

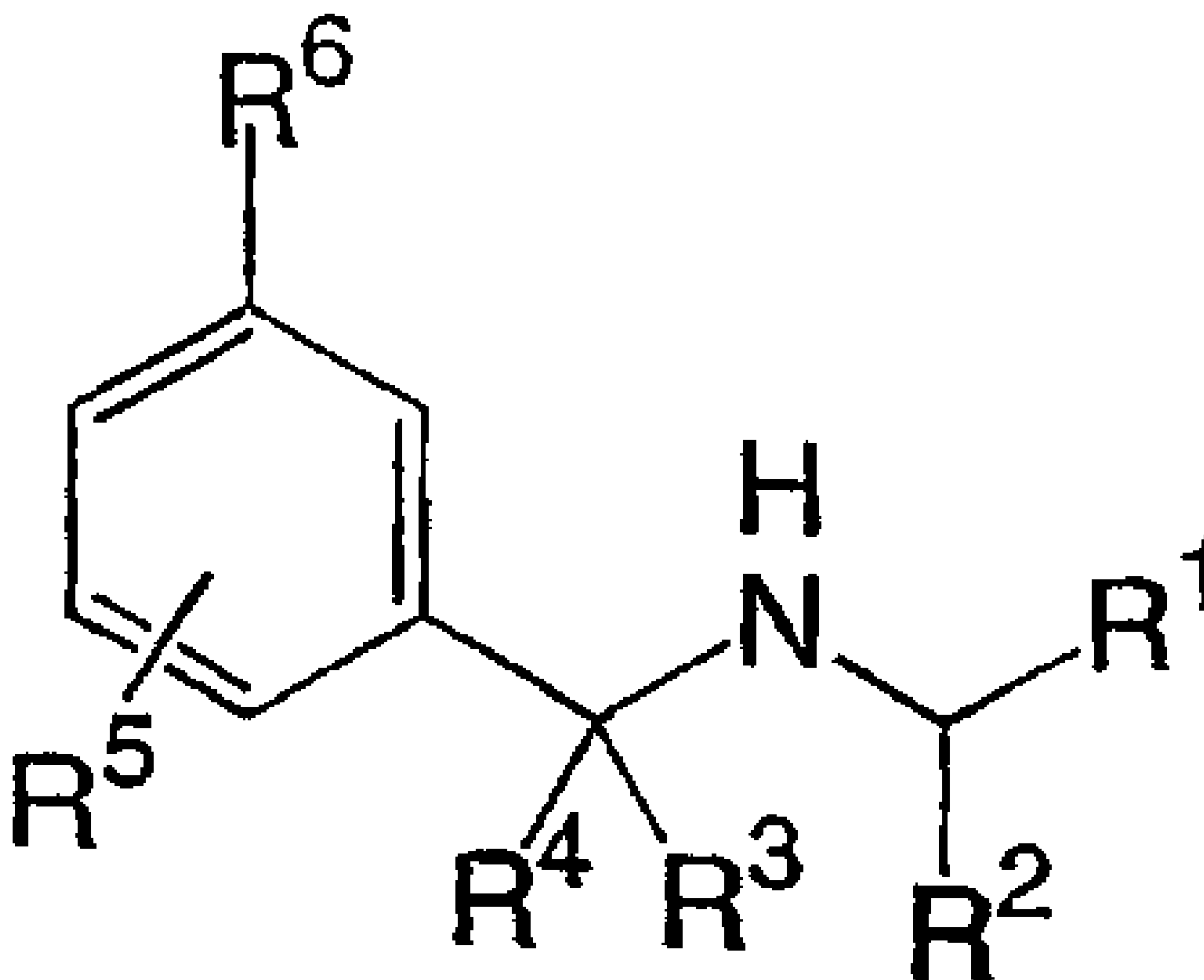


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(72) Inventeurs/Inventors:
KELLY, MICHAEL G., US;
XU, SHIMIN, US;
XI, NING, US;
MILLER, PHILIP, GB;
...

(54) Titre : AGENTS REGULANT LE RECEPTEUR DU CALCIUM
(54) Title: CALCIUM RECEPTOR MODULATING AGENTS



(57) Abrégé/Abstract:

The compounds of the invention are represented by the following general structure (I) or a pharmaceutically acceptable salt thereof, and compositions containing them, wherein the variables are defined herein, and their use to reduce or inhibit PTH



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(72) Inventeurs(suite)/Inventors(continued): KINCAID, JOHN F., US; GHIRON, CHIARA, GB; COULTER, THOMAS S., GB

(73) Propriétaires(suite)/Owners(continued): AMGEN INC., US

(74) Agent: GOWLING LAFLEUR HENDERSON LLP

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secretion, including methods for reducing or inhibiting PTH secretion and methods for treatment or prophylaxis of diseases associated with bone disorders, such as osteoporosis, or associated with excessive secretion of PTH, such as hyperparathyroidism. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

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OX1 5JS (GB). **COULTER, Thomas**; 45 Mably Grove,
Wantage, Oxfordshire OX1 29XW (GB).

(74) Agents: **ODRE, Steven, M.** et al.; Amgen Inc., One Am-
gen Center Drive, M/S 27-4-A, Thousand Oaks, CA 91320-
1799 (US).

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(71) Applicant: **AMGEN INC.** [US/US]; One Amgen Center
Drive, Thousand Oaks, CA 91320-1799 (US).

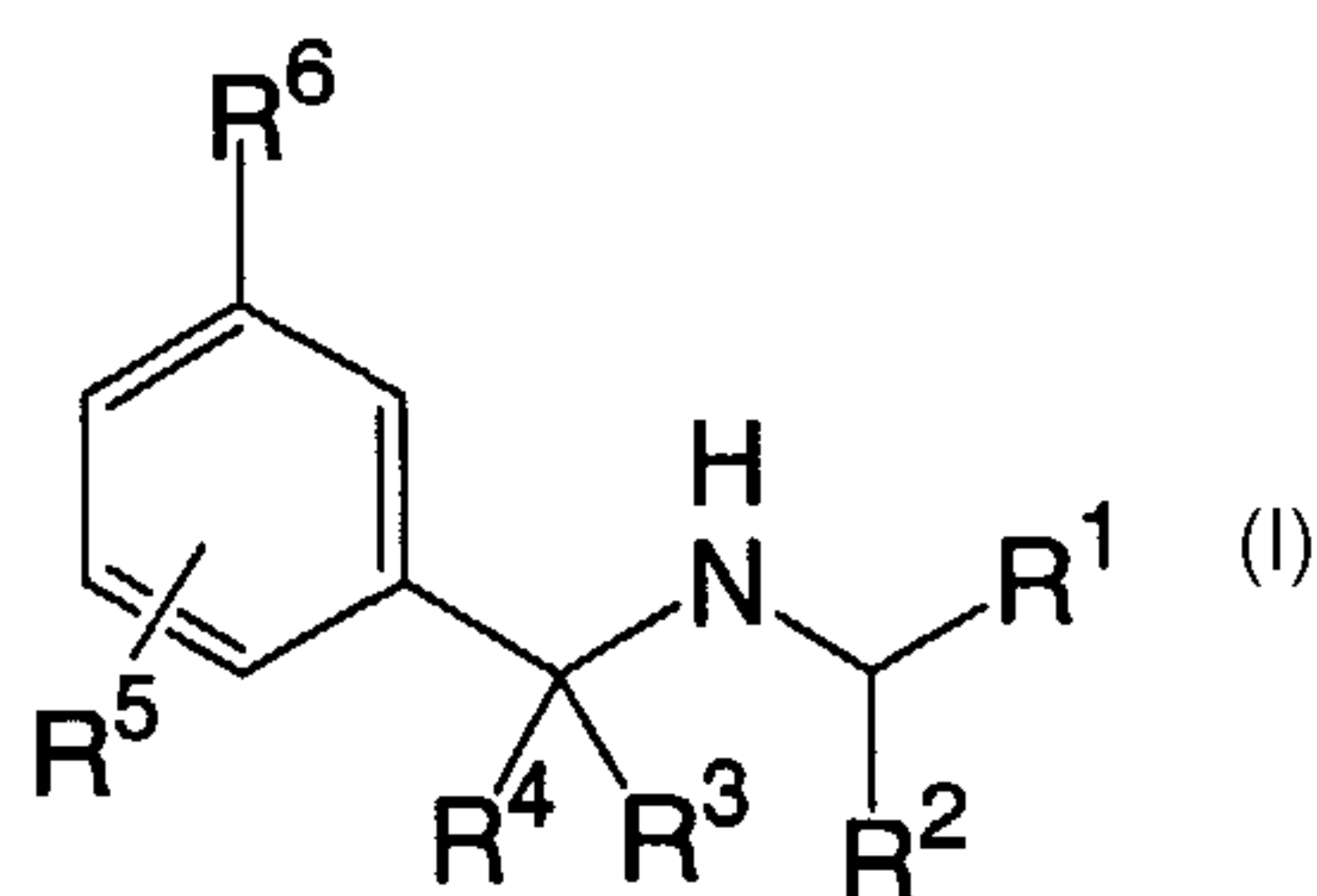
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(72) Inventors: **KELLY, Michael, G.**; 790 Sandoval Place,
Thousand Oaks, CA 91360 (US). **XU, Shimin**; 600 Spring
Road, Apt. #106, Moorpark, CA 93021 (US). **XI, Ning**;
565 Timberwood Avenue, Thousand Oaks, CA 91360
(US). **MILLER, Philip**; 5 Linden Court, Holyoake Road,
Headington, Oxford OX3 8AS (GB). **KINCAID, John, F.**;
9949 Azuaga Street #G202, San Diego, CA 92129 (US).
GHIRON, Chiara; 149 Cumnor Road, Wootton, Oxford

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(54) Title: CALCIUM RECEPTOR MODULATING ARYLALKYLAMINES



(57) Abstract: The compounds of the invention are represented by the following gen-
eral structure (I) or a pharmaceutically acceptable salt thereof, and compositions con-
taining them, wherein the variables are defined herein, and their use to reduce or in-
hibit PTH secretion, including methods for reducing or inhibiting PTH secretion and
methods for treatment or prophylaxis of diseases associated with bone disorders, such
as osteoporosis, or associated with excessive secretion of PTH, such as hyperparathy-
roidism. The subject invention also relates to processes for making such compounds as
well as to intermediates useful in such processes.



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CALCIUM RECEPTOR MODULATING AGENTS

Background of the Invention

Extracellular calcium ion concentration is involved in a variety of
10 biological processes, such as blood clotting, nerve and muscle excitability and
bone formation (Cell Calcium 11:319, 1990). Calcium ion receptors, which are
present on the membranes of various cells in the body, such as parathyroid and
kidney cells (Nature 366:574, 1993; J. Bone Miner. Res. 9, Supple. 1, s282, 1994;
J. Bone Miner. Res. 9, Supple. 1, s409, 1994; Endocrinology 136:5202, 1995), are
15 important to the regulation of the extracellular calcium ion concentration. For
example, concentration of extracellular calcium ion regulates the bone resorption
by osteoclasts (Bioscience Reports 10:493, 1990), secretion of parathyroid
hormone (PTH) from parathyroid cells and secretion of calcitonin from C-cells
(Cell Calcium 11:323, 1990). Parathyroid hormone (PTH) is an important factor
20 in regulating extracellular calcium ion concentration. Secretion of PTH increases
extracellular calcium ion concentration by acting on various cells, such as bone
and kidney cells, and the extracellular calcium ion concentration reciprocally
inhibits the secretion of PTH by acting on parathyroid cells.

Several classes of calcimimetic compounds have been disclosed for
25 regulating extracellular calcium ion concentration, particularly for reducing or
inhibiting secretion of PTH. For example, U.S. Patent Nos. 6,011,068 and
5,981,599 disclose arylalkylamines that are calcium receptor active molecules. EP
933354; WO 0021910, WO 96/12697; WO 95/11221; WO 94/18959; WO
93/04373; Endocrinology 128:3047, 1991; Biochem. Biophys. Res. Commun.
30 167:807, 1990; J. Bone Miner. Res. 5:581, 1990; and Nemeth et al.,
"Calcium-binding Proteins in Health and Disease," Academix Press, Inc., pp.
33-35 (1987) disclose various agents that interact with calcium receptors.

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Dauban et al., Bioorg. Med. Chem. Let. 10:2001-4, 2000, disclose various N1-arylsulfonyl-N2-(1-aryl)ethyl-3-phenylpropane-1,2-diamine compounds as calcimimetics acting on the calcium sensing receptor.

Oikawa et al., in U.S. Patent No. 6,403,832, and publication No.

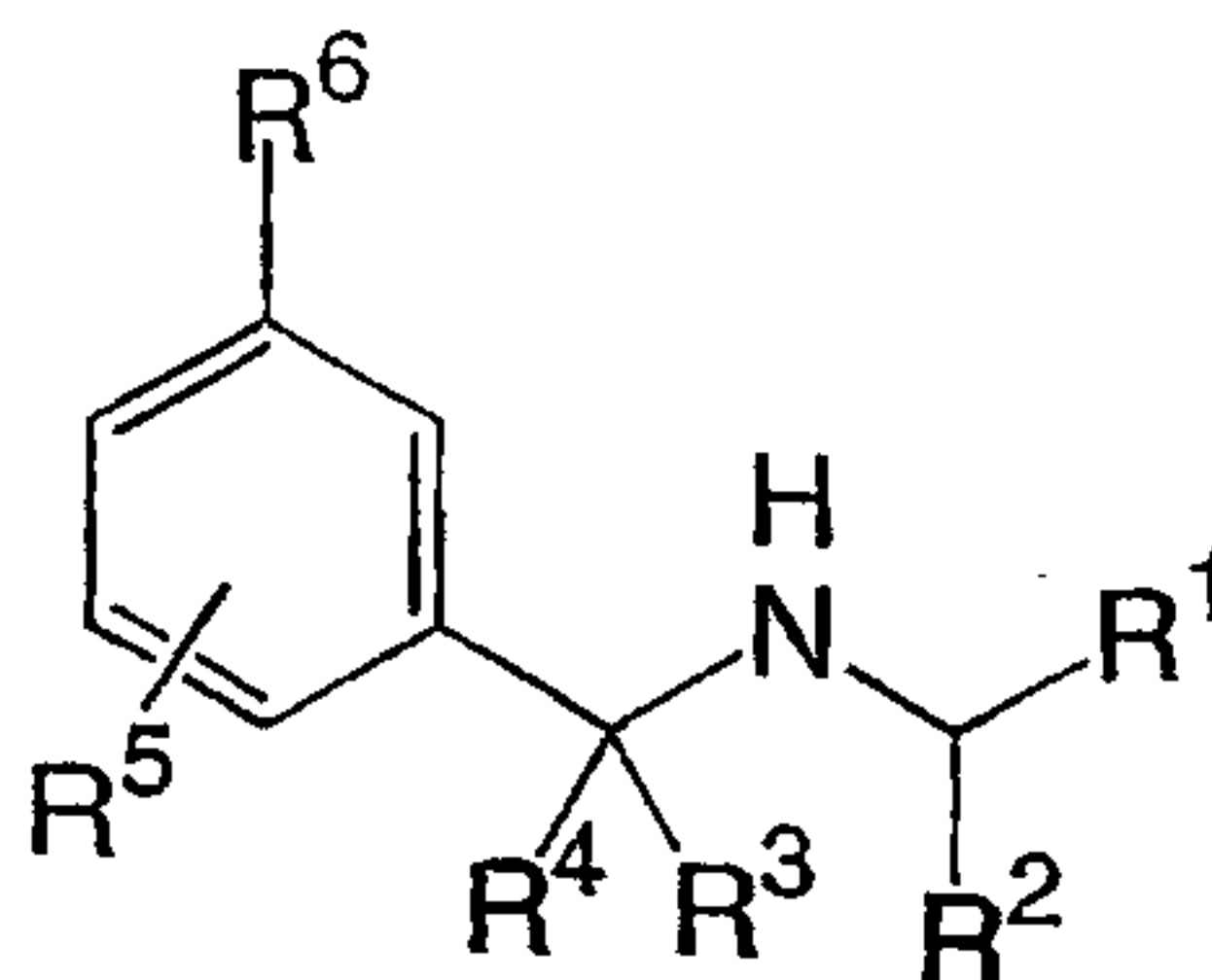
- 5 US2002/143212, describes aryl amine compounds useful as chiral intermediates in the synthesis of optically active propionic acid derivatives. Chassot et al., U.S. Patent No. 6,436,152, describes arylalkylamine compounds useful as hair dye precursor compounds.

- 10 Bös et al., U.S. Patent No. 6,407,111, describes phenyl substituted pyridine and benzene derivates that are antagonistic to the NK-1 receptor.

Summary of the Invention

- The present invention relates to selected calcimimetic compounds and pharmaceutically acceptable salts thereof. The invention compounds
15 advantageously reduce or inhibit PTH secretion. Therefore, this invention also encompasses pharmaceutical compositions, methods for reducing or inhibiting PTH secretion and methods for treatment or prophylaxis of diseases associated with bone disorders, such as osteoporosis, or associated with excessive secretion of PTH, such as hyperparathyroidism. The subject invention also relates to
20 processes for making such compounds as well as to intermediates useful in such processes.

The compounds of the invention are represented by the following general structure:



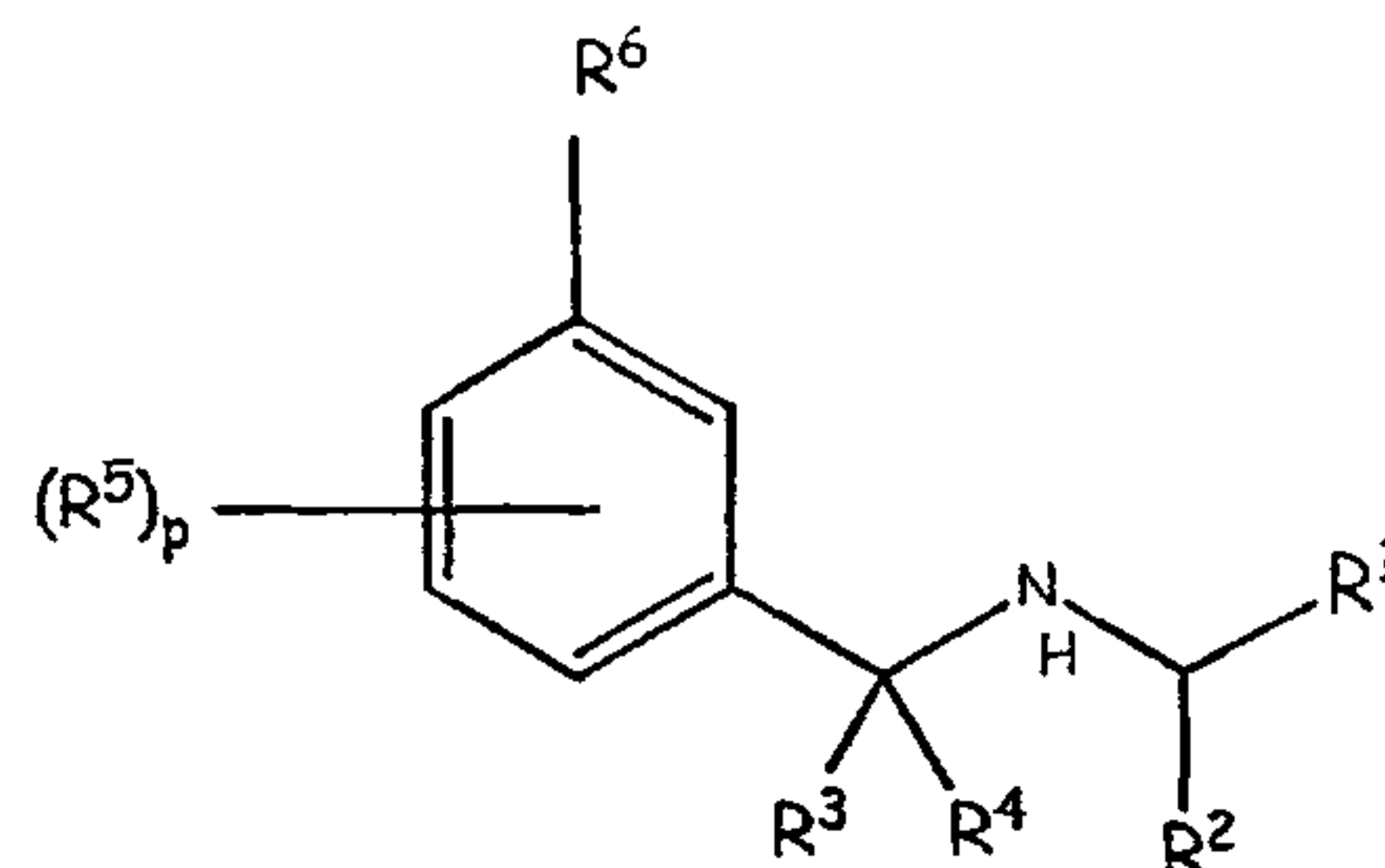
- 25 or a pharmaceutically acceptable salt thereof, wherein the variables are defined below.

The foregoing merely summarizes certain aspects of the invention and is not intended, nor should it be construed, as limiting the invention in any way.

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Detailed Description

5 The invention provides compounds of Formula (I):



(I)

10 or a pharmaceutically acceptable salt thereof,
wherein:

R^1 is aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, cycloalkyl, or substituted cycloalkyl;

R^2 is alkyl or haloalkyl;

15 R^3 is H, alkyl, or haloalkyl;

R^4 is H, alkyl, or haloalkyl;

each R^5 present is independently selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, halogen, $-C(=O)OH$, $-CN$, $-NR^dS(=O)_mR^d$, $-NR^dC(=O)NR^dR^d$, $-NR^dS(=O)_mNR^dR^d$, or $-NR^dC(=O)R^d$;

20

R^6 is aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, cycloalkyl, or substituted cycloalkyl;

each R^a is, independently, H, alkyl or haloalkyl;

each R^b is, independently, aryl, aralkyl, heterocyclyl, or

25

heterocyclylalkyl, each of which may be unsubstituted or substituted by up to 3 substituents selected from the group consisting of alkyl, halogen, haloalkyl, alkoxy, cyano, and nitro;

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each R^c is, independently, alkyl, haloalkyl, phenyl or benzyl, each of which may be substituted or unsubstituted;

each R^d is, independently, H, alkyl, aryl, aralkyl, heterocyclyl, or heterocyclalkyl wherein the alkyl, aryl, aralkyl, heterocyclyl, and heterocyclalkyl are substituted by 0, 1, 2, 3 or 4 substituents selected from alkyl, halogen, haloalkyl, alkoxy, cyano, nitro, R^b , $-C(=O)R^c$, $-OR^b$, $-NR^aR^a$, $-NR^aR^b$, $-C(=O)OR^c$, $-C(=O)NR^aR^a$, $-OC(=O)R^c$, $-NR^aC(=O)R^c$, $-NR^aS(=O)_nR^c$ and $-S(=O)_nNR^aR^a$;

m is 1 or 2;

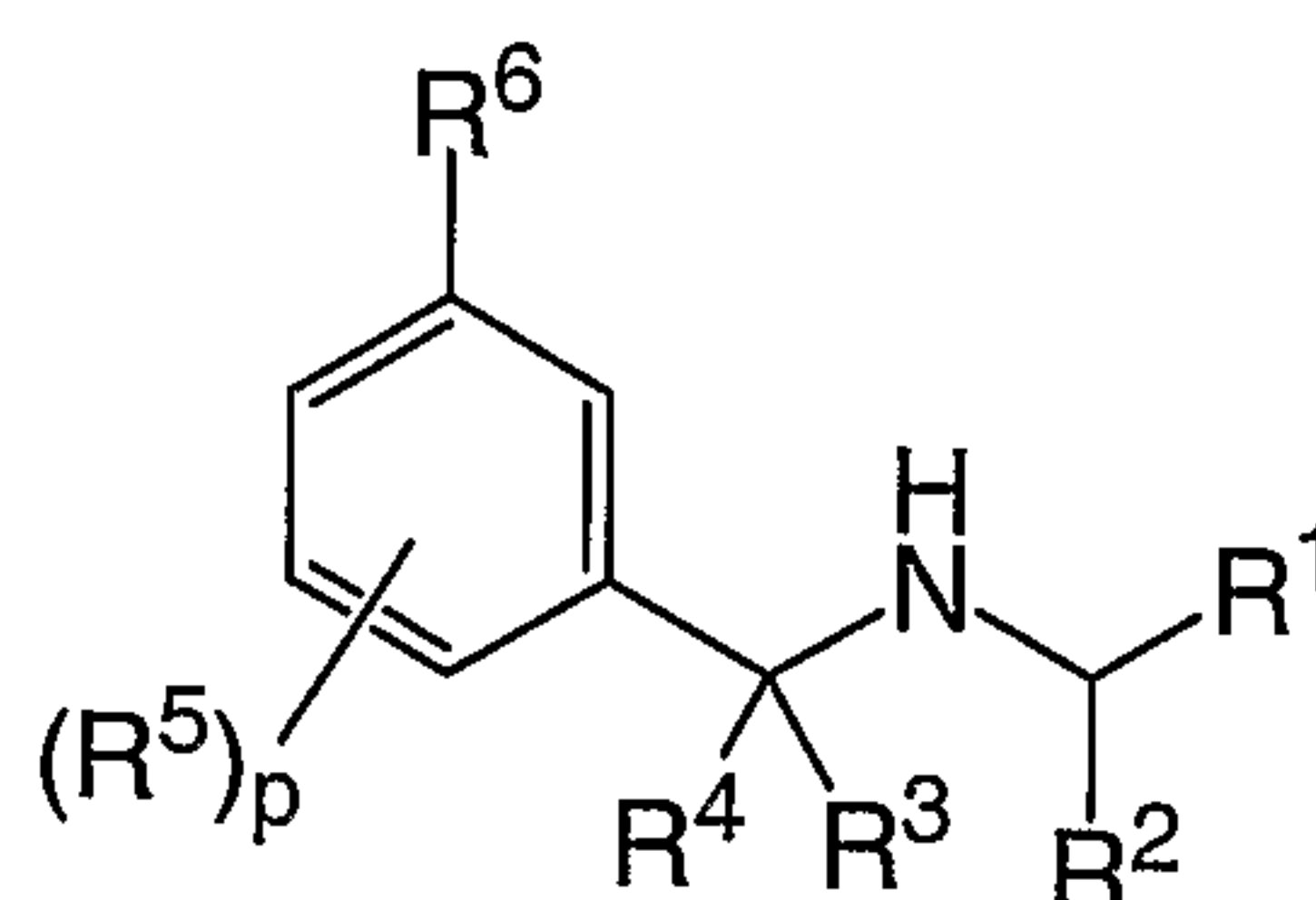
n is 0, 1 or 2; and

p is 0, 1, 2, 3, or 4;

provided that if R^2 is methyl, p is 0, and R^6 is unsubstituted phenyl, then R^1 is not 2,4-dihalophenyl, 2,4-dimethylphenyl, 2,4-diethylphenyl, 2,4,6-trihalophenyl, or 2,3,4-trihalophenyl.

15

Another aspect of the invention relates to compounds having the general structure II:



20

(II)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is phenyl, benzyl, naphthyl or a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the phenyl, benzyl or heterocycle are substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl, $-OC_{1-6}$ alkyl, cyano and nitro;

25

R^2 is C_{1-8} alkyl or C_{1-4} haloalkyl;

R^3 is H, C_{1-4} haloalkyl or C_{1-8} alkyl;

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R^4 is H, C_{1-4} haloalkyl or C_{1-8} alkyl;

R^5 is, independently, in each instance, H, C_{1-8} alkyl, C_{1-4} haloalkyl, halogen, cyano, $-NR^aR^d$, $-NS(=O)_2R^c$, $-NR^aC(=O)NR^aR^d$, $-NR^dC(=O)R^d$ or $-OC_{1-6}$ alkyl substituted by 0, 1, 2 or 3 substituents selected from halogen, $-OC_{1-6}$ alkyl, $-NR^aR^d$,
 5 $-NS(=O)_2R^c$, $-NR^aC(=O)NR^aR^d$, $-NR^dC(=O)R^d$ or cyano;

R^6 is phenyl, benzyl, naphthyl, a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, or a saturated or unsaturated 8-, 9-, 10- or 11-membered heterobicycle containing 1, 2, 3, 4 or 5
 10 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the phenyl, benzyl, naphthyl, heterocycle and heterobicycle are substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl, $-OC_{1-6}$ alkyl, $-OC_{1-4}$ haloalkyl, $-NR^aR^a$, $-NR^aC(=O)C_{1-6}$ alkyl, $-S(=O)_nC_{1-6}$ alkyl, cyano and nitro;

15 R^a is, independently, at each instance, H, C_{1-4} haloalkyl or C_{1-6} alkyl;

R^b is, independently, aryl, aralkyl, heterocyclyl, or heterocyclylalkyl, each of which may be unsubstituted or substituted by up to 3 substituents selected from the group consisting of alkyl, halogen, haloalkyl, alkoxy, cyano, and nitro;

20 R^c is, independently, at each instance, C_{1-6} alkyl, C_{1-4} haloalkyl, phenyl or benzyl;

R^d is, independently, at each instance, H, C_{1-6} alkyl, phenyl, benzyl or a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the C_{1-6} alkyl, phenyl, benzyl, naphthyl and heterocycle are
 25 substituted by 0, 1, 2, 3 or 4 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl, $-OC_{1-6}$ alkyl, cyano and nitro, R^b , $-C(=O)R^c$, $-OR^b$, $-NR^aR^a$, $-NR^aR^b$, $-C(=O)OR^c$, $-C(=O)NR^aR^a$, $-OC(=O)R^c$, $-NR^aC(=O)R^c$, $-NR^aS(=O)_mR^c$ and $-S(=O)_mNR^aR^a$;

m is 1 or 2;

30 n is 0, 1 or 2; and

p is 0, 1, 2, 3 or 4.

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In one embodiment, in conjunction with any one of the above and below embodiments, R^1 is phenyl substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl, $-OC_{1-6}$ alkyl, cyano and nitro.

5 In another embodiment, in conjunction with any one of the above and below embodiments, R^1 is benzyl substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl, $-OC_{1-6}$ alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R^1 is naphthyl substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl, $-OC_{1-6}$ alkyl, cyano and nitro.

10 In another embodiment, in conjunction with any one of the above and below embodiments, R^1 a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the heterocycle is substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl,
15 $-OC_{1-6}$ alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R^6 is phenyl, wherein the phenyl is substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl, $-OC_{1-6}$ alkyl, $-OC_{1-4}$ haloalkyl, $-NR^aR^a$, $-NR^aC(=O)C_{1-6}$ alkyl, $-S(=O)_nC_{1-6}$ alkyl, cyano and nitro.

20 In another embodiment, in conjunction with any one of the above and below embodiments, R^6 is benzyl, wherein the benzyl is substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl, $-OC_{1-6}$ alkyl, $-OC_{1-4}$ haloalkyl, $-NR^aR^a$, $-NR^aC(=O)C_{1-6}$ alkyl, $-S(=O)_nC_{1-6}$ alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R^6 is naphthyl, wherein the naphthyl is substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl, $-OC_{1-6}$ alkyl, $-OC_{1-4}$ haloalkyl, $-NR^aR^a$, $-NR^aC(=O)C_{1-6}$ alkyl, $-S(=O)_nC_{1-6}$ alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R^6 is a saturated or unsaturated 5- or 6-membered ring
30 heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the heterocycle is substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl,

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-OC₁₋₆alkyl, -OC₁₋₄haloalkyl, -NR^aR^a, -NR^aC(=O)C₁₋₆alkyl, -S(=O)_nC₁₋₆alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R⁶ is a saturated or unsaturated 8-, 9-, 10- or 11-membered heterobicycle containing 1, 2, 3, 4 or 5 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the heterobicycle is substituted by 0, 1, 2 or 3 substituents selected from C₁₋₆alkyl, halogen, C₁₋₄haloalkyl, -OC₁₋₆alkyl, -OC₁₋₄haloalkyl, -NR^aR^a, -NR^aC(=O)C₁₋₆alkyl, -S(=O)_nC₁₋₆alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R¹ is phenyl, naphthyl or (OC₁₋₄alkyl)phenyl.

In another embodiment, in conjunction with any one of the above and below embodiments, R¹ is phenyl substituted by 2 or 3 substituents selected from C₁₋₆alkyl, halogen, C₁₋₄haloalkyl, -OC₁₋₆alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R¹ is benzyl substituted by 1, 2 or 3 substituents selected from C₁₋₆alkyl, halogen, C₁₋₄haloalkyl, -OC₁₋₆alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R¹ is naphthyl substituted by 1, 2 or 3 substituents selected from C₁₋₆alkyl, halogen, C₁₋₄haloalkyl, -OC₁₋₆alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R¹ is a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the heterocycle is substituted by 1, 2 or 3 substituents selected from C₁₋₆alkyl, halogen, C₁₋₄haloalkyl, -OC₁₋₆alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, one of R³ or R⁴ is C₁₋₄haloalkyl or C₁₋₈alkyl.

In another embodiment, in conjunction with any one of the above and below embodiments, R⁵ is C₁₋₈alkyl, C₁₋₄haloalkyl, halogen or -OC₁₋₆alkyl.

In another embodiment, in conjunction with any one of the above and below embodiments, R⁶ is phenyl, wherein the phenyl is substituted by 1, 2 or 3

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substituents selected from C₁₋₆alkyl, halogen, C₁₋₄haloalkyl, -OC₁₋₆alkyl, -OC₁₋₄haloalkyl, -NR^aR^a, -NR^aC(=O)C₁₋₆alkyl, -S(=O)_nC₁₋₆alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R⁶ is benzyl, wherein the benzyl is substituted by 1, 2 or 3
 5 substituents selected from C₁₋₆alkyl, halogen, C₁₋₄haloalkyl, -OC₁₋₆alkyl, -OC₁₋₄haloalkyl, -NR^aR^a, -NR^aC(=O)C₁₋₆alkyl, -S(=O)_nC₁₋₆alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R⁶ is naphthyl, wherein the naphthyl is substituted by 0, 1, 2 or 3 substituents selected from C₁₋₆alkyl, halogen, C₁₋₄haloalkyl, -OC₁₋₆alkyl,
 10 -OC₁₋₄haloalkyl, -NR^aR^a, -NR^aC(=O)C₁₋₆alkyl, -S(=O)_nC₁₋₆alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R⁶ is a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the heterocycle is substituted
 15 by 1, 2 or 3 substituents selected from C₁₋₆alkyl, halogen, C₁₋₄haloalkyl, -OC₁₋₆alkyl, -OC₁₋₄haloalkyl, -NR^aR^a, -NR^aC(=O)C₁₋₆alkyl, -S(=O)_nC₁₋₆alkyl, cyano and nitro.

In another embodiment, in conjunction with any one of the above and below embodiments, R⁶ is a saturated or unsaturated 8-, 9-, 10- or 11-membered
 20 heterobicycle containing 1, 2, 3, 4 or 5 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the heterobicycle is substituted by 1, 2 or 3 substituents selected from C₁₋₆alkyl, halogen, C₁₋₄haloalkyl, -OC₁₋₆alkyl, -OC₁₋₄haloalkyl, -NR^aR^a, -NR^aC(=O)C₁₋₆alkyl, -S(=O)_nC₁₋₆alkyl, cyano and nitro.

25 Another aspect of the invention involves a pharmaceutical composition comprising a pharmaceutically acceptable amount of a compound according to any one of the above embodiments and a pharmaceutically acceptable diluent or carrier.

Another aspect of the inventions involve the use of a compound according
 30 to any one of the above embodiments as a medicament.

Another aspect of the invention involves the use of a compound according to any one of the above embodiments in the manufacture of a medicament for the

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treatment of diseases associated with bone disorders or associated with excessive secretion of PTH.

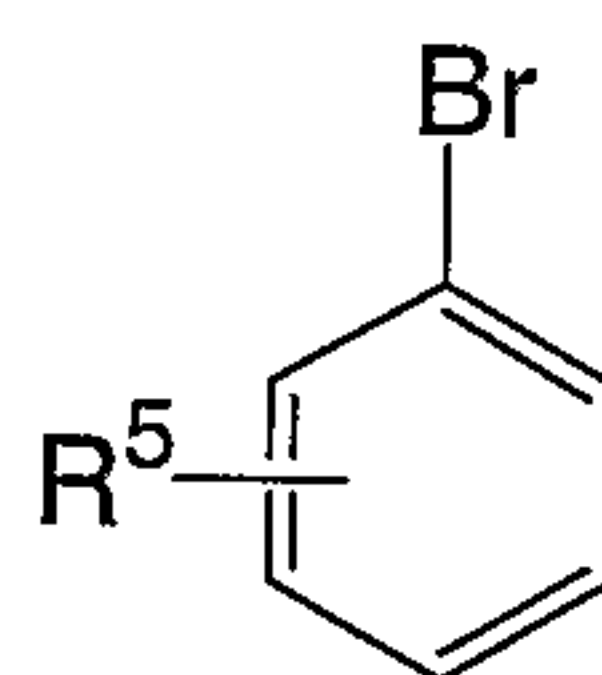
Another aspect of the invention involves the use of a compound according to any one of the above embodiments in the manufacture of a medicament for the treatment of osteoporosis or hyperparathyroidism.

Another aspect of the invention involves a method of using a compound according to any one of the above embodiments for the treatment of diseases associated with bone disorders or associated with excessive secretion of PTH.

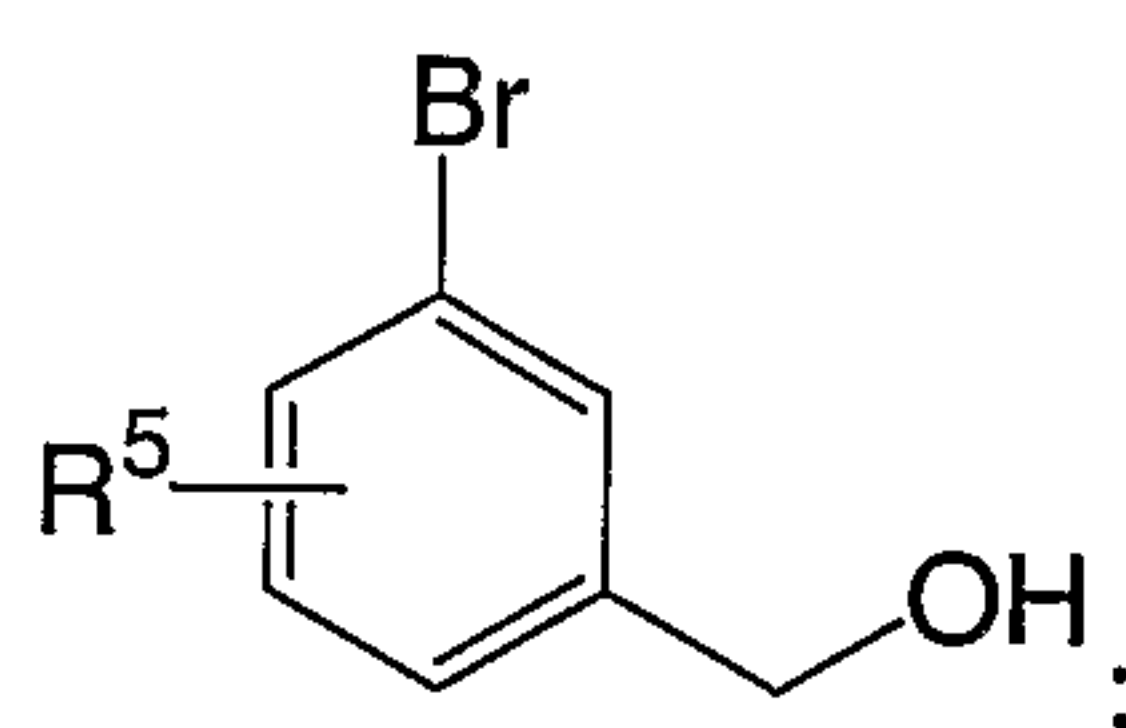
Another aspect of the invention involves a method of using a compound according to any one of the above embodiments for the treatment of osteoporosis or hyperparathyroidism.

Another aspect of the invention involves a process for making a compound according to Claim 1 wherein R^3 and R^4 are both hydrogen comprising the steps of:

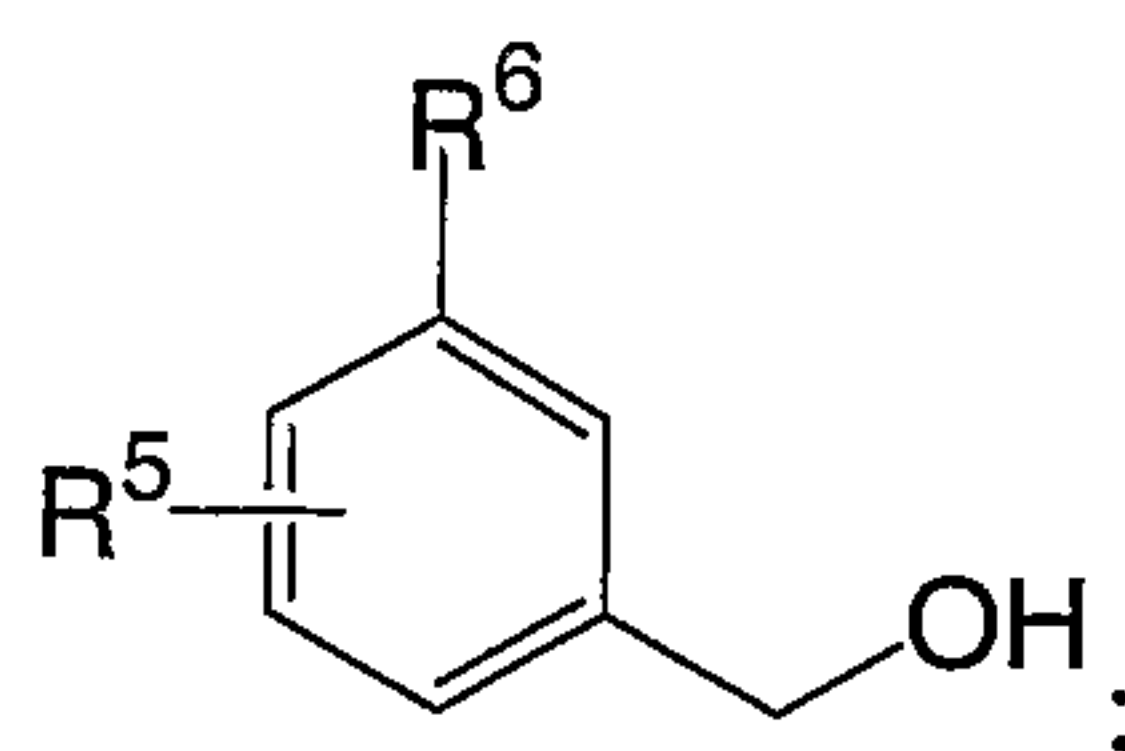
placing a compound having the structure



in the presence of acid followed by treatment with a hydride and methanol to form

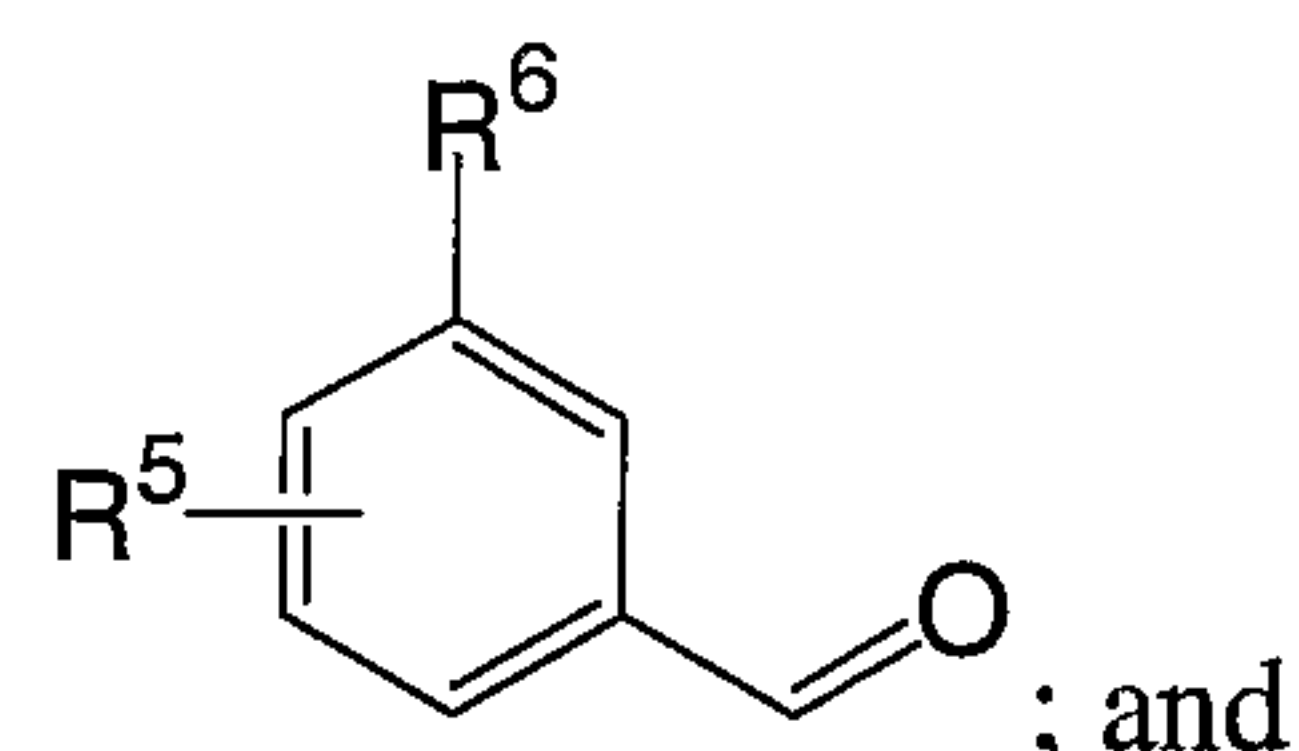


reacting the resulting alcohol with $R^6-B(OH)_2$ to form

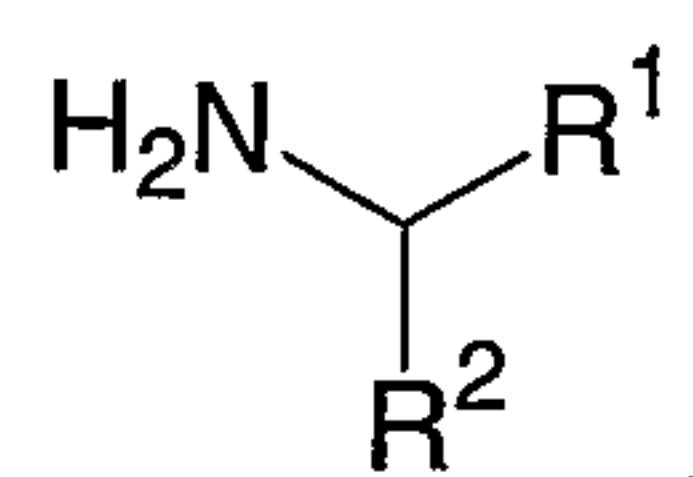


oxidizing the alcohol to form

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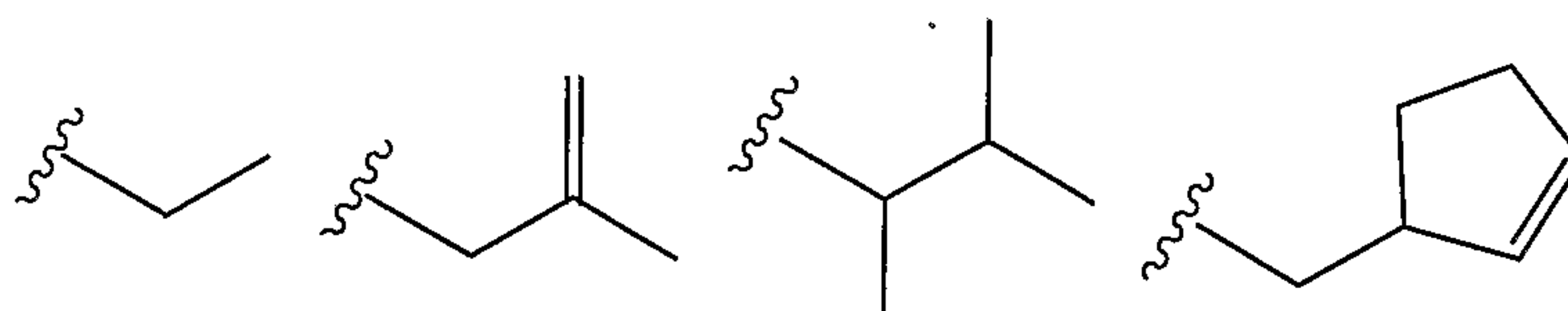


reacting the aldehyde with an amine having the structure



Unless otherwise specified, the following definitions apply to terms found
5 in the specification and claims:

“Alkyl” and the prefix “alk-“ refer to alkyl groups or substituents wherein the carbon atoms are in a branched, cyclical or linear relationship or any combination of the three. The alkyl groups described in this section contain from 1 to 10 carbon atoms unless otherwise specified and may also contain a double or
10 triple bond. “C_{V-W}alkyl” means an alkyl group comprising from V to W carbon atoms. Examples of C₁₋₆alkyl include, but are not limited to the following:



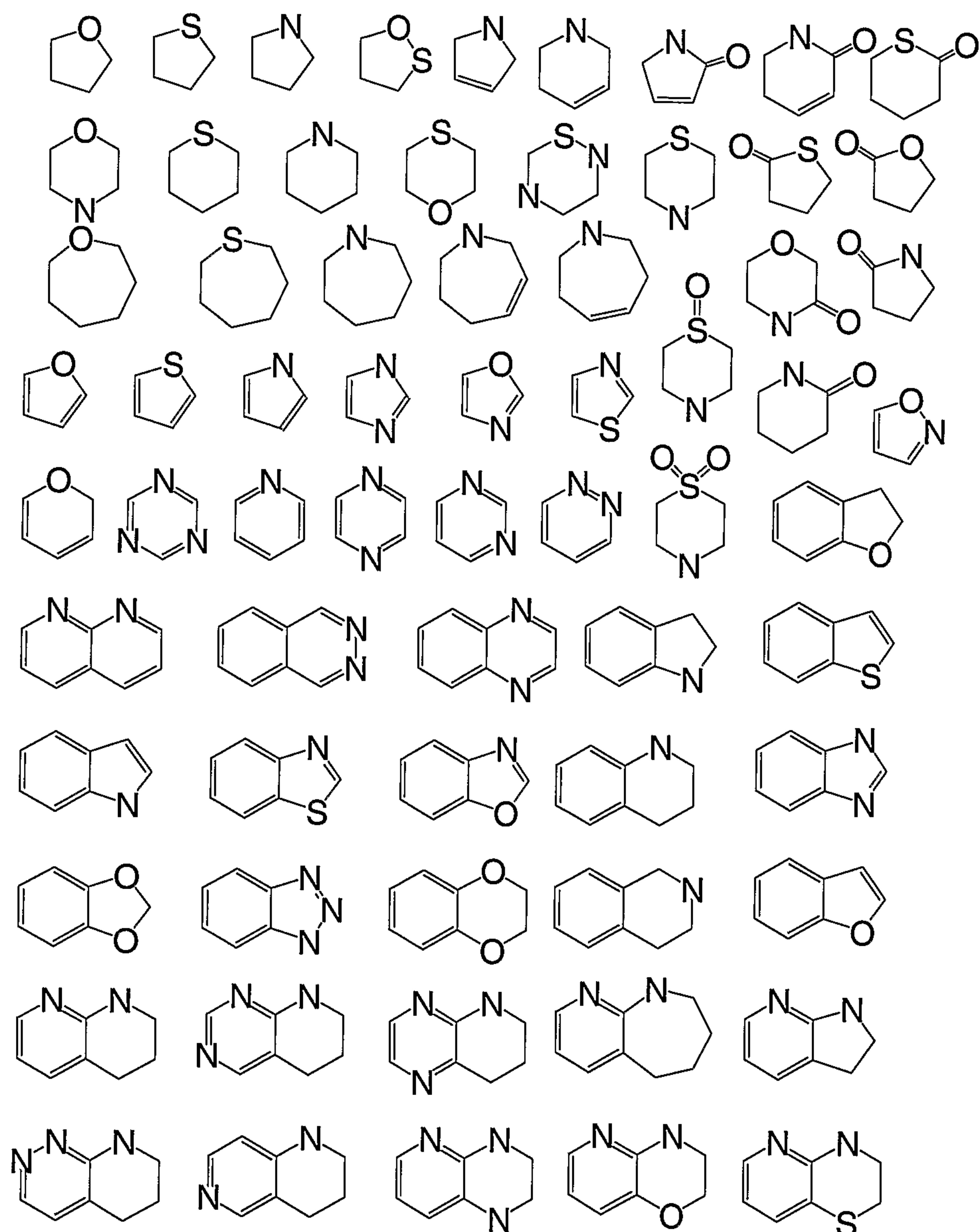
“Aryl” means a carbocyclic aromatic ring or ring system. Examples of aryl groups include phenyl, naphthyl, indenyl, fluorenyl, biphenyl, anthracenyl, 9-
15 (9-phenylfluorenyl), phenanthrenyl, and the like.

“Halogen” means a halogen atom selected from F, Cl, Br and I.

“Haloalkyl”, “haloalk-“ and “C_{V-W}haloalkyl” mean an alkyl group, as described above, wherein any number--at least one--of the hydrogen atoms attached to the alkyl group or chain are replaced by F, Cl, Br or I.

20 “Heterocycle” means a ring or ring system comprising at least one carbon atom and at least one other atom selected from N, O and S. Heterocyclic groups can be saturated, unsaturated or aromatic. Aromatic heterocyclic groups are also referred to as “heteroaryl” rings or ring systems. Examples of heterocycles that may be found in the claims include, but are not limited to, the following:

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Unless otherwise specified, the term “substituted” means that a group is substituted by one or more substituents independently selected from the group consisting of hydroxy, alkyl, alkoxy, alkylthio, halogen, haloalkyl, haloalkoxy, alkylcarbonyl, haloalkylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, -CN, -C(=O)OH, alkoxycarbonyl, alkanoyloxy, alkanoylthio, nitro, -N(R^a)₂, -N(R^a)(R^b), NR^dS(=O)₂R^d, -NR^dC(=O)NR^dR^d, -NR^dS(=O)₂NR^dR^d, or -NR^dC(=O)R^d and, in the case of heterocyclyl cycloalkyl groups, oxo.

Preferred compounds include:

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- (1R)-N-((6-fluoro-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 5 (1R)-N-((3',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- 10 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)ethanamine;
- (1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 15 (1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)ethanamine;
- 20 (1R)-N-((3-(1-methyl-1H-benzimidazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(6-(ethyloxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 25 (1R)-N-((3-(6-(ethyloxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1H-pyrrol-1-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 30 (1R)-N-((3-(1-methyl-1H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(1-methyl-1H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 35 (1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1H-pyrrol-1-yl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(4-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- 40 ethyl 4-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-3,6-dihydro-1(2H)-pyridinecarboxylate;
- (1R)-N-((6-(methyloxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 45 (1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;

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- (1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 5 (1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((6-chloro-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 10 (1R)-N-((6-chloro-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-quinolinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 15 (1R)-N-((4-(methyloxy)-3-(6-quinolinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1-(2,2,2-trifluoroethyl)-1H-indol-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 20 (1R)-N-((4-chloro-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 25 (1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 30 (1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4'-fluoro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-fluorophenyl)ethanamine;
- 35 (1R)-N-((4',6-bis(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3-(2,1,3-benzothiadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2,1,3-benzothiadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 40 (1R)-N-((3-(1-benzothien-3-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 1-(3-fluorophenyl)-N-((6-(methyloxy)-4'-((trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 45 1-(3-bromophenyl)-N-((6-(methyloxy)-4'-((trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 1-(3,5-difluorophenyl)-N-((6-(methyloxy)-4'-((trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;

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- (1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((6-chloro-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- 5 (1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-quinoxaliny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 10 (1R)-N-((6-iodo-4'-((trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((6-iodo-4'-((trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 15 (1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(2-methyl-1,3-oxazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2-methyl-1,3-oxazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 20 ethyl 2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate;
- ethyl 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate;
- 25 4-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1,3-thiazol-2-amine;
- (1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((6-(methyloxy)-4'-((trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 30 (1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-((tetrahydro-2-furanylmethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- 35 (1R)-N-((3-(2-fluoro-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- N,N-dimethyl-5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinamine;
- (1R)-N-((4-(methyloxy)-3-(1-methyl-2-(trifluoromethyl)-1H-benzimidazol-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 40 (1R)-N-((4-(methyloxy)-3-(1-methyl-2-(trifluoromethyl)-1H-benzimidazol-5-yl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 45 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)ethanamine;

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- (1R)-N-((4-(methyloxy)-3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 5 (1R)-N-((3-(1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(2-methyl-1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 10 2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile;
- (1R)-N-((6-(methyloxy)-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-1-(3-fluorophenyl)-N-((6-(methyloxy)-4'-((trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 15 (1R)-N-((6-(ethyloxy)-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 20 (1R)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-1-(3-chlorophenyl)-N-((6-(methyloxy)-4'-((trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine
- 25 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(3-pyridinyl)phenyl)methyl)ethanamine;
- 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile;
- (1R)-N-((2'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;
- 30 (1R)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 35 (1R)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-((tetrahydro-2-furanylmethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-(4-morpholinyl)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- 40 (1R)-N-((3-(1-methyl-1H-imidazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1-pyrrolidinyl)phenyl)methyl)-1-phenylethanamine;
- 45 ethyl 2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate;
- N-((6-(methyloxy)-4'-((trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-methylphenyl)ethanamine;

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- (1R)-N-((6-fluoro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 5 N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;
- N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;
- N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;
- 10 (1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 15 (1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-5-pyrimidinyl)phenyl)methyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-quinoxaliny)phenyl)methyl)-1-phenylethanamine;
- 20 (1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 25 (1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-phenylethanamine;
- 30 (1R)-N-((6-chloro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(1-(2,2,2-trifluoroethyl)-1H-indol-5-yl)phenyl)methyl)-1-phenylethanamine;
- 35 (1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-quinolinyl)phenyl)methyl)ethanamine;
- 40 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carboxamide;
- (1R)-1-(1-naphthalenyl)-N-((3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)ethanamine;
- 45 (1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((6-(methyloxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;

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(1R)-N-((4-(methyloxy)-3-(2-methyl-1,3-thiazol-4-yl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
 (1R)-N-((4-((difluoromethyl)oxy)-3-(3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 5 (1R)-N-((3-(2-methyl-2H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 (1R)-N-((4-(methyloxy)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 (1R)-N-((4-chloro-3-(3-pyridinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
 10 (1R)-N-((3-(2-ethyl-2H-1,2,3-benzotriazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine; and
 (1R)-N-((4',6-difluoro-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

15 Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional
 20 processes, *e.g.*, by formation of diastereoisomeric salts, by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric, and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for
 25 separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of the invention with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be
 30 separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of the invention can likewise be obtained by using active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt. The (R) isomer is generally preferred.

35 Likewise, the compounds of this invention may exist as isomers, that is compounds of the same molecular formula but in which the atoms, relative to one another, are arranged differently. In particular, the alkylene substituents of the

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compounds of this invention, are normally and preferably arranged and inserted into the molecules as indicated in the definitions for each of these groups, being read from left to right. However, in certain cases, one skilled in the art will appreciate that it is possible to prepare compounds of this invention in which these substituents are reversed in orientation relative to the other atoms in the molecule. That is, the substituent to be inserted may be the same as that noted above except that it is inserted into the molecule in the reverse orientation. One skilled in the art will appreciate that these isomeric forms of the compounds of this invention are to be construed as encompassed within the scope of the present invention.

10 The compounds of the present invention can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. The salts include, but are not limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, mandelate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 2-phenylpropionate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate, mesylate, and undecanoate. Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases. When compounds of the invention include an acidic function such as a carboxy group, then suitable pharmaceutically acceptable cation pairs for the carboxy group are well known to those skilled in the art and include alkaline, alkaline earth, ammonium, quaternary ammonium cations and the like. For additional examples of "pharmacologically acceptable salts," *see infra* and Berge et al., J. Pharm. Sci. 66:1 (1977).

Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and

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iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Also encompassed in the scope of the present invention are pharmaceutically acceptable esters of a carboxylic acid or hydroxyl containing group, including a metabolically labile ester or a prodrug form of a compound of this invention. A metabolically labile ester is one which may produce, for example, an increase in blood levels and prolong the efficacy of the corresponding non-esterified form of the compound. A prodrug form is one which is not in an active form of the molecule as administered but which becomes therapeutically active after some in vivo activity or biotransformation, such as metabolism, for example, enzymatic or hydrolytic cleavage. For a general discussion of prodrugs involving esters see Svensson and Tunek Drug Metabolism Reviews 165 (1988) and Bundgaard Design of Prodrugs, Elsevier (1985). Examples of a masked carboxylate anion include a variety of esters, such as alkyl (for example, methyl, ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-methoxybenzyl), and alkylcarbonyloxyalkyl (for example, pivaloyloxymethyl). Amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases in vivo releasing the free drug and formaldehyde (Bungard J. Med. Chem. 2503 (1989)). Also, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard Design of Prodrugs, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little, 4/11/81) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use. Esters of a compound of this invention, may include, for example, the methyl, ethyl, propyl, and butyl esters, as well as other suitable esters formed between an acidic moiety and a hydroxyl containing moiety. Metabolically labile esters, may include, for example, methoxymethyl, ethoxymethyl, iso-propoxymethyl, α -methoxyethyl, groups such as α -((C₁-C₄)alkyloxy)ethyl; for example, methoxyethyl, ethoxyethyl, propoxyethyl, iso-propoxyethyl, etc.; 2-oxo-1,3-dioxolen-4-ylmethyl groups, such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl, etc.; C₁-C₃ alkylthiomethyl groups, for example, methylthiomethyl, ethylthiomethyl, isopropylthiomethyl, etc.; acyloxymethyl

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groups, for example, pivaloyloxymethyl, α -acetoxymethyl, etc.; ethoxycarbonyl-1-methyl; or α -acyloxy- α -substituted methyl groups, for example α -acetoxylethyl.

Further, the compounds of the invention may exist as crystalline solids which can be crystallized from common solvents such as ethanol, N,N-dimethyl-
5 formamide, water, or the like. Thus, crystalline forms of the compounds of the invention may exist as solvates and/or hydrates of the parent compounds or their pharmaceutically acceptable salts. All of such forms likewise are to be construed as falling within the scope of the invention.

"Leaving group" generally refers to groups readily displaceable by a
10 nucleophile, such as an amine, a thiol or an alcohol nucleophile. Such leaving groups are well known in the art. Examples of such leaving groups include, but are not limited to, N-hydroxysuccinimide, N-hydroxybenzotriazole, halides, triflates, tosylates and the like. Preferred leaving groups are indicated herein where appropriate.

15 "Protecting group" generally refers to groups well known in the art which are used to prevent selected reactive groups, such as carboxy, amino, hydroxy, mercapto and the like, from undergoing undesired reactions, such as nucleophilic, electrophilic, oxidation, reduction and the like. Preferred protecting groups are indicated herein where appropriate. Examples of amino protecting groups include,
20 but are not limited to, aralkyl, substituted aralkyl, cycloalkenylalkyl and substituted cycloalkenyl alkyl, allyl, substituted allyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, silyl and the like. Examples of aralkyl include, but are not limited to, benzyl, ortho-methylbenzyl, trityl and benzhydryl, which can be optionally substituted with halogen, alkyl, alkoxy, hydroxy, nitro, acylamino, acyl and the like, and salts, such
25 as phosphonium and ammonium salts. Examples of aryl groups include phenyl, naphthyl, indanyl, anthracenyl, 9-(9-phenylfluorenyl), phenanthrenyl, durenyl and the like. Examples of cycloalkenylalkyl or substituted cycloalkenylalkyl radicals, preferably have 6-10 carbon atoms, include, but are not limited to, cyclohexenyl methyl and the like. Suitable acyl, alkoxycarbonyl and aralkoxycarbonyl groups
30 include benzyloxycarbonyl, t-butoxycarbonyl, iso-butoxycarbonyl, benzoyl, substituted benzoyl, butyryl, acetyl, tri-fluoroacetyl, tri-chloro acetyl, phthaloyl and the like. A mixture of protecting groups can be used to protect the same amino

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group, such as a primary amino group can be protected by both an aralkyl group and an aralkoxycarbonyl group. Amino protecting groups can also form a heterocyclic ring with the nitrogen to which they are attached, for example, 1,2-bis(methylene)benzene, phthalimidyl, succinimidyl, maleimidyl and the like and where these heterocyclic groups can further include adjoining aryl and cycloalkyl rings. In addition, the heterocyclic groups can be mono-, di- or tri-substituted, such as nitrophthalimidyl. Amino groups may also be protected against undesired reactions, such as oxidation, through the formation of an addition salt, such as hydrochloride, toluenesulfonic acid, trifluoroacetic acid and the like. Many of the amino protecting groups are also suitable for protecting carboxy, hydroxy and mercapto groups. For example, aralkyl groups. Alkyl groups are also suitable groups for protecting hydroxy and mercapto groups, such as tert-butyl.

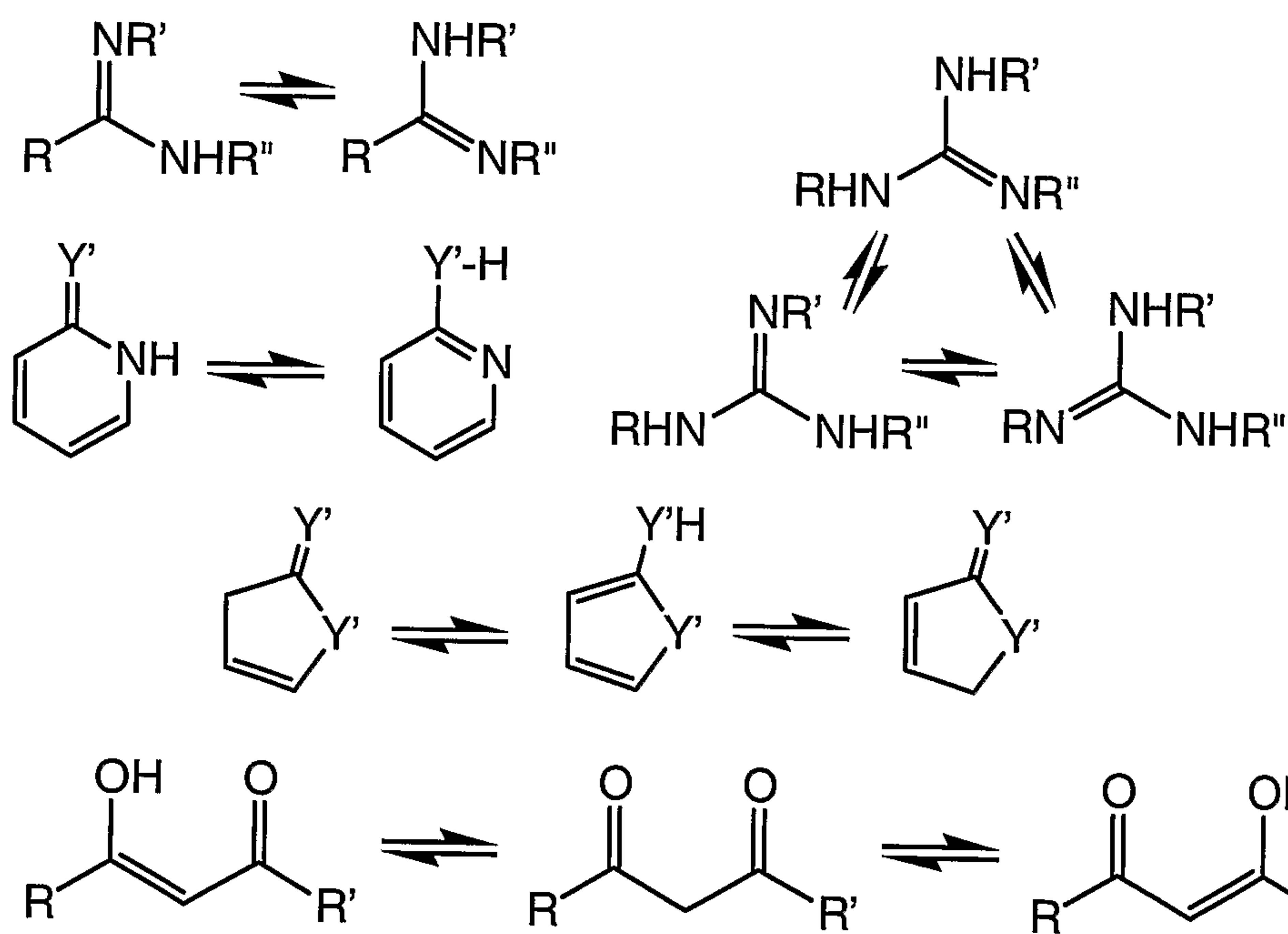
Silyl protecting groups are silicon atoms optionally substituted by one or more alkyl, aryl and aralkyl groups. Suitable silyl protecting groups include, but are not limited to, trimethylsilyl, triethylsilyl, tri-isopropylsilyl, tert-butyl dimethylsilyl, dimethylphenylsilyl, 1,2-bis(dimethylsilyl)benzene, 1,2-bis(dimethylsilyl)ethane and diphenylmethylsilyl. Silylation of an amino groups provide mono- or di-silylamino groups. Silylation of aminoalcohol compounds can lead to a N,N,O-tri-silyl derivative. Removal of the silyl function from a silyl ether function is readily accomplished by treatment with, for example, a metal hydroxide or ammonium fluoride reagent, either as a discrete reaction step or in situ during a reaction with the alcohol group. Suitable silylating agents are, for example, trimethylsilyl chloride, tert-butyl-dimethylsilyl chloride, phenyldimethylsilyl chloride, diphenylmethyl silyl chloride or their combination products with imidazole or DMF. Methods for silylation of amines and removal of silyl protecting groups are well known to those skilled in the art. Methods of preparation of these amine derivatives from corresponding amino acids, amino acid amides or amino acid esters are also well known to those skilled in the art of organic chemistry including amino acid/amino acid ester or aminoalcohol chemistry.

Protecting groups are removed under conditions which will not affect the remaining portion of the molecule. These methods are well known in the art and

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include acid hydrolysis, hydrogenolysis and the like. A preferred method involves removal of a protecting group, such as removal of a benzyloxycarbonyl group by hydrogenolysis utilizing palladium on carbon in a suitable solvent system such as an alcohol, acetic acid, and the like or mixtures thereof. A t-
 5 butoxycarbonyl protecting group can be removed utilizing an inorganic or organic acid, such as HCl or trifluoroacetic acid, in a suitable solvent system, such as dioxane or methylene chloride. The resulting amino salt can readily be neutralized to yield the free amine. Carboxy protecting group, such as methyl, ethyl, benzyl, tert-butyl, 4-methoxyphenylmethyl and the like, can be removed
 10 under hydrolysis and hydrogenolysis conditions well known to those skilled in the art.

It should be noted that compounds of the invention may contain groups that may exist in tautomeric forms, such as cyclic and acyclic amidine and guanidine groups, heteroatom substituted heteroaryl groups ($Y' = O, S, NR$), and
 15 the like, which are illustrated in the following examples:



and though one form is named, described, displayed and/or claimed herein, all the tautomeric forms are intended to be inherently included in such name, description, display and/or claim.

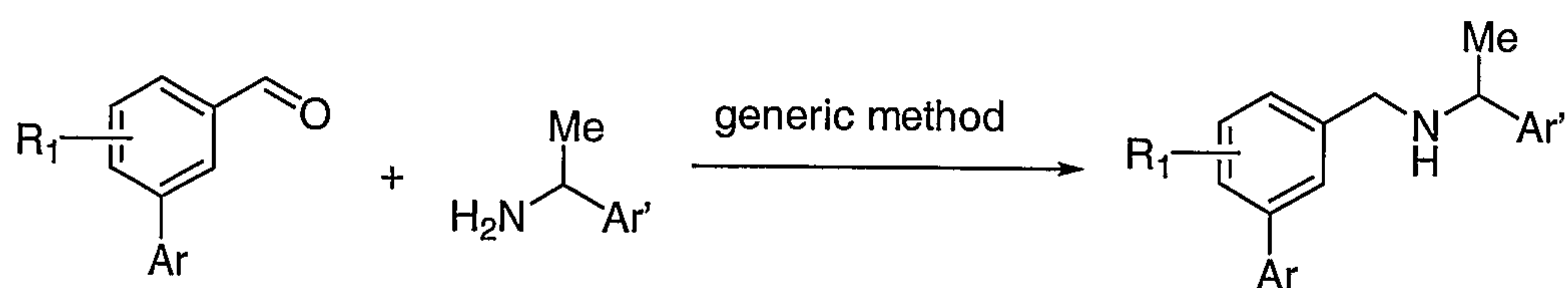
20 A "derivative" of a compound of the invention includes salts, isomers, enantiomers, prodrugs, and metabolites of the compound.

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Prodrugs of the compounds of this invention are also contemplated by this invention. A prodrug is an active or inactive compound that is modified chemically through in vivo physiological action, such as hydrolysis, metabolism and the like, into a compound of this invention following administration of the prodrug to a patient. The suitability and techniques involved in making and using prodrugs are well known by those skilled in the art. For a general discussion of prodrugs involving esters see Svensson and Tunek, Drug Metabolism Reviews 165 (1988) and Bundgaard, Design of Prodrugs, Elsevier (1985). One method of preparing a prodrug of a compound is by masking one or more potentially reactive groups on the compound, such as carboxylates, hydroxy groups, and amines. Examples of a masked carboxylate anion include a variety of esters, such as alkyl (for example, methyl, ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-methoxybenzyl), and alkylcarbonyloxyalkyl (for example, pivaloyloxymethyl). Amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases in vivo releasing the free drug and formaldehyde (Bundgaard, J. Med. Chem. 2503 (1989)). Also, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard, Design of Prodrugs, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little, 4/11/81) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

Experimental

General:



Method A: the aldehyde (1.6 mmol) is dissolved in methanol (5 mL) and the amine (1.9 mmol) is added. The reaction is shaken for 24 hours or until imine formation is complete (as monitored by LCMS), then solid supported borohydride is added (prepared according to Kabalka, G. W.; Wadgaonkar, P. P.; Chatla, N.; *Synth. Commun.*; (1990), 20 (2), 293-299) (ca 2.5mmol/g; 3.1 mmol) and the

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mixture is shaken for 24 hours or until reduction is complete (as monitored by LCMS). Dichloromethane (*ca* 3 mL) is then added followed by Wang-aldehyde resin (4-benzyloxybenzaldehyde, polymer-bound; *ca* 1.25mmol/g; 0.6mmol) and the mixture is shaken for further 24 hours. The resins are filtered off and the solvents are evaporated under reduced pressure, to afford an oil which is purified by column chromatography (usually Hexane/AcOEt 7/3 or DCM/MeOH 95/5). The free-base oil is then treated with 1.5-2.5 1N HCl in diethyl ether and the solvents are evaporated under reduced pressure to afford the *mono* or *bis*-HCl salt.

Method B: the aldehyde (1.6 mmol) is dissolved in methanol (5 mL) and the amine (1.9 mmol) is added. The reaction is heated to reflux for 10 minutes then left to cool overnight until imine formation is complete (as monitored by LCMS). Solid supported cyanoborohydride is added (prepared according to Sande, A. R.; Jagadale, M. H.; Mane, R. B.; Salunkhe, M. M.; *Tetrahedron Lett.* (1984), 25(32), 3501-4) (*ca* 2.5 mmol/g; 3.1 mmol) and the mixture is heated at 50 C for 15 hours or until reduction is complete (as monitored by LCMS). Dichloromethane (*ca* 3 mL) is then added followed by Wang-aldehyde resin (4-benzyloxybenzaldehyde, polymer-bound; *ca* 1.25 mmol/g; 0.6 mmol) and the mixture is shaken for further 24 hours. The resins are filtered off and the solvents are evaporated under reduced pressure, to afford an oil which is purified by column chromatography (usually Hexane/AcOEt 7/3 or DCM/MeOH 95/5). The free-base oil is then treated with 1.5-2.5 1N HCl in diethyl ether and the solvents are evaporated under reduced pressure to afford the *mono* or *bis*-HCl salt.

Method C: The aldehyde (1.6 mmol) is dissolved in 1,2-dichloroethane (12 mL) and the amine (1.9 mmol) is added, followed by acetic acid (0.09 mL, 1.6 mmol) and finally sodium triacetoxyborohydride (500 mg, 2.4 mmol). The mixture is stirred overnight or until complete by TLC; upon reaction completion, the mixture is diluted with ethyl acetate, washed with saturated NaHCO₃ then with saturated brine, and finally dried over sodium sulphate. The solvents are evaporated under reduced pressure, to afford an oil which is purified by column chromatography on silica gel (usually Hexane/AcOEt 7/3 or DCM/MeOH 95/5). The free-base oil is then treated with 1.5-2.5 equivalents 1N HCl in diethyl ether

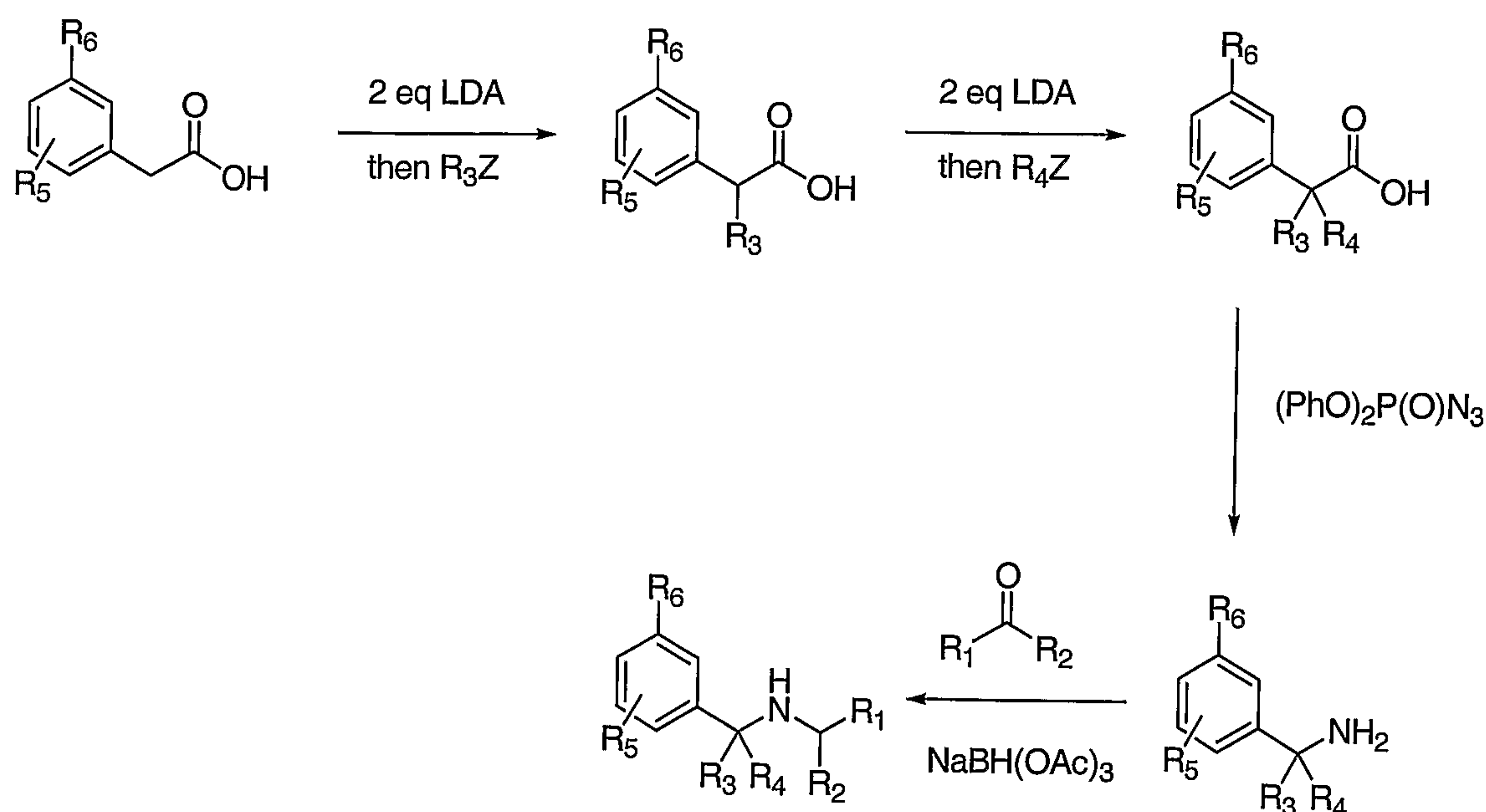
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and the solvents are evaporated under reduced pressure to afford the *mono* or *bis*-HCl salt.

Method D: Compounds wherein both R^3 and R^4 are other than hydrogen can be prepared by combining an appropriately substituted phenylacetic acid with a strong base such as lithium diisopropylamide or the like at a temperature between -78 and 20°C to yield a red dianion. The dianion is then reacted with an alkylating agent of formula $R^3\text{-Z}$, wherein Z is a halide, a sulfonate, or other suitable leaving group to provide an R^3 substituted compound. Treatment of the compound thus obtained with a strong base such as lithium diisopropylamide or the like at a temperature between -78 and 20°C yields a second red dianion, which is reacted with an alkylating agent of formula $R^4\text{-Z}$, wherein Z is a halide, a sulfonate, or other suitable leaving group to yield the R^3, R^4 disubstituted compound. Treatment of the resultant carboxylic acid with diphenylphosphoryl azide in a refluxing solvent (for example toluene, benzene, chlorobenzene, 1,4-dioxane or the like), followed by aqueous workup yields the R^3 substituted R^4 amine. Reductive coupling of the amine with an aldehyde or ketone according to Method C affords the final product.

Method E: Compounds wherein only one of R^3 and R^4 is hydrogen can be prepared by reacting the α -monosubstituted carboxylic acid obtained by reacting an appropriately substituted phenylacetic acid with a strong base such as lithium diisopropylamide and then with an alkylating agent of formula $R^3\text{-Z}$ as described above with diphenylphosphoryl azide in a refluxing solvent such as, for example, toluene, benzene, chlorobenzene, 1, 4-dioxane, etc. followed by an aqueous workup to yield a mono- α -substituted amine. This amine can then be reacted with an aldehyde or ketone according to Method C to obtain the final product.

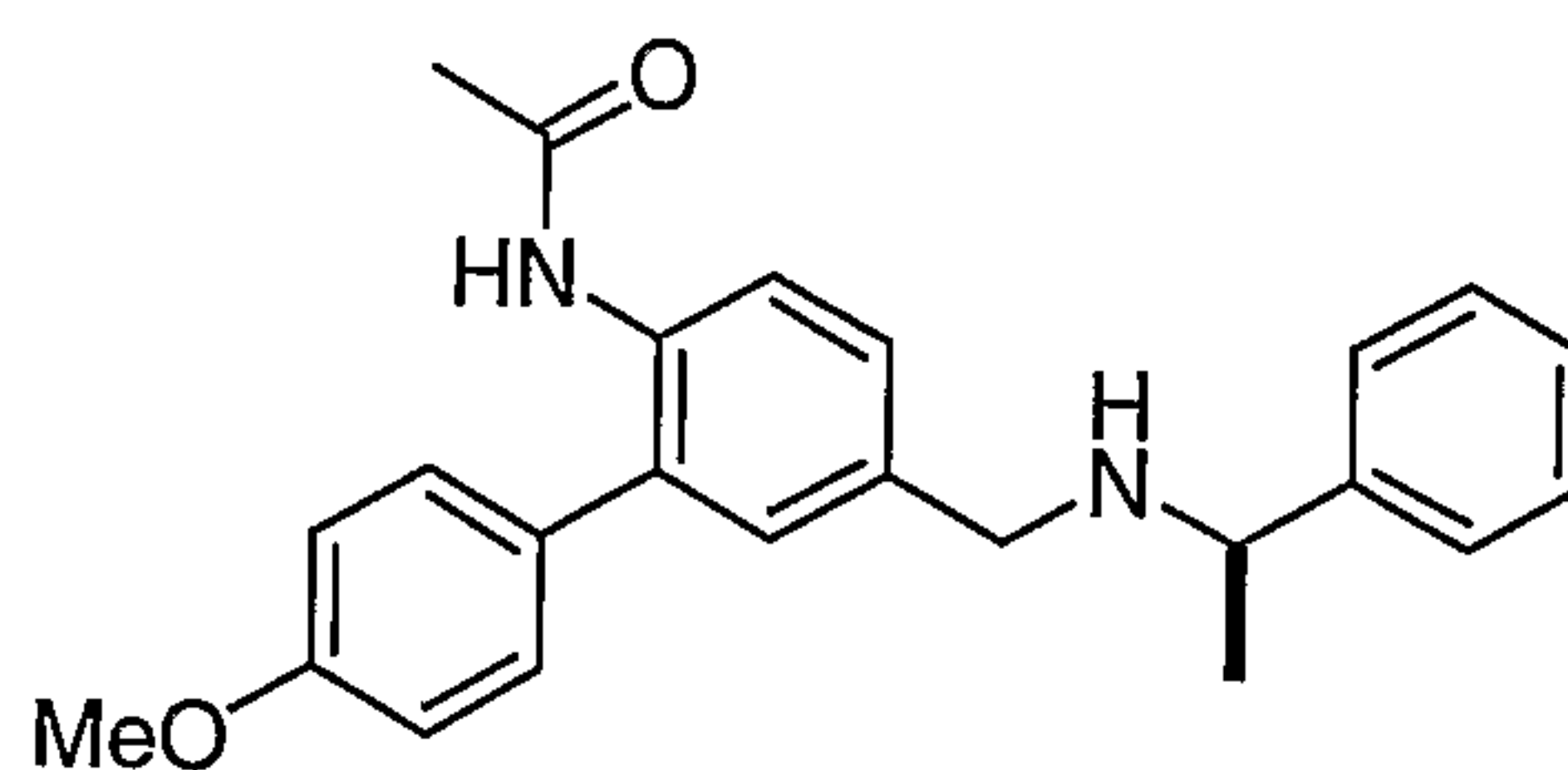
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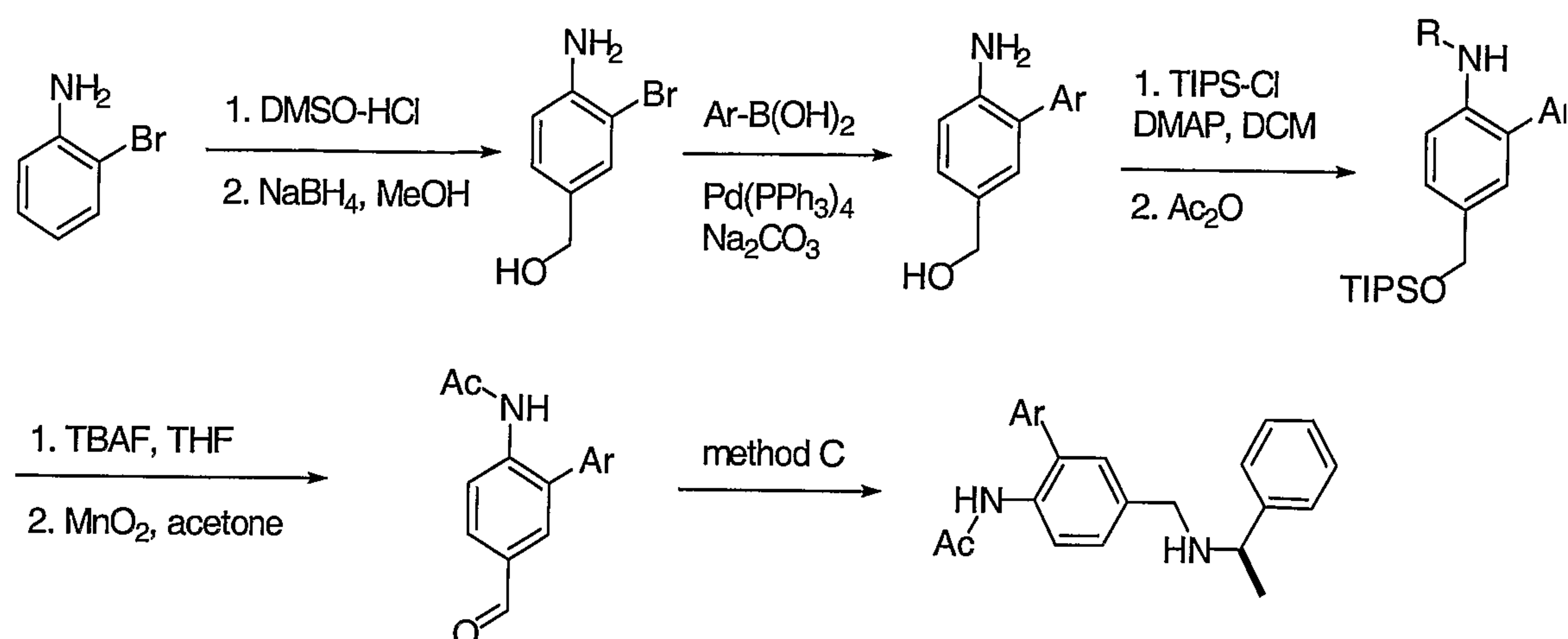
The following examples are representative of the invention, but are not to be construed as limiting the claimed invention in any way. The structure of the prepared compounds is verified by mass spectral data; C^{13} NMR data is also provided for some compounds. For some compounds, ions having mass greater than $M+H$ are reported. These ions generally represent dimers or trimers of the synthesized compound, and in some instances represent trifluoroacetate adducts generated from the mobile phase of the LC/MS. The trifluoroacetate adducts will have a weight of $M+115$.

Example 1

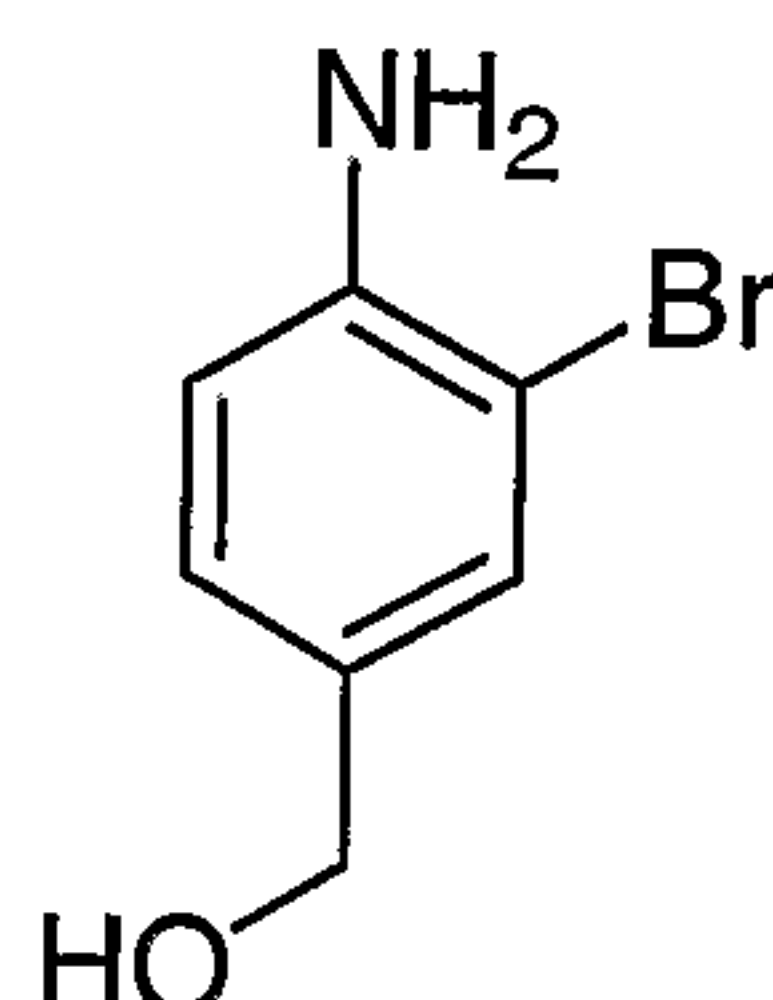
(R)-N-(1-phenylethyl)-N-((4-acetamido-3-(4-methoxyphenyl)phenyl)methyl)amine



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Step1) 2-bromo-4-hydroxymethylaniline:



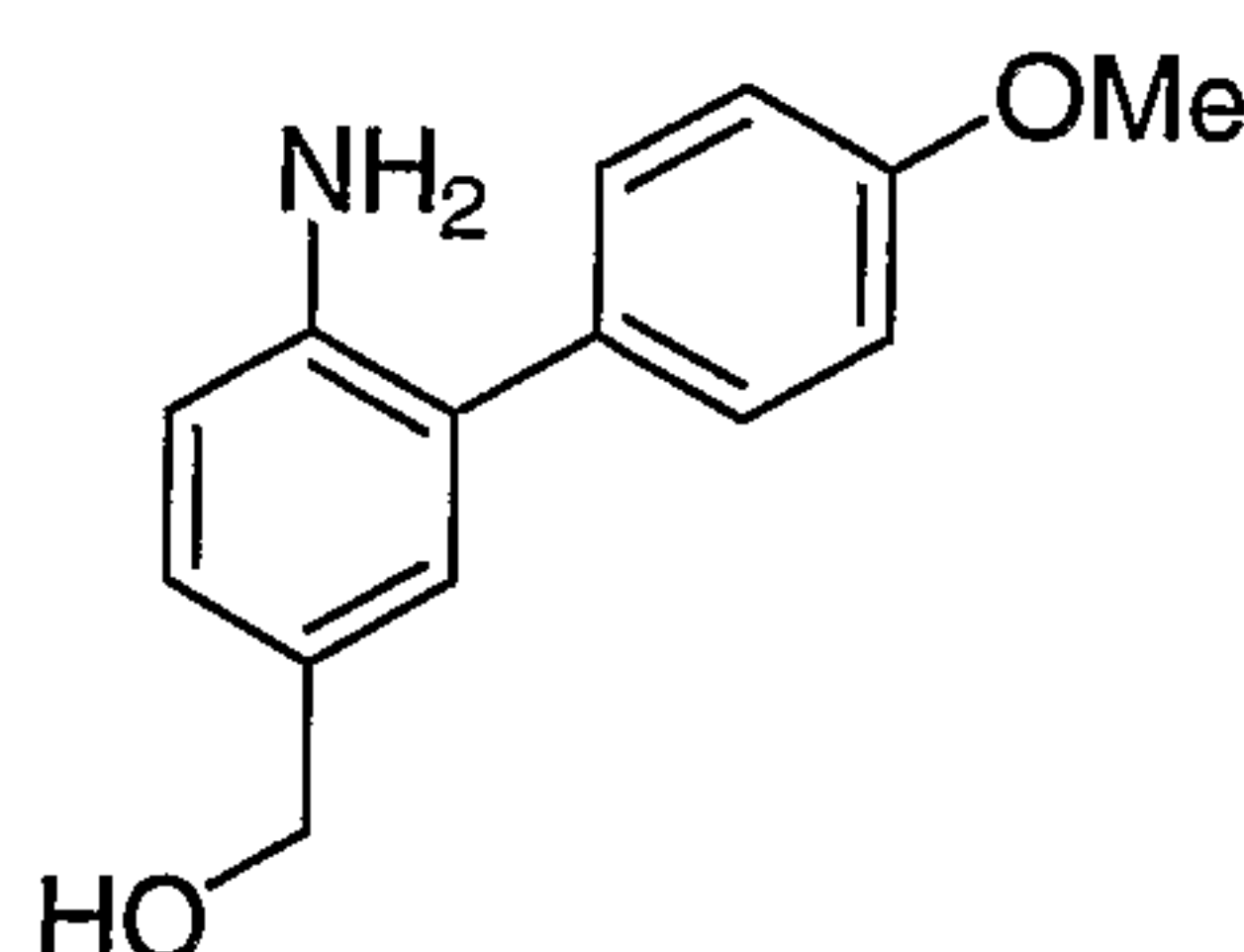
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To a solution of 4-amino-3-bromobenzaldehyde (2.6 g, 13 mmol) (prepared as in *J. Chem. Soc., Perkin Trans. 1* (1992), 2235) in methanol (130 mL) solid supported borohydride 6.2 g, 15.5 mmol) was added. The reaction was stirred for 1.5 hours at room temperature, then the resin filtered off and rinsed with little methanol. The filtrate was concentrated in vacuo to give 2.58 g of a brown oil. C_7H_8BrNO Mass (calculated) [202.05]; (found) $[M^+] = 202$ (bromine); Lc Rt = 0.63, 89%.

10

Step 2) 4-Hydroxymethyl-2-(4'-methoxyphenyl)aniline:

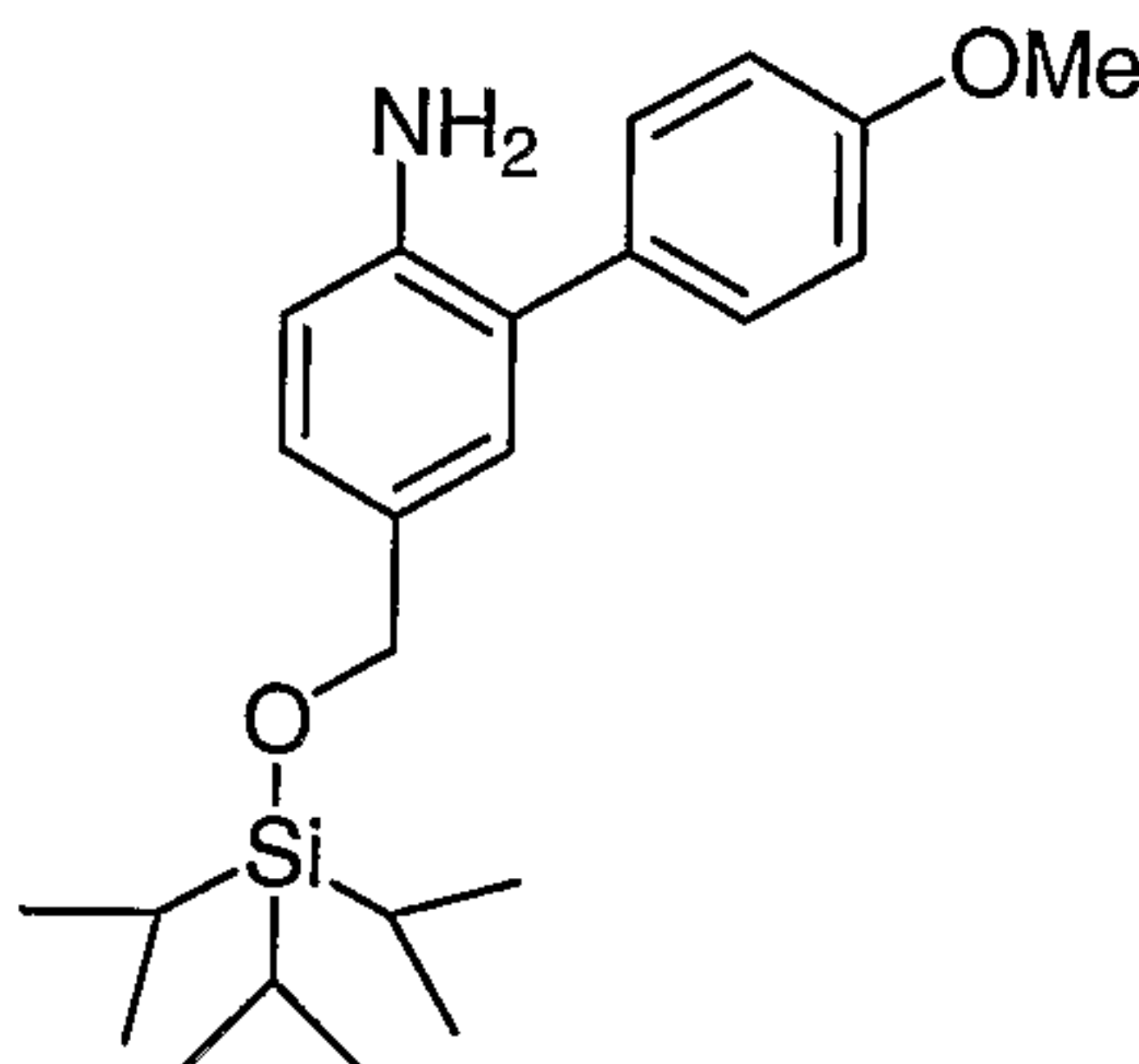
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To a degassed solution of crude 2-bromo-4-hydroxymethylaniline (3.2 g, 15.8 mmol), 4-methoxybenzeneboronic acid (2.89 g, 19 mmol) and potassium carbonate (4.77 g, 34.8 mmol) in toluene/ethanol 2/1 (45 mL) a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ (0.2 g, 1mmol%) was added and the mixture was heated at 90 C for 5 hours. The residue was extracted into ethyl acetate and washed with water and then saturated brine and dried over sodium sulphate. The solvent was removed under reduced pressure to afford 5 g of crude product. $\text{C}_{14}\text{H}_{15}\text{BNO}_2$ Mass (calculated) [229.28]; (found) $[\text{M}+\text{H}^+] = 230$ Lc Rt = 0.88, 89%. NMR (400 MHz, CDCl_3): 3.75 (3H, s, MeO); 4.5 (2H, s, CH_2O); 6.65 (1H, d, $J = 8.5$ Hz, aryl-H); 6.9 (2H, d, $J = 8.5$ Hz, aryl-H); 7-7.1 (2H, m, aryl-H); 7.25 (2H, d, $J = 8.5$ Hz, aryl-H).

Step 3) 4-Tri-isopropoxymethyl-2-(4'-methoxyphenyl)aniline:



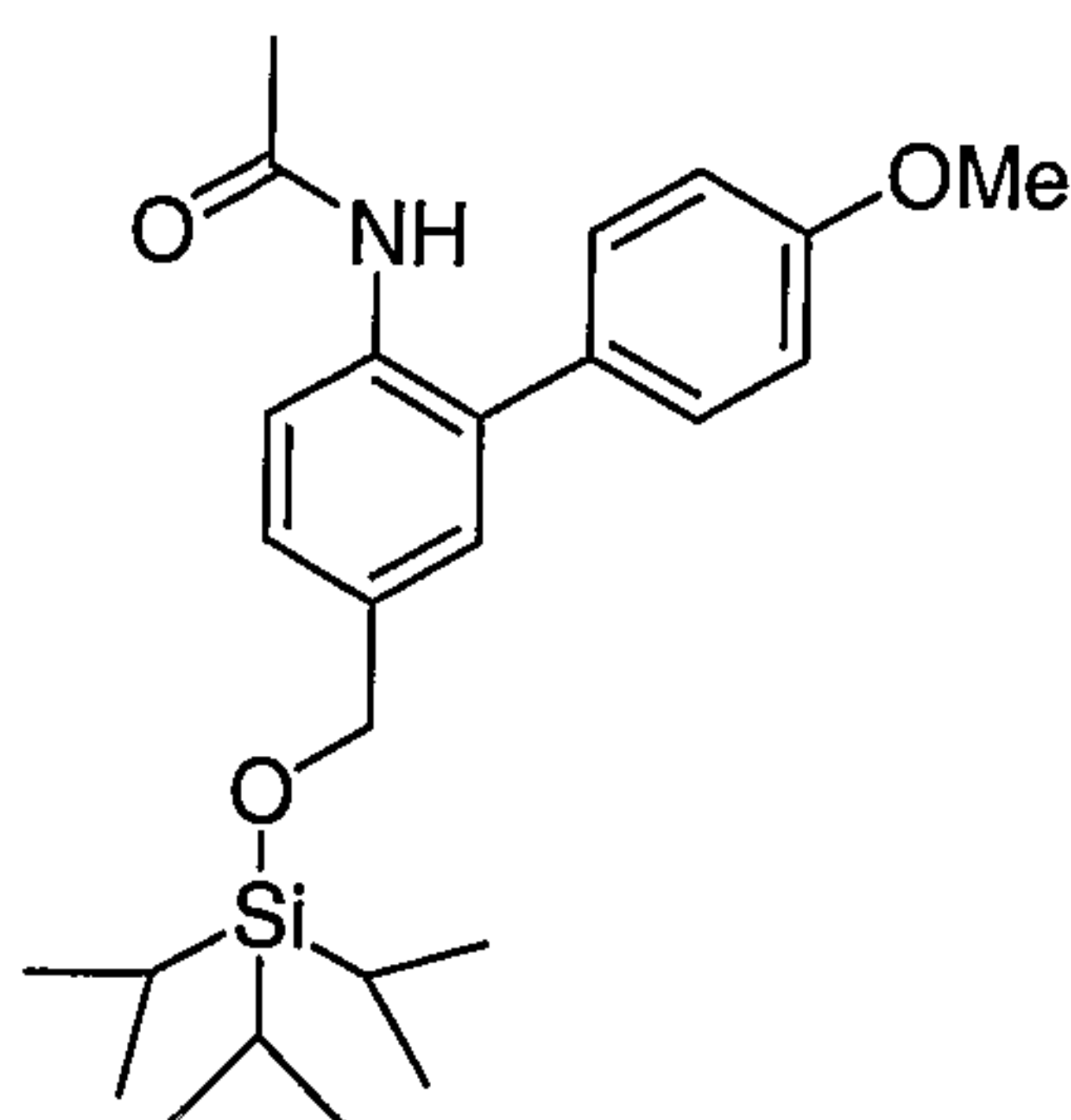
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To a solution of the crude alcohol from Step2 and 4-dimethylaminopyridine (2.12 g, 17.4 mmol) in dichloromethane (45 mL) tri-isopropylsilyl chloride (3.05 g, 15.8 mmol) was added. The reaction was stirred at room temperature for 16 hours and then diluted with dichloromethane and washed with water. The organic phase was dried over sodium sulphate and the solvent removed in vacuo. The crude was purified by column (silica, 5%-10 AcOEt in hexane to 10% methanol in AcOEt) to give 4.70 g of title compound.

$\text{C}_{23}\text{H}_{35}\text{NO}_2\text{Si}$ Mass (calculated) [385.63]; (found) $[\text{M}+\text{H}^+] = 386$ Lc Rt = 1.77.

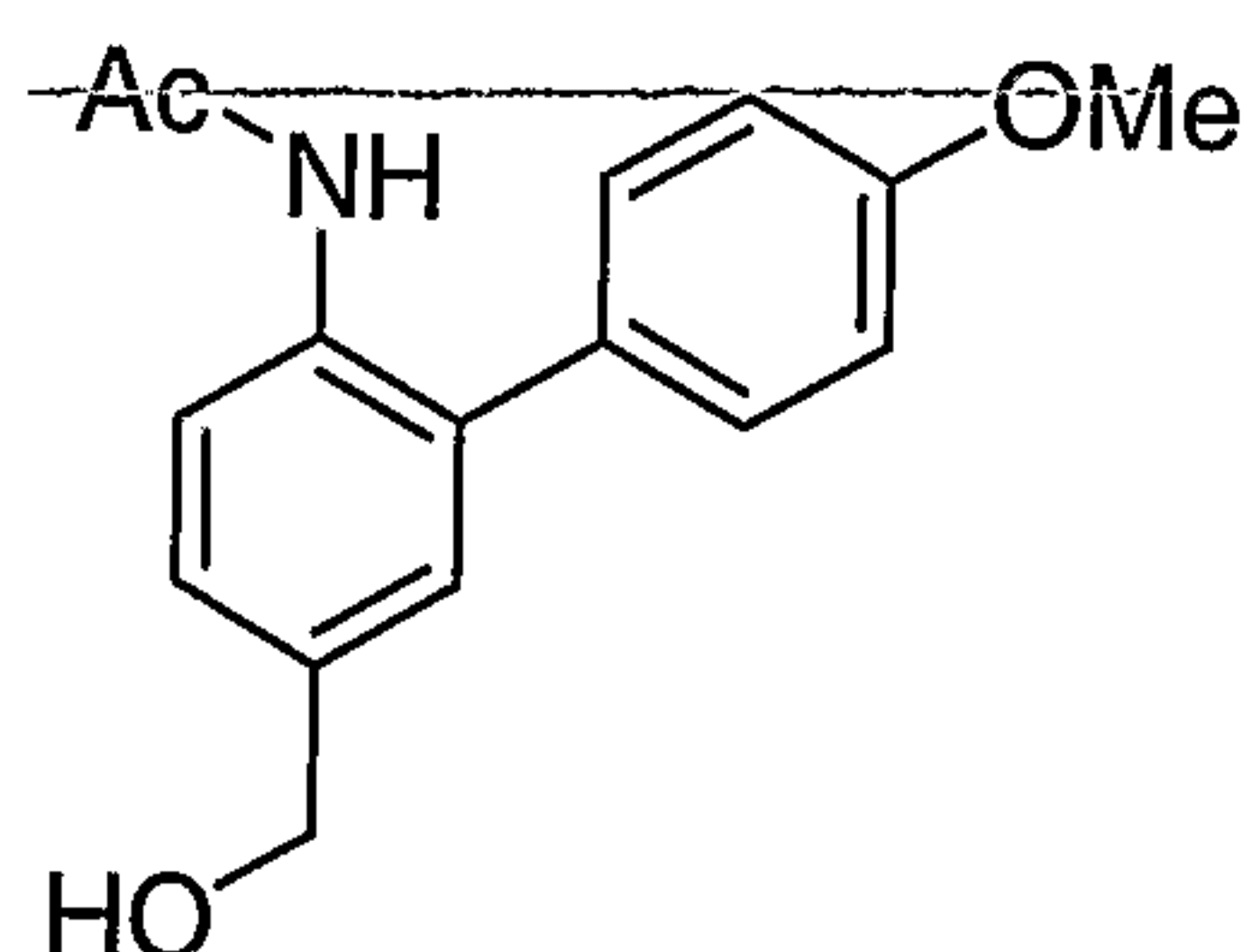
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Step 4) 4-Tri-*isopropoxymethyl*-2-(4'-methoxyphenyl)acetanilide:

To a solution of 4-tri-*isopropoxymethyl*-2-(4'-methoxyphenyl)aniline (1.57 g, 4.07 mmol) and 4-pyridine (0.35 mg, 4.48 mmol) in dichloromethane (9 mL), acetic anhydride (0.4 mL, 4.27 mmol) was added and the reaction stirred at room temperature for 72 hours. The reaction mixture was then diluted with dichloromethane and washed with saturated ammonium chloride and water, then dried over sodium sulphate to afford 1.87 g of a solid.

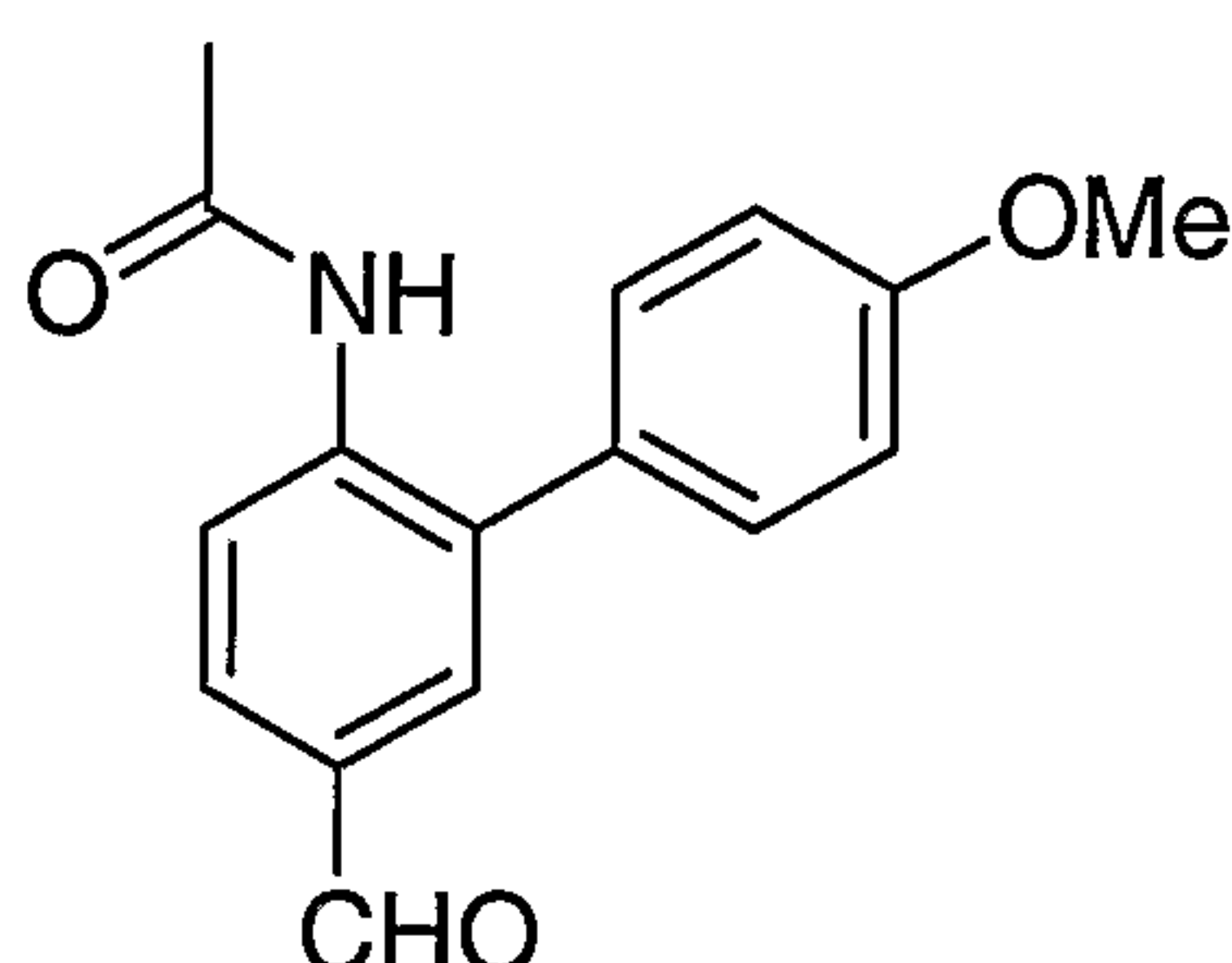
$C_{25}H_{37}NO_3Si$ Mass (calculated) [427.66]; (found) $[M+H^+] = 428$; Lc Rt = 2.10.

Step 5) 4-Hydroxymethyl-2-(4'-methoxyphenyl)acetanilide:

Tetra-butylammonium fluoride (4.48 mL of a 1M solution in THF) was added to a solution of 4-tri-*isopropoxymethyl*-2-(4'-methoxyphenyl)acetanilide (1.87 g, 4.07 mmol) in THF (12 mL) and stirred for 2 hours. The reaction was diluted with ethyl acetate and washed with saturated ammonium chloride then water and finally dried over sodium sulphate. The solvent was evaporated to afford 1.66 g of a yellow oil.

$C_{16}H_{17}NO_3$ Mass (calculated) [271.32]; (found) $[M+H^+] = 272$; Lc Rt = 0.95.

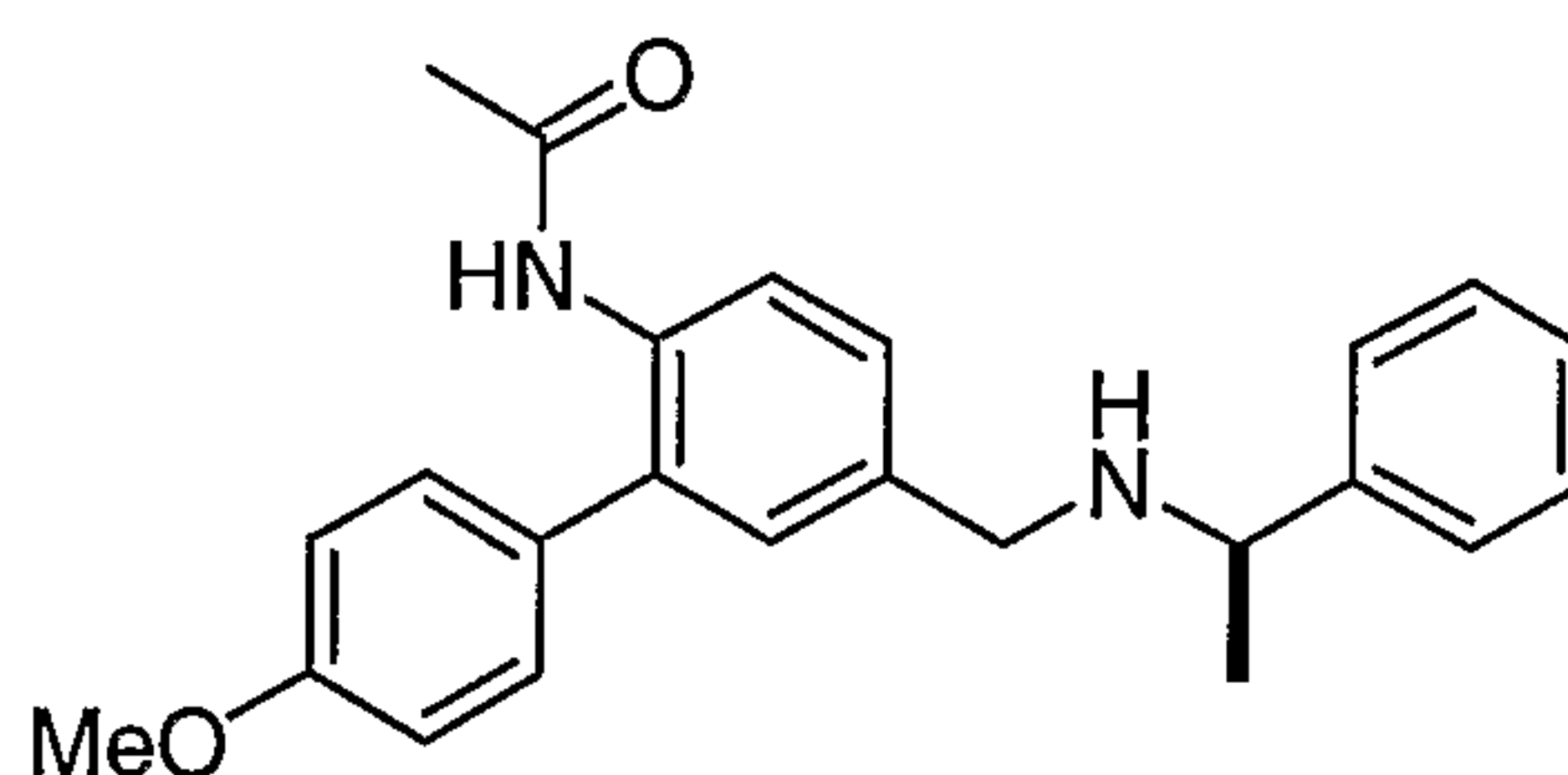
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Step 6) 4-Acetamido-3-(4'-methoxyphenyl)benzaldehyde:

Manganese dioxide (1.77 g, 20.3 mmol) was added portionwise to a stirred
 5 solution of the crude alcohol (1.66 g) from step 5 in acetone (12 mL). The reaction
 was stirred at room temperature for 20 hours, then refluxed for a further 8 hours.
 The reaction mixture was then filtered on paper and the solvent removed under
 reduced pressure. The crude was purified on silica (hexane/AcOEt 3/1) to give 0.6
 g of title product.

10 $C_{16}H_{15}NO_3$ Mass (calculated) [269.30]; (found) $[M+H^+] = 270$; Lc Rt = 1.21.
 NMR (400 MHz, $CDCl_3$): 2.6 (3H, s, CH_3CO); 3.86 (3H, s, MeO); 6.96 (2H, d,
 $J = 8.5$ Hz, aryl-H); 7.3 (2H, d, $J = 8.5$ Hz, aryl-H); 7.44 (1H, bs, NH); 7.72 ((1H,
 d, $J = 2$ Hz, aryl-H); 7.84 (1H, dd, $J = 2$ and 8.5 Hz, aryl-H); 8.6 (1H, bd, $J = 8.5$
 Hz, aryl-H); 9.5 (1H, s, CHO).

15

Step 7) (R)-N-(1-Phenylethyl)-N-((4-acetamido-3-(4-methoxyphenyl)phenyl)methyl)amine:

The title compound was prepared from N-[4-formyl-2-(4-
 20 methoxyphenyl)phenyl]acetamide and (R)- α -methylbenzylamine according to
 general procedure C.

 $C_{24}H_{26}N_2O_2$ Mass (calculated): [374]; (found): $[M+H^+] = 375$.

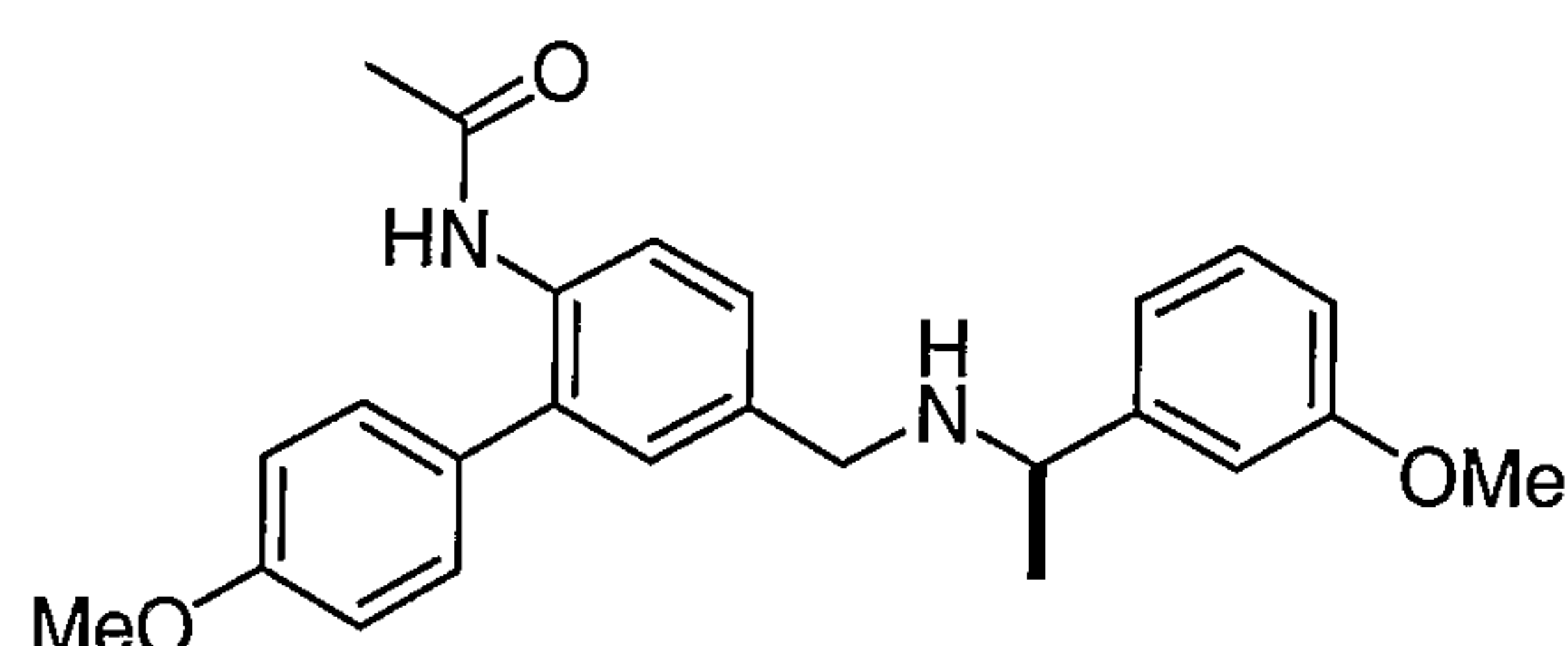
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NMR (400 MHz, CDCl₃): 1.3 (3H, d, $J = 6$ Hz, NCHCH₃); 1.95 (3H, s, CH₃CO); 3.5 and 3.55 (2H, dd, $J = 12$ Hz, CH₂N); 3.7 (1H, q, $J = 6$ Hz, NCHMe); 3.75 (3H, s, MeO); 6.9 (2H, d, $J = 8$ Hz, aryl-H); 7-7.1 (2H, m, aryl-H); 7.1-7.35 (7H, m, aryl-H); 8.1 (1H, d, $J = 8$ Hz, aryl-H).

5

Example 2

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-acetamido-3-(4-methoxyphenyl)phenyl)methyl)amine



10 The title compound was prepared from N-[4-formyl-2-(4-methoxyphenyl)phenyl]acetamide and (R)-3-methoxy- α -methylbenzylamine according to general procedure C.

$C_{25}H_{28}N_2O_3$

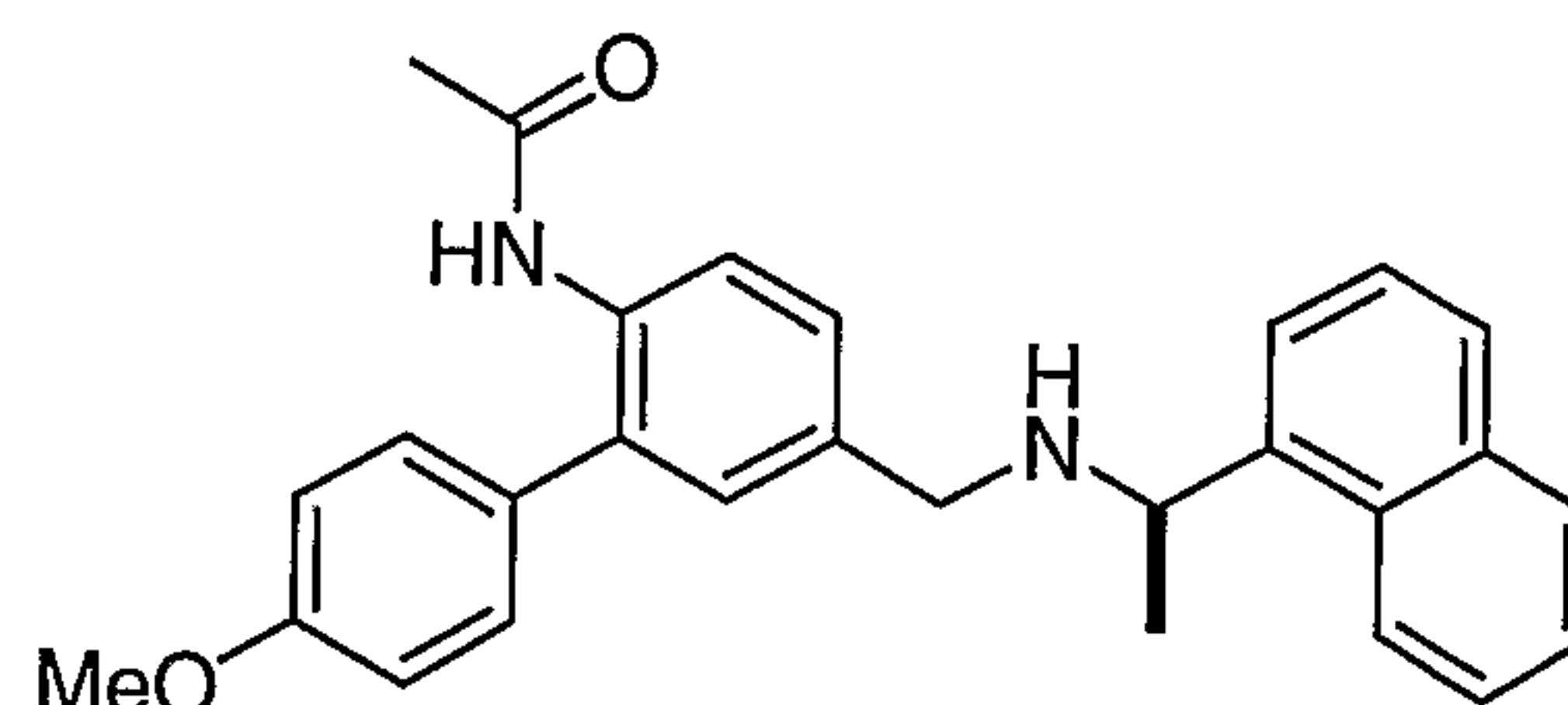
Mass (calculated): [404]; (found): $[M+H^+] = 254, 405$.

15 NMR (400 MHz, CDCl₃): 1.3 (3H, d, $J = 6$ Hz, NCHCH₃); 1.95 (3H, s, CH₃CO); 3.5 and 3.55 (2H, dd, $J = 12$ Hz, CH₂N); 3.7-3.75 (4H, m, MeO and NCHMe); 3.75 (3H, s, MeO); 6.7 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 6.75-6.8 (2H, m, aryl-H); 6.9 (2H, d, $J = 8$ Hz, aryl-H); 7-7.1 (2H, m, aryl-H); 7.1-7.35 (3H, m, aryl-H); 8.1 (1H, d, $J = 8$ Hz, aryl-H).

20

Example 3

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-acetamido-3-(4-methoxyphenyl)phenyl)methyl)amine



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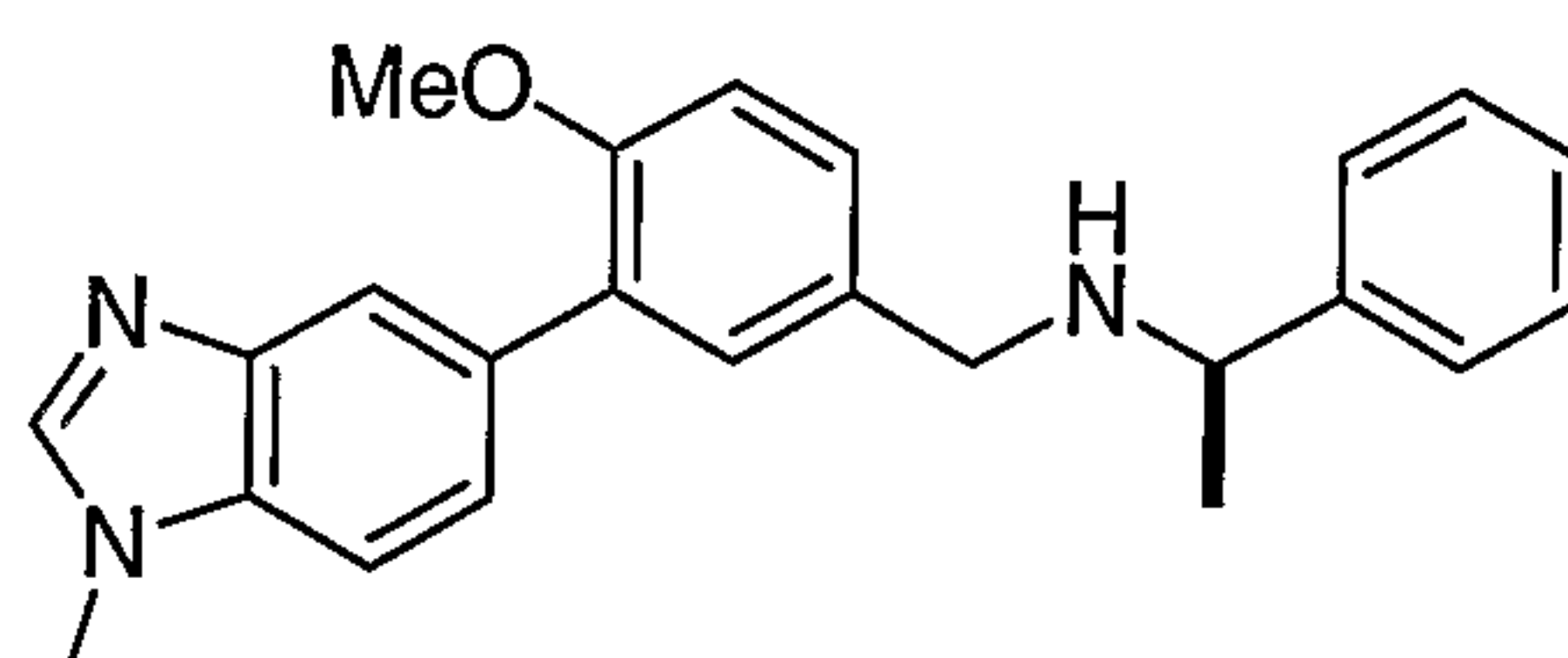
The title compound was prepared from N-[4-formyl-2-(4-methoxyphenyl)-phenyl]acetamide and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

$C_{28}H_{28}N_2O_2$

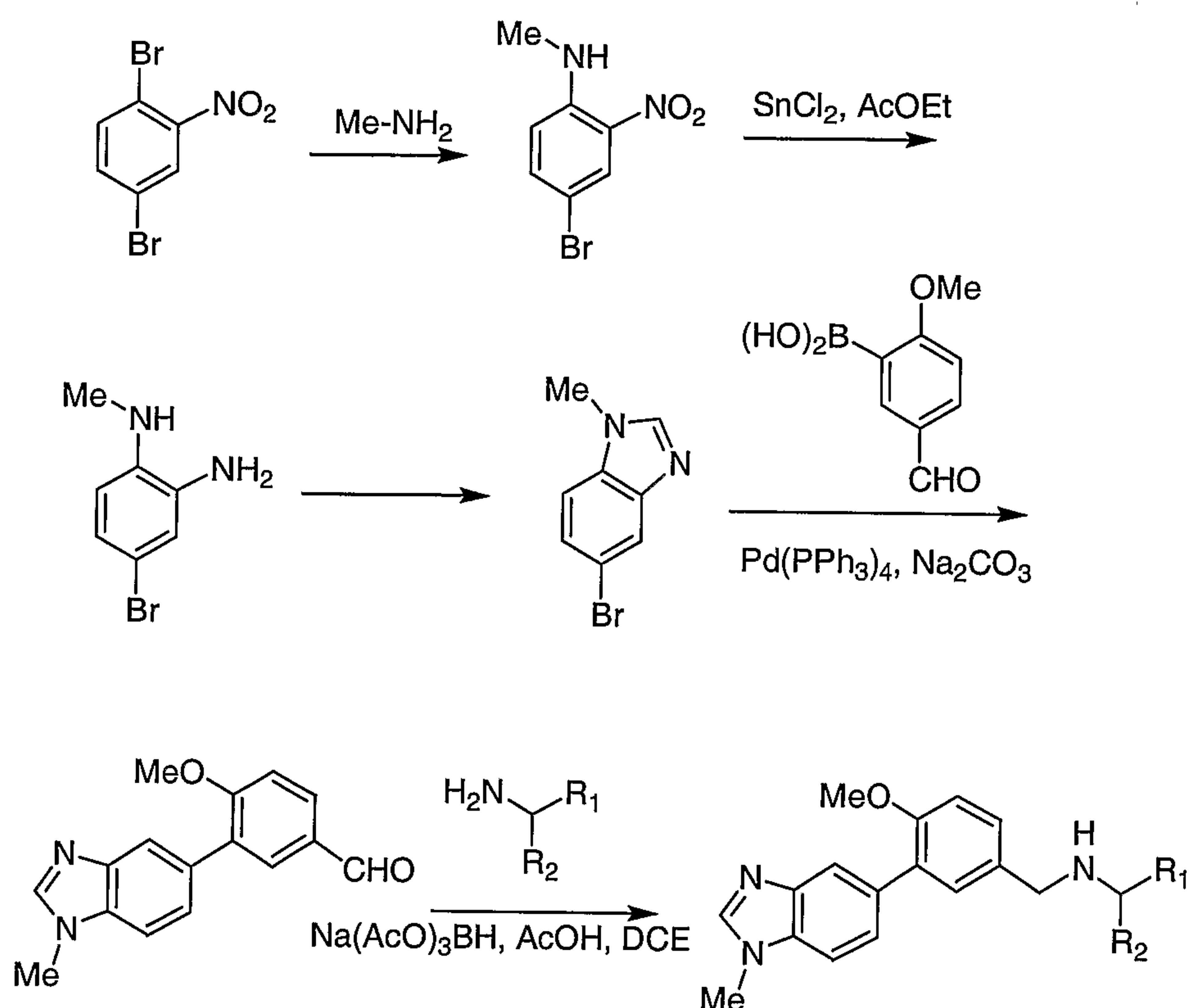
- 5 Mass (calculated): [424]; (found): $[M+H^+] = 425, 254$.
NMR (400 MHz, $CDCl_3$): 1.45 (3H, d, $J = 6$ Hz, $NCHCH_3$); 1.95 (3H, s, CH_3CO); 3.6 and 3.65 (2H, dd, $J = 12$ Hz, CH_2N); 3.8 (3H, s, MeO); 4.65 (1H, q, $J = 6$ Hz, $NCHMe$); 6.9 (2H, d, $J = 8$ Hz, aryl-H); 7.0-7.05 (2H, m, aryl-H); 7.1-7.15 (2H, m, aryl-H); 7.35-7.5 (3H, m, aryl-H); 7.7 (2H, d, $J = 8$ Hz, aryl-H); 7.75-7.85 (1H, m, aryl-H); 8-8.05 (1H, m, aryl-H); 8.1 (1H, d, $J = 8$ Hz, aryl-H).
- 10

Example 4

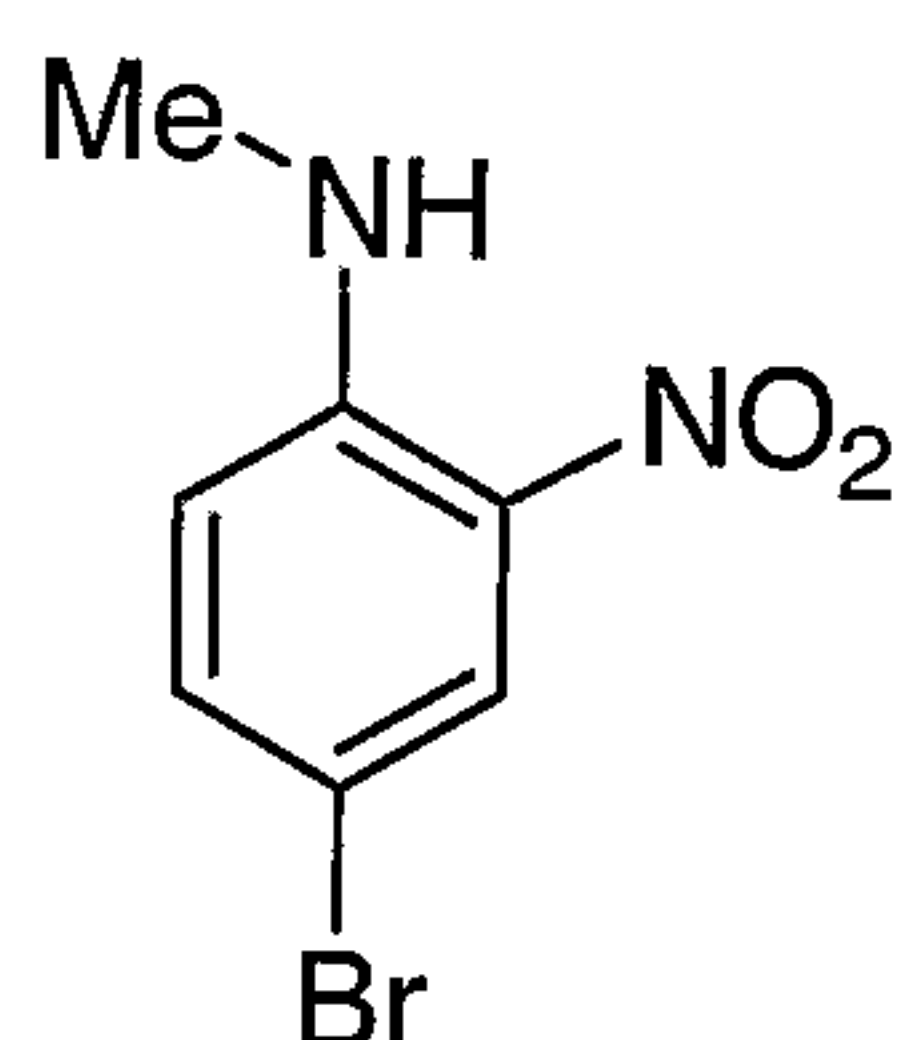
(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(1-methylbenzimidazol-5-yl)phenyl)methyl)amine



- 33 -



Step1) *N*-Methyl-4-bromo-2-nitroaniline/(4-Bromo-2-nitrophenyl)methylamine



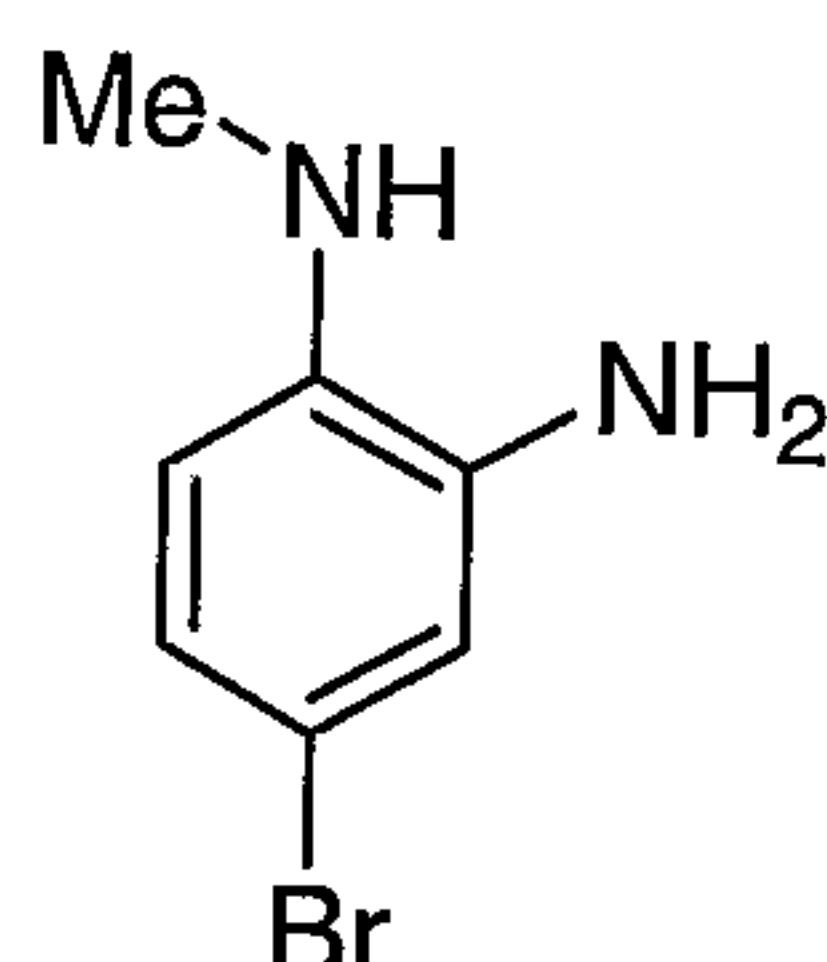
5

2,5-Dibromobenzene (5 g, 17.8 mmol) was added to a solution of methylamine (13.8 mL of a 40% aq. solution) and the mixture was stirred for 16 hours, then 8 mL of THF were added and the reaction was stirred for 2 hours at room temperature and then for further 2 hours at 50°C. The reaction mixture was then cooled and extracted twice into ethyl acetate. The solvent was removed under reduced pressure and the crude was chromatographed (silica, AcOEt 2-10% in hexane) to afford 2 g of orange crystals.

- 34 -

NMR (400 MHz, CDCl_3): 2.95 (3H, d, , $J = 5$ Hz, NCH_3); 3.92 (3H, s, MeN); 6.7 (d, $J = 8.5$ Hz, aryl-H); 7.45 (1H, dd, , $J = 2$ and 8.5 Hz, aryl-H); 7.9 (1H, bs, NH); 8.2 (1H, d, , $J = 2$ Hz, aryl-H).

5 Step 2) 2-N-Methylamino-5-bromoaniline/(2-Amino-4-bromophenyl)methylamine

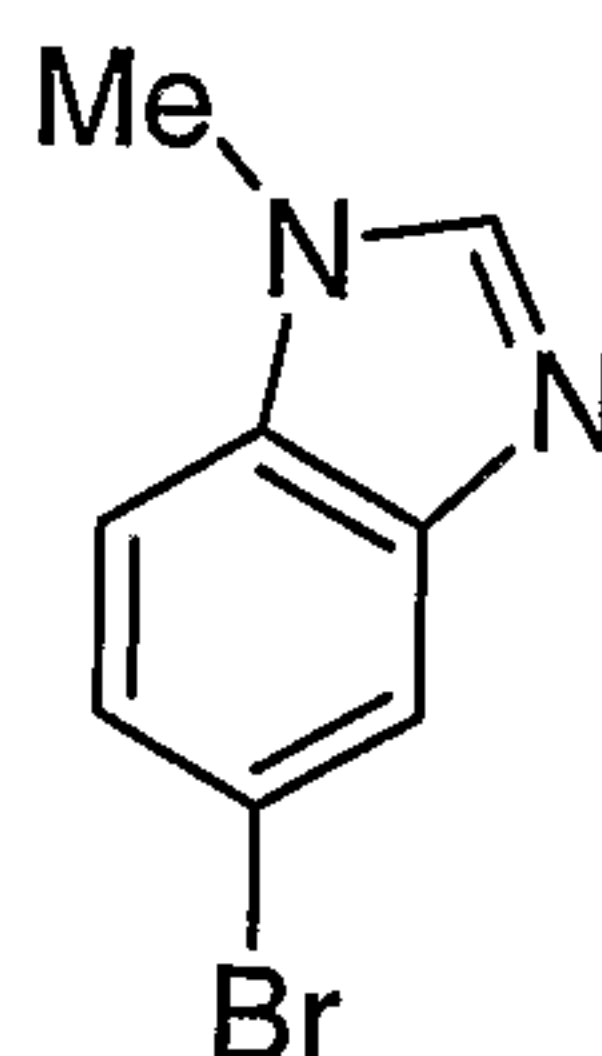


A solution of the nitroaniline from Step 1 (1.56 g, 6.75 mmol) and tin(II) chloride (7.62 g, 33.7 mmol) in ethyl acetate (40 mL) was refluxed under nitrogen for 3
 10 hours. The mixture was then poured onto ice, neutralized with saturated NaHCO_3 and extracted into ethyl acetate. The organic layer was washed with brine and dried over sodium sulphate to afford 1.5 g of crude red oil which was used without further purification.

$\text{C}_7\text{H}_9\text{BrO}_2$ Mass (calculated): [201.07]; (found): $[\text{M}^+] = 201$ (bromine).

15 NMR (400 MHz, MeOH-d_4): 3.88 (3H, s, MeO); 2.8 (3H, s, MeN); 6.7 (1H, d, $J = 8.5$ Hz, aryl-H); 6.85 (1H, dd, , $J = 2$ and 8.5 Hz, aryl-H); 6.9 (1H, d, , $J = 2$ Hz, aryl-H).

Step 3) 5-Bromo-1-methylbenzimidazole:



20

A solution of 2-N-methylamino-5-bromoaniline (1 g, 4.97 mmol) in triethyl orthoformate (30 mL) was refluxed for 5 hours. The solvent was removed under reduced pressure to afford 1 g of the title bromobenzimidazole.

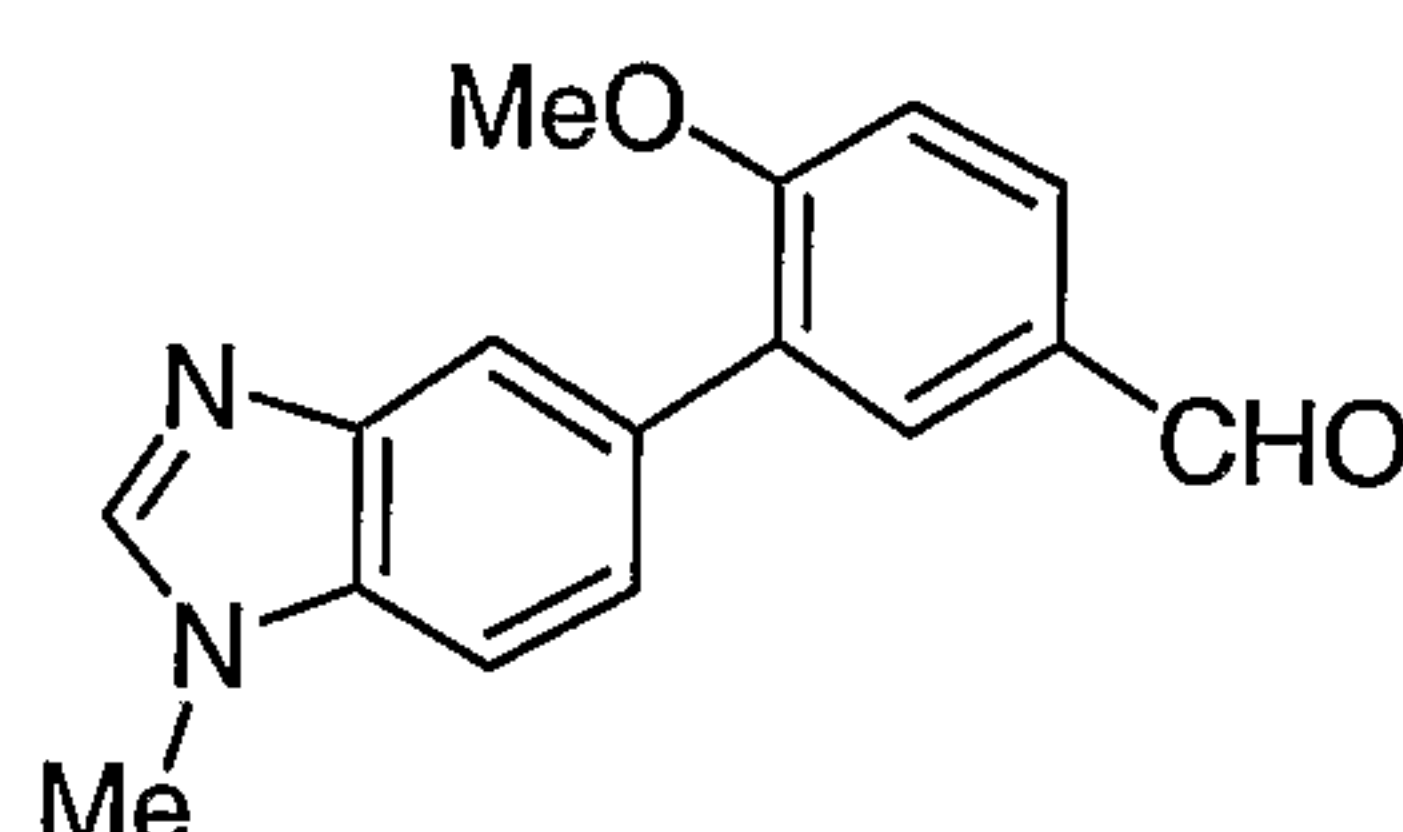
- 35 -

$C_8H_7BrN_2$ Mass (calculated): [211.06]; (found): $[M^+] = 211$ (bromine).

NMR (400 MHz, $MeOH-d_4$): 3.88 (3H, s, MeO); 2.8 (3H, s, MeN); 6.7 (1H, d, $J = 8.5$ Hz, aryl-H); 6.85 (1H, dd, $J = 2$ and 8.5 Hz, aryl-H); 6.9 (1H, d, $J = 2$ Hz, aryl-H).

5

Step 4) 4-Methoxy-3-(1'-methylbenzimidazol-5'-yl)benzenecarboxaldehyde/4-Methoxy-3-(1-methylbenzimidazol-5-yl)benzaldehyde:



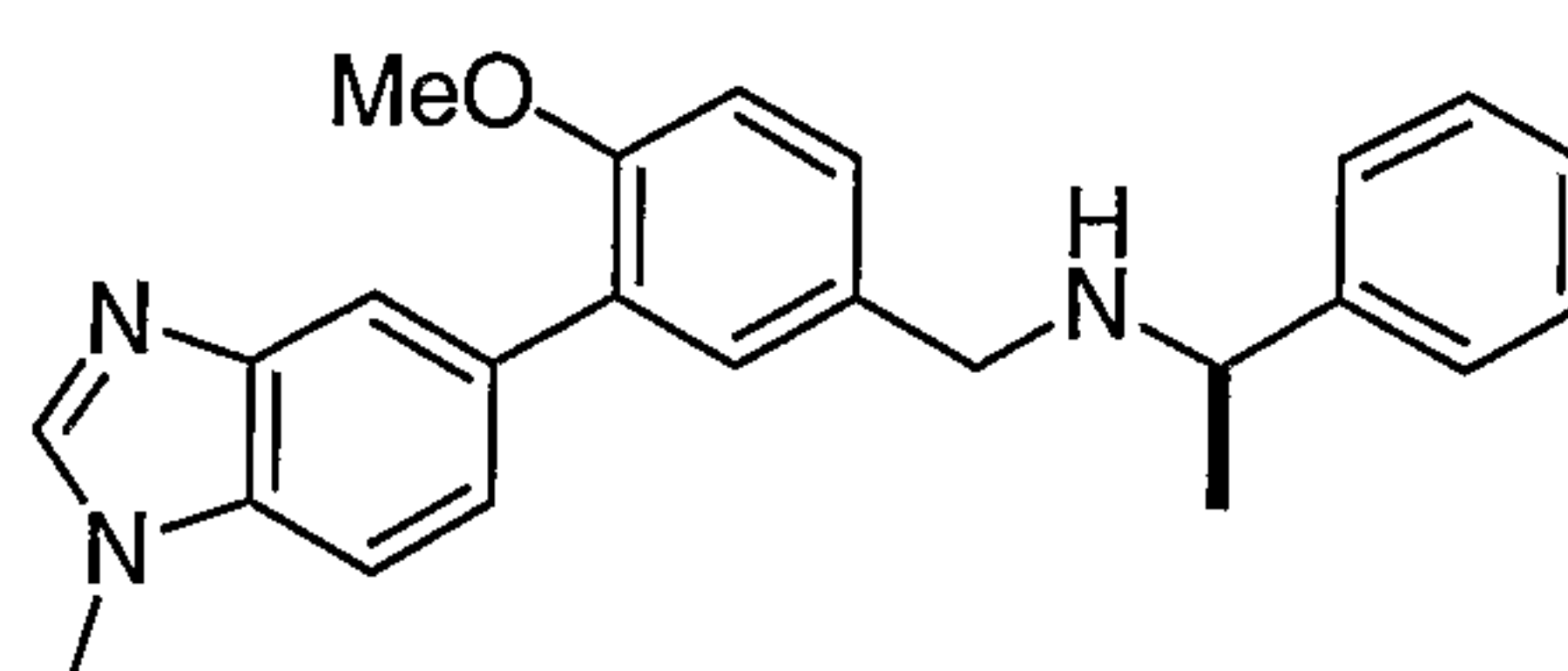
- 10 To a degassed solution of 5-bromo-1-methylbenzimidazole (0.56 g, 2.63 mmol), 5-formyl-2-methoxybenzeneboronic acid (0.57 g, 3.2 mmol) and potassium carbonate (0.91 g, 6.6 mmol) in toluene/ethanol 2/1 (30 mL) a catalytic amount of $Pd(PPh_3)_4$ (0.03 g, 1 mmol%) was added and the solution was degassed for further 5 minutes. The mixture was refluxed for 5 hours. The residue was extracted into
- 15 ethyl acetate and washed with water and then saturated brine and dried over sodium sulphate. The solvent was removed under reduced pressure and the crude was purified by column (silica, EtOAc to 5% MeOH in AcOEt) to afford 0.6 g of product.

$C_8H_7BrN_2$

- 20 Mass (calculated): [266.30]; (found): $[M^+] = 267$.
NMR (400 MHz, $CDCl_3$): 3.88 (3H, s, MeO); 3.92 (3H, s, MeN); 7.12 (1H, d, $J = 8.5$ Hz, aryl-H); 7.4-7.5 (2H, m, aryl-H); 7.8-7.95 (3H, m, aryl-H); 7.98 (1H, s, imidazole N=CHN); 9.95 (1H, s, CHO).

- 25 Step 5) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(1-methylbenzimidazol-5-yl)phenyl)methyl)amine

- 36 -



The title compound was prepared from 4-methoxy-3-(1-methylbenzimidazol-5-yl)benzaldehyde and (R)- α -methylbenzylamine according to general procedure C.

5 $C_{24}H_{25}N_3O$

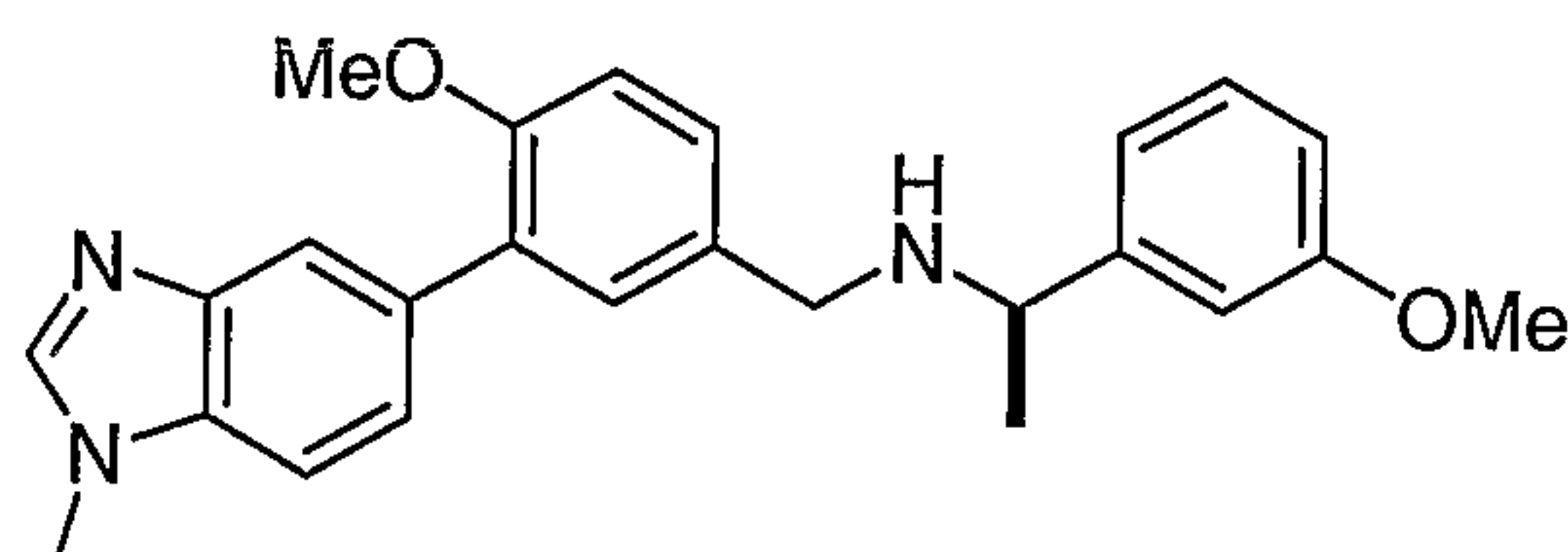
Mass (calculated): [371]; (found): $[M+H^+] = 251, 372, 268$.

NMR (400 MHz, $CDCl_3$): 1.3 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.55 and 3.6 (2H, dd, $J = 12$ Hz, CH_2N); 3.7 (3H, s, NMe); 3.75-3.85 (4H, m and s, $NCHMe$ and MeO); 6.9 (2H, d, $J = 8$ Hz, aryl-H); 7.25-7.3 (3H, m, aryl-H); 7.3-7.4 (5H, m, aryl-H);
 10 7.45 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 7.8 (1H, aryl-H); 7.9 (1H, m, aryl-H).

Example 5

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(1-methylbenzimidazol-5-yl)phenyl)methyl)amine

15



The title compound was prepared from 4-methoxy-3-(1-methylbenzimidazol-5-yl)benzaldehyde and (R)-3-methoxy- α -methylbenzylamine according to general procedure C.

20 $C_{25}H_{27}N_3O_2$

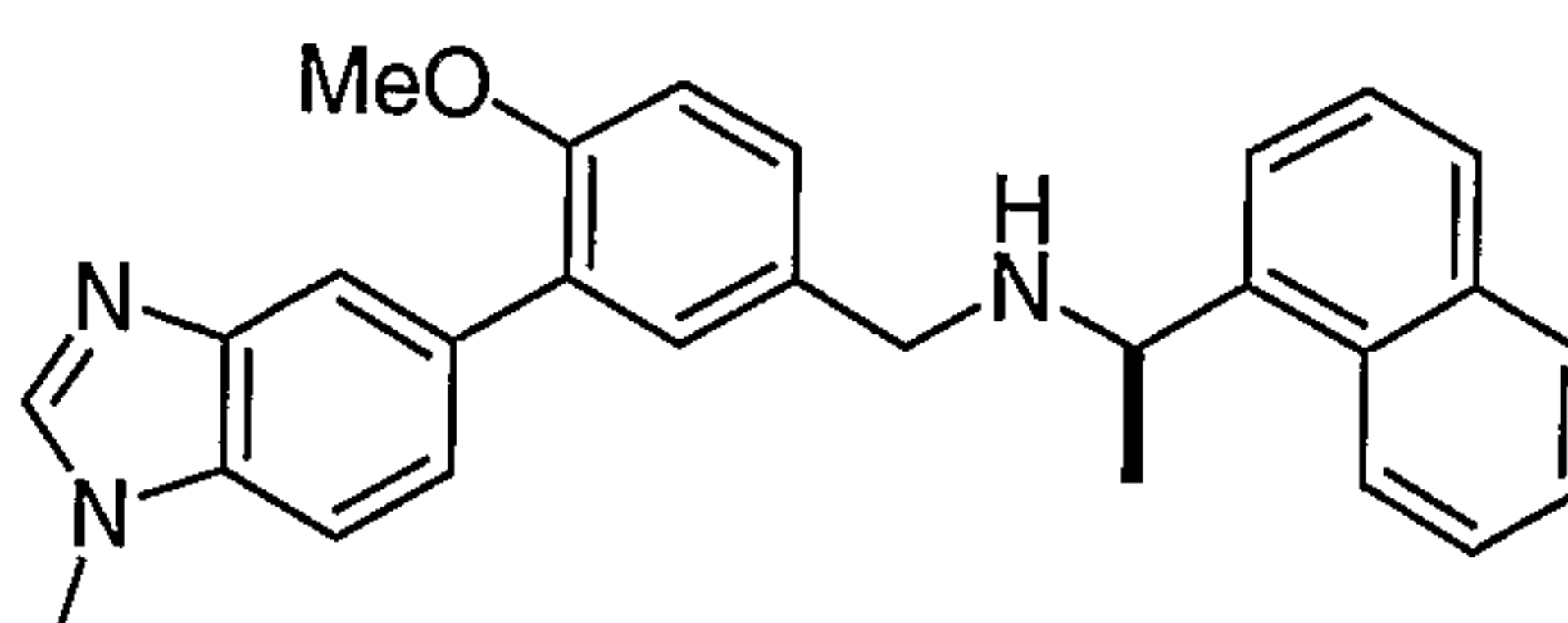
Mass (calculated): [401]; (found): $[M+H^+] = 402, 251, 268$.

NMR (400 MHz, $CDCl_3$): 1.3 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.55 and 3.6 (2H, dd, $J = 12$ Hz, CH_2N); 3.7-3.9 (10H, m and 2s, $NCHMe$, NMe and MeO); 6.7 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 6.85-6.95 (3H, m, aryl-H); 7.15-7.3 (3H, m, aryl-H); 7.35
 25 (1H, m, aryl-H); 7.45 (1H, m, aryl-H); 7.8-7.95 (2H, m, aryl-H).

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Example 6

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(1-methylbenzimidazol-5-yl)phenyl)methyl)amine



5

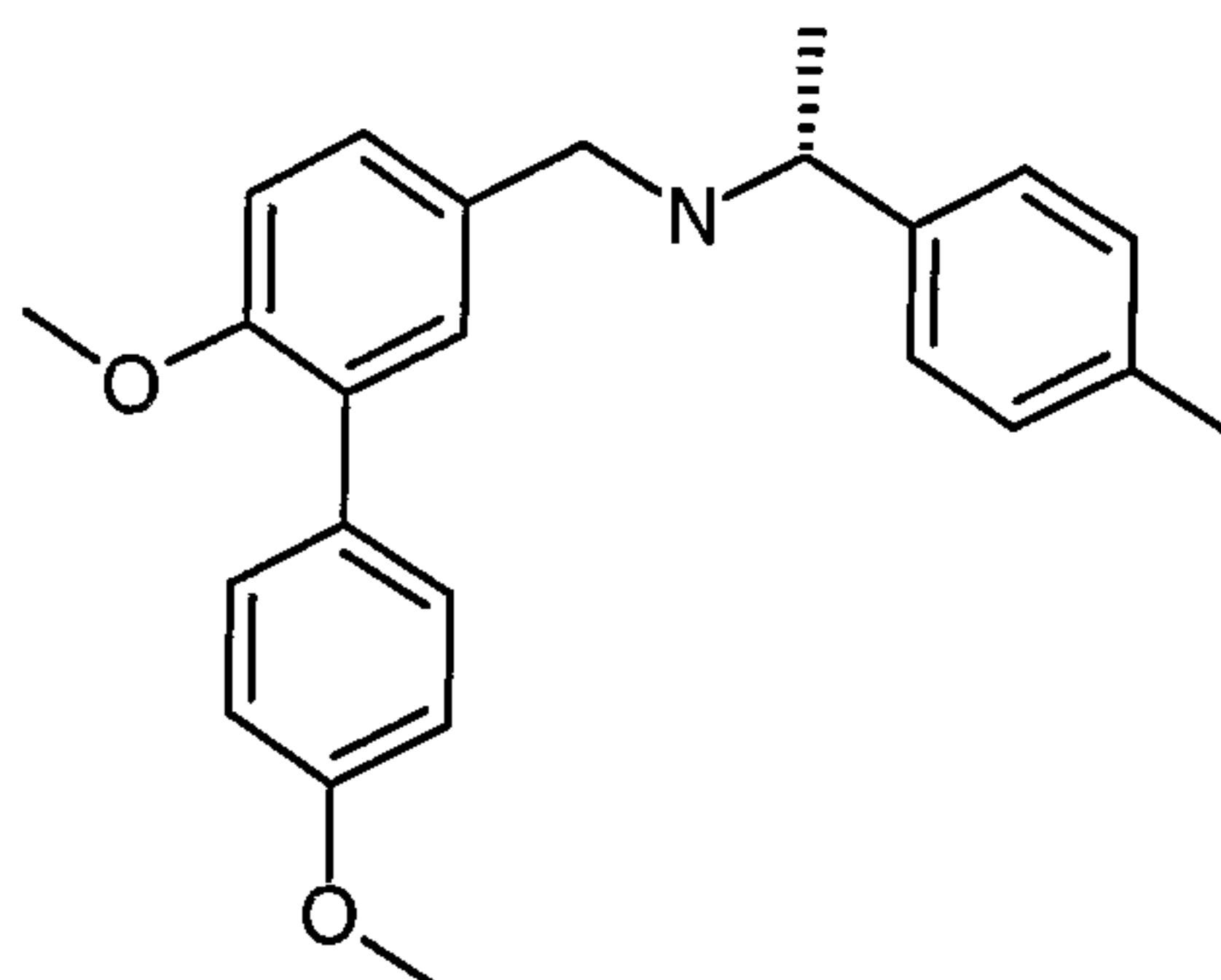
The title compound was prepared from 4-methoxy-3-(1-methylbenzimidazol-5-yl)benzaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

$C_{28}H_{27}N_3O$

- 10 Mass (calculated): [371]; (found): $[M+H^+] = 155, 422, 268, 251$.
 NMR (400 MHz, $CDCl_3$): 1.6 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.6-3.7 (4H, m, CH_2N and Nme); 3.7-3.8 (4H, m, CH_2N and MeO); 4.8 (1H, q, $J = 6$ Hz, $NCHCH_3$); 6.8 (1H, d, $J = 8$ Hz, aryl-H); 7.15 (1H, d, $J = 1$ Hz, aryl-H); 7.2-7.3 (1H, m, aryl-H); 7.3-7.35 (2H, m, aryl-H); 7.35-7.5 (2H, m, aryl-H); 7.5 (1H, t, $J = 7$ Hz, aryl-H);
 15 7.7 (1H, d, $J = 8$ Hz, aryl-H); 7.8-7.95 (5H, m, aryl-H).

Example 7

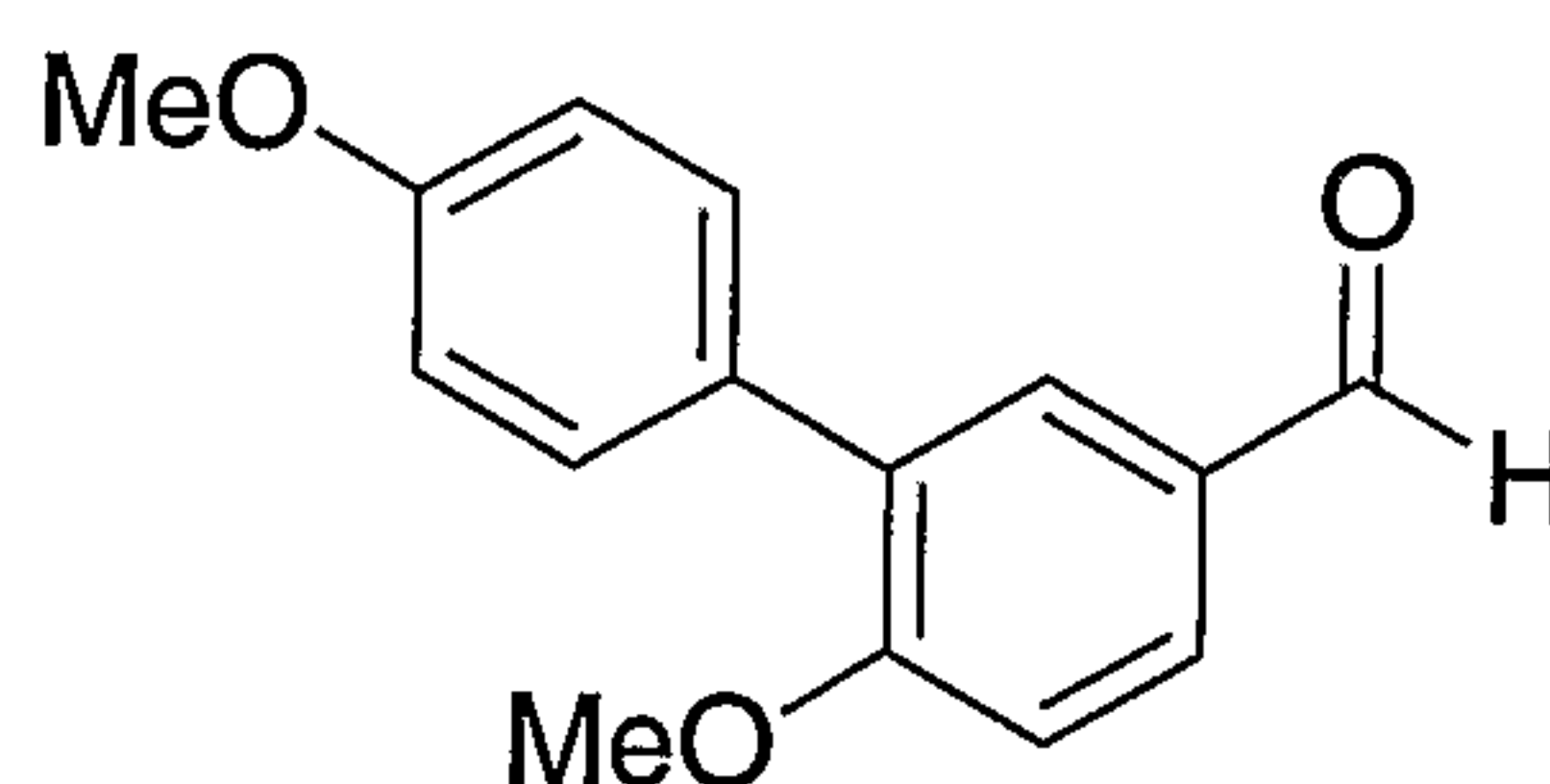
(R)-N-(1-(4-Methylphenyl)ethyl)-N-((4-methoxy-3-(4'-methoxyphenyl)phenyl)methyl)amine



20

Step 1) 4-Methoxy-3-(4-methoxyphenyl)benzaldehyde

- 38 -

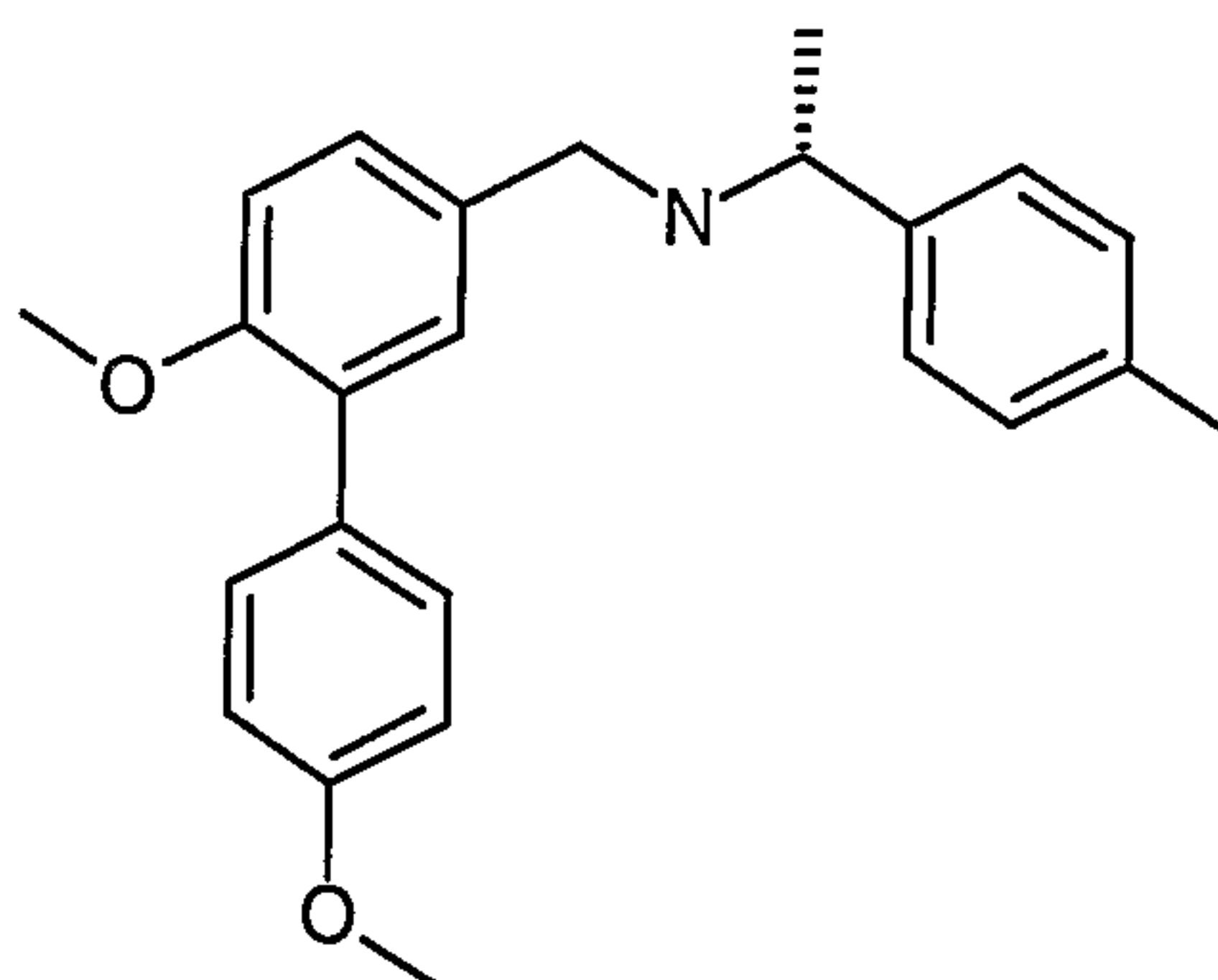


3-Bromo-4-methoxybenzaldehyde (1.92 g, 9 mmol, Aldrich) and 4-methoxyphenylboronic acid (1.52 g, 10 mmol, Aldrich) were dissolved in
 5 ethylene glycol dimethyl ether (15 mL, Aldrich). To the solution was added lithium chloride (0.72 g, 30 mmol, Aldrich) and aqueous 2 M sodium carbonate solution (15 mL, 30 mmol). After the mixture was bubbled with nitrogen for 10 min at room temperature, tetrakis(triphenylphosphine)palladium(0) (1.15 g, 1.0 mmol, Aldrich) was added to the mixture. The mixture was stirred under nitrogen
 10 at 80 C for overnight then the reaction was cooled at room temperature and diluted in ethyl acetate (50 mL). The solid portion was filtered out through Celite pad. The organic phase was separated and washed by water (30 mL) and brine (30 mL). The resulting organic layer was dried over anhydrous magnesium sulfate and concentrated via vacuo. The title compound was purified by column
 15 chromatography (silica gel, hexane/ethyl acetate 5/1) to give the title compound as white solid in 88% yield (2.12 g, 8.8 mmol).

$C_{15}H_{14}O_3$

MS (ESI, pos. ion) m/z: 243.1 (M+1); MS (ESI, neg. ion) m/z: 241.0 (M-1).

20 Step 2) (R)-N-(1-(4-Methylphenyl)ethyl)-N-((4-methoxy-3-(4'-methoxyphenyl)-phenylmethyl)amine



- 39 -

The title compound was prepared from 4-methoxy-3-(4-methoxyphenyl)-benzaldehyde and (R)-4-methyl- α -methylbenzylamine according to general procedure A.

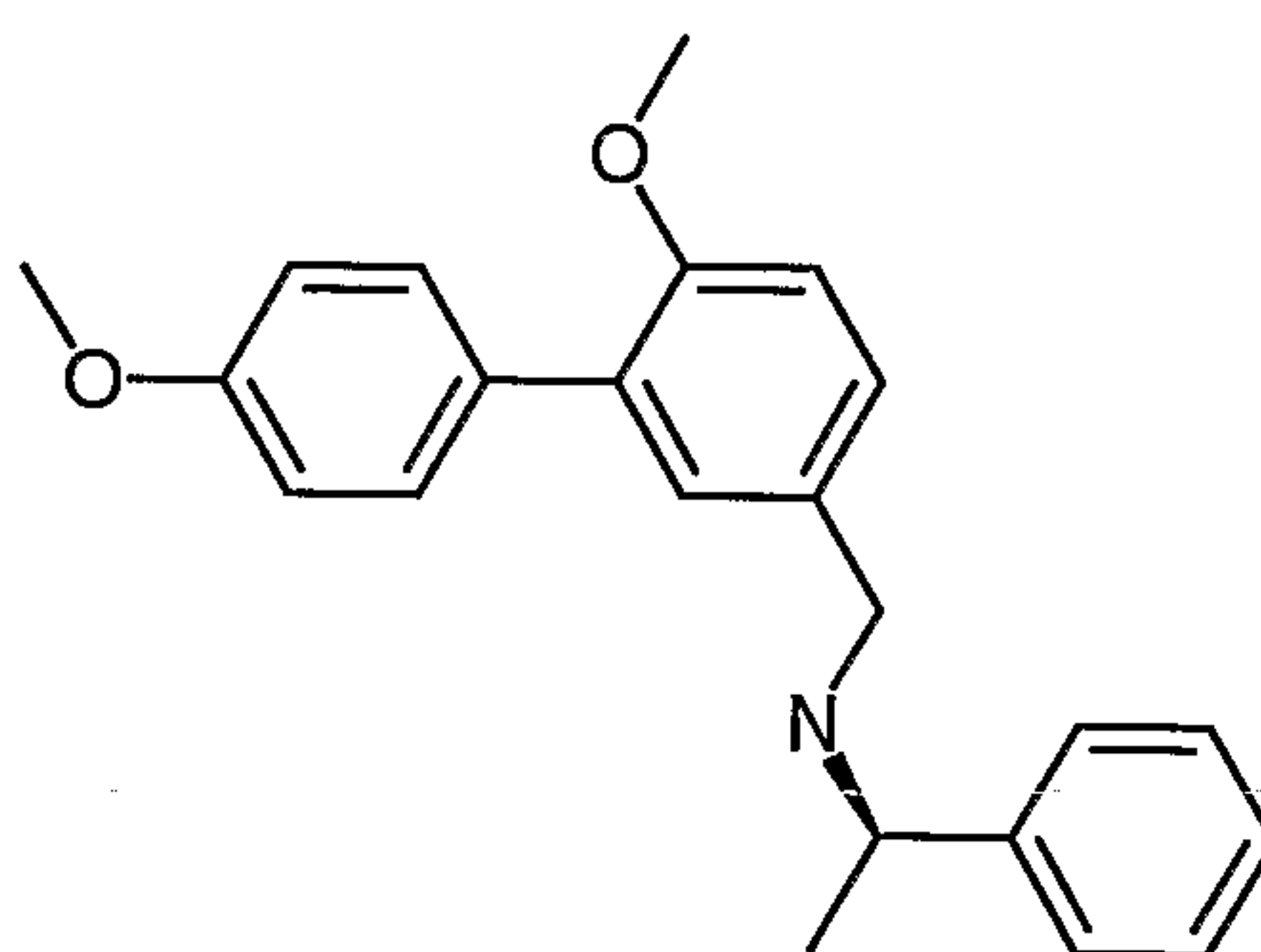
$C_{24}H_{27}NO_2$

- 5 Mass (calculated): [361]; (found): $[M+H^+] = 262$;
 NMR (400 MHz, MeOH- d_4): 1.55 (3H, d, $J=7$ Hz, NCHCH₃); 2.5 (3H, s, aryl-CH₃) 3.65 and 3.75 (2H, dd, $J=12$ Hz, CH₂N); 3.9 (3H, s, MeO); 3.9 (1H, m, NCHMe); 3.95 (3H, s, MeO); 7.05-7.15 (3H, m, aryl-H); 7.3-7.45 (6H, m, aryl-H); 7.62 (2H, d, $J=7$ Hz, aryl-H).

10

Example 8

(R)-*N*-(1-Phenylethyl)-*N*-((4-methoxy-3-(4'-methoxyphenyl)phenyl)methyl)amine



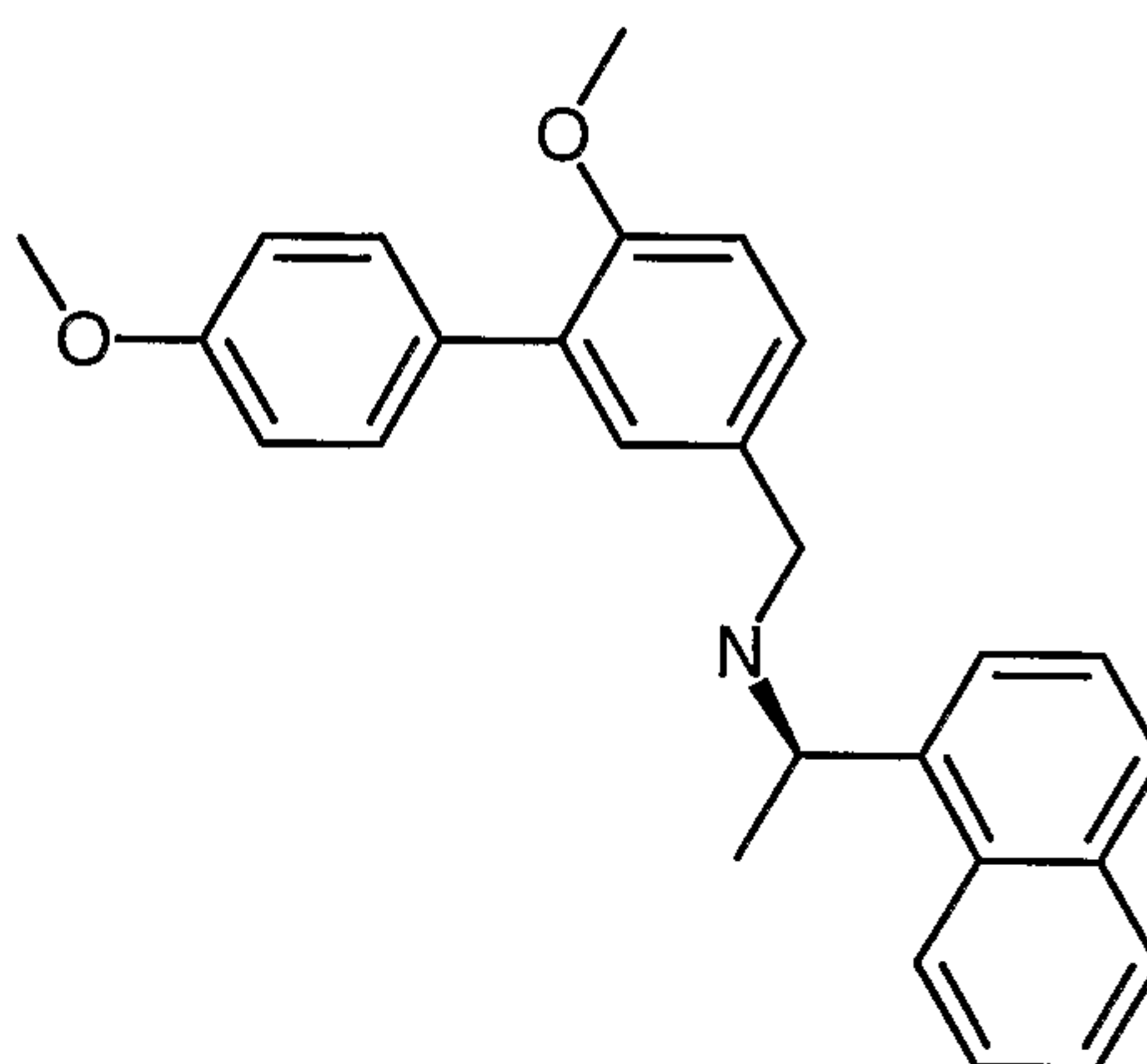
- 15 The title compound was prepared from 4-methoxy-3-(4-methoxyphenyl)-benzaldehyde and (R)- α -methylbenzylamine according to general procedure A.
 $C_{23}H_{25}NO_2$
 Mass (calculated): [347]; (found): $[M+H^+] = 348$.
 NMR (400 MHz, MeOH- d_4): 1.55 (3H, d, $J=7$ Hz, NCHCH₃); 2.5 (3H, s, aryl-CH₃) 3.65 and 3.75 (2H, dd, $J=12$ Hz, CH₂N); 3.9 (3H, s, MeO); 3.9 (1H, m, NCHMe); 3.95 (3H, s, MeO); 7.05-7.15 (3H, m, aryl-H); 7.3-7.45 (6H, m, aryl-H); 7.62 (2H, d, $J=7$ Hz, aryl-H).

25

- 40 -

Example 9

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(4'-methoxyphenyl)-phenylmethyl)amine



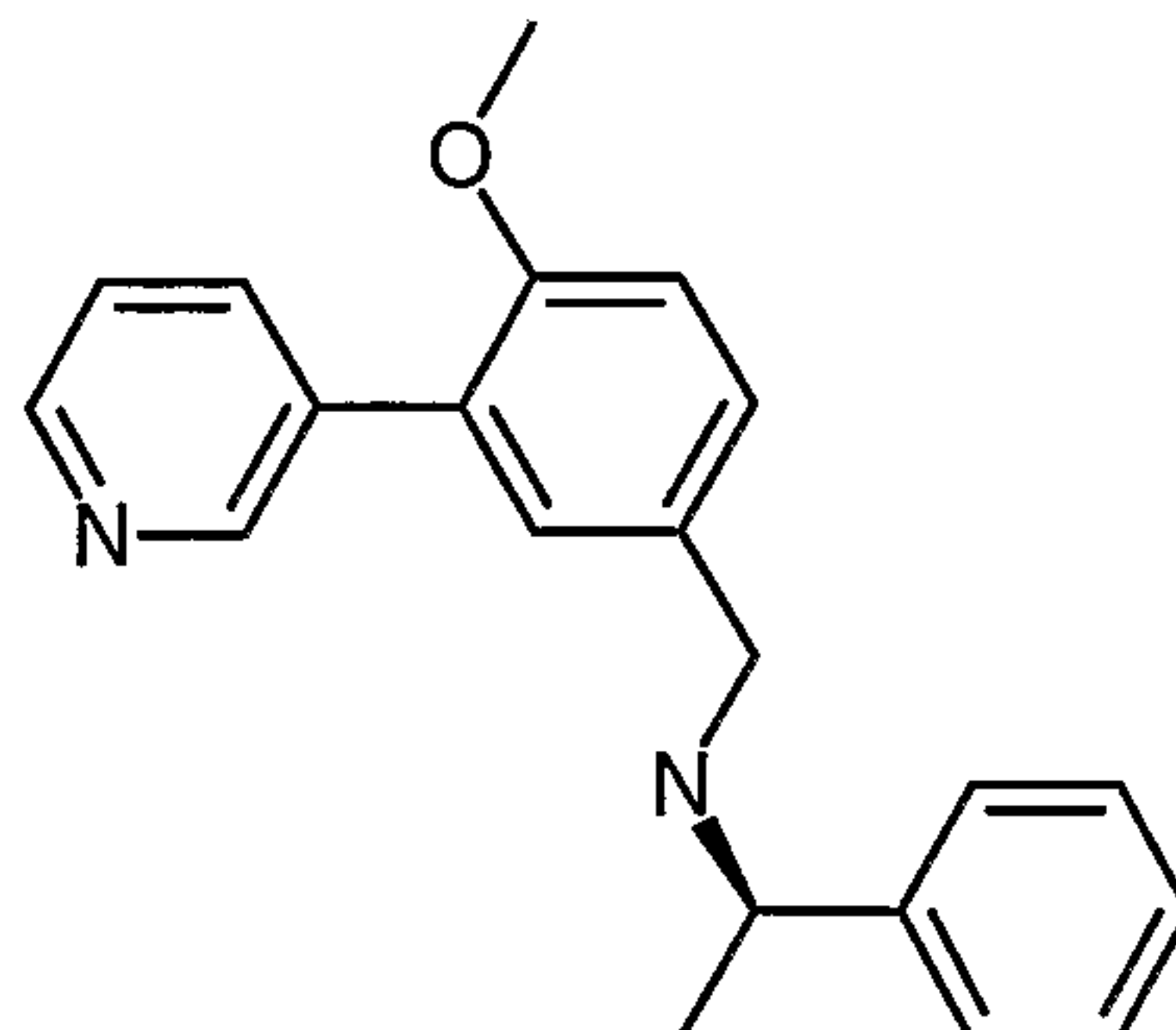
5

The title compound was prepared from 4-methoxy-3-(4-methoxyphenyl)-benzaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure A.

$C_{27}H_{27}NO_2$

- 10 Mass (calculated): [397]; (found): $[M+H^+] = 398$.
 NMR (400 MHz, MeOH- d_4): 1.65 (3H, d, $J=7$ Hz, NCHCH₃); 3.8 and 3.85 (2H, dd, $J=15$ Hz, CH₂N); 3.9 (3H, s, MeO); 4 (3H, s, MeO); 3.9 (1H, m, NCHMe); 4.85 (1H, q, $J=7$ Hz, NCHMe); 7.05 (2H, d, $J=7$ Hz, aryl-H); 7.15 (1H, d, $J=7$ Hz, aryl-H); 7.25 (1H, d, $J=1$ Hz, aryl-H); 7.35 (1H, dd, $J=1$ and 7 Hz, aryl-H); 7.5 (2H, d, $J=7$ Hz, aryl-H); 7.55-7.7 (2H, m, naphthyl-H); 7.7 (1H, t, $J=7$ Hz, naphthyl-H); 7.9 (1H, d, $J=7$ Hz, naphthyl-H); 7.95 (1H, d, $J=7$ Hz, naphthyl-H); 8.05 (1H, d, $J=7$ Hz, naphthyl-H); 8.15 (1H, d, $J=7$ Hz, naphthyl-H).
- 15

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Example 10**(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(pyrid-3-yl)phenyl)methyl)amine**

The title compound was prepared from 4-methoxy-3-(3-pyridyl)benzaldehyde and
 5 (R)- α -methylbenzylamine according to general procedure A.

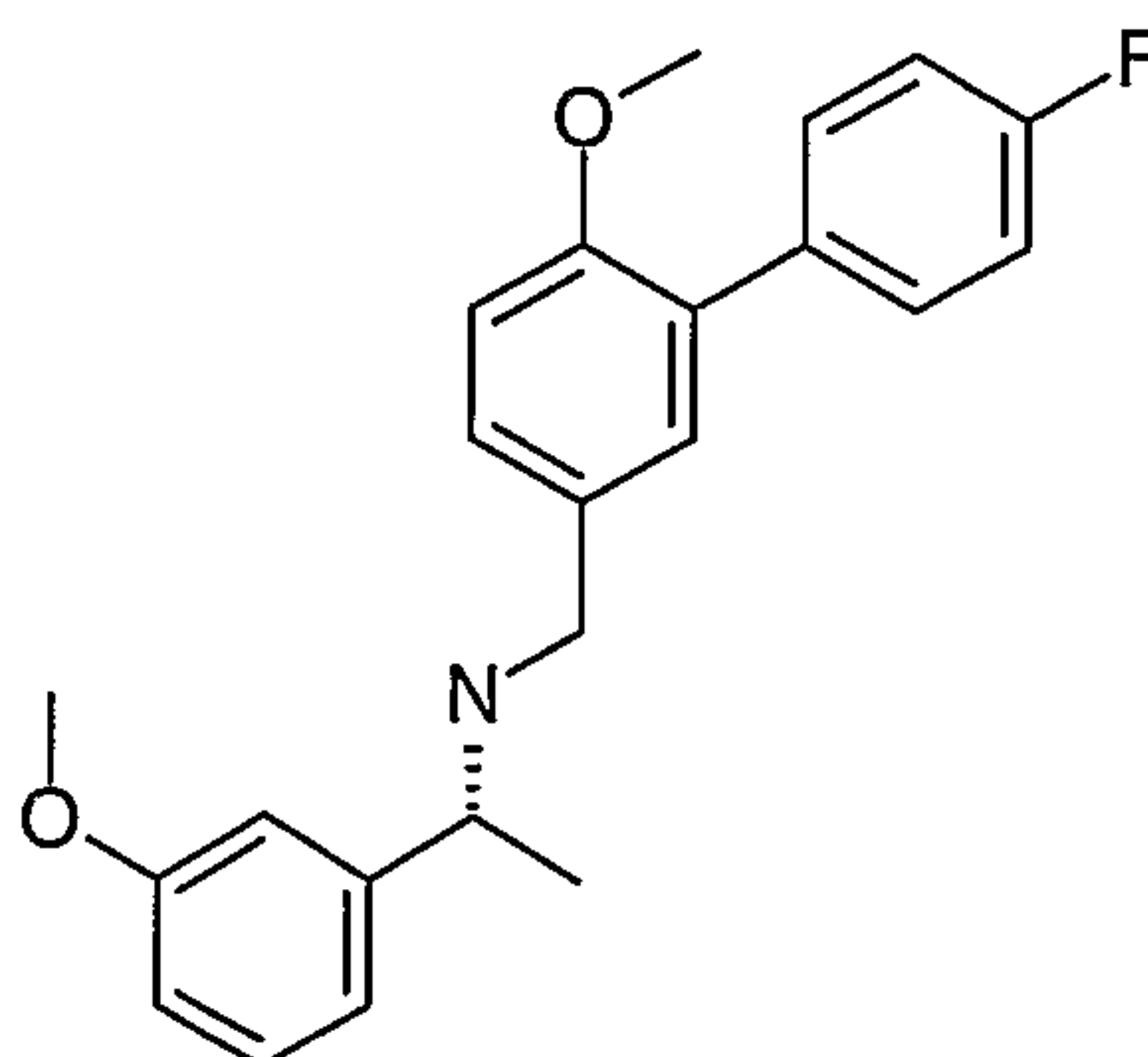
$C_{21}H_{22}N_2O$

Mass (calculated): [318]; (found): $[M+H^+] = 319, 198$.

NMR (400 MHz, MeOH- d_4): 1.75 (3H, d, $J=7$ Hz, NCHCH₃); 3.92 (3H, s, MeO);
 3.55 and 4.2 (2H, dd, $J=10$ Hz, CH₂N); 4.5 (1H, q, $J=4.5$ Hz; NCHMe); 3.95
 10 (3H, s, MeO); 7.3 (1H, d, $J=7$ Hz, aryl-H); 7.45-7.65 (7H, m, aryl-H); 8.05 (1H,
 bt, pyridyl-H); 7.75 (1H, d, $J=7$ Hz, pyridyl-H); 8.8 (1H, bs, pyridyl-H); 9.05
 (1H, bs, pyridyl-H).

Example 11

15 **(R)-N-(1-((3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(4'-fluorophenyl)-
 phenyl)methyl)amine**



- 42 -

The title compound was prepared from 3-(4-fluorophenyl)-4-methoxybenzaldehyde and (R)-3-methoxy- α -methylbenzylamine according to general procedure C.

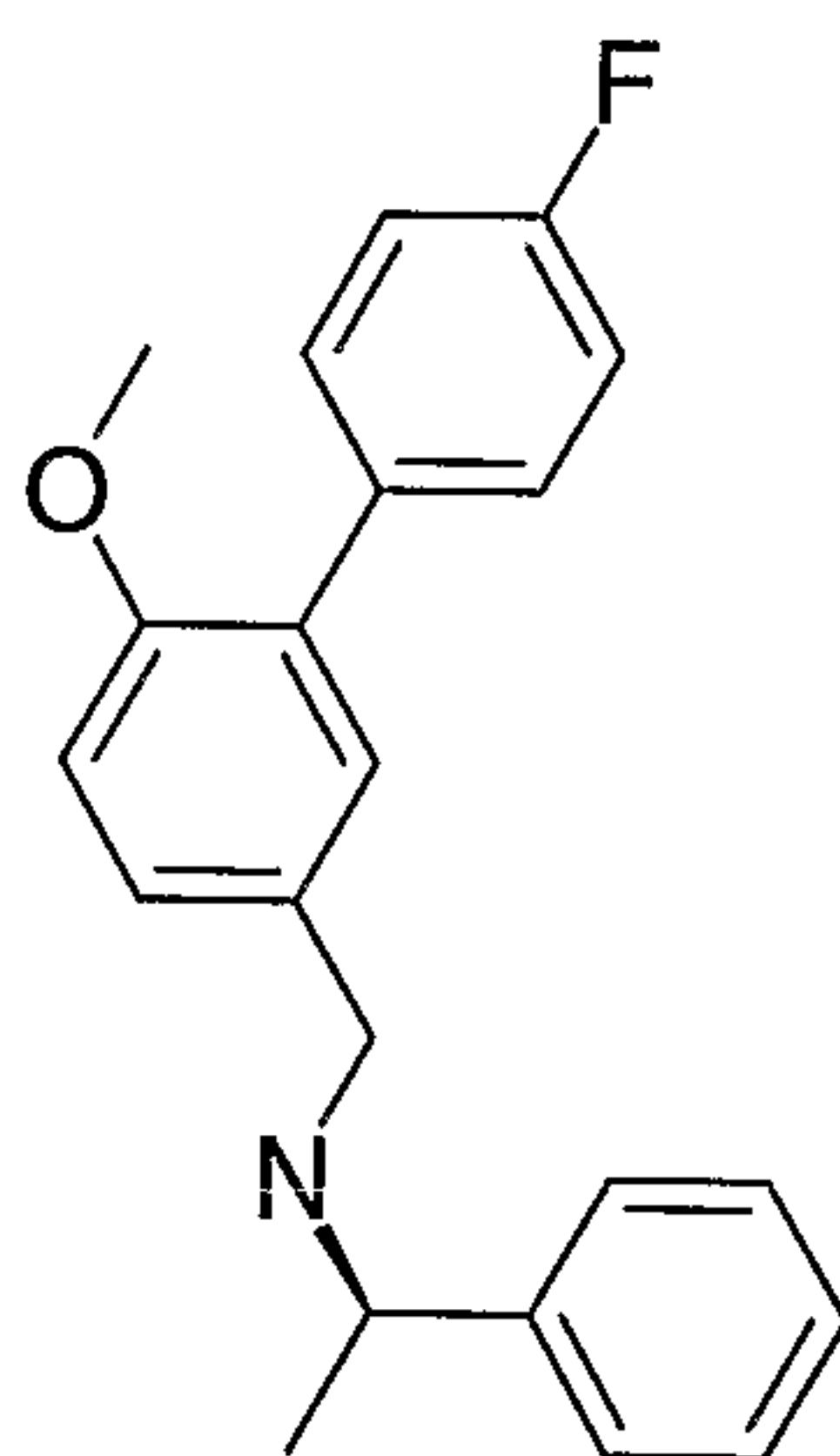
$C_{23}H_{24}FNO_2$ Mass (calculated): [365]; (found): $[M+H^+] = 366$, 215 base peak

5 NMR (400 MHz, $CDCl_3$): 1.4 (3H, d, $J=7$ Hz, $NCHCH_3$); 3.65 and 3.75 (2H, dd, $J=12$ Hz, CH_2N); 3.82 (3H, s, MeO); 3.85 (3H, s, MeO); 3.8-3.9 (1H, m, $NCHMe$); 6.85 (1H, dd, $J=7$ and 2 Hz, aryl-H); 6.9-7.0 (3H, m, aryl-H); 7.1-7.2 (2H, m, aryl-H); 7.2-7.35 (3H, m, aryl-H); 7.5-7.55 (2H, m, aryl-H).

10

Example 12

(R)-*N*-(1-Phenylethyl)-*N*-((4-methoxy-3-(4'-fluorophenyl)phenyl)methyl)amine



The title compound was prepared from 3-(4-fluorophenyl)-4-methoxybenzaldehyde and (R)- α -methylbenzylamine according to general procedure C.

$C_{22}H_{22}FNO$ Mass (calculated): [335]; (found): $[M+H^+] = 336$, 215 base peak

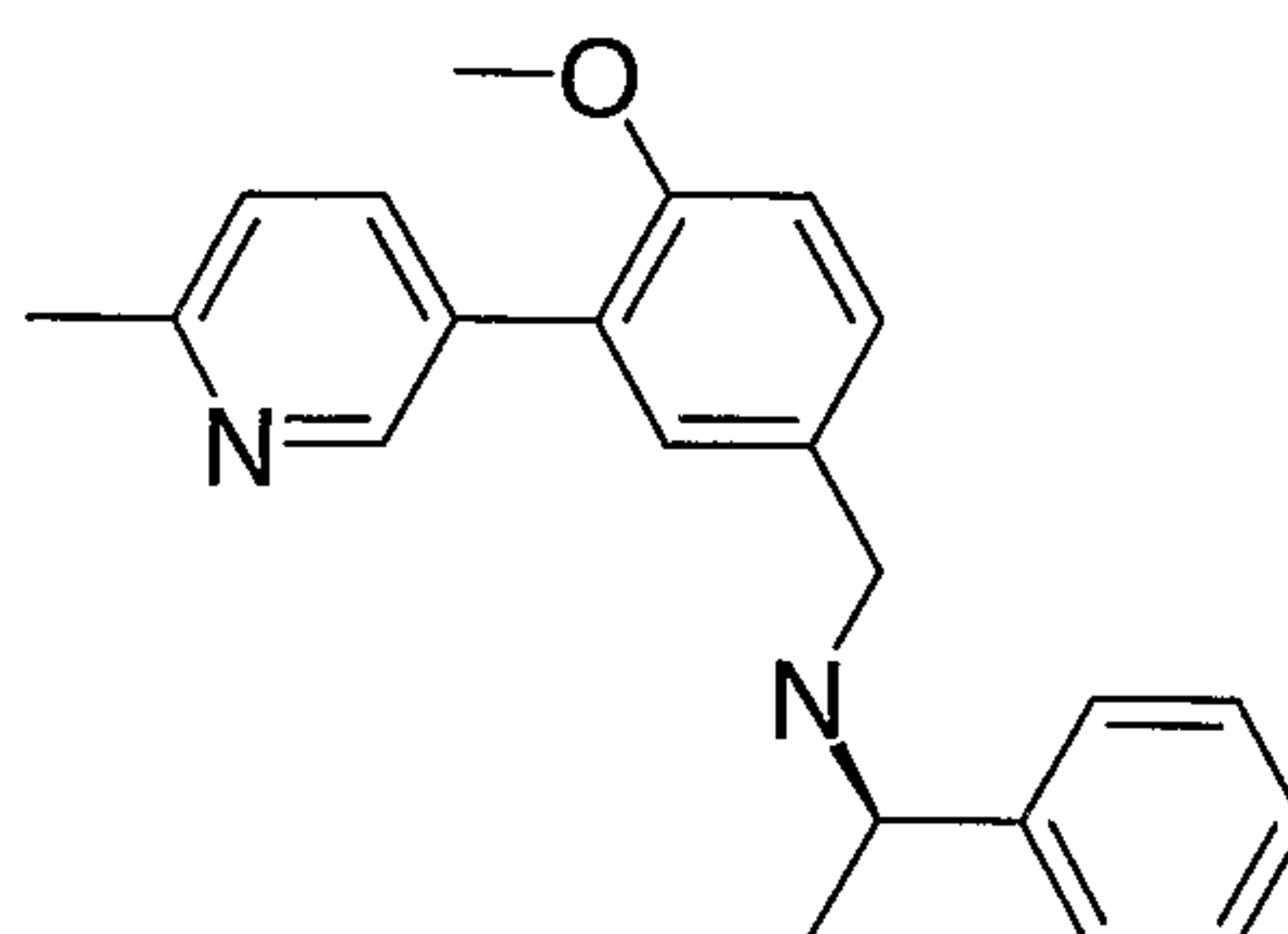
15 NMR (400 MHz, $CDCl_3$): 1.35 (3H, d, $J=7$ Hz, $NCHCH_3$); 3.5 and 3.6 (2H, dd, $J=11$ Hz, $J=7$ Hz; CH_2N); 3.7 (3H, s, MeO); 4.82 (1H, q, $J=7$ Hz; $NCHMe$); 6.85 (1H, d, $J=7$, aryl-H); 7.0 (2H, t, $J=7$ Hz; aryl-H); 7.15 (1H, d, $J=2$ Hz, aryl-H);

20 7.15-7.25 (2H, m, aryl-H); 7.25-7.35 (4H, m, aryl-H); 7.5 (2H, dd, $J=7$ and 6 Hz, aryl-H).

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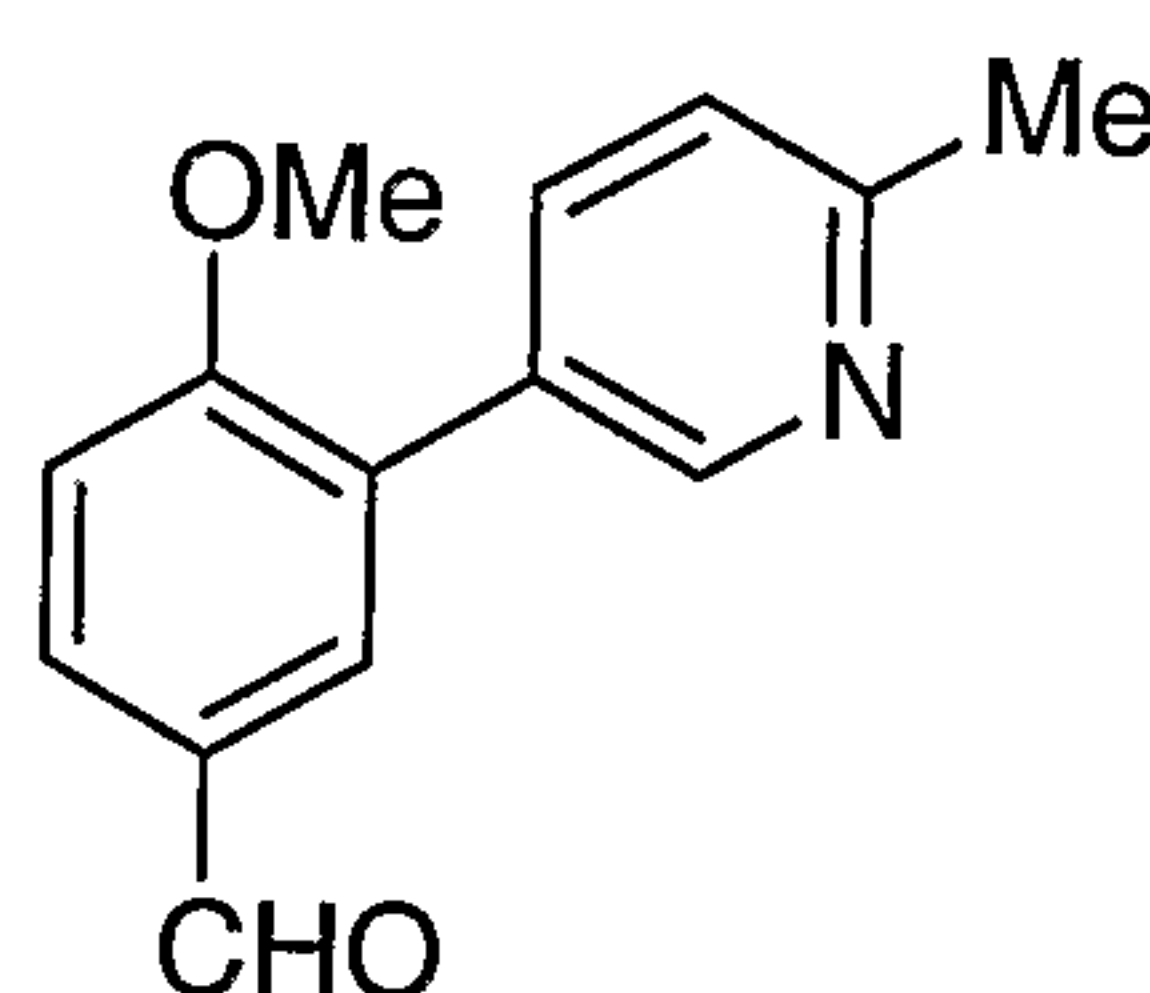
Example 13

R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(2'-methylpyrid-5'-yl)phenylmethyl)-amine



5 (

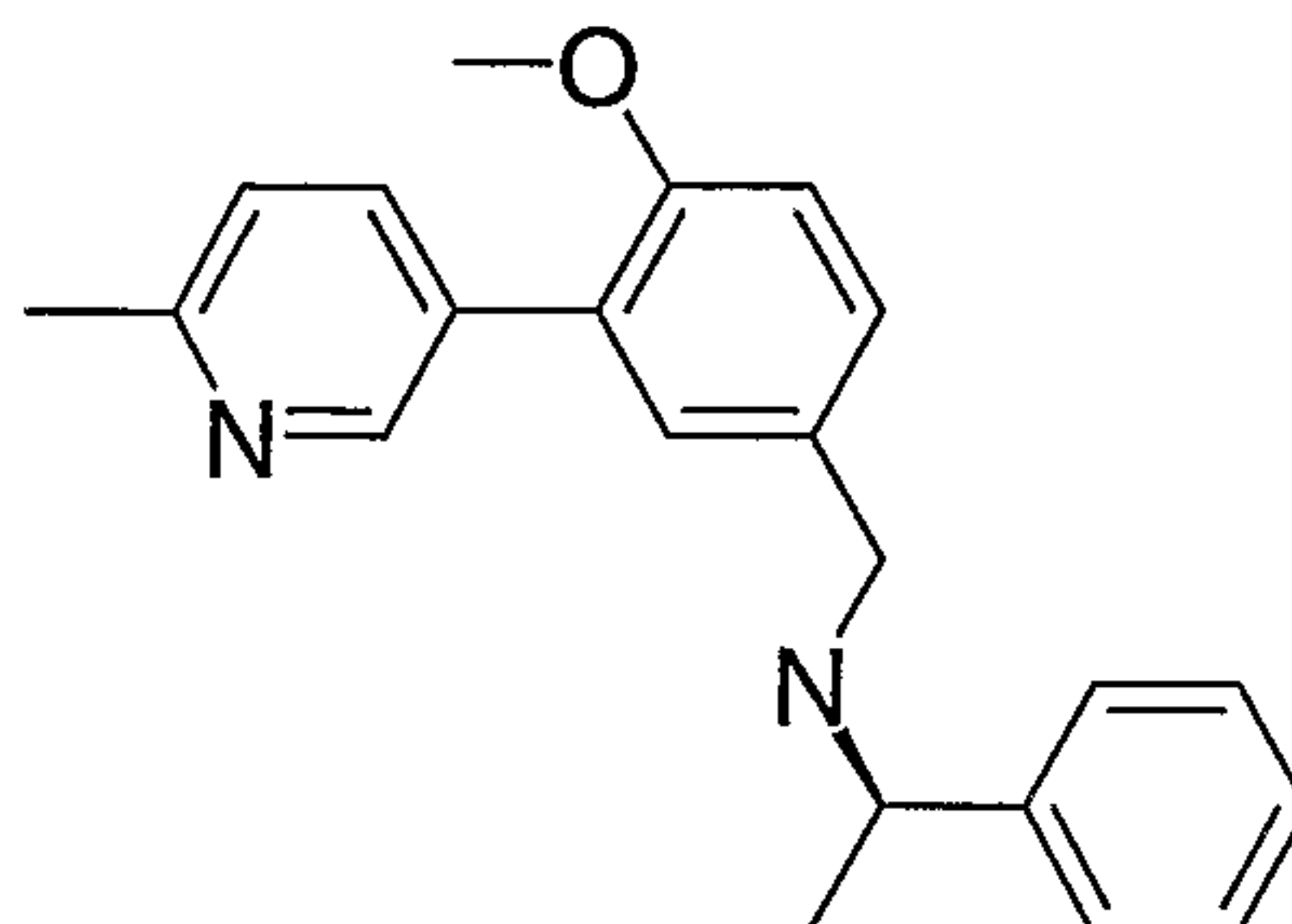
Step 1) 4-Methoxy-3-(1-methylpyrid-5-yl)benzenecarboxaldehyde:



- 10 To a degassed solution of 5-bromo-2-methylpyridine (2.75 g, 15 mmol) and potassium carbonate (4.5 g, 33 mmol) in toluene (70 mL) a catalytic amount of Pd(PPh₃)₄ (0.17 g, 0.15 mmol) was added and the solution was degassed for further 5 minutes. A degassed solution of 5-formyl-2-methoxybenzeneboronic acid (prepared according to Keseru, G.M. *et al. Tetrahedron* (48), 2, 913-922
- 15 (1992))(2.7 g, 15 mmol) in ethanol (30 mL) was then added and the mixture was refluxed for 15 hours. The residue was extracted into ethyl acetate and washed with saturated sodium bicarbonate solution and dried over sodium sulphate. The solvent was removed under reduced pressure and the crude was purified by column chromatography (silica, THF/DCM 2/1) to afford 2 g of pale yellow solid.
- 20 C₁₄H₁₃NO₂ Mass (calculated) [227]; (found) [M+H⁺] = 228; Lc Rt = 1.0, 92%. NMR (400 MHz, MeOH-d₄): 2.65 (3H, s, Me-pyridine); 4.05 (3H, s, MeO); 7.35 (1H, d, J=10Hz, pyridyl-H); 7.45 (1H, 2, J=7Hz, aryl-H); 7.95 (1H, m, pyridyl-H); 8 (1H, d, J=2Hz ; aryl-H); 8.1 (1H, dd, J=2 and 7 Hz, aryl-H); 8.65 (1H, d, J=2Hz, -H); 10 (1H, s, CHO).

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Step 2) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(2'-methylpyrid-5'-yl)-phenylmethyl)-amine



5

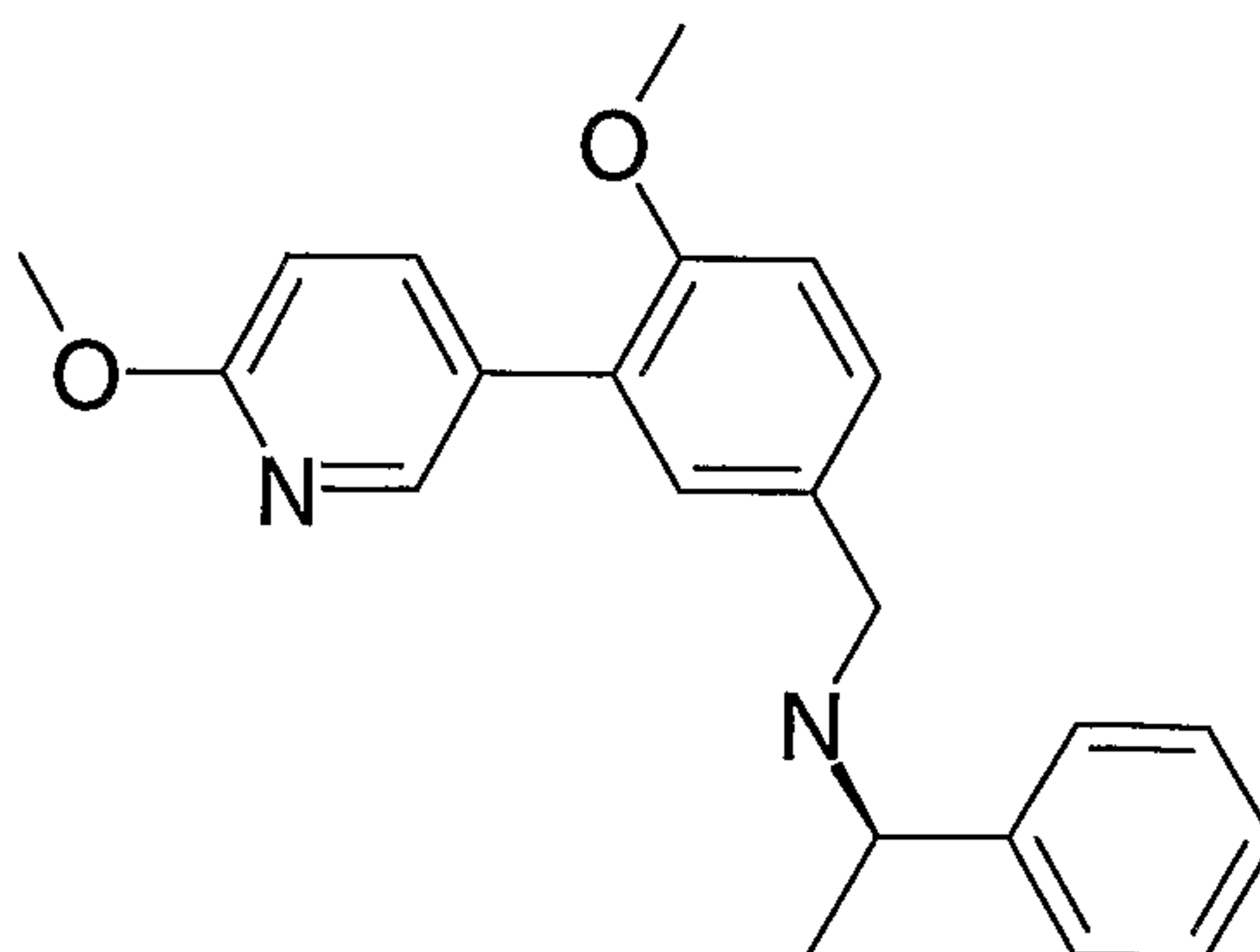
The title compound was prepared from 4-methoxy-3-(1-methylpyrid-5-yl)-benzenecarboxaldehyde and (R)- α -methylbenzylamine according to general procedure C.

10 $C_{22}H_{24}N_2O$ Mass (calculated): [332]; (found):): $[M+H^+] = 333$ NMR (400 MHz, $CDCl_3$): 1.4 (3H, d, $J=6.5$ Hz, $NCHCH_3$); 2.65 (3H, s, pyridyl- CH_3); 3.61 and 3.67 (2H, dd, $J = 13$ Hz, CH_2N); 3.82 (3H, s, MeO); 3.86 (1H, q, $J=6.5$ Hz, CH_3CH); 6.45 (1H, d, $J=8.5$ Hz); 7.2-7.35 (4H, m, aryl-H); 7.35-7.4 (4H, m, aryl-H); 7.77 (dd, 1H, $J=2.2$ and 8.1 Hz, aryl-H); 8.66 (1H, d, $J=1.8$ Hz, aryl-H).

15

Example 14

(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(2'-methoxypyrid-5'-yl)phenylmethyl)-amine



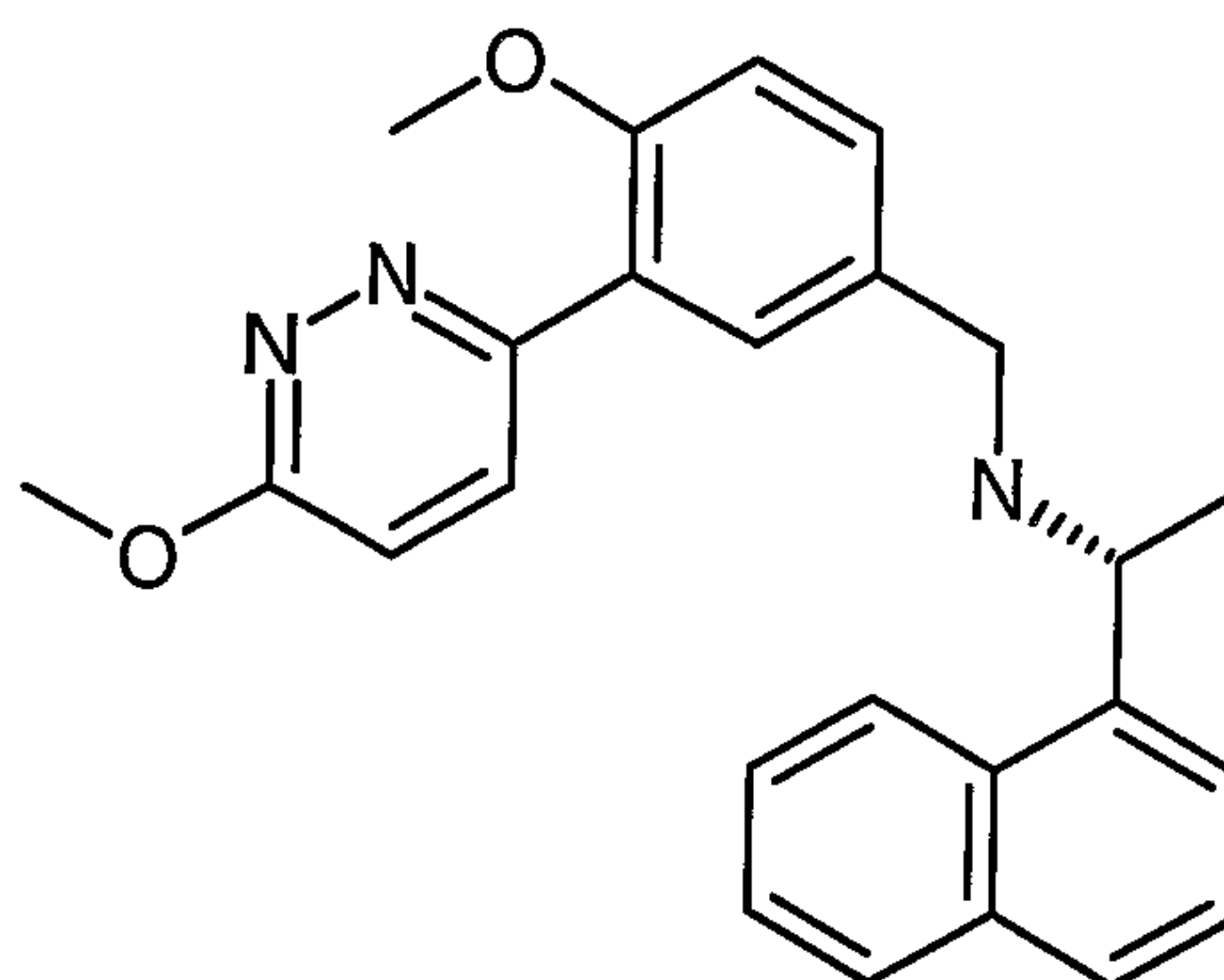
20 The title compound was prepared from 4-methoxy-3-(6-methoxy(3-pyridyl))-benzaldehyde and (R)- α -methylbenzylamine according to general procedure C.

- 45 -

$C_{22}H_{24}N_2O_2$ Mass (calculated): [348]; (found): $[M+H^+] = 349$, 228; NMR (400 MHz, $CDCl_3$): 1.32 (3H, d, $J = 6.8$ Hz, $NCHCH_3$); 3.5 and 3.57 (2H, dd, $J = 13$ Hz, CH_2N); 3.72 (3H, s, OCH_3); 3.78 (1H, q, $J = 6.8$ Hz, $CHCH_3$); 6.7 (1H, dd, $J = 0.6$ and 8.6 Hz, aryl-H); 6.8 (1H, d, $J = 8.4$ Hz, aryl-H); 7.10-6.35 (7H, m, aryl-H); 7.7 (1H, dd, $J = 2.5$ and 8.6 Hz, aryl-H); 8.2 (1H, dd, $J = 1.8$ and 8.2 Hz, aryl-H).

Example 15

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(6'-methoxypyridazin-3'-yl))phenylmethyl)amine

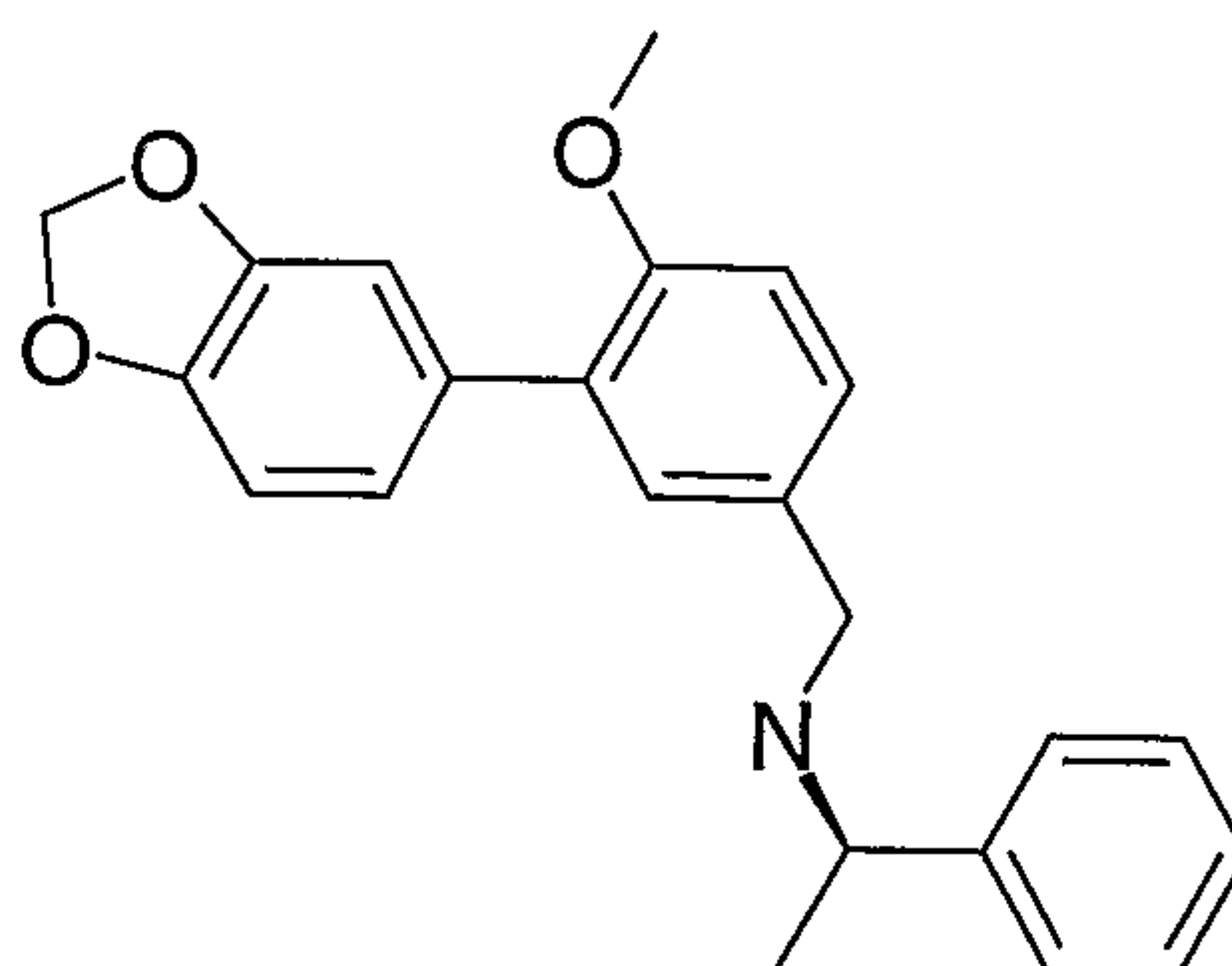


The title compound was prepared from 4-methoxy-3-(6-methoxypyridazin-3-yl)benzaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure A.

$C_{25}H_{25}N_3O_2$ Mass (calculated): [399]; (found): $[M+H^+] = 400$, $[2M+H^+] = 799$.

Example 16

(R)-N-(1-(Phenylethyl)-N-((4-methoxy-3-(3,4-methylenedioxyphenyl))phenylmethyl)amine



- 46 -

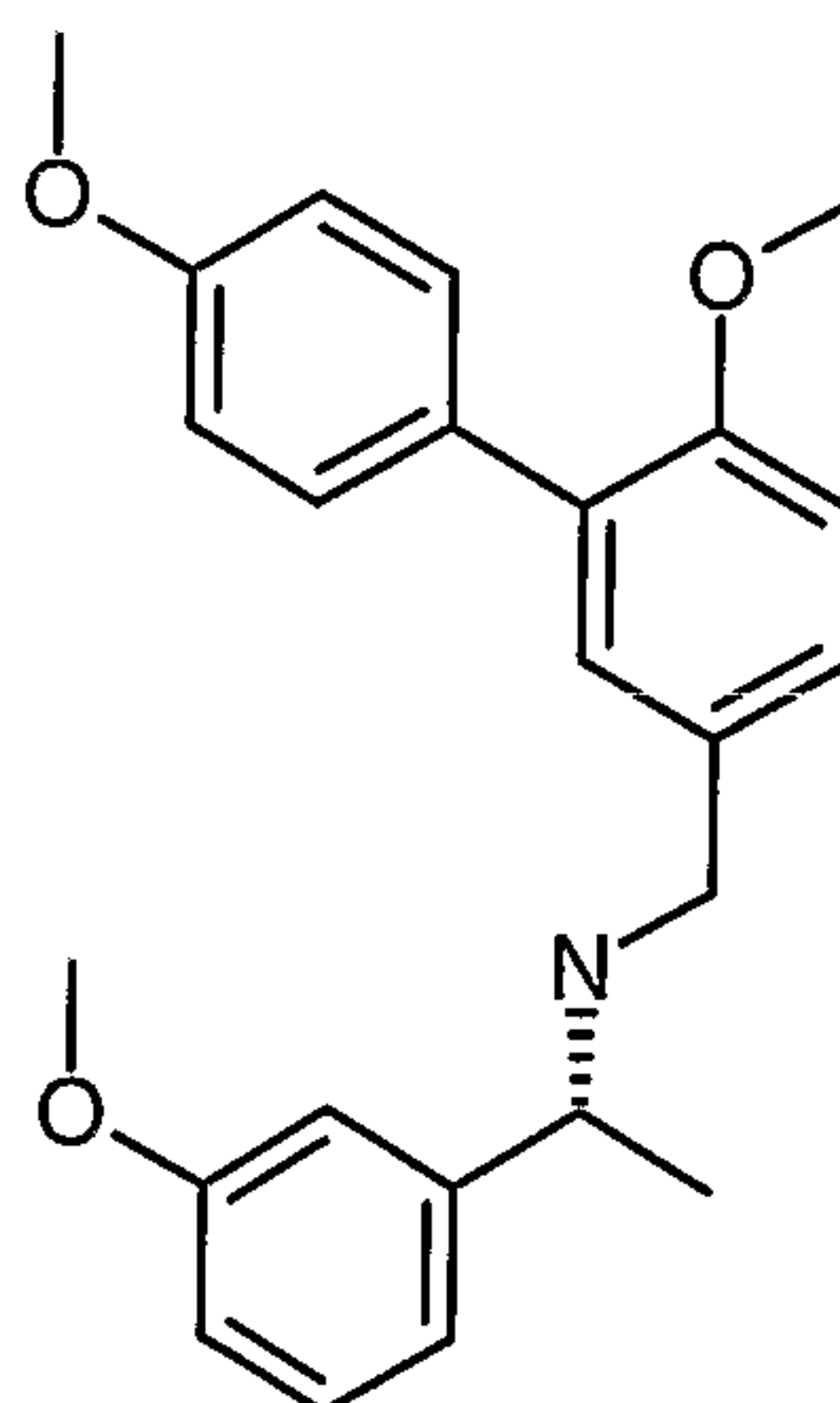
The title compound was prepared from 3-(2H-benzo[d]1,3-dioxolan-5-yl)-4-methoxybenzaldehyde and (R)- α -methylbenzylamine according to general procedure B.

$C_{23}H_{23}NO_3$ Mass (calculated): [361]; (found): $[M+H^+] = 362$, 241 NMR (400
 5 MHz, $CDCl_3$): 1.29 (3H, d, $J = 6.8$ Hz, $CHCH_3$); 3.50 and 3.54 (2H, dd, $J = 13$ Hz, CH_2N); 3.72 (3H, s, CH_3O); 3.75 (1H, q, $J = 6.8$ Hz, $CHCH_3$); 5.90 (2H, s, OCH_2O); 6.78 (1H, d, $J = 7.7$ Hz, aryl-H); 6.83 (1H, d, $J = 7.7$ Hz, aryl-H); 6.9 (1H, dd, $J = 1.7$ and 7.7 Hz, aryl-H); 6.97 (1H, d, $J = 1.7$ Hz, aryl-H); 7.10-7.15 (2H, m, aryl-H); 7.15-7.22 (1H, m, aryl-H); 7.24-7.31 (4H, m, aryl-H).

10

Example 17

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(4'-methoxyphenyl)phenyl)methyl)amine



15

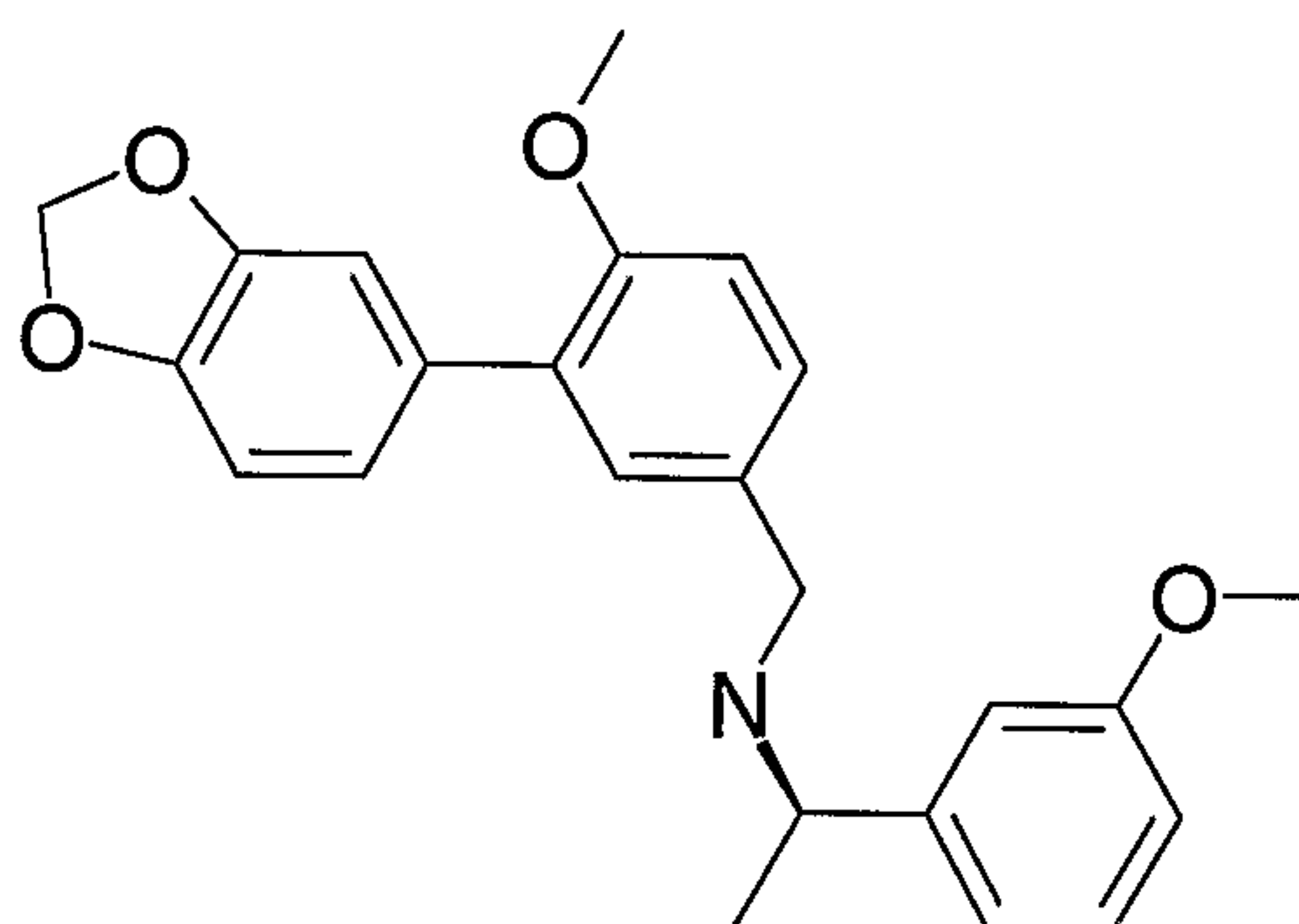
The title compound was prepared from 4-methoxy-3-(4-methoxyphenyl)-benzaldehyde and (R)-3-methoxy- α -methylbenzylamine according to general procedure A.

$C_{24}H_{27}NO_3$ Mass (calculated): [377]; (found): $[M+H^+] = 378$, $[M+MeCN + H^+] =$
 20 419.

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Example 18

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(4,5-methylenedioxyphenyl)phenyl)methyl)amine



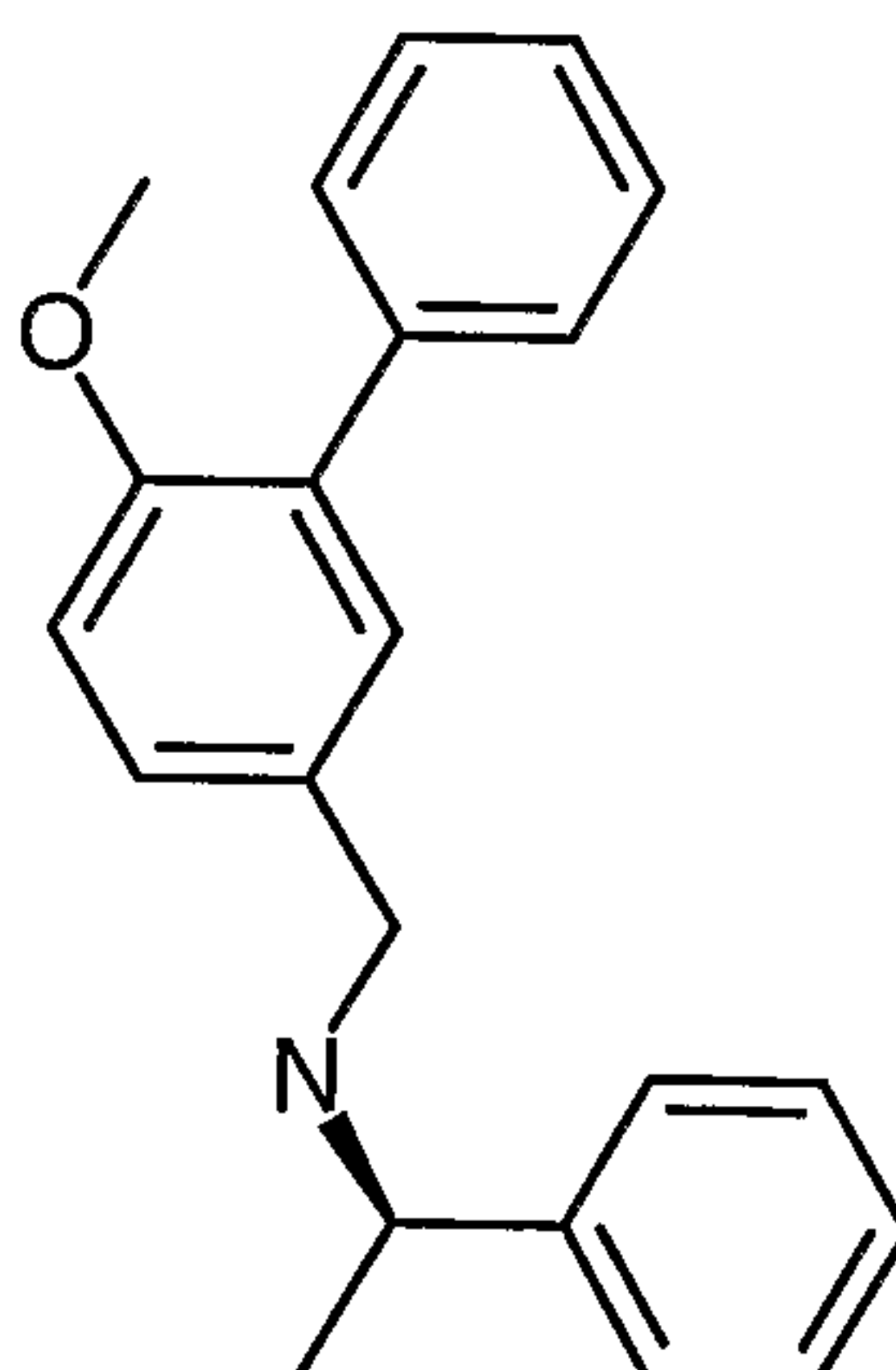
5

The title compound was prepared from 3-(2H-benzo[d]1,3-dioxolan-5-yl)-4-methoxybenzaldehyde and (R)-3-methoxy- α -methylbenzylamine according to general procedure B.

10 $C_{24}H_{25}NO_4$ Mass (calculated): [391]; (found): $[M+H^+] = 392$. NMR (400 MHz, $CDCl_3$): 1.35 (3H, d, $J = 6.8$ Hz, $NCHCH_3$); 3.4-3.8 (9H, m, OCH_3 , OCH_3 , $CHCH_3$, CH_2N); 5.9 (2H, s, OCH_2O); 6.7-7 (8H, m, aryl-H); 7.1-7.2 (2H, m, aryl-H).

Example 19

15 (R)-N-(1-Phenylethyl)-N-(4-methoxy-3-phenyl)phenylmethyl)amine



The title compound was prepared from 4-methoxy-3-phenylbenzaldehyde and (R)- α -methylbenzylamine according to general procedure A.

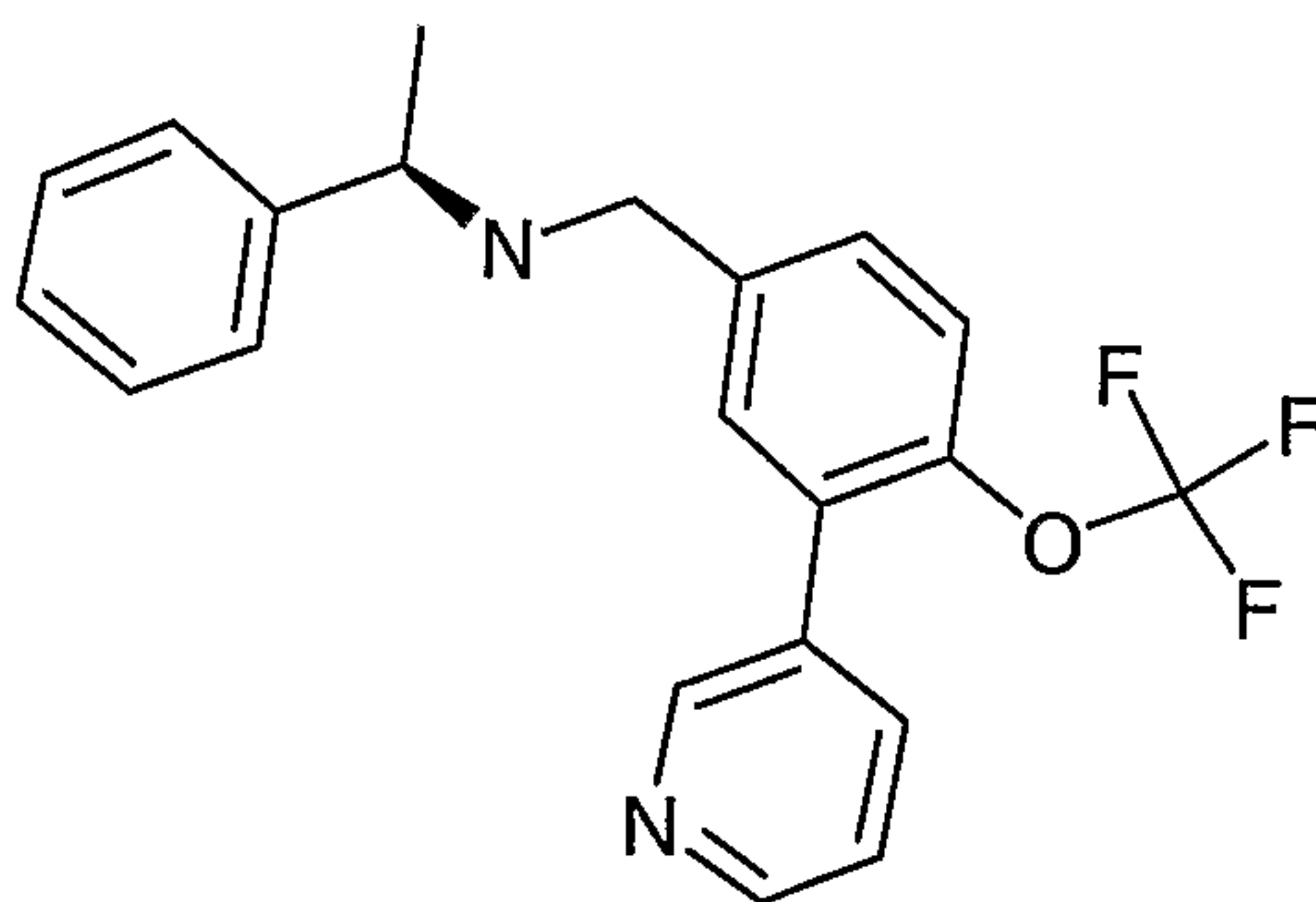
- 48 -

$C_{22}H_{23}NO$ Mass (calculated): [317]; (found): $[M+H^+] = 318, 197$ (base peak).

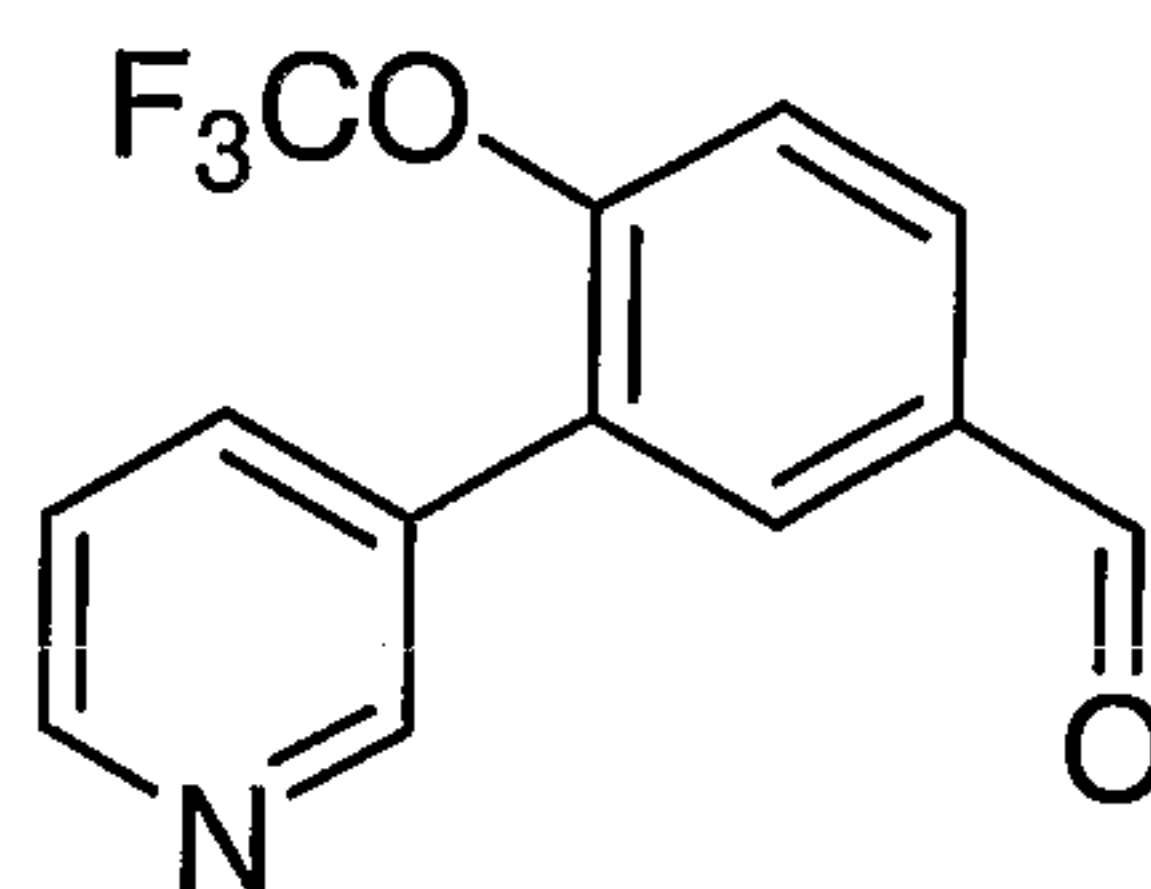
Example 20

(R)-N-(1-Phenylethyl)-N-((4-trifluoromethoxy-3-(pyrid-3-yl)phenyl)methyl)amine

5

Step 1) 4-Trifluoromethoxy-3-(pyrid-3-yl)benzaldehyde

10



A solution of 3-chloro-4-trifluoromethoxybenzaldehyde (3 g, 13.3 mmol) and 3-pyridylboronic acid (1.97 g, 16.0 mmol) in dioxane (70 mL) and 2M K_2CO_3 (20 mL) is degassed with nitrogen prior to addition of $Pd(PPh_3)_4$ (1.5 g, 1.33 mmol). The mixture was stirred at 100°C under nitrogen for 40 hours, then cooled and filtered on celite/silica and the filtrate concentrated under reduced pressure. The crude was purified by column chromatography (2/1 heptane/ethyl acetate) to give 1.51 g of title compound.

$C_{13}H_8F_3NO_2$ Mass (calculated): [267]; (found) $[M+H^+] = 268$ NMR (400 MHz, $CDCl_3$): 7.3-7.35 (1H, m, aryl-H); 7.4-7.45 (1H, m, aryl-H); 7.7-7.75 (1H, m, aryl-H); 7.9-8 (2H, n, aryl-H); 8.65 (1H, bs, aryl-H); 8.7 (1H, bs, aryl-H).

20

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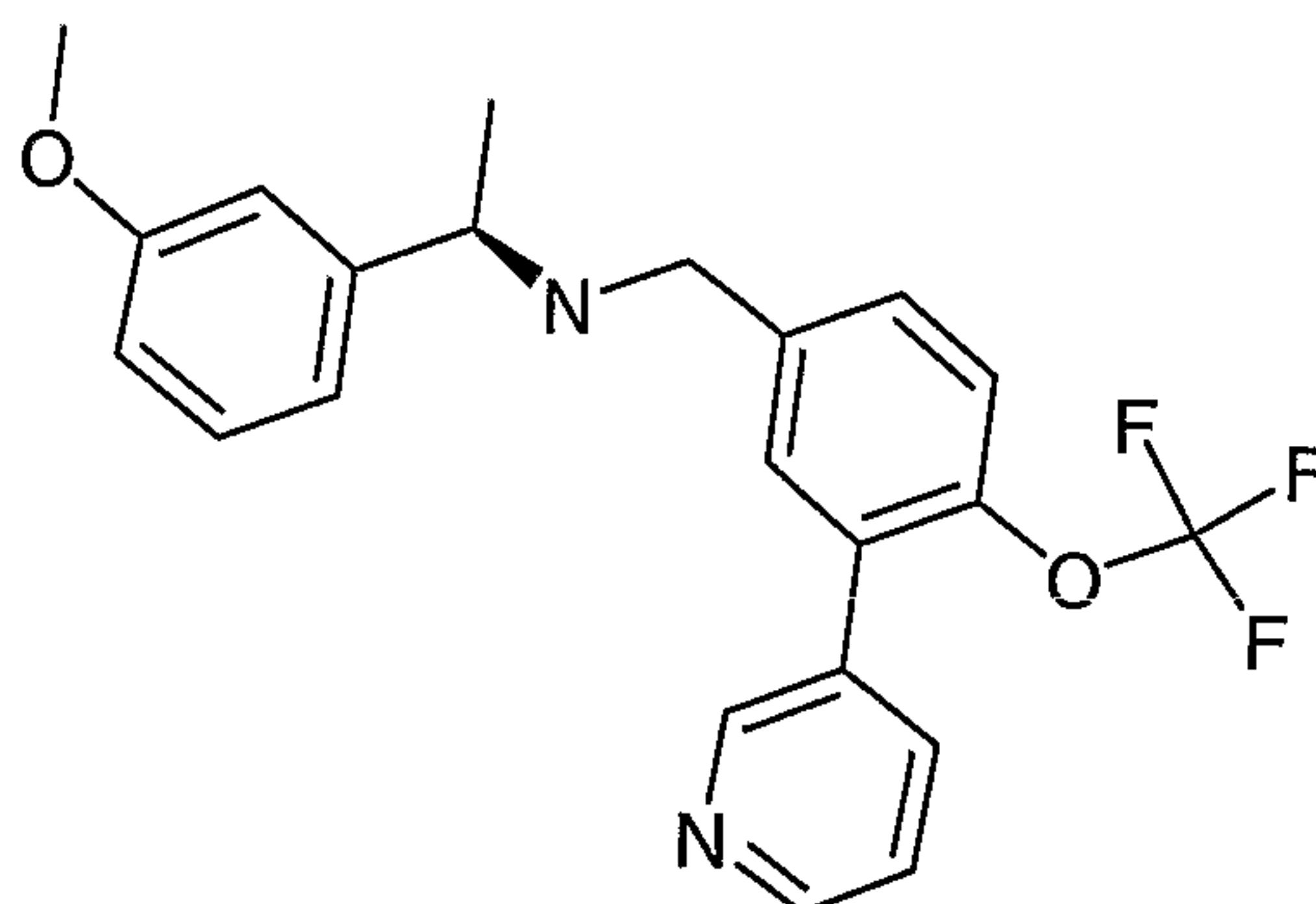
Step 2) (R)-N-(1-Phenylethyl)-N-((4-trifluoromethoxy-3-(pyrid-3-yl)phenylmethyl)amine

The title compound was prepared from 4-trifluoromethoxy-3-(pyrid-3-yl)benzenecarboxaldehyde and (R)- α -methylbenzylamine according to general procedure C.

$C_{21}H_{19}F_3N_2O$ Mass (calculated): [372]; (found): $[M+H^+] = 373$ NMR (400 MHz, $CDCl_3$): 1.3 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.6 (2H, s, CH_2N); 3.8 (1H, q, $J = 6$ Hz; $NCHMe$); 7.20-7.40 (9H, m, aryl-H); 7.7 (1H, dt, $J = 1$ and 8 Hz, aryl-H); 8.55 (1H, d, $J = 3$ Hz, aryl-H); 8.65 (1H, bs, aryl-H).

Example 21

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-trifluoromethoxy-3-(pyrid-3-yl)phenylmethyl)amine



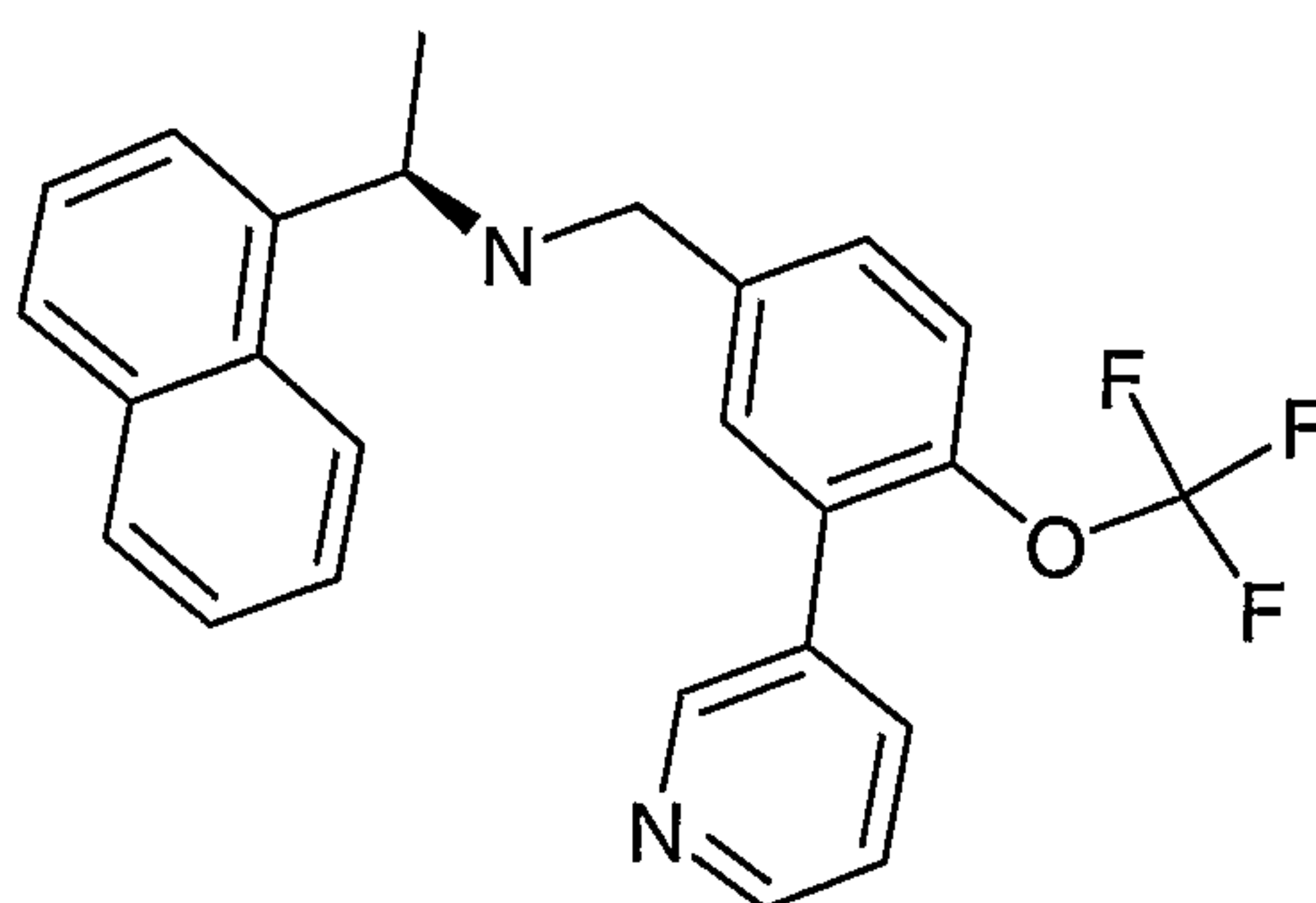
The title compound was prepared from 4-trifluoromethoxy-3-(pyrid-3-yl)benzenecarboxaldehyde and (R)-3-methoxy- α -methylbenzylamine according to general procedure C.

$C_{22}H_{21}F_3N_2O_2$ Mass (calculated): [402]; (found): $[M+H^+] = 403$ NMR (400 MHz, $CDCl_3$): 1.3 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.6 (2H, m, CH_2N); 3.7-3.8 (4H, m, $NCHMe$ and CH_3O); 6.7 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 6.8-6.9 (2H, m, aryl-H); 7.20-7.40 (5H, m, aryl-H); 7.7 (1H, dt, $J = 1$ and 8 Hz, aryl-H); 8.55 (1H, d, $J = 3$ Hz, aryl-H); 8.65 (1H, bs, aryl-H).

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Example 22

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-trifluoromethoxy-3-(pyrid-3-yl)phenyl)methyl)amine



5

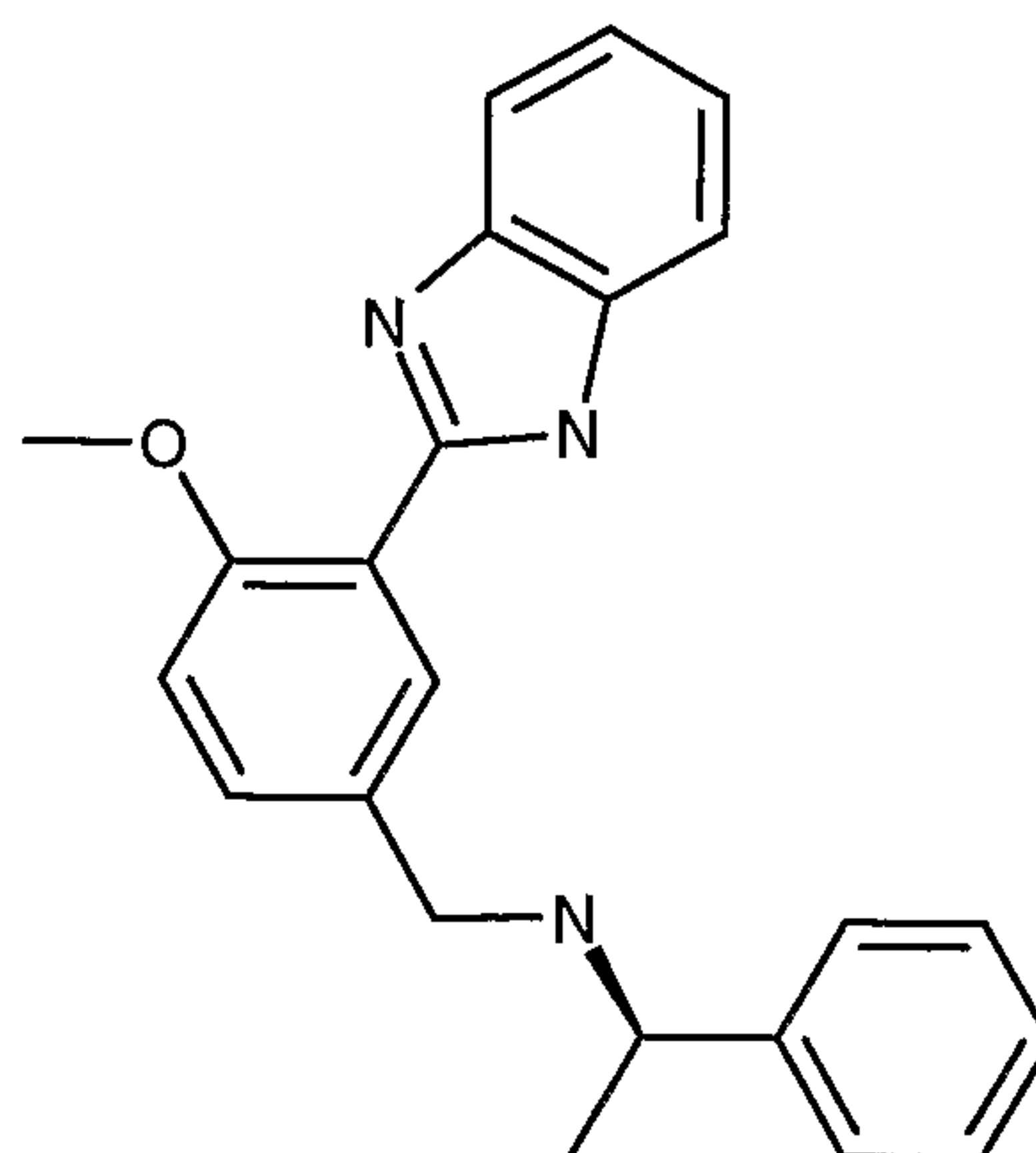
The title compound was prepared from 4-trifluoromethoxy-3-(pyrid-3-yl)benzene-carboxaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

$C_{25}H_{21}F_3N_2O$ Mass (calculated): [422]; (found): $[M+H^+] = 423$ NMR (400 MHz, $CDCl_3$): 1.45 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.65 and 3.75 (2H, dd, $J = 12$ Hz CH_2N); 4.65 (1H, q, $J = 6$ Hz; $NCHMe$); 7.30-7.40 (4H, m, aryl-H); 7.40-7.5 (3H, m, aryl-H); 7.6-7.7 (3H, m, aryl-H); 7.8-7.85 (1H, m, aryl-H); 8.05-8.1 (1H, m, aryl-H); 8.55 (1H, d, $J = 3$ Hz, aryl-H); 8.65 (1H, bs, aryl-H).

15

Example 23

(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(benzimidazol-2-yl)methyl)amine



Step 1) 4-Methoxy-3-(benzimidazol-2-yl)benzenecarboxaldehyde

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Pd(Ph₃)₄ (72 mg, 0.062 mmol) was added to a degassed solution of 2-chlorobenzimidazole (0.95 g, 6.25 mmol) in 1,2-dimethoxyethane (25 mL), followed by 2M Na₂CO₃ (15 mL) and 5-formyl-2-methoxybenzeneboronic acid (1.35 g, 7.5 mmol). The mixture was stirred at 115 C for 16 hours then more catalyst was added (2% mol) and reaction stirred for further 4 hours. The mixture was cooled and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure and the residue purified by column chromatography (1/1 hexane/ethyl acetate) to afford 0.285 g of title compound. C₁₅H₁₂N₂O₂ Mass (calculated): [252]; (found) [M+H⁺] = 253 NMR (400 MHz, CDCl₃): 4.1 (3H, s, CH₃O); 7.2 (1H, d, *J* = 8 Hz, aryl-H); 7.3-7.35 (2H, m, aryl-H); 7.5 (1H, m, aryl-H); 7.8 (1H, m, aryl-H); 8 (1H, dd, *J* = 2 and 8 Hz, aryl-H); 9 (1H, d, *J* = 1 Hz, aryl-H); 10 (1H, s, CHO); 10.4 (1H, bd, NH).

Step 2) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(benzimidazol-2-yl)methyl)amine

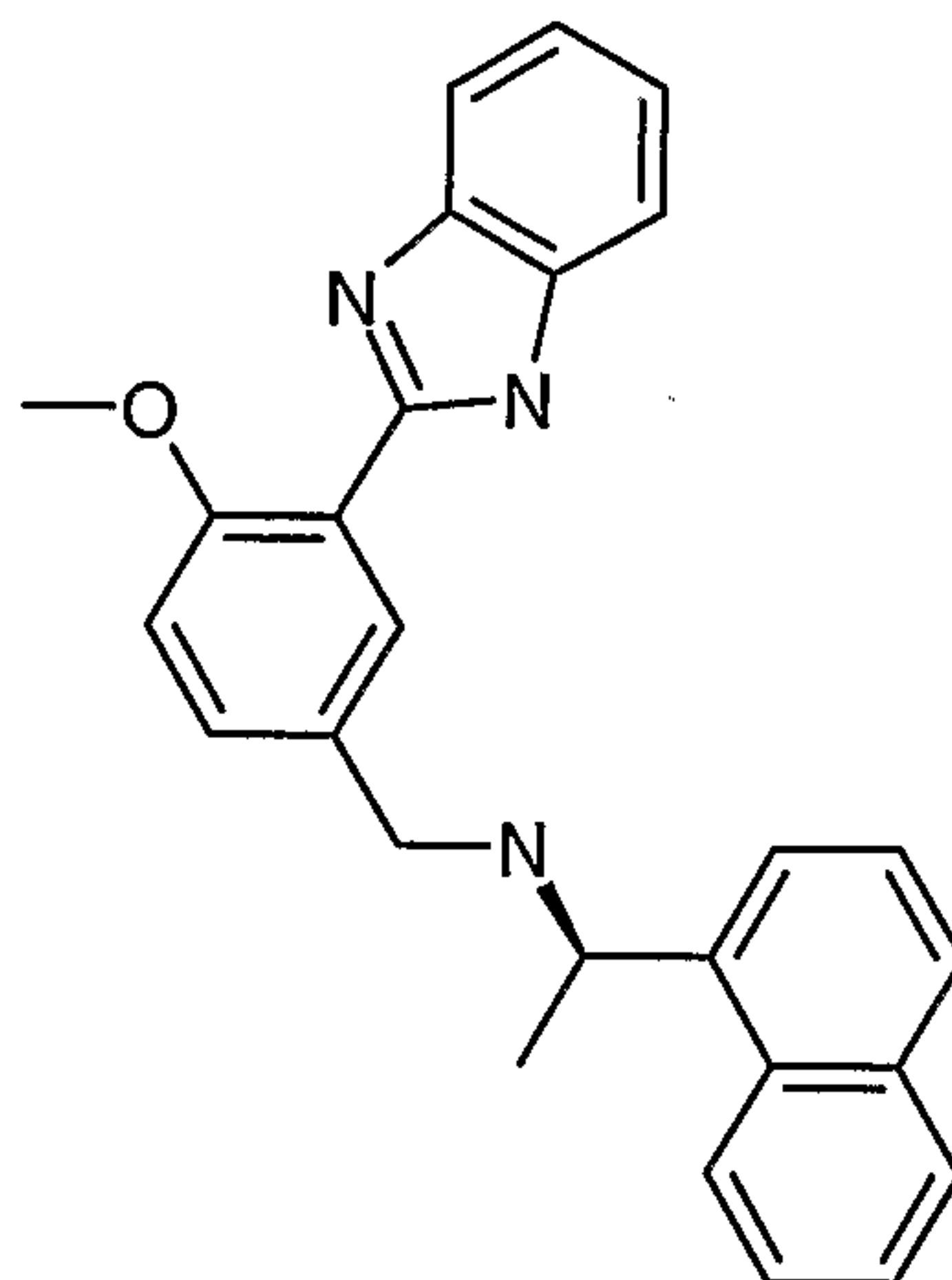
The title compound was prepared from 4-methoxy-3-(benzimidazol-2-yl)benzenecarboxaldehyde and (R)-α-methylbenzylamine according to general procedure C.

C₂₃H₂₃N₃O Mass (calculated): [357]; (found): [M+H⁺] = 358, 715 NMR (400 MHz, CDCl₃): 1.3 (3H, d, *J* = 6 Hz, NCHCH₃); 3.55 and 3.65 (2H, dd, *J* = 12 Hz, CH₂N); 3.75 (1H, q, *J* = 6 Hz; NCHMe); 4.0 (3H, s, CH₃O); 6.95 (1H, d, *J* = 8 Hz, aryl-H); 7.15-7.25 (3H, m, aryl-H); 7.25-7.35 (5H, m, aryl-H); 7.45 (1H, bd, aryl-H); 7.75 (1H, bd, aryl-H); 8.3 (1H, d, *J* = 1 Hz, aryl-H).

25

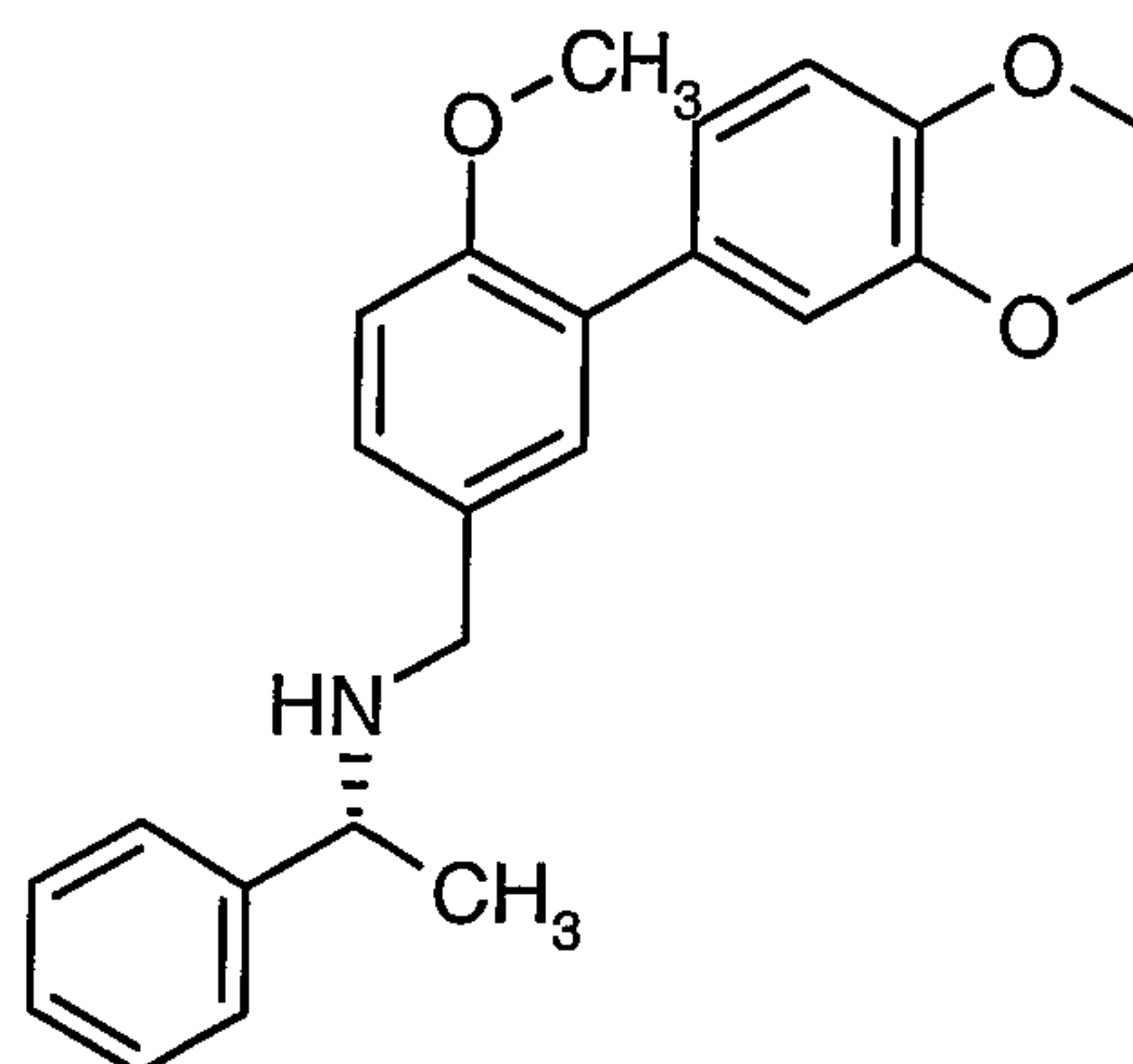
30

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Example 24**(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(benzimidazol-2-yl)lmethyl)amine**

The title compound was prepared from 4-methoxy-3-(benzimidazol-2-yl)benzenecarboxaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

$C_{27}H_{25}N_3O$ Mass (calculated): [407]; (found): $[M+H^+] = 408$ NMR (400 MHz, $CDCl_3$): 1.5 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.75 and 3.8 (2H, dd, $J = 12$ Hz, CH_2N); 4.1 (3H, s, CH_3O); 4.75 (1H, q, $J = 6$ Hz; $NCHMe$); 7.0 (1H, d, $J = 8$ Hz, aryl-H); 7.25-7.3 (2H, m, aryl-H); 7.45-7.55 (4H, m, aryl-H); 7.75-7.9 (4H, m, aryl-H); 8.2 (1H, d, $J = 8$ Hz, aryl-H); 8.55 (1H, d, $J = 1$ Hz, aryl-H).

Example 25**(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(1,4-benzodioxan-5-yl)lmethyl)amine**

Step 1) 4-methoxy-3-(1,4-benzodioxan-5-yl)benzenecarboxaldehyde

- 53 -

- A solution of 5-formyl-2-methoxybenzeneboronic acid (1 g, 5.6 mmol), 3,4-ethylenedioxybromobenzole (1 g, 4.65 mmol) and K_2CO_3 (1.6 g, 11.6 mmol) in ethanol (20 mL) and toluene (40 mL) was degassed prior to addition of $Pd(Ph_3)_4$ (54 mg, 0.046 mmol). The mixture was refluxed for 24 hours then cooled and
- 5 filtered through diatomaceous earth. The filtrate was concentrated in vacuo, extracted with ethyl acetate, washed with water and the organic layer dried over sodium sulphate. The crude was purified by column chromatography (heptane/ethyl acetate 7/3) to give 1 g of title compound. $C_{16}H_{14}O_4$ Mass (calculated): [270]; (found): $[M+H^+] = 271, 312$
- 10 NMR (400 MHz, $CDCl_3$): 3.95 (3H, s, CH_3O); 4.3 (4H, s, OCH_2CH_2O); 6.9-7.15 (4H, m, aryl-H); 7.9-7.95 (2H, m, aryl-H); 10 (1H, s, CHO).

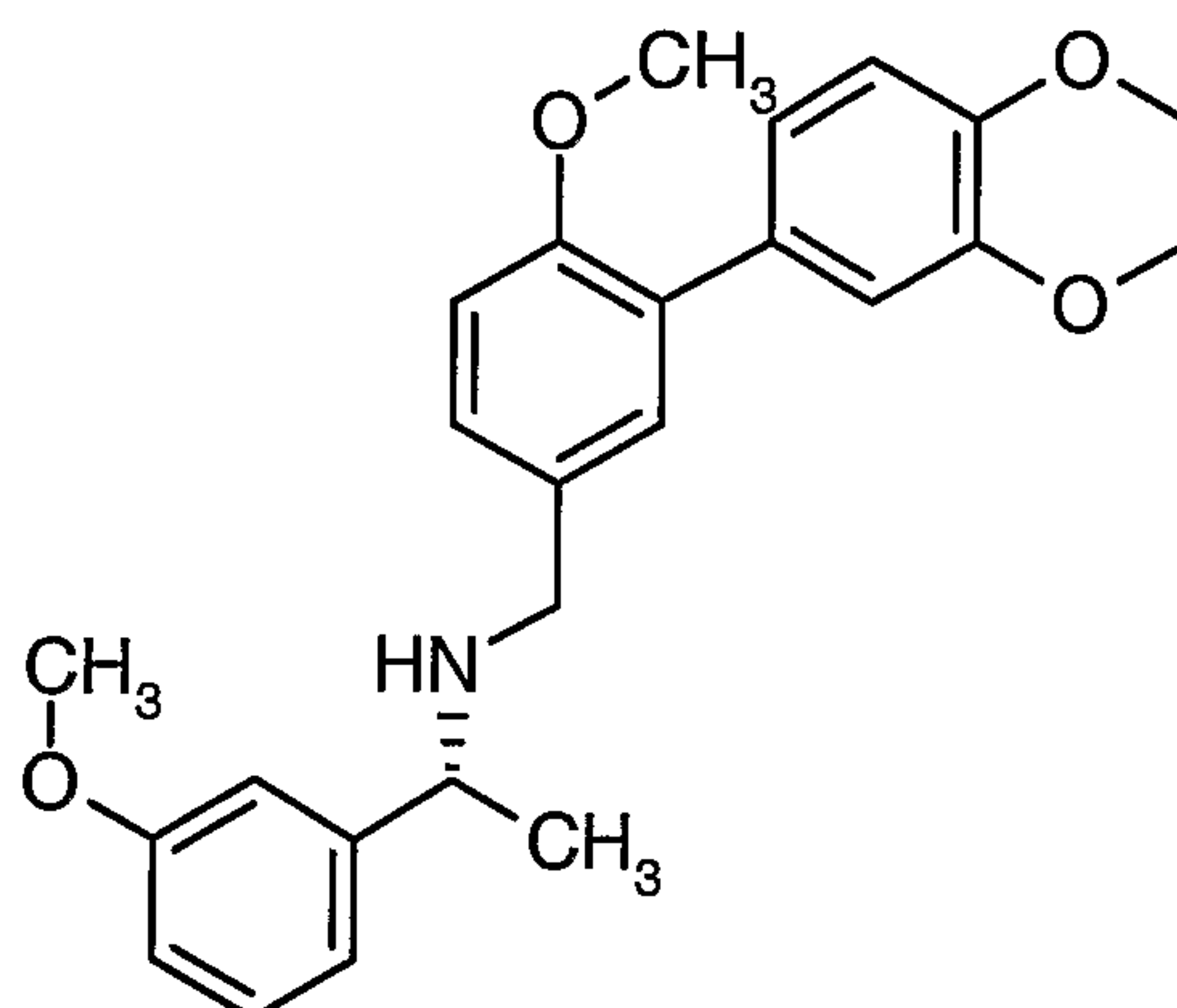
Step 2) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(1,4-benzodioxan-5-yl)methyl)amine

- 15 The title compound was prepared from 4-methoxy-3-(1,4-benzodioxan-5-yl)benzenecarboxaldehyde and (R)- α -methylbenzylamine according to general procedure C.
- $C_{24}H_{25}NO_3$ Mass (calculated): [375]; (found): $[M+H^+] = 376, 255$ NMR (400 MHz, $CDCl_3$): 1.3 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.55 and 3.65 (2H, dd, $J = 12$ Hz, CH_2N); 3.7 (3H, s, CH_3O); 3.75 (1H, q, $J = 6$ Hz; $NCHMe$); 4.2 (4H, s, OCH_2CH_2O); 6.8 (2H, m, aryl-H); 6.95 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 7.05 (1H, d, $J = 1$ Hz, aryl-H); 7.15-7.3 (3H, m, aryl-H); 7.35-7.45 (4H, m, aryl-H).
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Example 26

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(1,4-benzodioxan-5-yl)methyl)amine



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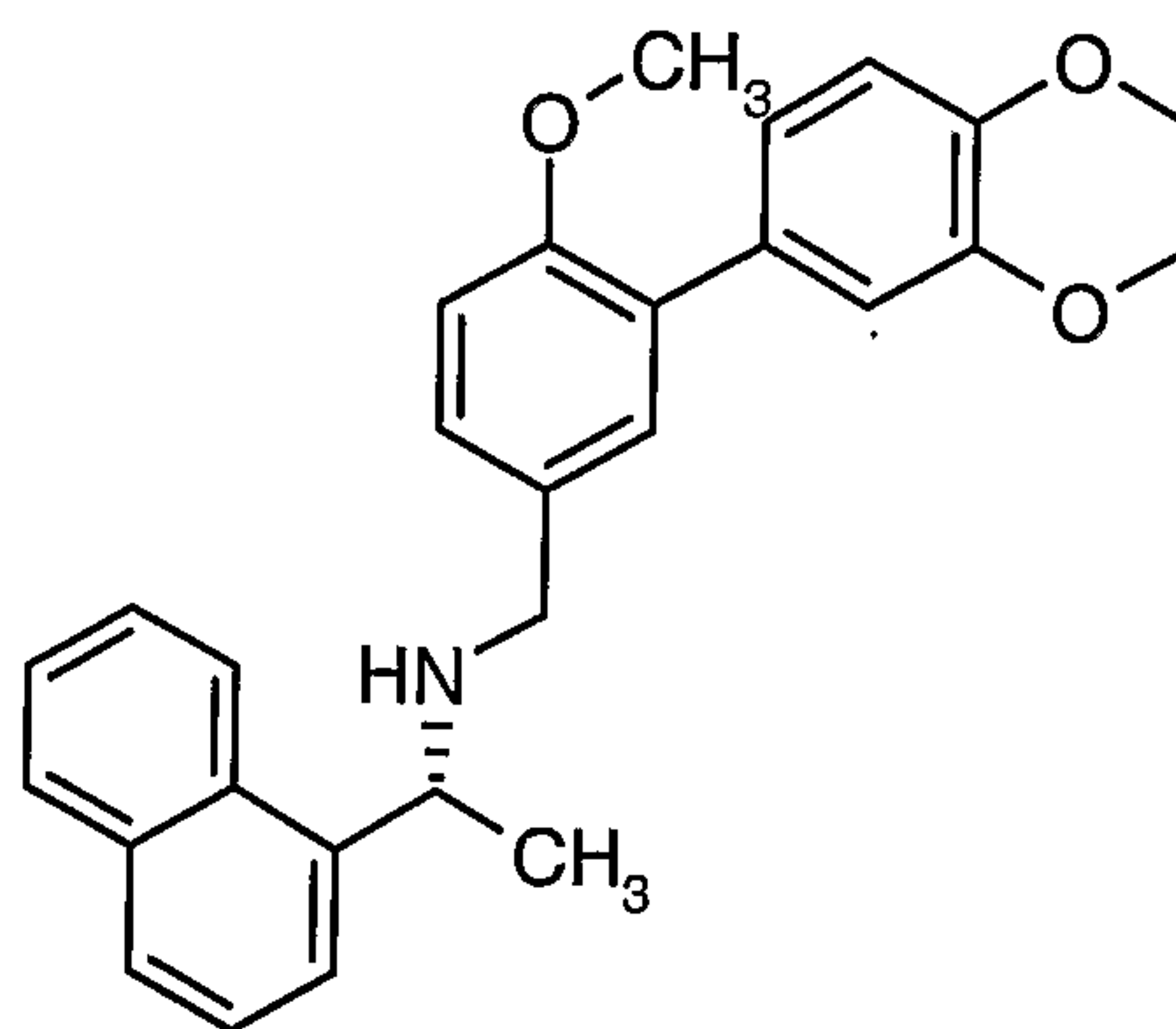
The title compound was prepared from 4-methoxy-3-(1,4-benzodioxan-5-yl)benzenecarboxaldehyde and (R)-3-methoxy- α -methylbenzylamine according to general procedure C.

10 $C_{25}H_{27}NO_4$ Mass (calculated): [405]; (found): $[M+H^+] = 406$, 255 NMR (400 MHz, $CDCl_3$): 1.3 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.55 and 3.65 (2H, dd, $J = 12$ Hz, CH_2N); 3.75 (3H, s, CH_3O); 3.77 (3H, s, CH_3O); 3.75 (1H, m; $NCHMe$); 4.2 (4H, s, OCH_2CH_2O); 6.7 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 6.8-6.9 (4H, m, aryl-H); 7.0 (1H, dd, dd, $J = 1$ and 8 Hz, aryl-H); 7.1 (1H, d, $J = 1$ Hz, aryl-H); 7.25-7.3 (3H, m, aryl-H).

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Example 27

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(1,4-benzodioxan-5-yl)-methyl)amine



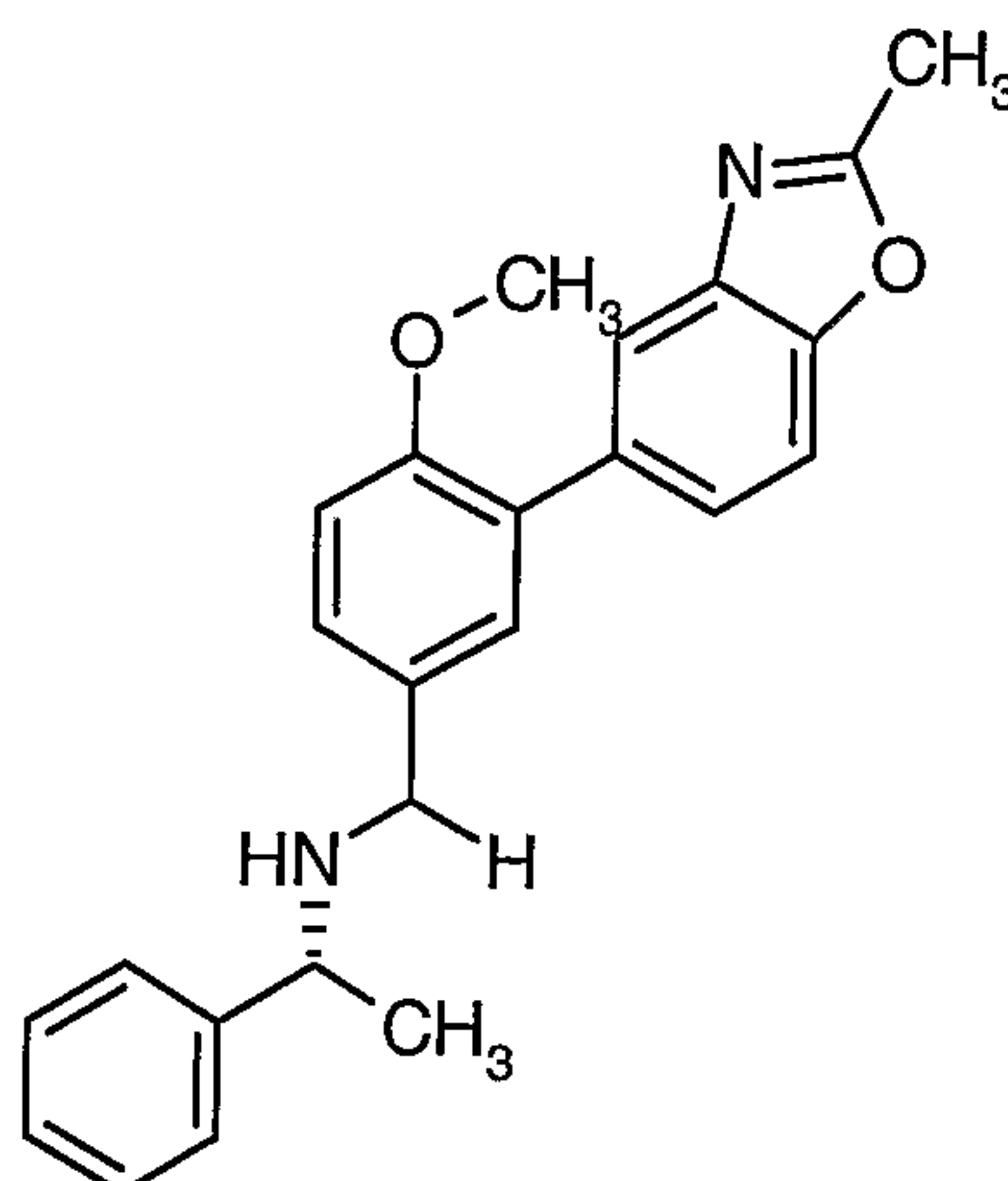
5

The title compound was prepared from 4-methoxy-3-(1,4-benzodioxan-5-yl)benzenecarboxaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

10 $C_{28}H_{28}NO_3$ Mass (calculated): [425]; (found): $[M+H^+] = 426, 255$. NMR (400 MHz, $CDCl_3$): 1.45 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.55 and 3.65 (2H, dd, $J = 12$ Hz, CH_2N); 3.7 (3H, s, CH_3O); 4.2 (4H, s, OCH_2CH_2O); 4.65 (1H, q, $J = 6$ Hz; $NCHMe$); 6.8 (2H, m, aryl-H); 6.9 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 7.0 (1H, d, $J = 1$ Hz, aryl-H); 7.1-7.15 (2H, m, aryl-H); 7.35-7.45 (3H, m, aryl-H); 7.7 (2H, d, $J = 8$ Hz, aryl-H); 7.8 (1H, m, aryl-H); 8.0 (1H, m, aryl-H).

15

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Example 28**(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(2-methylbenzoxazol-5-yl)methyl)amine**Step 1) 2-Amino-4-bromophenol:

- 5 A solution of 4-bromo-2-nitrophenol (2 g, 9.17 mmol) and tin (II) chloride (10.35 g, 45.9 mmol) in ethanol (20 mL) was heated at 70°C for 2 hours, then cooled, poured onto ice, neutralized with NaHCO₃. The aqueous phase was then extracted with ethyl acetate, dried over sodium sulphate and the solvent removed in vacuo to afford 1.61 g of the title compound. C₆H₆BrNO Mass (calculated): [188];
- 10 (found): [M+H⁺] = 188, 190 (Br) NMR (400 MHz, dmso-d₆): 4.8 (2H, bs, NH₂); 6.5 (1H, dd, *J* = 2 and 8 Hz, aryl-H); 6.6 (1H, d, *J* = 8 Hz, aryl-H); 6.75 (1H, d, *J* = 2 Hz, aryl-H); 9.3 (1H, bs, OH).

Step 2) 2-methyl-5-bromobenzoxazole:

- 15 A solution of 2-amino-4-bromophenol (1 g, 5.32 mmol) in trimethyl orthoacetate (20 mL) was refluxed for 1.5 hours. The reaction was then cooled and the solvent removed under reduced pressure to give 1.1 g of title compound.

C₈H₆BrNOMass (calculated): [212]; (found): [M+H⁺] = 212, 214 (Br).

- 20 NMR (400 MHz, dmso-d₆): 2.55 (3H, s, CH₃); 7.3 (1H, d, *J* = 8 Hz, aryl-H); 7.35 (1H, dd, *J* = 1 and 8 Hz, aryl-H); 7.75 (1H, d, *J* = 2 Hz, aryl-H).

Step 3) 4-methoxy-3-(2-methylbenzoxazol-5-yl)benzenecarboxaldehyde

A solution of 5-formyl-2-methoxybenzeneboronic acid (1 g, 5.6 mmol), 2-methyl-5-bromobenzoxazole (1 g, 4.72 mmol) and K₂CO₃ (1.63 g, 11.8 mmol) in

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ethanol (20 mL) and toluene (40 mL) was degassed prior to addition of $\text{Pd}(\text{Ph}_3)_4$ (55 mg, 0.047 mmol). The mixture was refluxed for 20 hours then cooled and filtered through diatomaceous earth. The filtrate was concentrated in vacuo, extracted with ethyl acetate, washed with water and the organic layer dried over sodium sulphate. The crude was purified by column chromatography (heptane/ethyl acetate 7/3 to 6/4) to give 1.13 g of title compound.



Mass (calculated): [267]; (found): $[\text{M}+\text{H}^+]$: 268.

NMR (400 MHz, CDCl_3): 2.6 (3H, s, CH_3); 3.85 (3H, s, CH_3O); 7.05 (1H, d, $J = 8$ Hz, aryl-H); 7.35 (1H, d, $J = 8$ Hz, aryl-H); 7.45 (1H, d, $J = 8$ Hz, aryl-H); 7.75 (1H, s, aryl-H); 7.8-7.85 (2H, m, aryl-H); 9.9 (1H, s, CHO).

Step 4) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(2-methylbenzoxazol-5-yl)methyl)amine:

The title compound was prepared from 4-methoxy-3-(benzimidazol-2-yl)benzenecarboxaldehyde and (R)- α -methylbenzylamine according to general procedure C.



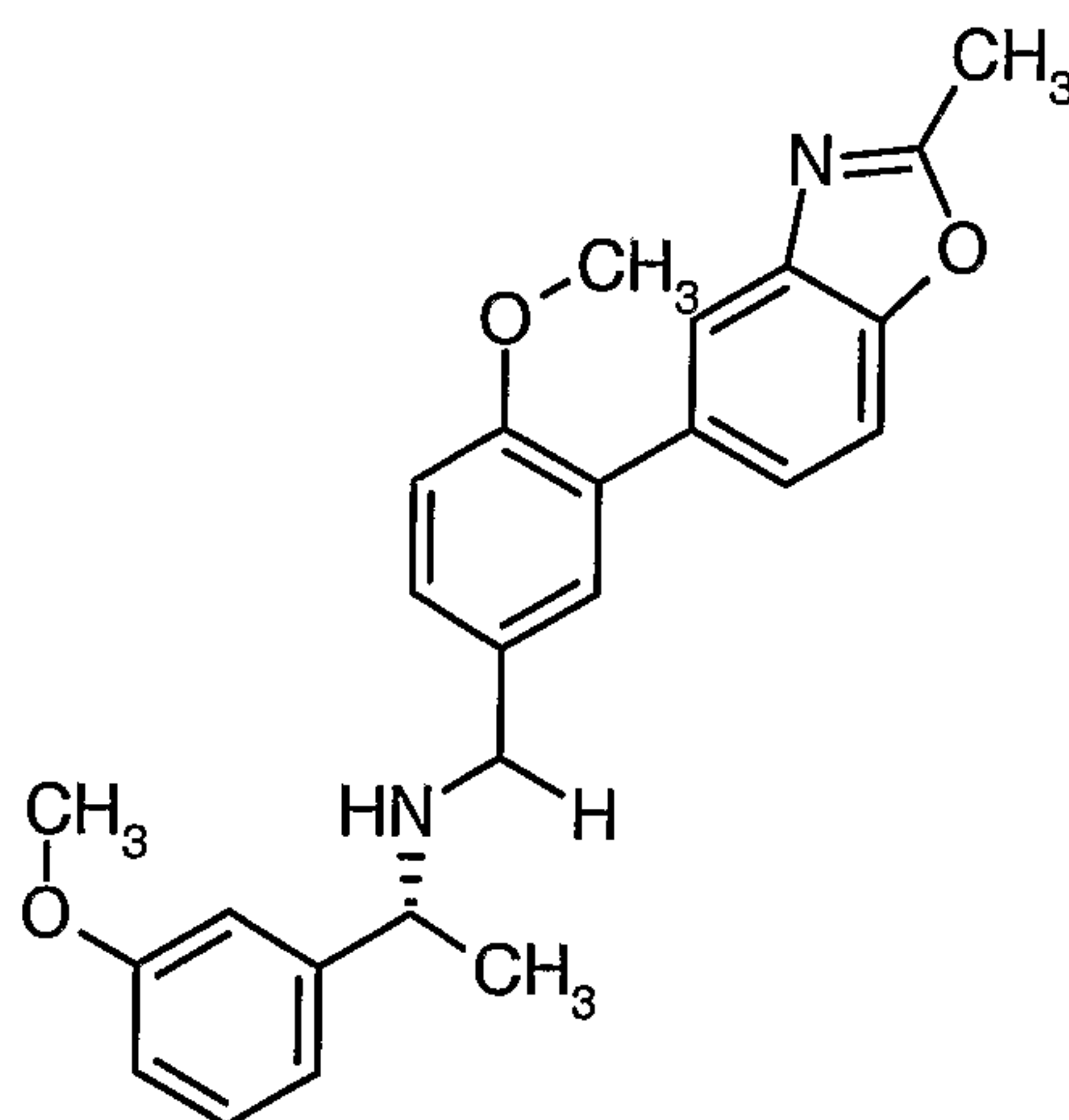
Mass (calculated): [372]; (found): $[\text{M}+\text{H}^+] = 373$.

NMR (400 MHz, CDCl_3): 1.3 (3H, d, $J = 6$ Hz, NCHCH_3); 2.6 (3H, s, CH_3); 3.55 and 3.6 (2H, dd, $J = 12$ Hz, CH_2N); 3.7 (3H, s, CH_3O); 3.75 (1H, q, $J = 6$ Hz, NCHMe); 6.8 (1H, d, $J = 8$ Hz, aryl-H); 7.2-7.3 (3H, m, aryl-H); 7.3-7.35 (4H, m, aryl-H); 7.4 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 7.45 (1H, d, $J = 8$ Hz, aryl-H); 7.7 (1H, d, $J = 1$ Hz, aryl-H).

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Example 29

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(2-methylbenzoxazol-5-yl)methyl)amine



5

The title compound was prepared from 4-methoxy-3-(2-methylbenzoxazol-5-yl)benzenecarboxyaldehyde and (R)-3-methoxy- α -methylbenzylamine according to general procedure C.

$C_{25}H_{26}N_2O_3$

10 Mass (calculated): [402]; (found): $[M+H^+] = 403$.

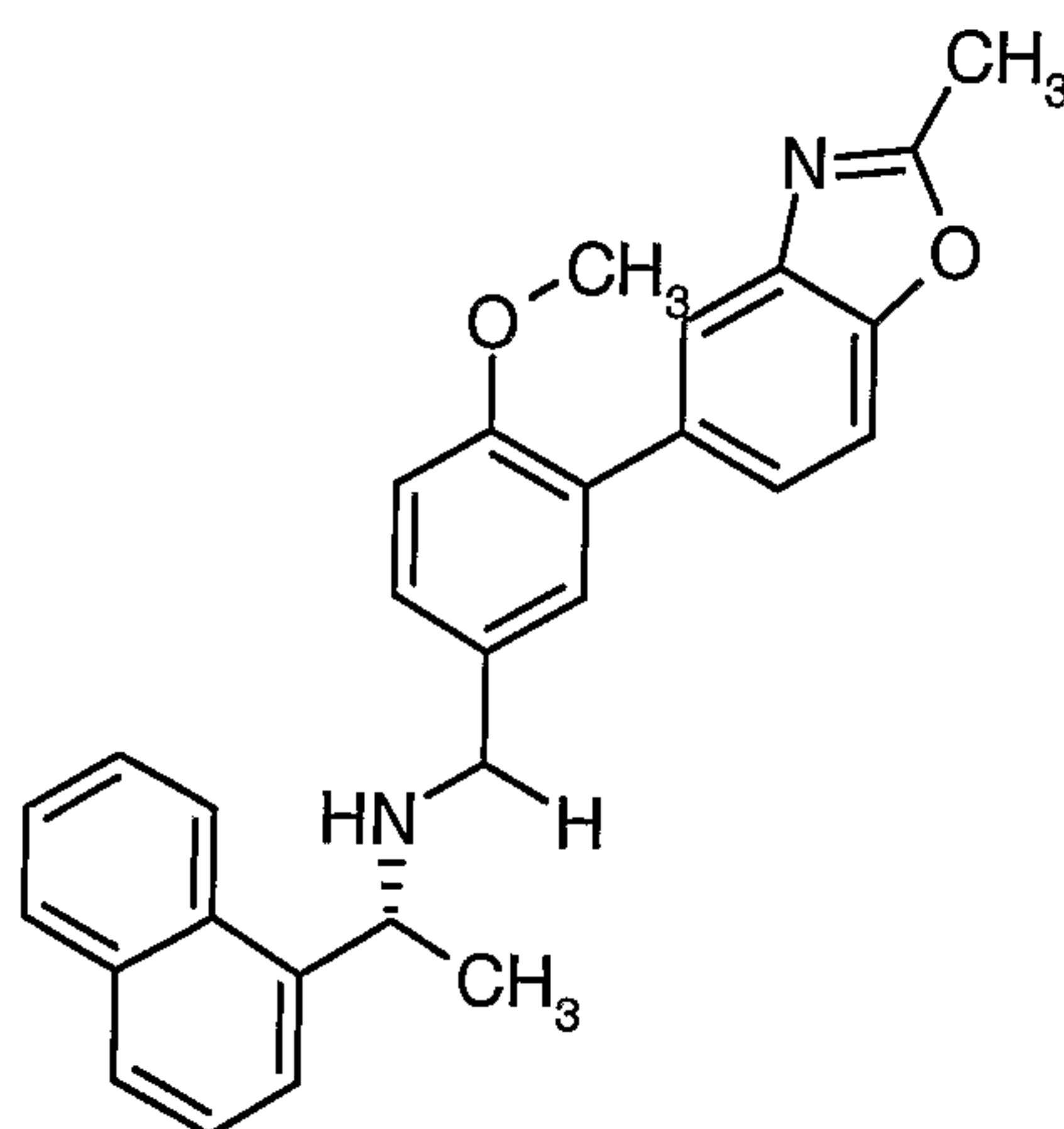
NMR (400 MHz, $CDCl_3$): 1.3 (3H, bd, $J = 6$ Hz, $NCHCH_3$); 2.6 (3H, s, CH_3); 3.55 and 3.6 (2H, dd, $J = 12$ Hz, CH_2N); 3.7 (3H, s, CH_3O); 3.72 (3H, s, CH_3O); 3.75 (1H, q, $J = 6$ Hz; $NCHMe$); 6.75 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 6.8-6.9 (3H, m, aryl-H); 7.2-7.3 (3H, m, aryl-H); 7.4 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 7.45 (1H, d, $J = 8$ Hz, aryl-H); 7.7 (1H, d, $J = 1$ Hz, aryl-H).

15

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Example 30

(R)-N-(1-(1-Naphthylethyl)-N-((4-methoxy-3-(2-methylbenzoxazol-5-yl)methyl)amine



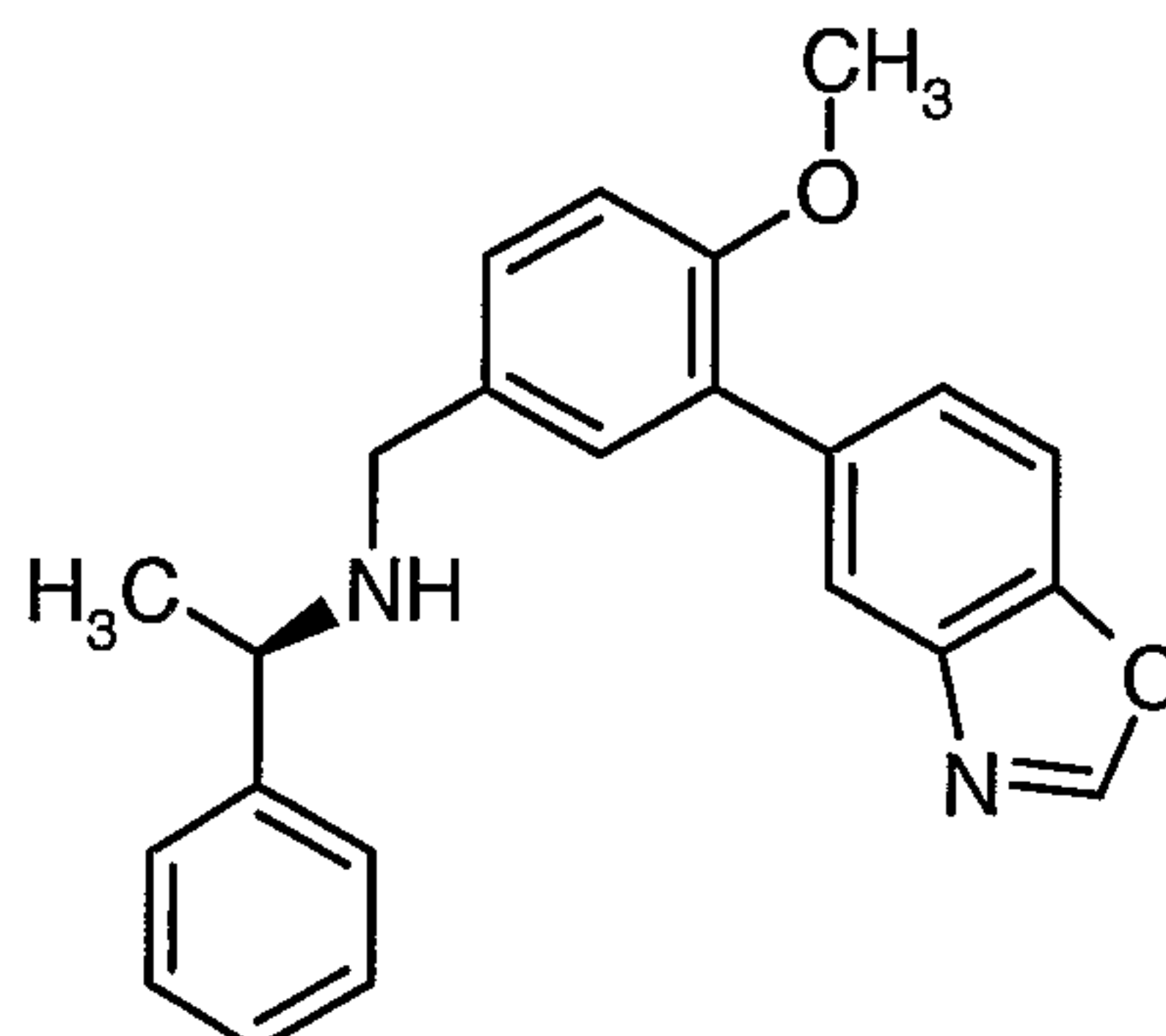
5

The title compound was prepared from 4-methoxy-3-(2-methylbenzoxazol-5-yl)benzenecarboxyaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

$C_{28}H_{26}N_2O_2$

- 10 Mass (calculated): [422]; (found): $[M+H^+] = 423$.
 NMR (400 MHz, $CDCl_3$): 1.45 (3H, d, $J = 6$ Hz, $NCHCH_3$); 2.6 (3H, s, CH_3); 3.6 and 3.65 (2H, dd, $J = 12$ Hz, CH_2N); 3.7 (3H, s, CH_3O); 4.6 (1H, q, $J = 6$ Hz; $NCHMe$); 6.8 (1H, d, $J = 8$ Hz, aryl-H); 7.2-7.3 (3H, m, aryl-H); 7.35 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 7.4-7.5 (3H, m, aryl-H); 7.7-7.75 (3H, m, aryl-H); 7.8-7.85
 15 (1H, m, aryl-H); 8.05-8.1 (1H, m, aryl-H).

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Example 31**(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(benzoxazol-5-yl)methyl)amine**Step 1) 5-Bromobenzoxazole:

- 5 A solution of 2-amino-4-bromophenol (2 g, 10.6 mmol) in triethylorthoformate (40 mL) was refluxed for 1.5 hours. The reaction was then cooled and the solvent removed under reduced pressure to give a crude which was purified by washing through a plug of silica eluting with hexane/ethyl acetate 3/2 to afford 1.1 g of title compound. C_7H_4BrNO Mass (calculated): [198]; (found): $[M+H^+] = 198, 200$
- 10 (Br) NMR (400 MHz, $CDCl_3$): 7.25-7.3 (2H, m, aryl-H); 7.8 (1H, d, $J = 1$, aryl-H); 8.0 (1H, s, aryl-H).

Step 2) 4-Methoxy-3-(benzoxazol-5-yl)benzenecarboxyaldehyde:

- A solution of 5-formyl-2-methoxybenzeneboronic acid (1 g, 5.6 mmol), 2-methyl-5-bromobenzoxazole (1 g, 4.72 mmol) and K_2CO_3 (1.63 g, 11.8 mmol) in ethanol (20 mL) and toluene (40 mL) was degassed prior to addition of $Pd(Ph_3)_4$ (55 mg, 0.047 mmol). The mixture was refluxed for 20 hours then cooled and filtered through diatomaceous earth. The filtrate was concentrated in vacuo, extracted with ethyl acetate, washed with water and the organic layer dried over sodium sulphate. The crude was purified by column chromatography (heptane/ethyl acetate 7/3 to 6/4) to give 1.13 g of title compound.

 $C_{15}H_{11}NO_3$ Mass (calculated): [253]; (found): $[M+H^+]$: 254, 295.

- NMR (400 MHz, $CDCl_3$): 2.6 (3H, s, CH_3); 3.95 (3H, s, CH_3O); 7.15 (1H, d, $J = 8$ Hz, aryl-H); 7.55 (1H, d, $J = 8$ Hz, aryl-H); 7.65 (1H, d, $J = 8$ Hz, aryl-H); 7.85-7.95 (2H, aryl-H); 8 (1H, s, aryl-H); 8.15 (1H, s, aryl-H); 10.0 (1H, s, CHO).

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Step 3) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(benzoxazol-5-yl)methyl)amine:

The title compound was prepared from 4-methoxy-3-(benzoxazol-5-yl)benzenecarboxyaldehyde and (R)- α -methylbenzylamine according to general
 5 procedure C.

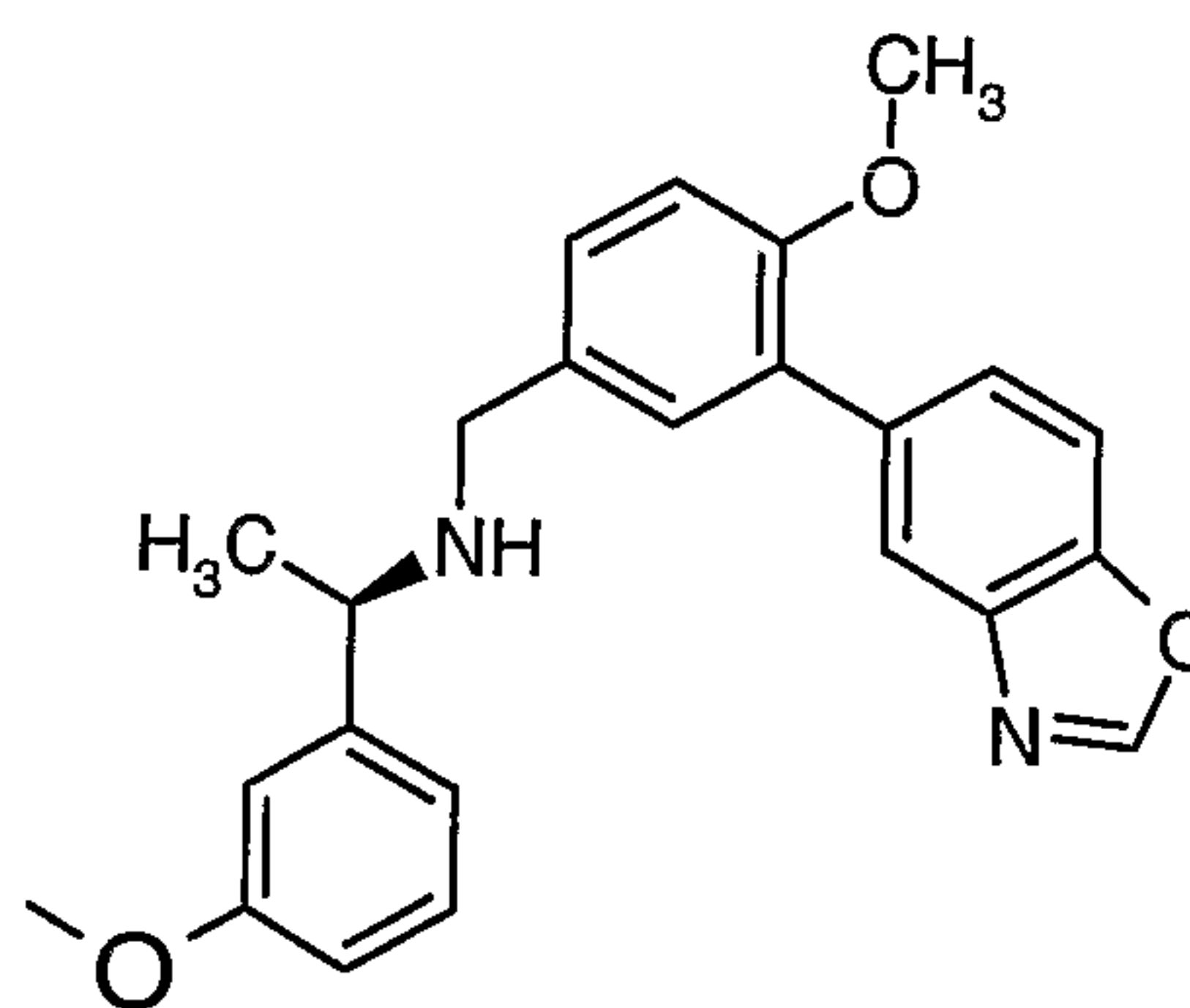
$$\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_2$$

Mass (calculated): [358]; (found): $[\text{M}+\text{H}^+] = 359, 831$.

NMR (400 MHz, CDCl_3): 1.3 (3H, d, $J = 6$ Hz, NCHCH_3); 2.6 (3H, s, CH_3); 3.5
 and 3.55 (2H, dd, $J = 12$ Hz, CH_2N); 3.7 (3H, s, CH_3O); 3.75 (1H, q, $J = 6$ Hz;
 10 NCHMe); 6.85 (1H, d, $J = 8$ Hz, aryl-H); 7.1-7.2 (3H, m, aryl-H); 7.2-7.3 (4H, m,
 aryl-H); 7.45 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 7.5 (1H, d, $J = 8$ Hz, aryl-H); 7.8
 (1H, d, $J = 1$ Hz, aryl-H); 8 (1H, s, aryl-H).

Example 32

15 (R)-N-(1-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(benzoxazol-5-yl)methyl)amine



The title compound was prepared from 4-methoxy-3-(benzoxazol-5-yl)benzene-
 20 carboxyaldehyde and (R)-3-methoxy- α -methylbenzylamine according to general
 procedure C.

$$\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_3$$

Mass (calculated): [388]; (found): $[\text{M}+\text{H}^+] = 389, 891$.

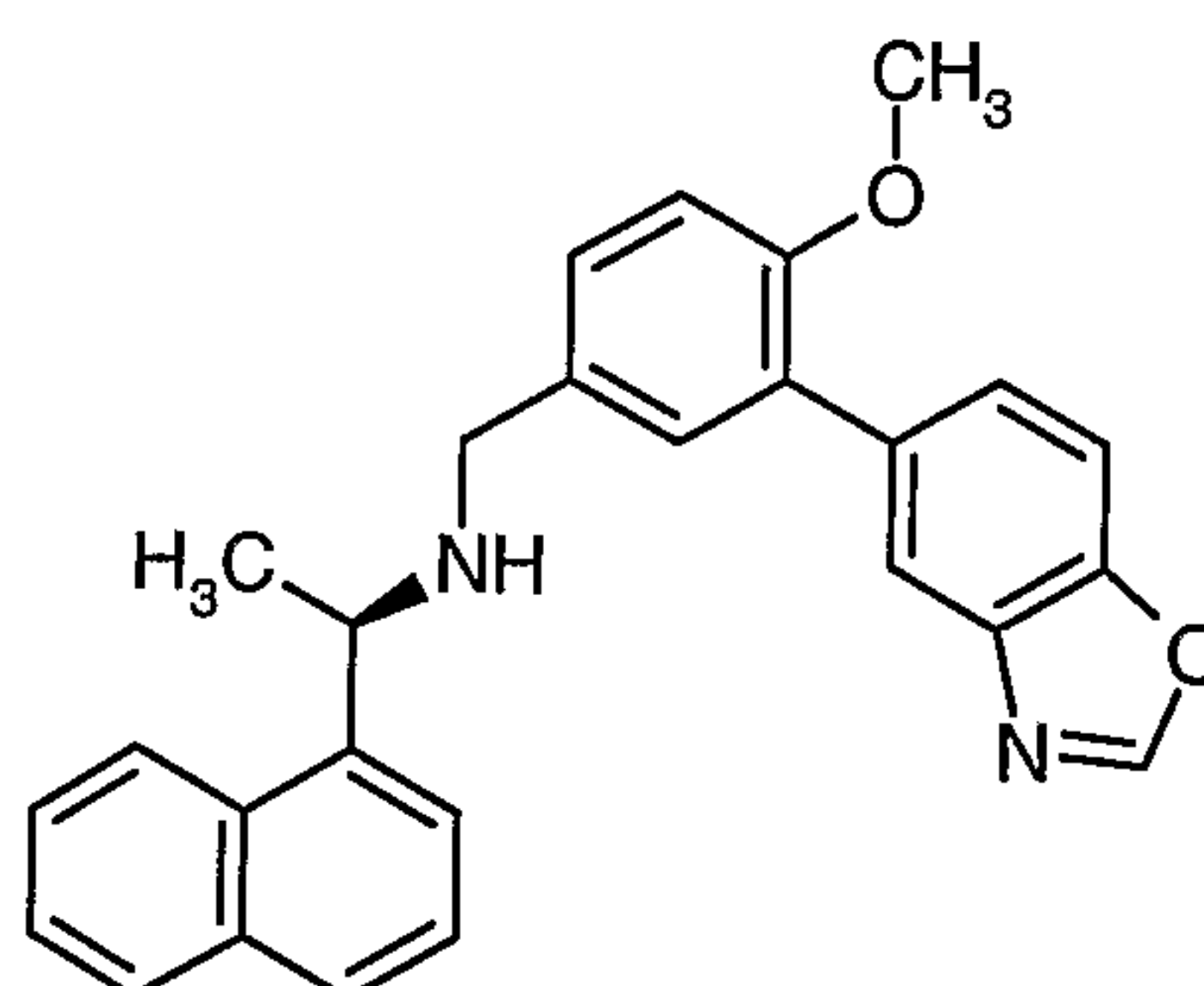
NMR (400 MHz, CDCl_3): 1.3 (3H, d, $J = 6$ Hz, NCHCH_3); 2.6 (3H, s, CH_3); 3.5
 25 and 3.55 (2H, dd, $J = 12$ Hz, CH_2N); 3.7-3.8 (4H, m, CH_3O and NCHMe); 6.7
 (1H, dd, $J = 2$ and 8 Hz, aryl-H); 6.8-6.9 (3H, m, aryl-H); 7.15-7.25 (3H, m, aryl-

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H); 7.45 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 7.5 (1H, d, $J = 8$ Hz, aryl-H); 7.85 (1H, d, $J = 1$ Hz, aryl-H); 8 (1H, s, aryl-H).

Example 33

5 (R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(benzoxazol-5-yl)methyl)amine



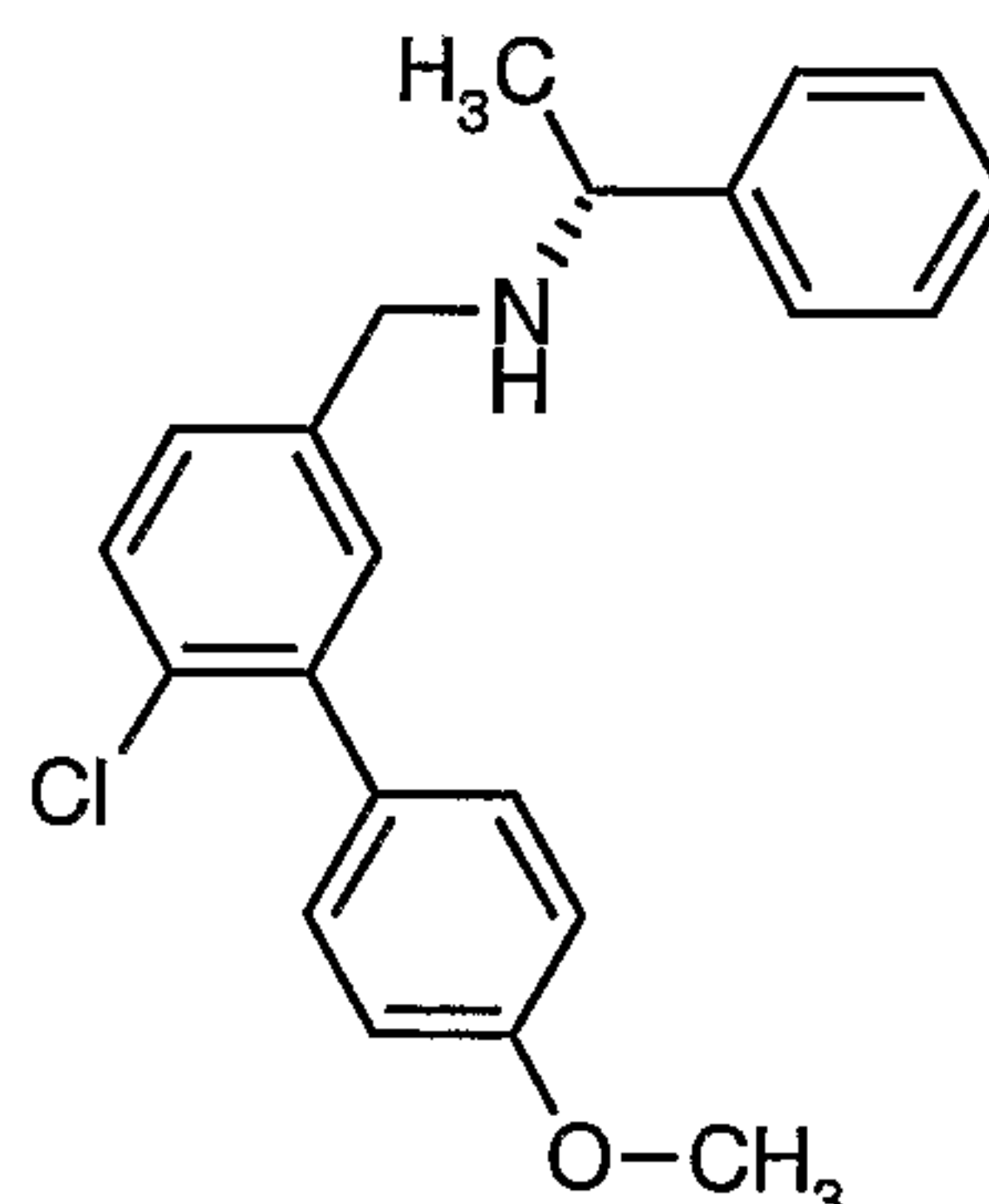
The title compound was prepared from 4-methoxy-3-(benzoxazol-5-yl)benzene-carboxyaldehyde and (R)-1-(1-naphthyl)ethylamine according to general
10 procedure C.

$C_{27}H_{24}N_2O_2$

Mass (calculated): [408]; (found): $[M+H^+] = 409, 931$.

¹H NMR (400 MHz, CDCl₃): 1.45 (3H, d, $J = 6$ Hz, NCHCH₃); 3.6 and 3.65 (2H, dd, $J = 12$ Hz, CH₂N); 3.7 (3H, s, CH₃O); 4.65 (1H, q, $J = 6$ Hz; NCHMe); 6.85 (1H, d, $J = 8$ Hz, aryl-H); 7.2-7.3 (2H, m, aryl-H); 7.4-7.5 (4H, m, aryl-H); 7.5 (1H, d, $J = 6$ Hz, aryl-H); 7.7-7.75 (2H, m, aryl-H); 7.75-7.8 (1H, m, aryl-H); 7.85 (1H, d, $J = 1$ Hz, aryl-H); 8 (1H, s, aryl-H); 8.05-8.1 (1H, m, aryl-H).

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Example 34**(R)-N-(1-Phenylethyl)-N-((4-chloro-3-(4'-methoxyphenyl)phenyl)methyl)amine**5 Step 1) 3-Bromo-4-chlorobenzyl alcohol:

A solution of 3-bromo-4-chlorobenzoic acid (3.53 g, 15 mmol) was dissolved in anhydrous THF (20 mL) and cooled to 0 C prior to addition of borane (1M soln in THF, 20 mL, 20 mmol). The solution was then heated at 65 C for 12 hours then cooled to 0 C and methanol was added dropwise to quench excess borane. The solvent was evaporated under reduced pressure, the residue was redissolved in ethyl acetate and washed with saturated NH₄Cl then brine, dried over sodium sulphate. The solvent was removed in vacuo to afford 3.23 g of title compound.

C₇H₆BrClO

Mass (calculated): [221], MH⁺ not found.

15 NMR (400 MHz, CDCl₃): 4.6 (2H, s, CH₂OH); 7.15 (1H, dd, *J* = 1 and 8 Hz, aryl-H); 7.35 (1H, d, *J* = 8 Hz, aryl-H); 7.55 (1H, d, *J* = 1 Hz, aryl-H).

Step 2) 3-Bromo-4-chlorobenzaldehyde:

20 A solution of 3-bromo-4-chlorobenzyl alcohol (3.24 g, 14.6 mmol) in acetone (100 mL) was treated with MnO₂ (16.2 g, 73 mmol) and the mixture stirred for 3 days then filtered over diatomaceous earth. The filtrate was concentrated under reduced pressure to afford 2.0 g of title compound.

C₇H₄BrClO

Mass (calculated): [219]; MH⁺ not found.

25 NMR (400 MHz, CDCl₃): 7.55 (1H, d, *J* = 8 Hz, aryl-H); 7.7 (1H, dd, *J* = 1 and 8 Hz, aryl-H); ; 8.05 (1H, d, *J* = 1 Hz, aryl-H); 9.85 (1H, s, CHO).

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Step 3) 4-chloro-3-(4-methoxyphenyl)benzenecarboxaldehyde:

To a degassed solution of 4-methoxybenzeneboronic acid (1.51 g, 10 mmol), 3-bromo-4-chlorobenzaldehyde (2 g, 9.13 mmol), and potassium carbonate (3.13 g, 22.8 mmol) in toluene/ethanol 2/1, (60 mL), Pd(PPh₃)₄ (130 mg, 1mol%) is added
5 and the mixture is degassed for further 5 minutes. The mixture is then refluxed for 2 days. The mixture was partitioned between ethyl acetate and water and extracted. The organic solvent was dried over sodium sulphate, removed under reduced pressure, and the residue purified by column chromatography (heptane/ethyl acetate 19/1 to afford 1.41 g of product.

10 C₁₄H₁₁ClO₂

Mass (calculated): [246]; MH⁺ not found.

NMR (400 MHz, CDCl₃): 3.8 (3H, s, MeO); 6.9 (2H, d, *J* = 8 Hz, aryl-H); 7.35 (2H, d, *J* = 8 Hz, aryl-H); 7.55 (1H, d, *J* = 8 Hz, aryl-H); 7.7 (1H, dd, *J* = 2 and 8 Hz, aryl-H); 7.75 (1H, d, *J* = 2 Hz, aryl-H); 9.9 (1H, s, CHO).

15

Step 4) (R)-N-(1-Phenylethyl)-N-((4-chloro-3-(4'-methoxyphenyl)phenyl)methyl)amine:

The title compound was prepared from 4-chloro-3-(4-methoxyphenyl)benzenecarboxaldehyde and (R)-α-methylbenzylamine according to general
20 procedure C.

C₂₂H₂₂ClNO

Mass (calculated): [351]; (found): [M+H⁺] = 352, 354 (Cl).

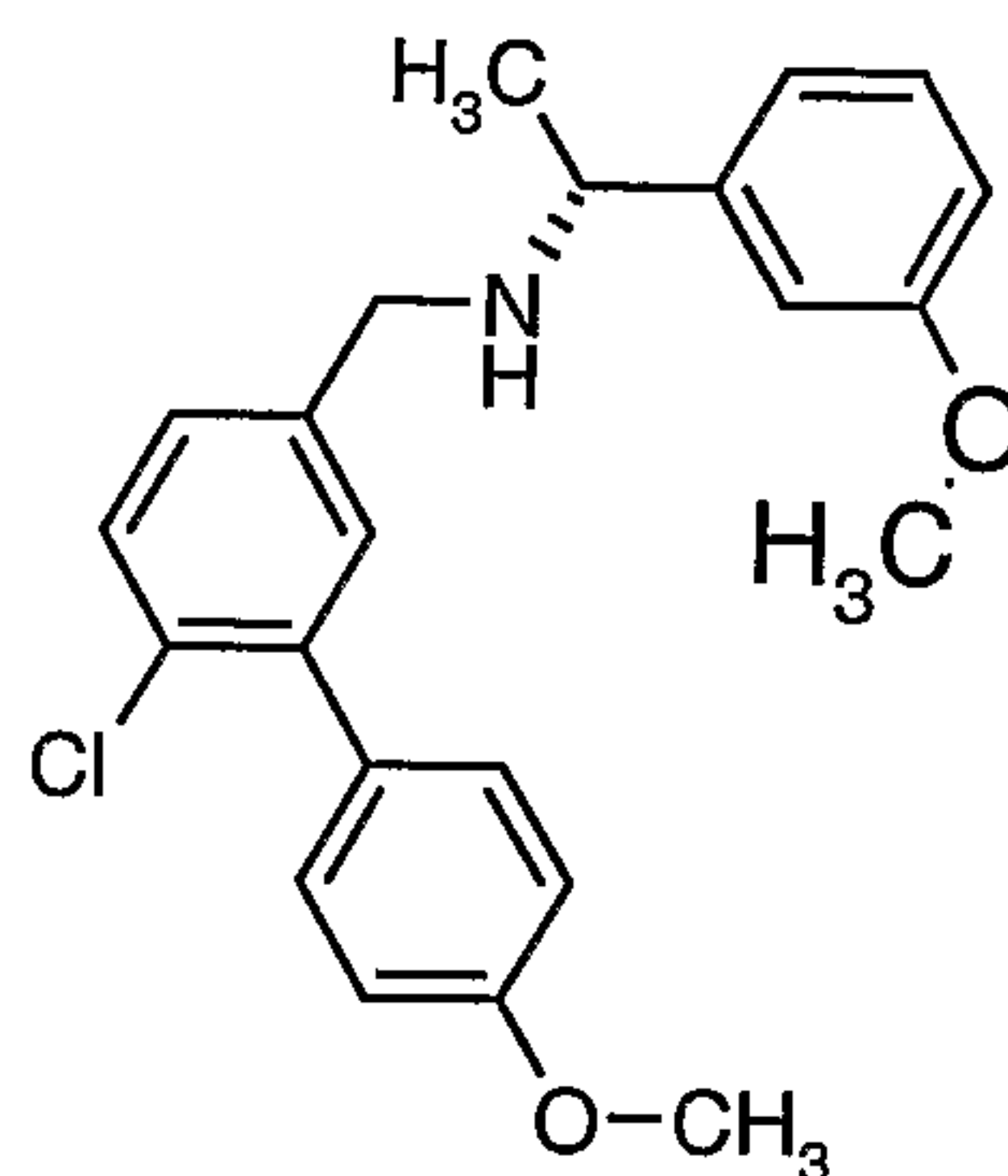
NMR (400 MHz, CDCl₃): 1.15 (3H, d, *J* = 6 Hz, NCHCH₃); 3.4 and 3.45 (2H, dd, *J*=12 Hz, CH₂N); 3.55 (1H, m, NCHMe); 3.6 (3H, s, MeO); 6.8 (2H, d, *J* = 8 Hz, aryl-H); 7 (1H, dd, *J* = 1 and 8 Hz, aryl-H); 7.05-7.1 (2H, m, aryl-H); 7.15-7.25 (7H, m, aryl-H).

25

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Example 35

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-chloro-3-(4'-methoxyphenyl)-phenylmethyl)amine



5

The title compound was prepared from 4-chloro-3-(4-methoxyphenyl)benzene-carboxaldehyde and (R)-3-methoxy- α -methylbenzylamine according to general procedure C.

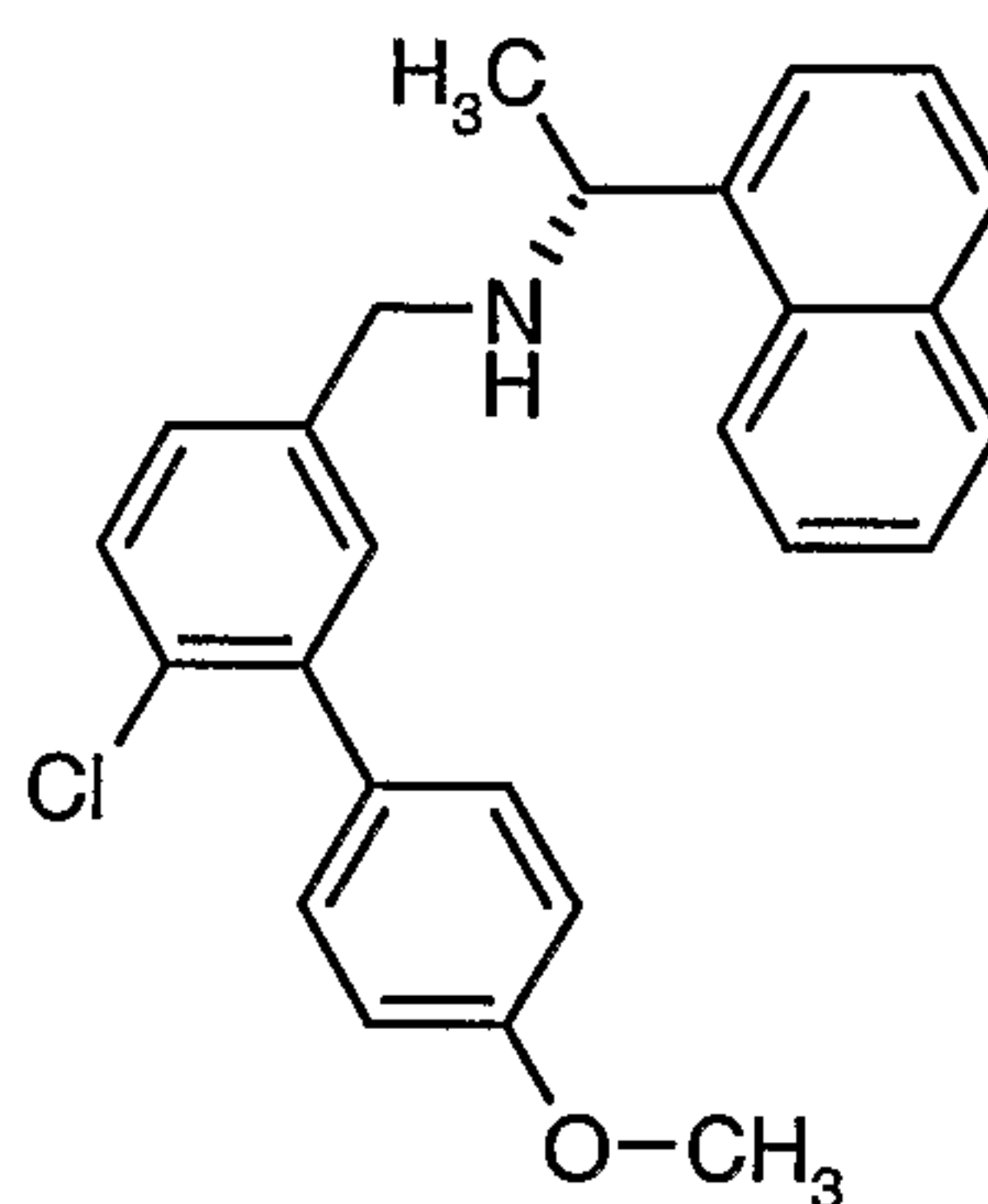
$C_{23}H_{23}ClNO_2$

- 10 Mass (calculated): [381]; (found): $[M+H^+] = 382, 384$ (Cl).
 NMR (400 MHz, $CDCl_3$): 1.3 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.55 and 3.6 (2H, dd, $J=12$ Hz, CH_2N); 3.7-3.75 (4H, m, $NCHMe$ and MeO); 3.8 (3H, s, MeO); 6.75 (1H, dd, $J = 2$ and 8 Hz, aryl-H); 7.85 (1H, d, $J = 1$ Hz, aryl-H); 7.9 (2H, d, $J = 8$ Hz, aryl-H); 7.15 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 7.15-7.25 (2H, m, aryl-H); 7.3-7.4 (3H, m, aryl-H).
- 15

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Example 36

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-chloro-3-(4'-methoxyphenyl)phenyl)methyl)amine



5

The title compound was prepared from 4-chloro-3-(4-methoxyphenyl)benzene-carboxaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

$C_{26}H_{24}ClNO$

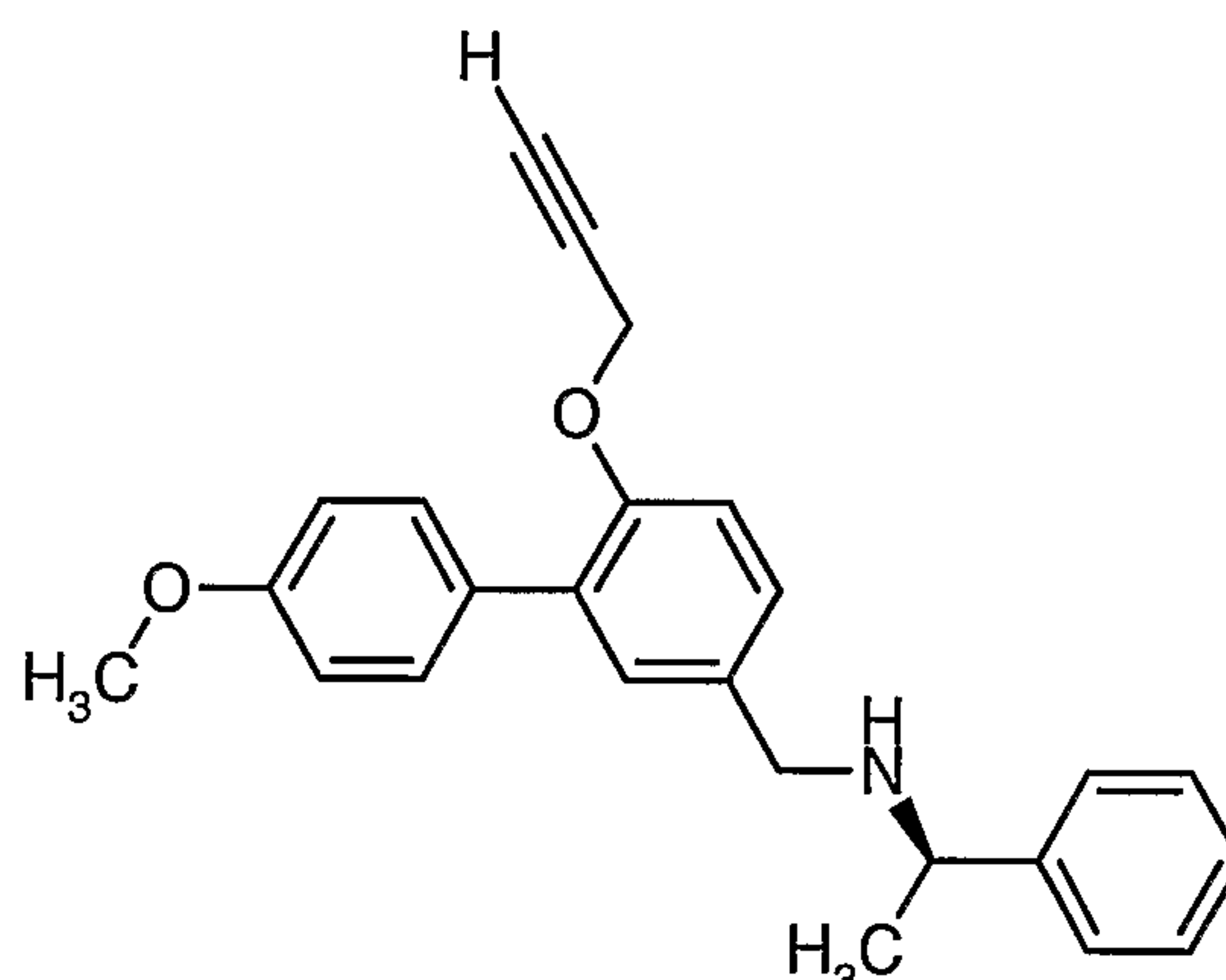
- 10 Mass (calculated): [401]; (found): $[M+H^+] = 402, 404$ (Cl).
 NMR (400 MHz, $CDCl_3$): 1.45 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.6 and 3.65 (2H, dd, $J = 12$ Hz, CH_2N); 3.75 (3H, s, MeO); 4.6 (1H, m, $NCHMe$); 6.85 (2H, d, $J = 8$ Hz, aryl-H); 7.1 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 7.2 (1H, d, $J = 1$ Hz, aryl-H); 7.3-7.35 (3H, m, aryl-H); 7.4-7.45 (3H, m, aryl-H); 7.65-7.7 (2H, m, aryl-H); 7.8-7.85 (1H, m, aryl-H); 8.05-8.1 (1H, m, aryl-H).
- 15

Example 37

(R)-N-(1-Phenylethyl)-N-((4-propargyloxy-3-(4'-methoxyphenyl)phenyl)methyl)amine

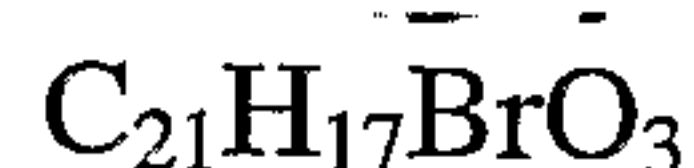
20

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Step 1) Benzyl 4-benzyloxy-3-bromobenzoate:

A 500mL round bottom flask was charged with DMF (250 mL), 3-bromo-4-hydroxybenzoic acid (8.68 g, 40 mmol), potassium carbonate (22.06 g, 160 mmol)
 5 potassium iodide (50 mg) and benzyl bromide (9.26 mL, 78 mmol). The mixture was heated at 75 C for 3 days, then cooled, the solvent removed under reduced pressure and the residue redissolved in ethyl acetate and washed with aqueous potassium carbonate, then brine. The organic layer was dried over sodium sulphate then removed under reduced pressure to give an off-white solid which
 10 was purified by column chromatography (eluting with DCM/hexane 1/1) to give 12.1 g of title compound).



Mass (calculated): [397]; found 397, 399 (Br).

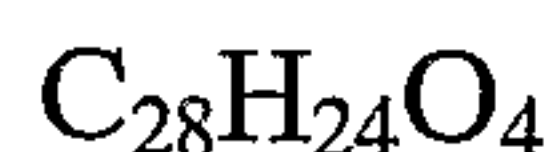
NMR (400 MHz, CDCl_3): 5.15 (2H, s, OCH_2Ph); 5.25 (2H, s, OCH_2Ph); 6.85 (1H, d, $J = 8$ Hz, aryl-H); 7.3-7.5 (10H, m, aryl-H); 7.9 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 8.2 (1H, d, $J = 1$ Hz, aryl-H).

Step 2) Benzyl 4-benzyloxy-3-(4-methoxyphenyl)benzoate:

To a degassed solution of 4-methoxybenzeneboronic acid (5.0 g, 32.9 mmol),
 20 benzyl 4-benzyloxy-3-bromobenzoate (12.1 g, 30.5 mmol), and potassium carbonate (10.4 g, 76.2 mmol) in toluene/ethanol 2/1, (140 mL), $\text{Pd}(\text{PPh}_3)_4$ (400 mg, 1mol%) was added and the mixture is degassed for further 5 minutes. The mixture is then refluxed for 12 hours. The mixture was partitioned between ethyl acetate and water and extracted. The organic solvent was dried over sodium
 25 sulphate, removed under reduced pressure, and the residue purified by column

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chromatography (9/1 DCM/hexane) to afford 0.73 g of pure title compound, 9.74 g of a 4:6 mixture of title compound and the corresponding ethyl ester, and 0.71 g of the ethyl ester derivative.



5 NMR (400 MHz, CDCl_3): $\text{C}_{28}\text{H}_{24}\text{O}_4$

Ethyl ester: NMR (400 MHz, CDCl_3): 1.3 (3H, t, $J = 6$ Hz, OCH_2CH_3); 3.75 (3H, s, CH_3O); 4.3 (2H, q, $J = 6$ Hz, OCH_2CH_3); 5.1 (2H, s, OCH_2Ph); 6.95 (2H, m, aryl-H); 7.2-7.3 (2H, m, aryl-H); 7.45 (2H, m, aryl-H); 7.85 (1H, dd, $J = 1$ and 8 Hz, aryl-H).

10 Benzyl ester: NMR (400 MHz, CDCl_3): 3.75 (3H, s, CH_3O); 4.65 (2H, s, OCH_2Ph); 5.1 (2H, s, OCH_2Ph); 7 (2H, m, aryl-H); 7.2-7.3 (2H, m, aryl-H); 7.45 (2H, m, aryl-H); 8.05 (1H, dd, $J = 1$ and 8 Hz, aryl-H).

Step 3) Ethyl 4-hydroxy-3-(4-methoxyphenyl)benzoate and 4-hydroxy-3-(4-methoxyphenyl)benzoic acid:

15 A mixture of benzyl and ethyl 4-benzyloxy-3-(4-methoxyphenyl)benzoates (9.74 g, ca, 22.9 mmol) was hydrogenated in THF/ethanol (100 mL) under atmospheric pressure for 60 hours, then the catalyst removed by filtration and the solvent evaporated in vacuo to afford 6.62 g of a mixture of the title compounds.

20 $\text{C}_{12}\text{H}_{14}\text{O}_4$

Mass (calculated): [244]; found: 245.

NMR (400 MHz, CDCl_3): 3.8 (3H, s, CH_3O); 5.8 (1H, bs, OH); 6.95 (3H, m, aryl-H); 7.35 (2H, d, $J = 8$ Hz, aryl-H); 7.9-8 (2H, m, aryl-H).



25 Mass (calculated): [272]; found: 273.

NMR (400 MHz, CDCl_3): 1.3 (3H, t, $J = 6$ Hz, $\text{CH}_3\text{CH}_2\text{O}$); 3.8 (3H, s, CH_3O); 4.3 (2H, q, $J = 6$ Hz, $\text{CH}_3\text{CH}_2\text{O}$); 5.75 (1H, s, OH); 6.9-7 (3H, m, aryl-H); 7.35 (2H, d, $J = 8$ Hz, aryl-H); 7.9-7.95 (2H, m, aryl-H).

Step 4) 4-hydroxy-3-(4-methoxyphenyl)benzyl alcohol:

30 A solution of Ethyl 4-hydroxy-3-(4-methoxyphenyl)benzoate and 4-hydroxy-3-(4-methoxyphenyl)benzoic acid (5.3 g, 19.47 mmol) in anhydrous THF (100 mL) was cooled to 0°C and treated with LiAlH_4 (2.95 g, 77.8 mmol); the mixture was

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then heated at 65 C for one hour then cooled and aqueous NaOH (5%, 19.4 mL) was added drop wise. The resulting precipitate was filtered off and the filtrate concentrated under reduced pressure to afford 5.54 g of crude product.



5 Mass (calculated): [230]; found: 213 [$\text{MH}^+ - \text{OH}$].

NMR (400 MHz, CDCl_3): 3.8 (3H, s, CH_3O); 4.55 (2H, s, CH_2); 6.9 (1H, d, $J = 8$ Hz, aryl-H); 6.9-7 (2H, m, aryl-H); 7.25-7.35 (2H, m, aryl-H); 7.4-7.45 (2H, m, aryl-H).

10 Step 5) 4-Hydroxy-3-(4-methoxyphenyl)benzaldehyde:

A solution of 4-hydroxy-3-(4-methoxyphenyl)benzyl alcohol (5.54 g, 24 mmol) in acetone (250 mL) was treated with MnO_2 and the mixture stirred for 3 days. The solid was filtered on diatomaceous earth and the filtrate was concentrated under reduced pressure to afford 5.96 g of title compound as a pale green oil, impure with manganese salts.



Mass (calculated): [228]; found: 229.

Step 6) 4-Propargyloxy-3-(4-methoxyphenyl)benzaldehyde:

20 A solution of 4-hydroxy-3-(4-methoxyphenyl)benzaldehyde (1.14 g, 5 mmol) in DMF (10 mL) was treated with potassium carbonate (2.48 g, 18 mmol), potassium iodide (10 mg) and propargyl bromide (0.67 mL, 6 mmol). The mixture was heated at 80 C for 3 days, then cooled and the solvent removed under reduced pressure. The residue was redissolved in ethyl acetate and washed water then
25 brine. The organic layer was dried over sodium sulphate then the solvent removed under reduced pressure and the residue purified by column chromatography (3/1 hexane/ethyl acetate) to afford 0.078 g of title compound.



Mass (calculated): [266]; found: 267.

30 NMR (400 MHz, CDCl_3): 2.45 (1H, t, $J = 1$ Hz, $\text{C}\equiv\text{CH}$); 3.75 (3H, s, CH_3O); 4.7 (2H, d, $J = 1$ Hz, $\text{C}\equiv\text{CCH}_2\text{O}$); 6.85 (2H, d, $J = 8$ Hz, aryl-H); 7.15 (1H, d, $J = 8$ Hz, aryl-H); 7.4 (2H, d, $J = 8$ Hz, aryl-H); 7.75-7.85 (2H, m, aryl-H).

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Step 7) (R)-N-(1-Phenylethyl)-N-((4-propargyloxy-3-(4'-methoxyphenyl)phenylmethyl)amine:

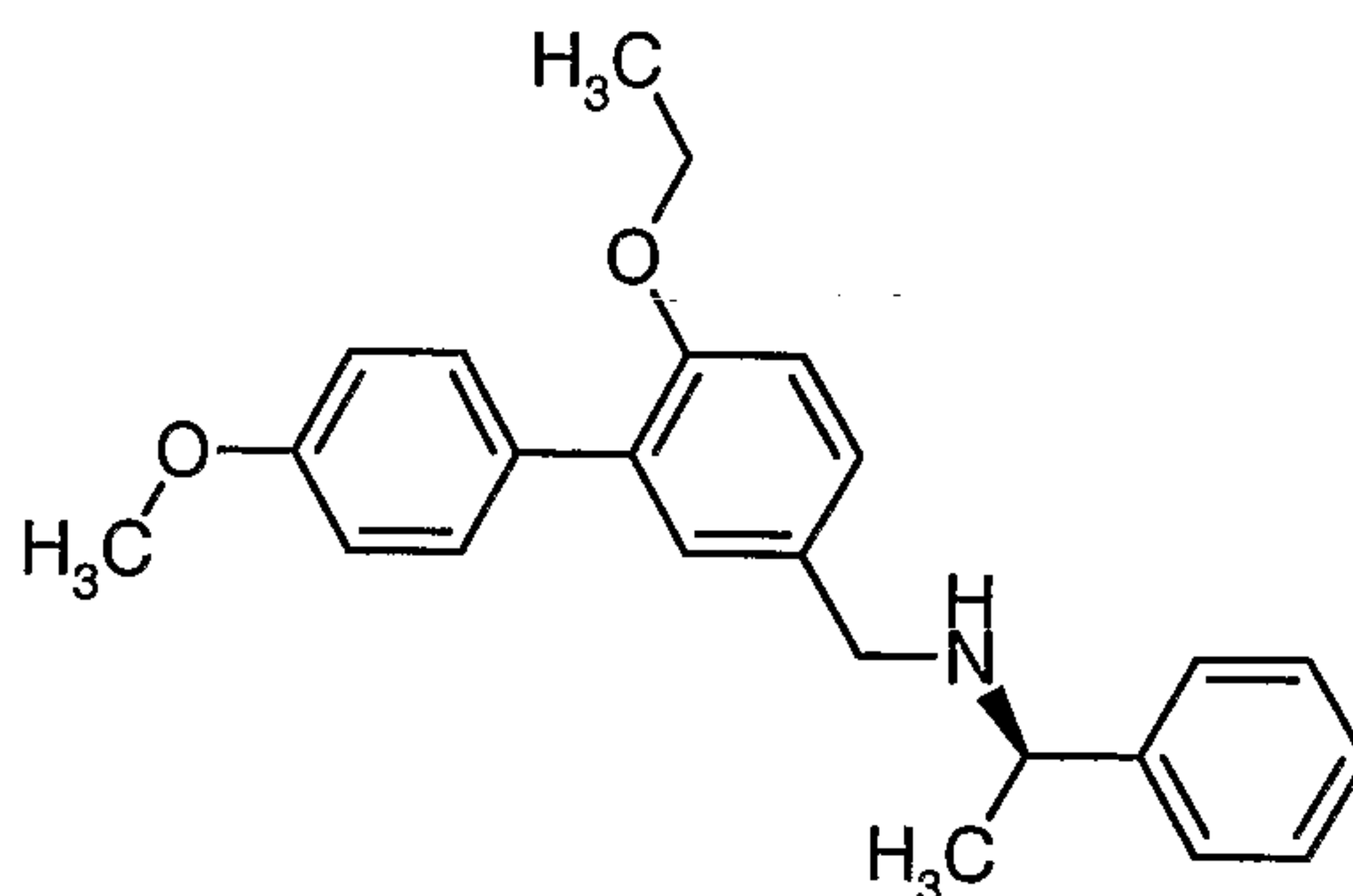
The title compound was prepared from 4-propargyloxy-3-(4-methoxyphenyl)-
5 benzaldehyde and (R)- α -methylbenzylamine according to general procedure C.
 $C_{25}H_{25}NO_2$

Mass (calculated): [371]; (found): $[M+H^+] = 372$.

NMR (400 MHz, $CDCl_3$): 1.3 (3H, d, $J = 6$ Hz, $NCHCH_3$); 2.3 (1H, t, $J = 1$ Hz, $C\equiv CH$); 3.5 and 3.55 (2H, dd, $J = 12$ Hz, CH_2N); 3.75-3.8 (4H, m, $NCHMe$ and
10 MeO); 4.55 (2H, d, $J = 1$ Hz, $C\equiv CCH_2O$); 6.85 (2H, d, $J = 8$ Hz, aryl-H); 7 (1H, d, $J = 8$ Hz, aryl-H); 7.1-7.2 (3H, m, aryl-H); 7.25-7.35 (4H, m, aryl-H); 7.4 (2H, d, $J = 8$ Hz, aryl-H).

Example 38

15 (R)-N-(1-Phenylethyl)-N-((4-ethoxy-3-(4'-methoxyphenyl)phenylmethyl)amine



Step 1) 4-Ethoxy-3-(4-methoxyphenyl)benzaldehyde:

A solution of 4-hydroxy-3-(4-methoxyphenyl)benzaldehyde (0.5 g, 2.19 mmol) in
20 DMF (5 mL) was treated with potassium carbonate (0.9 g, 6.57 mmol), potassium
iodide (10 mg) and ethyl iodide (0.21 mL, 0.263 mmol). The mixture was heated at
80 °C for 3 days, then cooled and the solvent removed under reduced pressure.
The residue was redissolved in ethyl acetate and washed water then brine. The
organic layer was dried over sodium sulphate then the solvent removed under
25 reduced pressure and the residue purified by column chromatography (3/1
hexane/ethyl acetate) to afford 0.043 g of title compound.

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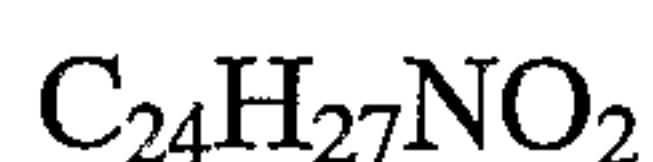


Mass (calculated): [256]; found: 257.

NMR (400 MHz, CDCl_3): 1.3 (3H, t, $J = 6$ Hz, $\text{CH}_3\text{CH}_2\text{O}$); 3.75 (3H, s, CH_3O); 4.1 (2H, q, $J = 6$ Hz, $\text{CH}_3\text{CH}_2\text{O}$); 6.85 (2H, d, $J = 8$ Hz, aryl-H); 6.95 (1H, d, $J = 8$ Hz, aryl-H); 7.4 (2H, d, $J = 8$ Hz, aryl-H); 7.7 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 7.75 (1H, d, $J = 1$ Hz, aryl-H).

Step 2) (R)-N-(1-Phenylethyl)-N-((4-ethoxy-3-(4'-methoxyphenyl)phenyl)methyl)amine

10 The title compound was prepared from 4-ethoxy-3-(4-methoxyphenyl)benzaldehyde and (R)- α -methylbenzylamine according to general procedure C.



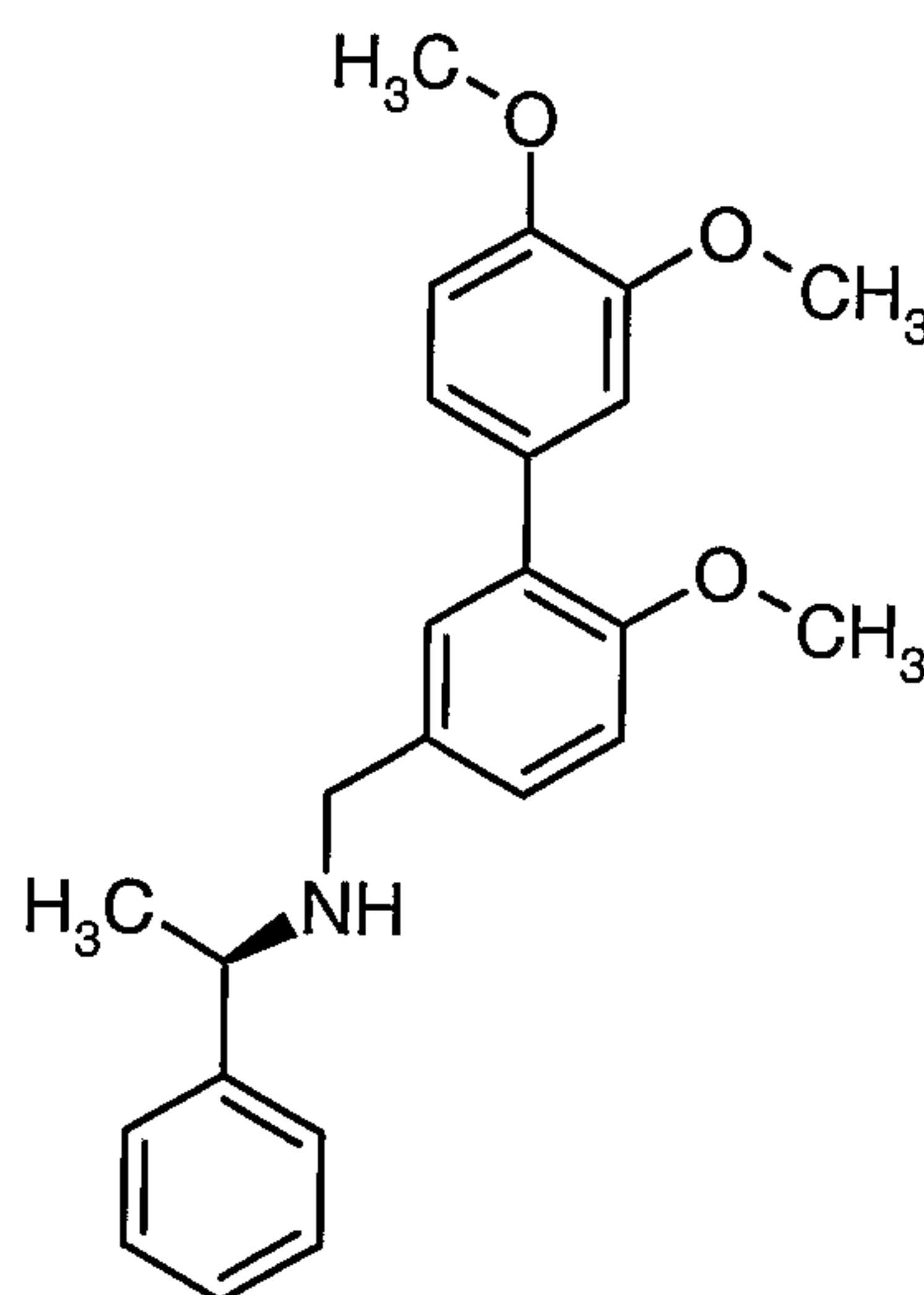
Mass (calculated): [361]; (found): $[\text{M}+\text{H}^+] = 362$.

15 NMR (400 MHz, CDCl_3): 1.25 (3H, t, $J = 6$ Hz, OCH_2CH_3) 1.3 (3H, d, $J = 6$ Hz, NCHCH_3); 3.5 and 3.55 (2H, dd, $J=12$ Hz, CH_2N); 3.75-3.8 (4H, m, NCHMe and MeO); 3.95 (2H, q, $J = 6$ Hz, OCH_2CH_3); 6.8 (1H, d, $J = 8$ Hz, aryl-H); 6.85 (2H, d, $J = 8$ Hz, aryl-H); 7.15-7.35 (2H, m, aryl-H); 7.35-7.4 (4H, m, aryl-H); 7.45 (2H, d, $J = 8$ Hz, aryl-H).

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Example 39

(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(3,4-dimethoxyphenyl)phenyl)methyl)amine



5

Step 1) 4-Methoxy-3-(3,4-dimethoxyphenyl)benzenecarboxaldehyde:

To a degassed solution of 3,4-dimethoxybenzeneboronic acid (2.18 g, 12 mmol), 3-bromo-4-methoxybenzaldehyde (3.23 g, 15 mmol) and potassium carbonate (5.18 g, 37.5 mmol) in toluene/ethanol 2/1 (72 mL), Pd(PPh₃)₄ (173 mg, 1.2 mol%) was added and the mixture was degassed for further 5 minutes. The mixture was then refluxed for 15 hours. The solid was filtered off and the filtrate concentrated under reduced pressure. The residue was dissolved in AcOEt, partitioned between ethyl acetate and water and extracted then washed with brine. The organic solvent was dried over sodium sulphate, removed under reduced pressure, and the residue purified by column chromatography (heptane/ethyl acetate 1/1) to afford 2.95 of title compound.

C₁₆H₁₆O₄

Mass (calculated): [272]; found: 273.

NMR (400 MHz, CDCl₃): 3.85-3.87 (9H, 3s, 3 CH₃O); 6.9 (1H, d, *J* = 8 Hz, aryl-H); 6.9-7.05 (3H, m, aryl-H); 7.85-7.9 (2H, m, aryl-H); 9.85 (1H, s, CHO).

20

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Step 2) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(3,4-dimethoxyphenyl)-phenylmethyl)amine:

The title compound was prepared from 4-methoxy-3-(3,4-dimethoxyphenyl)benzenecarboxaldehyde and (R)- α -methylbenzylamine according to general procedure C.

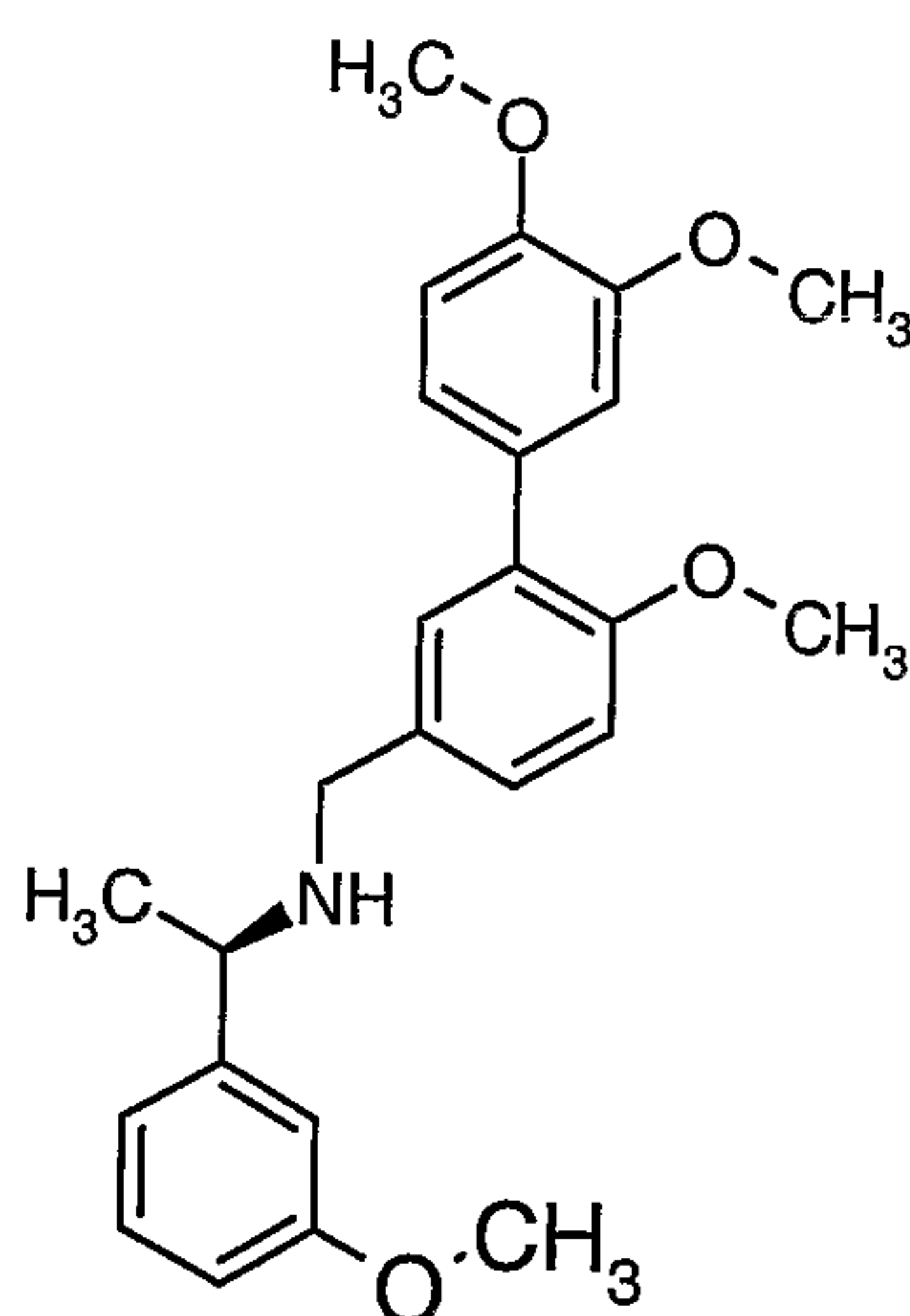


Mass (calculated): [377]; (found): $[\text{M}+\text{H}^+] = 378$.

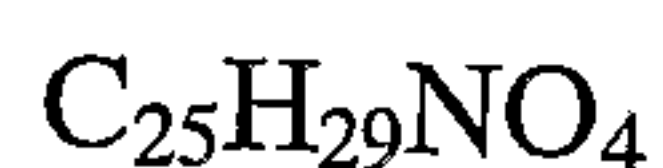
NMR (400 MHz, CDCl_3): 1.3 (3H, t, $J = 6$ Hz, NCHCH_3); 3.55 and 3.6 (2H, dd, $J=12$ Hz, CH_2N); 3.7 (3H, s, CH_3O); 3.8-4 (7H, m, NCHMe and 2 MeO); 6.8-6.85 (2H, m, aryl-H); 6.95-7.05 (2H, m, aryl-H); 7.1-7.15 (2H, m, aryl-H); 7.25-7.4 (4H, m, aryl-H).

Example 40

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(3,4-dimethoxyphenyl)phenylmethyl)amine



The title compound was prepared from 4-methoxy-3-(3,4-dimethoxyphenyl)benzenecarboxaldehyde and (R)-3-methoxy- α -methylbenzylamine according to general procedure C.



Mass (calculated): [407]; (found): $[\text{M}+\text{H}^+] = 408$.

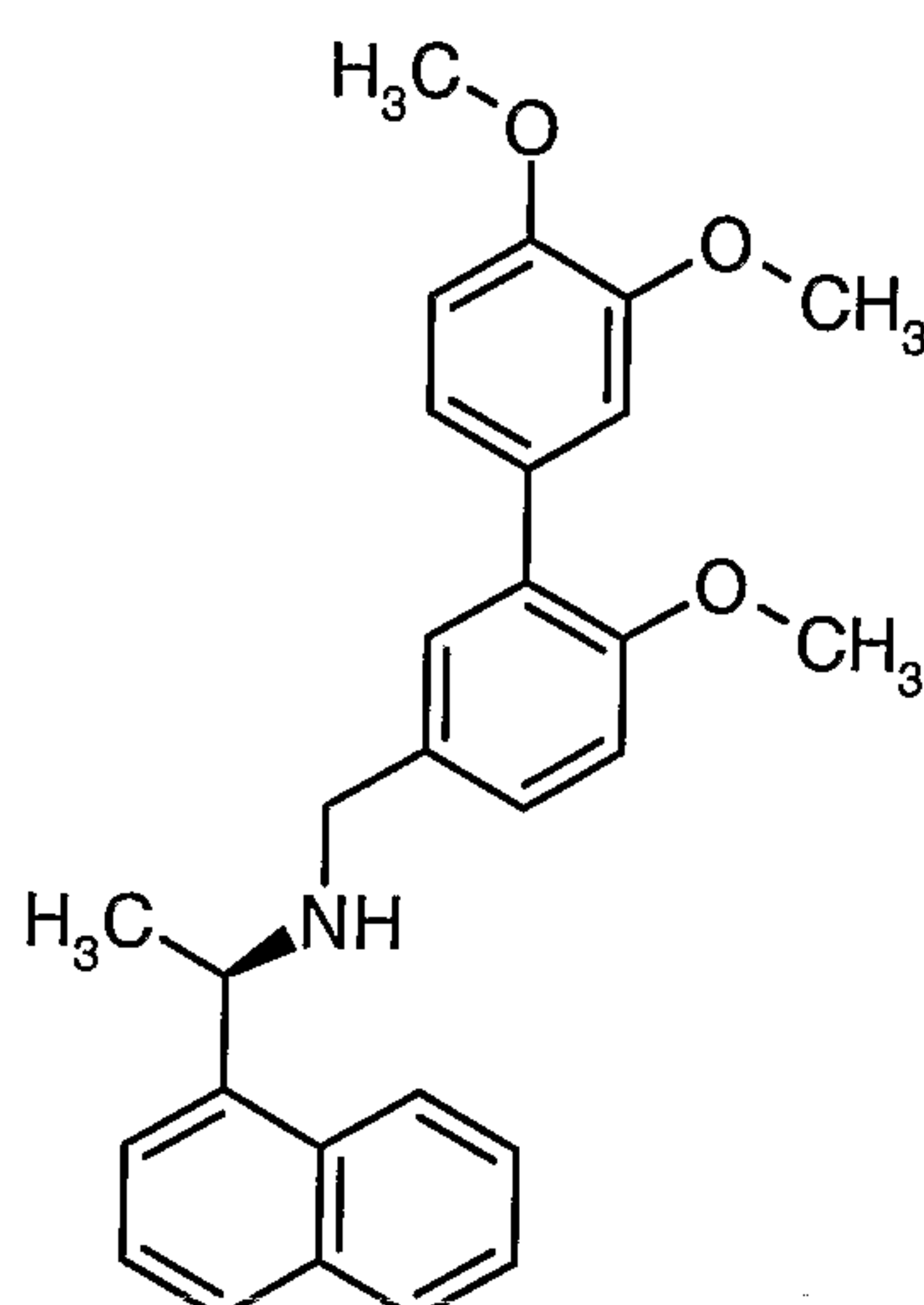
- 74 -

NMR (400 MHz, CDCl_3): 1.3 (3H, t, $J = 6$ Hz, NCHCH_3); 3.55 and 3.6 (2H, dd, $J=12$ Hz, CH_2N); 3.7 and 3.72 (6H, 2 s, 2 CH_3O); 3.8-3.9 (4H, m, NCHMe and CH_3O); 6.8 (1H, dd, $J = 2$ and 8 Hz, aryl-H); 6.8-6.9 (2H, m, aryl-H); 6.9-7 (2H, m, aryl-H); 7-7.05 (2H, m, aryl-H); 7.15-7.3 (3H, m, aryl-H).

5

Example 41

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(3,4-dimethoxyphenyl)-phenyl)methyl)amine



10

The title compound was prepared from 4-methoxy-3-(3,4-dimethoxyphenyl) benzenecarboxaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

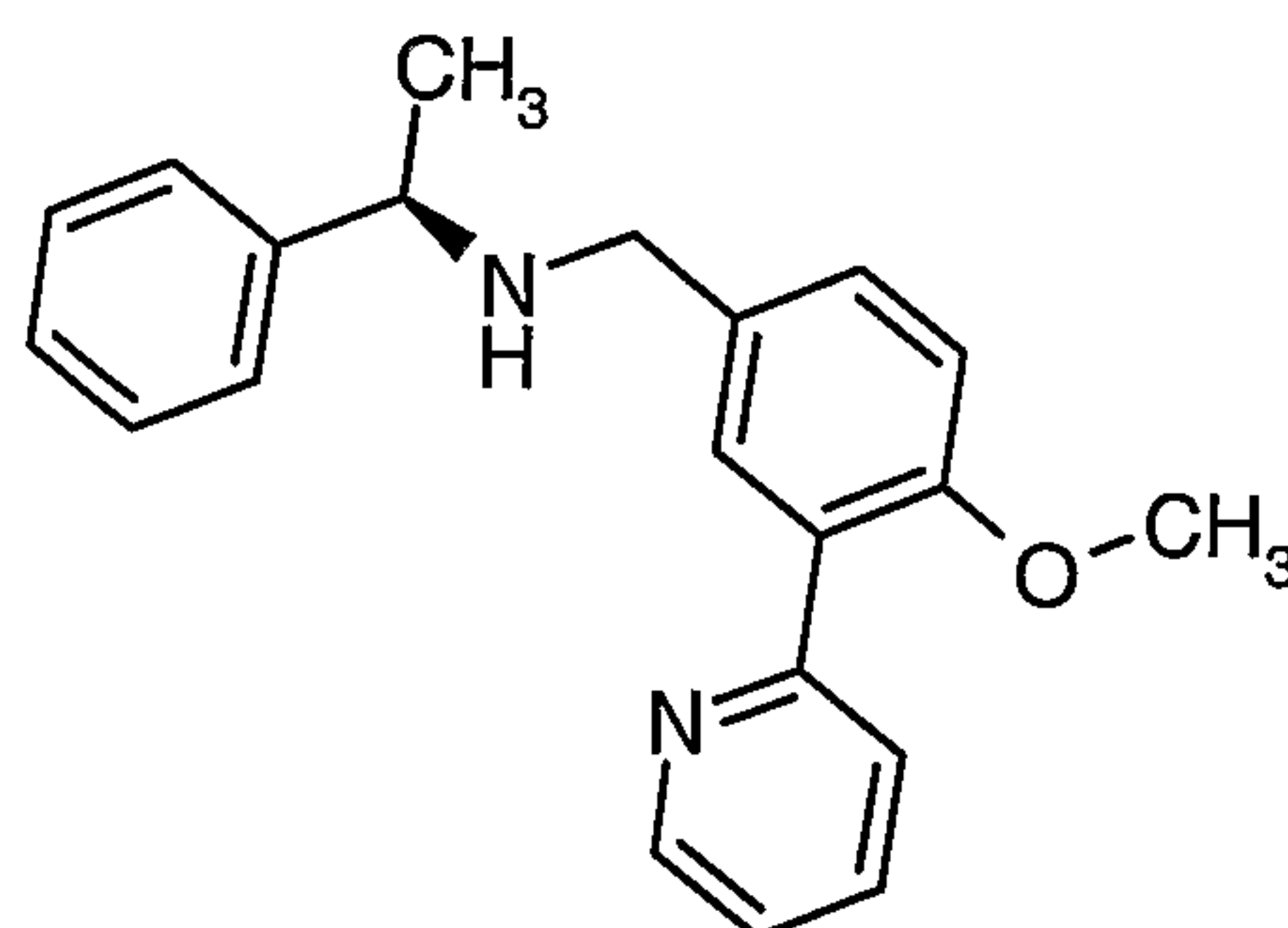
$\text{C}_{28}\text{H}_{29}\text{NO}_3$

15 Mass (calculated): [427]; (found): $[\text{M}+\text{H}^+] = 428, 257, 155$.

NMR (400 MHz, CDCl_3): 1.4 (3H, t, $J = 6$ Hz, NCHCH_3); 3.55 and 3.6 (2H, dd, $J=12$ Hz, CH_2N); 3.7 (3H, s, CH_3O); 3.8 and 3.82 (6H, 2 s, 2 CH_3O); 6.8-6.85 (2H, m, aryl-H); 6.95-7.0 (2H, m, aryl-H); 7.1-7.2 (2H, m, aryl-H); 7.3-7.5 (3H, m, aryl-H); 7.65-7.7 (2H, m, aryl-H); 7.75-7.8 (1H, m, aryl-H); 8.05-8.1 (1H, m, aryl-H).

20

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Example 42**(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(pyrid-2-yl)phenyl)methyl)amine**

5

Step 1) 4-Methoxy-3-(pyrid-2-yl)benzenecarboxaldehyde:

A degassed solution of 2-bromopyridine (1.0 g, 6.33 mmol), 3-borono-4-methoxybenzaldehyde (1.37 g, 7.6 mmol) and $[(PPh_3)_2PdCl_2]$ (64 mg, 0.09 mmol) in dimethoxyethane (30 mL), methanol (5 mL) and Na_2CO_3 (2M, 20 mL) was heated at 75 °C for 16 hours. The mixture was then cooled, diluted with water and extracted with DCM. The organic layer was dried over sodium sulphate and the solvent removed under reduced pressure. The crude was purified by column chromatography (heptane/AcOEt 7/3 to 6/4) to afford 1.31 g of title compound.

15 Mass (calculated): [213]; (found) $[M+H^+] = 214$.

NMR (400 MHz, $CDCl_3$): 3.85 (3H, s, MeO); 7.05 (1H, d, $J = 8$ Hz, aryl/pyridyl-H); 7.2 (1H, m, aryl/pyridyl -H); 7.65 (1H, m, aryl/pyridyl -H); 7.75 (1H, m, aryl/pyridyl-H); 7.85 (1H, m, aryl/pyridyl-H); 8.2 (1H, s, aryl/pyridyl-H); 8.65 (1H, s, aryl/pyridyl-H); 9.9 (1H, s, CHO).

20

Step 2) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(pyrid-2-yl)phenyl)methyl)amine

The title compound was prepared from 4-methoxy-3-(pyrid-2-yl)benzenecarboxaldehyde and (R)- α -methylbenzylamine according to general procedure C.

25 $C_{21}H_{22}N_2O$

Mass (calculated): [318]; (found): $[M+H^+] = 319, 198$.

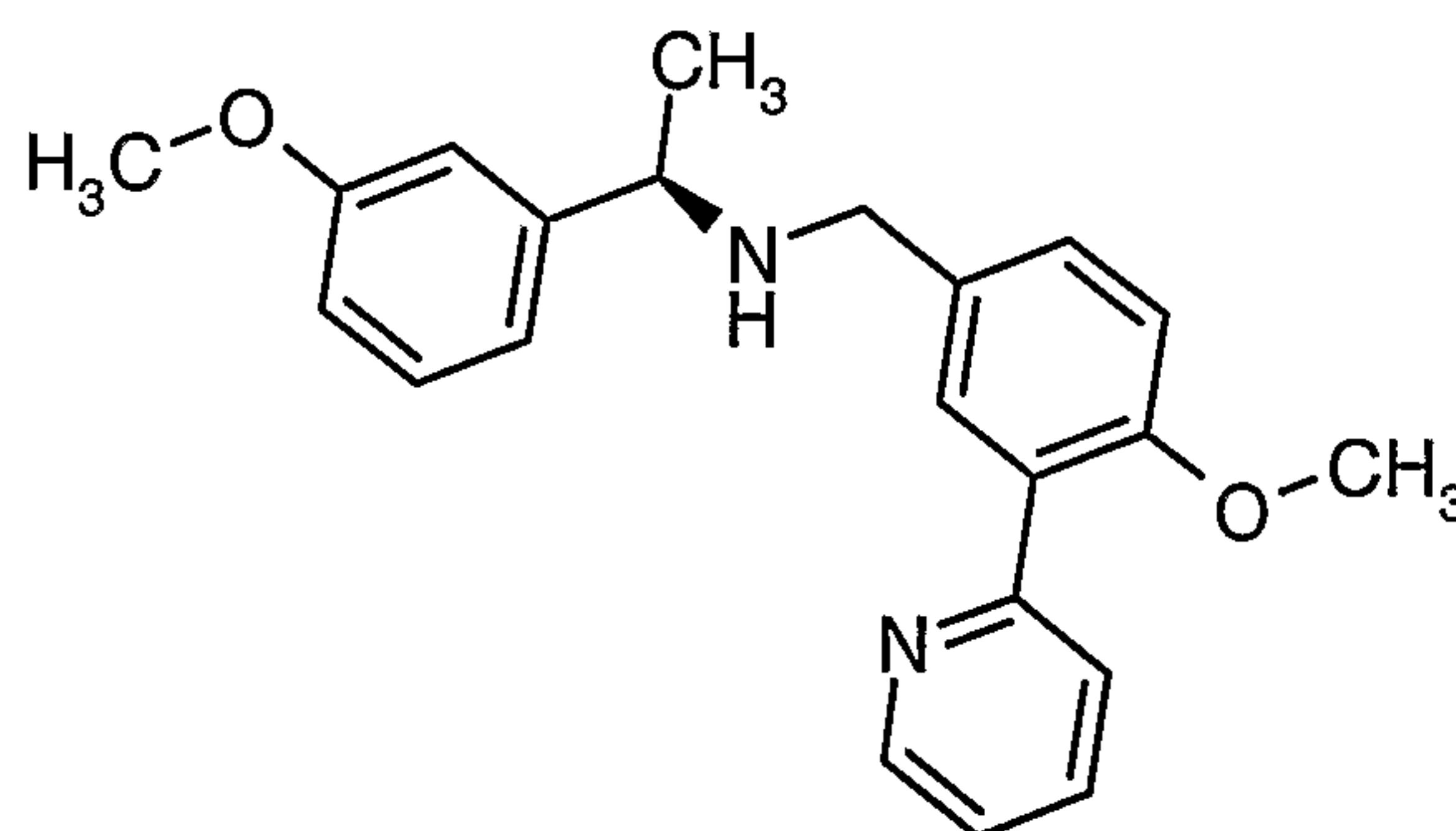
- 76 -

NMR (400 MHz, CDCl₃): 1.3 (3H, d, $J = 6$ Hz, NCHCH₃); 3.5 and 3.55 (2H, dd, $J = 12$ Hz, CH₂N); 3.7 (3H, s, MeO); 3.75 (1H, q, $J = 7$ Hz, NCHMe); 6.8 (1H, d, $J = 8$ Hz, aryl-H); 7.05-7.1 (1H, m, aryl-H); 7.15-7.35 (6H, m, aryl-H); 7.55-7.6 (2H, m, aryl-H); 7.7 (1H, d, $J = 8$ Hz, aryl-H); 8.55-8.6 (1H, m, pyridyl-H).

5

Example 43

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(pyrid-2-yl)phenyl)methyl)amine



10

The title compound was prepared from 4-methoxy-3-(pyrid-2-yl)benzenecarboxaldehyde and (R)-3-methoxy- α -methylbenzylamine according to general procedure C.

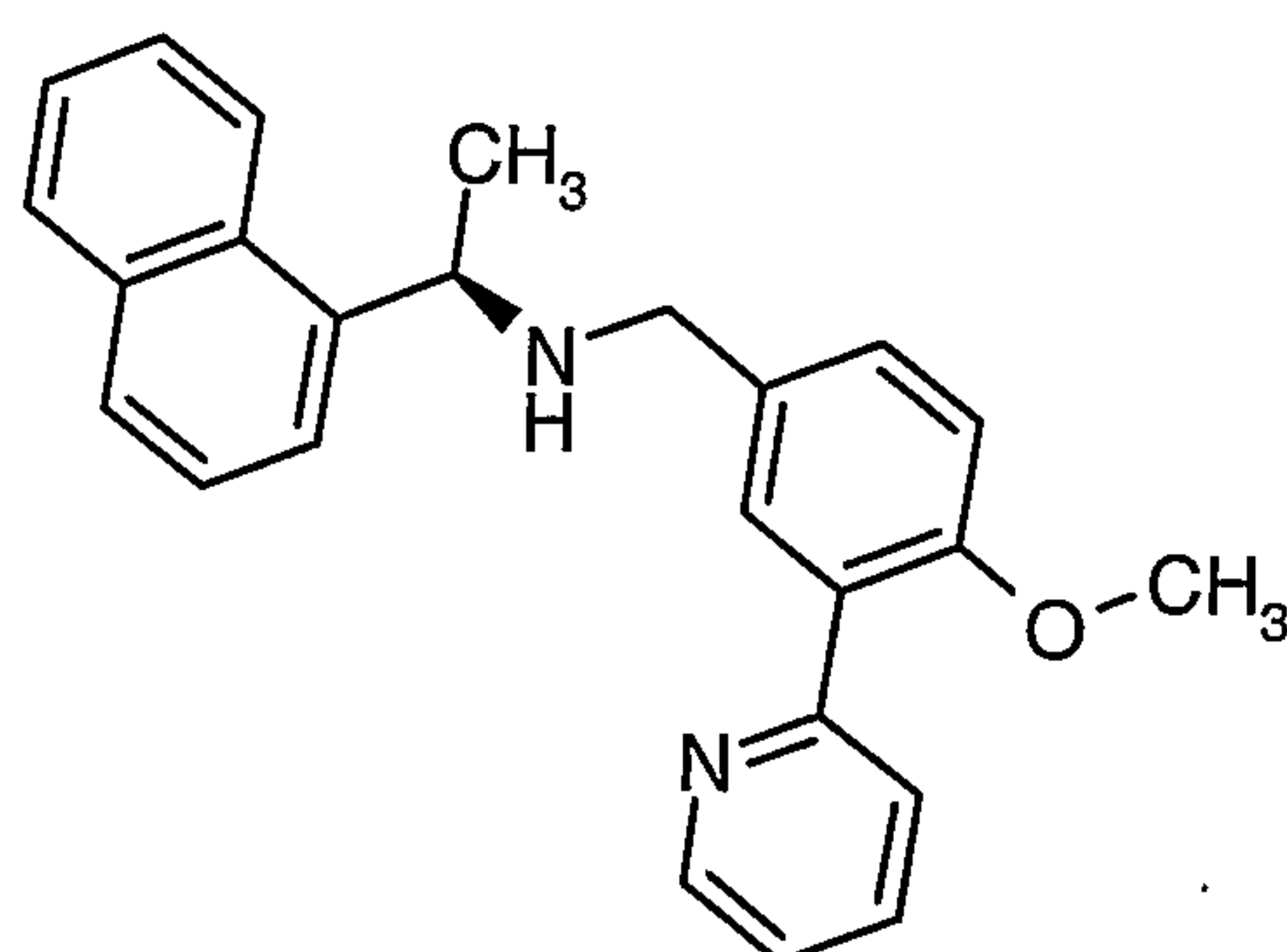
C₂₂H₂₄N₂O₂

15 Mass (calculated): [348]; (found): [M+H⁺] = 349, 198.

NMR (400 MHz, CDCl₃): 1.3 (3H, d, $J = 6$ Hz, NCHCH₃); 3.55 and 3.6 (2H, dd, $J = 12$ Hz, CH₂N); 3.7-3.8 (7H, m, 2 MeO and NCHMe); 6.7 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 6.8-6.9 (3H, m, aryl-H); 7.05-7.3 (3H, m, aryl-H); 7.55-7.65 (2H, m, aryl-H); 7.75 (1H, d, $J = 8$ Hz, aryl-H); 7.7 (1H, d, $J = 8$ Hz, aryl-H); 8.6 (1H, m, pyridyl-H).

20

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Example 44**(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(pyrid-2-yl)phenylmethyl)amine**

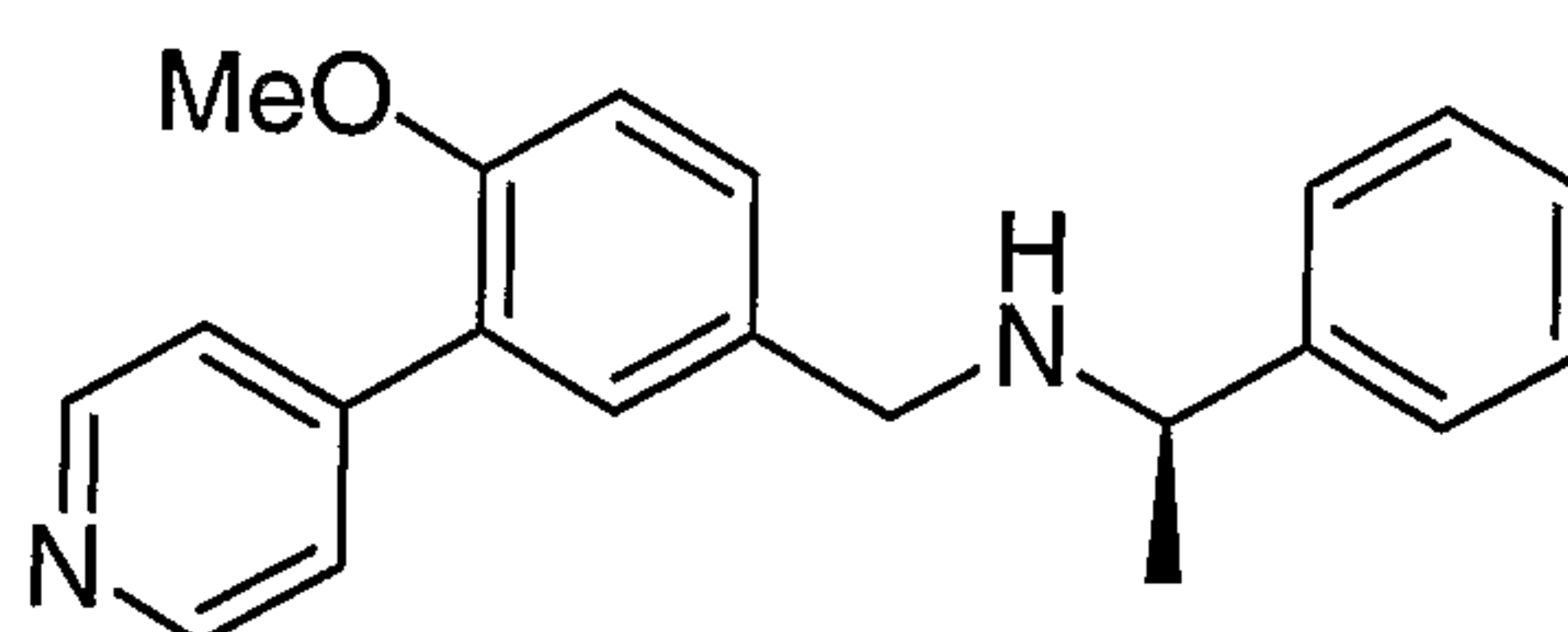
- 5 The title compound was prepared from 4-methoxy-3-(pyrid-2-yl)benzenecarboxaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

$C_{25}H_{24}N_2O$

Mass (calculated): [368]; (found): $[M+H^+] = 369, 198$.

- 10 NMR (400 MHz, $CDCl_3$): 1.45 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.6 and 3.65 (2H, dd, $J=12$ Hz, CH_2N); 3.75 (3H, s, MeO); 4.65 (1H, q, $J = 7$ Hz; $NCHMe$); 6.8 (1H, d, $J = 8$ Hz, aryl-H); 7.05-7.1 (1H, m, aryl-H); 7.15-7.25 (1H, m, aryl-H); 7.3-7.45 (3H, m, aryl-H); 7.5-7.6 (2H, m, aryl-H); 7.6-7.75 (3H, m, aryl-H); 7.75-7.8 (1H, m, aryl-H); 8-8.05 (1H, m, aryl-H); 8.55-8.6 (1H, m, pyridyl-H).

15

Example 45**(R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(pyrid-4-yl)phenylmethyl)amine**

20

Step 1) 4-Methoxy-3-(pyrid-4-yl)benzenecarboxaldehyde:

A degassed solution of 4-bromopyridine hydrochloride (1.36 g, 7 mmol), 3-borono-4-methoxybenzaldehyde (1.37 g, 7.6 mmol) and $[(PPh_3)_2PdCl_2]$ (246 mg, 0.35 mmol) in dimethoxyethane (30 mL), methanol (5 mL) and Na_2CO_3 (2M, 20

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mL) was heated at 75 °C for 16 hours. The mixture was then cooled, diluted with water and extracted with DCM. The organic layer was dried over sodium sulphate and the solvent removed under reduced pressure. The crude was purified by column chromatography (heptane/AcOEt 3/1) to afford 1.18 g of title compound

5 $C_{13}H_{11}NO_2$

Mass (calculated): [213]; (found) $[M+H^+] = 214$.

NMR (400 MHz, $CDCl_3$): 3.85 (3H, s, MeO); 7.05 (1H, d, $J = 8$ Hz, aryl-H); 7.4 (2H, d, $J = 7$ Hz, pyridyl-H); 7.8 (1H, d, $J = 1$ Hz, aryl-H); 7.85 (1H, dd, $J = 1$ and 8 Hz); 8.6 (2H, d, $J = 7$ Hz, pyridyl-H).

10

Step 2) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(pyrid-4-yl)phenylmethyl)amine:

The title compound was prepared from 4-methoxy-3-(pyrid-4-yl)benzenecarboxaldehyde and (R)- α -methylbenzylamine according to general procedure C.

$C_{21}H_{22}N_2O$

15 Mass (calculated): [318]; (found): $[M+H^+] = 319, 215$.

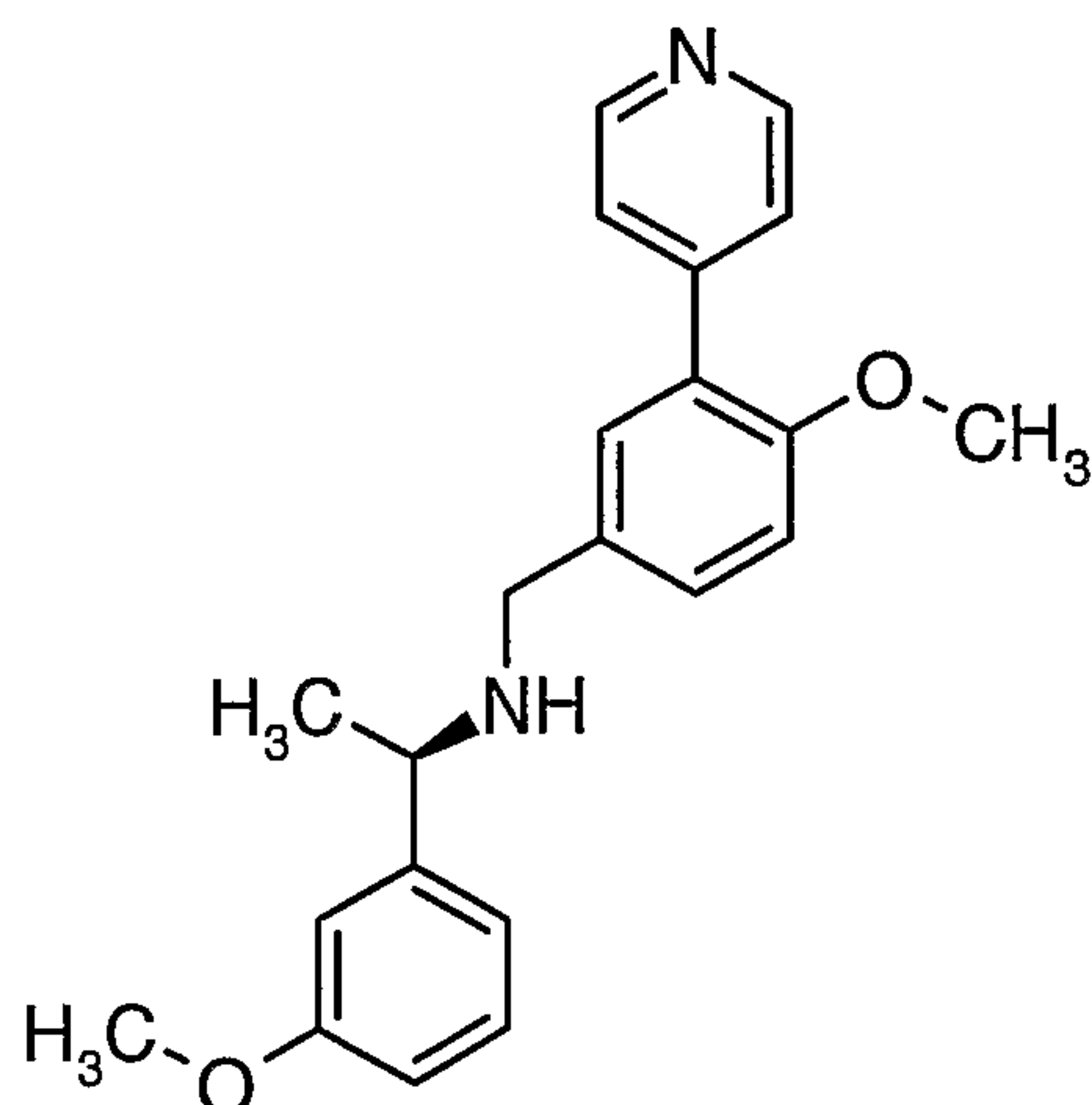
NMR (400 MHz, $CDCl_3$): 1.3 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.55 (2H, bq, CH_2N); 3.75 (3H, s, MeO); 3.8 (1H, bq, $NCHMe$); 6.85 (1H, d, $J = 8$ Hz, aryl-H); 7.15-7.25 (3H, m, aryl-H); 7.25-7.3 (4H, m, aryl-H); 7.45 (2H, bs, pyridyl-H); 8.4-8.6 (2H, bs, pyridyl-H).

20

Example 46

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(pyrid-4-yl)phenylmethyl)amine

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The title compound was prepared from 4-methoxy-3-(pyrid-4-yl)benzene-carboxaldehyde and (R)-3-methoxy- α -methylbenzylamine according to general procedure C.

5 $C_{22}H_{24}N_2O_2$

Mass (calculated): [348]; (found): $[M+H^+] = 349, 215$.

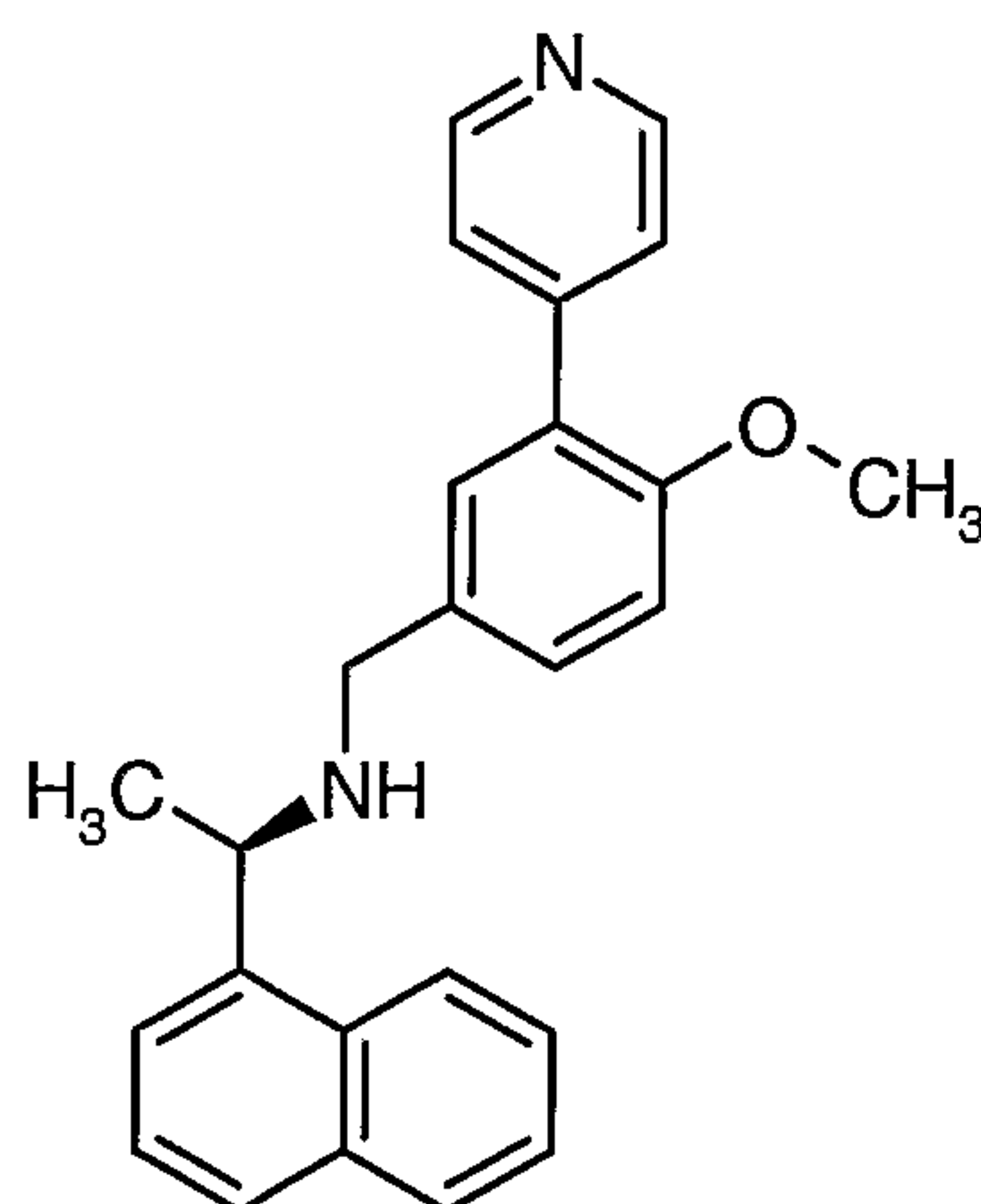
NMR (400 MHz, $CDCl_3$): 1.3 (3H, d, $J = 7$ Hz, $NCHCH_3$); 3.55 and 3.6 (2H, dd, $J = 12$ Hz, CH_2N); 3.75 (3H, s, MeO); 3.8 (1H, q, $J = 7$ Hz, $NCHMe$); 6.75 (1H, d, $J = 8$ Hz, aryl-H); 6.85-6.9 (3H, m, aryl-H); 7.15-7.25 (3H, m, aryl-H); 7.4 (2H, bd, pyridyl-H); 8.5 (2H, bs, pyridyl-H).

10

Example 47

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(pyrid-4-yl)phenyl)methyl)amine

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The title compound was prepared from 4-methoxy-3-(pyrid-4-yl)benzenecarboxaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

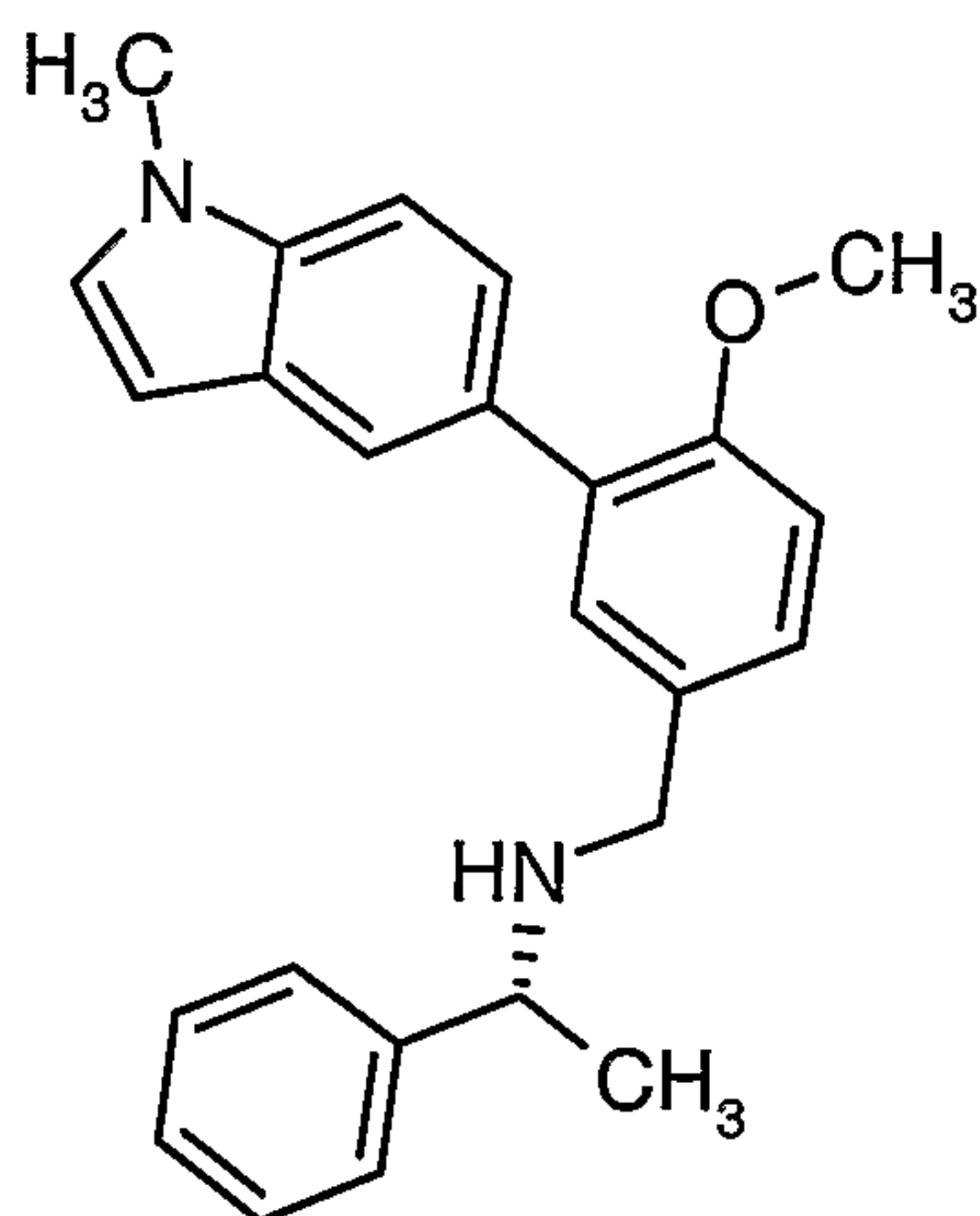
5 $C_{25}H_{24}N_2O$

Mass (calculated): [368]; (found): $[M+H^+] = 369, 215$.

NMR (400 MHz, $CDCl_3$): 1.5 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.55 and 3.6 (2H, dd, $J = 12$ Hz, CH_2N); 3.75 (3H, s, MeO); 4.7 (1H, bq, $NCHMe$); 6.85 (1H, d, $J = 8$ Hz, aryl-H); 7.15 (1H, d, $J = 1$ Hz, aryl-H); 7.3 (1H, dd, $J = 1$ and 8 Hz, aryl-H);
 10 7.35 (2H, d, $J = 5$ Hz, pyridyl-H); 7.35-7.5 (3H, m, aryl-H); 7.65-7.7 (2H, m, aryl-H); 7.85 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 8 (1H, d, $J = 8$ Hz, aryl-H); 8.5 (2H, bd, pyridyl-H).

Example 48

15 ((1R)-1-Phenylethyl){[4-methoxy-3-(1-methylindol-5-yl)phenyl]methyl}amine



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Step 1) 3-(Indol-5-yl)-4-methoxybenzaldehyde:

A solution of 5-formyl-2-methoxybenzeneboronic acid (5 g, 28.5 mmol), 5-bromoindole (5 g, 25.5 mmol) and K_2CO_3 (7.7 g, 56 mmol) in ethanol (25 mL) and toluene (50 mL) was degassed prior to addition of $Pd(Ph_3)_4$ (300 mg, 0.25 mmol). The mixture was refluxed for 16 hours then cooled and concentrated in vacuo, extracted with dichloromethane, washed with water and the organic layer dried over sodium sulphate. The crude was purified by column chromatography (hexane/ethyl acetate 6/4) to give 4.5 g of title compound.

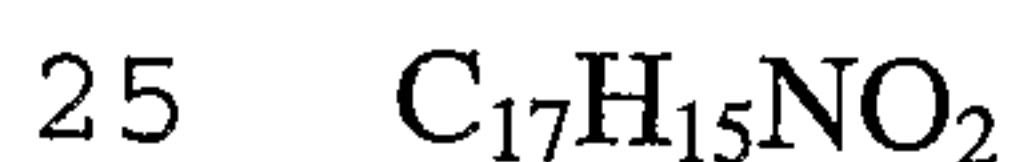


Mass (calculated): [251]; (found): $[M+H^+] = 252$.

NMR (400 MHz, $CDCl_3$): 3.75 (3H, s, CH_3O); 6.45 (1H, m, indole-H); 6.95 (1H, d, $J = 8$ Hz, aryl-H); 7.05-7.15 (1H, m, aryl-H); 7.3 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 7.4 (1H, d, $J = 8$ Hz, aryl-H); 7.65 (1H, s, aryl-H); 7.7 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 7.75 (1H, d, $J = 1$ Hz, aryl-H); 8.1 (1H, bs, NH); 9.8 (1H, s, CHO).

Step 2) 3-(1-Methylindol-5-yl)-4-methoxybenzaldehyde:

A solution of 3-(indol-5-yl)-4-methoxybenzaldehyde (0.50 g, 2.0 mmol) in DMF (10 mL) was cooled to 0 °C and NaH (60% dispersion in mineral oil, 0.14 g, 3.0 mmol) was added. The mixture was stirred at 0 °C for 45 minutes, then methyl iodide (0.34 g, 4.4 mmol) was added and the reaction was stirred for 16 hours at room temperature. The mixture was then poured into water and extracted with ethyl acetate, washed with water and dried over sodium sulphate. The solvent was removed in vacuo and the crude was purified by column chromatography (hexane/ethyl acetate 7/3) to give 0.48 g of title compound.



Mass (calculated): [265]; (found): $[M+H^+] = 266$.

NMR (400 MHz, $CDCl_3$): 3.85 (3H, s, CH_3O); 3.95 (3H, s, CH_3N); 6.65 (1H, m, indole-H); 7.10-7.25 (2H, m, aryl-H); 7.4-7.5 (2H, m, aryl-H); 7.8 (1H, s, aryl-H); 7.9 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 8 (1H, d, $J = 1$ Hz, aryl-H); 10 (1H, s, CHO).

Step 3) ((1R)-1-Phenylethyl){[4-methoxy-3-(1-methylindol-5-yl)phenyl]methyl}amine:

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The title compound was prepared from 3-(1-methylindol-5-yl)-4-methoxybenzaldehyde and (R)- α -methylbenzylamine according to general procedure C.

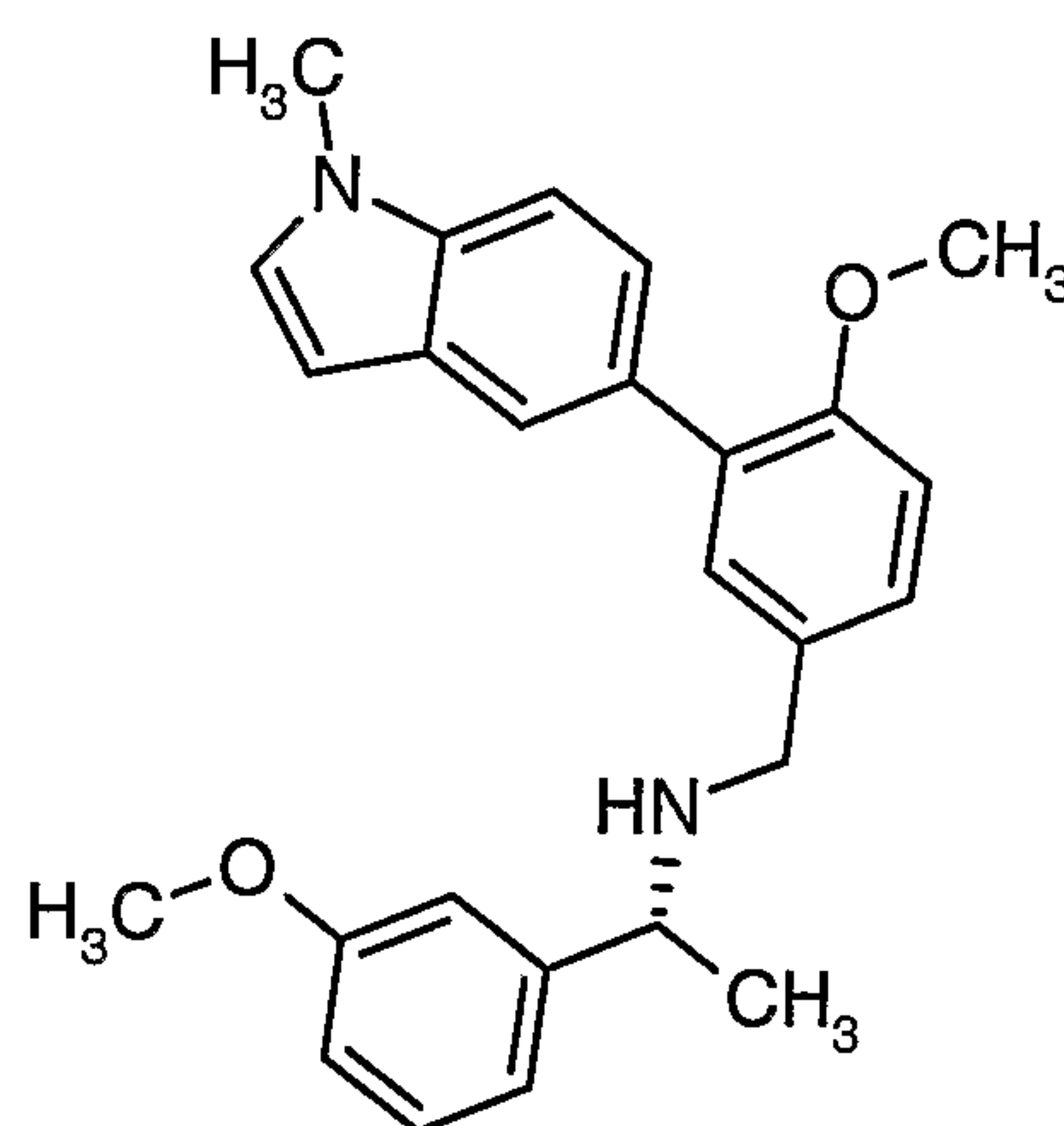
$C_{25}H_{26}N_2O$

5 Mass (calculated): [370]; (found): $[M+H^+] = 371, 250$.

Example 49

[(1R)-1-(3-Methoxyphenyl)ethyl]{[4-methoxy-3-(1-methylindol-5-yl)phenyl]methyl} amine

10



The title compound was prepared from 3-(1-methylindol-5-yl)-4-methoxybenzaldehyde and (R)-3-methoxy- α -methylbenzylamine according to general procedure C.

15 $C_{26}H_{28}N_2O_2$

Mass (calculated): [400]; (found): $[M+H^+] = 401$.

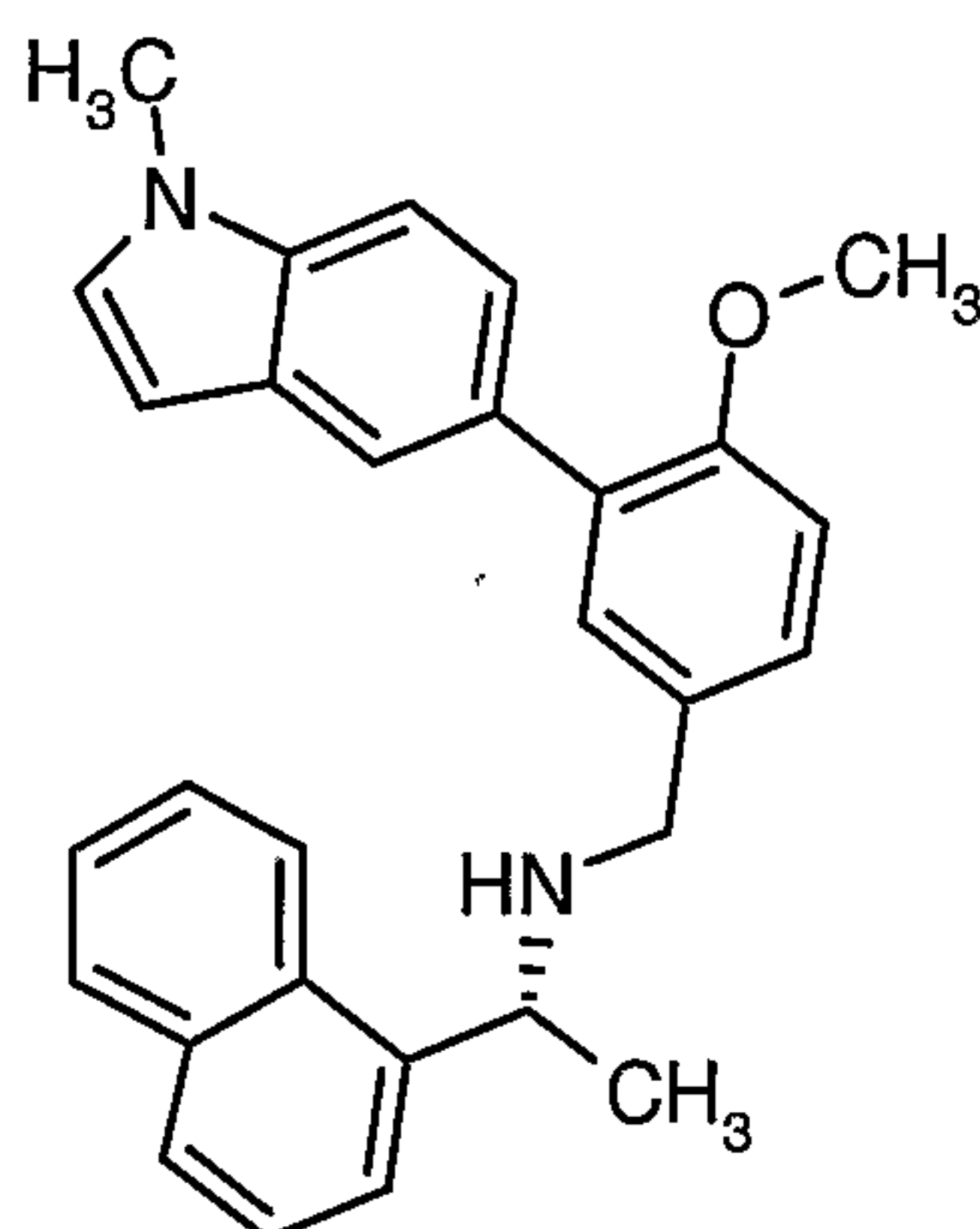
NMR (400 MHz, $CDCl_3$): 1.3 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.55 and 3.6 (2H, dd, $J = 12$ Hz, CH_2N); 3.65-3.8 (10H, m, 3 MeO and $NCHMe$); 6.4 (1H, d, $J = 5$ Hz, indole-H); 6.7 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 6.8-6.9 (3H, m, aryl-H); 6.95 (1H, d, $J = 2$ Hz, aryl-H); 7.1-7.3 (4H, m, aryl-H); 7.35 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 7.65 (1H, d, $J = 1$ Hz, aryl-H).

20

Example 50

((1R)-1-Naphthylethyl){[4-methoxy-3-(1-methylindol-5-yl)phenyl]methyl} amine

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The title compound was prepared from 3-(1-methylindol-5-yl)-4-methoxybenzaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure C.

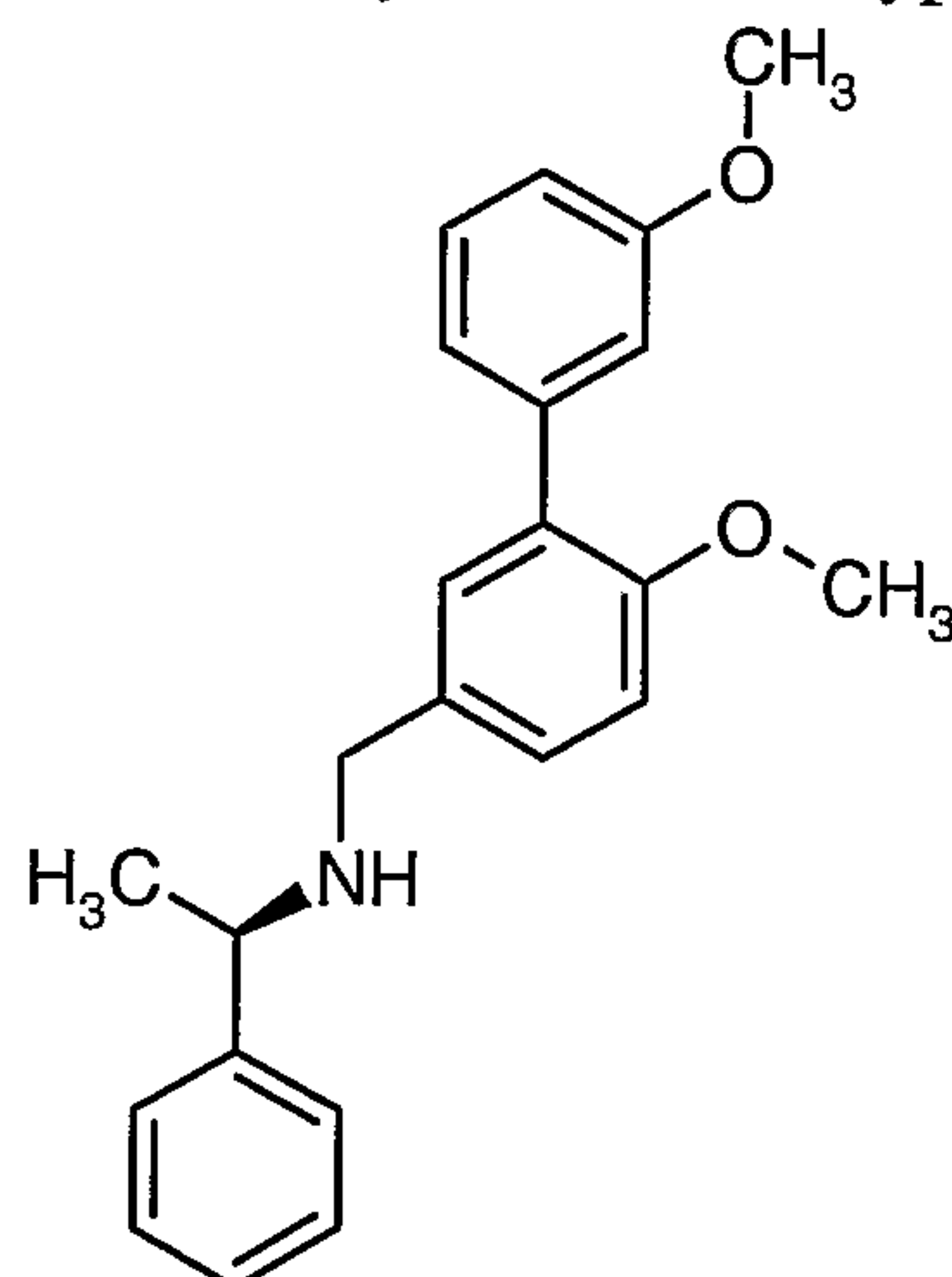
5 $C_{29}H_{28}N_2O$

Mass (calculated): [420]; (found): $[M+H^+] = 421$.

NMR (400 MHz, $CDCl_3$): 1.6 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.8 and 3.85 (2H, dd, $J = 12$ Hz, CH_2N); 3.85 and 3.87 (6H, m, 2 MeO); 4.8 (1H, q, $J = 6$ Hz, $NCHMe$); 6.6 (1H, d, $J = 5$ Hz, indole-H); 7 (1H, d, $J = 8$ Hz, aryl-H); 7.1 (1H, d, $J = 1$ Hz, aryl-H); 7.3 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 7.35-7.4 (2H, m, aryl-H); 7.5 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 7.5-7.6 (3H, m, aryl-H); 7.8-7.9 (3H, m, aryl-H); 7.95-7.8 (1H, m, aryl-H); 8.2-8.3 (1H, m, aryl-H).

Example 51

15 (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(3-methoxyphenyl)phenyl)methyl)amine



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Step 1) 4-Methoxy-3-(3-methoxyphenyl)benzenecarboxaldehyde:

A degassed solution of 3-bromoanisole (1.31 g, 7 mmol), 3-borono-4-methoxybenzaldehyde (1.38 g, 7.4 mmol) and [(PPh₃)₂PdCl₂] (246 mg, 0.35 mmol) in dimethoxyethane (35 mL), methanol and Na₂CO₃ 2M (20 mL) was heated at 75 °C for 24 hours. The mixture was then cooled, diluted with water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate and the solvent removed under reduced pressure. The crude was purified by column chromatography (heptane/AcOEt 4/1) to afford 1.14 g of title compound.



Mass (calculated): [242]; (found): [M+H⁺] = 243; [M+H⁺+MeCN] = 284.
NMR (400 MHz, CDCl₃): 3.85 (3H, s, MeO); 3.95 (3H, s, MeO); 6.9 (1H, dd, *J* = 1 and 8 Hz, aryl-H); 7.05-7.15 (1H, m, aryl-H); 7.35 (1H, t, *J* = 8 Hz, aryl-H); 7.85-7.95 (2H, m, aryl-H); 9.85 (1H, s, CHO).

Step 2) (R)-N-(1-Phenylethyl)-N-((4-methoxy-3-(3-methoxyphenyl)phenylmethyl)amine:

The title compound was prepared from 4-methoxy-3-(3-methoxyphenyl)benzenecarboxaldehyde and (R)-α-methylbenzylamine according to general procedure C.

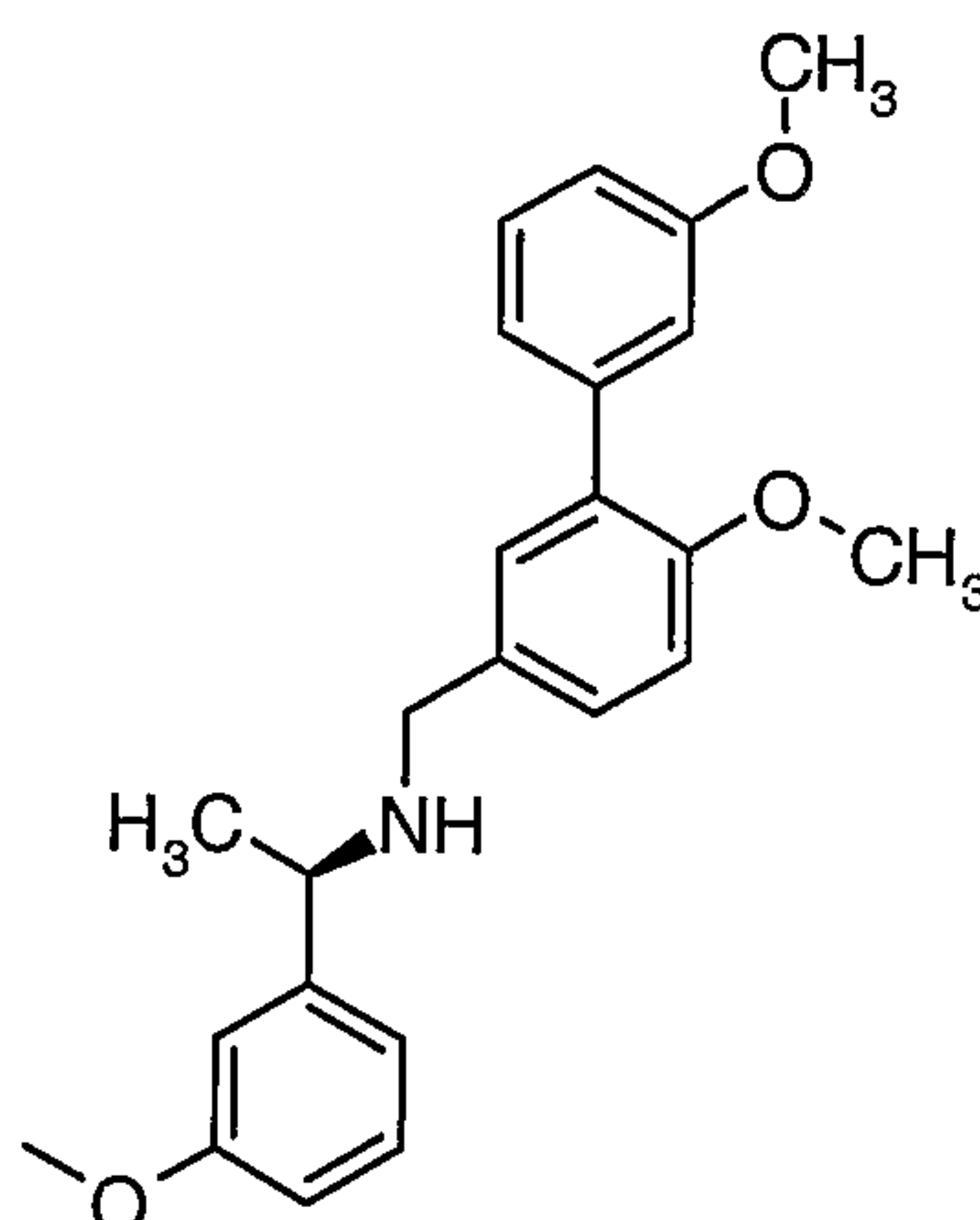


Mass (calculated): [347]; (found): [M+H⁺] = 348.
NMR (400 MHz, CDCl₃): 1.3 (3H, d, *J* = 6 Hz, NCHCH₃); 3.5 and 3.55 (2H, dd, *J* = 12 Hz, CH₂N); 3.7 (3H, s, MeO); 3.75-3.85 (4H, m, NCHMe and MeO); 6.75-6.9 (2H, m, aryl-H); 7-7.1 (2H, m, aryl-H); 7.1-7.2 (3H, m, aryl-H); 7.2-7.3 (5H, m, aryl-H).

Example 52

(R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-methoxy-3-(3-methoxyphenyl)phenylmethyl)amine

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The title compound was prepared from 4-methoxy-3-(3-methoxyphenyl)benzene-carboxaldehyde and (R)-3-methoxy- α -methylbenzylamine according to general procedure C.

5 $C_{24}H_{27}NO_3$

Mass (calculated): [377]; (found): $[M+H^+] = 378$.

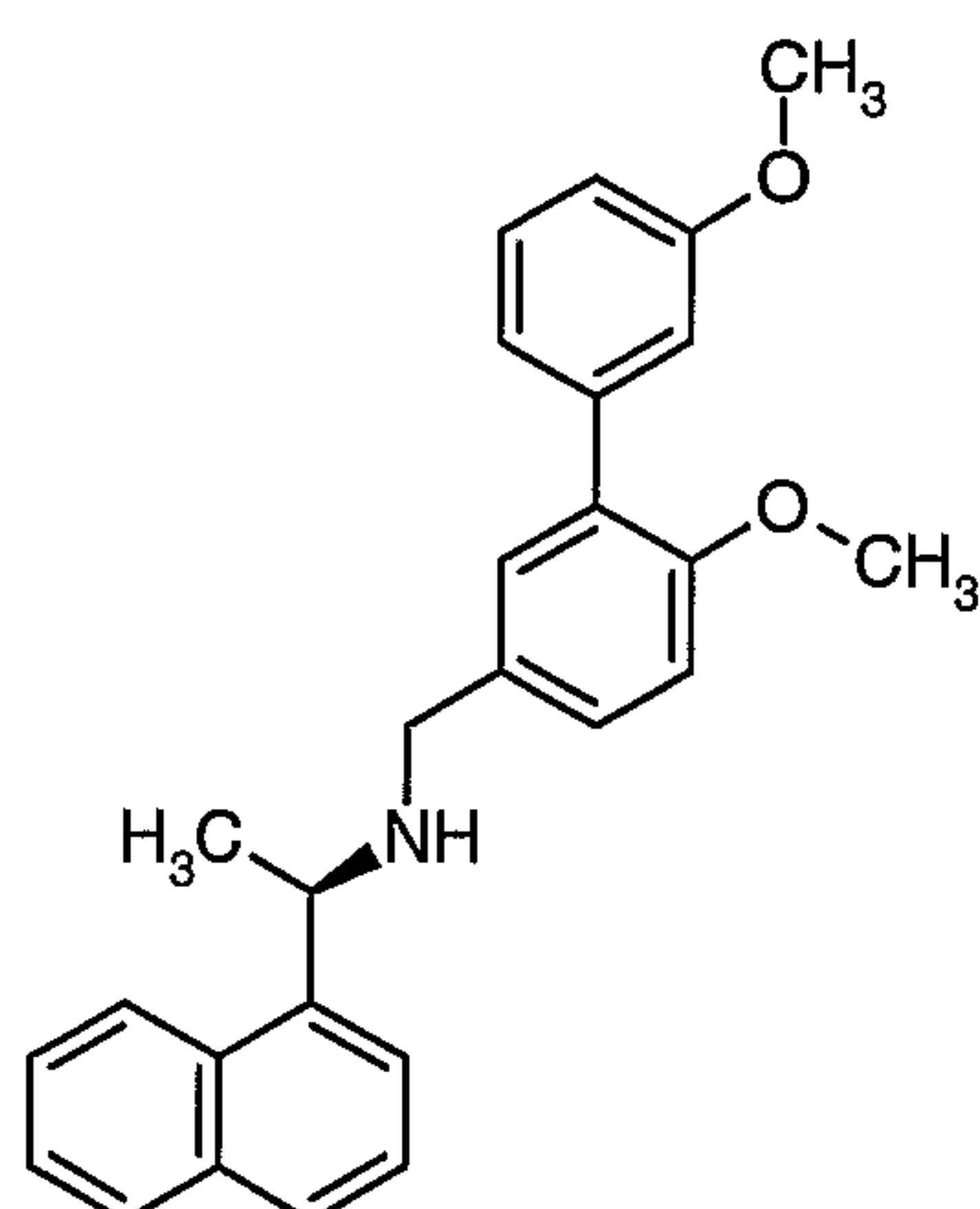
NMR (400 MHz, $CDCl_3$): 1.4 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.6 and 3.65 (2H, dd, $J = 12$ Hz, CH_2N); 3.8-3.9 (10H, 3 s and m, $NCHMe$ and 3 MeO); 6.8 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 6.9 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 6.95-7 (3H, m, aryl-H);

10 7.1-7.2 (2H, m, aryl-H); 7.2-7.4 (4H, m, aryl-H).

Example 53

(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-methoxy-3-(3-methoxyphenyl)phenyl)methyl)amine

- 86 -



The title compound was prepared from 4-methoxy-3-(3-methoxyphenyl)benzene-carboxaldehyde and (R)-1-(1-naphthyl)ethylamine according to general
 5 procedure C.

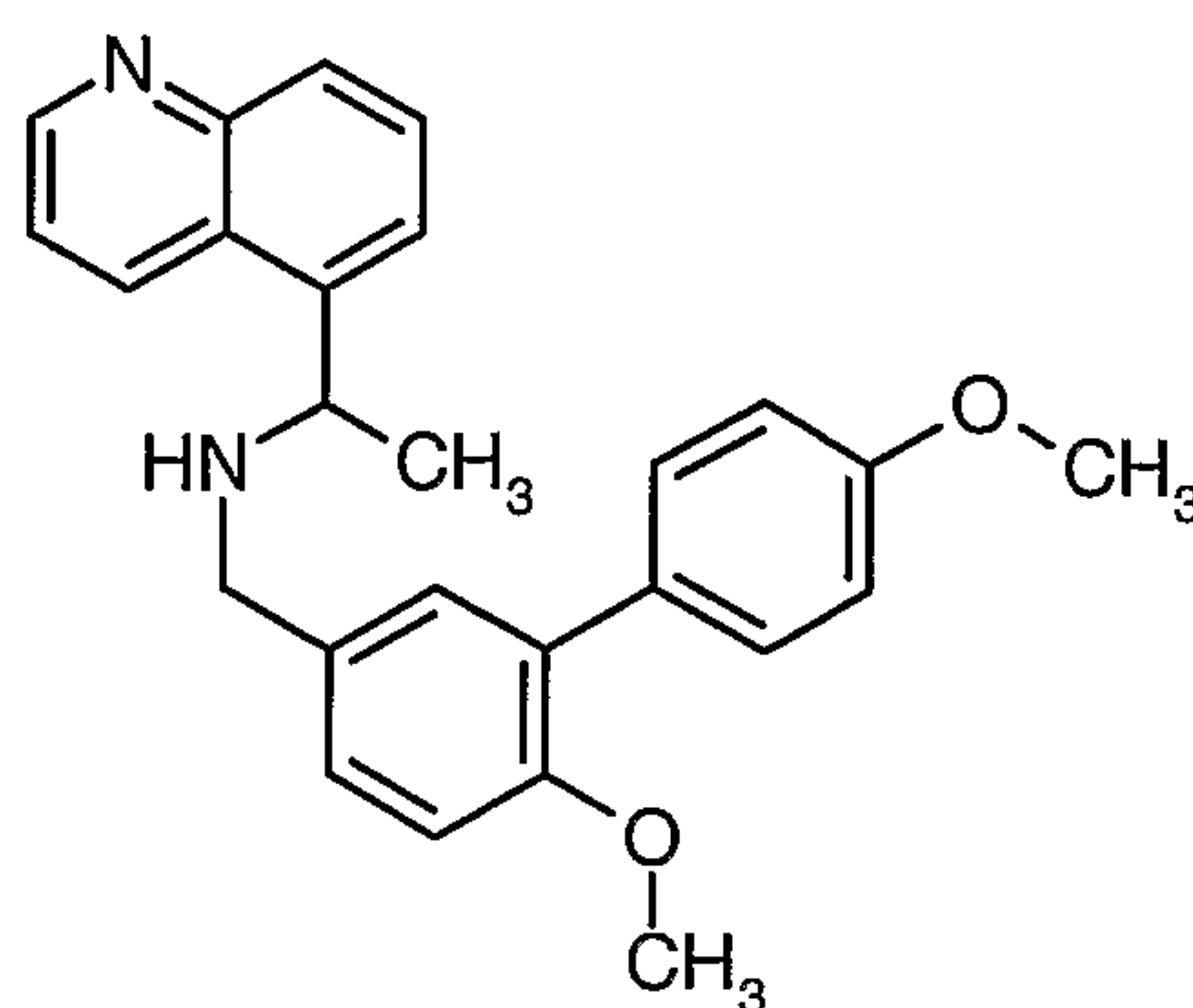
$C_{27}H_{27}NO_2$

Mass (calculated): [397]; (found): $[M+H^+] = 398$.

NMR (400 MHz, $CDCl_3$): 1.45 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.6 and 3.65 (2H, dd, $J = 12$ Hz, CH_2N); 3.7 and 3.75 (6H, 2 s, 2 MeO); 4.65 (1H, q, $J = 6$ Hz,
 10 $NCHMe$); 6.75-6.9 (2H, m, aryl-H); 7-7.1 (2H, m, aryl-H); 7.1-7.25 (3H, m, aryl-H); 7.4-7.45 (3H, m, aryl-H); 7.7 (2H, d, $J = 8$ Hz, aryl-H); 7.75-7.8 (1H, m, aryl-H); 8.05-8.1 (1H, m, aryl-H).

Example 54

15 *N*-(1-(Quinol-5-yl)ethyl)-*N*-((4-methoxy-3-(4'-methoxyphenyl)phenyl)methyl)amine



Step 1) 5-Trifluoromethanesulphonyloxyquinoline:

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A solution of 5-hydroxyquinoline (0.5 g, 3.4 mmol) in DCM (5 mL) was treated with pyridine (1.08 g, 13.7 mmol) and then trifluoromethanesulphone anhydride (1.1 g, 4.12 mmol). The mixture was stirred overnight then diluted with dichloromethane and washed with water. The organic layer was concentrated under reduced pressure and the excess pyridine azeotropically removed with toluene, to afford 0.47 g of title compound.

Step 2) 5-Acetylquinoline:

A degassed solution of 5-trifluoromethanesulphonyloxyquinoline (0.41 g, 1.47 mmol), butyl vinyl ether (0.38 mL, 2.94 mmol), palladium acetate (10 mg, 0.043 mmol), potassium carbonate (0.24 g, 1.76 mmol), 1,3-bis(diphenylphosphino)propane (40 mg, 0.097 mmol) in DMF (3.67 mL) and water (0.88 mL) was heated in a sealed tube at 100 °C for 16 hours.. The reaction mixture was then cooled and treated with 1M HCl and the mixture stirred for 30 minutes, then basified and extracted with dichloromethane. The organic layer was then evaporated under reduced pressure to afford the title compound.

Step 3) 4-Methoxy-3-(4-methoxyphenyl)benzyl alcohol:

A solution of 4-methoxy-3-(4-methoxyphenyl)benzenecarboxaldehyde (1 g, 4.13 mmol) in methanol (12 mL) was treated with polymer-supported borohydride (10.3 mmol) and the mixture shaken for 16 hours. The resin was then filtered and the filtrate concentrated under reduced pressure to afford 0.88 g of title compound.

Step 4) 4-Methoxy-3-(4-methoxyphenyl)benzylazide:

A solution of 4-methoxy-3-(4-methoxyphenyl)benzyl alcohol (0.88 g, 3.59 mmol) and diphenylphosphoryl azide (1.18 g, 4.32 mmol) in anhydrous THF (15 mL) was cooled in an ice-bath prior to addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (0.87 g, 5.76 mmol). The resulting mixture was then stirred at room temperature for 48 hours. More diphenylphosphoryl azide was added (1.4 mol, 0.39 g) and the mixture stirred for further 16 hours. The solvent was then evaporated, the residue taken into dichloromethane and washed with acid. The organic layer was

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separated and the solvent removed under reduced pressure to afford 0.82 g of title compound.

Step 5) 4-Methoxy-3-(4-methoxyphenyl)benzylamine:

- 5 A solution of 4-methoxy-3-(4-methoxyphenyl)benzylazide (0.82 g, 3.07 mmol) in ethanol (50 mL) was hydrogenated under atmospheric pressure for 16 hours. The catalyst was filtered off, the solvent removed under reduced pressure and the crude purified by column chromatography (hexane/ethyl acetate 6/1) to afford 400 mg of title compound.

10 $C_{15}H_{17}NO_2$

Mass (calculated): [243]; found: 227 ($MH^+ - NH_2$).

NMR (400 MHz, $CDCl_3$): 3.65 (3H, s, CH_3O); 3.7-3.8 (5H, m, CH_3O and aryl- CH_2O); 5.45 (2H, bs, NH_2); 6.75-6.95 (3H, m, aryl-H); 7.1-7.25 (2H, m, aryl-H); 7.4 (2H, d, $J = 8$ Hz, aryl-H).

15

Step 6) *N*-(1-(Quinol-5-yl)ethyl)-*N*-((4-methoxy-3-(4'-methoxyphenyl)phenyl)methyl)amine:

- A solution of 4-methoxy-3-(4-methoxyphenyl)benzylamine (243 mg, 1, mmol) and 5-acetylquinoline (152 mg, 0.89 mmol) in methanol (3 mL) was treated with
20 acetic acid (0.05 mL) and polymer-supported cyanoborohydride (0.9 g, 2.25 mmol). The mixture was stirred at 50 C for 20 hours, then cooled. The solid was filtered off and the filtrate concentrated in vacuo. The crude was purified by column chromatography (AcOEt/cyHex 7/3 to 100%AcOEt) to afford 91 mg of title compound.

25 $C_{26}H_{26}N_2O_2$

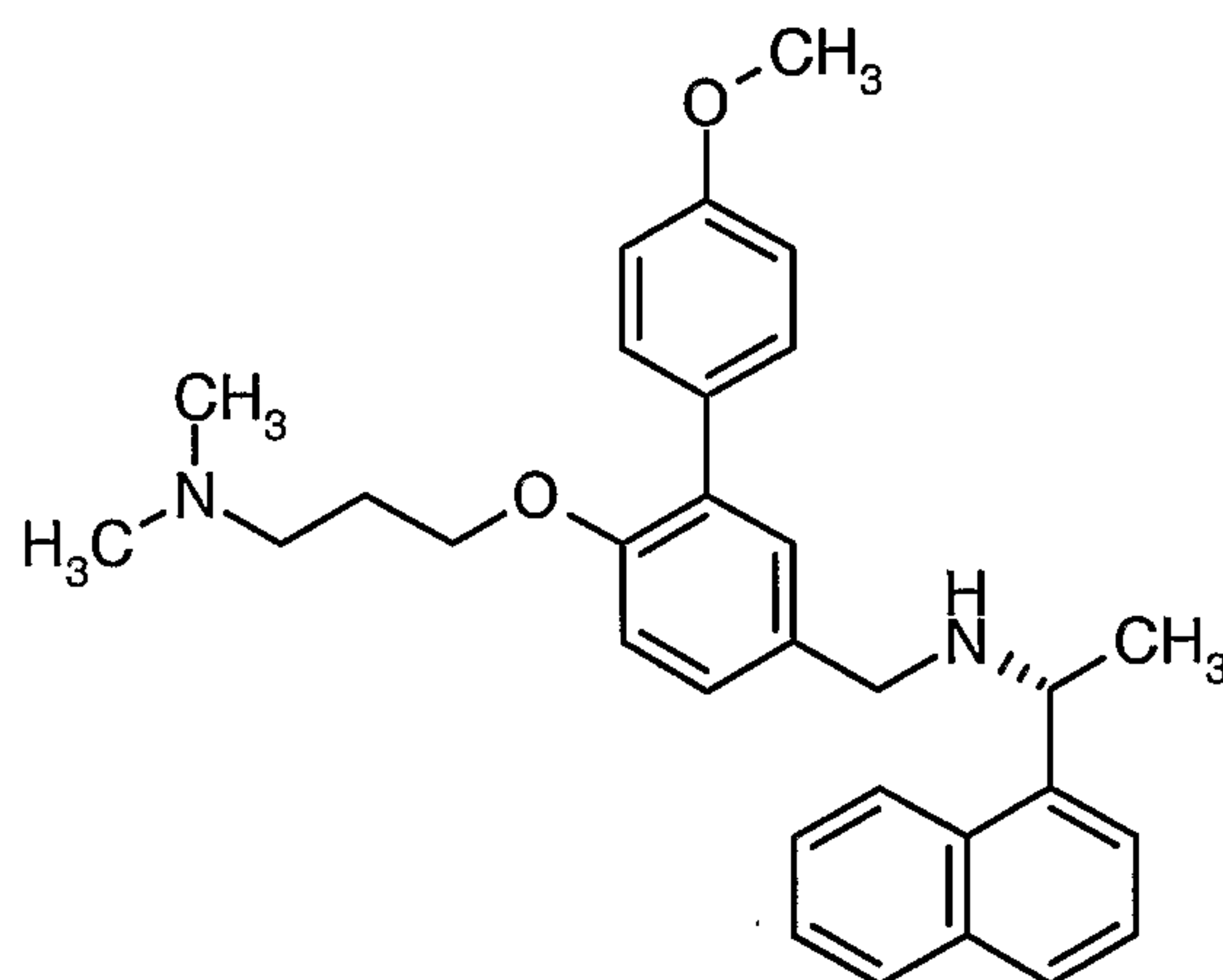
Mass (calculated): [398]; found: 399, 797.

- NMR (400 MHz, $CDCl_3$): 1.45 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.6 and 3.65 (2H, dd, $J = 12$ Hz, CH_2N); 3.7 and 3.75 (6H, 2 s, 2 MeO); 4.55 (1H, q, $J = 6$ Hz, $NCHCH_3$); 6.8-6.9 (3H, m, aryl-H); 7.1-7.2 (2H, m, aryl-H); 7.3 (1H, dd, $J = 4$
30 and 8 Hz, aryl-H); 7.35 (2H, $J = 8$ Hz, aryl-H); 7.75 (1H, t, $J = 6$ Hz, aryl-H); 7.75 (1H, d, $J = 8$ Hz, aryl-H); 7.95 (1H, d, $J = 8$ Hz, aryl-H); 8.55 (1H, d, $J = 8$ Hz, aryl-H); 8.8-8.9 (1H, m, aryl-H).

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Example 55

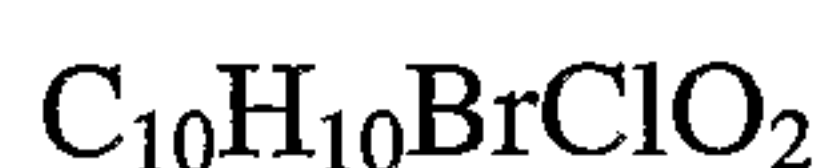
(R)-N-(1-(1-Naphthyl)ethyl)-N-((4-(3-N,N-dimethylamino)propoxy-3-(4-methoxyphenyl)phenyl)methyl)amine



5

Step 1) 3-Bromo-4-(3-chloropropoxy)benzaldehyde:

A solution of 3-bromo-4-hydroxybenzaldehyde (1.88 g, 9.36 mmol) 1-bromo-3-chloropropane (9.25 mL, 93.6 mmol) and potassium carbonate (3.22 g, 23.4 mmol) in acetonitrile (15 mL) was heated at 80 C for 2 days. The solid was filtered
10 through a plug of silica eluting with MeCN. The filtrate was evaporated to yield 2.46 g of title compound.

Step 2) 3-Bromo-4-(3-N,N-dimethylamino)propoxybenzaldehyde:

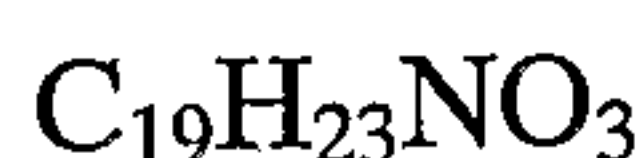
A suspension of 3-bromo-4-(3-chloropropoxy)benzaldehyde (2.47 g, 8.08 mmol) dimethylamine hydrochloride (6.58 g, 80.8 mmol) and potassium carbonate (11.1 g, 80.8 mmol) in acetonitrile (120 mL) was stirred for 2 days at room temperature, then more Me₂NH HCl 6.58 g, 80.8 mmol) was added together with KI (50 mg). After 4 days the mixture was filtered and the filtrate concentrated under reduced
20 pressure. The residue was dissolved in ethyl acetate and washed with water then brine. The organic layer was dried over MgSO₄ then evaporated to give a crude which was purified by column chromatography (DCM/MeOH 9/1) to give 1.24 g of title compound.



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Step 3) 4-(3-*N,N*-Dimethylamino)propoxy-3-(4-methoxyphenyl)benzaldehyde:

A solution of 4-methoxybenzeneboronic acid (0.79 g, 5.19 mmol), 3-bromo-4-(3-*N,N*-dimethylamino)propoxybenzaldehyde (1.28 g, 4.33 mmol) and K₂CO₃ (1.78 g, 12.9 mmol) in ethanol (12 mL) and toluene (24 mL) was degassed prior to addition of Pd(Ph₃)₄ (100 mg, 1 mmol%). The mixture was refluxed for 18 hours then cooled and filtered through diatomaceous earth. The filtrate was concentrated in vacuo, extracted with ethyl acetate, washed with water and the organic layer dried over sodium sulphate. The crude was purified by column chromatography (DCM/MeOH 85/15) to give 0.4 g of title compound.

Step 4) (R)-*N*-(1-(1-Naphthyl)ethyl)-*N*-((4-(3-*N,N*-dimethylamino)propoxy-3-(4-methoxyphenyl)phenylmethyl)amine:

The title compound was prepared from 4-(3-*N,N*-dimethylamino)propoxy-3-(4-methoxyphenyl)benzaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure B.



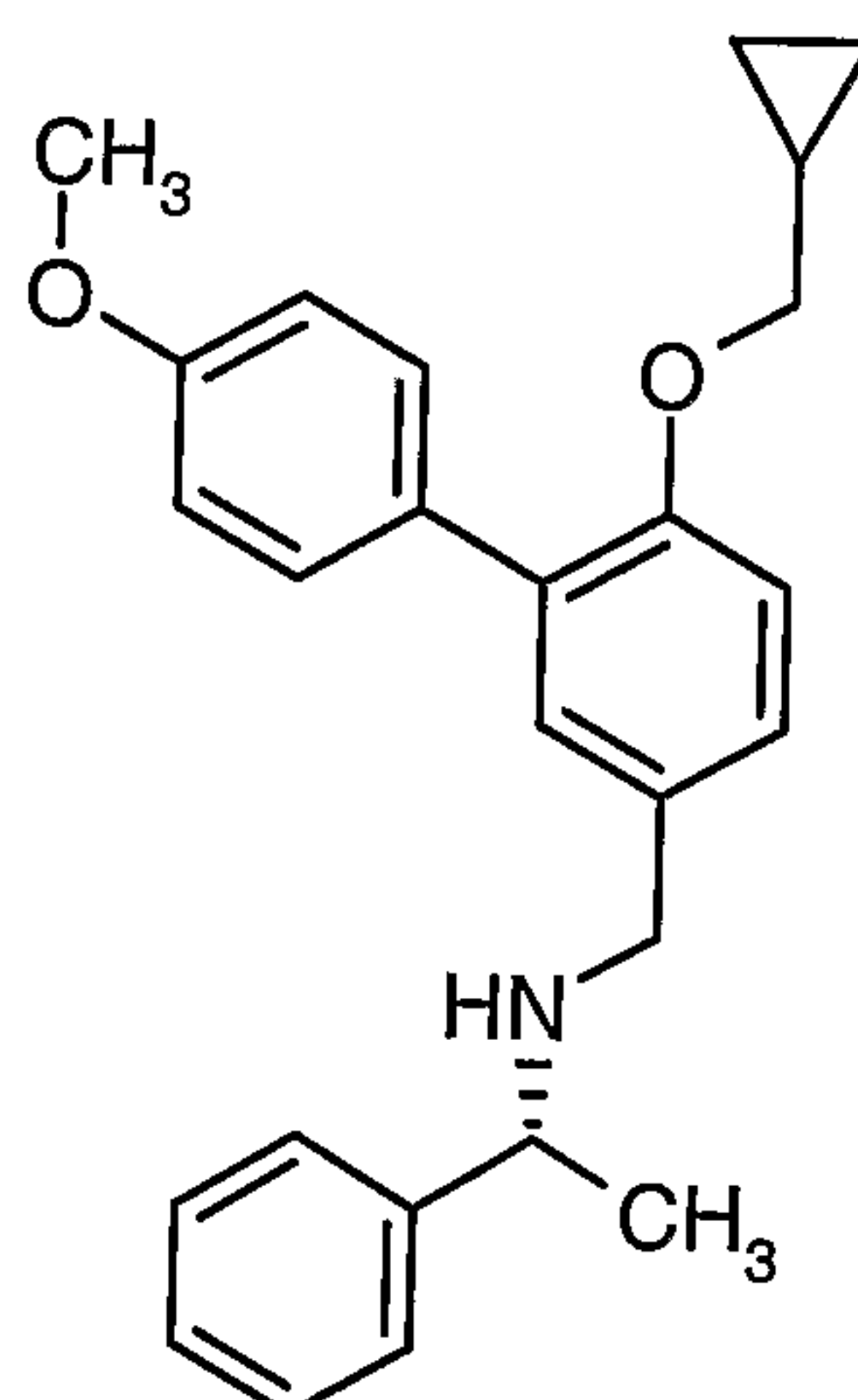
Mass (calculated): [468]; (found): [M+H⁺] = 469.

NMR (400 MHz, CDCl₃): 1.45 (3H, d, *J* = 6 Hz, NCHCH₃); 1.85-1.95 (2H, m, OCH₂CH₂CH₂N); 2.25 (6H, s, Me₂N); 2.4-2.5 (2H, m, OCH₂CH₂CH₂N);); 3.6 and 3.65 (2H, dd, *J* = 12 Hz, CH₂N); 3.7 (3H, s, CH₃O); 3.9 (2H, t, *J* = 6 Hz, OCH₂CH₂CH₂N); 4.65 (1H, q, *J* = 6 Hz, NCHCH₃); 6.8-6.9 (3H, m, aryl-H); 7.1-7.2 (2H, m, aryl-H); 7.3-7.5 (5H, m, aryl-H); 7.7 (2H, d, *J* = 8 Hz, aryl-H); 7.8-7.85 (1H, m, aryl-H); 8.05-8.1 (1H, m, aryl-H).

Example 56

(R)-*N*-(1-Phenylethyl)-*N*-((4-(cyclopropylmethoxy-3-(4-methoxyphenyl)-phenylmethyl)amine

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Step 1) 3-bromo-4-cyclopropylmethoxybenzaldehyde:

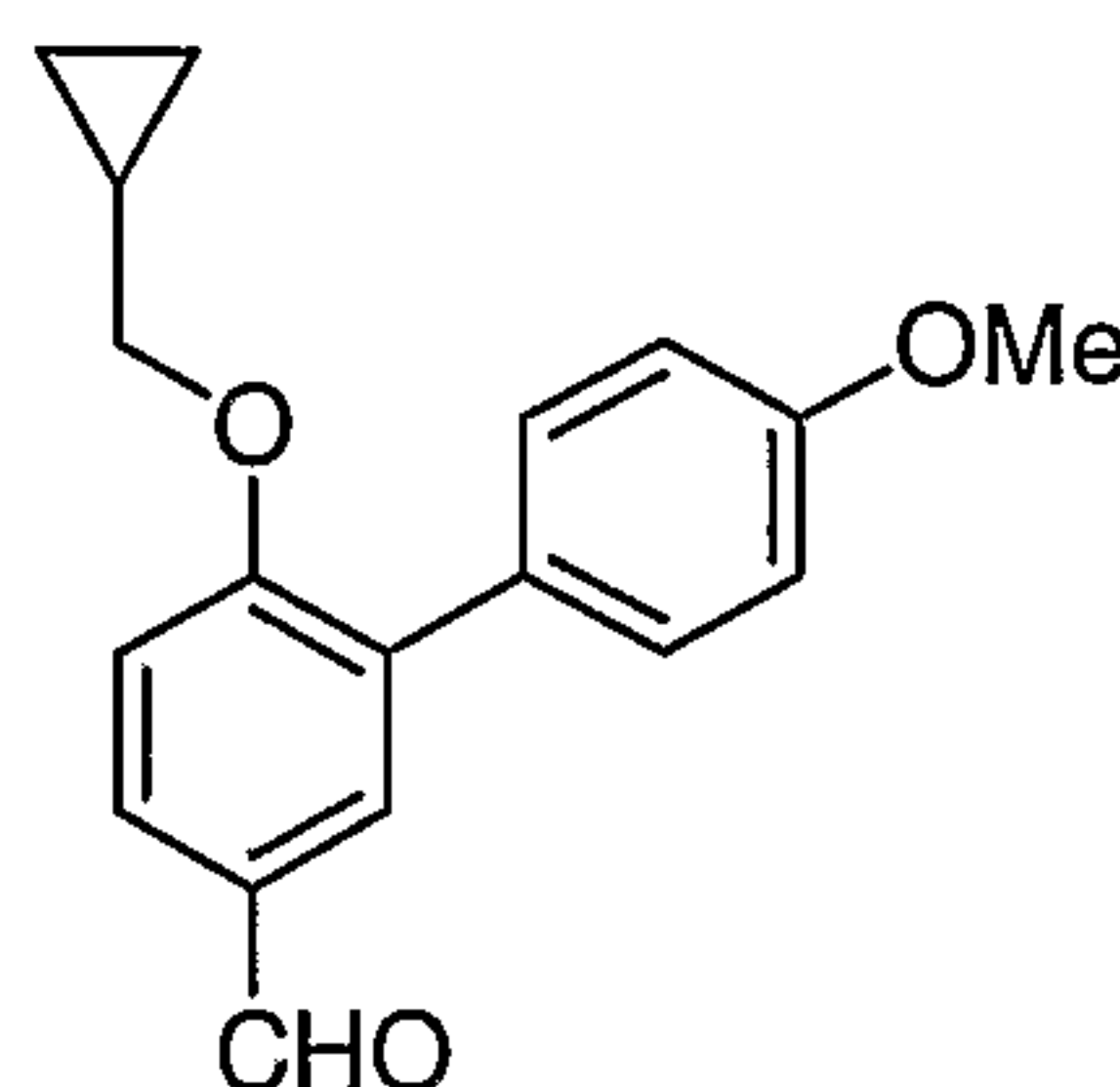
A suspension of 3-bromo-4-hydroxybenzaldehyde (5.03 g, 25 mmol),
 5 bromomethylcyclopropane (28 mmol, 2.72 mL) and potassium carbonate (37.5
 mmol, 5.14 g) in DMF (30 mL) was heated at 110 C for three days. The solid was
 filtered off and the solvent was removed under reduced pressure, to give an orange
 residue which was taken into ethyl acetate and washed with water and then
 saturated brine. The organic phase was dried over Mg_2SO_4 and solvent removed to
 10 afford 5.56 g of the title material.

$C_{11}H_{11}BrO_2$ Mass (calculated): [255]; (found): 255, 257 and 296, 298 (M +
 MeCN).

NMR (400 MHz, $CDCl_3$): 0.15-0.2 (2H, m, cyclopropyl- CH_2); 0.4-0.5 (2H, m,
 cyclopropyl- CH_2); 1-1.15 (1H, m, cyclopropyl-CH); 3.8 (2H, d, $J=7$ Hz, OCH_2);
 15 7.75 (1H, d, $J=8$ Hz, aryl-H); 7.55 (1H, dd, $J=2$ and 8 Hz, aryl-H); 7.9 (1H, d, $J=$
 2 Hz, aryl-H); 9.6 (1H, s, CHO).

Step 2) 4-Cyclopropylmethoxy-3-(4'-methoxyphenyl)benzenecarboxaldehyde:

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To a degassed solution of 3-bromo-4-cyclopropylmethoxybenzaldehyde (1.53 g, 6 mmol), 4-methoxybenzeneboronic acid (1.22 g, 8 mmol) and potassium carbonate (2.74 g, 20 mmol) in toluene/ethanol 2/1 (40 mL), Pd(PPh₃)₄ (100 mg) was added and the mixture was degassed for further 5 minutes. The mixture was then refluxed for 12 hours. The solid is filtered off, and the solvent partitioned between ethyl acetate and water and extracted. The organic solvent was removed under reduced pressure, dried over sodium sulphate and purified by column chromatography on silica (hexane/ethyl acetate 8/2) to afford 1.52 g of product.

10 C₁₈H₁₈O₃

Mass (calculated): [282]; (found): [M+H⁺] = 283; LC Rt = 1.65, 97%.

NMR (400 MHz, CDCl₃): 0.15-0.25 (2H, m, cyclopropyl-CH₂); 0.45-0.55 (2H, m, cyclopropyl-CH₂); 1.05-1.15 (1H, m, cyclopropyl-CH); 3.75 (3H, s, MeO); 3.8 (2H, d, *J* = 7 Hz, arylOCH₂); 6.9 (2H, 2, *J* = 7 Hz, 8.5 Hz, aryl-H); 7.9 (1H, d, *J* = 8.5 Hz, aryl-H); 7.4 (2H, d, *J* = 8.5 Hz, aryl-H); 7.65 (1H, dd, *J* = 2 and 8.5 Hz, aryl-H); 7.75 (1H, d, *J* = 2 Hz, aryl-H); 9.8 (1H, s, CHO).

Step 3) (R)-N-(1-Phenylethyl)-N-((4-(cyclopropylmethoxy)-3-(4-methoxyphenyl)-phenyl)methyl)amine:

20 The title compound was prepared from 4-cyclopropylmethoxy-3-(4'-methoxyphenyl)benzenecarboxaldehyde and (R)-α-methylbenzylamine according to general procedure A.

C₂₆H₂₉NO₂

Mass (calculated): [387]; (found): [M+H⁺] = 267, 388.

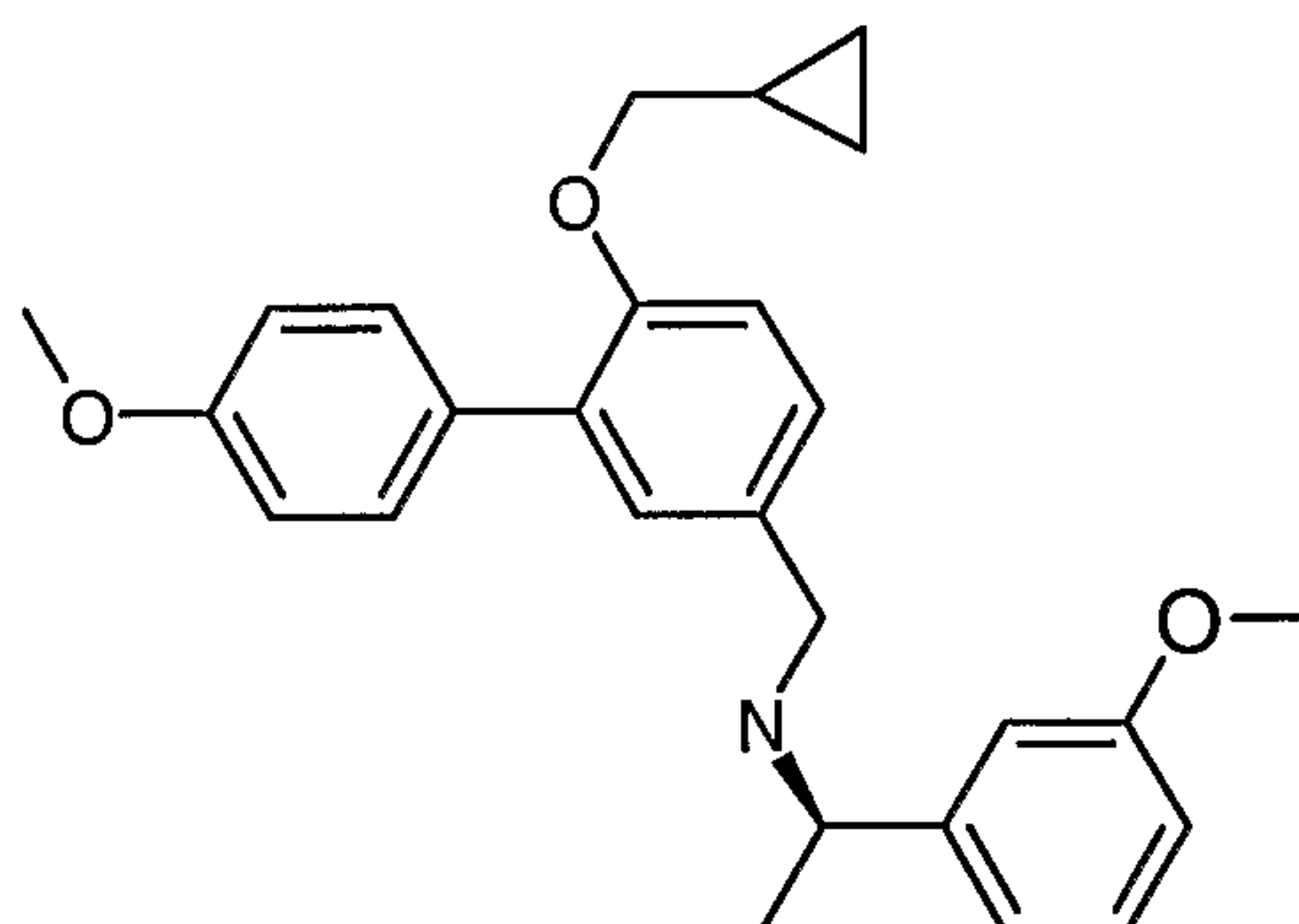
25 NMR (400 MHz, CDCl₃): 0.2 (2H, m, cyclopropyl-H); 0.45 (2H, m, cyclopropyl-H); 1.15 (1H, m, cyclopropyl-H); 1.3 (3H, d, *J* = 6 Hz, NCHCH₃); 3.5 and 3.55 (2H, dd, *J* = 12 Hz, CH₂N); 3.7 (2H, d, *J* = 6 Hz, cyclopropylCH₂O); 3.7-3.8 (4H, m, MeO and NCHMe); 6.8 (1H, d, *J* = 8 Hz, aryl-H); 6.85 (2H, d, *J* = 8 Hz, aryl-

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H); 7.1 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 7.15-7.25 (2H, m, aryl-H); 7.25-7.35 (4H, m, aryl-H); 7.45 (2H, d, $J = 8$ Hz, aryl-H).

Example 57

5 (R)-N-(1-(3-Methoxyphenyl)ethyl)-N-((4-cyclopropylmethoxy-3-(4'-methoxyphenyl)phenyl)methyl)amine



10 The title compound was prepared from 4-cyclopropylmethoxy-3-(4'-methoxyphenyl)benzenecarboxaldehyde and (R)-3-methoxy- α -methylbenzylamine according to general procedure A.

$C_{27}H_{31}NO_3$

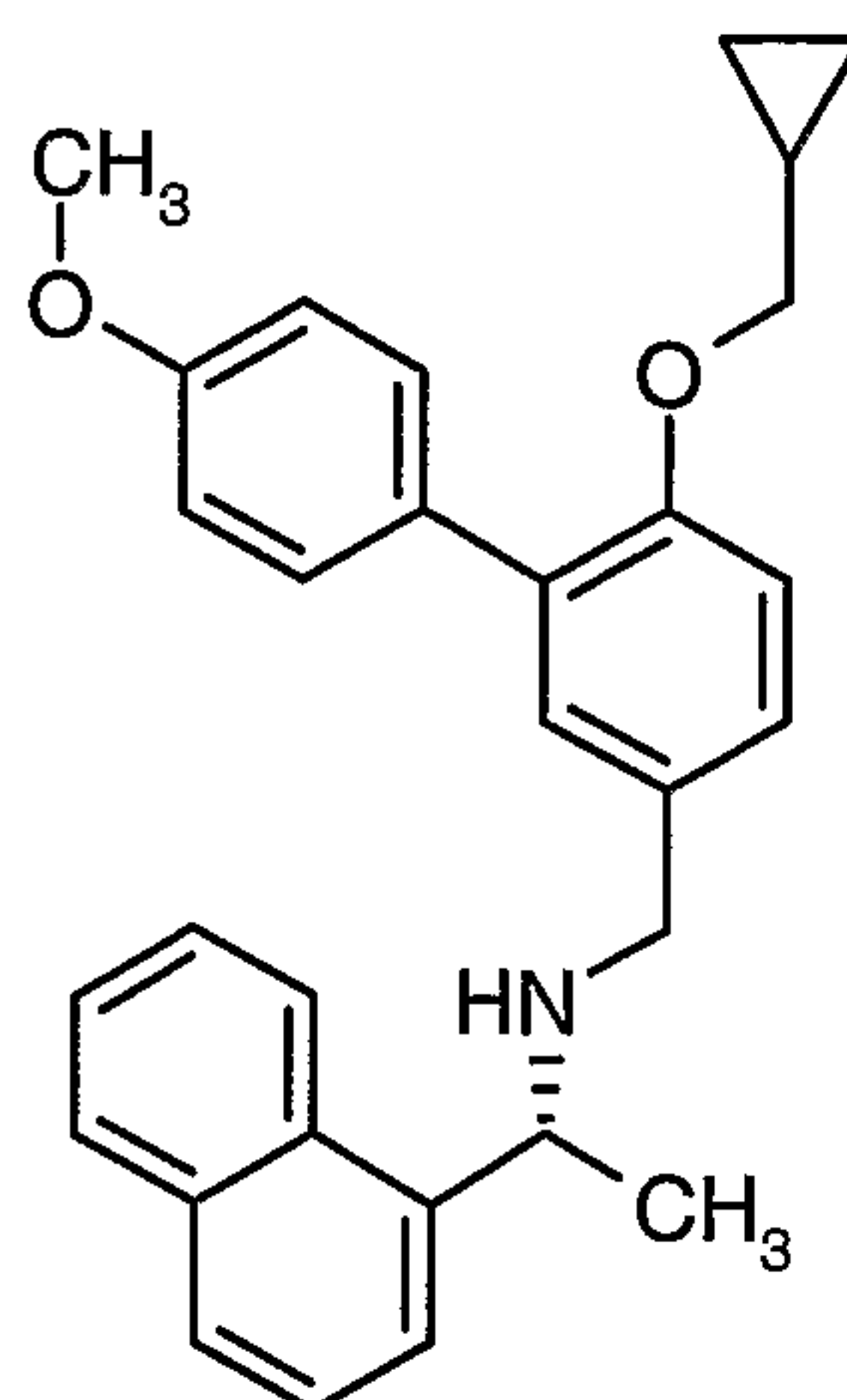
Mass (calculated): [417]; (found): $[M+H^+] = 267, 418$.

15 NMR (400 MHz, $CDCl_3$): 0.2 (2H, m, cyclopropyl-H); 0.45 (2H, m, cyclopropyl-H); 1.1 (1H, m, cyclopropyl-H); 1.3 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.5 and 3.55 (2H, dd, $J = 12$ Hz, CH_2N); 3.65 (2H, d, $J = 6$ Hz, cyclopropyl CH_2O); 3.7 (3H, s, CH_3O); 3.75-3.85 (4H, m, MeO and $NCHMe$); 6.75 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 6.8 (1H, d, $J = 8$ Hz, aryl-H); 6.85-6.95 (4H, m, aryl-H); 7.1 (1H, dd, $J = 1$ and 8 Hz, aryl-H); 7.15 (1H, d, $J = 1$ Hz, aryl-H); 7.15-7.25 (1H, m, aryl-H); 7.45 (2H, d, $J = 8$ Hz, aryl-H).

Example 58

25 (R)-N-(1-(1-Naphthyl)ethyl)-N-((4-(cyclopropylmethoxy-3-(4-methoxyphenyl)phenyl)methyl)amine

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The title compound was prepared from 4-cyclopropylmethoxy-3-(4'-methoxyphenyl)benzenecarboxaldehyde and (R)-1-(1-naphthyl)ethylamine according to general procedure A.

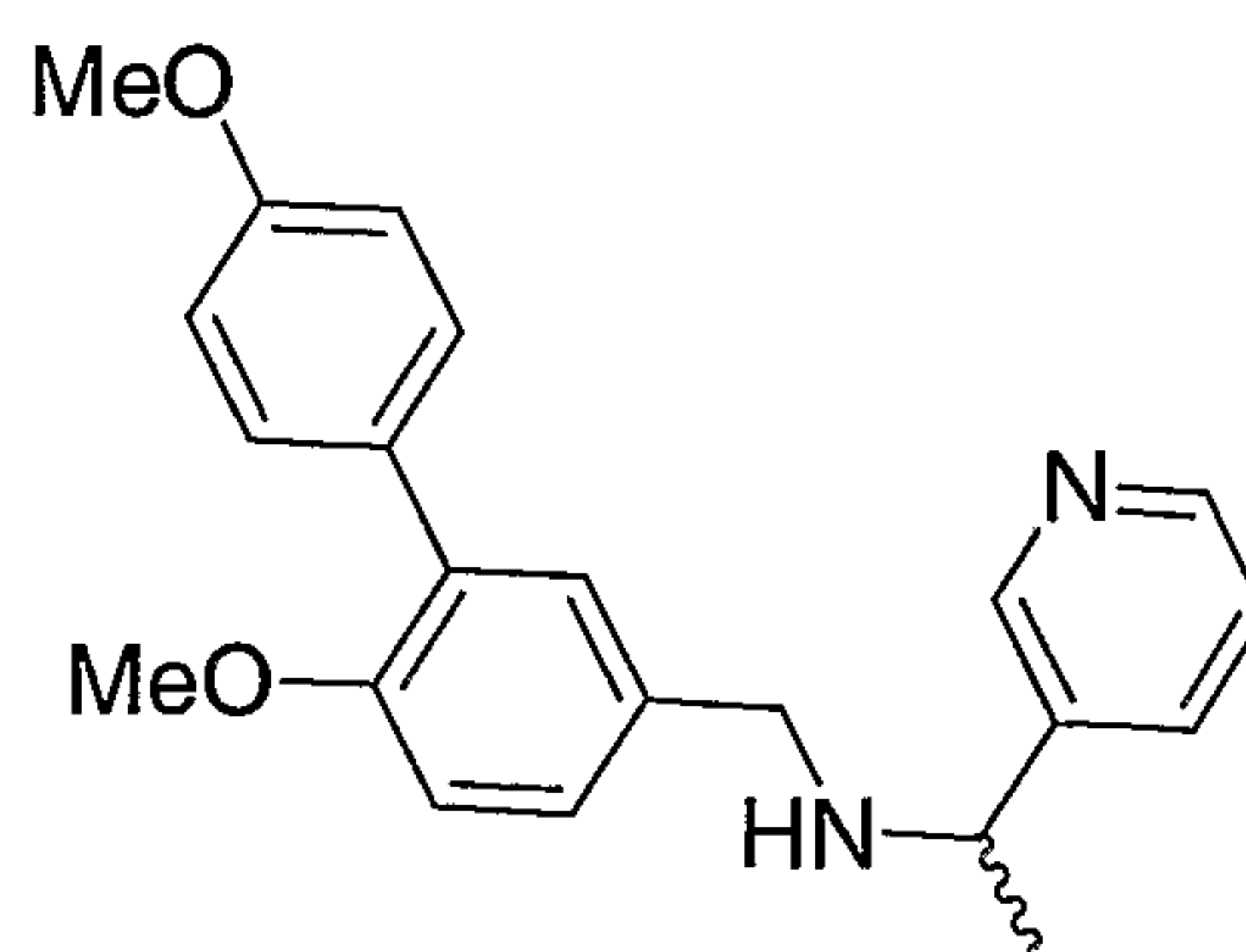
$C_{30}H_{31}NO_2$

Mass (calculated): [437]; (found): $[M+H^+] = 438, 267, 875$.

NMR (400 MHz, $CDCl_3$): 0.2 (2H, m, cyclopropyl-H); 0.45 (2H, m, cyclopropyl-H); 1.15 (1H, m, cyclopropyl-H); 1.45 (3H, d, $J = 6$ Hz, $NCHCH_3$); 3.6 (1H, d, $J = 12$ Hz, CH_2N); 3.65-3.75 (3H, m, CH_2N and cyclopropyl CH_2O); 3.75 (3H, s, MeO); 4.65 (1H, q, $J = 6$ Hz, $NCHMe$); 6.75-6.9 (3H, m, aryl-H); 7.1-7.2 (2H, m, aryl-H); 7.35-7.5 (5H, m, aryl-H); 7.65-7.5 (2H, m, aryl-H); 7.8-7.9 (1H, m, aryl-H); 8.0-8.1 (1H, m, aryl-H).

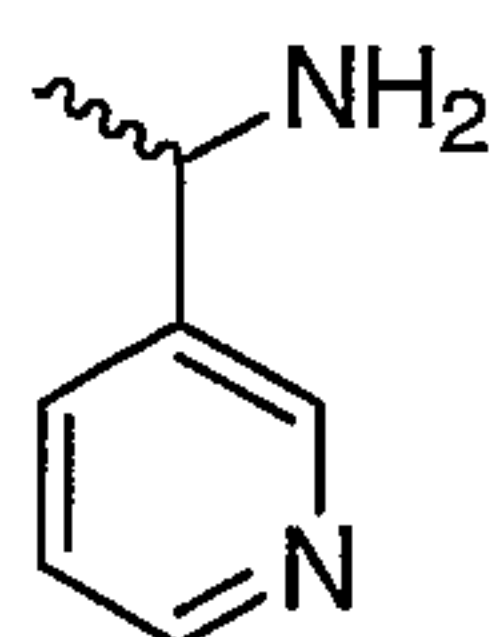
Example 59

(6,4'-Dimethoxy-biphenyl-3-ylmethyl)-(1-pyridin-3-yl-ethyl)-amine



Step 1) 1-Pyridin-3-yl-ethylamine:

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3-Acetylpyridine (2.4 g, 20 mmol, Aldrich) was dissolved in 2M ammonia solution in methyl alcohol (50 mL, 100 mmol, Aldrich) and acetic acid (15 mL, J.T. Baker) was slowly added at 0 C. After stirring for 3 h at room temperature, the sodium cyanoborohydride (5.0 g, 80 mmol, Aldrich) was added to the solution at 0 C. The mixture was stirred under nitrogen at room temperature for overnight then the reaction was cooled at ice bath and quenched with aqueous 5 N sodium hydroxide (30 mL, 150 mmol, J.T. Baker). The methyl alcohol was removed from the mixture via vacuo. The residue was extracted by diethyl ether (30 mL x 4). The combined organic phases were dried over anhydrous magnesium sulfate and concentrated via vacuo to give crude 1-pyridin-3-yl-ethylamine as light yellow oil in 44% yield (1.07 g, 8.8 mmol).



MS (ESI, pos. ion) m/z: 123.0 (M+1); MS (ESI, neg. ion) m/z: 121.0 (M-1).

Step 2) (6,4'-Dimethoxy-biphenyl-3-ylmethyl)-(1-pyridin-3-yl-ethyl)-amine:

1-Pyridin-3-yl-ethylamine (245 mg, 2 mmol) and 6,4'-Dimethoxy-biphenyl-3-carbaldehyde (121 mg, 0.5 mmol) were dissolved in dichloroethane (10 mL). After stirring for 6 h at room temperature, the sodium triacetoxyborohydride (212 mg, 1.0 mmol, Aldrich) was added to the solution at 0 C. The mixture was stirred under nitrogen at room temperature for overnight then the reaction was cooled at ice bath and quenched with saturated aqueous sodium bicarbonate (10 mL). The organic phase was separated and the aqueous phase was extracted with dichloroethane (10 mL x 3). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated via vacuo. The crude was purified by column chromatography (silica gel, ethyl acetate) to give the title compound as white solid in 50% yield (87 mg, 0.25 mmol).

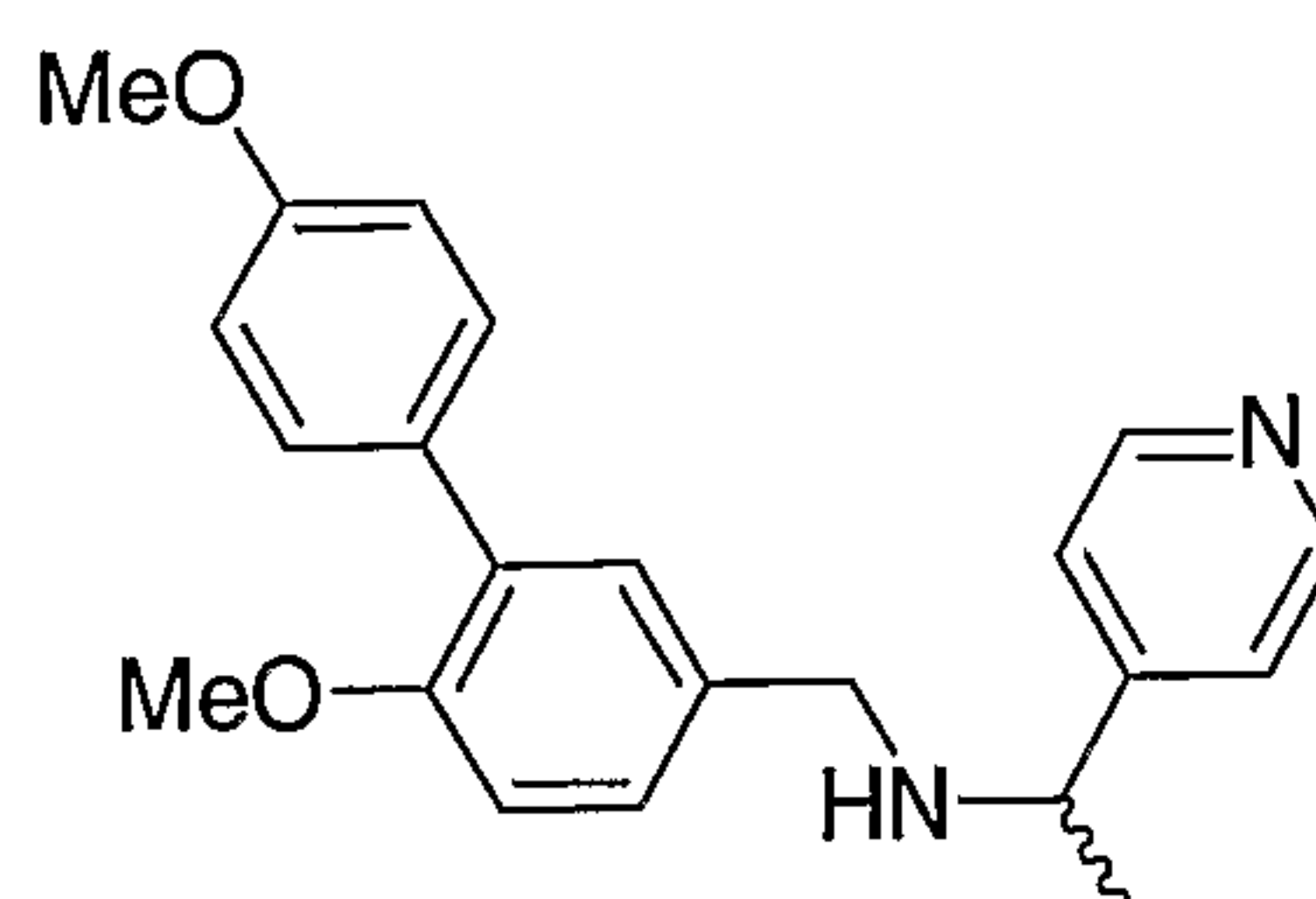


MS (ESI, pos. ion) m/z: 349.2 (M+1); MS (ESI, neg. ion) m/z: 347.2 (M-1).

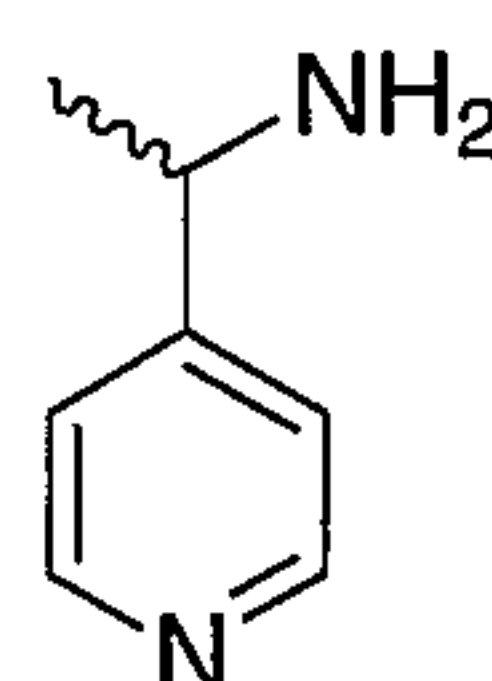
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Example 60

(6,4'-Dimethoxy-biphenyl-3-ylmethyl)-(1-pyridin-4-yl-ethyl)-amine



5

Step 1) 1-Pyridin-4-yl-ethylamine:

10 The title compound was prepared by the same procedure for preparing 1-pyridin-3-yl-ethylamine from 4-acetylpyridine (2.4 g, 20 mmol, Aldrich), 2 M ammonia solution in methyl alcohol (50 mL, 100 mmol, Aldrich), acetic acid (15 mL, J.T. Baker) and sodium cyanoborohydride (5.0 g, 80 mmol, Aldrich). The title compound was obtained in form as light yellow oil in 51% yield (1.25 g, 10.2 mmol).



MS (ESI, pos. ion) m/z: 123.0 (M+1); MS (ESI, neg. ion) m/z: 121.0 (M-1).

Step 2) (6,4'-Dimethoxy-biphenyl-3-ylmethyl)-(1-pyridin-4-yl-ethyl)-amine:

20 The title compound was prepared by the same procedure for preparing (6,4'-dimethoxy-biphenyl-3-ylmethyl)-(1-pyridin-3-yl-ethyl)-amine from 1-Pyridin-4-yl-ethylamine (245 mg, 2 mmol), 6,4'-Dimethoxy-biphenyl-3-carbaldehyde (121 mg, 0.5 mmol) and sodium triacetoxymethylborohydride (212 mg, 1.0 mmol, Aldrich). The title compound was purified by column chromatography (silica gel, ethyl acetate) in form as white solid in 51% yield (89 mg, 0.26 mmol).



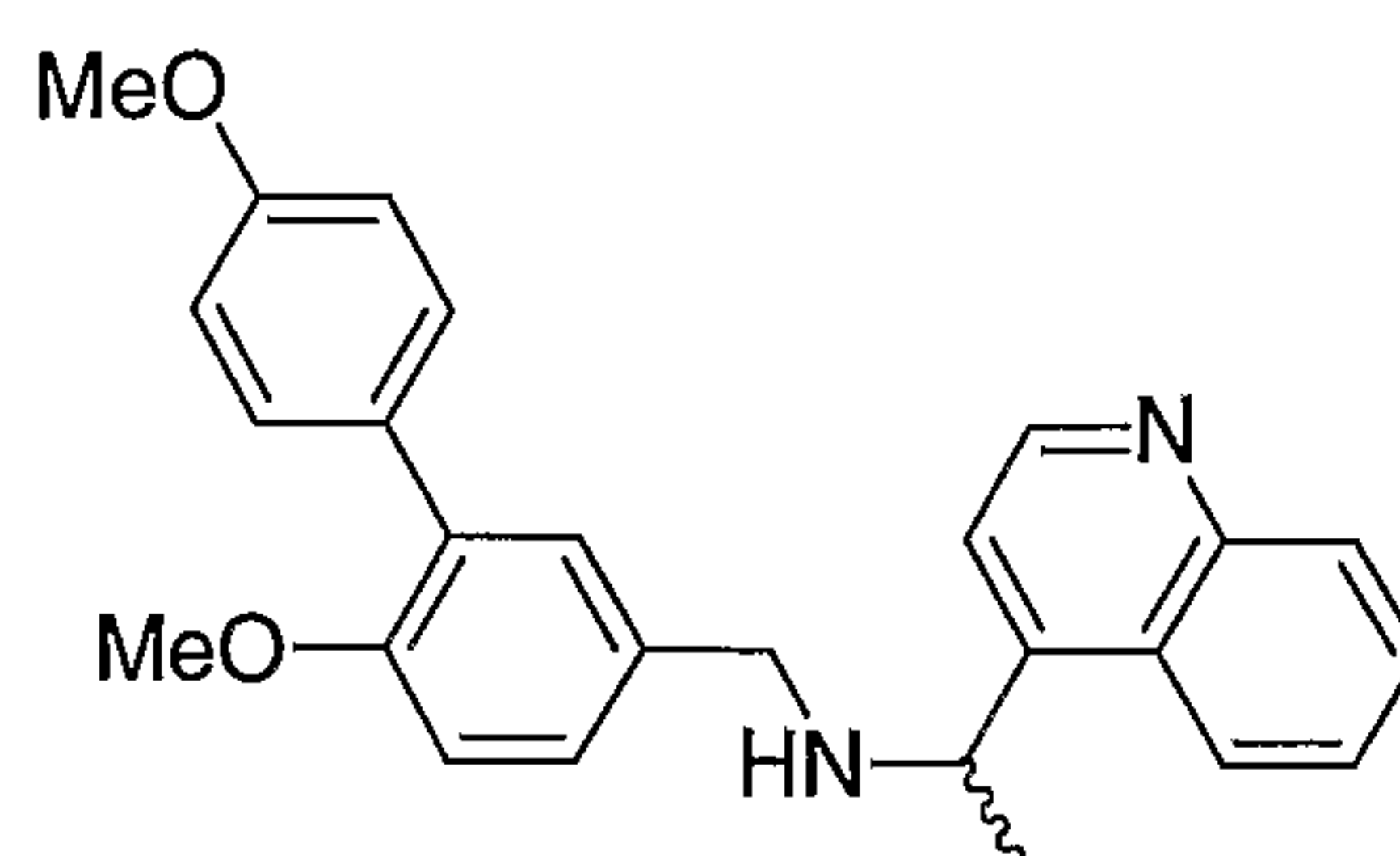
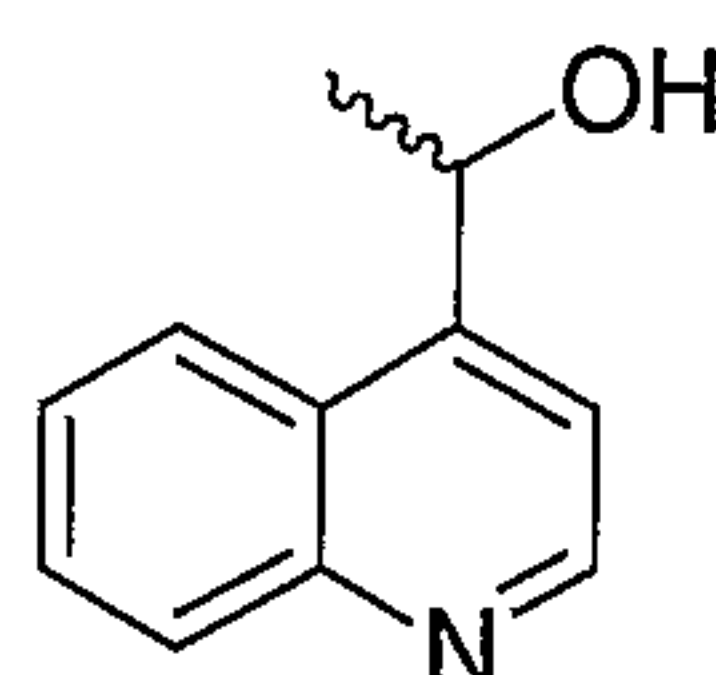
MS (ESI, pos. ion) m/z: 349.2 (M+1); MS (ESI, neg. ion) m/z: 347.2 (M-1).

25

- 97 -

Example 61**(6,4'-Dimethoxy-biphenyl-3-ylmethyl)-(1-quinolin-4-yl-ethyl)-amine**

5

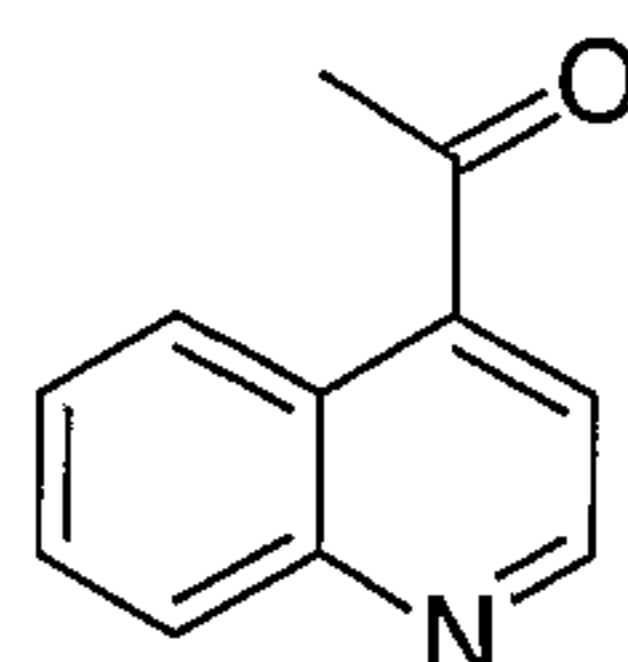
Step 1) 1-Quinolin-4-yl-ethanol:

10 4-Quinolinecarboxaldehyde (1.57 g, 10 mmol, Aldrich) was dissolved in anhydrous THF (30 mL) and cooled to -78°C . The 3 M methyl magnesium iodide solution in diethyl ether (5 mL, 15 mmol, Aldrich) was slowly added to the reaction solution in dry ice bath. The reaction mixture was allowed to stir under nitrogen at room temperature for overnight then the reaction was cooled at ice

15 bath and quenched with saturated aqueous ammonium chloride (30 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (30 mL x 2). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated via vacuo to give crude title compound as light yellow syrup in 100% yield (1.73 g, 10 mmol).

20 $\text{C}_{11}\text{H}_{11}\text{NO}$

MS (ESI, pos. ion) m/z: 174.4 (M+1); MS (ESI, neg. ion) m/z: 172.2 (M-1).

Step 2) 1-Quinolin-4-yl-ethanone:

25

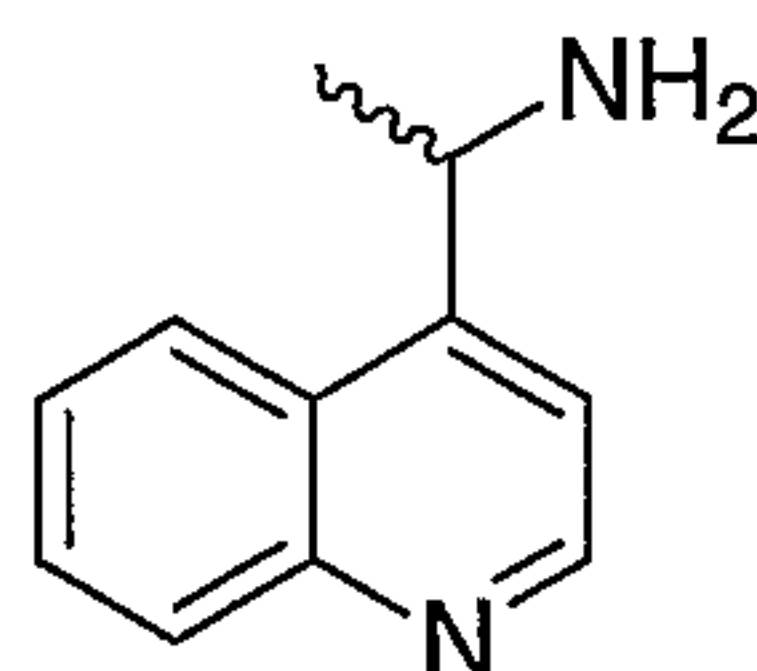
- 98 -

To the mixture of manganese oxide (8.69 g, 100 mmol, Aldrich) in dichloromethane (80 mL) was added 1-quinolin-4-yl-ethanol (1.73 g, 10 mmol). The reaction mixture was refluxed for overnight and then cooled to room temperature. The solid was filtered out through Celite pad. The organic solution
 5 dried over anhydrous magnesium sulfate and concentrated via vacuo to give crude title compound as light yellow solid in 100% yield (1.71 g, 10.0 mmol).

$C_{11}H_9NO$

MS (ESI, pos. ion) m/z: 172.10 (M+1); MS (ESI, neg. ion) m/z: 170.0 (M-1).

10 Step 3) 1-Quinolin-4-yl-ethylamine:

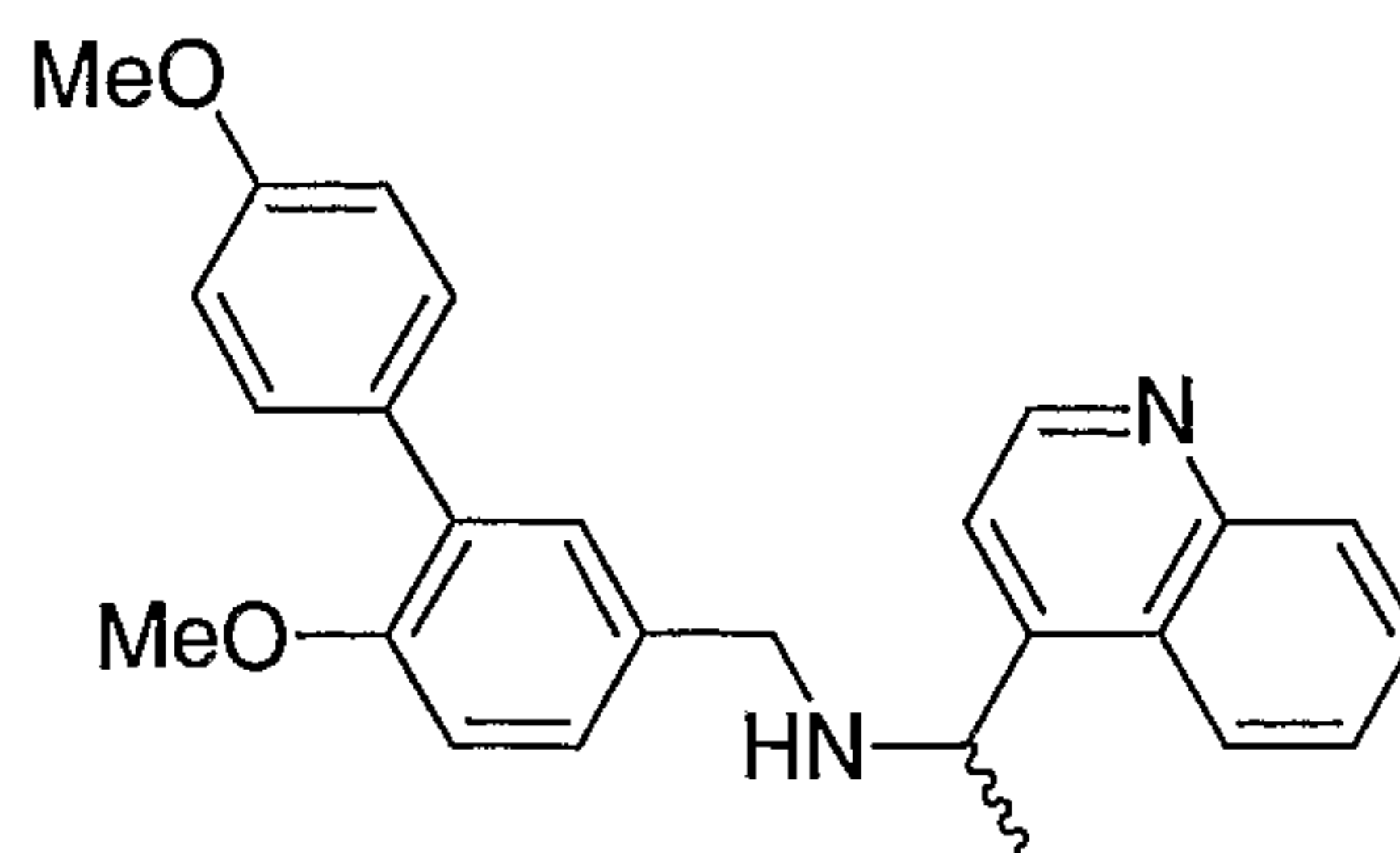


The title compound was prepared by the same procedure for preparing 1-pyridin-3-yl-ethylamine from 1-quinolin-4-yl-ethanone, (1.71 g, 10 mmol, Aldrich), 2 M ammonia solution in methyl alcohol, (40 mL, 80 mmol, Aldrich), acetic acid (10
 15 mL, J.T. Baker) and sodium cyanoborohydride (5.0 g, 80 mmol, Aldrich). The title compound obtained in form as light yellow solid in 100% yield (1.72 g, 10 mmol).

$C_{11}H_{12}N_2$

20 MS (ESI, pos. ion) m/z: 173.0 (M+1); MS (ESI, neg. ion) m/z: 171.0 (M-1).

Step 4) (6,4'-Dimethoxy-biphenyl-3-ylmethyl)-(1-quinolin-4-yl-ethyl)-amine:



25 The 1-quinolin-4-yl-ethylamine (510 mg, 3 mmol) and 6,4'-dimethoxy-biphenyl-3-carbaldehyde (242 mg, 1.0 mmol) were stirred with acetic acid (300 mg,

- 99 -

J.T.Baker) in methyl alcohol (15 mL) at room temperature for 4 h. To the reaction solution was added sodium cyanoborohydride (1.0 g, 16 mmol, Aldrich) at 0°C.

The mixture was stirred under nitrogen at room temperature for overnight then the reaction was cooled at ice bath and quenched with saturated aqueous sodium

5 bicarbonate (30 mL). The methyl alcohol was removed from the mixture via vacuo. The residue was extracted by ethyl acetate (30 mL x 4). The combined organic phases were dried over anhydrous magnesium sulfate and concentrated via vacuo. The title compound was purified by column chromatography (silica gel, ethyl acetate) in form as white solid in 72% yield (287 mg, 0.72 mmol).

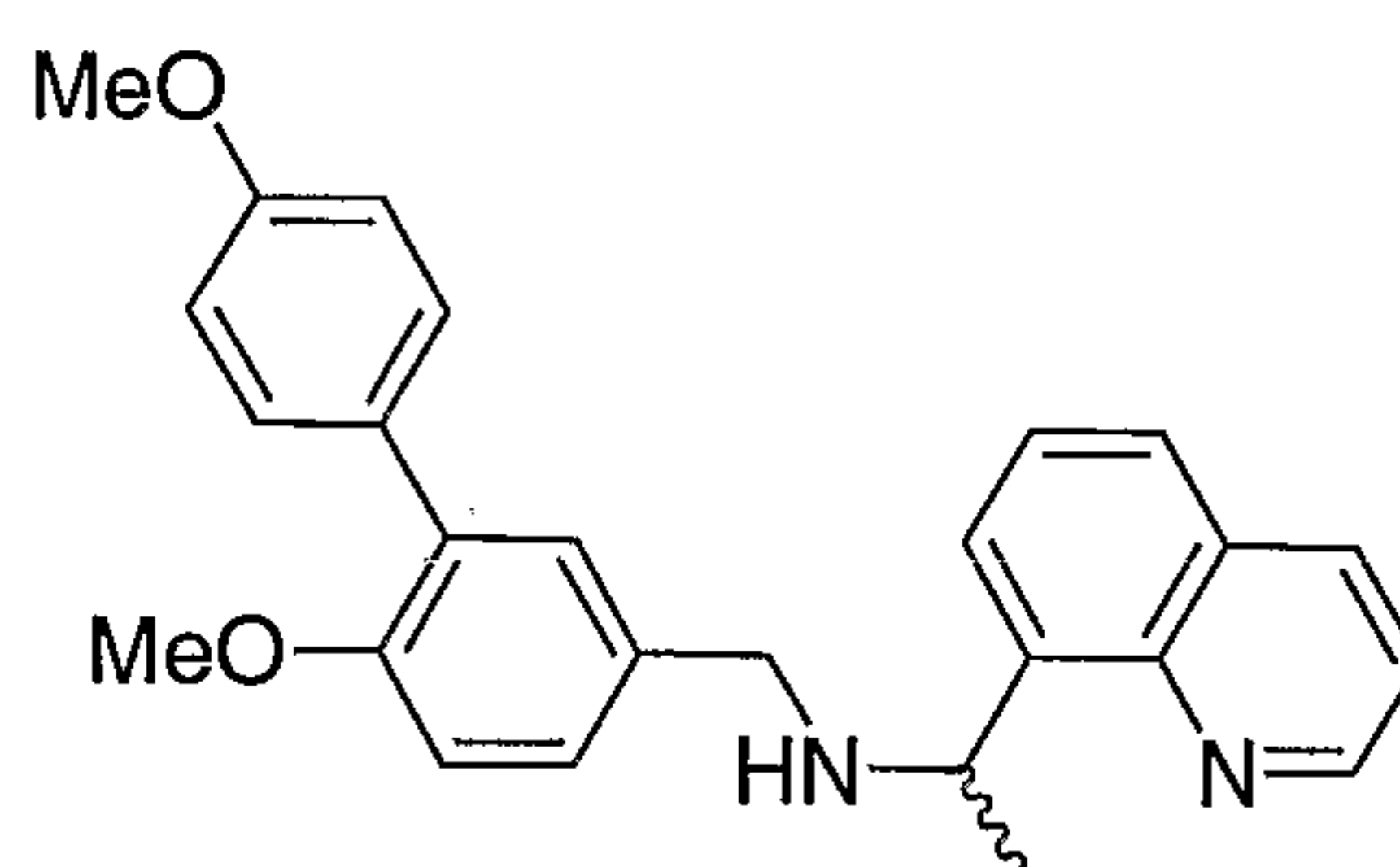
10 $C_{26}H_{26}N_2O_2$

MS (ESI, pos. ion) m/z: 399.2 (M+1); MS (ESI, neg. ion) m/z: 397.2 (M-1).

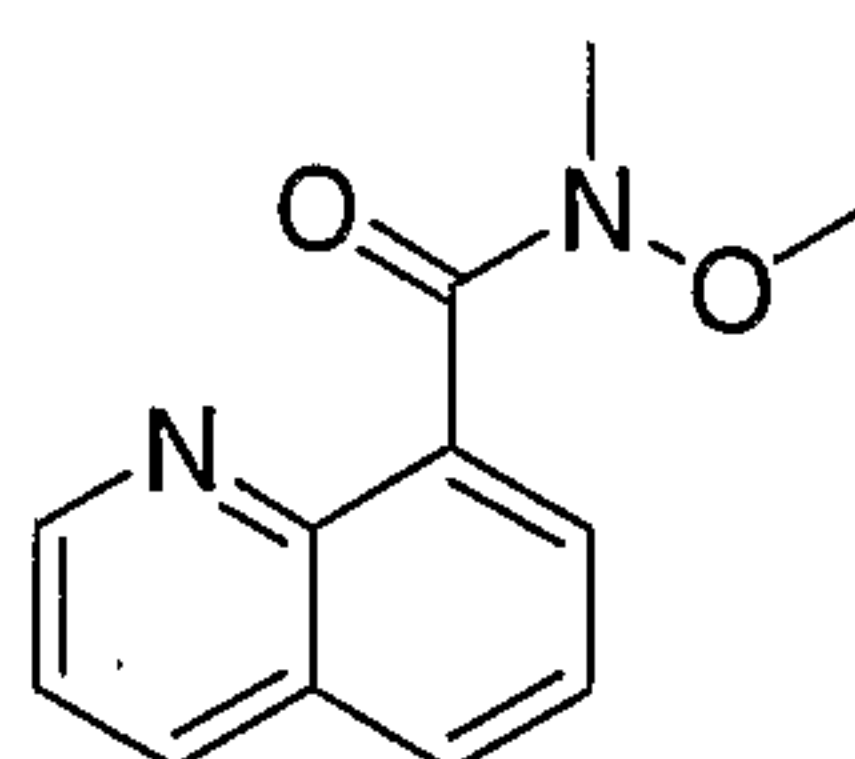
Example 62

(6,4'-Dimethoxy-biphenyl-3-ylmethyl)-(1-quinolin-8-yl-ethyl)-amine

15



Step 1) Quinoline-8-carboxylic acid methoxy-methyl-amide:



20

To the solution of 1-isoquinolonecarboxylic acid (1.73 g, 10 mmol, Aldrich) in anhydrous N, N –dimethylformamide (30 mL) were added N, N-

diisopropylethylamine (5.29 g, 40 mmol, Aldrich), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (7.6 g, 20 mmol, PerSeptive

25 Biosystems GmbH), N,O-dimethylhydroxylamine hydrochloride (1.8 g, 20 mmol,

- 100 -

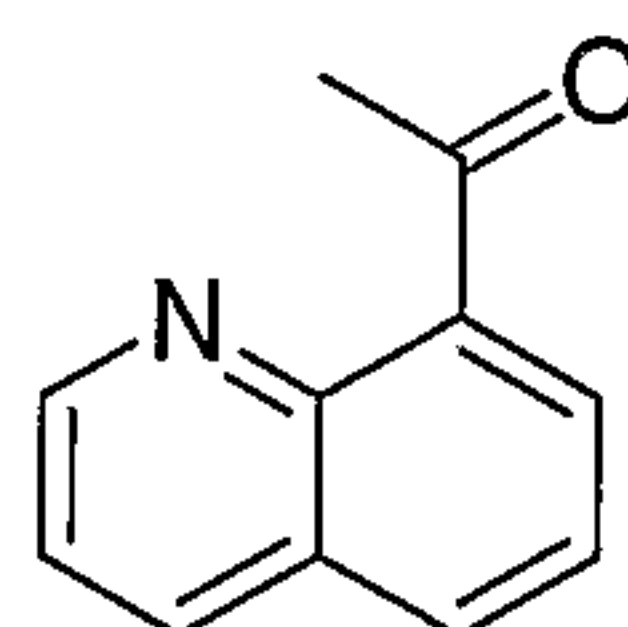
Aldrich) subsequently at room temperature. The reaction solution was allowed to stir for overnight at room temperature. The N, N –Dimethylformamide was removed via vacuo and the resulting residue was diluted in ethyl acetate (50 mL). After being washed by saturate aqueous sodium bicarbonate (50 mL) and
5 brine (50 mL), the organic portion was dried over anhydrous magnesium sulfate and concentrated. The title compound was purified by column chromatography (silica gel, ethyl acetate) in form as yellow syrup in 94% yield (2.04 g, 9.4 mmol).

$C_{12}H_{12}N_2O_2$

MS (ESI, pos. ion) m/z: 217.1 (M+1); MS (ESI, neg. ion) m/z: 215.0 (M-1).

10

Step 2) 1-Quinolin-8-yl-ethanone:



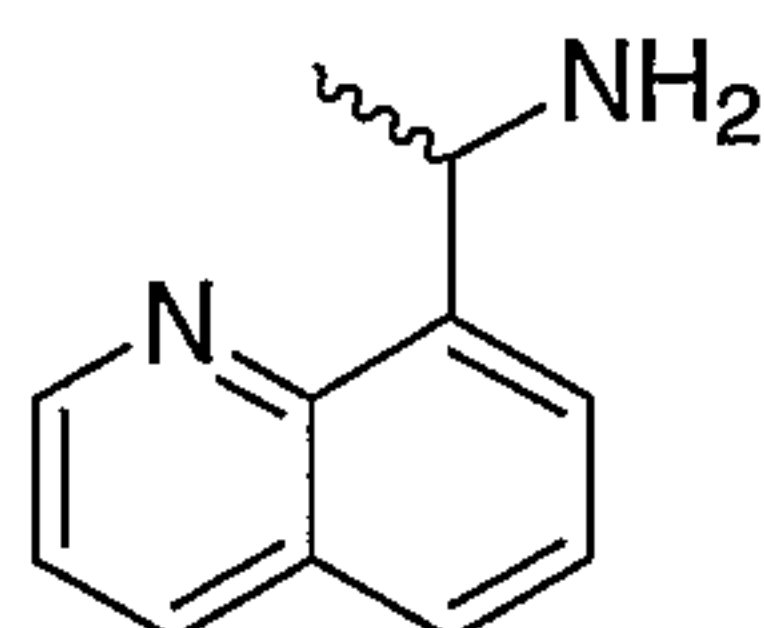
15 Quinoline-8-carboxylic acid methoxy-methyl-amide (2.16 g, 10 mmol) was dissolved in anhydrous THF (40 mL) and cooled to -78°C . The 3 M methyl magnesium iodide solution in diethyl ether (4.0 mL, 12 mmol, Aldrich) was slowly added to the reaction solution in dry ice bath. The reaction mixture was allowed to stir under nitrogen at room temperature for overnight then the reaction
20 was cooled at ice bath and quenched with saturated aqueous ammonium chloride (40 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (30 mL x 2). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated via vacuo to give crude title compound as light yellow solid in 83% yield (1.42 g, 8.3 mmol).

25 $C_{11}H_9NO$

MS (ESI, pos. ion) m/z: 172.0 (M+1); MS (ESI, neg. ion) m/z: 170.1 (M-1).

Step 3) 1-Quinolin-8-yl-ethylamine:

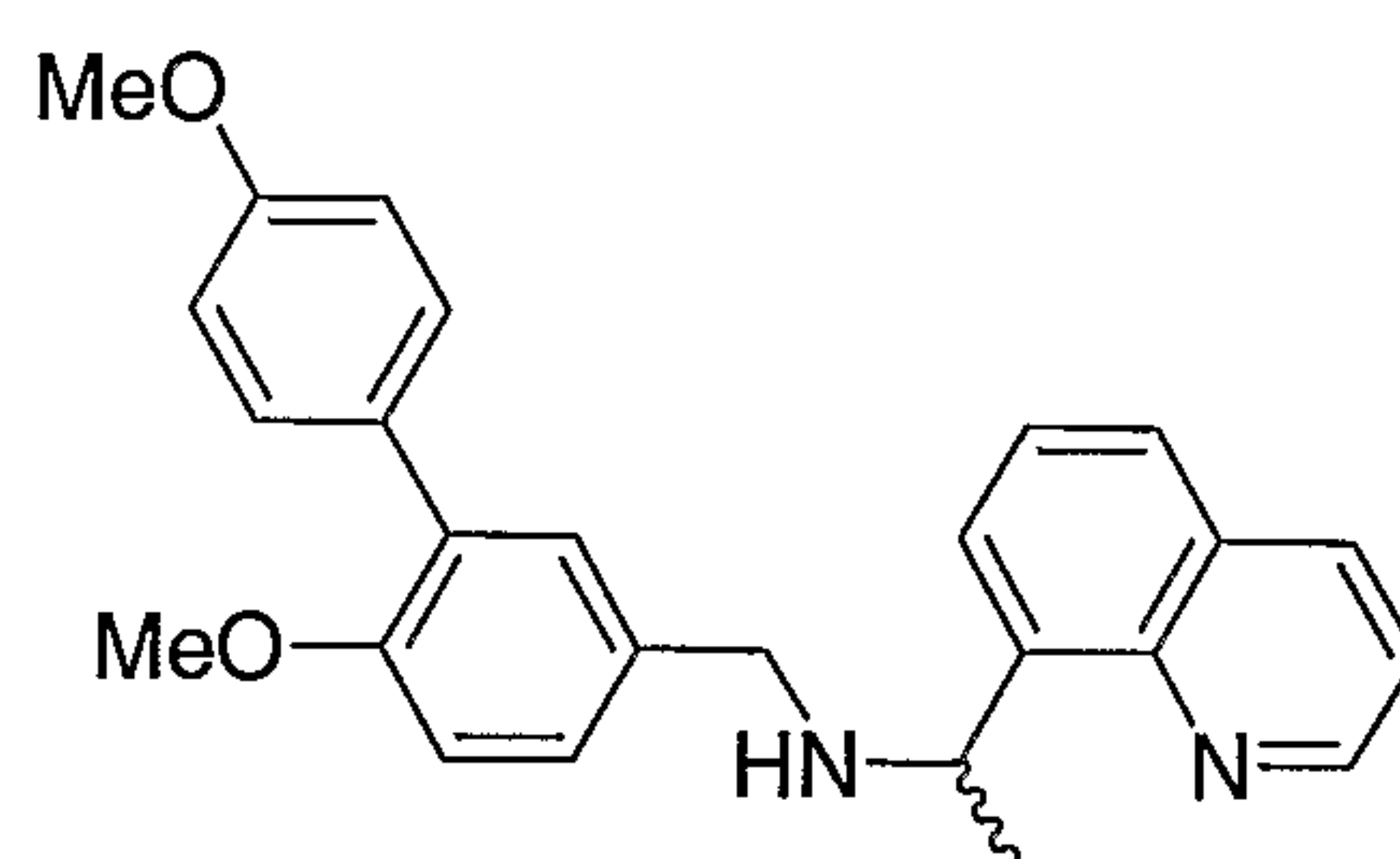
- 101 -



The title compound was prepared by the same procedure for preparing 1-pyridin-3-yl-ethylamine from 1-quinolin-8-yl-ethanone (1.71 g, 10 mmol), 2 M ammonia solution in methyl alcohol, acetic acid (25 mL, 50 mmol, Aldrich) and sodium cyanoborohydride (2.5 g, 40 mmol, Aldrich). The title compound was purified by column chromatography (silica gel, ethyl acetate) in form as light yellow solid in 98% yield (1.68 g, 9.8 mmol). MS (ESI, pos. ion) m/z: 173.2 (M+1); MS (ESI, neg. ion) m/z: 171.0 (M-1).

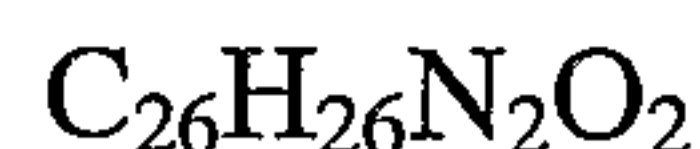
10

Step 4) (6,4'-Dimethoxy-biphenyl-3-ylmethyl)-(1-quinolin-8-yl-ethyl)-amine:



The title compound was prepared by the same procedure for (6,4'-dimethoxybiphenyl-3-ylmethyl)-(1-quinolin-4-yl-ethyl)-amine from 1-quinolin-8-yl-ethylamine (510 mg, 3.0 mmol), 6,4'-Dimethoxy-biphenyl-3-carbaldehyde (242 mg, 1.0 mmol) and sodium cyanoborohydride (1.0 g, 16 mmol, Aldrich). The title compound was purified by column chromatography (silica gel, ethyl acetate) in form as white solid in 72% yield (287 mg, 0.72 mmol).

20

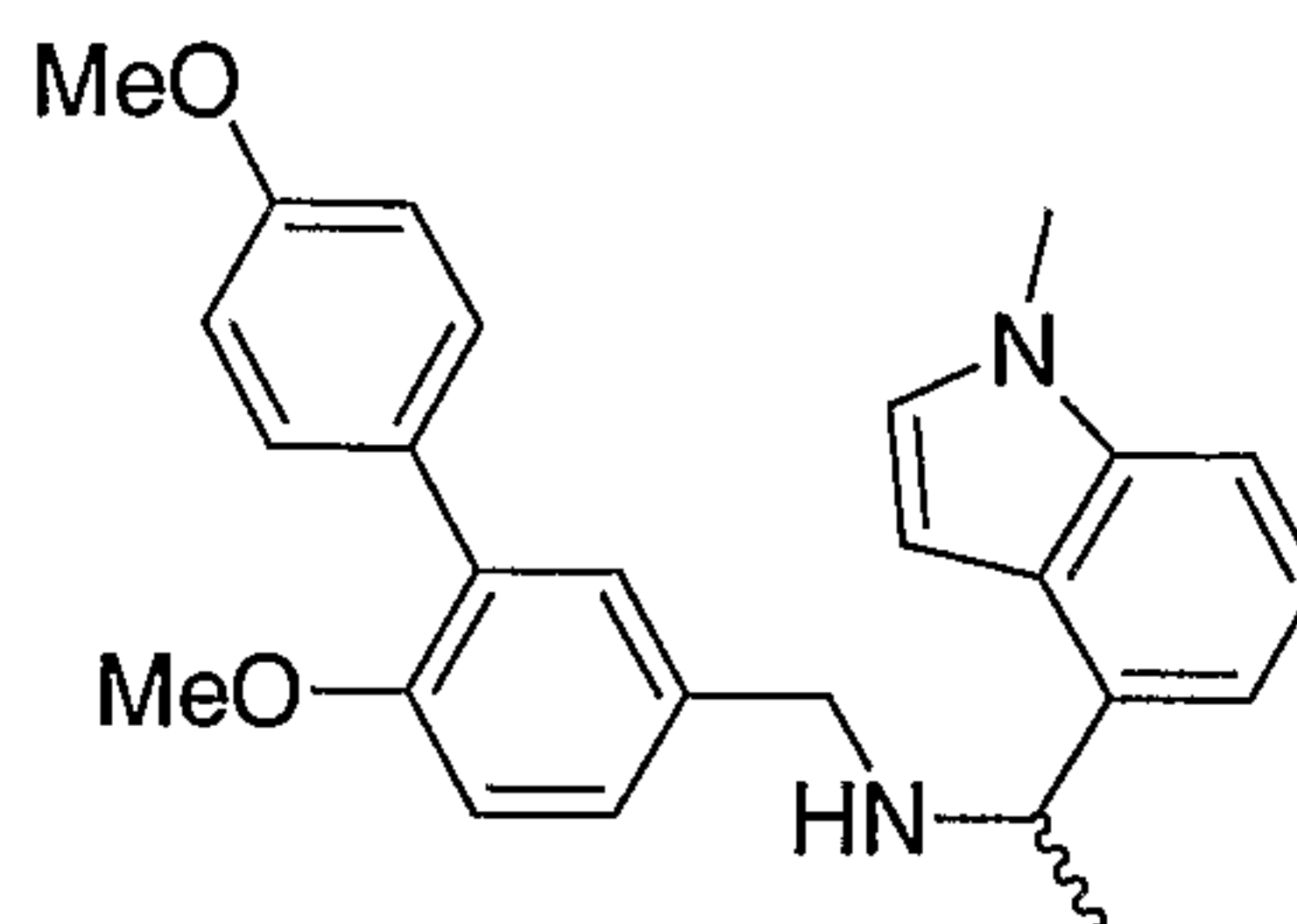


MS (ESI, pos. ion) m/z: 399.2 (M+1); MS (ESI, neg. ion) m/z: 397.2 (M-1).

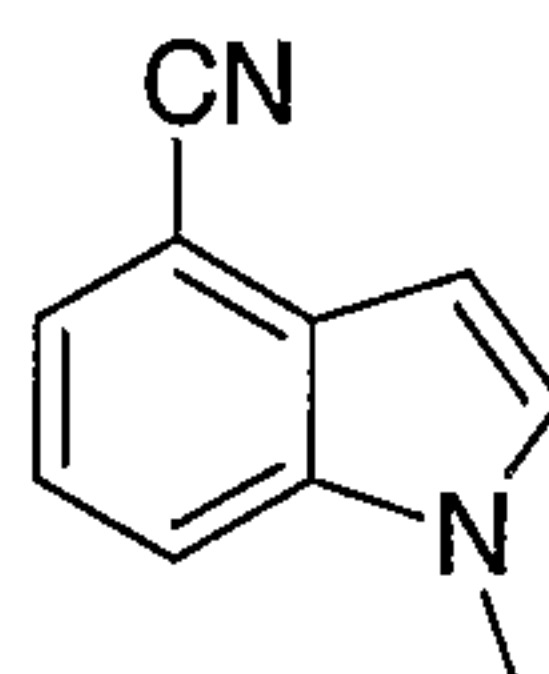
- 102 -

Example 63

(6,4'-Dimethoxy-biphenyl-3-ylmethyl)-[1-(1-methyl-1H-indol-4-yl)-ethyl]-amine



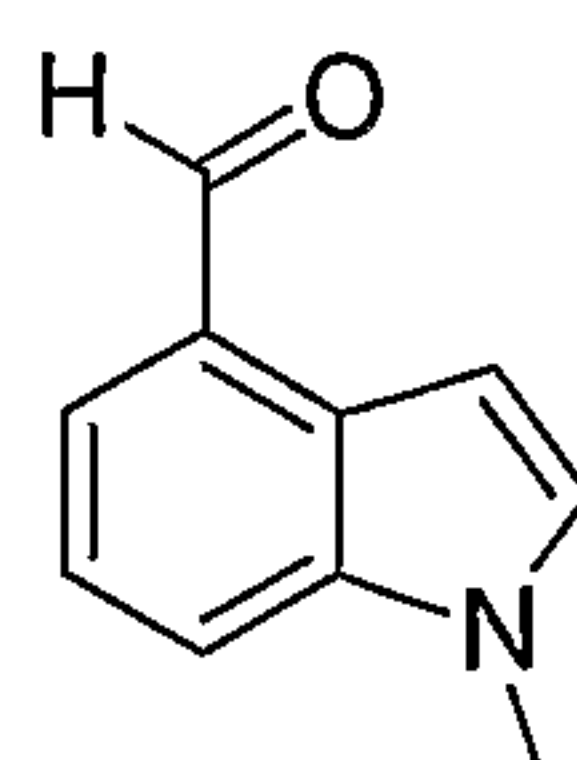
5

Step 1) 1-Methyl-1H-indole-4-carbonitrile:

4-Cyanoindole (2.8 g, 20 mmol, Biosynth International) was dissolved in N, N –
 10 Dimethylformamide (25 mL). To the solution were added potassium carbonate
 powder (5.5 g, 40 mmol, 325 mesh, Aldrich) and iodomethane (3.4 g, 24 mmol,
 Aldrich). The mixture was stirred at room temperature for 48 h then the N, N –
 Dimethylformamide was removed via vacuo and the residue was diluted in ethyl
 acetate (100 mL). The organic solution was washed by water (50 mL), brine (50
 15 mL). The resulting organic solution was dried over anhydrous magnesium sulfate
 and concentrated via vacuo. The title compound was purified by column
 chromatography (silica gel, hexane/ethyl acetate 3/2) in form as white solid in
 97% yield (3.02 g, 19.4 mmol).

 $C_{10}H_8N_2$

20 MS (ESI, pos. ion) m/z: 157.0 (M+1); MS (ESI, neg. ion) m/z: 155.0 (M-1).

Step 2) 1-Methyl-1H-indole-4-carbaldehyde:

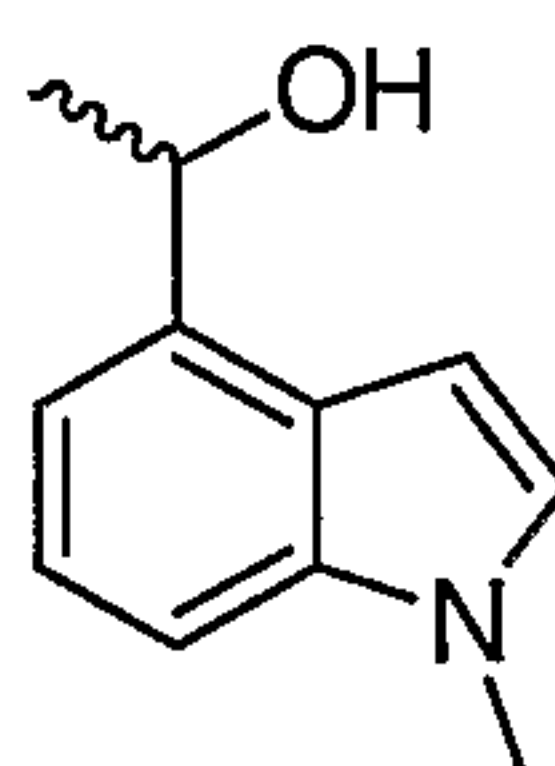
- 103 -

1-Methyl-1H-indole-4-carbonitrile (3.02 g, 19 mmol) was dissolved in anhydrous dichloromethane (30 mL) and the solution was cooled to -78°C . To the reaction solution was slowly added 1.5 M diisobutylaluminum hydride in toluene (12.6 mL, 19 mmol, Aldrich). The reaction mixture was allowed to stir under nitrogen at room temperature for 6 h then it was cooled again in ice bath and quenched with methyl alcohol (4 mL). The resulting solution was poured to 15% aqueous sulfuric acid solution (40 mL) at 0°C . After stirring vigorously for 1 h, the mixture was added aqueous 5 N sodium hydroxide to adjust $\text{PH} > 12$. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (40 mL x 3). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated via vacuo. The title compound was purified by column chromatography (silica gel, hexane/ethyl acetate 2/3) in form as light yellow oil in 92% yield (2.8 g, 17.6 mmol).

$\text{C}_{10}\text{H}_9\text{NO}$

MS (ESI, pos. ion) m/z : 160.1 (M+1); MS (ESI, neg. ion) m/z : 158.0 (M-1).

Step 3) 1-(1-Methyl-1H-indol-4-yl)-ethanol:



20

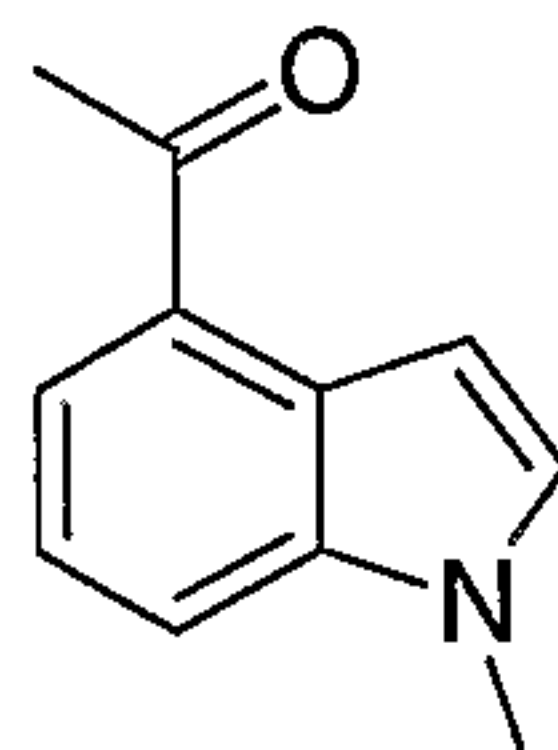
The title compound was prepared by the same procedure for 1-quinolin-4-yl-ethanol from 1-methyl-1H-indole-4-carbaldehyde (2.8 g, 17.6 mmol), 3 M methyl magnesium iodide solution in diethyl ether (10 mL, 30 mmol, Aldrich) and anhydrous tetrahydrofuran (20 mL). The crude title compound obtained in form as yellow oil in 97% yield (3.0 g, 17.1 mmol).

$\text{C}_{11}\text{H}_{13}\text{NO}$

MS (ESI, pos. ion) m/z : 176.0 (M+1); MS (ESI, neg. ion) m/z : 174.0 (M-1).

Step 4) 1-(1-Methyl-1H-indol-4-yl)-ethanone:

- 104 -

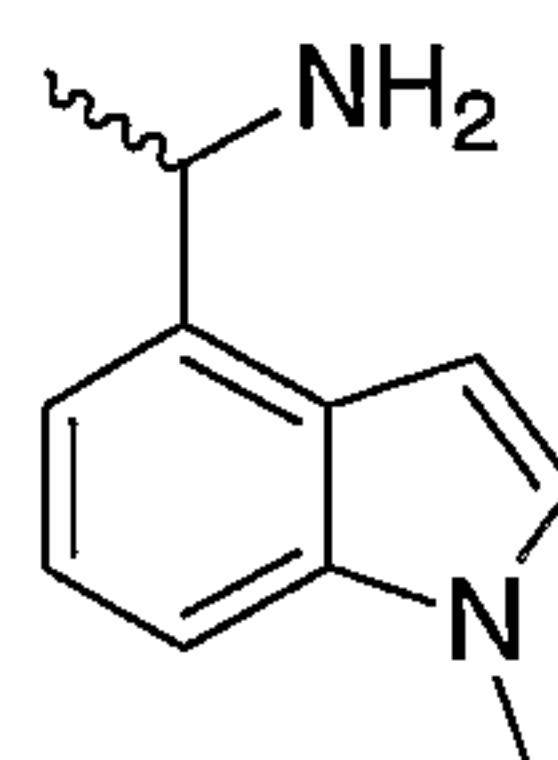


The title compound was prepared by the same procedure for 1-quinolin-4-yl-ethanone from 1-(1-Methyl-1H-indol-4-yl)-ethanol (3.0 g, 17 mmol), manganese
 5 oxide (8.69 g, 100 mmol, Aldrich) and dichloromethane (50 mL). The crude title compound was obtained in form as yellow oil in 98% yield (2.9 g, 16.7 mmol).

$C_{11}H_{11}NO$

MS (ESI, pos. ion) m/z: 174.0 (M+1); MS (ESI, neg. ion) m/z: 172.0 (M-1).

10 Step 5) 1-(1-Methyl-1H-indol-4-yl)-ethylamine:



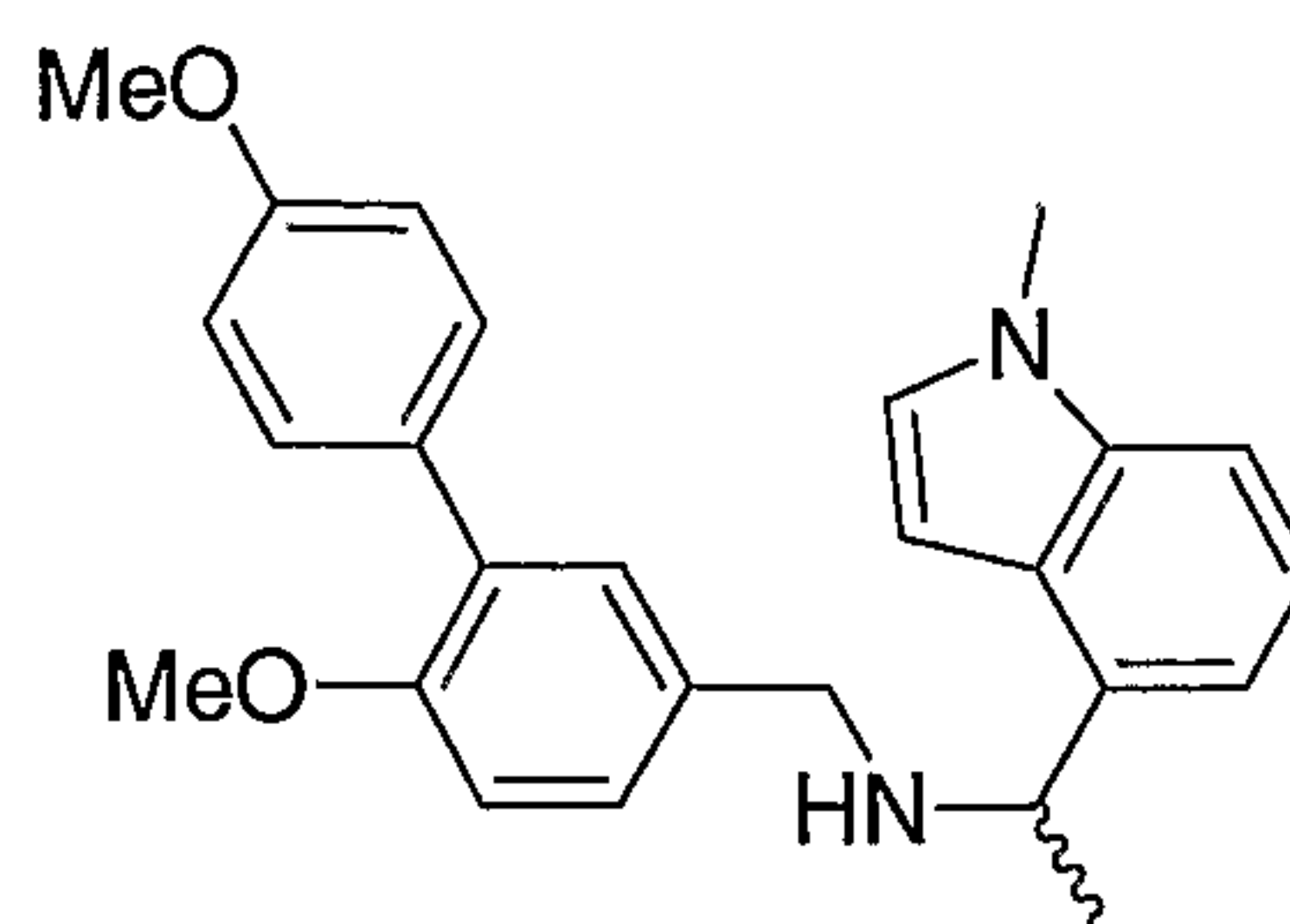
The title compound was prepared by the same procedure for preparing 1-pyridin-3-yl-ethylamine from 1-(1-methyl-1H-indol-4-yl)-ethanone (1.75 g, 10 mmol), 2
 15 M ammonia solution in methyl alcohol (25 mL, 50 mmol, Aldrich), acetic acid (15 mL, J.T. Baker) and sodium cyanoborohydride (2.5 g, 40 mmol, Aldrich). The title compound was purified by column chromatography (silica gel, 2 M ammonia solution in methyl alcohol/ethyl acetate 1/10) in form as light yellow oil in 48% yield (0.83 g, 4.8 mmol).

20 $C_{11}H_{14}N_2$

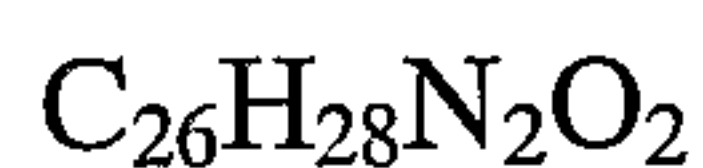
MS (ESI, pos. ion) m/z: 175.0 (M+1); MS (ESI, neg. ion) m/z: 173.0 (M-1).

Step 6) (6,4'-Dimethoxy-biphenyl-3-ylmethyl)-[1-(1-methyl-1H-indol-4-yl)-ethyl]-amine:

- 105 -



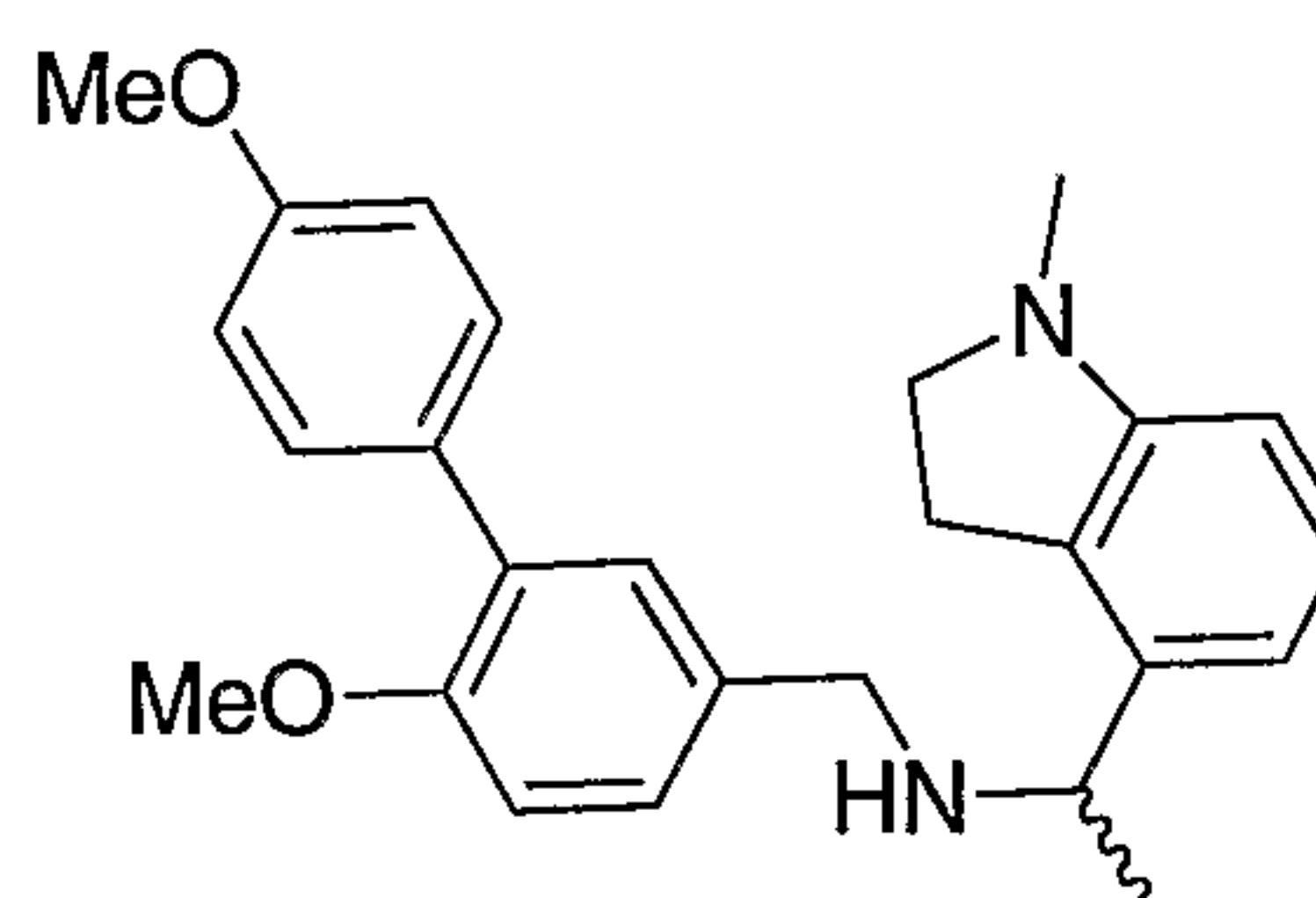
The title compound was prepared by the same procedure for (6,4'-dimethoxy-biphenyl-3-ylmethyl)-(1-quinolin-4-yl-ethyl)-amine from 1-(1-Methyl-1H-indol-4-yl)-ethylamine (522 mg, 3.0 mmol), 6,4'-Dimethoxy-biphenyl-3-carbaldehyde (242 mg, 1.0 mmol) and sodium cyanoborohydride (1.0 g, 16 mmol, Aldrich). The title compound was purified by column chromatography (silica gel, hexane/ethyl acetate 3/2) in form as white solid in 74% yield (296 mg, 0.74 mmol).



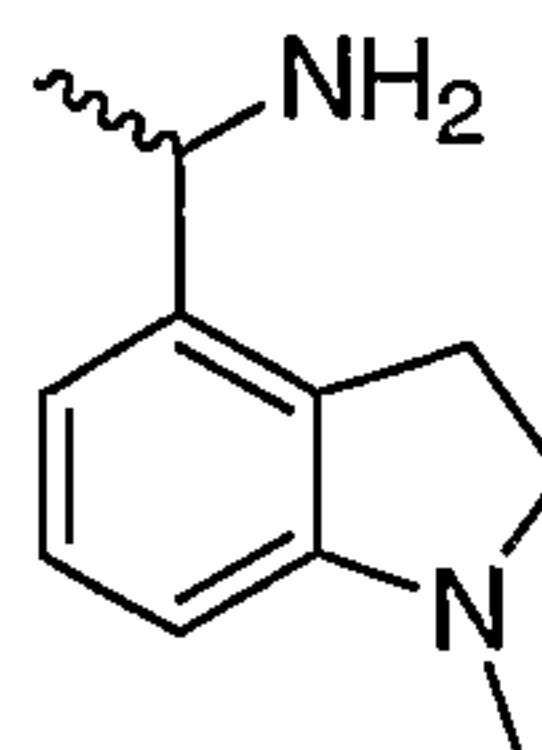
MS (ESI, pos. ion) m/z: 401.6 (M+1); MS (ESI, neg. ion) m/z: 399.2 (M-1).

Example 64

(6,4'-Dimethoxy-biphenyl-3-ylmethyl)-[1-(1-methyl-2,3-dihydro-1H-indol-4-yl)-ethyl]-amine



Step 1) 1-(1-Methyl-2,3-dihydro-1H-indol-4-yl)-ethylamine:



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To the solution of 1-(1-Methyl-1H-indol-4-yl)-ethylamine (1.74 g, 10 mmol) with acetic acid (10 mL, J.T. Baker) was added sodium cyanoborohydride (1.0 g, 16 mmol, Aldrich) at 0 C. The reaction mixture was stirred at room temperature for 4 h then quenched with saturate aqueous sodium bicarbonate (40 mL). The aqueous phase was extracted with ethyl acetate (30 mL x 4). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated via vacuo. The title crude compound was obtained in form as light yellow oil in 78% yield (1.37, 7.8 mmol).



MS (ESI, pos. ion) m/z: 177.2 (M+1); MS (ESI, neg. ion) m/z: 175.0 (M-1).

Step 2) (6,4'-Dimethoxy-biphenyl-3-ylmethyl)-[1-(1-methyl-2,3-dihydro-1H-indol-4-yl)-ethyl]-amine:

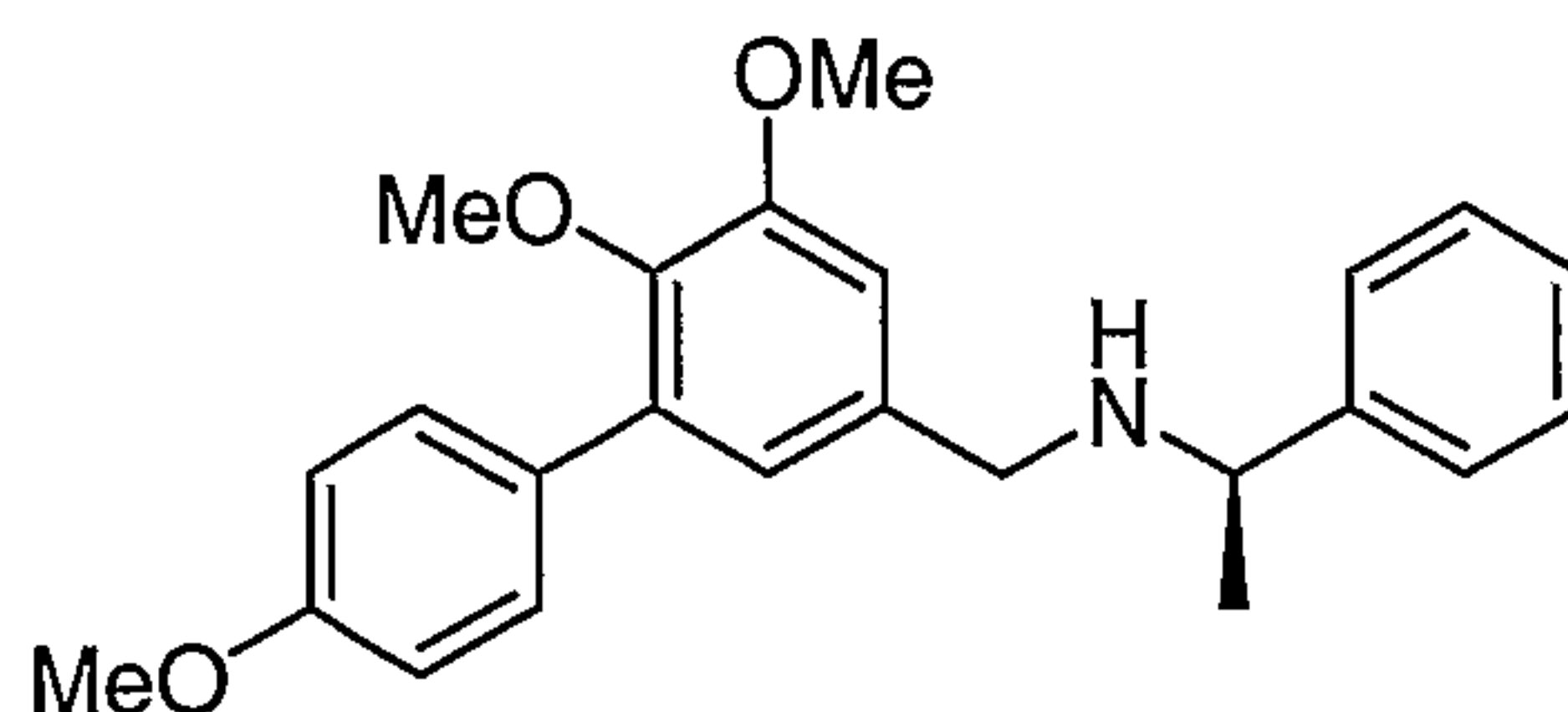
The title compound was prepared by the same procedure for (6,4'-dimethoxy-biphenyl-3-ylmethyl)-(1-quinolin-4-yl-ethyl)-amine from 1-(1-Methyl-2,3-dihydro-1H-indol-4-yl)-ethylamine (528 mg, 3.0 mmol), 6,4'-Dimethoxy-biphenyl-3-carbaldehyde (242 mg, 1.0 mmol) and sodium cyanoborohydride (1.0 g, 16 mmol, Aldrich). The title compound was purified by column chromatography (silica gel, ethyl acetate) in form as white solid in 55% yield (221 mg, 5.5 mmol).



MS (ESI, pos. ion) m/z: 403.3 (M+1); MS (ESI, neg. ion) m/z: 401.4 (M-1).

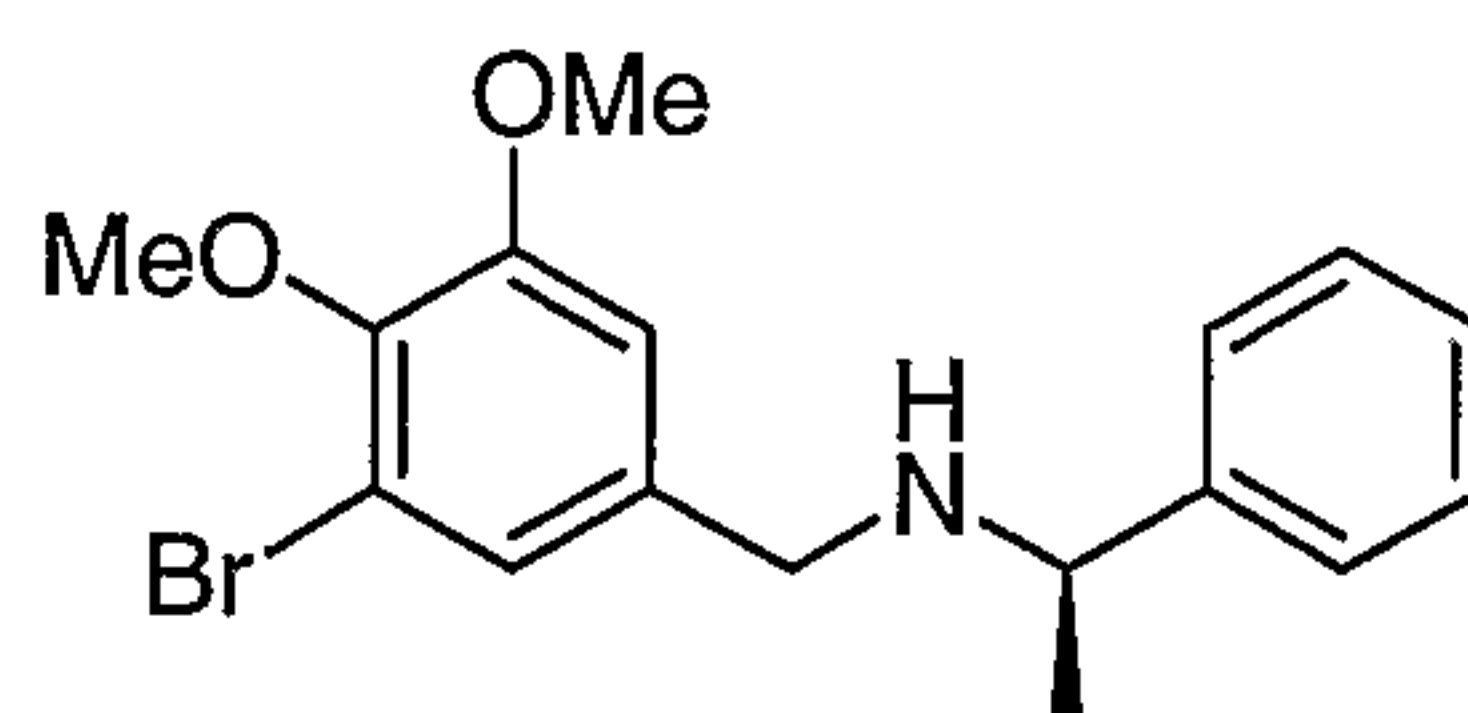
Example 65

((1R)-1-Phenylethyl){[4,5-dimethoxy-3-(4-methoxyphenyl)phenyl]methyl}amine



Step 1) ((1R)-1-Phenylethyl)[(3-bromo-4,5-dimethoxyphenyl)methyl]amine:

- 107 -

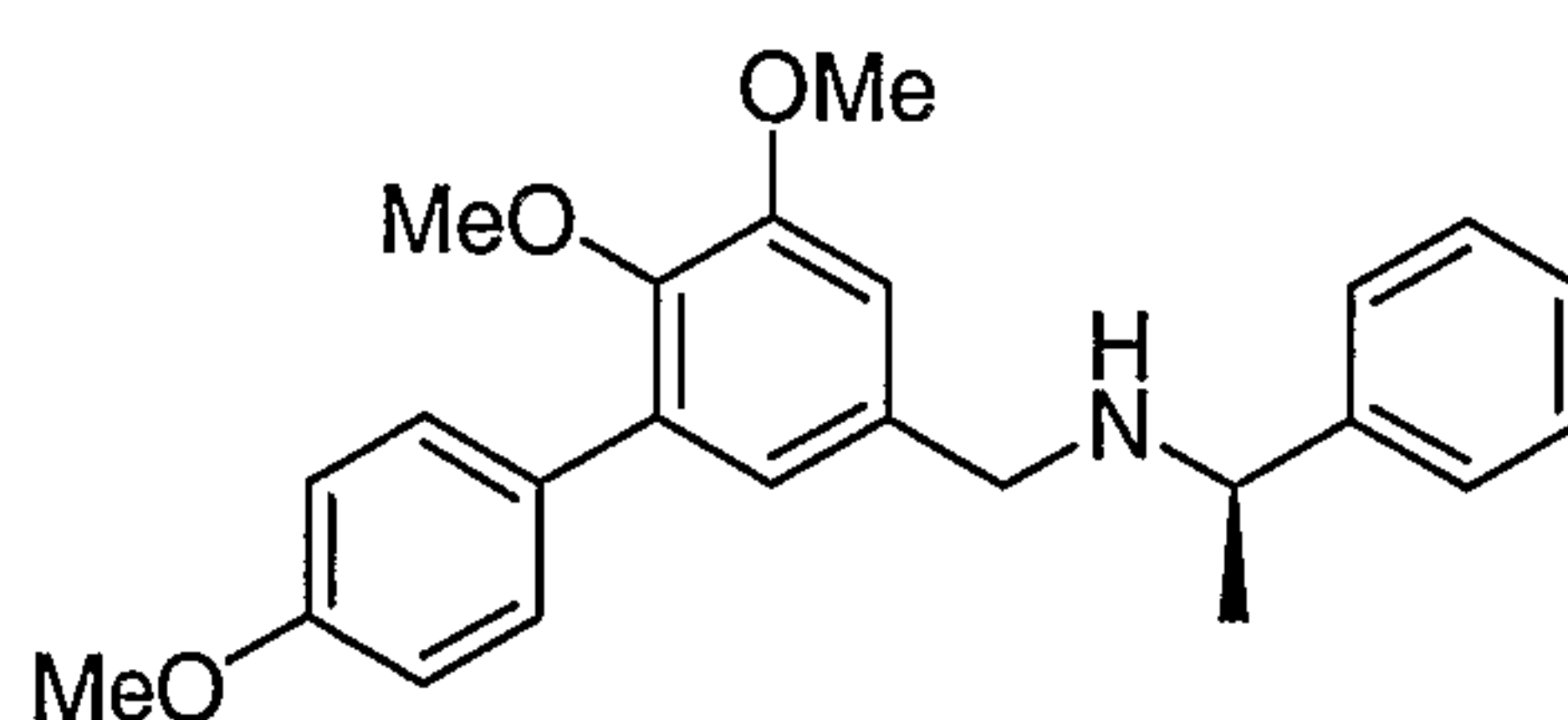


To a solution of 3-bromo-4,5-dimethoxybenzaldehyde (5 g, 0.020 mol, Aldrich), (R)- α -methylbenzylamine (2.6 mL, 0.020 mol) and AcOH (5 mL) in 70 mL of MeOH was stirred at RT for 2 hours. The reaction solution was then cooled to 0 C and NaBH₃CN (2.51 g, 0.040 mol) was added. The reaction was warmed up to RT in 2 hours and continued to stir for 16 hours. The reaction solution was concentrated *in vacuo* and the residue was re-dissolved in 150 mL of EtOAc. The organic solution was washed with 50 mL of saturated NaHCO₃ aqueous solution, followed by 50 mL of brine. The organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by a silica gel column chromatography (50% EtOAc in hexane) to provide white waxy solid (5.1 g).

C₁₇H₂₀BrNO₂

MS (ESI, pos. ion) m/z: 350.2 (M+1).

Step 2) ((1R)-1-Phenylethyl){[4,5-dimethoxy-3-(4-methoxyphenyl)phenyl]methyl}amine:



To a mixture of ((1R)-1-phenylethyl)[(3-bromo-4,5-dimethoxyphenyl)-methyl]amine (1.1 g, 3.15 mmol), 4-methoxyphenylboronic acid (0.479 g, 3.15 mmol), 2M Na₂CO₃ (5 mL). 4 mL of EtOH in 10 mL of toluene was added 83 mg of PPh₃ (0.315 mmol) and 0.364 g of Pd (PPh₃)₄ (0.315 mmol). The mixture was then heated to 80 C under N₂ for 16 hours. The mixture was cooled to RT and was diluted with 50 mL of EtOAc and 20 mL of sat. NaHCO₃ aq. solution. The

- 108 -

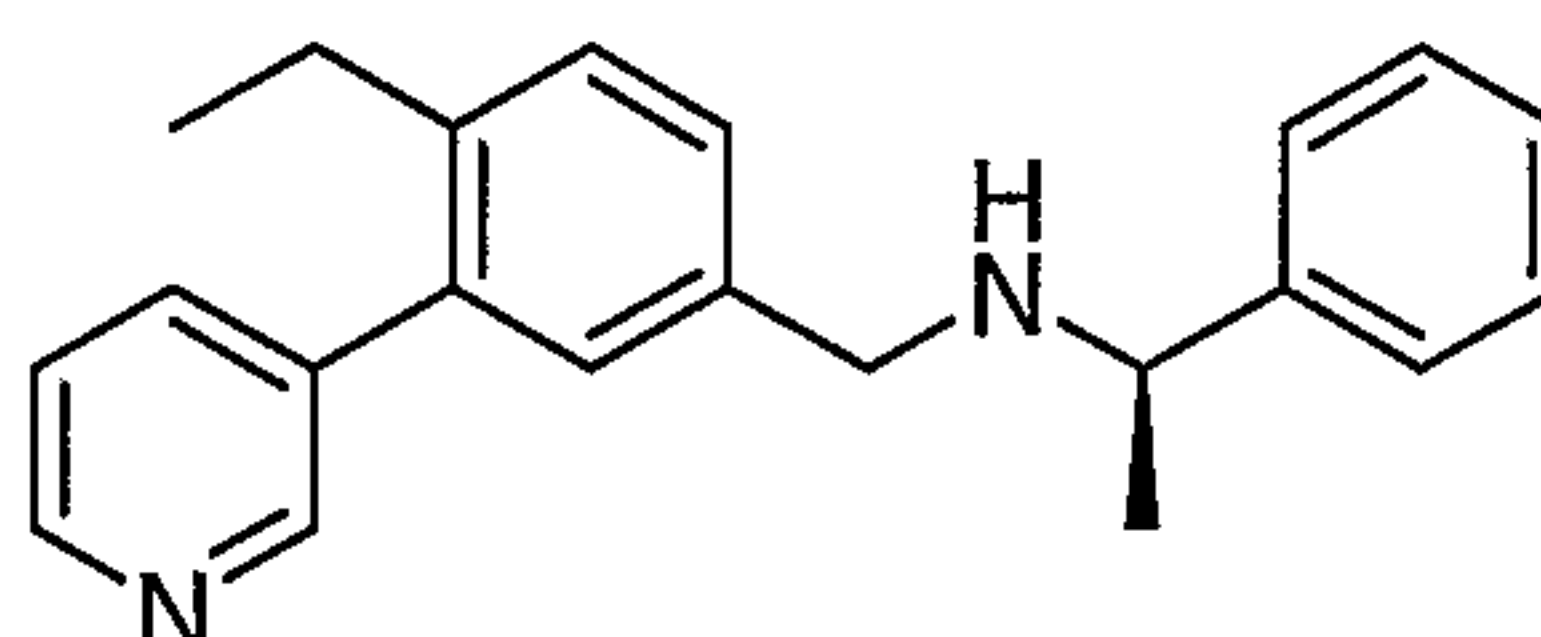
organic phase was washed with 30 mL of brine, dried over Na₂SO₄ and concentrated *in vacuo*. The light yellow oil was chromatographed (silica gel, 10% to 50% EtOAc in hexane) to provide light yellow oil (0.5 g). The product was treated with 1N HCl in Et₂O to afford the HCl salt, which was re-crystallized in EtOAc to afford light yellow solid (0.5 g).

C₂₄H₂₇BNO₃

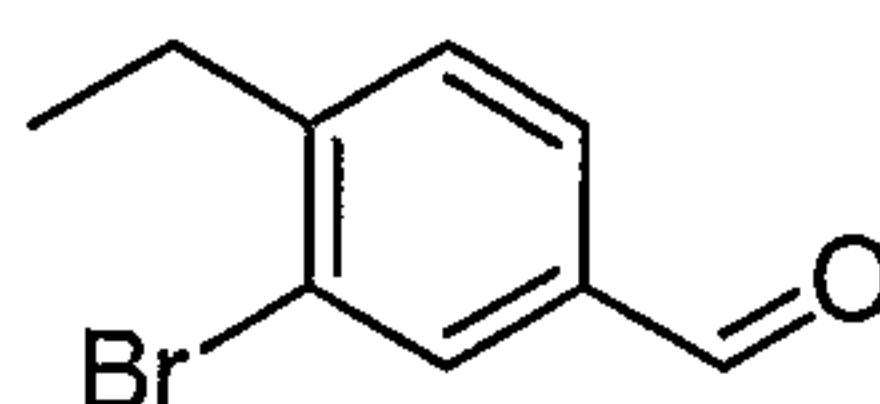
MS (ESI, pos. ion) m/z: 378.4 (M+1).

Example 66

((1R)-1-Phenylethyl)[(4-ethyl-3-(3-pyridyl)phenyl)methyl]amine



Step 1) 3-Bromo-4-ethylbenzaldehyde



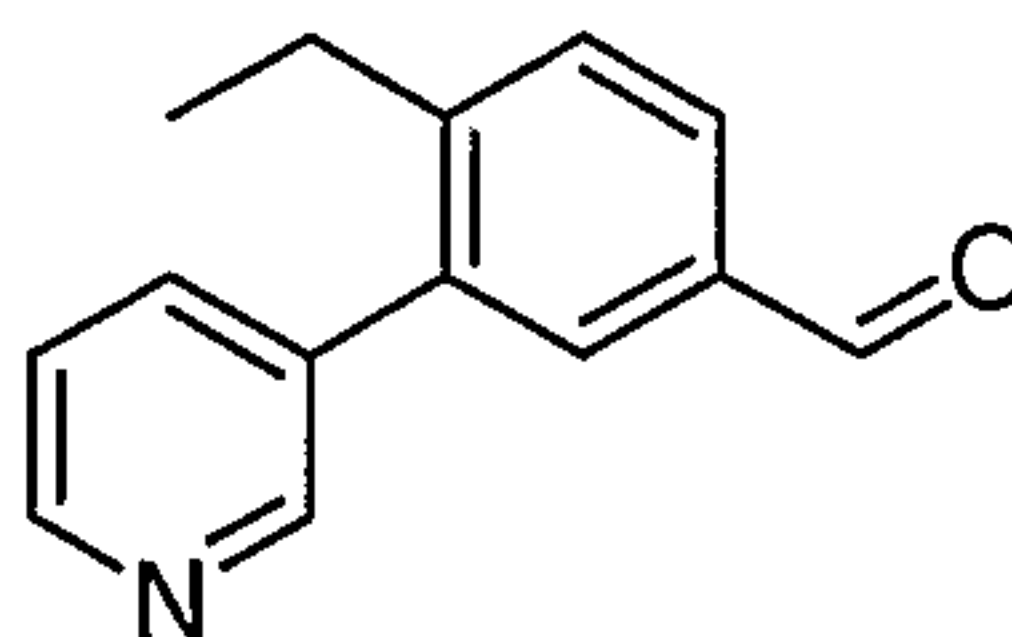
To a solution of 4-ethylbenzaldehyde (10 g, 0.0745mol, Aldrich) in TFA/98% H₂SO₄ (4/1, 125 mL) mixture was added NBS (13.26 g, 0.0745 mol, Aldrich) at RT and continued to stir for 16 hours. The solvent was then removed *in vacuo* and the residue was dissolved in 200 mL of EtOAc. 1N NaOH solution (about 150 mL) was added to the solution and the organic phase was separated, washed with 100 mL of brine, dried over Na₂SO₄ and concentrated *in vacuo*. The oily residue was chromatographed (silica gel, 50% EtOAc in hexane) to afford orange oil as desired product (11.55 g).

C₉H₉BrO

MS (ESI, pos. ion) m/z: 227.0 (M+15).

Step 2) 4-Ethyl-3-(3-pyridyl)benzaldehyde:

- 109 -

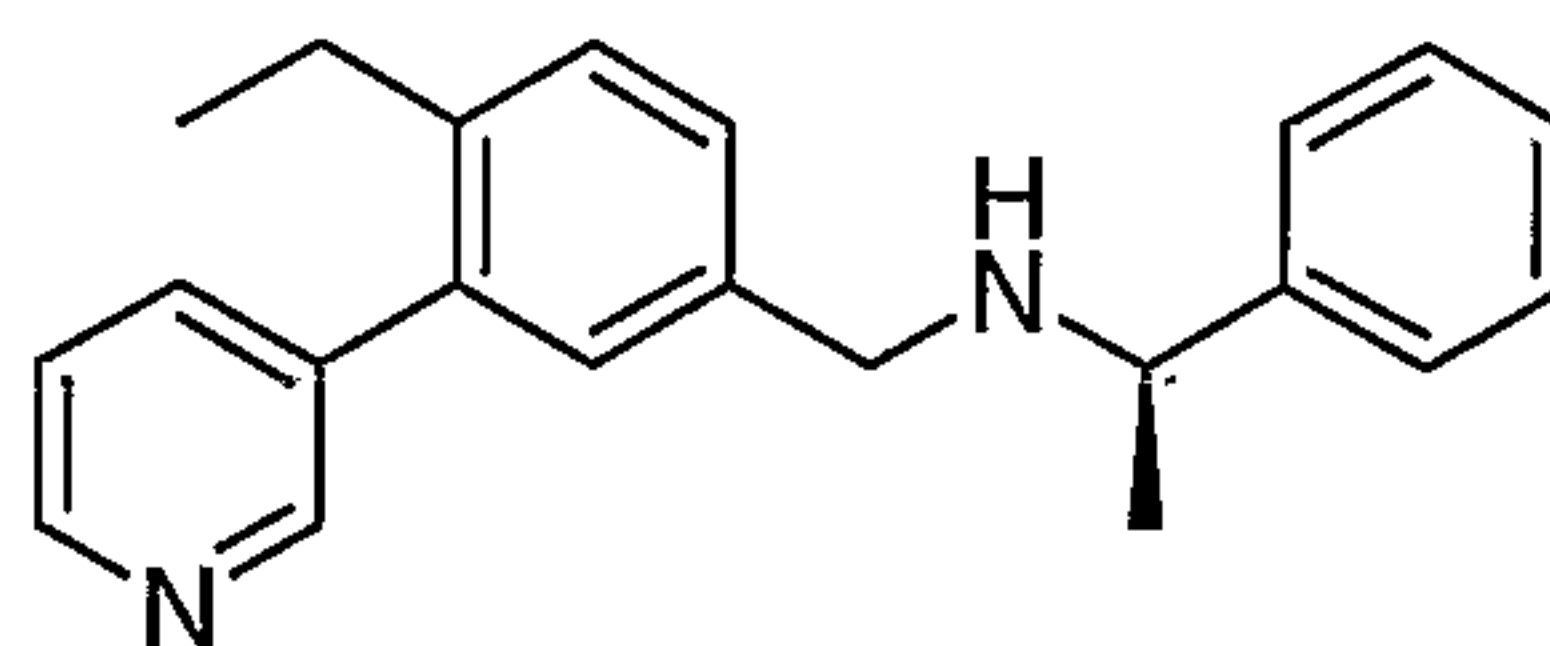


To a mixture of 3-bromo-4-ethylbenzaldehyde (2.45 g, 0.0115 mol), pyridine 3-boronic acid (1.42 g, 0.0115 mol, Matrix Scientific), 2M Na₂CO₃ (15 mL) in 30 mL of toluene was added 1.33 g of Pd (PPh₃)₄ (1.15 mmol, Aldrich). The mixture
 5 was then heated to 80 C under N₂ for 16 hours. The mixture was cooled to RT and was diluted with 100 mL of EtOAc and 40 mL of sat. NaHCO₃ aq. solution. The organic phase was washed with 40 mL of brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was chromatographed (silica gel, 20% EtOAc in hexane) to provide yellow oil (1.2 g).

10 C₁₄H₁₃NO

MS (ESI, pos. ion) m/z: 212.4 (M+1).

Step 3) ((1R)-1-Phenylethyl)[(4-ethyl-3-(3-pyridyl)phenyl)methyl]amine:



15

A solution of 4-ethyl-3-(3-pyridyl)benzaldehyde (0.2 g, 0.95 mmol), (R)- α -methylbenzylamine (0.121 mL, 0.95 mmol) and AcOH (1 mL) in 10 mL of MeOH was stirred at RT for 3 hours. The reaction solution was then cooled to 0 C and NaBH₃CN (0.18 g, 2.85 mmol) was added. The reaction was warmed up
 20 to RT continued to stir 3 hours. The reaction solution was concentrated *in vacuo* and the residue was re-dissolved in 50 mL of EtOAc. The organic solution was washed with 20 mL of saturated NaHCO₃ aqueous solution, followed by 20 mL of brine. The organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by a silica gel column chromatography (20% of EtOAc
 25 in hexane) to provide colorless oil (0.2 g). The product was treated with 1N HCl in Et₂O and the HCl salt was re-crystallized in MeOH/Et₂O (1:10) mixture to provide white solid (0.2 g).

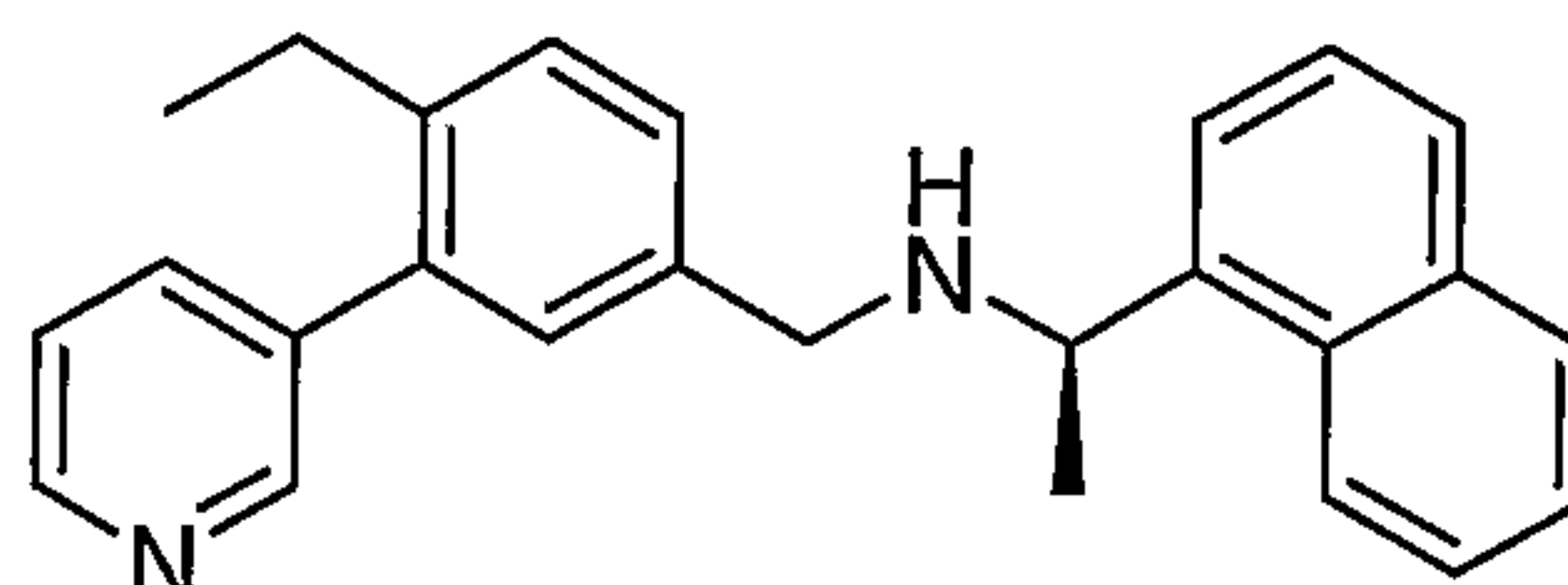
- 110 -

 $C_{22}H_{24}N_2$

MS (ESI, pos. ion) m/z: 317.3 (M+1).

Example 67

5 ((1R)-1-Naphthylethyl)[(4-ethyl-3-(3-pyridyl)phenyl)methyl]amine



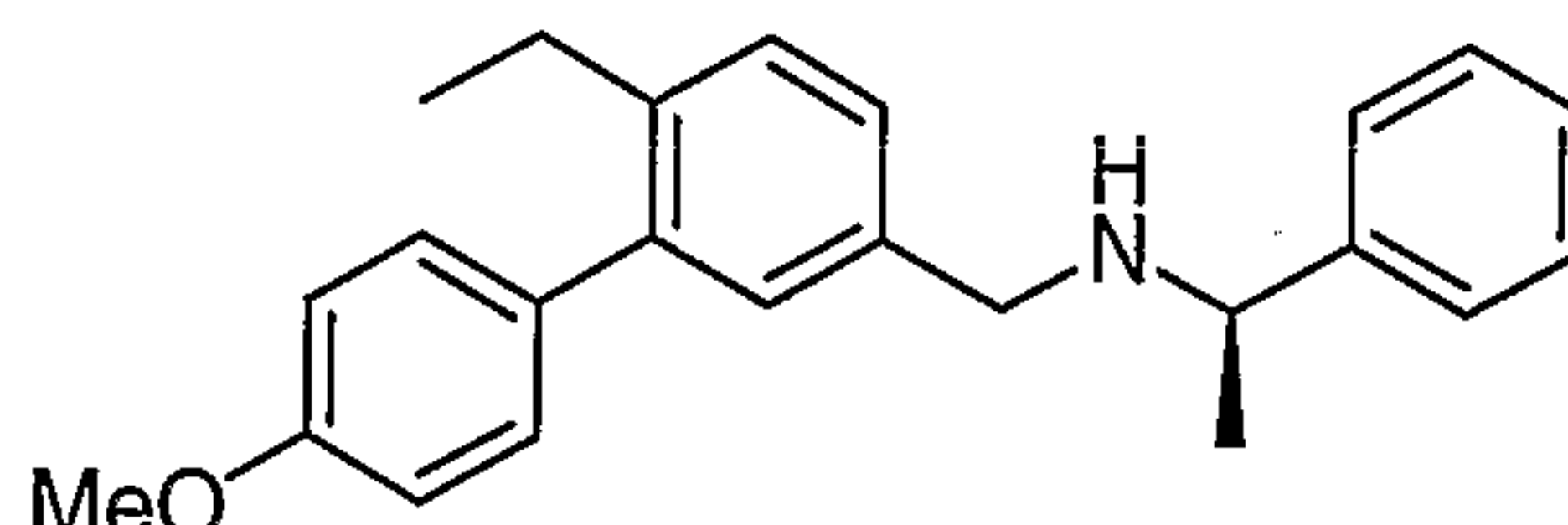
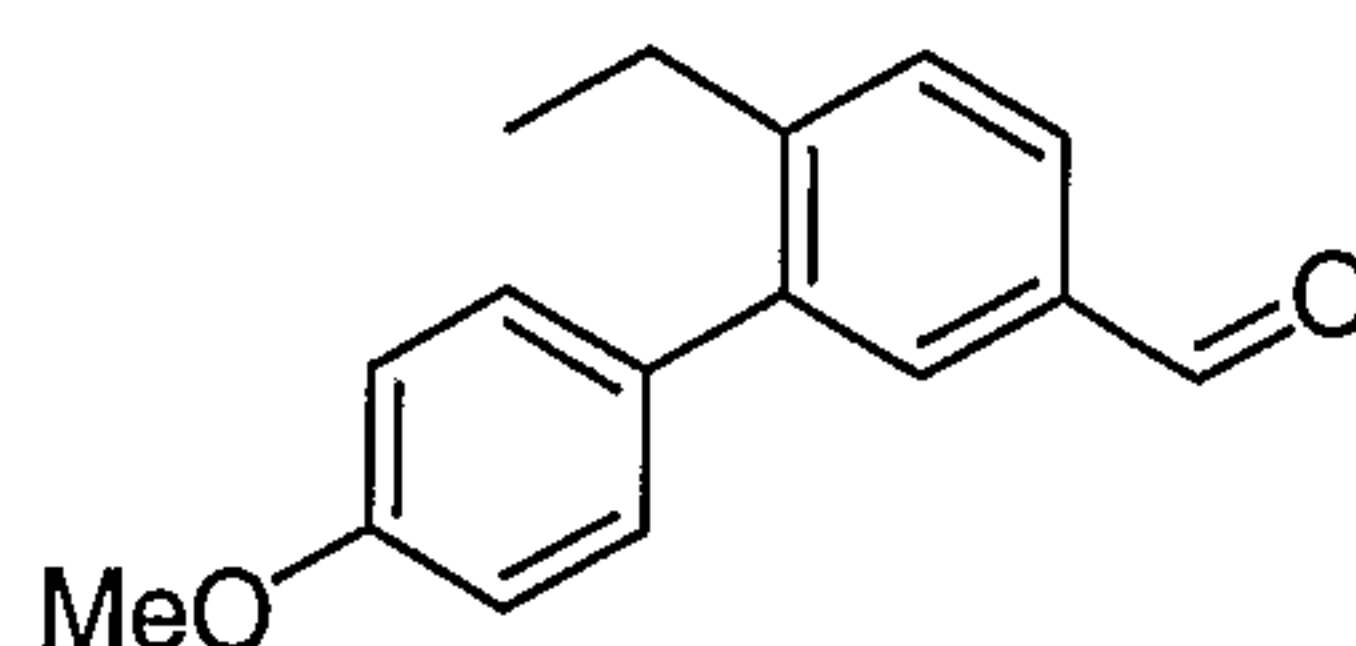
The title compound (0.22 g, white solid as HCl salt) was prepared from 4-ethyl-3-(3-pyridyl)benzaldehyde (0.22 g) and (R)-1-(1-naphthyl)ethylamine (0.17 mL) analogously to Example 66, step 3.

 $C_{26}H_{26}N_2$

MS (ESI, pos. ion) m/z: 367.3 (M+1).

Example 68

15 ((1R)-1-phenylethyl){[4-ethyl-3-(4-methoxyphenyl)phenyl]methyl}amine

20 Step 1) 4-Ethyl-3-(4-methoxyphenyl)benzaldehyde:

To a mixture of 3-bromo-4-ethylbenzaldehyde (1.5 g, 7.07 mmol), 4-methoxyphenylboronic acid (1.075 g, 7.07 mmol), 2M Na_2CO_3 (10 mL) in 20 mL of toluene was added 0.817 g of Pd (PPh_3)₄ (0.707 mmol). The mixture was then heated to 80 C under N_2 for 16 hours. The mixture was cooled to RT and was diluted with 100 mL of EtOAc and 50 mL of sat. $NaHCO_3$ aq. solution. The

- 111 -

organic phase was washed with 40 mL of brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was chromatographed (silica gel, 10% EtOAc in hexane) to provide light yellow solid (2.1 g).

C₁₆H₁₆O₂

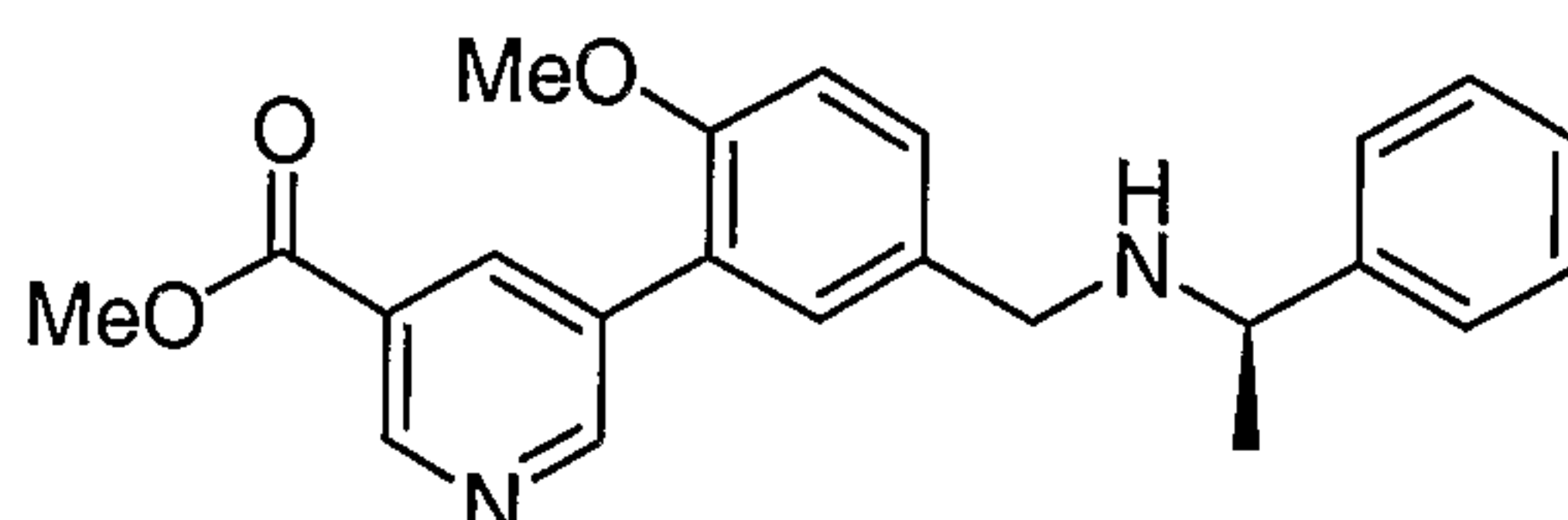
5 MS (ESI, pos. ion) m/z: 241.1 (M+1).

Step 2) ((1R)-1-phenylethyl){[4-ethyl-3-(4-methoxyphenyl)phenyl]methyl}amine:

The title compound (0.2 g, white solid as HCl salt) was prepared from 4-ethyl-3-(4-methoxyphenyl)benzaldehyde (0.5 g) and (R)- α -methylbenzylamine (0.265 mL) analogously to Example 66, step 3.

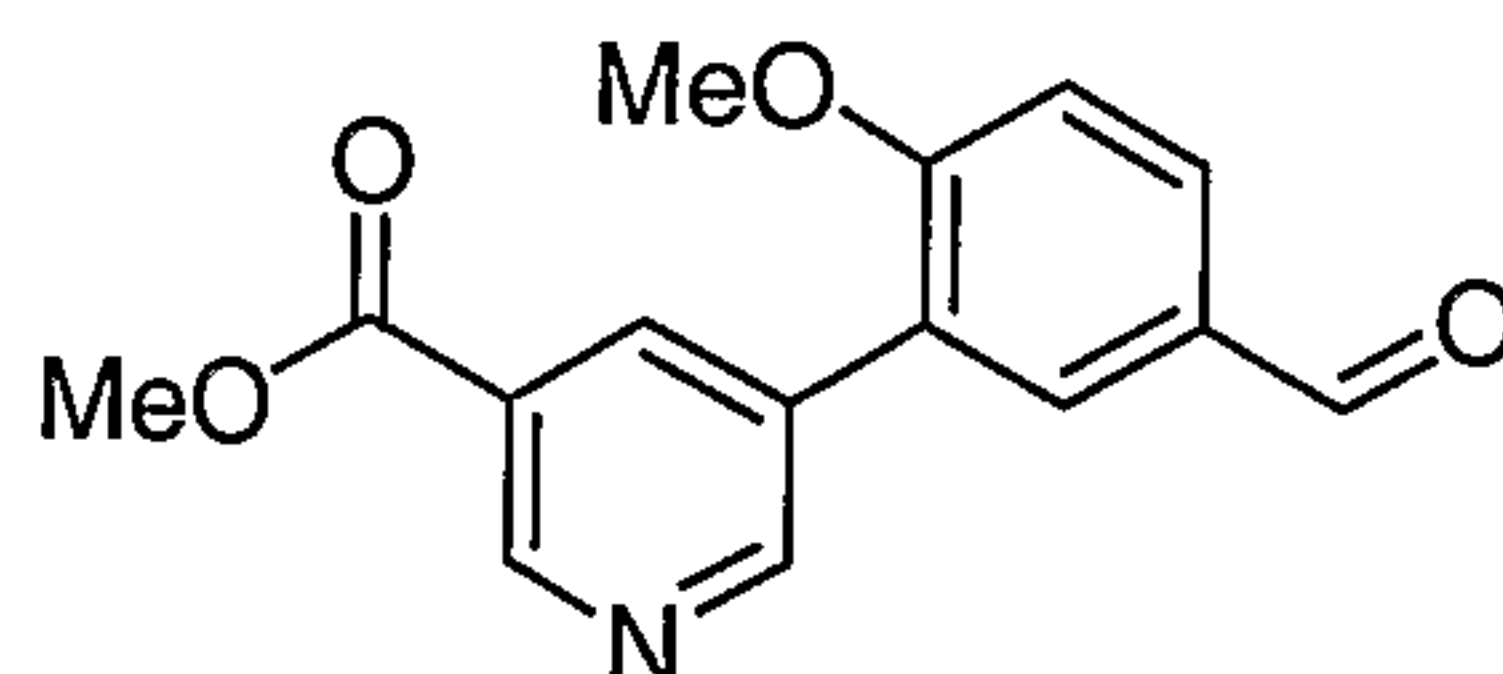
Example 69

15 Methyl 5-(5-{[((1R)-1-phenylethyl)amino]methyl}-2-methoxyphenyl)pyridine-3-carboxylate



20

Step 1) Methyl 5-(3-formyl-6-methoxyphenyl)pyridine-3-carboxylate:



To a mixture of 5-bromonicotinate (2.16 g, 0.01 mol, Avocado Research) and (5-formyl-2-methoxyphenyl)boronic acid (1.79 g, 0.01 mol, Matrix Scientific), 2M Na₂CO₃ (10 mL) in 20 mL of toluene was added 1.15 g of Pd (PPh₃)₄ (1.0 mmol). The mixture was then heated to 80 C under N₂ for 16 hours. The mixture was cooled to RT and was diluted with 100 mL of EtOAc and 50 mL of sat. NaHCO₃

- 112 -

aq. solution. The organic phase was washed with 40 mL of brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was chromatographed (silica gel, 50% EtOAc in hexane) to provide white solid (1.2 g).

$\text{C}_{15}\text{H}_{13}\text{NO}_4$

5 MS (ESI, pos. ion) m/z : 272.3 ($M+1$).

Step 2) Methyl 5-(5-{[[(1R)-1-phenylethyl]amino]methyl}-2-methoxyphenyl)pyridine-3-carboxylate:

The title compound (0.4 g, white solid as HCl salt) was prepared from 4-ethyl-3-(4-methoxyphenyl)benzaldehyde (0.5 g) and (R)- α -methylbenzylamine (0.265 mL) analogously to Example 66, step 3.

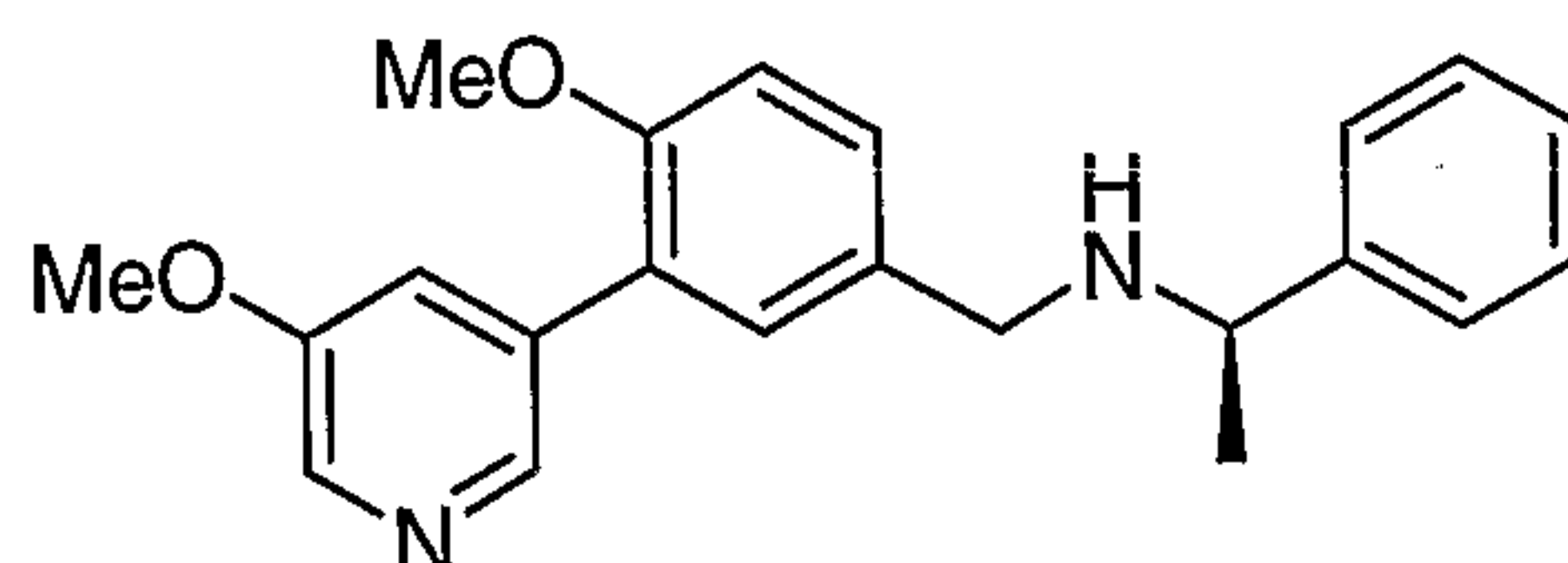
$\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_3$

MS (ESI, pos. ion) m/z : 377.5 ($M+1$).

15

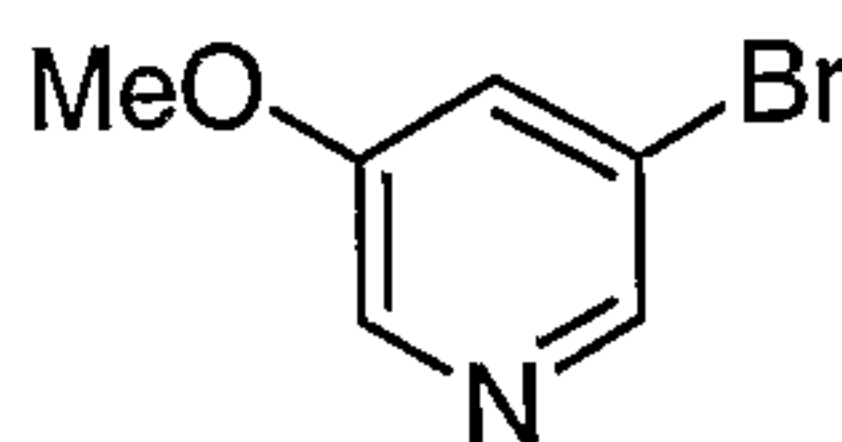
Example 70

((1R)-1-Phenylethyl){[4-methoxy-3-(5-methoxy(3-pyridyl))phenyl]methyl}amine



20

Step 1) 3-Bromo-5-methoxypyridine:



1.45 g of Na (0.063 mol) were added to 100 mL of MeOH and the resulted solution was stirred at RT for 30 minutes. The solution was then concentrated at 65 C *in vacuo* for 40 minutes. The white solid obtained was dissolved in 100 mL of DMF. 15 g of 3,5-dibromopyridine (0.063 mol) were added and the reaction was heated to 65 C for 16 hours. The reaction was cooled to RT and diluted with 200 mL of EtOAc and 100 mL of sat. aq. NaHCO_3 solution. The organic phase

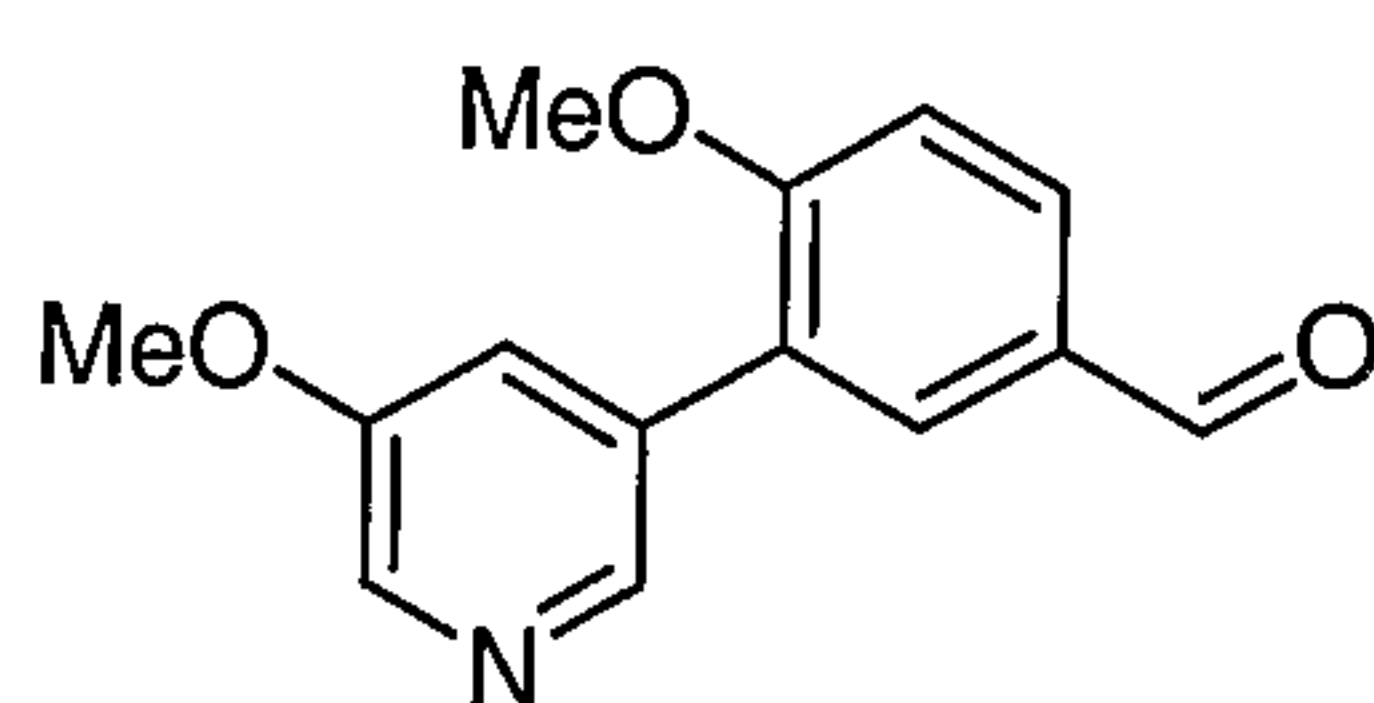
- 113 -

was separated and was washed with 100 mL of brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was chromatographed (silica gel, 10% EtOAc in hexane) to provide colorless crystals (10 g).

C₆H₆BrNO

5 MS (ESI, pos. ion) m/z: 188.1 (M+1).

Step 2) 4-Methoxy-3-(5-methoxy(3-pyridyl))benzaldehyde:



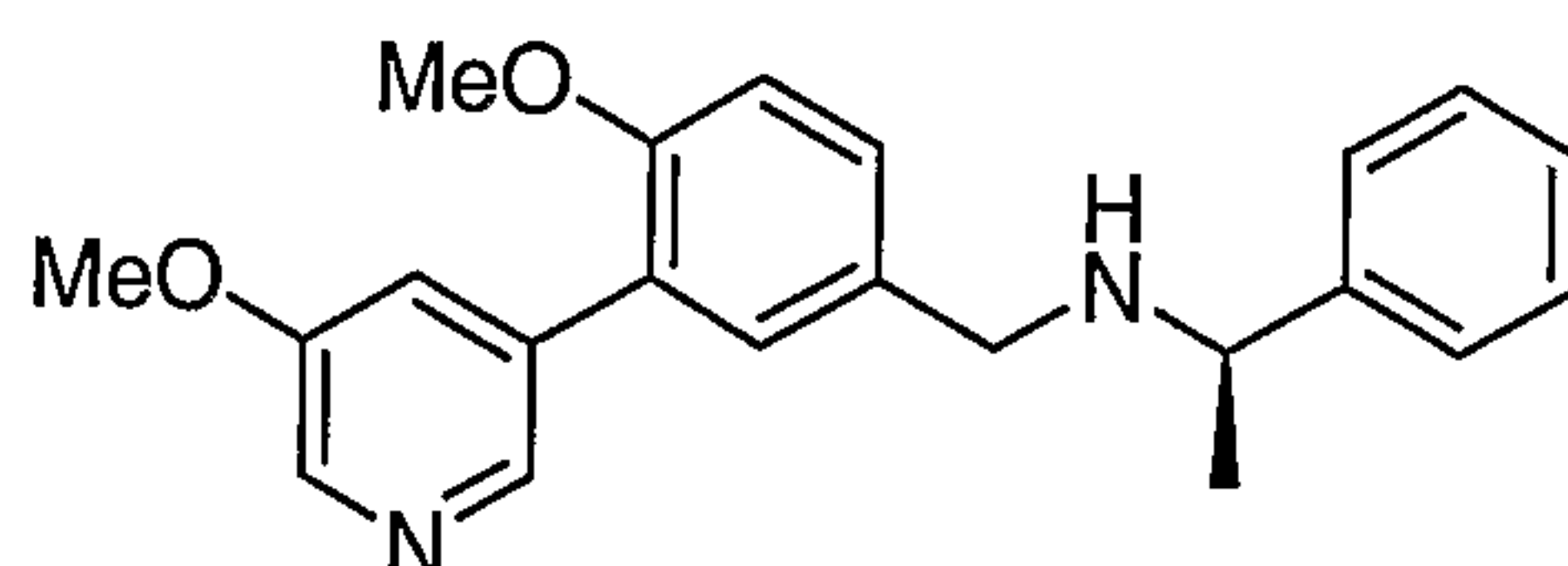
10 The title compound (2.5 g, white solid) was prepared from 3-Bromo-5-methoxypyridine (2.17 g, 0.0116 mol) and (5-formyl-2-methoxyphenyl)boronic acid (2.5 g, 0.014 mol, Matrix Scientific) analogously to Example 69, step 1.

C₁₄H₁₃NO₃

MS (ESI, pos. ion) m/z: 244.4 (M+1).

15

Step 3) ((1R)-1-Phenylethyl){[4-methoxy-3-(5-methoxy(3-pyridyl))phenyl]methyl}amine:



20 The title compound (0.8 g, white solid as HCl salt) was prepared from 4-methoxy-3-(5-methoxy(3-pyridyl))benzaldehyde (0.71 g) and (R)-α-methylbenzylamine (0.371 mL) analogously to Example 66, step 3.

C₂₂H₂₄N₂O₂

MS (ESI, pos. ion) m/z: 349.4 (M+1).

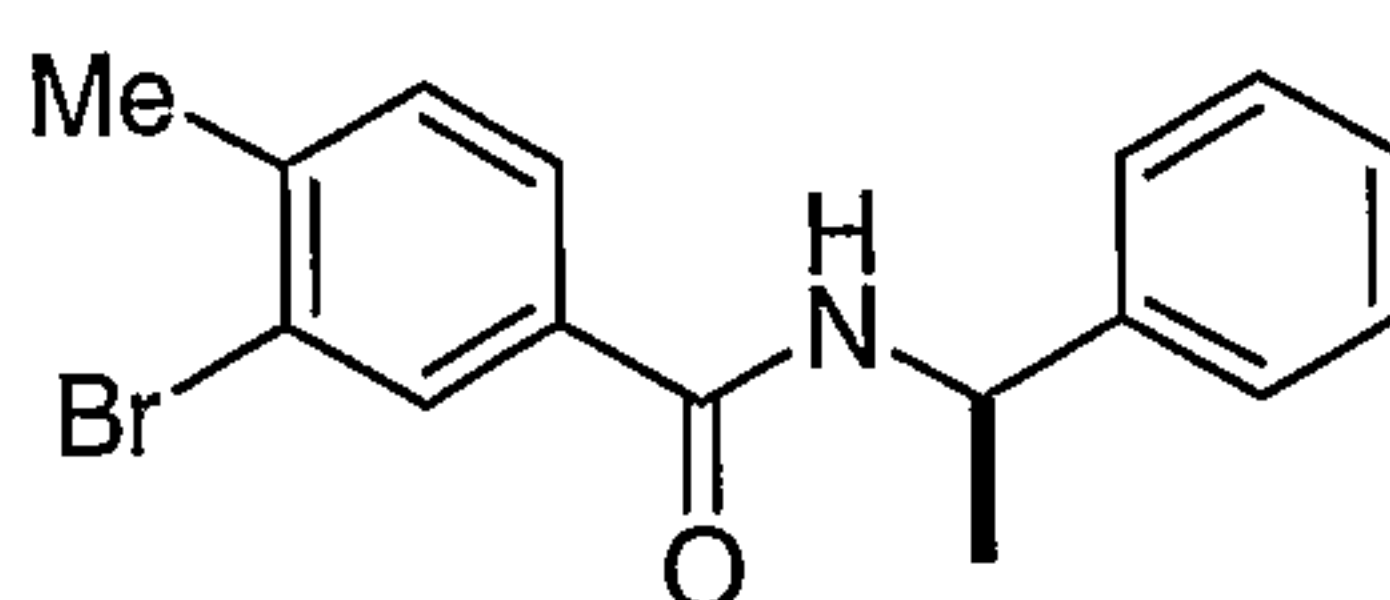
25

Example 71

((1R)-1-Phenylethyl){[3-(4-methoxyphenyl)-4-methylphenyl]methyl}amine
and

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4-(5-[[((1R)-1-Phenylethyl)amino]methyl]-2-methylphenyl)phenol

Step 1) N-((1R)-1-Phenylethyl)(3-bromo-4-methylphenyl)carboxamide:

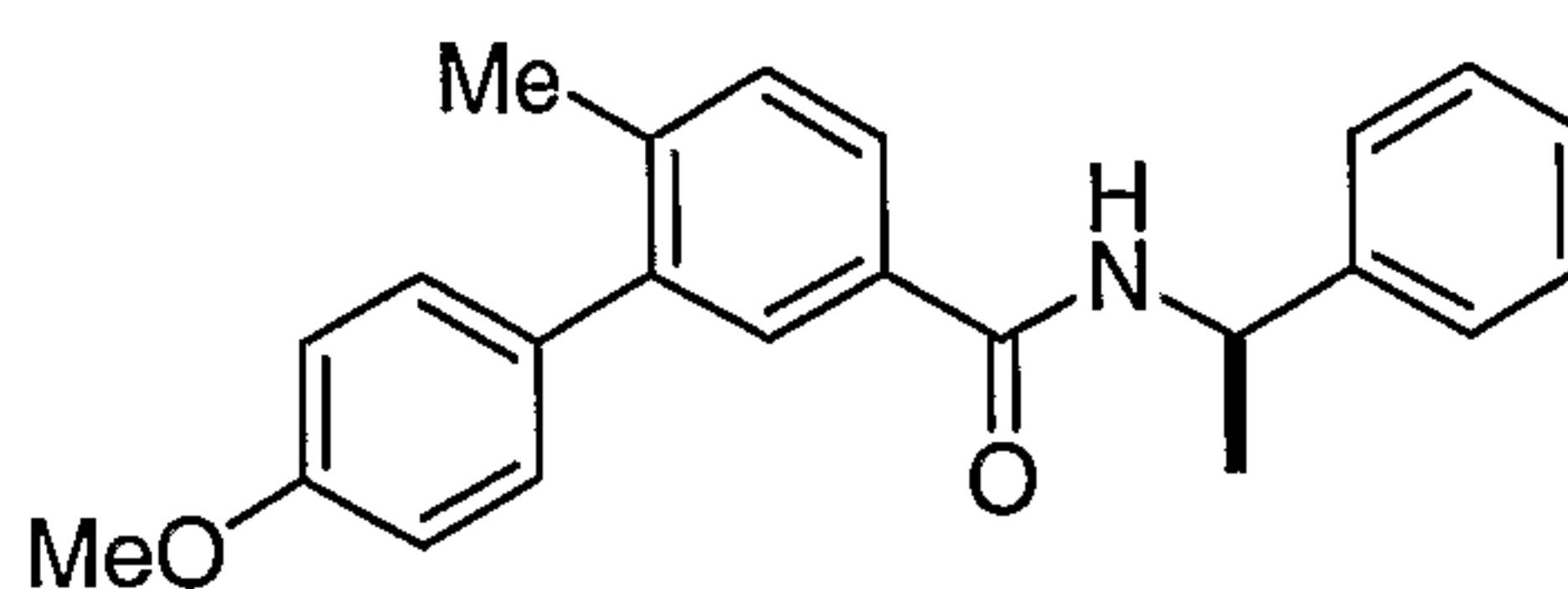
5

To a solution of 3-bromo-4-methylbenzoic acid (5.0 g, 0.023 mol) in CH₂CH₂ (100 mL) was added oxalyl chloride (8.67 g, 0.069 mol). After 10 minutes, 1.0 mL of DMF was added slowly and the mixture was continued to stir at RT for 2 hours. The volatile was removed *in vacuo*. The residue was re-dissolved in CH₂CH₂ (100 mL) and transferred to a 125 mL additional funnel.

To a 500 mL Erlenmeyer flask equipped with a stir bar was added 100 mL of sat. aq. NaHCO₃ solution followed by 2.79 g of (R)- α -methylbenzylamine (0.023 mol) in 100 mL of CH₂CH₂. 3-Bromo-4-methylbenzoyl chloride in CH₂Cl₂ (from above) was added dropwise to the Erlenmeyer flask and the reaction mixture was continued to stir at RT for 16 hours. The organic phase was diluted with 50mL of CH₂CH₂, separated from aqueous phase, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was washed with 50mL of Et₂O and dried in an oven at 40 C overnight to afford light yellow solid (7.0 g, 0.022mol, 96%).

C₁₆H₁₆BrNO

20 MS (ESI, pos. ion) m/z: 316.1 (M+1).

Step 2) N-((1R)-1-Phenylethyl)[3-(4-methoxyphenyl)-4-methylphenyl]carboxamide:

25 To a mixture of N-((1R)-1-phenylethyl)(3-bromo-4-methylphenyl)carboxamide (1.38 g, 4.32 mmol) and 4-methoxyphenylboronic acid (0.53 g, 4.32 mmol) in 10 mL of 2M Na₂CO₃ aq. soln and 20 mL of toluene was bubbled through N₂ for 5 min. Catalyst Pd(PPh₃)₄ (0.36 g, 0.314 mmol) was then added and the mixture

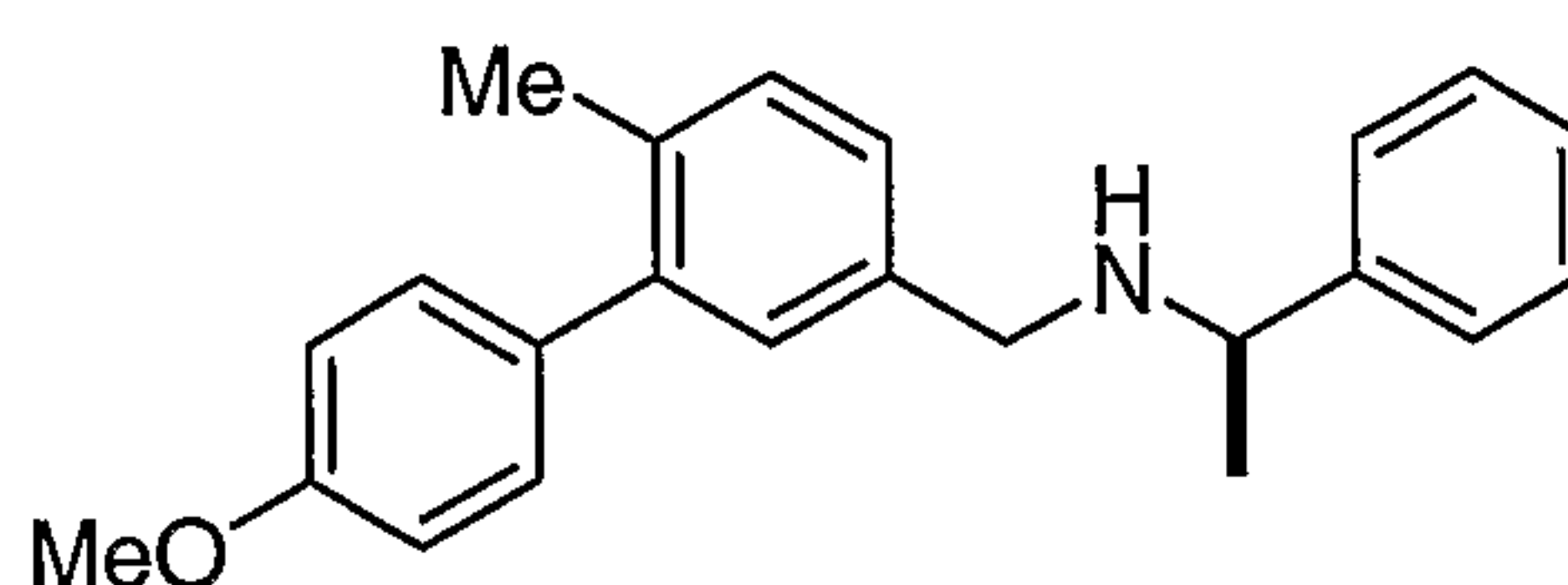
- 115 -

was heated to 80 C for 19 hours under N₂. The reaction mixture was cooled to RT and was diluted with 100 mL of EtOAc and 50 mL of water. The organic layer was separated and washed with 50 mL of brine, and dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (CHCl₃ to EtOAc) to provide yellow solid (1.0 g, 2.9 mmol, 92%).

C₂₃H₂₃NO₂

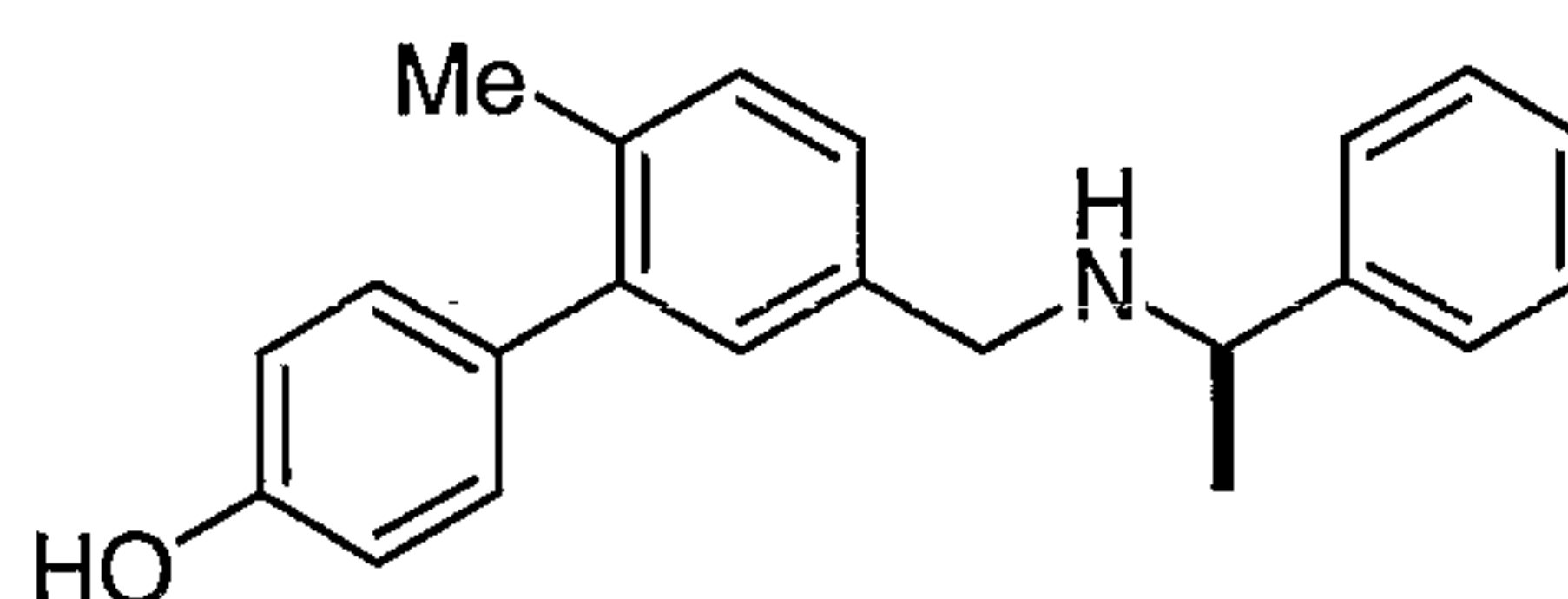
MS (ESI, pos. ion) m/z: 346.3 (M+1).

10 Step 3) ((1R)-1-Phenylethyl){[3-(4-methoxyphenyl)-4-methylphenyl]methyl}amine



and

4-(5-[[((1R)-1-Phenylethyl)amino]methyl]-2-methylphenyl)phenol



15

To a solution of N-((1R)-1-phenylethyl)[3-(4-methoxyphenyl)-4-methylphenyl]carboxamide (0.12 g, 0.34 mmol) in 10mL of toluene was added DIBAL-H (1mL, 1.5mmol). The reaction was then heated to 100 C for 16 hours and cooled to RT. The reaction was quenched with 5 mL of 2N NaOH aq. soln. 100 mL of CH₂Cl₂ was used to extract the product. The organic phase was washed with 30 mL of brine, dried over Na₂SO₃ and concentrated *in vacuo*. The desired products were separated by silica gel column chromatography (30% to 60% EtOAc in hexane) provide ((1R)-1-phenylethyl){[3-(4-methoxyphenyl)-4-methylphenyl]methyl}amine and 4-(5-[[((1R)-1-phenylethyl)amino]methyl]-2-methylphenyl)phenol, which were treated with 1N HCl in Et₂O separately to provide the HCl salts as white solids.

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((1R)-1-Phenylethyl){[3-(4-methoxyphenyl)-4-methylphenyl]methyl}amine

$C_{23}H_{25}NO$

MS (ESI, pos. ion) m/z: 332.3 (M+1).

4-(5-{[((1R)-1-Phenylethyl)amino]methyl}-2-methylphenyl)phenol

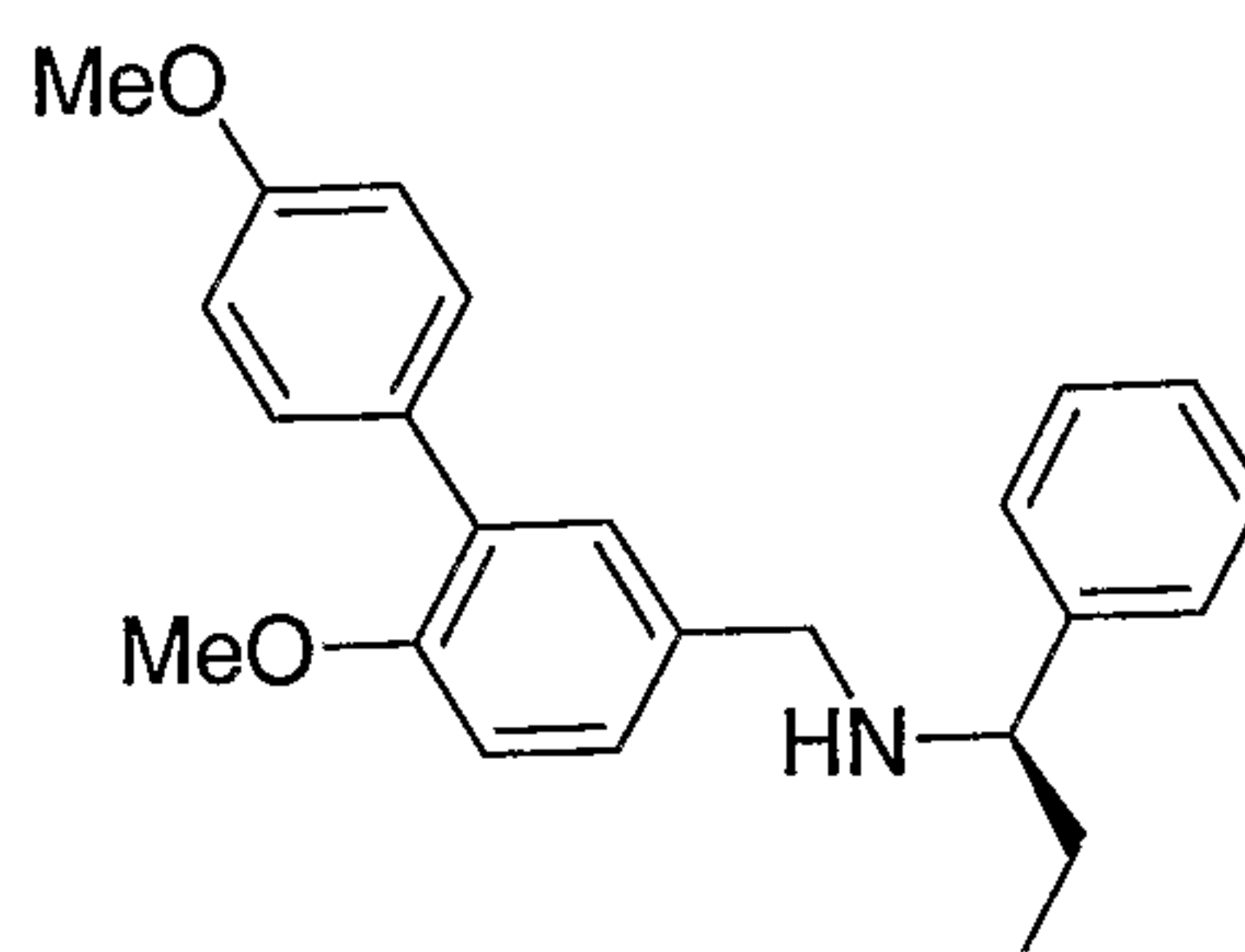
5 $C_{22}H_{23}NO$

MS (ESI, pos. ion) m/z: 318.2 (M+1); MS (ESI, neg. ion) m/z: 316.2 (M-1).

Example 72

((1R)-1-Phenylpropyl){[4-methoxy-3-(4-methoxyphenyl)phenyl]methyl}amine

10



The title compound was prepared by the same procedure for (6,4'-dimethoxy-biphenyl-3-ylmethyl)-(1-quinolin-4-yl-ethyl)-amine from (R)-(+)-1-phenyl-propylamine (405 mg, 3.0 mmol, Lancaster Synthesis Ltd.), 6,4'-Dimethoxy-biphenyl-3-carbaldehyde (242 mg, 1.0 mmol) and sodium cyanoborohydride (1.0 g, 16 mmol, Aldrich). The title compound was purified by column chromatography (silica gel, hexane/ethyl acetate 2/3) in form as white solid in 52% yield (187 mg, 0.52 mmol).

20 $C_{24}H_{27}NO_2$

MS (ESI, pos. ion) m/z: 362.4 (M+1); MS (ESI, neg. ion) m/z: 360.3 (M-1).

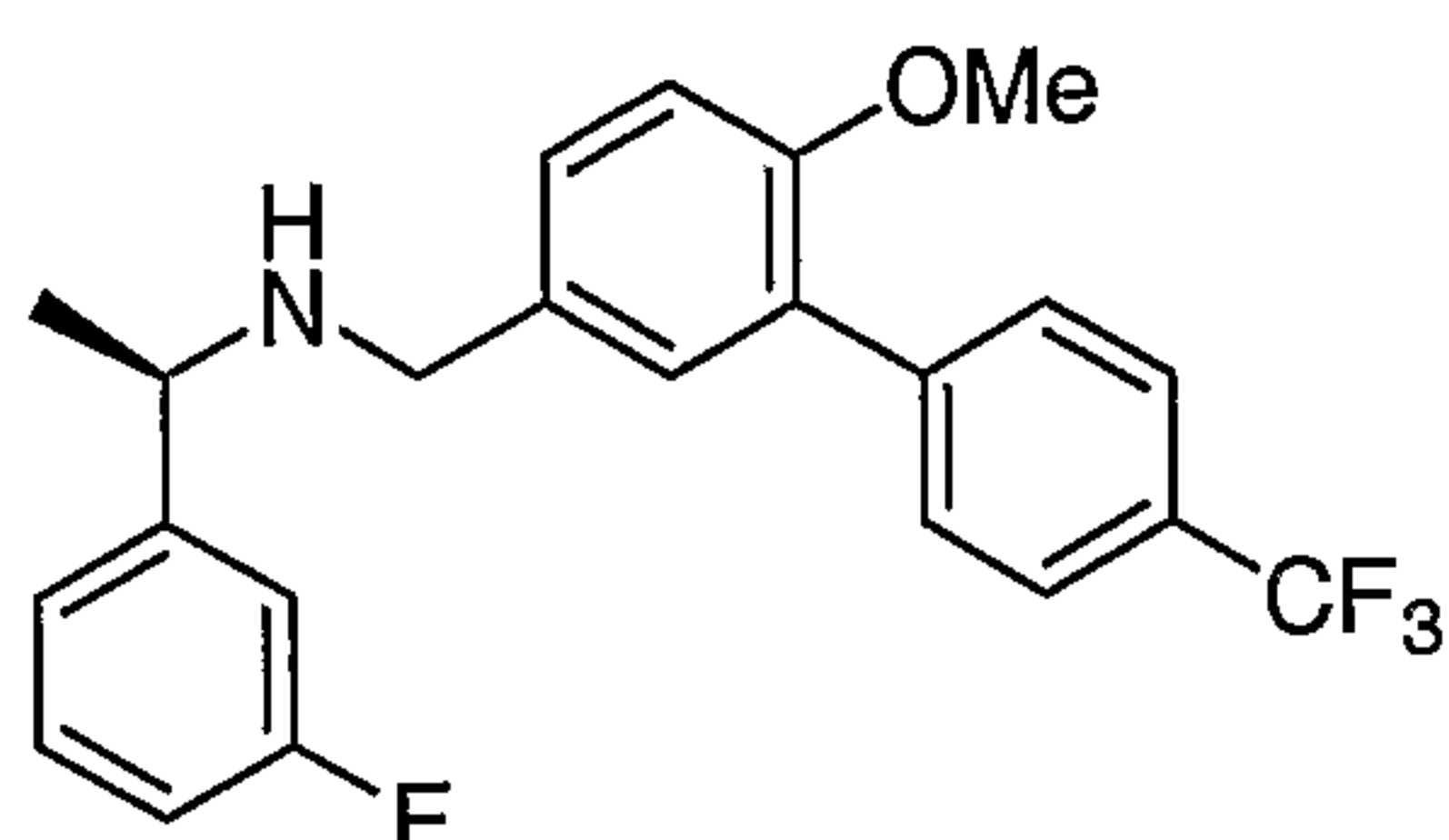
The final products disclosed in Examples 73 to 109 were prepared according to Method C described earlier.

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Example 73

(1R)-1-(3-fluorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine

5



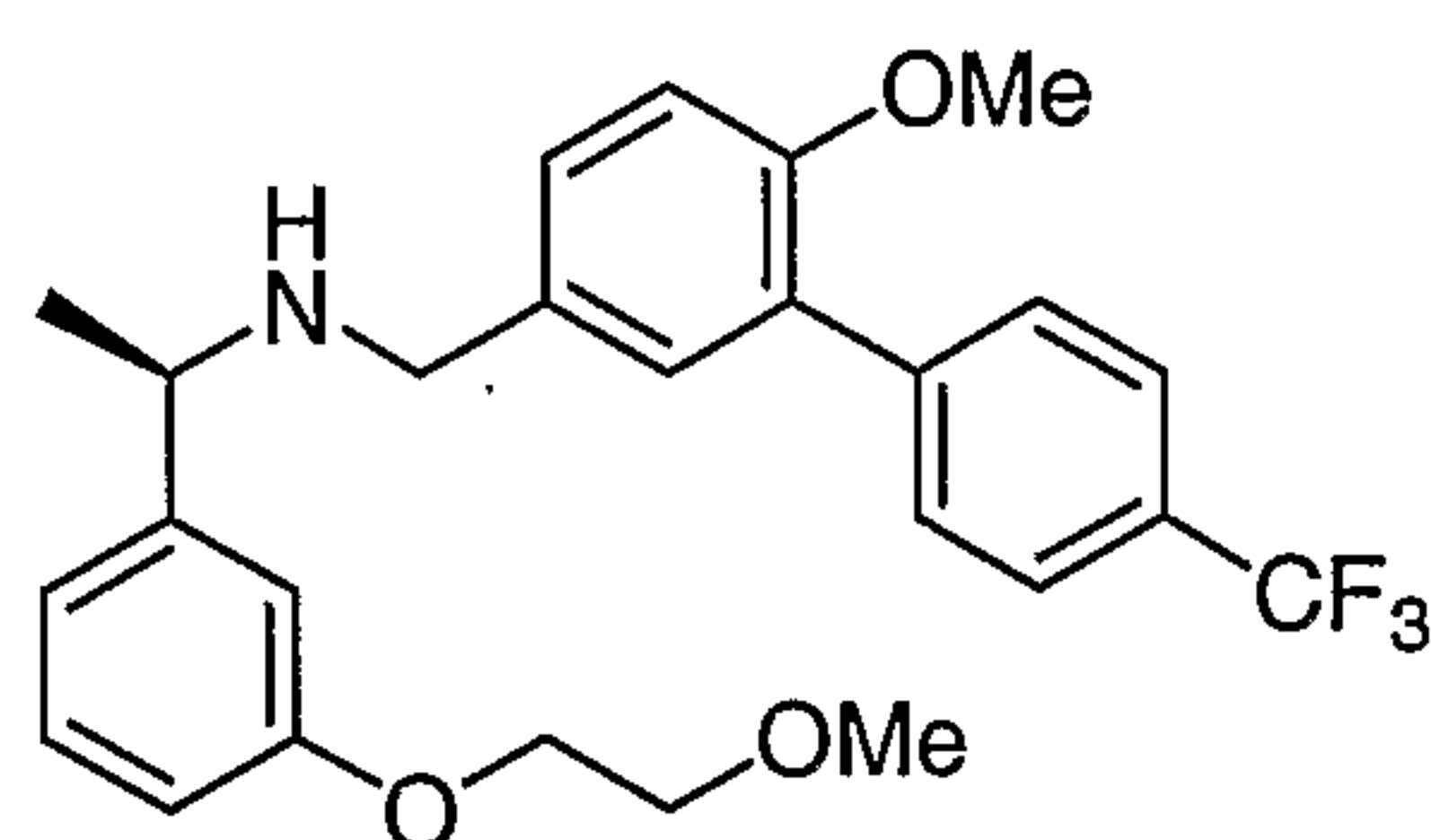
MS(EI) calcd for $C_{23}H_{22}F_4NO$ (MH^+) 404.1, Found 404.1, 265.1.

10

Example 74

(1R)-1-(3-((2-(methyloxy)ethyl)oxy)phenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine

15



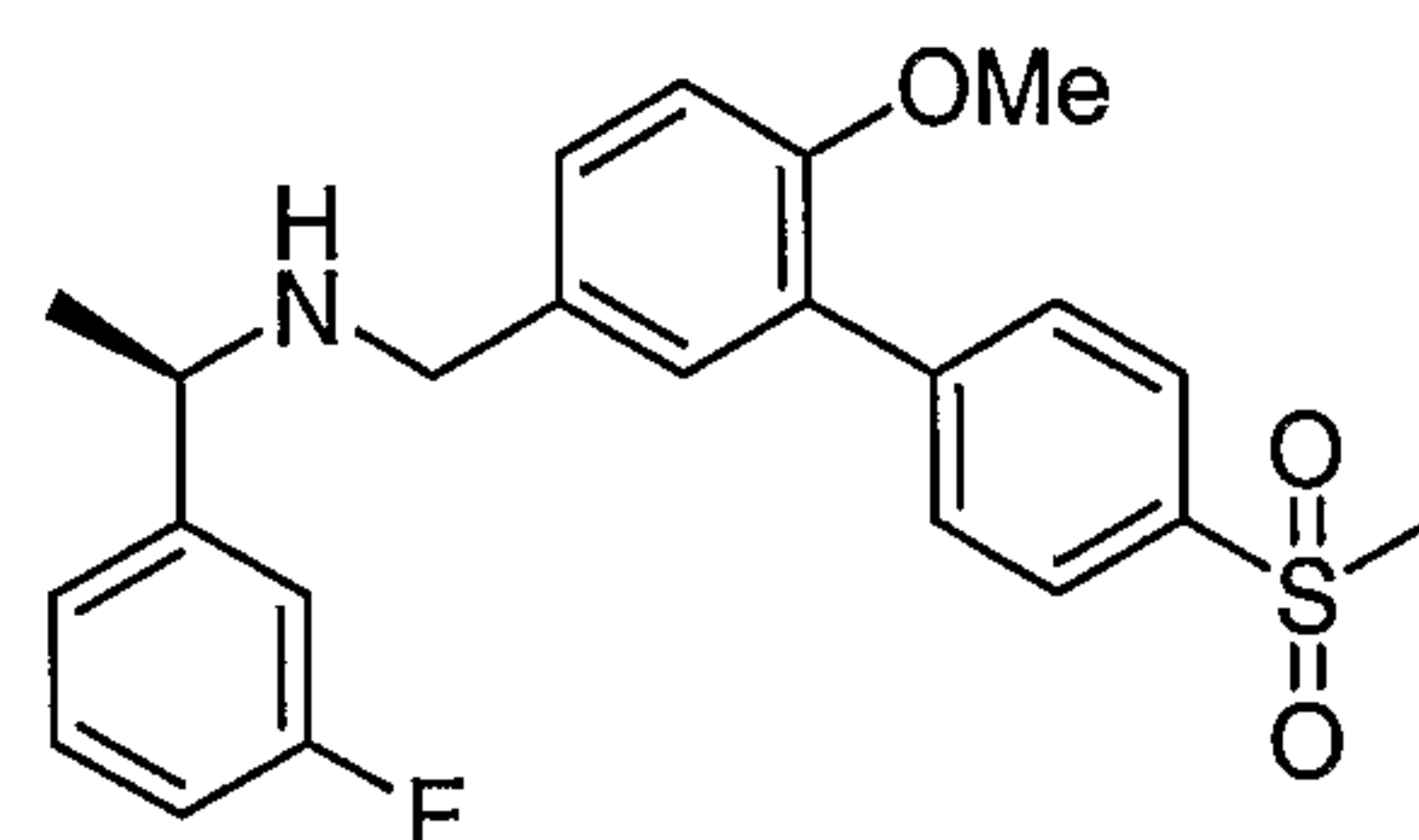
MS(EI) calcd for $C_{26}H_{29}F_3NO_3$ (MH^+) 460.2, Found 460.2, 265.1.

20

Example 75

(1R)-1-(3-fluorophenyl)-N-((6-(methyloxy)-4'-(methylsulfonyl)-1,1'-biphenyl-3-yl)methyl)ethanamine

25



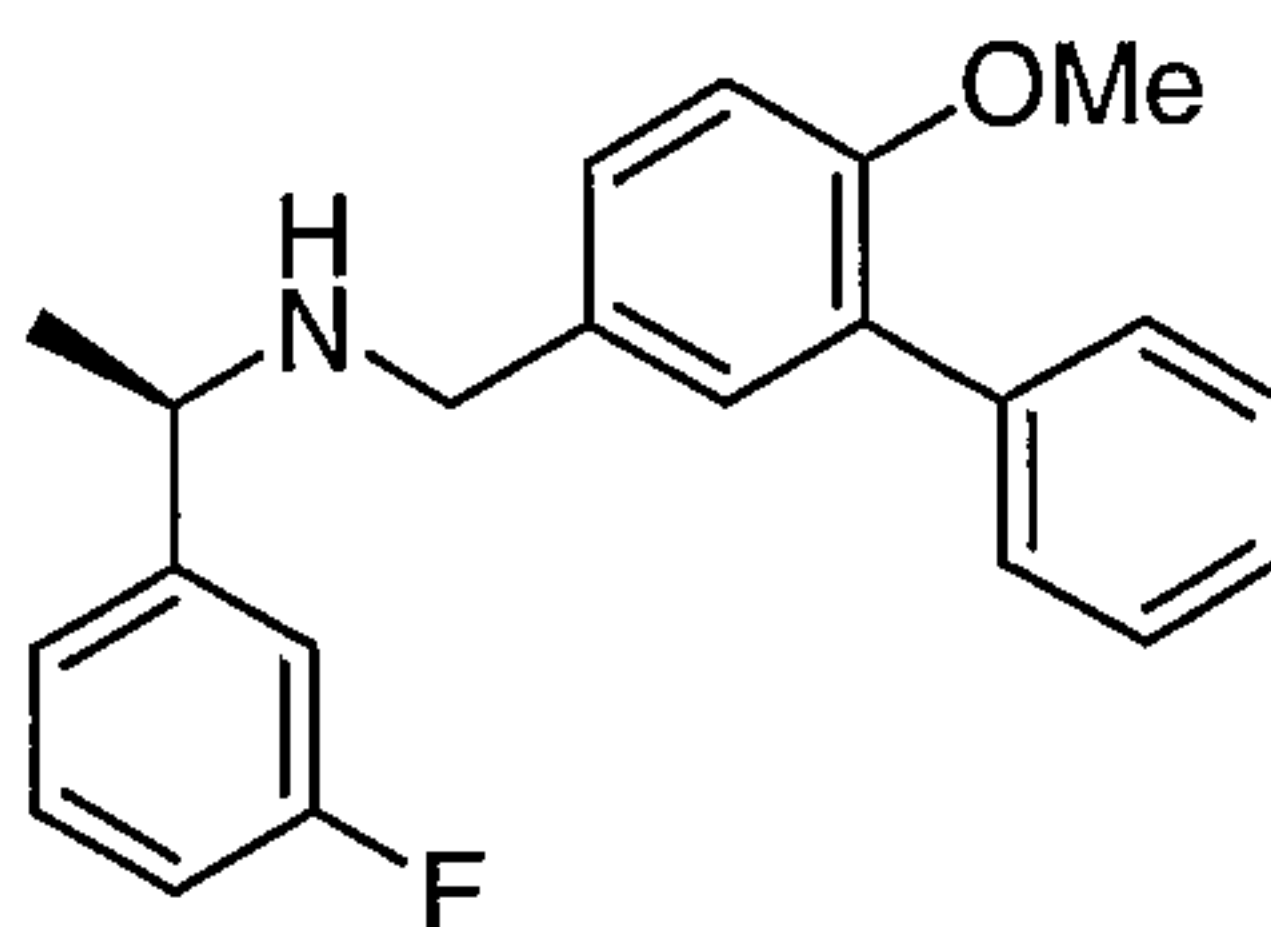
MS(EI) calcd for $C_{23}H_{25}FNO_3S$ (MH^+) 414.1, Found 414.2, 275.2.

30

Example 76

- 118 -

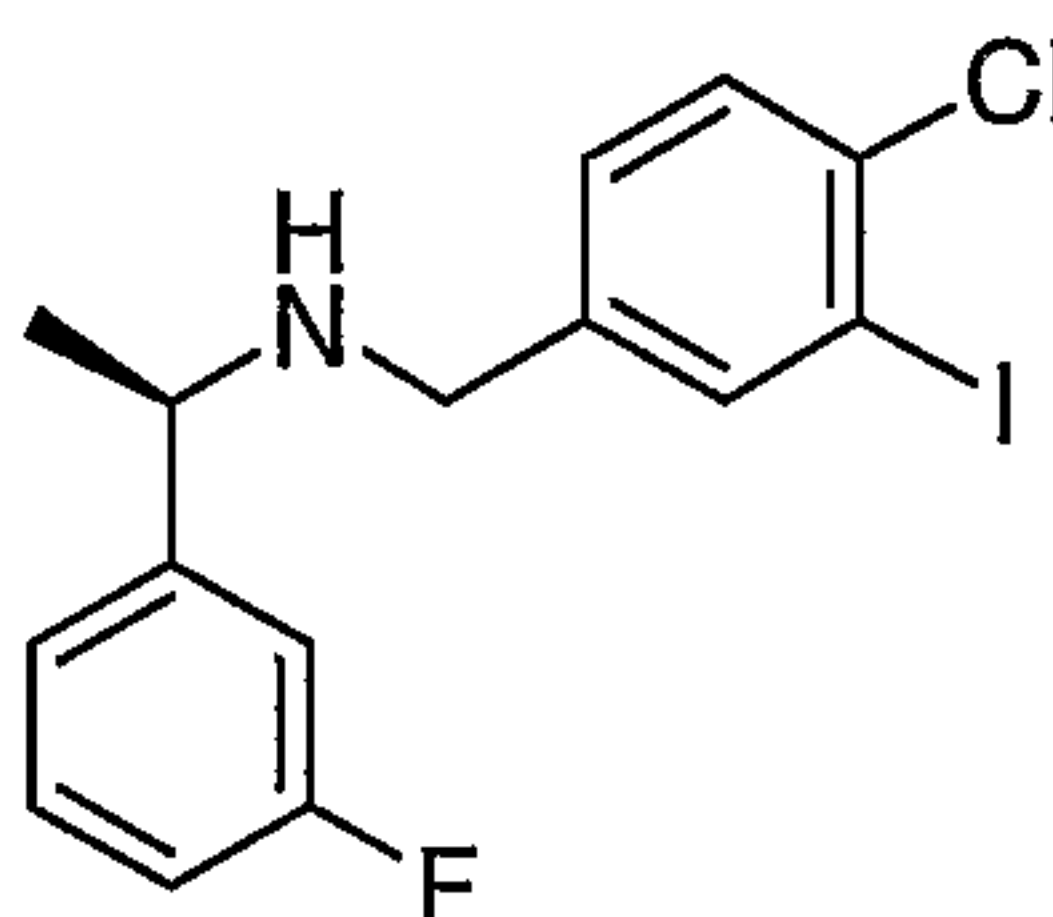
(1R)-1-(3-fluorophenyl)-N-((6-(methoxy)-1,1'-biphenyl-3-yl)methyl)ethanamine



5 MS(EI) calcd for $C_{22}H_{23}FNO$ (MH^+) 336.2, Found 336.2, 197.1.

Example 77

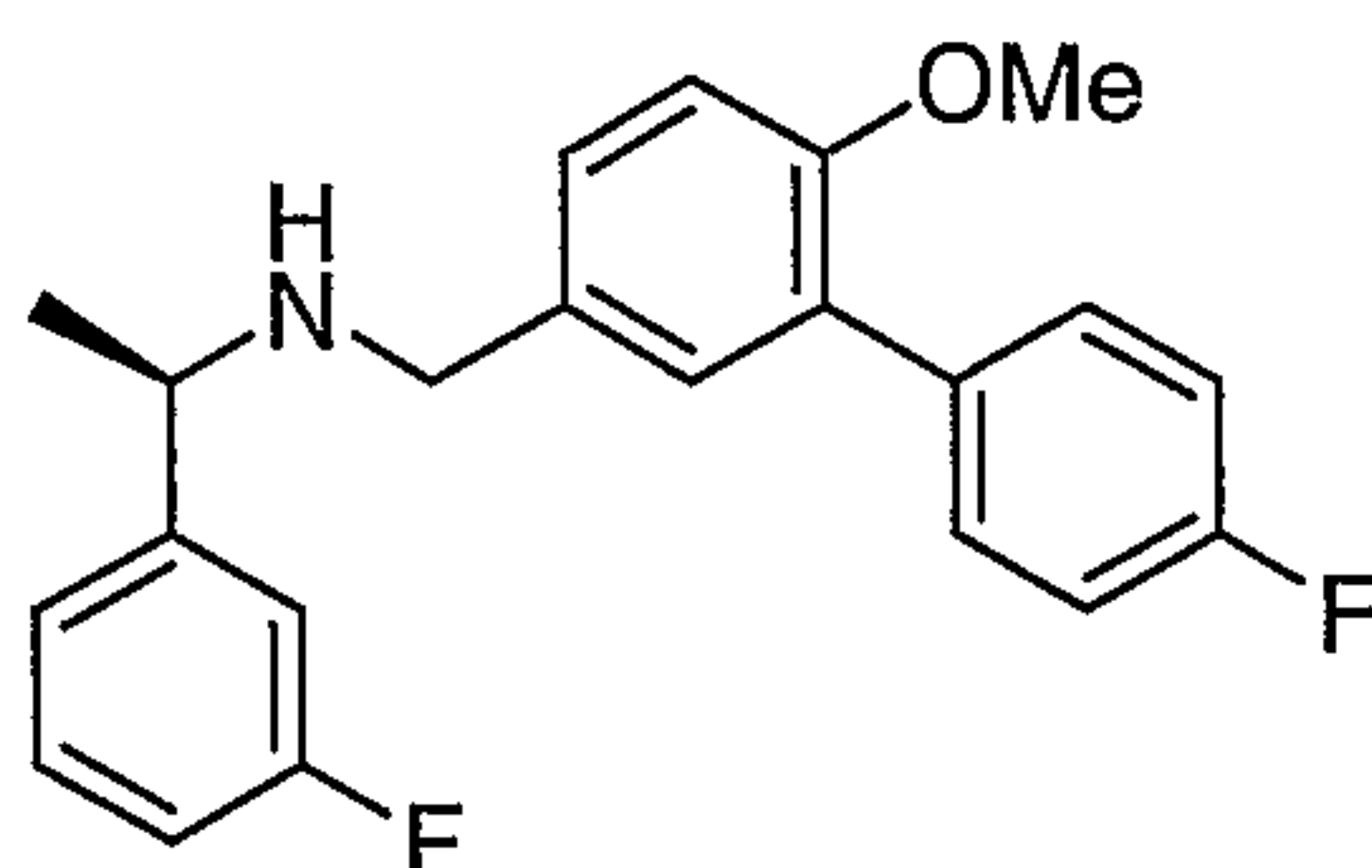
10 (1R)-N-((4-chloro-3-iodophenyl)methyl)-1-(3-fluorophenyl)ethanamine



15 MS(EI) calcd for $C_{15}H_{15}ClFIN$ (MH^+) 390.0, Found 390.0, 251.0, 123.1.

Example 78

20 (1R)-N-((4'-fluoro-6-(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-fluorophenyl)ethanamine

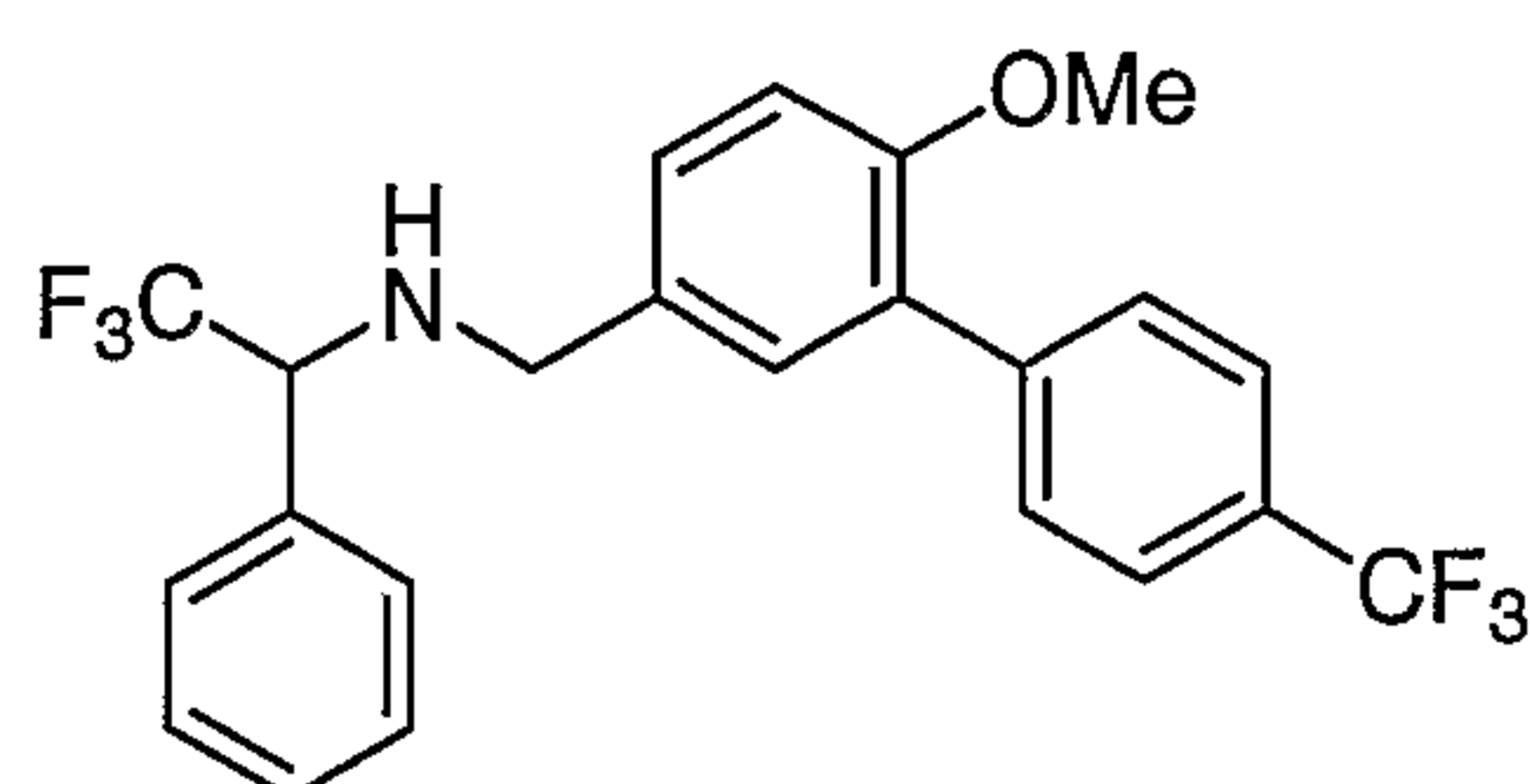


25 MS(EI) calcd for $C_{22}H_{22}F_2NO$ (MH^+) 354.1, Found 354.1, 215.1.

Example 79

30 2,2,2-trifluoro-N-((6-(methoxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

- 119 -

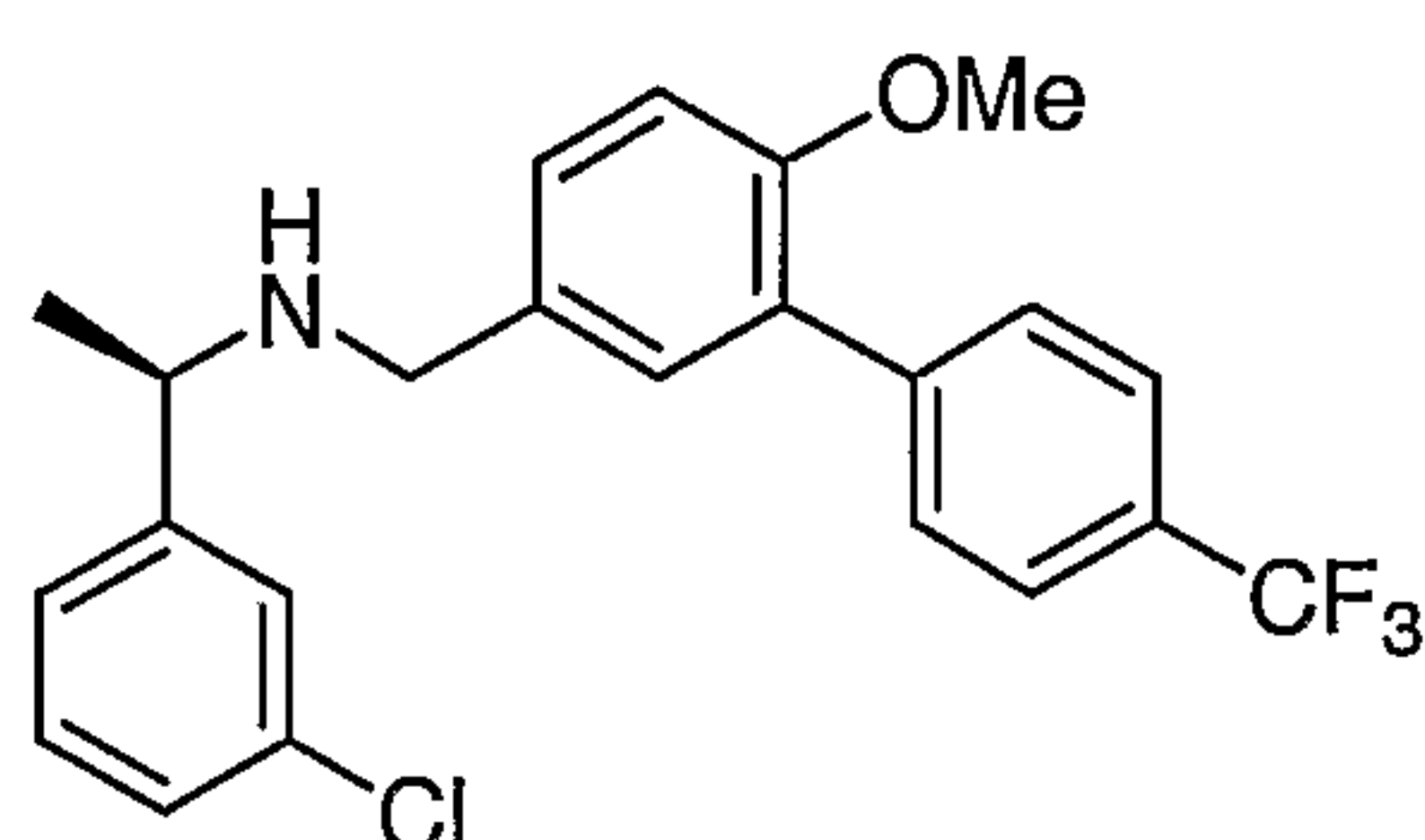


MS(EI) calcd for $C_{23}H_{20}F_6NO$ (MH^+) 440.0, Found 439.9, 264.7.

5

Example 80

(1R)-1-(3-chlorophenyl)-N-(((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine



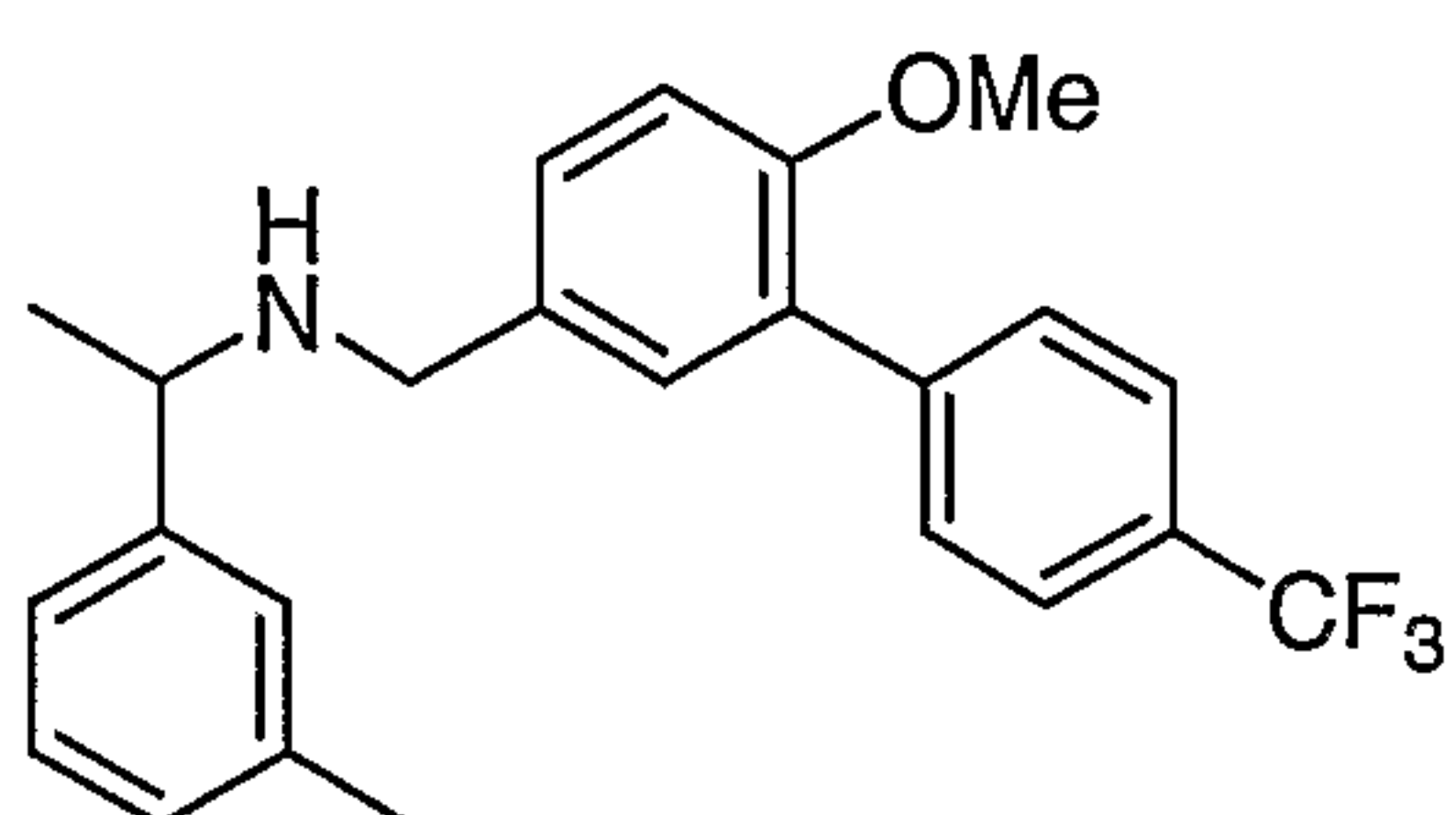
10

MS(EI) calcd for $C_{23}H_{21}ClF_3NO$ 420.87 (MH^+), Found: 420.1; 422.1 265.1

15

Example 81

N-(((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-methylphenyl)ethanamine



20

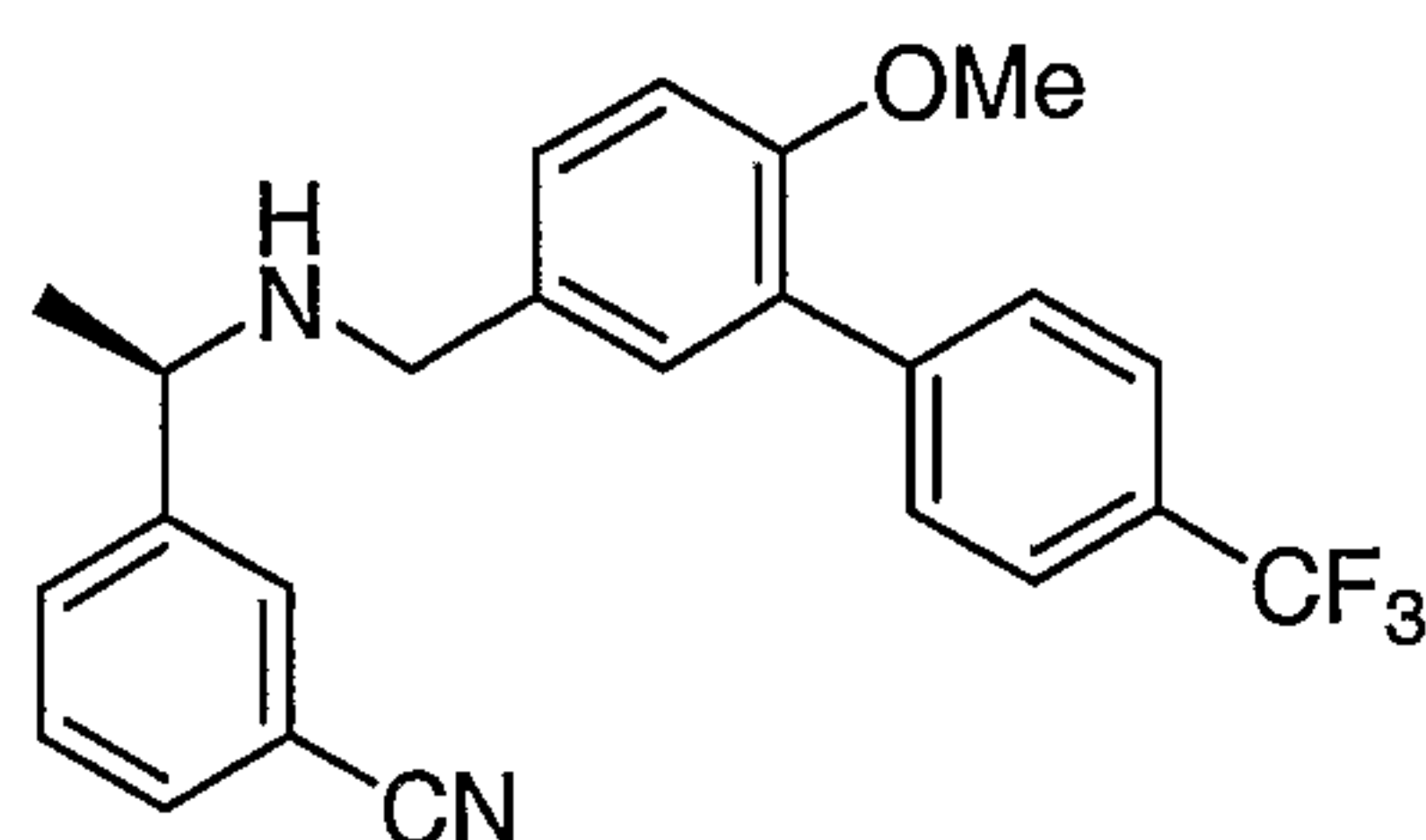
MS(EI) calcd for $C_{24}H_{24}F_3NO$ 400.45 (MH^+), Found: 400.1; 265.1

25

Example 82

3-(1-(((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)amino)ethyl)benzonitrile

- 120 -



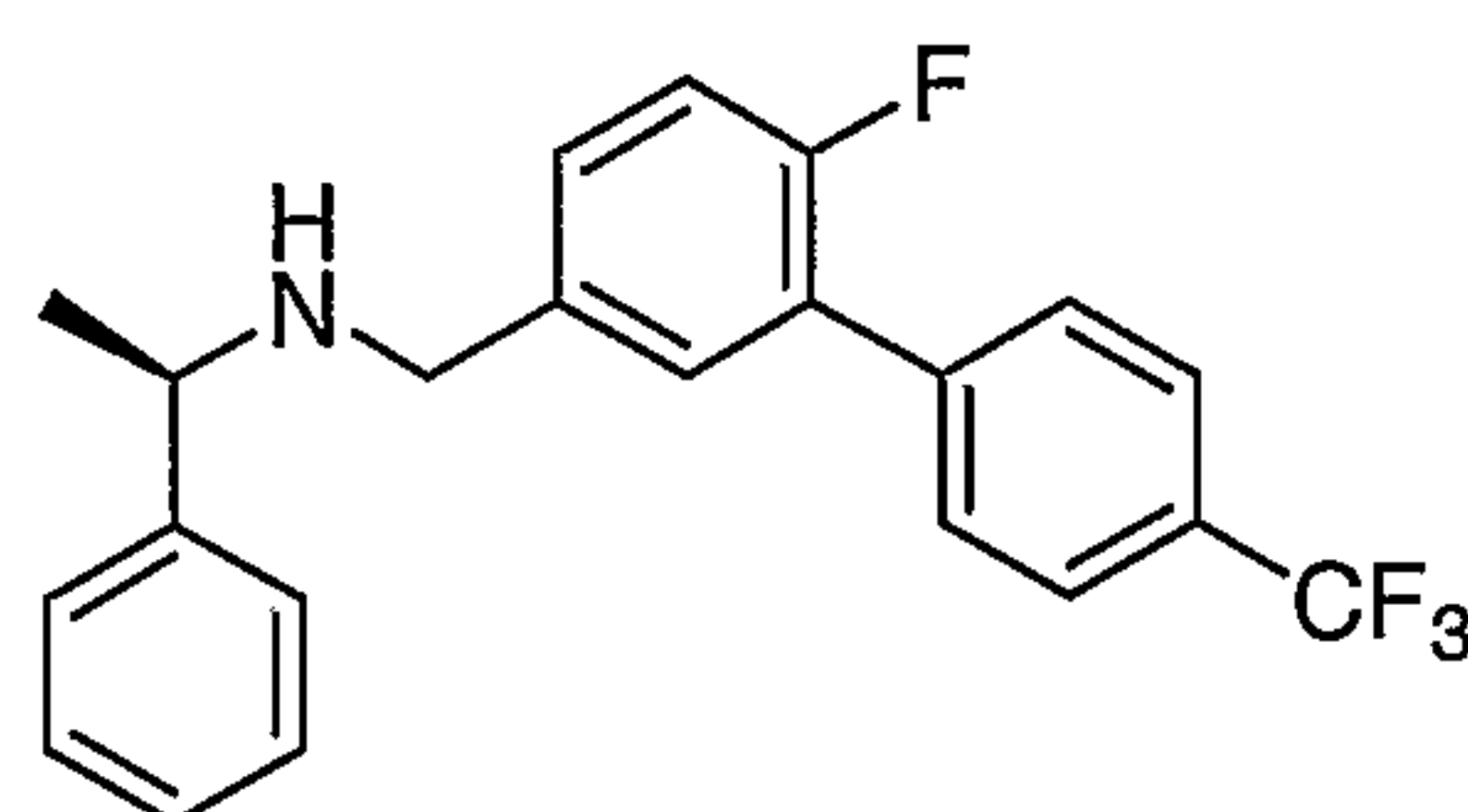
MS(EI) calcd for $C_{24}H_{21}F_3N_2O$ 411.44 (MH+) Found: 411.3; 265.1

5

Example 83

(1R)-N-((6-fluoro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

10



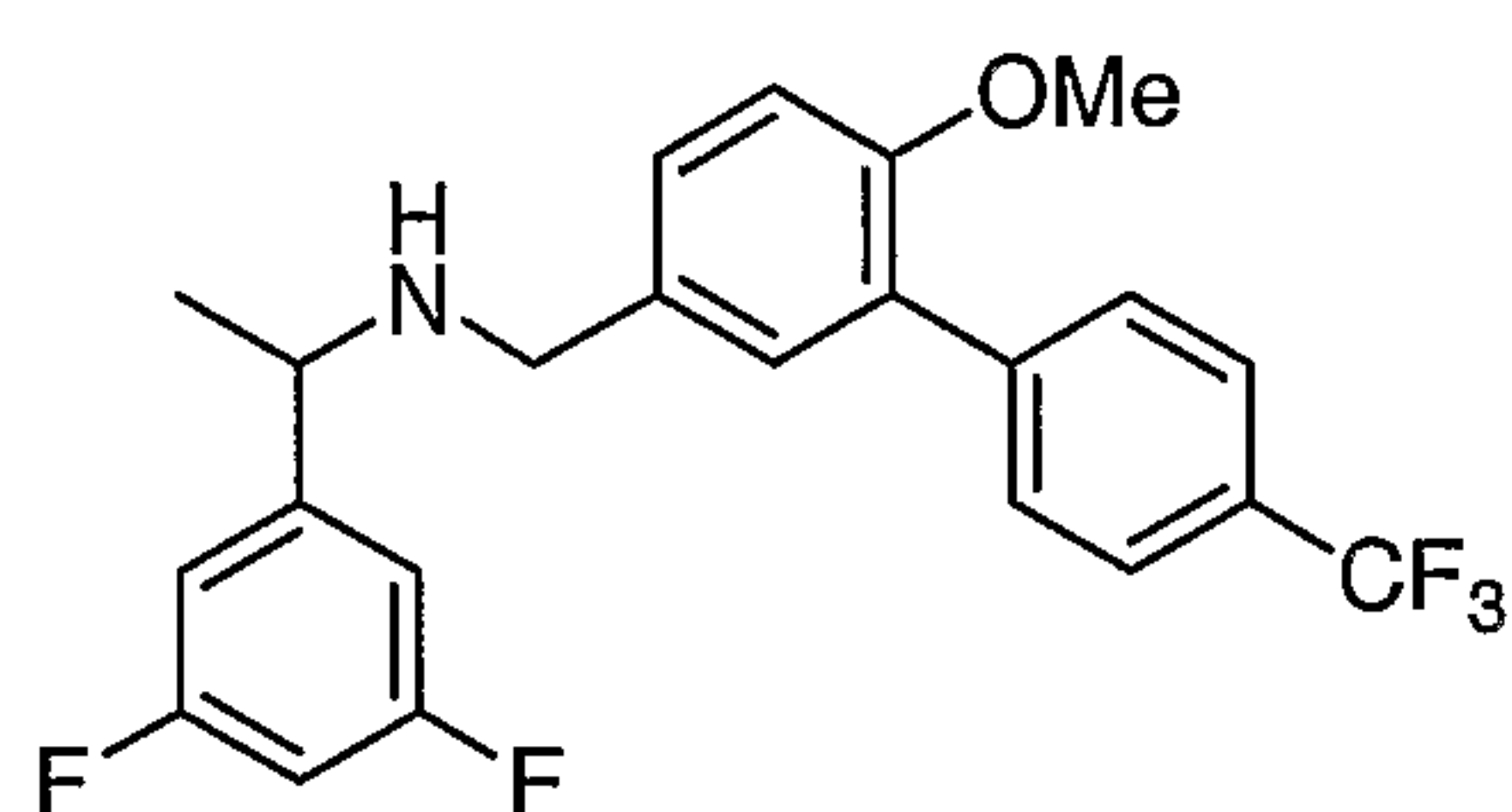
MS(EI) calcd for $C_{22}H_{19}F_4N$ 374.30 (MH+) Found: 374.2;

15

Example 84

1-(3,5-difluorophenyl)-N-((6-(methoxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine

20



MS(EI) calcd for $C_{23}H_{20}F_5NO$ 422.41 (MH+) Found: 422.2; 265.2

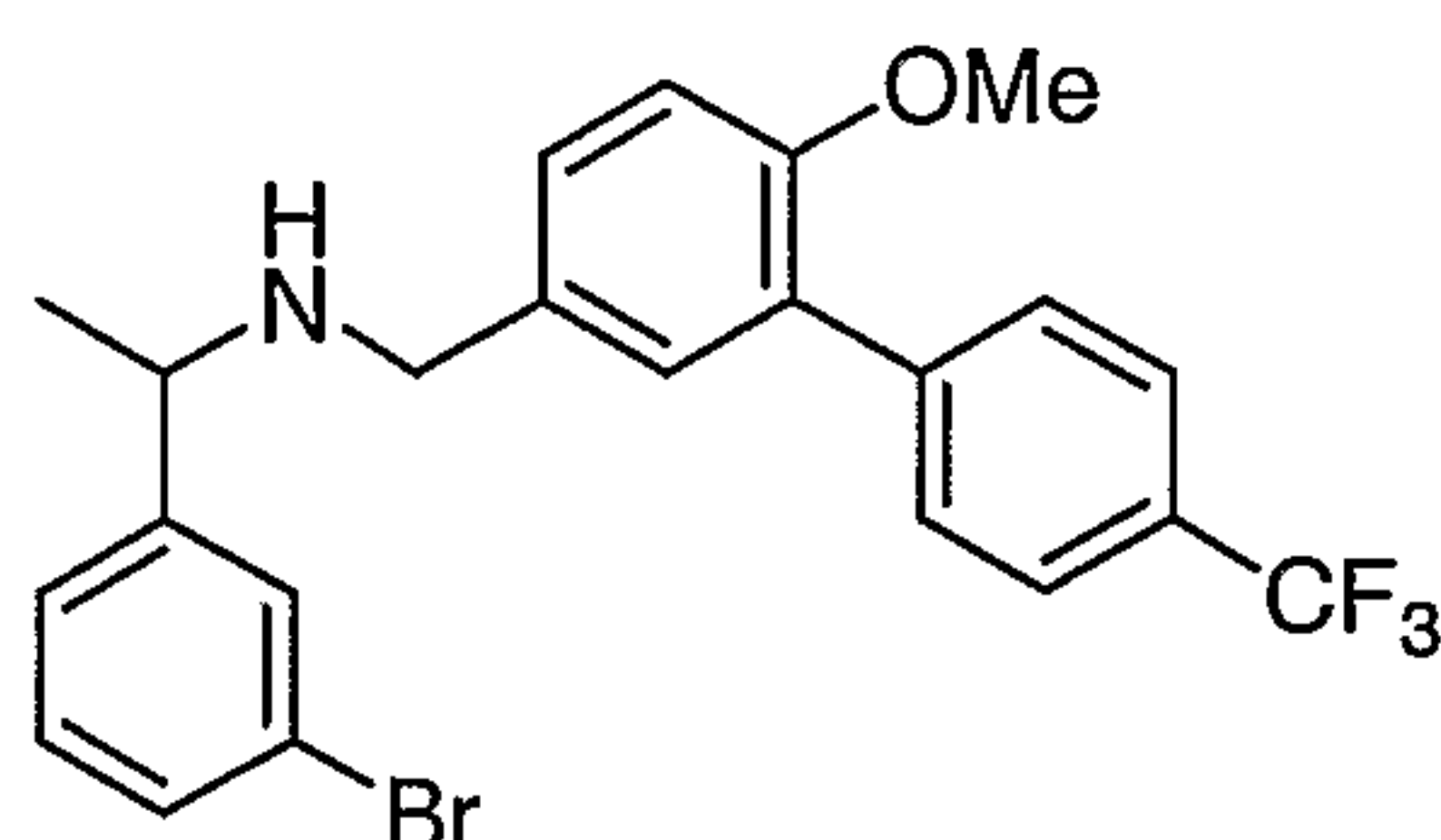
25

Example 85

1-(3-bromophenyl)-N-((6-(methoxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine

30

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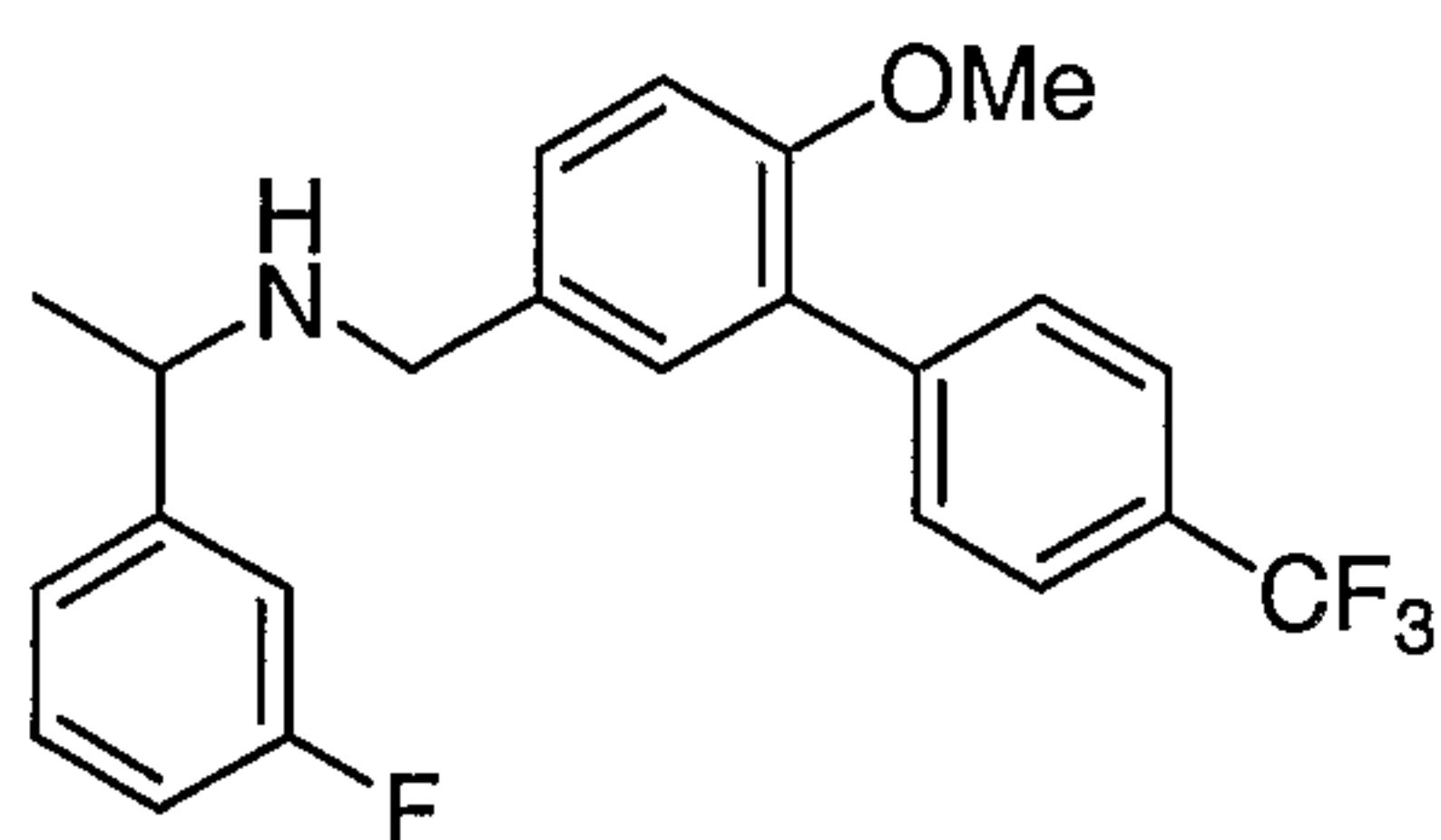
MS(EI) calcd for $C_{23}H_{21}BrF_3NO$ 465.32 (MH⁺) Found: 466.0; 265.1

5

Example 86

1-(3-fluorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine

10



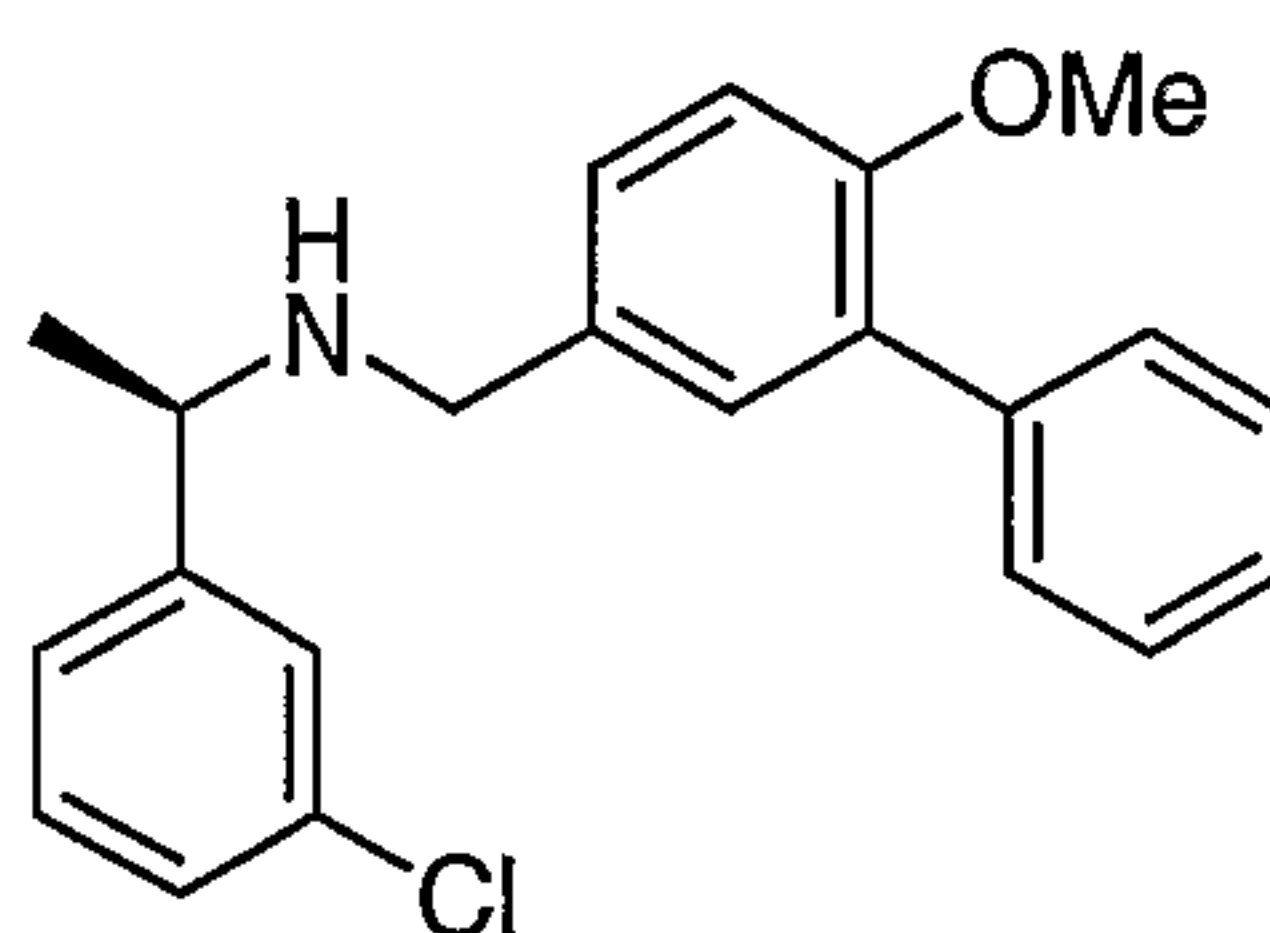
MS(EI) calcd for $C_{23}H_{21}F_4NO$ 404.42 (MH⁺) Found: 404.2; 265.1

15

Example 87

(1R)-1-(3-chlorophenyl)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)ethanamine

20



MS(EI) calcd for $C_{22}H_{22}ClNO$ 352.88 (MH⁺) Found: 353.1; 197.1

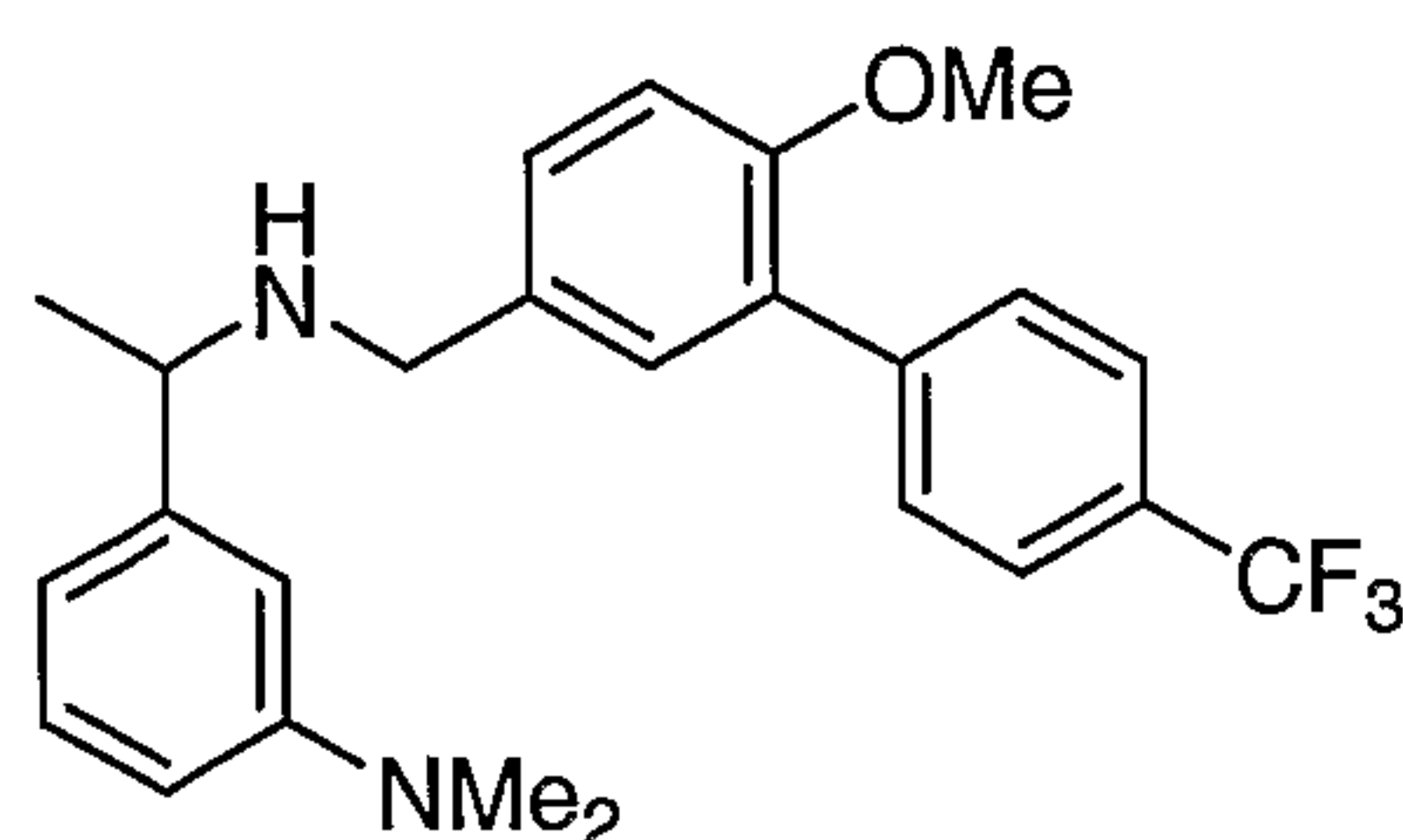
25

Example 88

N-1-(3-(dimethylamino)phenyl)ethyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)amine

30

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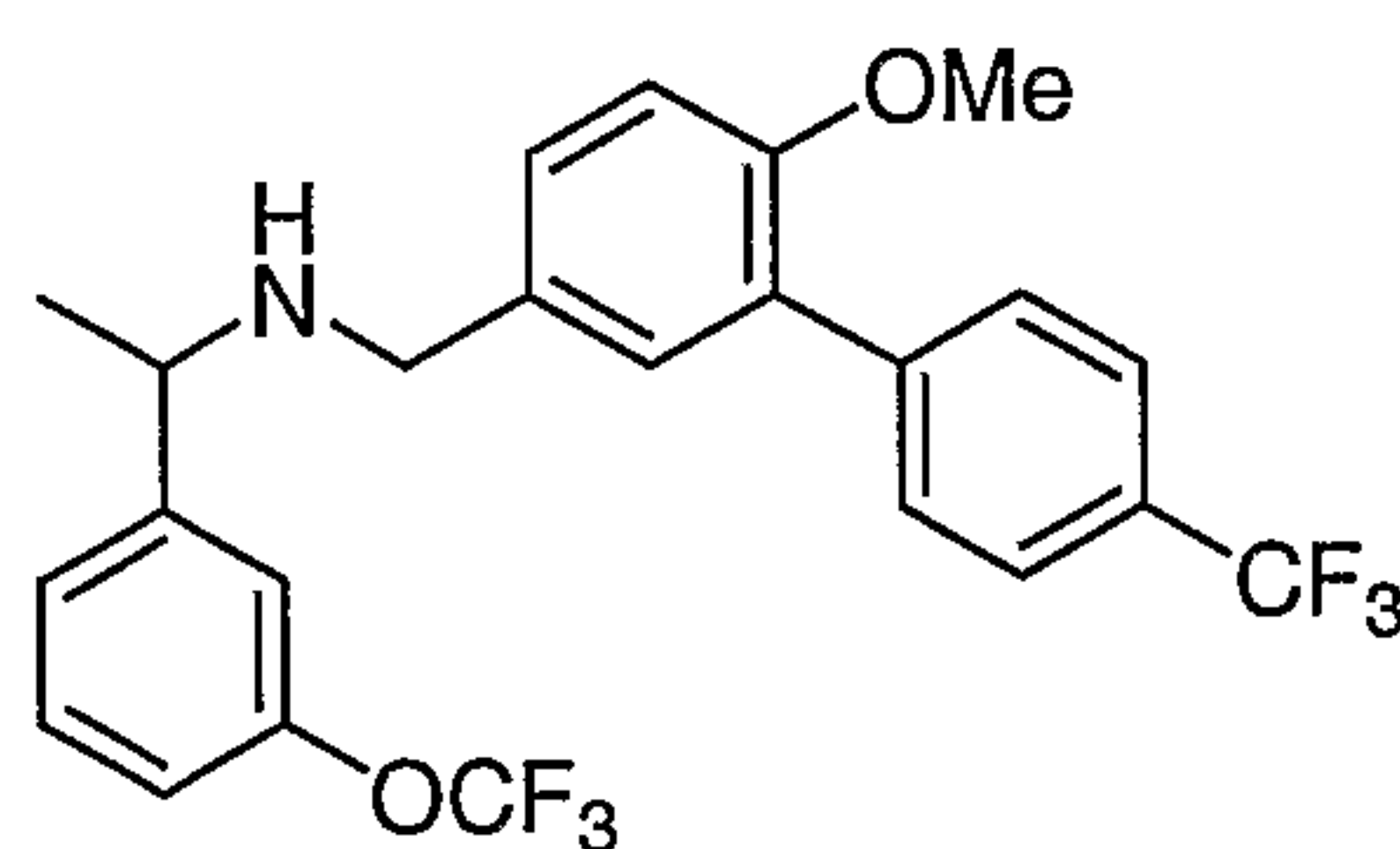
MS(EI) calcd for $C_{25}H_{27}F_3 N_2O$ 429.50 (MH+) Found: 429.2; 265.1

5

Example 89

N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-((trifluoromethyl)oxy)phenyl)ethanamine

10



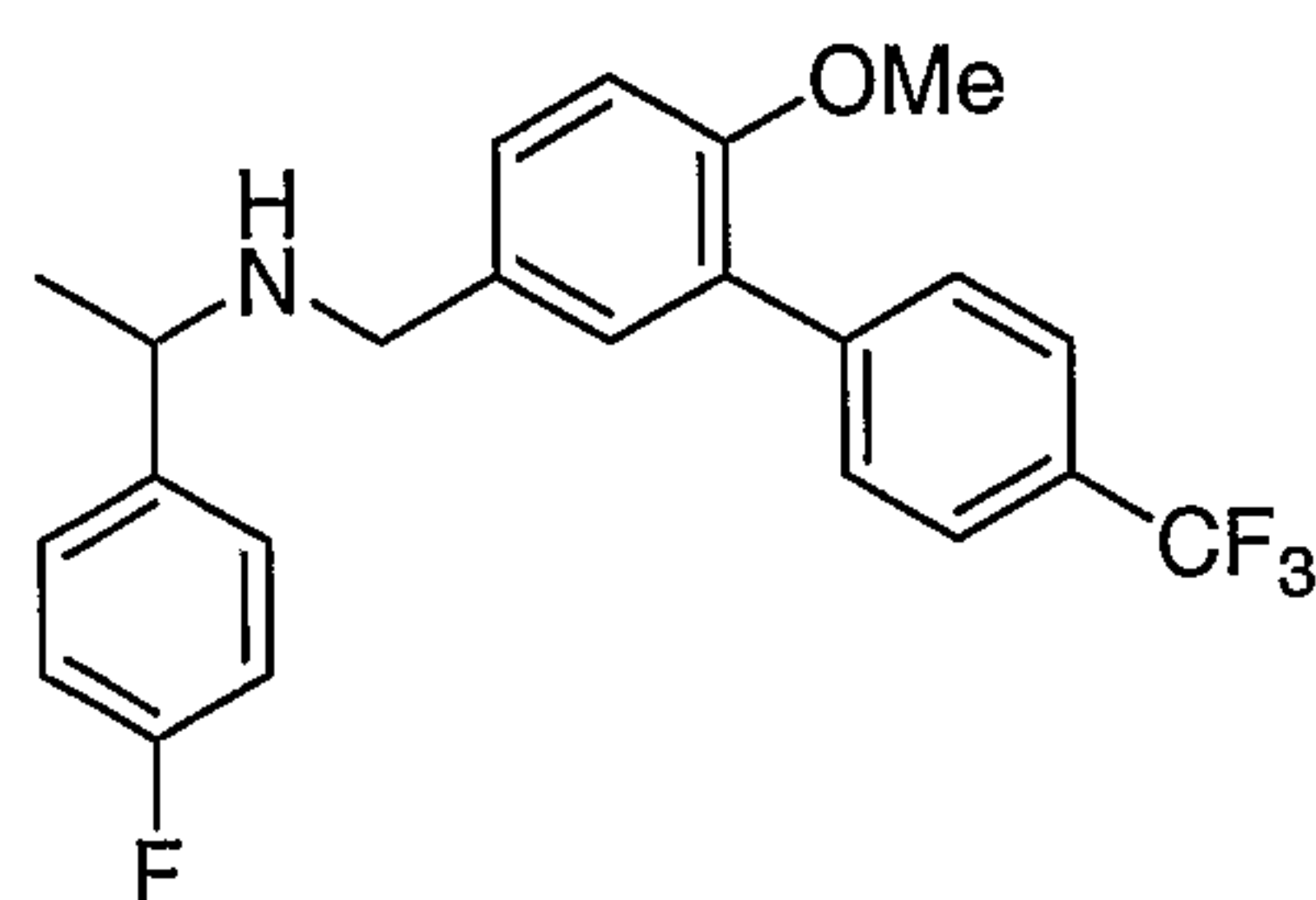
MS(EI) calcd for $C_{24}H_{21}F_6NO_2$ 470.42 (MH+) Found: 470.1; 265.1

15

Example 90

1-(4-fluorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine

20



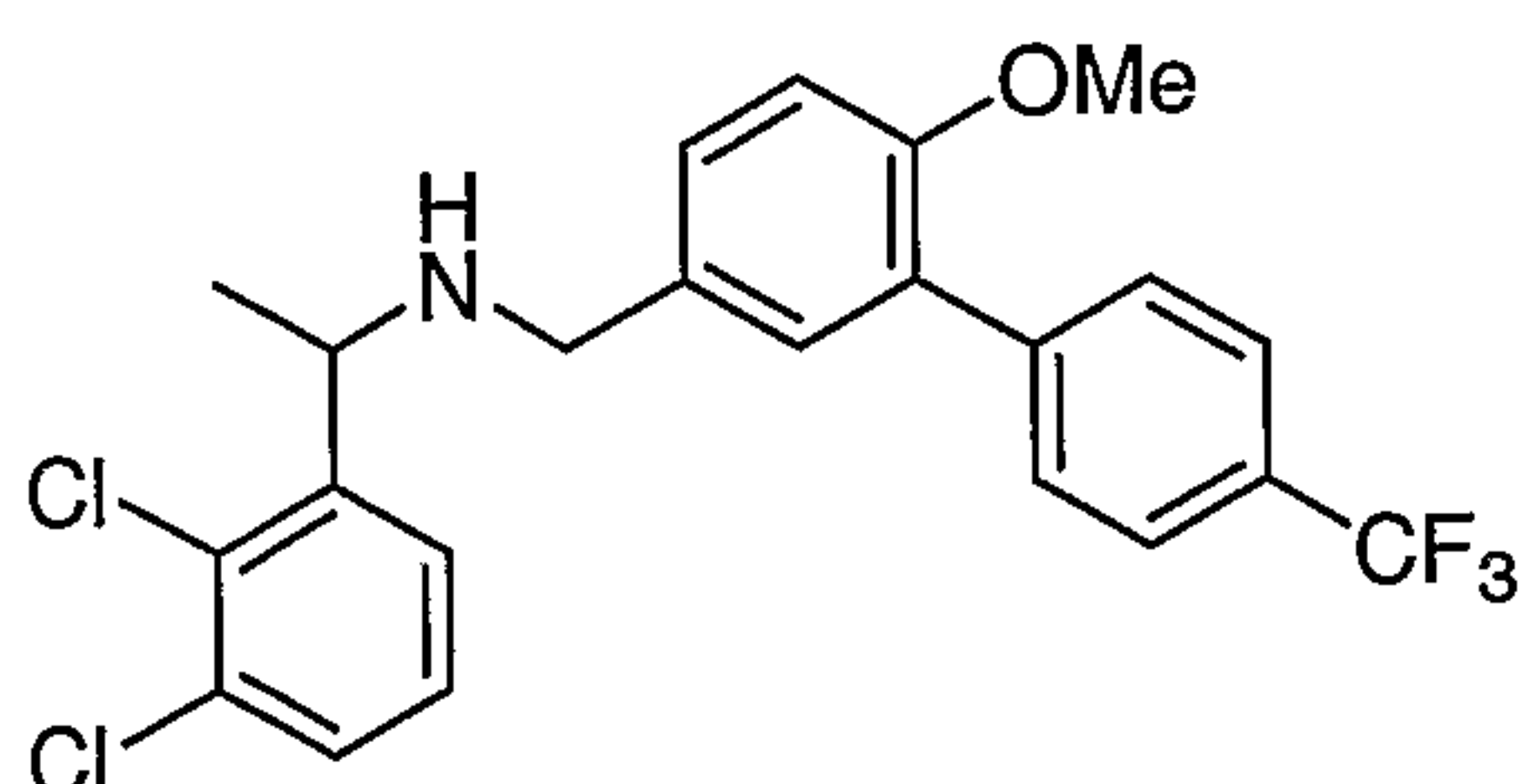
MS(EI) calcd for $C_{23}H_{21}F_4NO$ 404.42 (MH+) Found: 404.2; 265.1

25

Example 91

1-(2,3-dichlorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine

- 123 -



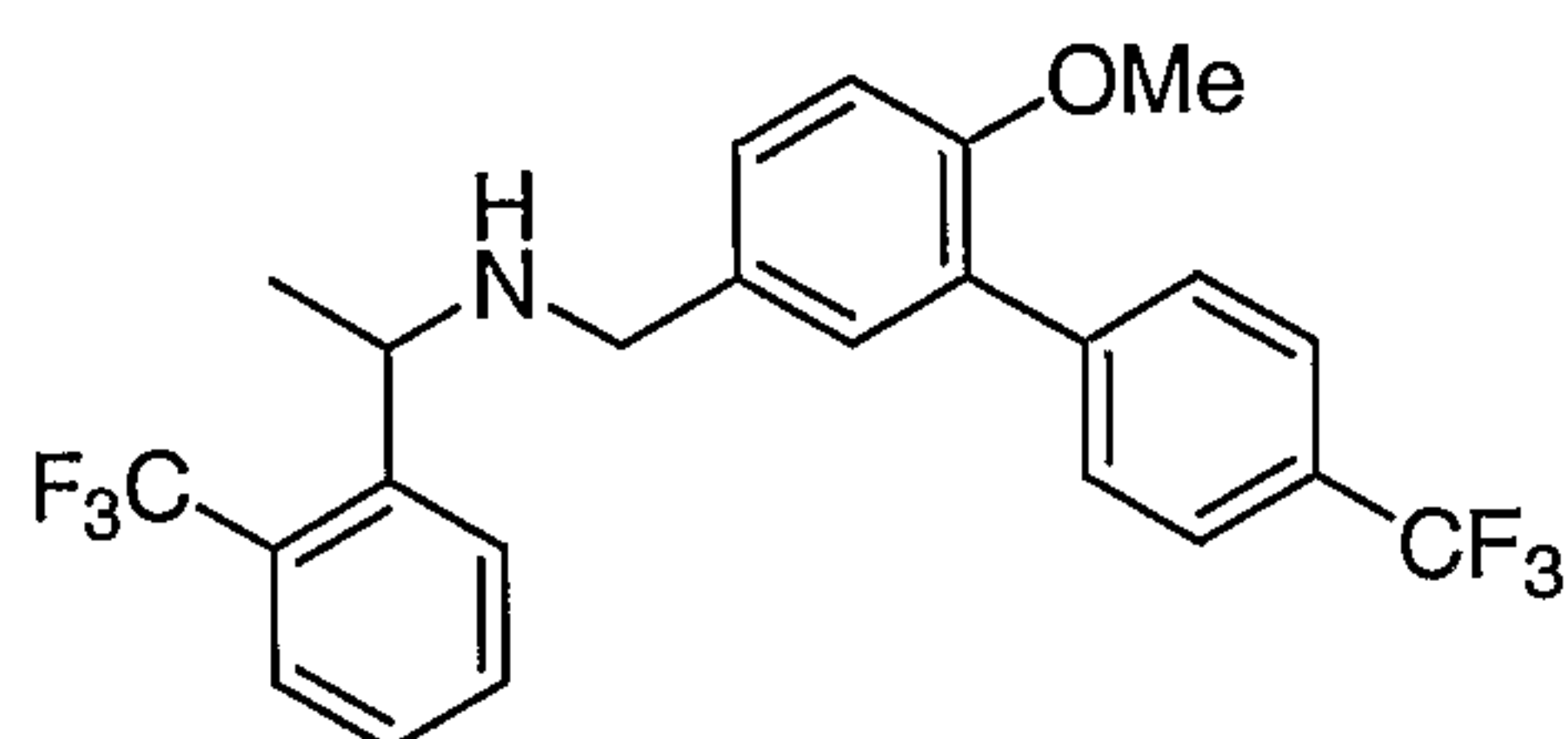
MS(EI) calcd for $C_{23}H_{20}Cl_2F_3NO$ 455.32 (MH⁺) Found: 454.0; 456.0

5

Example 92

N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(2-(trifluoromethyl)phenyl)ethanamine

10



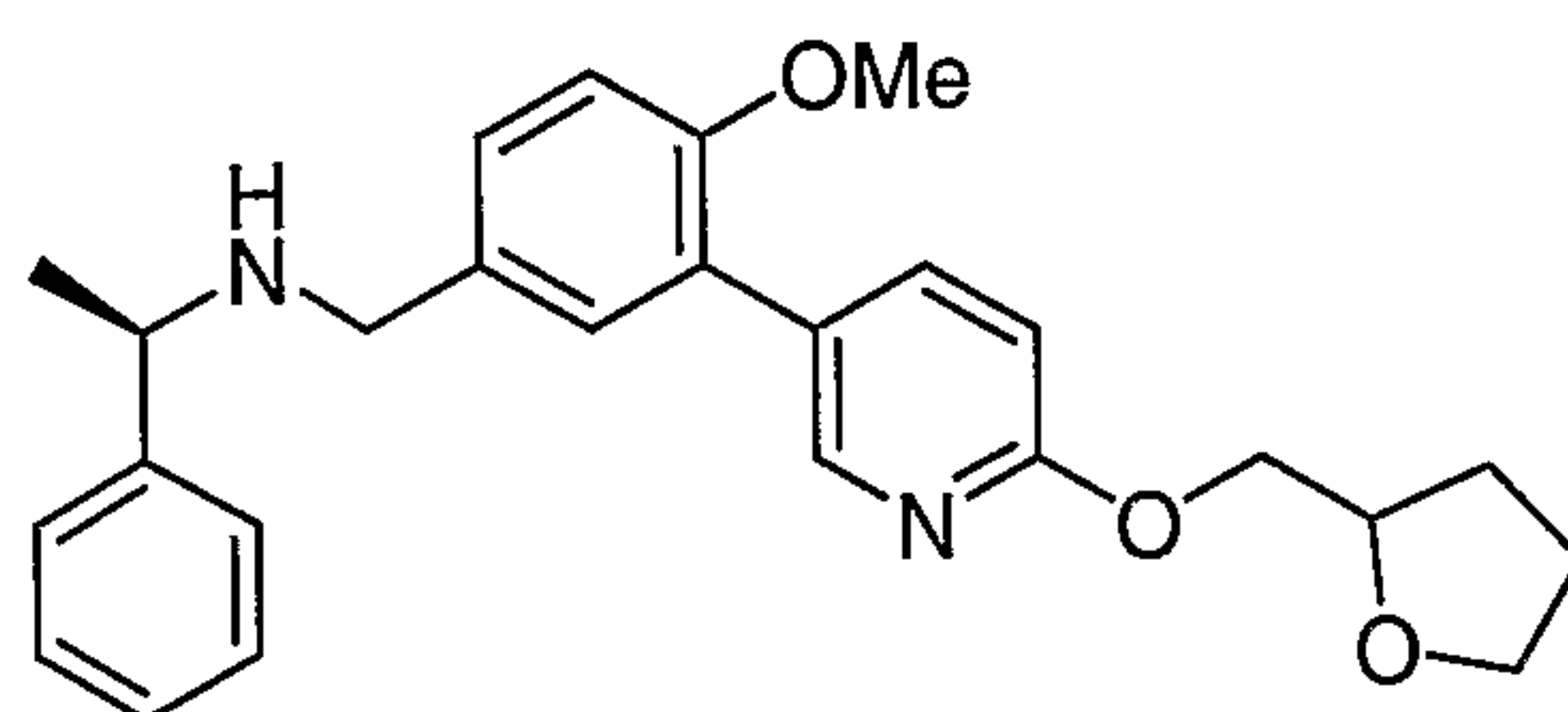
MS(EI) calcd for $C_{24}H_{21}F_6NO$ 454.42 (MH⁺) Found: 454.2; 265.1

15

Example 93

(1R)-N-((4-(methyloxy)-3-(6-((tetrahydro-2-furanylmethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine

20



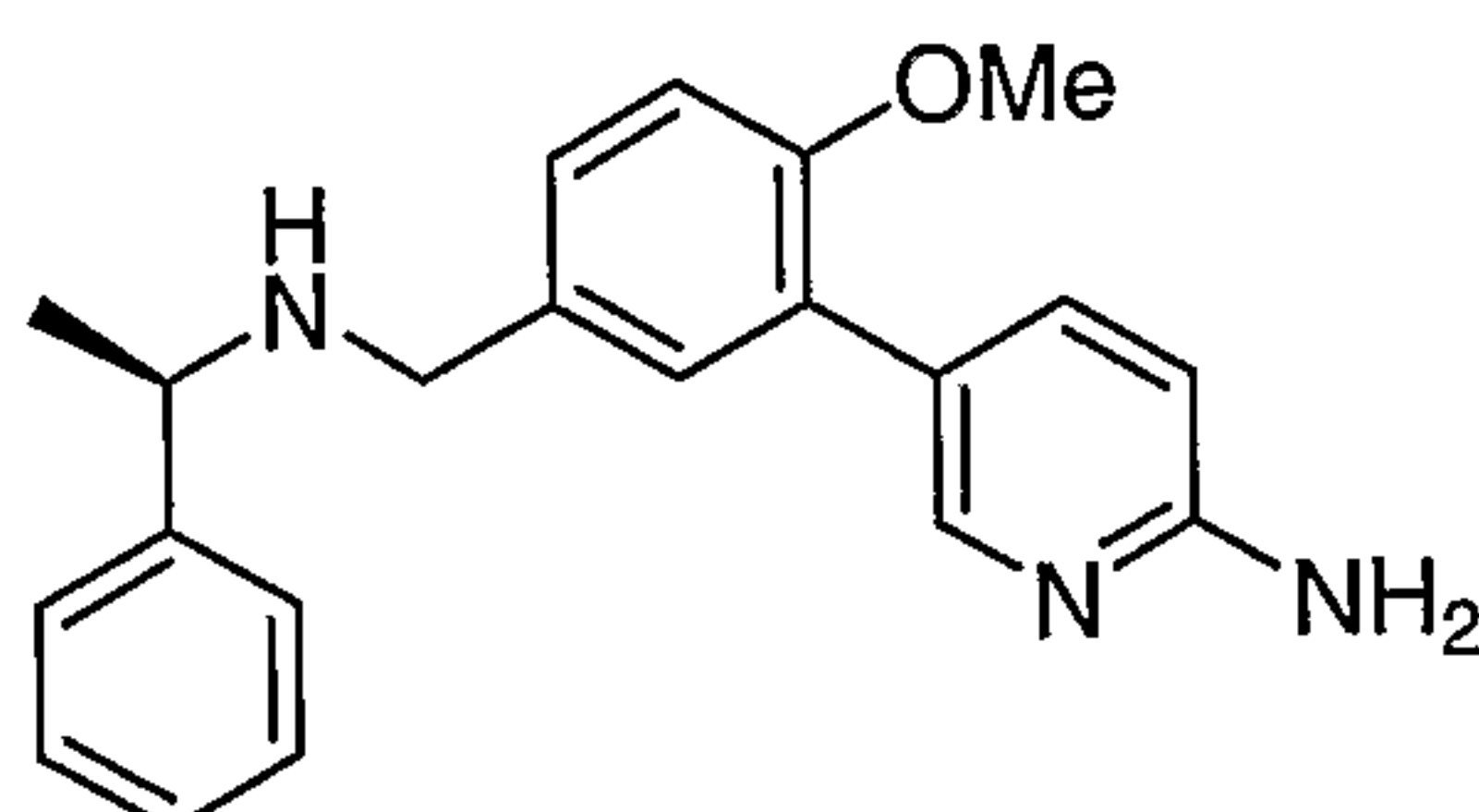
MS (ESI, pos. ion) *m/z*: Calc'd for $C_{26}H_{30}N_2O_3$: 418.5 g/mol. Found: (M+1) 418.7, 334.9, 297.7

25

Example 94

5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinamine

- 124 -



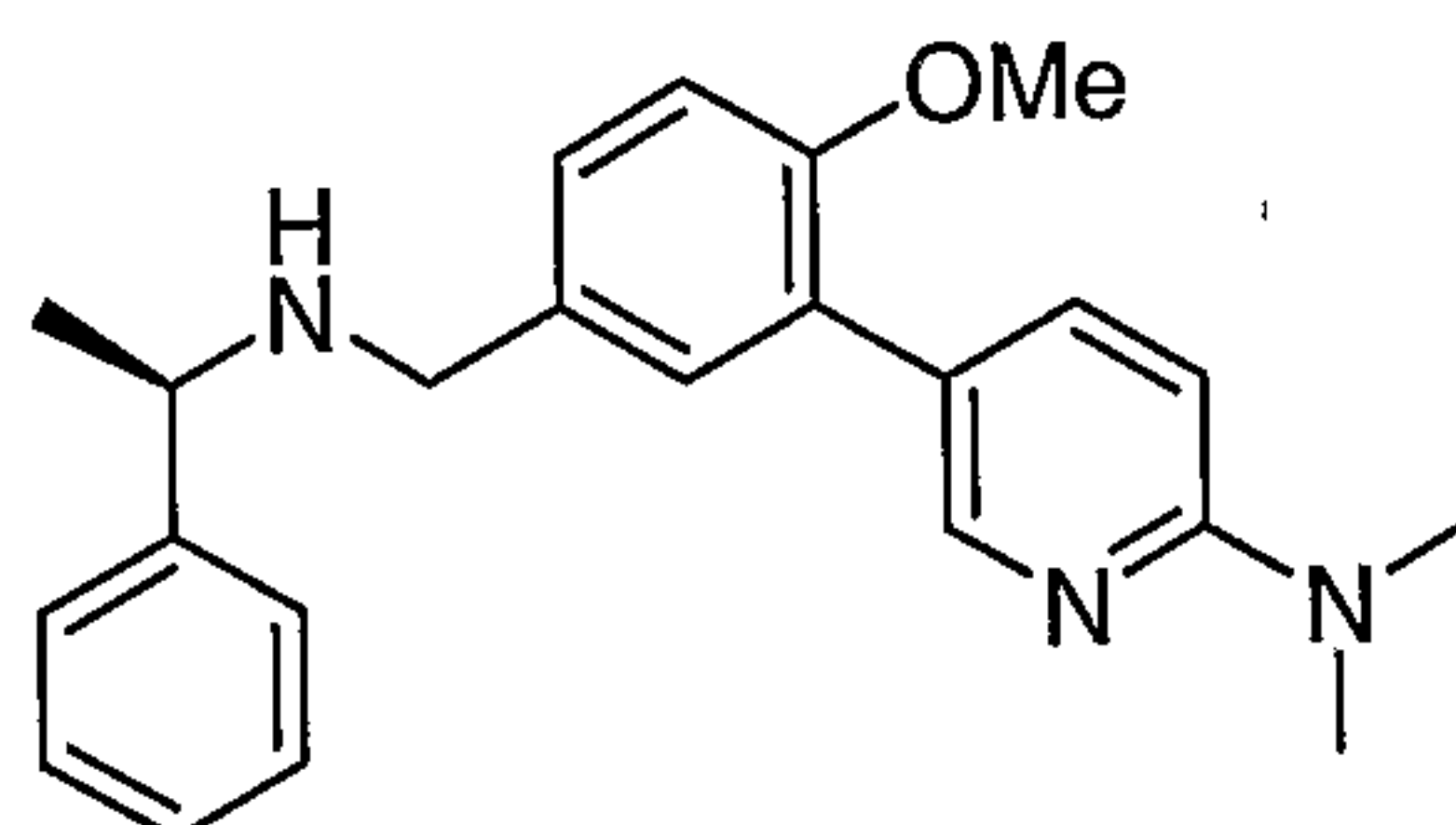
MS (ESI, pos. ion) m/z : Calc'd for $C_{21}H_{23}N_3O$: 333.43 g/mol. Found: (M+1) 334.1, 213.2

5

Example 95

N,N-dimethyl-5-(2-(methyloxy)-5-(((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinamine

10



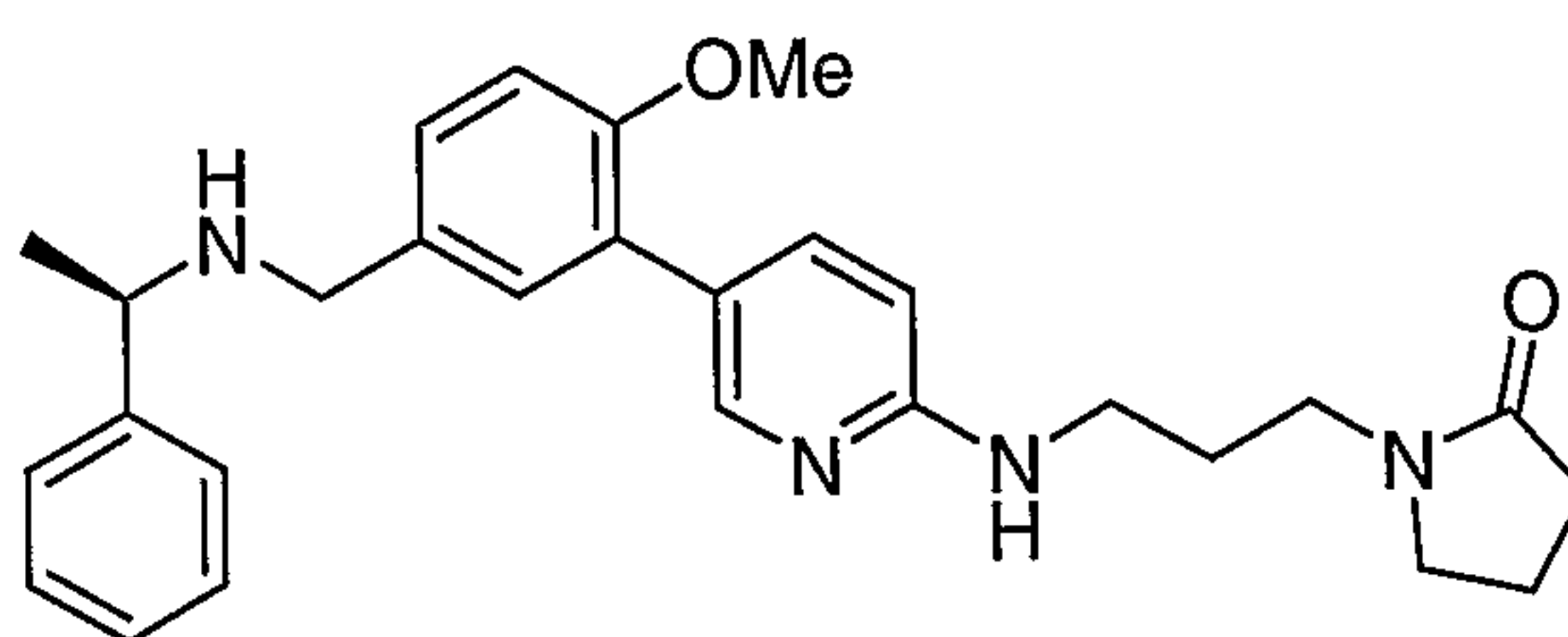
MS (ESI, pos. ion) m/z : Calc'd for $C_{23}H_{27}N_3O$: 361.48 g/mol. Found: (M+1) 362.0, 241.2

15

Example 96

1-(3-((5-(2-(methyloxy)-5-(((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinyl)amino)propyl)-2-pyrrolidinone

20



MS (ESI, pos. ion) m/z : Calc'd for $C_{28}H_{34}N_4O_2$: 458.60 g/mol. Found: (M+1) 458.8, 355.0, 337.7, 306.0, 239.1

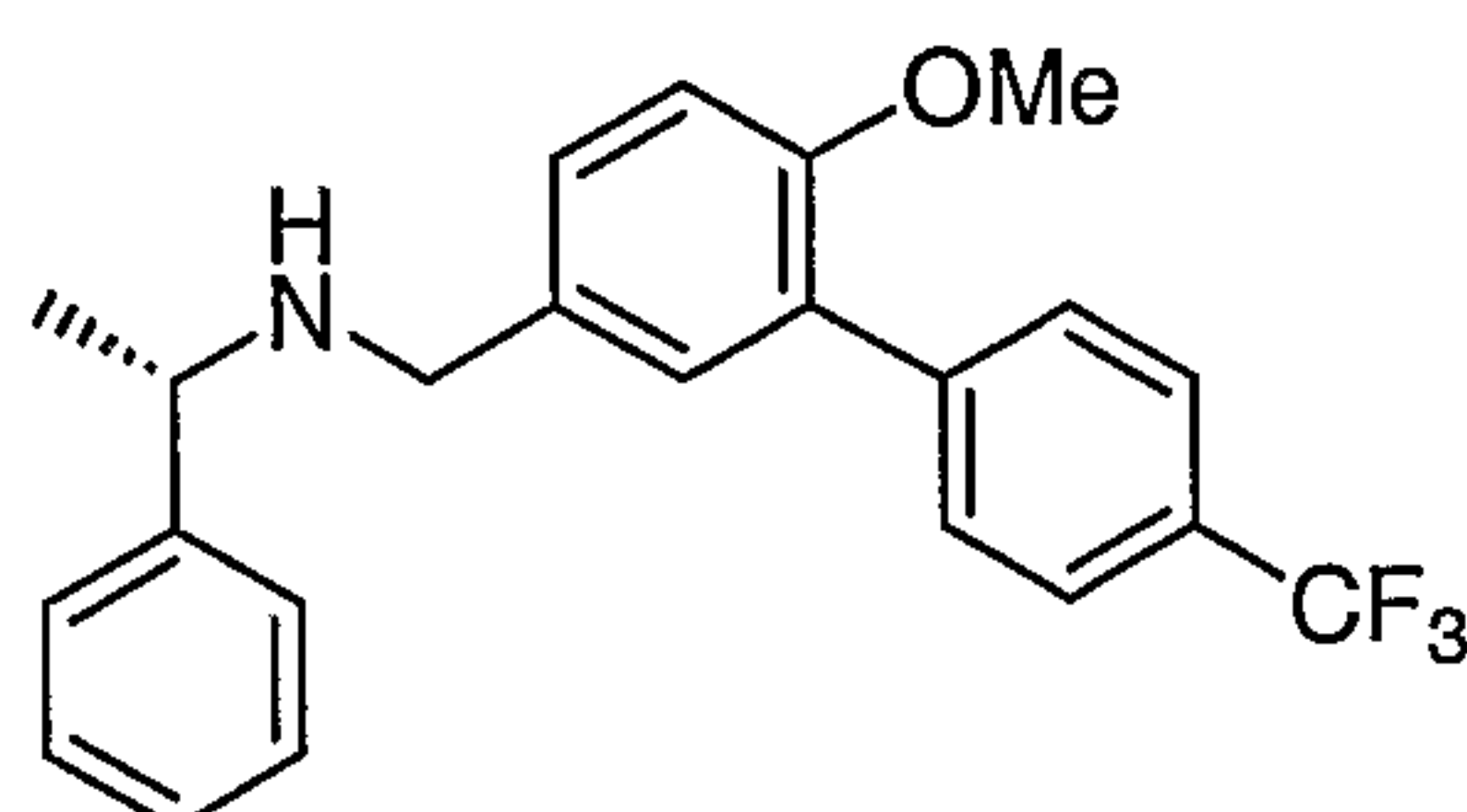
25

Example 97

(1S)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

30

- 125 -



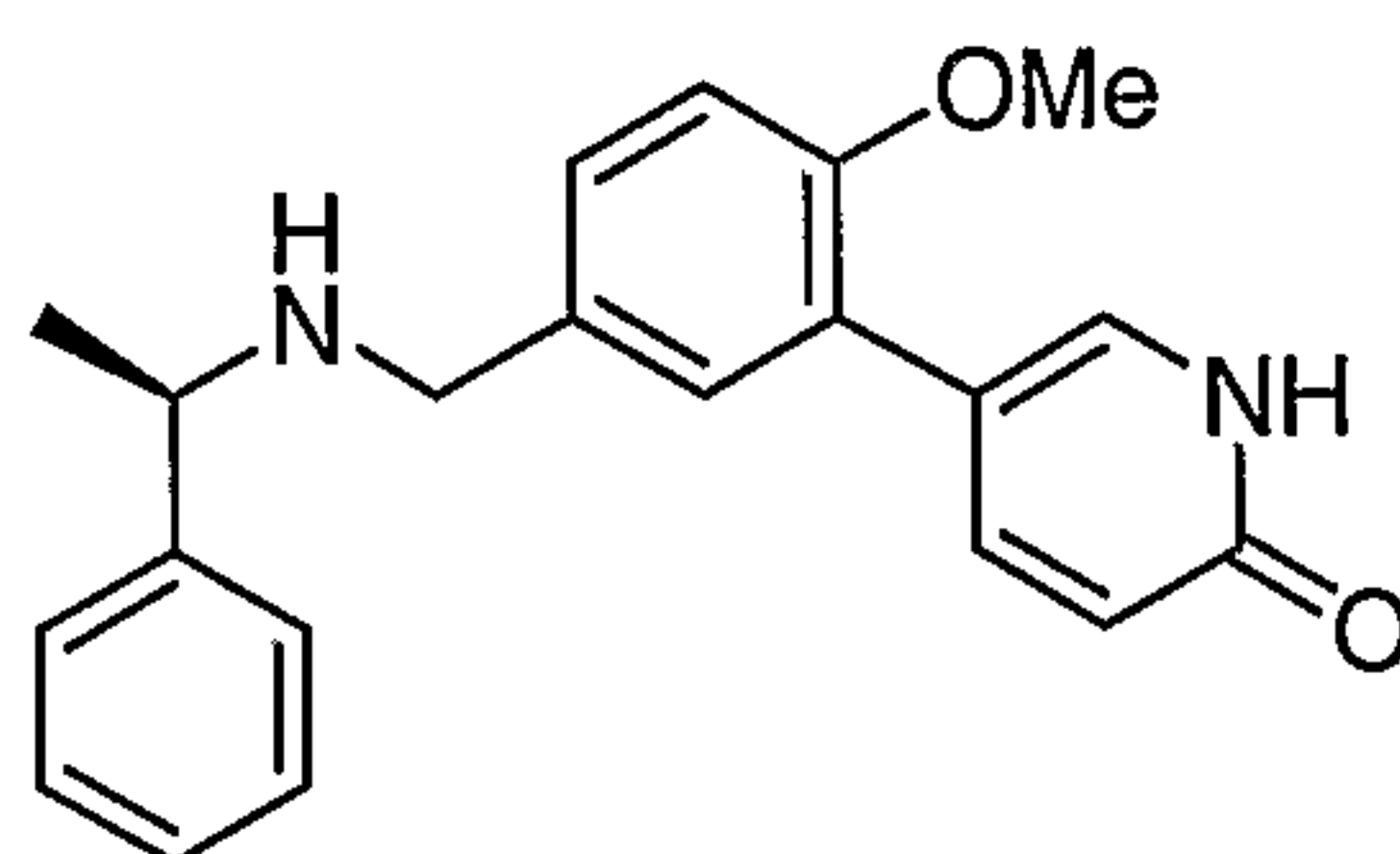
MS (ESI, pos. ion) *m/z*: Calc'd for C₂₃H₂₂F₃NO: 385.43 g/mol. Found: (M+1) 385.9, 264.6, 245.2

5

Example 98

5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2(1H)-pyridinone

10



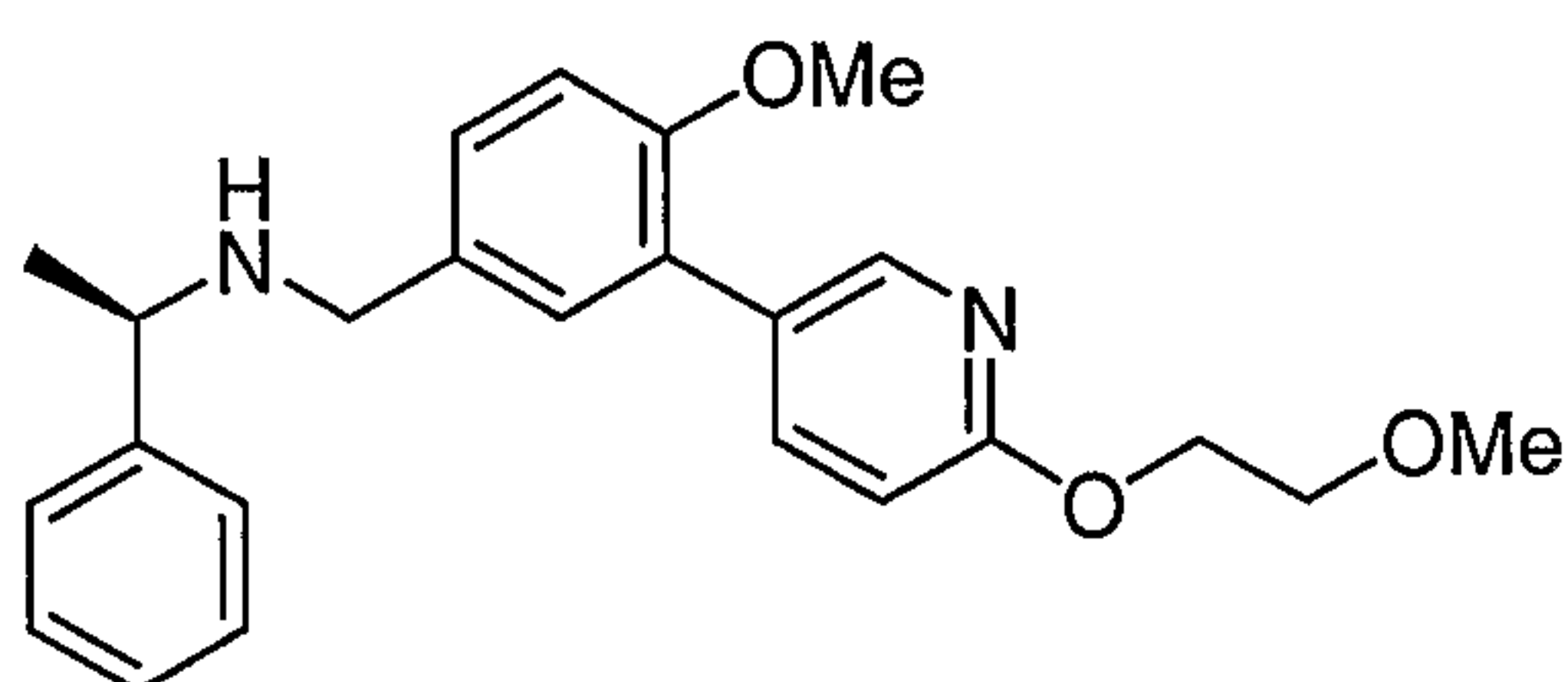
MS (ESI, pos. ion) *m/z*: Calc'd for C₂₁H₂₂N₂O₂: 334.42 g/mol. Found: (M+1) 334.9, 214.2

15

Example 99

(1R)-N-((4-(methyloxy)-3-(6-((2-(methyloxy)ethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine

20



MS (ESI, pos. ion) *m/z*: Calc'd for C₂₄H₂₈N₂O₃: 392.50 g/mol. Found: (M+1) 392.9, 334.9, 271.9, 226.2

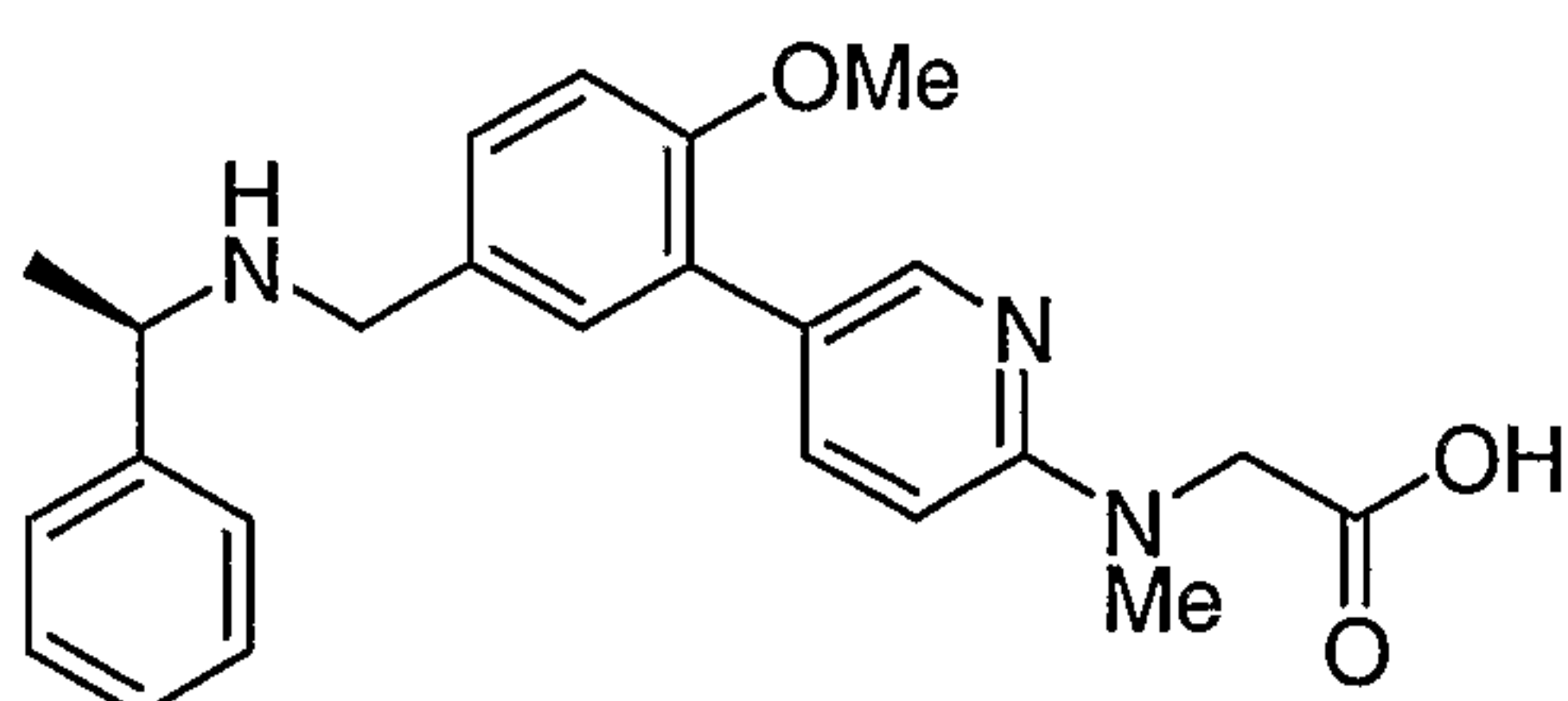
25

Example 100

N-methyl-N-(5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinyl)glycine

30

- 126 -



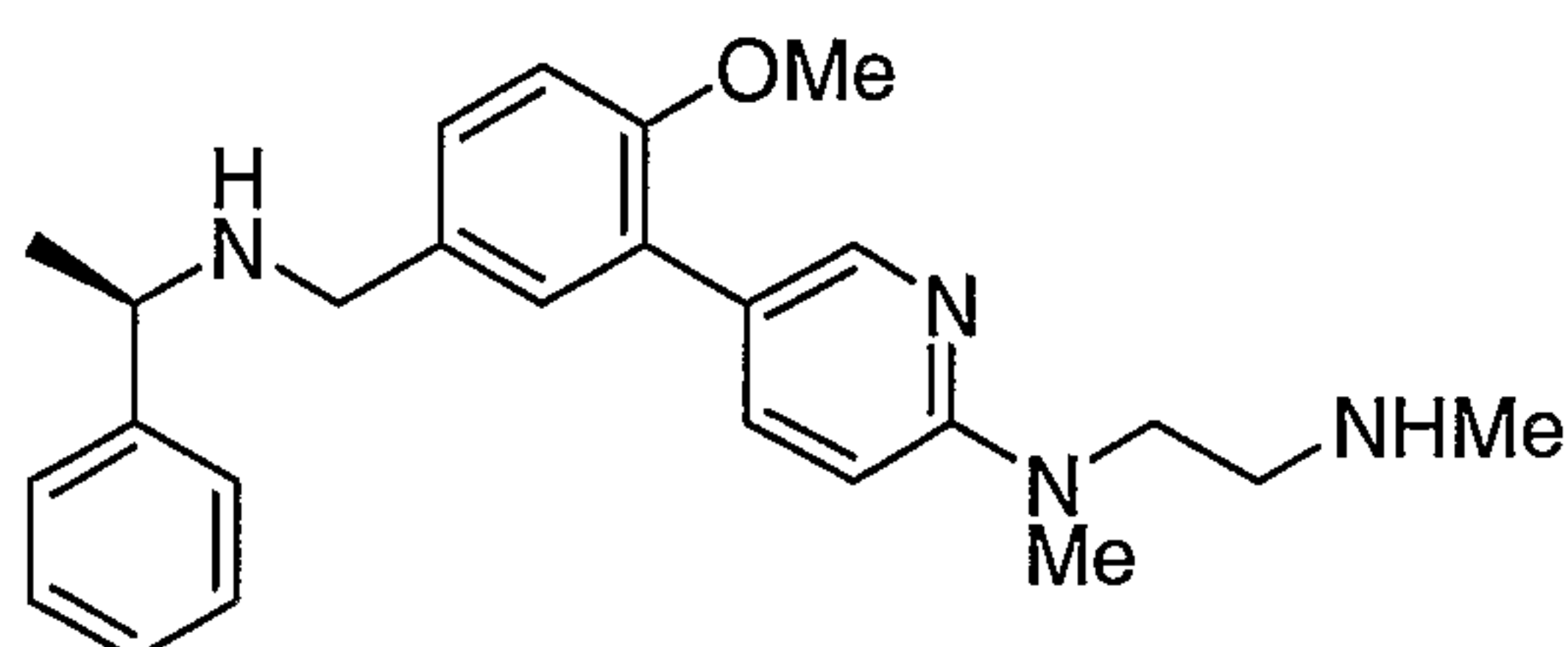
MS (ESI, pos. ion) m/z : Calc'd for $C_{24}H_{27}N_3O_3$: 405.50 g/mol. Found: (M+1) 406.3, 284.9

5

Example 101

N-1-,N-2-dimethyl-N-1-(5-(2-(methyloxy)-5-(((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinyl)-1,2-ethanediamine

10



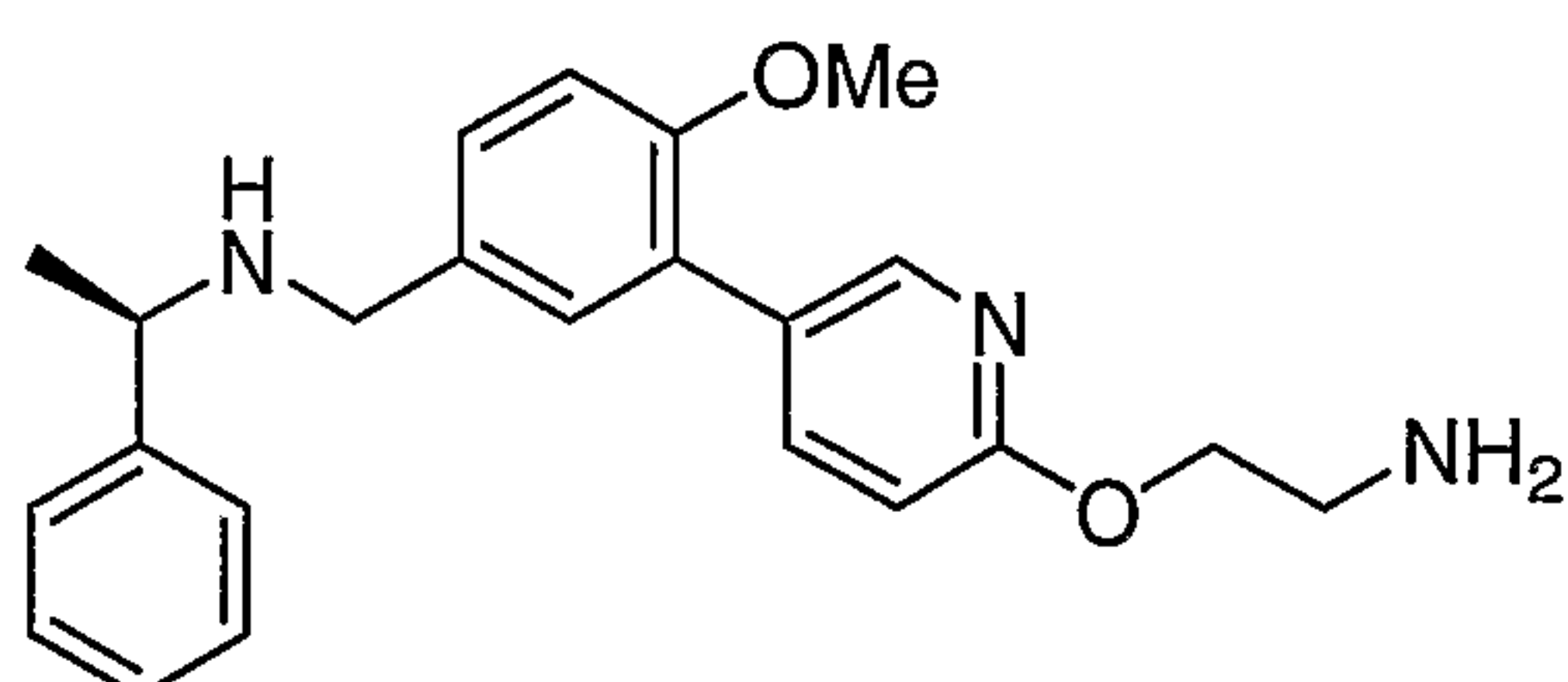
MS (ESI, pos. ion) m/z : Calc'd for $C_{25}H_{32}N_4O$: 404.56 g/mol. Found: (M+1) 404.8, 373.7, 301.0, 284.0, 270.0

15

Example 102

(1R)-N-((3-(6-((2-aminoethyl)oxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine

20



MS (ESI, pos. ion) m/z : Calc'd for $C_{23}H_{27}N_3O_2$: 377.49 g/mol. Found: (M+1) 377.8, 274.1, 256.9

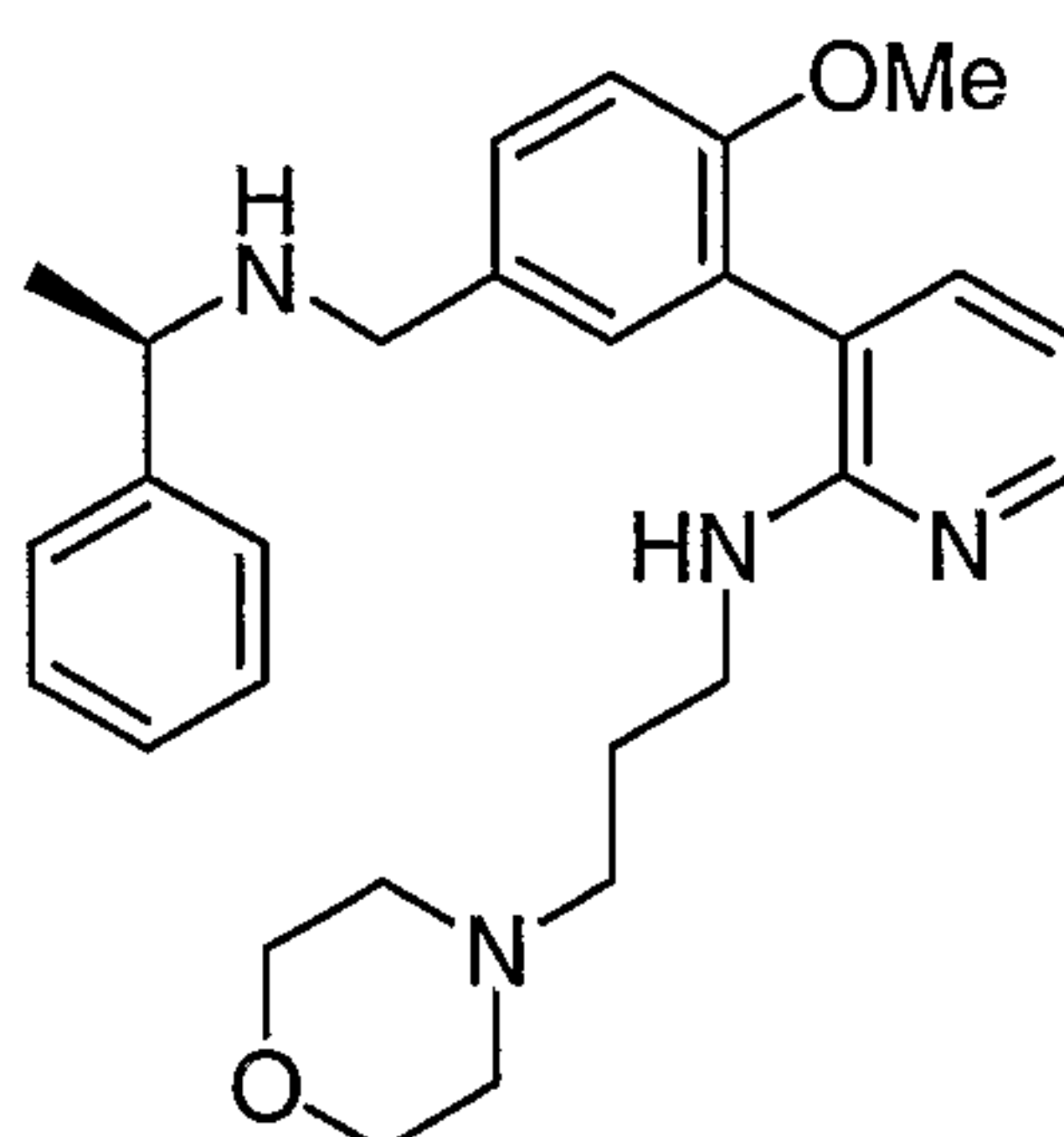
25

Example 103

3-(2-(methyloxy)-5-(((1R)-1-phenylethyl)amino)methyl)phenyl)-N-(3-(4-morpholinyl)propyl)-2-pyridinamine

30

- 127 -

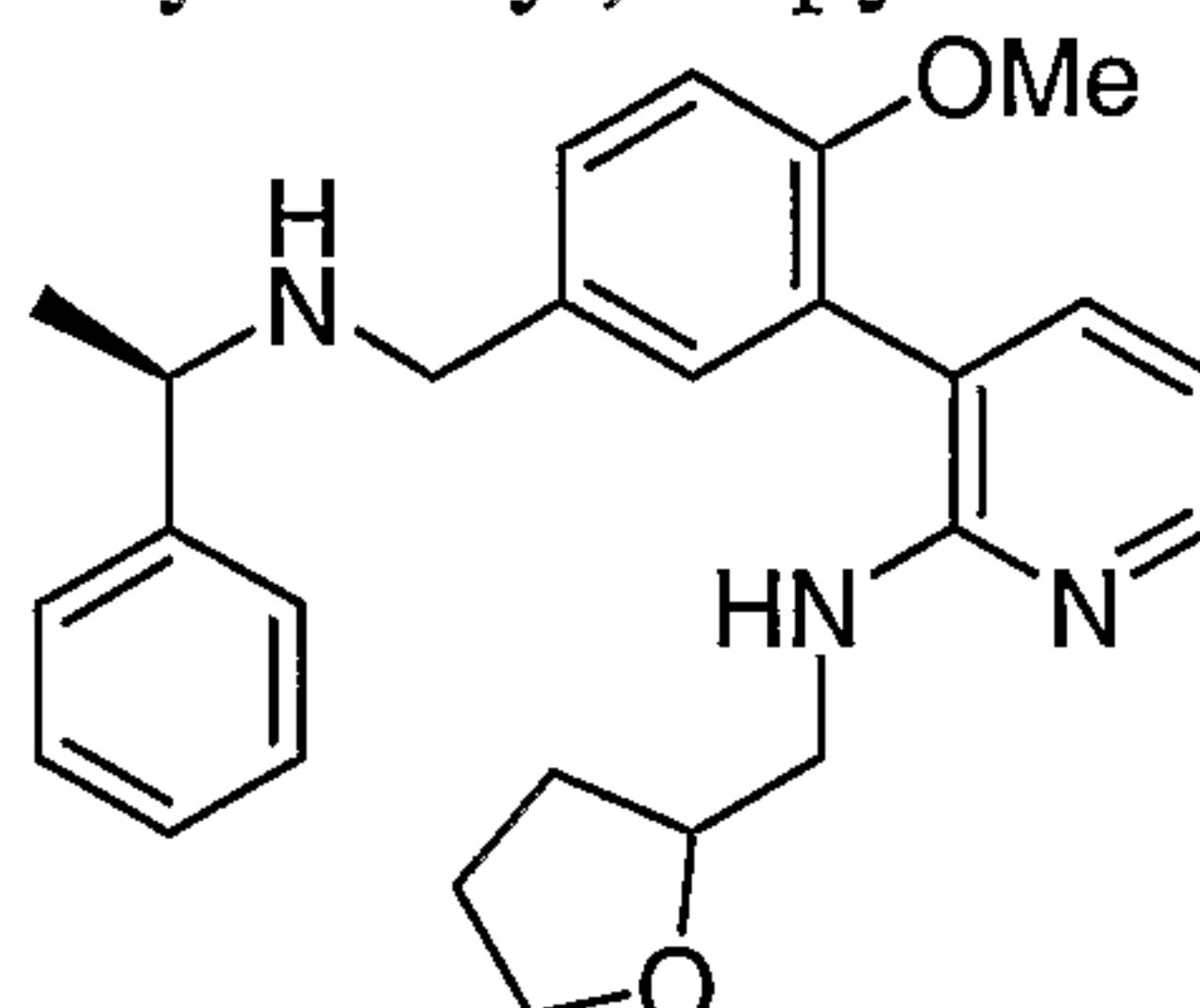


MS (ESI, pos. ion) *m/z*: Calc'd for C₂₈H₃₆N₄O₂: 460.62 g/mol. Found: (M+1) 461.1, 356.8

5

Example 104

3-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-N-(tetrahydro-2-furanylmethyl)-2-pyridinamine



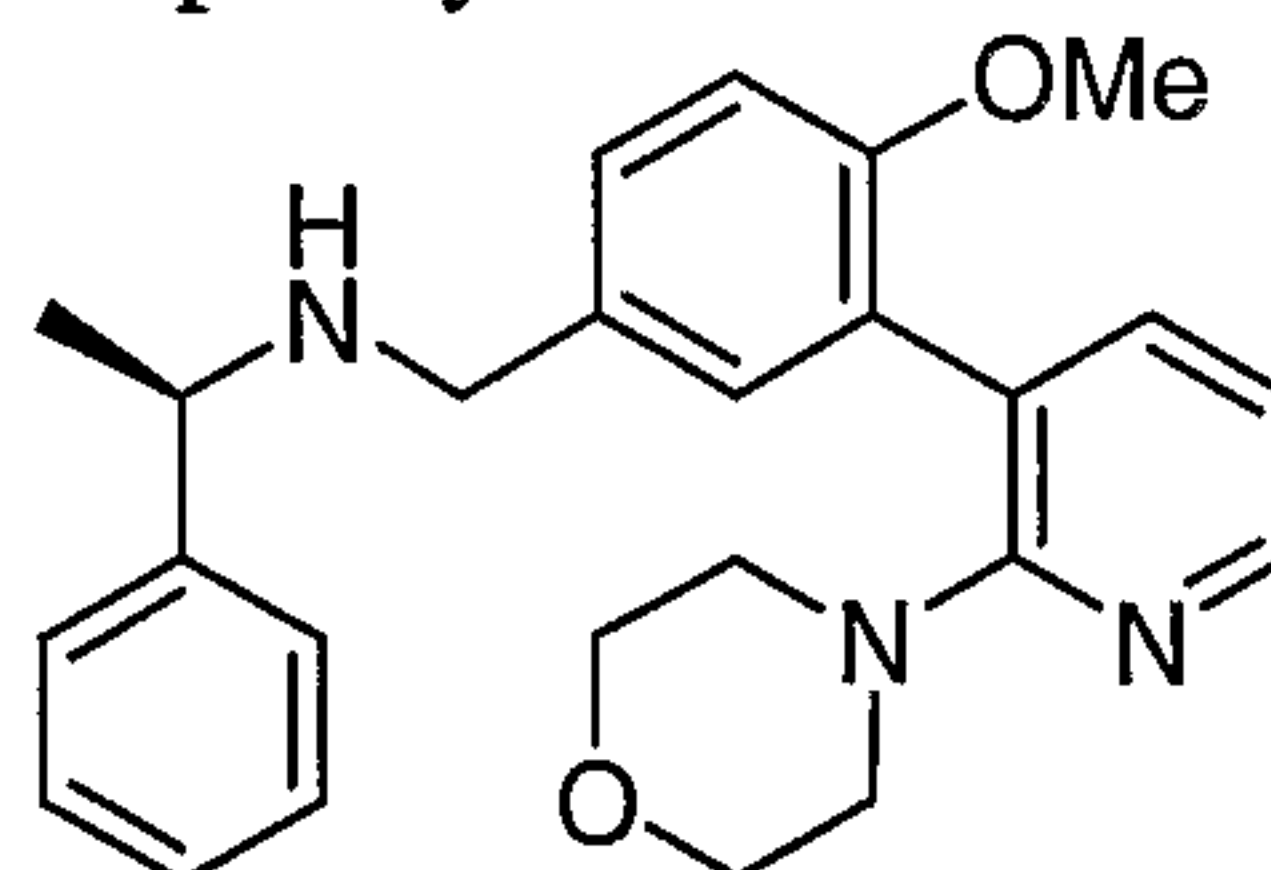
10

MS (ESI, pos. ion) *m/z*: Calc'd for C₂₆H₃₁N₃O₂: 417.55 g/mol. Found: (M+1) 418.1, 297.1, 265.1

15

Example 105

(1R)-N-((4-(methyloxy)-3-(2-(4-morpholinyl)-3-pyridinyl)phenyl)methyl)-1-phenylethylamine



20

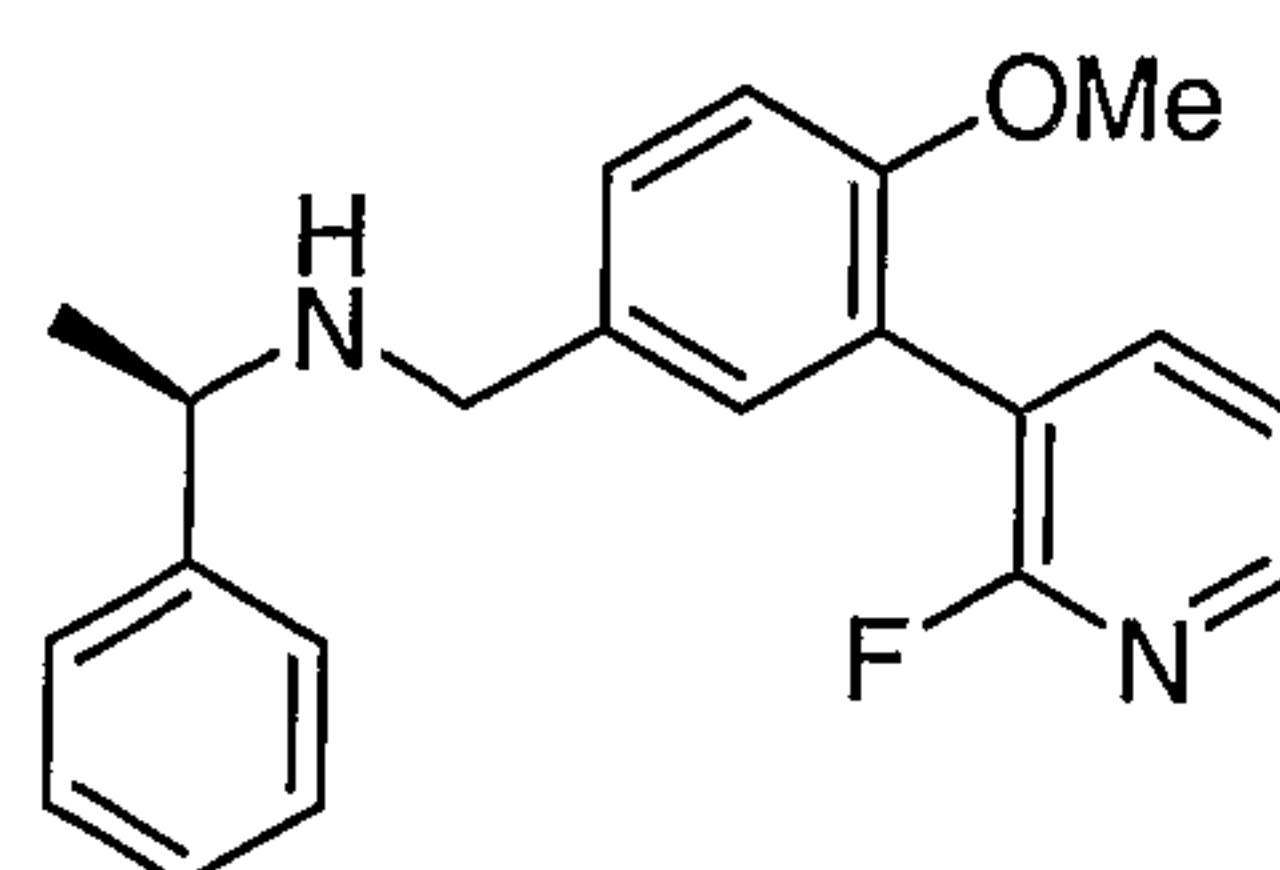
MS (ESI, pos. ion) *m/z*: Calc'd for C₂₅H₂₉N₃O₂: 403.52 g/mol. Found: (M+1) 404.2, 283.0

25

Example 106

(1R)-N-((3-(2-fluoro-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-phenylethylamine

- 128 -



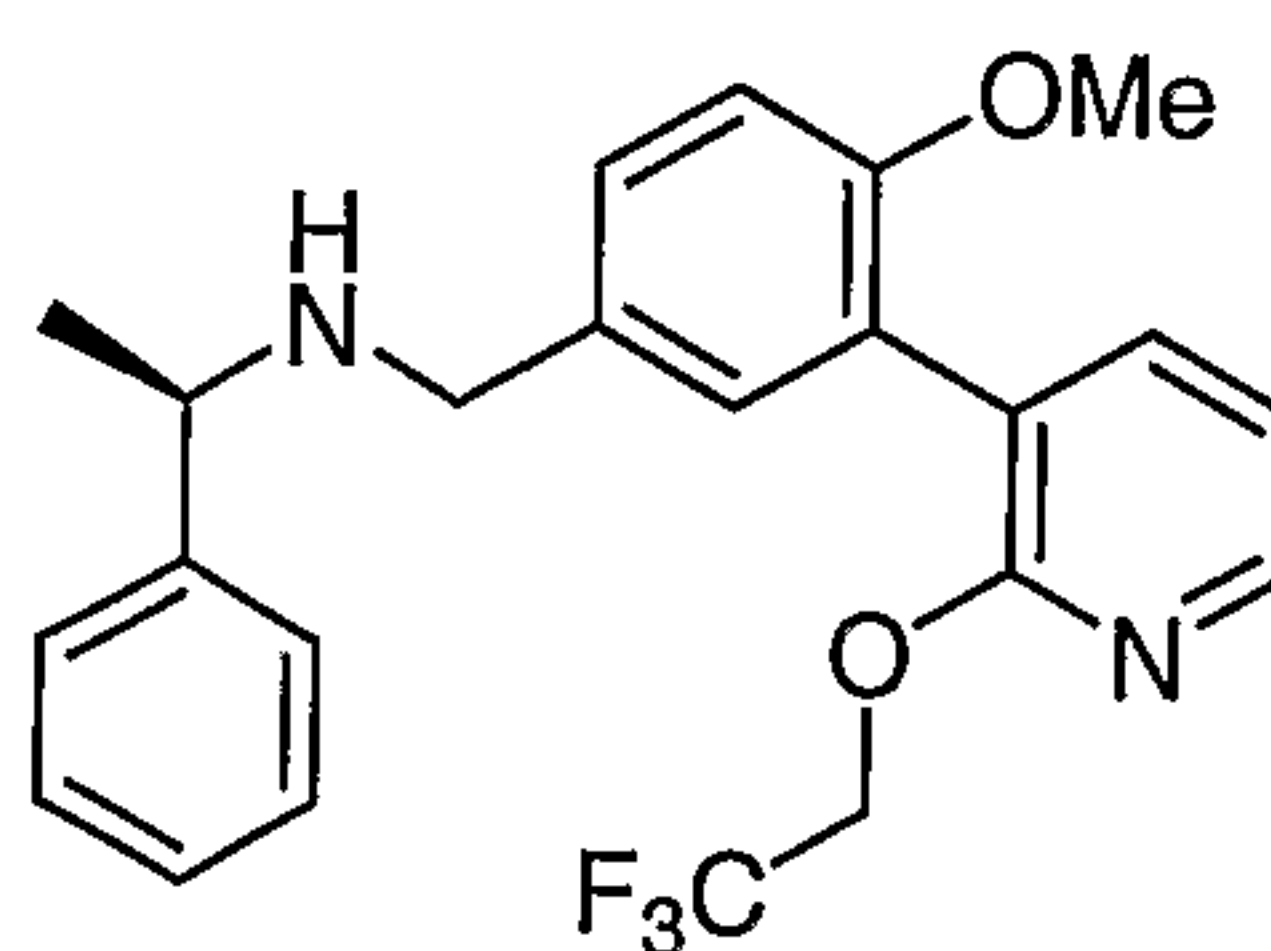
MS (ESI, pos. ion) m/z : Calc'd for $C_{21}H_{21}FN_2O$: 336.41 g/mol. Found: (M+1) 336.9, 233.1, 217.1

5

Example 107

(1R)-N-((4-(methyloxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine

10



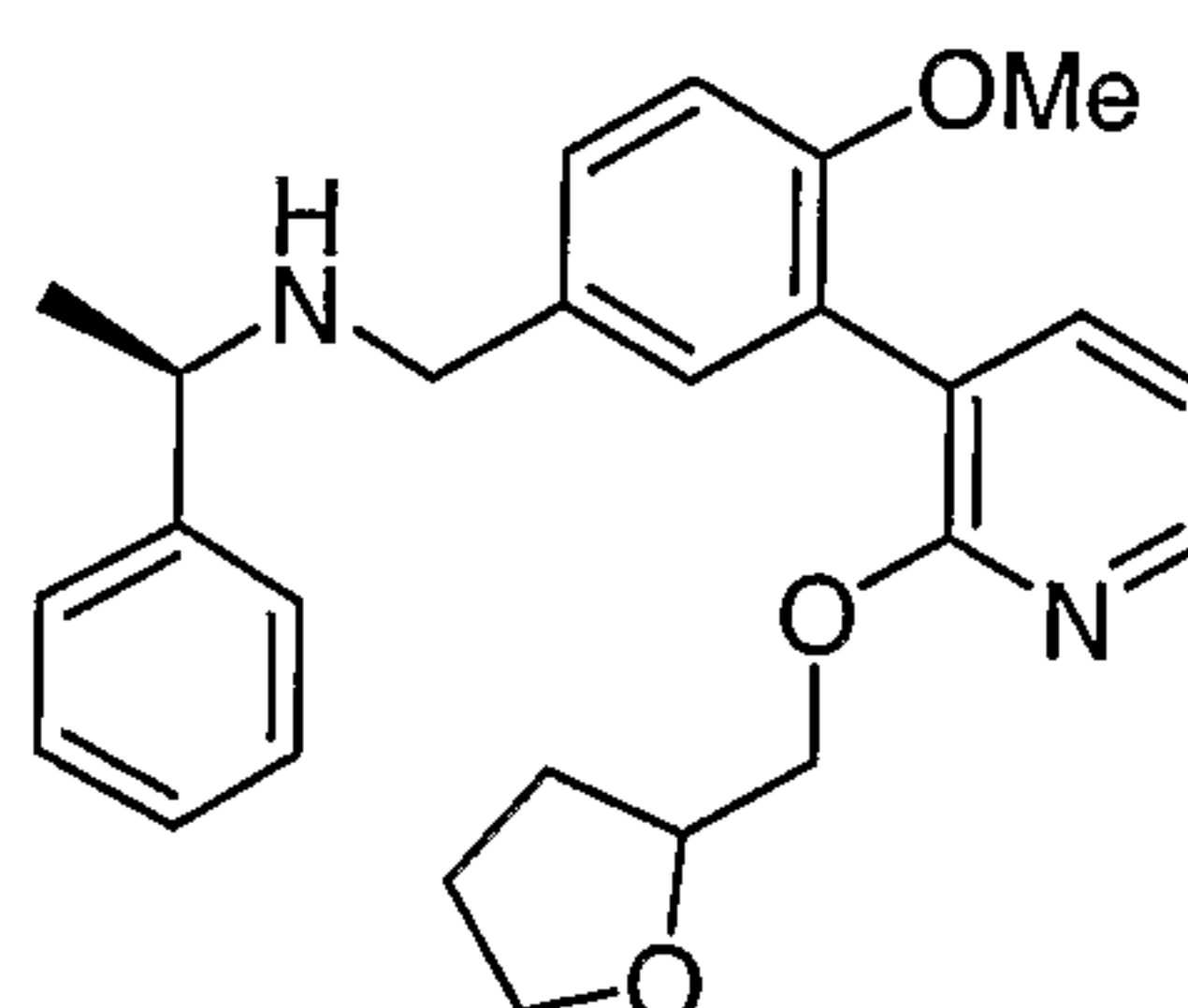
MS (ESI, pos. ion) m/z : Calc'd for $C_{23}H_{23}F_3N_2O_2$: 416.44 g/mol. Found: (M+1) 416.7, 295.8

15

Example 108

(1R)-N-((4-(methyloxy)-3-(2-((tetrahydro-2-furanylmethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine

20



MS (ESI, pos. ion) m/z : Calc'd for $C_{26}H_{30}N_2O_3$: 418.54 g/mol. Found: (M+1) 419.2, 298.1, 216.1

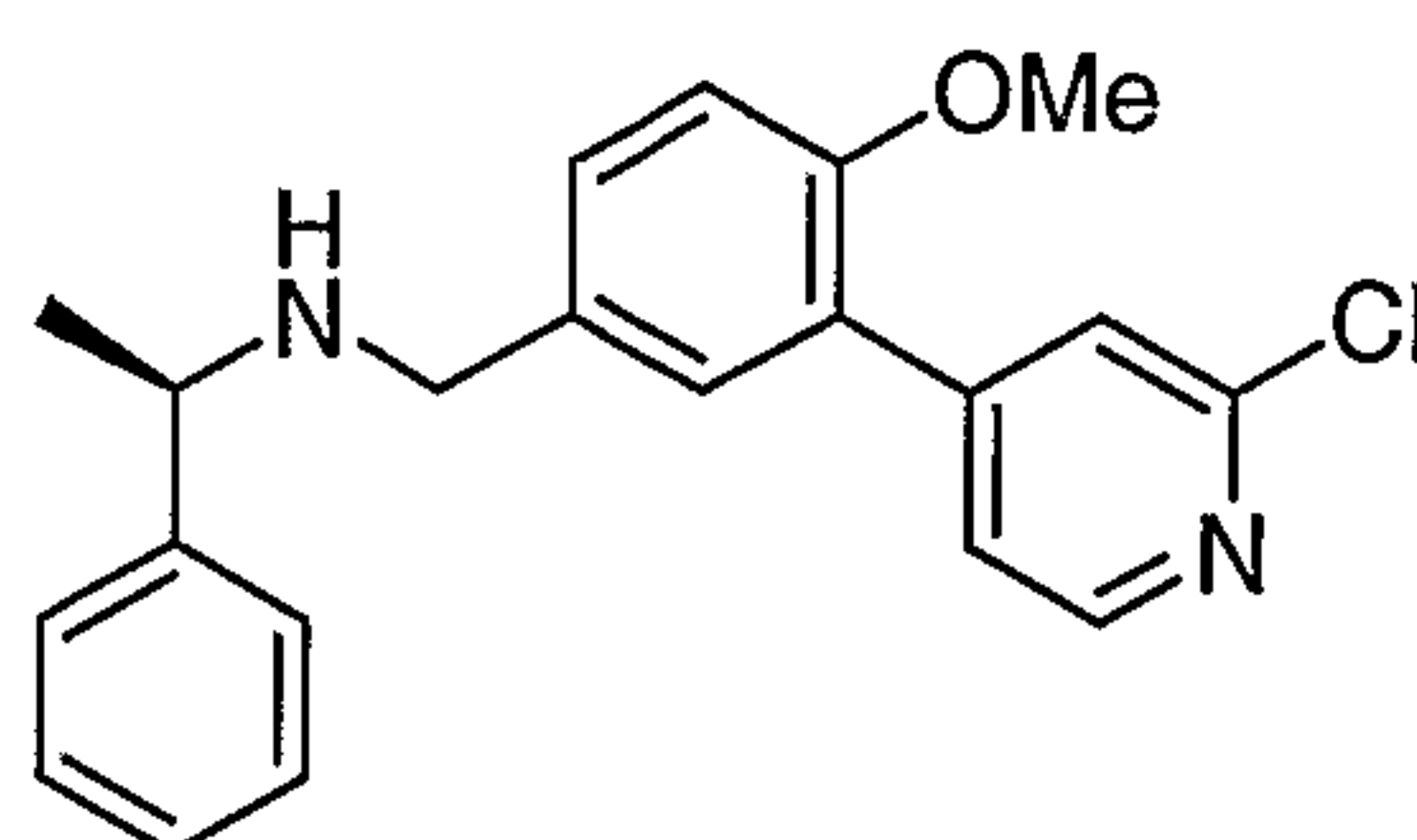
25

Example 109

(1R)-N-(3-(2-chloropyrid-4-yl)-4-methoxyphenyl)methyl-N-1-phenylethylamine

30

- 129 -



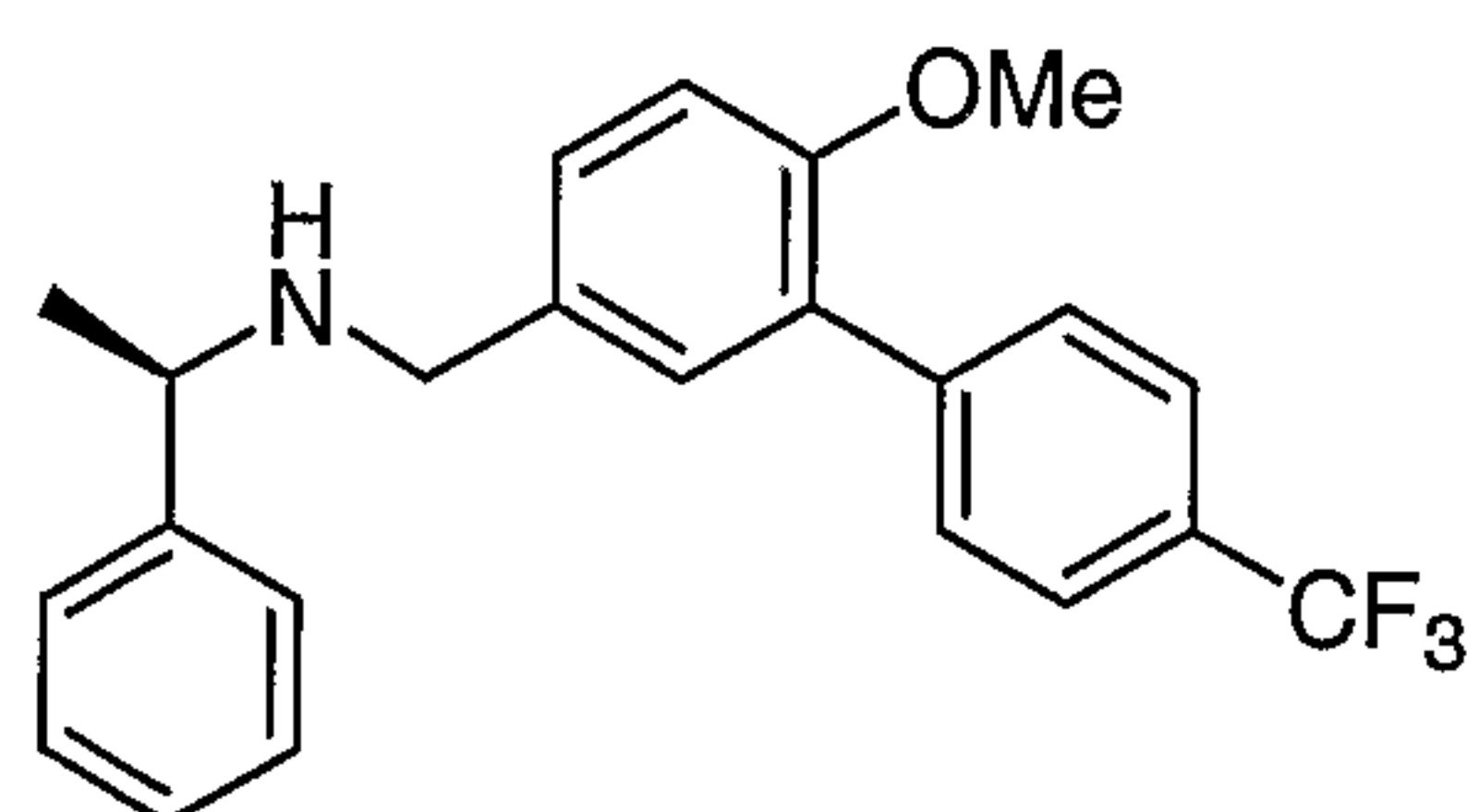
MS (ESI, pos. ion) m/z : Calc'd for $C_{21}H_{21}ClN_2O$: 352.86 g/mol. Found: (M+1) 353.0 (d), 231.9 (d)

5

Example 110

(1R)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine Prepared using Method C.

10



MW 385.427

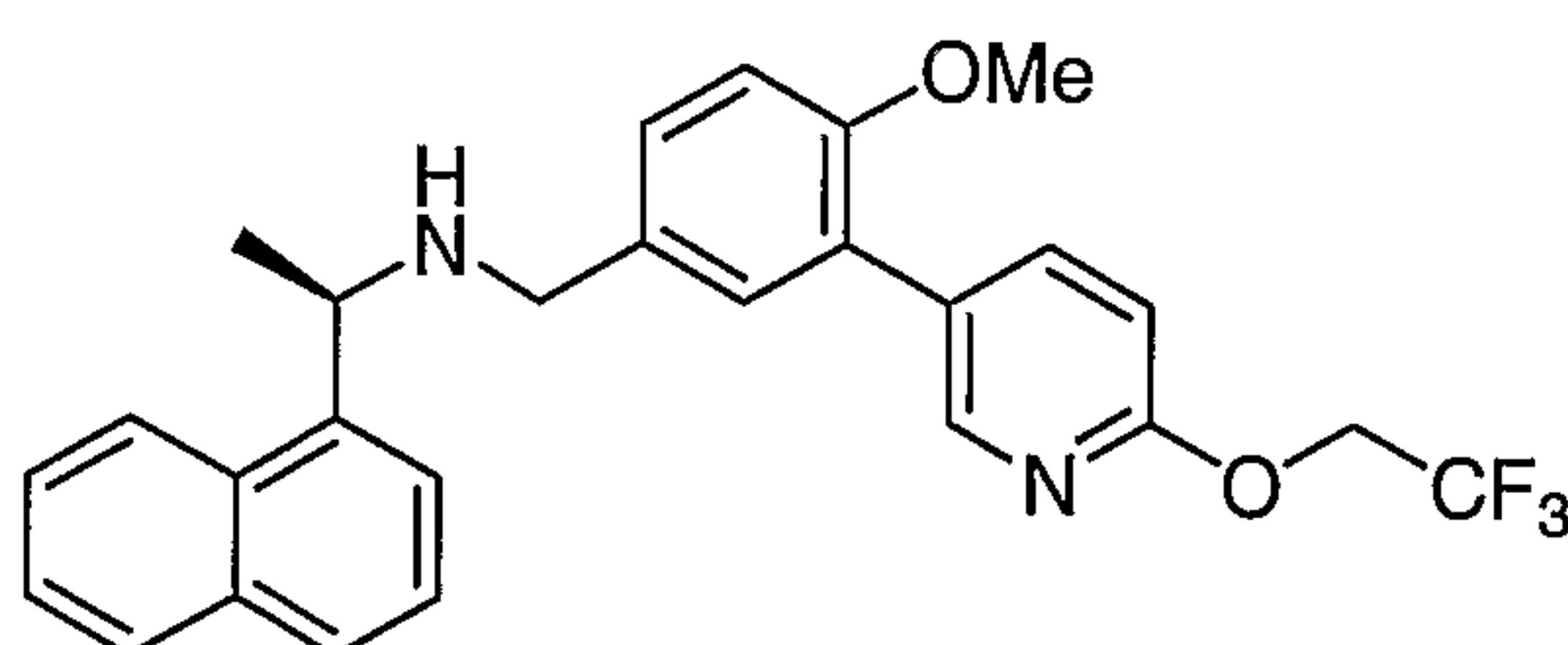
Mass found: 265, 386

15

Example 111

(1R)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine Prepared using Method C.

20



MW 466.5

Mass found: 467, 155

25

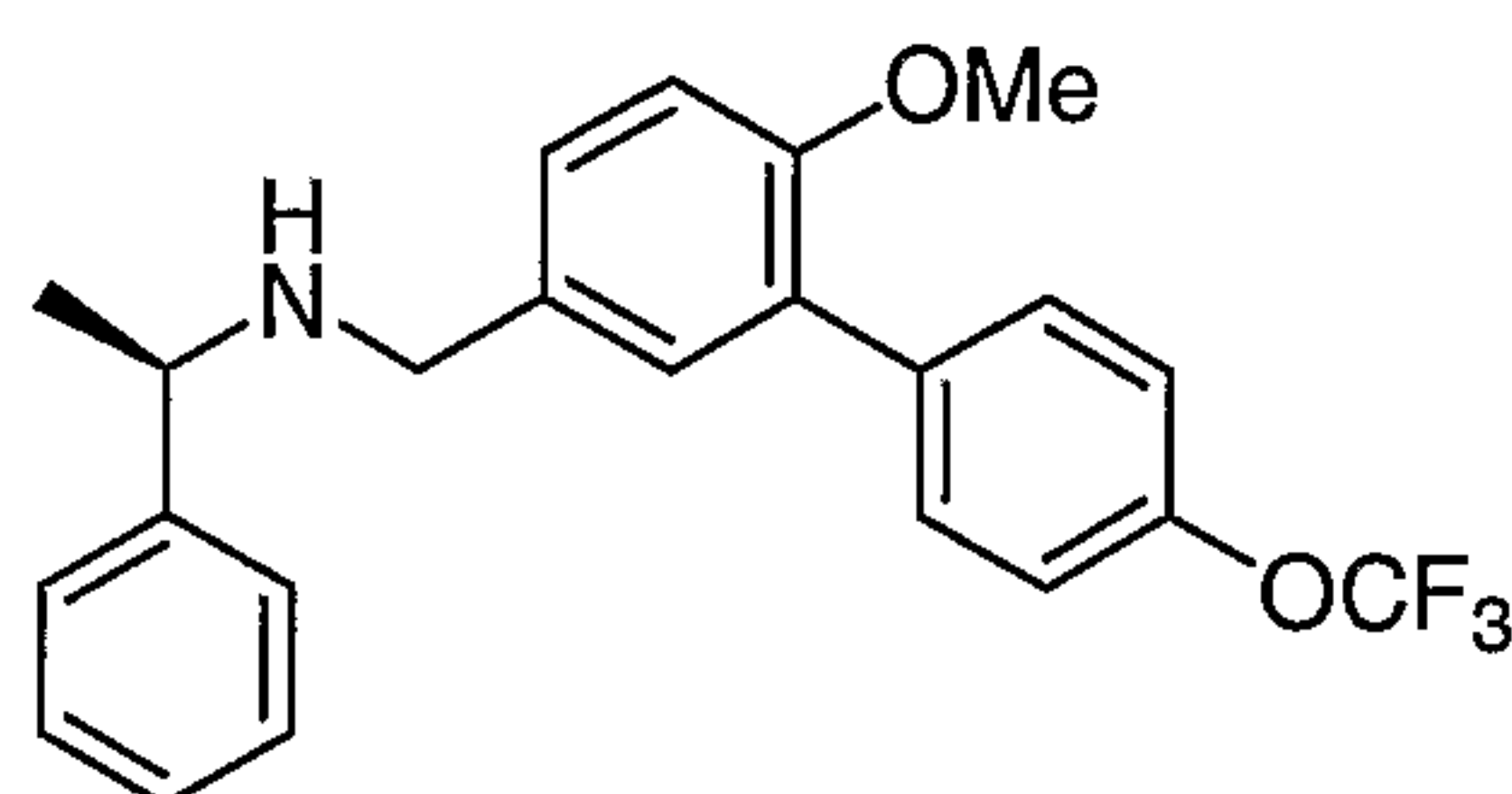
Example 112

(1R)-N-((6-(methyloxy)-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

30

Prepared using Method C.

- 130 -



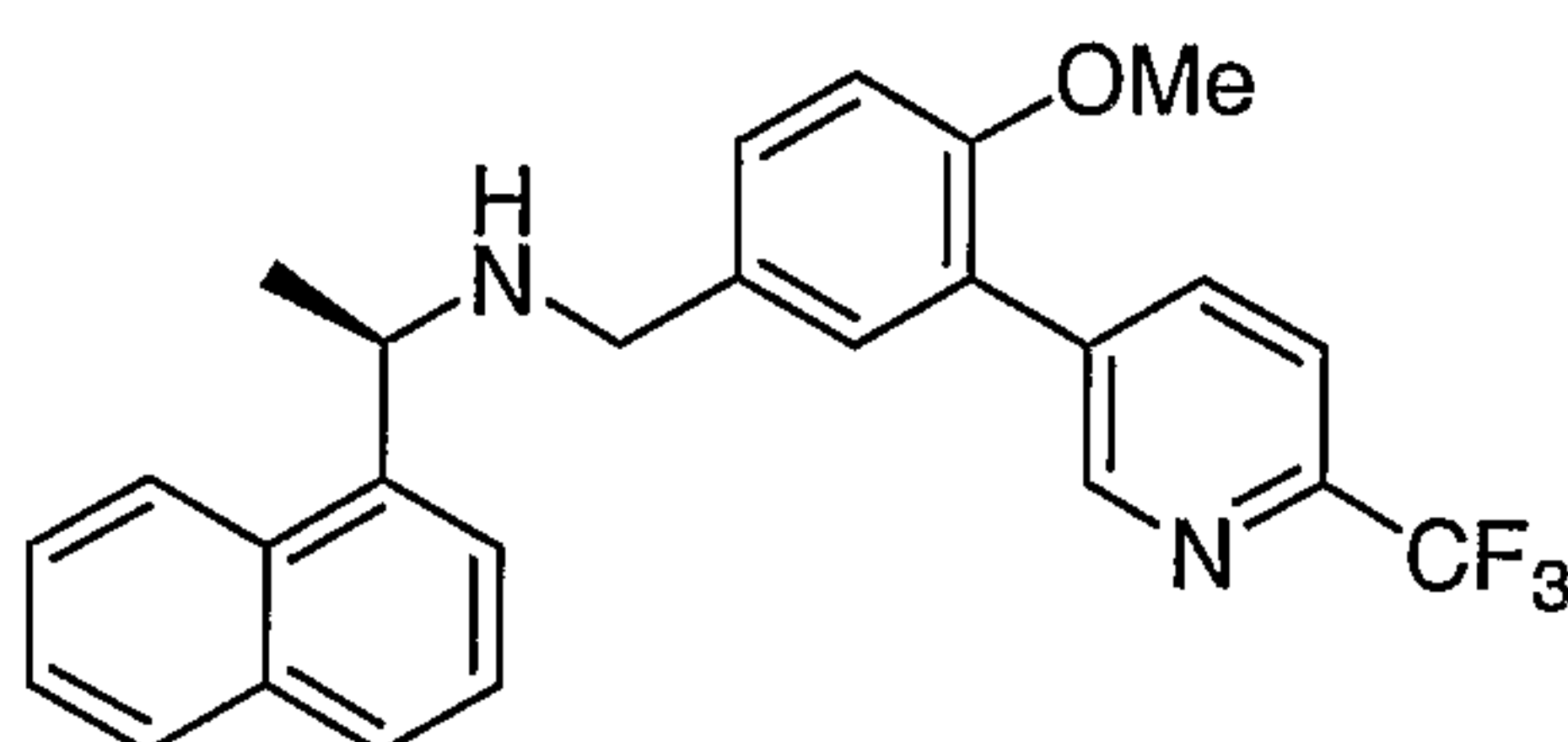
MW 401.426

Mass found: 402, 803, 917

Example 113

(1R)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

Prepared using Method C.



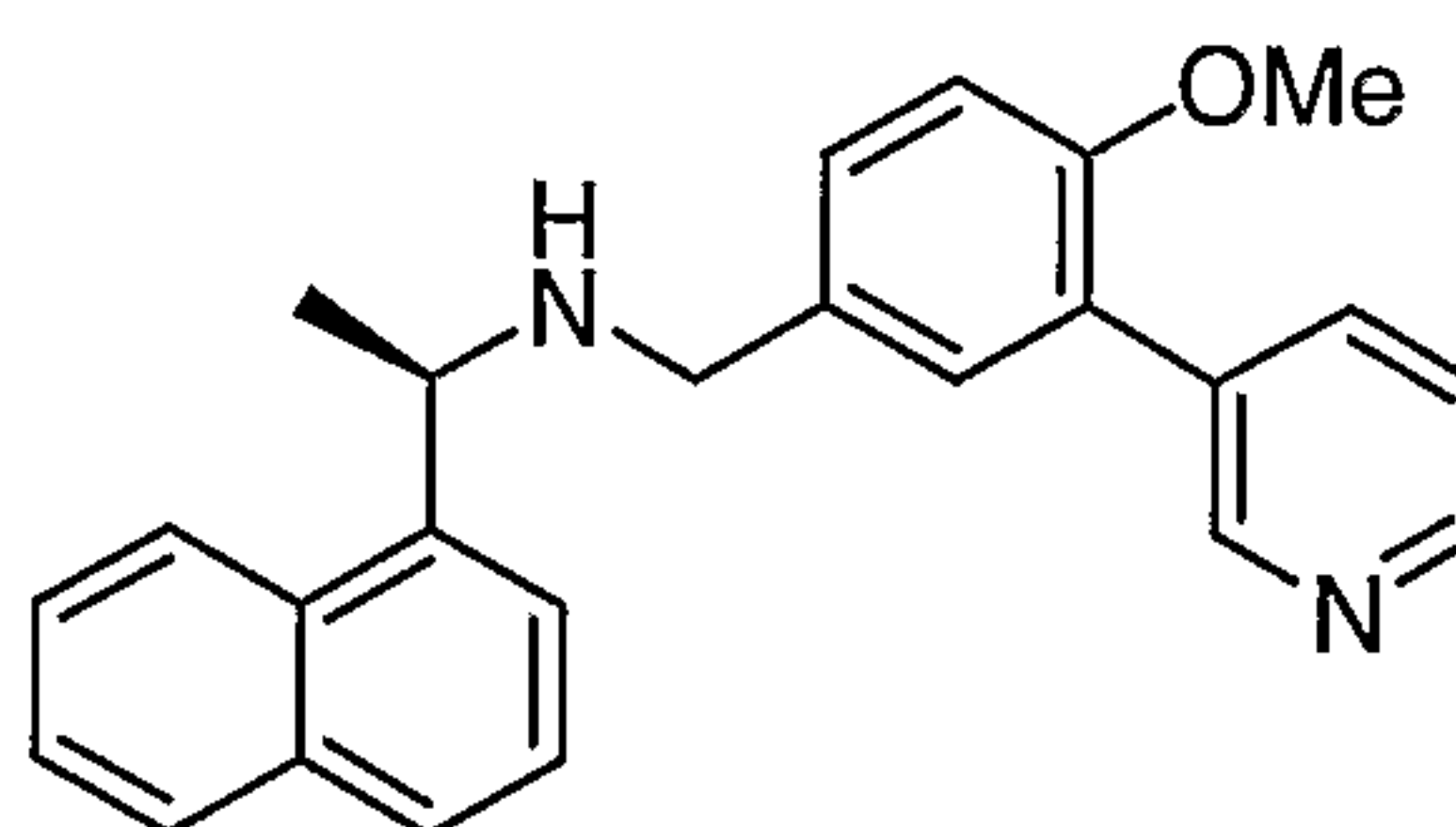
MW 436.475

Mass found: 437, 478

Example 114

(1R)-N-((4-(methyloxy)-3-(3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

Prepared using Method A.



MW 368.478

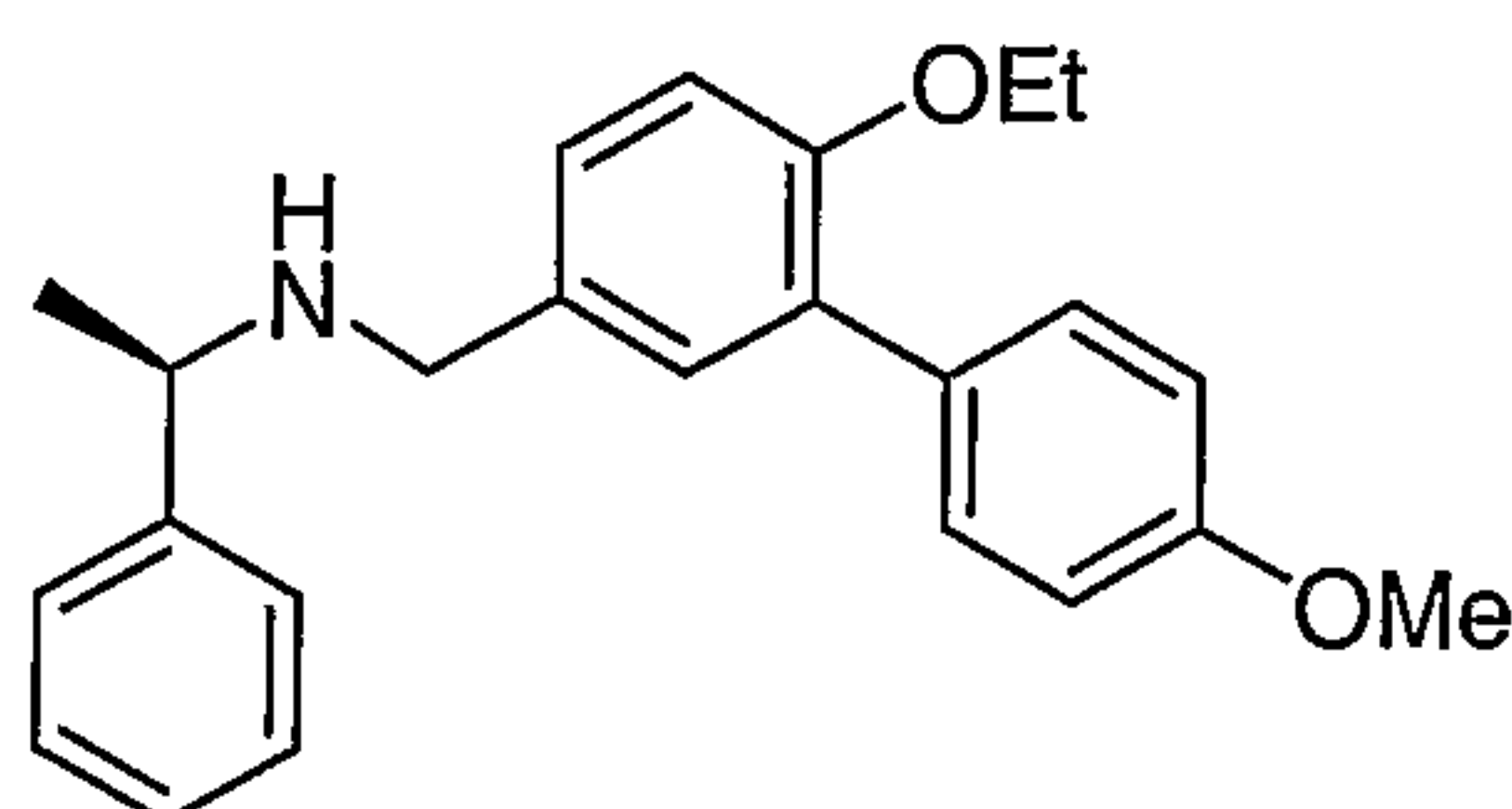
Mass found: 369, 155

Example 115

- 131 -

(1R)-N-((6-(ethoxy)-4'-(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

5 Prepared using Method C.

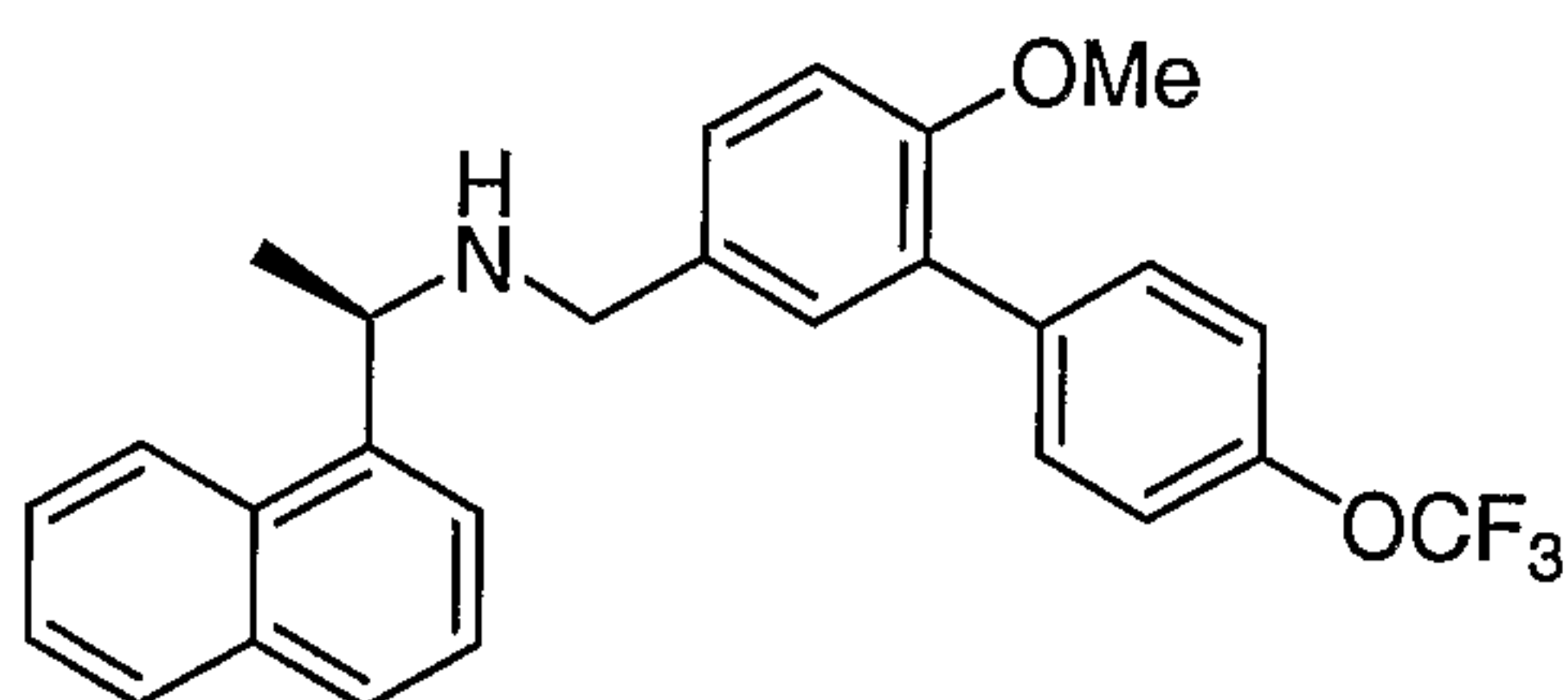


MW 361.482
Mass found: 362

Example 116

15 (1R)-N-((6-(methoxy)-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine

Prepared using Method C.



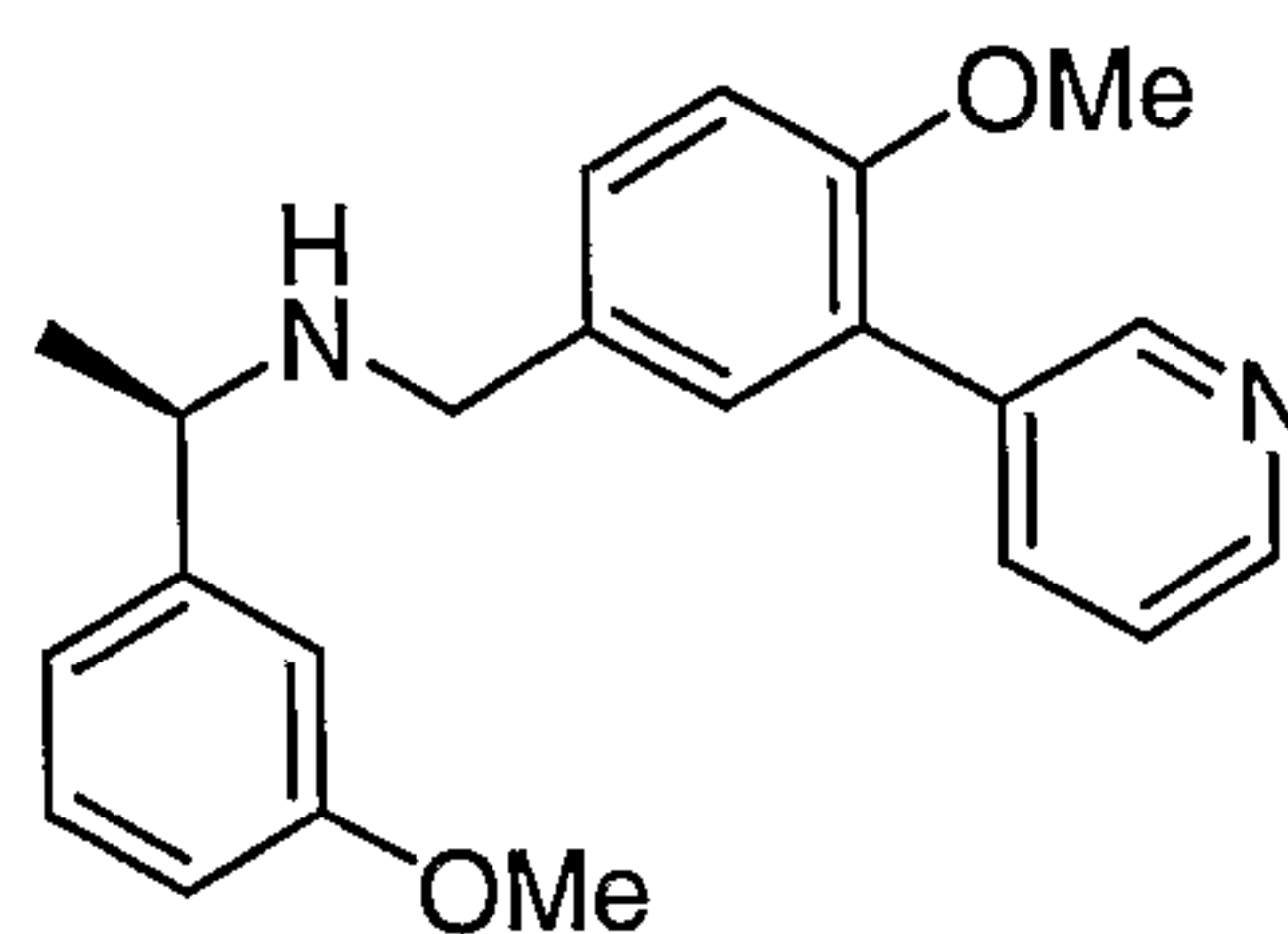
MW 451.486
Mass found: 452, 155

Examples 117-252 were prepared using Method A:

Example 117

(1R)-1-(3-(methoxy)phenyl)-N-((4-(methoxy)-3-(3-pyridinyl)phenyl)methyl)ethanamine

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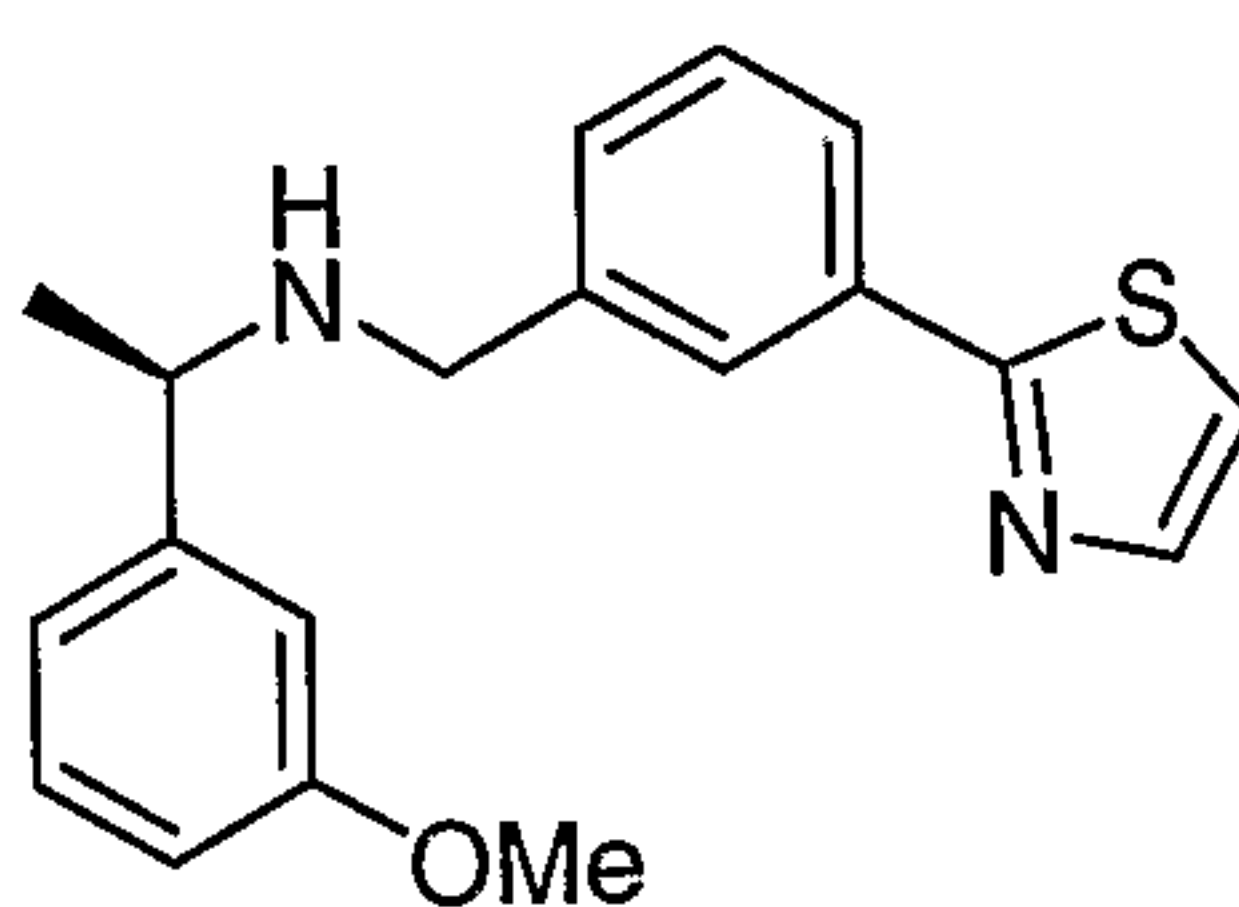
MW 348.444

Mass found: 198, 349

5

Example 118

(1R)-1-(3-(methoxy)phenyl)-N-((3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine



10

MW 324.446

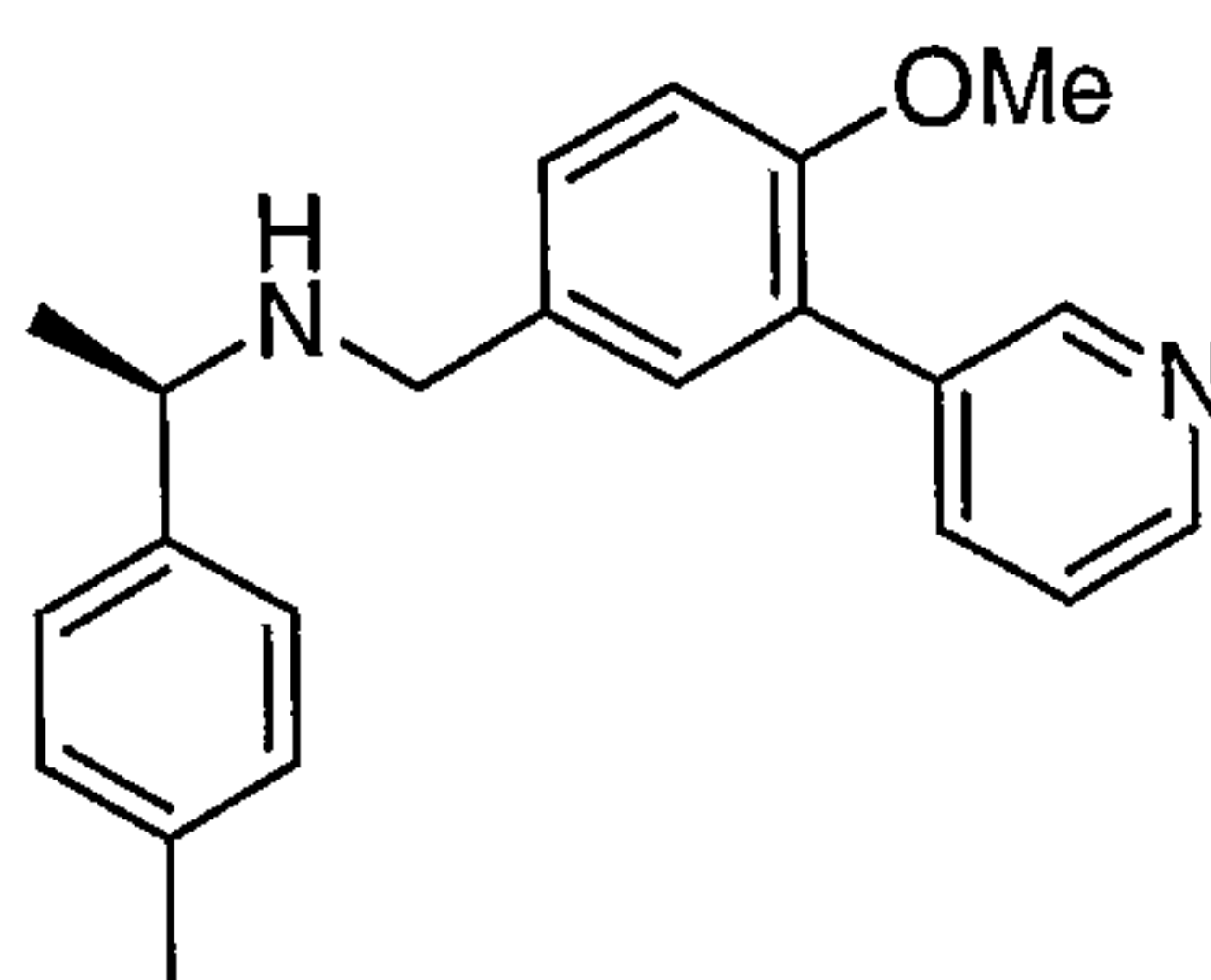
Mass found: 325, 649

15

Example 119

(1R)-N-((4-(methoxy)-3-(3-pyridinyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine

20



MW 332.445

Mass found: 333, 779

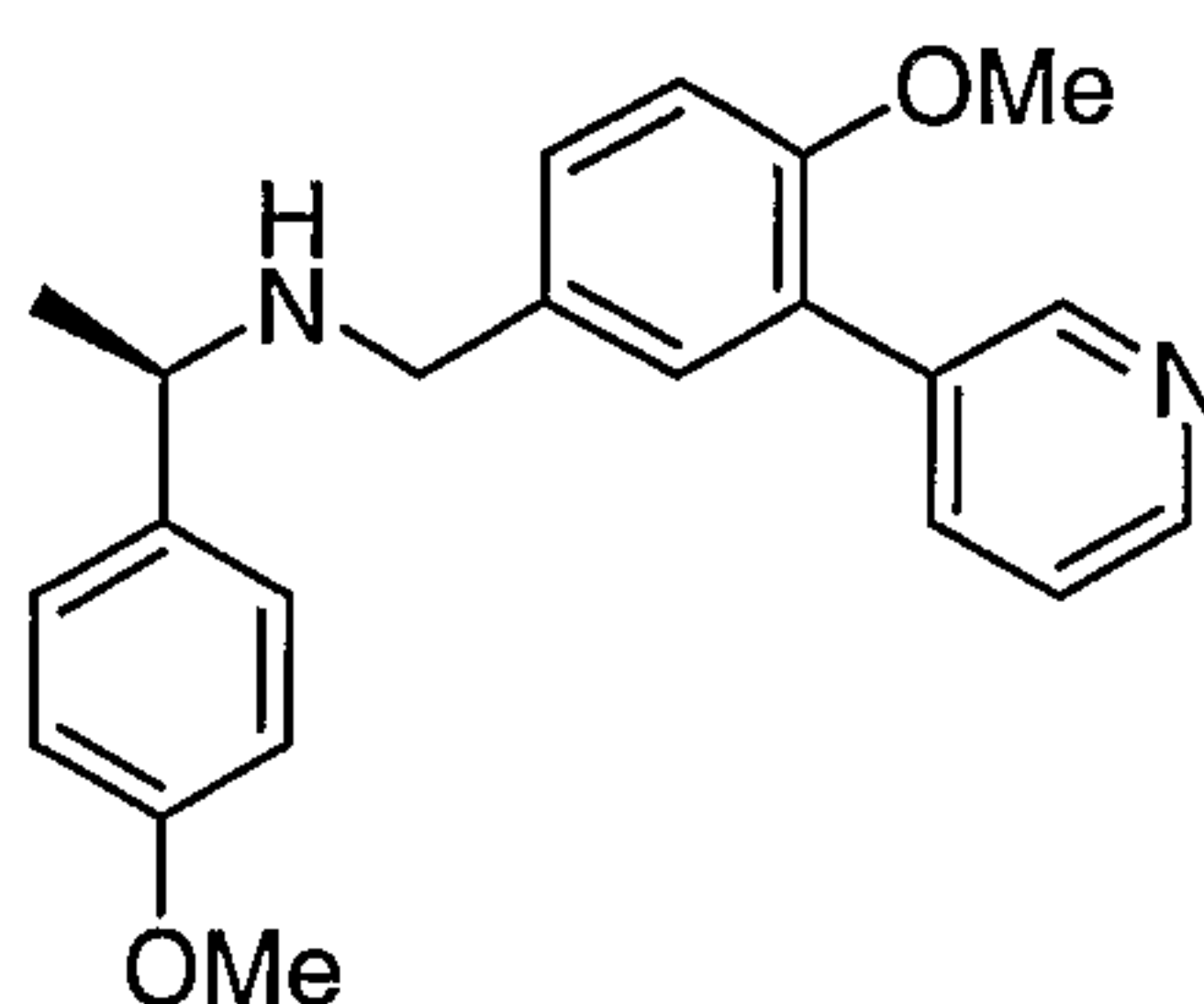
25

Example 120

(1R)-1-(4-(methoxy)phenyl)-N-((4-(methoxy)-3-(3-pyridinyl)phenyl)methyl)ethanamine

30

- 133 -

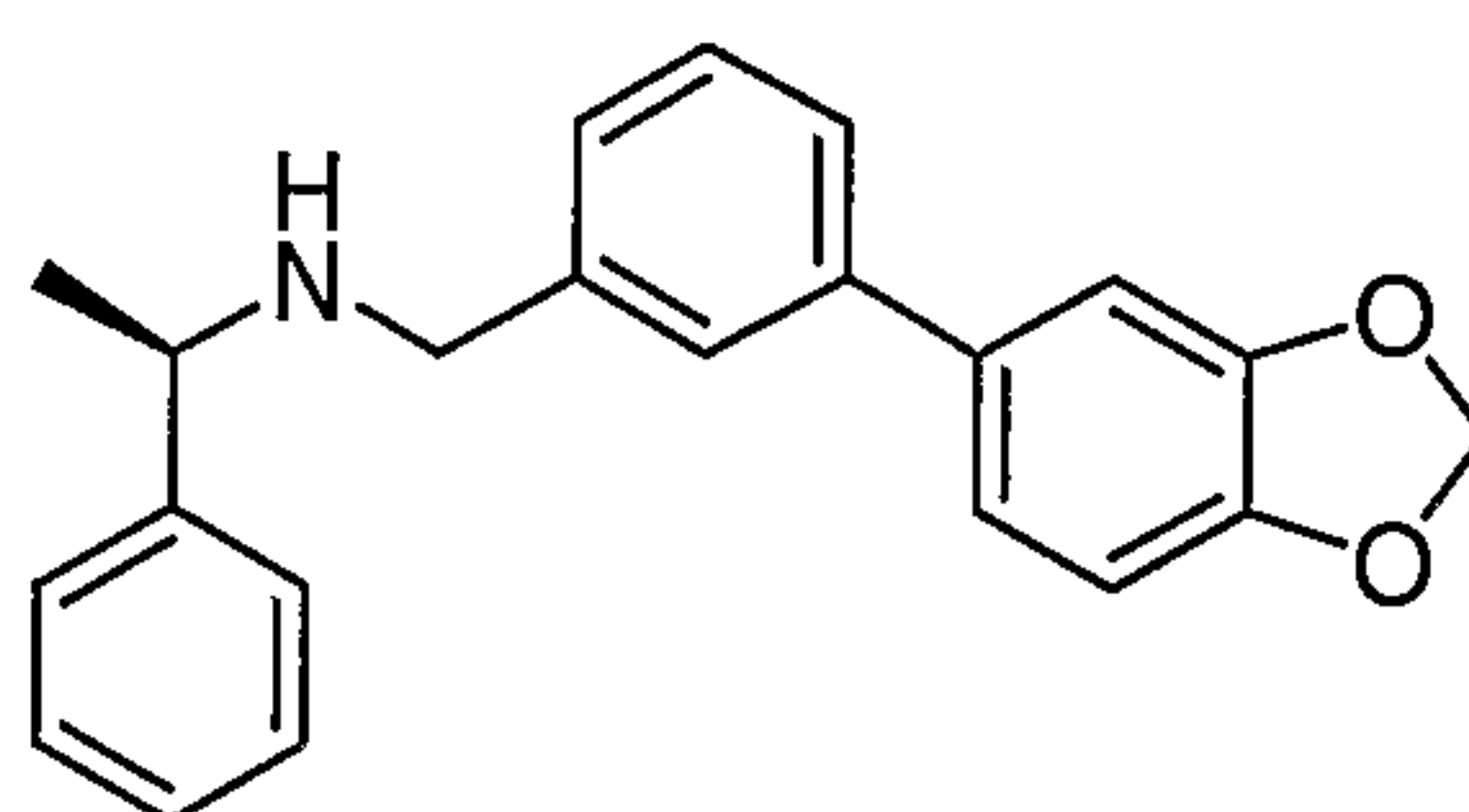


MW 348.444

Mass found: 349

Example 121

(1R)-N-((3-(1,3-benzodioxol-5-yl)phenyl)methyl)-1-phenylethanamine

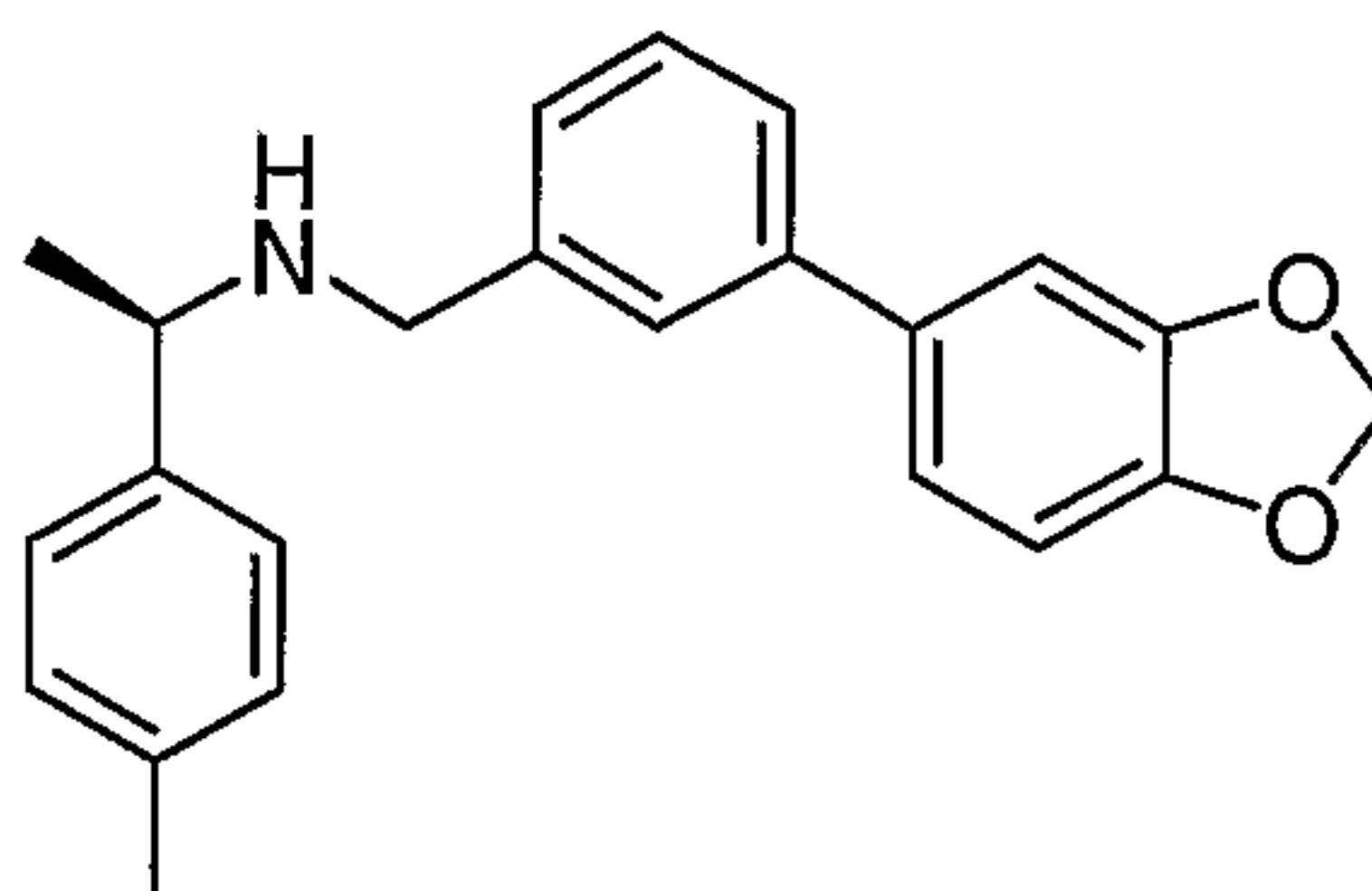


MW 331.413

Mass found: 332, 777

Example 122

(1R)-N-((3-(1,3-benzodioxol-5-yl)phenyl)methyl)-1-(4-methylphenyl)ethanamine



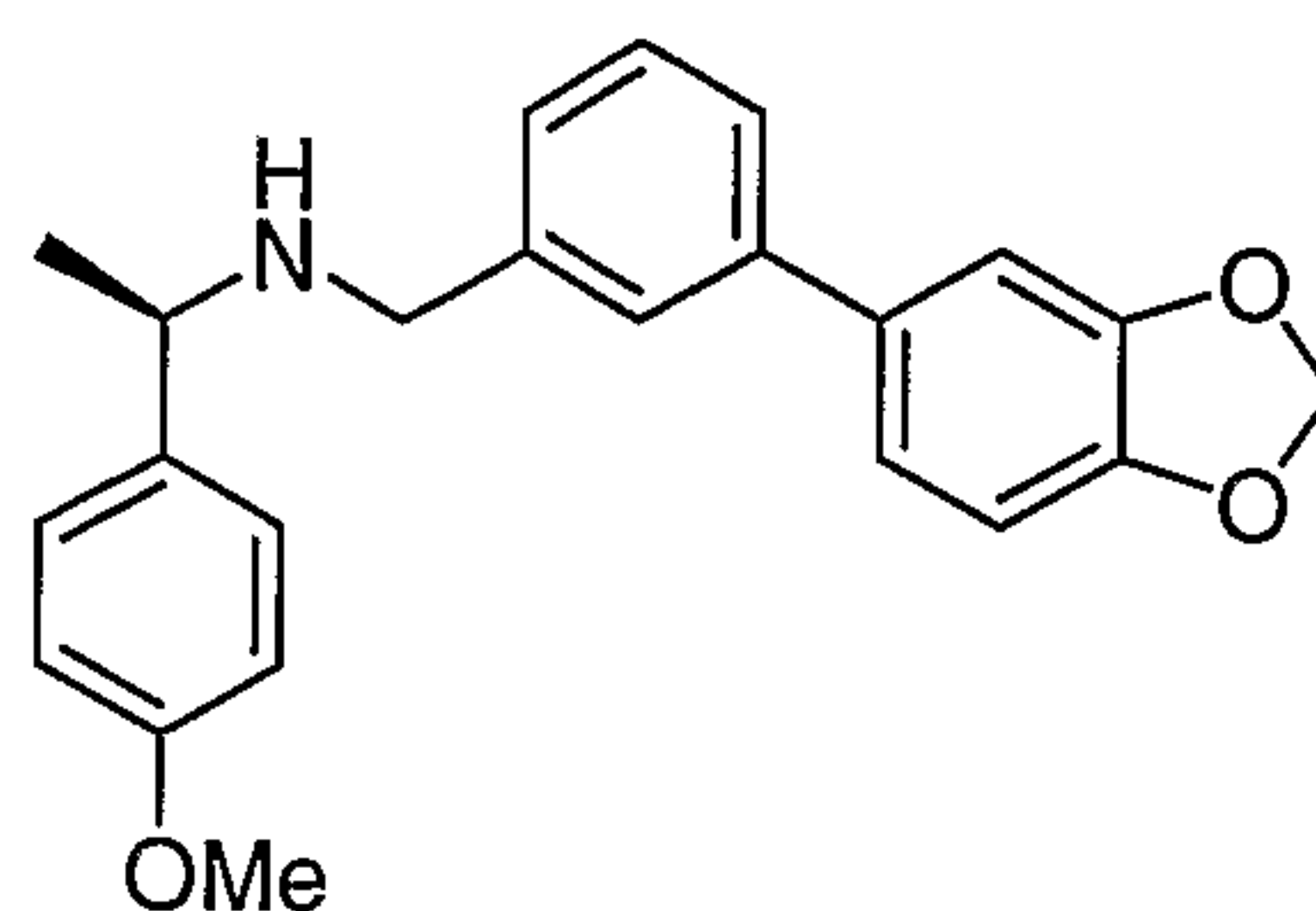
MW 345.44

Mass found: 346

Example 123

(1R)-N-((3-(1,3-benzodioxol-5-yl)phenyl)methyl)-1-(4-(methyloxy)phenyl)ethanamine

- 134 -



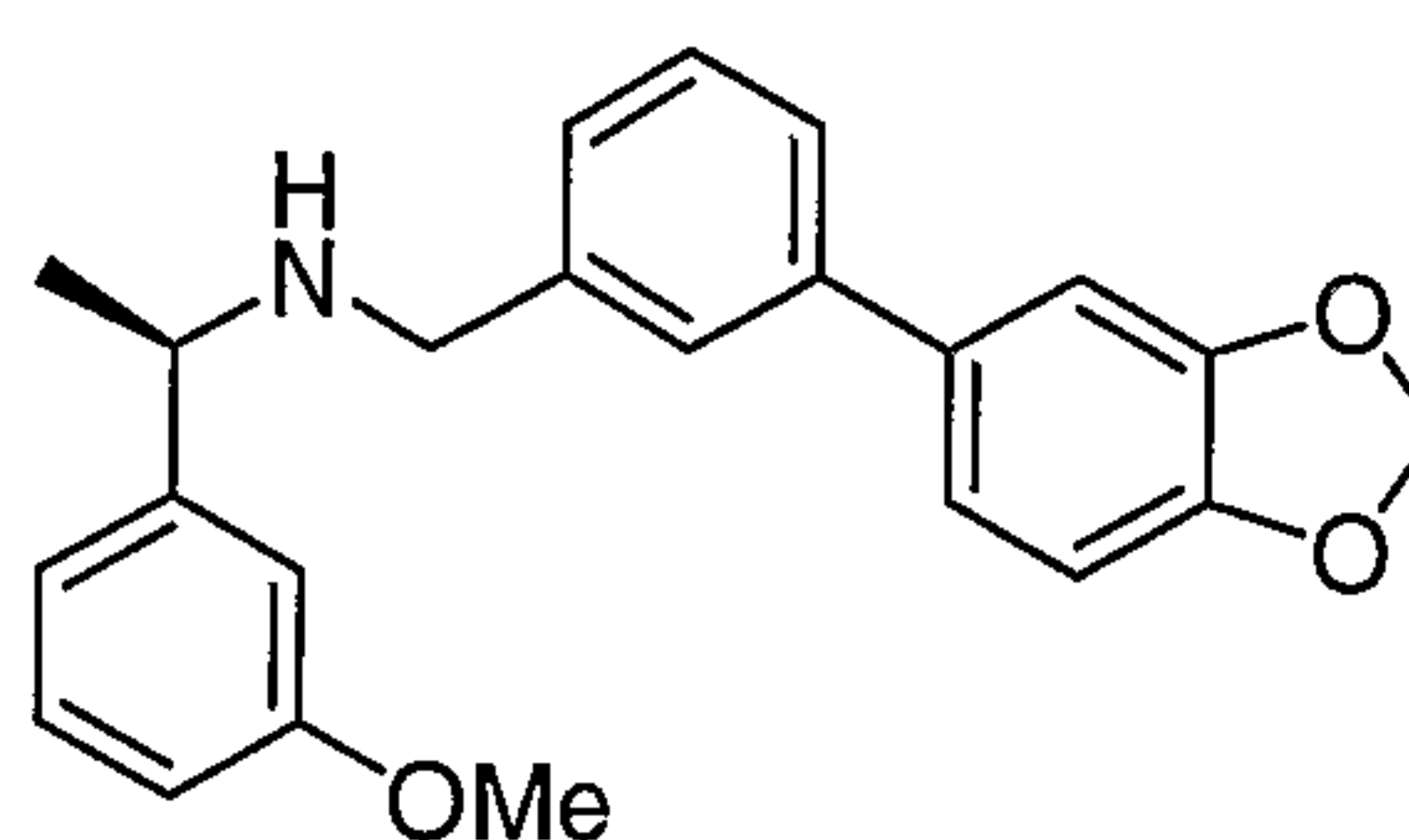
MW 361.439
Mass found: 362

5

Example 124

(1R)-N-((3-(1,3-benzodioxol-5-yl)phenyl)methyl)-1-(4-(methyloxy)phenyl)ethanamine

10



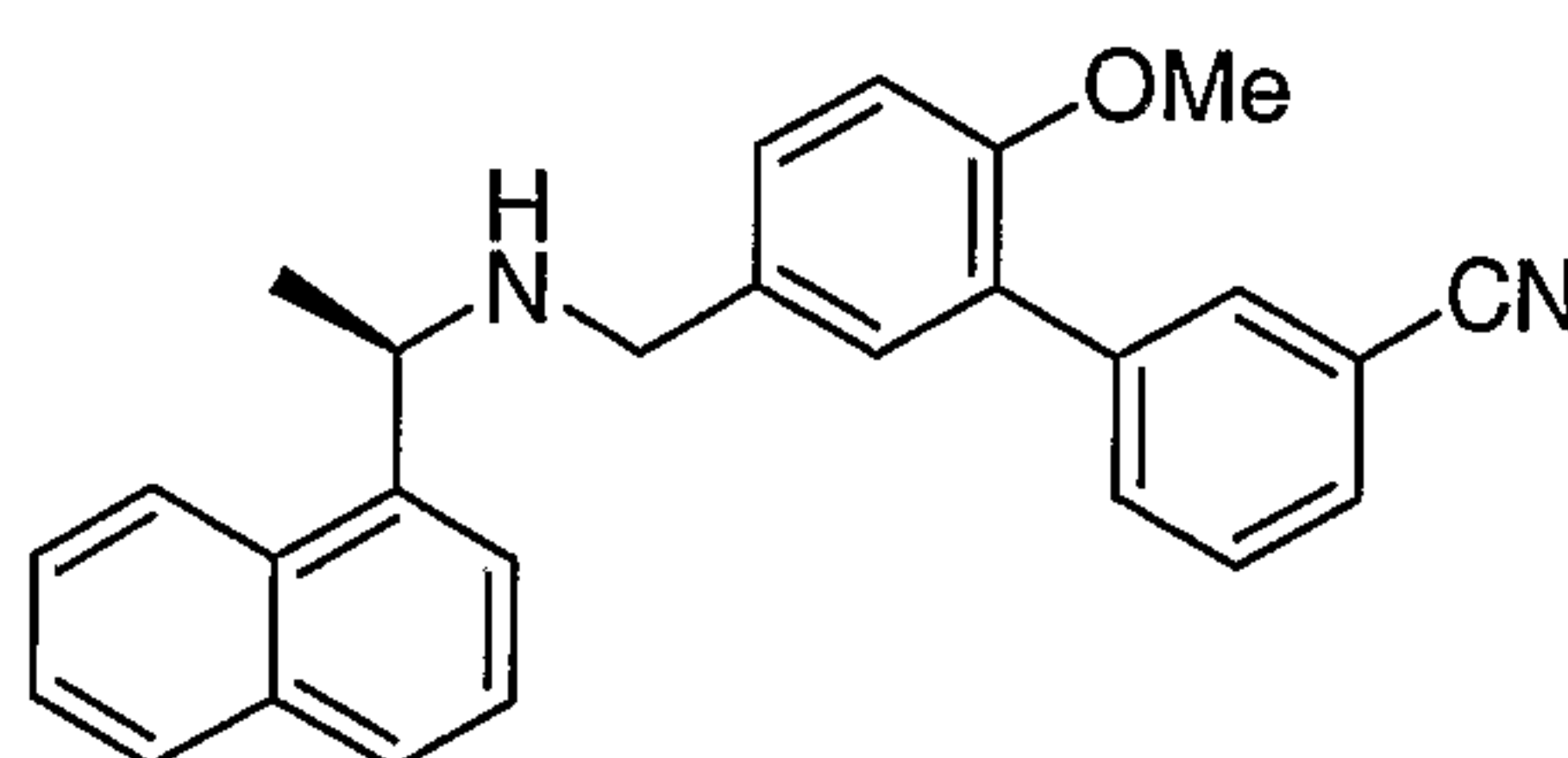
MW 361.439
Mass found: 362

15

Example 125

2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile

20



MW 392.5
Mass found: 393

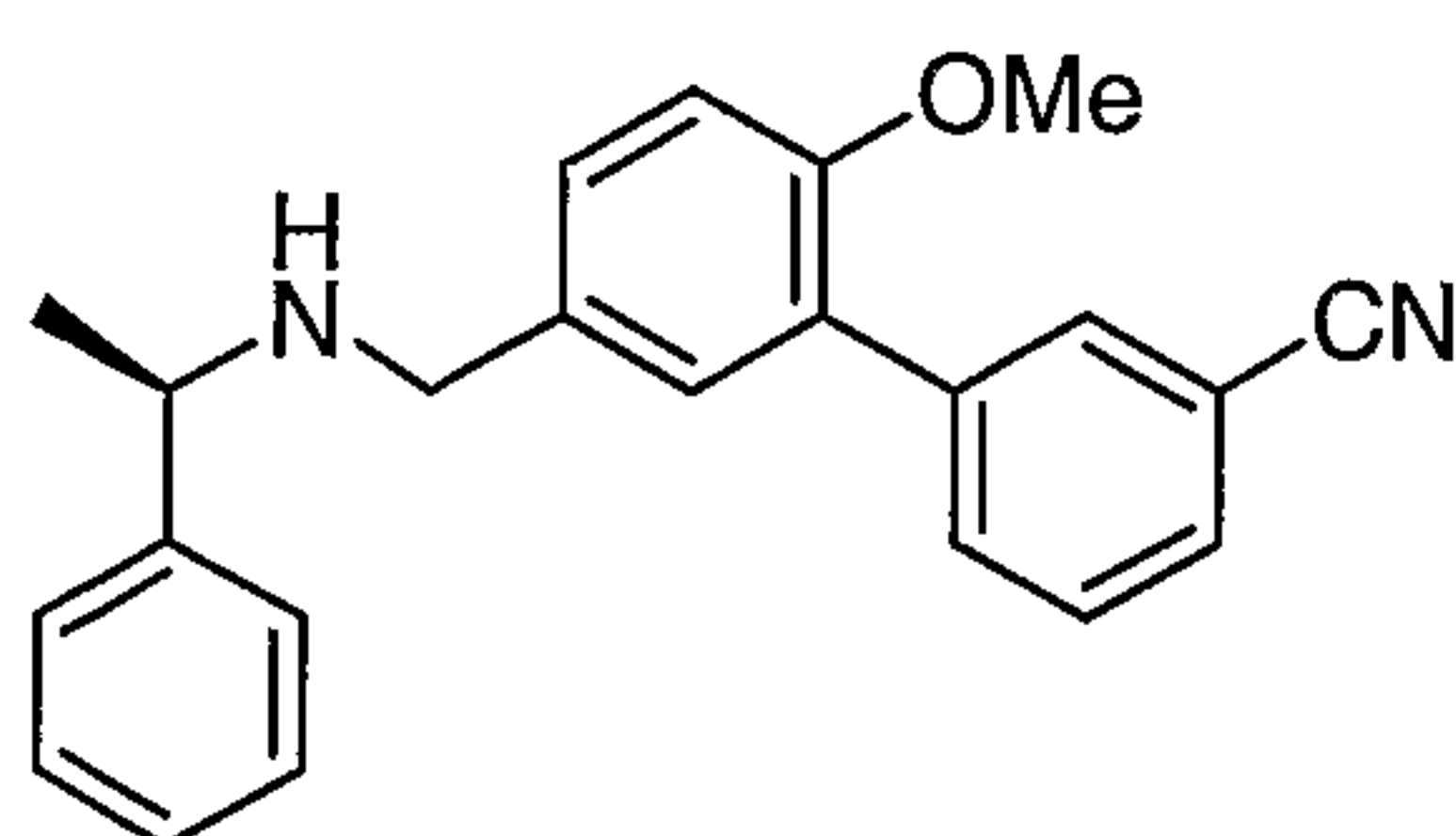
25

Example 126

2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile

30

- 135 -



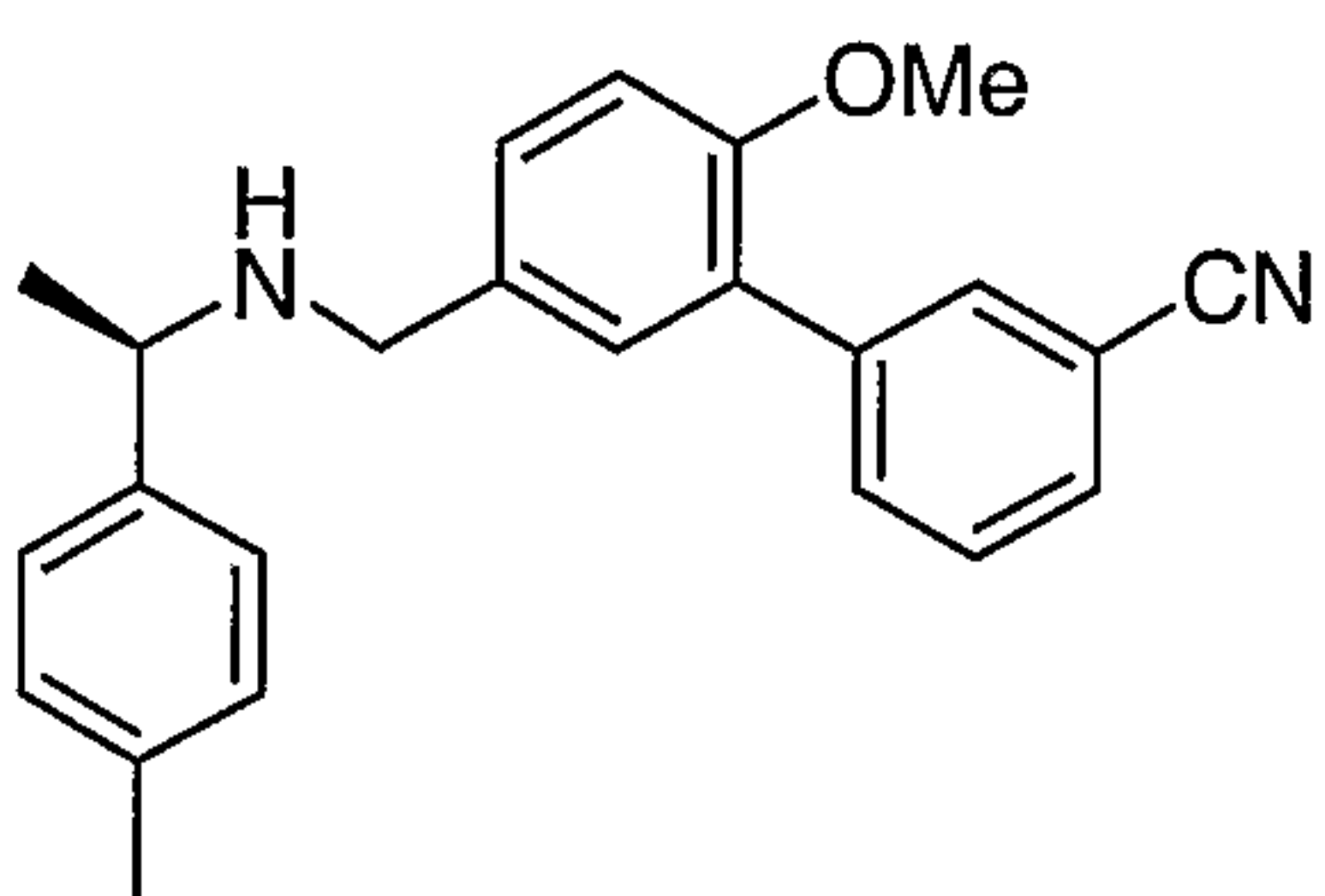
MW 342.44

Mass found: 343, 384

5

Example 127

10 2'-(methyloxy)-5'-((((1R)-1-(4-methylphenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile



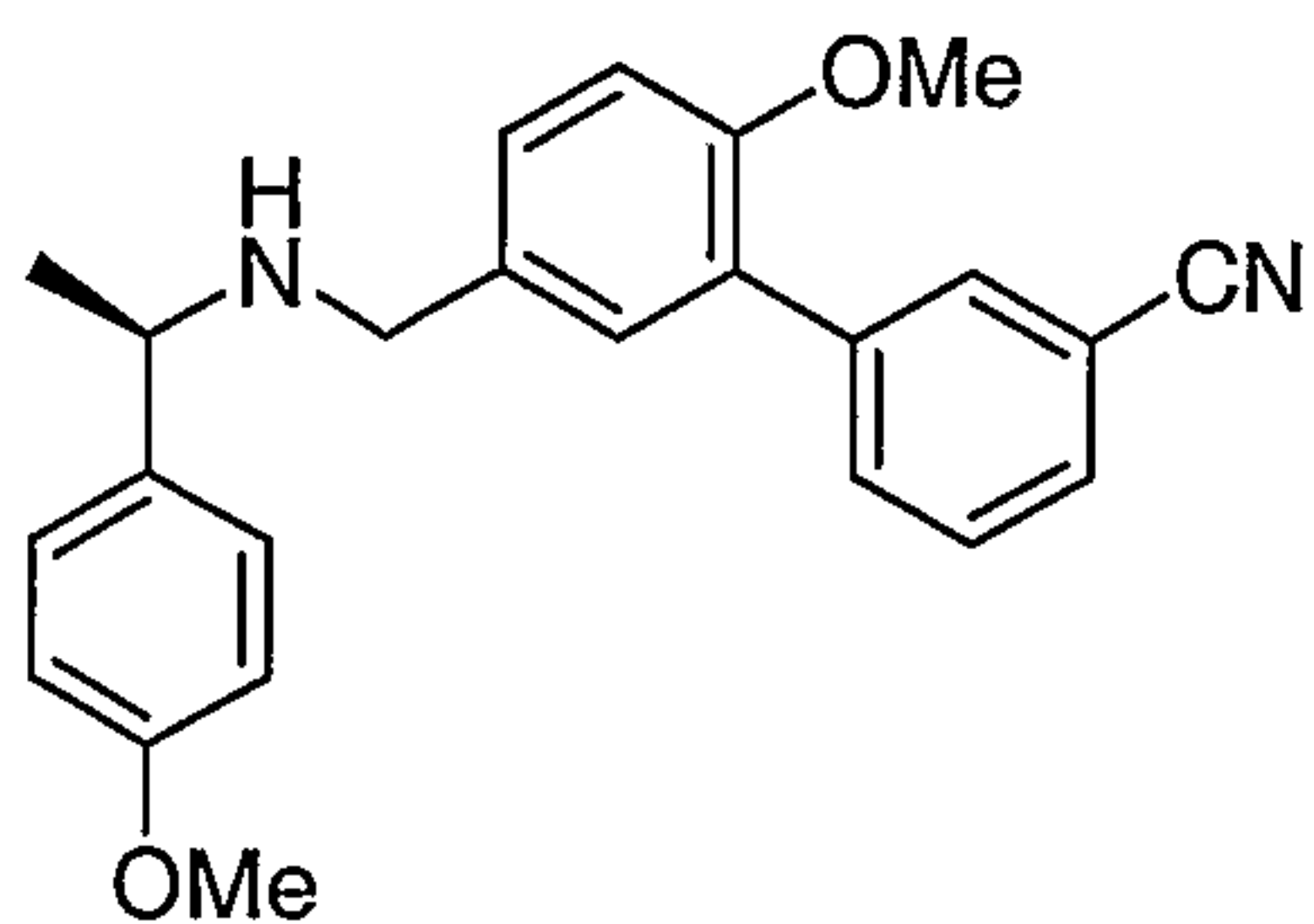
MW 356.467

Mass found: 357, 398

15

Example 128

20 2'-(methyloxy)-5'-((((1R)-1-(4-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile



MW 372.466

Mass found: 373, 414

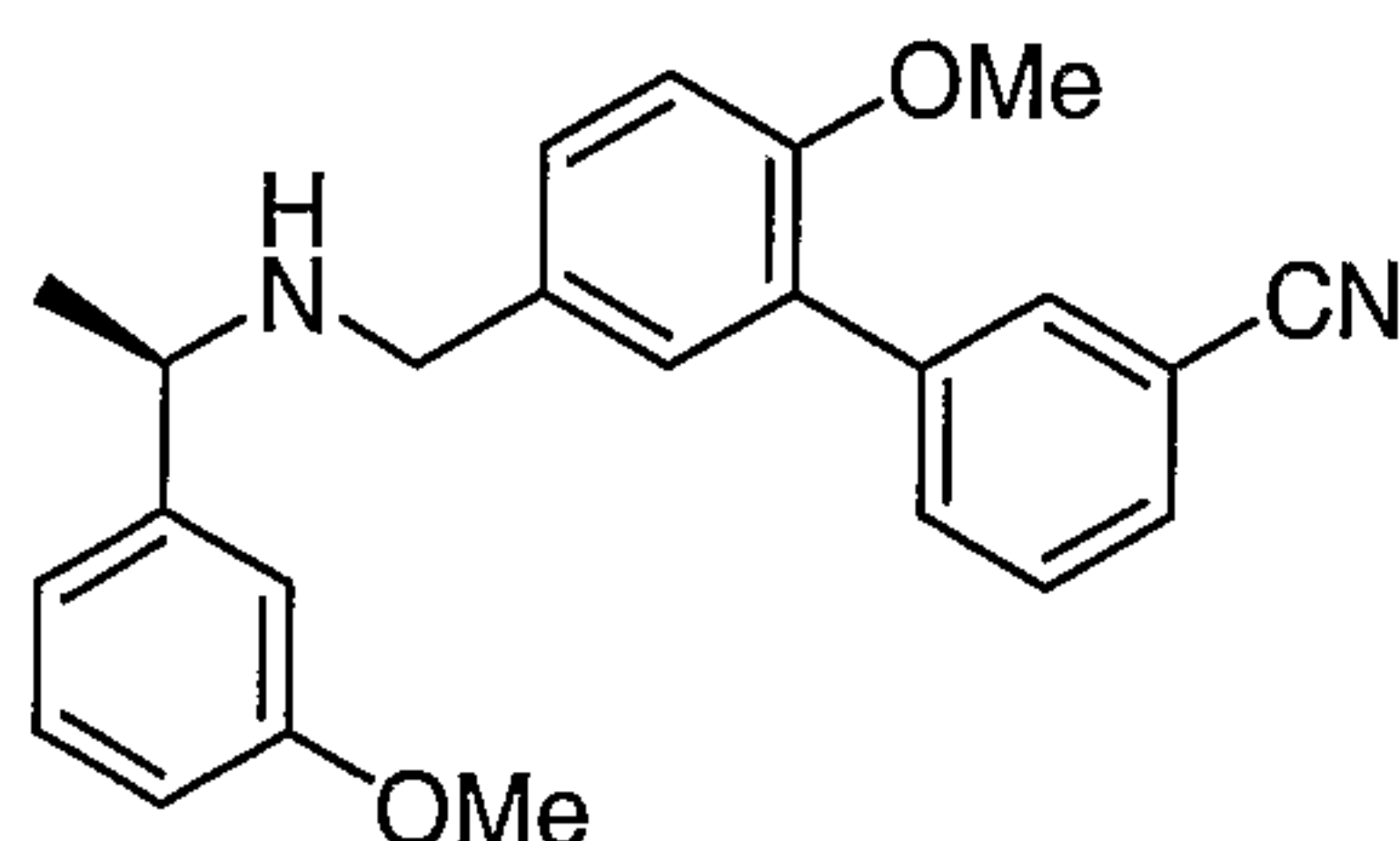
25

30

Example 129

- 136 -

2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile



5

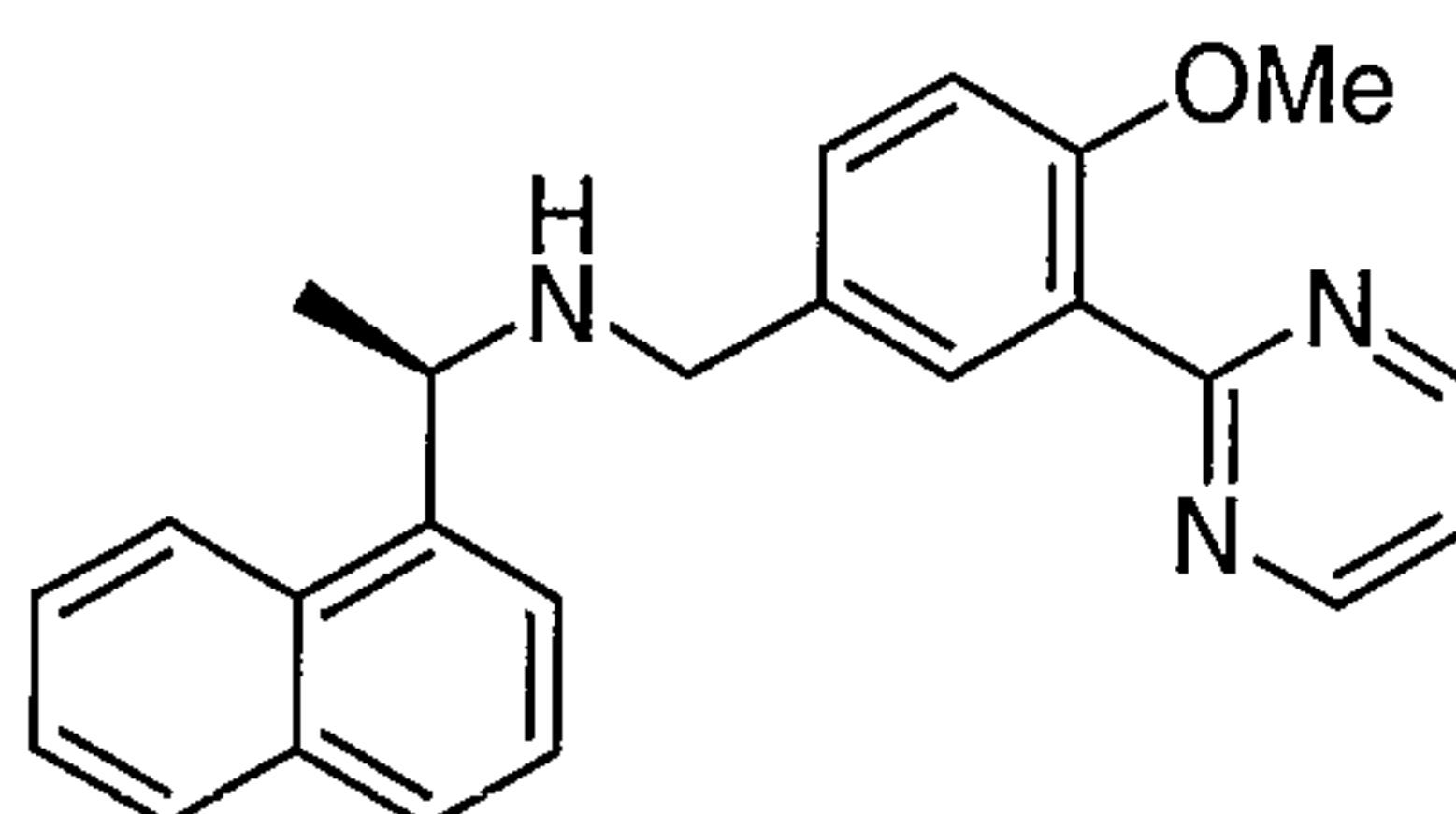
MW 372.466
Mass found: 373, 414

10

Example 130

(1R)-N-((4-(methyloxy)-3-(2-pyrimidinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

15



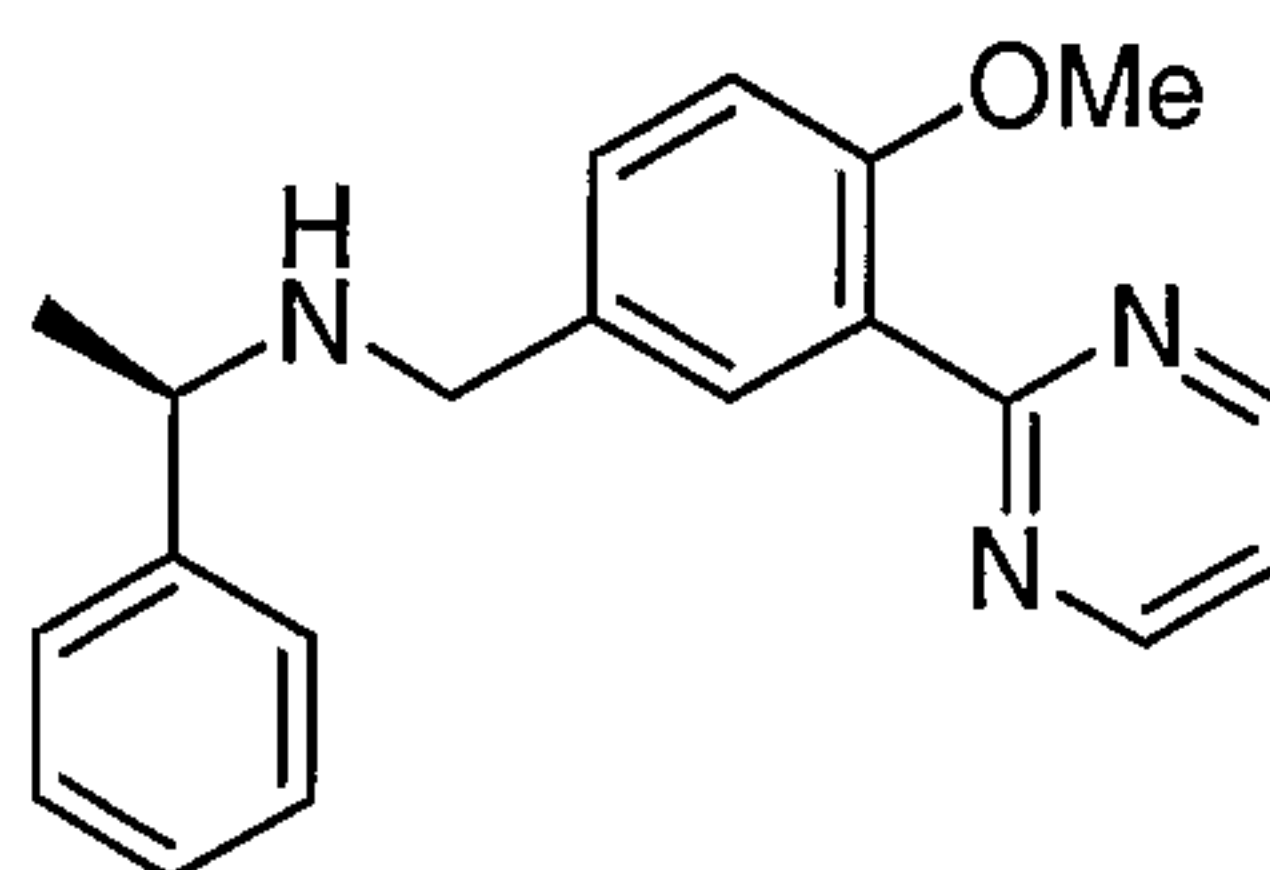
20

MW 369.466
Mass found: 370, 739

Example 131

(1R)-N-((4-(methyloxy)-3-(2-pyrimidinyl)phenyl)methyl)-1-phenylethanamine

25



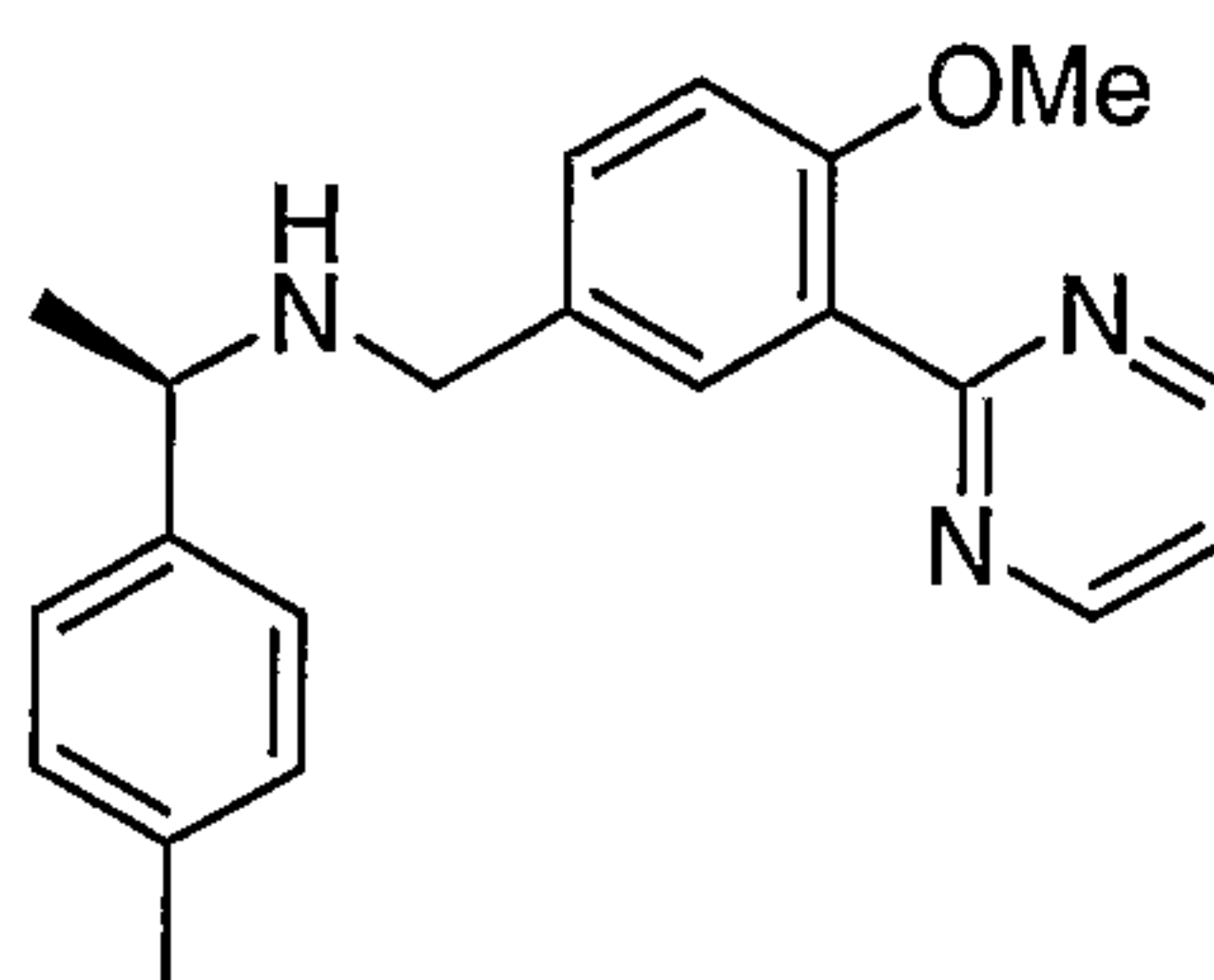
30

MW 319.406
Mass found: 320

Example 132

- 137 -

(1R)-N-((4-(methyloxy)-3-(2-pyrimidinyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine



5

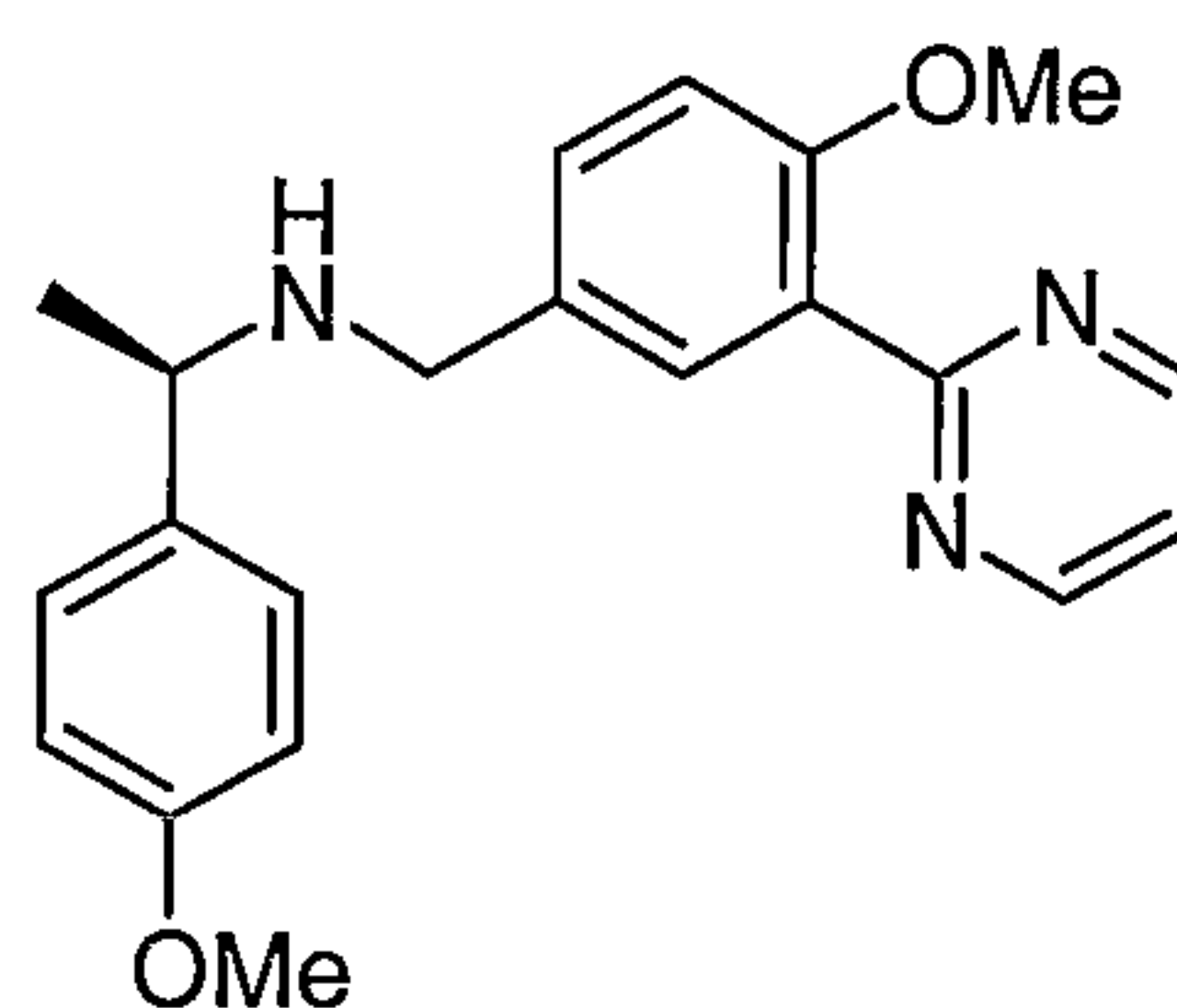
MW 333.433
Mass found: 334, 667

10

Example 133

(1R)-1-(4-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-pyrimidinyl)phenyl)methyl)ethanamine

15



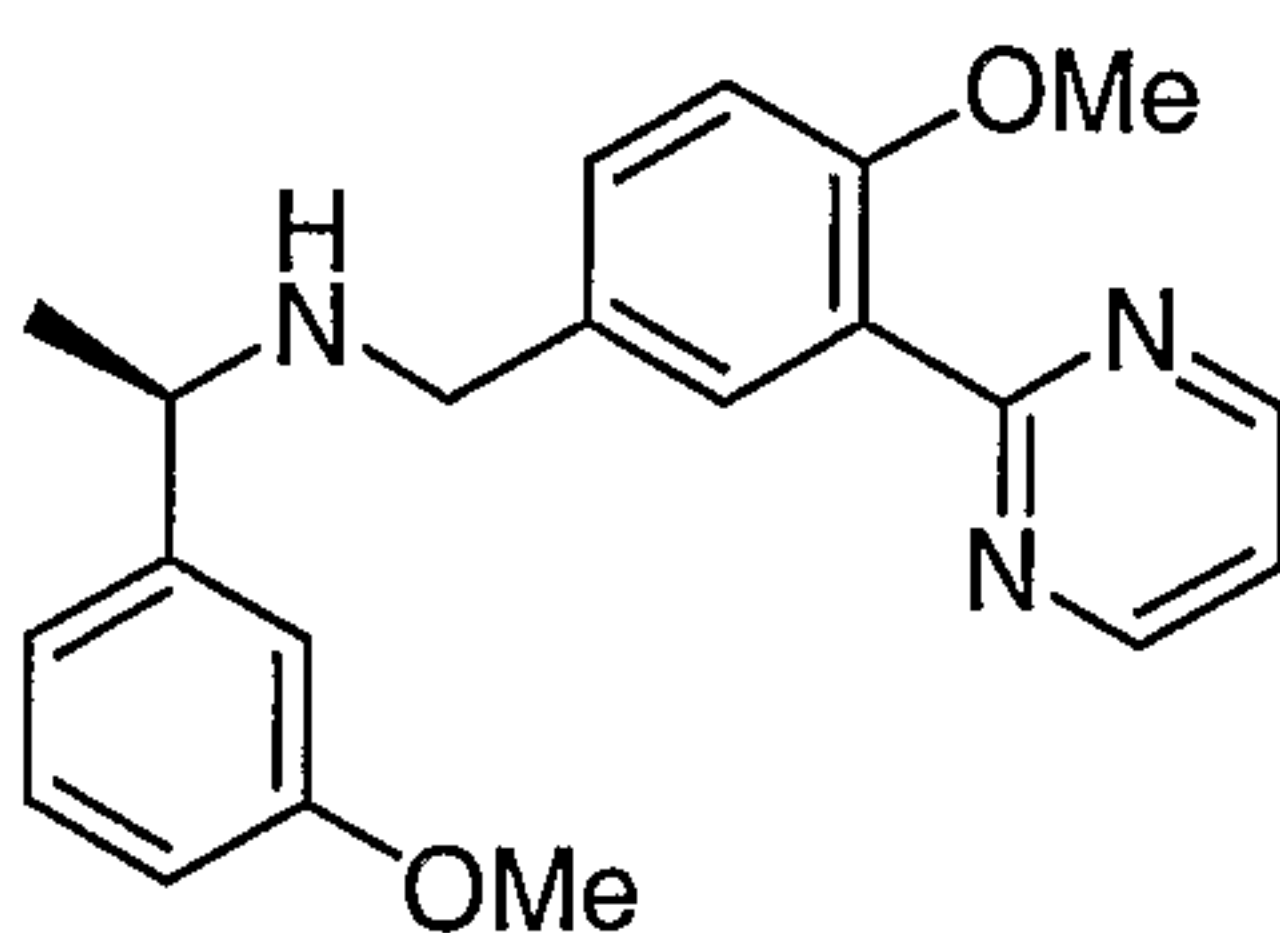
MW 349.432
Mass found: 350, 699

20

Example 134

(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-pyrimidinyl)phenyl)methyl)ethanamine

25



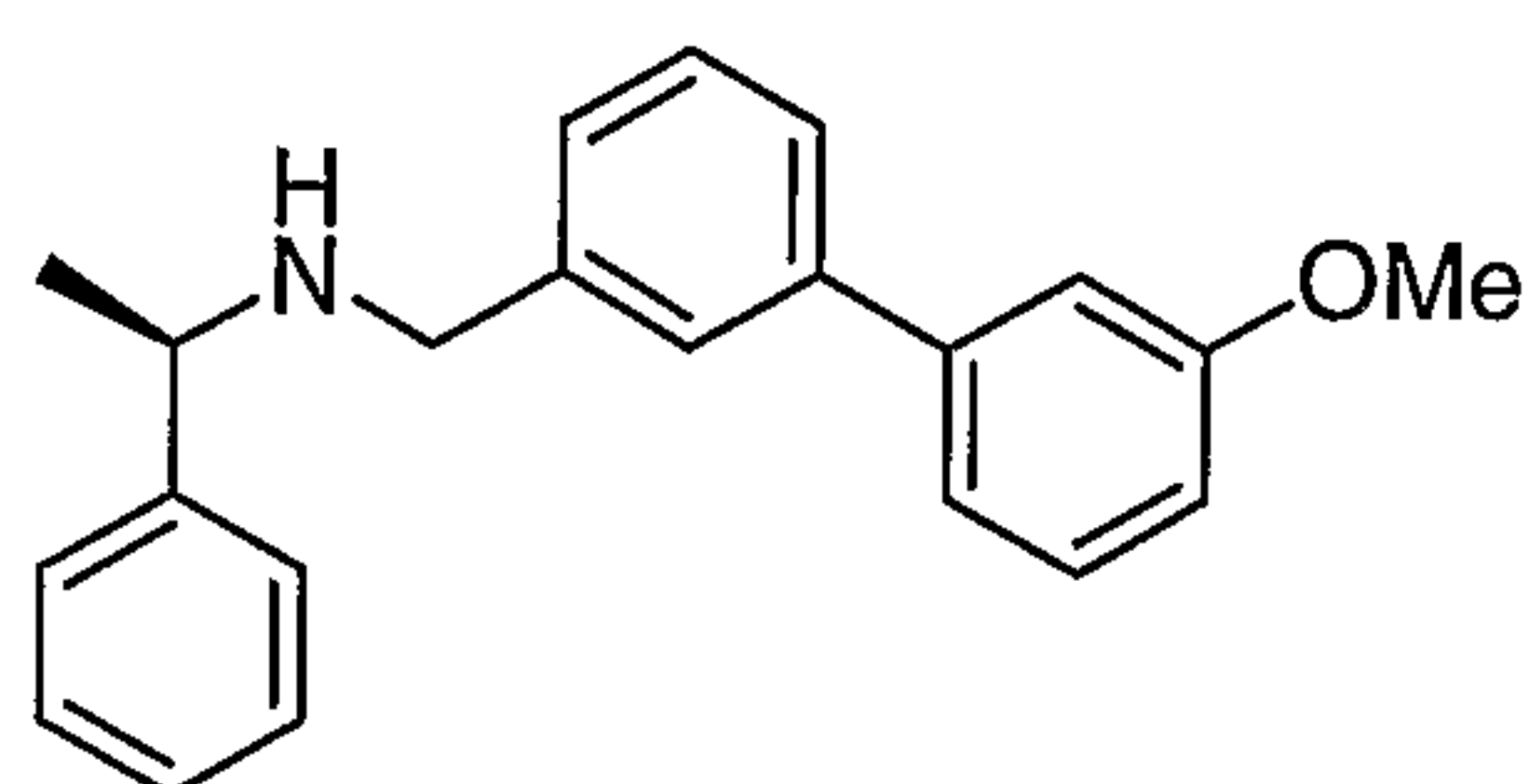
MW 349.432
Mass found: 350, 699

30

- 138 -

Example 135

5 (1R)-N-((3'-(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine



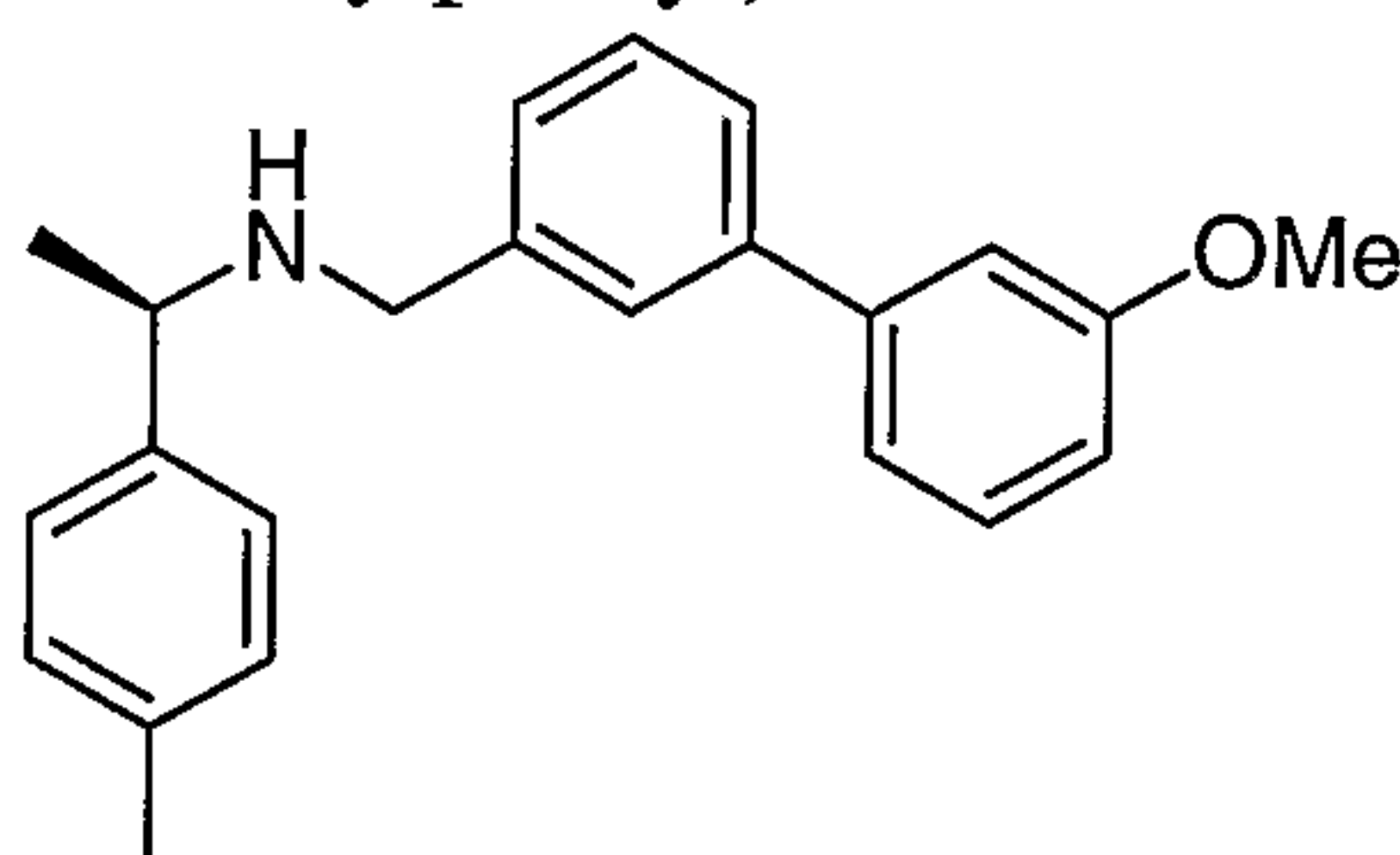
MW 317.43

Mass found: 318, 197, 214

10

Example 136

15 (1R)-N-((3'-(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine



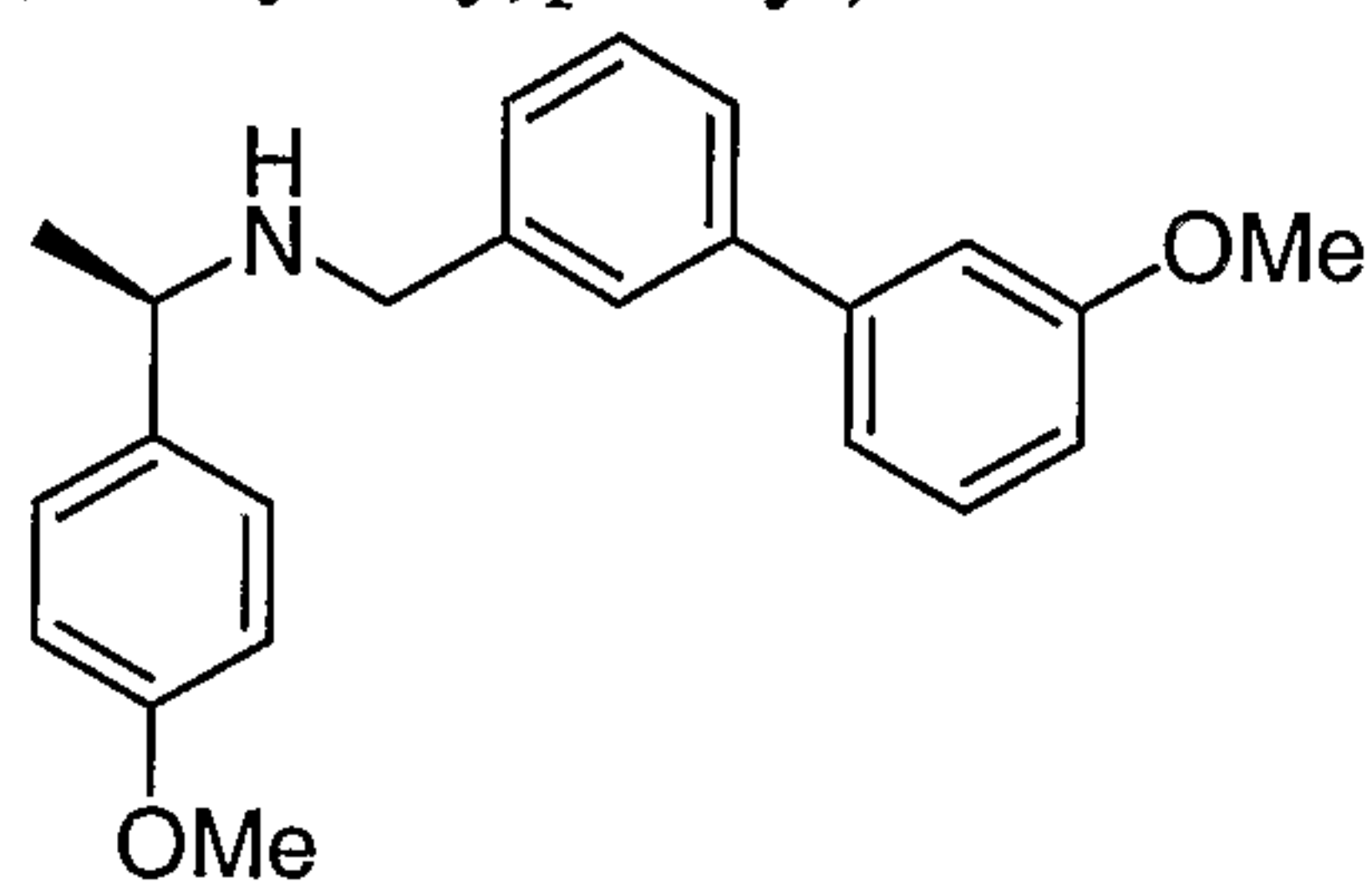
MW 331.457

Mass found: 332, 214

20

Example 137

25 (1R)-N-((3'-(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methoxy)phenyl)ethanamine



MW 347.456

Mass found: 348, 214

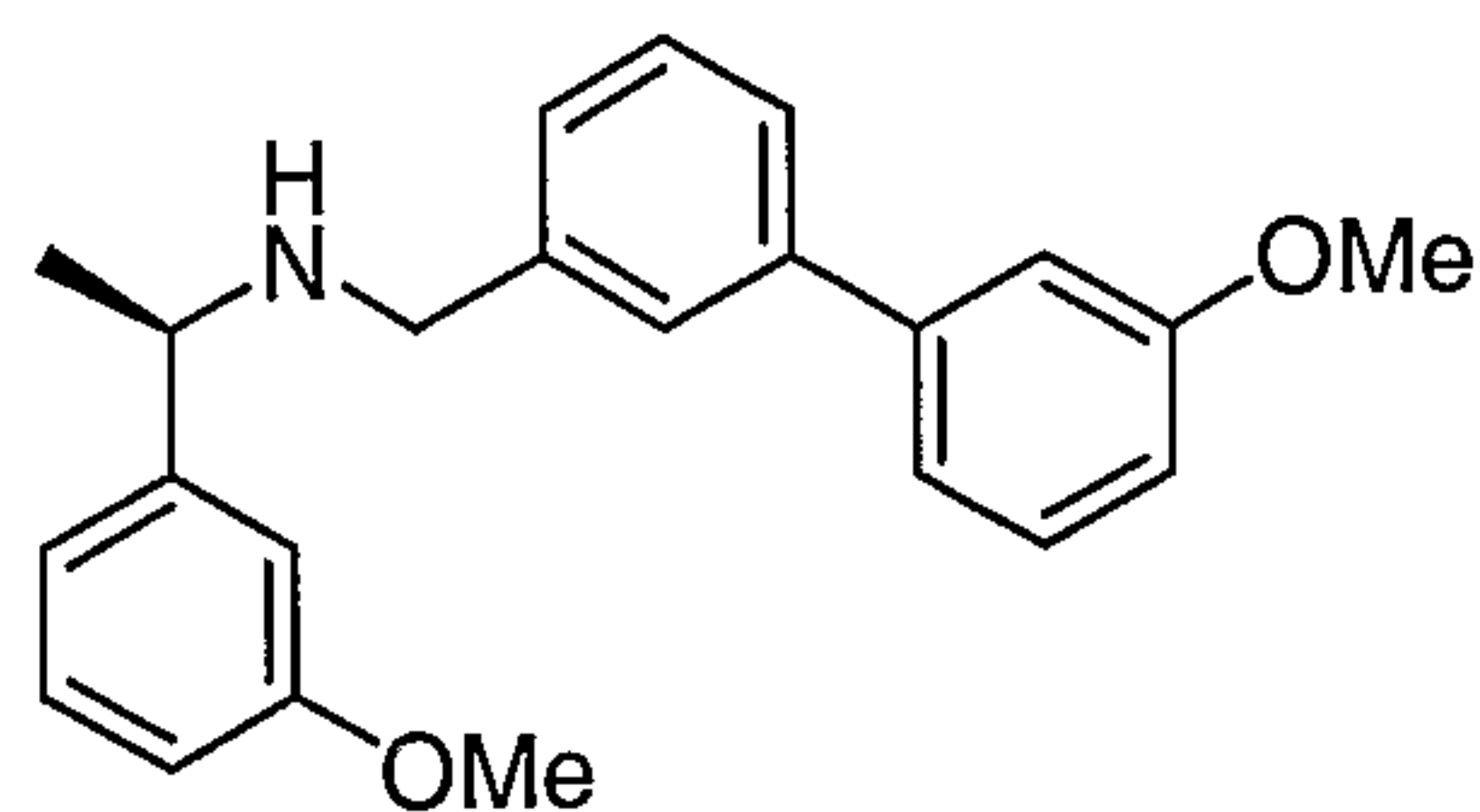
30

- 139 -

Example 138

(1R)-N-((3'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

5



MW 347.456

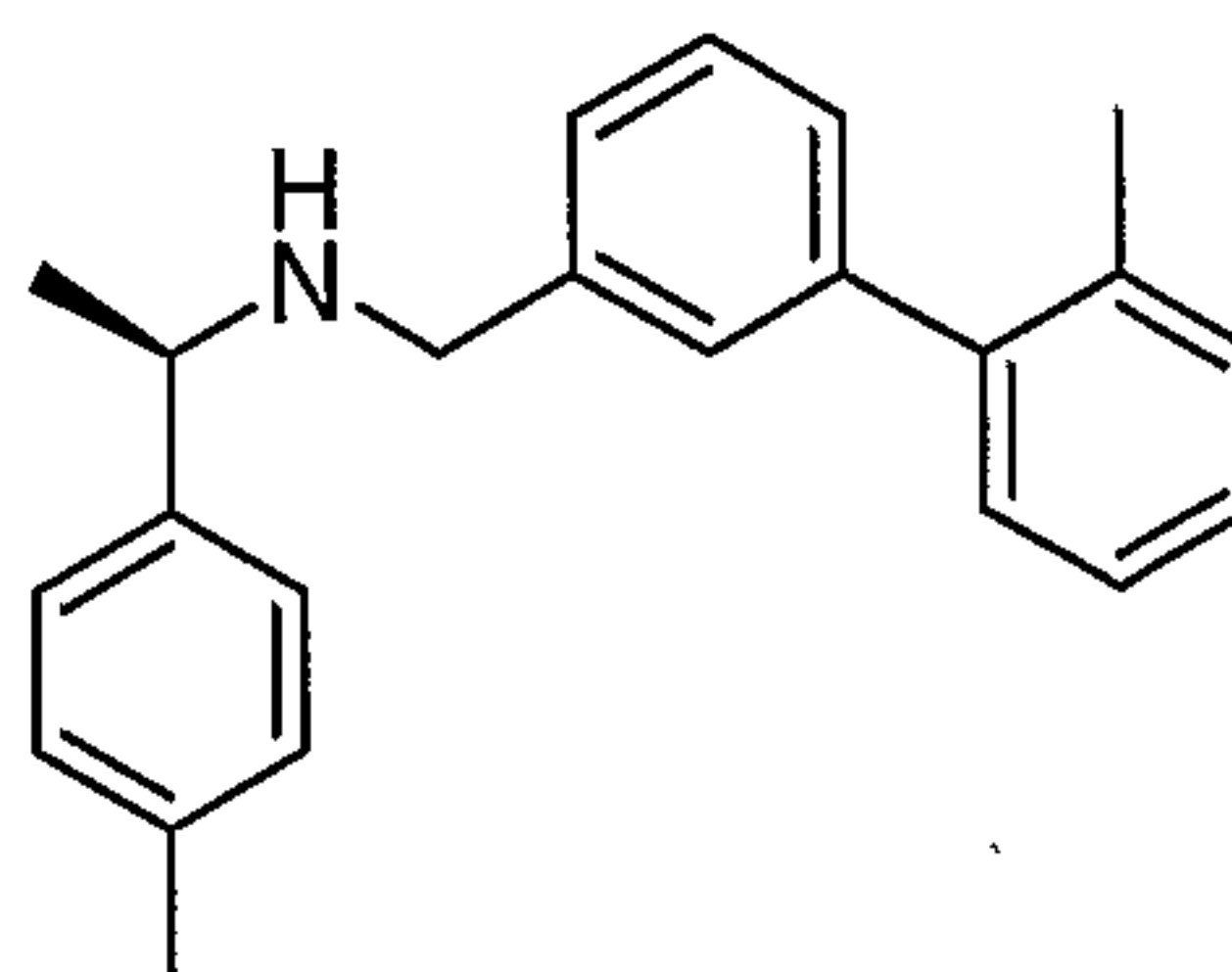
Mass found: 348, 214, 255

10

Example 139

(1R)-N-((2'-methyl-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine

15



MW 315.457

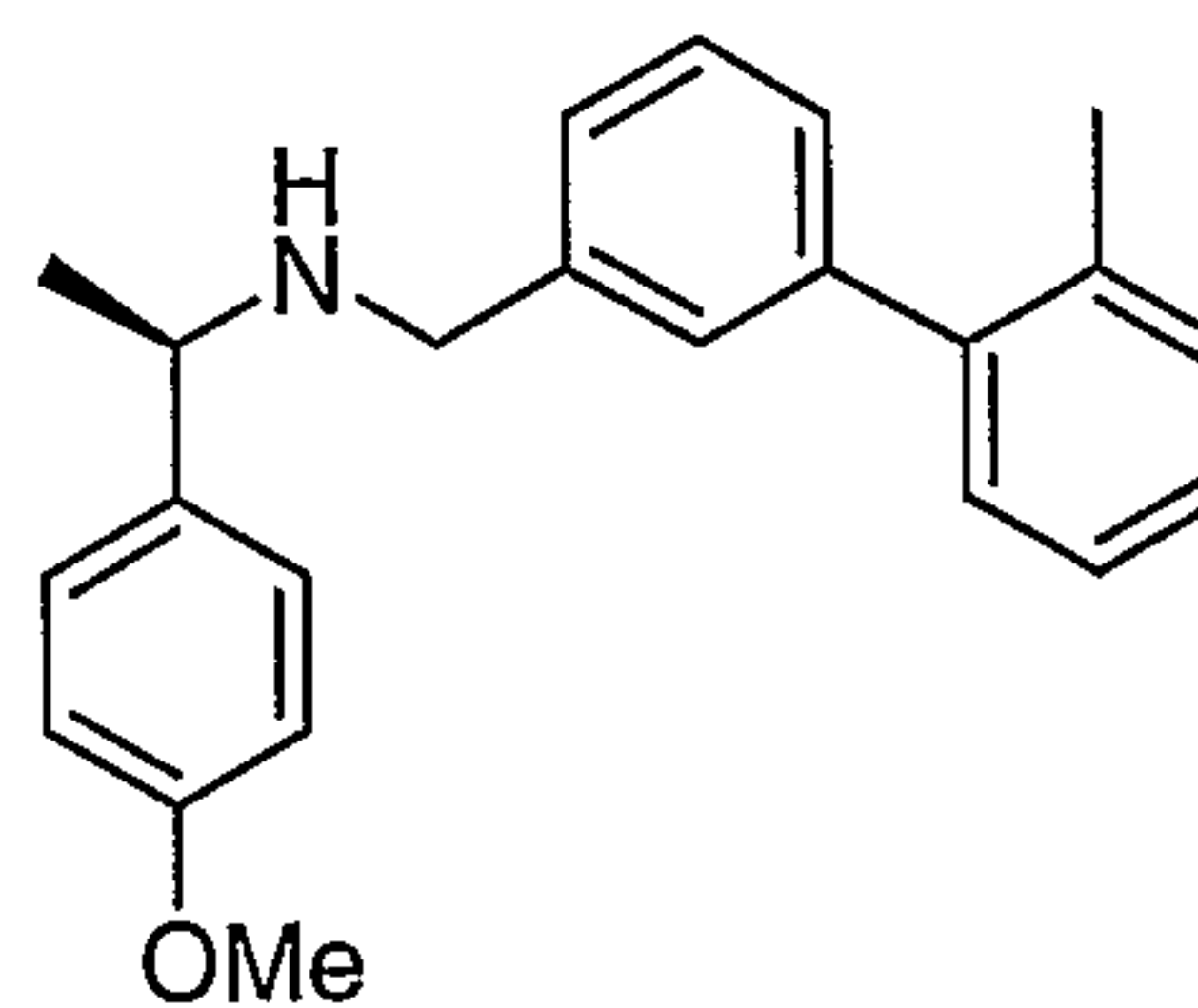
Mass found: 181, 316, 198

20

Example 140

(1R)-N-((2'-methyl-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine

25



MW 331.457

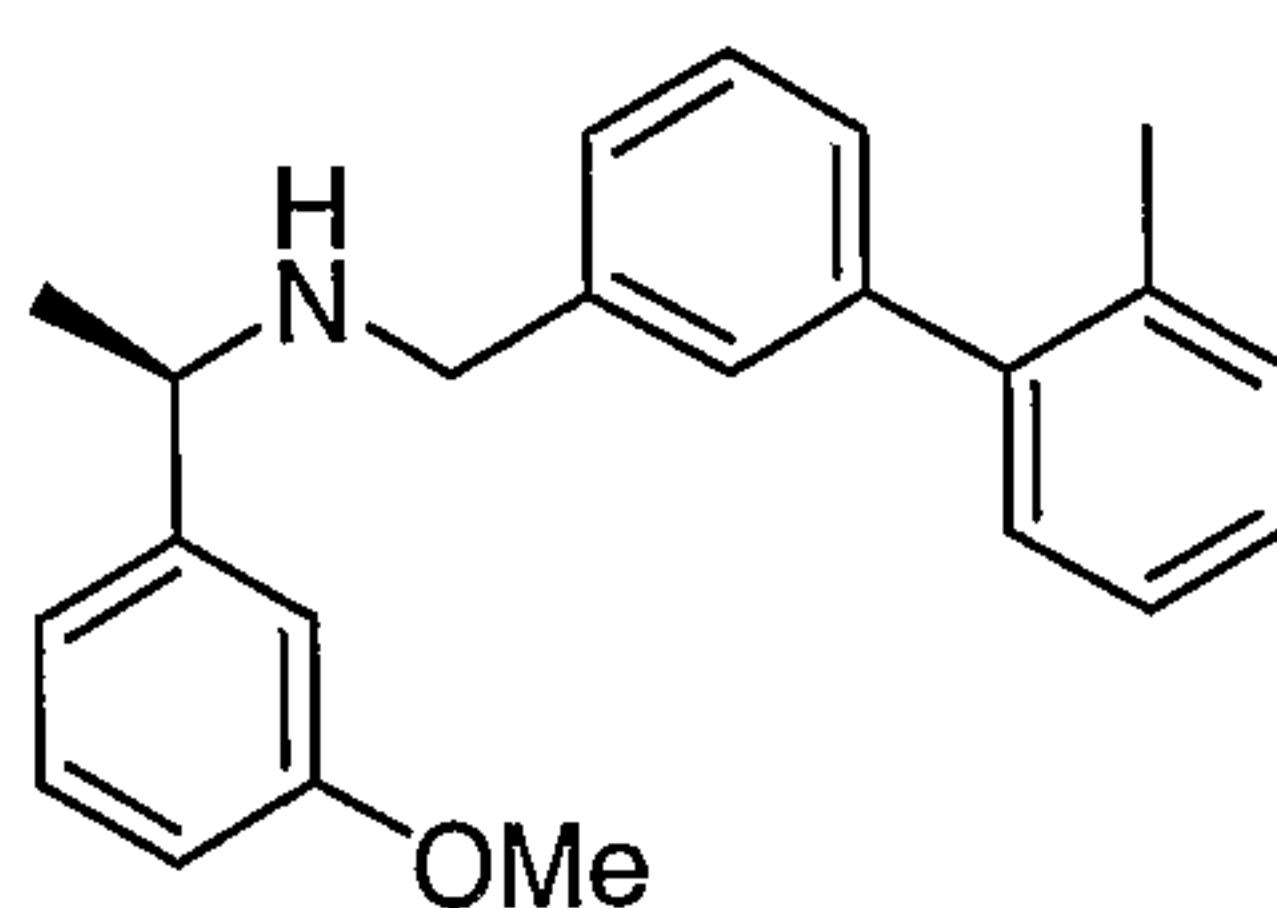
Mass found: 332, 181, 198

30

- 140 -

Example 141

(1R)-N-((2'-methyl-1,1'-biphenyl-3-yl)methyl)-1-(3-(methoxy)phenyl)ethanamine

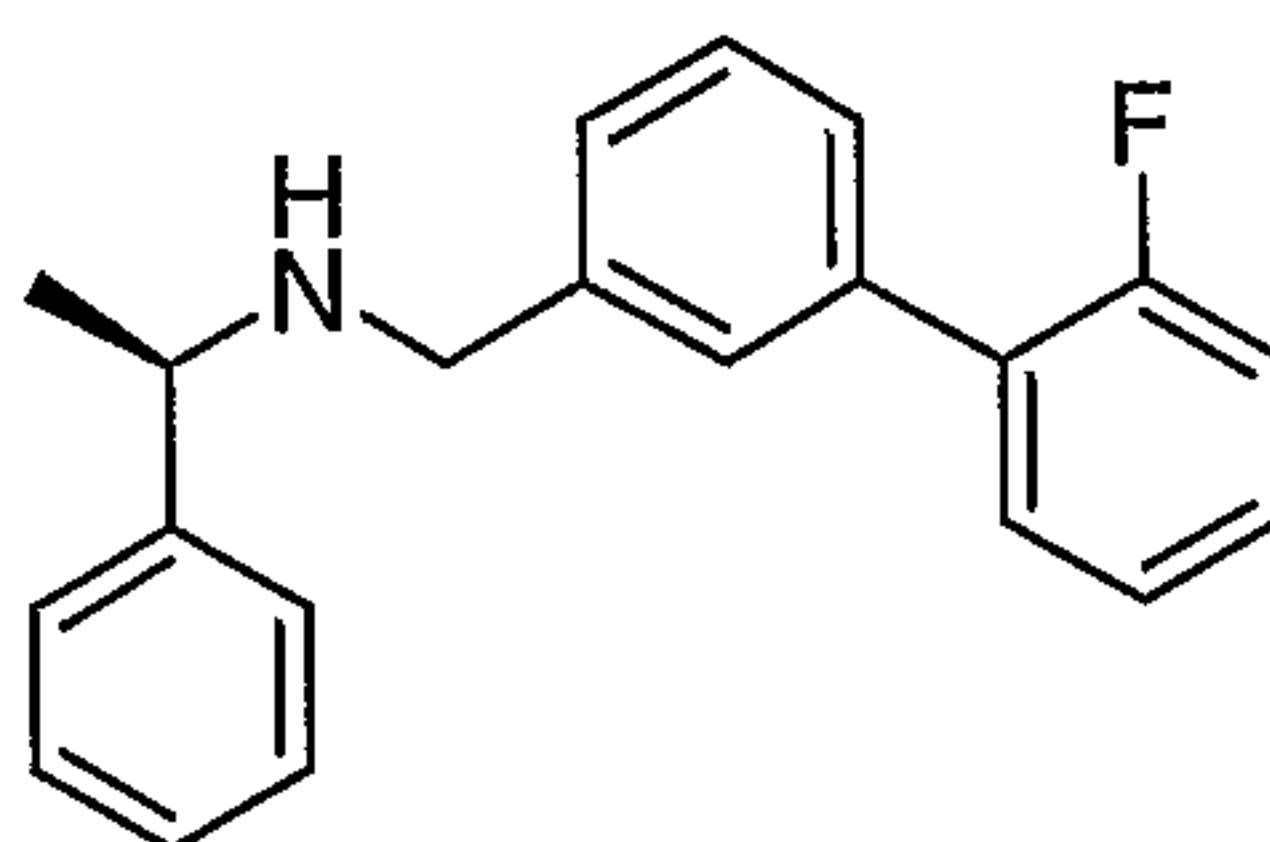


MW 331.457

Mass found: 332, 198, 181

Example 142

(1R)-N-((2'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

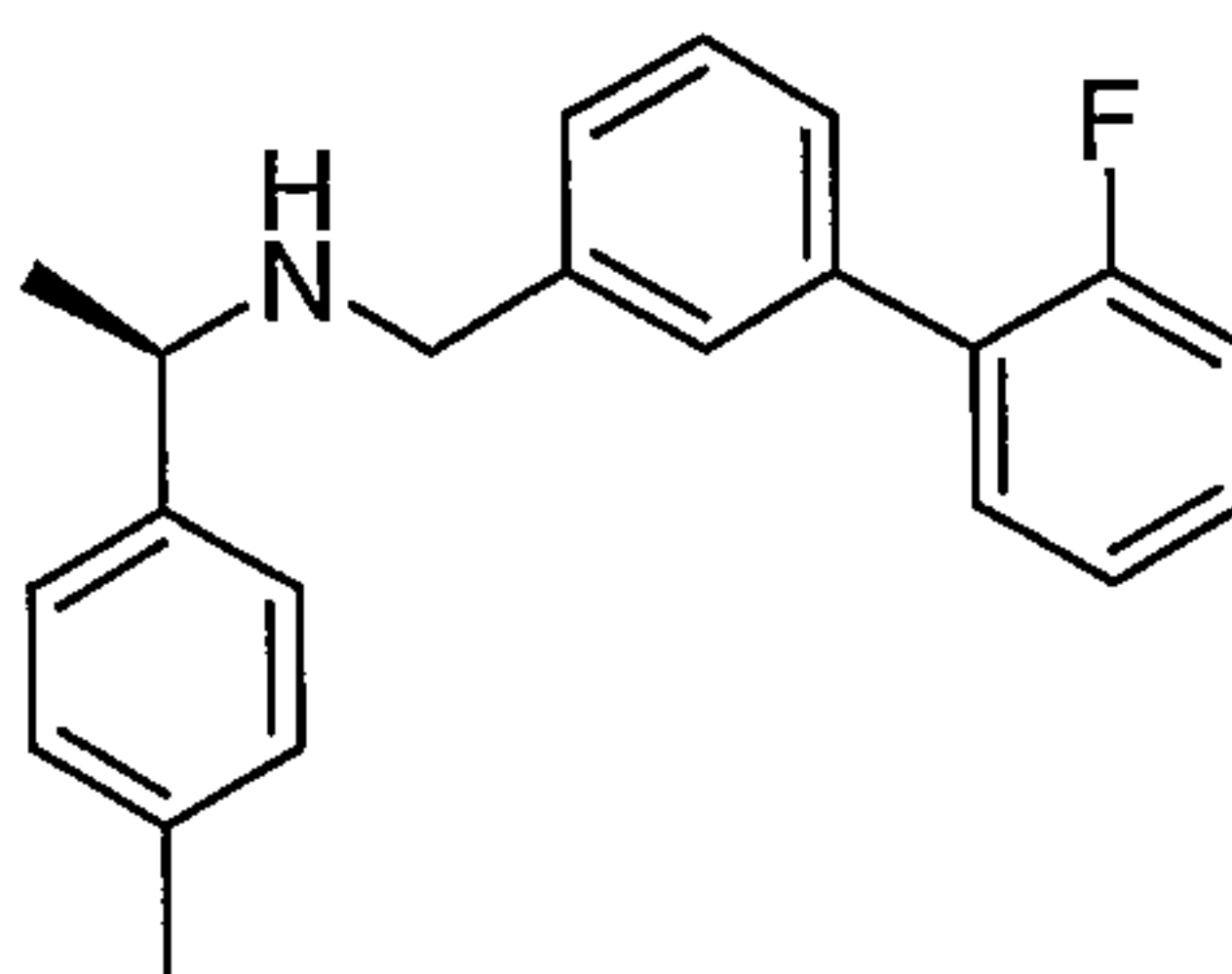


MW 305.394

Mass found: 202, 306, 243

Example 143

(1R)-N-((2'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine



MW 319.421

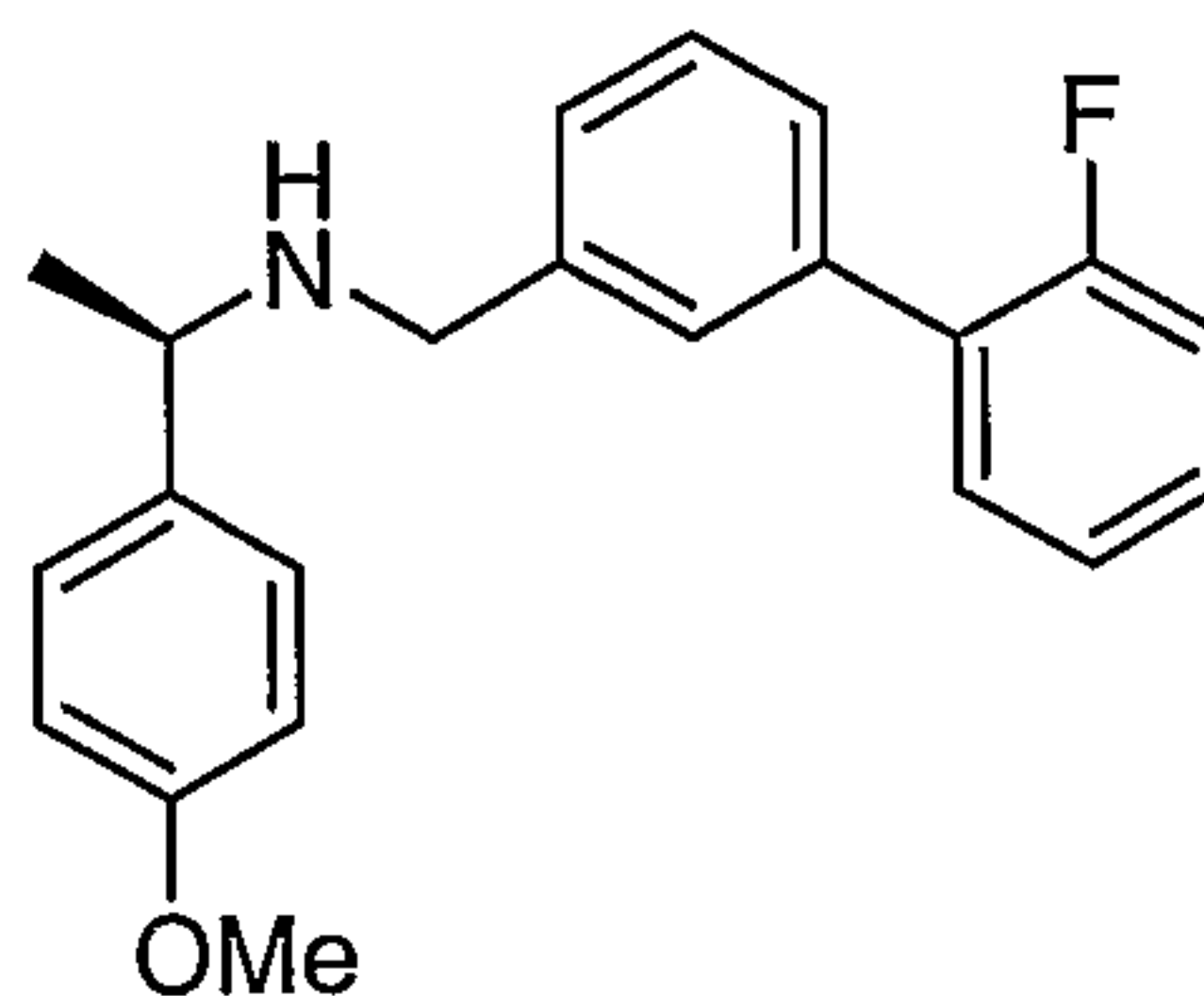
Mass found: 202, 320, 243

- 141 -

Example 144

(1R)-N-((2'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-(methoxy)phenyl)ethanamine

5



MW 335.42

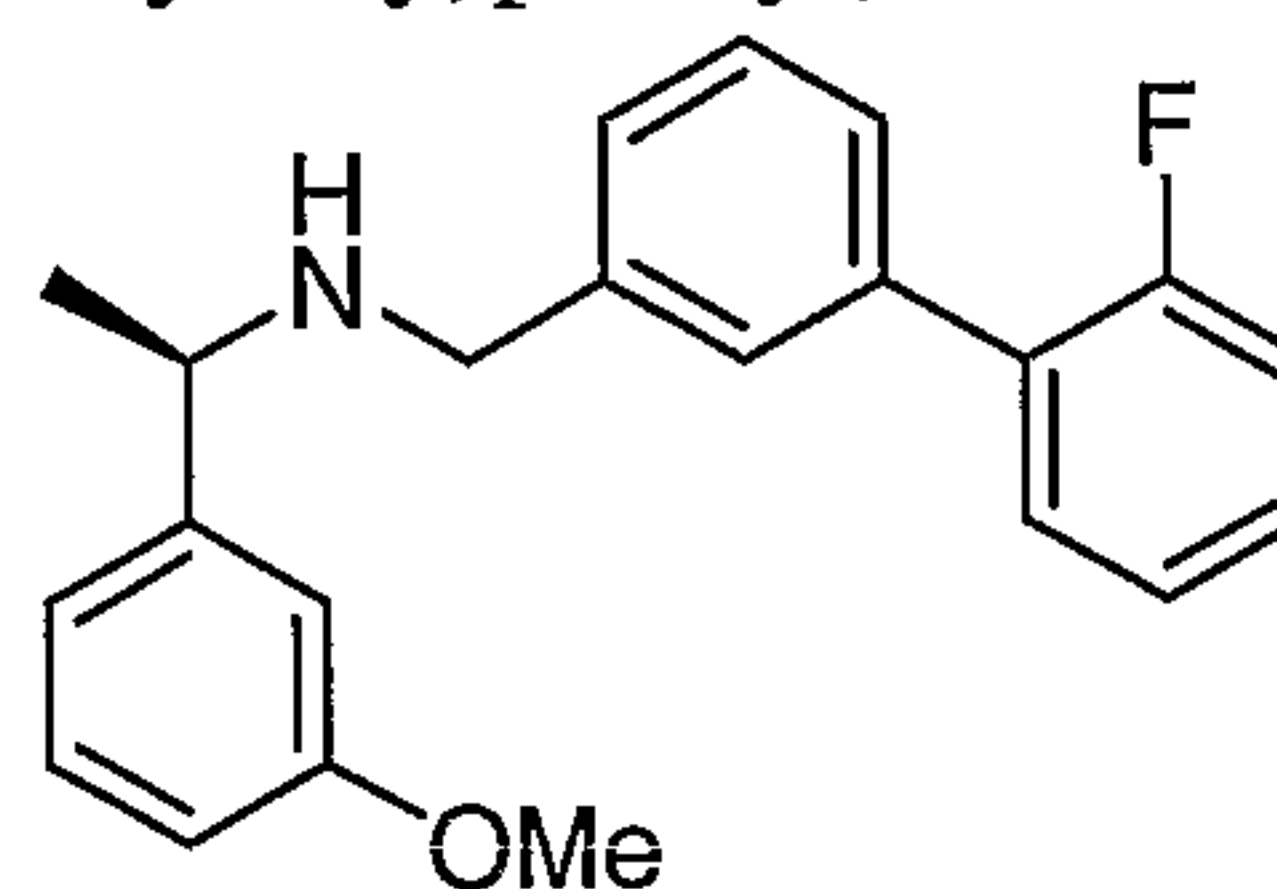
Mass found: 336, 202, 243

10

Example 145

(1R)-N-((2'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(3-(methoxy)phenyl)ethanamine

15



MW 335.42

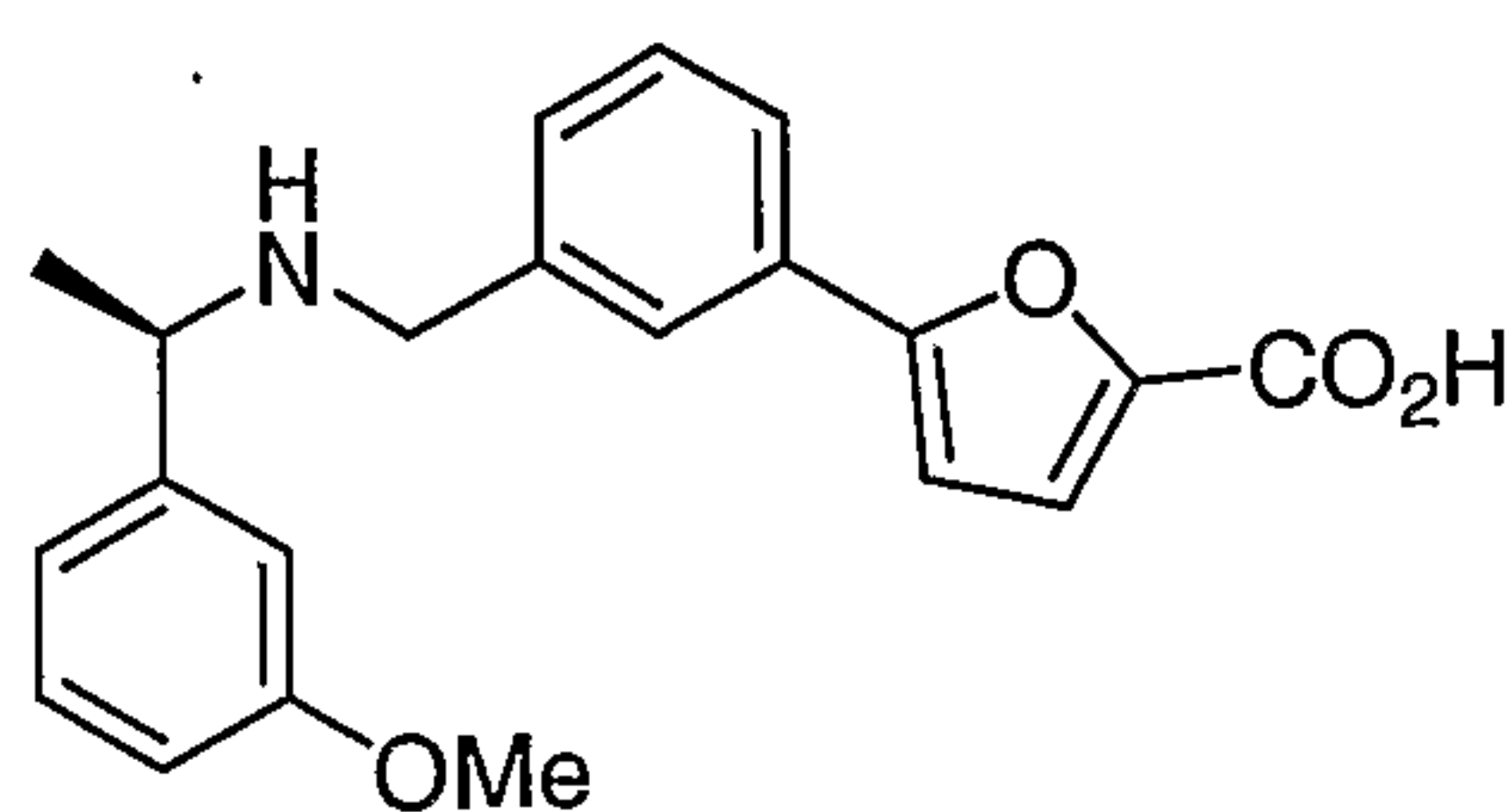
Mass found: 202, 336, 243

20

Example 146

5-(2-(methoxy)-5-((((1R)-1-(3-(methoxy)phenyl)ethyl)amino)methyl)phenyl)-2-furancarboxylic acid

25



MW 381.426

Mass found: 382, 423

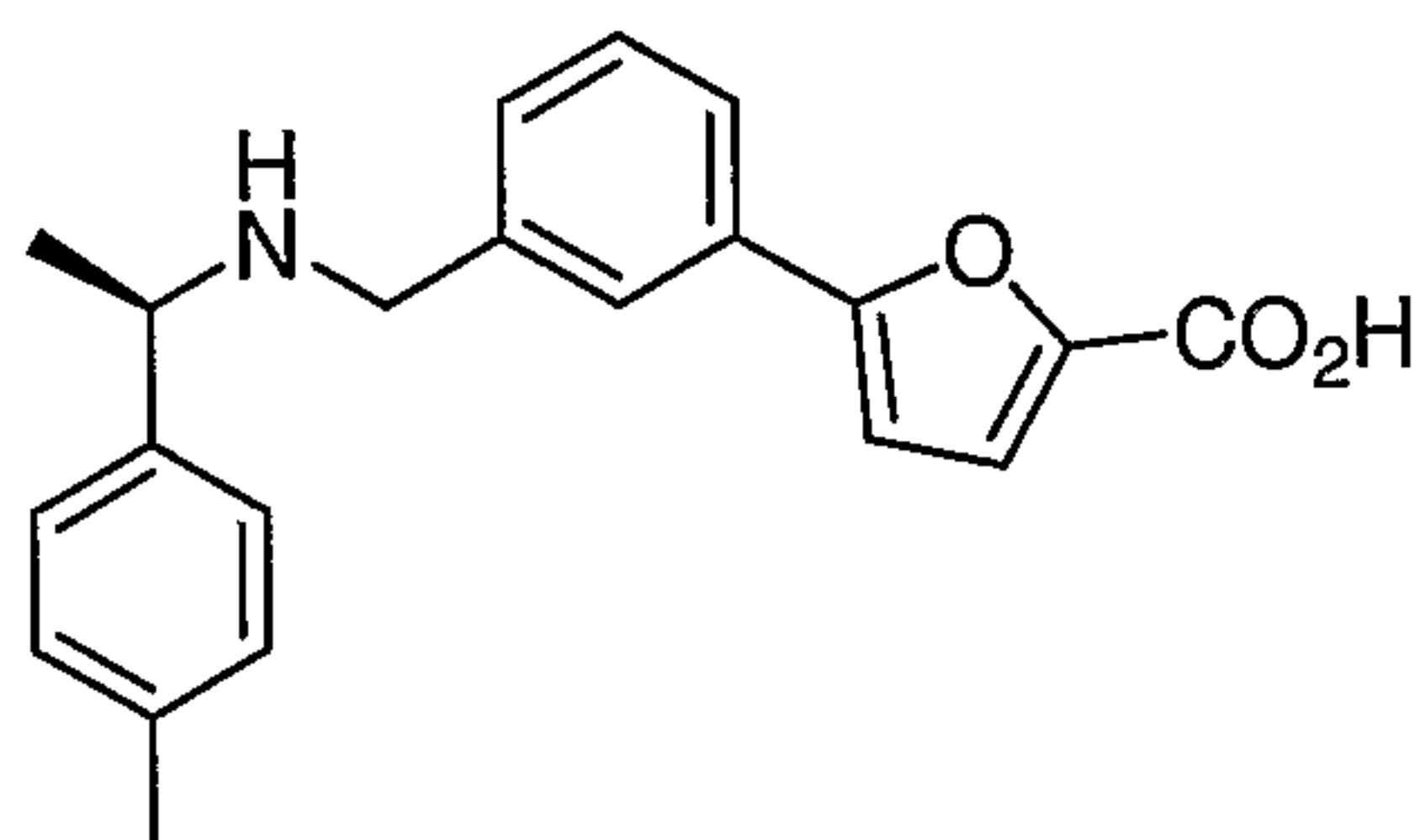
30

- 142 -

Example 147

5-(2-(methyloxy)-5-((((1R)-1-(4-methylphenyl)ethyl)amino)methyl)phenyl)-2-furancarboxylic acid

5



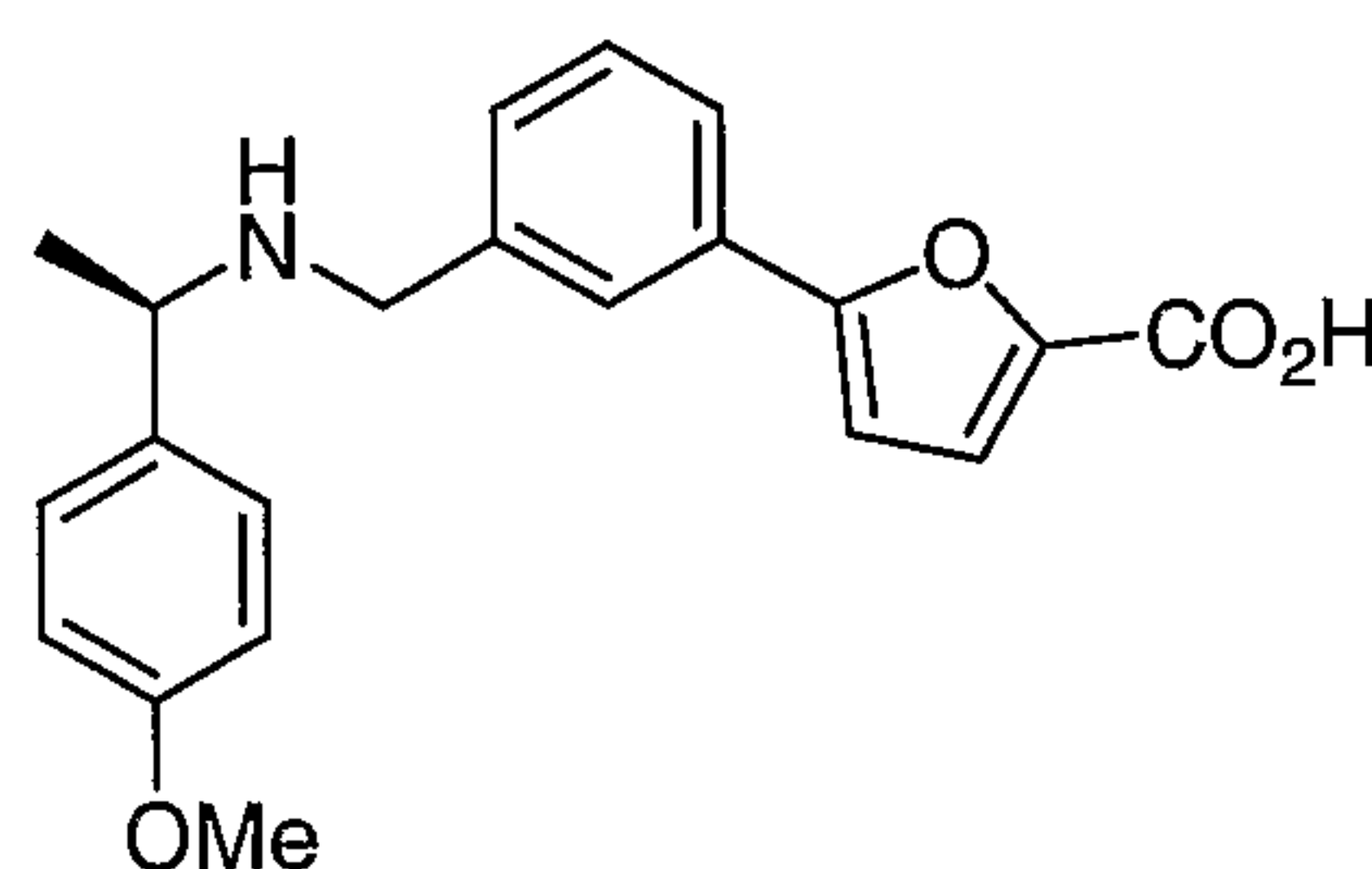
MW 365.427
Mass found: 366, 731

10

Example 148

5-(2-(methyloxy)-5-((((1R)-1-(4-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2-furancarboxylic acid

15



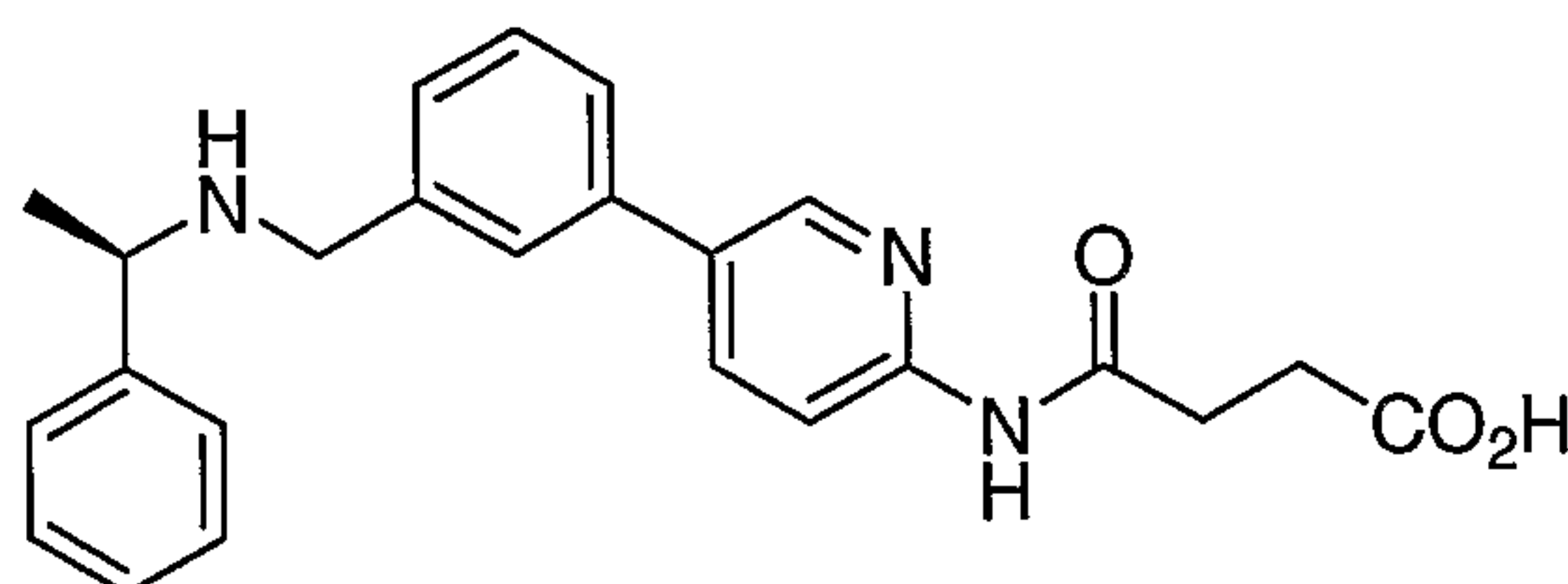
MW 381.426
Mass found: 352, 393

20

Example 149

4-oxo-4-((5-(3-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinyl)amino)butanoic acid

25



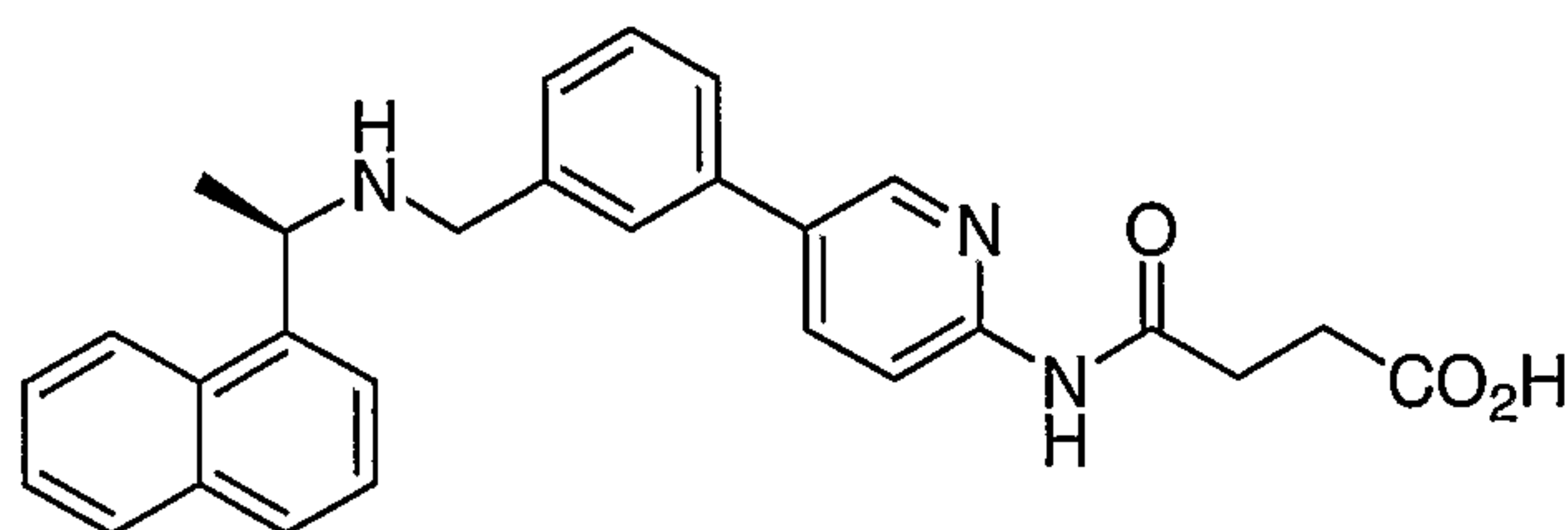
MW 403.479
Mass found: 404, 300

30

- 143 -

Example 150

5 4-((5-(3-(((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-2-pyridinyl)amino)-4-oxobutanoic acid



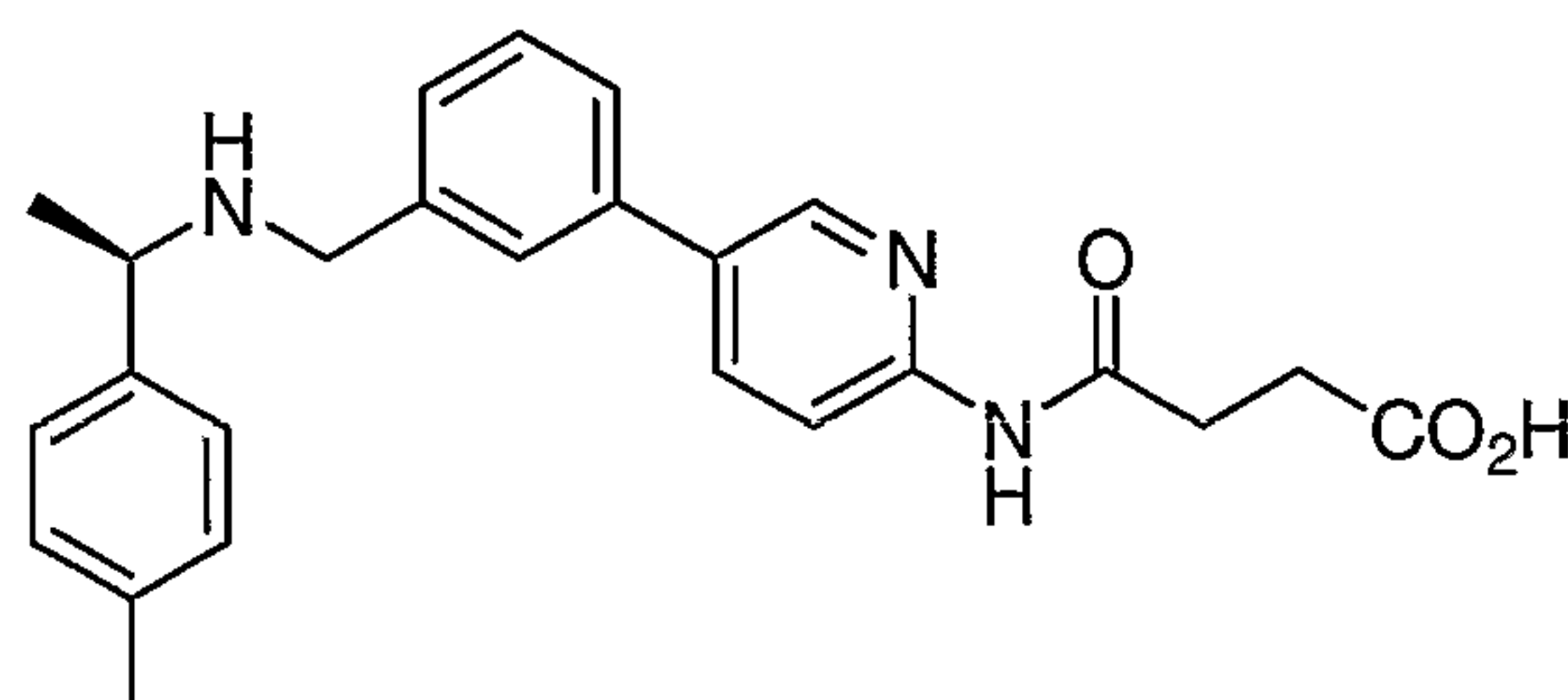
10

MW 453.539
Mass found: 454, 300

Example 151

15

4-((5-(3-(((1R)-1-(4-methylphenyl)ethyl)amino)methyl)phenyl)-2-pyridinyl)amino)-4-oxobutanoic acid



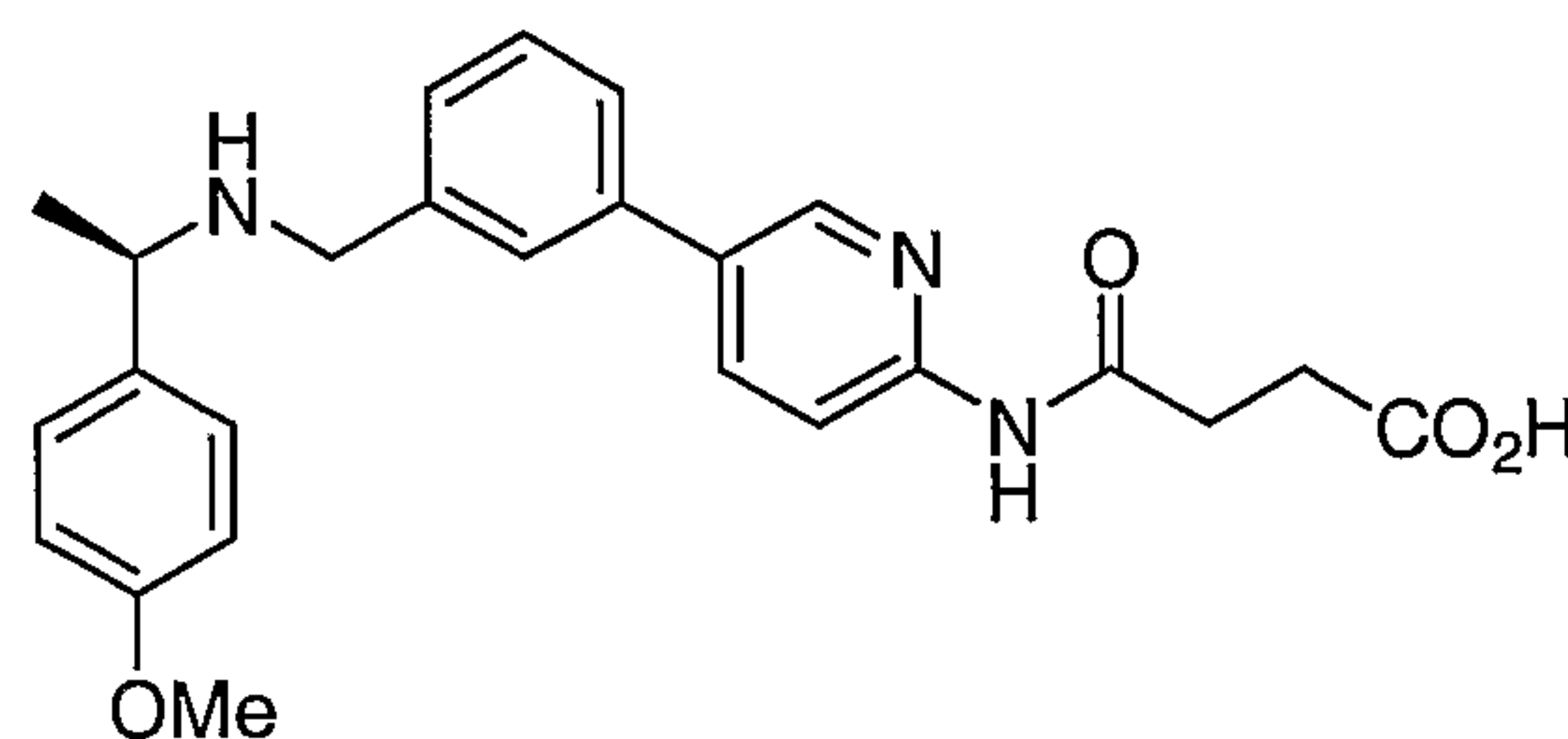
20

MW 417.506
Mass found: 418, 300

Example 152

25

4-((5-(3-(((1R)-1-(4-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2-pyridinyl)amino)-4-oxobutanoic acid



30

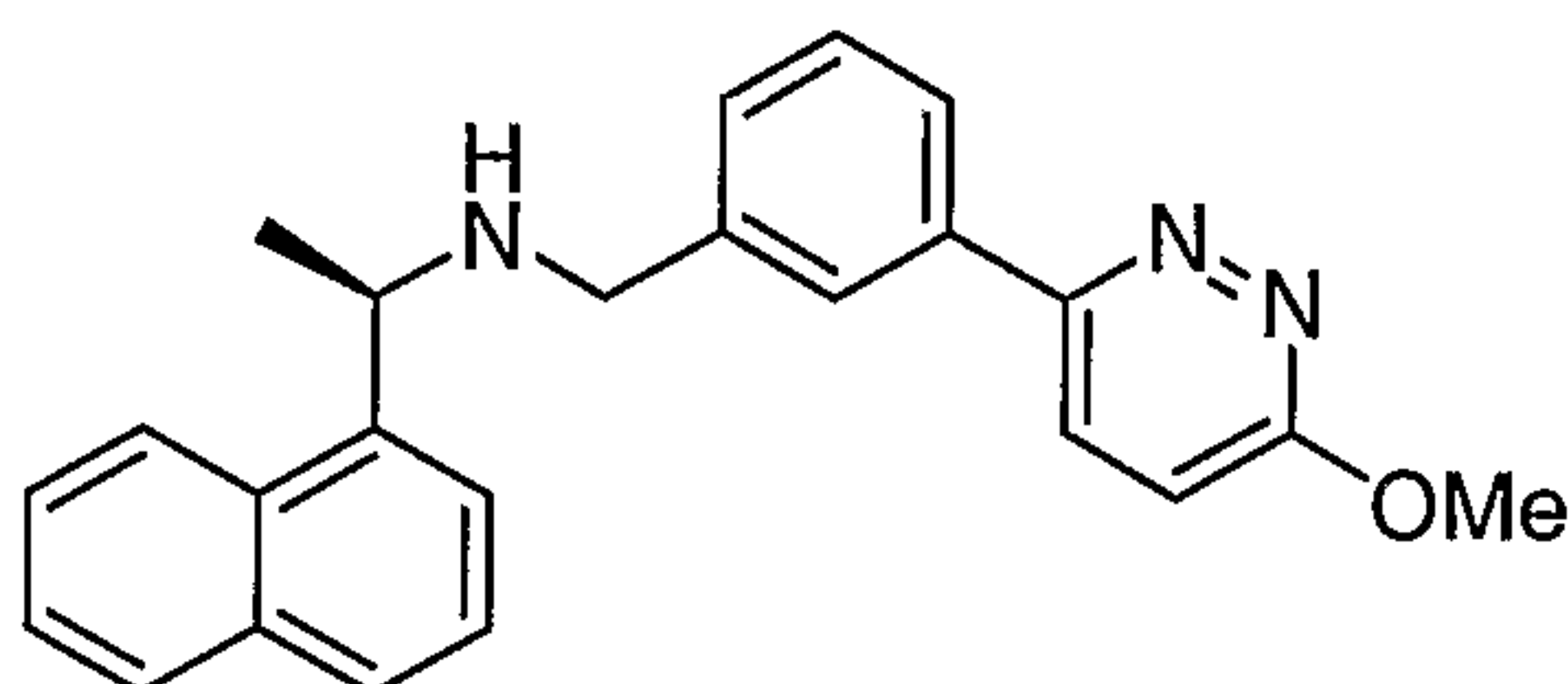
- 144 -

MW 433.505

Mass found: 434, 300

Example 153

5 (1R)-N-((3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



10

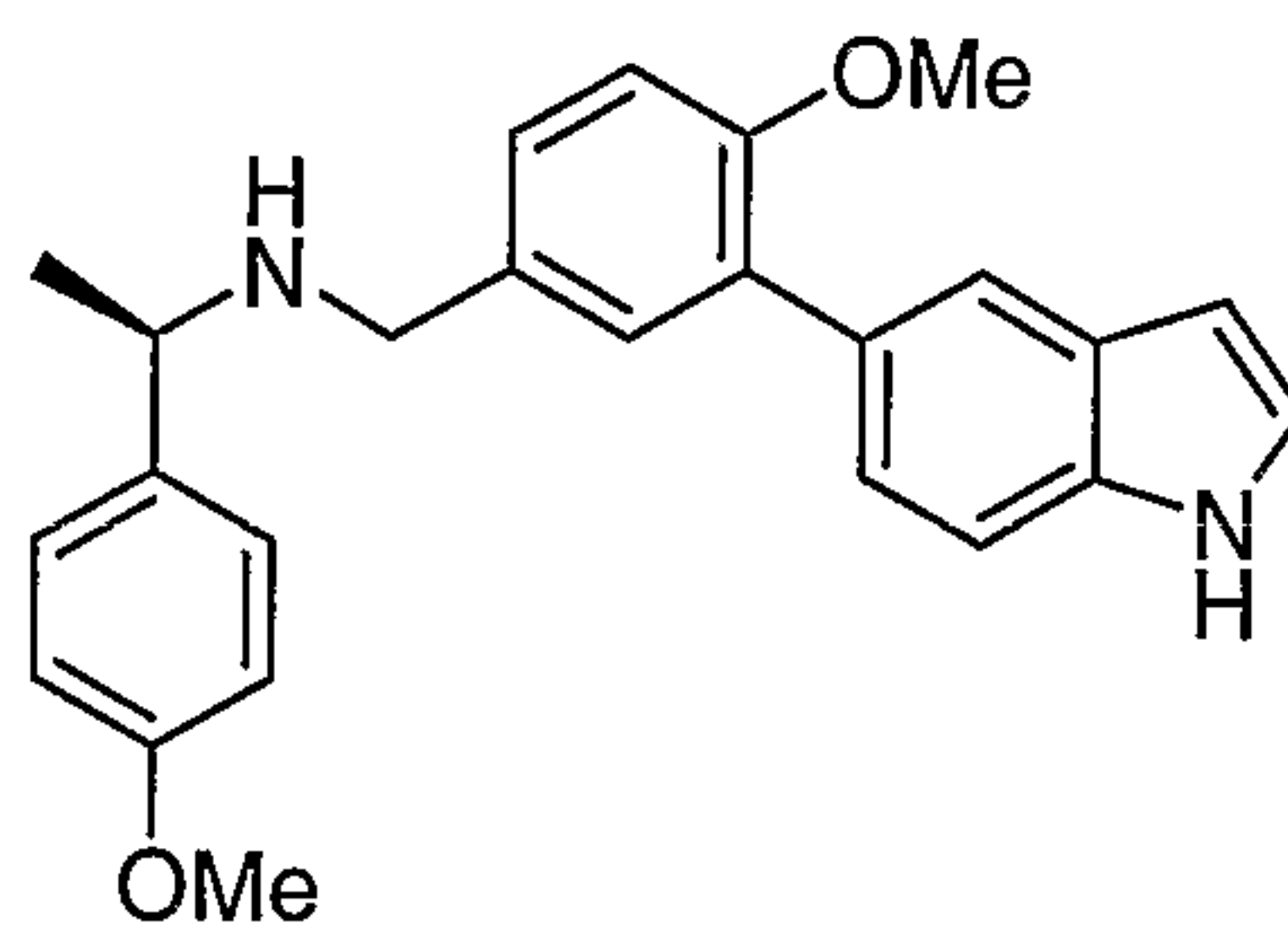
MW 369.466

Mass found: 370, 739

Example 154

15

(1R)-N-((3-(1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(4-(methyloxy)phenyl)ethanamine



20

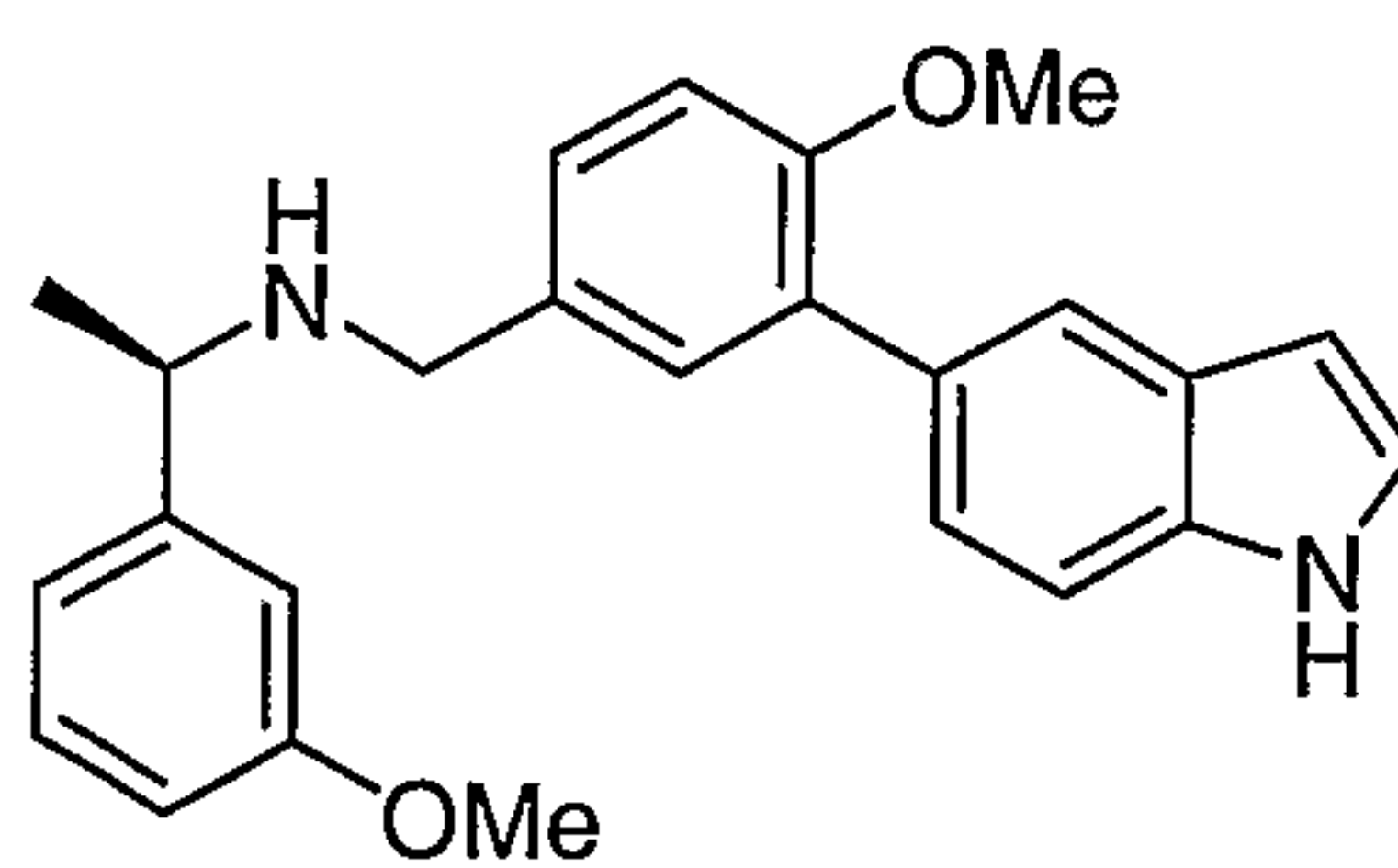
MW 386.492

Mass found: 387, 773

25

Example 155

(1R)-N-((3-(1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine



30

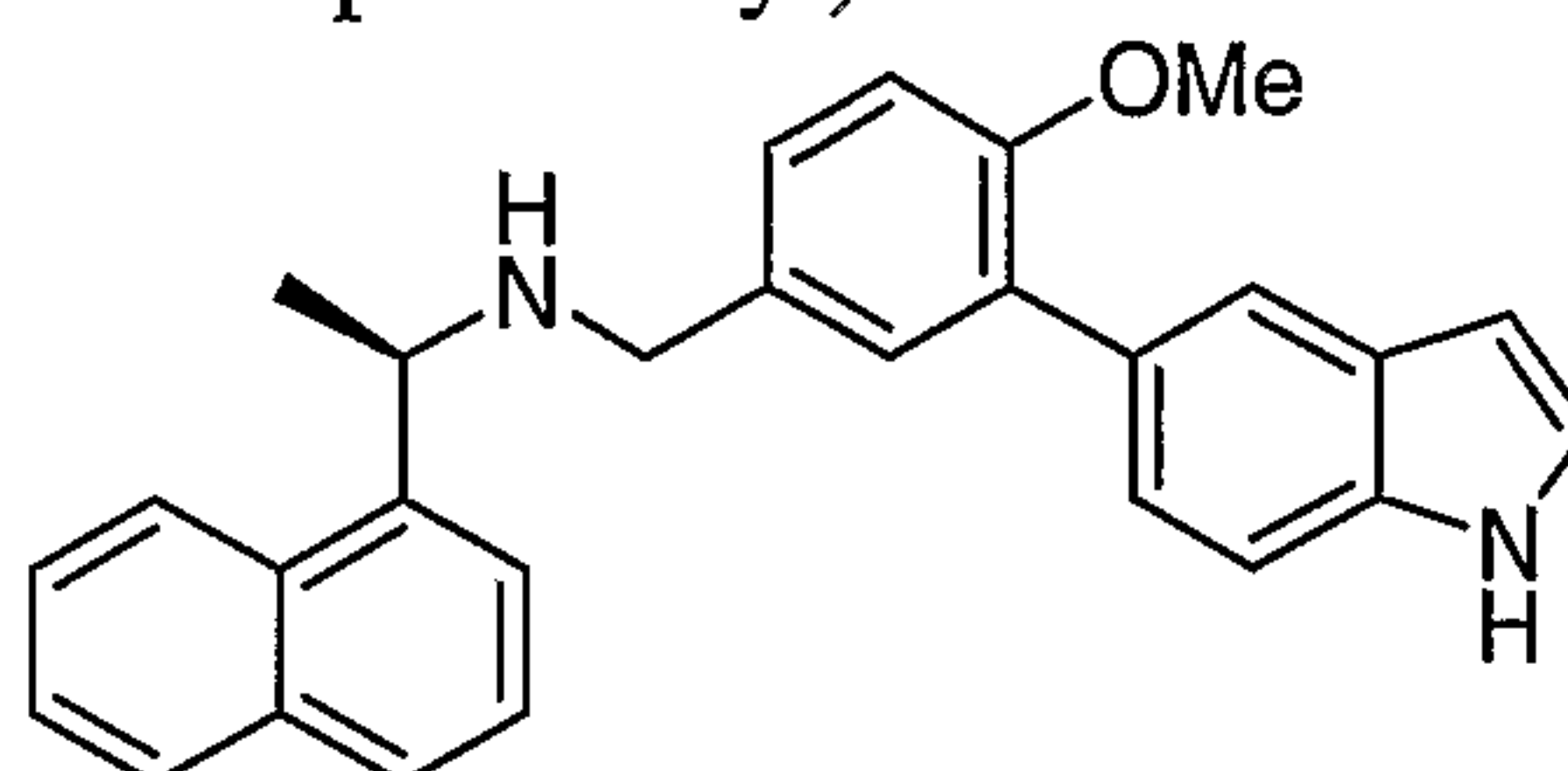
- 145 -

MW 386.492

Mass found: 387, 773

Example 156

5 (1R)-N-((3-(1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(2-naphthalenyl)ethanamine



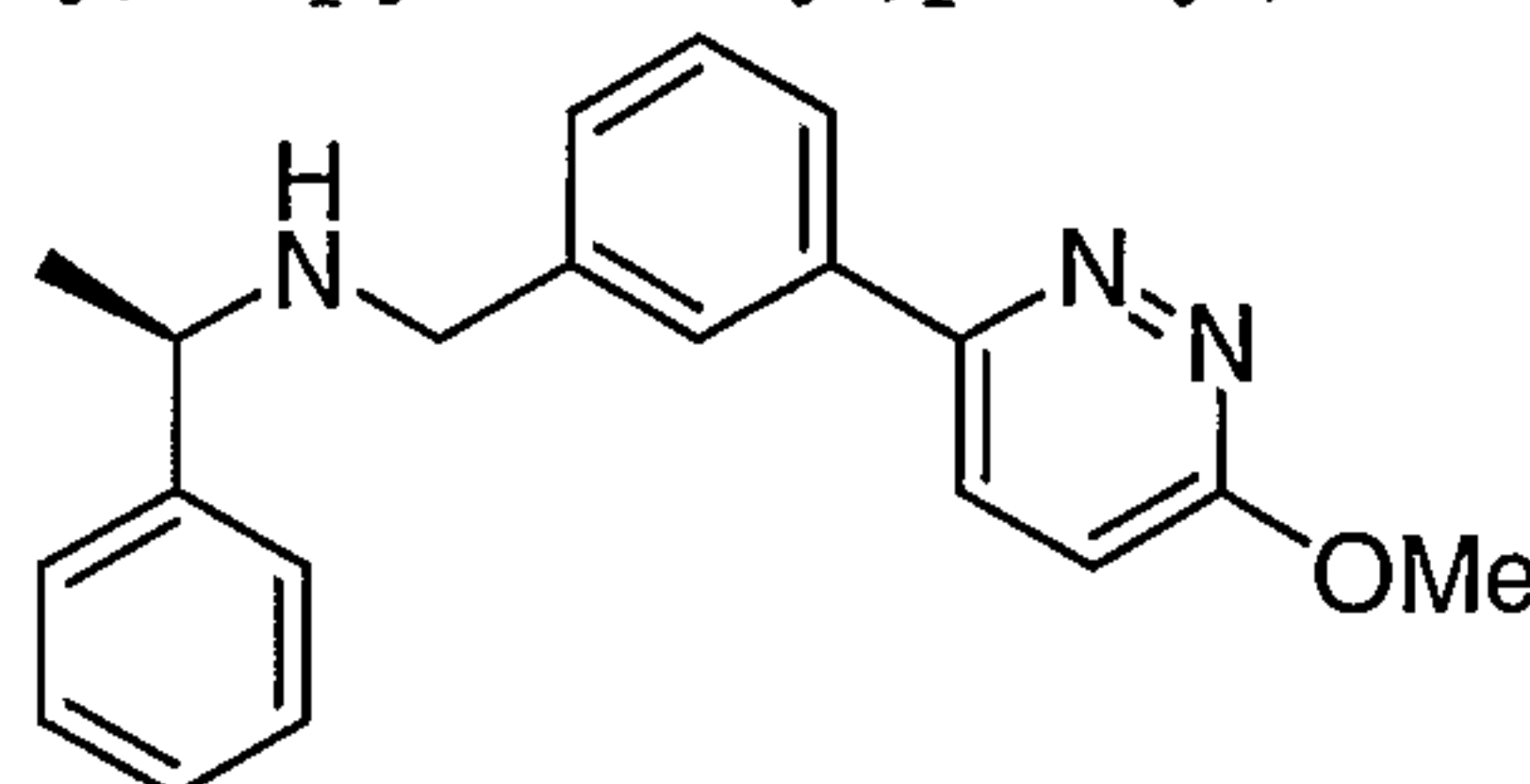
MW 406.526

Mass found: 371, 407, 326

10

Example 157

15 (1R)-N-((3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-phenylethanamine



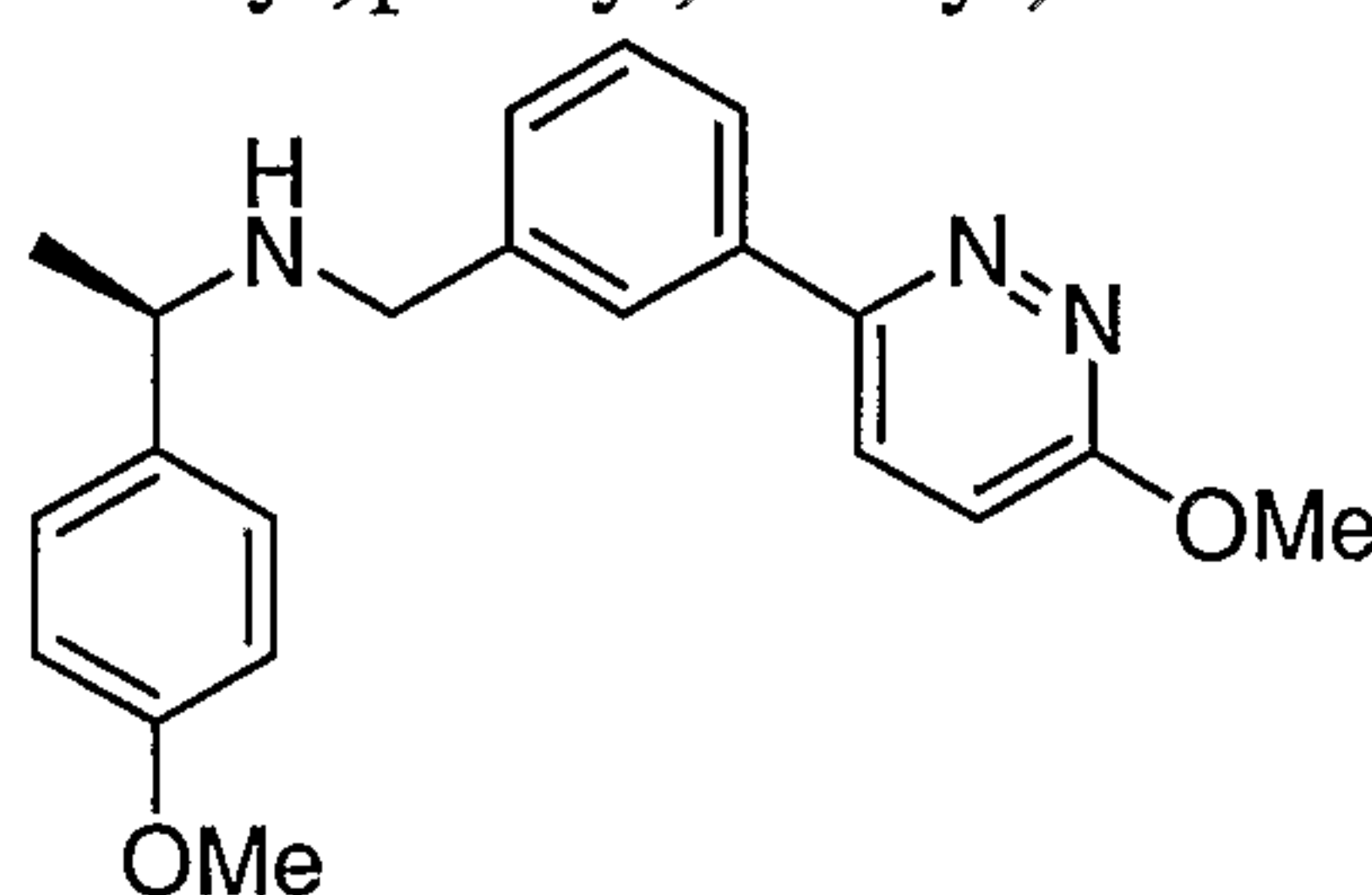
MW 319.406

Mass found: 320, 639

20

Example 158

25 (1R)-1-(4-(methyloxy)phenyl)-N-((3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)ethanamine



MW 349.432

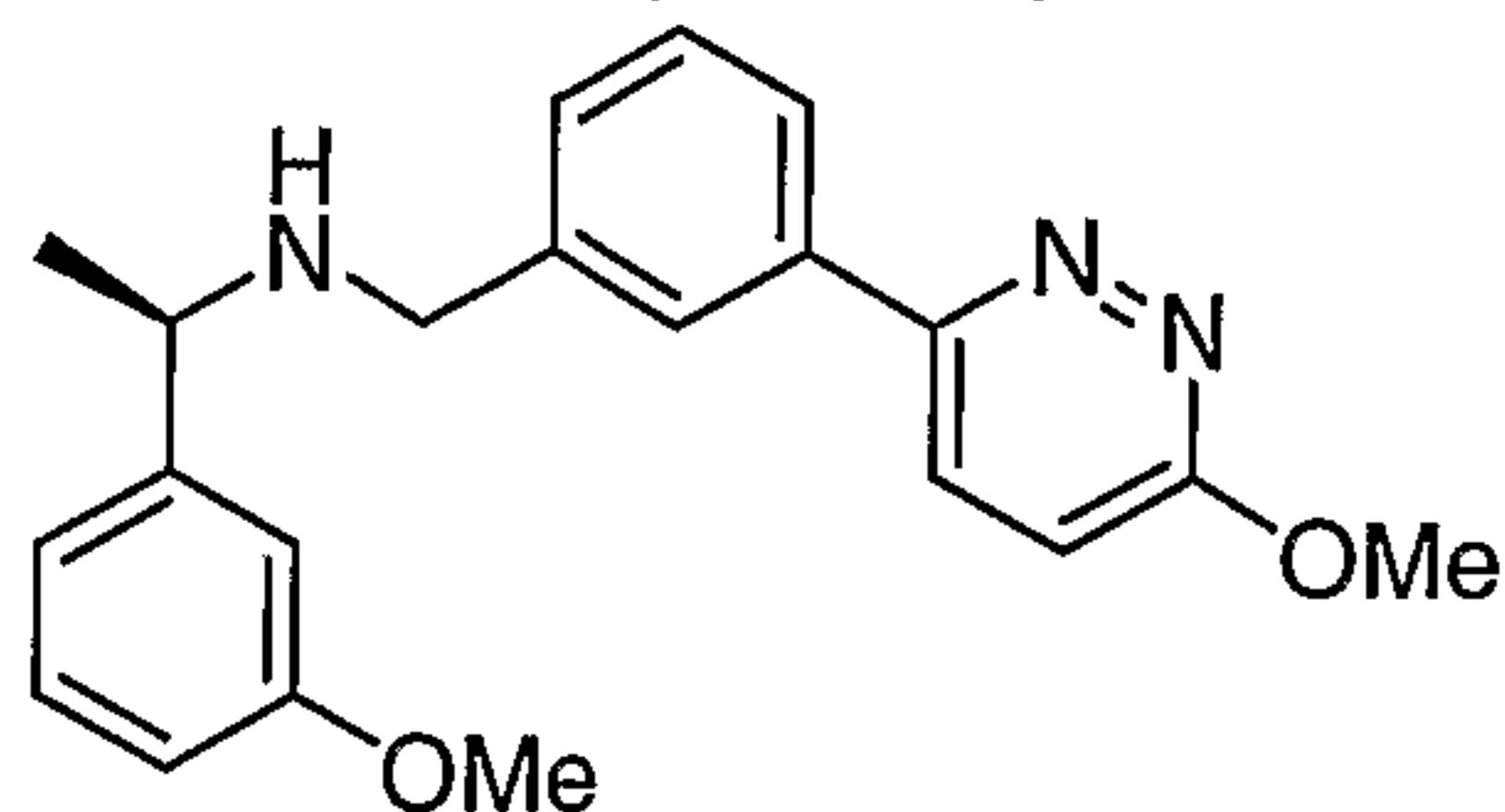
Mass found: 350, 699

30

Example 159

- 146 -

(1R)-1-(3-(methyloxy)phenyl)-N-((3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)ethanamine



5

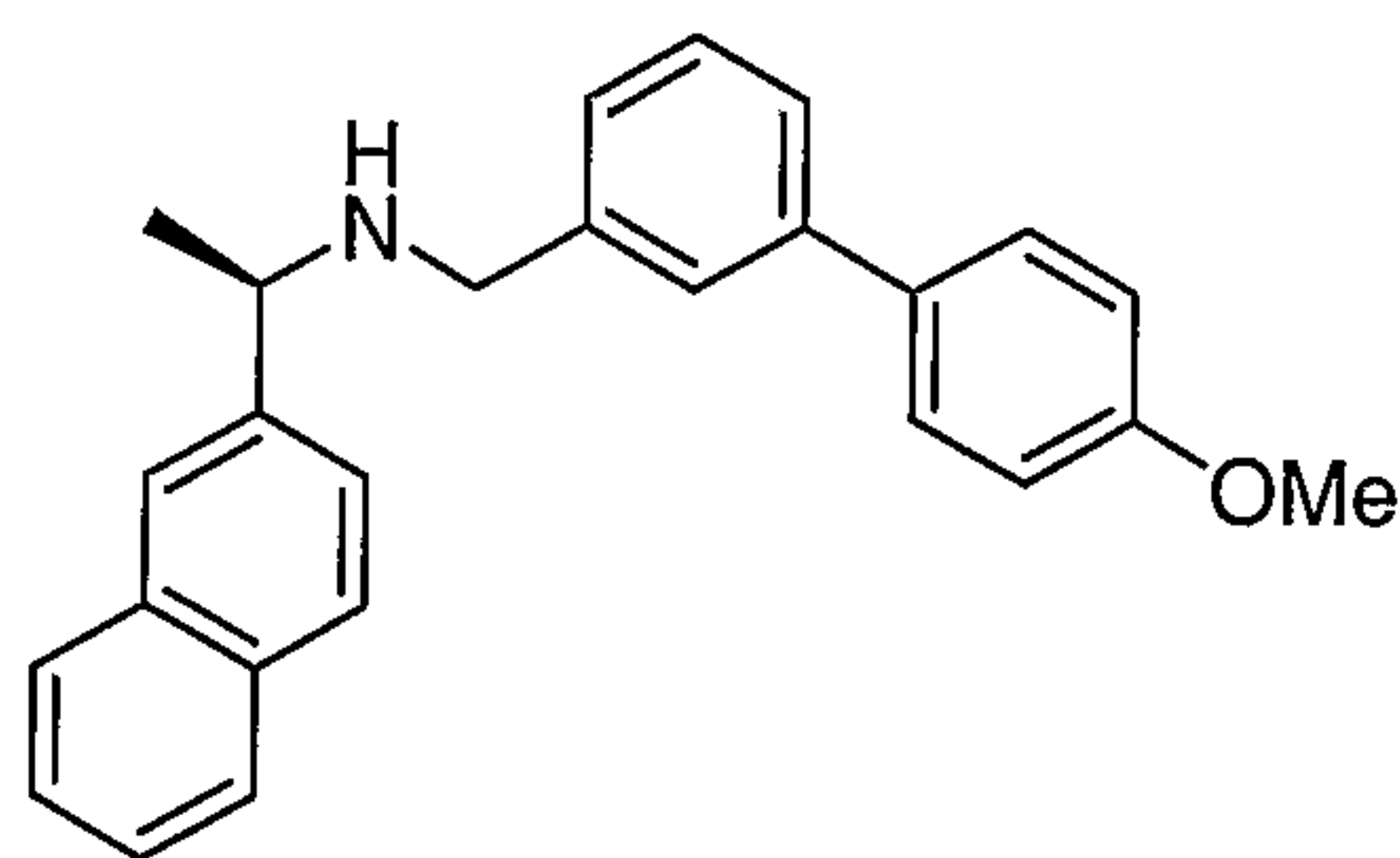
MW 349.432

Mass found: 350, 699

10

Example 160

(1R)-N-((4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(2-naphthalenyl)ethanamine



15

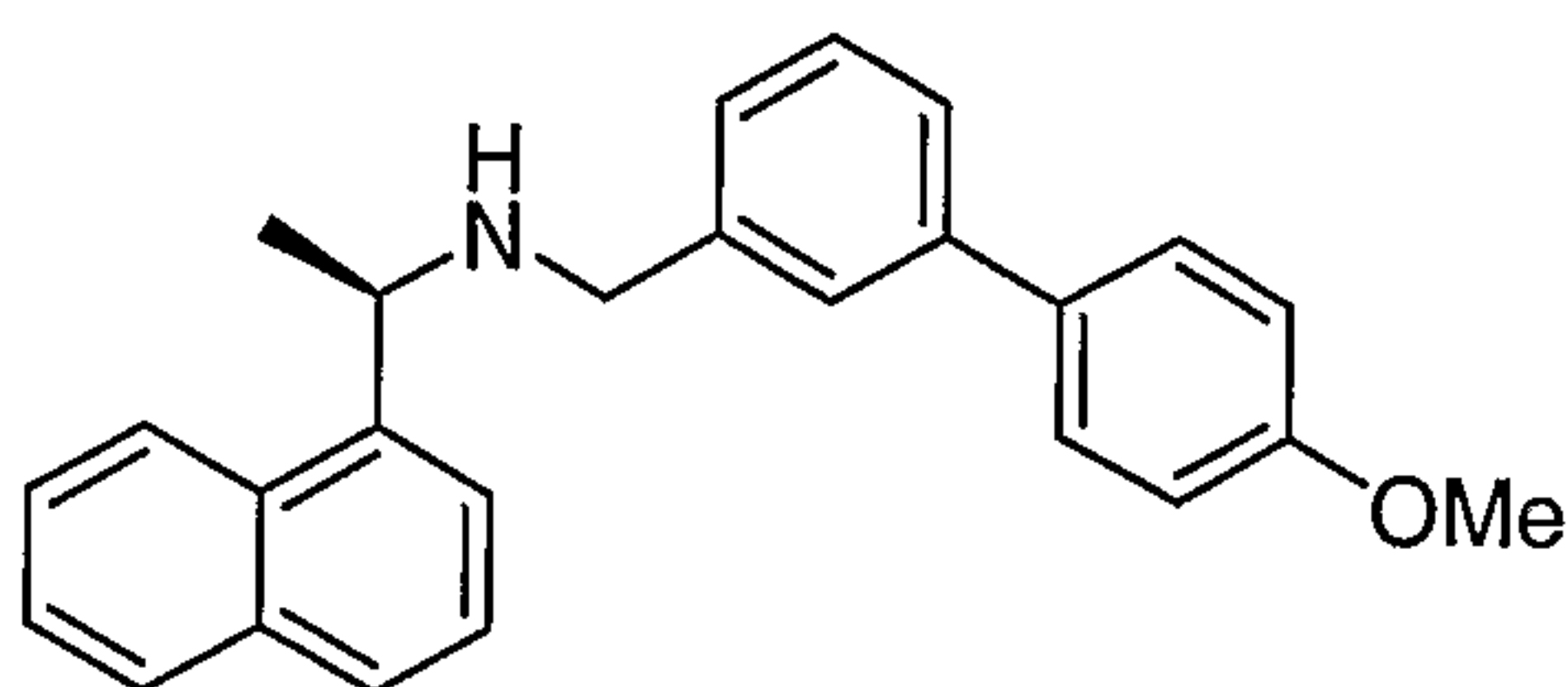
MW 367.49

Mass found: 368

20

Example 161

(1R)-N-((4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine



25

MW 367.49

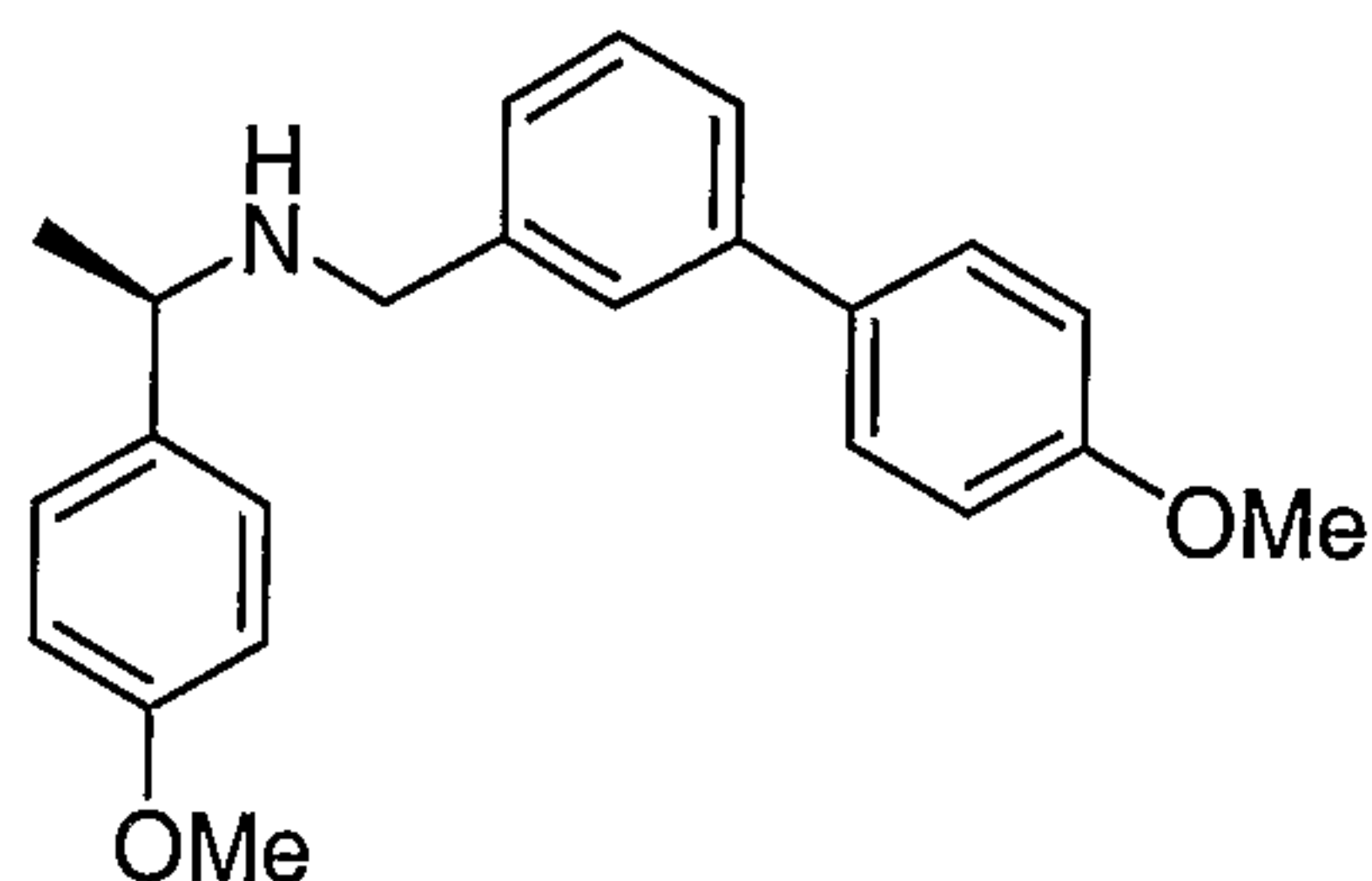
Mass found: 368, 735

30

Example 162

- 147 -

(1R)-N-((4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine



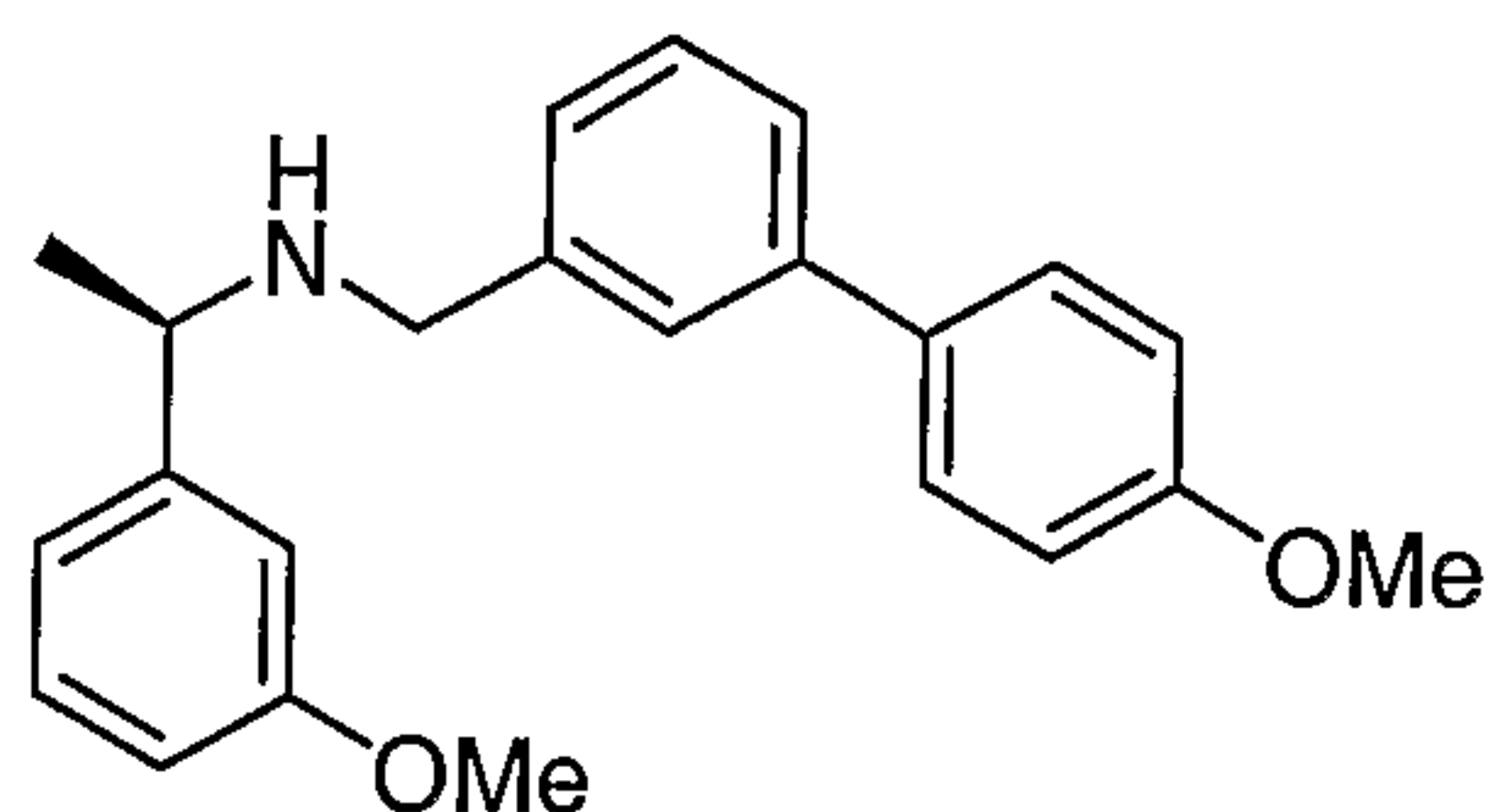
5

MW 347.456
Mass found: 348, 695

10

Example 163

(1R)-N-((4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine



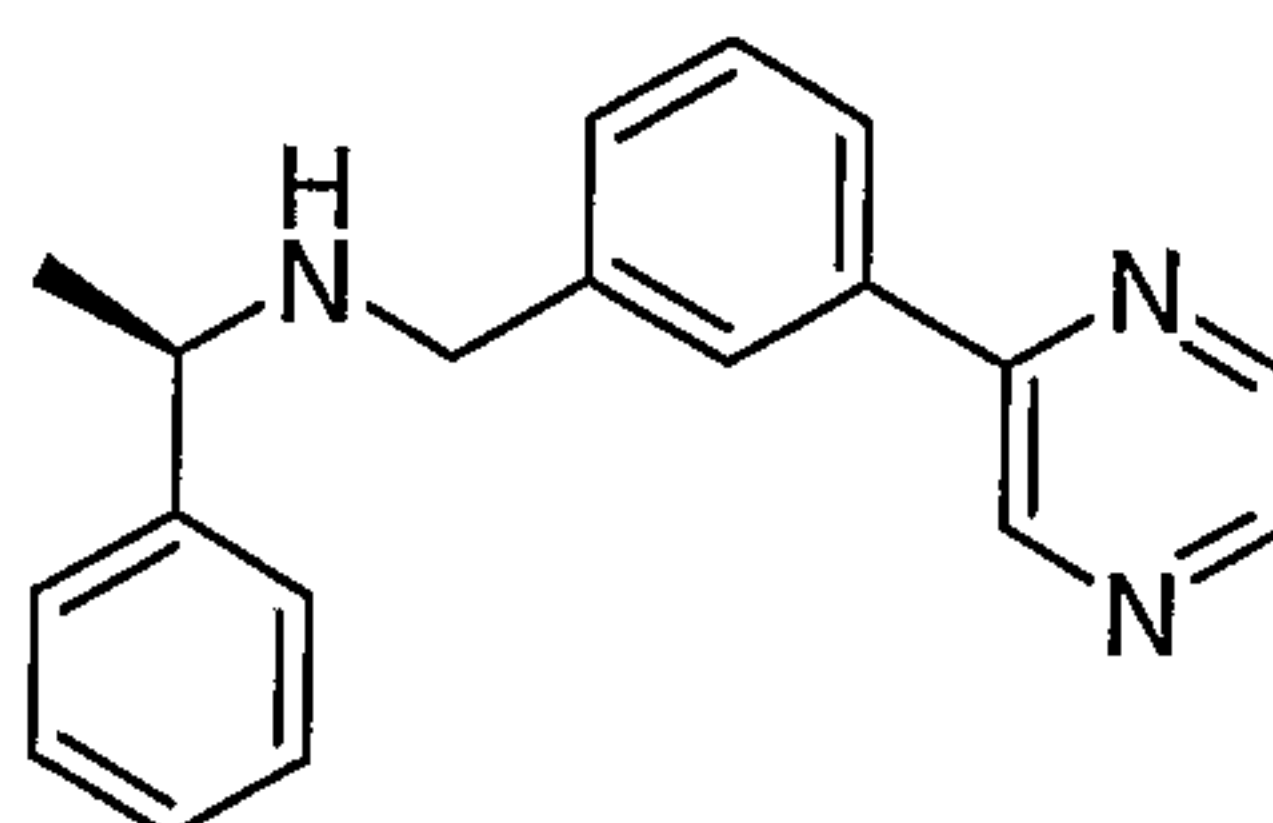
15

MW 347.456
Mass found: 348, 695

20

Example 164

(1R)-1-phenyl-N-((3-(2-pyrazinyl)phenyl)methyl)ethanamine



25

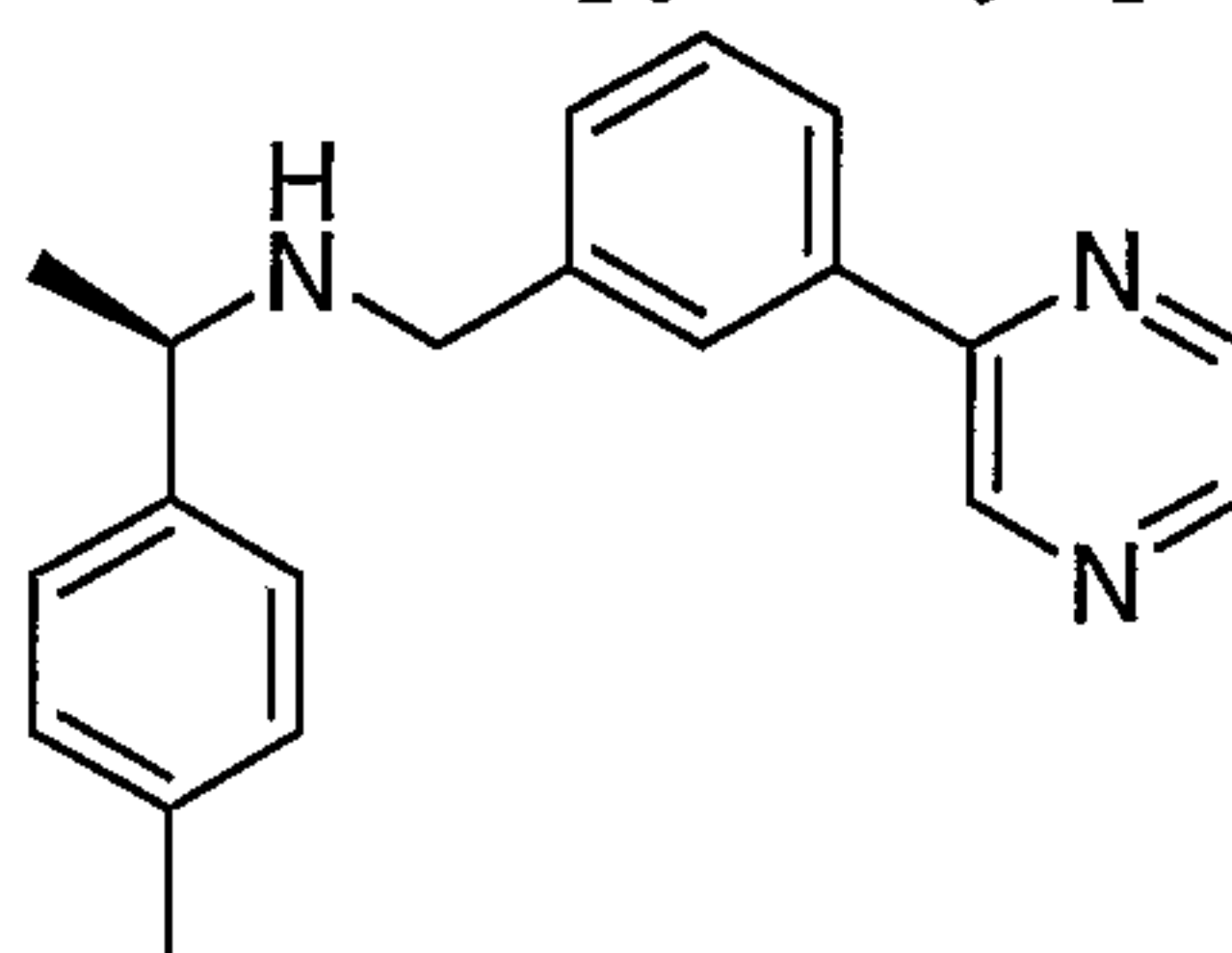
MW 289.38
Mass found: 290, 579, 693

30

Example 165

- 148 -

(1R)-1-(4-methylphenyl)-N-((3-(2-pyrazinyl)phenyl)methyl)ethanamine



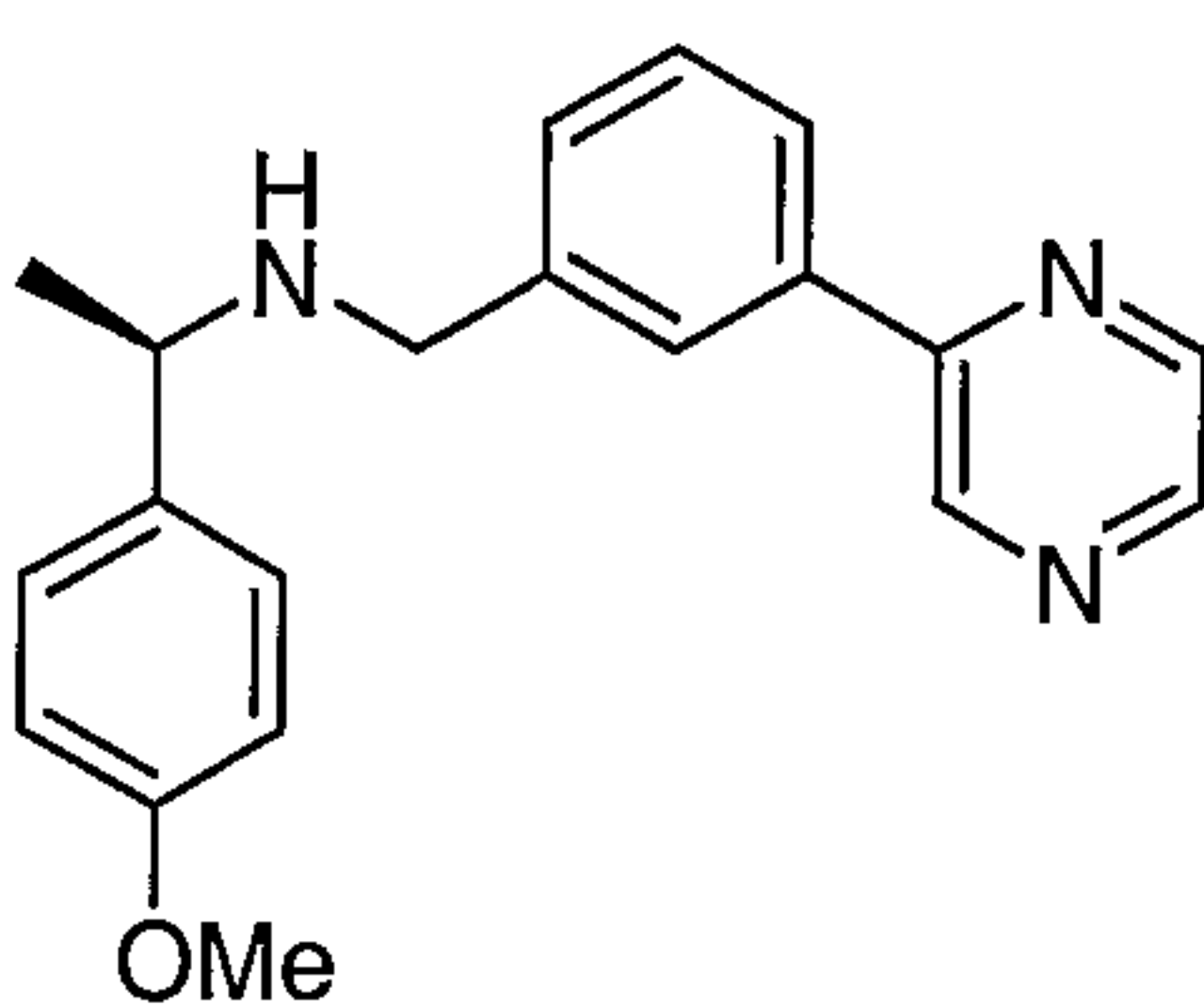
MW 303.407

Mass found: 304, 607, 721

5

Example 166

(1R)-1-(4-(methyloxy)phenyl)-N-((3-(2-pyrazinyl)phenyl)methyl)ethanamine



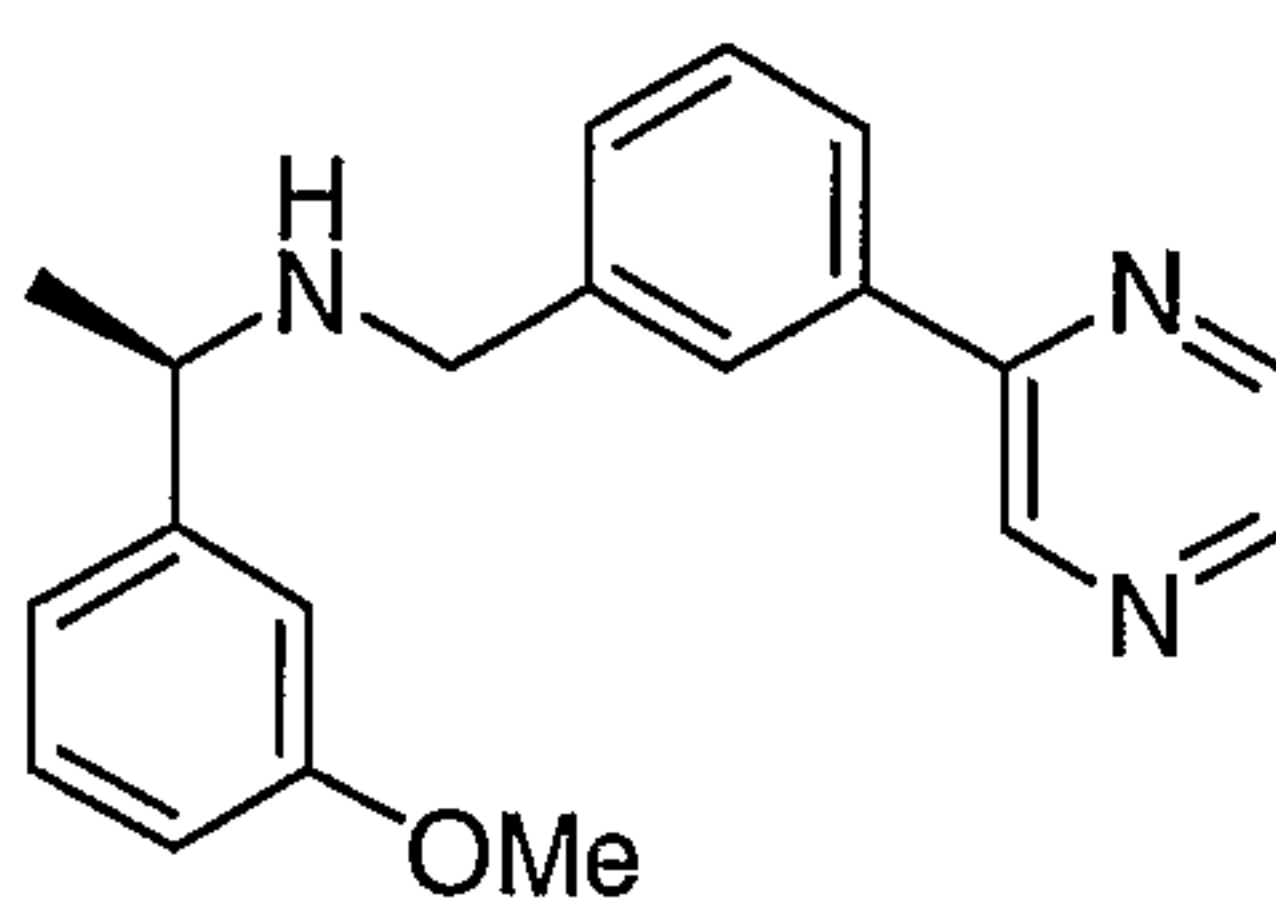
MW 319.406

Mass found: 320, 639, 753

15

Example 167

(1R)-1-(3-(methyloxy)phenyl)-N-((3-(2-pyrazinyl)phenyl)methyl)ethanamine



MW 319.406

Mass found: 320, 639, 753

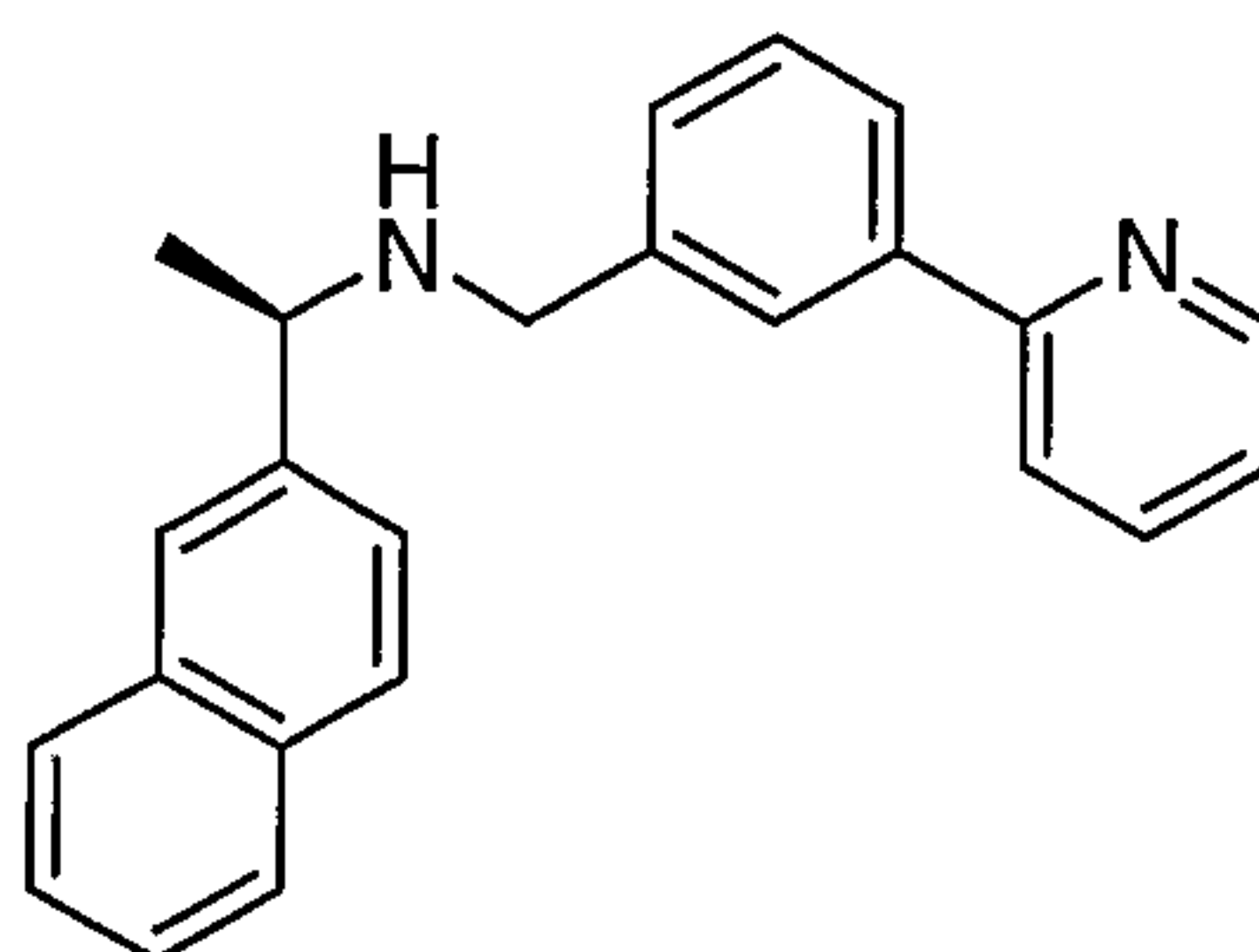
25

Example 168

(1R)-1-(2-naphthalenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine

30

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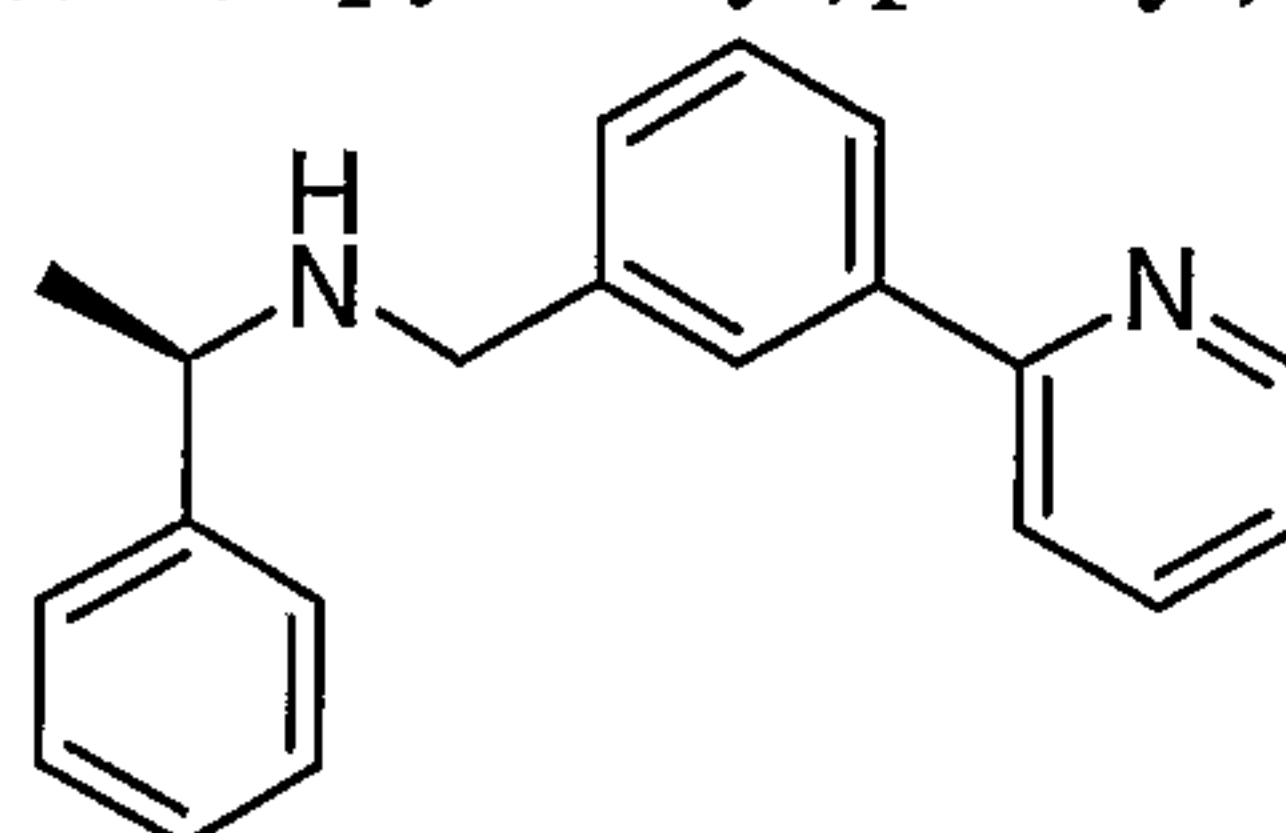


MW 338.452
Mass found: 339, 677

5

Example 169

(1R)-1-phenyl-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine



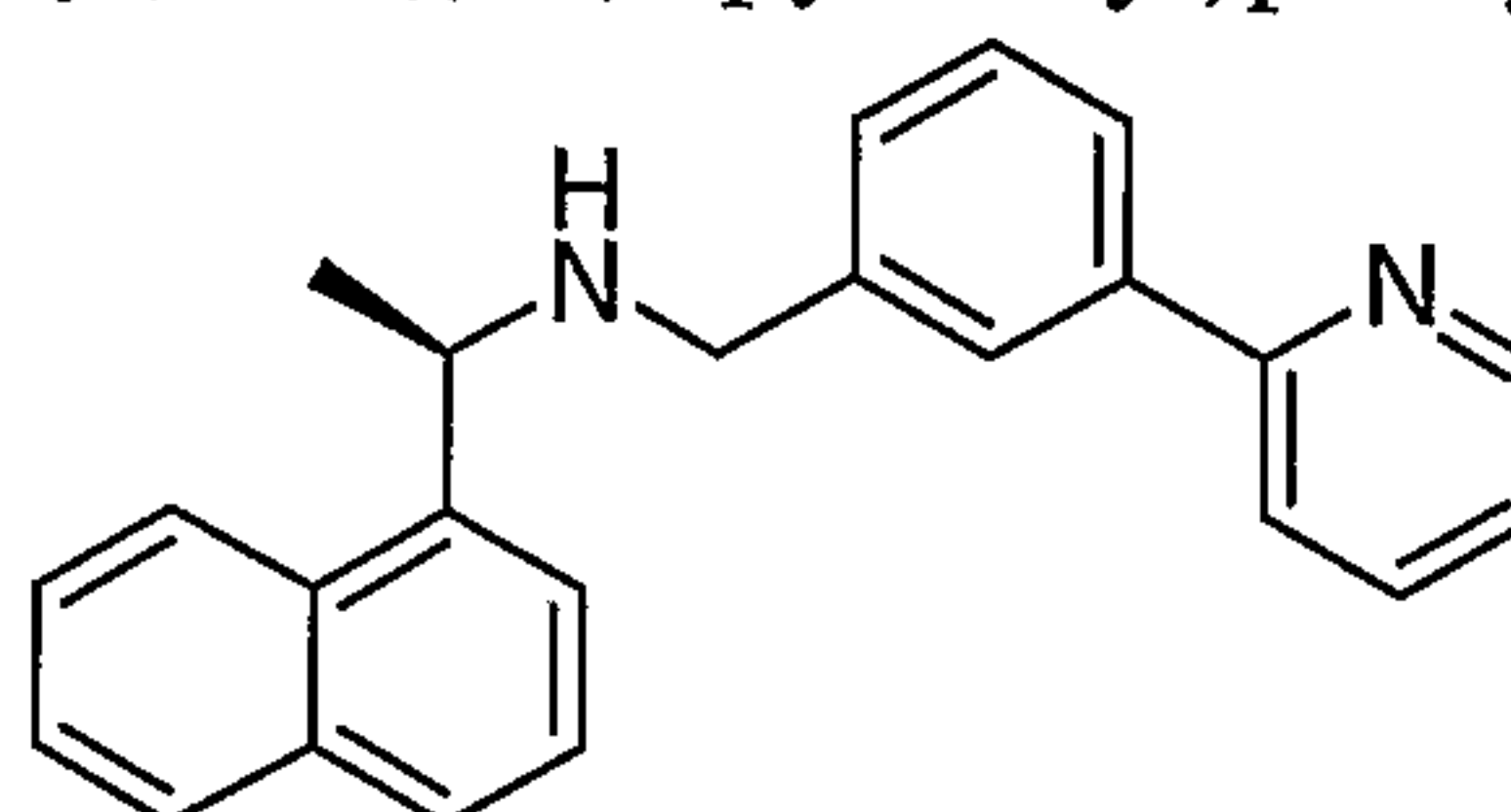
10

MW 288.392
Mass found: 289, 577

15

Example 170

(1R)-1-(1-naphthalenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine



20

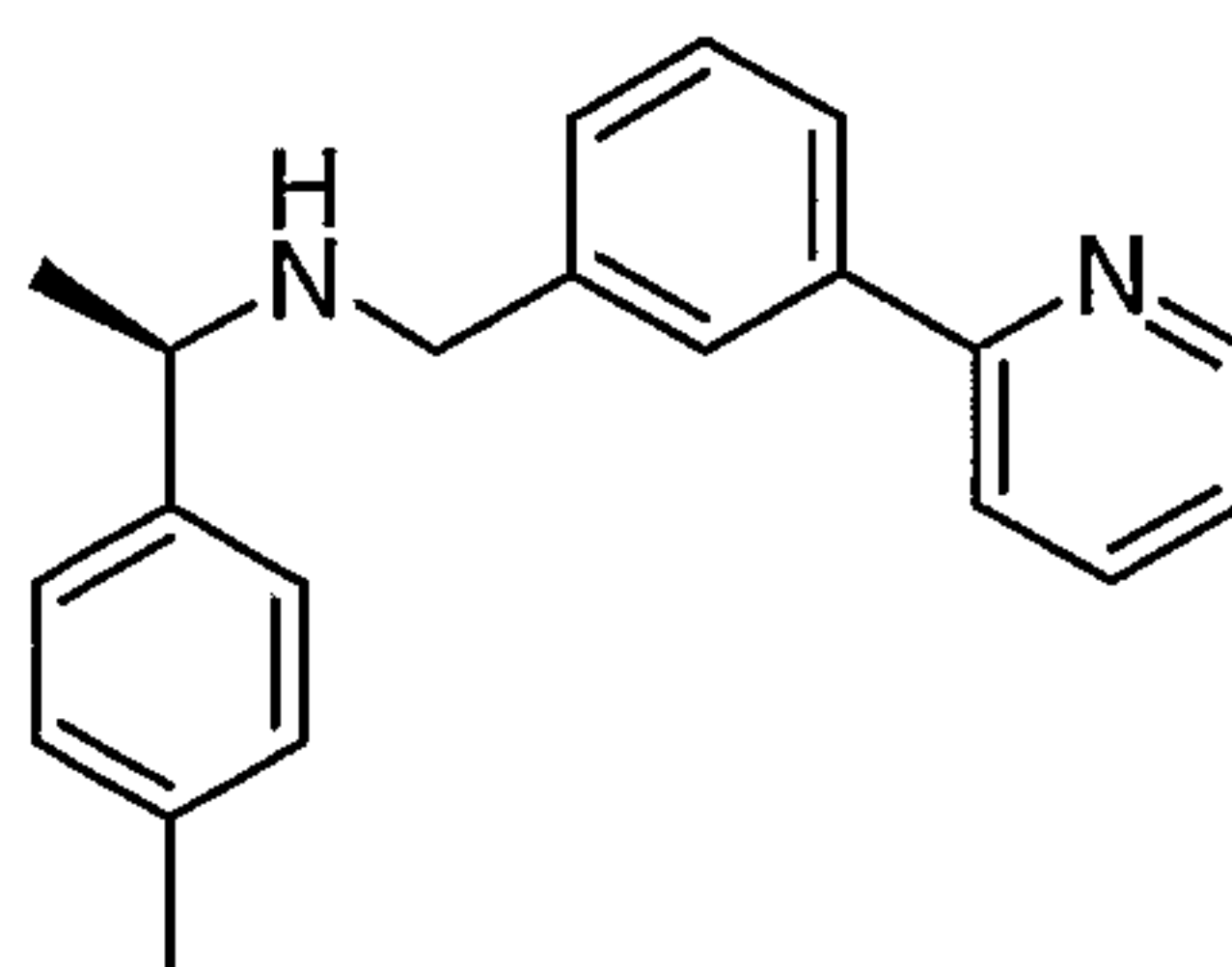
MW 338.452
Mass found: 339, 677

25

Example 171

(1R)-1-(4-methylphenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine

- 150 -



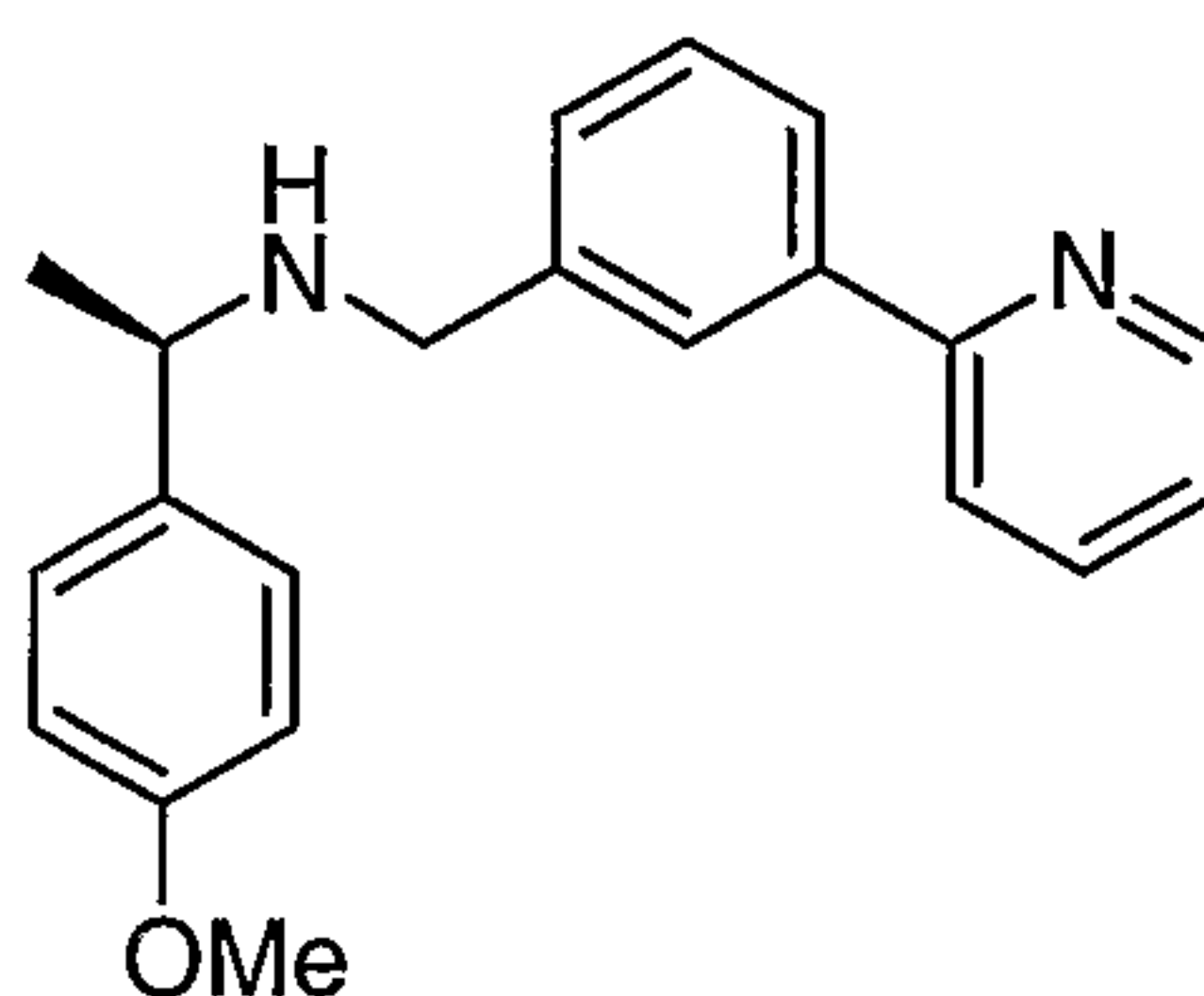
MW 302.419
Mass found: 303, 605

5

Example 172

(1R)-1-(4-(methyloxy)phenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine

10



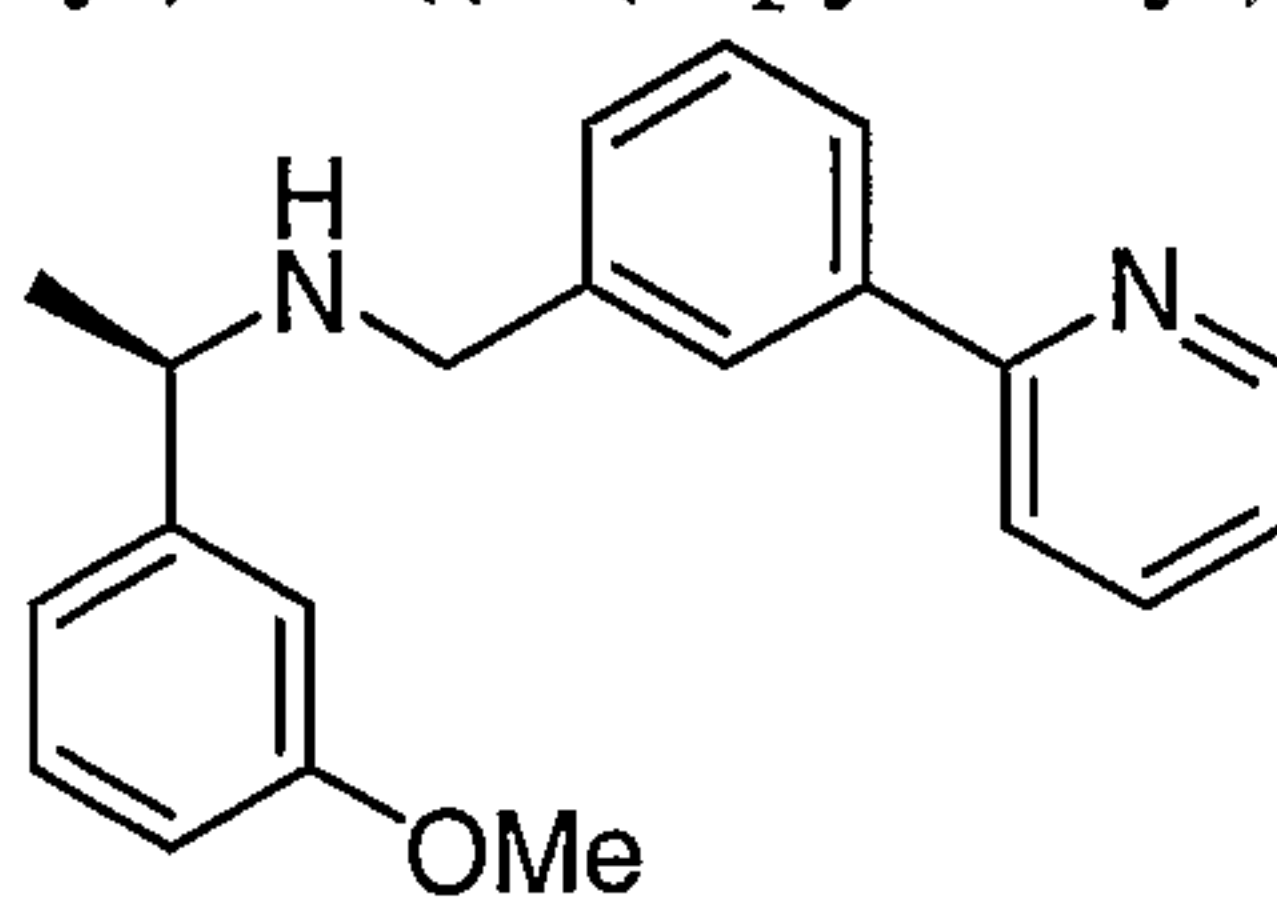
MW 318.418
Mass found: 319, 637

15

Example 173

(1R)-1-(3-(methyloxy)phenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine

20



MW 318.418
Mass found: 319, 637

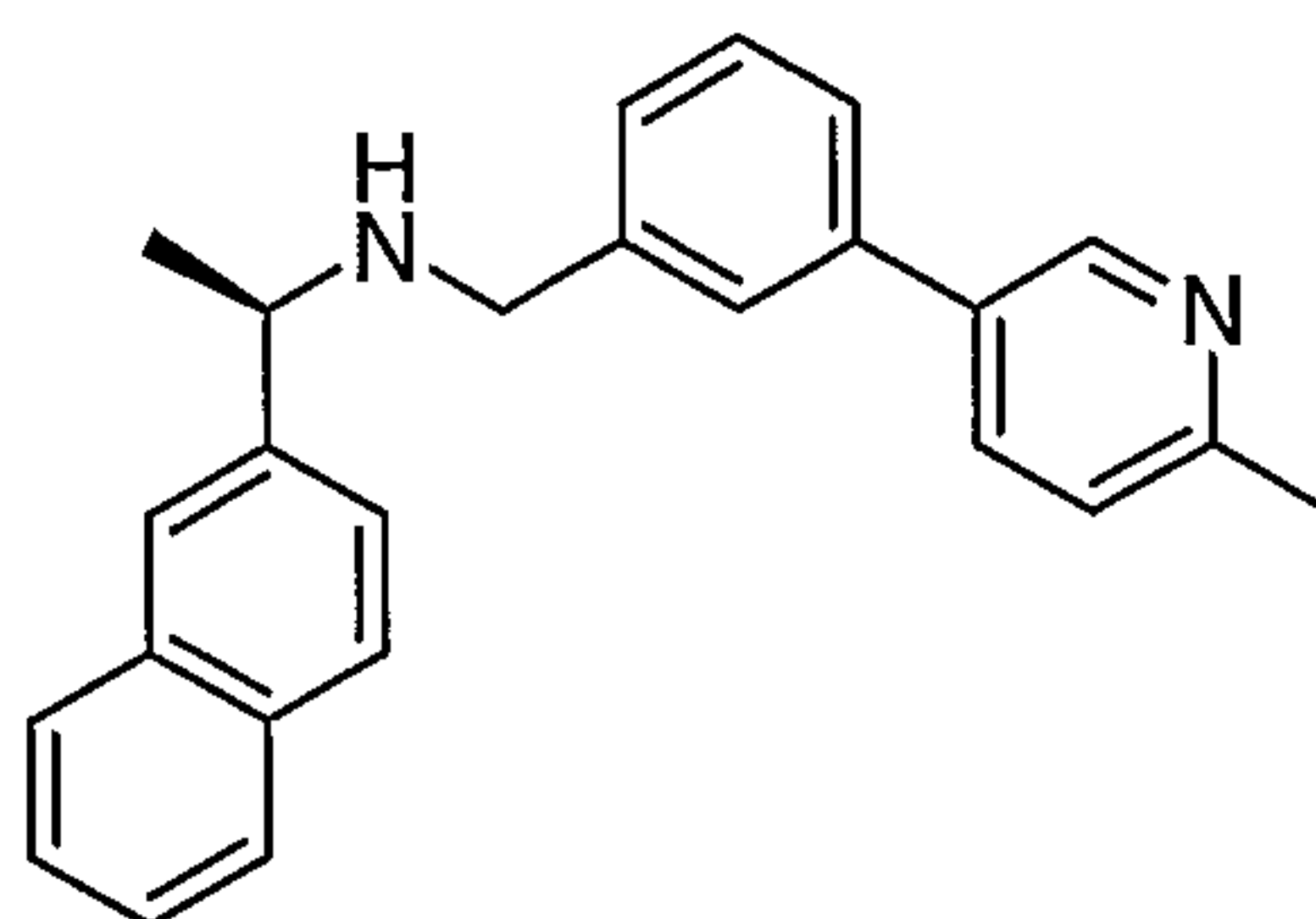
25

Example 174

(1R)-N-((3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine

30

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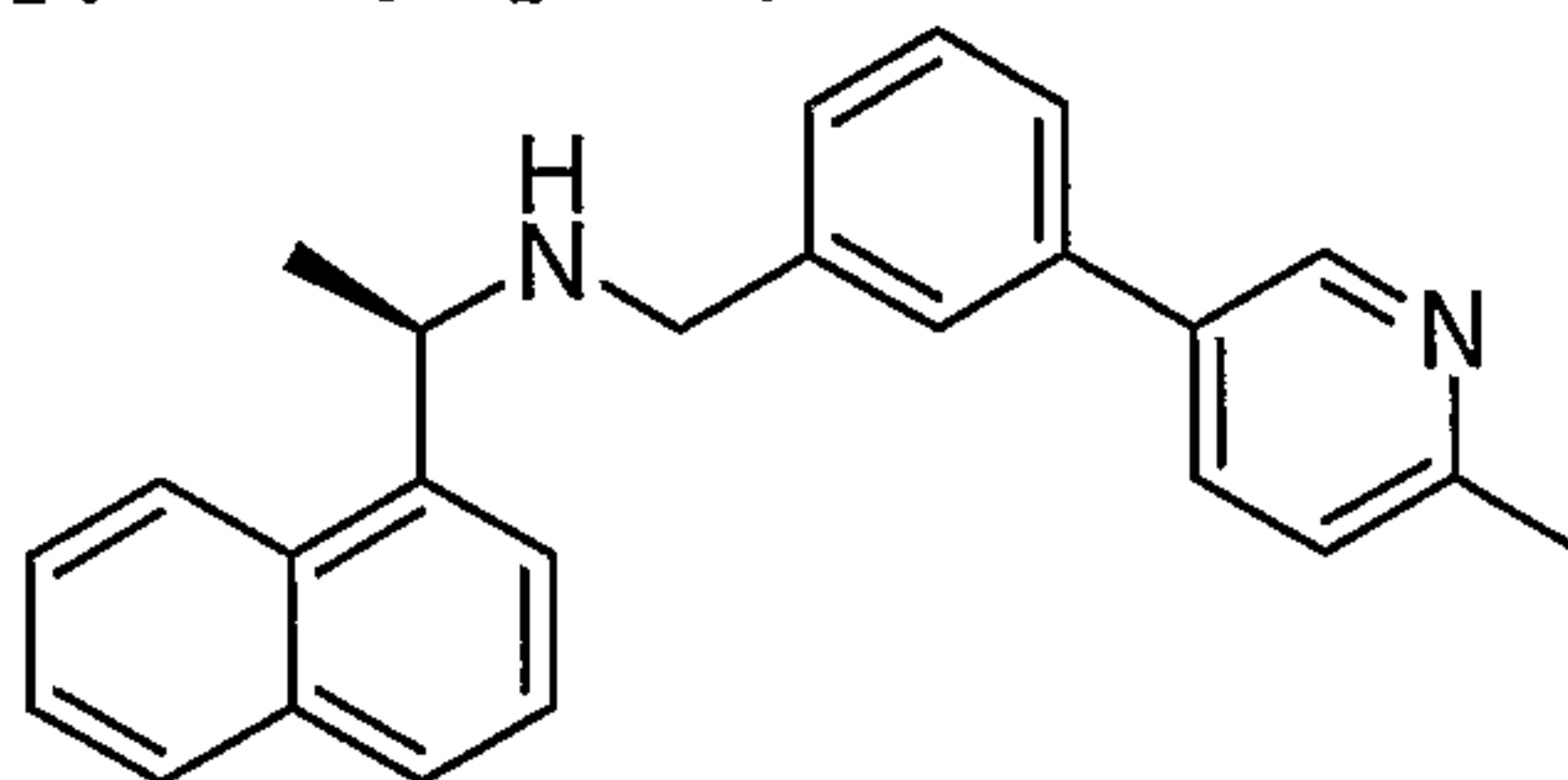


MW 352.479
Mass found: 353, 705

5

Example 175

(1R)-N-((3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



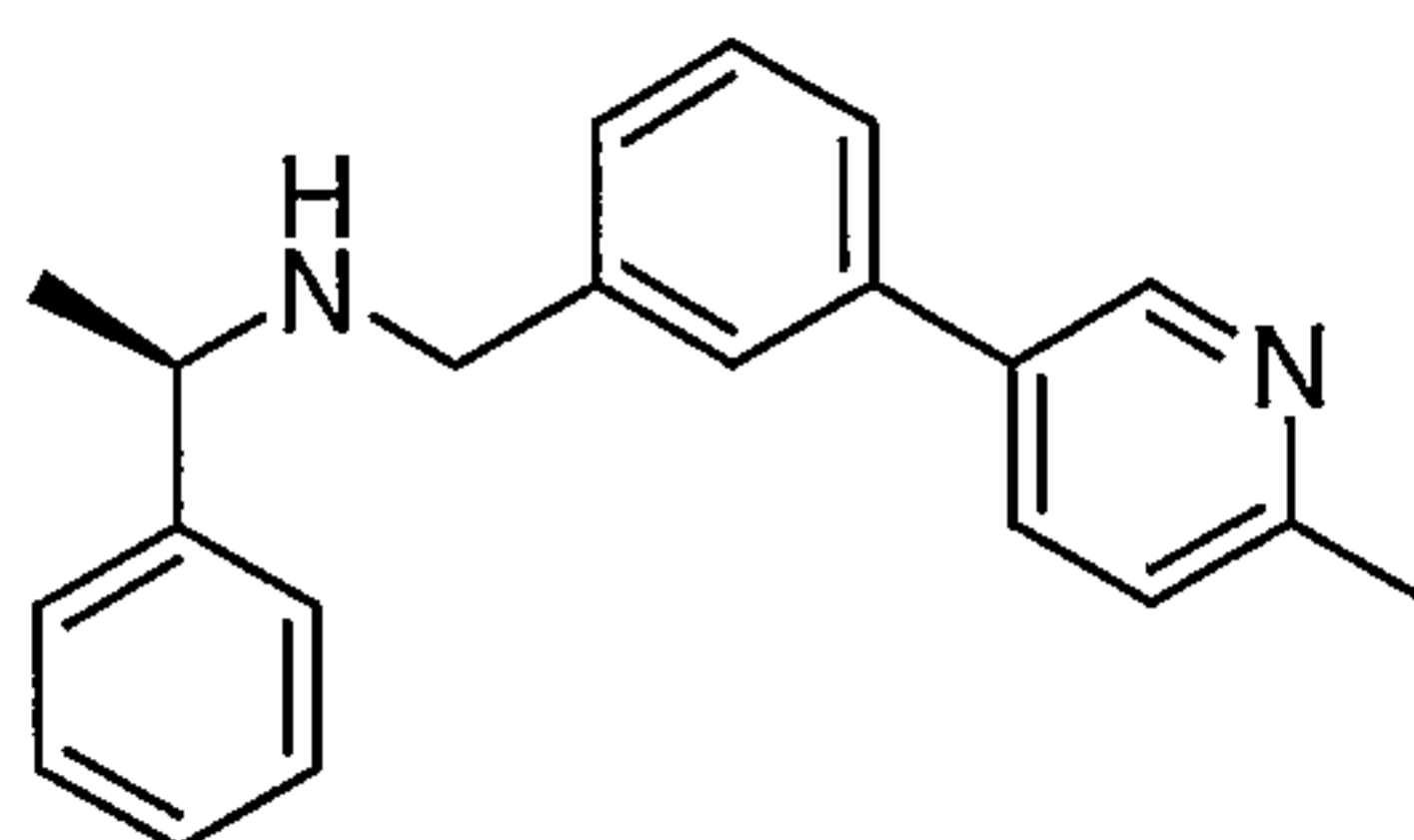
10

MW 352.479
Mass found: 353, 705

15

Example 176

(1R)-N-((3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-phenylethanamine



20

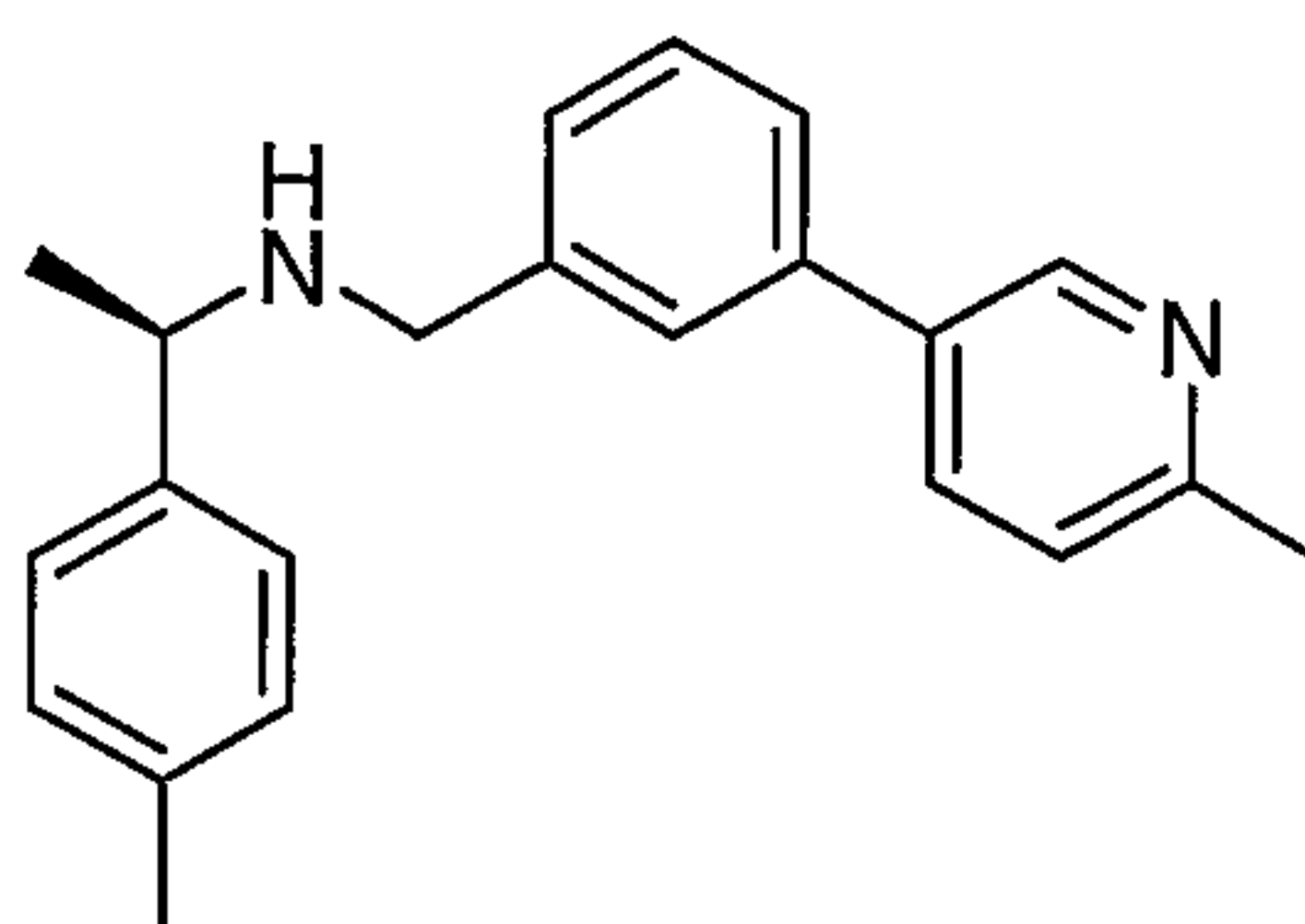
MW 302.419
Mass found: 303, 719

25

Example 177

(1R)-1-(4-methylphenyl)-N-((3-(6-methyl-3-pyridinyl)phenyl)methyl)ethanamine

- 152 -



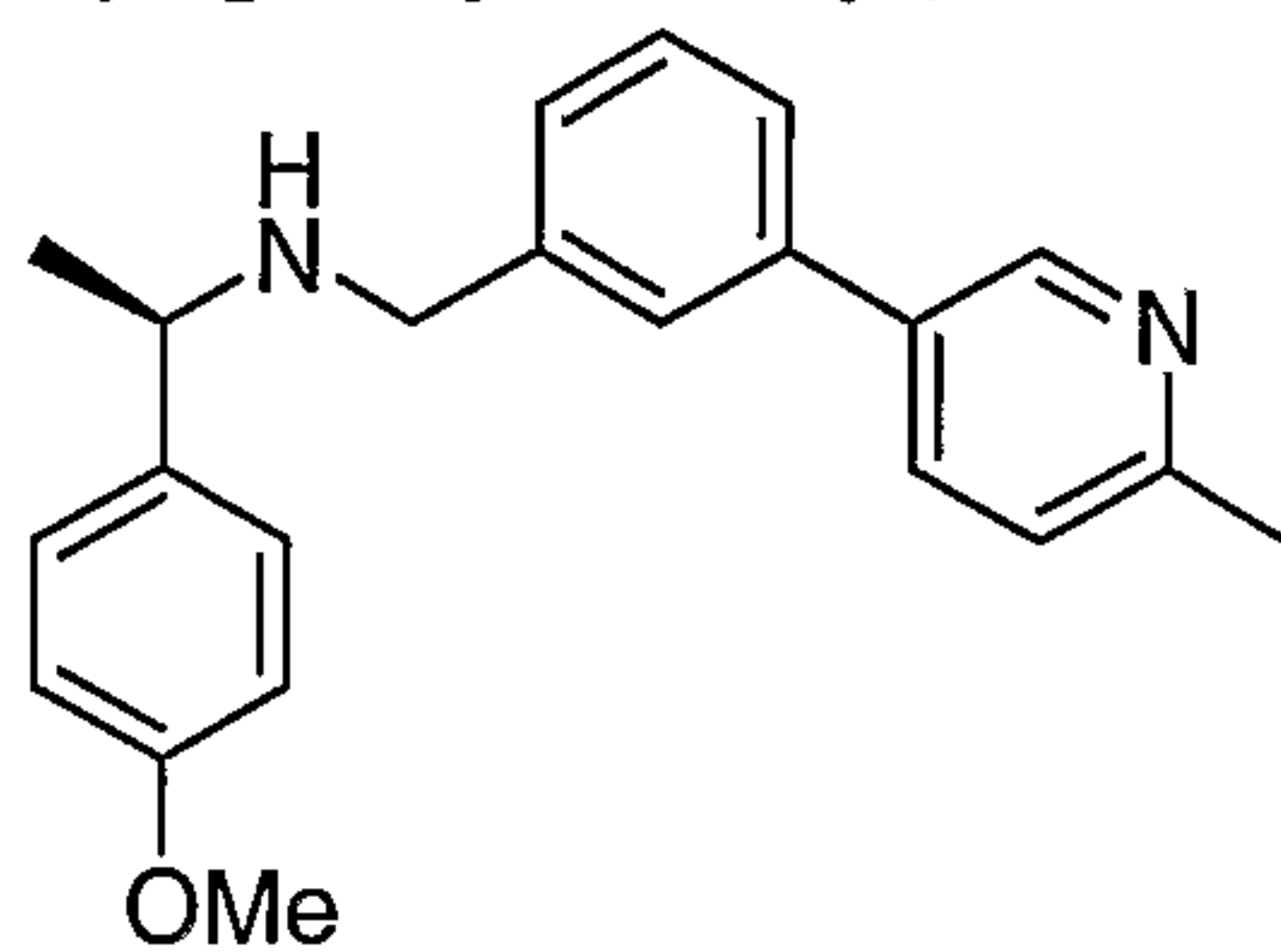
MW 316.446
Mass found: 317, 747

5

Example 178

(1R)-1-(4-(methyloxy)phenyl)-N-((3-(6-methyl-3-ylridinyl)phenyl)methyl)ethanamine

10



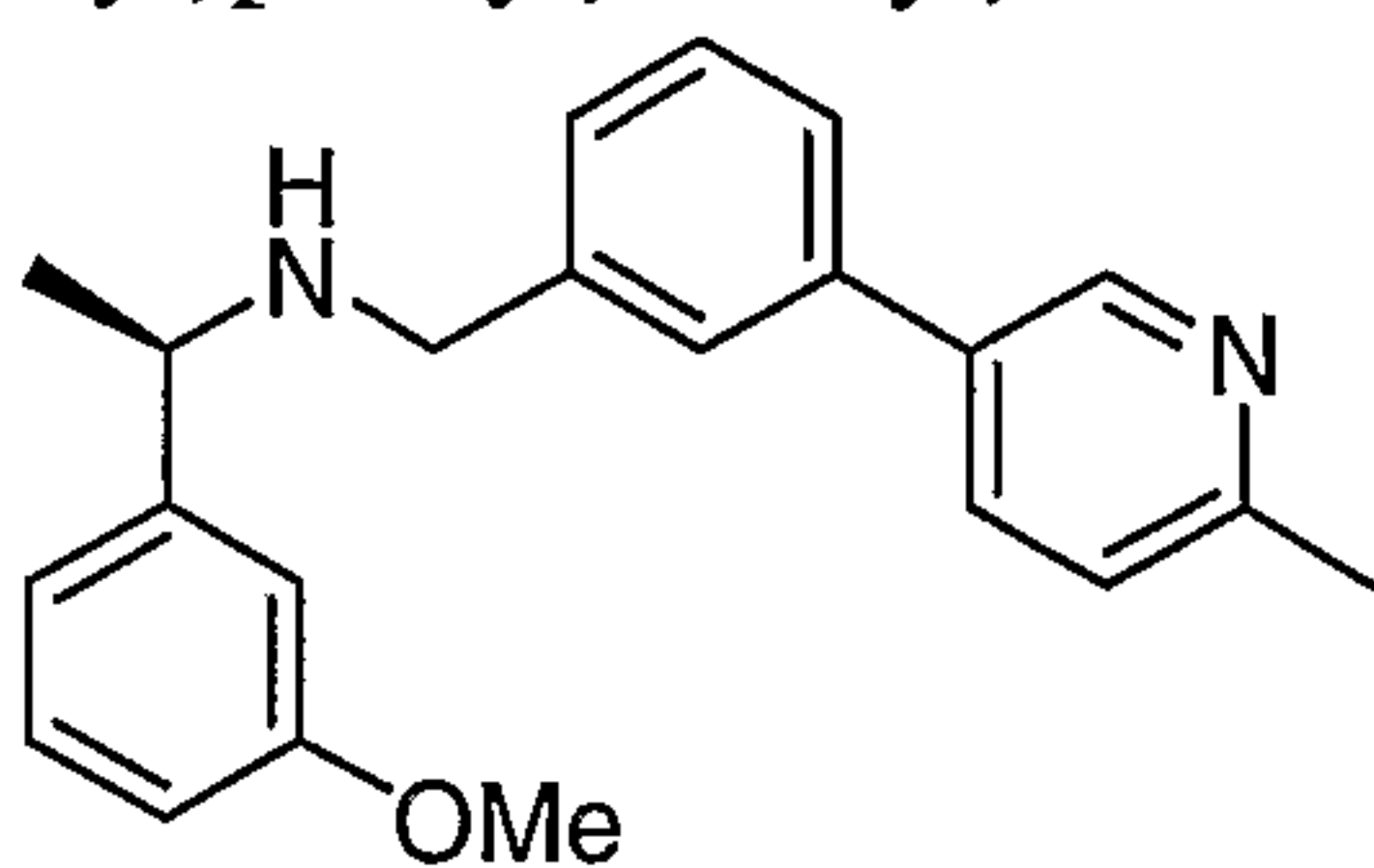
MW 332.445
Mass found: 333, 779, 665

15

Example 179

(1R)-1-(3-(methyloxy)phenyl)-N-((3-(6-methyl-3-ylridinyl)phenyl)methyl)ethanamine

20



MW 332.445
Mass found: 333, 779, 665

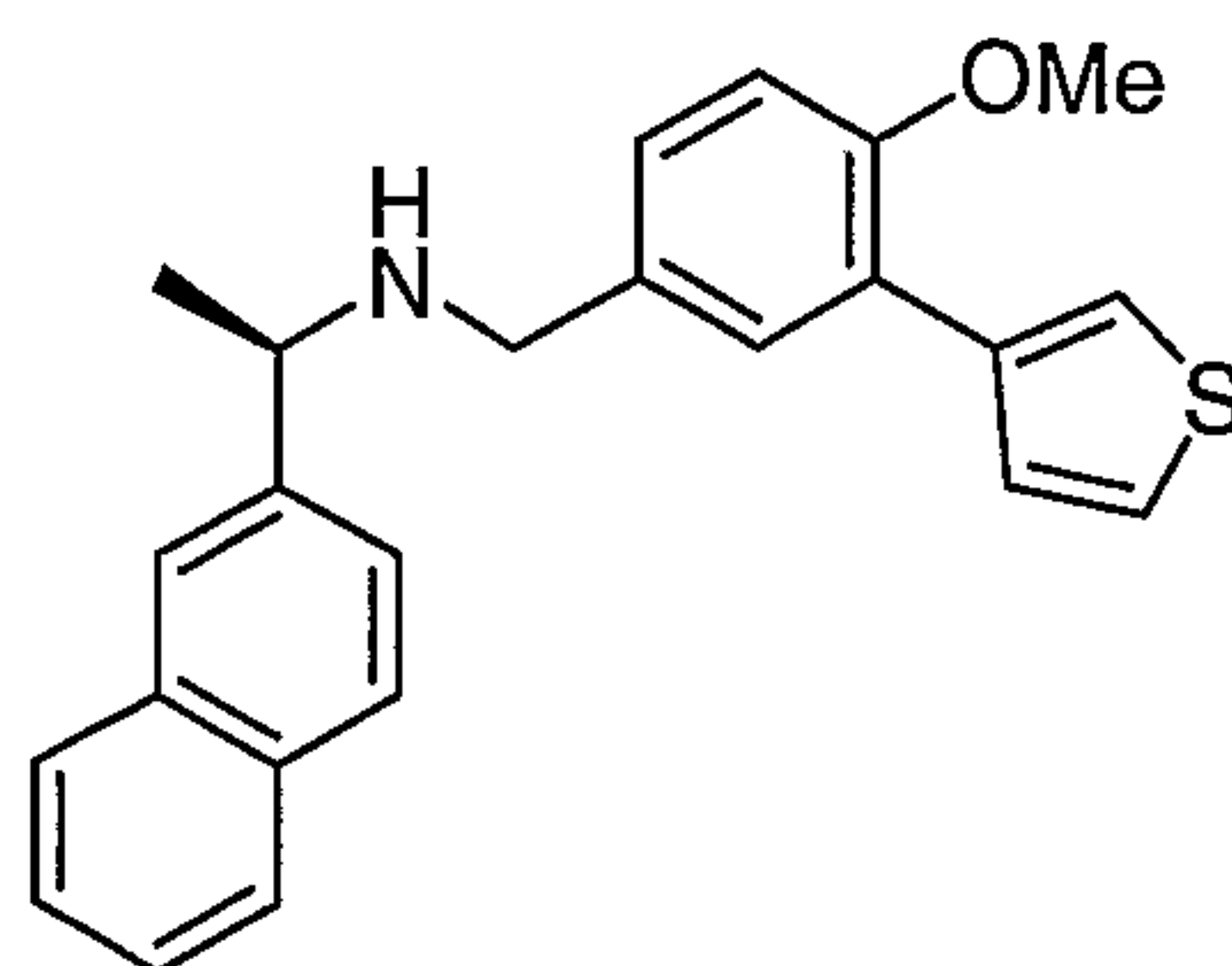
25

Example 180

(1R)-N-((4-(methyloxy)-3-(3-thienyl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine

30

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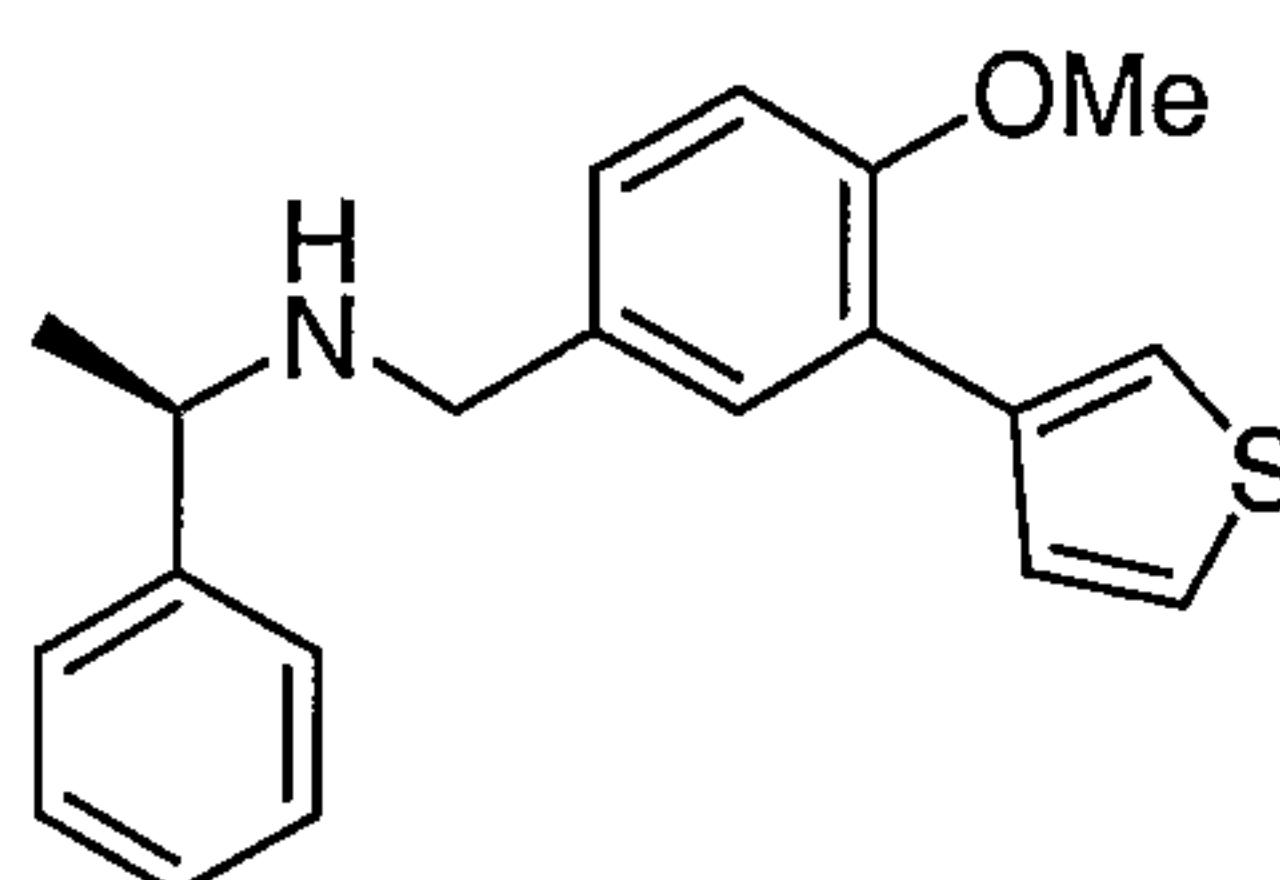
MW 373.518
Mass found: 374, 747

5

Example 181

(1R)-N-((4-(methyloxy)-3-(3-thienyl)phenyl)methyl)-1-phenylethanamine

10



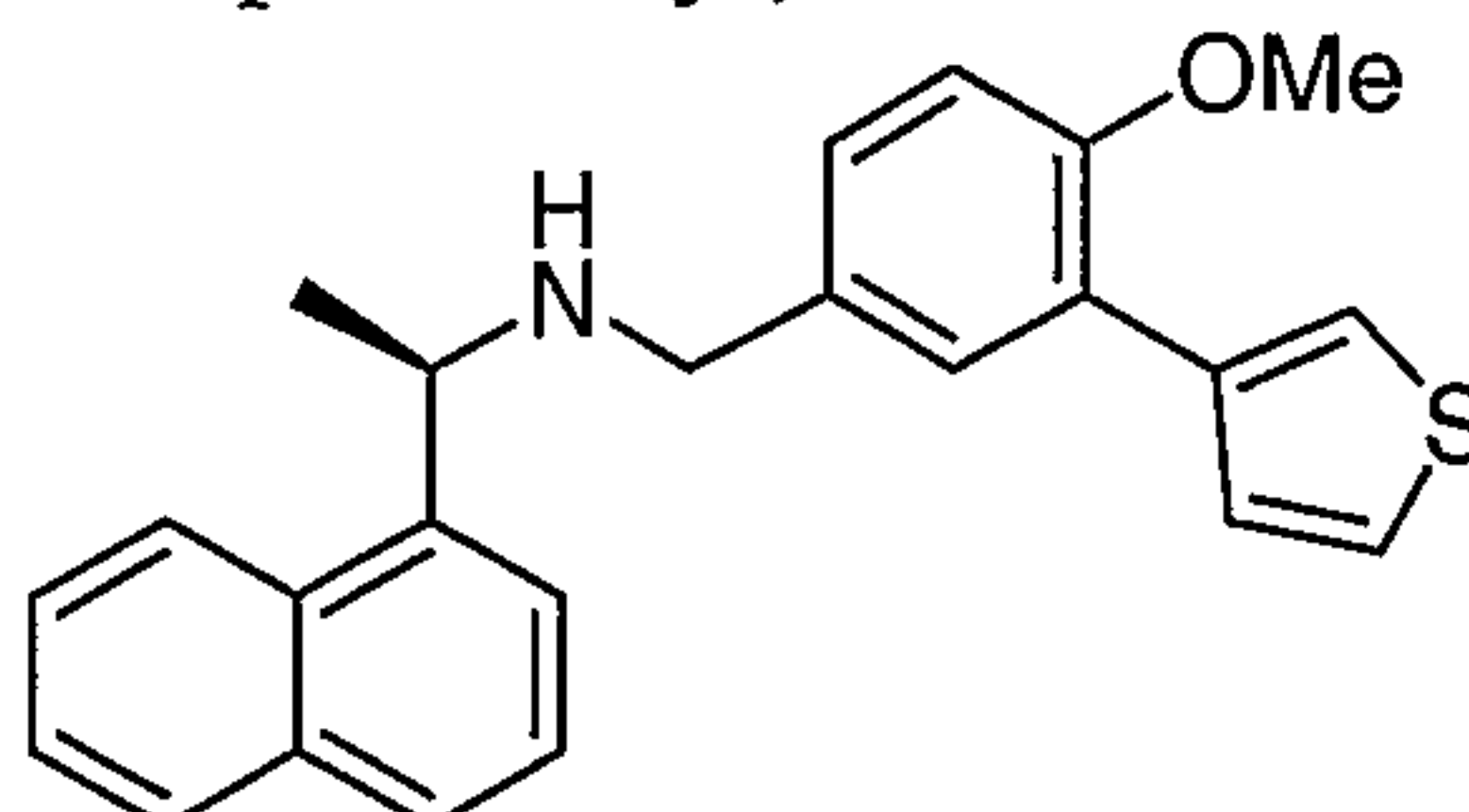
MW 323.458
Mass found: 324, 647, 761

15

Example 182

(1R)-N-((4-(methyloxy)-3-(3-thienyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

20



MW 373.518
Mass found: 374, 747

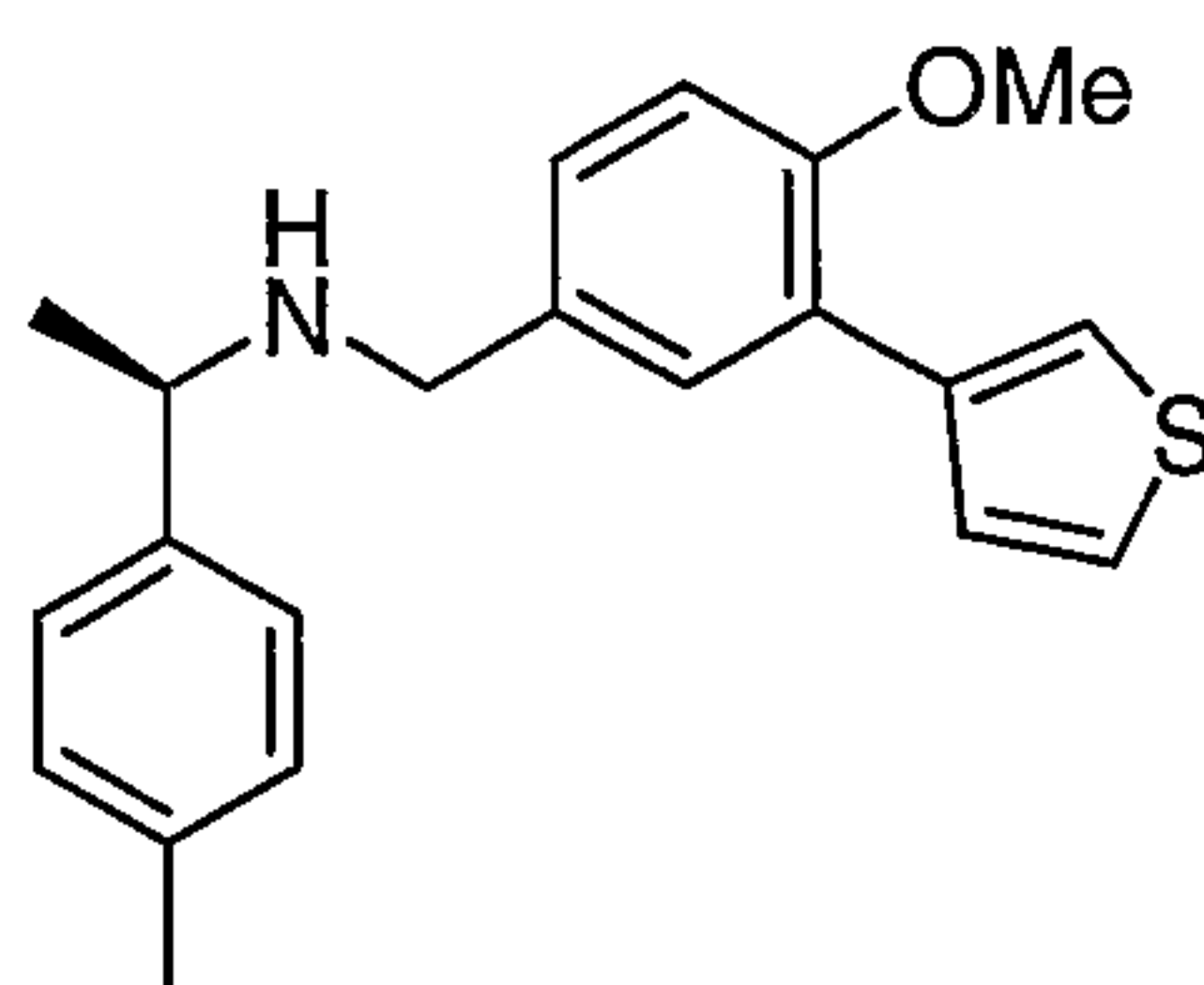
25

Example 183

(1R)-N-((4-(methyloxy)-3-(3-thienyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine

30

- 154 -



MW 337.485

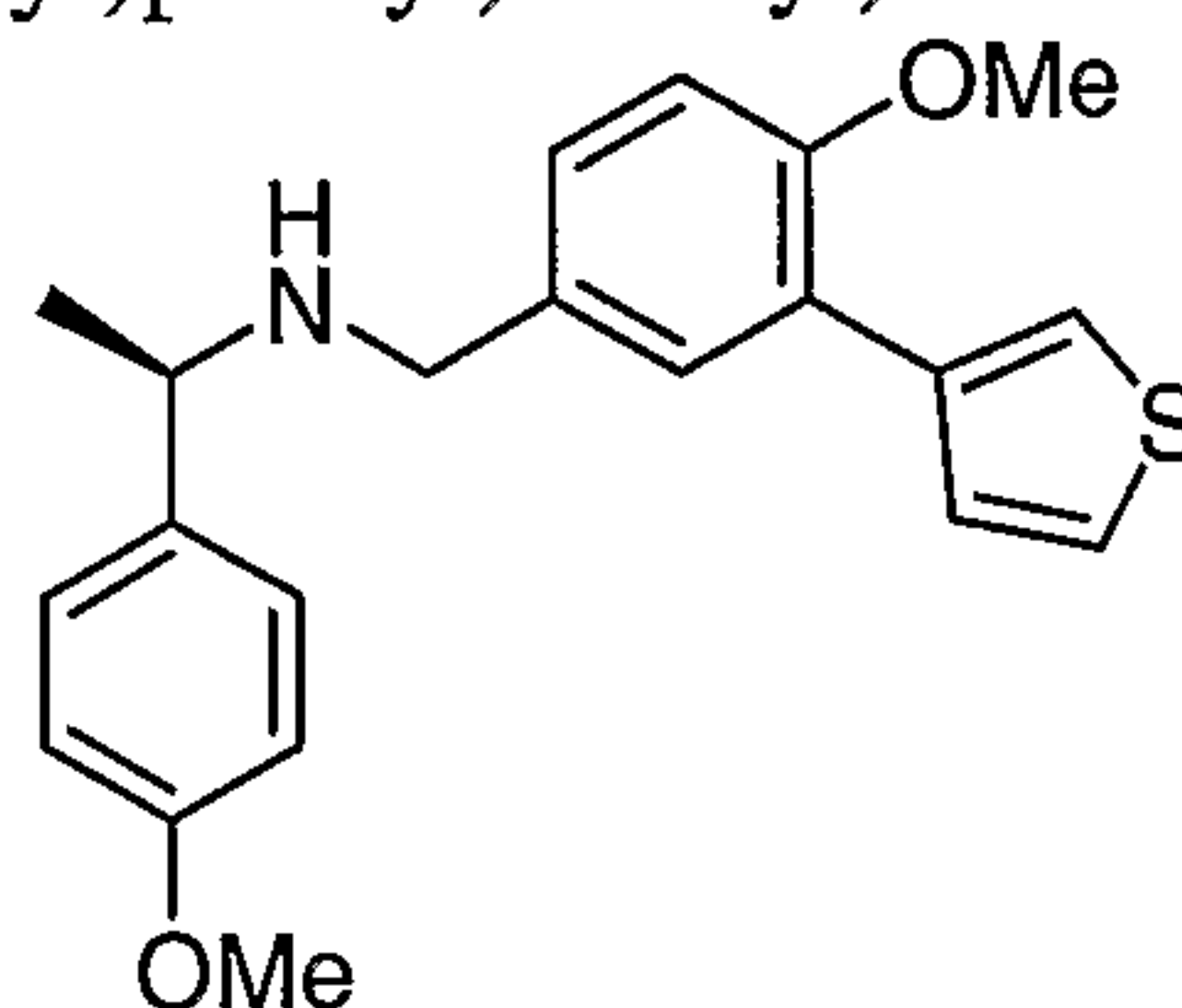
Mass found: 338, 675

5

Example 184

(1R)-1-(4-(methoxy)phenyl)-N-((4-(methoxy)-3-(3-thienyl)phenyl)methyl)ethanamine

10



MW 353.484

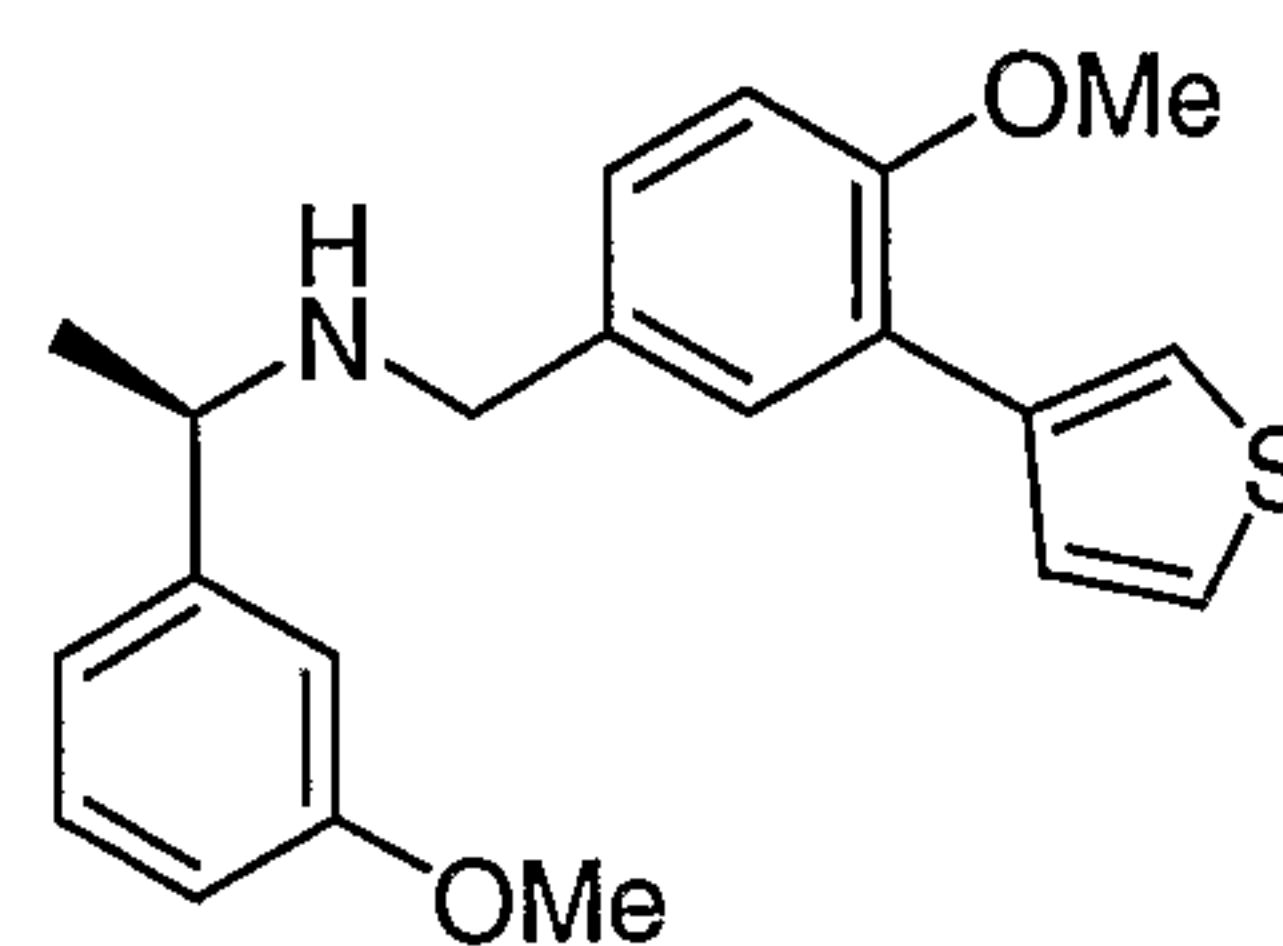
Mass found: 354, 707

15

Example 185

(1R)-1-(3-(methoxy)phenyl)-N-((4-(methoxy)-3-(3-thienyl)phenyl)methyl)ethanamine

20



MW 353.484

Mass found: 354, 707

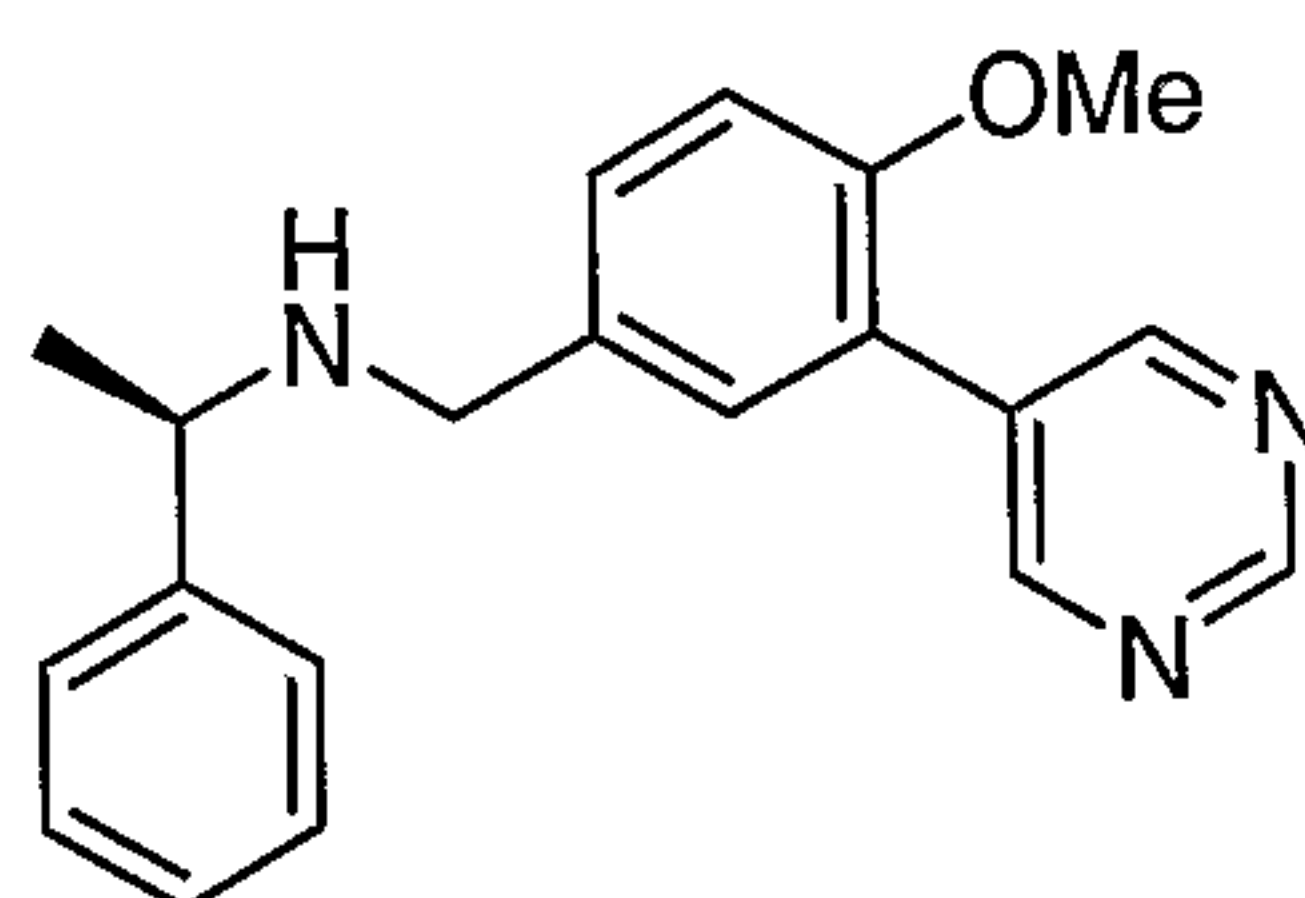
25

Example 186

(1R)-N-((4-(methoxy)-3-(5-pyrimidinyl)phenyl)methyl)-1-phenylethanamine

30

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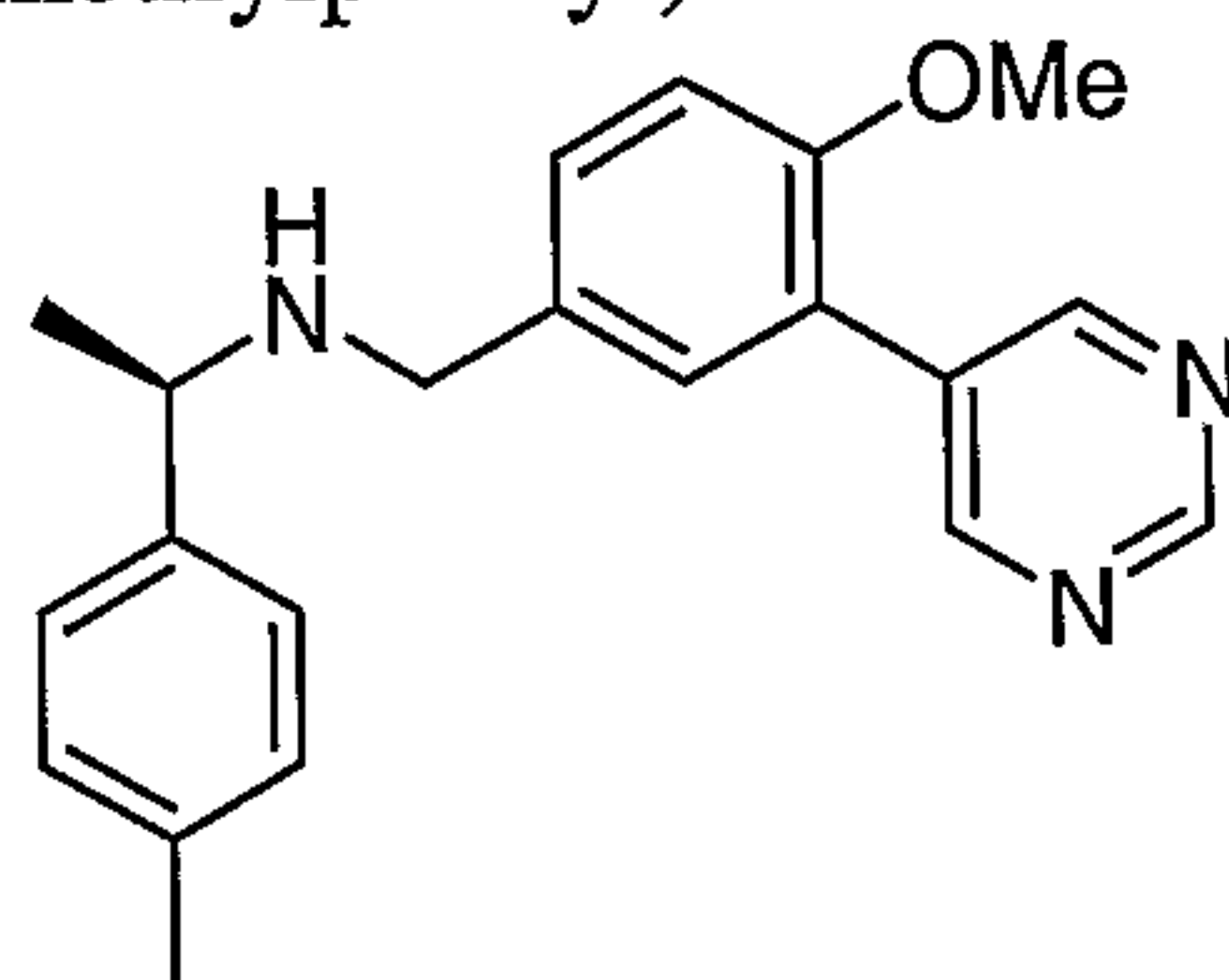
MW 319.406
Mass found: 320, 361, 753

5

Example 187

(1R)-N-((4-(methyloxy)-3-(5-pyrimidinyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine

10



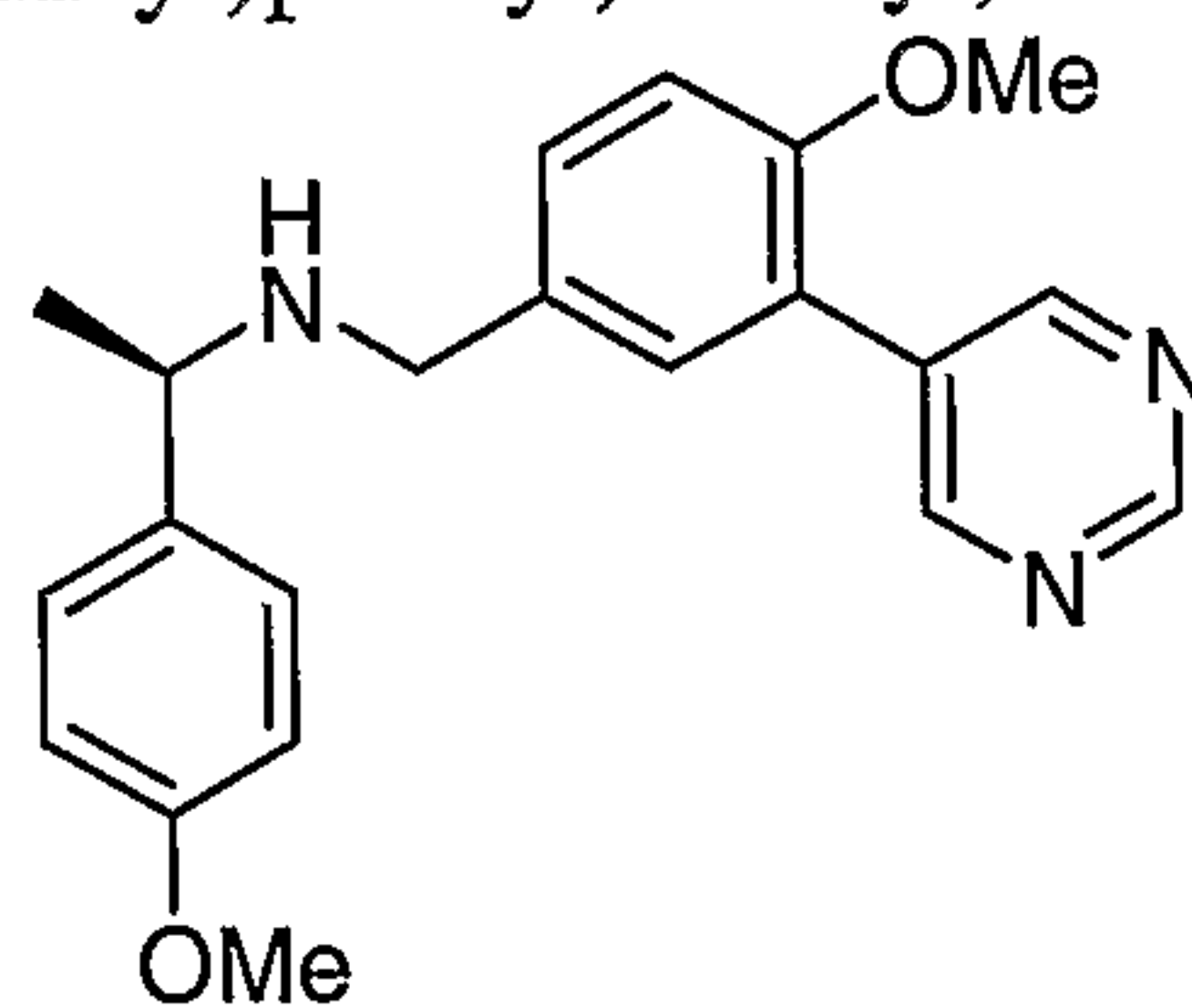
MW 333.433
Mass found: 334, 781

15

Example 188

(1R)-1-(4-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(5-pyrimidinyl)phenyl)methyl)ethanamine

20



MW 349.432
Mass found: 350, 699

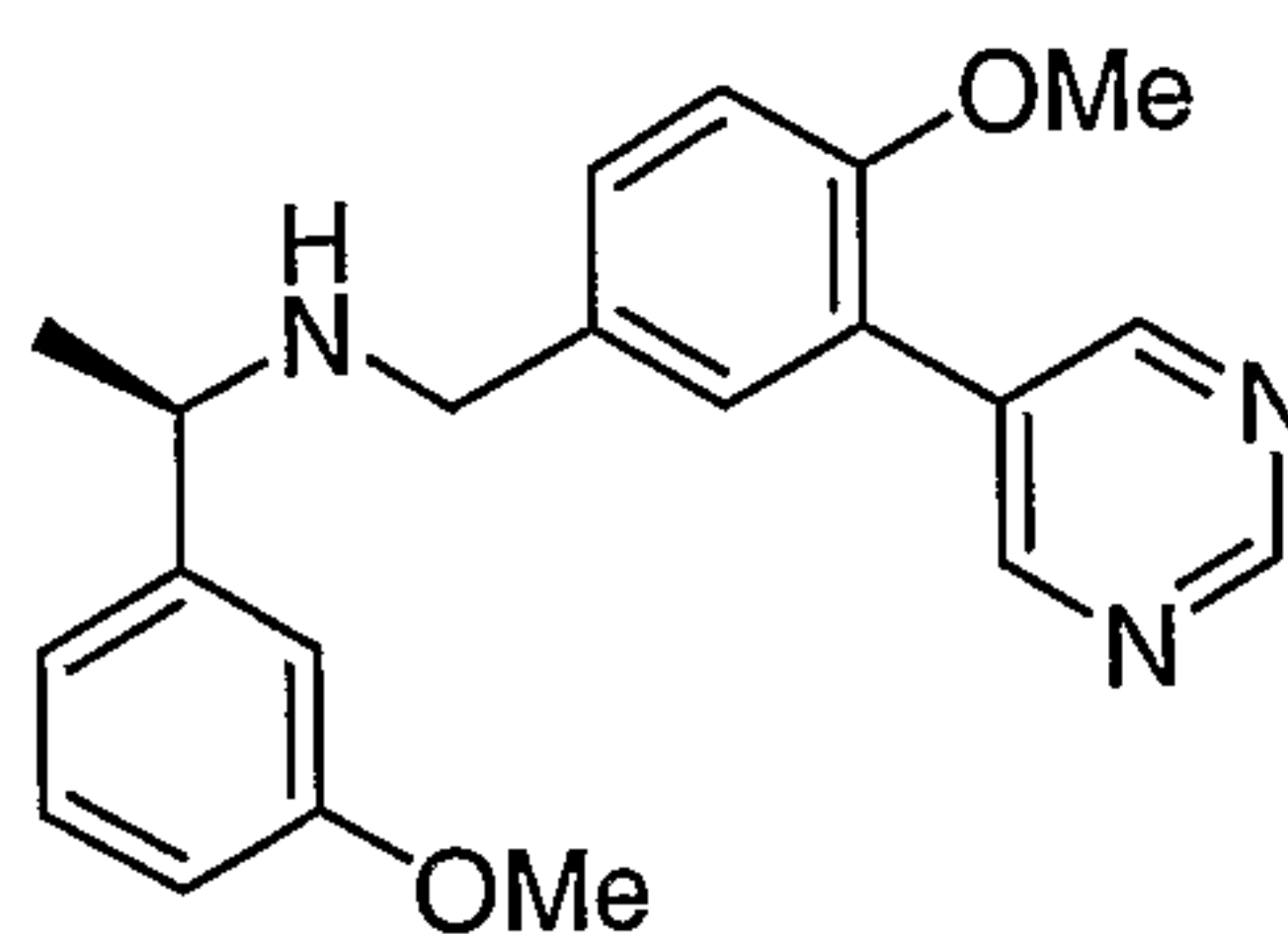
25

Example 189

(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(5-pyrimidinyl)phenyl)methyl)ethanamine

30

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MW 349.432

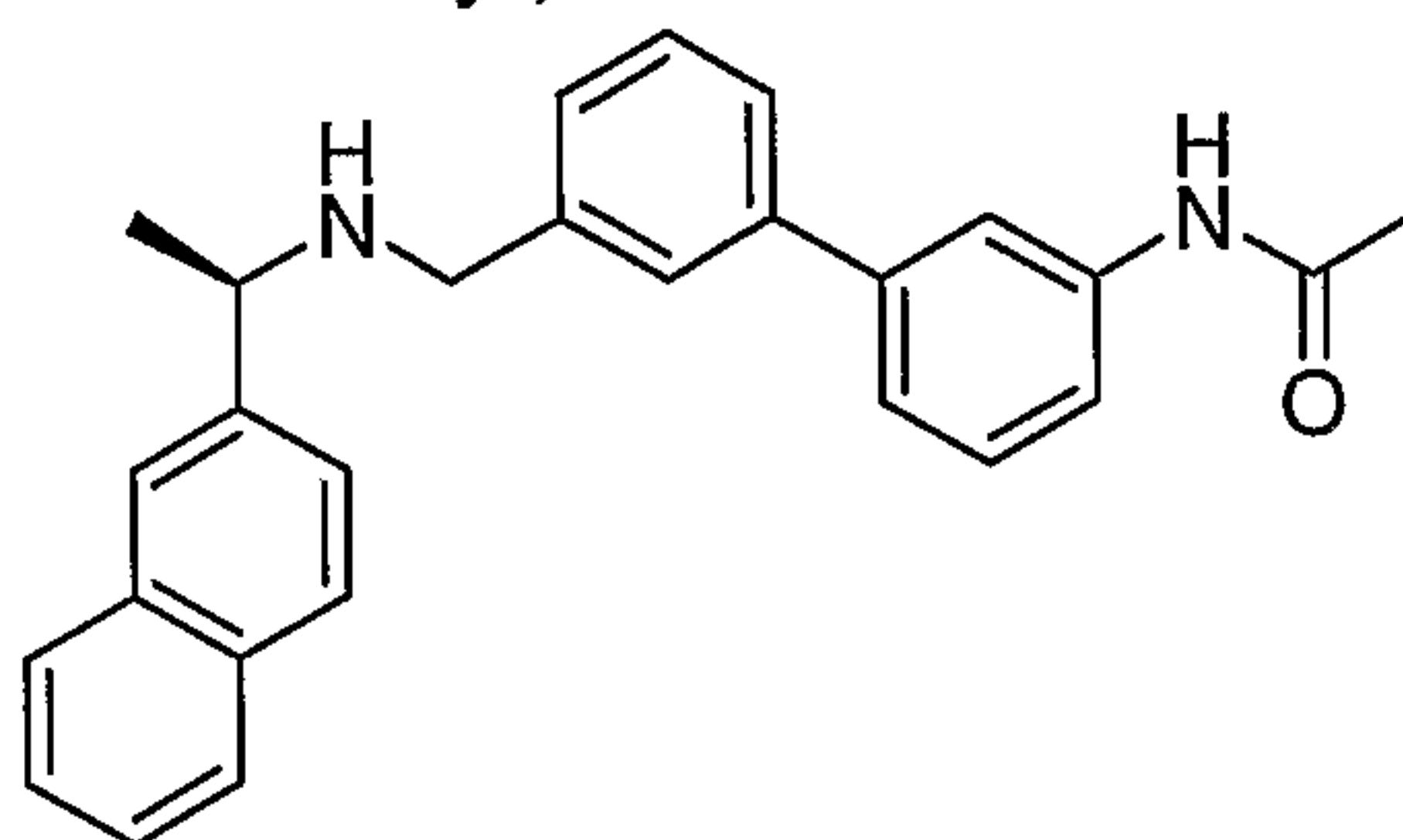
Mass found: 350, 699

5

Example 190

N-(3'-((((1R)-1-(2-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-yl)acetamide

10



MW 394.515

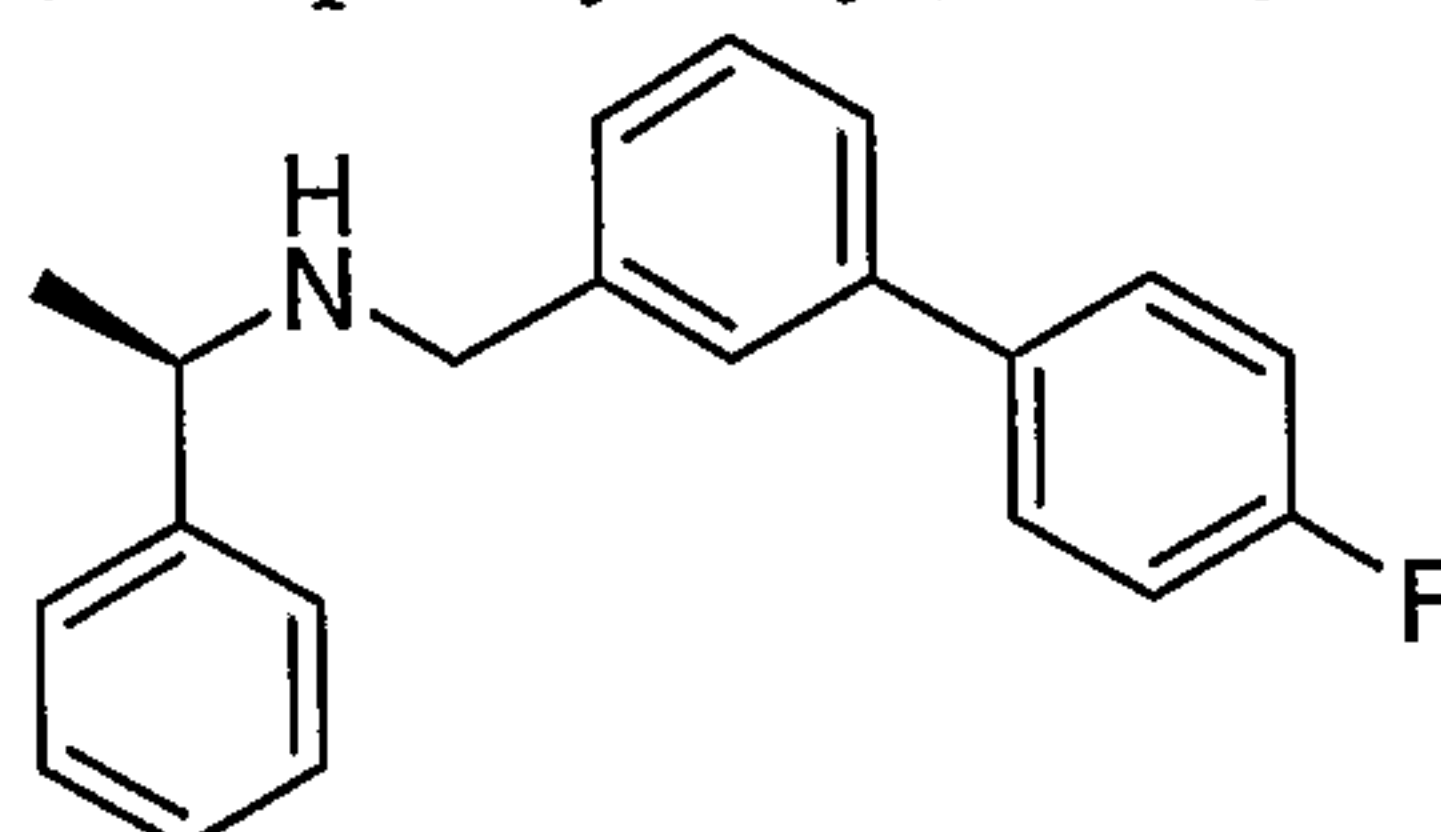
Mass found: 395, 789

15

Example 191

(1R)-N-((4'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

20



MW 305.394

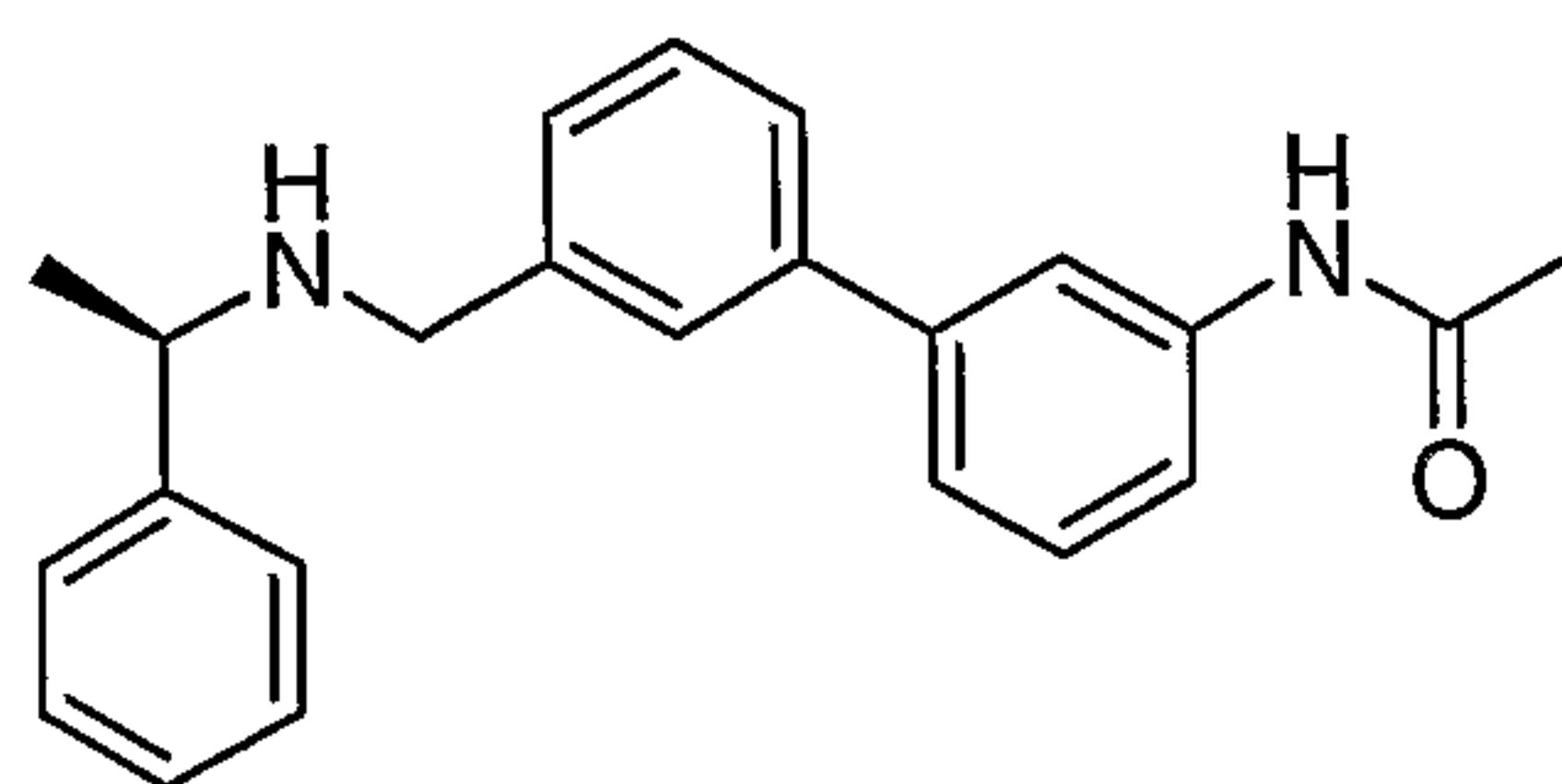
Mass found: 306, 202, 243

25

Example 192

N-(3'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-yl)acetamide

- 157 -



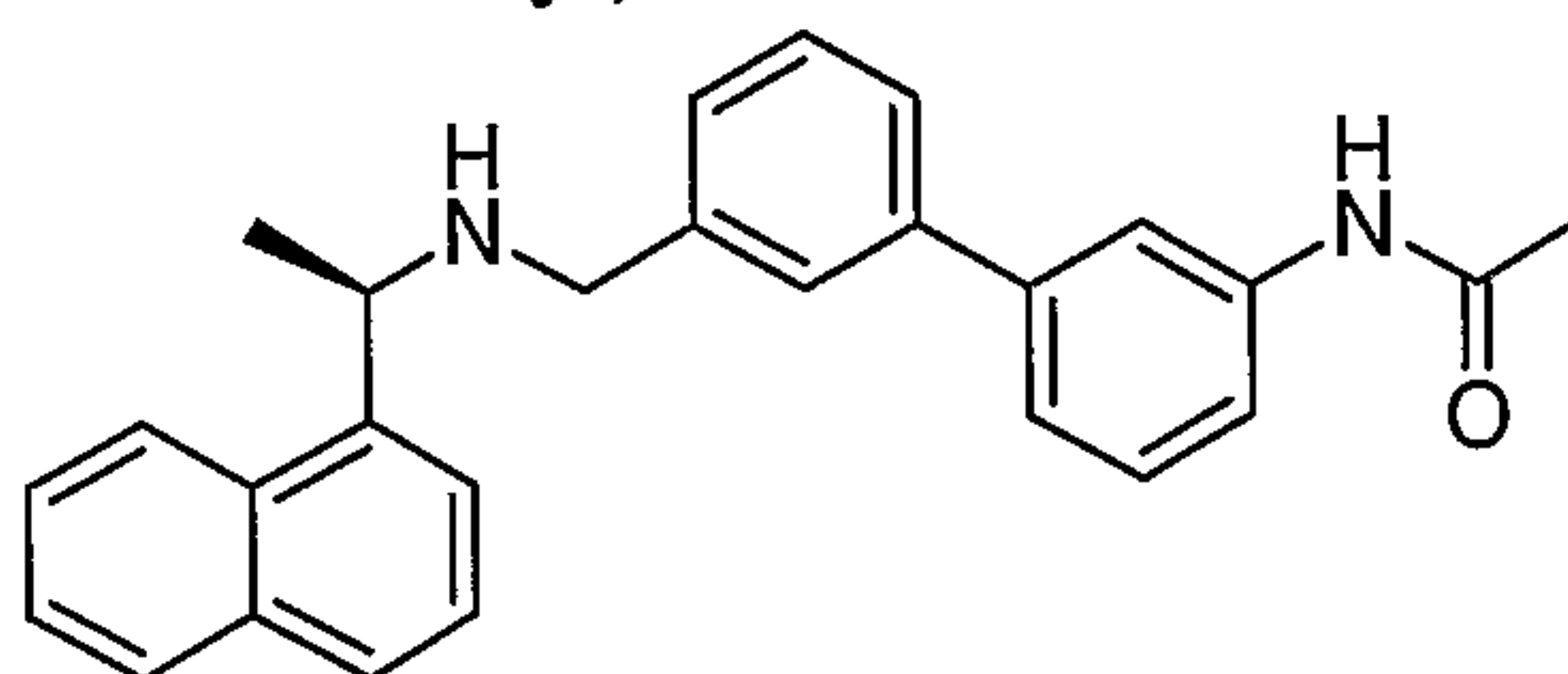
MW 344.456
Mass found: 345, 689

5

Example 193

N-(3'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-yl)acetamide

10



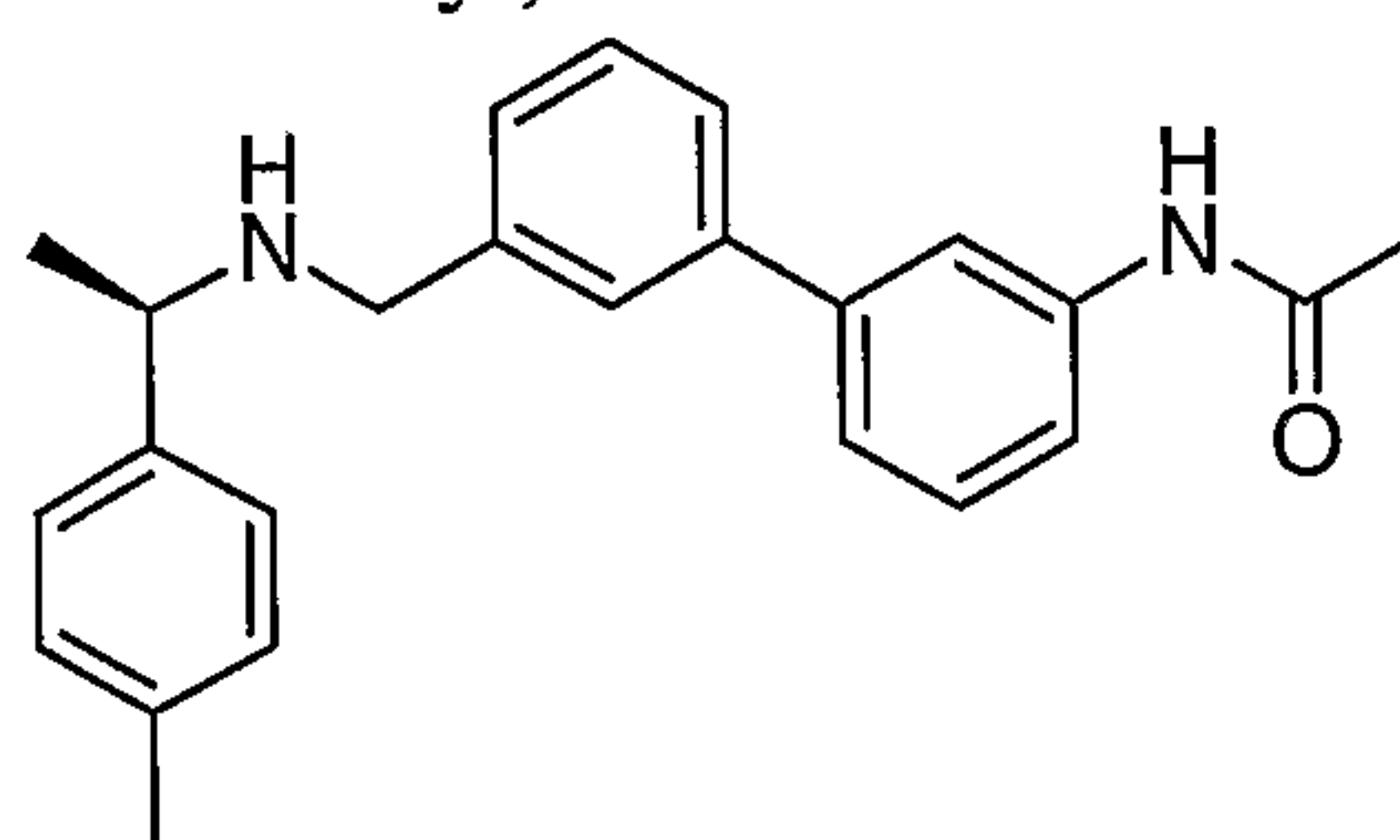
MW 394.515
Mass found: 395, 789

15

Example 194

N-(3'-((((1R)-1-(4-methylphenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-yl)acetamide

20



MW 358.482
Mass found: 359, 717

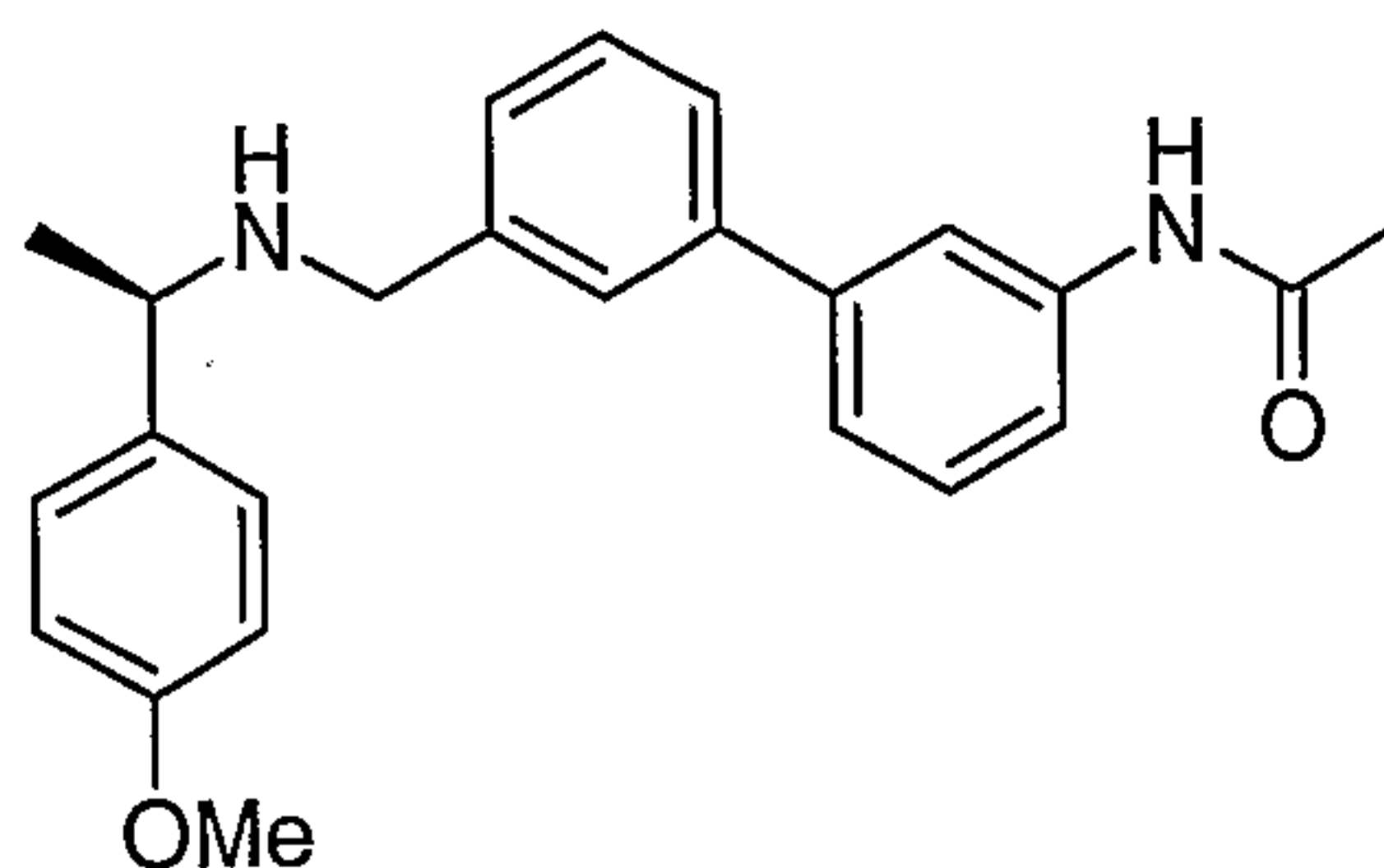
25

Example 195

N-(3'-((((1R)-1-(4-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-yl)acetamide

30

- 158 -



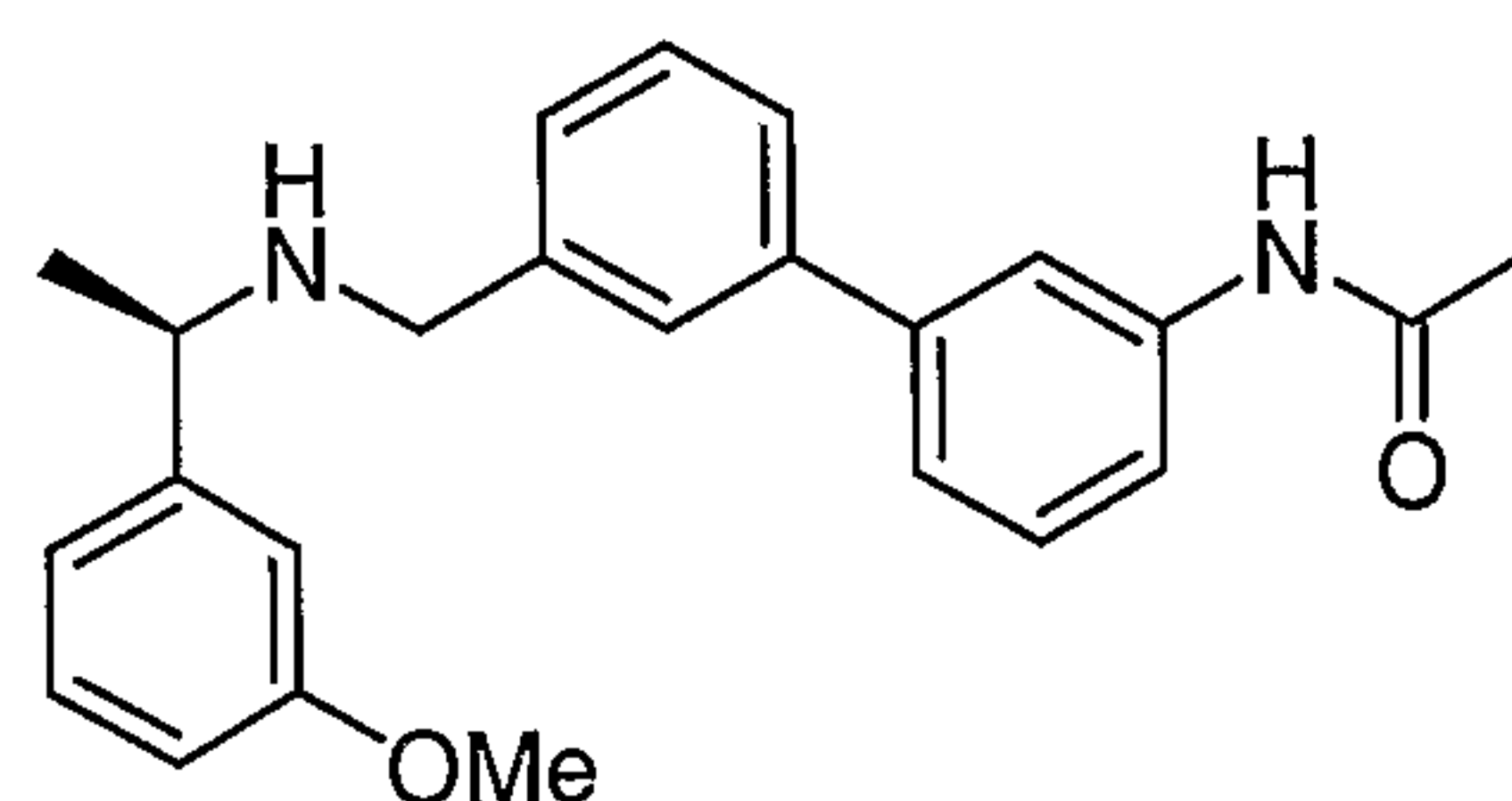
MW 374.481
Mass found: 375, 749

5

Example 196

N-(3'-((((1R)-1-(3-(methoxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-yl)acetamide

10

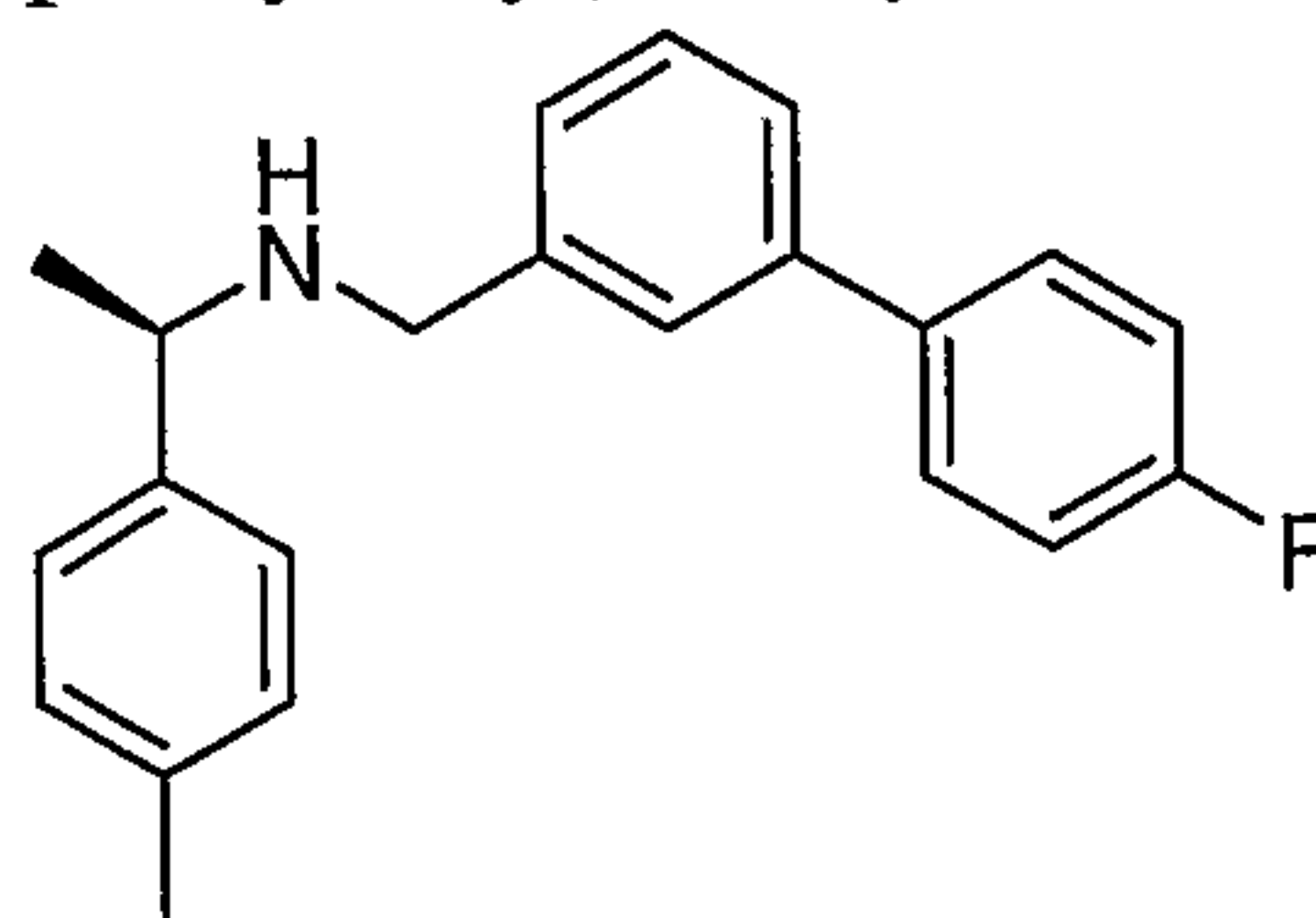


MW 374.481
Mass found: 375, 749, 416

15

Example 197

(1R)-N-((4'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine



MW 319.421
Mass found: 320, 202, 243

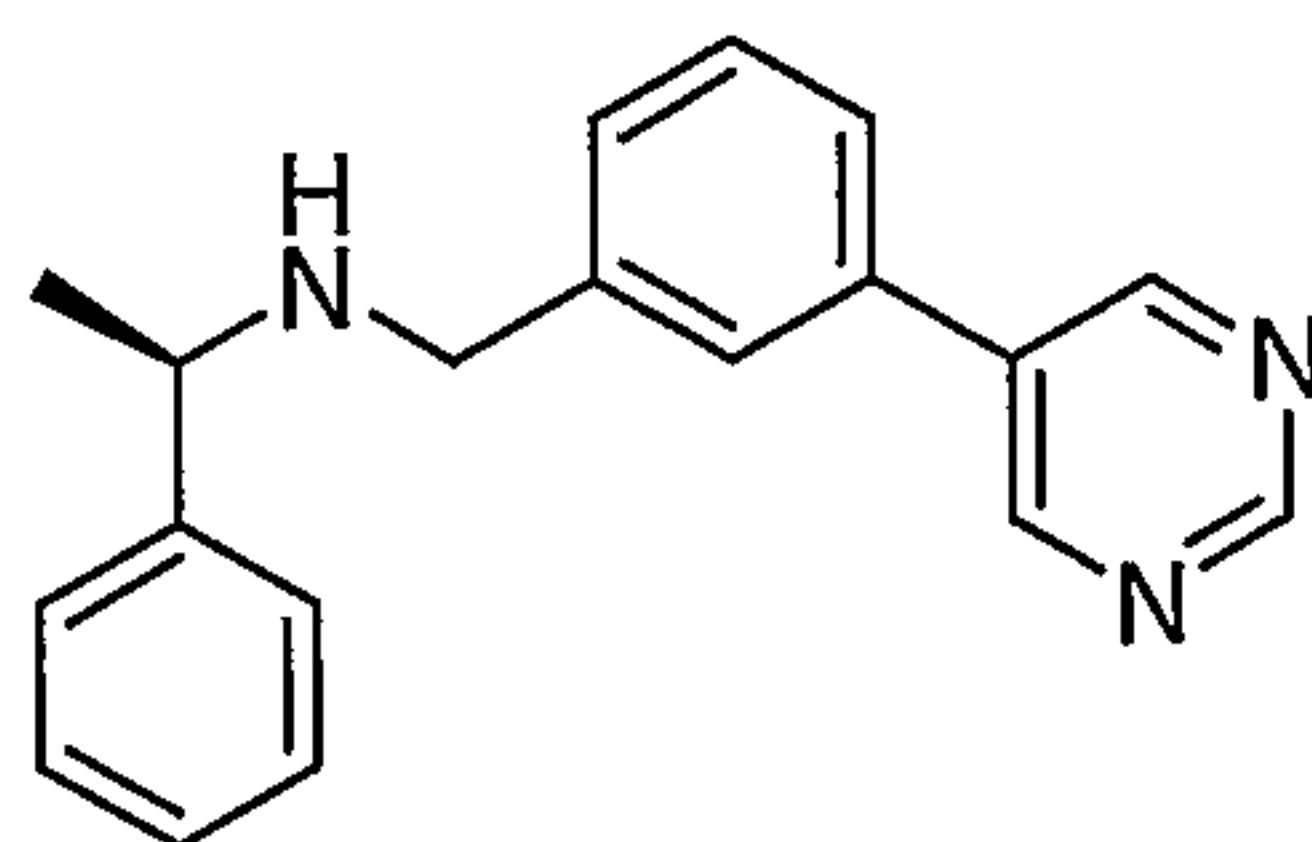
20

Example 198

(1R)-1-phenyl-N-((3-(5-pyrimidinyl)phenyl)methyl)ethanamine

25

- 159 -



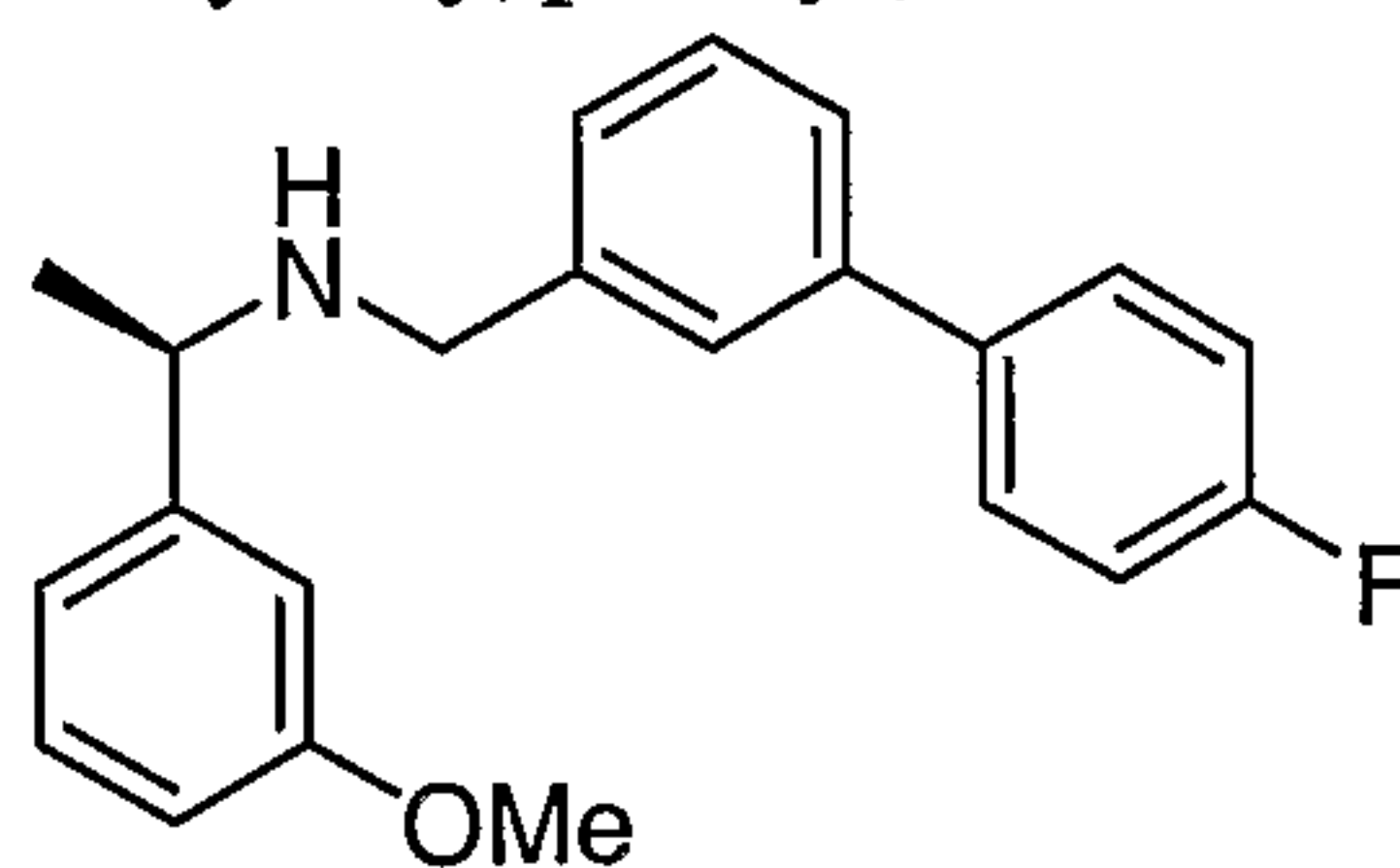
MW 289.38
Mass found: 290, 693, 331

5

Example 199

(1R)-N-((4'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(3-(methoxy)phenyl)ethanamine

10

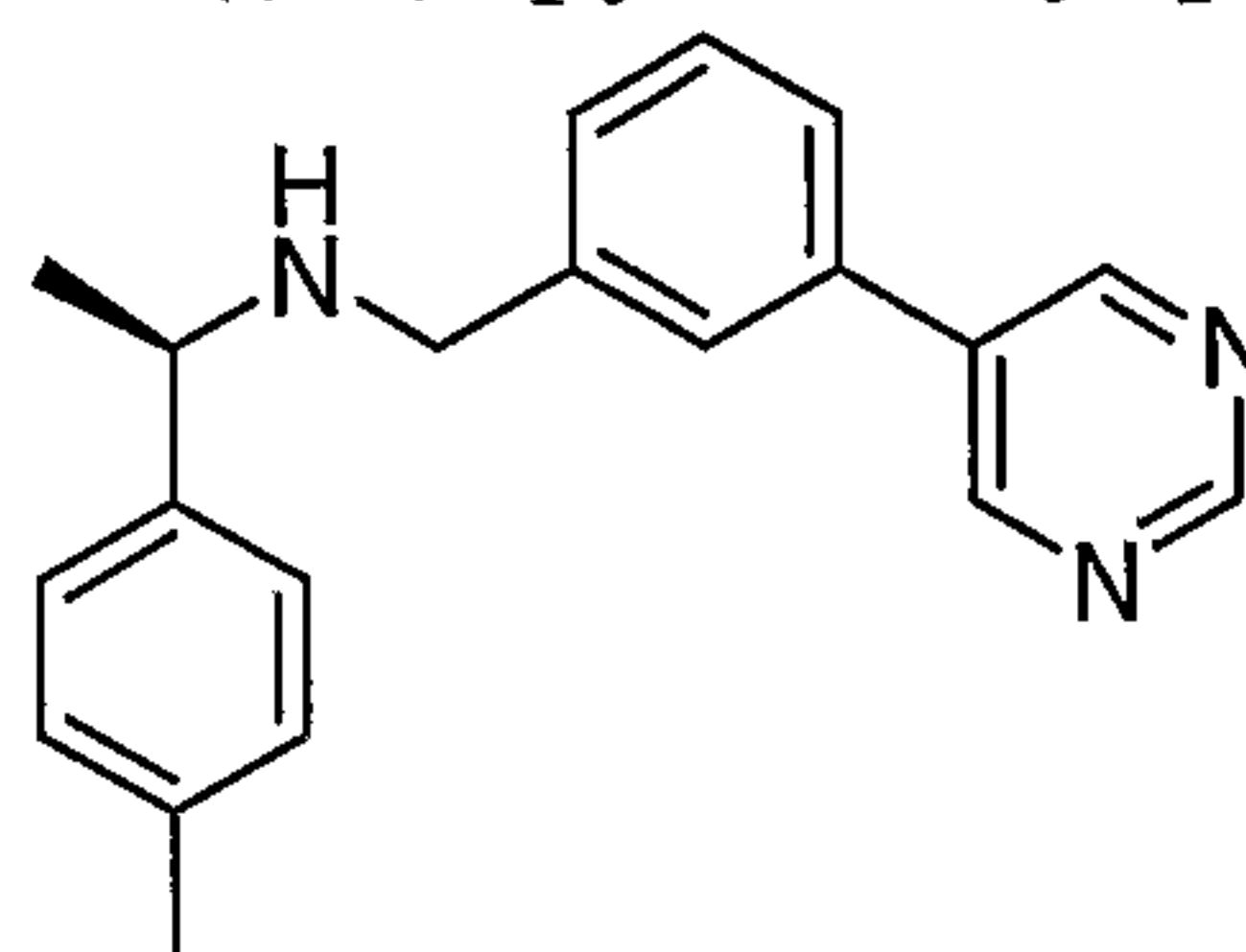


MW 335.42
Mass found: 336, 202, 243

15

Example 200

(1R)-1-(4-methylphenyl)-N-((3-(5-pyrimidinyl)phenyl)methyl)ethanamine



20

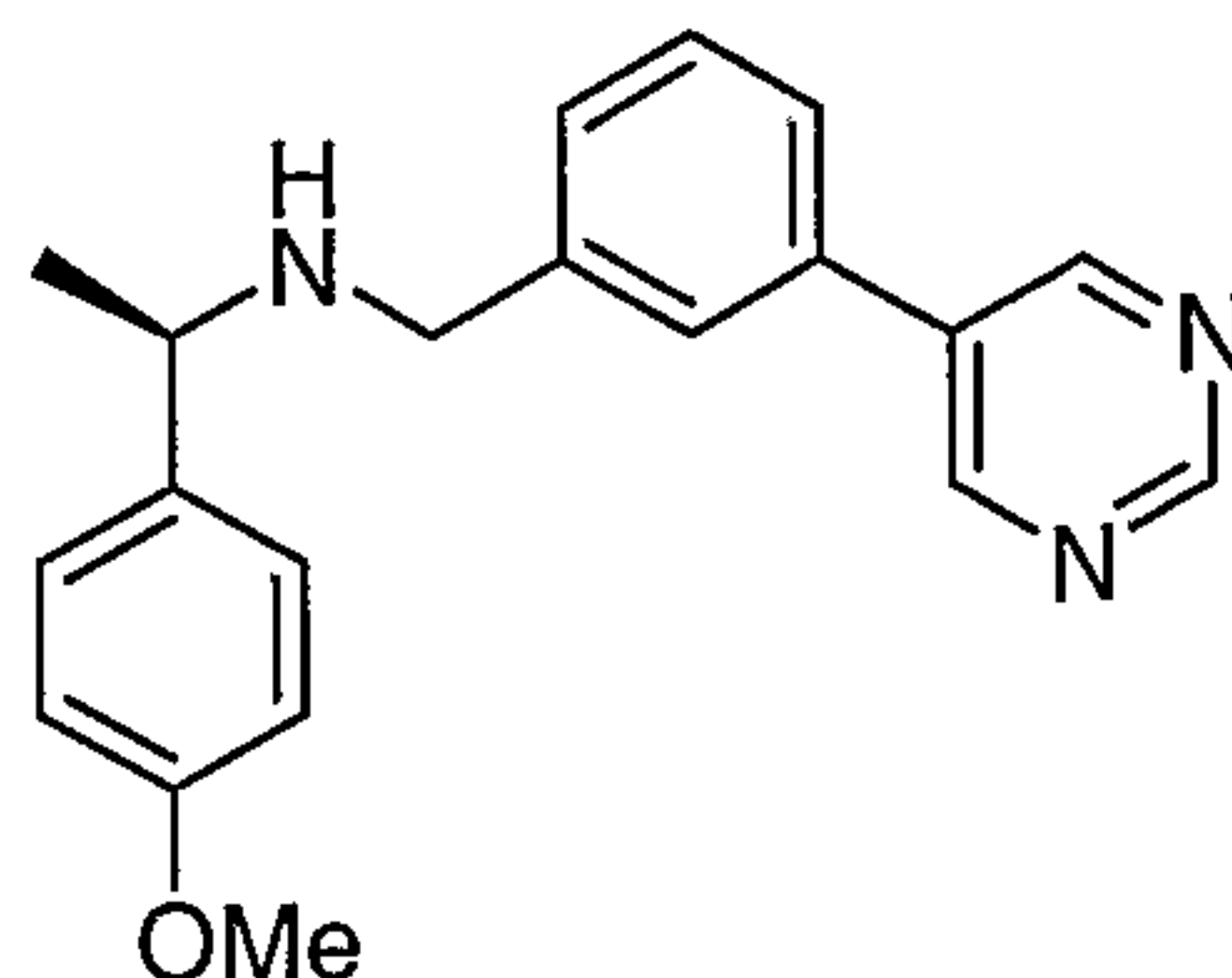
MW 303.407
Mass found: 304, 721, 345

25

Example 201

(1R)-1-(4-(methoxy)phenyl)-N-((3-(5-pyrimidinyl)phenyl)methyl)ethanamine

- 160 -



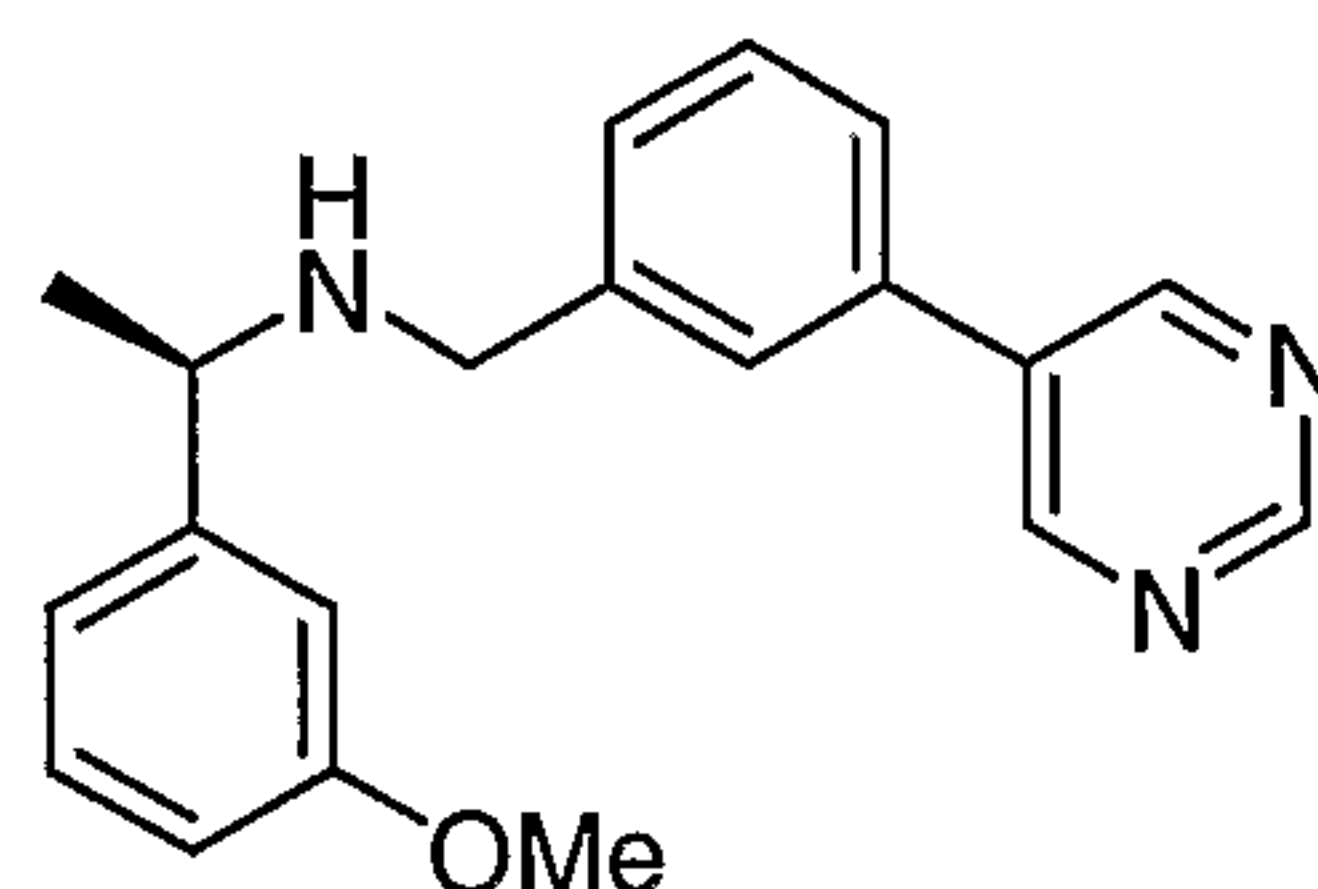
MW 319.406
Mass found: 320, 753

5

Example 202

(1R)-1-(3-(methyloxy)phenyl)-N-((3-(5-pyrimidinyl)phenyl)methyl)ethanamine

10



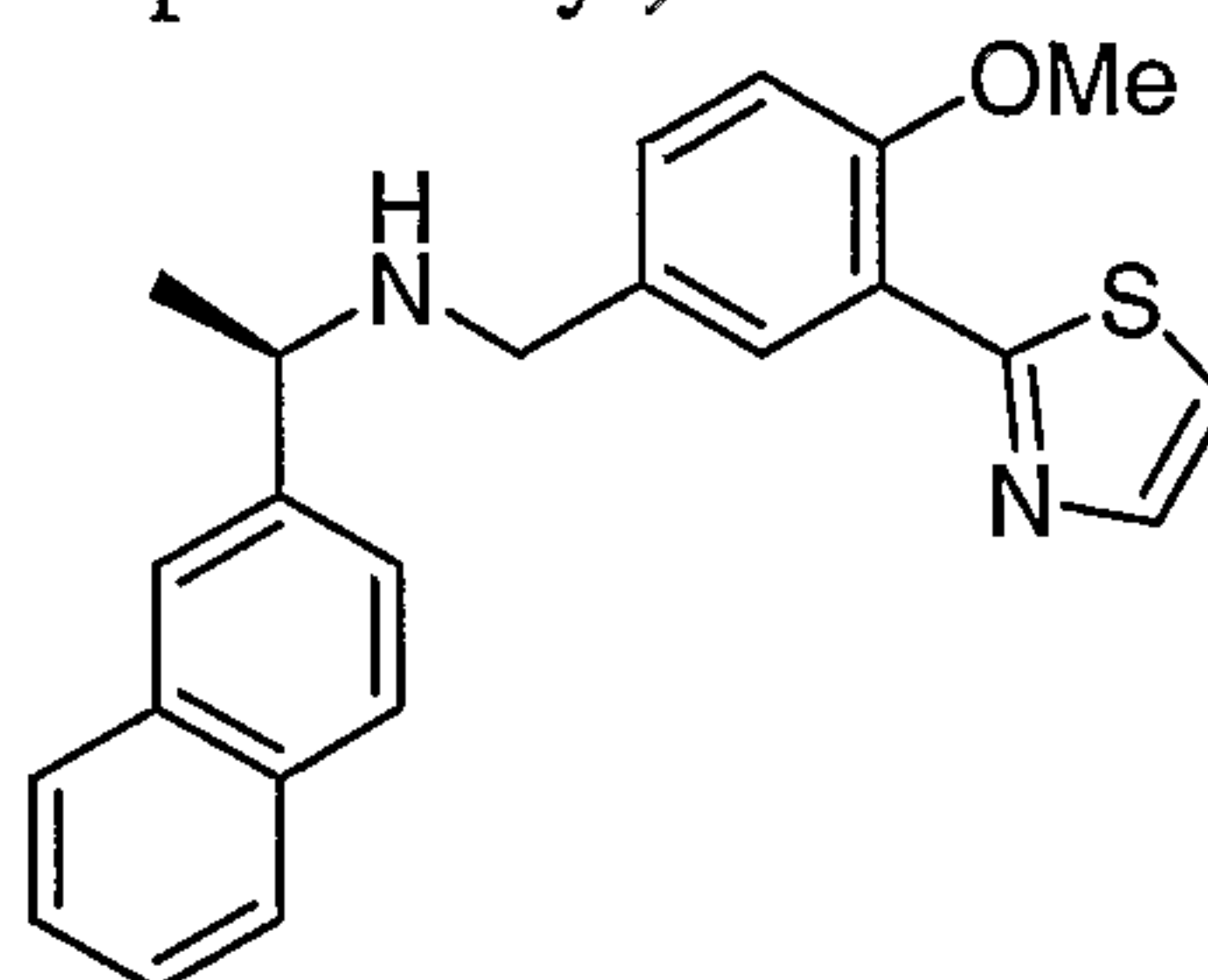
MW 319.406
Mass found: 320, 753, 361

15

Example 203

(1R)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine

20



MW 374.506
Mass found: 375, 749

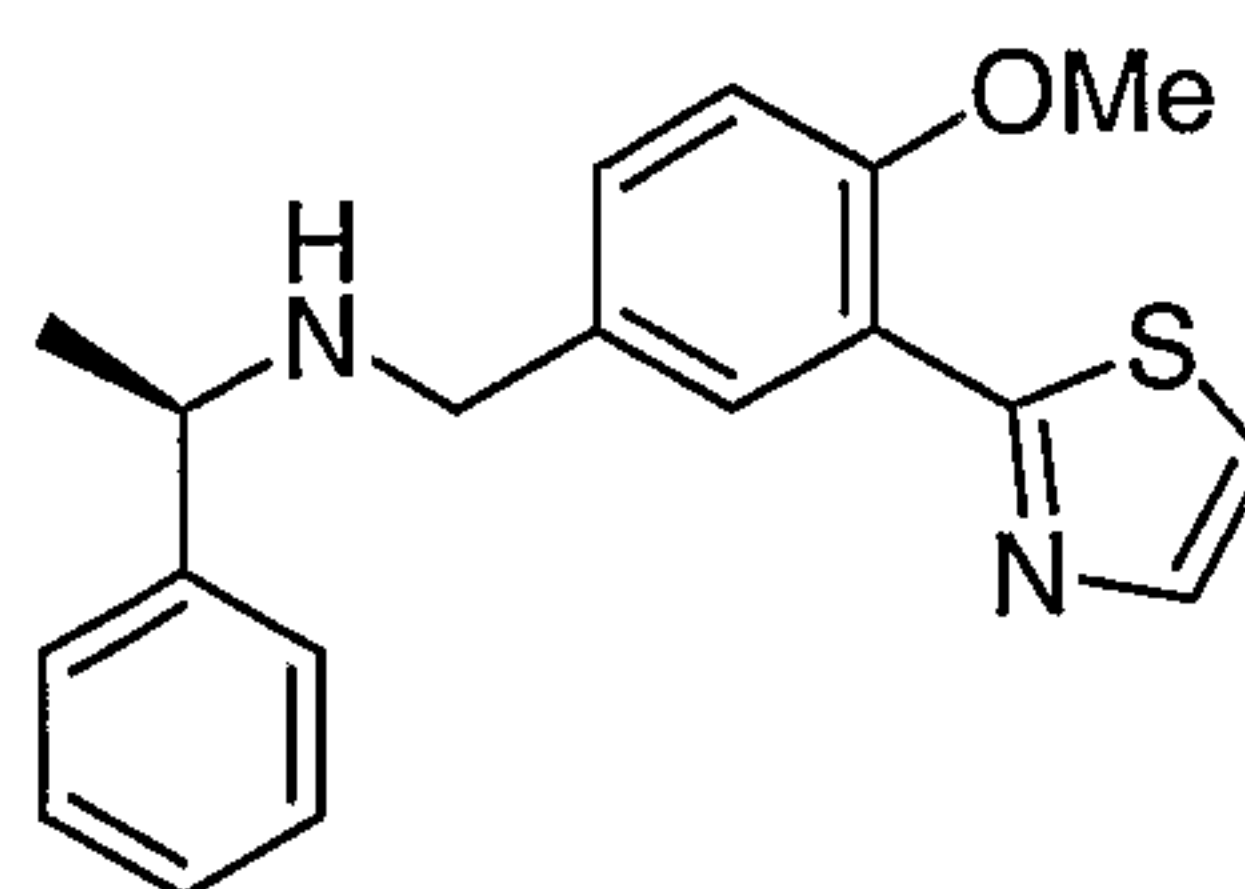
25

Example 204

(1R)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)-1-phenylethanamine

30

- 161 -



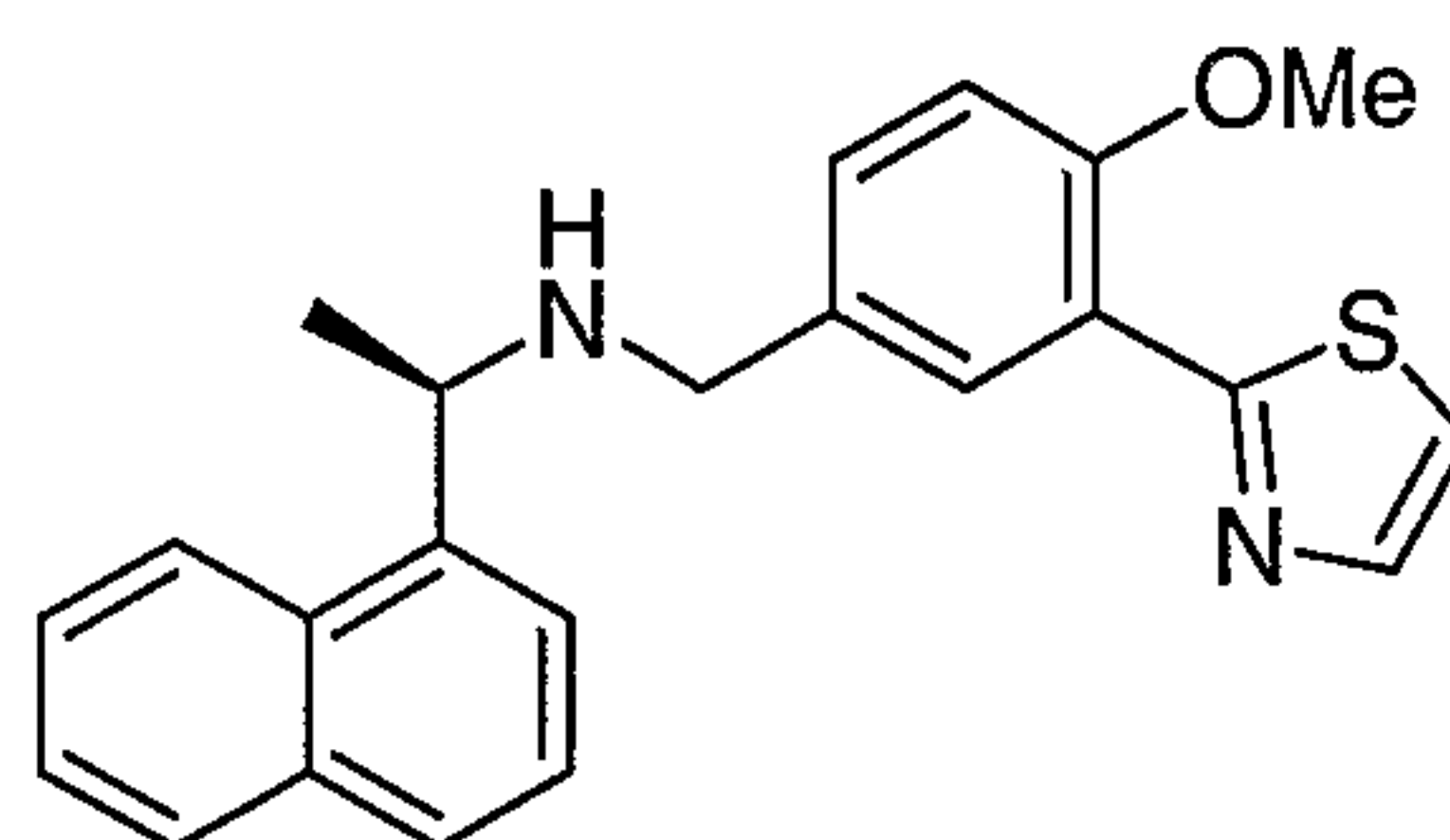
MW 324.446

Mass found: 325, 649

5

Example 205

10 (1R)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



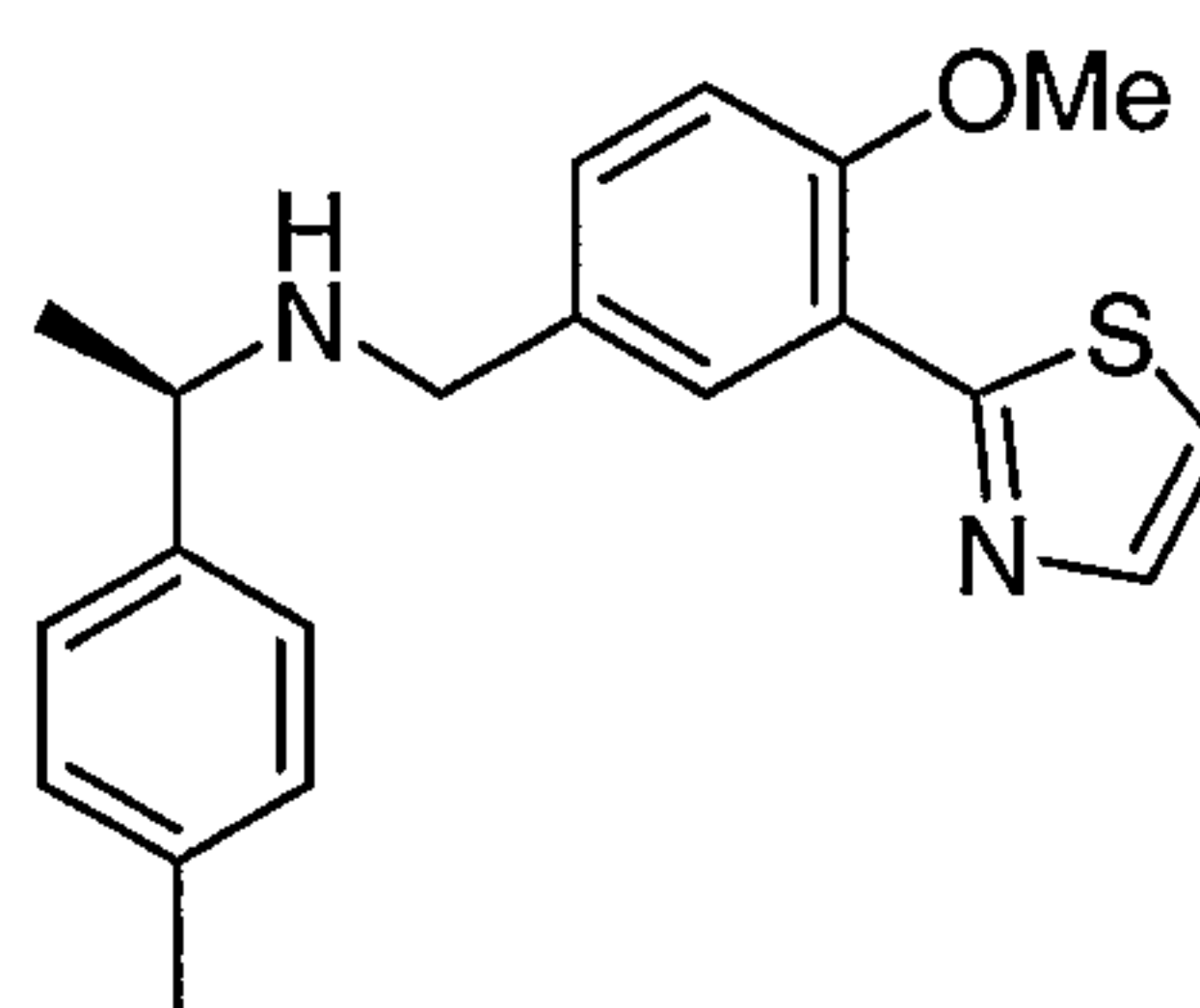
MW 374.506

Mass found: 375, 749

15

Example 206

20 (1R)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)-1-(4-methylphenyl)ethanamine



MW 338.473

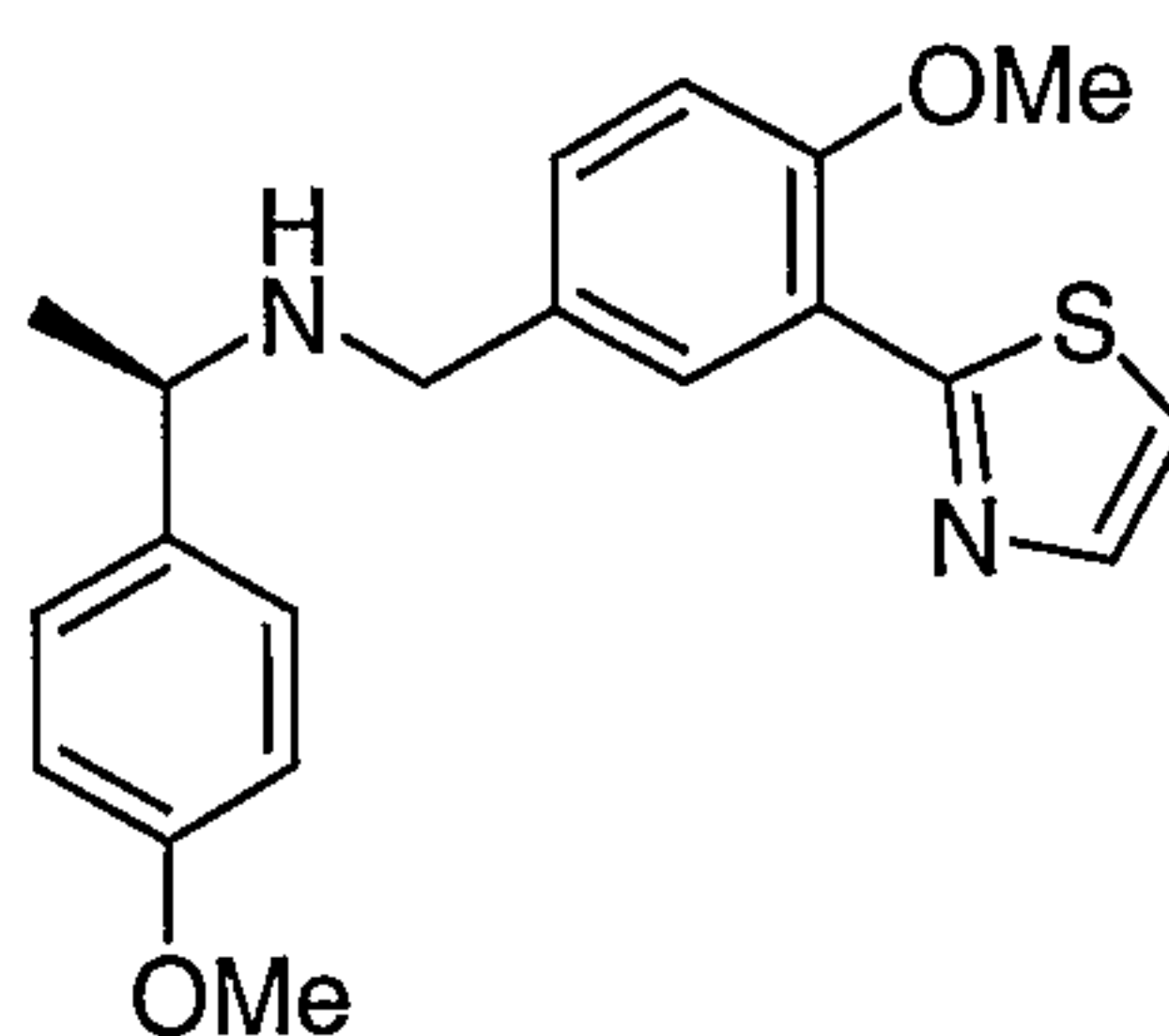
Mass found: 339, 677

25

Example 207

30 (1R)-1-(4-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine

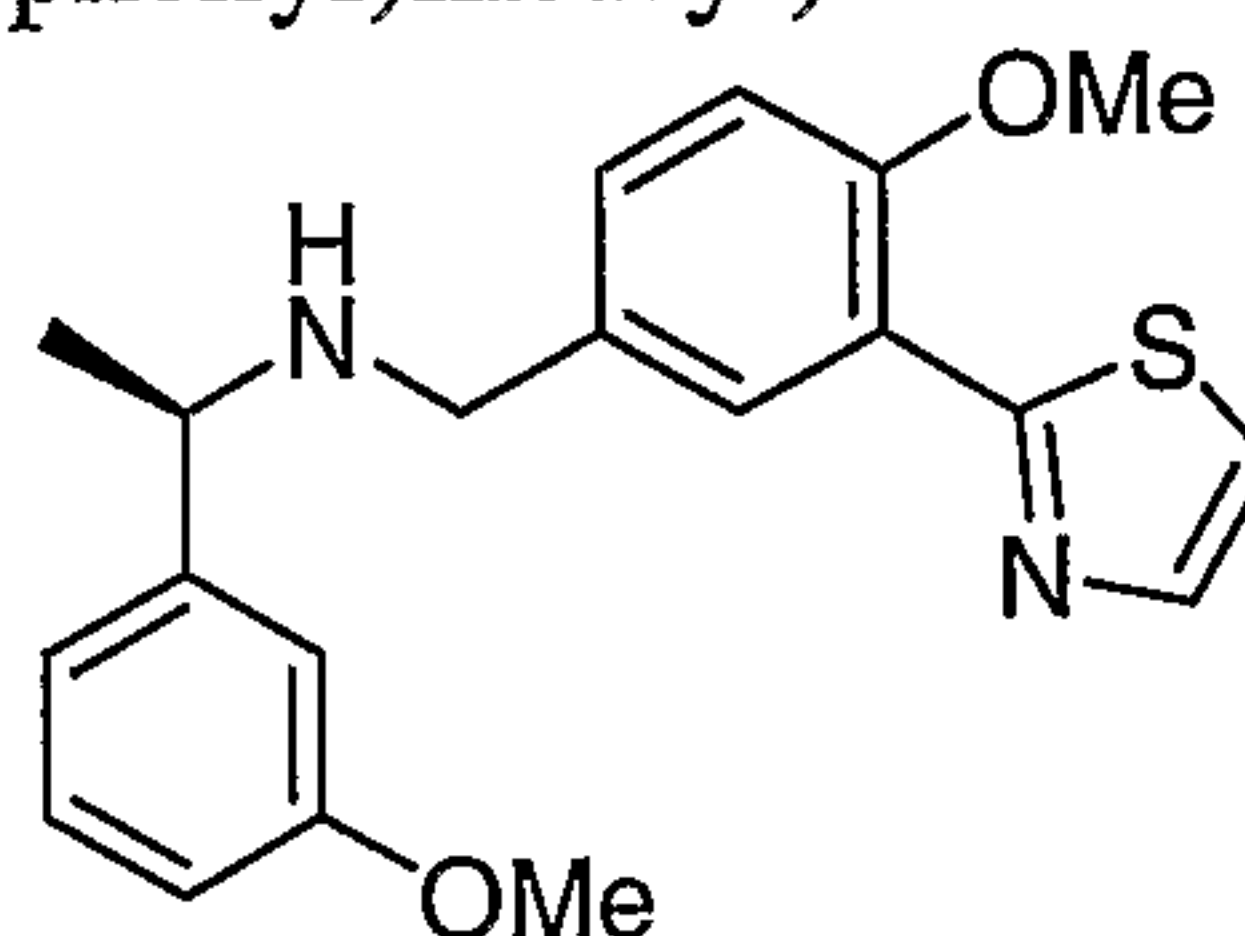
- 162 -



MW 354.472
Mass found: 355, 709

Example 208

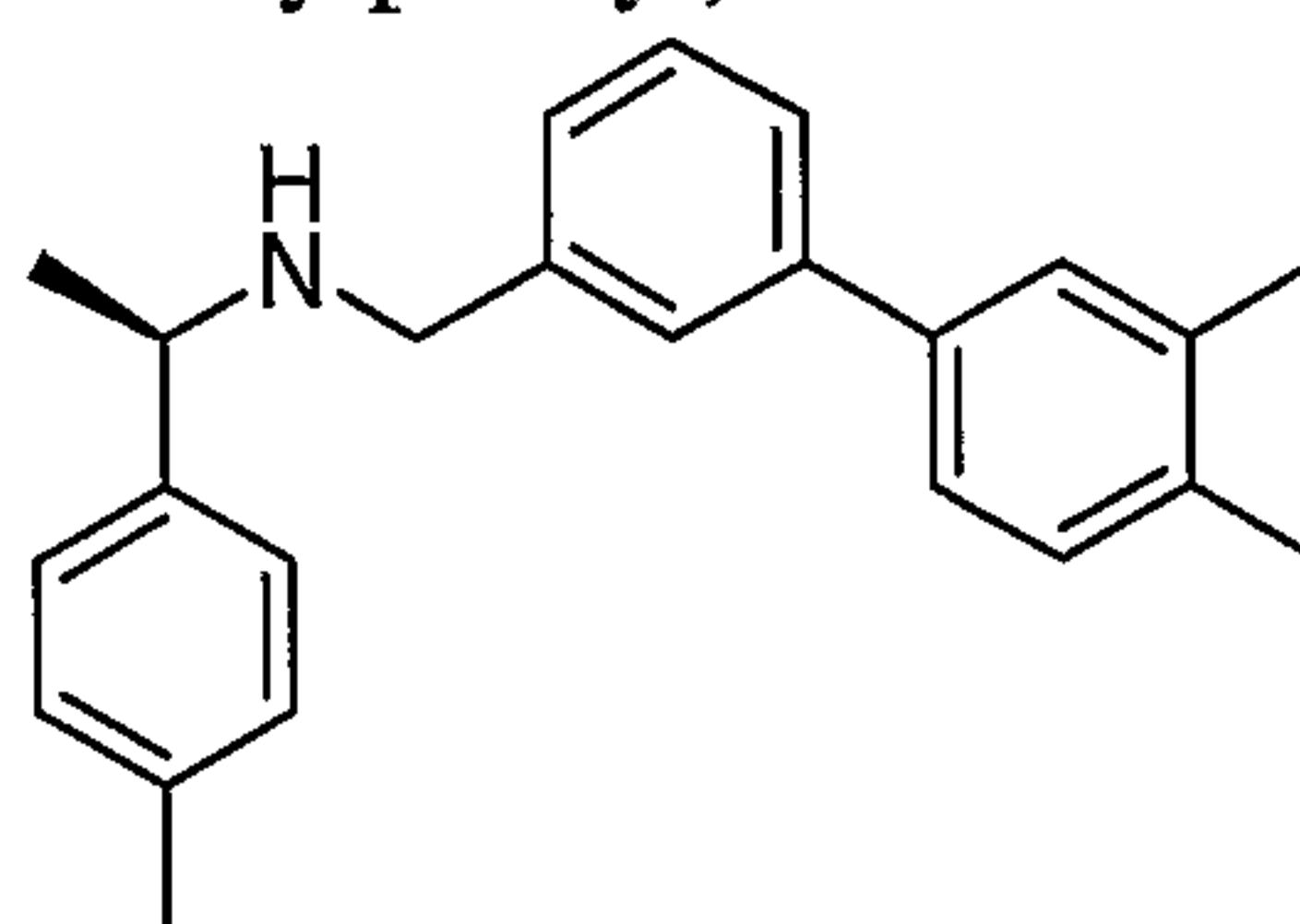
(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine



MW 354.472
Mass found: 355, 709

Example 209

(1R)-N-((3',4'-dimethyl-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine

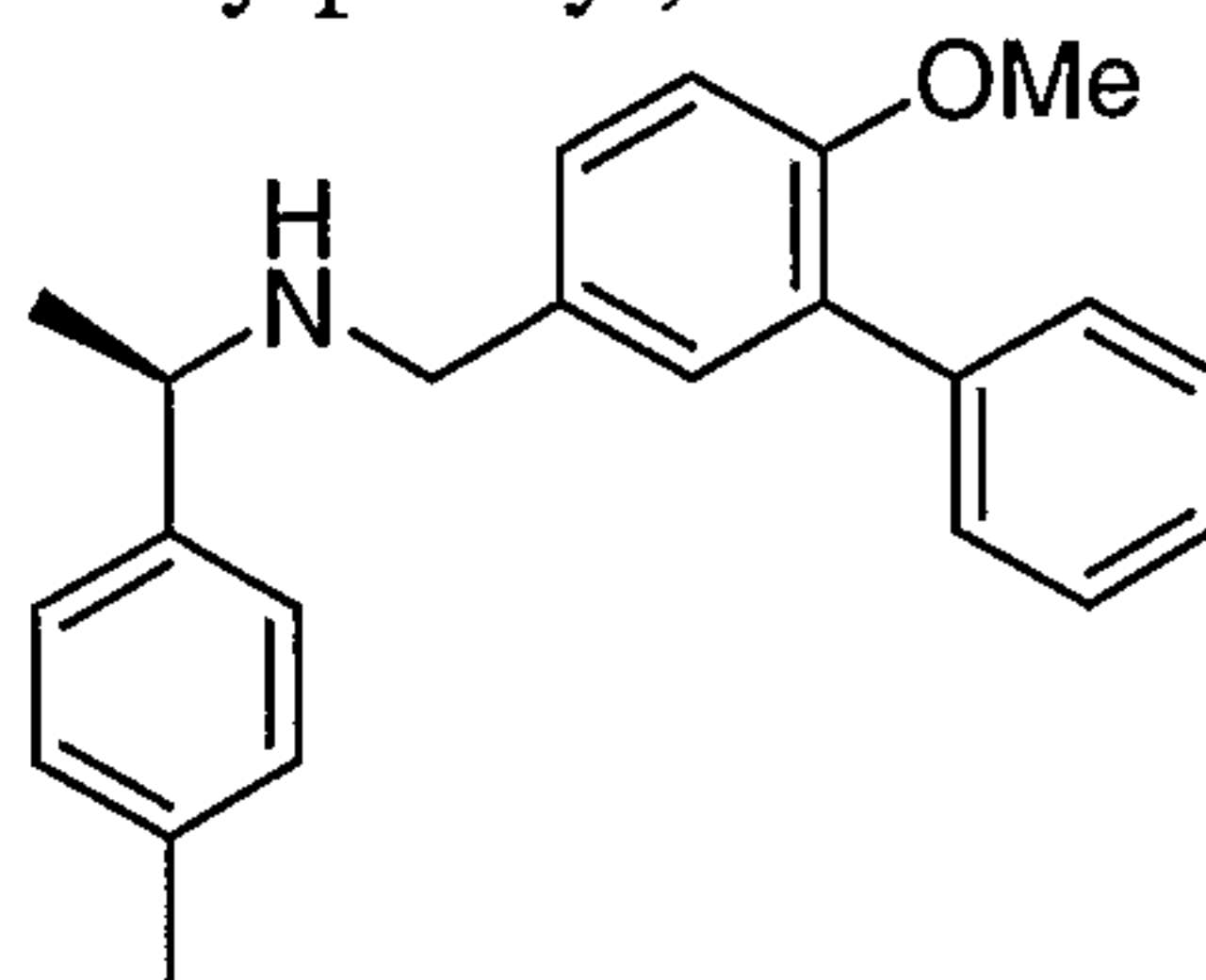


MW 329.484
Mass found: 330, 195, 212

Example 210

- 163 -

(1R)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine



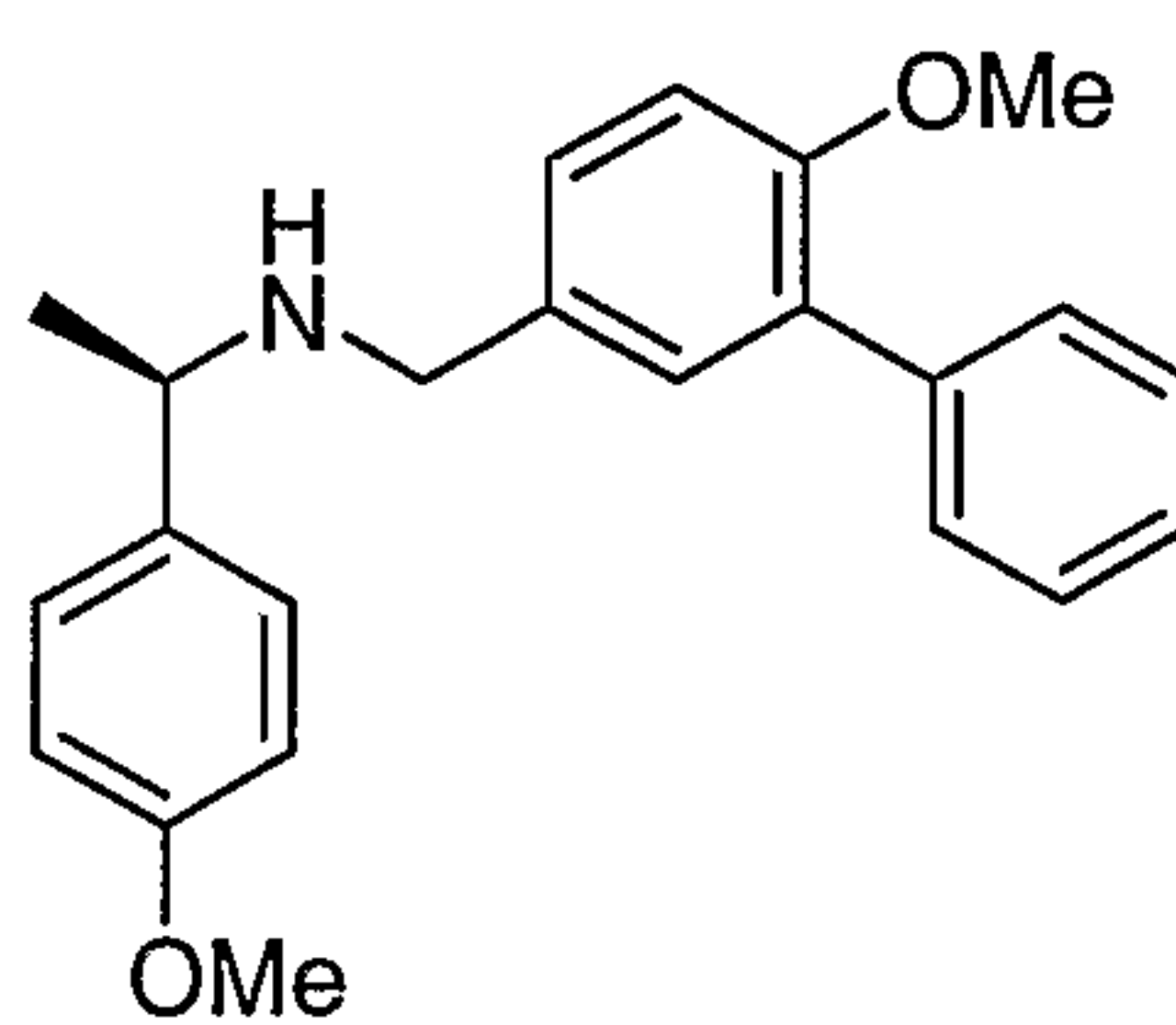
5

MW 331.457
Mass found: 197, 332

Example 211

10

(1R)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine



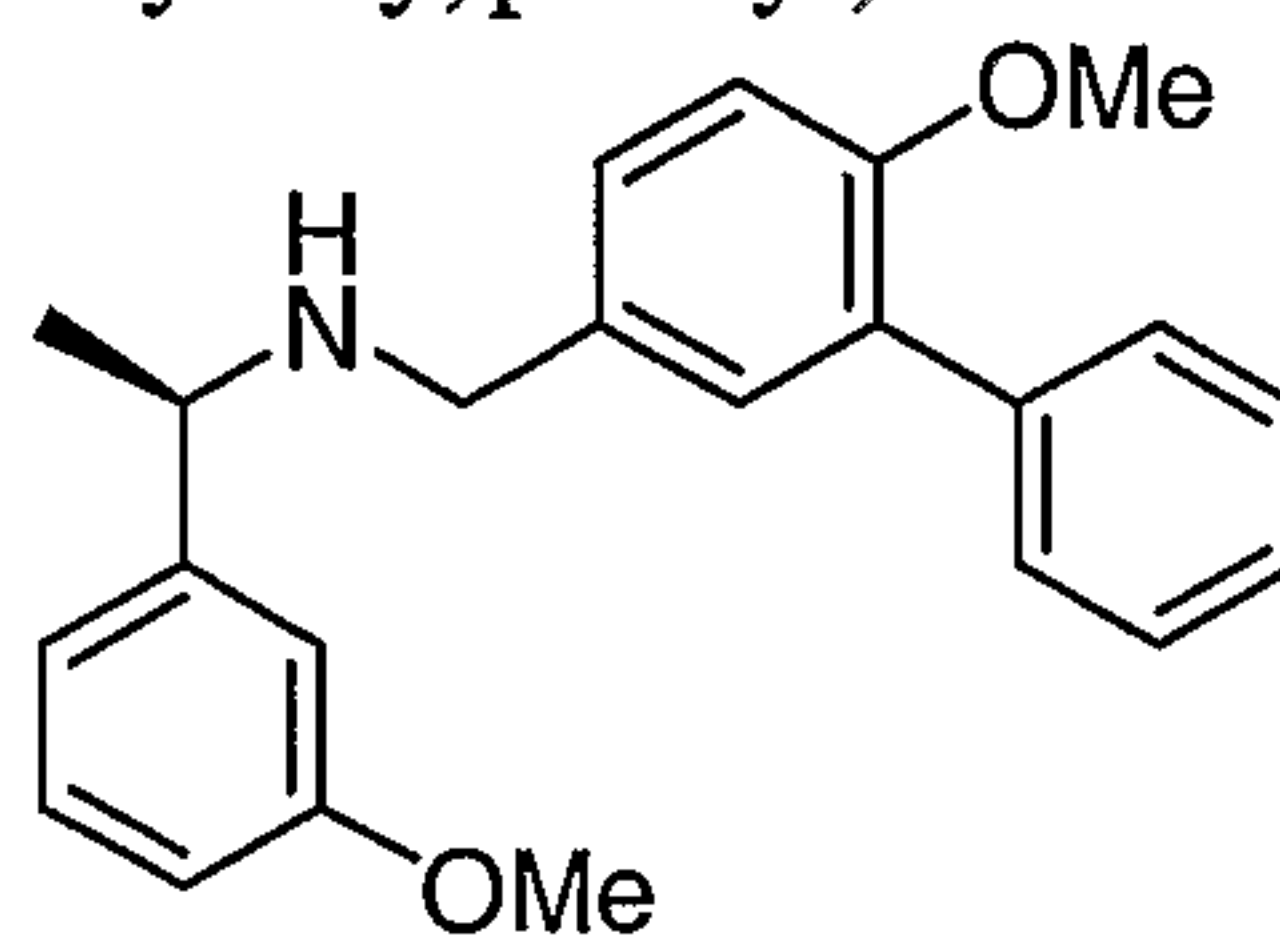
15

MW 347.456
Mass found: 197, 348

Example 212

20

(1R)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine



25

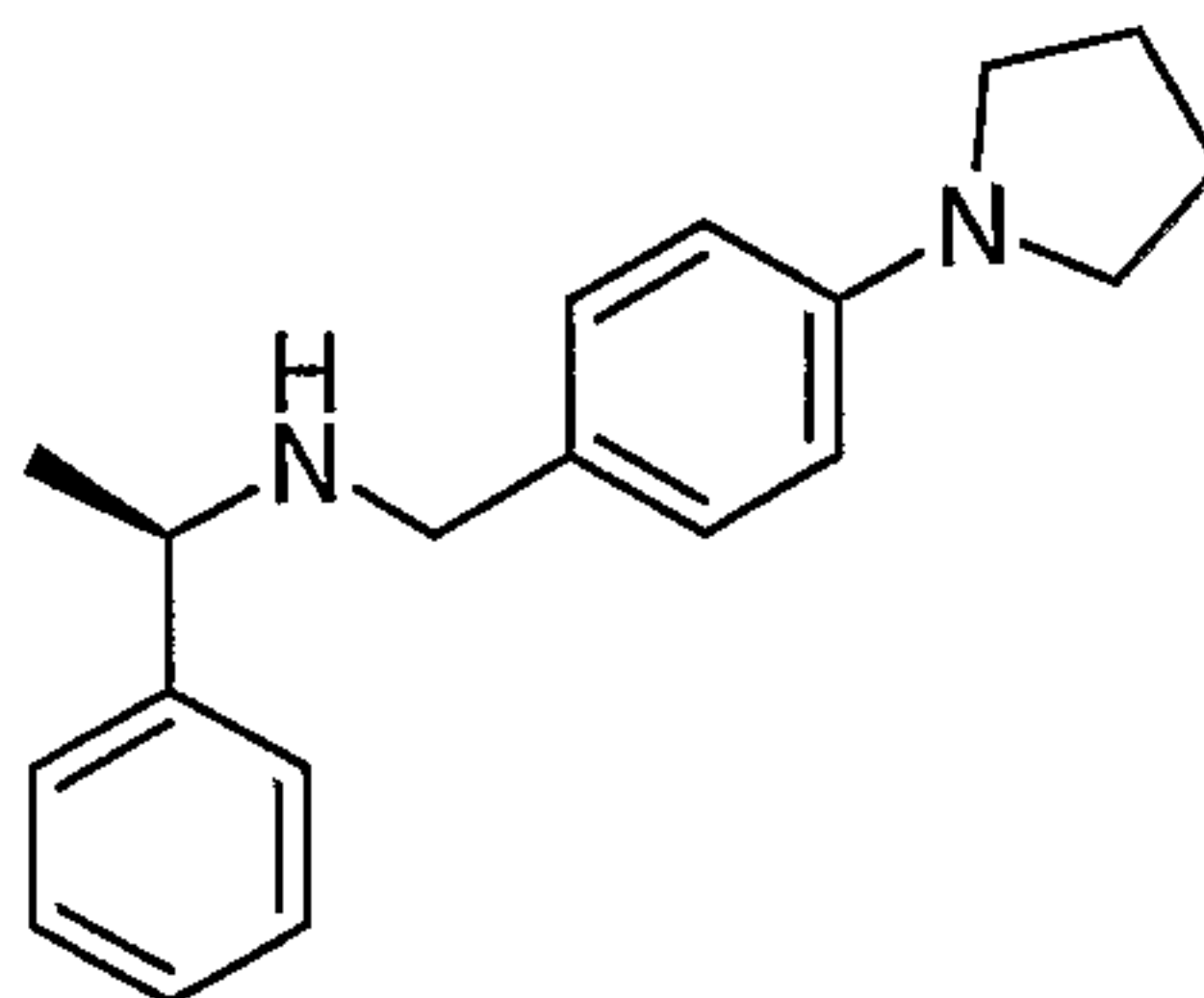
MW 347.456
Mass found: 197, 348

Example 213

30

- 164 -

(1R)-1-phenyl-N-((4-(1-pyrrolidinyl)phenyl)methyl)ethanamine



5

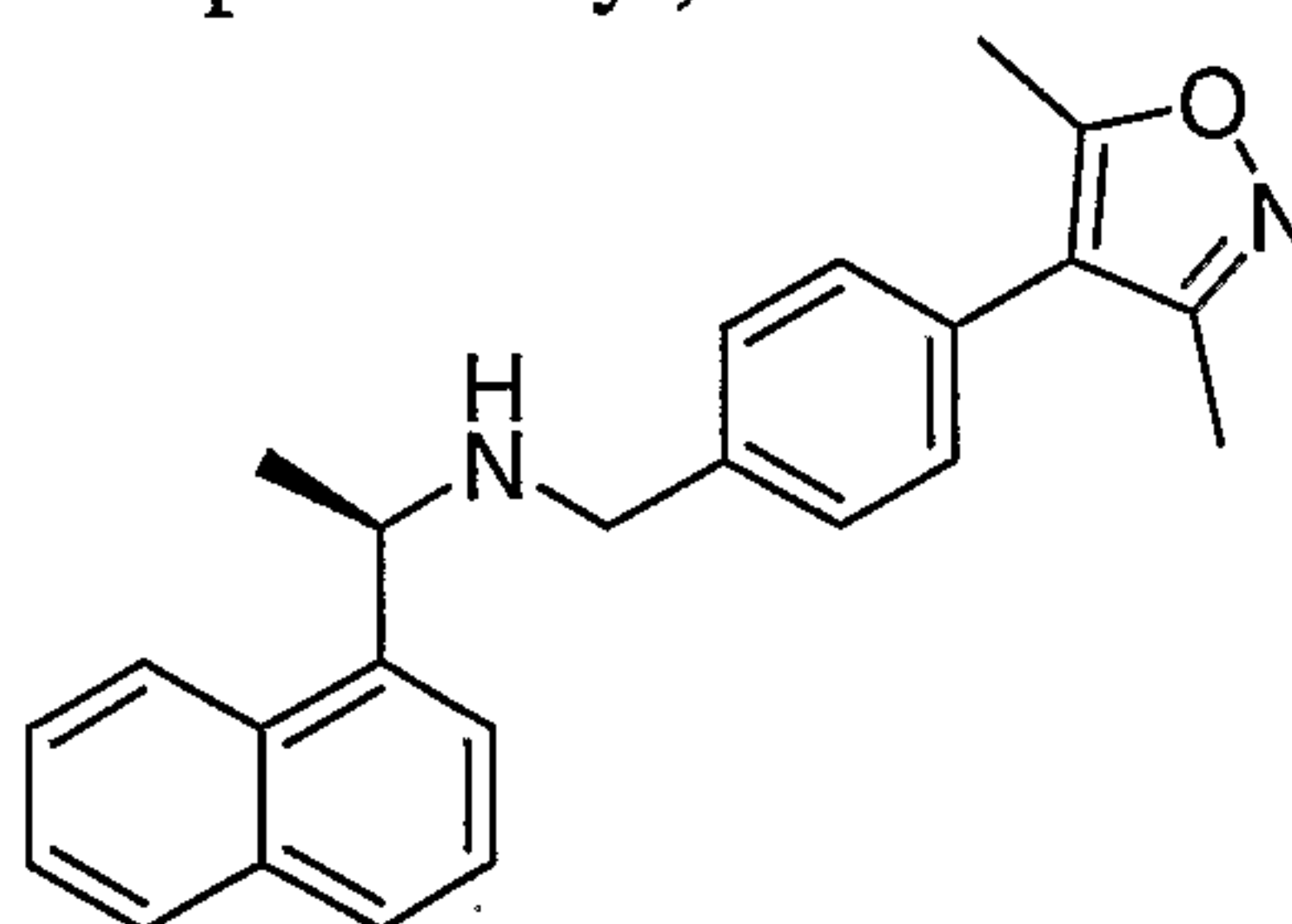
MW 280.413

Mass found: 160, 561, 281

10

Example 214

(1R)-N-((4-(3,5-dimethyl-4-isoxazolyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



15

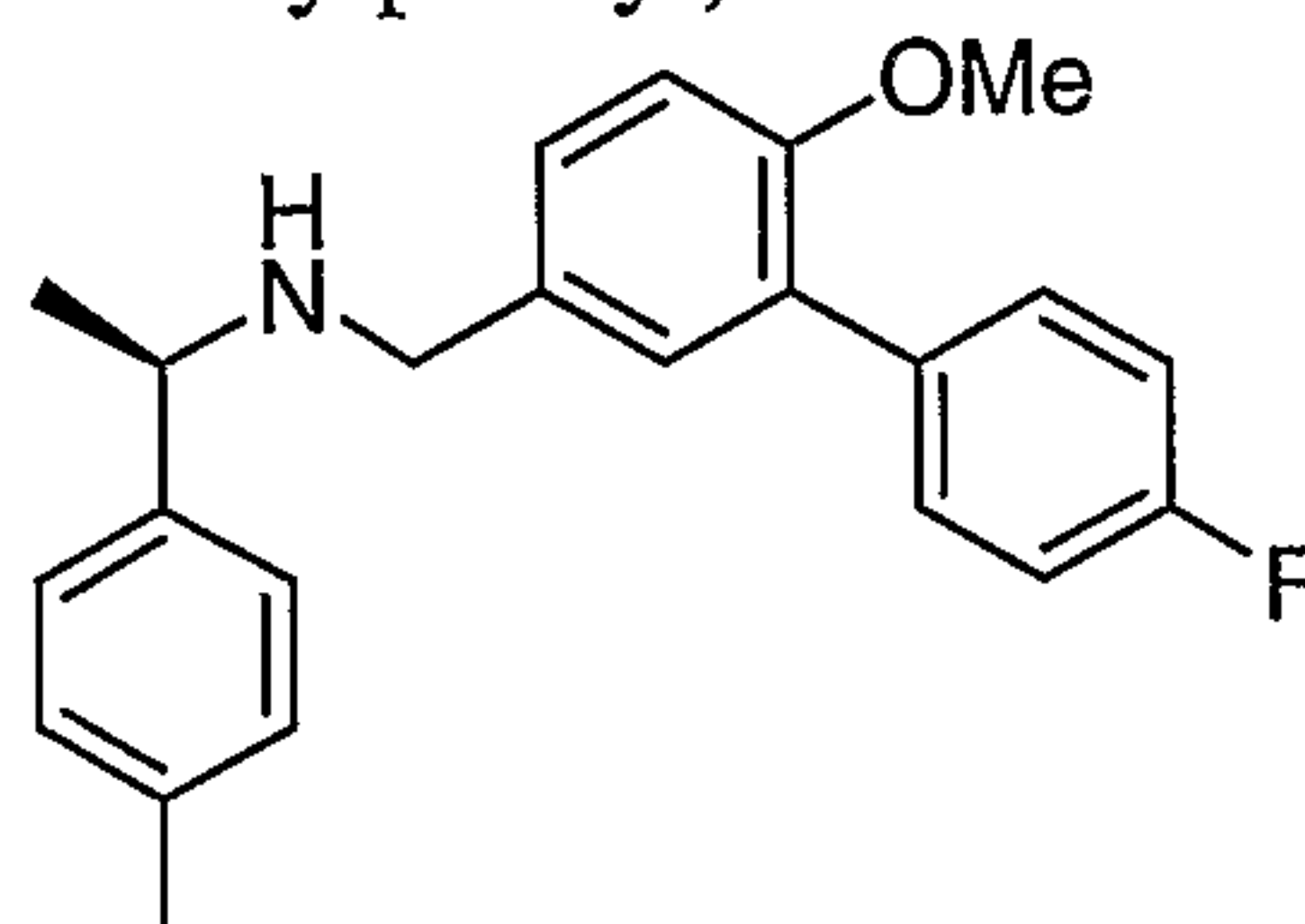
MW 356.467

Mass found: 155, 357, 203

20

Example 215

(1R)-N-((4'-fluoro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine



25

MW 349.447

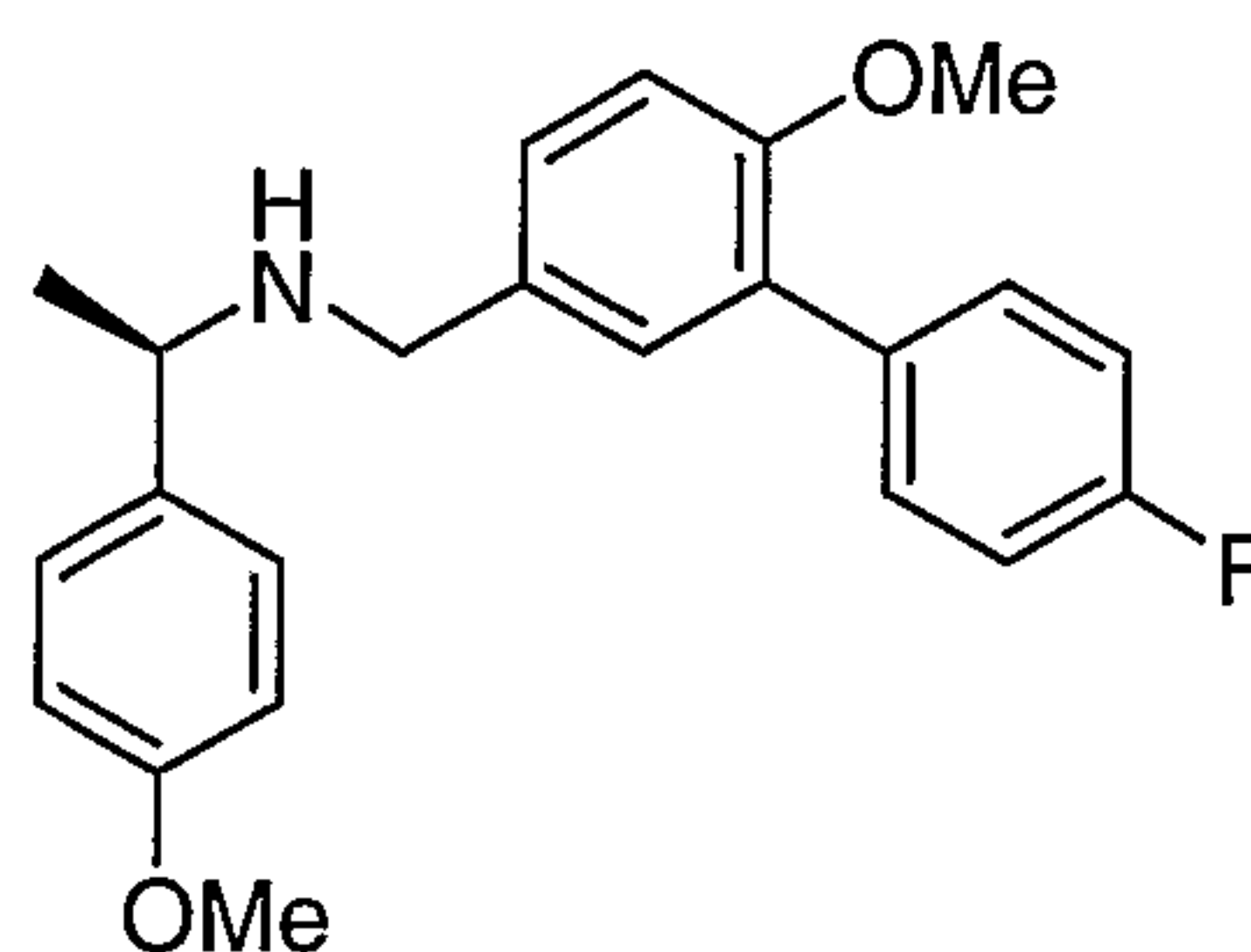
Mass found: 350

- 165 -

Example 216

(1R)-N-((4'-fluoro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine

5



MW 365.446

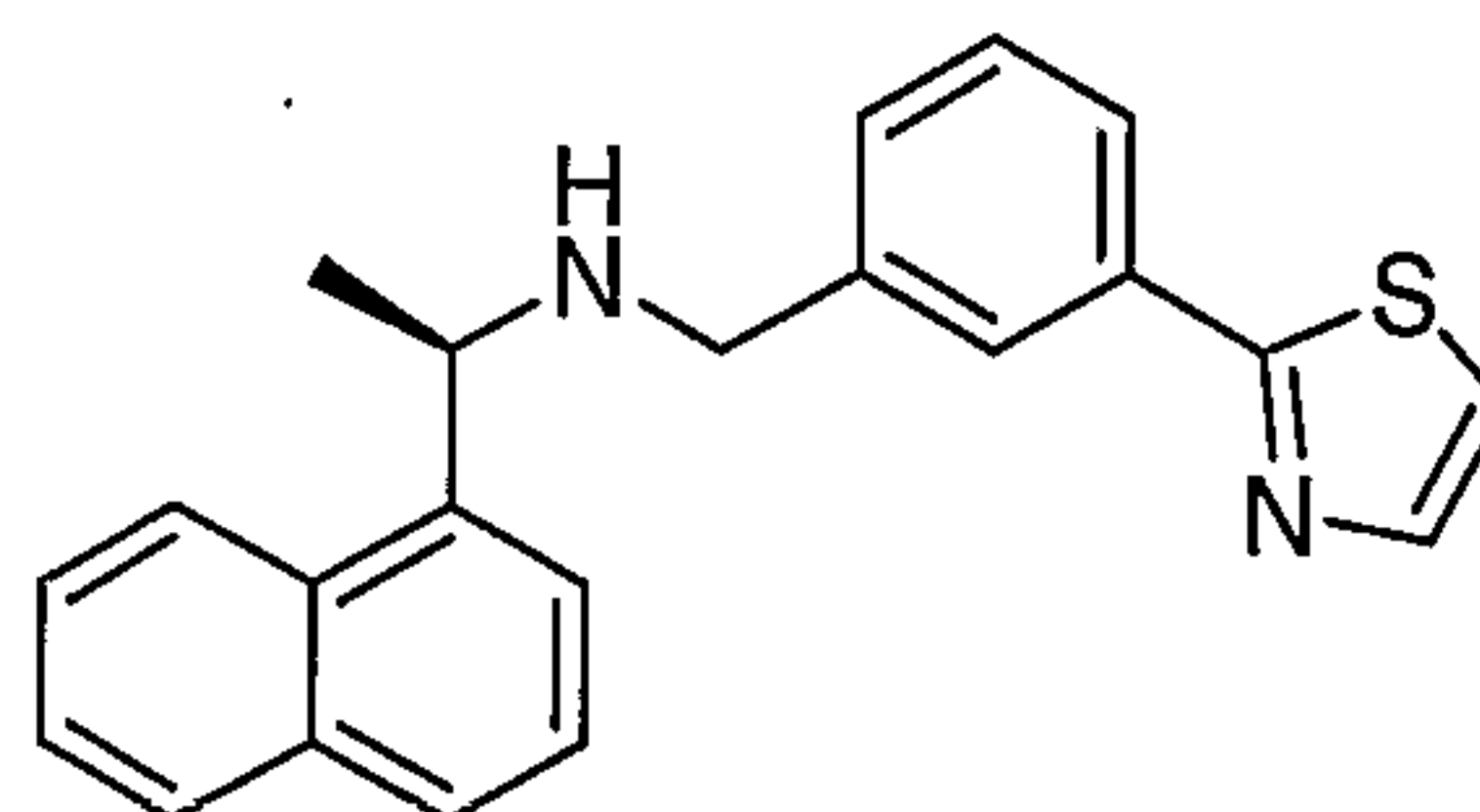
Mass found: 366

10

Example 217

(1R)-1-(1-naphthalenyl)-N-((3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine

15



MW 344.48

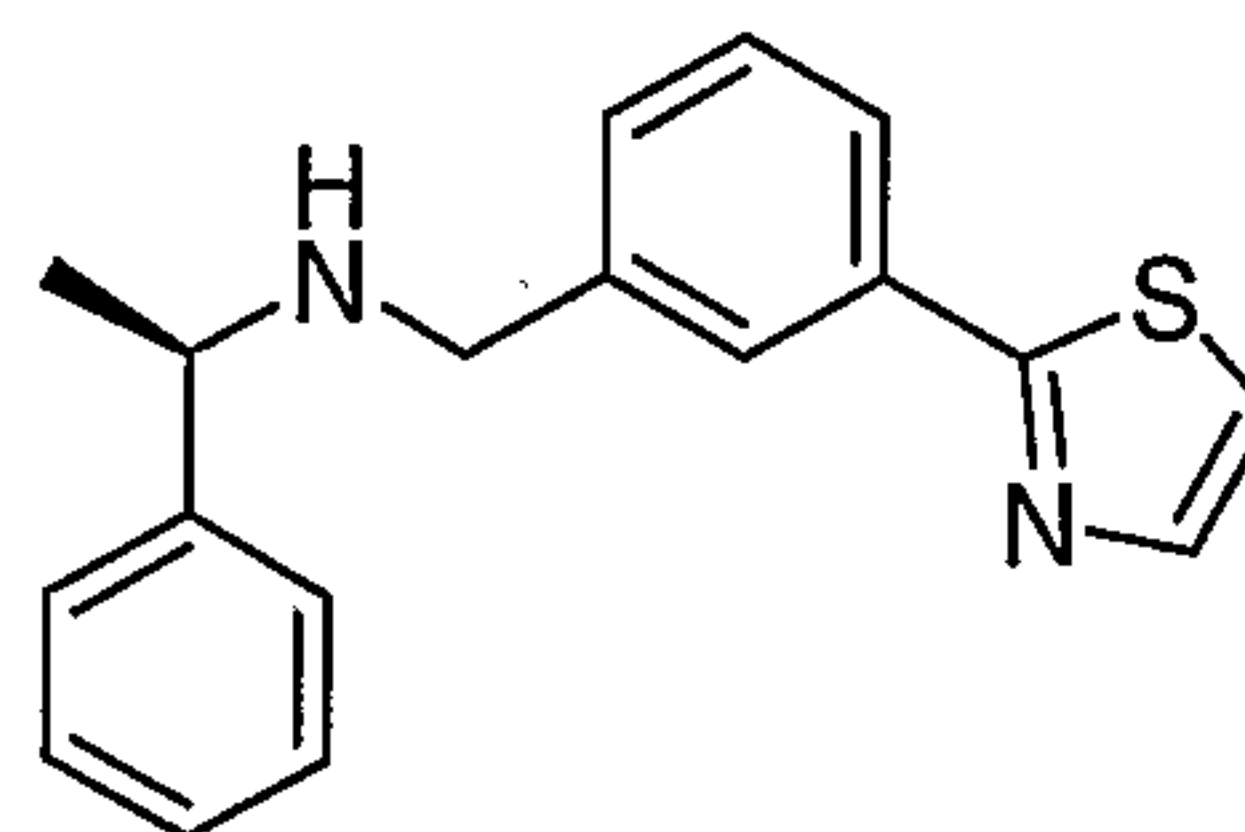
Mass found: 345, 689

20

Example 218

(1R)-1-phenyl-N-((3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine

25



MW 294.42

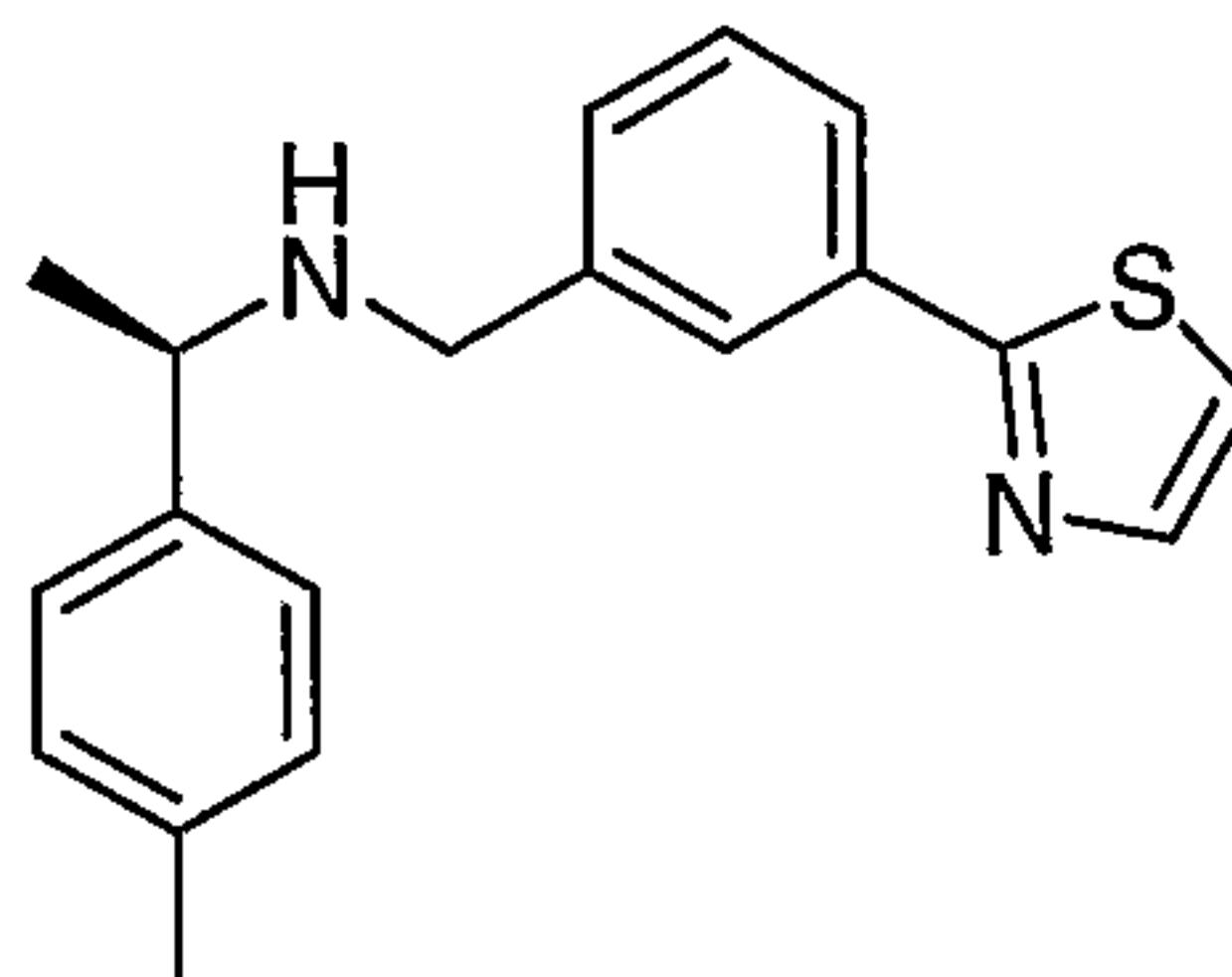
Mass found: 295, 589

30

Example 219

- 166 -

(1R)-1-(4-methylphenyl)-N-((3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine



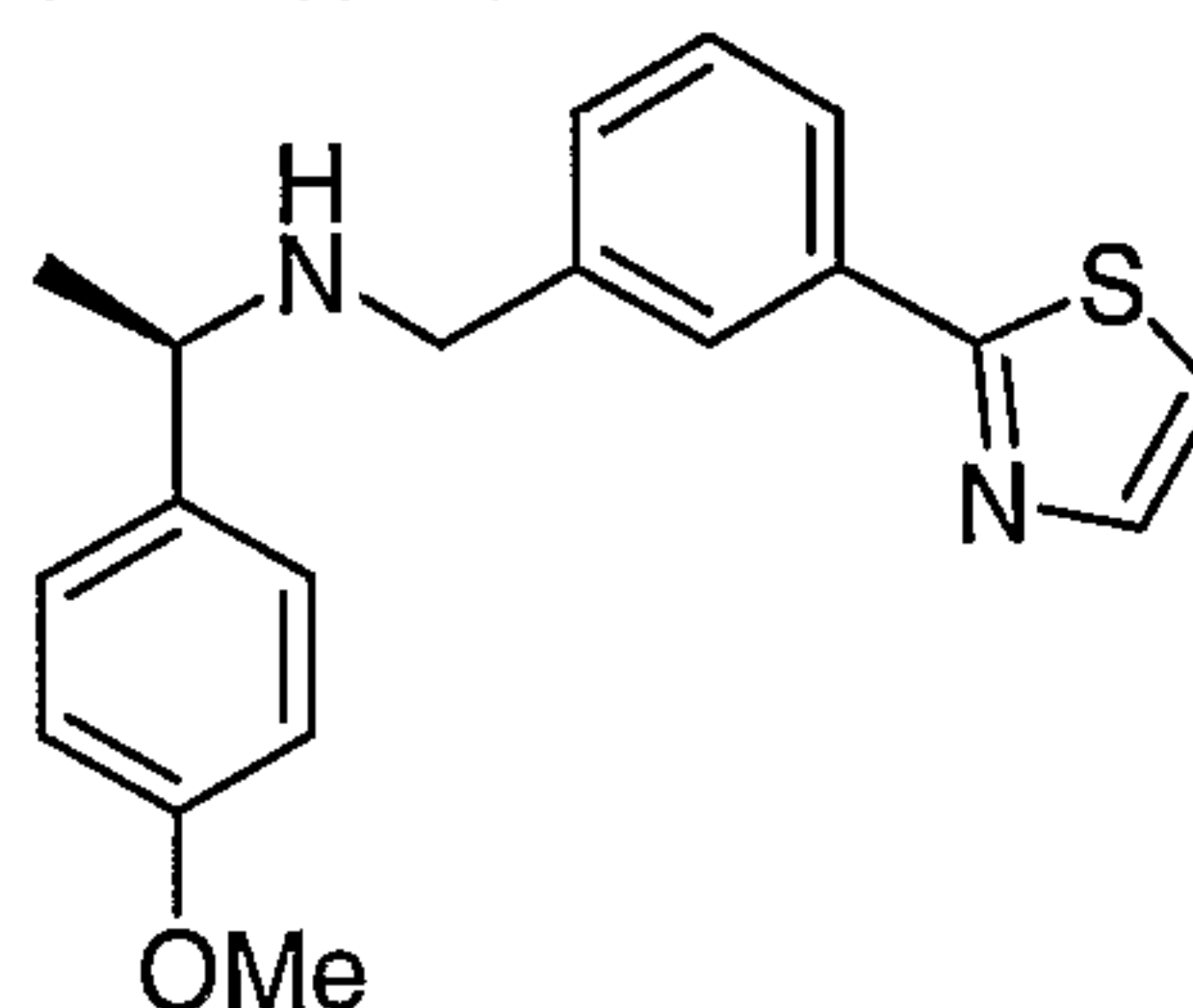
5

MW 303.407

Mass found: 304, 607

Example 220

10 (1R)-1-(4-(methyloxy)phenyl)-N-((3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine



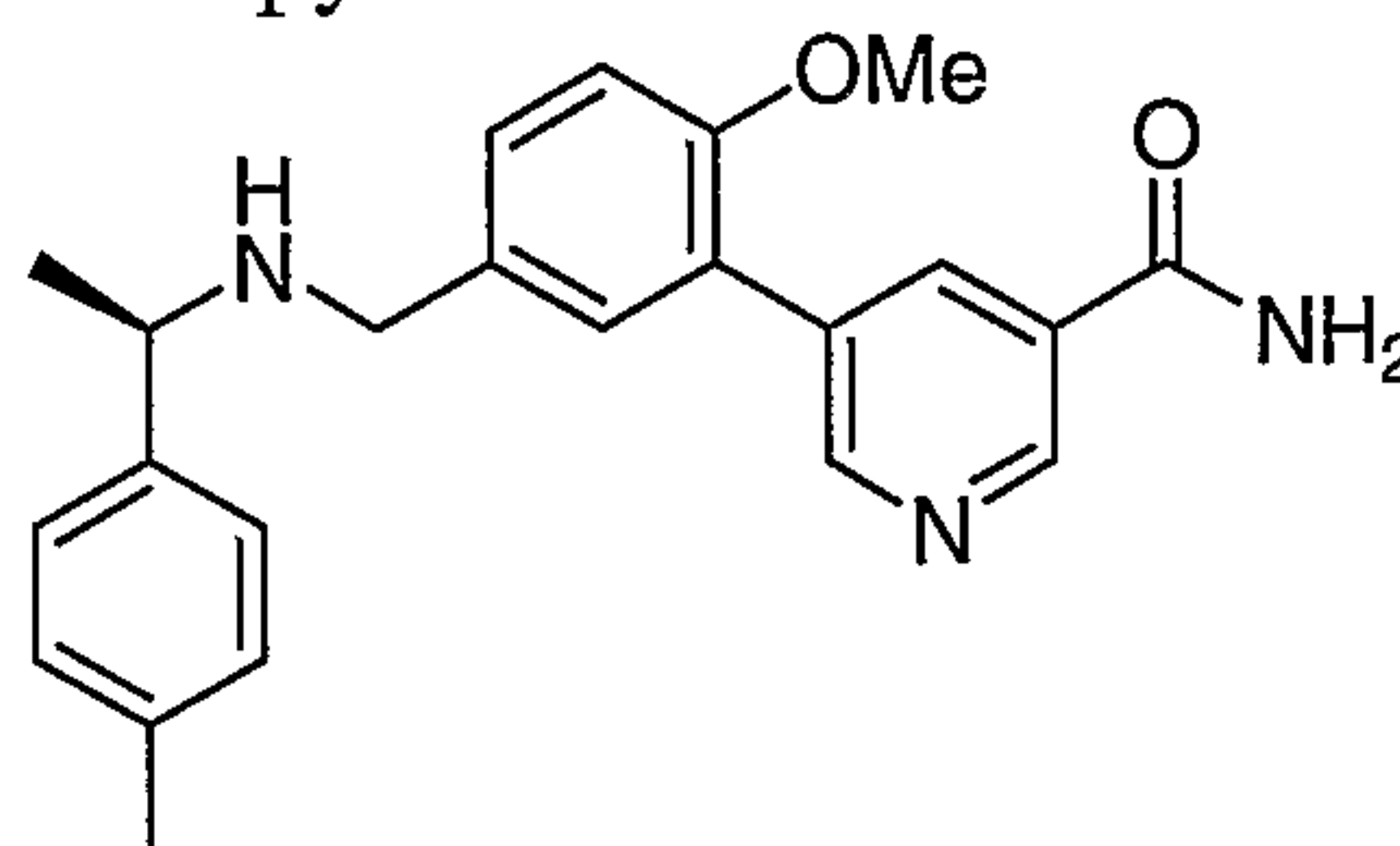
15

MW 324.446

Mass found: 325, 649

Example 221

20 5-(2-(methyloxy)-5-((((1R)-1-(4-methylphenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide



25

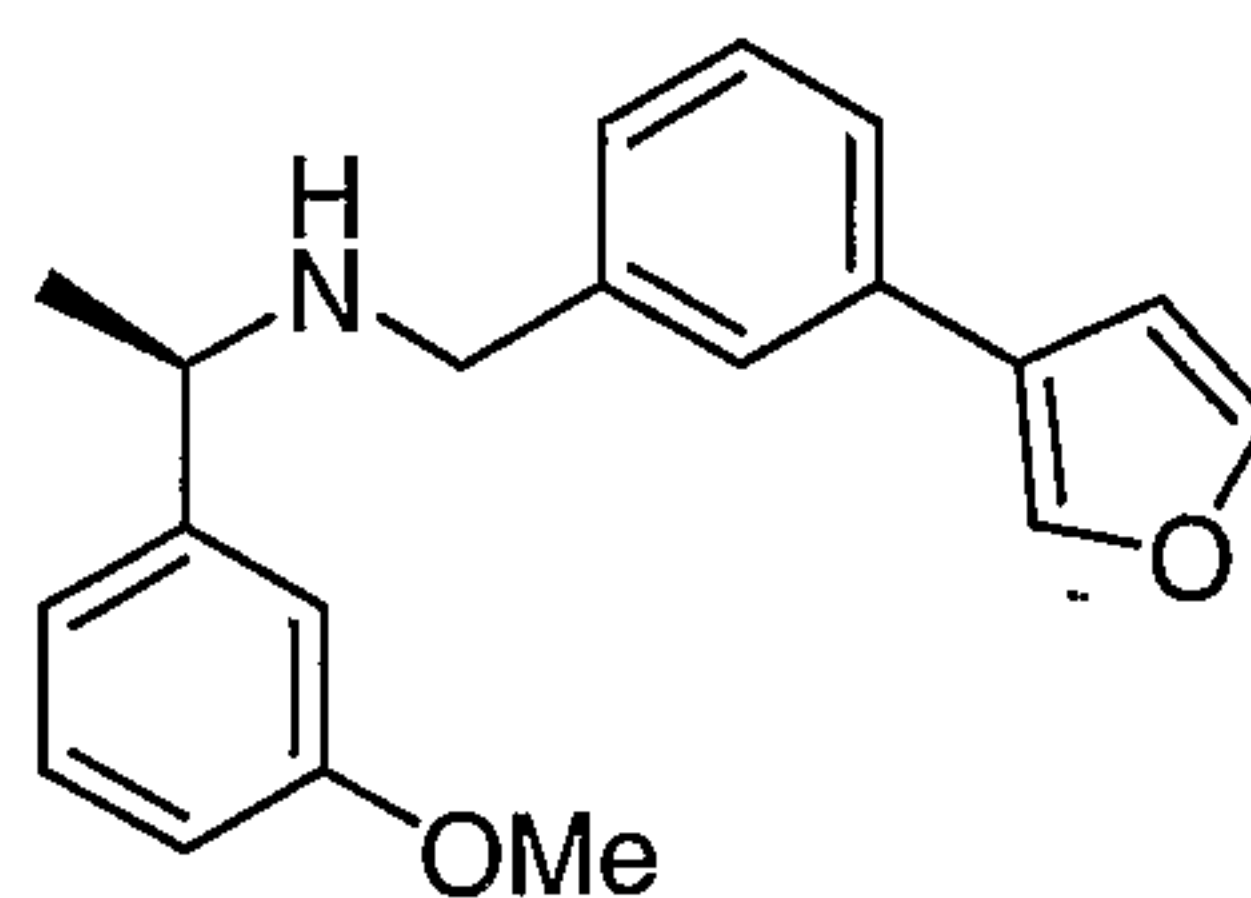
MW 375.47

Mass found: 376, 417, 751, 865

Example 222

(1R)-N-((3-(3-furanyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

- 167 -



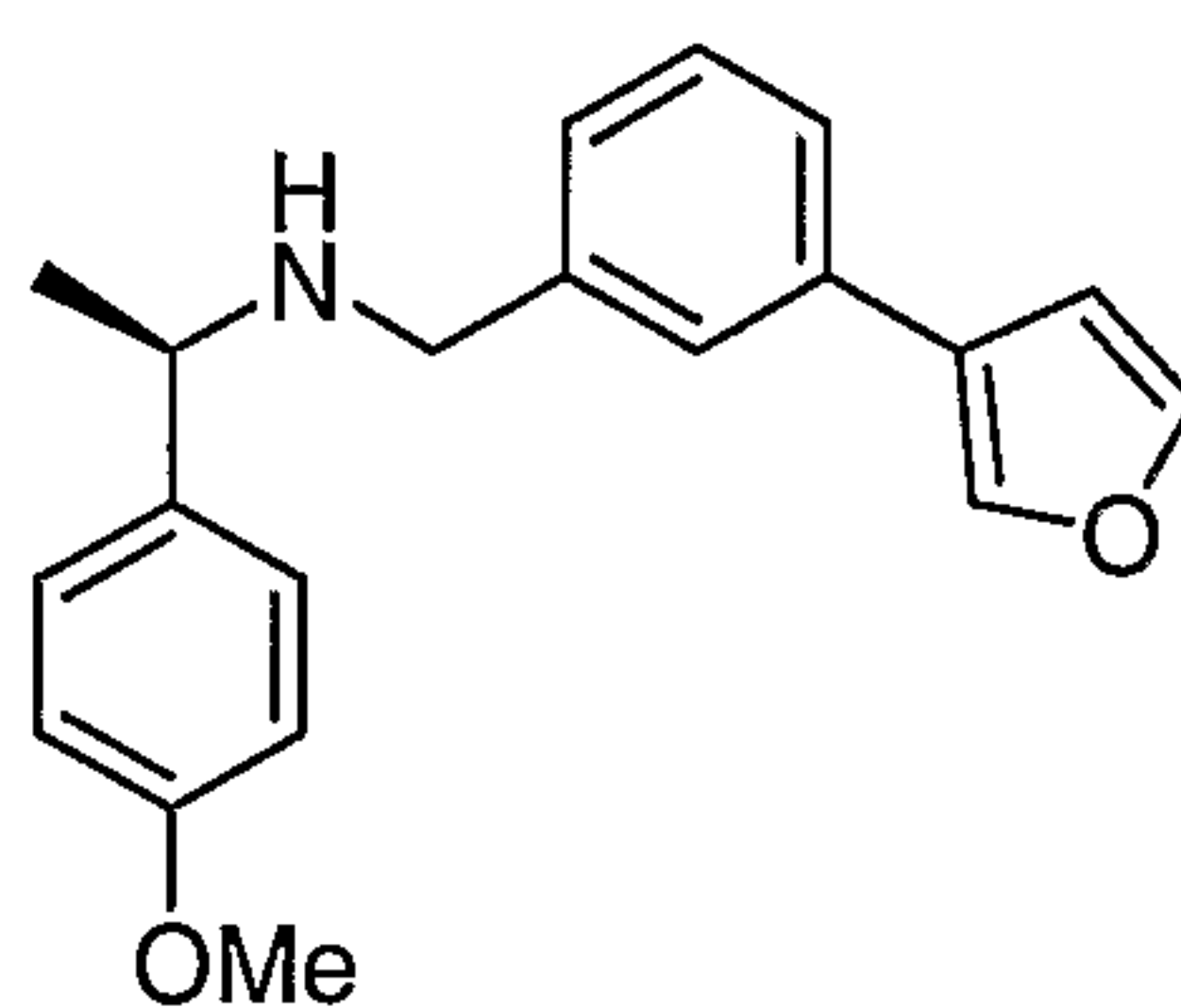
MW 307.391
Mass found: 308, 615

5

Example 223

(1R)-N-((3-(3-furanyl)phenyl)methyl)-1-(4-(methoxy)phenyl)ethanamine

10

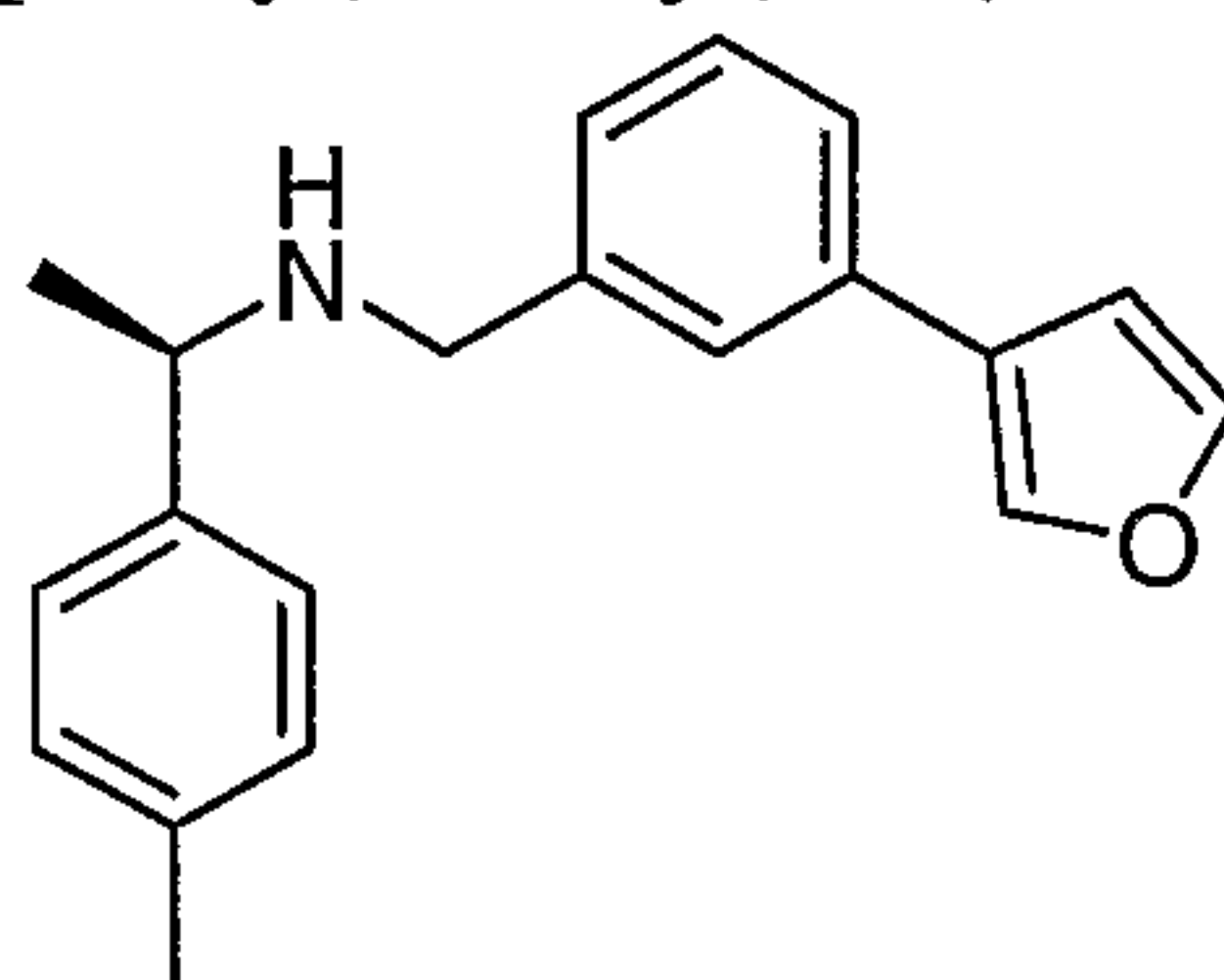


MW 307.391
Mass found: 308, 615

15

Example 224

(1R)-N-((3-(3-furanyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine



MW 291.392
Mass found: 292, 583

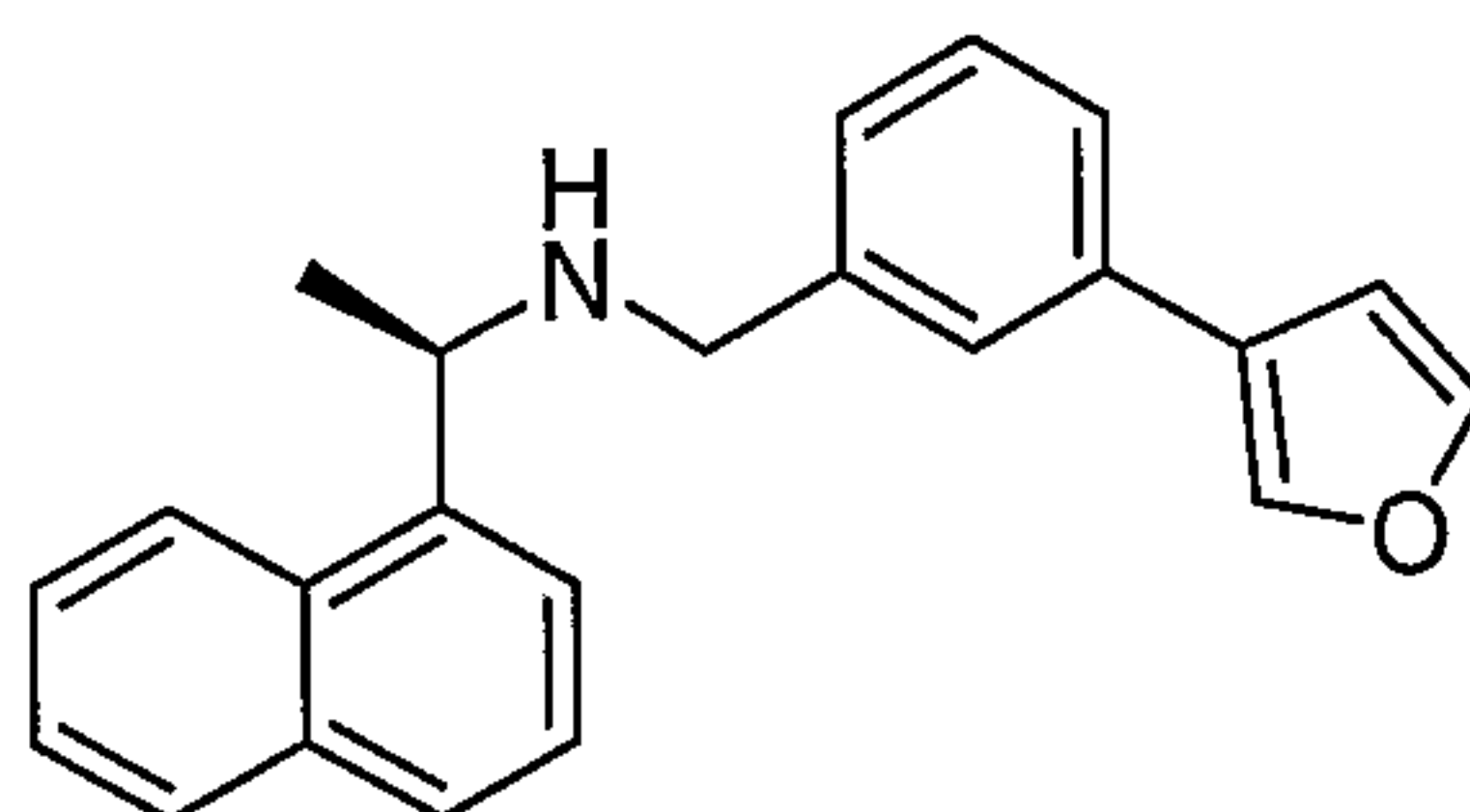
20

Example 225

(1R)-N-((3-(3-furanyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

25

- 168 -

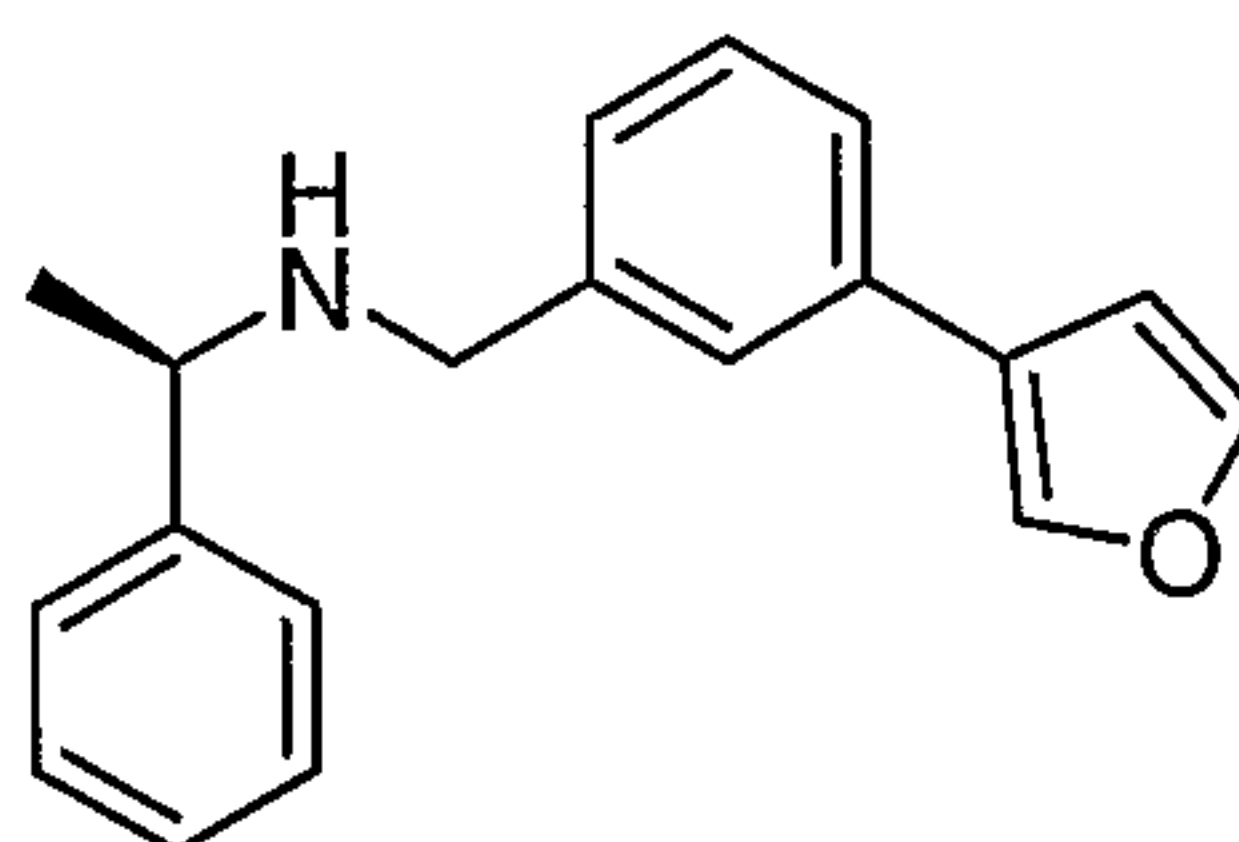


MW 327.425
Mass found: 328, 655

5

Example 226

10 (1R)-N-((3-(3-furanyl)phenyl)methyl)-1-phenylethanamine

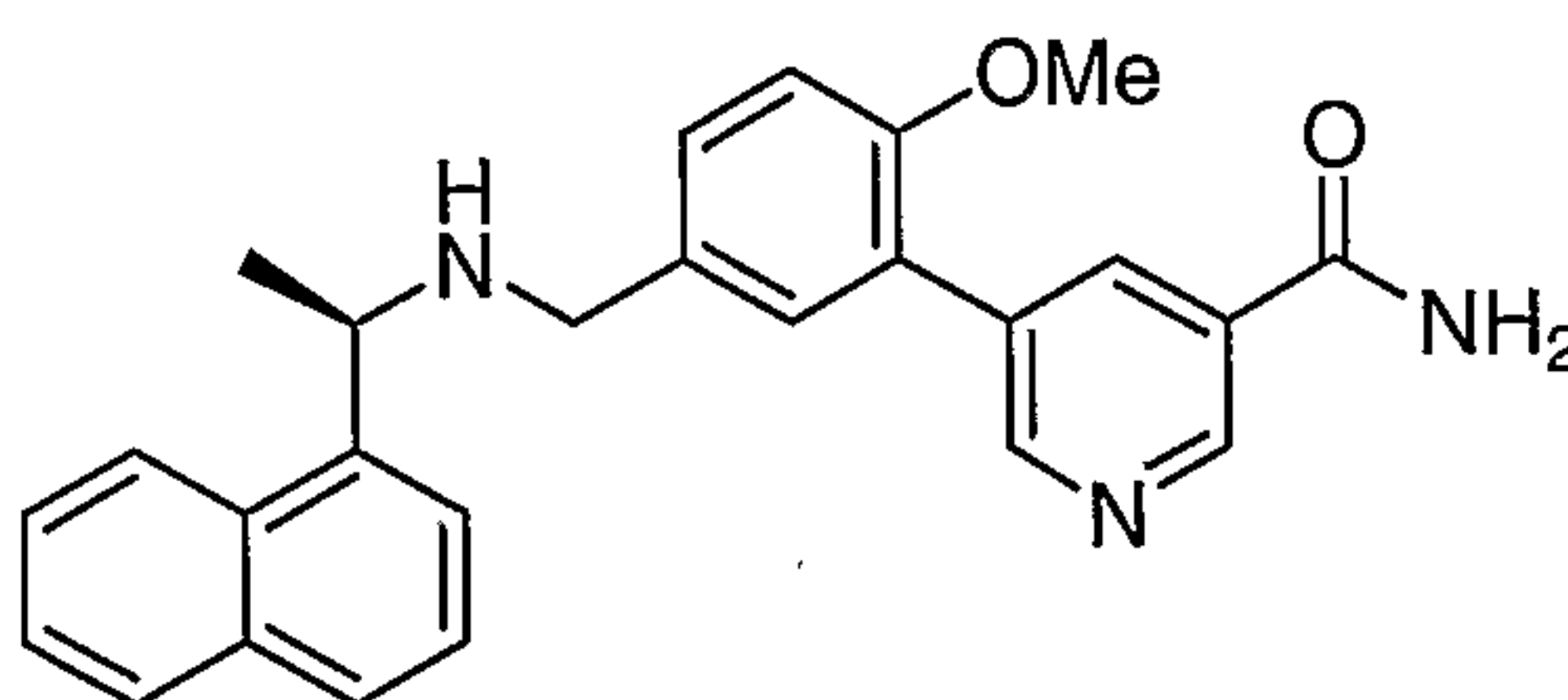


MW 277.365
Mass found: 278, 555

15

Example 227

20 5-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide



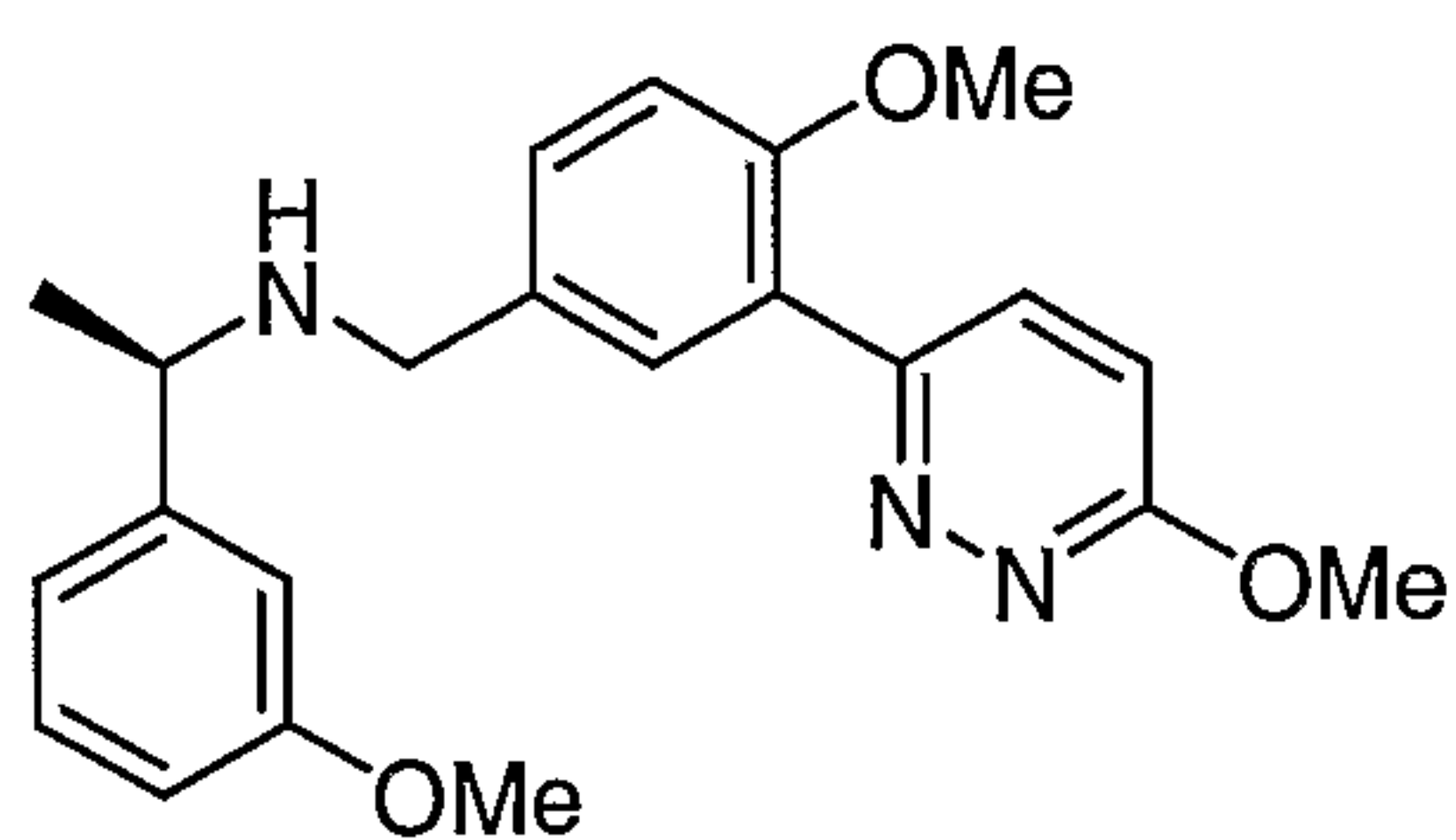
MW 411.503
Mass found: 412, 823

25

Example 228

30 (1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

- 169 -



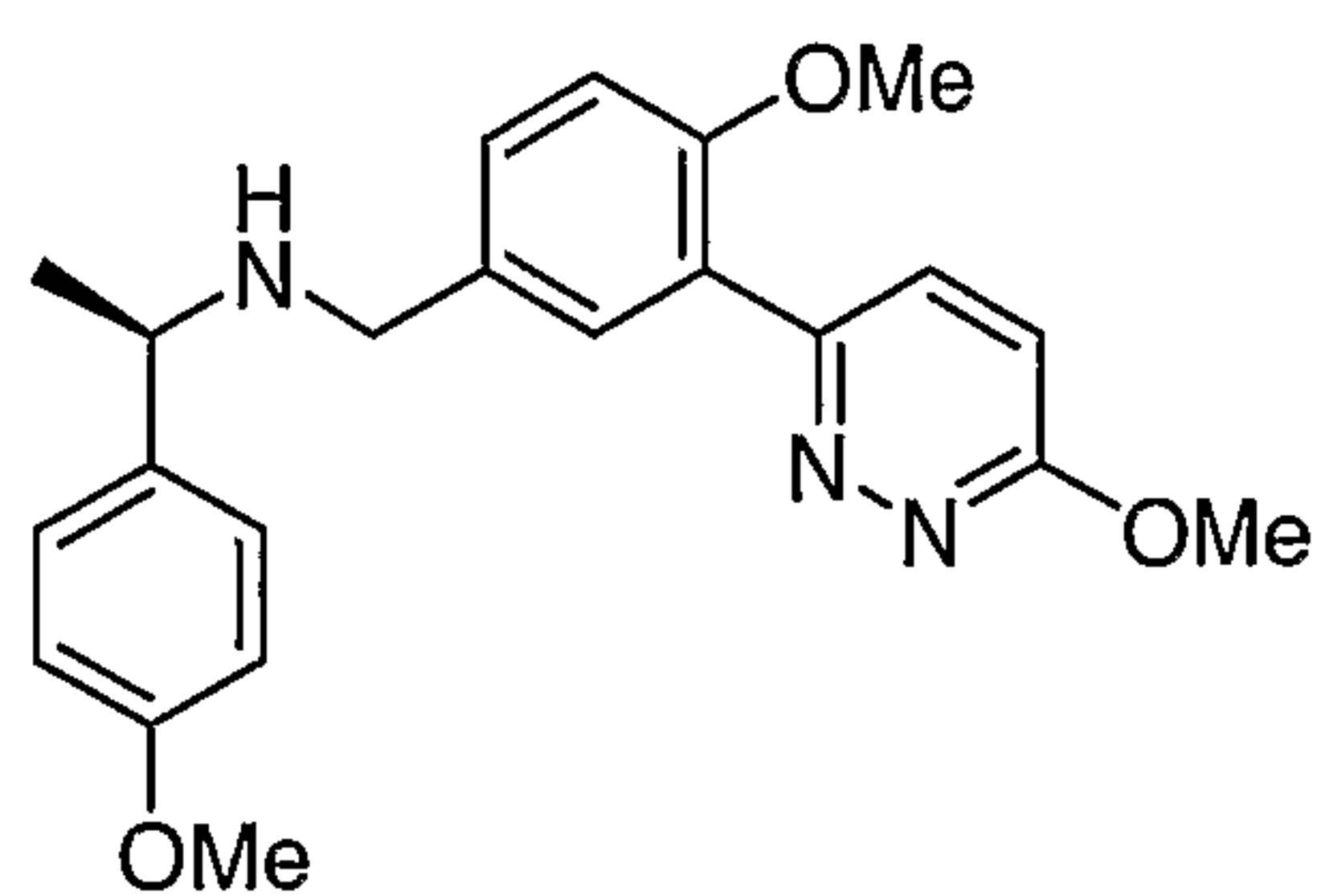
MW 379.457

Mass found: 380, 759

5

Example 229

10 (1R)-N-((4-(methoxy)-3-(6-(methoxy)-3-pyridazinyl)phenyl)methyl)-1-(4-(methoxy)phenyl)ethanamine



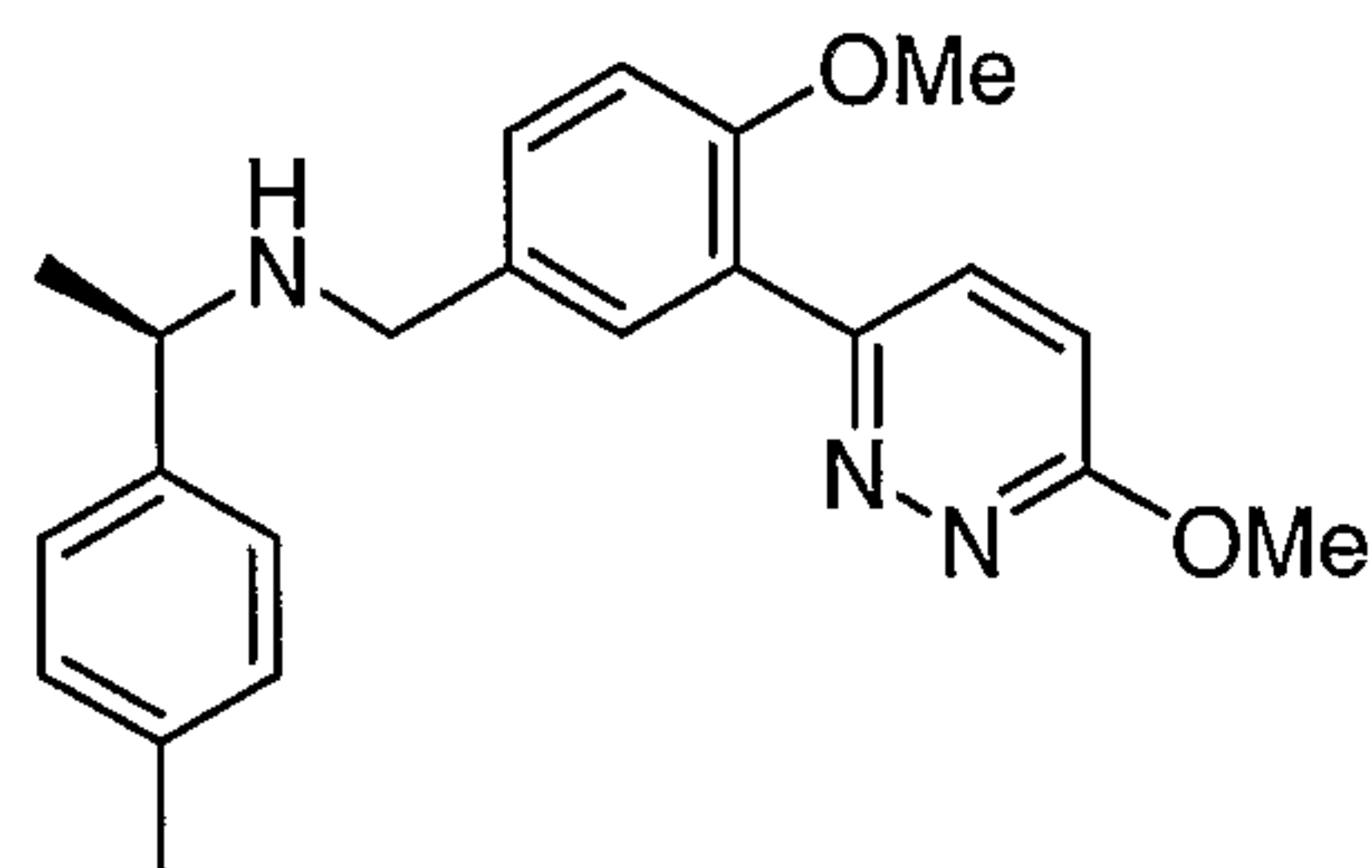
MW 379.457

Mass found: 380, 759

15

Example 230

20 (1R)-N-((4-(methoxy)-3-(6-(methoxy)-3-pyridazinyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine



MW 363.458

Mass found: 364, 727

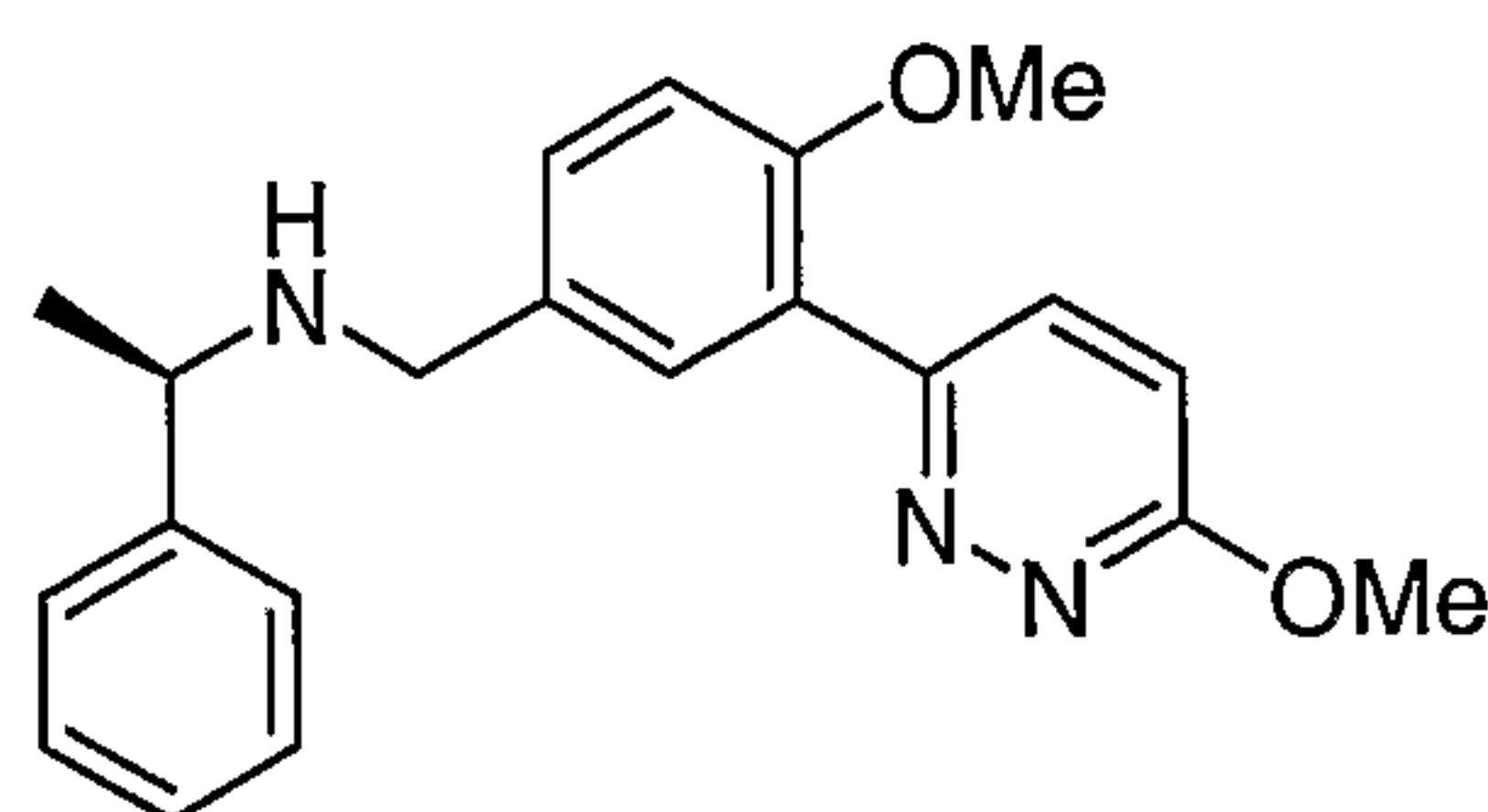
25

Example 231

30

- 170 -

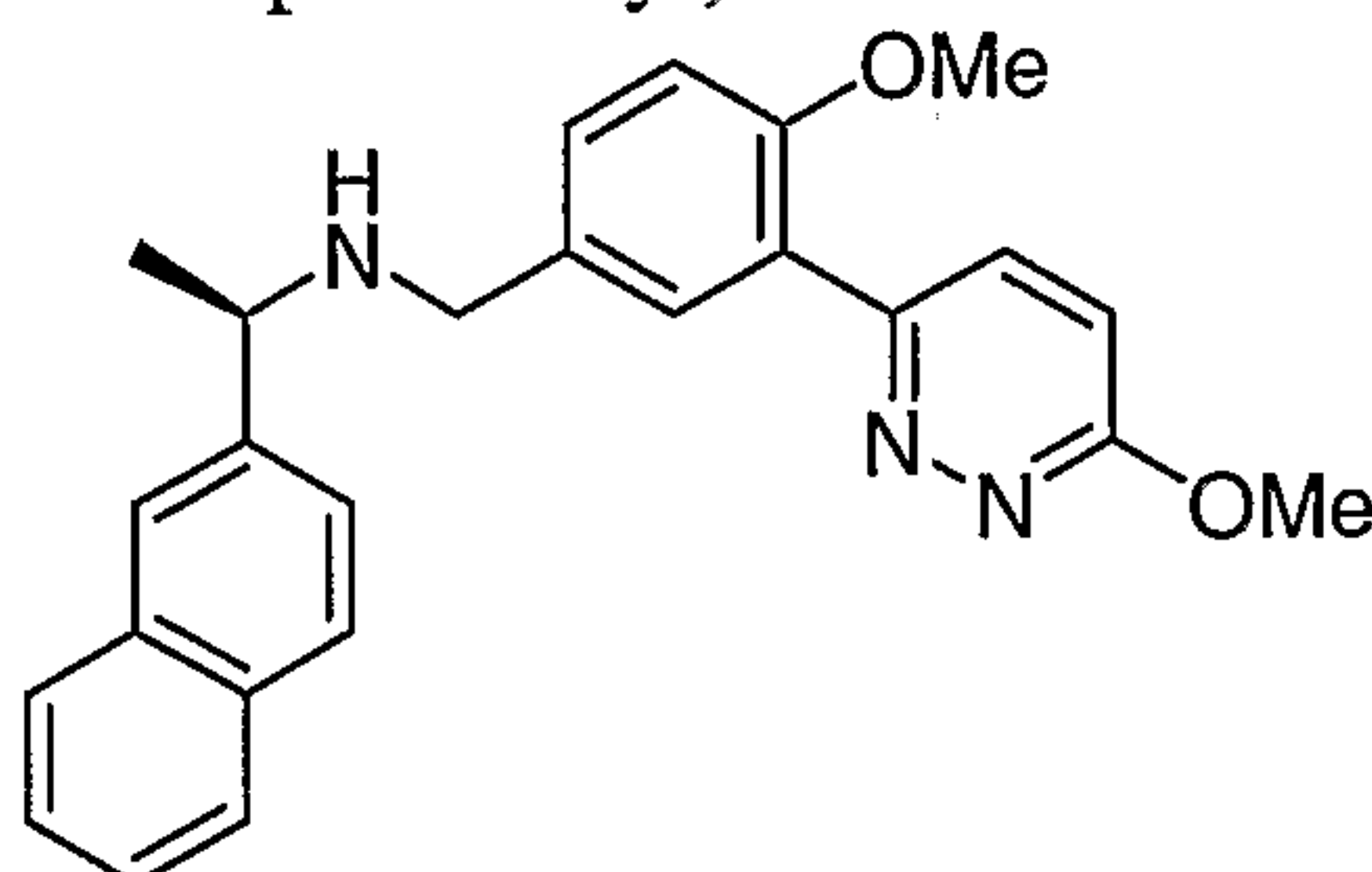
(1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-phenylethanamine



MW 349.432
Mass found: 350, 699

Example 232

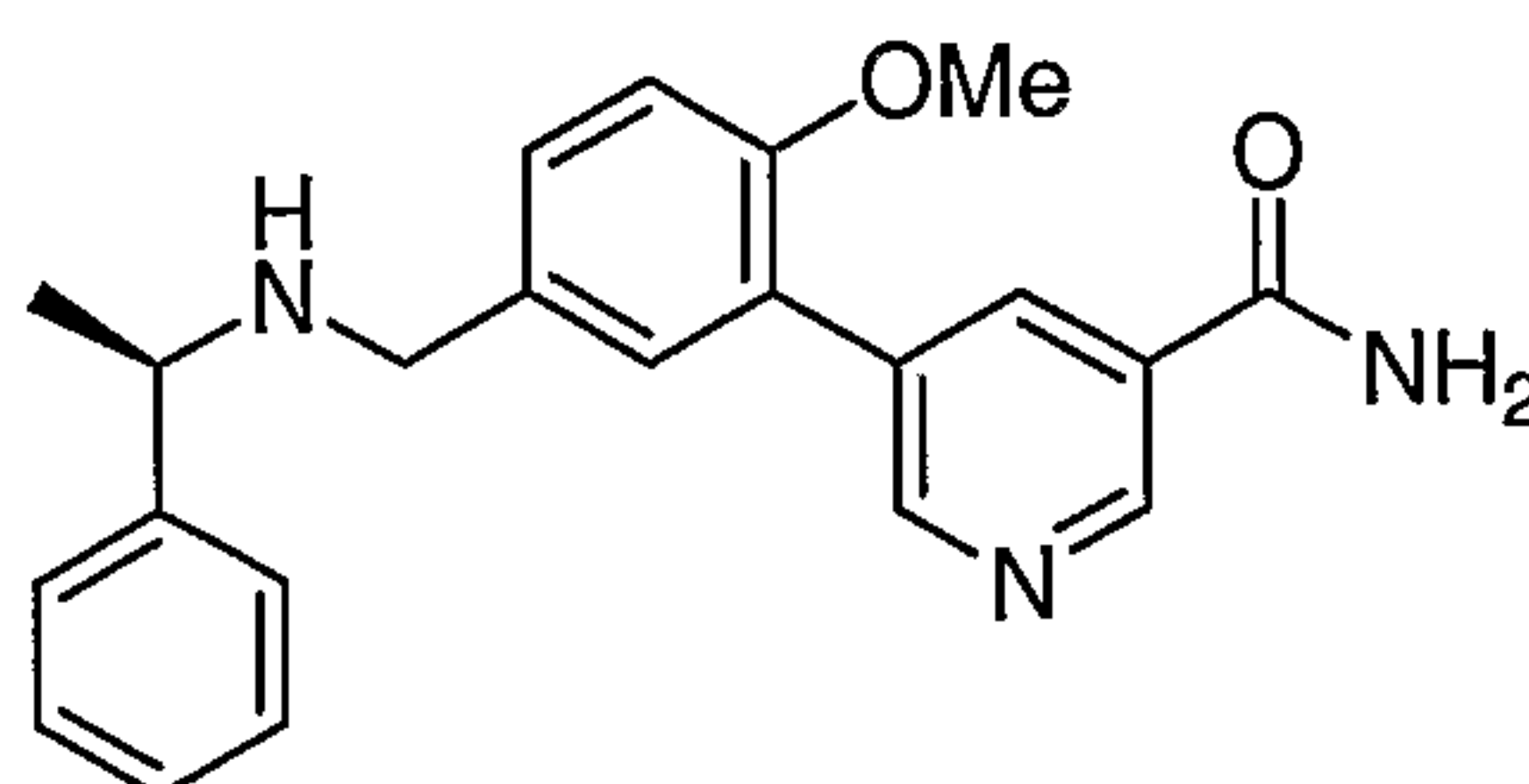
(1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine



MW 399.491
Mass found: 400, 799

Example 233

5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-3-pyridinecarboxamide



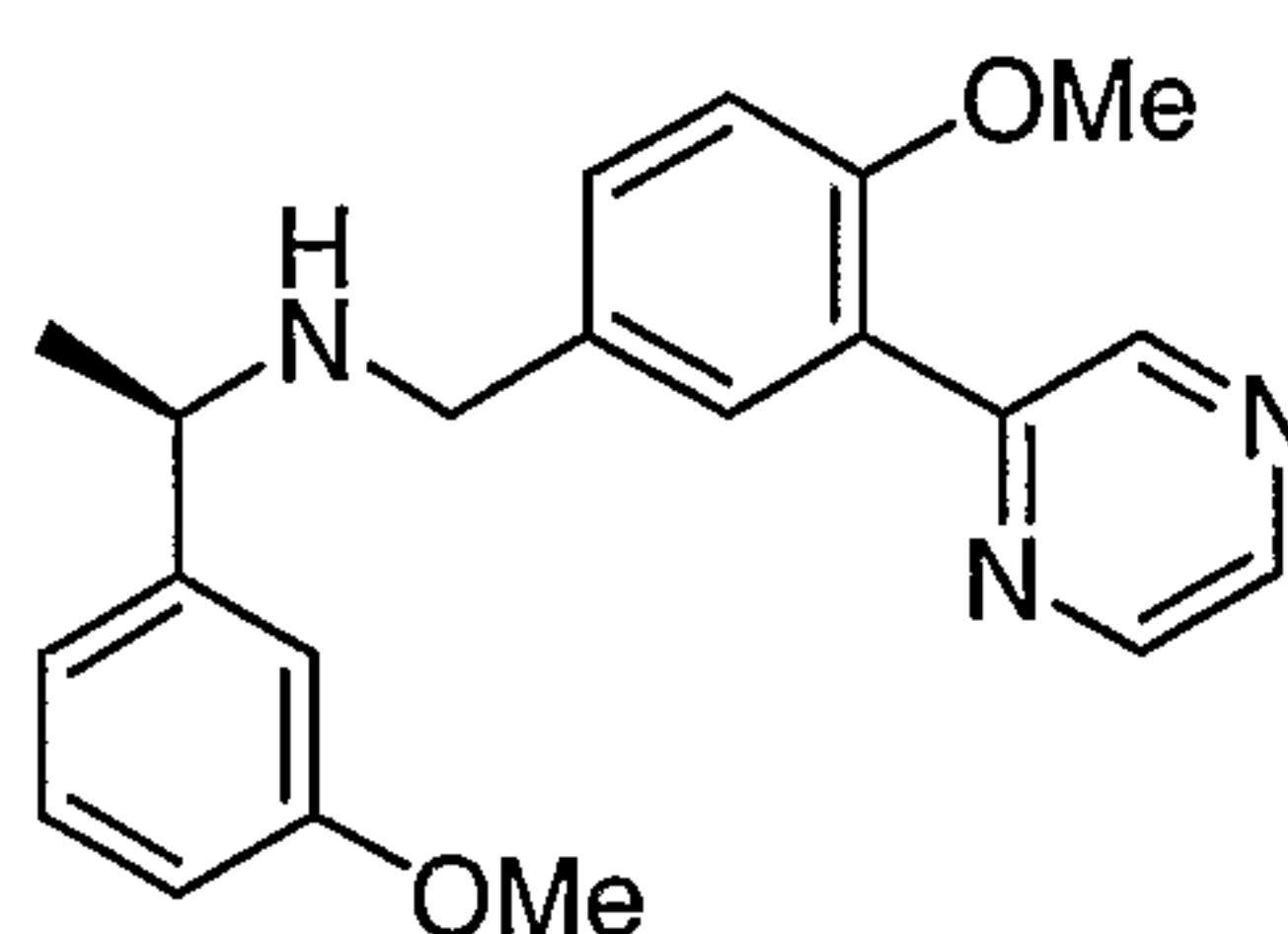
MW 361.443
Mass found: 362, 403, 723, 837

- 171 -

Example 234

5

(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)ethanamine



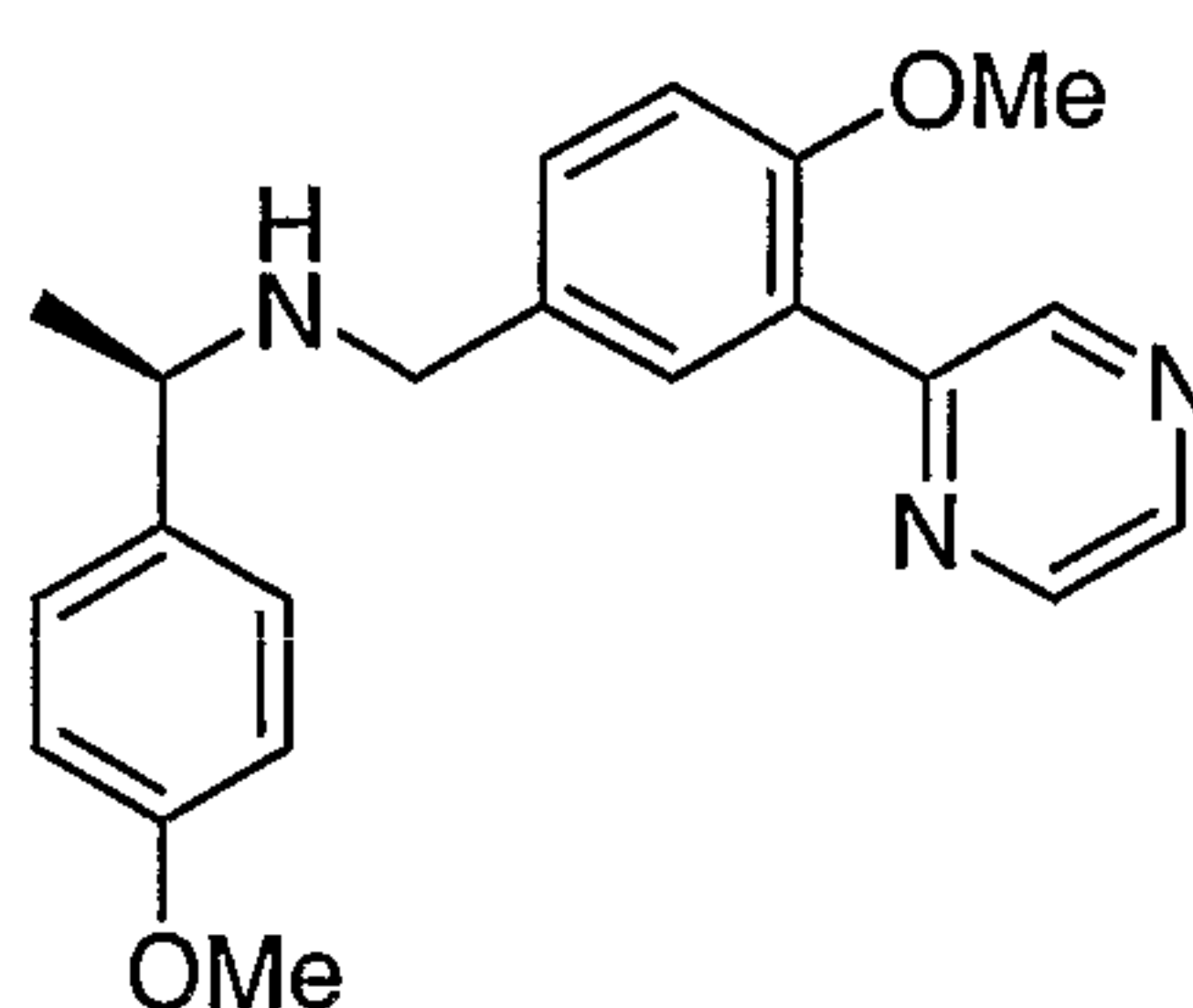
10

MW 349.432
Mass found: 350, 699

Example 235

15

(1R)-1-(4-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)ethanamine



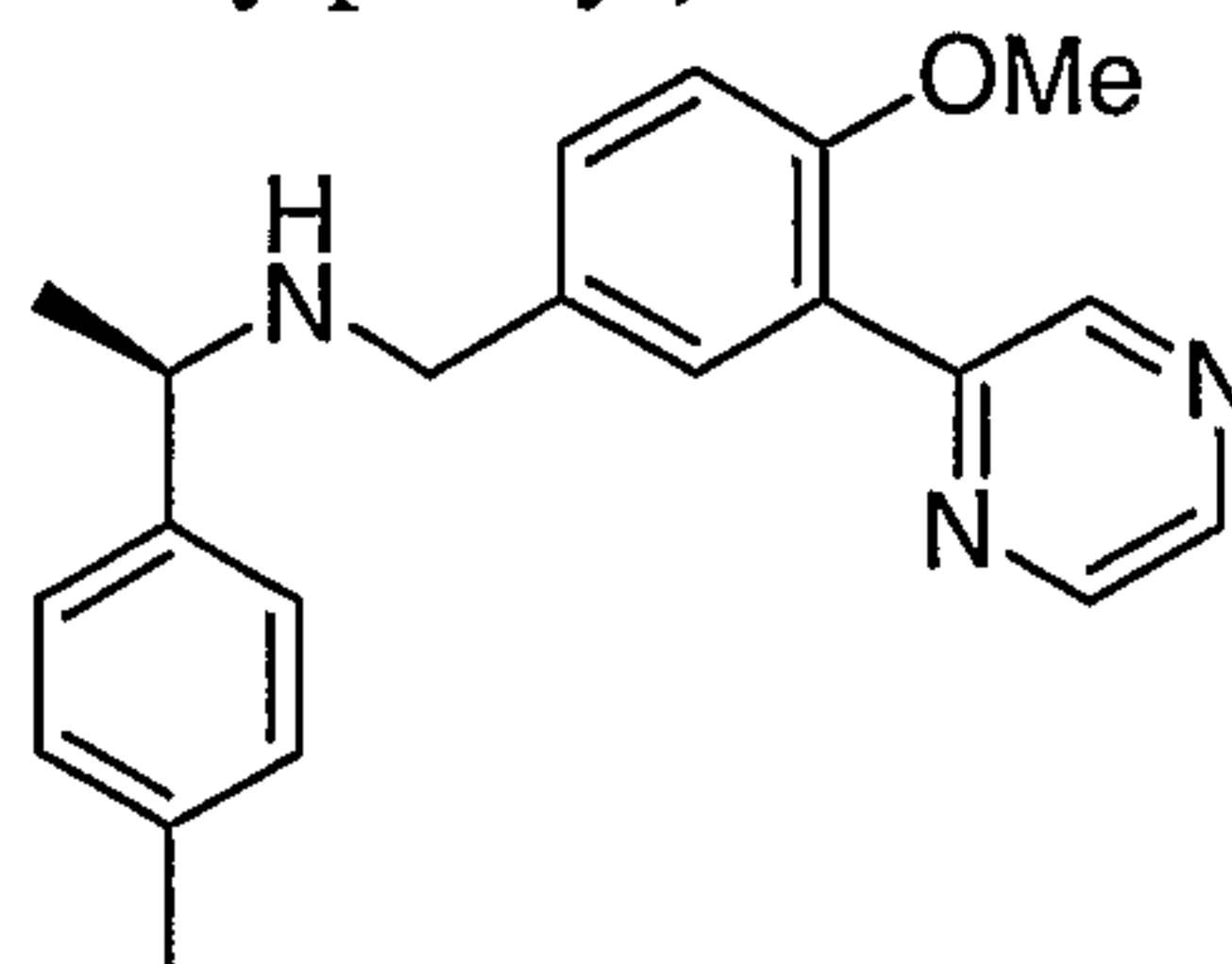
20

MW 349.432
Mass found: 350, 699

Example 236

25

(1R)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine



30

MW 333.433

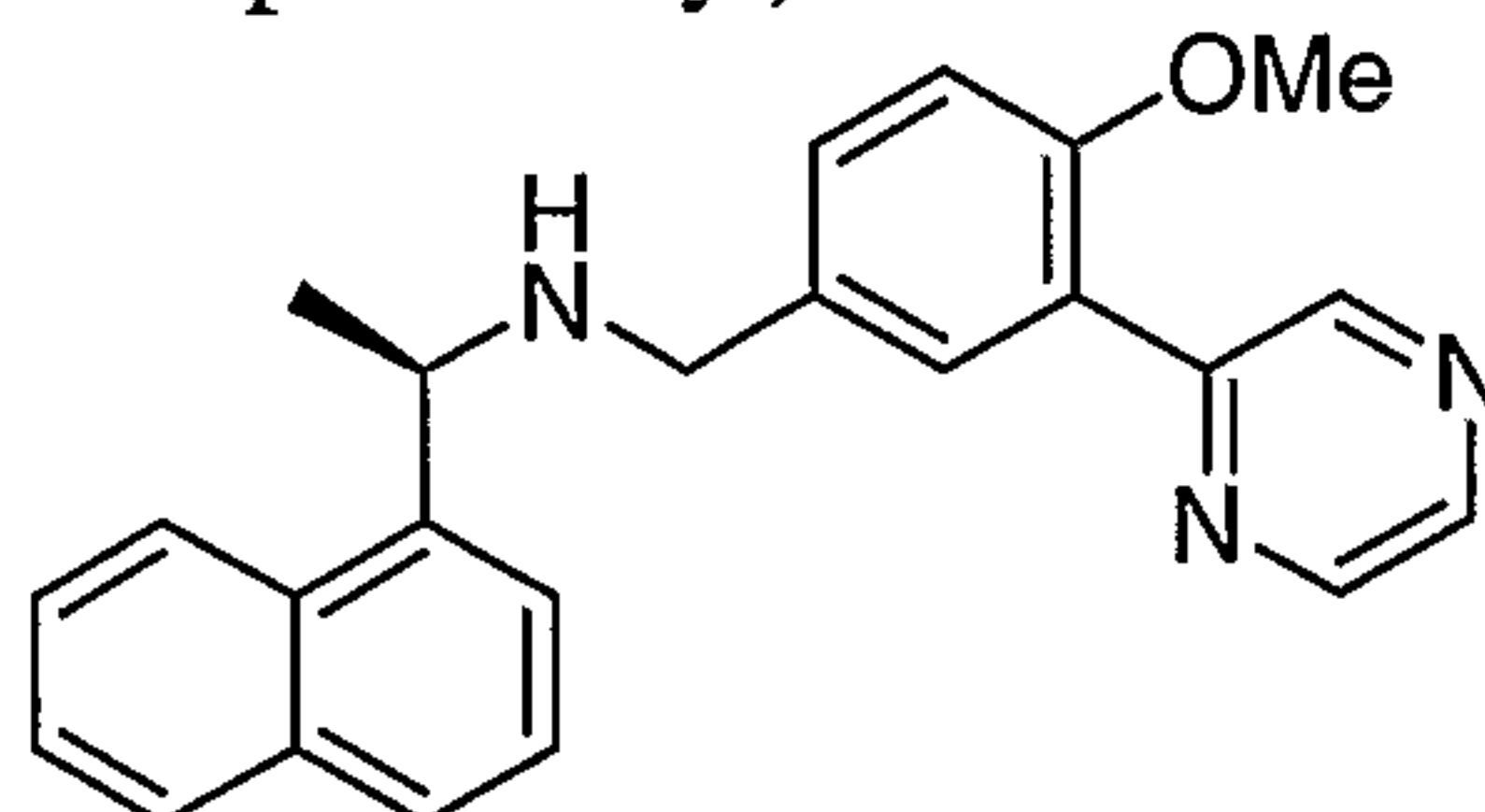
- 172 -

Mass found: 334, 667

Example 237

5

(1R)-N-((4-(methoxy)-3-(2-pyrazinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



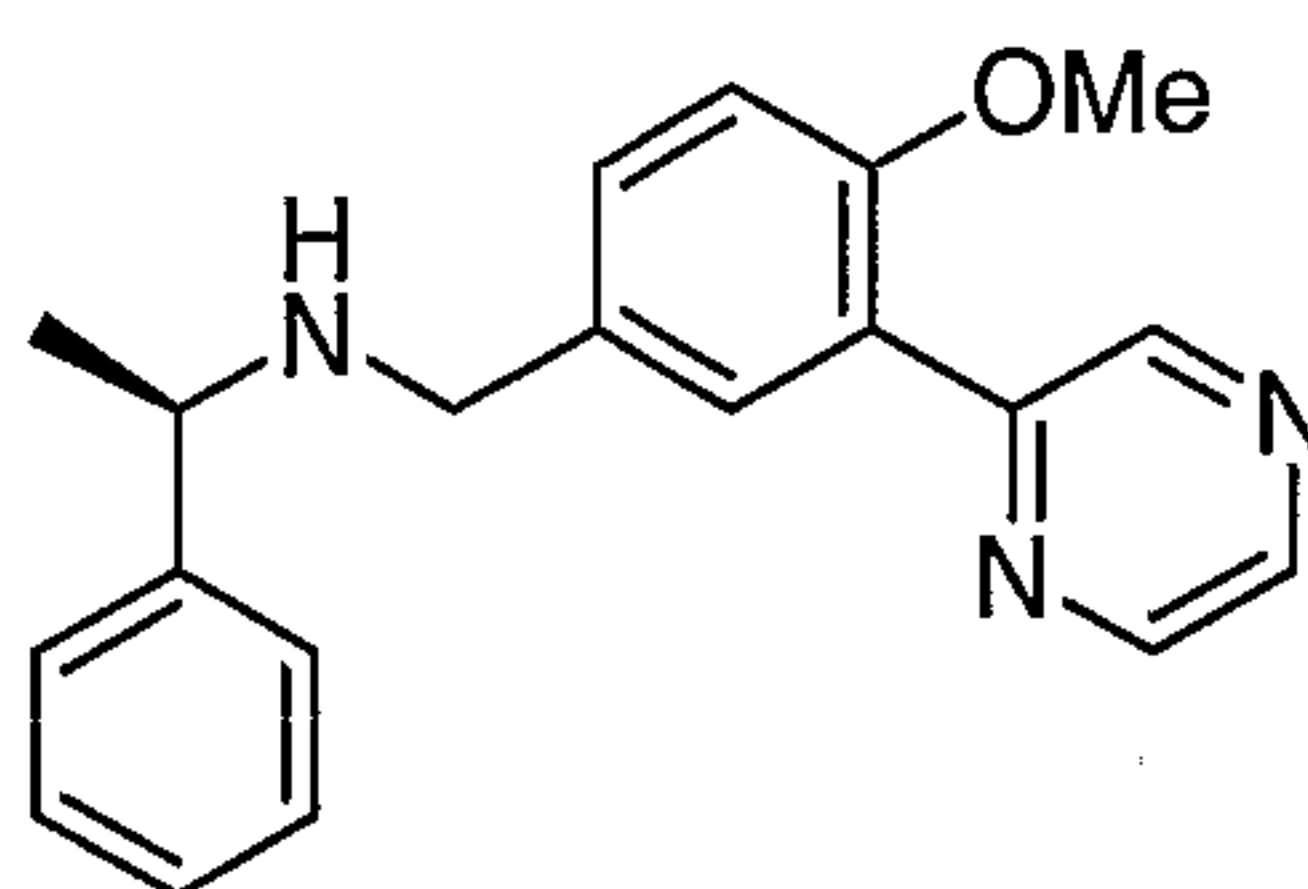
10

MW 369.466
Mass found: 370, 739

Example 238

15

(1R)-N-((4-(methoxy)-3-(2-pyrazinyl)phenyl)methyl)-1-phenylethanamine



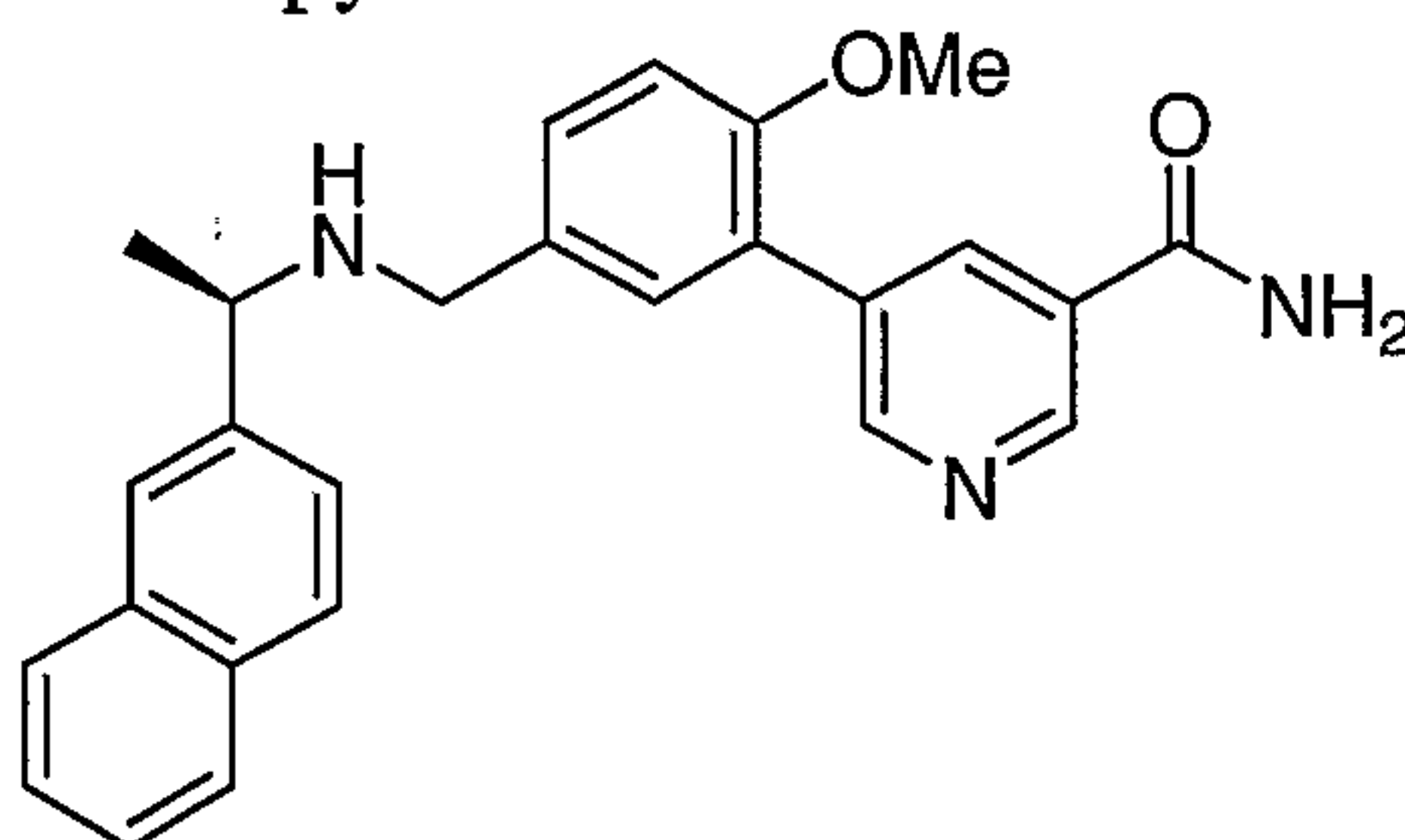
20

MW 319.406
Mass found: 320, 639

Example 239

25

5-(2-(methoxy)-5-((((1R)-1-(2-naphthalenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide



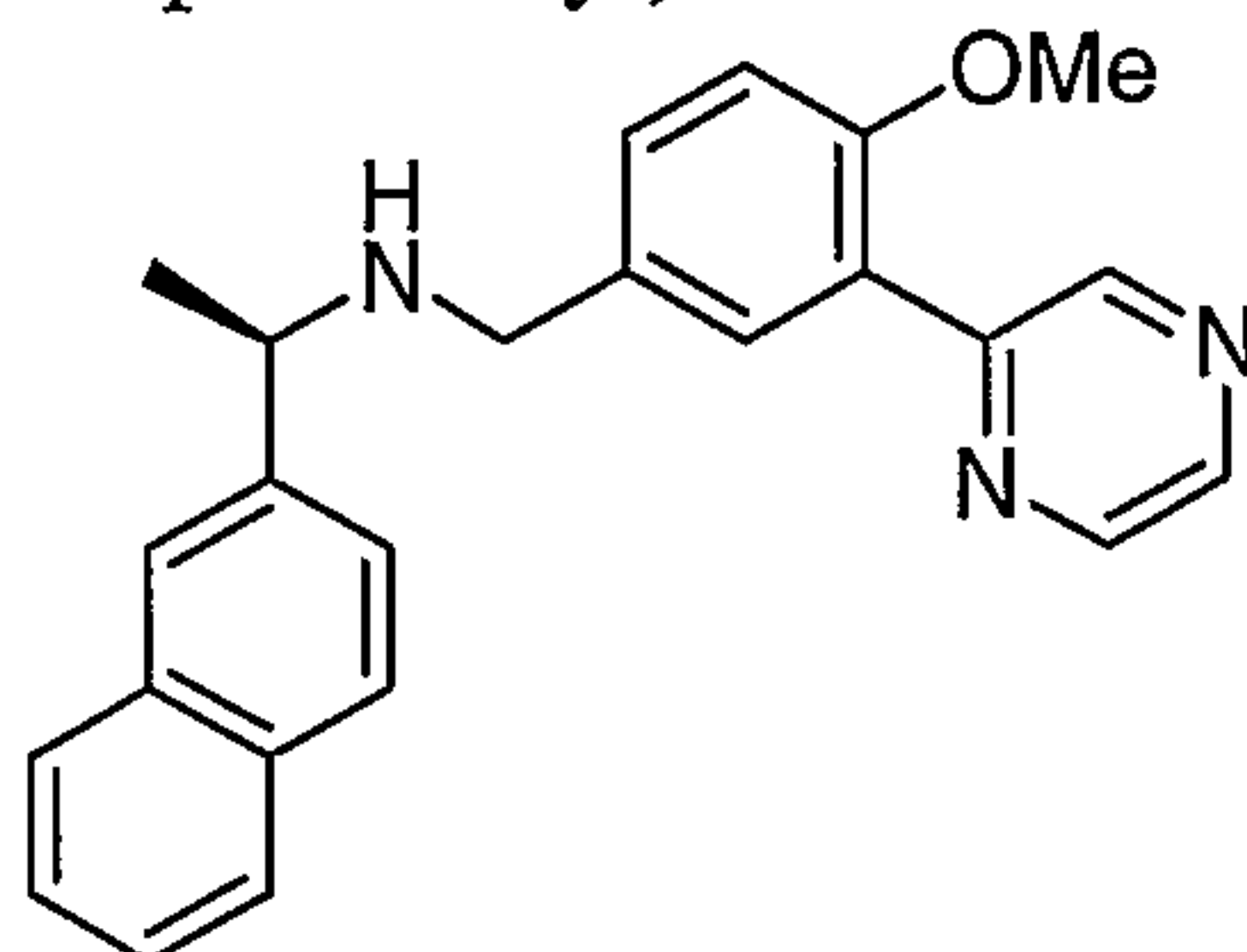
30

MW 411.503
Mass found: 412, 453, 823, 937

- 173 -

Example 240

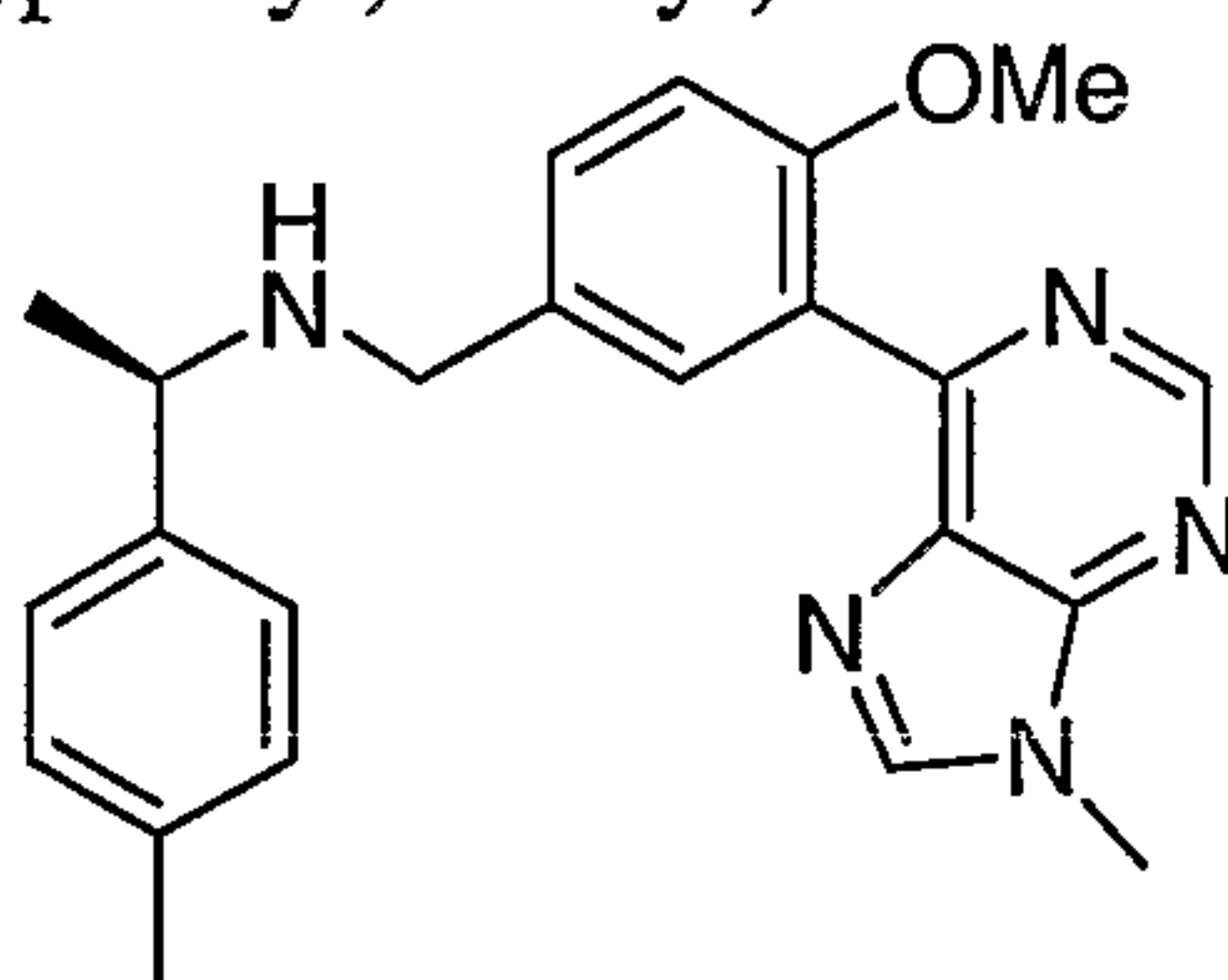
(1R)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine



MW 369.466
Mass found: 370, 739

Example 241

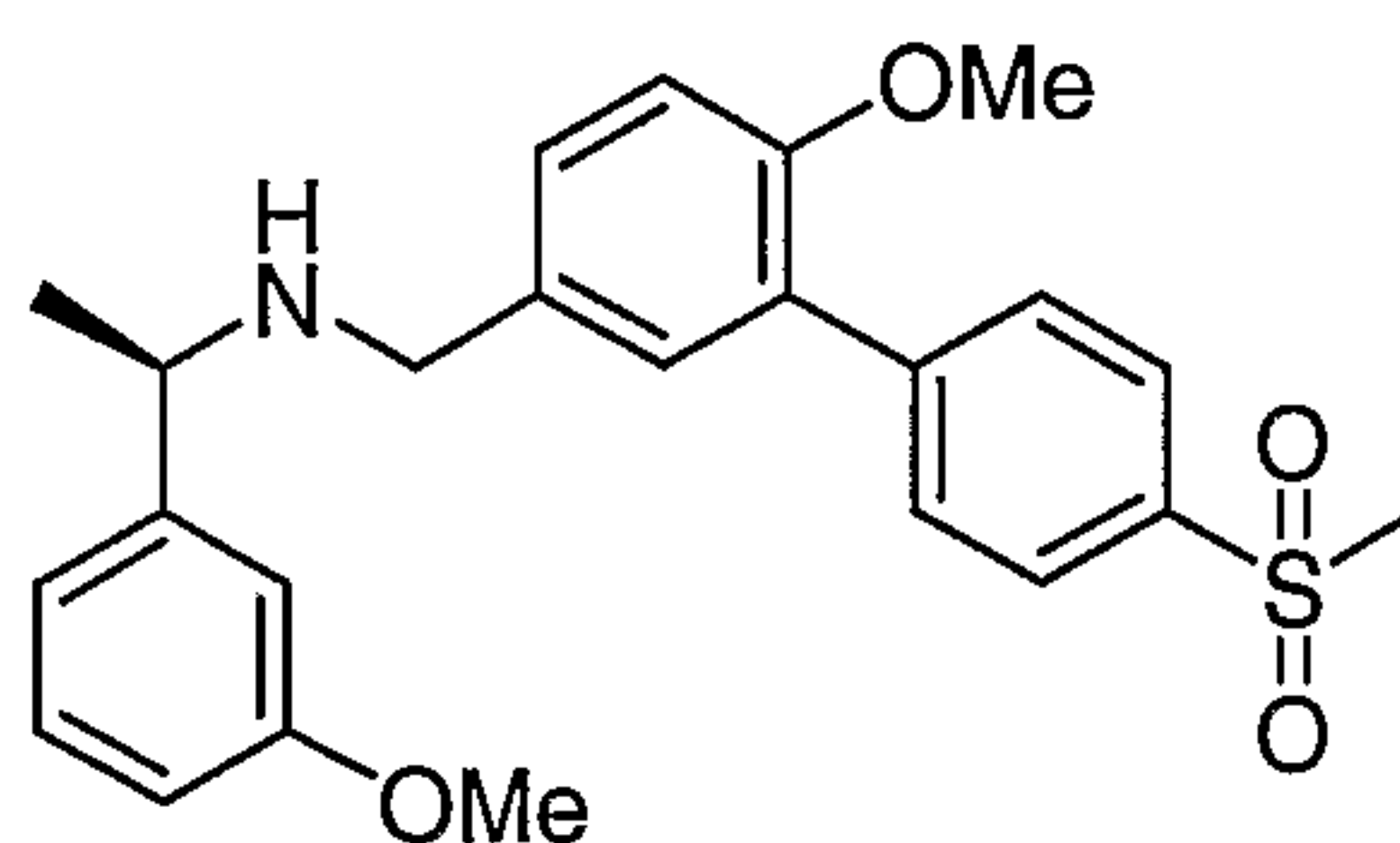
(1R)-1-(4-methylphenyl)-N-((3-(9-methyl-9H-purin-6-yl)phenyl)methyl)ethanamine



MW 357.459
Mass found: 358, 715

Example 242

(1R)-N-((6-(methyloxy)-4'-(methylsulfonyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine



MW 425.546

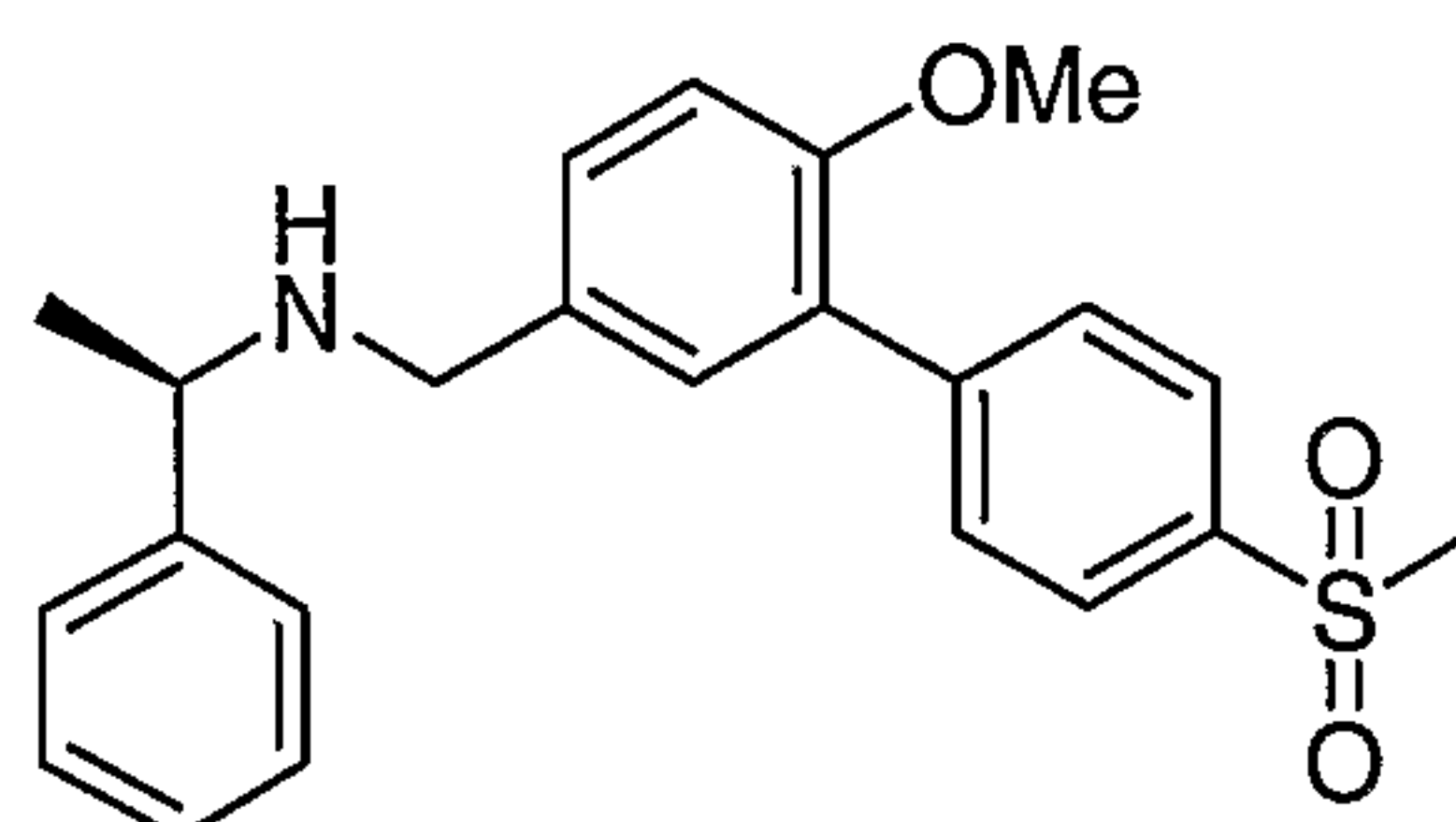
- 174 -

Mass found: 426, 851

Example 243

5

(1R)-N-((6-(methyloxy)-4'-(methylsulfonyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine



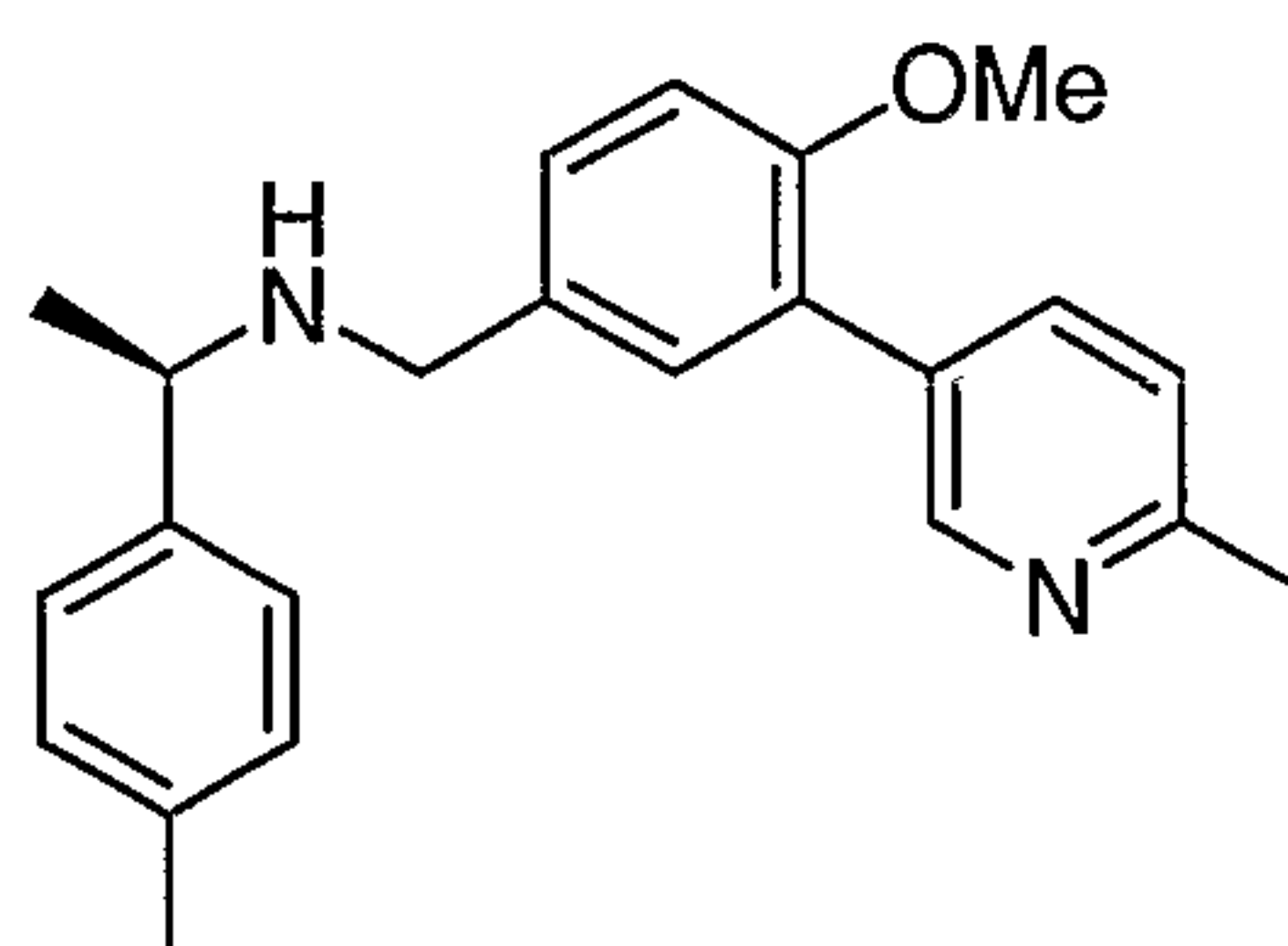
10

MW 395.521
Mass found: 396, 437

15

Example 244

(1R)-N-((4-(methyloxy)-3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine



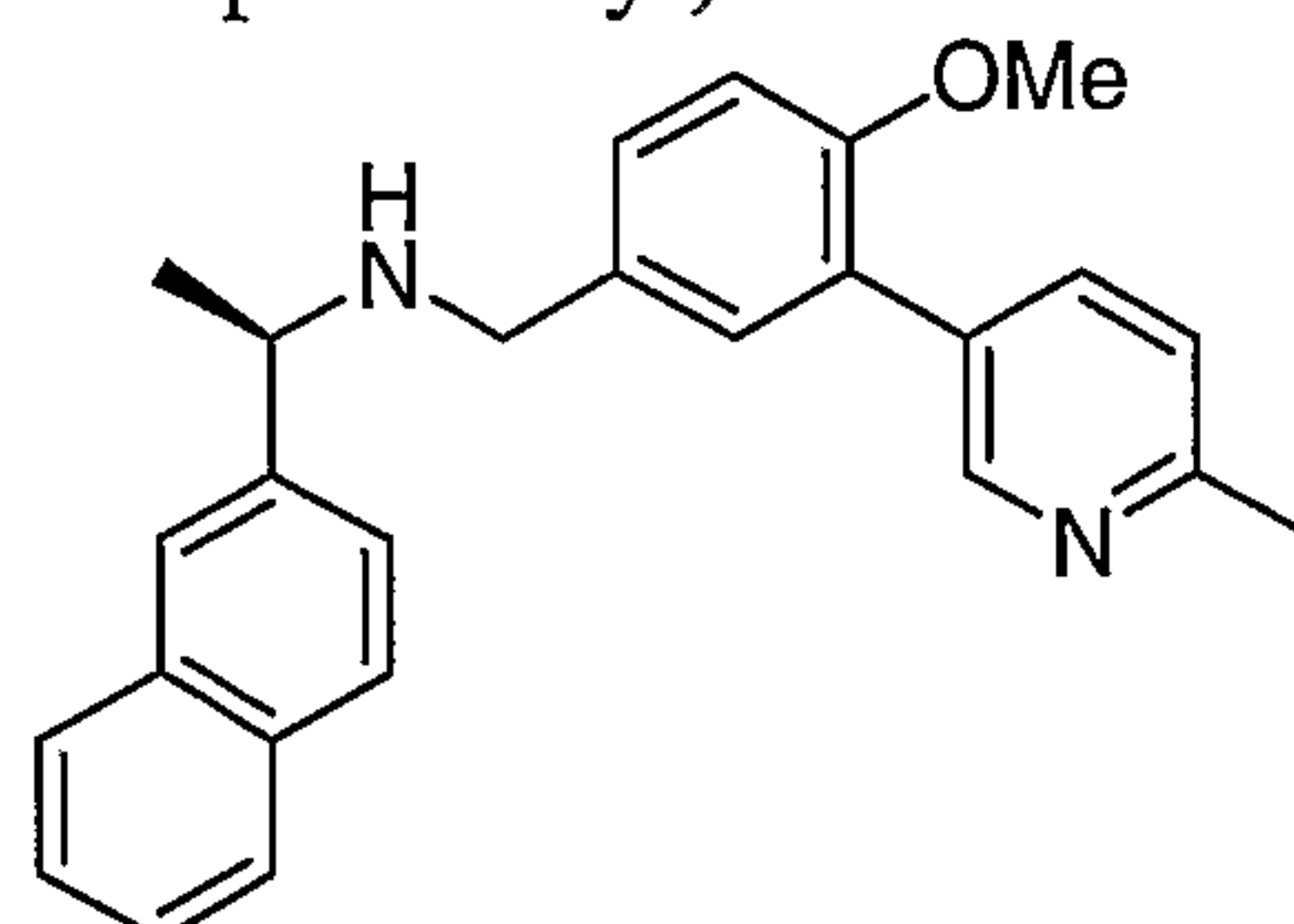
20

MW 346.471
Mass found: 347, 807, 693

25

Example 245

(1R)-N-((4-(methyloxy)-3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine



30

- 175 -

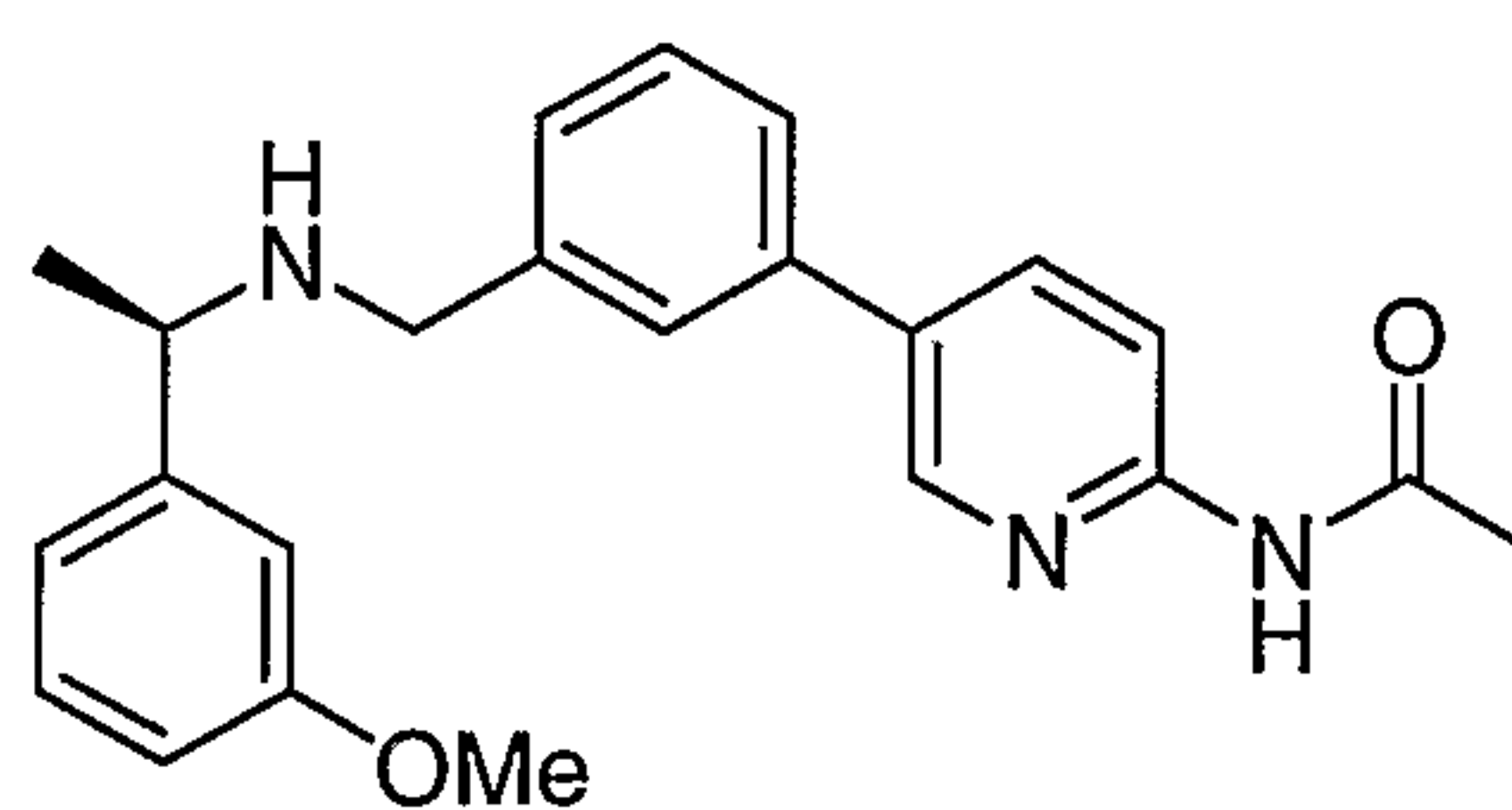
MW 382.504
Mass found: 383, 879, 765

5

Example 246

N-(5-(3-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2-pyridinyl)acetamide

10



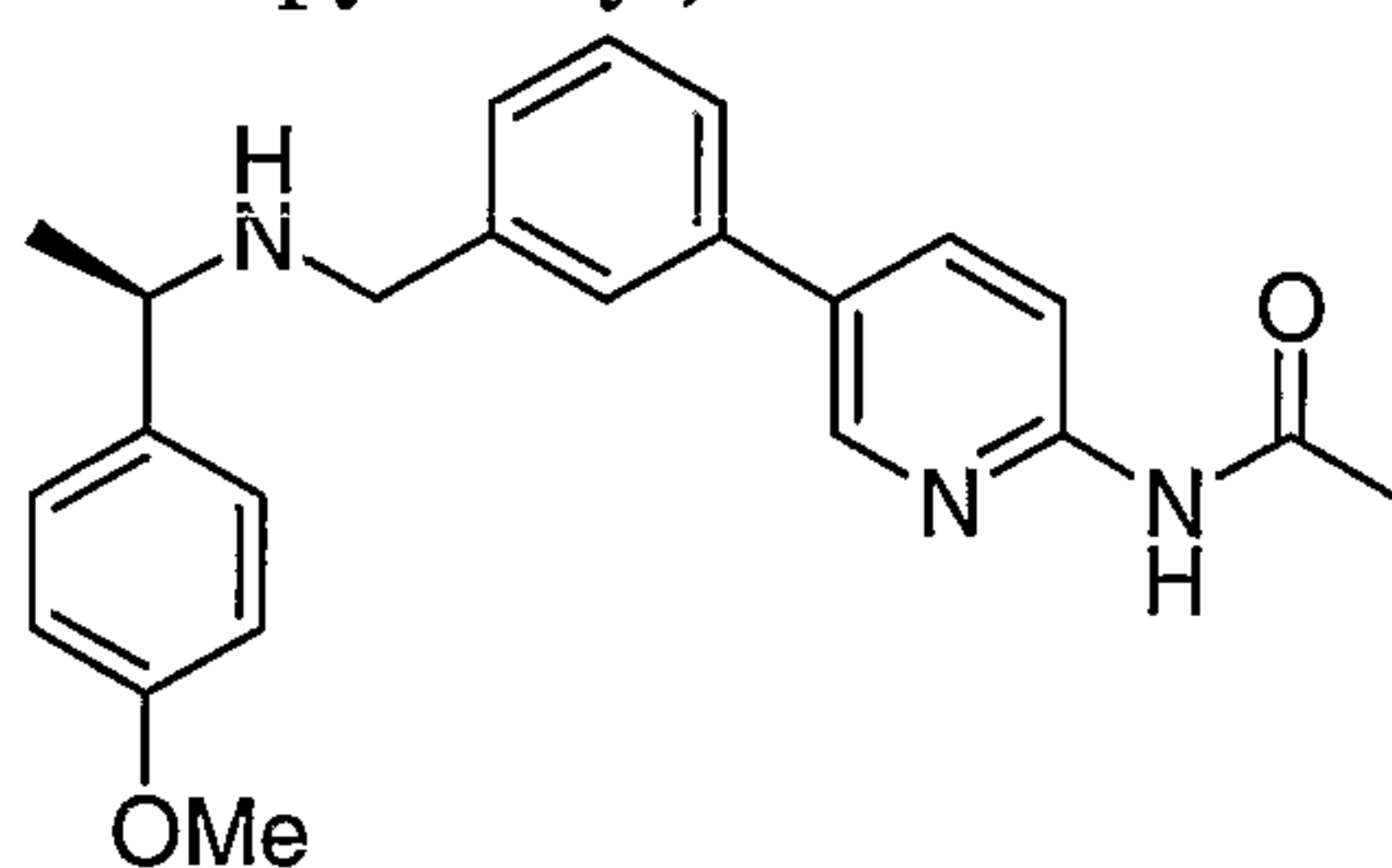
MW 375.47
Mass found: 242, 376

15

Example 247

N-(5-(3-((((1R)-1-(4-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2-pyridinyl)acetamide

20



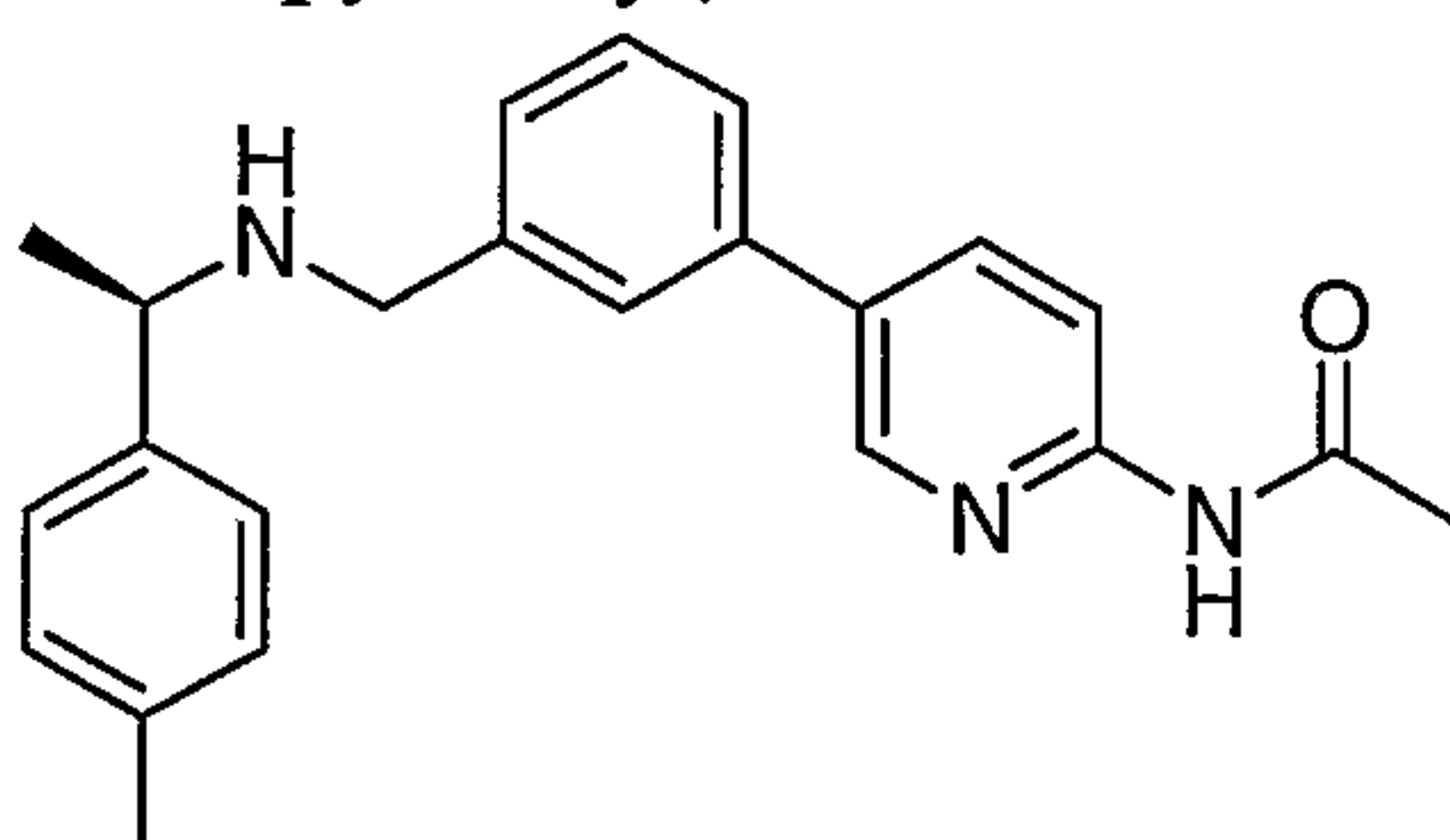
MW 375.47
Mass found: 375, 242, 751

25

Example 248

N-(5-(3-((((1R)-1-(4-methylphenyl)ethyl)amino)methyl)phenyl)-2-pyridinyl)acetamide

30



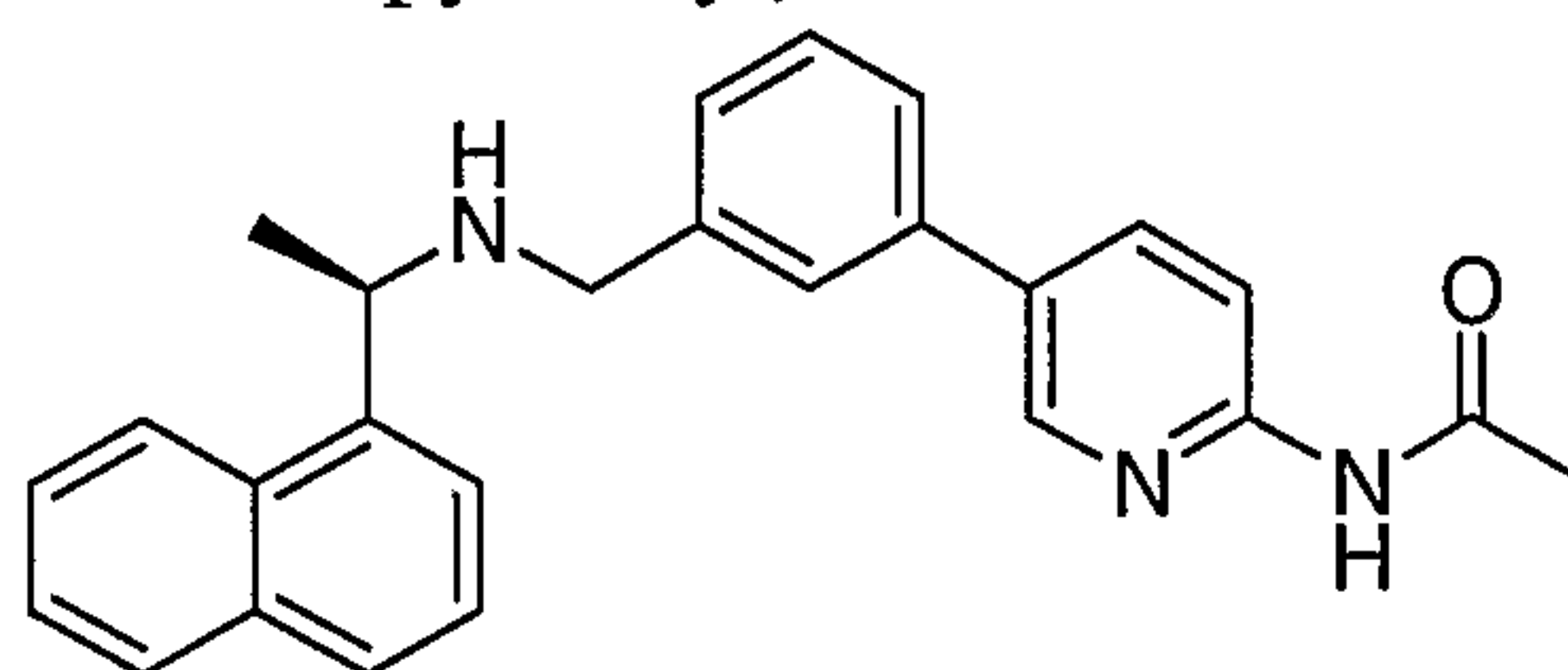
- 176 -

MW 359.47
Mass found: 242, 360

5

Example 249

N-(5-(3-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-2-pyridinyl)acetamide



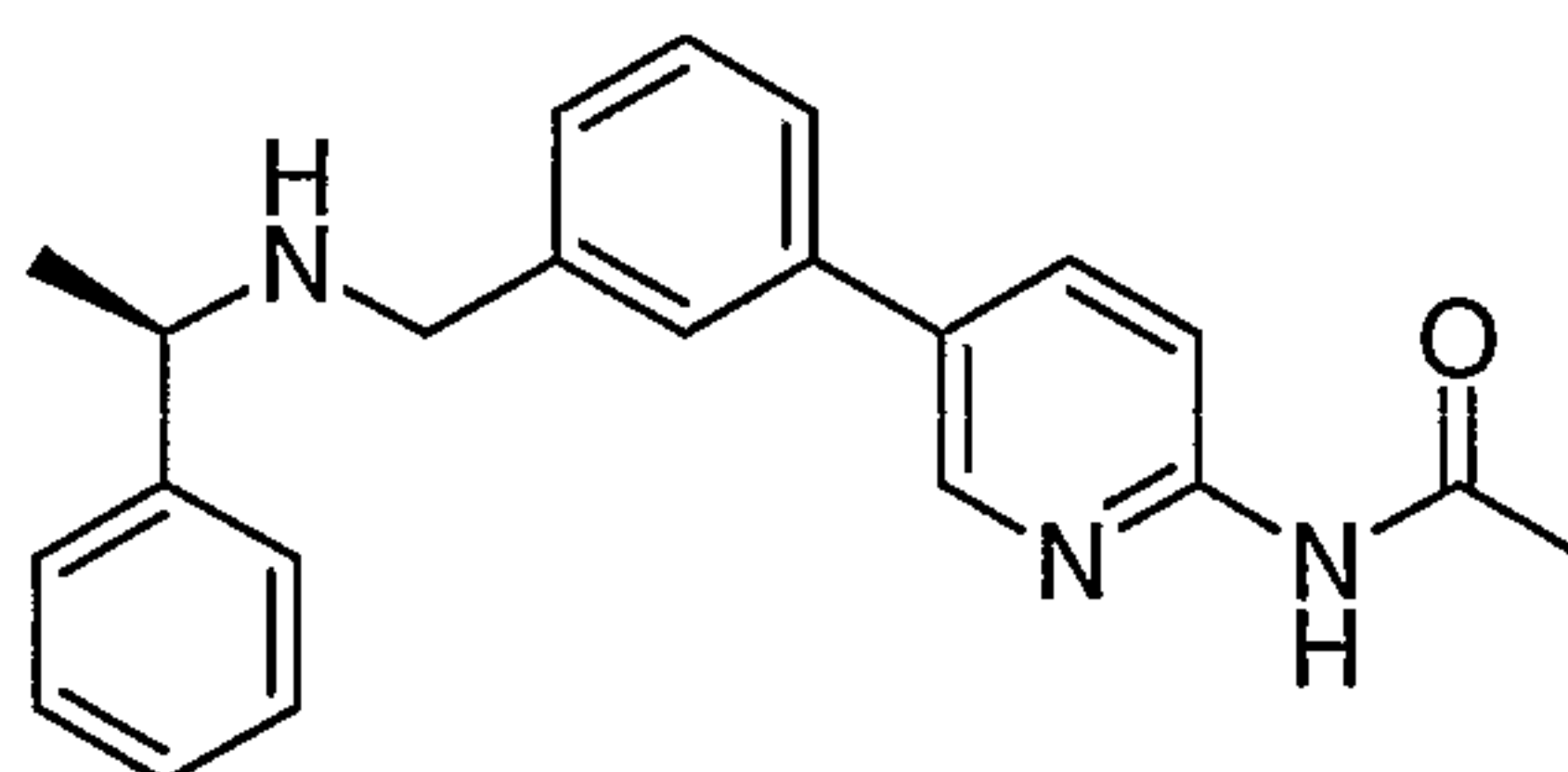
10

MW 395.504
Mass found: 155, 242, 396

15

Example 250

N-(5-(3-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinyl)acetamide



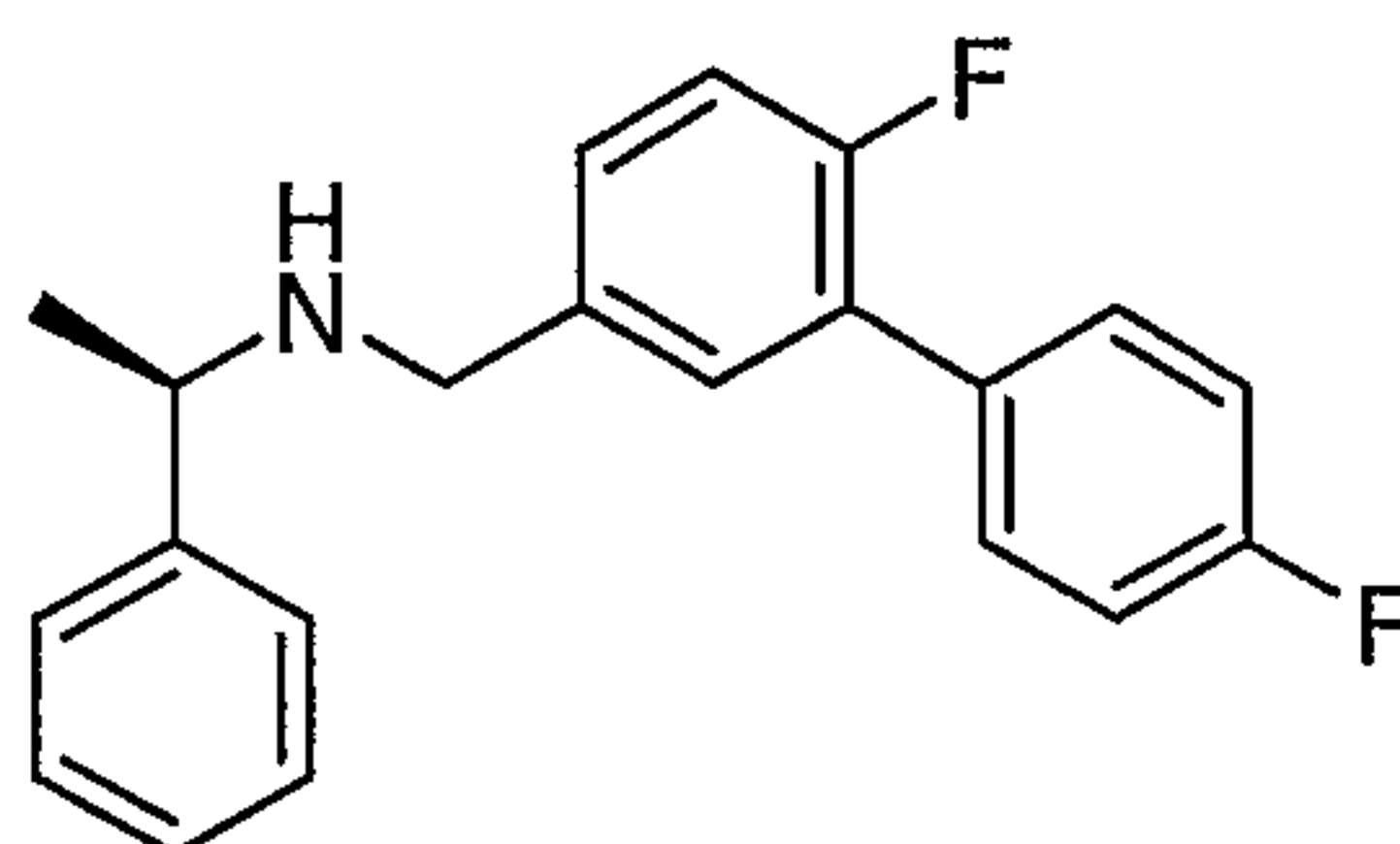
20

MW 345.444
Mass found: 242, 346

25

Example 251

(1R)-N-((4',6-difluoro-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine



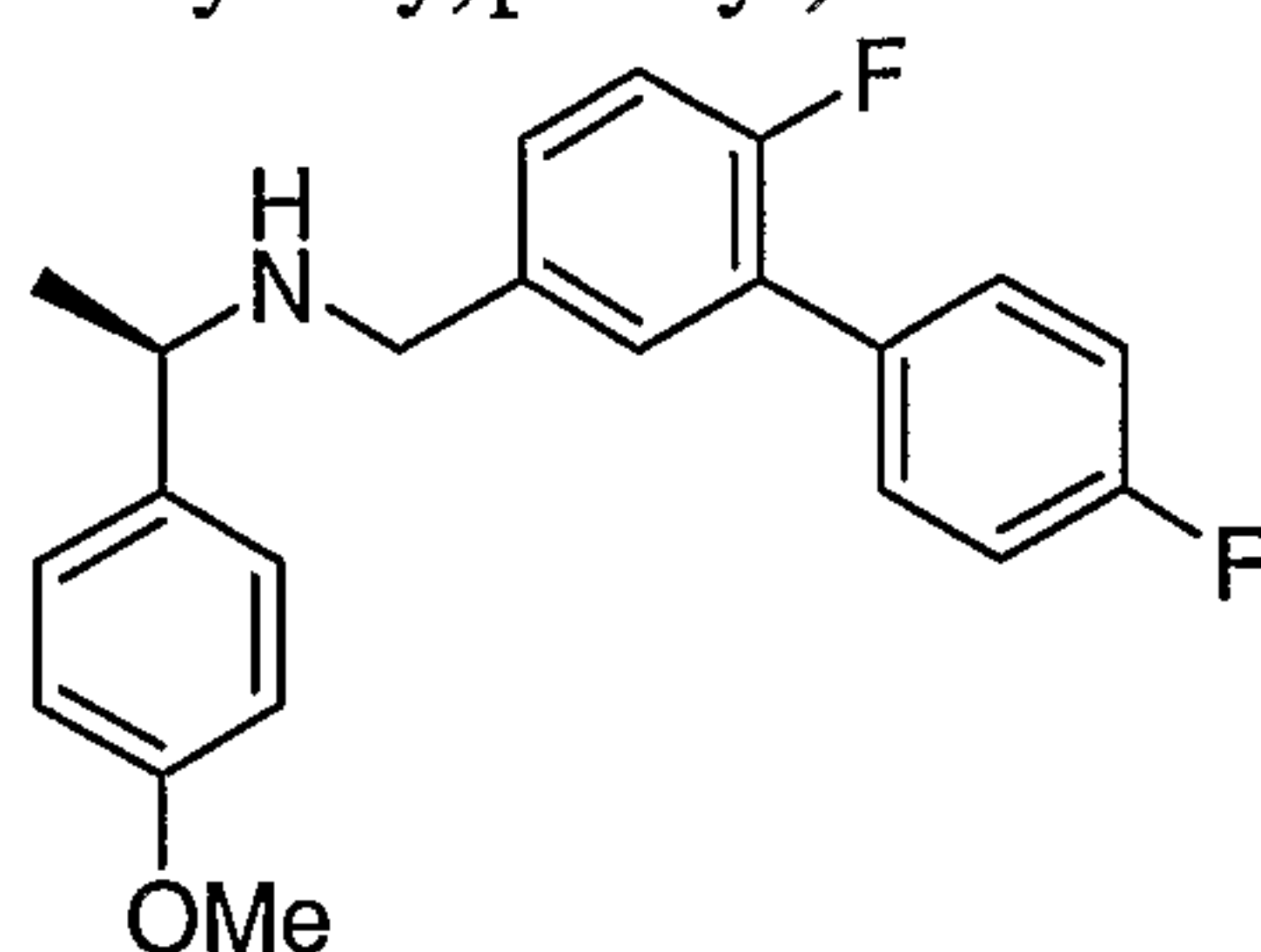
30

MW 323.384
Mass found: 324, 647, 761

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Example 252

5 (1R)-N-((4',6-difluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine



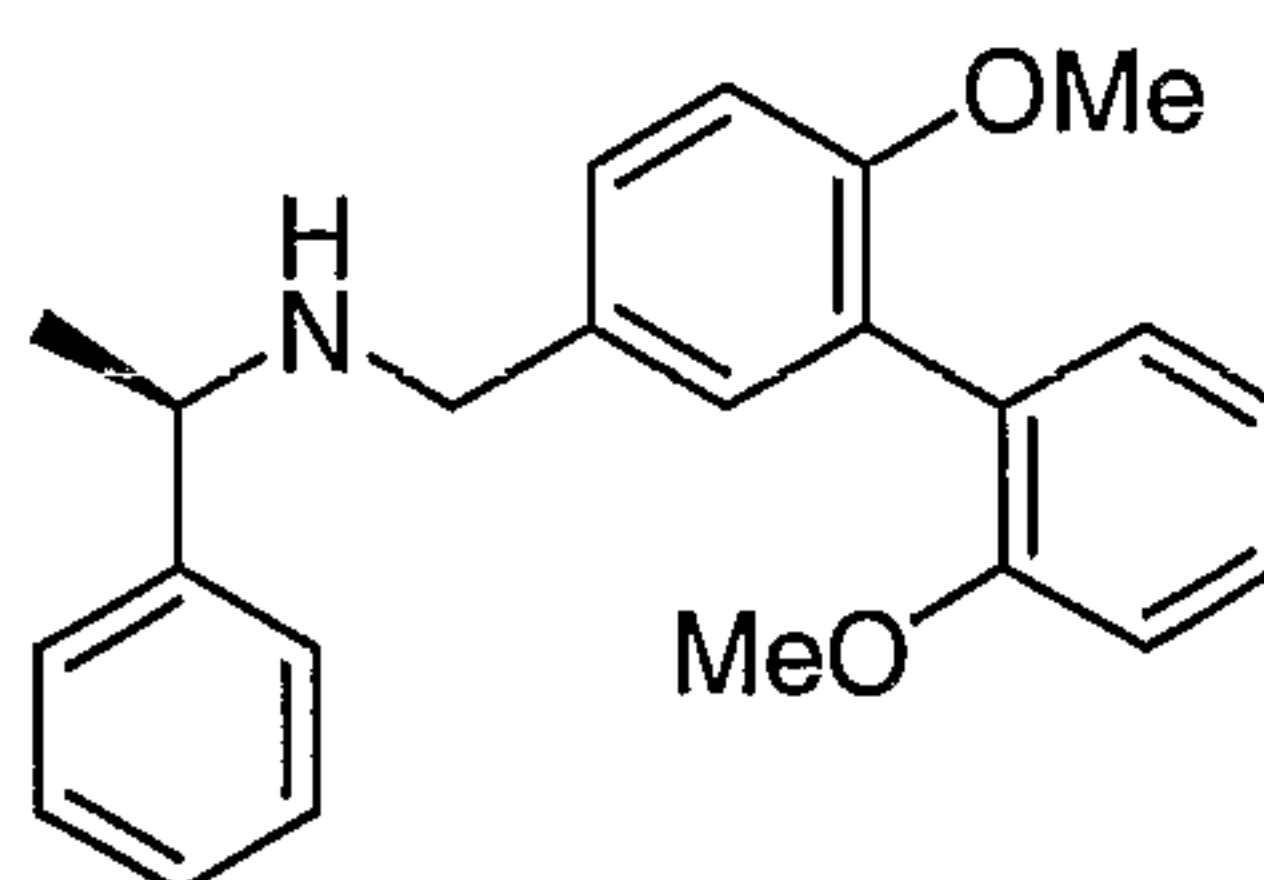
MW 353.41

10 Mass found: 354, 707, 821

Examples 253-451 were prepared using Method C:

15 **Example 253**

(1R)-N-((2',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine



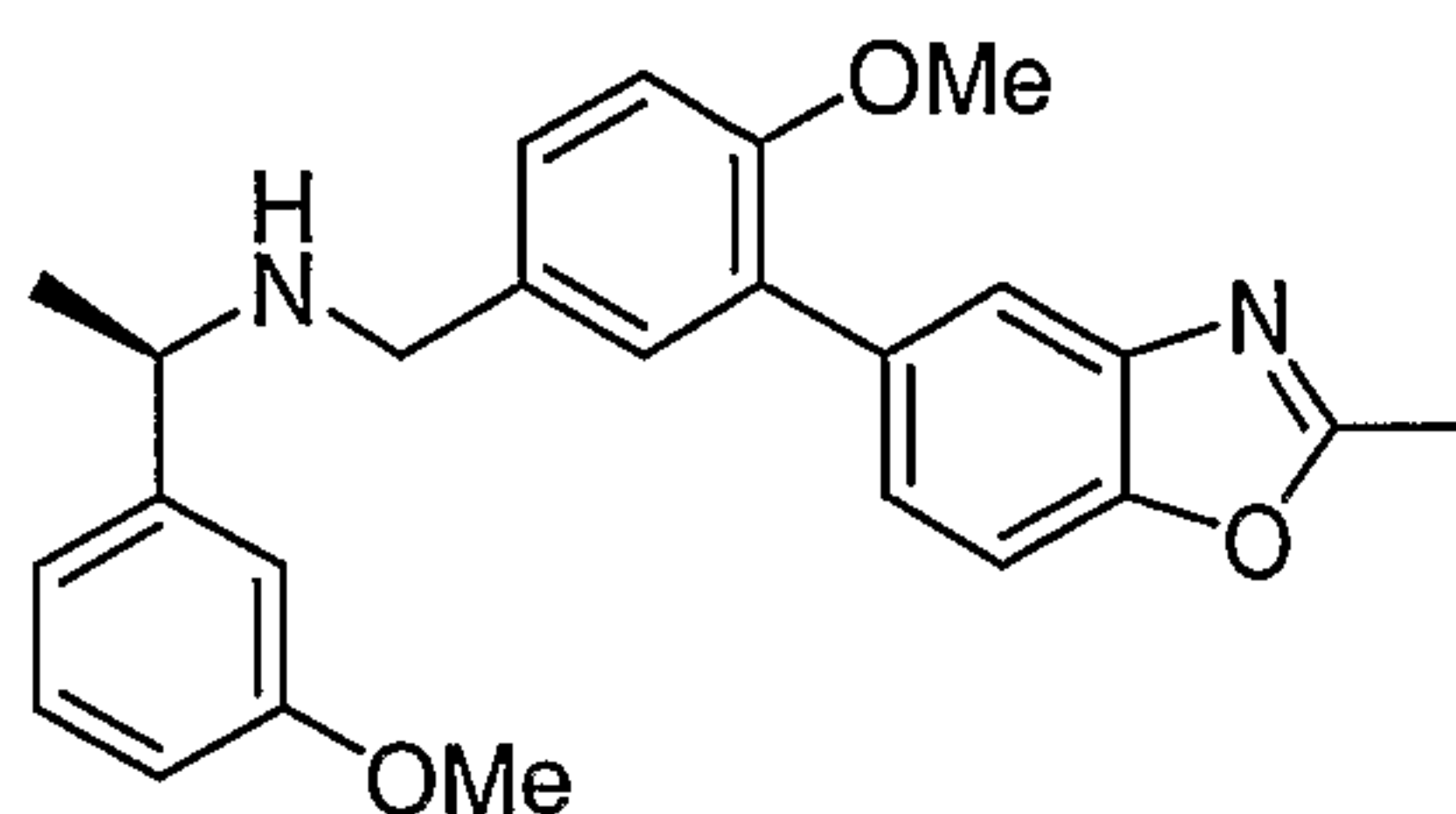
20

MW 347.456

Mass found: 227, 348

Example 254

25 (1R)-N-((3-(2-methyl-1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine



30

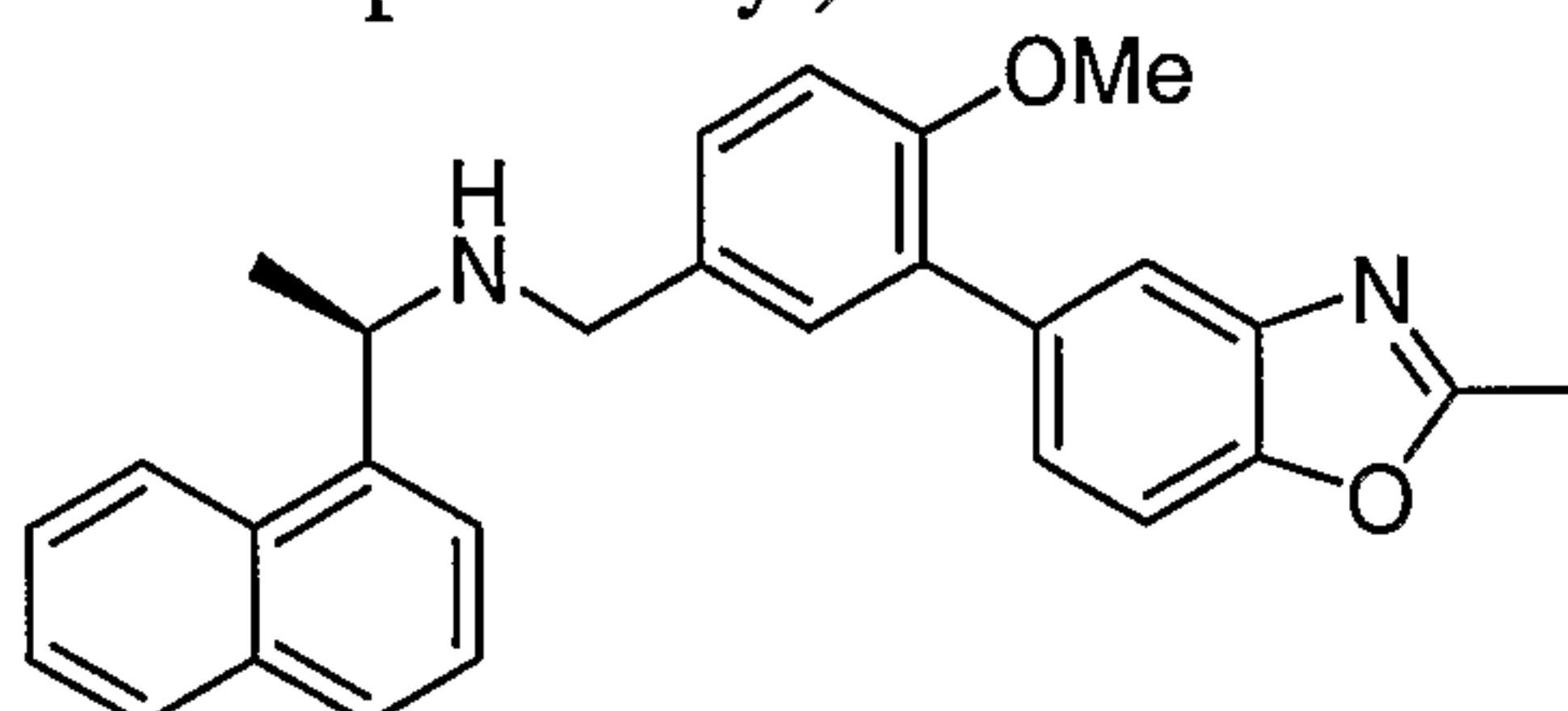
MW 402.491

Mass found: 403

- 178 -

Example 255

5 (1R)-N-((3-(2-methyl-1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



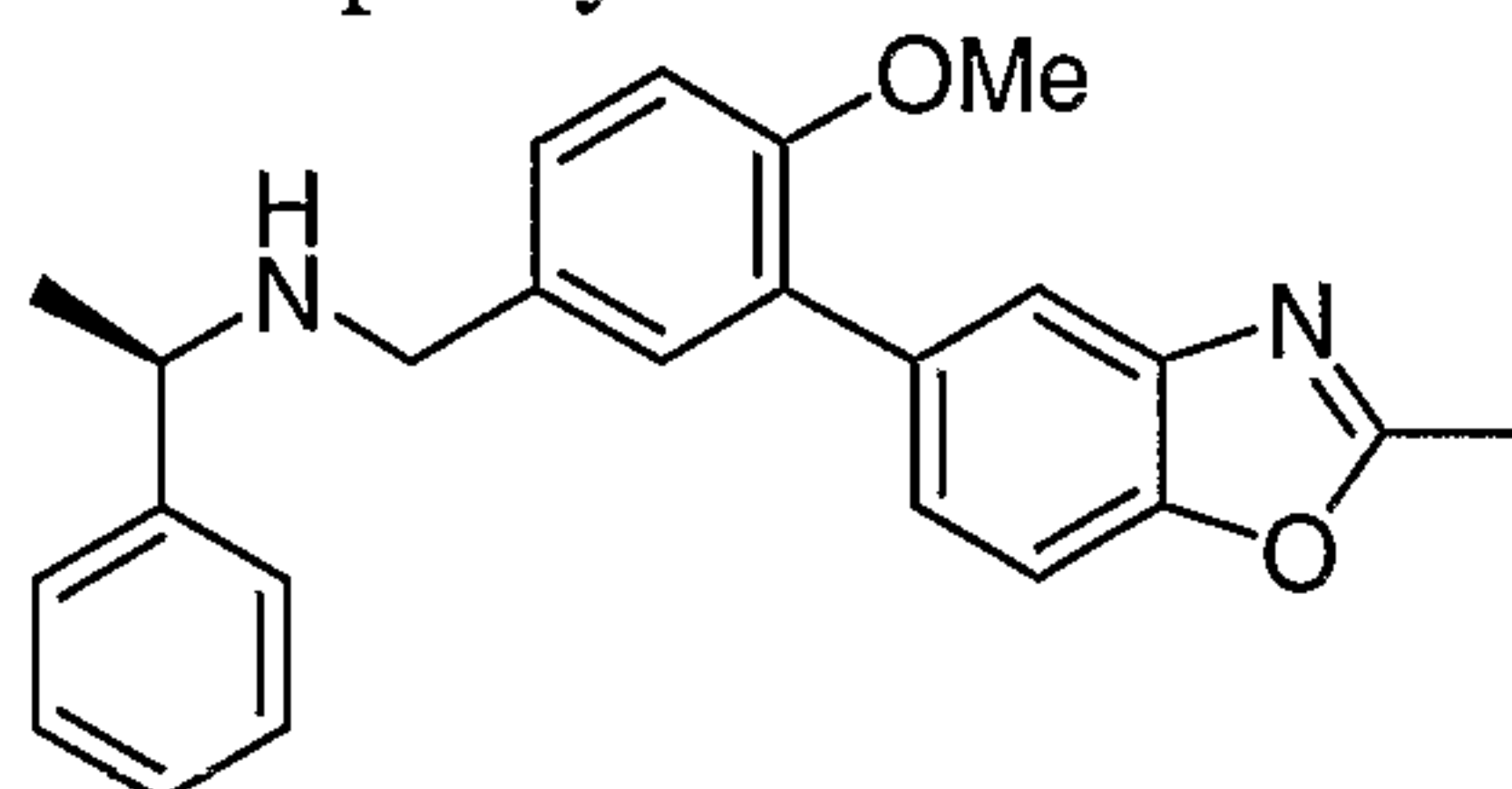
MW 422.525

Mass found: 423

10

Example 256

15 (1R)-N-((3-(2-methyl-1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine



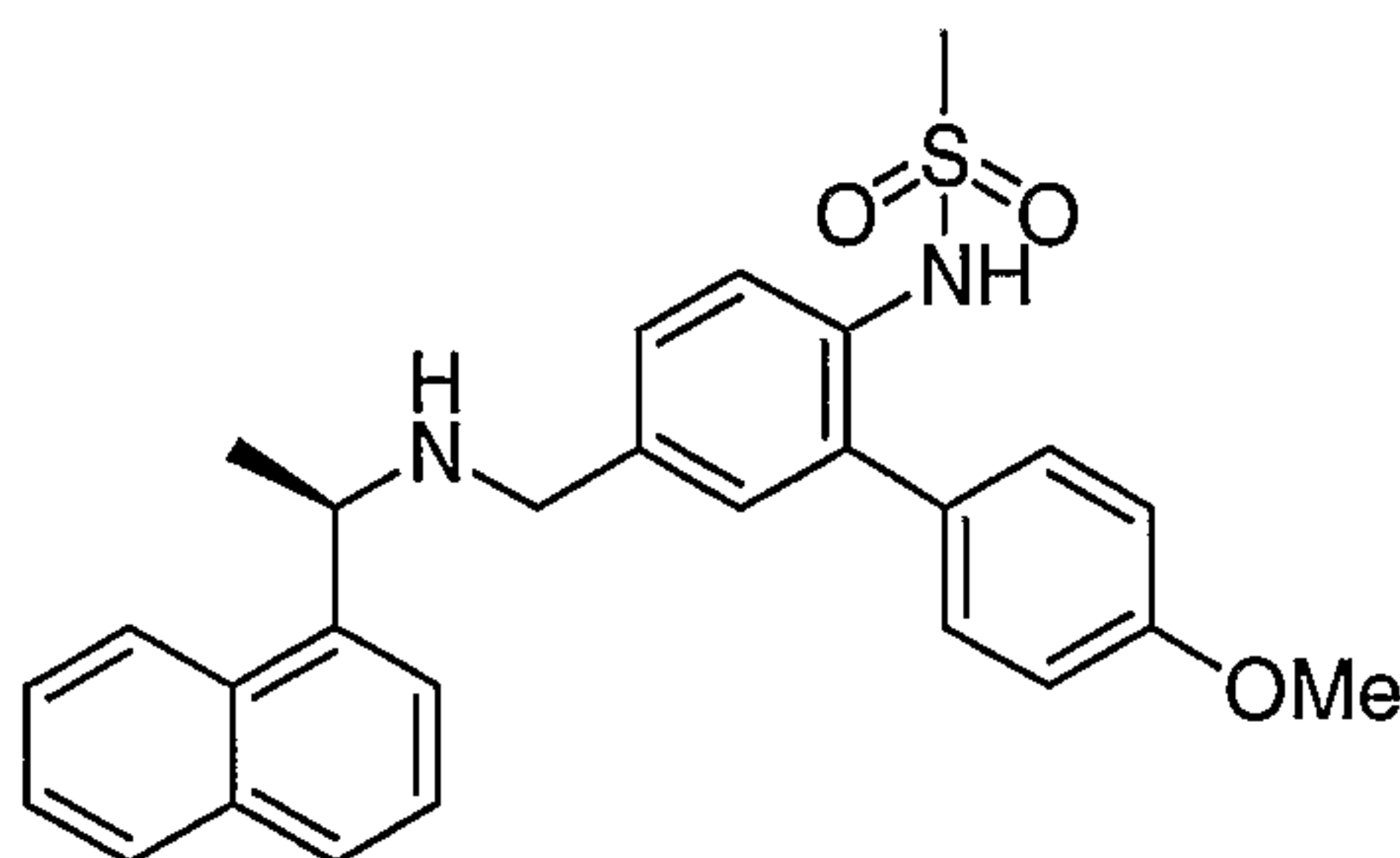
MW 372.466

Mass found: 373

20

Example 257

25 N-(4'-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-2-yl)methanesulfonamide



MW 460.595

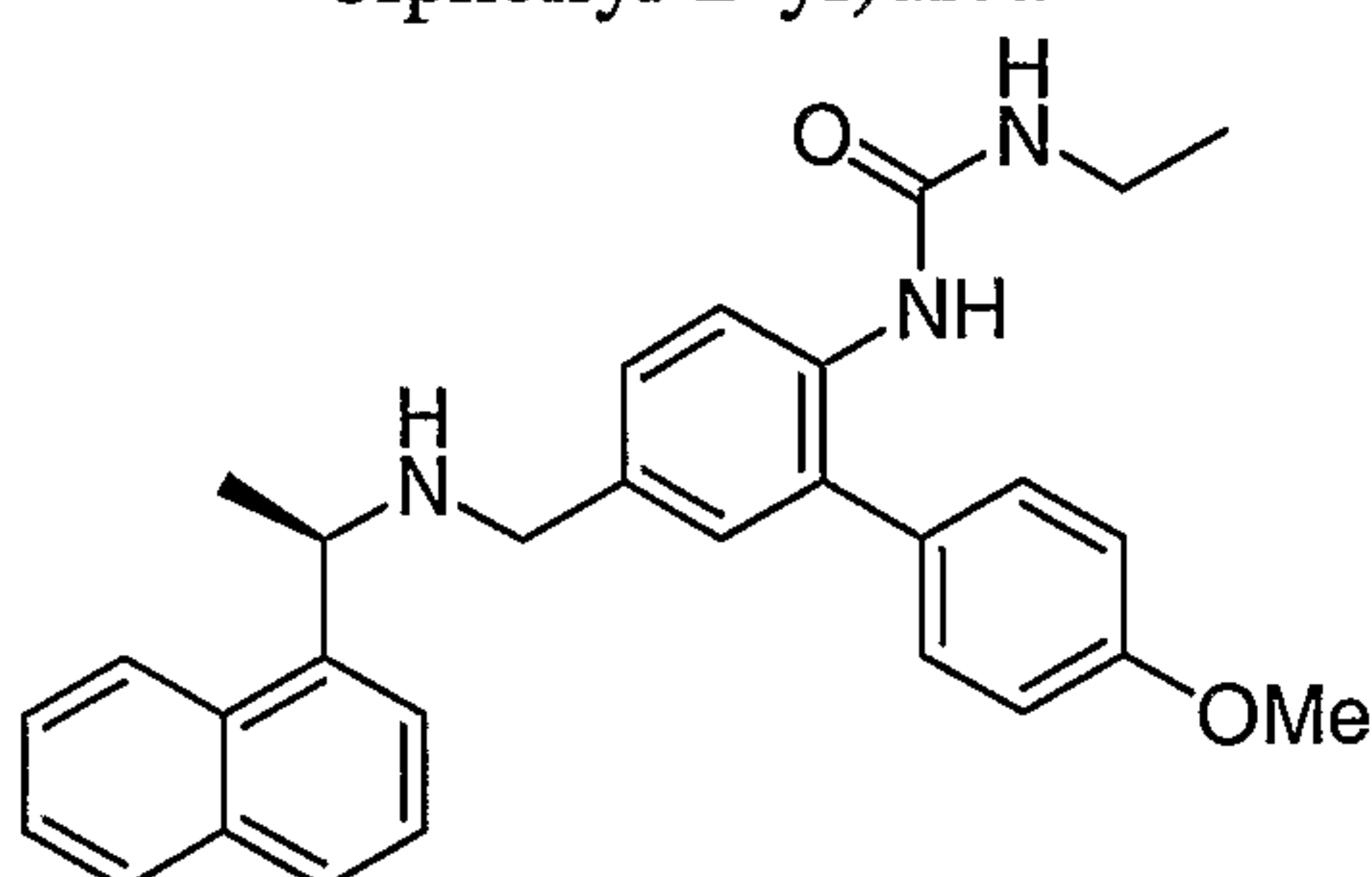
Mass found: 155, 290, 461

30

- 179 -

Example 258

5 N-ethyl-N'-(4'-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-2-yl)urea



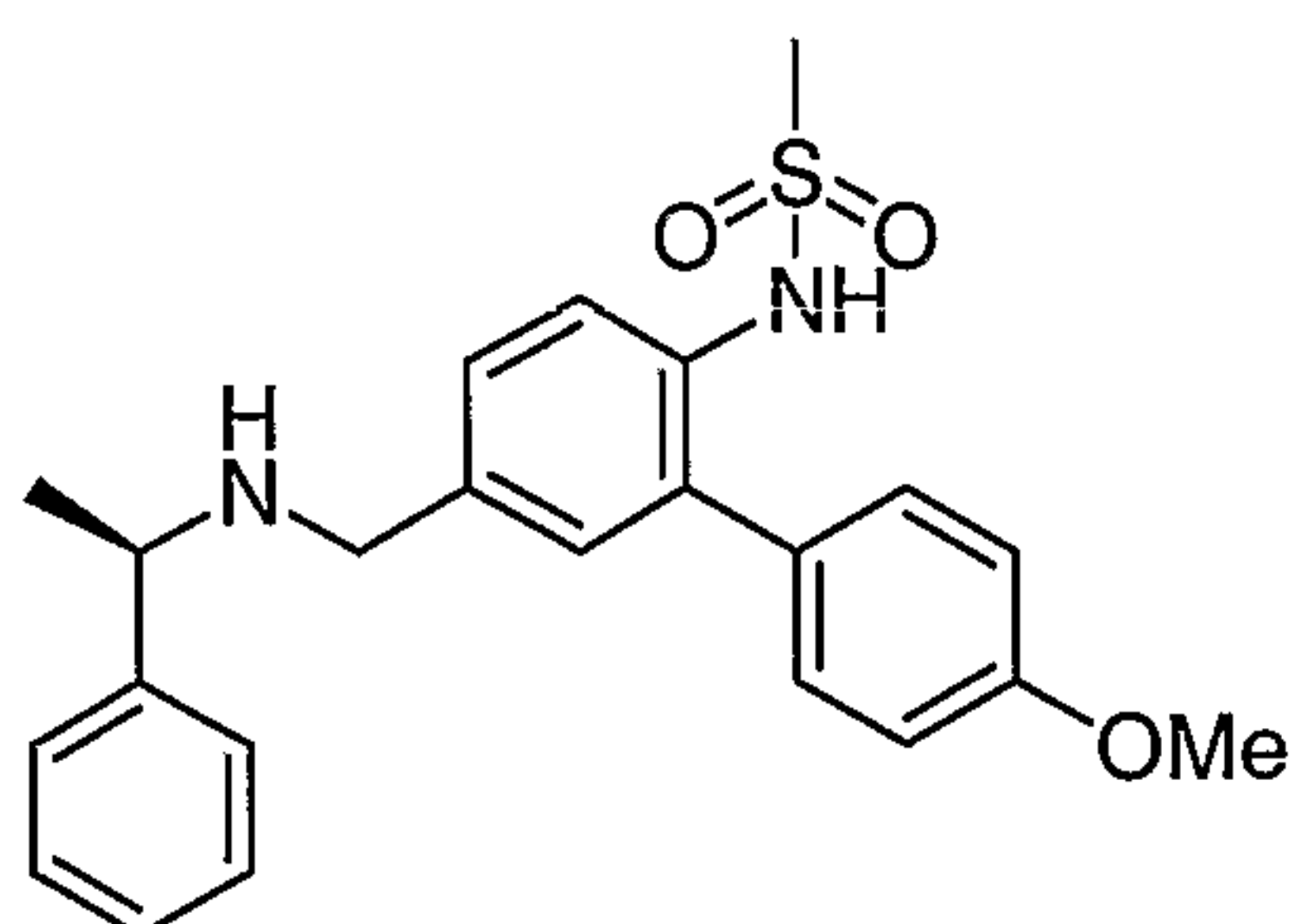
MW 453.583

Mass found: 283, 454

10

Example 259

15 N-(4'-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-2-yl)methanesulfonamide



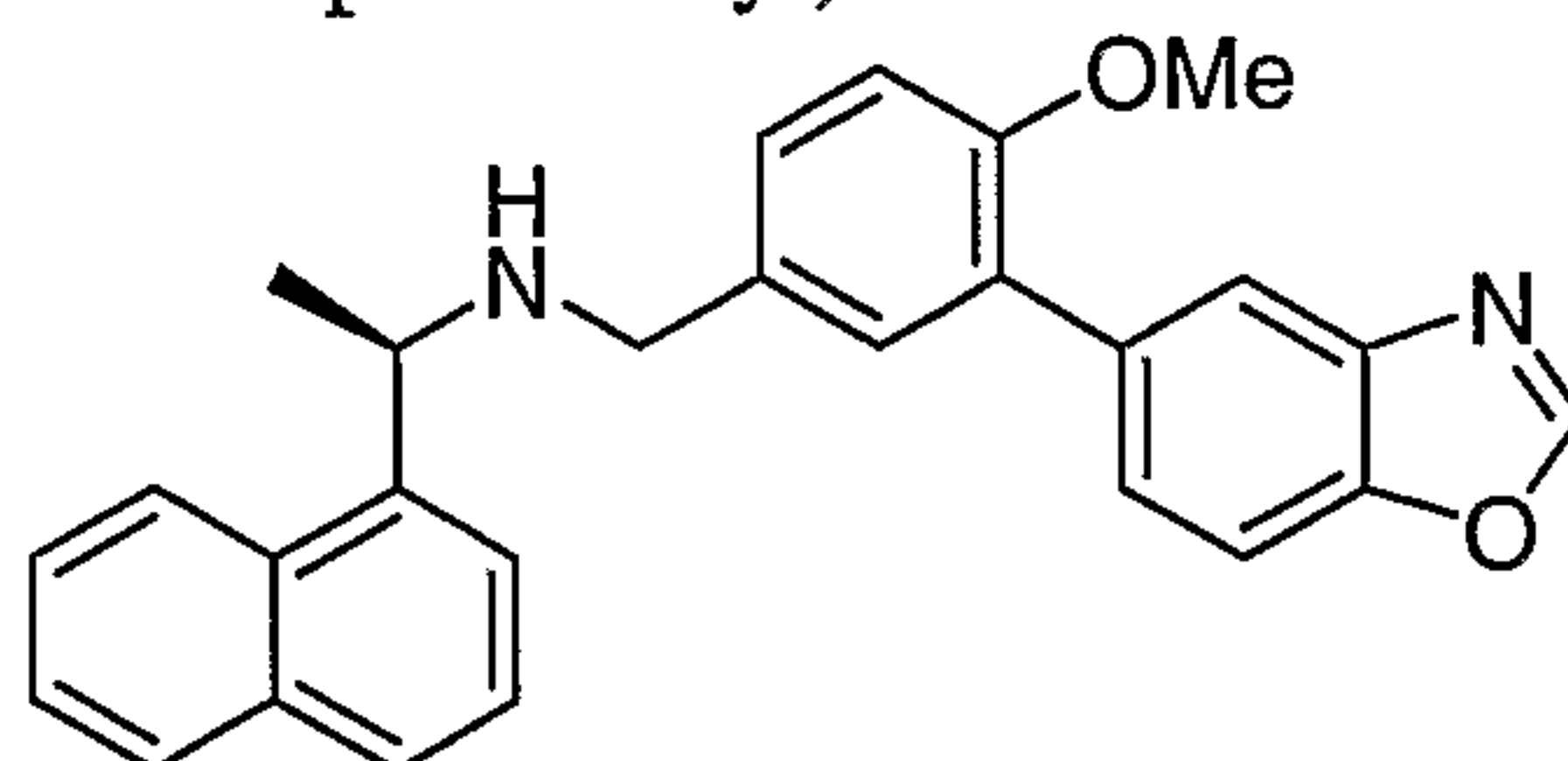
MW 410.535

Mass found: 411

20

Example 260

25 (1R)-N-((3-(1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



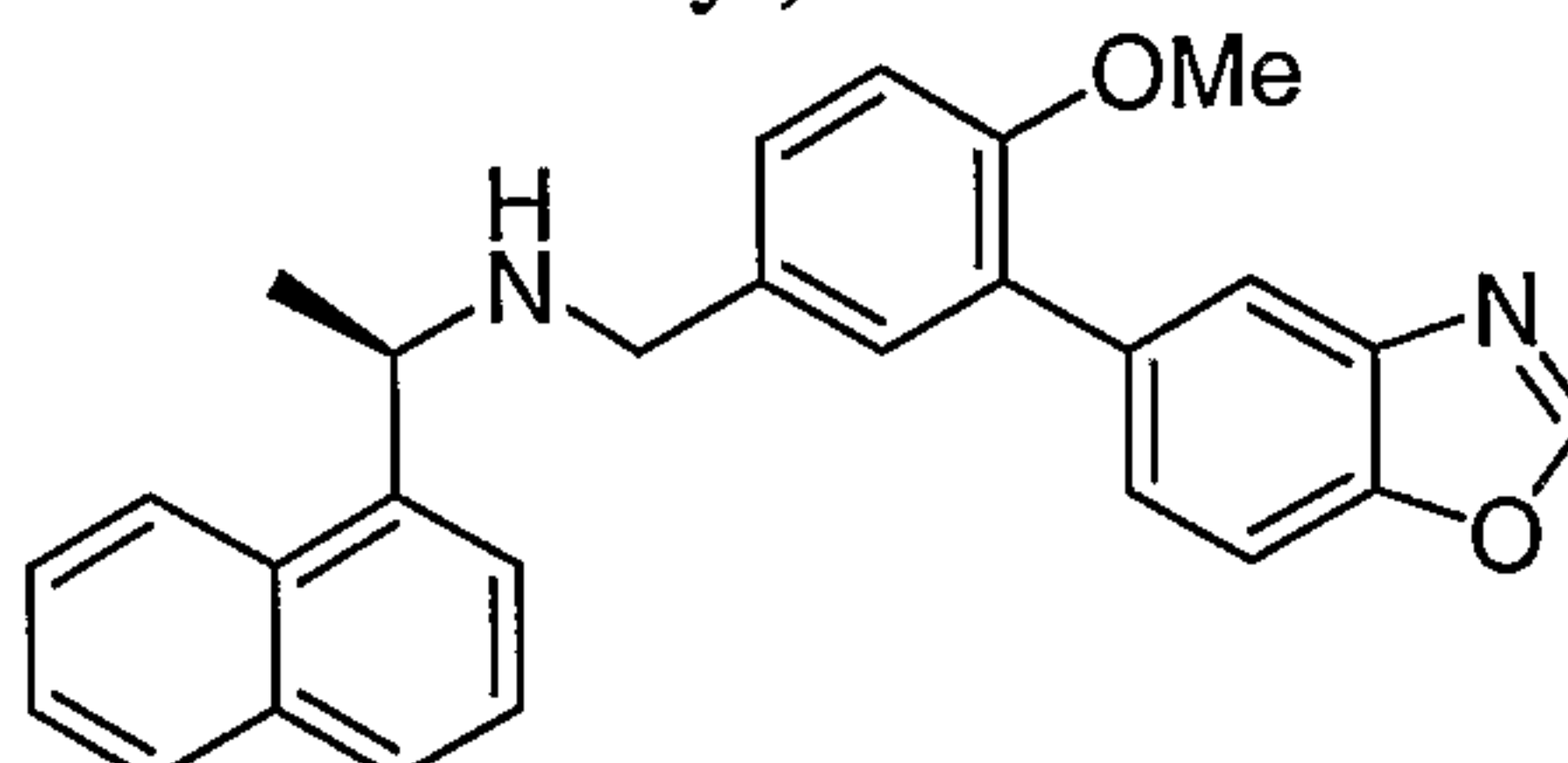
- 180 -

MW 408.499
Mass found: 409

5

Example 261

N-ethyl-N'-(4'-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-2-yl)urea



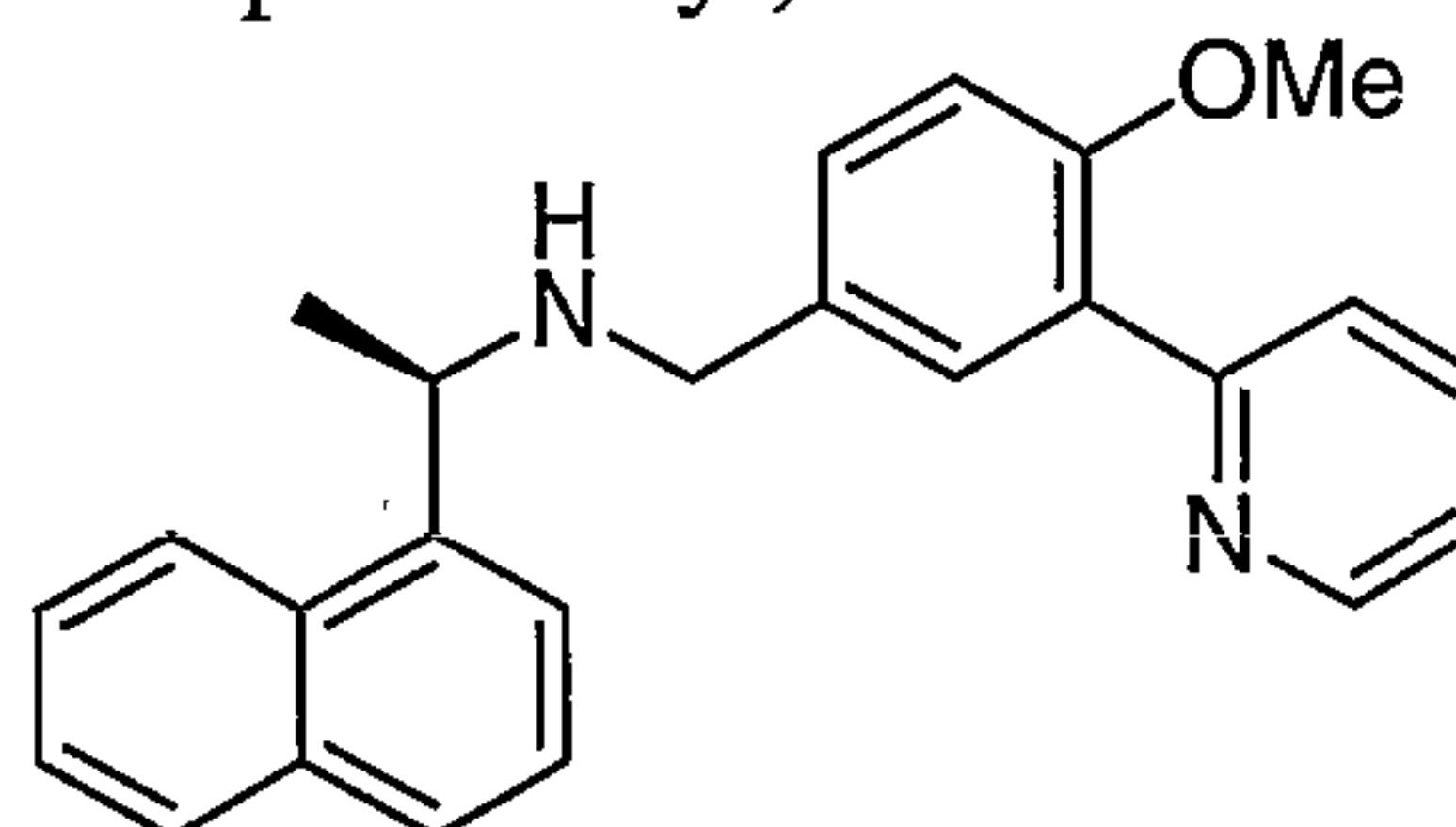
10

MW 403.523
Mass found: 404, 283

15

Example 262

(1R)-N-((4-(methyloxy)-3-(2-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



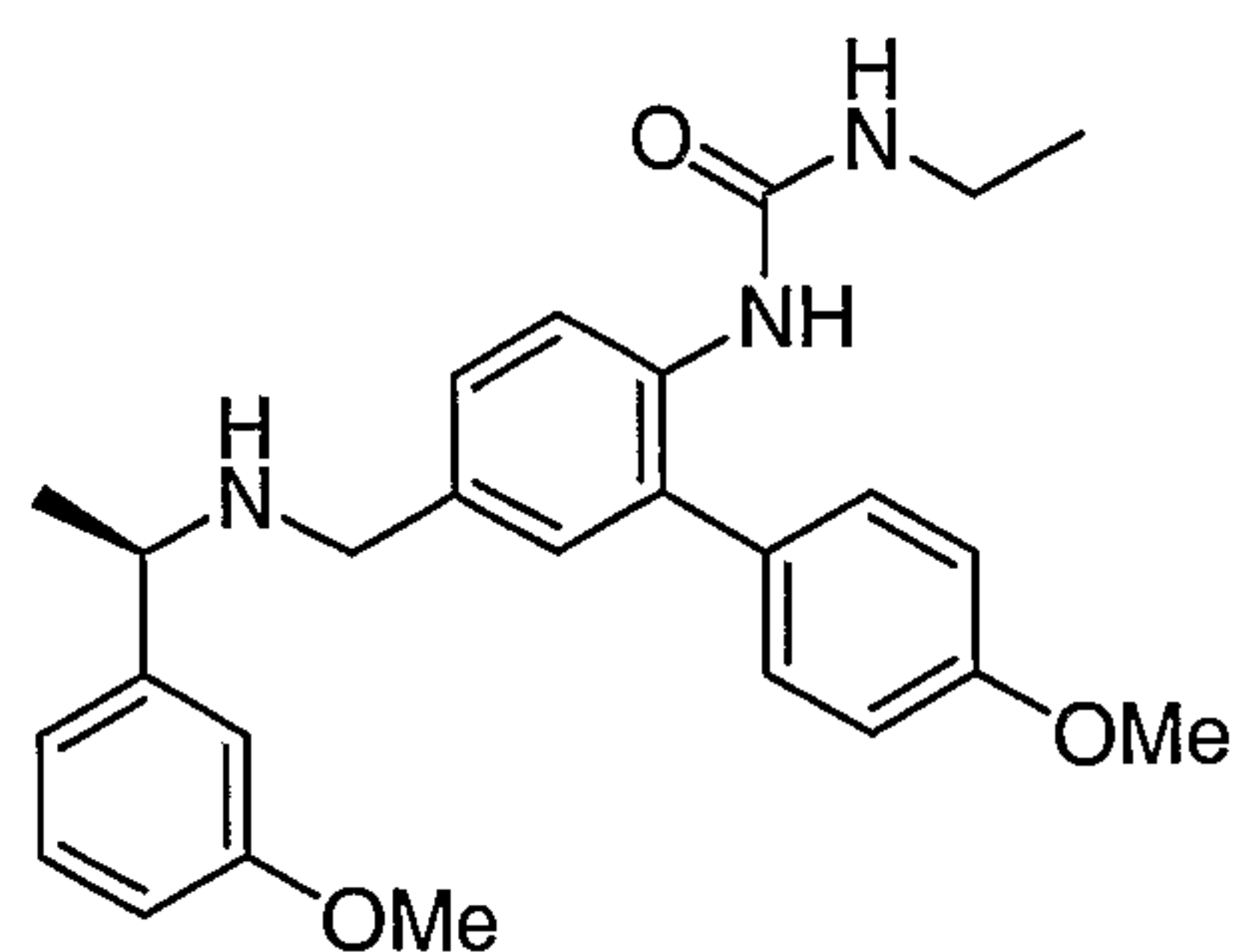
20

MW 368.478
Mass found: 369, 737

25

Example 263

N-ethyl-N'-(4'-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-2-yl)urea



30

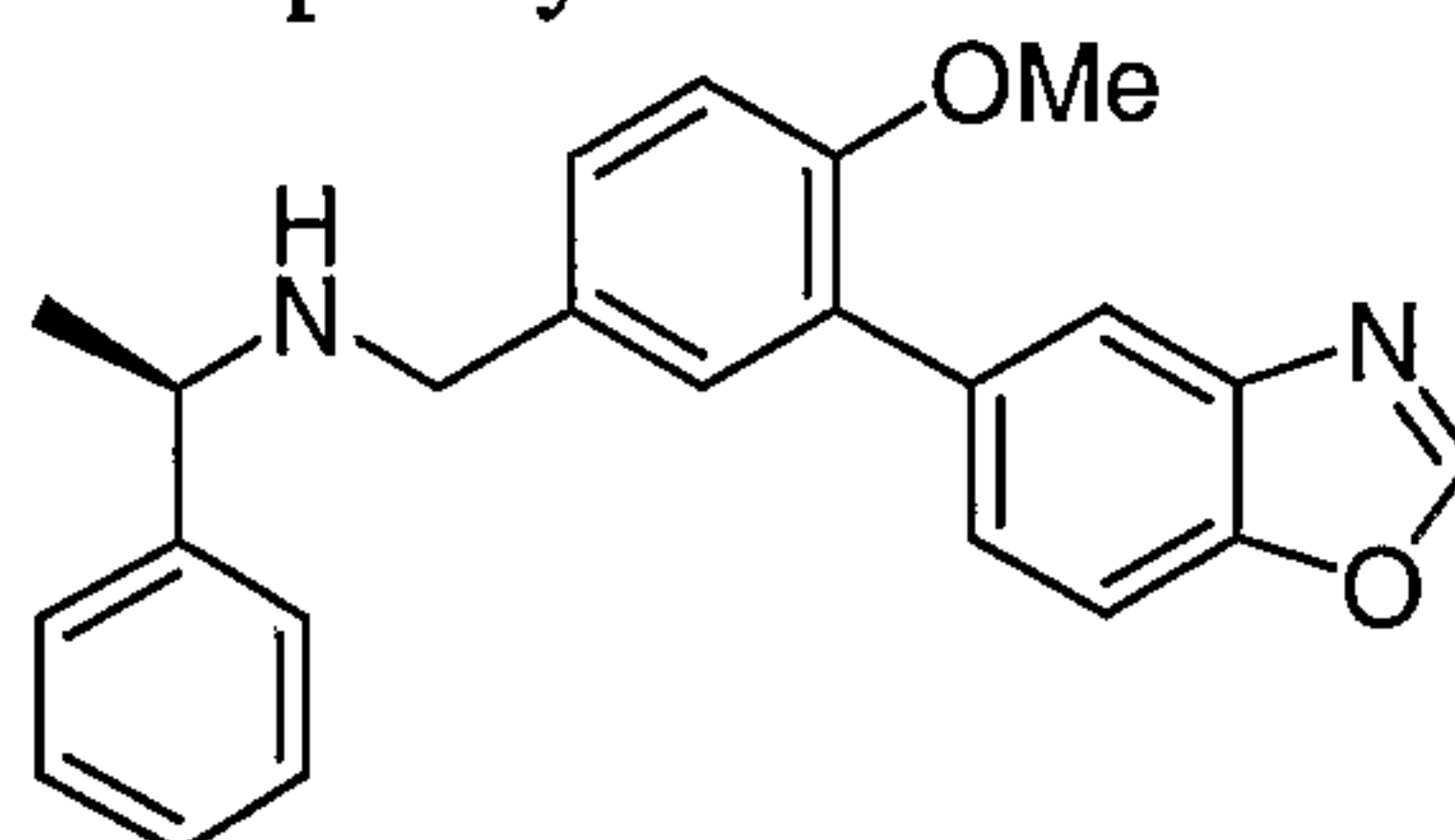
- 181 -

MW 433.549
Mass found: 434

5

Example 264

(1R)-N-((3-(1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine



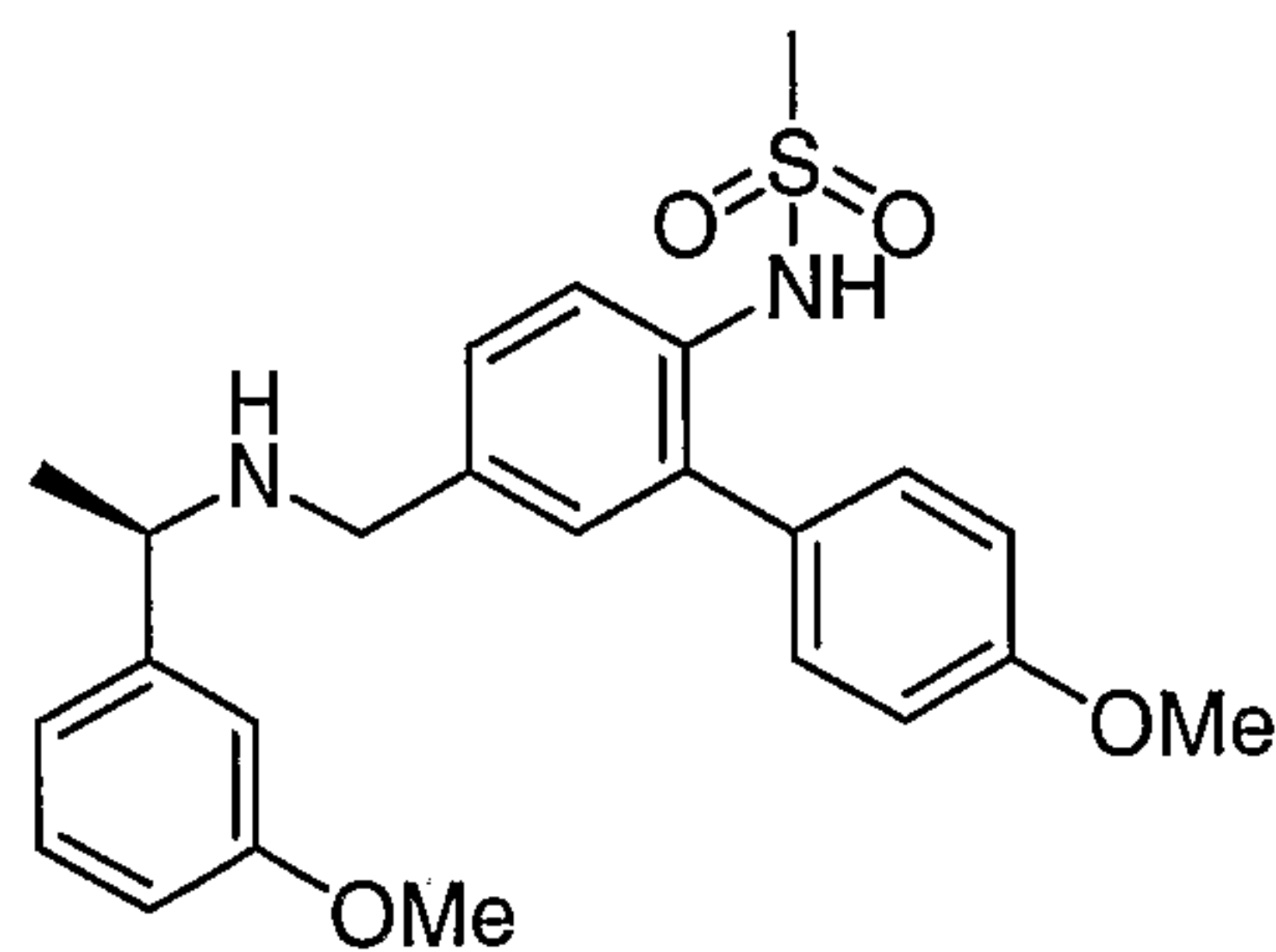
10

MW 358.439
Mass found: 359

15

Example 265

N-(4'-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-2-yl)methanesulfonamide



20

MW 440.561
Mass found: 290, 441

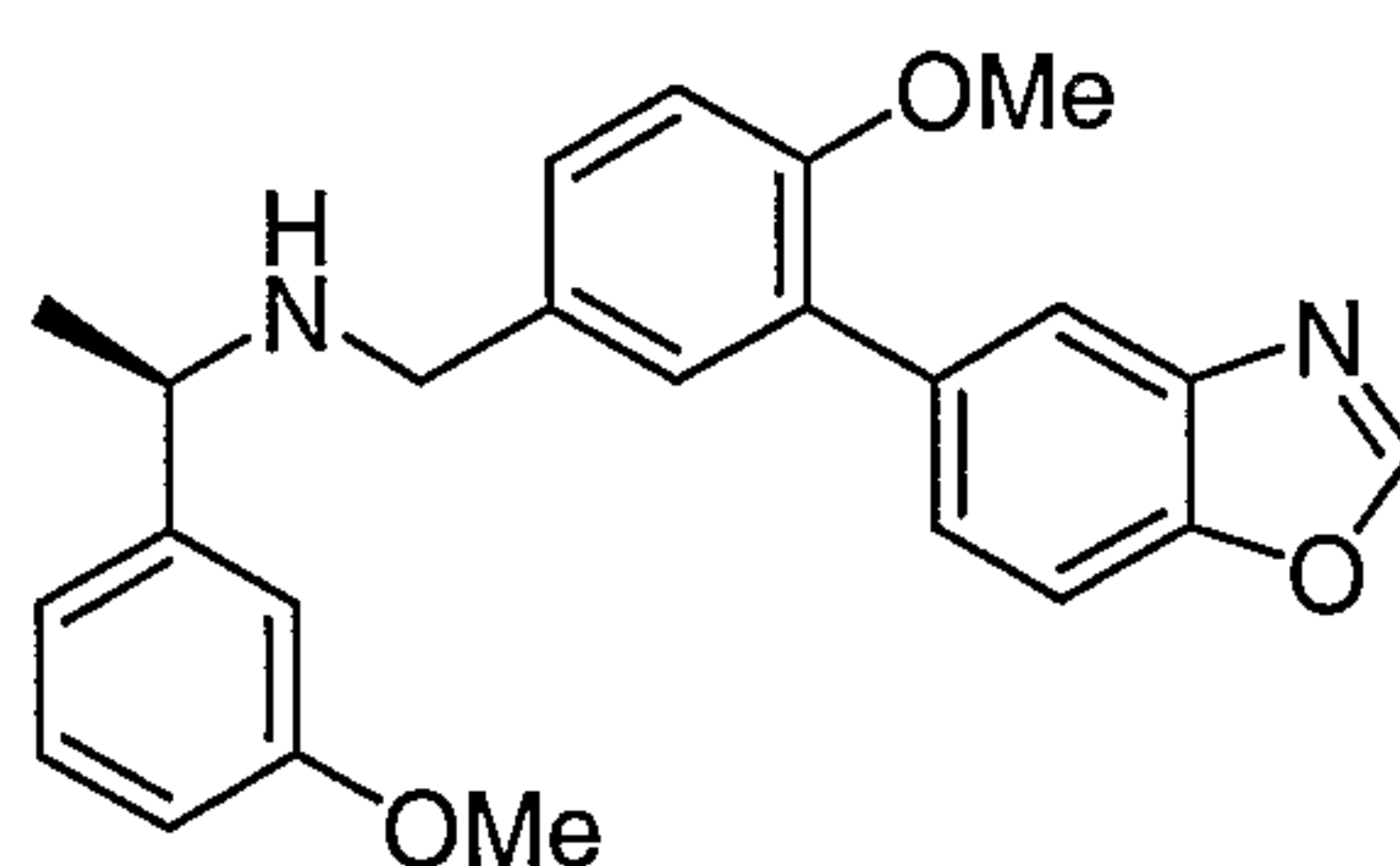
25

Example 266

(1R)-N-((3-(1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

30

- 182 -



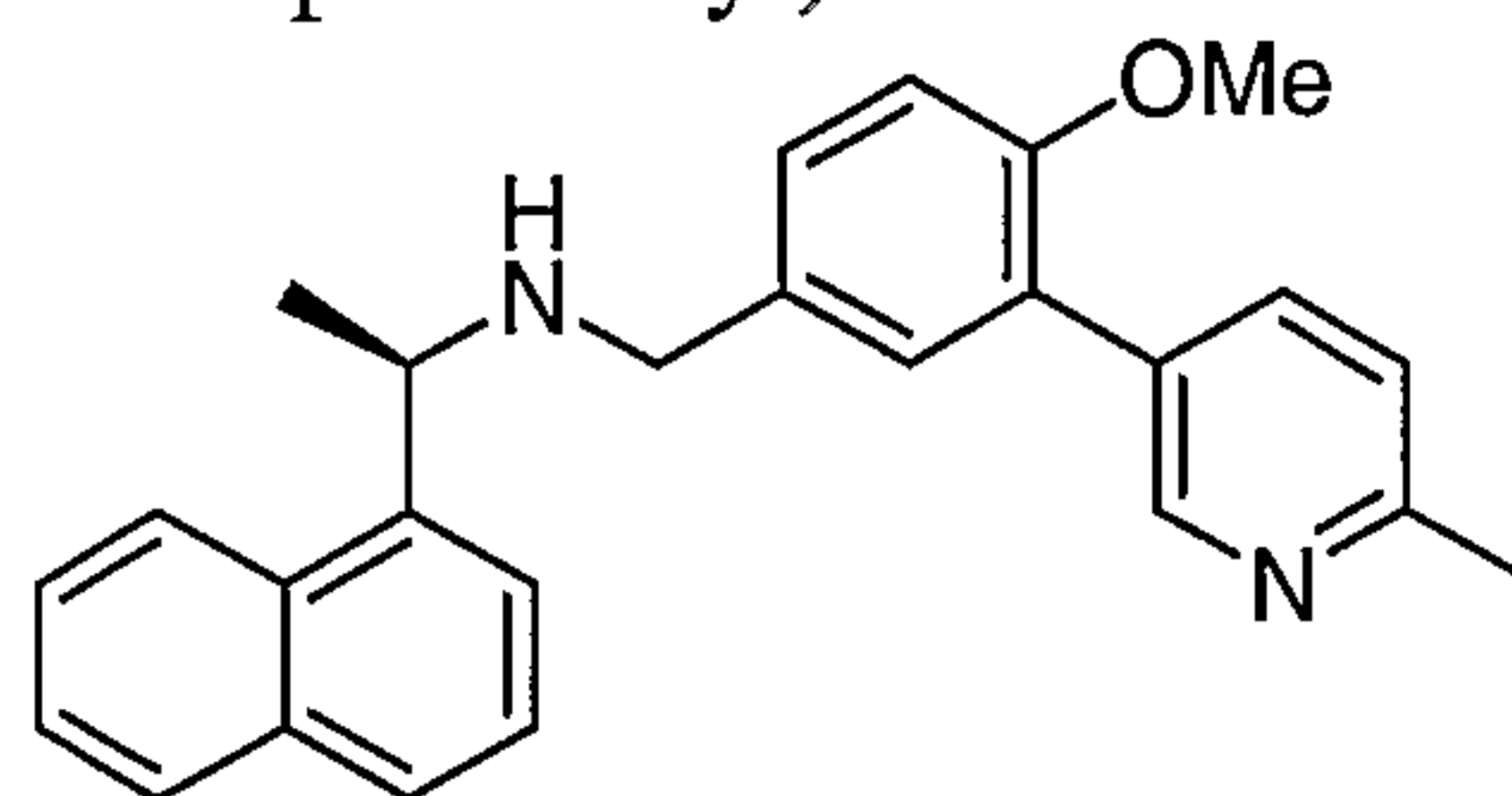
MW 388.465
Mass found: 389, 891

5

Example 267

(1R)-N-((4-(methoxy)-3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

10



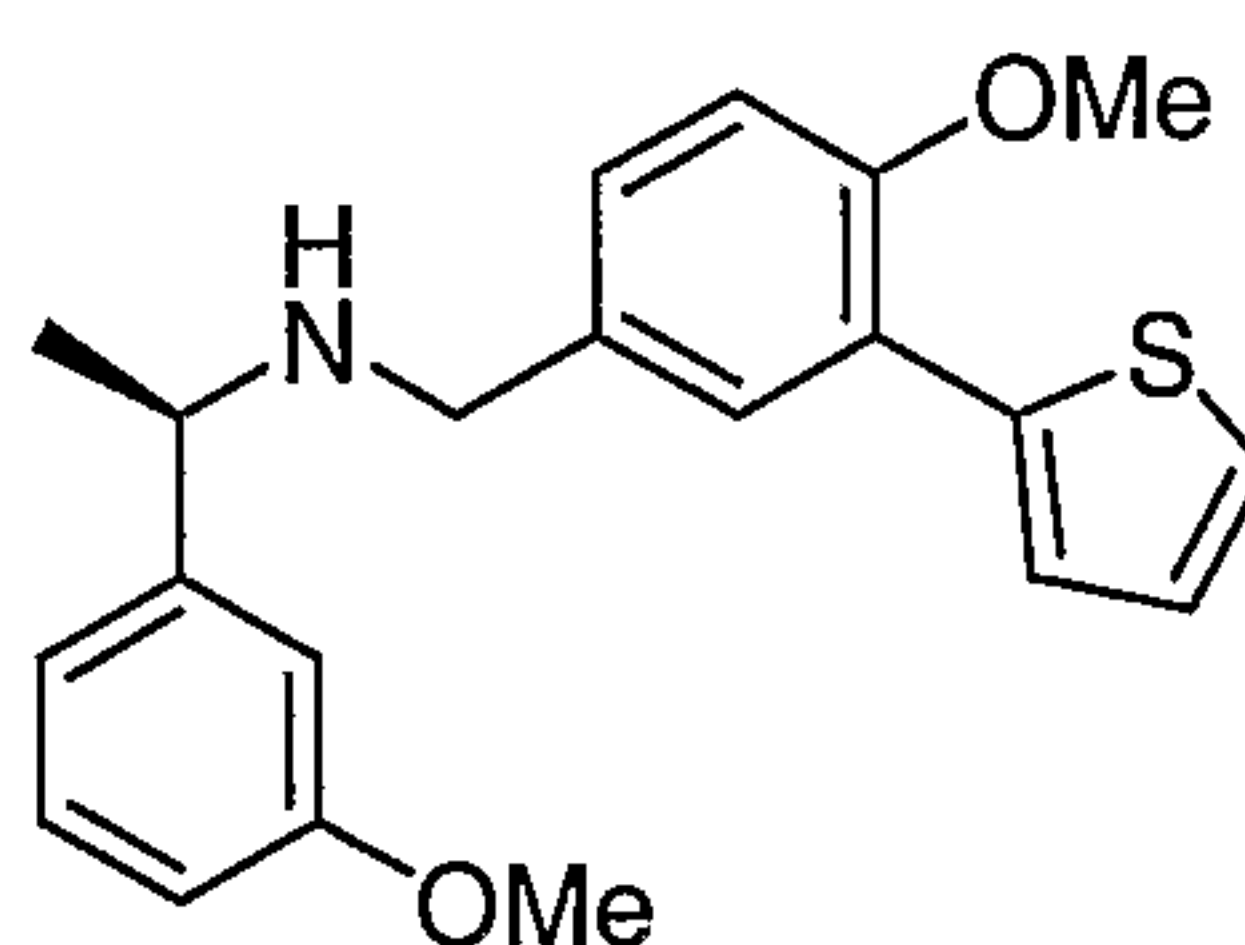
MW 382.504
Mass found: 383, 229, 155

15

Example 268

(1R)-1-(3-(methoxy)phenyl)-N-((4-(methoxy)-3-(2-thienyl)phenyl)methyl)ethanamine

20



MW 353.484
Mass found: 354

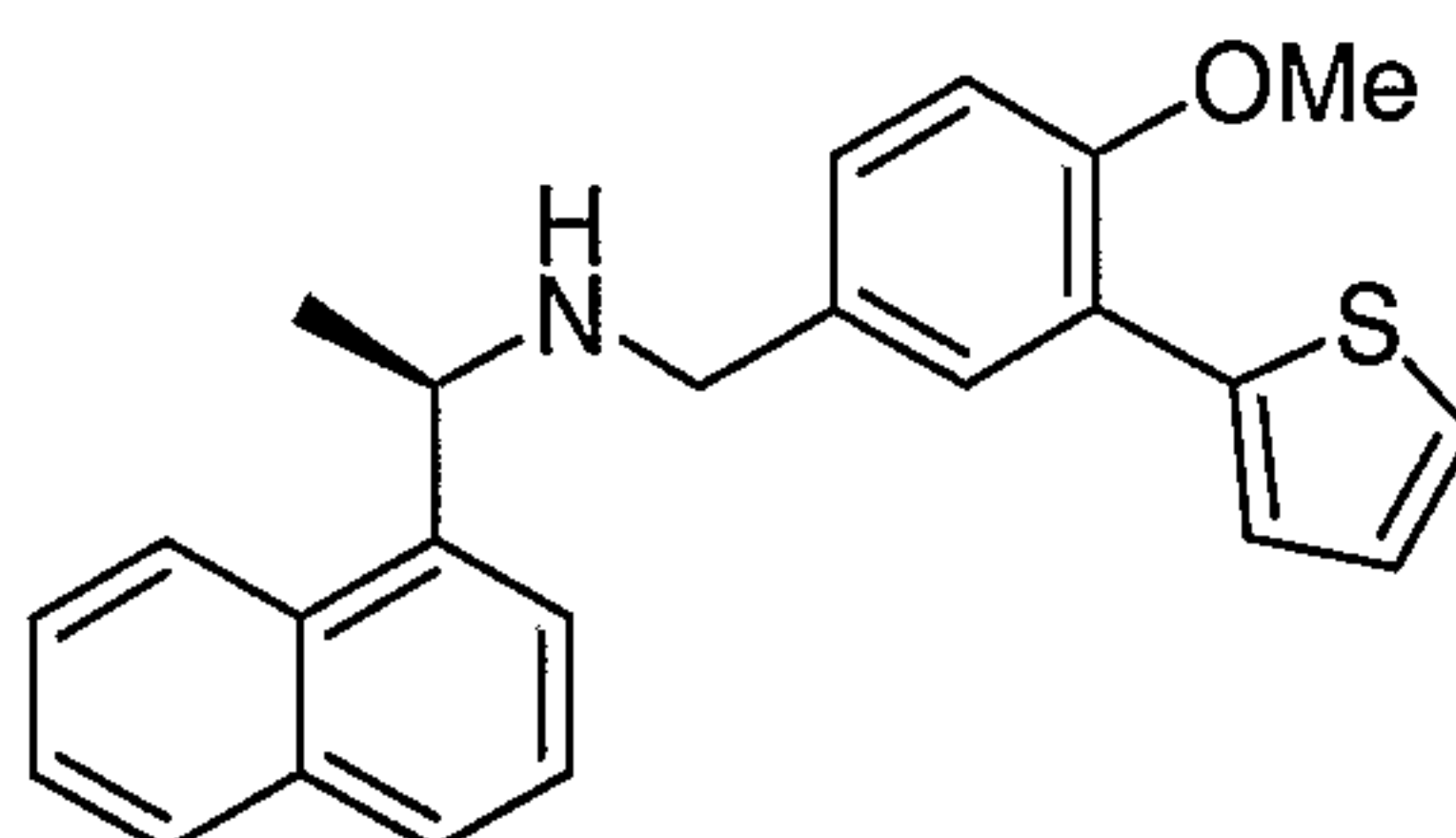
25

Example 269

(1R)-N-((4-(methoxy)-3-(2-thienyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

30

- 183 -



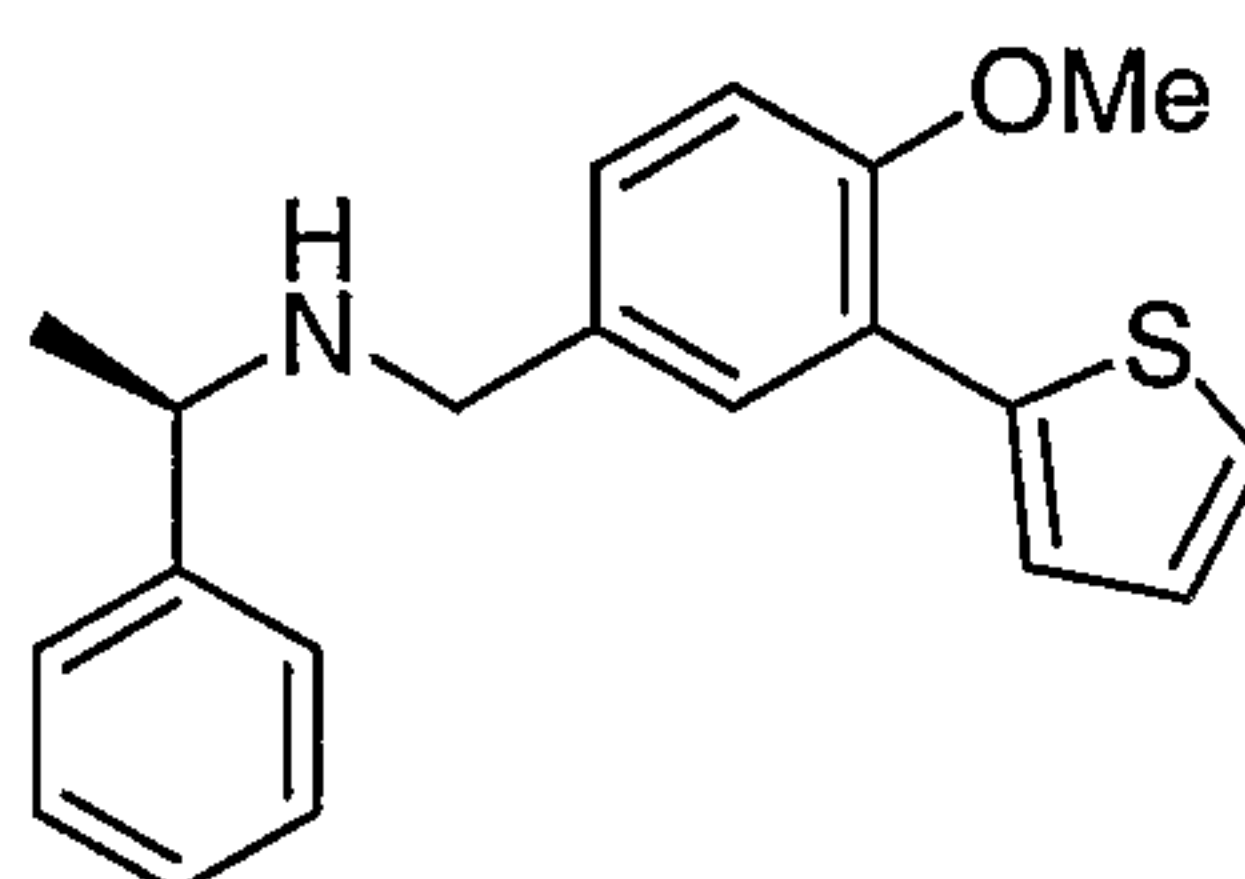
MW 373.518
Mass found: 374

5

Example 270

(1R)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)-1-phenylethanamine

10



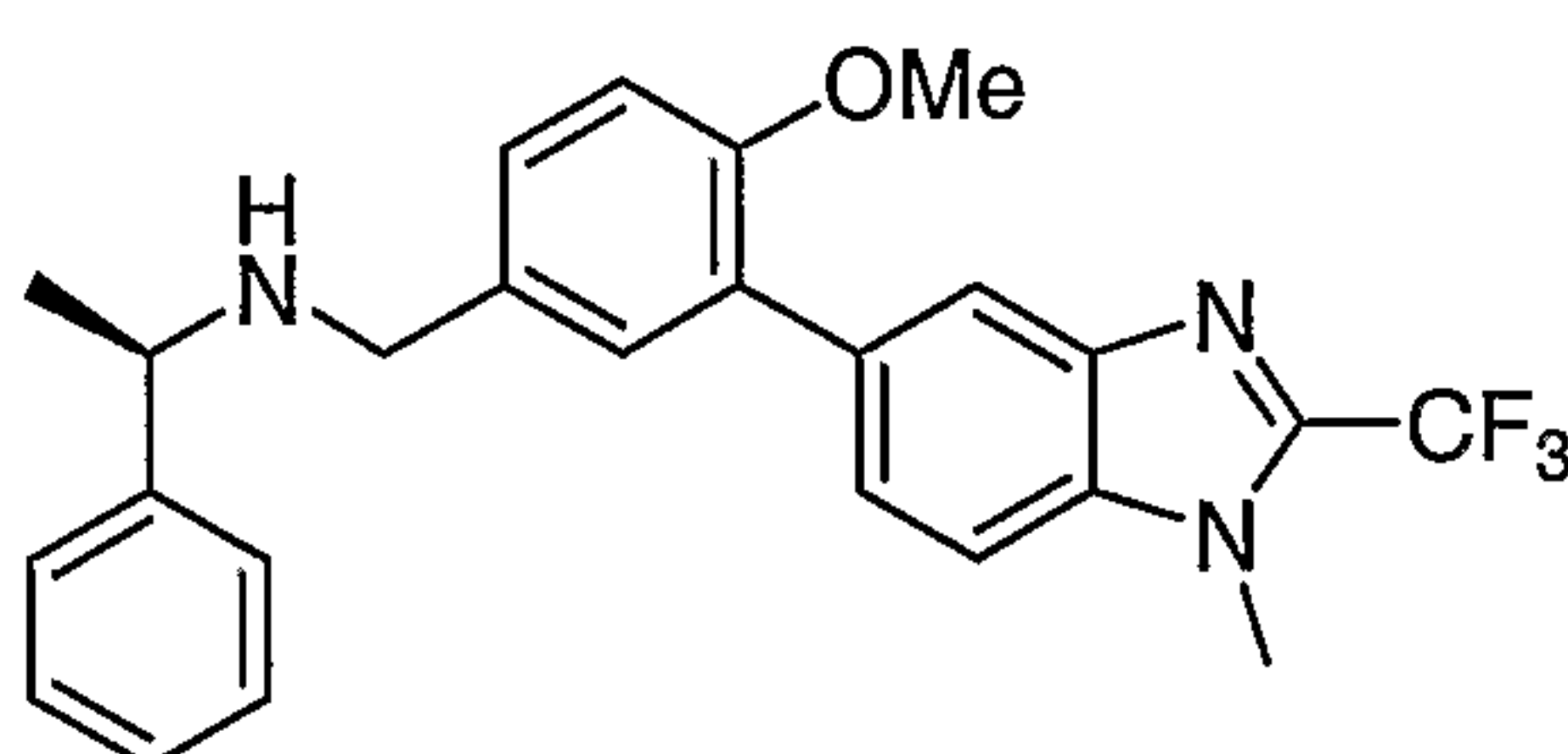
MW 323.458
Mass found: 324, 203, 647

15

Example 271

(1R)-N-((4-(methyloxy)-3-(1-methyl-2-(trifluoromethyl)-1H-benzimidazol-5-yl)phenyl)methyl)-1-phenylethanamine

20



MW 439.479
Mass found: 440, 481

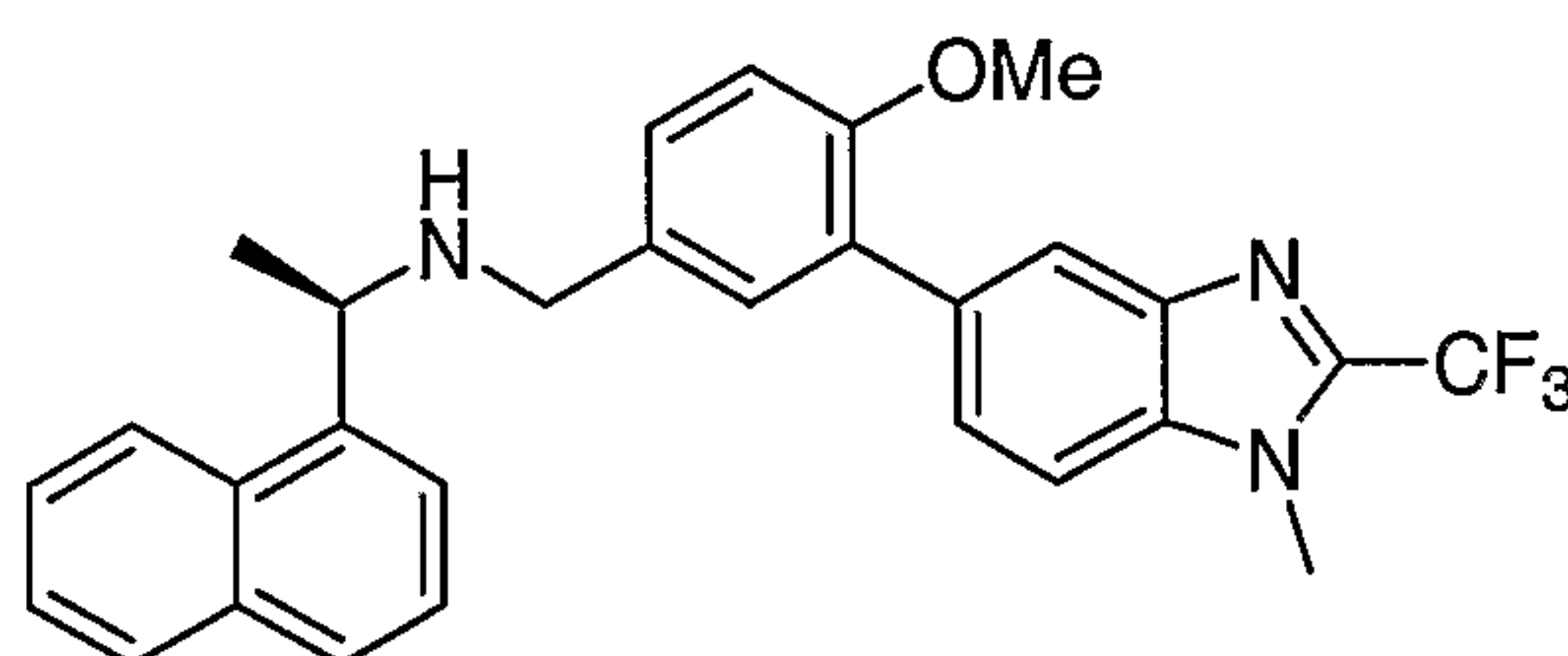
25

Example 272

(1R)-N-((4-(methyloxy)-3-(1-methyl-2-(trifluoromethyl)-1H-benzimidazol-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

30

- 184 -

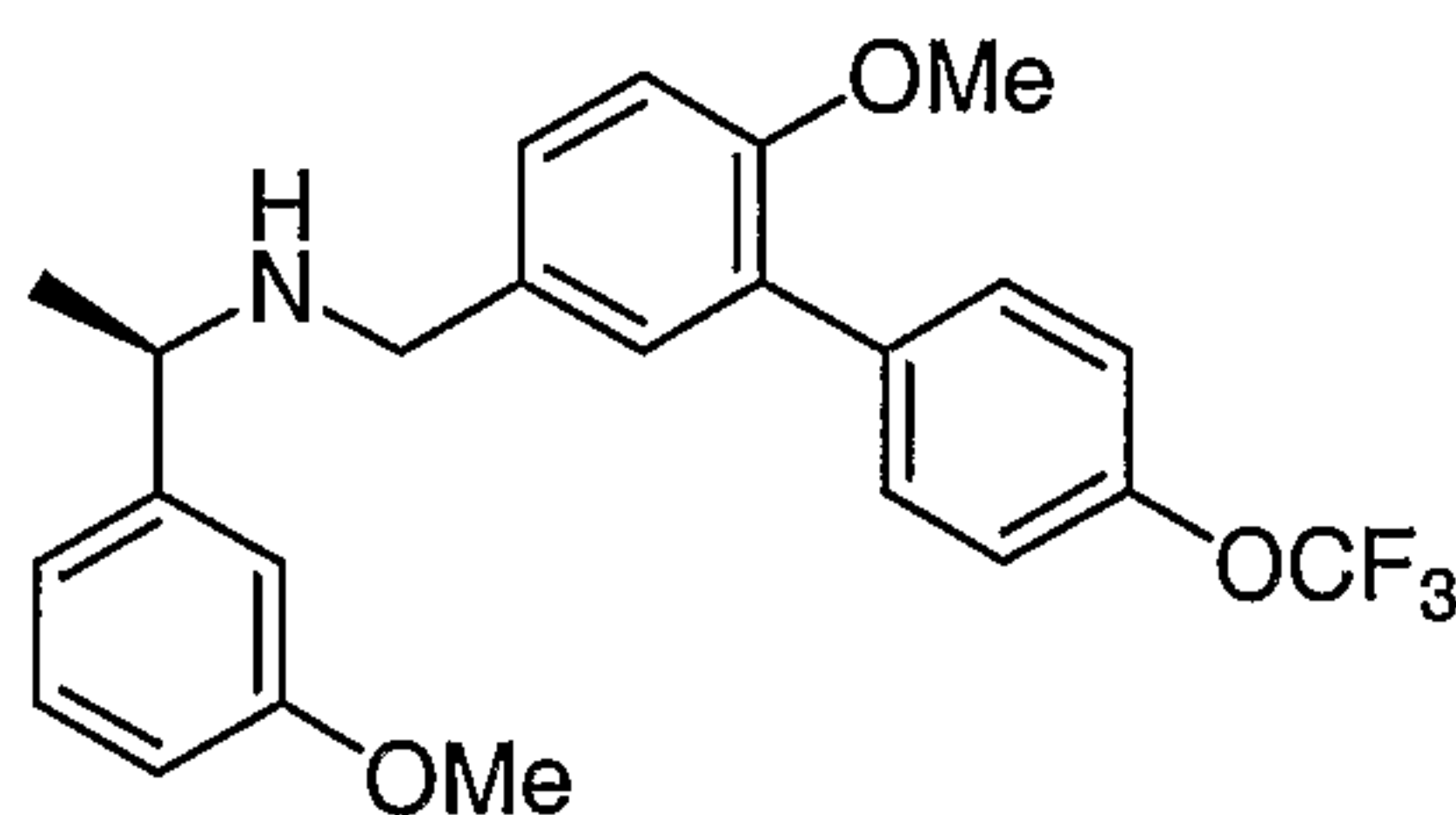


MW 489
Mass found: 490, 155

5

Example 273

10 (1R)-1-(3-(methoxy)phenyl)-N-((6-(methoxy)-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)ethanamine

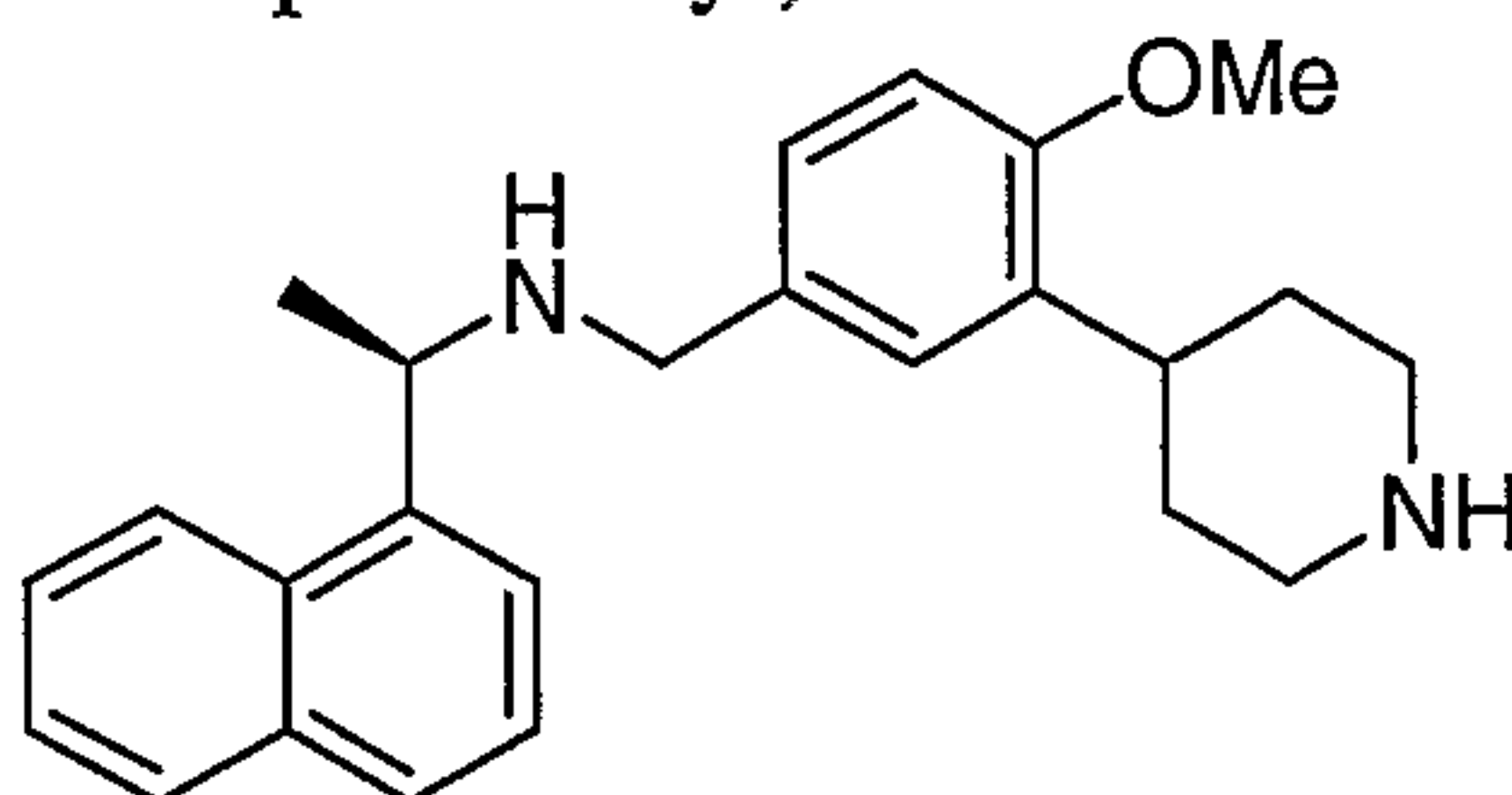


MW 431.452
Mass found: 432

15

Example 274

20 (1R)-N-((4-(methoxy)-3-(4-piperidiny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



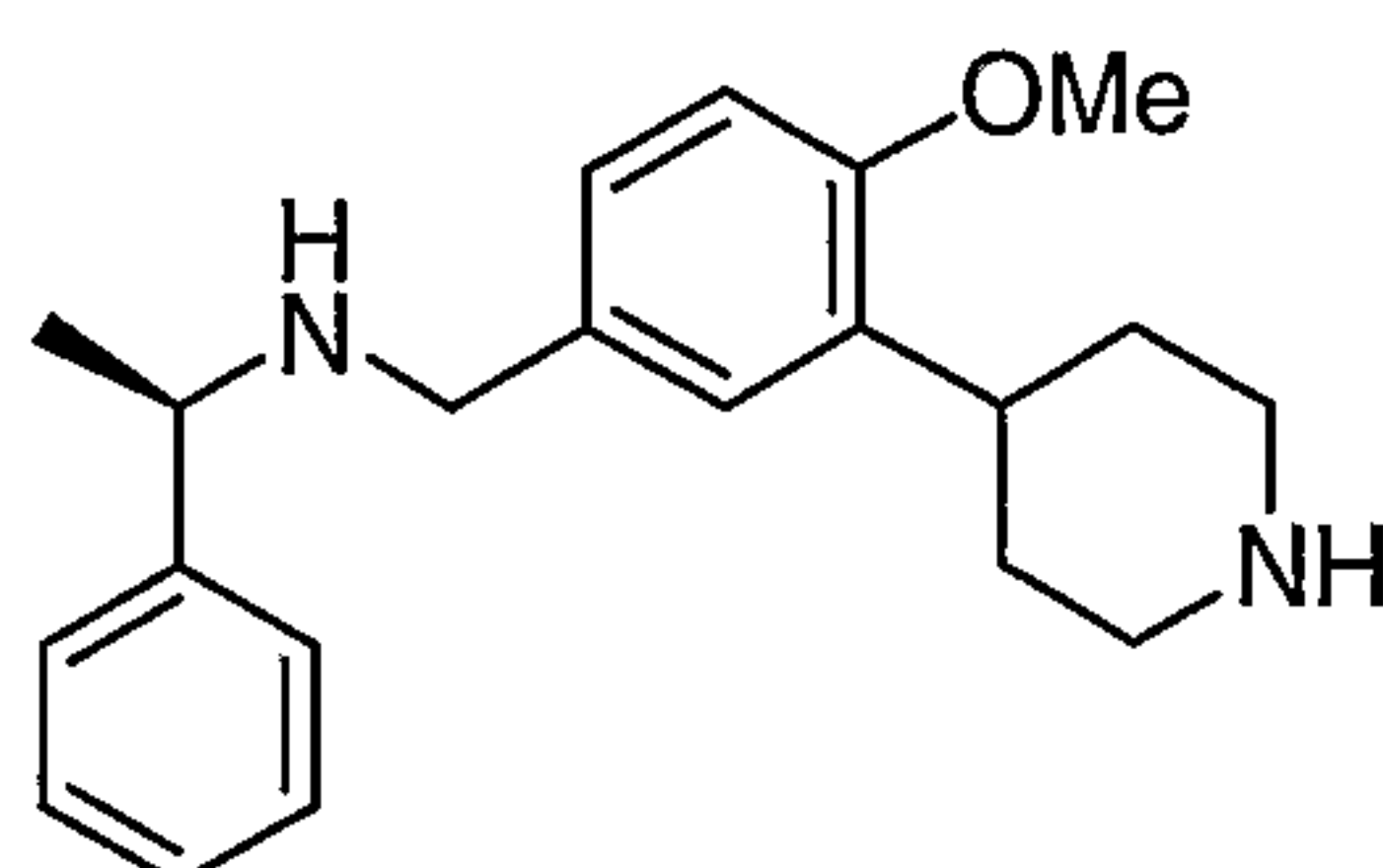
MW 374.525
Mass found: 375, 489, 155

25

Example 275

30 (1R)-N-((4-(methoxy)-3-(4-piperidiny)phenyl)methyl)-1-phenylethanamine

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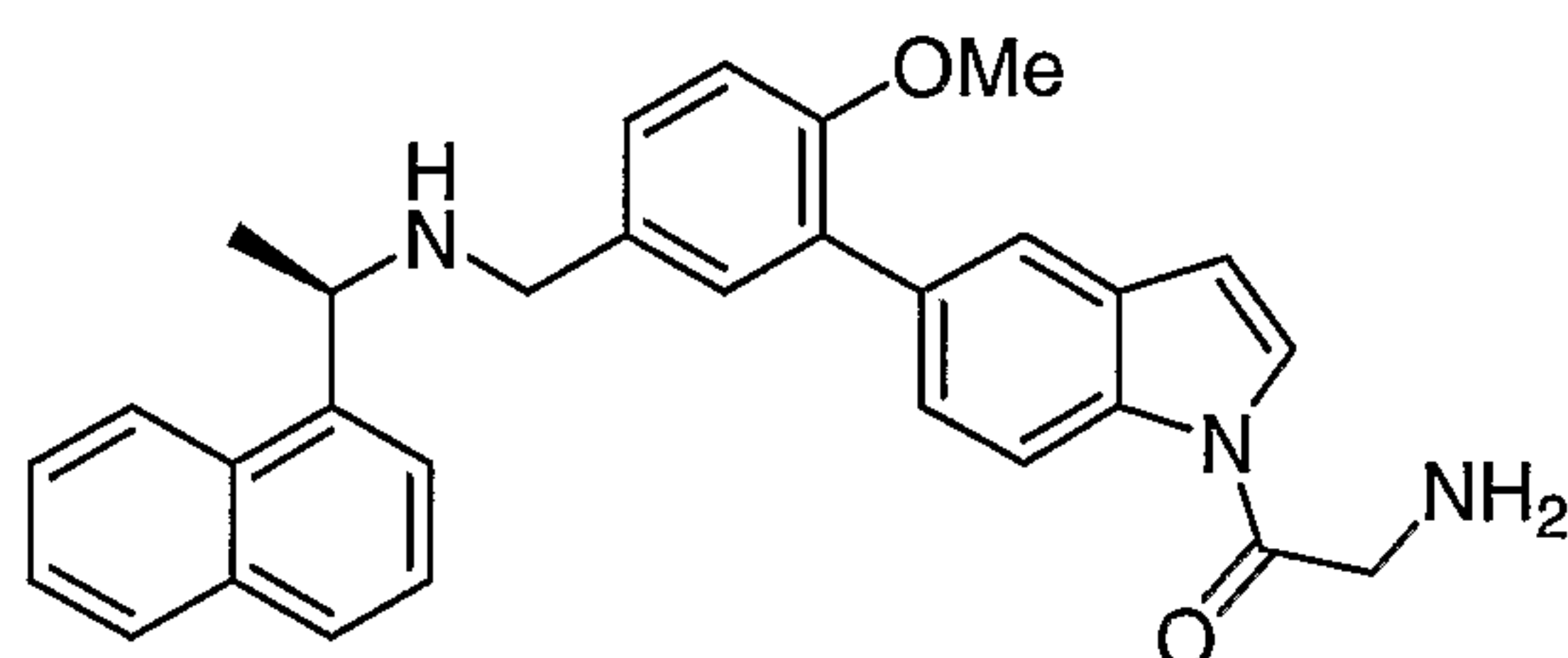
MW 324.465
Mass found: 325, 439

5

Example 276

2-(5-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-1H-indol-1-yl)acetamide

10



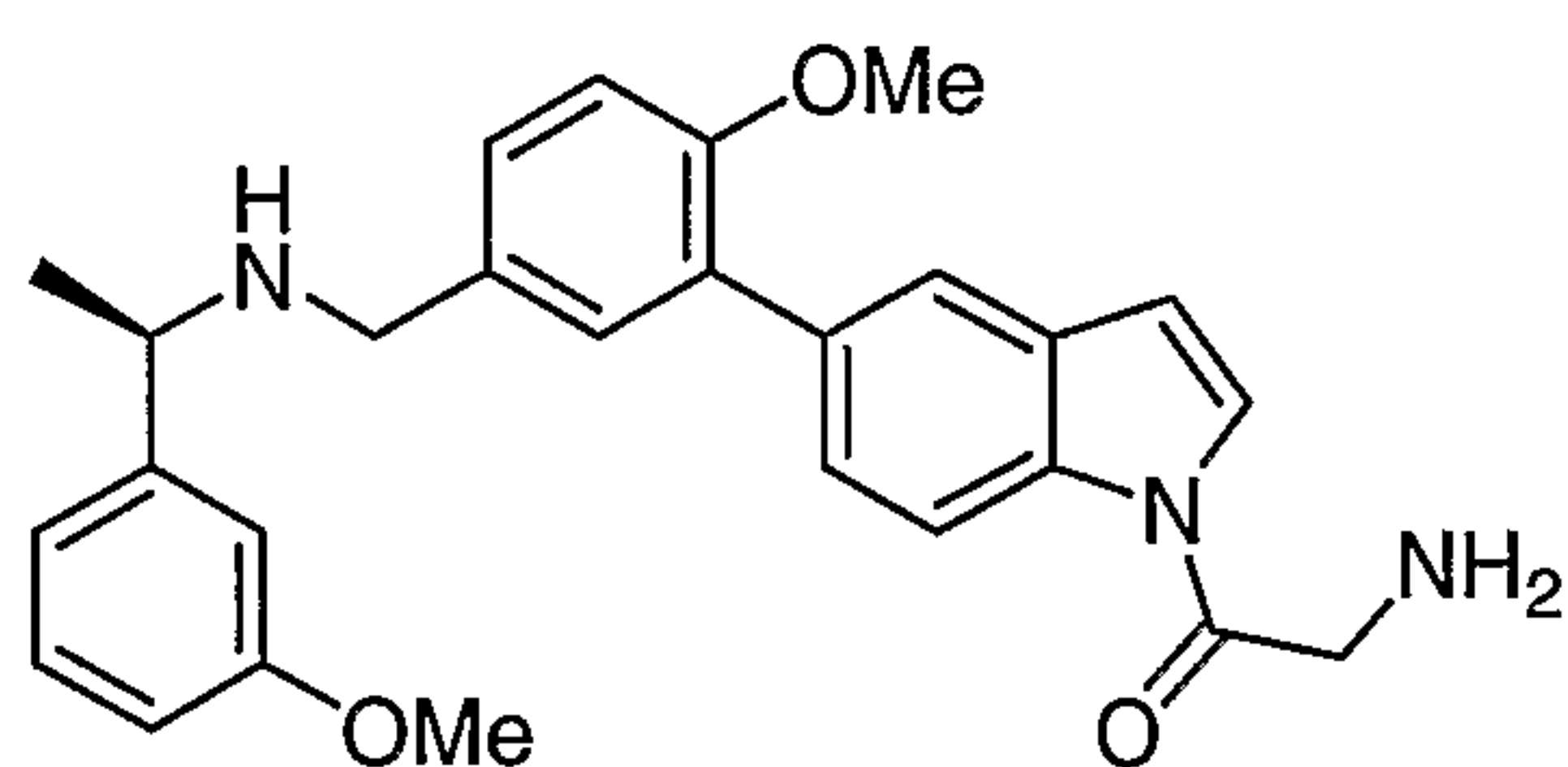
MW 463.578
Mass found: 464

15

Example 277

2-(5-(2-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-1H-indol-1-yl)acetamide

20



MW 443.544
Mass found: 444

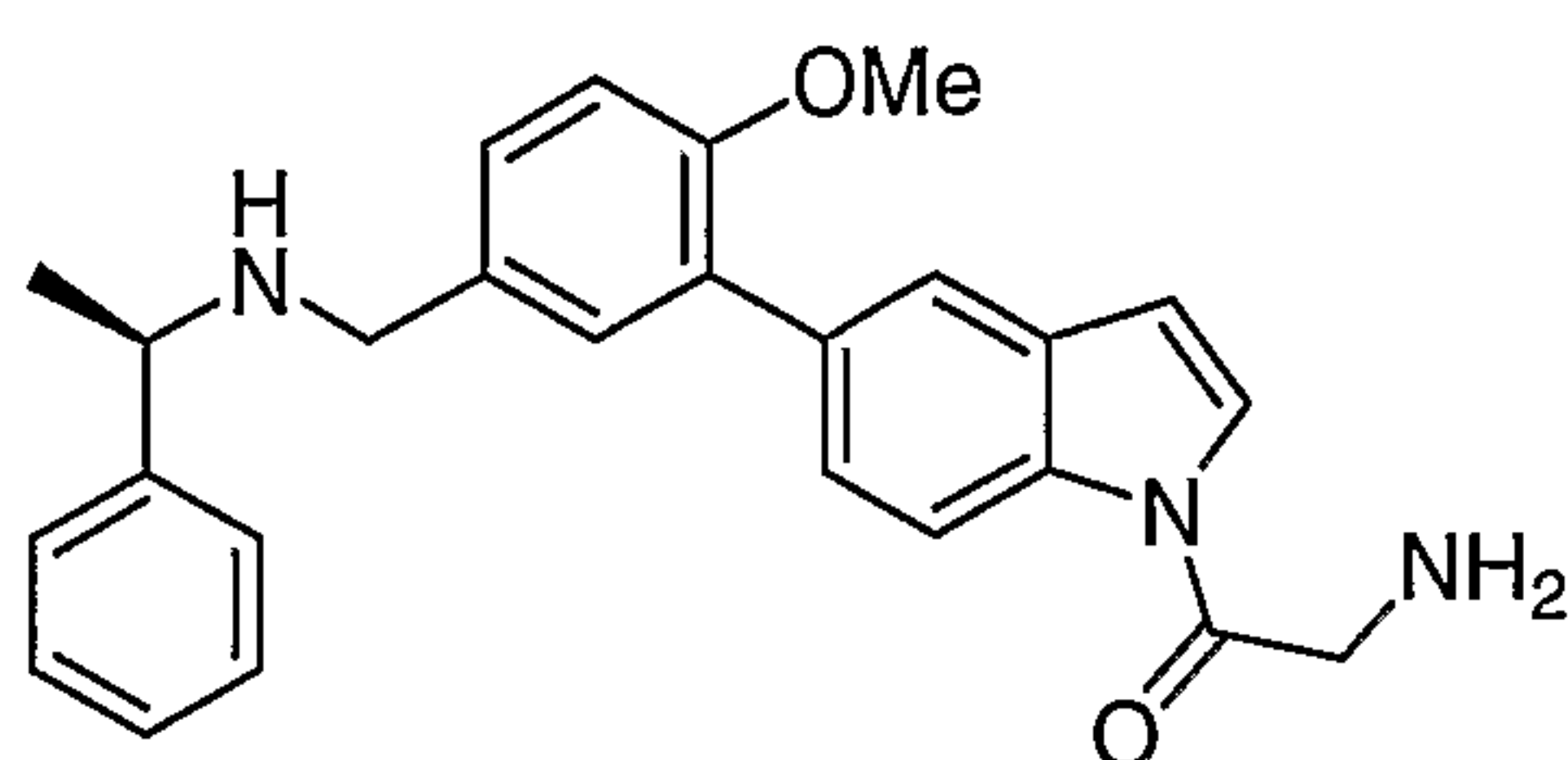
25

Example 278

2-(5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1H-indol-1-yl)acetamide

30

- 186 -

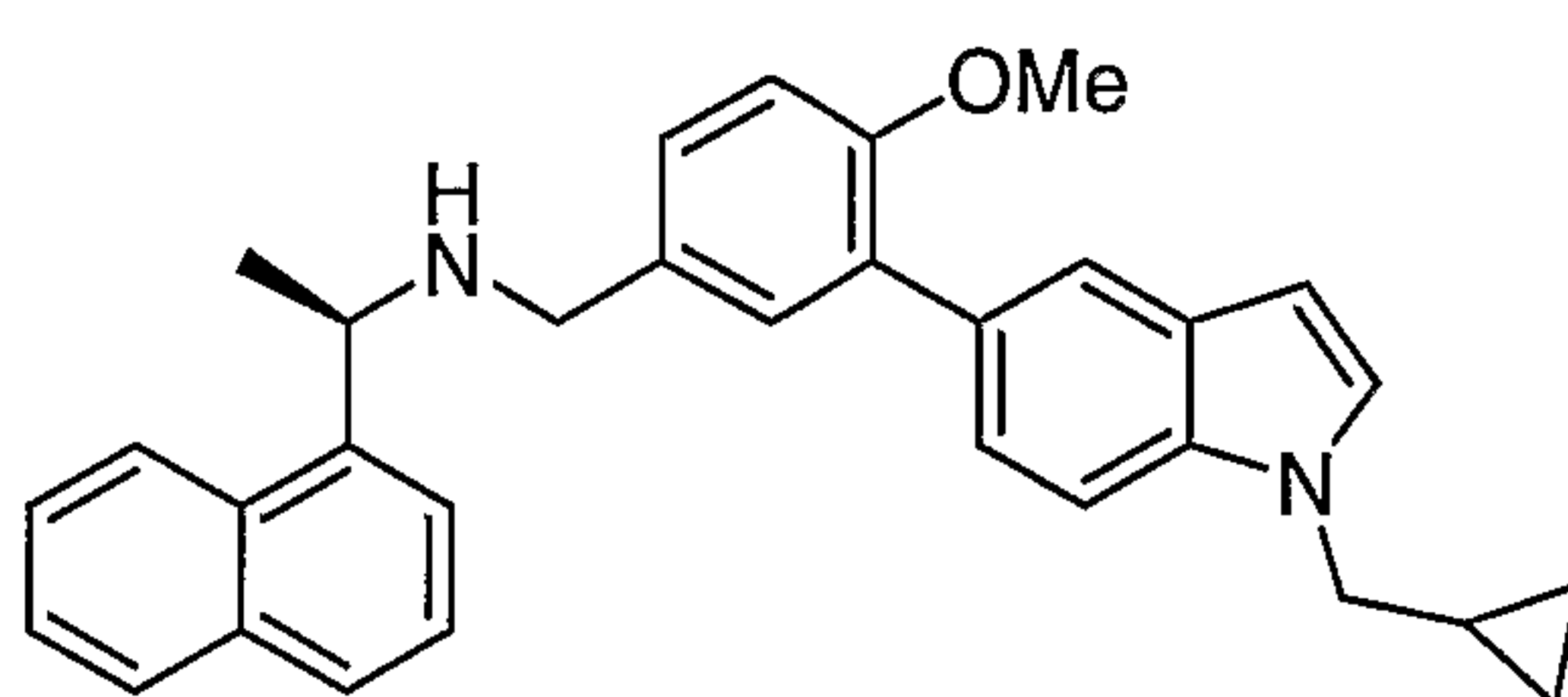


MW 413.518
Mass found: 414

5

Example 279

10 (1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-
1-(1-naphthalenyl)ethanamine

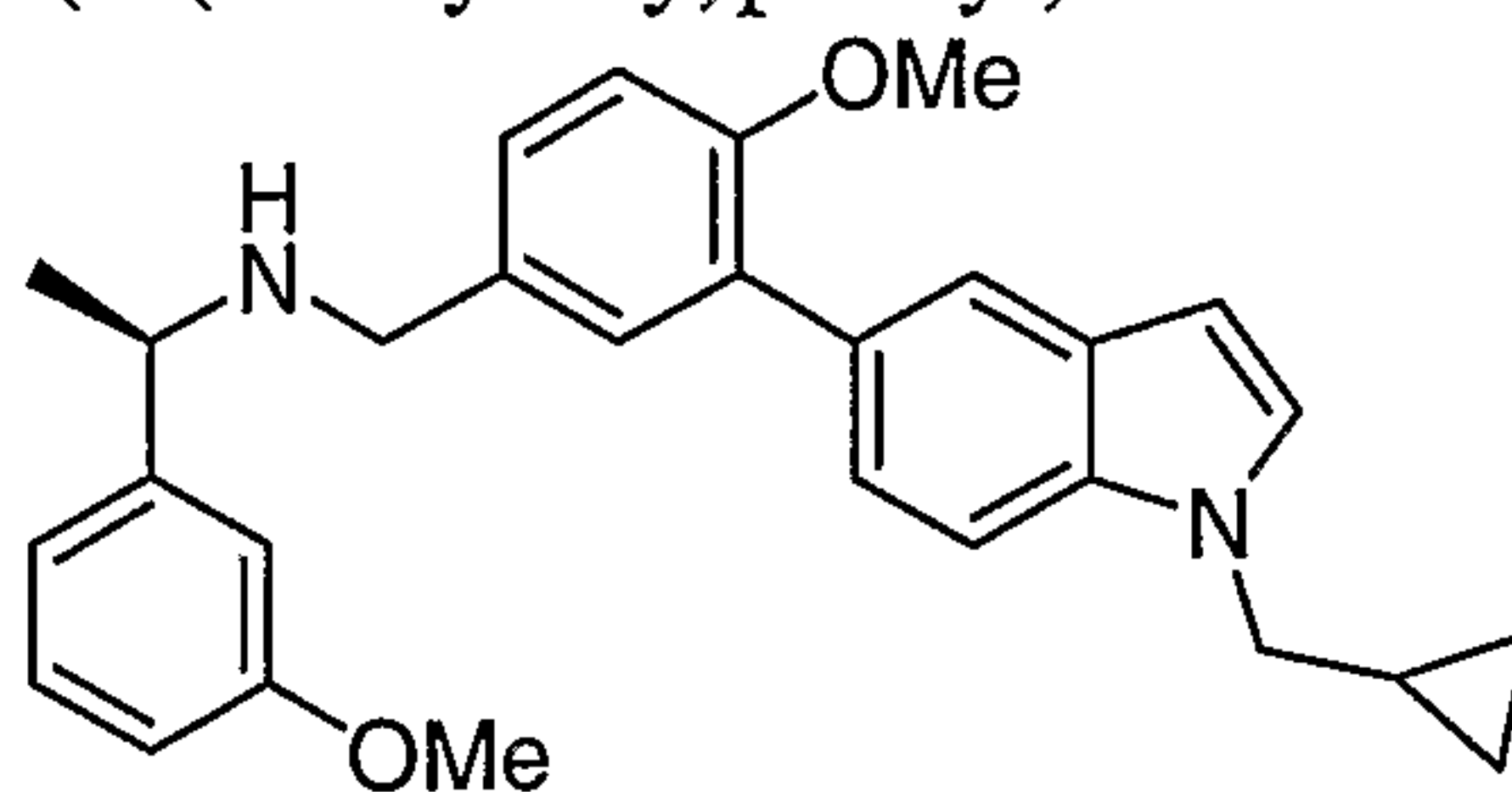


MW 460.618
Mass found: 491

15

Example 280

20 (1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-
1-(3-(methyloxy)phenyl)ethanamine



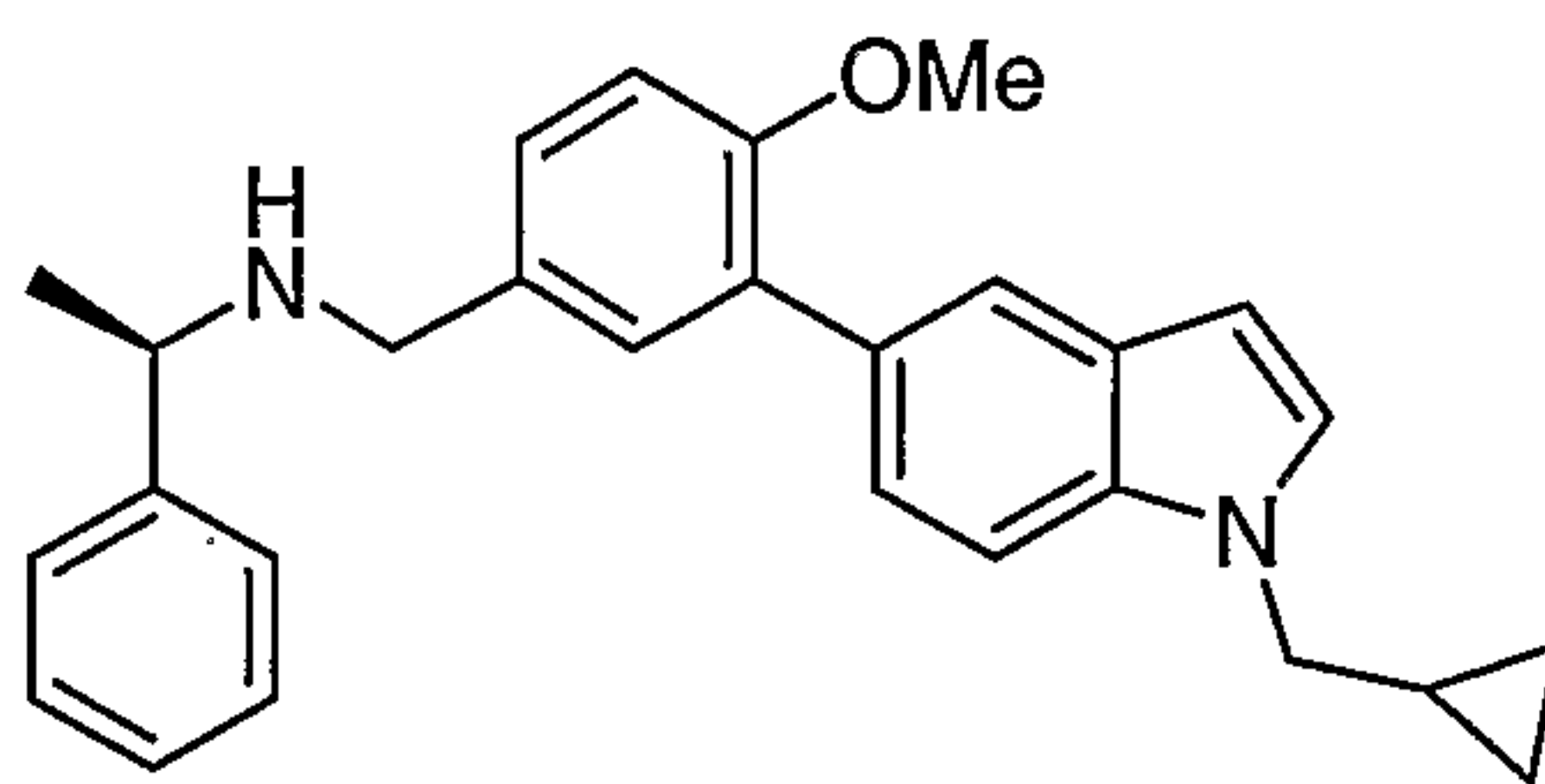
MW 440.584
Mass found: 441

25

Example 281

30 (1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-
1-phenylethanamine

- 187 -

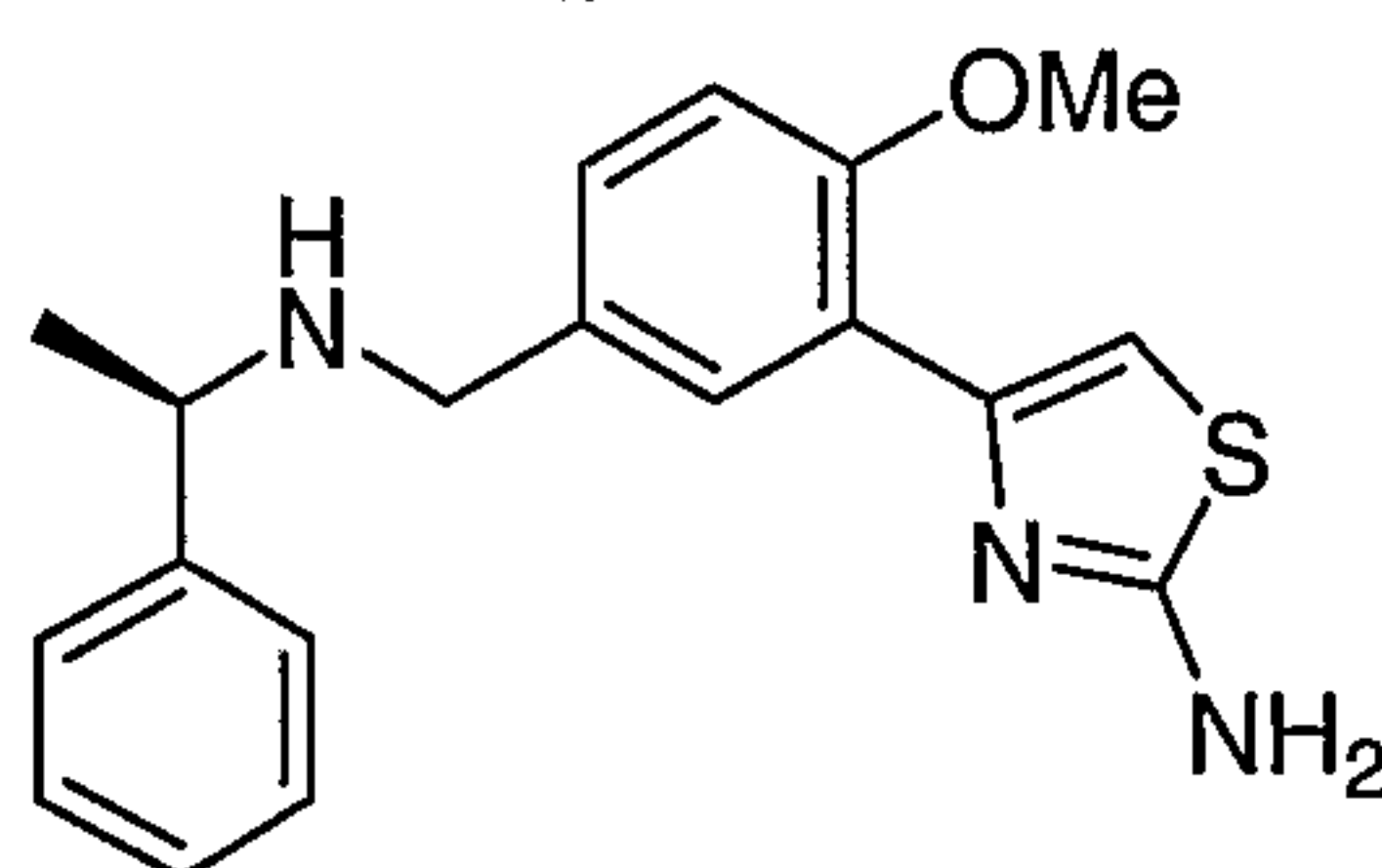


MW 410.558
Mass found: 411

- 188 -

Example 282

4-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1,3-thiazol-2-amine

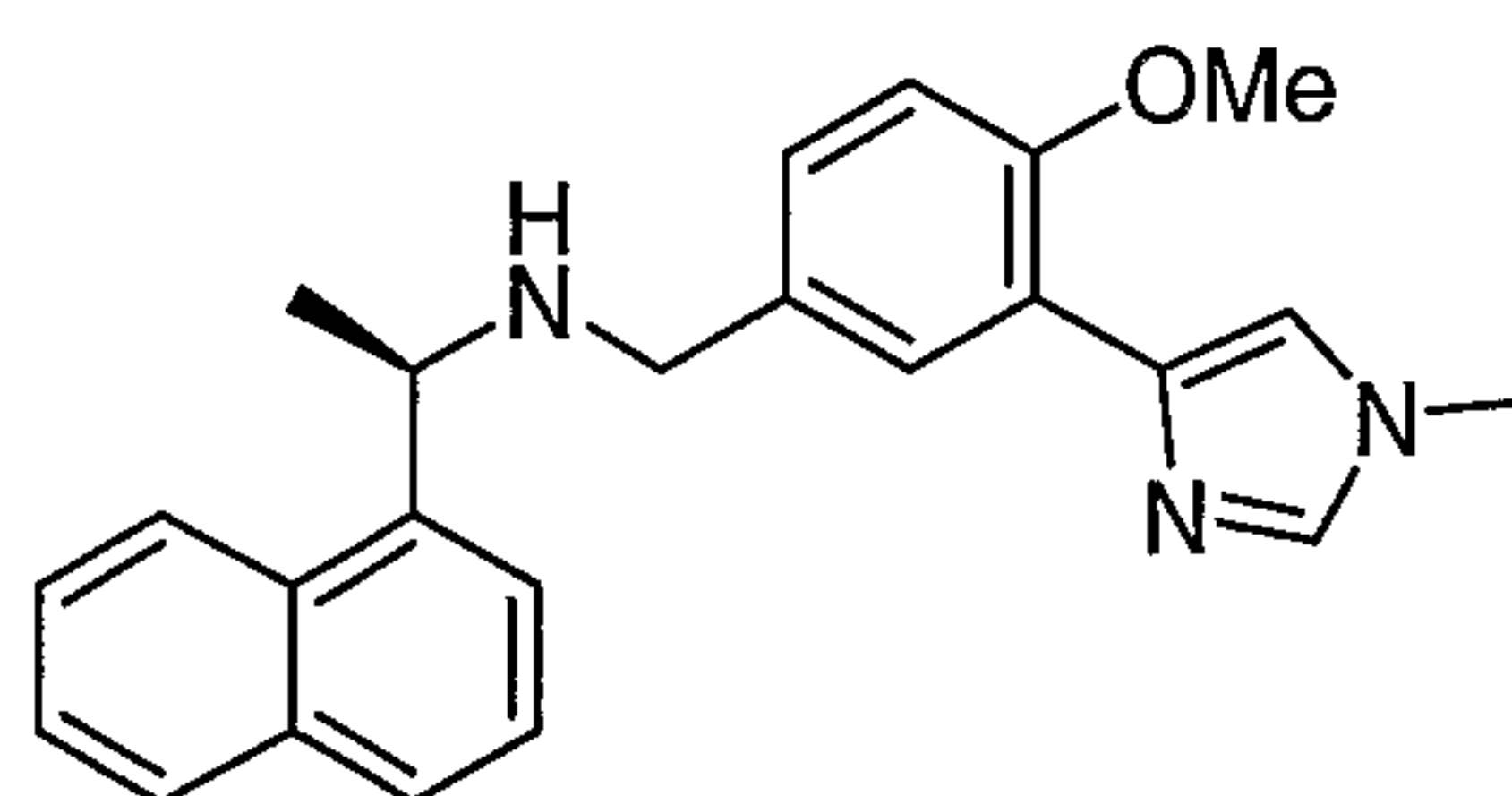


MW 339.461

Mass found: 340, 679

Example 283

(1R)-N-((3-(1-methyl-1H-imidazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

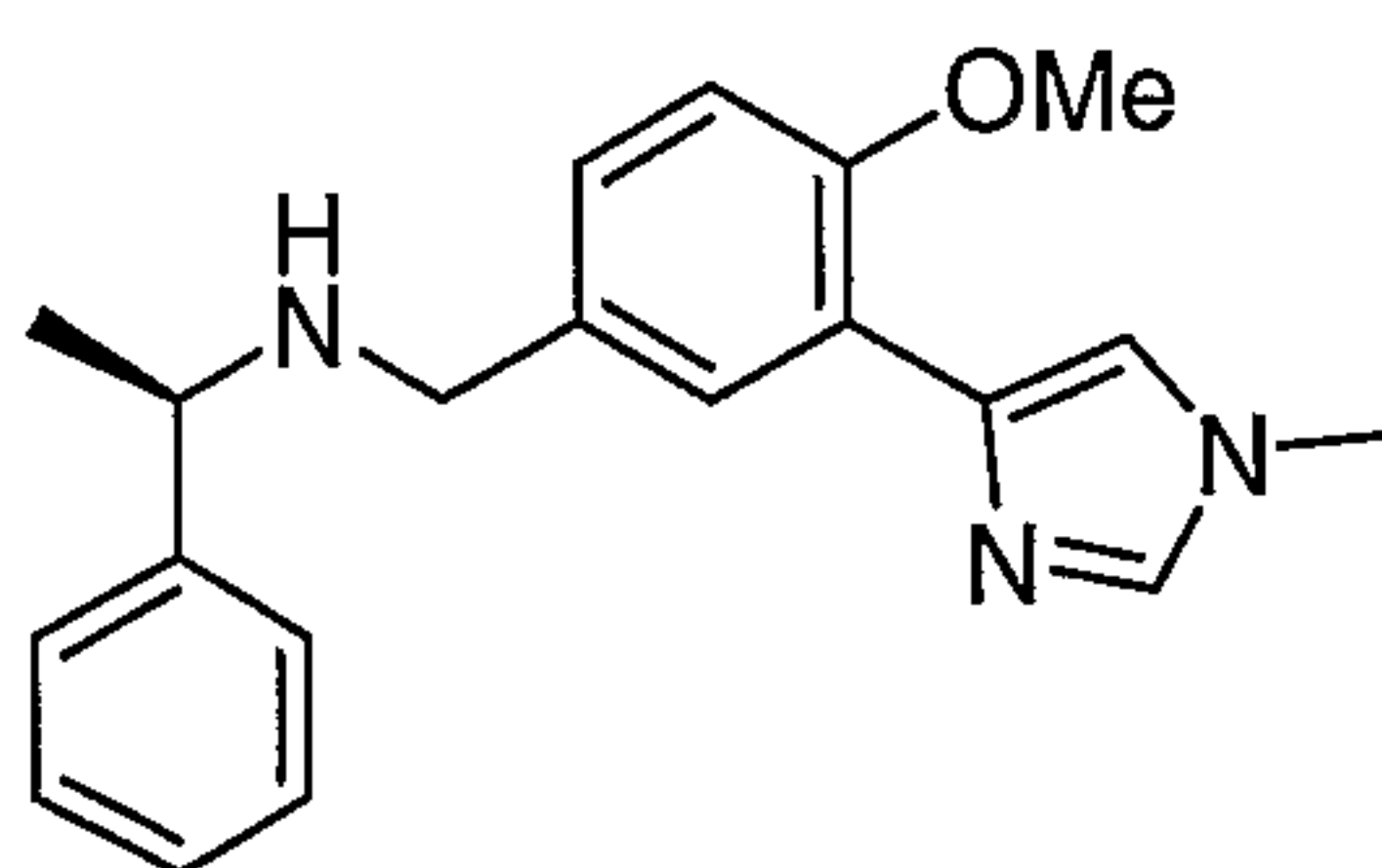


MW 371.482

Mass found: 372, 155, 743

Example 284

(1R)-N-((3-(1-methyl-1H-imidazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine



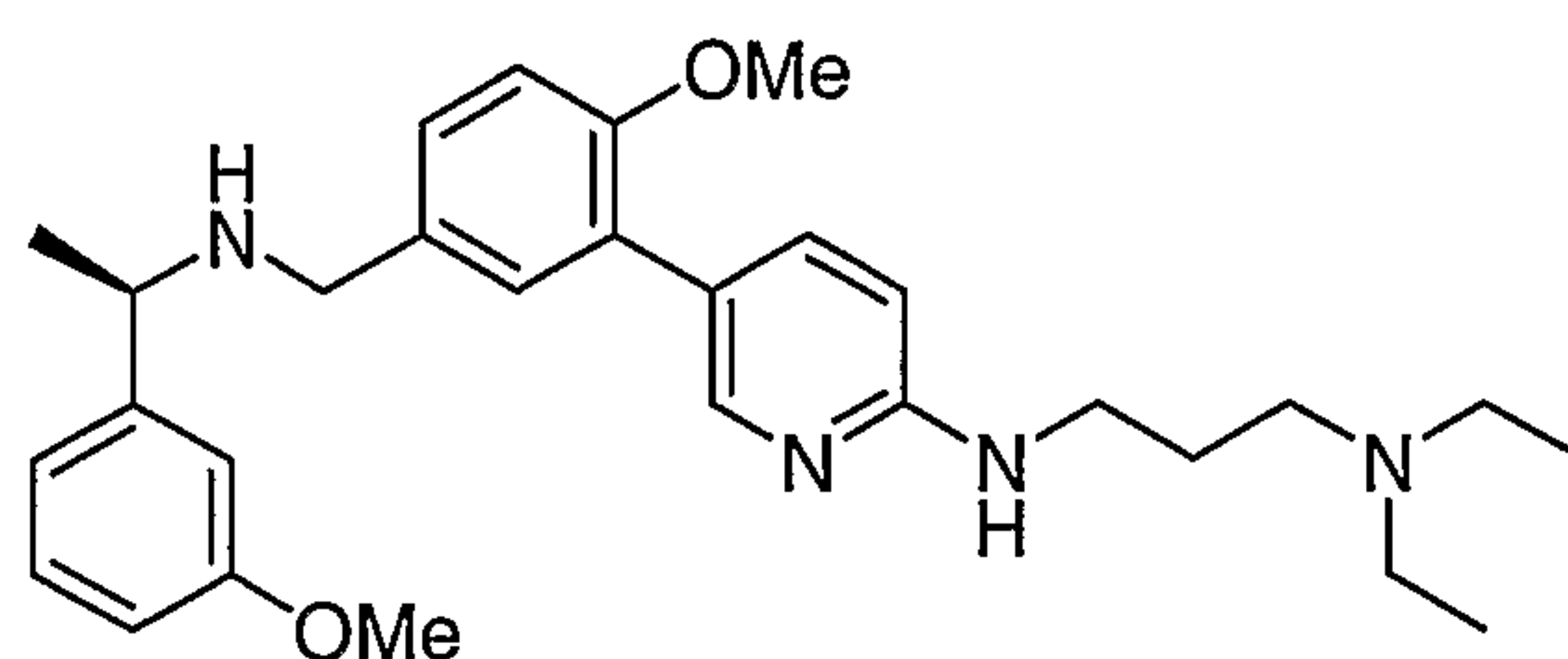
MW 321.422

Mass found: 322, 643

Example 285

- 189 -

N-((3-(6-((3-(diethylamino)propyl)oxy)-3-pyridinyl)-4-(methoxy)phenyl)methyl)-N-((1R)-1-(3-(methoxy)phenyl)ethyl)amine

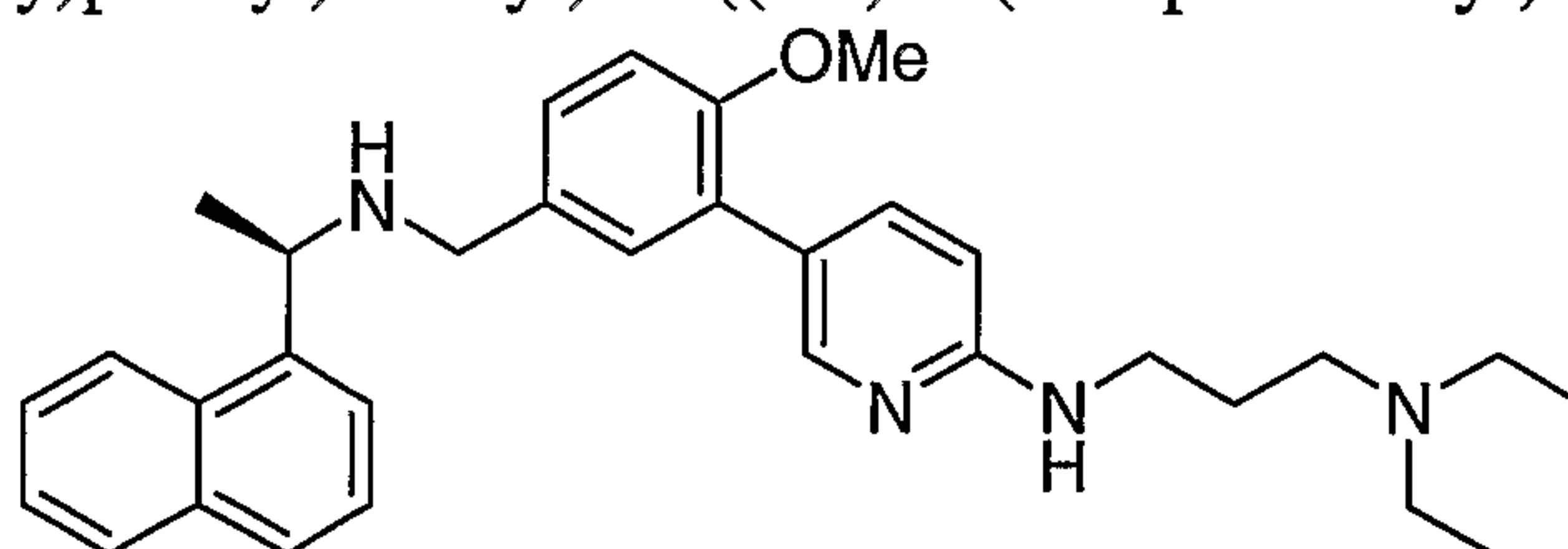


MW 477.645
Mass found: 478, 344

10

Example 286

N-((3-(6-((3-(diethylamino)propyl)oxy)-3-pyridinyl)-4-(methoxy)phenyl)methyl)-N-((1R)-1-(1-naphthalenyl)ethyl)amine

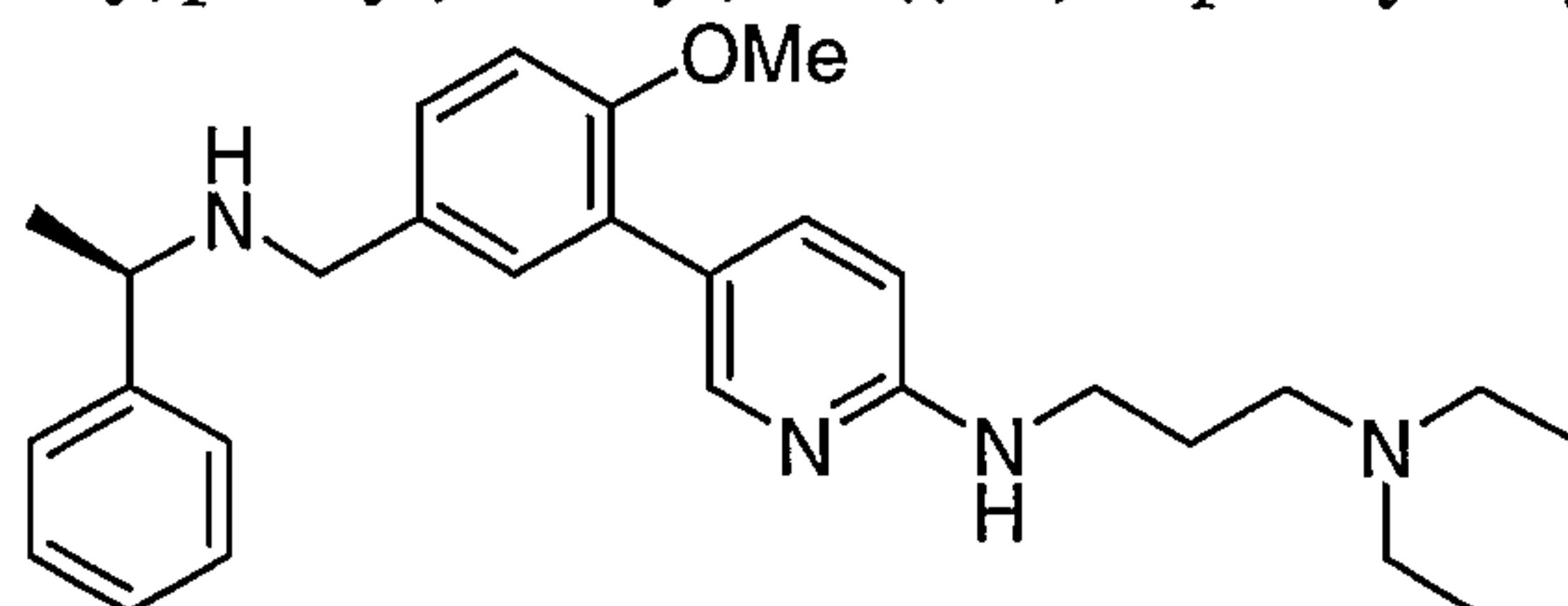


MW 497.679
Mass found: 498, 155, 344

20

Example 287

N-((3-(6-((3-(diethylamino)propyl)oxy)-3-pyridinyl)-4-(methoxy)phenyl)methyl)-N-((1R)-1-phenylethyl)amine



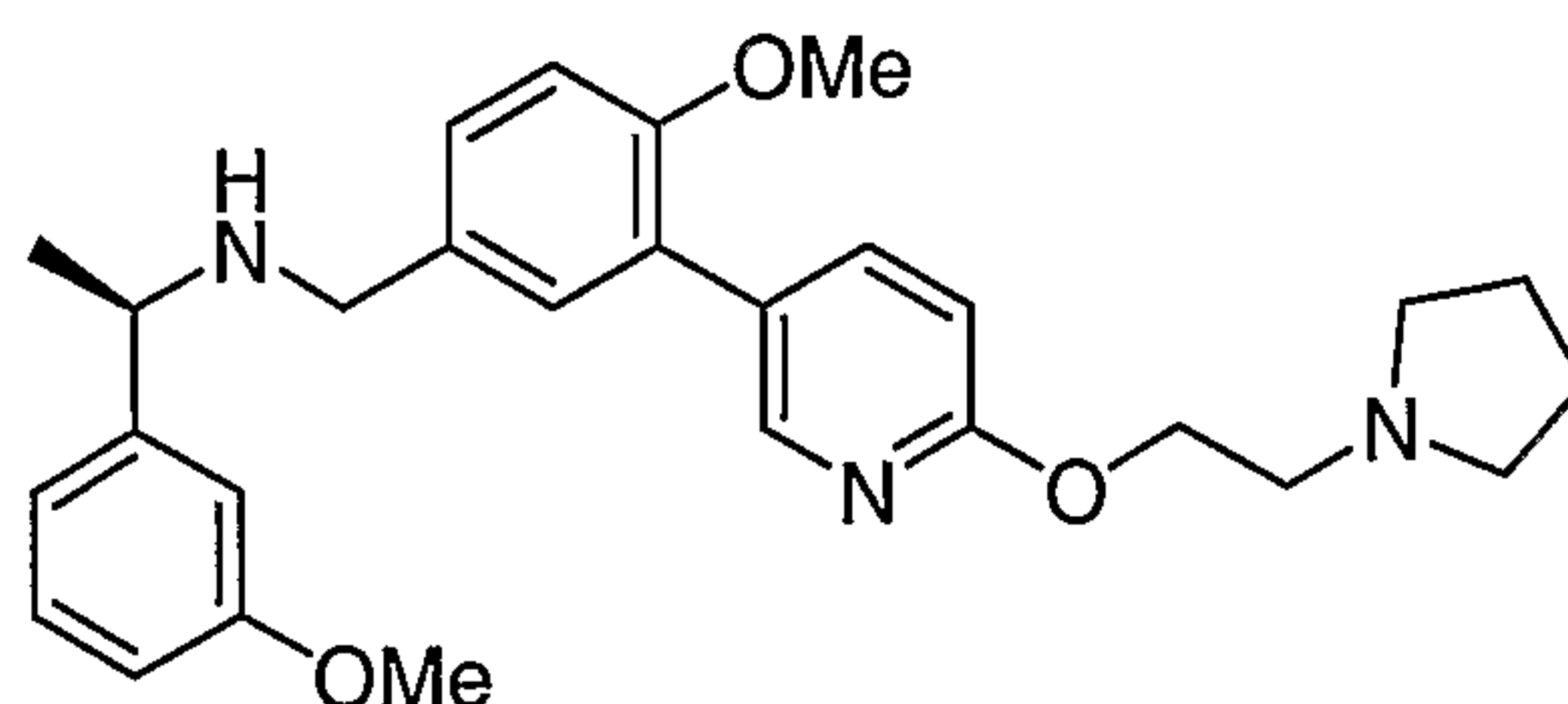
MW 447.619
Mass found: 448, 344

30

Example 288

- 190 -

(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-((2-(1-pyrrolidinyl)ethyl)oxy)-3-pyridinyl)phenyl)methyl)ethanamine



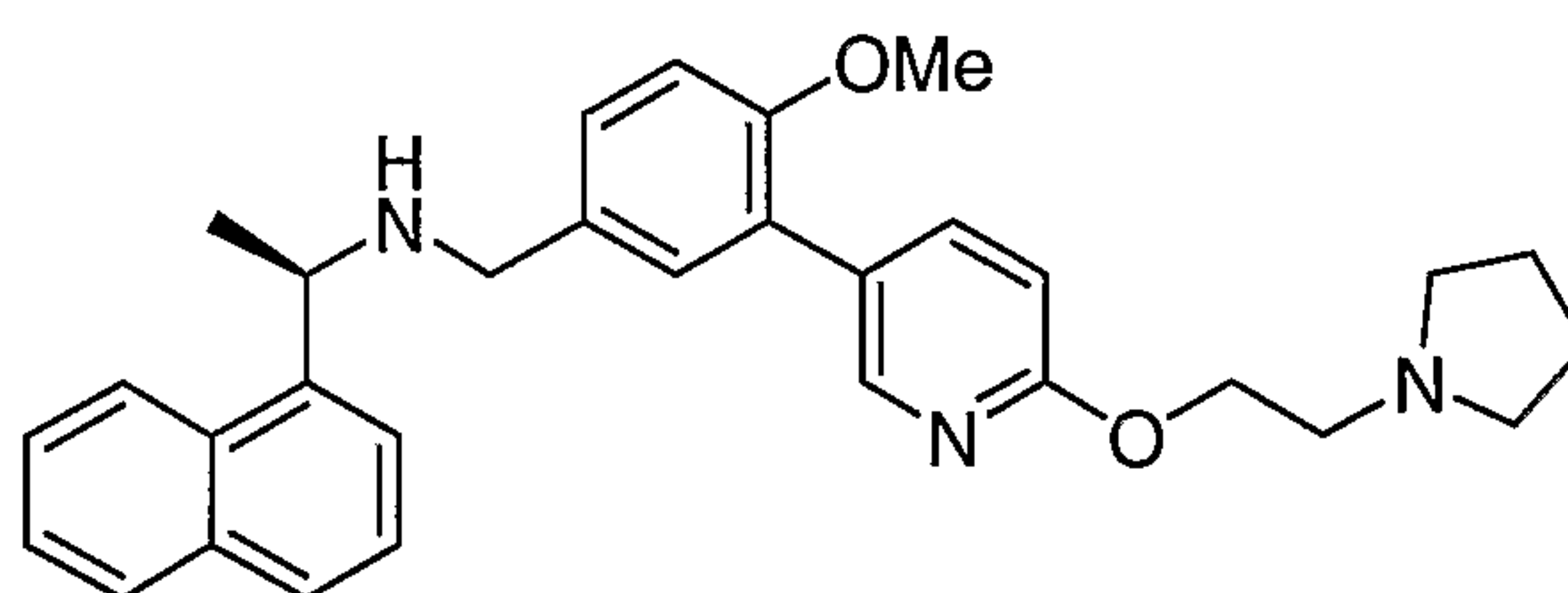
5

MW 461.603
Mass found: 462, 328

10

Example 289

(1R)-N-((4-(methyloxy)-3-(6-((2-(1-pyrrolidinyl)ethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



15

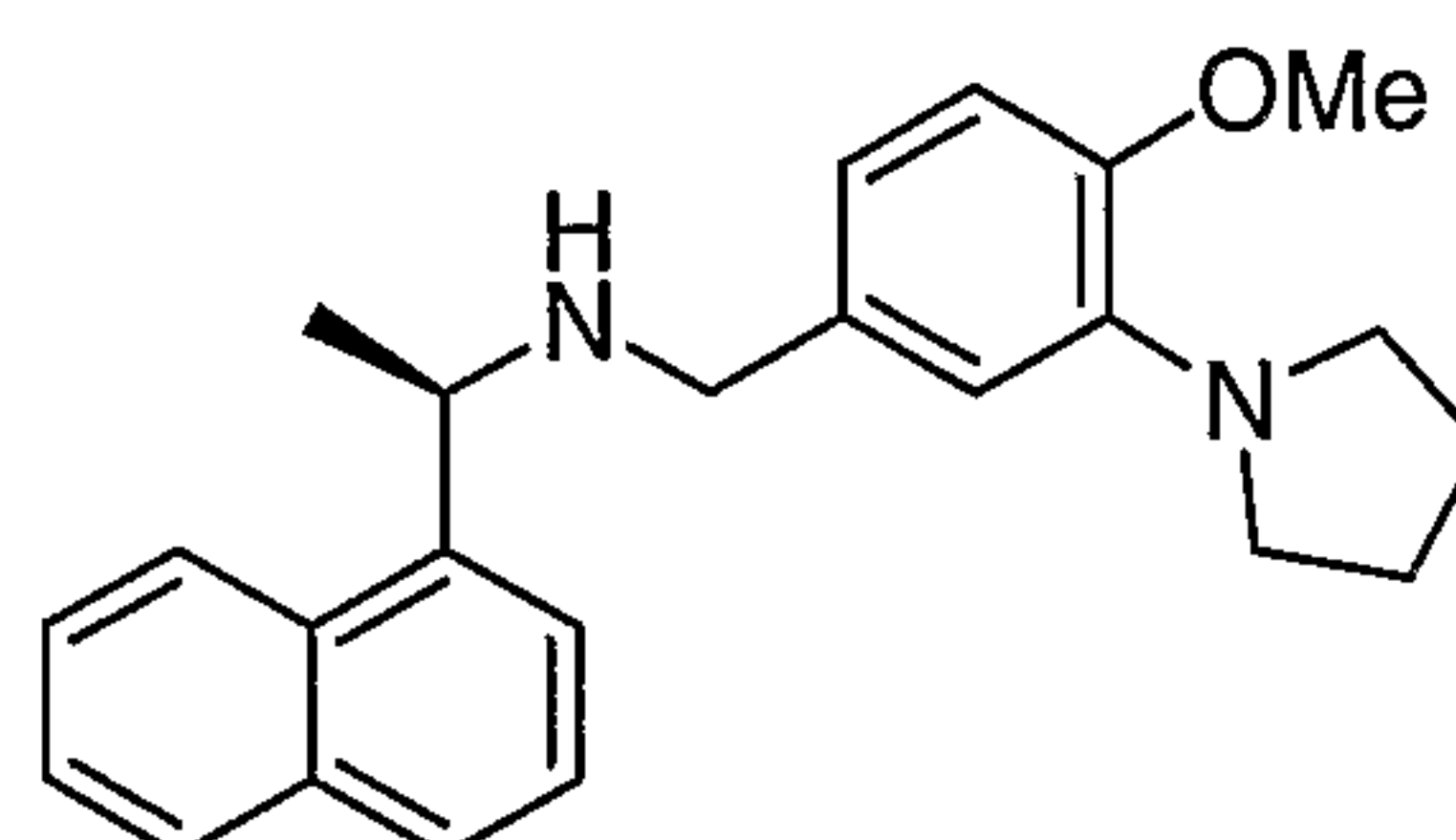
MW 481.637
Mass found: 155, 482, 328

20

Example 290

(1R)-N-((4-(methyloxy)-3-(1-pyrrolidinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

25



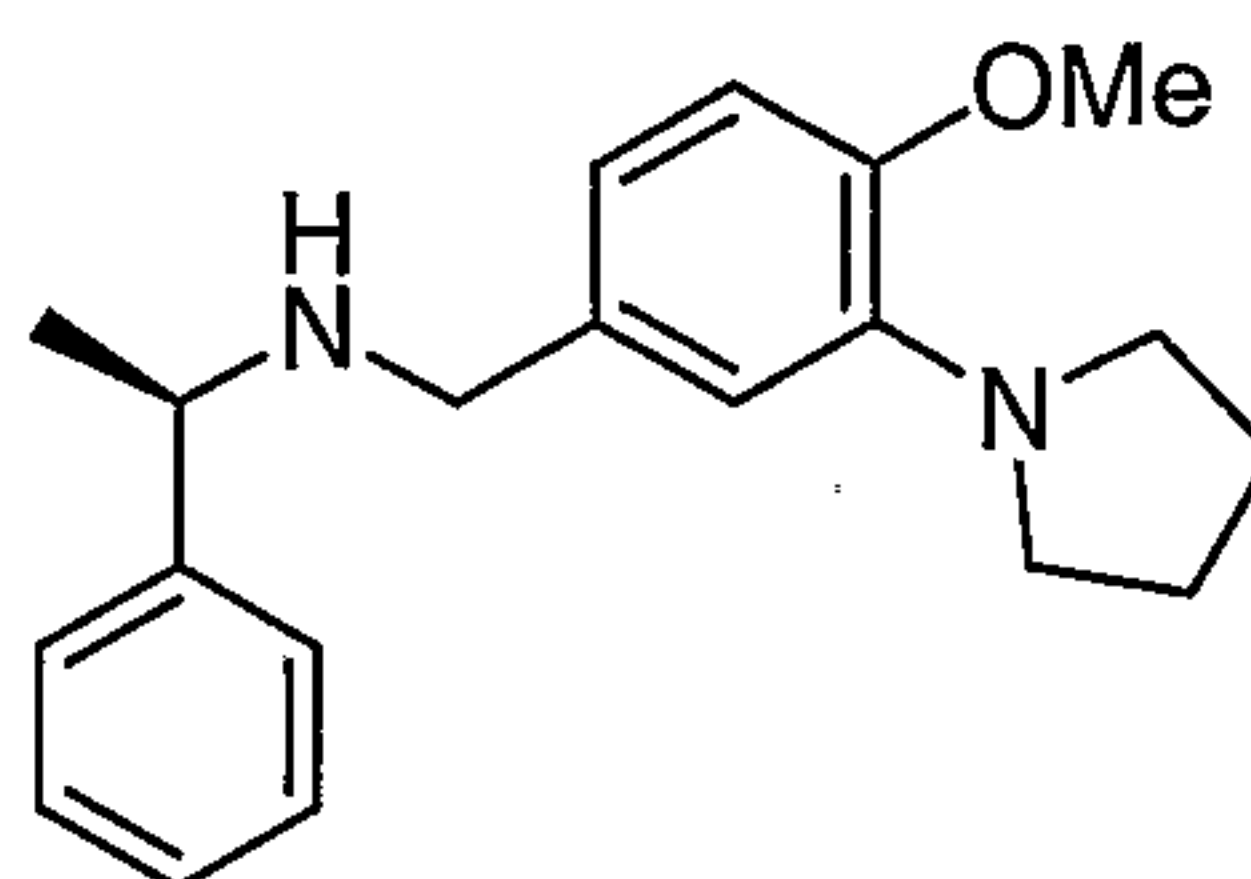
MW 360.498
Mass found: 361, 721

30

Example 291

(1R)-N-((4-(methyloxy)-3-(1-pyrrolidinyl)phenyl)methyl)-1-phenylethanamine

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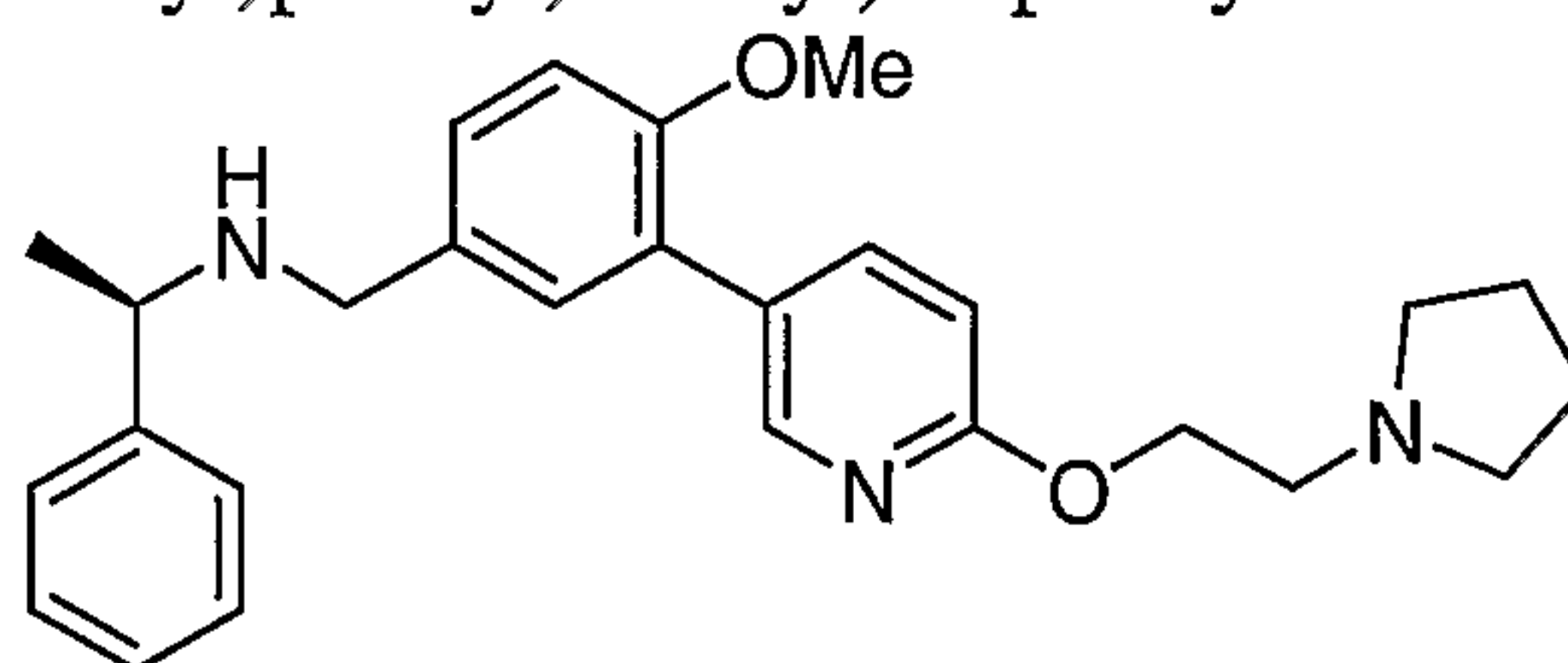
MW 310.438
Mass found: 311, 621

5

Example 292

(1R)-N-((4-(methyloxy)-3-(6-((2-(1-pyrrolidinyl)ethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine

10



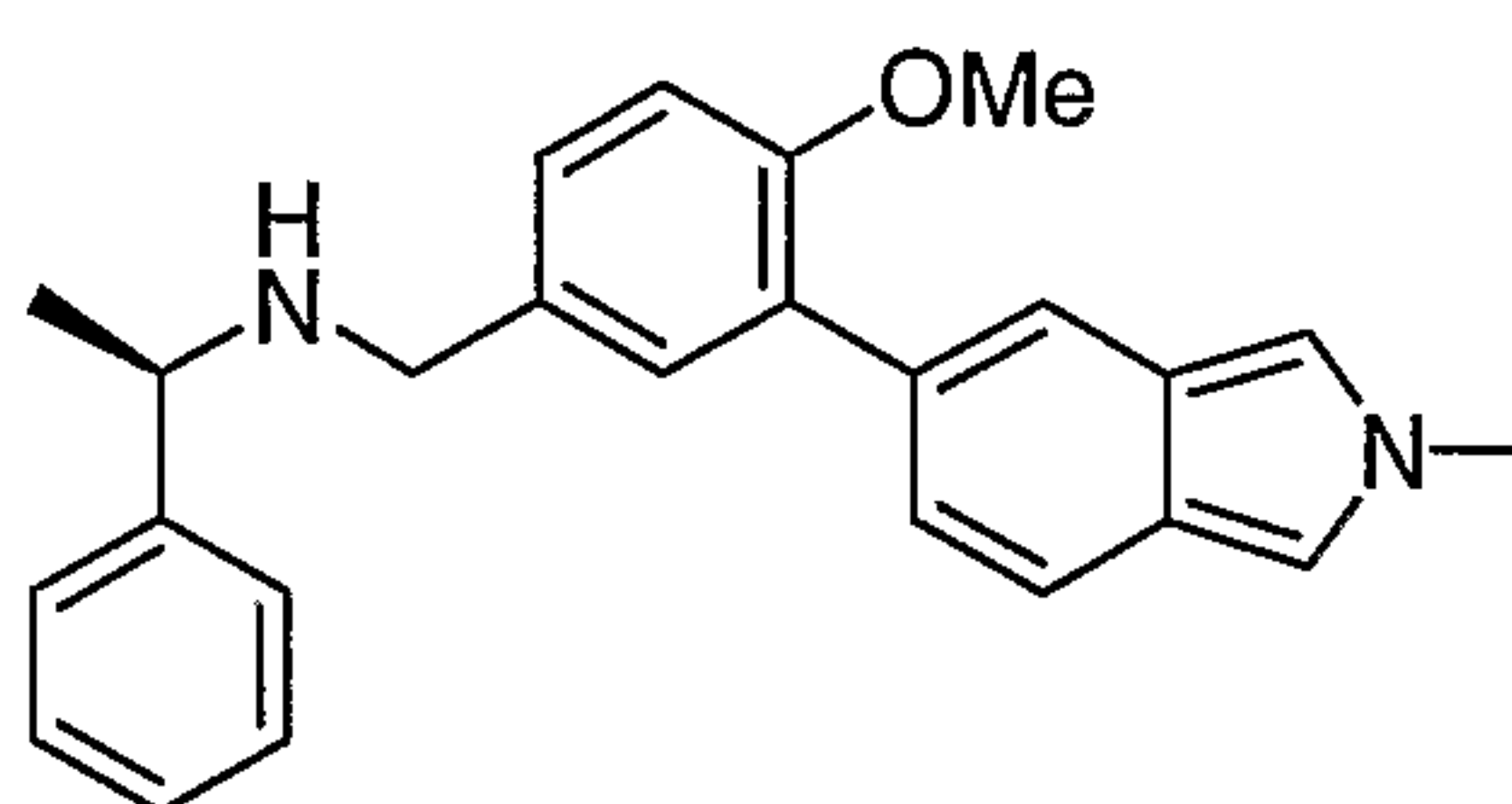
MW 431.577
Mass found: 432, 328

15

Example 293

(1R)-N-((3-(2-methyl-2H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine

20



MW 371.482
Mass found: 372, 744, 858

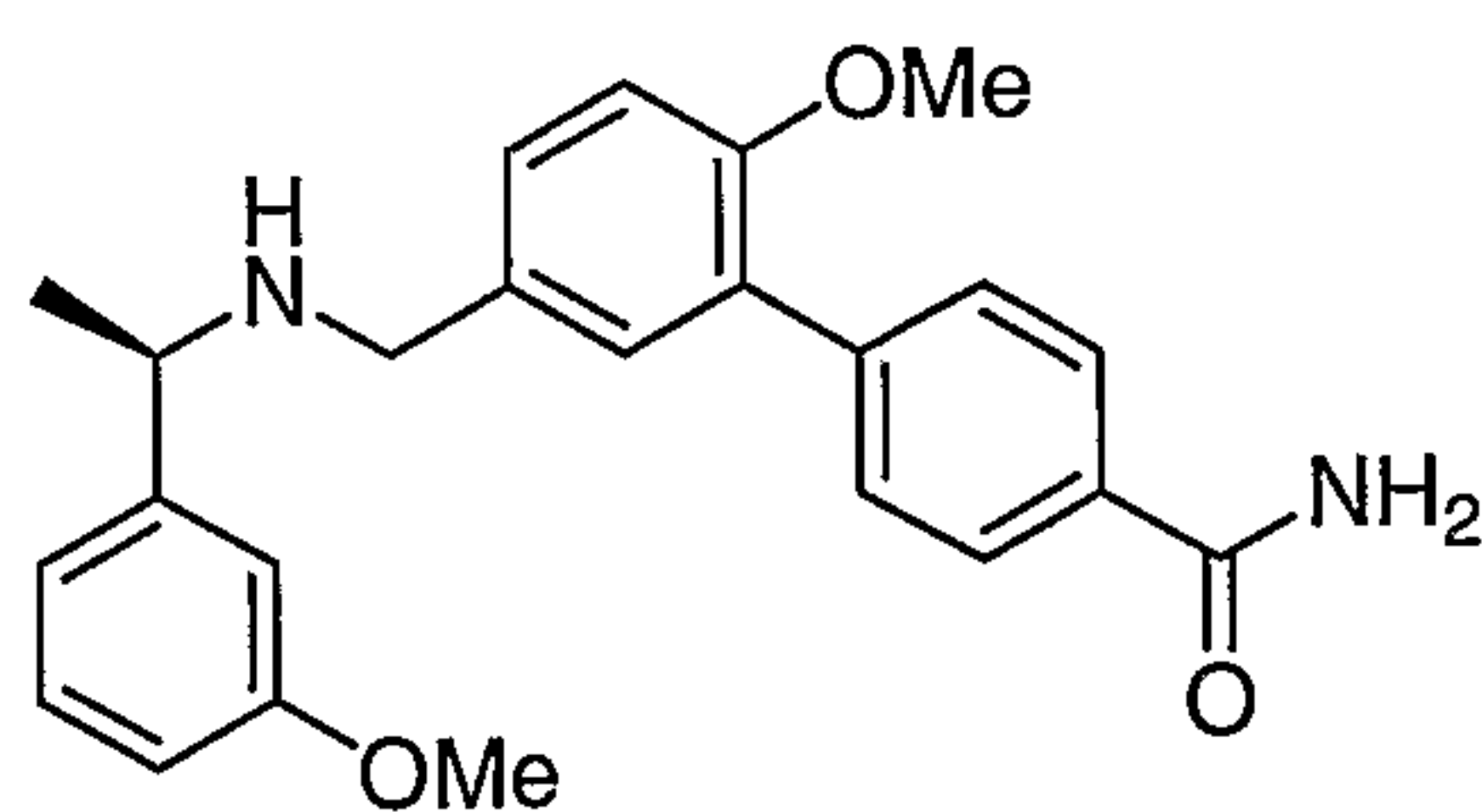
25

Example 294

2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide

30

- 192 -



MW 390.48

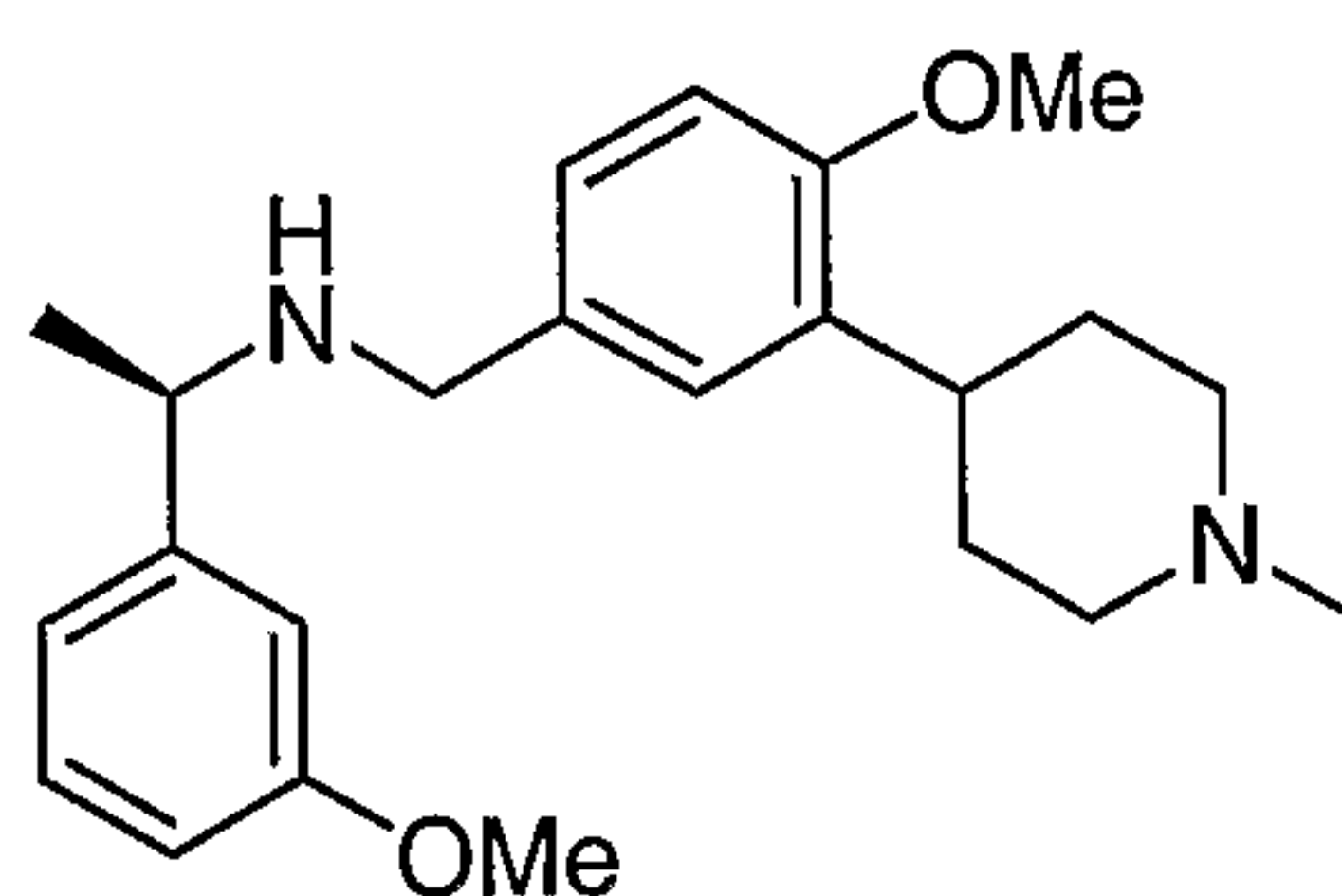
Mass found: 240, 391, 781

5

Example 295

(1R)-N-((4-(methoxy)-3-(1-methyl-4-piperidinyl)phenyl)methyl)-1-(3-(methoxy)phenyl)ethanamine

10



MW 368.518

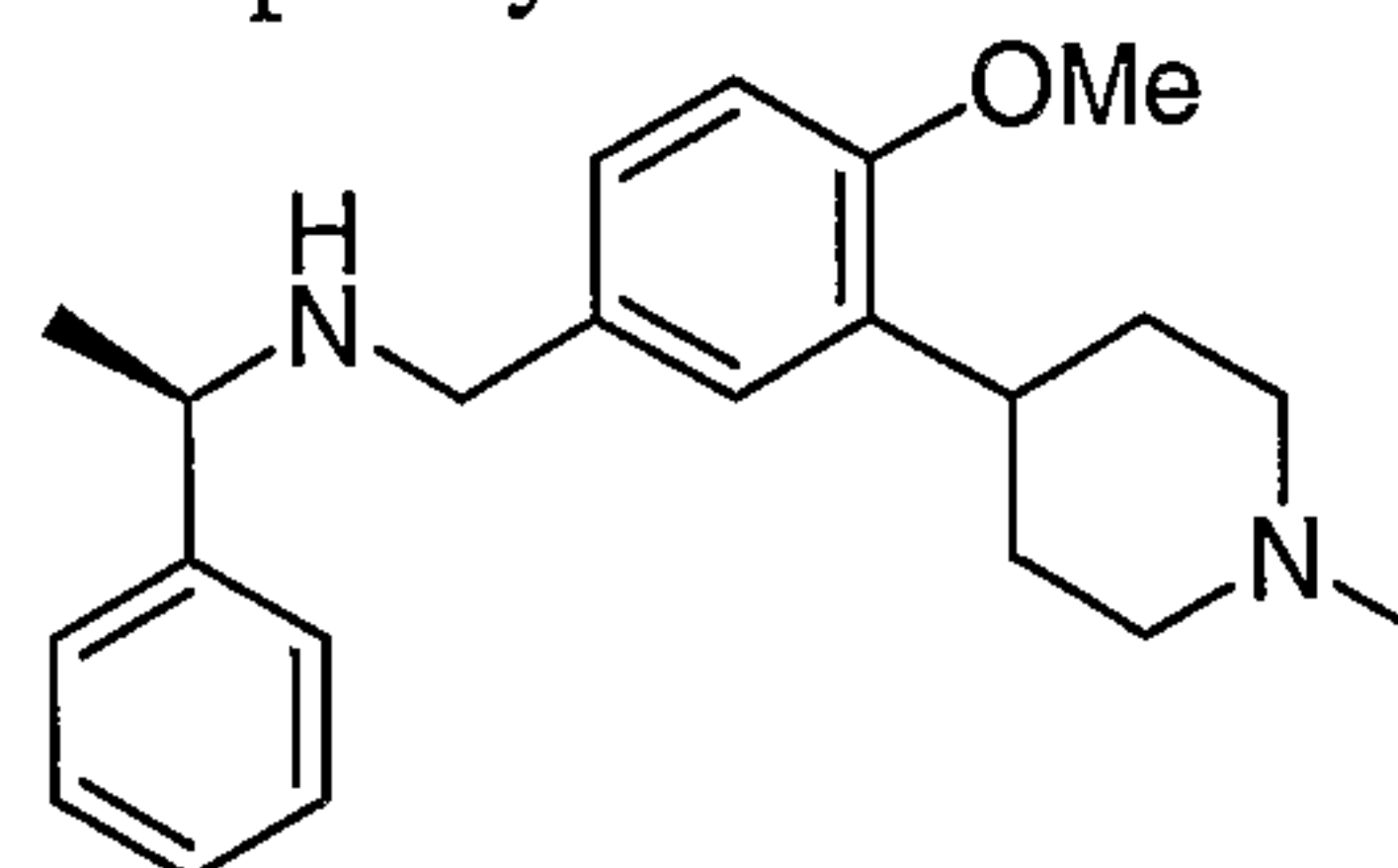
Mass found: 369, 483

15

Example 296

(1R)-N-((4-(methoxy)-3-(1-methyl-4-piperidinyl)phenyl)methyl)-1-phenylethanamine

20



MW 338.492

Mass found: 339, 453

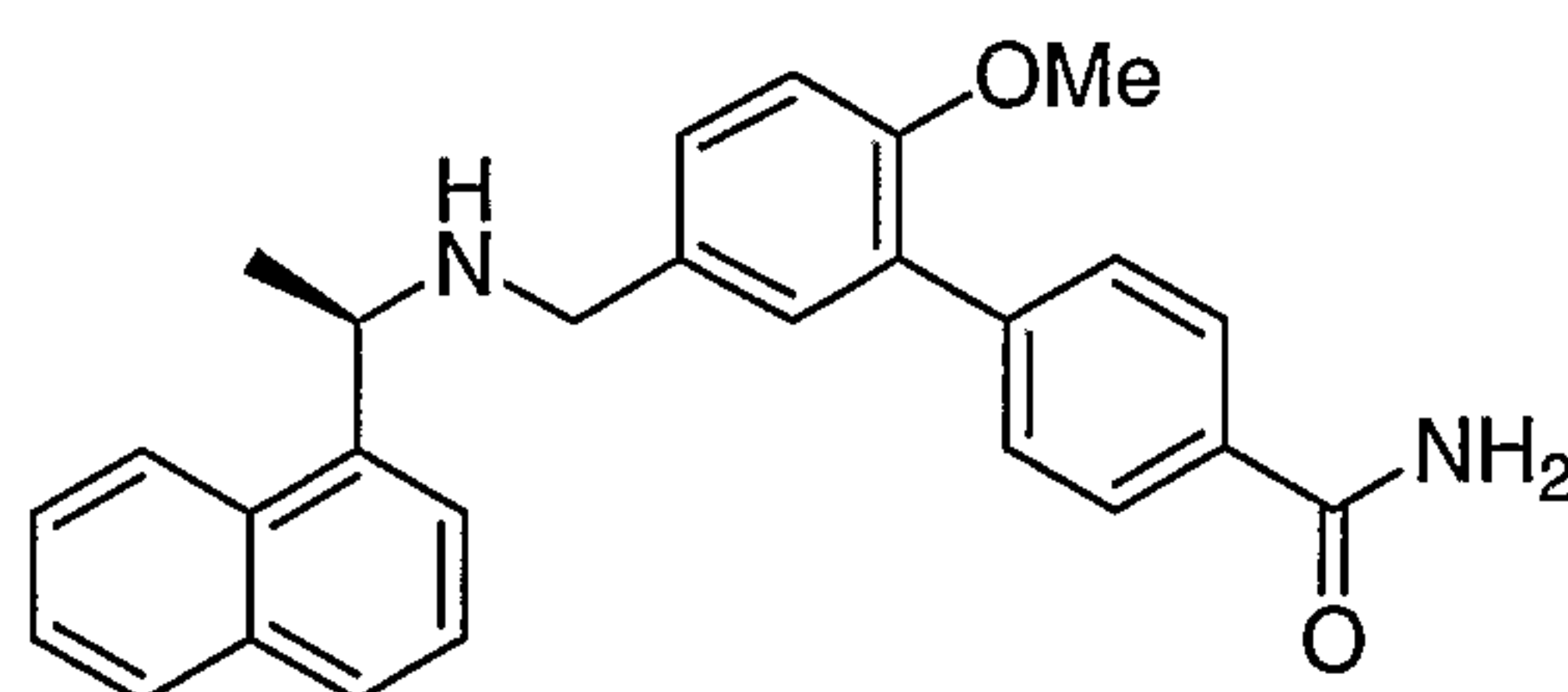
25

Example 297

2'-(methoxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide

30

- 193 -



MW 410.514

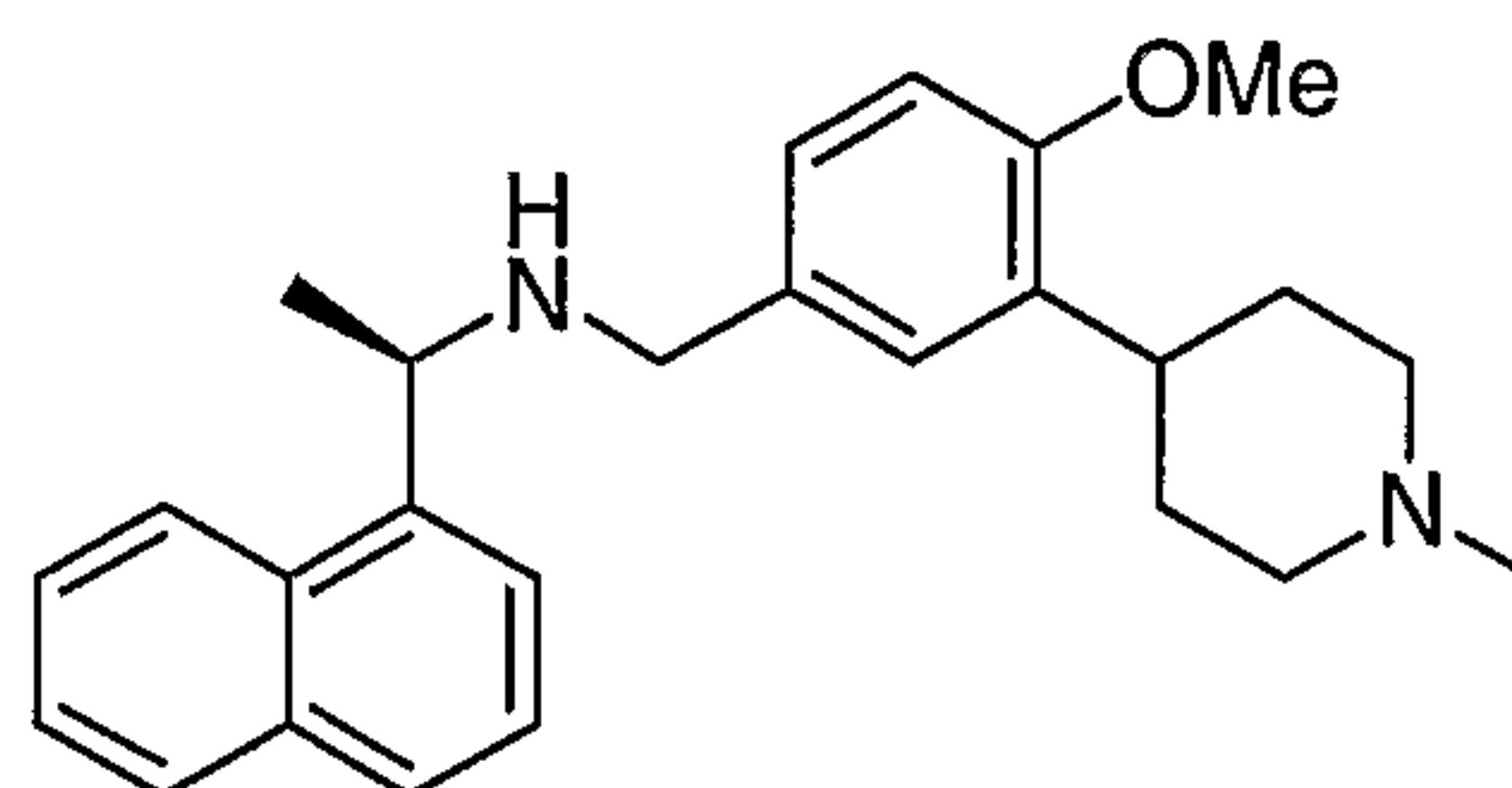
Mass found: 155, 411, 240, 257

5

Example 298

(1R)-N-((4-(methoxy)-3-(1-methyl-4-piperidiny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

10



MW 388.552

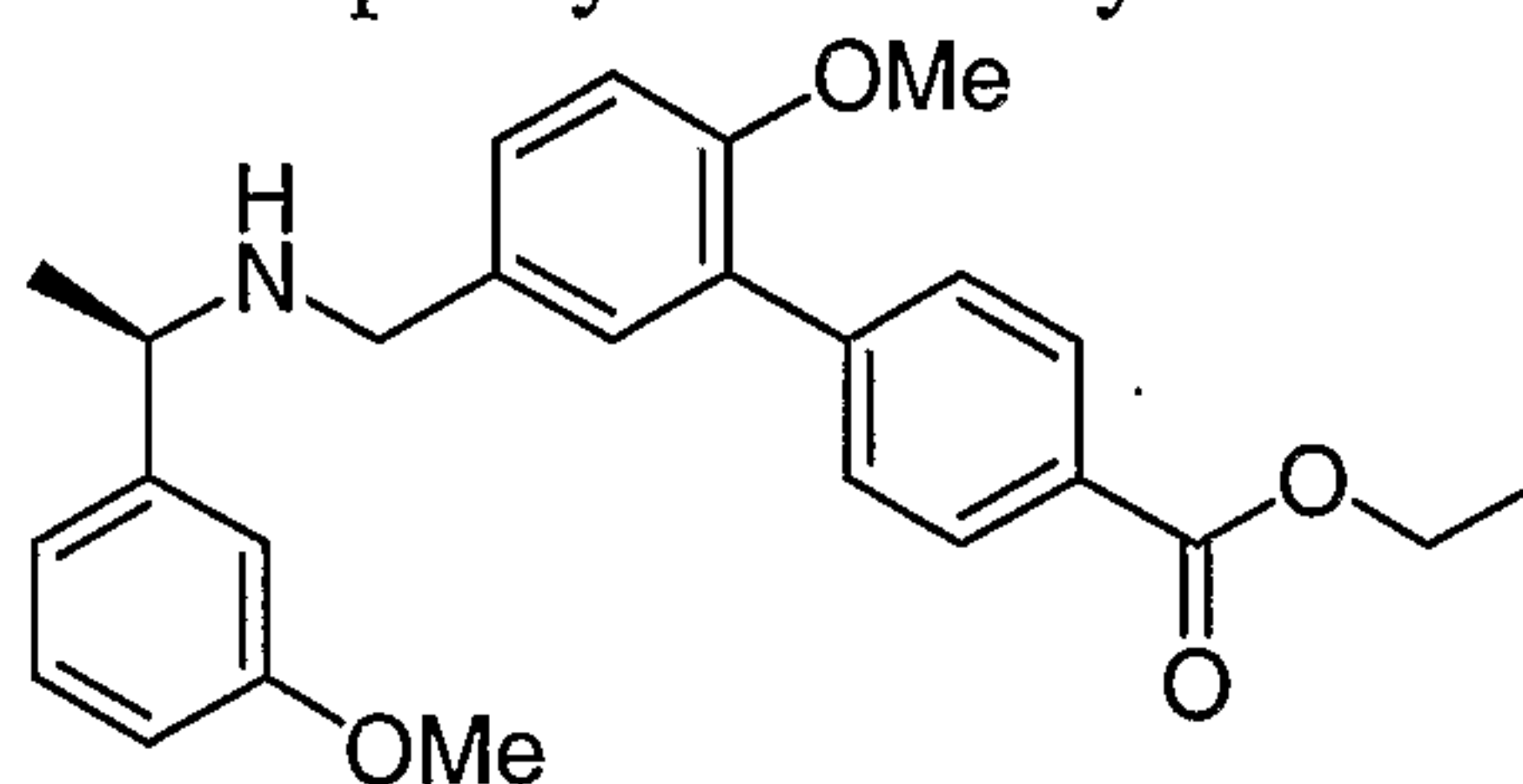
Mass found: 389, 503

15

Example 299

ethyl 2'-(methoxy)-5'-((((1R)-1-(3-(methoxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate

20



MW 419.518

Mass found: 953, 420

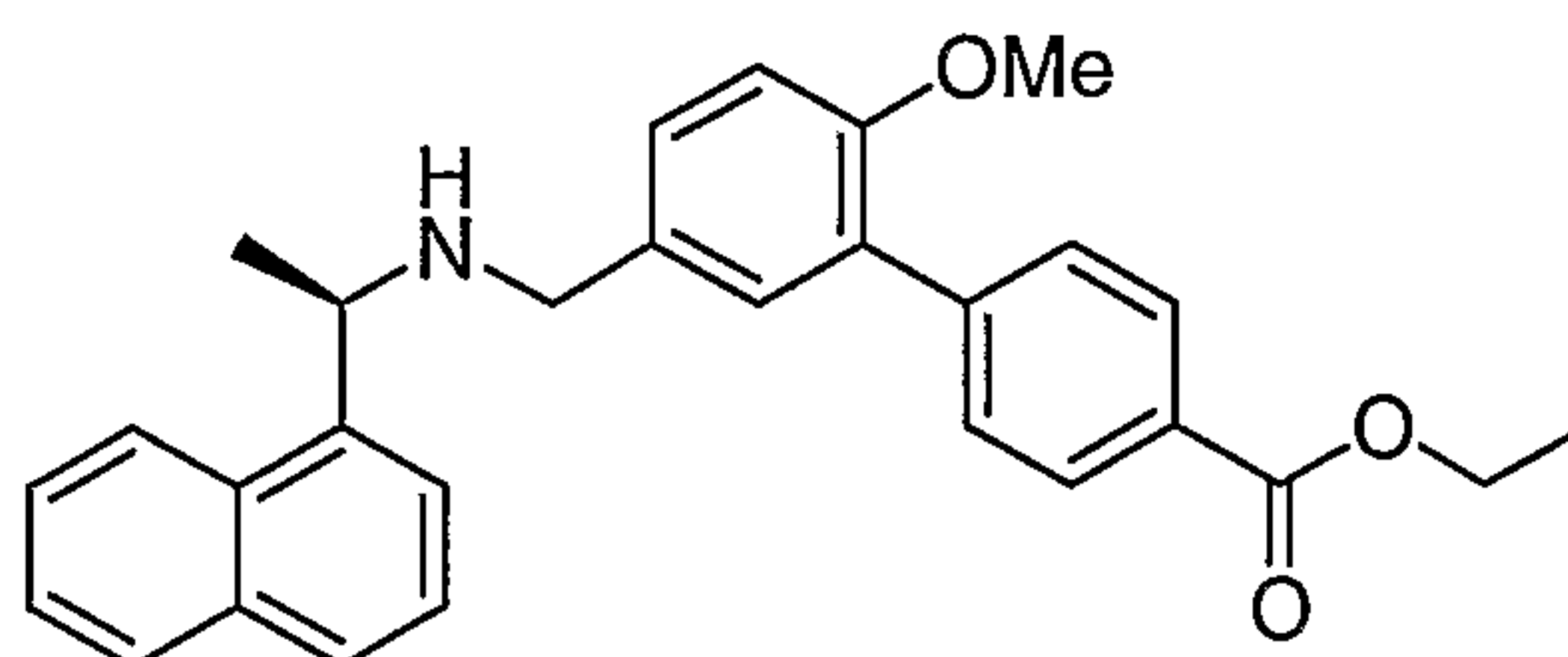
25

Example 300

ethyl 2'-(methoxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate

30

- 194 -



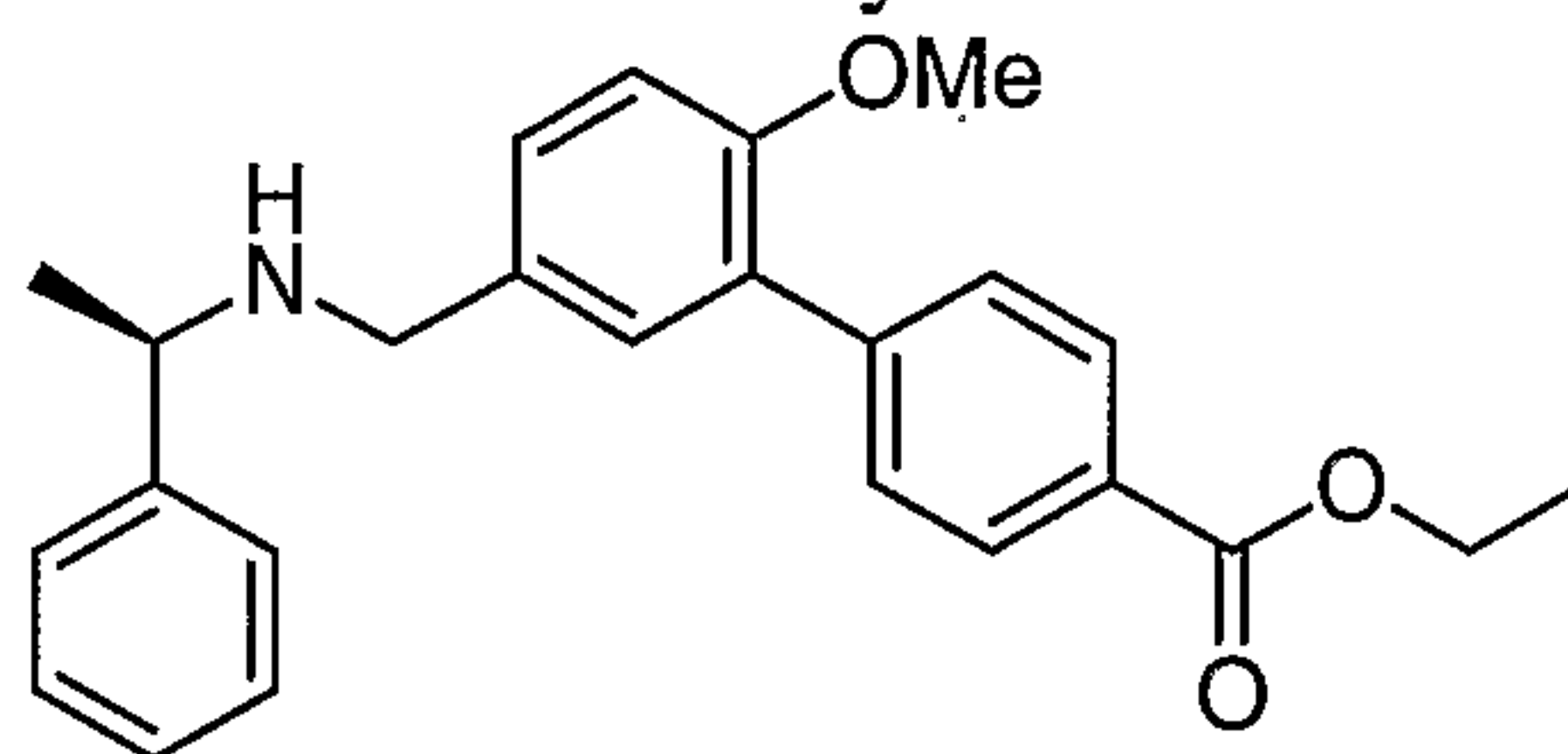
MW 439.552
Mass found: 440, 993

5

Example 301

ethyl 2'-(methoxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-
carboxylate

10



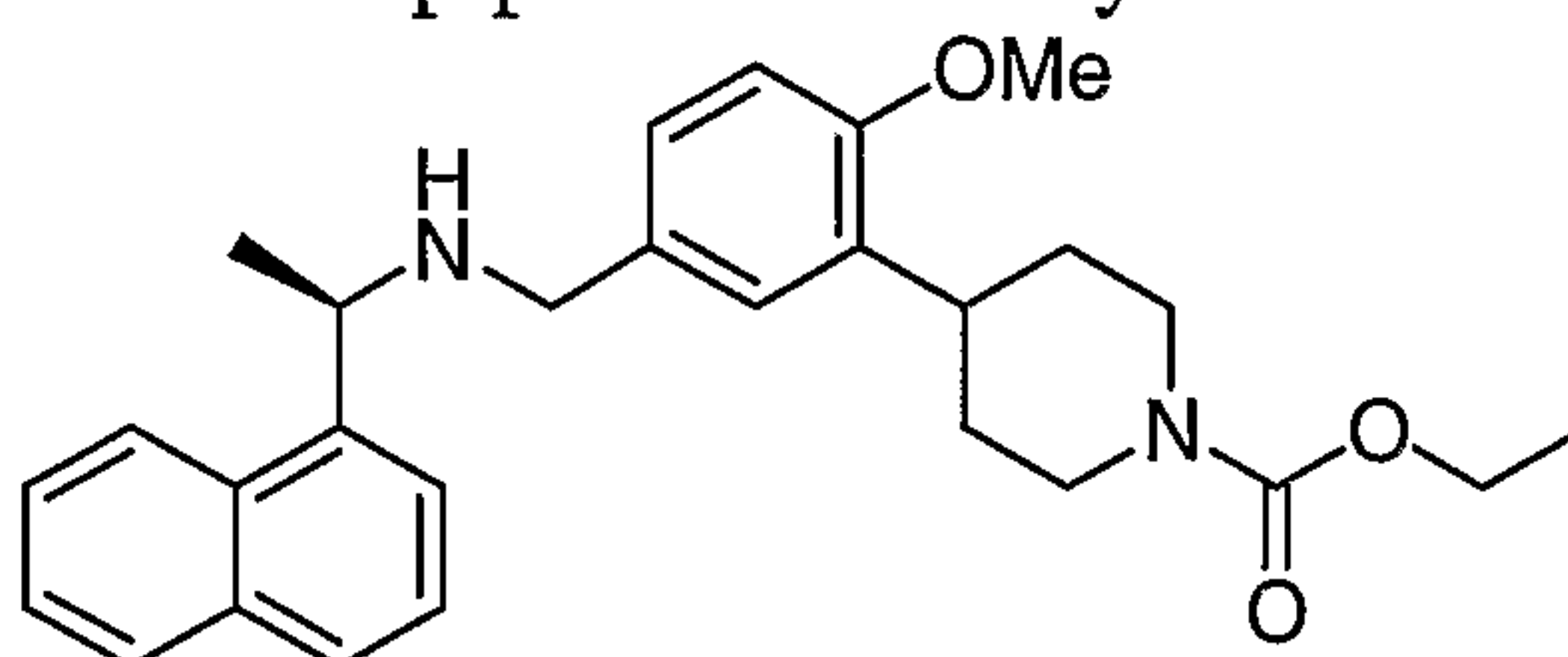
MW 389.492
Mass found: 390, 893

15

Example 302

ethyl 4-(2-(methoxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-
1-piperidinecarboxylate

20



MW 446.588
Mass found: 447

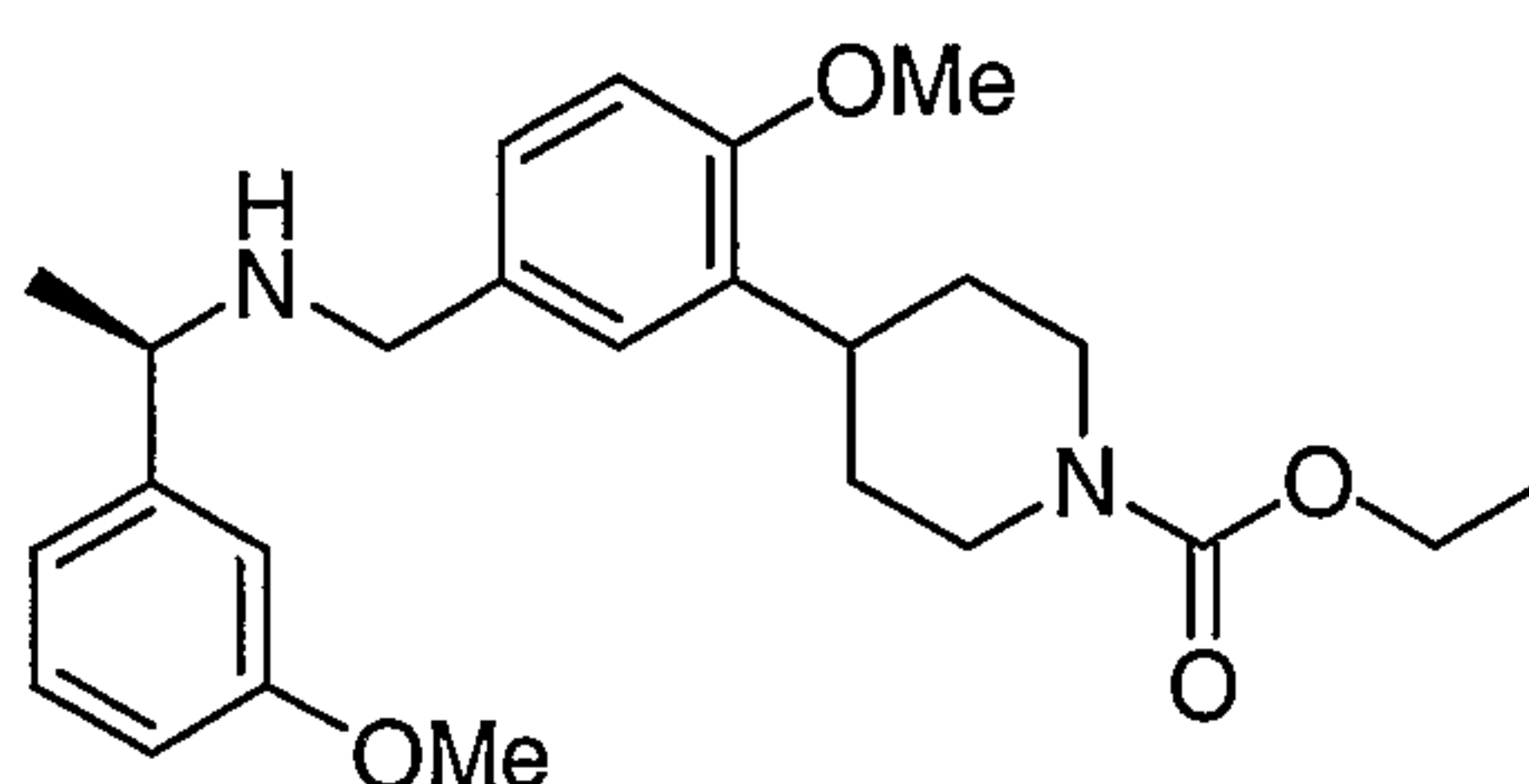
25

Example 303

ethyl 4-(2-(methoxy)-5-((((1R)-1-(3-
(methoxy)phenyl)ethyl)amino)methyl)phenyl)-1-piperidinecarboxylate

30

- 195 -



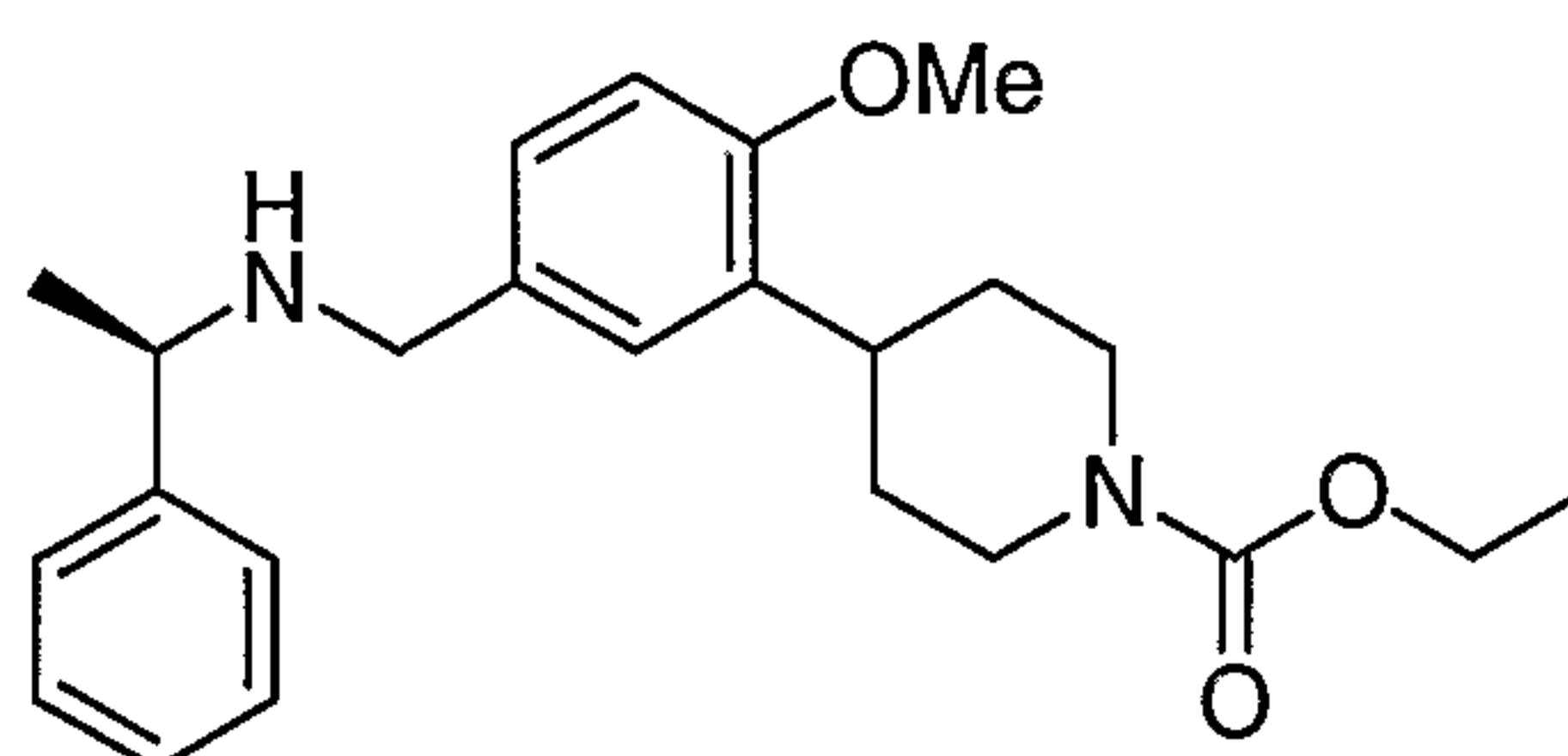
MW 426.554
Mass found: 427, 967

5

Example 304

ethyl 4-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1-piperidinecarboxylate

10



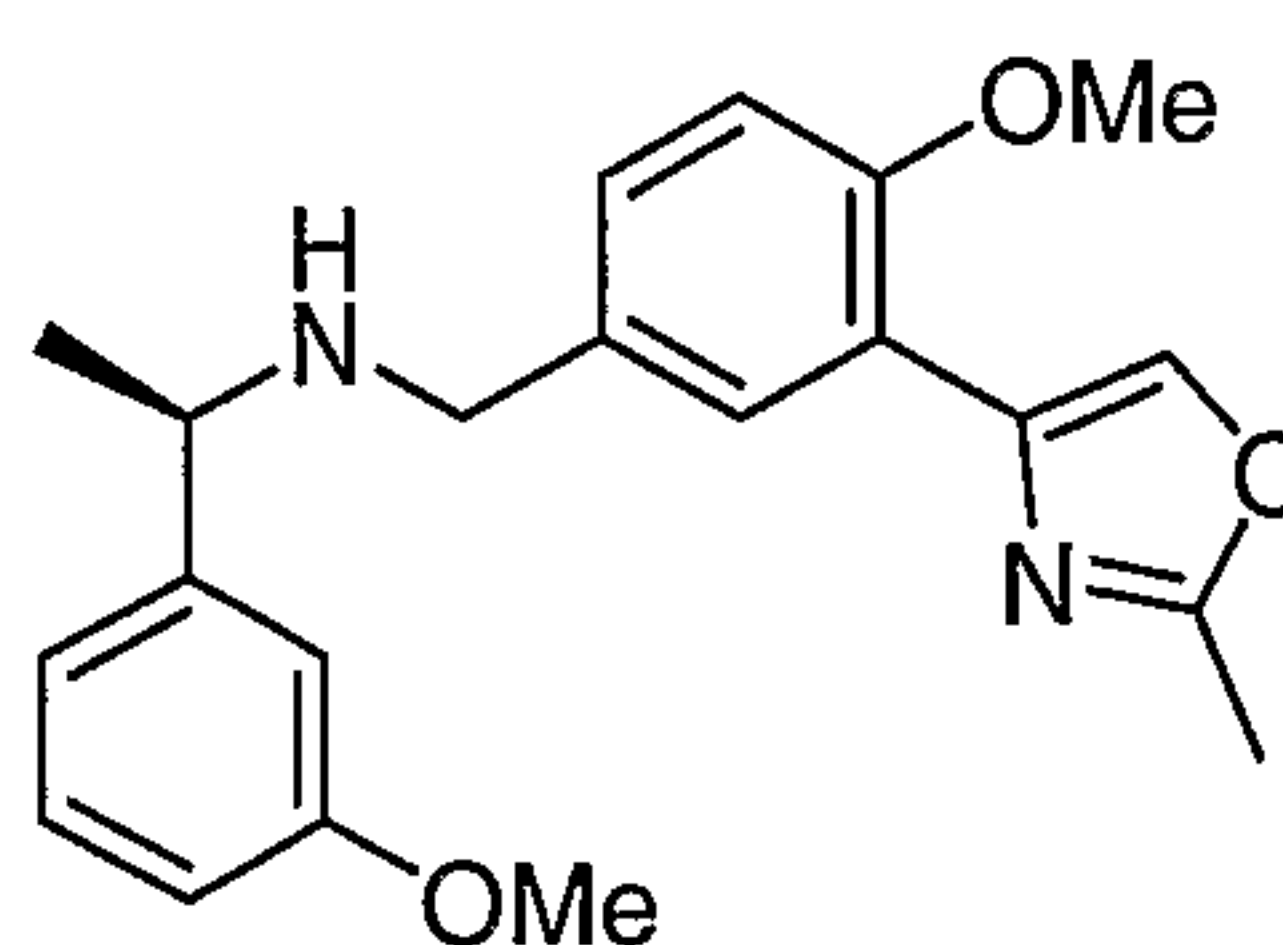
MW 396.528
Mass found: 397, 907

15

Example 305

(1R)-N-((3-(2-methyl-1,3-oxazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

20



MW 352.432
Mass found: 353, 705

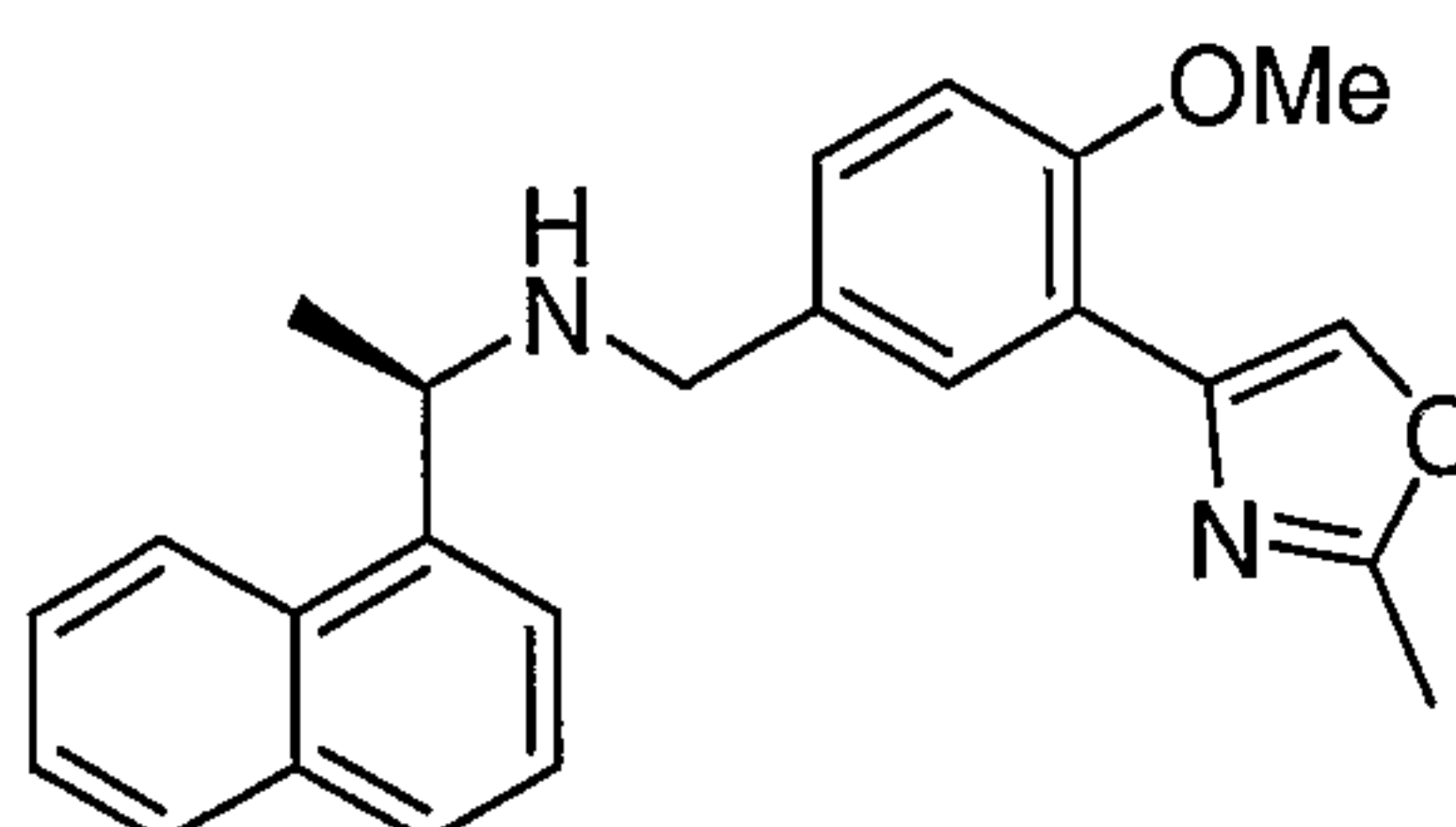
25

Example 306

(1R)-N-((3-(2-methyl-1,3-oxazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

30

- 196 -



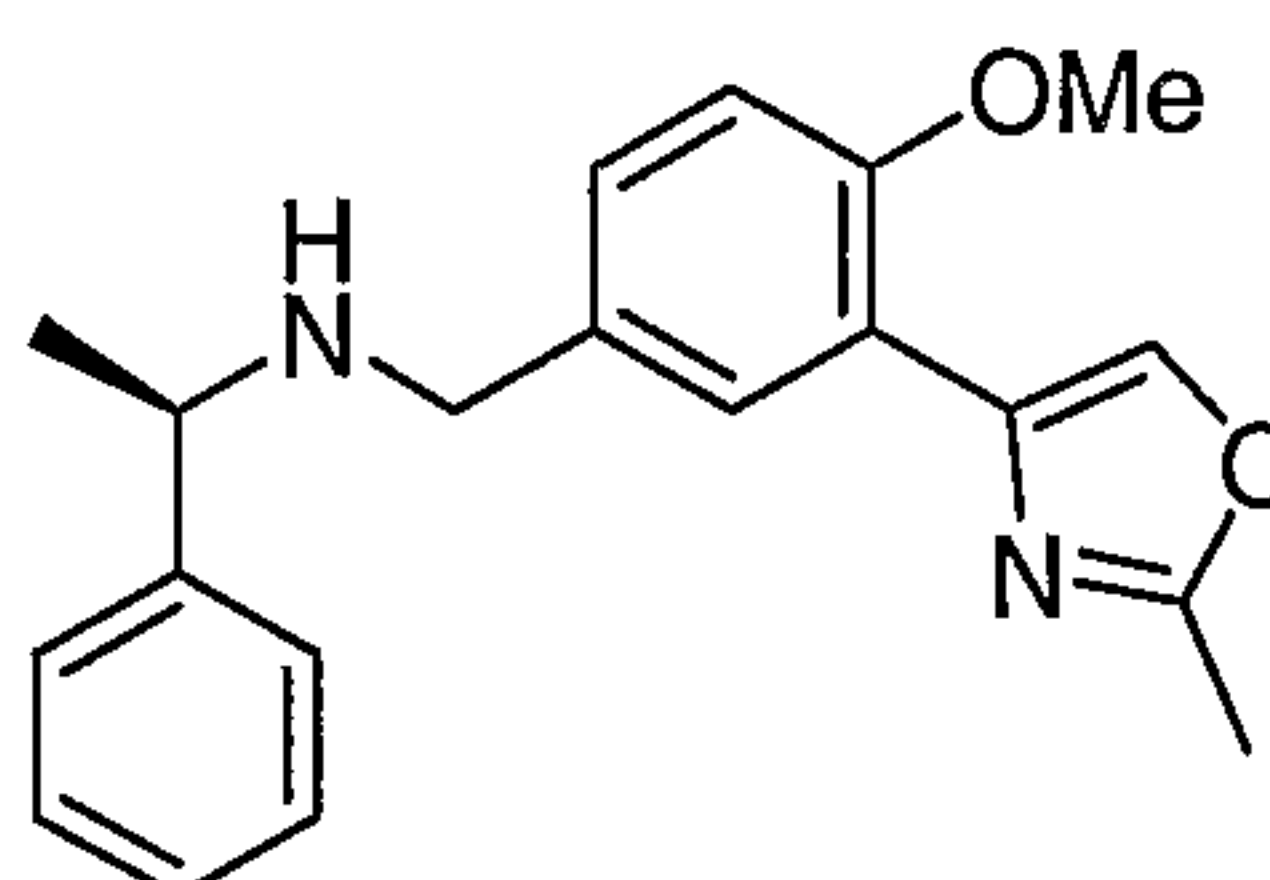
MW 372.466
Mass found: 373, 745

5

Example 307

(1R)-N-((3-(2-methyl-1,3-oxazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine

10



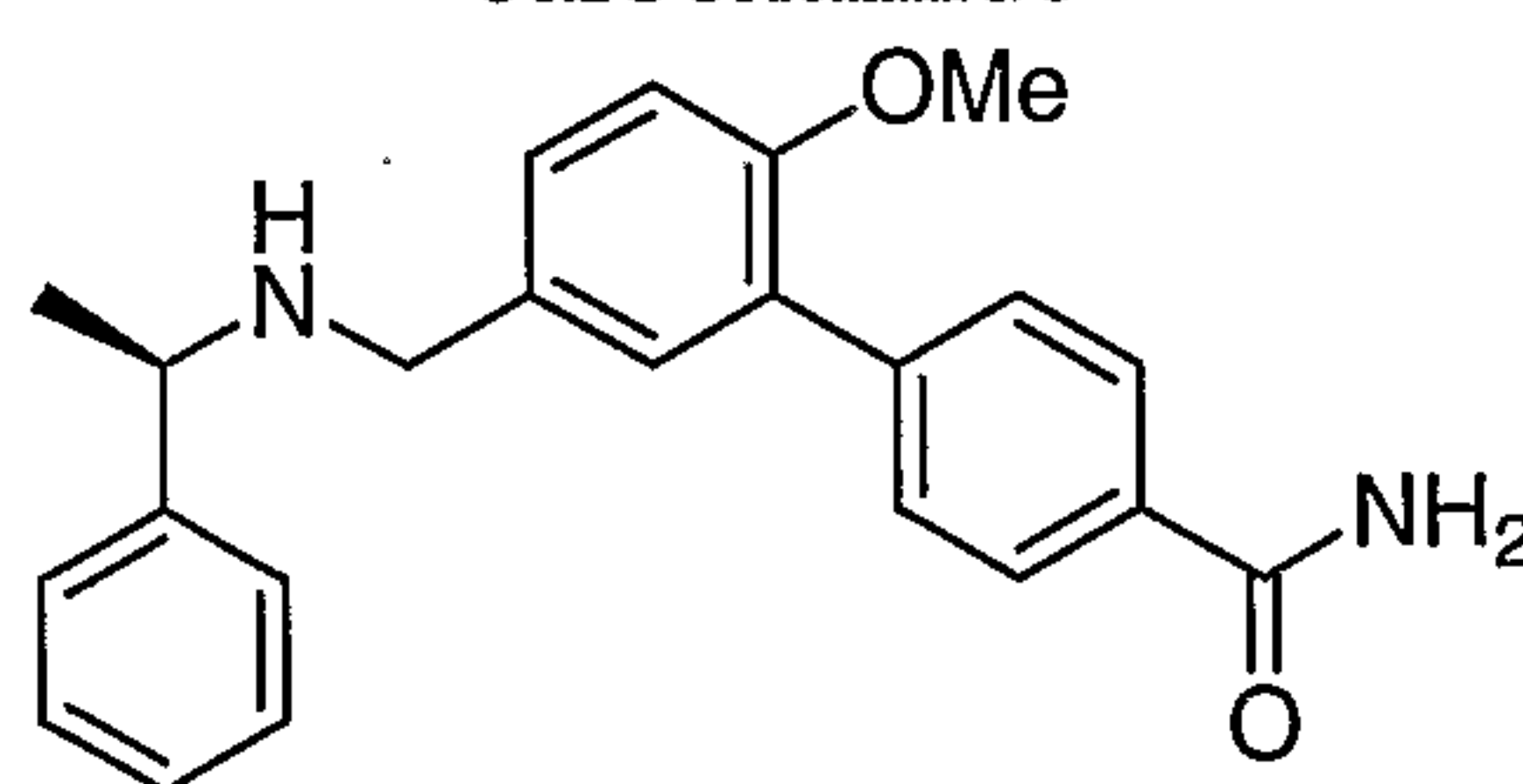
MW 322.406
Mass found: 323, 645

15

Example 308

2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide

20



MW 360.455
Mass found: 835, 361

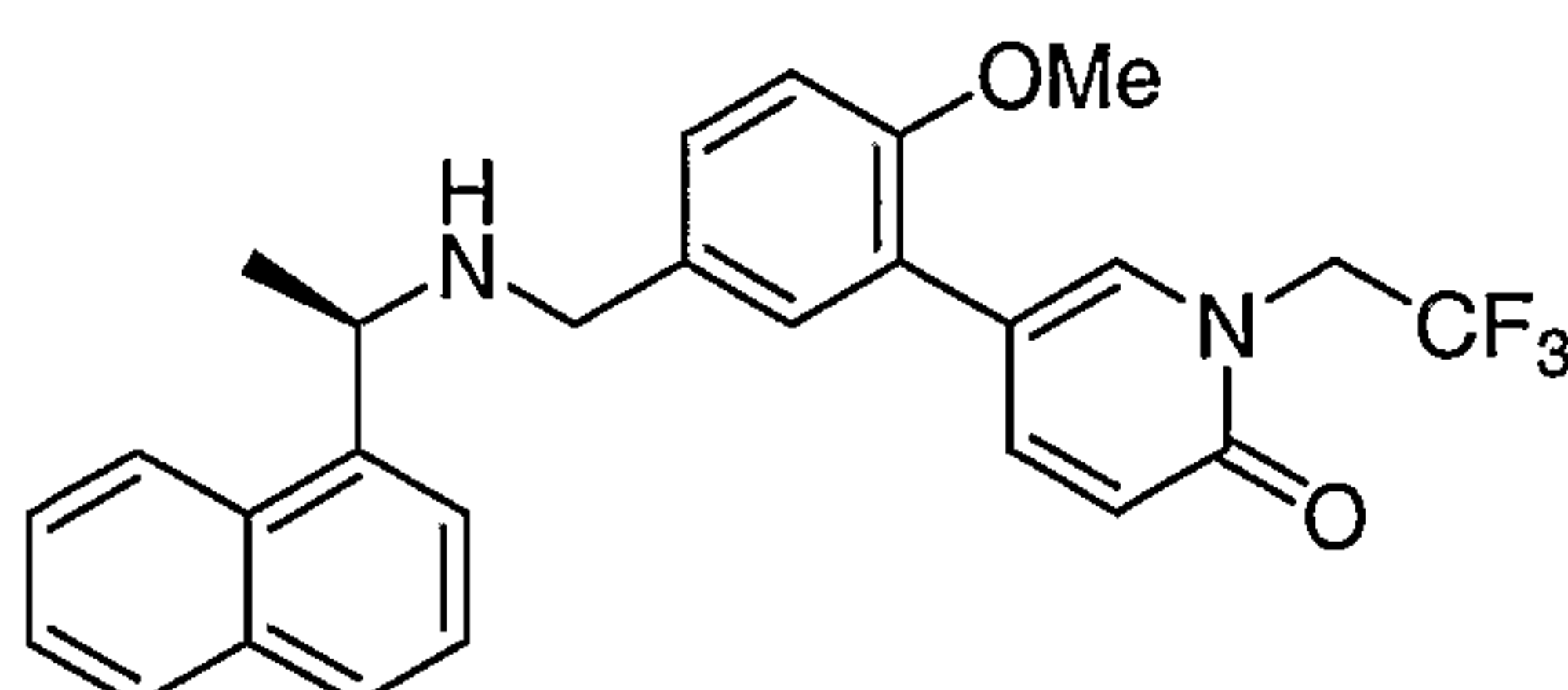
25

Example 309

5-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-1-(2,2,2-trifluoroethyl)-2(1H)-pyridinone

30

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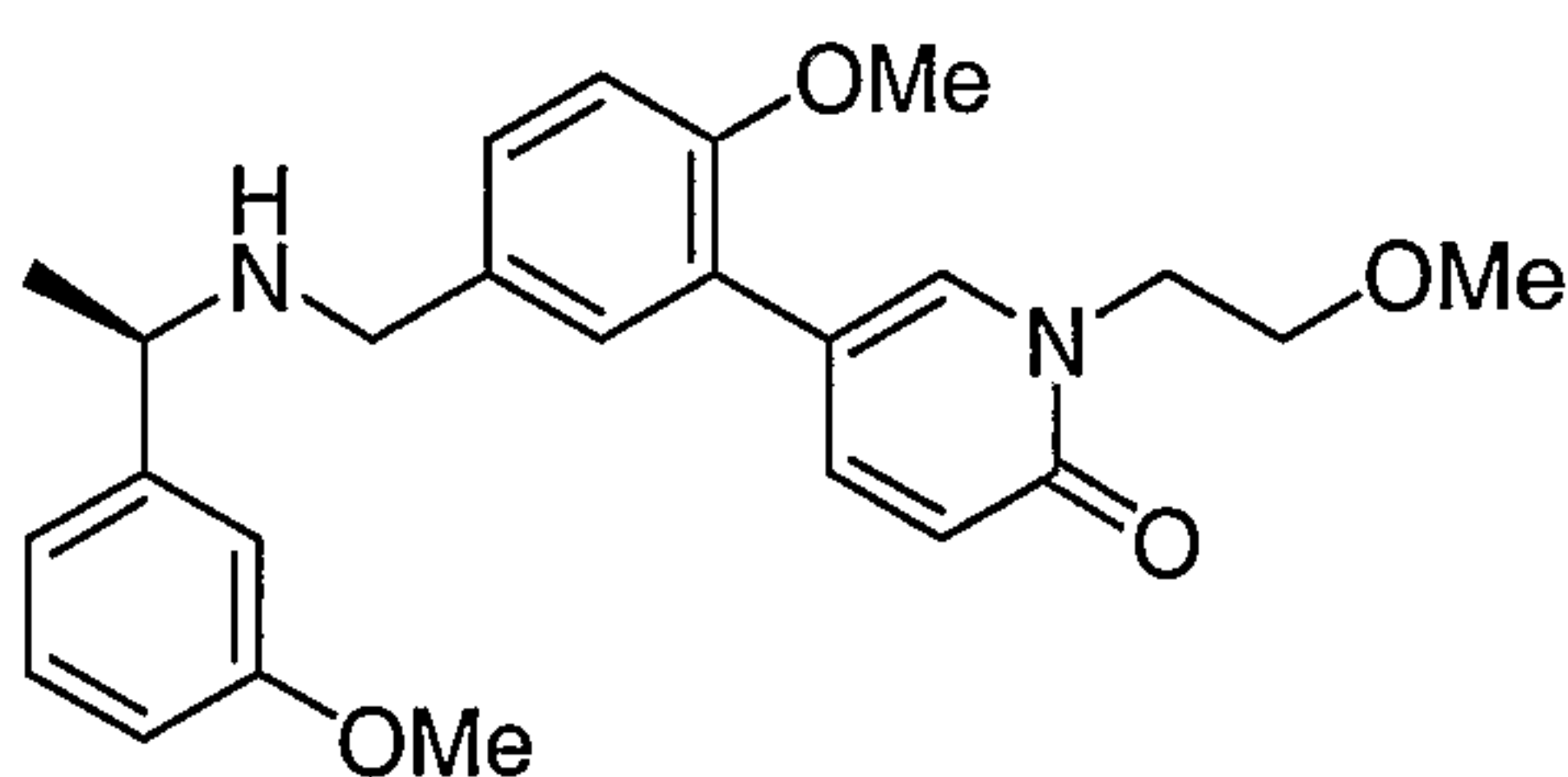


MW 466.5
Mass found: 155, 296, 467

5

Example 310

10 1-(2-(methyloxy)ethyl)-5-(2-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2(1H)-pyridinone

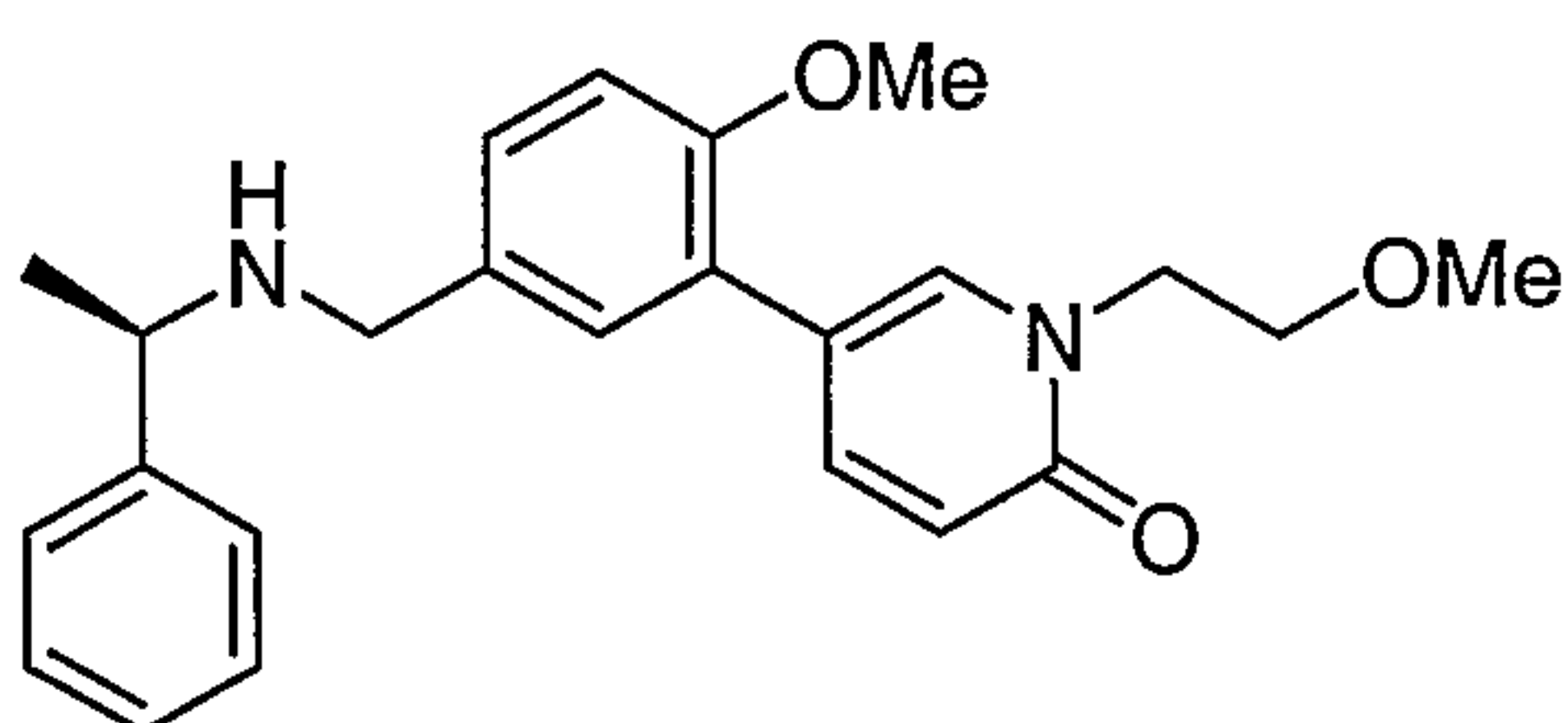


MW 422.522
Mass found: 272, 423, 290

15

Example 311

20 1-(2-(methyloxy)ethyl)-5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2(1H)-pyridinone



MW 392.496
Mass found: 272, 393

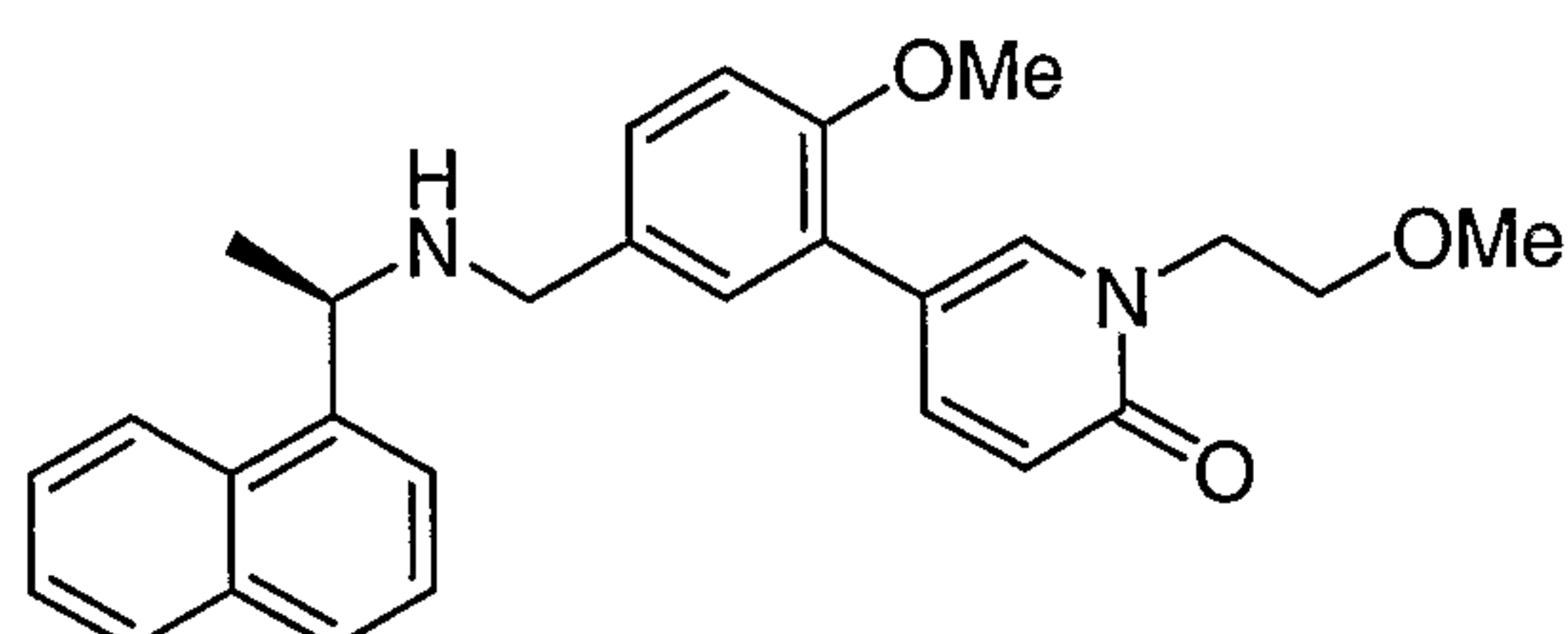
25

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Example 312

1-(2-(methyloxy)ethyl)-5-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-2(1H)-pyridinone

5



MW 442.556

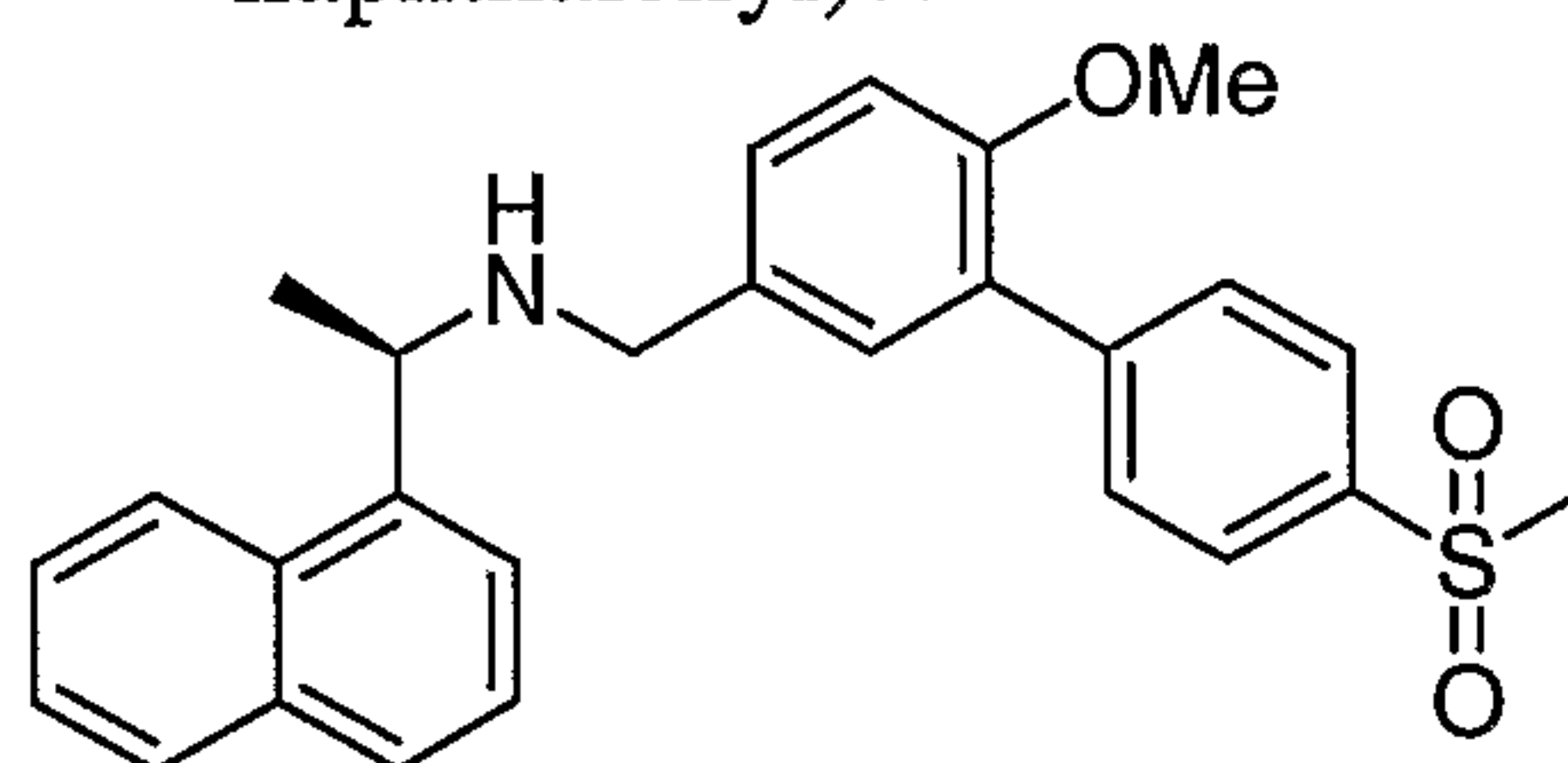
Mass found: 289, 272, 443

10

Example 313

(1R)-N-((6-(methyloxy)-4'-(methylsulfonyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine

15



MW 445.58

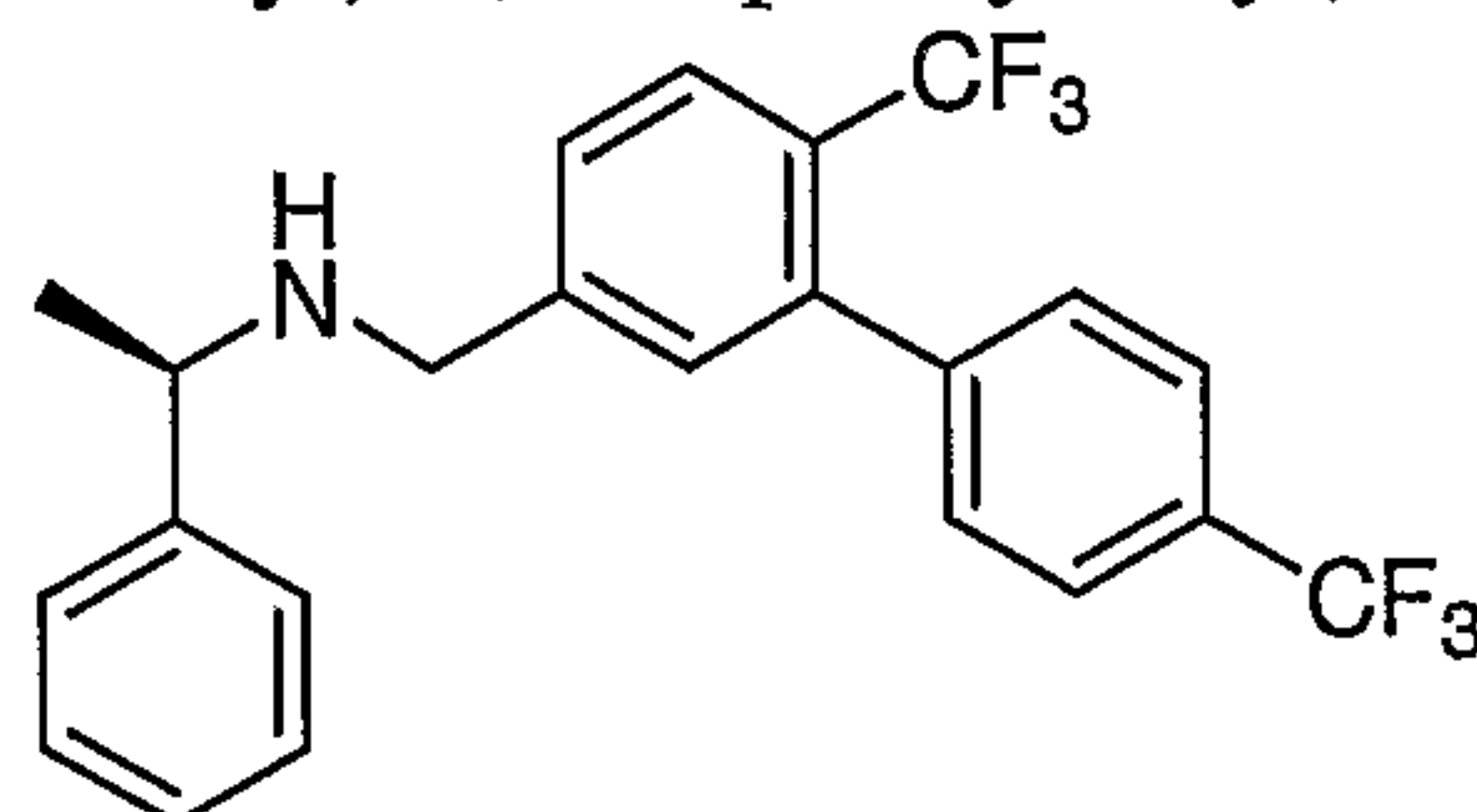
Mass found: 155, 446, 275

20

Example 314

(1R)-N-((4',6-bis(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

25



MW 423.398

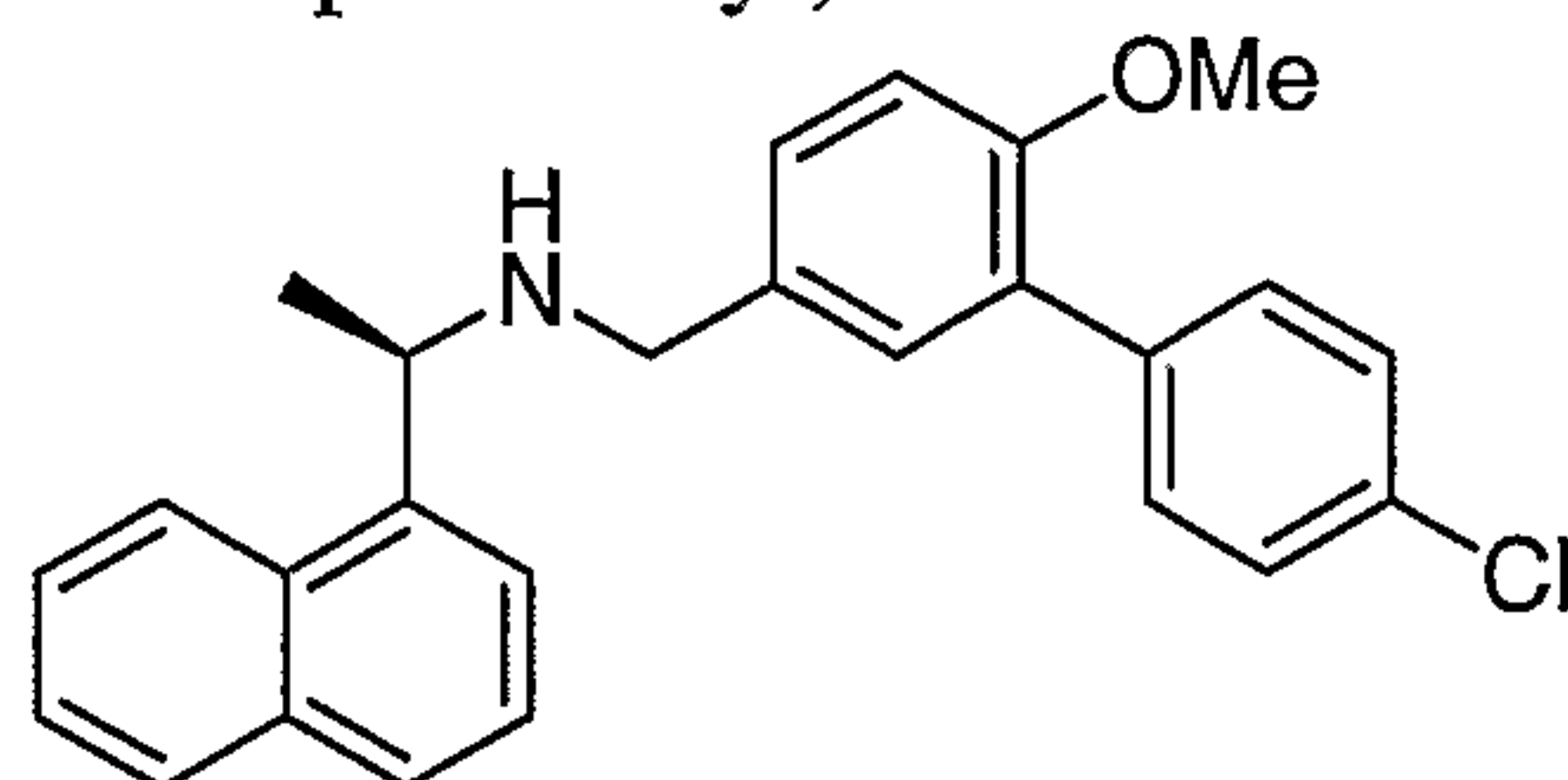
Mass found: 424, 361

30

Example 315

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(1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine



5

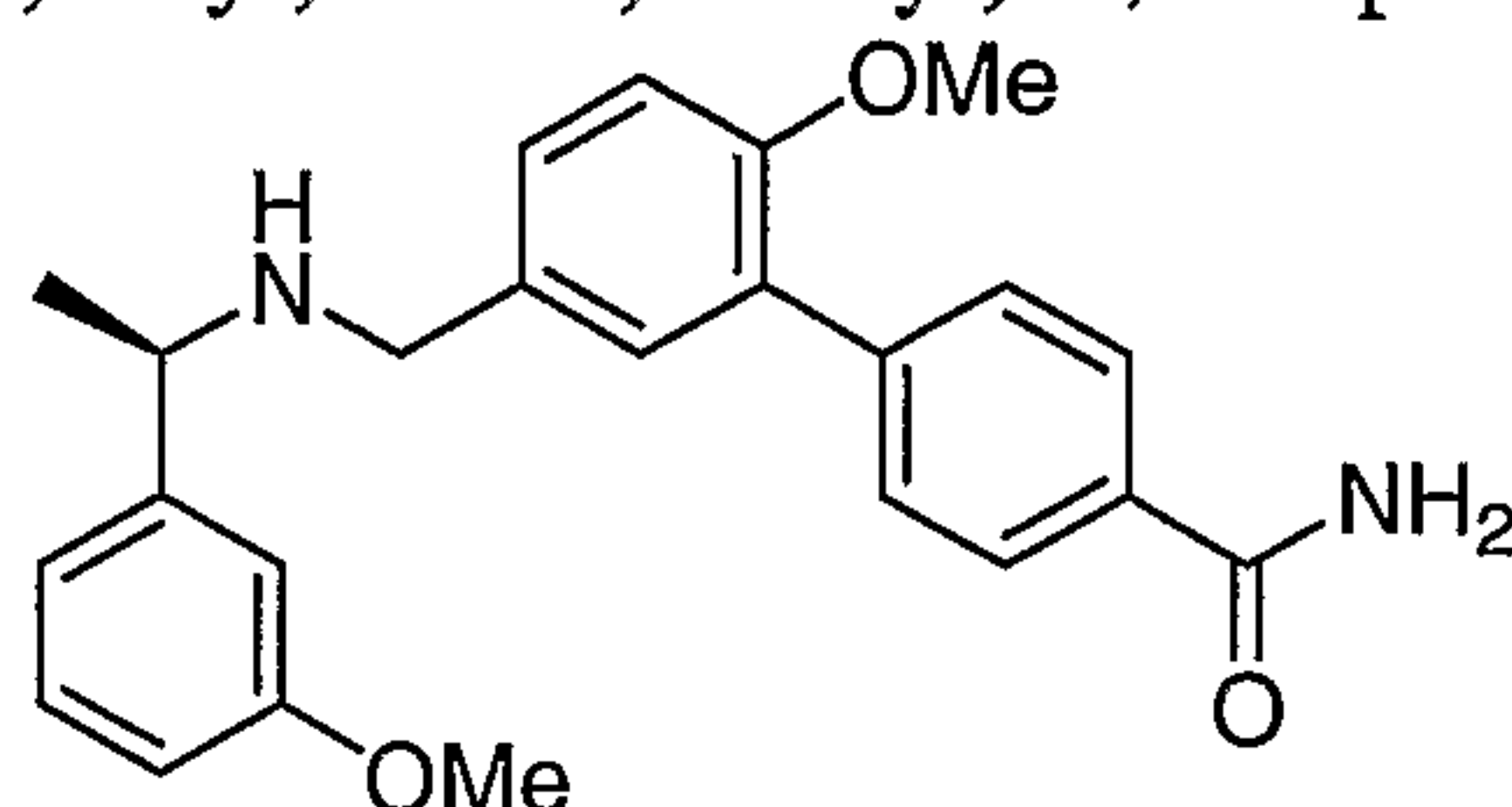
MW 401.935

Mass found: 155, 231, 402

Example 316

10

N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide



15

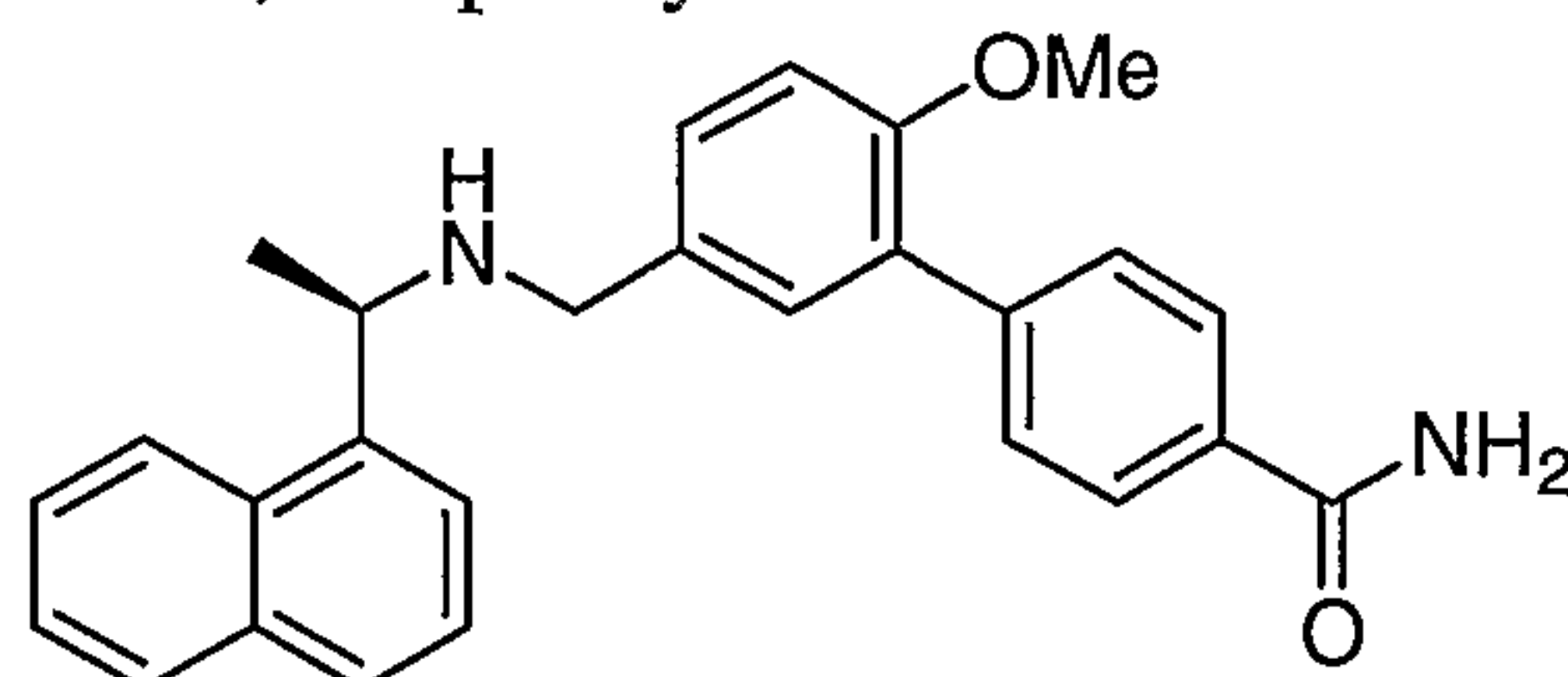
MW 418.534

Mass found: 286, 268, 441, 419

Example 317

20

N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide



25

MW 438.568

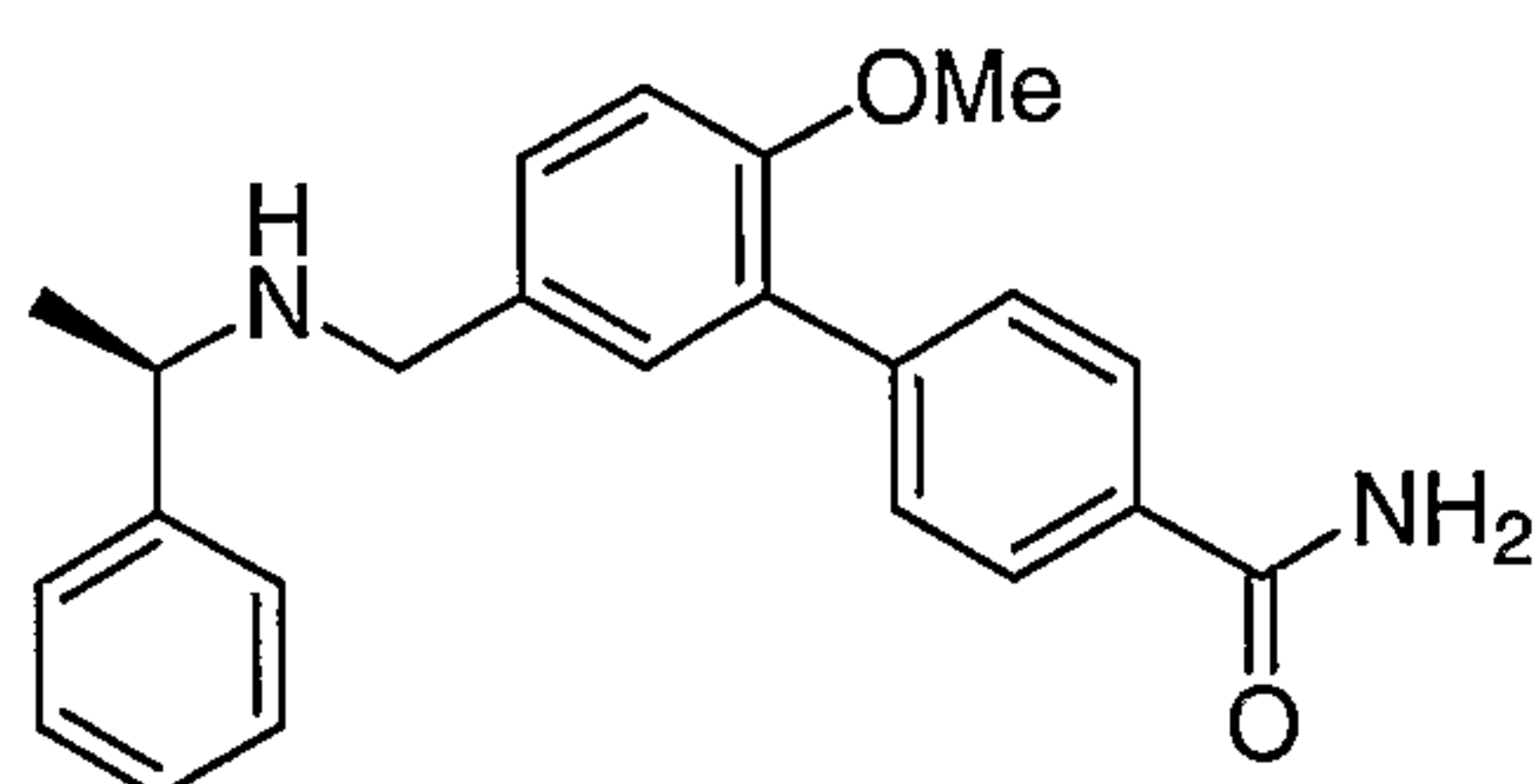
Mass found: 268, 155, 461, 439

Example 318

30

N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide

- 200 -



MW 388.508

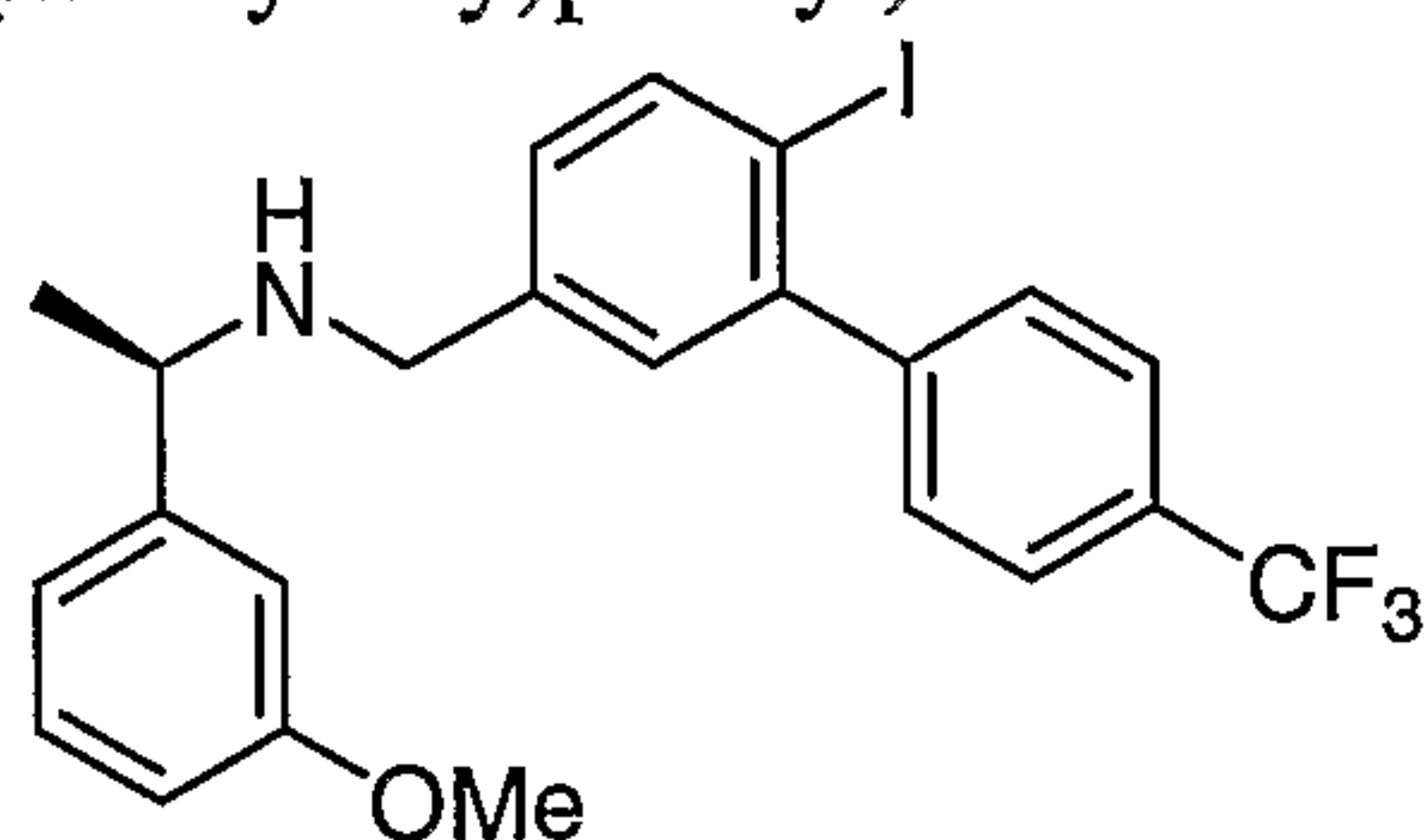
Mass found: 286, 268, 389, 411

5

Example 319

(1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methoxy)phenyl)ethanamine

10



MW 511.319

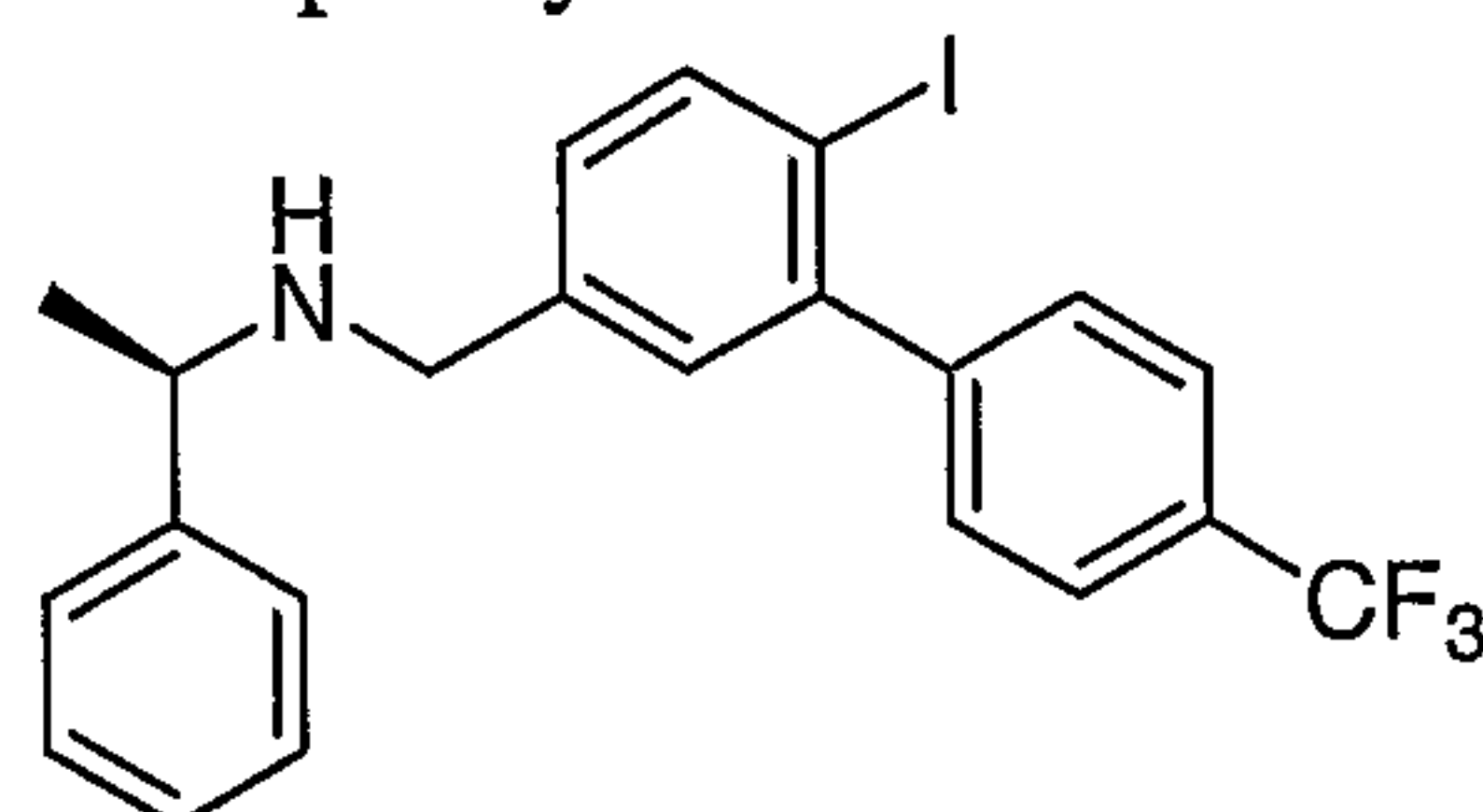
Mass found: 512, 402, 361

15

Example 320

(1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethylamine

20



MW 481.293

Mass found: 482, 523

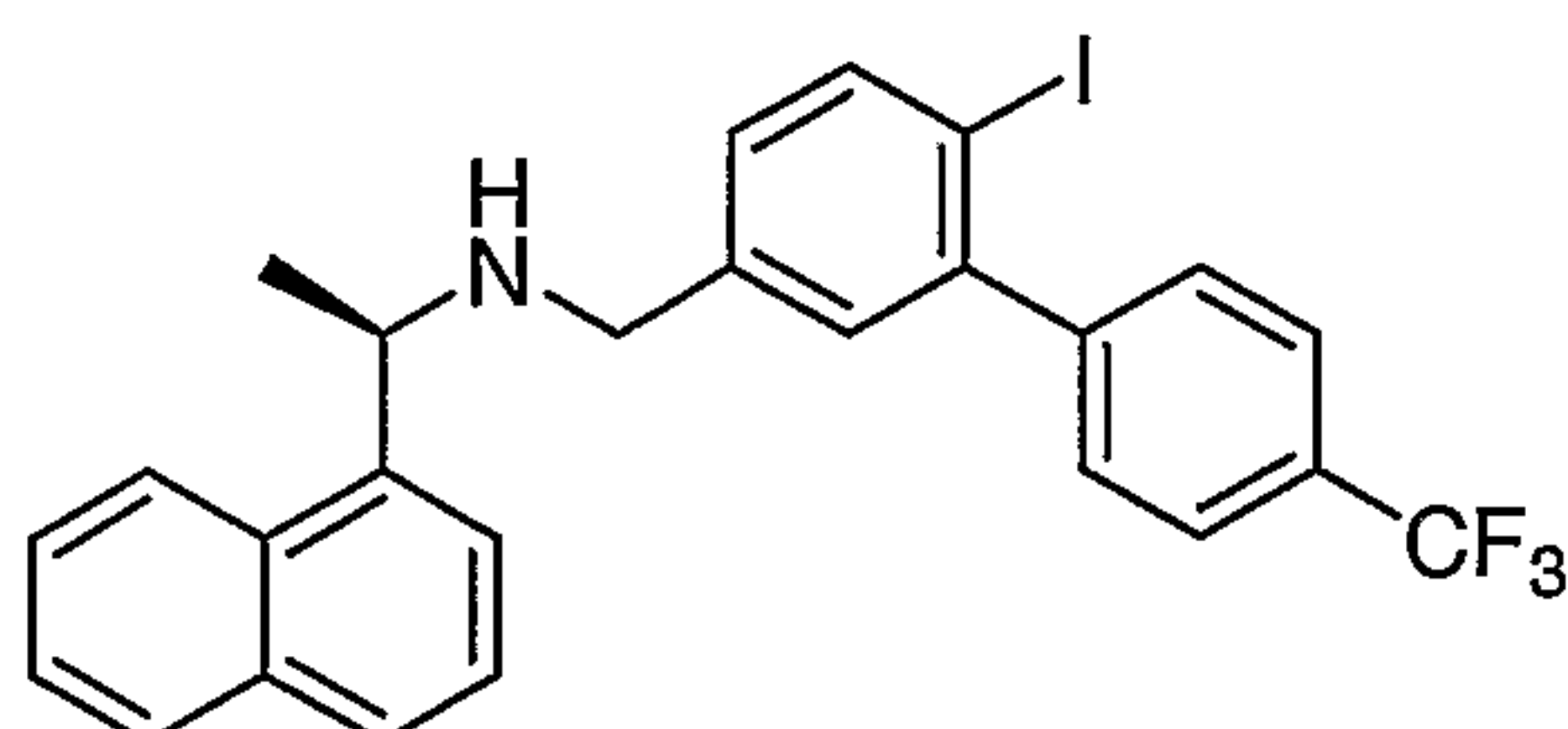
25

Example 321

(1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine

30

- 201 -

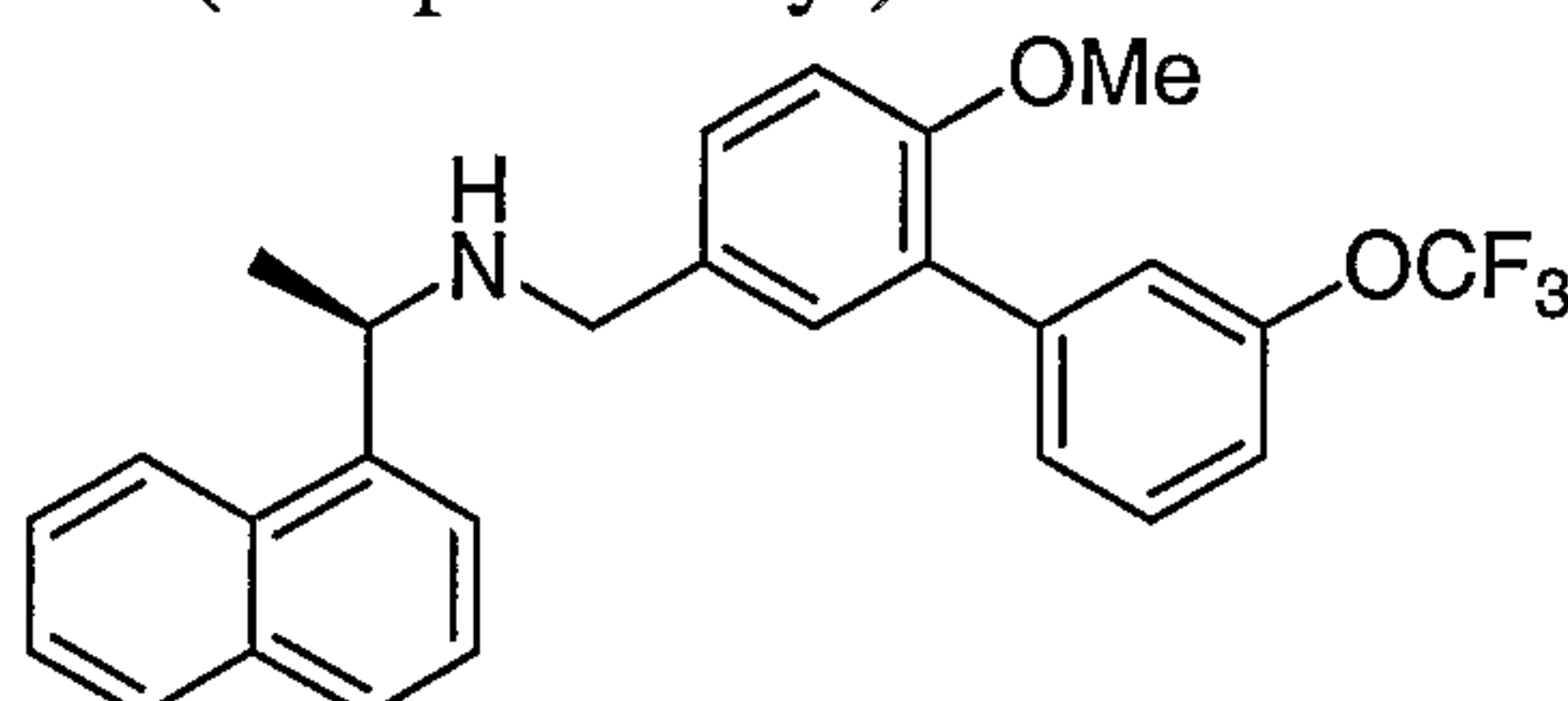


MW 531.353
Mass found: 155, 532

5

Example 322

10 (1R)-N-((6-(methoxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine

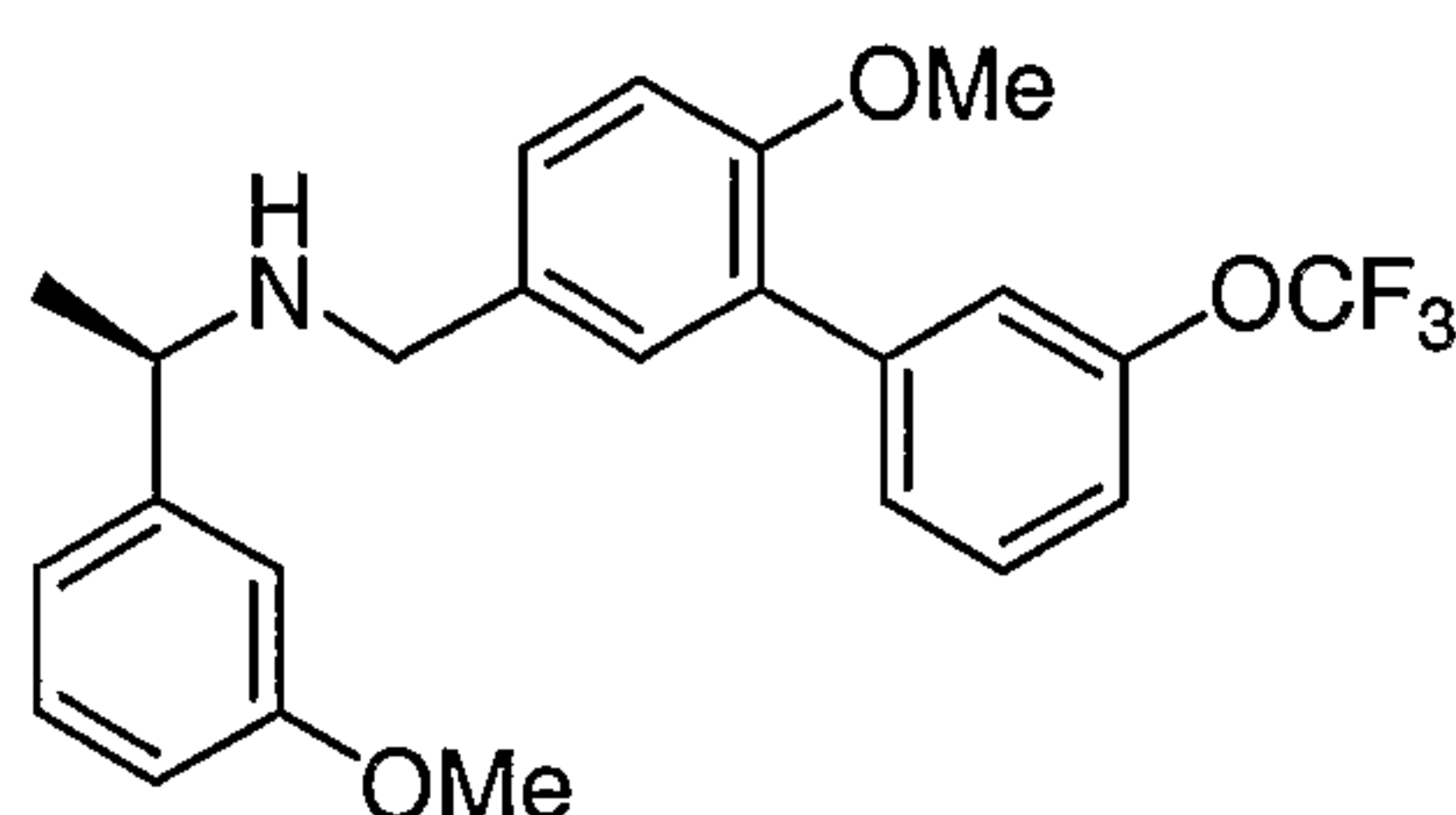


MW 451.486
Mass found: 155, 452, 281

15

Example 323

20 (1R)-1-(3-(methoxy)phenyl)-N-((6-(methoxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)ethanamine



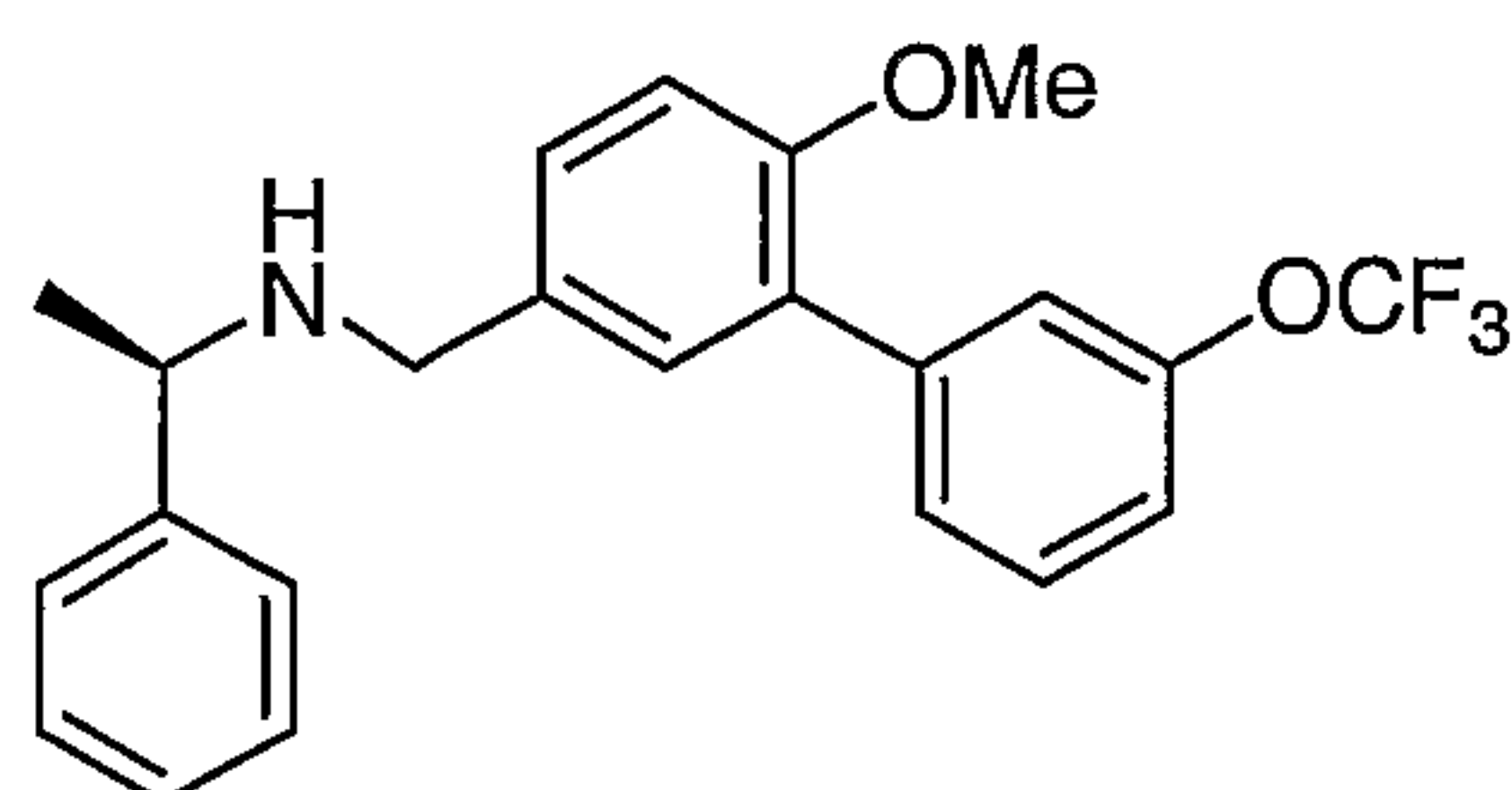
MW 431.452
Mass found: 432, 281

25

Example 324

30 (1R)-N-((6-(methoxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

- 202 -



MW 401.426

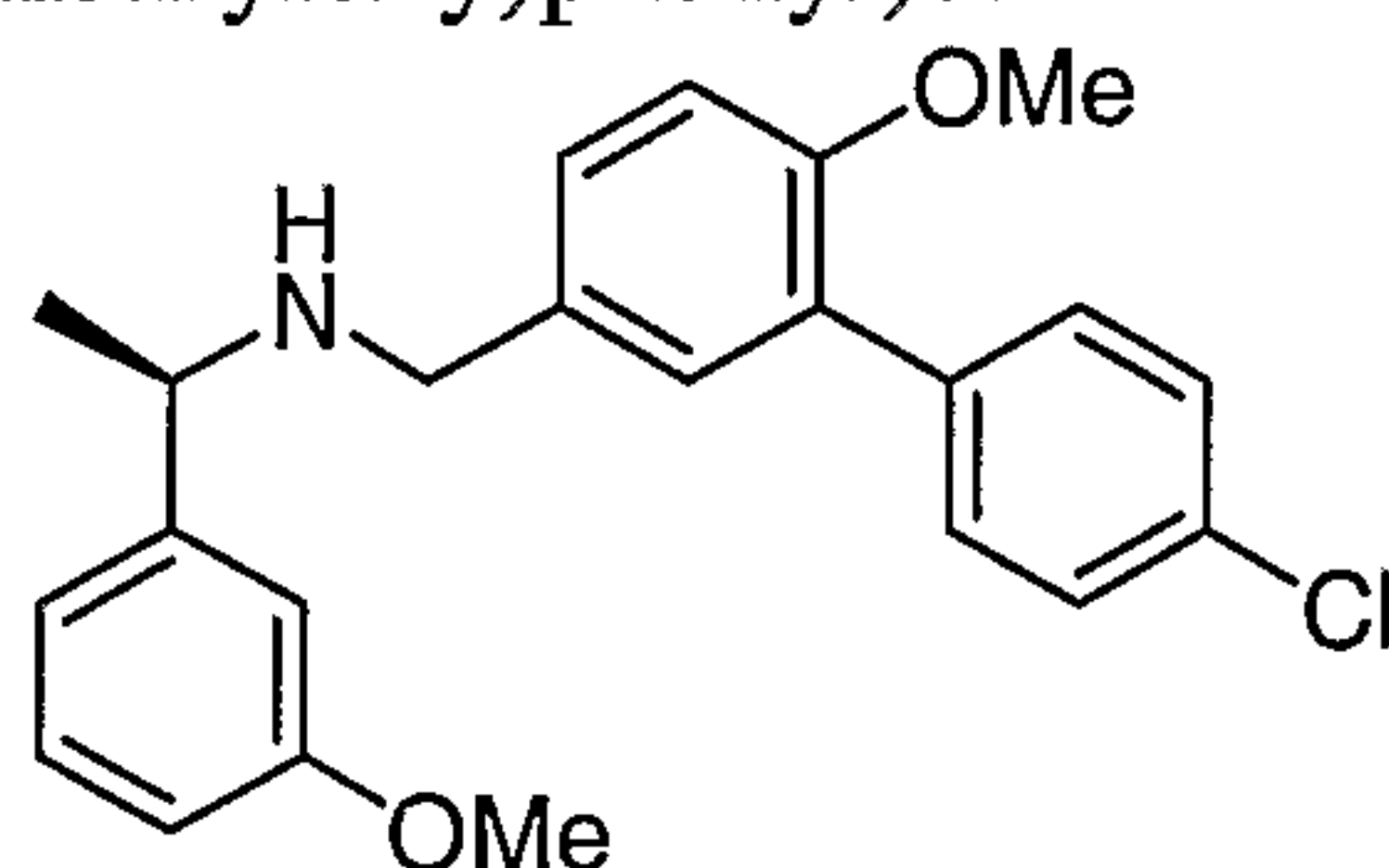
Mass found: 281, 402

5

Example 325

(1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

10



MW 381.901

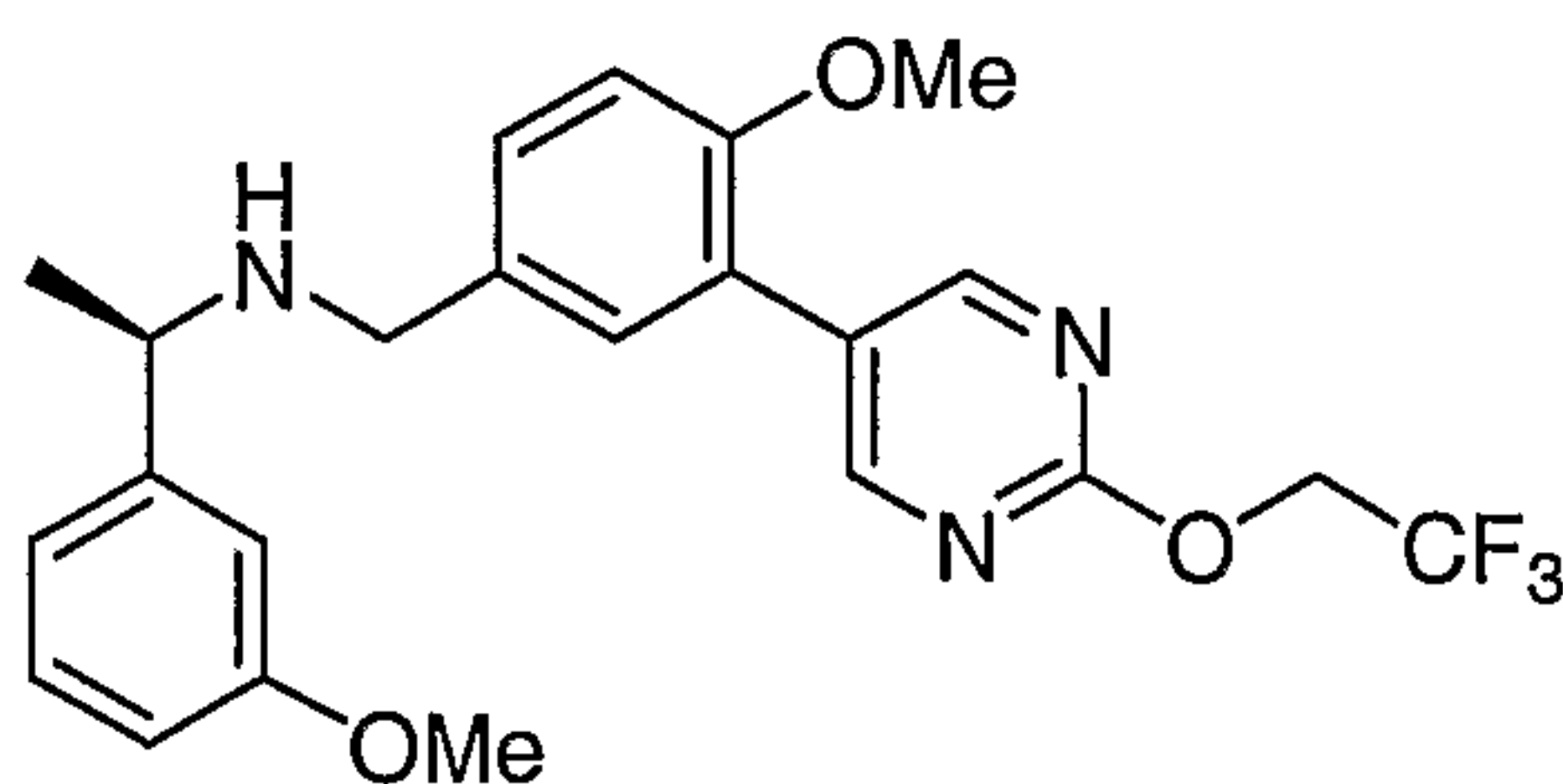
Mass found: 231, 382

15

Example 326

(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-5-pyrimidinyl)phenyl)methyl)ethanamine

20



MW 447.455

Mass found: 448

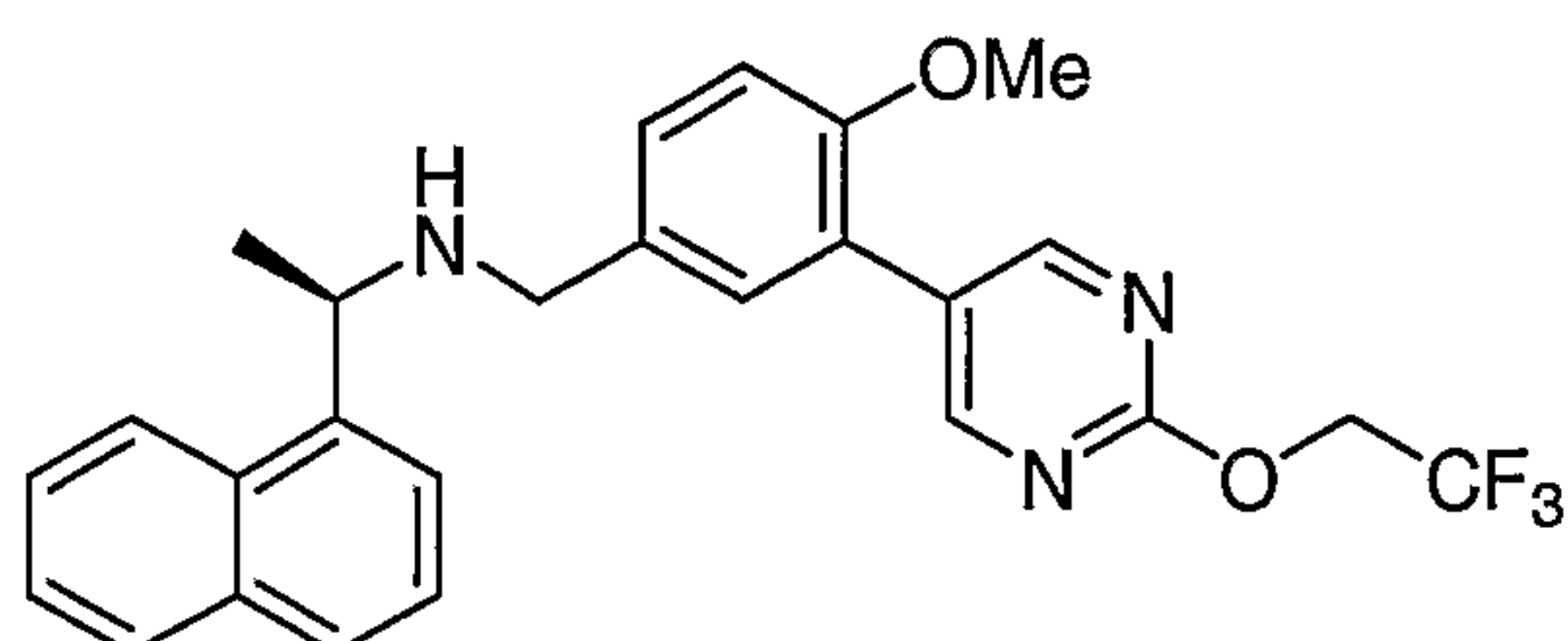
25

Example 327

(1R)-N-((4-(methyloxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-5-pyrimidinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

30

- 203 -



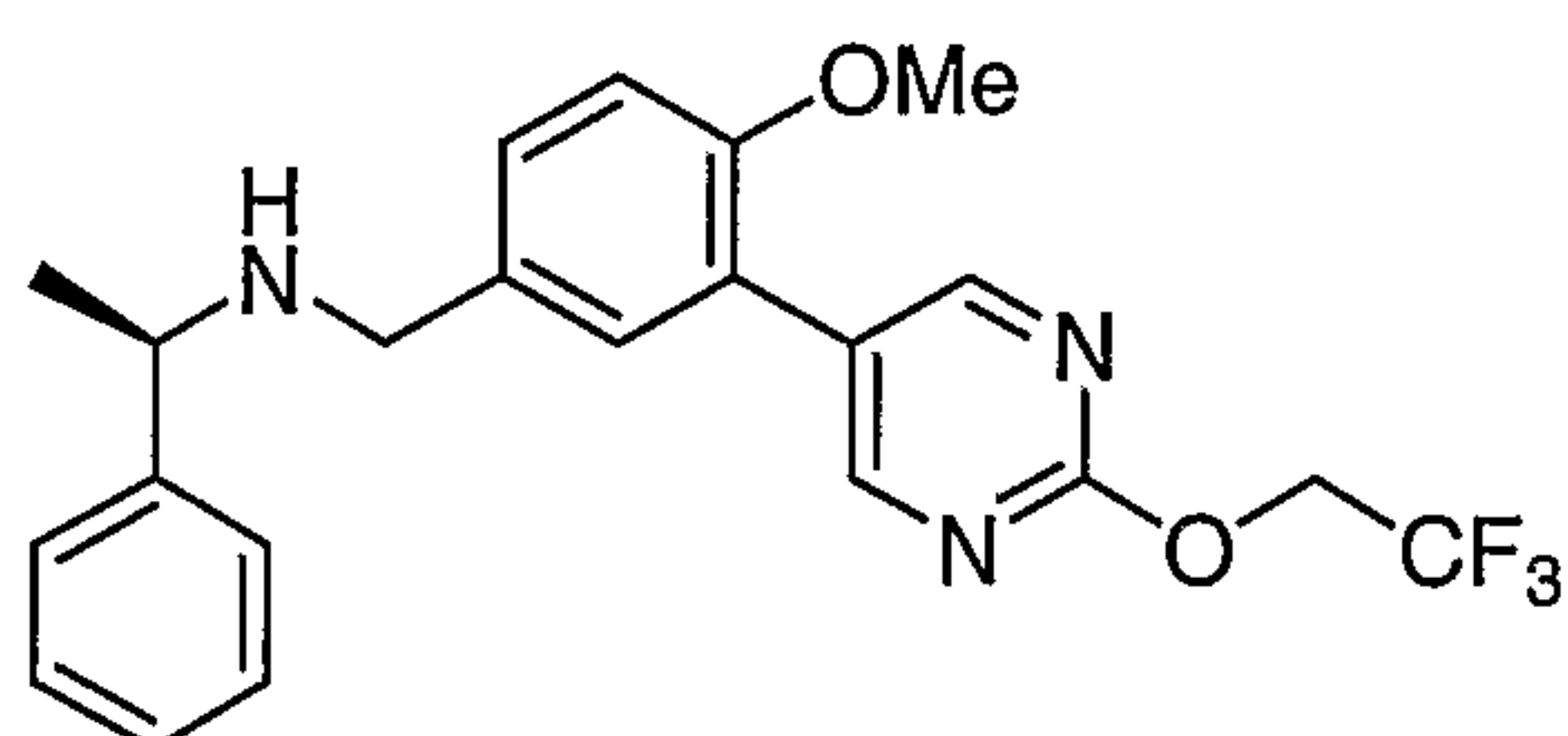
MW 467.489
Mass found: 155, 468

5

Example 328

(1R)-N-((4-(methyloxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-5-pyrimidinyl)phenyl)methyl)-1-phenylethanamine

10



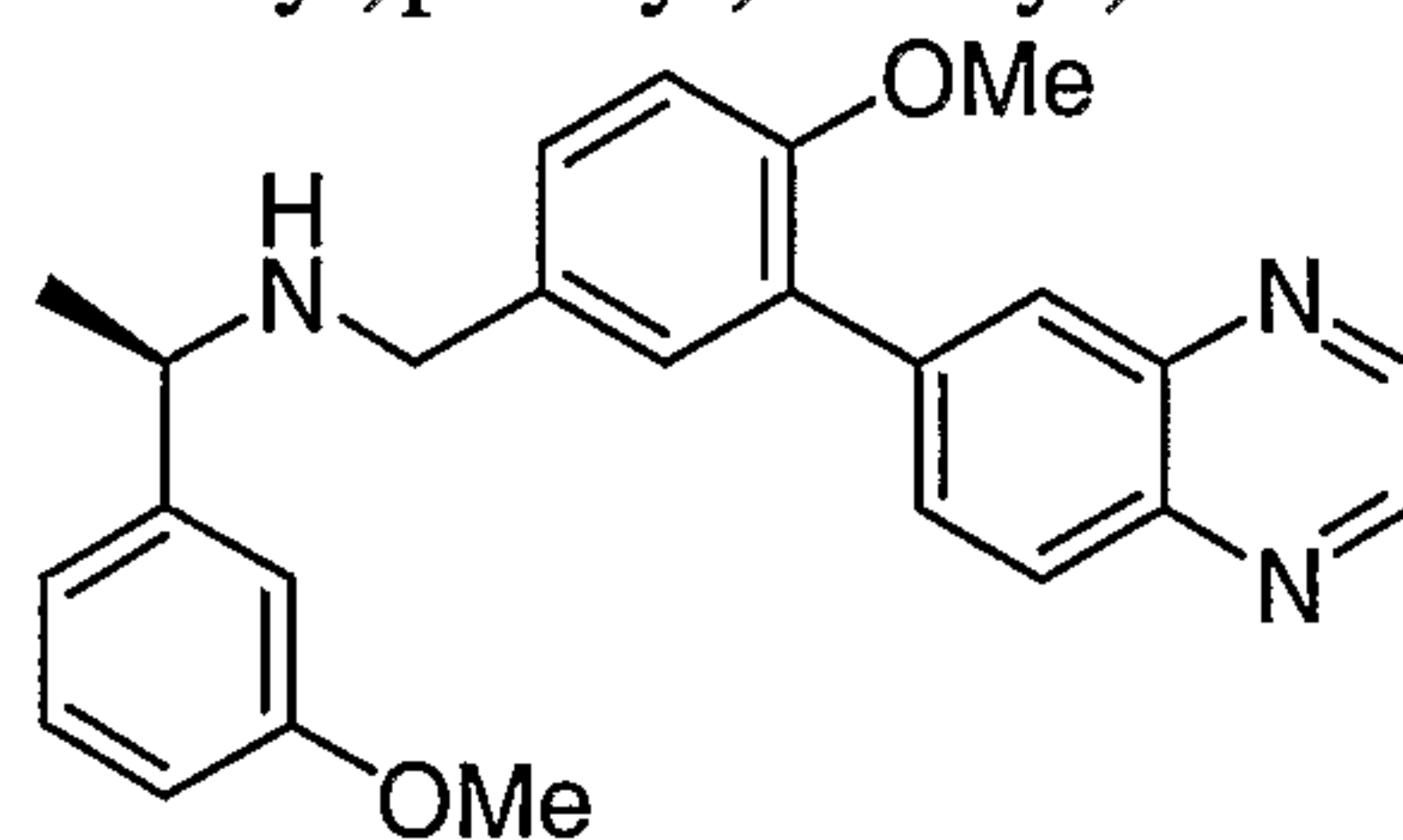
MW 417.429
Mass found: 418, 297

15

Example 329

(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-quinoxaliny)phenyl)methyl)ethanamine

20



MW 399.491
Mass found: 249, 400

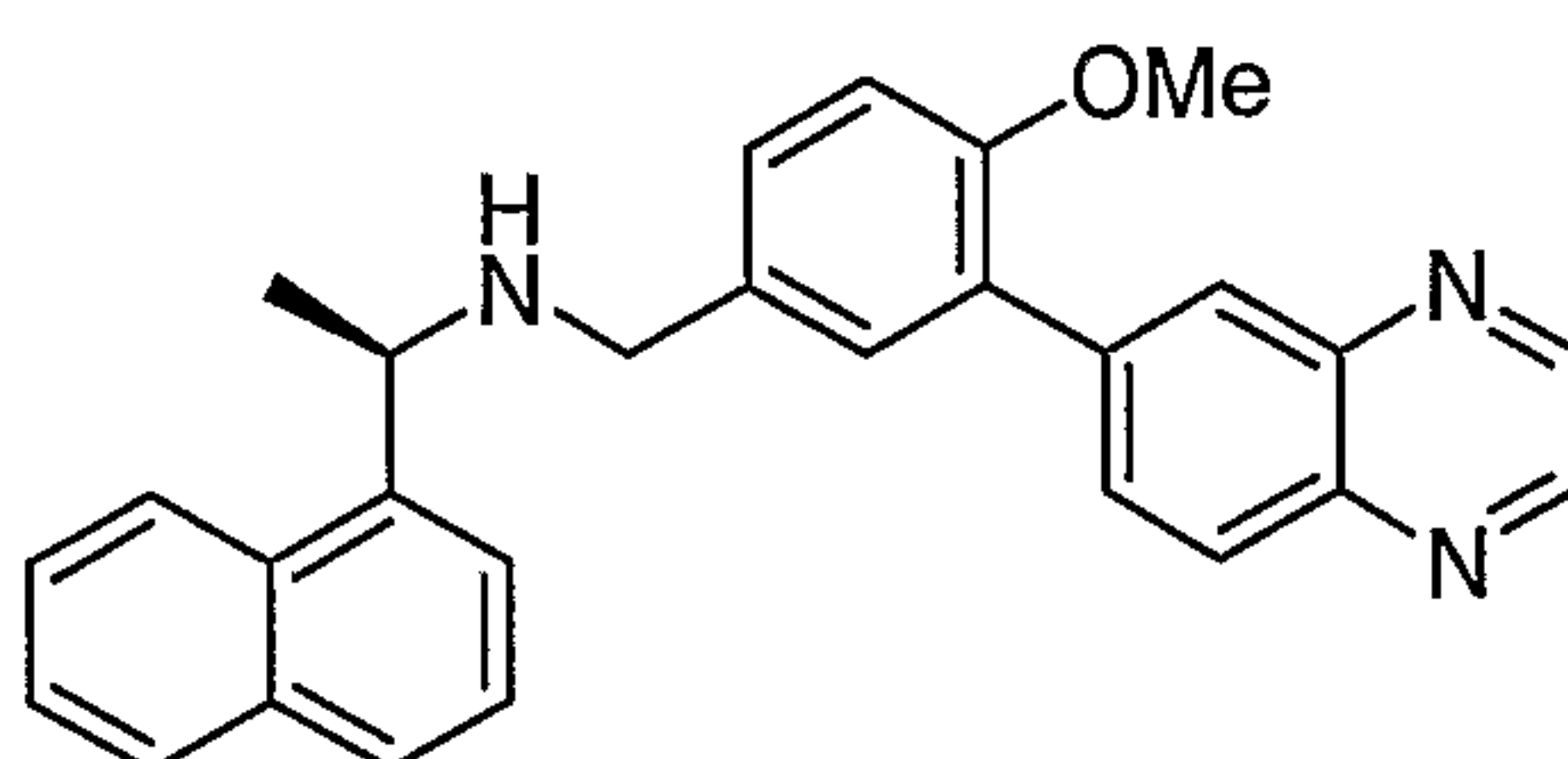
25

Example 330

(1R)-N-((4-(methyloxy)-3-(6-quinoxaliny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

30

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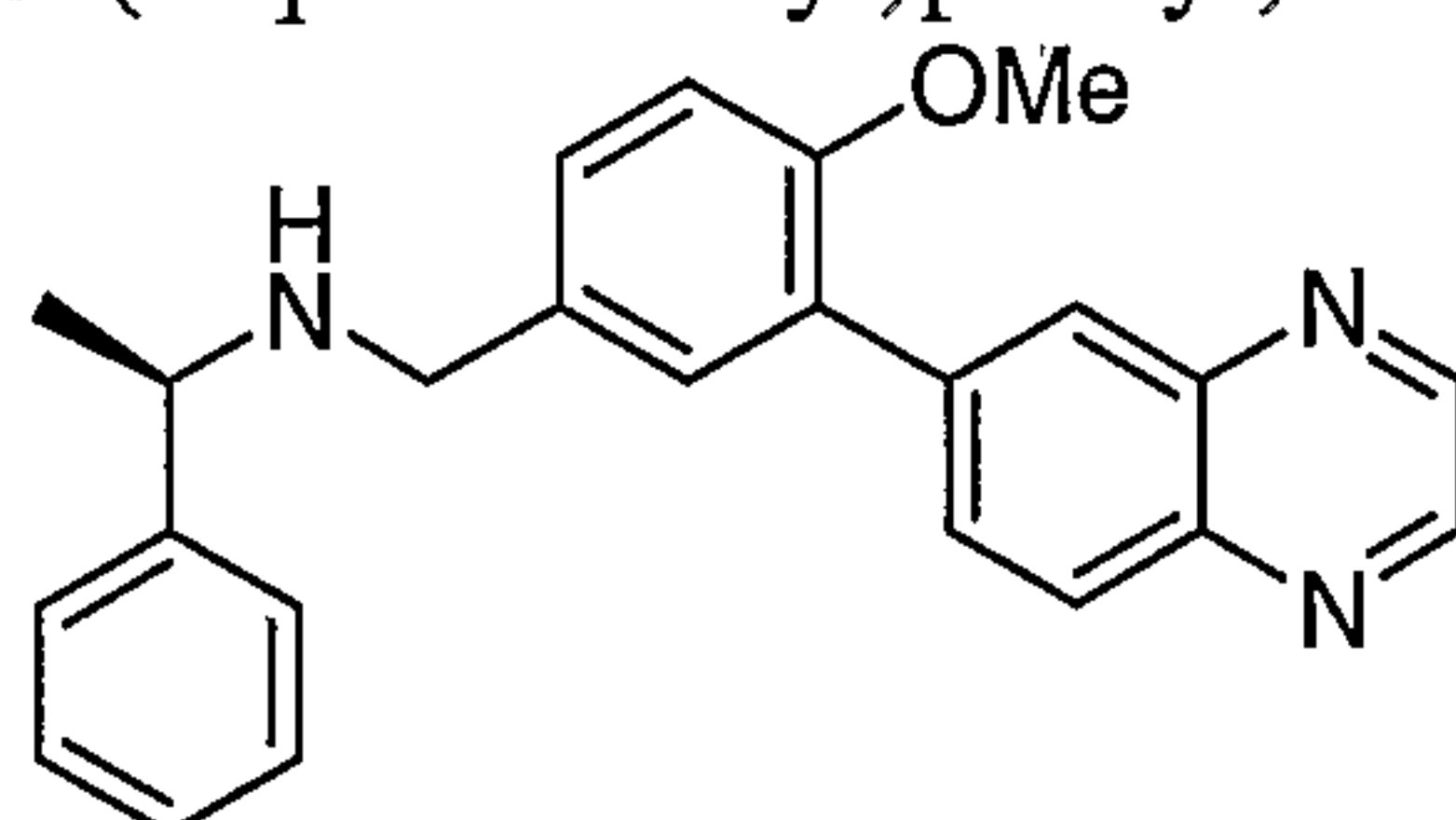


MW 419.526
Mass found: 420, 249, 155

5

Example 331

(1R)-N-((4-(methoxy)-3-(6-quinoxaliny)phenyl)methyl)-1-phenylethylamine



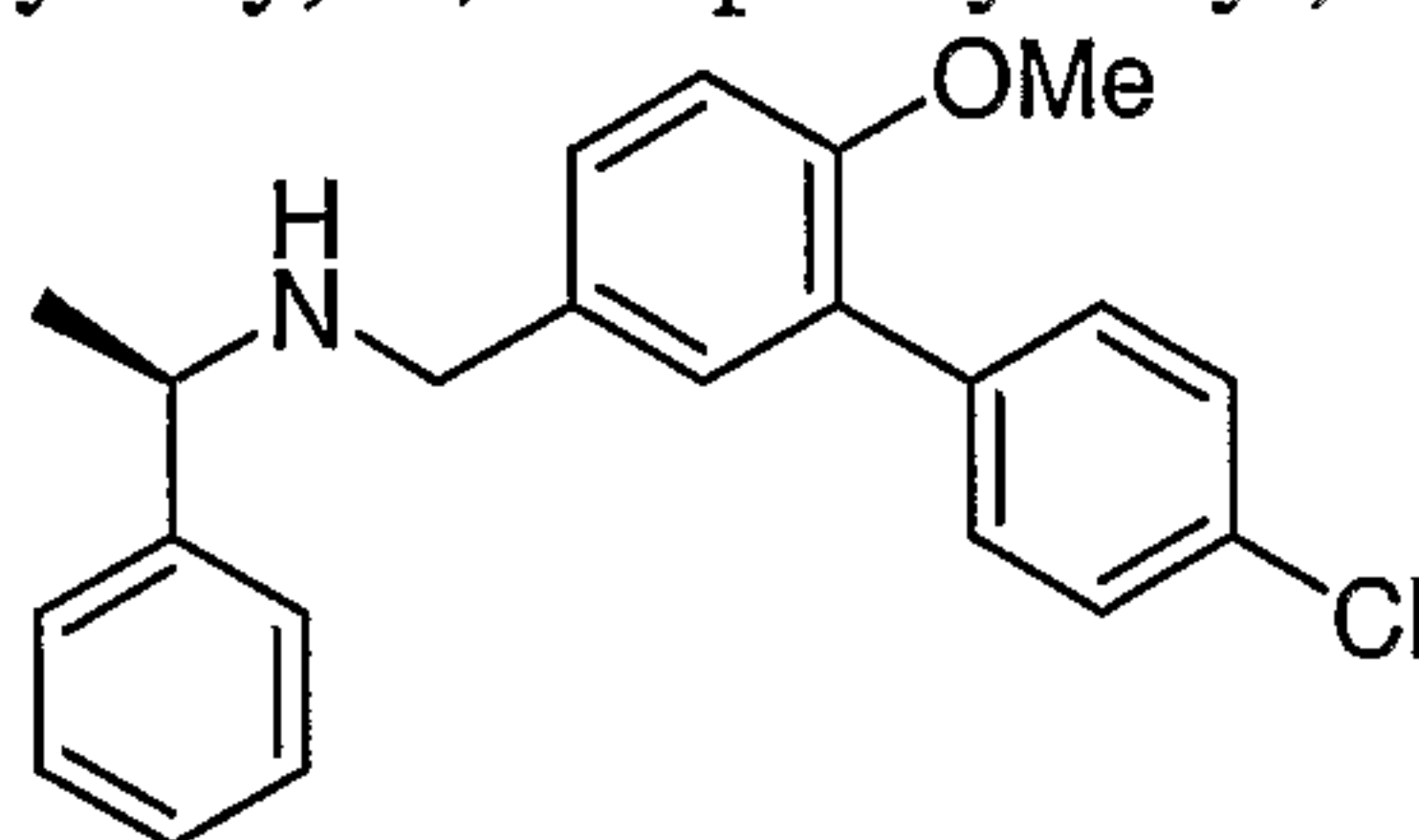
10

MW 369.466
Mass found: 370, 249

15

Example 332

(1R)-N-((4'-chloro-6-(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethylamine



20

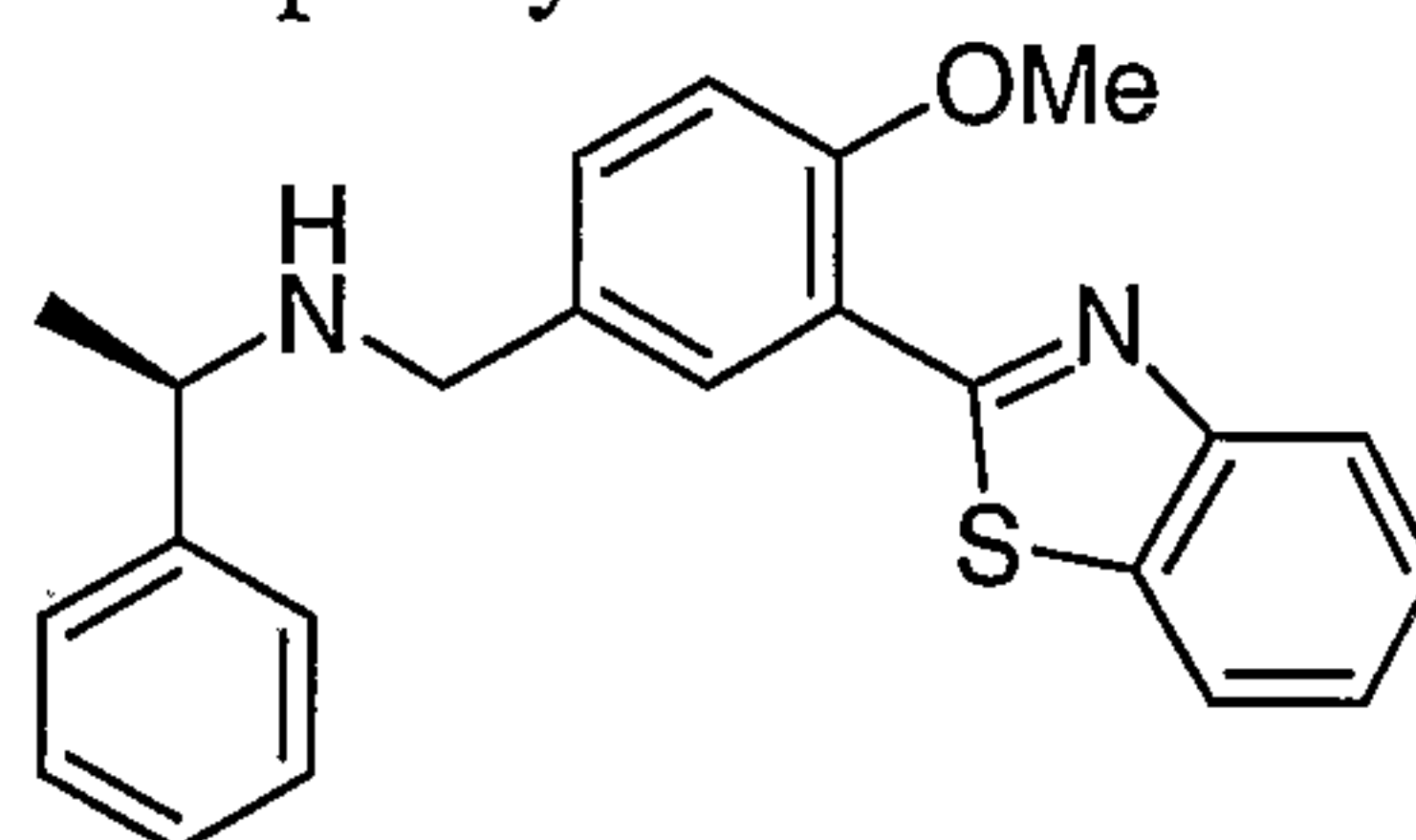
MW 351.875
Mass found: 231, 352

25

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Example 333

(1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methoxy)phenyl)methyl)-1-phenylethanamine

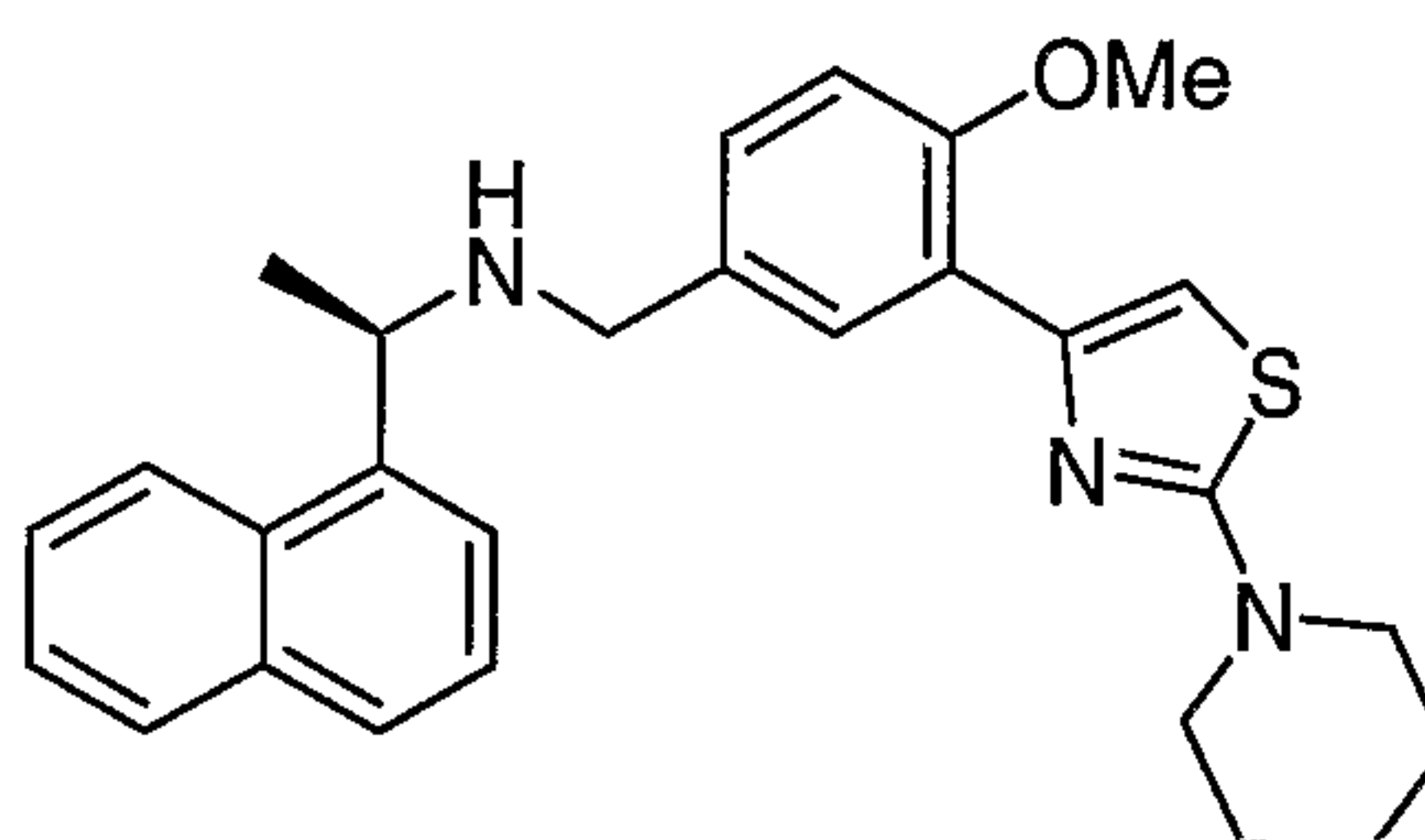


MW 374.506

Mass found: 375, 749

Example 334

(1R)-N-((4-(methoxy)-3-(2-(1-piperidiny)-1,3-thiazol-4-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

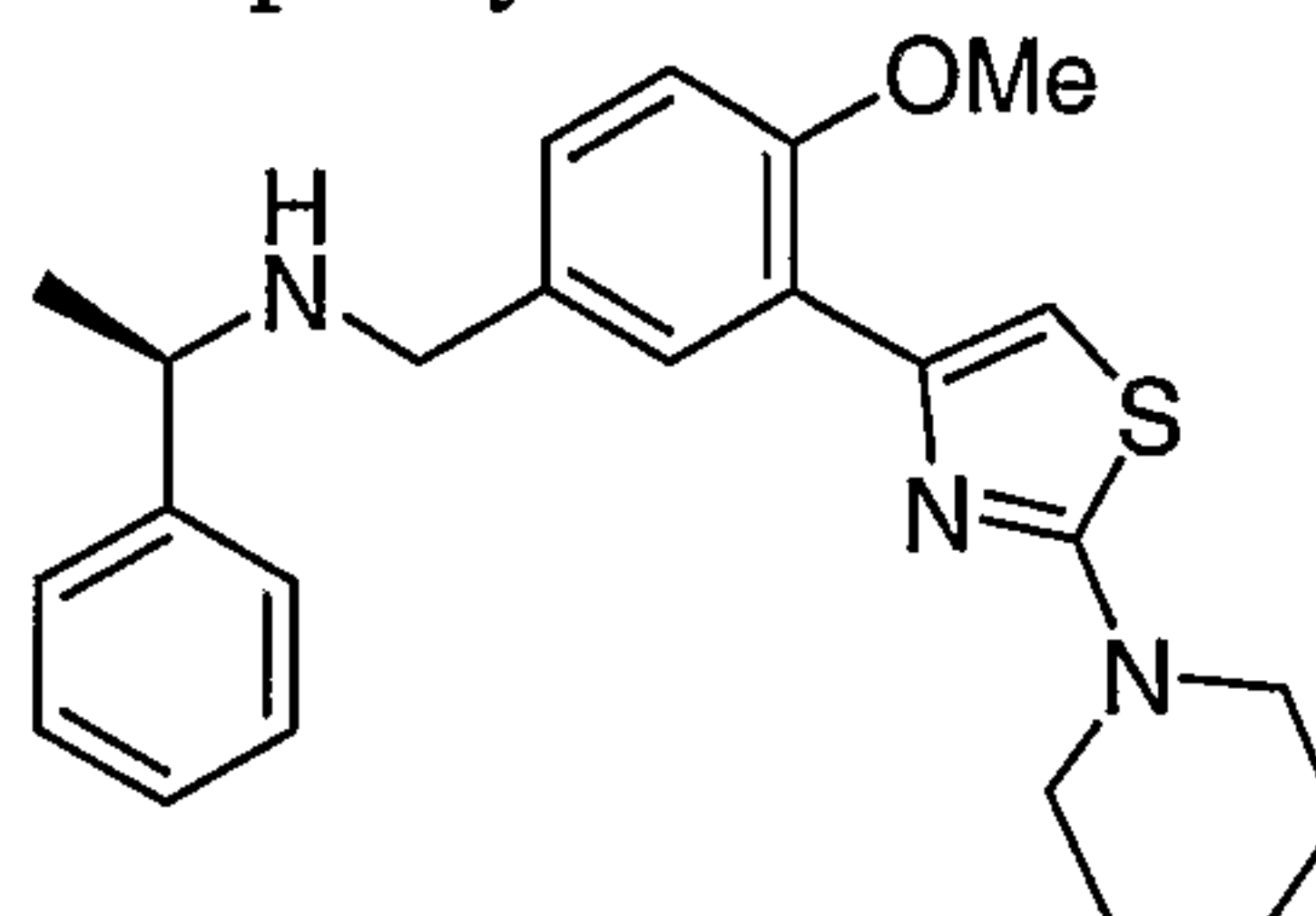


MW 457.639

Mass found: 458, 155

Example 335

(1R)-N-((4-(methoxy)-3-(2-(1-piperidiny)-1,3-thiazol-4-yl)phenyl)methyl)-1-phenylethanamine



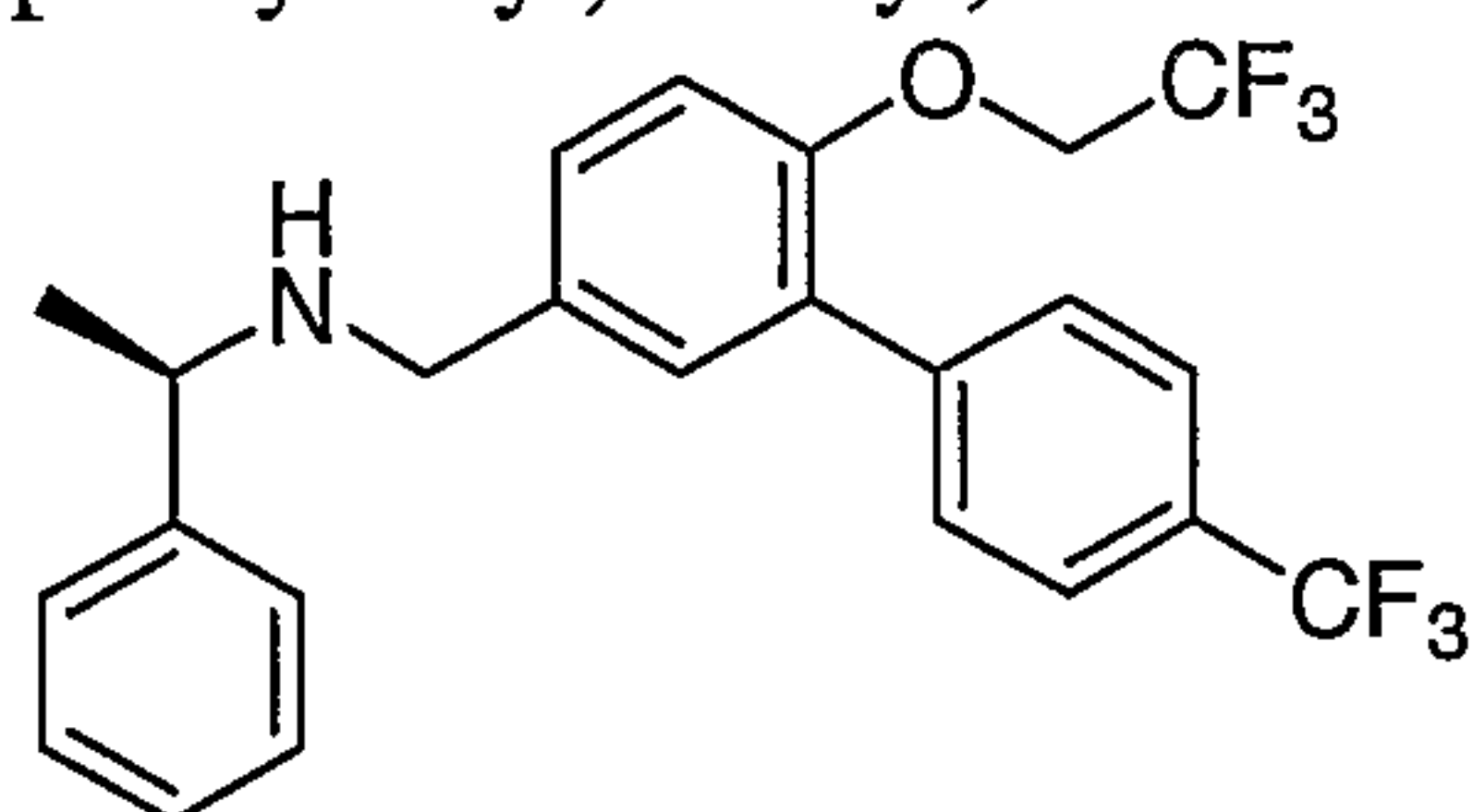
MW 407.579

Mass found: 408, 304

Example 336

- 206 -

(1R)-1-phenyl-N-((6-((2,2,2-trifluoroethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine



5

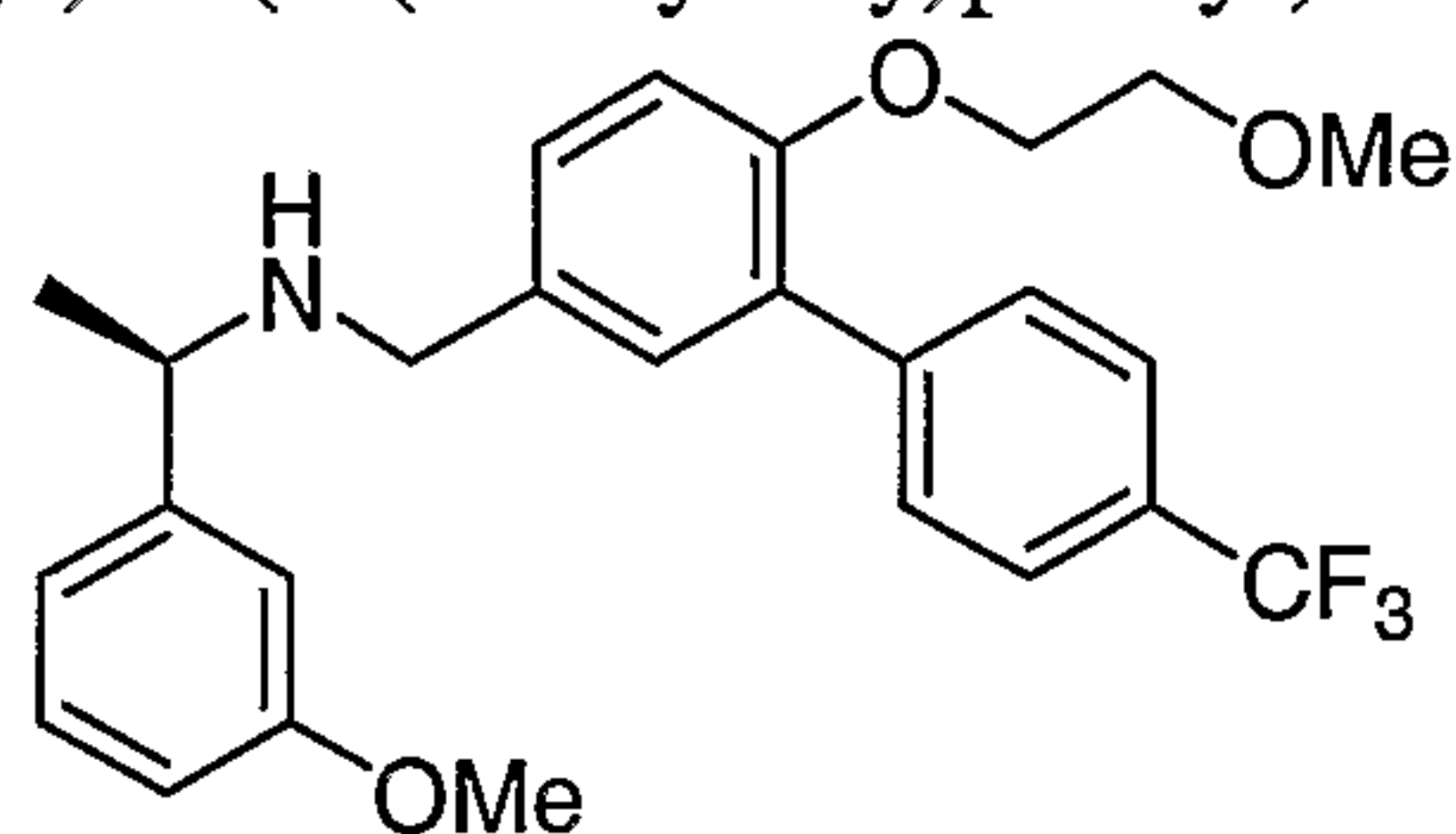
MW 453.424

Mass found: 454, 333

Example 337

10

(1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine



15

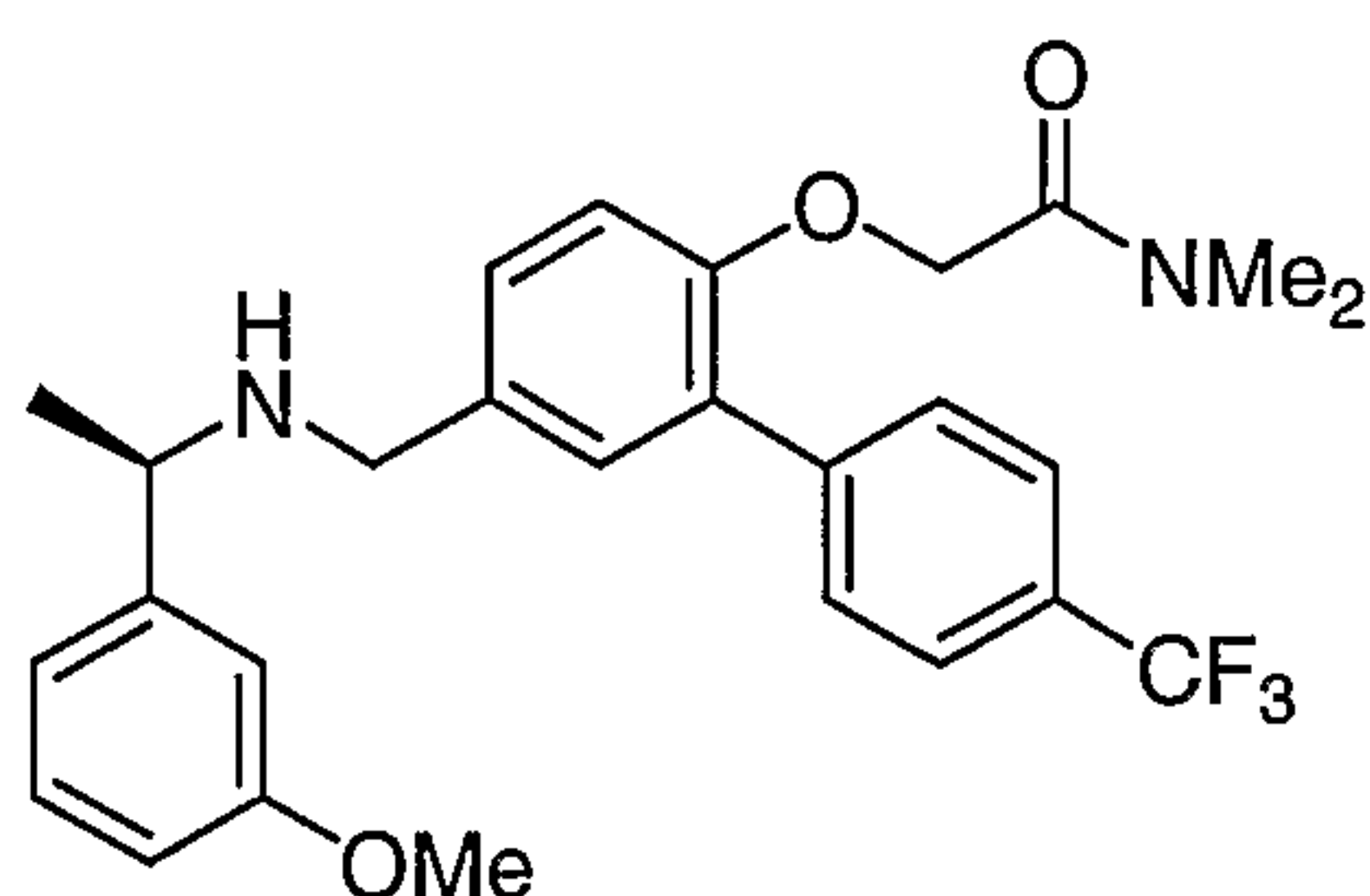
MW 459.505

Mass found: 460, 309

Example 338

20

N,N-dimethyl-2-((5-(((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-4'-(trifluoromethyl)-1,1'-biphenyl-2-yl)oxy)acetamide



25

MW 486.531

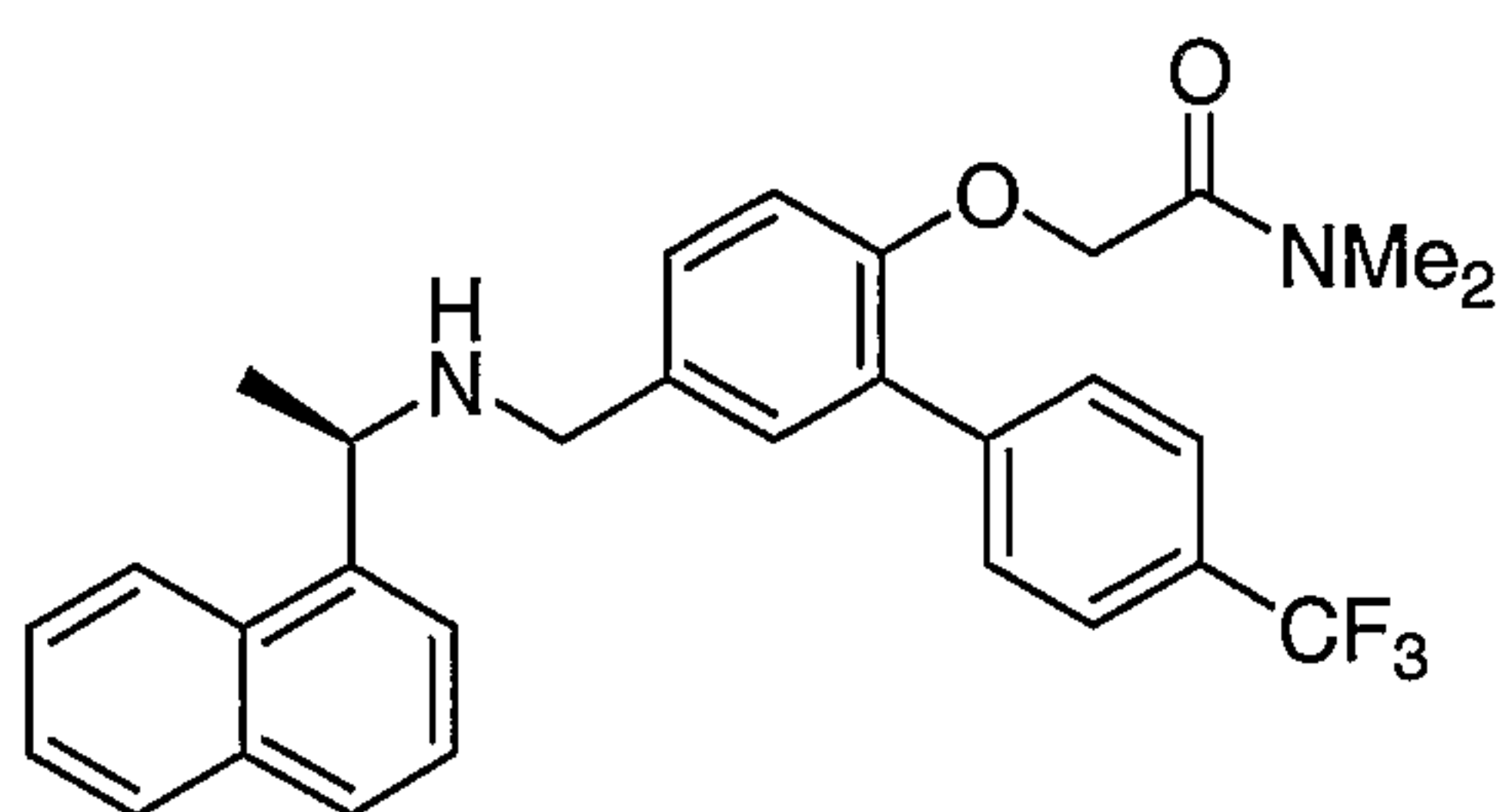
Mass found: 487, 336, 509

Example 339

30

N,N-dimethyl-2-((5-(((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-4'-(trifluoromethyl)-1,1'-biphenyl-2-yl)oxy)acetamide

- 207 -

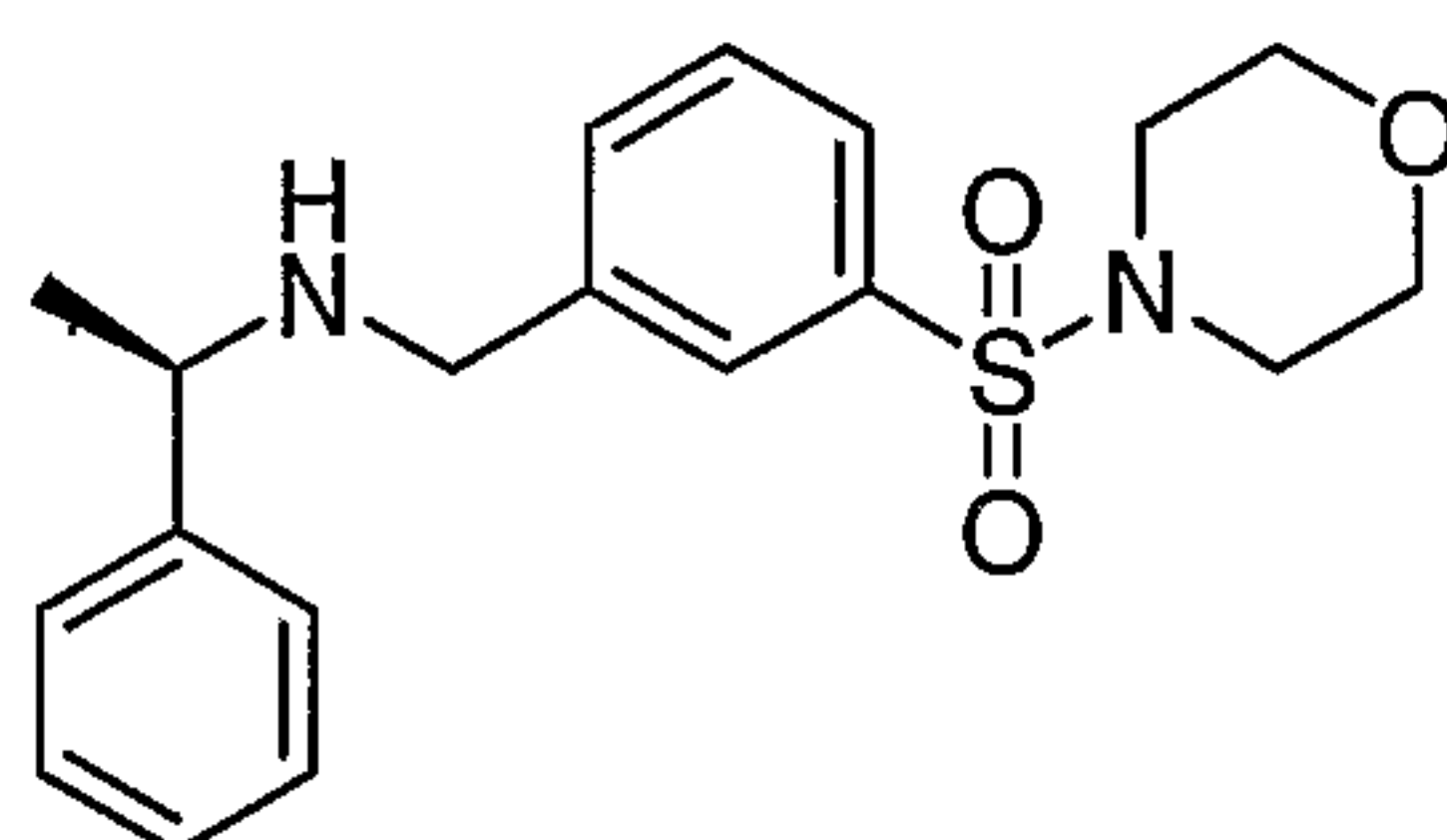


MW 506.565

Mass found: 507, 336, 529

Example 340

(1R)-N-((3-(4-morpholinesulfonyl)phenyl)methyl)-1-phenylethanamine

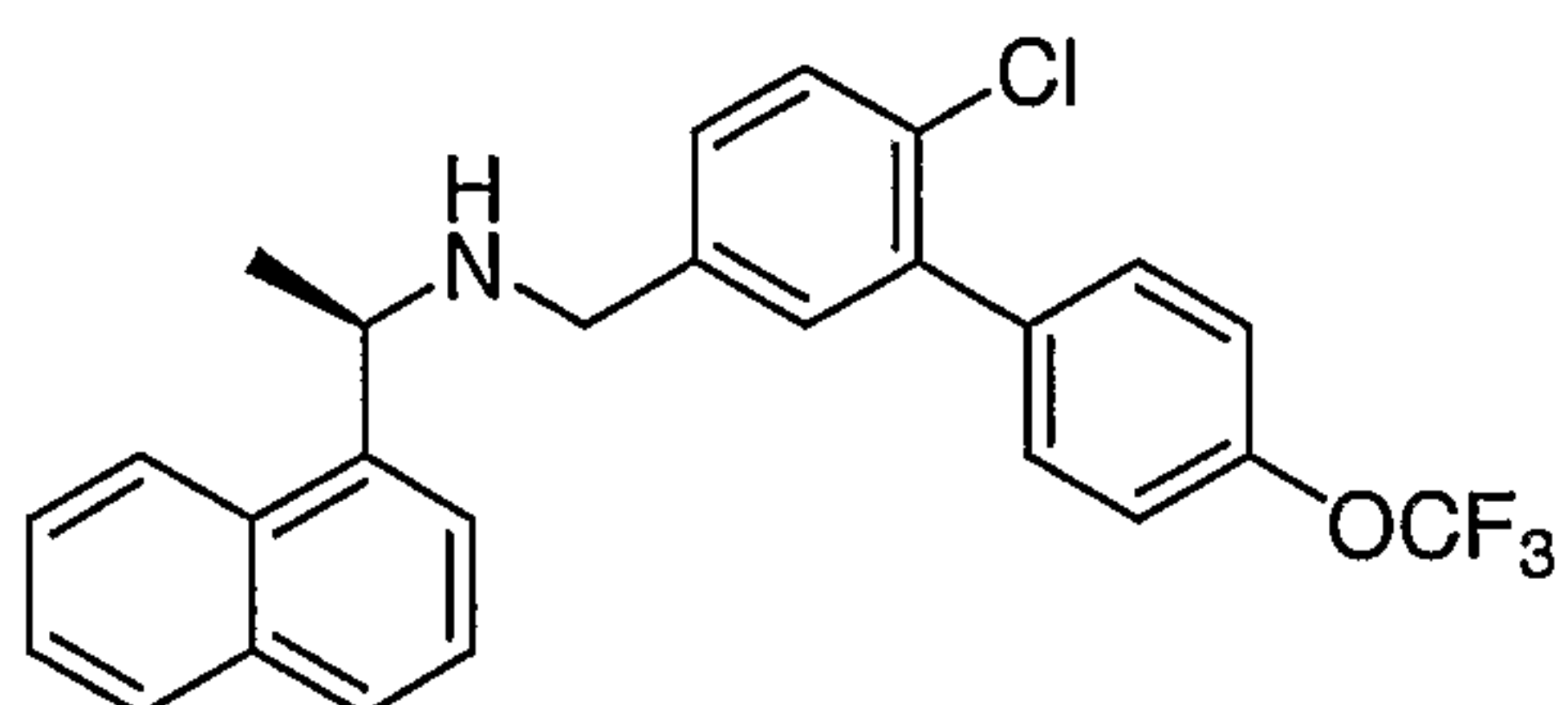


MW 360.476

Mass found: 298, 361, 402

Example 341

(1R)-N-((6-chloro-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine



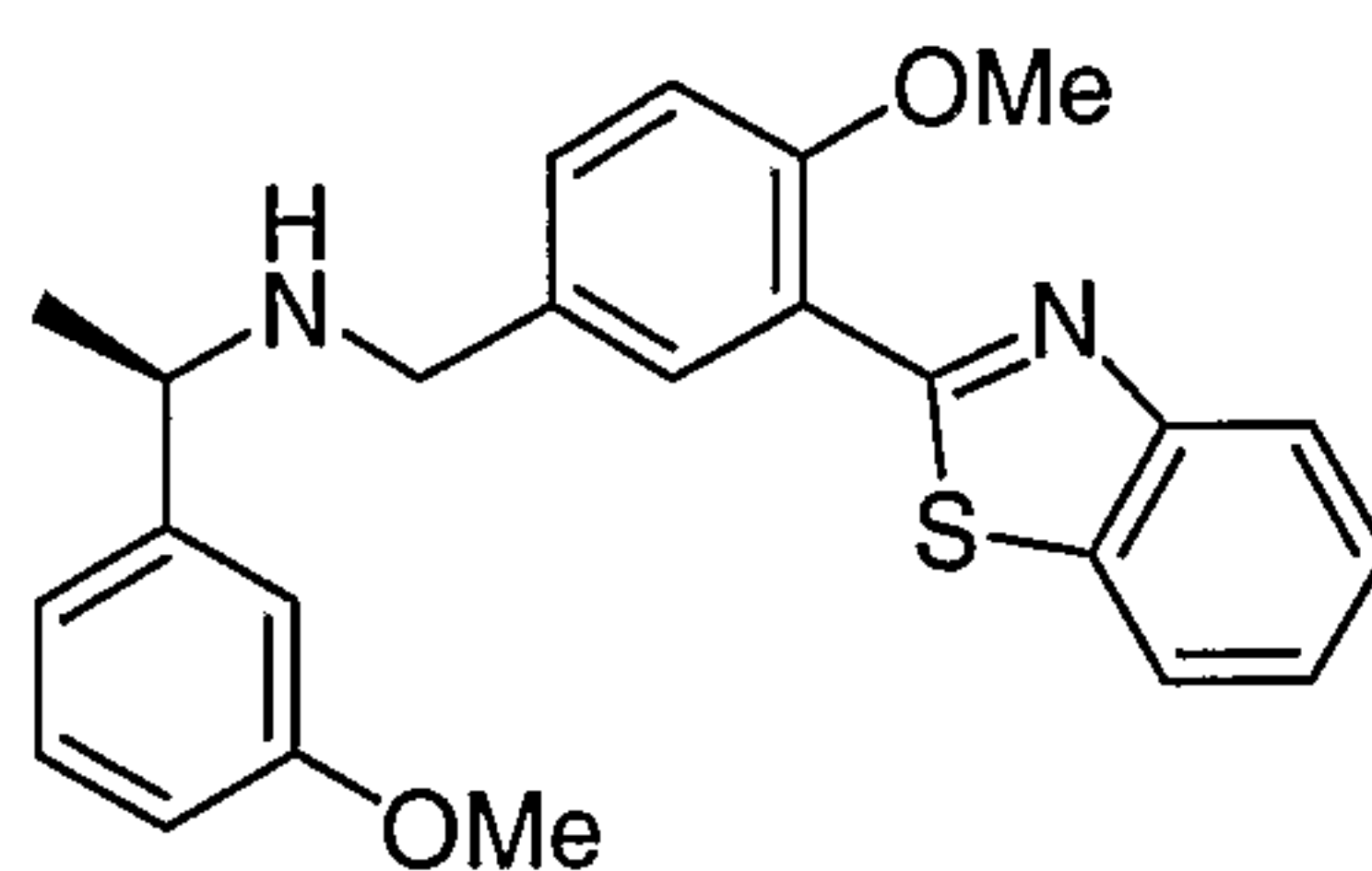
MW 455.905

Mass found: 456, 911

Example 342

(1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methoxy)phenyl)methyl)-1-(3-(methoxy)phenyl)ethanamine

- 208 -



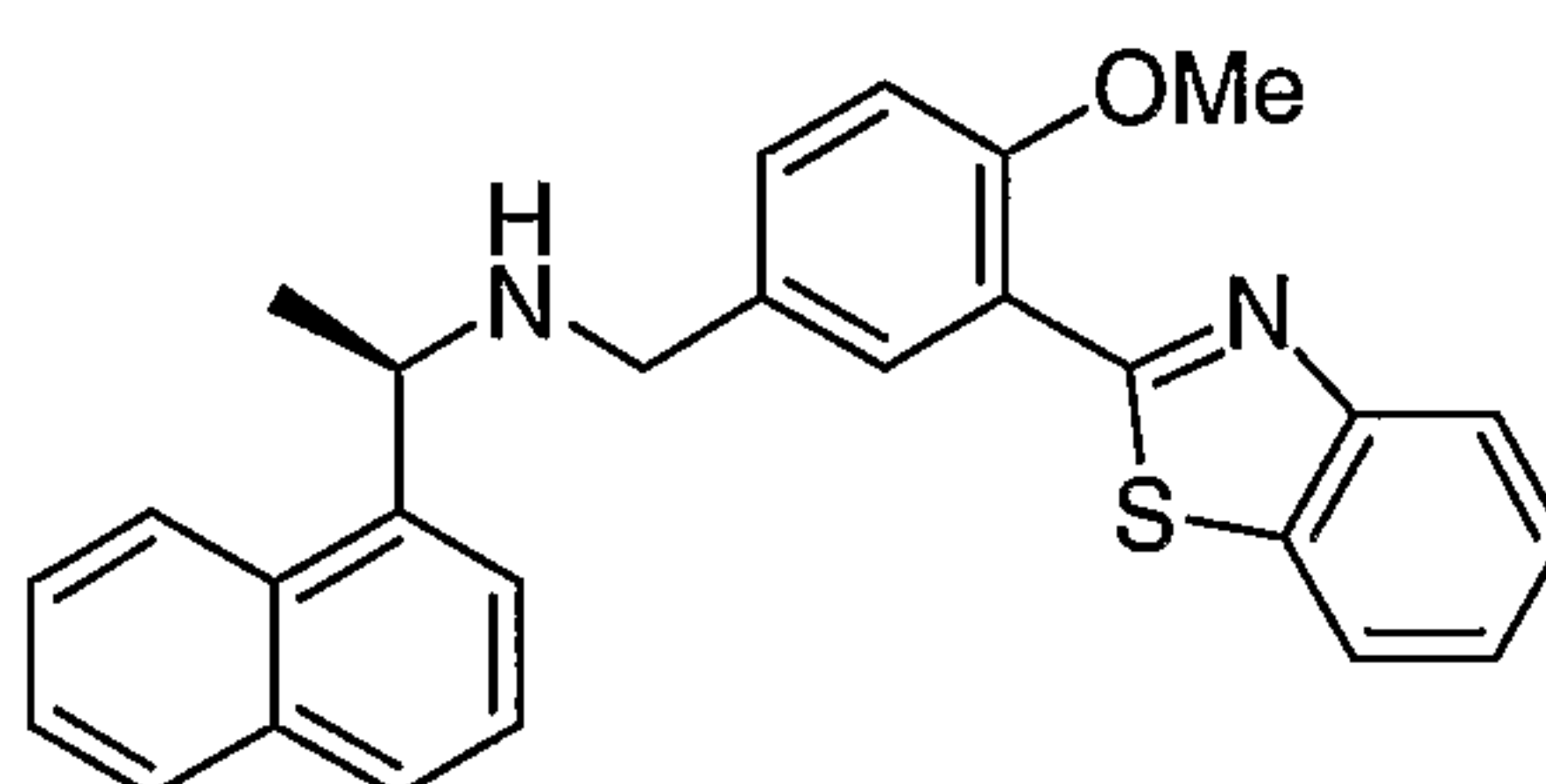
MW 404.532
Mass found: 405, 809

5

Example 343

(1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methoxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

10



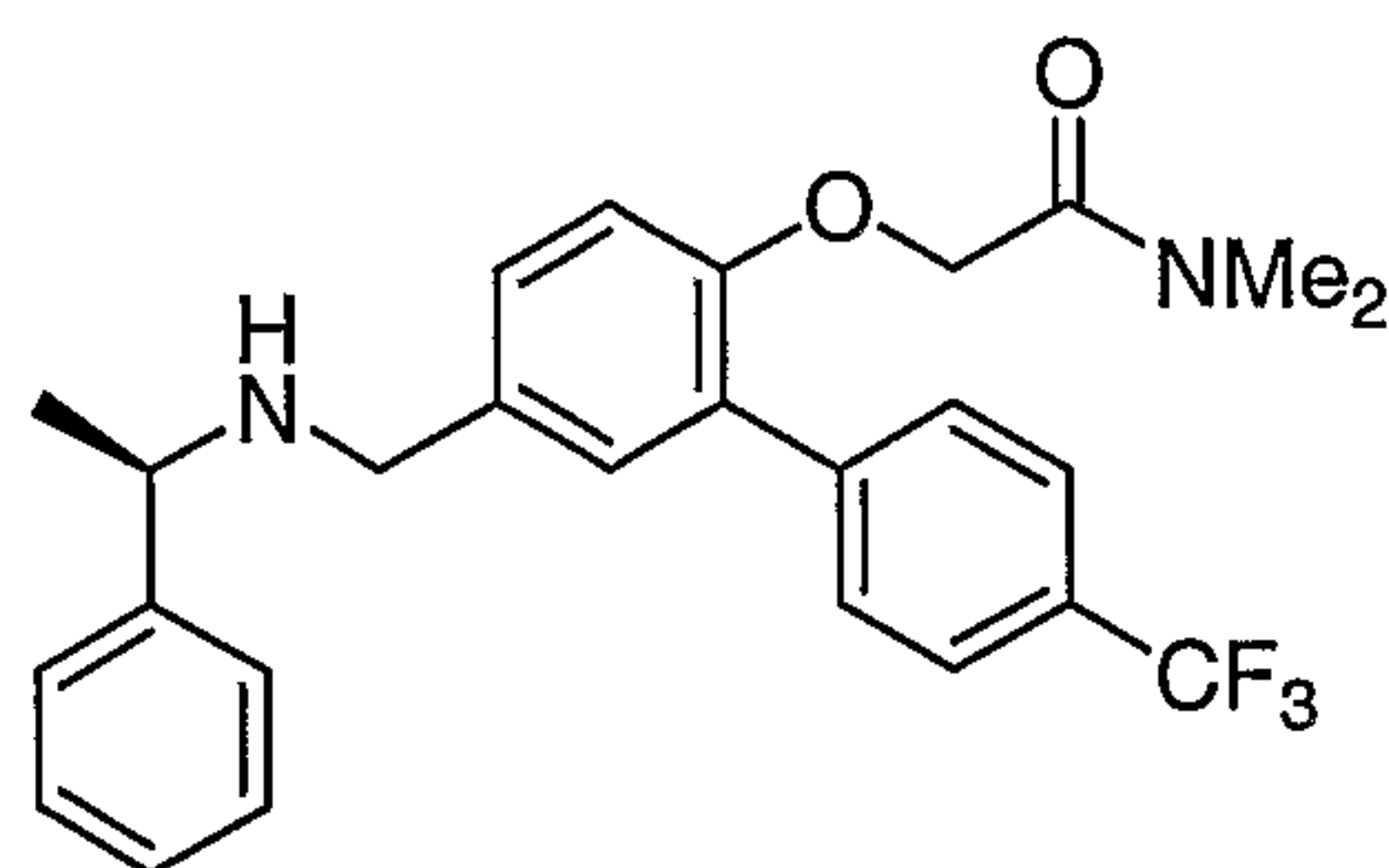
MW 424.566
Mass found: 425, 849

15

Example 344

N,N-dimethyl-2-((5-((((1R)-1-phenylethyl)amino)methyl)-4'-(trifluoromethyl)-1,1'-biphenyl-2-yl)oxy)acetamide

20



MW 456.505
Mass found: 336, 457, 354

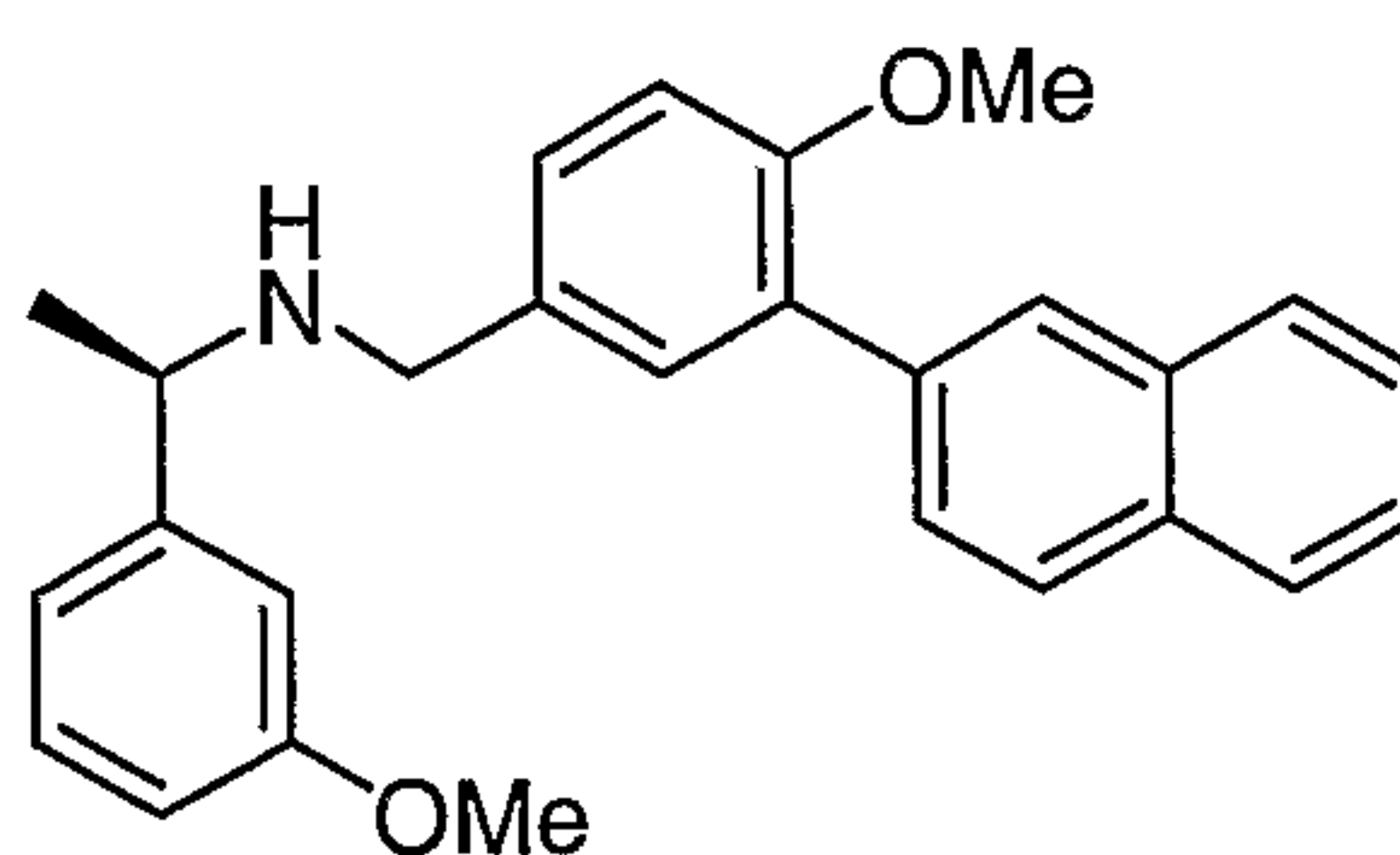
25

Example 345

(1R)-N-((4-(methoxy)-3-(2-naphthalenyl)phenyl)methyl)-1-(3-(methoxy)phenyl)ethanamine

30

- 209 -



MW 433.98

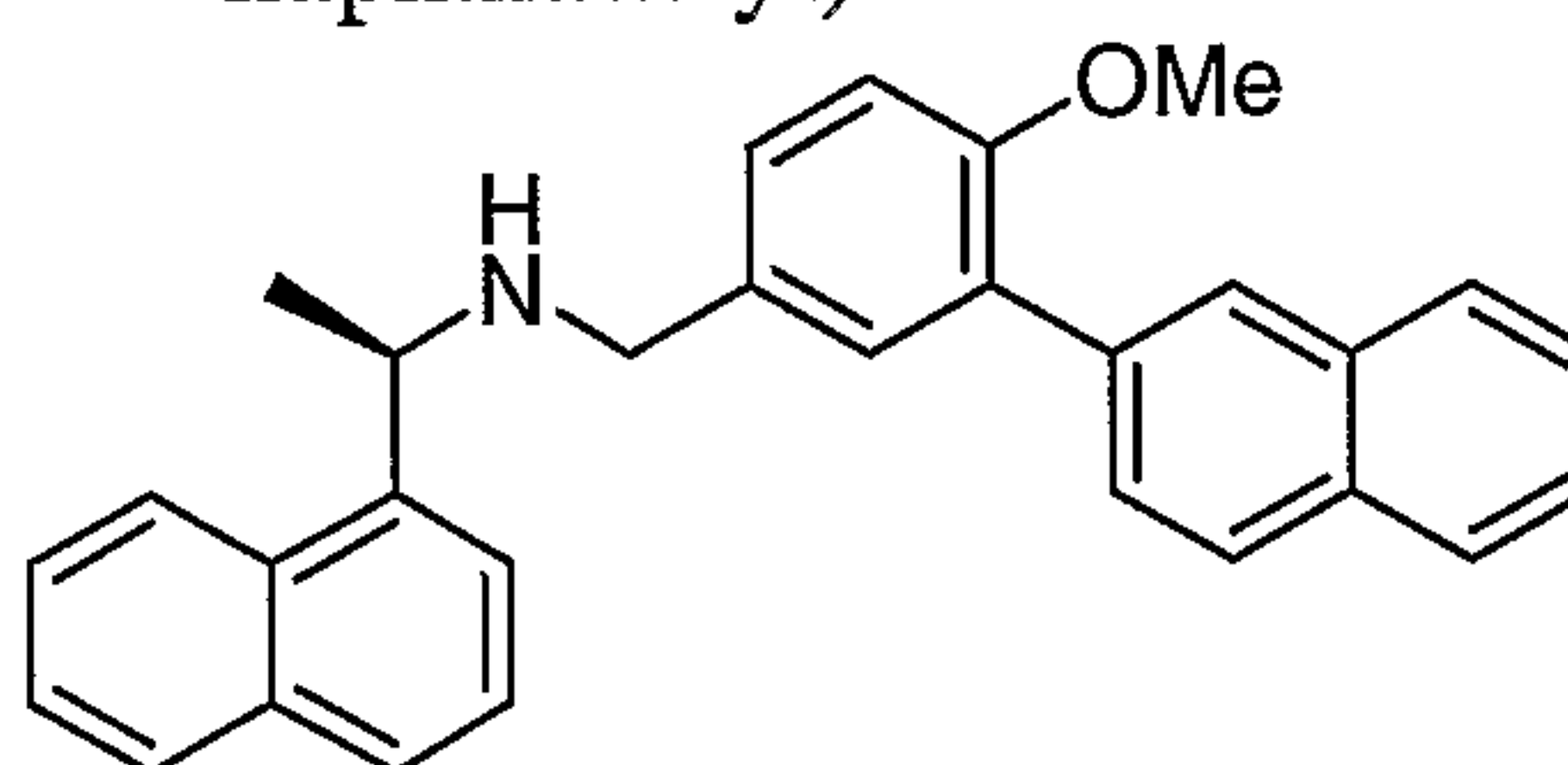
Mass found: 247, 398

5

Example 346

(1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

10



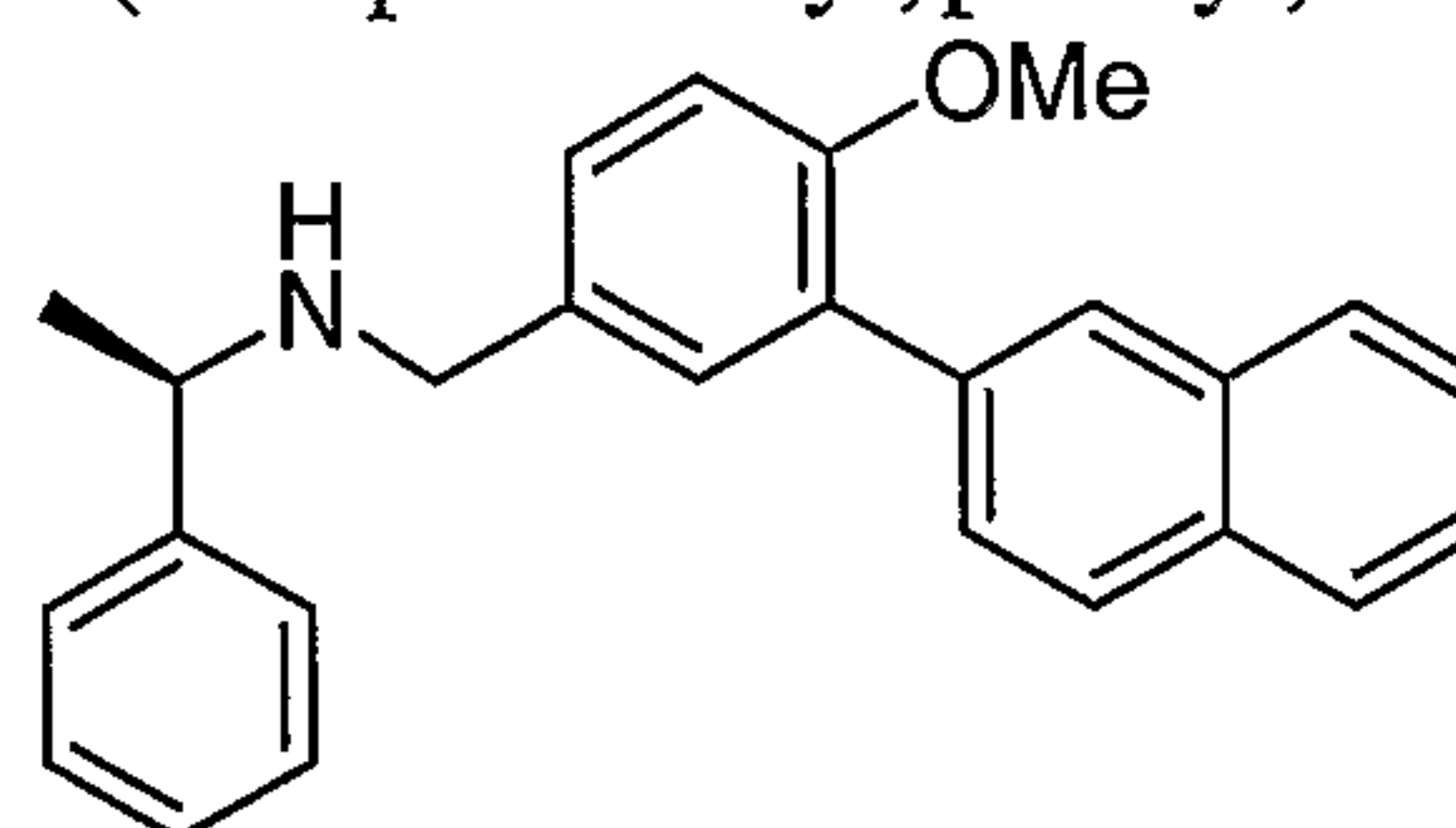
MW 454.02

Mass found: 247, 155, 418

15

Example 347

(1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-phenylethanamine



20

MW 403.96

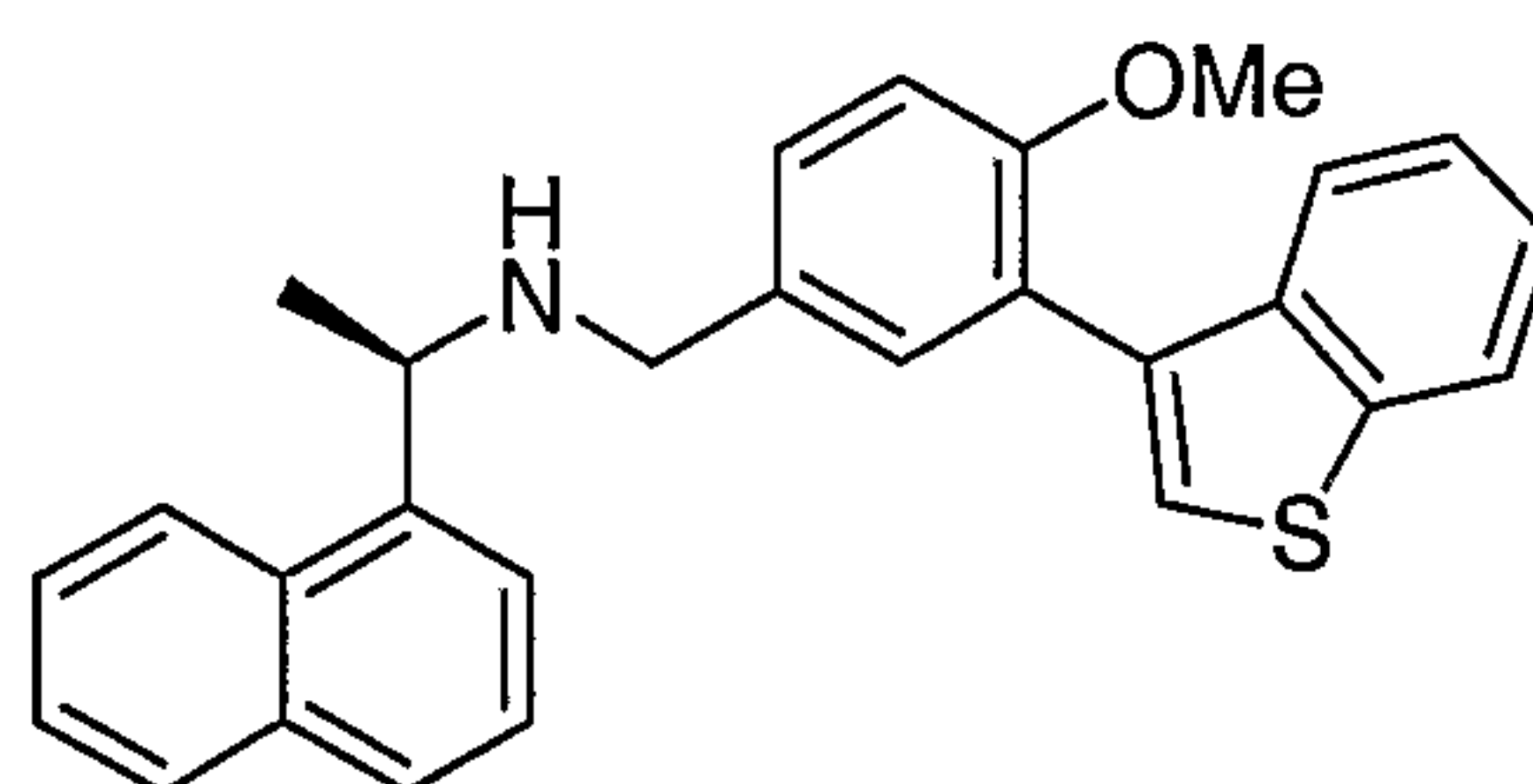
Mass found: 247, 368

25

Example 348

(1R)-N-((3-(1-benzothien-3-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

- 210 -



MW 460.04

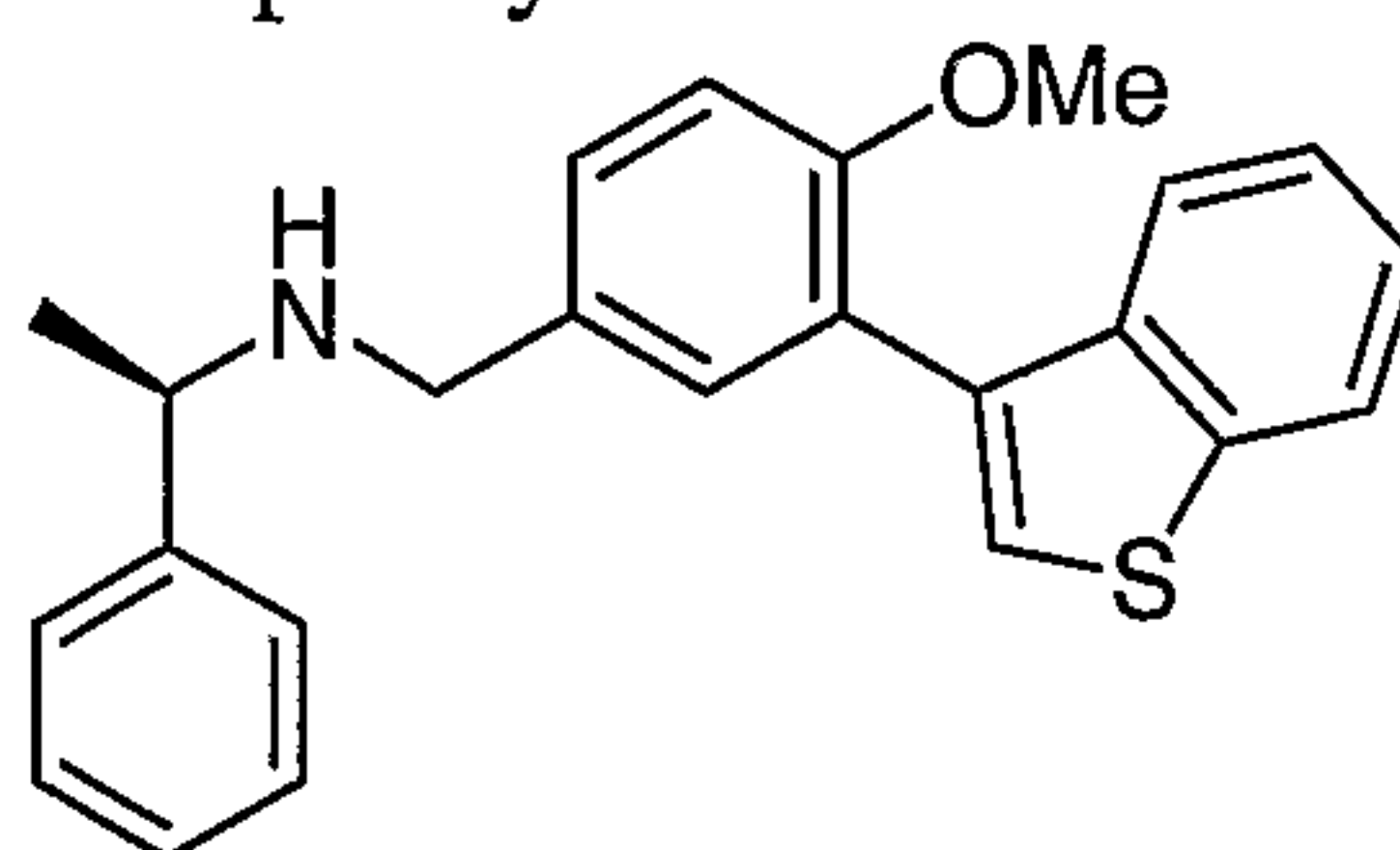
Mass found: 253, 155, 424

5

Example 349

(1R)-N-((3-(1-benzothiophen-3-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine

10



MW 409.98

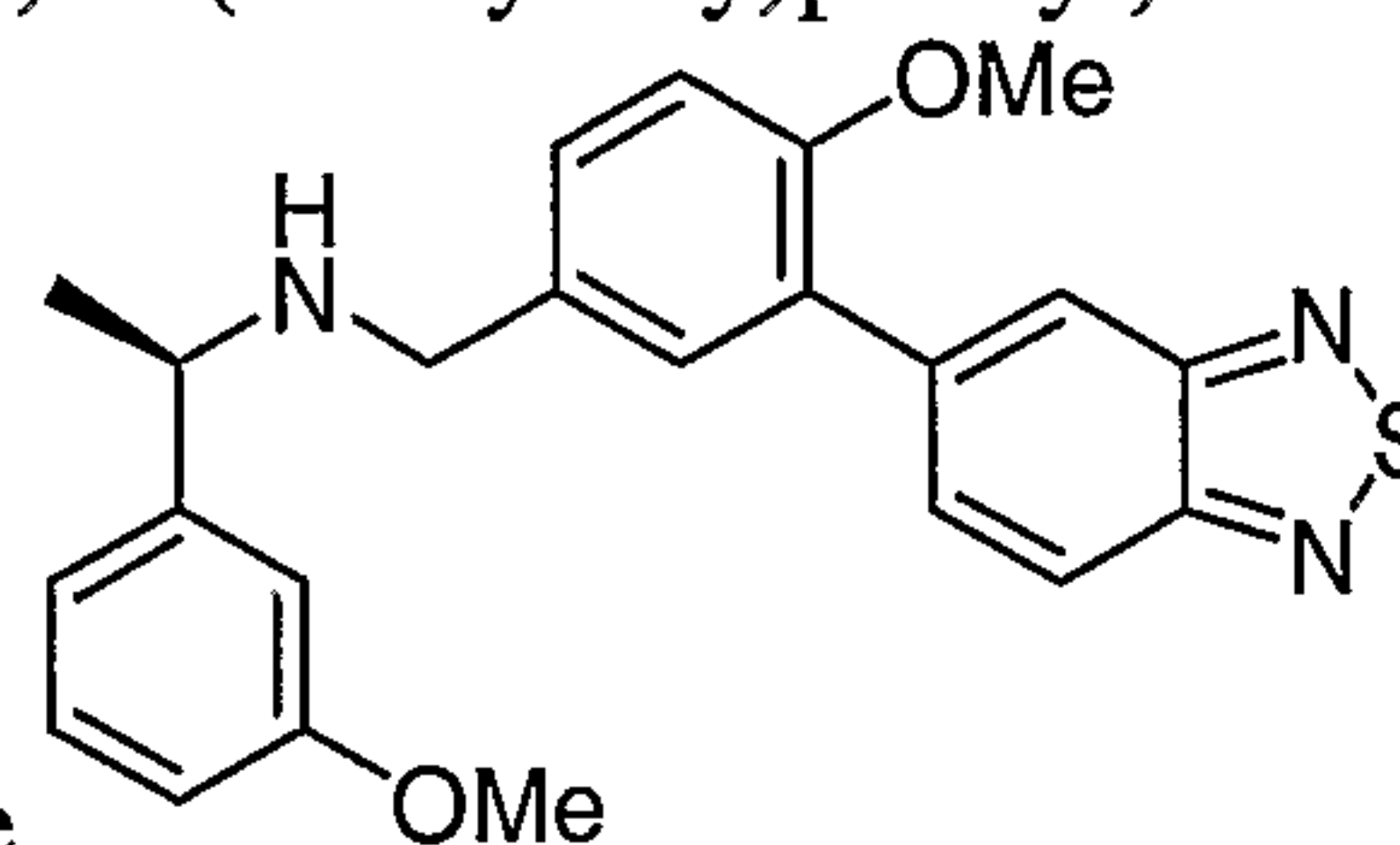
Mass found: 253, 374

15

Example 350

(1R)-N-((3-(2,1,3-benzothiadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

20



MW 441.98

Mass found: 273, 255, 406

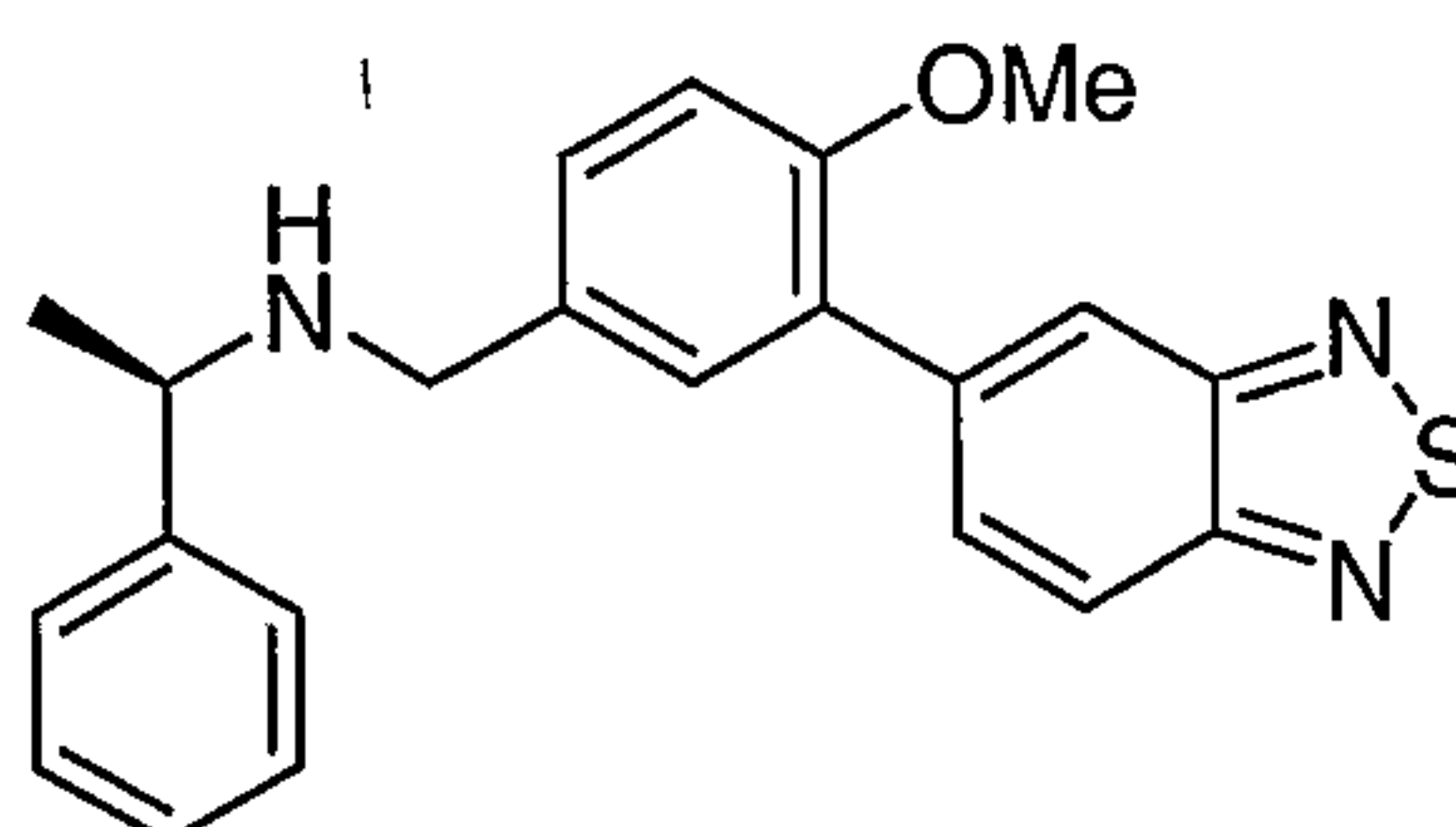
25

Example 351

(1R)-N-((3-(2,1,3-benzothiadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine

30

- 211 -



MW 411.96

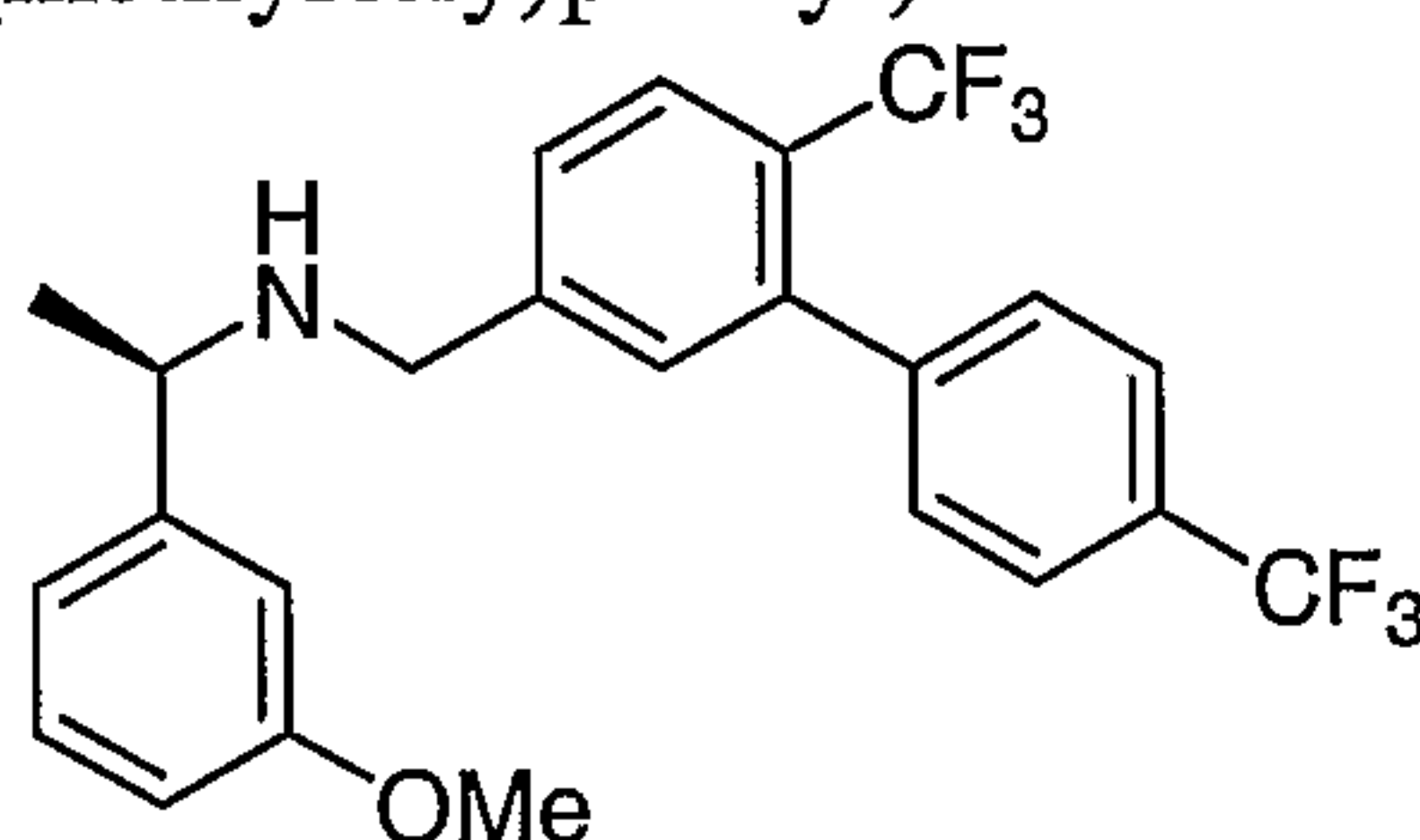
Mass found: 273, 255, 376

5

Example 352

(1R)-N-((4',6-bis(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

10



MW 489.89

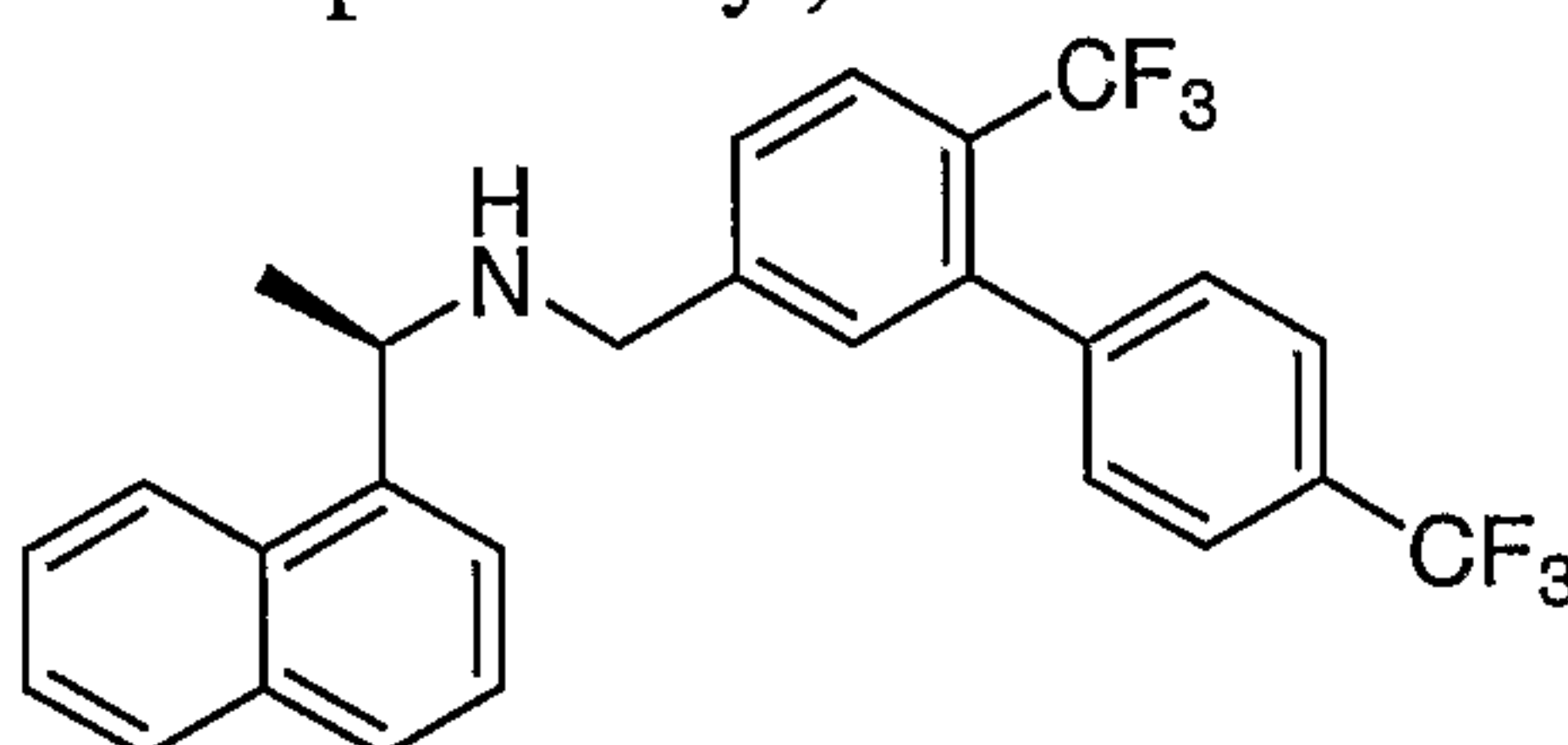
Mass found: 454, 361, 344

15

Example 353

(1R)-N-((4',6-bis(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine

20



MW 509.93

Mass found: 155

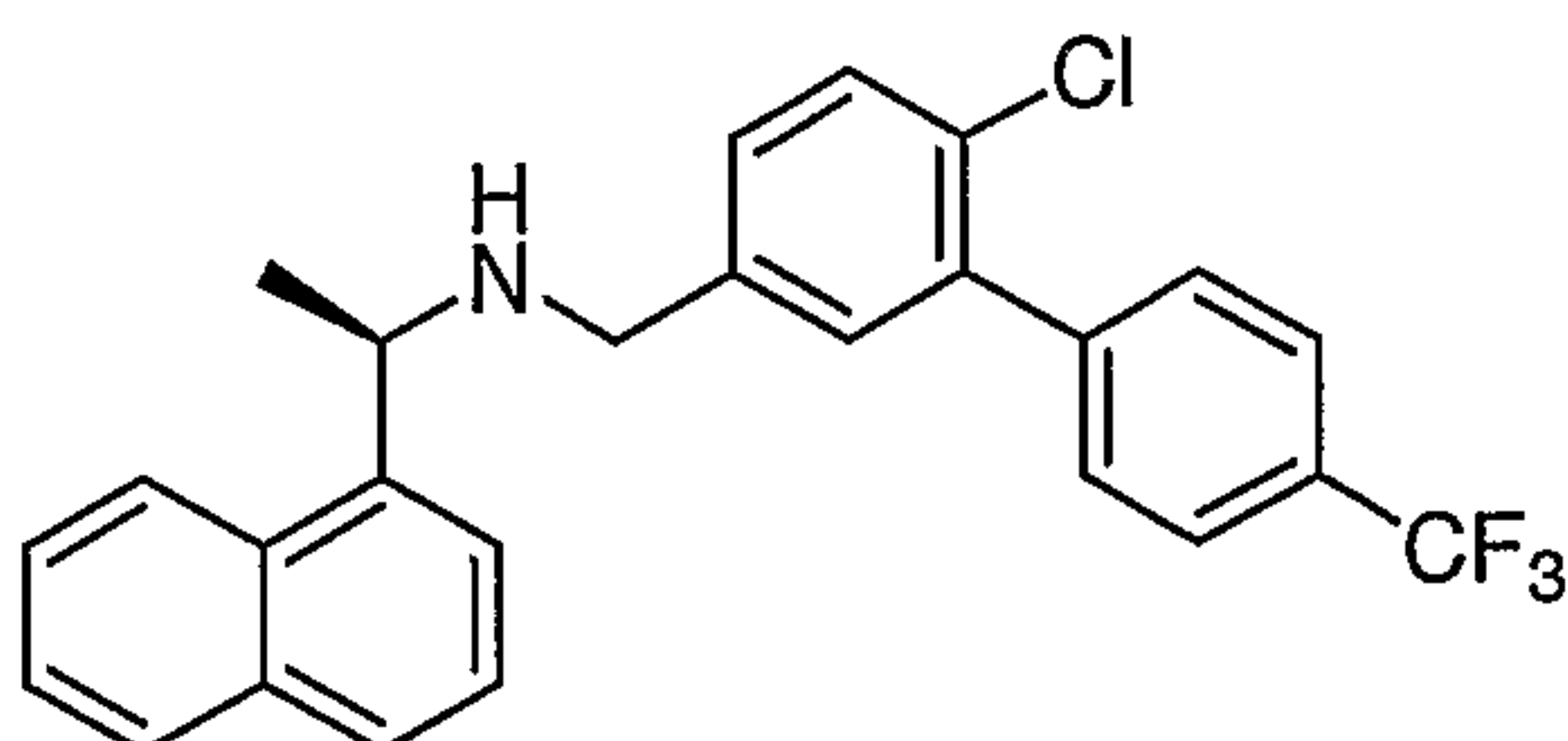
25

Example 354

(1R)-N-((6-chloro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine

30

- 212 -



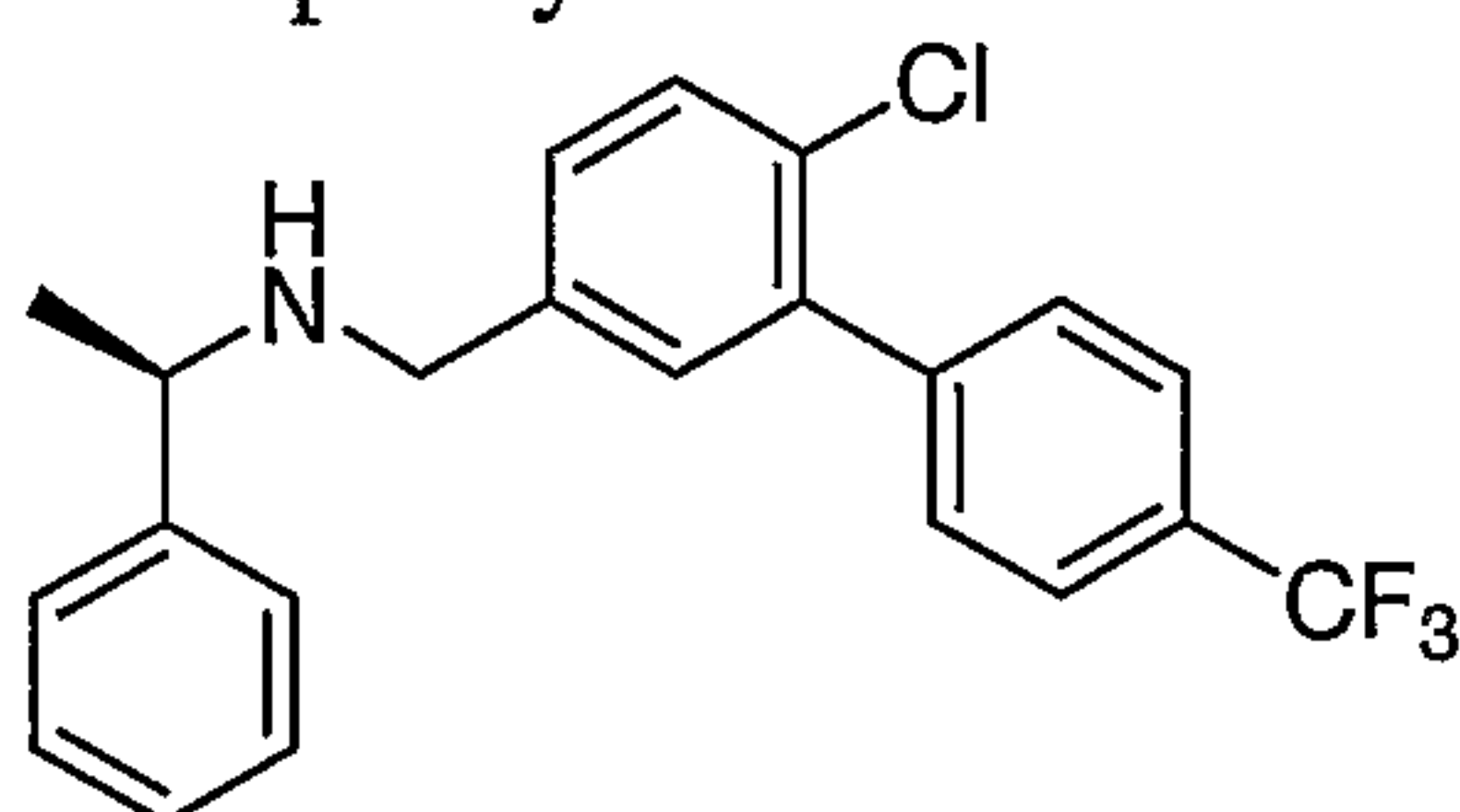
MW 439.91
Mass found: 155

5

Example 355

(1R)-N-((6-chloro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethylamine

10

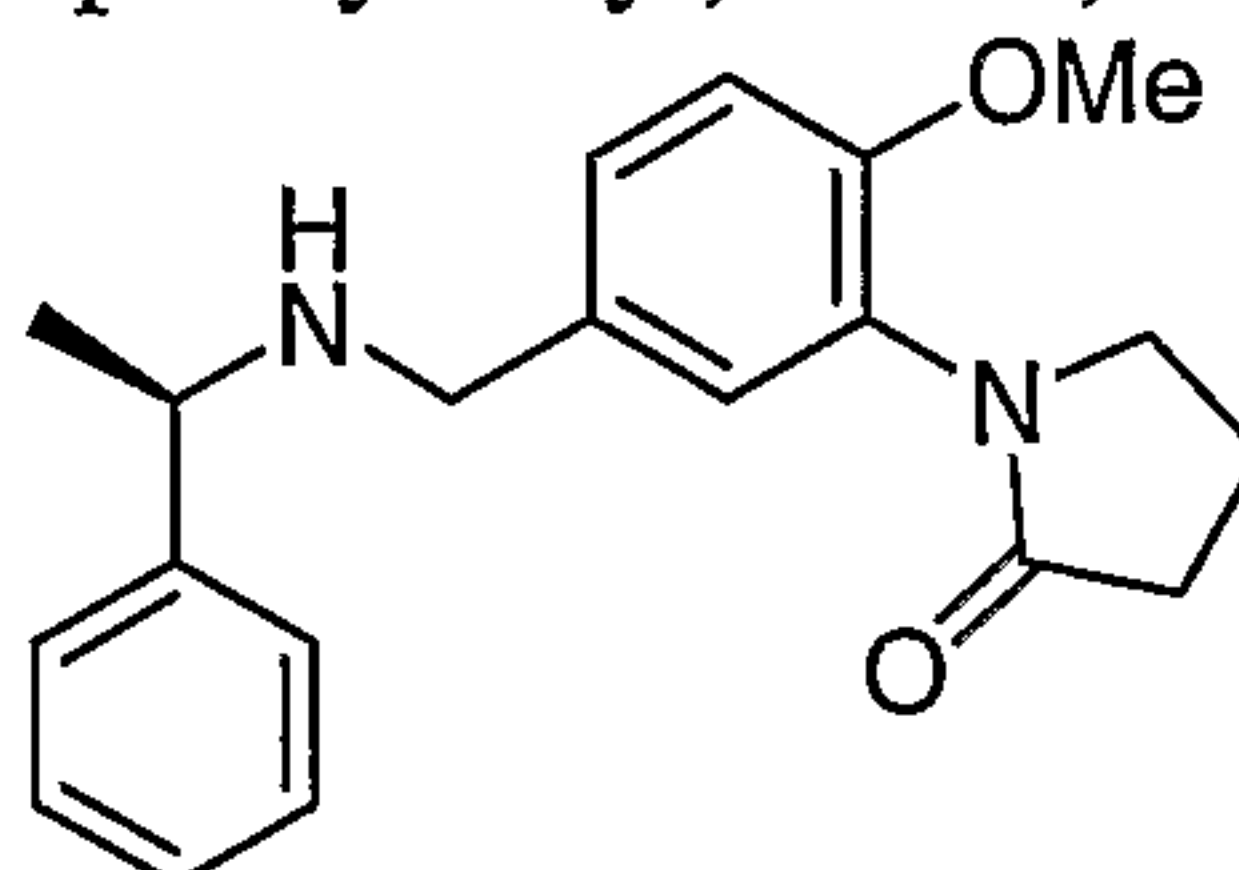


MW 389.95
Mass found: 390, 269, 310

15

Example 356

1-(2-(methoxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyrrolidinone



20

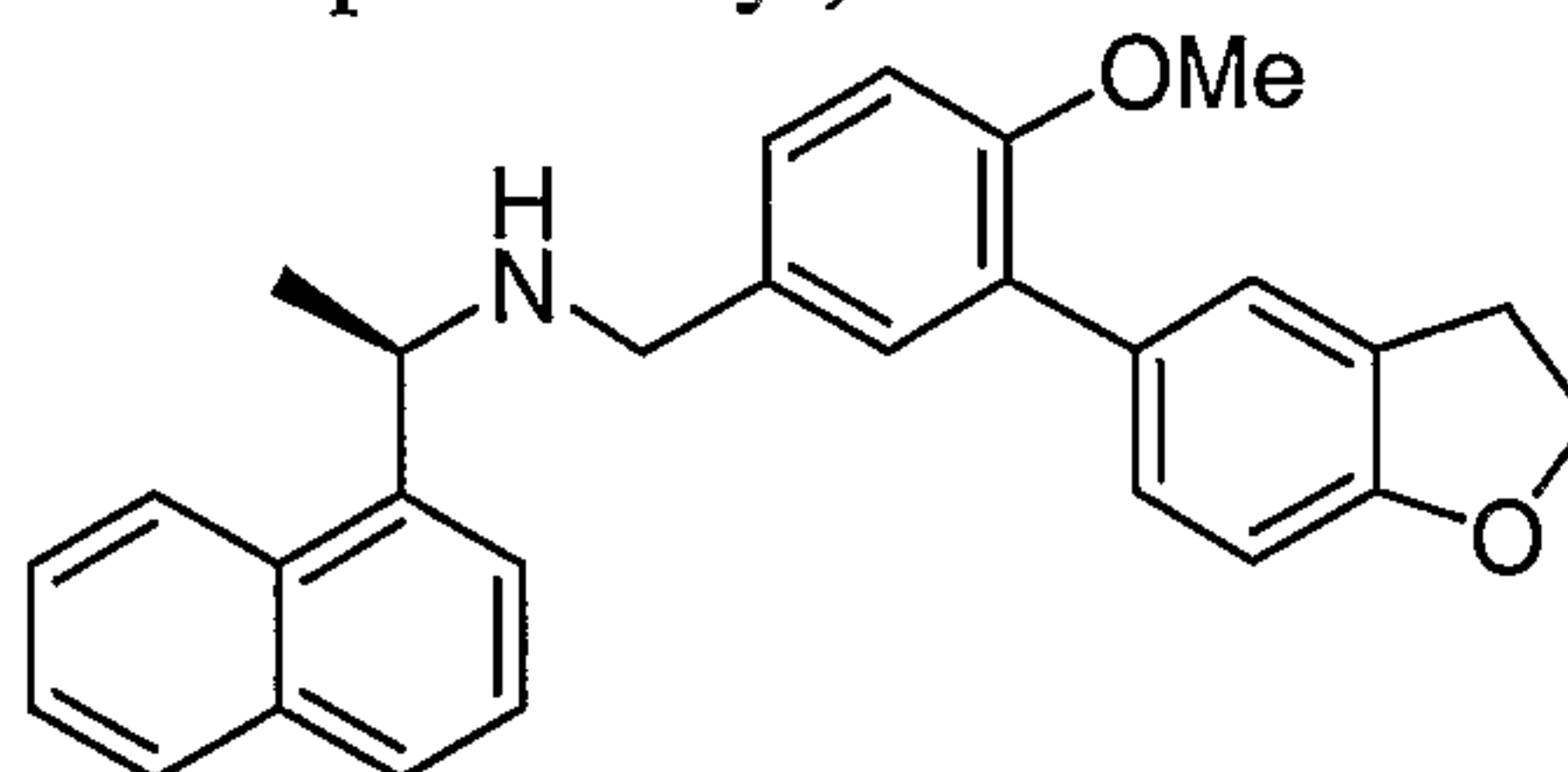
MW 324.43
Mass found: 204, 347, 325

25

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Example 357

(1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

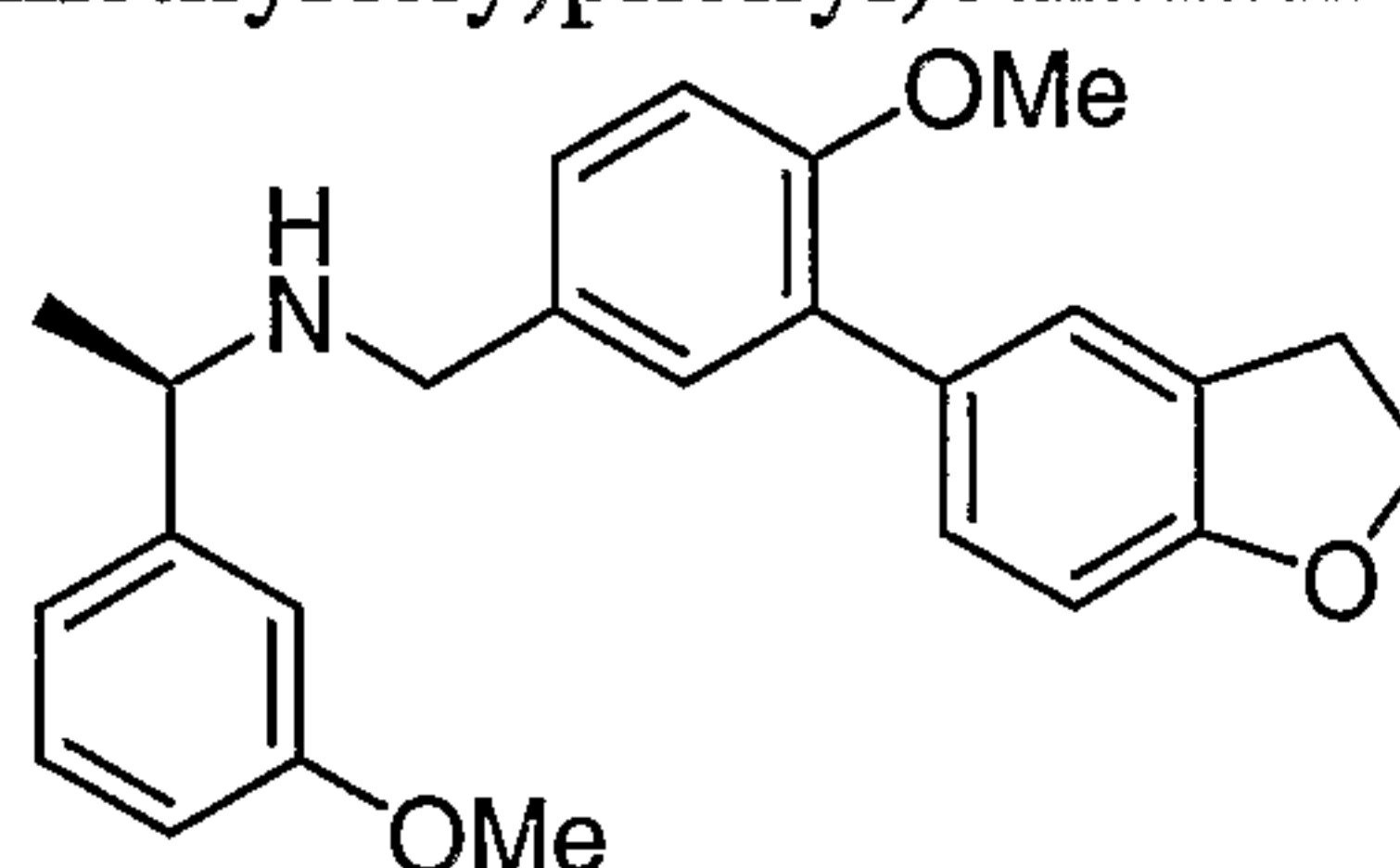


MW 409.53

Mass found: 239, 410

Example 358

(1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

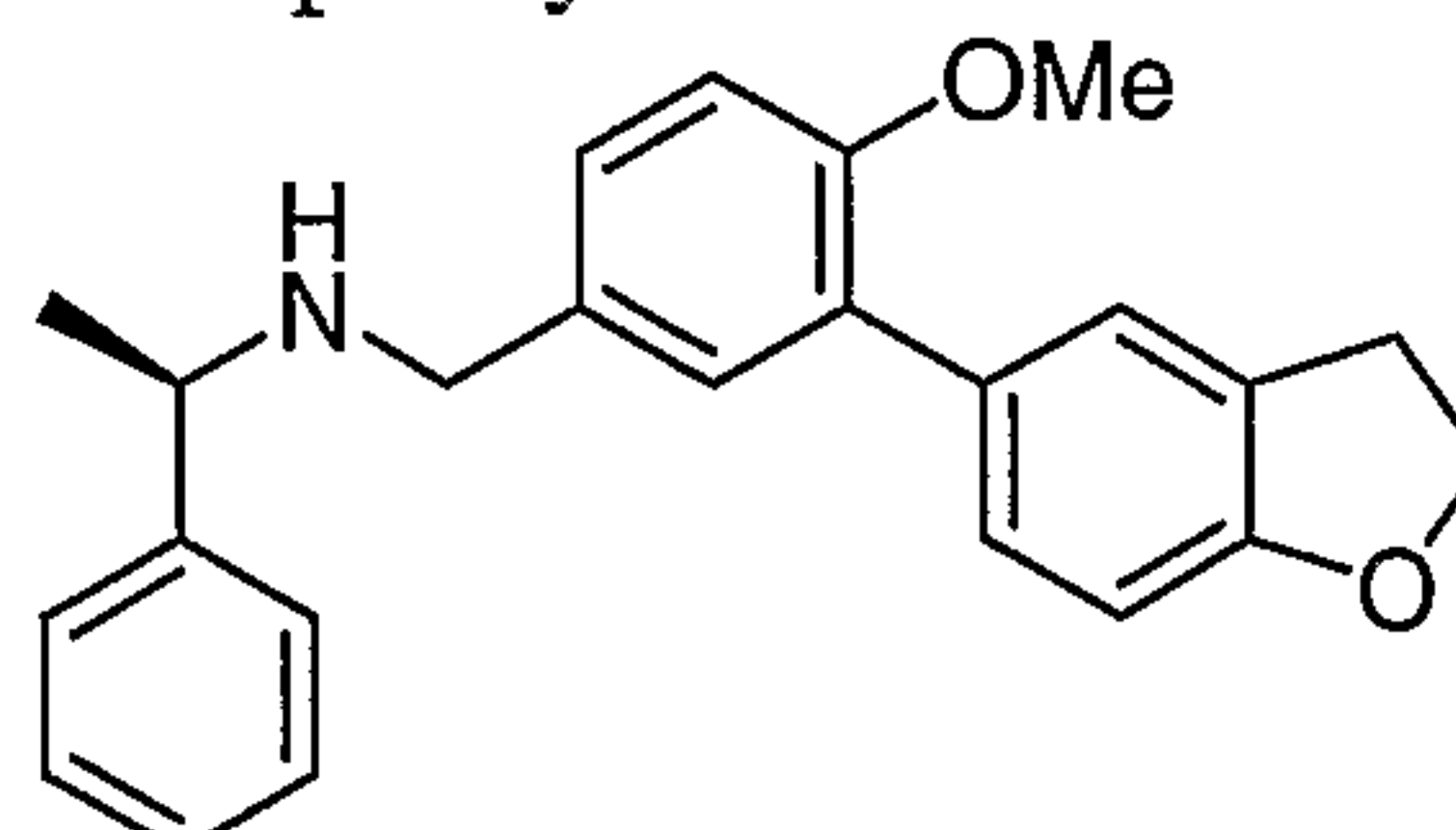


MW 389.50

Mass found: 239, 390

Example 359

(1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine



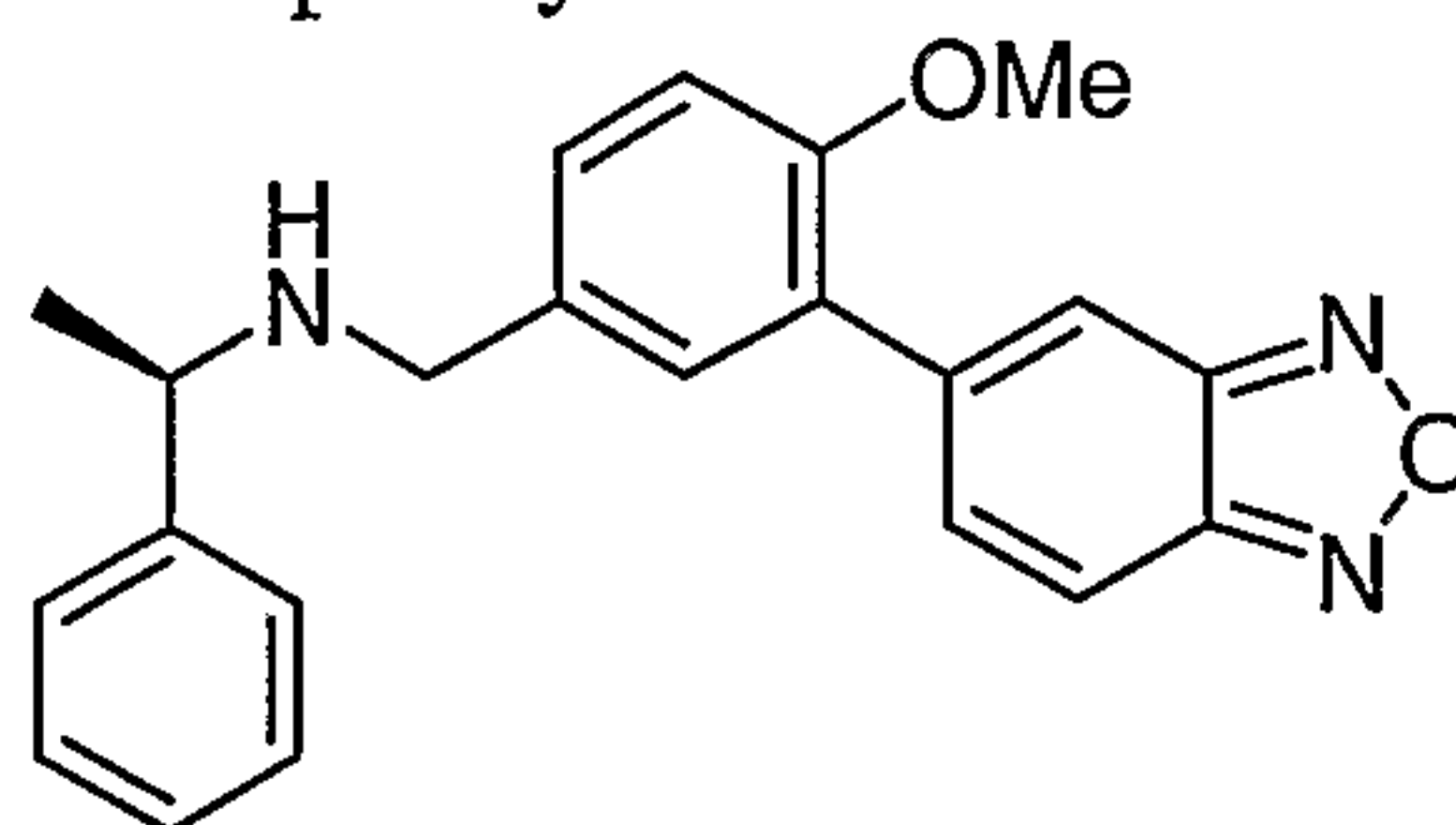
MW 359.47

Mass found: 239, 360

Example 360

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(1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine



5

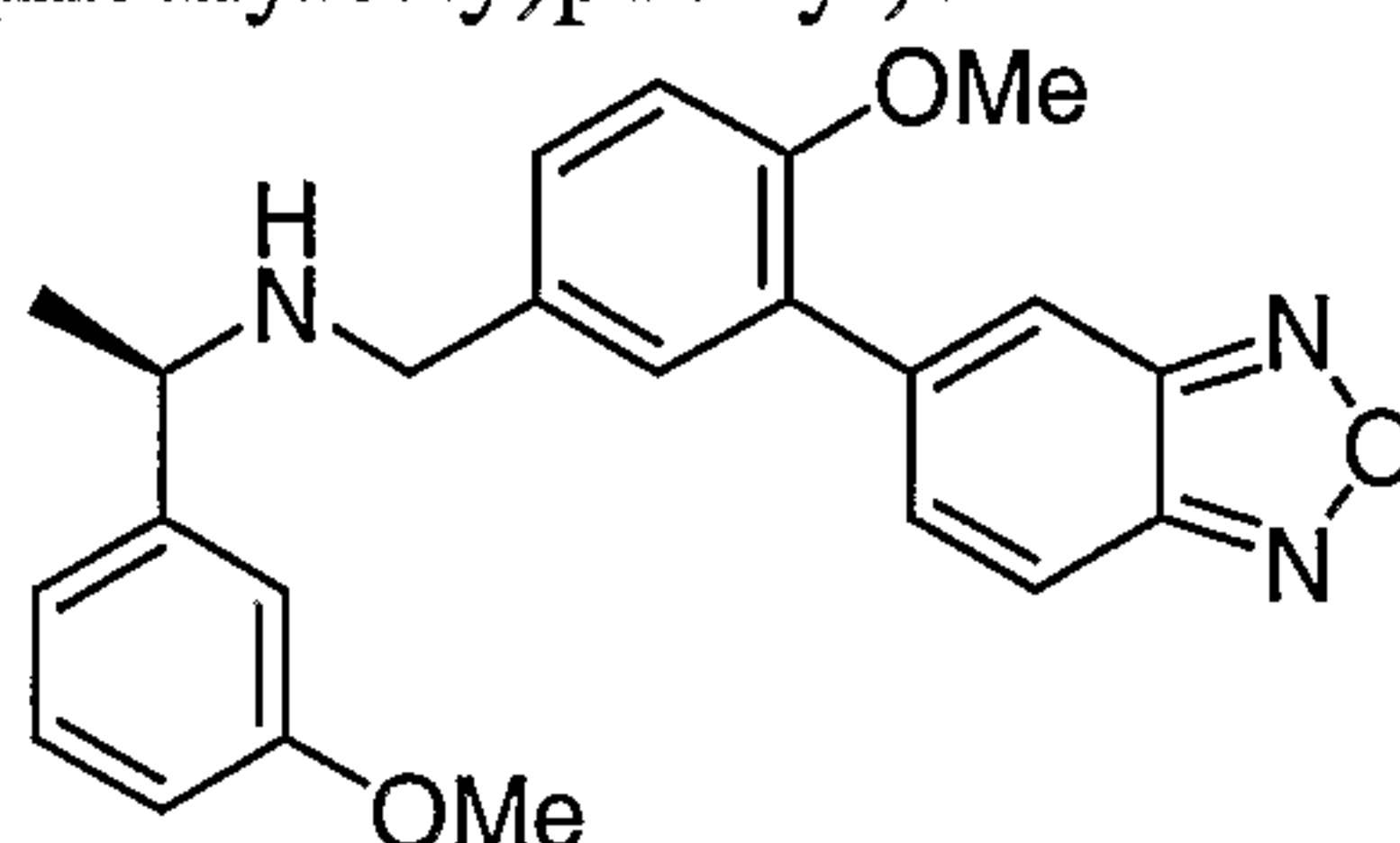
MW 359.43

Mass found: 239, 360, 401

Example 361

10

(1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine



15

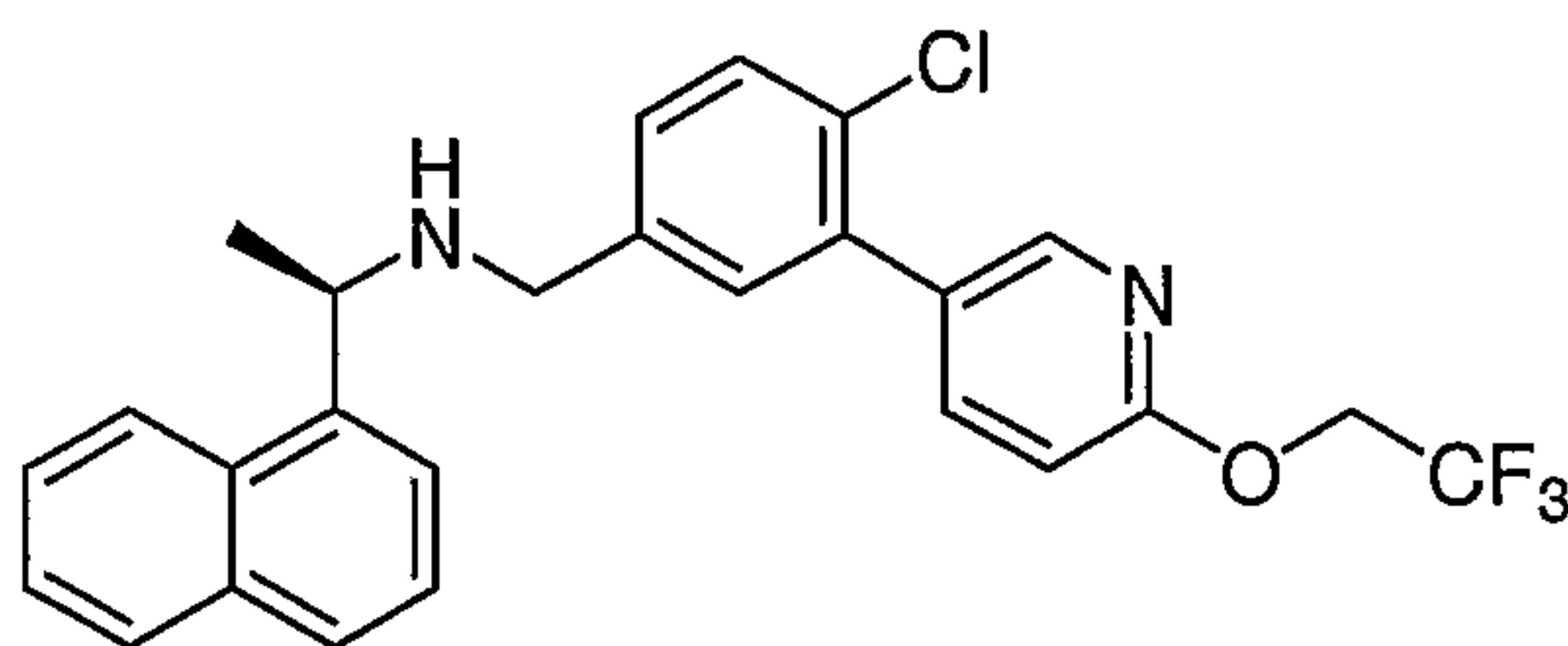
MW 389.46

Mass found: 390, 431, 779

Example 362

20

(1R)-N-((4-chloro-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



25

MW 470.93

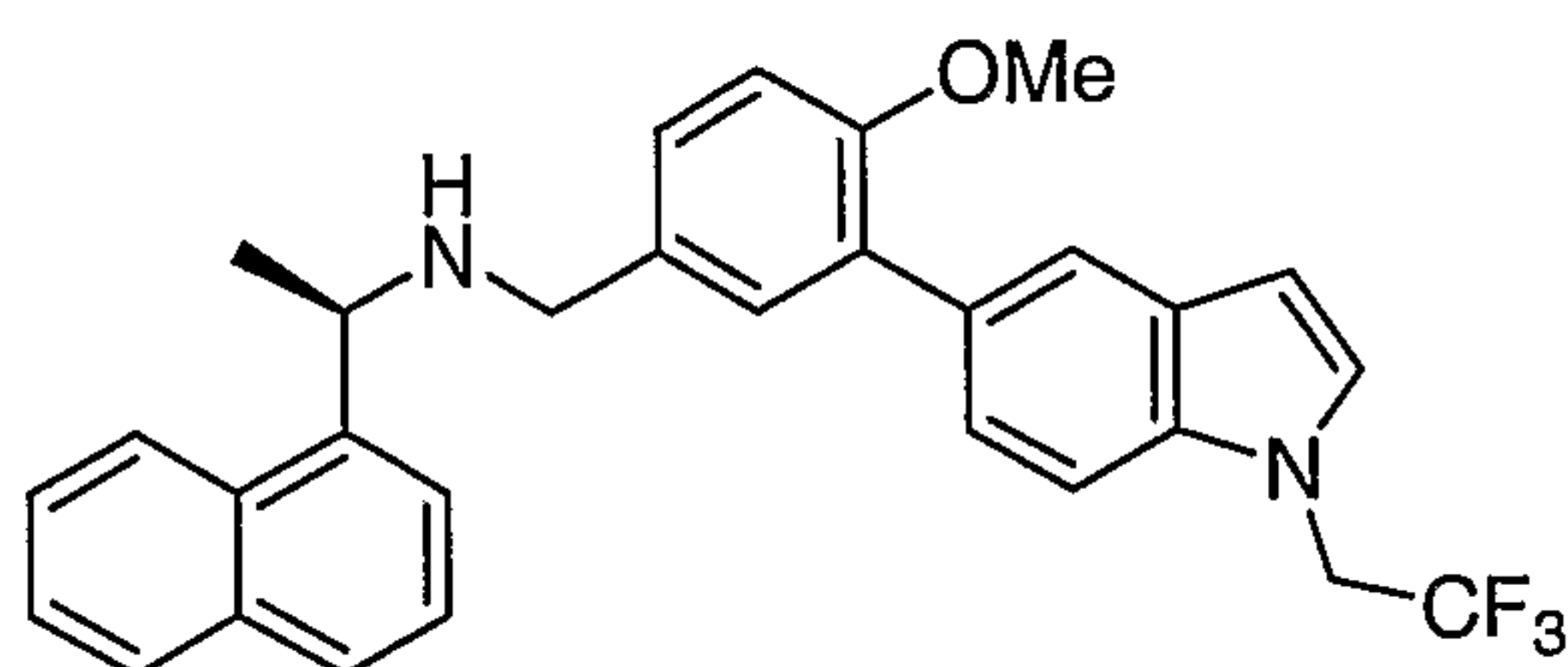
Mass found: 155, 472

Example 363

30

(1R)-N-((4-(methyloxy)-3-(1-(2,2,2-trifluoroethyl)-1H-indol-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

- 215 -



MW 488.55

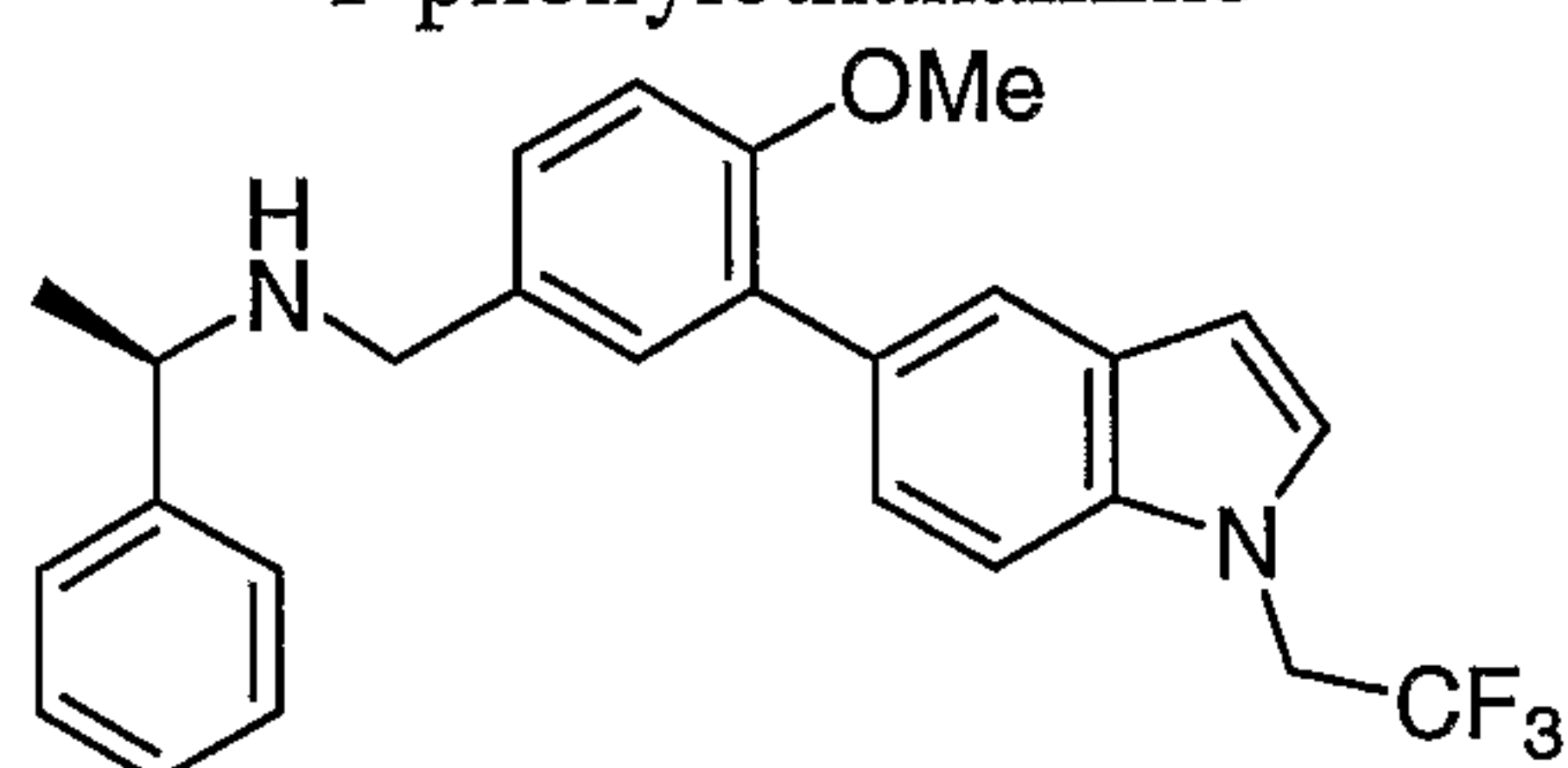
Mass found: 318, 489

5

Example 364

(1R)-N-((4-(methoxy)-3-(1-(2,2,2-trifluoroethyl)-1H-indol-5-yl)phenyl)methyl)-1-phenylethanamine

10



MW 438.491

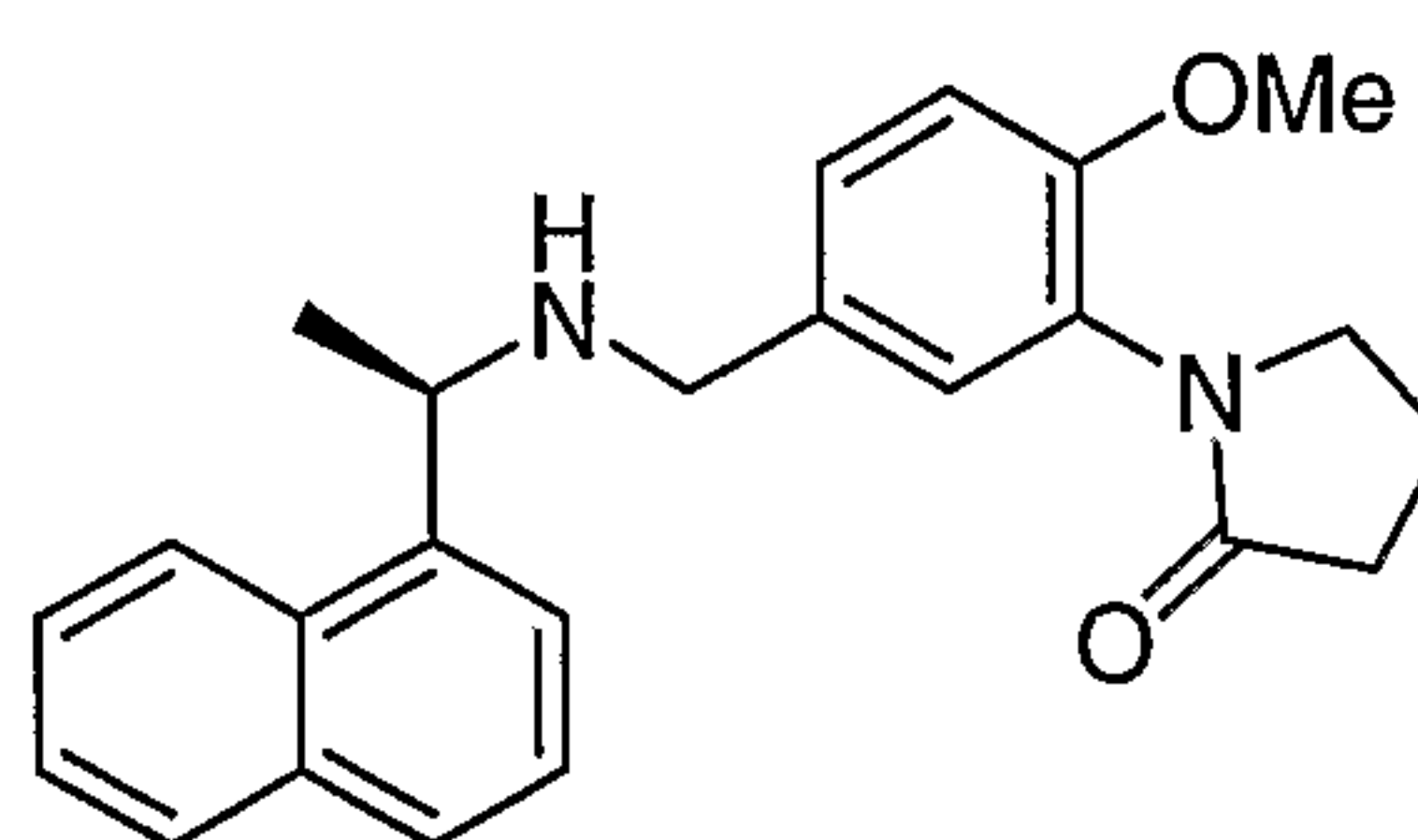
Mass found: 318, 439

15

Example 365

1-(2-(methoxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-2-pyrrolidinone

20



MW 374.49

Mass found: 240, 375, 397, 749

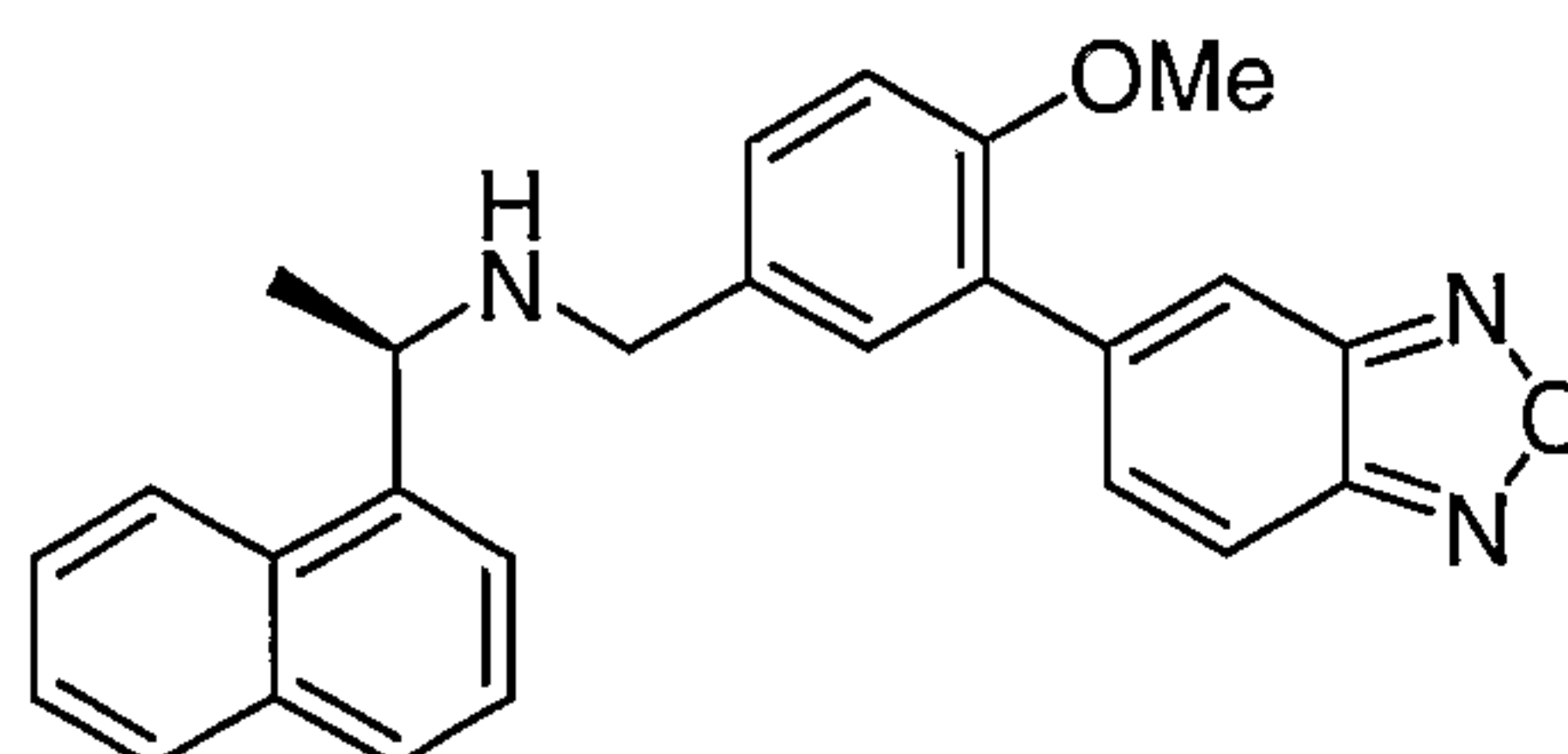
25

Example 366

(1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methoxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

30

- 216 -



MW 409.49

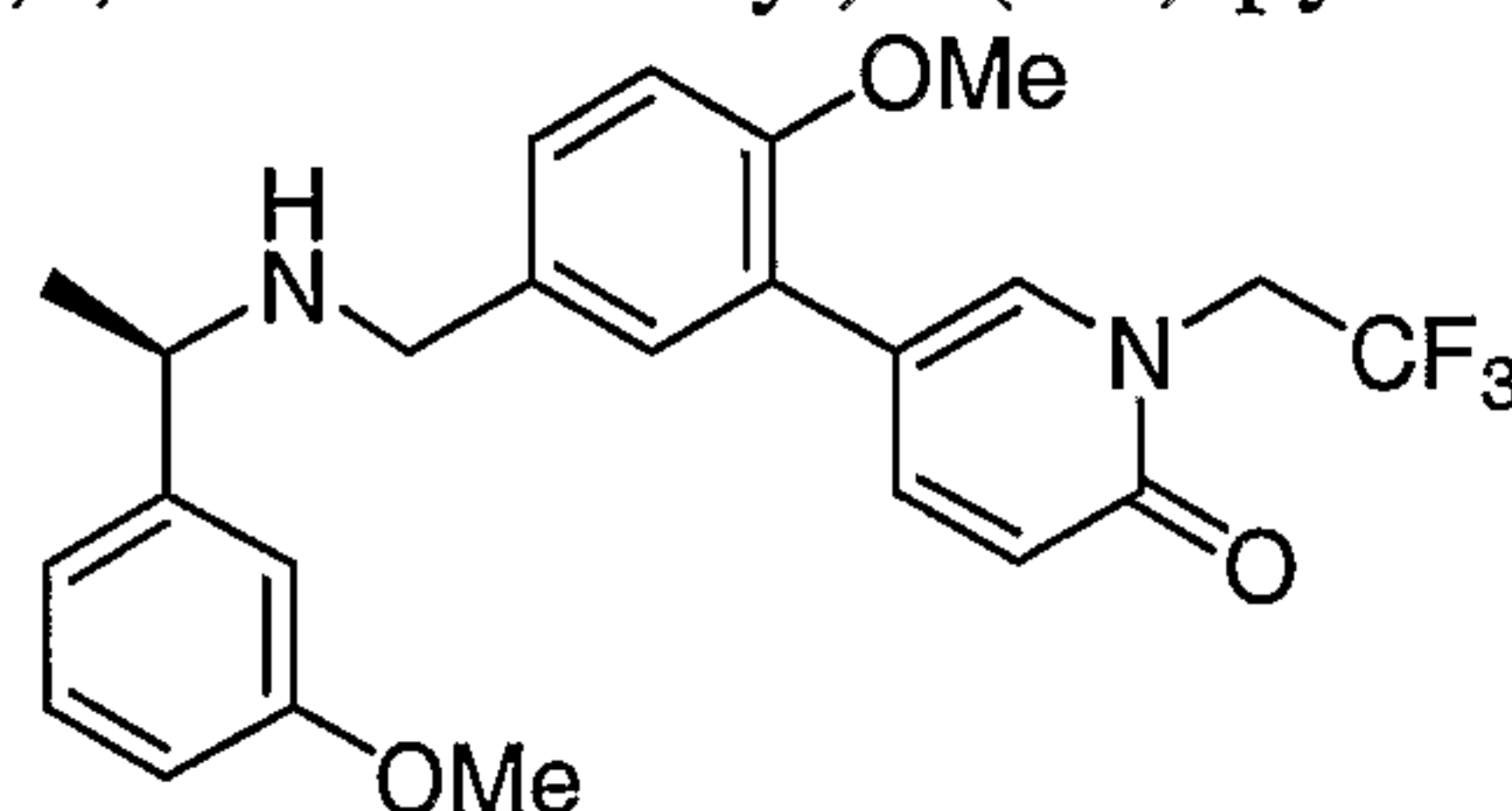
Mass found: 155, 410, 239

5

Example 367

5-(2-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-
1-(2,2,2-trifluoroethyl)-2(1H)-pyridinone

10



MW 446.466

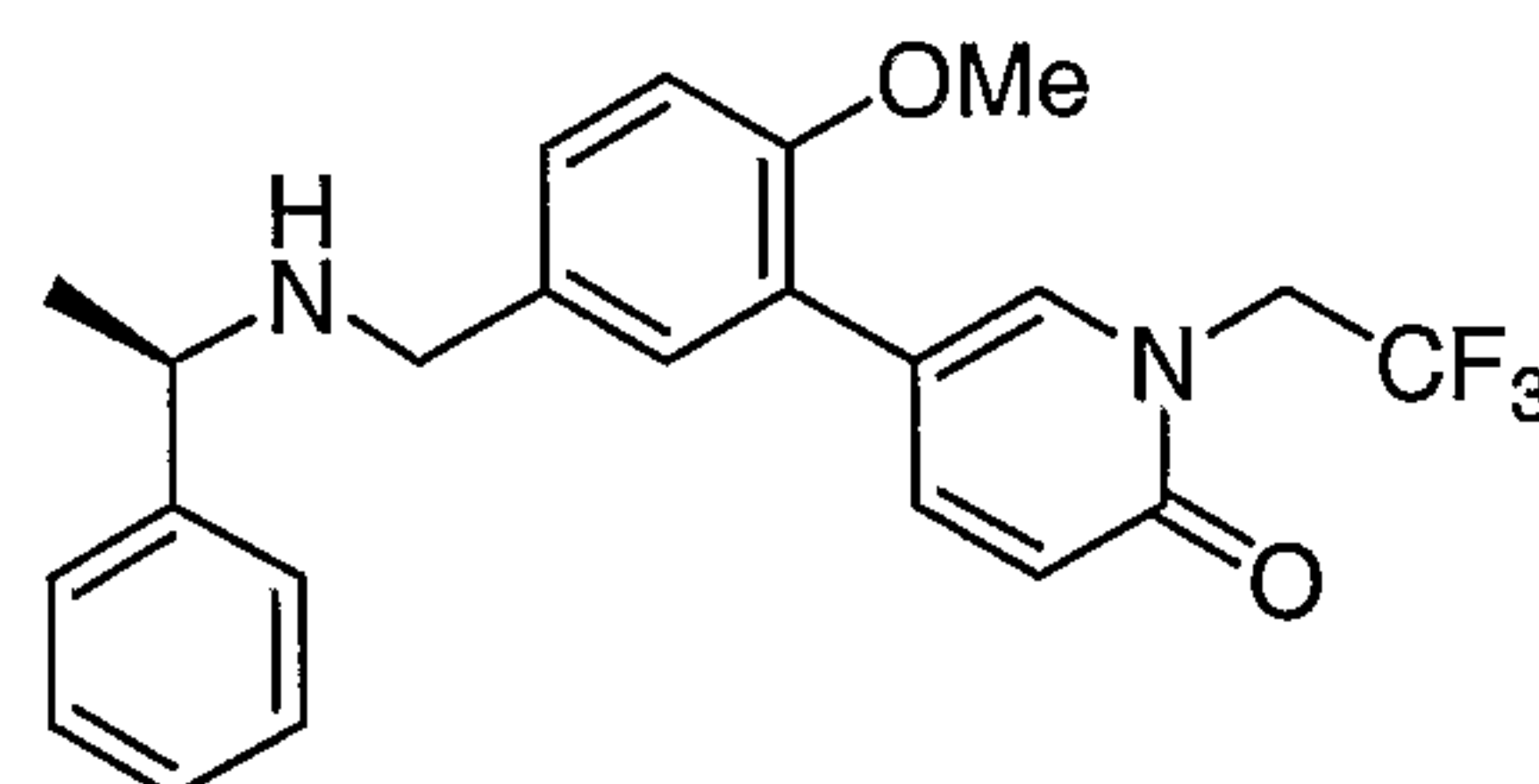
Mass found: 296, 447, 314

15

Example 368

5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1-(2,2,2-
trifluoroethyl)-2(1H)-pyridinone

20



MW 416.441

Mass found: 296, 314, 417

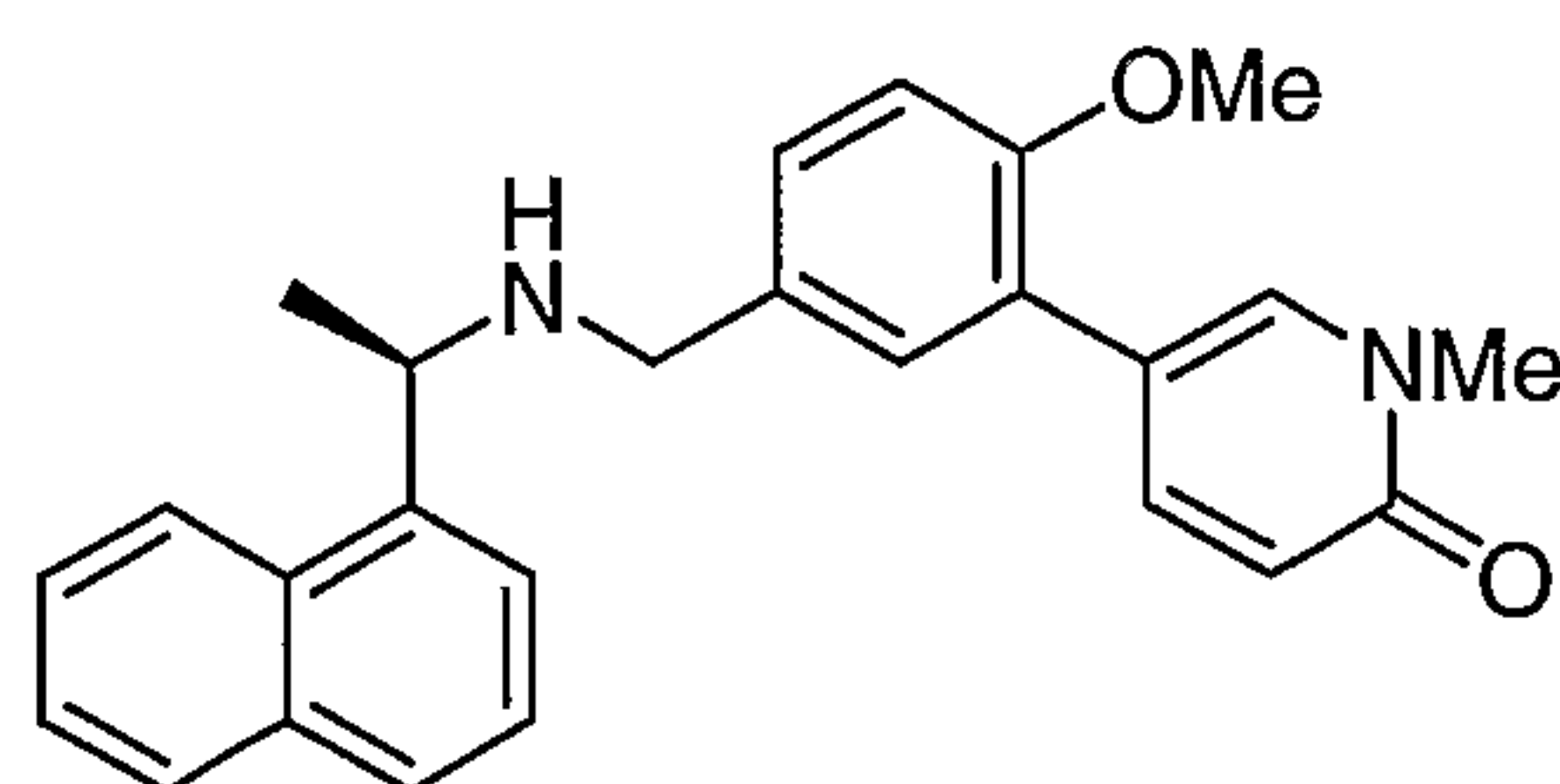
25

Example 369

1-methyl-5-(2-(methyloxy)-5-((((1R)-1-(1-
naphthalenyl)ethyl)amino)methyl)phenyl)-2(1H)-pyridinone

30

- 217 -



MW 398.503

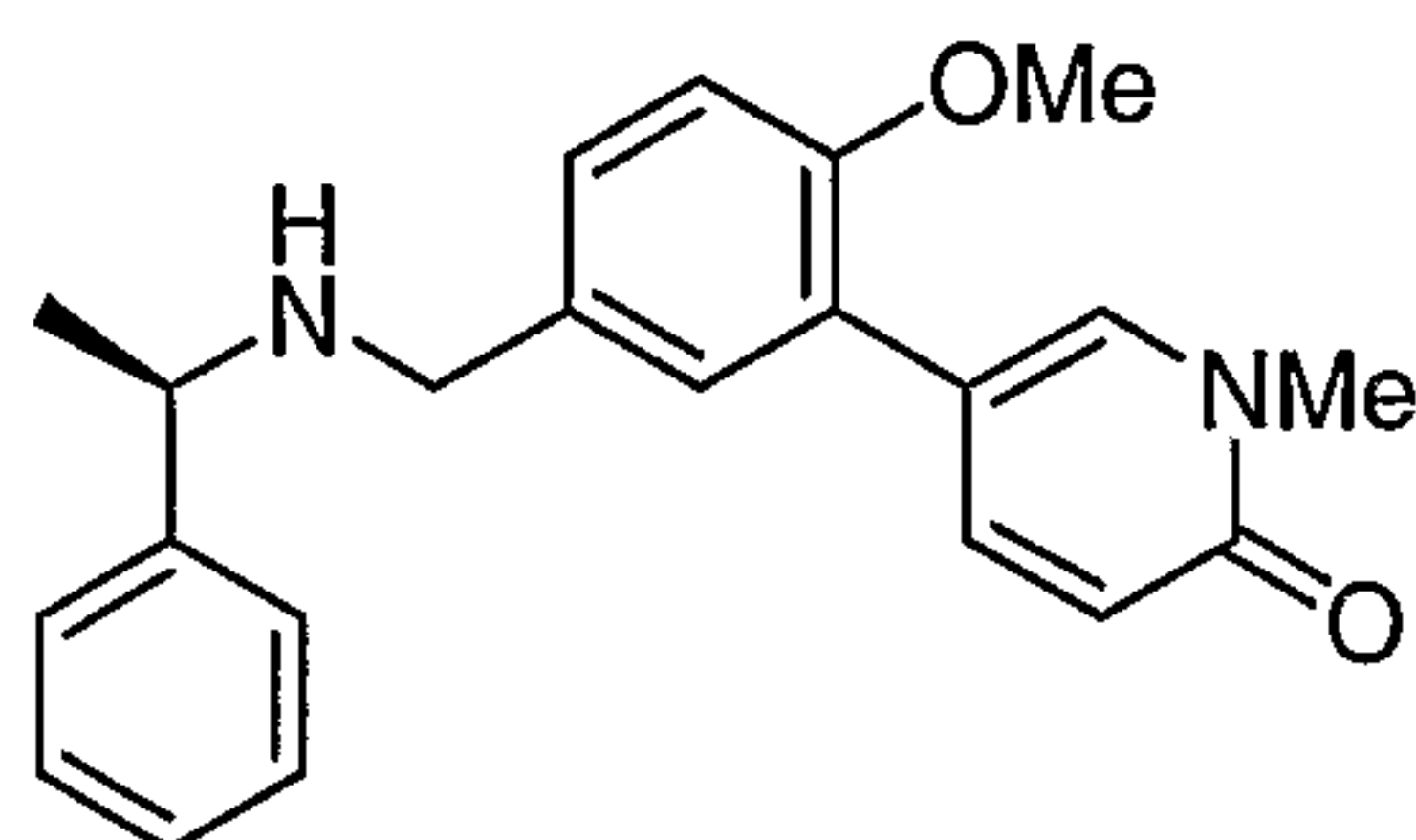
Mass found: 245, 399, 228, 155

5

Example 370

1-methyl-5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-
2(1H)-pyridinone

10



MW 348.444

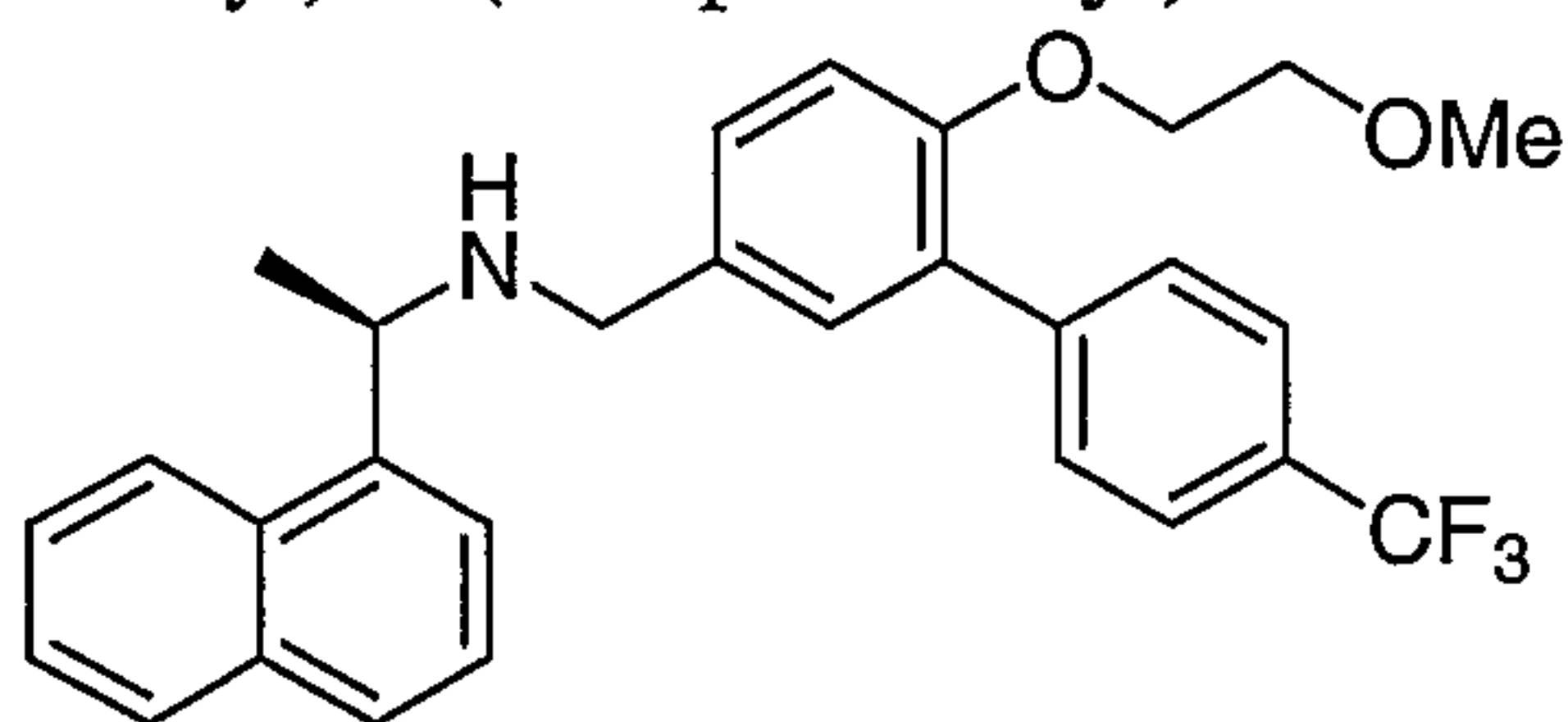
Mass found: 228, 349

15

Example 371

(1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-
yl)methyl)-1-(1-naphthalenyl)ethanamine

20



MW 479.539

Mass found: 480, 959

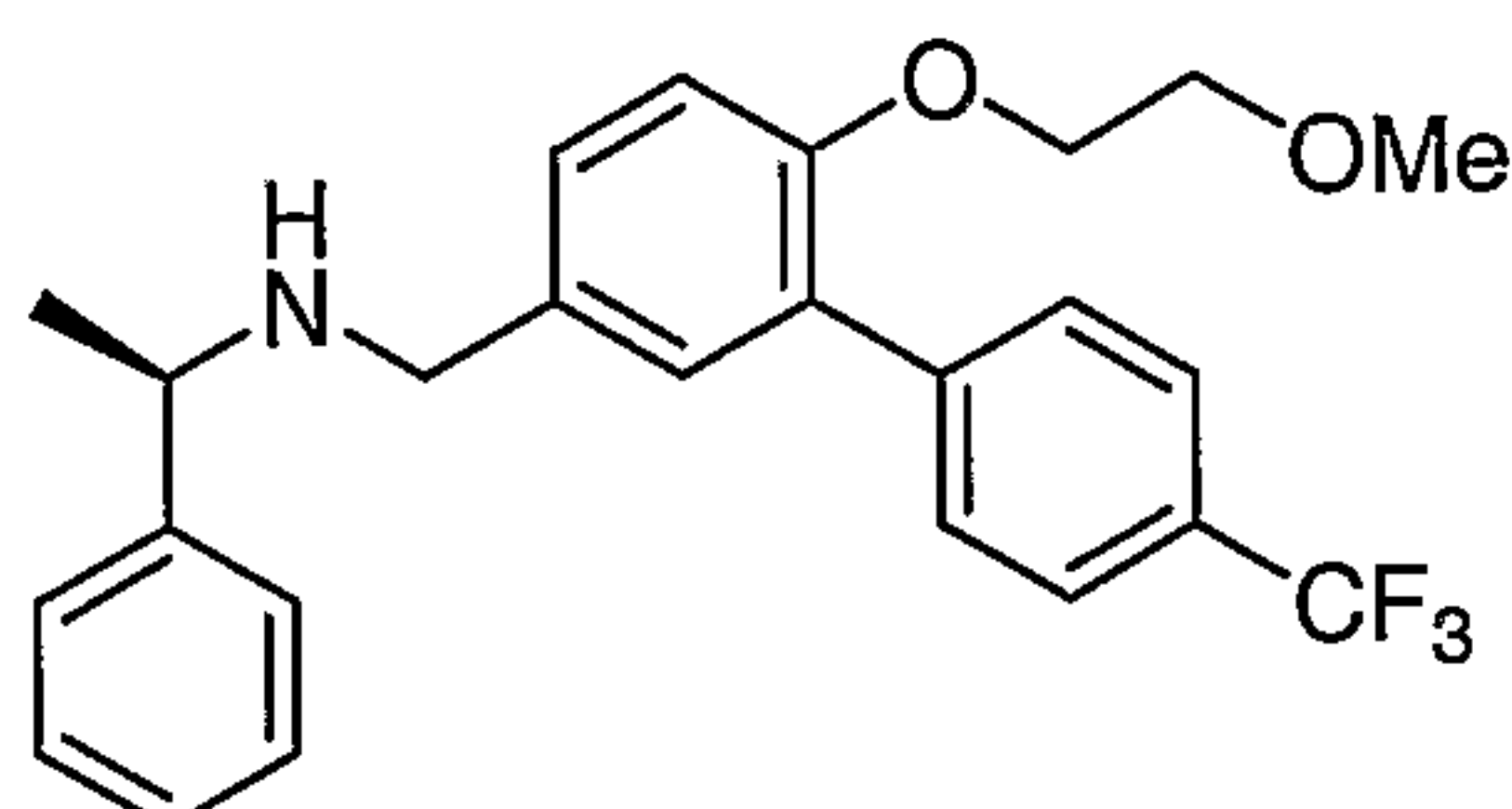
25

- 218 -

Example 372

(1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

5



MW 429.479

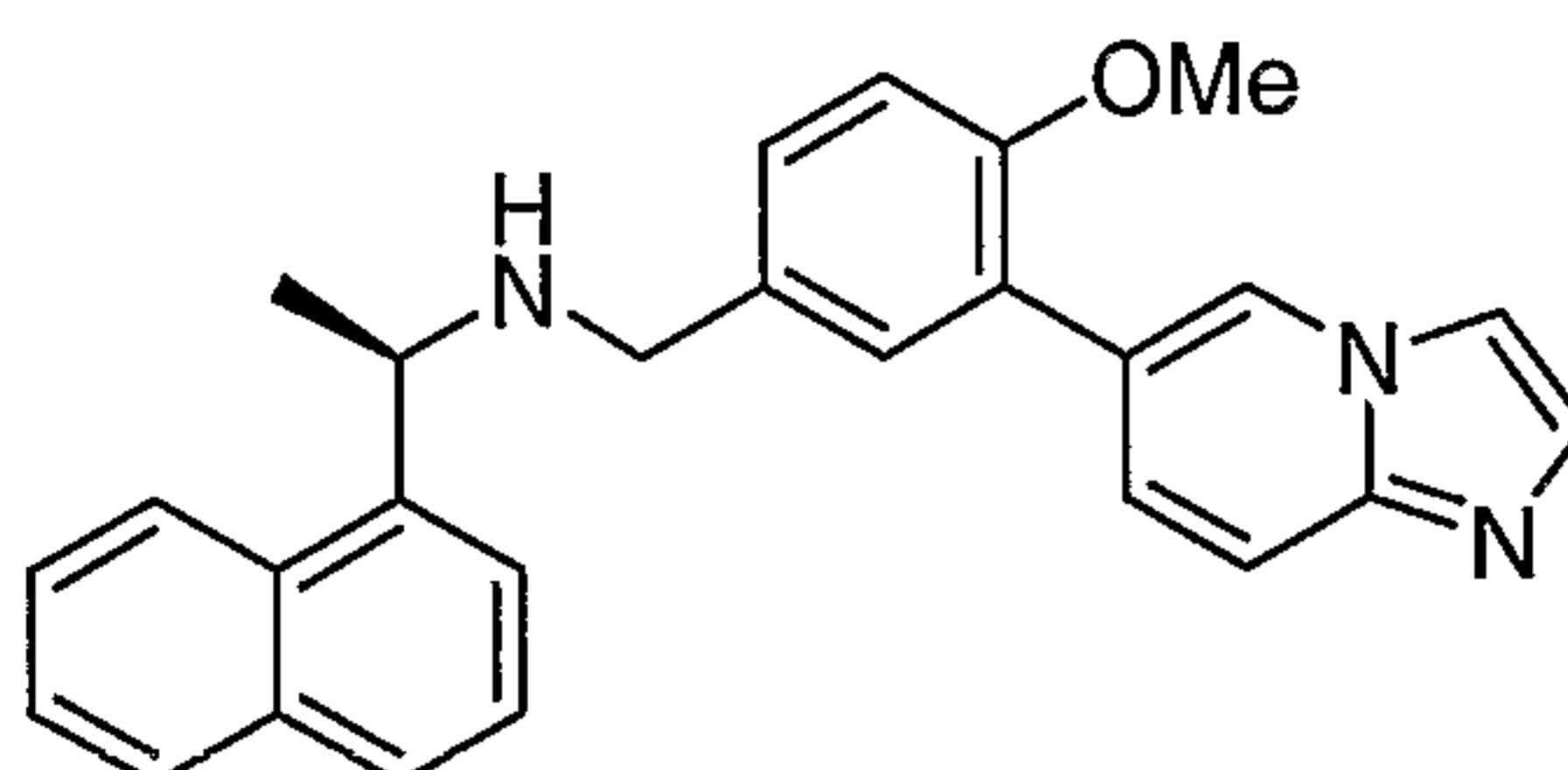
Mass found: 309, 430

10

Example 373

(1R)-N-((3-imidazo[1,2-a]pyridin-6-yl-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

15



MW 407.514

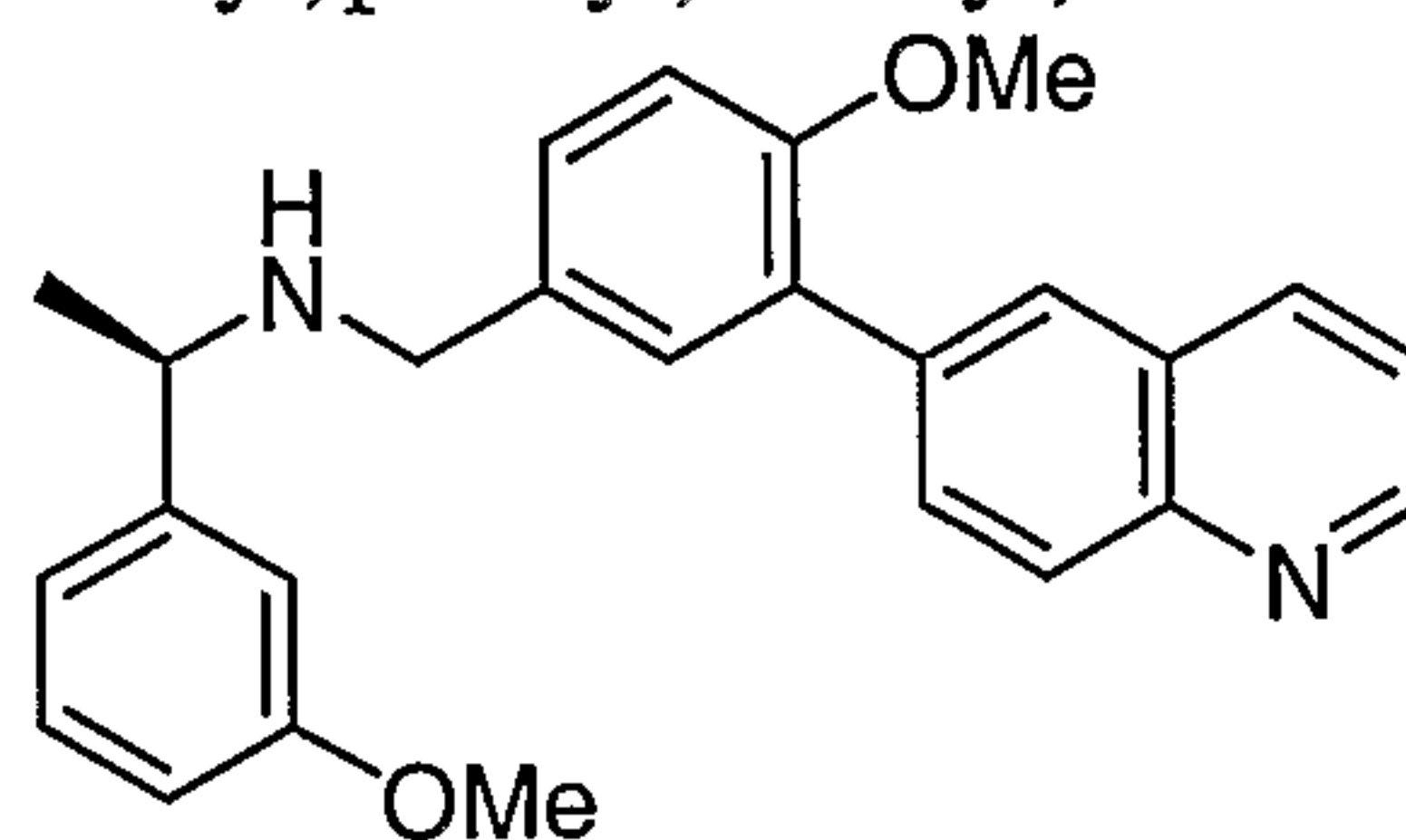
Mass found: 408, 254, 155

20

Example 374

(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-quinolinyl)phenyl)methyl)ethanamine

25



MW 398.503

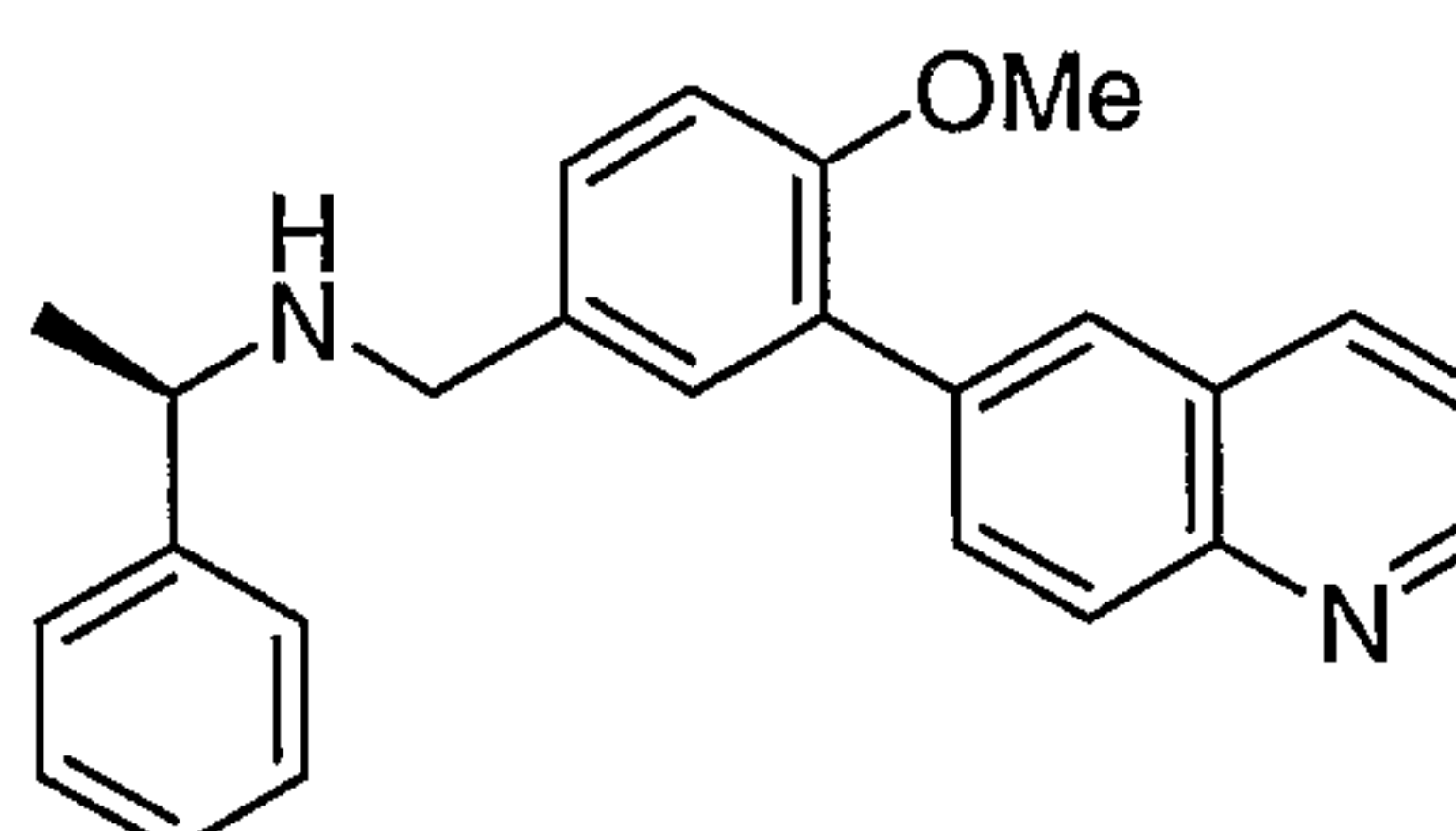
Mass found: 399, 248, 265

30

Example 375

- 219 -

(1R)-N-((4-(methyloxy)-3-(6-quinoliny)phenyl)methyl)-1-phenylethanamine



5

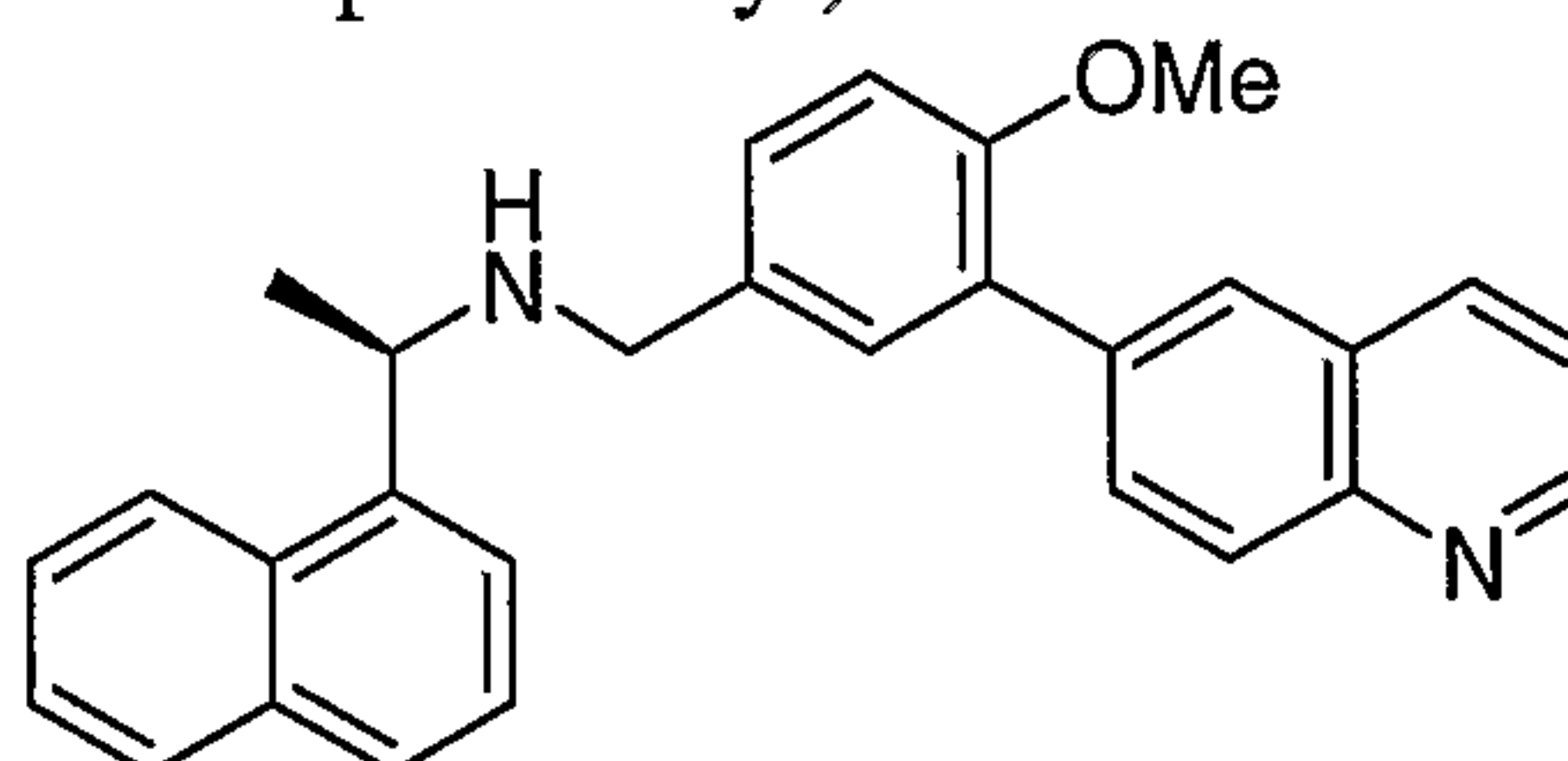
MW 368.478

Mass found: 248, 369, 265

10

Example 376

(1R)-N-((4-(methyloxy)-3-(6-quinoliny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



15

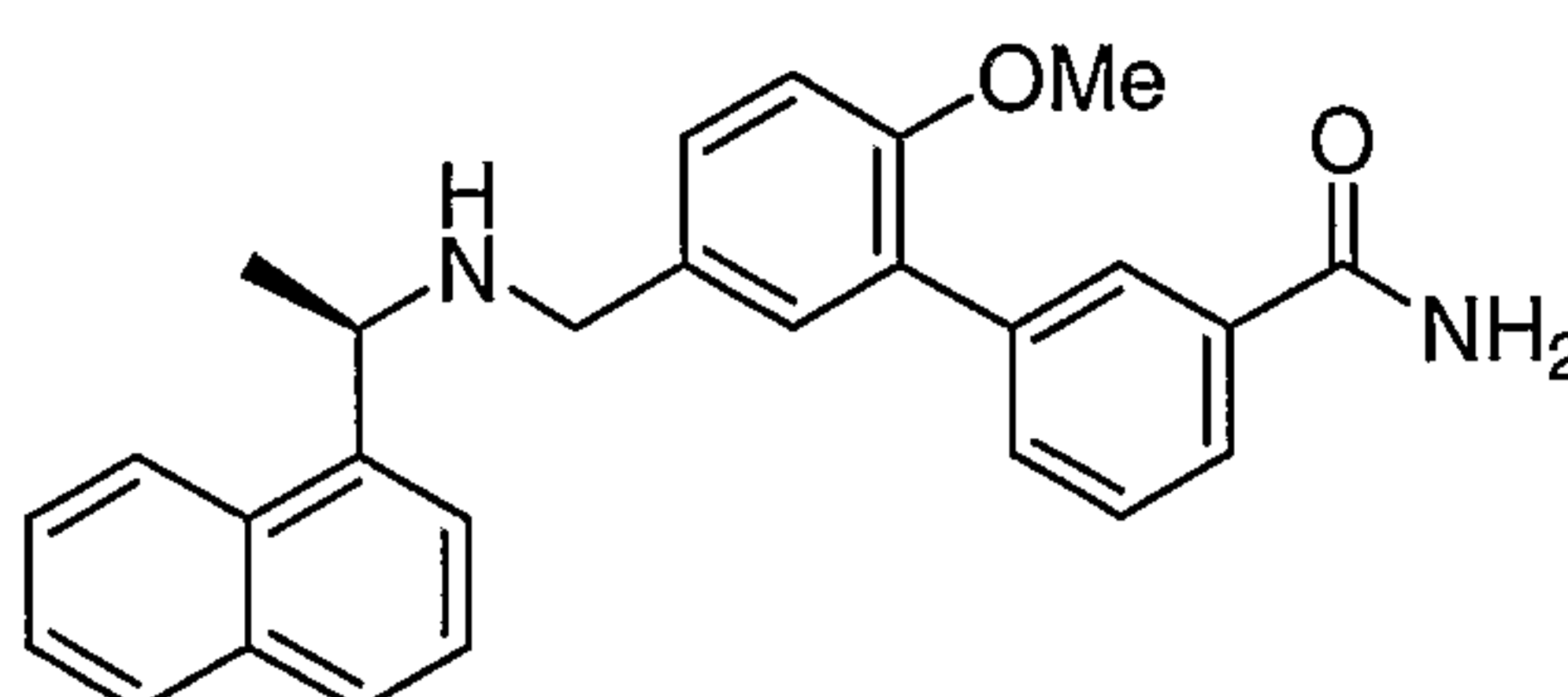
MW 418.537

Mass found: 419, 248, 265

20

Example 377

2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carboxamide



25

MW 410.514

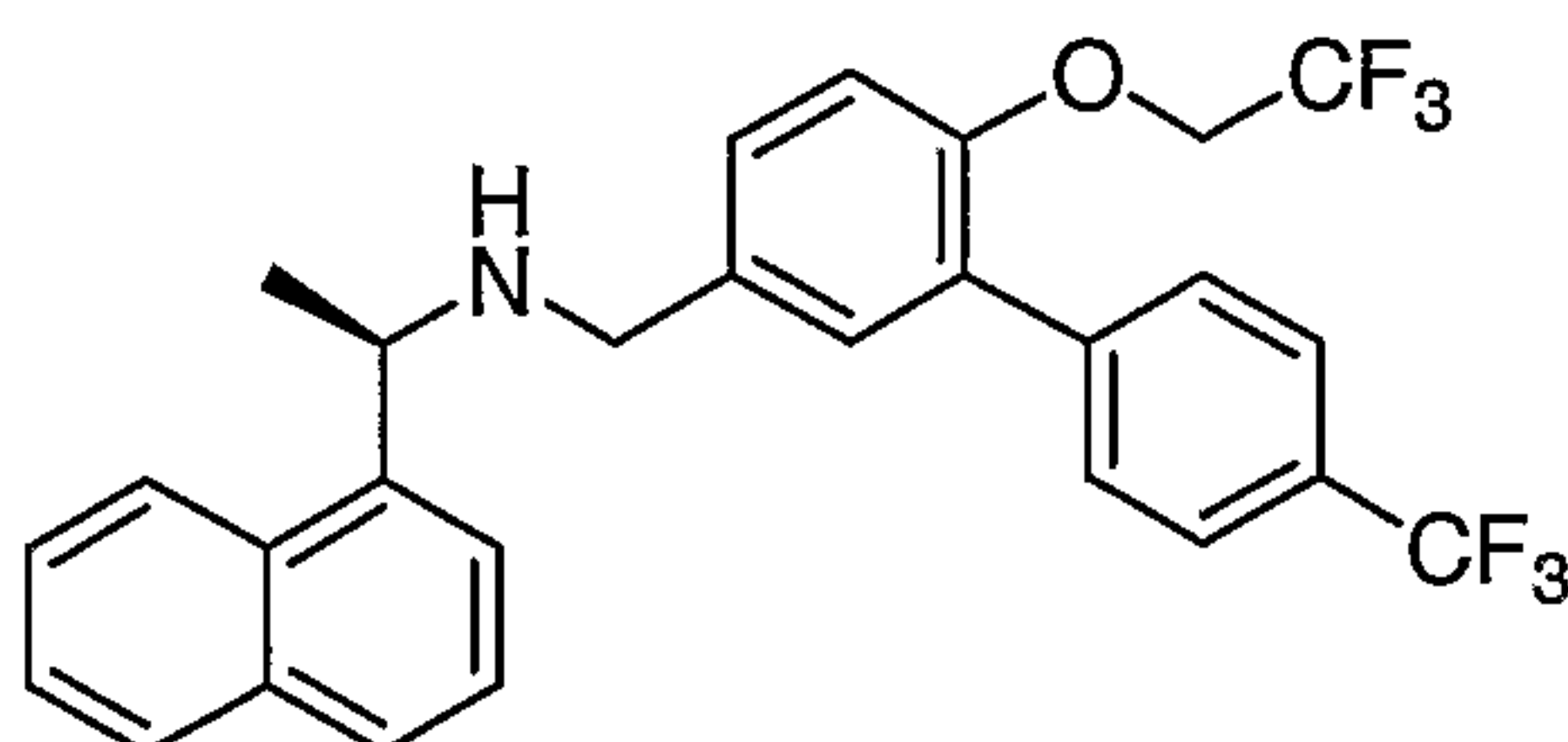
Mass found: 411, 821

30

Example 378

- 220 -

(1R)-1-(1-naphthalenyl)-N-((6-((2,2,2-trifluoroethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine



5

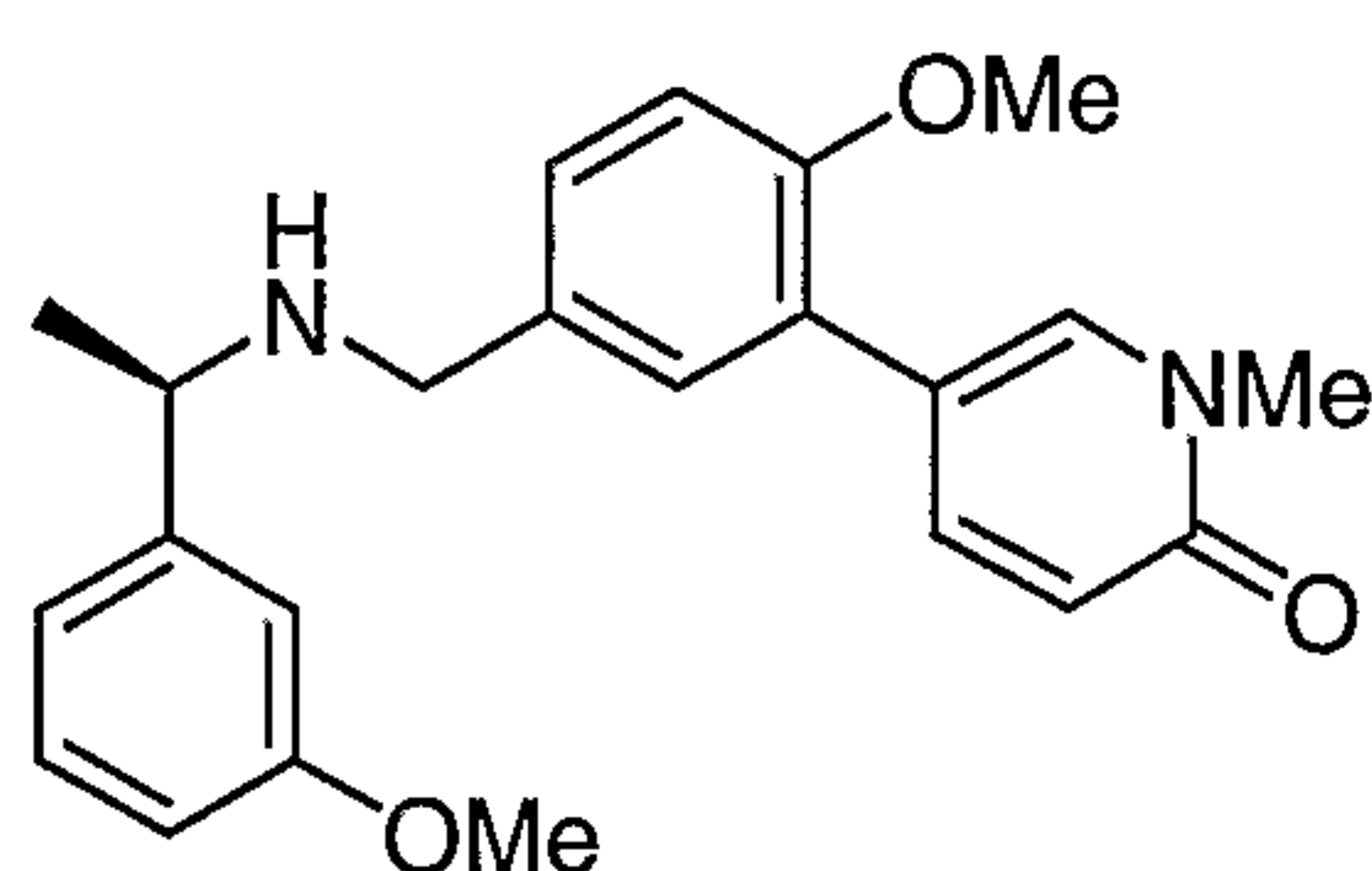
MW 503.484

Mass found: 155, 504

10

Example 379

1-methyl-5-(2-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2(1H)-pyridinone



15

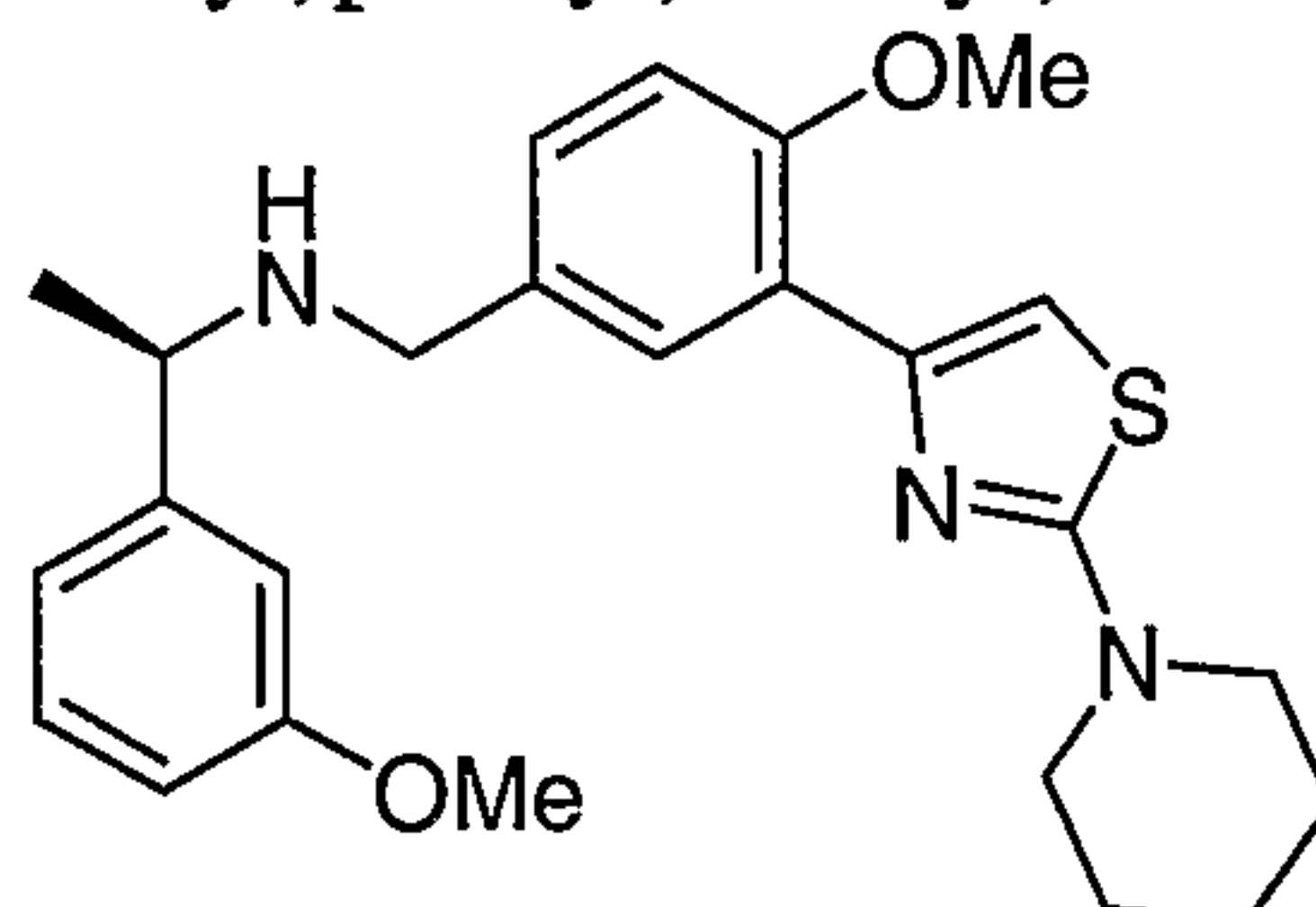
MW 378.469

Mass found: 228, 379

20

Example 380

(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-(1-piperidinyl)-1,3-thiazol-4-yl)phenyl)methyl)ethanamine



25

MW 437.605

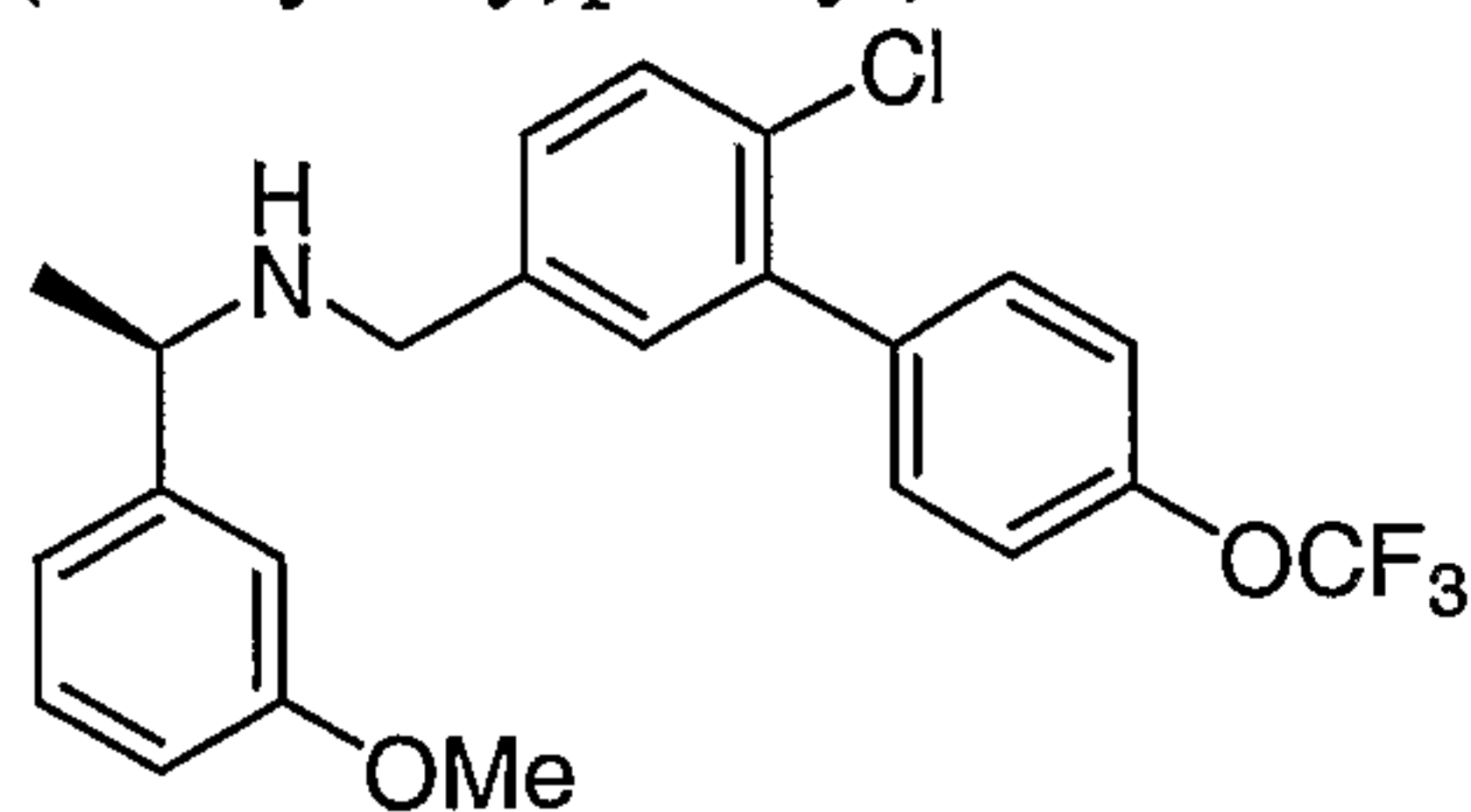
Mass found: 438, 875

30

Example 381

- 221 -

(1R)-N-((6-chloro-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine



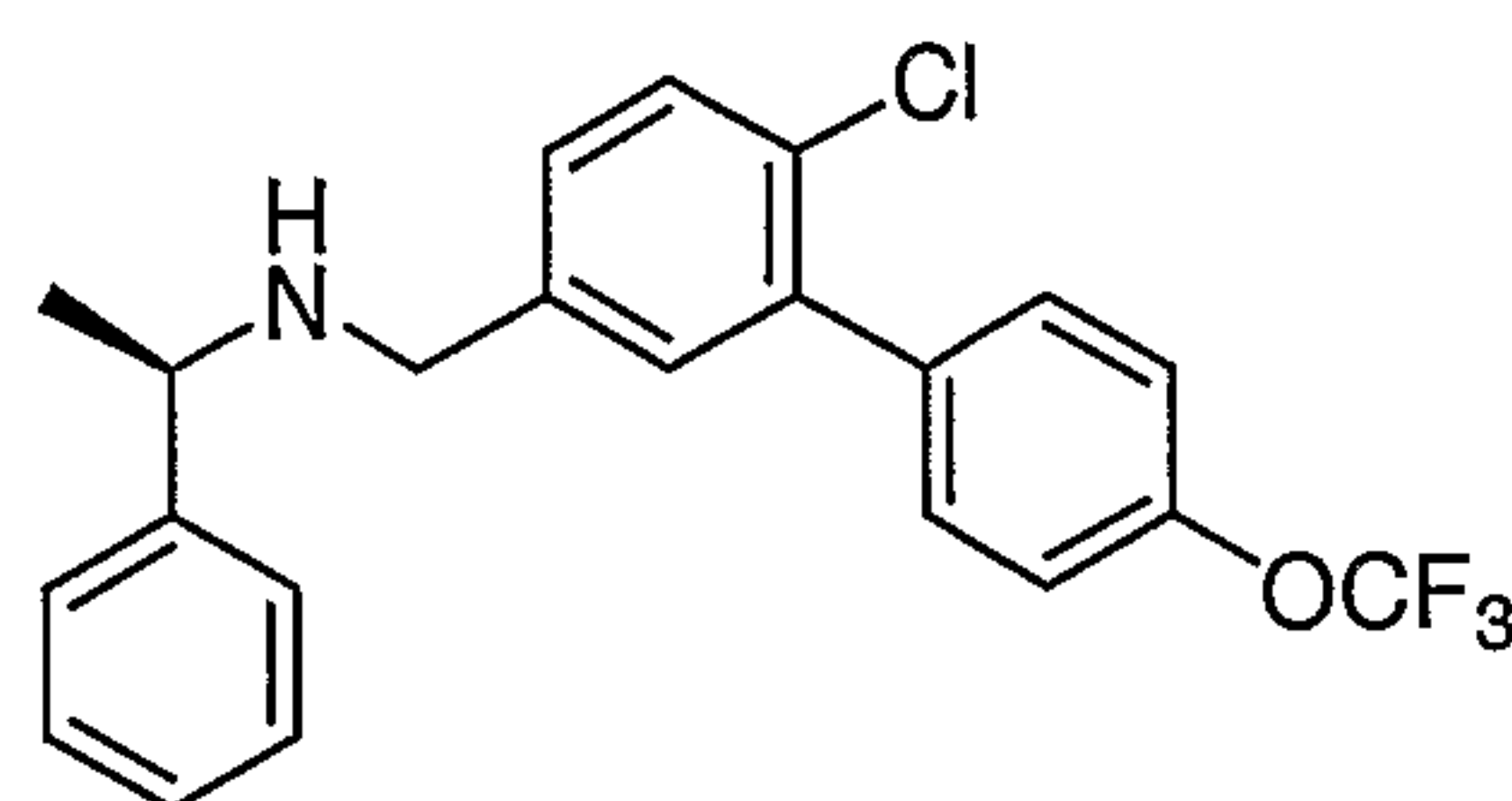
5

MW 435.871
Mass found: 436, 477

Example 382

10

(1R)-N-((6-chloro-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine



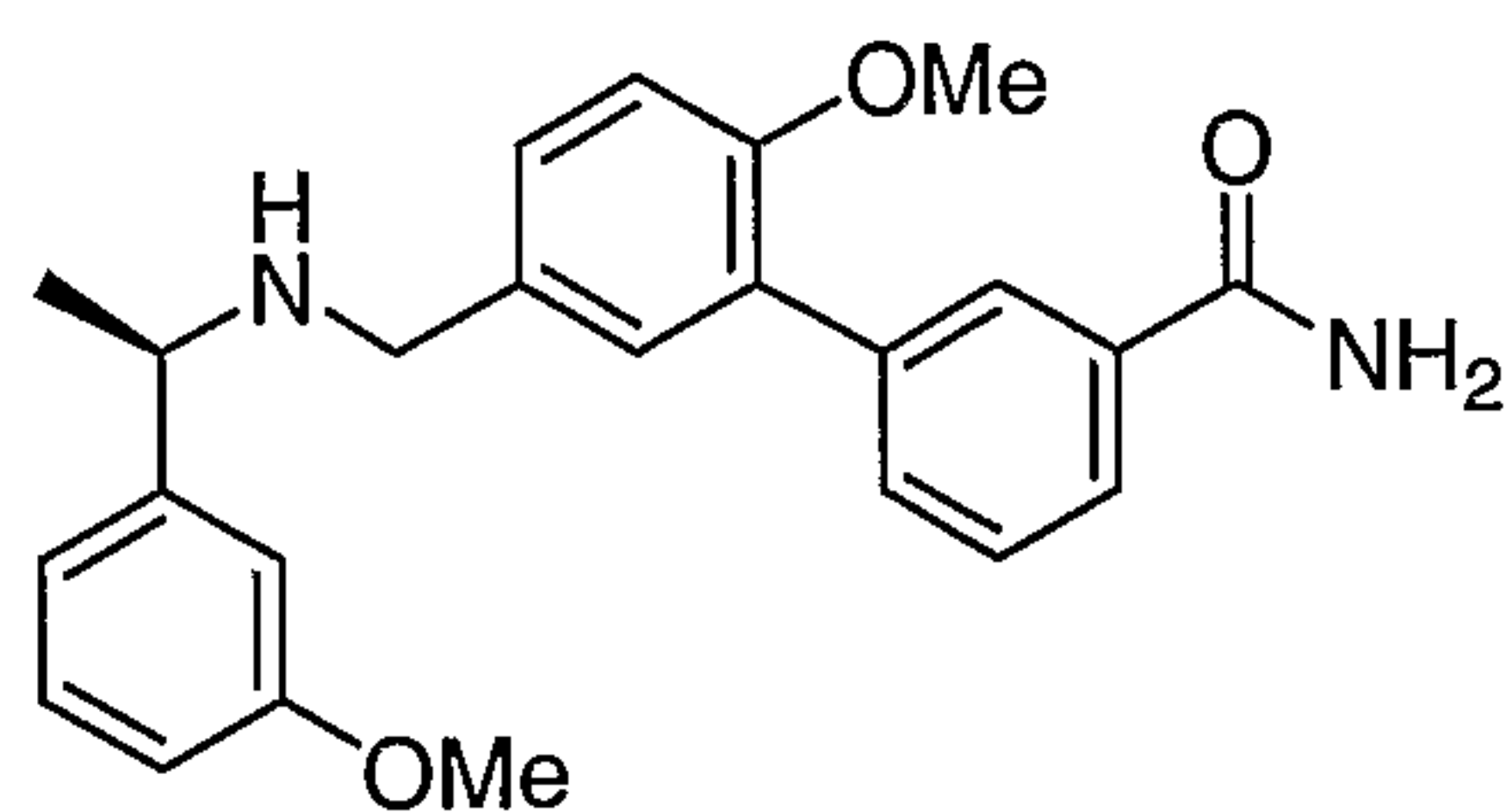
15

MW 405.845
Mass found: 406

Example 383

20

2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carboxamide



25

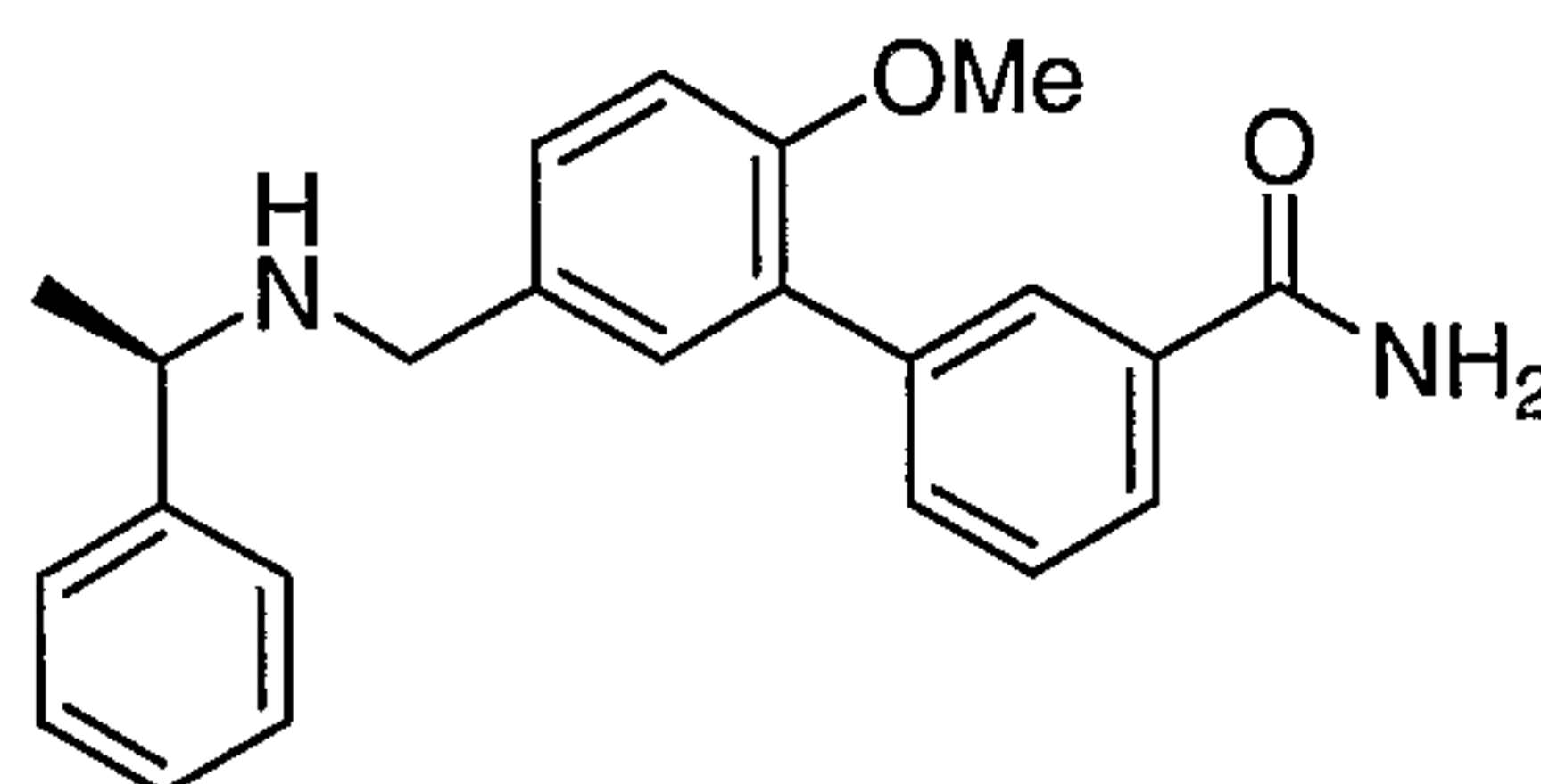
MW 390.48
Mass found: 391, 432, 781, 895

Example 384

30

- 222 -

2'-(methoxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-carboxamide



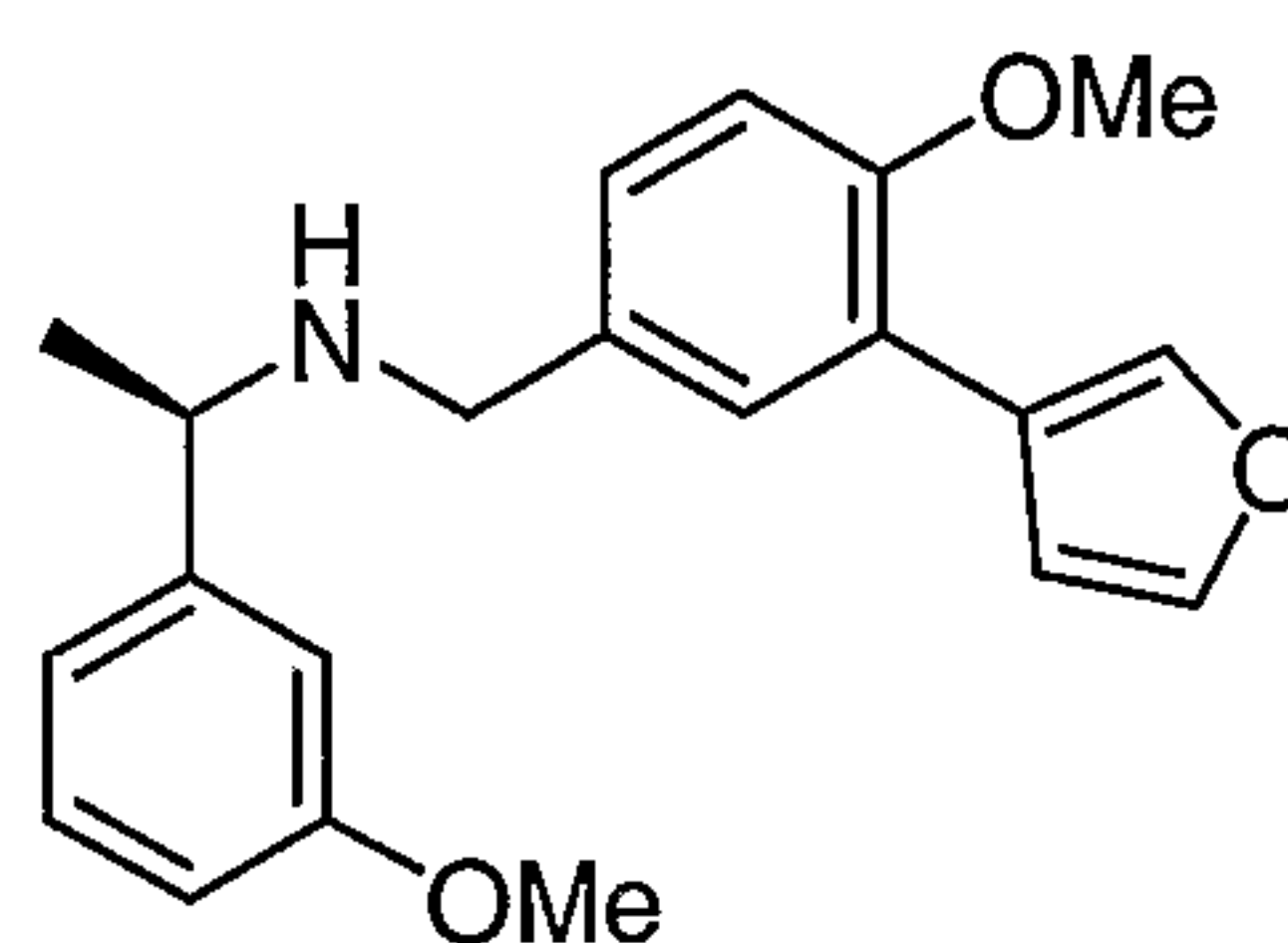
5

MW 360.455
Mass found: 361, 721, 402

Example 385

10

(1R)-N-((3-(3-furanyl)-4-(methoxy)phenyl)methyl)-1-(3-(methoxy)phenyl)ethanamine



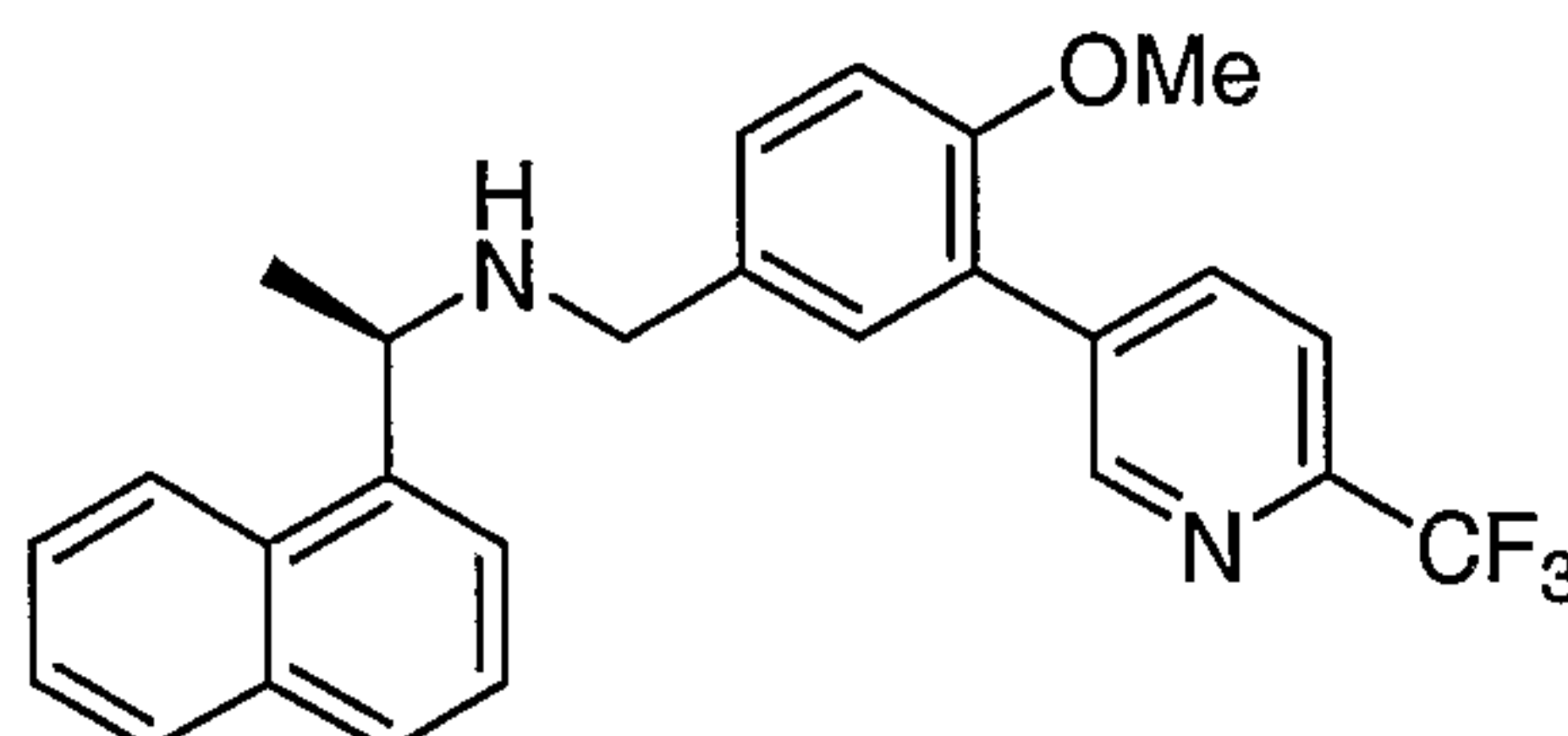
15

MW 337.417
Mass found: 187, 338

Example 386

20

(1R)-1-(1-naphthalenyl)-N-((3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)ethanamine



25

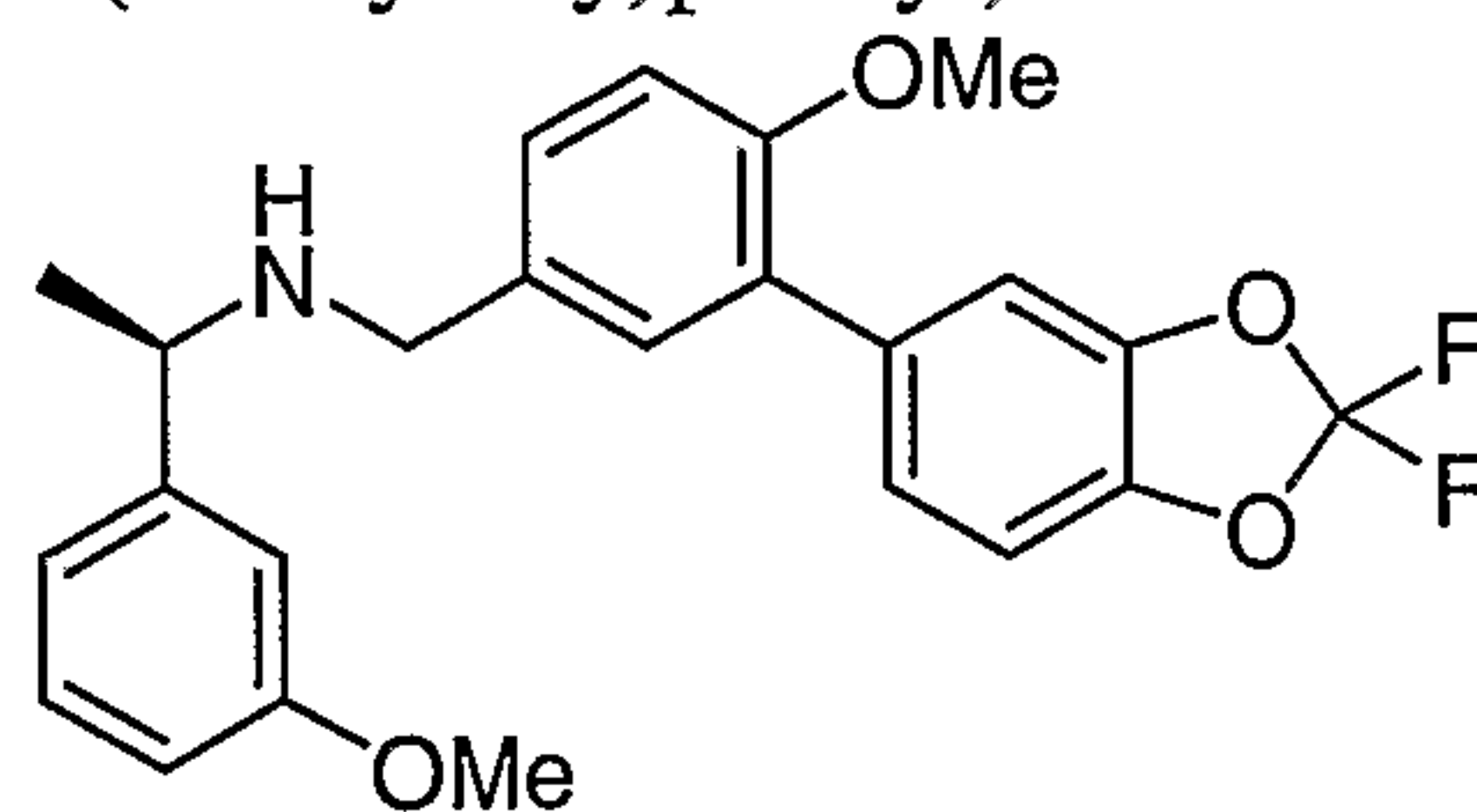
MW 406.449
Mass found: 155, 407

30

- 223 -

Example 387

(1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methoxy)phenyl)methyl)-1-(3-(methoxy)phenyl)ethanamine



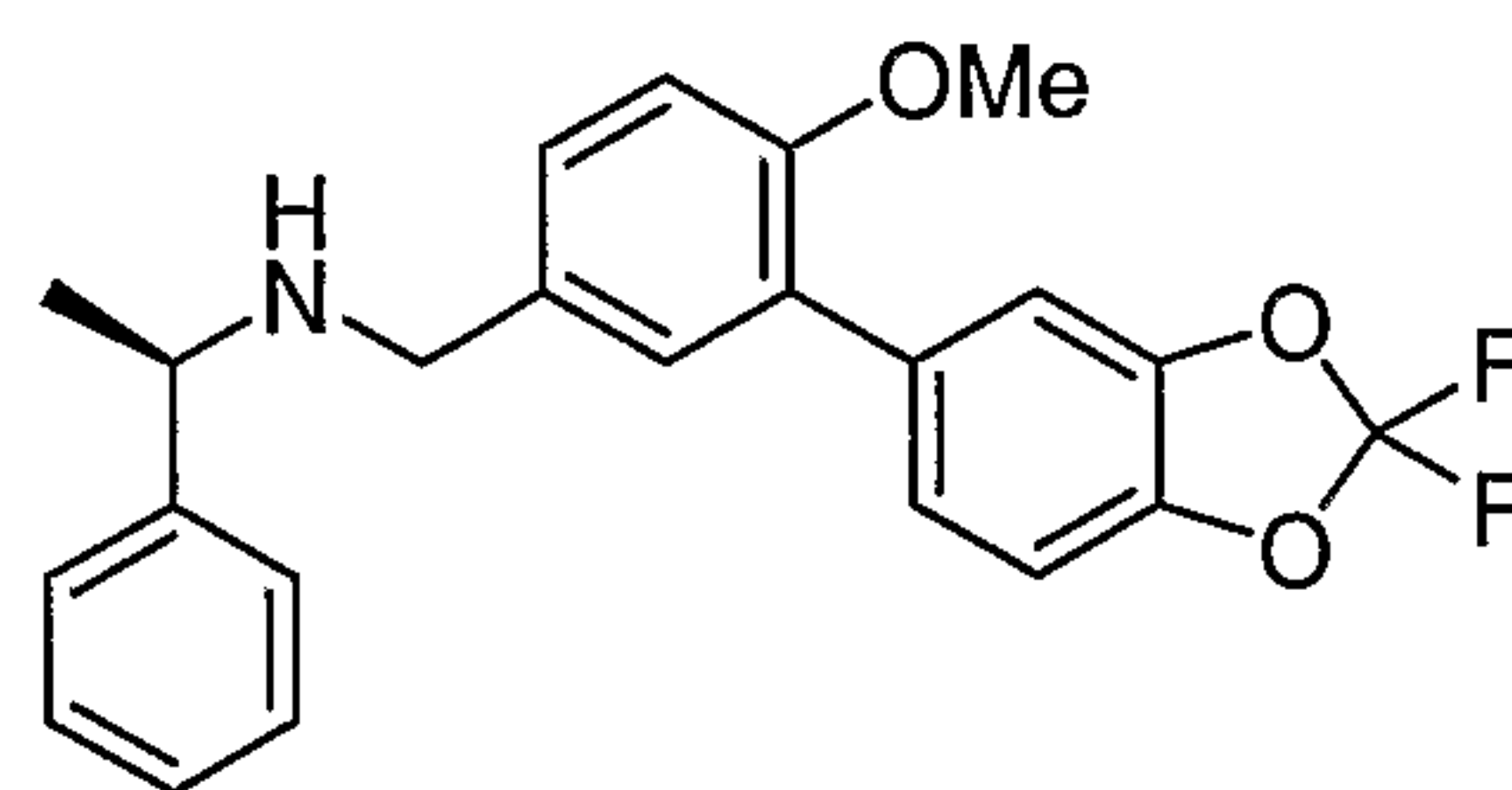
5

MW 427.445
Mass found: 428, 855, 969

10

Example 388

(1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methoxy)phenyl)methyl)-1-phenylethanamine



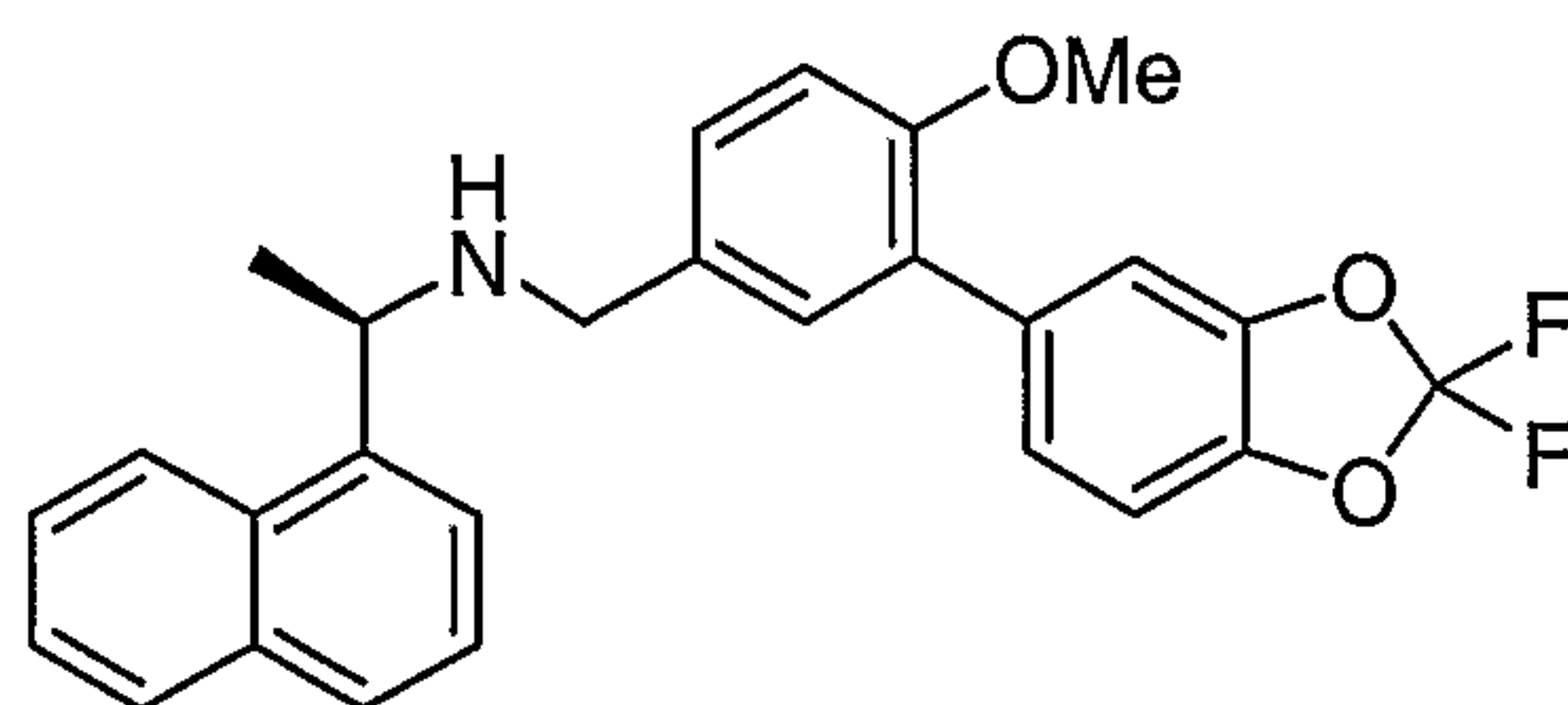
15

MW 397.419
Mass found: 398, 277

20

Example 389

(1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methoxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



25

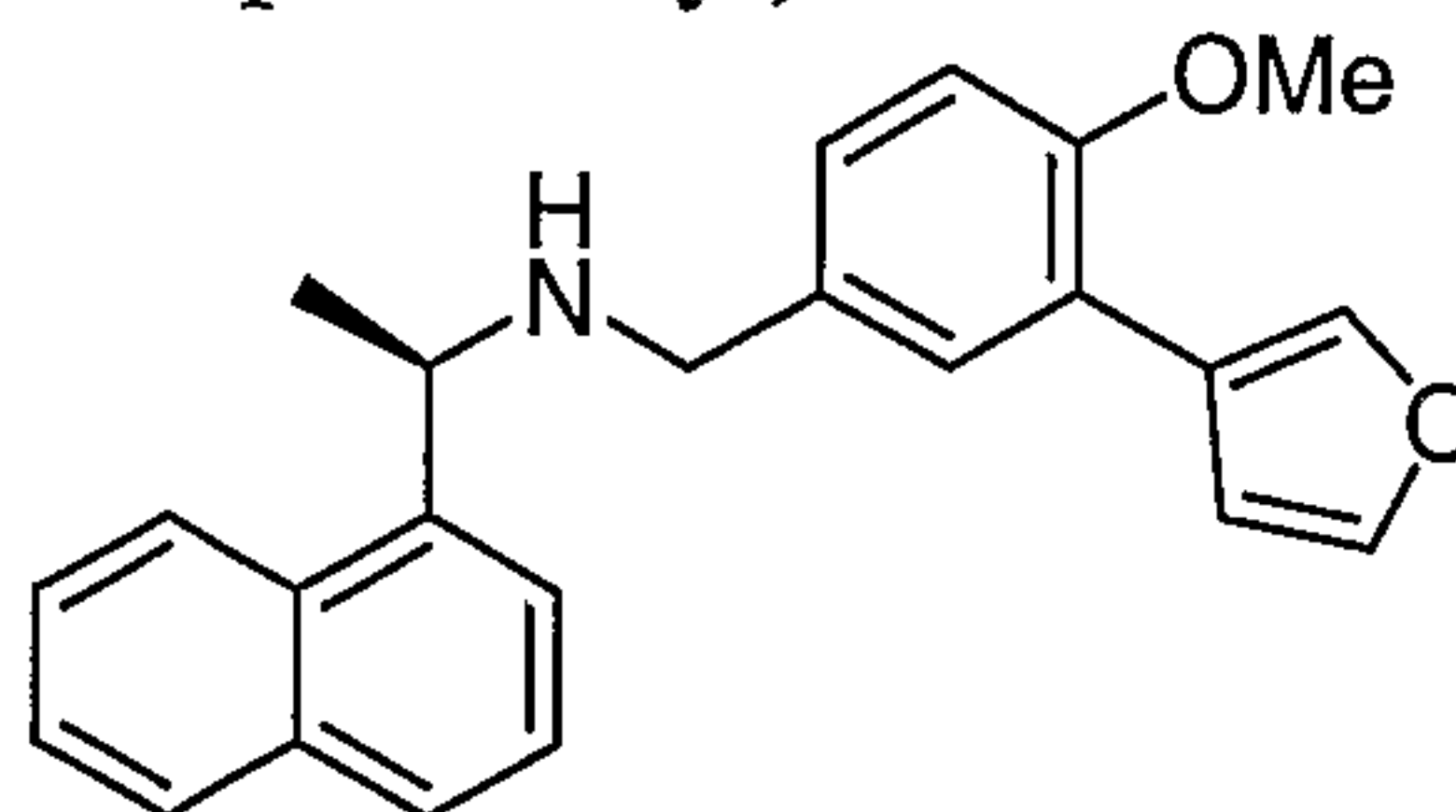
MW 447.479
Mass found: 448, 895

30

Example 390

- 224 -

(1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



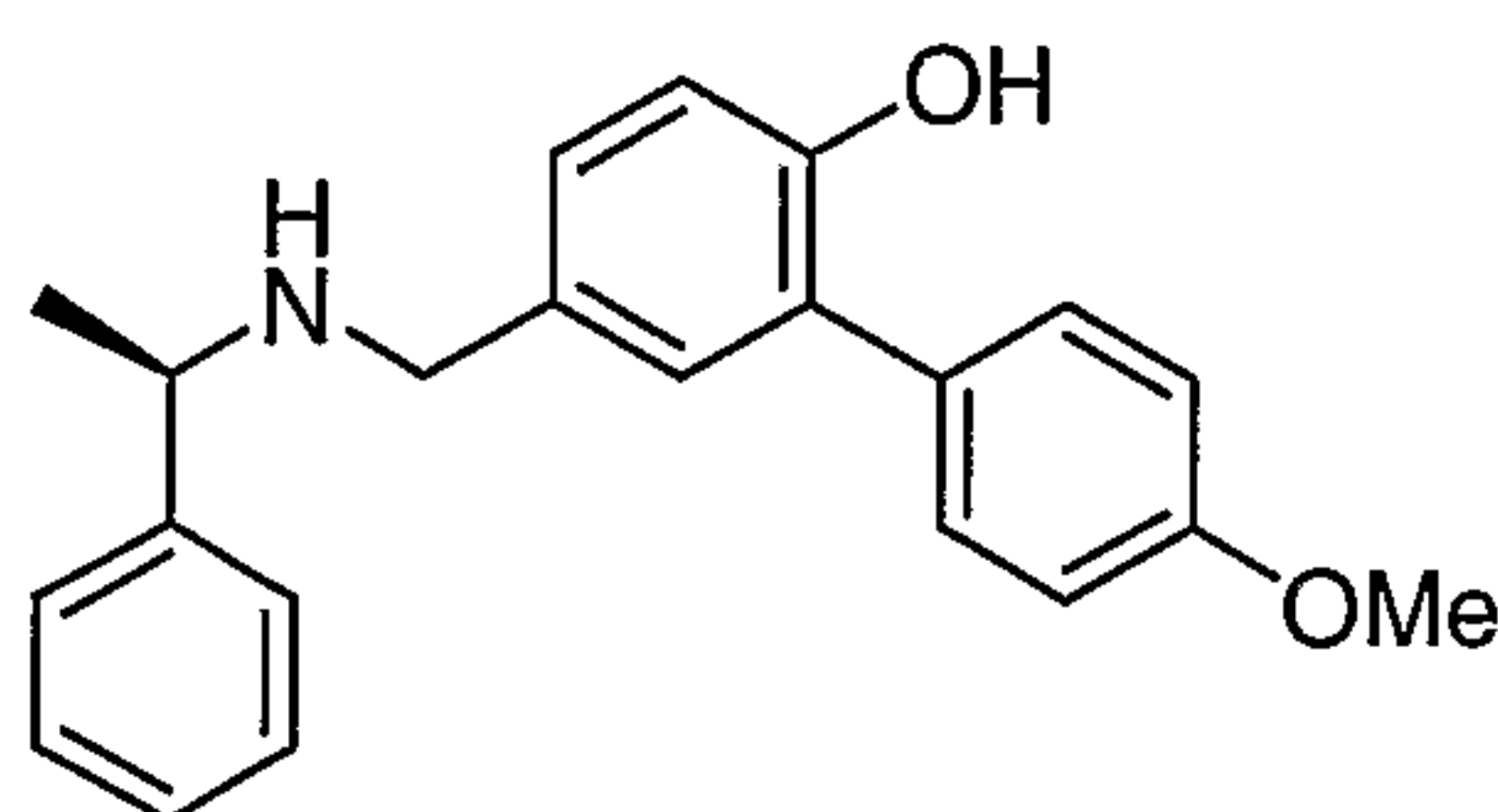
5

MW 357.451
Mass found: 358

10

Example 391

4'-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-2-ol



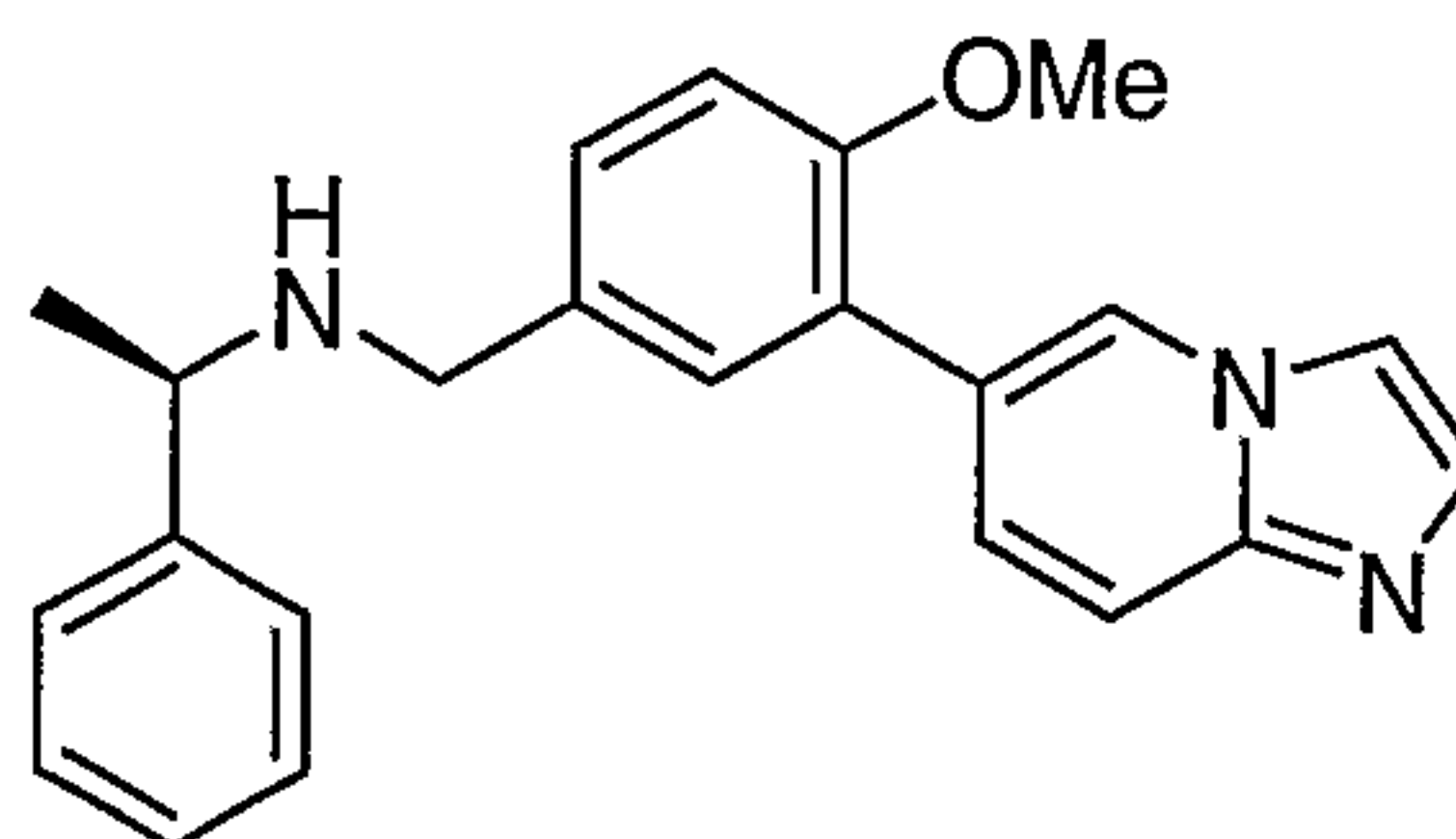
15

MW 333.429
Mass found: 334, 213

20

Example 392

(1R)-N-((3-imidazo[1,2-a]pyridin-6-yl-4-(methyloxy)phenyl)methyl)-1-phenylethanamine



25

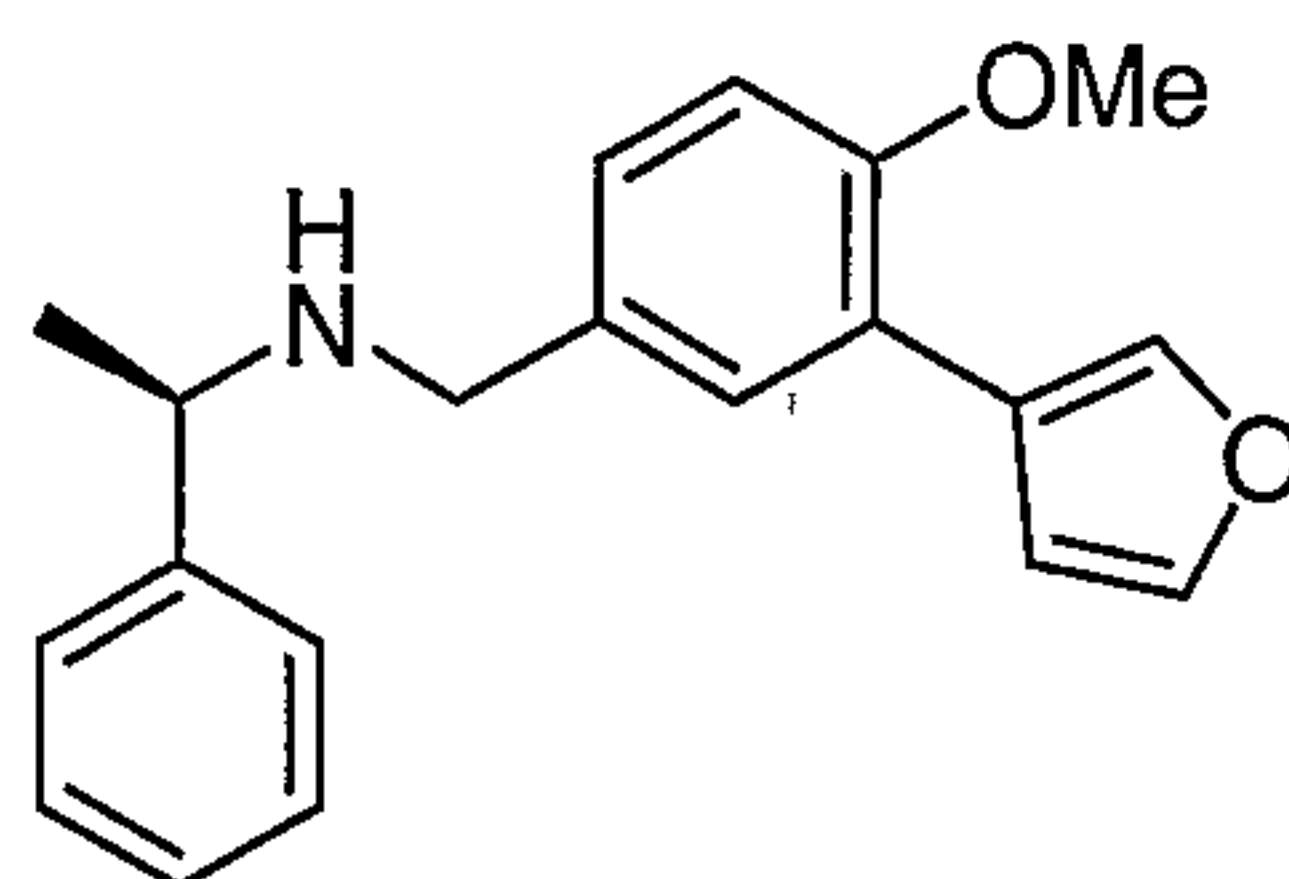
MW 357.455
Mass found: 358

30

Example 393

- 225 -

(1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine

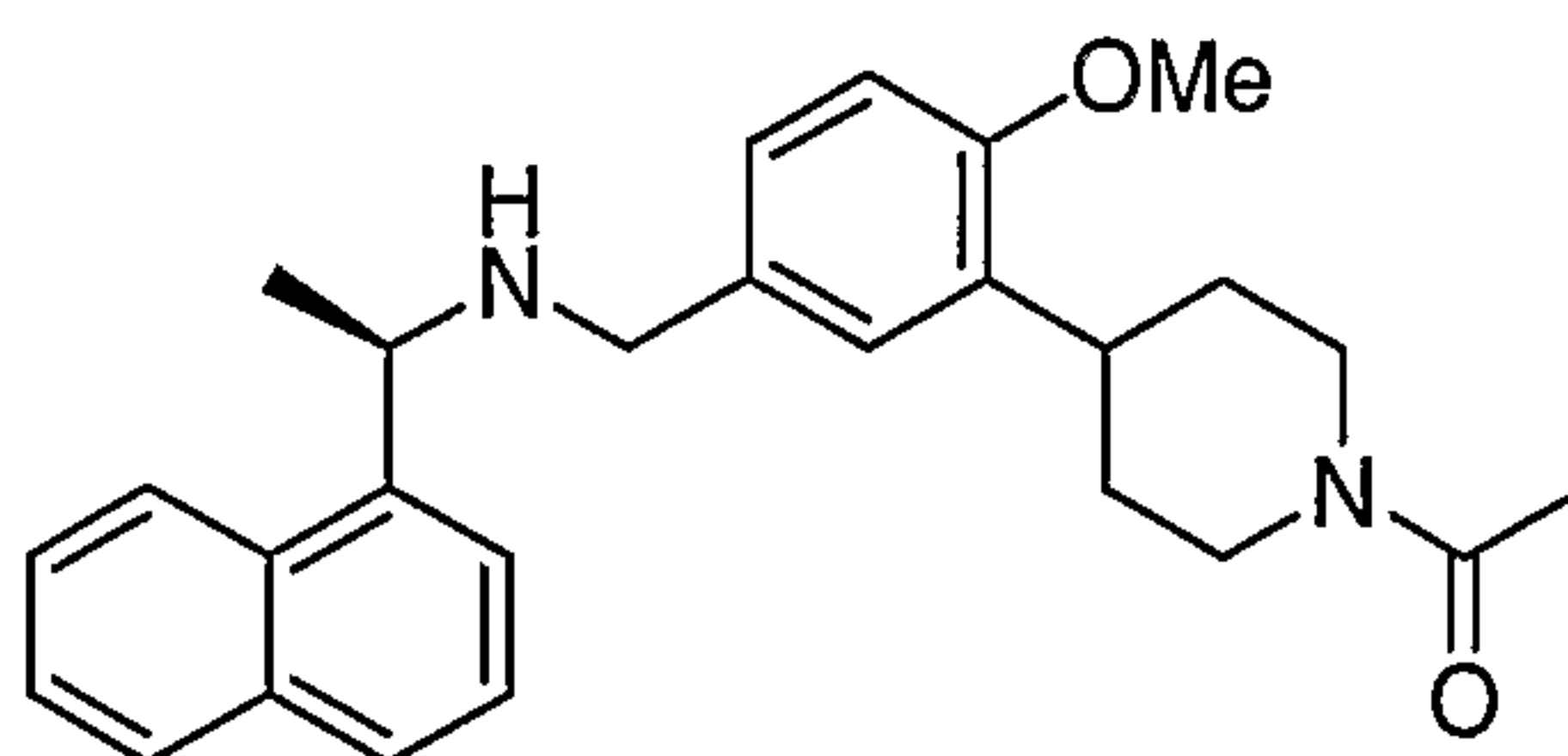


5

MW 307.391
Mass found: 308, 187**Example 394**

10

(1R)-N-((3-(1-acetyl-4-piperidiny)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

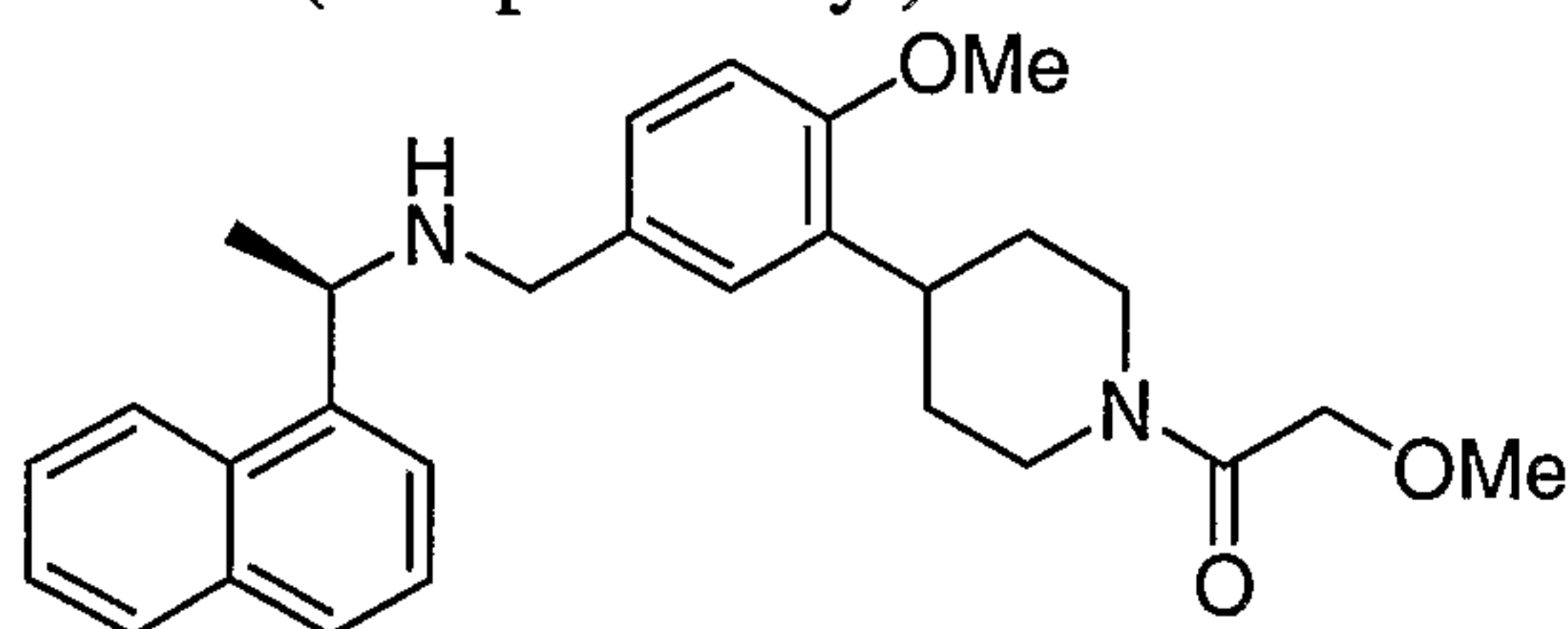


15

MW 416.562
Mass found: 417**Example 395**

20

(1R)-N-((4-(methyloxy)-3-(1-((methyloxy)acetyl)-4-piperidiny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



25

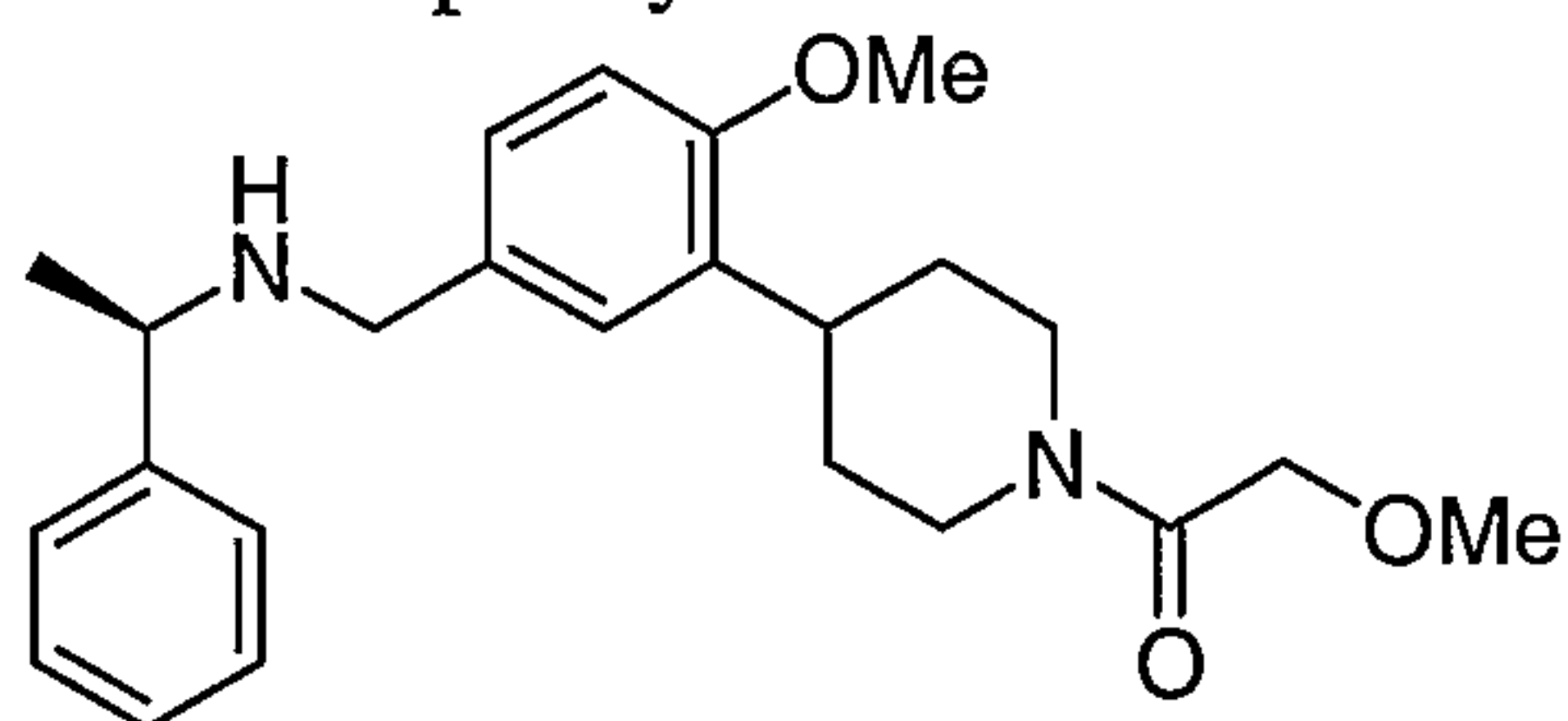
MW 446.588
Mass found: 447

30

Example 396

- 226 -

(1R)-N-((4-(methyloxy)-3-(1-((methyloxy)acetyl)-4-piperidiny)phenyl)methyl)-1-phenylethanamine



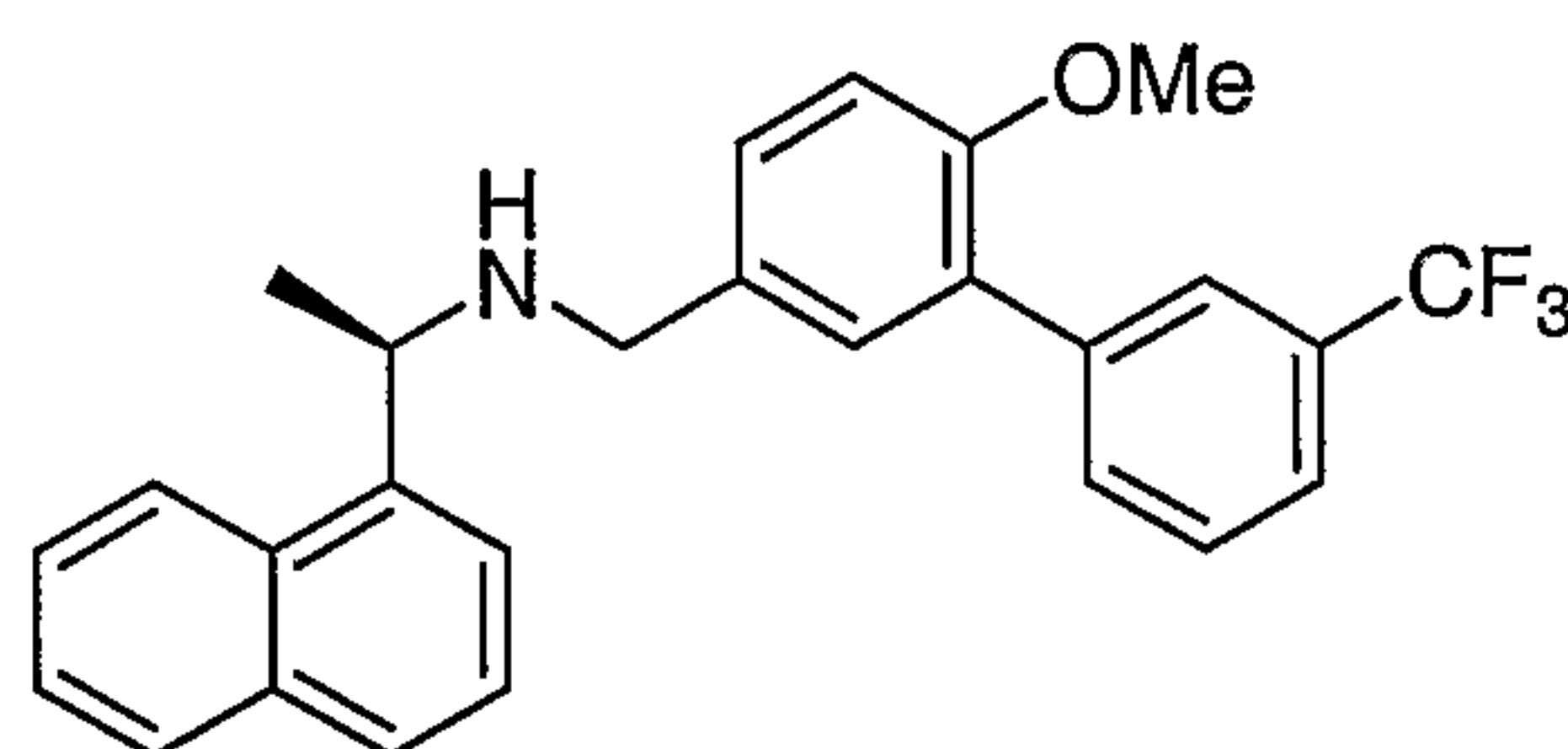
5

MW 396.528
Mass found: 397

Example 397

10

(1R)-N-((6-(methyloxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine



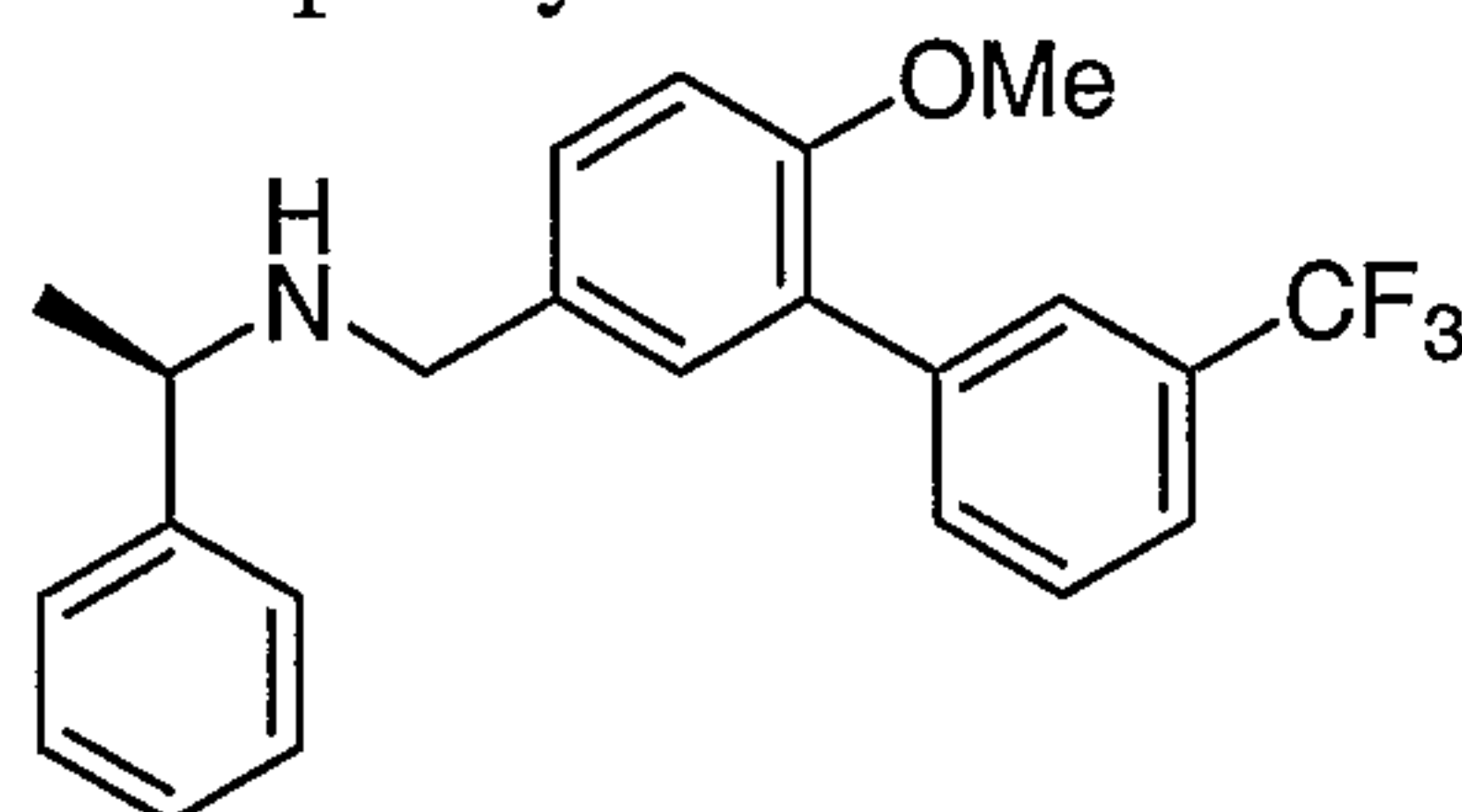
15

MW 435.487
Mass found: 155, 436

Example 398

20

(1R)-N-((6-(methyloxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine



25

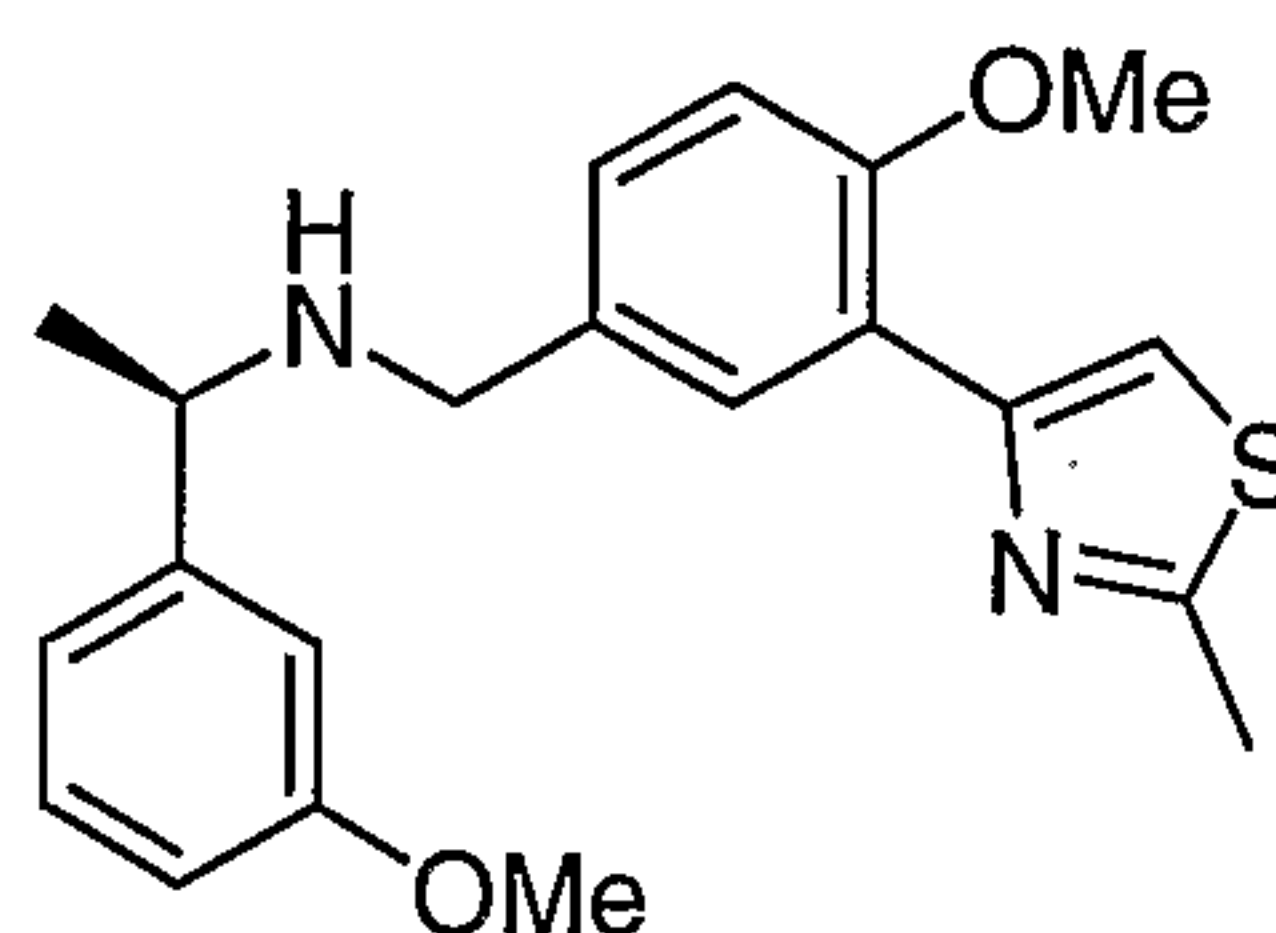
MW 385.427
Mass found: 386, 265

Example 399

30

(1R)-N-((4-(methyloxy)-3-(2-methyl-1,3-thiazol-4-yl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

- 227 -

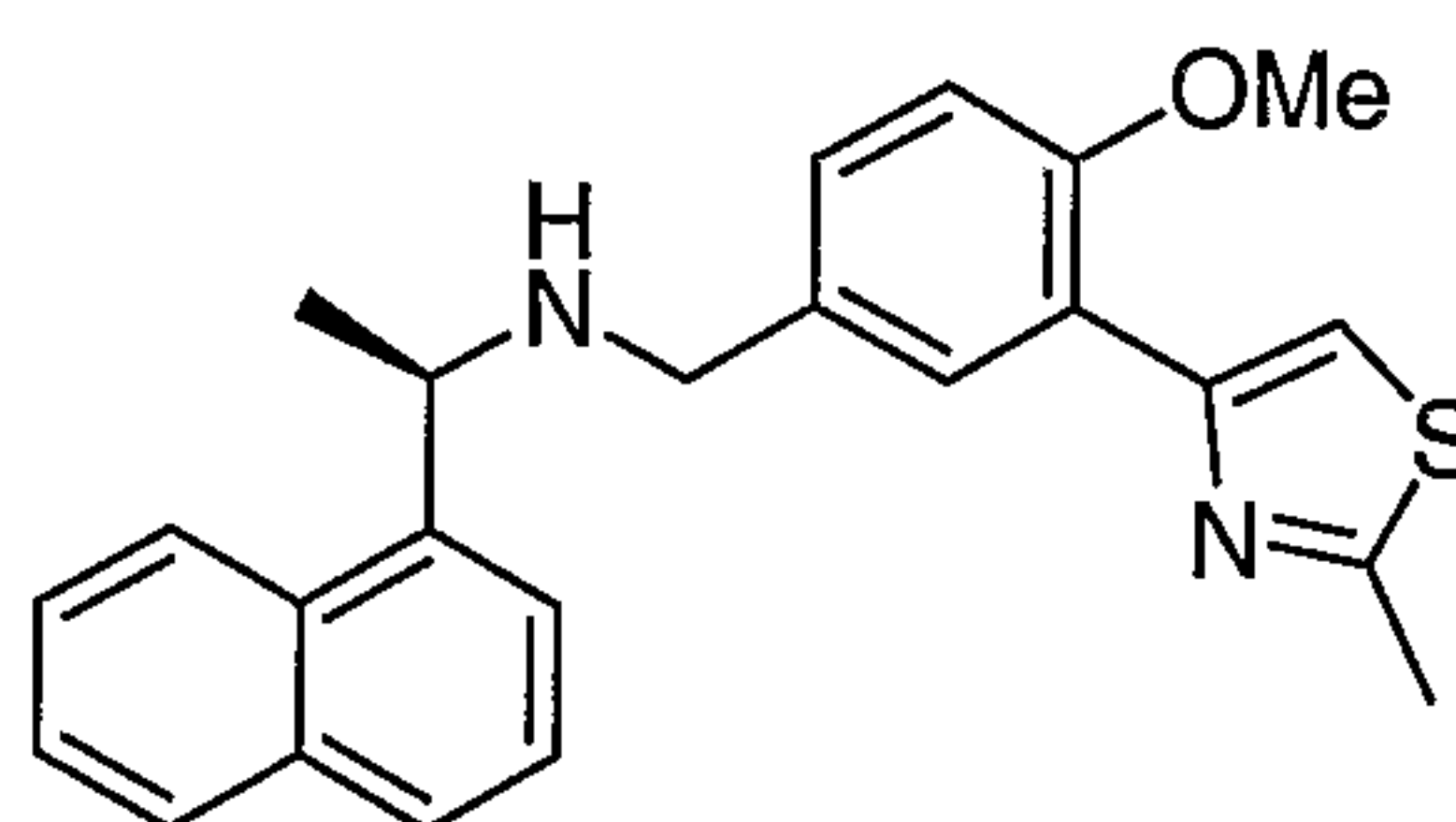


MW 368.499
Mass found: 369, 218

5

Example 400

10 (1R)-N-((4-(methoxy)-3-(2-methyl-1,3-thiazol-4-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

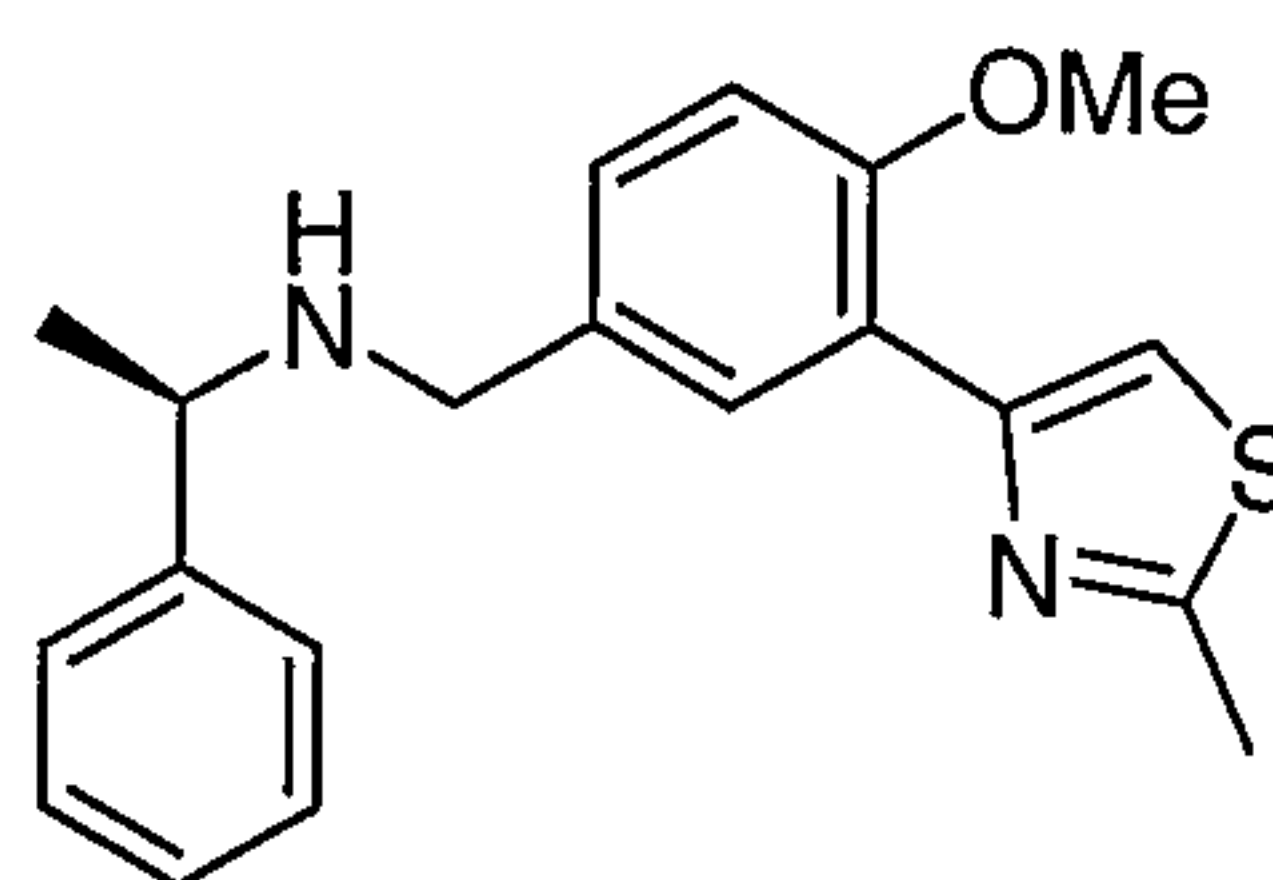


MW 388.533
Mass found: 389, 218

15

Example 401

20 (1R)-N-((4-(methoxy)-3-(2-methyl-1,3-thiazol-4-yl)phenyl)methyl)-1-phenylethanamine



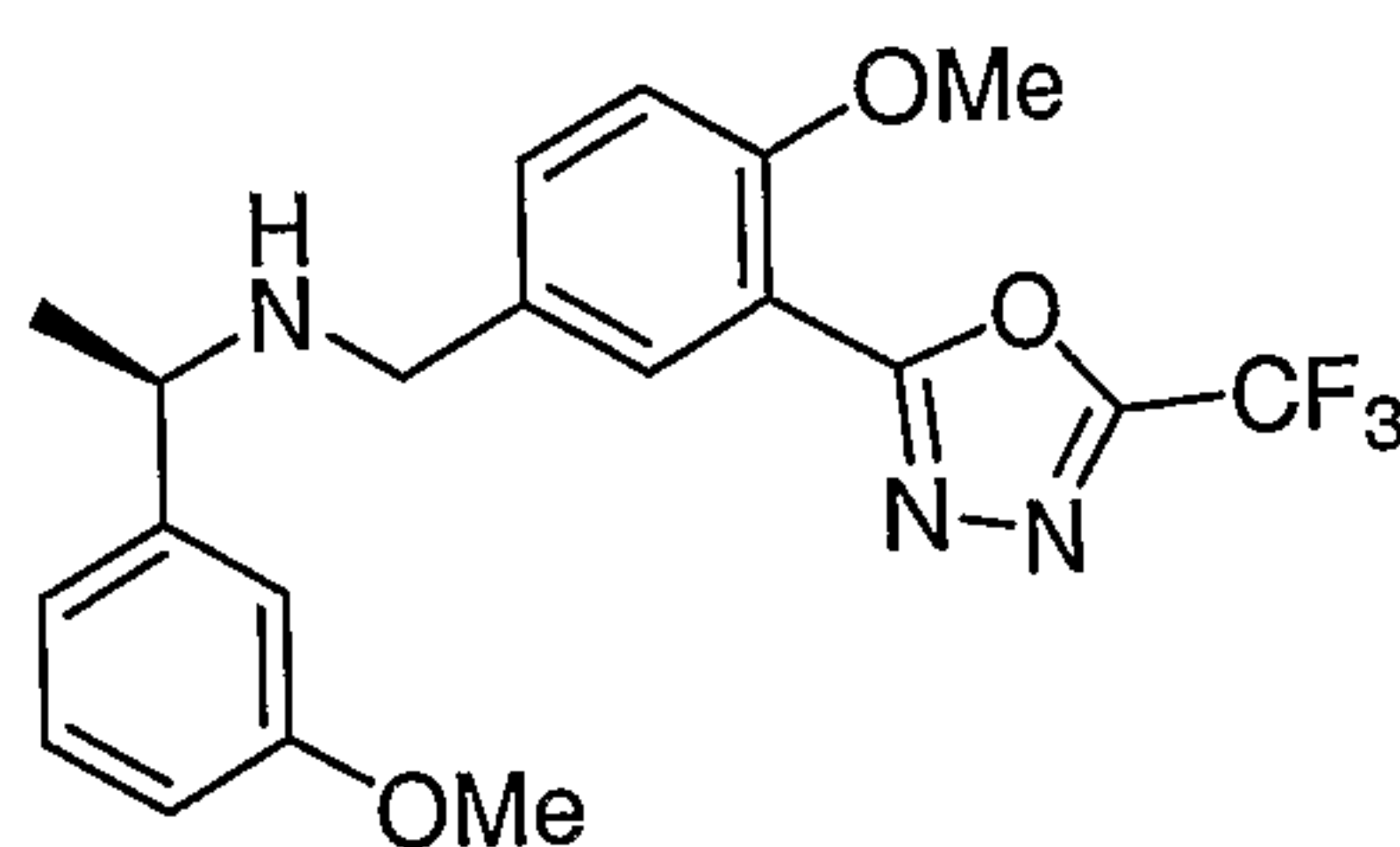
MW 338.473
Mass found: 218, 339

25

Example 402

30 (1R)-1-(3-(methoxy)phenyl)-N-((4-(methoxy)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)phenyl)methyl)ethanamine

- 228 -



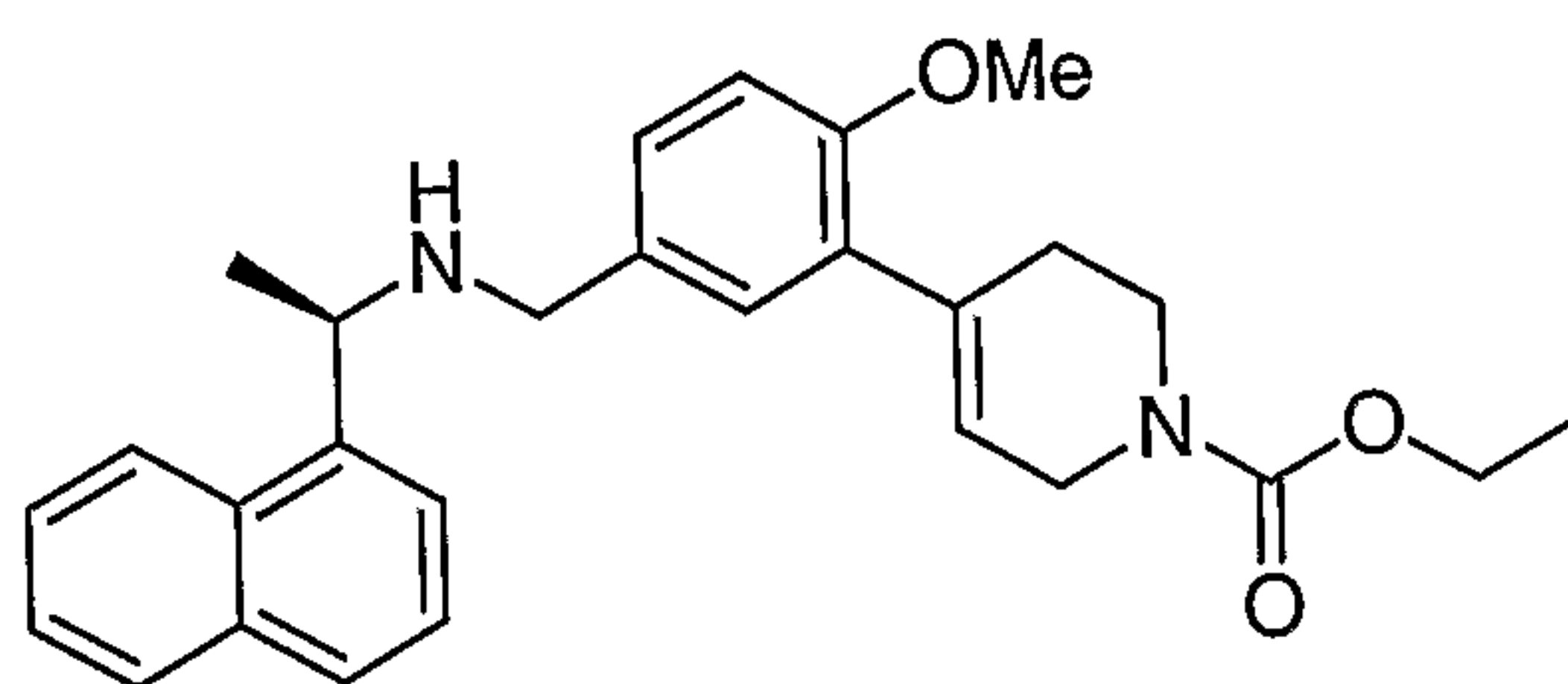
MW 407.39

Mass found: 408, 274

5

Example 403

10 ethyl 4-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-
3,6-dihydro-1(2H)-pyridinecarboxylate



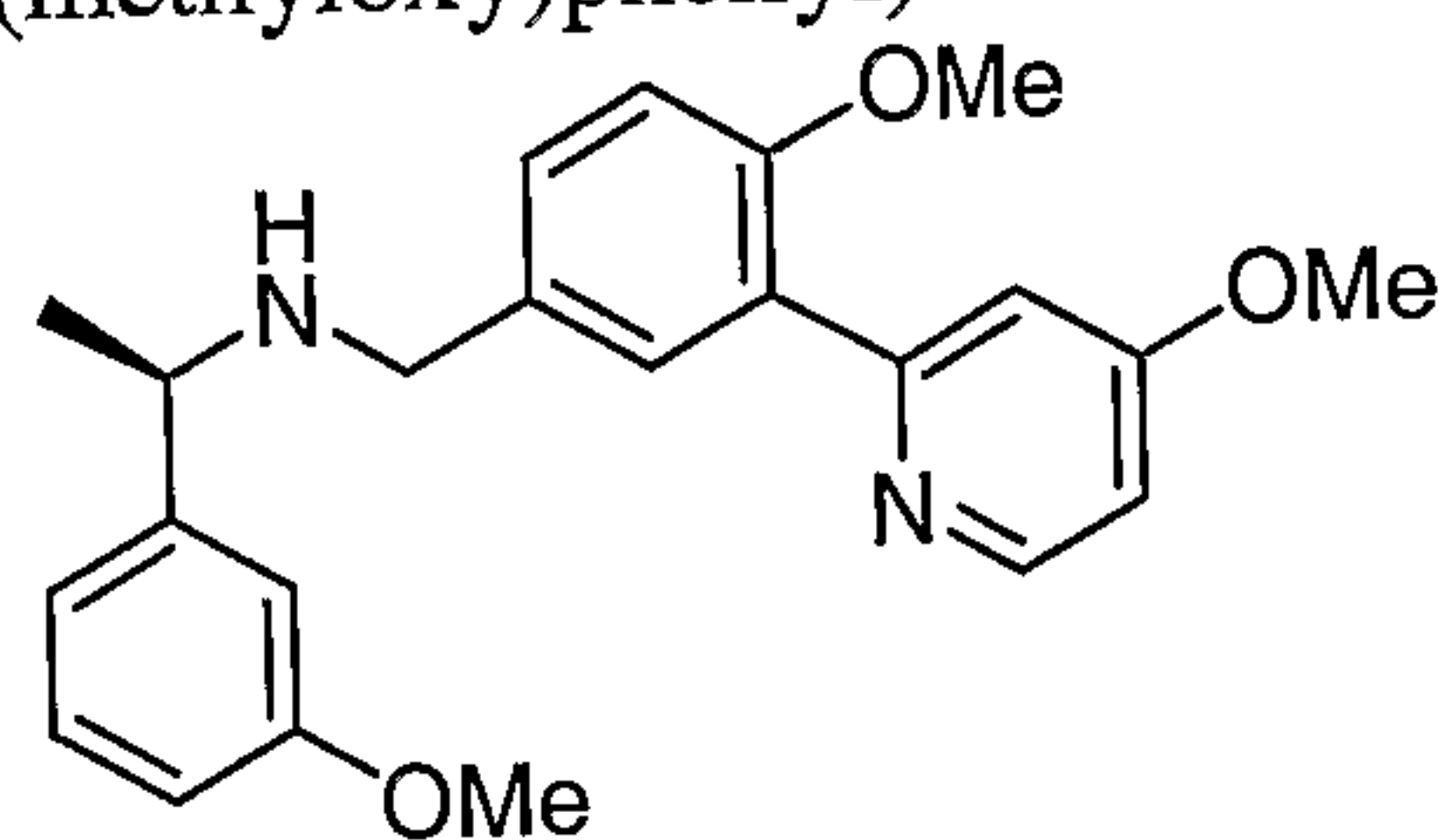
MW 444.572

Mass found: 445, 274, 155

15

Example 404

20 (1R)-N-((4-(methyloxy)-3-(4-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-(3-
(methyloxy)phenyl)ethanamine



MW 378.469

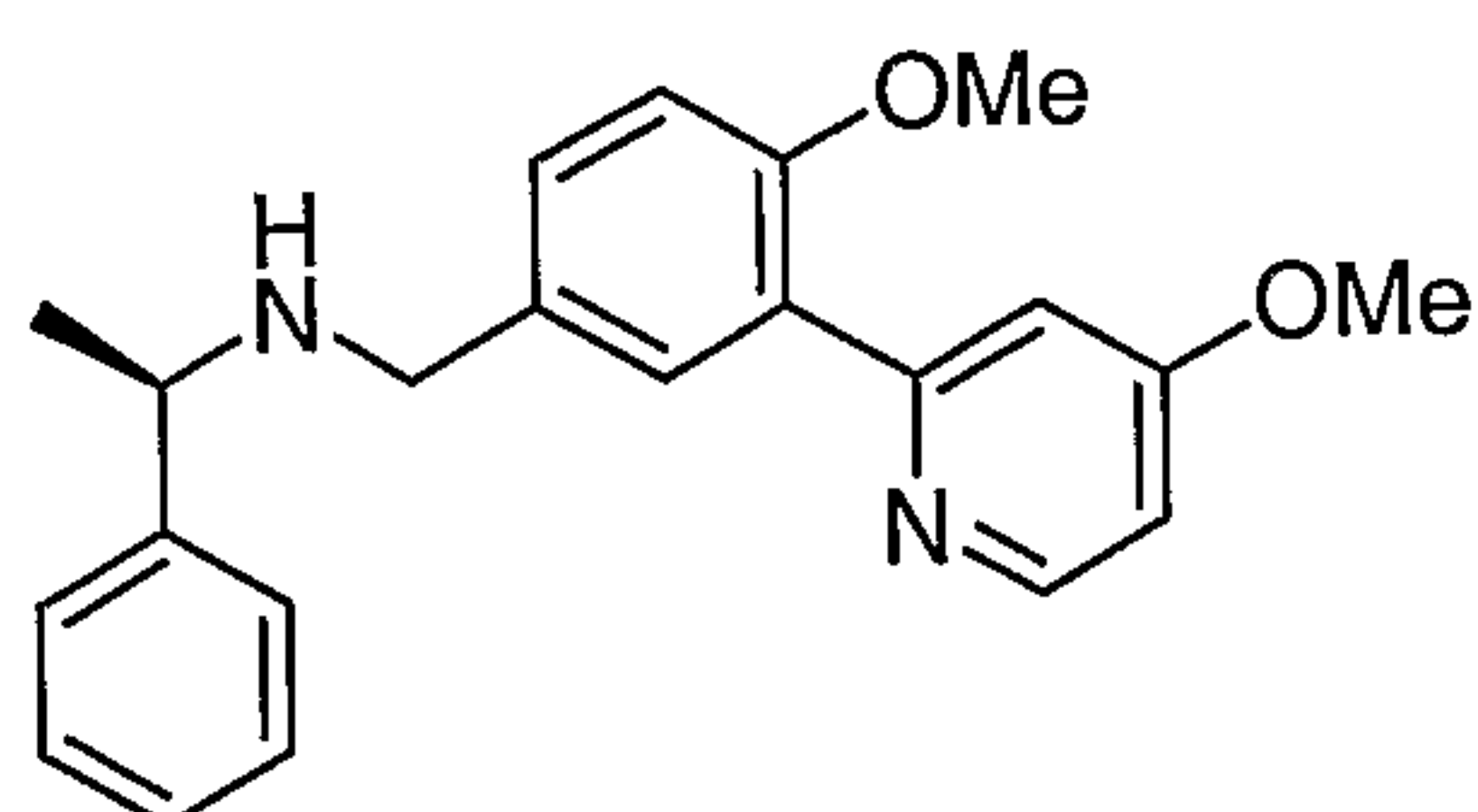
Mass found: 379

25

Example 405

30 (1R)-N-((4-(methyloxy)-3-(4-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-
phenylethanamine

- 229 -



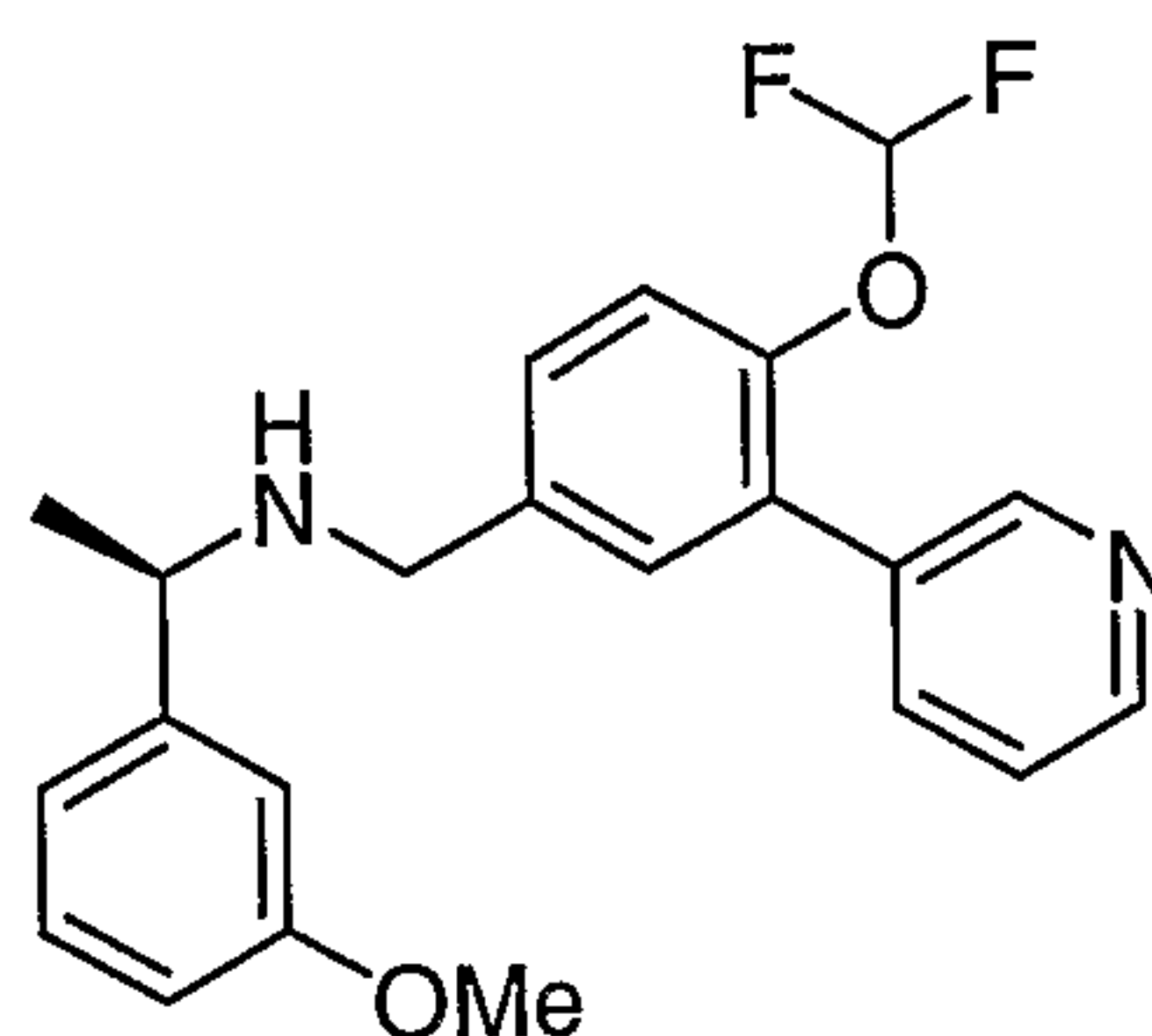
MW 348.444
Mass found: 349

5

Example 406

(1R)-N-((4-((difluoromethyl)oxy)-3-(3-pyridinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

10



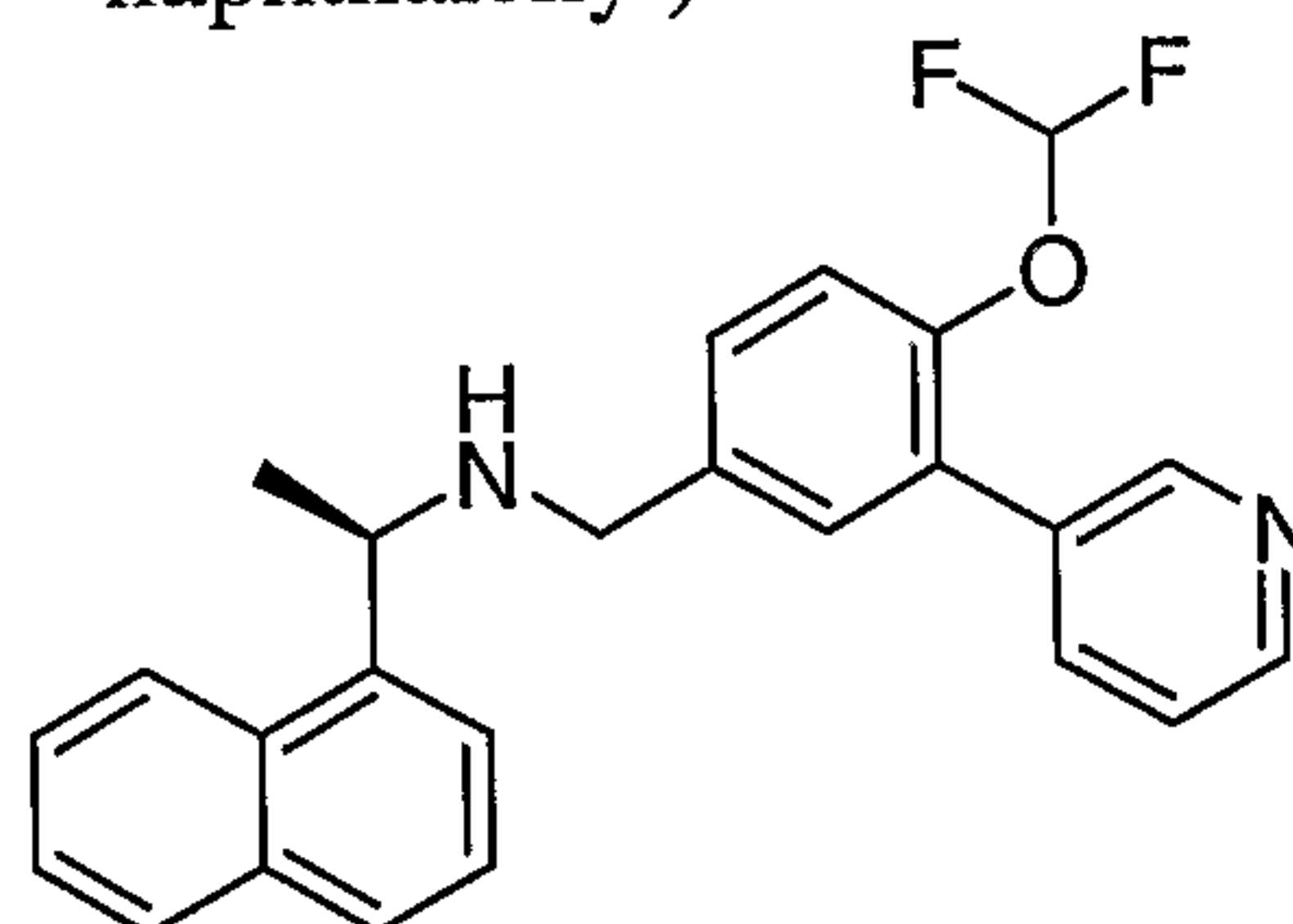
MW 384.424
Mass found: 385, 251

15

Example 407

(1R)-N-((4-((difluoromethyl)oxy)-3-(3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

20



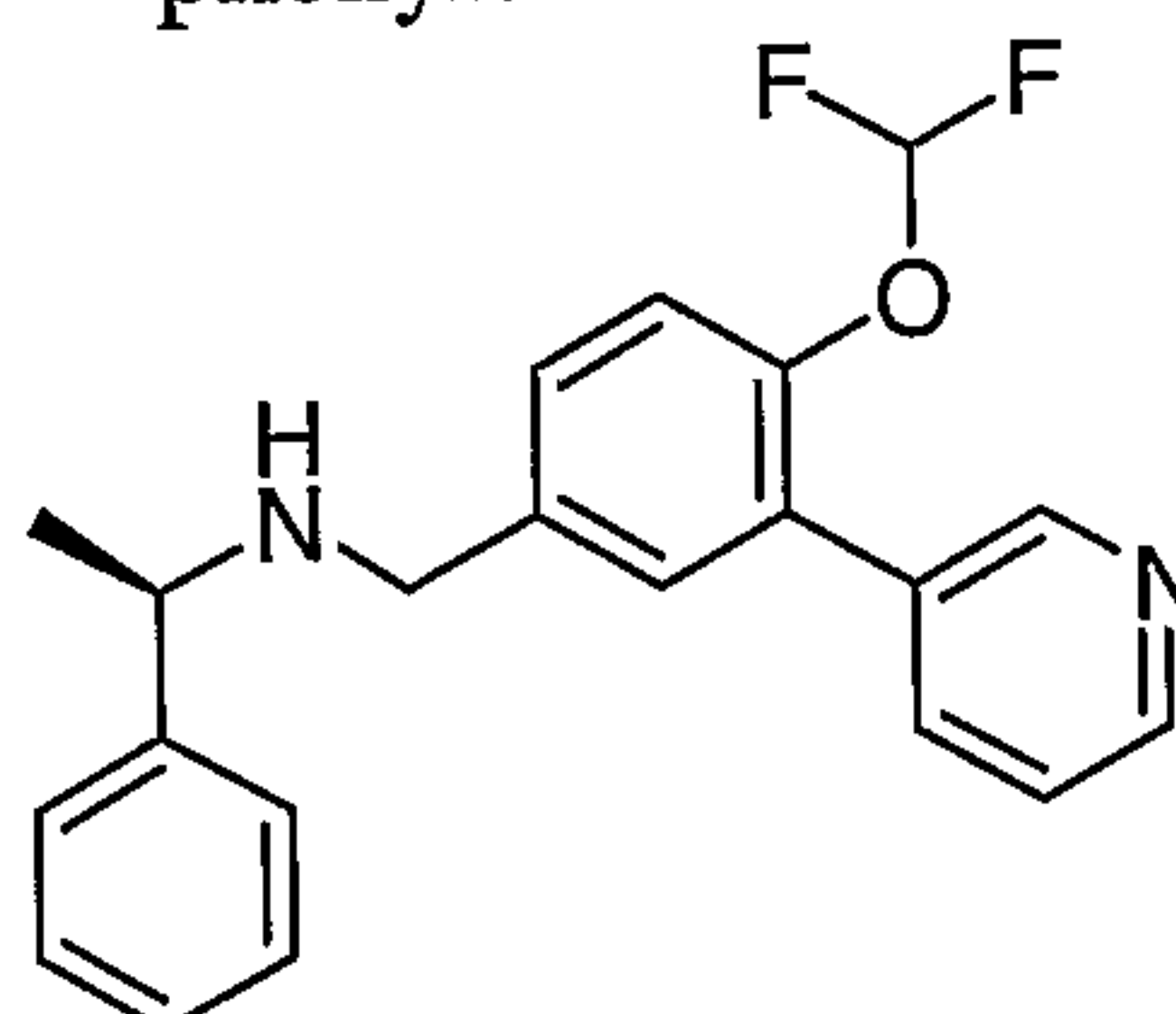
MW 404.458
Mass found: 405, 155

25

Example 408

- 230 -

(1R)-N-((4-((difluoromethyl)oxy)-3-(3-pyridinyl)phenyl)methyl)-1-phenylethanamine



5

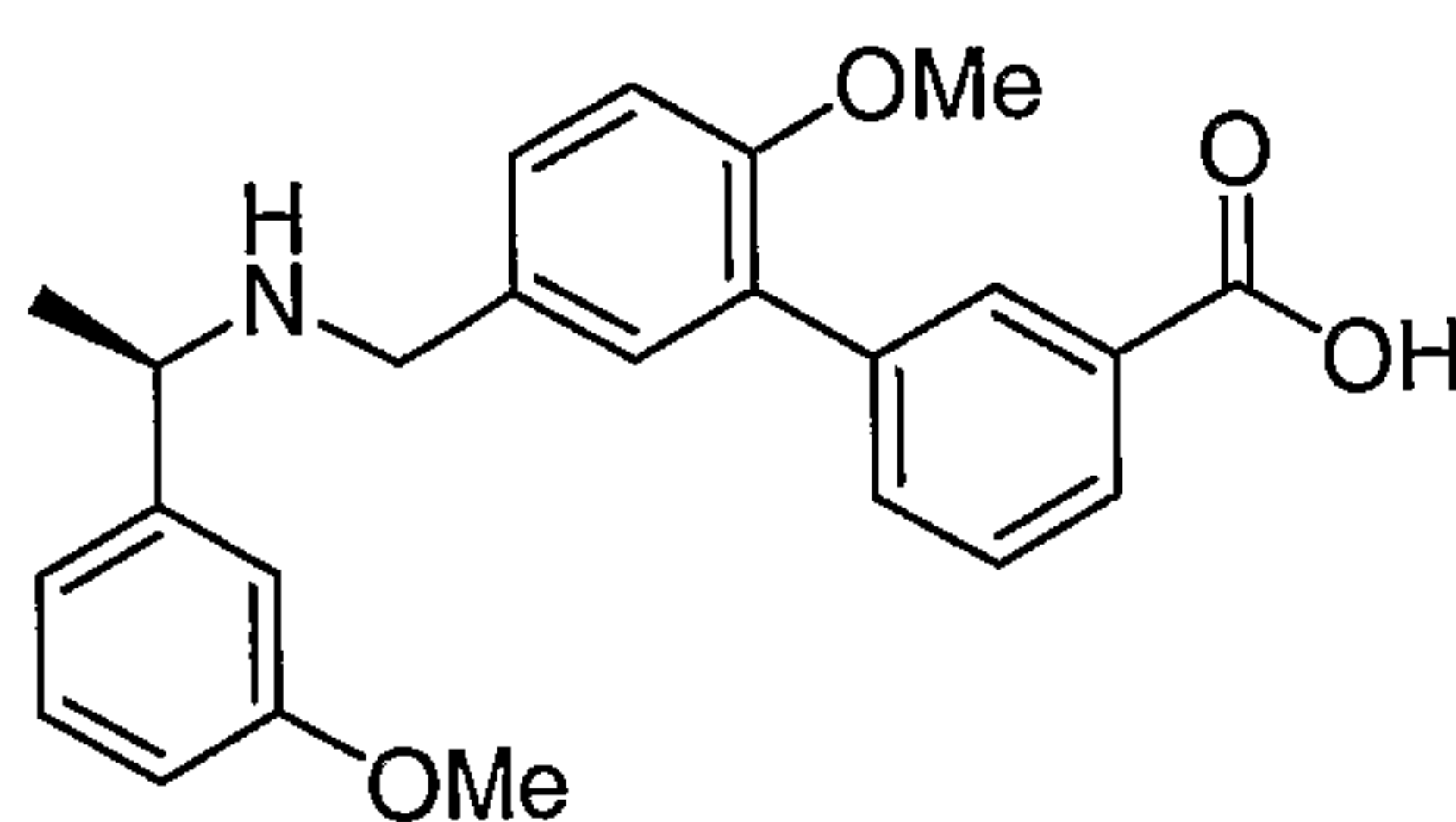
MW 354.398

Mass found: 355, 251

Example 409

10

2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carboxylic acid



15

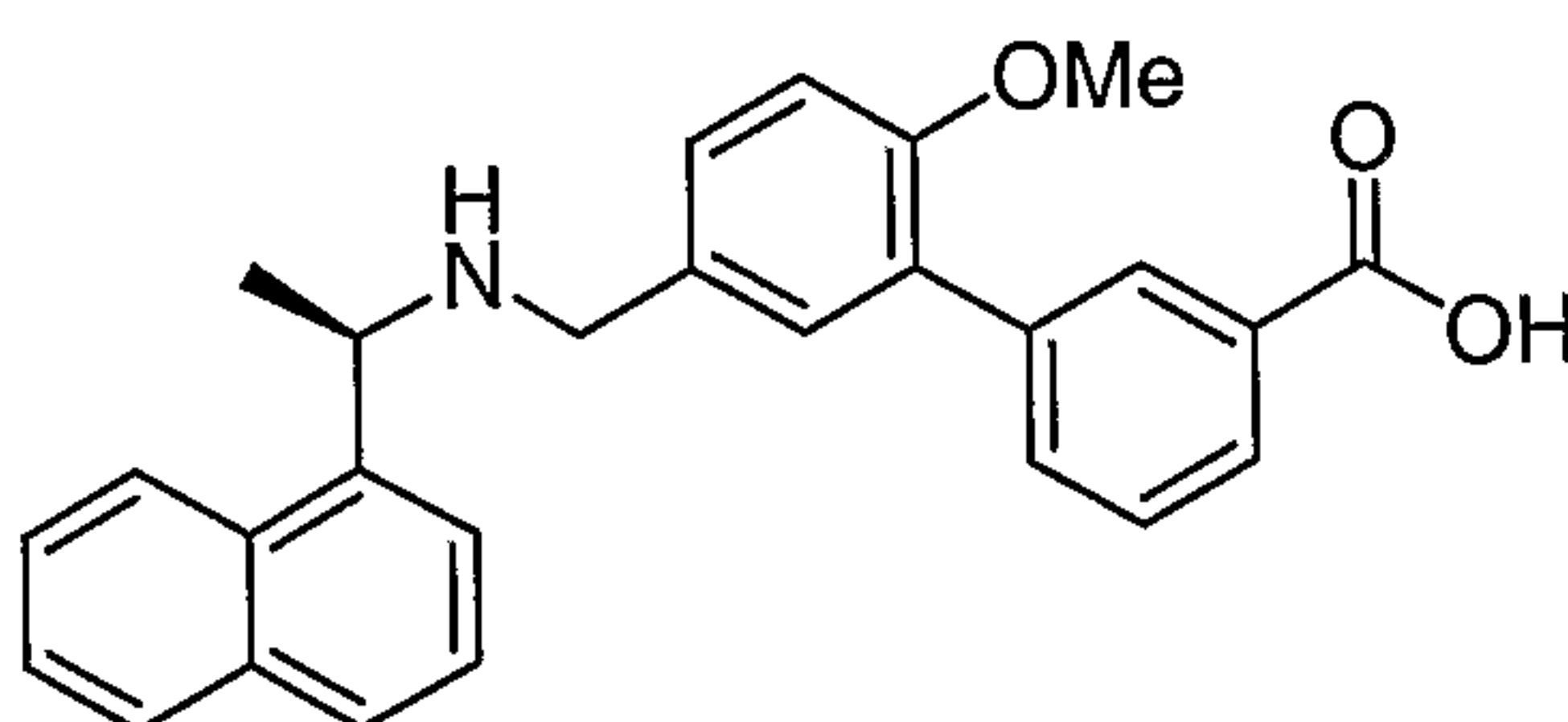
MW 391.465

Mass found: 241, 392

Example 410

20

2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carboxylic acid



25

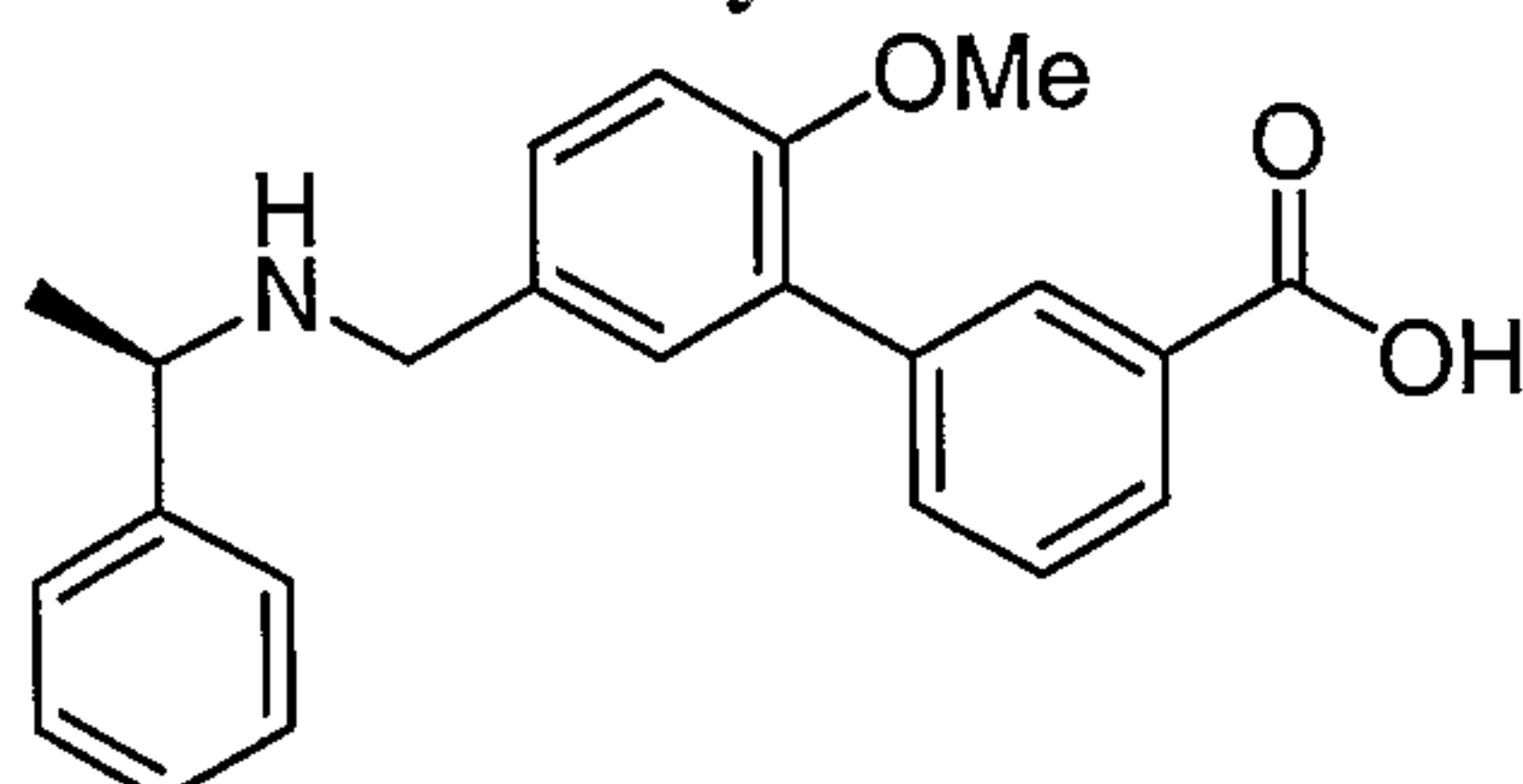
MW 411.499

Mass found: 155, 412, 241

30

Example 411

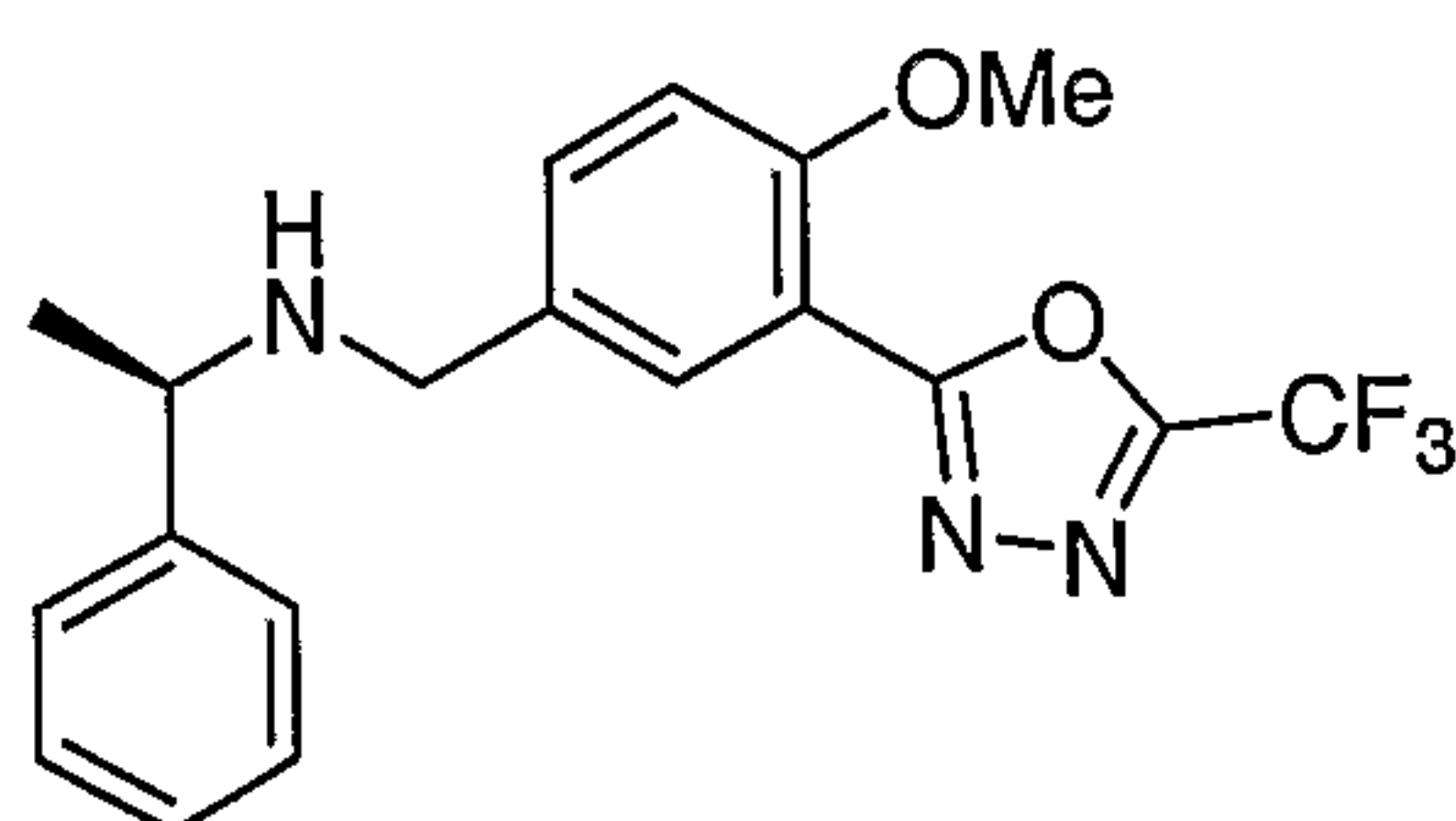
2'-(methoxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-carboxylic acid



Mass found: 241, 362

Example 412

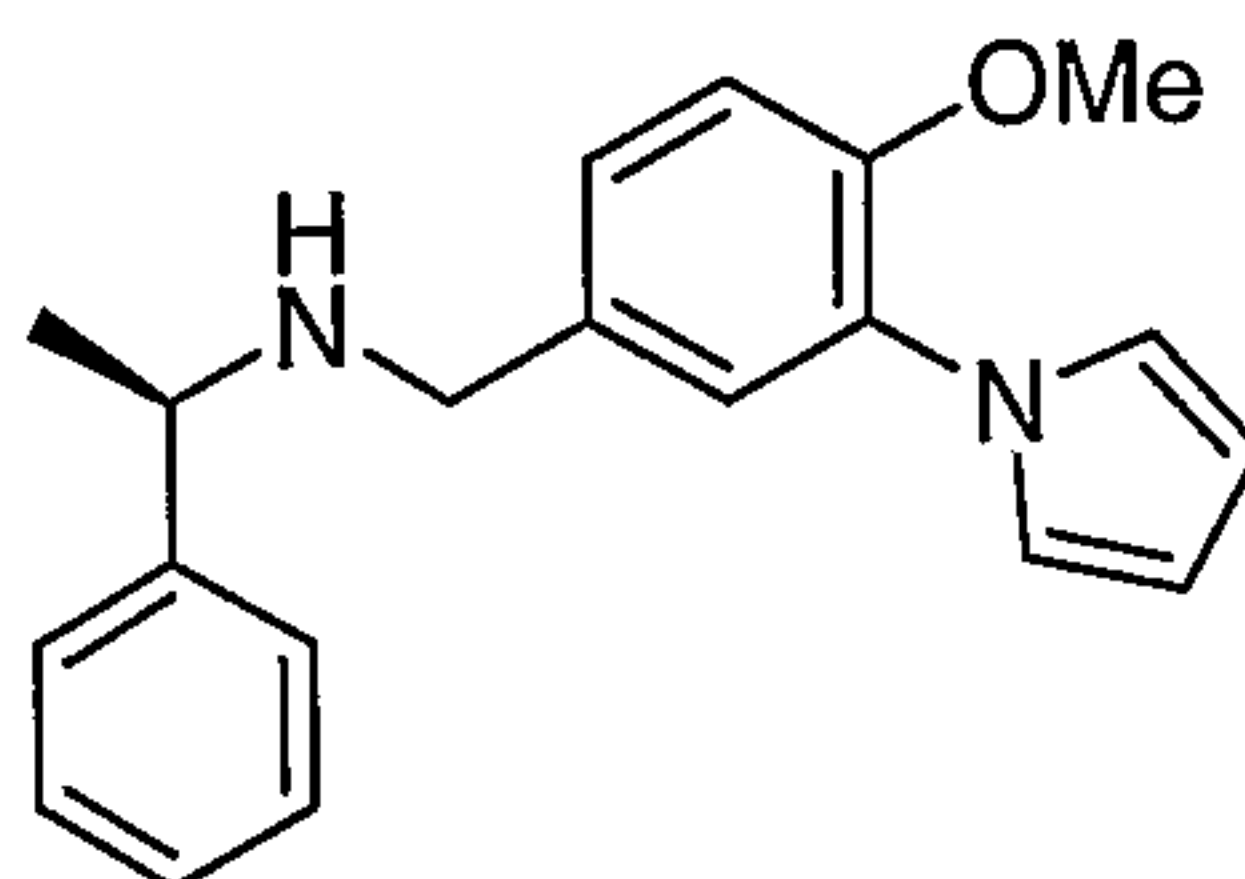
(1R)-N-((4-(methyloxy)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)phenyl)methyl)-1-phenylethanamine



Mass found: 274,378

Example 413

(1R)-N-((4-(methyloxy)-3-(1H-pyrrol-1-yl)phenyl)methyl)-1-phenylethanamine

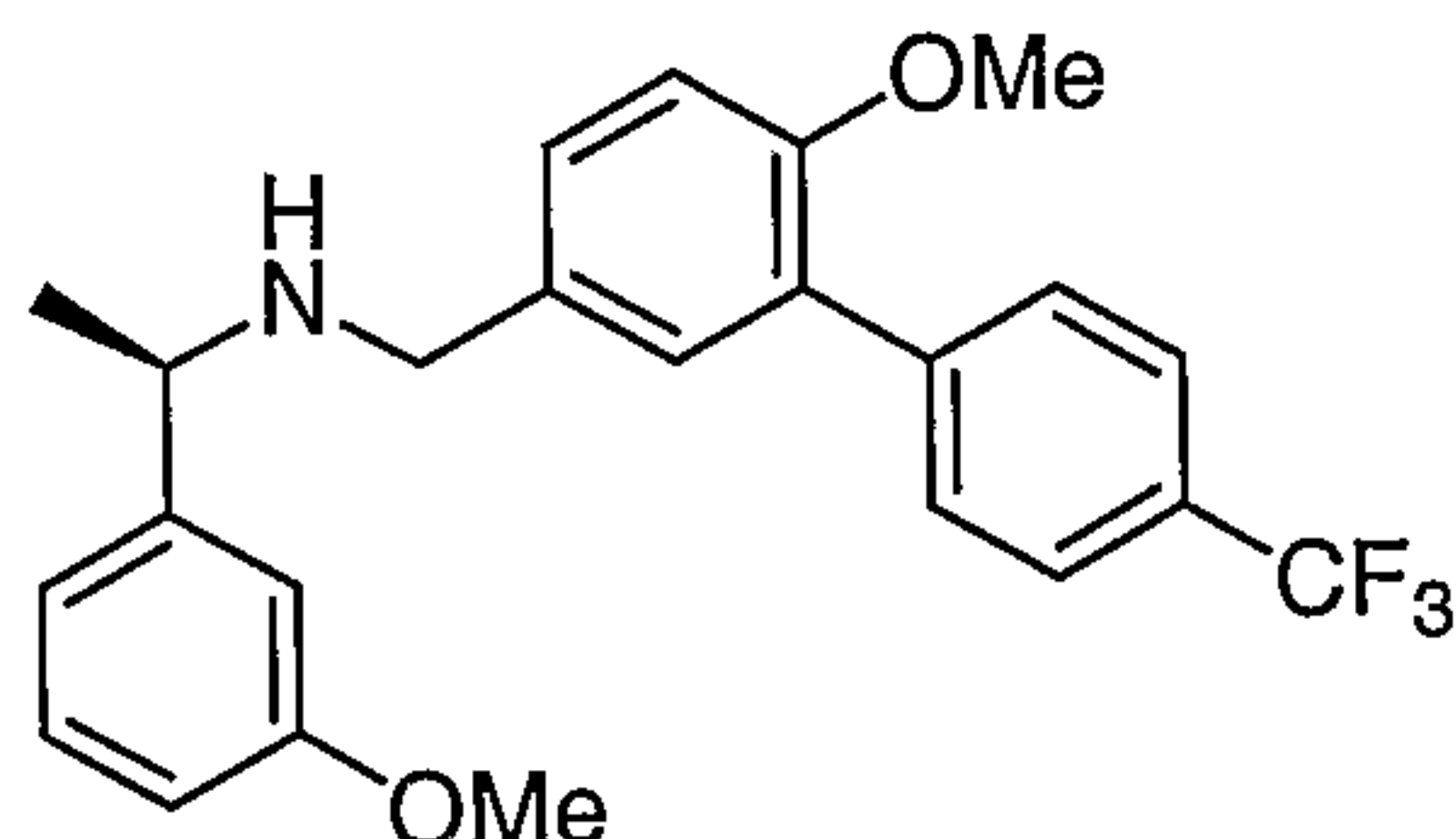


Mass found: 186, 307

Example 414

- 232 -

(1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine



5

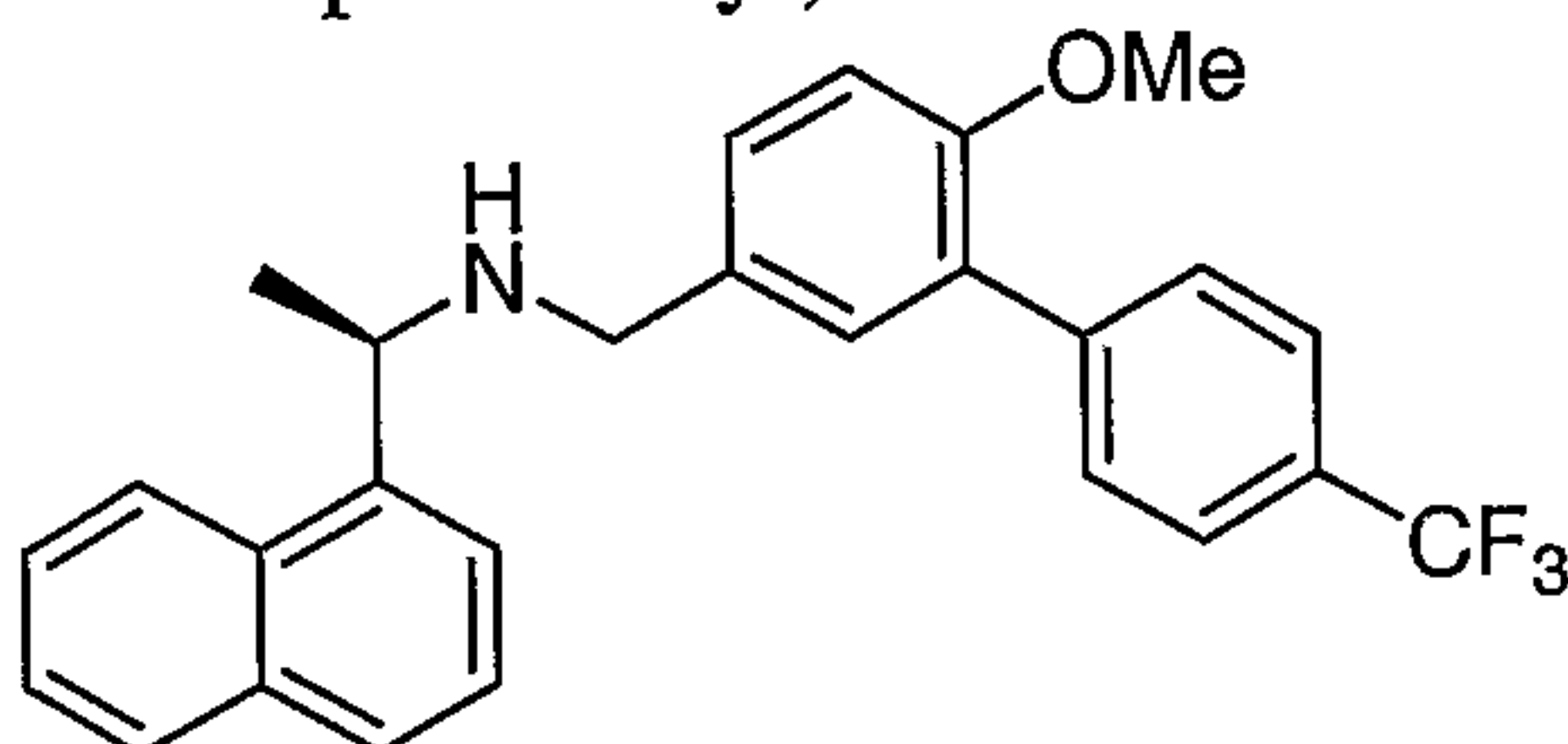
MW 415.453

Mass found: 265, 416

10

Example 415

(1R)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine



15

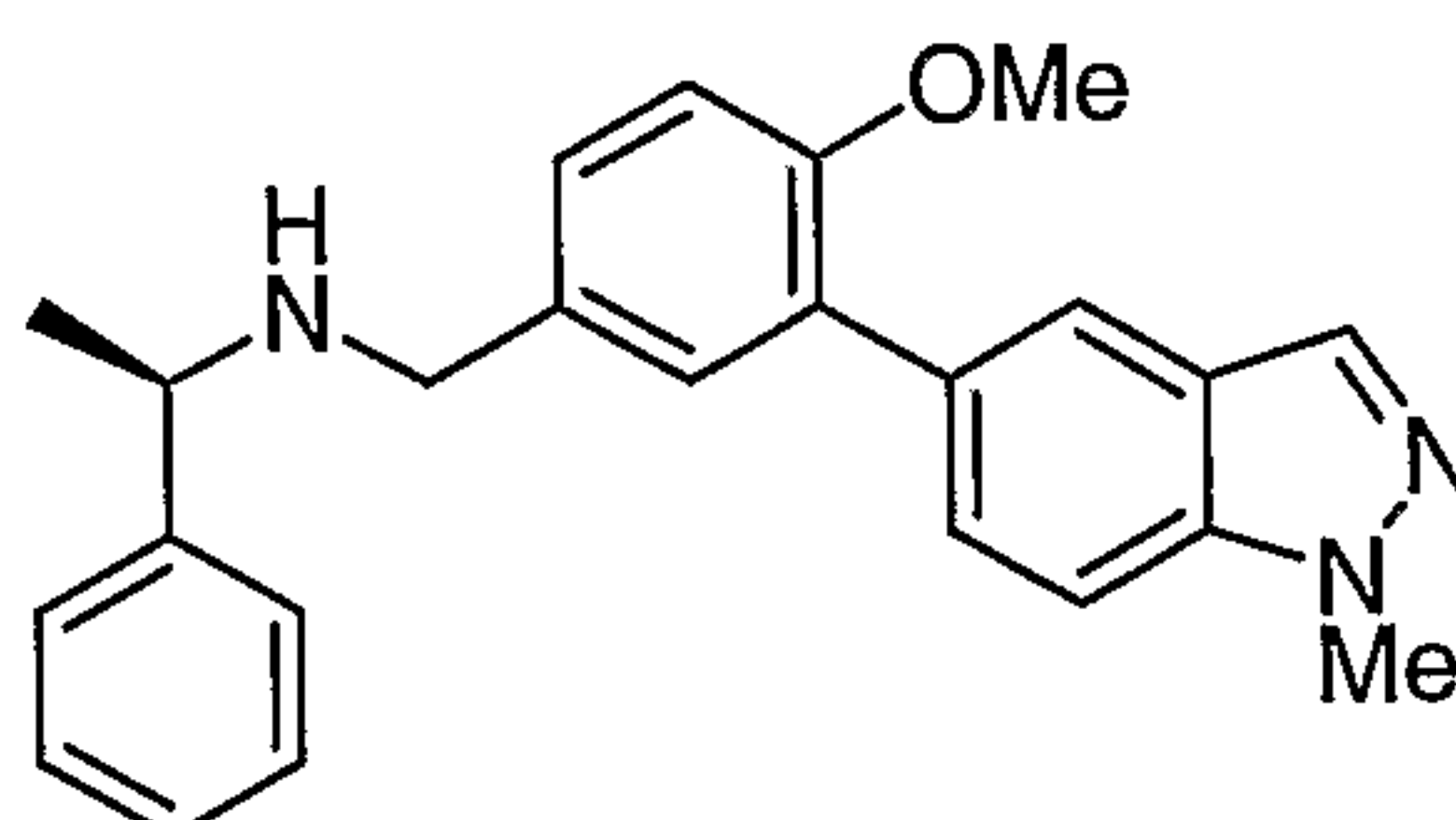
MW 435.487

Mass found: 155, 436

20

Example 416

(1R)-N-((3-(1-methyl-1H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine



25

MW 371.482

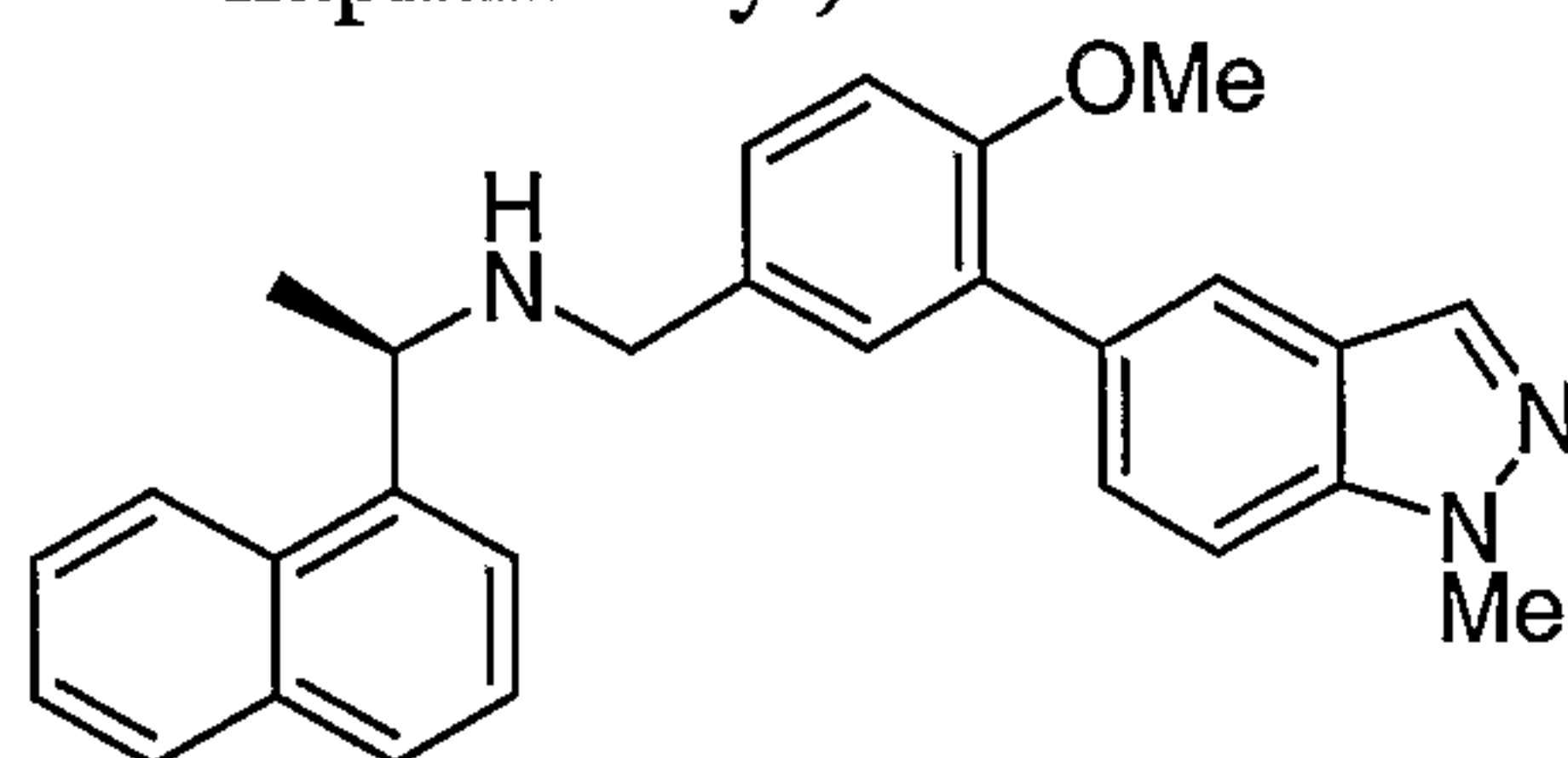
Mass found: 251, 372

30

Example 417

- 233 -

(1R)-N-((3-(1-methyl-1H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



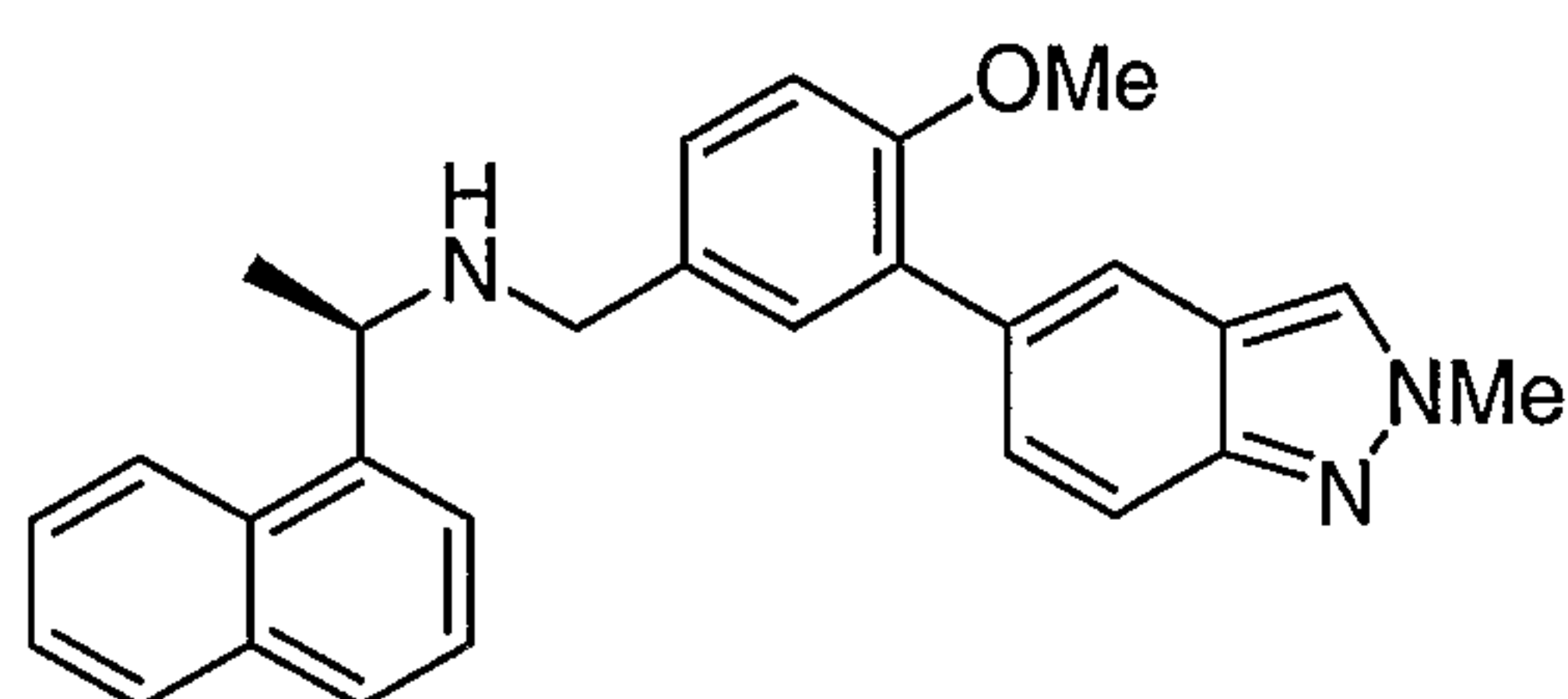
5

MW 421.541
Mass found: 251, 422

Example 418

10

(1R)-N-((3-(2-methyl-2H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



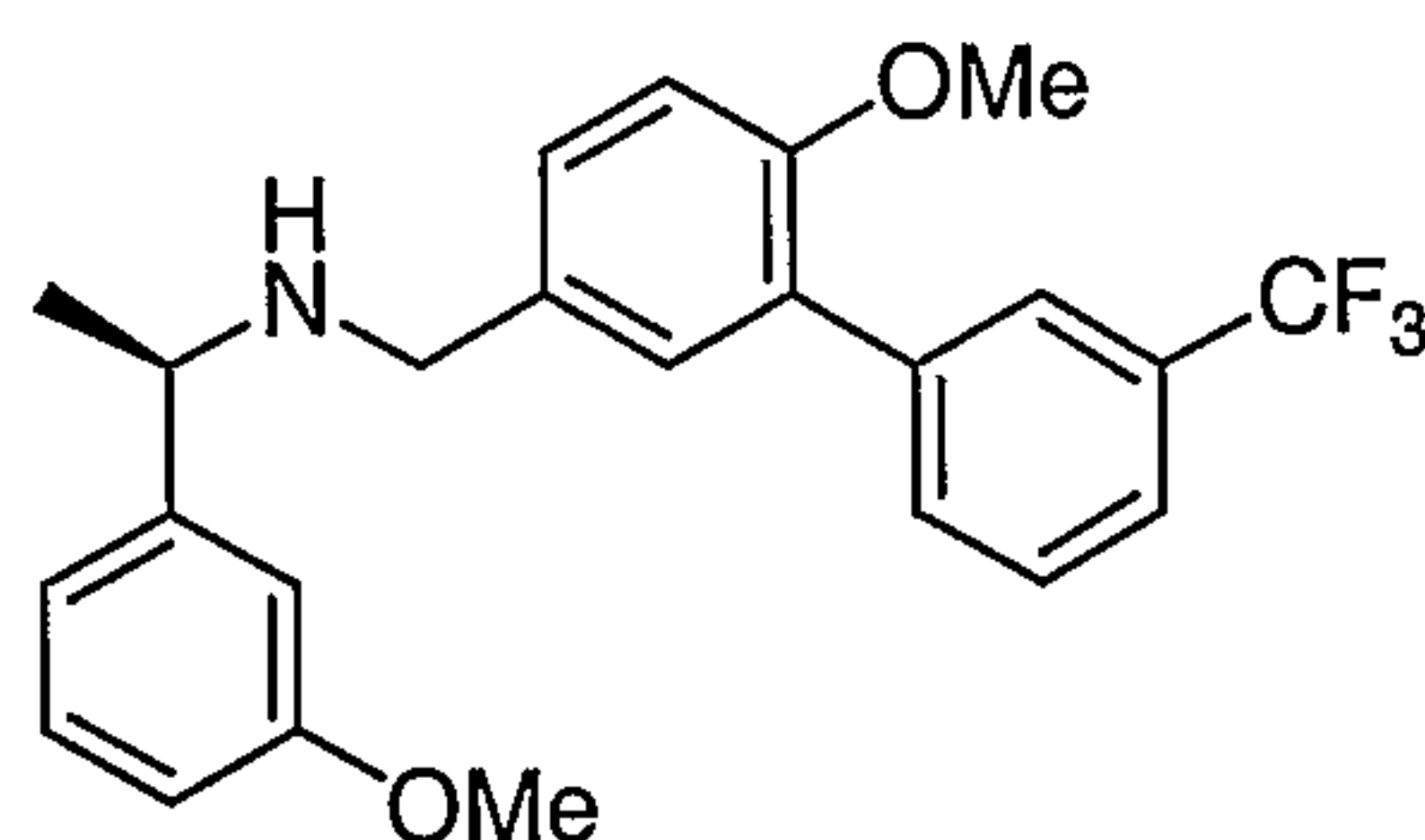
15

MW 421.541
Mass found: 422, 251, 155

Example 419

20

(1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine



25

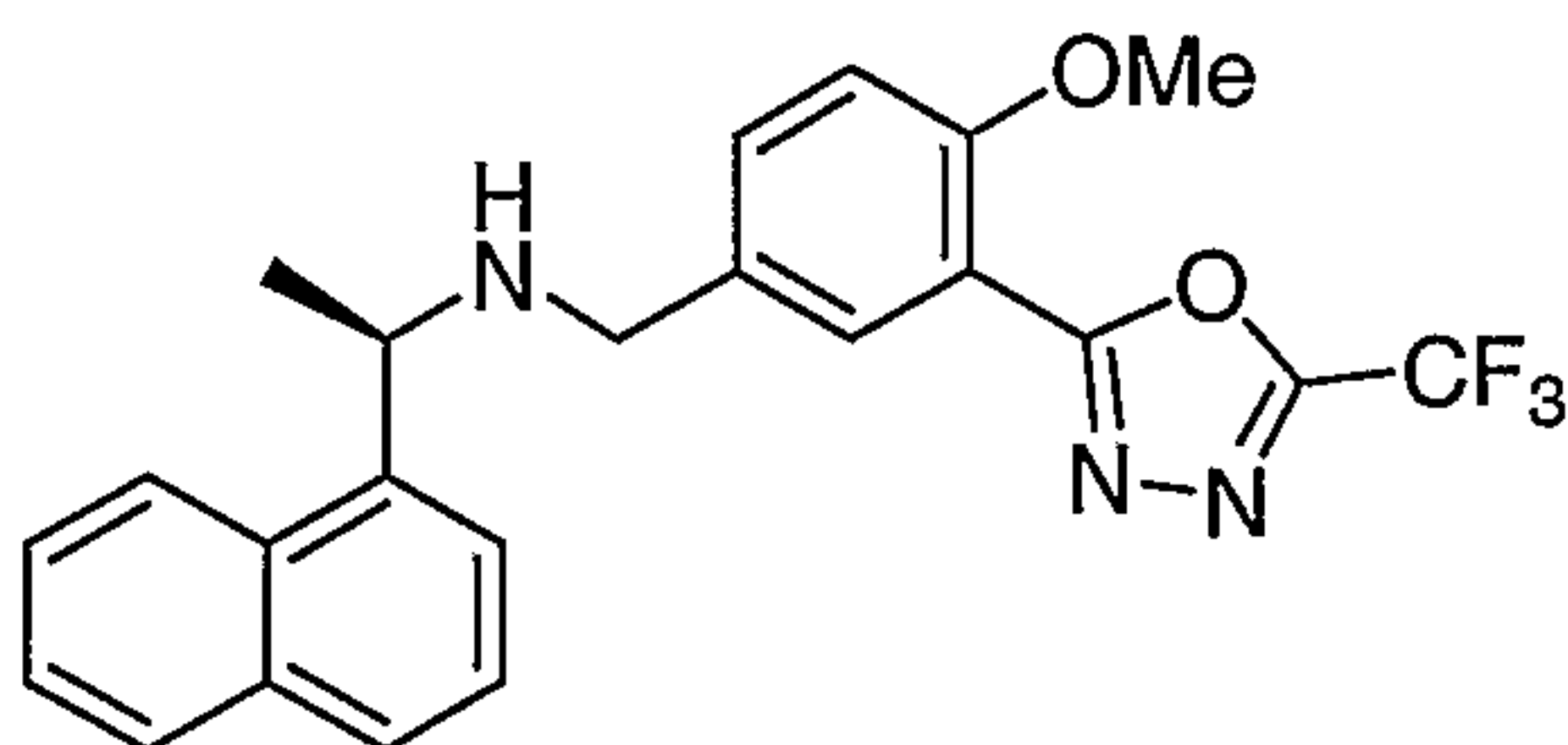
MW 415.453
Mass found: 416, 265

30

Example 420

- 234 -

(1R)-N-((4-(methyloxy)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



5

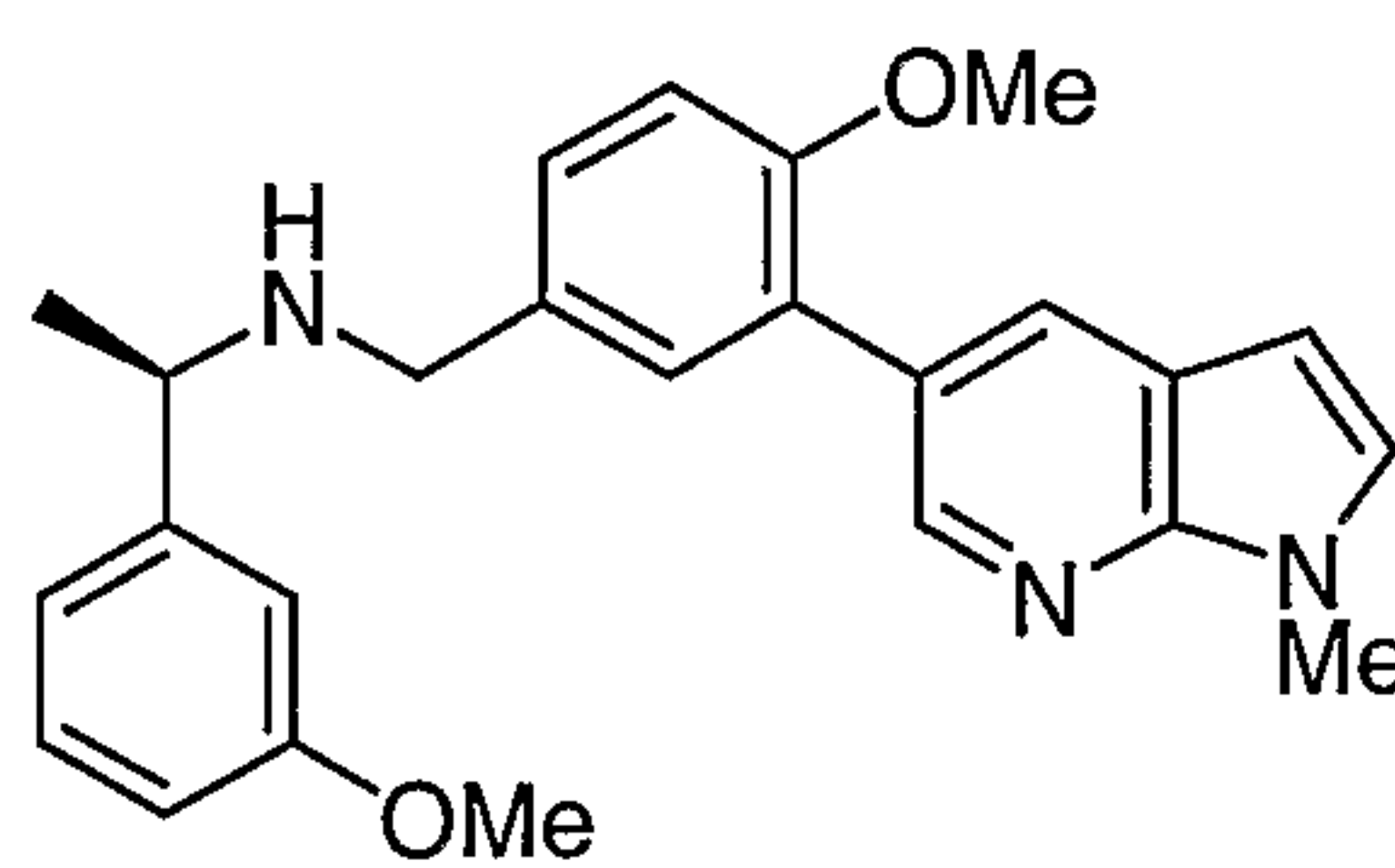
MW 427.424

Mass found: 155, 428

10

Example 421

(1R)-N-((4-(methyloxy)-3-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine



15

MW 401.507

Mass found: 251, 402, 268

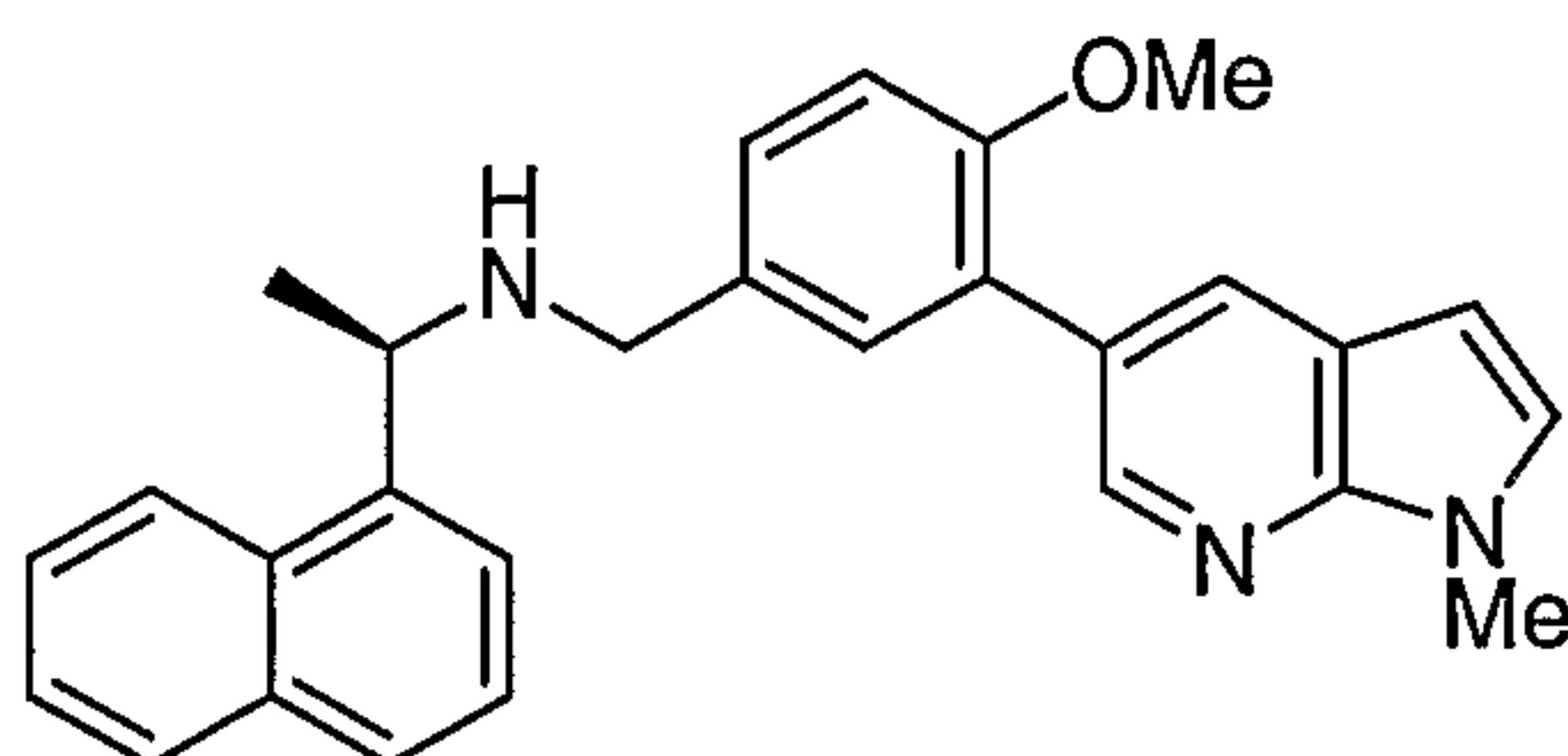
20

- 235 -

Example 422

(1R)-N-((4-(methyloxy)-3-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

5



MW 421.541

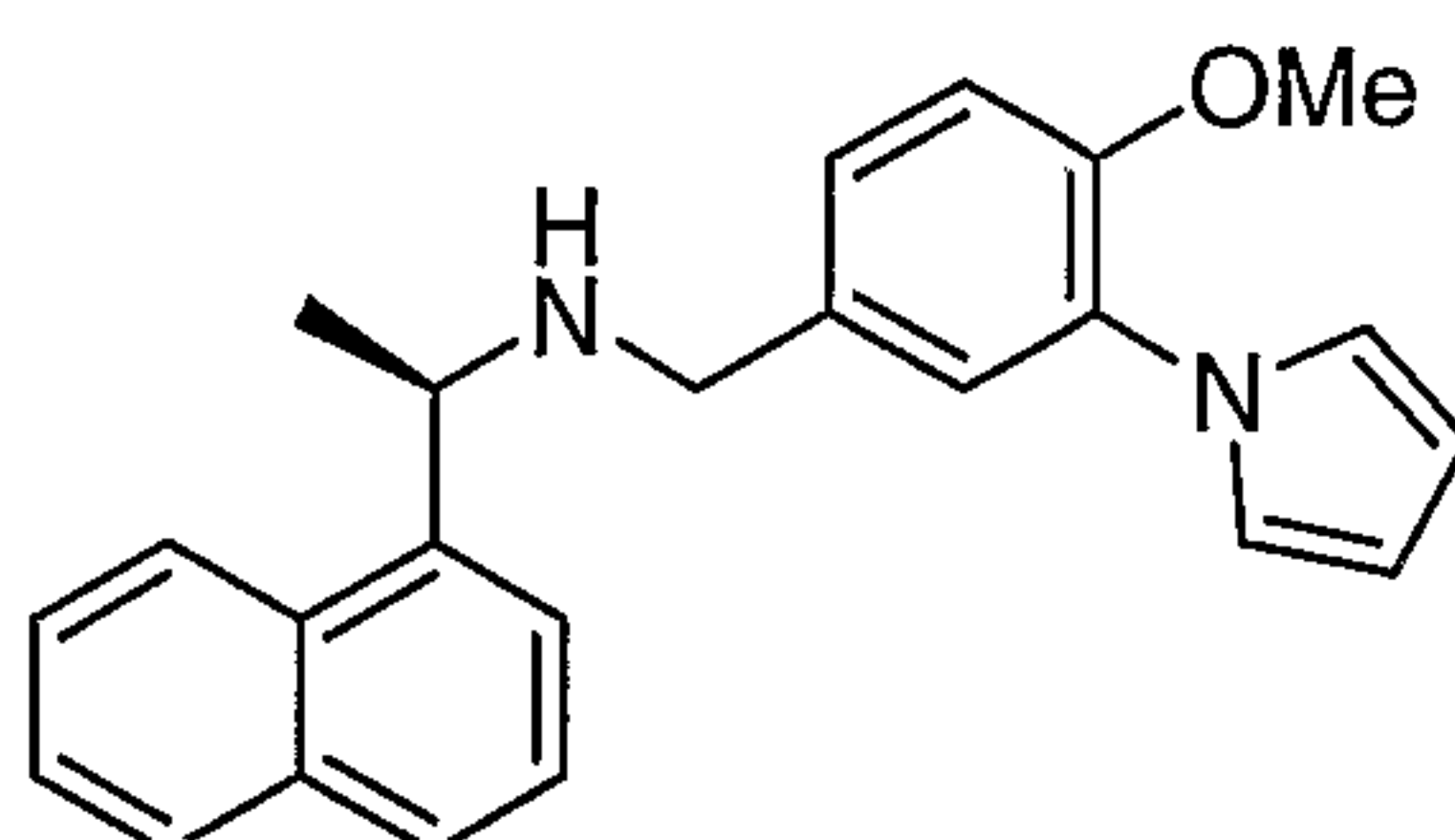
Mass found: 422, 251, 155, 268

10

Example 423

(1R)-N-((4-(methyloxy)-3-(1H-pyrrol-1-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

15



MW 356.467

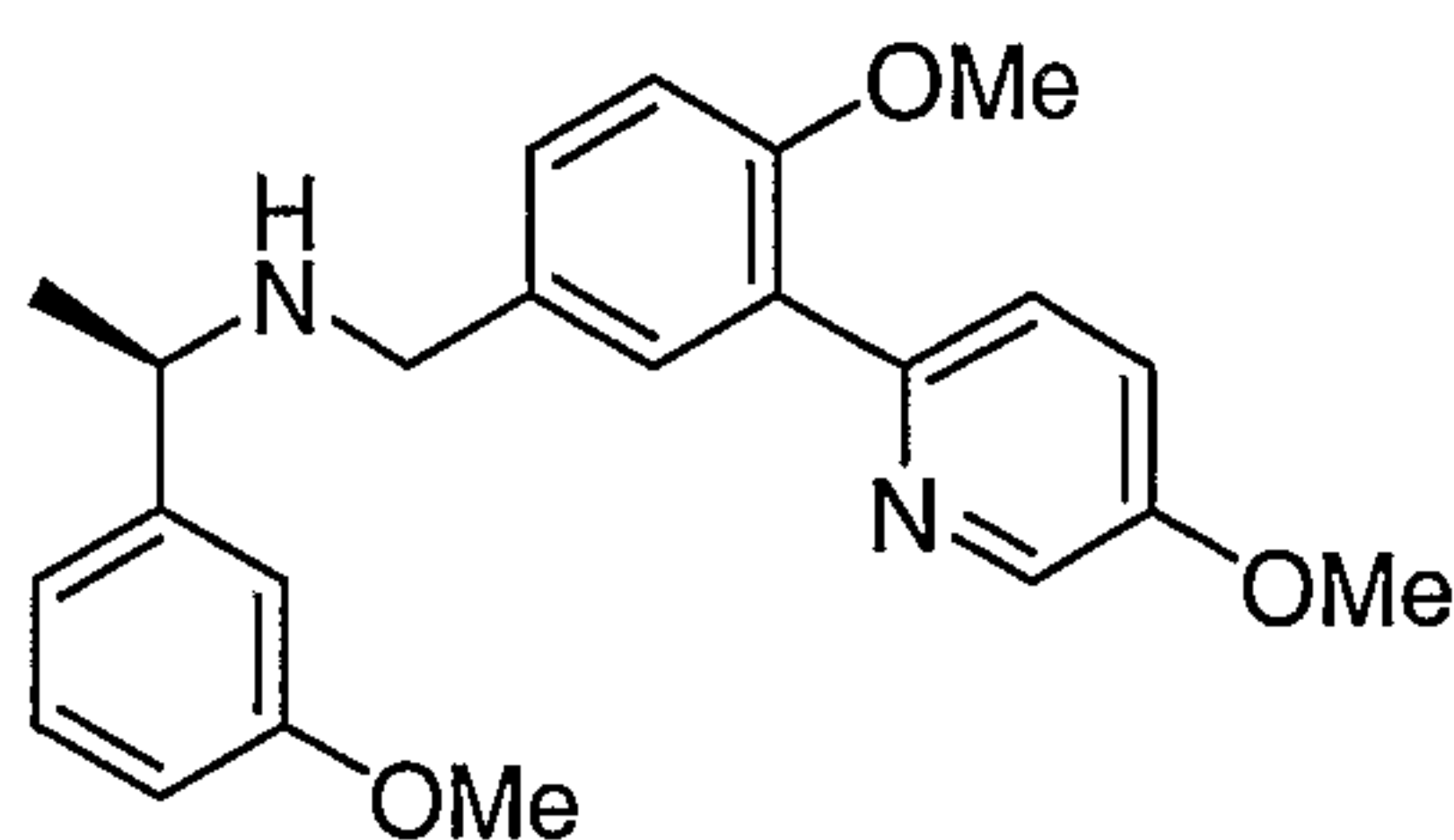
Mass found: 155, 357

20

Example 424

(1R)-N-((4-(methyloxy)-3-(5-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

25



MW 378.469

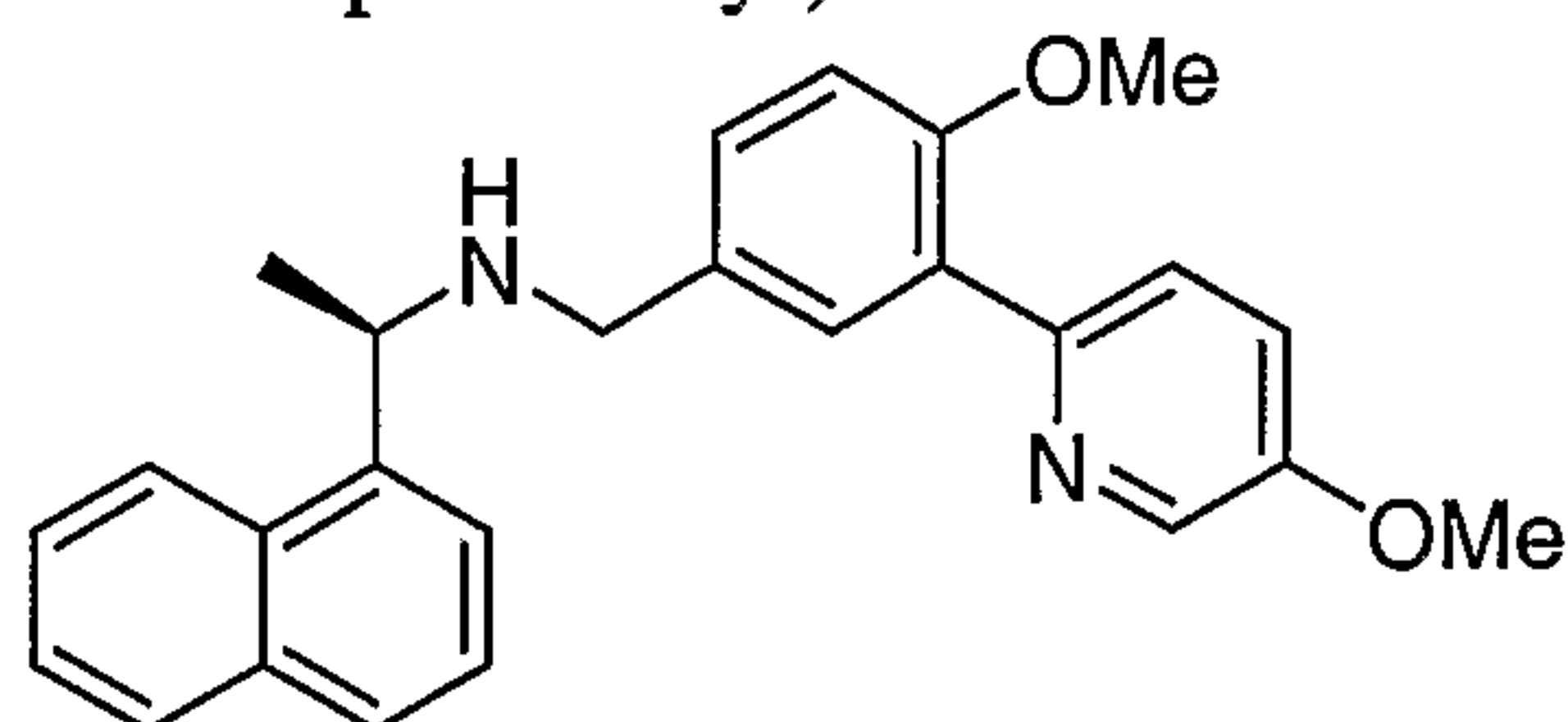
Mass found: 379, 757

30

- 236 -

Example 425

(1R)-N-((4-(methyloxy)-3-(5-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

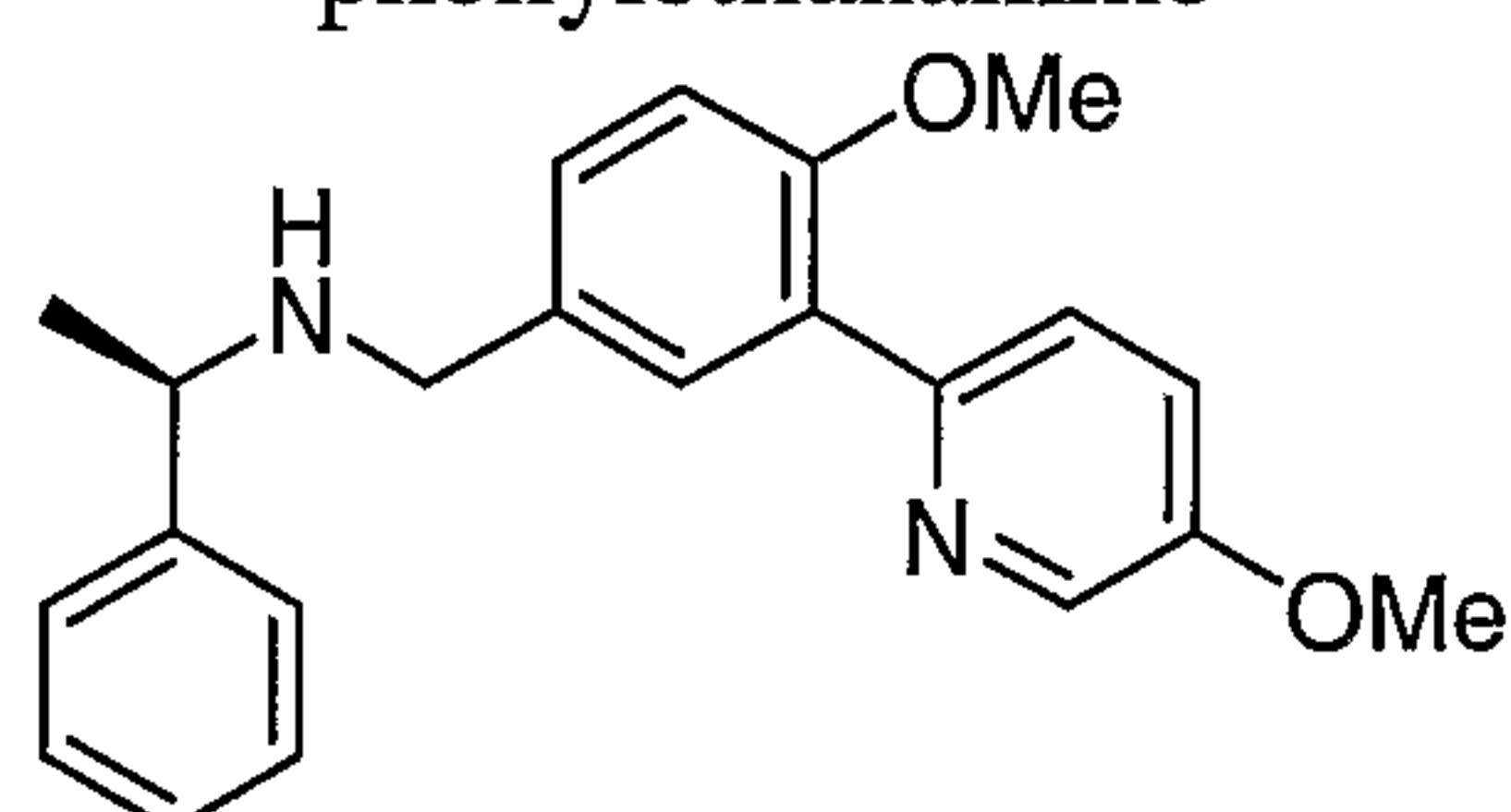


MW 398.503

Mass found: 399, 797

Example 426

(1R)-N-((4-(methyloxy)-3-(5-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-phenylethanamine

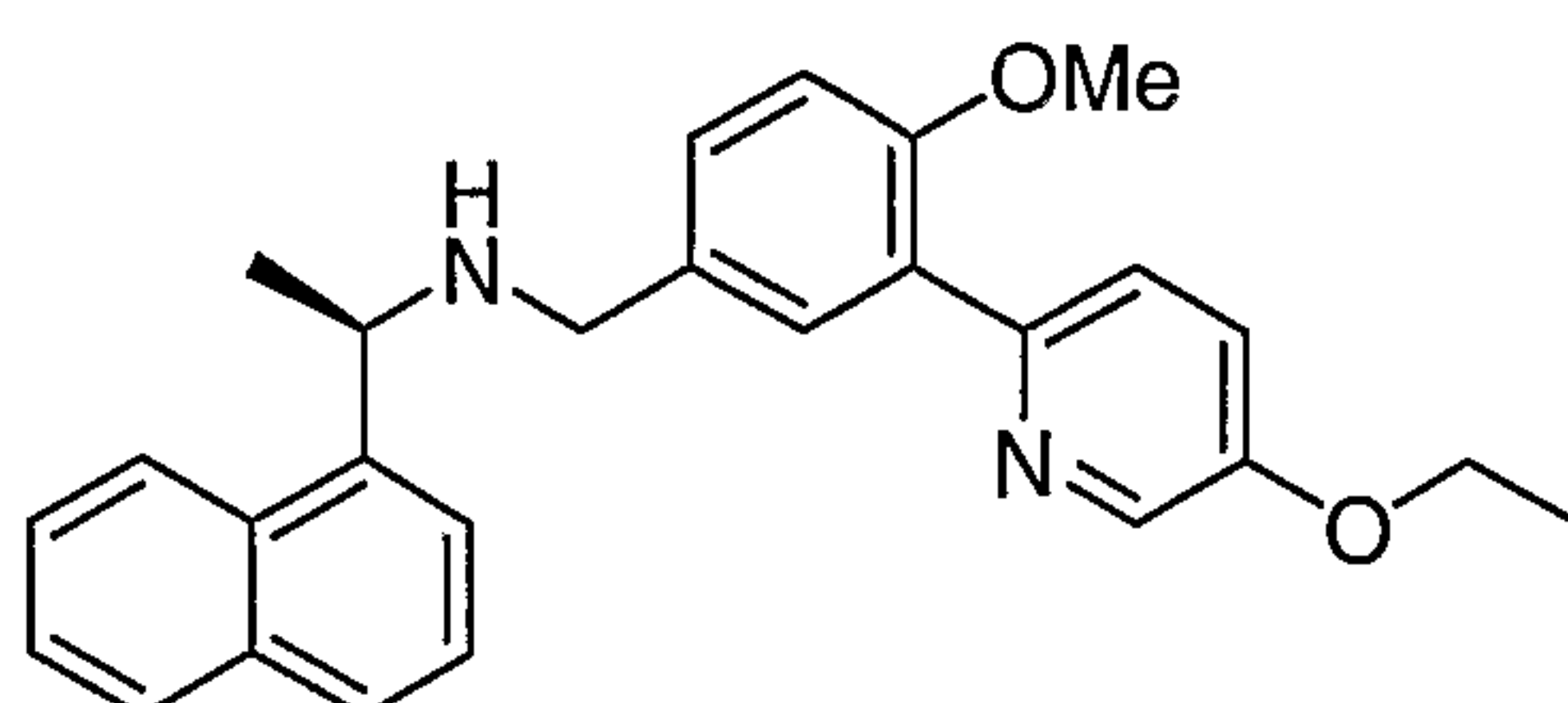


MW 348.444

Mass found: 349, 697

Example 427

(1R)-N-((3-(6-(ethyloxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



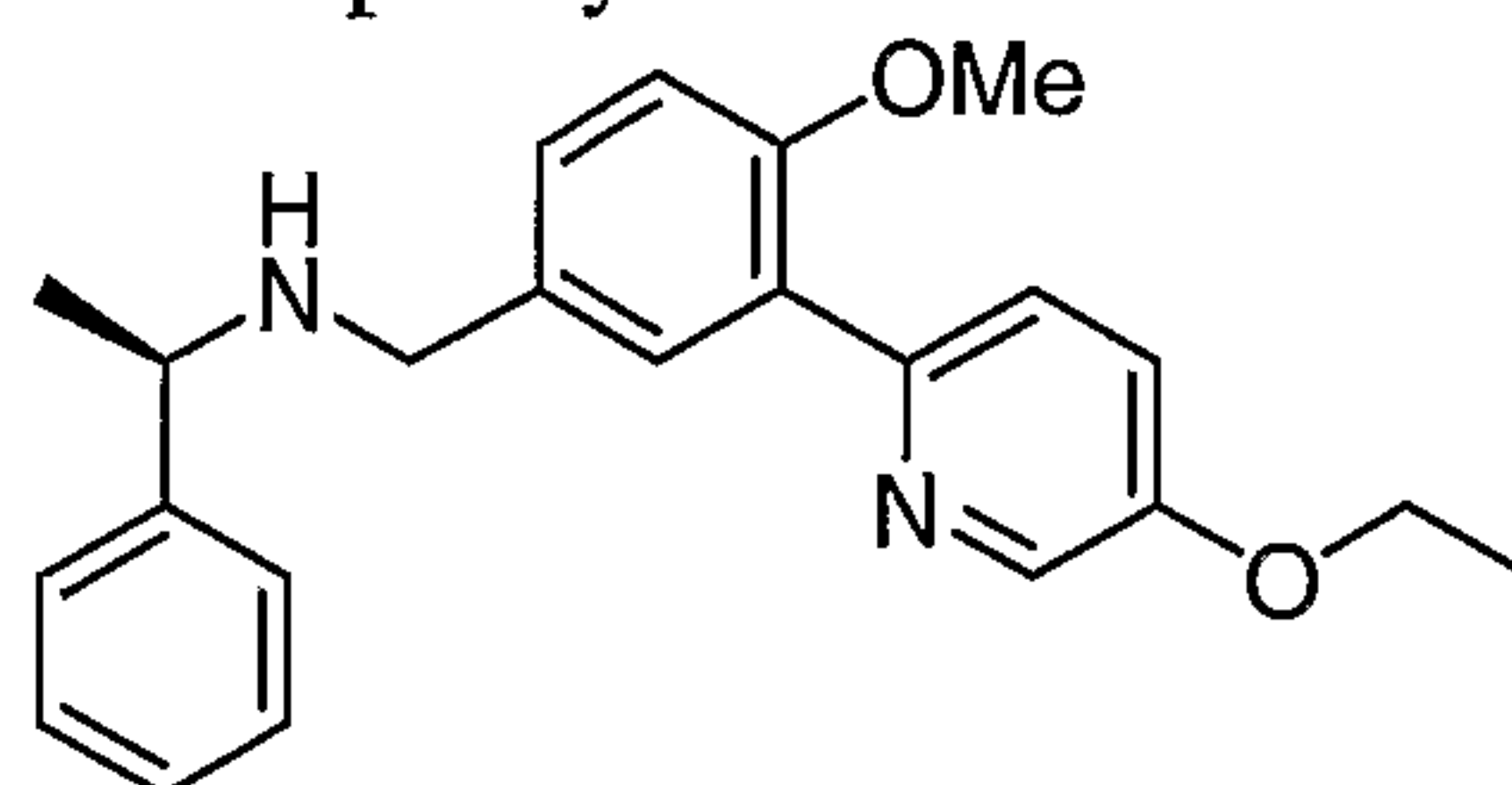
MW 412.53

Mass found: 413, 155, 242, 259

Example 428

- 237 -

(1R)-N-((3-(6-(ethyloxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine



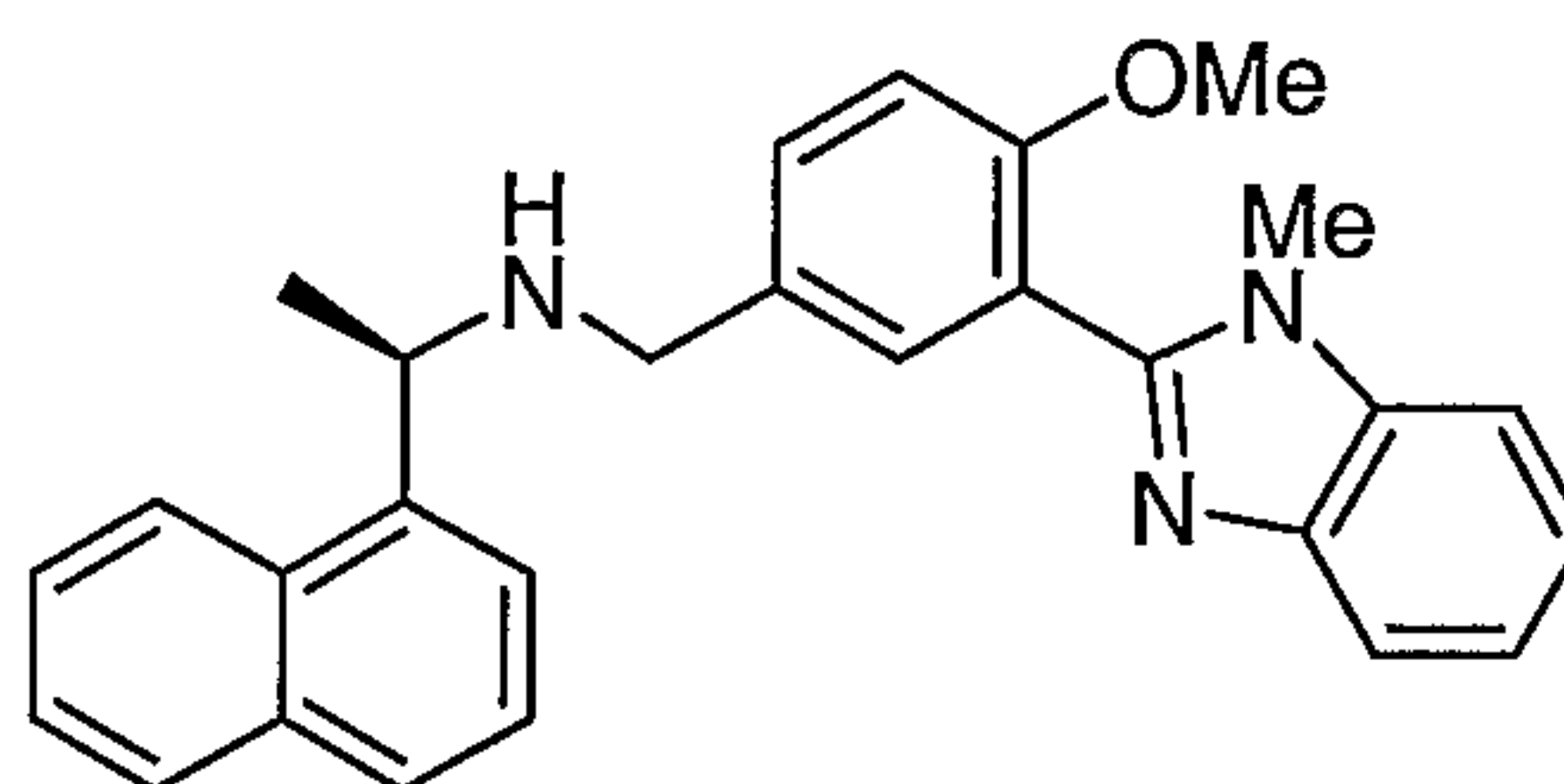
5

MW 362.47
Mass found: 242, 363, 725

Example 429

10

(1R)-N-((3-(1-methyl-1H-benzimidazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



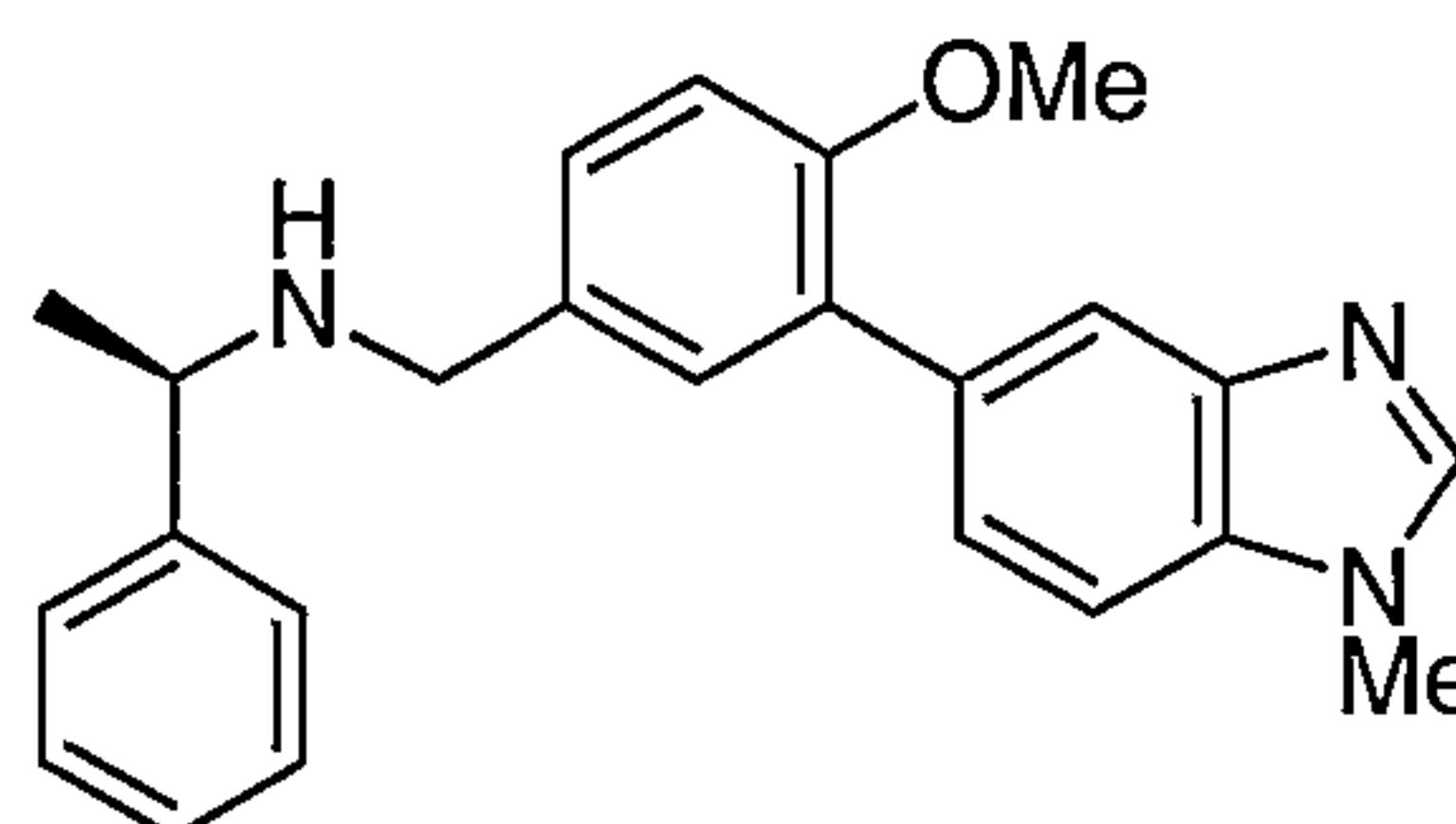
15

MW 421.541
Mass found: 422, 155

20

Example 430

(1R)-N-((3-(1-methyl-1H-benzimidazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine



25

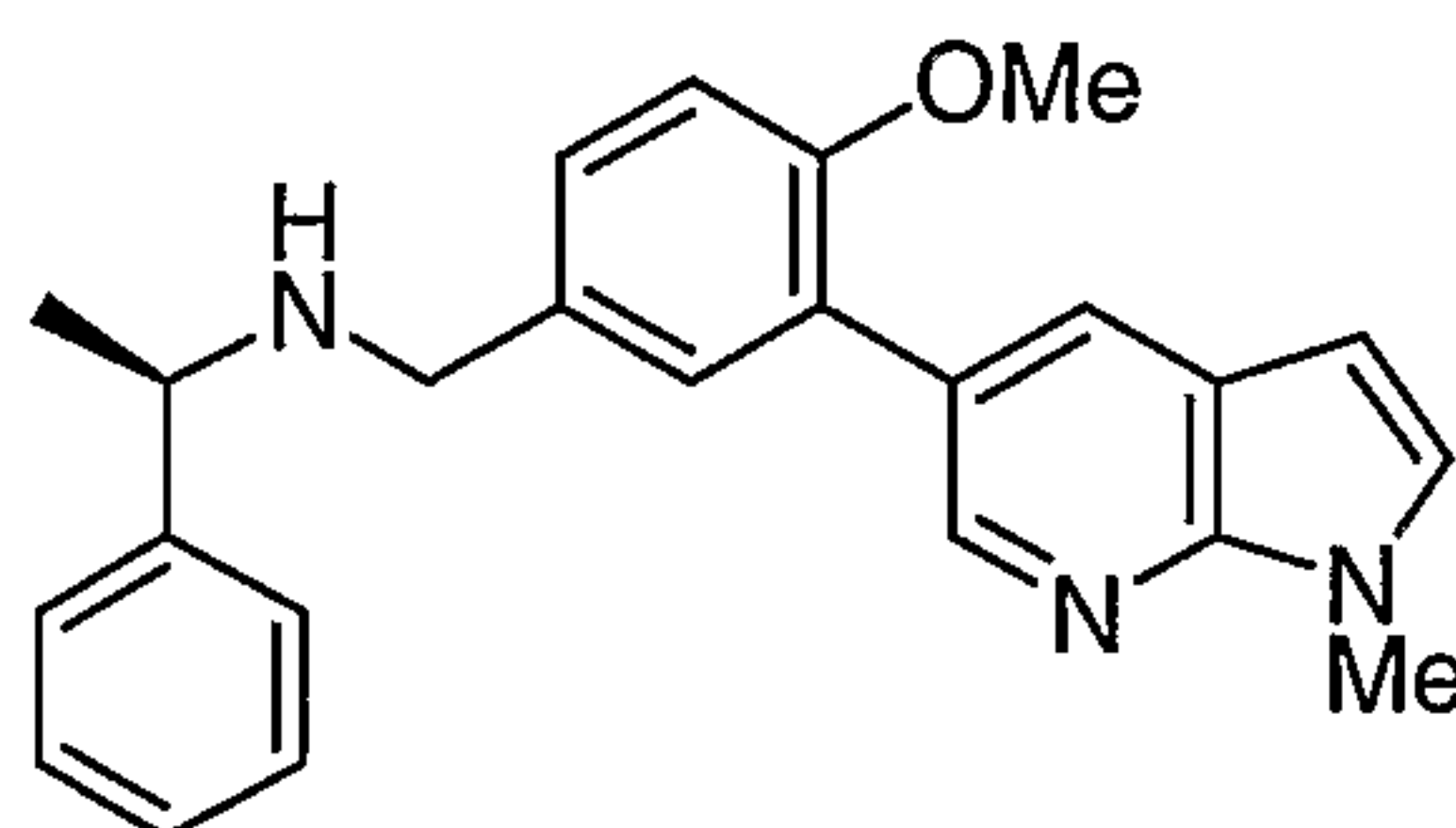
MW 371.482
Mass found: 251, 268, 372, 743

30

Example 431

- 238 -

(1R)-N-((4-(methyloxy)-3-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl)methyl)-1-phenylethanamine



5

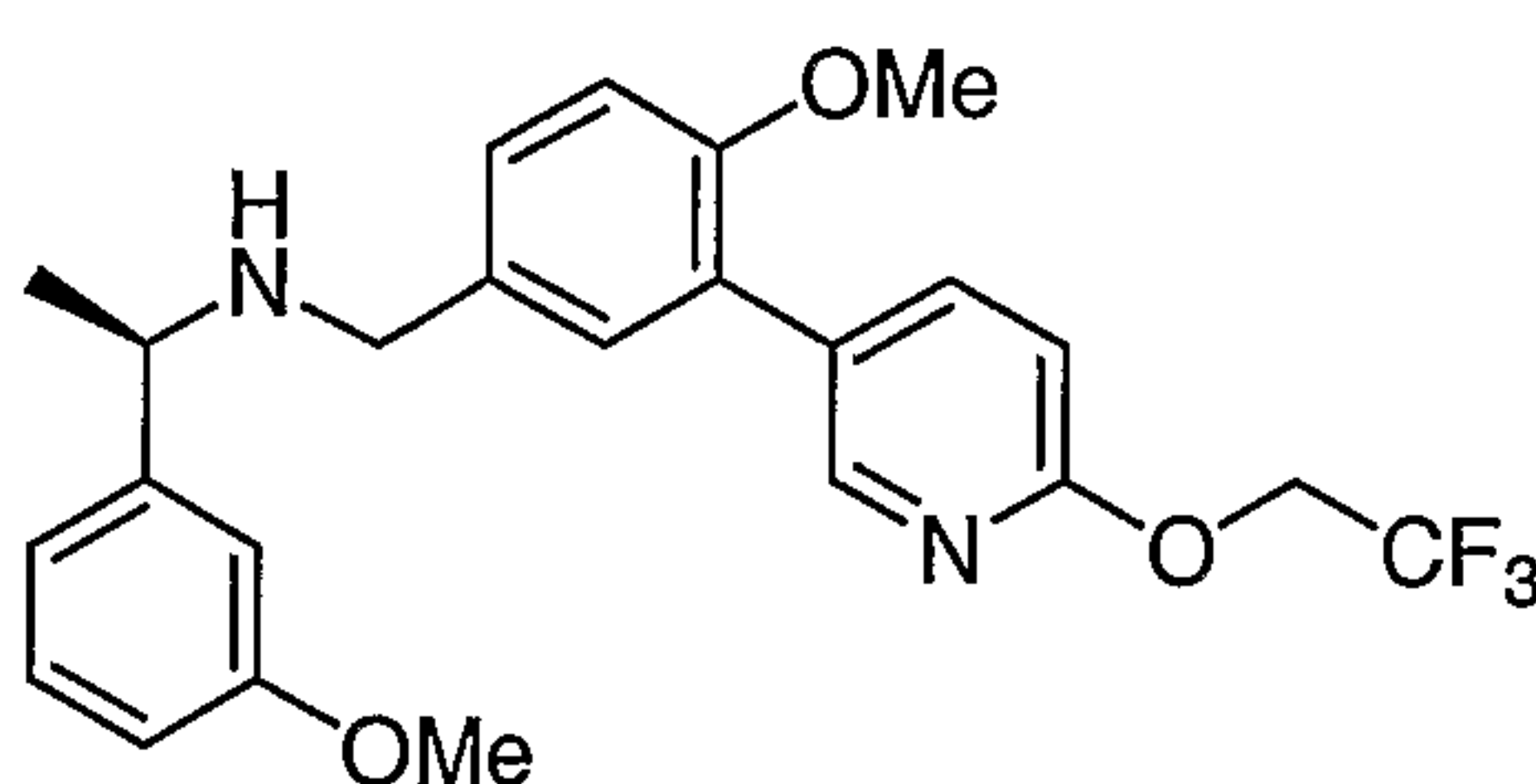
MW 371.482

Mass found: 251, 372, 268

10

Example 432

(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)ethanamine



15

MW 446.466

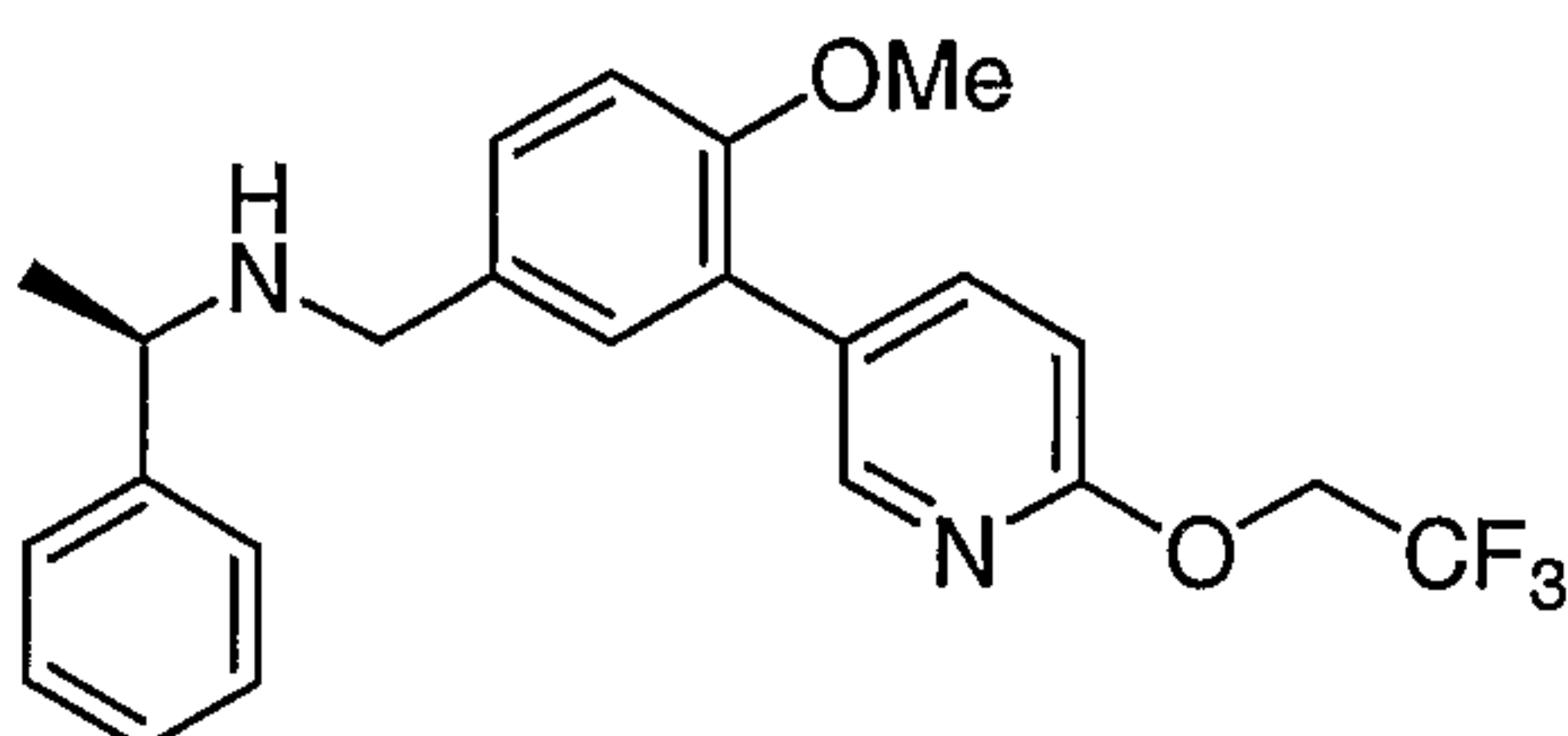
Mass found: 447, 296

20

Example 433

(1R)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine

25



30

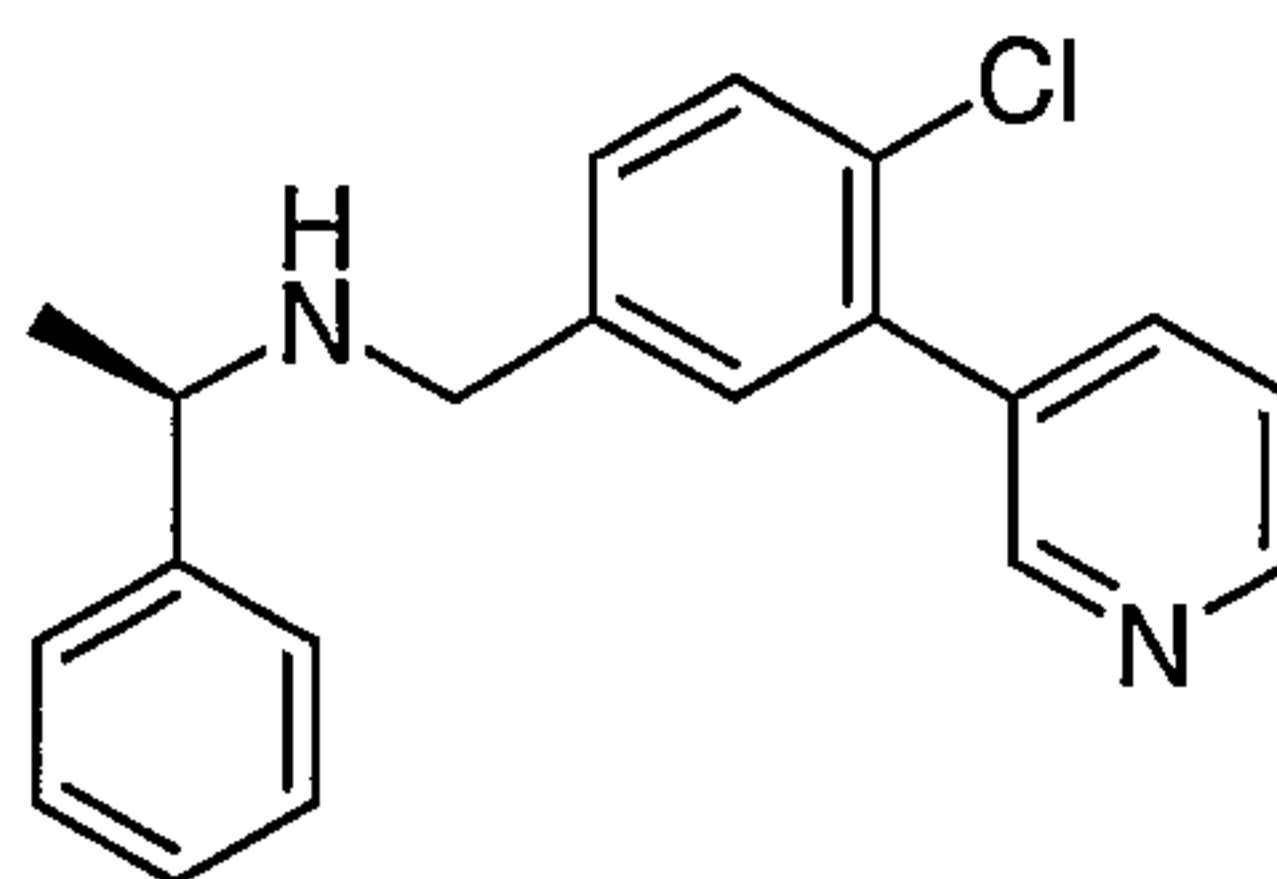
MW 416.441

Mass found: 417, 296

Example 434

- 239 -

(1R)-N-((4-chloro-3-(3-pyridinyl)phenyl)methyl)-1-phenylethanamine



5

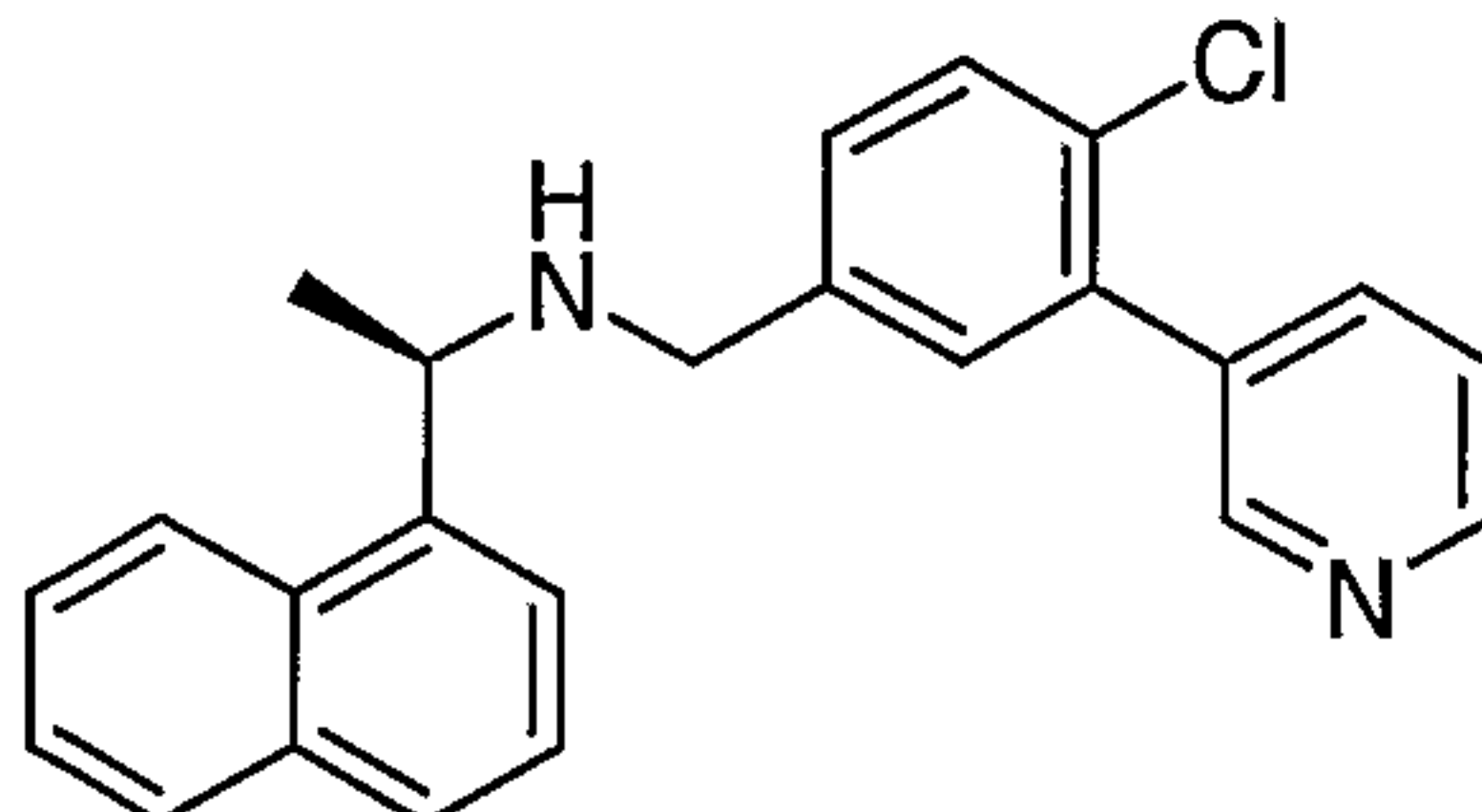
MW 322.837

Mass found: 323, 219, 645

Example 435

10

(1R)-N-((4-chloro-3-(3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine



15

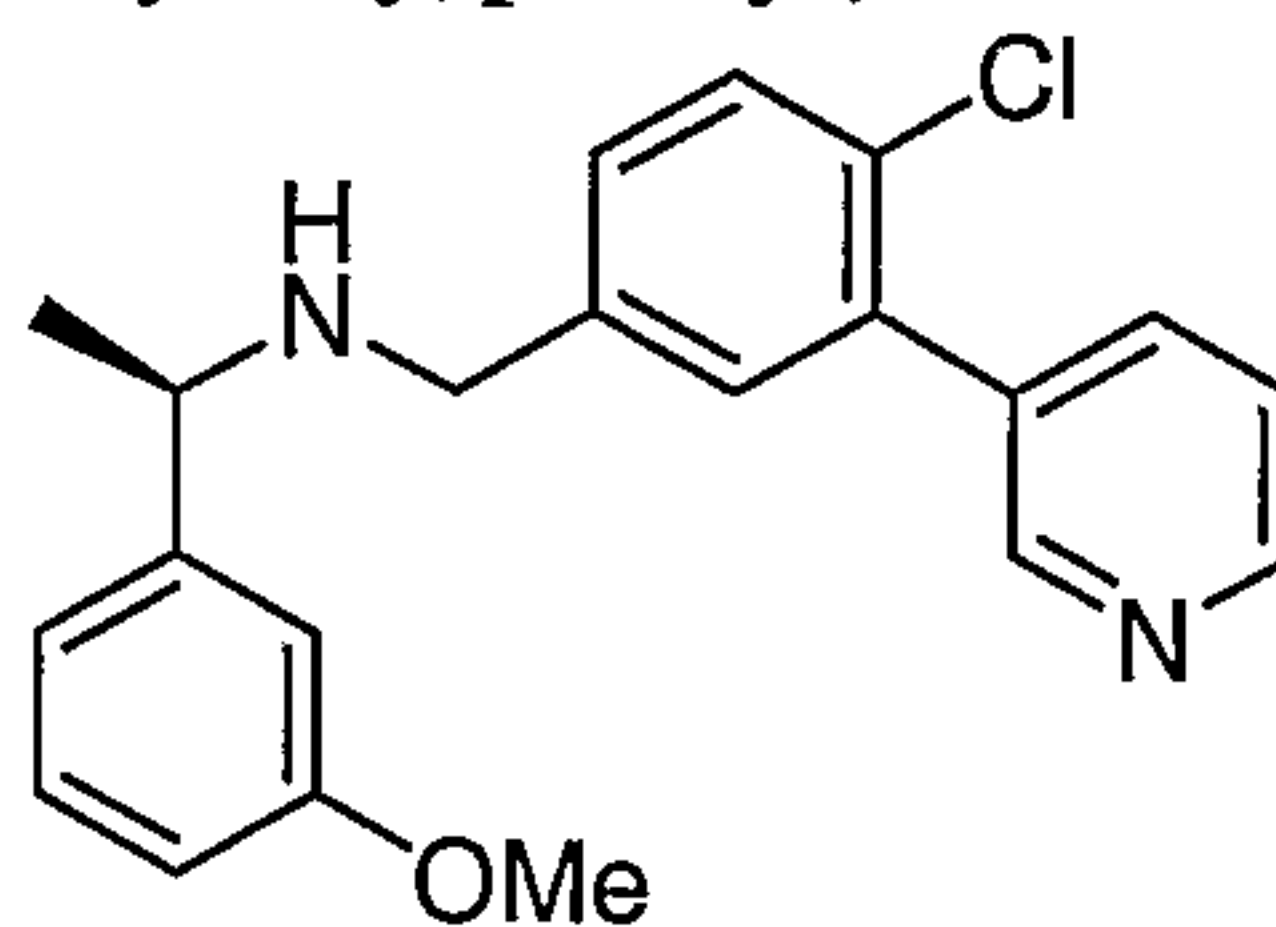
MW 372.897

Mass found: 155, 373, 219

Example 436

20

(1R)-N-((4-chloro-3-(3-pyridinyl)phenyl)methyl)-1-(3-(methoxy)phenyl)ethanamine



25

MW 352.863

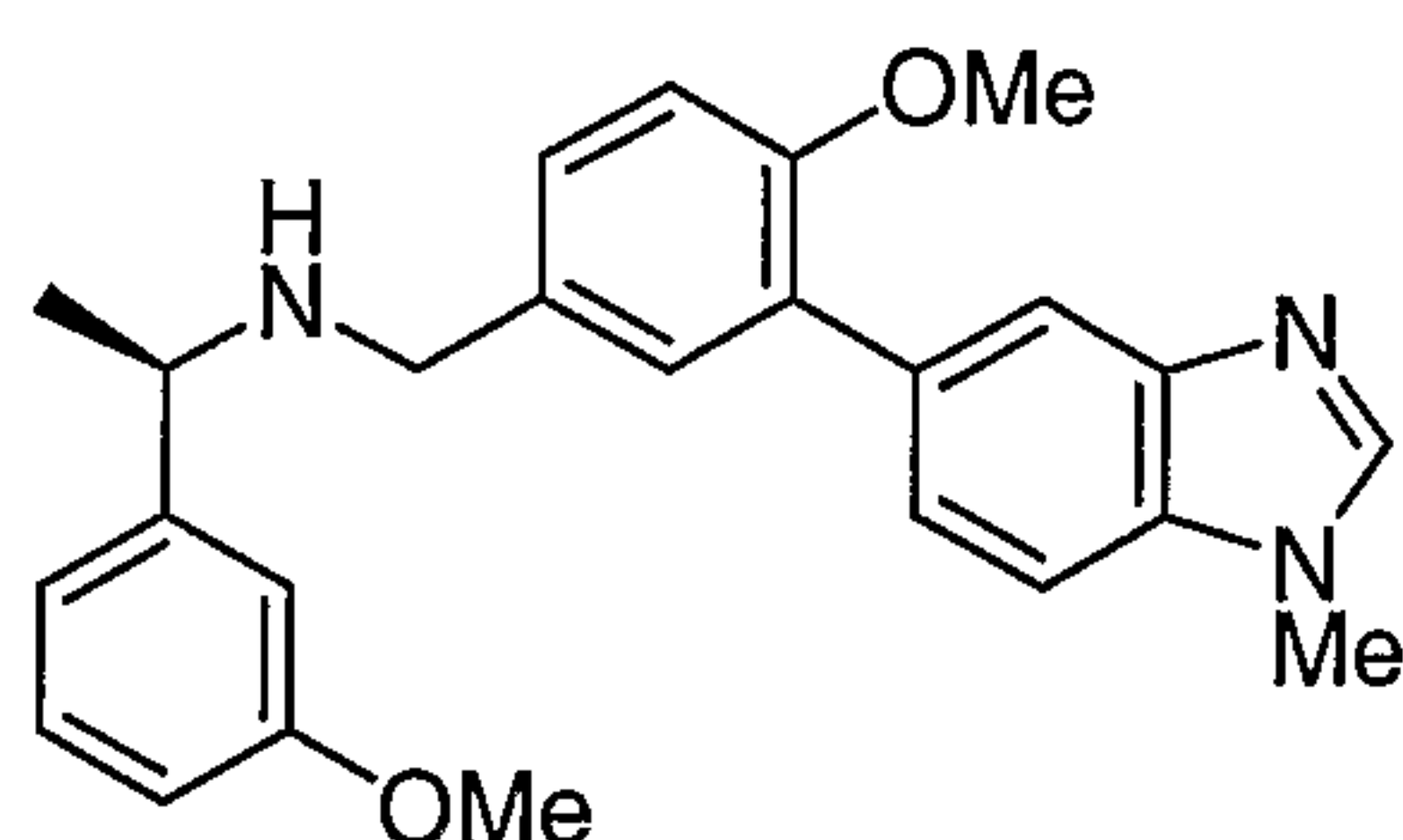
Mass found: 353, 219

- 240 -

Example 437

(1R)-N-((3-(1-methyl-1H-benzimidazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

5



MW 401.507

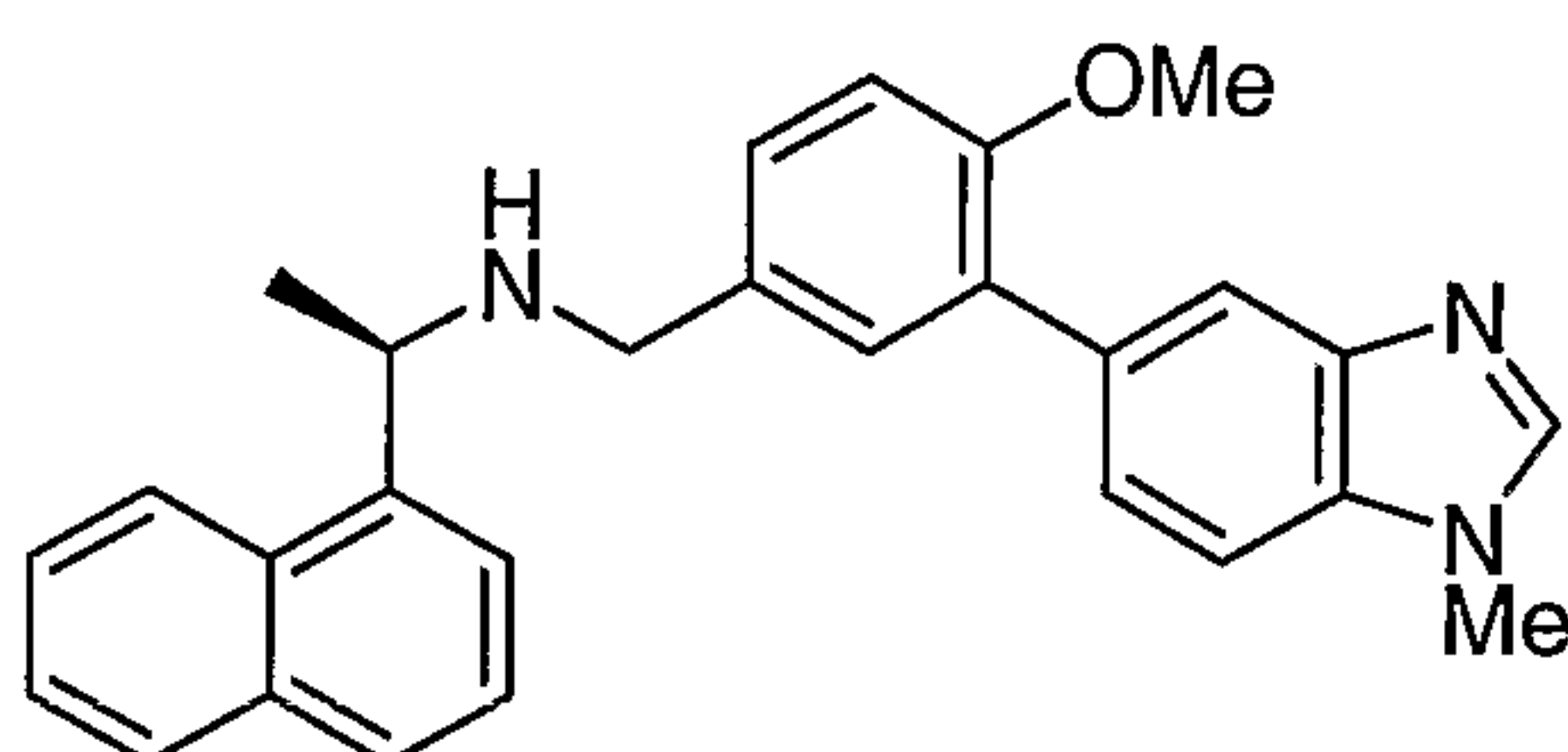
Mass found: 402, 251, 268

10

Example 438

(1R)-N-((3-(1-methyl-1H-benzimidazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

15



MW 421.541

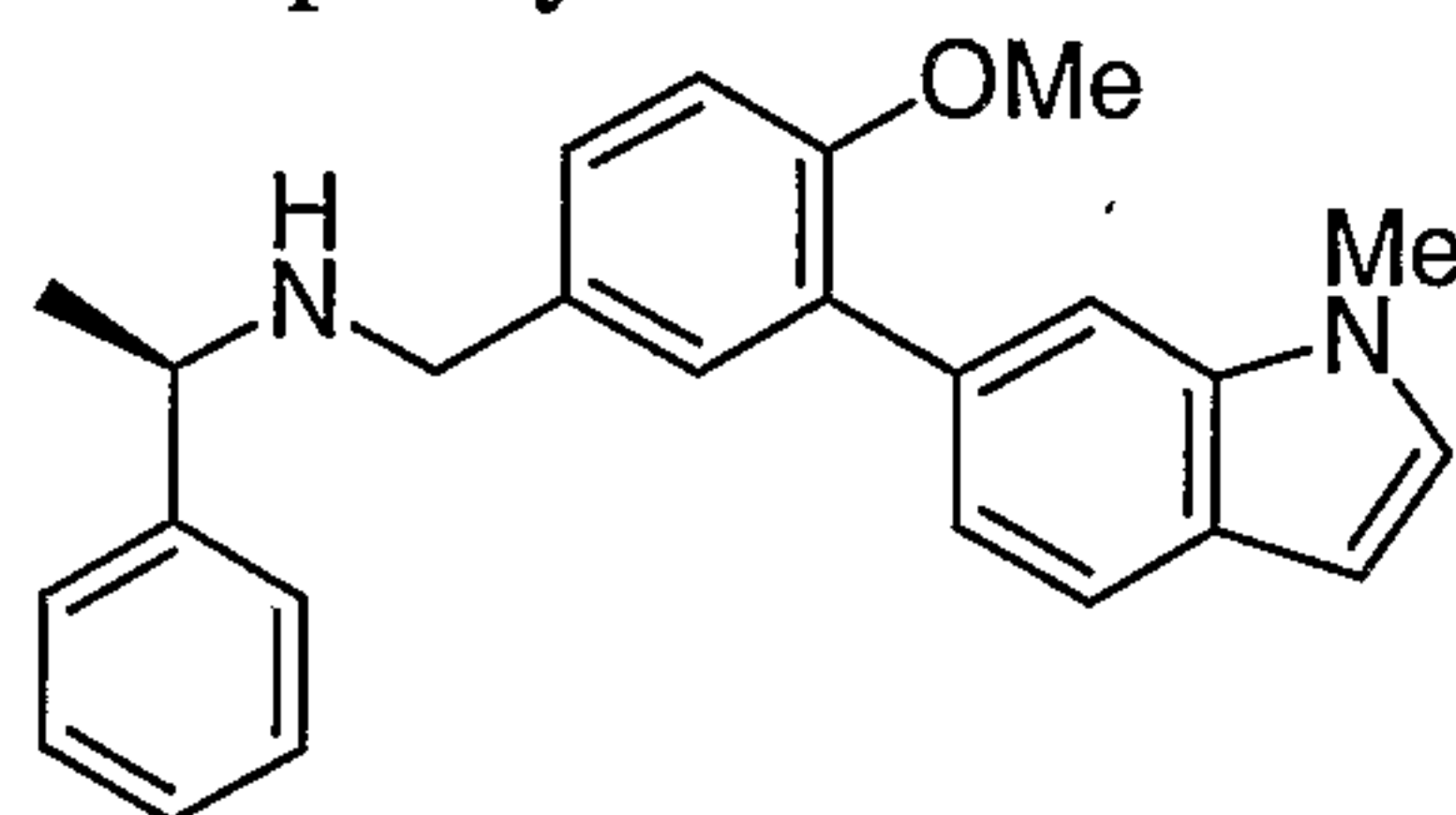
Mass found: 155, 422, 251, 268

20

Example 439

(1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine

25



MW 370.493

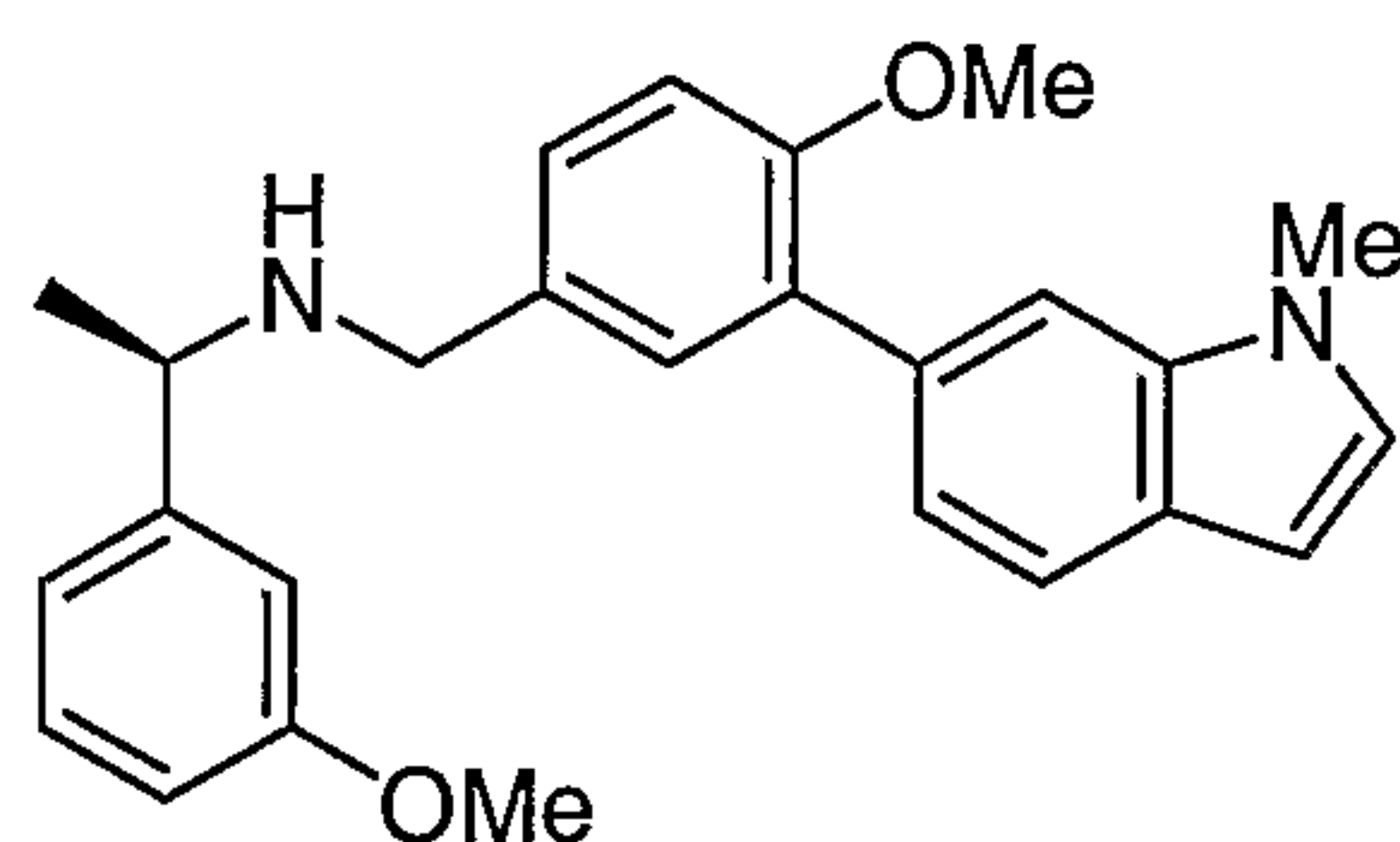
Mass found: 250, 371

30

Example 440

- 241 -

(1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methoxy)phenyl)methyl)-1-(3-(methoxy)phenyl)ethanamine



5

MW 400.519

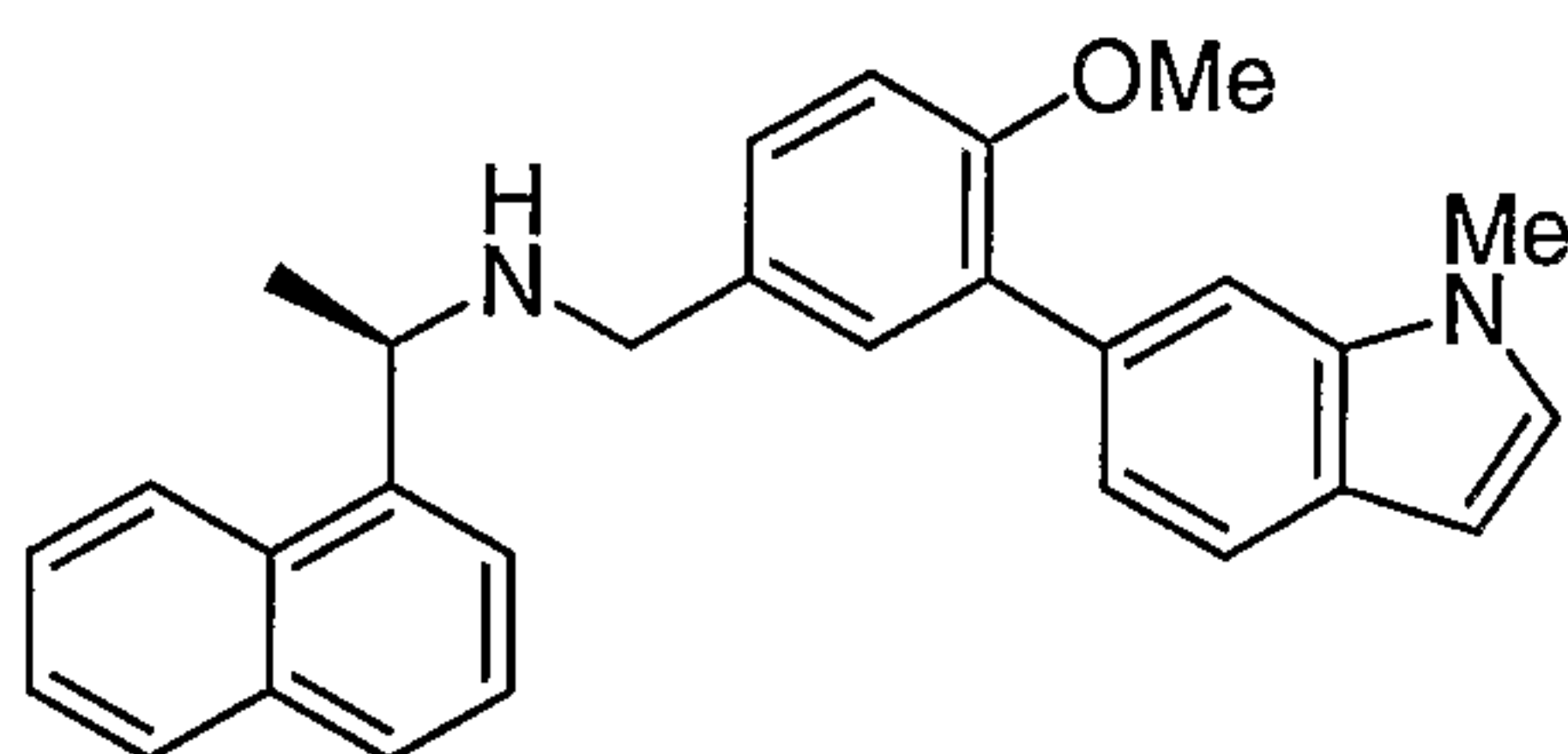
Mass found: 401, 250

10

Example 441

(1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methoxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

15



MW 420.553

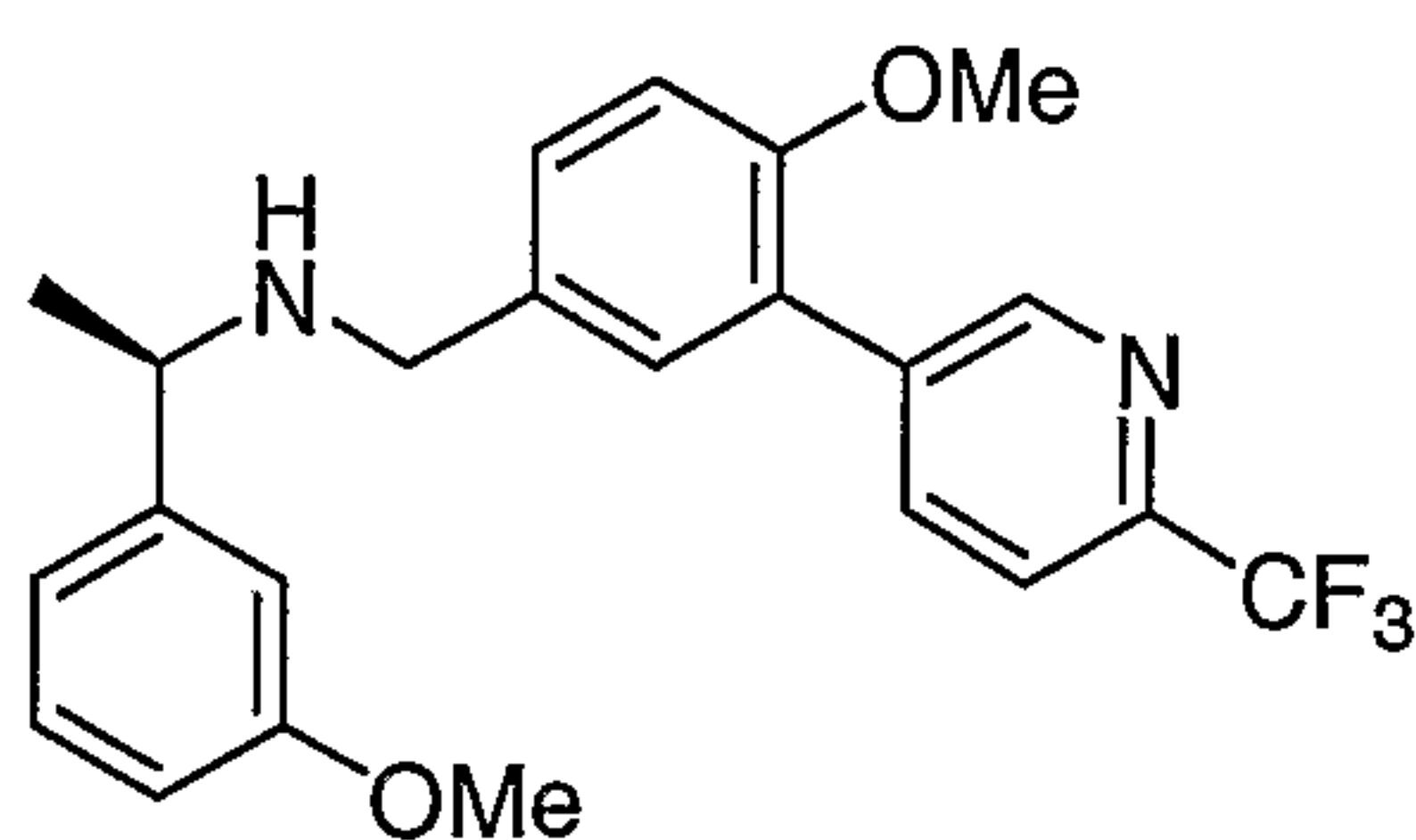
Mass found: 421, 250

20

Example 442

(1R)-1-(3-(methoxy)phenyl)-N-((4-(methoxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)ethanamine

25



MW 416.441

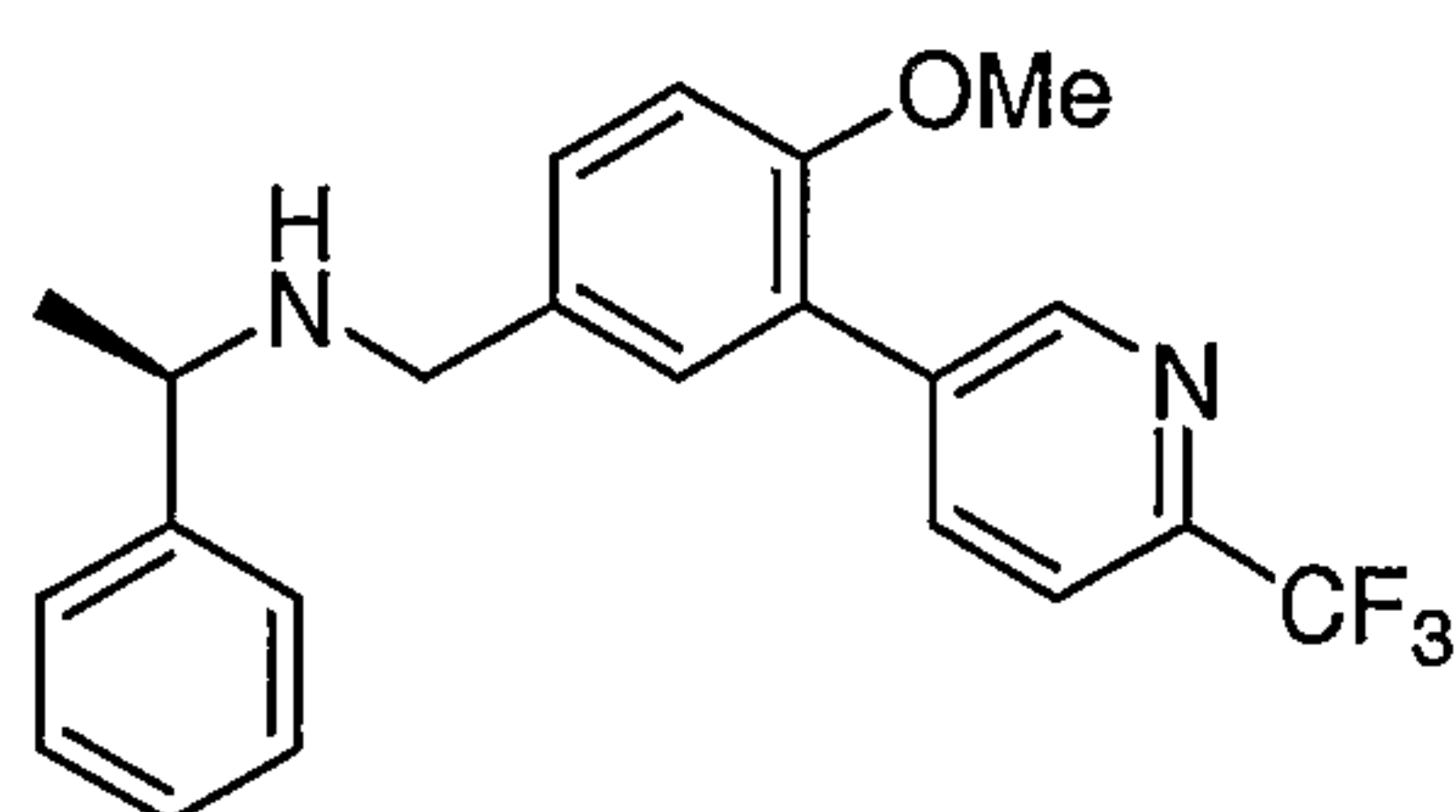
Mass found: 417, 947

30

Example 443

- 242 -

(1R)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine



5

MW 386.415

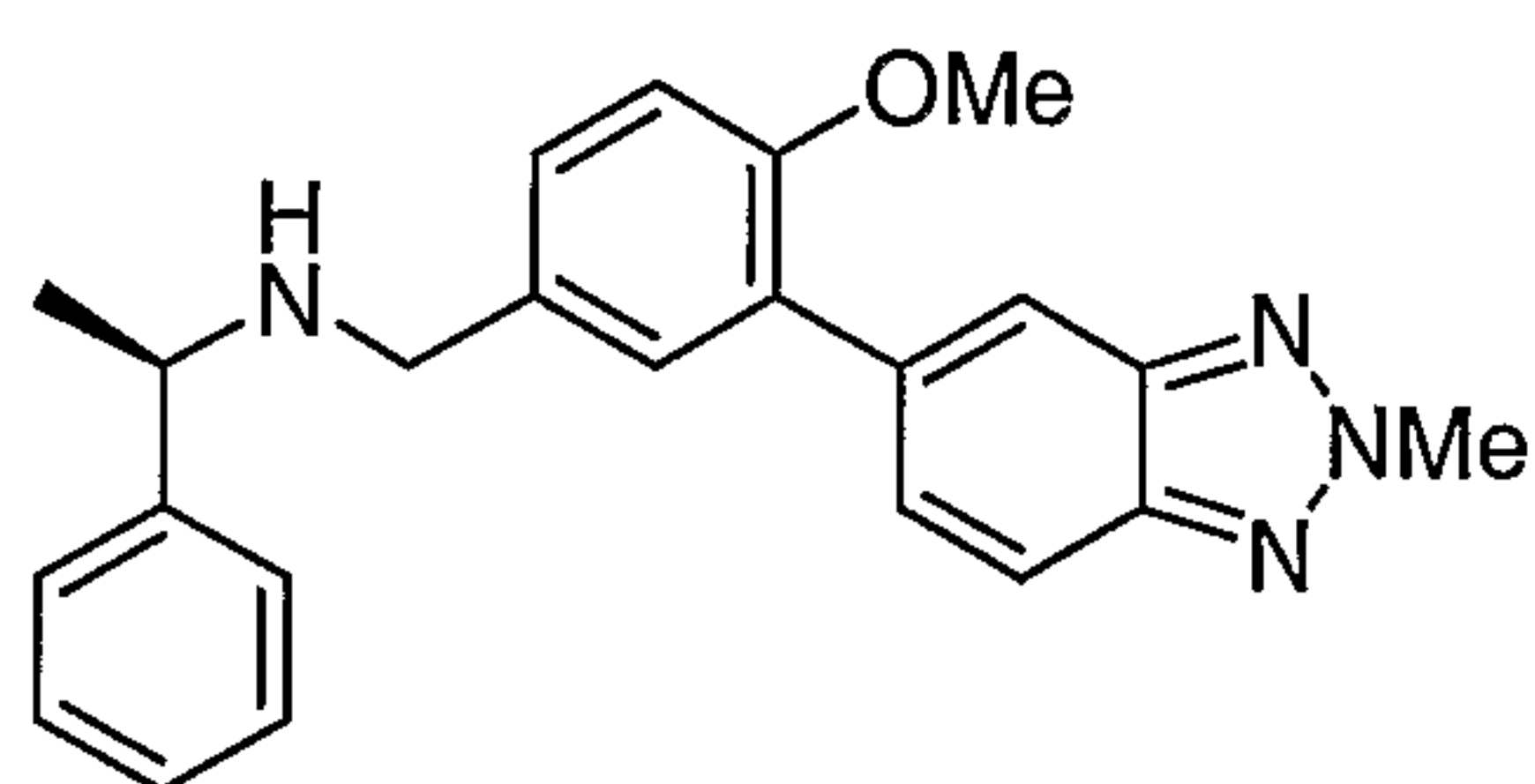
Mass found: 887, 387, 428

10

Example 444

(1R)-N-((3-(2-ethyl-2H-1,2,3-benzotriazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine

15



MW 386.496

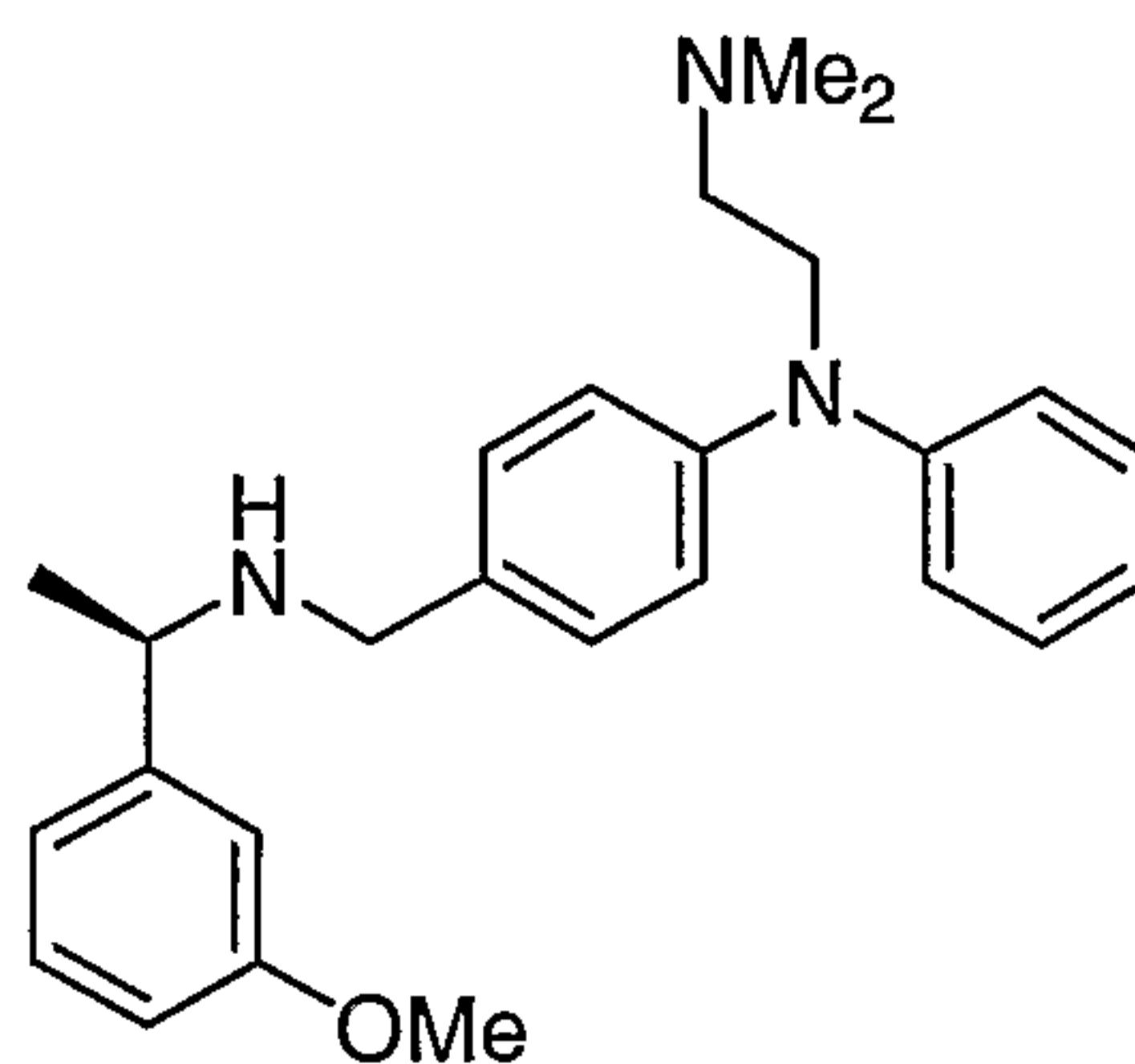
Mass found: 887, 387

20

Example 445

N-1,N-1-dimethyl-N-2-(4-(((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-N-2-phenyl-1,2-ethanediamine

25



MW 403.567

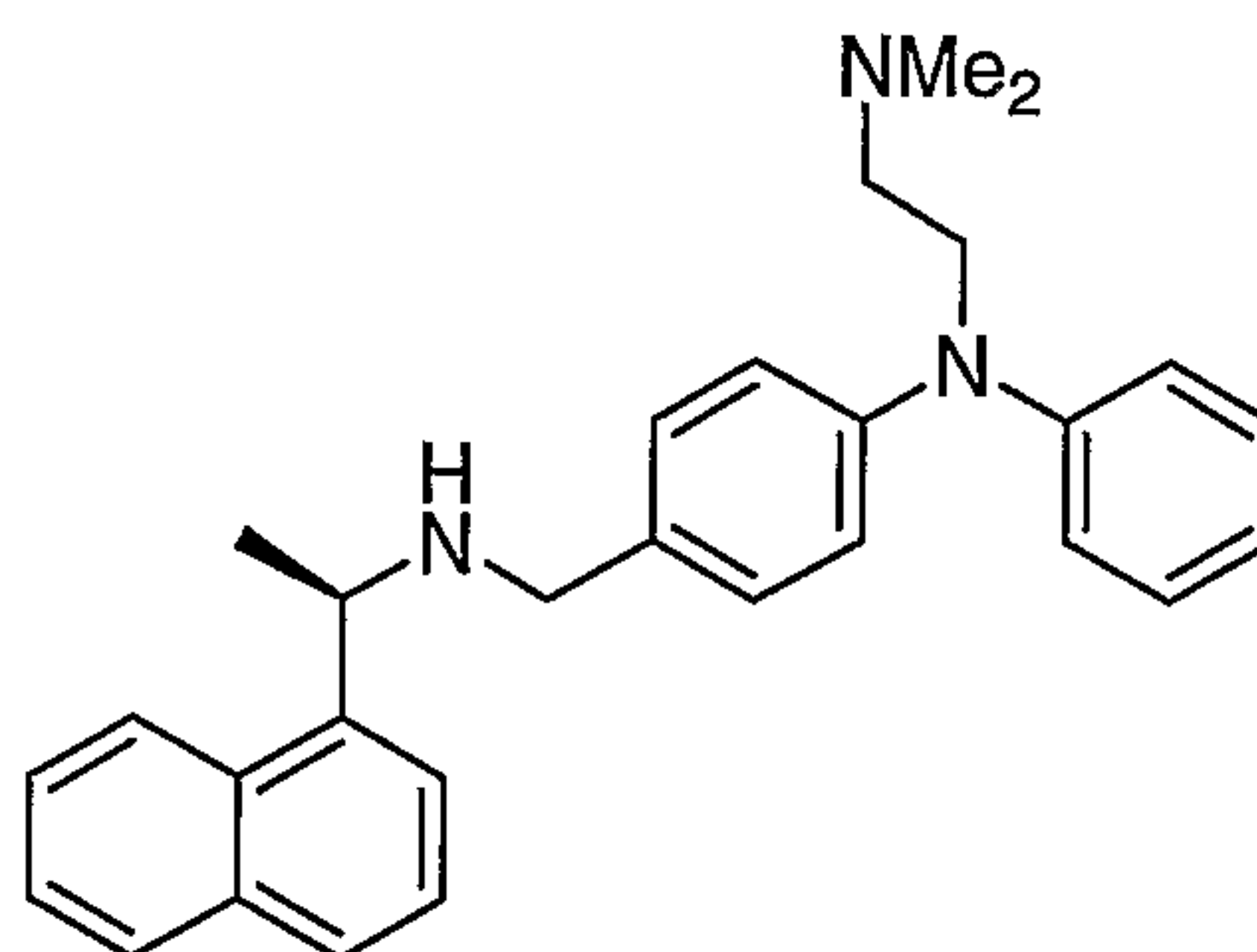
Mass found: 253, 404

30

- 243 -

Example 446

5 N-1,N-1-dimethyl-N-2-(4-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-
N-2-phenyl-1,2-ethanediamine



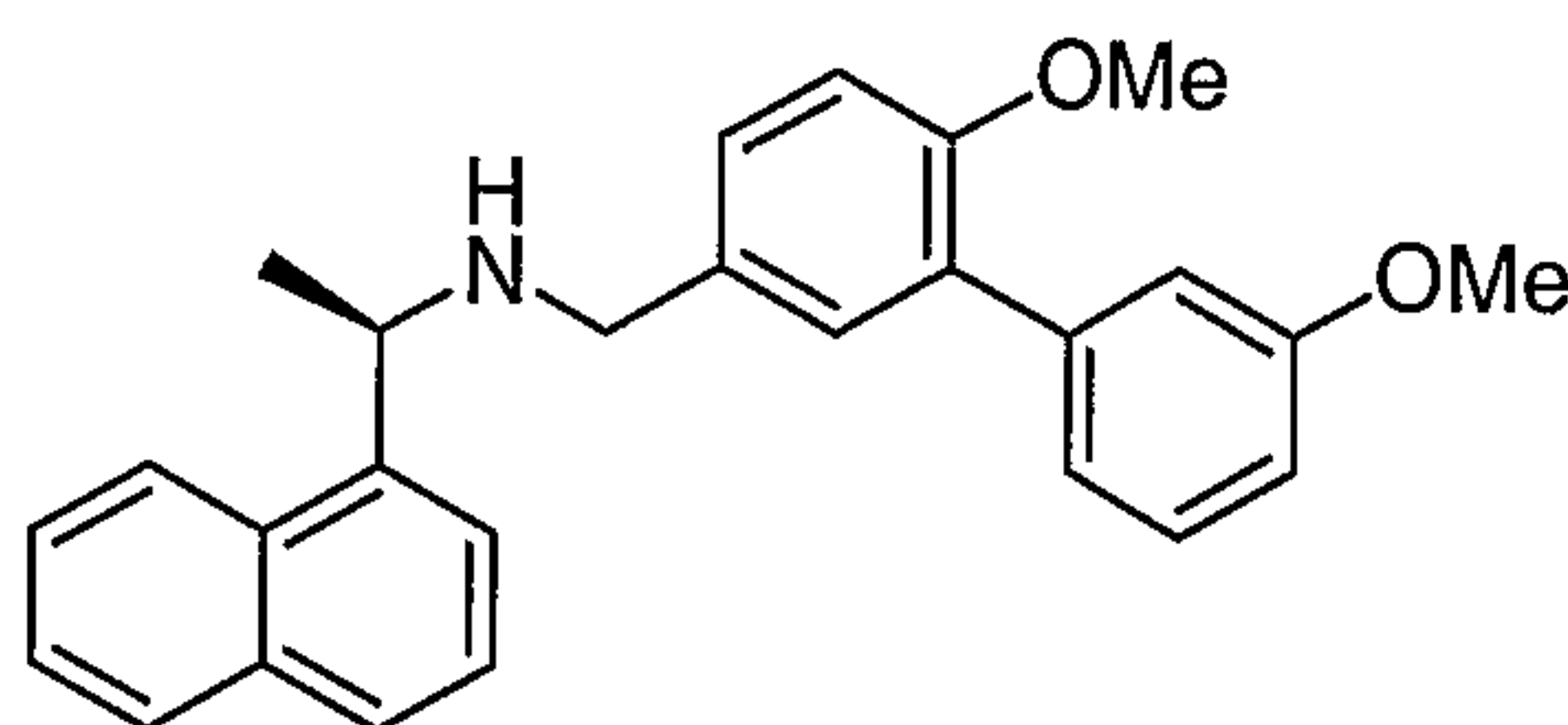
10

MW 423.601
Mass found: 253, 424

Example 447

15

(1R)-N-((3',6-bis(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-
naphthalenyl)ethanamine



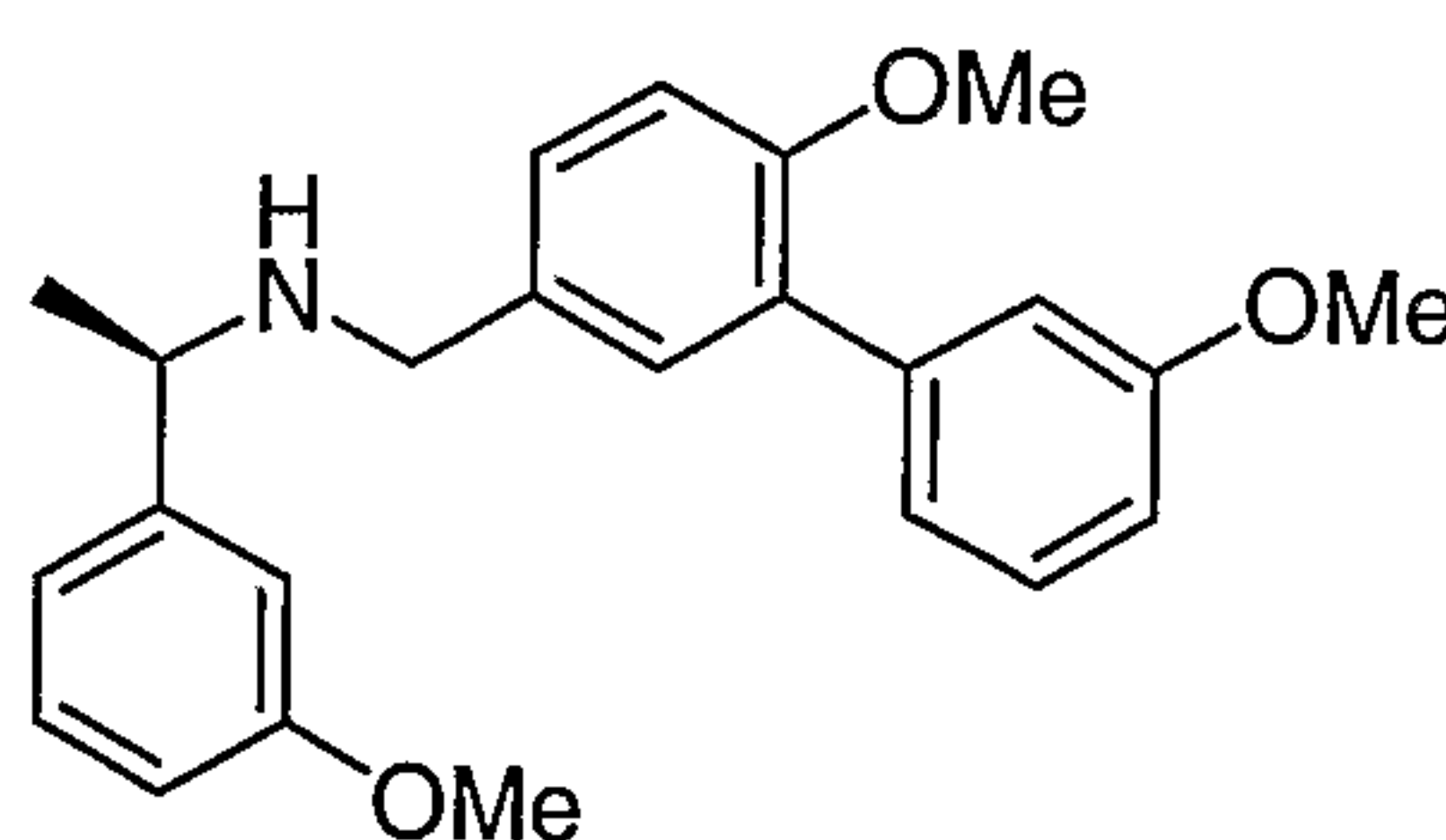
20

MW 397.515
Mass found: 398

Example 448

25

(1R)-N-((3',6-bis(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-
(methoxy)phenyl)ethanamine



30

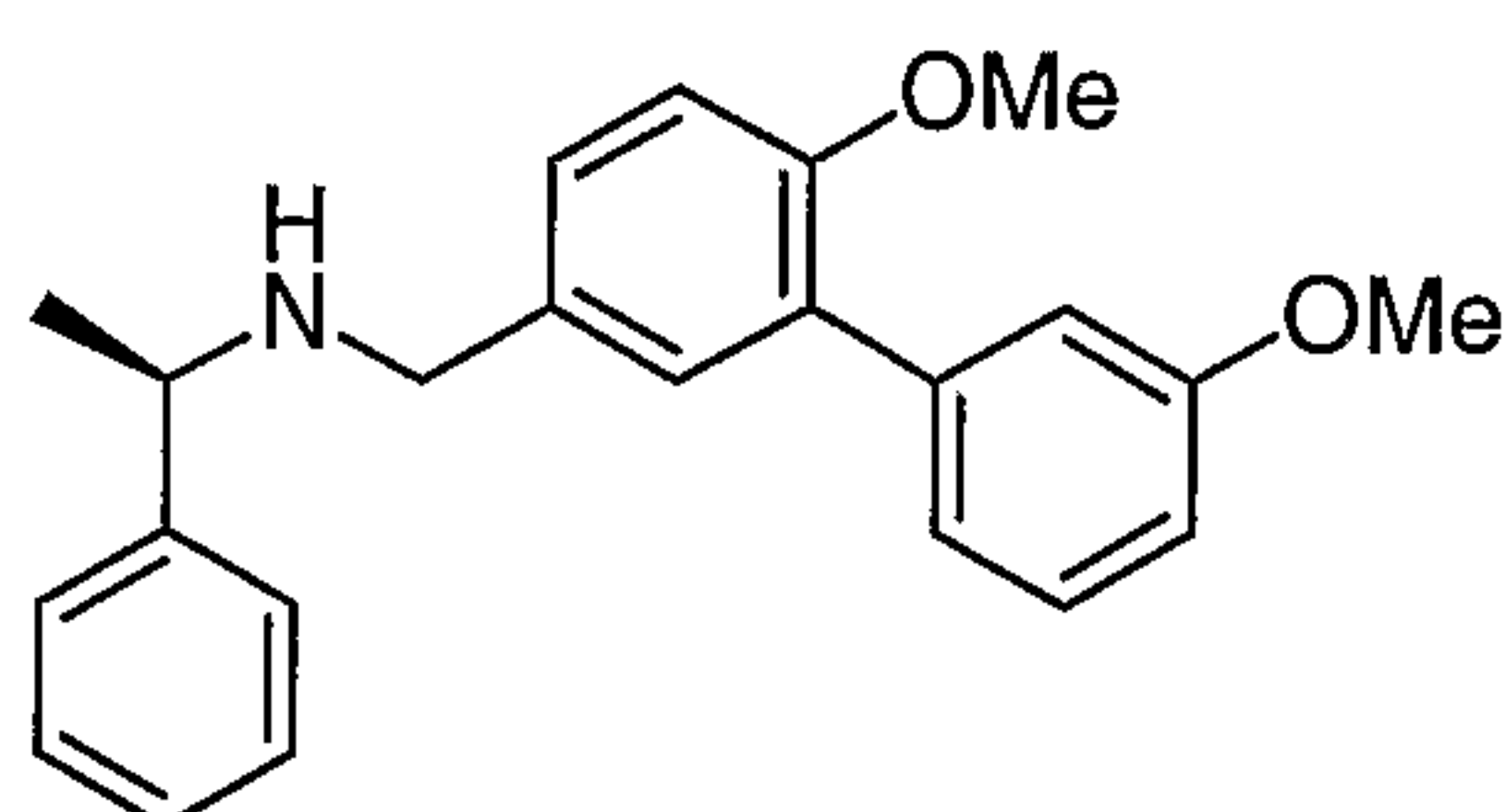
- 244 -

MW 377.481
Mass found: 378

5

Example 449

(1R)-N-((3',6-bis(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine



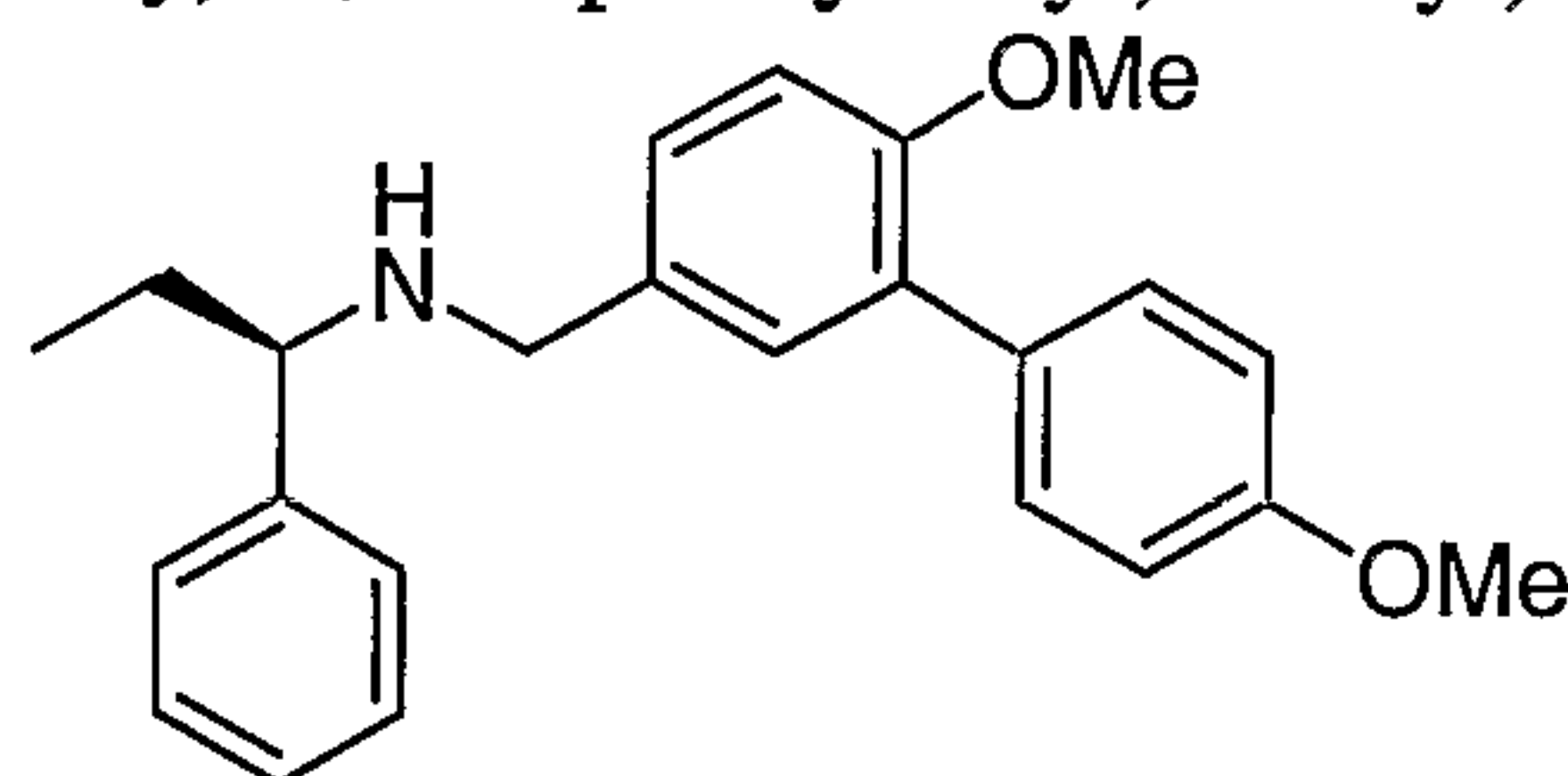
10

MW 347.456
Mass found: 348

15

Example 450

(1R)-N-((4',6-bis(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-phenyl-1-propanamine



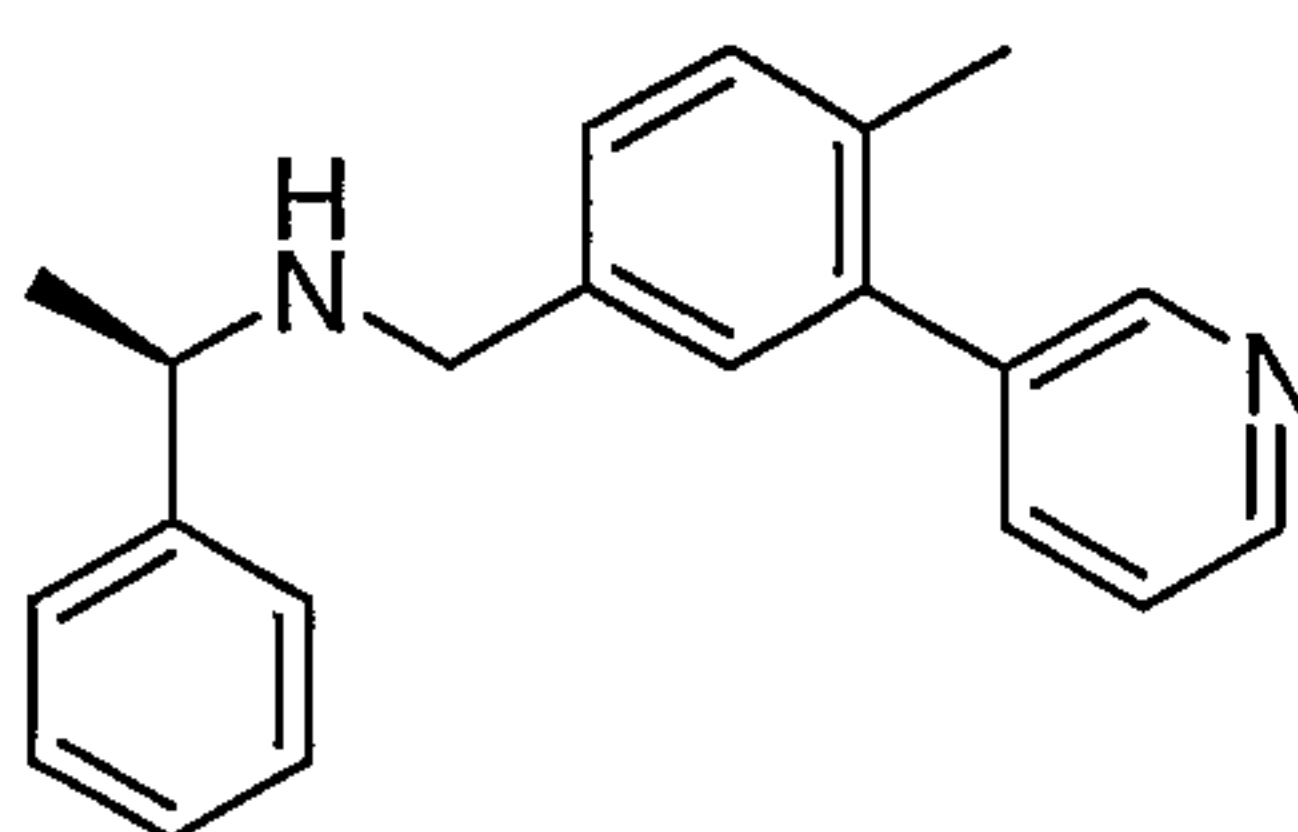
20

MW 361.482
Mass found: MS(EI) calcd for C₂₄H₂₇NO₂ 362 (MH⁺), Found: 362, 227, 212

25

Example 451

(1R)-N-((4-methyl-3-(3-pyridinyl)phenyl)methyl)-1-phenylethanamine



30

MW 302.419
Mass found: MS(EI) calcd for C₂₁H₂₂N₂ 303 (MH⁺) Found: 303, 199, 183

- 245 -

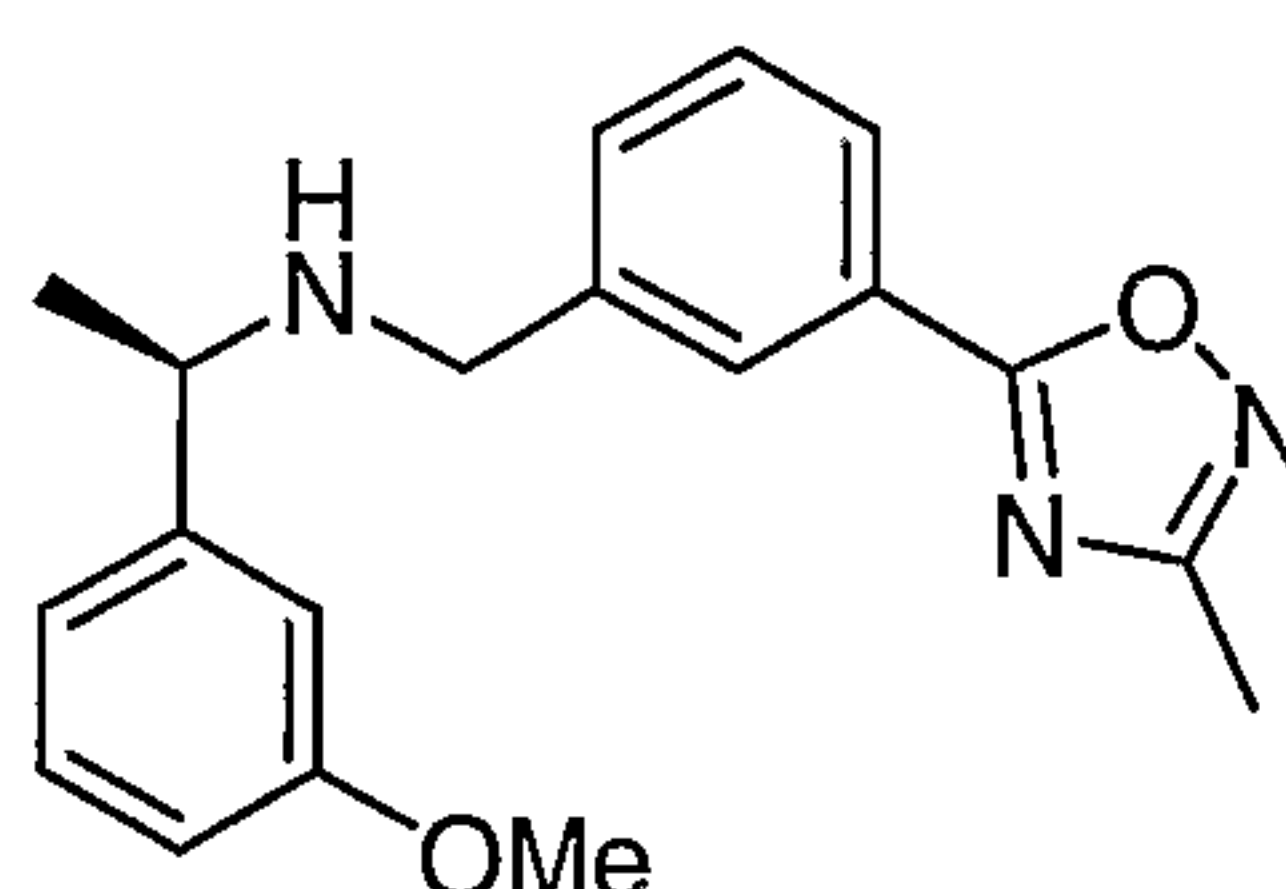
Examples 452-465 were prepared using Method A:

5

Example 452

(1R)-N-((3-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

10



MW 323.394

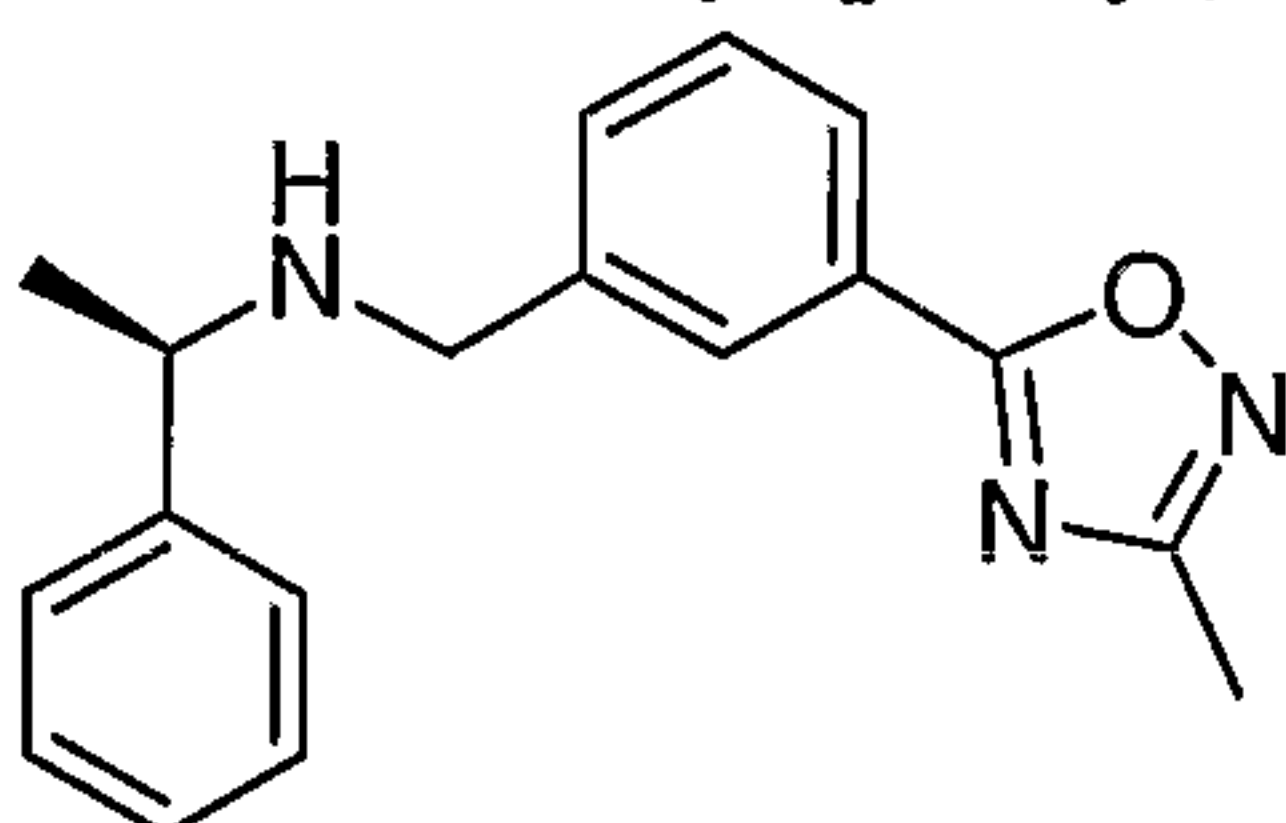
Mass found: 324, 231, 190

15

Example 453

(1R)-N-((3-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)methyl)-1-phenylethanamine

20



MW 293.368

Mass found: 294, 231, 190

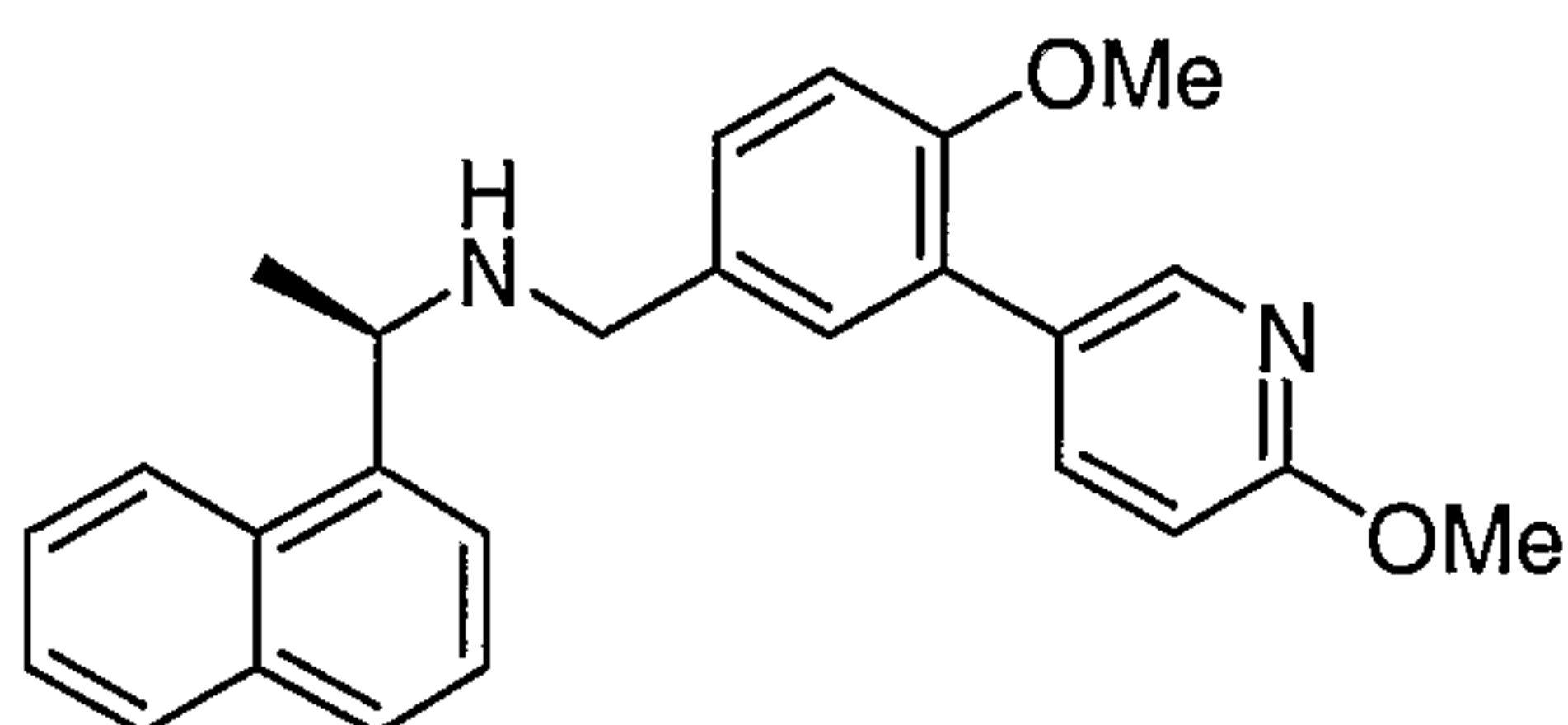
25

- 246 -

Example 454

(1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine

5



MW 398.503

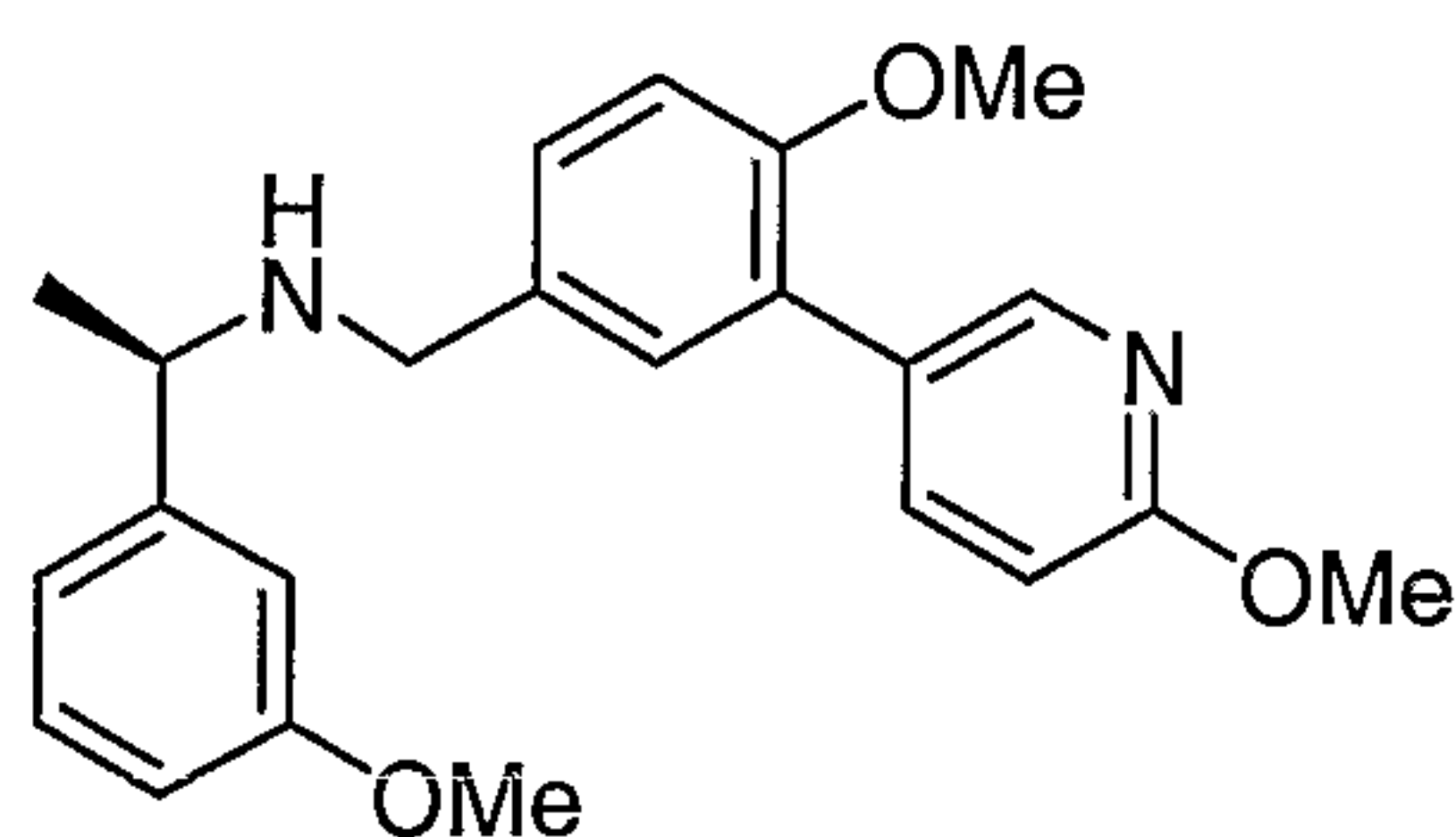
Mass found: 399, 155, 245, 228

10

Example 455

(1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

15



MW 378.469

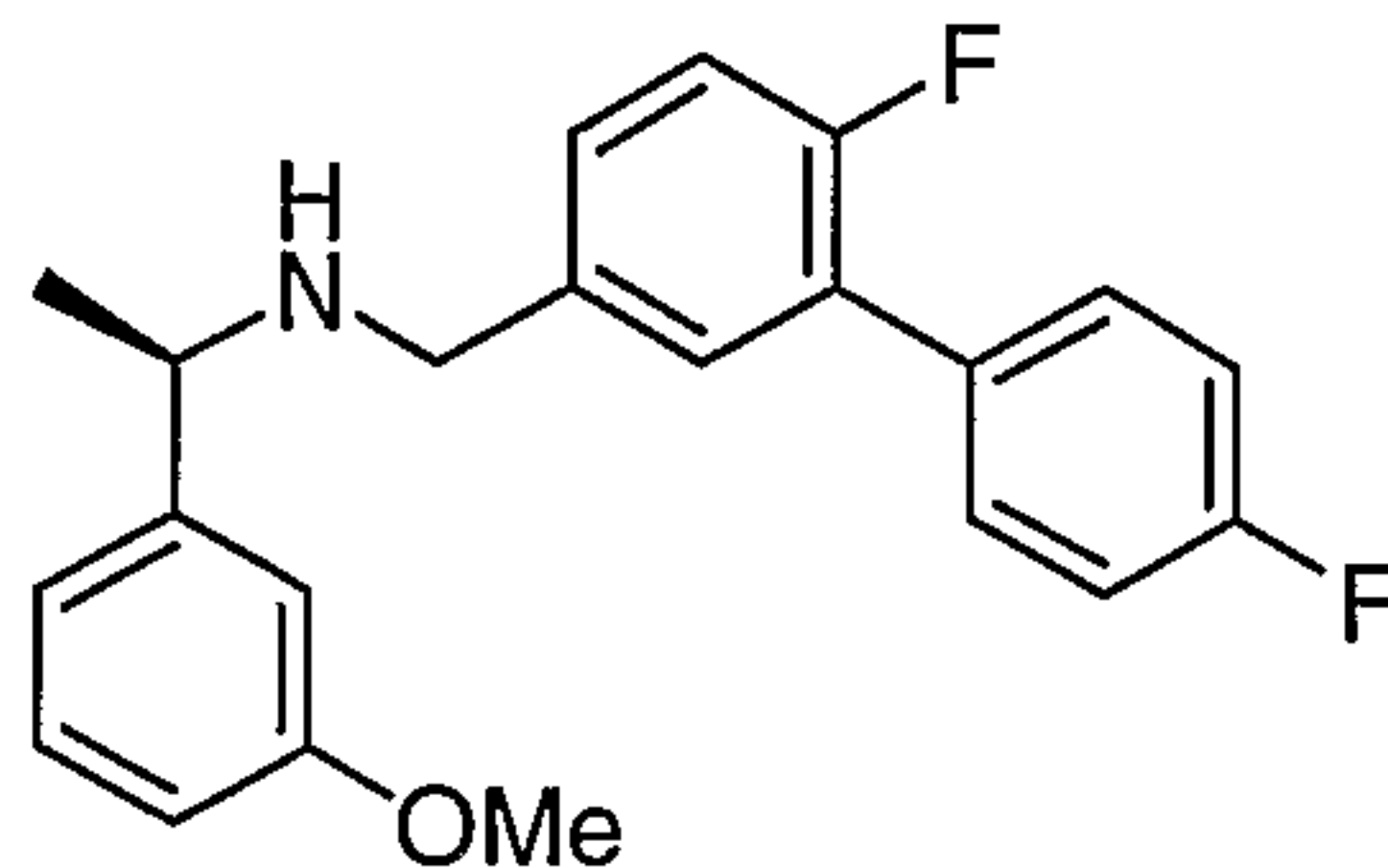
Mass found: 379

20

Example 456

(1R)-N-((4',6-difluoro-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

25



MW 353.41

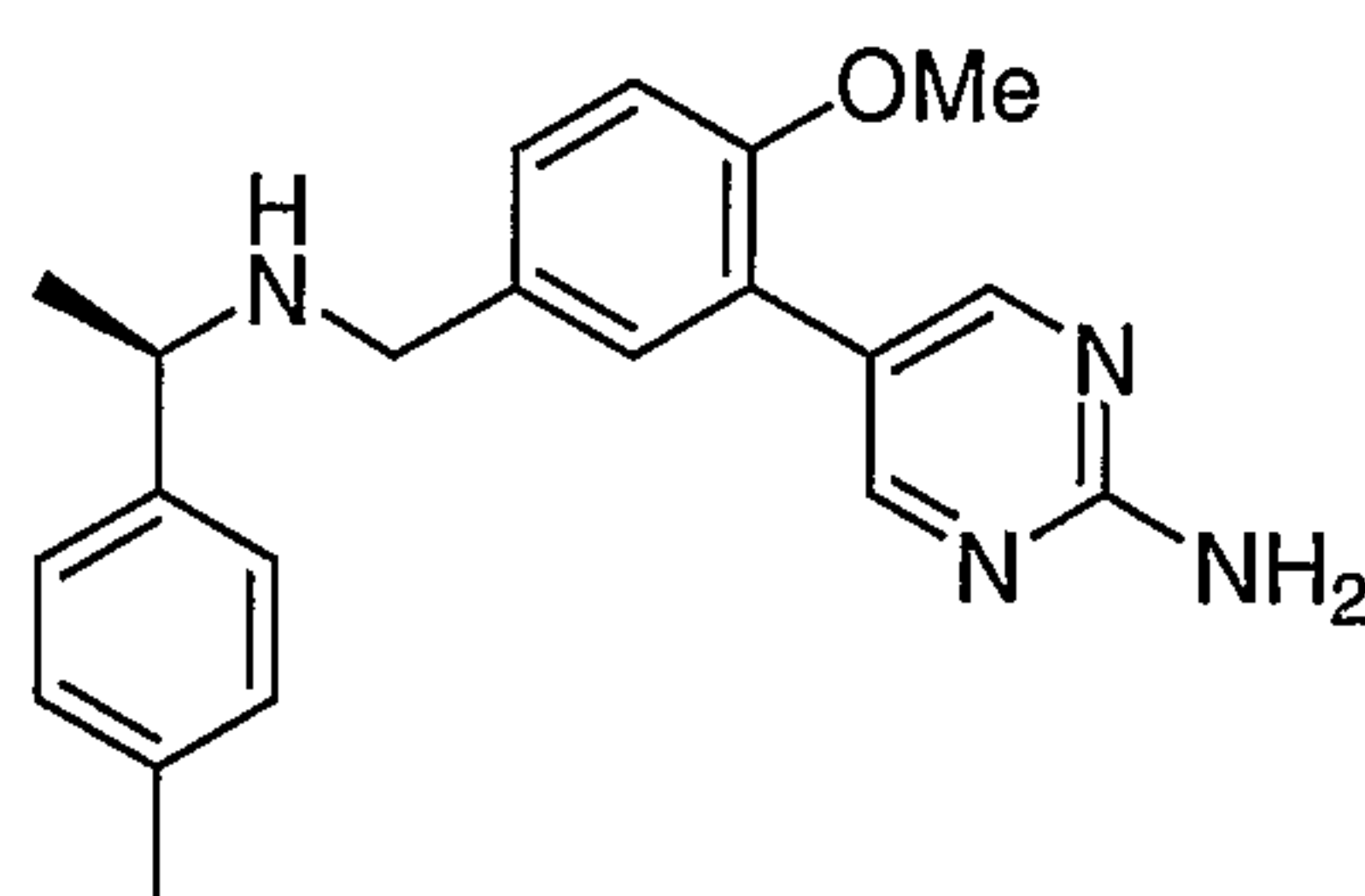
Mass found: 354

30

Example 457

- 247 -

5-(2-(methyloxy)-5-((((1R)-1-(4-methylphenyl)ethyl)amino)methyl)phenyl)-2-pyrimidinamine



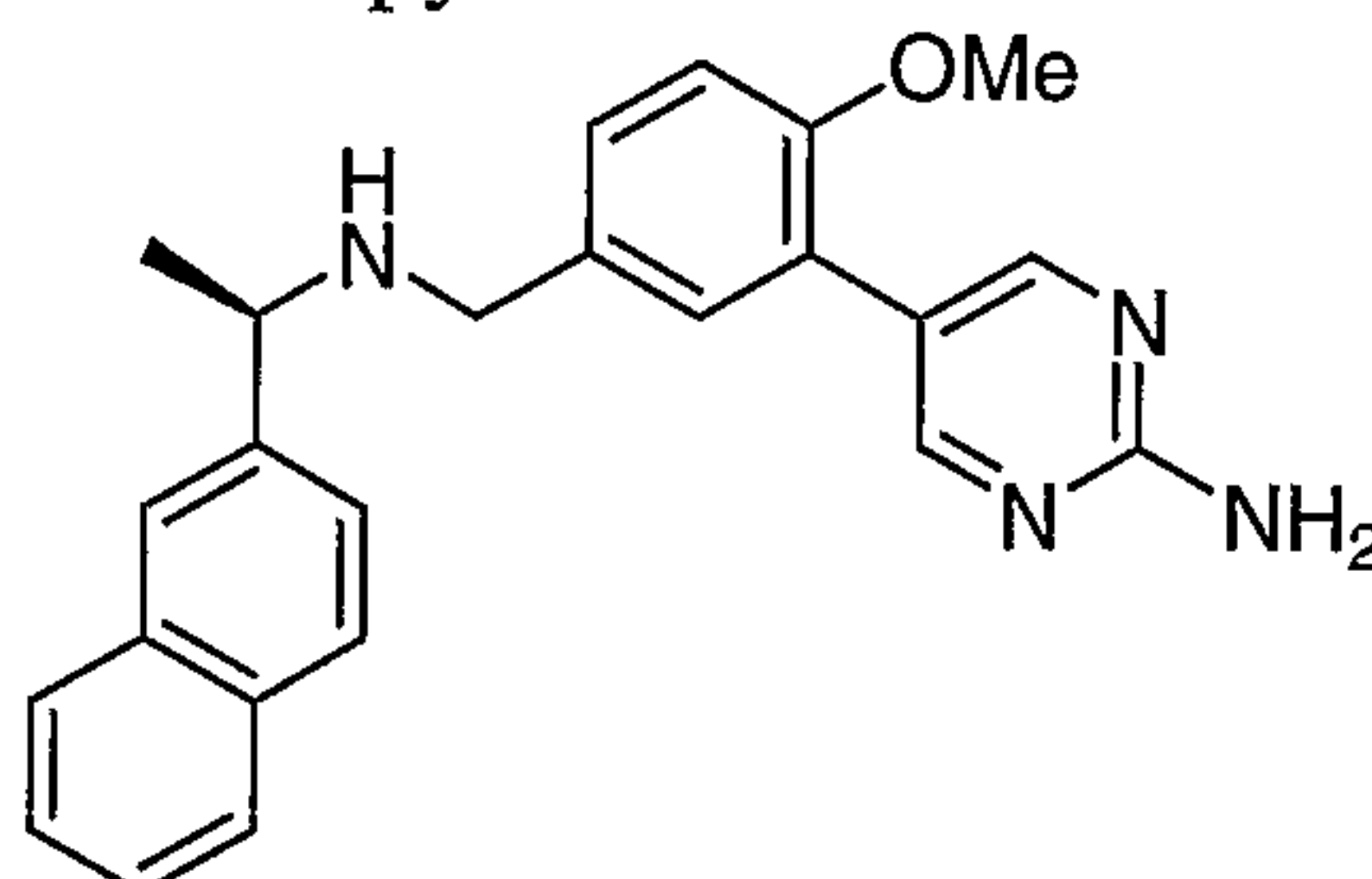
5

MW 348.448
Mass found: 214, 349, 231

10

Example 458

5-(2-(methyloxy)-5-((((1R)-1-(2-naphthalenyl)ethyl)amino)methyl)phenyl)-2-pyrimidinamine



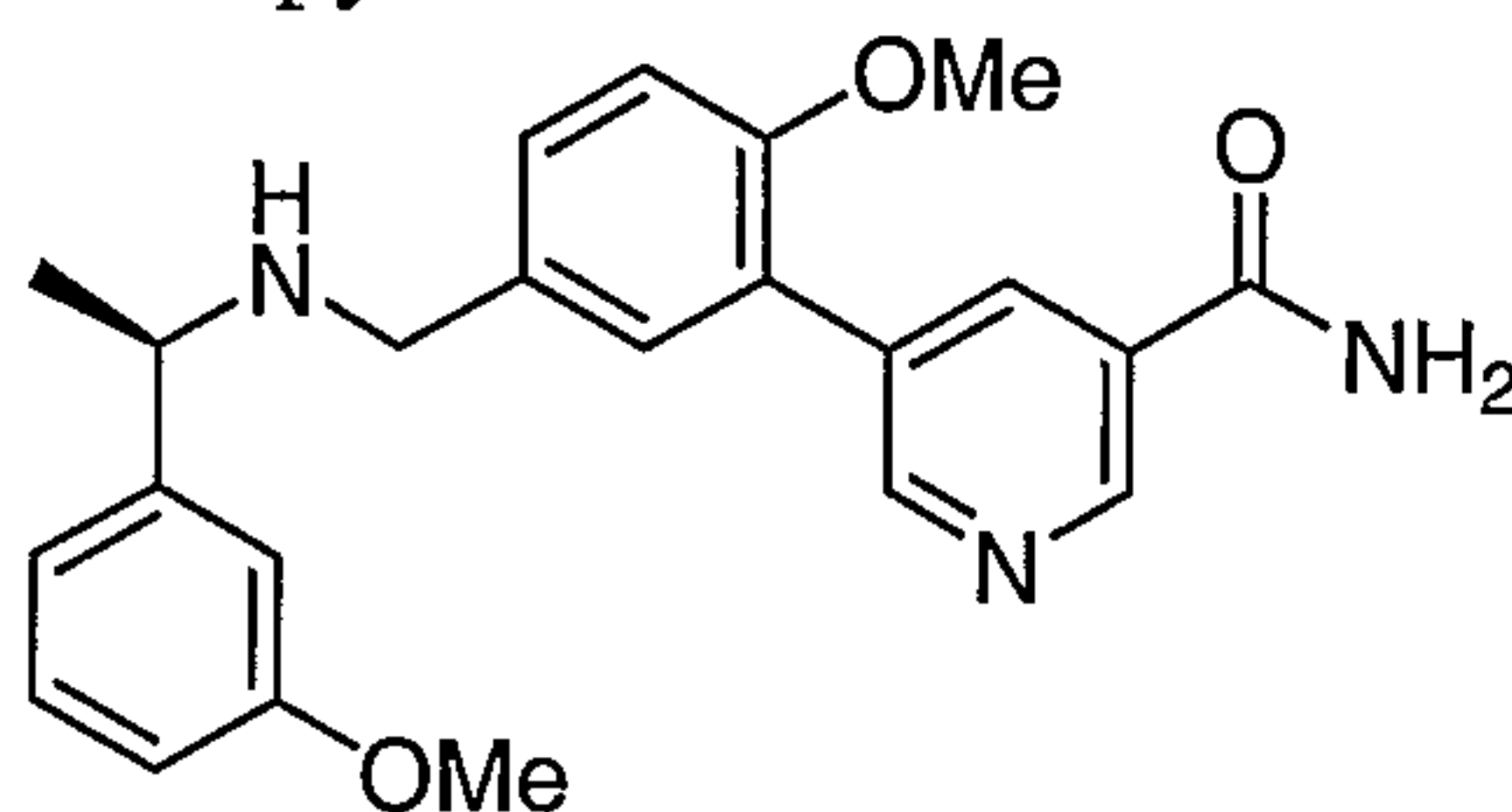
15

MW 384.481
Mass found: 155, 385, 231

20

Example 459

5-(3-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide



25

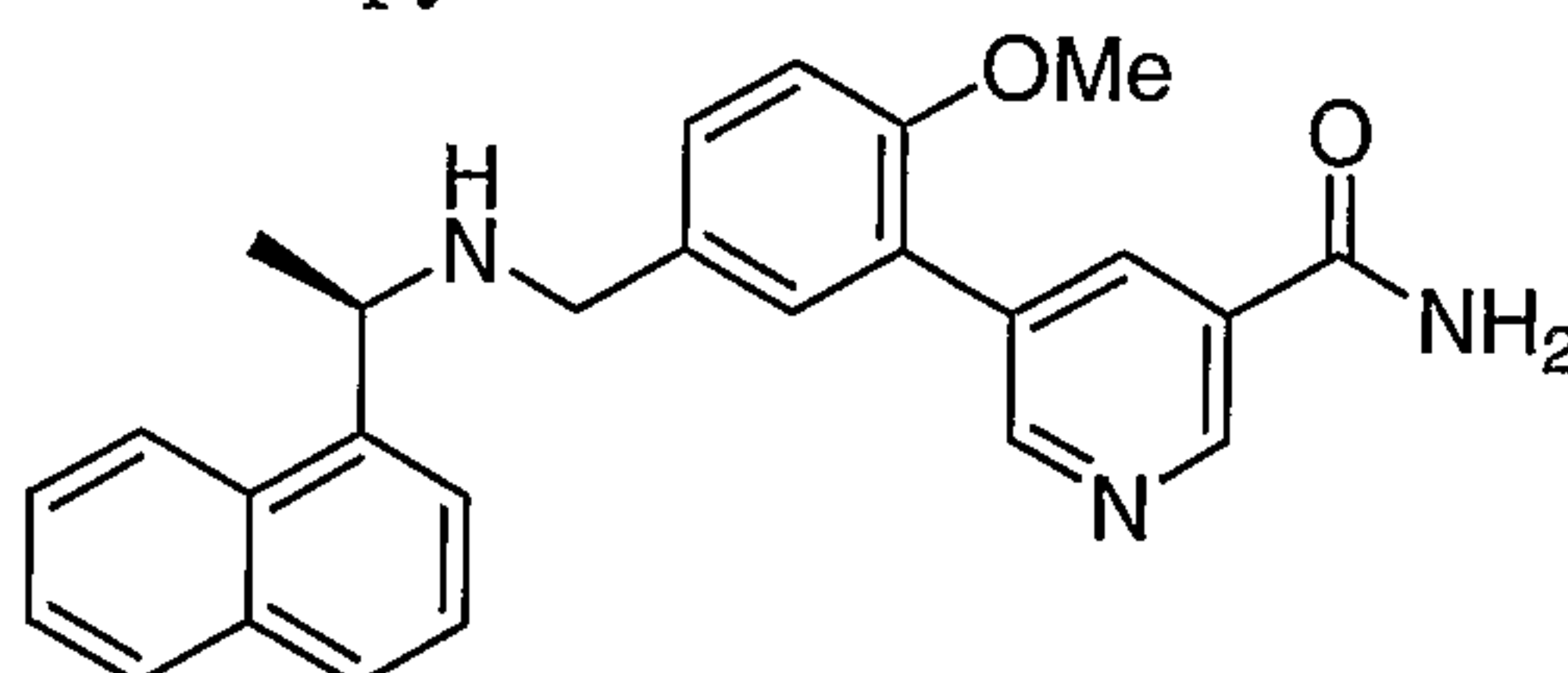
MW 361.443
Mass found: 362, 228

30

- 248 -

Example 460

5 5-(3-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide



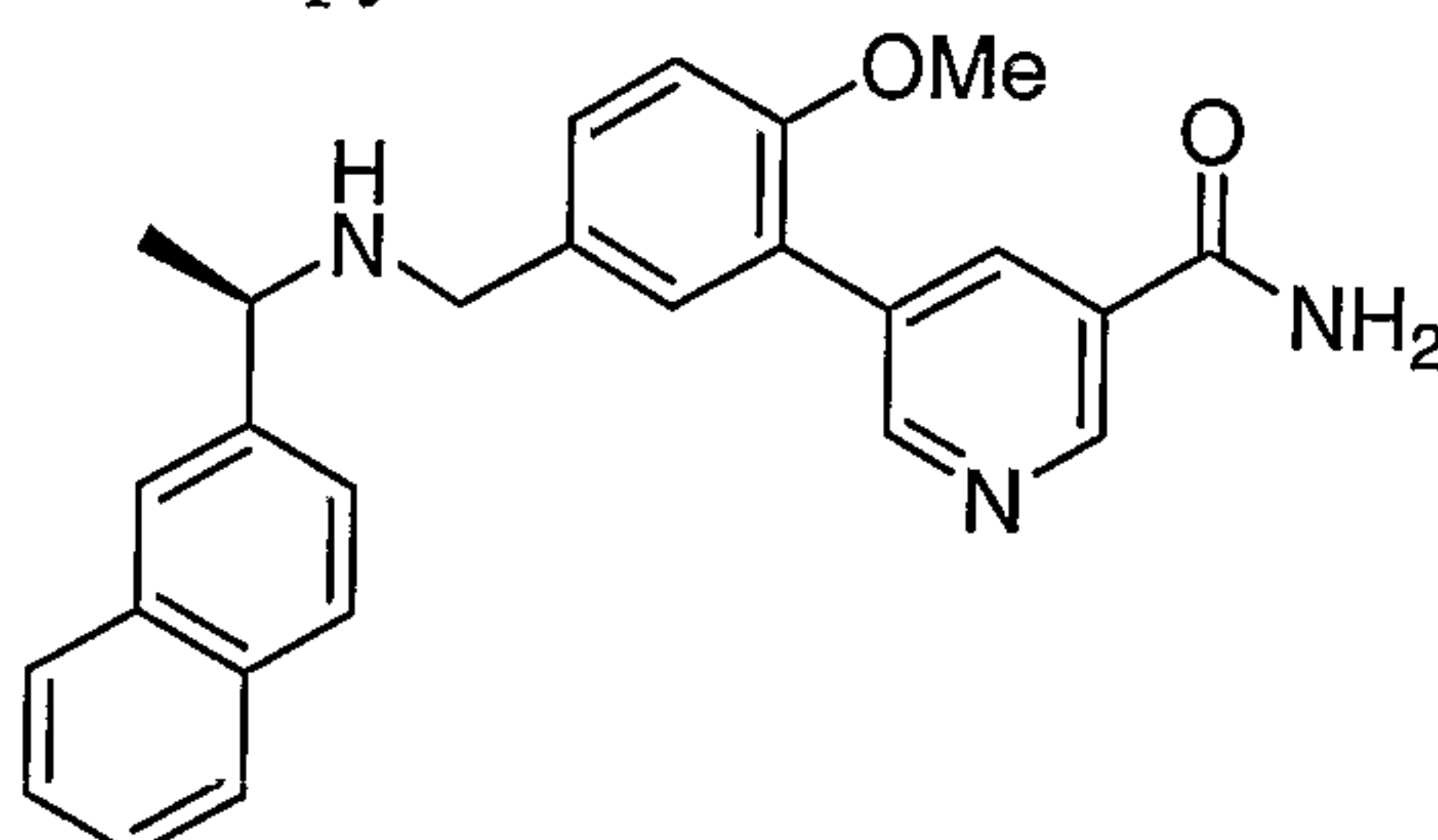
MW 381.477

Mass found: 155, 382, 228

10

Example 461

15 5-(3-((((1R)-1-(2-naphthalenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide



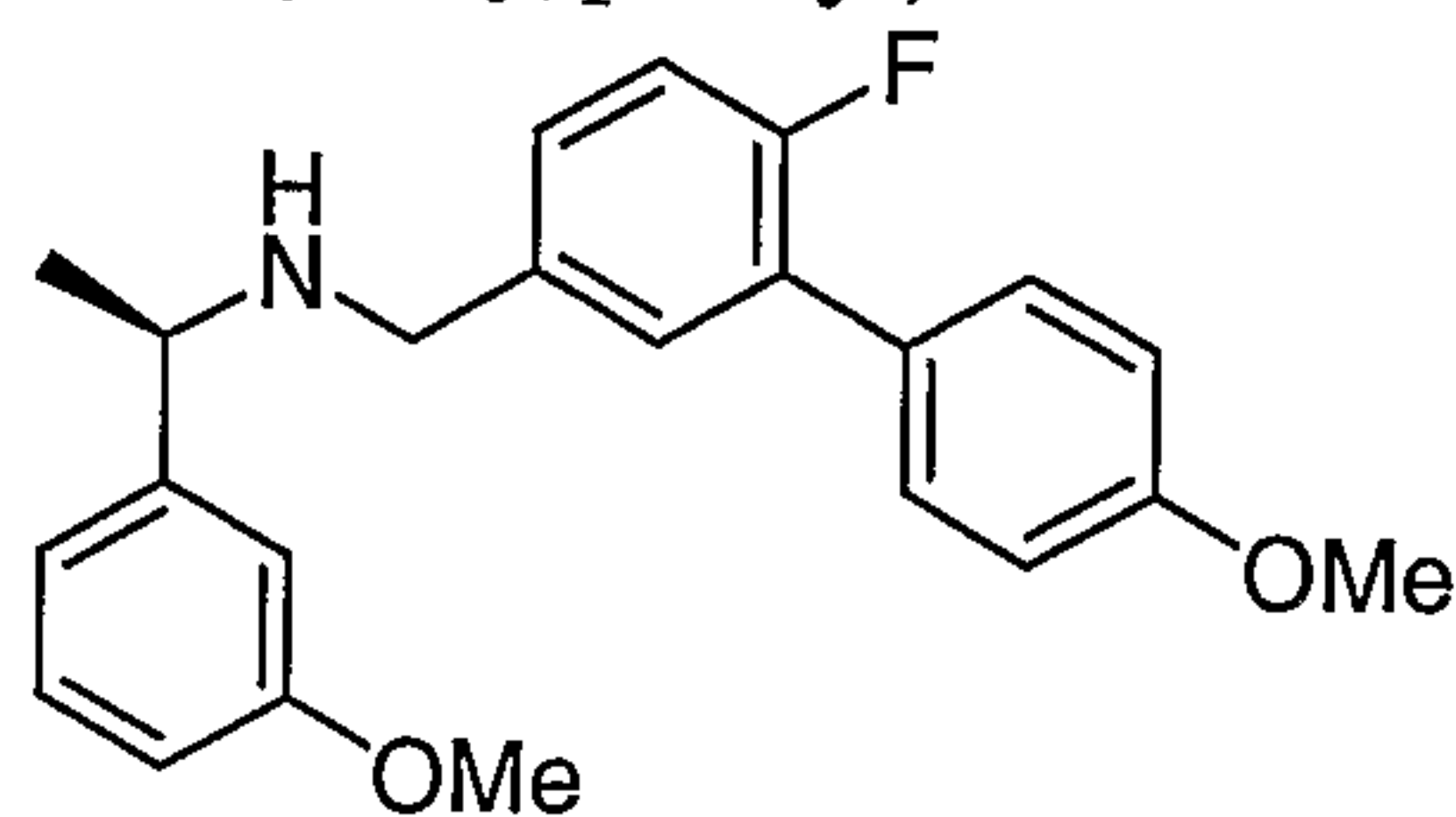
MW 381.477

Mass found: 155, 382, 228

20

Example 462

25 (1R)-N-((6-fluoro-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine



MW 365.446

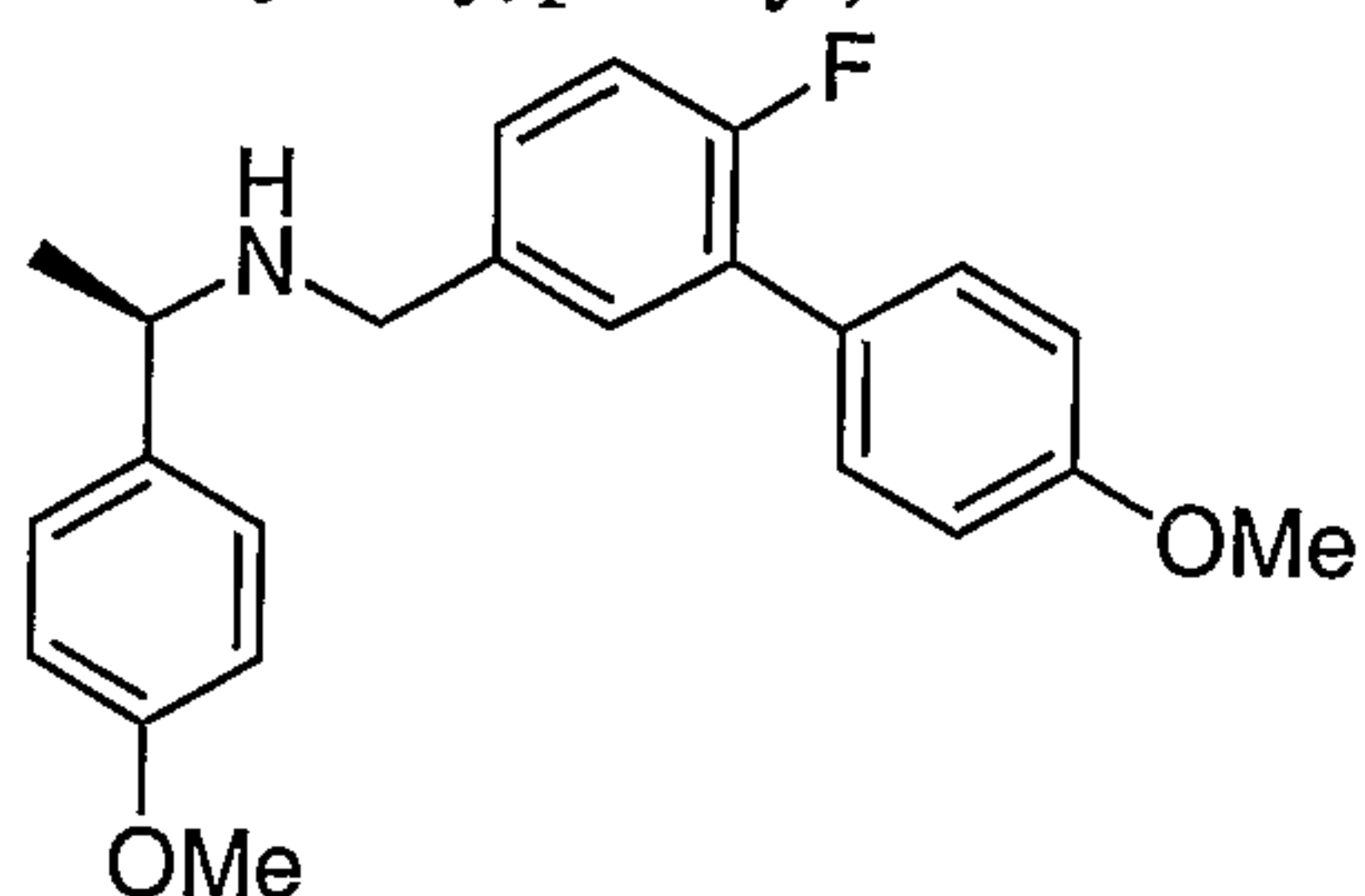
Mass found: 366, 215

30

- 249 -

Example 463

(1R)-N-((6-fluoro-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine



5

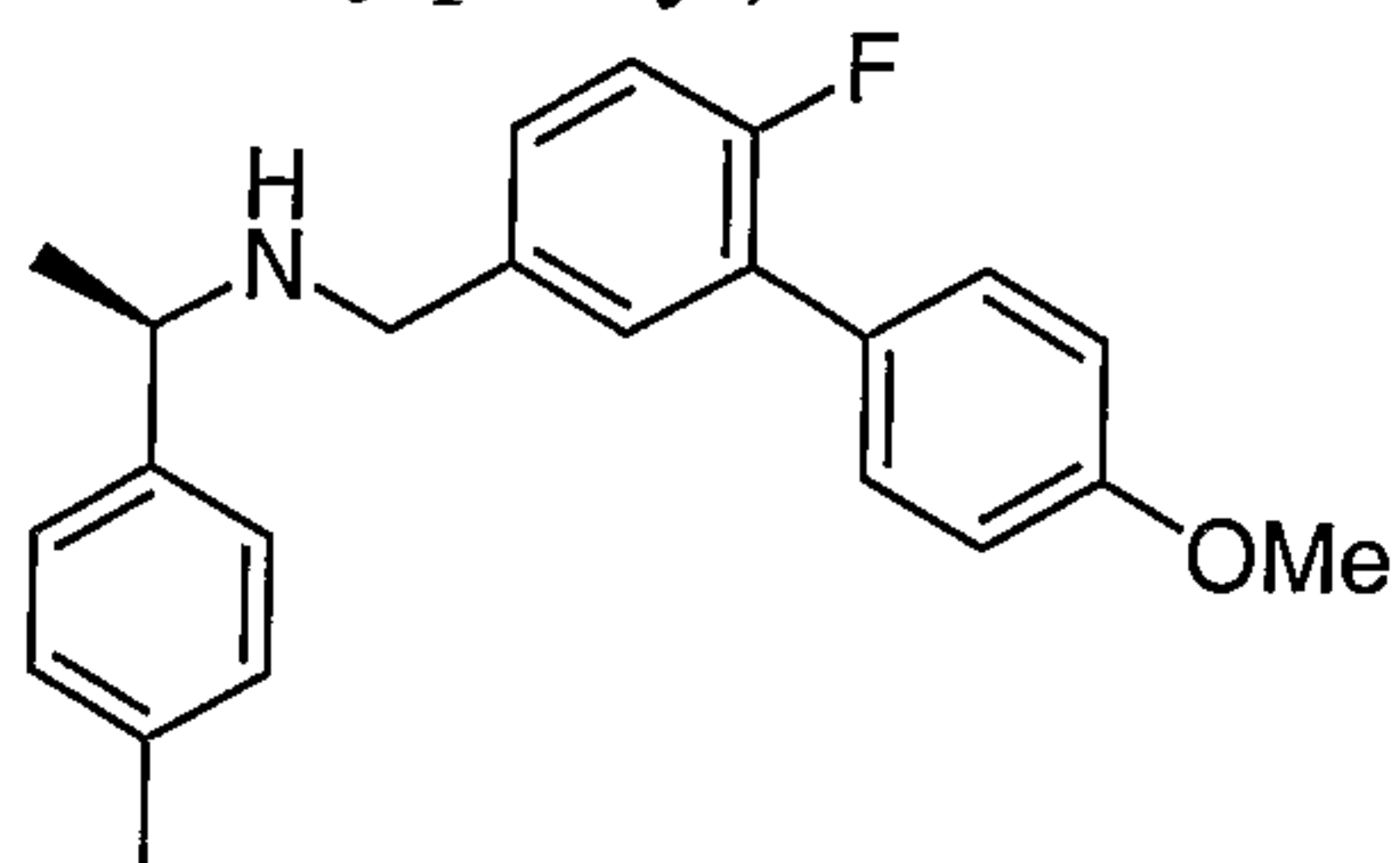
MW 365.446

Mass found: 366, 215

10

Example 464

(1R)-N-((6-fluoro-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine



15

MW 349.447

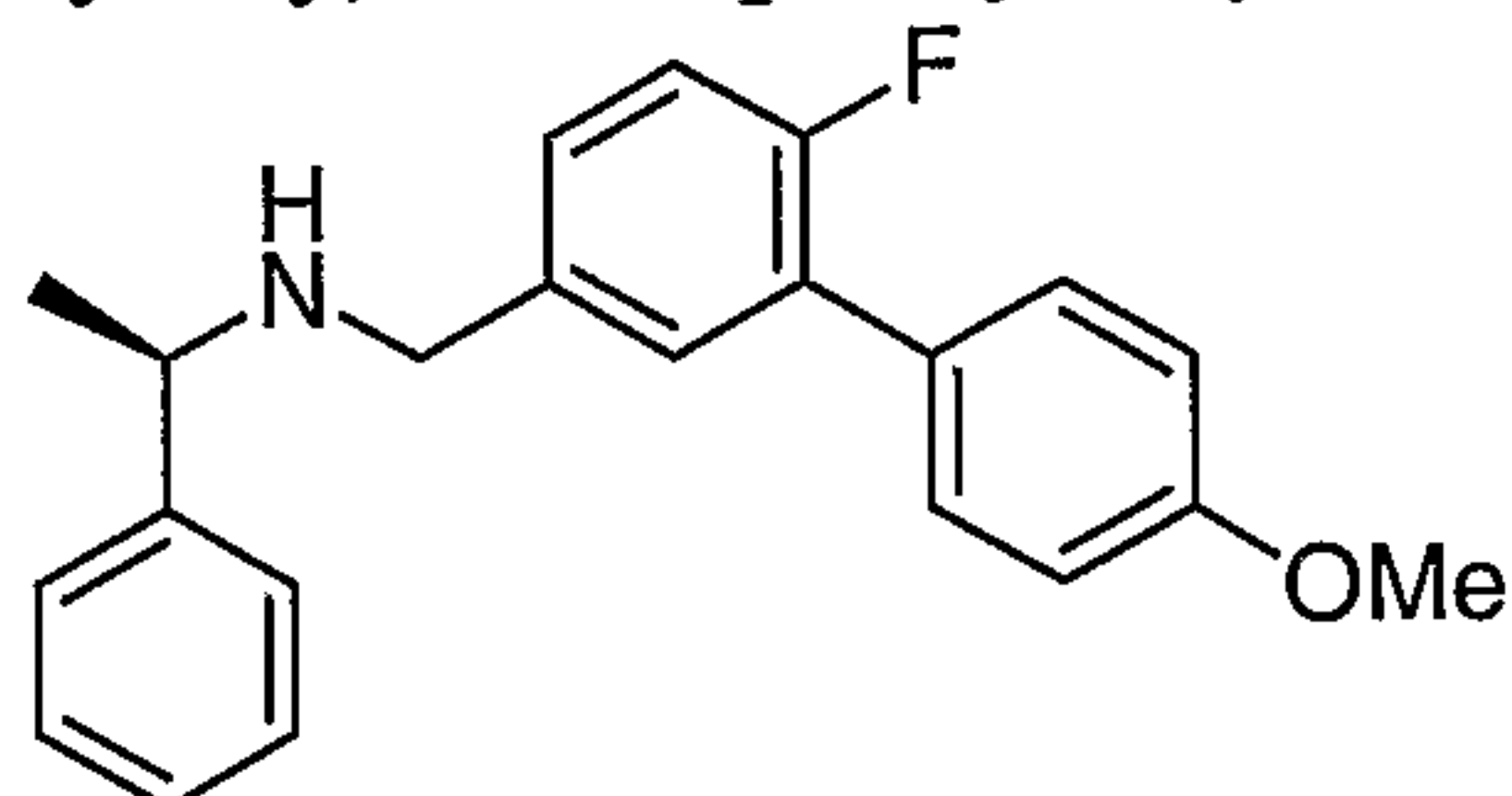
Mass found: 350, 215

20

- 250 -

Example 465

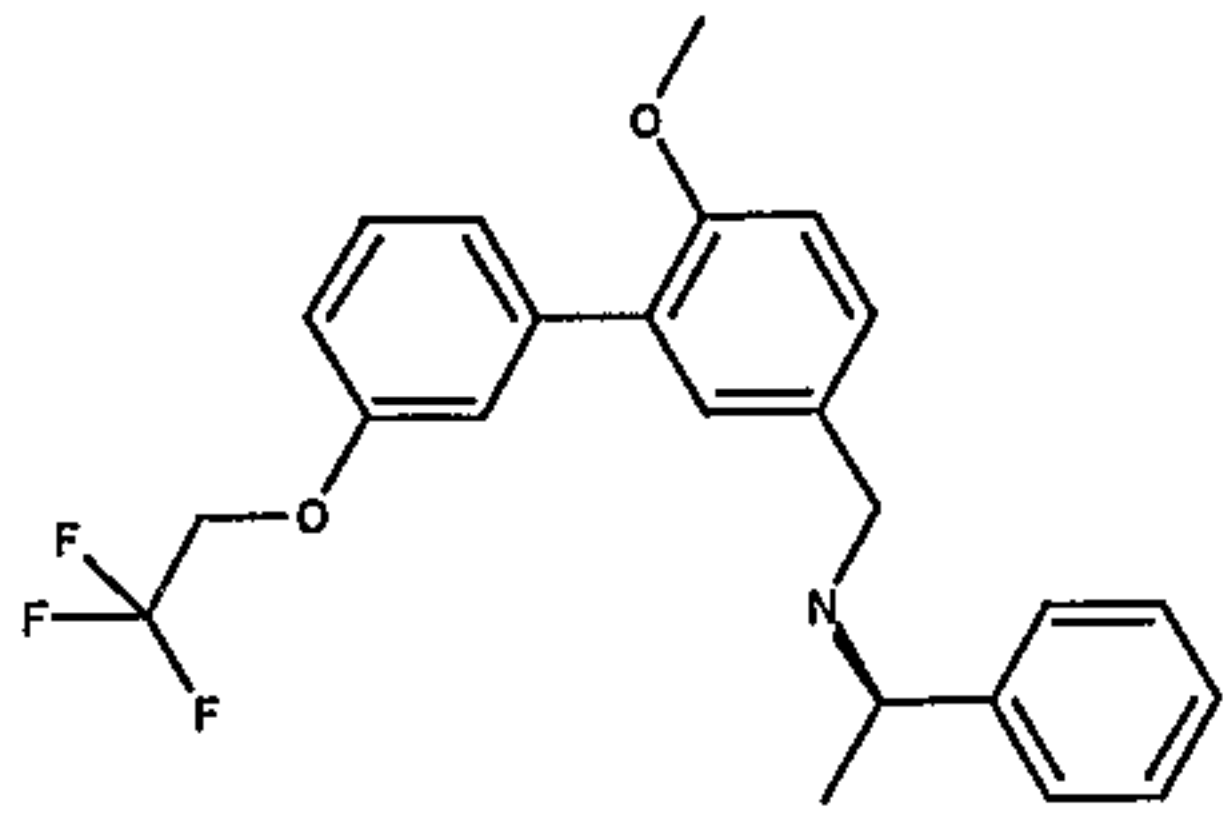
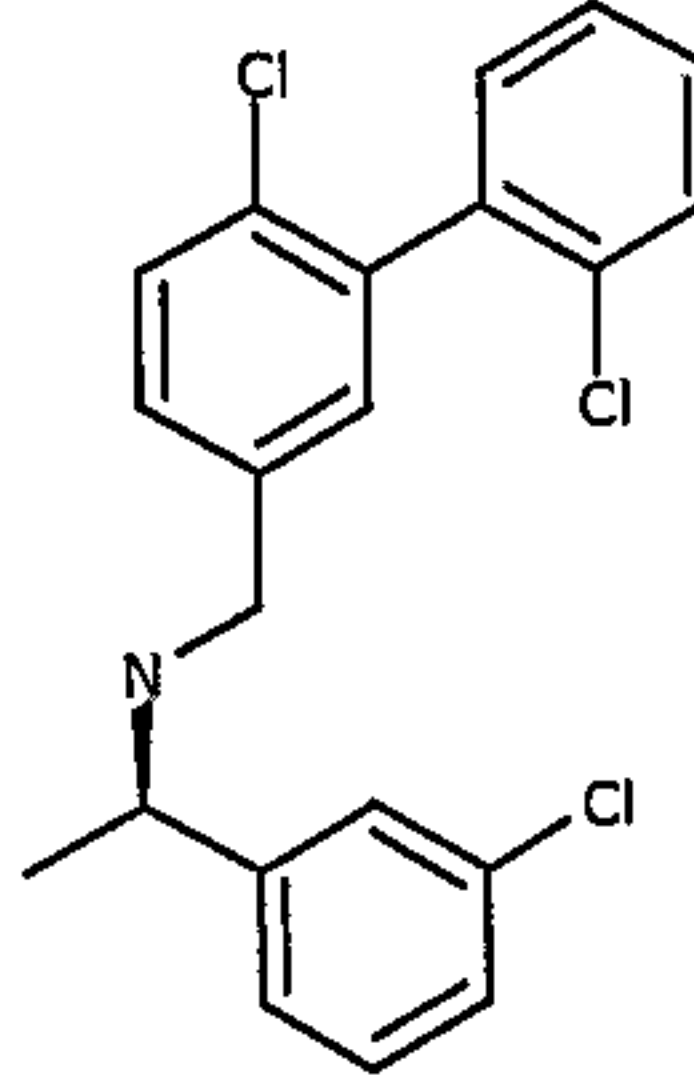
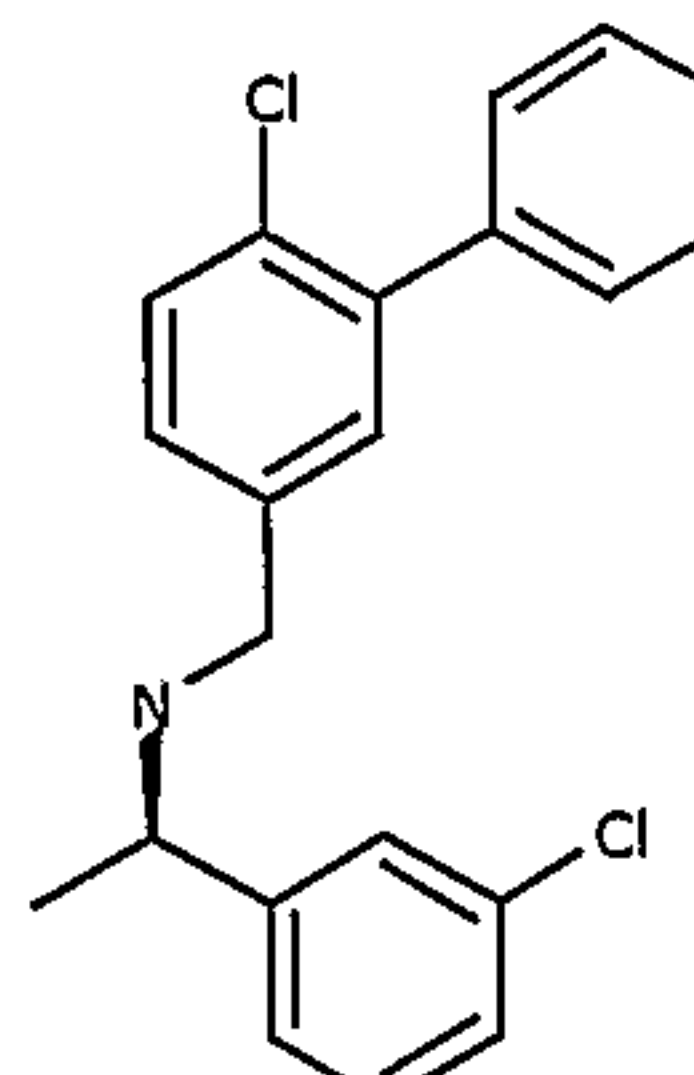
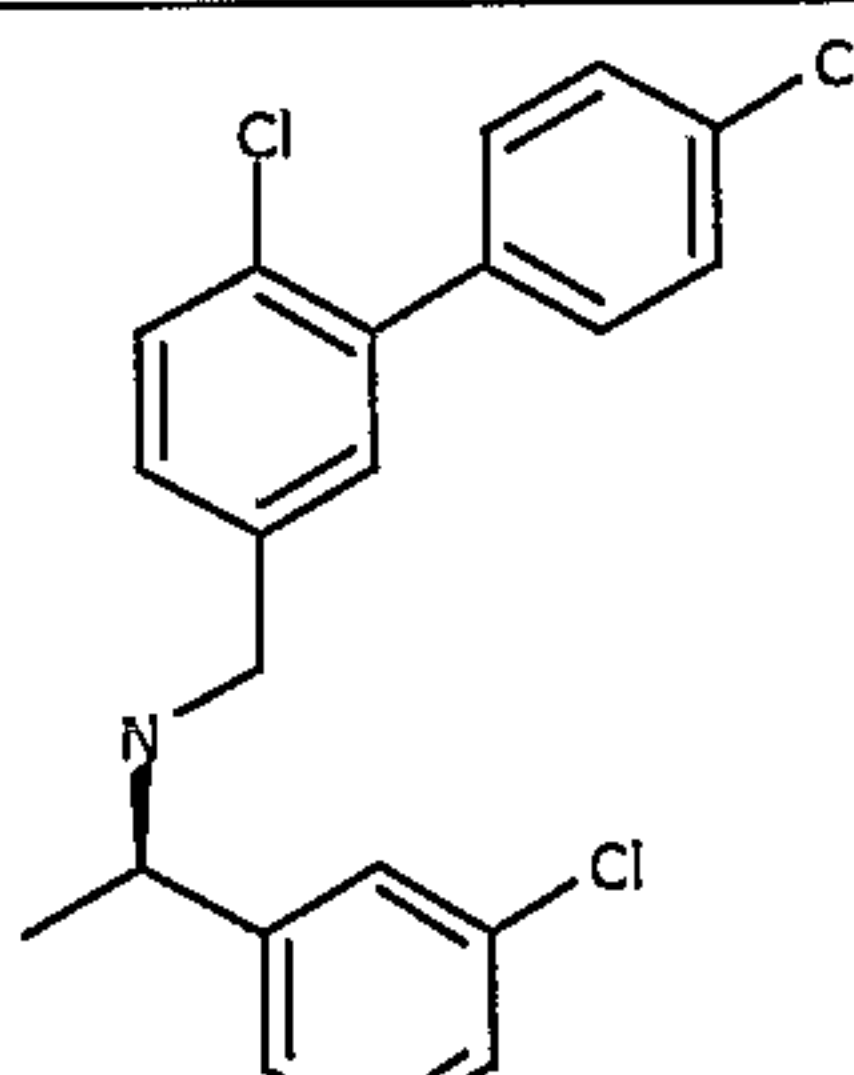
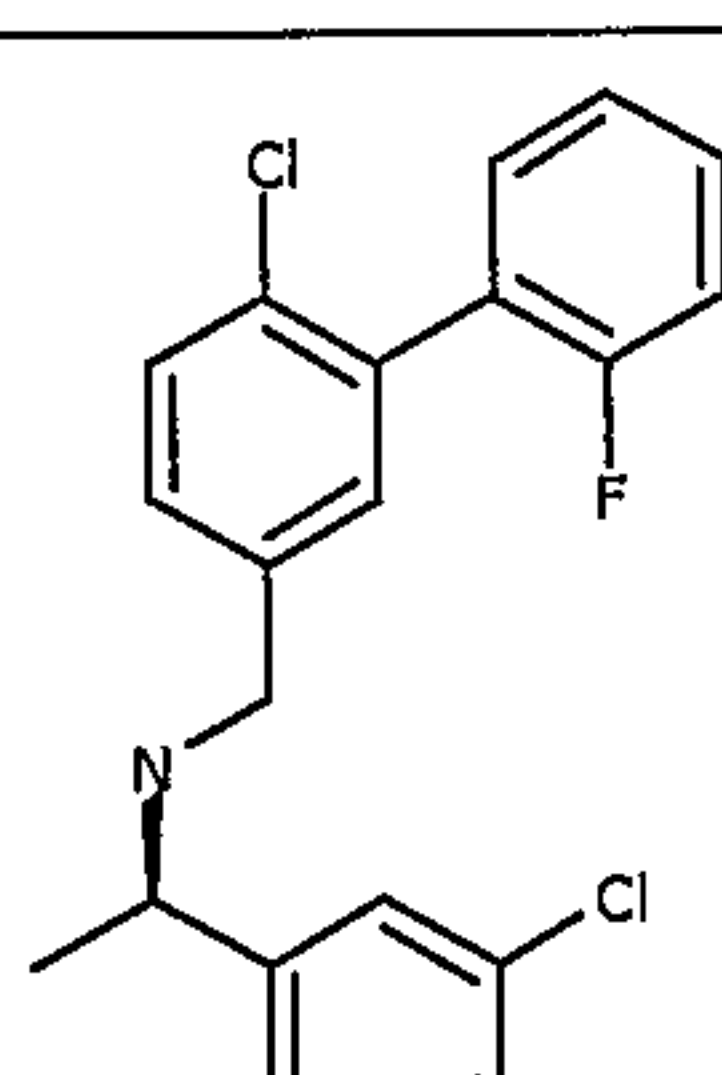
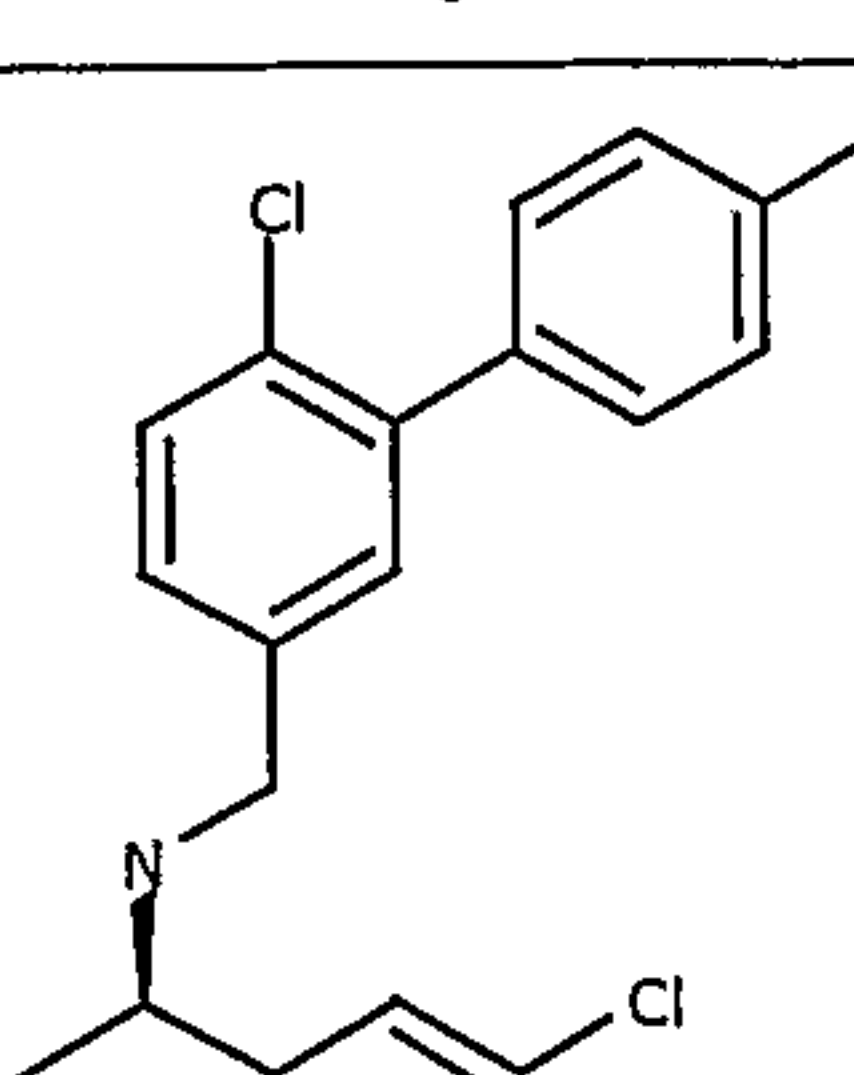
(1R)-N-((6-fluoro-4'-(methoxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine

MW 335.42
Mass found: 336, 215

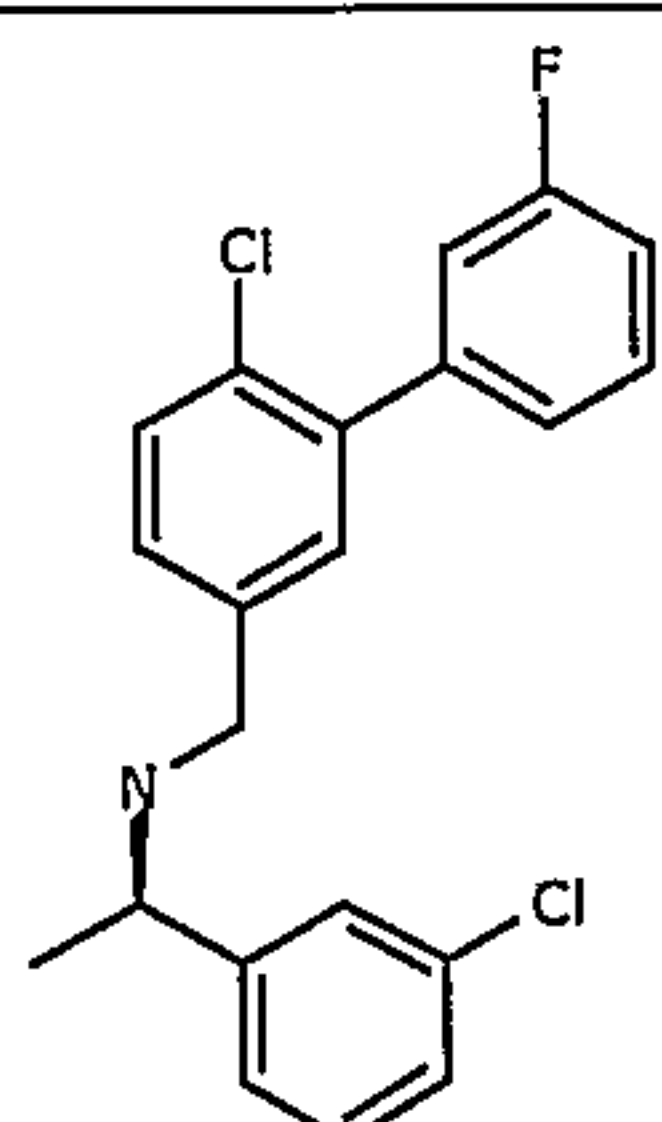
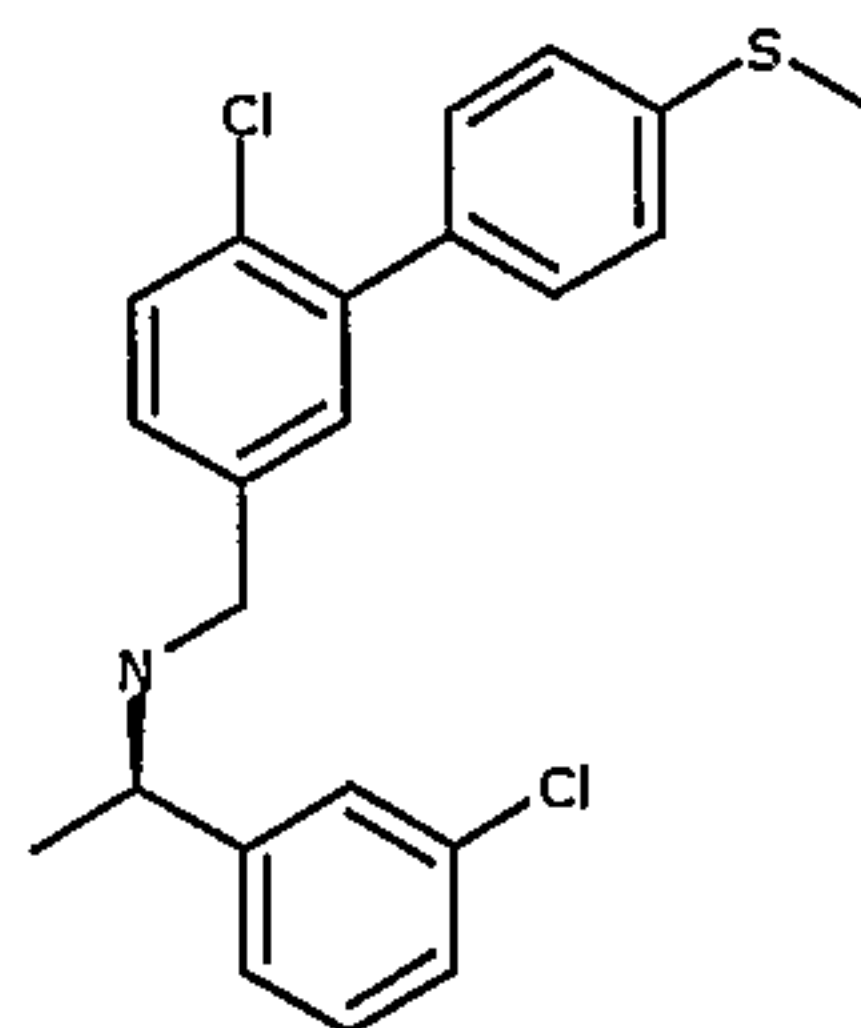
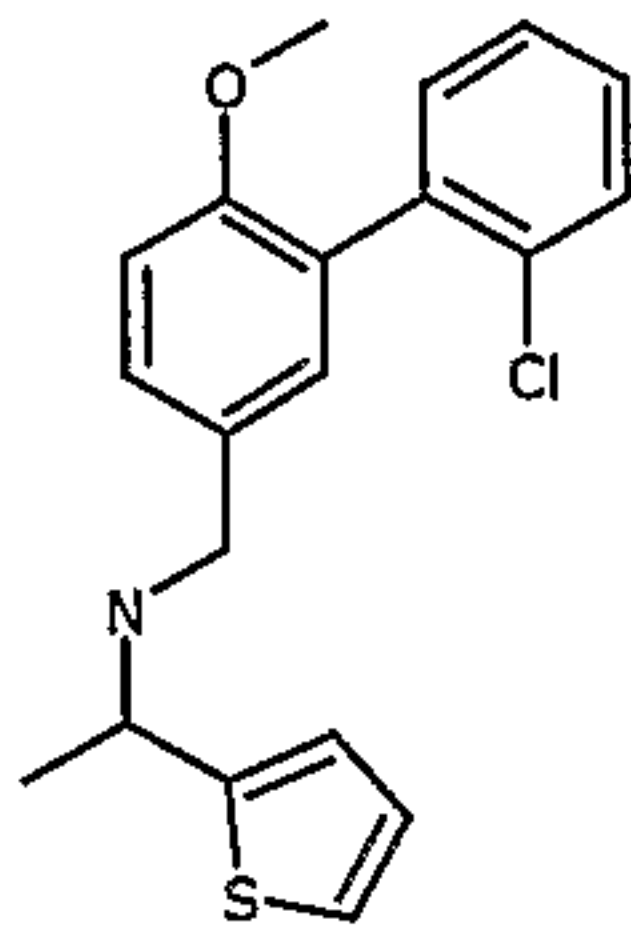
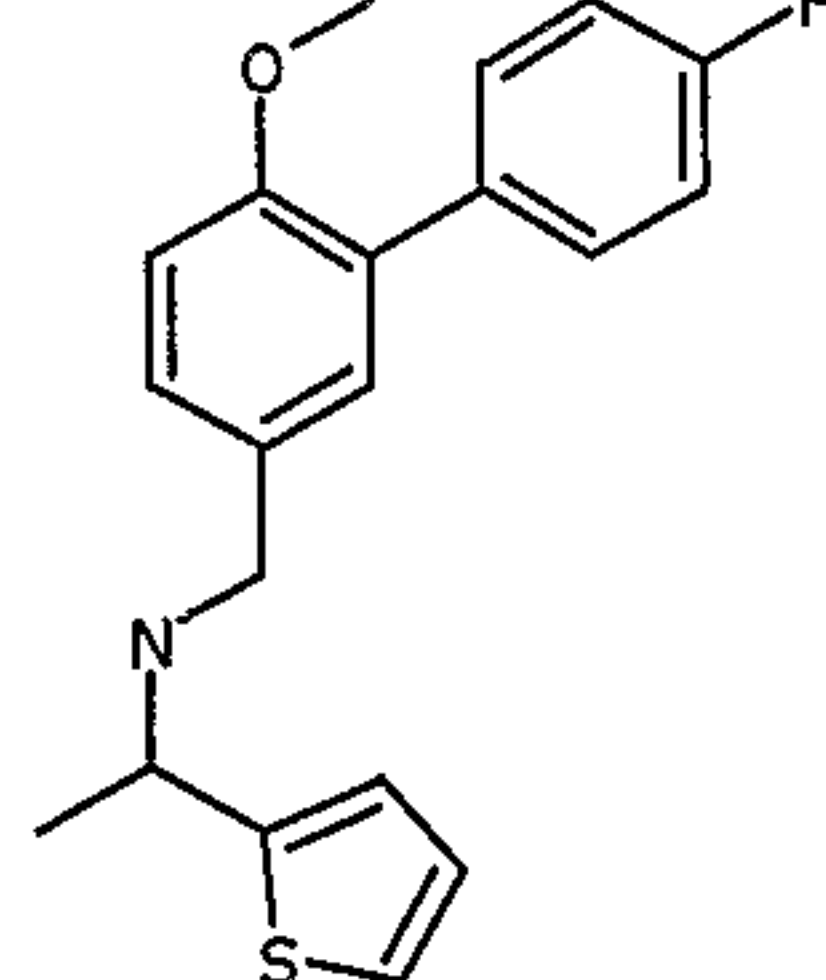
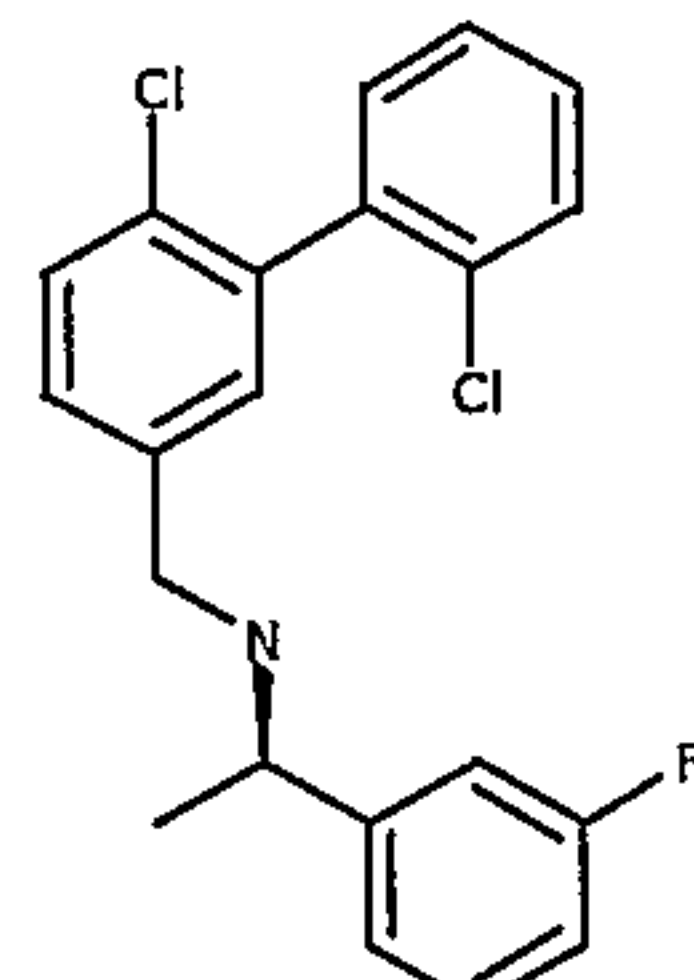
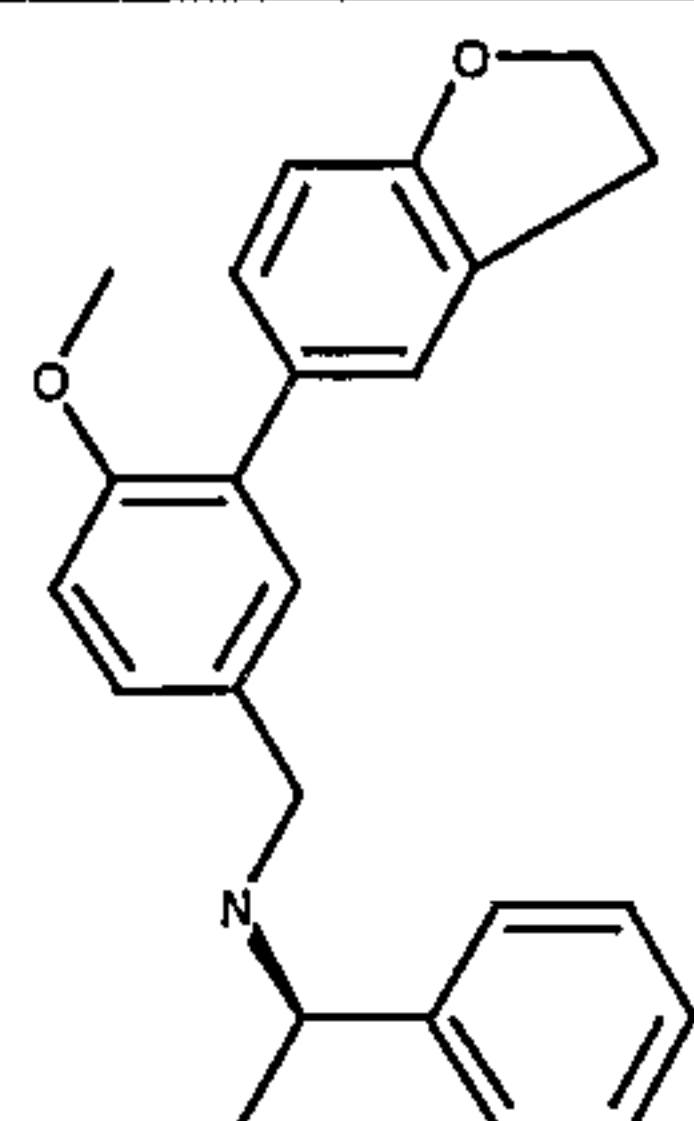
The following compounds were prepared using Synthetic Method C:

Example No:	Structure
466	
467	
468	
469	

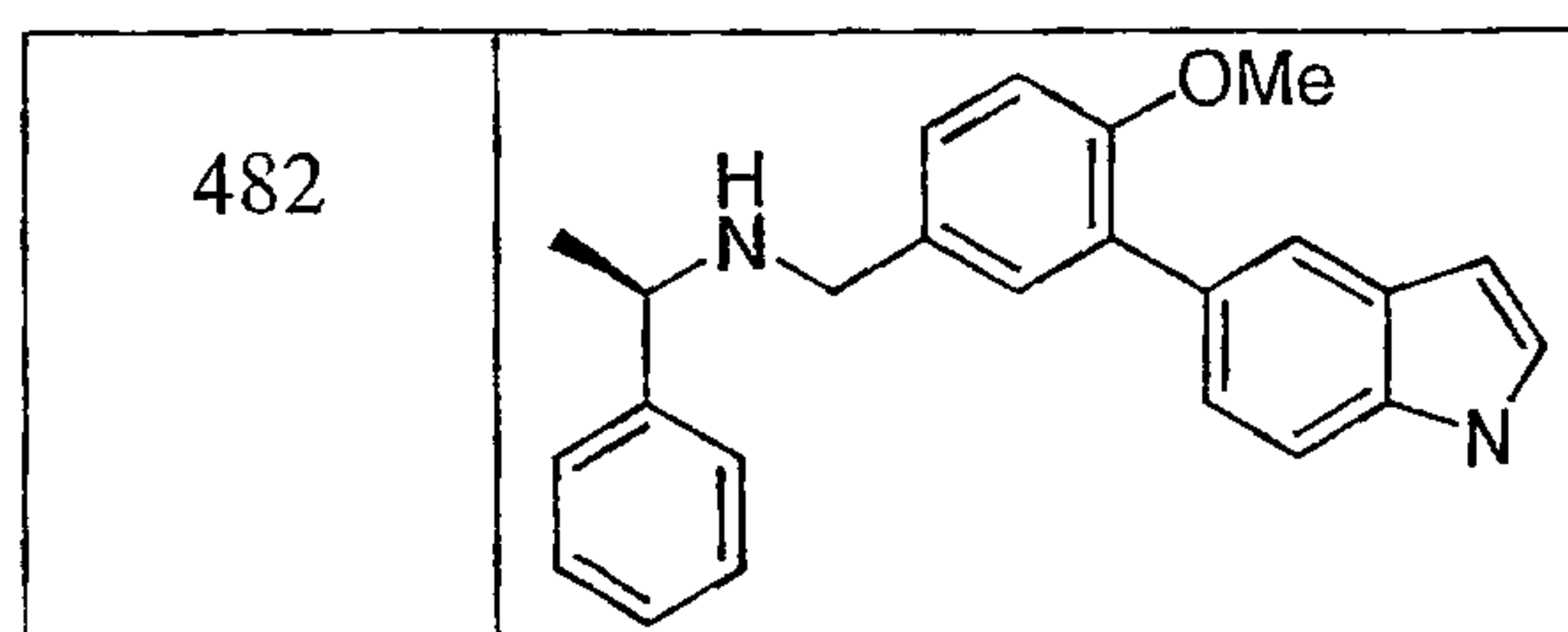
- 251 -

470	
471	
472	
473	
474	
475	

- 252 -

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481	

- 253 -



Biological Activity

The activities of the compounds of the present invention on calcium
 5 receptors were measured. In one embodiment, the measurement was performed in
 accordance with the method described in Example 4 of Nemeth et al.,
 PCT/US95/13704 (International Publication No. WO96/12697).

A 4.0-kb *NotI*-*HindIII* fragment of the human parathyroid cell Ca^{2+}
 10 receptor (hPCaR) cDNA was subcloned into the mammalian expression vector
 pCEP4 (Invitrogen) containing the hygromycin-resistant gene as a selectable
 marker. This plasmid was transfected into HEK 293 cells by calcium phosphate
 precipitation. Transfected cells were grown in Dulbecco's modified Eagle's
 medium containing 10% fetal bovine serum and hygromycin (200 $\mu\text{g/mL}$).
 15 Hygromycin-resistant colonies were subcloned and assayed for hPCaR mRNA by
 solution hybridization using a ^{32}P -labeled RNA probe complementary to the (4.0
 kb) hPCaR sequence (Garrett, et al., J. Biol. Chem. 270, 12919-12925 (1995)).
 Clone 7 was used to assess the effects of compounds on $[\text{Ca}^{2+}]_i$. This stably
 transfected cell line is termed HEK 293 4.0-7. For measurements of $[\text{Ca}^{2+}]_i$, the
 20 cells were recovered from tissue culture flasks by brief treatment with 0.02%
 EDTA and then washed and resuspended in PCB containing 1mM CaCl_2 and
 0.1% Bovine Serum Albumin ("BSA"). The cells were loaded with fluo-3 by
 incubation for 30 min at 37 °C, with parathyroid cell buffer (126mM NaCl, 4mM
 KCl, 1mM MgSO_4 , 0.7mM $\text{K}_2\text{HPO}_4/\text{KH}_2\text{PO}_4$, 20mM HEPES-NaOH (pH 7.45))
 25 containing 0.5% BSA in 1mM CaCl_2 and 2 μM fluo-3 acetoxymethyl ester. The
 cells were subsequently washed, each test compound was added to the cells and
 the fluorescence was recorded by using excitation and emission wavelengths of
 485 and 530 nm, respectively.

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The following compounds of the invention were tested according to the procedure described above and found to have an EC₅₀ of 10 μ M or less:

- (1R)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 5 (1R)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((6-(methyloxy)-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)-1-(1-
10 naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((6-(ethyloxy)-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 15 (1R)-1-(3-chlorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- (1R)-1-(3-fluorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- (1R)-N-((6-(methyloxy)-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-
20 (1-naphthalenyl)ethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(3-pyridinyl)phenyl)methyl)ethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(3-pyridinyl)phenyl)methyl)-1-(4-
25 methylphenyl)ethanamine;
- (1R)-1-(4-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(3-pyridinyl)phenyl)methyl)ethanamine;
- (1R)-N-((3-(1,3-benzodioxol-5-yl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(1,3-benzodioxol-5-yl)phenyl)methyl)-1-(4-methylphenyl)ethanamine;
- 30 (1R)-N-((3-(1,3-benzodioxol-5-yl)phenyl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;

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- (1R)-N-((3-(1,3-benzodioxol-5-yl)phenyl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;
- 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile;
- 5 2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile;
- 2'-(methyloxy)-5'-((((1R)-1-(4-methylphenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile;
- 2'-(methyloxy)-5'-((((1R)-1-(4-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-
- 10 biphenyl-3-carbonitrile;
- 2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile;
- (1R)-N-((4-(methyloxy)-3-(2-pyrimidinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 15 (1R)-N-((4-(methyloxy)-3-(2-pyrimidinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-pyrimidinyl)phenyl)methyl)ethanamine;
- (1R)-N-((3'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((3'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-
- 20 methylphenyl)ethanamine;
- (1R)-N-((3'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 25 (1R)-N-((2'-methyl-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;
- (1R)-N-((2'-methyl-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;
- (1R)-N-((2'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;
- (1R)-N-((2'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-
- 30 (methyloxy)phenyl)ethanamine;
- (1R)-N-((2'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;

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- 5-(2-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2-furancarboxylic acid;
- 4-oxo-4-((5-(3-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinyl)amino)butanoic acid;
- 5 4-((5-(3-((((1R)-1-(4-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2-pyridinyl)amino)-4-oxobutanoic acid;
- (1R)-N-((3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(4-
- 10 (methyloxy)phenyl)ethanamine;
- (1R)-N-((3-(1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3-(1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(2-naphthalenyl)ethanamine;
- 15 (1R)-N-((3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-1-(4-(methyloxy)phenyl)-N-((3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)ethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)ethanamine;
- 20 (1R)-N-((4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(2-naphthalenyl)ethanamine;
- (1R)-N-((4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-
- 25 (methyloxy)phenyl)ethanamine;
- (1R)-N-((4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-1-phenyl-N-((3-(2-pyrazinyl)phenyl)methyl)ethanamine;
- (1R)-1-(4-(methyloxy)phenyl)-N-((3-(2-pyrazinyl)phenyl)methyl)ethanamine;
- 30 (1R)-1-(3-(methyloxy)phenyl)-N-((3-(2-pyrazinyl)phenyl)methyl)ethanamine;
- (1R)-1-(2-naphthalenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine;
- (1R)-1-phenyl-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine;

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- (1R)-1-(1-naphthalenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine;
(1R)-1-(4-methylphenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine;
(1R)-1-(4-(methyloxy)phenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine;
(1R)-1-(3-(methyloxy)phenyl)-N-((3-(2-pyridinyl)phenyl)methyl)ethanamine;
5 (1R)-N-((3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine;
(1R)-N-((3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
(1R)-N-((3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
(1R)-1-(4-methylphenyl)-N-((3-(6-methyl-3-pyridinyl)phenyl)methyl)ethanamine;
(1R)-1-(4-(methyloxy)phenyl)-N-((3-(6-methyl-3-
10 yridinyl)phenyl)methyl)ethanamine;
(1R)-1-(3-(methyloxy)phenyl)-N-((3-(6-methyl-3-
yridinyl)phenyl)methyl)ethanamine;
(1R)-N-((4-(methyloxy)-3-(3-thienyl)phenyl)methyl)-1-(2-
naphthalenyl)ethanamine;
15 (1R)-N-((4-(methyloxy)-3-(3-thienyl)phenyl)methyl)-1-phenylethanamine;
(1R)-N-((4-(methyloxy)-3-(3-thienyl)phenyl)methyl)-1-(1-
naphthalenyl)ethanamine;
(1R)-N-((4-(methyloxy)-3-(3-thienyl)phenyl)methyl)-1-(4-
methylphenyl)ethanamine;
20 (1R)-1-(4-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(3-
thienyl)phenyl)methyl)ethanamine;
(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(3-
thienyl)phenyl)methyl)ethanamine;
(1R)-N-((4-(methyloxy)-3-(5-pyrimidinyl)phenyl)methyl)-1-phenylethanamine;
25 (1R)-N-((4-(methyloxy)-3-(5-pyrimidinyl)phenyl)methyl)-1-(4-
methylphenyl)ethanamine;
(1R)-1-(4-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(5-
pyrimidinyl)phenyl)methyl)ethanamine;
(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(5-
30 pyrimidinyl)phenyl)methyl)ethanamine;
(1R)-N-((4'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
N-(3'-(((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-yl)acetamide;

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- N-(3'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-yl)acetamide;
- N-(3'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-yl)acetamide;
- 5 (1R)-N-((4'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;
- (1R)-N-((4'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((3-(5-pyrimidinyl)phenyl)methyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine;
- 10 (1R)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)-1-(4-methylphenyl)ethanamine;
- 15 (1R)-1-(4-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine;
- 20 (1R)-N-((3',4'-dimethyl-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;
- (1R)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;
- (1R)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;
- 25 (1R)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4'-fluoro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;
- 30 (1R)-N-((4'-fluoro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;
- (1R)-1-(1-naphthalenyl)-N-((3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine;

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- (1R)-1-phenyl-N-((3-(1,3-thiazol-2-yl)phenyl)methyl)ethanamine;
(1R)-1-phenyl-N-((4-(1-pyrrolidinyl)phenyl)methyl)ethanamine;
(1R)-N-((4-(3,5-dimethyl-4-isoxazolyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 5 5-(2-(methyloxy)-5-((((1R)-1-(4-methylphenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide;
(1R)-N-((3-(3-furanyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
(1R)-N-((3-(3-furanyl)phenyl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;
(1R)-N-((3-(3-furanyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine;
- 10 (1R)-N-((3-(3-furanyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
(1R)-N-((3-(3-furanyl)phenyl)methyl)-1-phenylethanamine;
5-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide;
(1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(3-
- 15 (methyloxy)phenyl)ethanamine;
(1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;
(1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-phenylethanamine;
- 20 (1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine;
5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-3-pyridinecarboxamide;
(1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-
- 25 pyrazinyl)phenyl)methyl)ethanamine;
(1R)-1-(4-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)ethanamine;
(1R)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)-1-(4-methylphenyl)ethanamine;
- 30 (1R)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
(1R)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)-1-phenylethanamine;

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- 5-(2-(methyloxy)-5-((((1R)-1-(2-naphthalenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide;
 (1R)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)-1-(2-naphthalenyl)ethanamine;
 5 (1R)-1-(4-methylphenyl)-N-((3-(9-methyl-9H-purin-6-yl)phenyl)methyl)ethanamine;
 (1R)-N-((6-(methyloxy)-4'-(methanesulfonyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
 (1R)-N-((6-(methyloxy)-4'-(methanesulfonyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
 10 N-(5-(3-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2-pyridinyl)acetamide;
 N-(5-(3-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-2-pyridinyl)acetamide;
 15 N-(5-(3-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinyl)acetamide;
 (1R)-N-((4',6-difluoro-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
 (1R)-N-((4',6-difluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;
 (1R)-N-((2',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
 20 (1R)-N-((3-(2-methyl-1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
 (1R)-N-((3-(2-methyl-1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 (1R)-N-((3-(2-methyl-1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
 25 N-(4'-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-2-yl)methanesulfonamide;
 N-ethyl-N'-(4'-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-2-yl)urea;
 30 N-(4'-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-2-yl)methanesulfonamide;

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(1R)-N-((3-(1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;

N-ethyl-N'-(4'-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-2-yl)urea;

5 (1R)-N-((4-(methyloxy)-3-(2-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;

N-ethyl-N'-(4'-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-2-yl)urea;

10 (1R)-N-((3-(1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;

N-(4'-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-2-yl)methanesulfonamide;

(1R)-N-((4-(methyloxy)-3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;

15 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)ethanamine;

(1R)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;

(1R)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)-1-phenylethanamine;

20 (1R)-N-((4-(methyloxy)-3-(1-methyl-2-(trifluoromethyl)-1H-benzimidazol-5-yl)phenyl)methyl)-1-phenylethanamine;

(1R)-N-((4-(methyloxy)-3-(1-methyl-2-(trifluoromethyl)-1H-benzimidazol-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;

25 (1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)ethanamine;

3-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-N-(3-(4-morpholinyl)propyl)-2-pyridinamine;

(1R)-N-((4-(methyloxy)-3-(6-((tetrahydro-2-furanylmethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;

30 3-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-N-(tetrahydro-2-furanylmethyl)-2-pyridinamine;

5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinamine;

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- N,N-dimethyl-5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinamine;
- (1R)-N-((4-(methyloxy)-3-(4-piperidinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 5 2-(5-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-1H-indol-1-yl)acetamide;
- 2-(5-(2-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-1H-indol-1-yl)acetamide;
- 2-(5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1H-indol-1-yl)acetamide;
- 10 (1R)-N-((4-(methyloxy)-3-(2-(4-morpholinyl)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2-fluoro-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 15 (1R)-N-((4-(methyloxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-((tetrahydro-2-furanylmethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 20 (1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 25 4-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1,3-thiazol-2-amine;
- (1R)-N-((3-(1-methyl-1H-imidazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(1-methyl-1H-imidazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 30 N-((3-(6-((3-(diethylamino)propyl)oxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-N-((1R)-1-(3-(methyloxy)phenyl)ethyl)amine;

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- N-((3-(6-((3-(diethylamino)propyl)oxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-N-((1R)-1-(1-naphthalenyl)ethyl)amine;
- (1R)-N-((4-(methyloxy)-3-(6-((2-(1-pyrrolidinyl)ethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 5 (1R)-N-((4-(methyloxy)-3-(1-pyrrolidinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1-pyrrolidinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-((2-(1-pyrrolidinyl)ethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- 10 (1R)-N-((3-(2-methyl-2H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;
- (1R)-N-((4-(methyloxy)-3-(1-methyl-4-piperidinyl)phenyl)methyl)-1-(3-
- 15 (methyloxy)phenyl)ethanamine;
- 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;
- (1R)-N-((4-(methyloxy)-3-(1-methyl-4-piperidinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 20 ethyl 2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate;
- ethyl 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate;
- ethyl 2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-
- 25 carboxylate;
- ethyl 4-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-1-piperidinecarboxylate;
- ethyl 4-(2-(methyloxy)-5-((((1R)-1-(3-
- (methyloxy)phenyl)ethyl)amino)methyl)phenyl)-1-piperidinecarboxylate;
- 30 ethyl 4-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1-piperidinecarboxylate;

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- (1R)-N-((3-(2-methyl-1,3-oxazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(2-methyl-1,3-oxazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 5 2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;
- 1-(2-(methyloxy)ethyl)-5-(2-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2(1H)-pyridinone;
- 1-(2-(methyloxy)ethyl)-5-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-2(1H)-pyridinone;
- 10 (1R)-N-((6-(methyloxy)-4'-(methylsulfonyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4',6-bis(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 15 N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-methylphenyl)ethanamine;
- 3-(1-(((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)amino)ethyl)benzonitrile;
- (1R)-1-(3-((2-(methyloxy)ethyl)oxy)phenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 20 (1R)-N-((6-fluoro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- 25 N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;
- N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;
- N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;
- 30 (1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;

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- (1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- 5 (1R)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- (1R)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 10 (1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-5-pyrimidinyl)phenyl)methyl)ethanamine;
- 15 (1R)-N-((4-(methyloxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-5-pyrimidinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-5-pyrimidinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-quinoxaliny)phenyl)methyl)ethanamine;
- 20 (1R)-N-((4-(methyloxy)-3-(6-quinoxaliny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-quinoxaliny)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 25 (1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-(1-piperidinyl)-1,3-thiazol-4-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 30 (1R)-N-((4-(methyloxy)-3-(2-(1-piperidinyl)-1,3-thiazol-4-yl)phenyl)methyl)-1-phenylethanamine;

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- (1R)-1-phenyl-N-((6-((2,2,2-trifluoroethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- (1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 5 (1R)-N-((6-chloro-4'-(trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-(1-
- 10 naphthalenyl)ethanamine;
- 1-(3,5-difluorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 1-(3-bromophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 15 1-(3-fluorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- (1S)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-(3-(2-chloropyrid-4-yl)-4-methoxyphenyl)methyl-N-1-phenylethylamine;
- 20 (1R)-1-(3-fluorophenyl)-N-((6-(methyloxy)-4'-(methylsulfonyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- (1R)-1-(3-fluorophenyl)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- (1R)-1-(3-chlorophenyl)-N-((6-(methyloxy)-1,1'-biphenyl-3-
- 25 yl)methyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 30 (1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(1-benzothien-3-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;

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- (1R)-N-((3-(1-benzothien-3-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2,1,3-benzothiadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 5 (1R)-N-((3-(2,1,3-benzothiadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4',6-bis(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4',6-bis(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- 10 (1R)-N-((4'-fluoro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-fluorophenyl)ethanamine;
- (1R)-N-((6-chloro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- 15 (1R)-N-((6-chloro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 20 (1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 25 (1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4-chloro-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1-(2,2,2-trifluoroethyl)-1H-indol-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 30 (1R)-N-((4-(methyloxy)-3-(1-(2,2,2-trifluoroethyl)-1H-indol-5-yl)phenyl)methyl)-1-phenylethanamine;

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- (1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- N-1-(3-(dimethylamino)phenyl)ethyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)amine;
- 5 N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-((trifluoromethyl)oxy)phenyl)ethanamine;
- 5-(2-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-1-(2,2,2-trifluoroethyl)-2(1H)-pyridinone;
- 5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1-(2,2,2-trifluoroethyl)-2(1H)-pyridinone;
- 10 1-(4-fluorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 1-(2,3-dichlorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 15 1-methyl-5-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-2(1H)-pyridinone;
- 1-methyl-5-(2-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2(1H)-pyridinone;
- (1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- 20 (1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethyl)ethanamine;
- (1R)-N-((3-imidazo[1,2-a]pyridin-6-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 25 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-quinolinyl)phenyl)methyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-quinolinyl)phenyl)methyl)-1-phenylethyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-quinolinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 30 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carboxamide;

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- (1R)-1-(1-naphthalenyl)-N-((6-((2,2,2-trifluoroethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 1-methyl-5-(2-(methyloxy)-5-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-2(1H)-pyridinone;
- 5 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-(1-piperidinyl)-1,3-thiazol-4-yl)phenyl)methyl)ethanamine;
- (1R)-N-((6-chloro-4'-(trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((6-chloro-4'-(trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 10 2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carboxamide;
- 2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-carboxamide;
- 15 (1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-1-(1-naphthalenyl)-N-((3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)ethanamine;
- (1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 20 (1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 25 (1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 4'-(methyloxy)-5-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-2-ol;
- (1R)-N-((3-imidazo[1,2-a]pyridin-6-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 30 (1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(1-acetyl-4-piperidinyl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;

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- (1R)-N-((4-(methyloxy)-3-(1-((methyloxy)acetyl)-4-piperidinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-((2-(methyloxy)ethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- 5 (1R)-N-((6-(methyloxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((6-(methyloxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-methyl-1,3-thiazol-4-yl)phenyl)methyl)-1-(3-
- 10 (methyloxy)phenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-methyl-1,3-thiazol-4-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-methyl-1,3-thiazol-4-yl)phenyl)methyl)-1-phenylethanamine;
- 15 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)phenyl)methyl)ethanamine;
- ethyl 4-(2-(methyloxy)-5-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-3,6-dihydro-1(2H)-pyridinecarboxylate;
- (1R)-N-((4-(methyloxy)-3-(4-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-(3-
- 20 (methyloxy)phenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(4-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-((difluoromethyl)oxy)-3-(3-pyridinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 25 (1R)-N-((4-((difluoromethyl)oxy)-3-(3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-((difluoromethyl)oxy)-3-(3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- 2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-
- 30 biphenyl-3-carboxylic acid;
- 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carboxylic acid;

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2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-carboxylic acid;

(1R)-N-((4-(methyloxy)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)phenyl)methyl)-1-phenylethylamine;

5 (1R)-N-((4-(methyloxy)-3-(1H-pyrrol-1-yl)phenyl)methyl)-1-phenylethylamine;

(1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;

(1R)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;

10 (1R)-N-((3-(1-methyl-1H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethylamine;

(1R)-N-((3-(1-methyl-1H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;

(1R)-N-((3-(2-methyl-2H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-

15 naphthalenyl)ethanamine;

(1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;

(1R)-N-((4-(methyloxy)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;

20 (1R)-N-((4-(methyloxy)-3-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;

(1R)-N-((4-(methyloxy)-3-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;

(1R)-N-((4-(methyloxy)-3-(1H-pyrrol-1-yl)phenyl)methyl)-1-(1-

25 naphthalenyl)ethanamine;

(1R)-N-((4-(methyloxy)-3-(5-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;

(1R)-N-((4-(methyloxy)-3-(5-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;

30 (1R)-N-((4-(methyloxy)-3-(5-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-phenylethylamine;

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- (1R)-N-((3-(6-(ethyloxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(6-(ethyloxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 5 (1R)-N-((3-(1-methyl-1H-benzimidazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(1-methyl-1H-benzimidazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl)methyl)-1-phenylethanamine;
- 10 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- 15 (1R)-N-((4-chloro-3-(3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-chloro-3-(3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-chloro-3-(3-pyridinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3-(1-methyl-1H-benzimidazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 20 (1R)-N-((3-(1-methyl-1H-benzimidazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 25 (1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)ethanamine;
- 30 (1R)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;

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- (1R)-N-((3-(2-ethyl-2H-1,2,3-benzotriazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- 5 (1R)-N-((3',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((4',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenyl-1-propanamine;
- 10 (1R)-N-((4-methyl-3-(3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 15 (1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4',6-difluoro-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 20 5-(2-(methyloxy)-5-((((1R)-1-(4-methylphenyl)ethyl)amino)methyl)phenyl)-2-pyrimidinamine;
- 5-(2-(methyloxy)-5-((((1R)-1-(2-naphthalenyl)ethyl)amino)methyl)phenyl)-2-pyrimidinamine;
- 5-(3-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide;
- 25 5-(3-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide;
- 5-(3-((((1R)-1-(2-naphthalenyl)ethyl)amino)methyl)phenyl)-3-pyridinecarboxamide;
- 30 (1R)-N-((6-fluoro-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;

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(1R)-N-((6-fluoro-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;

(1R)-N-((6-fluoro-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine; and

5 (1R)-N-((6-fluoro-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;

For the treatment of bone disorders, such as osteoporosis, excessive secretion of PTH, such as hyperparathyroidism, and the like, the compounds of the present invention may be administered orally, parentally, by inhalation spray,
10 rectally, or topically in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles. The term "parenteral" as used herein includes, subcutaneous, intravenous, intramuscular, intrasternal, infusion techniques or intraperitoneally.

Treatment of diseases and disorders herein is intended to also include the
15 prophylactic administration of a compound of the invention, a pharmaceutical salt thereof, or a pharmaceutical composition of either to a subject (*i.e.*, an animal, preferably a mammal, most preferably a human) believed to be in need of preventative treatment, such as, for example, pain, inflammation and the like.

The dosage regimen for treating the disclosed diseases with the
20 compounds of this invention and/or compositions of this invention is based on a variety of factors, including the type of disease, the age, weight, sex, medical condition of the patient, the severity of the condition, the route of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. Dosage levels of
25 the order from about 0.01 mg to 30 mg per kilogram of body weight per day, preferably from about 0.1 mg to 10 mg/kg, more preferably from about 0.25 mg to 1 mg/kg are useful for all methods of use disclosed herein.

The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal
30 agents for administration to patients, including humans and other mammals.

For oral administration, the pharmaceutical composition may be in the form of, for example, a capsule, a tablet, a suspension, or liquid. The

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pharmaceutical composition is preferably made in the form of a dosage unit containing a given amount of the active ingredient. For example, these may contain an amount of active ingredient from about 1 to 2000 mg, preferably from about 1 to 500 mg, more preferably from about 5 to 150 mg. A suitable daily
5 dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods.

The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water. The daily
10 parenteral dosage regimen will be from about 0.1 to about 30 mg/kg of total body weight, preferably from about 0.1 to about 10 mg/kg, and more preferably from about 0.25 mg to 1 mg/kg.

Injectable preparations, such as sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known are using suitable
15 dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition,
20 sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by
25 mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

A suitable topical dose of active ingredient of a compound of the invention is 0.1 mg to 150 mg administered one to four, preferably one or two times daily.
30 For topical administration, the active ingredient may comprise from 0.001% to 10% w/w, *e.g.*, from 1% to 2% by weight of the formulation, although it may

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comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably from 0.1% to 1% w/w of the formulation.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (*e.g.*, liniments, lotions, ointments, creams, or pastes) and drops suitable for administration to the eye, ear, or nose.

For administration, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate for the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, acacia, gelatin, sodium alginate, polyvinyl-pyrrolidone, and/or polyvinyl alcohol, and tableted or encapsulated for conventional administration. Alternatively, the compounds of this invention may be dissolved in saline, water, polyethylene glycol, propylene glycol, ethanol, corn oil, peanut oil, cottonseed oil, sesame oil, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well known in the pharmaceutical art. The carrier or diluent may include time delay material, such as glyceryl monostearate or glyceryl distearate alone or with a wax, or other materials well known in the art.

The pharmaceutical compositions may be made up in a solid form (including granules, powders or suppositories) or in a liquid form (*e.g.*, solutions, suspensions, or emulsions). The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, *e.g.*, lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also

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comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert
5 diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

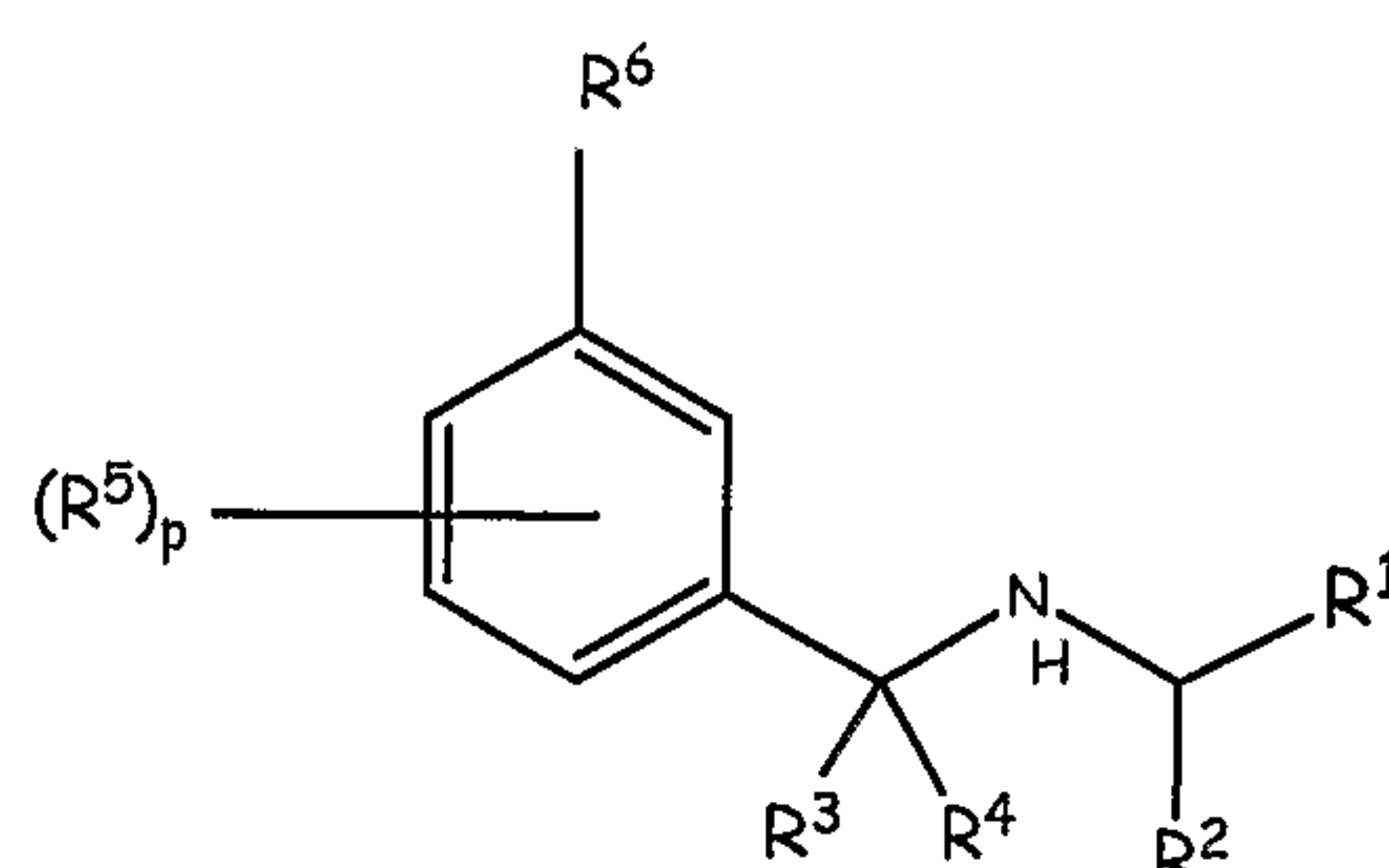
While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or
10 more compounds of the invention or other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to
15 limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

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WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, cycloalkyl, or substituted cycloalkyl;

R^2 is alkyl or haloalkyl;

R^3 is H, alkyl, or haloalkyl;

R^4 is H, alkyl, or haloalkyl;

each R^5 present is independently alkyl, substituted alkyl, alkoxy, substituted alkoxy, halogen, $-C(=O)OH$, $-CN$, $-NR^dS(=O)_mR^d$, $-NR^dC(=O)NR^dR^d$, $-NR^dS(=O)_mNR^dR^d$, or $-NR^dC(=O)R^d$;

R^6 is aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, cycloalkyl, or substituted cycloalkyl;

each R^a is, independently, H, alkyl or haloalkyl;

each R^b is, independently, aryl, aralkyl, heterocyclyl, or

heterocyclylalkyl, each of which may be unsubstituted or

substituted by up to 3 substituents selected from the group

consisting of alkyl, halogen, haloalkyl, alkoxy, cyano, and nitro;

each R^c is, independently, alkyl, haloalkyl, phenyl or benzyl, each of which may be substituted or unsubstituted;

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each R^d is, independently, H, alkyl, aryl, aralkyl, heterocyclyl, or heterocyclylalkyl wherein the alkyl, aryl, aralkyl, heterocyclyl, and heterocyclylalkyl are substituted by 0, 1, 2, 3 or 4 substituents selected from alkyl, halogen, haloalkyl, alkoxy, cyano, nitro, R^b ,
 5 $-C(=O)R^c$, $-OR^b$, $-NR^aR^a$, $-NR^aR^b$, $-C(=O)OR^c$, $-C(=O)NR^aR^a$,
 $-OC(=O)R^c$, $-NR^aC(=O)R^c$, $-NR^aS(=O)_nR^c$ and $-S(=O)_nNR^aR^a$;

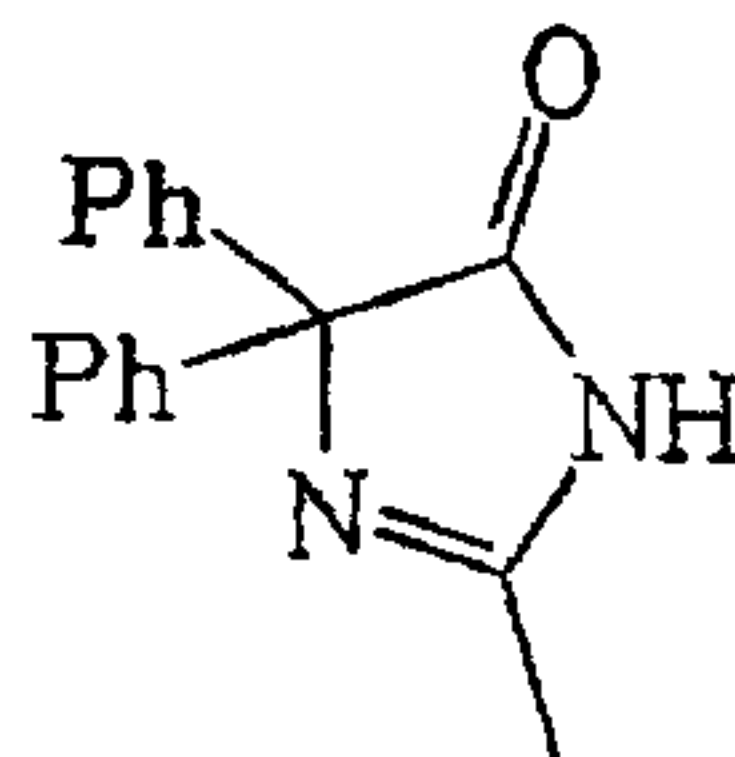
m is 1 or 2;

n is 0, 1 or 2; and

p is 0, 1, 2, 3, or 4,

10 provided that if R^2 is methyl, p is 0, and R^6 is unsubstituted phenyl, then R^1 is not 2,4-dihalophenyl, 2,4-dimethylphenyl, 2,4-diethylphenyl, 2,4,6-trihalophenyl, or 2,3,4-trihalophenyl

wherein when R^1 is phenyl and R^2 is methyl, R^6 is not



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2. A compound or salt of claim 1 wherein R^1 is aryl or substituted aryl.
- 15 3. A compound or salt of claim 1 wherein R^1 is phenyl, substituted phenyl, naphthyl, or substituted naphthyl.
4. A compound or salt of claim 1 wherein R^1 is phenyl or substituted phenyl.
5. A compound or salt of claim 1 wherein R^1 is phenyl that is unsubstituted or substituted by a substituent selected from the group consisting of
20 halogen, C_{1-4} alkyl, C_{1-4} alkoxy, and cyano.
6. A compound or salt of claim 1 wherein R^1 is phenyl substituted by a halogen, methyl, or methoxy group.
7. A compound or salt of claim 6 wherein the substituent is in the 3-position.
8. A compound or salt of claim 1 wherein R^1 is heteroaryl or substituted
25 heteroaryl.
9. A compound or salt of claim 1 wherein R^6 is heterocyclyl or substituted heterocyclyl.
10. A compound or salt of claim 1 wherein R^6 is a 2-pyridyl or 3-pyridyl group that is substituted or unsubstituted.
- 30 11. A compound or salt of claim 1 wherein R^6 is phenyl, substituted phenyl, naphthyl, or substituted naphthyl.
12. A compound or salt of claim 1 wherein R^6 is phenyl or substituted phenyl.

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13. A compound or salt of claim 1 wherein R^6 is phenyl that is unsubstituted or substituted by 1 or 2 substituents selected from the group consisting of C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{1-4} alkoxy, methylenedioxy, cyano, C_{1-4} alkyl, $-NH-C(=O)-C_{1-4}$ alkyl, $-(CH_2)_{0-3}-C(=O)-NH_2$, $-S(=O)_2-C_{1-4}$ alkyl, $-(CH_2)_{0-3}-C(=O)O-C_{1-4}$ alkyl, and $-(CH_2)_{0-3}-C(=O)-OH$.
14. A compound or salt of claim 1 wherein R^6 is phenyl that is unsubstituted or substituted by a halogen, methoxy, trifluoromethyl, or trifluoromethoxy group.
15. A compound or salt of claim 1 wherein R^6 is a phenyl group that is substituted at the 4-position and may be further substituted.
16. A compound or salt of claim 1 wherein each R^5 present is independently selected from the group consisting of halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $-NR^d-S(=O)_2-C_{1-4}$ alkyl, $-NR^d-C(=O)-NR^d-C_{1-4}$ alkyl.
17. A compound or salt of claim 1 wherein p is 0.
18. A compound or salt of claim 1 wherein p is 1 and R^5 is methoxy.
19. A compound or salt of claim 18 wherein R^5 is in the 4-position.
20. A compound or salt of claim 19 wherein R^1 is phenyl, substituted phenyl, or naphthyl.
21. A compound or salt of claim 19 wherein R^6 is phenyl or substituted phenyl.
22. A compound or salt of claim 19 wherein R^6 is phenyl that is unsubstituted or substituted by a halogen, methoxy, trifluoromethyl, or trifluoromethoxy group.
23. A compound or salt of claim 22 wherein R^1 is phenyl, 1-naphthyl, or 2-naphthyl that is unsubstituted or substituted by 1 or 2 substituents selected from the group consisting of halogen, C_{1-4} alkyl, C_{1-4} alkoxy, and cyano.
24. A compound or salt of claim 22 wherein R^1 is phenyl substituted by 1 or 2 substituents selected from the group consisting of halogen, methyl, methoxy, and cyano.
25. A compound or salt of claim 1 wherein R^2 is methyl.
26. A compound or salt of claim 23 wherein R^2 is methyl.

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27. A compound or salt of claim 1 wherein R³ and R⁴ are both hydrogen.

28. A compound or salt of claim 26 wherein R³ and R⁴ are both hydrogen.

29. A compound selected from the group consisting of:

- 5 (1R)-N-((6-fluoro-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-(methyloxy)phenyl)ethanamine;
 (1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 (1R)-N-((3',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
 10 (1R)-N-((3',6-bis(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
 (1R)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)ethanamine;
 15 (1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 (1R)-N-((3-(1-methyl-1H-indol-6-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
 20 (1R)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)ethanamine;
 (1R)-N-((3-(1-methyl-1H-benzimidazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 25 (1R)-N-((3-(6-(ethyloxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
 (1R)-N-((3-(6-(ethyloxy)-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 30 (1R)-N-((4-(methyloxy)-3-(1H-pyrrol-1-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 (1R)-N-((4-(methyloxy)-3-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
 (1R)-N-((3-(1-methyl-1H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 35 (1R)-N-((3-(1-methyl-1H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
 (1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
 40 (1R)-N-((4-(methyloxy)-3-(1H-pyrrol-1-yl)phenyl)methyl)-1-phenylethanamine;
 (1R)-N-((4-(methyloxy)-3-(4-(methyloxy)-2-pyridinyl)phenyl)methyl)-1-phenylethanamine;
 ethyl 4-(2-(methyloxy)-5-(((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)phenyl)-3,6-dihydro-1(2H)-
 45 pyridinecarboxylate;

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- (1R)-N-((6-(methyloxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 5 (1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 10 (1R)-N-((3-(2,2-difluoro-1,3-benzodioxol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((6-chloro-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 15 (1R)-N-((6-chloro-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-quinoliny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-quinoliny)phenyl)methyl)-1-phenylethanamine;
- 20 (1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1-(2,2,2-trifluoroethyl)-1H-indol-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 25 (1R)-N-((4-chloro-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridiny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((3-(2,1,3-benzoxadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 30 (1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 35 (1R)-N-((3-(2,3-dihydro-1-benzofuran-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4'-fluoro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-fluorophenyl)ethanamine;
- (1R)-N-((4',6-bis(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 40 (1R)-N-((3-(2,1,3-benzothiadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2,1,3-benzothiadiazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 45 (1R)-N-((3-(1-benzothien-3-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 1-(3-fluorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;

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- 1-(3-bromophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 1-(3,5-difluorophenyl)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- 5 (1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((6-chloro-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 10 (1R)-N-((4-(methyloxy)-3-(6-quinoxaliny)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 15 (1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- 20 (1R)-N-((3-(2-methyl-1,3-oxazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2-methyl-1,3-oxazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 25 ethyl 2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate;
- ethyl 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate;
- 4-(2-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)phenyl)-1,3-thiazol-2-amine;
- 30 (1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 35 (1R)-N-((3-(1-(cyclopropylmethyl)-1H-indol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-((tetrahydro-2-furanylmethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(2-fluoro-3-pyridinyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 40 N,N-dimethyl-5-(2-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)phenyl)-2-pyridinamine;
- (1R)-N-((4-(methyloxy)-3-(1-methyl-2-(trifluoromethyl)-1H-benzimidazol-5-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- 45 (1R)-N-((4-(methyloxy)-3-(1-methyl-2-(trifluoromethyl)-1H-benzimidazol-5-yl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)-1-phenylethanamine;

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- (1R)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-thienyl)phenyl)methyl)ethanamine;
 5 (1R)-N-((4-(methyloxy)-3-(6-methyl-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 (1R)-N-((4-(methyloxy)-3-(2-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 10 (1R)-N-((3-(1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 (1R)-N-((3-(2-methyl-1,3-benzoxazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
 2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile;
 15 (1R)-N-((6-(methyloxy)-4'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
 (1R)-1-(3-fluorophenyl)-N-((6-(methyloxy)-4'-((trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine;
 (1R)-N-((6-(ethyloxy)-4'-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
 20 (1R)-N-((4-(methyloxy)-3-(3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 (1R)-N-((4-(methyloxy)-3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 25 (1R)-N-((4-(methyloxy)-3-(6-((2,2,2-trifluoroethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine; and
 (1R)-1-(3-chlorophenyl)-N-((6-(methyloxy)-4'-((trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)ethanamine
 30 or a pharmaceutically acceptable salt thereof.
30. A compound selected from the group consisting of:
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(3-pyridinyl)phenyl)methyl)ethanamine;
 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carbonitrile;
 35 (1R)-N-((2'-fluoro-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;
 (1R)-N-((6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(4-methylphenyl)ethanamine;
 40 (1R)-N-((4-(methyloxy)-3-(6-(methyloxy)-3-pyridazinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
 (1R)-N-((4-(methyloxy)-3-(2-pyrazinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 (1R)-N-((4-(methyloxy)-3-(6-((tetrahydro-2-furanylmethyl)oxy)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;
 45 (1R)-N-((4-(methyloxy)-3-(2-(4-morpholinyl)-3-pyridinyl)phenyl)methyl)-1-phenylethanamine;

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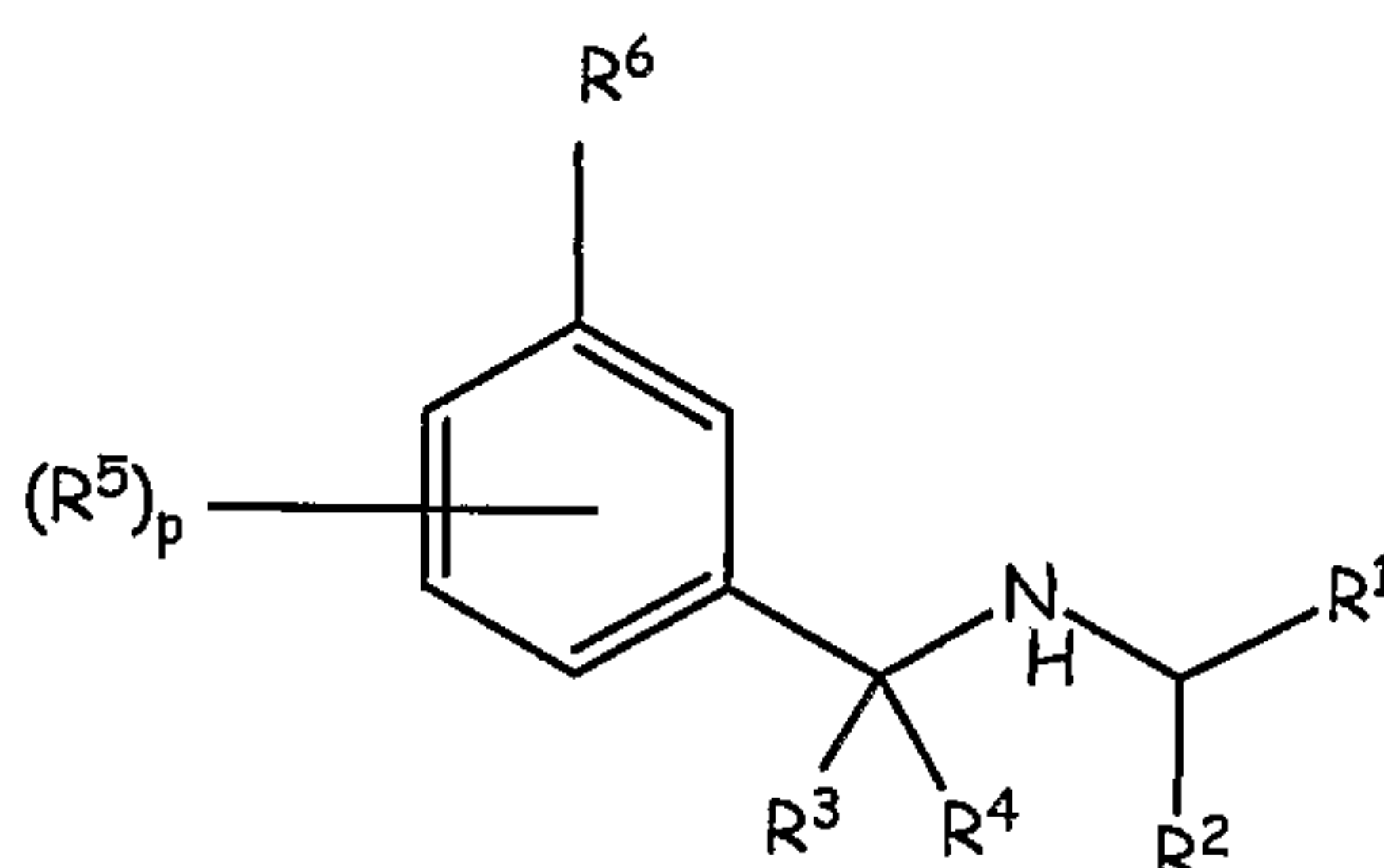
- (1R)-N-((3-(1-methyl-1H-imidazol-4-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(1-pyrrolidinyl)phenyl)methyl)-1-phenylethanamine;
- 5 ethyl 2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxylate;
- N-((6-(methyloxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-methylphenyl)ethanamine;
- (1R)-N-((6-fluoro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 10 N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-(3-(methyloxy)phenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;
- N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;
- 15 N,N-dimethyl-2'-(methyloxy)-5'-((((1R)-1-phenylethyl)amino)methyl)-1,1'-biphenyl-4-carboxamide;
- (1R)-N-((6-iodo-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- 20 (1R)-1-(3-(methyloxy)phenyl)-N-((6-(methyloxy)-3'-((trifluoromethyl)oxy)-1,1'-biphenyl-3-yl)methyl)ethanamine;
- (1R)-N-((4'-chloro-6-(methyloxy)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 25 (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(2-((2,2,2-trifluoroethyl)oxy)-5-pyrimidinyl)phenyl)methyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(6-quinoxaliny)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((3-(1,3-benzothiazol-2-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
- 30 (1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
- 35 (1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
- (1R)-N-((4-(methyloxy)-3-(2-naphthalenyl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((6-chloro-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- 40 (1R)-N-((4-(methyloxy)-3-(1-(2,2,2-trifluoroethyl)-1H-indol-5-yl)phenyl)methyl)-1-phenylethanamine;
- (1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
- 45 (1R)-N-((6-((2-(methyloxy)ethyl)oxy)-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-phenylethanamine;
- (1R)-1-(3-(methyloxy)phenyl)-N-((4-(methyloxy)-3-(6-quinoliny)phenyl)methyl)ethanamine;

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- 2'-(methyloxy)-5'-((((1R)-1-(1-naphthalenyl)ethyl)amino)methyl)-1,1'-biphenyl-3-carboxamide;
 (1R)-1-(1-naphthalenyl)-N-((3-(6-(trifluoromethyl)-3-pyridinyl)phenyl)methyl)ethanamine;
 5 (1R)-N-((3-(3-furanyl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine;
 (1R)-N-((6-(methyloxy)-3'-(trifluoromethyl)-1,1'-biphenyl-3-yl)methyl)-1-(1-naphthalenyl)ethanamine;
 (1R)-N-((4-(methyloxy)-3-(2-methyl-1,3-thiazol-4-yl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
 10 (1R)-N-((4-((difluoromethyl)oxy)-3-(3-pyridinyl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 (1R)-N-((3-(2-methyl-2H-indazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 15 (1R)-N-((4-(methyloxy)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)phenyl)methyl)-1-(1-naphthalenyl)ethanamine;
 (1R)-N-((4-chloro-3-(3-pyridinyl)phenyl)methyl)-1-(3-(methyloxy)phenyl)ethanamine;
 (1R)-N-((3-(2-ethyl-2H-1,2,3-benzotriazol-5-yl)-4-(methyloxy)phenyl)methyl)-1-phenylethanamine; and
 20 (1R)-N-((4',6-difluoro-1,1'-biphenyl-3-yl)methyl)-1-(3-(methyloxy)phenyl)ethanamine

or a pharmaceutically acceptable salt thereof.

31. A composition comprising a pharmaceutically acceptable amount of a compound of the formula Ia:



(Ia)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, or substituted heterocyclyl;

R^2 is alkyl or haloalkyl;

R^3 is H, alkyl, or haloalkyl;

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R^4 is H, alkyl, or haloalkyl;

each R^5 present is independently alkyl, substituted alkyl, haloalkyl, alkoxy, substituted alkoxy, halogen, $-C(=O)OH$, $-CN$, $-NR^aR^d$, $-NR^dS(=O)_mR^d$, $-NR^dC(=O)NR^dR^d$, $-NR^dS(=O)_mNR^dR^d$, or $-NR^dC(=O)R^d$;

5 R^6 is aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, or substituted heterocyclyl;

each R^a is, independently, H, alkyl or haloalkyl;

each R^b is, independently, aryl, aralkyl, heterocyclyl, or heteroaryl, each of which may be unsubstituted or substituted by up to 3

10 substituents selected from the group consisting of alkyl, halogen, haloalkyl, alkoxy, cyano, and nitro;

each R^c is, independently, alkyl, haloalkyl, phenyl or benzyl;

each R^d is, independently, H, alkyl, aryl, aralkyl, or heterocyclyl, wherein the alkyl, aryl, aralkyl, and heterocycle are substituted by

15 0, 1, 2, 3 or 4 substituents selected from alkyl, halogen, haloalkyl, alkoxy, cyano, nitro, R^b , $-C(=O)R^c$, $-OR^b$, $-NR^aR^a$, $-NR^aR^b$, $-C(=O)OR^c$, $-C(=O)NR^aR^a$, $-OC(=O)R^c$, $-NR^aC(=O)R^c$, $-NR^aS(=O)_nR^c$ and $-S(=O)_nNR^aR^a$;

m is 1 or 2;

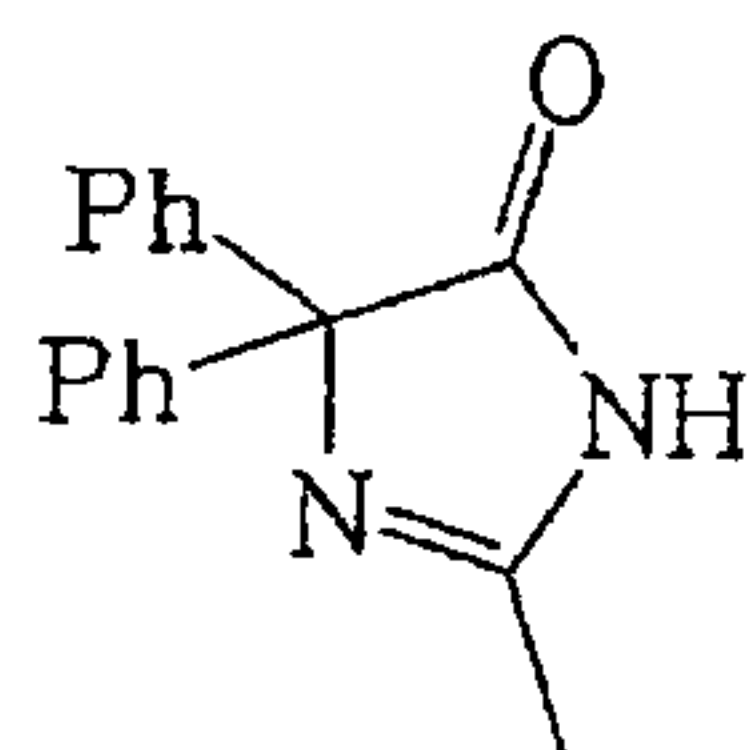
20 n is 0, 1 or 2; and

p is 0, 1, 2, 3, or 4, in combination with a pharmaceutically acceptable carrier

provided that if R^2 is methyl, p is 0, and R^6 is unsubstituted phenyl, then

R^1 is not 2,4-dihalophenyl, 2,4-dimethylphenyl, 2,4-diethylphenyl, 2,4,6-trihalophenyl, or 2,3,4-trihalophenyl

wherein when R^1 is phenyl and R^2 is methyl, R^6 is not

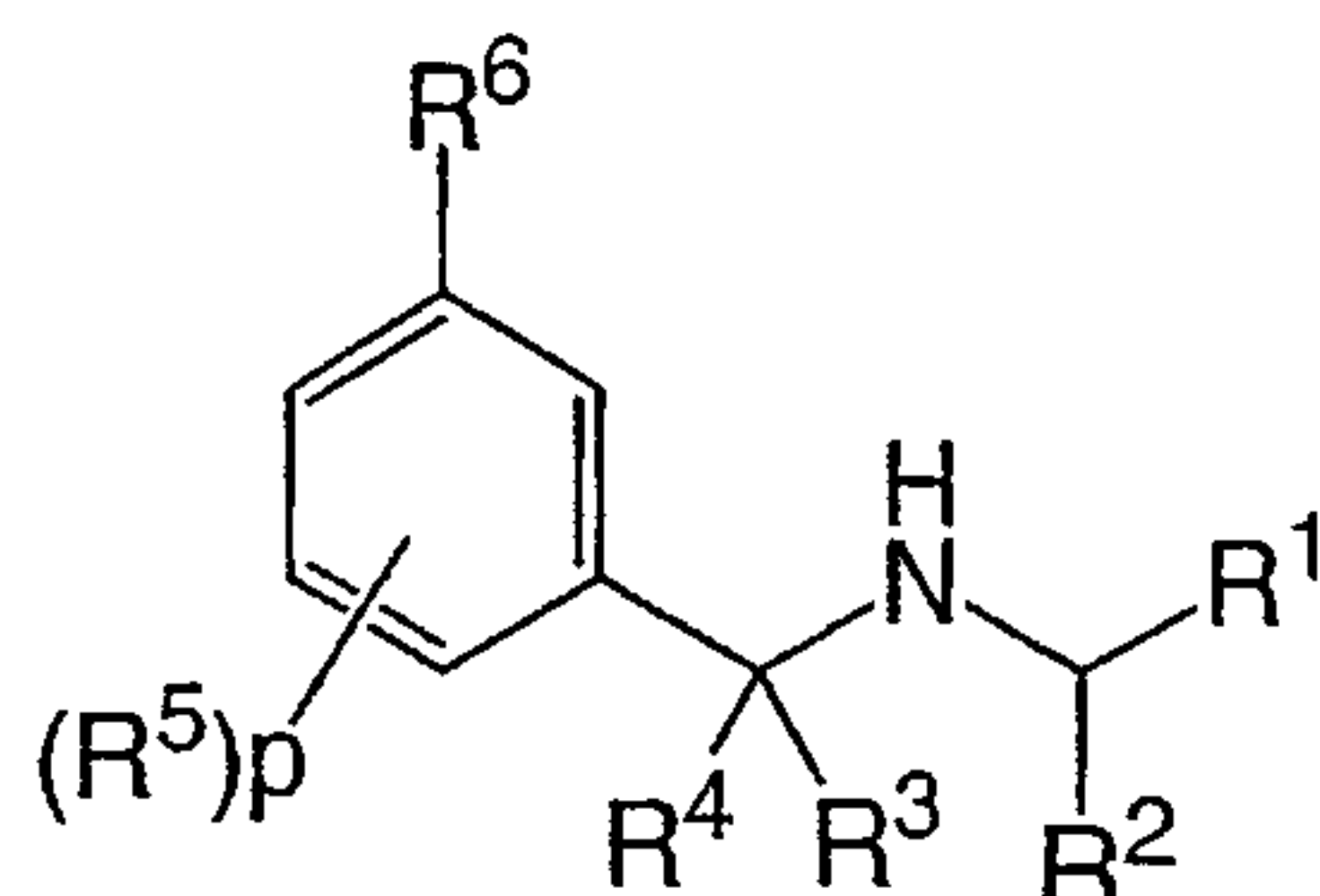


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32. A use of a therapeutically effective amount of a composition of claim 31 for treating a disease associated with excess secretion of PTH in a patient in need thereof.
33. A use of a therapeutically effective amount of a composition of claim 31 for the preparation of a medicament for treating a disease associated with excess secretion of PTH in a patient in need thereof.
34. A use of a therapeutically effective amount of a composition of claim 31 for treating osteoporosis or hyperparathyroidism in a patient in need thereof.
35. A use of a therapeutically effective amount of a composition of claim 31 for the preparation of a medicament for treating osteoporosis or hyperparathyroidism in a patient in need thereof.

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36. A compound having the formula



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is phenyl, benzyl, naphthyl or a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the phenyl, benzyl, naphthyl or heterocycle are substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl, $-OC_{1-6}$ alkyl, cyano and nitro;

R^2 is C_{1-8} alkyl or C_{1-4} haloalkyl;

R^3 is H, C_{1-4} haloalkyl or C_{1-8} alkyl;

R^4 is H, C_{1-4} haloalkyl or C_{1-8} alkyl;

R^5 is, independently, in each instance, H, C_{1-8} alkyl, C_{1-4} haloalkyl, halogen, cyano, $-NR^aR^d$, $-NS(=O)_2R^c$, $-NR^aC(=O)NR^aR^d$, $-NR^dC(=O)R^d$ or

$-OC_{1-6}$ alkyl substituted by 0, 1, 2 or 3 substituents selected from halogen, $-OC_{1-6}$ alkyl, $-NR^aR^d$, $-NS(=O)_2R^c$, $-NR^aC(=O)NR^aR^d$, $-NR^dC(=O)R^d$ or cyano;

R^6 is phenyl, benzyl, naphthyl, a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, or a saturated or unsaturated 8-, 9-, 10- or 11-membered heterobicycle containing 1, 2, 3, 4 or 5 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the phenyl, benzyl, naphthyl, heterocycle and heterobicycle are substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl, $-OC_{1-6}$ alkyl, $-OC_{1-4}$ haloalkyl, $-NR^aR^a$, $-NR^aC(=O)C_{1-6}$ alkyl, $-S(=O)_nC_{1-6}$ alkyl, cyano and nitro;

R^a is, independently, at each instance, H, C_{1-4} haloalkyl or C_{1-6} alkyl;

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R^b is, independently, aryl, aralkyl, heterocyclyl, or heterocyclalkyl, each of which may be unsubstituted or substituted by up to 3 substituents selected from the group consisting of alkyl, halogen, haloalkyl, alkoxy, cyano, and nitro;

5 R^c is, independently, at each instance, C_{1-6} alkyl, C_{1-4} haloalkyl, phenyl or benzyl, each of which may be unsubstituted or substituted;

R^d is, independently, at each instance, H, C_{1-6} alkyl, phenyl, benzyl, naphthyl, or a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms
10 selected from O and S, wherein the C_{1-6} alkyl, phenyl, benzyl, naphthyl and heterocycle are substituted by 0, 1, 2, 3 or 4 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl, $-OC_{1-6}$ alkyl, cyano and nitro, R^b , $-C(=O)R^c$, $-OR^b$, $-NR^aR^a$, $-NR^aR^b$, $-C(=O)OR^c$, $-C(=O)NR^aR^a$, $-OC(=O)R^c$, $-NR^aC(=O)R^c$, $-NR^aS(=O)_mR^c$ and $-S(=O)_mNR^aR^a$;

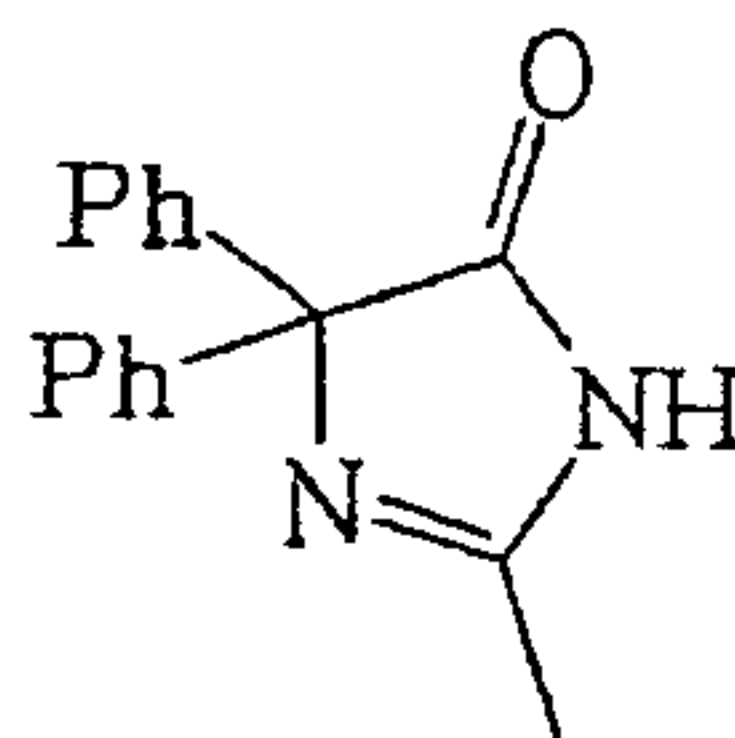
15 m is 1 or 2;

n is 0, 1 or 2 and

p is 0, 1, 2, 3, or 4,

provided that if R^2 is methyl, p is 0, and R^6 is unsubstituted phenyl, then R^1 is not 2,4-dihalophenyl, 2,4-dimethylphenyl, 2,4-diethylphenyl, 2,4,6-trihalophenyl, or 2,3,4-trihalophenyl

wherein when R^1 is phenyl and R^2 is methyl, R^6 is not



37. A compound according to claim 36 wherein R¹ is phenyl, naphthyl or a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the phenyl, benzyl, naphthyl or heterocycle are substituted by 0, 1, 2 or 3 substituents selected from C₁₋₆alkyl, halogen, C₁₋₄haloalkyl, -OC₁₋₆alkyl, cyano and nitro and R⁶ is phenyl, naphthyl, a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, or a saturated or unsaturated 8-, 9-, 10- or 11-membered heterobicycle containing 1, 2, 3, 4 or 5 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the phenyl, benzyl, naphthyl, heterocycle and heterobicycle are substituted by 0, 1, 2 or 3 substituents selected from C₁₋₆alkyl, halogen, C₁₋₄haloalkyl, -OC₁₋₆alkyl, -OC₁₋₄haloalkyl, -NR^aR^a, -NR^aC(=O)C₁₋₆alkyl, -S(=O)_nC₁₋₆alkyl, cyano and nitro.

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38. A compound according to Claim 36, wherein R^1 is phenyl substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl, $-OC_{1-6}$ alkyl, cyano and nitro.
- 5 39. A compound according to Claim 36, wherein R^1 is benzyl substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl, $-OC_{1-6}$ alkyl, cyano and nitro.
- 10 40. A compound according to Claim 36, wherein R^1 is naphthyl substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl, $-OC_{1-6}$ alkyl, cyano and nitro.
- 15 41. A compound according to Claim 36, wherein R^1 is a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the heterocycle is substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl, $-OC_{1-6}$ alkyl, cyano and nitro.
- 20 42. A compound according to Claim 36, wherein R^6 is phenyl, wherein the phenyl is substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl, $-OC_{1-6}$ alkyl, $-OC_{1-4}$ haloalkyl, $-NR^aR^a$, $-NR^aC(=O)C_{1-6}$ alkyl, $-S(=O)_nC_{1-6}$ alkyl, cyano and nitro.
- 25 43. A compound according to Claim 36, wherein R^6 is benzyl, wherein the benzyl is substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl, halogen, C_{1-4} haloalkyl, $-OC_{1-6}$ alkyl, $-OC_{1-4}$ haloalkyl, $-NR^aR^a$, $-NR^aC(=O)C_{1-6}$ alkyl, $-S(=O)_nC_{1-6}$ alkyl, cyano and nitro.
- 30 44. A compound according to Claim 36, wherein R^6 is naphthyl, wherein the naphthyl is substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl,

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halogen, C₁₋₄haloalkyl, -OC₁₋₆alkyl, -OC₁₋₄haloalkyl, -NR^aR^a,
 -NR^aC(=O)C₁₋₆alkyl, -S(=O)_nC₁₋₆alkyl, cyano and nitro.

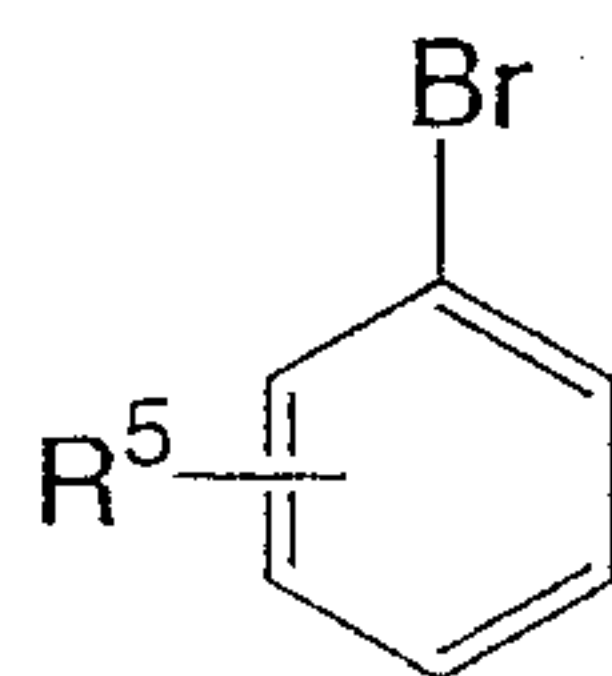
45. A compound according to Claim 36, wherein R⁶ is a saturated or
 5 unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms
 selected from N, O and S, with no more than 2 of the atoms selected from
 O and S, wherein the heterocycle is substituted by 0, 1, 2 or 3 substituents
 selected from C₁₋₆alkyl, halogen, C₁₋₄haloalkyl, -OC₁₋₆alkyl,
 -OC₁₋₄haloalkyl, -NR^aR^a, -NR^aC(=O)C₁₋₆alkyl, -S(=O)_nC₁₋₆alkyl, cyano
 10 and nitro.
46. A compound according to Claim 36, wherein R⁶ is a saturated or
 unsaturated 8-, 9-, 10- or 11-membered heterobicycle containing 1, 2, 3, 4
 or 5 atoms selected from N, O and S, with no more than 2 of the atoms
 15 selected from O and S, wherein the heterobicycle is substituted by 0, 1, 2
 or 3 substituents selected from C₁₋₆alkyl, halogen, C₁₋₄haloalkyl,
 -OC₁₋₆alkyl, -OC₁₋₄haloalkyl, -NR^aR^a, -NR^aC(=O)C₁₋₆alkyl, -S(=O)_n
 C₁₋₆alkyl, cyano and nitro.
- 20 47. A compound according to Claim 36, wherein R¹ is phenyl, naphthyl or
 (OC₁₋₄alkyl)phenyl.
48. A compound according to Claim 36, wherein R¹ is phenyl substituted by 2
 or 3 substituents selected from C₁₋₆alkyl, halogen, C₁₋₄haloalkyl,
 25 -OC₁₋₆alkyl, cyano and nitro.
49. A compound according to Claim 36, wherein R¹ is benzyl substituted by 1,
 2 or 3 substituents selected from C₁₋₆alkyl, halogen, C₁₋₄haloalkyl,
 -OC₁₋₆alkyl, cyano and nitro.

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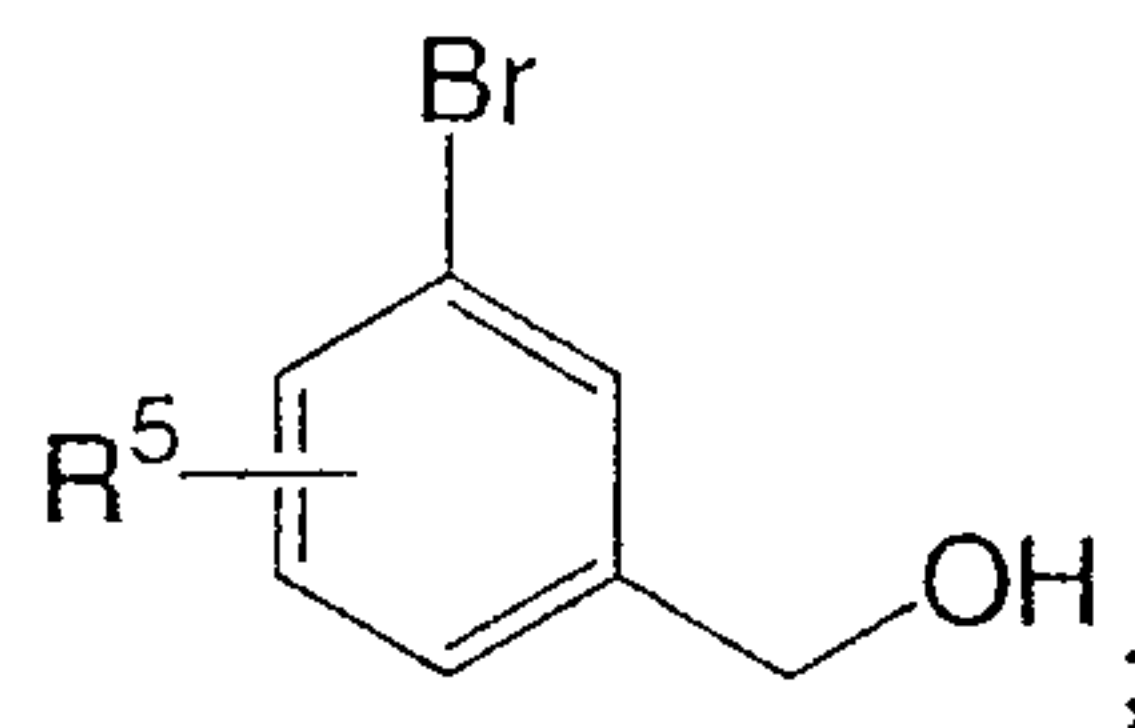
50. A compound according to Claim 36, wherein R¹ is naphthyl substituted by 1, 2 or 3 substituents selected from C₁₋₆alkyl, halogen, C₁₋₄haloalkyl, -OC₁₋₆alkyl, cyano and nitro.
- 5 51. A compound according to Claim 36, wherein R¹ a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1, 2 or 3 atoms selected from N, O and S, with no more than 2 of the atoms selected from O and S, wherein the heterocycle is substituted by 1, 2 or 3 substituents selected from C₁₋₆alkyl, halogen, C₁₋₄haloalkyl, -OC₁₋₆alkyl, cyano and nitro.
- 10 52. A compound according to Claim 36, wherein one of R³ or R⁴ is C₁₋₄haloalkyl or C₁₋₈alkyl.
- 15 53. A compound according to Claim 36, wherein R⁵ is C₁₋₈alkyl, C₁₋₄haloalkyl, halogen or -OC₁₋₆alkyl.
54. A pharmaceutical composition comprising a compound according to Claim 36 and a pharmaceutically acceptable diluent or carrier.
- 20 55. The use of a compound according to Claim 36 in the manufacture of a medicament for the treatment of diseases associated with bone disorders or associated with excessive secretion of PTH.
- 25 56. The use of a compound according to Claim 36 for the treatment of diseases associated with bone disorders or associated with excessive secretion of PTH.
57. The use of a compound according to Claim 36 in the manufacture of a medicament for the treatment of osteoporosis or hyperparathyroidism.
- 30 58. The use of a compound according to Claim 36, for the treatment of osteoporosis or hyperparathyroidism.

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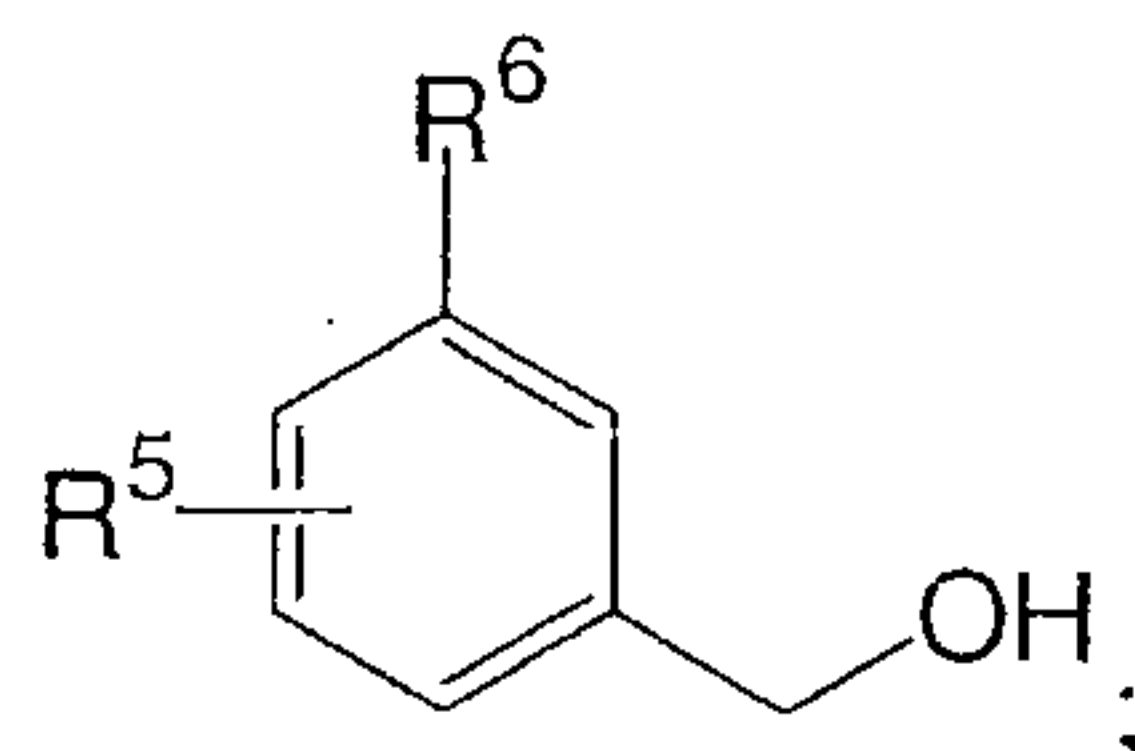
59. A process for making a compound according to Claim 1, wherein R^3 and R^4 are both H comprising the steps of:
 5 placing a compound having the structure



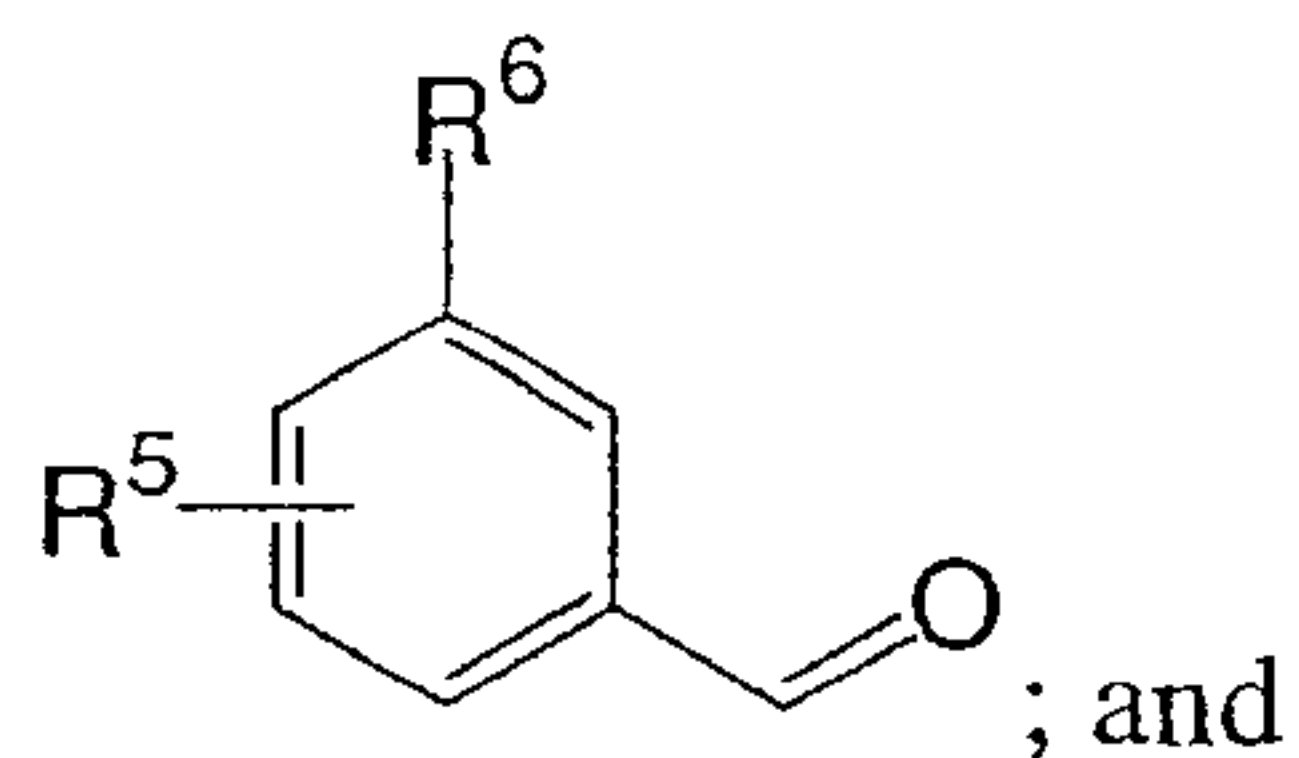
in the presence of acid followed by treatment with a hydride and methanol to form



10 reacting the resulting alcohol with $R^6-B(OH)_2$ to form



oxidizing the alcohol to form



- 15 reacting the aldehyde with an amine having the structure

