal of a tert-butoxycarbonyl group to produce compound (Ib).

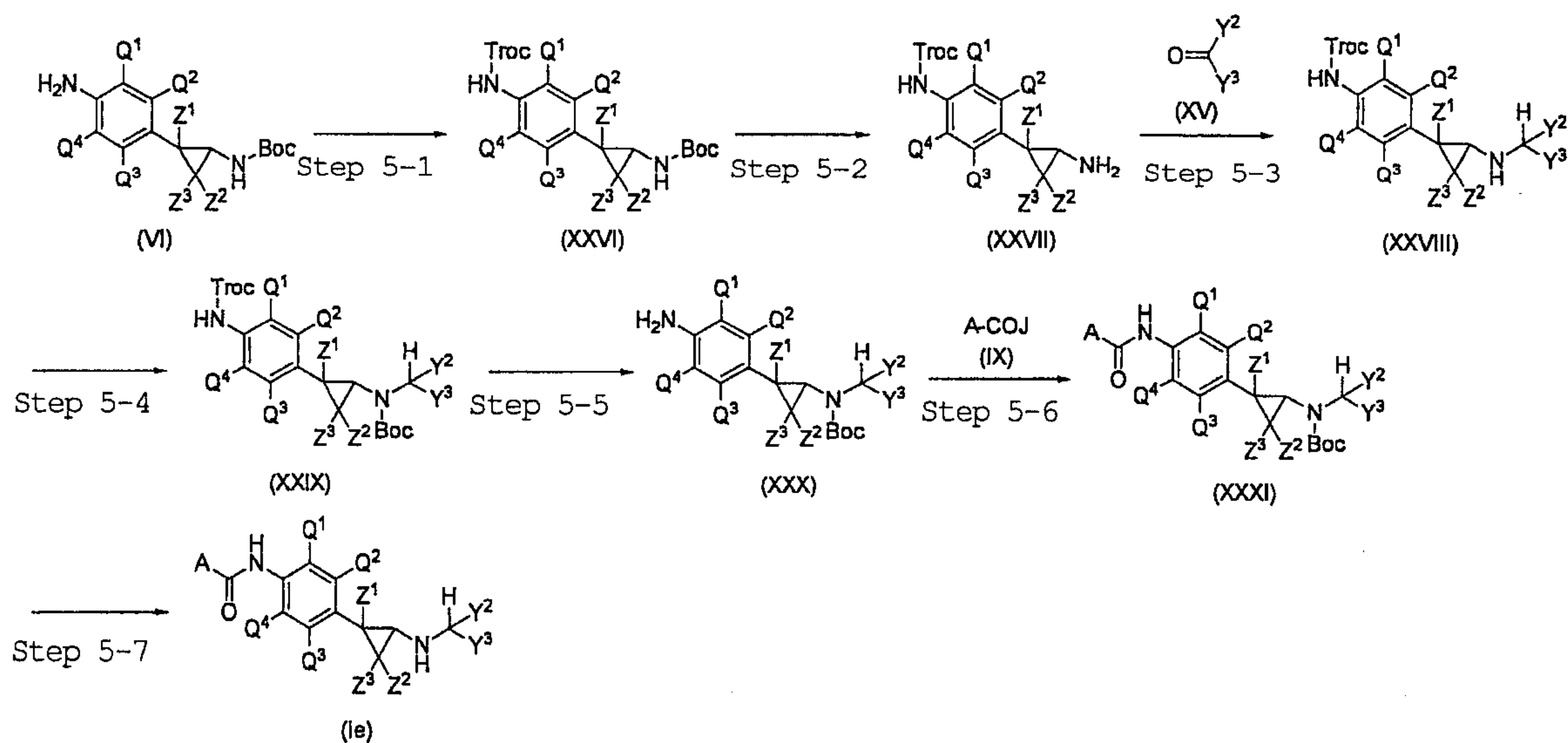
15 This reaction can be carried out in the same manner as in the aforementioned Step 1-8.

[0205]

[Production method 5]

Compound (Ie) which is compound (I) wherein $R=H$, $X=H$, $Y^1=H$ can also be produced by the following production method or a method analogous thereto. Compound (Ie) is encompassed in compound (I).

[0206]



25 [0207]

wherein each symbol is as defined above, J is a halogen atom (e.g., F, Cl, Br, I), OTs, OMs or OH, and Troc is 2,2,2-trichloroethoxycarbonyl.

[0208]

5 [Step 5-1]

In this Step, compound (VI) is reacted with 2,2,2-trichloroethyl chloroformate under basic conditions to produce compound (XXVI).

The amount of the 2,2,2-trichloroethyl chloroformate to
10 be used is generally 0.1 - 10 molar equivalents relative to compound (VI).

This reaction is generally performed in the presence of a base in an inert solvent.

Examples of the base include triethylamine,
15 diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, potassium carbonate, sodium carbonate, cesium carbonate, potassium tert-butoxide, sodium hydroxide and the like. Among these, triethylamine, diisopropylethylamine and potassium carbonate are preferable.

20 The amount of the base to be used is generally not less than 1 molar equivalent relative to compound (VI).

Examples of the inert solvent include tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethyl sulfoxide, acetone, methylene chloride
25 and the like. Two or more kinds of these solvents may be used in an appropriate ratio.

The reaction temperature is generally about 0 - 150°C.

While the reaction time is not particularly limited, it is generally 0.1 - 100 hr, preferably 0.5 - 72 hr.

30 [0209]

[Step 5-2]

In this Step, compound (XXVI) is subjected to a reaction for removal of a tert-butoxycarbonyl group to produce compound (XXVII).

35 This reaction can be carried out in the same manner as in

the aforementioned Step 1-8.

[0210]

[Step 5-3]

In this Step, compound (XXVII) is reacted with compound
5 (XV) in the presence of a reducing agent to produce compound
(XXVIII).

This reaction can be carried out in the same manner as in
the aforementioned Step 1-12.

[0211]

10 [Step 5-4]

In this Step, compound (XXVIII) is reacted with di-tert-
butyl dicarbonate under basic conditions to produce compound
(XXIX).

This reaction can be carried out in the same manner as in
15 the aforementioned Step 4-1.

[0212]

[Step 5-5]

In this Step, compound (XXIX) is subjected to a reaction
for removal of a 2,2,2-trichloroethoxycarbonyl group to produce
20 compound (XXX).

This reaction is generally performed in the presence of
an acid and a metal reagent in a polar solvent.

Examples of the acid include acetic acid, citric acid,
trifluoroacetic acid, hydrochloric acid, hydrobromic acid and
25 the like. Among these, acetic acid is preferable.

The amount of the acid to be used is generally 1 - 1000
molar equivalents relative to compound (XXIX).

Examples of the metal reagent include zinc, iron, tin,
cadmium and the like. Among these, zinc is preferable.

30 The amount of the metal reagent to be used is generally 1
- 1000 molar equivalents relative to compound (XXIX).

Examples of the polar solvent include water, methanol,
ethanol, isopropanol, tetrahydrofuran, 1,4-dioxane, N,N-
dimethylformamide, N,N-dimethylacetamide, acetonitrile,
35 dimethyl sulfoxide, acetic acid, trifluoroacetic acid and the

like. Two or more kinds of these solvents may be used in an appropriate ratio.

The reaction temperature is generally about 0 - 150°C.

While the reaction time is not particularly limited, it is generally 0.1 - 100 hr, preferably 0.5 - 72 hr.

[0213]

[Step 5-6]

In this Step, compound (XXX) is reacted with compound (IX) to produce compound (XXXI).

This reaction can be carried out in the same manner as in the aforementioned Step 1-6.

[0214]

[Step 5-7]

In this Step, compound (XXXI) is subjected to a reaction for removal of a tert-butoxycarbonyl group to produce compound (Ie).

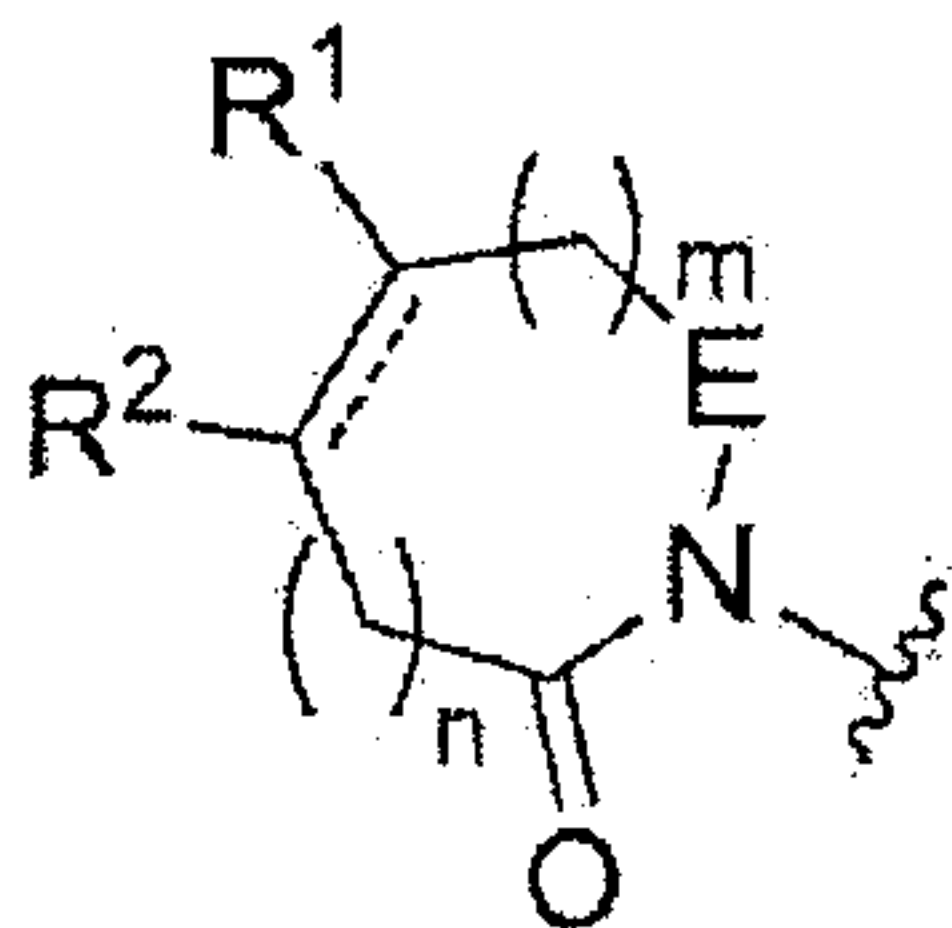
This reaction can be carried out in the same manner as in the aforementioned Step 1-8.

[0215]

[Production method 6]

Compound (If) which is compound (I) wherein A-CON(R)- is a group represented by

[0216]

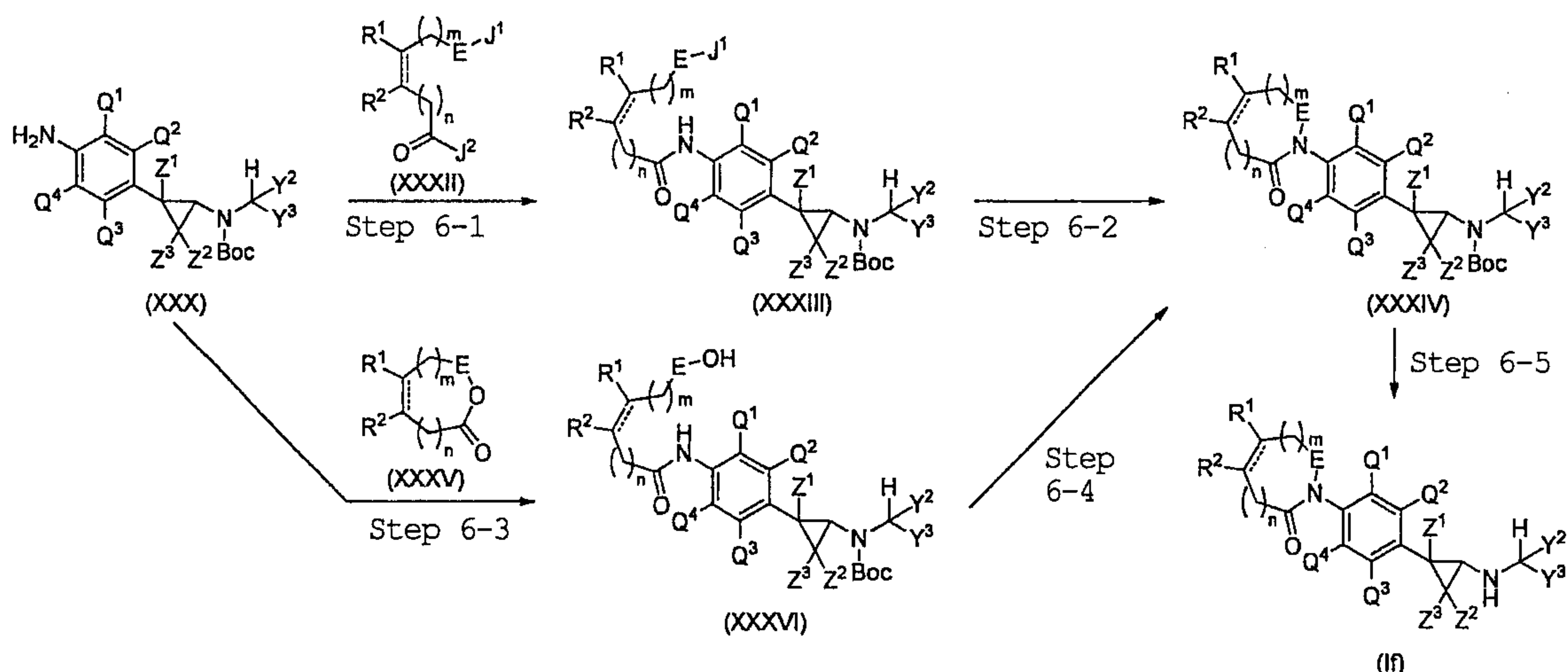


[0217]

wherein R¹ and R² are each independently an optionally fused hydrocarbon group optionally having substituent(s), E is a methylene group optionally having substituent(s) or a carbonyl group, and m and n are each independently an integer of 0 to 3, and Y¹=H can also be produced by the following production method or a method analogous thereto. Compound (If) is

encompassed in compound (I).

[0218]



[0219]

5 wherein each symbol is as defined above, and J^1 and J^2 are each independently a halogen atom (e.g., F, Cl, Br, I), OTs, OMs or OH.

[0220]

[Step 6-1]

10 In this Step, compound (XXX) is reacted with compound (XXXII) to produce compound (XXXIII).

Compound (XXXII) may be a commercially available product, or can be produced by a method known per se [for example, the method described in "Advanced Organic Chemistry, 4th Ed." (by
15 Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (by Richard C. Larock) and the like] or a method analogous thereto.

This reaction can be carried out in the same manner as in the aforementioned Step 1-6.

20 [0221]

[Step 6-2]

In this Step, compound (XXXIII) is cyclized to produce compound (XXXIV).

This reaction is generally performed in the presence of a
25 base in an inert solvent.

Examples of the base include triethylamine,

diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, potassium carbonate, sodium carbonate, cesium carbonate, potassium tert-butoxide, sodium hydroxide and the like. Among these, triethylamine, diisopropylethylamine, and potassium
5 carbonate are preferable.

The amount of the base to be used is generally not less than 1 molar equivalent relative to compound (XXXIII).

Examples of the inert solvent include tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide,
10 acetonitrile, dimethyl sulfoxide, acetone, methylene chloride and the like. Two or more kinds of these solvents may be used in an appropriate ratio.

When carboxylic acid ($E=CO$, $J^1=OH$) is used as compound (XXXIII), the reaction can be accelerated by adding a
15 condensing agent to the reaction system.

Examples of the condensing agent include 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide, 1,1'-carbonyldiimidazole,
20 benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like.

25 The amount of the condensing agent to be used is generally 1 - 10 molar equivalents relative to compound (XXXIII).

In this reaction, a suitable condensation accelerator (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide, N,N-
30 dimethyl-4-aminopyridine etc.) can be used as necessary.

The amount of the condensation accelerator to be used is generally 0.1 - 10 molar equivalents relative to compound (XXXIII).

The reaction temperature is generally about 0 - 150°C.

35 While the reaction time is not particularly limited, it

is generally 0.1 - 100 hr, preferably 0.5 - 72 hr.

Compound (XXXIV) can also be produced by one step from compound (XXX) without via compound (XXXIII).

[0222]

5 [Step 6-3]

In this Step, compound (XXX) is reacted with compound (XXXV) to produce compound (XXXVI).

Compound (XXXV) may be a commercially available product, or can be produced by a method known per se [for example, the
10 method described in "Advanced Organic Chemistry, 4th Ed." (by Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (by Richard C. Larock) and the like] or a method analogous thereto.

This reaction can be carried out in the same manner as in
15 the aforementioned Step 1-5.

[0223]

[Step 6-4]

In this Step, compound (XXXVI) is cyclized to produce compound (XXXIV).

20 This reaction is generally performed in the presence of an acid or condensing agent in an inert solvent.

Examples of the acid include hydrochloric acid, hydrobromic acid, acetic acid, p-toluenesulfonic acid, sulfuric acid, pyrophosphoric acid and the like. Among these,
25 hydrochloric acid and p-toluenesulfonic acid are preferable.

The amount of the acid to be used is generally 0.01 - 10 molar equivalents relative to compound (XXXVI).

Examples of the inert solvent include tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide,
30 acetonitrile, dimethyl sulfoxide, acetone, methylene chloride and the like. Two or more kinds of these solvents may be used in an appropriate ratio.

Examples of the condensing agent include acetic anhydride, trifluoroacetic anhydride, p-toluenesulfonyl chloride,
35 Mitsunobu reagent (mixture of dialkyl azodicarboxylate and

trialkylphosphine or triarylphosphine), 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide, 1,1'-carbonyldiimidazole,
 5 benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like.

10 The amount of the condensing agent to be used is generally 1 - 10 molar equivalents relative to compound (XXXVI).

In this reaction, a suitable condensation accelerator (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide, N,N-dimethyl-4-aminopyridine etc.) can be used as necessary.

15 The amount of the condensation accelerator to be used is generally 0.1 - 10 molar equivalents relative to compound (XXXVI).

The reaction temperature is generally about 0 - 200°C.

While the reaction time is not particularly limited, it
 20 is generally 0.1 - 100 hr, preferably 0.5 - 72 hr.

Compound (XXXIV) can also be produced by one step from compound (XXX) without via compound (XXXVI).

[0224]

[Step 6-5]

25 In this Step, compound (XXXIV) is subjected to a reaction for removal of a tert-butoxycarbonyl group to produce compound (If).

This reaction can be carried out in the same manner as in the aforementioned Step 1-8.

30 [0225]

It is also possible to produce a compound encompassed in the present invention by further applying substituent introduction or functional group conversion to compound (I) according to a means known per se. Substituent introduction
 35 and functional group conversion are performed according to

known conventional methods such as conversion to carboxy group by ester hydrolysis, conversion to carbamoyl group by amidation of carboxy group, conversion to hydroxymethyl group by reduction of carboxy group, conversion to alcohol compound by reduction or alkylation of carbonyl group, reductive amination of carbonyl group, oximation of carbonyl group, acylation, ureation, sulfonylation or alkylation of amino group, amination of activated halogen with amine, conversion to amino group by reduction of nitro group, and acylation, carbamation, sulfonylation or alkylation of hydroxy group. When a reactive substituent causing an unintended reaction during substituent introduction and functional group conversion is present, a protecting group may be introduced in advance into the reactive substituent as necessary according to a means known per se, the object reaction is performed and the protecting group is removed according to a means known per se, whereby compounds encompassed in the present invention can be produced.

[0226]

In each of the above-mentioned reactions, when the starting compounds have an amino group, a carboxyl group, a hydroxy group or a carbonyl group as a substituent, such groups may be protected with the protecting groups generally used in peptide chemistry, etc. In such case, if necessary, such protecting groups can be removed after the reactions to obtain the objective compounds.

[0227]

Examples of the amino-protecting group include formyl, and C₁₋₆ alkylcarbonyl (e.g., acetyl, ethylcarbonyl etc.), phenylcarbonyl, C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl etc.), phenyloxycarbonyl, C₇₋₁₀ aralkyl-carbonyl (e.g., benzylcarbonyl etc.), trityl, phthaloyl, N,N-dimethylaminomethylene and the like, each of which optionally has substituent(s). Examples of the substituent of the "amino-protecting group" include a halogen atom (e.g., fluorine, chlorine, bromine, iodine), C₁₋₆ alkyl-

carbonyl (e.g., methylcarbonyl, ethylcarbonyl, butylcarbonyl etc.), a nitro group and the like, wherein the number of the substituents is 1 to several (e.g., 3).

[0228]

5 Examples of the carboxyl-protecting group include a C₁₋₆ alkyl group, a C₇₋₁₁ aralkyl group (e.g., benzyl), a phenyl group, a trityl group, a substituted silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyl dimethylsilyl, tert-butyl diethylsilyl), a C₂₋₆ alkenyl
10 group (e.g., 1-allyl) and the like. These groups are optionally substituted by 1 to 3 halogen atoms, a C₁₋₆ alkoxy group, a nitro group etc.

[0229]

 Examples of the hydroxy-protecting group include a C₁₋₆
15 alkyl group, a phenyl group, a trityl group, a C₇₋₁₀ aralkyl group (e.g., benzyl), a formyl group, a C₁₋₆ alkyl-carbonyl group, a benzoyl group, a C₇₋₁₀ aralkyl-carbonyl group (e.g., benzylcarbonyl), a 2-tetrahydropyranyl group, a 2-tetrahydrofuranyl group, a substituted silyl group (e.g.,
20 trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyl dimethylsilyl, tert-butyl diethylsilyl), a C₂₋₆ alkenyl group (e.g., 1-allyl) and the like. These groups are optionally substituted by 1 to 3 halogen atoms, a C₁₋₆ alkyl group, a C₁₋₆ alkoxy group, a nitro group etc.

25 [0230]

 Examples of the carbonyl-protecting group include cyclic acetal (e.g., 1,3-dioxane), non-cyclic acetal (e.g., di-C₁₋₆ alkyl acetal) and the like.

[0231]

30 Removal of the above-mentioned protecting group can be performed according to a known method, for example, the method described in 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-
35 methyldithiocarbamate, tetrabutylammonium fluoride, palladium

acetate, trialkylsilyl halide (e.g., trimethylsilyl iodide, trimethylsilyl bromide) and the like, a reduction method and the like can be used.

Examples

5 [0232]

The present invention is explained in detail in the following by referring to Examples, Experimental Examples and Formulation Examples. However, the examples do not limit the present invention and the present invention can be modified
10 within the scope of the present invention.

[0233]

The "room temperature" in the following Examples is generally about 10°C to about 35°C. The ratio for a mixed solvent is, unless otherwise specified, a volume mixing ratio
15 and % means wt% unless otherwise specified.

[0234]

In silica gel column chromatography, the indication of NH means use of aminopropylsilane-bonded silica gel. In HPLC (high performance liquid chromatography), the indication of C18
20 means use of octadecyl-bonded silica gel. The ratio of elution solvents is, unless otherwise specified, a volume mixing ratio.

[0235]

¹H NMR (proton nuclear magnetic resonance spectrum) was measured by Fourier-transform NMR. For the analysis,
25 ACD/SpecManager (trade name) and the like were used. Very mild peaks showing protons of hydroxyl group, amino group and the like are not described.

[0236]

MS (mass spectrum) was measured by LC/MS (liquid
30 chromatography mass spectrometer). As the ionization method, ESI (ElectroSpray Ionization) method or APCI (Atmospheric Pressure Chemical Ionization) method was used as API (Atmospheric Pressure Ionization), and the measurement was performed in a positive mode (API+) or negative mode (API-).
35 The data indicates measured values (found). Generally, a

molecular ion peak is observed, but an ion peak added with a solvent such as acetonitrile (CH_3CN) and the like or sodium ion (Na^+) is sometimes observed. When a compound having a tert-butoxycarbonyl group ($-\text{Boc}$) is used, a peak free of a tert-butoxycarbonyl group or tert-butyl group may be observed as a fragment ion. In addition, when a compound having a hydroxyl group ($-\text{OH}$) is used, a peak free of H_2O may be observed as a fragment ion. In the case of a salt, generally, a molecular ion peak of a free form or a fragment ion peak is observed.

10 [0237]

In the following Examples, the following abbreviations are used.

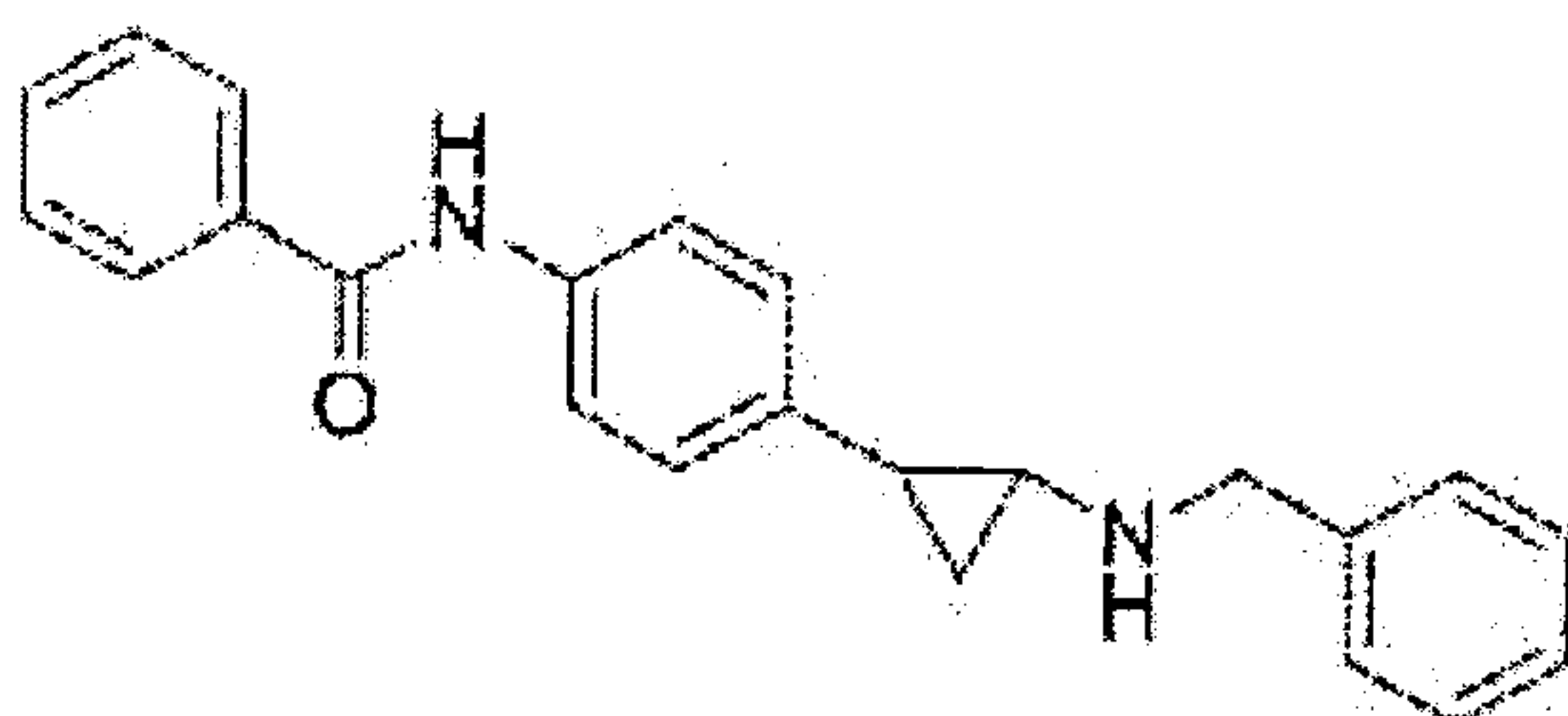
TFA: trifluoroacetic acid, DMSO: dimethyl sulfoxide, DMF: N,N-dimethylformamide, THF: tetrahydrofuran.

15 [0238]

Example 1

N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}benzamide

[0239]



20 [0240]

A) tert-butyl (trans-2-{4-[(phenylcarbonyl)amino]phenyl}cyclopropyl)carbamate

To a solution of tert-butyl [trans-2-(4-aminophenyl)cyclopropyl]carbamate (150 mg) described in a document (J. Am. Chem. Soc., 2010, 132, 6827.) in acetonitrile (6 mL) were added benzoyl chloride (84 μL) and triethylamine (101 μL). The mixture was stirred at room temperature overnight and water was added. The mixture was extracted with ethyl acetate, and the extract was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel

column chromatography (hexane/ethyl acetate) to give the title compound (212 mg).

¹H NMR (400 MHz, DMSO-d₆) δ 1.07 (2H, brs), 1.38 (9H, s), 1.88 (1H, brs), 2.56-2.65 (1H, m), 7.07 (2H, d, J = 8.6 Hz), 7.24
5 (1H, brs), 7.48-7.62 (3H, m), 7.66 (2H, d, J = 7.6 Hz), 7.94 (2H, d, J = 7.6 Hz), 10.18 (1H, s).

[0241]

B) N-[4-(trans-2-aminocyclopropyl)phenyl]benzamide hydrochloride

10 tert-Butyl (trans-2-{4-
[(phenylcarbonyl)amino]phenyl}cyclopropyl)carbamate (212 mg)
was dissolved in 4N hydrochloric acid/ethyl acetate solution (2 mL), and the mixture was stirred at room temperature for 2 hr and the solvent was evaporated under reduced pressure to give
15 the title compound (148 mg).

¹H NMR (400 MHz, DMSO-d₆) δ 1.13-1.25 (1H, m), 1.32-1.44 (1H, m), 2.24-2.35 (1H, m), 2.79 (1H, brs), 7.14 (2H, d, J = 8.1 Hz), 7.47-7.65 (3H, m), 7.72 (2H, d, J = 7.8 Hz), 7.95 (2H, d, J = 7.3 Hz), 8.38 (3H, brs), 10.25 (1H, s).

20 [0242]

C) N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}benzamide

To a solution of N-[4-(trans-2-aminocyclopropyl)phenyl]benzamide hydrochloride (70 mg) in methanol (2 mL) were added benzaldehyde (25 µL) and sodium
25 hydrogen carbonate (30.5 mg). The reaction mixture was stirred at 70°C for 1 hr, and ice-cooled to 0°C and sodium borohydride (13.8 mg) was added. The mixture was stirred for 1 hr and water was added. The mixture was extracted with ethyl acetate, and the extract was washed with saturated brine and dried over
30 anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was recrystallized (hexane/ethyl acetate) to give the title compound (49.1 mg).

MS (API+): [M+H]⁺ 343.3.

¹H NMR (400 MHz, CDCl₃) δ 0.96 (1H, brs), 1.11 (1H, brs), 1.92
35 (1H, brs), 2.37 (1H, brs), 3.89 (2H, brs), 7.00 (2H, d, J = 7.8

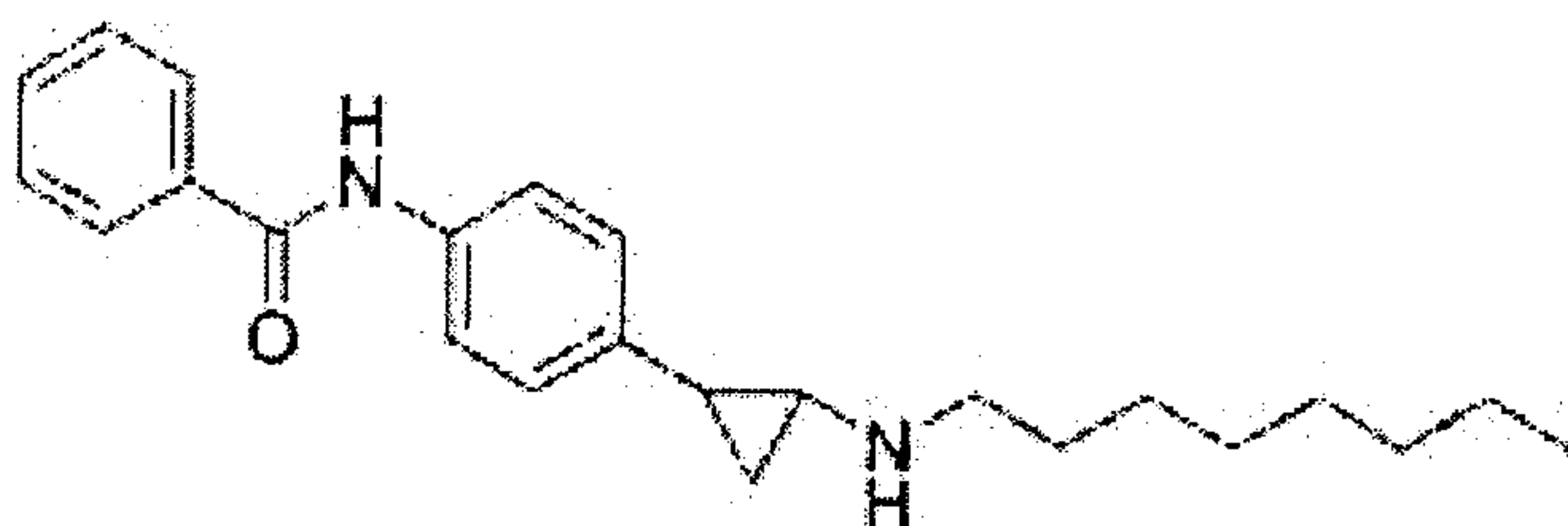
Hz), 7.21-7.36 (4H, m), 7.45-7.60 (5H, m), 7.73 (1H, brs),
7.82-7.91 (2H, m).

[0243]

Example 2

5 N-{4-[trans-2-(octylamino)cyclopropyl]phenyl}benzamide

[0244]



[0245]

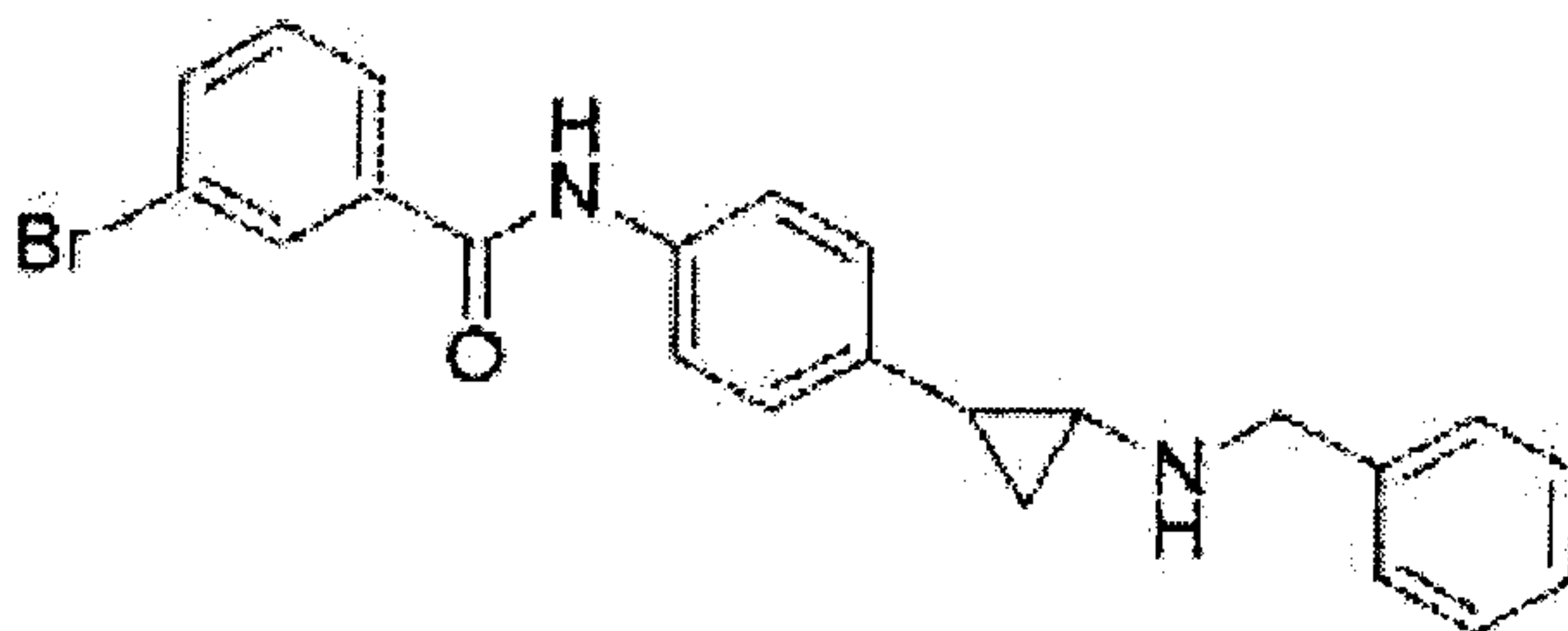
By a method similar to Example 1, Step C, the title
10 compound (59.4 mg) was obtained from N-[4-(trans-2-
aminocyclopropyl)phenyl]benzamide hydrochloride (100 mg) and
octylaldehyde (44.4 mg).

¹H NMR (400 MHz, DMSO-d₆) δ 0.81-0.97 (5H, m), 1.24 (10H, brs),
1.39 (2H, brs), 1.70-1.79 (1H, m), 2.12-2.31 (2H, m), 2.54-2.62
15 (2H, m), 7.02 (2H, s), 7.48-7.55 (2H, m), 7.55-7.59 (1H, m),
7.60-7.66 (2H, m), 7.93 (2H, d, J = 7.3 Hz), 10.15 (1H, s).

[0246]

Example 3

N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-bromobenzamide
20 [0247]



[0248]

A) tert-butyl [trans-2-(4-{[(3-
bromophenyl)carbonyl]amino}phenyl)cyclopropyl]carbamate

25 To a solution of tert-butyl [trans-2-(4-
aminophenyl)cyclopropyl]carbamate (300 mg) described in a
document (J. Am. Chem. Soc., 2010, 132, 6827.) in acetonitrile
(12 mL) were added 3-bromobenzoyl chloride (191 μL) and

triethylamine (202 μ L). The mixture was stirred at room temperature overnight and water was added. The mixture was extracted with ethyl acetate, and the extract 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 (hexane/ethyl acetate) to give the title compound (407 mg).

^1H NMR (400 MHz, CDCl_3) δ 1.15 (2H, t, $J = 5.6$ Hz), 1.46 (9H, s), 2.04 (1H, s), 2.70 (1H, brs), 4.86 (1H, brs), 7.15 (2H, d, $J = 7.6$ Hz), 7.36 (1H, t, $J = 7.9$ Hz), 7.52 (2H, d, $J = 7.6$ Hz), 7.67 (1H, d, $J = 8.1$ Hz), 7.71-7.81 (2H, m), 8.00 (1H, s).

[0249]

B) N-[4-(trans-2-aminocyclopropyl)phenyl]-3-bromobenzamide hydrochloride

tert-Butyl [trans-2-(4-((3-bromophenyl)carbonyl)amino)phenyl)cyclopropyl]carbamate (407 mg) was dissolved in 4N hydrochloric acid/ethyl acetate solution (2 mL), and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure to give the title compound (320 mg).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.15-1.24 (1H, m), 1.32-1.40 (1H, m), 2.29 (1H, brs), 2.76-2.84 (1H, m), 7.15 (2H, d, $J = 8.1$ Hz), 7.50 (1H, t, $J = 7.9$ Hz), 7.70 (2H, d, $J = 8.1$ Hz), 7.80 (1H, d, $J = 7.8$ Hz), 7.95 (1H, d, $J = 8.1$ Hz), 8.13 (1H, s), 8.33 (3H, brs), 10.35 (1H, s).

[0250]

C) N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-bromobenzamide

To a solution of N-[4-(trans-2-aminocyclopropyl)phenyl]-3-bromobenzamide hydrochloride (80 mg) in methanol (2 mL) were added benzaldehyde (22 μ L) and sodium hydrogen carbonate (27.4 mg). The mixture was stirred at 70°C for 1 hr, and ice-cooled to 0°C and sodium borohydride (12.4 mg) was added. The mixture was stirred for 1 hr and water was added. The mixture was extracted with ethyl acetate, and the extract 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 (hexane/ethyl acetate) and recrystallized (hexane/ethyl acetate) to give the
 5 title compound (21.0 mg).

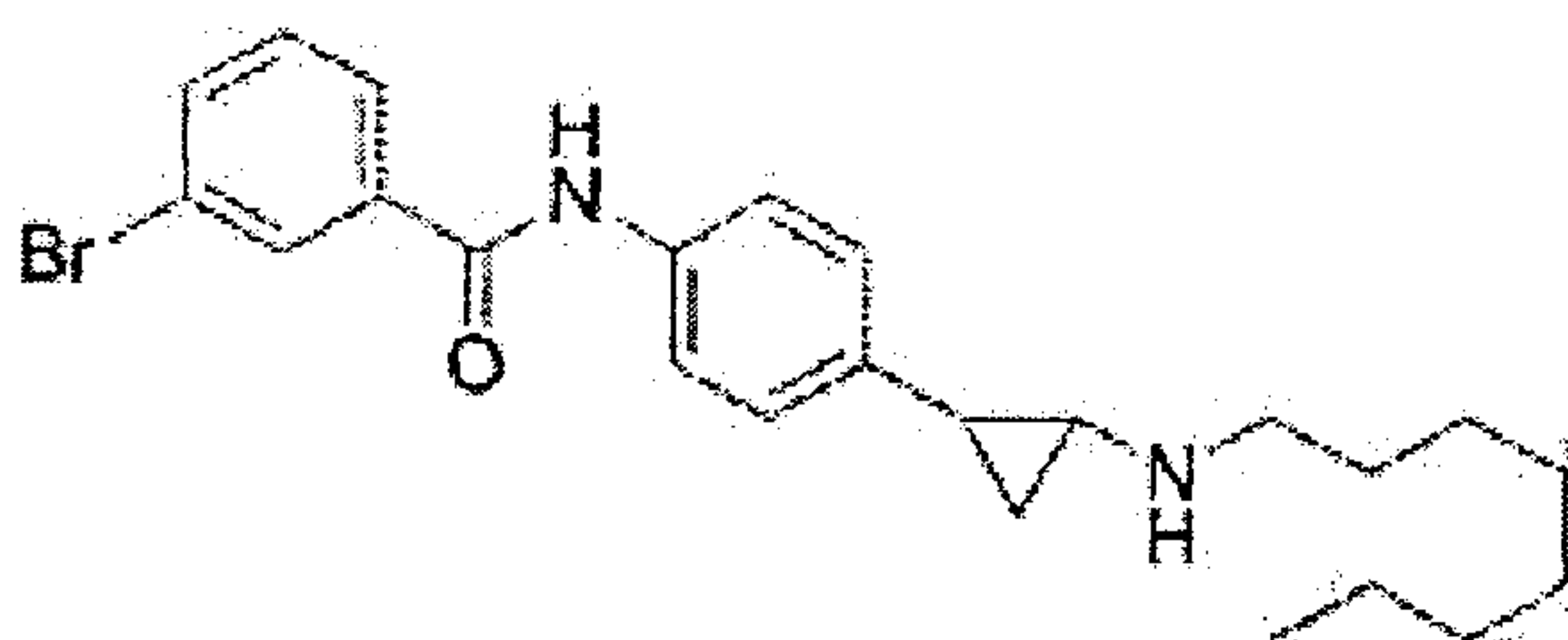
MS (API+): $[M+H]^+$ 421.2.

^1H NMR (400 MHz, CDCl_3) δ 0.96 (1H, dt, $J = 6.9, 5.6$ Hz), 1.11 (1H, dt, $J = 9.1, 4.9$ Hz), 1.88-1.95 (2H, m), 2.33-2.40 (1H, m), 3.89 (2H, d, $J = 2.4$ Hz), 6.98 (2H, d, $J = 8.6$ Hz), 7.22-7.38
 10 (6H, m), 7.48 (2H, d, $J = 8.6$ Hz), 7.66 (1H, ddd, $J = 7.9, 1.9, 1.0$ Hz), 7.77 (2H, d, $J = 6.4$ Hz), 7.98 (1H, t, $J = 1.7$ Hz).

[0251]

Example 4

3-bromo-N-{4-[trans-2-(octylamino)cyclopropyl]phenyl}benzamide
 15 [0252]



[0253]

To a solution of N-[4-(trans-2-aminocyclopropyl)phenyl]-3-bromobenzamide hydrochloride (80 mg) in methanol (2 mL) were
 20 added octylaldehyde (34 μL) and sodium hydrogen carbonate (27.4 mg). The reaction mixture was stirred at 70°C for 1 hr, and ice-cooled to 0°C and sodium borohydride (12.4 mg) was added. The mixture was stirred for 1 hr and water was added. The mixture was extracted with ethyl acetate, and the extract was
 25 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 (hexane/ethyl acetate) and recrystallized (hexane/ethyl acetate) to give the title compound (48.3 mg).

30 MS (API+): $[M+H]^+$ 443.3.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 0.80-0.96 (5H, m), 1.24 (10H, s),

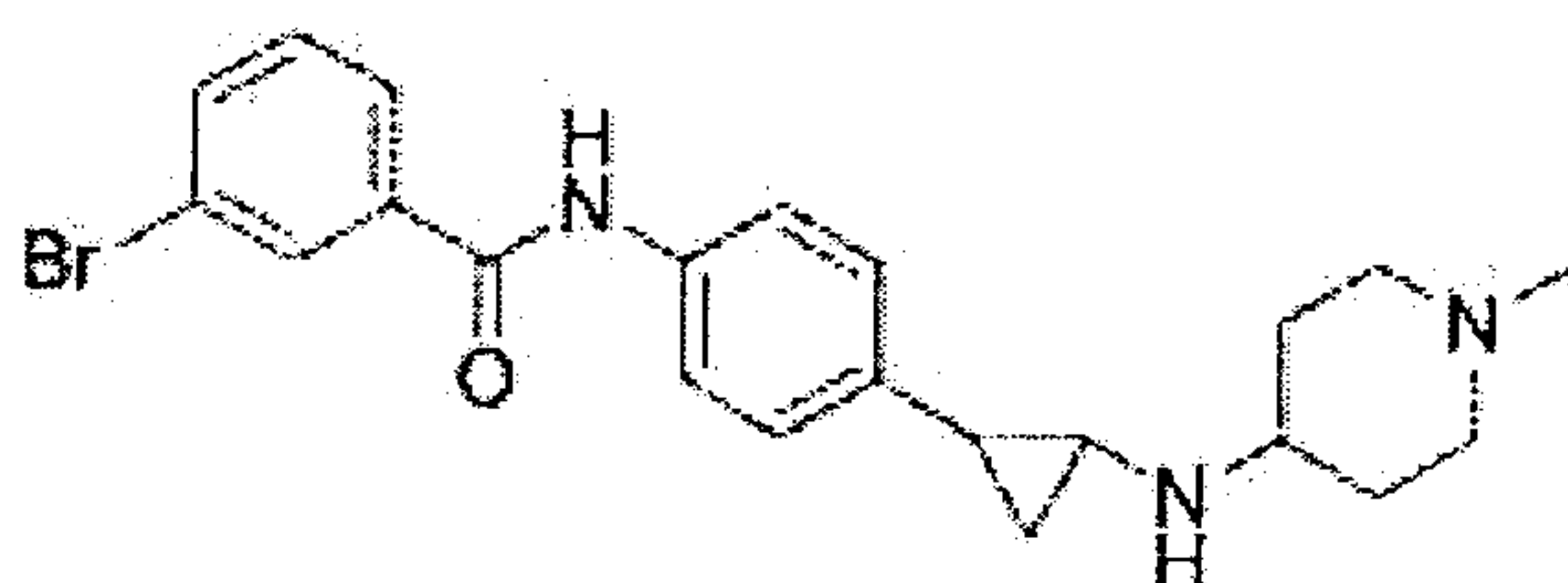
1.38 (2H, d, $J = 7.1$ Hz), 1.70-1.80 (1H, m), 2.13-2.22 (1H, m),
 2.22-2.30 (1H, m), 2.57 (2H, t, $J = 6.8$ Hz), 7.02 (2H, d, $J =$
 8.6 Hz), 7.49 (1H, t, $J = 7.9$ Hz), 7.61 (2H, d, $J = 8.6$ Hz),
 7.79 (1H, d, $J = 8.1$ Hz), 7.94 (1H, d, $J = 8.1$ Hz), 8.08-8.15
 5 (1H, m), 10.25 (1H, s).

[0254]

Example 5

3-bromo-N-(4-{trans-2-[(1-methylpiperidin-4-
 yl)amino]cyclopropyl}phenyl)benzamide

10 [0255]



[0256]

To a solution of N-[4-(trans-2-aminocyclopropyl)phenyl]-
 3-bromobenzamide hydrochloride (80 mg) in methanol (2 mL) were
 15 added 1-methylpiperidin-4-one (24.6 mg) and sodium hydrogen
 carbonate (27.4 mg). The mixture was stirred at 70°C for 1 hr,
 and ice-cooled to 0°C and sodium borohydride (12.4 mg) was
 added. The mixture was stirred for 1 hr and water was added.
 The mixture was extracted with ethyl acetate, and the extract
 20 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
 (ethyl acetate) and recrystallized (ethyl acetate) to give the
 title compound (10.0 mg).

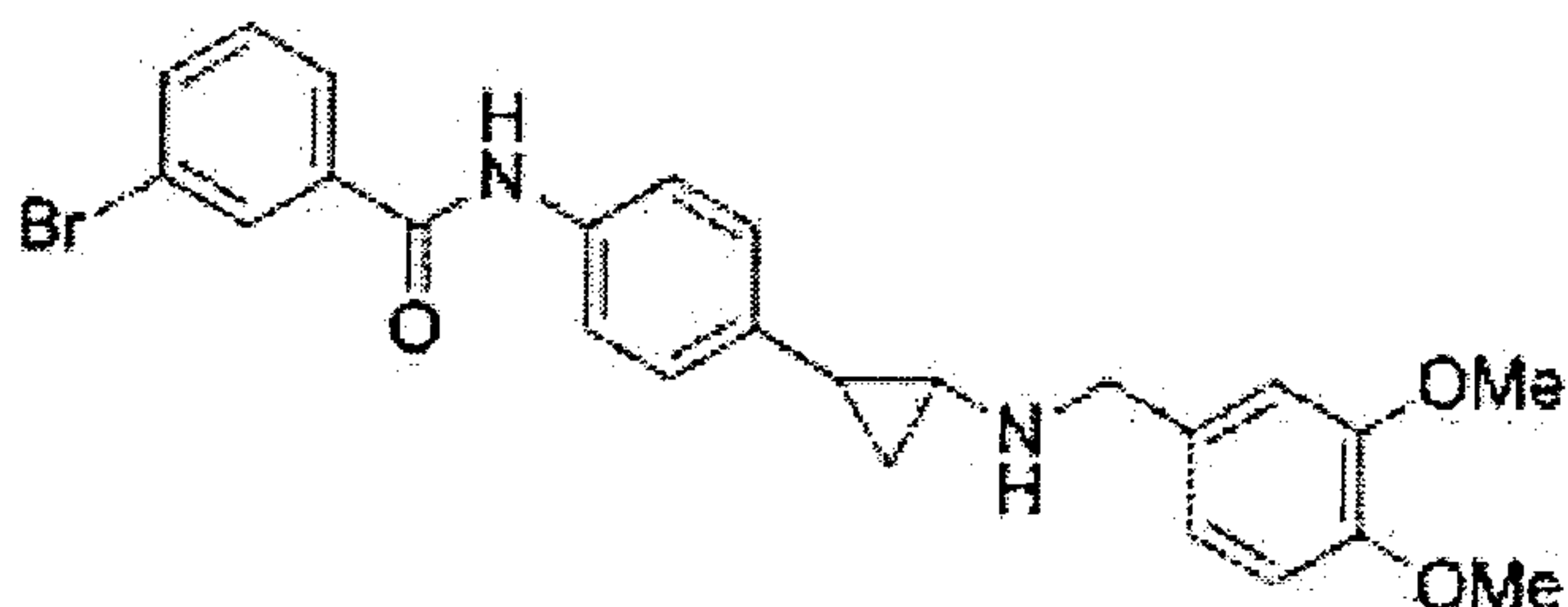
25 MS (API⁺): $[M+H]^+$ 428.3.

¹H NMR (400 MHz, DMSO-d₆) δ 0.89-0.96 (2H, m), 1.20-1.35 (2H,
 m), 1.68-1.79 (3H, m), 1.86 (2H, t, $J = 10.5$ Hz), 2.11 (3H, s),
 2.14-2.21 (1H, m), 2.47 (2H, brs), 2.62-2.70 (2H, m), 7.01 (2H,
 d, $J = 8.6$ Hz), 7.50 (1H, t, $J = 7.9$ Hz), 7.61 (2H, d, $J = 8.6$
 30 Hz), 7.79 (1H, d, $J = 7.1$ Hz), 7.94 (1H, d, $J = 8.1$ Hz), 8.12
 (1H, s), 10.25 (1H, s).

[0257]

Example 6

3-bromo-N-(4-{trans-2-[(3,4-dimethoxybenzyl)amino]cyclopropyl}phenyl)benzamide
[0258]



[0259]

To a solution of N-[4-(trans-2-aminocyclopropyl)phenyl]-3-bromobenzamide hydrochloride (80 mg) in methanol (2 mL) were added 3,4-dimethoxybenzaldehyde (36.2 mg) and sodium hydrogen
10 carbonate (27.4 mg). The mixture was stirred at 70°C for 1 hr, and ice-cooled to 0°C and sodium borohydride (12.4 mg) was added. The mixture was stirred for 1 hr and water was added. The mixture was extracted with ethyl acetate, and the extract was washed with saturated brine and dried over anhydrous sodium
15 sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate) and recrystallized (ethyl acetate) to give the title compound (44.2 mg).

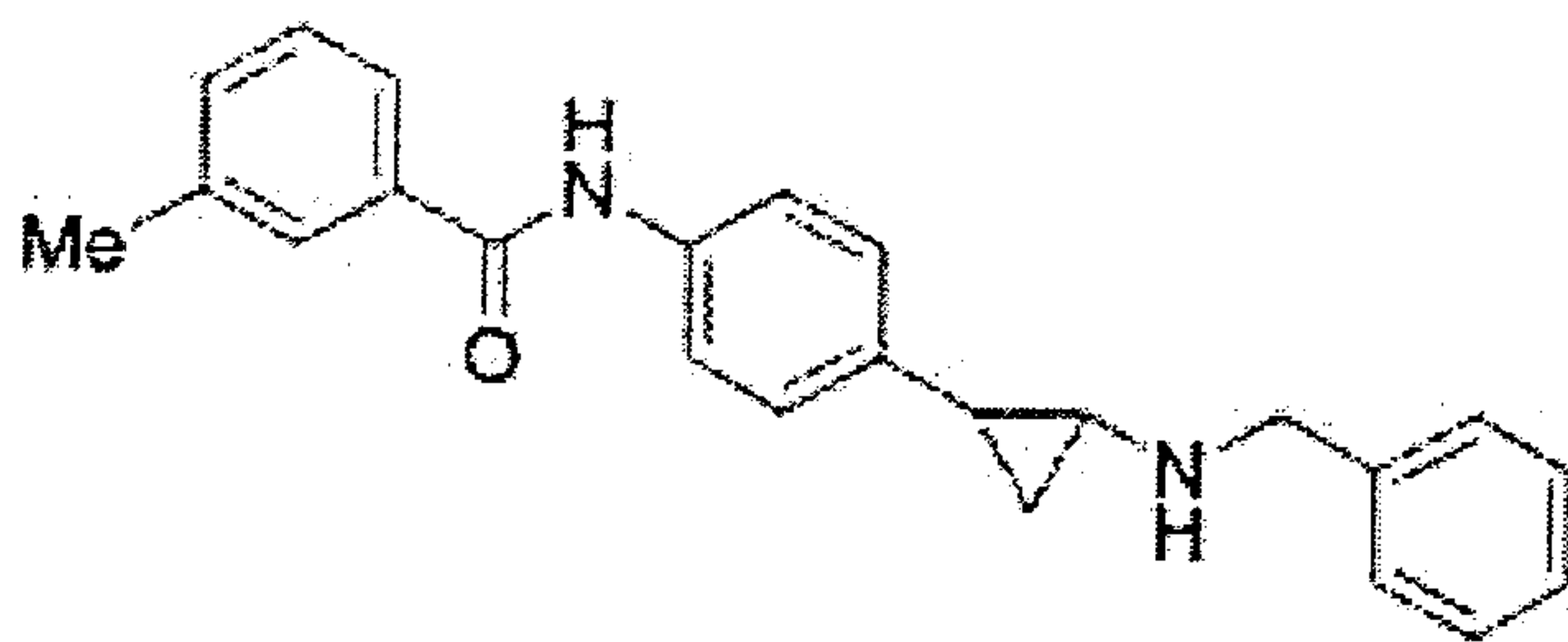
MS (API+): [M+H]⁺ 481.3.

20 ¹H NMR (400 MHz, DMSO-d₆) δ 0.86-1.06 (2H, m), 1.80 (1H, brs), 2.15 (1H, brs), 2.79 (1H, brs), 3.62-3.75 (8H, m), 6.74-6.91 (3H, m), 6.97 (2H, d, J = 8.3 Hz), 7.49 (1H, t, J = 7.8 Hz), 7.60 (2H, d, J = 8.1 Hz), 7.79 (1H, d, J = 7.8 Hz), 7.94 (1H, d, J = 7.3 Hz), 8.12 (1H, s), 10.25 (1H, s).

25 [0260]

Example 7

N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-methylbenzamide
[0261]



[0262]

A) tert-butyl [trans-2-(4-((3-methylphenyl)carbonyl)amino)phenyl)cyclopropyl]carbamate

5 To a solution of tert-butyl [trans-2-(4-aminophenyl)cyclopropyl]carbamate (100 mg) described in a document (J. Am. Chem. Soc., 2010, 132, 6827.) in acetonitrile (4 mL) were added 3-methylbenzoyl chloride (62.3 mg) and triethylamine (56 μ L). The mixture was stirred at room
10 temperature for 1 hr and water was added. The mixture was extracted with ethyl acetate, and the extract 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 (hexane/ethyl
15 acetate) to give the title compound (141 mg).

^1H NMR (400 MHz, CDCl_3) δ 1.10–1.20 (2H, m), 1.46 (9H, s), 2.05 (1H, s), 2.43 (3H, s), 2.71 (1H, brs), 4.85 (1H, brs), 7.15 (2H, d, $J = 7.8$ Hz), 7.34–7.39 (2H, m), 7.54 (2H, d, $J = 8.1$ Hz), 7.64 (1H, d, $J = 4.4$ Hz), 7.68 (1H, s), 7.76 (1H, brs).

20 [0263]

B) N-[4-(trans-2-aminocyclopropyl)phenyl]-3-methylbenzamide hydrochloride

tert-Butyl [trans-2-(4-((3-methylphenyl)carbonyl)amino)phenyl)cyclopropyl]carbamate (141
25 mg) was dissolved in 4N hydrochloric acid/ethyl acetate solution (2 mL). The mixture was stirred at room temperature for 2 hr and the solvent was evaporated under reduced pressure to give the title compound (51.6 mg).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.15–1.24 (1H, m), 1.35 (1H, brs),
30 2.28 (1H, brs), 2.40 (3H, s), 2.79 (1H, d, $J = 3.7$ Hz), 7.14 (2H, d, $J = 8.6$ Hz), 7.38–7.43 (2H, m), 7.66–7.78 (4H, m), 8.33

(3H, brs), 10.19 (1H, s).

[0264]

C) N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-methylbenzamide

5 To a solution of N-[4-(trans-2-aminocyclopropyl)phenyl]-3-methylbenzamide hydrochloride (113 mg) in methanol (3 mL) were added benzaldehyde (38 μ L) and sodium hydrogen carbonate (47.0 mg). The mixture was stirred at 70°C for 1 hr, and ice-cooled to 0°C and sodium borohydride (21.2 mg) was added. The
10 mixture was stirred for 1 hr and water was added. The mixture was extracted with ethyl acetate, and the extract 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 (hexane/ethyl
15 acetate) and recrystallized (hexane/ethyl acetate) to give the title compound (85.6 mg).

MS (API+): $[M+H]^+$ 357.1.

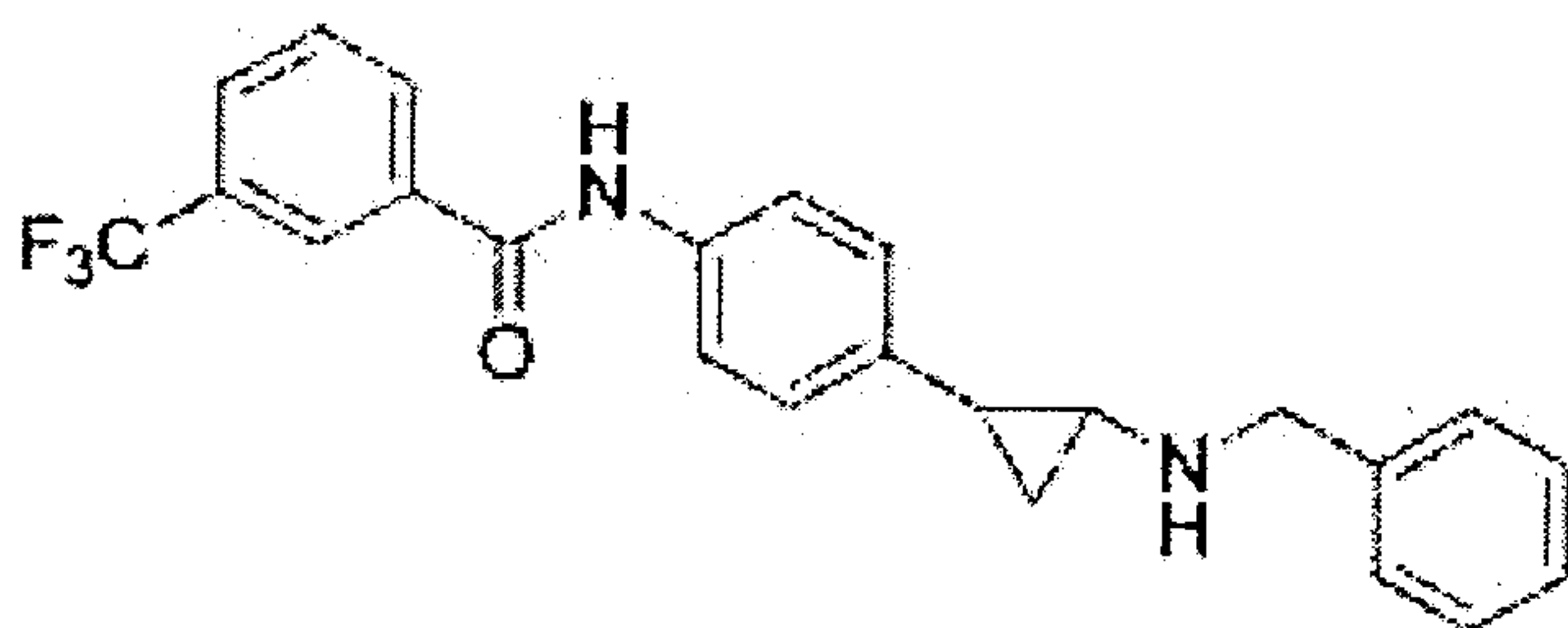
^1H NMR (400 MHz, DMSO- d_6) δ 0.87-0.94 (1H, m), 0.94-1.02 (1H, m), 1.76-1.85 (1H, m), 2.14-2.21 (1H, m), 2.39 (3H, s), 2.81-
20 2.92 (1H, m), 3.76 (2H, s), 6.95 (2H, d, $J = 8.6$ Hz), 7.18-7.25 (1H, m), 7.26-7.34 (4H, m), 7.37-7.43 (2H, m), 7.60 (2H, d, $J = 8.6$ Hz), 7.69-7.77 (2H, m), 10.10 (1H, s).

[0265]

Example 8

25 N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-(trifluoromethyl)benzamide

[0266]



[0267]

30 A) tert-butyl {trans-2-[4-({[3-(trifluoromethyl)phenyl]carbonyl}amino)phenyl]cyclopropyl}-

carbamate

To a solution of tert-butyl [trans-2-(4-aminophenyl)cyclopropyl]carbamate (100 mg) described in a document (J. Am. Chem. Soc., 2010, 132, 6827.) in acetonitrile (4 mL) were added 3-(trifluoromethyl)benzoyl chloride (126 mg) and triethylamine (84 μ L). The mixture was stirred at room temperature for 30 min and water was added. The mixture was extracted with ethyl acetate, and the extract was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was crystallized (hexane/ethyl acetate) to give the title compound (161 mg).

^1H NMR (400 MHz, CDCl_3) δ 1.17 (2H, brs), 1.46 (9H, s), 2.00-2.11 (1H, m), 2.66-2.76 (1H, m), 4.78-4.94 (1H, m), 7.17 (2H, d, $J = 7.3$ Hz), 7.54 (2H, d, $J = 7.6$ Hz), 7.64 (1H, s), 7.79 (2H, d, $J = 14.4$ Hz), 8.03-8.09 (1H, m), 8.12 (1H, s).

[0268]

B) N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride

tert-Butyl {trans-2-[4-({[3-(trifluoromethyl)phenyl]carbonyl}amino)phenyl]cyclopropyl}-carbamate (161 mg) was dissolved in 4N hydrochloric acid/ethyl acetate solution (2 mL), and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure to give the title compound (130 mg).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.16-1.26 (1H, m), 1.36 (1H, d, $J = 3.9$ Hz), 2.29 (1H, brs), 2.80 (1H, brs), 7.17 (2H, d, $J = 8.1$ Hz), 7.71 (2H, d, $J = 8.3$ Hz), 7.79 (1H, t, $J = 7.2$ Hz), 7.97 (1H, d, $J = 7.6$ Hz), 8.21-8.38 (5H, m), 10.48 (1H, s).

[0269]

C) N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-(trifluoromethyl)benzamide

To a solution of N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (107 mg) in methanol (2 mL) were added benzaldehyde (30 μ L) and sodium hydrogen

carbonate (37.8 mg). The mixture was stirred at 70°C for 1 hr, and ice-cooled to 0°C and sodium borohydride (17.0 mg) was added. The mixture was stirred for 1 hr and water was added. The mixture was extracted with ethyl acetate, and the extract
 5 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 (hexane/ethyl acetate) and recrystallized (hexane/ethyl acetate) to give the title compound (66.0 mg).

10 MS (API+): $[M+H]^+$ 411.3.

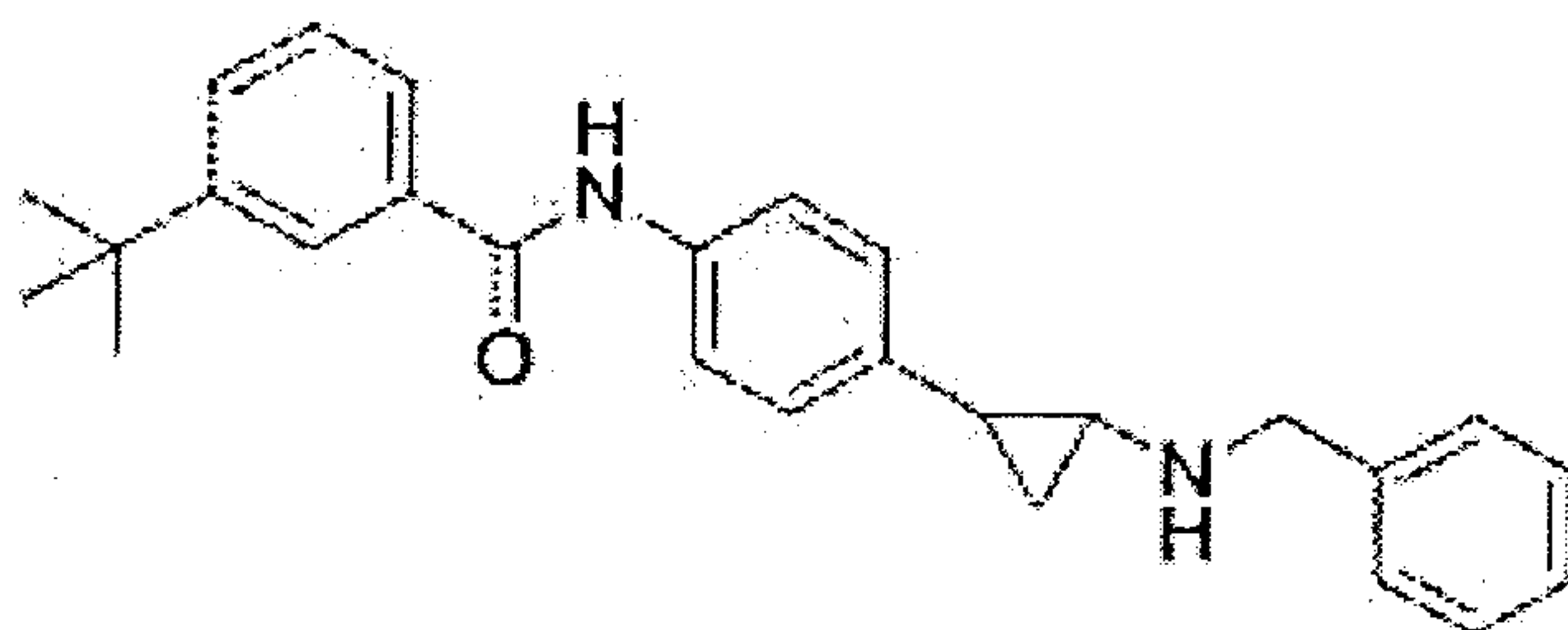
^1H NMR (400 MHz, DMSO- d_6) δ 0.93 (1H, d, J = 6.1 Hz), 0.96-1.03 (1H, m), 1.81 (1H, brs), 2.20 (1H, d, J = 3.4 Hz), 3.77 (2H, s), 6.98 (2H, d, J = 8.6 Hz), 7.18-7.25 (1H, m), 7.26-7.34 (4H, m), 7.61 (2H, d, J = 8.3 Hz), 7.75-7.82 (1H, m), 7.96 (1H, d, J =
 15 7.6 Hz), 8.22-8.29 (2H, m), 10.37 (1H, s).

[0270]

Example 9

N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-tert-butylbenzamide

20 [0271]



[0272]

A) tert-butyl [trans-2-(4-{{(3-tert-butylphenyl)carbonyl}-amino}phenyl)cyclopropyl]carbamate

25 By a method similar to Example 28, Step A, the title compound (100 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl]carbamate (100 mg) and 3-tert-butylbenzoic acid (86 mg).

^1H NMR (400 MHz, CDCl_3) δ 1.08-1.20 (2H, m), 1.35 (9H, s), 1.46
 30 (9H, s), 2.05 (1H, br. s), 2.71 (1H, brs), 4.86 (1H, brs), 7.15 (2H, d, J = 7.8 Hz), 7.36-7.46 (1H, m), 7.50-7.65 (4H, m), 7.72

(1H, s), 7.92 (1H, s).

[0273]

B) N-[4-(trans-2-aminocyclopropyl)phenyl]-3-tert-butylbenzamide hydrochloride

5 By a method similar to Example 1, Step B, the title compound (64.3 mg) was obtained from tert-butyl [trans-2-(4-[(3-tert-butylphenyl)carbonyl]amino)phenyl]cyclopropyl]-carbamate (99 mg).

¹H NMR (400 MHz, DMSO-d₆) δ 1.16-1.24 (1H, m), 1.32-1.40 (10H, m), 2.29 (1H, ddd, J = 9.9, 6.5, 3.4 Hz), 2.79 (1H, dt, J = 7.6, 4.1 Hz), 7.15 (2H, d, J = 8.6 Hz), 7.42-7.48 (1H, m), 7.60-7.65 (1H, m), 7.70 (2H, d, J = 8.6 Hz), 7.76 (1H, d, J = 7.8 Hz), 7.92 (1H, t, J = 1.8 Hz), 8.34 (3H, brs), 10.21 (1H, s).

[0274]

15 C) N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-tert-butylbenzamide

By a method similar to Example 1, Step C, the title compound (15.0 mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]-3-tert-butylbenzamide hydrochloride (62.6 mg).

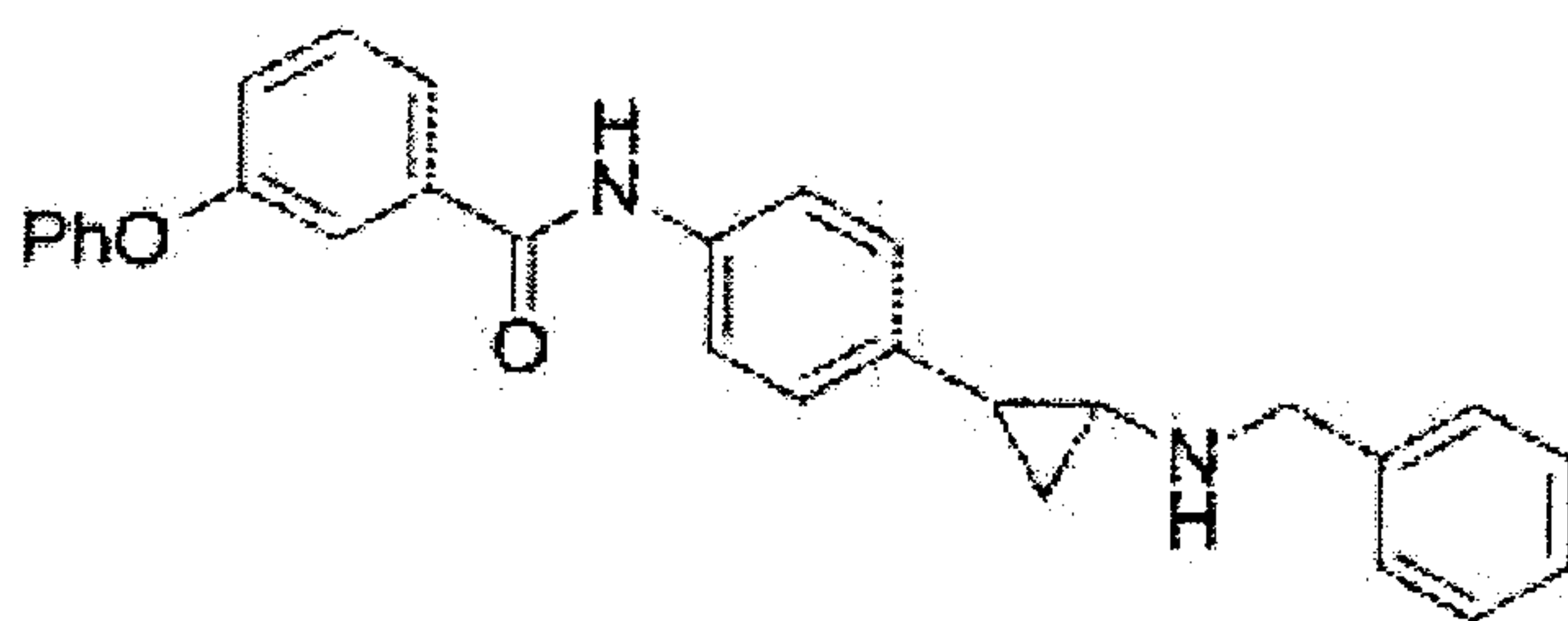
¹H NMR (400 MHz, CDCl₃) δ 0.97 (1H, dt, J = 7.0, 5.5 Hz), 1.07-1.15 (1H, m), 1.36 (9H, s), 1.92 (2H, ddd, J = 9.2, 5.9, 3.2 Hz), 2.37 (1H, ddd, J = 7.2, 4.1, 3.2 Hz), 3.85-3.94 (2H, m), 6.96-7.01 (2H, m), 7.22-7.35 (4H, m), 7.37-7.43 (1H, m), 7.51 (2H, d, J = 8.3 Hz), 7.55-7.63 (2H, m), 7.75 (1H, brs), 7.92 (1H, t, J = 1.7 Hz).

[0275]

Example 10

N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-phenoxybenzamide

[0276]



[0277]

A) tert-butyl [trans-2-(4-{[(3-phenoxyphenyl)carbonyl]amino}phenyl)cyclopropyl]carbamate

5 By a method similar to Example 28, Step A, the title compound (93.8 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl]carbamate (100 mg) and 3-phenoxybenzoic acid (104 mg).

¹H NMR (400 MHz, CDCl₃) δ 1.10-1.19 (2H, m), 1.46 (9H, s), 2.04
10 (1H, brs), 2.70 (1H, brs), 4.85 (1H, brs), 7.02-7.07 (2H, m), 7.11-7.20 (4H, m), 7.34-7.40 (2H, m), 7.44 (1H, t, J = 7.9 Hz), 7.48-7.54 (3H, m), 7.56 (1H, d, J = 7.8 Hz), 7.71 (1H, s).

[0278]

B) N-[4-(trans-2-aminocyclopropyl)phenyl]-3-phenoxybenzamide
15 hydrochloride

By a method similar to Example 1, Step B, the title compound (51.9 mg) was obtained from tert-butyl [trans-2-(4-{[(3-phenoxyphenyl)carbonyl]amino}phenyl)cyclopropyl]carbamate (92 mg).

20 ¹H NMR (400 MHz, DMSO-d₆) δ 1.15-1.23 (1H, m), 1.32-1.40 (1H, m), 2.29 (1H, ddd, J = 10.1, 6.4, 3.5 Hz), 2.79 (1H, brs), 7.07 (2H, dd, J = 8.6, 1.0 Hz), 7.14 (2H, d, J = 8.8 Hz), 7.16-7.26 (2H, m), 7.40-7.47 (2H, m), 7.51-7.59 (2H, m), 7.69 (2H, d, J = 8.6 Hz), 7.75 (1H, d, J = 8.1 Hz), 8.38 (3H, brs), 10.27 (1H,
25 s).

[0279]

C) N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-phenoxybenzamide

By a method similar to Example 1, Step C, the title
30 compound (8.3 mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]-3-phenoxybenzamide hydrochloride (27.1

mg).

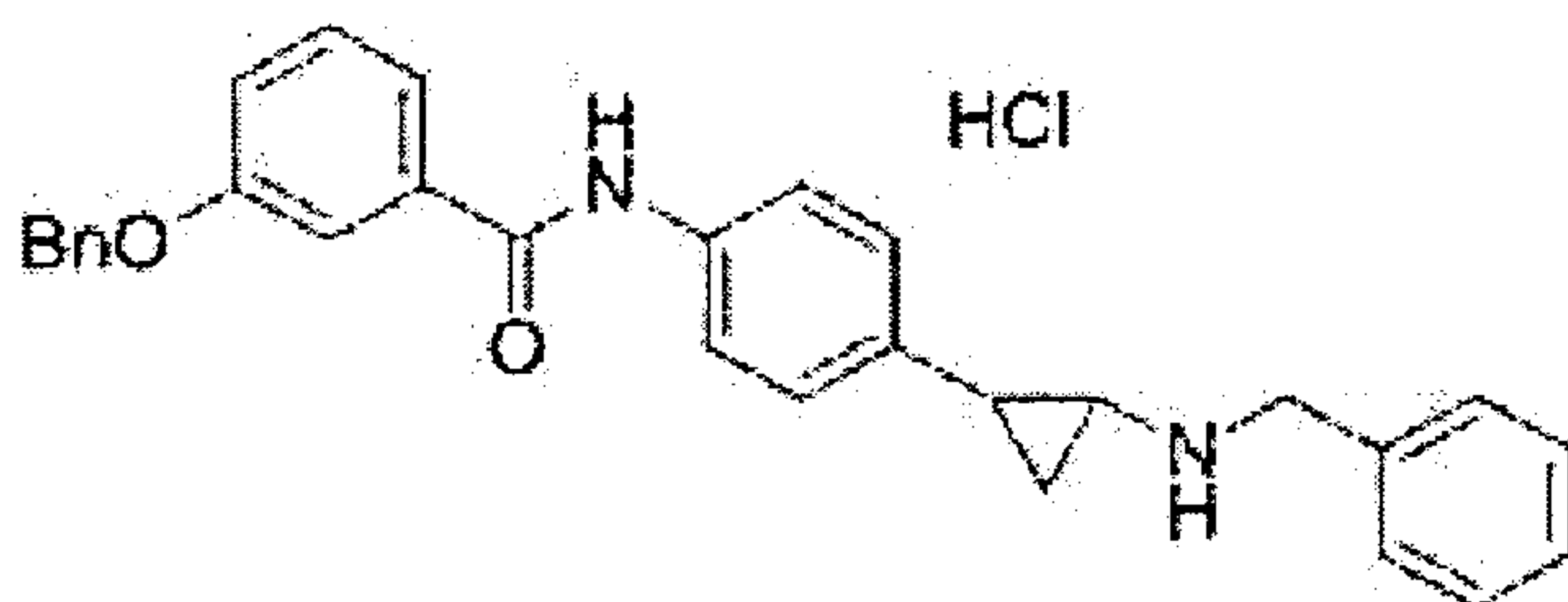
¹H NMR (400 MHz, DMSO-d₆) δ 0.87-0.94 (1H, m), 0.98 (1H, dt, J = 9.2, 4.5 Hz), 1.75-1.83 (1H, m), 2.14-2.21 (1H, m), 2.86 (1H, brs), 3.76 (2H, s), 6.94 (2H, d, J = 8.6 Hz), 7.04-7.09 (2H, m),
 5 7.16-7.24 (3H, m), 7.25-7.33 (4H, m), 7.40-7.47 (2H, m), 7.50-7.61 (4H, m), 7.73 (1H, d, J = 8.1 Hz), 10.16 (1H, s).

[0280]

Example 11

N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-
 10 (benzyloxy)benzamide hydrochloride

[0281]



[0282]

A) tert-butyl {trans-2-[4-({[3-
 15 (benzyloxy)phenyl]carbonyl}amino)phenyl]cyclopropyl}carbamate

By a method similar to Example 28, Step A, the title compound (164 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl]carbamate (100 mg) and 3-(benzyloxy)benzoic acid (110 mg).

20 ¹H NMR (400 MHz, DMSO-d₆) δ 0.99-1.13 (2H, m), 1.38 (9H, s), 1.83-1.92 (1H, m), 2.59 (1H, brs), 5.19 (2H, s), 7.07 (2H, d, J = 8.6 Hz), 7.20-7.27 (2H, m), 7.32-7.38 (1H, m), 7.38-7.45 (3H, m), 7.45-7.51 (2H, m), 7.54 (1H, d, J = 7.6 Hz), 7.58 (1H, d, J = 1.7 Hz), 7.65 (2H, d, J = 8.6 Hz), 10.14 (1H, s).

25 [0283]

B) N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(benzyloxy)benzamide hydrochloride

By a method similar to Example 1, Step B, the title compound (115 mg) was obtained from tert-butyl {trans-2-[4-
 30 ({[3-(benzyloxy)phenyl]carbonyl}amino)phenyl]cyclopropyl}-carbamate (164 mg).

¹H NMR (400 MHz, DMSO-d₆) δ 1.19 (1H, d, J = 6.8 Hz), 1.30-1.38 (1H, m), 2.28 (1H, brs), 2.76-2.83 (1H, m), 5.19 (2H, s), 7.14 (2H, d, J = 8.6 Hz), 7.24 (1H, dd, J = 7.9, 2.1 Hz), 7.36 (1H, d, J = 7.1 Hz), 7.38-7.51 (5H, m), 7.54 (1H, d, J = 7.8 Hz),
 5 7.58 (1H, d, J = 2.0 Hz), 7.71 (2H, d, J = 8.6 Hz), 8.30 (3H, brs), 10.21 (1H, s).

[0284]

C) N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-(benzyloxy)benzamide hydrochloride

10 By a method similar to Example 1, Step C, 4N hydrochloric acid/ethyl acetate solution was added to N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-(benzyloxy)benzamide obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(benzyloxy)benzamide hydrochloride (109 mg) and benzaldehyde
 15 (29.3 μL), and the resulting solid was collected by filtration to give the title compound (96.1 mg).

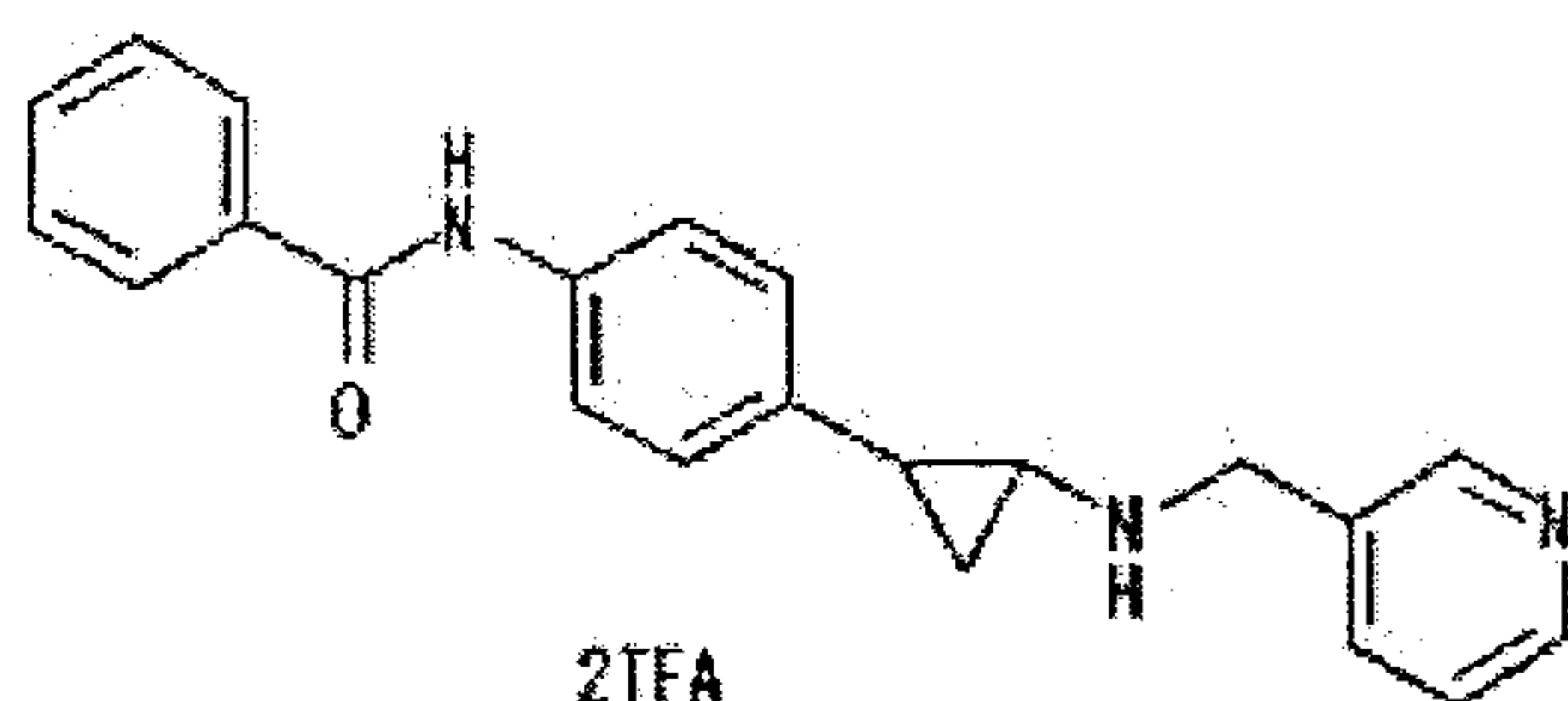
¹H NMR (400 MHz, DMSO-d₆) δ 1.22-1.34 (1H, m), 1.46 (1H, brs), 2.41 (1H, brs), 2.89 (1H, brs), 4.29 (2H, brs), 5.19 (2H, s), 7.11 (2H, d, J = 8.6 Hz), 7.24 (1H, dd, J = 8.3, 2.0 Hz), 7.30-
 20 7.63 (13H, m), 7.70 (2H, d, J = 8.3 Hz), 9.44 (2H, br. s), 10.20 (1H, s).

[0285]

Example 12

N-(4-{trans-2-[(pyridin-3-ylmethyl)amino]cyclopropyl}phenyl)-
 25 benzamide bis(trifluoroacetate)

[0286]



[0287]

To a solution of N-[4-(trans-2-
 30 aminocyclopropyl)phenyl]benzamide hydrochloride (23 mg) and 3-pyridinecarboxyaldehyde (17 mg) in methanol (0.5 mL) were added

acetic acid (0.1 mL) and a solution of 2-picoline borane (23 mg) in methanol (0.4 mL). The reaction mixture was stirred at 60°C overnight, and the solvent was evaporated by an air blowing apparatus. The residue was purified by HPLC (C18, 5 mobile phase: water/acetonitrile (with 0.1% TFA)) to give the title compound (2.8 mg).

MS (API+): $[M+H]^+$ 344.2.

[0288]

The compounds produced by the method described in the 10 above-mentioned Example 12 or a method analogous thereto are shown in the following Tables. In the Tables, MS shows measured values.

[0289]

[Table 1-1]

Ex. No.	IUPAC name	structure	salt	MS
13	N-(4-{trans-2-[(thiophen-2-ylmethyl)amino]-cyclopropyl}-phenyl)benzamide		CF ₃ COOH	349.1
14	N-(4-{trans-2-[(3-phenylpropyl)amino]-cyclopropyl}-phenyl)benzamide		CF ₃ COOH	371.3
15	N-(4-{trans-2-[(2-fluorobenzyl)amino]-cyclopropyl}-phenyl)benzamide		CF ₃ COOH	361.2
16	N-(4-{trans-2-[(biphenyl-4-ylmethyl)amino]-cyclopropyl}-phenyl)benzamide		CF ₃ COOH	419.3
17	N-(4-{trans-2-[(2,2-dimethylpropyl)amino]-cyclopropyl}-phenyl)benzamide		CF ₃ COOH	323.3
18	N-(4-{trans-2-[(naphthalen-2-ylmethyl)amino]-cyclopropyl}-phenyl)benzamide		CF ₃ COOH	393.3
19	N-(4-{trans-2-[(1-phenylethyl)amino]-cyclopropyl}-phenyl)benzamide		CF ₃ COOH	357.2
20	N-{4-[trans-2-(2,3-dihydro-1H-inden-1-ylamino)cyclopropyl]phenyl}benzamide		CF ₃ COOH	369.3

[0290]

[Table 1-2]

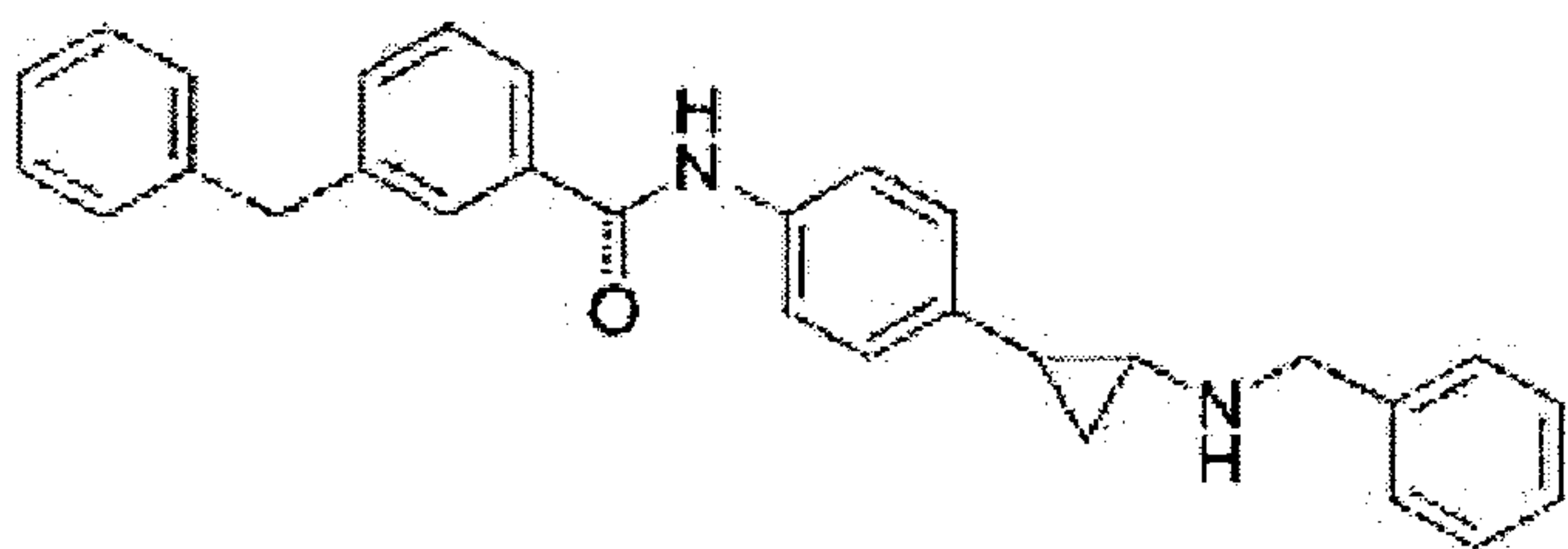
Ex. No.	IUPAC name	structure	salt	MS
21	N-{4-[trans-2-(9H-fluoren-9-ylamino)cyclopropyl]phenyl}-benzamide		CF ₃ COOH	417.3
22	N-{4-[trans-2-(dodecylamino)-cyclopropyl]-phenyl}benzamide		CF ₃ COOH	421.4
23	N-{4-[trans-2-(cycloheptylamino)cyclopropyl]phenyl}-benzamide		CF ₃ COOH	349.3
24	N-{4-[trans-2-(cyclooctylamino)cyclopropyl]phenyl}-benzamide		CF ₃ COOH	363.3
25	N-(4-{trans-2-[(1-benzylpiperidin-4-yl)amino]cyclopropyl}phenyl)-benzamide		2CF ₃ COOH	426.3
26	N-[4-(trans-2-{[2-(benzyloxy)ethyl]amino}-cyclopropyl)-phenyl]benzamide		CF ₃ COOH	387.3
27	N-{4-[trans-2-(dimethylamino)-cyclopropyl]-phenyl}benzamide		CF ₃ COOH	281.1

[0291]

Example 28

3-benzyl-N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}benzamide

5 [0292]



[0293]

A) tert-butyl [trans-2-(4-{[(3-benzylphenyl)carbonyl]amino}phenyl)cyclopropyl]carbamate

10 To a solution of tert-butyl [trans-2-(4-aminophenyl)cyclopropyl]carbamate (100 mg) described in a document (J. Am. Chem. Soc., 2010, 132, 6827.) in acetonitrile (4 mL) were added 3-benzylbenzoic acid (103 mg) described in a document (J. Org. Chem. 2001, 66, 2874.), N-ethyl-N'-(3-

15 dimethylaminopropyl)carbodiimide hydrochloride (93 mg), 1-hydroxybenzotriazole (65.3 mg) and triethylamine (140 μ L). The mixture was stirred at room temperature overnight and water was added. The mixture was extracted with ethyl acetate, and the extract was washed with saturated brine and dried over

20 anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was recrystallized (hexane/ethyl acetate) to give the title compound (126 mg).

^1H NMR (400 MHz, CDCl_3) δ 1.13 (2H, t, J = 6.6 Hz), 1.45 (9H, s), 1.97-2.03 (1H, m), 2.68 (1H, brs), 4.03 (2H, s), 4.89 (1H, brs), 7.11 (2H, d, J = 8.6 Hz), 7.15-7.24 (3H, m), 7.25-7.32 (2H, m), 7.35 (2H, s), 7.51 (2H, d, J = 8.3 Hz), 7.65-7.69 (1H, m), 7.71 (1H, s), 7.88 (1H, brs).

[0294]

B) N-[4-(trans-2-aminocyclopropyl)phenyl]-3-benzylbenzamide

30 hydrochloride

tert-Butyl [trans-2-(4-{[(3-

benzylphenyl)carbonyl]amino}phenyl)cyclopropyl]carbamate (125 mg) was dissolved in 4N hydrochloric acid/ethyl acetate solution (2 mL), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to give the title compound (54.7 mg).

MS (API+): $[M+H]^+$ 343.1.

[0295]

C) 3-benzyl-N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}benzamide

To a solution of N-[4-(trans-2-aminocyclopropyl)phenyl]-3-benzylbenzamide hydrochloride (69.6 mg) in methanol (1.5 mL) were added benzaldehyde (19 μ L) and sodium hydrogen carbonate (23.2 mg). The mixture was stirred at 70°C for 1 hr, and ice-cooled to 0°C and sodium borohydride (10.4 mg) was added. The mixture was stirred for 1 hr and water was added. The mixture was extracted with ethyl acetate, and the extract 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 (hexane/ethyl acetate) and crystallized (hexane/ethyl acetate) to give the title compound (29.7 mg).

MS (API+): $[M+H]^+$ 433.3.

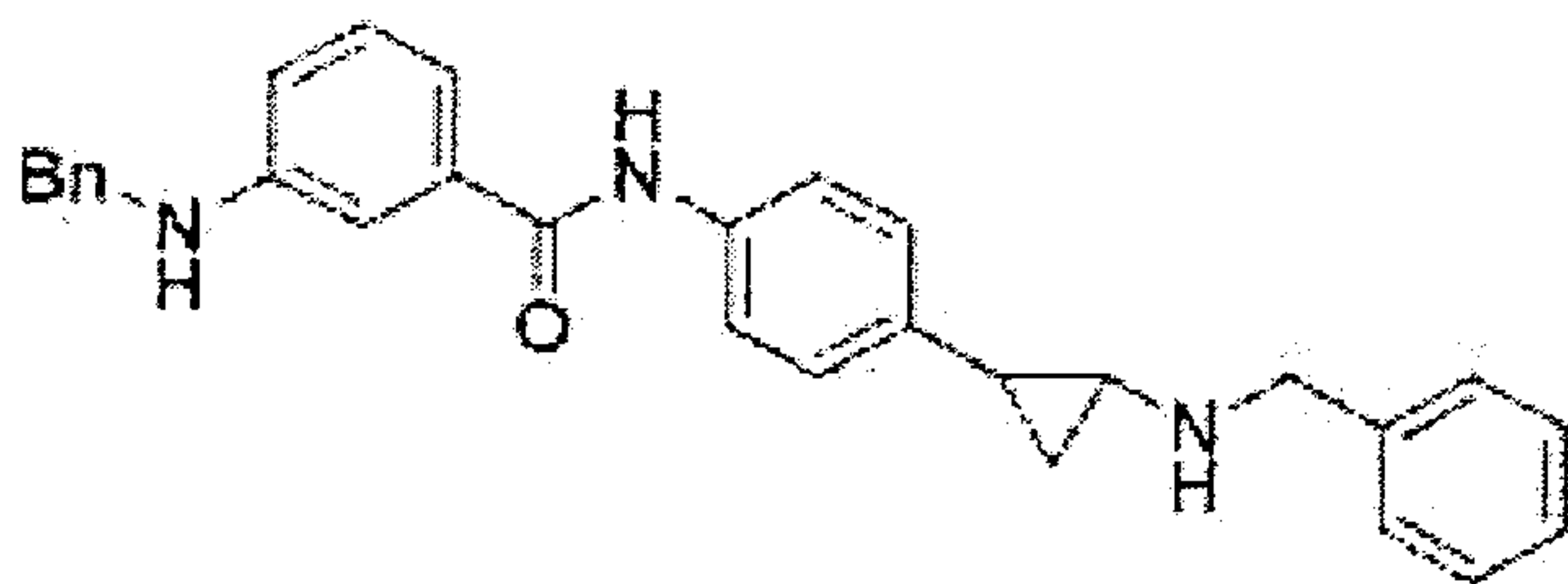
^1H NMR (400 MHz, DMSO- d_6) δ 0.88-0.94 (1H, m), 0.98 (1H, dt, J = 9.0, 4.5 Hz), 1.75-1.83 (1H, m), 2.14-2.20 (1H, m), 2.86 (1H, brs), 3.76 (2H, s), 4.03 (2H, s), 6.95 (2H, d, J = 8.6 Hz), 7.16-7.24 (2H, m), 7.24-7.33 (8H, m), 7.43 (2H, d, J = 4.6 Hz), 7.58 (2H, d, J = 8.3 Hz), 7.76 (1H, t, J = 4.0 Hz), 7.80 (1H, s), 10.11 (1H, s).

[0296]

Example 29

3-(benzylamino)-N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}benzamide

[0297]



[0298]

A) methyl 3-[benzyl(tert-butoxycarbonyl)amino]benzoate

To a solution of methyl 3-(tert-butoxycarbonylamino)benzoate (1.08 g) described in a document (Bioorg. Med. Chem. 2010, 18, 3175.) in DMF (40 mL) was added sodium hydride (258 mg). The reaction mixture was stirred at room temperature for 15 min, and benzyl bromide (613 μ L) was added. The mixture was stirred for 1 hr and water was added. The mixture was extracted with ethyl acetate, and the extract 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 (hexane/ethyl acetate) to give the title compound (125 mg). ^1H NMR (400 MHz, CDCl_3) δ 1.42 (9H, s), 3.89 (3H, s), 4.86 (2H, s), 7.19-7.34 (7H, m), 7.80-7.85 (1H, m), 7.88 (1H, s).

[0299]

B) 3-[benzyl(tert-butoxycarbonyl)amino]benzoic acid

By a method similar to Example 33, Step A, the title compound (121 mg) was obtained from methyl 3-[benzyl(tert-butoxycarbonyl)amino]benzoate (125 mg). ^1H NMR (400 MHz, CDCl_3) δ 1.46 (9H, s), 4.90 (2H, s), 7.22-7.27 (3H, m), 7.30-7.43 (4H, m), 7.91 (1H, dd, $J = 8.7, 1.6$ Hz), 7.96 (1H, s).

[0300]

C) tert-butyl benzyl{3-[(4-{trans-2-[(tert-butoxycarbonyl)amino]cyclopropyl}phenyl)carbamoyl]phenyl}-carbamate

By a method similar to Example 28, Step A, the title compound (81.6 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl]carbamate (110 mg) and 3-[benzyl(tert-

butoxycarbonyl)amino]benzoic acid (121 mg).

¹H NMR (400 MHz, CDCl₃) δ 1.08-1.18 (2H, m), 1.41-1.48 (18H, m),
1.86-1.97 (1H, m), 2.63-2.76 (1H, m), 4.85 (2H, s), 6.52-6.65
(1H, m), 6.89-6.99 (1H, m), 7.11 (2H, d, J = 8.6 Hz), 7.18-7.40
5 (4H, m), 7.44-7.55 (2H, m), 7.64 (2H, s), 7.75-7.83 (1H, m),
7.87-8.00 (1H, m).

[0301]

D) N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(benzylamino)benzamide dihydrochloride

10 By a method similar to Example 1, Step B, the title compound (35.7 mg) was obtained from tert-butyl benzyl{3-[(4-{trans-2-[(tert-butoxycarbonyl)amino]cyclopropyl}-phenyl)carbamoyl]phenyl}carbamate (82 mg).

¹H NMR (400 MHz, DMSO-d₆) δ 1.18 (1H, d, J = 7.8 Hz), 1.36 (1H,
15 t, J = 4.3 Hz), 2.24-2.34 (1H, m), 2.78 (1H, dd, J = 8.2, 4.0 Hz), 4.34 (2H, s), 6.79 (1H, d, J = 8.1 Hz), 7.07-7.27 (6H, m), 7.29-7.41 (4H, m), 7.68 (2H, d, J = 8.6 Hz), 8.41 (3H, d, J = 4.4 Hz), 10.07 (1H, s).

[0302]

20 E) 3-(benzylamino)-N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}benzamide

By a method similar to Example 1, Step C, the title compound (5.0 mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(benzylamino)benzamide hydrochloride
25 (40 mg).

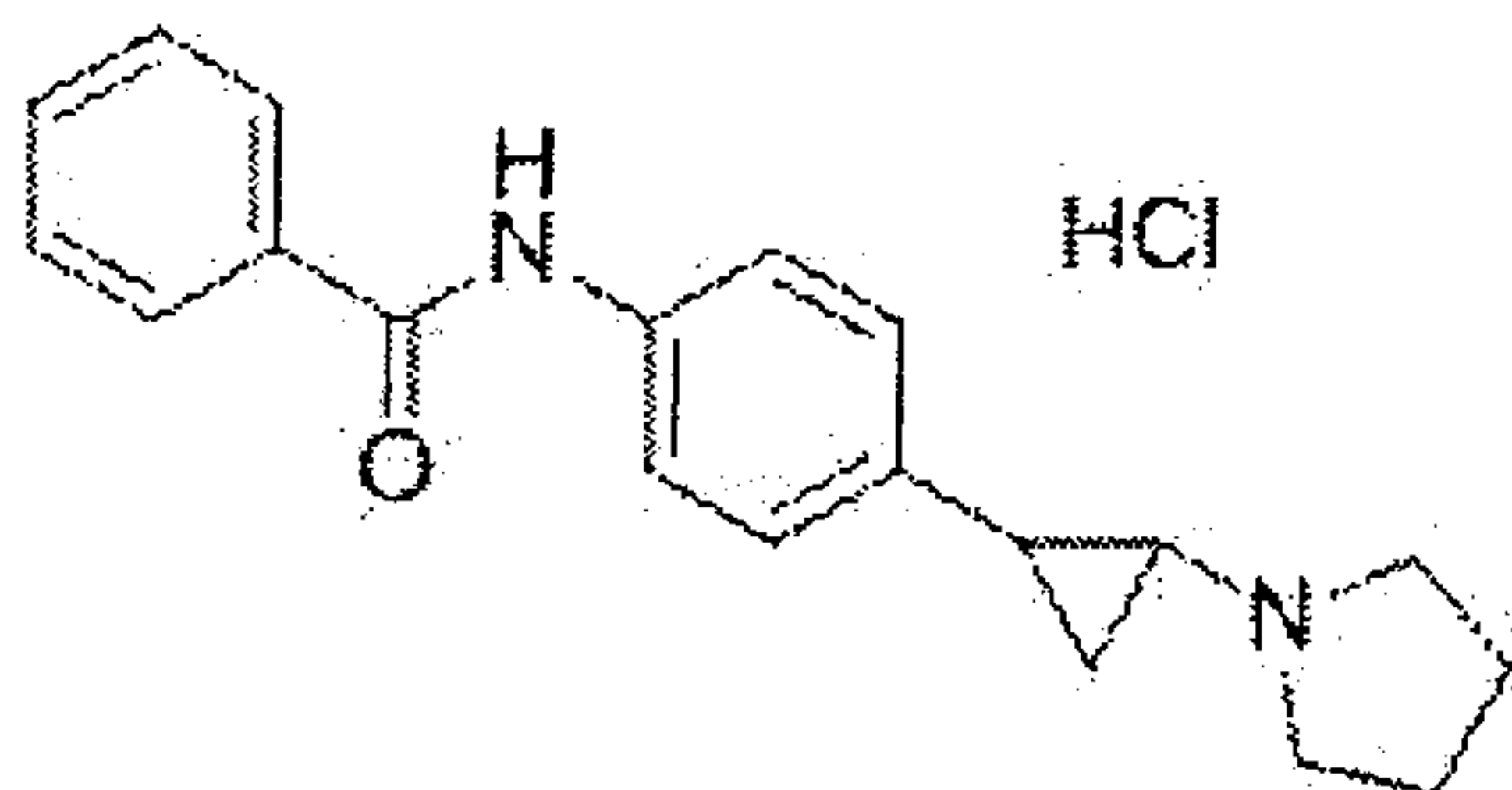
¹H NMR (400 MHz, DMSO-d₆) δ 1.22-1.31 (1H, m), 1.45-1.53 (1H, m), 2.41-2.48 (1H, m), 2.85-2.93 (1H, m), 4.27-4.32 (2H, m), 4.34 (2H, s), 6.76-6.81 (1H, m), 7.09 (4H, s), 7.16-7.26 (2H, m), 7.33 (2H, s), 7.36-7.40 (2H, m), 7.40-7.45 (3H, m), 7.50-
30 7.58 (2H, m), 7.67 (2H, d, J = 8.6 Hz), 9.53-9.67 (2H, m), 10.03-10.10 (1H, m).

[0303]

Example 30

N-{4-[trans-2-(pyrrolidin-1-yl)cyclopropyl]phenyl}benzamide
35 hydrochloride

[0304]



[0305]

To a mixture of N-[4-(trans-2-aminocyclopropyl)phenyl]benzamide hydrochloride (100 mg), triethylamine (0.145 mL), and N,N-dimethylformamide (2.0 mL) was added 1,4-dibromobutane (0.050 mL), and the mixture was stirred at 60°C for 2 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted twice with ethyl acetate. The organic layers were combined, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol), and the fractions containing the object product were collected and concentrated. The residue was dissolved in methanol (5.0 mL), 10% hydrochloric acid methanol solution (1.0 mL) was added, and the mixture was concentrated under reduced pressure to give the title compound (9.8 mg).

MS (API+): $[M+H]^+$ 307.3.

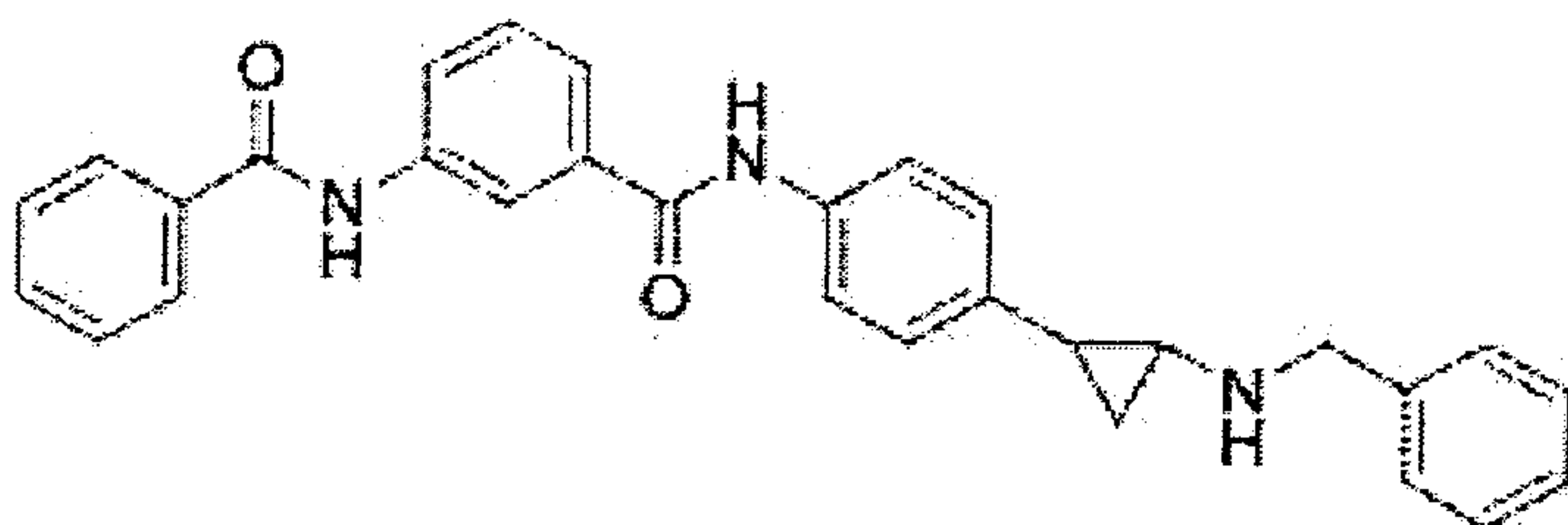
^1H NMR (300 MHz, CD_3OD) δ 1.36-1.48 (1H, m), 1.63 (1H, ddd, $J = 10.7, 6.7, 4.3$ Hz), 2.00-2.14 (2H, m), 2.14-2.32 (2H, m), 2.64 (1H, ddd, $J = 10.4, 6.7, 3.5$ Hz), 3.05-3.20 (1H, m), 3.26-3.41 (2H, m), 3.64-3.88 (2H, m), 7.16-7.23 (2H, m), 7.49-7.59 (3H, m), 7.62-7.70 (2H, m), 7.88-7.95 (2H, m).

[0306]

Example 31

N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-[(phenylcarbonyl)amino]benzamide

[0307]



[0308]

A) tert-butyl (trans-2-{4-[(3-
[(phenylcarbonyl)amino]phenyl)carbonyl)amino]phenyl}-
5 cyclopropyl)carbamate

To a solution of tert-butyl [trans-2-(4-
aminophenyl)cyclopropyl]carbamate (124 mg) described in a
document (J. Am. Chem. Soc., 2010, 132, 6827.) in acetonitrile
(4 mL) were added 3-[(phenylcarbonyl)amino]benzoic acid (100
10 mg), N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide
hydrochloride (95 mg), 1-hydroxybenzotriazole (67.2 mg) and
triethylamine (69 μ L). The mixture was stirred at room
temperature overnight and water was added. Ethyl acetate was
added to the mixture, and the resulting solid was collected by
15 filtration to give the title compound (188 mg).

^1H NMR (400 MHz, DMSO- d_6) δ 1.00-1.13 (2H, m), 1.39 (9H, s),
1.83-1.92 (1H, m), 2.60 (1H, brs), 7.08 (2H, d, J = 8.6 Hz),
7.24 (1H, brs), 7.47-7.71 (7H, m), 7.98-8.05 (3H, m), 8.30 (1H,
s), 10.22 (1H, s), 10.45 (1H, s).

20 [0309]

B) N-[4-(trans-2-aminocyclopropyl)phenyl]-3-
[(phenylcarbonyl)amino]benzamide hydrochloride

tert-Butyl (trans-2-{4-[(3-
[(phenylcarbonyl)amino]phenyl)carbonyl)amino]phenyl}-
25 cyclopropyl)carbamate (188 mg) was dissolved in 4N hydrochloric
acid/ethyl acetate solution (2 mL), and the mixture was stirred
at room temperature for 2 hr. The solvent was evaporated under
reduced pressure to give the title compound (107 mg).

^1H NMR (400 MHz, DMSO- d_6) δ 1.16-1.24 (1H, m), 1.31-1.40 (1H,
30 m), 2.23-2.33 (1H, m), 2.77-2.84 (1H, m), 7.15 (2H, d, J = 8.6
Hz), 7.48-7.65 (4H, m), 7.65-7.75 (3H, m), 7.96-8.03 (3H, m),

8.21-8.37 (4H, m), 10.28 (1H, s), 10.47 (1H, s).

[0310]

C) N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-[(phenylcarbonyl)amino]benzamide

5 To a solution of N-[4-(trans-2-aminocyclopropyl)phenyl]-3-[(phenylcarbonyl)amino]benzamide hydrochloride (85.5 mg) in methanol (2 mL) were added benzaldehyde (21 μ L) and sodium hydrogen carbonate (26.4 mg). The mixture was stirred at 70°C for 1 hr, and ice-cooled to 0°C and sodium borohydride (11.9
10 mg) was added. The mixture was stirred for 1 hr and water was added. The mixture was extracted with ethyl acetate, and the extract 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
15 column chromatography (hexane/ethyl acetate) and crystallized (hexane/ethyl acetate) to give the title compound (6.2 mg).

MS (API+): $[M+H]^+$ 462.2.

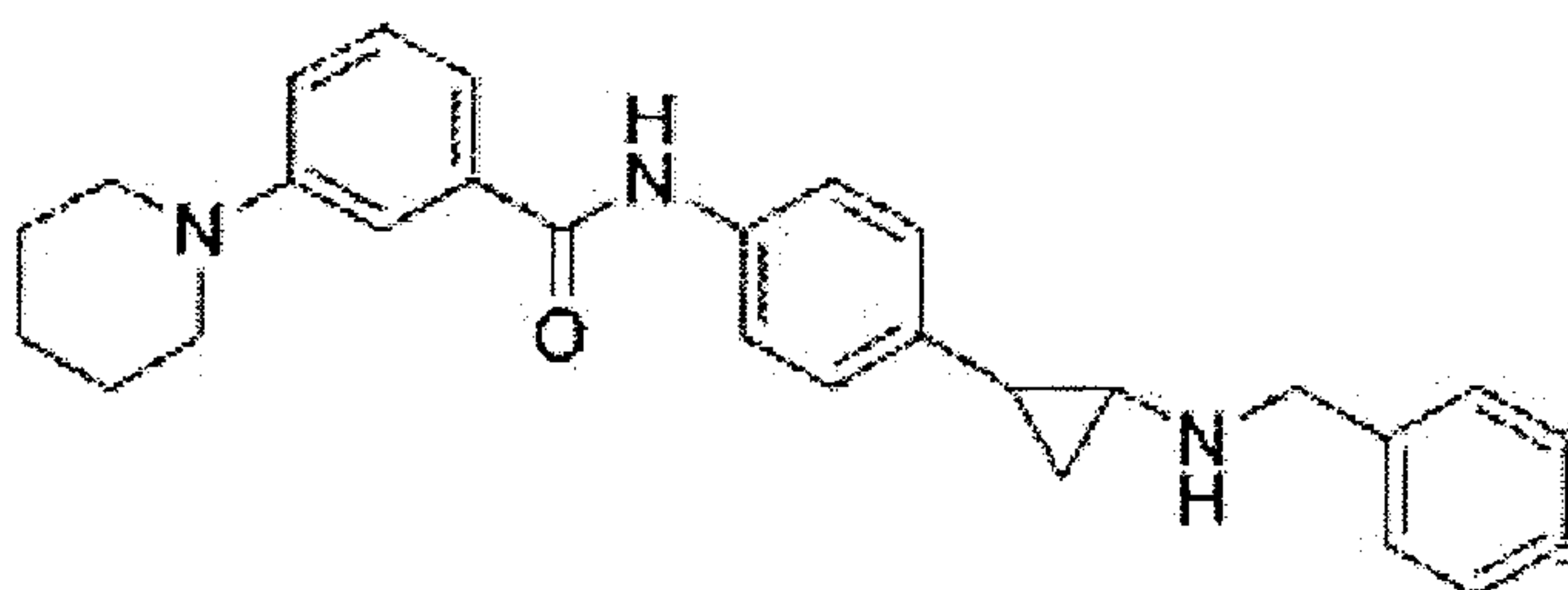
^1H NMR (400 MHz, CDCl_3) δ 0.92-0.99 (1H, m), 1.10 (1H, dt, J = 9.2, 4.8 Hz), 1.91 (1H, ddd, J = 9.2, 5.9, 3.2 Hz), 2.33-2.39
20 (1H, m), 3.84-3.94 (2H, m), 6.98 (2H, d, J = 8.6 Hz), 7.22-7.35 (5H, m), 7.43-7.54 (5H, m), 7.54-7.60 (1H, m), 7.63 (1H, d, J = 7.8 Hz), 7.82-7.91 (3H, m), 8.01 (1H, s), 8.07 (1H, s), 8.15 (1H, s).

[0311]

25 Example 32

N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-piperidin-1-ylbenzamide

[0312]



30 [0313]

A) tert-butyl {trans-2-[4-({[3-(piperidin-1-

yl)phenyl]carbonyl}amino)phenyl]cyclopropyl}carbamate

To a solution of tert-butyl [trans-2-(4-aminophenyl)cyclopropyl]carbamate (105 mg) described in a document (J. Am. Chem. Soc., 2010, 132, 6827.) in acetonitrile (3 mL) were added 3-(piperidin-1-yl)benzoic acid (105 mg) described in a document (J. Med. Chem. 1997, 40, 331.), N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (81 mg), 1-hydroxybenzotriazole (57.2 mg) and triethylamine (59 μ L). The mixture was stirred at room temperature overnight and water was added. The mixture was extracted with ethyl acetate, and the extract 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 (hexane/ethyl acetate) to give the title compound (142 mg).

^1H NMR (400 MHz, DMSO- d_6) δ 0.99-1.11 (2H, m), 1.35-1.41 (9H, m), 1.51-1.60 (2H, m), 1.63 (4H, d, $J = 4.9$ Hz), 1.87 (1H, brs), 2.55-2.63 (1H, m), 3.18-3.24 (4H, m), 4.83 (1H, s), 7.06 (2H, d, $J = 8.6$ Hz), 7.09-7.15 (1H, m), 7.28-7.35 (2H, m), 7.42 (1H, s), 7.63 (2H, d, $J = 8.6$ Hz), 10.06 (1H, s).

[0314]

B) N-{4-[trans-2-aminocyclopropyl]phenyl}-3-(piperidin-1-yl)benzamide dihydrochloride

tert-Butyl {trans-2-[4-({[3-(piperidin-1-yl)phenyl]carbonyl}amino)phenyl]cyclopropyl}carbamate (142 mg) was dissolved in 4N hydrochloric acid/ethyl acetate solution (2 mL), and the mixture was stirred at room temperature for 3 hr. The solvent was evaporated under reduced pressure to give the title compound (121 mg).

^1H NMR (400 MHz, DMSO- d_6) δ 1.14-1.27 (1H, m), 1.31-1.45 (1H, m), 1.63 (2H, brs), 1.81 (4H, brs), 2.25-2.36 (1H, m), 2.79 (1H, brs), 3.29-3.48 (4H, m), 7.15 (2H, d, $J = 8.8$ Hz), 7.26 (1H, s), 7.52 (2H, brs), 7.71 (2H, d, $J = 8.6$ Hz), 8.38-8.53 (3H, m), 10.31 (1H, brs).

[0315]

C) N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-(piperidin-1-yl)benzamide

To a solution of N-{4-[trans-2-aminocyclopropyl]phenyl}-3-(piperidin-1-yl)benzamide dihydrochloride (64.2 mg) in
 5 methanol (2 mL) were added benzaldehyde (16 μ L) and sodium hydrogen carbonate (19.8 mg). The reaction mixture was stirred at 70°C for 1 hr, and ice-cooled to 0°C and sodium borohydride (8.9 mg) was added. The mixture was stirred for 1 hr and water was added. The mixture was extracted with ethyl acetate, and
 10 the extract 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 (hexane/ethyl acetate) to give the title compound (51.0 mg).

15 MS (API+): $[M+H]^+$ 426.3.

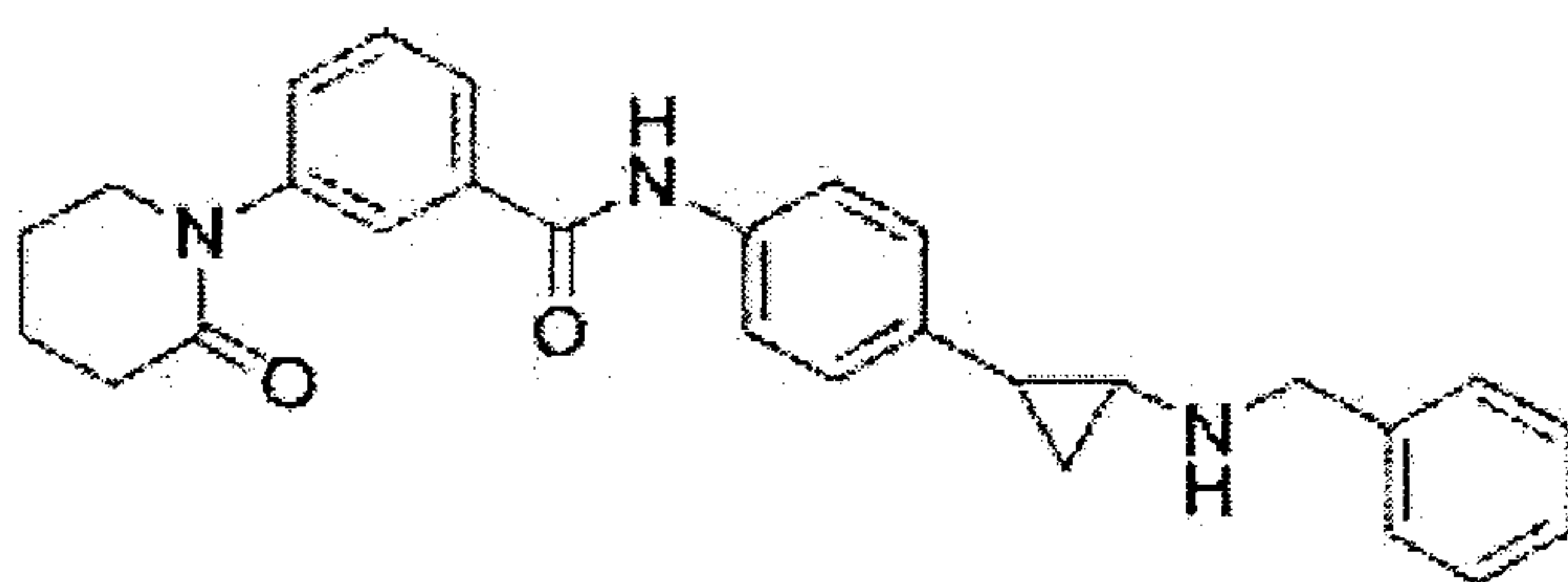
^1H NMR (400 MHz, CDCl_3) δ 0.92-0.99 (1H, m), 1.10 (1H, dt, $J = 9.4, 4.7$ Hz), 1.55-1.63 (2H, m), 1.71 (4H, quin, $J = 5.6$ Hz), 1.88-1.94 (1H, m), 2.36 (1H, dt, $J = 7.2, 3.6$ Hz), 3.19-3.25 (4H, m), 3.84-3.93 (2H, m), 6.97 (2H, d, $J = 8.6$ Hz), 7.07 (1H, dd, $J = 8.2, 2.6$ Hz), 7.17 (1H, d, $J = 7.6$ Hz), 7.22-7.35 (6H, m), 7.45 (1H, t, $J = 2.0$ Hz), 7.50 (2H, d, $J = 8.6$ Hz), 7.79 (1H, brs).

[0316]

Example 33

25 N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-(2-oxopiperidin-1-yl)benzamide

[0317]



[0318]

30 A) 3-(2-oxopiperidin-1-yl)benzoic acid

To a solution of methyl 3-(2-oxopiperidin-1-yl)benzoate

(114 mg) described in a document (J. Med. Chem. 1997, 40, 331.) in THF (3.0 mL) - water (0.5 mL) was added lithium hydroxide monohydrate (61.5 mg). The mixture was stirred at room temperature overnight, and 10% citric acid solution was added.

5 The mixture was extracted with ethyl acetate, and the extract was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give the title compound (34.7 mg).

¹H NMR (400 MHz, DMSO-d₆) δ 1.67-1.98 (4H, m), 2.40 (2H, t, J = 6.5 Hz), 3.63 (2H, t, J = 5.5 Hz), 7.39-7.60 (2H, m), 7.73-7.90 (2H, m), 12.39 (1H, brs).

[0319]

B) tert-butyl {trans-2-[4-({[3-(2-oxopiperidin-1-yl)phenyl]carbonyl}amino)phenyl]cyclopropyl}carbamate

15 To a solution of tert-butyl [trans-2-(4-aminophenyl)cyclopropyl]carbamate (230 mg) described in a document (J. Am. Chem. Soc., 2010, 132, 6827.) in acetonitrile (7 mL) were added 3-(2-oxopiperidin-1-yl)benzoic acid (169 mg), N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (177 mg), 1-hydroxybenzotriazole (125 mg) and triethylamine (128 µL). The mixture was stirred at room temperature overnight and water was added. The mixture was extracted with ethyl acetate, and the extract was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was
25 evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (53.4 mg).

¹H NMR (400 MHz, CDCl₃) δ 1.09-1.18 (2H, m), 1.46 (9H, s), 1.81-1.91 (2H, m), 1.91-2.07 (3H, m), 2.58 (2H, t, J = 5.5 Hz), 2.69 (1H, brs), 3.65 (2H, brs), 4.90 (1H, brs), 7.11 (2H, d, J = 8.6 Hz), 7.32-7.38 (1H, m), 7.38-7.46 (1H, m), 7.53 (2H, d, J = 8.6 Hz), 7.68-7.75 (2H, m), 8.40 (1H, brs).

[0320]

C) N-{4-[trans-2-aminocyclopropyl]phenyl}-3-(2-oxopiperidin-1-yl)benzamide hydrochloride
35

A mixed solution of tert-butyl {trans-2-[4-({[3-(2-oxopiperidin-1-yl)phenyl]carbonyl}amino)phenyl]cyclopropyl}-carbamate (53.4 mg) in 4N hydrochloric acid/ethyl acetate solution (2 mL) was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure to give the title compound (38.5 mg).

¹H NMR (400 MHz, CD₃OD) δ 1.31-1.48 (2H, m), 1.96-2.08 (4H, m), 2.39 (1H, brs), 2.58 (2H, t, J = 6.2 Hz), 2.82-2.90 (1H, m), 3.76 (2H, t, J = 5.6 Hz), 7.21 (2H, d, J = 8.6 Hz), 7.49-7.55 (1H, m), 7.56-7.63 (1H, m), 7.67 (2H, d, J = 8.6 Hz), 7.81-7.92 (2H, m).

[0321]

D) N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-(2-oxopiperidin-1-yl)benzamide

To a solution of N-{4-[trans-2-aminocyclopropyl]phenyl}-3-(2-oxopiperidin-1-yl)benzamide hydrochloride (27.1 mg) in methanol (1 mL) were added benzaldehyde (7.14 μL) and sodium hydrogen carbonate (8.9 mg). The mixture was stirred at 70°C for 1 hr, and ice-cooled to 0°C and sodium borohydride (4.0 mg) was added. The mixture was stirred for 1 hr and water was added. The mixture was extracted with ethyl acetate, and the extract 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 (hexane/ethyl acetate) to give the title compound (10.9 mg).

MS (API+): [M+H]⁺ 440.3.

¹H NMR (400 MHz, CDCl₃) δ 0.92-0.99 (1H, m), 1.10 (1H, dt, J = 9.2, 4.8 Hz), 1.88-2.01 (6H, m), 2.33-2.39 (1H, m), 2.58 (2H, t, J = 5.7 Hz), 3.61-3.69 (2H, m), 3.89 (2H, d, J = 1.7 Hz), 6.97 (2H, d, J = 8.6 Hz), 7.22-7.37 (6H, m), 7.39-7.45 (1H, m), 7.51 (2H, d, J = 8.6 Hz), 7.68-7.73 (2H, m), 8.35 (1H, brs).

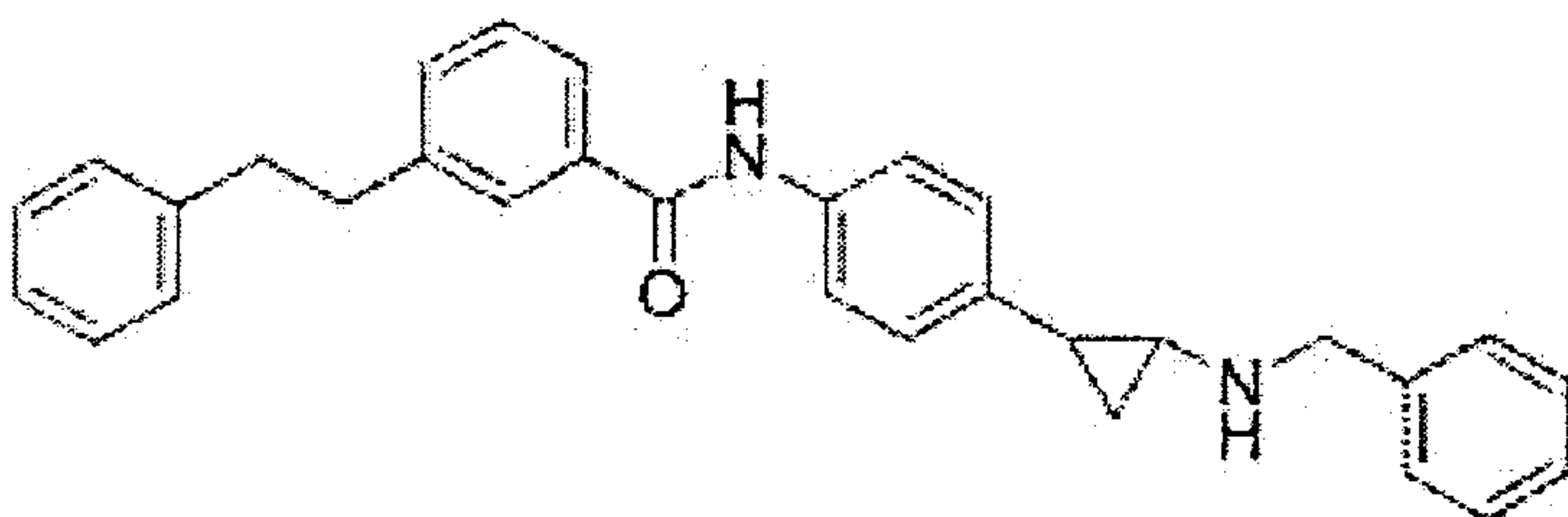
[0322]

Example 34

N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-(2-

phenylethyl)benzamide

[0323]



[0324]

5 A) tert-butyl {trans-2-[4-({[3-(2-phenylethyl)phenyl]carbonyl}amino)phenyl]cyclopropyl}carbamate

By a method similar to Example 28, Step A, the title compound (232 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl]carbamate (191 mg) and 3-(2-phenylethyl)benzoic acid (145 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.98-1.13 (2H, m), 1.38 (9H, s), 1.82-1.93 (1H, m), 2.58 (1H, brs), 2.87-3.02 (4H, m), 7.06 (2H, d, J = 8.3 Hz), 7.14-7.32 (6H, m), 7.36 (2H, d, J = 8.3 Hz), 7.65 (2H, d, J = 8.7 Hz), 7.86 (2H, d, J = 8.3 Hz), 10.08 (1H, s).

[0325]

B) N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(2-phenylethyl)benzamide hydrochloride

By a method similar to Example 1, Step B, the title compound (154 mg) was obtained from tert-butyl {trans-2-[4-({[3-(2-phenylethyl)phenyl]carbonyl}amino)phenyl]cyclopropyl}-carbamate (232 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.11-1.25 (1H, m), 1.30-1.41 (1H, m), 2.21-2.36 (1H, m), 2.73-2.83 (1H, m), 2.86-3.02 (4H, m), 7.07-7.40 (9H, m), 7.70 (2H, d, J = 8.7 Hz), 7.85 (2H, d, J = 8.3 Hz), 8.34 (3H, brs) 10.14 (1H, s).

[0326]

C) N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-3-(2-phenylethyl)benzamide

By a method similar to Example 1, Step C, the title compound (85.4 mg) was obtained from N-[4-(trans-2-

aminocyclopropyl)phenyl]-3-(2-phenylethyl)benzamide
hydrochloride (100 mg).

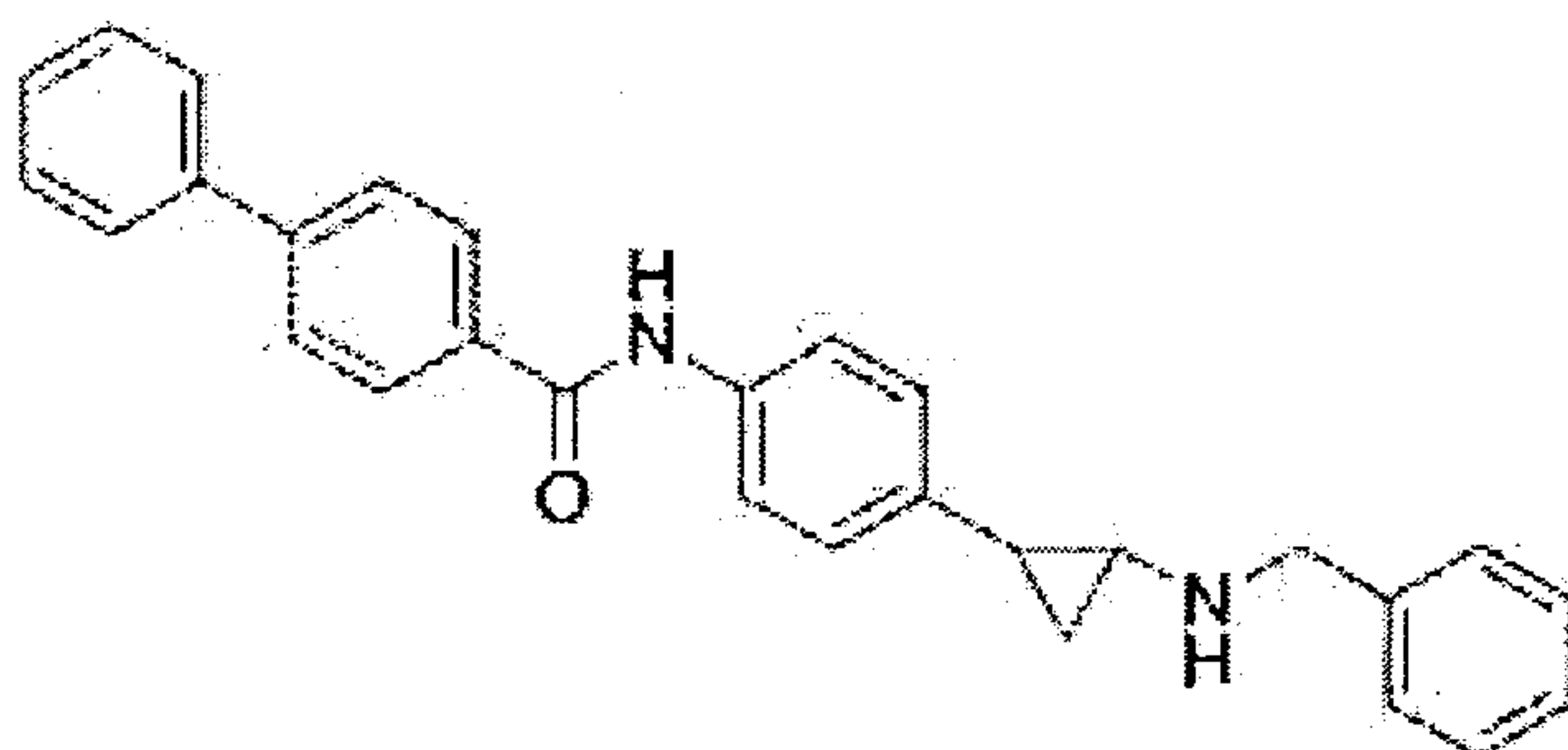
¹H NMR (300 MHz, DMSO-d₆) δ 0.83-1.03 (2H, m), 1.80 (1H, ddd, J = 9.0, 5.8, 3.0 Hz), 2.18 (1H, dt, J = 6.7, 3.6 Hz), 2.83-3.03
5 (4H, m), 3.77 (2H, s), 6.94 (2H, d, J = 8.3 Hz), 7.13 - 7.40
(12H, m), 7.60 (2H, d, J = 8.7 Hz), 7.85 (2H, d, J = 8.3 Hz),
10.04 (1H, s).

[0327]

Example 35

10 N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}biphenyl-4-
carboxamide

[0328]



[0329]

15 A) tert-butyl (trans-2-{4-[(biphenyl-4-
ylcarbonyl)amino]phenyl}cyclopropyl)carbamate

To a solution of tert-butyl [trans-2-(4-
aminophenyl)cyclopropyl]carbamate (150 mg) described in a
document (J. Am. Chem. Soc., 2010, 132, 6827.) in acetonitrile
20 (6 mL) were added biphenyl-4-carboxylic acid (100 mg), N-ethyl-
N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (116 mg),
1-hydroxybenzotriazole (82 mg) and triethylamine (84 µL). The
mixture was stirred at room temperature overnight and water was
added. The mixture was extracted with ethyl acetate, and the
25 extract was washed with saturated brine and dried over
anhydrous sodium sulfate. The solvent was evaporated under
reduced pressure. The residue was recrystallized
(methanol/ethyl acetate) to give the title compound (131 mg).
MS (API+): [M-tBu+2H]⁺ 373.2.

30 [0330]

B) N-[4-(trans-2-aminocyclopropyl)phenyl]biphenyl-4-carboxamide hydrochloride

tert-Butyl (trans-2-{4-[(biphenyl-4-ylcarbonyl)amino]phenyl}cyclopropyl)carbamate (154 mg) was dissolved in 4N hydrochloric acid/ethyl acetate solution (2 mL), and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure to give the title compound (81.9 mg).

MS (API+): $[M+H]^+$ 329.2.

10 [0331]

C) N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}biphenyl-4-carboxamide

To a solution of N-[4-(trans-2-aminocyclopropyl)phenyl]biphenyl-4-carboxamide hydrochloride (82 mg) in methanol (2 mL) were added benzaldehyde (25 μ L) and sodium hydrogen carbonate (31.5 mg). The reaction mixture was stirred at 70°C for 1 hr, and ice-cooled to 0°C and sodium borohydride (14.2 mg) was added. The mixture was stirred for 1 hr and water was added. The mixture was extracted with ethyl acetate, and the extract 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 (hexane/ethyl acetate) to give the title compound (6.4 mg).

25 MS (API+): $[M+H]^+$ 419.2.

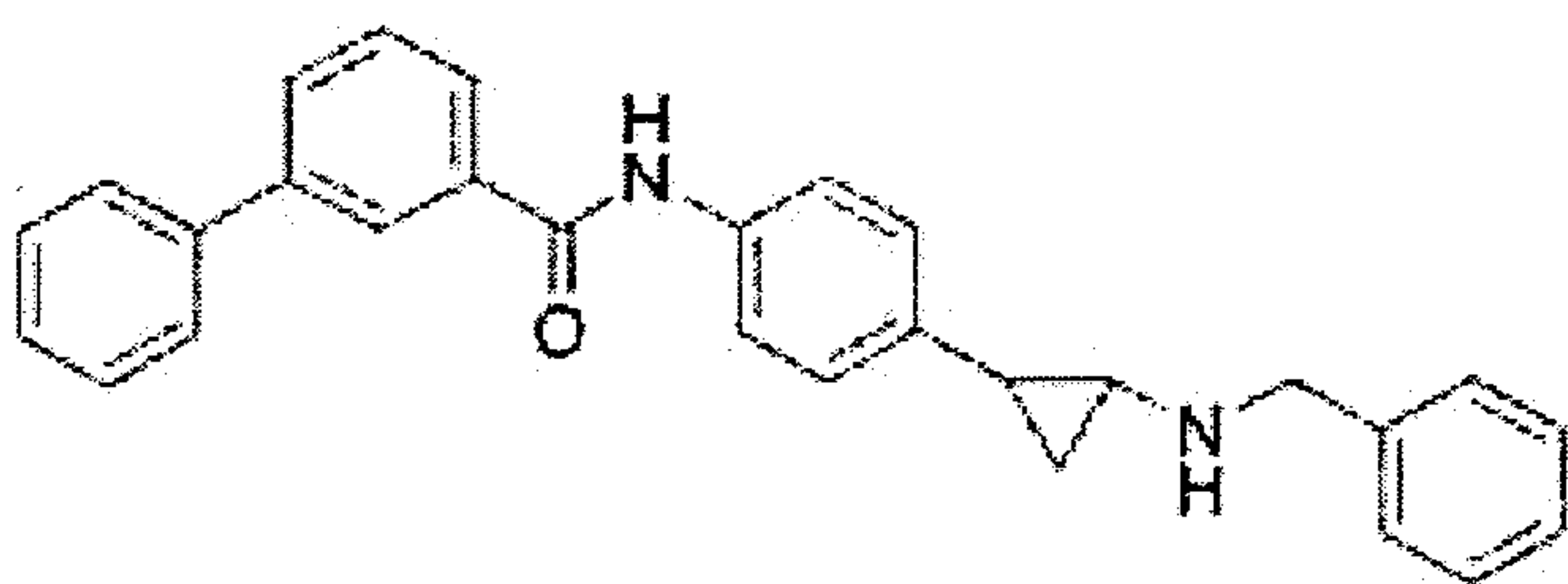
^1H NMR (400 MHz, DMSO- d_6) δ 0.88 - 1.03 (2H, m), 1.81 (1H, s), 2.16 - 2.24 (1H, m), 3.77 (2H, s), 6.97 (2H, d, J = 8.6 Hz), 7.22 (1H, d, J = 6.9 Hz), 7.27 - 7.34 (4H, m), 7.44 (1H, d, J = 7.3 Hz), 7.48 - 7.55 (2H, m), 7.64 (2H, d, J = 8.6 Hz), 7.74 - 7.79 (2H, m), 7.83 (2H, d, J = 8.6 Hz), 8.04 (2H, d, J = 8.6 Hz), 10.19 (1H, s).

[0332]

Example 36

N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}biphenyl-3-carboxamide

[0333]



[0334]

A) tert-butyl (trans-2-{4-[(biphenyl-3-
5 ylcarbonyl)amino]phenyl}cyclopropyl)carbamate

To a solution of tert-butyl [trans-2-(4-aminophenyl)cyclopropyl]carbamate (100 mg) described in a document (J. Am. Chem. Soc., 2010, 132, 6827.) in acetonitrile (4 mL) were added biphenyl-3-carbonyl chloride (131 mg) and
10 triethylamine (61.1 mg). The mixture was stirred at room temperature overnight and water was added. To the reaction mixture was added ethyl acetate, and the resulting solid was collected by filtration to give the title compound (154 mg).
MS (API+): [M-^tBu+2H]⁺ 373.2.

15 [0335]

B) N-[4-(trans-2-aminocyclopropyl)phenyl]biphenyl-3-carboxamide hydrochloride

tert-Butyl (trans-2-{4-[(biphenyl-3-ylcarbonyl)amino]phenyl}cyclopropyl)carbamate (154 mg) was
20 dissolved in 4N hydrochloric acid/ethyl acetate solution (2 mL), and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure to give the title compound (130 mg).
MS (API+): [M+H]⁺ 329.2.

25 [0336]

C) N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}biphenyl-3-carboxamide

To a solution of N-[4-(trans-2-aminocyclopropyl)phenyl]biphenyl-3-carboxamide hydrochloride
30 (130 mg) in methanol (4 mL) were added benzaldehyde (40 µL) and sodium hydrogen carbonate (49.9 mg). The mixture was stirred

at 70°C for 1 hr, and ice-cooled to 0°C and sodium borohydride (22.5 mg) was added. The mixture was stirred for 1 hr and water was added. The mixture was extracted with ethyl acetate, and the extract was washed with saturated brine and dried over
 5 anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was recrystallized (hexane/ethyl acetate) to give the title compound (60.4 mg).

MS (API+): $[M+CH_3CN+H]^+$ 460.4.

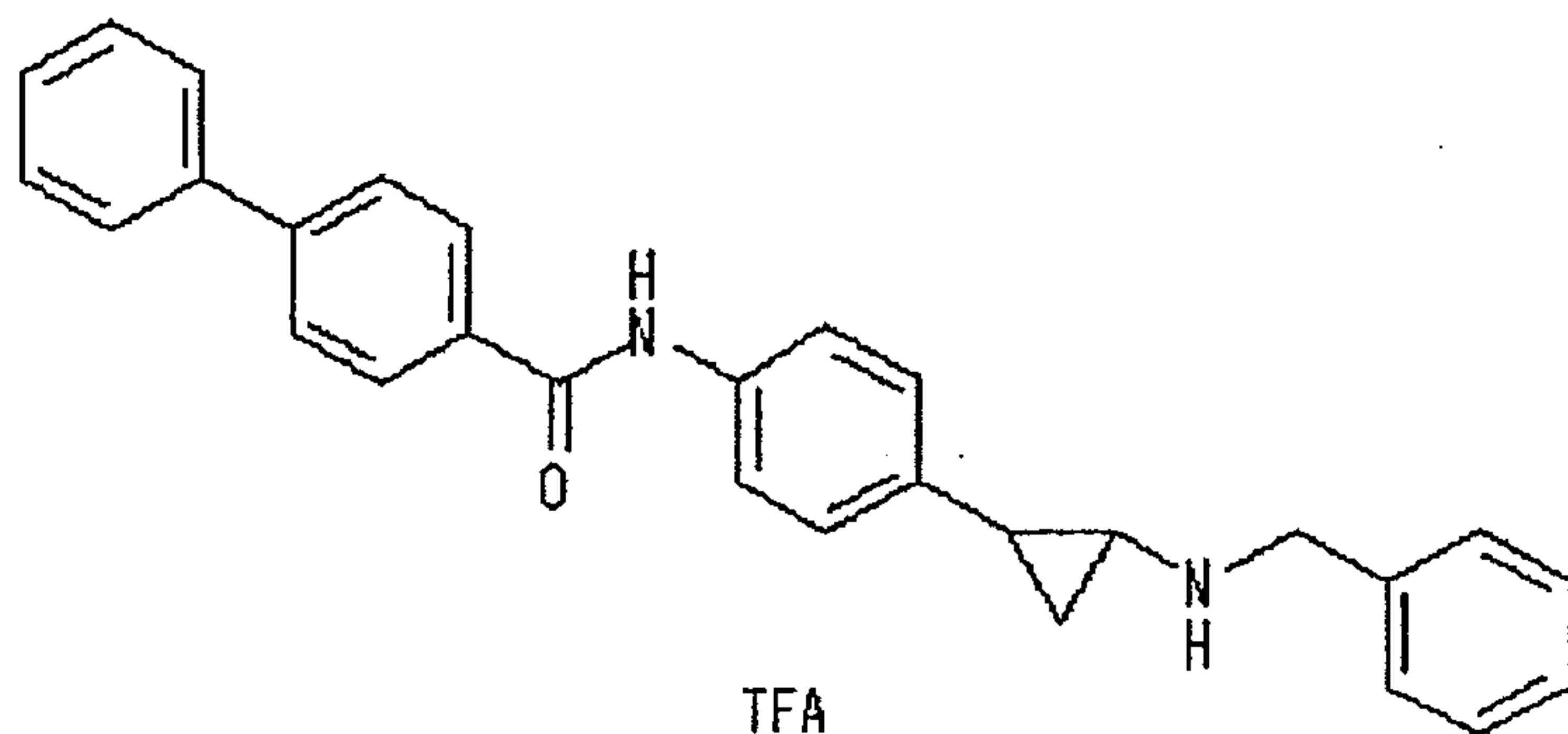
^1H NMR (400 MHz, DMSO- d_6) δ 0.85-1.06 (2H, m), 1.76-1.86 (1H, m), 2.16-2.23 (1H, m), 2.81-2.96 (1H, m), 3.77 (2H, s), 6.97
 10 (2H, d, $J = 8.6$ Hz), 7.18-7.26 (1H, m), 7.26-7.35 (4H, m), 7.43 (1H, d, $J = 7.3$ Hz), 7.49-7.56 (2H, m), 7.63 (3H, d, $J = 8.3$ Hz), 7.77 (2H, d, $J = 7.3$ Hz), 7.90 (2H, dd, $J = 18.3, 7.8$ Hz), 8.20 (1H, s), 10.24 (1H, s).

15 [0337]

Example 37

N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}biphenyl-4-carboxamide trifluoroacetate

[0338]



20

[0339]

To a solution of N-[4-(trans-2-aminocyclopropyl)phenyl]biphenyl-4-carboxamide hydrochloride (26 mg) and benzaldehyde (10 mg) in methanol (1 mL) was added
 25 acetic acid (0.1 mL), and the mixture was stirred at 45°C for 1 hr and 2-picoline borane (17 mg) was added. The mixture was stirred at 60°C overnight, and the solvent was evaporated by an air blowing apparatus. The residue was purified by HPLC (C18,

mobile phase: water/acetonitrile (with 0.1% TFA)) to give the title compound (3.3 mg).

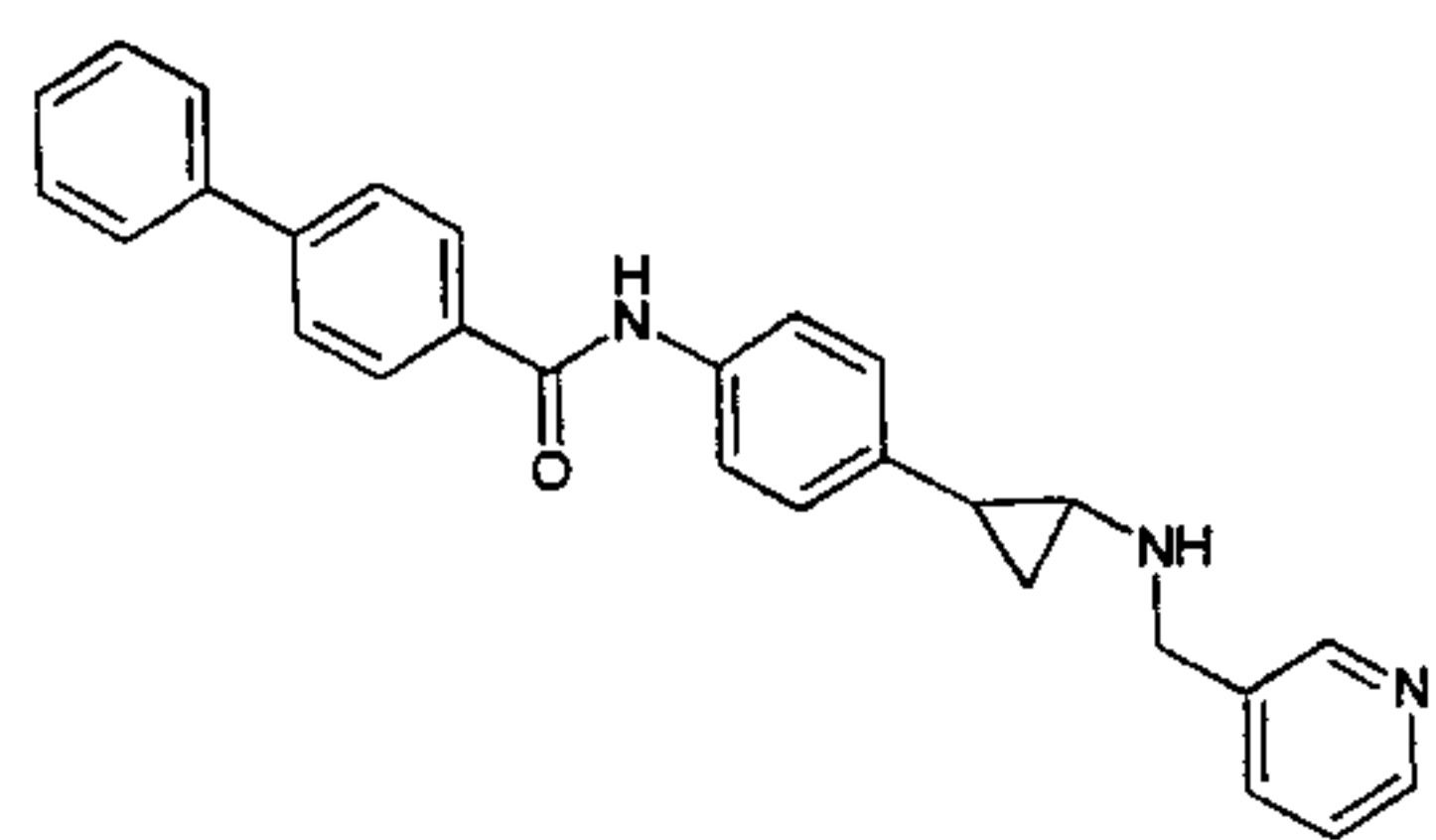
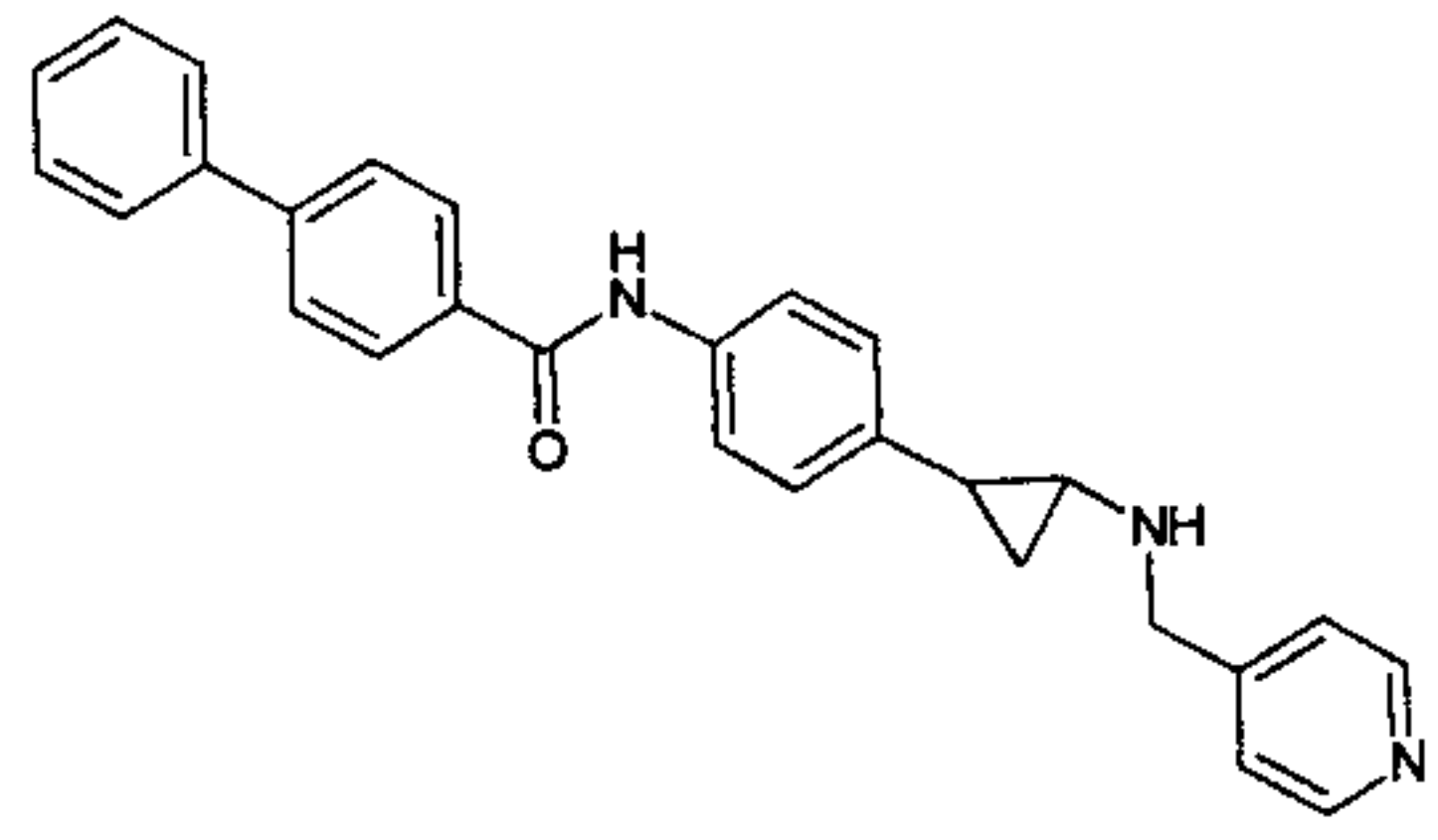
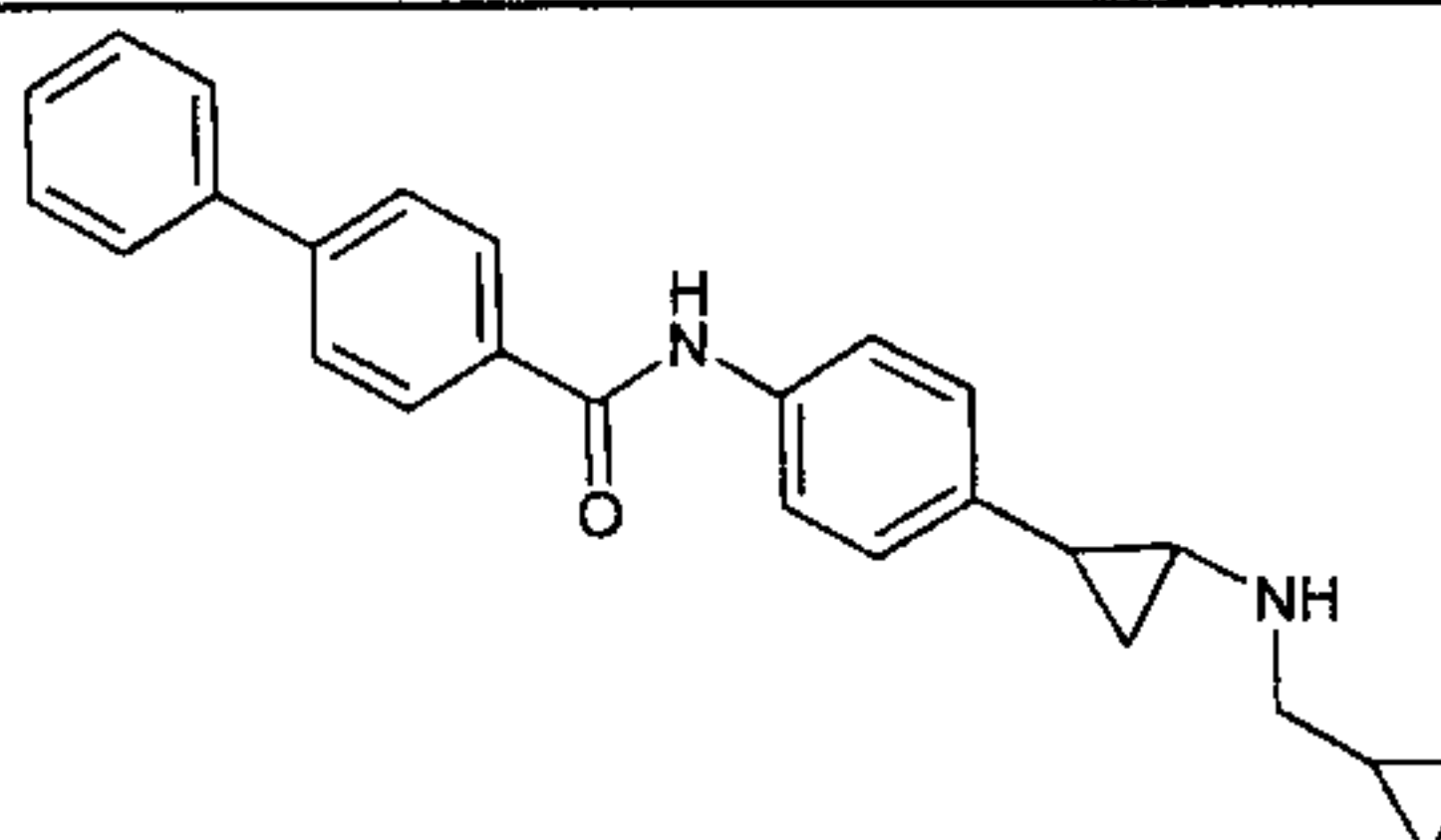
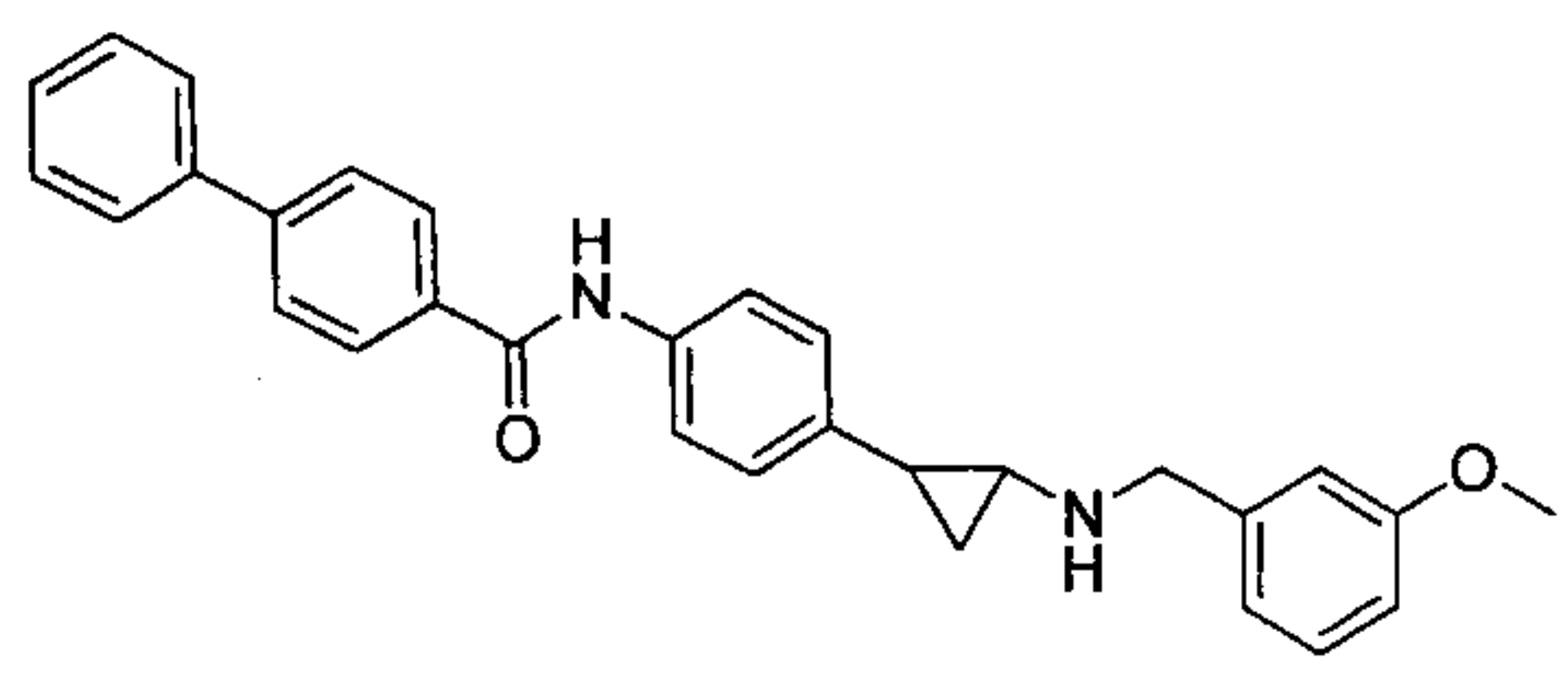
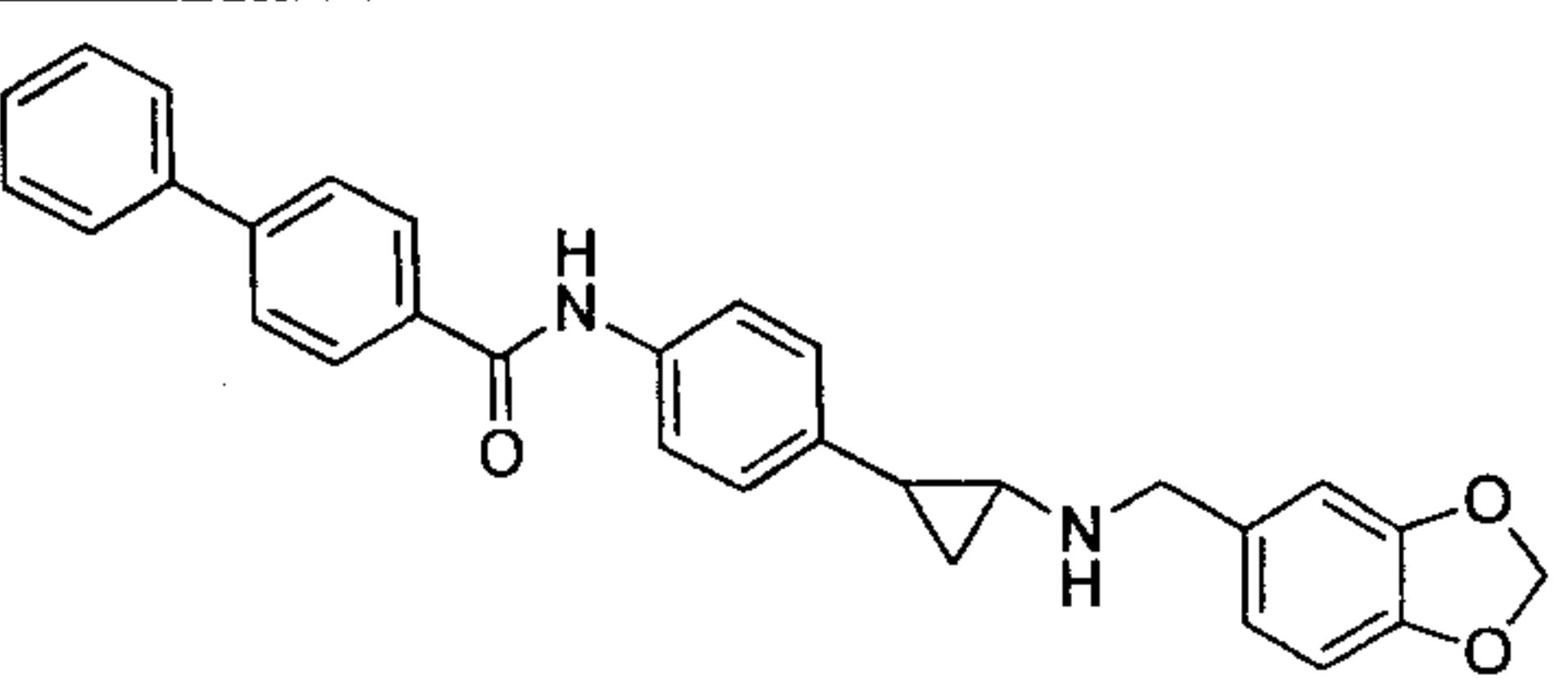
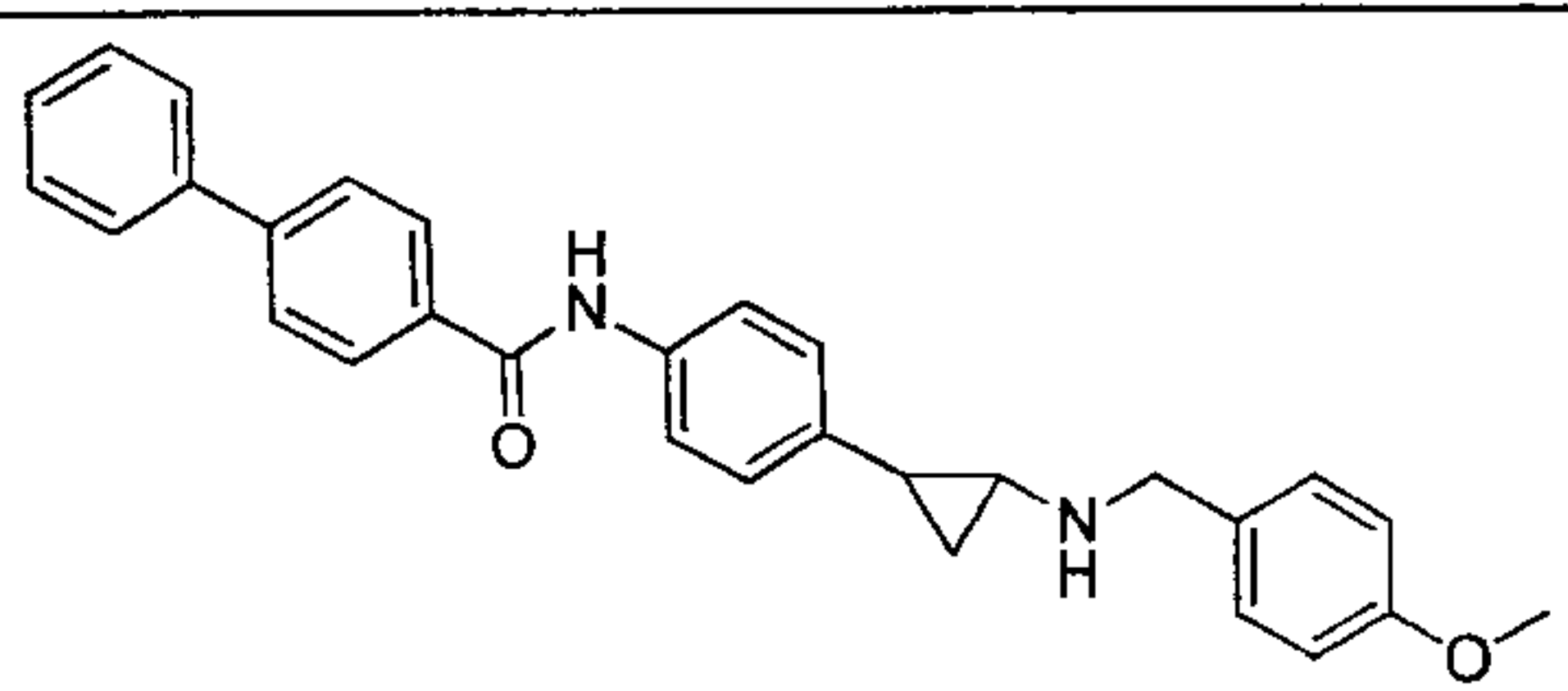
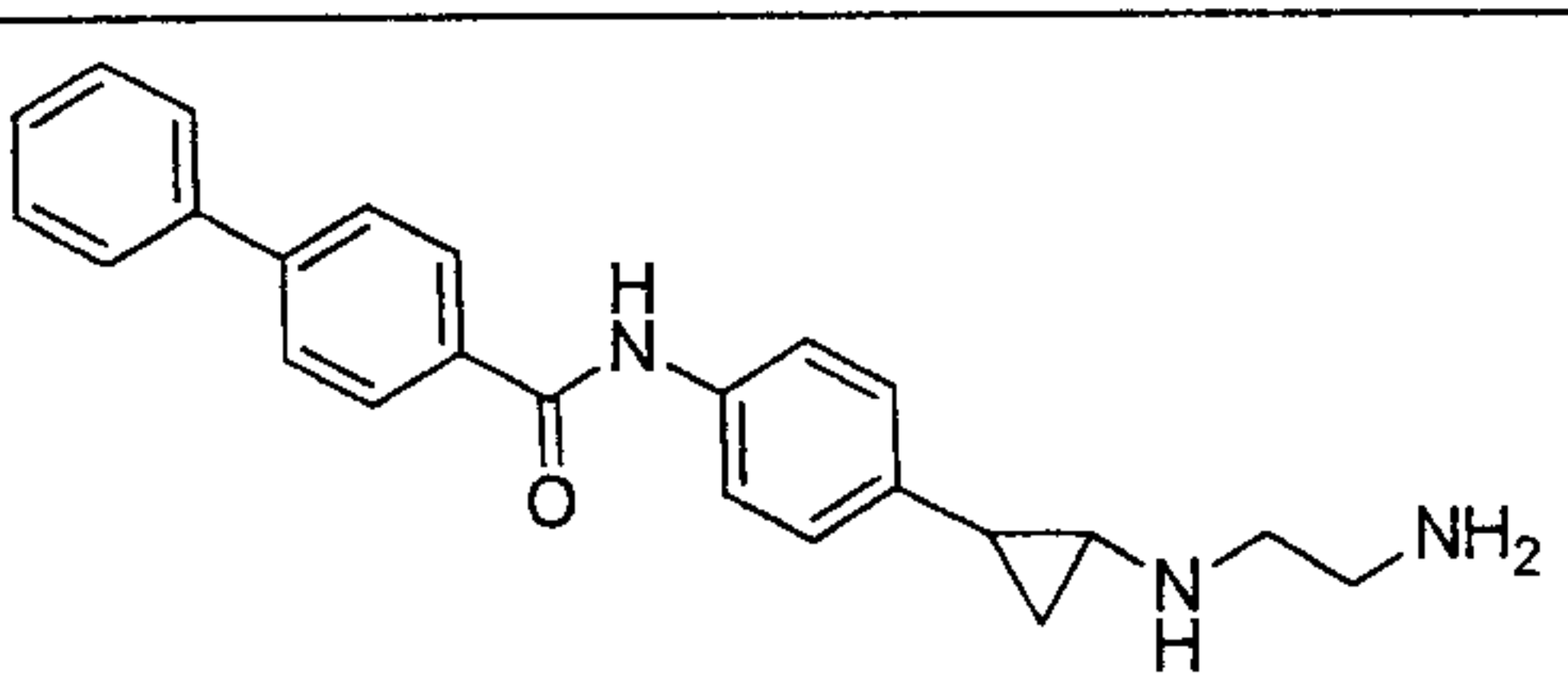
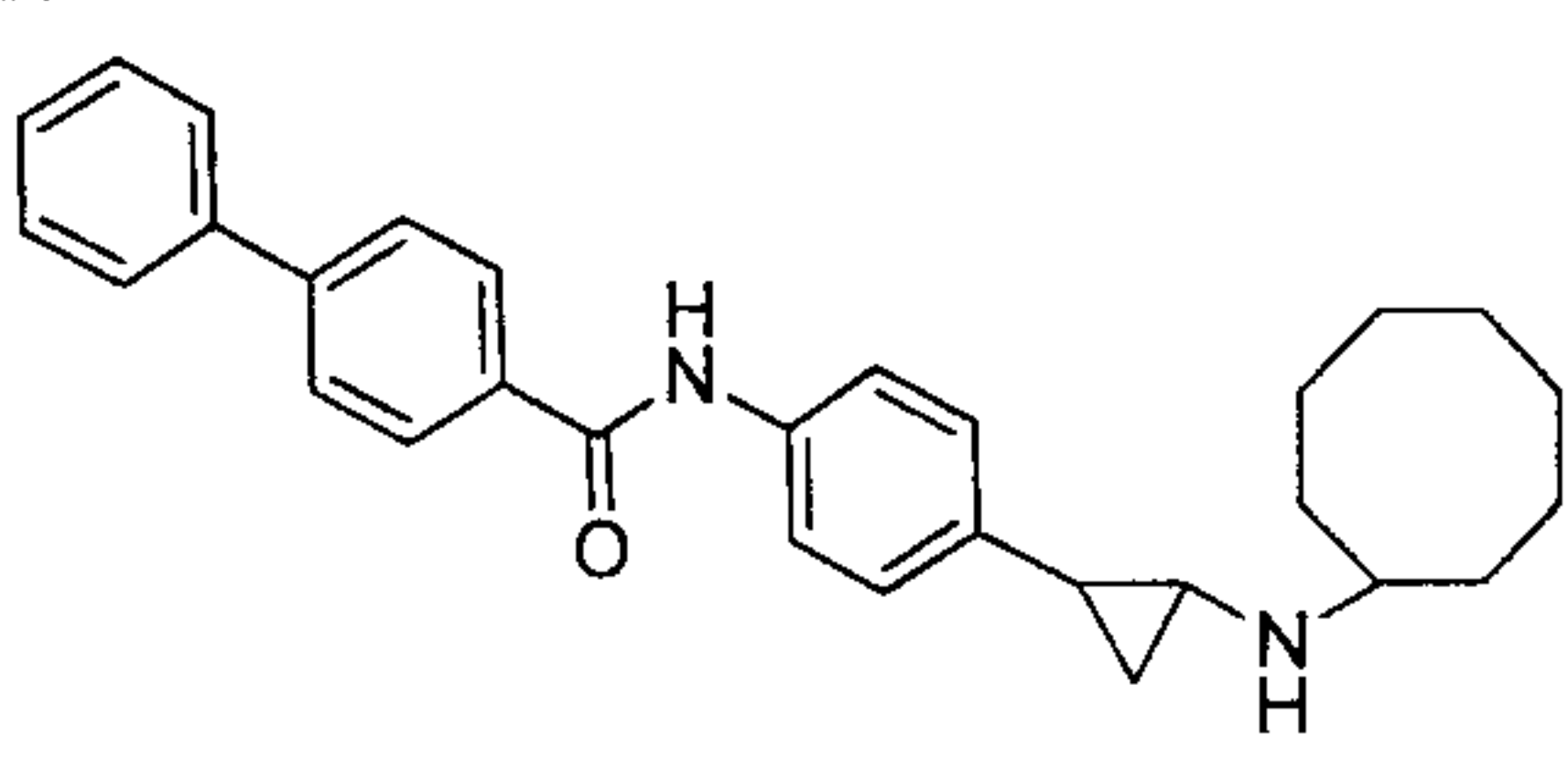
MS (API+): $[M+H]^+$ 419.3

[0340]

- 5 The compounds produced by the method described in the above-mentioned Example 37 or a method analogous thereto are shown in the following Tables. In the Tables, MS shows measured values.

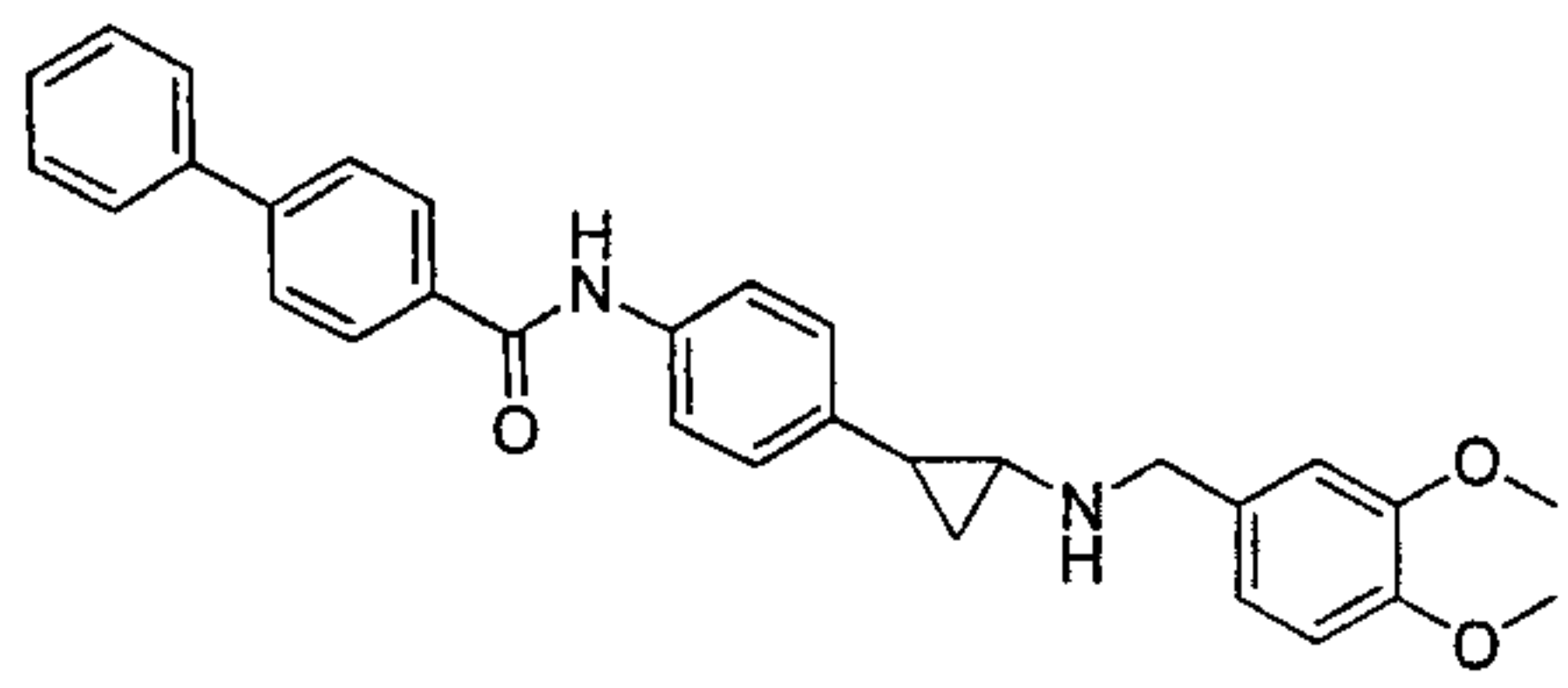
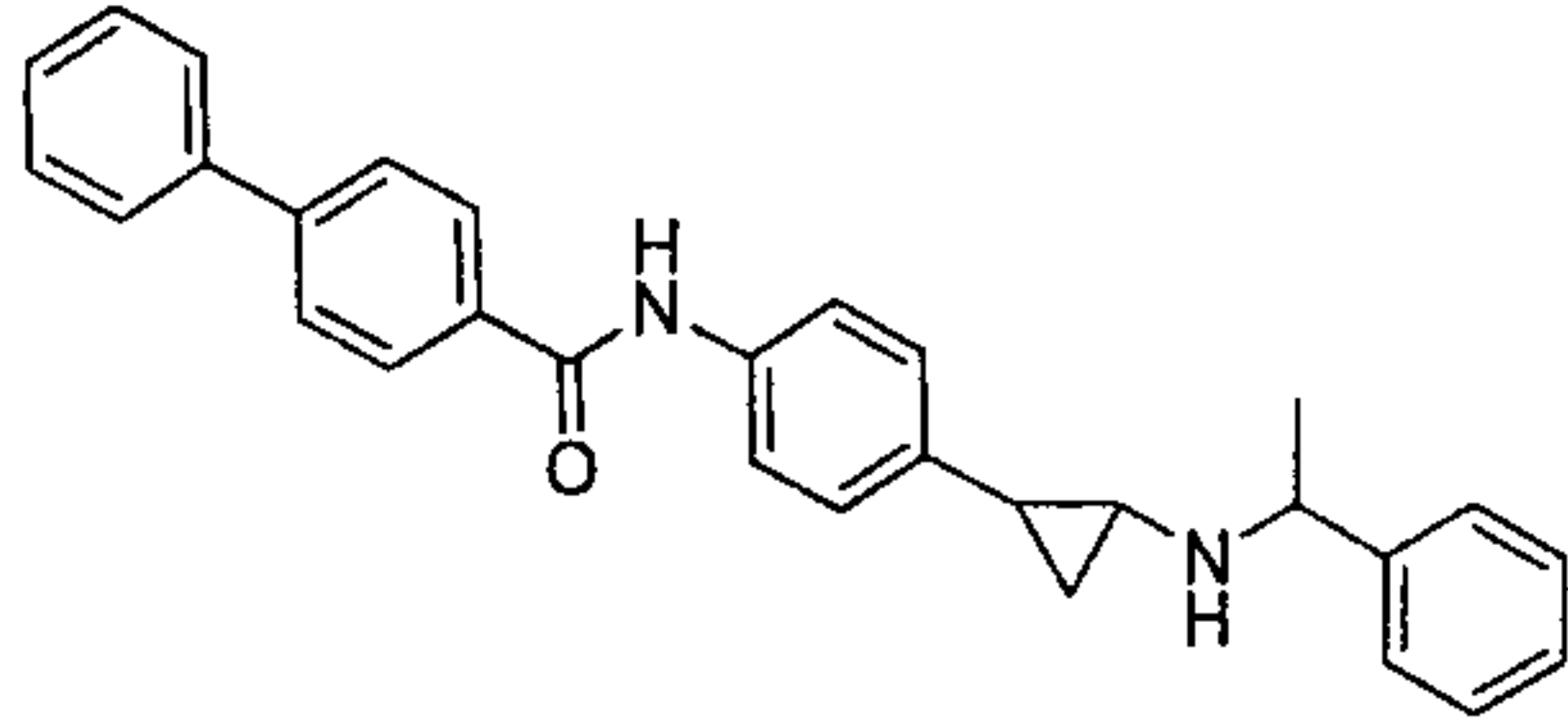
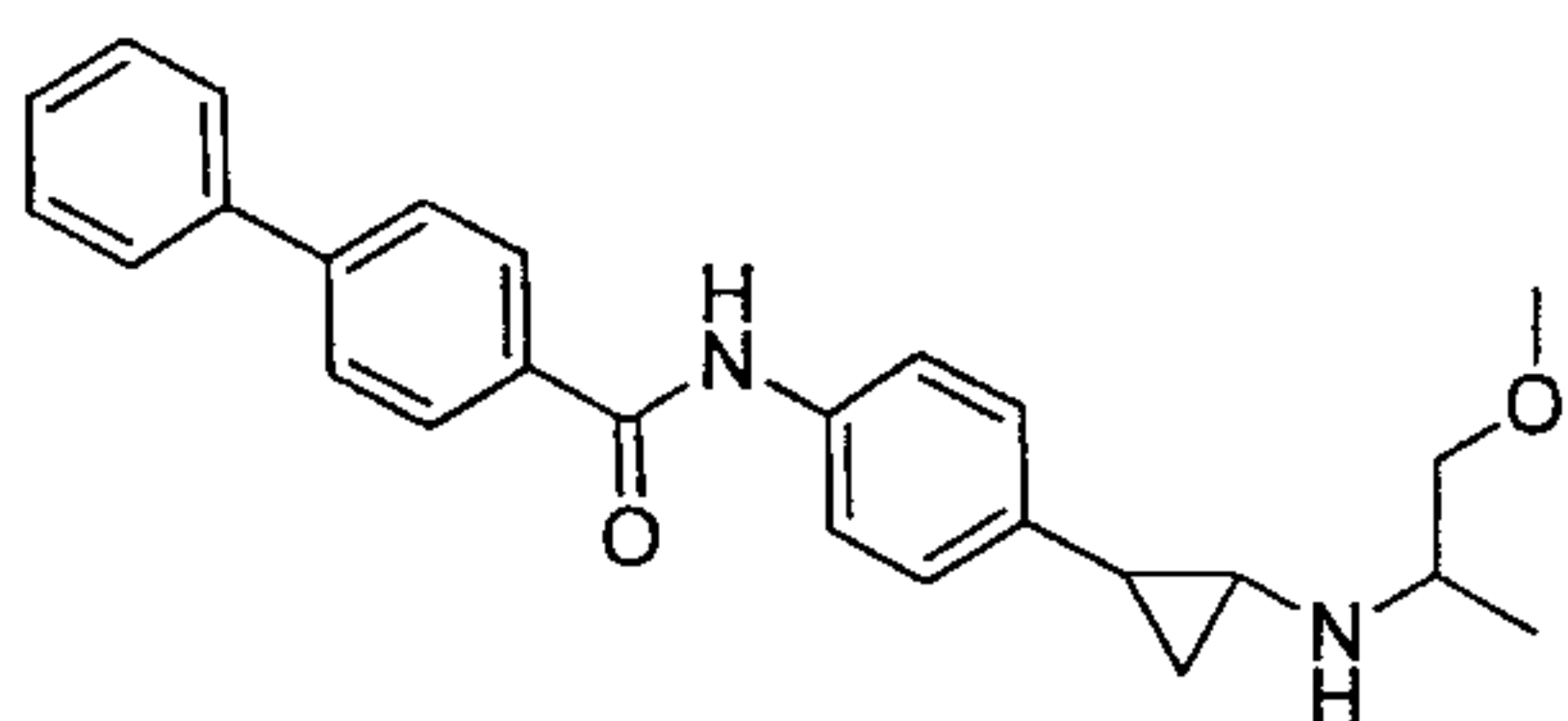
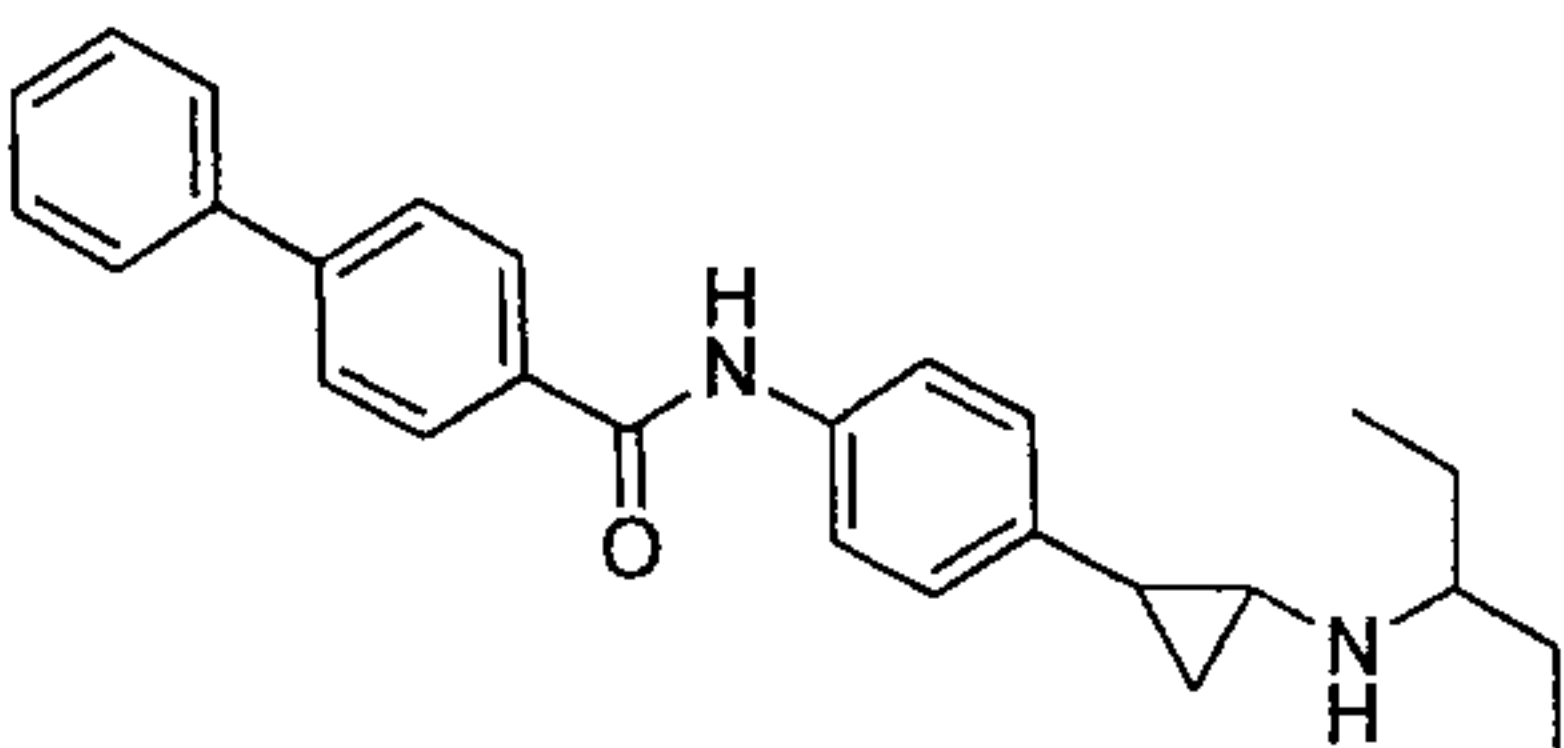
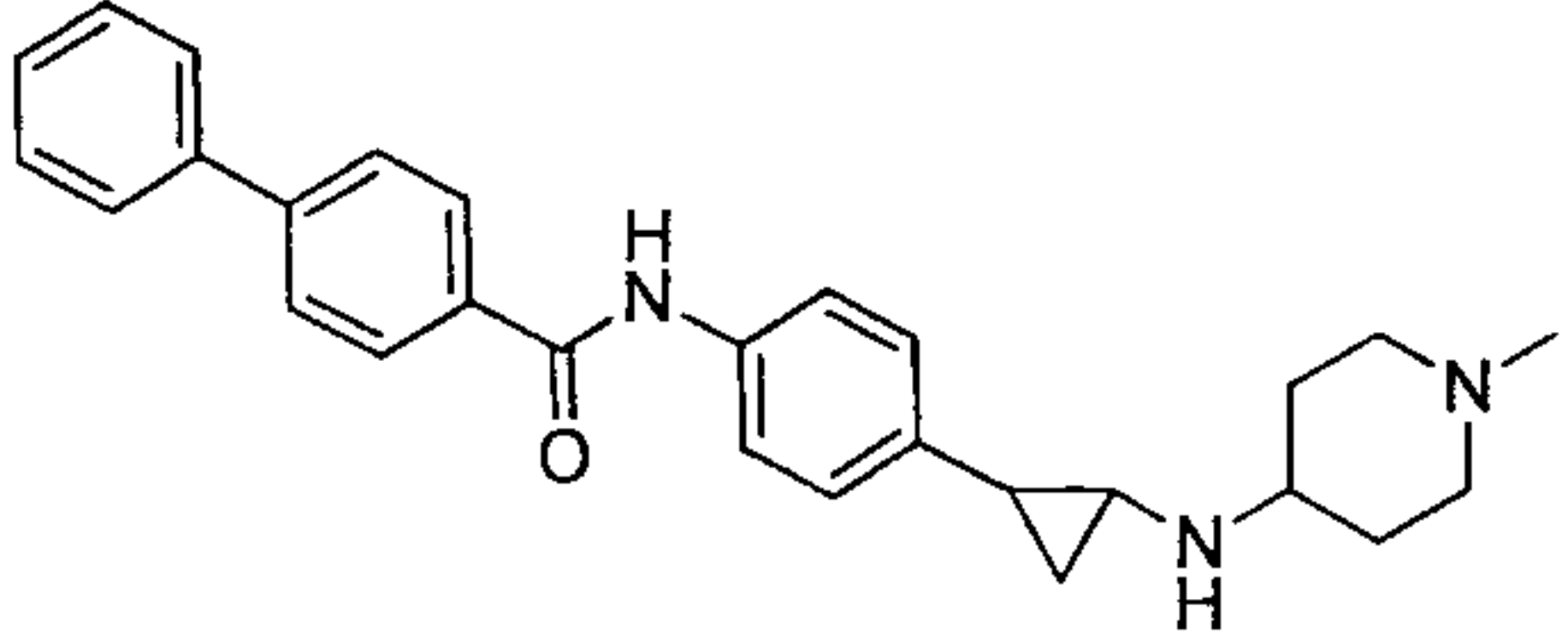
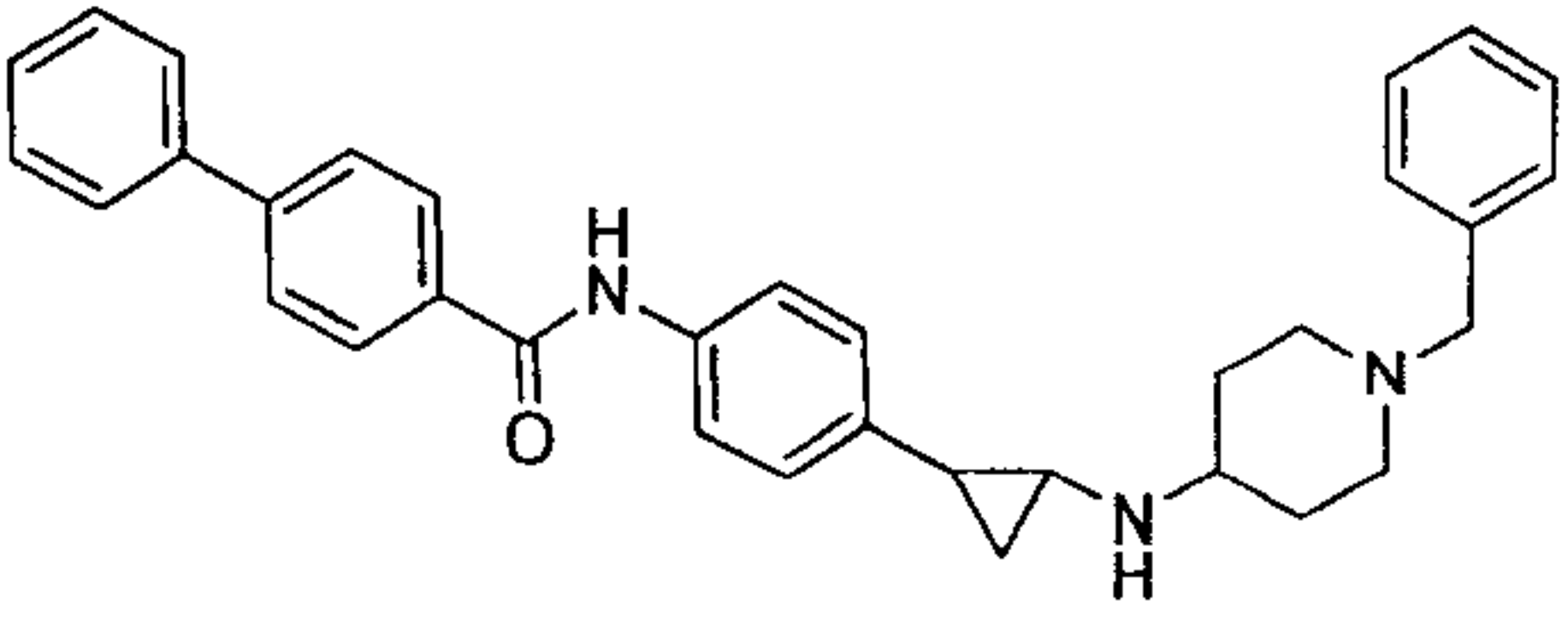
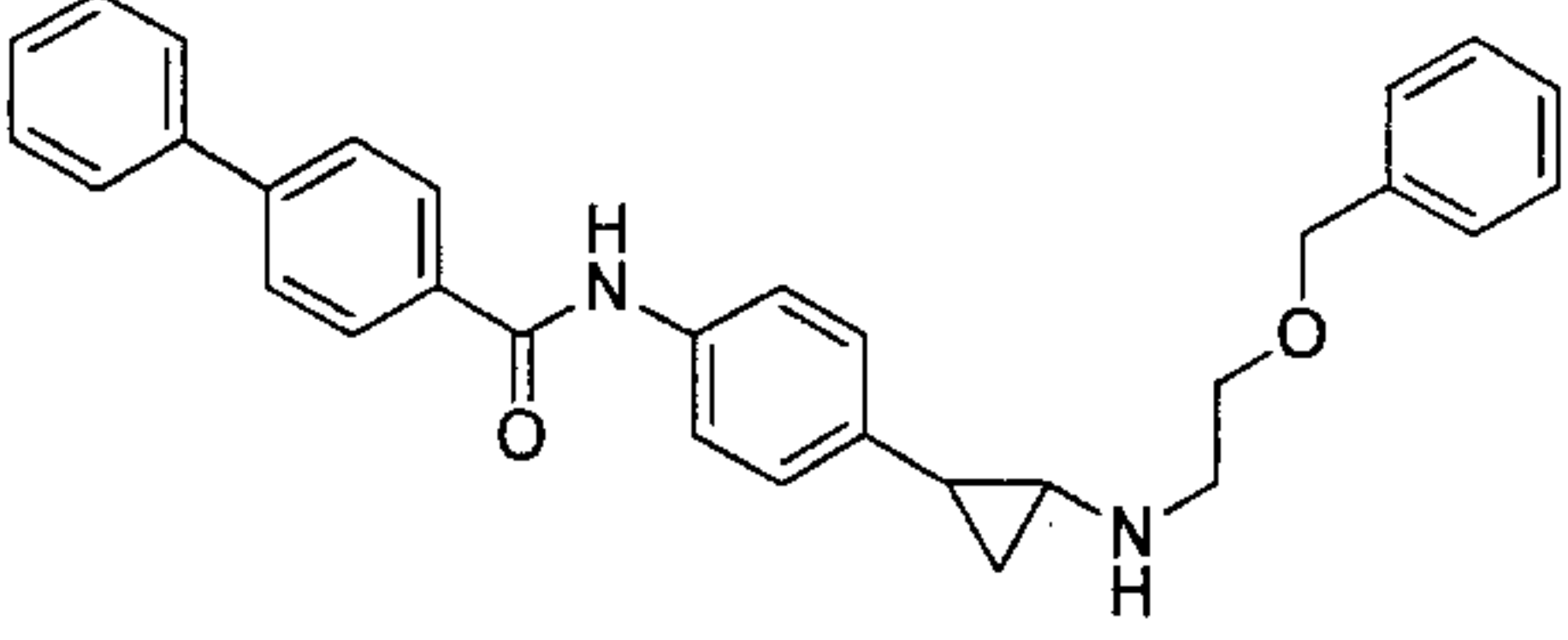
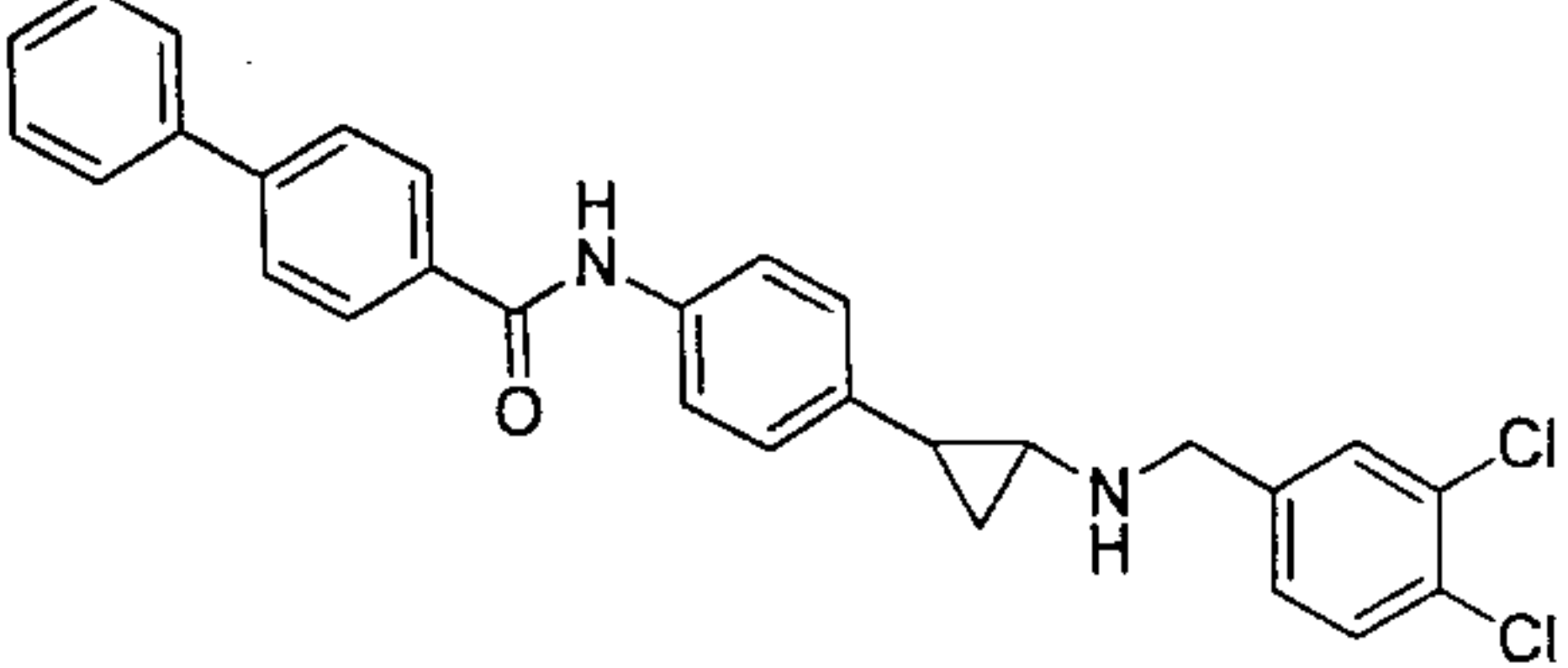
[0341]

[Table 1-3]

Ex. No.	IUPAC name	structure	salt	MS
38	N-(4-{trans-2-[(pyridin-3-ylmethyl)amino]-cyclopropyl}-phenyl)biphenyl-4-carboxamide		2CF ₃ COOH	420.3
39	N-(4-{trans-2-[(pyridin-4-ylmethyl)amino]-cyclopropyl}-phenyl)biphenyl-4-carboxamide		2CF ₃ COOH	420.3
40	N-(4-{trans-2-[(cyclopropylmethyl)amino]-cyclopropyl}-phenyl)biphenyl-4-carboxamide		CF ₃ COOH	383.3
41	N-(4-{trans-2-[(3-methoxybenzyl)amino]cyclopropyl}phenyl)biphenyl-4-carboxamide		CF ₃ COOH	449.3
42	N-(4-{trans-2-[(1,3-benzodioxol-5-ylmethyl)amino]-cyclopropyl}-phenyl)biphenyl-4-carboxamide		CF ₃ COOH	463.3
43	N-(4-{trans-2-[(4-methoxybenzyl)amino]cyclopropyl}phenyl)biphenyl-4-carboxamide		CF ₃ COOH	449.3
44	N-(4-{trans-2-[(2-aminoethyl)amino]cyclopropyl}phenyl)biphenyl-4-carboxamide		2CF ₃ COOH	372.3
45	N-{4-[trans-2-(cyclooctylamino)cyclopropyl]phenyl}biphenyl-4-carboxamide		CF ₃ COOH	439.3

[0342]

[Table 1-4]

Ex. No.	IUPAC name	structure	salt	MS
46	N-(4-{trans-2-[(3,4-dimethoxybenzyl)amino]cyclopropyl}phenyl)-biphenyl-4-carboxamide		CF ₃ COOH	479.3
47	N-(4-{trans-2-[(1-phenylethyl)amino]cyclopropyl}phenyl)-biphenyl-4-carboxamide		CF ₃ COOH	433.3
48	N-(4-{trans-2-[(2-methoxy-1-methylethyl)amino]cyclopropyl}phenyl)-biphenyl-4-carboxamide		CF ₃ COOH	401.3
49	N-(4-{trans-2-[(1-ethylpropyl)amino]cyclopropyl}phenyl)-biphenyl-4-carboxamide		CF ₃ COOH	399.3
50	N-(4-{trans-2-[(1-methylpiperidin-4-yl)amino]cyclopropyl}phenyl)-biphenyl-4-carboxamide		2CF ₃ COOH	426.4
51	N-(4-{trans-2-[(1-benzylpiperidin-4-yl)amino]cyclopropyl}phenyl)-biphenyl-4-carboxamide		2CF ₃ COOH	502.4
52	N-{4-[trans-2-{[2-(benzyloxy)ethyl]amino}cyclopropyl]phenyl}biphenyl-4-carboxamide		CF ₃ COOH	463.3
53	N-(4-{trans-2-[(3,4-dichlorobenzyl)amino]cyclopropyl}phenyl)-biphenyl-4-carboxamide		CF ₃ COOH	487.3

[0343]

[Table 1-5]

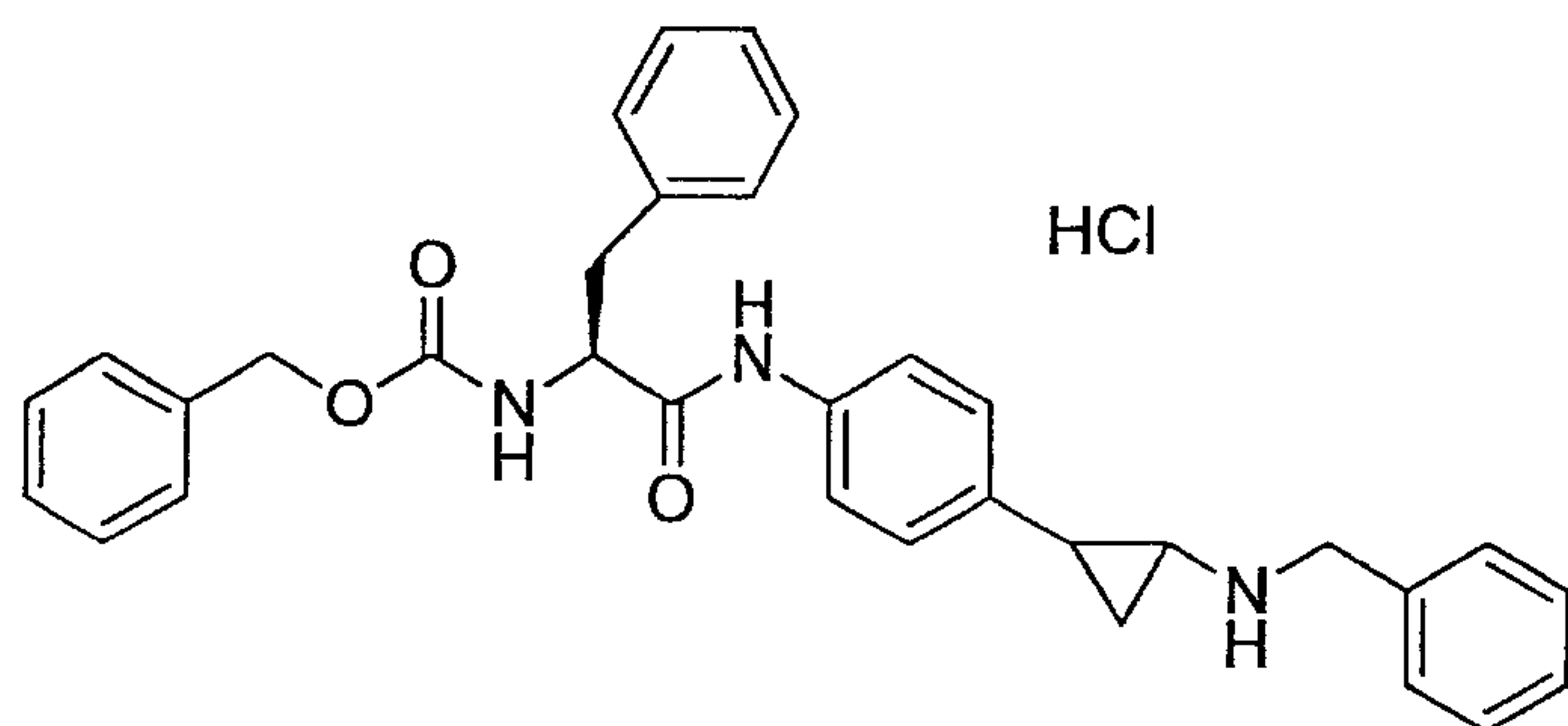
Ex. No.	IUPAC name	structure	salt	MS
54	N-{4-[trans-2-{{(6-methoxypyridin-3-yl)methyl}amino}-cyclopropyl]-phenyl}biphenyl-4-carboxamide		2CF ₃ COOH	450.3
55	allyl 4-{{trans-2-{{4-[(biphenyl-4-yl-carbonyl)amino]-phenyl}cyclopropyl}amino}-piperidine-1-carboxylate		CF ₃ COOH	496.4
56	N-(4-{trans-2-[(1-methyl-2-phenoxyethyl)-amino]cyclopropyl}phenyl)-biphenyl-4-carboxamide		CF ₃ COOH	463.3

[0344]

5 Example 57

N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-N α -[(benzyloxy)carbonyl]-L-phenylalaninamide hydrochloride

[0345]



10 [0346]

To a mixture of N-[4-(trans-2-aminocyclopropyl)phenyl]-N α -[(benzyloxy)carbonyl]-L-phenylalaninamide hydrochloride (100 mg) described in a document (J. Am. Chem. Soc. 2010, 132, 6827.), sodium hydrogen carbonate (27.0 mg), and methanol (2.00 mL) was added benzaldehyde (0.022 mL), and the mixture was

stirred at 70°C for 1 hr. The reaction mixture was cooled in an ice bath, sodium borohydride (12.2 mg) was added and the mixture was stirred at 0°C for 1.5 hr. The reaction mixture was diluted with dehydrated THF (4.00 mL), and cooled in an ice bath, and sodium borohydride (8.12 mg) was added. The ice bath was removed, and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with methanol (2.00 mL) and dehydrated THF (2.00 mL), and cooled in an ice bath, sodium borohydride (8.12 mg) was added, and the mixture was stirred at 0°C for 3 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate, and the mixture was concentrated under reduced pressure. To the residue was added water, and the mixture was extracted twice with ethyl acetate. The organic layers were combined, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate), and the fractions containing the object product were combined and concentrated. The residue was dissolved in methanol (5.00 mL), 10% hydrochloric acid methanol solution (1.00 mL) was added, and the mixture was concentrated under reduced pressure to give the title compound (82.3 mg).

MS (API+): $[M+H]^+$ 520.4.

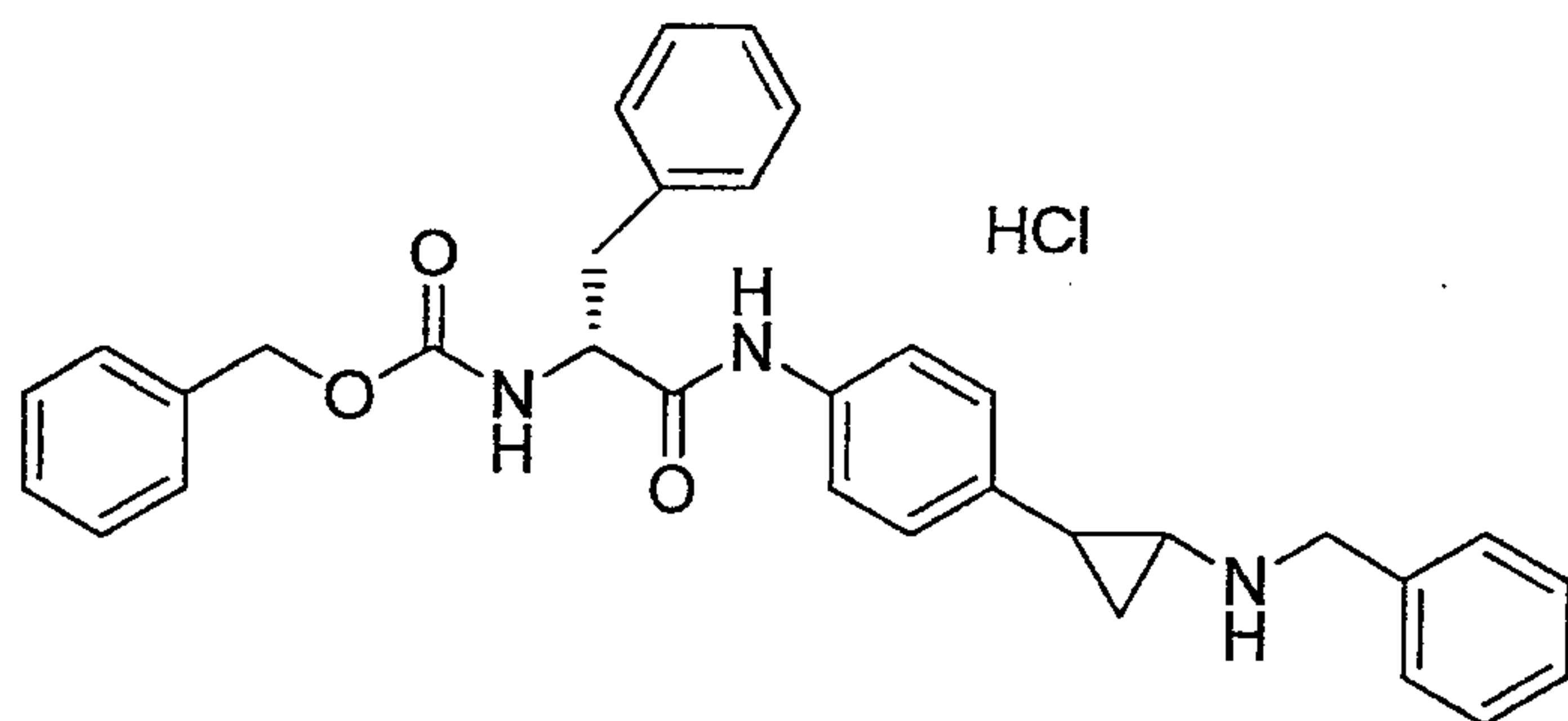
^1H NMR (300 MHz, CD_3OD) δ 1.25-1.41 (1H, m), 1.49 (1H, ddd, $J = 10.5, 6.6, 4.4$ Hz), 2.42 (1H, ddd, $J = 10.2, 6.6, 3.5$ Hz), 2.89-3.03 (2H, m), 3.03-3.19 (1H, m), 4.37 (2H, s), 4.48 (1H, t, $J = 7.5$ Hz), 4.97-5.12 (2H, m), 7.05 (2H, d, $J = 8.5$ Hz), 7.14-7.35 (10H, m), 7.35-7.54 (7H, m).

[0347]

30 Example 58

N-{4-[trans-2-(benzylamino)cyclopropyl]phenyl}-N α -[(benzyloxy)carbonyl]-D-phenylalaninamide hydrochloride

[0348]



[0349]

To a mixture of N-[4-(trans-2-aminocyclopropyl)phenyl]-N α -[(benzyloxy)carbonyl]-D-phenylalaninamide hydrochloride (100 mg) described in a document (J. Am. Chem. Soc. 2010, 132, 6827.), sodium hydrogen carbonate (27.0 mg), and methanol (4.00 mL) was added benzaldehyde (0.022 mL), and the mixture was stirred at 70°C for 1 hr. The reaction mixture was diluted with dehydrated THF (6.00 mL), and cooled in an ice bath.

10 Sodium borohydride (24.4 mg) was added and the mixture was stirred at 0°C for 2 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate, and the mixture was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted twice with ethyl

15 acetate. The organic layers were combined, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate), and the fractions containing the object product were combined and

20 concentrated. The residue was dissolved in methanol (5.00 mL), 10% hydrochloric acid methanol solution (1.00 mL) was added, and the mixture was concentrated under reduced pressure to give the title compound (84.6 mg).

MS (API+): [M+H]⁺ 520.4.

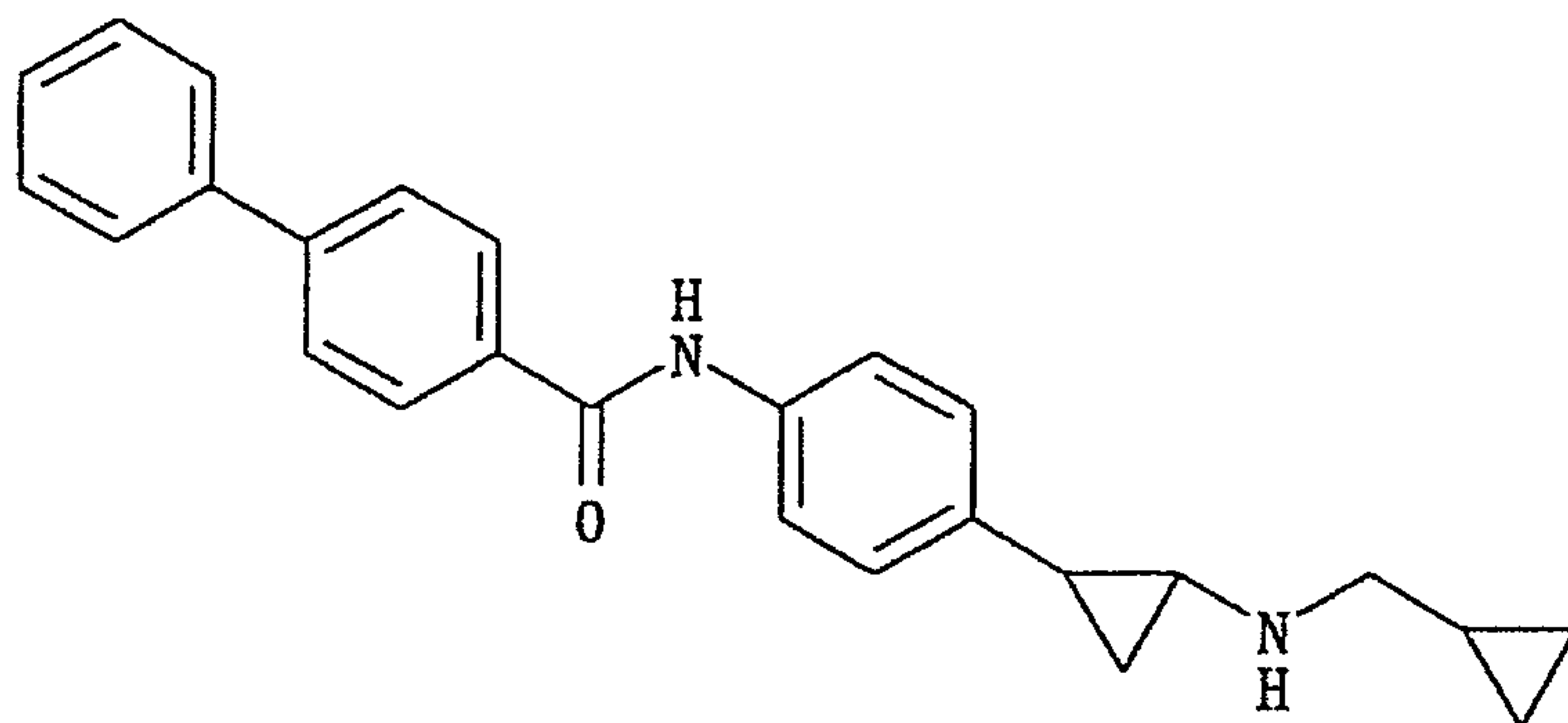
25 ¹H NMR (300 MHz, CD₃OD) δ 1.25-1.41 (1H, m), 1.42-1.55 (1H, m), 2.35-2.48 (1H, m), 2.88-3.03 (2H, m), 3.03-3.20 (1H, m), 4.37 (2H, s), 4.47 (1H, t, J = 7.4 Hz), 4.96-5.13 (2H, m), 7.05 (2H, d, J = 8.5 Hz), 7.15-7.36 (10H, m), 7.36-7.53 (7H, m).

[0350]

In the following Examples, description of salts (e.g., HCl, 2HCl, TFA, 2TFA) in the structural formulas is omitted.

Example 59

N-(4-{trans-2-
5 [(cyclopropylmethyl)amino]cyclopropyl}phenyl)biphenyl-4-carboxamide hydrochloride
[0351]



[0352]

10 A solution of N-[4-(trans-2-aminocyclopropyl)phenyl]biphenyl-4-carboxamide hydrochloride (2.2 g) in methanol (75 mL)/THF (75 mL) was ice-cooled, and cyclopropanecarbaldehyde (549 mg) and sodium hydrogen carbonate (1.01 g) were added. The mixture was stirred at 60°C for 1 hr,
15 and ice-cooled to 0°C and sodium borohydride (456 mg) was added. The mixture was stirred for 1 hr, and saturated aqueous sodium hydrogen carbonate solution was added. The mixture was extracted with ethyl acetate, and the extract was washed with saturated brine and dried over anhydrous sodium sulfate. The
20 solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate, ethyl acetate/methanol). 10% Hydrochloric acid methanol solution was added and the solvent was evaporated under reduced pressure. The residue was recrystallized from
25 methanol/diisopropyl ether to give the title compound (1.62 g).
MS (API+): [M+H]⁺ 383.1.

¹H NMR (300 MHz, CD₃OD) δ 0.38-0.48 (2H, m), 0.69-0.78 (2H, m), 1.06-1.21 (1H, m), 1.35-1.55 (2H, m), 2.47 (1H, ddd, J = 10.1,

6.5, 3.5 Hz), 2.96-3.04 (1H, m), 3.09 (2H, dd, $J = 7.5, 2.1$ Hz), 7.21 (2H, d, $J = 8.7$ Hz), 7.36-7.44 (1H, m), 7.45-7.53 (2H, m), 7.65-7.73 (4H, m), 7.78 (2H, d, $J = 8.5$ Hz), 8.02 (2H, d, $J = 8.7$ Hz).

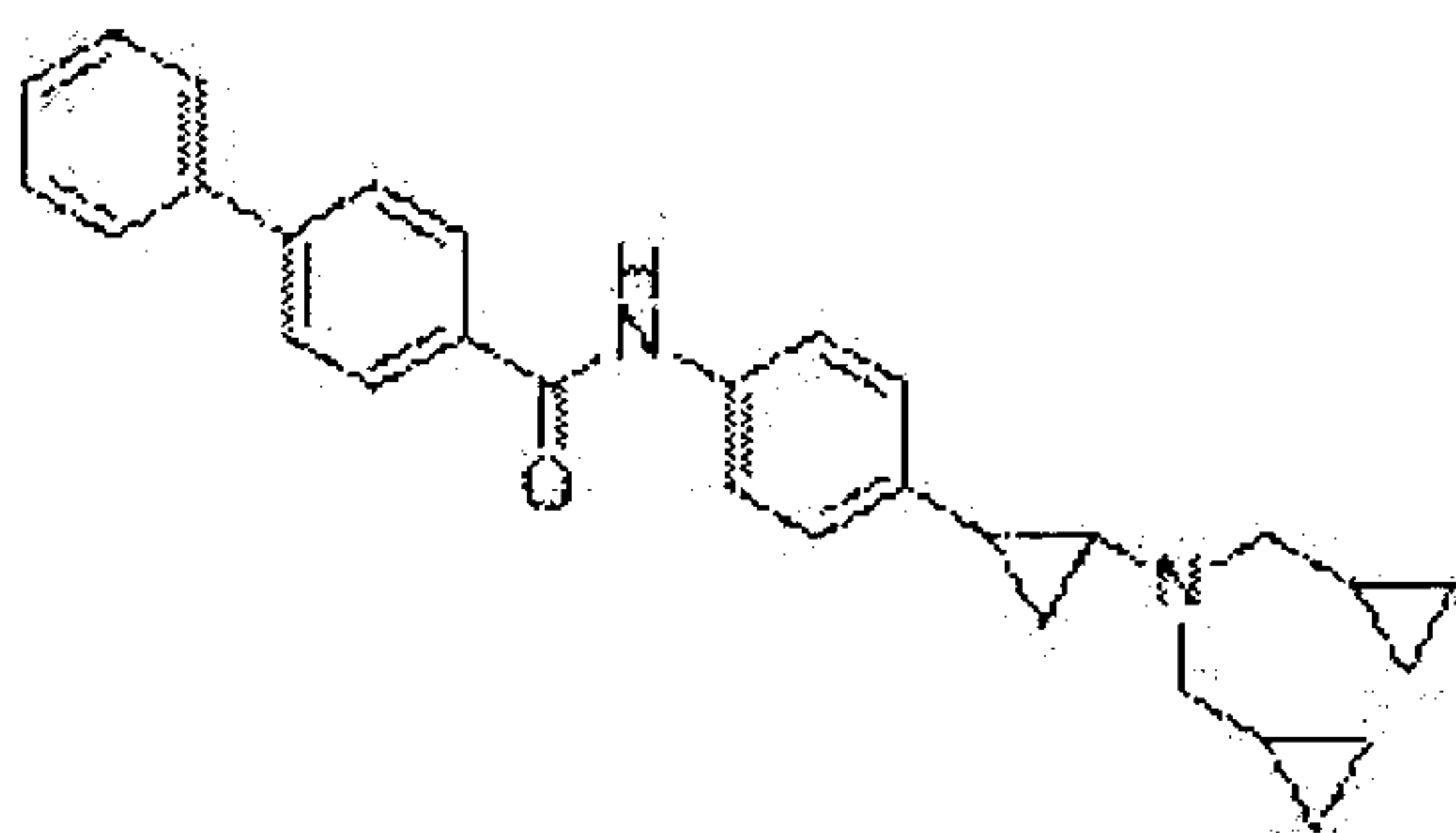
5 [0353]

Example 60

N-(4-{trans-2-

[bis(cyclopropylmethyl)amino]cyclopropyl}phenyl)biphenyl-4-carboxamide hydrochloride

10 [0354]



[0355]

To a solution of N-[4-(trans-2-aminocyclopropyl)phenyl]biphenyl-4-carboxamide hydrochloride
 15 (100 mg) in methanol (5.4 mL) were added acetic acid (0.6 mL), cyclopropanecarbaldehyde (0.023 mL) and 2-picoline-borane complex (44 mg). The mixture was stirred at room temperature for 21 hr, and DMF (4 mL) and 2-picoline-borane complex (29.3 mg) were added. The mixture was stirred at room temperature
 20 for 2 hr, and cyclopropanecarbaldehyde (0.010 mL) was added. The mixture was stirred at room temperature for 3 hr, and cyclopropanecarbaldehyde (0.008 mL) was added. The mixture was stirred at room temperature for 1 hr, water and ethyl acetate were added, and the mixture was concentrated under reduced
 25 pressure. To the residue was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted twice with ethyl acetate. The extracts were combined, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure.
 30 The residue was purified by silica gel column chromatography

(hexane/ethyl acetate), and 10% hydrochloric acid methanol solution (1.0 mL) was added to the obtained product. The solvent was evaporated under reduced pressure to give the title compound (26.1 mg).

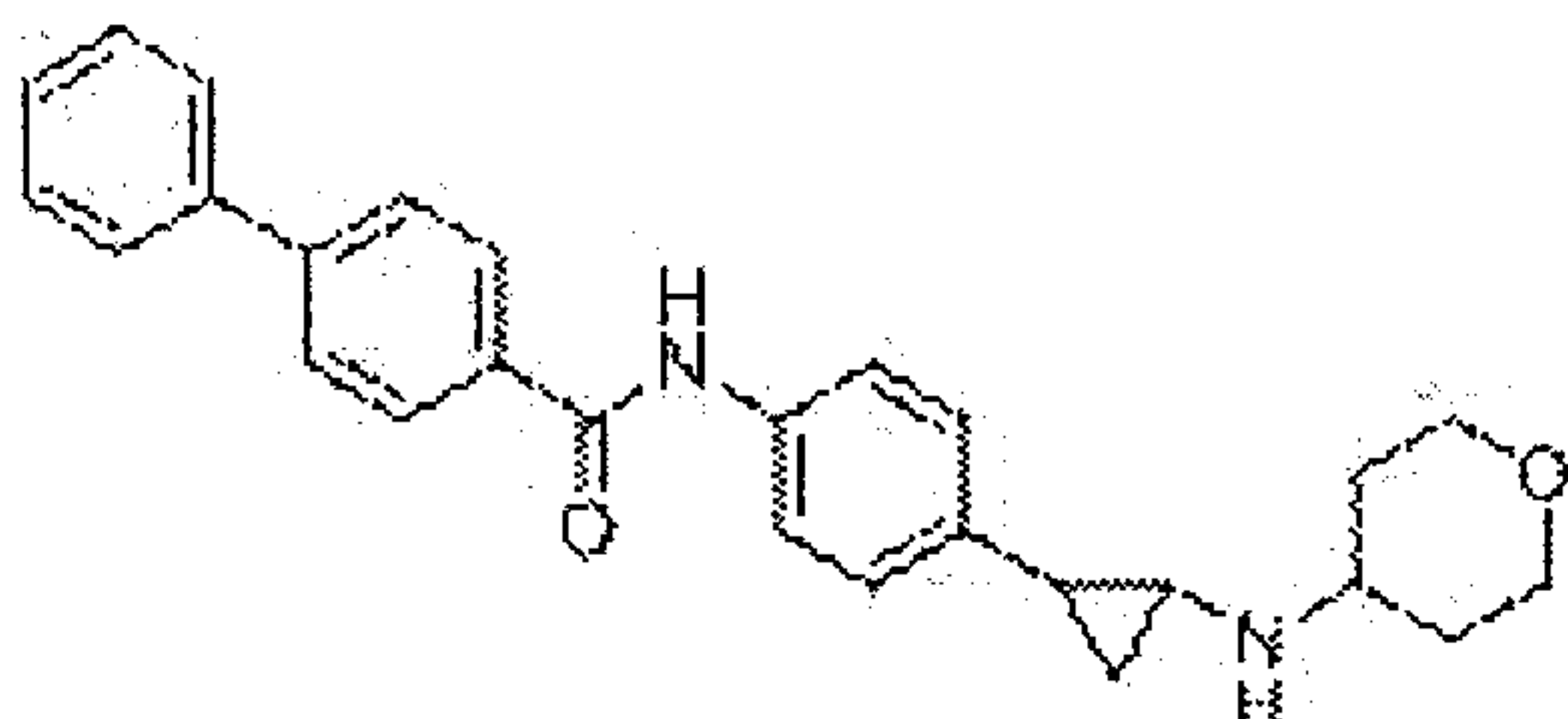
5 MS (API+): $[M+H]^+$ 437.3.

^1H NMR (300 MHz, CD_3OD) δ 0.27-0.61 (4H, m), 0.61-0.96 (4H, m), 1.03-1.39 (2H, m), 1.52 (1H, brs), 1.77 (1H, brs), 2.71 (2H, s), 3.11-3.55 (4H, m), 7.20 (2H, d, $J = 7.6$ Hz), 7.34-7.55 (3H, m), 7.63-7.84 (6H, m), 8.03 (2H, d, $J = 8.1$ Hz).

10 [0356]

Example 61

N-{4-[trans-2-(tetrahydro-2H-pyran-4-ylamino)cyclopropyl]phenyl}biphenyl-4-carboxamide hydrochloride
[0357]



15

[0358]

By a method similar to Example 59, the title compound (39 mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]biphenyl-4-carboxamide hydrochloride
20 (120 mg) and tetrahydro-4H-pyran-4-one (32.9 mg).

MS (API+): $[M+H]^+$ 413.4.

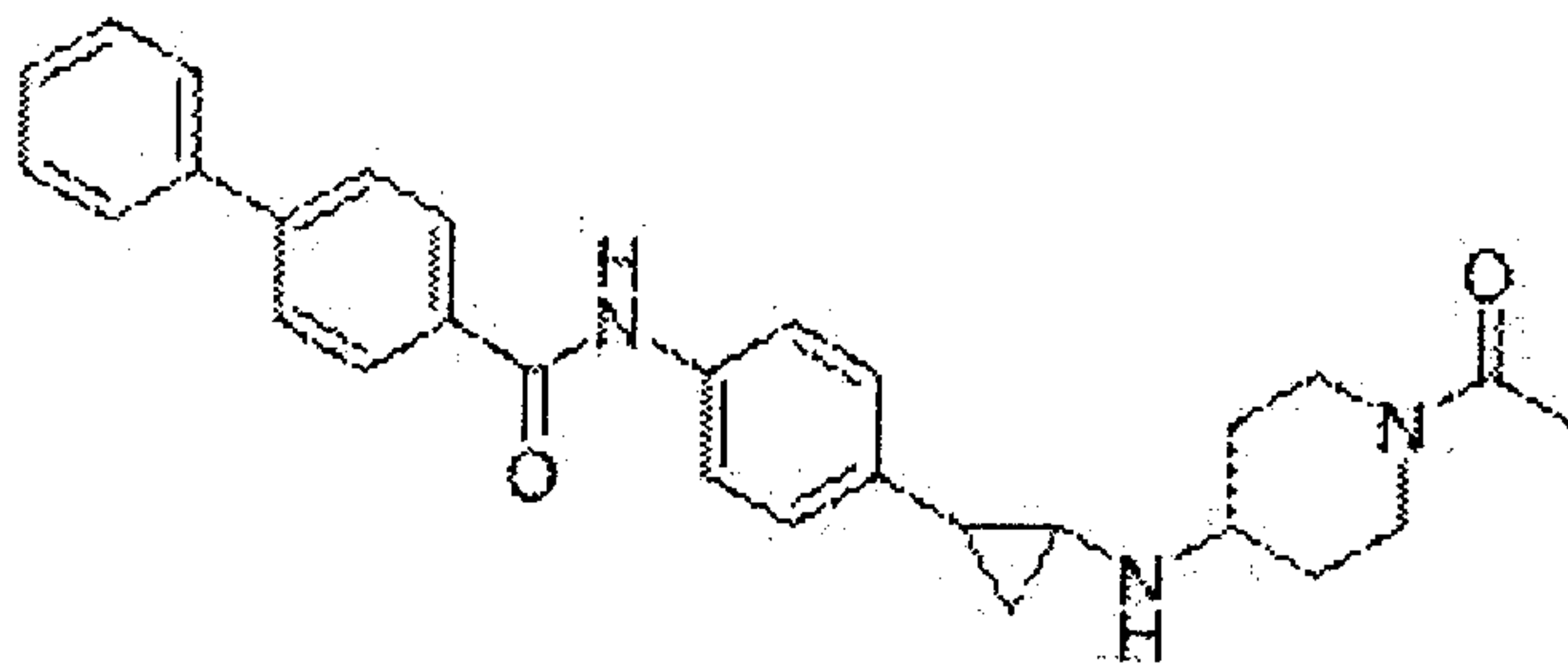
^1H NMR (300 MHz, CD_3OD) δ 1.37-1.58 (2H, m), 1.64-1.83 (2H, m), 2.10 (2H, d, $J = 11.6$ Hz), 2.42-2.57 (1H, m), 2.93-3.05 (1H, m), 3.41-3.67 (3H, m), 4.04 (2H, d, $J = 8.1$ Hz), 7.21 (2H, d, $J =$
25 8.0 Hz), 7.34-7.55 (3H, m), 7.65-7.82 (6H, m), 8.01 (2H, d, $J =$
8.1 Hz).

[0359]

Example 62

N-(4-{trans-2-[(1-acetylpiperidin-4-yl)amino]cyclopropyl}phenyl)biphenyl-4-carboxamide
30 hydrochloride

[0360]



[0361]

By a method similar to Example 59, the title compound (31
5 mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]biphenyl-4-carboxamide hydrochloride (120 mg) and 1-acetylpiperidin-4-one (46.4 mg).

MS (API+): $[M+H]^+$ 454.3.

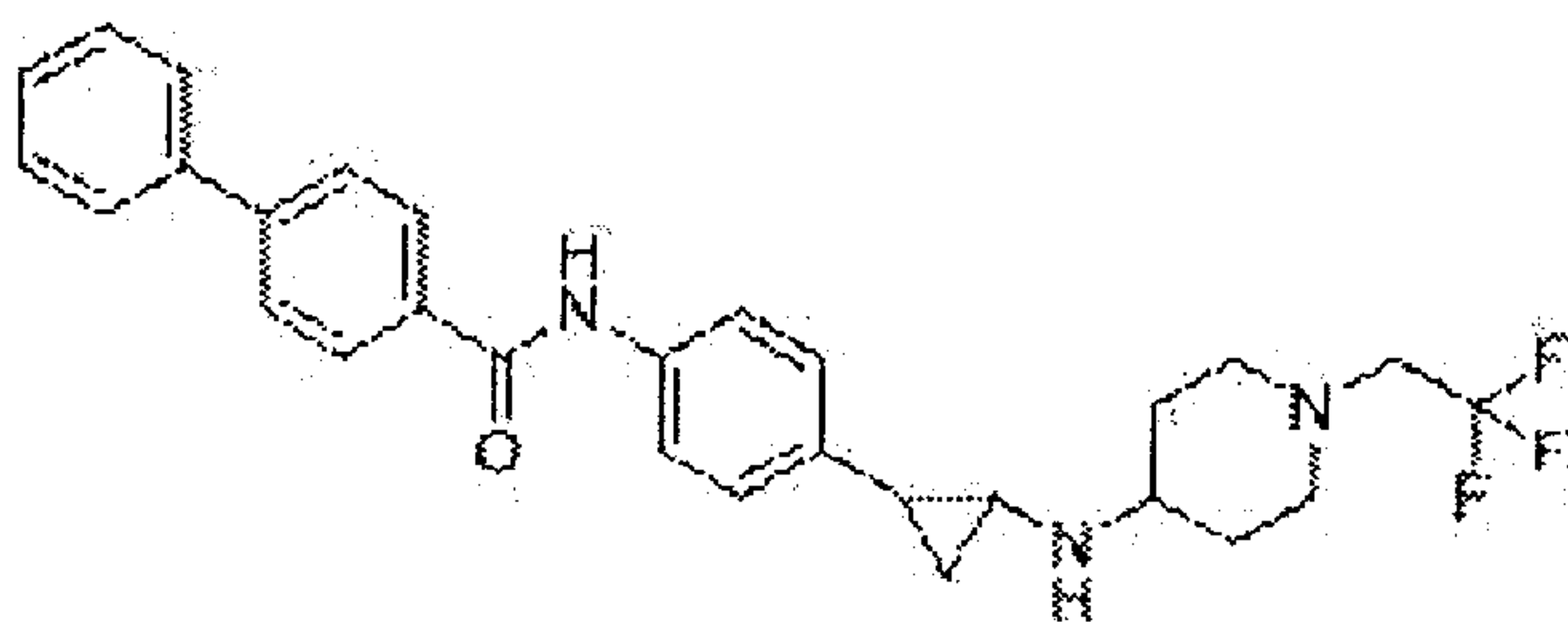
^1H NMR (300MHz, CD_3OD) δ 1.06-1.88 (5H, m), 2.03-2.43 (5H, m),
10 2.51-3.16 (3H, m), 3.50-3.87 (1H, m), 3.97-4.25 (1H, m), 4.49-4.78 (1H, m), 7.19-7.53 (5H, m), 7.66-7.81 (6H, m), 8.03 (2H, d, $J = 7.4$ Hz).

[0362]

Example 63

15 N-{4-[trans-2-{[1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino}cyclopropyl]phenyl}biphenyl-4-carboxamide hydrochloride

[0363]



20 [0364]

By a method similar to Example 59, the title compound (23
mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]biphenyl-4-carboxamide hydrochloride (164 mg) and 1-(2,2,2-trifluoroethyl)piperidin-4-one (91 mg).

25 MS (API+): $[M+H]^+$ 494.3

^1H NMR (300MHz, CD_3OD) δ 1.43-1.60 (2H, m), 1.82-1.98 (2H, m),
2.20-2.32 (2H, m), 2.45-2.57 (1H, m), 2.69-2.85 (3H, m), 2.98-

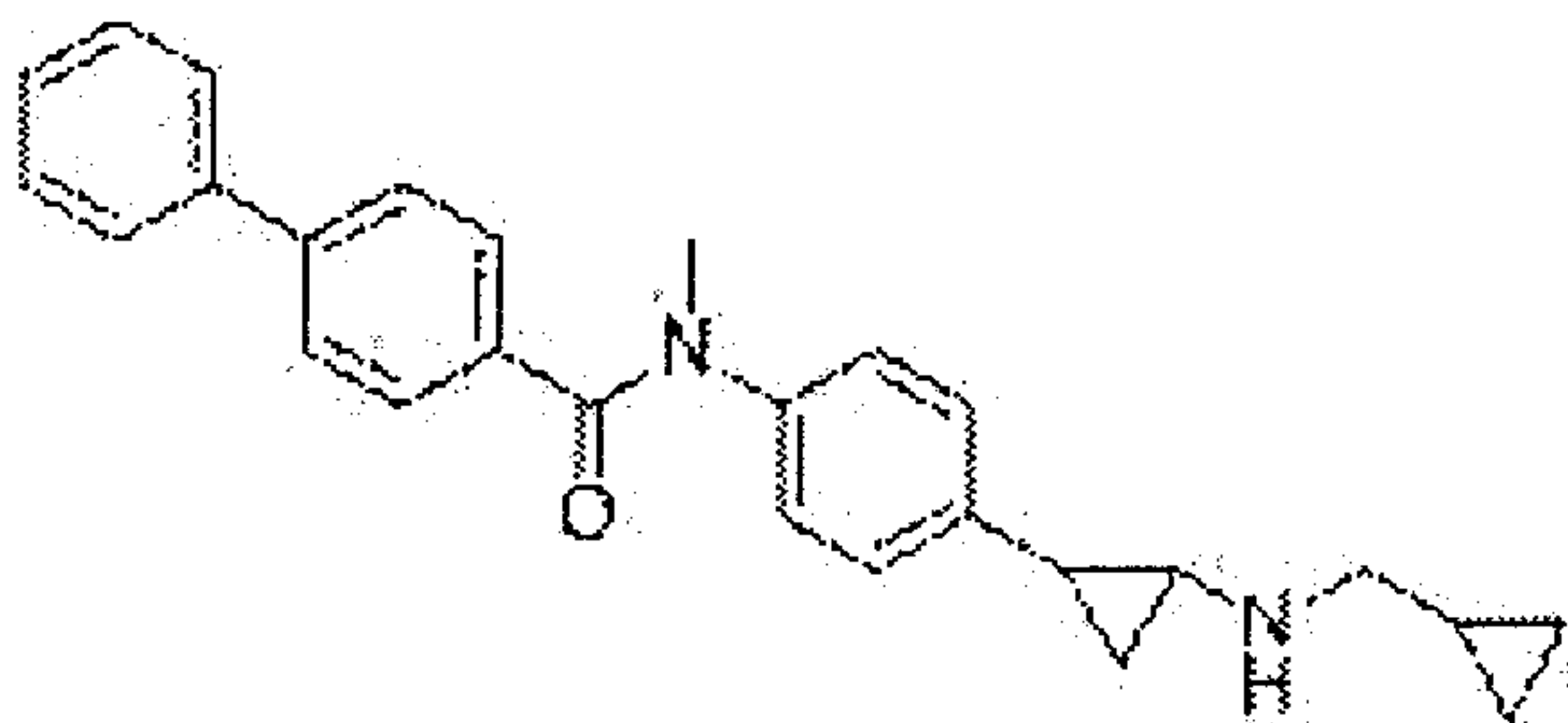
3.06 (1H, m), 3.36-3.75 (4H, m), 7.23 (2H, d, $J = 8.6$ Hz),
7.39-7.44 (1H, m), 7.47-7.53 (2H, m), 7.68-7.73 (4H, m), 7.79
(2H, d, $J = 8.7$ Hz), 8.01-8.06 (2H, m).

[0365]

5 Example 64

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-N-methylbiphenyl-4-carboxamide hydrochloride

[0366]



10 [0367]

A) tert-butyl (trans-2-{4-[(biphenyl-4-ylcarbonyl) (methyl)amino]phenyl}cyclopropyl) (cyclopropylmethyl) carbamate

To a solution of N-(4-{trans-2-
15 [(cyclopropylmethyl)amino]cyclopropyl}phenyl)biphenyl-4-carboxamide hydrochloride (90 mg) and triethylamine (43.5 mg) in THF (2 mL) was added di-tert-butyl dicarbonate (60.9 mg) under ice-cooling. The mixture was stirred at room temperature overnight and water was added. The mixture was extracted with
20 ethyl acetate, and the extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in DMF (2.5 mL), sodium hydride (12.9 mg) was added under ice-cooling, and the mixture was stirred for 1 hr. To the reaction
25 mixture was added methyl iodide (52.9 mg) under ice-cooling, and the mixture was stirred at room temperature overnight, and poured into saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted with ethyl acetate, and the extract was washed with saturated brine, and dried over
30 anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel

column chromatography (hexane/ethyl acetate) to give the title compound (105 mg).

MS (API+): $[M-tBu+2H]^+$ 441.3.

[0368]

- 5 B) N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-N-methylbiphenyl-4-carboxamide hydrochloride

To a solution of tert-butyl (trans-2-{4-[(biphenyl-4-ylcarbonyl) (methyl)amino]phenyl}cyclopropyl) (cyclopropylmethyl) carbamate (248 mg) in THF (5 mL) was added 10% hydrochloric
10 acid methanol (20 mL) under ice-cooling, and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure. The residue was recrystallized from methanol/diisopropyl ether to give the title compound (62 mg).

15 MS (API+): $[M+H]^+$ 397.3.

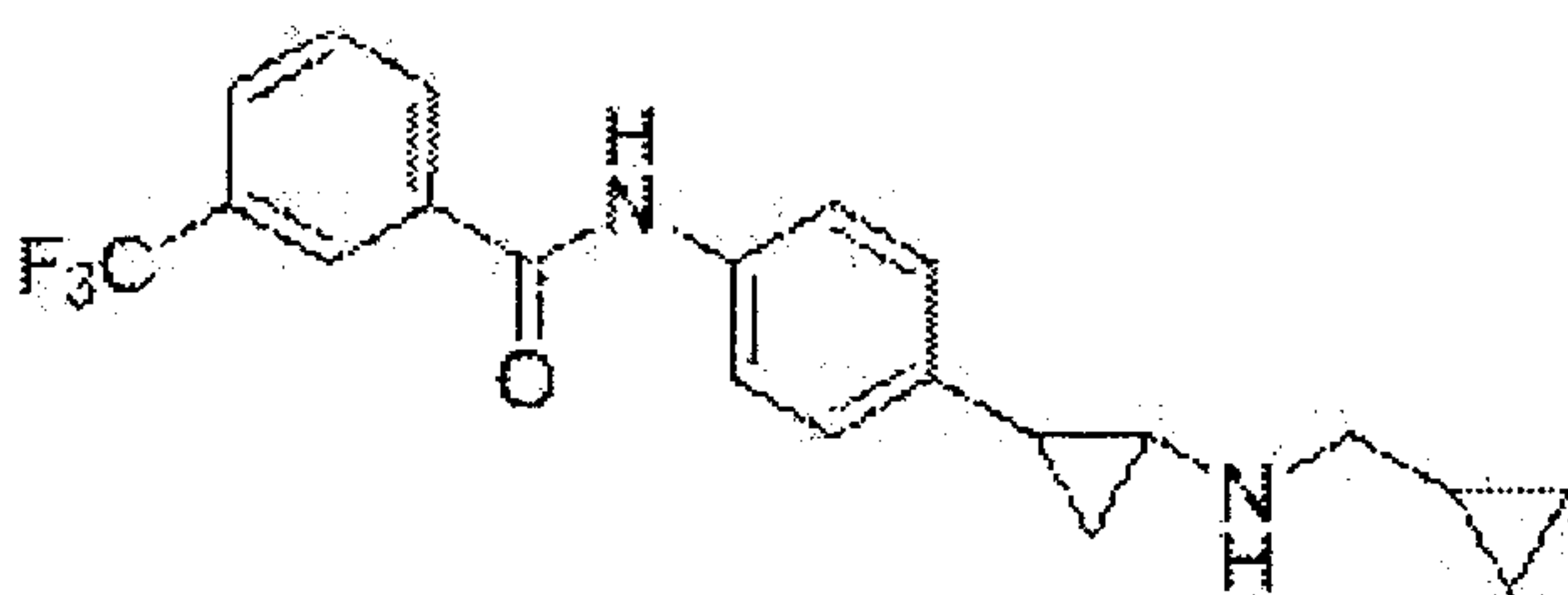
^1H NMR (300 MHz, CD_3OD) δ 0.19-0.29 (2H, m), 0.50-0.61 (2H, m), 0.87-1.02 (1H, m), 1.16-1.30 (1H, m), 1.31-1.43 (1H, m), 2.30 (1H, ddd, $J = 10.2, 6.5, 3.7$ Hz), 2.82 (1H, dt, $J = 7.8, 4.0$ Hz), 2.90 (2H, d, $J = 7.5$ Hz), 3.37 (3H, s), 6.97-7.08 (4H, m),
20 7.19-7.41 (7H, m), 7.42-7.48 (2H, m).

[0369]

Example 65

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide hydrochloride

25 [0370]



[0371]

To a solution of N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (150 mg) in methanol
30 (10 mL)/THF (10 mL) were added cyclopropanecarbaldehyde (38.3 mg) and sodium hydrogen carbonate (70.6 mg). The mixture was

stirred at 60°C for 1 hr, and ice-cooled to 0°C and sodium borohydride (31.8 mg) was added. The mixture was stirred at room temperature for 2 hr, and ice-cooled to 0°C, and aqueous sodium hydrogen carbonate solution was added. The mixture was
 5 extracted with ethyl acetate, and the extract was washed with water 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 (ethyl acetate/methanol). To the obtained product was added
 10 10% hydrochloric acid methanol solution, and the solvent was evaporated under reduced pressure. The residue was recrystallized from methanol/diisopropyl ether to give the title compound (79 mg).

MS (API+): $[M+H]^+$ 375.2.

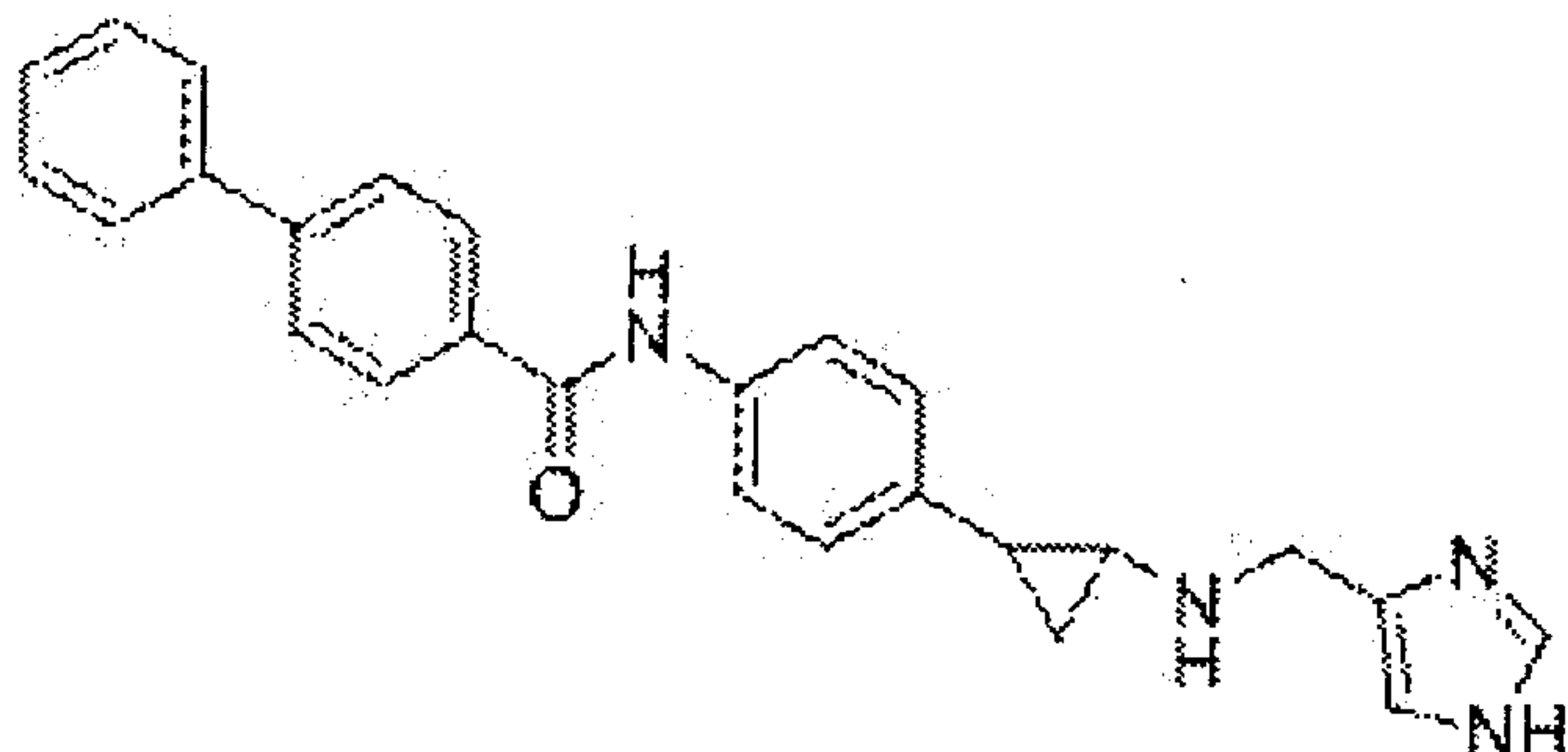
15 ^1H NMR (300MHz, CD_3OD) δ 0.42 (2H, m), 0.68-0.78 (2H, m), 1.05-1.18 (1H, m), 1.34-1.54 (2H, m), 2.46 (1H, ddd, $J = 10.2, 6.5, 3.3$ Hz), 2.98 (1H, m), 3.08 (2H, dd, $J = 7.5, 2.1$ Hz), 7.20 (2H, d, $J = 8.5$ Hz), 7.63-7.77 (3H, m), 7.89 (1H, d, $J = 7.7$ Hz), 8.13-8.28 (2H, m).

20 [0372]

Example 66

N-(4-{trans-2-[(1H-imidazol-4-ylmethyl)amino]cyclopropyl}phenyl)biphenyl-4-carboxamide dihydrochloride

25 [0373]



[0374]

By a method similar to Example 59, the title compound (78 mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]biphenyl-4-carboxamide hydrochloride
 30

(150 mg) and 1H-imidazole-4-carbaldehyde (39.5 mg).

MS (API+): $[M+H]^+$ 409.0.

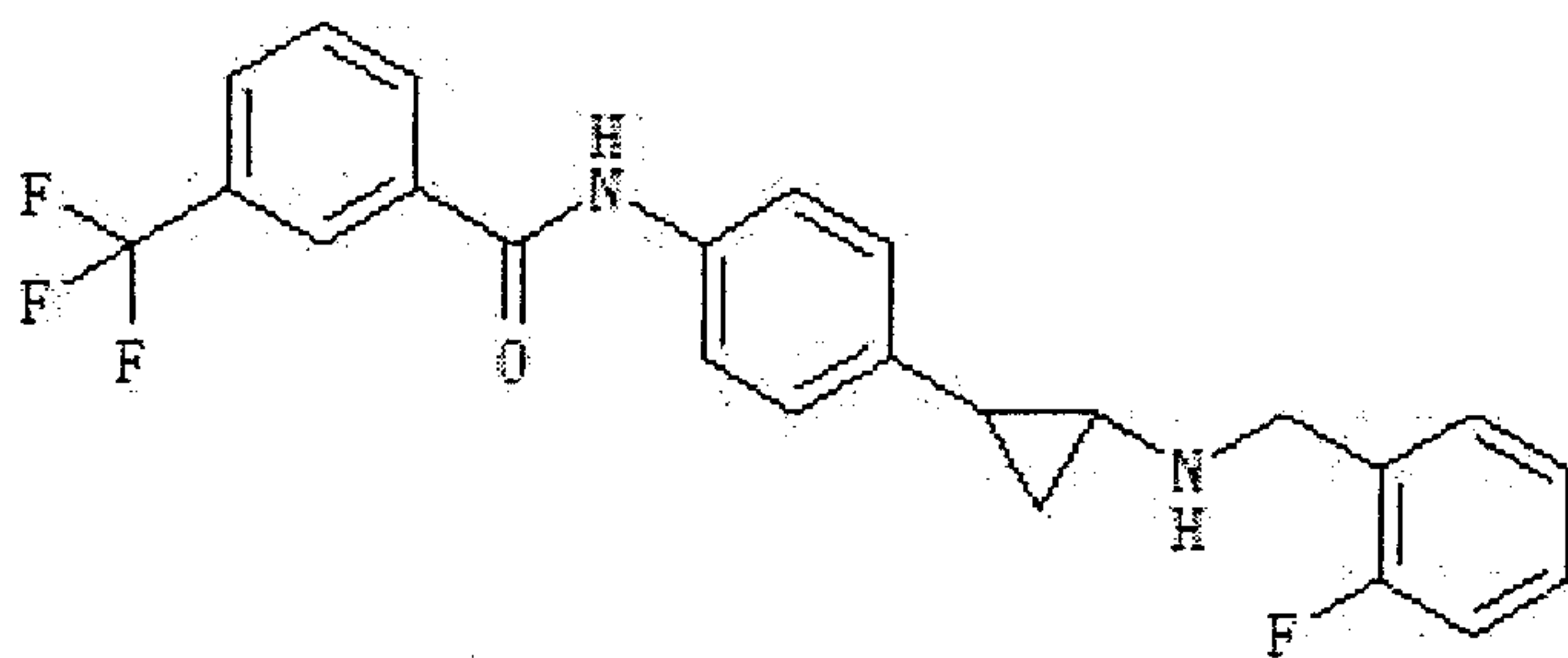
^1H NMR (300MHz, CD_3OD) δ 1.40-1.49 (1H, m), 1.60 (1H, ddd, J = 10.6, 6.7, 4.3 Hz), 2.51-2.61 (1H, m), 3.08 (1H, dq, J = 4.3, 3.2 Hz), 4.61 (2H, d, J = 2.1 Hz), 7.16 (2H, d, J = 8.5 Hz), 7.36-7.43 (1H, m), 7.44-7.52 (2H, m), 7.65-7.73 (4H, m), 7.75-7.82 (3H, m), 8.01 (2H, d, J = 8.5 Hz), 9.02 (1H, d, J = 1.1 Hz).

[0375]

10 Example 67

N-(4-{trans-2-[(2-fluorobenzyl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide hydrochloride

[0376]



15 [0377]

By a method similar to Example 65, the title compound (90 mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (120 mg) and 2-fluorobenzaldehyde (54.3 mg).

20 MS (API+): $[M+H]^+$ 429.0.

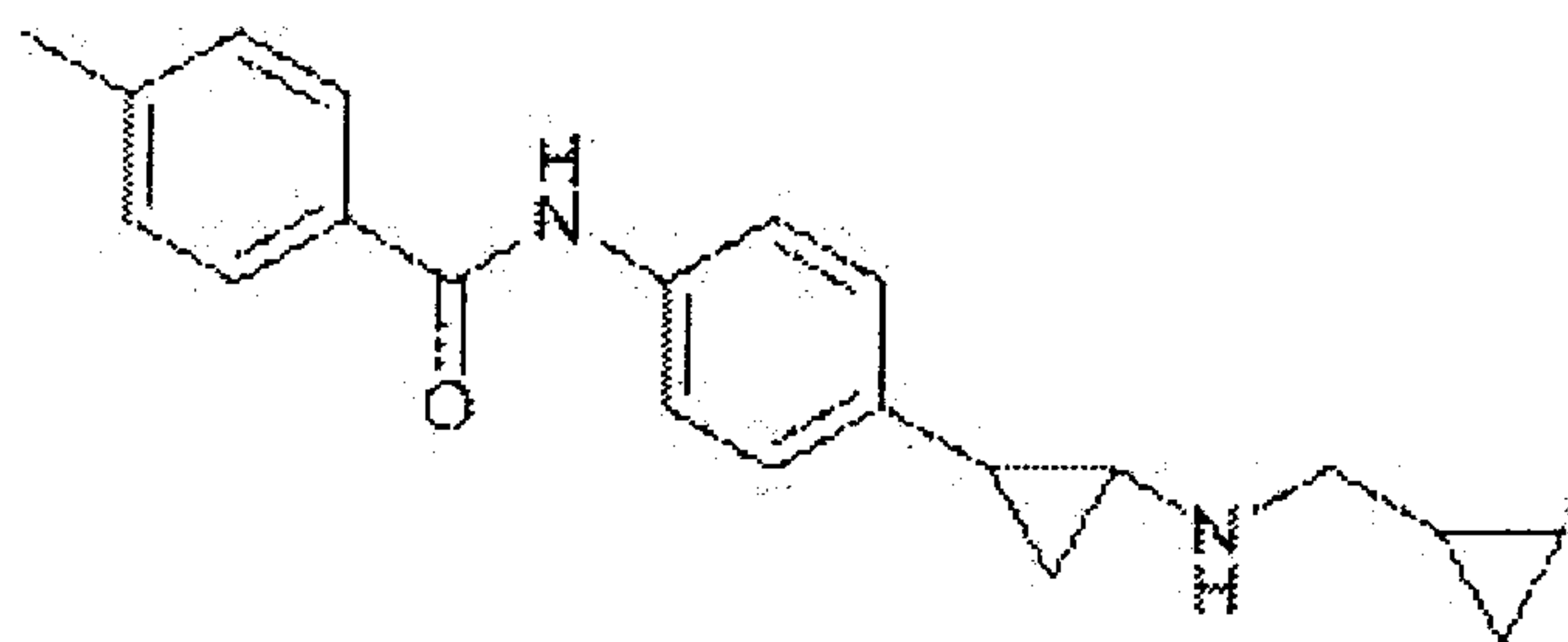
^1H NMR (300MHz, CD_3OD) δ 1.36-1.55 (2H, m), 2.36-2.48 (1H, m), 3.03 (1H, dt, J = 7.5, 3.8 Hz), 4.47 (2H, s), 7.15 (2H, d, J = 7.9 Hz), 7.20-7.34 (2H, m), 7.47-7.60 (2H, m), 7.63-7.80 (3H, m), 7.91 (1H, d, J = 7.9 Hz), 8.16-8.30 (2H, m).

25 [0378]

Example 68

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-4-methylbenzamide hydrochloride

[0379]



[0380]

A) 2,2,2-trichloroethyl (4-{trans-2-[(tert-butoxycarbonyl)amino]cyclopropyl}phenyl)carbamate

5 To a solution of tert-butyl [trans-2-(4-aminophenyl)cyclopropyl]carbamate (16.8 g) described in a document (J. Am. Chem. Soc., 2010, 132, 6827.) and triethylamine (11.32 mL) in THF (338 mL) was added 2,2,2-trichloroethyl chloroformate (11.2 mL). The mixture was
10 stirred at room temperature overnight, and poured into saturated aqueous ammonium chloride solution. The reaction mixture was extracted with ethyl acetate, and the extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure.
15 The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (19.0 g).
¹H NMR (300 MHz, CDCl₃) δ 1.07-1.19 (2H, m), 1.45 (9H, s), 1.95-2.08 (1H, m), 2.68 (1H, brs), 4.81 (3H, brs), 6.84 (1H, brs), 7.11 (2H, d, J = 7.8 Hz), 7.31 (2H, d, J = 7.8 Hz).

20 [0381]

B) 2,2,2-trichloroethyl [4-(trans-2-aminocyclopropyl)phenyl]carbamate hydrochloride

2,2,2-Trichloroethyl (4-{trans-2-[(tert-butoxycarbonyl)amino]cyclopropyl}phenyl)carbamate (19.0 g) was
25 dissolved in 4N hydrochloric acid/cyclopentyl methyl ether solution (188 mL), and the mixture was stirred at room temperature for 3 hr. The solvent was evaporated under reduced pressure to give the title compound (16.2 g).

¹H NMR (300 MHz, DMSO-d₆) δ 1.09-1.22 (1H, m), 1.24-1.37 (1H, m), 2.16-2.30 (1H, m), 2.69-2.81 (1H, m), 4.93 (2H, s), 7.11
30 (2H, d, J = 8.3 Hz), 7.43 (2H, d, J = 8.3 Hz), 8.21 (3H, brs),

10.11 (1H, brs).

[0382]

C) 2,2,2-trichloroethyl (4-{trans-2-[(tert-butoxycarbonyl)(cyclopropylmethyl)amino]cyclopropyl}phenyl)-
5 carbamate

To a solution of 2,2,2-trichloroethyl [4-(trans-2-aminocyclopropyl)phenyl]carbamate hydrochloride (16.2 g) and sodium hydrogen carbonate (7.56 g) in THF (112 mL)/methanol (112 mL) was added cyclopropanecarbaldehyde (4.37 mL). The
10 mixture was stirred at 60°C for 2 hr, and ice-cooled to 0°C and sodium borohydride (3.4 g) was added. The mixture was stirred at room temperature for 1 hr, and di-tert-butyl dicarbonate (14.7 g) was added. The mixture was stirred at room
temperature overnight, and poured into water. The mixture was
15 extracted with ethyl acetate, and the extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (15.9 g).

20 ¹H NMR (300 MHz, DMSO-d₆) δ 0.05-0.15 (1H, m), 0.16-0.27 (1H, m), 0.32-0.51 (2H, m), 0.89-1.04 (1H, m), 1.12-1.25 (2H, m), 1.35 (9H, s), 2.00-2.08 (1H, m), 2.62-2.75 (1H, m), 2.99 (1H, dd, J = 14.2, 6.9 Hz), 3.17 (1H, dd, J = 14.2, 6.9 Hz), 4.93 (2H, s), 7.08 (2H, d, J = 8.7 Hz), 7.40 (2H, d, J = 8.1 Hz),
25 10.06 (1H, brs).

[0383]

D) tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate

To a solution of 2,2,2-trichloroethyl (4-{trans-2-[(tert-butoxycarbonyl)(cyclopropylmethyl)amino]cyclopropyl}phenyl)-
30 carbamate (15.9 g) in THF (166 mL) were added zinc powder (32.6 g) and acetic acid (5 mL). The reaction mixture was stirred at room temperature for 5 hr, 1N aqueous sodium hydroxide solution (100 mL) and ethyl acetate (500 mL) were added, and the mixture
35 was filtered through celite. The organic layer was separated

from the mother liquor, washed successively with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (NH,
 5 hexane/ethyl acetate) to give the title compound (6.83 g).

¹H NMR (300 MHz, DMSO-d₆) δ 0.06-0.16 (1H, m), 0.16-0.26 (1H, m), 0.33-0.48 (2H, m), 0.89-1.12 (3H, m), 1.36 (9H, s), 1.85-1.95 (1H, m), 2.53-2.60 (1H, m), 2.97 (1H, dd, J = 14.2, 6.8 Hz), 3.15 (1H, dd, J = 14.2, 6.8 Hz), 4.83 (2H, s), 6.46 (2H, d,
 10 J = 7.9 Hz), 6.80 (2H, d, J = 7.9 Hz).

[0384]

E) tert-butyl (cyclopropylmethyl)(trans-2-{4-[(4-methylbenzoyl)amino]phenyl}cyclopropyl)carbamate

To a solution of tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (75.0 mg)
 15 and triethylamine (41.5 µL) in THF (1.24 mL) was added 4-toluoyl chloride (39.4 µL). The mixture was stirred at room temperature overnight, and poured into saturated aqueous ammonium chloride solution. The mixture was extracted with
 20 ethyl acetate, and the extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the title compound (104.3 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.06-0.16 (1H, m), 0.18-0.29 (1H, m), 0.34-0.51 (2H, m), 0.91-1.04 (1H, m), 1.11-1.25 (2H, m), 1.36 (9H, s), 2.01-2.11 (1H, m), 2.38 (3H, s), 2.67-2.76 (1H, m), 3.00 (1H, dd, J = 14.3, 7.0 Hz), 3.19 (1H, dd, J = 14.3, 7.1 Hz), 7.11 (2H, d, J = 8.1 Hz), 7.33 (2H, d, J = 7.7 Hz), 7.66 (2H, d, J = 8.2 Hz), 7.86 (2H, d, J = 7.7 Hz), 10.08 (1H,
 30 s).

[0385]

F) N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-4-methylbenzamide hydrochloride

tert-Butyl (cyclopropylmethyl)(trans-2-{4-[(4-methylbenzoyl)amino]phenyl}cyclopropyl)carbamate (104.3 mg) was
 35

dissolved in 4N hydrochloric acid/cyclopentyl methyl ether solution (4 mL), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure. The residue was recrystallized from
 5 methanol/diisopropyl ether to give the title compound (65.0 mg).

MS (API+): $[M+H]^+$ 321.2.

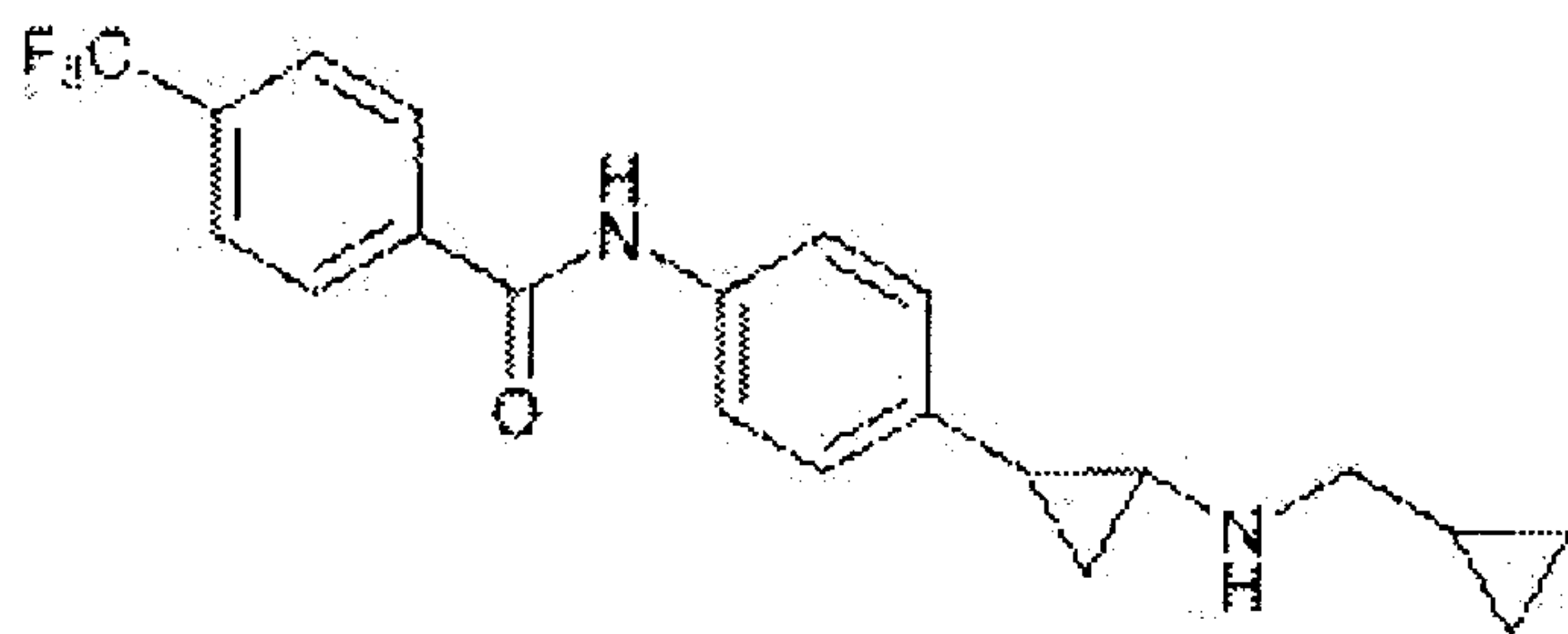
^1H NMR (300 MHz, DMSO- d_6) δ 0.32-0.41 (2H, m), 0.52-0.63 (2H, m), 0.99-1.13 (1H, m), 1.21-1.32 (1H, m), 1.42-1.56 (1H, m), 2.38 (3H, s), 2.41-2.47 (1H, m), 2.84-3.04 (3H, m), 7.15 (2H, d, $J = 7.6$ Hz), 7.33 (2H, d, $J = 7.6$ Hz), 7.71 (2H, d, $J = 7.9$ Hz),
 10 7.86 (2H, d, $J = 7.9$ Hz), 9.15 (2H, brs), 10.14 (1H, s).

[0386]

Example 69

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-4-
 15 (trifluoromethyl)benzamide hydrochloride

[0387]



[0388]

By a method similar to Example 68, Steps E and F, the
 20 title compound (65.9 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl] (cyclopropylmethyl) carbamate (73.0 mg) and 4-(trifluoromethyl)benzoyl chloride (43.0 μL).

MS (API+): $[M+H]^+$ 375.4.

^1H NMR (300 MHz, DMSO- d_6) δ 0.31-0.43 (2H, m), 0.50-0.64 (2H, m), 1.01-1.15 (1H, m), 1.23-1.33 (1H, m), 1.43-1.60 (1H, m), 2.43-2.48 (1H, m), 2.83-3.03 (3H, m), 7.18 (2H, d, $J = 8.2$ Hz), 7.72 (2H, d, $J = 8.2$ Hz), 7.92 (2H, d, $J = 8.2$ Hz), 8.15 (2H, d, $J = 8.2$ Hz), 9.27 (2H, brs), 10.48 (1H, s).

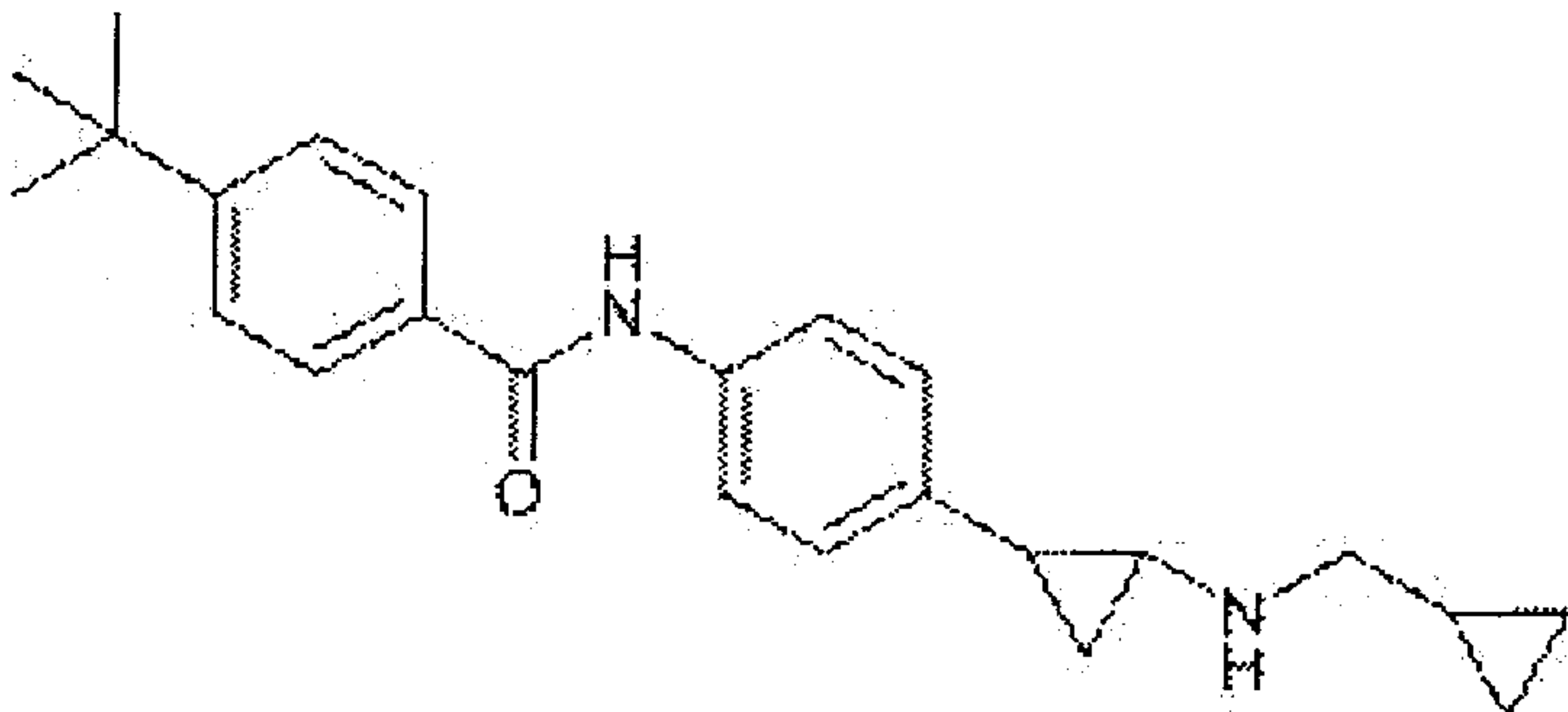
[0389]

30 Example 70

4-tert-butyl-N-(4-{trans-2-

[(cyclopropylmethyl)amino]cyclopropyl}phenyl)benzamide
hydrochloride

[0390]



5 [0391]

By a method similar to Example 68, Steps E and F, the title compound (67.6 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (71.3 mg) and 4-tert-butylbenzoyl chloride (55.3 μ L).

10 MS (API+): $[M+H]^+$ 363.4.

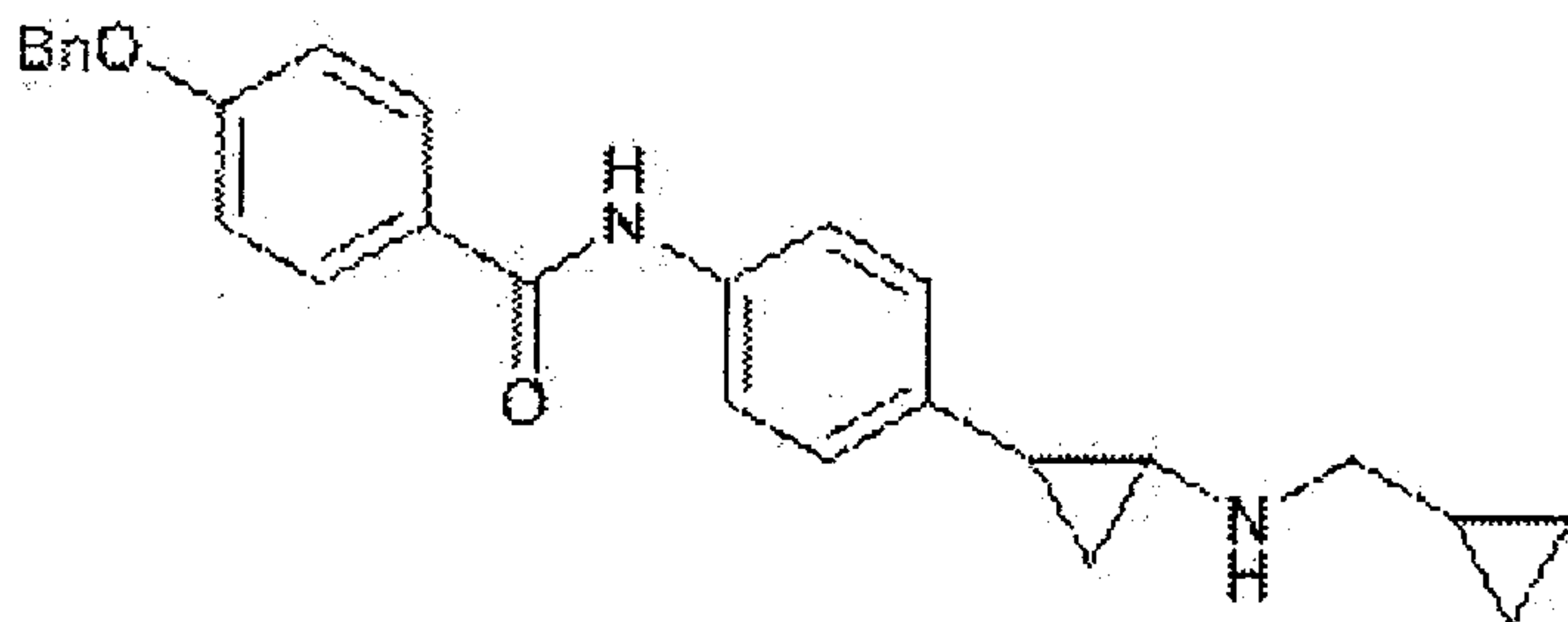
^1H NMR (300 MHz, DMSO- d_6) δ 0.32-0.41 (2H, m), 0.53-0.65 (2H, m), 0.98-1.13 (1H, m), 1.21-1.29 (1H, m), 1.32 (9H, s), 1.41-1.55 (1H, m), 2.39-2.48 (1H, m), 2.81-3.05 (3H, m), 7.15 (2H, d, $J = 8.1$ Hz), 7.54 (2H, d, $J = 8.1$ Hz), 7.71 (2H, d, $J = 8.1$ Hz),
15 7.88 (2H, d, $J = 8.1$ Hz), 9.16 (2H, brs), 10.16 (1H, s).

[0392]

Example 71

4-(benzyloxy)-N-(4-{trans-2-
[(cyclopropylmethyl)amino]cyclopropyl}phenyl)benzamide
20 hydrochloride

[0393]



[0394]

By a method similar to Example 68, Steps E and F, the
25 title compound (50.2 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (70.9

mg) and 4-(benzyloxy)benzoyl chloride (69.4 mg).

MS (API+): $[M+H]^+$ 413.3.

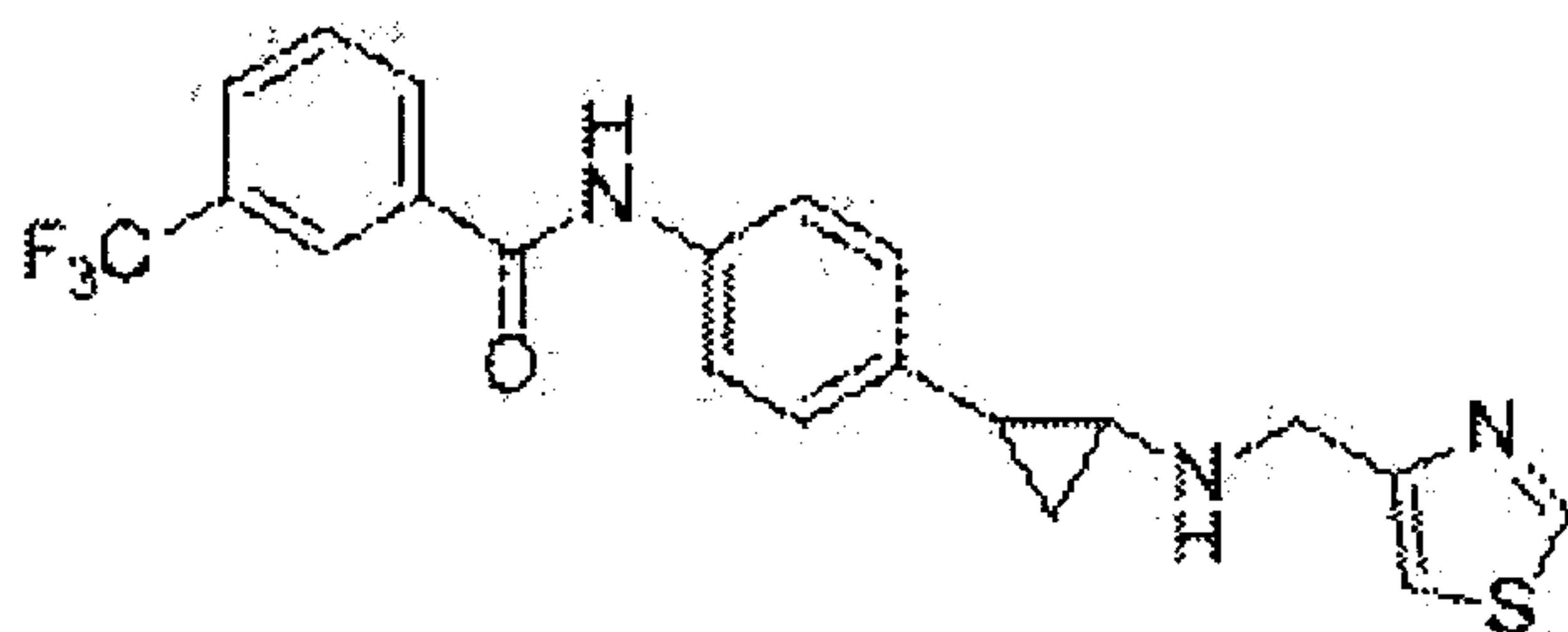
^1H NMR (300 MHz, DMSO- d_6) δ 0.30-0.40 (2H, m), 0.51-0.63 (2H, m), 0.96-1.13 (1H, m), 1.21-1.32 (1H, m), 1.39-1.53 (1H, m),
 5 2.42 (1H, m), 2.85-3.04 (3H, m), 5.21 (2H, s), 7.05-7.20 (4H, m), 7.30-7.51 (5H, m), 7.70 (2H, d, J = 7.8 Hz), 7.94 (2H, d, J = 8.2 Hz), 9.03 (2H, brs), 10.07 (1H, s).

[0395]

Example 72

10 N-(4-{trans-2-[(1,3-thiazol-4-ylmethyl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide dihydrochloride

[0396]



15 [0397]

By a method similar to Example 65, the title compound (40 mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (80 mg) and 1,3-thiazole-4-carbaldehyde (33 mg).

20 MS (API+): $[M+H]^+$ 417.9.

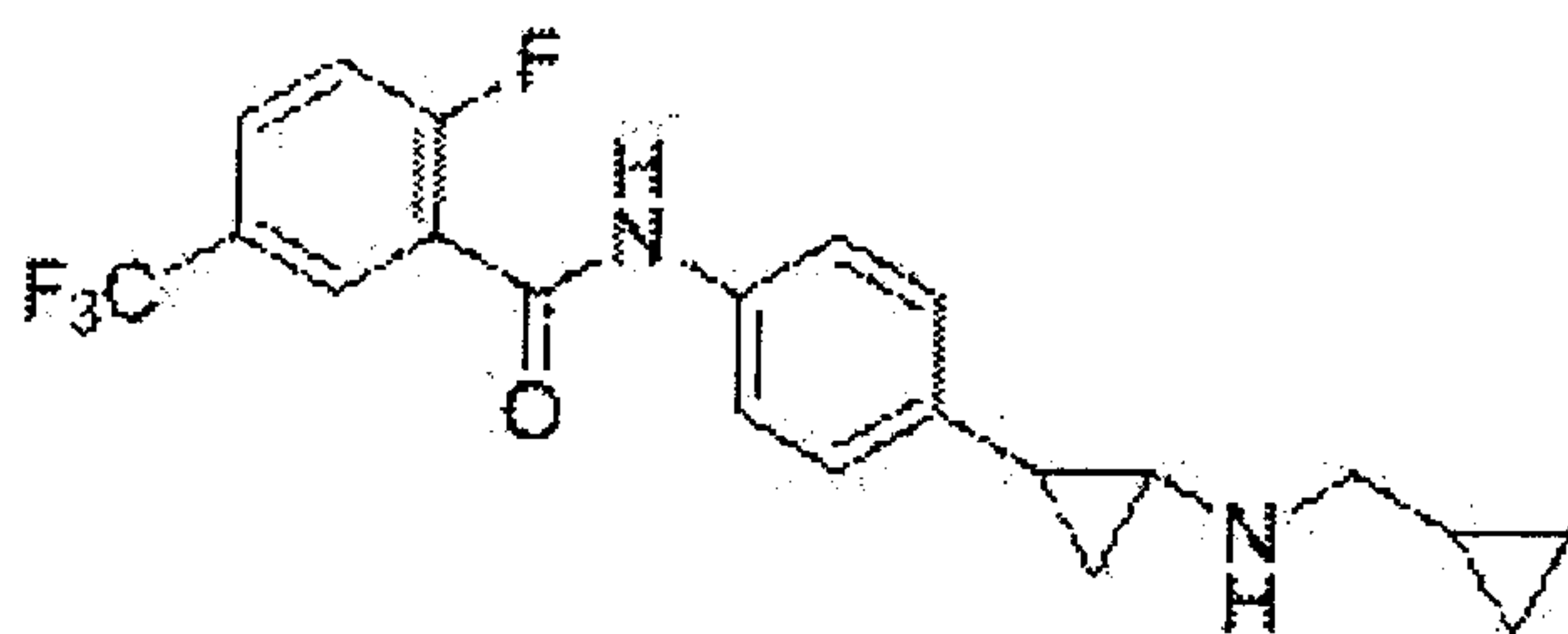
^1H NMR (300MHz, CD $_3$ OD) δ 1.34-1.55 (2H, m), 2.40-2.50 (1H, m), 3.04 (1H, td, J = 4.3, 3.4 Hz), 4.58 (2H, s), 7.14 (2H, d, J = 8.5 Hz), 7.64-7.79 (4H, m), 7.90 (1H, d, J = 7.9 Hz), 8.16-8.29 (2H, m), 9.10 (1H, d, J = 1.9 Hz).

25 [0398]

Example 73

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-2-fluoro-5-(trifluoromethyl)benzamide hydrochloride

[0399]



[0400]

A) tert-butyl (cyclopropylmethyl) [trans-2-(4-{[2-fluoro-5-(trifluoromethyl)benzoyl]amino}phenyl)cyclopropyl]carbamate

5 A solution of tert-butyl [trans-2-(4-aminophenyl)cyclopropyl] (cyclopropylmethyl)carbamate (80.0 mg) and triethylamine (32.1 mg) in acetonitrile (3 mL) was ice-cooled, and 2-fluoro-5-(trifluoromethyl)benzoyl chloride (71.9 mg) was added. The mixture was stirred at room temperature for
10 2 hr, and poured into water under ice-cooling. The mixture was extracted with ethyl acetate, and the extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl
15 acetate) to give the title compound (115 mg).

MS (API+): [M-tBu+2H]⁺ 437.0.

¹H NMR (300 MHz, CDCl₃) δ 0.12-0.31 (2H, m), 0.37-0.54 (2H, m), 0.93-1.12 (1H, m), 1.22-1.30 (2H, m), 1.45 (9H, s), 2.07-2.16 (1H, m), 2.78-2.88 (1H, m), 2.99-3.13 (1H, m), 3.19-3.35 (1H,
20 m), 7.16 (2H, d, J = 8.1 Hz), 7.28-7.38 (1H, m), 7.57 (2H, d, J = 8.0 Hz), 7.75-7.84 (1H, m), 8.38 (1H, d, J = 14.4 Hz), 8.49 (1H, d, J = 6.7 Hz).

[0401]

B) N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-
25 2-fluoro-5-(trifluoromethyl)benzamide hydrochloride

A solution of tert-butyl (cyclopropylmethyl) [trans-2-(4-{[2-fluoro-5-(trifluoromethyl)benzoyl]amino}phenyl)-cyclopropyl]carbamate (110 mg) in THF (1 mL) was ice-cooled, and 4N hydrochloric acid/cyclopentyl methyl ether solution (15
30 mL) was added. The mixture was stirred at room temperature overnight and the solvent was evaporated under reduced pressure.

The residue was recrystallized from methanol/diisopropyl ether to give the title compound (72.0 mg).

MS (API+): $[M+H]^+$ 393.0.

^1H NMR (300 MHz, CD_3OD) δ 0.38-0.48 (2H, m), 0.69-0.79 (2H, m),
 5 1.09-1.18 (1H, m), 1.36-1.58 (2H, m), 2.49 (1H, ddd, $J = 10.0$,
 6.5, 3.7 Hz), 2.96-3.04 (1H, m), 3.09 (2H, dd, $J = 7.5$, 2.1 Hz),
 7.21 (2H, d, $J = 8.7$ Hz), 7.48 (1H, t, $J = 9.2$ Hz), 7.66 (2H, d,
 $J = 8.7$ Hz), 7.86-7.97 (1H, m), 8.04 (1H, dd, $J = 6.2$, 2.3 Hz).

[0402]

10 Example 74

N-(4-{trans-2-[(1-benzylpiperidin-4-yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide dihydrochloride

[0403]



[0404]

By a method similar to Example 65, the title compound (65 mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (80 mg) and 1-
 20 benzylpiperidin-4-one (55.2 mg).

MS (API+): $[M+H]^+$ 494.2.

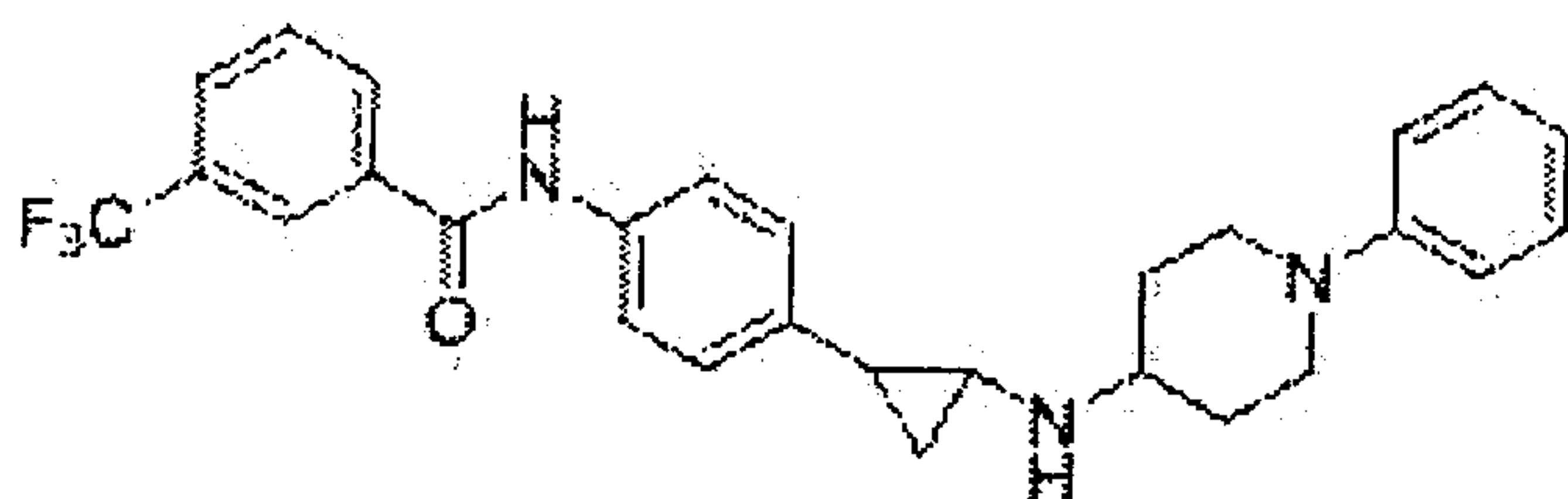
^1H NMR (300MHz, CD_3OD) δ 1.42-1.63 (2H, m), 2.02-2.21 (2H, m),
 2.39-2.59 (3H, m), 3.03 (1H, brs), 3.14-3.25 (2H, m), 3.56-3.74
 (3H, m), 4.37 (2H, brs), 7.23 (2H, d, $J = 8.2$ Hz), 7.50-7.61
 25 (5H, m), 7.66-7.80 (3H, m), 7.92 (1H, d, $J = 7.7$ Hz), 8.16-8.29
 (2H, m).

[0405]

Example 75

N-(4-{trans-2-[(1-phenylpiperidin-4-yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide dihydrochloride

[0406]



[0407]

By a method similar to Example 65, the title compound (45 mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (80 mg) and 1-phenylpiperidin-4-one (51.1 mg).

MS (API+): $[M+H]^+$ 480.1.

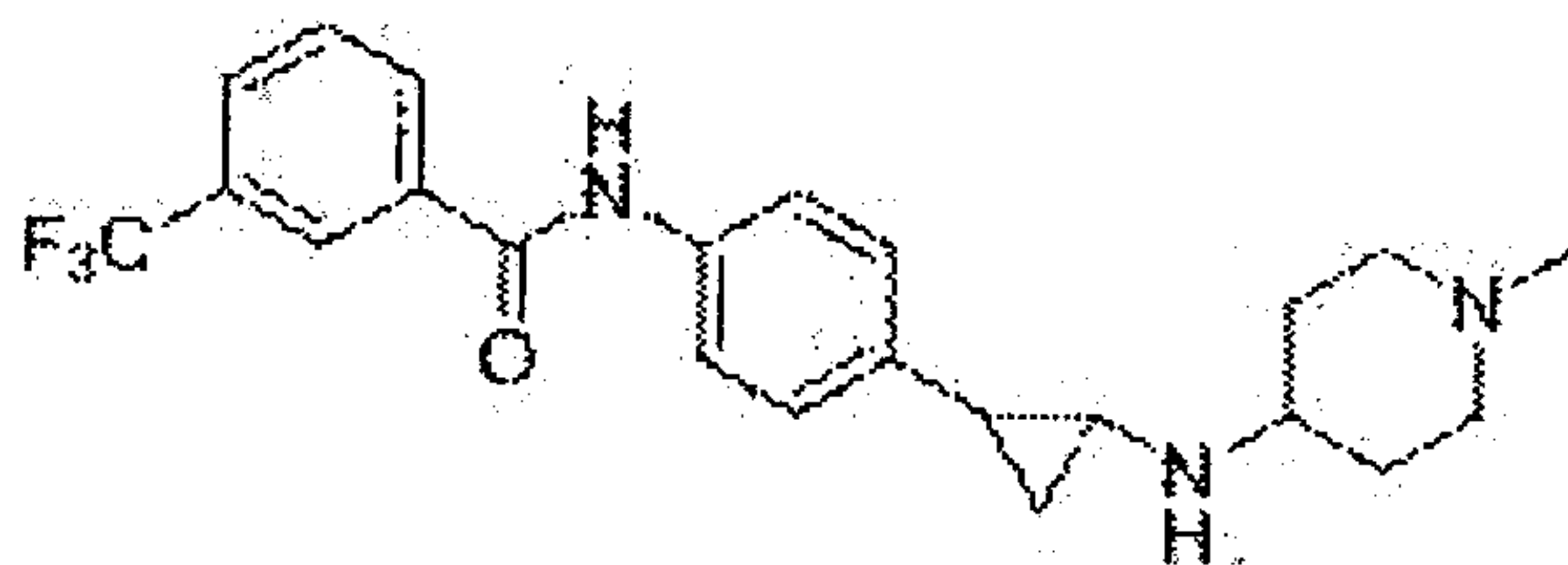
^1H NMR (300MHz, CD_3OD) δ 1.46-1.69 (2H, m), 2.22-2.44 (2H, m), 2.46-2.66 (3H, m), 3.06-3.16 (1H, m), 3.59-3.97 (5H, m), 7.27
10 (2H, d, $J = 8.3$ Hz), 7.43-7.51 (1H, m), 7.53-7.61 (2H, m), 7.62-7.68 (2H, m), 7.69-7.79 (3H, m), 7.91 (1H, d, $J = 7.8$ Hz), 8.16-8.30 (2H, m).

[0408]

Example 76

15 N-(4-{trans-2-[(1-methylpiperidin-4-yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide dihydrochloride

[0409]



20 [0410]

To a solution of N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (80 mg) in methanol (3 mL)/THF (3 mL) were added 1-methylpiperidin-4-one (33.0 mg) and sodium hydrogen carbonate (37.7 mg). The mixture was
25 stirred at 60°C for 2 hr, and ice-cooled to 0°C and sodium borohydride (17.0 mg) was added. The mixture was stirred at room temperature for 2 hr, and ice-cooled to 0°C, and saturated aqueous sodium hydrogen carbonate solution was added. The mixture was extracted with ethyl acetate, and the extract was

washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate, ethyl acetate/methanol). 10%

5 Hydrochloric acid methanol solution was added and the solvent was evaporated under reduced pressure. The residue was recrystallized from methanol/diisopropyl ether to give the title compound (40 mg).

MS (API+): $[M+H]^+$ 418.0.

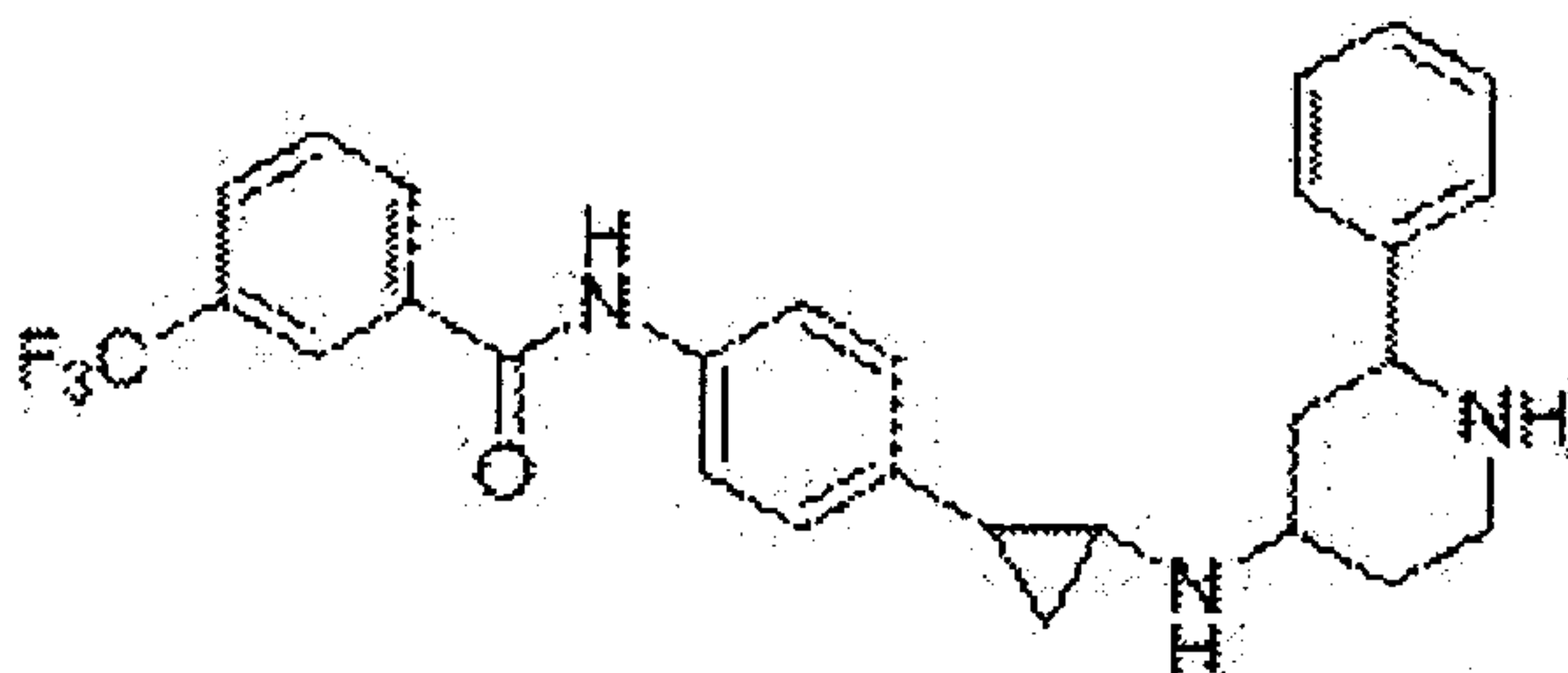
10 ^1H NMR (300MHz, CD_3OD) δ 1.42-1.65 (2H, m), 2.02-2.22 (2H, m), 2.34-2.63 (3H, m), 2.92 (3H, s), 3.01-3.27 (3H, m), 3.60-3.78 (3H, m), 7.24 (2H, d, $J = 8.3$ Hz), 7.67-7.79 (3H, m), 7.91 (1H, d, $J = 7.5$ Hz), 8.17-8.28 (2H, m).

[0411]

15 Example 77

N-(4-{trans-2-[(2-phenylpiperidin-4-yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide dihydrochloride

[0412]



20

[0413]

A) tert-butyl 2-phenyl-4-[[trans-2-(4-[[3-(trifluoromethyl)benzoyl]amino]phenyl)cyclopropyl]amino]-piperidine-1-carboxylate

25 To a solution of N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (60 mg) in methanol (1.5 mL)/THF (1.5 mL) were added tert-butyl 4-oxo-2-phenylpiperidine-1-carboxylate (60.2 mg) and sodium hydrogen carbonate (28.3 mg). The mixture was stirred at 60°C for 1 hr,
30 and ice-cooled to 0°C and sodium borohydride (12.7 mg) was added. The mixture was stirred at room temperature for 2 hr,

and ice-cooled to 0°C and saturated aqueous sodium hydrogen carbonate solution was added. The mixture was extracted with ethyl acetate, and the extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was
 5 evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (62 mg).

MS (API+): [M-Boc+H]⁺ 480.1.

[0414]

10 B) N-(4-{trans-2-[(2-phenylpiperidin-4-yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide dihydrochloride

tert-Butyl 2-phenyl-4-{[trans-2-(4-{[3-(trifluoromethyl)benzoyl]amino}phenyl)cyclopropyl]amino}-
 15 piperidine-1-carboxylate (62 mg) was dissolved in THF (0.5 mL), and the mixture was ice-cooled to 0°C. 4N Hydrochloric acid/cyclopentyl methyl ether solution (5.0 mL) was added, and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure. The residue was
 20 recrystallized from methanol/diisopropyl ether to give the title compound (24 mg).

MS (API+): [M+H]⁺ 480.1.

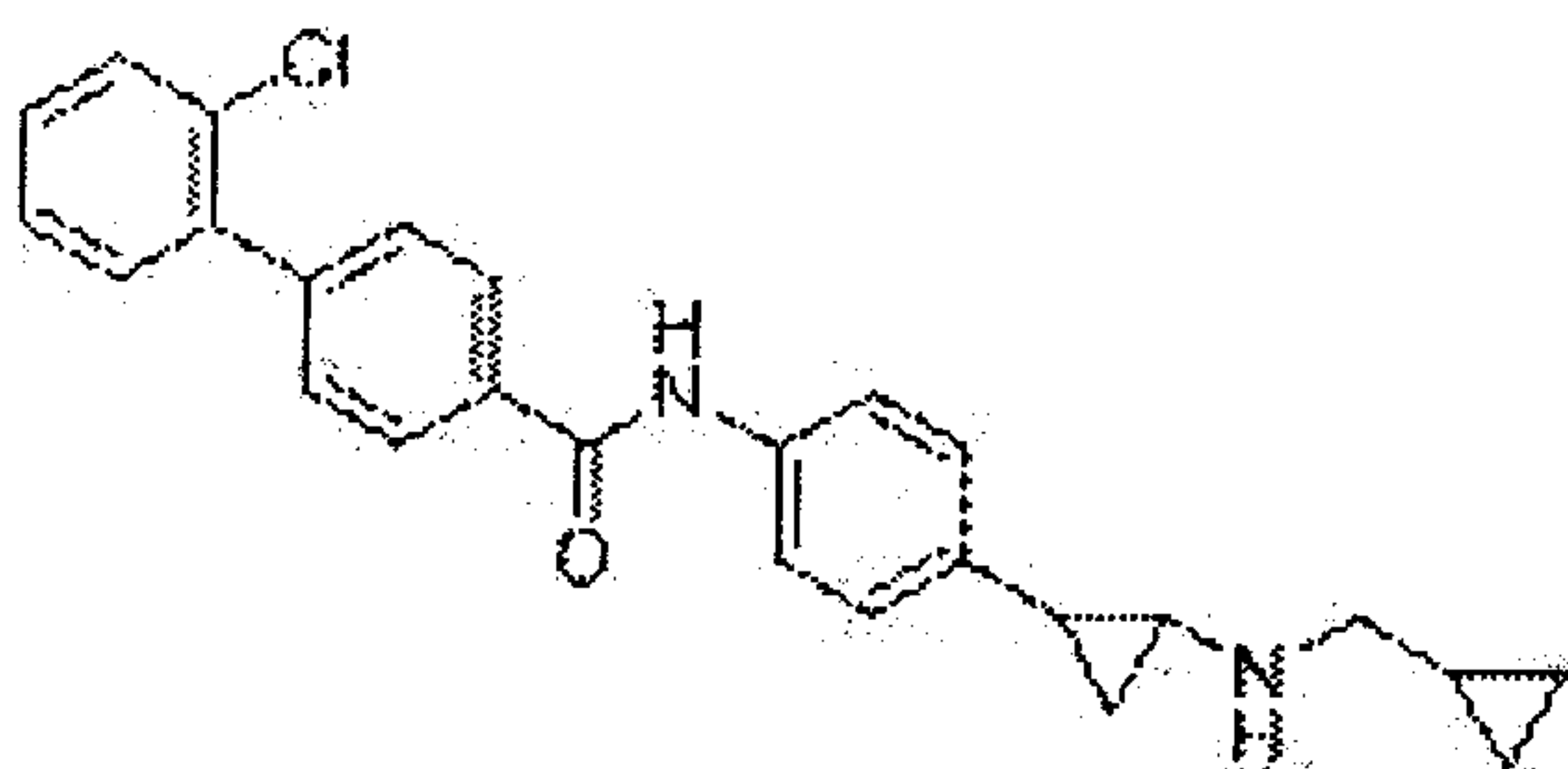
¹H NMR (300MHz, CD₃OD) δ 1.43-1.55 (1H, m), 1.56-1.67 (1H, m), 2.05-2.21 (1H, m), 2.31 (1H, d, J = 12.1 Hz), 2.47-2.67 (3H, m),
 25 3.07 (1H, d, J = 3.4 Hz), 3.35-3.40 (1H, m), 3.62-3.72 (1H, m), 3.83-3.98 (1H, m), 4.49 (1H, d, J = 12.6 Hz), 7.22 (2H, t, J = 9.8 Hz), 7.48-7.59 (5H, m), 7.64-7.78 (3H, m), 7.90 (1H, d, J = 8.1 Hz), 8.15-8.31 (2H, m).

[0415]

30 Example 78

2'-chloro-N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)biphenyl-4-carboxamide hydrochloride

[0416]



[0417]

A) tert-butyl [trans-2-(4-((2'-chlorobiphenyl-4-yl)carbonyl)amino)phenyl)cyclopropyl](cyclopropylmethyl)-
5 carbamate

By a method similar to Example 79, Step A, the title compound (115 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (75.0 mg) and 2'-chlorobiphenyl-4-carboxylic acid (69.2 mg).

10 MS (API+): [M-tBu+2H]⁺ 461.0.

[0418]

B) 2'-chloro-N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)biphenyl-4-carboxamide hydrochloride

15 tert-Butyl [trans-2-(4-((2'-chlorobiphenyl-4-yl)carbonyl)amino)phenyl)cyclopropyl](cyclopropylmethyl)-carbamate (115 mg) was dissolved in THF (0.5 mL), and the mixture was ice-cooled to 0°C. 4N Hydrochloric acid/cyclopentyl methyl ether solution (5 mL) was added, and
20 the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure. The residue was recrystallized from methanol/diisopropyl ether to give the title compound (65.0 mg).

MS (API+): [M+H]⁺ 417.0.

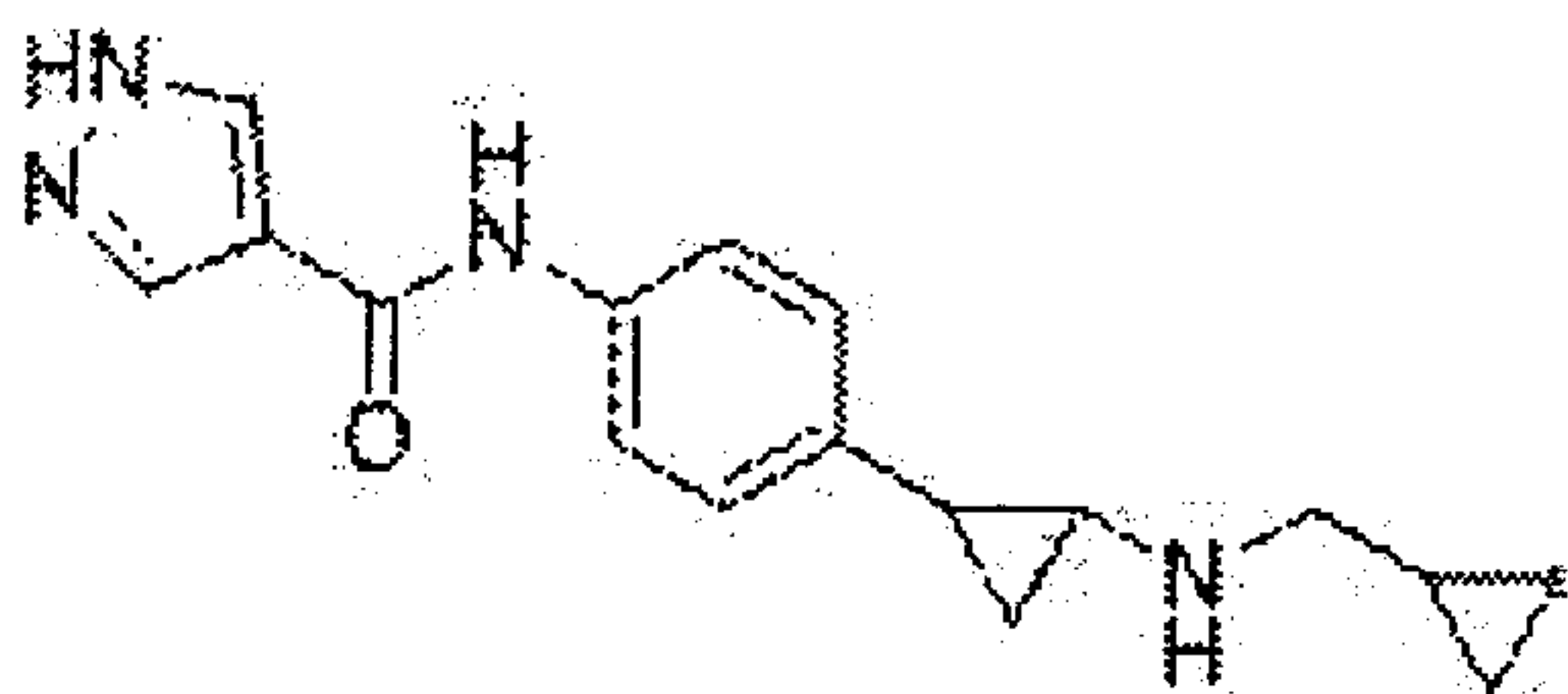
25 ¹H NMR (300MHz, CD₃OD) δ 0.38-0.52 (2H, m), 0.69-0.80 (2H, m), 1.14 (1H, tt, J = 7.8, 4.8 Hz), 1.40 (1H, m), 1.48-1.59 (1H, m), 2.50 (1H, ddd, J = 10.2, 6.6, 3.6 Hz), 3.00 (1H, m), 3.06-3.16 (2H, m), 7.21 (2H, d, J = 8.7 Hz), 7.34-7.47 (3H, m), 7.49-7.63 (3H, m), 7.70 (2H, d, J = 8.7 Hz), 8.00 (2H, d, J = 8.5 Hz).

30 [0419]

Example 79

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-1H-pyrazole-4-carboxamide hydrochloride

[0420]



5 [0421]

A) tert-butyl (cyclopropylmethyl) (trans-2-{4-[(1H-pyrazol-4-ylcarbonyl)amino]phenyl}cyclopropyl) carbamate

A solution of tert-butyl [trans-2-(4-aminophenyl)cyclopropyl] (cyclopropylmethyl) carbamate (75 mg) in
 10 DMF (3 mL) was ice-cooled, and 1H-pyrazole-4-carboxylic acid (33.4 mg), N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (143 mg), 1-hydroxybenzotriazole (49.4 mg) and diisopropylethylamine (80 mg) were added. The mixture was stirred at room temperature overnight, and saturated aqueous
 15 sodium hydrogen carbonate solution was added under ice-cooling. The mixture was extracted with ethyl acetate, and the extract was washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel
 20 column chromatography (hexane/ethyl acetate) to give the title compound (72 mg).

MS (API+): [M-tBu+2H]⁺ 341.0.

[0422]

B) N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-
 25 1H-pyrazole-4-carboxamide hydrochloride

tert-Butyl (cyclopropylmethyl) (trans-2-{4-[(1H-pyrazol-4-ylcarbonyl)amino]phenyl}cyclopropyl) carbamate (72 mg) was dissolved in THF (0.5 mL), and the mixture was ice-cooled to 0°C. 4N Hydrochloric acid/cyclopentyl methyl ether solution
 30 (4.5 mL) was added, and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure. The residue was recrystallized from

methanol/diisopropyl ether to give the title compound (45 mg).

MS (API+): $[M+H]^+$ 297.0.

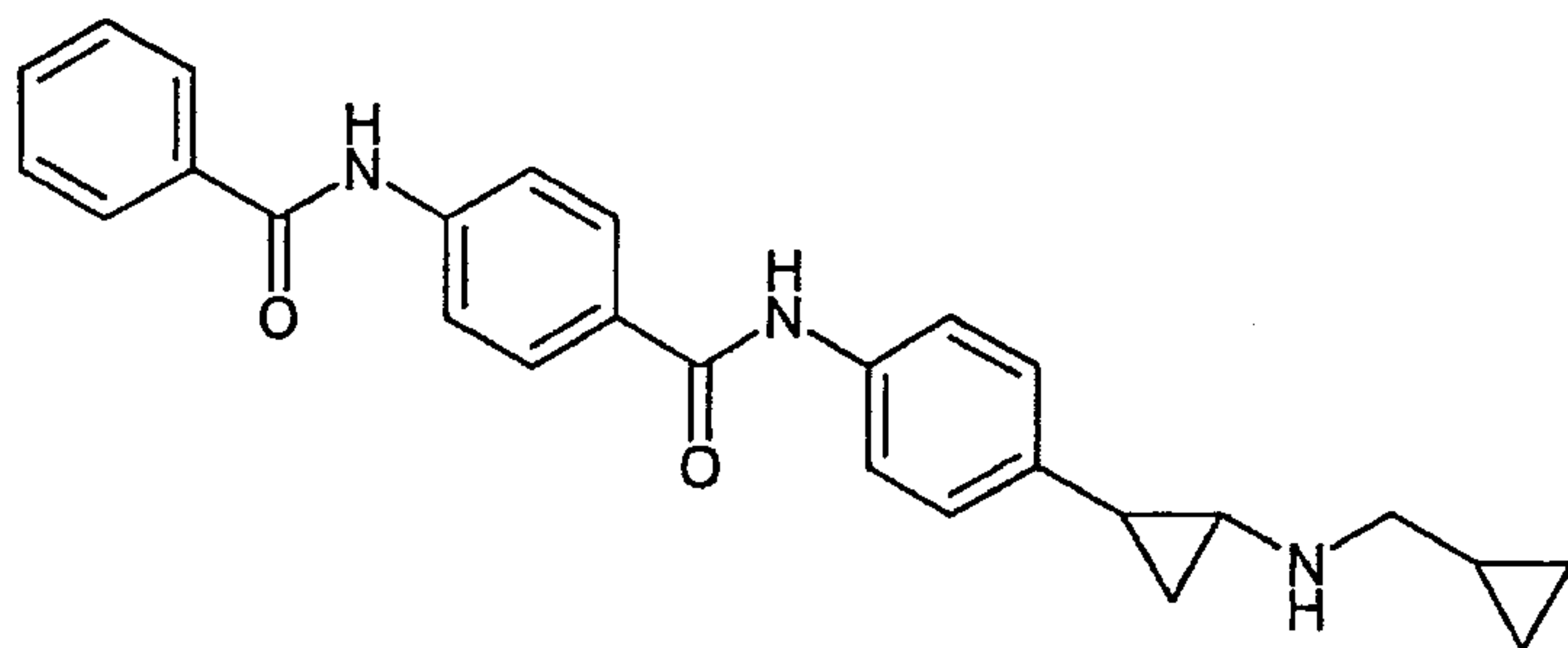
^1H NMR (300MHz, CD_3OD) δ 0.37-0.47 (2H, m), 0.68-0.76 (2H, m),
1.04-1.22 (1H, m), 1.33-1.43 (1H, m), 1.45-1.55 (1H, m), 2.48
5 (1H, ddd, $J = 10.1, 6.5, 3.6$ Hz), 2.93-3.01 (1H, m), 3.08 (2H,
dd, $J = 7.4, 1.6$ Hz), 6.87 (1H, brs), 7.17 (2H, d, $J = 8.3$ Hz),
7.67 (2H, d, $J = 8.5$ Hz), 7.74 (1H, brs).

[0423]

Example 80

10 N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-4-
[(phenylcarbonyl)amino]benzamide hydrochloride

[0424]



[0425]

15 A) tert-butyl [trans-2-(4-{[4-(benzoylamino)benzoyl]amino}-
phenyl)cyclopropyl](cyclopropylmethyl)carbamate

To a solution of tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (90.9 mg),
4-benzamidobenzoic acid (87 mg) and 1-hydroxybenzotriazole
20 (60.9 mg) in DMF (1.5 mL) was added N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (86 mg). The
reaction mixture was stirred at room temperature for 2 hr, and
poured into 0.5N hydrochloric acid. The mixture was extracted
with ethyl acetate, and the extract was washed successively
25 with water, saturated aqueous sodium hydrogen carbonate
solution and saturated brine, and dried over anhydrous
magnesium sulfate. The solvent was evaporated under reduced
pressure. The residue was washed with ethyl
acetate/diisopropyl ether to give the title compound (98.0 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.07-0.17 (1H, m), 0.18-0.29 (1H, m), 0.34-0.52 (2H, m), 0.91-1.02 (1H, m), 1.15-1.28 (2H, m), 1.37 (9H, s), 2.01-2.12 (1H, m), 2.67-2.76 (1H, m), 3.00 (1H, dd, J = 14.5, 7.0 Hz), 3.20 (1H, dd, J = 14.5, 6.9 Hz), 7.12
5 (2H, d, J = 8.7 Hz), 7.50-7.63 (3H, m), 7.67 (2H, d, J = 8.7 Hz), 7.91-8.01 (6H, m), 10.09 (1H, s), 10.51 (1H, s).

[0426]

B) 4-(benzoylamino)-N-(4-{trans-2-[(cyclopropylmethyl)amino]-cyclopropyl}phenyl)benzamide hydrochloride

10 tert-Butyl [trans-2-(4-{[4-(benzoylamino)benzoyl]amino}phenyl)cyclopropyl]-(cyclopropylmethyl)carbamate (98.0 mg) was dissolved in 4N hydrochloric acid/cyclopentyl methyl ether solution (1 mL), and the mixture was stirred at room temperature for 2 hr. The
15 solvent was evaporated under reduced pressure. The residue was recrystallized from methanol/diisopropyl ether to give the title compound (44.6 mg).

MS (API+): [M+H]⁺ 426.4.

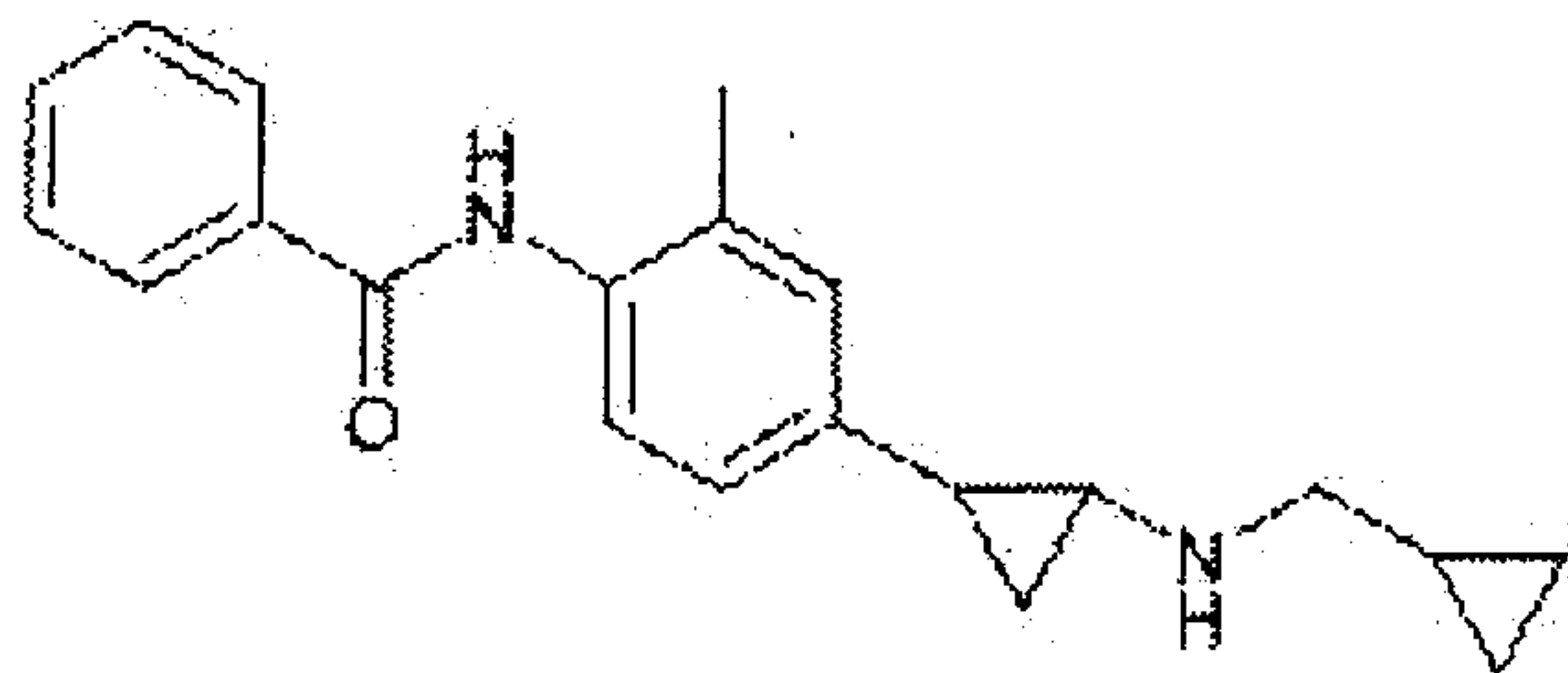
¹H NMR (300 MHz, DMSO-d₆) δ 0.32-0.41 (2H, m), 0.54-0.64 (2H, m), 0.98-1.14 (1H, m), 1.23-1.33 (1H, m), 1.43-1.55 (1H, m),
20 2.39-2.47 (1H, m), 2.85-3.05 (3H, m), 7.16 (2H, d, J = 8.4 Hz), 7.51-7.66 (3H, m), 7.73 (2H, d, J = 8.3 Hz), 7.89-8.05 (6H, m), 9.13 (2H, brs), 10.15 (1H, s), 10.53 (1H, s).

[0427]

25 Example 81

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}-2-methylphenyl)benzamide hydrochloride

[0428]



30 [0429]

A) N-(4-bromo-2-methylphenyl)benzamide

To a solution of 4-bromo-2-methylaniline (3.55 g) in pyridine (95 mL) was added benzoyl chloride (2.66 mL). The mixture was stirred at room temperature for 1 hr and the solvent was evaporated under reduced pressure. To the residue
5 was added 2N hydrochloric acid. The mixture was extracted with ethyl acetate, and the extract was washed successively with 1N hydrochloric acid, saturated aqueous sodium hydrogen carbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced
10 pressure. The residue was washed with diisopropyl ether to give the title compound (4.35 g).

¹H NMR (300 MHz, DMSO-d₆) δ 2.24 (3H, s), 7.33 (1H, d, J = 8.5 Hz), 7.41 (1H, dd, J = 8.5, 2.5 Hz), 7.49-7.64 (4H, m), 7.94-8.00 (2H, m), 9.90 (1H, brs).

15 [0430]

B) ethyl trans-2-[4-(benzoylamino)-3-methylphenyl]cyclopropanecarboxylate

To a solution of N-(4-bromo-2-methylphenyl)benzamide (4.35 g) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (2.54 g)
20 in THF (64.3 mL)/water (10.7 mL) were added 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride-dichloromethane complex (0.367 g) and triethylamine (4.18 mL). The reaction mixture was stirred at 60°C overnight, and poured into saturated aqueous ammonium chloride solution. The
25 reaction mixture was extracted with ethyl acetate, and the extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give a mixture
30 (4.42 g) containing N-(2-methyl-4-vinylphenyl)benzamide. To a solution of the mixture (4.42 g) and copper(I) chloride (0.233 g) in toluene (36 mL)/THF (5 mL) was added dropwise a solution of ethyl diazoacetate (9.79 mL) in toluene (25 mL) at 80°C over 1 hr or longer. The mixture was stirred at 80°C overnight,
35 cooled to room temperature, and filtered through celite. The

mother liquor was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (1.29 g).

¹H NMR (300 MHz, DMSO-d₆) δ 1.21 (3H, t, J = 6.7 Hz), 1.34-1.53 (2H, m), 1.87-2.01 (1H, m), 2.20 (3H, s), 2.35-2.46 (1H, m), 4.11 (2H, q, J = 6.7 Hz), 7.01 (1H, d, J = 8.0 Hz), 7.09 (1H, s), 7.23 (1H, d, J = 8.0 Hz), 7.47-7.62 (3H, m), 7.97 (2H, d, J = 7.5 Hz), 9.83 (1H, s).

[0431]

10 C) trans-2-[4-(benzoylamino)-3-methylphenyl]cyclopropanecarboxylic acid

To a solution of ethyl trans-2-[4-(benzoylamino)-3-methylphenyl]cyclopropanecarboxylate (1.29 g) in ethanol (7.98 mL) was added 1N aqueous sodium hydroxide solution (7.98 mL).

15 The reaction mixture was stirred at 50°C for 6.5 hr, 1N hydrochloric acid (10 mL) was added under ice-cooling, and the mixture was stirred under ice-cooling for 1 hr. The precipitate was collected by filtration to give the title compound (576.9 mg).

20 ¹H NMR (300 MHz, DMSO-d₆) δ 1.30-1.47 (2H, m), 1.74-1.85 (1H, m), 2.20 (3H, s), 2.31-2.44 (1H, m), 7.00 (1H, d, J = 8.3 Hz), 7.07 (1H, s), 7.19-7.27 (1H, m), 7.46-7.67 (3H, m), 7.97 (2H, d, J = 7.6 Hz), 9.82 (1H, s), 12.30 (1H, brs).

[0432]

25 D) tert-butyl {trans-2-[4-(benzoylamino)-3-methylphenyl]cyclopropyl}carbamate

To trans-2-[4-(benzoylamino)-3-methylphenyl]cyclopropanecarboxylic acid (576.0 mg) was added toluene (200 mL), and the solvent was evaporated under reduced pressure. The residue was suspended in toluene (10 mL), and triethylamine (0.326 mL), THF (2 mL) and diphenylphosphoryl azide (0.504 mL) were added. The reaction mixture was stirred at room temperature for 1 hr, and tert-butyl alcohol (1.83 mL) was added. The mixture was stirred at 80°C overnight, and 35 poured into saturated aqueous ammonium chloride solution. The

reaction mixture was extracted with ethyl acetate, and the extract was washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under
5 reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (125.8 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.01-1.14 (2H, m), 1.39 (9H, s), 1.80-1.94 (1H, m), 2.19 (3H, s), 2.54-2.67 (1H, m), 6.92 (1H,
10 dd, J = 8.1, 1.5 Hz), 6.99 (1H, d, J = 1.5 Hz), 7.19 (1H, d, J = 8.1 Hz), 7.22-7.28 (1H, m), 7.46-7.63 (3H, m), 7.97 (2H, d, J = 6.6 Hz), 9.81 (1H, s).

[0433]

E) N-[4-(trans-2-aminocyclopropyl)-2-methylphenyl]benzamide
15 hydrochloride

tert-Butyl {trans-2-[4-(benzoylamino)-3-methylphenyl]cyclopropyl}carbamate (125.8 mg) was dissolved in 4N hydrochloric acid/cyclopentyl methyl ether solution (1.5 mL), and the mixture was stirred at room temperature for 2 hr. The
20 solvent was evaporated under reduced pressure to give the title compound (95.9 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.16-1.29 (1H, m), 1.31-1.42 (1H, m), 2.21 (3H, s), 2.24-2.33 (1H, m), 2.77-2.86 (1H, m), 7.01 (1H, dd, J = 8.1, 1.9 Hz), 7.06 (1H, d, J = 1.9 Hz), 7.26 (1H,
25 d, J = 8.1 Hz), 7.45-7.67 (3H, m), 7.97 (2H, d, J = 6.8 Hz), 8.32 (3H, brs), 9.85 (1H, s).

[0434]

F) N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}-2-methylphenyl)benzamide hydrochloride

30 To a solution of N-[4-(trans-2-aminocyclopropyl)-2-methylphenyl]benzamide hydrochloride (90.1 mg) and sodium hydrogen carbonate (50.0 mg) in THF (1.49 mL)/methanol (1.49 mL) was added cyclopropanecarbaldehyde (0.029 mL). The reaction mixture was stirred at 60°C for 1 hr, and ice-cooled
35 to 0°C and sodium borohydride (22.51 mg) was added. The

mixture was stirred at room temperature overnight, and poured into saturated aqueous sodium hydrogen carbonate solution. The reaction mixture was extracted with ethyl acetate, and the extract was washed with saturated brine, and dried over
 5 anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (5 mL), and 4N hydrochloric
 10 acid/ethyl acetate solution (0.5 mL) was added. The solvent was evaporated under reduced pressure, and the residue was recrystallized from methanol/diisopropyl to give the title compound (55.9 mg).

MS (API+): $[M+H]^+$ 321.2.

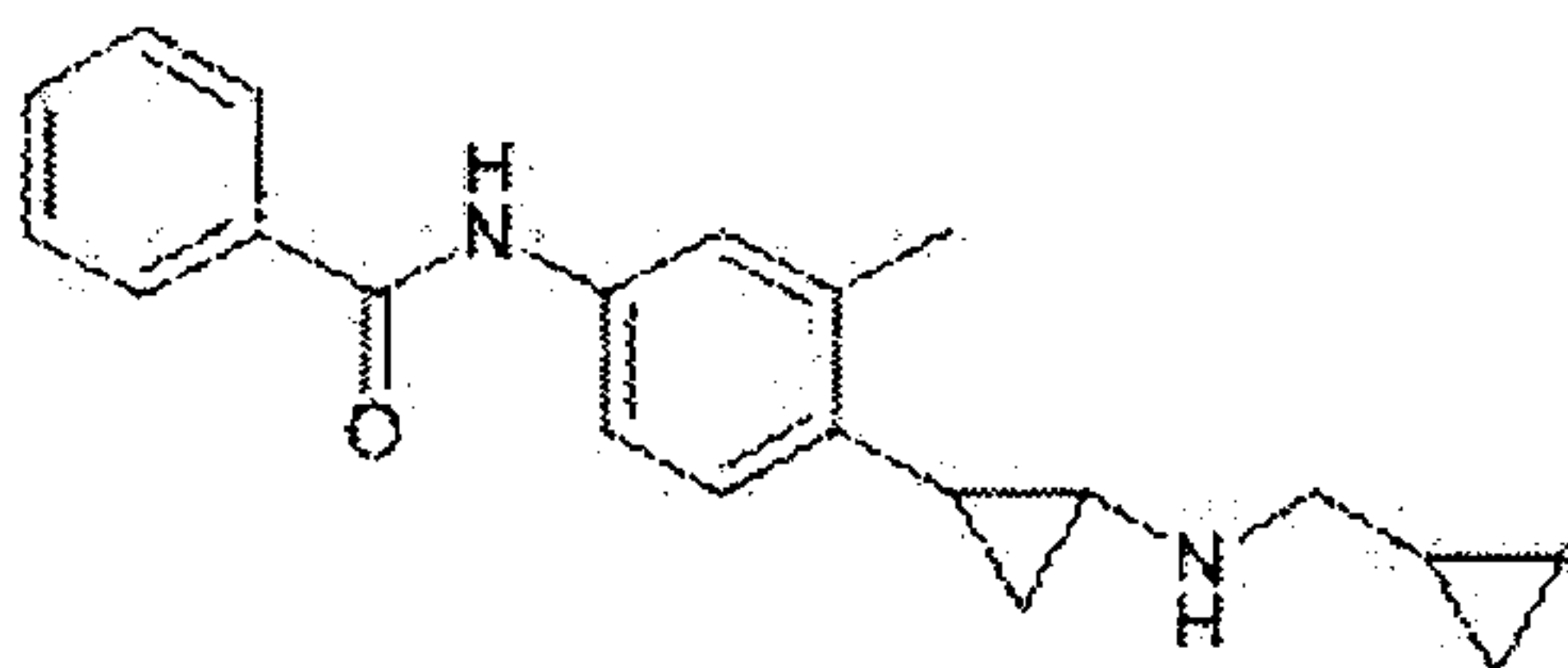
15 ^1H NMR (300 MHz, DMSO- d_6) δ 0.33-0.41 (2H, m), 0.54-0.64 (2H, m), 1.00-1.14 (1H, m), 1.23-1.34 (1H, m), 1.47-1.57 (1H, m), 2.21 (3H, s), 2.42-2.48 (1H, m), 2.86-3.05 (3H, m), 7.02 (1H, d, $J = 8.1$ Hz), 7.08 (1H, s), 7.26 (1H, d, $J = 8.1$ Hz), 7.44-7.64 (3H, m), 7.97 (2H, d, $J = 7.4$ Hz), 9.24 (2H, brs), 9.85 (1H, s).

20 [0435]

Example 82

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}-3-methylphenyl)benzamide hydrochloride

[0436]



25

[0437]

By a method similar to Example 81, the title compound (50.1 mg) was obtained from 4-bromo-3-methylaniline (3.55 g).

MS (API+): $[M+H]^+$ 321.4.

30 ^1H NMR (300 MHz, DMSO- d_6) δ 0.34-0.43 (2H, m), 0.54-0.67 (2H, m), 0.98-1.27 (2H, m), 1.37-1.51 (1H, m), 2.39 (3H, s), 2.41-2.46 (1H, m), 2.89-3.06 (3H, m), 6.99 (1H, d, $J = 8.5$ Hz),

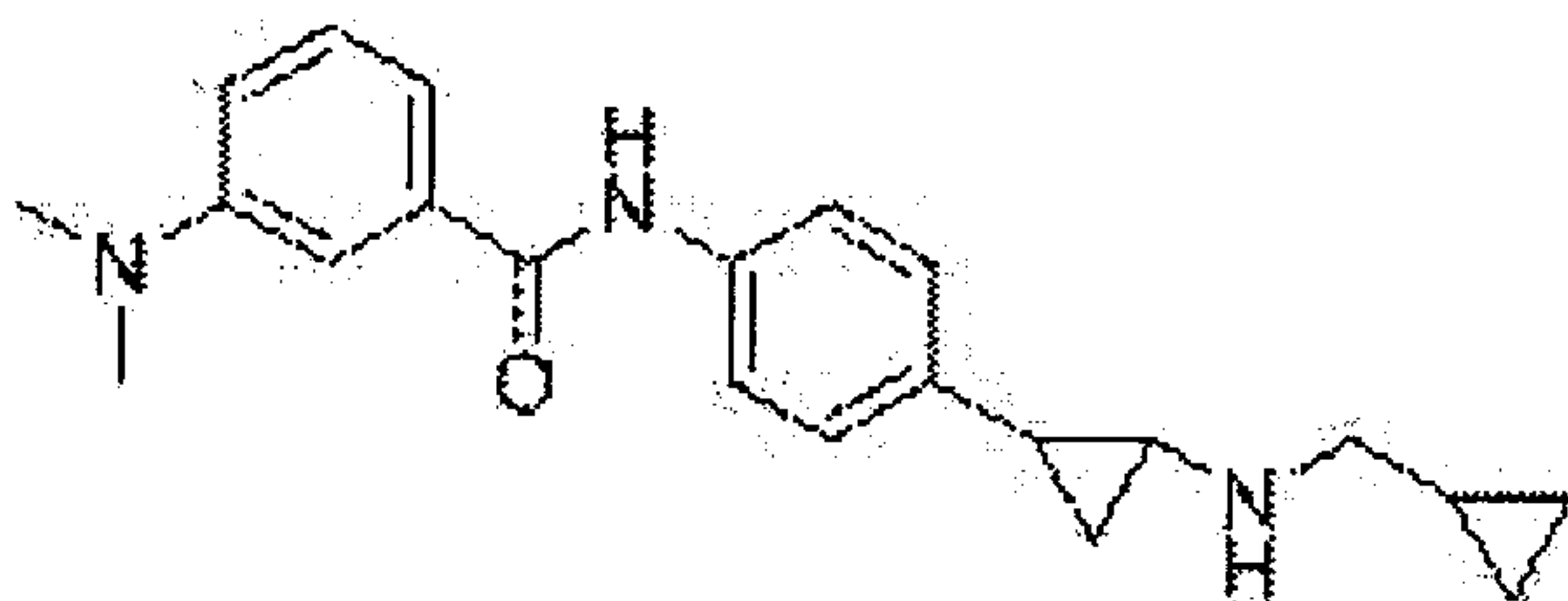
7.46-7.66 (5H, m), 7.94 (2H, d, $J = 7.4$ Hz), 9.04 (2H, brs), 10.16 (1H, s).

[0438]

Example 83

5 N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-3-(dimethylamino)benzamide bis(trifluoroacetate)

[0439]



[0440]

10 To tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (30 mg) were added a solution of 3-(dimethylamino)benzoic acid (33 mg) in DMF (1 mL), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (76 mg), and N,N-diisopropylethylamine (26 mg), and the mixture was stirred at room temperature overnight. To the reaction mixture were added water (1 mL) and ethyl acetate (3 mL) and the mixture was stirred. The organic layer was passed through a phase separation filter, and the solvent was evaporated from the separate liquid by an air blowing apparatus. To the residue was added trifluoroacetic acid (200 μ L) and the mixture was stirred for 1 hr. The solvent was evaporated by an air blowing apparatus. The residue was purified by HPLC (column: YMC Triart C18, mobile phase: 0.1% trifluoroacetic acid-acetonitrile/0.1% aqueous trifluoroacetic acid solution) to give the title compound (12.6 mg).

MS (API+): $[M+H]^+$ 350.1.

[0441]

30 The compounds produced by the method described in the above-mentioned Example 83 or a method analogous thereto are shown in the following Tables. In the Tables, MS shows measured values.

[0442]

[Table 1-6]

Ex. No.	IUPAC name	structure	salt	MS
84	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}-phenyl)-4-(dimethylamino)-benzamide		2CF ₃ COOH	350.1
85	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}-phenyl)-5,6,7,8-tetrahydronaphthalene-2-carboxamide		CF ₃ COOH	361.1
86	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}-phenyl)-4-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide		CF ₃ COOH	403.1
87	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}-phenyl)-4-(methylsulfonyl)-benzamide		CF ₃ COOH	385.0
88	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}-phenyl)-4-sulfamoylbenzamide		CF ₃ COOH	386.0
89	4-cyclohexyl-N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}-phenyl)benzamide		CF ₃ COOH	389.1
90	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}-phenyl)-1,3-benzothiazole-6-carboxamide		CF ₃ COOH	364.0
91	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}-phenyl)-3-(methylsulfonyl)-benzamide		CF ₃ COOH	385.0

[0443]

[Table 1-7]

Ex. No.	IUPAC name	structure	salt	MS
92	N-(4-{trans-2-[(cyclopropylmethyl)-amino]cyclopropyl}-phenyl)-4-(1H-imidazol-1-yl)benzamide		2CF ₃ COOH	373.0
93	N-(4-{trans-2-[(cyclopropylmethyl)-amino]cyclopropyl}-phenyl)-5-phenyl-1,2-oxazole-3-carboxamide		CF ₃ COOH	374.0
94	N-(4-{trans-2-[(cyclopropylmethyl)-amino]cyclopropyl}-phenyl)-4-(1H-pyrazol-1-yl)benzamide		2CF ₃ COOH	373.0
95	N-(4-{trans-2-[(cyclopropylmethyl)-amino]cyclopropyl}-phenyl)-4-(1,3-oxazol-5-yl)benzamide		CF ₃ COOH	374.0
96	N-(4-{trans-2-[(cyclopropylmethyl)-amino]cyclopropyl}-phenyl)-4-(pyridin-4-yl)benzamide		2CF ₃ COOH	384.1
97	N-(4-{trans-2-[(cyclopropylmethyl)-amino]cyclopropyl}-phenyl)-2-(3-thienyl)-1H-benzimidazole-6-carboxamide		CF ₃ COOH	429.1
98	N-(4-{trans-2-[(cyclopropylmethyl)-amino]cyclopropyl}-phenyl)-2-(2-furyl)-1H-benzimidazole-6-carboxamide		CF ₃ COOH	413.1
99	N-(4-{trans-2-[(cyclopropylmethyl)-amino]cyclopropyl}-phenyl)-1H-indazole-5-carboxamide		2CF ₃ COOH	347.0

[0444]

[Table 1-8]

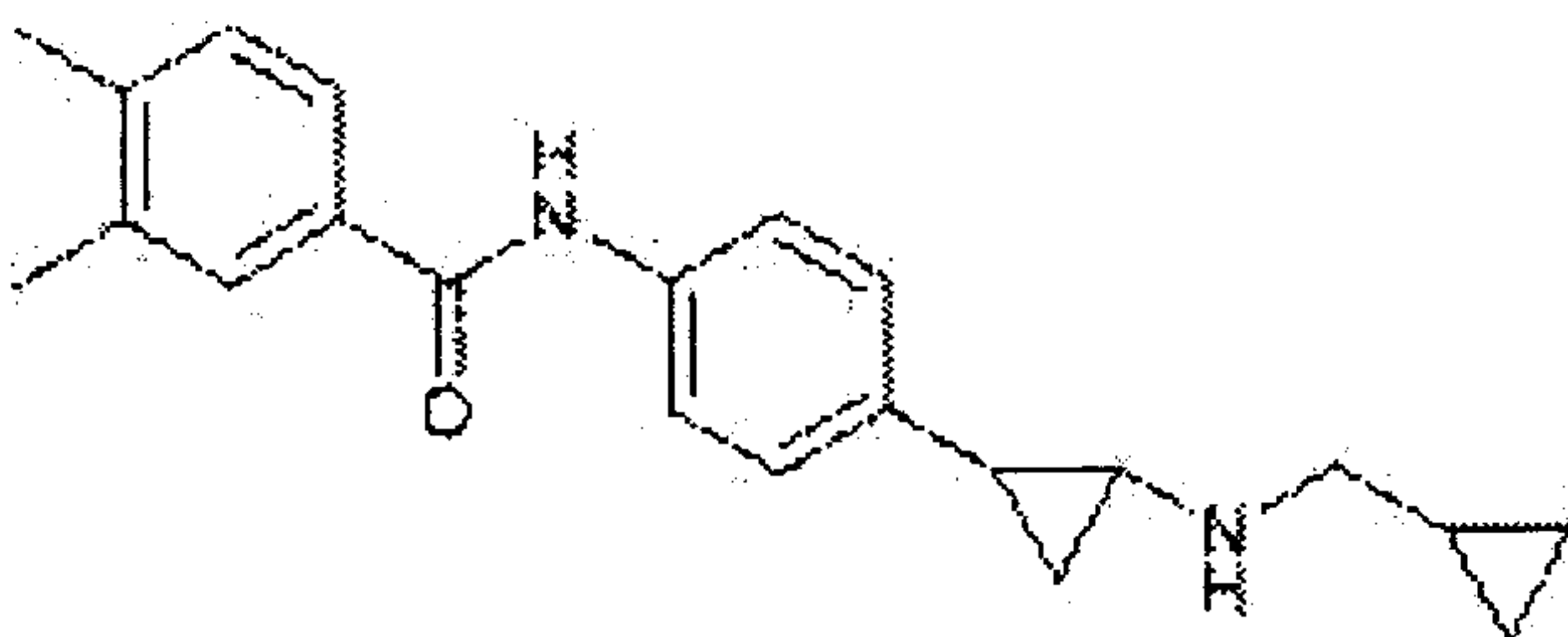
Ex. No.	IUPAC name	structure	salt	MS
100	N-(4-{trans-2-[(cyclopropylmethyl)-amino]cyclopropyl}-phenyl)-3-(1H-tetrazol-1-yl)benzamide		CF3COOH	375.0
101	N-(4-{trans-2-[(cyclopropylmethyl)-amino]cyclopropyl}-phenyl)-3-(2-methyl-1,3-thiazol-4-yl)benzamide		CF3COOH	404.1
102	N-(4-{trans-2-[(cyclopropylmethyl)-amino]cyclopropyl}-phenyl)-4-(1H-tetrazol-5-yl)benzamide		CF3COOH	375.0
103	N-(4-{trans-2-[(cyclopropylmethyl)-amino]cyclopropyl}-phenyl)-2-phenyl-1,3-oxazole-4-carboxamide		CF3COOH	374.0
104	N-(4-{trans-2-[(cyclopropylmethyl)-amino]cyclopropyl}-phenyl)-2-phenyl-1,3-oxazole-5-carboxamide		CF3COOH	374.0

[0445]

5 Example 105

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-
3,4-dimethylbenzamide hydrochloride

[0446]



10 [0447]

By a method similar to Example 80, the title compound (54.7 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (94.0 mg) and 3,4-dimethylbenzoic acid (56.0 mg).

5 MS (API+): $[M+H]^+$ 335.3.

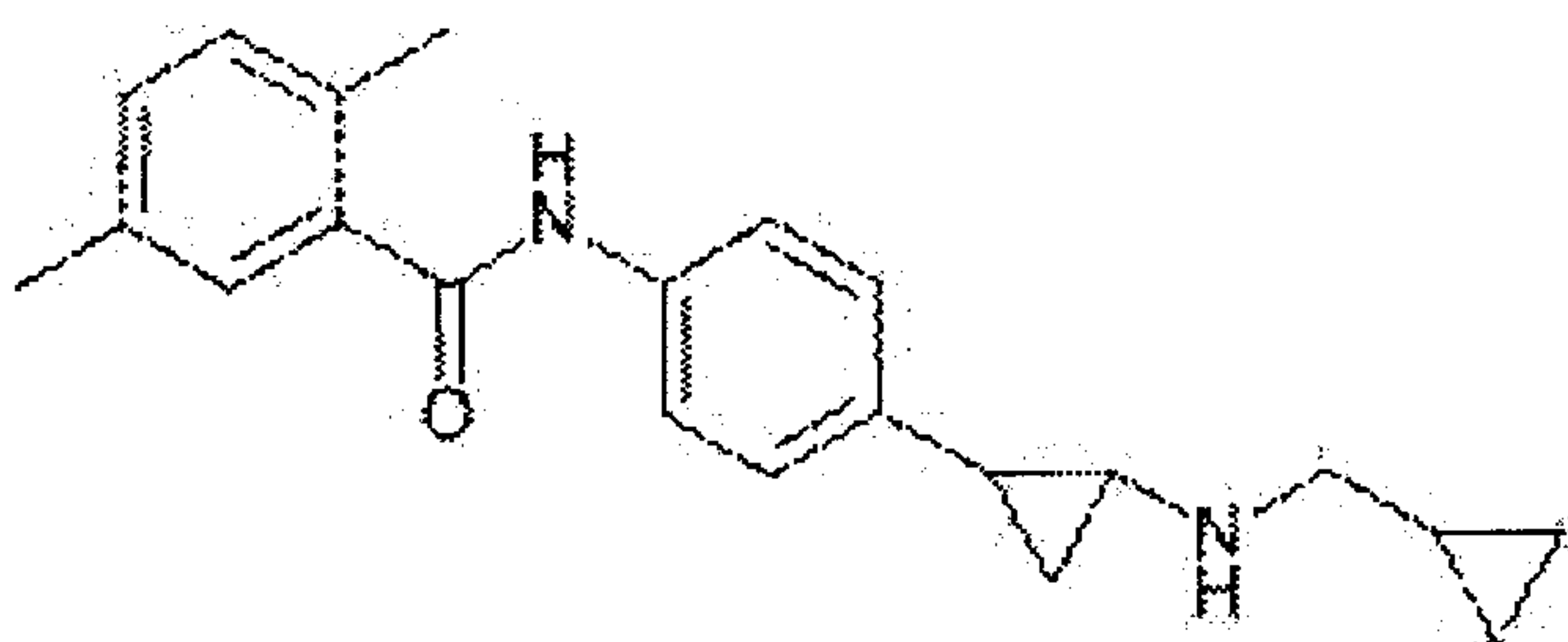
^1H NMR (300 MHz, DMSO- d_6) δ 0.25-0.44 (2H, m), 0.53-0.62 (2H, m), 0.98-1.13 (1H, m), 1.19-1.32 (1H, m), 1.41-1.52 (1H, m), 2.30 (6H, brs), 2.36-2.47 (1H, m), 2.83-2.99 (3H, m), 7.15 (2H, d, $J = 7.9$ Hz), 7.28 (1H, d, $J = 8.0$ Hz), 7.63-7.78 (4H, m),
10 9.00 (2H, brs), 10.10 (1H, s).

[0448]

Example 106

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-2,5-dimethylbenzamide hydrochloride

15 [0449]



[0450]

By a method similar to Example 80, the title compound (50.9 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (94.6 mg) and 2,5-dimethylbenzoic acid (56.4 mg).

MS (API+): $[M+H]^+$ 335.3.

^1H NMR (300 MHz, DMSO- d_6) δ 0.33-0.41 (2H, m), 0.53-0.64 (2H, m), 1.00-1.12 (1H, m), 1.19-1.31 (1H, m), 1.42-1.55 (1H, m), 2.31 (6H, s), 2.39-2.47 (1H, m), 2.83-3.05 (3H, m), 7.09-7.27 (5H, m), 7.66 (2H, d, $J = 7.9$ Hz), 9.17 (2H, brs), 10.23 (1H, s).

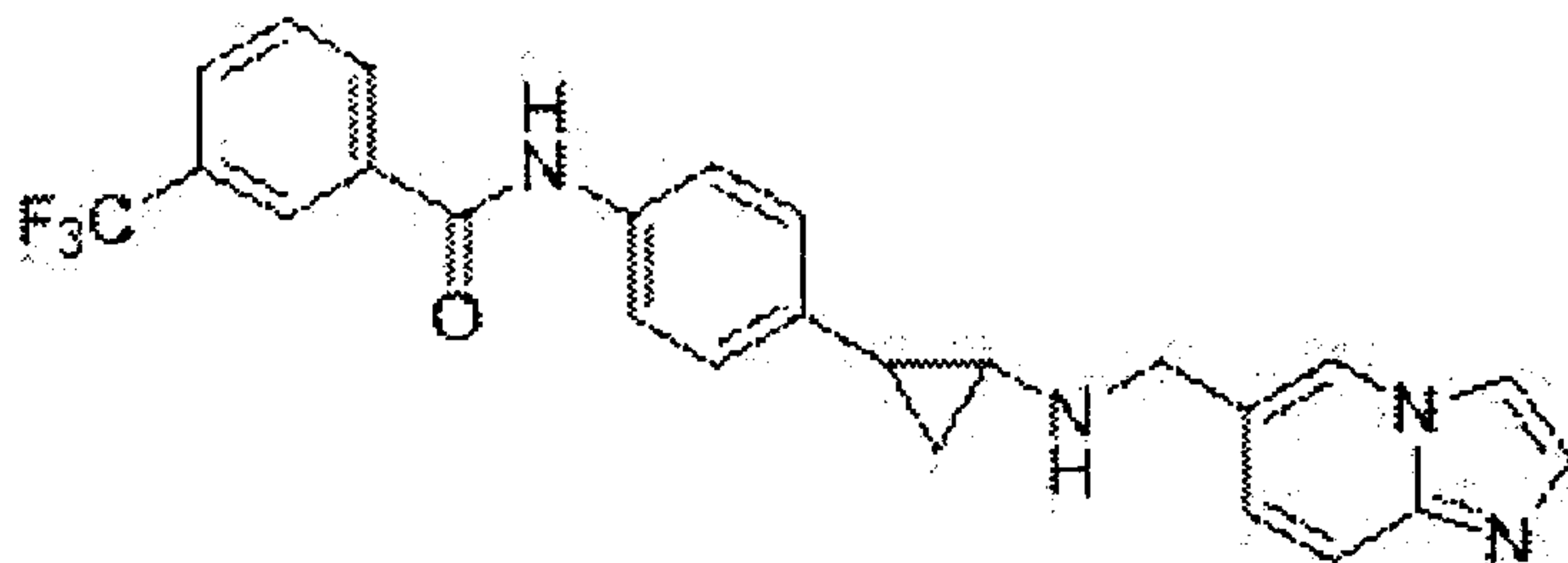
[0451]

Example 107

30 N-(4-{trans-2-[(imidazo[1,2-a]pyridin-6-ylmethyl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide

dihydrochloride

[0452]



[0453]

5 By a method similar to Example 65, the title compound (33 mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (80 mg) and imidazo[1,2-a]pyridine-6-carbaldehyde (42.6 mg).

MS (API+): $[M+H]^+$ 451.0.

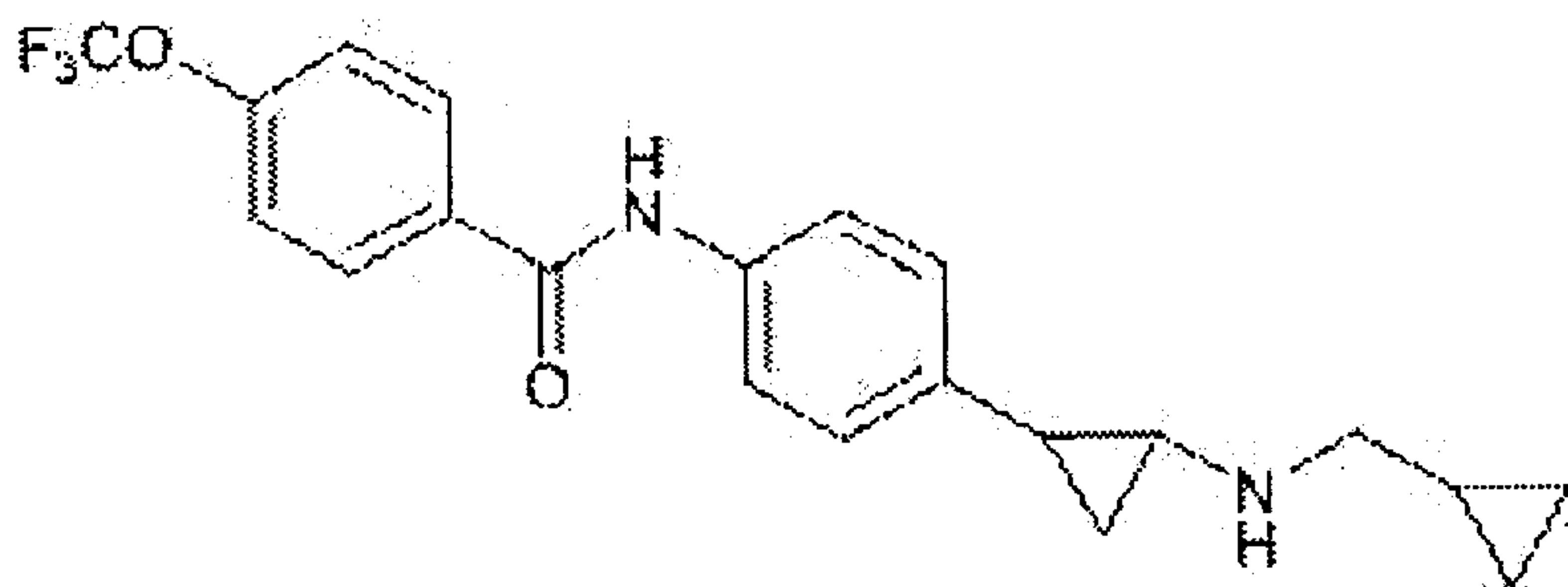
10 ^1H NMR (300 MHz, CD_3OD) δ 1.34-1.44 (1H, m), 1.56-1.69 (1H, m), 2.40-2.51 (1H, m), 3.03-3.11 (1H, m), 4.54-4.70 (2H, m), 7.02 (2H, d, $J = 8.5$ Hz), 7.58 (2H, d, $J = 8.7$ Hz), 7.70 (1H, t, $J = 7.7$ Hz), 7.83-7.89 (1H, m), 7.96-8.07 (2H, m), 8.13-8.25 (4H, m), 9.01-9.05 (1H, m).

15 [0454]

Example 108

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-4-(trifluoromethoxy)benzamide hydrochloride

[0455]



20

[0456]

By a method similar to Example 80, the title compound (55.7 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (87.2 mg) and 4-(trifluoromethoxy)benzoic acid (71.3 mg).

MS (API+): $[M+H]^+$ 391.3.

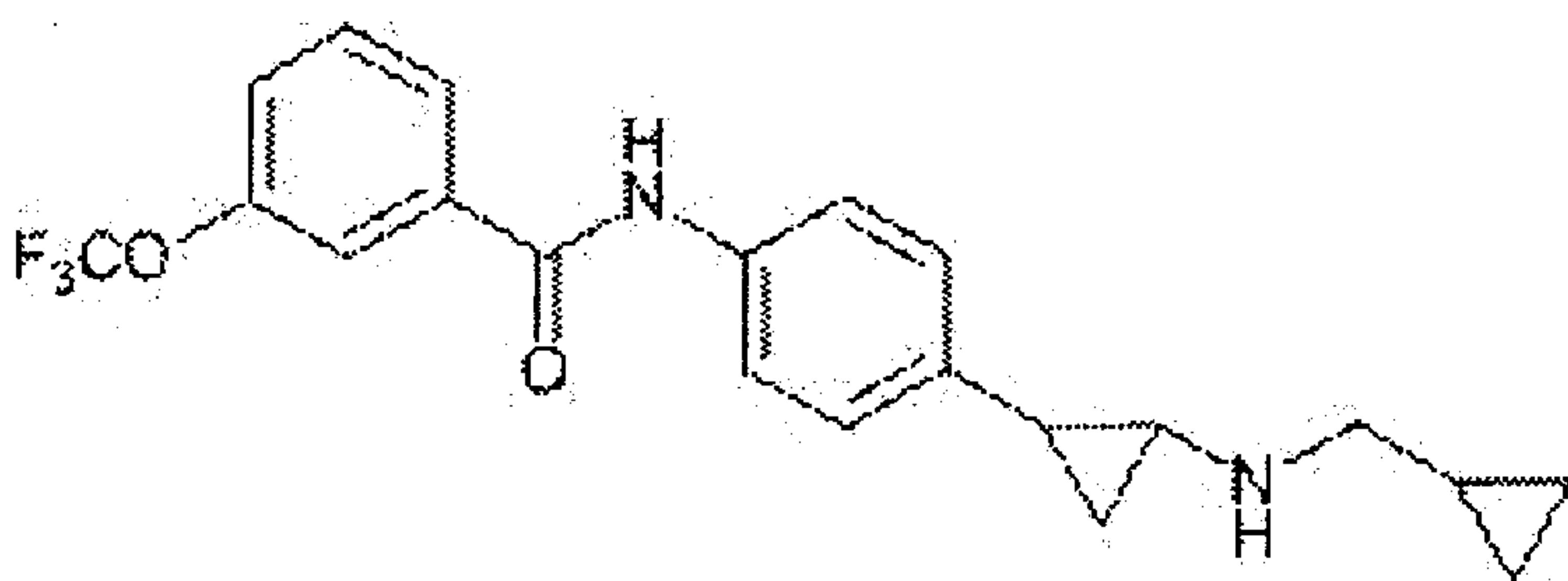
¹H NMR (300 MHz, DMSO-d₆) δ 0.30-0.41 (2H, m), 0.51-0.65 (2H, m), 0.93-1.13 (1H, m), 1.19-1.36 (1H, m), 1.38-1.55 (1H, m), 2.33-2.46 (1H, m), 2.82-3.04 (3H, m), 7.17 (2H, d, J = 8.1 Hz), 7.53 (2H, d, J = 8.1 Hz), 7.70 (2H, d, J = 8.1 Hz), 8.07 (2H, d, J = 8.1 Hz), 8.90 (2H, brs), 10.33 (1H, s).

[0457]

Example 109

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-3-(trifluoromethoxy)benzamide hydrochloride

10 [0458]



[0459]

By a method similar to Example 80, the title compound (82.8 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (88.4 mg) and 3-(trifluoromethoxy)benzoic acid (72.3 mg).

MS (API+): [M+H]⁺ 391.3.

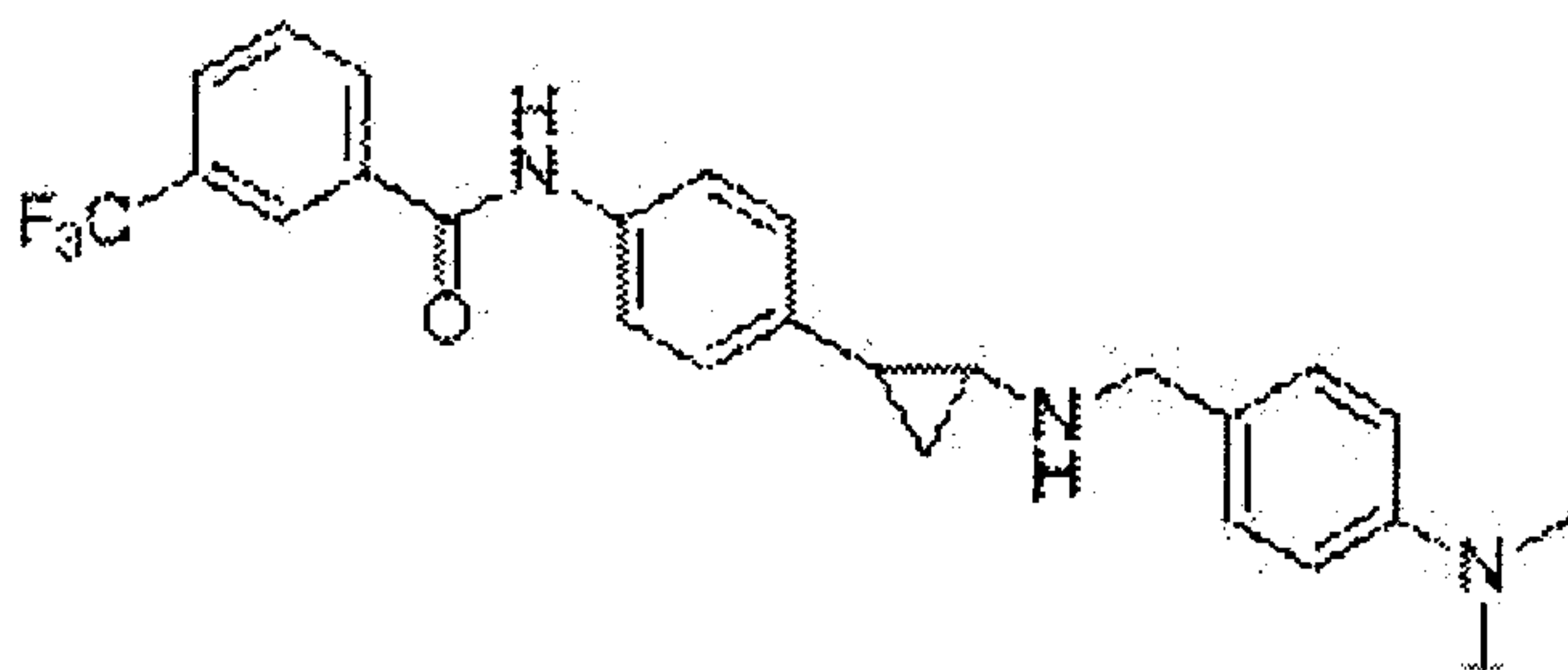
¹H NMR (300 MHz, DMSO-d₆) δ 0.30-0.40 (2H, m), 0.52-0.63 (2H, m), 0.95-1.11 (1H, m), 1.21-1.32 (1H, m), 1.37-1.55 (1H, m), 2.31-2.46 (1H, m), 2.79-3.08 (3H, m), 7.18 (2H, d, J = 8.5 Hz), 7.56-7.76 (4H, m), 7.90 (1H, s), 8.01 (1H, d, J = 7.8 Hz), 8.96 (2H, brs), 10.37 (1H, s).

[0460]

Example 110

25 N-[4-(trans-2-{[4-(dimethylamino)benzyl]amino}cyclopropyl)phenyl]-3-(trifluoromethyl)benzamide dihydrochloride

[0461]



[0462]

By a method similar to Example 65, the title compound (30 mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (80 mg) and 4-(dimethylamino)benzaldehyde (43.5 mg).

MS (API+): $[M+H]^+$ 454.0.

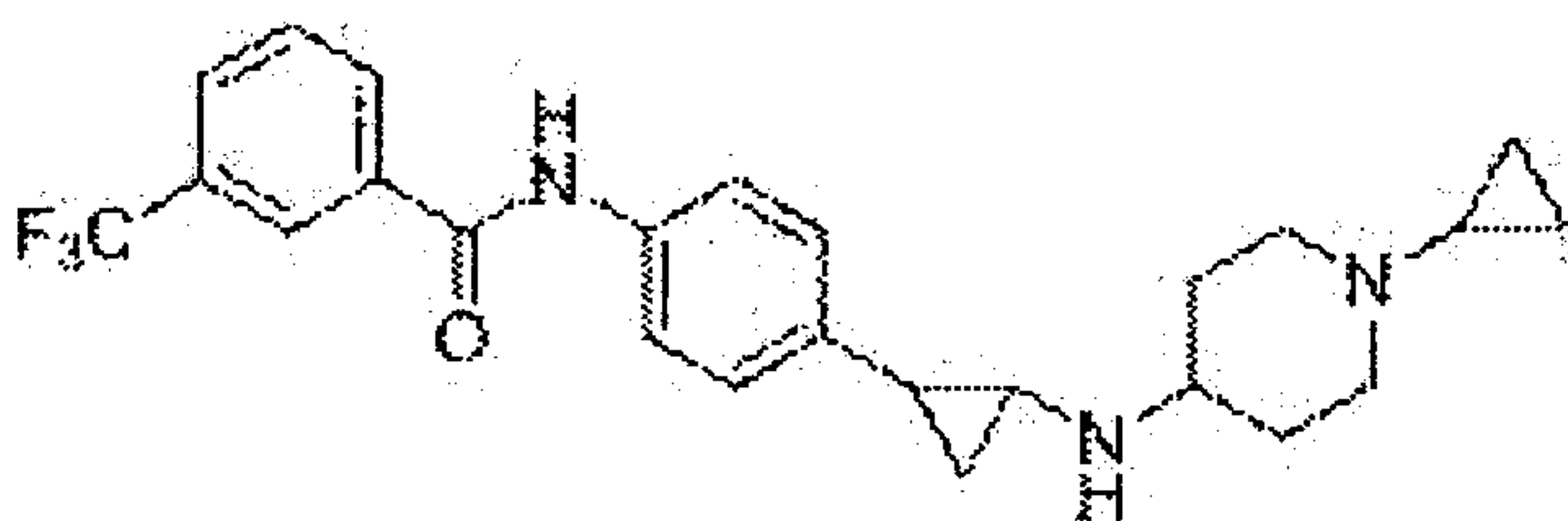
^1H NMR (300MHz, CD_3OD) δ 1.35-1.45 (1H, m), 1.47-1.58 (1H, m), 2.36-2.47 (1H, m), 2.91-3.03 (1H, m), 3.07-3.24 (6H, m), 4.40 (2H, d, $J = 2.8$ Hz), 7.09-7.16 (2H, m), 7.33 (2H, d, $J = 8.5$ Hz), 7.57 (2H, d, $J = 8.7$ Hz), 7.67 (2H, d, $J = 8.5$ Hz), 7.71-7.77 (1H, m), 7.90 (1H, d, $J = 7.9$ Hz), 8.18-8.26 (2H, m).

[0463]

Example 111

N-(4-{trans-2-[(1-cyclopropylpiperidin-4-yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide dihydrochloride

[0464]



[0465]

By a method similar to Example 65, the title compound (50 mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (60 mg) and 1-cyclopropylpiperidin-4-one (30.4 mg).

MS (API+): $[M+H]^+$ 444.3.

^1H NMR (300MHz, CD_3OD) δ 0.89-1.00 (2H, m), 1.02-1.10 (2H, m), 1.46 (1H, q, $J = 6.8$ Hz), 1.52-1.62 (1H, m), 2.01-2.16 (2H, m), 2.35-2.47 (2H, m), 2.52 (1H, ddd, $J = 10.0, 6.5, 3.5$ Hz), 2.68-

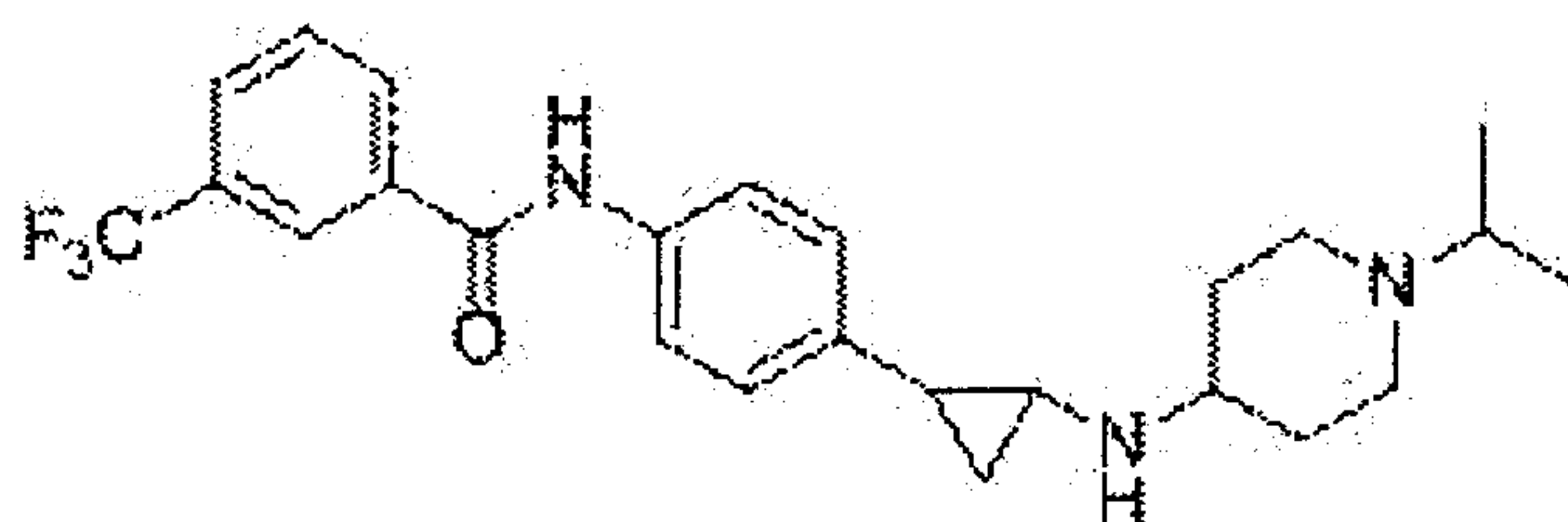
2.82 (1H, m), 3.02 (1H, dt, $J = 7.6, 3.8$ Hz), 3.17-3.29 (2H, m),
3.62-3.81 (3H, m), 7.24 (2H, d, $J = 8.3$ Hz), 7.67-7.78 (3H, m),
7.90 (1H, d, $J = 7.9$ Hz), 8.16-8.27 (2H, m).

[0466]

5 Example 112

N-[4-(trans-2-{[1-(1-methylethyl)piperidin-4-yl]amino}cyclopropyl)phenyl]-3-(trifluoromethyl)benzamide
dihydrochloride

[0467]



10

[0468]

By a method similar to Example 65, the title compound (51 mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (60 mg) and 1-
15 isopropylpiperidin-4-one (30.9 mg).

MS (API+): $[M+H]^+$ 446.1.

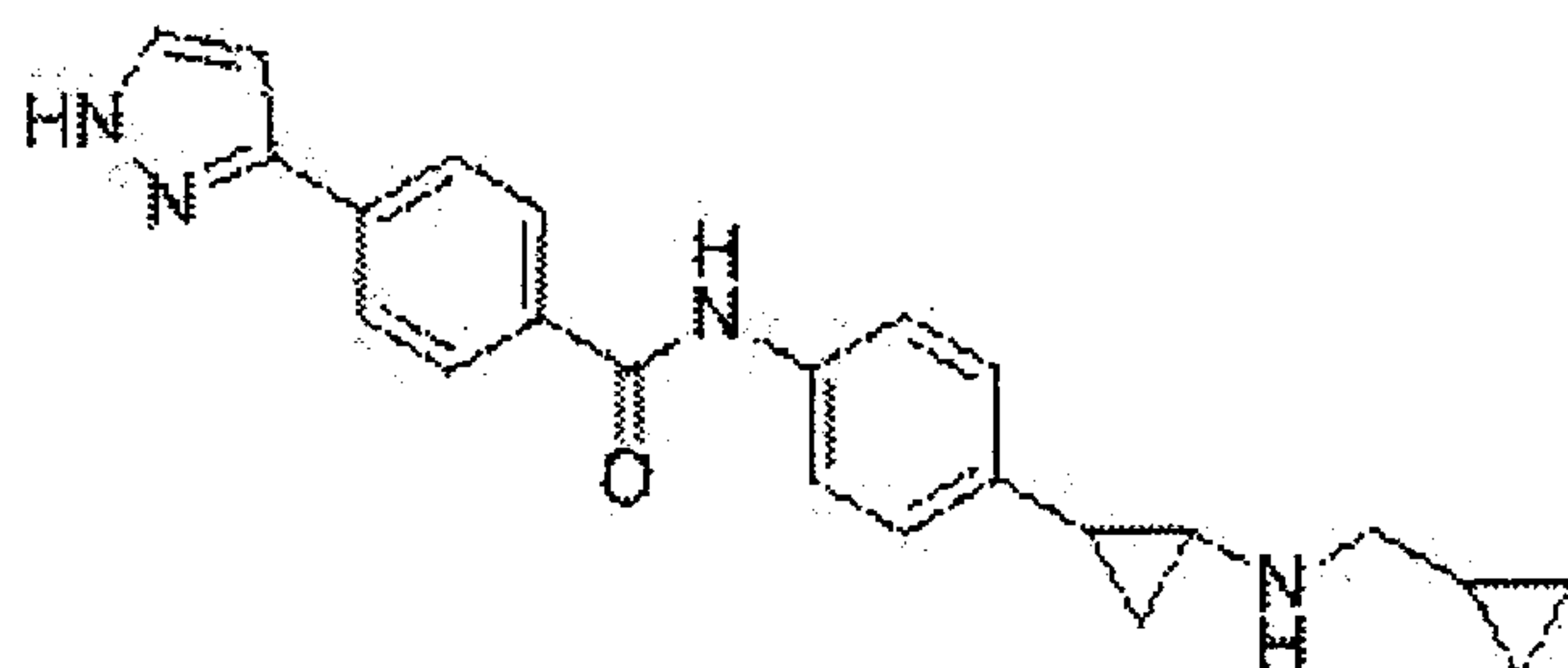
^1H NMR (300MHz, CD_3OD) δ 1.36-1.52 (7H, m), 1.56-1.68 (1H, m),
2.09-2.29 (2H, m), 2.43-2.54 (2H, m), 2.55-2.64 (1H, m), 3.01-
3.09 (1H, m), 3.14-3.28 (2H, m), 3.50-3.81 (4H, m), 7.24 (2H, d,
20 $J = 8.7$ Hz), 7.63-7.79 (3H, m), 7.90 (1H, d, $J = 7.9$ Hz), 8.16-
8.28 (2H, m).

[0469]

Example 113

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-4-(
25 1H-pyrazol-3-yl)benzamide hydrochloride

[0470]



[0471]

By a method similar to Example 79, the title compound (78 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (100 mg) and 4-(1H-pyrazol-3-yl)benzoic acid (93 mg).

5 MS (API+): $[M+H]^+$ 373.0.

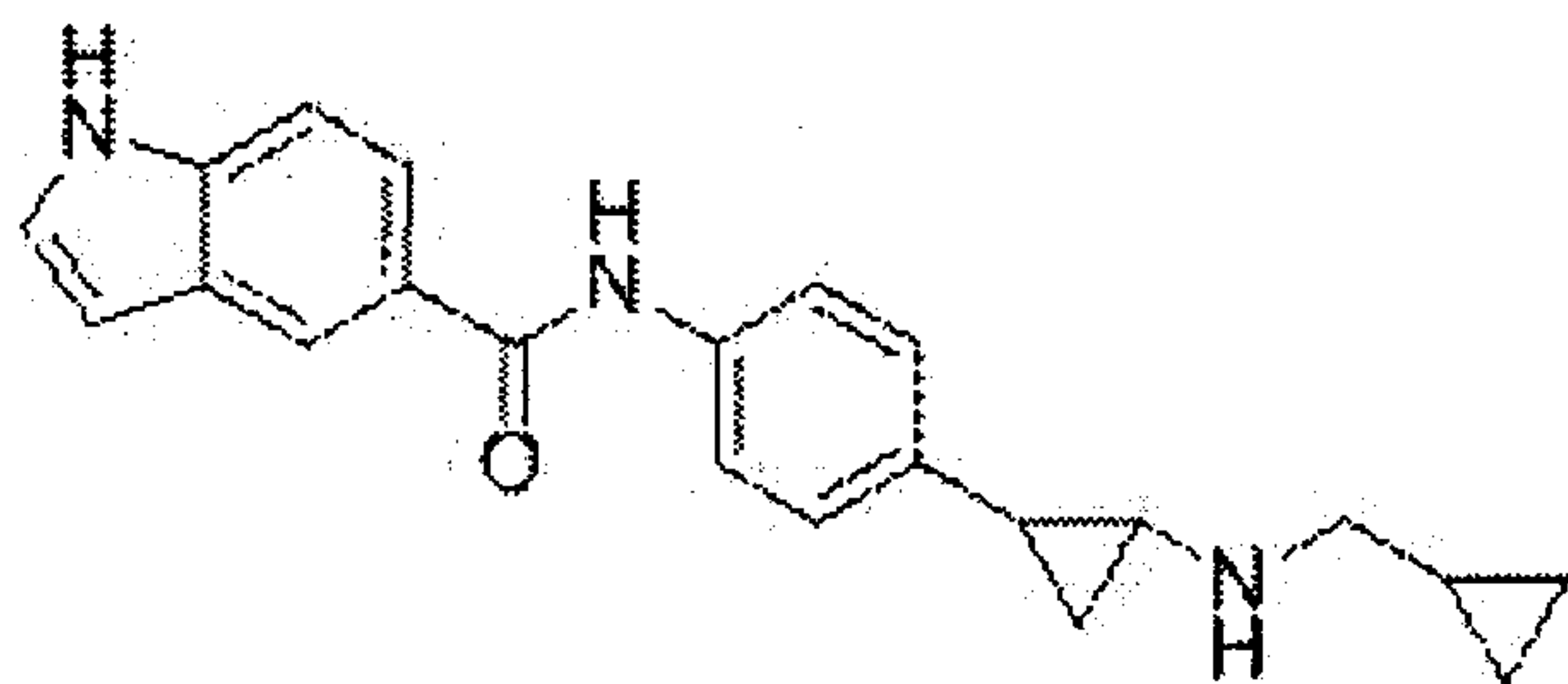
^1H NMR (300MHz, CD_3OD) δ 0.42 (2H, q, $J = 4.8$ Hz), 0.68-0.77 (2H, m), 1.05-1.19 (1H, m), 1.39 (1H, q, $J = 6.8$ Hz), 1.45-1.55 (1H, m), 2.48 (1H, ddd, $J = 10.3, 6.6, 3.7$ Hz), 2.99 (1H, dt, $J = 7.8, 4.1$ Hz), 3.05-3.13 (2H, m), 6.91-6.96 (1H, m), 7.19 (2H, d, $J = 8.7$ Hz), 7.67 (2H, d, $J = 8.7$ Hz), 7.90-7.98 (3H, m), 8.02 (2H, d, $J = 7.5$ Hz).

[0472]

Example 114

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-1H-indole-5-carboxamide trifluoroacetate

15 [0473]



[0474]

To tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (30 mg) were added a solution of indole-5-carboxylic acid (32 mg) in DMF (1 mL), N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (28.8 mg) and 1-hydroxybenzotriazole (20 mg), and the mixture was stirred at room temperature overnight. To the reaction solution were added water (1 mL) and ethyl acetate (3 mL) and the mixture was stirred. The organic layer was passed through a phase separation filter, and the solvent was evaporated from the separated liquid by an air blowing apparatus. To the residue was added trifluoroacetic acid (200 μL) and the mixture was stirred for 1 hr. The solvent was evaporated by an air blowing apparatus. The residue was

purified by HPLC (column: YMC Triart C18, mobile phase: 0.1% trifluoroacetic acid-acetonitrile/0.1% aqueous trifluoroacetic acid solution) to give the title compound (18.1 mg).

MS (API+): $[M+H]^+$ 345.9.

5 [0475]

The compounds produced by the method described in the above-mentioned Example 114 or a method analogous thereto are shown in the following Tables. In the Tables, MS shows measured values.

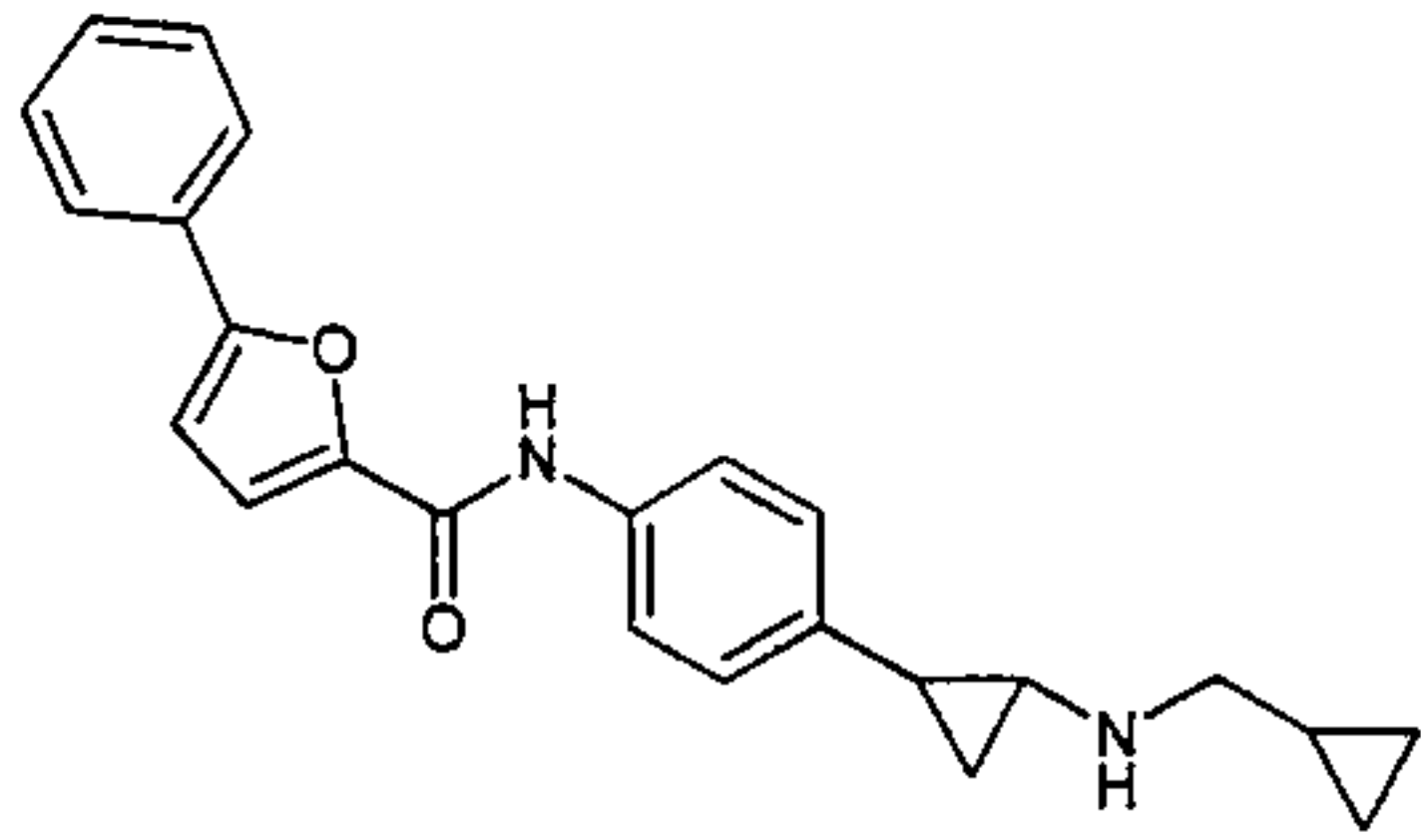
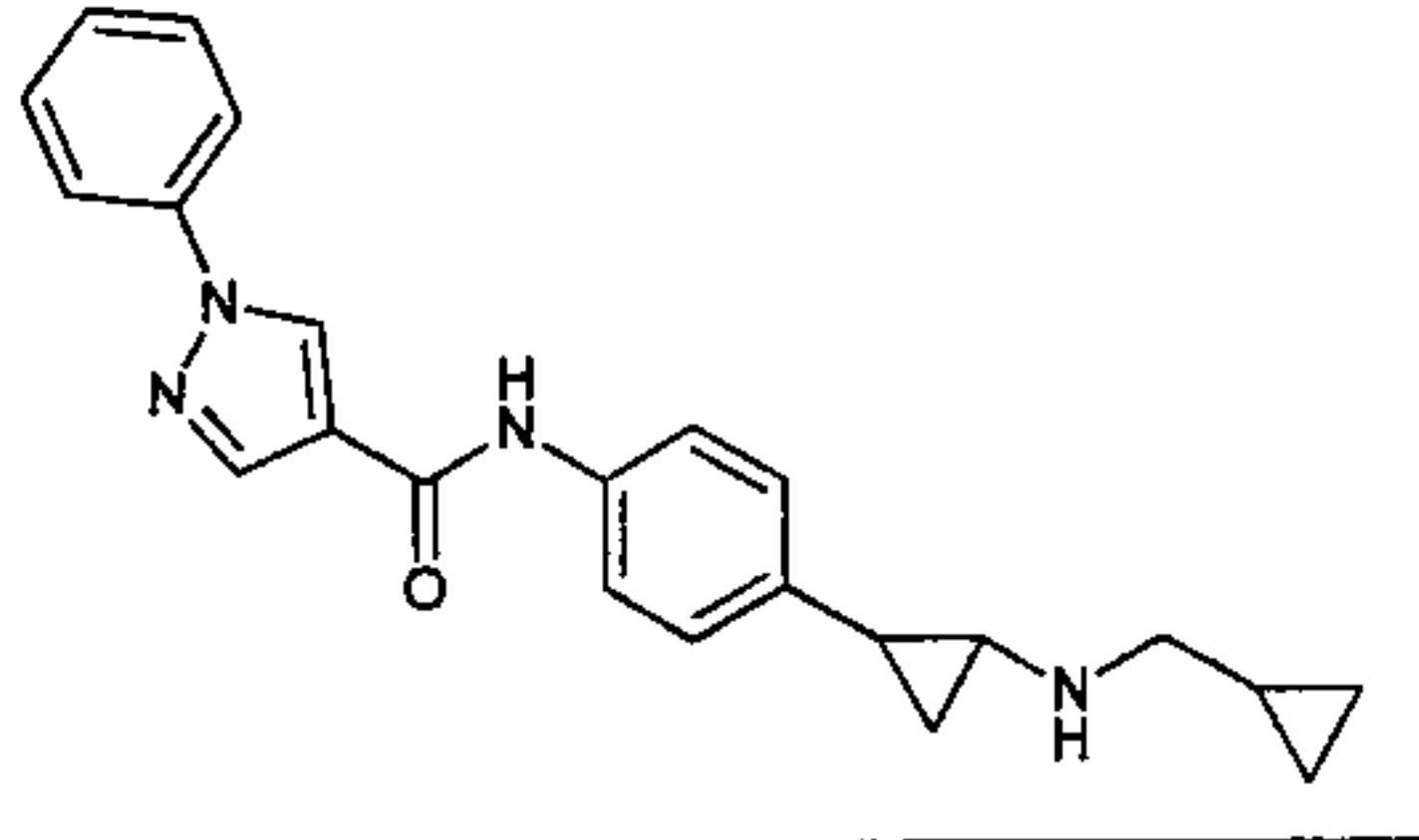
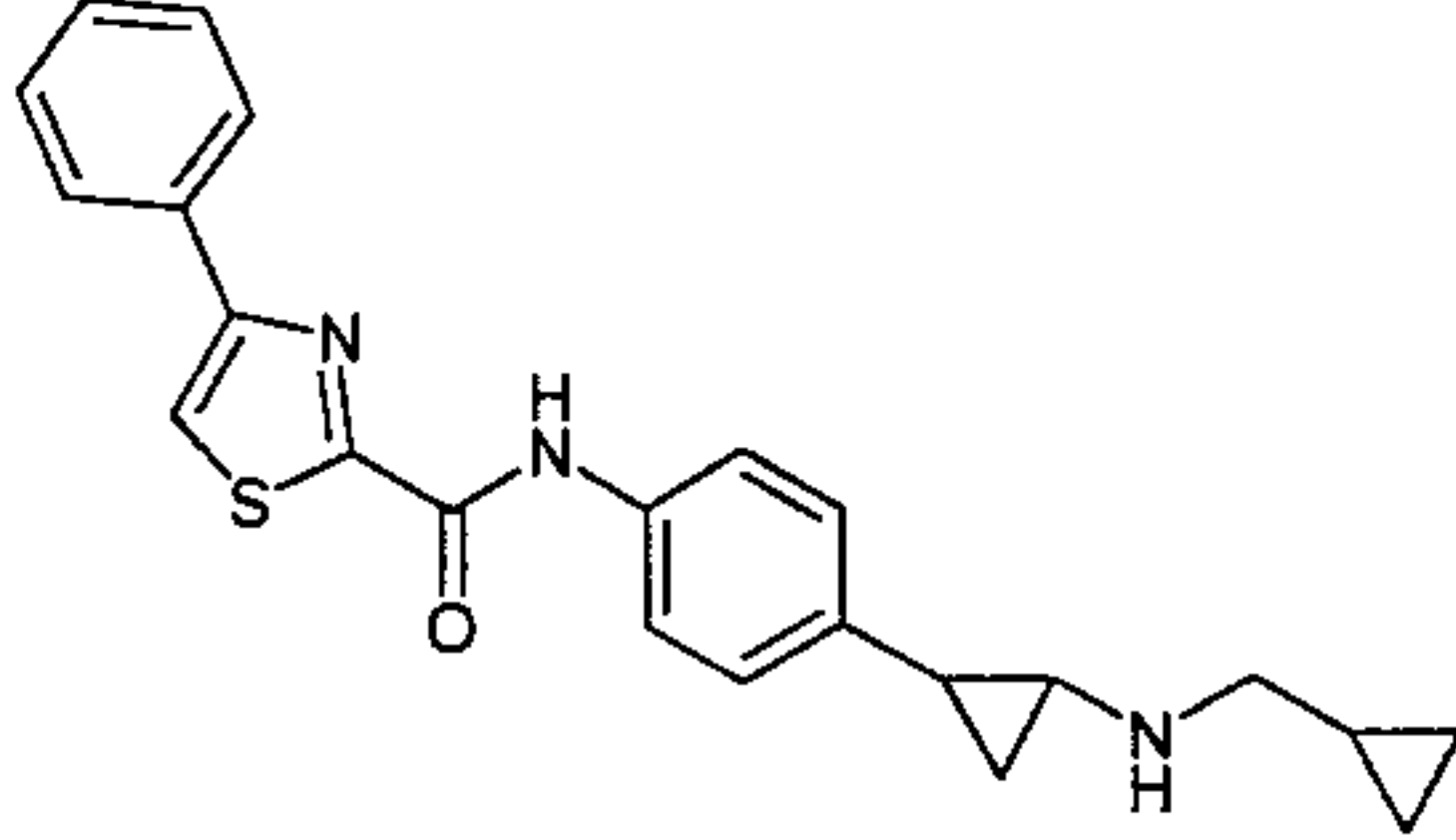
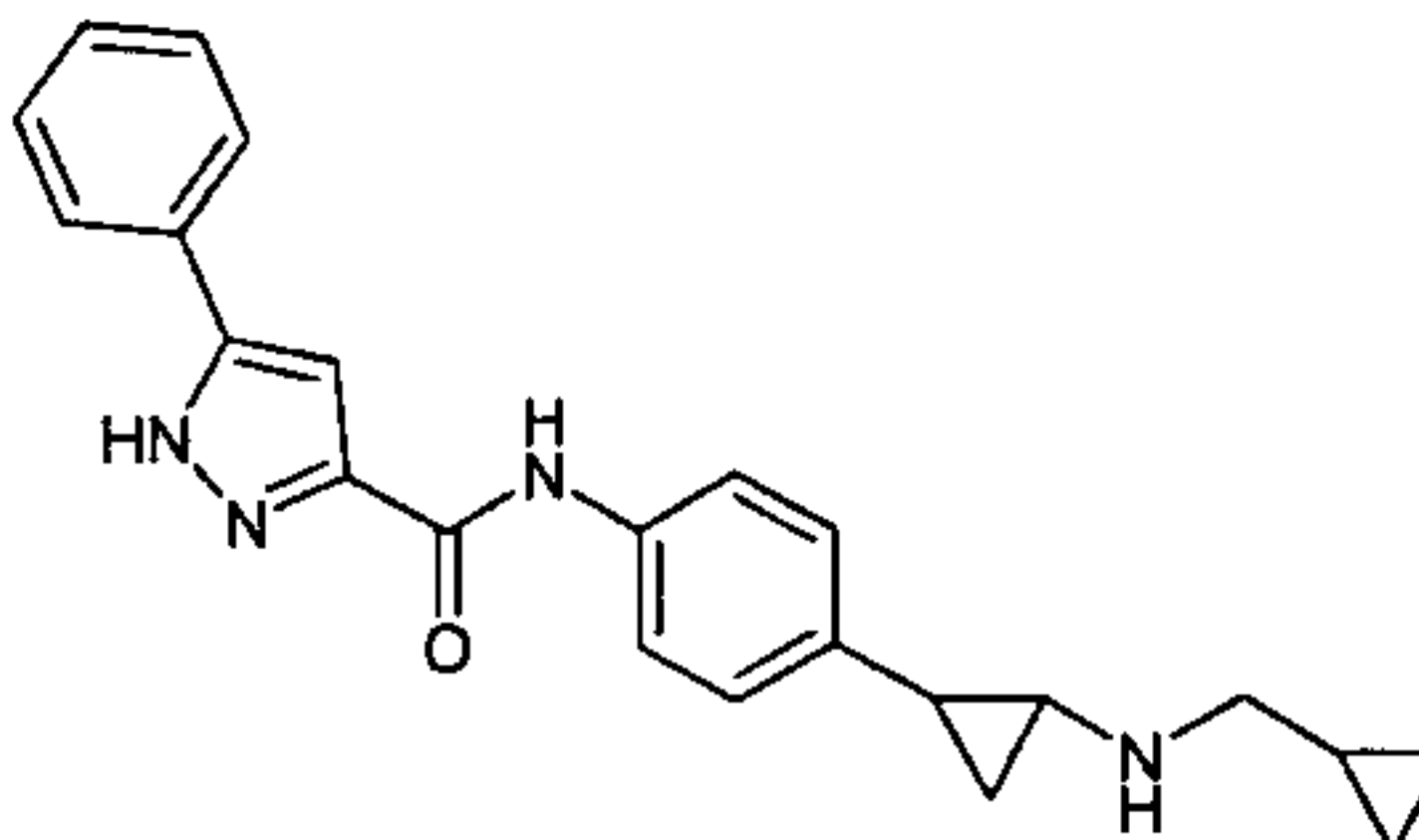
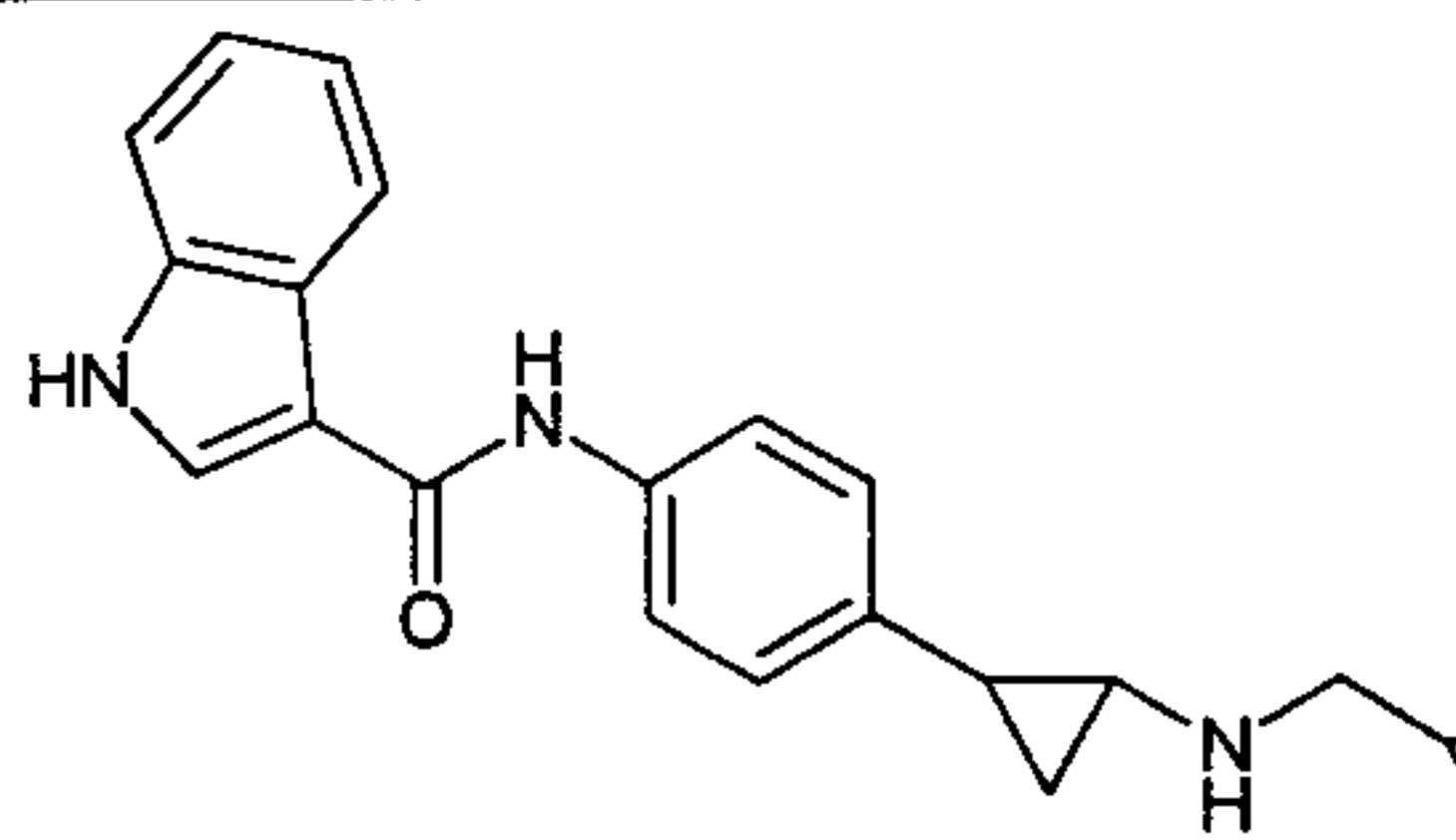
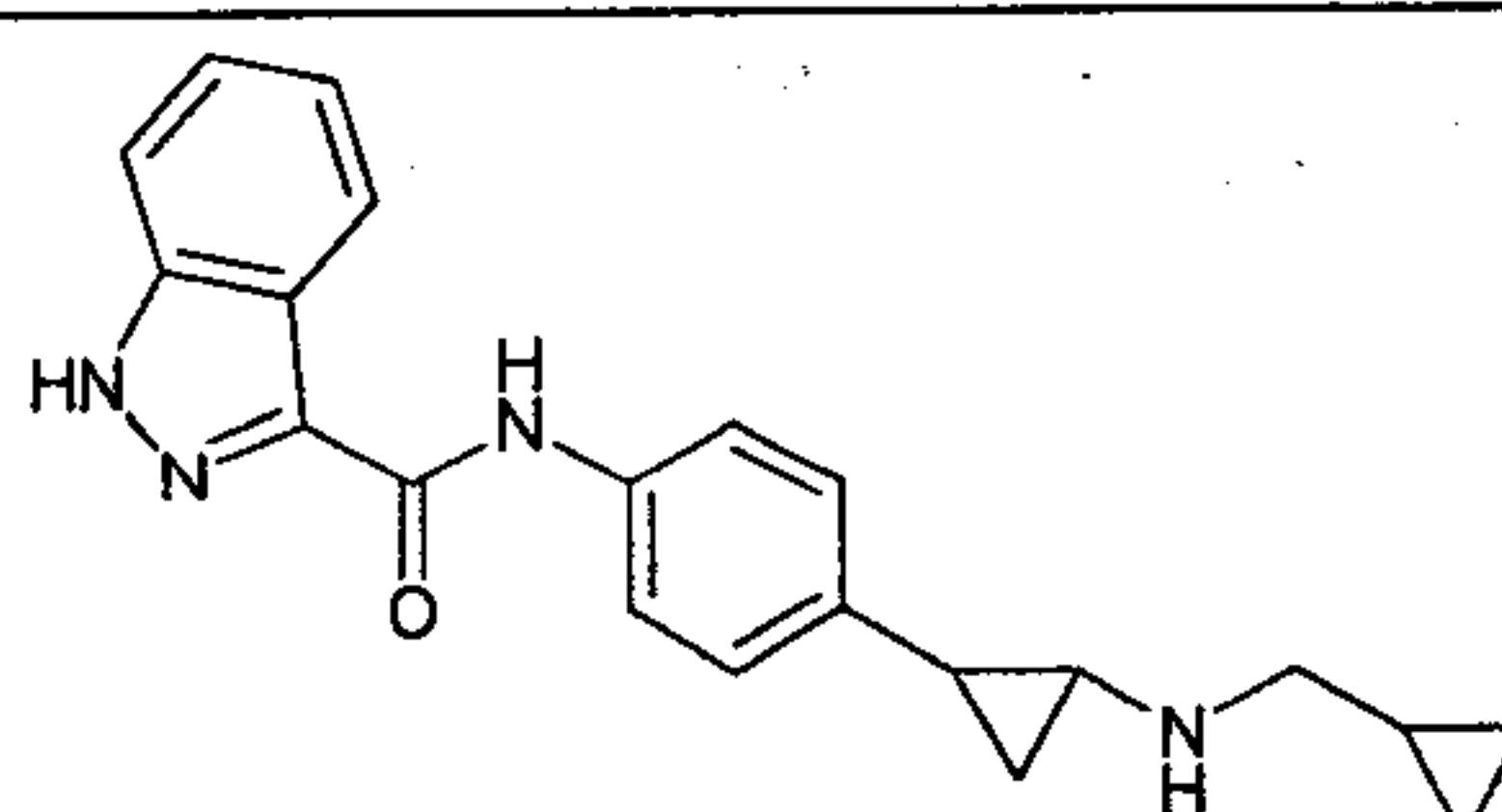
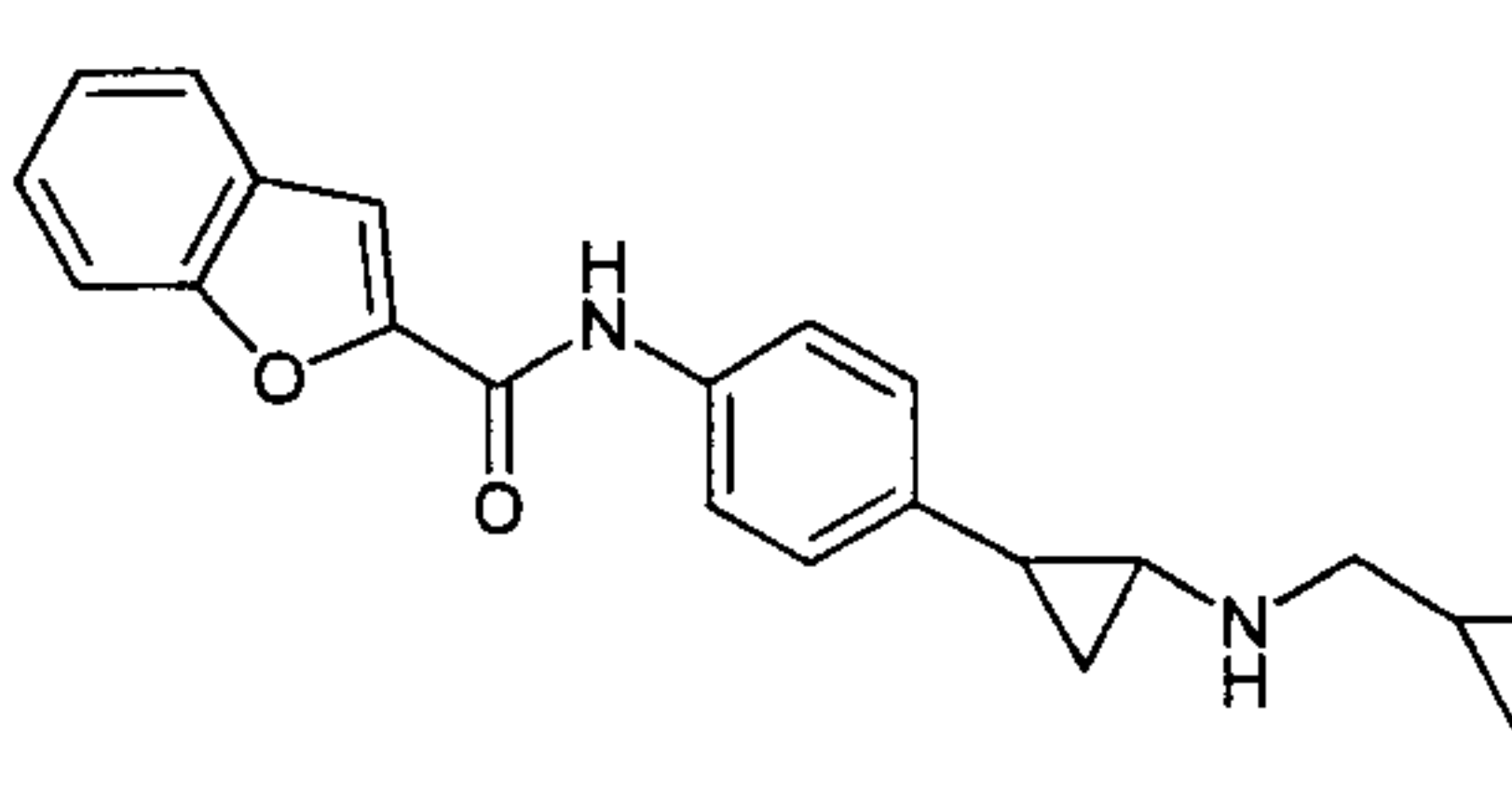
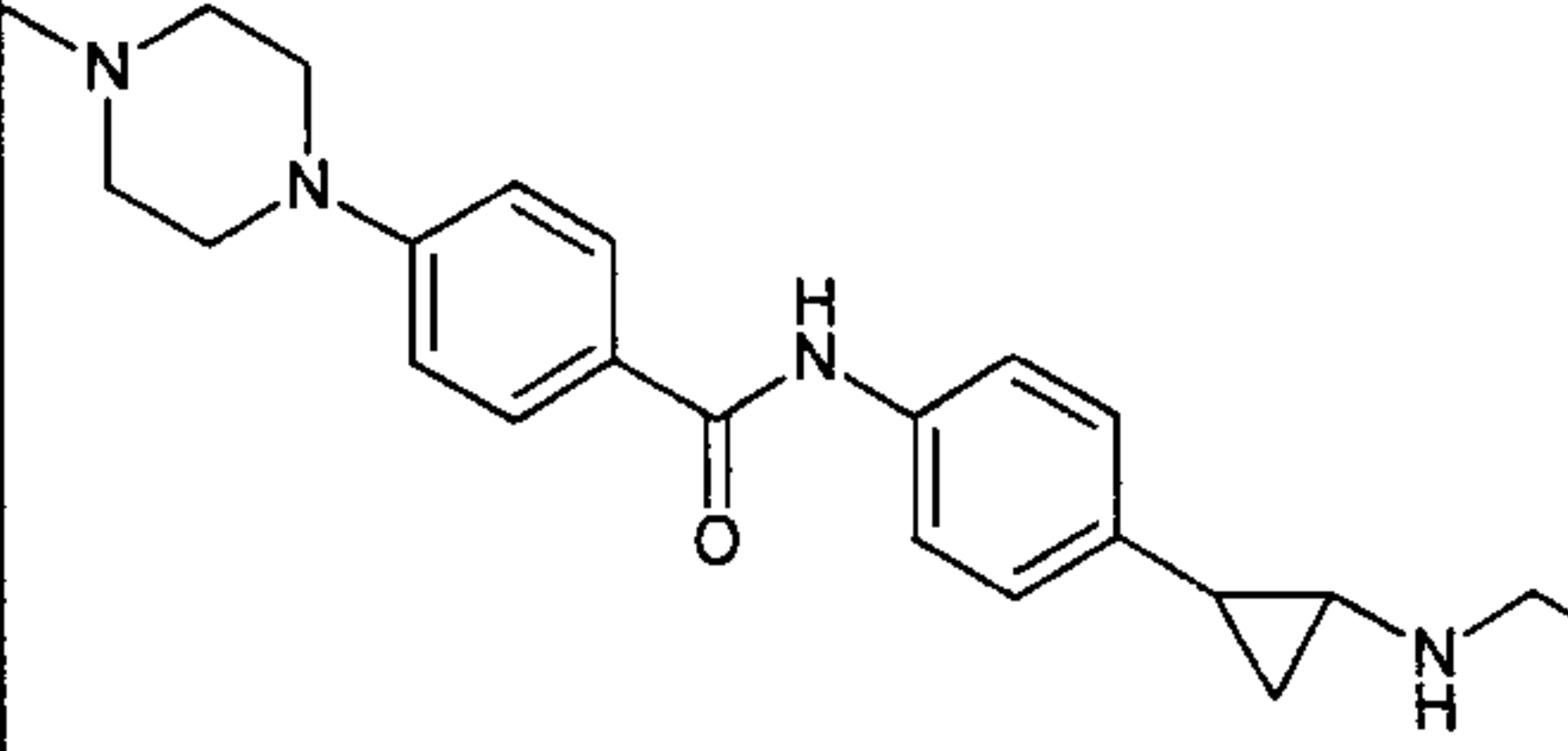
[0476]

[Table 1-9]

Ex. No.	IUPAC name	structure	salt	MS
115	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}-phenyl)-1H-indole-6-carboxamide		CF ₃ COOH	345.9
116	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}-phenyl)-4'-propylbiphenyl-4-carboxamide		CF ₃ COOH	425.1
117	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}-phenyl)-4-(1H-pyrrol-1-yl)benzamide		2CF ₃ COOH	372.0
118	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}-phenyl)-4'-methylbiphenyl-4-carboxamide		CF ₃ COOH	397.1
119	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}-phenyl)-4-(1,2,3-thiadiazol-4-yl)benzamide		CF ₃ COOH	390.9
120	4'-tert-butyl-N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}-phenyl)biphenyl-4-carboxamide		CF ₃ COOH	439.1
121	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}-phenyl)-5-methyl-1-phenyl-1H-pyrazole-4-carboxamide		2CF ₃ COOH	387.0
122	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}-phenyl)-5-methyl-2-phenyl-1,3-oxazole-4-carboxamide		CF ₃ COOH	388.0

[0477]

[Table 1-10]

Ex. No.	IUPAC name	structure	salt	MS
123	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-5-phenyl-2-furamide		CF ₃ COOH	372.9
124	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-1-phenyl-1H-pyrazole-4-carboxamide		2CF ₃ COOH	373.0
125	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-4-phenyl-1,3-thiazole-2-carboxamide		CF ₃ COOH	389.9
126	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-5-phenyl-1H-pyrazole-3-carboxamide		2CF ₃ COOH	373.0
127	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-1H-indole-3-carboxamide		CF ₃ COOH	345.9
128	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-1H-indazole-3-carboxamide		CF ₃ COOH	346.9
129	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-1-benzofuran-2-carboxamide		CF ₃ COOH	346.9
130	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-4-(4-methylpiperazin-1-yl)benzamide		3CF ₃ COOH	405.1

[0478]

[Table 1-11]

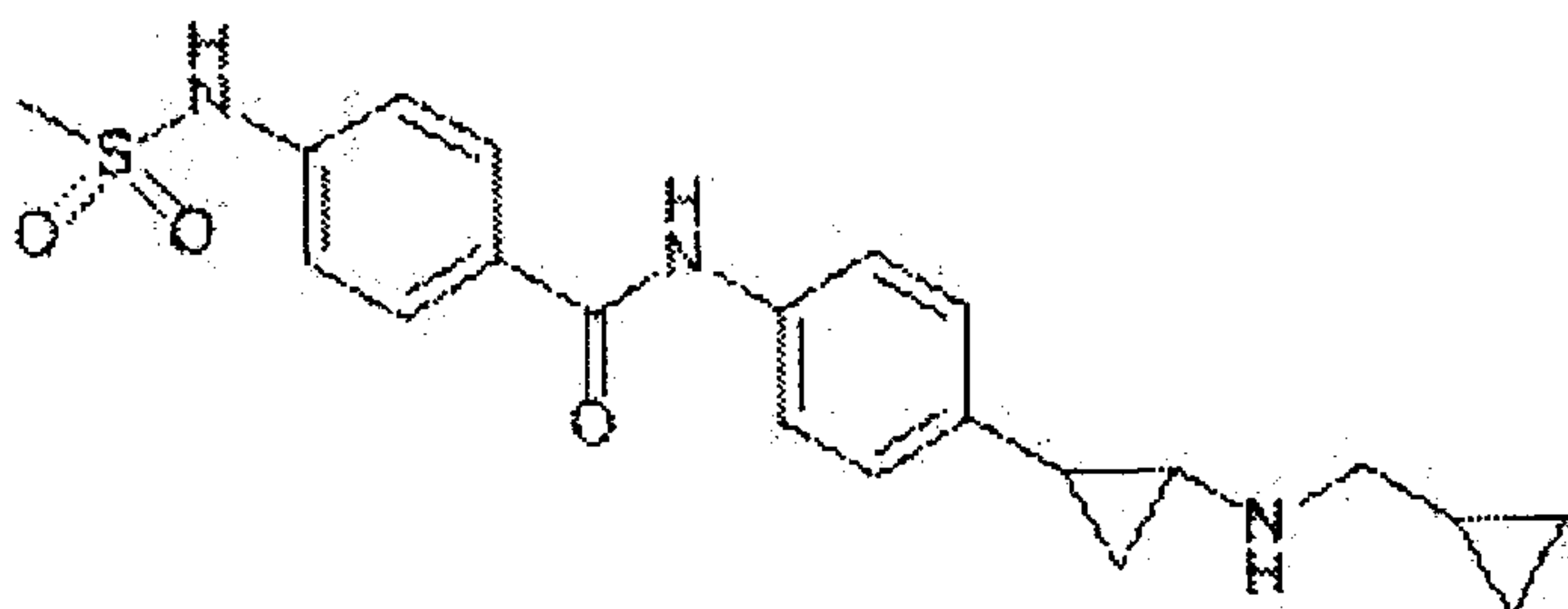
Ex. No.	IUPAC name	structure	salt	MS
131	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-3-(4-methylpiperazin-1-yl)benzamide		3CF3COOH	405.1
132	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-4-(pyridin-3-yl)benzamide		2CF3COOH	384.0
133	N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-3-phenyl-1,2-oxazole-5-carboxamide		CF3COOH	373.9
134	2-acetyl-N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-8-carboxamide		CF3COOH	418.1

[0479]

5 Example 135

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-4-[(methylsulfonyl)amino]benzamide hydrochloride

[0480]



10 [0481]

By a method similar to Example 80, the title compound (81.1 mg) was obtained from tert-butyl [trans-2-(4-

aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (96.9 mg)
and 4-(methanesulfonamido)benzoic acid (83 mg).

MS (API+): $[M+H]^+$ 400.3.

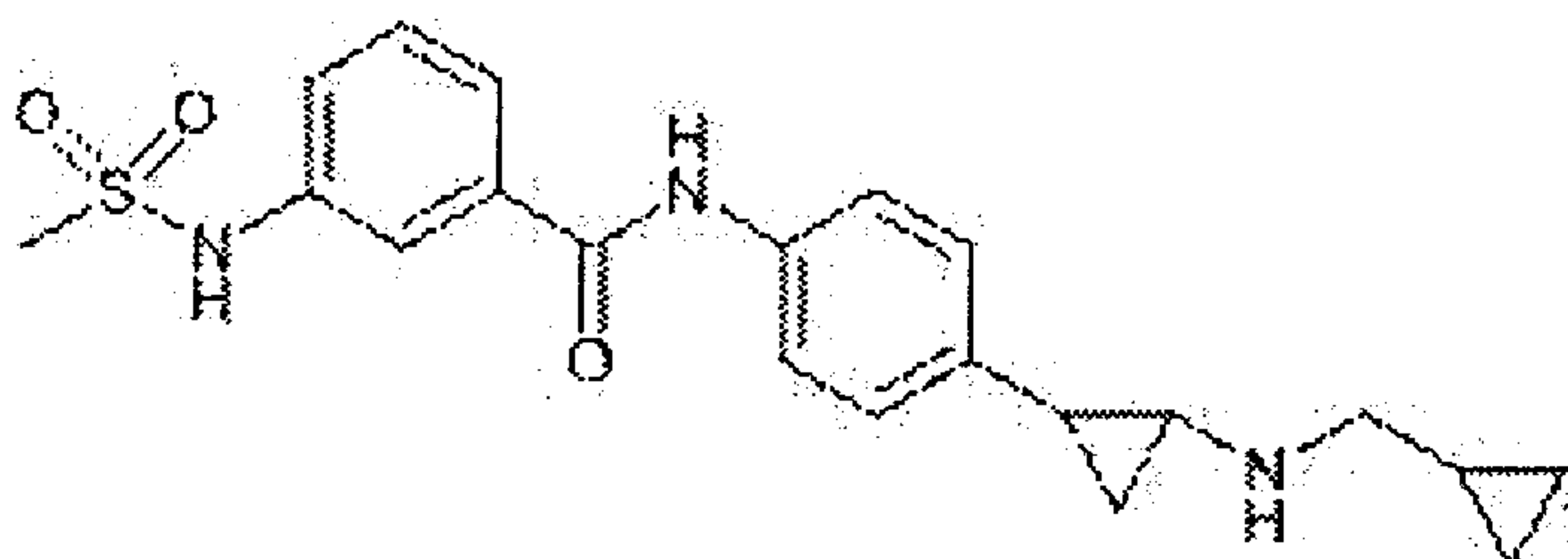
^1H NMR (300 MHz, DMSO- d_6) δ 0.32-0.40 (2H, m), 0.53-0.62 (2H, m), 0.97-1.12 (1H, m), 1.21-1.33 (1H, m), 1.41-1.53 (1H, m), 2.36-2.46 (1H, m), 2.82-3.01 (3H, m), 3.09 (3H, s), 7.15 (2H, d, $J = 8.7$ Hz), 7.30 (2H, d, $J = 8.9$ Hz), 7.69 (2H, d, $J = 8.7$ Hz), 7.93 (2H, d, $J = 8.9$ Hz), 9.08 (2H, brs), 10.14 (2H, s).

[0482]

10 Example 136

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-3-[(methylsulfonyl)amino]benzamide hydrochloride

[0483]



15 [0484]

By a method similar to Example 80, the title compound (75.4 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (95.3 mg) and 3-(methanesulfonamido)benzoic acid (81 mg).

20 MS (API+): $[M+H]^+$ 400.3.

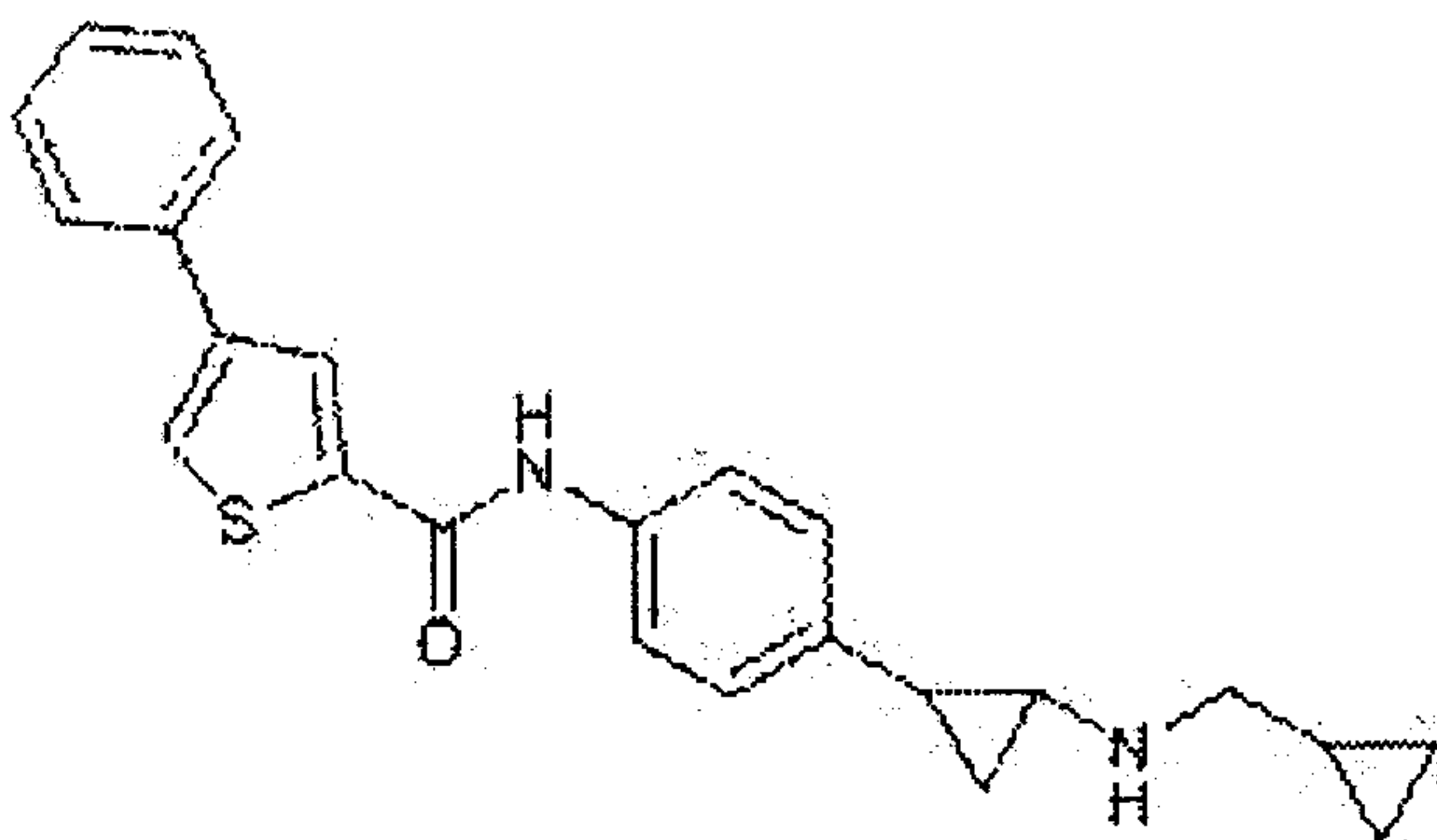
^1H NMR (300 MHz, DMSO- d_6) δ 0.26-0.42 (2H, m), 0.51-0.65 (2H, m), 0.93-1.14 (1H, m), 1.18-1.33 (1H, m), 1.37-1.54 (1H, m), 2.32-2.47 (1H, m), 2.83-2.99 (3H, m), 3.04 (3H, s), 7.16 (2H, d, $J = 8.5$ Hz), 7.37-7.55 (2H, m), 7.63-7.76 (4H, m), 9.03 (2H, brs), 9.98 (1H, brs), 10.27 (1H, s).

[0485]

Example 137

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-4-phenylthiophene-2-carboxamide hydrochloride

30 [0486]



[0487]

By a method similar to Example 80, the title compound (46.8 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (83.1 mg) and 4-phenylthiophene-2-carboxylic acid (67.3 mg).

MS (API+): $[M+H]^+$ 389.2.

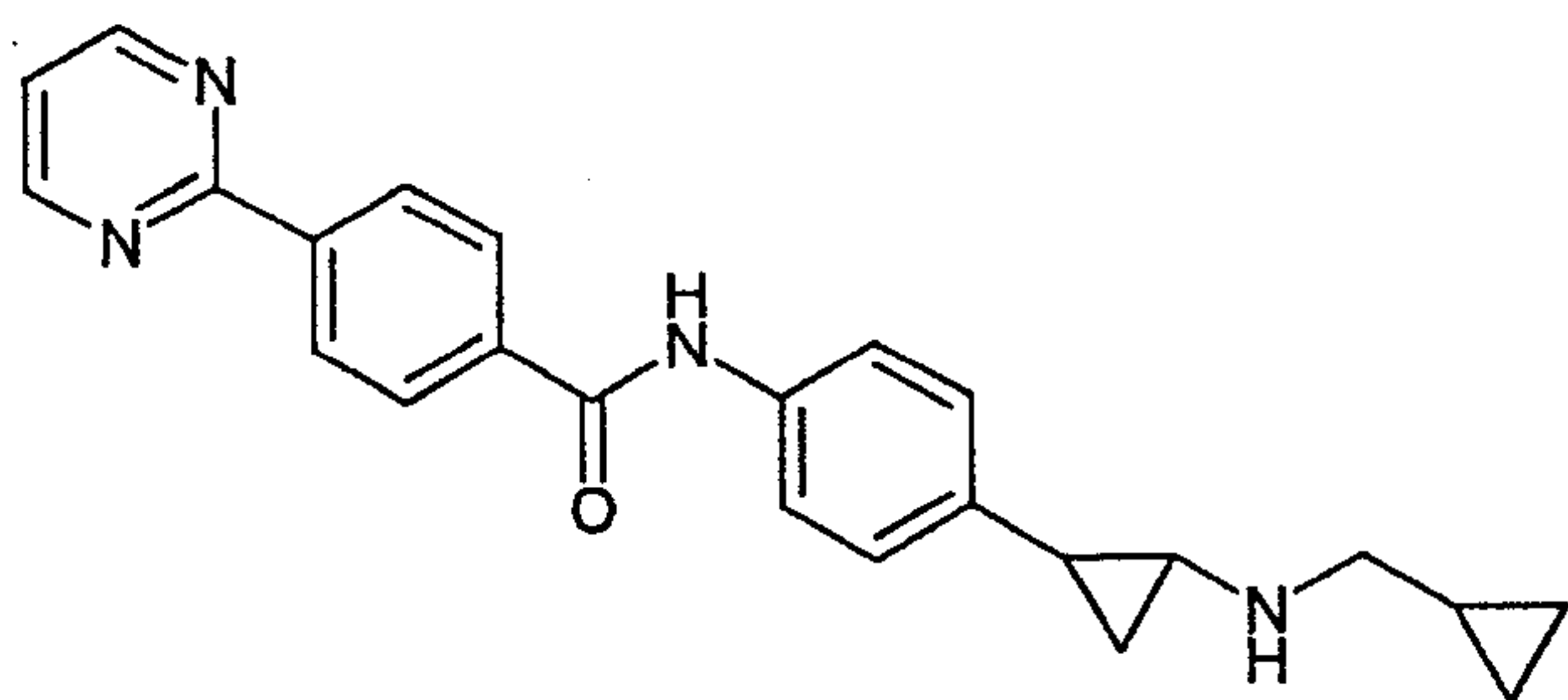
^1H NMR (300 MHz, DMSO- d_6) δ 0.27-0.44 (2H, m), 0.53-0.64 (2H, m), 0.95-1.15 (1H, m), 1.21-1.34 (1H, m), 1.40-1.54 (1H, m), 2.35-2.46 (1H, m), 2.84-3.01 (3H, m), 7.19 (2H, d, $J = 8.5$ Hz), 7.35 (1H, t, $J = 7.4$ Hz), 7.48 (2H, dd, $J = 7.4, 7.3$ Hz), 7.69 (2H, d, $J = 8.5$ Hz), 7.75 (2H, d, $J = 7.3$ Hz), 8.18 (1H, d, $J = 1.4$ Hz), 8.52 (1H, brs), 9.01 (1H, brs), 10.32 (1H, brs).

[0488]

15 Example 138

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-4-(pyrimidin-2-yl)benzamide hydrochloride

[0489]



20 [0490]

By a method similar to Example 80, the title compound (34.3 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (87.7 mg) and 4-(pyrimidin-2-yl)benzoic acid (69.7 mg).

MS (API+): $[M+H]^+$ 385.1.

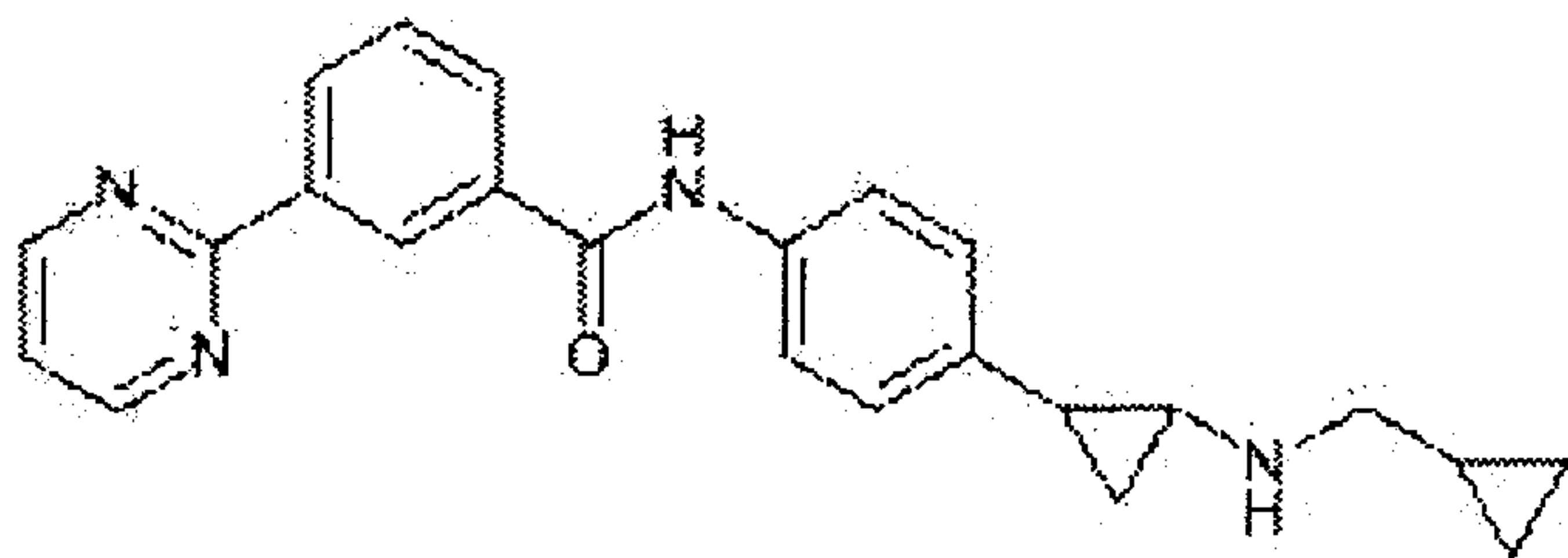
^1H NMR (300 MHz, DMSO- d_6) δ 0.30-0.42 (2H, m), 0.53-0.66 (2H, m), 0.98-1.12 (1H, m), 1.24-1.35 (1H, m), 1.43-1.55 (1H, m), 2.39-2.46 (1H, m), 2.86-3.07 (3H, m), 7.19 (2H, d, J = 8.6 Hz), 7.53 (1H, t, J = 4.9 Hz), 7.75 (2H, d, J = 8.7 Hz), 8.11 (2H, d, J = 8.6 Hz), 8.53 (2H, d, J = 8.6 Hz), 8.97 (2H, d, J = 4.9 Hz), 9.06 (2H, brs), 10.37 (1H, s).

[0491]

Example 139

10 N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-3-(pyrimidin-2-yl)benzamide hydrochloride

[0492]



[0493]

15 By a method similar to Example 80, the title compound (38.9 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (93.0 mg) and 3-(pyrimidin-2-yl)benzoic acid (73.9 mg).

MS (API+): $[M+H]^+$ 385.1.

20 ^1H NMR (300 MHz, DMSO- d_6) δ 0.32-0.42 (2H, m), 0.53-0.65 (2H, m), 0.98-1.11 (1H, m), 1.23-1.35 (1H, m), 1.41-1.55 (1H, m), 2.40-2.47 (1H, m), 2.87-3.08 (3H, m), 7.19 (2H, d, J = 8.6 Hz), 7.52 (1H, t, J = 4.9 Hz), 7.70 (1H, dd, J = 7.8, 7.6 Hz), 7.75 (2H, d, J = 8.6 Hz), 8.10 (1H, ddd, J = 7.6, 1.7, 1.5 Hz), 8.59 (1H, ddd, J = 7.8, 1.6, 1.5 Hz), 8.95 (1H, dd, J = 1.7, 1.6 Hz), 8.97 (2H, d, J = 4.9 Hz), 9.05 (2H, brs), 10.45 (1H, s).

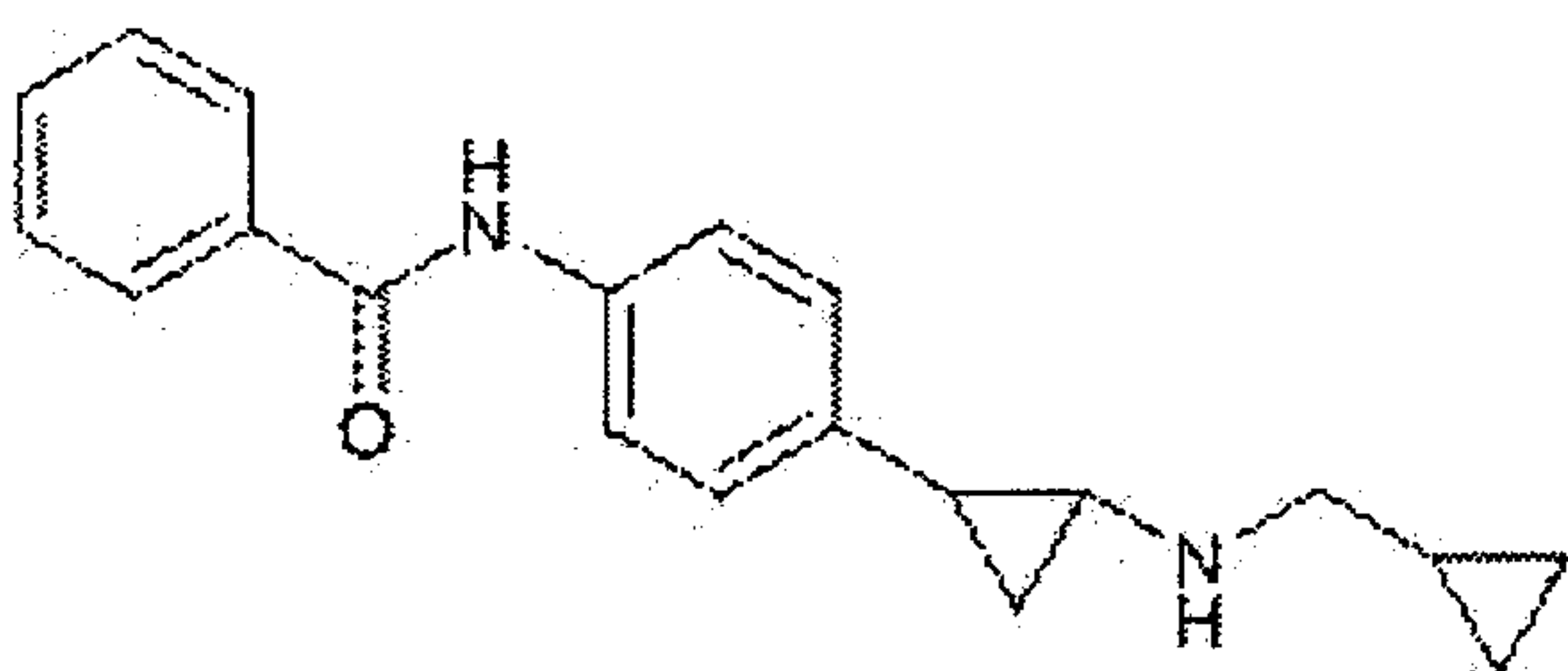
[0494]

Example 140

N-(4-{trans-2-

30 [(cyclopropylmethyl)amino]cyclopropyl}phenyl)benzamide hydrochloride

[0495]



[0496]

By a method similar to Example 68, Steps E and F, the
 5 title compound (79.3 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (91.8 mg) and benzoyl chloride (42.3 μ L).

MS (API+): $[M+H]^+$ 307.3.

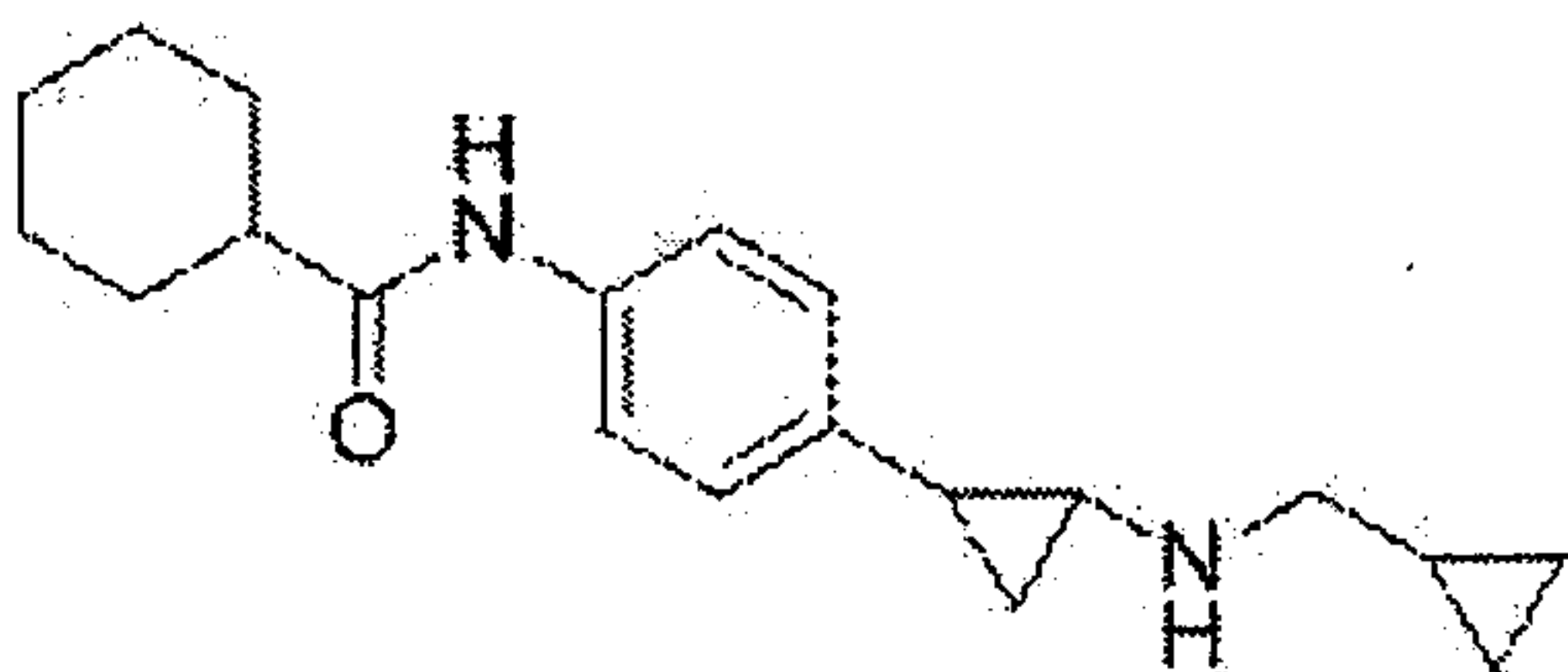
^1H NMR (300 MHz, DMSO- d_6) δ 0.22-0.38 (2H, m), 0.46-0.63 (2H, m),
 10 0.90-1.11 (1H, m), 1.13-1.30 (1H, m), 1.31-1.49 (1H, m), 2.28-2.46 (1H, m), 2.78-2.97 (3H, m), 7.15 (2H, d, $J = 8.7$ Hz), 7.47-7.63 (3H, m), 7.64-7.75 (2H, m), 7.90-7.98 (2H, m), 10.22 (1H, brs).

[0497]

15 Example 141

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-cyclohexanecarboxamide hydrochloride

[0498]



20 [0499]

By a method similar to Example 73, the title compound (145 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (170 mg) and cyclohexanecarbonyl chloride (99.0 mg).

25 MS (API+): $[M+H]^+$ 313.1.

^1H NMR (300MHz, CD $_3$ OD) δ 0.41 (2H, q, $J = 5.0$ Hz), 0.65-0.76 (2H, m), 1.03-1.17 (1H, m), 1.33-1.60 (7H, m), 1.67-1.76 (1H, m), 1.78-1.90 (4H, m), 2.27-2.50 (2H, m), 2.94 (1H, dt, $J = 7.8$,

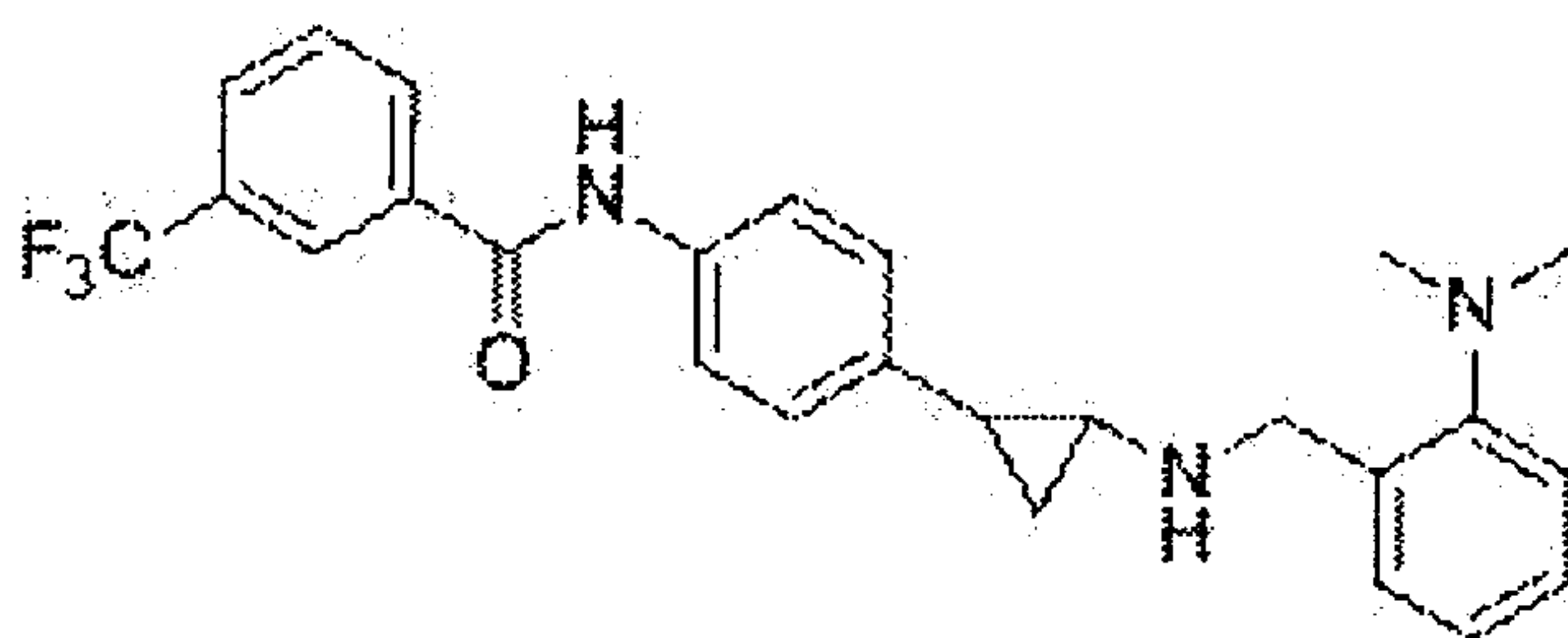
4.0 Hz), 3.06 (2H, dd, $J = 7.5, 2.1$ Hz), 7.11 (2H, d, $J = 8.5$ Hz), 7.50 (2H, d, $J = 8.7$ Hz).

[0500]

Example 142

5 N-{4-[trans-2-{[2-(dimethylamino)benzyl]amino}cyclopropyl]phenyl}-3-(trifluoromethyl)benzamide hydrochloride

[0501]



10 [0502]

By a method similar to Example 65, the title compound (40 mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (100 mg) and 2-(dimethylamino)benzaldehyde (41.8 mg).

15 MS (API⁺): $[M+H]^+$ 454.0.

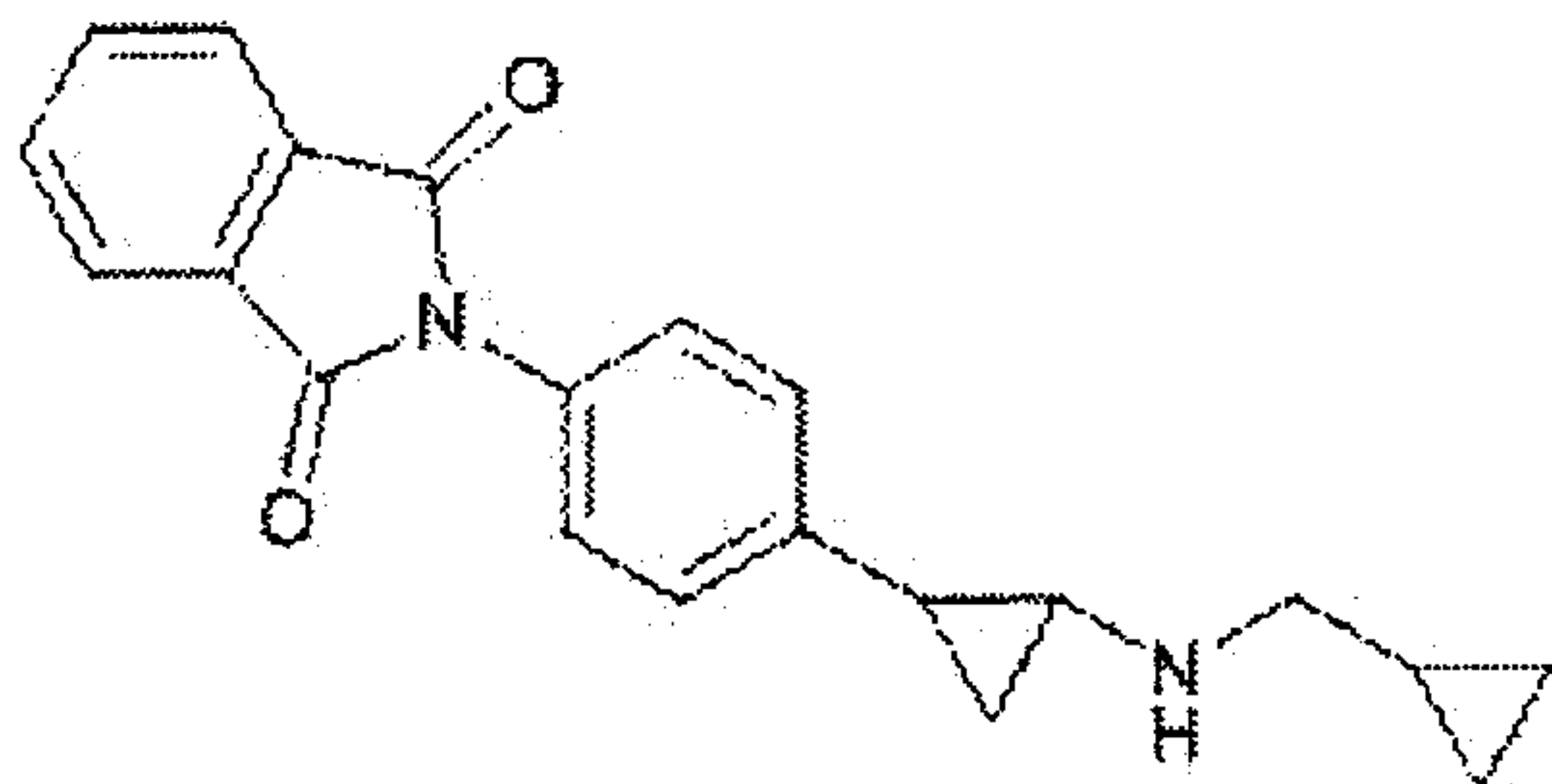
¹H NMR (300 MHz, DMSO- d_6) δ 1.22-1.34 (1H, m), 1.56-1.71 (1H, m), 2.54-2.64 (1H, m), 2.82 (6H, s), 2.98-3.11 (1H, m), 4.52 (2H, brs), 7.13 (2H, d, $J = 8.5$ Hz), 7.24-7.38 (1H, m), 7.42-7.57 (2H, m), 7.67-7.82 (4H, m), 7.97 (1H, d, $J = 7.7$ Hz),
20 8.22-8.33 (2H, m), 9.84 (2H, brs), 10.52 (1H, s).

[0503]

Example 143

2-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-1H-isoindole-1,3(2H)-dione hydrochloride

25 [0504]



[0505]

A) tert-butyl (cyclopropylmethyl){trans-2-[4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]cyclopropyl}carbamate

To a solution of tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (177.9 mg) and triethylamine (98 μ L) in THF (2.94 mL) was added phthalic anhydride (105 mg). The mixture was stirred at room temperature overnight and the solvent was evaporated under reduced pressure. The residue was dissolved in acetic anhydride (3 mL), and the mixture was stirred at 80°C for 5 hr. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (252.7 mg).

^1H NMR (300 MHz, DMSO- d_6) δ 0.07-0.18 (1H, m), 0.19-0.31 (1H, m), 0.33-0.56 (2H, m), 0.90-1.07 (1H, m), 1.25-1.34 (2H, m), 1.38 (9H, s), 2.10-2.24 (1H, m), 2.75-2.85 (1H, m), 3.01 (1H, dd, J = 14.4, 6.7 Hz), 3.22 (1H, dd, J = 14.4, 6.7 Hz), 7.22-7.39 (4H, m), 7.85-7.99 (4H, m).

[0506]

B) 2-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-1H-isoindole-1,3(2H)-dione hydrochloride

tert-Butyl (cyclopropylmethyl){trans-2-[4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]cyclopropyl}carbamate (252.7 mg) was dissolved in 4N hydrochloric acid/cyclopentyl methyl ether solution (3 mL), and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure. The residue was recrystallized from methanol/diisopropyl ether to give the title compound (176.2 mg).

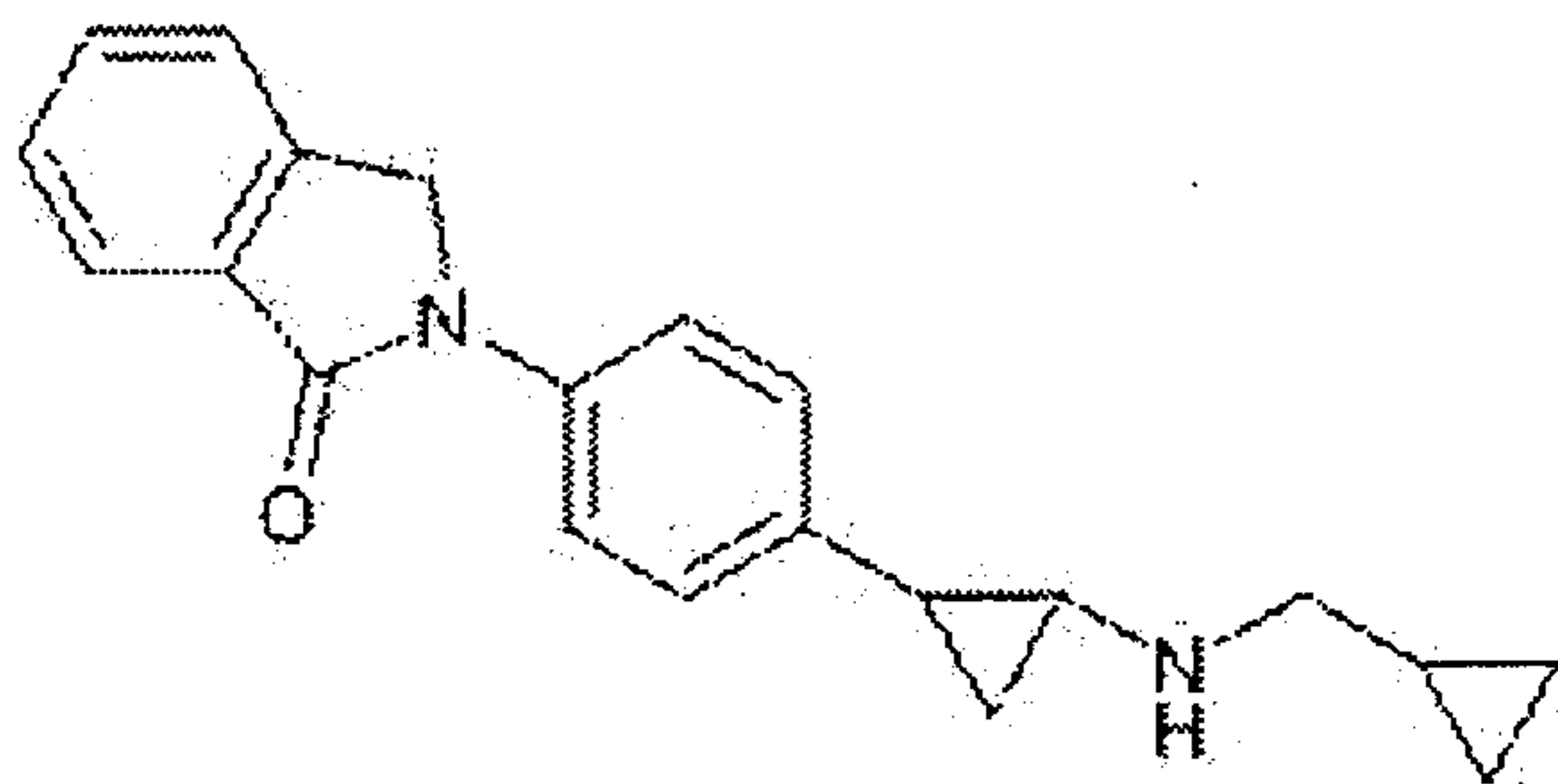
MS (API+): $[M+H]^+$ 333.2.

^1H NMR (300 MHz, DMSO- d_6) δ 0.34-0.43 (2H, m), 0.55-0.64 (2H, m), 1.02-1.16 (1H, m), 1.31-1.43 (1H, m), 1.53-1.66 (1H, m), 2.54-2.63 (1H, m), 2.90-3.07 (3H, m), 7.21-7.50 (4H, m), 7.84-8.03 (4H, m), 9.37 (2H, brs).

[0507]

Example 144

2-(4-{trans-2-
 [(cyclopropylmethyl)amino]cyclopropyl}phenyl)isoindolin-1-one
 hydrochloride
 [0508]



5

[0509]

A) tert-butyl (cyclopropylmethyl){trans-2-[4-(1-oxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]cyclopropyl}carbamate

To a solution of tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (126.8 mg) and triethylamine (70.1 μ L) in THF (2.1 mL) was added 2-(chloromethyl)benzoyl chloride (95 mg). The mixture was stirred at room temperature overnight, and saturated aqueous ammonium chloride solution was added. The mixture was extracted with ethyl acetate, and the extract was washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give a mixture (260.5 mg) containing the title compound and tert-butyl [trans-2-(4-{[2-(chloromethyl)benzoyl]amino}phenyl)cyclopropyl]-(cyclopropylmethyl)carbamate. To a solution of this mixture and tetrabutylammonium iodide (15.51 mg) in DMF (4.2 mL) was added sodium hydride (20.16 mg). The mixture was stirred at room temperature for 2 hr and poured into water. The mixture was extracted with ethyl acetate, and the extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (123.7 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.07-0.17 (1H, m), 0.18-0.28 (1H, m), 0.33-0.53 (2H, m), 0.90-1.08 (1H, m), 1.14-1.27 (2H, m), 1.37 (9H, s), 2.07 (1H, ddd, J = 9.4, 6.5, 3.2 Hz), 2.65-2.78 (1H, m), 3.00 (1H, dd, J = 14.4, 6.8 Hz), 3.20 (1H, dd, J = 14.4, 6.8 Hz), 5.49 (2H, s), 7.09 (2H, d, J = 8.5 Hz), 7.17 (2H, d, J = 8.5 Hz), 7.50-7.73 (4H, m).

[0510]

B) 2-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)isoindolin-1-one hydrochloride

tert-Butyl (cyclopropylmethyl){trans-2-[4-(1-oxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]cyclopropyl}carbamate (123.7 mg) was dissolved in 4N hydrochloric acid/cyclopentyl methyl ether solution (1.5 mL), and the mixture was stirred at room temperature for 4 hr. The solvent was evaporated under reduced pressure. The residue was recrystallized from methanol/diisopropyl ether to give the title compound (76.4 mg). MS (API+): [M+H]⁺ 319.3.

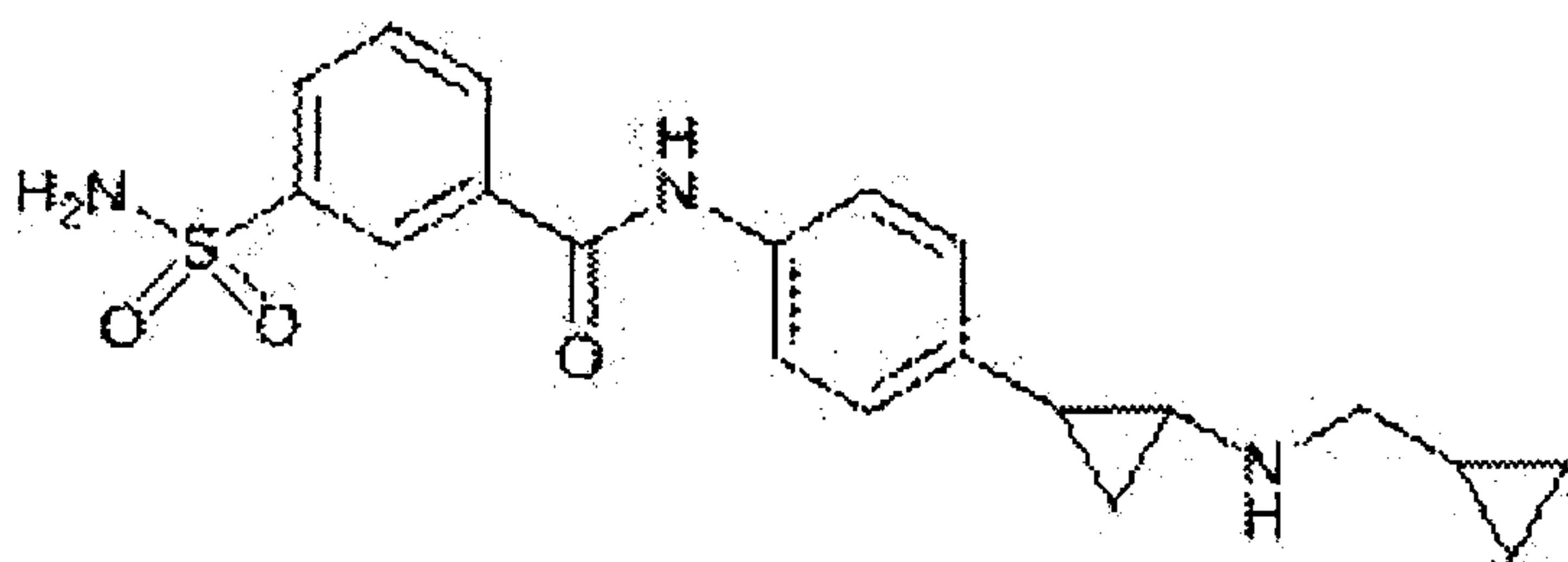
¹H NMR (300 MHz, DMSO-d₆) δ 0.32-0.42 (2H, m), 0.52-0.64 (2H, m), 0.99-1.17 (1H, m), 1.22-1.36 (1H, m), 1.45-1.63 (1H, m), 2.53-2.59 (1H, m), 2.82-3.06 (3H, m), 5.65 (2H, brs), 7.08-7.44 (4H, m), 7.46-7.84 (3H, m), 7.98-8.41 (1H, m), 9.33 (2H, brs).

[0511]

Example 145

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-3-sulfamoylbenzamide hydrochloride

[0512]



[0513]

A) tert-butyl (cyclopropylmethyl)(trans-2-{4-[(3-sulfamoylbenzoyl)amino]phenyl}cyclopropyl)carbamate

By a method similar to Example 80, Step A, the title compound (125.0 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (76.0 mg) and 3-sulfamoylbenzoic acid (60.7 mg).

5 ¹H NMR (300 MHz, DMSO-d₆) δ 0.07-0.16 (1H, m), 0.18-0.28 (1H, m), 0.33-0.51 (2H, m), 1.02 (1H, brs), 1.20-1.28 (2H, m), 1.37 (9H, s), 2.07 (1H, ddd, J = 9.6, 6.5, 3.1 Hz), 2.69-2.76 (1H, m), 3.00 (1H, dd, J = 14.4, 6.7 Hz), 3.20 (1H, dd, J = 14.4, 6.7 Hz), 7.14 (2H, d, J = 8.6 Hz), 7.47-7.51 (2H, m), 7.67 (2H, 10 d, J = 8.6 Hz), 7.73 (1H, dd, J = 7.7, 7.6 Hz), 7.98-8.08 (1H, m), 8.10-8.22 (1H, m), 8.38 (1H, t, J = 1.6 Hz), 10.43 (1H, s).
[0514]

B) N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-3-sulfamoylbenzamide hydrochloride

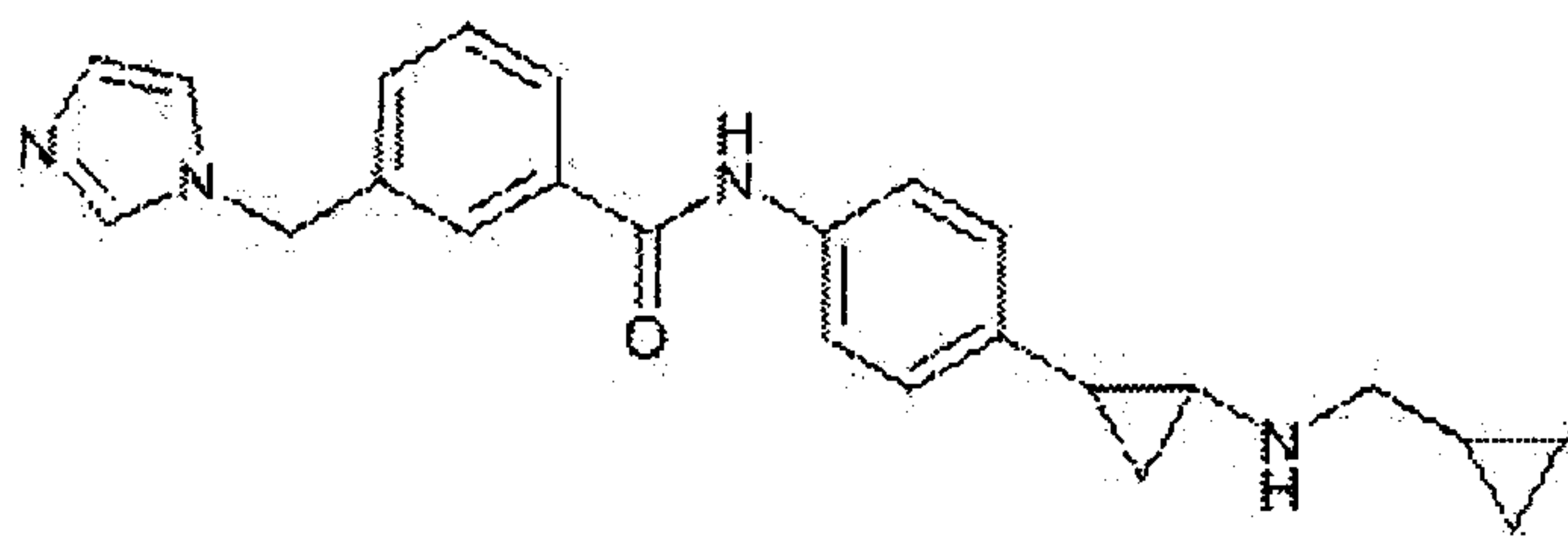
15 tert-Butyl (cyclopropylmethyl)(trans-2-{4-[(3-sulfamoylbenzoyl)amino]phenyl}cyclopropyl)carbamate (125.0 mg) was dissolved in 4N hydrochloric acid/ethyl acetate solution (1.25 mL), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure.
20 The residue was recrystallized from methanol/diisopropyl ether to give the title compound (69.5 mg).

MS (API+): [M+H]⁺ 386.3.

¹H NMR (300 MHz, DMSO-d₆) δ 0.28-0.40 (2H, m), 0.54-0.62 (2H, m), 0.95-1.11 (1H, m), 1.17-1.34 (1H, m), 1.35-1.52 (1H, m), 25 2.34-2.45 (1H, m), 2.86-3.02 (3H, m), 7.18 (2H, d, J = 8.5 Hz), 7.49 (2H, s), 7.67-7.79 (3H, m), 8.00-8.04 (1H, m), 8.14-8.19 (1H, m), 8.37 (1H, t, J = 1.7 Hz), 8.90 (2H, s), 10.48 (1H, s).
[0515]

Example 146

30 N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-3-(1H-imidazol-1-ylmethyl)benzamide hydrochloride
[0516]



[0517]

By a method similar to Example 145, the title compound (21.0 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (76.6 mg) and 3-(1H-imidazol-1-ylmethyl)benzoic acid (61.5 mg).

MS (API+): $[M+H]^+$ 387.4.

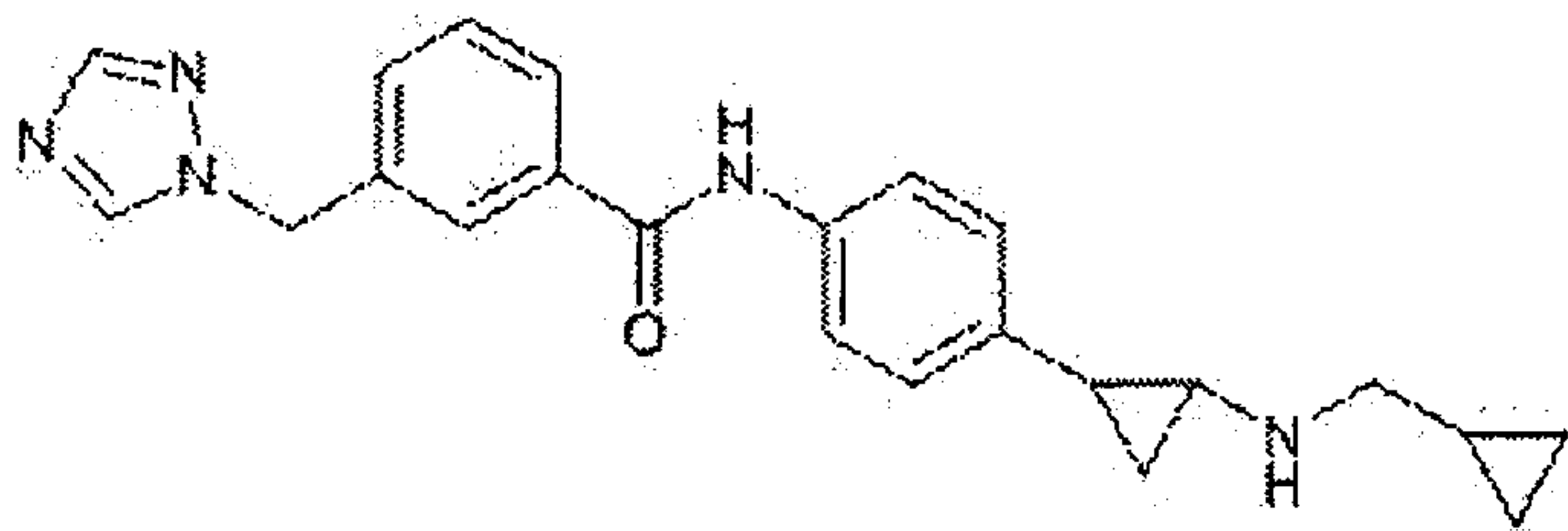
^1H NMR (300 MHz, DMSO- d_6) δ 0.29-0.45 (2H, m), 0.53-0.62 (2H, m), 1.05-1.12 (1H, m), 1.21-1.31 (1H, m), 1.47-1.60 (1H, m), 2.42-2.47 (1H, m), 2.85-3.00 (3H, m), 5.52 (2H, s), 7.17 (2H, d, $J = 8.3$ Hz), 7.52-7.65 (2H, m), 7.67-7.76 (3H, m), 7.81-7.88 (1H, m), 7.94-8.08 (2H, m), 9.22-9.45 (3H, m), 10.37 (1H, s).

[0518]

Example 147

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-3-(1H-1,2,4-triazol-1-ylmethyl)benzamide hydrochloride

[0519]



[0520]

By a method similar to Example 145, the title compound (15.3 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (76.6 mg) and 3-(1H-1,2,4-triazol-1-ylmethyl)benzoic acid (61.8 mg).

MS (API+): $[M+H]^+$ 388.3.

^1H NMR (300 MHz, DMSO- d_6) δ 0.33-0.40 (2H, m), 0.55-0.62 (2H, m), 1.00-1.12 (1H, m), 1.23-1.33 (1H, m), 1.42-1.54 (1H, m), 2.40-2.46 (1H, m), 2.87-3.03 (3H, m), 5.51 (2H, s), 7.17 (2H, d, $J = 8.7$ Hz), 7.45-7.58 (2H, m), 7.69 (2H, d, $J = 8.7$ Hz), 7.82-

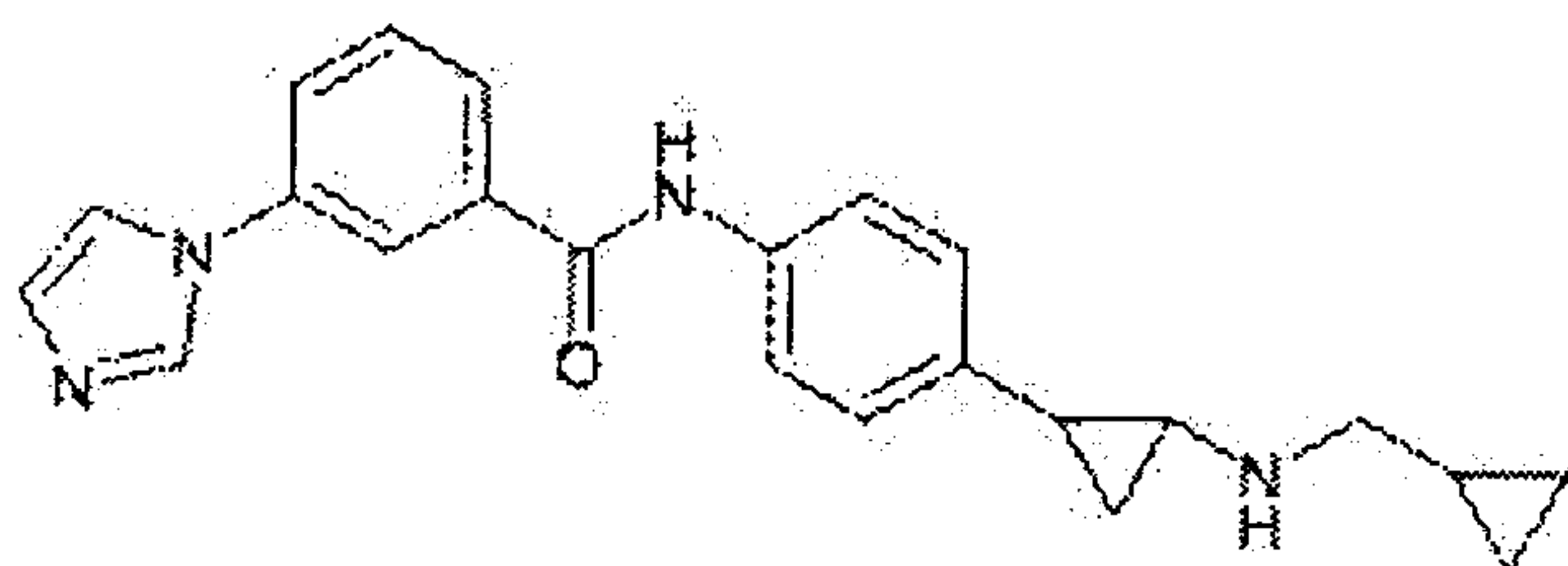
7.94 (2H, m), 8.01 (1H, s), 8.72 (1H, s), 9.08 (2H, brs), 10.27 (1H, s).

[0521]

Example 148

5 N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-3-(1H-imidazol-1-yl)benzamide hydrochloride

[0522]



[0523]

10 By a method similar to Example 145, the title compound (48.2 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (77.3 mg) and 3-(1H-imidazol-1-yl)benzoic acid (48.1 mg).

MS (API+): [M+H]⁺ 373.3.

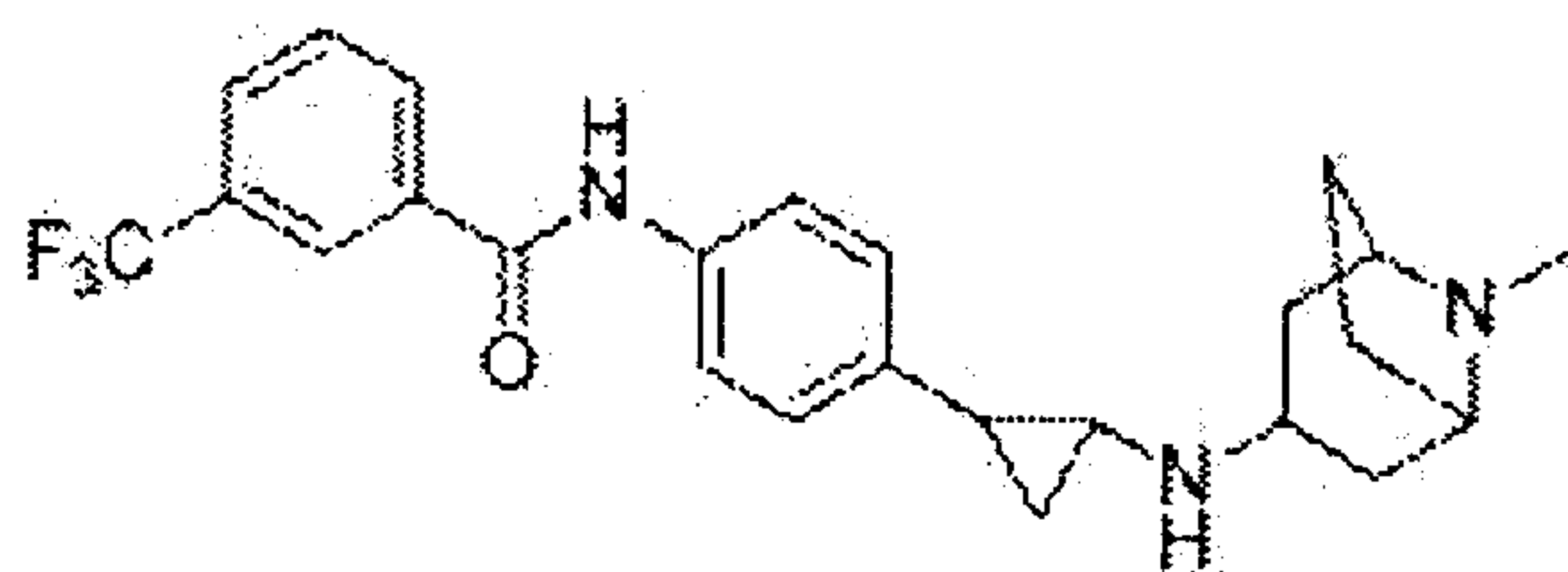
15 ¹H NMR (300 MHz, DMSO-d₆) δ 0.38 (2H, m), 0.53-0.62 (2H, m), 1.08-1.15 (1H, m), 1.22-1.32 (1H, m), 1.50-1.60 (1H, m), 2.52-2.58 (1H, m), 2.88-3.01 (3H, m), 7.19 (2H, d, J = 8.6 Hz), 7.76-7.85 (3H, m), 7.90 (1H, s), 8.03 (1H, dd, J = 8.1, 1.6 Hz), 8.12 (1H, d, J = 8.1 Hz), 8.48 (2H, d, J = 19.1 Hz), 9.42 (2H, 20 brs), 9.81 (1H, brs), 10.68 (1H, s).

[0524]

Example 149

N-(4-{trans-2-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide 25 dihydrochloride

[0525]



[0526]

By a method similar to Example 65, the title compound (50

mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (100 mg) and 8-methyl-8-azabicyclo[3.2.1]octan-3-one (50.7 mg).

MS (API+): $[M+H]^+$ 444.1.

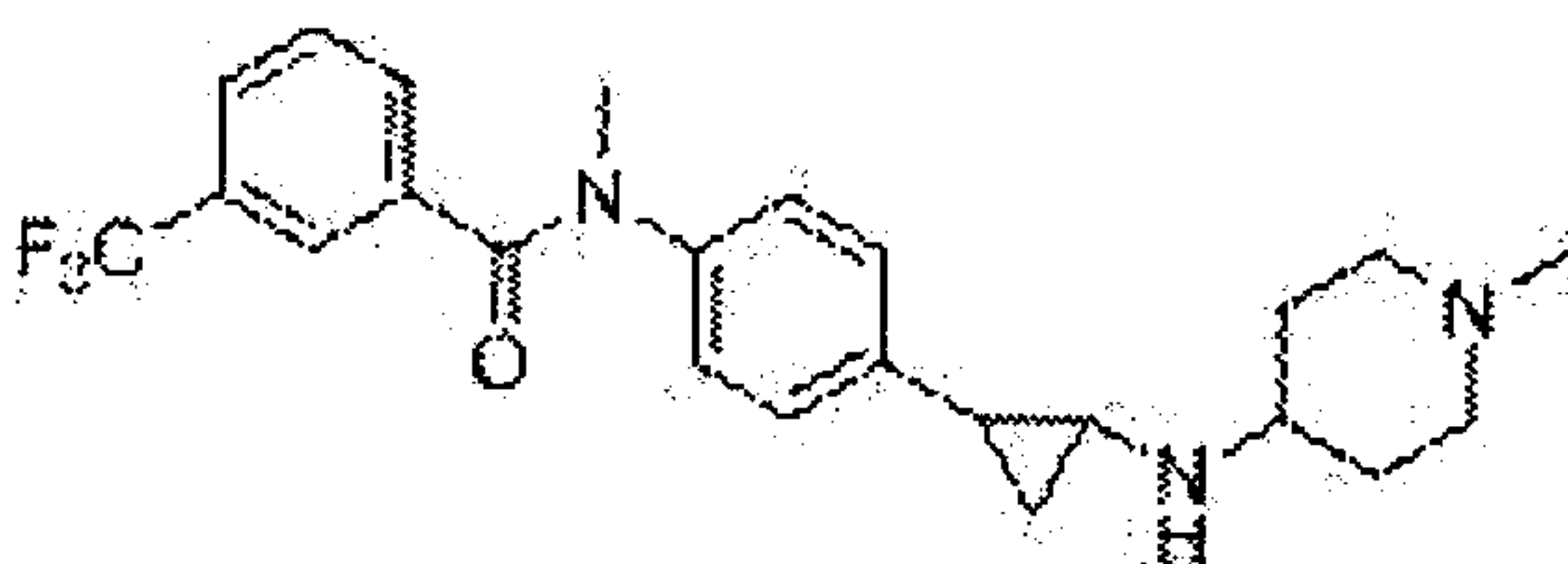
5 ^1H NMR (300MHz, CD_3OD) δ 1.44-1.61 (3H, m), 1.66-1.78 (3H, m), 2.21-2.26 (1H, m), 2.37-2.56 (3H, m), 2.68-2.76 (1H, m), 2.80-2.86 (3H, m), 3.15-3.25 (1H, m), 3.80-4.30 (3H, m), 7.25 (2H, d, $J = 7.9$ Hz), 7.65-7.78 (3H, m), 7.90 (1H, d, $J = 7.8$ Hz), 8.18-8.28 (2H, m).

10 [0527]

Example 150

N-methyl-N-(4-{trans-2-[(1-methylpiperidin-4-yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide dihydrochloride

15 [0528]



[0529]

By a method similar to Example 64, the title compound (3 mg) was obtained from N-(4-{trans-2-[(1-methylpiperidin-4-yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide hydrochloride (160 mg).

MS (API+): $[M+H]^+$ 432.1.

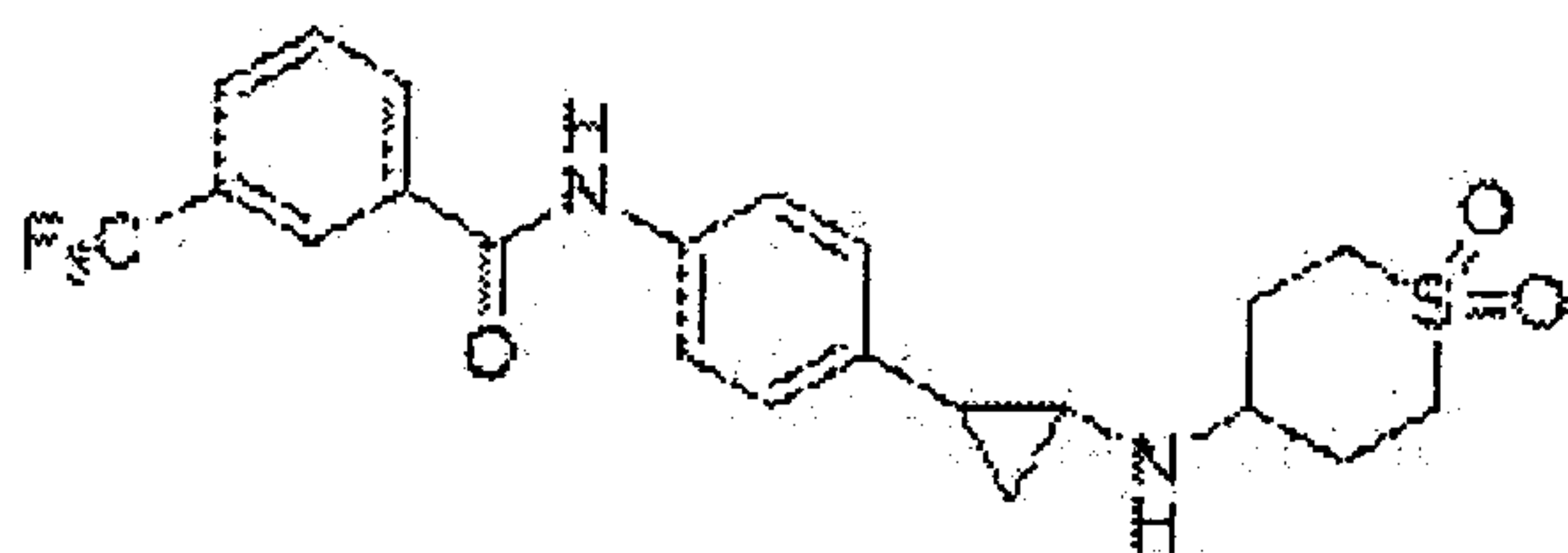
18 ^1H NMR (300MHz, CD_3OD) δ 1.18-1.43 (2H, m), 1.48-1.62 (1H, m), 1.91-2.11 (2H, m), 2.31-2.58 (3H, m), 2.84-3.21 (5H, m), 3.46
25 (3H, s), 3.56-3.73 (3H, m), 7.05-7.19 (4H, m), 7.37-7.48 (1H, m), 7.51-7.63 (3H, m).

[0530]

Example 151

N-(4-{trans-2-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide hydrochloride

[0531]



[0532]

To a solution of N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (75 mg), tetrahydro-4H-thiopyran-4-one 1,1-dioxide (37.4 mg) and acetic acid (0.2 mL) in methanol (2 mL) was added 2-picoline-borane complex (38.2 mg). The mixture was stirred at room temperature overnight, and saturated aqueous sodium hydrogen carbonate solution was added under ice-cooling. The mixture was
 10 extracted with ethyl acetate, and the extract was washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate, ethyl acetate/methanol) and 10%
 15 hydrochloric acid methanol solution was added. The solvent was evaporated under reduced pressure. The residue was recrystallized from methanol/diisopropyl ether to give the title compound (32.0 mg).

MS (API+): [M+H]⁺ 453.1.

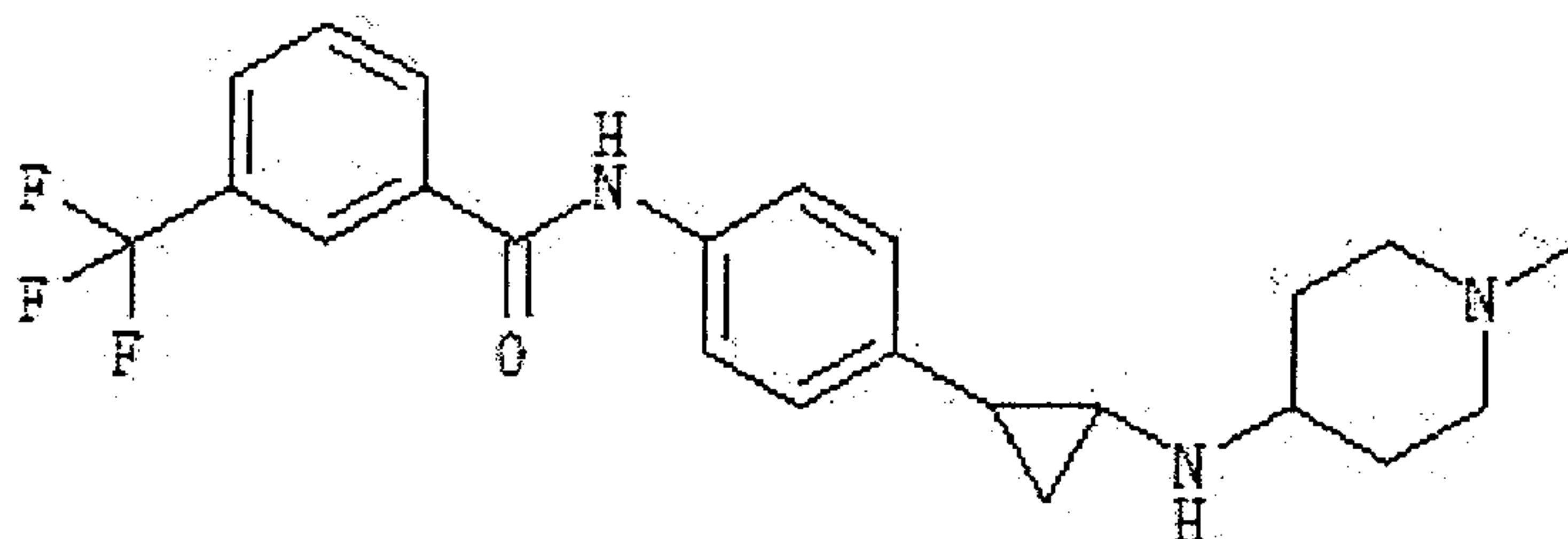
20 ¹H NMR (300MHz, CD₃OD) δ 1.39-1.61 (2H, m), 2.25 (2H, d, J = 12.8 Hz), 2.43-2.63 (3H, m), 3.03 (1H, dt, J = 7.7, 4.1 Hz), 3.14-3.25 (2H, m), 3.32-3.42 (2H, m), 3.61-3.76 (1H, m), 7.22 (2H, d, J = 8.5 Hz), 7.65-7.78 (3H, m), 7.89 (1H, d, J = 7.7 Hz), 8.15-8.26 (2H, m).

25 [0533]

Example 152

N-(4-((1R,2S) or (1S,2R)-2-[(1-methylpiperidin-4-yl)amino]cyclopropyl)phenyl)-3-(trifluoromethyl)benzamide dihydrochloride

30 [0534]



[0535]

N-(4-{trans-2-[(1-Methylpiperidin-4-yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide
 5 dihydrochloride (113 mg) was fractionated by HPLC (CHIRALCEL (registered trademark) OD (CA002), 50 mmID x 500 mmL, manufactured by Daicel Corporation, mobile phase: hexane/ethanol/diethylamine = 900/100/0.5), a fraction containing the object product and having a shorter retention
 10 time was concentrated under reduced pressure, and the residue was ice-cooled to 0°C. 4N Hydrochloric acid/cyclopentyl methyl ether solution (3.0 mL) was added, and the mixture was concentrated under reduced pressure to give the title compound (43 mg).

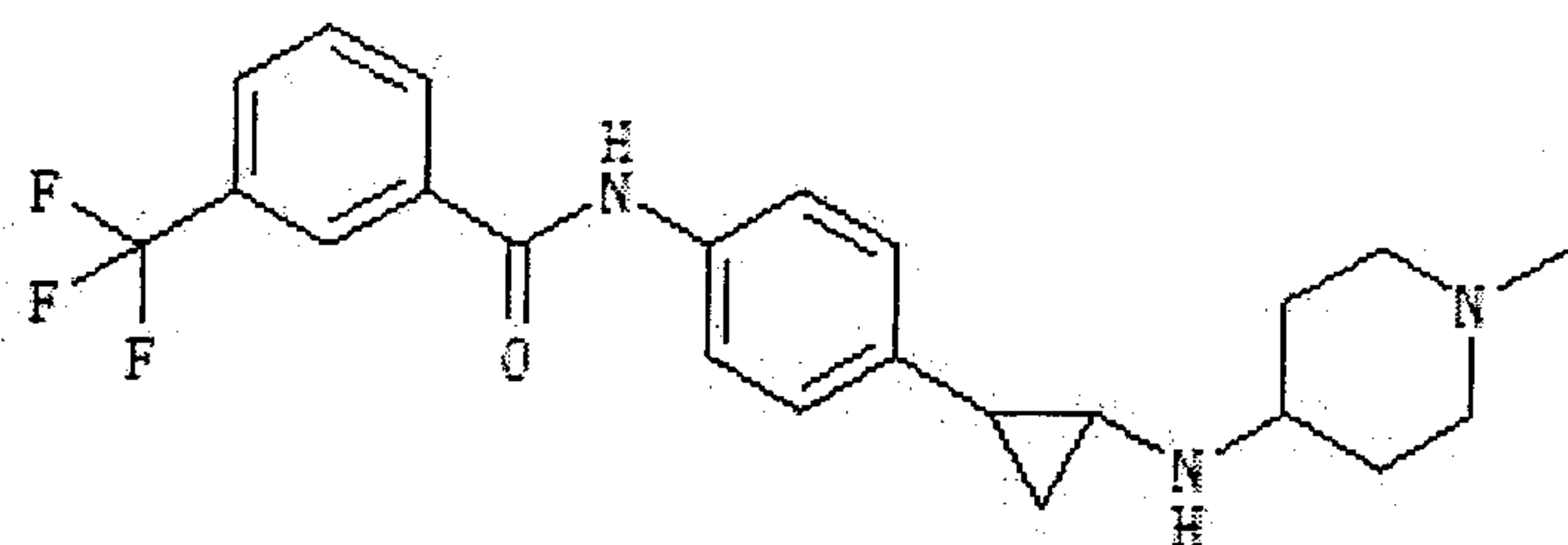
15 optical purity: 99.9% ee, retention time: 9.284 min (CHIRACEL (registered trademark) OD3 (NL022), 4.6 mmID x 250 mmL, manufactured by Daicel Corporation, mobile phase: hexane/ethanol/diethylamine = 900/100/0.1)
¹H NMR (300MHz, CD₃OD) δ 1.41-1.52 (1H, m), 1.54-1.64 (1H, m),
 20 2.00-2.19 (2H, m), 2.38-2.63 (3H, m), 2.91 (3H, s), 2.99-3.06 (1H, m), 3.10-3.27 (2H, m), 3.59-3.75 (3H, m), 7.23 (2H, d, J = 8.5 Hz), 7.64-7.77 (3H, m), 7.90 (1H, d, J = 7.9 Hz), 8.17-8.27 (2H, m).

[0536]

25 Example 153

N-(4-{(1S,2R) or (1R,2S)-2-[(1-methylpiperidin-4-yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide dihydrochloride

[0537]



[0538]

N-(4-{trans-2-[(1-Methylpiperidin-4-yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide
 5 dihydrochloride (113 mg) was fractionated by HPLC (CHIRALCEL (registered trademark) OD (CA002), 50 mmID x 500 mmL, manufactured by Daicel Corporation, mobile phase: hexane/ethanol/diethylamine = 900/100/0.5), a fraction containing the object product and having a longer retention
 10 time was concentrated under reduced pressure, and the residue was ice-cooled to 0°C. 4N Hydrochloric acid/cyclopentyl methyl ether solution (3.0 mL) was added, and the mixture was concentrated under reduced pressure to give the title compound (46 mg).

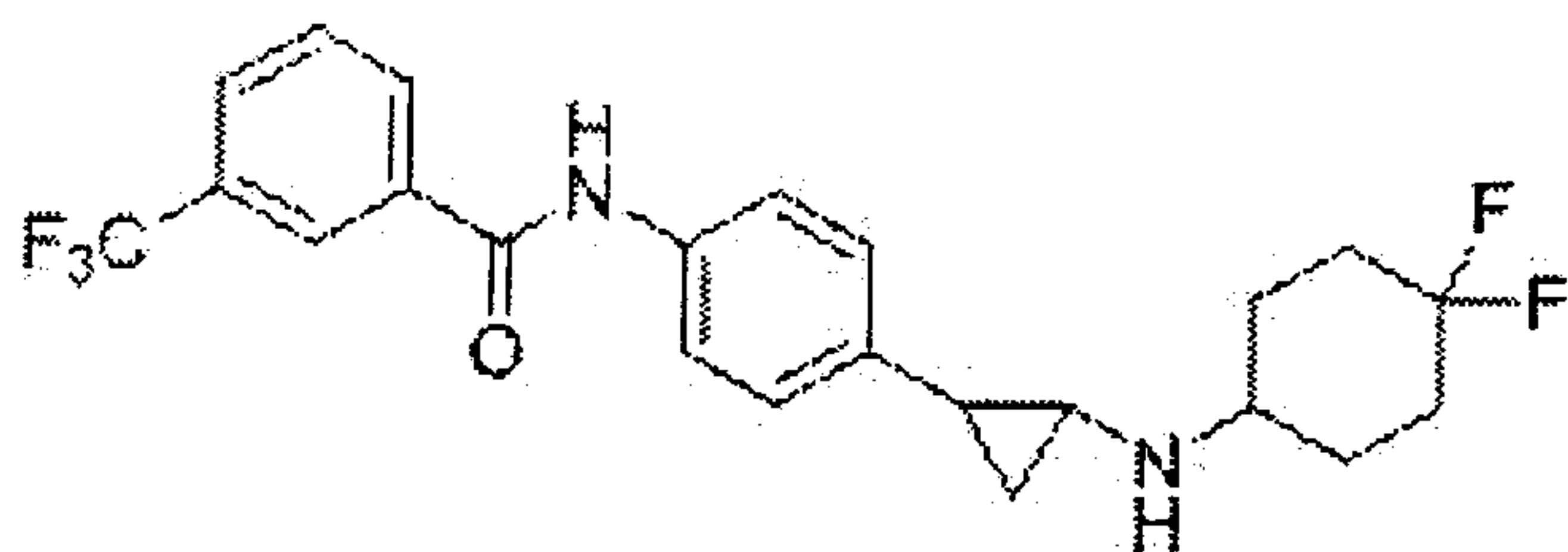
15 optical purity: 99.1% ee, retention time: 12.724 min (CHIRACEL (registered trademark) OD3 (NL022), 4.6 mmID x 250 mmL, manufactured by Daicel Corporation, mobile phase: hexane/ethanol/diethylamine = 900/100/0.1)
¹H NMR (300MHz, CD₃OD) δ 1.43-1.52 (1H, m), 1.54-1.64 (1H, m),
 20 1.98-2.19 (2H, m), 2.37-2.61 (3H, m), 2.91 (3H, s), 3.00-3.25 (3H, m), 3.59-3.76 (3H, m), 7.23 (2H, d, J = 8.7 Hz), 7.67-7.77 (3H, m), 7.90 (1H, d, J = 7.3 Hz), 8.16-8.27 (2H, m).

[0539]

Example 154

25 N-(4-{trans-2-[(4,4-difluorocyclohexyl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide hydrochloride

[0540]



[0541]

By a method similar to Example 151, the title compound (45 mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (75 mg) and 4,4-difluorocyclohexanone (33.8 mg). MS (API+): $[M+H]^+$ 439.0.

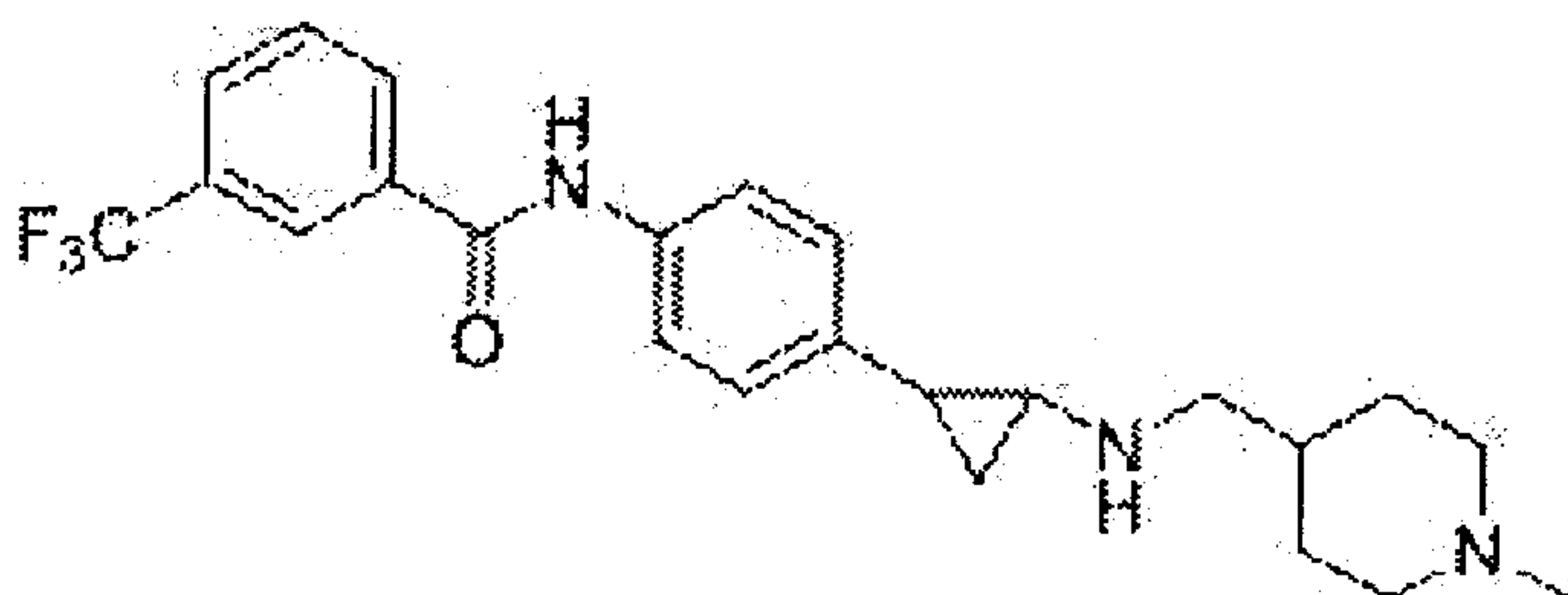
^1H NMR (300MHz, CD_3OD) δ 1.39-1.55 (2H, m), 1.73 (2H, q, $J = 12.2$ Hz), 1.83-2.08 (2H, m), 2.11-2.32 (4H, m), 2.44 (1H, ddd, $J = 10.1, 6.7, 3.6$ Hz), 2.95-3.03 (1H, m), 3.40-3.55 (1H, m), 7.20 (2H, d, $J = 8.7$ Hz), 7.65-7.77 (3H, m), 7.89 (1H, d, $J = 7.9$ Hz), 8.15-8.27 (2H, m).

[0542]

Example 155

N-{4-[trans-2-[(1-methylpiperidin-4-yl)methyl]amino}cyclopropyl]phenyl}-3-(trifluoromethyl)benzamide dihydrochloride

[0543]



20 [0544]

By a method similar to Example 65, the title compound (20 mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (80 mg) and 1-methylpiperidine-4-carbaldehyde (28.5 mg).

25 MS (API+): $[M+H]^+$ 432.1.

^1H NMR (300MHz, CD_3OD) δ 1.35-1.46 (1H, m), 1.51-1.73 (3H, m), 2.04-2.16 (3H, m), 2.51-2.61 (1H, m), 2.86-2.92 (3H, m), 2.97-3.11 (3H, m), 3.20 (2H, d, $J = 6.6$ Hz), 3.52-3.63 (2H, m), 7.21

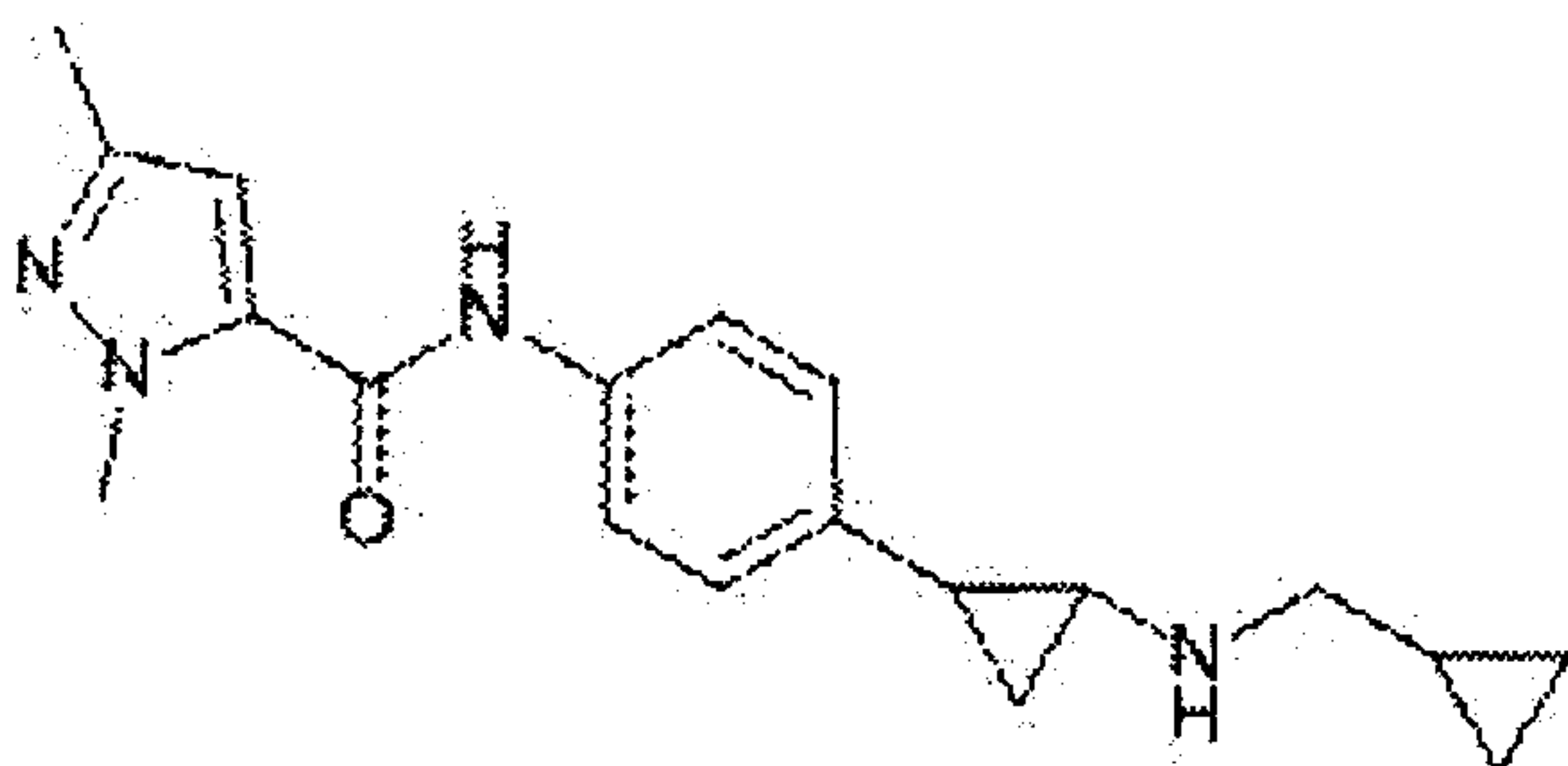
(2H, d, $J = 8.7$ Hz), 7.64-7.77 (3H, m), 7.89 (1H, d, $J = 7.9$ Hz), 8.15-8.29 (2H, m).

[0545]

Example 156

5 N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide dihydrochloride

[0546]



[0547]

10 By a method similar to Example 145, the title compound (89.6 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl] (cyclopropylmethyl)carbamate (88.6 mg) and 1,3-dimethyl-1H-pyrazole-5-carboxylic acid (49.3 mg).

MS (API+): $[M+H]^+$ 325.3.

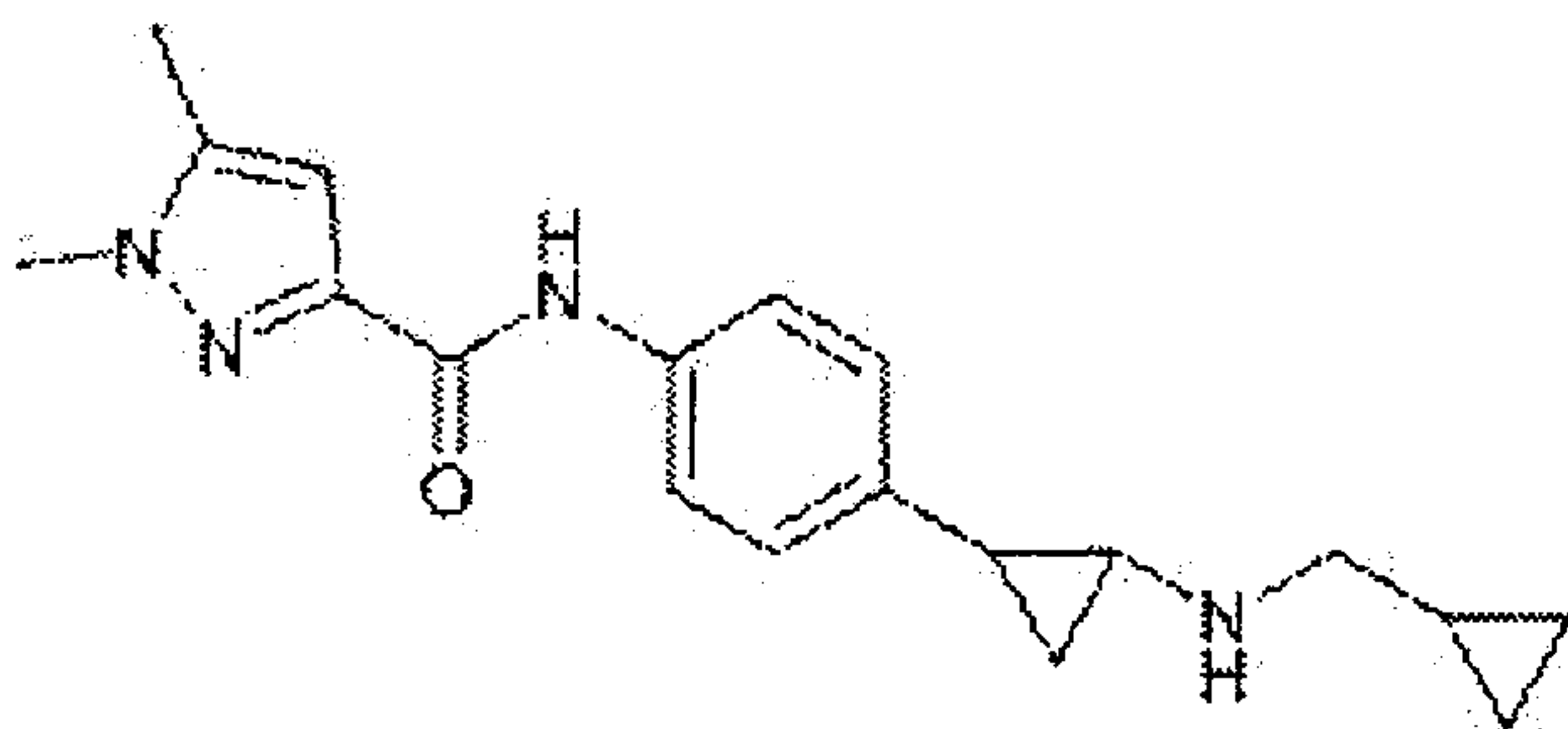
15 ^1H NMR (300 MHz, DMSO- d_6) δ 0.32-0.40 (2H, m), 0.52-0.64 (2H, m), 0.98-1.14 (1H, m), 1.22-1.32 (1H, m), 1.42-1.55 (1H, m), 2.19 (3H, s), 2.40-2.47 (1H, m), 2.87-3.03 (3H, m), 3.99 (3H, s), 6.82 (1H, s), 7.16 (2H, d, $J = 8.6$ Hz), 7.65 (2H, d, $J = 8.6$ Hz), 9.18 (2H, brs), 10.11 (1H, s).

20 [0548]

Example 157

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-1,5-dimethyl-1H-pyrazole-3-carboxamide dihydrochloride

[0549]



25

[0550]

By a method similar to Example 145, the title compound

(60.0 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (87.2 mg) and 1,5-dimethyl-1H-pyrazole-3-carboxylic acid (48.5 mg).

MS (API+): $[M+H]^+$ 325.3.

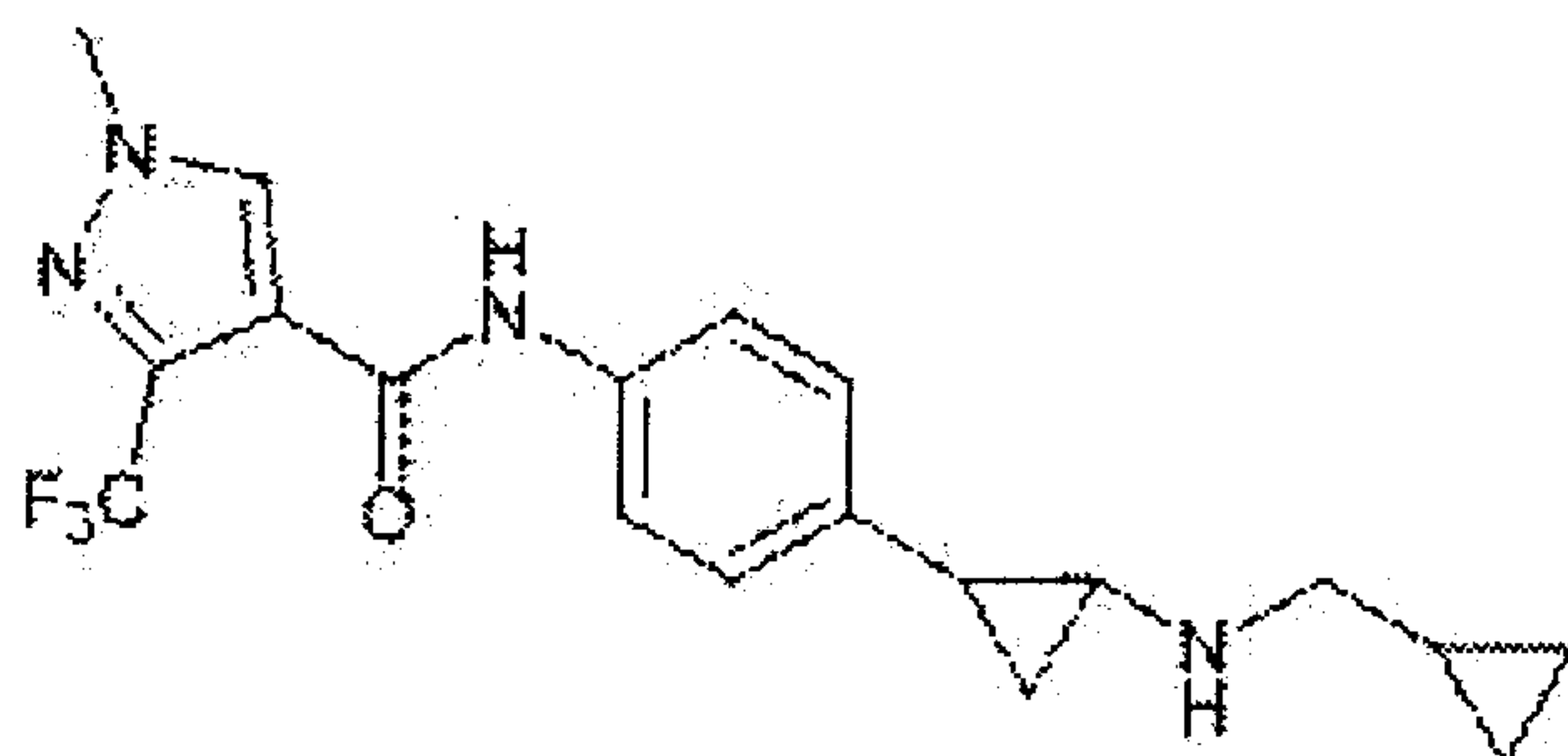
5 ^1H NMR (300 MHz, DMSO- d_6) δ 0.31-0.41 (2H, m), 0.53-0.63 (2H, m), 0.98-1.11 (1H, m), 1.18-1.33 (1H, m), 1.41-1.52 (1H, m), 2.30 (3H, s), 2.37-2.47 (1H, m), 2.85-3.03 (3H, m), 3.83 (3H, s), 6.53 (1H, s), 7.12 (2H, d, $J = 8.7$ Hz), 7.74 (2H, d, $J = 8.6$ Hz), 9.11 (2H, brs), 9.89 (1H, s).

10 [0551]

Example 158

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide hydrochloride

15 [0552]



[0553]

By a method similar to Example 145, the title compound (40.8 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (87.1 mg) and 1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (67.1 mg).

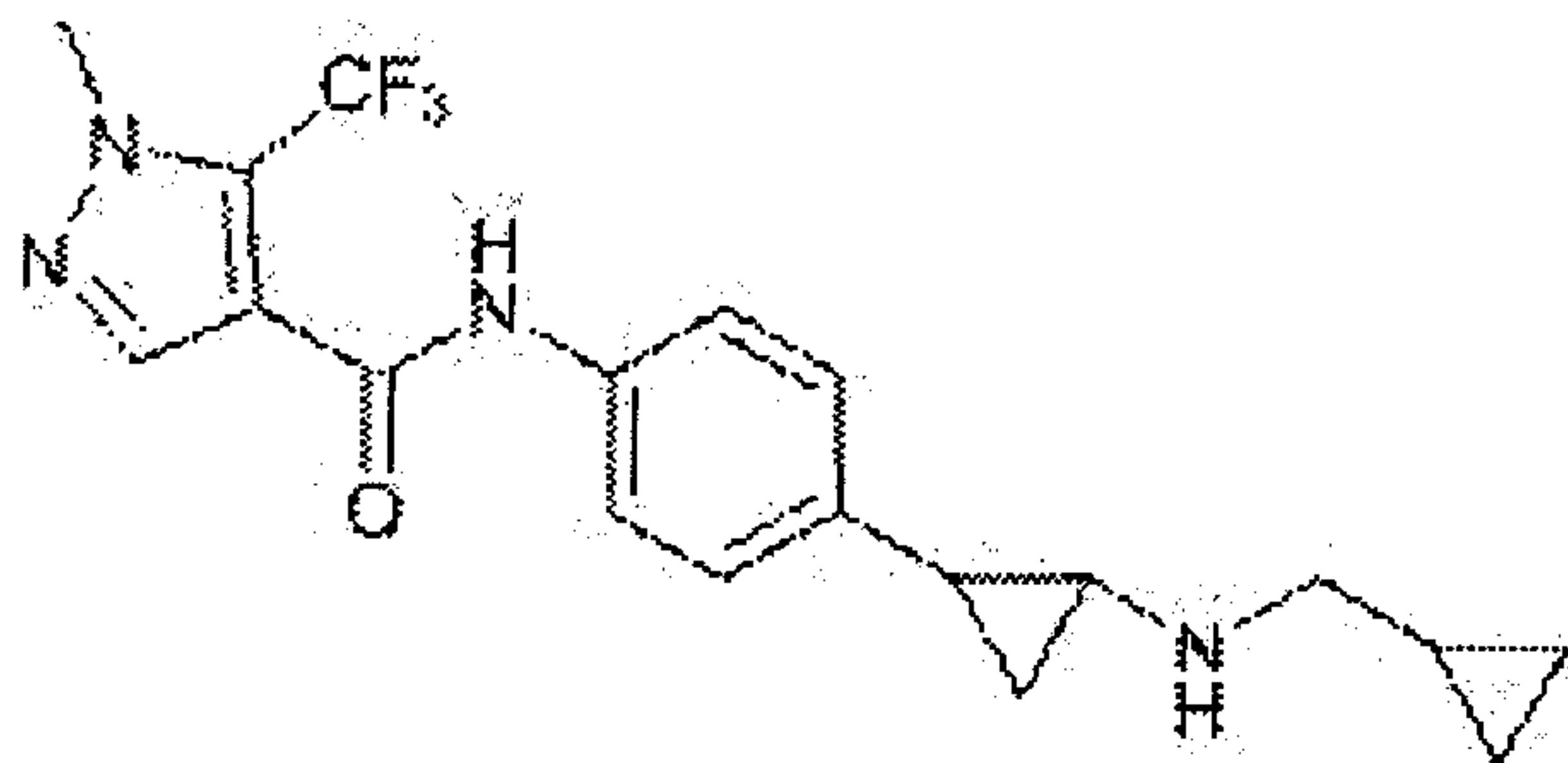
MS (API+): $[M+H]^+$ 379.3.

25 ^1H NMR (300 MHz, DMSO- d_6) δ 0.29-0.39 (2H, m), 0.52-0.62 (2H, m), 0.95-1.11 (1H, m), 1.17-1.30 (1H, m), 1.35-1.52 (1H, m), 2.31-2.45 (1H, m), 2.81-3.01 (3H, m), 3.98 (3H, s), 7.14 (2H, d, $J = 8.6$ Hz), 7.60 (2H, d, $J = 8.6$ Hz), 8.53 (1H, s), 8.95 (2H, brs), 10.11 (1H, s).

[0554]

30 Example 159

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-1-methyl-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide hydrochloride
[0555]



5

[0556]

By a method similar to Example 80, the title compound (56.1 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl] (cyclopropylmethyl)carbamate (82.8 mg) and 1-methyl-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (63.8 mg).

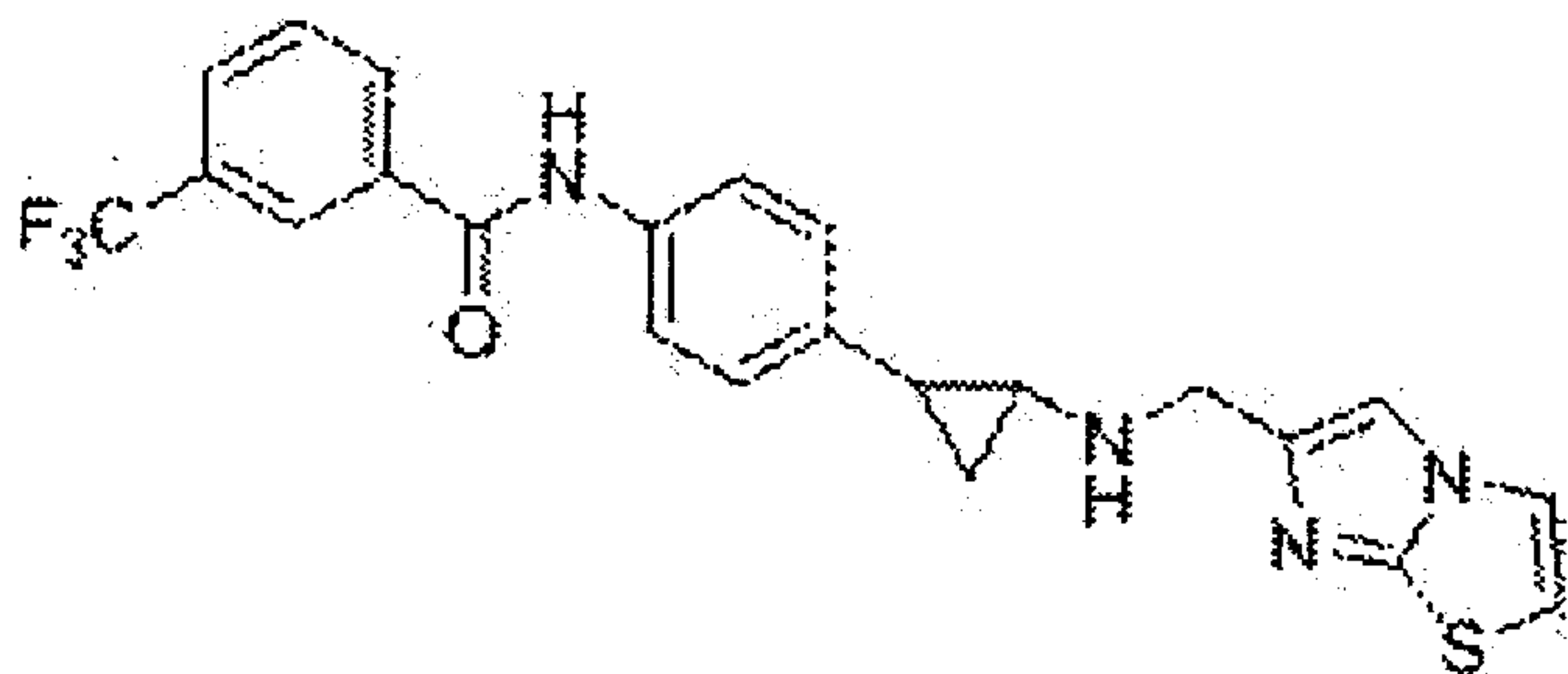
MS (API+): $[M+H]^+$ 379.3.
 ^1H NMR (300 MHz, DMSO- d_6) δ 0.29-0.40 (2H, m), 0.52-0.62 (2H, m), 0.95-1.11 (1H, m), 1.18-1.30 (1H, m), 1.39-1.52 (1H, m), 2.32-2.47 (1H, m), 2.82-3.02 (3H, m), 3.98 (3H, s), 7.14 (2H, d, $J = 8.6$ Hz), 7.61 (2H, d, $J = 8.6$ Hz), 8.54 (1H, s), 9.01 (2H, brs), 10.12 (1H, s).

[0557]

Example 160

N-(4-{trans-2-[(imidazo[2,1-b][1,3]thiazol-6-ylmethyl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide dihydrochloride

[0558]



25 [0559]

By a method similar to Example 65, the title compound (17

mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (75 mg) and imidazo[2,1-b][1,3]thiazole-6-carbaldehyde (41.6 mg).

MS (API+): $[M+H]^+$ 457.0.

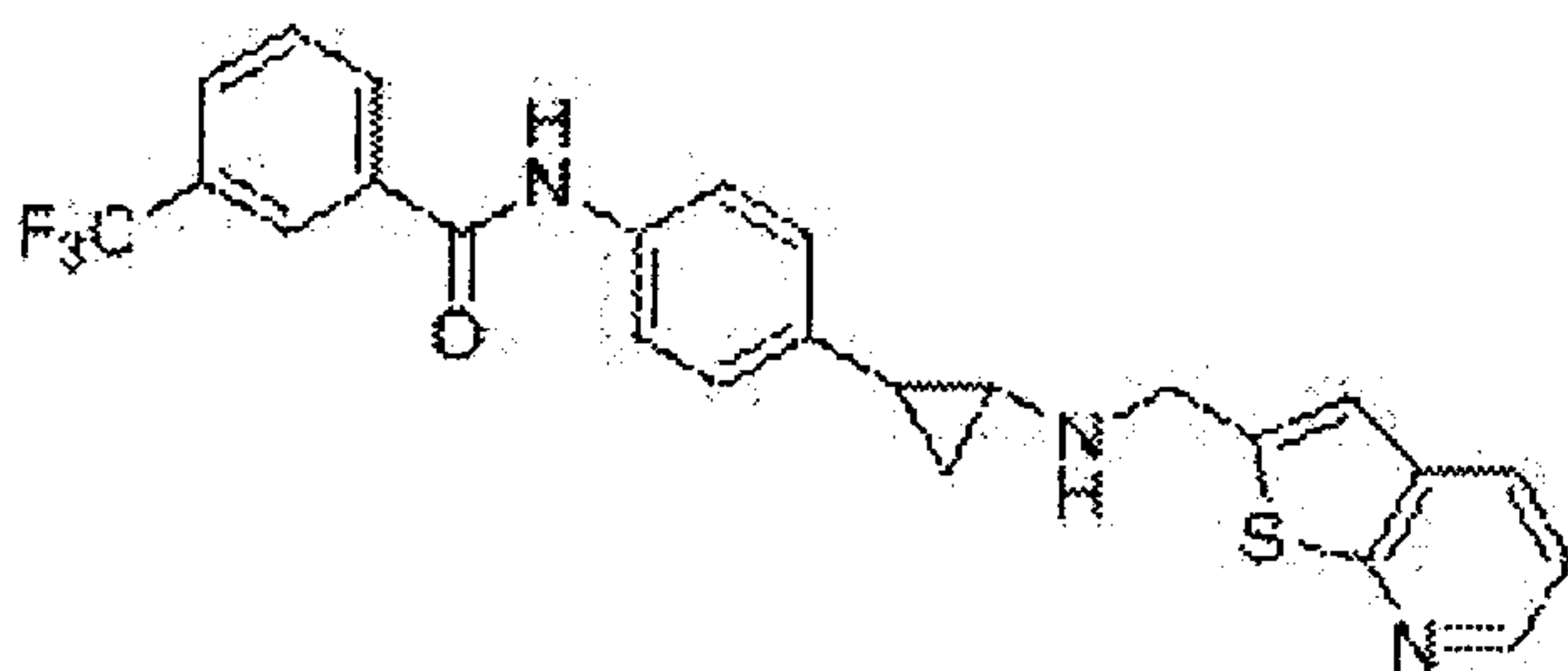
5 ^1H NMR (300 MHz, CD_3OD) δ 1.35 (1H, q, $J = 6.8$ Hz), 1.53-1.65 (1H, m), 2.50 (1H, s), 3.00-3.11 (1H, m), 4.60-4.66 (2H, m), 7.01 (2H, d, $J = 8.3$ Hz), 7.51-7.69 (4H, m), 7.80 (1H, d, $J = 7.7$ Hz), 8.00-8.26 (4H, m).

[0560]

10 Example 161

N-(4-{trans-2-[(thieno[2,3-b]pyridin-2-ylmethyl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide hydrochloride

[0561]



15

[0562]

By a method similar to Example 65, the title compound (10 mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (75 mg) and thieno[2,3-b]pyridine-2-carbaldehyde (44.6 mg).

MS (API+): $[M+H]^+$ 468.0.

16 ^1H NMR (300 MHz, CD_3OD) δ 1.36-1.57 (2H, m), 2.41 (1H, ddd, $J = 10.2, 6.5, 3.7$ Hz), 3.01 (1H, dt, $J = 7.6, 4.0$ Hz), 4.73 (2H, s), 7.07 (2H, d, $J = 8.7$ Hz), 7.44-7.54 (2H, m), 7.61 (2H, d, $J = 8.7$ Hz), 7.70-7.79 (1H, m), 7.90 (1H, d, $J = 7.9$ Hz), 8.15-8.30 (3H, m), 8.58 (1H, dd, $J = 4.7, 1.5$ Hz).

25

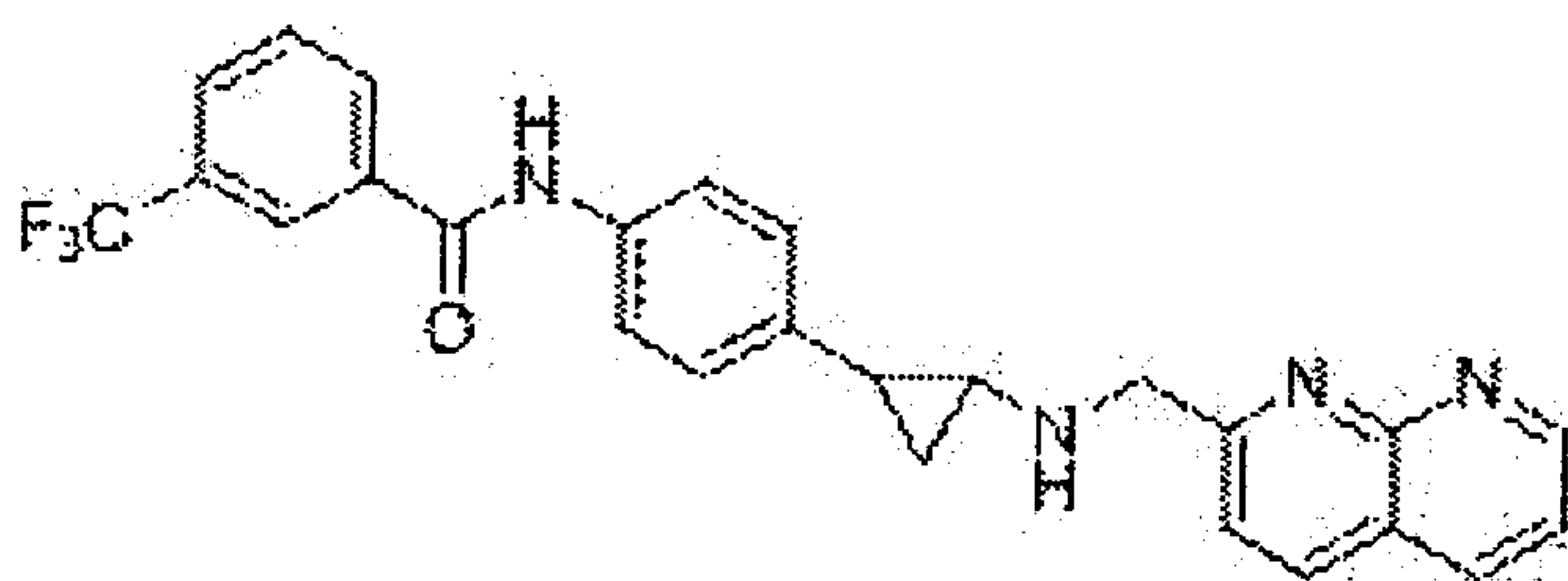
[0563]

Example 162

N-(4-{trans-2-[(1,8-naphthyridin-2-ylmethyl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide hydrochloride

30

[0564]



[0565]

By a method similar to Example 65, the title compound (16
5 mg) was obtained from N-[4-(trans-2-aminocyclopropyl)phenyl]-3-(trifluoromethyl)benzamide hydrochloride (75 mg) and 1,8-naphthyridine-2-carbaldehyde (43.2 mg).

MS (API+): $[M+H]^+$ 463.0.

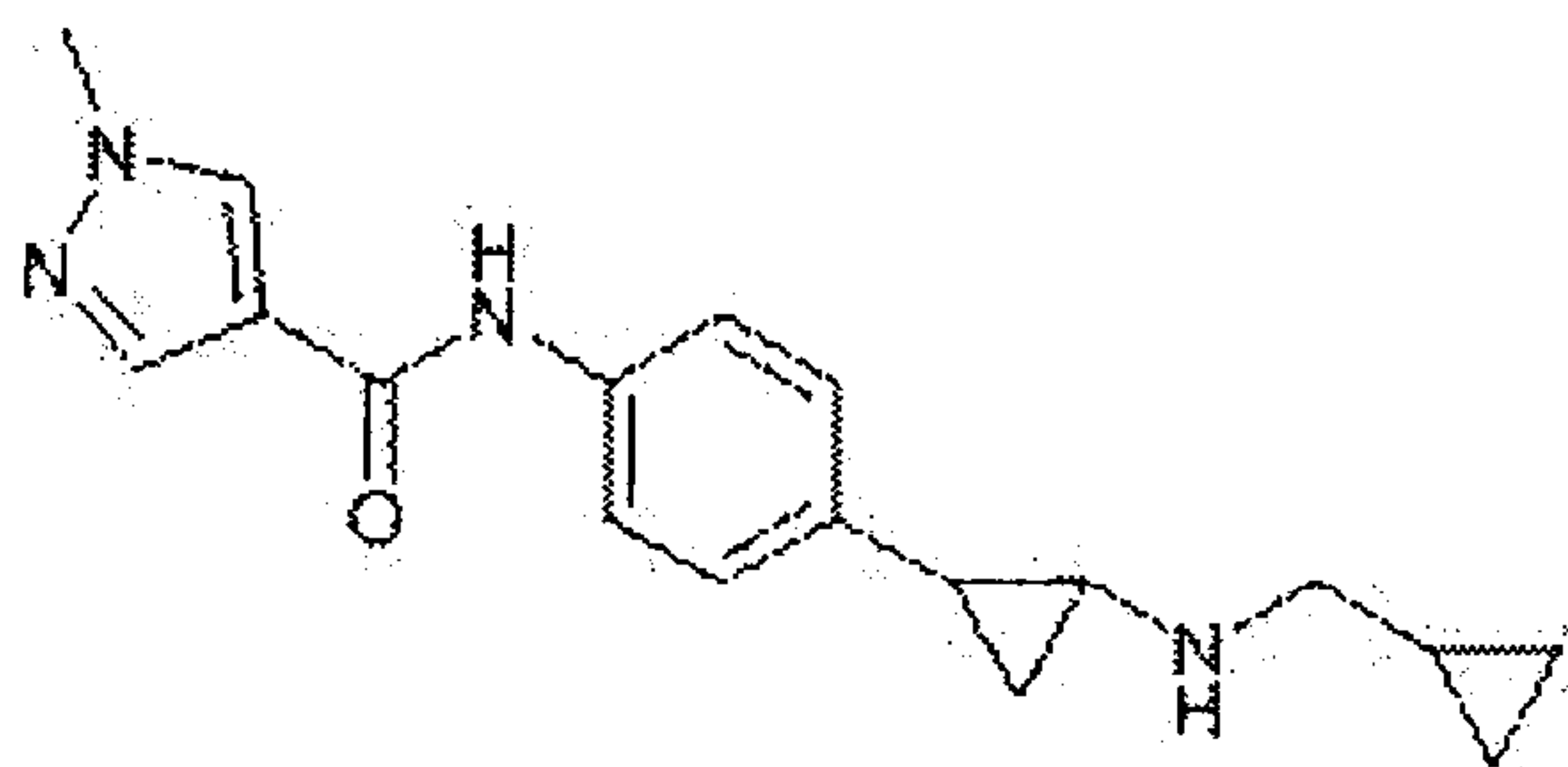
^1H NMR (300 MHz, CD_3OD) δ 1.42-1.53 (1H, m), 1.63-1.73 (1H, m),
10 2.59-2.70 (1H, m), 3.20-3.28 (1H, m), 4.95 (2H, s), 7.20 (2H, d, $J = 8.7$ Hz), 7.64-7.77 (3H, m), 7.83-7.97 (3H, m), 8.16-8.27 (2H, m), 8.69 (1H, d, $J = 8.5$ Hz), 8.85 (1H, dd, $J = 8.3, 1.7$ Hz), 9.19-9.32 (1H, m).

[0566]

15 Example 163

N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-1-methyl-1H-pyrazole-4-carboxamide hydrochloride

[0567]



20 [0568]

A) tert-butyl (cyclopropylmethyl)[trans-2-(4-{[(1-methyl-1H-pyrazol-4-yl)carbonyl]amino}phenyl)cyclopropyl]carbamate

To a solution of tert-butyl [trans-2-(4-aminophenyl)cyclopropyl](cyclopropylmethyl)carbamate (85.8 mg)
25 and 1-methyl-1H-pyrazole-4-carboxylic acid (42.9 mg) in DMF (1.42 mL) was added N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (82 mg). The

mixture was stirred at room temperature overnight, and poured into water. The mixture was extracted with ethyl acetate, and the extract was washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine, and
 5 dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the title compound (114.8 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.05-0.16 (1H, m), 0.16-0.28 (1H, m), 0.32-0.52 (2H, m), 0.89-1.05 (1H, m), 1.09-1.26 (2H, m),
 10 1.36 (9H, s), 2.00-2.10 (1H, m), 2.65-2.72 (1H, m), 2.98 (1H, dd, J = 14.2, 6.9 Hz), 3.19 (1H, dd, J = 14.2, 6.9 Hz), 3.88 (3H, s), 7.10 (2H, d, J = 8.5 Hz), 7.59 (2H, d, J = 8.7 Hz), 7.99 (1H, s), 8.28 (1H, s), 9.74 (1H, s).

[0569]

15 B) N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-1-methyl-1H-pyrazole-4-carboxamide hydrochloride

tert-Butyl (cyclopropylmethyl)[trans-2-(4-{[(1-methyl-1H-pyrazol-4-yl)carbonyl]amino}phenyl)cyclopropyl]carbamate (114.8 mg) was dissolved in 4N hydrochloric acid/cyclopentyl methyl
 20 ether solution (1 mL), and the mixture was stirred at room temperature for 1.5 hr. The solvent was evaporated under reduced pressure. The residue was recrystallized from methanol/diisopropyl ether to give the title compound (51.1 mg). MS (API+): [M+H]⁺ 311.3.

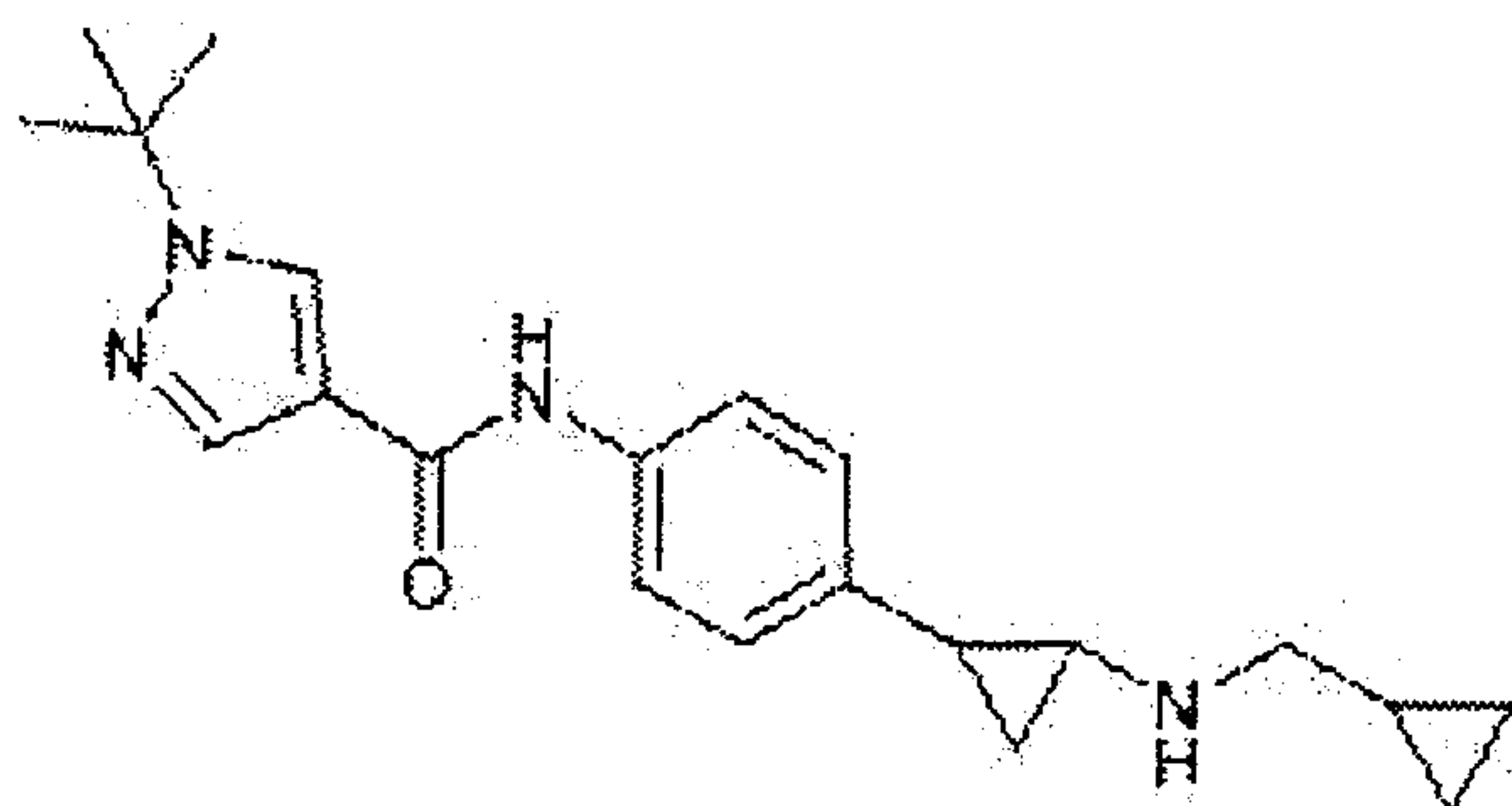
25 ¹H NMR (300 MHz, DMSO-d₆) δ 0.32-0.41 (2H, m), 0.51-0.62 (2H, m), 1.01-1.15 (1H, m), 1.19-1.30 (1H, m), 1.47-1.58 (1H, m), 2.43-2.49 (1H, m), 2.80-3.01 (3H, m), 3.89 (3H, s), 7.13 (2H, d, J = 8.7 Hz), 7.66 (2H, d, J = 8.7 Hz), 8.02 (1H, s), 8.33 (1H, s), 9.41 (2H, brs), 9.86 (1H, s).

30 [0570]

Example 164

1-tert-butyl-N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-1H-pyrazole-4-carboxamide hydrochloride

35 [0571]



[0572]

By a method similar to Example 163, the title compound (30.7 mg) was obtained from tert-butyl [trans-2-(4-aminophenyl)cyclopropyl] (cyclopropylmethyl) carbamate (76.5 mg) and 1-(tert-butyl)-1H-pyrazole-4-carboxylic acid (51.1 mg).

MS (API+): $[M+H]^+$ 353.2.

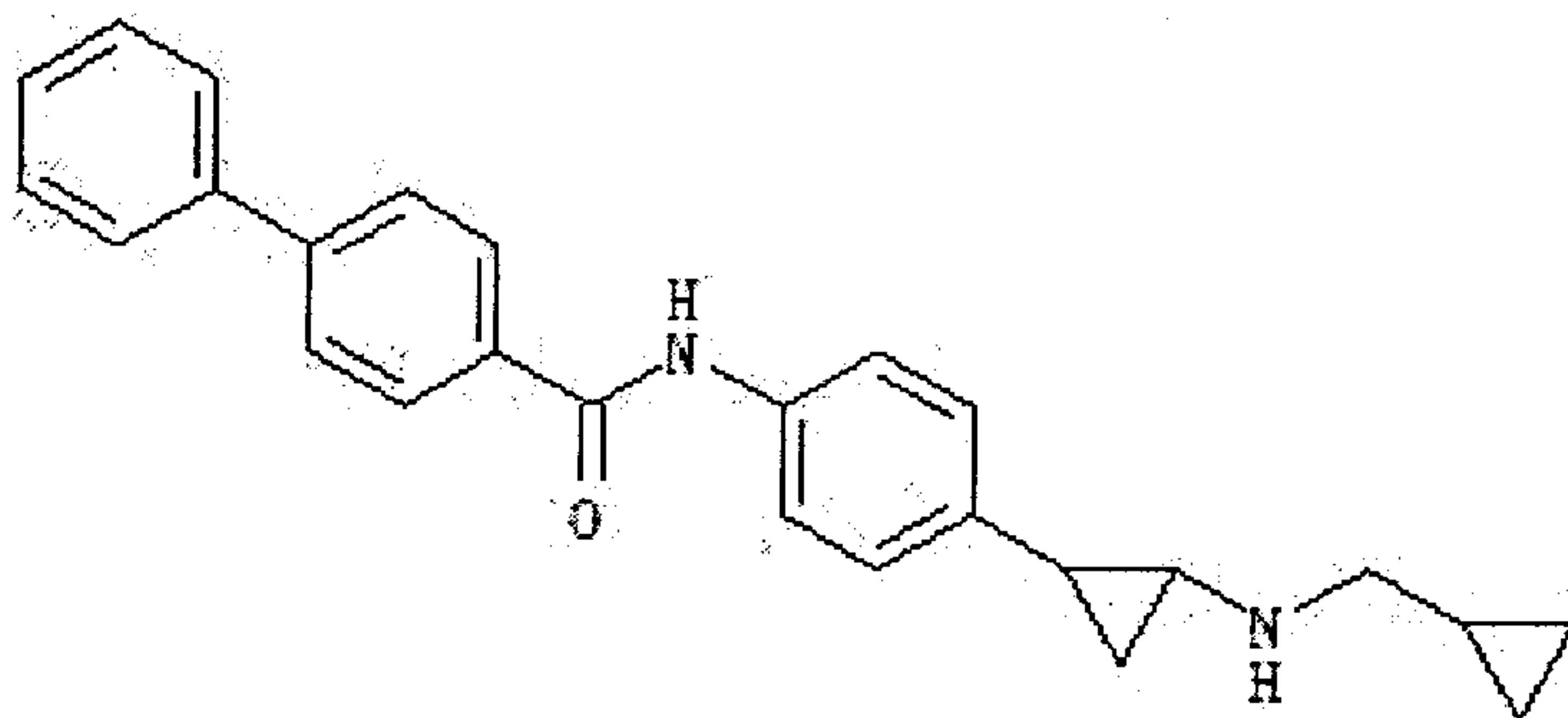
^1H NMR (300 MHz, DMSO- d_6) δ 0.27-0.42 (2H, m), 0.53-0.61 (2H, m), 0.99-1.13 (1H, m), 1.19-1.30 (1H, m), 1.42-1.51 (1H, m), 1.55 (9H, s), 2.36-2.47 (1H, m), 2.84-2.98 (3H, m), 7.14 (2H, d, $J = 8.5$ Hz), 7.64 (2H, d, $J = 8.5$ Hz), 8.01 (1H, s), 8.48 (1H, s), 9.09 (2H, brs), 9.79 (1H, s).

[0573]

Example 165

N-(4-{(1R,2S) or (1S,2R)-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)biphenyl-4-carboxamide hydrochloride

[0574]



[0575]

N-(4-{trans-2-[(Cyclopropylmethyl)amino]cyclopropyl}phenyl)biphenyl-4-carboxamide hydrochloride (273 mg) was fractionated by HPLC (CHIRALPAK (registered trademark) AD (JG001), 50 mmID x 500 mmL,

manufactured by Daicel Corporation, mobile phase: ethanol), a fraction containing the object product and having a shorter retention time was concentrated under reduced pressure, and the residue was ice-cooled to 0°C. 4N Hydrochloric

5 acid/cyclopentyl methyl ether solution (3.0 mL) was added, and the mixture was concentrated under reduced pressure to give the title compound (116 mg).

optical purity: 99.7% ee, retention time: 13.684 min (CHIRALPAK (registered trademark) AD (KF053), 4.6 mmID x 250 mmL,

10 manufactured by Daicel Corporation, mobile phase: ethanol)

¹H NMR (300 MHz, CD₃OD) δ 0.39-0.48 (2H, m), 0.69-0.78 (2H, m), 1.06-1.23 (1H, m), 1.31-1.55 (2H, m), 2.47 (1H, ddd, J = 10.3, 6.7, 3.6 Hz), 2.95-3.03 (1H, m), 3.06-3.13 (2H, m), 7.21 (2H, d, J = 9.8 Hz), 7.36-7.53 (3H, m), 7.66-7.73 (4H, m), 7.78 (2H, d, J = 8.1 Hz), 8.01 (2H, d, J = 9.0 Hz).

[0576]

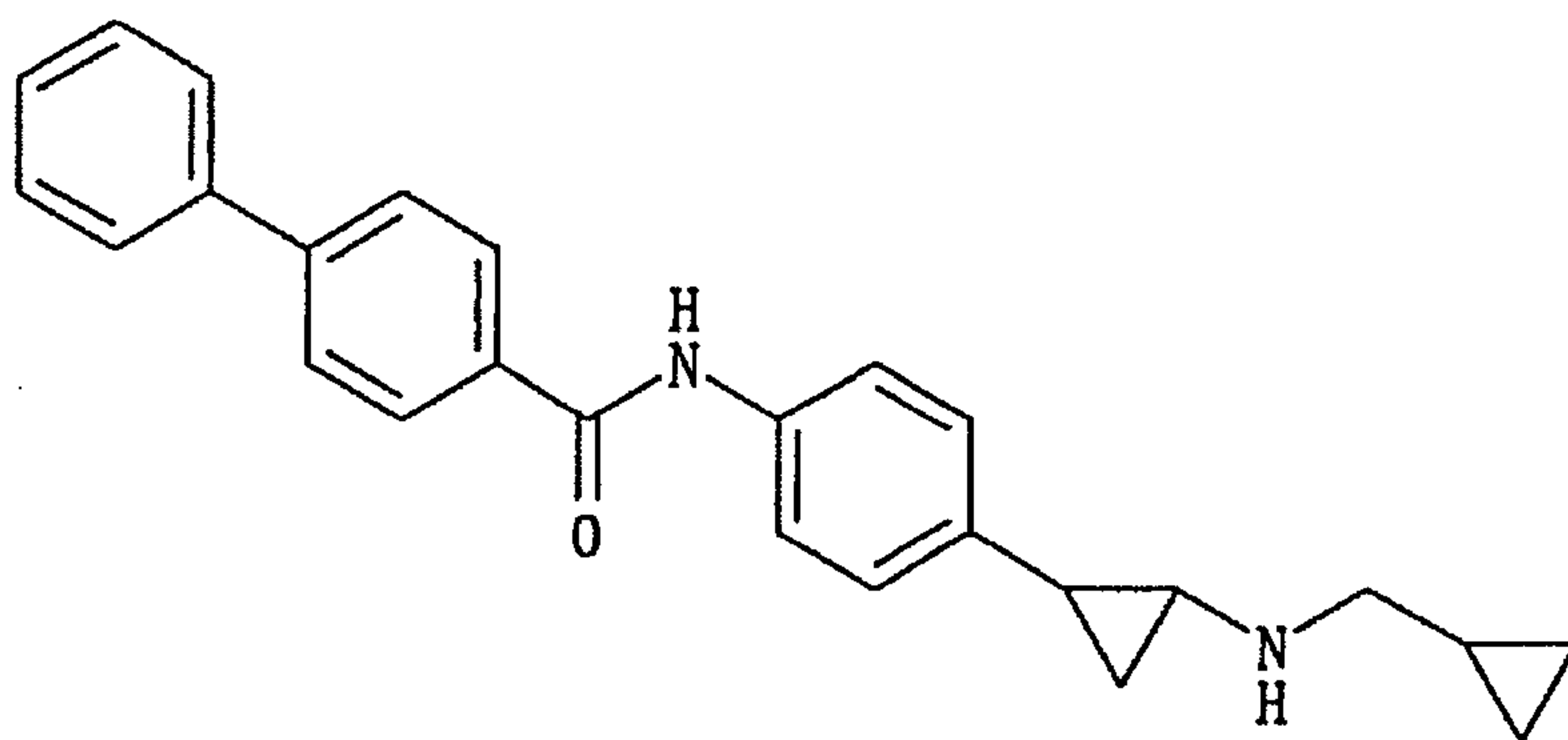
Example 166

N-(4-((1S,2R) or (1R,2S)-2-

[(cyclopropylmethyl)amino]cyclopropyl}phenyl)biphenyl-4-

20 carboxamide hydrochloride

[0577]



[0578]

N-(4-{trans-2-

25 [(Cyclopropylmethyl)amino]cyclopropyl}phenyl)biphenyl-4-

carboxamide hydrochloride (273 mg) was fractionated by HPLC

(CHIRALPAK (registered trademark) AD (JG001), 50 mmID x 500 mmL,

manufactured by Daicel Corporation, mobile phase: ethanol), a

fraction containing the object product and having a longer retention time was concentrated under reduced pressure, and the residue was ice-cooled to 0°C. 4N Hydrochloric acid/cyclopentyl methyl ether solution (3.0 mL) was added, and the mixture was concentrated under reduced pressure to give the title compound (128 mg).

optical purity: 99.1% ee, retention time: 16.256 min (CHIRALPAK (registered trademark) AD (KF053), 4.6 mmID x 250 mmL, manufactured by Daicel Corporation, mobile phase: ethanol)

¹H NMR (300 MHz, CD₃OD) δ 0.38-0.48 (2H, m), 0.69-0.79 (2H, m), 1.04-1.21 (1H, m), 1.36-1.55 (2H, m), 2.47 (1H, ddd, J = 10.2, 6.6, 3.4 Hz), 2.95-3.02 (1H, m), 3.09 (2H, dd, J = 7.5, 2.3 Hz), 7.21 (2H, d, J = 8.7 Hz), 7.36-7.44 (1H, m), 7.44-7.53 (2H, m), 7.66-7.73 (4H, m), 7.78 (2H, d, J = 8.9 Hz), 8.02 (2H, d, J = 8.5 Hz).

[0579]

Experimental Example 1

The genetic engineering method described below was performed according to the method described in a book (Maniatis et al., Molecular Cloning, Cold Spring Harbor Laboratory, 1989) or the method described in the protocol attached to the reagent.

(1) Construction of GST-tagged expression vector having TEV Protease cleavage sequence

A GST-tagged expression vector having TEV Protease cleavage sequence was constructed by successive 2 times of PCR method. Firstly, PCR was performed using pGEX6P1 (GE Healthcare) as a template, two primers

GST-Sw-F:

5'-AGAATCATTTAAATGGTGATCATGTAACCCATCCT-3'

[SEQ ID NO: 1]

GST-Tv-R1:

5'-CGCCCTGAAAGTACAGGTTCTCATCCGATTTTGGAGGATGGTCG-3'

[SEQ ID NO: 2]

and PrimeStar GXL DNA Polymerase (Takara Bio Inc.). Template DNA 0.5 μL, 5x Buffer 10 μL, 2.5 mM dNTP solution 4 μL, 10 μM

primer solution each 1.5 μ L, PrimeStar GXL DNA Polymerase 1 μ L, and sterilized distilled water 31.5 μ L were mixed. After a treatment at 98°C for 1 min, the PCR reaction was started with 35 repeats of a treatment at 98°C for 10 seconds, at 65°C for 5 seconds, and at 72°C for 25 seconds, followed by a treatment at 72°C for 1 min. Then, PCR was performed using the obtained PCR product as a template, two primers

GST-Sw-F:

5'-AGAATCATTTAAATGGTGATCATGTAACCCATCCT-3'

10 [SEQ ID NO: 1]

GST-Tv-R2:

5'-ATAATAGGATCCGCCCTGAAAGTACAGGTTCTC-3'

[SEQ ID NO: 3]

and PrimeStar GXL DNA Polymerase. Template DNA 0.5 μ L, 5x Buffer 10 μ L, 2.5 mM dNTP solution 4 μ L, 10 μ M primer solution each 1.5 μ L, PrimeStar GXL DNA Polymerase 1 μ L, and sterilized distilled water 31.5 μ L were mixed. After a treatment at 98°C for 1 min, the PCR reaction was started with 25 repeats of a treatment at 98°C for 10 seconds, at 65°C for 5 seconds, and at 72°C for 25 seconds, followed by a treatment at 72°C for 1 min. The obtained PCR product was electrophoresed on agarose gel (1%), and an about 0.3 kbp DNA fragment containing a part of GST gene was recovered from the gel. The recovered DNA fragment was cleaved with restriction enzymes Swa I (New England Biolabs) and Bam HI (Takara Bio Inc.), and inserted into the Swa I/Bam HI site of pGEX6P1 to prepare an expression vector pGEX7V1.

[0580]

(2) Cloning of human LSD1 (AOF2) gene

30 Human LSD1 gene was cloned by PCR method using brain cDNA Library (Takara Bio Inc.) as a template, two primers hLSD1-NheI-ko-F:

5'-TATTATGCTAGCGCCACCATGTTATCTGGGAAGAAGGCGGCAGC-3'

[SEQ ID NO: 4]

35 hLSD1-St-NotI-R:

5'-TATTATGCGGCCGCTCACATGCTTGGGGACTGCTGTGC-3'

[SEQ ID NO: 5]

and Pyrobest DNA Polymerase (Takara Bio Inc.). Template DNA 0.5 µL, 10x Buffer 5 µL, 2.5 mM dNTP solution 4 µL, 10 µM primer solution each 2.5 µL, Pyrobest DNA Polymerase 0.5 µL, and sterilized distilled water 34 µL were mixed. After a treatment at 98°C for 1 min, the PCR reaction was started with 35 repeats of a treatment at 98°C for 10 seconds, at 68°C for 5 seconds, and at 72°C for 2.5 min, followed by a treatment at 72°C for 1 min. The obtained PCR product was electrophoresed on agarose gel (1%), and an about 2.5 kbp DNA fragment containing human LSD1 gene was recovered from the gel. The recovered DNA fragment was cleaved with restriction enzymes Nhe I and Not I (Takara Bio Inc.), and inserted into the Nhe I/Not I site of pcDNA3.1(+) (Invitrogen) to prepare an expression plasmid pcDNA3.1/hLSD1.

[0581]

(3) Construction of expression plasmid for human LSD1(171-852) in *Escherichia coli*

A plasmid for expression of human LSD1(171-852) in *Escherichia coli* was produced by PCR method using pcDNA3.1/hLSD1 as a template, two primers hLSD1-171aa-Bgl2-F:

5'-TATTATAGATCTCCATCGGGTGTGGAGGGCGCA-3'

[SEQ ID NO: 6]

hLSD1-St-NotI-R:

5'-TATTATGCGGCCGCTCACATGCTTGGGGACTGCTGTGC-3'

[SEQ ID NO: 5]

and PrimeStar MAX DNA Polymerase (Takara Bio Inc.). Template DNA 1 µL, 2x Enzyme PreMix 25 µL, 10 µM primer solution each 1.5 µL, and sterilized distilled water 21 µL were mixed. After a treatment at 98°C for 1 min, the PCR reaction was started with 25 repeats of a treatment at 98°C for 10 seconds and at 68°C for 10 seconds, followed by a treatment at 72°C for 1 min. The obtained PCR product was electrophoresed on agarose gel

(1%), and an about 2 kbp DNA fragment containing human LSD1(171-852) gene was recovered from the gel. The recovered DNA fragment was cleaved with restriction enzymes Bgl II and Not I (Takara Bio Inc.), and inserted into the Bam HI/Not I
5 site of pGEX7V1 to prepare expression plasmid pGEX7V1/GST-hLSD1(171-852).

[0582]

(4) Preparation of LSD1

Escherichia coli C43(DE3) pLysS was transformed with the
10 expression plasmid pGEX7V1/GST-hLSD1(171-852) prepared in (3). The obtained recombinant Escherichia coli was inoculated in a TB medium (1.2% tryptone, 2.4% yeast extract, 0.4% glycerol, 0.5% glucose, 17 mM potassium dihydrogen phosphate and 72 mM dipotassium hydrogen phosphate) added with 100 mg/L ampicillin
15 and 30 mg/L chloramphenicol, and cultured at 37°C. When the turbidity reached 600 Klett units, the culture temperature was changed to 16°C, IPTG having a final concentration of 0.5 mM was added to induce expression, and the cells were cultured further for 21 hr. The culture medium was centrifuged at 9,000
20 g for 10 min, and Escherichia coli pellets were recovered.

[0583]

Escherichia coli pellets in 9 L of the culture medium were suspended in 1340 mL of an extraction buffer (PBS, 5%(V/V) Glycerol), and 6700 units of Benzonase (Merck) were added.
25 Using Branson ultrasonic disintegrator, the suspension was disrupted by ultrasonication for 3 min, and centrifuged at 33,000 g for 20 min, and the supernatant was recovered. To the supernatant was added 5 M NaCl solution to a final concentration of 0.15 M, and the mixture was applied to two
30 GSTrap 4B 5 mL columns (GE Healthcare) equilibrated in advance with PBS, 0.15 M NaCl, 5%(V/V) Glycerol (Buffer A), and the columns were each washed with 25 mL of Buffer A. GST-hLSD1(171-852) was eluted from each column with 20 mL of 0.1 M Tris (pH 8.0), 10 mM GSH, 0.15 M NaCl, 5%(V/V) Glycerol. The
35 eluate (14 mL) containing GST-hLSD1(171-852) was applied to

HiLoad 26/60 Superdex 200 pg column (GE Healthcare) equilibrated with Buffer A, and eluted with 300 mL of Buffer A. The fraction containing GST-hLSD1(171-852) was concentrated to 9 mL with AmiconUltra 15 (Japan Millipore) having a molecular weight cutoff of 30K to give purified GST-hLSD1(171-852). 1 mg of His-TEV protease was added relative to about 36 mg of GST-hLSD1(171-852), and the mixture was treated with 50 mM Tris (pH 8.0), 0.5 mM EDTA, 1 mM DTT at 4°C for 16 hr to cleave the GST tag. The reaction mixture after the cleavage reaction was applied to GSTrap 4B 5 mL column (GE Healthcare) equilibrated in advance with Buffer A, and a flow-through fraction containing hLSD1(171-852) free of GST tag was recovered. It was concentrated to 9 mL with AmiconUltra 15 (Japan Millipore), and purified with HiLoad 26/60 Superdex 200 pg column (GE Healthcare) equilibrated with Buffer A again to give hLSD1(171-852) purified product. The protein concentration of hLSD1(171-852) was measured by BCA Protein Assay Kit (Thermo Fisher Scientific K.K.) using bovine serum albumin as the standard. [0584]

(5) Measurement of LSD1 inhibitory activity

A test compound dissolved in 2.5% DMSO was added by 4 μ L to 3 μ L reaction solution (50 mM Tris-HCl (pH 8.0), 0.1% BSA, 1 mM DTT) containing 2.8 ng of LSD1, and the mixture was reacted at room temperature for 15 min. Biotin-histone H3 mono methylated K4 peptide solution (NH₂-ART(me-K)QTARKSTGGKAPRKQLAGGK(Biotin)-CONH₂) (3.3 μ M) was added by 3 μ L to start the reaction. After reaction at room temperature for 20 min, 1 mM 2-PCPA solution (5 μ L) was added to terminate the reaction. A detection solution (800 mM potassium fluoride, 0.1% BSA) containing europium-labeled antihistone H3 antibody (Wako Pure Chemical Industries, Ltd.) and Streptavidin-XL665 (Cisbio) was further added by 5 μ L, and the mixture was left standing for 60 min. A time-resolved fluorescence (excitation 320 nm, emission 615 nm, 665 nm) was measured by Envision (PerkinElmer). The LSD1 inhibitory rate (%) of the test

compound was calculated by the following formula.

$$\text{inhibitory rate (\%)} = (1 - (\text{test compound count} - \text{blank}) \div (\text{control} - \text{blank})) \times 100$$

The count of the LSD1 enzyme reaction mixture under
5 compound non-addition conditions is indicated as control, and
the count under compound non-addition and LSD1 enzyme non-
addition conditions is indicated as blank. The results are
shown in Table 2.

[0585]

10 Experimental Example 2

(1) Measurement of MAO-A inhibitory activity

The MAO-A inhibitory activity evaluation described below
followed the protocol of MAO-Glo (registered trademark) Assay
of Promega KK.

15 A test compound dissolved in 4% DMSO was added by 12.5 μ L
to 25 μ L reaction solution (100 mM HEPES (pH 7.5), 5% glycerol)
containing 400 ng of MAO-A enzyme (Sigma-Aldrich Co. LLC.), and
the mixture was reacted at room temperature for 10 min. MAO
substrate (Promega KK) (160 μ M) was added by 12.5 μ L to start
20 the reaction. After reaction at room temperature for 60 min,
Luciferine detection reagent (Promega KK) (50 μ L) was added to
terminate the reaction. After reaction at room temperature for
20 min with stirring, the luminescence was measured by Envision
(PerkinElmer). The MAO-A inhibitory rate (%) of the test
25 compound was calculated by the following formula.

$$\text{inhibitory rate (\%)} = (1 - (\text{test compound count} - \text{blank}) \div (\text{control} - \text{blank})) \times 100$$

The count of the MAO-A enzyme reaction mixture under
compound non-addition conditions is indicated as control, and
30 the count under compound non-addition and MAO-A enzyme non-
addition conditions is indicated as blank. The results are
shown in Table 2.

[0586]

(2) Measurement of MAO-B inhibitory activity

35 The MAO-B inhibitory activity evaluation described below

followed the protocol of MAO-Glo (registered trademark) Assay of Promega KK.

A test compound dissolved in 4% DMSO was added by 12.5 μ L to 25 μ L reaction solution (100 mM HEPES (pH 7.5), 5% glycerol, 10% DMSO) containing 400 ng of MAO-B enzyme (Sigma-Aldrich Co. LLC.), and the mixture was reacted at room temperature for 10 min. MAO substrate (Promega KK) (16 μ M) was added by 12.5 μ L to start the reaction. After reaction at room temperature for 60 min, Luciferine detection reagent (Promega KK) (50 μ L) was added to terminate the reaction. After reaction at room temperature for 20 min with stirring, the luminescence was measured by Envision (PerkinElmer). The MAO-B inhibitory rate (%) of the test compound was calculated by the following formula.

$$\text{inhibitory rate (\%)} = (1 - (\text{test compound count} - \text{blank}) \div (\text{control} - \text{blank})) \times 100$$

The count of the MAO-B enzyme reaction mixture under compound non-addition conditions is indicated as control, and the count under compound non-addition and MAO-B enzyme non-addition conditions is indicated as blank. The results are shown in Table 2.

[0587]

[Table 2-1]

Ex. No.	LSD1 IC ₅₀ value (μM)	MAO-A IC ₅₀ value (μM)	MAO-B IC ₅₀ value (μM)
1	<0.1	3.8	9.7
2	0.2	9.3	>10
3	<0.1	4.4	9
4	0.24	>10	>10
5	<0.1	7.7	>10
6	<0.1	>10	>10
7	<0.1	5.6	>10
8	<0.1	5.8	>10
9	0.28	>10	>10
10	0.14	3.3	>10
11	0.15	2.4	> 10
12	<0.1	4.7	>10
13	<0.1	>10	>10
14	<0.1	>10	>10
15	<0.1	6	>10
16	<0.1	4.7	>10
17	<0.1	>10	>10
18	<0.1	2.6	>10
19	<0.1	>10	3.2
20	<0.1	>10	>10
21	<0.1	>10	>10
22	0.41	3.6	2.6
23	<0.1	>10	>10
24	<0.1	>10	>10
25	<0.1	>10	>10
26	<0.1	9.2	>10
28	<0.1	3.5	>10
29	0.11	5.2	>10
30	0.58	1.7	>10

[0588]

[Table 2-2]

Ex. No.	LSD1 IC ₅₀ value (μM)	MAO-A IC ₅₀ value (μM)	MAO-B IC ₅₀ value (μM)
31	<0.1	>10	>10
32	<0.1	>10	>10
33	<0.1	>10	>10
34	0.19	>10	>10
35	0.13	1.3	>10
36	<0.1	4.6	>10
38	<0.1	9.1	>10
39	<0.1	>10	>10
40	<0.1	—	—
41	0.11	5.8	5.1
42	<0.1	>10	>10
43	0.11	3.3	4.7
44	<0.1	>10	9.3
45	0.29	>10	>10
46	<0.1	>10	>10
47	0.19	1.8	1.7
48	<0.1	4.3	3.8
49	<0.1	>10	>10
50	<0.1	>10	>10
51	0.1	>10	>10
52	0.16	>10	>10
53	0.23	4	3.4
54	<0.1	0.85	1.5
55	0.13	>10	>10
56	0.26	>10	>10
57	0.48	>10	>10
58	0.41	>10	>10
59	<0.1	7.1	>10
60	1.9	>10	>10

[0589]

[Table 2-3]

Ex. No.	LSD1 IC ₅₀ value (μM)	MAO-A IC ₅₀ value (μM)	MAO-B IC ₅₀ value (μM)
61	<0.1	2.2	3.3
62	<0.1	>10	>10
63	<0.1	>10	>10
64	0.2	8.5	>10
65	<0.1	8.6	9.6
66	<0.1	>10	>10
67	<0.1	>10	>10
68	<0.1	>10	>10
69	<0.1	>10	>10
70	<0.1	>10	>10
71	<0.1	>10	>10
72	<0.1	3.1	>10
73	<0.1	10.0	8.1
74	<0.1	>10	>10
75	<0.1	>10	>10
76	<0.1	>10	>10
77	<0.1	9.9	>10
78	<0.1	>10	>10
79	<0.1	>10	>10
80	<0.1	>10	>10
81	<0.1	>10	>10
82	<0.1	>10	>10
83	<0.1	>10	>10
84	<0.1	>10	>10
85	<0.1	9.1	4.9
86	1.0	>10	>10
87	<0.1	>10	>10
88	<0.1	>10	>10
89	0.1	>10	>10
90	<0.1	>10	>10

[0590]

[Table 2-4]

Ex. No.	LSD1 IC ₅₀ value (μM)	MAO-A IC ₅₀ value (μM)	MAO-B IC ₅₀ value (μM)
91	<0.1	>10	>10
92	<0.1	7.9	>10
93	<0.1	>10	>10
94	<0.1	>10	>10
95	<0.1	>10	>10
96	<0.1	>10	>10
97	<0.1	>10	>10
98	<0.1	>10	>10
99	<0.1	>10	>10
100	<0.1	>10	>10
101	<0.1	>10	>10
102	0.2	>10	>10
103	<0.1	>10	>10
104	<0.1	>10	>10
105	<0.1	>10	>10
106	<0.1	>10	>10
107	<0.1	4.3	>10
108	<0.1	>10	>10
109	<0.1	>10	>10
110	<0.1	>10	>10
111	<0.1	>10	>10
112	<0.1	>10	>10
113	<0.1	5.7	>10
114	<0.1	>10	>10
115	<0.1	>10	>10
116	1.8	>10	>10
117	<0.1	7.5	>10
118	0.1	>10	>10
119	<0.1	0.1	>10
120	1.6	>10	>10

[0591]

[Table 2-5]

Ex. No.	LSD1 IC ₅₀ value (μM)	MAO-A IC ₅₀ value (μM)	MAO-B IC ₅₀ value (μM)
121	<0.1	>10	>10
122	<0.1	>10	>10
123	<0.1	5.0	>10
124	<0.1	>10	>10
125	<0.1	2.5	>10
126	<0.1	>10	>10
127	0.1	>10	>10
128	<0.1	5.3	>10
129	<0.1	8.2	>10
130	<0.1	>10	>10
131	<0.1	>10	>10
132	<0.1	8.3	>10
133	<0.1	>10	>10
134	<0.1	>10	>10
135	0.1	>10	>10
136	<0.1	>10	>10
137	<0.1	4.2	>10
138	<0.1	>10	>10
139	<0.1	8.2	>10
140	<0.1	>10	>10
141	<0.1	>10	>10
142	0.1	>10	>10
143	<0.1	4.5	>10
144	0.2	>10	>10
145	<0.1	>10	>10
146	<0.1	6.7	>10
147	<0.1	>10	>10
148	<0.1	8.3	>10
149	<0.1	>10	>10
150	<0.1	>10	>10

[0592]

[Table 2-6]

Ex. No.	LSD1 IC ₅₀ value (μM)	MAO-A IC ₅₀ value (μM)	MAO-B IC ₅₀ value (μM)
151	<0.1	>10	>10
152	<0.1	>10	>10
153	<0.1	>10	>10
154	<0.1	>10	>10
155	<0.1	>10	>10
156	<0.1	>10	>10
157	0.1	>10	>10
158	<0.1	>10	>10
159	<0.1	>10	>10
160	<0.1	5.1	>10
161	<0.1	4.1	>10
162	<0.1	2.1	>10
163	0.1	>10	>10
164	0.2	>10	>10
165	<0.1	>10	>10
166	<0.1	>10	>10

[0593]

5 As shown in Table 2, the compound of the present invention has a superior LSD1 inhibitory activity. In addition, the MAO-A inhibitory activity and MAO-B inhibitory activity of the compound of the present invention are low, and the compound of the present invention has a selective LSD1 inhibitory
10 activity.

[0594]

Experimental Example 3

Tumor growth suppressive effect test using HEL92.1.7 acute myeloid leukemia cell

15 6-Week-old SCID mice were subcutaneously transplanted with 5×10^6 cells/100 μL of HEL92.1.7 acute myeloid leukemia

cells, and the mice were grouped according to the body weight and tumor volume after 15 to 17 days. Vehicle (0.5% methylcellulose) or compound A, compound B or compound C was administered orally to mice (5 mice per group). The administration was once per day and performed continuously during the dosing period. Setting the change in tumor volume of the vehicle-treated group as 100%, the change rate in tumor volume of the compound-treated group (T/C %) was calculated. The tumor volume was determined by measuring the long diameter and short diameter of the tumor with a vernier caliper, and calculating by the following calculation formula: (long diameter)x(short diameter)x(short diameter)/2. The results are shown in Table 3.

Compound A: N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)biphenyl-4-carboxamide hydrochloride

Compound B: N-(4-{trans-2-[(1-methylpiperidin-4-yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide dihydrochloride

Compound C: N-(4-{trans-2-[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-1H-pyrazole-4-carboxamide hydrochloride

[0595]

Table 3

compound	T/C (%)	dose (mg/kg)	dosing period (days)
A	12.54	30 mg/kg	14
B	-8.08	30 mg/kg	7
C	46.42	30 mg/kg	14

25

[0596]

As shown in Table 3, the compound of the present invention has a superior antitumor growth activity.

[0597]

30 Formulation Example 1

A medicament containing the compound of the present invention as an active ingredient can be produced, for example, according to the following formulation.

1. capsule

5	(1) compound obtained in Example 1	10 mg
	(2) lactose	90 mg
	(3) crystalline cellulose	70 mg
	(4) magnesium stearate	10 mg
	1 capsule	180 mg

10 The total amount of the above-mentioned (1), (2) and (3) and 5 mg of (4) are blended, and the mixture is granulated. Thereto is added the remaining 5 mg of (4), and the whole is sealed in a gelatin capsule.

[0598]

15 2. tablet

	(1) compound obtained in Example 1	10 mg
	(2) lactose	35 mg
	(3) cornstarch	150 mg
	(4) crystalline cellulose	30 mg
20	(5) magnesium stearate	5 mg
	1 tablet	230 mg

The total amount of the above-mentioned (1), (2) and (3), 20 mg of (4) and 2.5 mg of (5) are blended, and the mixture is granulated. Thereto are added the remaining 10 mg of (4) and 2.5 mg of (5), and the mixture is compression-molded to give a tablet.

Industrial Applicability

[0599]

The compound of the present invention has a superior LSD1 inhibitory action, and is useful as a medicament such as a prophylactic or therapeutic agent for cancer, schizophrenia, Alzheimer's disease, Parkinson's disease and Huntington's chorea, and the like.

[0600]

35 This application is based on patent application No. 2011-

174305 filed in Japan, the entire contents of which are incorporated by reference herein.

2781 Sequence Listing
SEQUENCE LISTING

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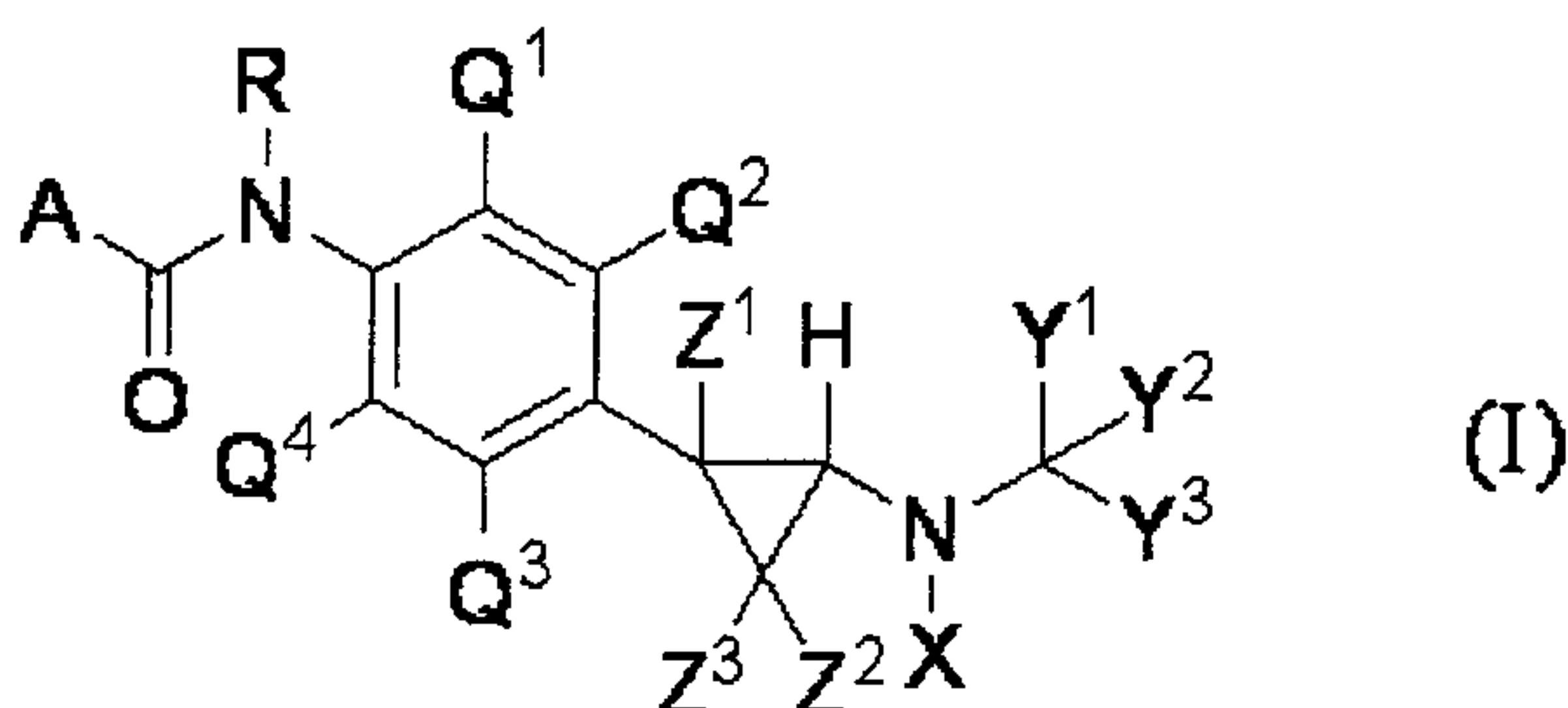
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33

CLAIMS

1. A compound represented by the formula



5 wherein A is a hydrocarbon group optionally having substituent(s), or a heterocyclic group optionally having substituent(s);

R is a hydrogen atom, a hydrocarbon group optionally having substituent(s), or a heterocyclic group optionally having
10 substituent(s); or

A and R are optionally bonded to each other to form a ring optionally having substituent(s);

Q¹, Q², Q³ and Q⁴ are each independently a hydrogen atom or a substituent; Q¹ and Q², and Q³ and Q⁴, are each optionally
15 bonded to each other to form a ring optionally having substituent(s);

X is a hydrogen atom, an acyclic hydrocarbon group optionally having substituent(s), or a saturated cyclic group optionally having substituent(s);

20 Y¹, Y² and Y³ are each independently a hydrogen atom, a hydrocarbon group optionally having substituent(s), or a heterocyclic group optionally having substituent(s);

X and Y¹, and Y¹ and Y², are each optionally bonded to each other to form a ring optionally having substituent(s); and

25 Z¹, Z² and Z³ are each independently a hydrogen atom or a substituent,
or a salt thereof.

2. The compound according to claim 1, wherein

30 A is

(1) a C₃₋₈ cycloalkyl group optionally having substituent(s),

- (2) a C₆₋₁₄ aryl group optionally having substituent(s),
 (3) a C₆₋₁₄ aryl C₁₋₆ alkyl group optionally having substituent(s),
 (4) a C₆₋₁₄ aryl C₁₋₆ alkyl C₆₋₁₄ aryl group optionally having substituent(s),
 (5) a 4- to 11-membered heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 3 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, and optionally having substituent(s), or
 (6) a C₁₀₋₁₄ cyclic hydrocarbon group optionally having substituent(s);
- R is a hydrogen atom or a C₁₋₆ alkyl group optionally having substituent(s); or
- A and R are optionally bonded to each other to form a 4- to 10-membered heterocycle optionally having substituent(s), or a salt thereof.

3. The compound according to claim 1, wherein Q¹ is a hydrogen atom or a C₁₋₆ alkyl group, and Q², Q³ and Q⁴ are each a hydrogen atom, or a salt thereof.

4. The compound according to claim 1, wherein X is a hydrogen atom or an optionally substituted C₁₋₆ alkyl group;

Y¹, Y² and Y³ are each independently

(1) a hydrogen atom,
 (2) a C₁₋₂₀ alkyl group optionally having substituent(s),
 (3) a C₃₋₈ cycloalkyl group optionally having substituent(s),
 (4) a C₆₋₁₄ aryl group optionally having substituent(s),
 (5) a C₆₋₁₄ aryl C₁₋₆ alkyl group optionally having substituent(s),
 (6) a 5- to 7-membered monocyclic aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom

and an oxygen atom, and optionally having substituent(s), or
(7) a bicyclic or tricyclic aromatic heterocyclic group
containing, as a ring-constituting atom besides carbon atom, 1
to 4 hetero atoms selected from a nitrogen atom, a sulfur atom
5 and an oxygen atom, and optionally having substituent(s);
X and Y¹ are optionally bonded to each other to form, together
with the adjacent nitrogen atom and carbon atom,
a 5- to 7-membered monocyclic nitrogen-containing nonaromatic
heterocycle containing, as a ring-constituting atom besides
10 carbon atom, one nitrogen atom, and optionally further
containing one hetero atom selected from a nitrogen atom, a
sulfur atom and an oxygen atom, and optionally having
substituent(s);
Y¹ and Y² are optionally bonded to each other to form, together
15 with the adjacent carbon atom,
(1) a 5- to 7-membered monocyclic nonaromatic heterocycle
containing, as a ring-constituting atom besides carbon atom,
one or two hetero atoms selected from a nitrogen atom, a sulfur
atom and an oxygen atom, and optionally having substituent(s),
20 or
(2) a 7- to 10-membered bridged heterocycle containing, as a
ring-constituting atom besides carbon atom, one or two hetero
atoms selected from a nitrogen atom, a sulfur atom and an
oxygen atom, and optionally having substituent(s),
25 or a salt thereof.

5. The compound according to claim 1, wherein
Z¹, Z² and Z³ are each a hydrogen atom, or a salt thereof.

30 6. The compound according to claim 1, wherein
A is
a phenyl-C₁₋₆ alkyl group,
a C₃₋₆ cycloalkyl group,
a tetrahydronaphthyl group,
35 a phenyl group,

- a biphenylyl group,
a furyl group,
a thienyl group,
an oxazolyl group,
5 an isoxazolyl group,
a thiazolyl group,
a pyrazolyl group,
an indazolyl group,
a benzofuryl group,
10 a benzimidazolyl group,
a benzothiazolyl group,
an indolyl group, or
a tetrahydrobenzazepinyl group, each of which optionally has 1
to 3 substituents selected from
15 (1) a halogen atom,
(2) a C₁₋₆ alkyl group optionally having 1 to 3 substituents
selected from a halogen atom, a phenyl group, an imidazolyl
group and a triazolyl group,
(3) a C₁₋₆ alkoxy group optionally having 1 to 3 substituents
20 selected from a halogen atom and a phenyl group,
(4) a C₁₋₆ alkyl-carbonyl group,
(5) a di-C₁₋₆ alkylamino group,
(6) a C₁₋₆ alkylsulfonyl group,
(7) a sulfamoyl group,
25 (8) a C₁₋₆ alkylsulfonylamino group,
(9) an oxo group,
(10) a C₃₋₆ cycloalkyl group,
(11) a phenyl group optionally having 1 to 3 substituents
selected from a halogen atom and a C₁₋₆ alkyl group,
30 (12) a phenoxy group,
(13) a phenylcarbonylamino group,
(14) a benzyloxycarbonylamino group,
(15) a benzoyl group,
(16) a benzylamino group,
35 (17) a pyrazolyl group,

- (18) a dihydropyrazolyl group optionally having 1 to 3 substituents selected from a C₁₋₆ alkyl group and an oxo group,
- (19) an oxazolyl group,
- (20) a thiazolyl group having 1 or 2 C₁₋₆ alkyl groups,
- 5 (21) a tetrazolyl group,
- (22) a pyrrolyl group,
- (23) a piperazinyl group having 1 to 3 C₁₋₆ alkyl groups,
- (24) an imidazolyl group,
- (25) a pyridyl group,
- 10 (26) a pyrimidinyl group,
- (27) a piperidyl group optionally having one oxo group,
- (28) a thienyl group,
- (29) a furyl group, and
- (30) a thiadiazolyl group;
- 15 R is a hydrogen atom or a C₁₋₆ alkyl group; or
- A and R are optionally bonded to each other to form a dihydroisoindole ring having 1 or 2 oxo groups;
- Q¹ is a hydrogen atom or a C₁₋₆ alkyl group;
- Q², Q³ and Q⁴ are each a hydrogen atom;
- 20 X is a hydrogen atom or a C₁₋₆ alkyl group optionally substituted by one C₃₋₆ cycloalkyl group;
- Y¹, Y² and Y³ are each independently
- (1) a hydrogen atom,
- (2) a C₁₋₂₀ alkyl group optionally having 1 to 3 substituents
- 25 selected from an amino group, a C₁₋₆ alkoxy group, a phenyl group, a phenyloxy group and a benzyloxy group,
- (3) a C₃₋₈ cycloalkyl group,
- (4) a phenyl group optionally having 1 to 3 substituents selected from a halogen atom, a C₁₋₆ alkoxy group, a C₁₋₃
- 30 alkylenedioxy group and a di-C₁₋₆ alkylamino group,
- (5) a pyridyl group optionally having 1 to 3 C₁₋₆ alkoxy groups,
- (6) a naphthyl group,
- (7) a biphenyl group,
- (8) a thienyl group,
- 35 (9) an imidazolyl group,

- (10) a thiazolyl group,
 - (11) a piperidyl group optionally having 1 to 3 C₁₋₆ alkyl groups,
 - (12) an imidazopyridyl group,
 - 5 (13) an imidazothiazolyl group,
 - (14) a thienopyridyl group, or
 - (15) a 1,8-naphthyridinyl group;
- Y¹ and Y² are optionally bonded to each other to form, together with the adjacent carbon atom,
- 10 a C₃₋₈ cycloalkane ring,
 - a pyrrolidine ring,
 - a piperidine ring,
 - a tetrahydropyran ring,
 - a 2,3-dihydroindene ring,
 - 15 a fluorene ring,
 - a 8-azabicyclo[3.2.1]octane ring, or
 - a tetrahydrothiopyran ring, each of which optionally has 1 to 3 substituents selected from
- (1) a halogen atom,
 - 20 (2) a C₁₋₆ alkyl group optionally having 1 to 3 substituents selected from a halogen atom and a phenyl group,
 - (3) a C₃₋₆ cycloalkyl group,
 - (4) an oxo group,
 - (5) a phenyl group,
 - 25 (6) a C₂₋₆ alkenyloxy-carbonyl group, and
 - (7) a C₁₋₆ alkyl-carbonyl group;
- X and Y¹ are optionally bonded to each other to form a pyrrolidine ring, together with the adjacent nitrogen atom and carbon atom; and
- 30 Z¹, Z² and Z³ are each a hydrogen atom,
 - or a salt thereof.

7. The compound according to claim 1, wherein

A is

- 35 a phenyl group optionally having 1 to 3 C₁₋₆ alkyl groups

substituted by 1 to 3 halogen atoms,
 a biphenyl group, or
 a pyrazolyl group;
 R is a hydrogen atom; or

5 A and R are optionally bonded to each other to form a
 dihydroisoindole ring having 1 or 2 oxo groups;

Q¹ is a hydrogen atom or a C₁₋₆ alkyl group;

Q², Q³ and Q⁴ are each a hydrogen atom;

X is a hydrogen atom;

10 Y¹, Y² and Y³ are each independently a hydrogen atom or a C₃₋₈
 cycloalkyl group;

Y¹ and Y² are optionally bonded to each other to form, together
 with the adjacent carbon atom,

a piperidine ring optionally having 1 to 3 C₁₋₆ alkyl groups;

15 and

Z¹, Z² and Z³ are each a hydrogen atom,

or a salt thereof.

8. N-(4-{trans-2-

20 [(cyclopropylmethyl)amino]cyclopropyl}phenyl)biphenyl-4-
 carboxamide or a salt thereof.

9. N-(4-{trans-2-[(1-methylpiperidin-4-

yl)amino]cyclopropyl}phenyl)-3-(trifluoromethyl)benzamide or a
 25 salt thereof.

10. N-(4-{trans-2-

[(cyclopropylmethyl)amino]cyclopropyl}phenyl)-1H-pyrazole-4-
 carboxamide or a salt thereof.

30

11. A medicament comprising the compound according to claim 1
 or a salt thereof.

12. The medicament according to claim 11, which is a
 35 prophylactic or therapeutic agent for cancer.

13. The medicament according to claim 11, which is an LSD1 inhibitor.

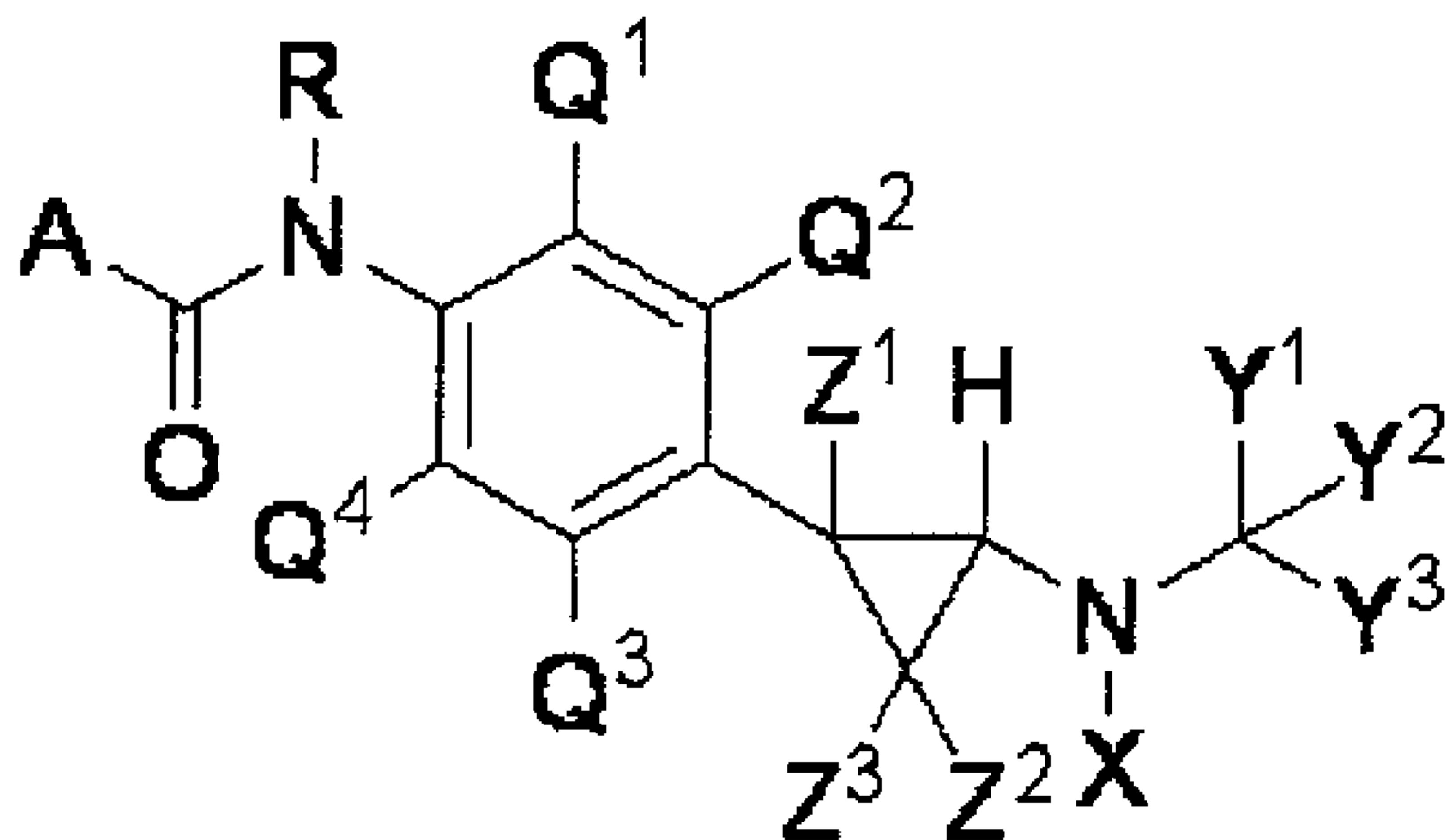
5 14. The medicament according to claim 11, which is a prophylactic or therapeutic agent for schizophrenia, Alzheimer's disease, Parkinson's disease or Huntington's chorea.

15. A method for the prophylaxis or treatment of schizophrenia,
10 Alzheimer's disease, Parkinson's disease or Huntington's chorea, comprising administering an effective amount of the compound according to claim 1 or a salt thereof to a mammal.

16. Use of the compound according to claim 1 or a salt thereof
15 for the production of a prophylactic or therapeutic agent for schizophrenia, Alzheimer's disease, Parkinson's disease or Huntington's chorea.

17. The compound according to claim 1 or a salt thereof for use
20 in the prophylaxis or treatment of schizophrenia, Alzheimer's disease, Parkinson's disease or Huntington's chorea.

18. A method of inhibiting LSD1, comprising administering an effective amount of the compound according to claim 1 or a salt
25 thereof to a mammal.



(I)