



(86) Date de dépôt PCT/PCT Filing Date: 2008/02/11
(87) Date publication PCT/PCT Publication Date: 2008/08/21
(85) Entrée phase nationale/National Entry: 2009/08/07
(86) N° demande PCT/PCT Application No.: US 2008/001776
(87) N° publication PCT/PCT Publication No.: 2008/100463
(30) Priorité/Priority: 2007/02/13 (US11/705,673)

(51) Cl.Int./Int.Cl. *A61K 31/4985* (2006.01),
A61K 31/42 (2006.01), *A61K 31/5383* (2006.01),
A61P 11/02 (2006.01), *A61P 25/24* (2006.01),
A61P 27/06 (2006.01), *A61P 29/00* (2006.01),
C07D 403/06 (2006.01), *C07D 413/06* (2006.01),
C07D 413/14 (2006.01), *C07D 417/06* (2006.01),
C07D 471/04 (2006.01), *C07D 498/04* (2006.01)

(71) Demandeurs/Applicants:
SCHERING CORPORATION, US;
PHARMACOEPIA, LLC, US

(72) Inventeurs/Inventors:
MCCORMICK, KEVIN D., US;
BOYCE, CHRISTOPHER W., US;

(54) Titre : AGONISTES DU RECEPTEUR ADRENERGIQUE ALPHA2C

(54) Title: 3,4-DIHYDRO-1,4-BENZOXAZINE, 3, 4-DIHYDRO-1, 4-BENZOTHIAZINE AND 1,2,3,4-TETRAHYDRO-
QUINOXALINE DERIVATIVES AS ALPHA2C ADRENORECEPTOR AGONISTS

(57) **Abrégé/Abstract:**

The present invention relates to a novel class of phenylmorpholine and phenyl thiomorpholine compounds useful as alpha2C adrenergic receptor agonists, pharmaceutical compositions containing the compounds, and methods of treatment, prevention, inhibition,- or amelioration of one or more diseases associated with the alpha2C adrenergic receptor agonists, such as allergic rhinitis, congestion, pain, diarrhea, glaucoma, congestive heart failure, cardiac ischemia, manic disorders, depression, anxiety and schizophrenia.

(72) **Inventeurs(suite)/Inventors(continued)**: SHIH, NENG-YANG, US; ASLANIAN, ROBERT G., US; FEVRIER, SALEM, US; MANGIARACINA, PIETRO, US; DE LERA RUIZ, MANUEL, US; YU, YOUNONG, US; ZHENG, JUNYING, US; HUANG, CHIA-YU, US; LIANG, BO, US; LIU, RONG-QIANG, US; LIU, RUIYAN, US; GUISE ZAWACKI, LISA, US

(74) **Agent**: OGILVY RENAULT LLP/S.E.N.C.R.L.,S.R.L.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 August 2008 (21.08.2008)

PCT

(10) International Publication Number
WO 2008/100463 A1

(51) International Patent Classification:

A61K 31/4985 (2006.01) C07D 471/04 (2006.01)
A61K 31/5383 (2006.01) C07D 498/04 (2006.01)
A61K 31/42 (2006.01) A61P 11/02 (2006.01)
C07D 403/06 (2006.01) A61P 29/00 (2006.01)
C07D 413/06 (2006.01) A61P 25/24 (2006.01)
C07D 413/14 (2006.01) A61P 27/06 (2006.01)
C07D 417/06 (2006.01)

(21) International Application Number:

PCT/US2008/001776

(22) International Filing Date:

11 February 2008 (11.02.2008)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

11/705,673 13 February 2007 (13.02.2007) US

(71) Applicants (for all designated States except US): **SCHERING CORPORATION** [US/US]; 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530 (US). **PHARMACOPEIA, INC.** [US/US]; 3000 Eastpark Boulevard, Cranbury, New Jersey 08512 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MCCORMICK, Kevin, D.** [US/US]; 15 Brookfield Drive, Basking Ridge, New Jersey 07920 (US). **BOYCE, Christopher, W.** [US/US]; 71 Bonnell Street, Flemington, New Jersey 08822 (US). **SHIH, Neng-yang** [US/US]; 2 Tyler Road, Lexington, Massachusetts 02420 (US). **ASLANIAN, Robert, G.** [US/US]; 144 Philip Drive, Rockaway, New Jersey 07866 (US). **FEVRIER, Salem** [US/US]; 8 Washington Place, Cranford, New Jersey 07016 (US). **MANGIARACINA, Pietro** [US/US]; 4 Montclair Avenue, Monsey, New York 10952 (US). **DE LERA RUIZ, Manuel** [ES/US]; 1236 Magnolia Lane, Branchburg, New Jersey 08876 (US). **YU, Younong** [CN/US]; 280

Bromley Place, East Brunswick, New Jersey 08816 (US). **ZHENG, Junying** [CN/US]; 49 Wexford Way, Bridgewater, New Jersey 08807 (US). **HUANG, Chia-yu** [US/US]; 319 Oak Lane, Princeton Junction, New Jersey 08550 (US). **LIANG, Bo** [CN/US]; 239 Bromley Place, East Brunswick, New Jersey 08816 (US). **LIU, Rong-Qiang** [US/US]; 15 Shepherd Way, Kendall Park, New Jersey 08824 (US). **LIU, Ruiyan** [US/US]; 496 Kings Road, Yardley, Pennsylvania 19067 (US). **GUISE ZAWACKI, Lisa** [US/US]; 1226 Pebble Court, Yardley, Pennsylvania 19067 (US).

(74) Agent: **RUSSELL, Mark, W.**; Schering-Plough Corporation, Patent Department, K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- with amended claims

Date of publication of the amended claims: 23 October 2008

(54) Title: 3,4-DIHYDRO-L,4-BENZOXAZINE, 3, 4-DIHYDRO-1, 4-BENZOTHIAZINE AND 1,2,3,4-TETRAHYDRO-QUINOXALINE DERIVATIVES AS ALPHA2C ADRENORECEPTOR AGONISTS

(57) Abstract: The present invention relates to a novel class of phenylmorpholine and phenyl thiomorpholine compounds useful as alpha2C adrenergic receptor agonists, pharmaceutical compositions containing the compounds, and methods of treatment, prevention, inhibition, or amelioration of one or more diseases associated with the alpha2C adrenergic receptor agonists, such as allergic rhinitis, congestion, pain, diarrhea, glaucoma, congestive heart failure, cardiac ischemia, manic disorders, depression, anxiety and schizophrenia.



WO 2008/100463 A1

3,4-DIHYDRO-1,4-BENZOXAZINE, 3,4-DIHYDRO-1,4-BENZOTHAZINE AND
1,2,3,4-TETRAHYDRO-QUINOXALINE DERIVATIVES AS ALPHA_{2C} ADRENORECEPTOR AGONISTS

Field of the Invention

The present invention relates to phenylmorpholine and phenylthiomorpholine compounds useful as α_2C adrenergic receptor agonists, pharmaceutical compositions containing the compounds, and methods of treatment and prevention using the compounds and compositions to treat disease states such as congestion (including
5 nasal congestion), migraine, congestive heart failure, cardiac ischemia, pain, glaucoma, and psychotic disorders without substantial adverse side effects associated with α_2A receptor agonist treatments.

Background of the Invention

10 The initial classification of adrenergic receptors into α - and β -families was first described by Ahlquist in 1948 (Ahlquist RP, "A Study of the Adrenergic Receptors," Am. J. Physiol. 153:586-600 (1948)). Functionally, the α -adrenergic receptors were shown to be associated with most of the excitatory functions (vasoconstriction, stimulation of the uterus and pupil dilation) and B-adrenergic receptors were implicated
15 in vasodilation, bronchodilation and myocardial stimulation (Lands et al., "Differentiation of Receptor Systems Activated by Sympathomimetic amines," Nature 214:597-598 (1967)). Since this early work, α -adrenergic receptors have been subdivided into α_1 - and α_2 -adrenergic receptors. Cloning and expression of α -adrenergic receptors have confirmed the presence of multiple subtypes of both α_1 -
20 (α_1A , α_1B , α_1D) and α_2 -(α_2A , α_2B , α_2C) adrenergic receptors (Michel et al., "Classification of α_1 -Adrenoceptor Subtypes," Naunyn-Schmiedeberg's Arch. Pharmacol, 352:1-10 (1995); Macdonald et al., "Gene Targeting--Homing in on α_2 -Adrenoceptor-Subtype Function," TIPS, 18:211-219 (1997)).

Current therapeutic uses of α_2 adrenergic receptor drugs involve the ability of
25 those drugs to mediate many of the physiological actions of the endogenous catecholamines. There are many drugs that act on these receptors to control hypertension, intraocular pressure, eye reddening and nasal congestion and induce analgesia and anesthesia.

α_2 adrenergic receptors can be found in the rostral ventrolateral medulla, and
30 are known to respond to the neurotransmitter norepinephrine and the antihypertensive

drug clonidine to decrease sympathetic outflow and reduce arterial blood pressure (Bousquet et al., "Role of the Ventral Surface of the Brain Stem in the Hypothetive Action of Clonidine," Eur. J. Pharmacol., 34:151-156 (1975); Bousquet et al., "Imidazoline Receptors: From Basic Concepts to Recent Developments," 26:S1-S6 (1995)). Clonidine and other imidazolines also bind to imidazoline receptors (formerly called imidazoline-guanidinium receptive sites or IGRS) (Bousquet et al., "Imidazoline Receptors: From Basic Concepts to Recent Developments," 26:S1-S6 (1995)). Some researchers have speculated that the central and peripheral effects of imidazolines as hypotensive agents may be related to imidazoline receptors (Bousquet et al., "Imidazoline Receptors: From Basic Concepts to Recent Developments," 26:S1-S6 (1995); Reis et al., "The Imidazoline Receptor: Pharmacology, Functions, Ligands, and Relevance to Biology and Medicine," Ann. N.Y. Acad. Sci., 763:1-703 (1995)).

Compounds which have adrenergic activity are well known in the art, and are described in numerous patents and scientific publications. The two main families of adrenergic receptor are termed alpha adrenergic receptors and beta adrenergic receptors in the art, and each of these two families is known to have subtypes, which are designated by letters of the alphabet, such as $\alpha 2A$, $\alpha 2B$, and $\alpha 2C$. It is generally known that adrenergic activity is useful for treating animals of the mammalian species, including humans, for curing or alleviating the symptoms and conditions of numerous diseases and conditions. In other words, it is generally accepted in the art that pharmaceutical compositions having an adrenergic compound or compounds as the active ingredient are useful for treating, among other things, glaucoma, chronic pain, migraines, heart failure, and psychotic disorders. It is also known that compounds having adrenergic activity, such as $\alpha 2A$ agonists, may be associated with undesirable side effects. Examples of such side effects include hyper-and hypotension, sedation, locomotor activity, and body temperature variations.

It has been discovered in accordance with the present invention that adrenergic compounds that act selectively, and preferably even specifically, as agonists of the $\alpha 2C$ or the $\alpha 2B/\alpha 2C$ (hereinafter referred to as $\alpha 2C$ or $\alpha 2B/2C$) receptor subtypes in preference over the $\alpha 2A$ receptor subtype, with adrenergic compounds that are functionally selective agonists of the $\alpha 2C$ receptor subtype in preference over the $\alpha 2A$ receptor subtype and $\alpha 2B/2C$ receptor subtype, possess desirable therapeutic properties associated with adrenergic receptors but without having one or more

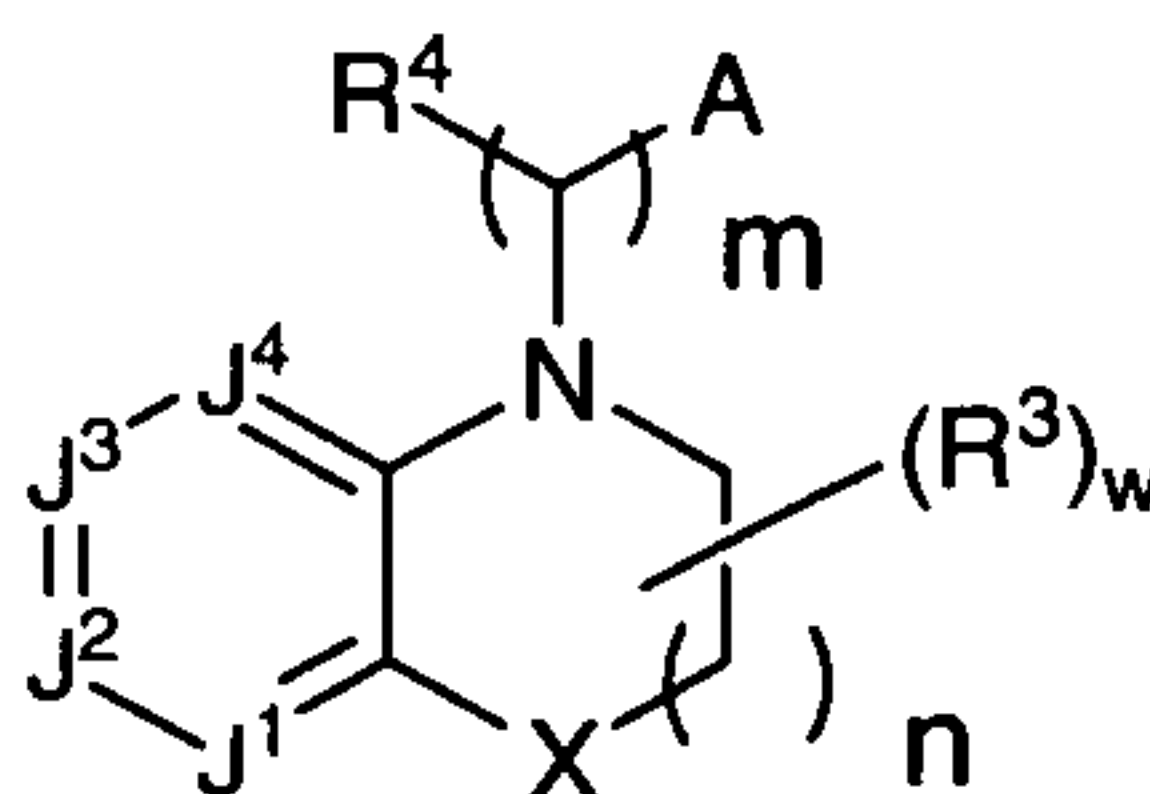
undesirable side effects such as changes in blood pressure (e.g., a hypertensive or hypotensive effect) or sedation. For the purposes of this present invention, a compound is defined to be an active agonist of the α_2C receptor subtype if the compound's efficacy at the α_2C receptor is $\geq 30\%$ E_{max} (GTP γ S assay). A compound is a functionally selective agonist of the α_2C receptor subtype over the α_2A receptor subtype if the compound's efficacy at the α_2C receptor is $\geq 30\%$ E_{max} (GTP γ S assay) and its efficacy at the α_2A receptor is $\leq 30\%$ E_{max} (GTP γ S assay).

There is a need for new compounds, formulations, treatments and therapies to treat diseases and disorders associated with α_2C adrenergic receptors. Furthermore, there is a need to develop compounds that are functionally selective for the α_2C receptor subtype with respect to the α_2A receptor subtype or the α_2B/α_2C receptor subtype. It is, therefore, an object of this invention to provide compounds useful in the treatment or prevention or amelioration of such diseases and disorders.

Summary of the Invention

In its many embodiments, the present invention provides a novel class of heterocyclic compounds as active or functionally selective α_2C adrenergic receptor agonists or metabolites, stereoisomers (e.g., enantiomers or diastereomers) salts, solvates or polymorphs thereof, methods of preparing such compounds, pharmaceutical compositions comprising one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention, inhibition or amelioration of one or more conditions associated with α_2C receptors using such compounds or pharmaceutical compositions.

In one aspect, the present application discloses a compound, or pharmaceutically acceptable salts or metabolites, solvates or polymorphs of said compound, said compound having the general structure shown in Formula I:



Formula 1

wherein:

A is a 5-membered heterocyclic ring containing 1-3 heteroatoms, and is optionally substituted with at least one R^5 and/or 1 or 2 (=O) (carbonyl) groups;

X is -O-, -S(O)_p-, or -N(R⁶)-;

J¹, J², J³, and J⁴ are independently -N-, -N(O)- or -C(R²)-, provided that 0-3 of J¹, J², J³ and J⁴ are -N-;

R² is independently selected from the group consisting of H, -OH, halo, -CN, -NO₂, -S(O)_pR⁷, -NR⁷R^{7'}, -[C(R^a)(R^b)]_qYR^{7'}, -[C(R^a)(R^b)]_qN(R⁷)YR^{7'}, C(R^a)(R^b)_qOYR^{7'}, -[C(R^a)(R^b)]_qON=CR⁷R^{7'}, -P(=O)(OR⁷)(OR^{7'}), -P(=O)NR⁷R^{7'}, and -P(=O)R⁸₂, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R⁵;

Y is selected from the group consisting of a bond, -C(=O)-, -C(=O)NR⁷-, C(=O)O-, -C(=NR⁷)-, -C(=O)-[C(R^a)(R^b)]_n-O-C(=O)-, -C(=O)N(R^c)-O-, -C(=NOR⁷)-, C(=NR⁷)NR⁷-, -C(=NR⁷)N(R^c)O-, -S(O)_p-, -SO₂NR⁷-, and -C(S)NR⁷-;

wherein R^a and R^b are independently selected from the group consisting of H, alkyl, alkoxy, and halo,

R^c is H or alkyl;

R³ is independently selected from the group consisting of H, (=O), AND halo, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R⁵, provided that when n is 3 or 4, no more than 2 of the R³ groups may be (=O);

R⁴ is independently selected from the group consisting of H, -CN, and halo, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R⁵;

R⁵ is independently selected from the group consisting of H, halo, -OH, -CN, -NO₂, -NR⁷R^{7'}, and -S(O)_pR⁷, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, -NO₂, -NR⁷R^{7'}, and -S(O)_pR⁷ substituents and/or 1 or 2 (=O) groups;

R⁶ is independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl,

heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, -NO₂, -NR⁷R^{7'}, and -S(O)_pR⁷ substituents and/or 1 or 2 (=O) groups, and -C(=O)R⁷, -C(=O)OR⁷, -C(=O)NR⁷R^{7'}, -SO₂R⁷ and -SO₂NR⁷R^{7'};

5 R⁷ is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl, groups, each of which is optionally substituted one or more times (preferably 1 to 5, more preferably 1 to 3) by R¹²;

10 R^{7'} is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl, groups, each of which is optionally substituted one or more times (preferably 1 to 5, more preferably 1 to 3) by R¹²; or

15 R⁷ and R^{7'} together with the nitrogen atom to which they are attached form a 3- to 8-membered heterocyclyl, heterocyclenyl or heteroaryl ring having, in addition to the N atom, 1 or 2 additional hetero atoms selected from the group consisting of O, N, -N(R⁹)- and S, wherein said rings are optionally substituted by 1 to 5 independently selected R⁵ moieties and/or 1 or 2 (=O) groups,

20 R⁸ is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, -NO₂, -N(R¹¹)₂, and -S(O)_pR¹¹ substituents and/or 1 or 2 (=O) groups;

25 R⁹ is independently selected from the group consisting of H, -C(O)-R¹⁰, -C(O)-OR¹⁰, and -S(O)_p-OR¹⁰ and alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, -NO₂, -N(R¹¹)₂, and -S(O)_pR¹¹ substituents and/or 1 or 2 (=O) groups; and

30 R¹⁰ is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, -NO₂, -N(R¹¹)₂, and -S(O)_pR¹¹ substituents and/or 1 or 2 (=O) groups;

R^{11} is a moiety independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, each of which is optionally substituted by at least one substituent independently selected from the group consisting of halo, -OH, -CN, -NO₂, -N(R^{11'})₂, and -S(O)_pR^{11'} and/or 1 or 2 (=O) groups;

$R^{11'}$ is independently selected from the group consisting of H, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

R^{12} is independently selected from the group consisting of H, halo, -OH, -CN, -NO₂, -N(R¹¹)₂, and -S(O)_pR¹¹ and/or 1 or 2 (=O) groups, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkenyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heterocyclyl, heterocyclenyl, heterocyclenyloxy, heterocyclylalkyl, heterocyclenylalkyl, arylalkoxy, heteroarylalkoxy, heterocyclylalkoxy, and heterocyclenylalkoxy groups, each of which in turn is optionally substituted by at least once (preferably 1 to 5, more preferably 1 to 3) by a substituent selected from the group consisting of H, alkyl, haloalkyl, halo, -OH, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, optionally substituted heterocyclenyloxy, -CN, -NO₂, -N(R¹¹)₂, and -S(O)_pR¹¹ and/or 1 or 2 (=O) groups, wherein said optionally substituted alkoxy, aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, and heterocyclenyloxy when substituted are substituted one or more (preferably 1 to 5, more preferably 1 to 3) times by R¹¹;

m is 1-5;

n is independently 1-3;

n' is independently 1-3

p is independently 0-2;

q is independently 0-6; and

w is 0-4

with the following provisos:

(a) if J¹-J⁴ are each -C(H)-, n is 1, m is 1, R⁴ is H, A is 3H-imidazol-4-yl, and X is -N(R⁶)-, then R⁶ is not -C(=O)-naphthyl;

(b) if J^1 - J^4 are each $-C(H)-$, n is 1, m is 1, R^4 is H, A is 1H-imidazol-4-yl, and X is $-N(R^6)-$, then R^6 is not $-S(O_2)$ -naphthyl; and

(c) if J^1 , J^2 , and J^4 are each $-C(H)-$, J^3 is $-C(Br)-$, n is 2, m is 1, R^3 is 3-benzyl, R^4 is H, A is 1H-imidazol-4-yl, and X is $-N(R^6)-$, then R^6 is not $-C(O_2)$ benzyl.

5 The compounds of Formula I can be useful as α_2C adrenergic receptor agonists, and can be useful in the treatment and prevention of allergic rhinitis, all types of congestion (including, but not limited to nasal congestion), migraine, congestive heart failure, cardiac ischemia, glaucoma, and psychotic disorders. Further, the compounds of Formula I can be useful in the treatment of pain (both chronic and
10 acute), such as pain that is caused by inflammation, neuropathy, arthritis (including osteo and rheumatoid arthritis), diabetes (e.g., diabetes mellitus or diabetes insipidus) or pain of an unknown origin. Examples of neuropathic pain may include but not limited to; diabetic neuropathy, neuralgia of any etiology (e.g. post-herpetic, trigeminal), chemotherapy-induced neuropathy, HIV, lower back pain of neuropathic
15 origin (e.g. sciatica), traumatic peripheral nerve injury of any etiology, central pain (e.g. post-stroke, thalamic, spinal nerve injury). Other pain that can be treated is nociceptive pain and pain that is visceral in origin or pain that is secondary to inflammation or nerve damage in other diseases. Other utilities for the inventive compounds could include stress-induced urinary incontinence and neuronal damage
20 from ischemia.

 Alternatively, the present invention provides for a method for the treatment of congestion in a mammal in need thereof which comprises administering to a mammal an effective dose of at least one compound having adrenergic activity wherein said compound is a functionally selective agonist of the α_2c receptor.

25 A further embodiment of the present invention is a method for the treatment of congestion in a mammal in need thereof which comprises administering to a mammal an effective dose of at least one compound having adrenergic activity wherein said compound is a selective agonist of the α_2c adrenergic receptor, wherein the functional selective agonist of the α_2c receptor has an efficacy that is greater than or equal to
30 30% E_{max} when assayed in the GTP γ S assay .

 Another embodiment of the present invention is a method for the treatment of congestion in a mammal in need thereof without modifying the systemic blood pressure at therapeutic doses which comprises administering to the mammal an

effective dose of at least one compound having adrenergic activity wherein said compound is a functionally selective agonist of the α_2c receptor.

Detailed Description

5 In an embodiment, the present invention discloses certain heterocyclic compounds which are represented by structural Formula I, or a pharmaceutically acceptable salt or solvate thereof, wherein the various moieties are as described above.

10 In another embodiment, if J^1 - J^4 are each $-C(H)-$, n is 1, m is 1, R^4 is H, A is 1H-imidazol-4-yl, and X is $-N(R^6)-$, then R^6 is not $-C(=O)$ -naphthyl.

In another embodiment, if J^1 - J^4 are each $-C(H)-$, n is 1, m is 1, R^4 is H, A is 1H-imidazol-4-yl, and X is $-N(R^6)-$, then R^6 is not $-S(O_2)$ -naphthyl.

15 In another embodiment, if J^1 , J^2 , and J^4 are each $-C(H)-$, J^3 is $-C(Br)-$, n is 2, m is 1, R^3 is 3-benzyl, R^4 is H, A is 1H-imidazol-4-yl, and X is $-N(R^6)-$, then R^6 is not $-C(O_2)$ benzyl.

In another embodiment, J^1 - J^4 are each $-C(R^2)-$, n is 1, A is imidazolyl, and X is $-O-$.

In another embodiment, J^1 - J^4 are each $-C(H)-$, n is 1, A is imidazolyl, and X is $-O-$.

20 In another embodiment, J^1 - J^4 are each $-C(R^2)-$, n is 1, A is imidazolyl, and X is $-N(R^6)-$.

In another embodiment, J^1 - J^4 are each $-C(R^2)-$, n is 1, A is imidazolyl, and X is $-S(O)_p-$.

In another embodiment, J^1 - J^3 are each $-C(R^2)-$, preferably $-CH-$;

25 In another embodiment, J^1 is $-N-$.

In another embodiment, J^2 is $-N-$.

In another embodiment, J^3 is $-N-$.

In another embodiment, J^4 is $-N-$.

30 In another embodiment, A is a 5-membered heterocyclic ring containing at least one ring nitrogen.

In another embodiment, A is a 5-membered heteroaryl, heterocyclyl or heterocyclenyl ring containing at least one ring nitrogen.

In another embodiment A is an optionally substituted 5-membered heteroaryl, heterocyclenyl or heterocyclyl ring. Preferred optionally substituted heteroaryl, heterocyclenyl or heterocyclyl 5-membered rings include, for example, imidazole, thiazole, pyrrole, isoxazole, oxazole, isothiazole, pyrazole, imadazoline, imidazol-2-one, imidazol-2-thione, 2-aminoimidazoline, oxazoline, oxazol-2-one, oxazol-2-thione, 2-aminooxazoline, thiazoline, thiazol-2-one, thiazol-2-thione, 2-aminothiazoline, pyrroline, pyrazoline, pyrrolidine, imidazolidine, and pyrazolidine. A more preferred set of 5-membered rings includes: imidazole, imadazoline, imidazol-2-one, imidazol-2-thione, 2-aminoimidazoline, oxazoline, oxazol-2-one, oxazol-2-thione, and 2-aminooxazoline. A most preferred set of 5-membered rings includes imidazole. Optionally substituents include any of the "ring system substituents" identified below.

In another embodiment, R^2 is independently selected from H, -OH, halo, -CN, -NO₂, -(CH₂)_qYR⁷, -(CH₂)_qN(R⁷)YR⁷, -(CH₂)_qOYR⁷, -(CH₂)_qON=CR⁷R⁷, -P(=O)(OR⁷)(OR⁷), -P(=O)(NR⁷R⁷)₂, -P(=O)R⁸₂, alkyl, alkoxy and polyhaloalkoxy.

In another embodiment R^2 is -(CH₂)_qYR⁷, -(CH₂)_qN(R⁷)YR⁷ and Y is -C(=O)-[C(R^a)(R^b)]_n-O-C(=O)- or -C(=O)N(R^c)-O-.

In another embodiment, J³ is -C(R²)-, R² is -(CH₂)_qN(R⁷)YR⁷, q = 0, Y is -C(=O)-, -C(=O)NR⁷-, or -C(=O)O-, and R⁷ is Me or Et.

In another embodiment, R³ is independently selected from H, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R⁵.

In another embodiment, R³ is independently selected from H, alkyl and haloalkyl.

In another embodiment, R⁴ is independently selected from H, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R⁵.

In another embodiment, R⁴ is independently selected from H, alkyl, allyl, and haloalkyl.

In another embodiment, R⁴ is independently selected from H and alkyl. In another embodiment, R⁵ is independently selected from H, halo, -NR⁷R⁷, -

$S(O)_pR^7$, alkyl, and alkoxy.

In another embodiment, R^6 is independently selected from H, alkyl, haloalkyl, cycloalkyl, $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^{7'}$, $-SO_2R^7$ and $-SO_2NR^7R^{7'}$.

5 In another embodiment, R^7 is independently chosen from H, alkyl, haloalkyl, cycloalkyl, aryl, and heteroaryl.

10 In another embodiment, R^7 is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted one or more times (preferably 1 to 5, more preferably 1 to 3) by R^{12} .

In another embodiment, $R^{7'}$ is independently chosen from H, alkyl, haloalkyl, cycloalkyl, aryl, and heteroaryl.

15 In another embodiment, $R^{7'}$ is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted one or more times (preferably 1 to 5, more preferably 1 to 3) by R^{12} .

20 In another embodiment, R^7 and $R^{7'}$ together with the N atom to which they are attached form a aziridine, azetidine, pyrrole, pyrrolidine, piperidine, piperazine or morpholine ring, each of which are optionally substituted by R^5 .

In another embodiment, R^8 is independently chosen from alkyl, haloalkyl, cycloalkyl, aryl, and heteroaryl.

25 In another embodiment R^{12} is independently an arylalkoxy, heteroarylalkoxy, heterocyclylalkoxy, and heterocyclenylalkoxy group, each of which in turn is optionally substituted by at least once (preferably 1 to 5, more preferably 1 to 3) by a substituent selected from the group consisting of H, alkyl, haloalkyl, halo, -OH, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, optionally substituted heterocyclenyloxy, -CN, -NO₂, -N(R^{11})₂, and $-S(O)_pR^{11}$, wherein said optionally substituted alkoxy, aryloxy, 30 optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, and heterocyclenyloxy when substituted are substituted one or more (preferably 1 to 5, more preferably 1 to 3) times by R^{11} .

In another embodiment R^{12} is independently selected from the group consisting of H, halo, -OH, -CN, -NO₂, -N(R¹¹)₂, and -S(O)_pR¹¹, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkenyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heterocyclyl, heterocyclenyl, heterocyclenyloxy, heterocyclylalkyl, heterocyclenylalkyl, groups, each of which in turn is optionally substituted by at least once (preferably 1 to 5, more preferably 1 to 3) by a substituent selected from the group consisting of H, alkyl, haloalkyl, halo, -OH, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, optionally substituted heterocyclenyloxy, -CN, -NO₂, -N(R¹¹)₂, and -S(O)_pR¹¹, wherein said optionally substituted alkoxy, aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, and heterocyclenyloxy when substituted are substituted one or more (preferably 1 to 5, more preferably 1 to 3) times by R¹¹.

In another embodiment J¹, J² and J⁴ are -CH-; X is -O- or -S-; m is 1 and n is 1 or 2.

In another embodiment R² is -(CH₂)_qYR⁷, or -(CH₂)_qN(R⁷)YR⁷, Y is -C(=O)-[C(R^a)(R^b)]_n-O-C(=O)-, n is 1 or 2, and R^a and R^b are independently H or alkyl (preferably methyl or ethyl).

In another embodiment, A is an optionally substituted imidazole;

R² is -(CH)_qN(R⁷)Y(R⁷);

Y is -C(=O)O-, -(C=O)N(R^c)-O- or -C(O)NR⁷; and

R⁷ is independently selected from the group consisting of H, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl, said groups being optionally substituted one or more times by a substituent independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, halo, -OH, -CN, -NO₂, -N(R¹¹)₂, -S(O)_pR¹¹, optionally substituted aryl, optionally substituted aryloxy and optionally substituted heteroaryloxy, said optionally substituted optionally substituted aryl, optionally substituted aryloxy and optionally substituted heteroaryloxy when substituted are independently substituted one or more times by a substituent selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, halo, -OH, NO₂, -N(R¹¹)₂ and -S(O)_pR¹¹.

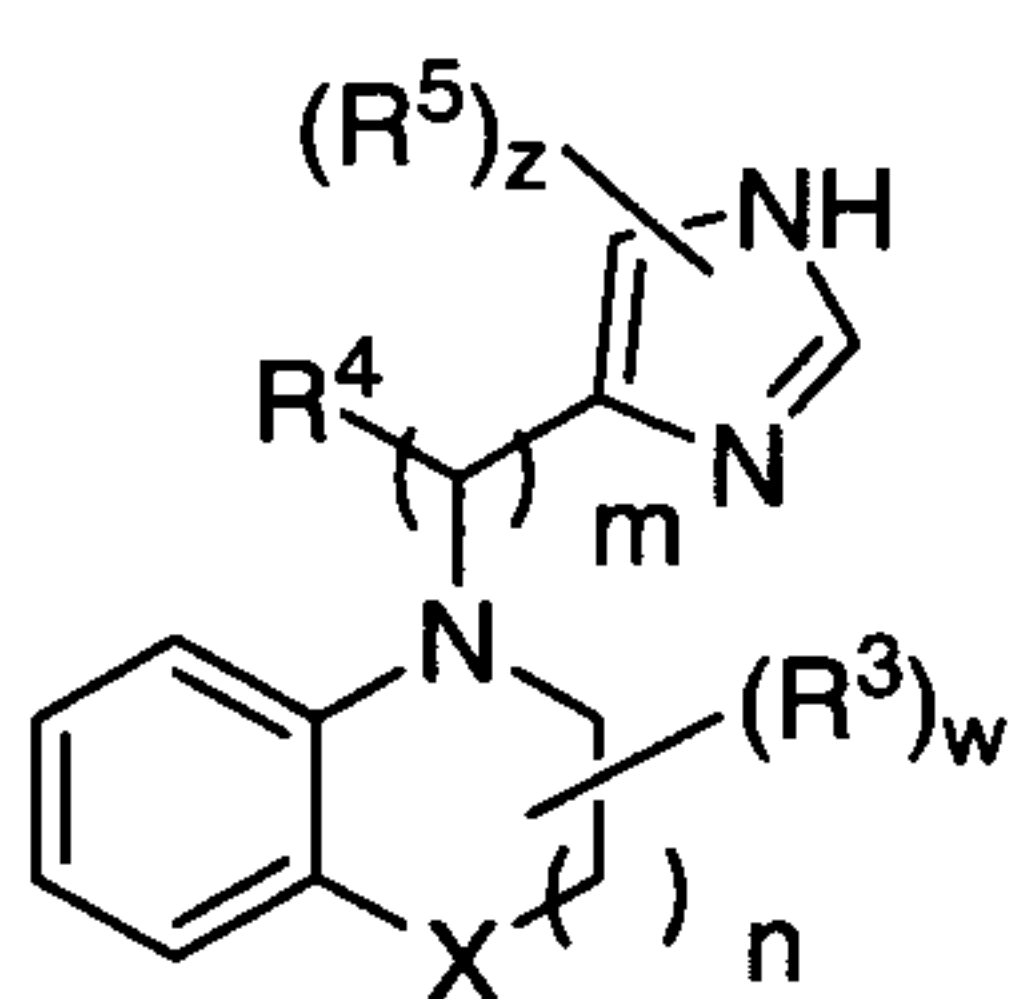
In another embodiment, m is 1 or 2.

In another embodiment, n is 1 or 2.

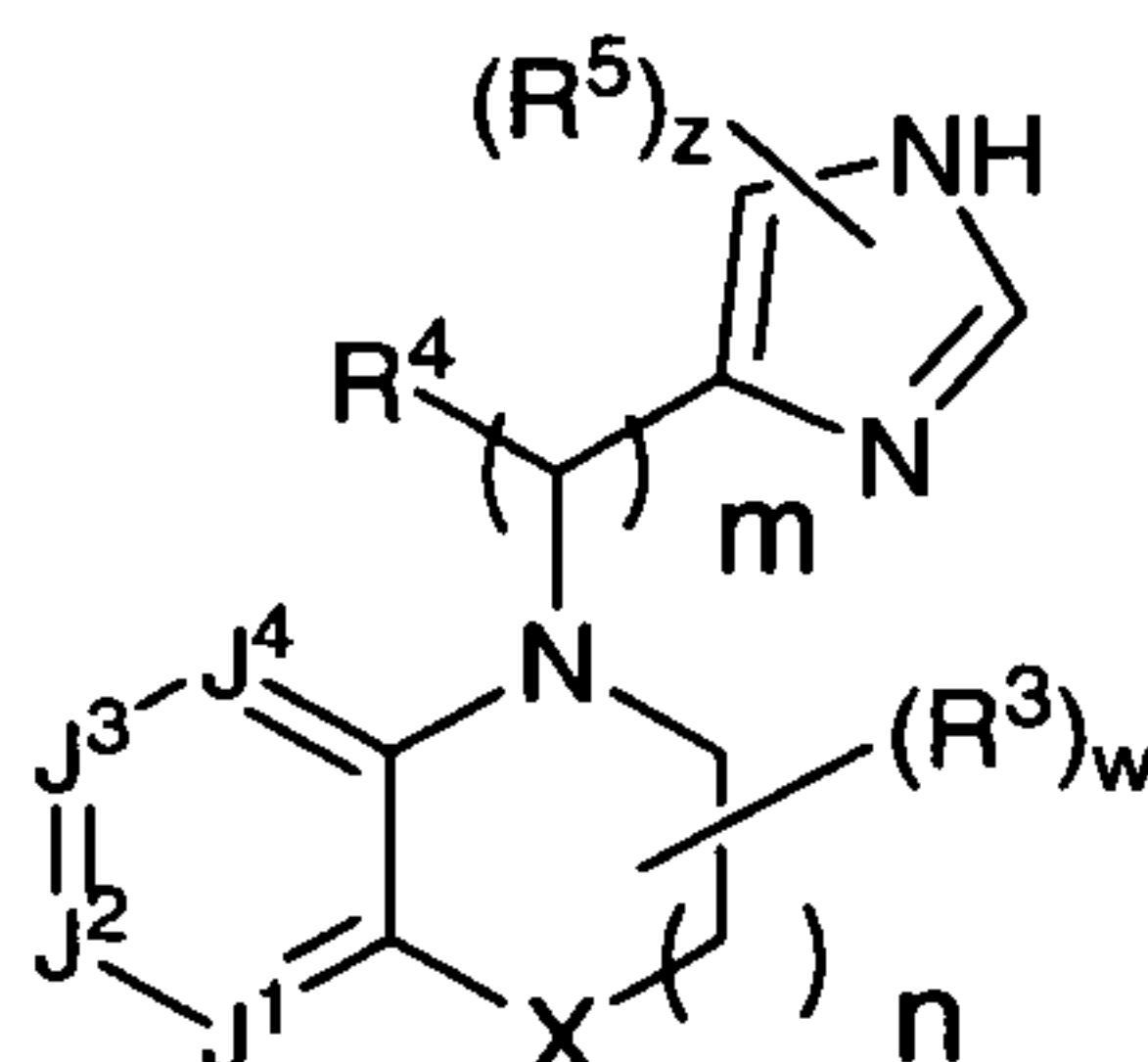
In another embodiment, n is 1.

In another embodiment, q is 0, 1, 2, or 3.

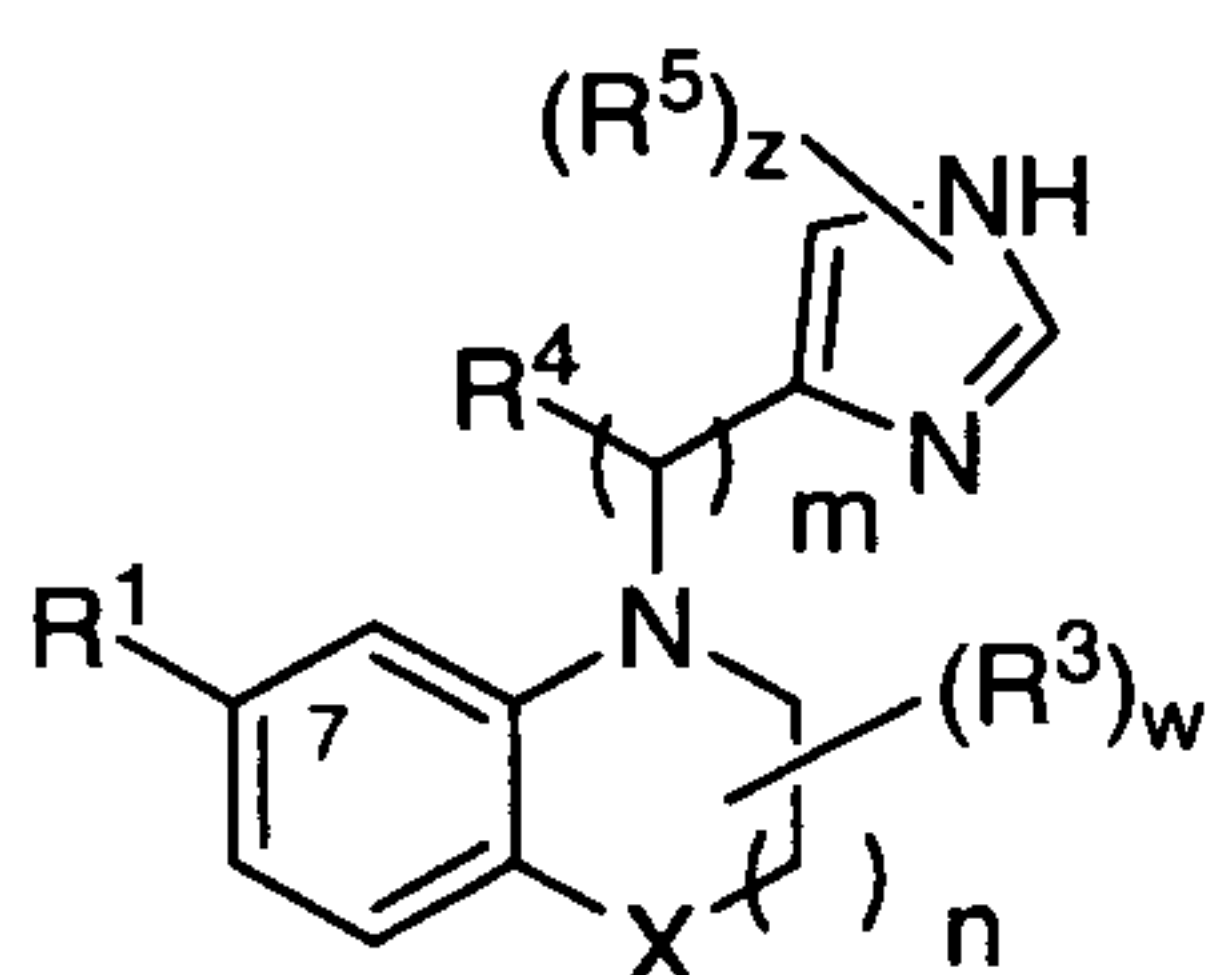
In another embodiment, the present invention discloses compounds which are represented by structural formulae II-V or a pharmaceutically acceptable salt, solvate
5 or ester thereof, wherein the various moieties are as described above:



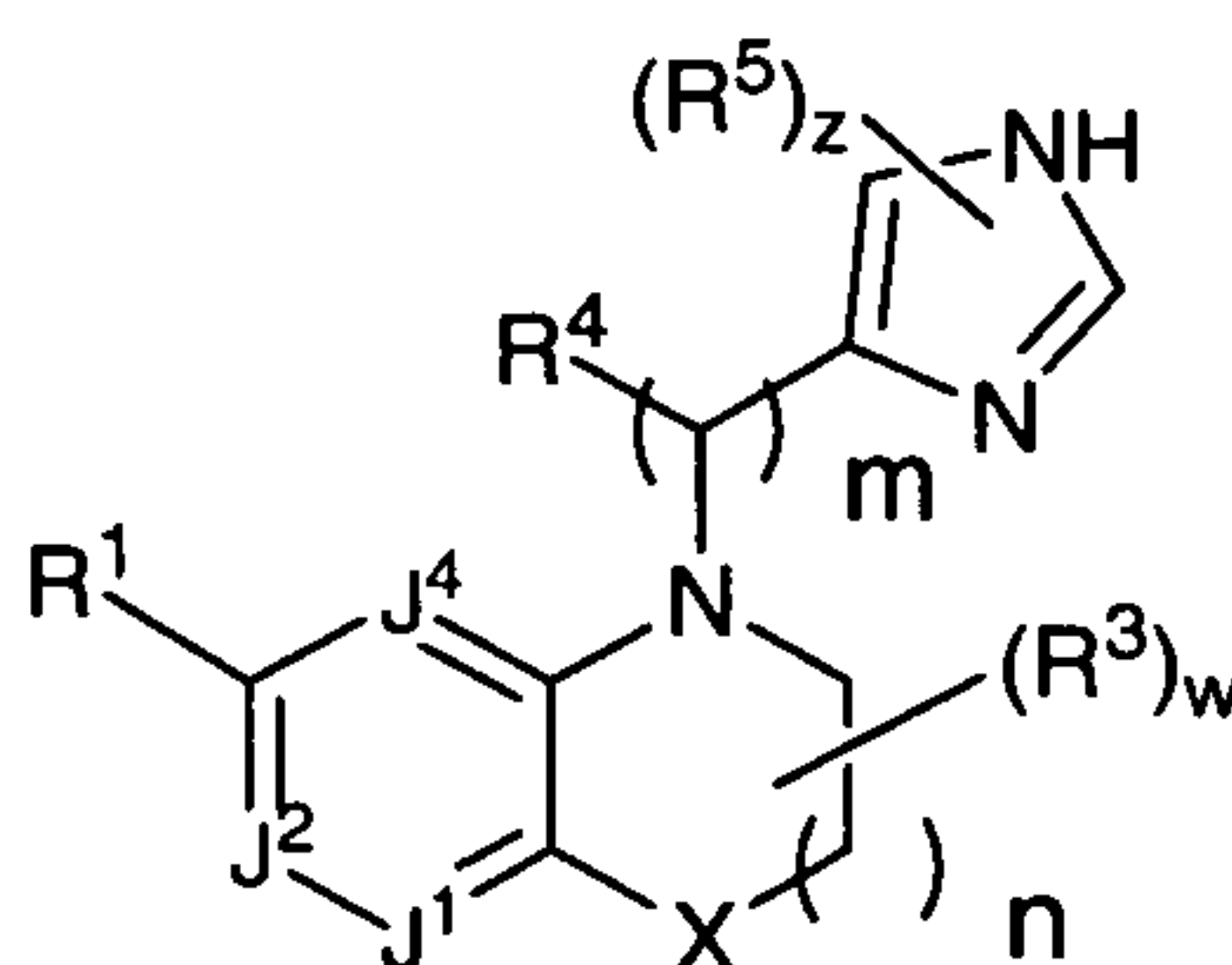
Formula II



Formula III



Formula IV



Formula V

wherein z is 0-3 and R¹ is selected from the group consisting of H, -OH, halo, -CN, -NO₂, -SR⁷, -S(O)_pR⁷, -(CH₂)_qYR⁷, -(CH₂)_qN(R⁷)YR⁷, -(CH₂)_qOYR⁷, -
10 (CH₂)_qON=C NR⁷R⁷, -P(=O)(OR⁷)(OR⁷), -P(=O)(NR⁷R⁷)₂, -P(=O)R⁸₂ and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R⁵.

In another embodiment in the above formulae R¹ is -(CH₂)_qYR⁷, or
15 -(CH₂)_qN(R⁷)YR⁷.

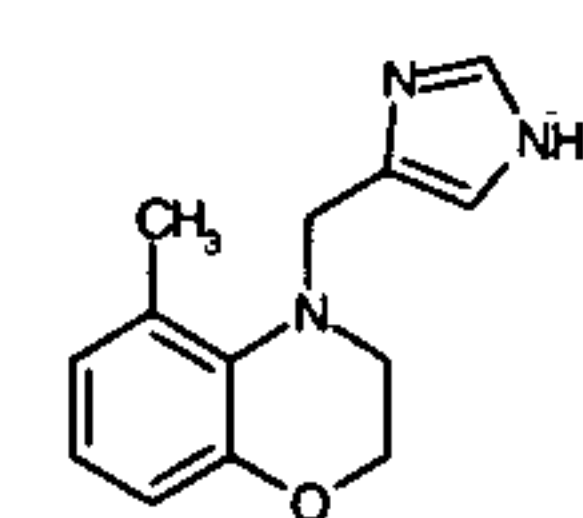
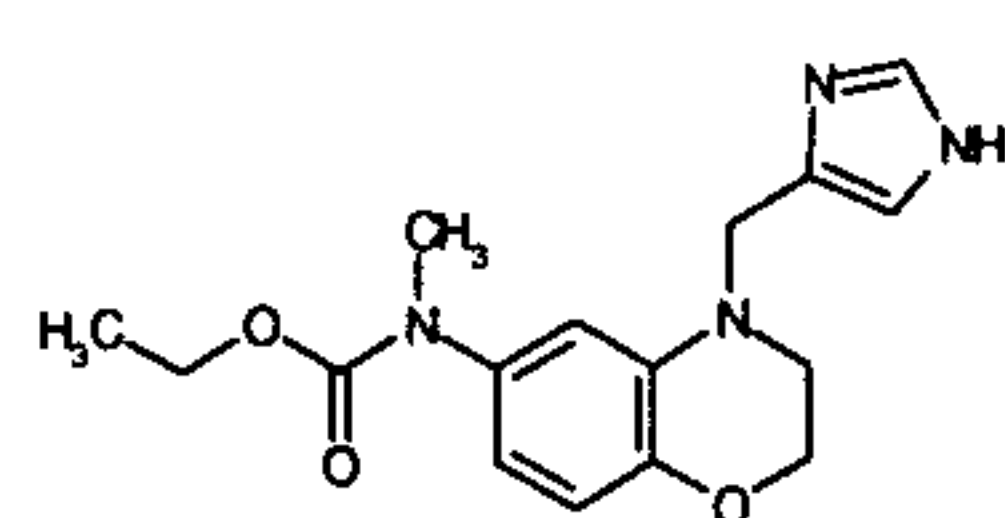
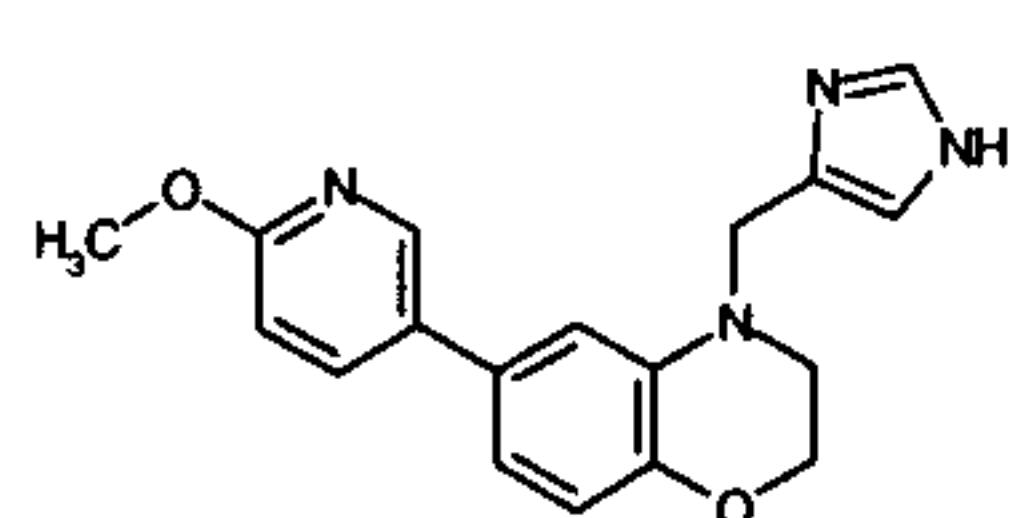
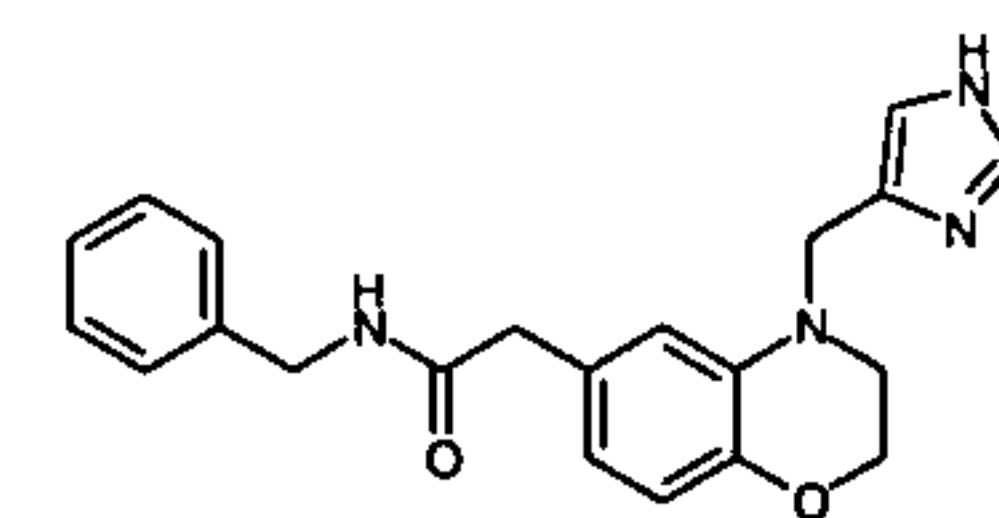
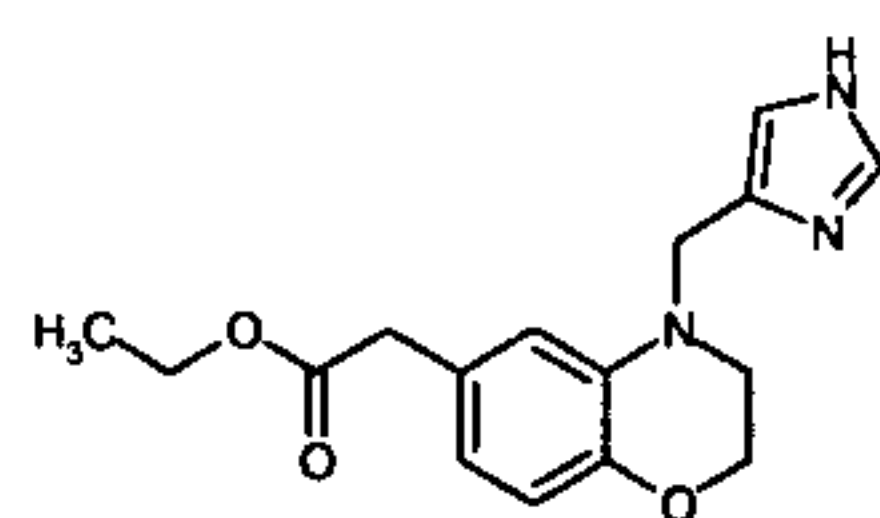
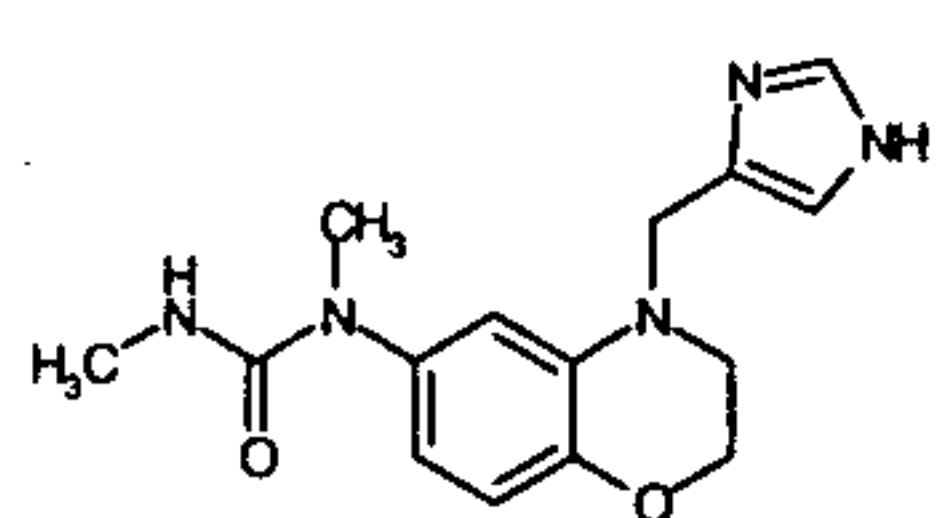
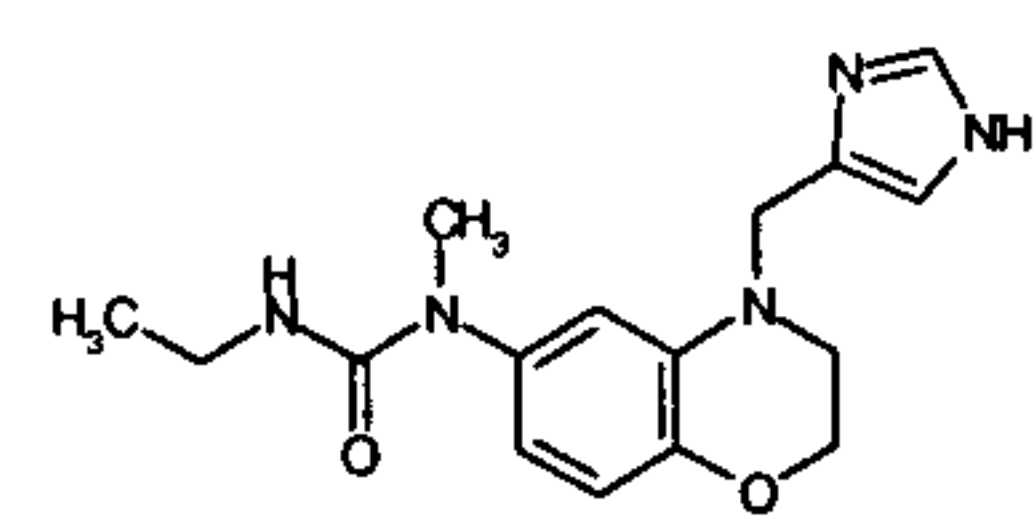
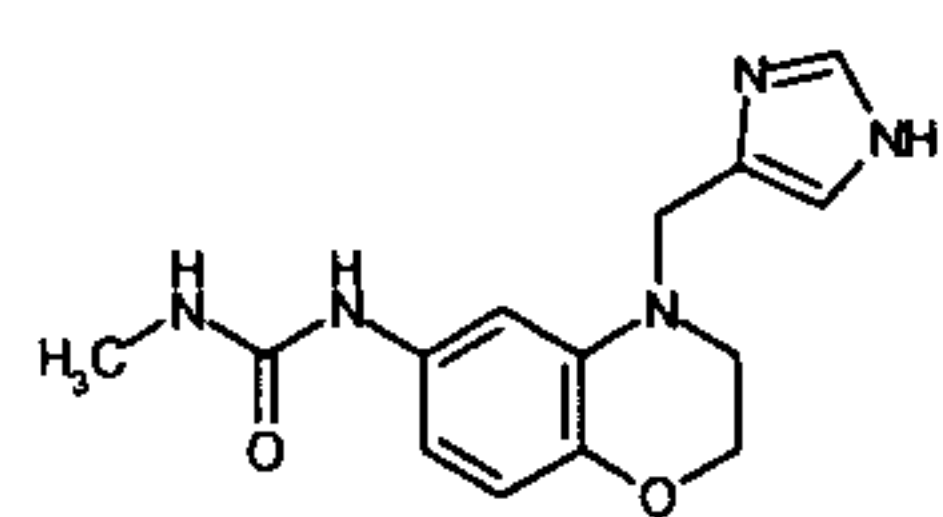
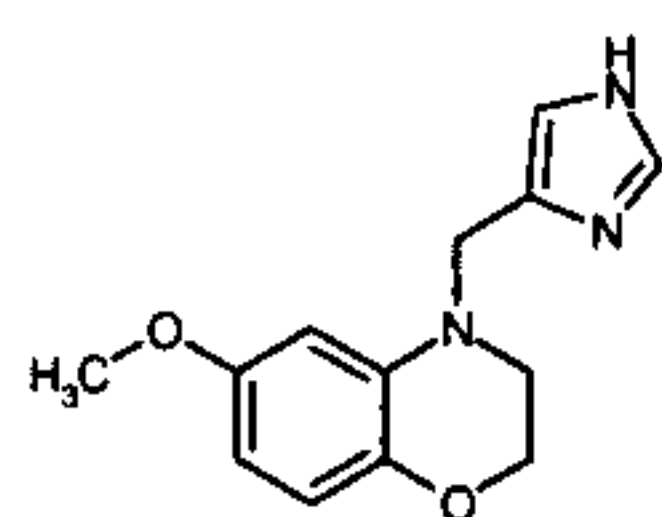
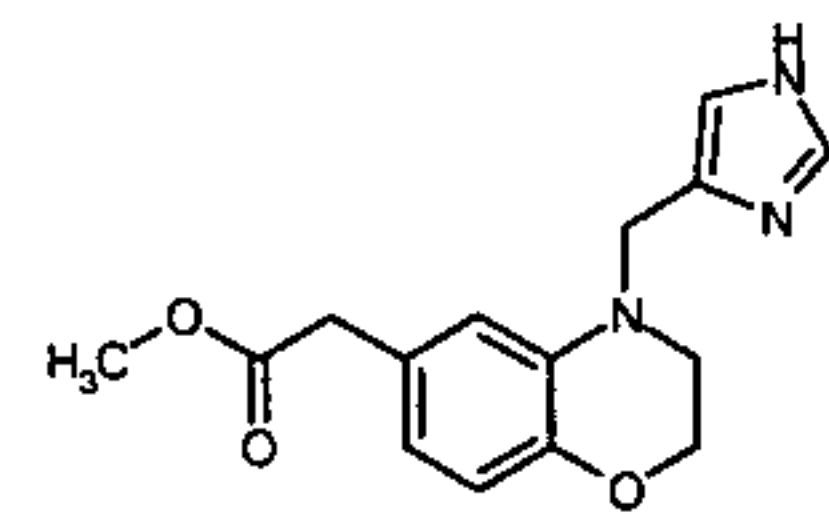
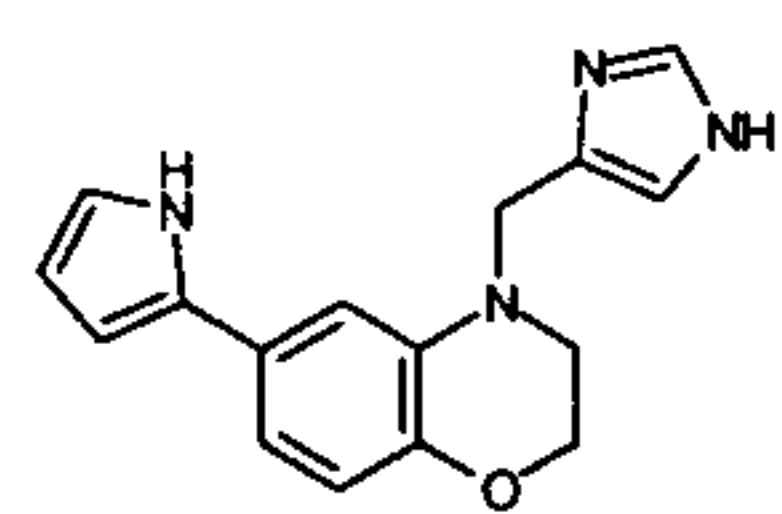
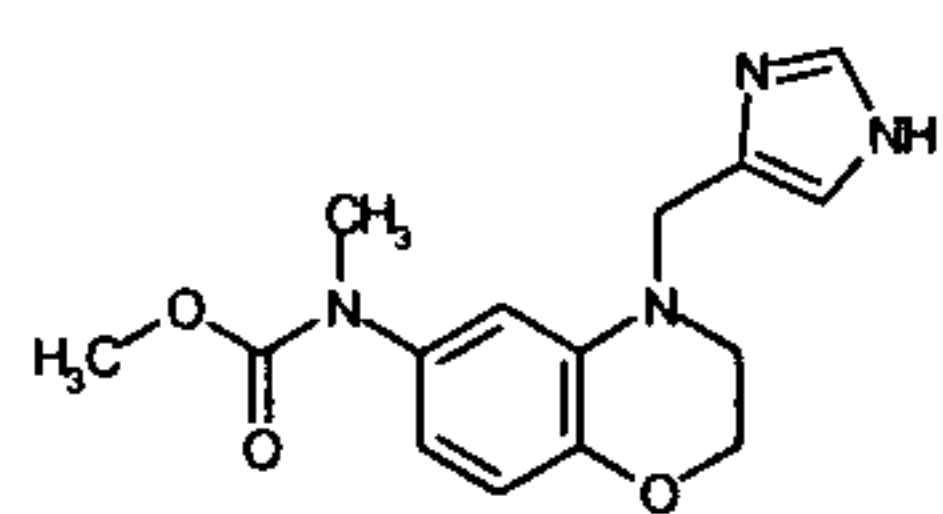
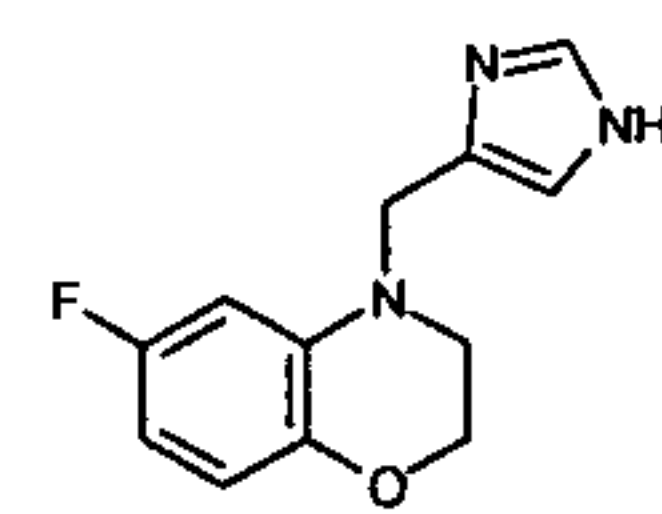
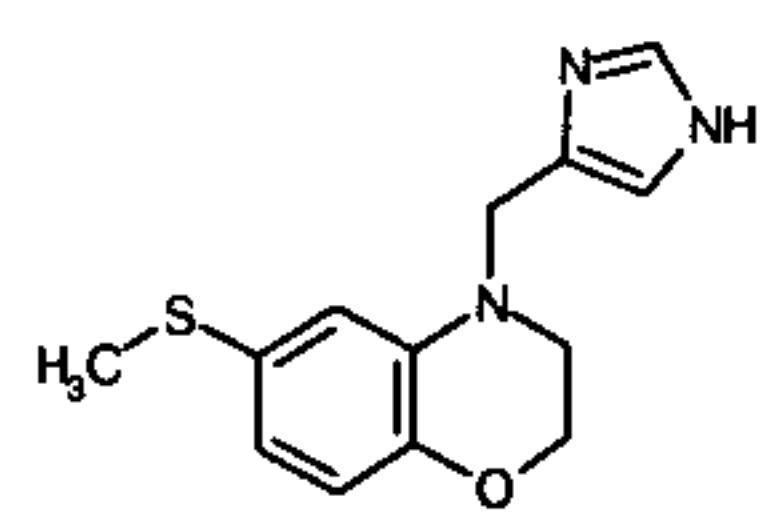
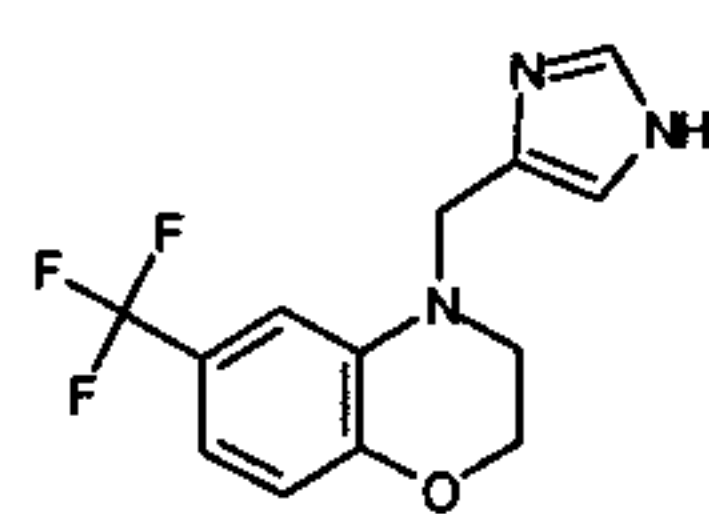
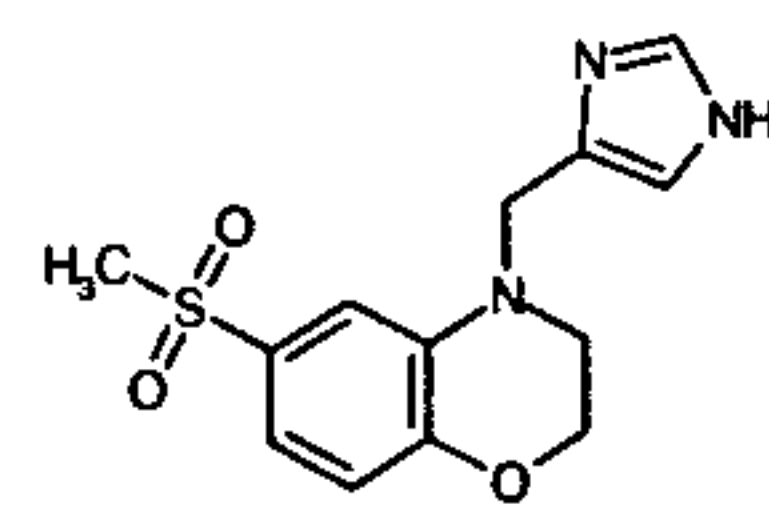
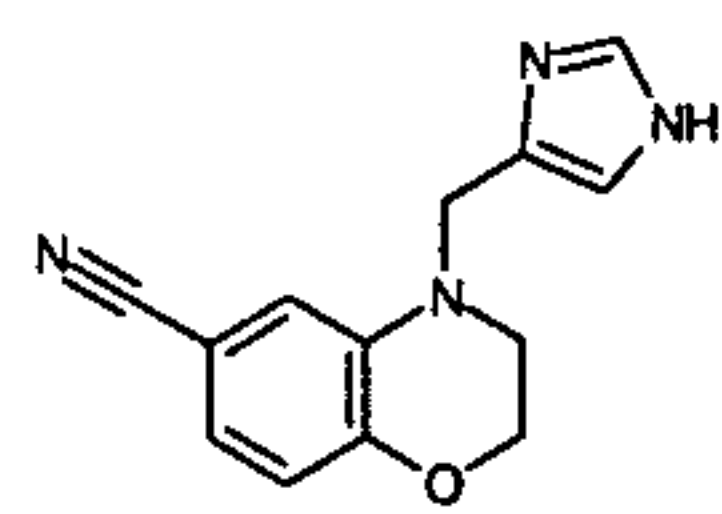
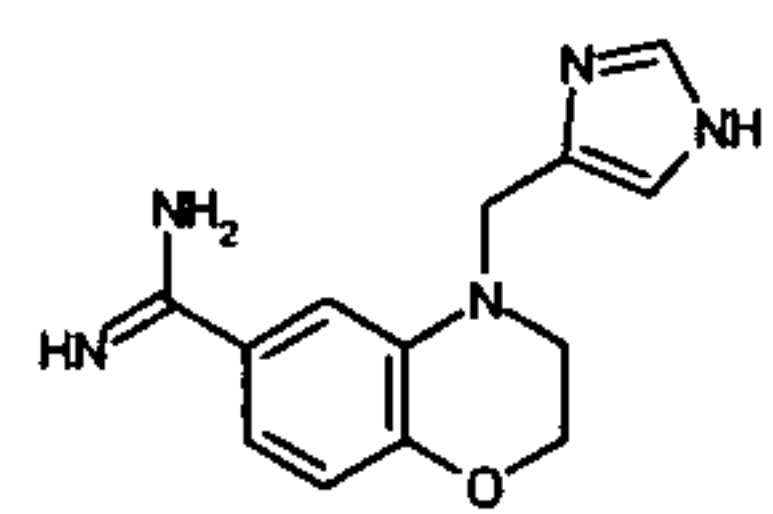
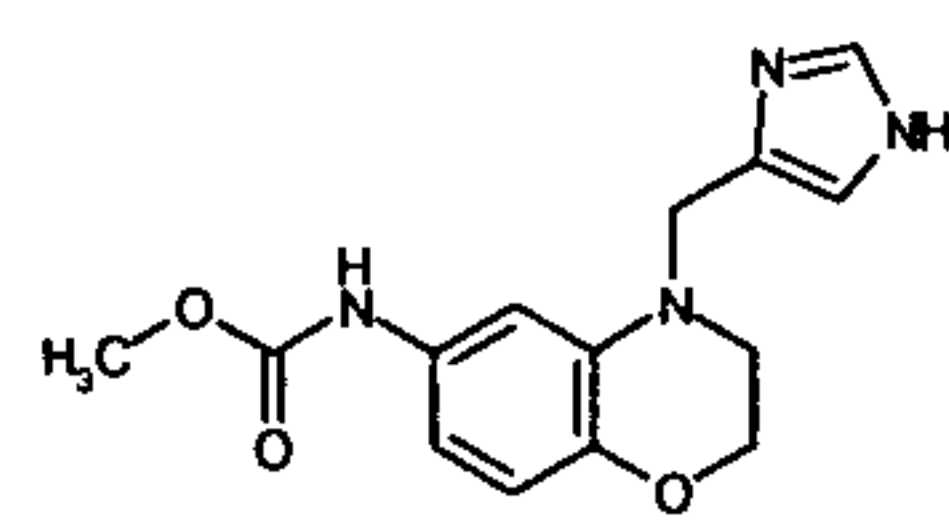
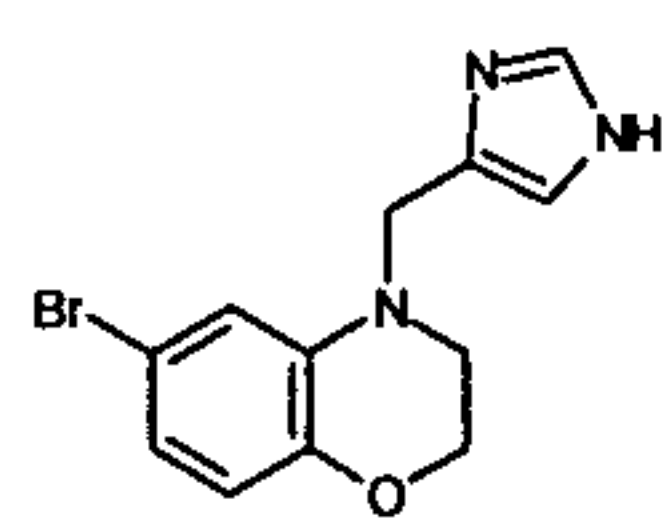
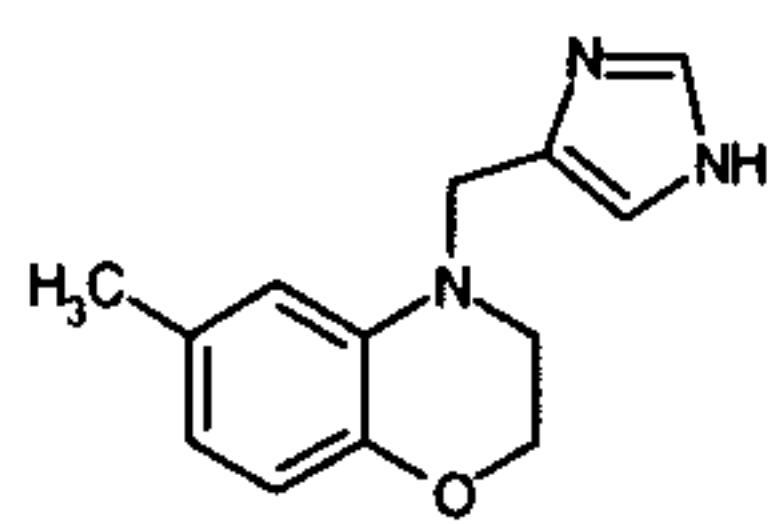
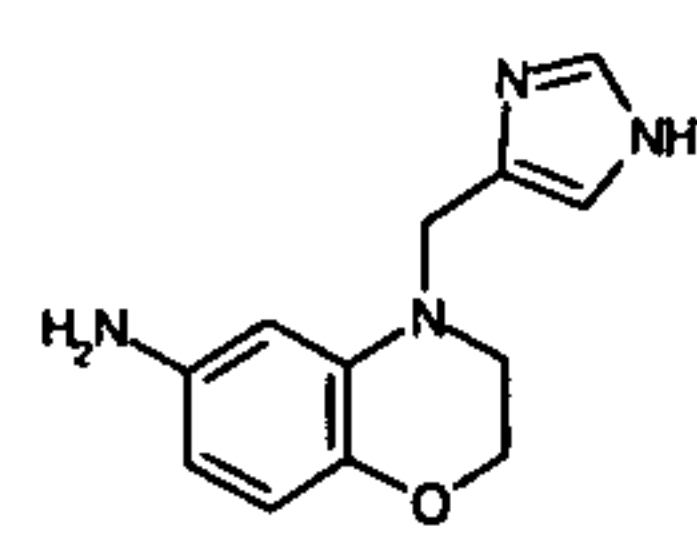
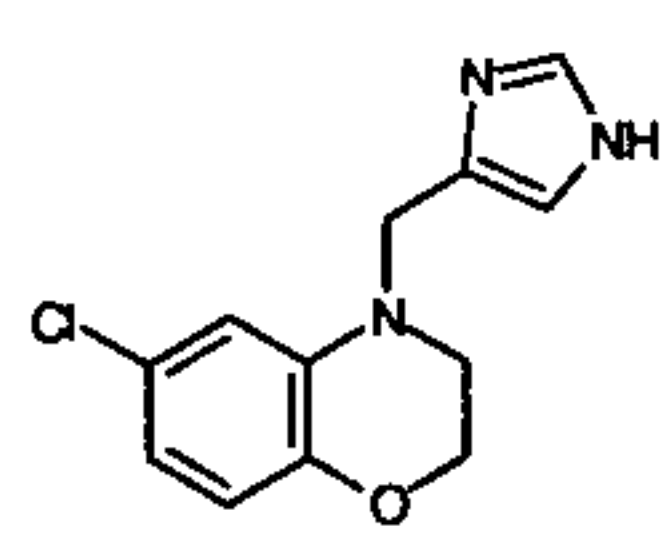
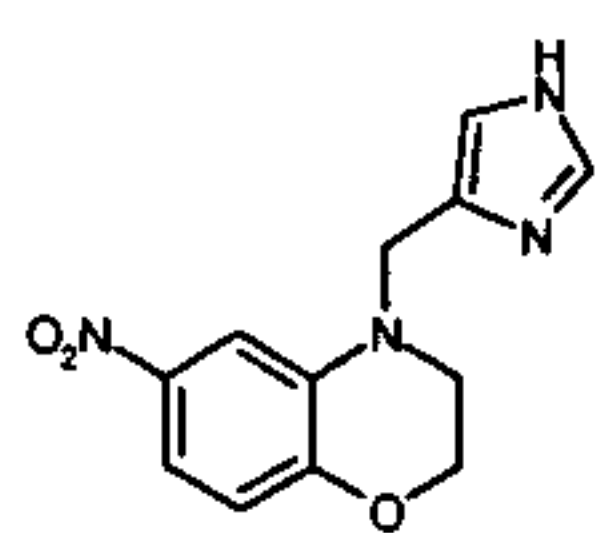
In another embodiment in the above formulae, Y is -(=O)O- or -(C=O)NR⁷.

In another embodiment in the above formulae, Y is -C(=O)-[C(R^a)(R^b)]_n-O-C(=O)-.

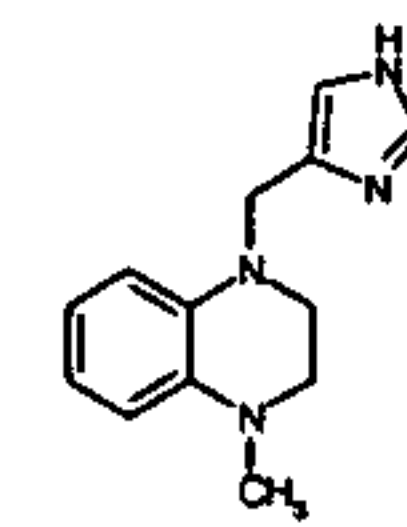
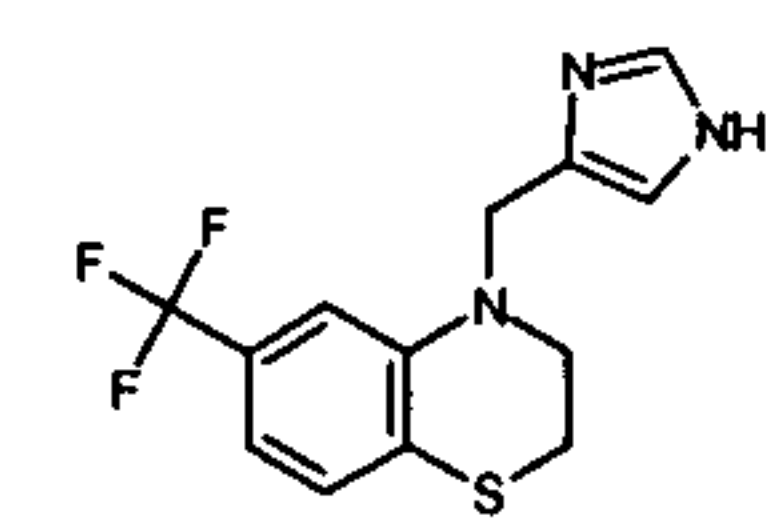
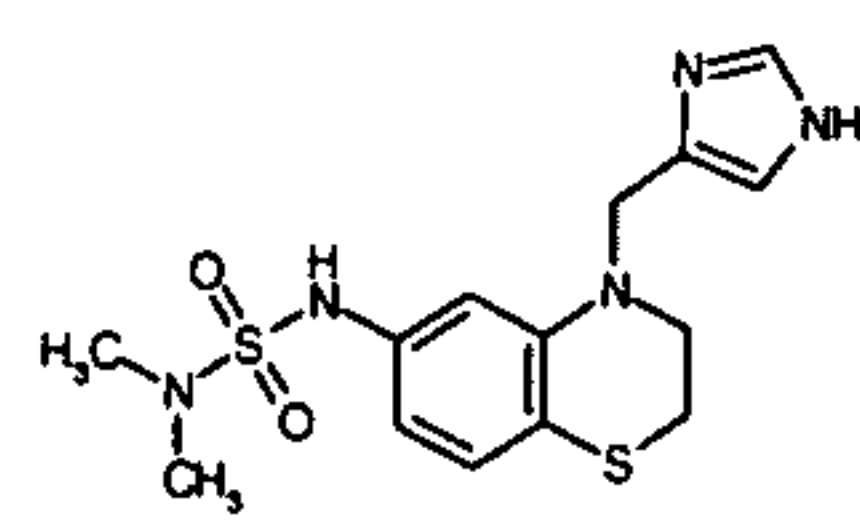
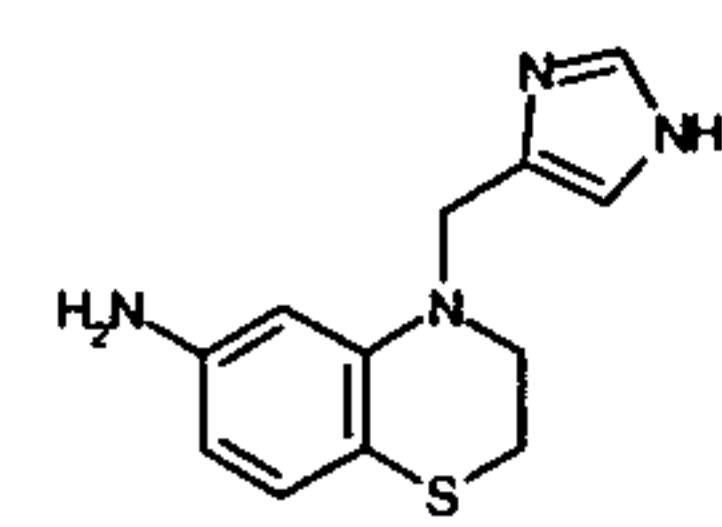
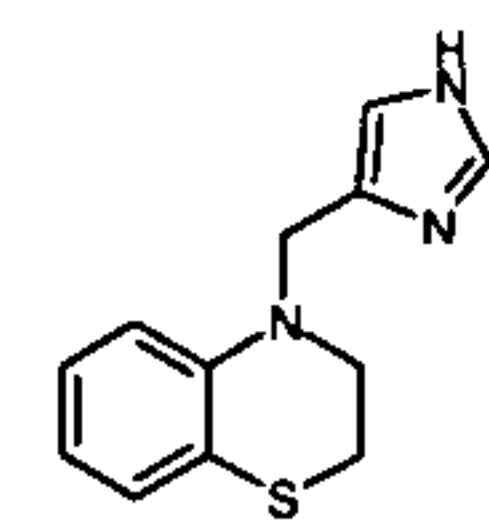
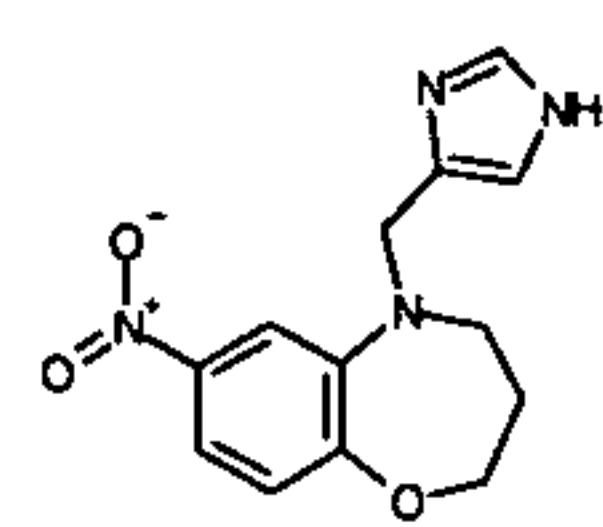
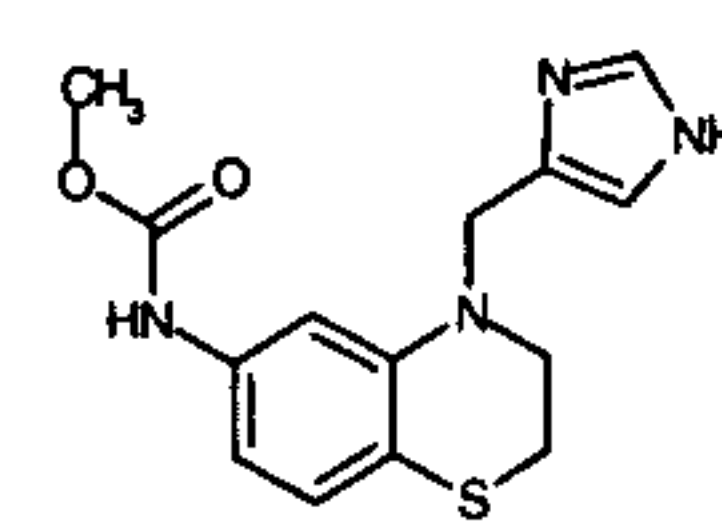
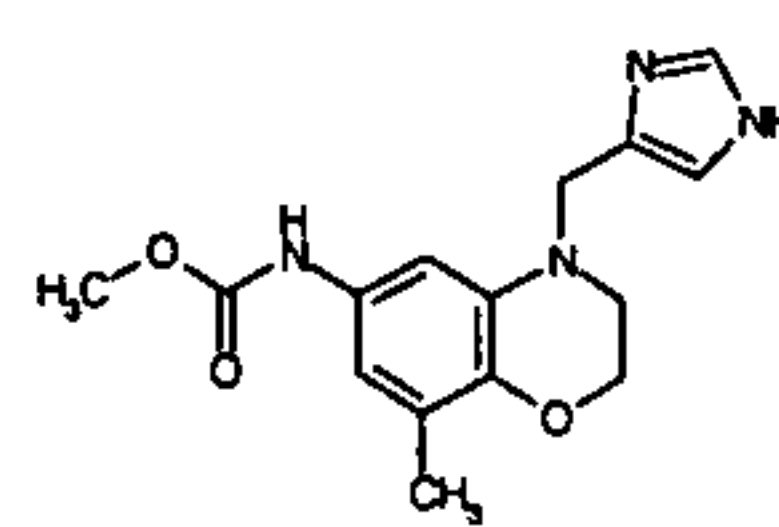
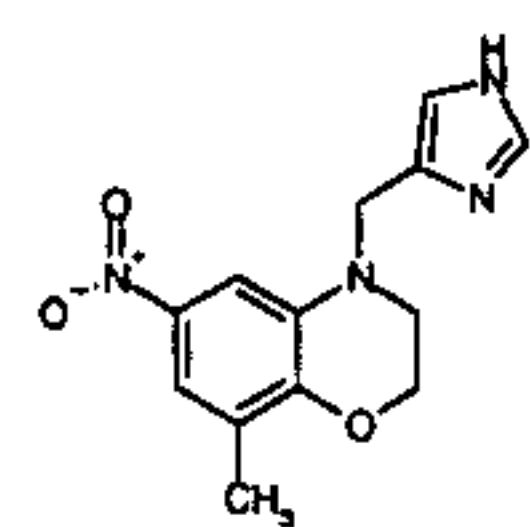
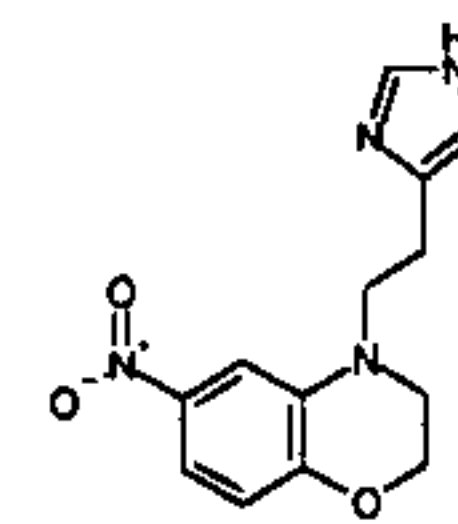
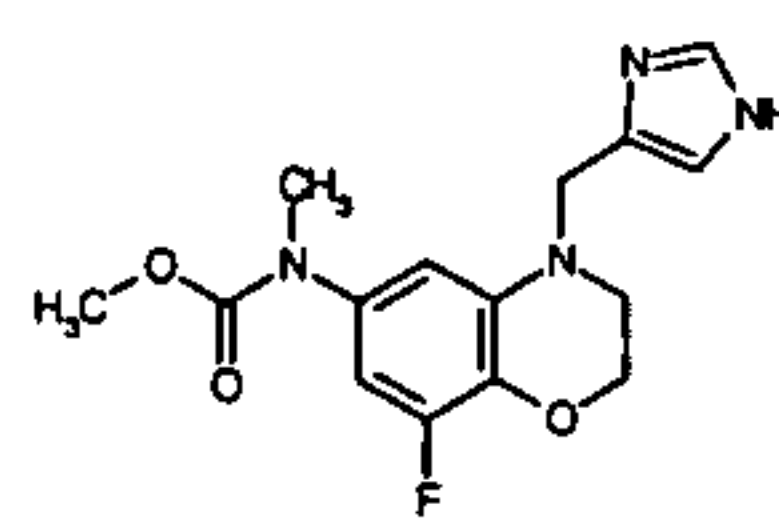
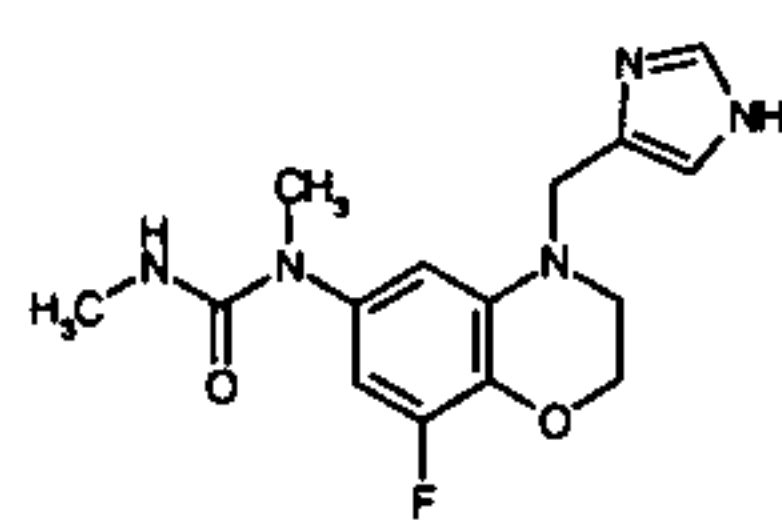
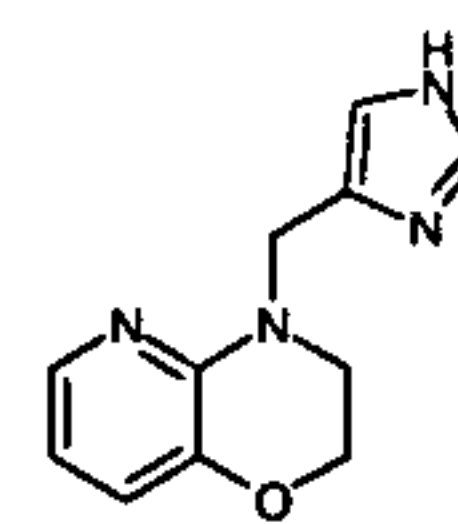
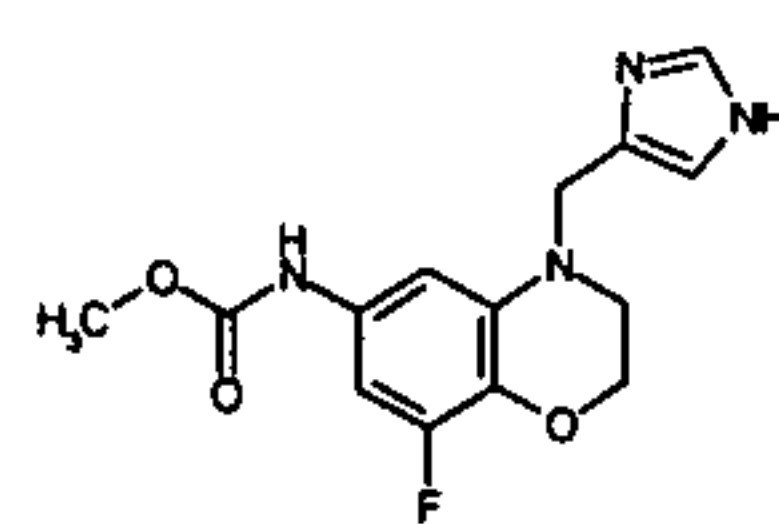
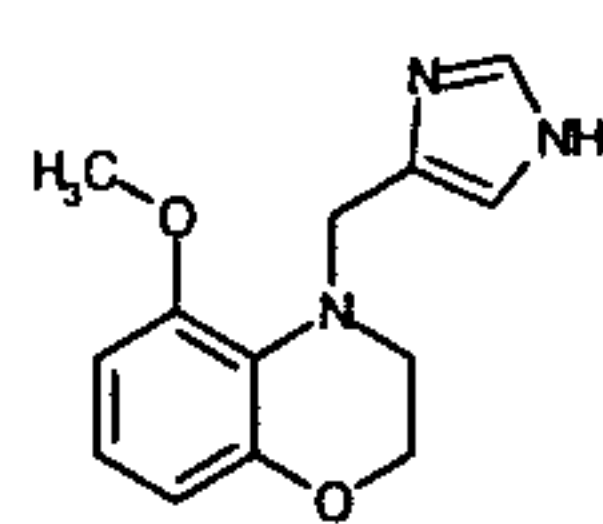
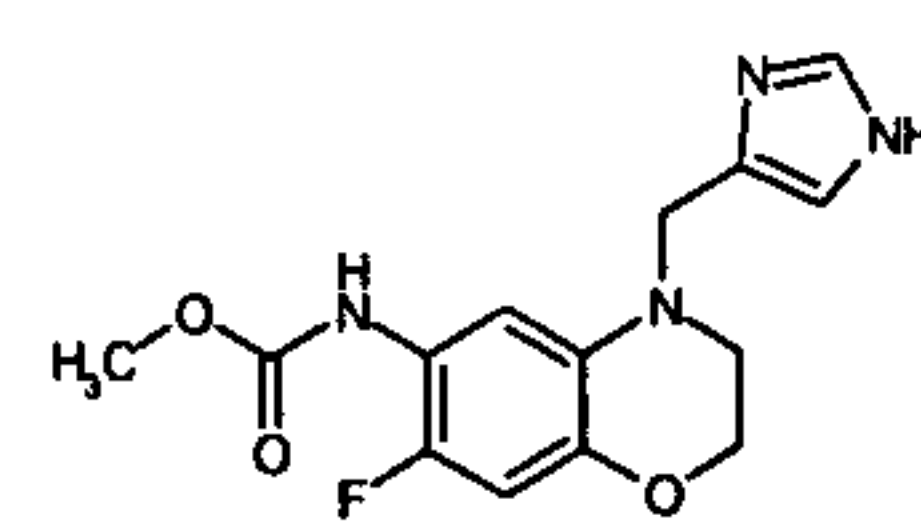
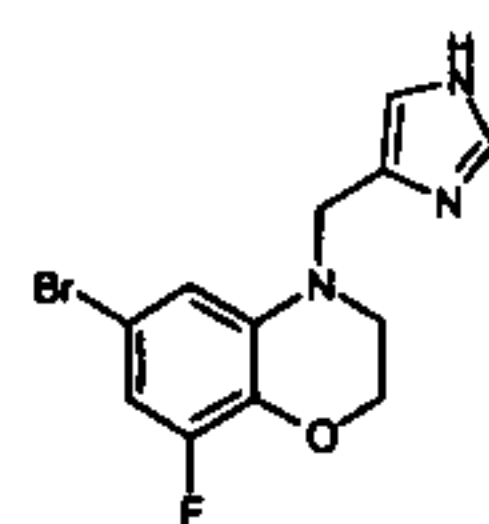
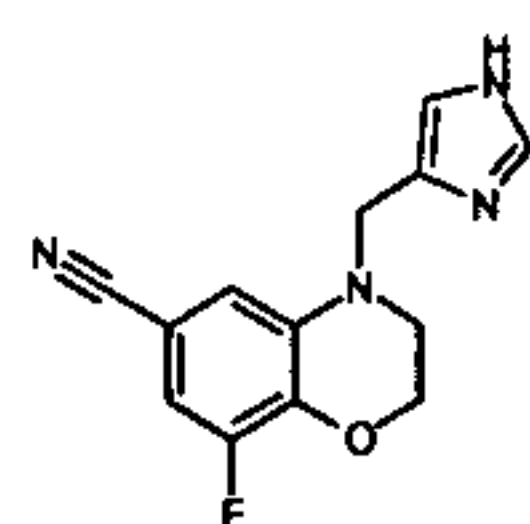
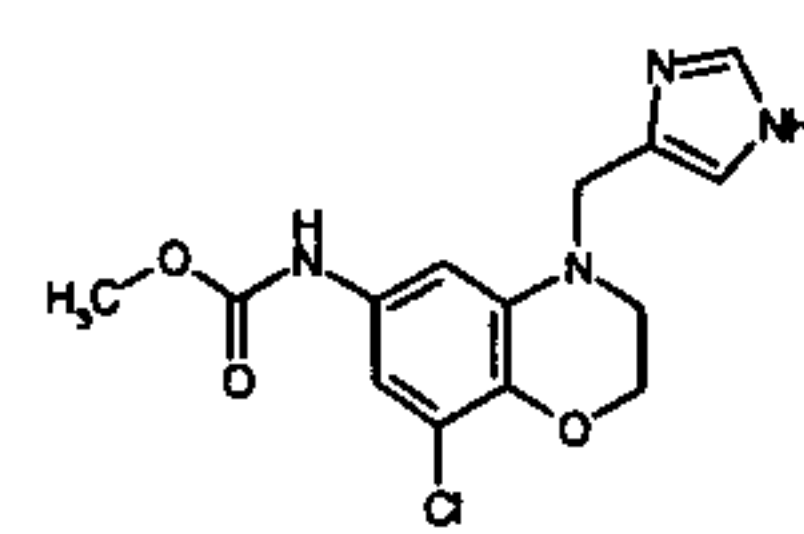
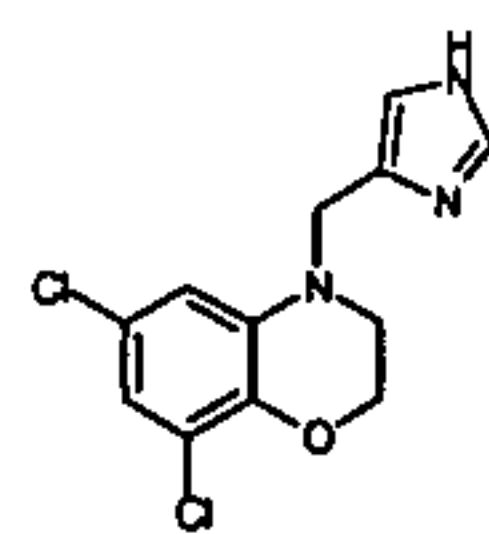
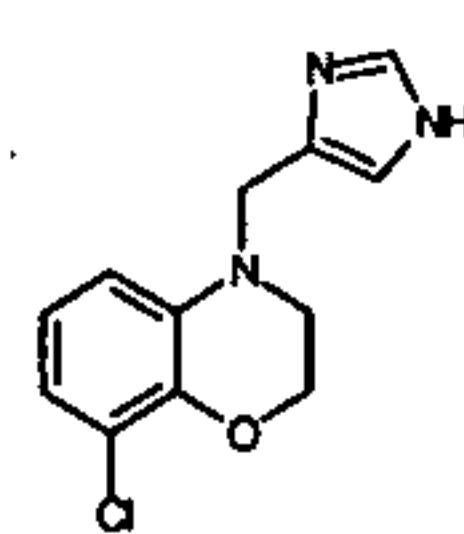
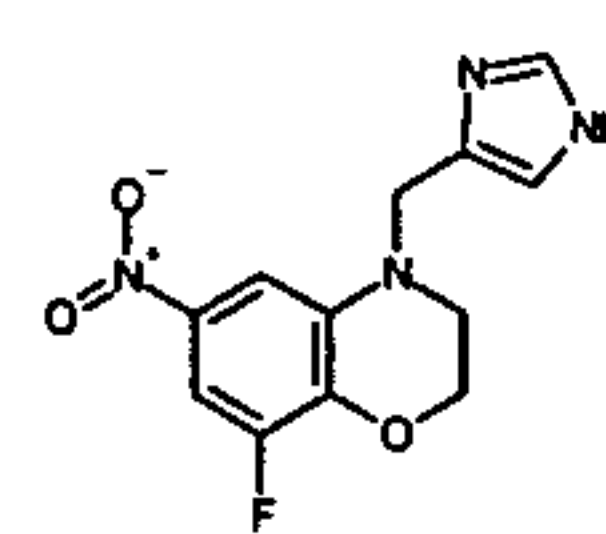
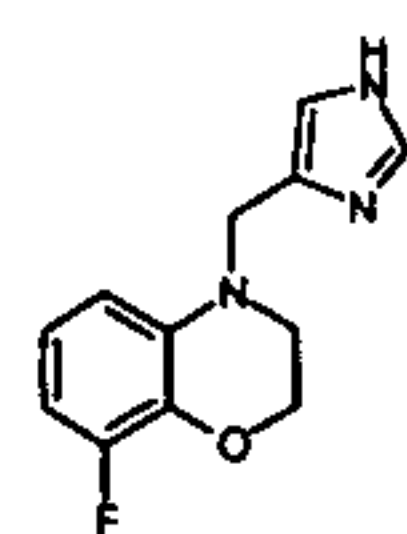
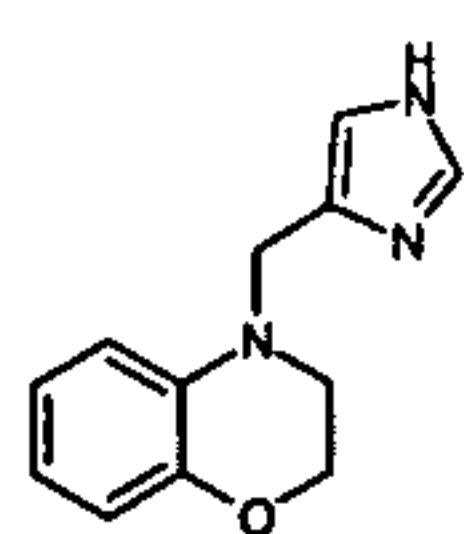
In another embodiment in the above formulae R¹ is -(CH₂)_qN(R⁷)YR⁷ and Y is -C(=O)N(R^c)-O-.

20 An inventive group of compounds is shown in below:

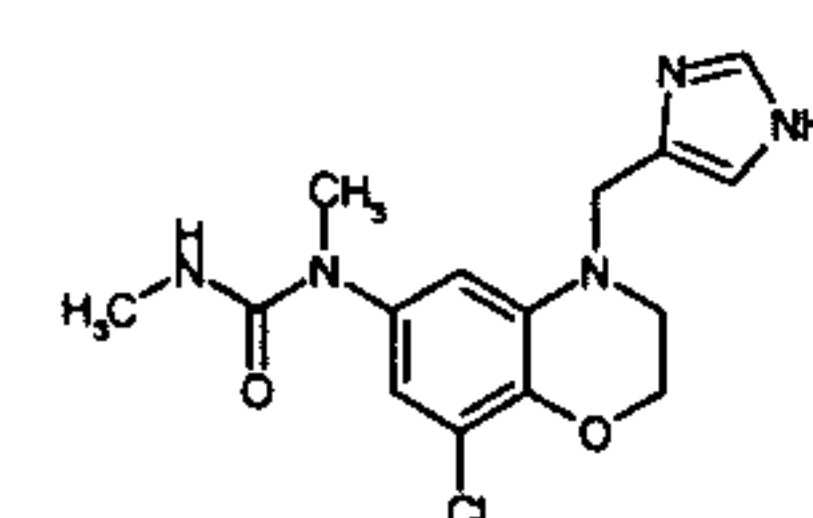
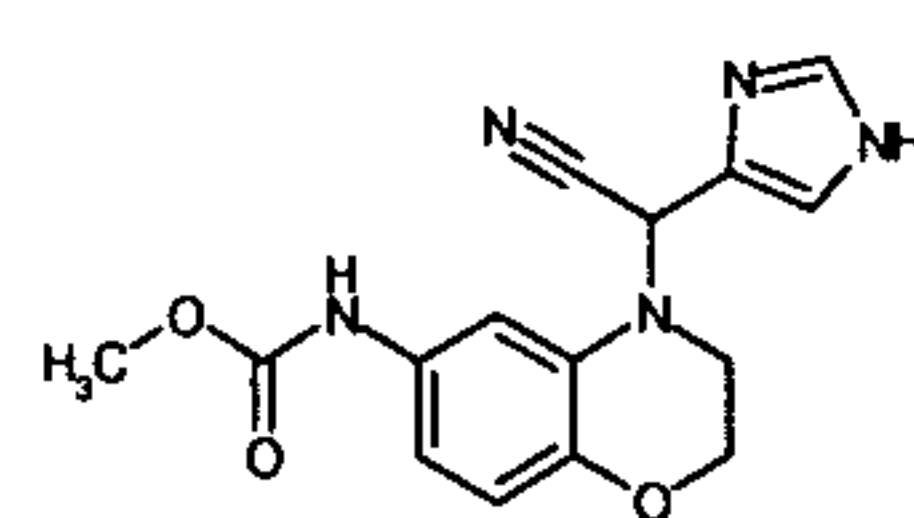
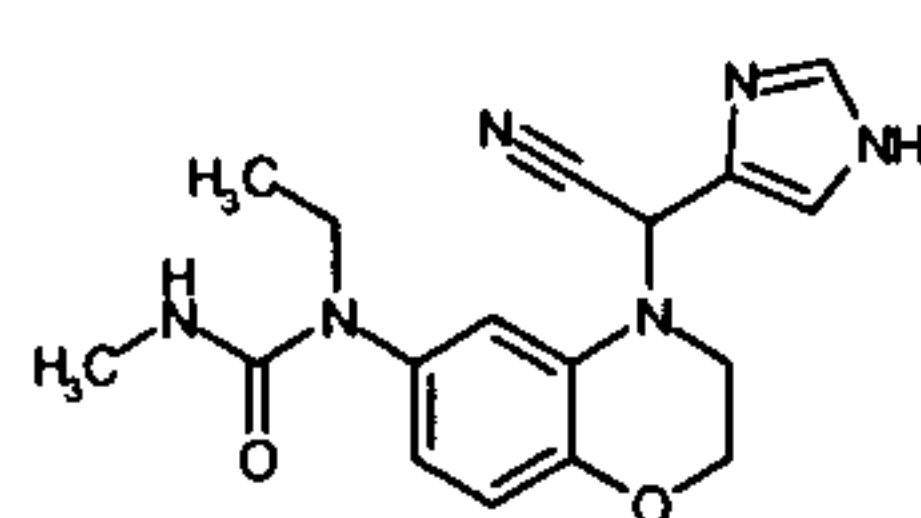
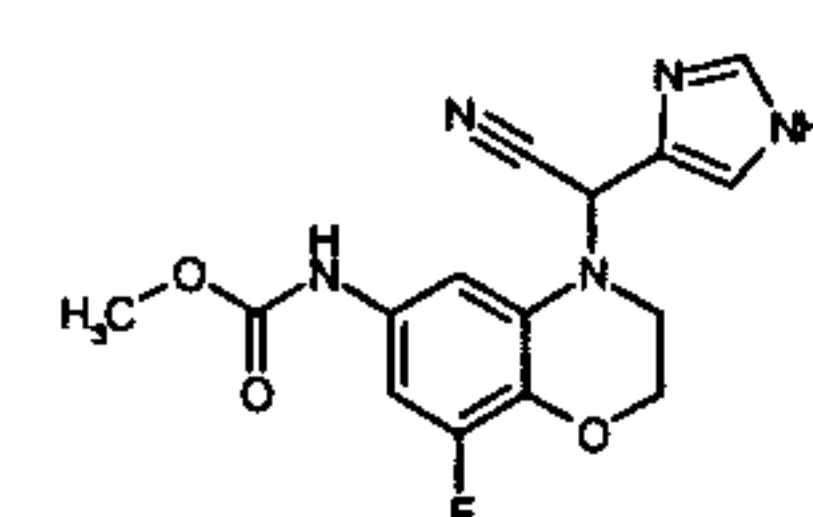
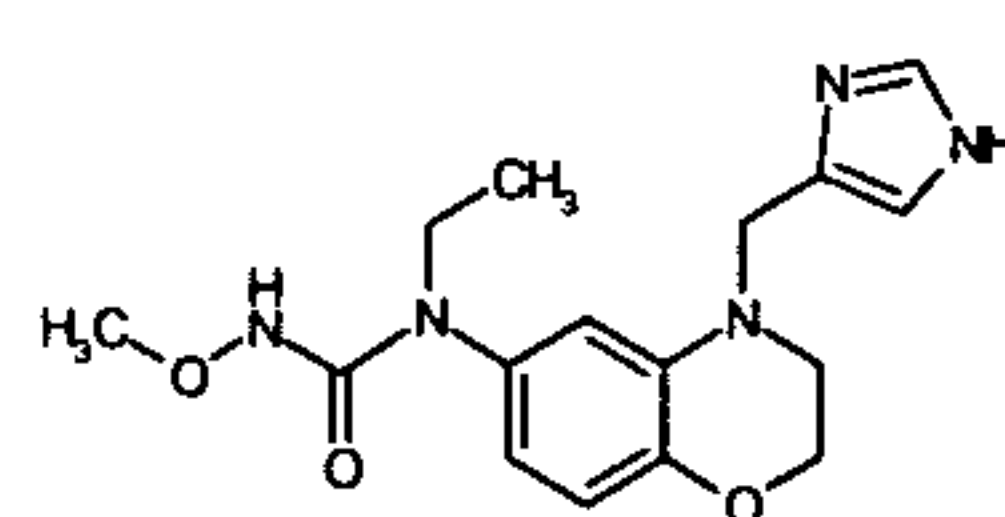
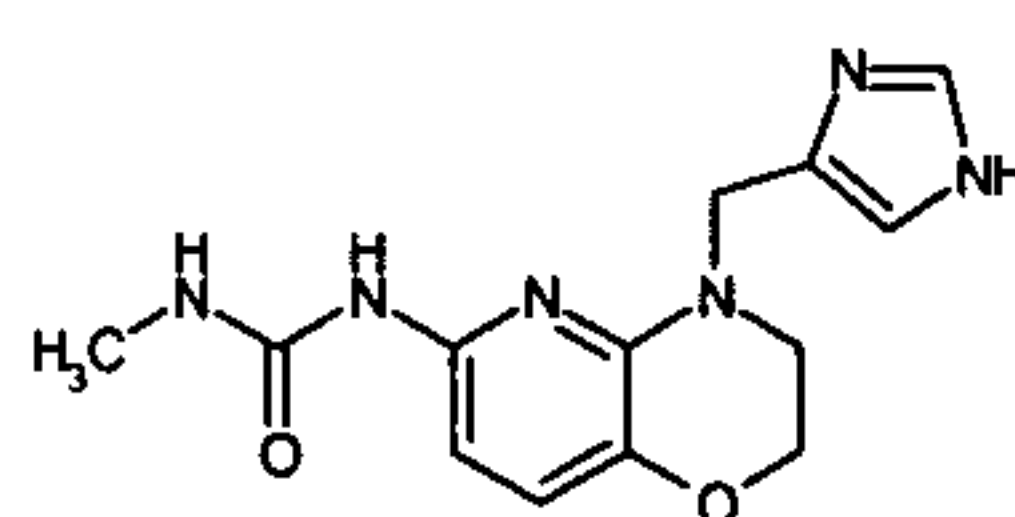
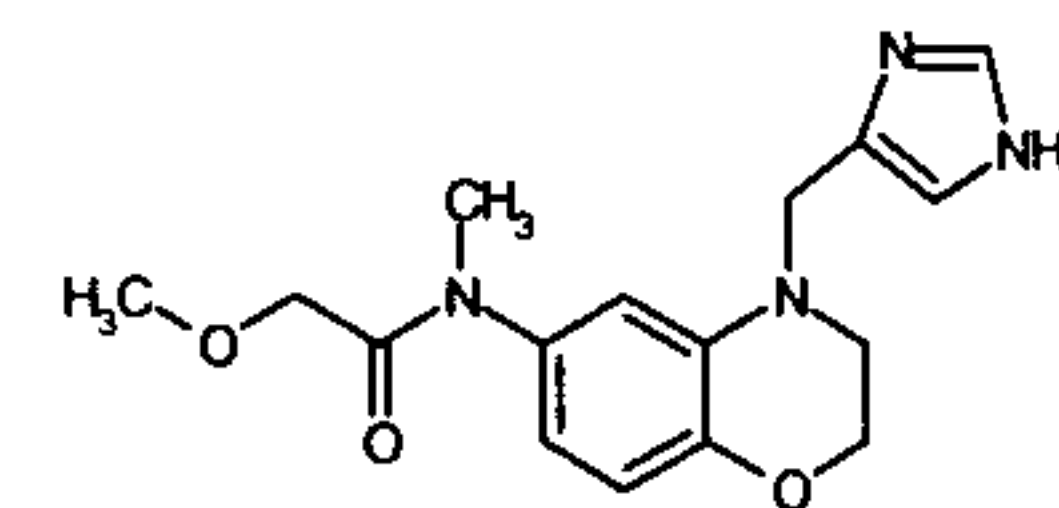
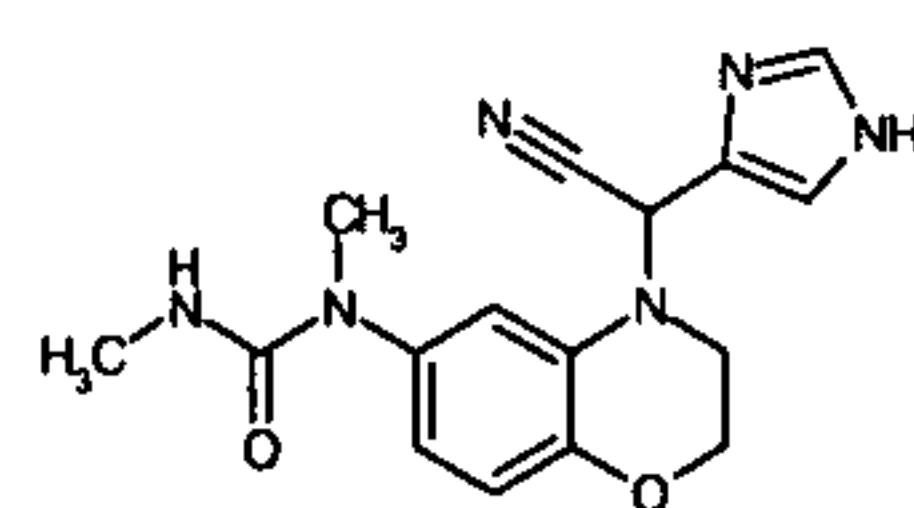
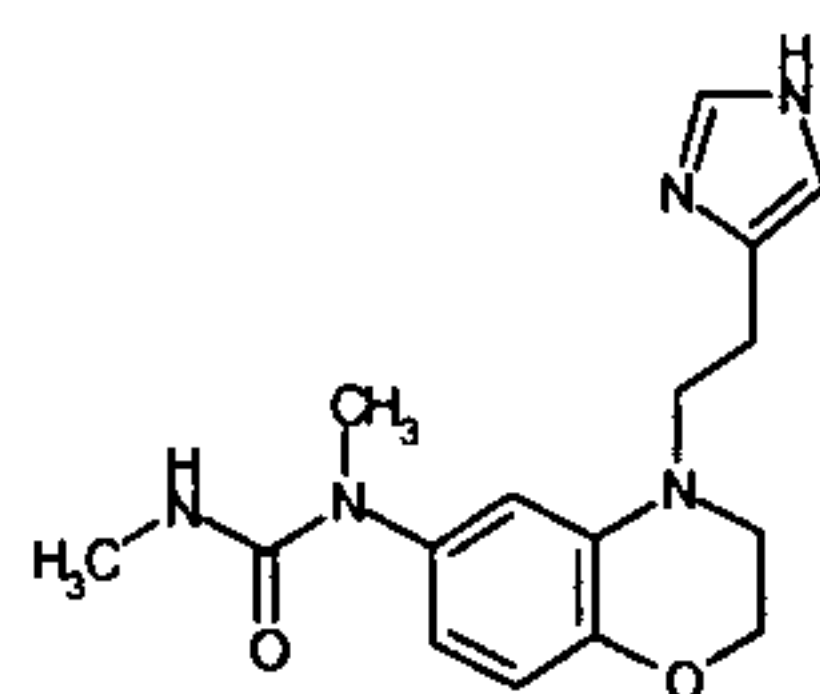
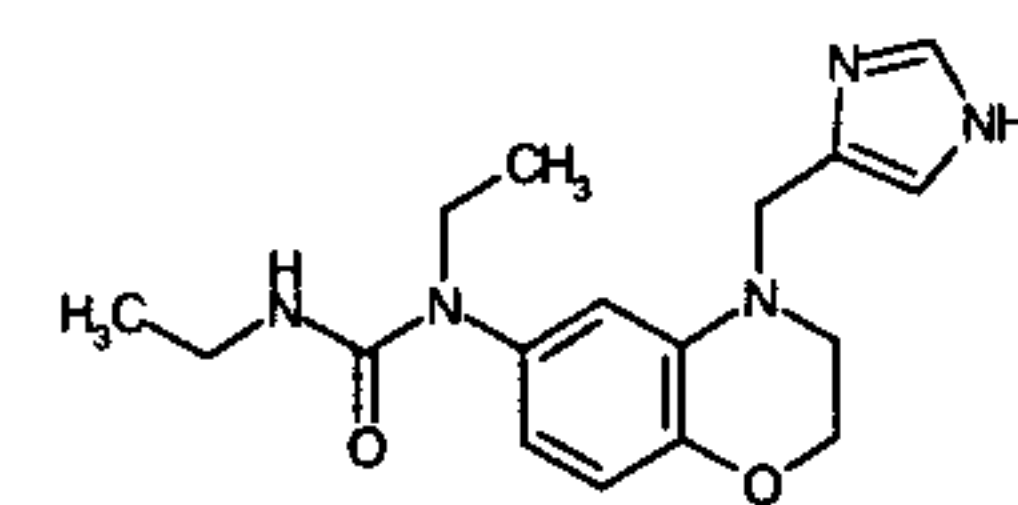
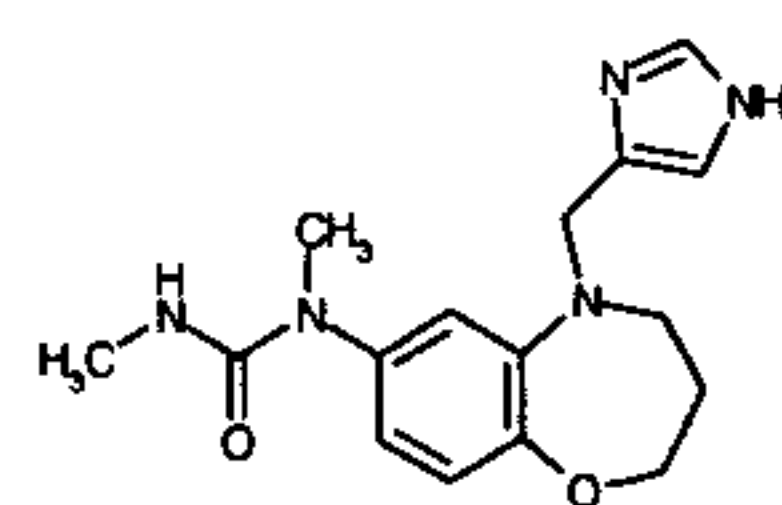
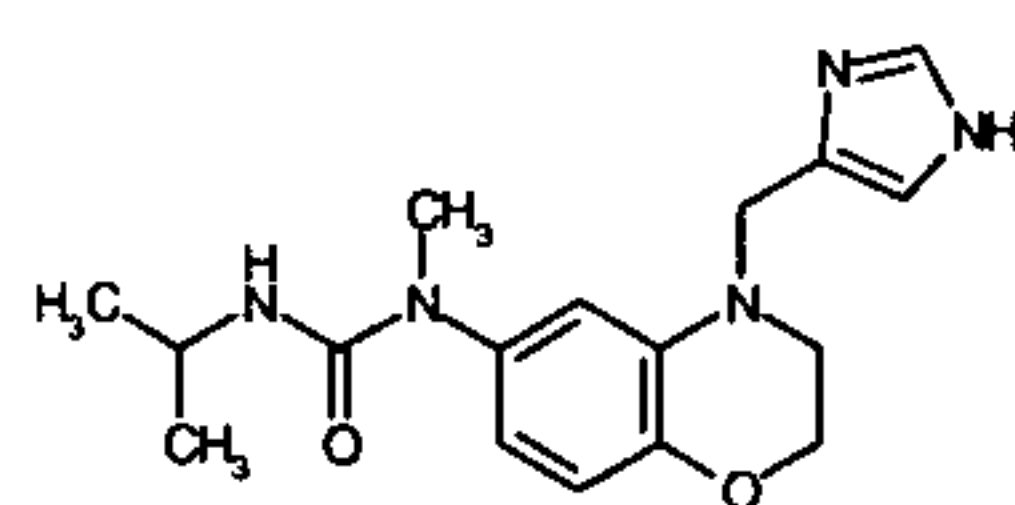
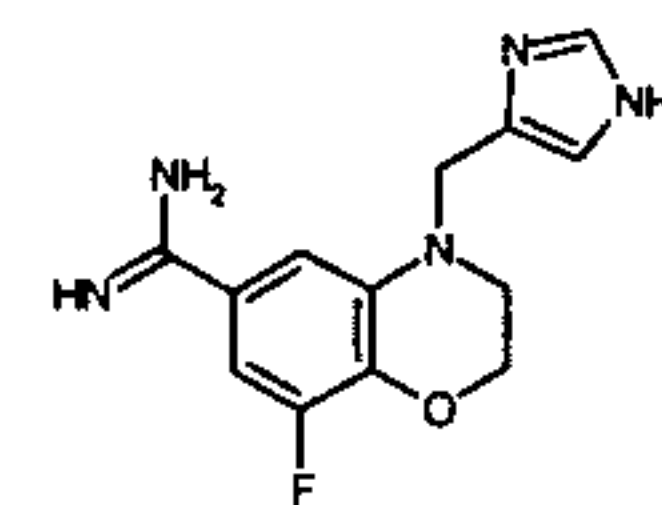
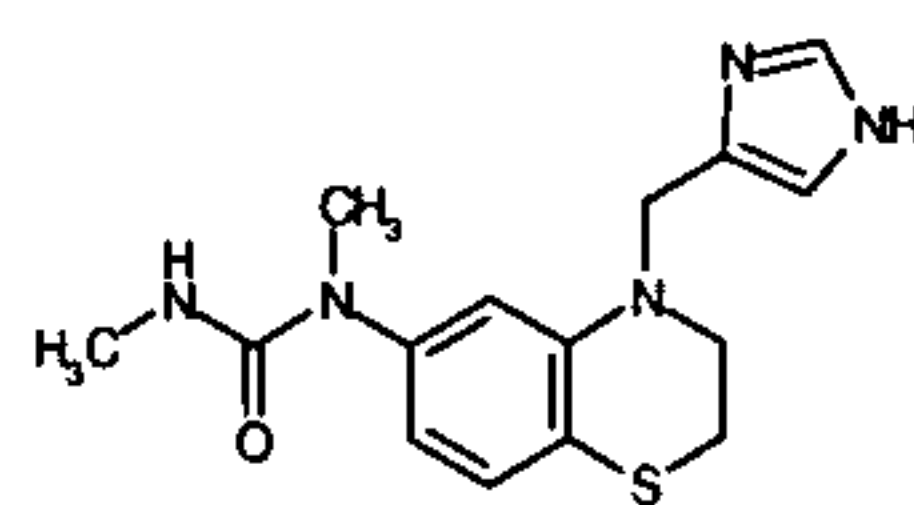
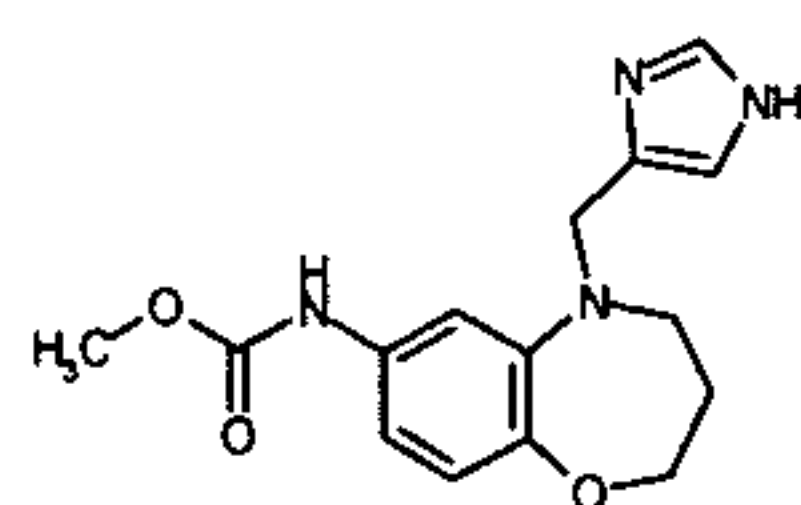
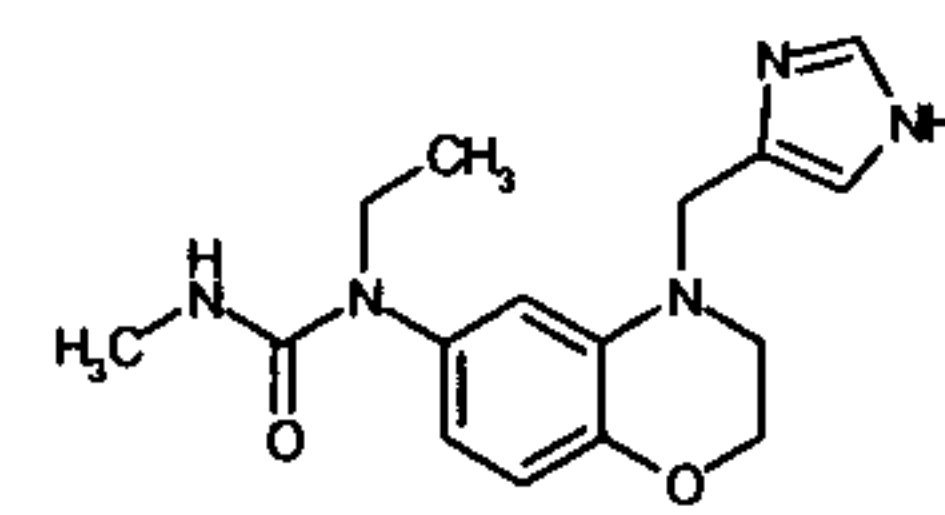
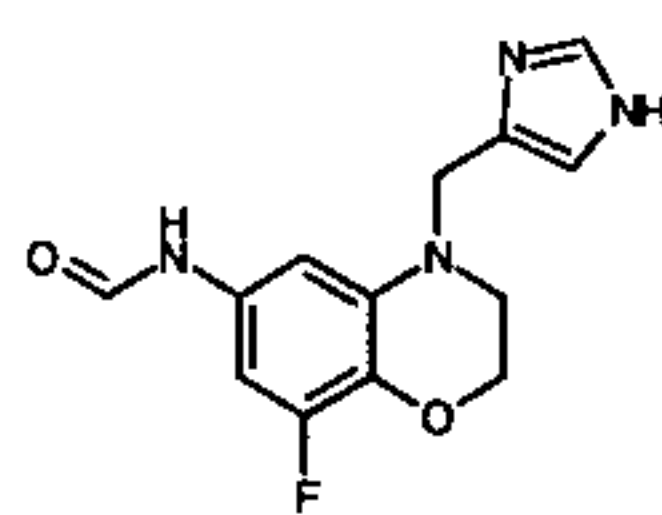
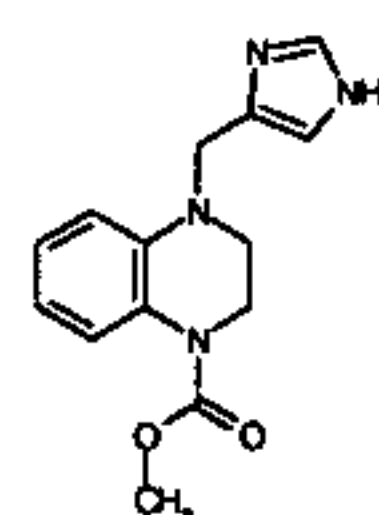
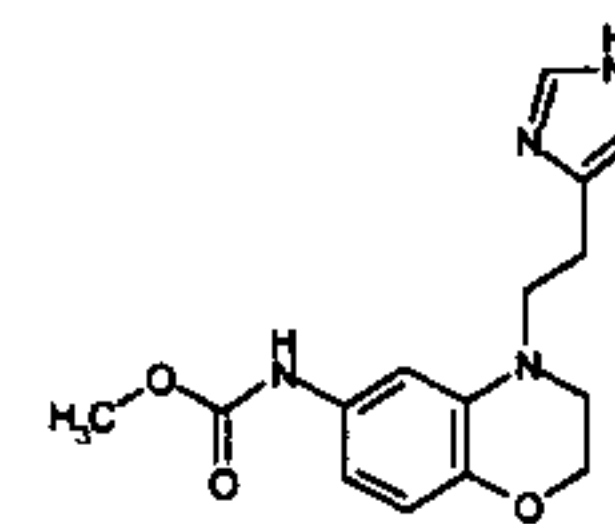
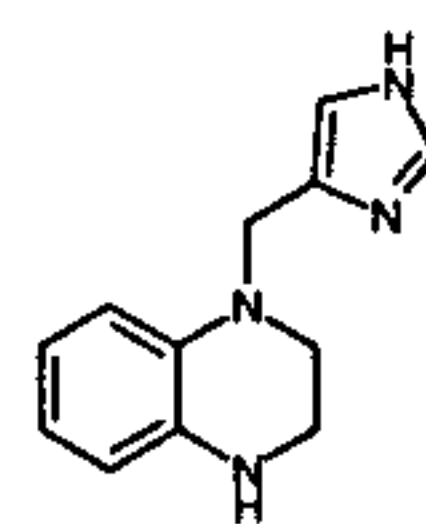
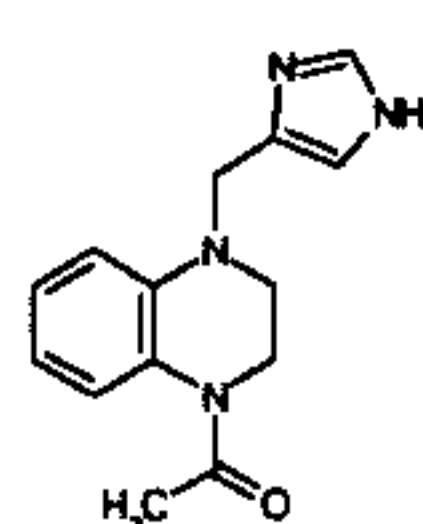
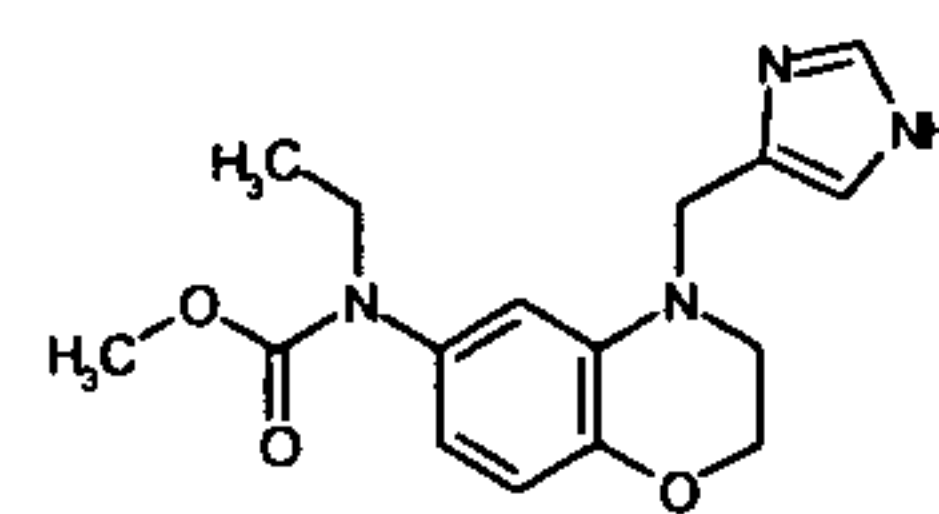
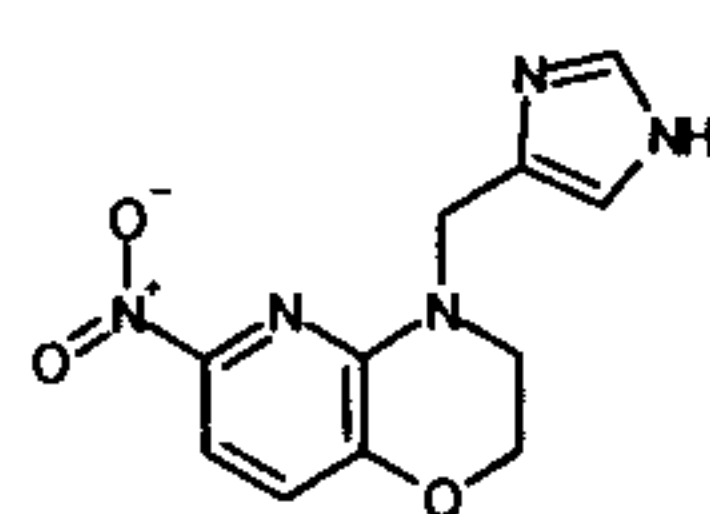
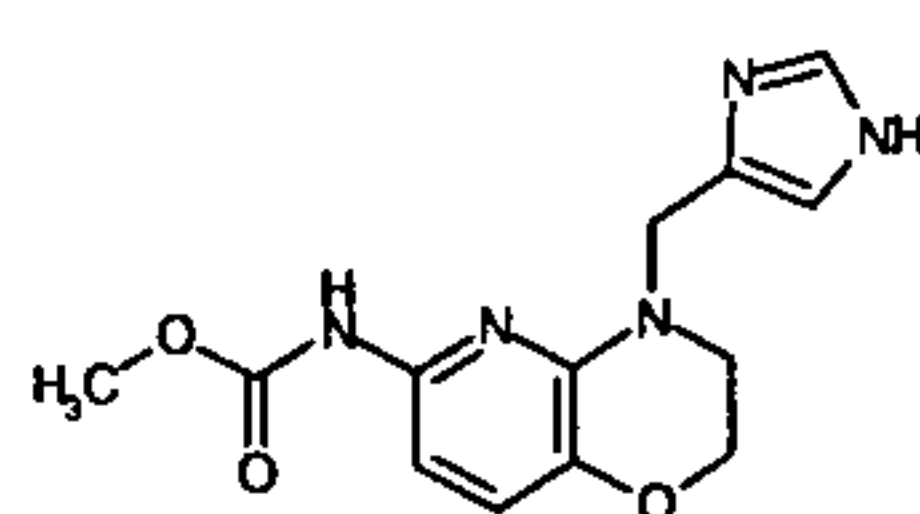
13



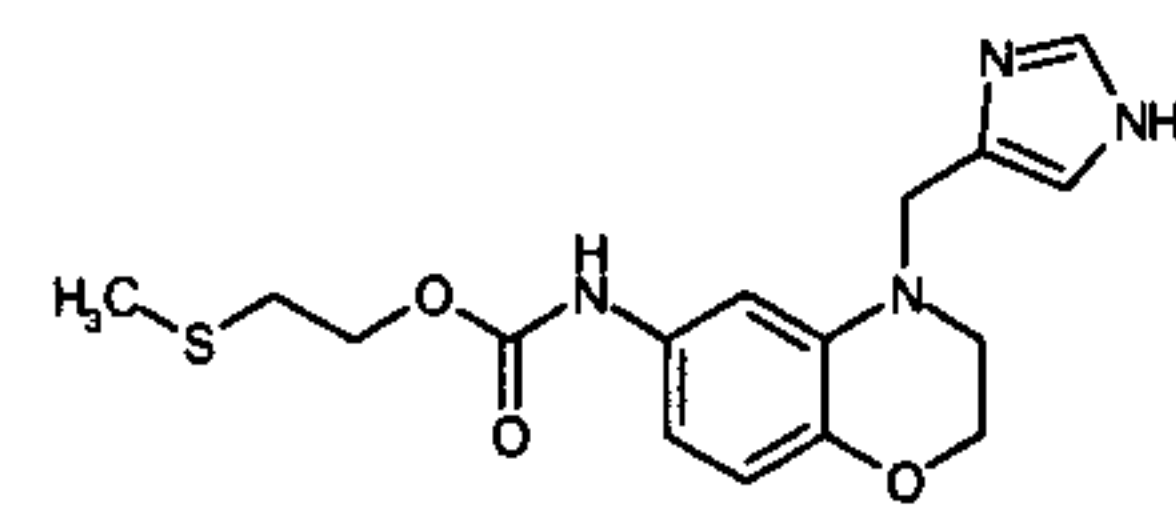
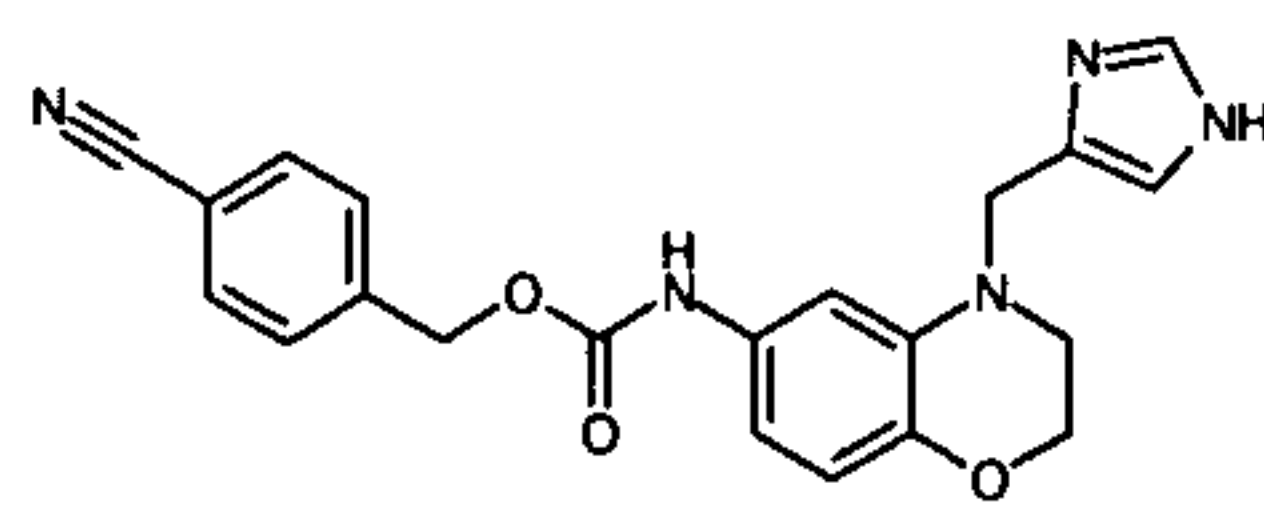
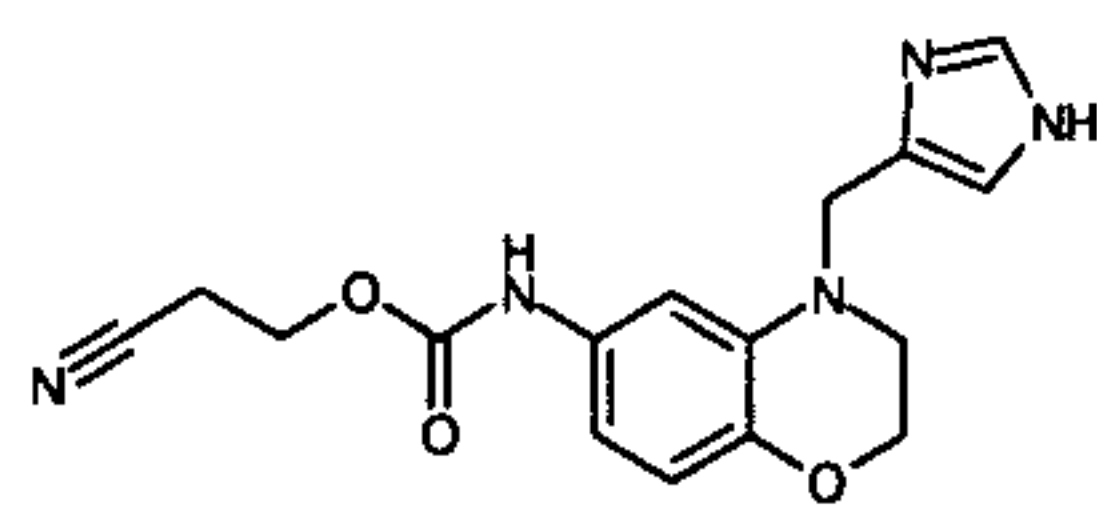
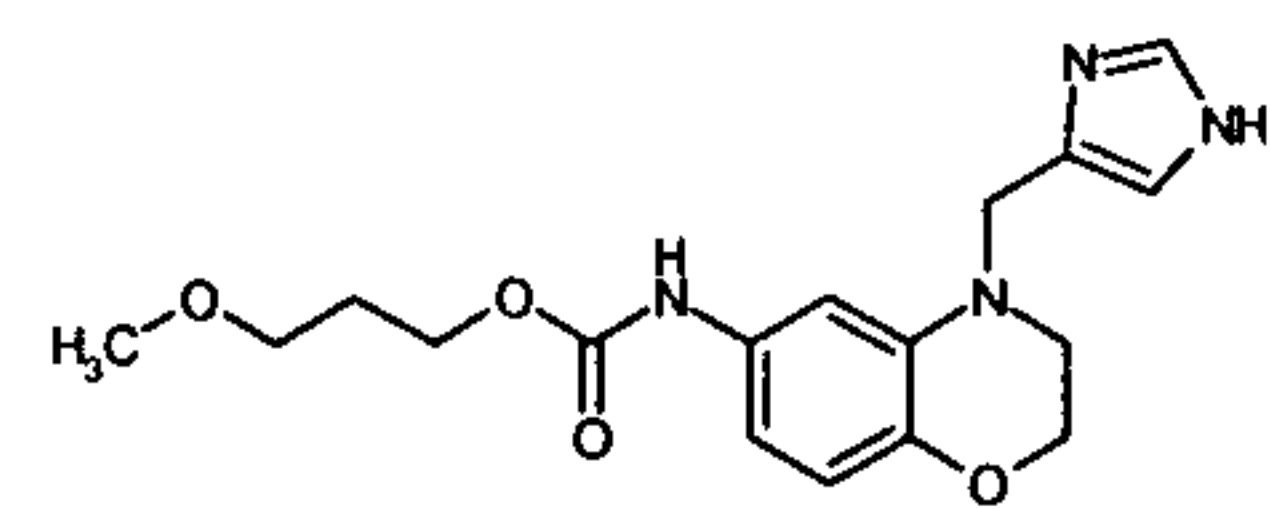
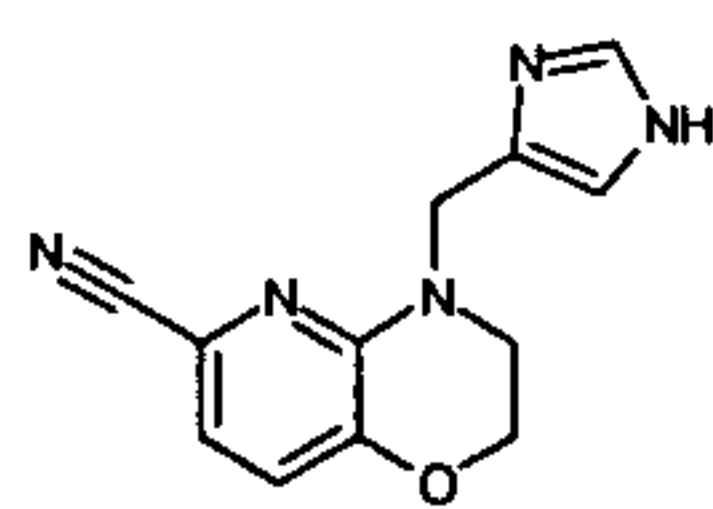
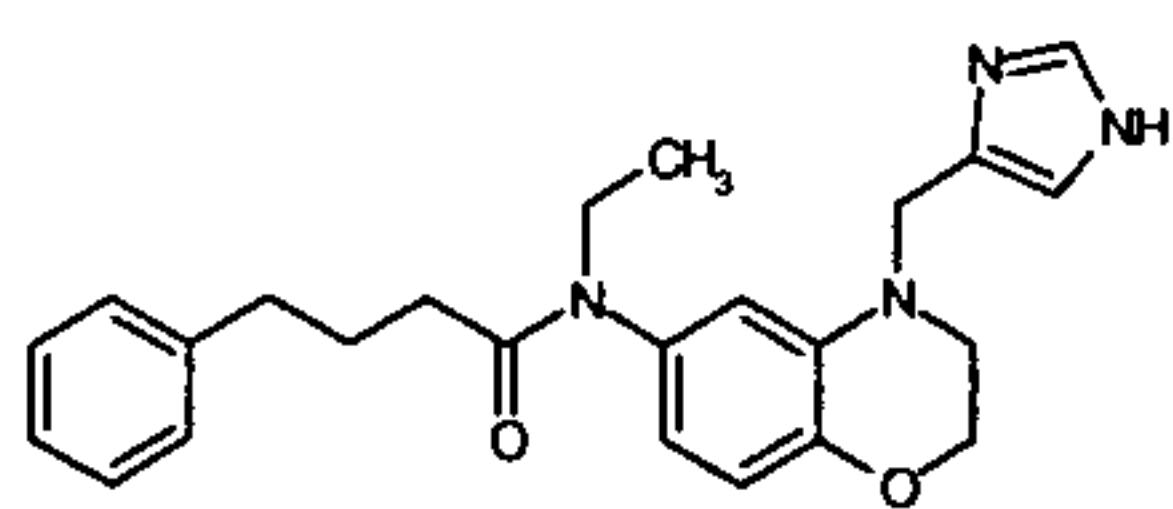
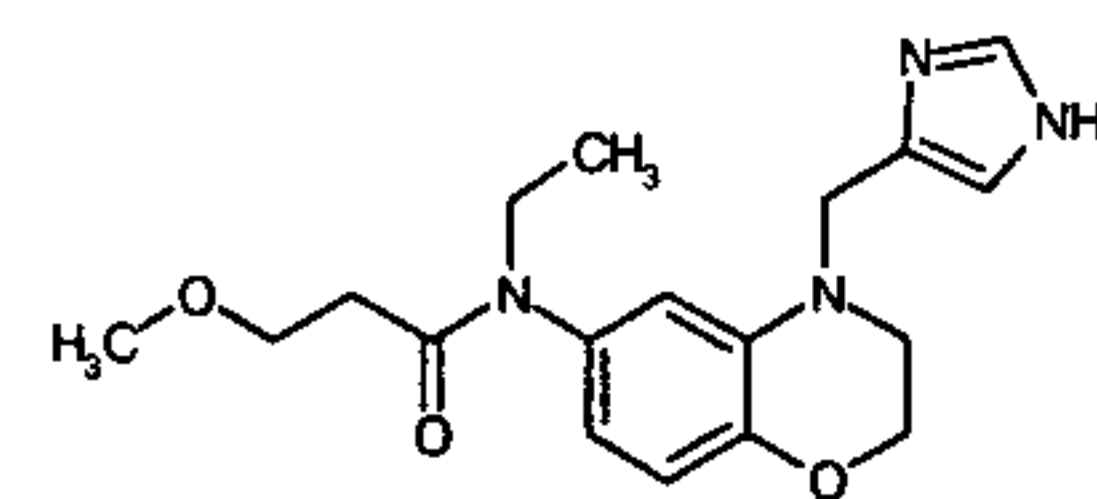
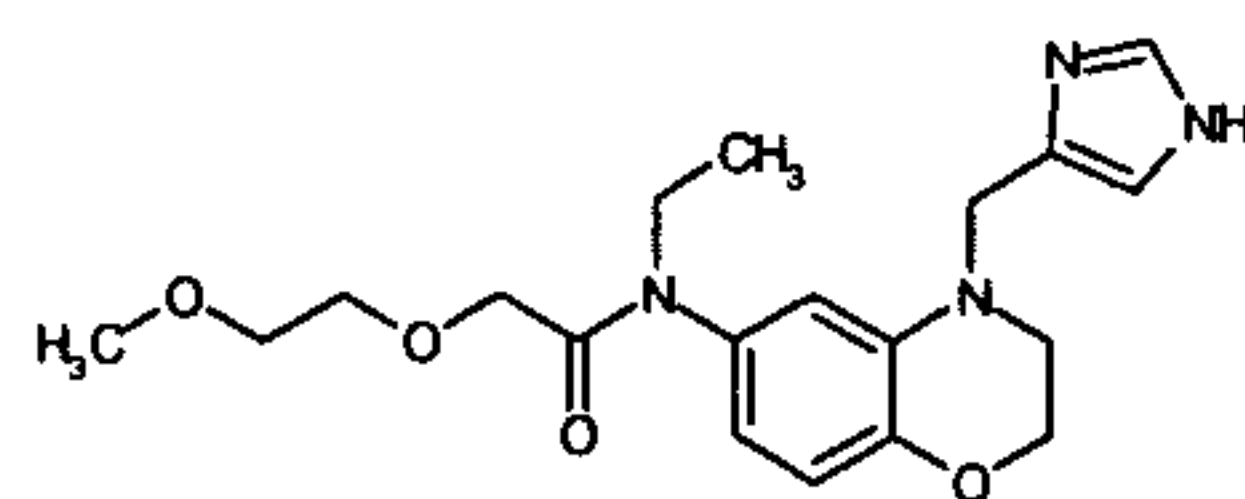
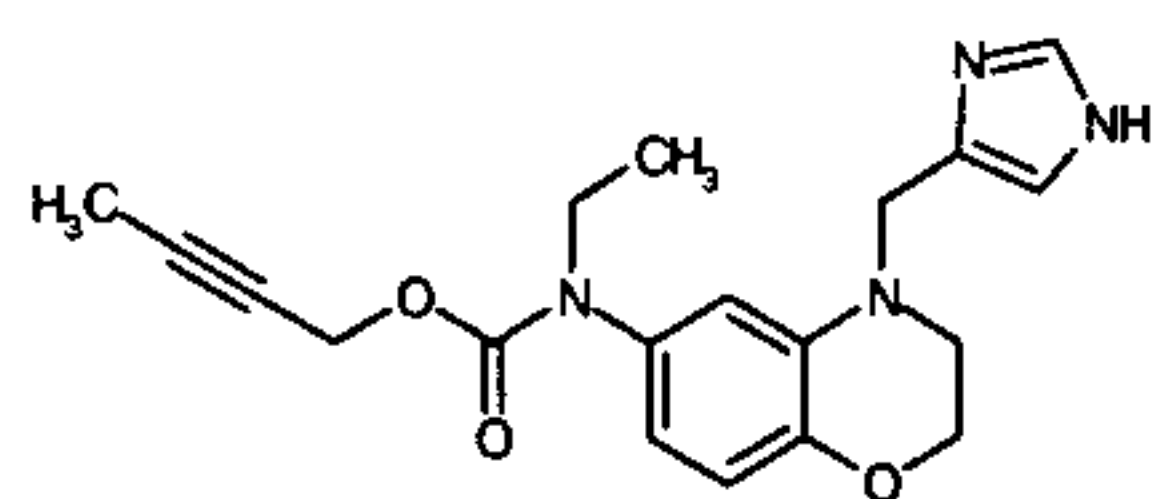
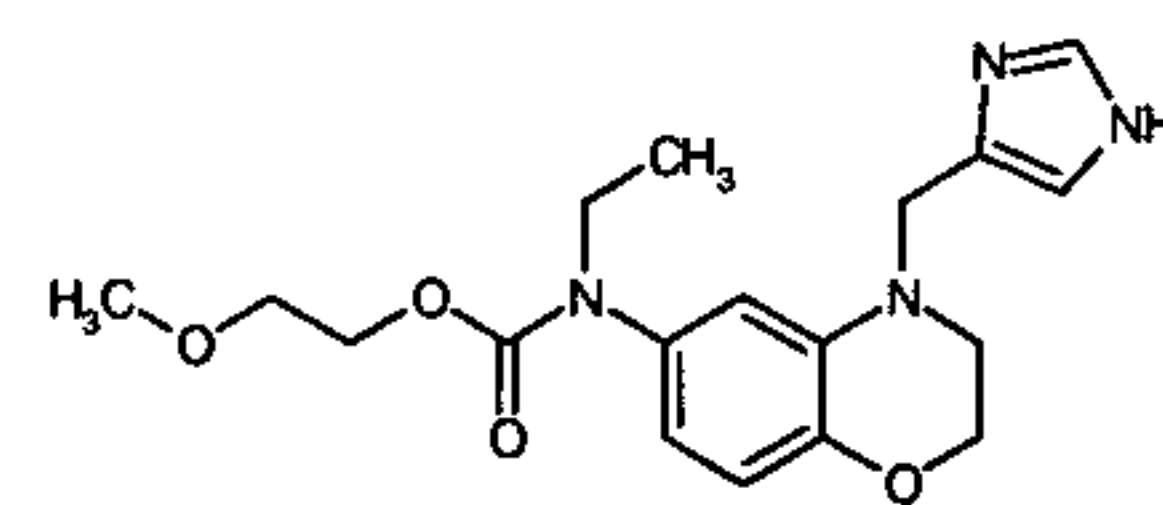
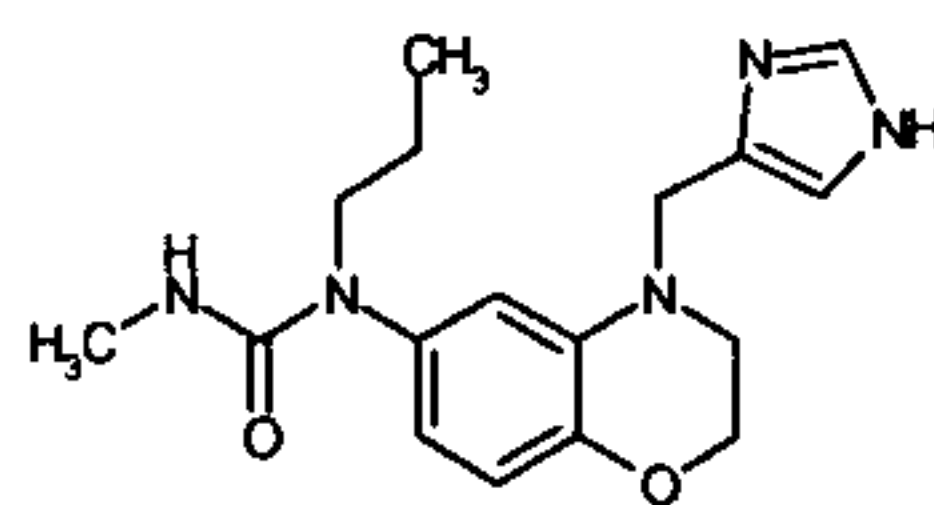
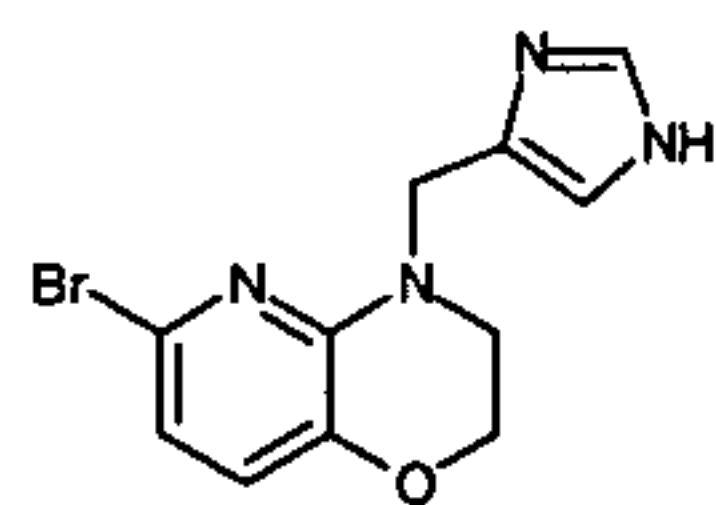
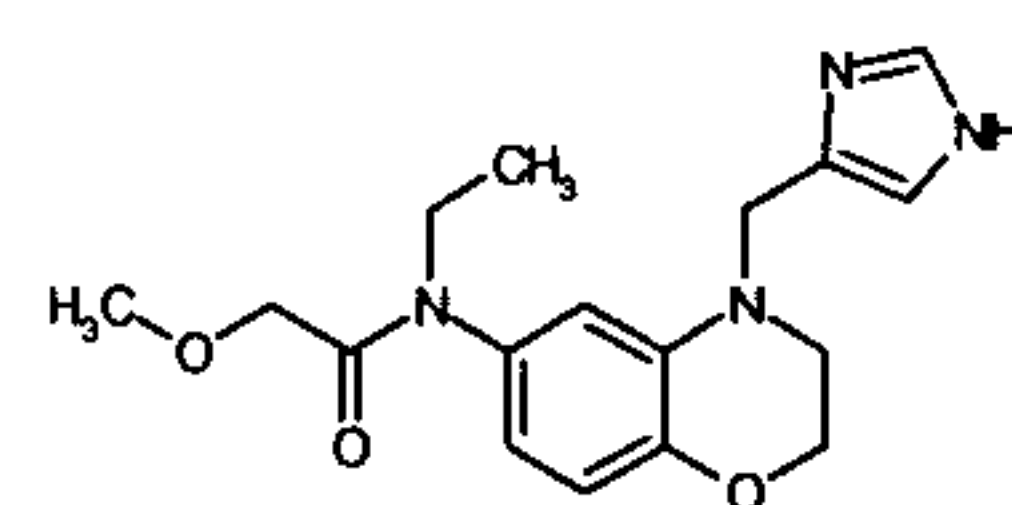
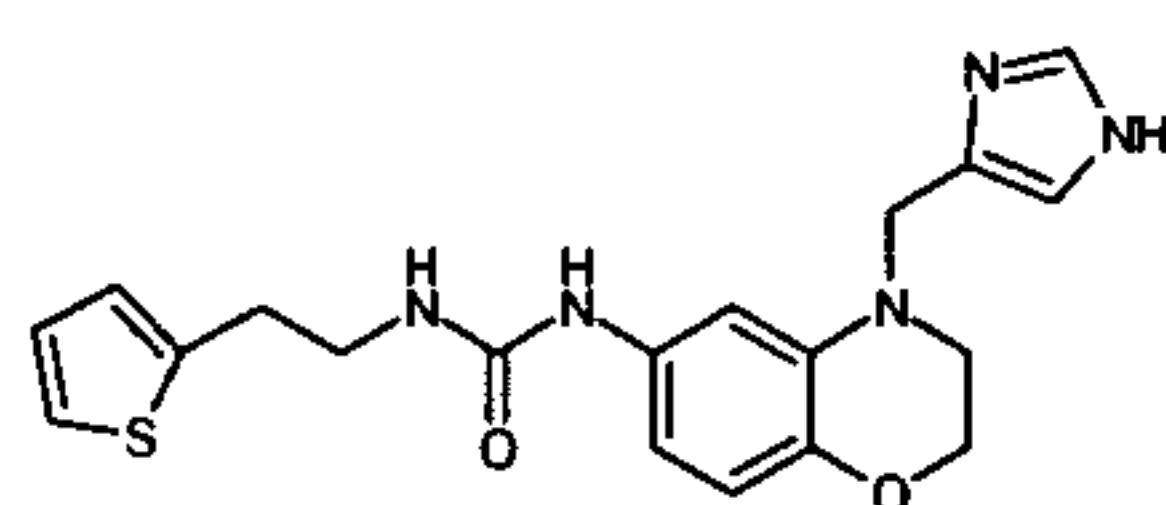
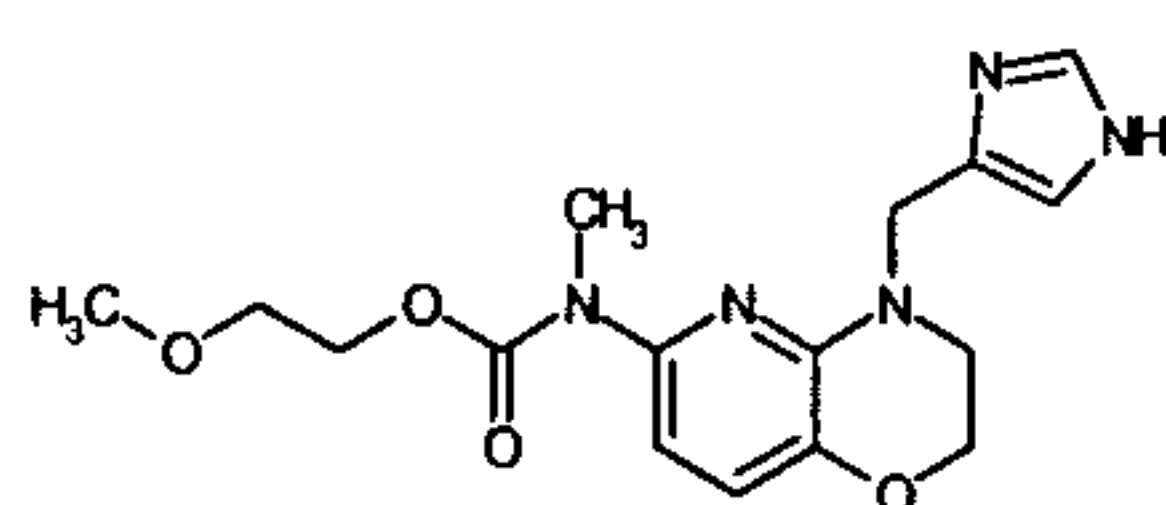
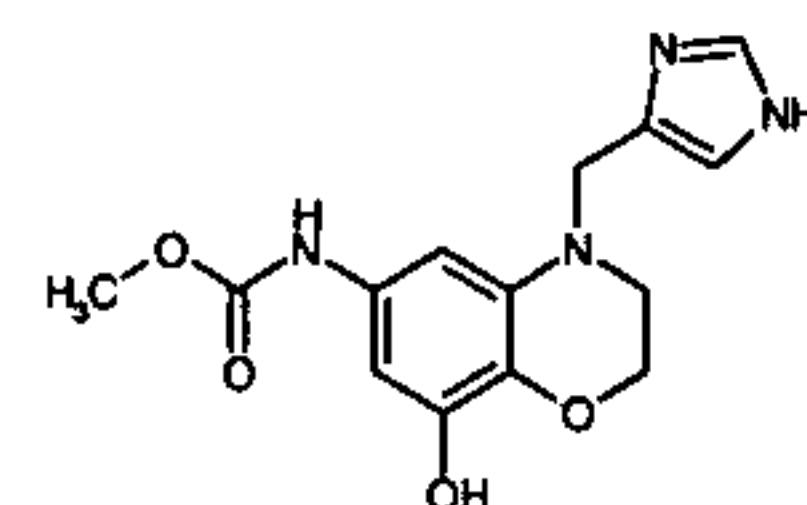
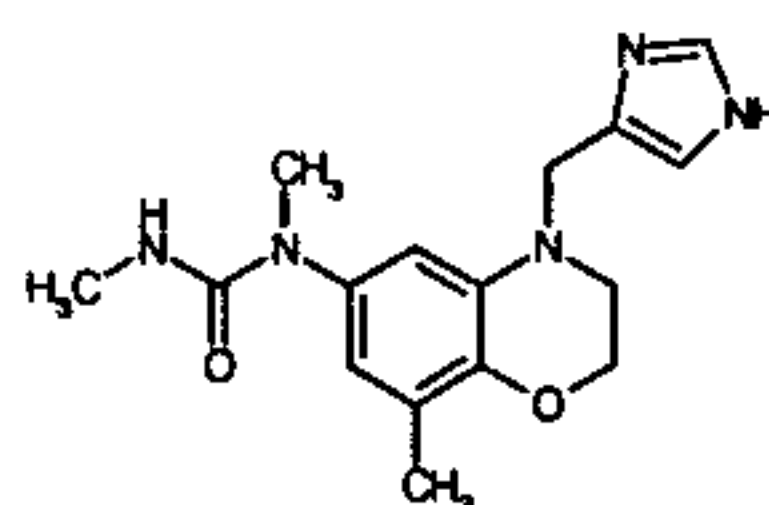
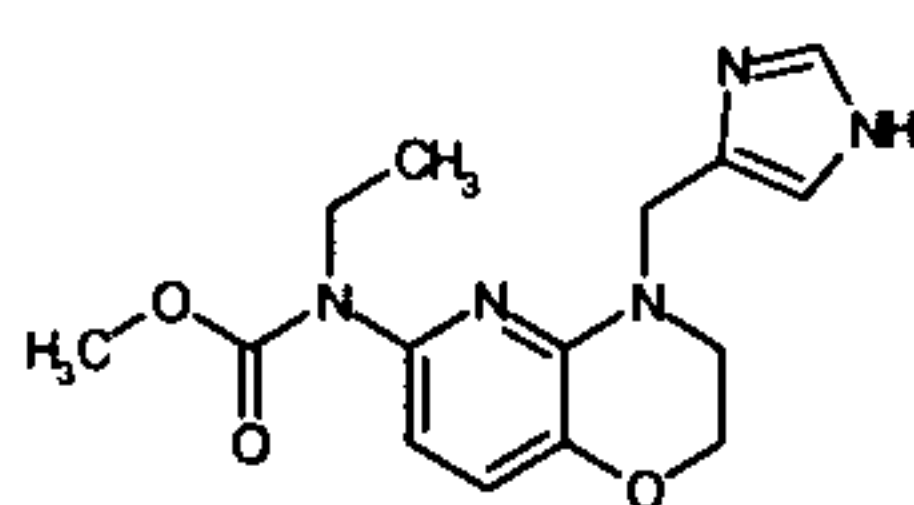
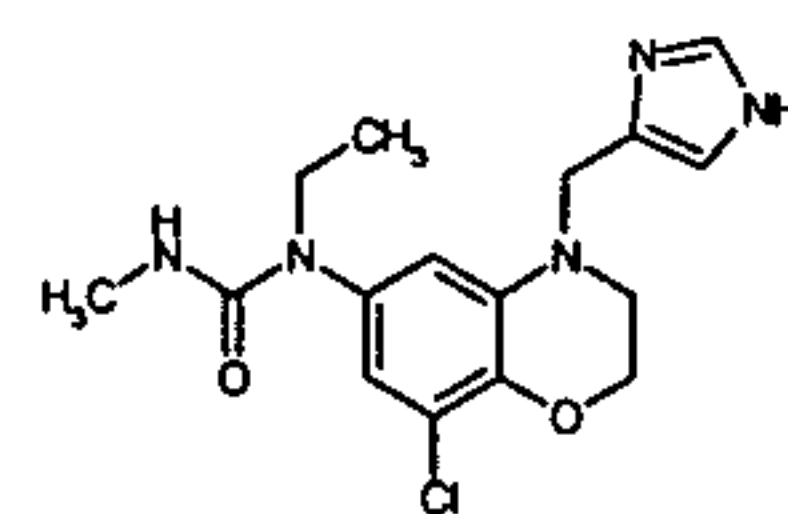
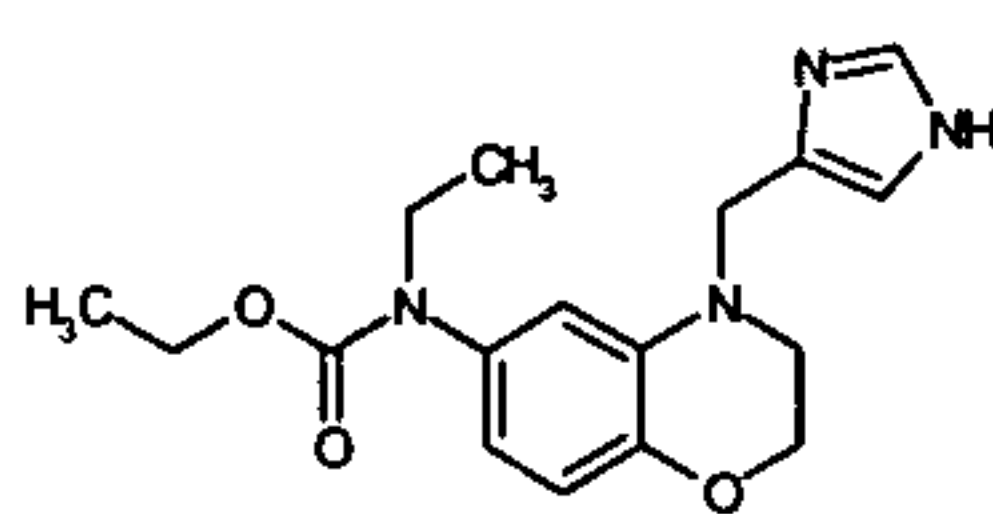
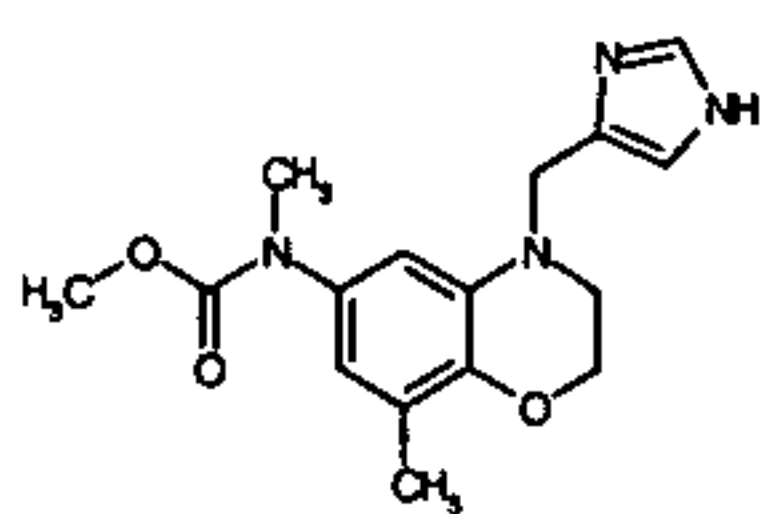
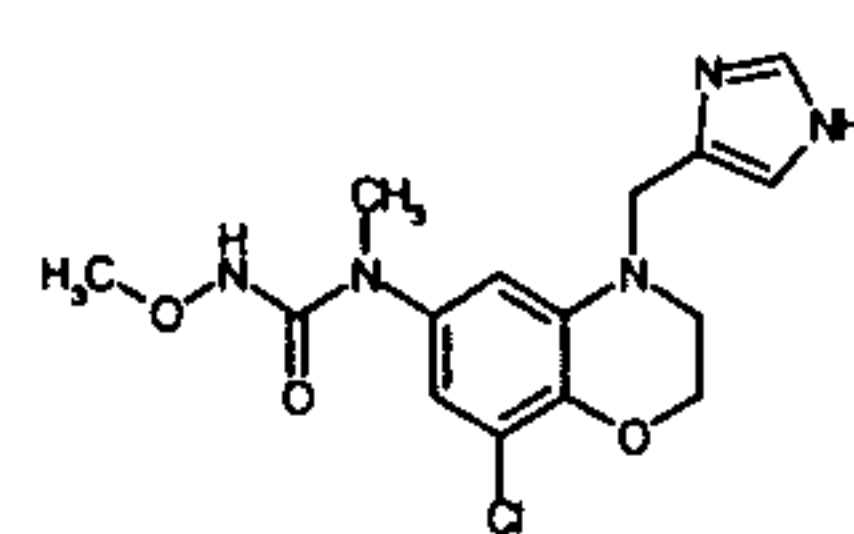
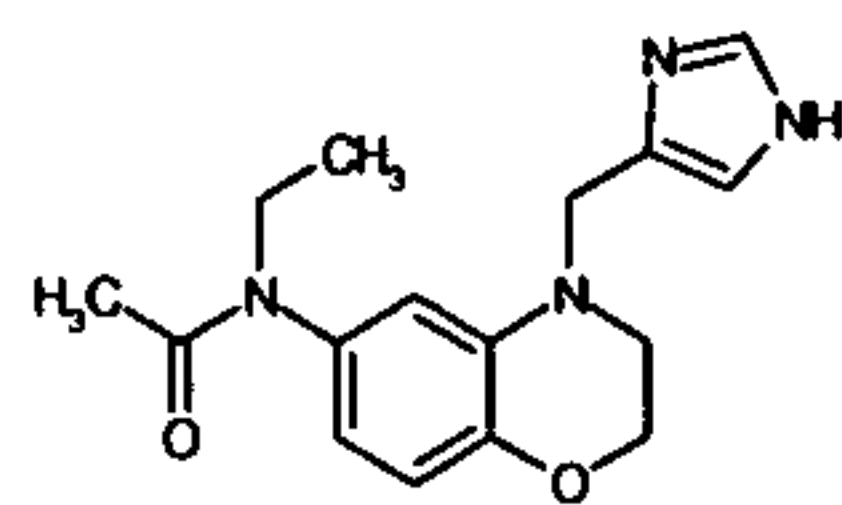
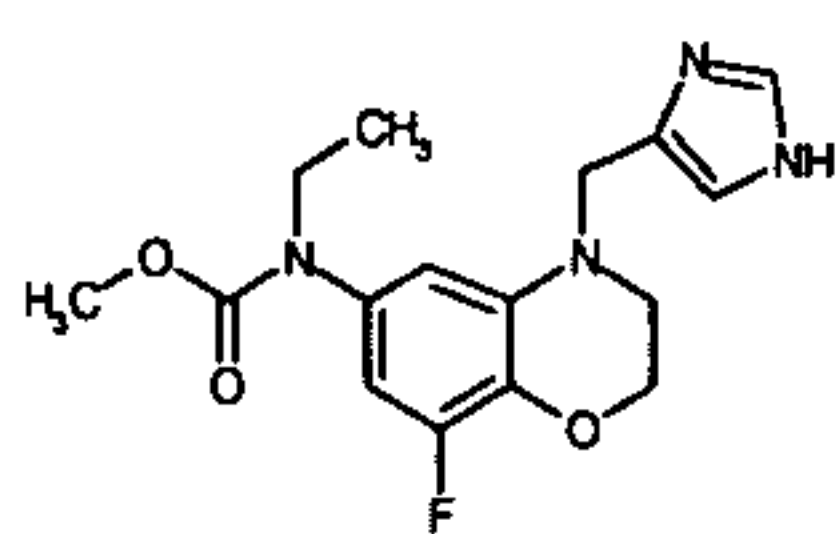
14

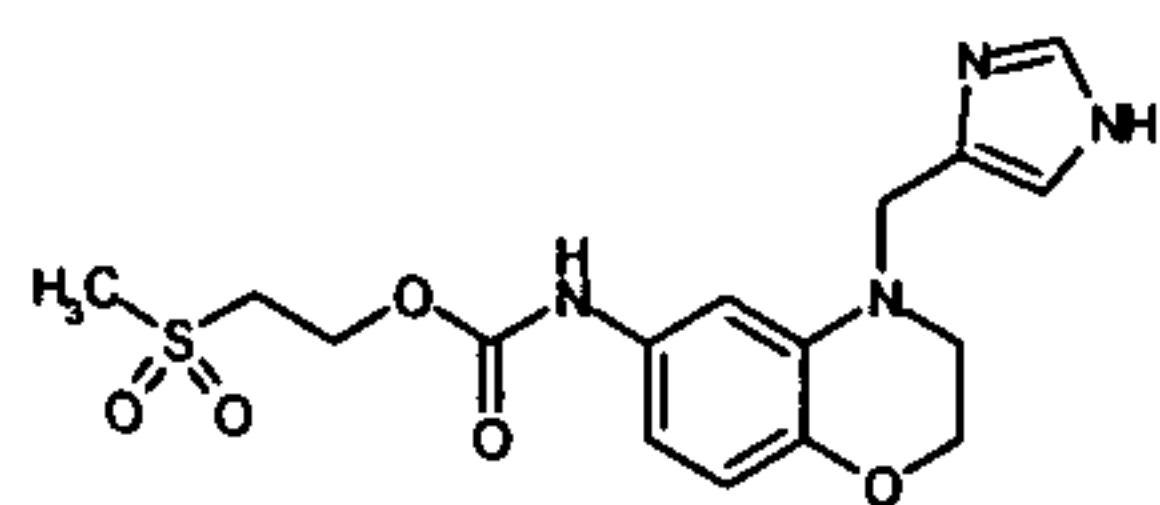


15



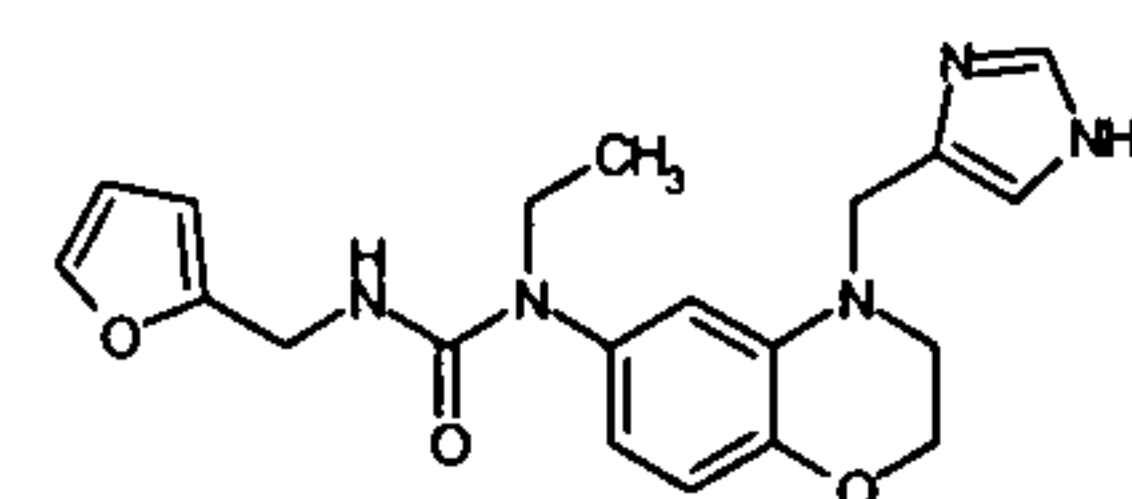
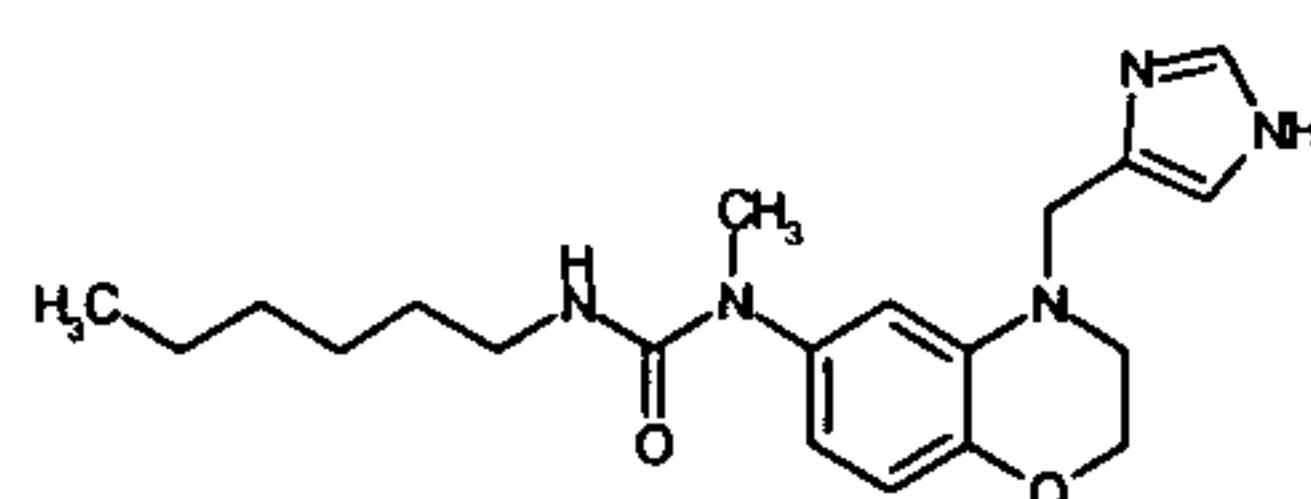
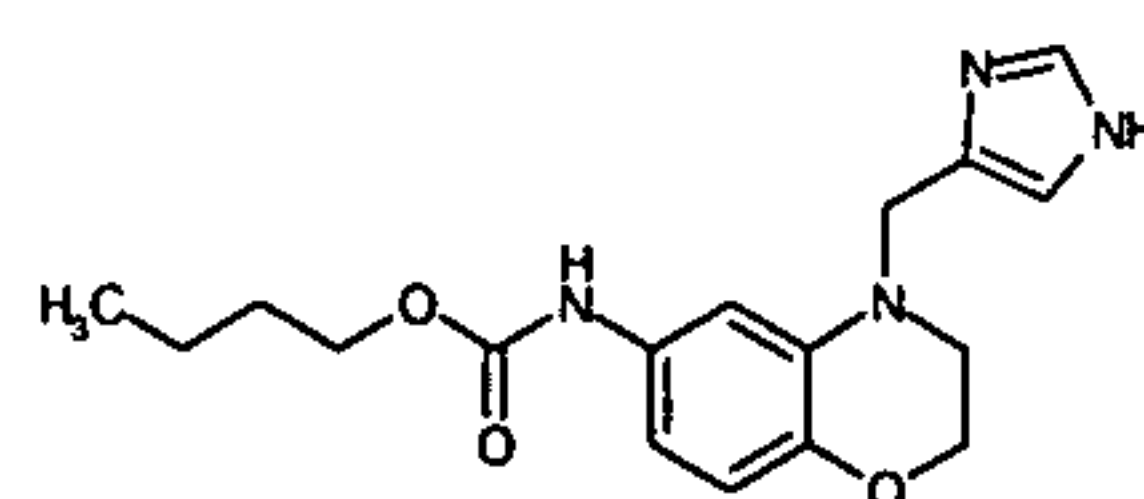
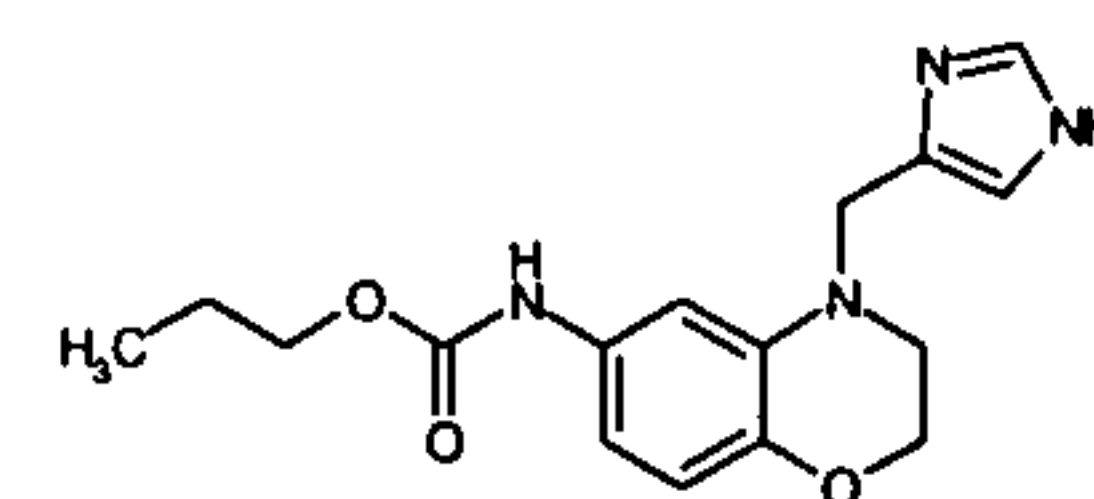
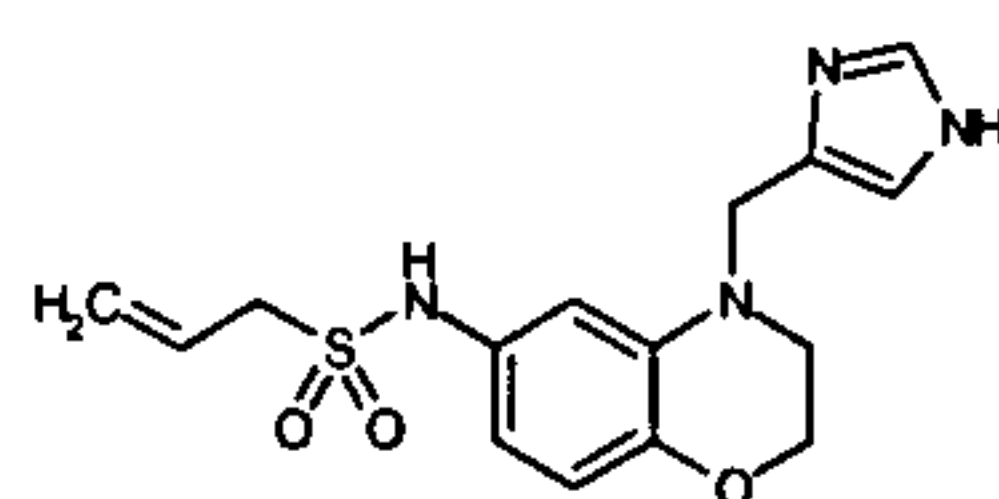
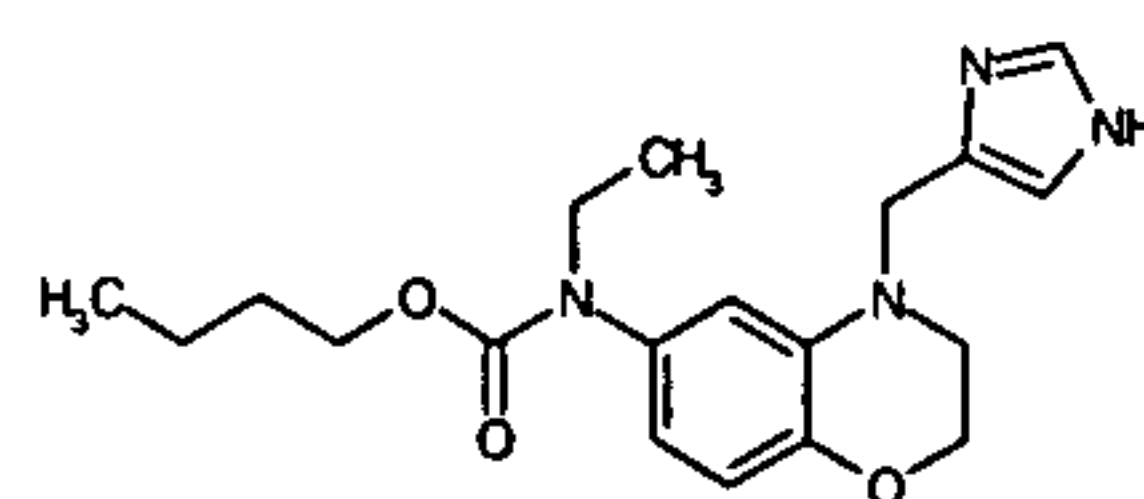
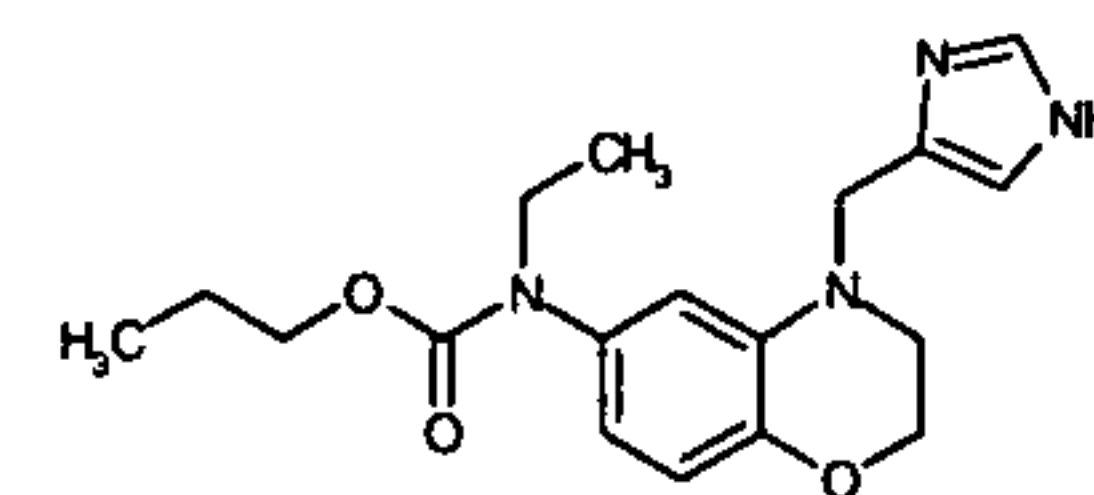
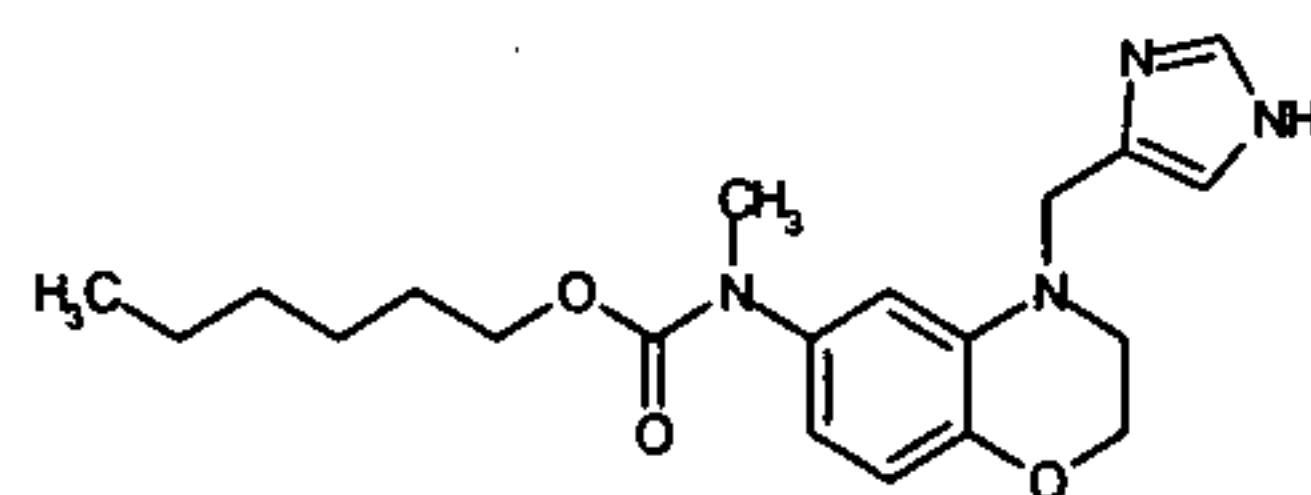
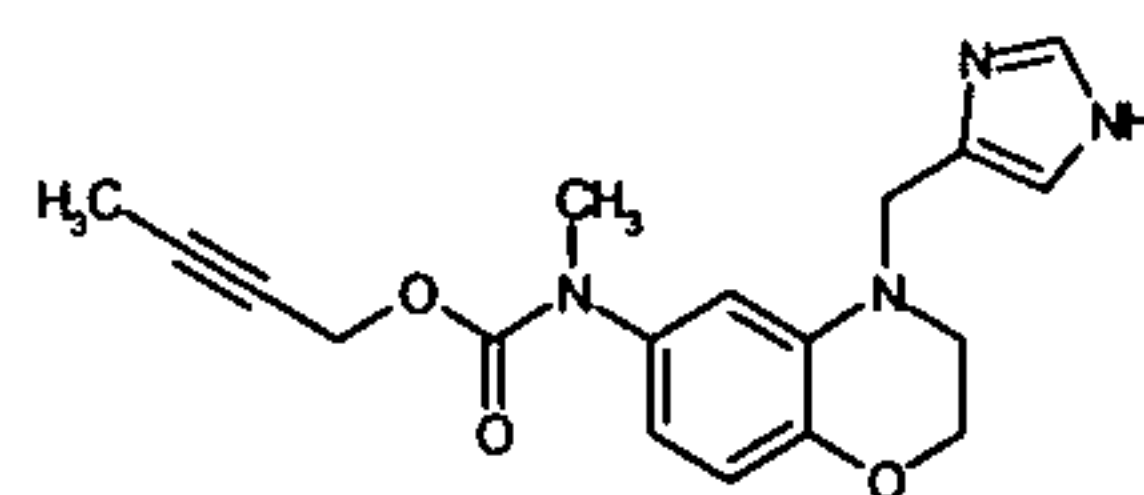
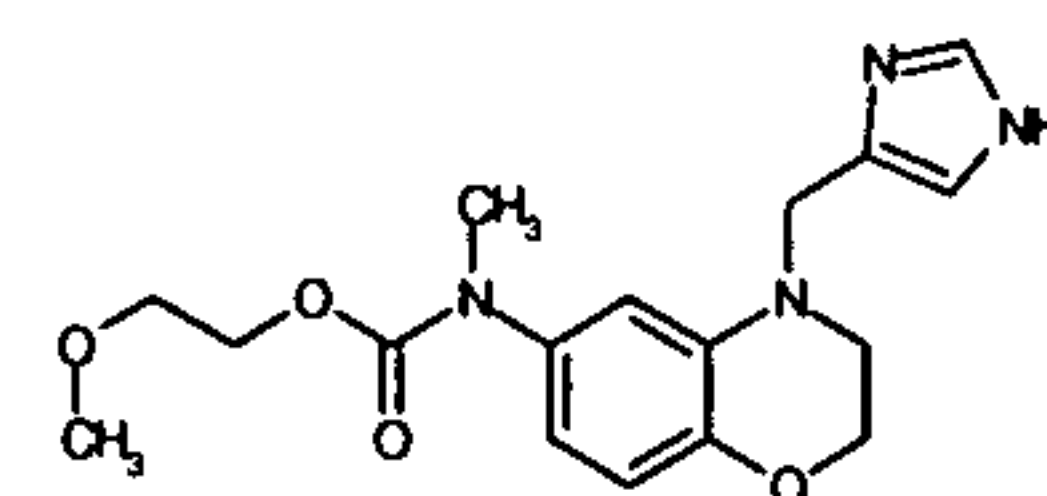
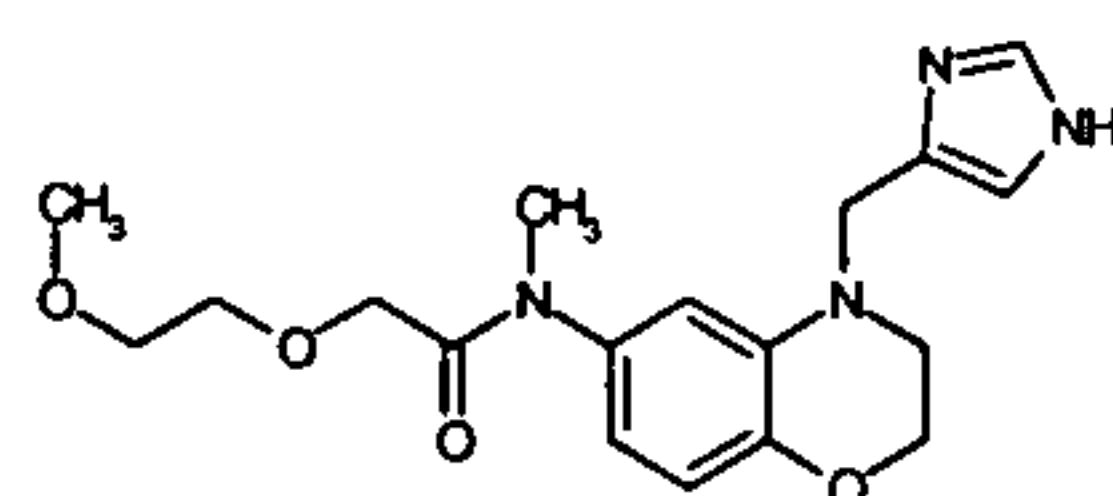
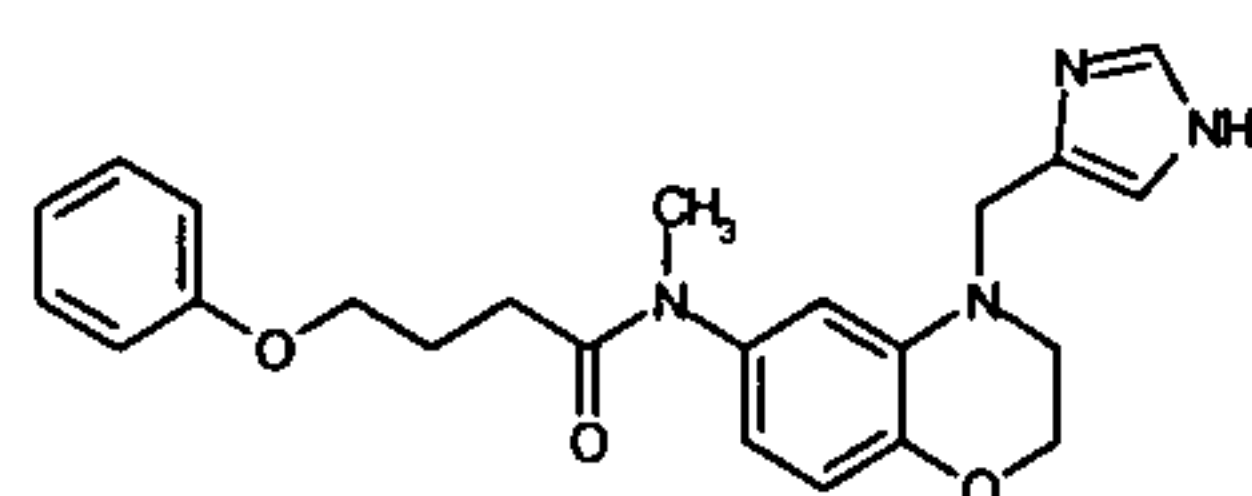
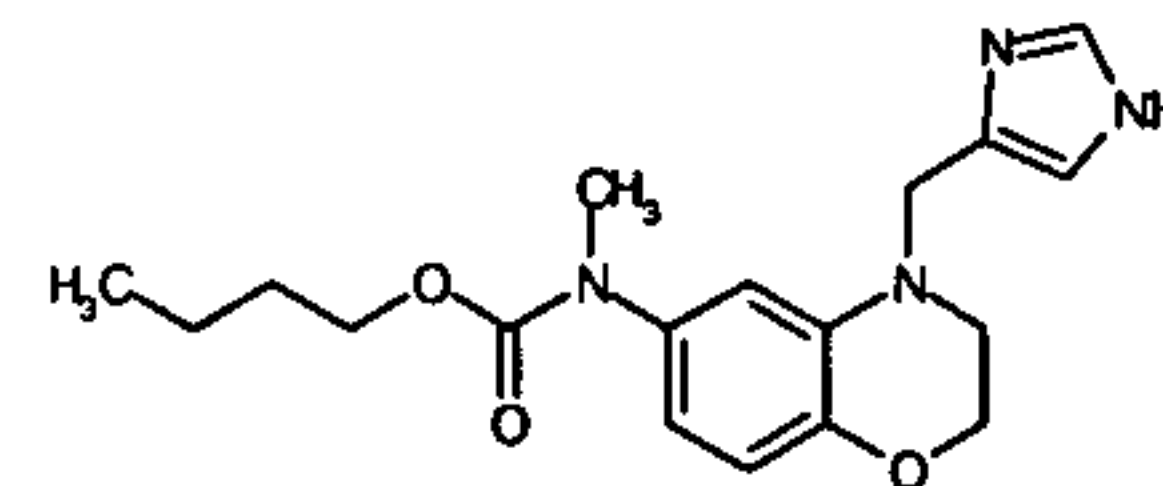
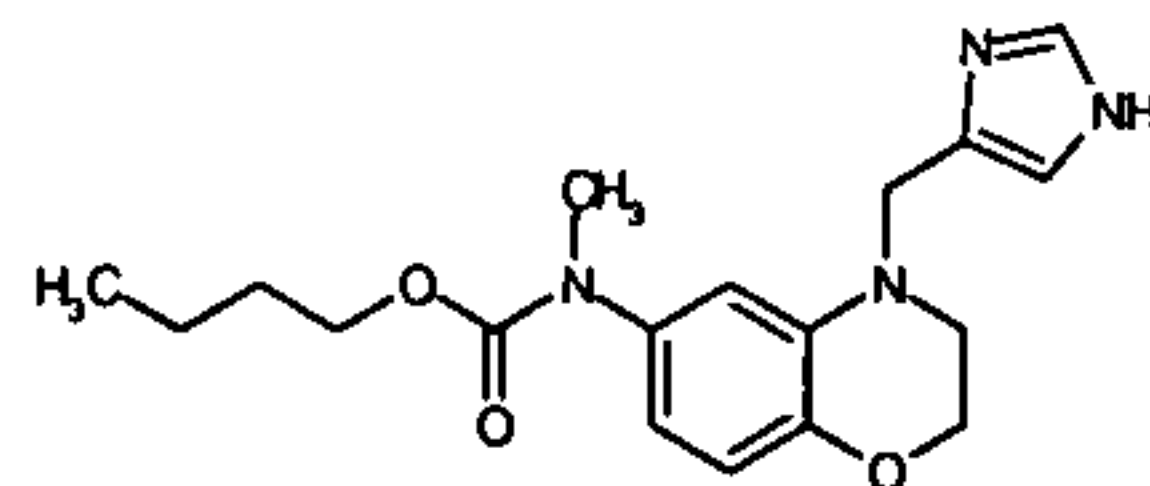
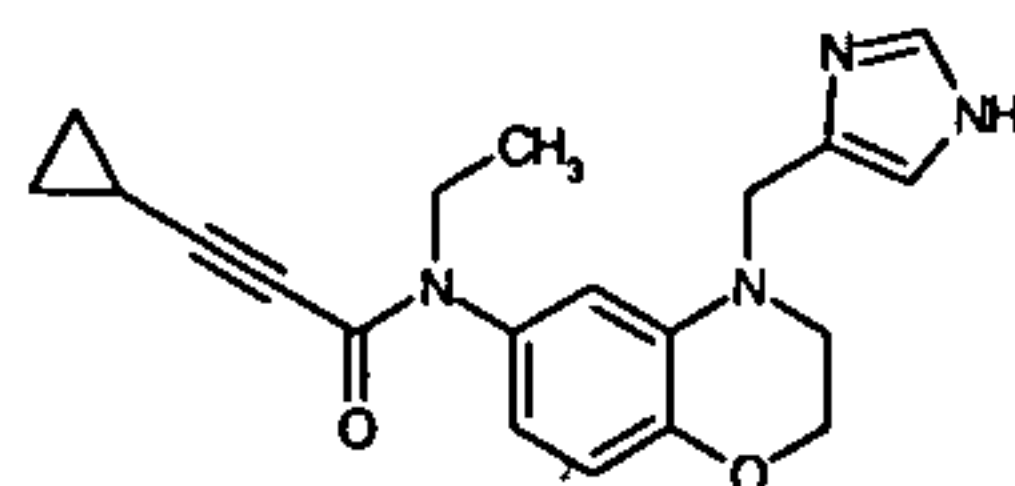
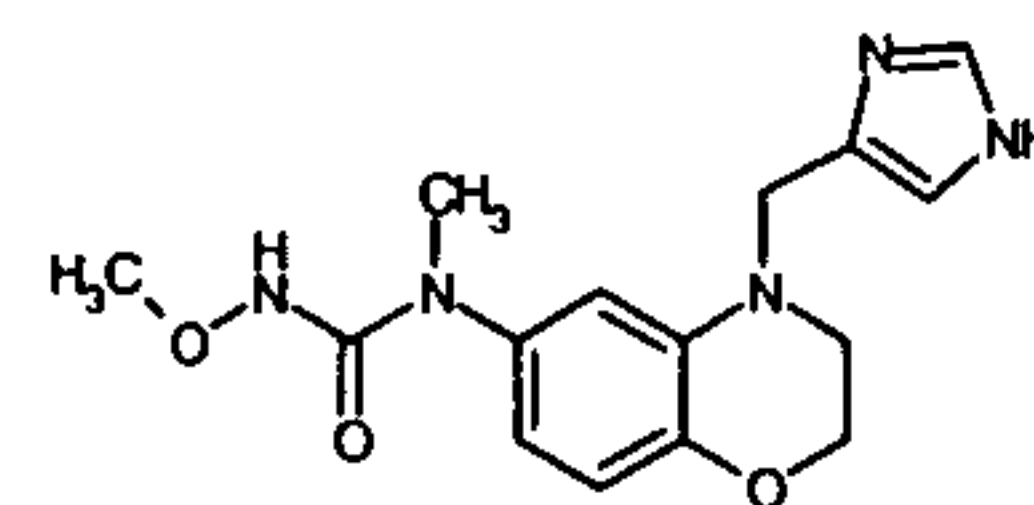
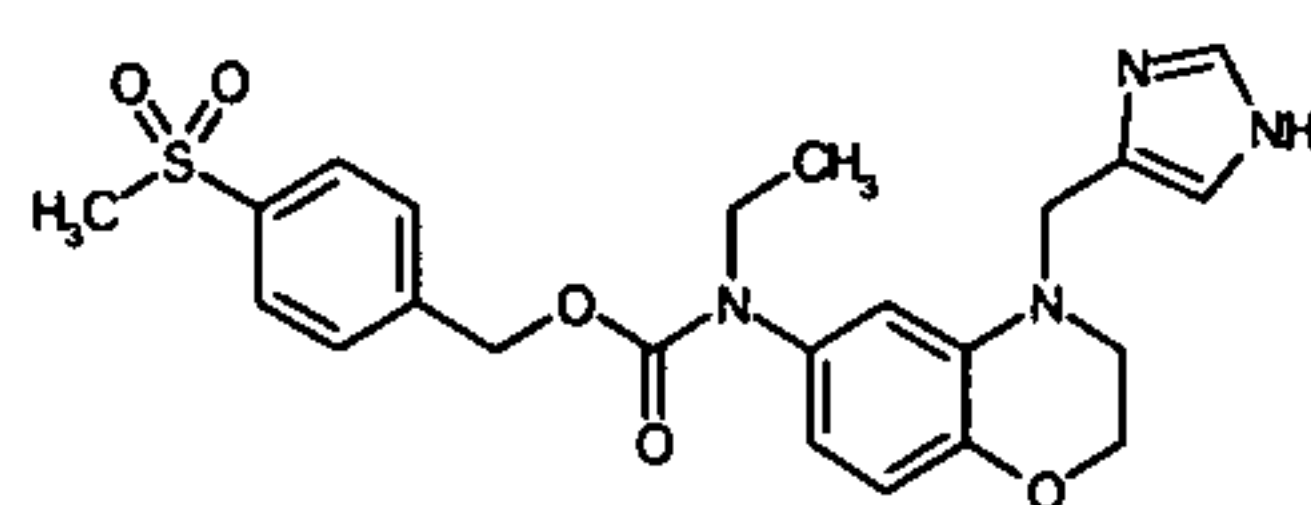
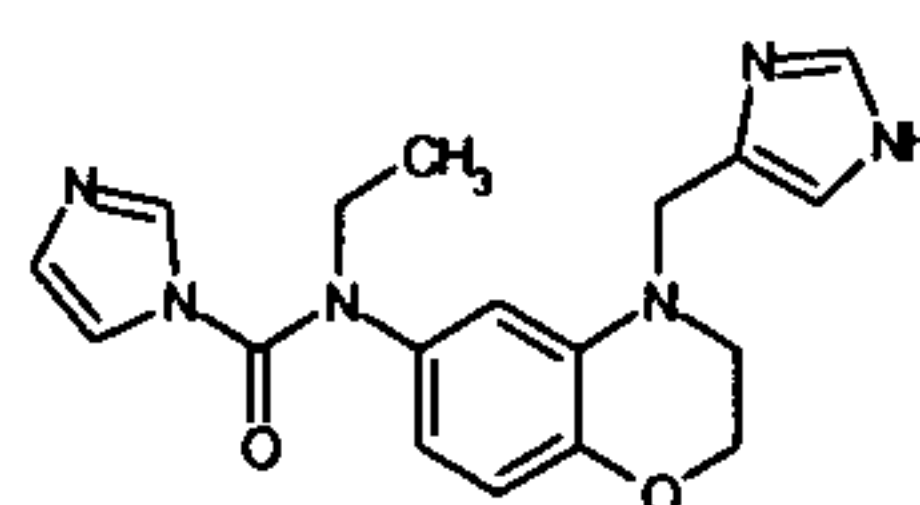
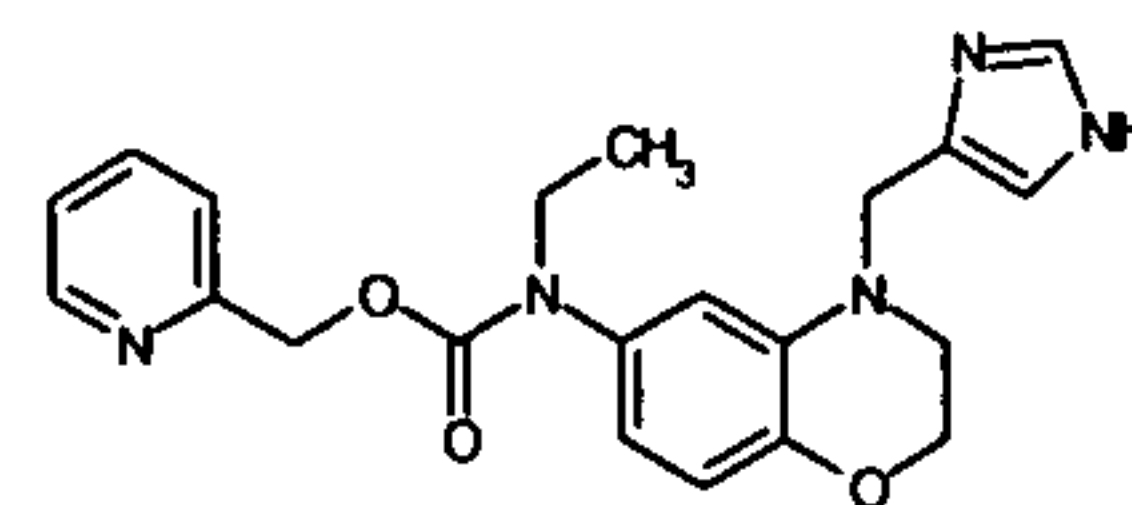
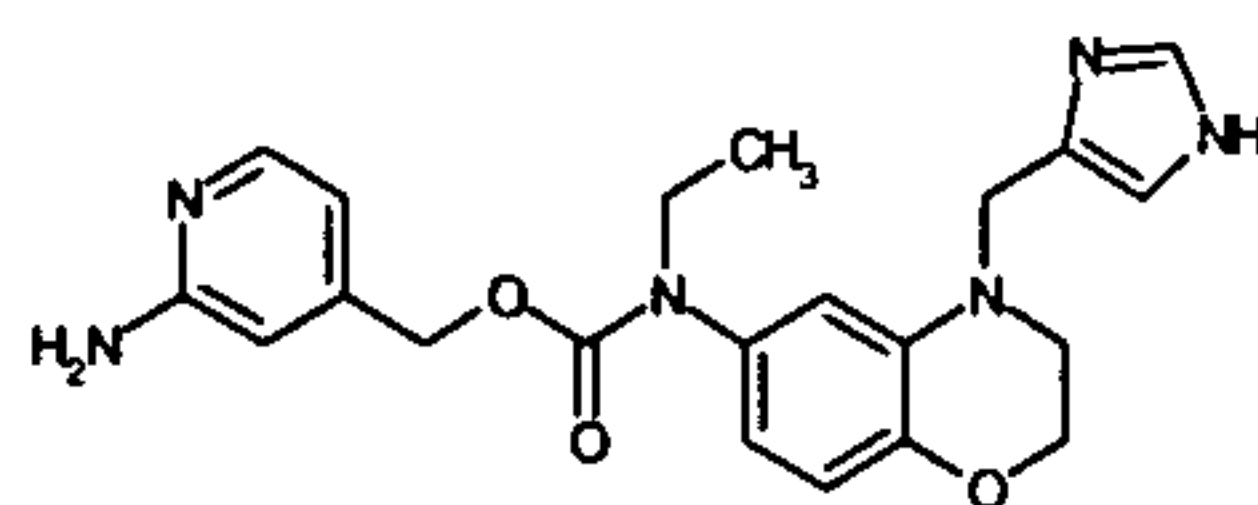
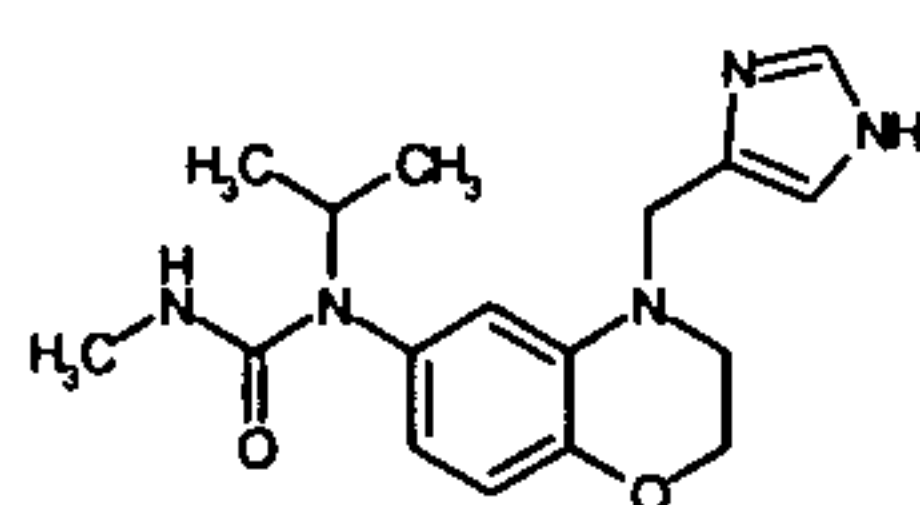
16

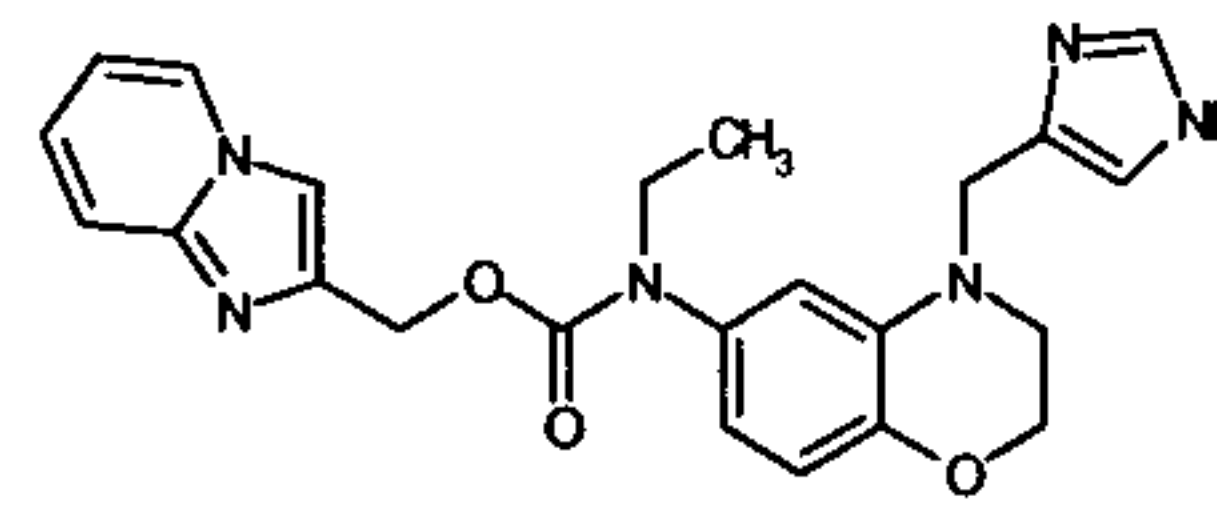
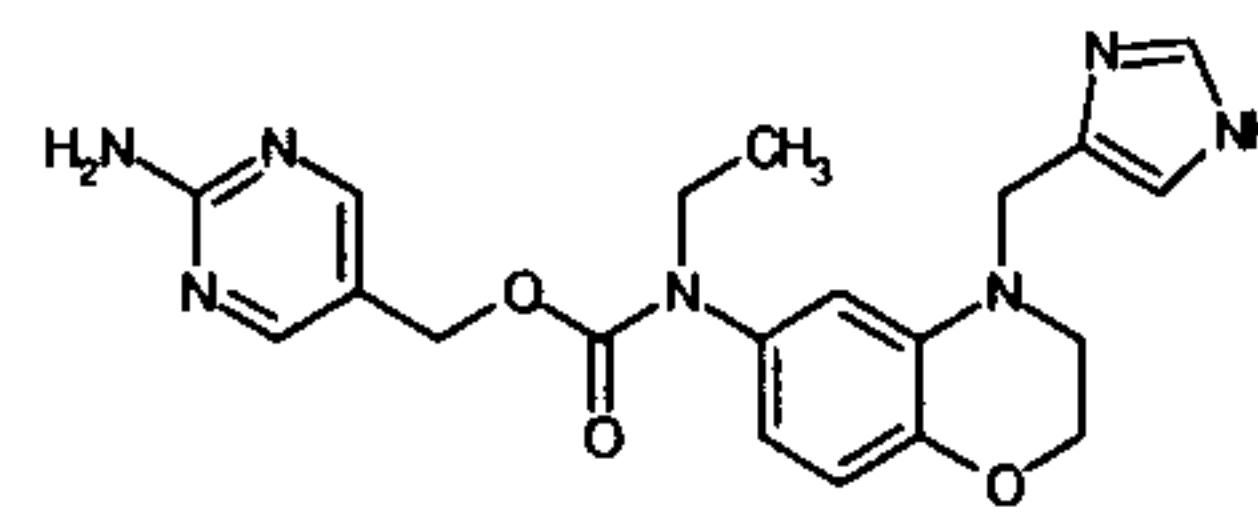
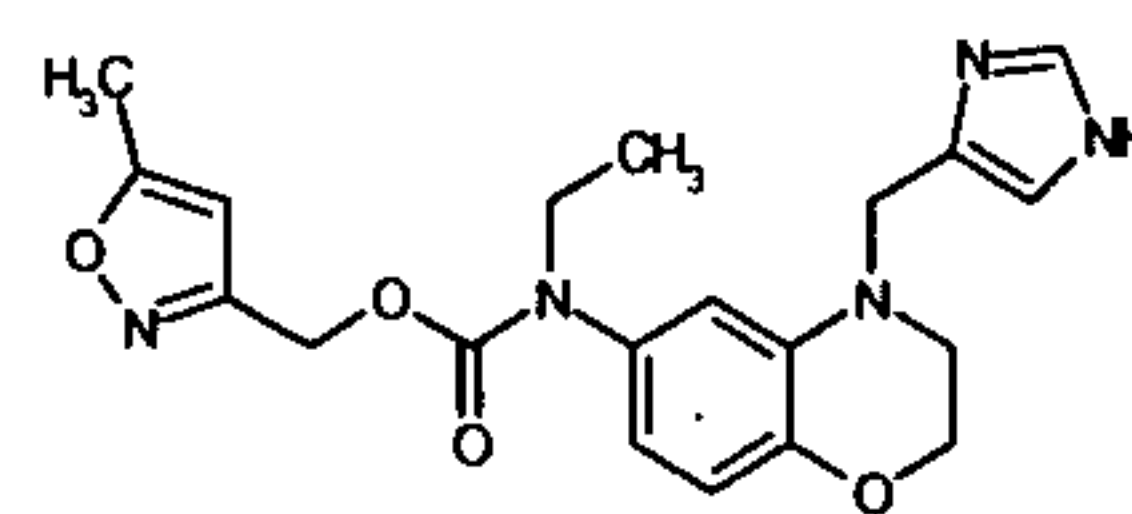




Another group of inventive compounds is as follows:

18





"Patient" includes both human and animals.

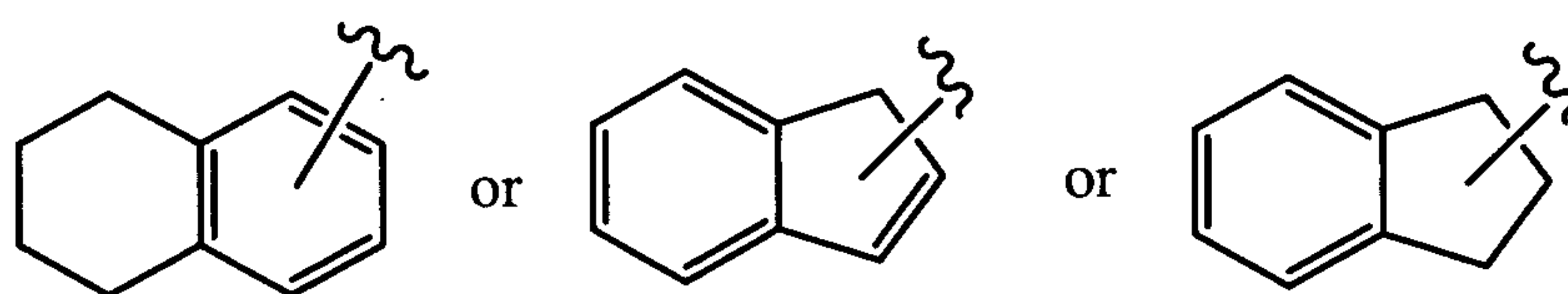
“Mammal” means humans and other mammalian animals.

“Congestion” refers to all type of congestion including, but not limited to, congestion associated with perennial allergic rhinitis, seasonal allergic rhinitis, non-allergic rhinitis, vasomotor rhinitis, rhinitis medicamentosa, sinusitis, acute rhinosinusitis, or chronic rhinosinusitis or when the congestion is caused by polyps or is virally induced, such as congestion associated with the common cold.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. The term "substituted alkyl" means that the alkyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)₂, carboxy and -C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butylnyl and 3-methylbutynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

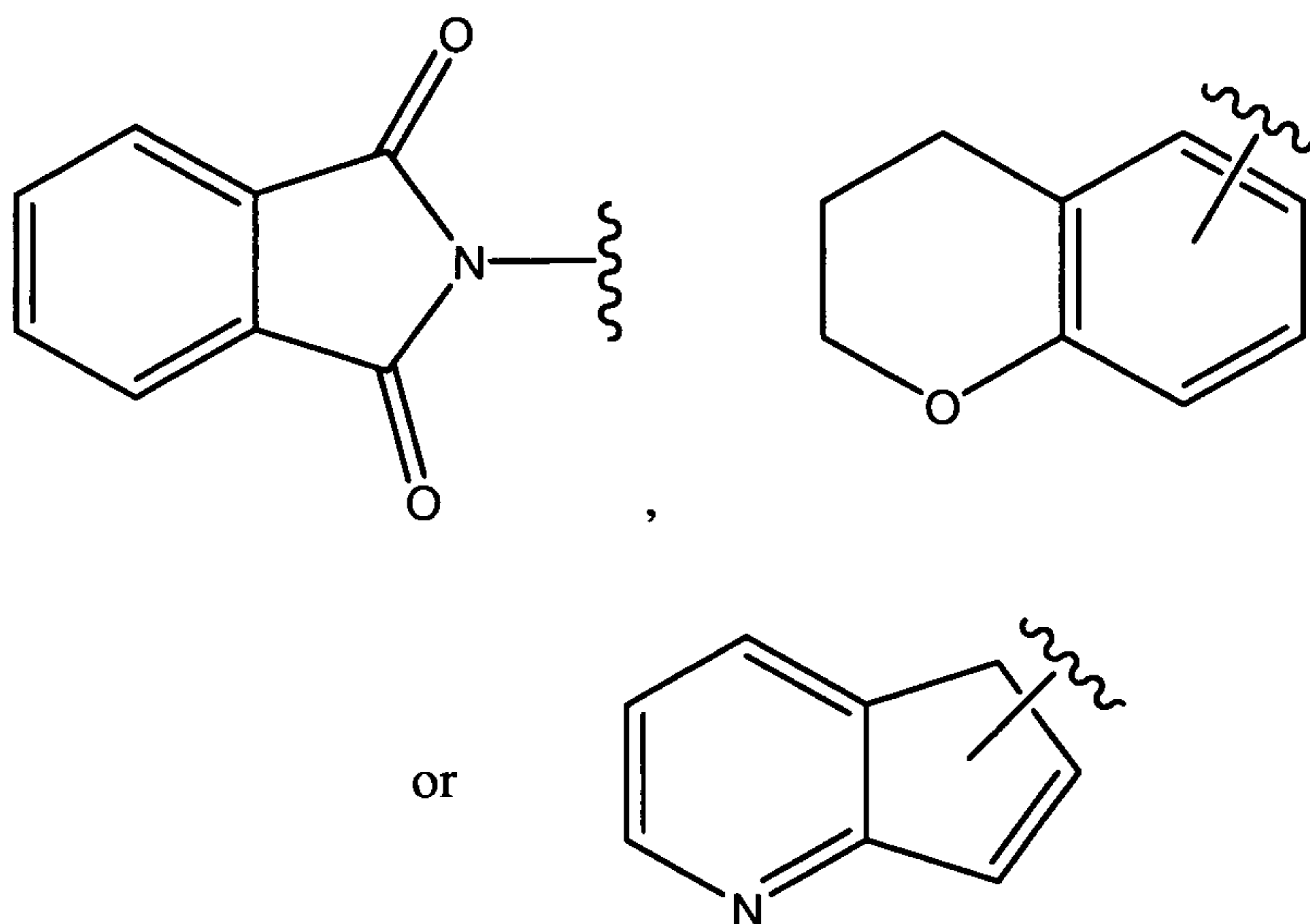
"Aryl" means an aromatic monocyclic or multicyclic ring system, in which at least one of the multicyclic rings is an aryl ring, comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl. Non-limiting examples of aryl multicyclic ring systems include:



"Heteroaryl" means an aromatic monocyclic or multicyclic ring system, in which at least one of the multicyclic rings is aromatic, comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, isoxazolyl,

isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalynyl, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolynyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolynyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like.

Non-limiting examples of heteroaryl multicyclic ring systems include:



"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like.

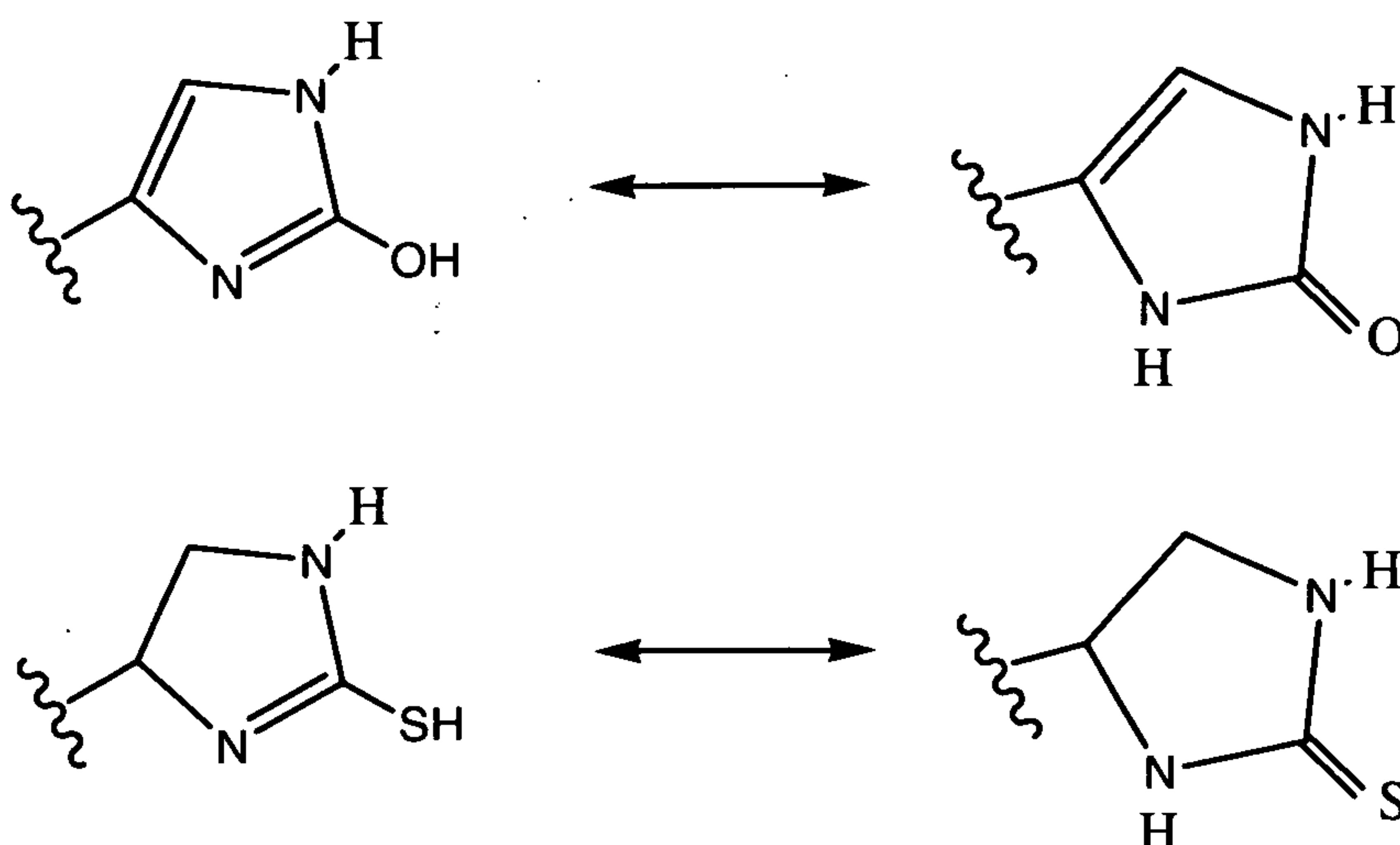
"Halogen" and "Halo" mean fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine or bromine, and more preferred are fluorine and chlorine.

"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, Y_1Y_2N- , Y_1Y_2N -alkyl-, $Y_1Y_2NC(O)-$ and $Y_1Y_2NSO_2-$, wherein Y_1 and Y_2 may be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl.

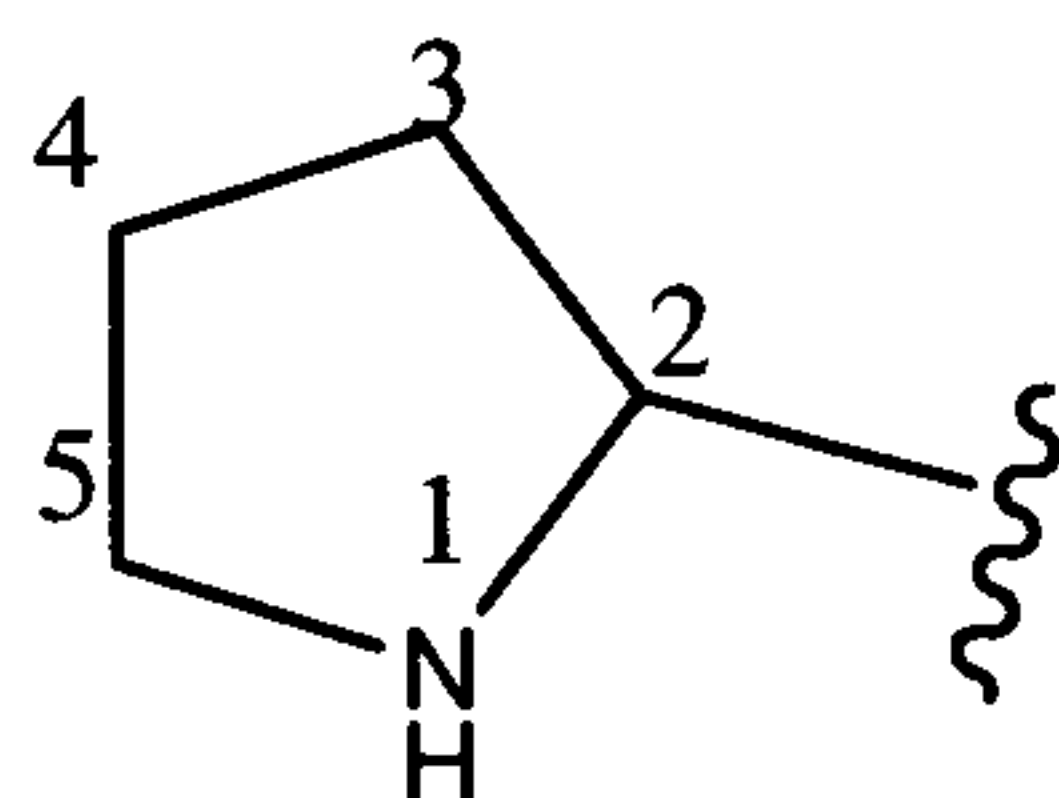
"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any $-NH$ in a heterocyclyl ring may exist protected such as, for example, as an $-N(Boc)$, $-N(CBz)$, $-N(Tos)$ group and the like; such protected moieties are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, and the like.

Compounds of Formula I and salts, esters, solvates and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention. Non-limiting examples of tautomeric forms that are part of this invention are as follows:

23



It should be noted that in saturated heterocyclyl containing systems of this invention, there are no hydroxyl, amino, or thiol groups on carbon atoms adjacent to a N, O or S atom. Thus, for example, in the ring:

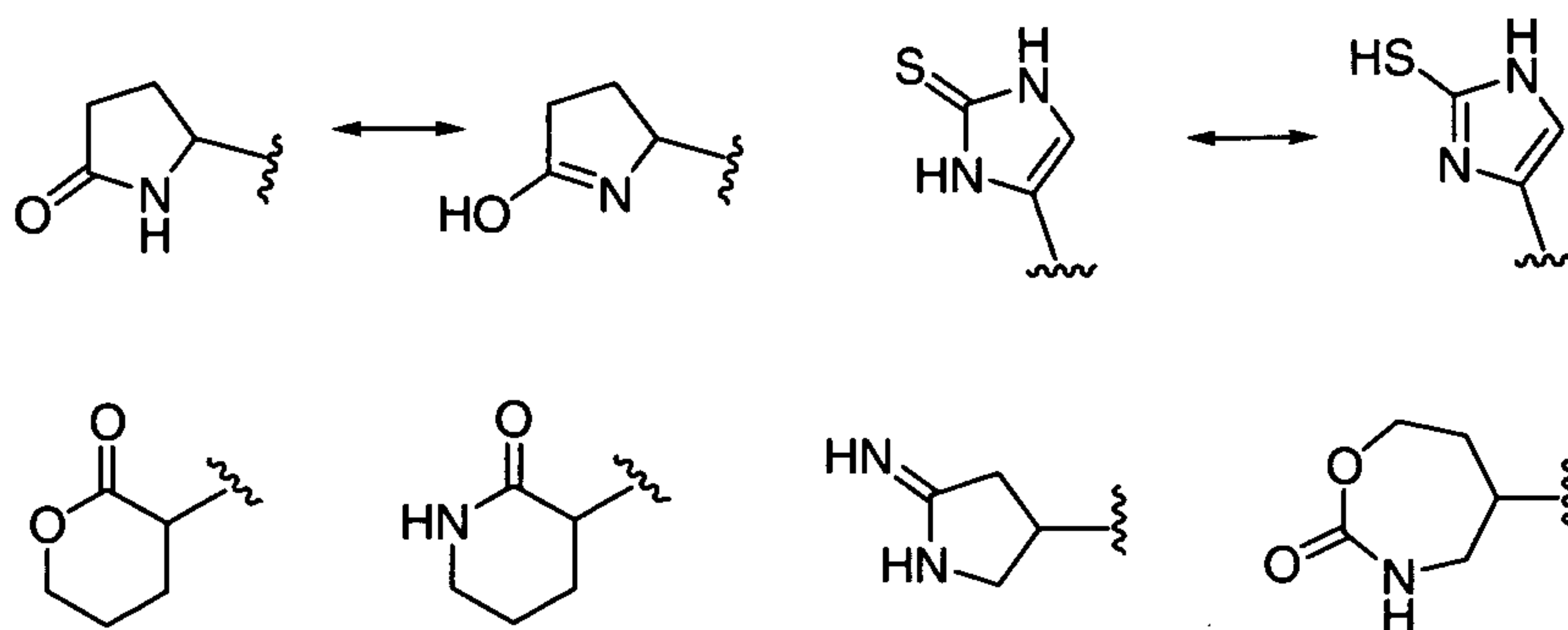


5

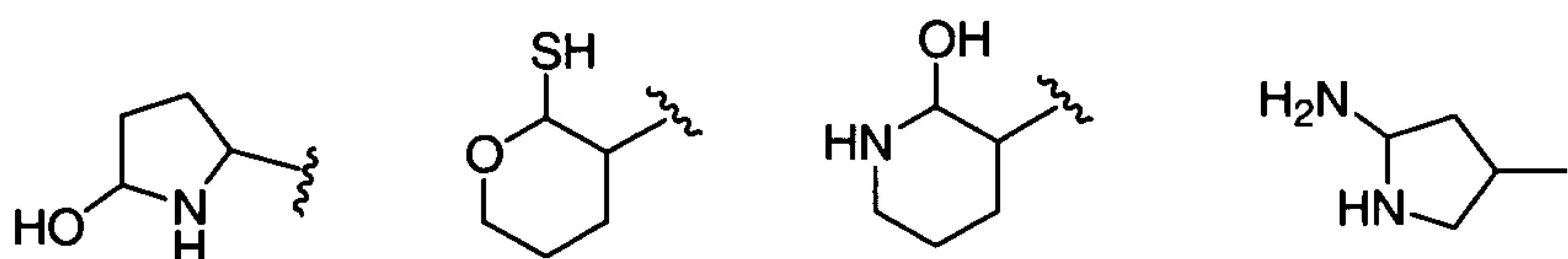
there is no -OH attached directly to carbons marked 2 and 5. It should also be noted that this definition does not preclude (=O), (=S), or (=N) substitutions, or their tautomeric forms, on C atoms adjacent to a N, O or S. Thus, for example, in the above ring, (=O) substitution on carbon 5, or its imino ether tautomer is allowed.

10

Non-limiting examples which illustrate the present invention are as follows:



The following non-limiting examples serve to illustrate radicals not contemplated by the present invention:



15

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

5 "Heteroaralkyl" or "heteroarylalkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

10 "Heterocyclalkyl" means a heterocycl-alkyl group in which the heterocycl and the alkyl are as previously described. Preferred heterocyclalkyls contain a lower alkyl group. Non-limiting examples of suitable heterocyclalkyl groups include piperidylmethyl, piperidylethyl, pyrrolidylmethyl, morpholinylpropyl, piperazinylethyl, azindylmethyl, azetidylethyl, oxiranylpropyl and the like. The bond to the parent
15 moiety is through the alkyl group.

"Heterocyclenyl" (or "heterocycloalkenyl") means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in
20 combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The
25 heterocyclenyl can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic azaheterocyclenyl groups include 1,2,3,4- tetrahydropyridyl, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-
30 tetrahydropyridyl, 1,4,5,6-tetrahydropyrimidyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolynyl, 2-pyrazolynyl, and the like. Non-limiting examples of suitable oxaheterocyclenyl groups include 3,4-dihydro-2H-pyran, dihydrofuranyl, fluorodihydrofuranyl, and the like. Non-limiting example of a suitable multicyclic oxaheterocyclenyl group is 7-

oxabicyclo[2.2.1]heptenyl. Non-limiting examples of suitable monocyclic thiaheterocyclenyl rings include dihydrothiophenyl, dihydrothiopyranyl, and the like.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Heterocyclenylalkyl" means a heterocyclenyl-alkyl group in which the heterocyclenyl and the alkyl are as previously described.

"Acyl" means an organic acid group in which the -OH of the carboxyl group is replaced by some other substituent. Suitable non-limiting examples include H-C(O)-, alkyl-C(O)-, cycloalkyl-C(O)-, heterocyclyl-C(O)-, and heteroaryl-C(O)- groups in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1-naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" or "arylalkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Heteroarylalkoxy" means a heteroarylalkyl-O-group in which the heteroarylalkyl group is as previously described.

"Heterocyclylalkoxy" means a heterocyclylalkyl-O group in which the heterocyclylalkyl group is as previously described.

"Heterocyclenylalkoxy" means a heterocyclenylalkyl-O group in which the heterocyclenylalkyl group is as previously described.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

5 "Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

10 "Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The
15 bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

20 "Alkylsulfonyl" means an alkyl-S(O₂)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-S(O₂)- group. The bond to the parent moiety is through the sulfonyl.

25 The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently
30 robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

It is noted that carbons of formula I can be replaced with 1-3 silicon atoms, provided all valency requirements are satisfied.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

It should also be noted that any heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the hydrogen atom to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R^2 , etc.) occurs more than one time in any constituent or formula, its definition on each occurrence is independent of its definition at every other occurrence.

Unless defined otherwise, all definitions for the variables follow the convention that the group to the right forms the point of attachment to the molecule; i.e., if a definition is arylalkyl, this means that the alkyl portion of the definition is attached to the molecule.

Further, all divalent variable are attached from left to right. For example when R^2 is $-(CH_2)_qN(R^7)YR^{7'}$, and Y is $-C(=O)-[C(R^a)(R^b)]_n-O-C(=O)-$, then R^2 forms the group $-(CH_2)_qN(R^7)-C(=O)-[C(R^a)(R^b)]_n-O-C(=O)-R^{7'}$.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of formula I or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) Volume 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B.

Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

For example, if a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a
 5 prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C₁-C₈)alkyl, (C₂-C₁₂)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl
 10 having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁-C₂)alkylamino(C₂-C₃)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C₁-C₂)alkyl, N,N-di (C₁-C₂)alkylcarbamoyl-(C₁-
 15 C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂-C₃)alkyl, and the like.

Similarly, if a compound of Formula (I) contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C₁-C₆)alkanoyloxymethyl, 1-((C₁-C₆)alkanoyloxy)ethyl, 1-methyl-1-((C₁-C₆)alkanoyloxy)ethyl, (C₁-
 20 C₆)alkoxycarbonyloxymethyl, N-(C₁-C₆)alkoxycarbonylaminomethyl, succinoyl, (C₁-C₆)alkanoyl, α-amino(C₁-C₄)alkanyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, -P(O)(OH)₂, -P(O)(O(C₁-C₆)alkyl)₂ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a
 25 carbohydrate), and the like.

If a compound of Formula I incorporates a -NH- functional group, such as a in a primary or secondary amine or in a nitrogen-containing heterocycle, such as imidazole or piperazine ring, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C₁-C₁₀)alkyl, (C₃-C₇) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, -C(OH)C(O)OY¹ wherein Y¹ is H, (C₁-C₆)alkyl or benzyl, -C(OY²)Y³ wherein Y² is (C₁-C₄) alkyl and Y³ is (C₁-C₆)alkyl, carboxy (C₁-C₆)alkyl, amino(C₁-C₄)alkyl or mono-N- or di-N,N-(C₁-

C₆)alkylaminoalkyl, -C(Y⁴)Y⁵ wherein Y⁴ is H or methyl and Y⁵ is mono-N- or di-N,N-(C₁-C₆)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

5 "Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

10 "Capsule" is meant to describe a special container or enclosure made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active ingredients. Hard shell capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins. The capsule itself may contain small amounts of dyes, opaquing agents, plasticizers and preservatives.

15 "Tablet" is meant to describe a compressed or molded solid dosage form containing the active ingredients with suitable diluents. The tablet can be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation or by compaction.

"Oral gels" is meant to describe to the active ingredients dispersed or solubilized in a hydrophillic semi-solid matrix.

"Powders for constitution" refers to powder blends containing the active ingredients and suitable diluents which can be suspended in water or juices.

20 "Diluent" refers to substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol and sorbitol; starches derived from wheat, corn, rice and potato; and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 10 to about 90% by weight of the total composition, preferably from about 25 to about 75%, more preferably from about 30 to about 60% by weight, even more preferably from about 12 to about 60%.

25 "Disintegrants" refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Suitable disintegrants include starches; "cold water soluble" modified starches such as sodium carboxymethyl starch; natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar; cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose; microcrystalline celluloses and cross-linked microcrystalline celluloses such as sodium croscarmellose; alginates such as alginic acid and sodium

30

alginate; clays such as bentonites; and effervescent mixtures. The amount of disintegrant in the composition can range from about 2 to about 15% by weight of the composition, more preferably from about 4 to about 10% by weight.

“Binders” refers to substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent.

Suitable binders include sugars such as sucrose; starches derived from wheat, corn rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; cellulosic materials such as methylcellulose and sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as magnesium aluminum silicate. The amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

“Lubricant” is meant to describe a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate; stearic acid; high melting point waxes; and water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and d'l-leucine. Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts of the tablet press. The amount of lubricant in the composition can range from about 0.2 to about 5% by weight of the composition, preferably from about 0.5 to about 2%, more preferably from about 0.3 to about 1.5% by weight.

“Glidents” means materials that prevent caking and improve the flow characteristics of granulations, so that flow is smooth and uniform. Suitable glidents include silicon dioxide and talc. The amount of glident in the composition can range from about 0.1% to about 5% by weight of the total composition, preferably from about 0.5 to about 2% by weight.

“Coloring agents” refers to excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes and food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The

amount of the coloring agent can vary from about 0.1 to about 5% by weight of the composition, preferably from about 0.1 to about 1%.

“Bioavailability” refers to the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed into the systemic circulation from an administered dosage form as compared to a standard or control. Conventional methods for preparing tablets are known. Such methods include dry methods such as direct compression and compression of granulation produced by compaction, or wet methods or other special procedures. Conventional methods for making other forms for administration such as, for example, capsules, suppositories and the like are also well known.

The compounds of Formula I can form salts which are also within the scope of this invention. Reference to a compound of Formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula III contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula I may be formed, for example, by reacting a compound of Formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of*

Pharmaceutics (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

5 Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents
10 such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically
15 acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of Formula I, and salts, solvates and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric
20 forms are contemplated herein as part of the present invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons or sulfurs on various substituents, including
25 enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention. For example, if a compound of Formula (I) incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Individual stereoisomers of the
30 compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms

"salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrugs of the inventive compounds.

Diasteromeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diasteromeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of Formula (I) may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

Polymorphic forms of the compounds of formula I, and of the salts, solvates and prodrugs of the compounds of formula I, are intended to be included in the present invention

The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively.

Certain isotopically-labelled compounds of Formula (I) (e.g., those labeled with ^3H , ^{11}C and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^3H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labelled compounds of Formula (I) can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples hereinbelow, by

substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent.

The compounds according to the invention have pharmacological properties; in particular, the compounds of Formula I can be useful as α_2C adrenoreceptor agonists.

5 A preferred dosage is about 0.001 to 500 mg/kg of body weight/day of the compound of Formula I. An especially preferred dosage is about 0.01 to 25 mg/kg of body weight/day of a compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound.

The compounds of this invention may also be useful in combination
10 (administered together or sequentially) with one or more therapeutic agents such as, for example, glucocorticosteroids, PDE-4 inhibitors, anti-muscarinic agents, cromolyn sodium, H_1 receptor antagonists, 5-HT₁ agonists, NSAIDs, angiotensin-converting enzyme inhibitors, angiotensin II receptor agonists, β -blockers, β -agonists (including both short and long acting), leukotriene antagonists, diuretics, aldosterone
15 antagonists, ionotropic agents, natriuretic peptides, pain management/analgesic agents, anti-anxiety agents, anti-migraine agents, and therapeutic agents suitable for treating heart conditions, psychotic disorders, and glaucoma.

Suitable steroids include prednisolone, fluticasone (including all esters such as the propionate or furoate esters), triamcinolone, beclomethasone, mometasone
20 (including any ester form such as mometasone furoate), budasamine, ciclesonide, betamethasone, dexamethasone, prednisone, flunisolide, and cortisone.

Suitable PDE-4 inhibitors include roflumilast, theophylline, rolipram, piclamilast, cilomilast, and CDP-840.

Suitable anti-muscarinic agents include ipratropium bromide and tiotropium
25 bromide.

Suitable H_1 antagonists include astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratidine, diphenhydramine, doxylamine, dimethindene, ebastine, epinastine, efletirizeine, fexofenadine,
30 hydroxyzine, ketotifen, loratidine, levocabastine, meclizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, meclizine, mizolastine, mequitazine, mianserin, noberastine, norastemizole, picumast, pyrilamine, promethazine, terfenadine, tripelennamine, temelastine, trimeprazine or triprolidine.

Suitable anti-inflammatory agents include aspirin, diclofenac, diflunisal, etodolac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, and tolmetin.

Suitable aldosterone antagonists include spironolactone.

5 Suitable ionotropic agents include digitalis.

Suitable angiotensin II receptor agonists include irbesartan and losartan.

Suitable diuretics include spironolactone, methyclothiazide, bumetanide, torsemide, hydroflumethiazide, trichlormethiazide, hydrochlorothiazide, triamterene, ethacrynic acid, methyclothiazide, hydrochlorothiazide, benzthiazide,
10 hydrochlorothiazide, quinethazone, hydrochlorothiazide, chlorthalidone, furosemide, indapamide, hydrochlorothiazide, triamterene, trichlormethiazide, hydrochlorothiazide, amiloride HCl, amiloride HCl, metolazone, trichlormethiazide, bendroflumethiazide, hydrochlorothiazide, polythiazide, hydroflumethiazide, chlorthalidone, and metolazone.

Suitable pain management/analgesic agents include; Celecoxib, amitriptyline,
15 ibuprofen, naproxen, tramadol, rofecoxib, oxycodone HCl, acetaminophenoxycodone HCl, carbamazepine, amitriptyline, diclofenac, diclofenac, etodolac, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac tromethamine, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, tolmetin sodium, valdecoxib, diclofenac/ misoprostol, oxycontin, vicodin, darvocet,
20 percocet, morphine sulfate, dilaudid, stadol, stadol NS, nalbuphine, acetaminophen with codeine, acetaminophen with codeine #4, Lidoderm[®] patches, ziconotide, duloxetine, roboxetine, gabapentin and pregabalin.

Suitable β -blockers include acebutolol, atenolol, atenolol/chlorthalidone, betaxolol, bisoprolol fumarate, bisoprolol/HCTZ, labetalol, metoprolol tartrate, nadolol,
25 pindolol, propranolol, propranolol/HCTZ, sotalol, and timolol.

Suitable β -agonists include dobutamine, ritodrine, salbutamol, levalbuterol, metaproterenol, formoterol, fenoterol, bambuterol, brocaterol, clenbuterol, terbutaline, tulobuterol, epinephrine, isoprenaline, and hexoprenaline.

Suitable leukotriene antagonists include levamisole.

30 Suitable anti-migraine agents include rovatriptan succinate, naratriptan HCl, rizatriptan benzoate, sumatriptan succinate, zolmitriptan, almotriptan malate, methysergide maleate, dihydroergotamine mesylate, ergotamine tartrate, ergotamine

tartrate/caffeine, Fioricet[®], Fiorinal[®], Depakene[®], and Depakote[®].

Suitable anti-anxiety and anti-depressant agents include amitriptyline HCl, bupropion HCl, citalopram hydrobromide, clomipramine HCl, desipramine, fluoxetine, fluvoxamine maleate, maprotiline HCl, mirtazapine, nefazodone HCl, nortriptyline, paroxetine HCl, protriptyline HCl, sertraline HCl, doxepin, and trimipramine maleate.

Suitable angiotensin converting enzyme inhibitors include Captopril, enalapril, enalapril/HCTZ, lisinopril, lisinopril/HCTZ, and Aceon[®].

The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. The exemplified pharmacological assays which are described later have been carried out with the compounds according to the invention and their salts.

This invention is also directed to pharmaceutical compositions which comprise at least one compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound and at least one pharmaceutically acceptable carrier.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), *Remington's Pharmaceutical Sciences*, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

5 The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

The compounds of this invention may also be delivered subcutaneously.

Preferably the compound is administered orally.

10 Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

15 The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 100 mg, preferably from about 1 mg to about 50 mg, more preferably from about 1 mg to about 25 mg, according to the particular application.

20 The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

25 The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 500 mg/day, preferably 1 mg/day to 200 mg/day, in two to four divided doses.

30 Another aspect of this invention is a kit comprising a therapeutically effective amount of at least one compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

Yet another aspect of this invention is a kit comprising an amount of at least one compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound and an amount of at least one therapeutic agent listed above, wherein the amounts of the two or more ingredients result in desired therapeutic effect.

5 The invention disclosed herein is exemplified by the following preparations and examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art.

10 Where NMR data are presented, ^1H spectra were obtained on either a Varian VXR-200 (200 MHz, ^1H), Varian Gemini-300 (300 MHz), Varian Mercury VX-400 (400MHz), or Bruker-Biospin AV-500 (500MHz), and are reported as ppm with number of protons and multiplicities indicated parenthetically. Where LC/MS data are presented, analyses was performed using an Applied Biosystems API-100 mass spectrometer and C18 column, 10-95% $\text{CH}_3\text{CN-H}_2\text{O}$ (with 0.05% TFA) gradient. The
15 observed parent ion is given.

The following solvents and reagents may be referred to by their abbreviations in parenthesis:

Me = methyl; Et = ethyl; Pr = propyl; Bu = butyl; Ph = phenyl, and Ac = acetyl
 μl = microliters

20 AcOEt or EtOAc = ethyl acetate

AcOH or HOAc = acetic acid

ACN = acetonitrile

atm = atmosphere

Boc or BOC = tert-butoxycarbonyl

25 DCE = dichloroethane

DCM or CH_2Cl_2 : dichloromethane:

DIPEA = diisopropylethylamine

DMAP = 4-dimethylaminopyridine

DMF = dimethylformamide

30 DMS = dimethylsulfide

DMSO = dimethyl sulfoxide

EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

Fmoc = 9-fluorenylmethoxycarbonyl

g = grams

h = hour

hal = halogen

HOBt = 1-hydroxybenzotriazole

5 LAH = lithium aluminum hydride

LCMS = liquid chromatography mass spectrometry

min = minute

mg = milligrams

mL = milliliters

10 mmol = millimoles

MCPBA = 3-chloroperoxybenzoic acid

MeOH = methanol

MS = mass spectrometry

NMR = nuclear magnetic resonance spectroscopy

15 RT or rt = room temperature (ambient, about 25°C)

TEA or Et₃N = triethylamine

TFA = trifluoroacetic acid

THF = tetrahydrofuran

TLC = thin layer chromatography

20 TMS = trimethylsilyl

Tr = triphenylmethyl

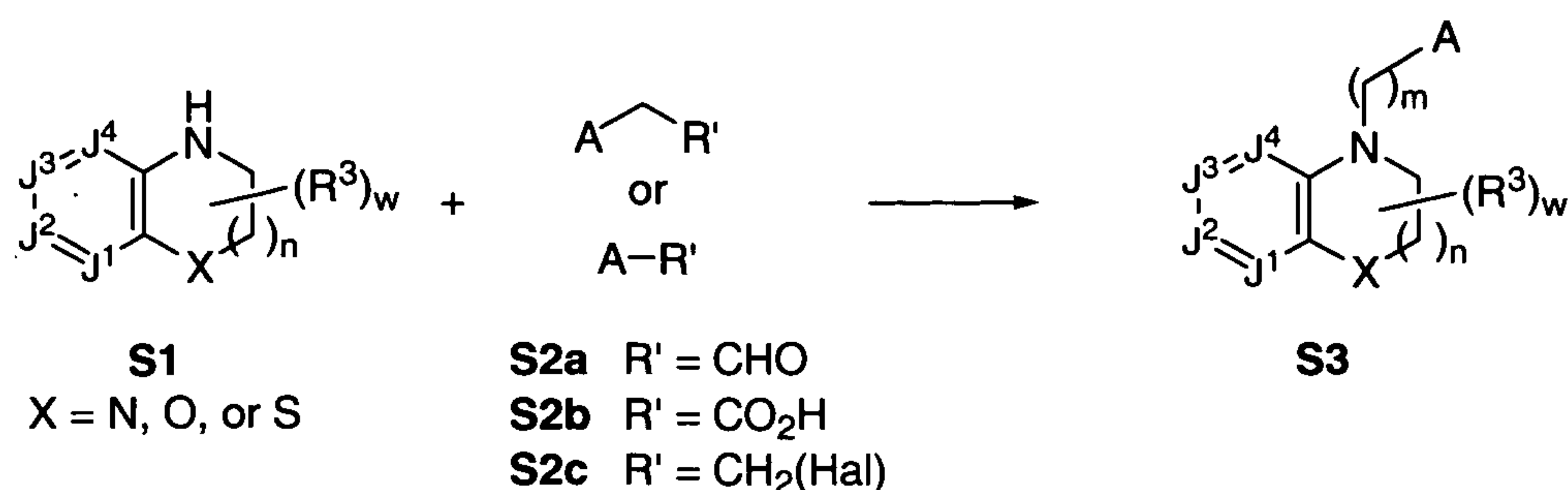
Examples

The compounds of this invention can be prepared as generally described in
25 Schemes 1 and 2, and the following examples. Scheme 1 shows an approach in
which **S1** and **S2** are joined together. Examples of these approaches include reaction
of **S1** with an electrophilic **S2** compound, where **R'** is a carboxaldehyde (coupling by
reductive amination), carboxylic acid (amide coupling) or halide (coupling by
alkylation).

30

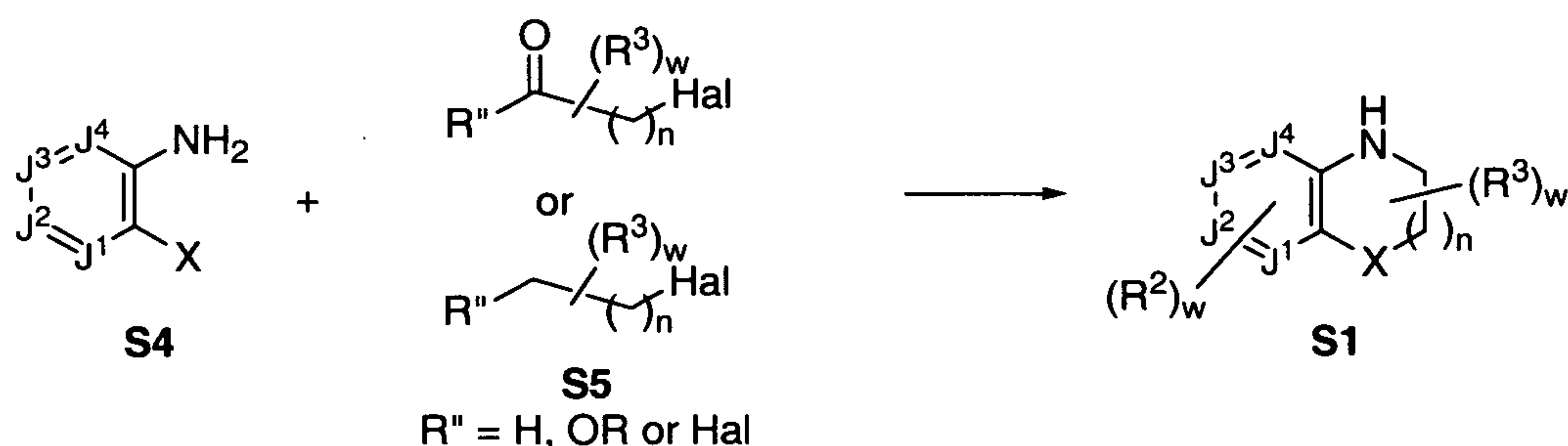
Scheme 1

40



Scheme 2 discloses a general approach for synthesizing **S1**, whereby an appropriately substituted aniline **S4** can be converted to **S1** through a single or multistep ring cyclization approach.

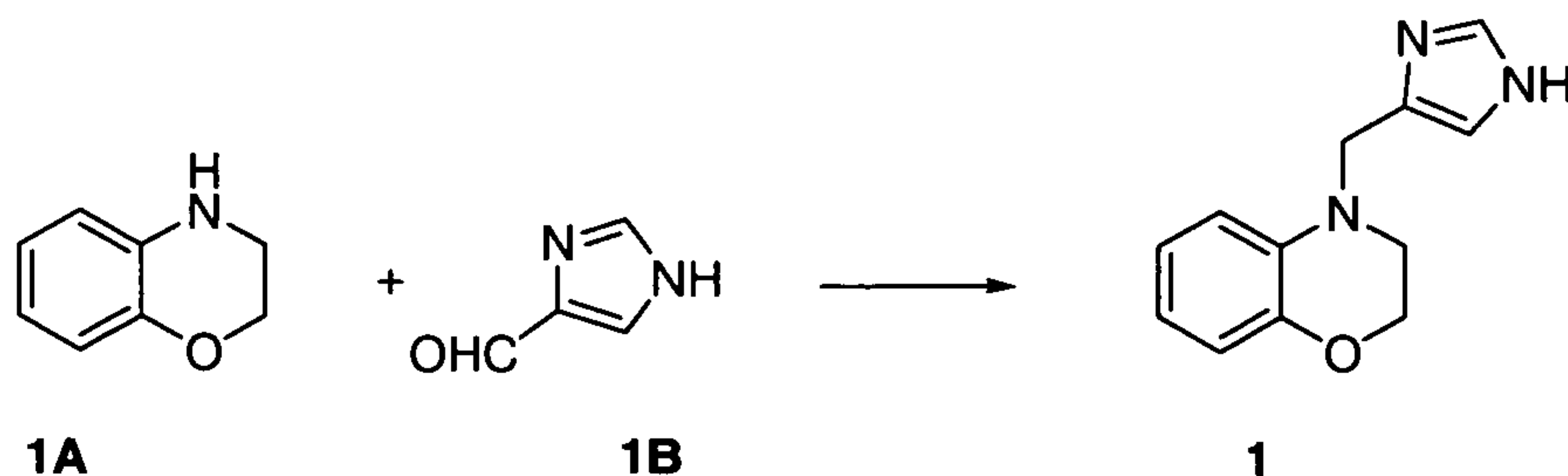
Scheme 2



Compounds of formula **S3** can be prepared by the general methods outlined above. Specifically exemplified compounds were prepared from **S4** or **S1** fragments as described in the examples below or from starting materials known in the art.

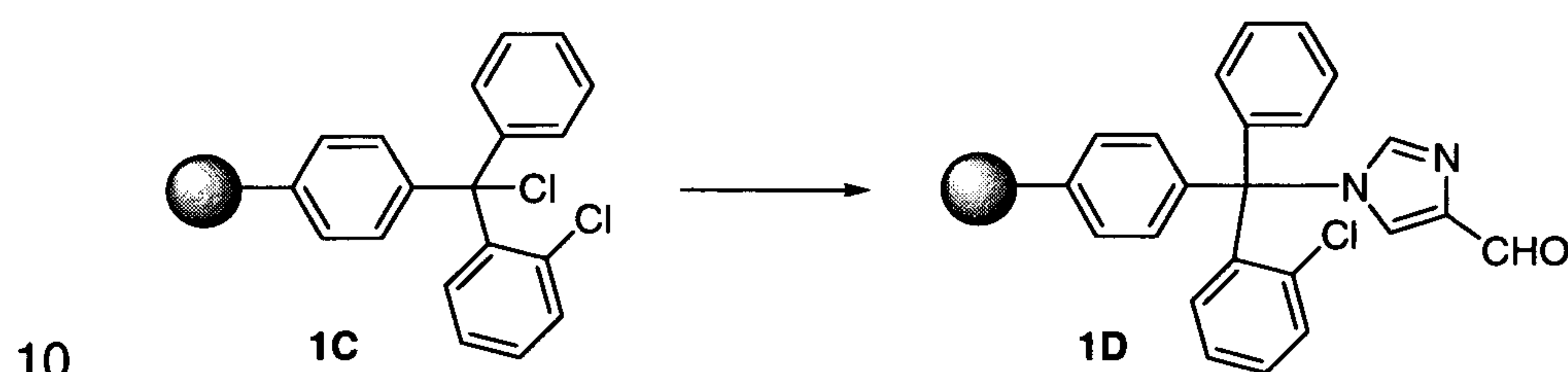
The starting materials and reagents used in preparing compounds described are either available from commercial suppliers such as Aldrich Chemical Co. (Wisconsin, USA) and Acros Organics Co. (New Jersey, USA) or were prepared by literature methods known to those skilled in the art. These examples are being provided to further illustrate the present invention. They are for illustrative purposes only; the scope of the invention is not to be considered limited in any way thereby.

PREPARATIVE EXAMPLE 1



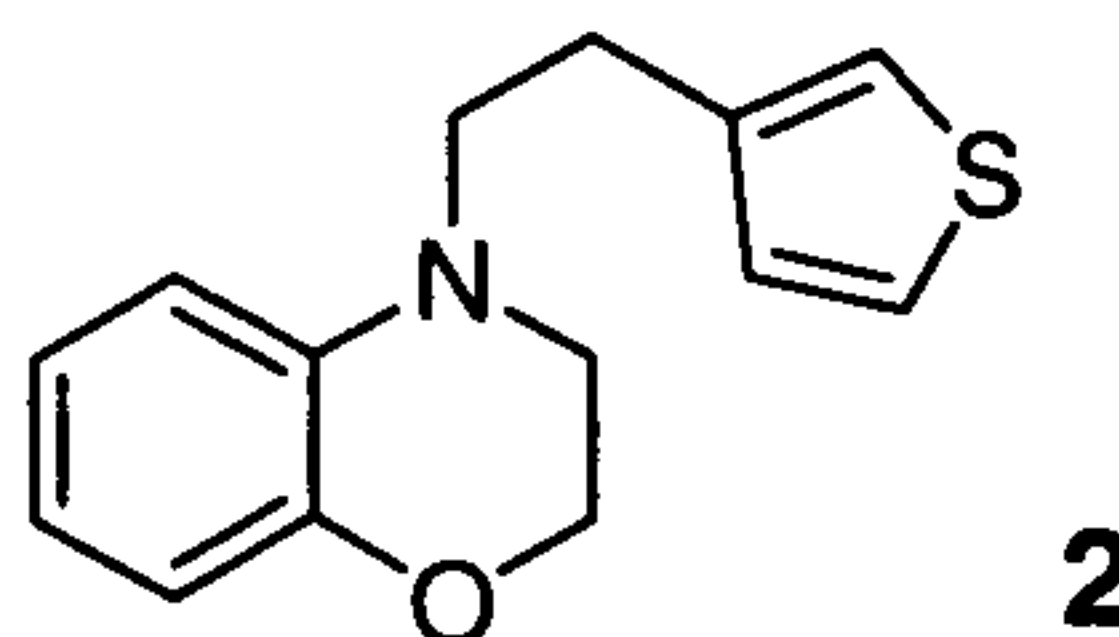
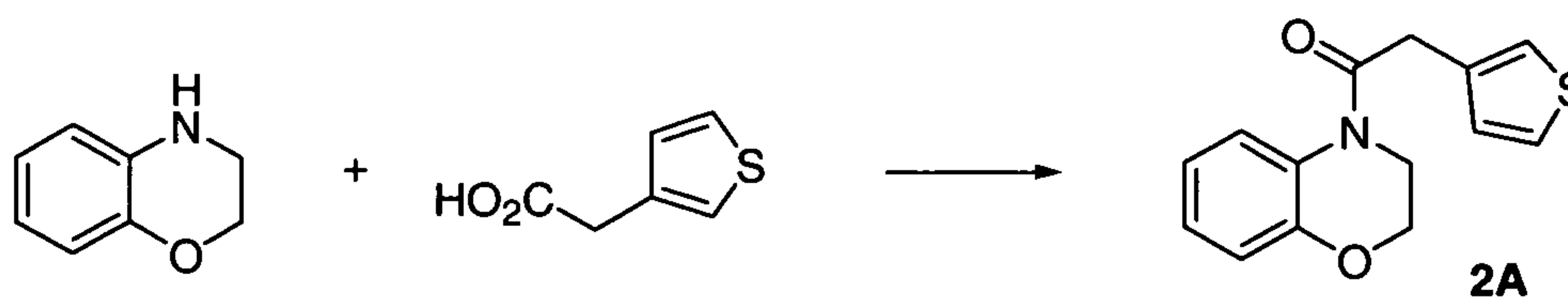
A solution of 3,4-dihydro-2H-1,4-benzoxazine **1A** (0.1 g, 0.75 mmol) in DCE (10 mL) was treated with imidazole-4-carboxaldehyde **1B** (0.11 g, 1.1 mmol), NaBH(OAc)₃ (0.47 g, 2.2 mmol), and AcOH (one drop) and stirred at 60 °C overnight. The reaction was then diluted with CH₂Cl₂, washed with saturated aqueous NaHCO₃, dried over Na₂SO₄, and concentrated. Chromatography (0-4% 7 N NH₃-MeOH/CH₂Cl₂) provided **1** as a beige solid (0.08 g, 50%). LMCS m/z 216 (MH⁺).

Alternatively, the title compound **1** can be synthesized by the reaction of **1A** and resin bound imidazole-4-carboxaldehyde **1D** as described below:



Novabiochem Resin **1C** (100-200 mesh, 1% DVB, 1.4 mmol/g, 5g) was suspended in anhydrous DMF (25 mL) and DCE (25 mL) and treated sequentially with **1B** (2 g, 21 mmol) and TEA (2.96 mL, 21 mmol). The resin was shaken overnight and washed with DMF (3x), MeOH (3x), and DCM (4x) then dried in vacuo overnight. The resulting resin **1D** (100 mg, 1.4 mmol/g, 0.14 mmol) was suspended in DCE (4 mL) and treated with **1A** (94.5mg, 0.7 mmol) and NaBH(OAc)₃ (148mg, 0.7 mmol). The reaction was shaken overnight and washed with DMF (3x), MeOH (3x), and DCM (4x), then dried in vacuo. The resulting resin was subjected to 30%TFA/DCM, stirred at RT for 2 h and the mixture was concentrated under vacuum. The residue was purified by Gilson prep-HPLC to afford compound **1** (12.3 mg).

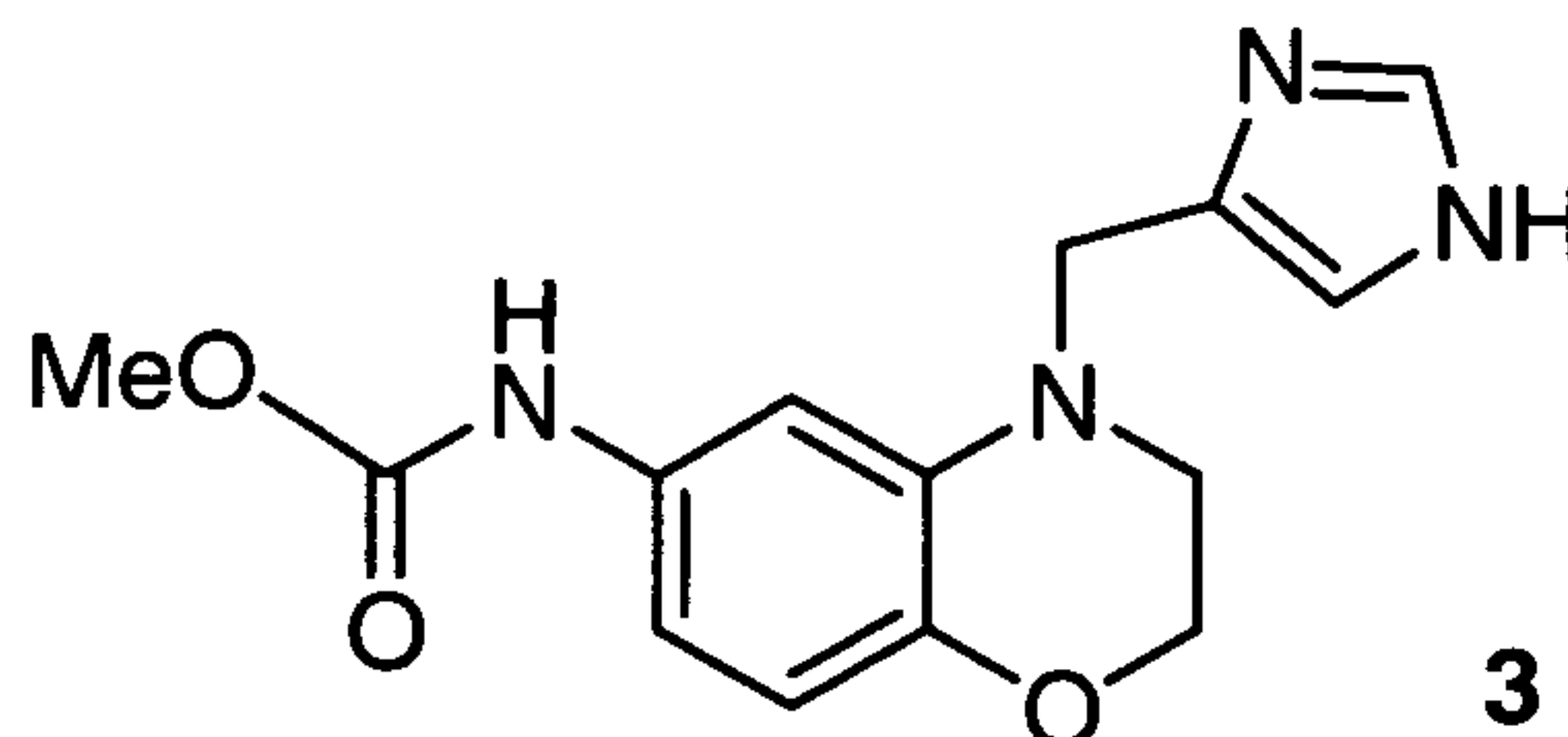
42

PREPARATIVE EXAMPLE 2**Step 1**

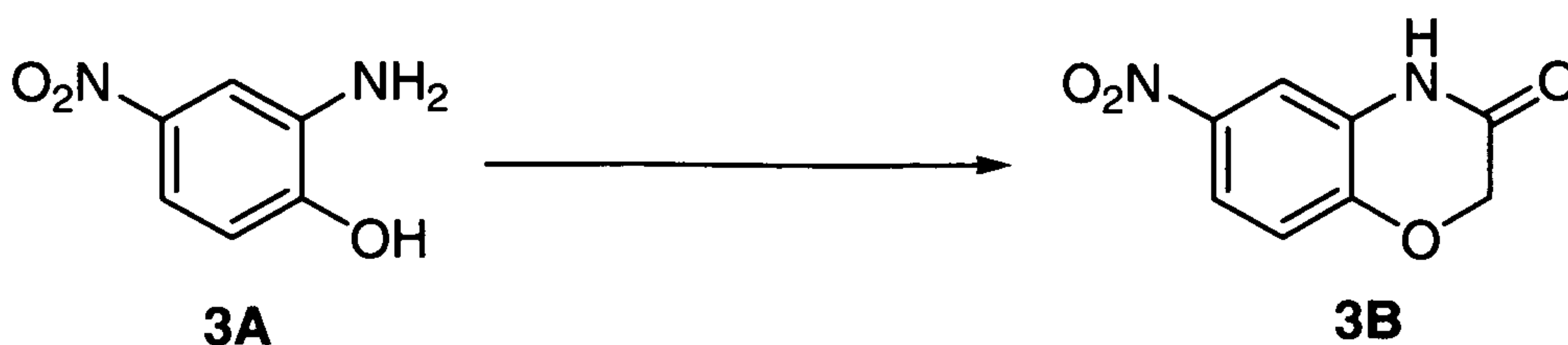
- 5 A solution of 3,4-dihydro-2H-1,4-benzoxazine (0.52 g, 3.8 mmol) and thiophene-3-acetic acid (0.82 g, 5.7 mmol) in 1:1 CH₂Cl₂:DMF (20 mL) was treated with DIPEA (2.6 ml, 15 mmol), HOBt (1.29 g, 9.5 mmol), and EDCI (1.83 g, 9.5 mmol) and stirred at 70 °C overnight. The reaction was then diluted with CH₂Cl₂, washed with saturated aqueous NaHCO₃, dried over Na₂SO₄, and concentrated.
- 10 Chromatography (0-10% 1 N NH₃-MeOH/EtOAc) provided **2A** as a red solid (0.54g, 55%)

Step 2

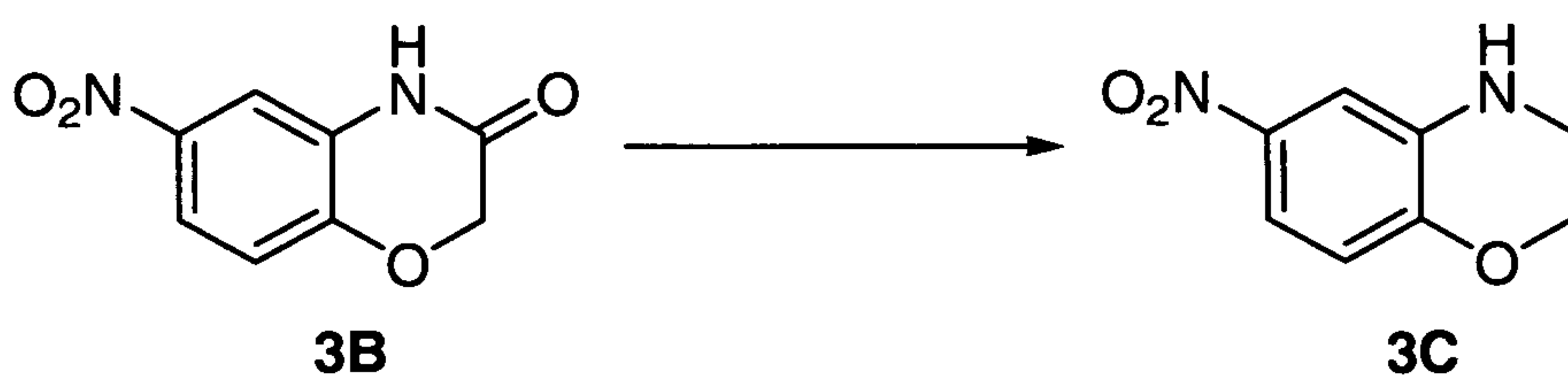
- 15 A solution of **2A** (0.094 g, 0.36 mmol) in THF (10 mL) was treated with BH₃-SMe₂ (2M/THF, 0.27 mL, 0.54 mmol) and stirred at reflux for 2h. The reaction was concentrated and subjected to chromatography (EtOAc) to provide **2** as a white solid (0.040 g, 45%). LMCS m/z 246 (MH⁺).

PREPARATIVE EXAMPLE 3

43

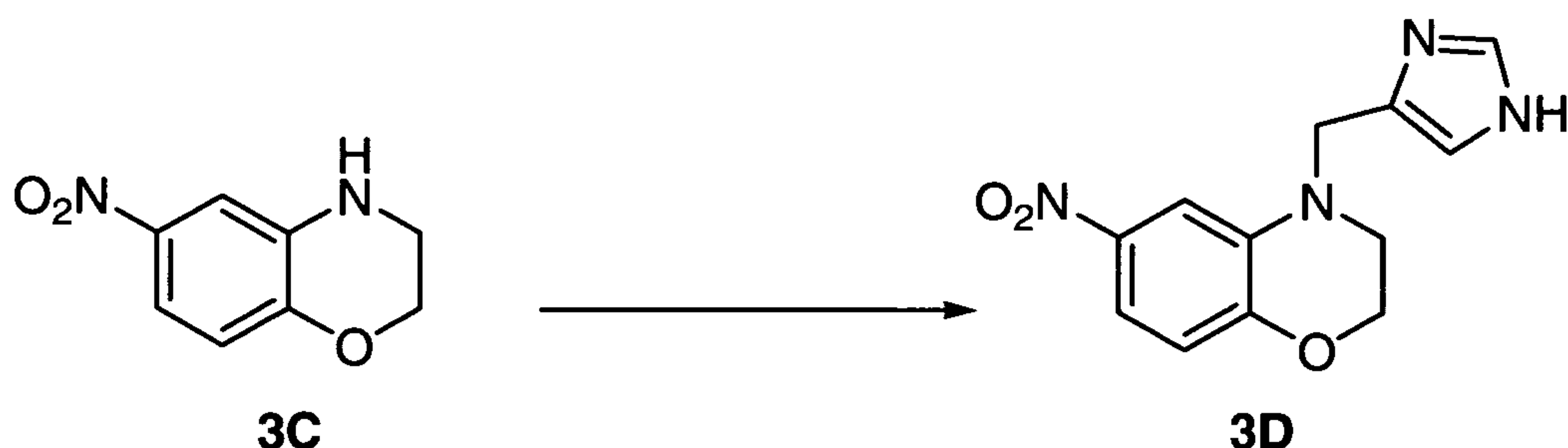
Step 1

A mixture of 2-amino-4-nitrophenol (**3A**, 25.03 g, 0.16 mol) in 4-methyl-2-pentanone and water (420 mL, 1:1) was treated with sodium bicarbonate (32.74g, 0.39mol), cooled to 0 °C, and treated then with chloroacetyl chloride (15.52 mL, 0.19 mol). The reaction mixture was heated to reflux overnight. After cooling to RT, the mixture was concentrated under vacuum. The residue was diluted with water (200 mL) and EtOAc (100 mL), and filtered to give the pale gray solid **3B** (26.05 g). The filtrate was separated and the aqueous was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water, and dried (MgSO₄), filtered, and concentrated under vacuum to give additional light gray solid **3B** (7.7 g). The resulting solid (quantitative yield) was used for next reaction without further purification.

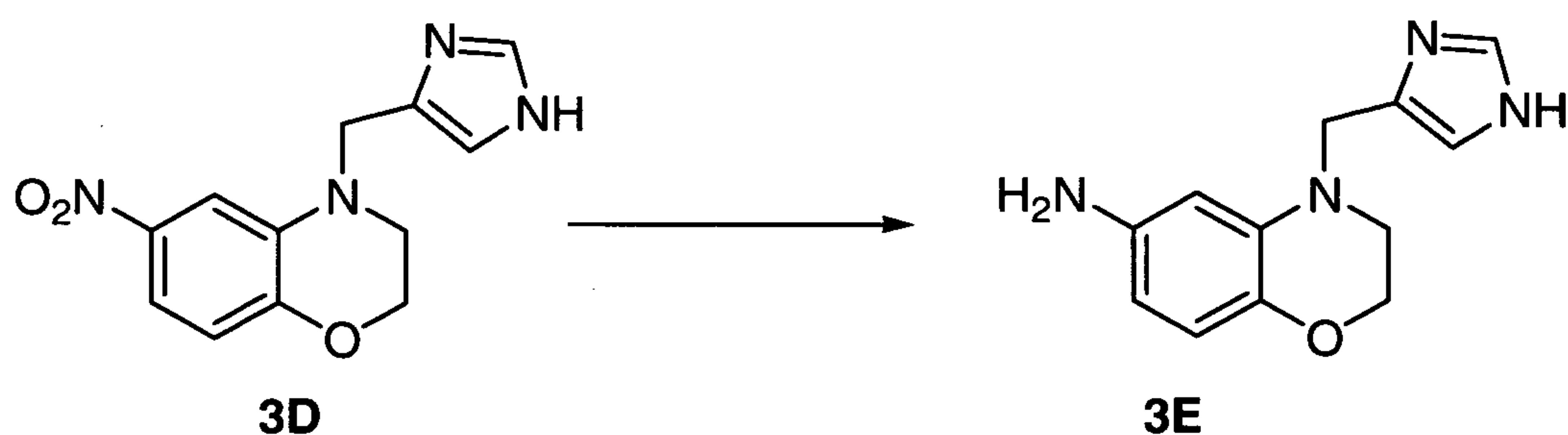
Step 2

To compound **3B** (6.76 g, 34.84 mmol) in anhydrous THF (200 mL) was added BH₃-SMe₂ (2.0M/THF, 35 mL, 69.68 mmol). The mixture was heated to reflux for 2 h. After cooling to RT, the mixture was quenched with MeOH (10 ml) and heated to reflux for another 10 minutes. The reaction mixture was concentrated under vacuum. Chromatography (10%-30% EtOAc/hexanes) provided **3C** (6.1 g, 97% for two steps).

44

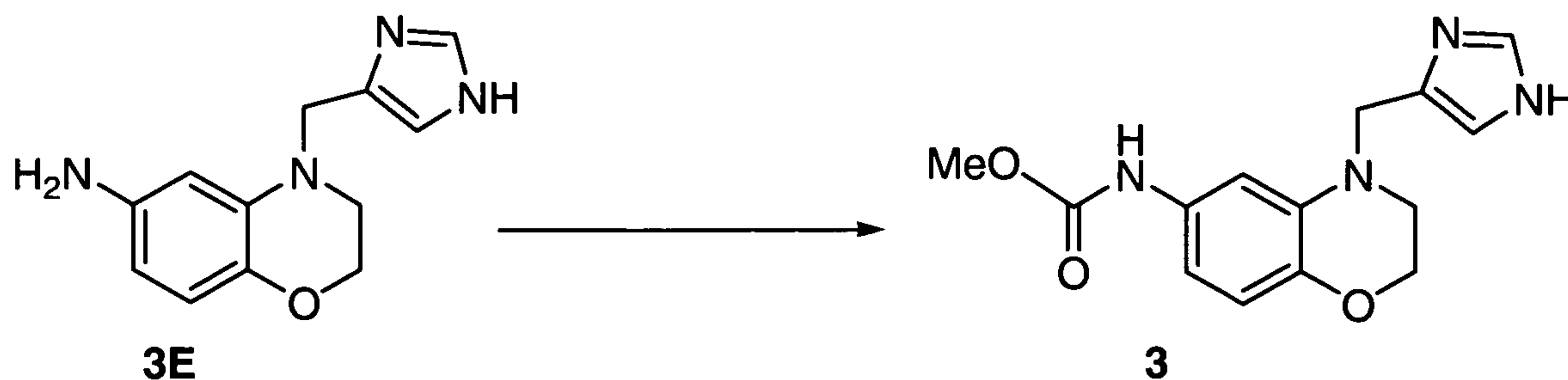
Step 3

A mixture of **3C** (4.35 g, 21.16 mmol) in anhydrous dichloroethane (60 mL) was treated with imidazole-4-carboxaldehyde (**1B**, 2.79 g, 28.99 mmol) and AcOH (0.35 mL, 6 mmol). The mixture was stirred at RT for 10 min and then treated with NaBH(OAc)₃ (15.36 g, 72.48 mmol). The reaction mixture was stirred at RT overnight, and quenched with 2N NaOH solution, concentrated under vacuum. The residue was diluted with water (50 mL) and extracted with EtOAc (4 x 100 mL). The organic layer was dried (MgSO₄), filtered, and concentrated under vacuum. Chromatography (DCM containing 1 to 5% of 7N NH₃ in MeOH) provided **3D** (5.56g, 89%). MS m/z 261 (MH⁺).

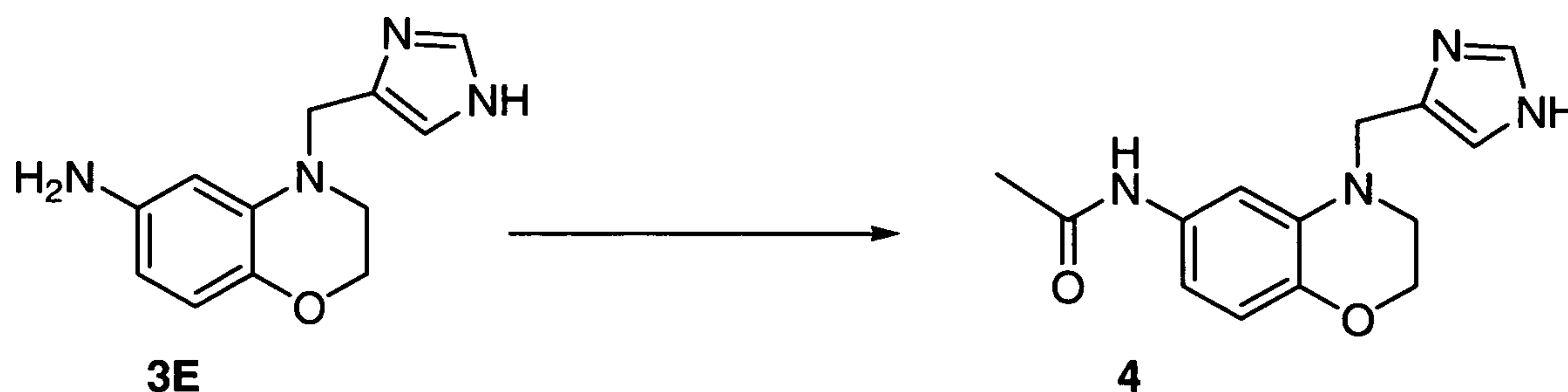
Step 4

Compound **3D** (5.56 g, 21.38 mmol) was dissolved in MeOH/EtOAc (300 mL, 1:1), 10% Pd/C (1.11 g, 20% by weight) was carefully added. The mixture was stirred at RT under a hydrogen balloon overnight and filtered. The solvent was evaporated off under vacuum to give a white solid **3E** (5.46 g, 100%). MS m/z 231 (MH⁺).

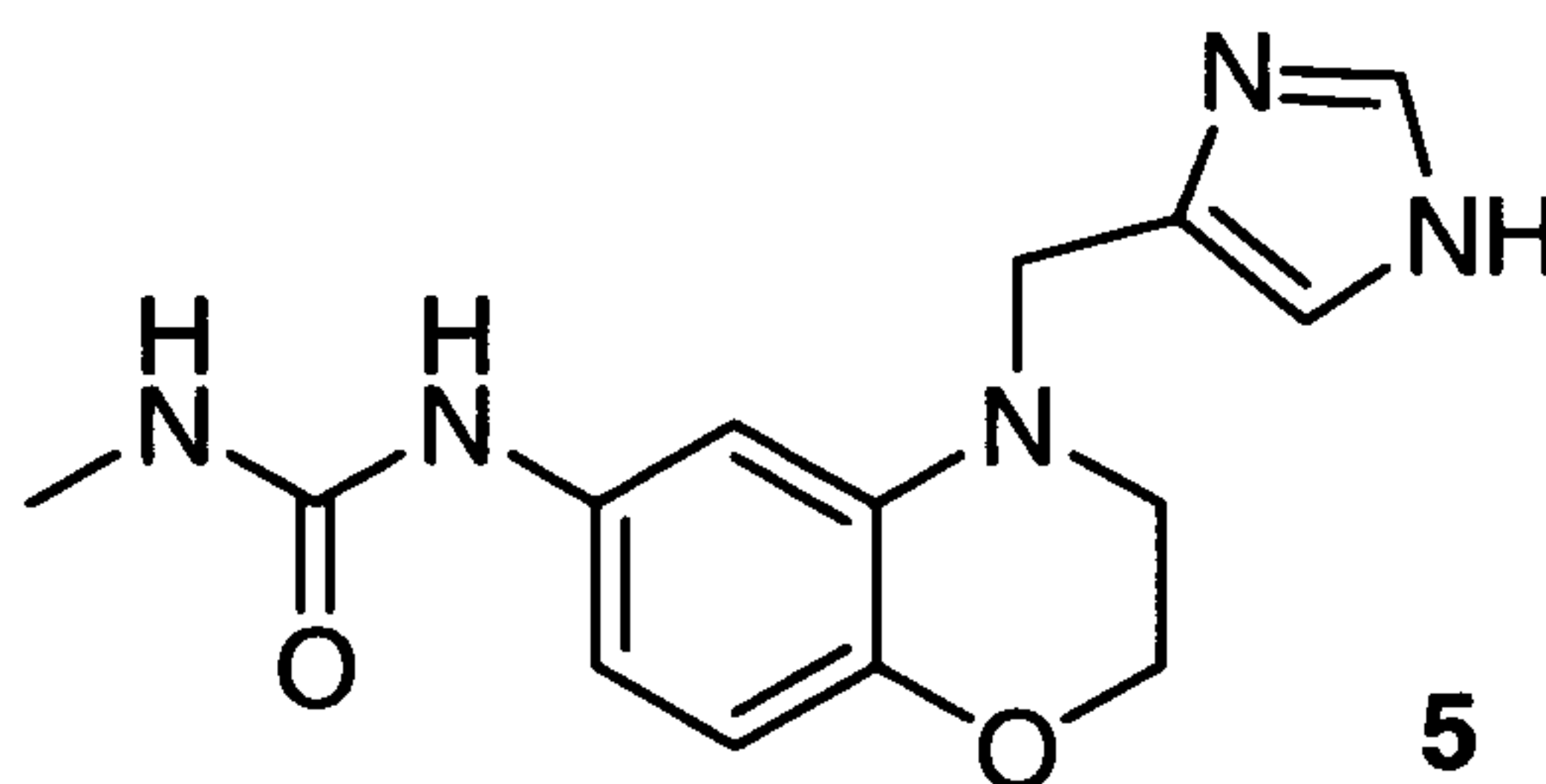
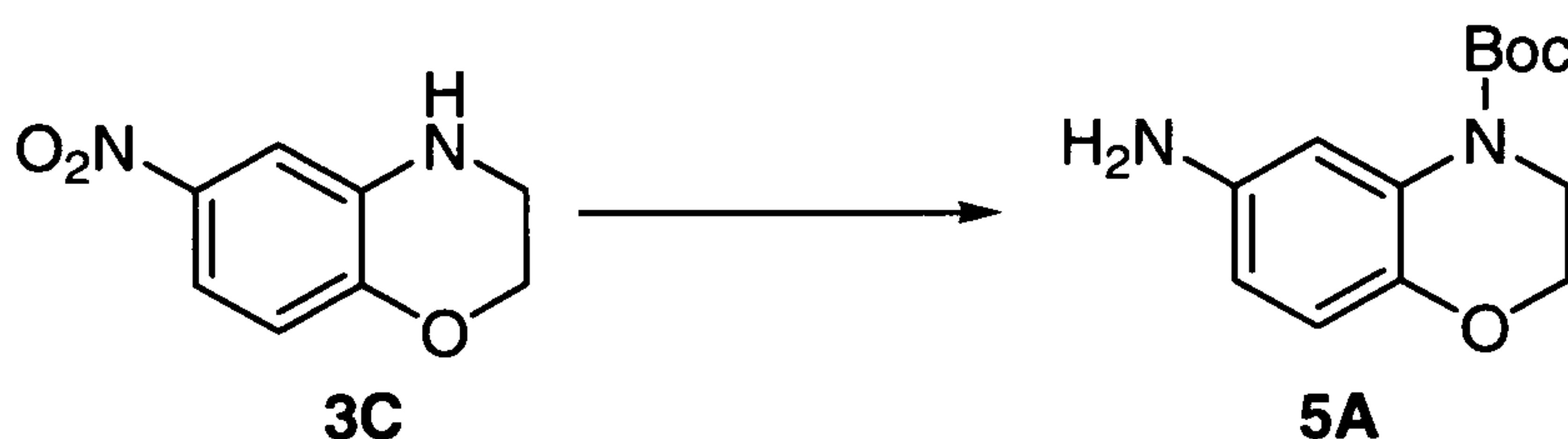
45

Step 5

A mixture of amine **3E** (2.14 g, 9.30 mmol) in anhydrous DCM (40 mL) was sequentially treated with TEA (3.24 mL, 23.3 mmol) and ClCO₂Me (1.43 mL, 18.6 mmol). The mixture was stirred at RT for 2 h, and then quenched with 2N NaOH solution. The resulting mixture was stirred for another 2 h and separated. The aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated under vacuum. Chromatography (DCM containing 1 to 4% of 7N NH₃/MeOH) provided **3** as a white solid (1.64 g, 61%). MS m/z 289 (MH⁺).

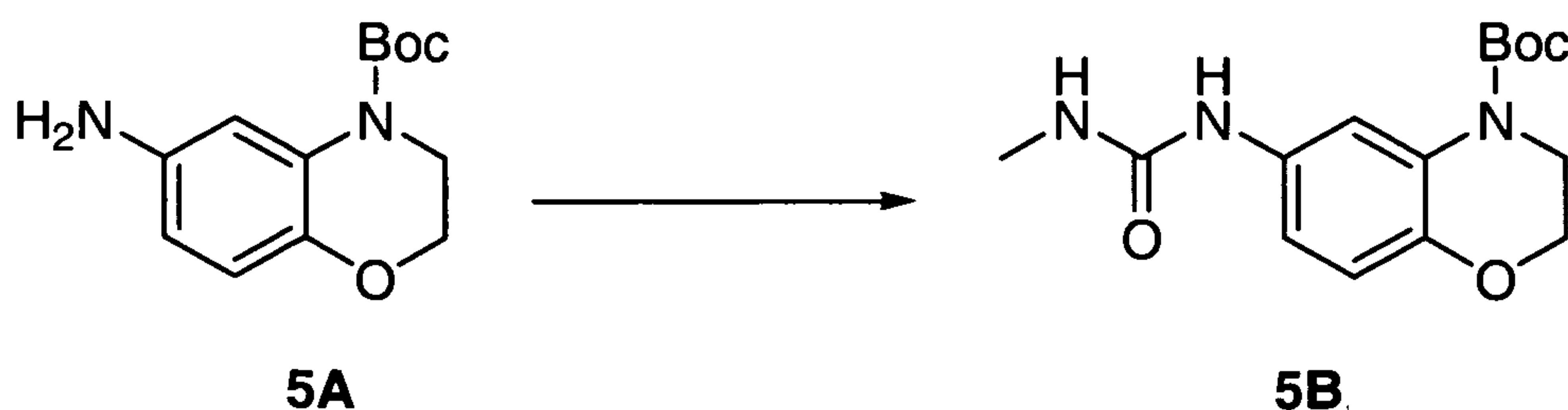
PREPARATIVE EXAMPLE 4

In a manner similar to Example 3, Step 5, amine **3E** was treated with TEA and AcCl to provide the compound **4**. MS m/z 273 (MH⁺).

PREPARATIVE EXAMPLE 5**5 Steps 1-2**

A solution of **3C** (3 g, 16.7 mmol) in anhydrous DCM (100 mL) was treated with Boc_2O (7.27g, 33.3 mmol), pyridine (5.39 mL, 66.7 mmol), and catalytic DMAP. The mixture was stirred at RT overnight and concentrated under vacuum. The residue
 10 was diluted with water (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (MgSO_4), concentrated and subjected to chromatography (5-5% EtOAc/hexanes, yield: 3g, 64%).

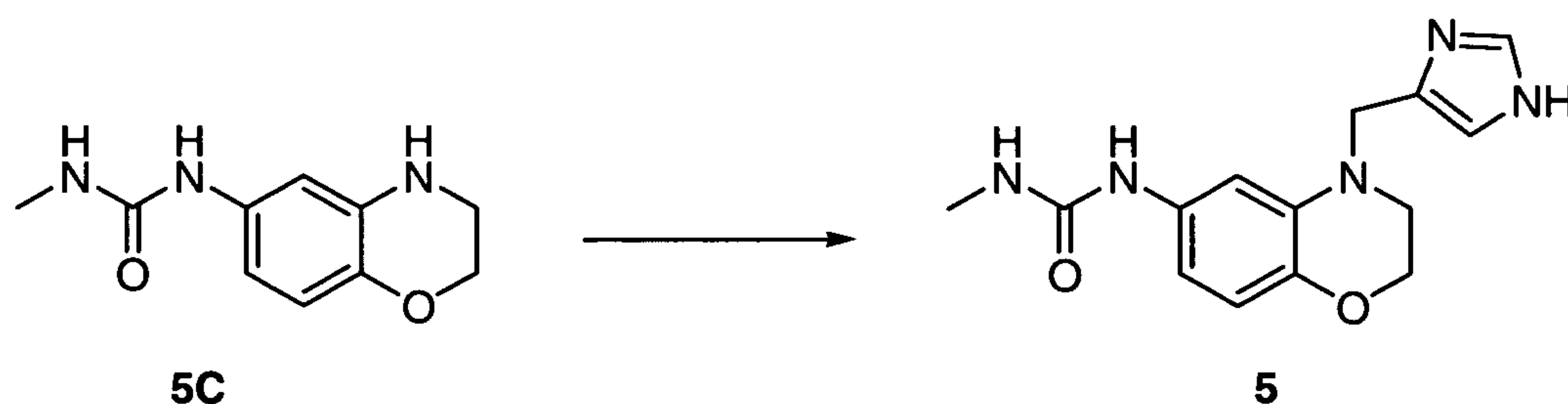
The resulting product was hydrogenated in a manner similar to that found in
 15 Example 3, Step 4 to provide **5A**.

Step 3

To amine **5A** (1.1 g, 4.4 mmol) in anhydrous THF (15 mL) was added MeNCO
 20 (215 mg, 4.4 mmol). The mixture was stirred at RT overnight and then concentrated. Chromatography (DCM containing 1 to 5% of 7N NH_3/MeOH) provided **5B** (890 mg, 66%).

Step 4

Compound **5B** (890 mg, 2.9 mmol) was stirred at RT in 30% TFA/DCM (14 mL) containing three drops of Et₃SiH for 1 h, and then quenched with 2N NaOH solution. The mixture was extracted with EtOAc (3 x 50 mL). The organic layer was dried (MgSO₄), filtered and concentrated under vacuum. The residue (**5C**, 600mg) was used in the next reaction without further purification.

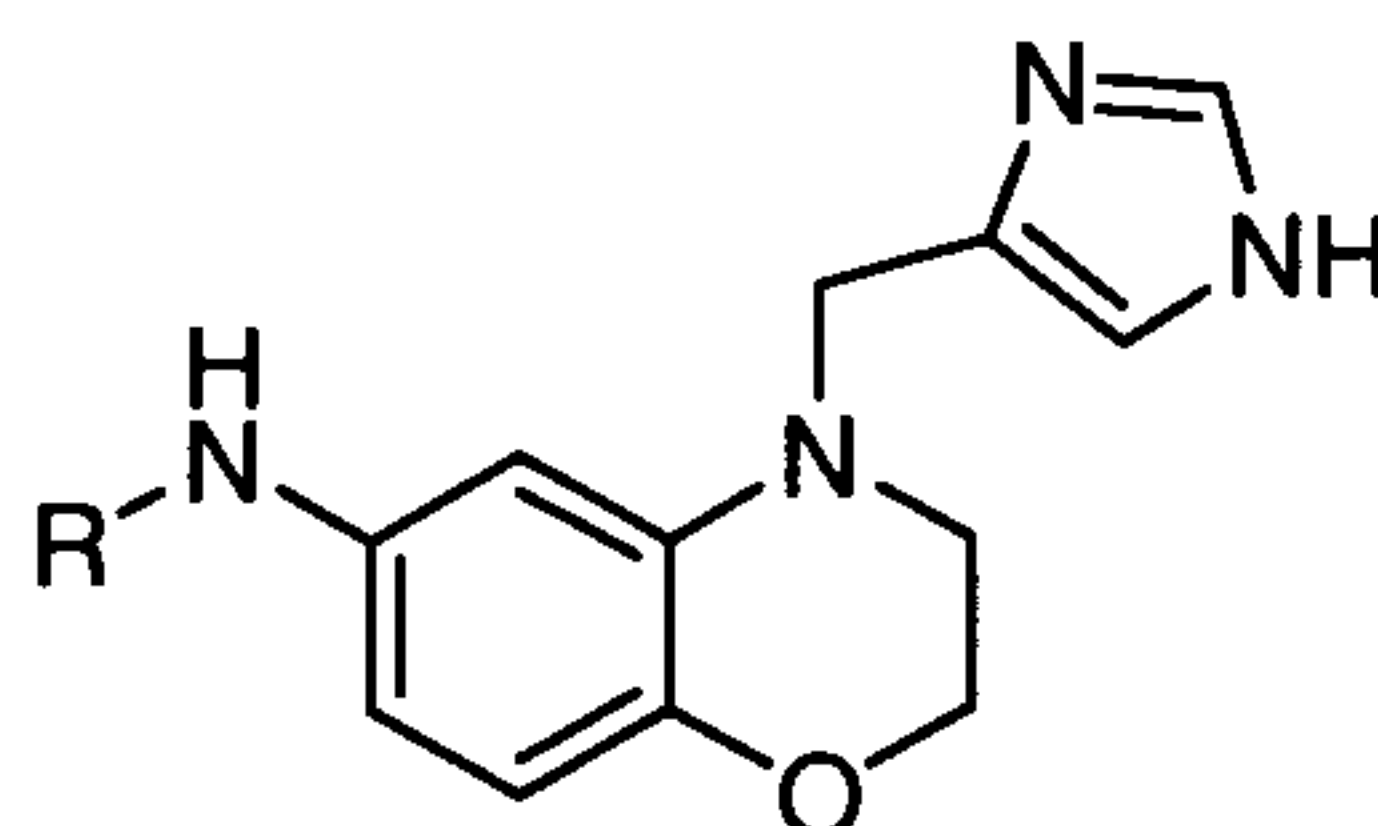
Step 5

In a manner similar to that described in Example 3 (Step 3), compound **5C** was treated with imidazole-4-carboxaldehyde (**1B**) to provide title compound **5** (56% for two steps). MS m/z 288 (MH⁺).

Compounds **5D-5F** in **Table 1** below can be prepared from compound **5A** using various capping reagents as shown, followed by Boc-deprotection and reductive alkylation as described above.

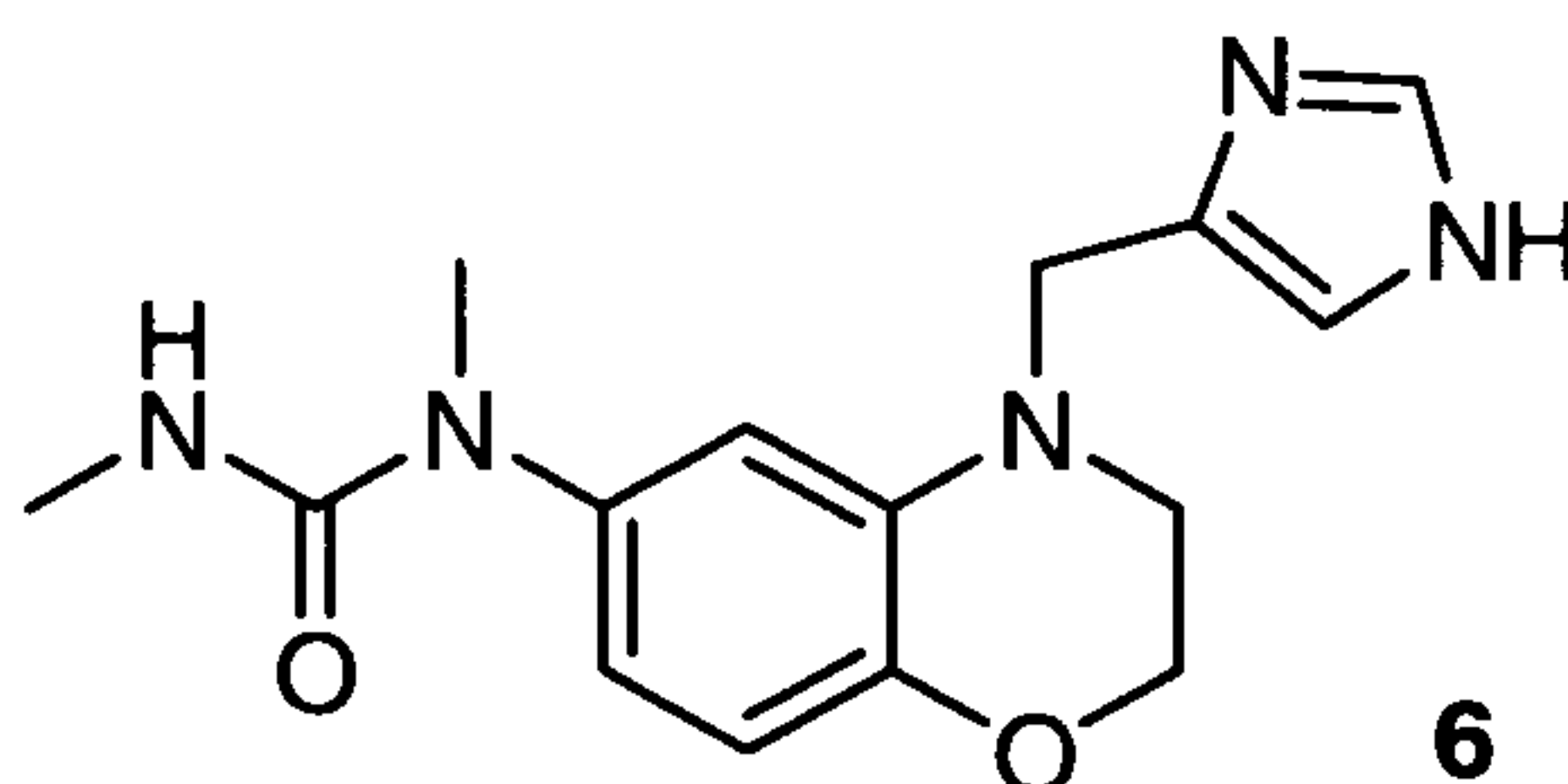
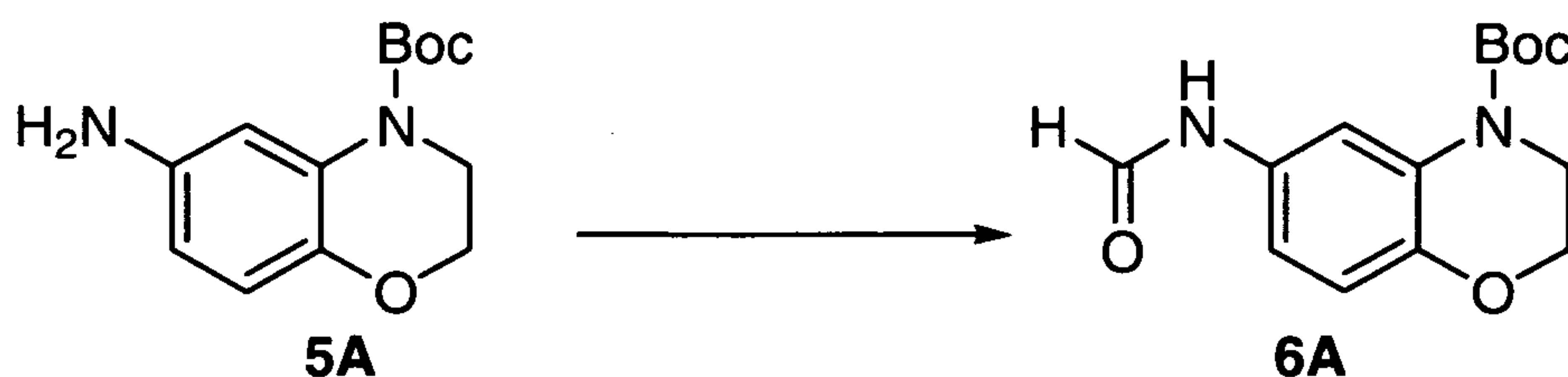
48

Table 1



Cpd	Reagent	R	MS (MH+)
5D	Methanesulfonic anhydride/pyridine		309
5E	 and pyridine		338
5F	 and pyridine		302

5

PREPARATIVE EXAMPLE 6**Step 1**

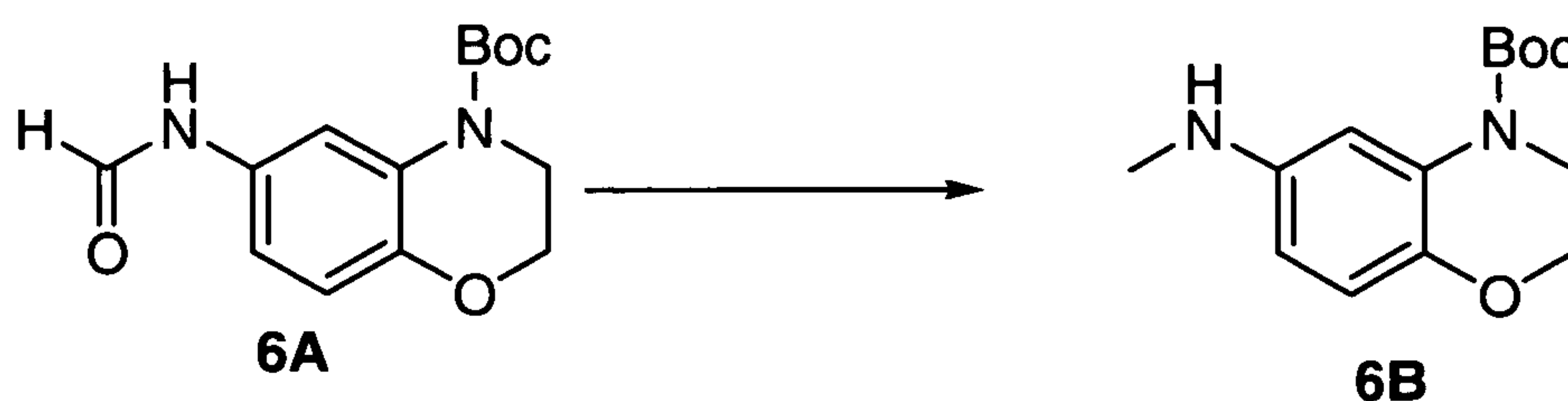
10 To a flask with Ac₂O (2.02 mL, 21.4 mmol) at 0 °C was added HCO₂H (0.82 mL, 21.4 mmol) by syringe. After stirring at 0 °C for 5 min, the mixture was heated up to 55 °C for 2h, and then was cooled to 0 °C again. Amine **5A** (2g, 8.0 mmol) in anhydrous THF (100 mL) was added and the mixture was stirred at 0 °C for 30 min. The reaction mixture was concentrated under vacuum and diluted with 2 N NaOH

15 solution to pH 9, extracted with EtOAc (3 x 50 mL). The organic layer was dried

(MgSO₄), filtered, and concentrated under vacuum to give a foam **6A** (quantitative yield).

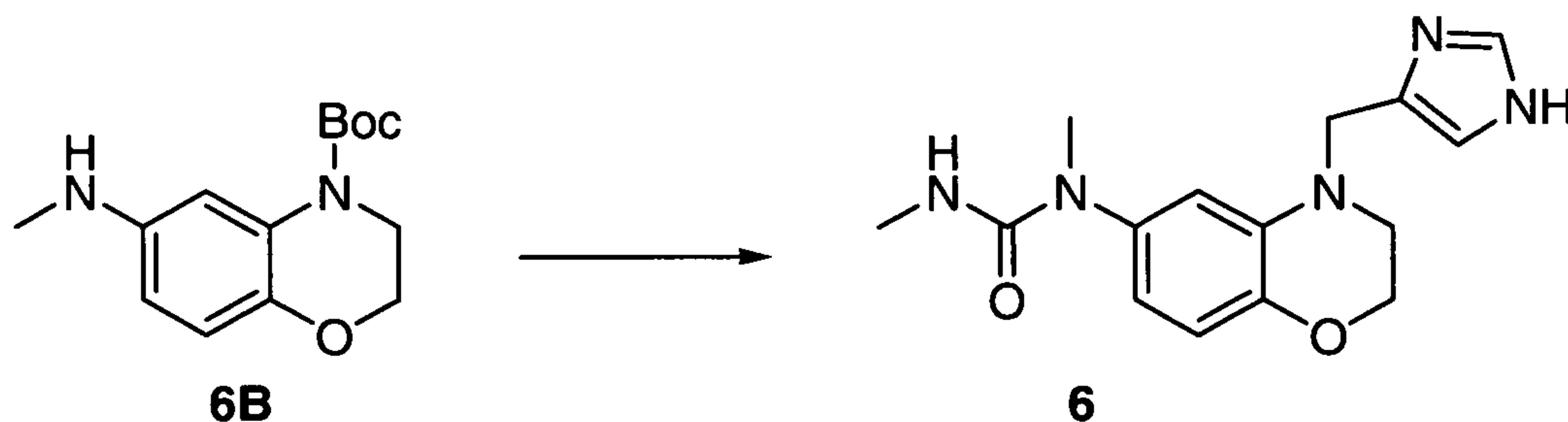
Alternatively, a mixture of compound **5A** (17.5 g, 69.9 mmol) in butyl formate (700 ml) was heated at 50°C for 3h and then left at RT overnight. The reaction mixture was then concentrated, added to 100 ml of 0.5N NaOH, extracted with CH₂Cl₂ (4X), dried with Na₂SO₄, and concentrated. Chromatography (10%-50% EtOAc/hexane) gave **6A** (9.19 g, 47 %) as a light brown sticky foam.

Step 2



A mixture of compound **6A** (2.75 g, 9.88 mmol) in THF (30 ml) was treated slowly with BH₃-DMS (2.0 M/THF, 7.8 ml) and then heated at reflux for 3h. The reaction mixture was concentrated, treated with K₂CO₃ (1.5 g) and EtOH, and then stirred overnight at RT. The reaction mixture was filtered, concentrated, added to H₂O and extracted with CH₂Cl₂ (4X). The combined organic layers were dried with Na₂SO₄, filtered and concentrated to provide **6B** as a clear oil (2.76 g).

Steps 3-5



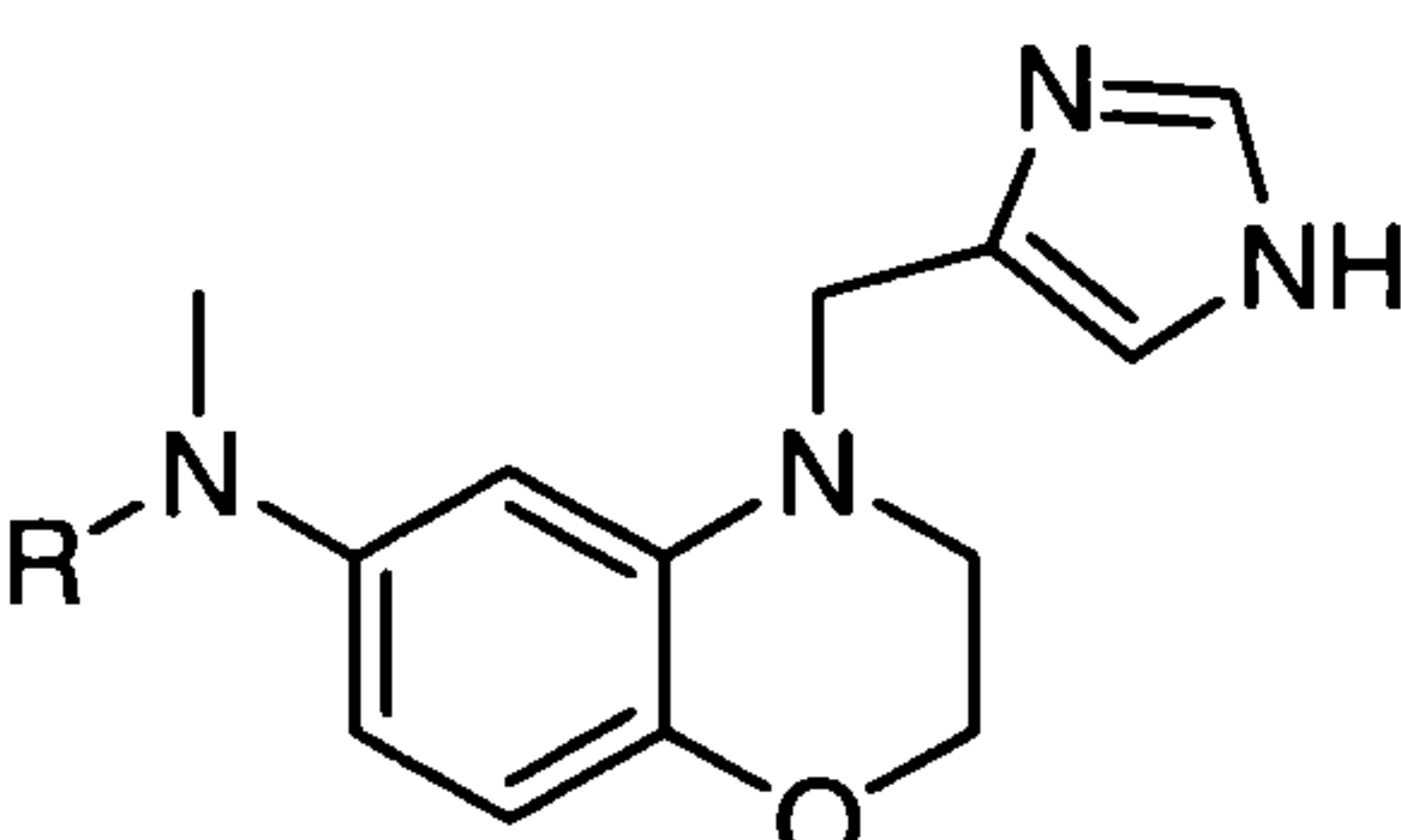
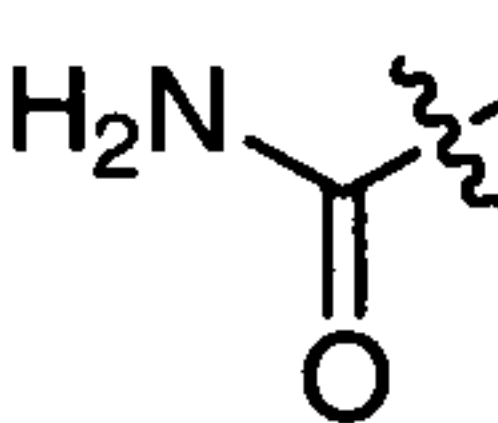
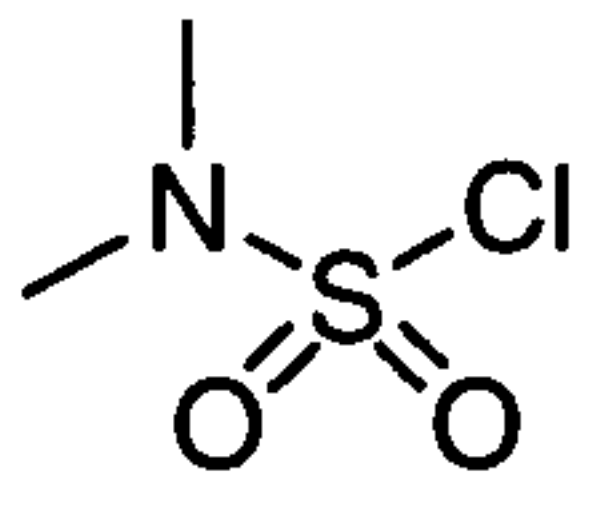
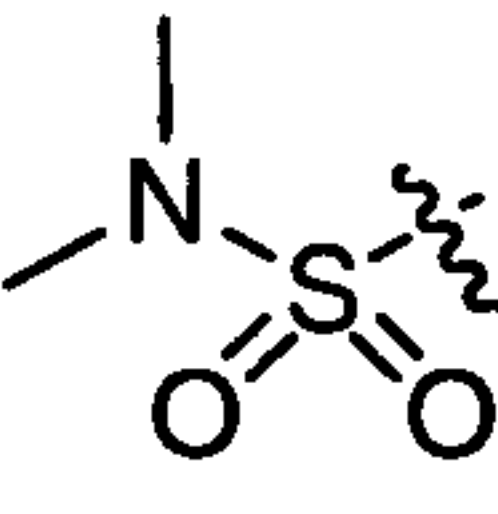
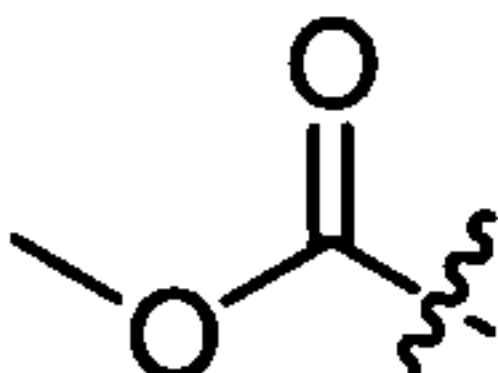
A solution of **6B** (2.76 g, crude) in CH₂Cl₂ (20 ml) was treated slowly with MeNCO (1.0 g, 12.5 mmol) and stirred at RT overnight. The reaction mixture was concentrated and chromatographed (50% to 80% EtOAc/hex, 3.10 g, 98% yield from **6A**). This product (3.10 g, 9.65 mmol) was taken up in CH₂Cl₂ (80 ml) and deprotected with TFA (11.5 ml) as described in Example 5, Step 4 (95% yield). A

50

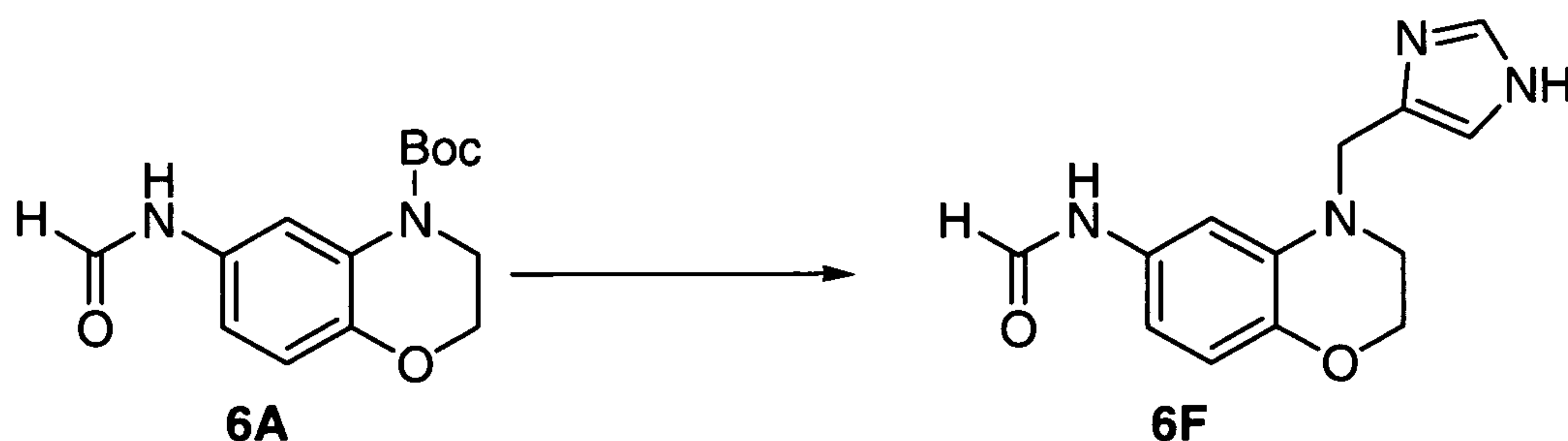
mixture of the resulting amine and aldehyde **1B** (1 eq) in a minimal amount of CH_2Cl_2 was treated with $\text{Ti}(\text{OiPr})_4$ (1.3 eq). After stirring for 2h at RT, NaBH_4 (1.2 eq) and EtOH were added. The reaction mixture was then stirred overnight, concentrated, treated with H_2O and extracted with CH_2Cl_2 (4X). The combined organic layers were
 5 dried with Na_2SO_4 , filtered, concentrated and chromatographed (silica gel, 5% MeOH/ CH_2Cl_2 w/ NH_3) to provide the title compound **6** (74% yield). MS m/z 302 (MH^+).

Compounds in **Table 2** below can be prepared from compound **6B** using the various capping reagents as shown, followed by Boc-deprotection and reductive alkylation as
 10 shown in Example 5.

Table 2

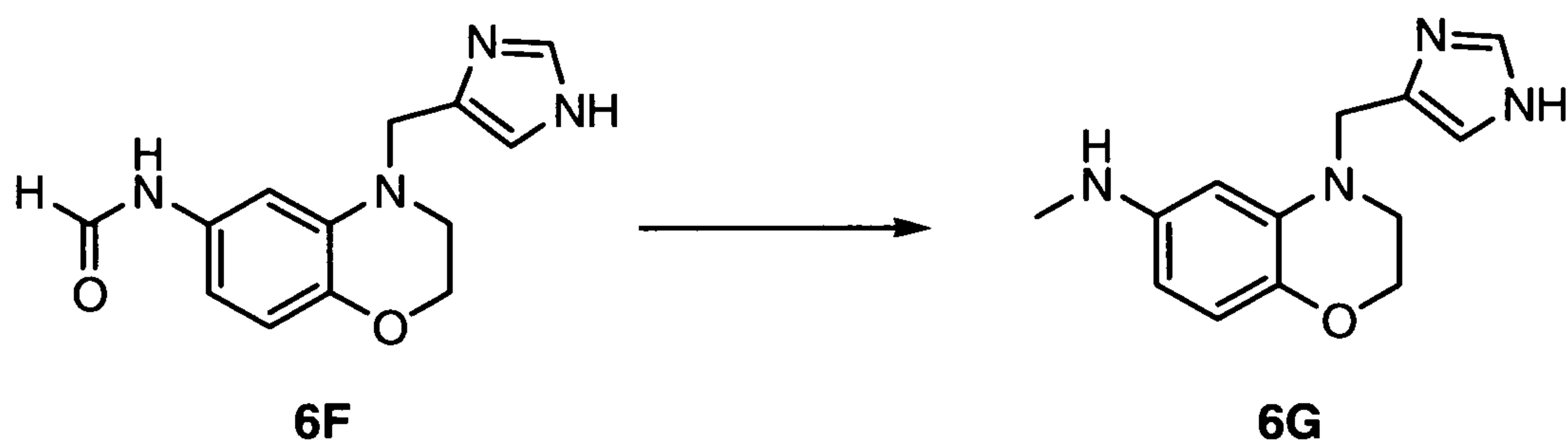
			
Cpd	Reagent	R	MS (MH^+)
6C	TMSNCO		288
6D	 /pyridine		352
6E	MeCOCl /pyridine		303

15



Compound **6F** was prepared as follows: **6A** was treated with TFA, followed by reductive alkylation with imidazole-4-carboxaldehyde (**1B**) as described previously in Example 5 (Step 4) and Example 3 (Step 3). MS m/z 259 (MH⁺).

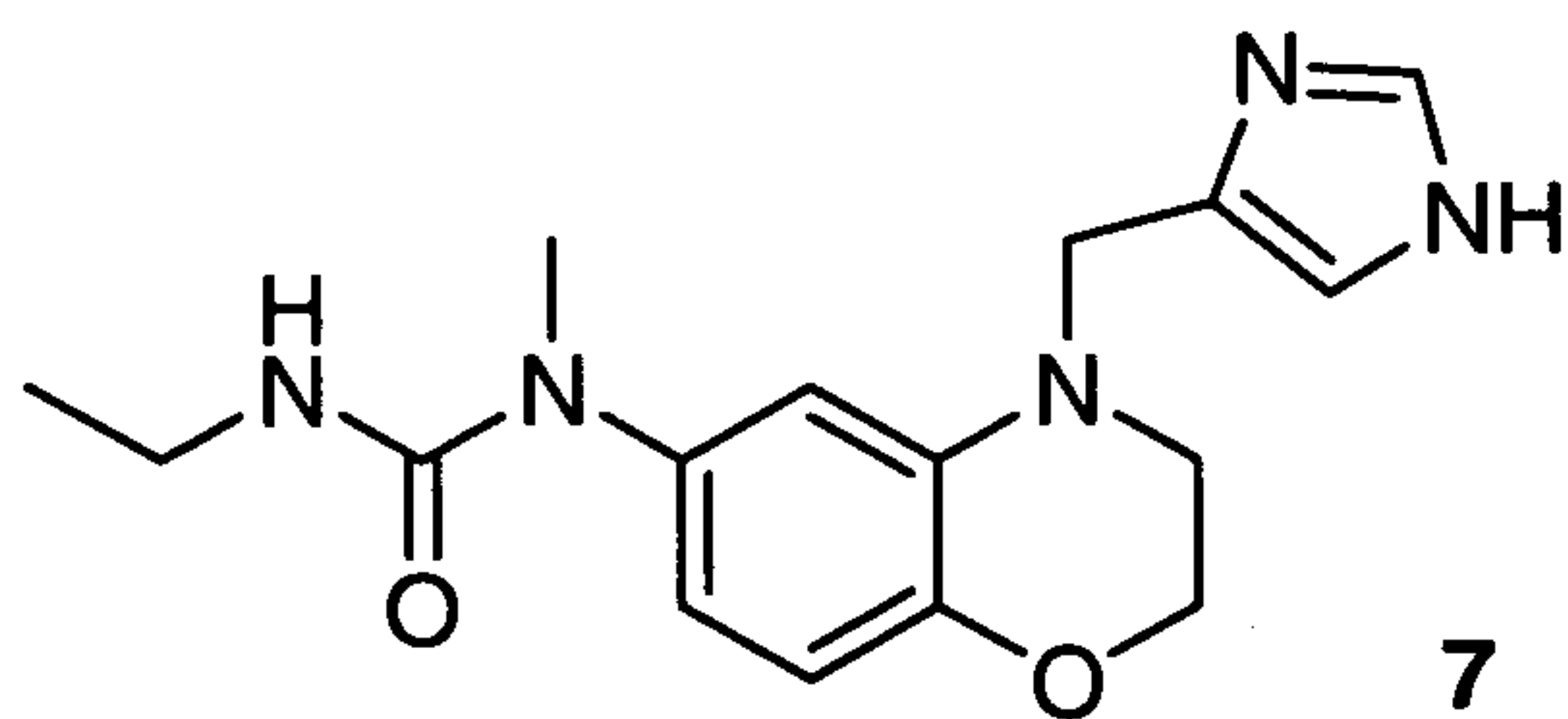
5



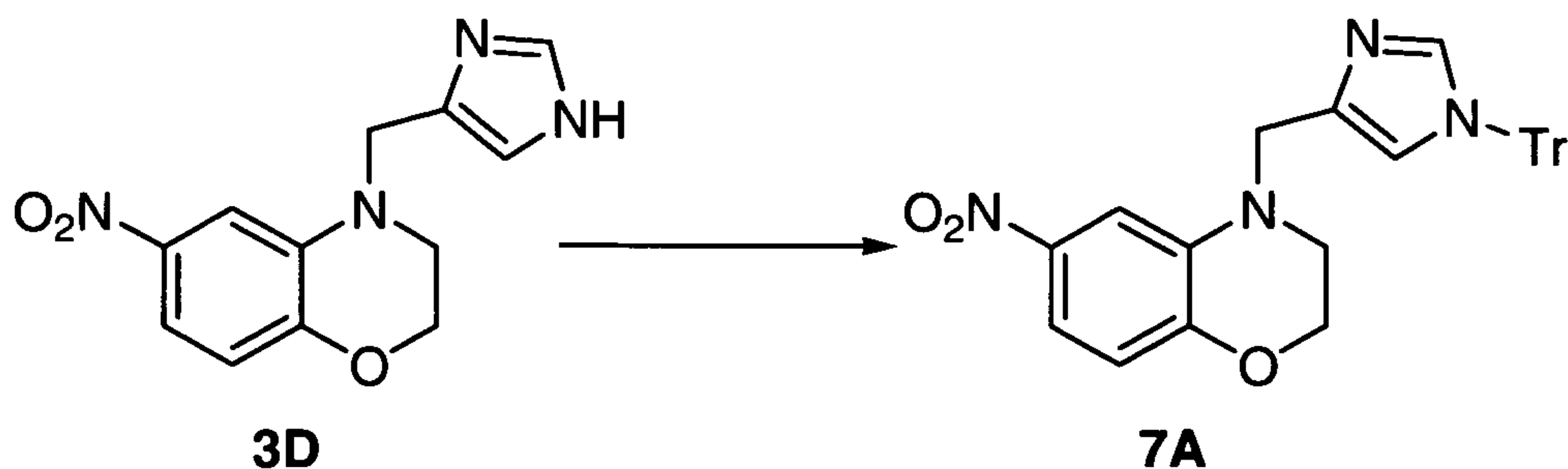
In a manner similar to Example 3, Step 2, compound **6F** was reduced with BH₃-SMe₂ to provide **6G**. MS m/z 245 (MH⁺).

10

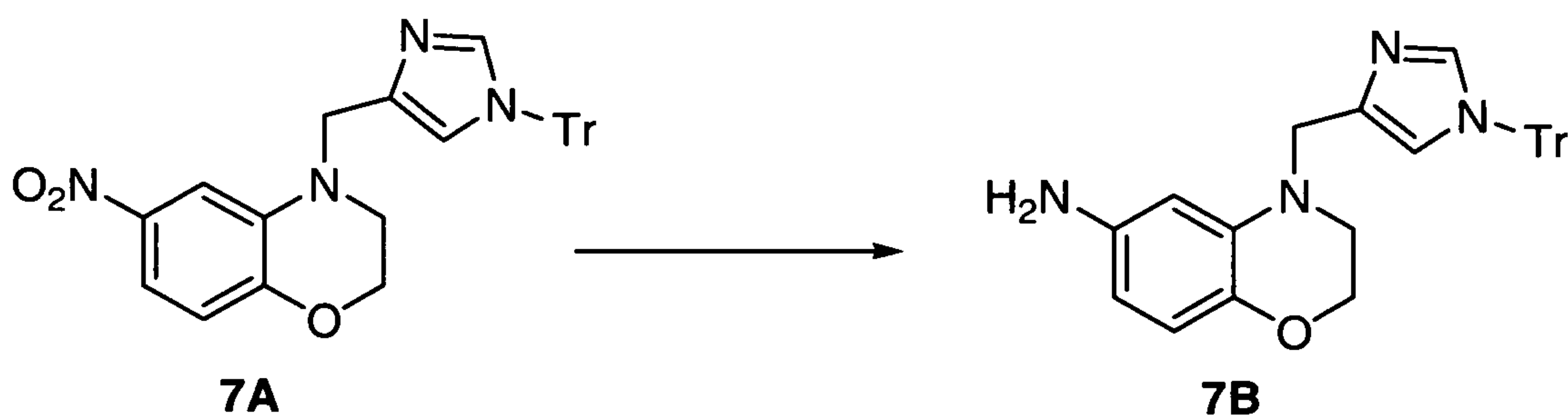
PREPARATIVE EXAMPLE 7



52

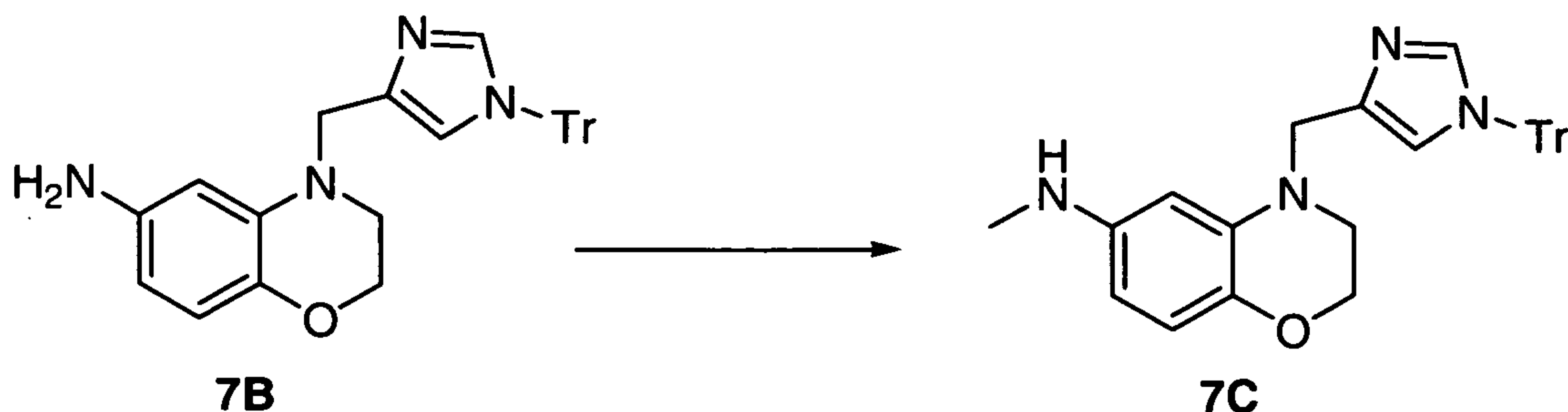
Step 1

To a suspension of compound **3D** (4.8 g, 18.46 mmol) in anhydrous DCM (200 mL) was sequentially added TrCl (5.15 g, 18.46 mmol) and TEA (7.7 mL, 55.37 mmol). The mixture was stirred at RT overnight, and quenched with saturated NH₄Cl solution. The solution was separated and the aqueous was extracted with DCM (3 x 100 mL). The combined organic layers were washed with water, dried (MgSO₄), filtered, and concentrated under vacuum to give red yellowish solid **7A** (9.13g, yield: 98%).

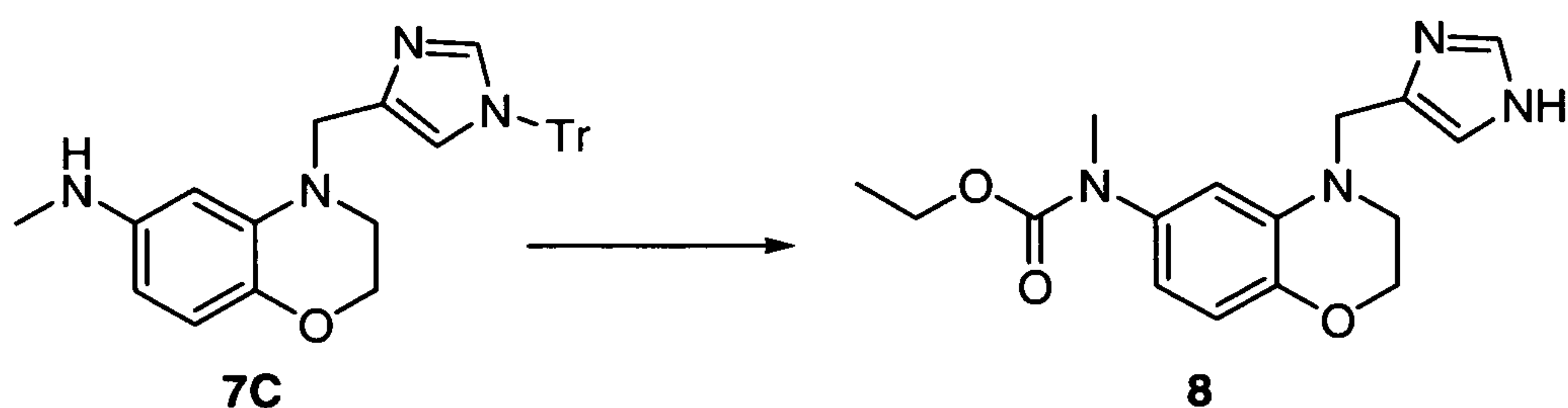
Step 2

To compound **7A** (4.55g, 9.06 mmol) in MeOH/EtOAc (400 mL, 1:1) in a hydrogenation bottle was added 10% Pd-C (1 g). The reaction vessel was shaken in the Parr shaker under 50 psi hydrogen for 4h. Then the catalyst was filtered off through a celite bed and washed with MeOH and EtOAc. The filtrate was concentrated under vacuum to give white solid **7B** (3.81 g, 89%).

53

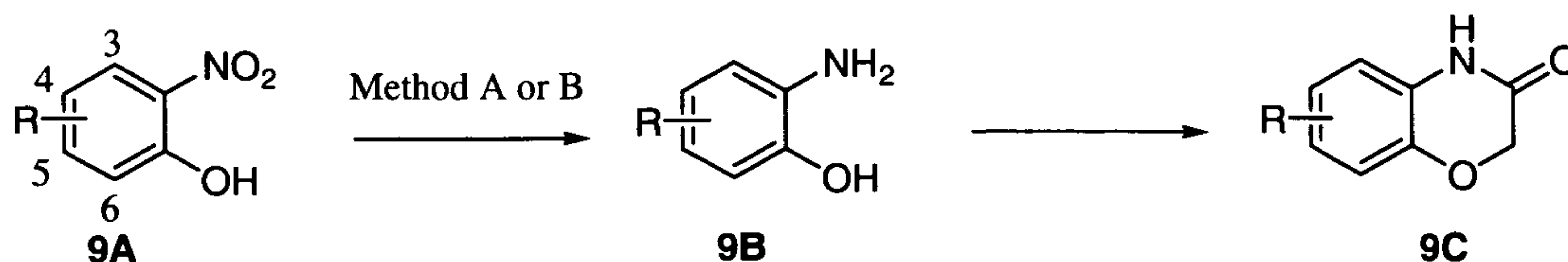
Steps 3-6

Following the approach outlined in Example 6 (Steps 1-2), **7B** was treated with $\text{Ac}_2\text{O}/\text{HCO}_2\text{H}$ and then reduced with $\text{BH}_3\text{-SMe}_2$ to afford **7C**. In a manner similar to that found in Example 5 (Steps 3-4), **7C** was further elaborated by treatment with EtNCO and deprotection with TFA to provide the title compound **7**. MS m/z 316 (MH^+).

10 PREPARATIVE EXAMPLE 8

To compound **7C** (1.5 g, 3.09 mmol) in anhydrous DCM (10 mL) was added pyridine (0.5 mL, 6.18 mmol) and ClCO_2Et (0.59 mL, 6.18 mmol) sequentially. The mixture was stirred at RT overnight, and then quenched with saturated NH_4Cl solution. The solution was concentrated and the aqueous was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried (MgSO_4), filtered, and concentrated under vacuum.

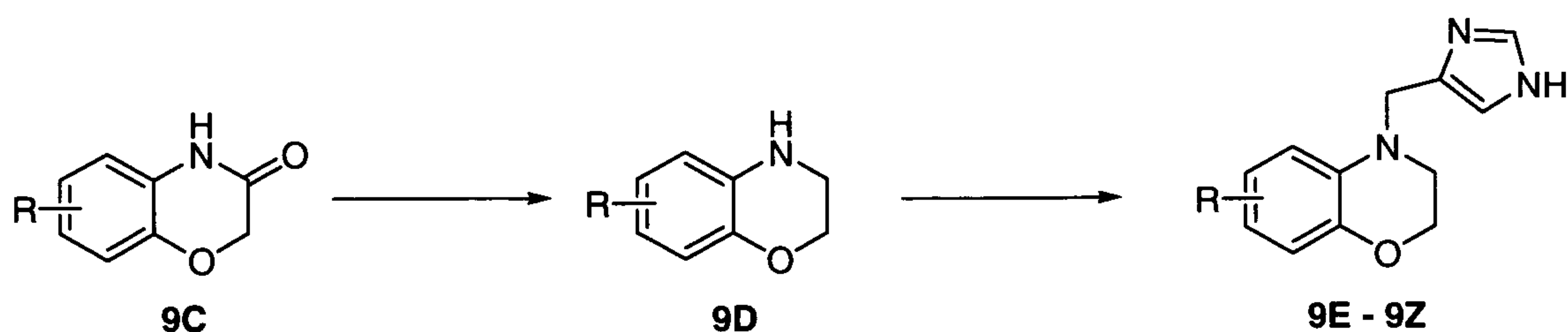
The residue was then deprotected with TFA, in a manner described in Example 5, Step 4, to afford compound **8** (145 mg, 15% for two steps). MS m/z 317 (MH^+).

PREPARATIVE EXAMPLE 9

- 5 The synthesis in Example 9 used starting materials **9A**, **9B** or **9C**. Compound **9B** can be synthesized from **9A** by using reduction method A or B:

Method A: To compound **9A** in MeOH was added 10% Pd/C and the mixture was stirred at RT under hydrogen balloon overnight. Then the catalyst was filtered off
10 through a celite bed and washed with MeOH. The filtrate was concentrated to give compound **9B** for next reaction without further purification.

Method B: To compound **9A** in EtOH was added SnCl₂·2H₂O (4eq.), and the mixture was heated to reflux for 2 h. The mixture was concentrated and poured into
15 ice, neutralized to pH 7 with sat. NaHCO₃. Then the solid was filter off and washed extensively with EtOAc. The filtrate was separated and the aqueous was extracted with (3x). The organic layer was dried (MgSO₄), filtered and concentrated to give compound **9B**.



20

Compounds **9E-9Z** (shown in **Table 3**) were synthesized starting from **9A**, **9B** or **9C** by following the procedures described in Example 3. The selective single-nitro reduction of starting material **9A13** (2,6-dinitrophenol) using Method A provided 2-amino-6-nitrophenol.

55

Table 3

Starting Material	R	Reduction method from 9A	Cpd	Spectral data MS (MH+) unless noted
9A1	4-F	A	9E	234
9A2	5-F	A	9F	234
9A3	6-F	A	9G	234
9A4	5,6-diF	A	9H	252
9B1	4-Cl	N.A.	9I	¹ H NMR (CDCl ₃): 7.60 (s, 1H), 6.90 (s, 1H), 6.75 (d, 1H), 6.66 (d, 1H), 6.55 (dd, 1H), 4.40 (s, 2H), 4.20 (t, 2H), 3.40 (t, 2H)
9B2	5-Cl	N. A.	9J	250
9A5	6-Cl	B	9K	250
9A6	4,6-diCl	B	9L	284
9C1	4-Me	N.A.	9M	230
9A7	3-Me	A	9N	230
9B3	4-Ph	N.A.	9O	292
9A8	4-Br	B	9P	294
9A9	4-CF ₃	A	9Q	284
9A10	3-OMe	A	9R	246
9A11	4-OMe	A	9S	246
9B4	5-OMe	N.A.	9T	246
9A12	6-OMe	A	9U	246
9B5	4-SO ₂ NH ₂	N.A.	9V	295
9B6	4-SO ₂ Et	N.A.	9W	308
9B7	5-NO ₂	N.A.	9X	261
9A13	6-NO ₂	A	9Y	261
9A14	4-CO ₂ CH ₃	B	9Z	274

Starting material **9A10** in **Table 3** was prepared as follows:

5 Dimethylsulfate (2.7 mL, 0.058 mmol) was added carefully to 2-nitrobenzene-1,3-diol (2.5 g, 0.232 mmol) and the mixture was stirred vigorously while 10% NaOH solution (21 mL) was added and the temperature was kept below 40 °C. After about

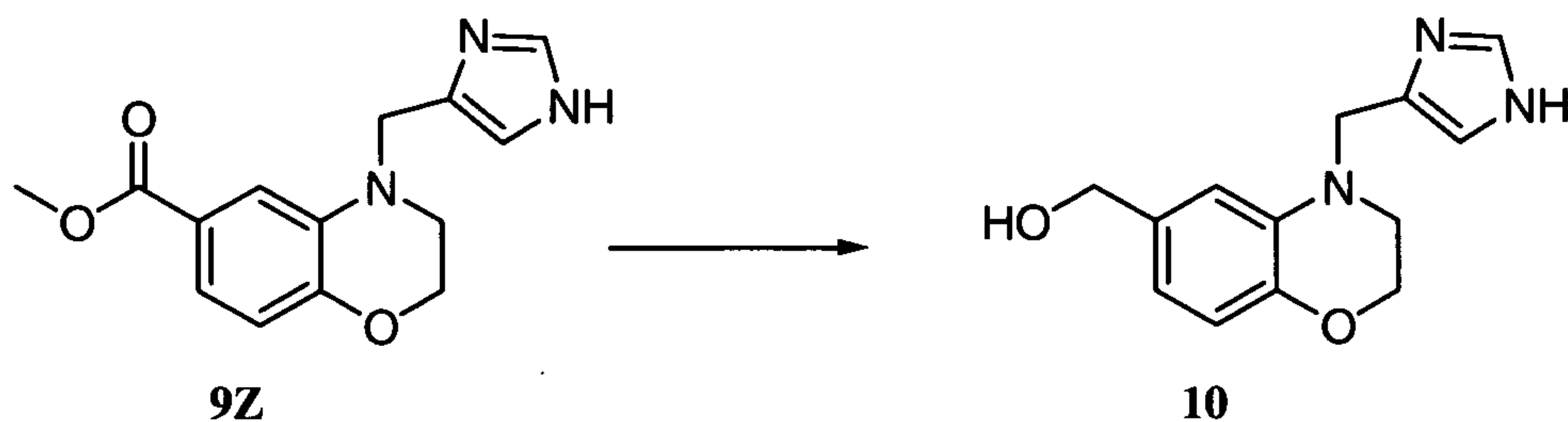
15 min, the mixture was cooled and then filtered. The filtrate was collected and acidified with 10% HCl, and extracted with ether (3 x 25 mL). The organic layer was dried (MgSO₄), filtered, and concentrated under vacuum. Chromatography (10-30% EtOAc/hexanes) provided **9A10** (1 g, 37%).

5

Starting material **9A12** in **Table 3** was prepared as follows:

Fuming HNO₃ (0.34 mL, 0.008 mmol) was carefully added to a mixture of 2-methoxyphenol (0.886 mL, 0.008 mmol) in anhydrous DCM (10 mL) at -20 °C. After stirring for 2 h at RT, the mixture was concentrated under vacuum. Chromatography (10-30% EtOAc/ hexanes) provided **9A12** (400 mg, 29%) and 2-methoxy-3-nitrophenol (400 mg, 29%).

PREPARATIVE EXAMPLE 10

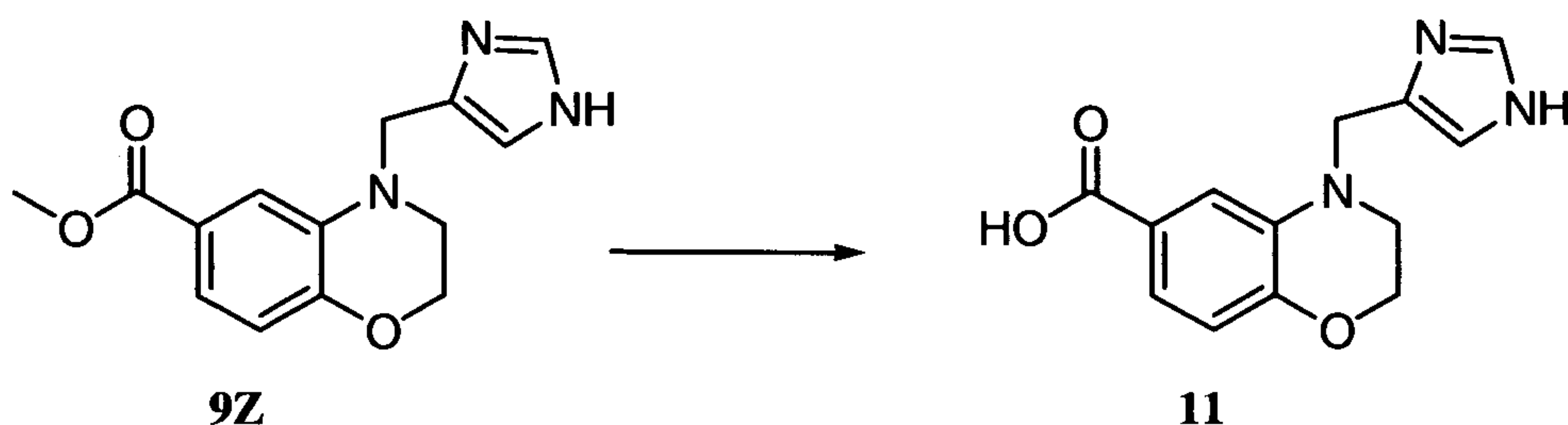


15

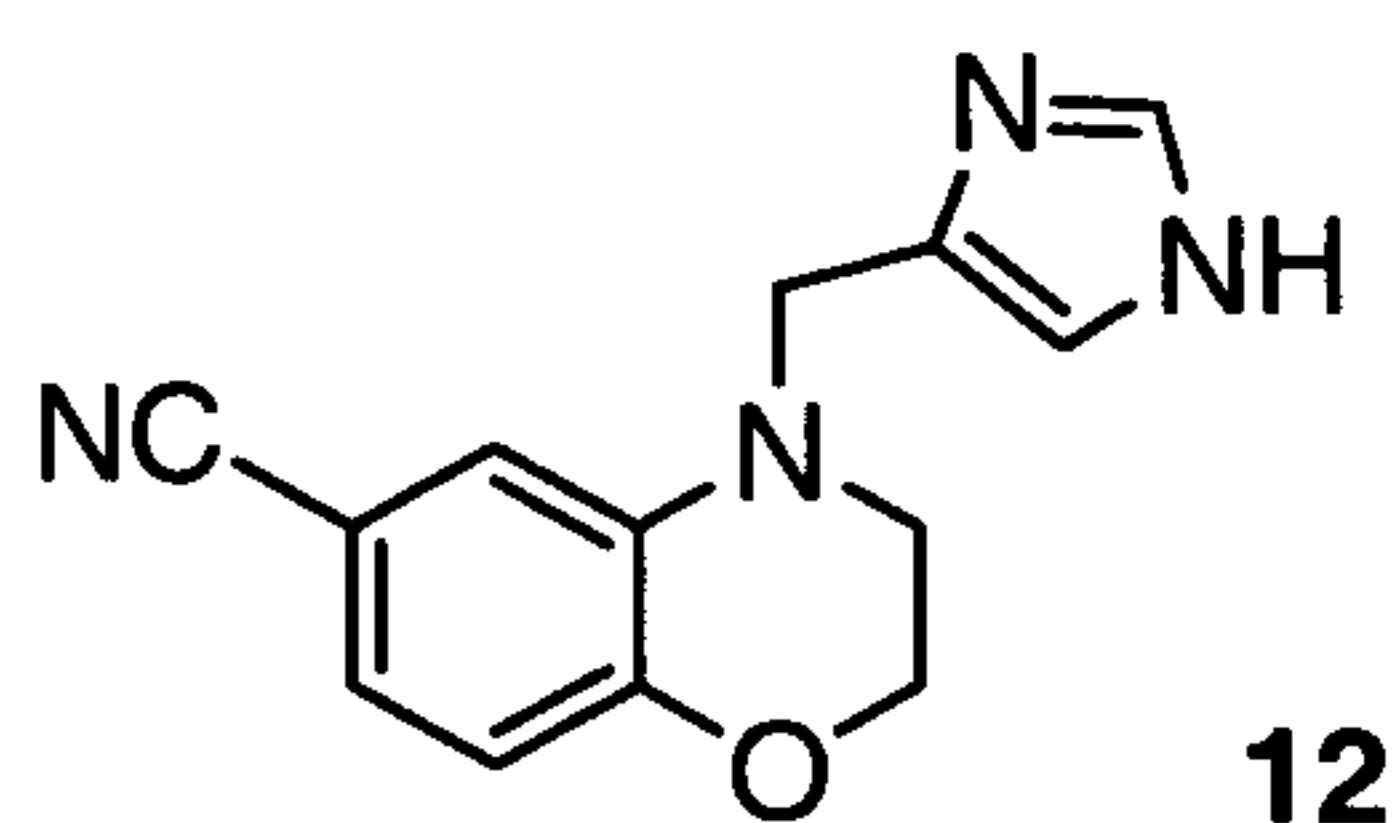
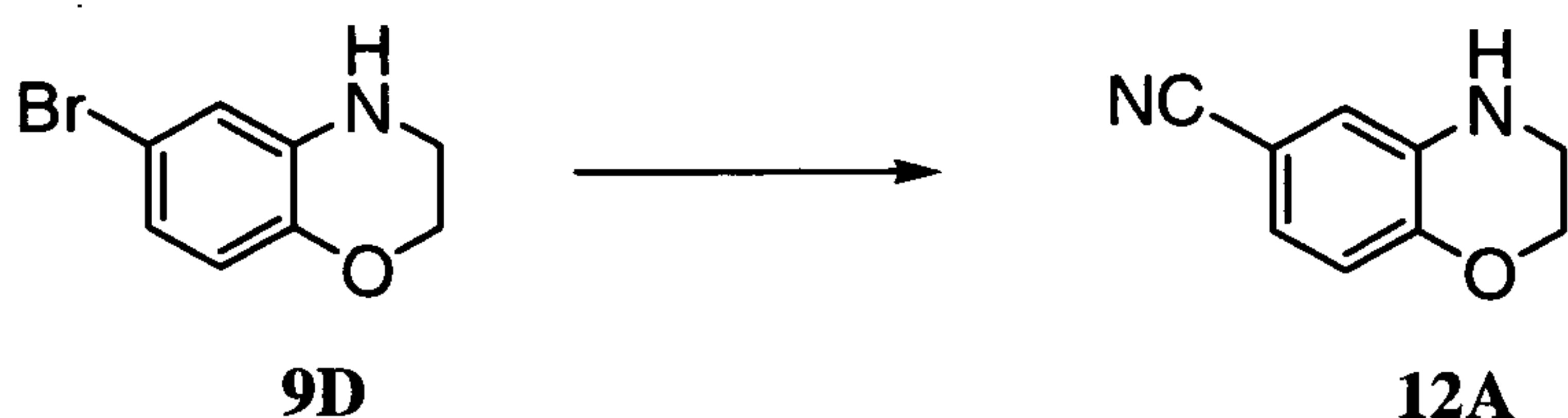
A mixture of compound **9Z** (46 mg, 0.24 mmol) in anhydrous THF (10 mL) at 0 °C was carefully treated with LAH powder (18 mg, 0.48 mmol) and then stirred for 2 h at RT. The reaction was quenched with 1N NaOH solution (2 mL), filtered and concentrated under vacuum. Chromatography (DCM with 3 to 5% of 7N NH₃-MeOH) provided **10** (47 mg, 80%). MS m/z 246(MH⁺).

20

57

PREPARATIVE EXAMPLE 11

A mixture of **9Z** (67 mg, 0.24 mmol) in MeOH (5 mL) was treated with NaOH (15 mg, 0.38 mmol) and stirred at RT overnight. The reaction was then neutralized with 10% HCl and concentrated under vacuum. The residue was taken up in MeOH, stirred for 1 h, filtered, and concentrated. Chromatography (Prep-HPLC) provided compound **11** (21 mg, 32%). MS m/z 260(MH⁺).

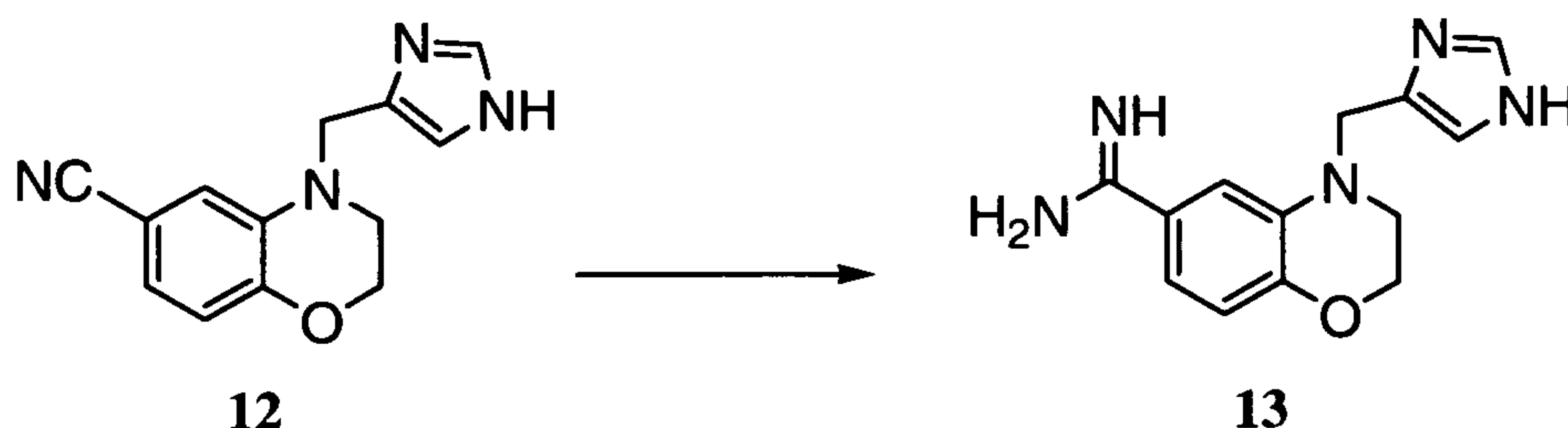
PREPARATIVE EXAMPLE 12**Steps 1**

A mixture of 6-bromo-3,4-dihydro-2H-benzo[1,4]oxazine (**9D**, 1.5 g, 7.05 mmol) and CuCN (1.58 g, 17.61 mmol) in anhydrous DMF (15 mL) was stirred at 130 °C for 3 h and then at 150 °C overnight. Then the mixture was cooled to RT, quenched with water and concentrated under vacuum. The residue was taken up in 2N NaOH and EtOAc (100 mL) and then agitated in a sonicator for 1 h. The precipitate was filtered off and washed with EtOAc. The filtrate and washings were combined and extracted with EtOAc (2 x 80 mL). The organic layer was dried (MgSO₄), filtered and concentrated under vacuum to give compound **12A** (1.062 g, 94%).

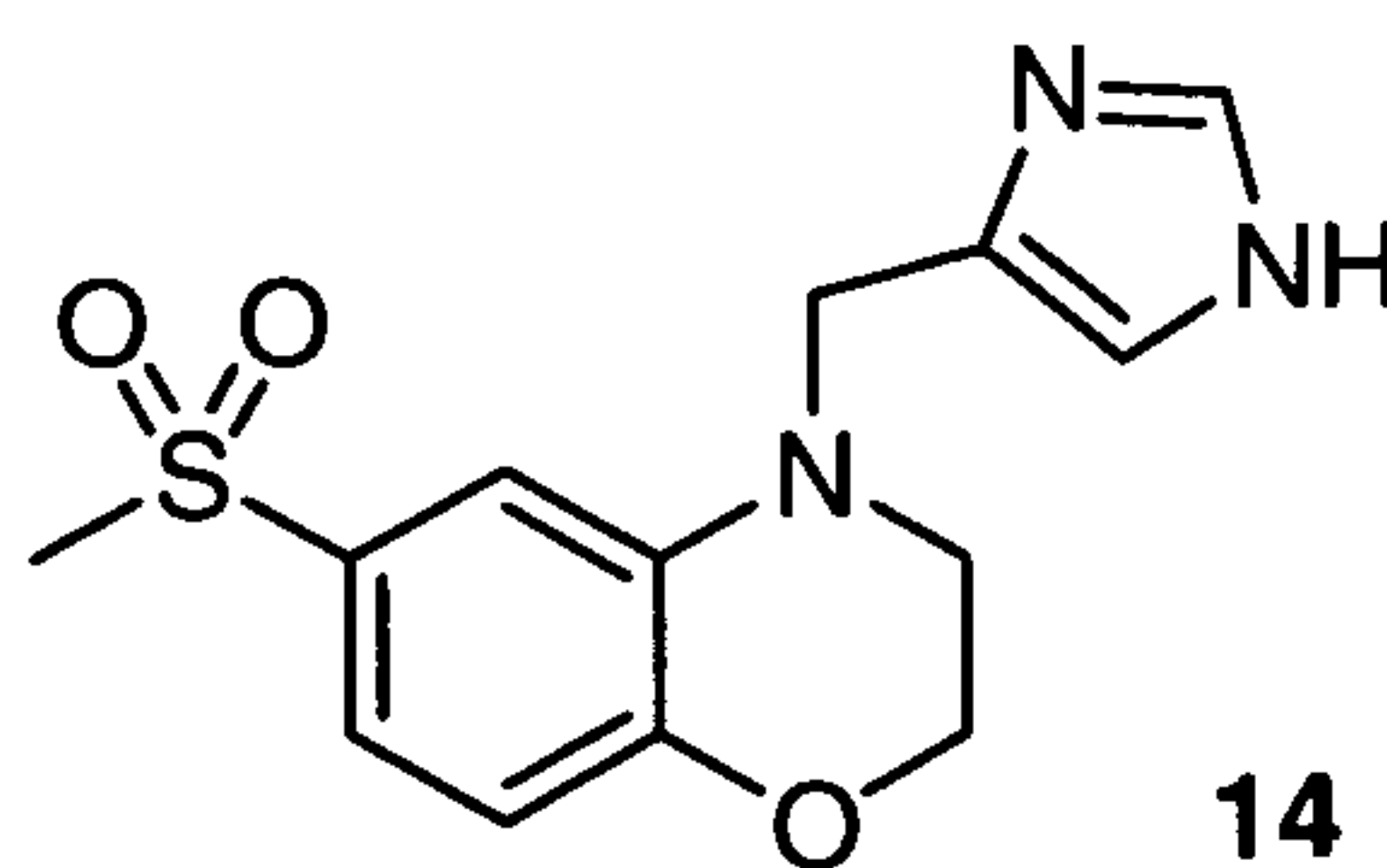
58

Step 2

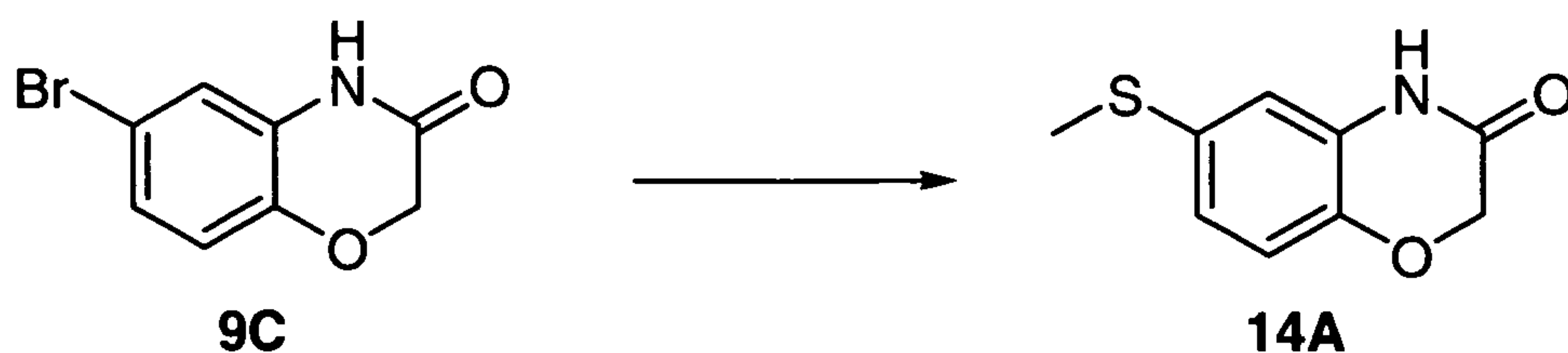
In a manner similar to that found in Example 3, Step 3, **12A** was converted to the title compound **12**. MS m/z 241 (MH⁺).

5 EXAMPLE 13

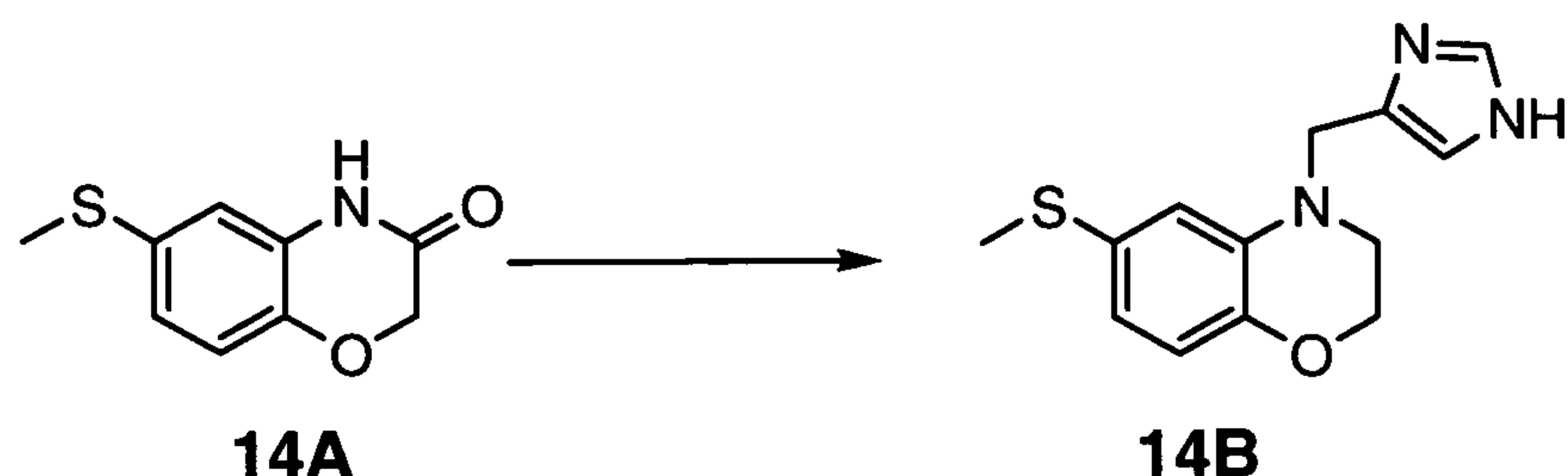
A solution of **12** (0.179 g, 0.75 mmol) in anhydrous EtOH (10 mL) was cooled to 0 °C and treated with bubbling HCl gas for 15 min. The mixture was stirred at 0 °C for 30 min, warmed to RT overnight, and concentrated. The residue was dissolved in 2.0 M NH₃-MeOH (5 mL), stirred at RT for 4 h, and then concentrated under vacuum. Chromatography (Ranin-Prep HPLC, Waters SunFire™ Prep C18 5 μM, 19-100 mm column, 5-90% CH₃CN/H₂O gradient) gave the compound **13** (36 mg: 19%). MS m/z 258 (MH⁺).

PREPARATIVE EXAMPLE 14

59

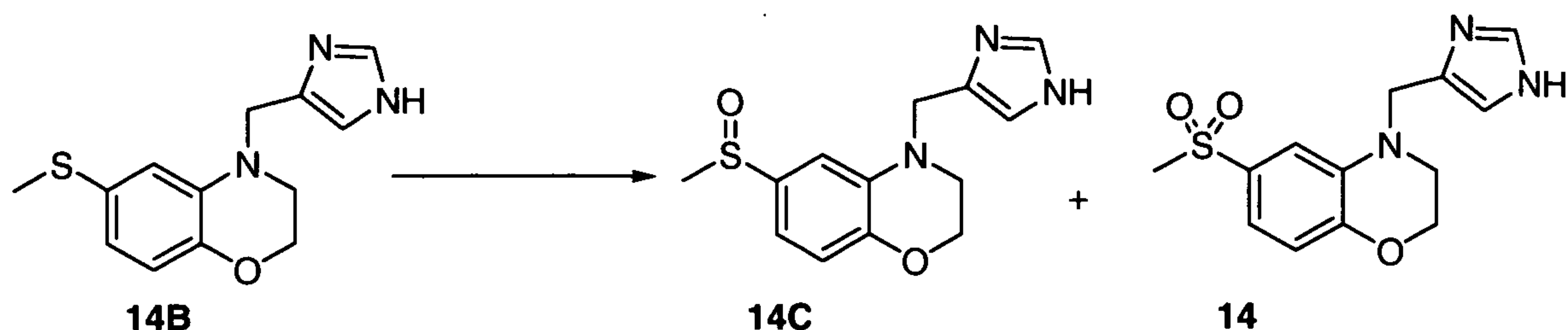
Step 1

To a suspension of KH (30% in mineral oil, washed with hexanes, 1.2 g, 8.98 mmol) in anhydrous THF (20 mL) at 0 °C under argon was added a solution of 6-bromo-4H-benzo[1,4]oxazin-3-one (**9C**, 1.02 g, 4.49 mmol) in THF (20 mL). After 15 min, the solution was cooled to -78 °C, and *t*-BuLi (1.7 M in pentane, 5.18 mL, 8.8 mmol) was added dropwise. The mixture was stirred for 15 min at -78 °C, and then treated with dimethyl disulfide dropwise. The solution was warmed gradually to RT and stirred overnight. The reaction was then quenched by sat. NH₄Cl (15 mL) carefully, and filtered. The filtrate was diluted with water and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated. Chromatography (5-25% EtOAc/ hexanes) provided **14A** (0.483 g, 55%).

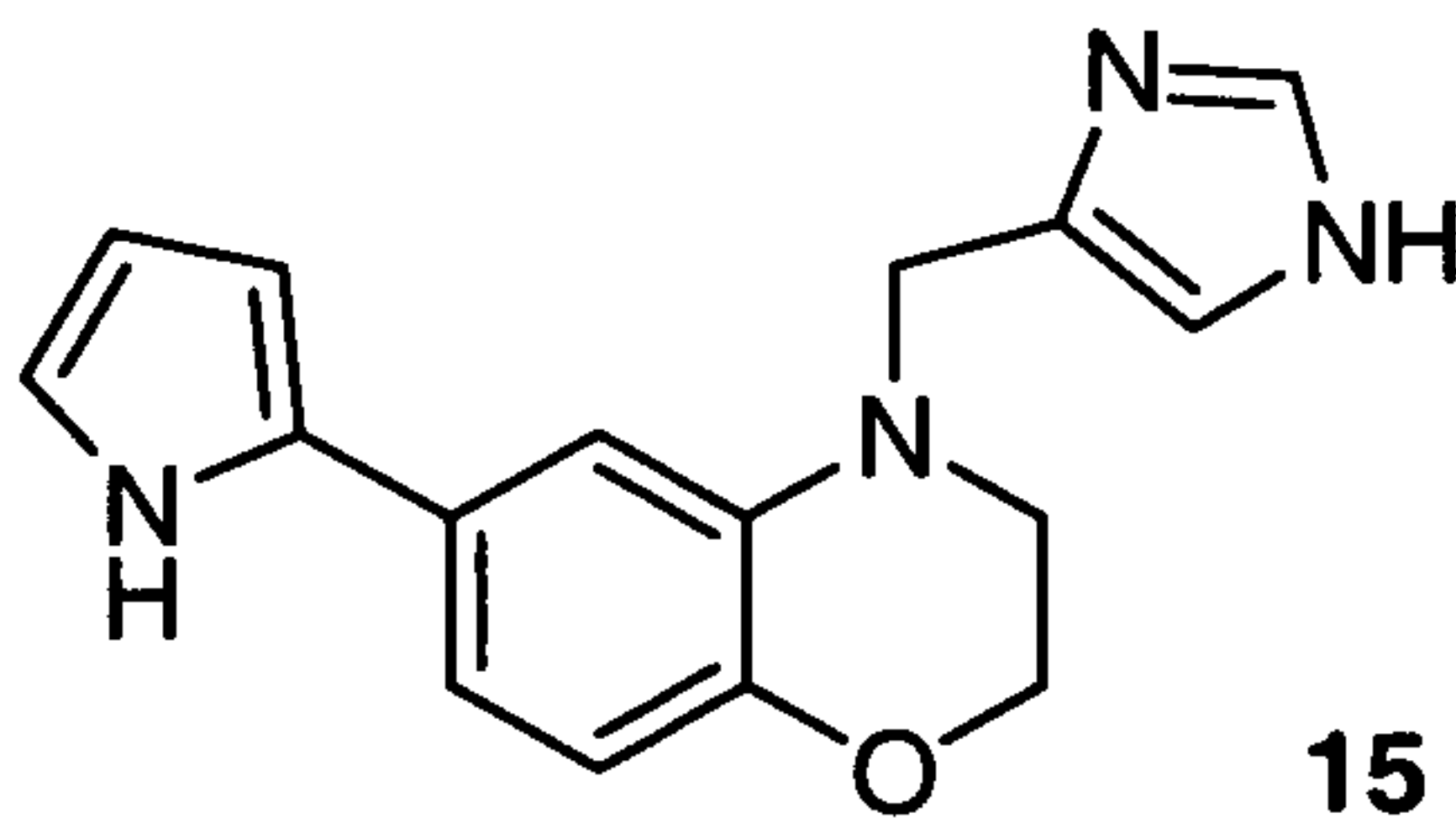
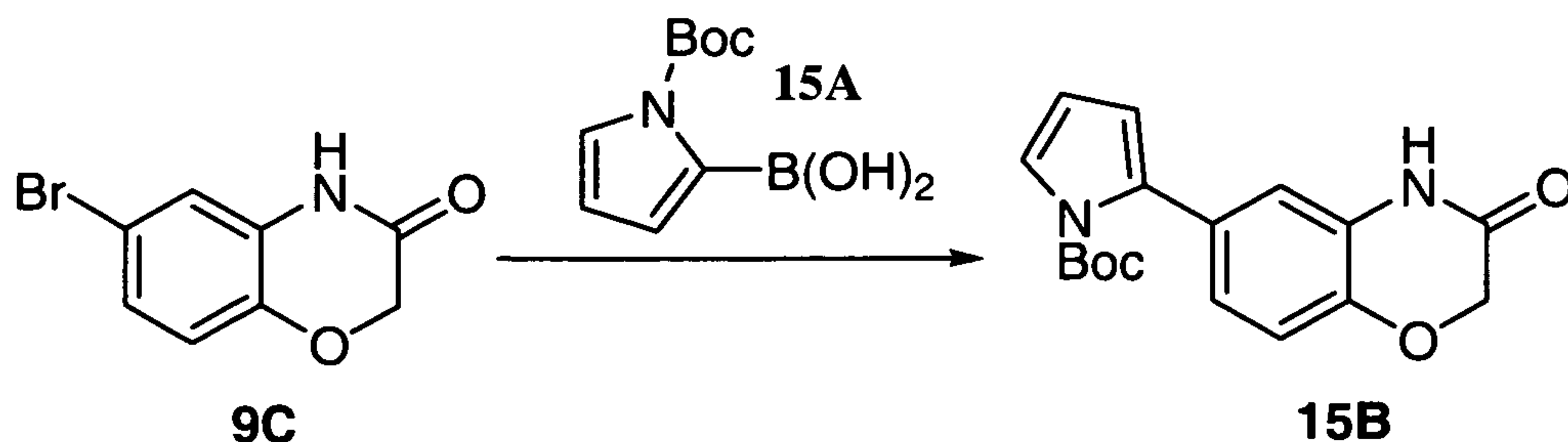
Steps 2-3

In a manner similar to that found in Example 3, Steps 2-3, **14A** was reduced with BH₃-SMe₂ and treated with imidazole-4-carboxaldehyde to provide **14B**. MS *m/z* 262(MH⁺).

60

Step 4

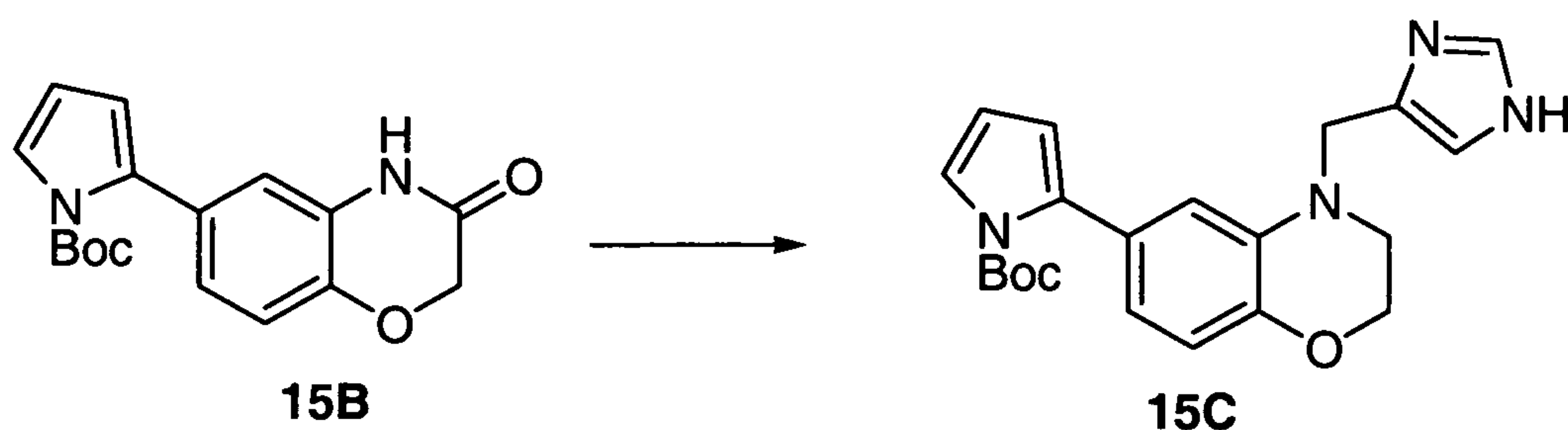
To compound **14B** (0.447 g, 1.71 mmol) in anhydrous DCM (10 mL) was added MCPBA (77%, 0.85g, 3.77 mmol), and the mixture was stirred at RT overnight. The reaction was quenched with sat. Na_2CO_3 solution and the solvent was removed under vacuum. The concentrated solution was extracted with EtOAc (3 x 10 mL). The organic layer was dried (MgSO_4), filtered, and concentrated under vacuum. Chromatography (DCM containing 1-7% of 7N NH_3 -MeOH) provided the title compound **14** (67 mg, 13%, MS m/z 294 MH^+) and a mixture of **14C** and **14**, which was purified by Ranin-preparative HPLC to provided **14C** (39 mg, 8%, MS m/z 278 MH^+).

PREPARATIVE EXAMPLE 15**Steps 1**

To compound 6-bromo-4H-benzo[1,4]oxazin-3-one (**9C**, 500 mg, 2.2 mmol) in toluene (44 mL) was added $\text{Pd}(\text{PPh}_3)_4$ (127 mg, 0.11 mmol). After stirring at RT for 30 min, boronic acid **15A** (697 mg, 3.3 mmol) in EtOH (13 mL, 0.25 M) and saturated NaHCO_3 solution (22 mL) were added and the solution was heated to reflux overnight.

Then the mixture was cooled to RT, and poured into saturated NaCl solution, and concentrated under vacuum. The residue was diluted with water and extracted with EtOAc (3 x 25 mL). The organic layer was dried (MgSO₄), filtered, and concentrated under vacuum. Chromatography (10 to 30% EtOAc/ hexanes) provided **15B** (320 mg, 46%).

Steps 2-3

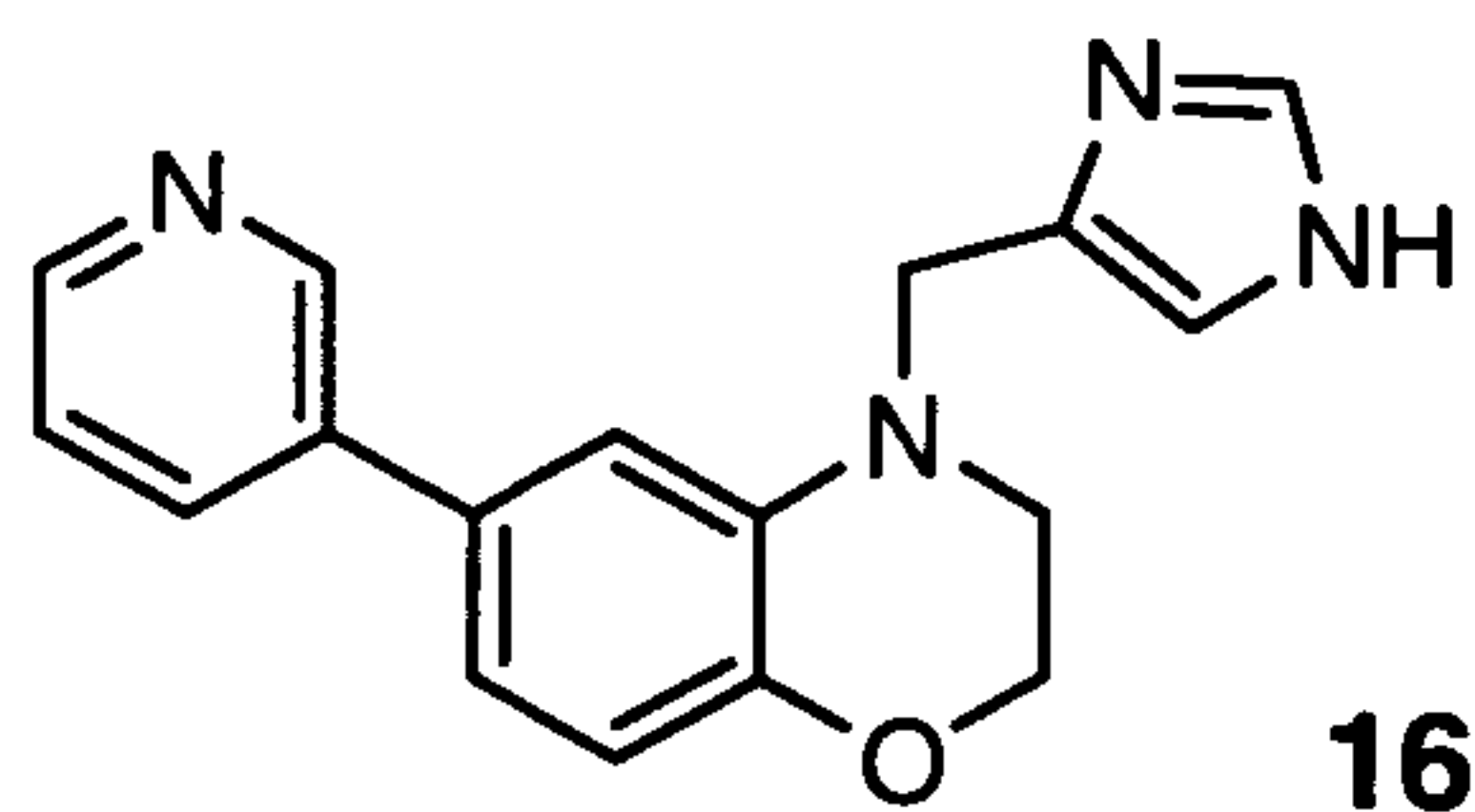


In a manner similar to that found in Example 3, Steps 2-3, **15B** was reduced with BH₃-SMe₂ and treated with imidazole-4-carboxaldehyde to provide **15C**. MS m/z 381 (MH⁺).

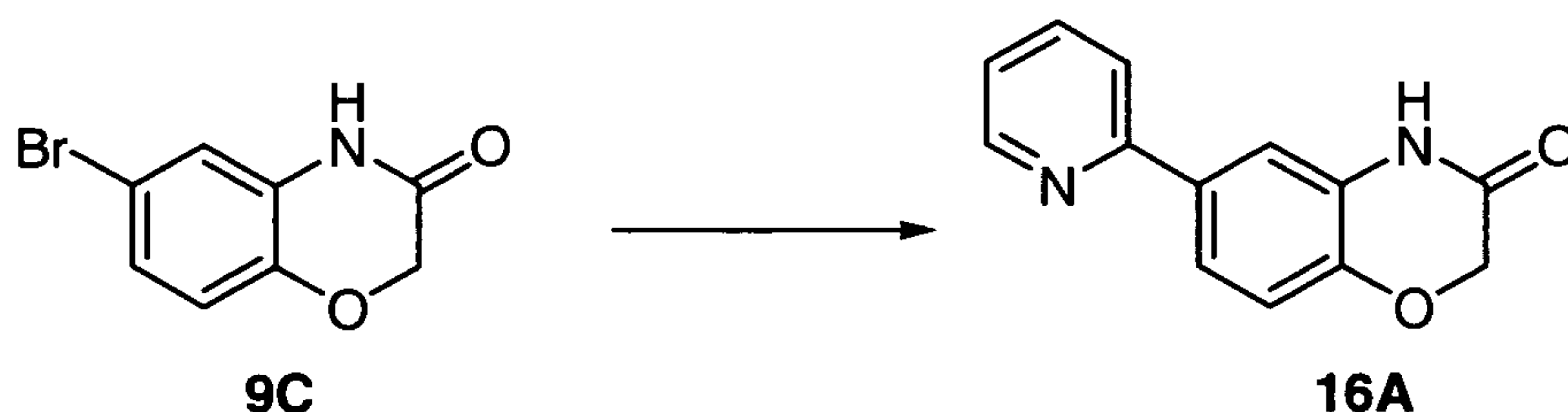
Step 4

A mixture of **15C** (143 mg, 0.37 mmol) in 4.0M HCl-dioxane (1.5 mL, 0.56 mmol) was stirred at RT overnight. The reaction was neutralized with 7N NH₃-MeOH and concentrated. The residue was purified by preparative TLC (DCM containing 10% of 7N NH₃-MeOH) to provide the title compound **15** (28 mg, 26%). MS m/z 281 (MH⁺).

PREPARATIVE EXAMPLE 16



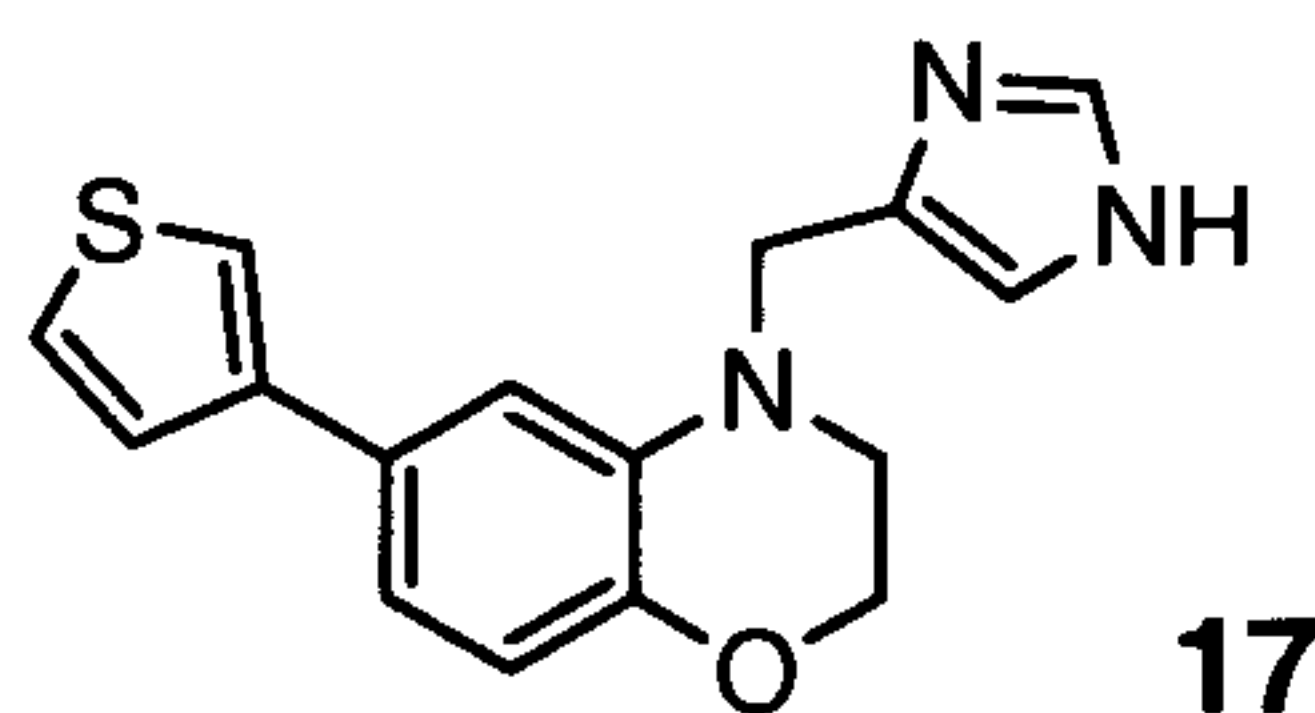
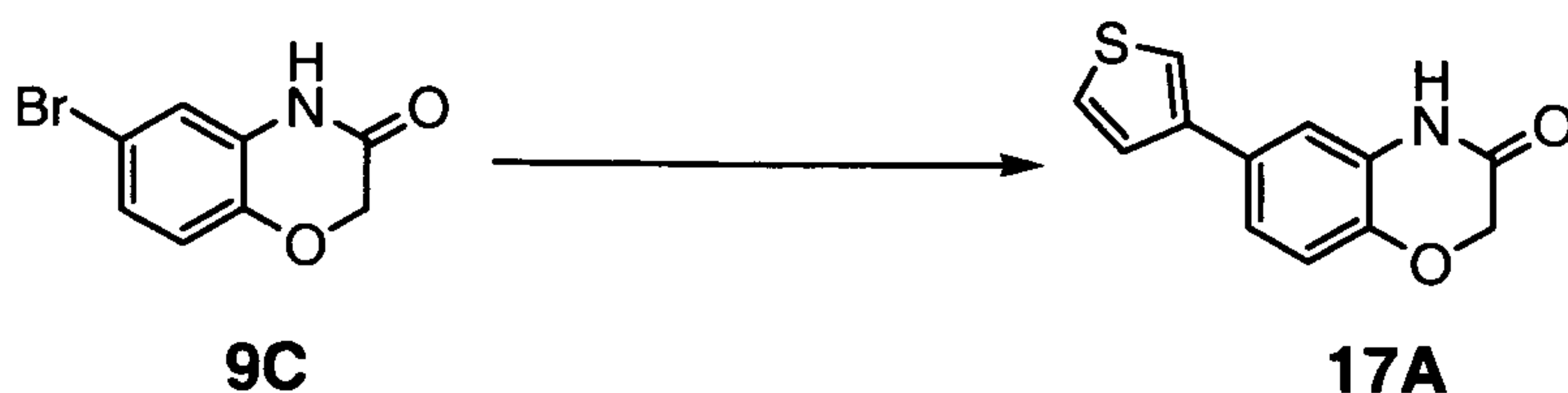
62

Step 1

To a stirred solution of Pd (OAc)₂ (3 mg, 0.0125 mmol) and PPh₃ (13 mg, 0.05 mmol) in anhydrous THF (2 mL) under argon was added 6-bromo-4H-benzo[1,4]oxazin-3-one (**9C**, 57 mg, 0.25 mmol). The mixture was stirred at RT for 10 min and treated sequentially with a solution of 3-pyridine boronic acid (62 mg, 0.5 mmol) in EtOH (1 mL) and aqueous NaHCO₃ solution (2 M, 2 mL). The mixture was heated to reflux for 2 h and then cooled to RT. The solution was poured into saturated NaCl solution, and then concentrated under vacuum. The residue was diluted with water (5 mL) and extracted with EtOAc (3 x 10 mL). The organic layer was dried (MgSO₄), filtered, and concentrated under vacuum. Chromatography (10-30% EtOAc/hexanes) provided **16A** (21mg, 37%).

Steps 2-3

Compound **16A** was converted to compound **16** by reduction with BH₃-SMe₂ and reductive alkylation with imidazole-4-carboxaldehyde as described in Example 3, Steps 2-3. MS m/z 293(MH⁺).

PREPARATIVE EXAMPLE 17**Step 1**

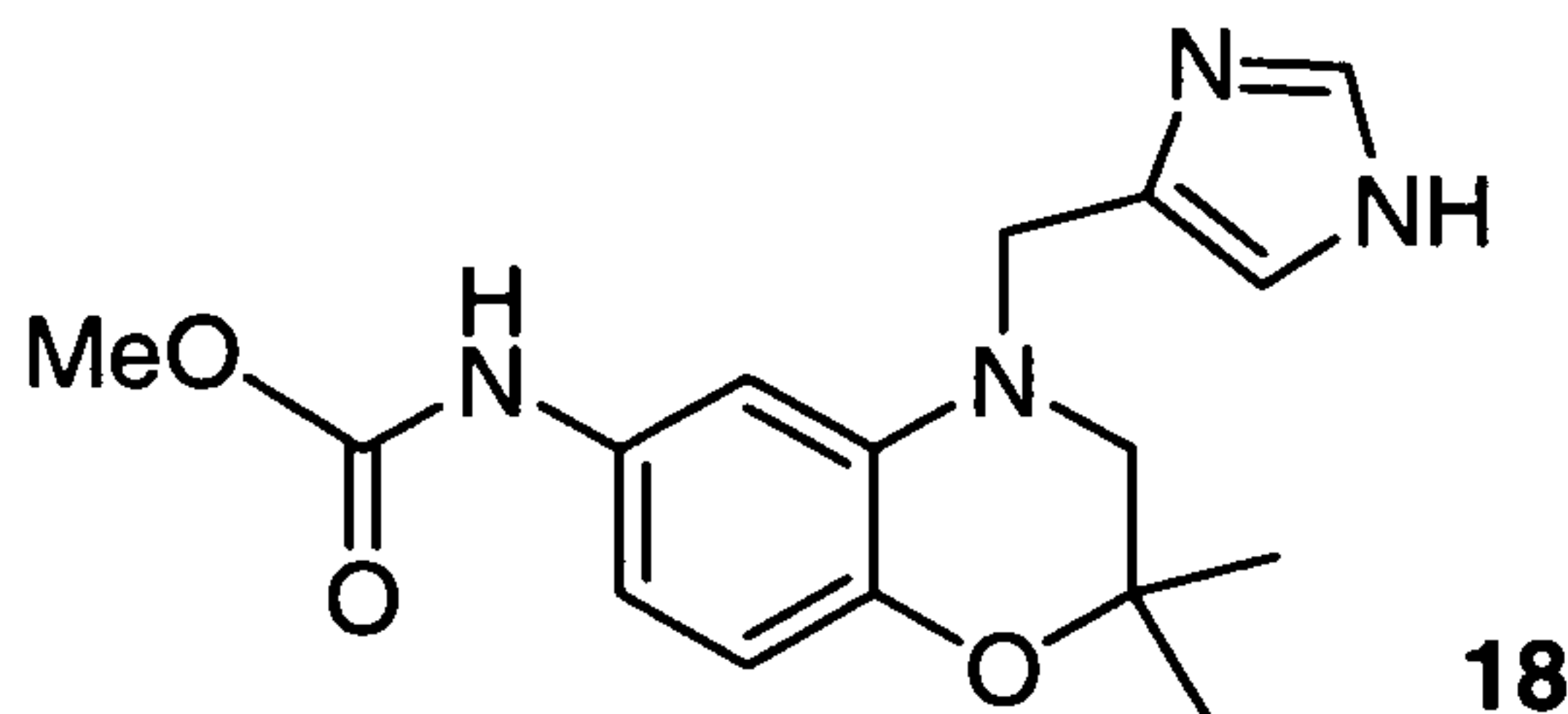
A Smith process vial (2-5 mL) was charged with a stir bar, 6-bromo-4H-benzo[1,4]oxazin-3-one (**9C**, 23 mg, 0.1 mmol), thiophen-3-ylboronic acid (17mg, 0.13

mmol) and EtOH (2 mL). Aqueous K₂CO₃ (1 M, 0.12 mL) and polymer-supported Pd (40 mg, 3 mol% Pd, FiberCat. 1000-D32, Pd% 4.26) were then added sequentially. The reaction vessel was sealed and heated to 110 °C for 1 h under microwave irradiation. After cooling, the reaction mixture was transferred to a prepacked column of Si-carbonate (2 g, 0.79 mmol/g), which had been conditioned with MeOH/DCM (1:1). The product was eluted with MeOH/DCM (1:1, 3 x 3 mL, gravity filtration) and concentrated to give compound **17A** (18 mg, 80%).

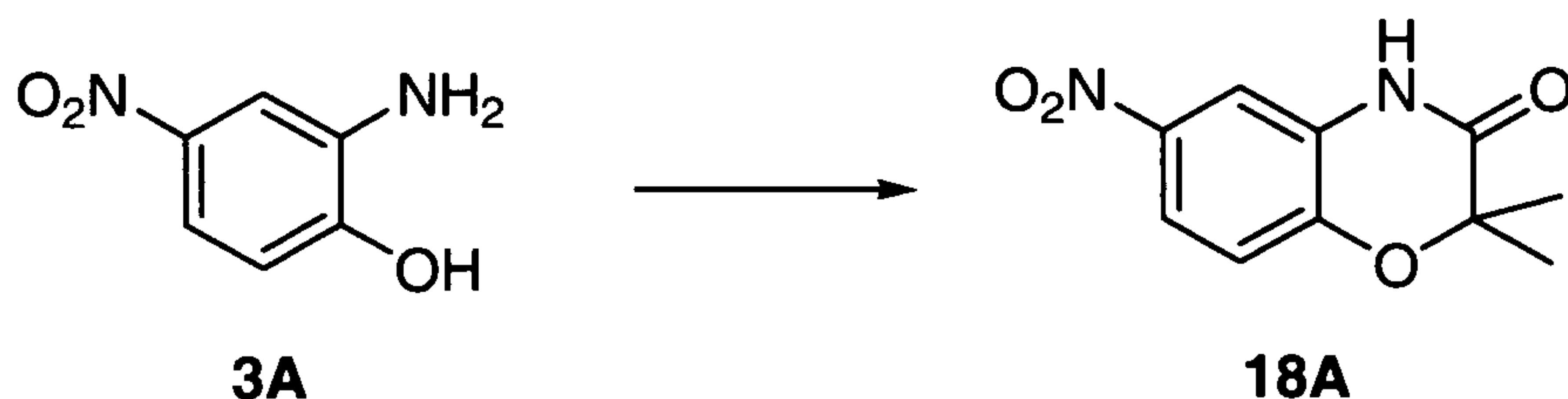
Steps 2-3

Compound **17A** was converted to **17** in a manner similar to that found in Example 3, Steps 2-3. MS m/z 298 (MH⁺).

PREPARATIVE EXAMPLE 18

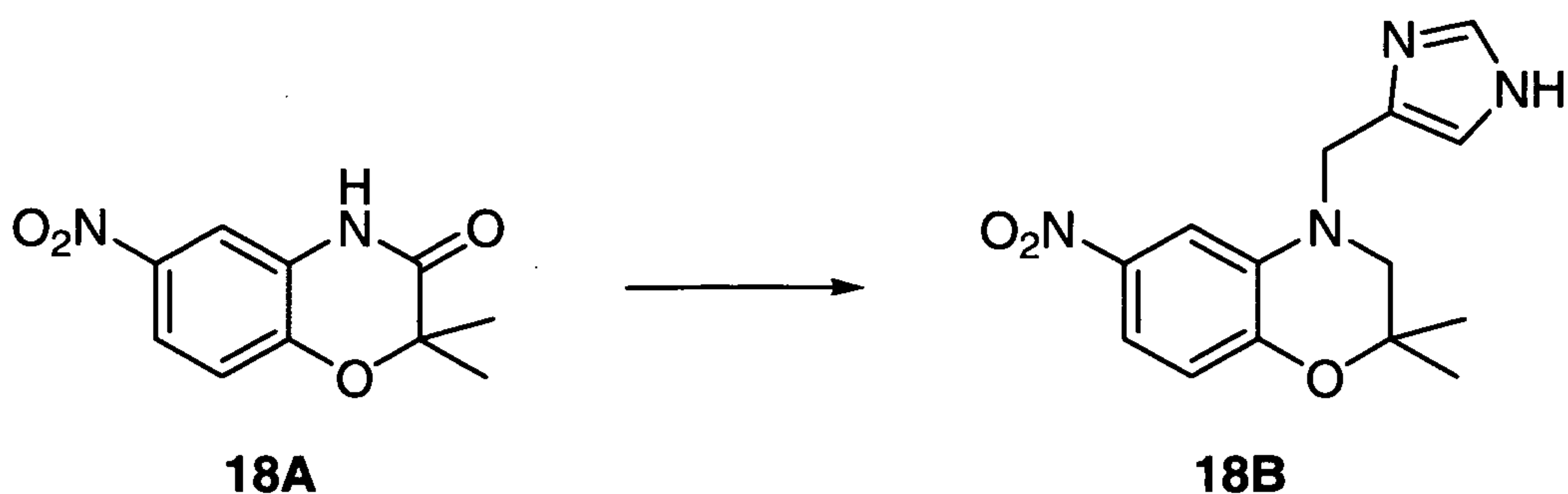


Step 1

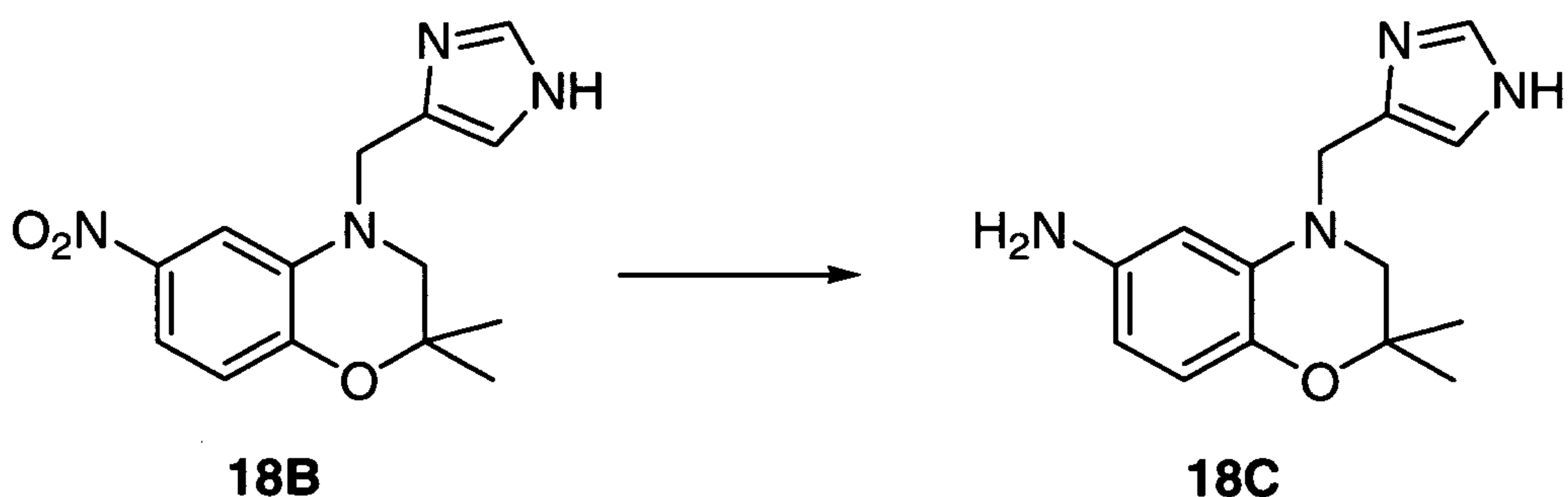


A Smith process vial (20 mL) was charged with a stir bar, compound **3A** (1 g, 6.49 mmol), ethyl 2-bromo-2-methylpropanoate (1 mL, 6.81 mmol), KF (1.13 g, 19.5 mmol) and DMF (10 mL). The reaction vessel was sealed and heated to 160 °C for 1 h under microwave irradiation. After cooling, the reaction mixture was poured into ice-water and extracted with EtOAc (3 x 50 mL). The organic layer was dried (MgSO₄), filtered, and concentrated under vacuum. Chromatography (10-30% EtOAc/hexanes) gave **18A** (0.245 g, 17%).

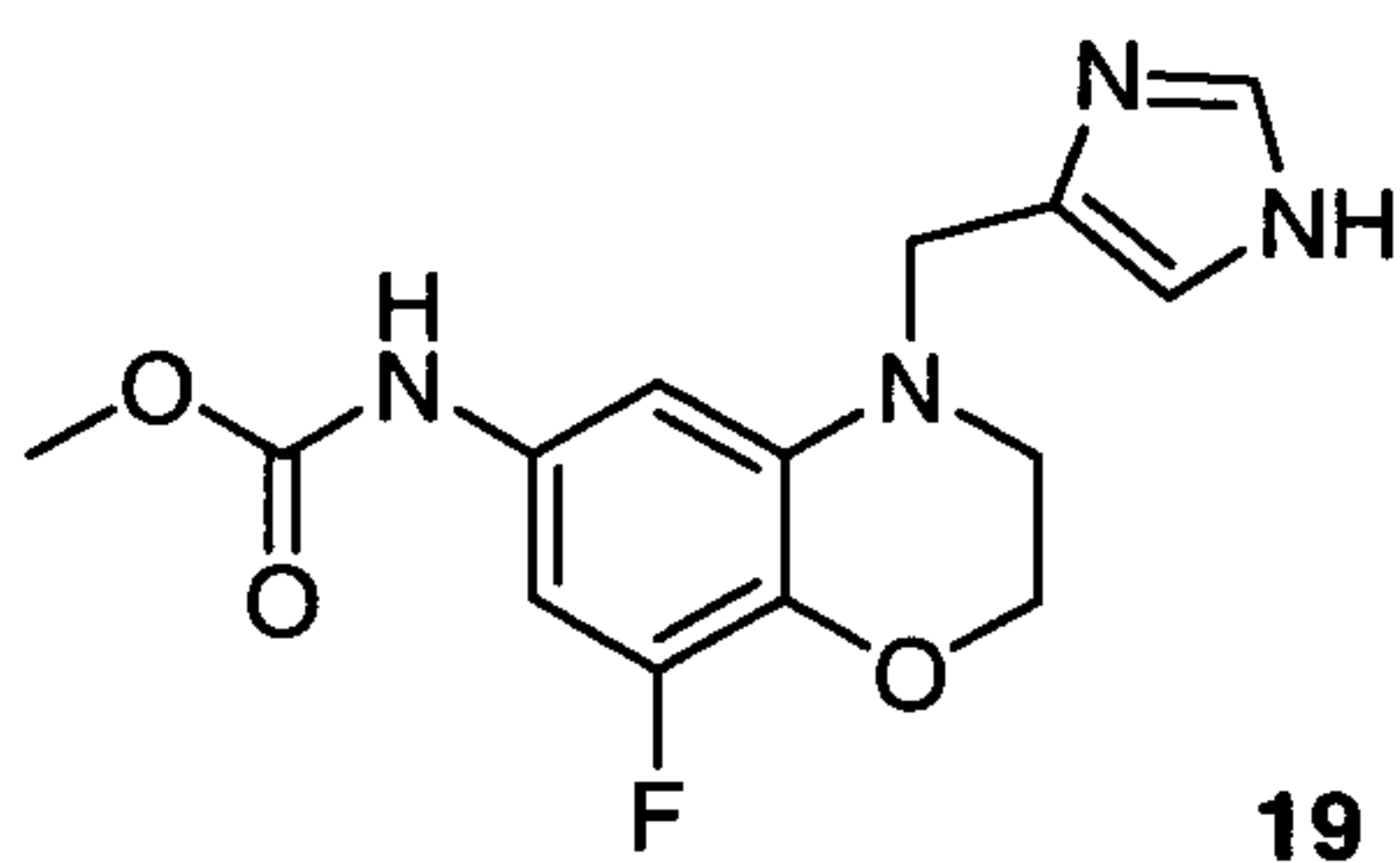
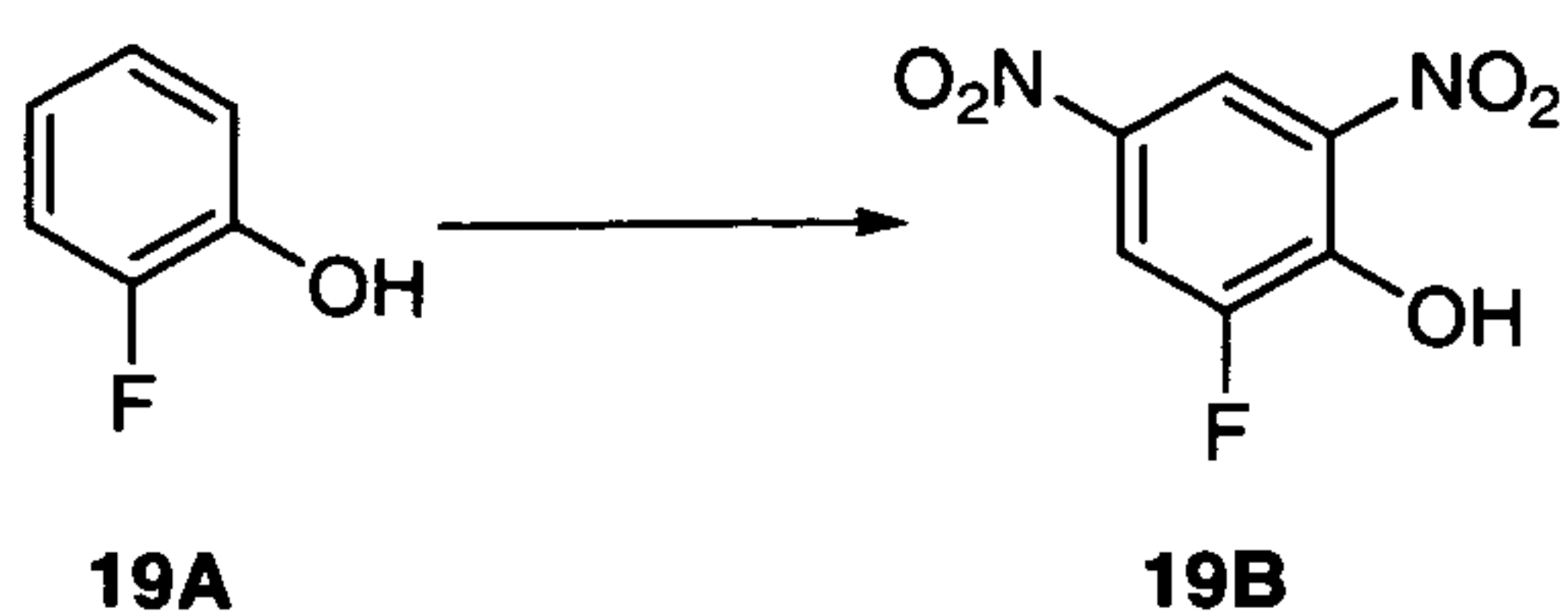
64

Step 2-3

In a manner similar to that found in Example 3, Steps 2-3, **18A** was reduced with $\text{BH}_3\text{-SMe}_2$ and reacted with imidazole-4-carboxaldehyde to provide **18B**. MS m/z 289 (MH^+).

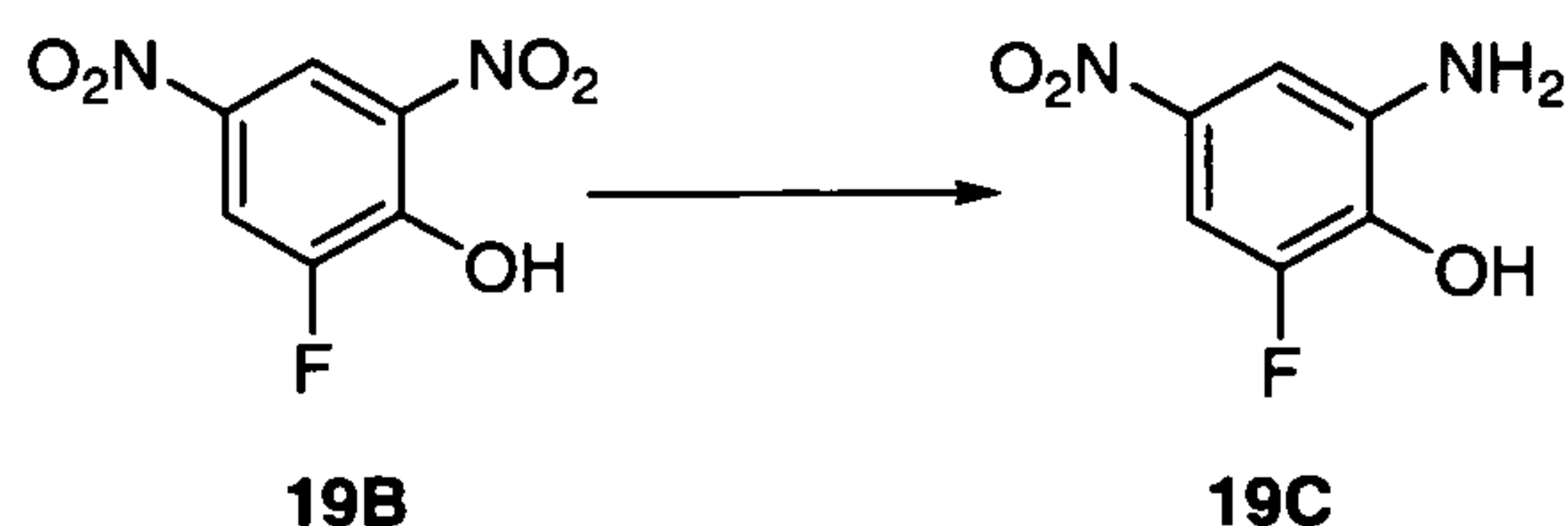
Step 4-5

Following the procedure found in Example 3, Step 4, **18B** was hydrogenated to give compound **18C**. In a manner similar to that found in Example 3, Step 5, **18C** was further reacted with ClCO_2Me to provide the title compound **18**. MS m/z 317 (MH^+).

PREPARATIVE EXAMPLE 19**Step 1**

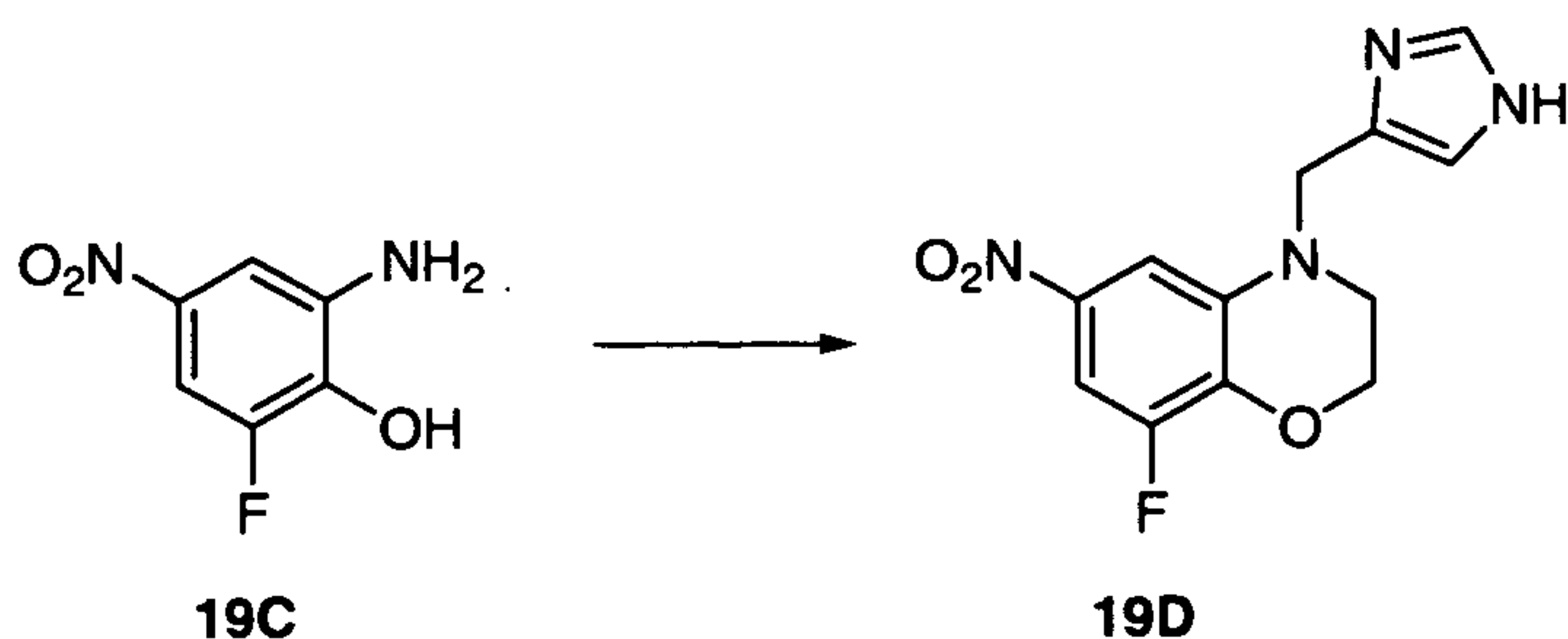
To 2-fluorophenol (**19A**, 8 mL, 86.4 mmol) in anhydrous DCM (70 mL) at 0 °C was added fuming HNO₃ (0.34 mL, 0.008 mmol) dropwise through an addition funnel. The mixture was warmed to RT and stirred for 2 h, then cooled to 0 °C again and
5 quenched with 2N NaOH solution to pH 5. The mixture was concentrated under vacuum, diluted with water, extracted with EtOAc (3 x 100 mL). The combined organic layer was dried (MgSO₄), filtered, and concentrated under vacuum to give compound **19B** (15.07 g, yield: 86.4%).

10 **Step 2**

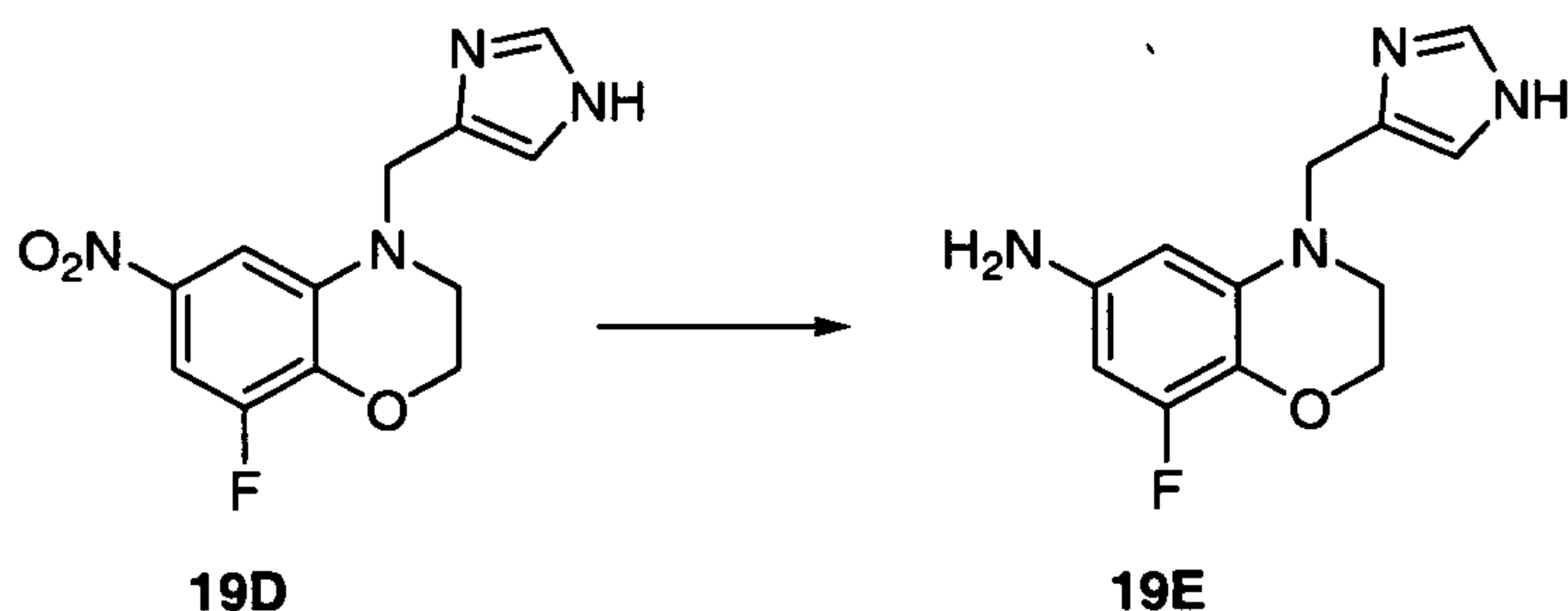


A solution of **19B** (15.07g, 74.6 mmol) in EtOH (300 mL) was treated with SnCl₂·2H₂O (50.5 g, 224 mmol) and heated to reflux for 2 h. The mixture was concentrated, poured into ice, and neutralized to pH 7 with 2N NaOH solution. The
15 solid was filtered off and washed with EtOAc (5 x 500 mL). The filtrate was separated and the aqueous was extracted with EtOAc (3 x 100 mL). The organic layer was dried (MgSO₄), filtered and concentrated under afford **19C** (12.59 g, 98%).

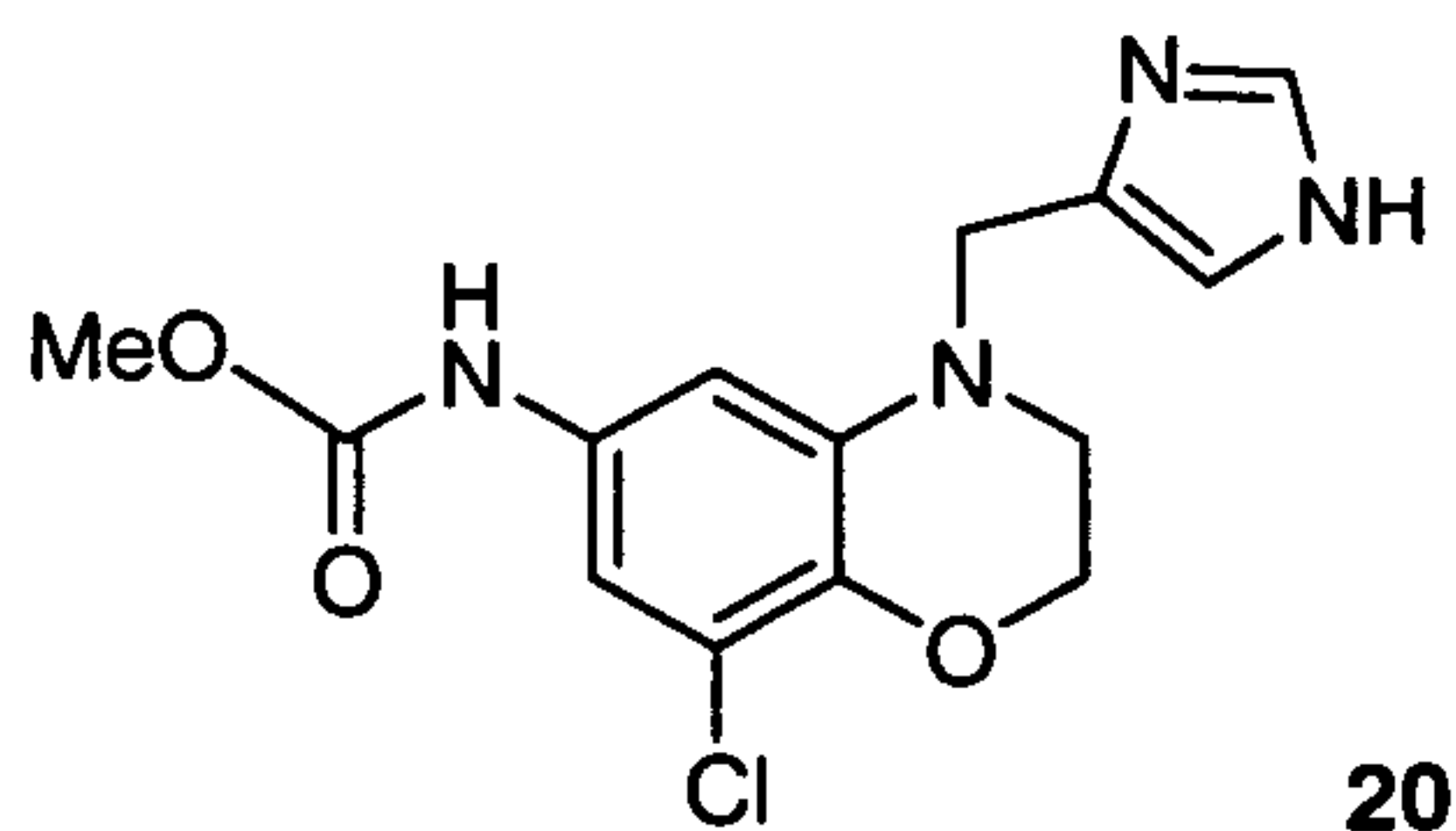
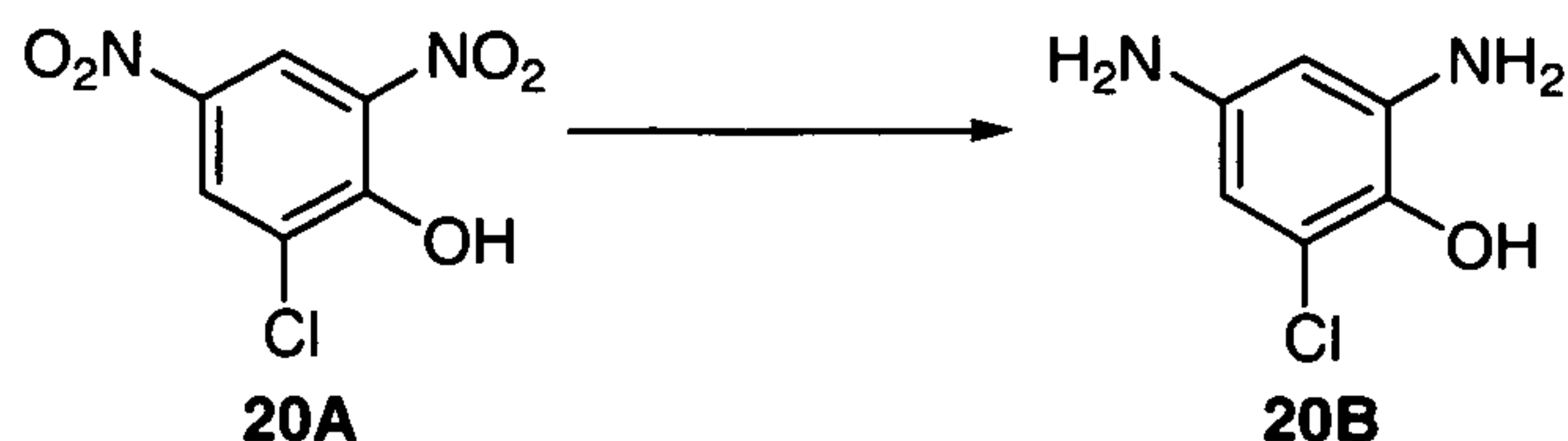
66

Steps 3-5

In a manner similar to that found in Example 3, Steps 1-3, **19C** was reacted with chloroacetyl chloride, reduced with $\text{BH}_3\text{-SMe}_2$, and treated with imidazole-4-carboxaldehyde to provide compound **19D**. MS m/z 279 (MH^+).

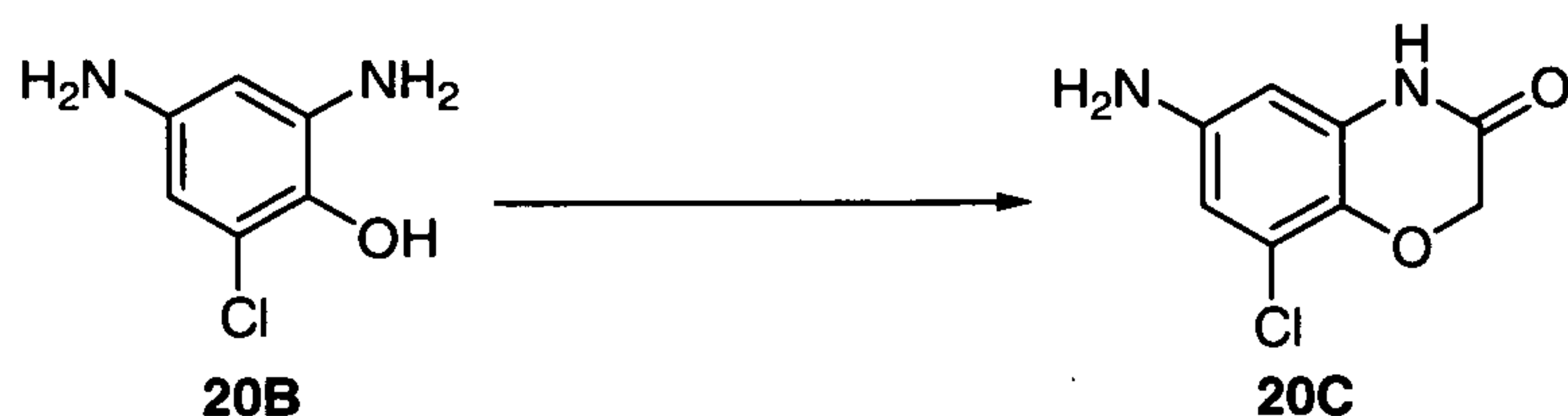
Steps 6-7

In a manner similar to that found in Example 3, Step 4, **19D** was hydrogenated to afford compound **19E**. MS m/z 249 (MH^+). Compound **19E** was further reacted with ClCO_2Me as described in Example 3, Step 5, to provide the title compound **19**. MS m/z 307 (MH^+).

PREPARATIVE EXAMPLE 20**Step 1**

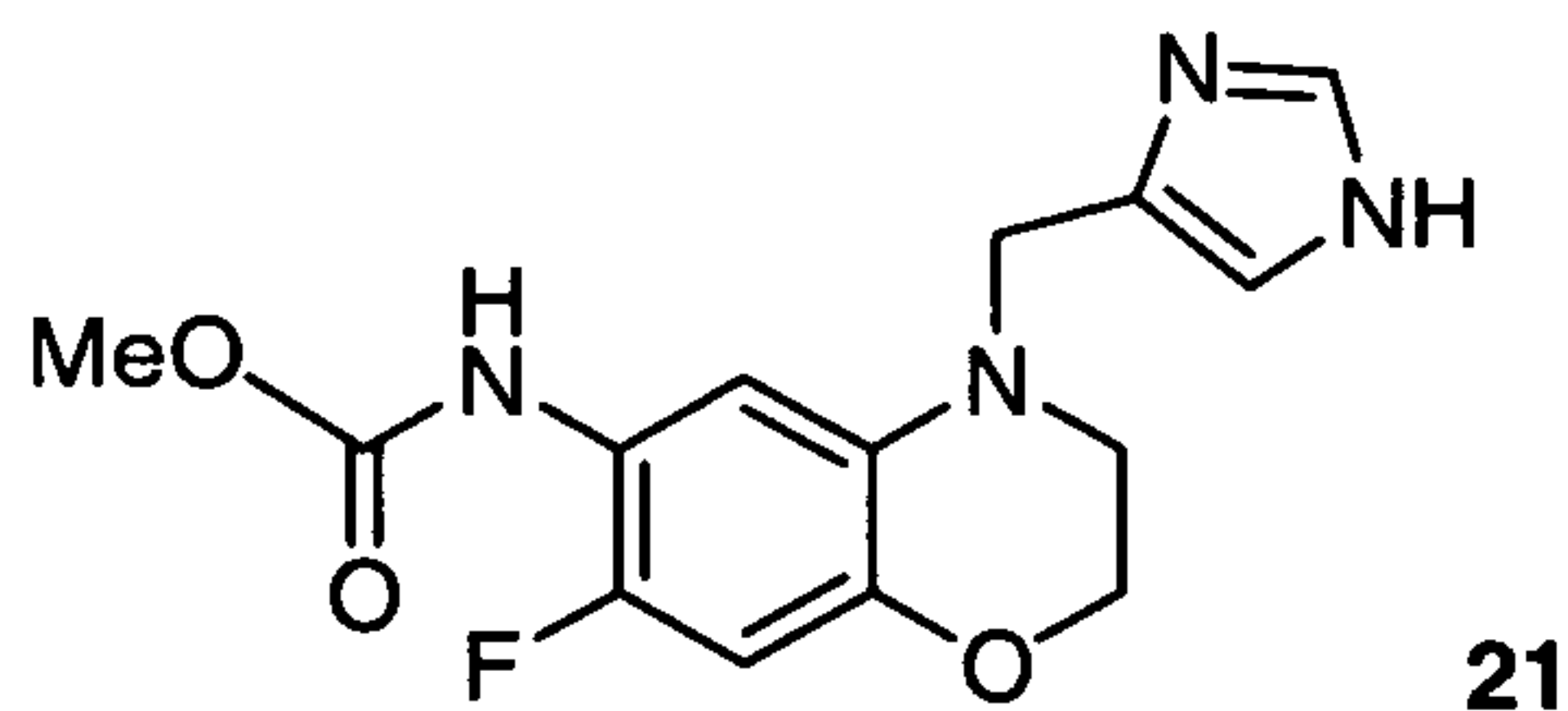
To 2-chloro-4,6-dinitrophenol (**20A**, 2 g, 9.18 mmol) in EtOH (100 mL) was added a scoop of Raney nickel (20% by weight) carefully. The mixture was stirred at RT under hydrogen balloon overnight and then filtered. The solvent was evaporated off under vacuum to give white solid **20B** (1.3 g, 89%) and used directly in the next reaction.

Steps 2-5

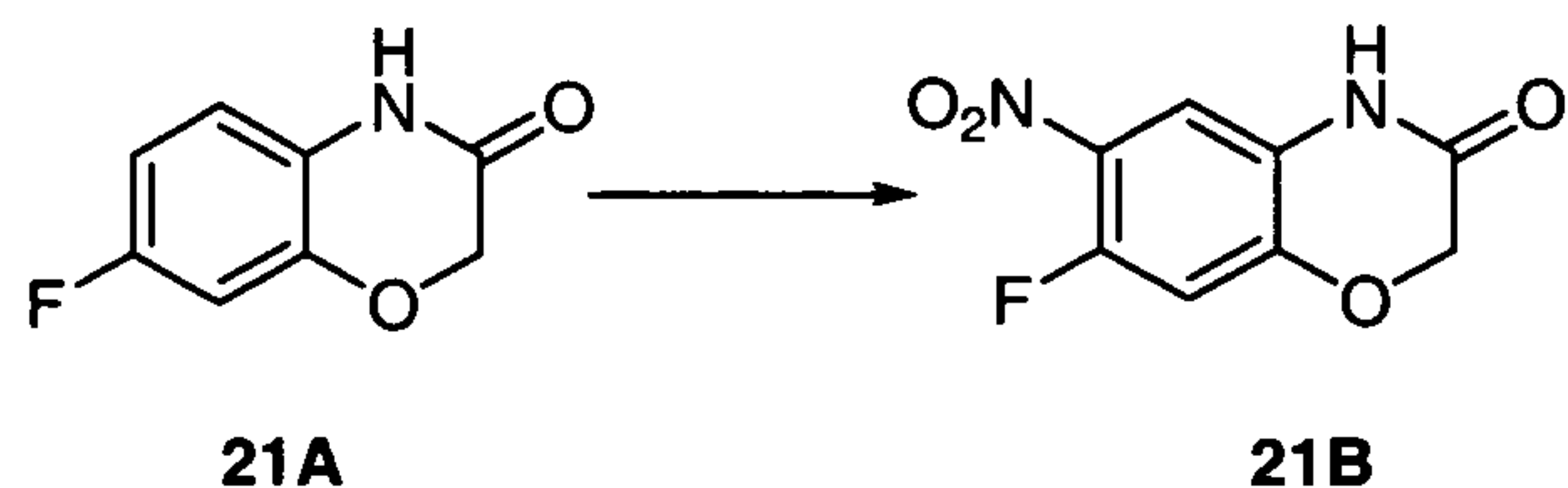


Following the procedure described in example 3, Step 1, **20B** was reacted with chloroacetyl chloride to provide **20C** (5%). Compound **20C** was treated with ClCO_2Me , reduced with $\text{BH}_3\text{-SMe}_2$, and reductively alkylated in a manner similar to that found in Example 8 and Example 3 (Steps 2-3) to afford the title compound **20**. MS m/z 323 (MH^+).

PREPARATIVE EXAMPLE 21

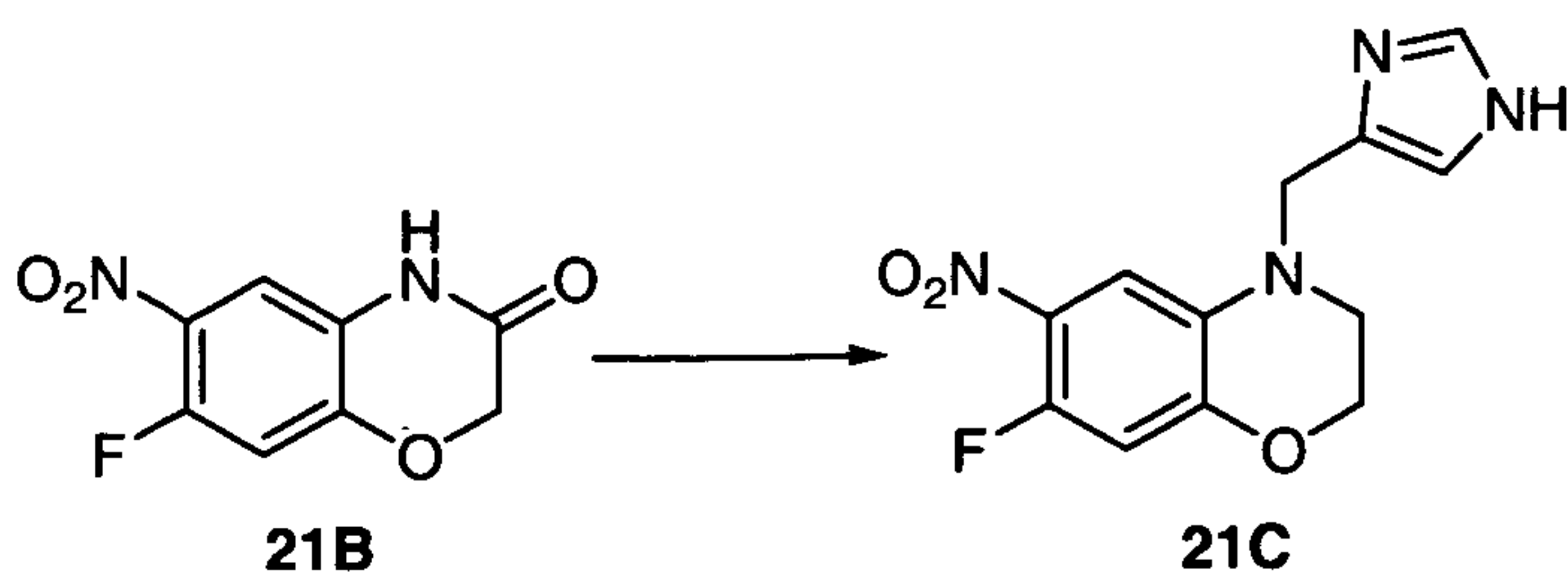


Step 1

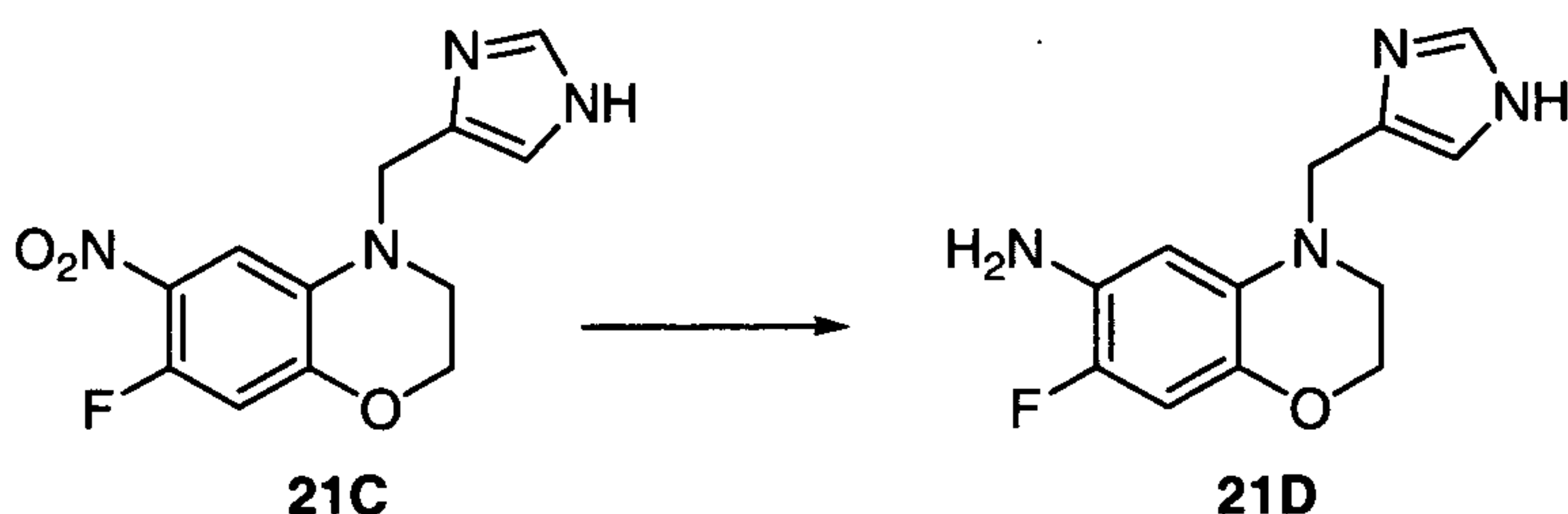


To compound **21A** (5 g, 30 mmol) in concentrated H_2SO_4 (17 mL) was added a 1:1 mixture of fuming HNO_3 and conc. H_2SO_4 (7 mL) over 15 min. The mixture was stirred for additional 30 min at RT and was slowly poured into ice water (500 mL). The mixture was filtered to collect solid and washed with water (4x). The solid was placed under high vacuum in an 80°C oil bath for 5 h to provide **21B** (3.82 g, 60%).

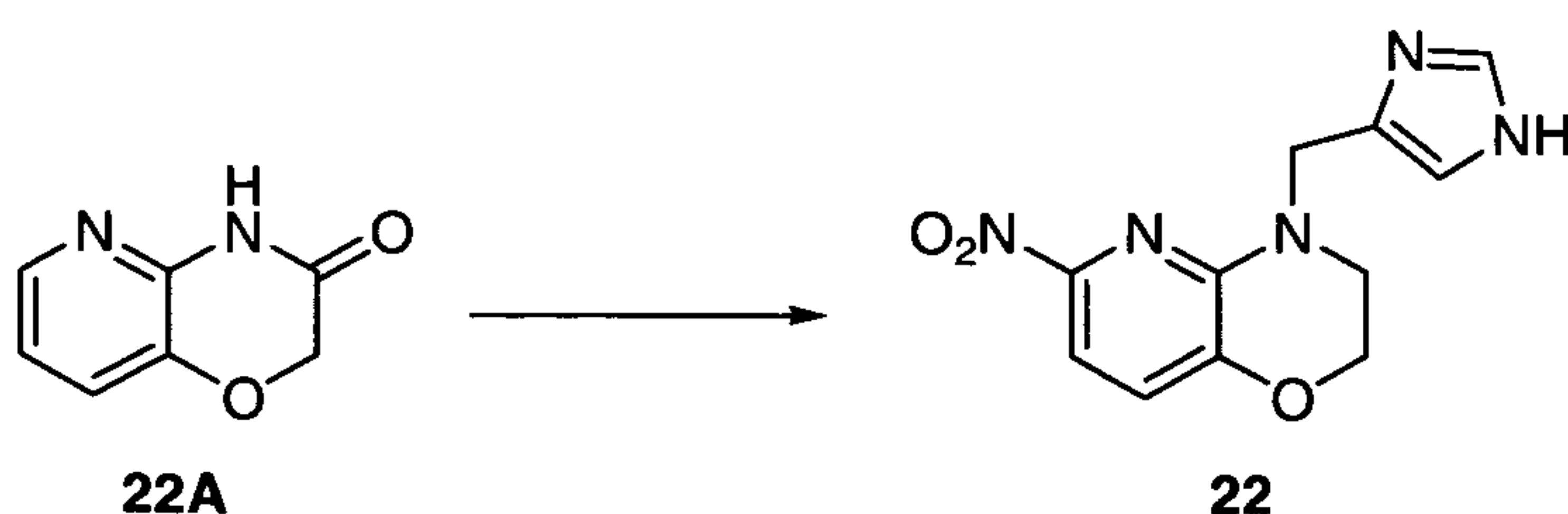
68

Steps 2-3

In a manner similar to that found in Example 3, Steps 2-3, **21B** was reduced with $\text{BH}_3\text{-SMe}_2$ and then treated with imidazole-4-carboxaldehyde to afford compound **21C**. MS m/z 279 (MH^+).

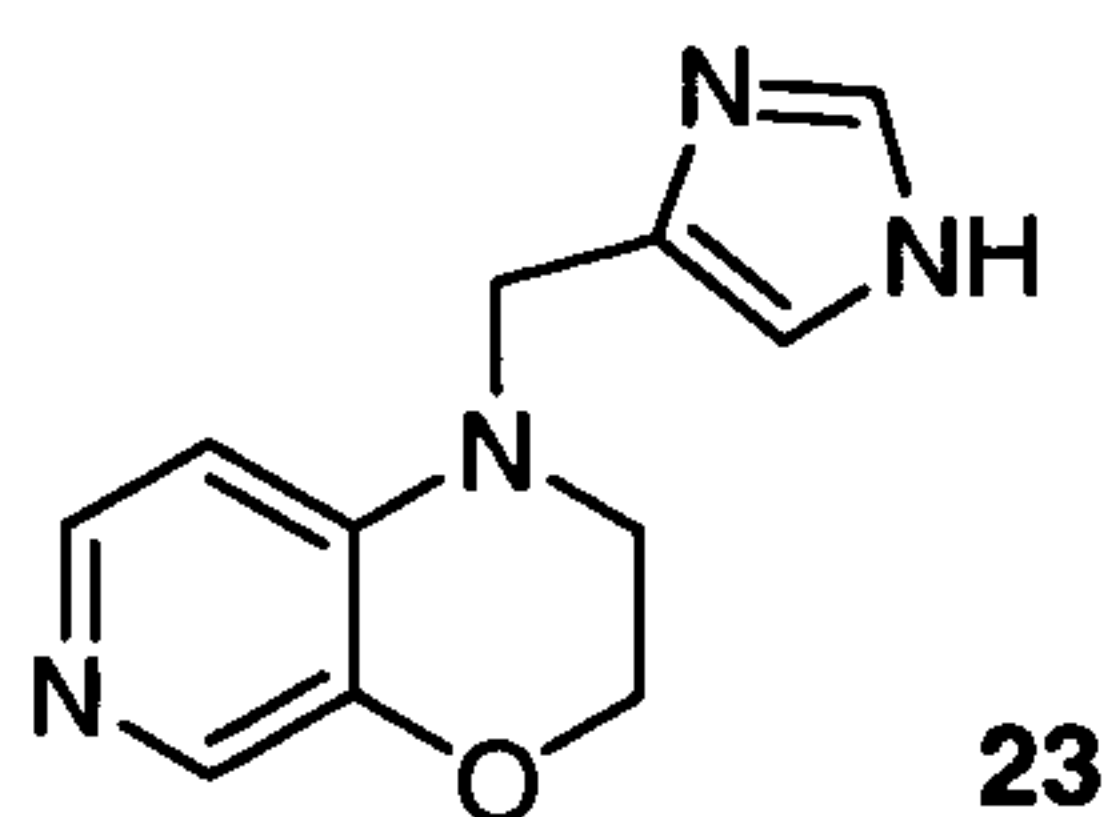
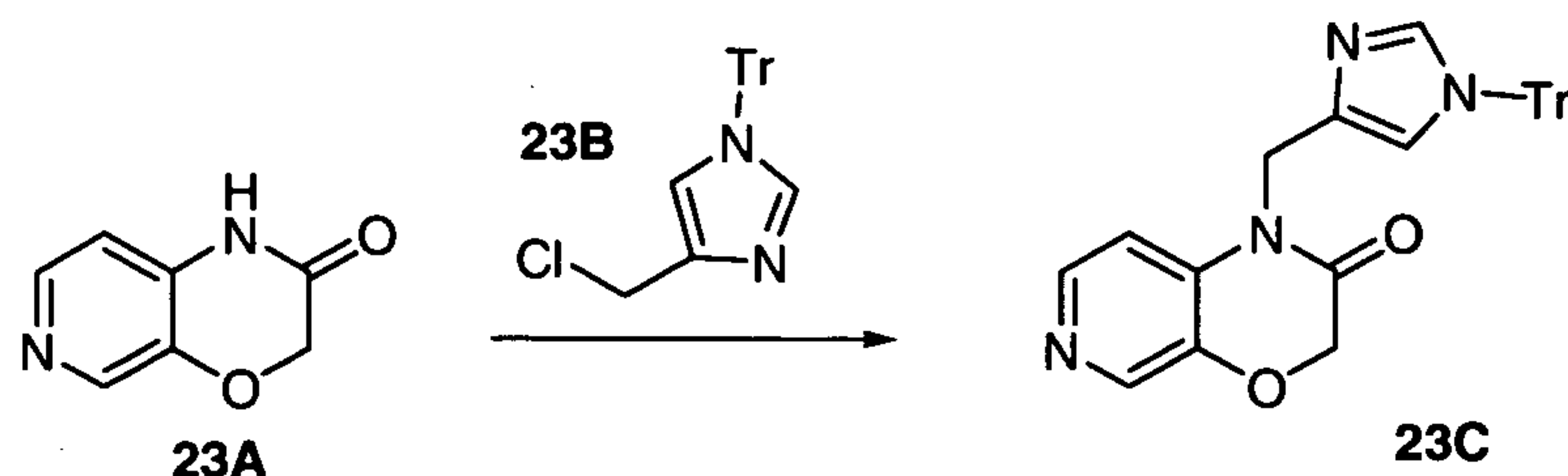
Steps 4-5

In a manner similar to that found in Example 3, Steps 4, **21C** was hydrogenated to provide compound **21D**. Compound **21D** was then converted to the title compound **21** as described in Example 3, Step 5. MS m/z 307 (MH^+).

PREPARATIVE EXAMPLE 22

Following the procedures described in Example 21 (Step 1) and Example 3 (Steps 2-3), **22A** was nitrated with HNO_3 , reduced with $\text{BH}_3\text{-SMe}_2$, and reacted with imidazole-4-carboxaldehyde to provide compound **22**. MS m/z 262 (MH^+).

69

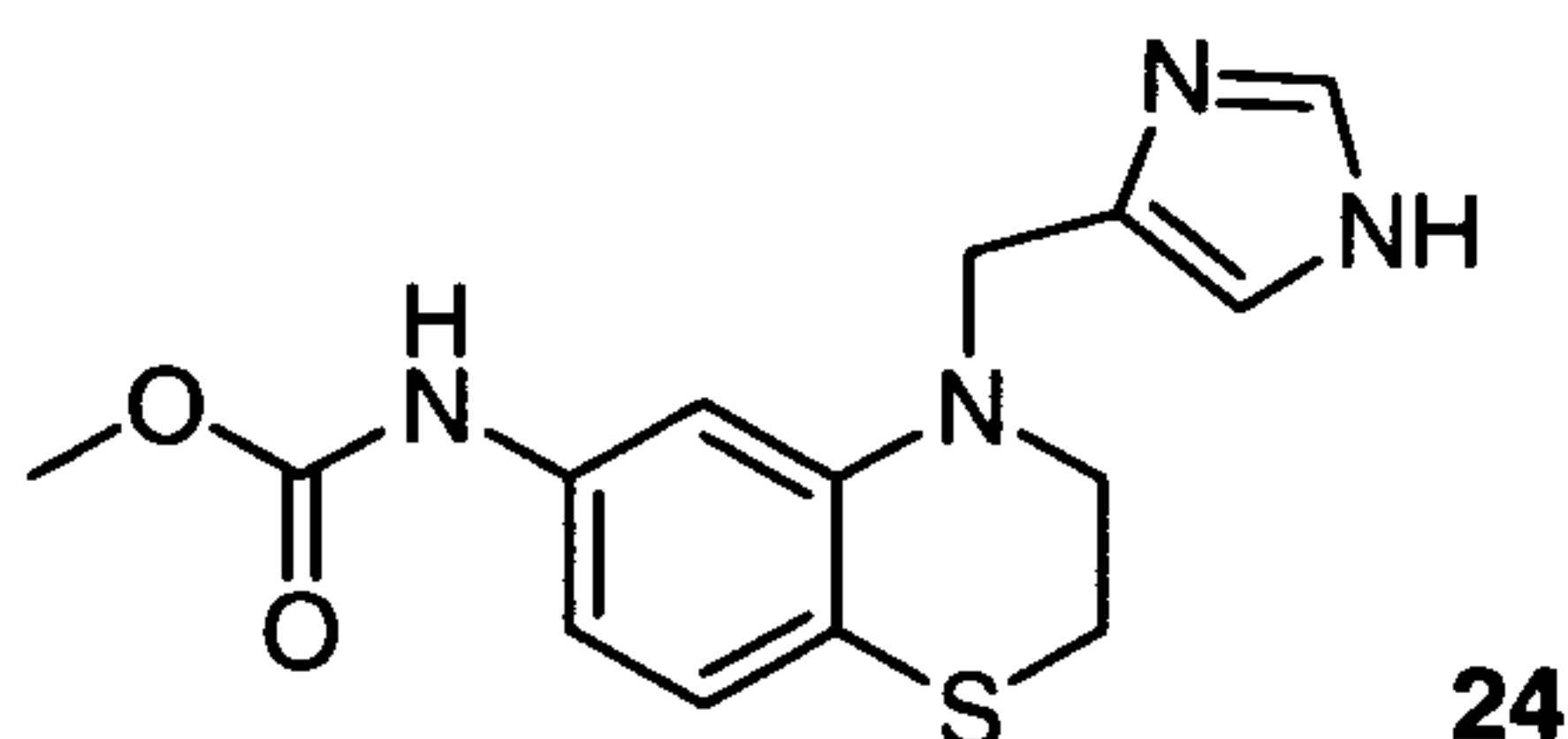
PREPARATIVE EXAMPLE 23**Step 1**

5 A solution of compound **23A** (330 mg, 2.2 mmol, U.S. Patent No. 5,652,363) in DMF (4 mL) was treated with NaH (60% in mineral oil, 88 mg, 2.2 mmol) at RT. The mixture was stirred for 20 min, followed by addition of a solution of compound **23B** (0.79 g, 2.2 mmol, J. Med. Chem., 2002, 45, 533) in DMF (4 mL). The mixture was stirred at 45 °C for 3 days, and then quenched with water and concentrated under vacuum.

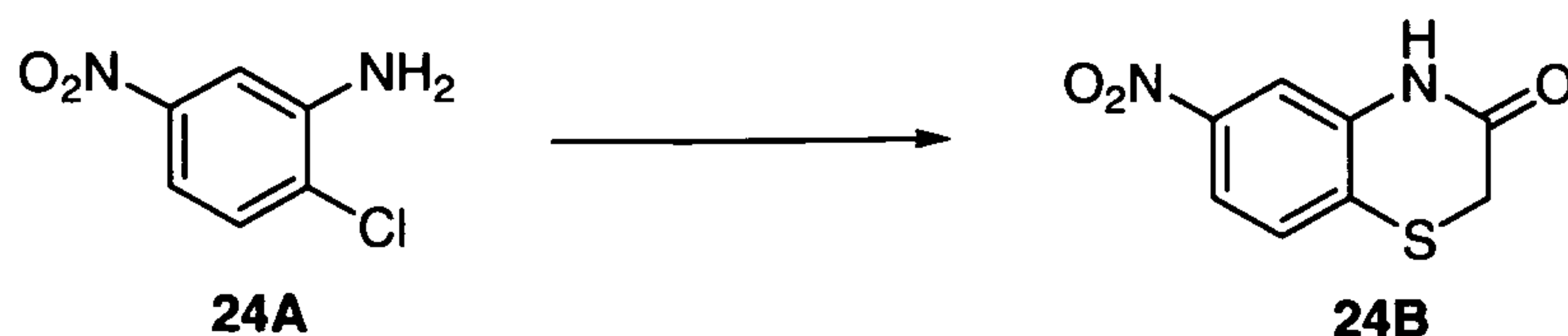
10 The residue was dissolved in EtOAc (50 mL), washed with water (2 x 10 mL). The organic layer was dried (Na₂SO₄), filtered, and concentrated under vacuum. Chromatography (DCM with 2-3% 7 N NH₃-MeOH) provided **23C** (519 mg, 50%). MS m/z 473 (MH⁺).

Steps 2-3

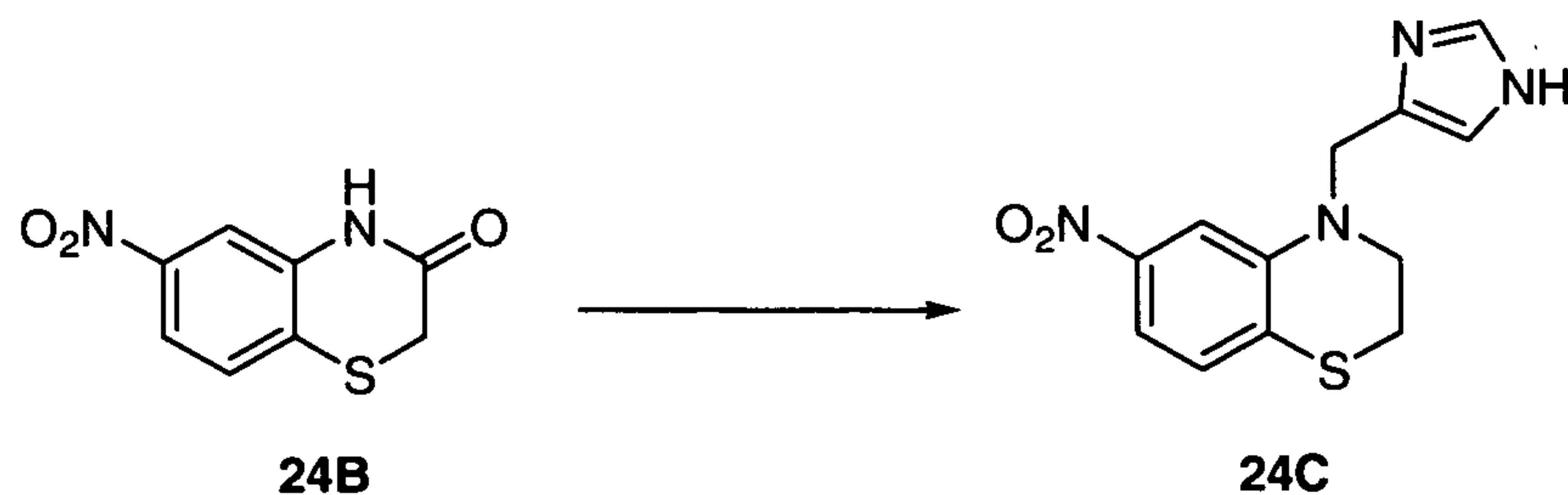
15 In a manner similar to that found in Example 2 (Step 2) and Example 15 (Step 4), **23C** was reduced with BH₂-SMe₂ (18 h at reflux) and then deprotected with HCl-dioxane (1 h at 60 °C) to provide the title compound **23**. MS m/z 217 (MH⁺).

20 PREPARATIVE EXAMPLE 24

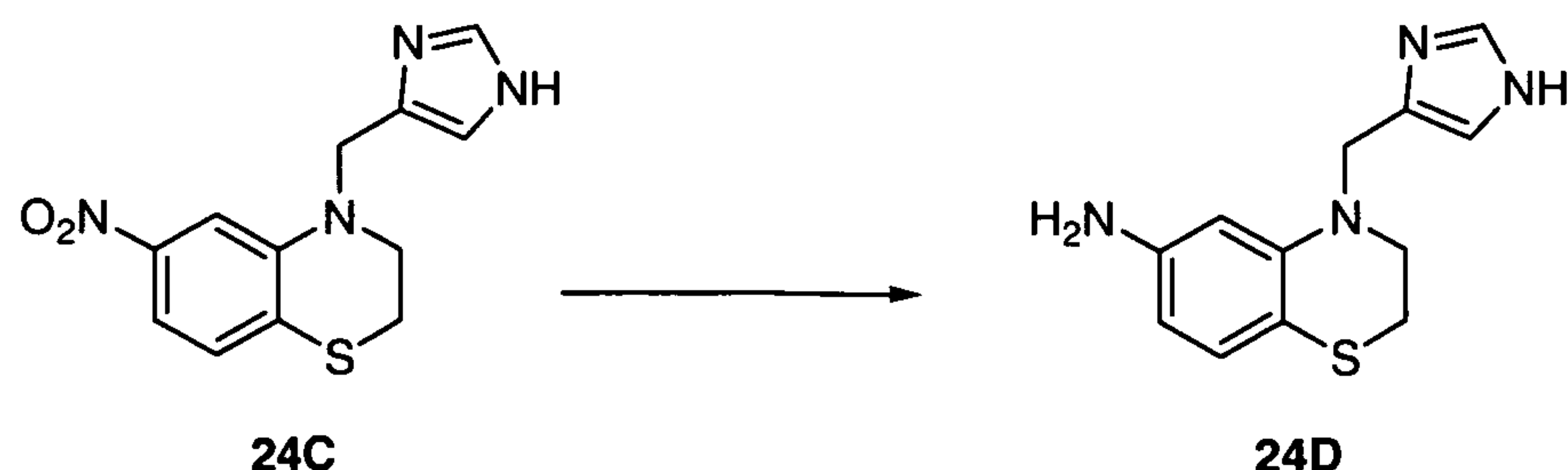
70

Step 1

A stirred solution of 2-chloro-5-nitroaniline **24A** (34.4 g, 0.2 mol) in absolute EtOH (200 mL) at 70 °C was treated gradually with a solution of sodium sulfide nonahydrate (48 g, 0.2 mol) and sulfur (9.6 g, 0.3 mol), which had been preheated to melting. The mixture was refluxed for 30 min and cooled to RT. The mixture was filtered to collect the solid, wash with water. The solid was dried under vacuum at 100 °C for 5 h. The resulting solid was taken up in water (200 mL) and treated with NaOH (8 g, 0.2 mol) and ClCH₂COOH (18.9g, 0.2 mol). The mixture was then heated to reflux for 1.5 h. After cooling down, the mixture was acidified with 10% HCl solution and filtered to collect brown-yellow solid, and washed with water to give compound **24B** (25 g, 60%).

Steps 2-3

Following the procedure described in Example 3, Steps 2-3, **24B** was reduced with BH₃-SMe₂ and treated with imidazole-4-carboxaldehyde to provide **24C**. MS m/z 277 (MH⁺).

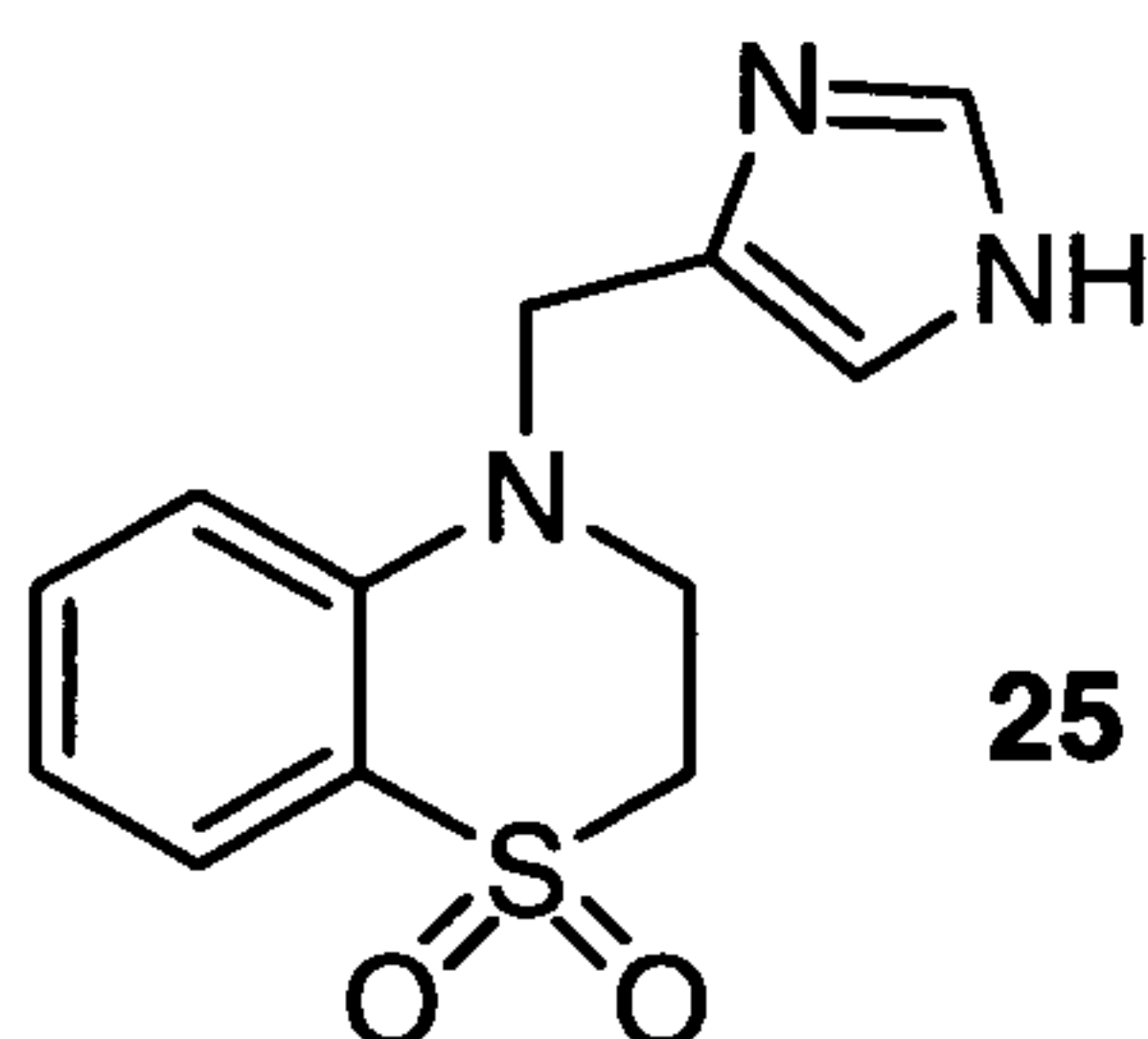
Steps 4-5

In a manner similar to that found in Example 3, Step 4, **24C** was hydrogenated to provide **24D**. MS m/z 247 (MH⁺). Compound **24D** was further treated with

71

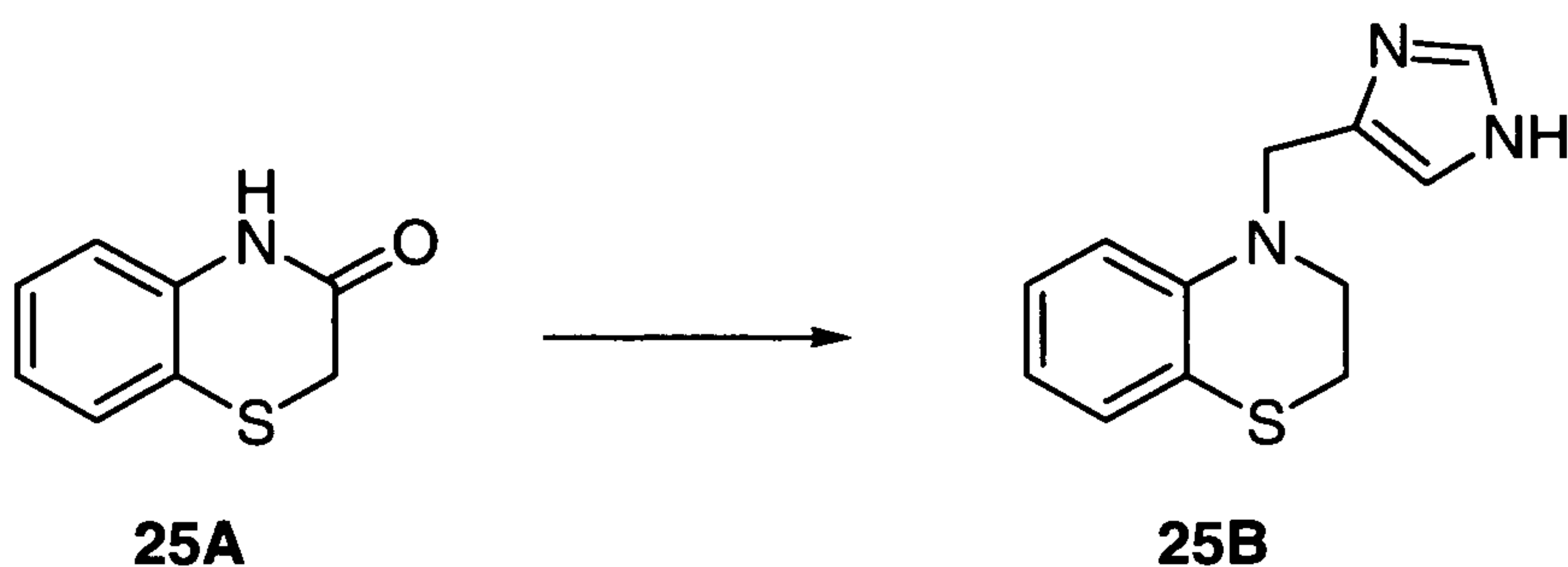
ClCO₂Me as described in Example 3, Step 5, to provide the title compound **24**. MS m/z 305 (MH⁺).

PREPARATIVE EXAMPLE 25



5

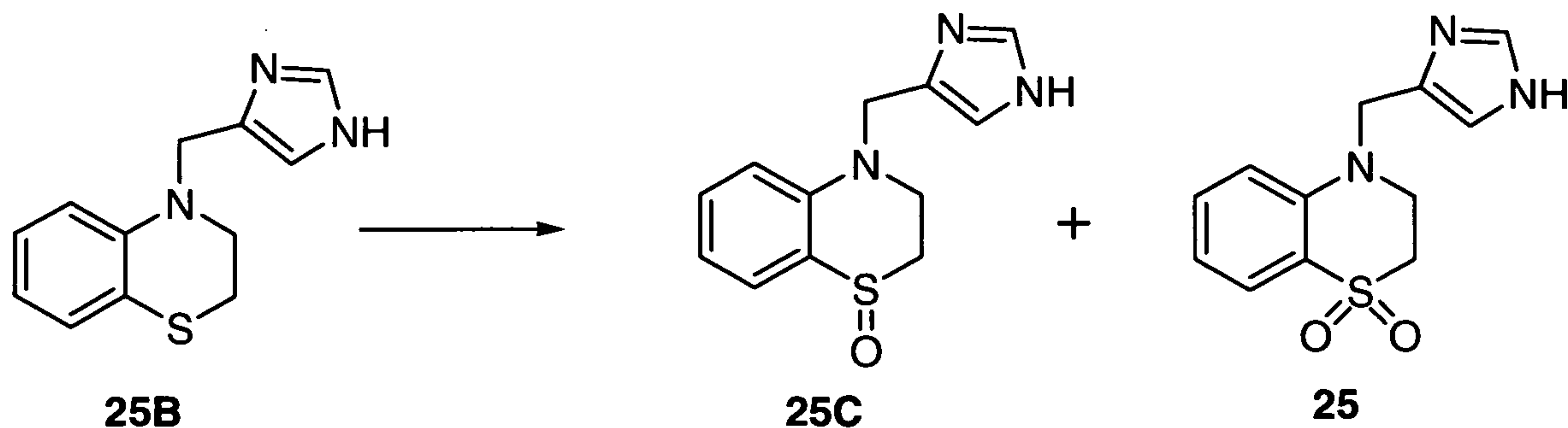
Steps 1-2



10

Following procedures described in Example 3 (Steps 2-3), compound **25A** was subjected to reduction with BH₃-SMe₂ and then reductive amination with imidazole-4-carboxaldehyde to provide compound **25B**. MS m/z 232 (MH⁺).

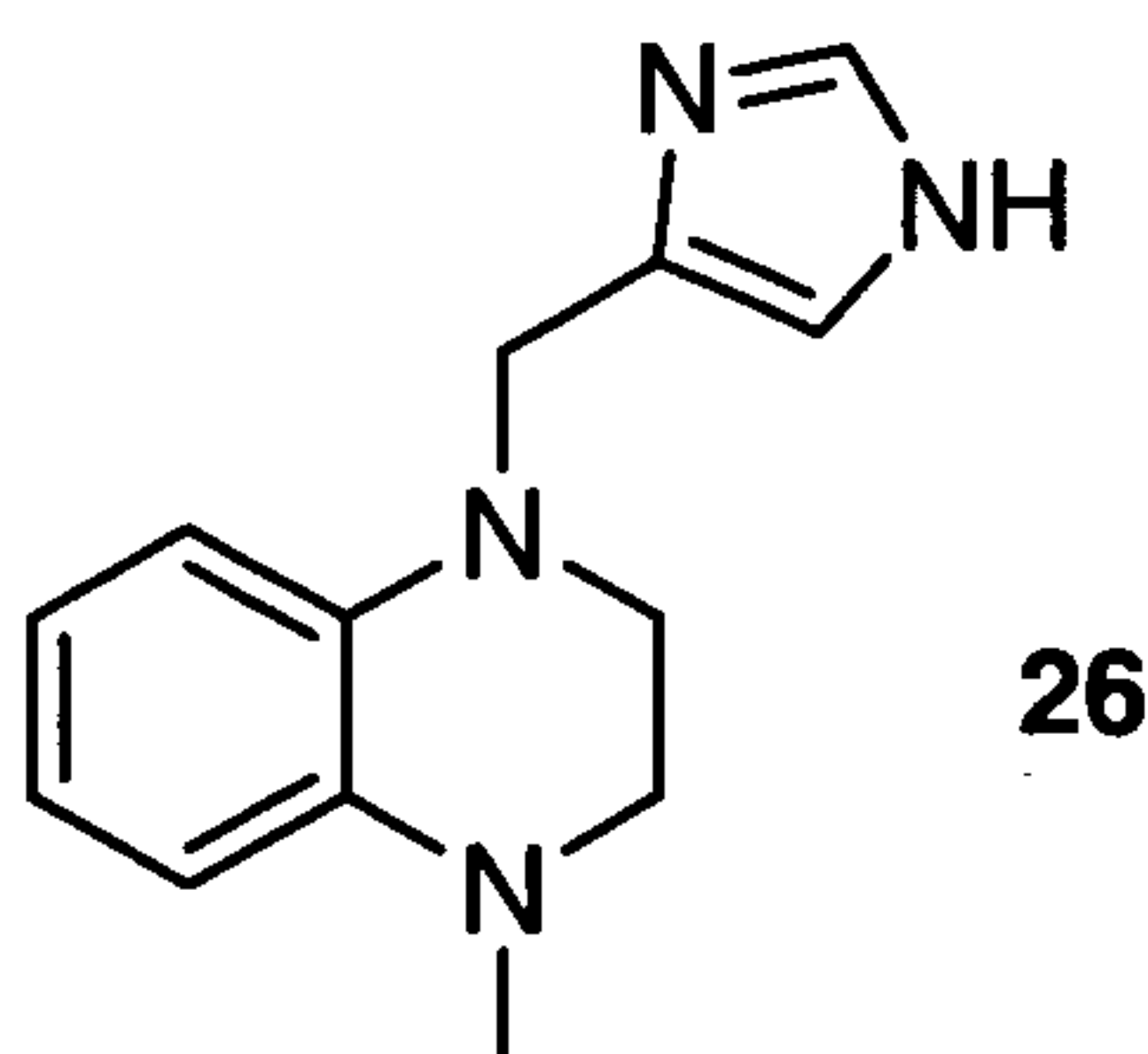
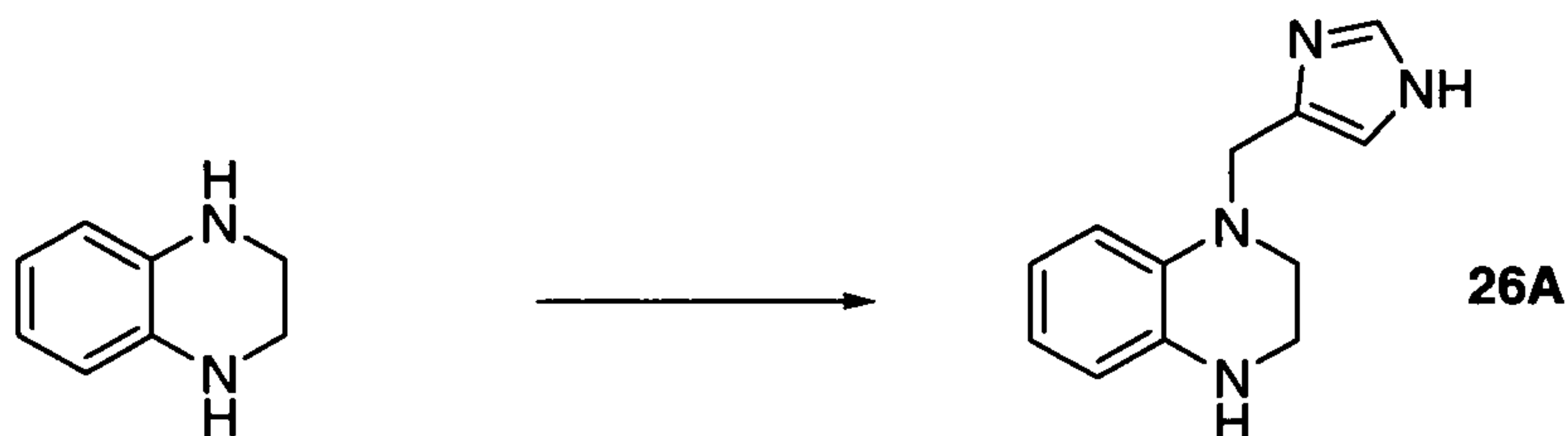
Step 3



15

In a manner similar to that found in Example 14, Step 4, **25B** was oxidized with MCPBA to afford compounds **25C** (MS m/z 248 MH⁺) and **25** (MS m/z 264 MH⁺).

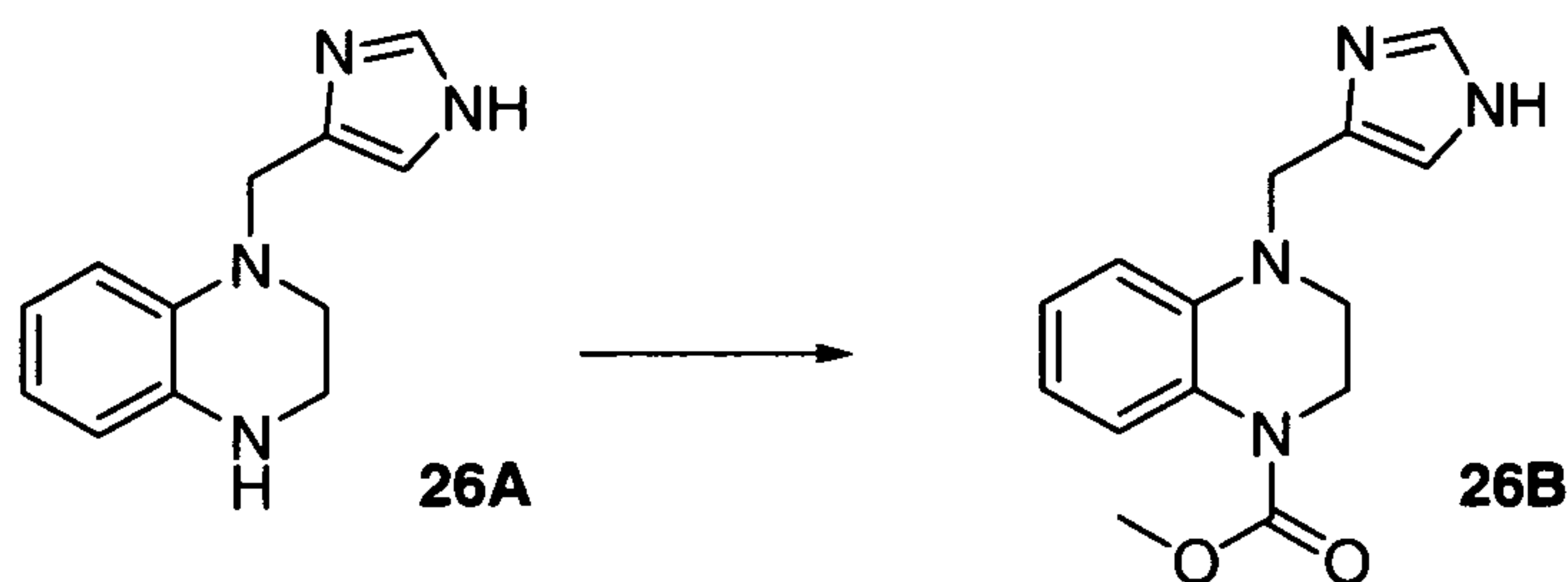
72

PREPARATIVE EXAMPLE 26**Step 1**

5 In a manner similar to that found in Example 1, 1,2,3,4-tetrahydro-quinoxaline and imidazole-4-carboxaldehyde **1B** underwent reductive amination to provide **26A**. LMCS m/z 215 (MH⁺).

Step 2

10



In a manner similar to that found in Example 3, Step 5, **26A** was converted to **26B**. LMCS m/z 273 (MH⁺).

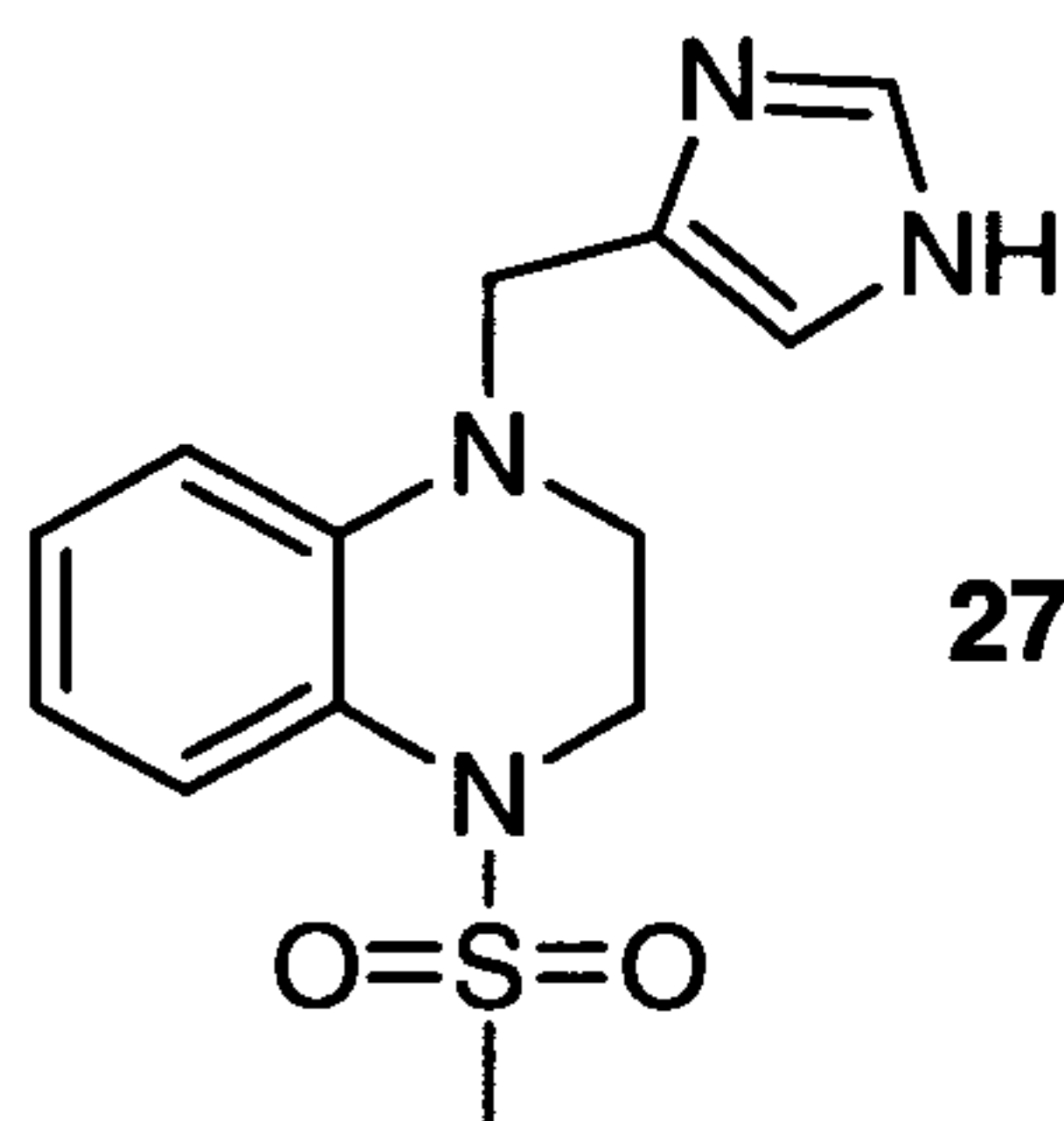
Step 3

15 Compound **26B** (120 mg) was added portionwise to a stirred slurry of LAH powder (500 mg) in Et₂O (15 mL) at 0 °C. The mixture was refluxed for 1 h and then cooled to 0 °C. The reaction was treated sequentially with H₂O (0.5 mL), 1 N NaOH (0.5 mL), and H₂O (1.5 mL). and then concentrated. Chromatography (DCM with 2 to
20 5% of 7N NH₃-MeOH) provided the title compound **26**. MS m/z 229(MH⁺).

73

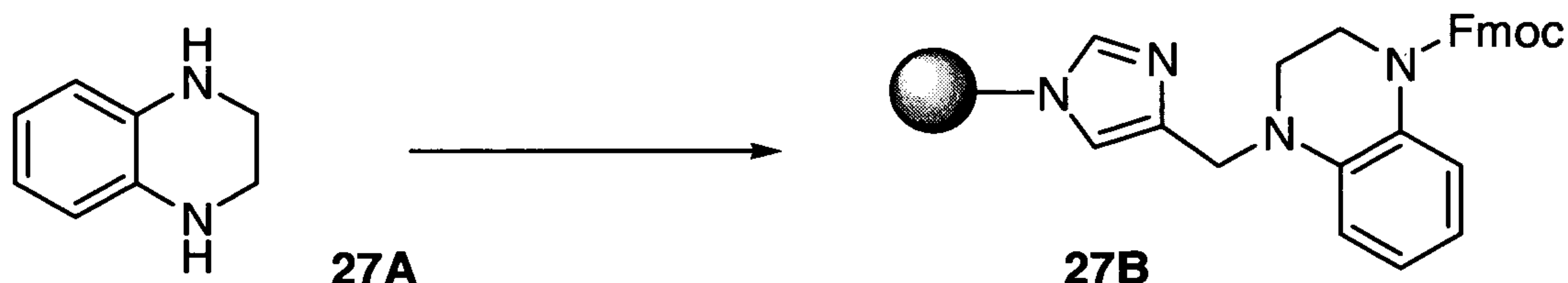
Alternatively, compounds in this class may be synthesized by a solid phase approach as described in the following Example 27.

PREPARATIVE EXAMPLE 27



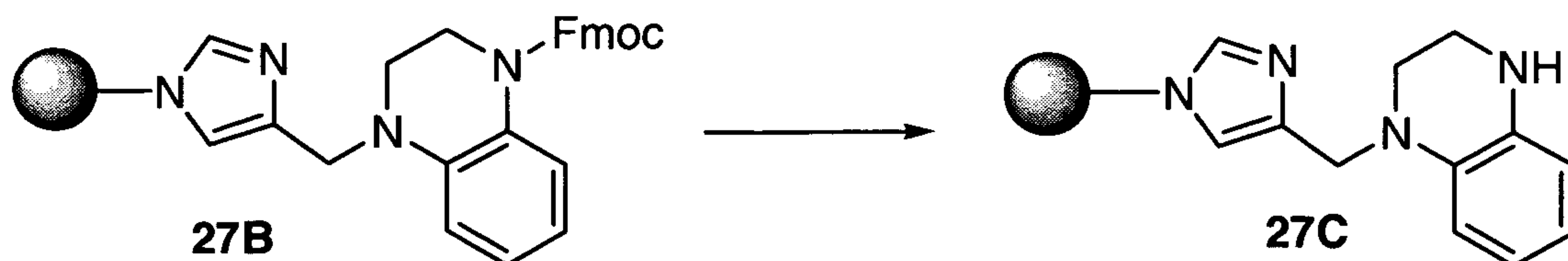
5

Steps 1-2



A mixture of 1,2,3,4-tetrahydroquinoline (**27A**, 2 g, 14.9 mmol) in dioxane (15 mL) and water (24 mL) at 0 °C was sequentially treated with Na₂CO₃ (1.58 g, 14.9 mmol) and FmocCl (3.84g, 14.9 mmol) in dioxane (20 mL, added dropwise). The mixture was warmed to RT gradually and stirred overnight. The reaction mixture was diluted with water (50 mL) and extracted with DCM (2 x 70 mL). The combined organic layers were dried (Na₂SO₄), concentrated, and subjected to chromatography (30-40% EtOAc/hexanes, yields 0.75g, 14%). Subsequent reaction with resin **1D** as described in Example 1 provided **27B**.

Steps 3-5



20

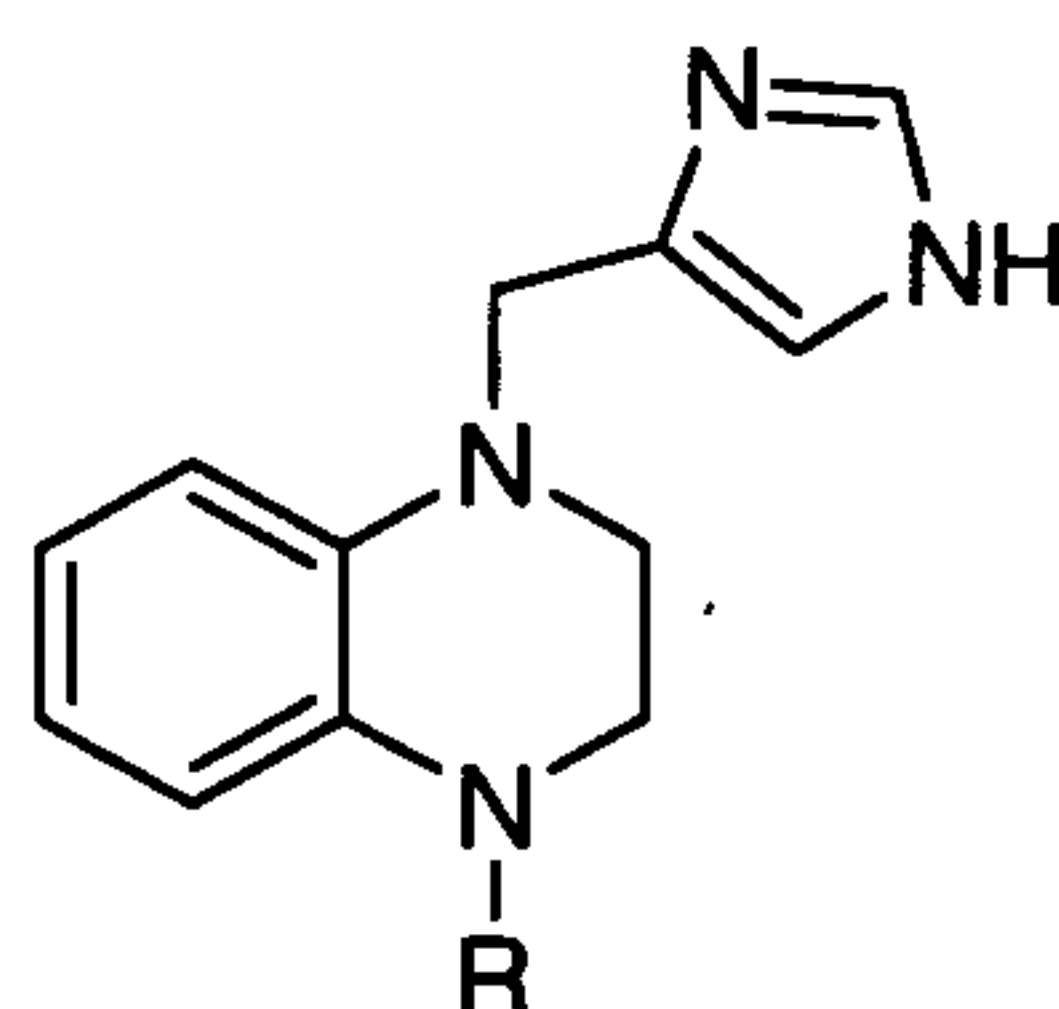
Compound **27B** (0.5 g, 1.4 mmol/g) was stirred in 30% piperidine/DMF overnight. The resin was washed with DMF (3x), MeOH (3x) and DCM and then dried in vacuo to provide **27C**. Resin **27C** (125mg, 1.4 mmol/g) was suspended in DCM (5

74

mL) and treated with pyridine (0.283 mL, 3.5 mmol) and MeSO₂Cl (0.135 mL, 1.75 mmol). The reaction was shaken overnight, then washed with MeOH (2x), DMF (2x), DCM (2x), MeOH (2x) and DCM (3x). Subsequent cleavage from the resin with TFA, as described in Example 1, provided the title compound **27**. MS m/z 293 (MH⁺).

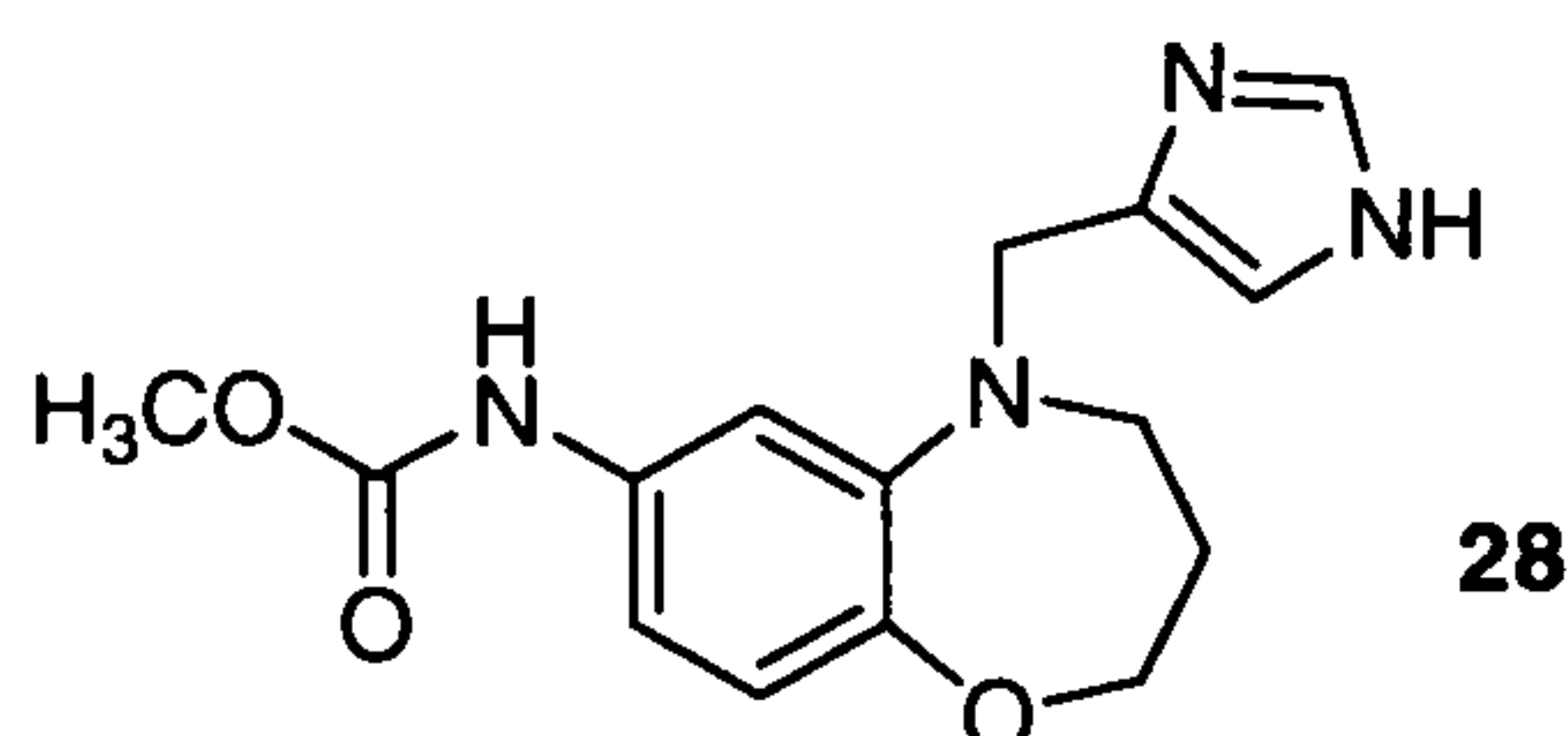
5

Compounds in **Table 4** can be prepared from Resin **27C** by reaction with the various reagents shown followed by TFA cleavage.

Table 4

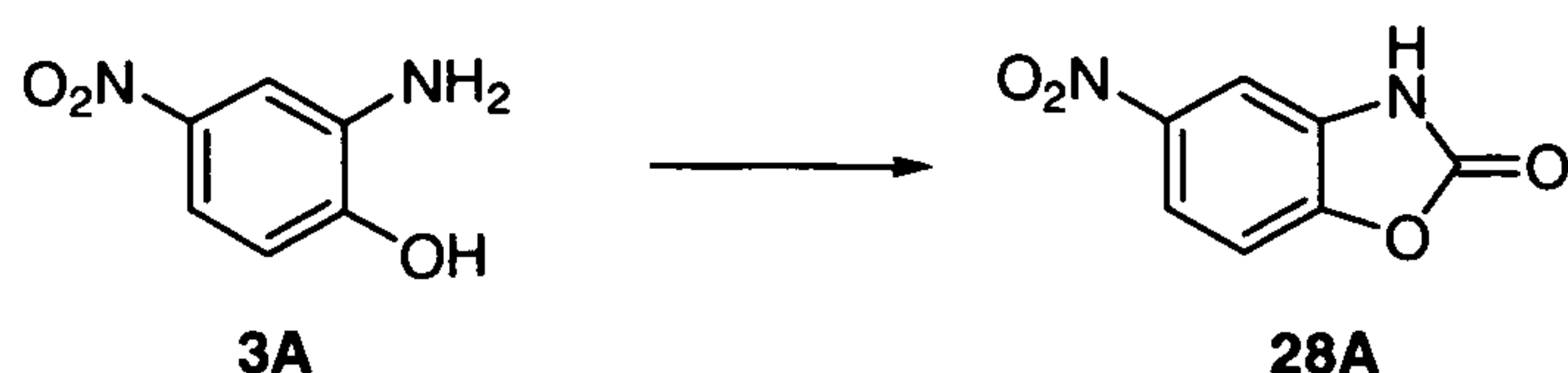
10

Cpd	Reagent	R	MS (MH ⁺)
27D	Me ₂ NSO ₂ Cl/ pyridine		322
27E	Ac ₂ O/ pyridine		257
27F	MeNCO		272

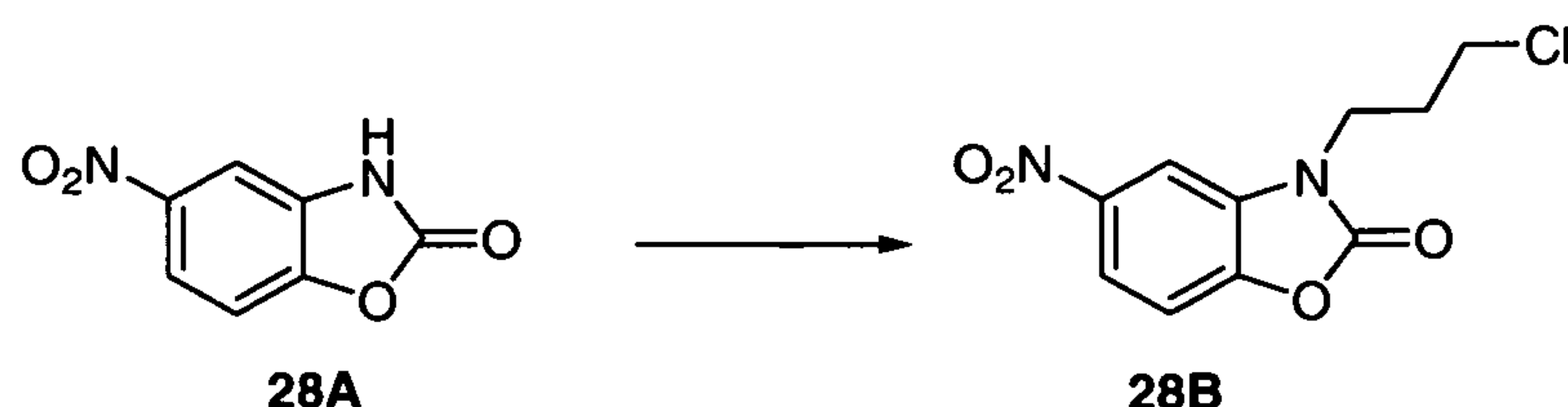
PREPARATIVE EXAMPLE 28**28**

15

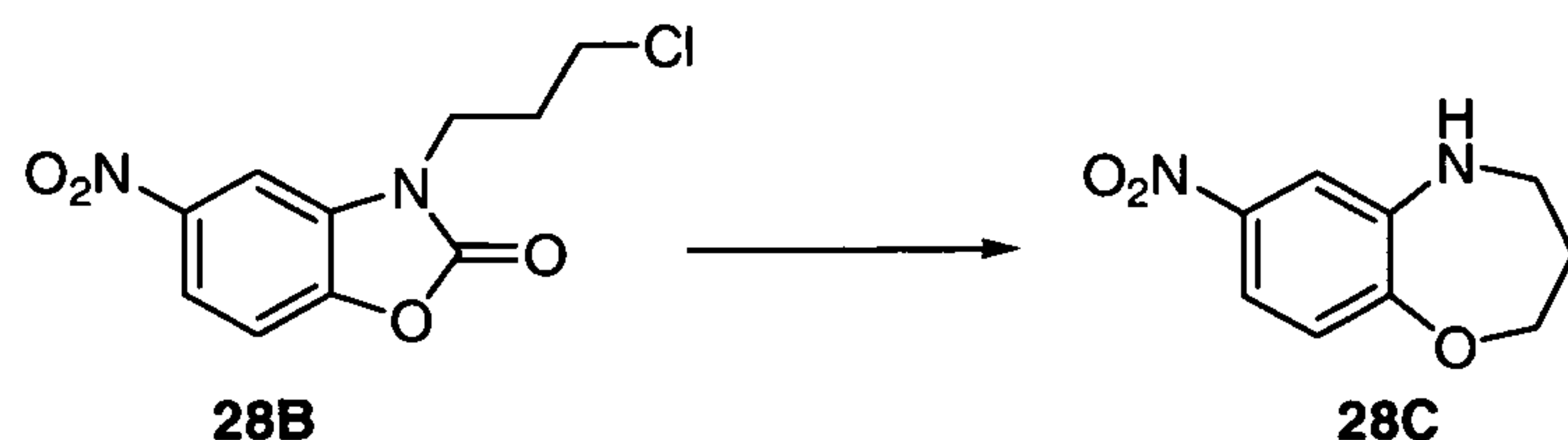
75

Step 1

To 6-nitro-2-aminophenol (**3A**, 3.03g, 19.7 mmol) in anhydrous DCM (50 mL) was added dipyrldylcarbonate (4.25 g, 19.7 mmol). The mixture was stirred at RT overnight, and then concentrated under vacuum. Chromatography (1-6% MeOH/DCM) afforded the solid **28A** (2.77 g, 78%).

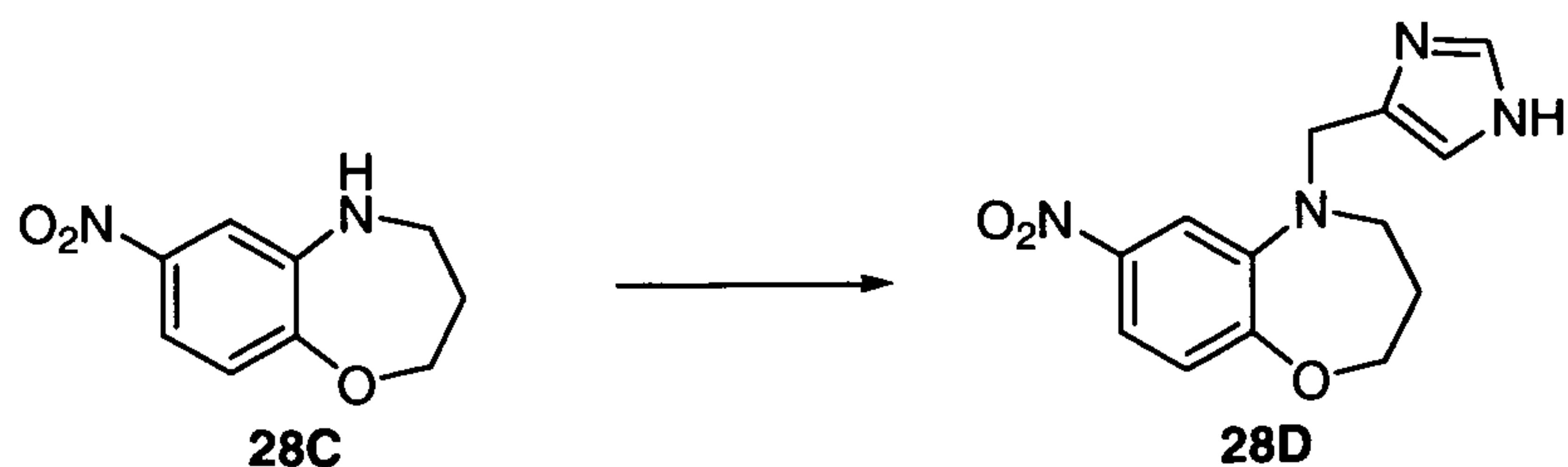
Step 2

A solution of **28A** (0.69 g, 3.83 mmol) in 2-ethoxyethanol (10 mL) was treated with KOH (0.22 g, 3.83 mmol) and stirred at RT for 1 h. The mixture was then heated to reflux and treated with 1-bromo-3-chloropropane (0.75 mL, 7.67 mmol). After refluxing for 4 h, the solution was filtered and concentrated to provide **28B**, which was taken on to Step 3 without further purification.

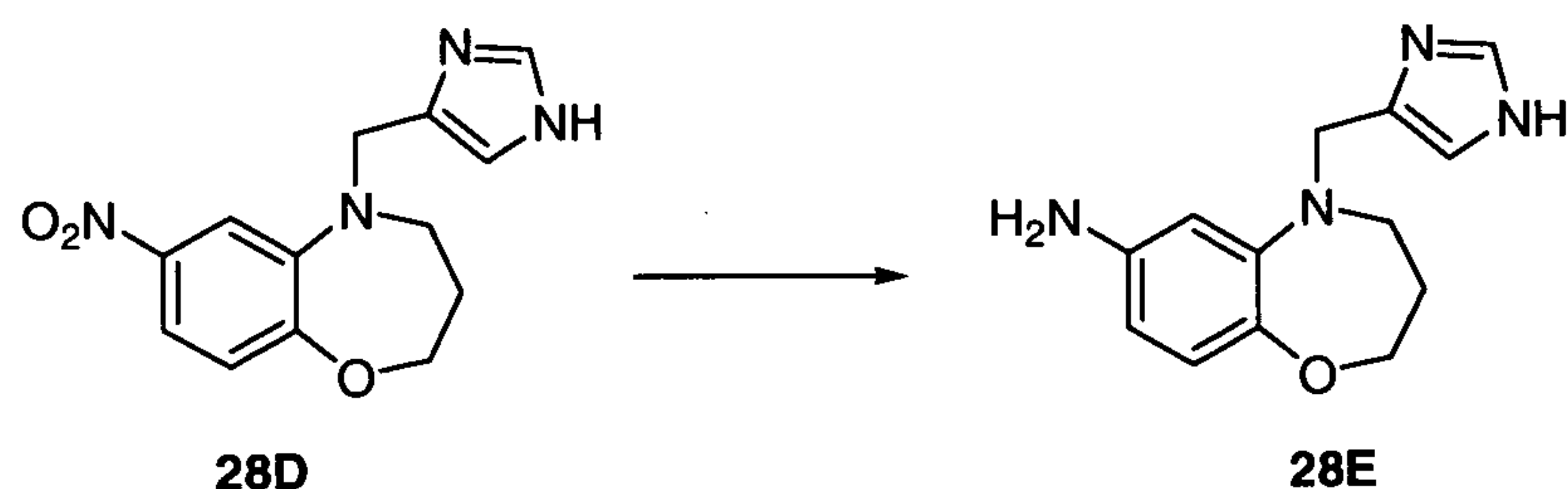
Step 3

A solution of **28B** in 2-ethoxyethanol and DMF (10 mL, 1:1) was transferred into a Smith process vial (20 mL) with a stir bar, and treated with KOH (0.86g, 15.32 mmol). The reaction vessel was sealed and heated to 220 °C for 1 h under microwave irradiation. After cooling, the reaction mixture was filtered and concentrated. The residue was diluted with water and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated under vacuum. Chromatography (DCM containing 1-5% 7N NH₃-MeOH) provided **28C** (124 mg, 17% for 2 steps).

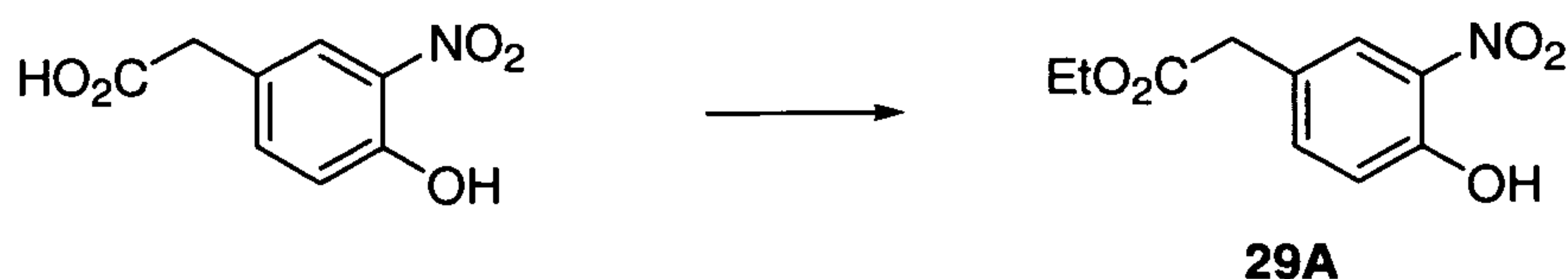
76

Step 4

In a manner similar to that found in Example 3 (Step 3), **28C** was reacted with
 5 imidazole-4-carboxaldehyde to provide compound **28D**. MS m/z 275 (MH⁺).

Steps 5-6

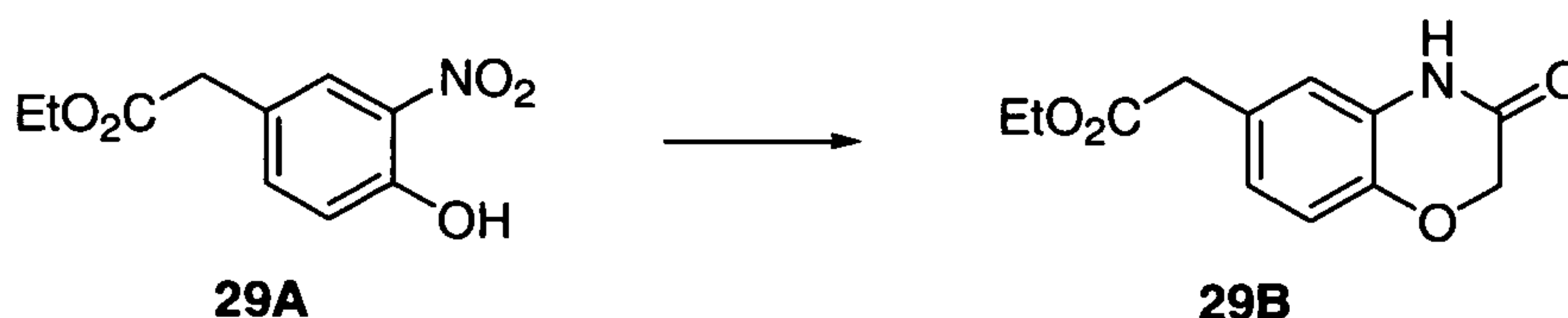
In a manner similar to that found in Example 3 (Step 4), **28D** was hydrogenated
 10 to afford compound **28E**. MS m/z 245 (MH⁺). Following the procedure found in
 Example 3 (Step 5), **28E** was further reacted with ClCO₂Me to provide the title
 compound **28**. MS m/z 303 (MH⁺).

PREPARATIVE EXAMPLE 29**Step 1**

A mixture of 4-hydroxy-3-nitrophenylacetic acid (10 g, 51 mmol) and 4M HCl-
 dioxane (40 mL) in EtOH (150 mL) was refluxed for 2 h and concentrated. The
 20 residue was then taken up in 1 N NaOH (50 mL) and extracted with CH₂Cl₂ (8x). The

combined organic layers were dried over Na_2SO_4 , and concentrated to provide **29A** (8.39 g, 73%) as a yellow oil.

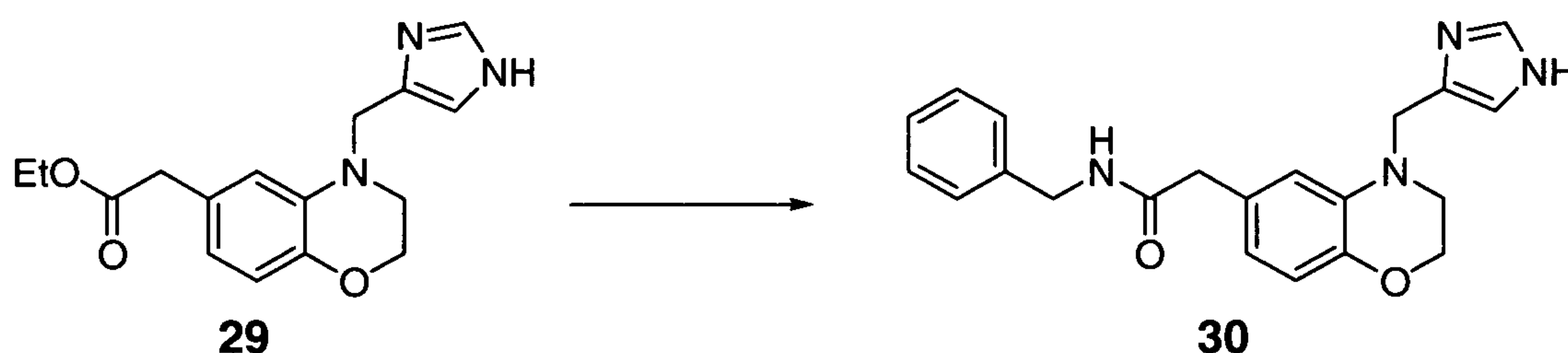
Steps 2-5



In a manner similar to that described in Example 20 (Step 1) and Example 3 (Step 1), **29A** was hydrogenated with Raney Ni (50 psi H_2) and then cyclized with chloroacetyl chloride to provide **29B**. Compound **29B** could be further elaborated to the title compound **29** following the procedure detailed in Example 3 (Steps 2-3).

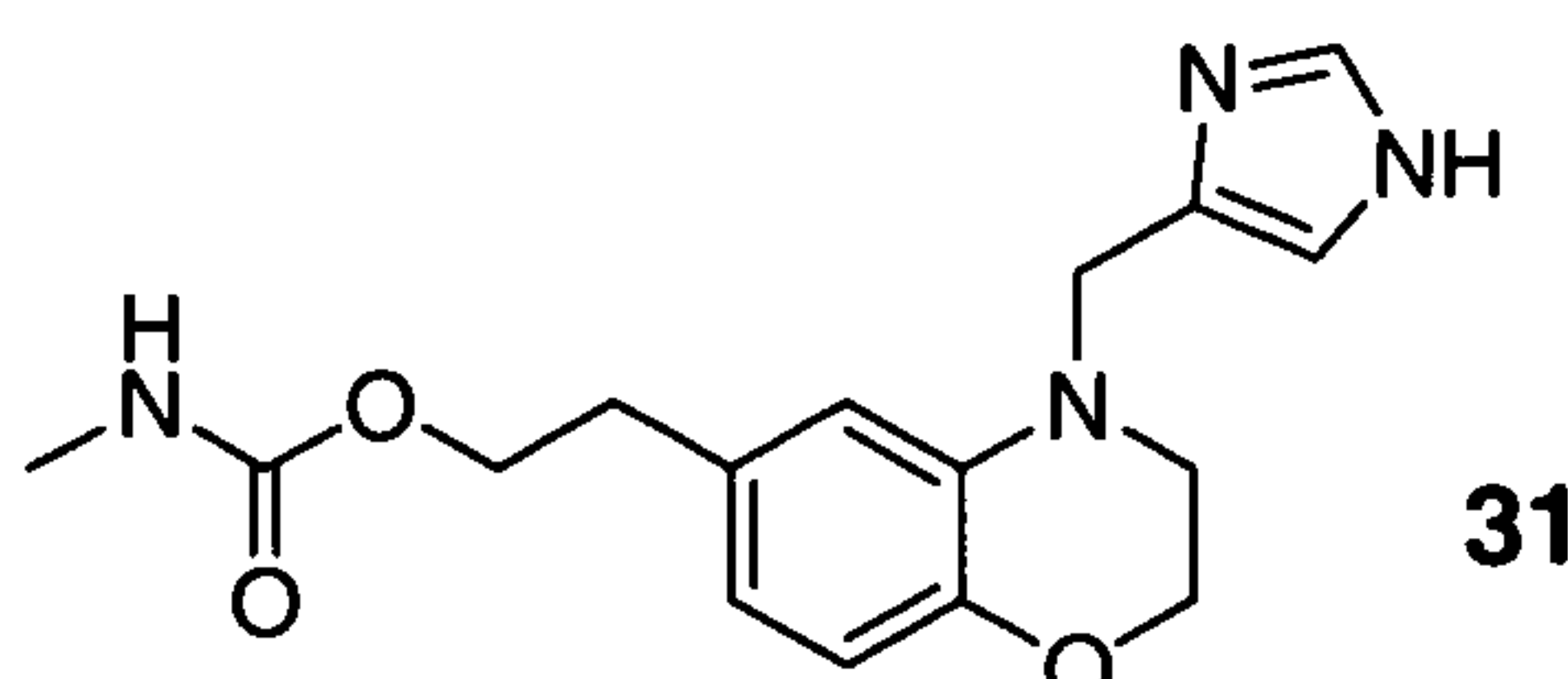
LMCS m/z 302 (MH^+).

PREPARATIVE EXAMPLE 30

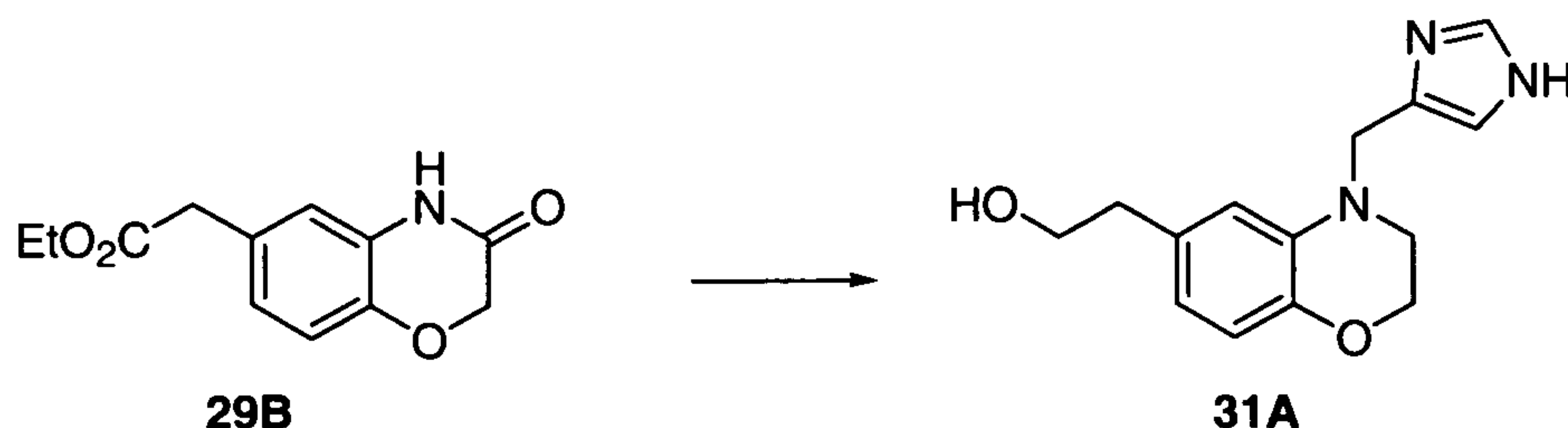


A stirred solution of benzylamine (0.070 mL, 0.66 mmol) in CH_2Cl_2 (10 mL) was treated dropwise with AlMe_3 (2M/toluene, 0.33 mL, 0.66 mmol) at 20 °C. After 20 min, a solution of **29** (0.10 g, 0.33 mmol) in CH_2Cl_2 (3 mL) was added slowly. The mixture was then heated at reflux overnight and cooled to 20 °C. The reaction was quenched with H_2O (0.5 mL), and stirred 1h. The mixture was then dried with Na_2SO_4 , filtered, and concentrated. Chromatography (2-5% 1 N NH_3 -MeOH/ CH_2Cl_2) provided **30** as a white film (0.115 g, 96%). LMCS m/z 363 (MH^+).

PREPARATIVE EXAMPLE 31



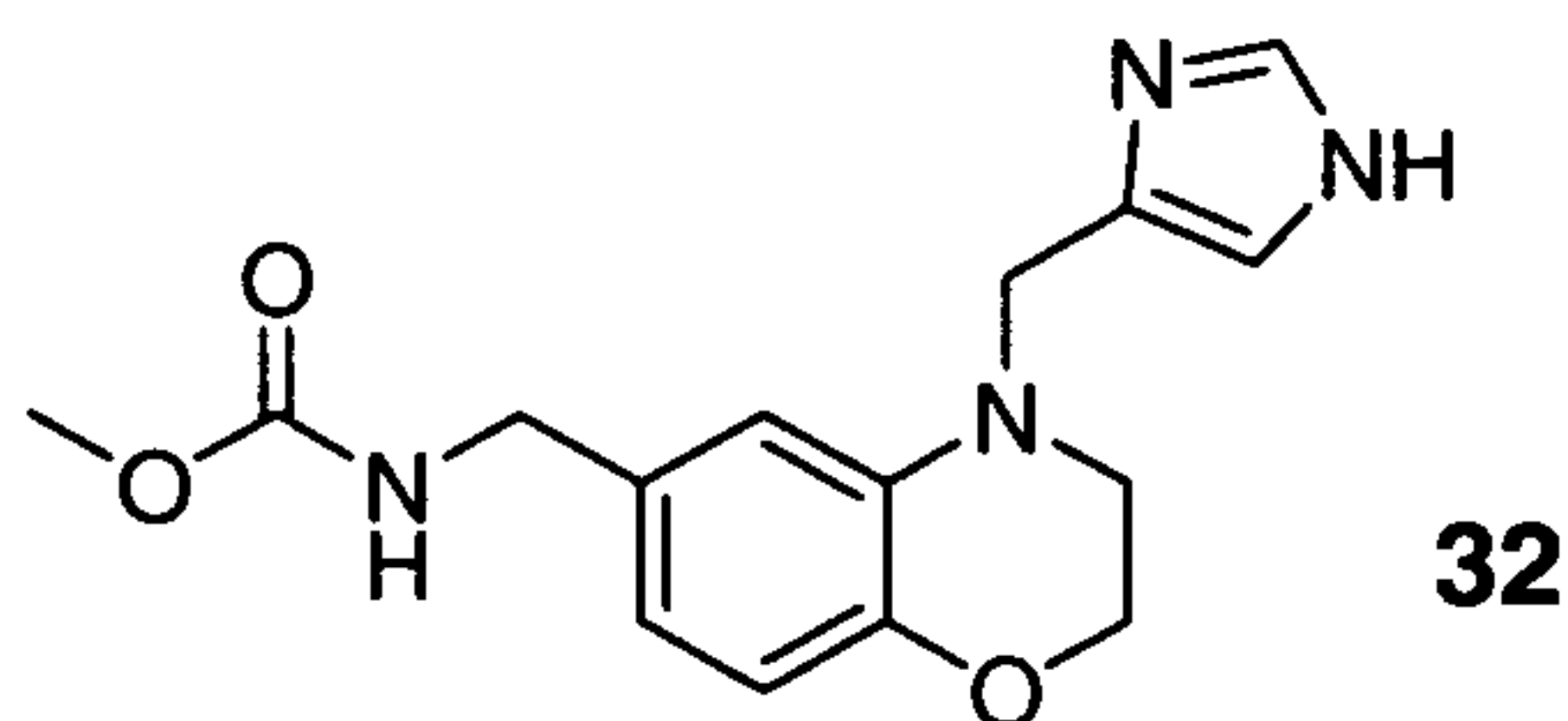
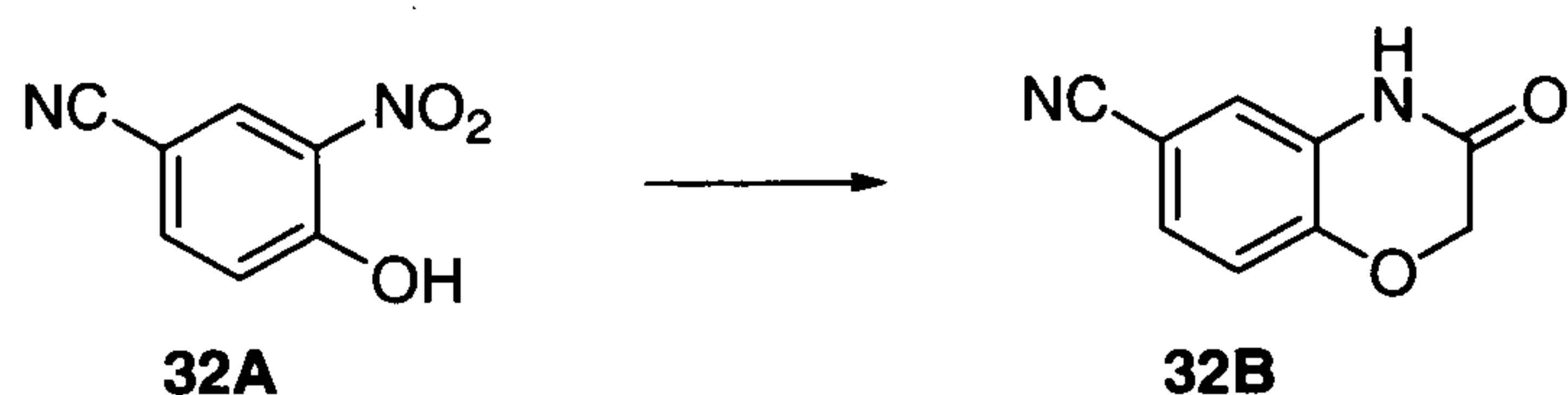
78

Steps 1-2

In a manner similar to that found in Example 26 (Step 3) and Example 1, **29B** was reduced with LAH and then treated with imidazole-4-carboxaldehyde to provide
 5 **31A**. LMCS m/z 260 (MH⁺).

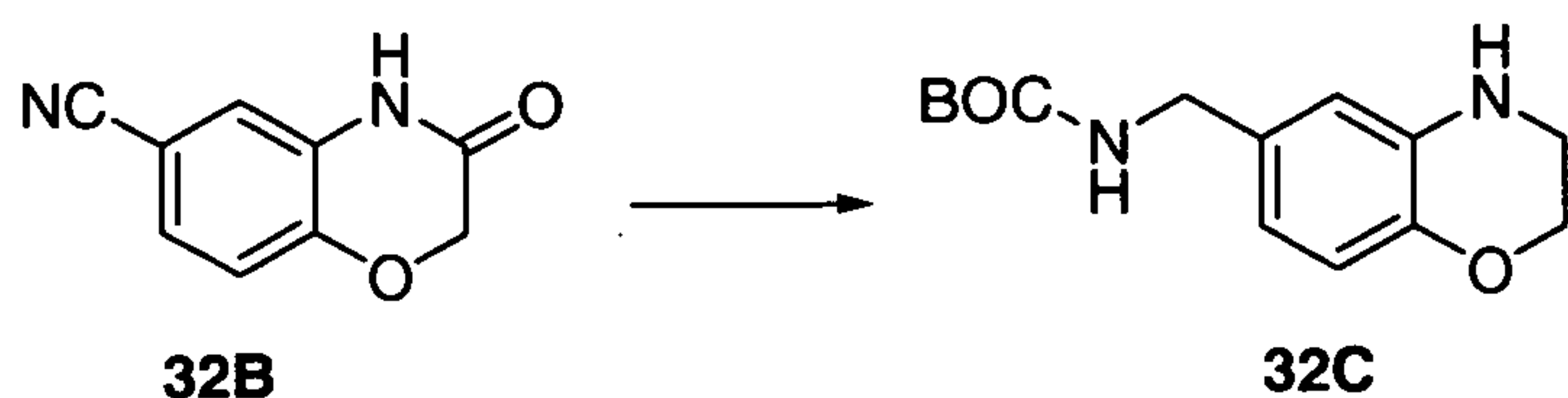
Step 3

A solution of **31A** (0.20 g, 77 mmol) in 1,2-dichloroethane (10 mL) was treated with Et₃N (0.20 mL, 1.5 mmol) and MeNCO (0.050 mL, 0.85 mmol) and stirred for 3h at 20 °C. The mixture was treated with H₂O (10 mL), extracted with CH₂Cl₂ (2x), and
 10 concentrated. The residue was subjected to chromatography (2-5% MeOH/ CH₂Cl₂) and then stirred in Et₂NH (5 mL) at 20 °C overnight. The mixture was concentrated, treated with 1 N NaOH, and extracted with CH₂Cl₂ (3x). The combined organic extracts were dried with Na₂SO₄, and concentrated. Chromatography (5% MeOH/CH₂Cl₂) provided **31** as a white film (0.080 g, 33%). LMCS m/z 317 (MH⁺).

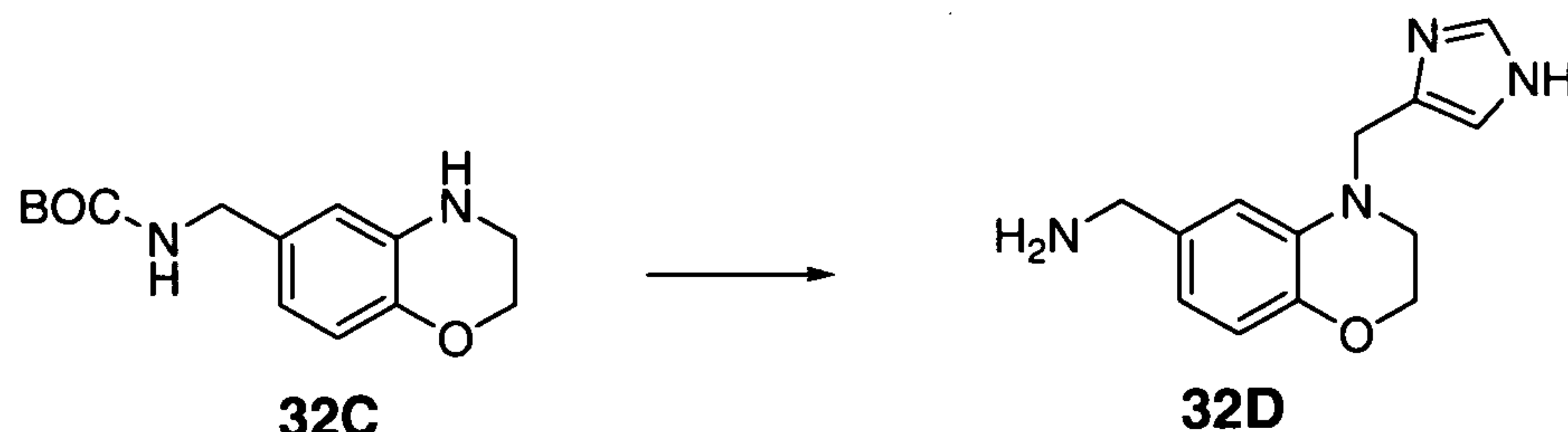
PREPARATIVE EXAMPLE 32**Step 1-2**

Following the procedures found in Example 20 (Step 1) and Example 3 (Step 1), **32A** was hydrogenated with Raney Ni (50 psi H₂) and then cyclized with chloroacetyl chloride to provide **32B**.

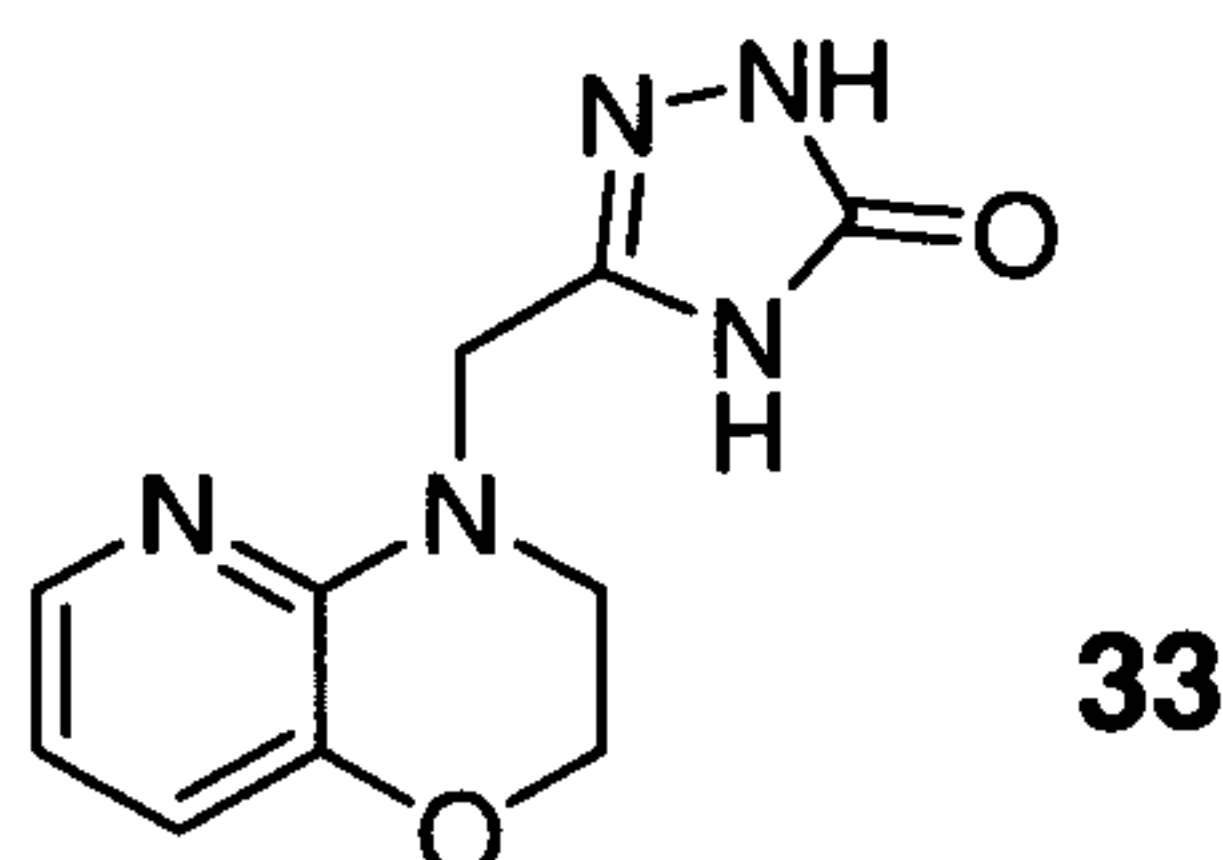
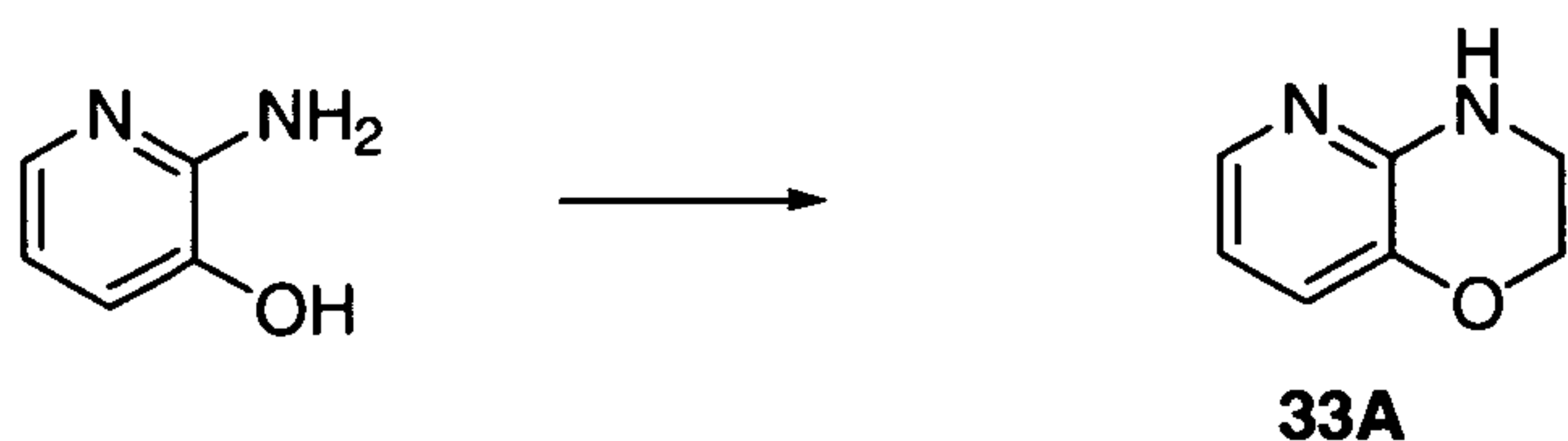
79

Steps 3-4

Following the procedure found in Example 26 (Step 3), the nitrile and amide found in compound **32B** were concomitantly reduced with LAH. The resultant product (0.83 g, 5.1 mmol) in CH₂Cl₂ (50 mL) was treated with BOC₂O (1.07 g, 5.1 mmol), stirred at 20 °C for 0.5 h and then concentrated. Chromatography (20-50% EtOAc/hexanes) provided **32C** as a white sticky foam (1.19 g, 89%)

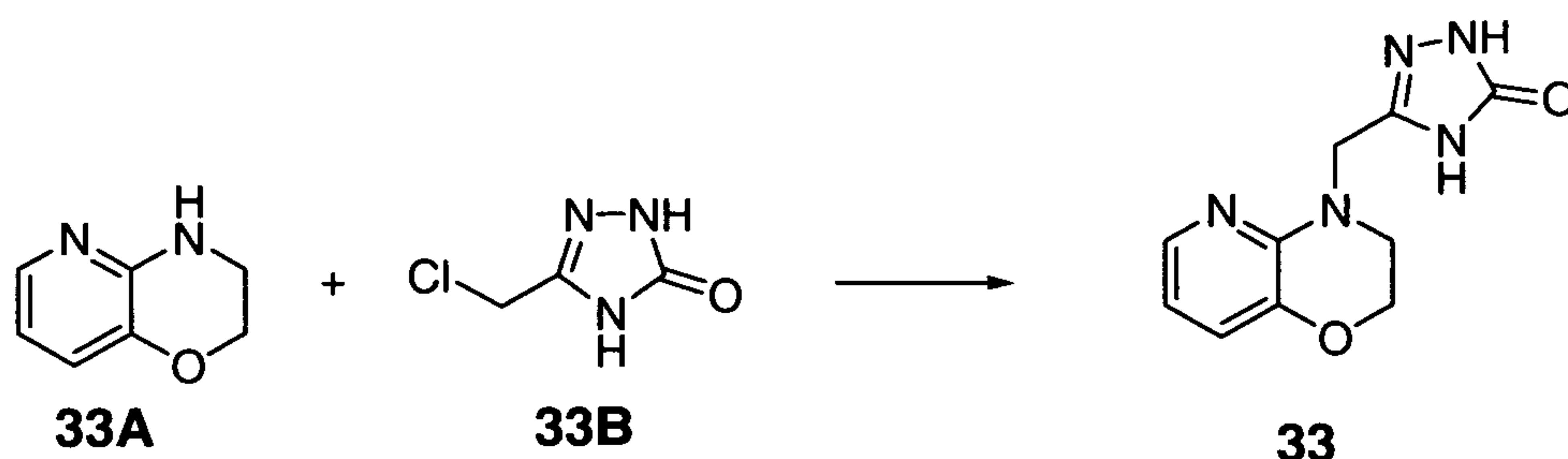
Steps 5-6

In a manner similar to that found in Example 1 and Example 15 (Step 4), **32C** was treated with imidazole-4-carboxaldehyde and then deprotected to afford **32D**. LMCS m/z 245 (MH⁺). Following the procedure described Example 3, Step 5, **32D** was treated with ClCO₂Me and converted to the title compound **32**. LMCS m/z 303 (MH⁺).

PREPARATIVE EXAMPLE 33**Step 1-2**

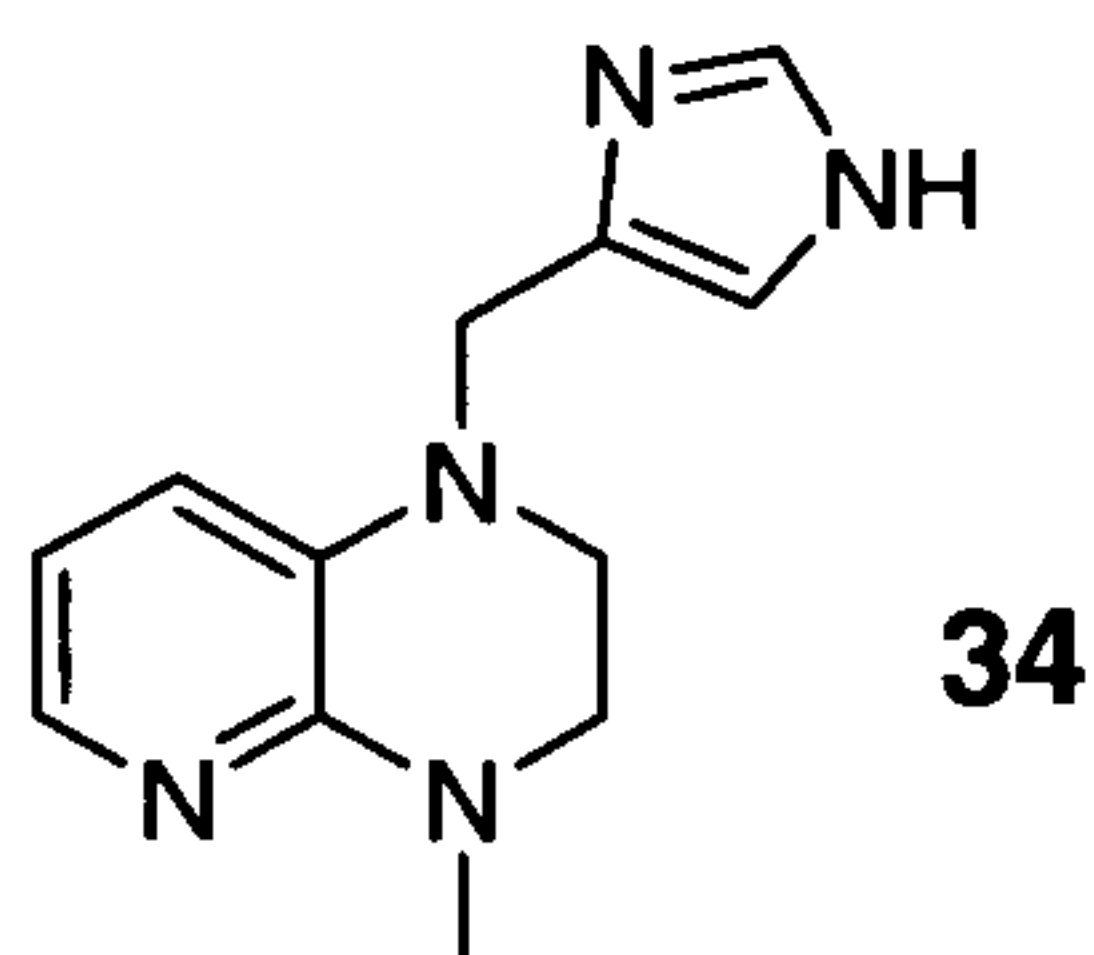
In a manner similar to that found in Example 3 (Step 1) and Example 26 (Step 3), 2-amino-3-hydroxypyridine was cyclized with chloroacetyl chloride and then reduced with LAH to afford **33A**.

5 Step 3

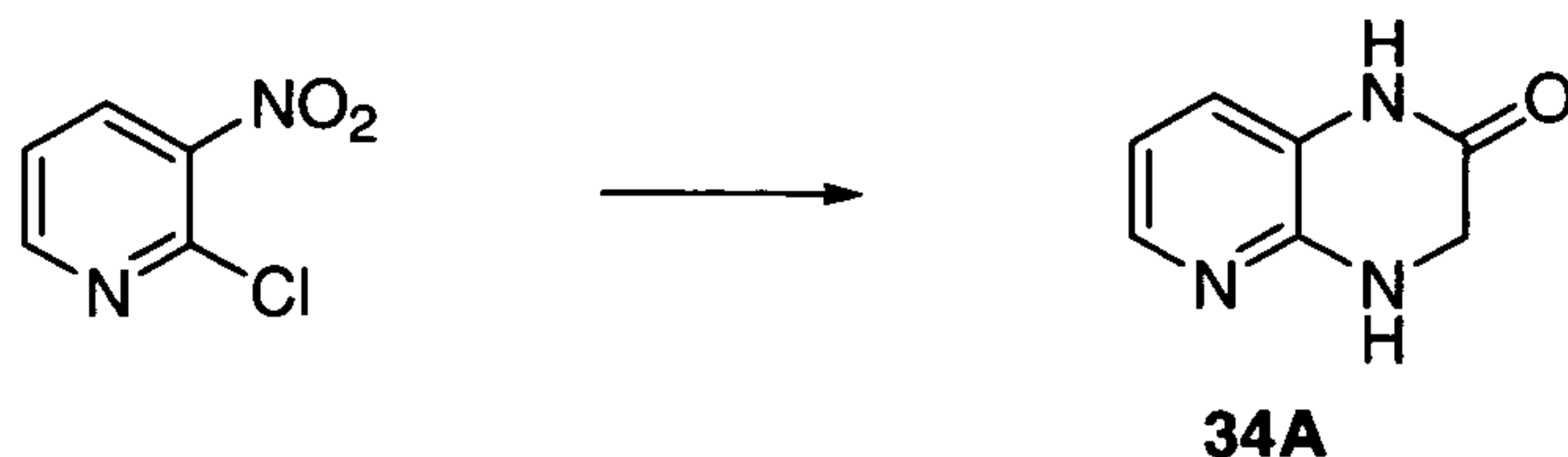


A solution of **33A** (0.105 g 0.77 mmol) in DMF (5 mL) was treated with $\text{KN}(\text{SiMe}_3)_2$ (0.5 M/toluene, 1.8 mL, 0.93 mmol), stirred at 0 °C for 20 min, and then treated with **33B** (0.155 g 1.16 mmol, Tetrahedron Letters **2000**, 41, 8661). The reaction was warmed to 20 °C, stirred 2h, and concentrated. The residue was then treated with 0.5 N NaOH (10 mL) and washed with CH_2Cl_2 (3x). The aqueous layer was concentrated and subjected to chromatography (20-80% EtOAc/hexanes) to provide **33** as a white solid (0.065 g, 36%). LMCS m/z 234 (MH^+).

15 PREPARATIVE EXAMPLE 34



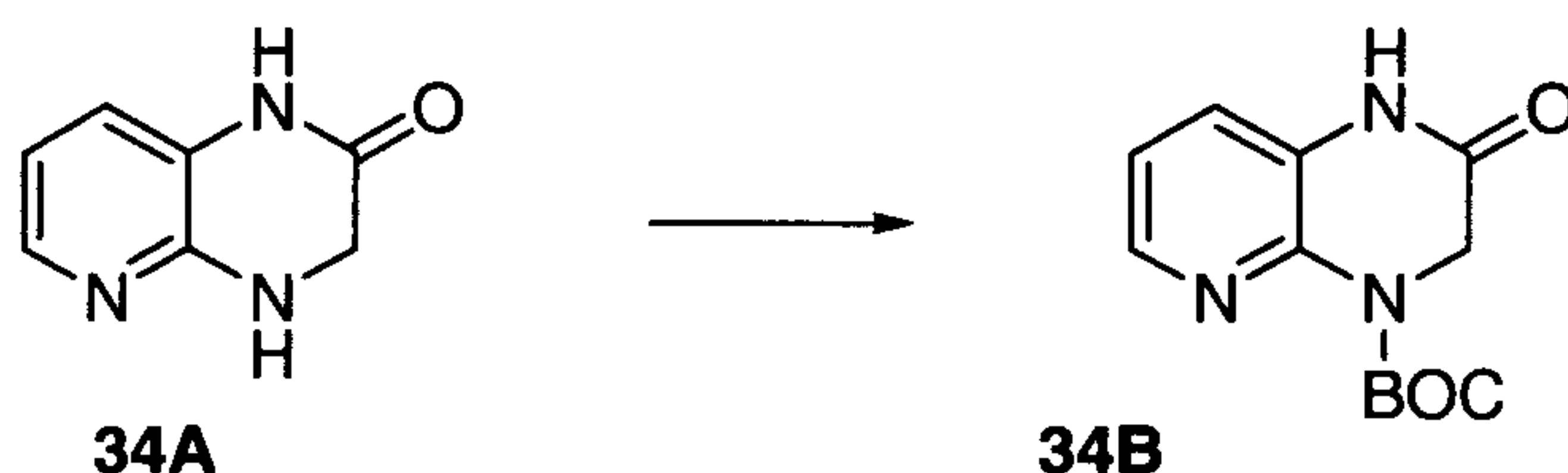
Step 1



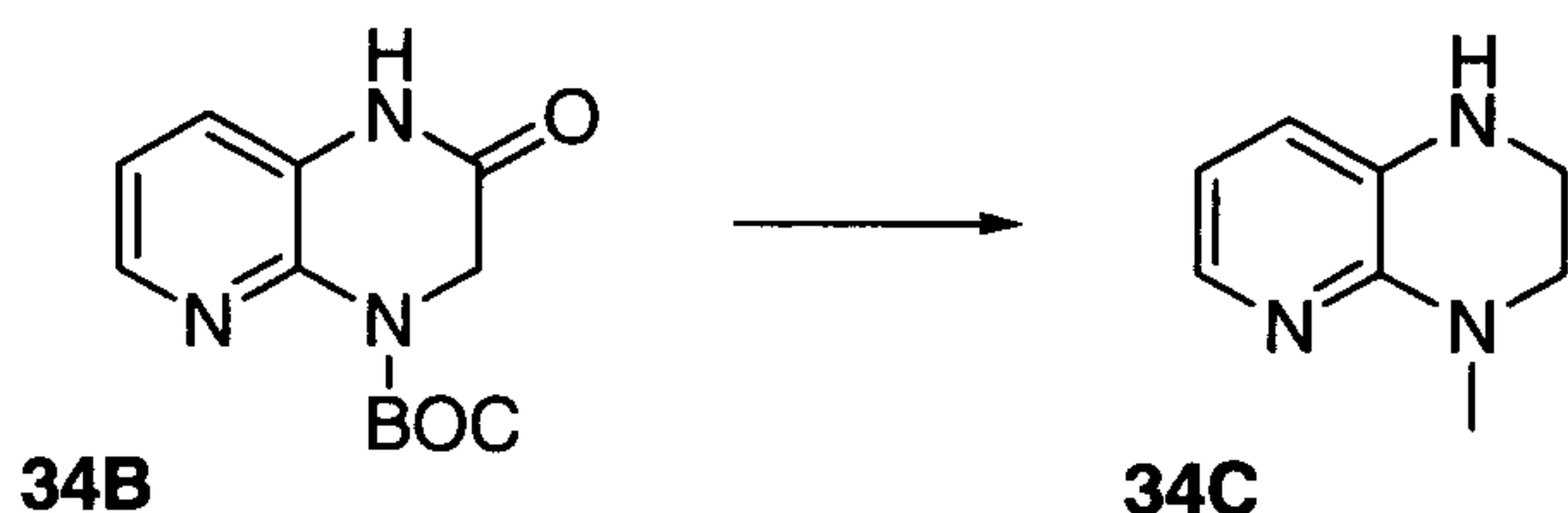
A mixture of 2-chloro-3-nitropyridine (9.4 g, 59 mmol), glycine ethyl ester hydrochloride (10.8 g, 77 mmol), and K_2CO_3 (21.3 g, 154 mmol) in toluene (100mL) was refluxed overnight. The mixture was then filtered, concentrated, and subjected to chromatography (20% EtOAc/hexanes). The resulting yellow solid was dissolved in

81

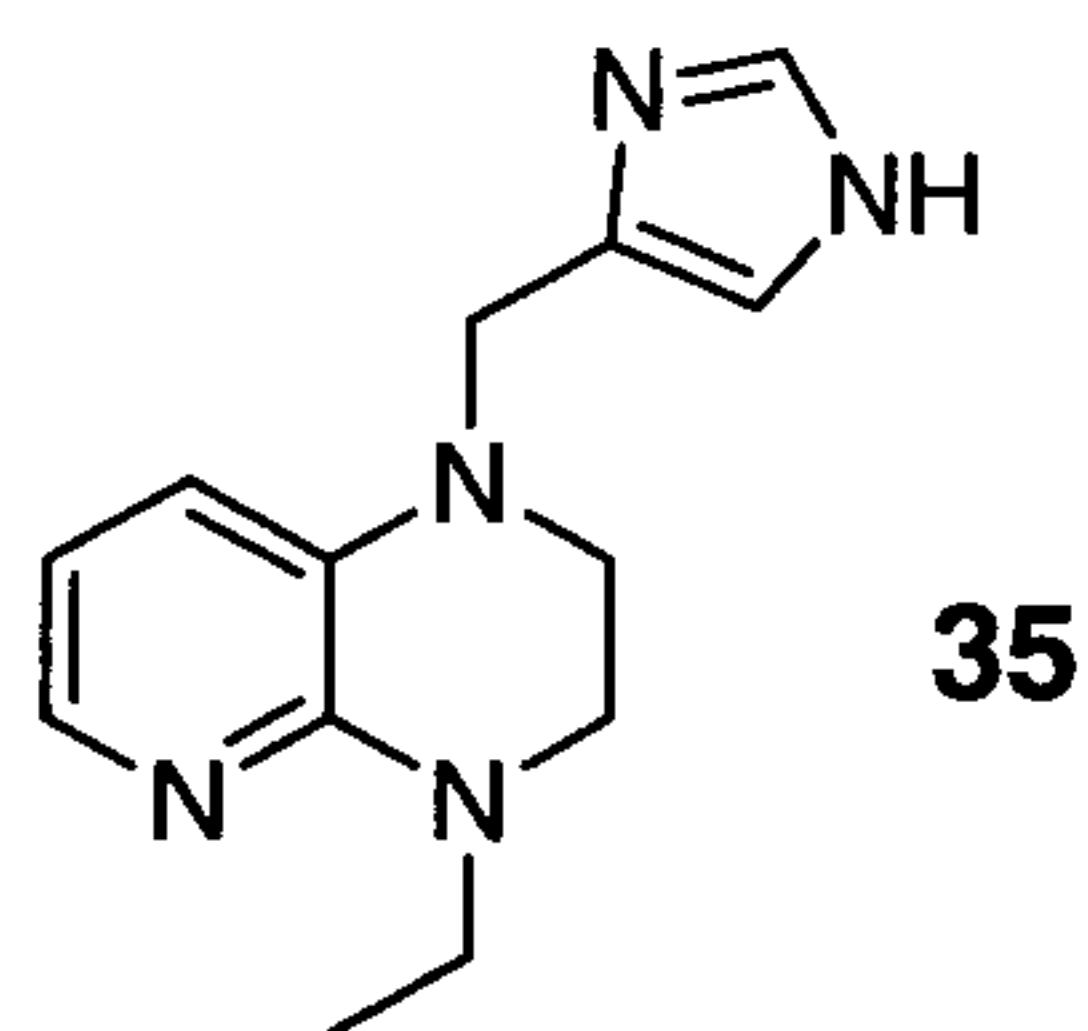
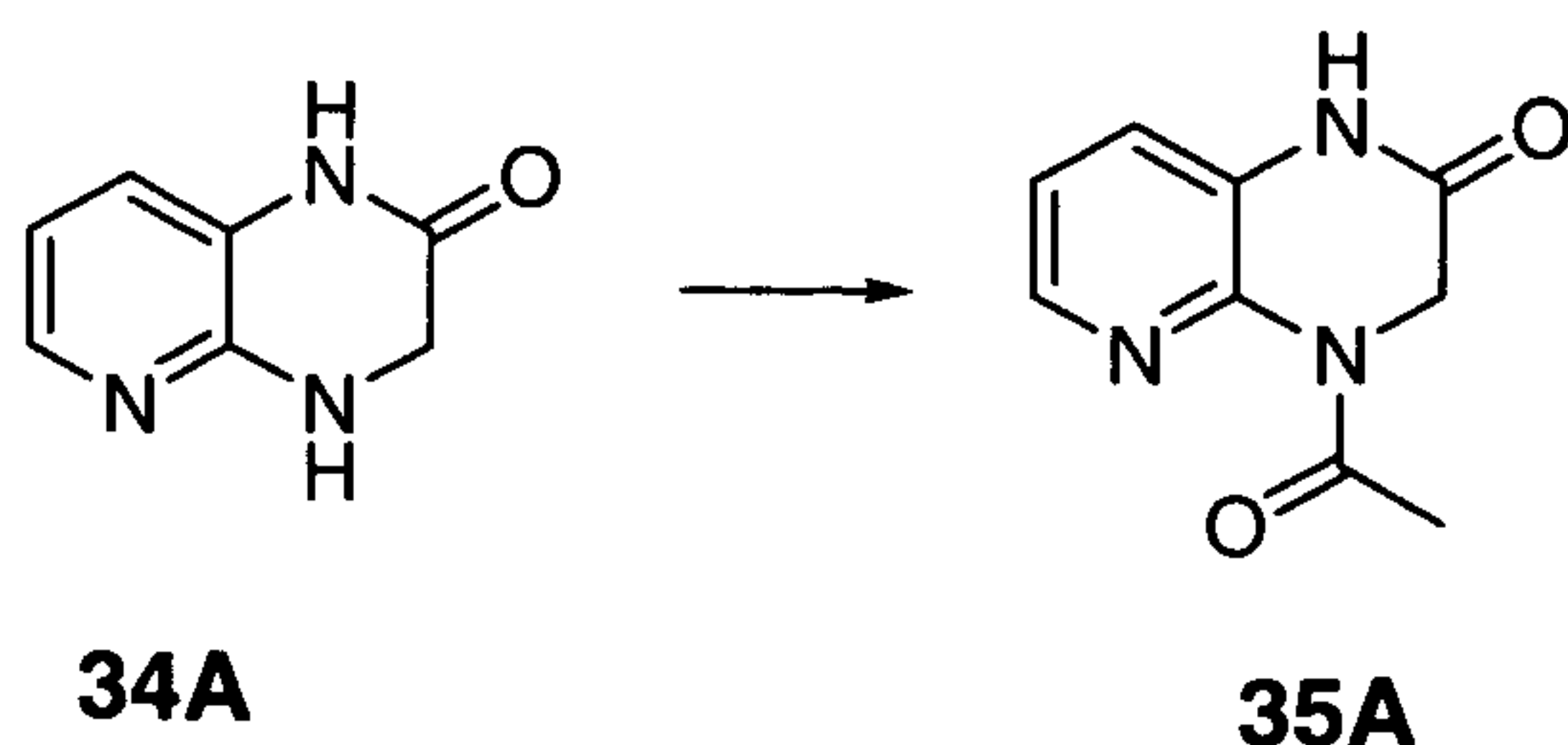
EtOH (300 mL), treated with Raney Ni (2 g) and hydrogenated at 40 psi H₂ overnight. The mixture was filtered, concentrated and chromatographed (2-5% MeOH/CH₂Cl₂) to provide **34A** (1.25 g, 14%) and N-(3-amino-2-pyridinyl)glycine ethyl ester (8.2 g, 71%).

5 **Step 2**

In a manner similar to that found in Example 5 (Step 1), **34A** was converted to **34B** (BOC₂O, DMAP and Et₃N in refluxing DCM).

10 **Step 3-4**

In a manner similar to that found in Example 26 (Step 3), **34B** was treated with LAH to provide **34C** as a white solid (0.040 g, 48%). Following the procedure found in Example 1, **34C** was then treated with imidazole-4-carboxaldehyde to provide the title compound **34**. LMCS m/z 230 (MH⁺).

PREPARATIVE EXAMPLE 35**Steps 1-3**

20

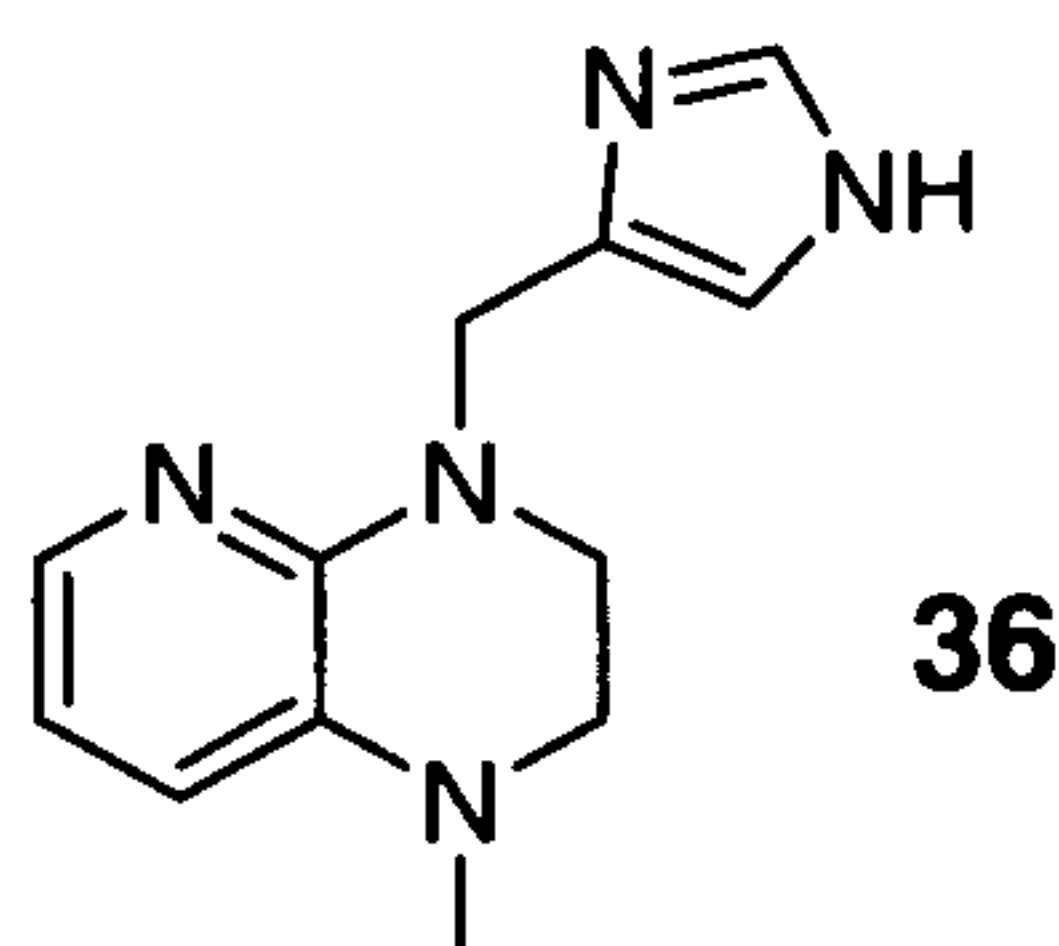
A solution of **34A** (0.260 g, 1.74 mmol) in THF (15 mL) was treated with Et₃N (1.2 mL, 8.7 mmol) and Ac₂O (0.33 mL, 3.5 mmol) and stirred overnight at 20 °C. The reaction was treated diluted with H₂O (10 mL) and extracted with 10% MeOH/CH₂Cl₂ (3x). The combined organic extracts were dried with Na₂SO₄ and concentrated.

5 Chromatography (20-50% EtOAc/hexanes) provided **35A** as a white solid (0.140 g, 42%).

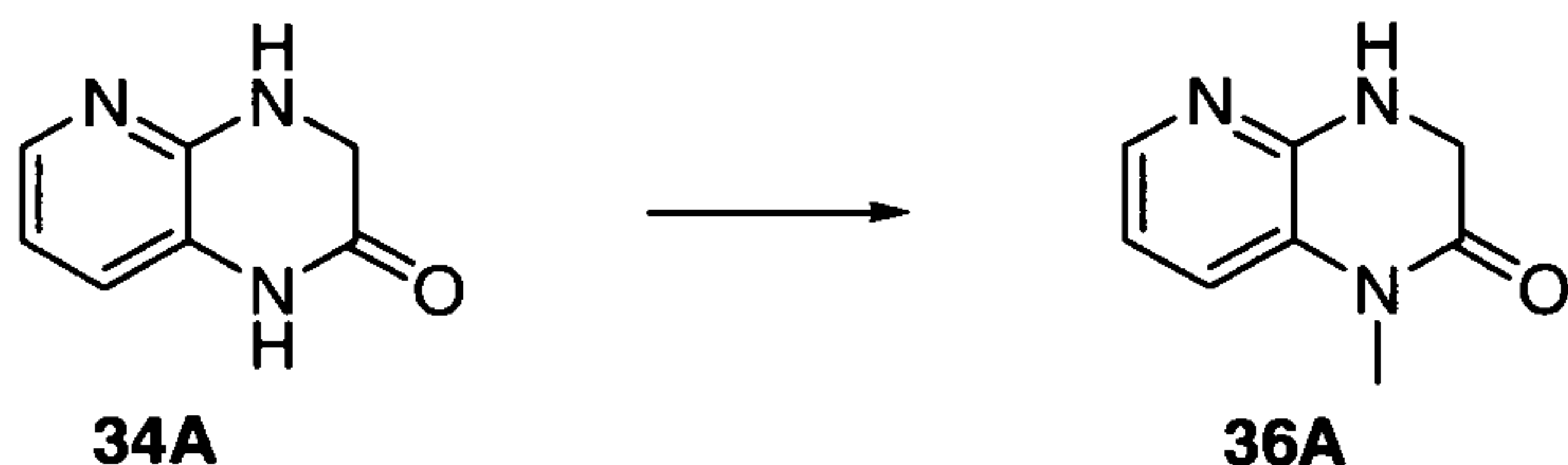
In a manner similar to that found in Example 26 (Step 3) and Example 1, **35A** was reduced with LAH and then treated with imidazole-4-carboxaldehyde to provide the title compound **35**. LMCS m/z 244 (MH⁺).

10

PREPARATIVE EXAMPLE 36



Steps 1-3



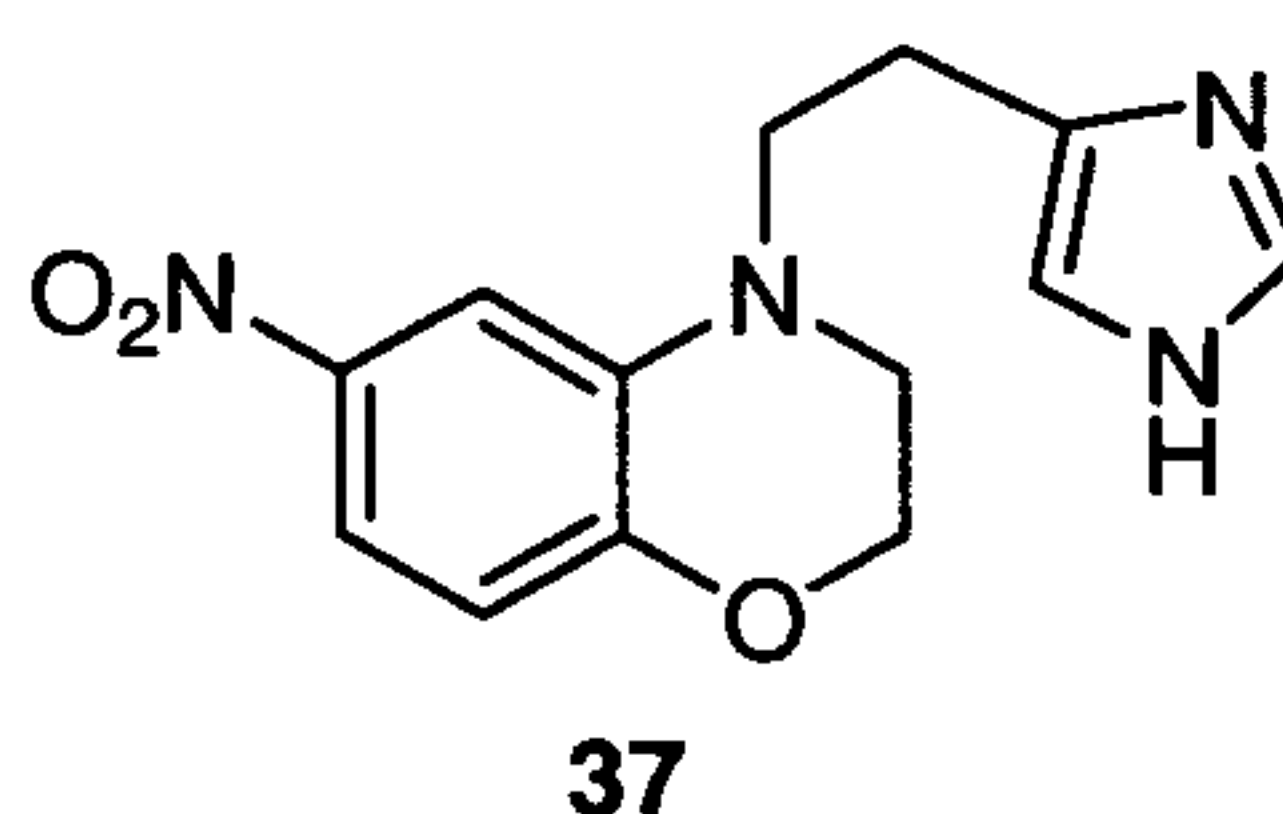
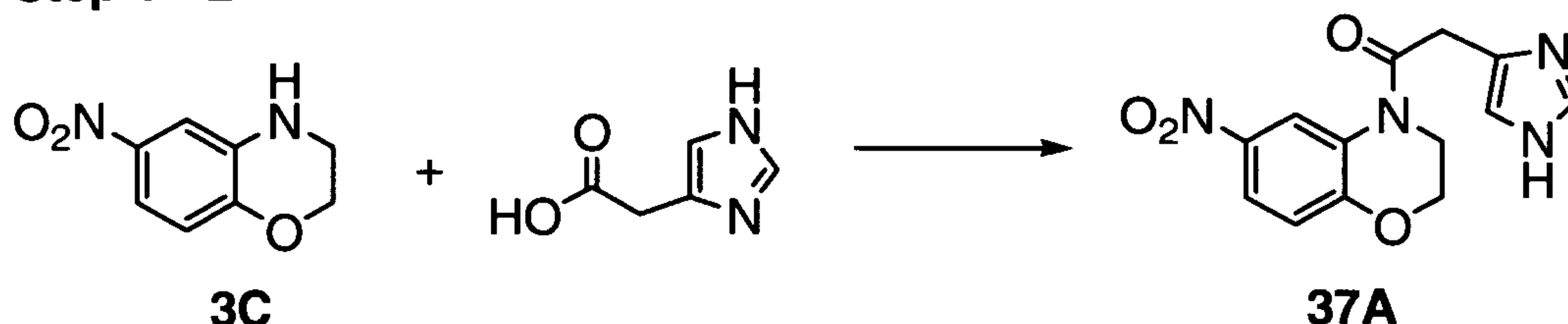
15

A solution of **34A** (0.200 g 1.33 mmol) in DMF (15 mL) was treated with KN(SiMe₃)₂ (0.5M/toluene, 3.2 mL, 0.93 mmol), stirred at 0 °C for 30 min, and then treated with CH₃I (0.12 mL, 2.00 mmol). The reaction was warmed to 20 °C, stirred overnight, and concentrated. The residue was then treated with 0.5 N NaOH (10 mL) and extracted with CH₂Cl₂ (3x). The combined organic layers were concentrated and subjected to chromatography (2-5% MeOH/CH₂Cl₂) to provide **36A** (0.120 g, 55%).

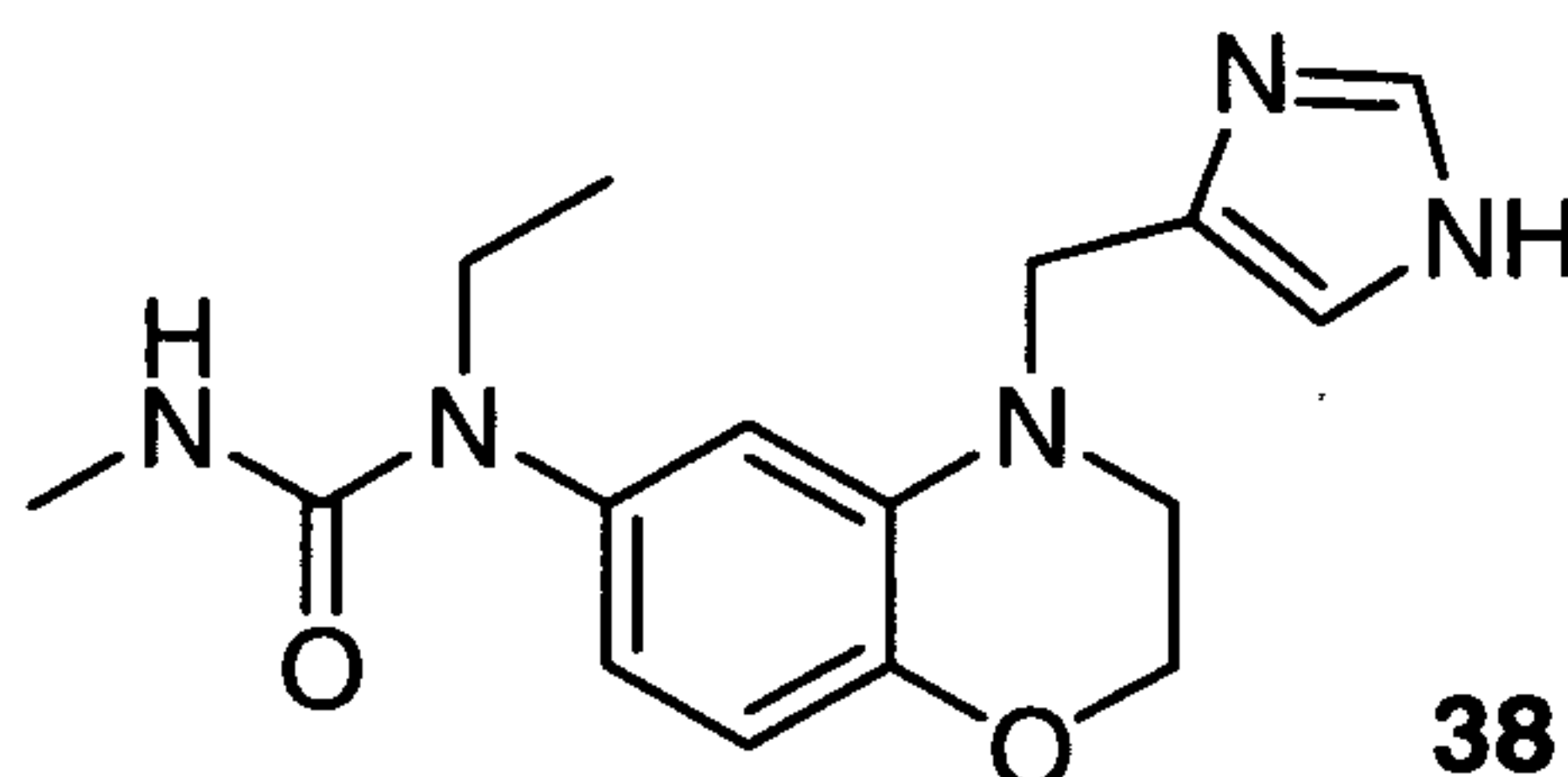
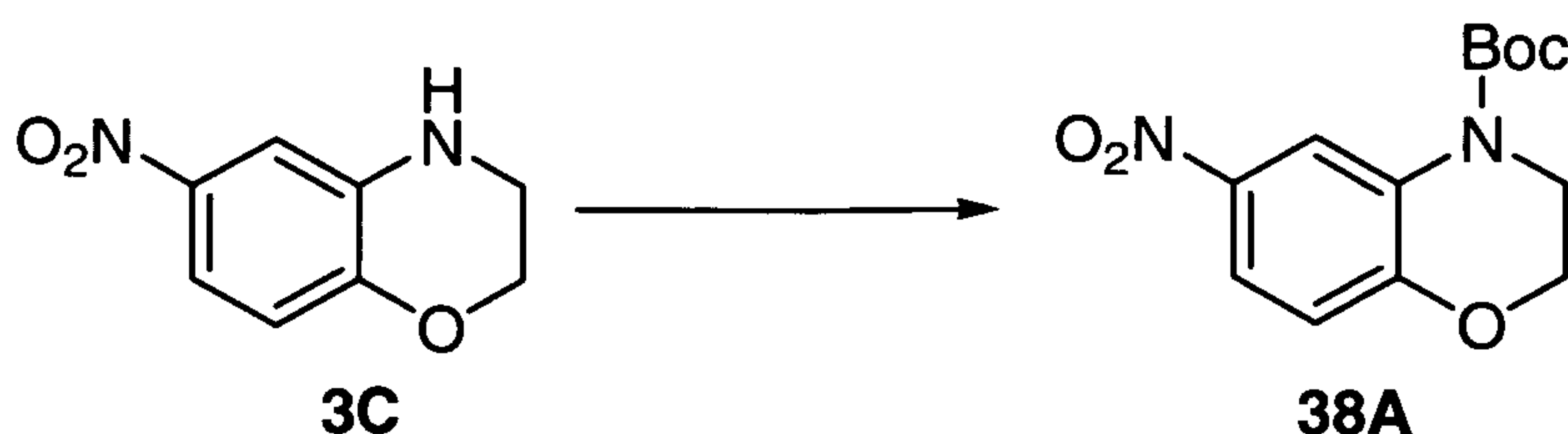
20

In a manner similar to that found in Example 26 (Step 3) and Example 1, **36A** was reduced with LAH and then reacted with imidazole-4-carboxaldehyde to provide **36**. LMCS m/z 230 (MH⁺).

83

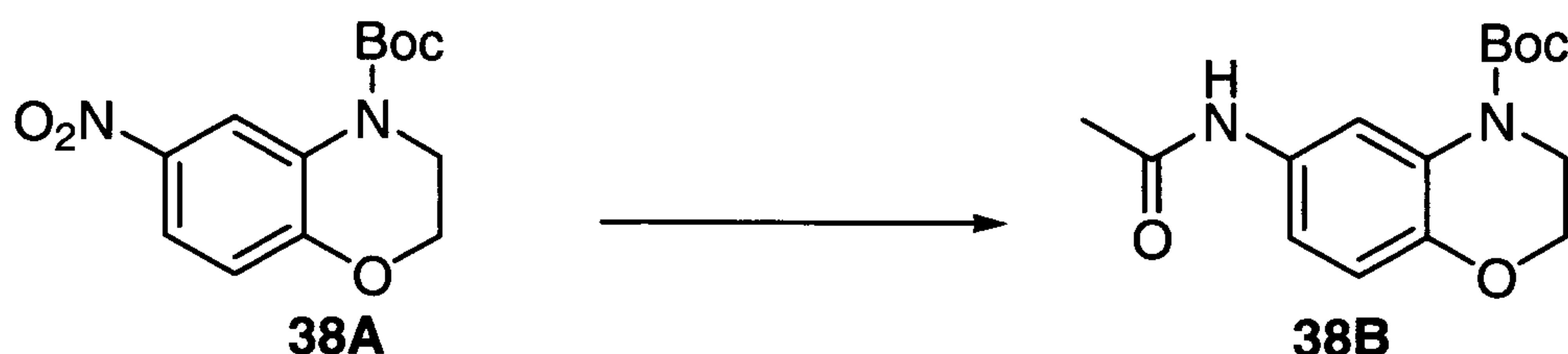
PREPARATIVE EXAMPLE 37**Step 1 - 2**

A mixture of **3C** (2g, 11.1 mmol) in anhydrous DMF (20 mL) was treated with 2-(1H-imidazol-4-yl)acetic acid (2g, 17.5 mmol), HATU (6.2g, 16.3 mmol) and DIEA (0.4 mL, 2.3 mmol) at 25 °C. The mixture was stirred at room temperature overnight and then concentrated under vacuum. Column chromatography (DCM containing 1 - 6% of 7N NH₃/MeOH) provided **37A** (1.2g, yield: 38%). In a manner similar to Example 2, Step 2, compound **37A** was reduced with BH₃-SMe₂ to provide compound **37**. MS m/z 275 (MH⁺).

PREPARATIVE EXAMPLE 38**Step 1**

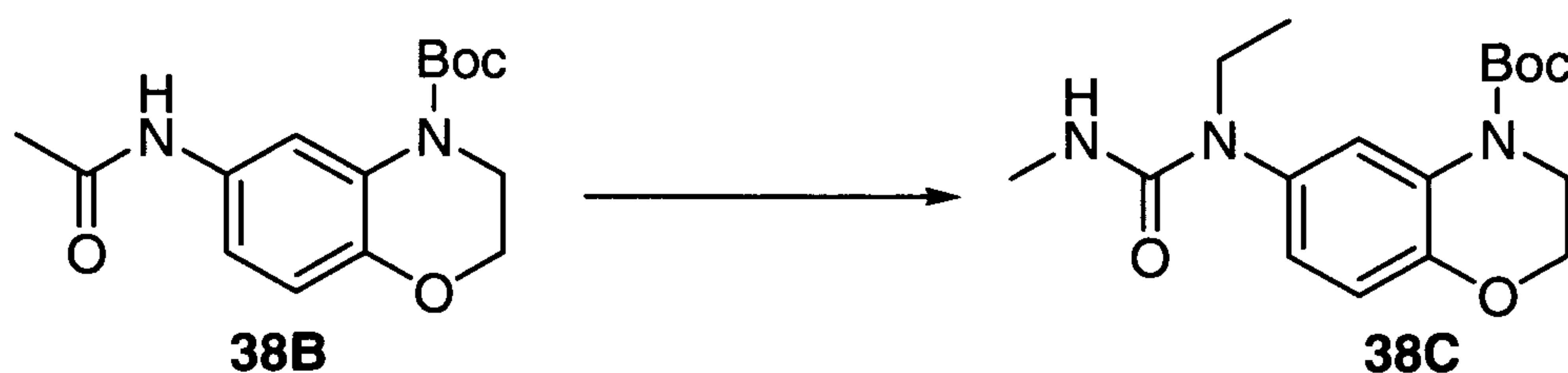
A solution of compound **3C** (14.1 g, 78 mmol) in MeCN (200 mL) was treated with (BOC)₂O (20.5 g, 94 mmol) and DMAP (0.5 g) and then refluxed overnight. The reaction mixture was concentrated and chromatographed (10% -50% EtOAc/hexanes) to give compound **38A** (16.1 g, 74%, typically 70-90%) and recovered starting material **3C**.

84

Steps 2-3

A mixture of compound **38A** (16.1 g, 58 mmol) in EtOH (300 ml) was treated with Raney Ni (~5 g) and hydrogenated (40 psi H₂) overnight. The reaction mixture was filtered and concentrated.

The resulting white solid (~15.3 g, 61 mmol) was suspended in anhydrous THF (200mL) and treated slowly with Ac₂O (~18mL, 173 mmol). After stirring for 2 h at 20 °C, the reaction mixture was concentrated in vacuo and taken up in 25% aqueous NaOH (100mL) and CH₂Cl₂. The layers were separated. The aqueous layer was further extracted with CH₂Cl₂ (3x). The organic layers were combined, dried with Na₂SO₄, and filtered to give **38B** as a gray solid (17.6 g, quantitative yield).

Steps 4-5

A solution of compound **38B** (21 g, 72 mmol) in THF (300 ml) at 0 °C was slowly treated with BH₃-DMS (60 ml, 2M/THF) and then heated to reflux overnight. The mixture was concentrated, treated with K₂CO₃ (9.9 g) and EtOH (300 mL) and then refluxed for 45 min. The reaction mixture was filtered, concentrated, added to H₂O and extracted with CH₂Cl₂ (4x). The combined organic layers were dried with Na₂SO₄, filtered and concentrated.

The resulting clear oil (21.9 g) was dissolved in anhydrous CH₂Cl₂ (300 ml), treated slowly with MeNCO (~5 g, 86 mmol), and then stirred at RT for 30 min. The

reaction mixture was concentrated and chromatographed (50%-80% EtOAc/hexanes) to give the product **38C** as a white solid (21.65 g, 90% yield for two steps).

Steps 6-7

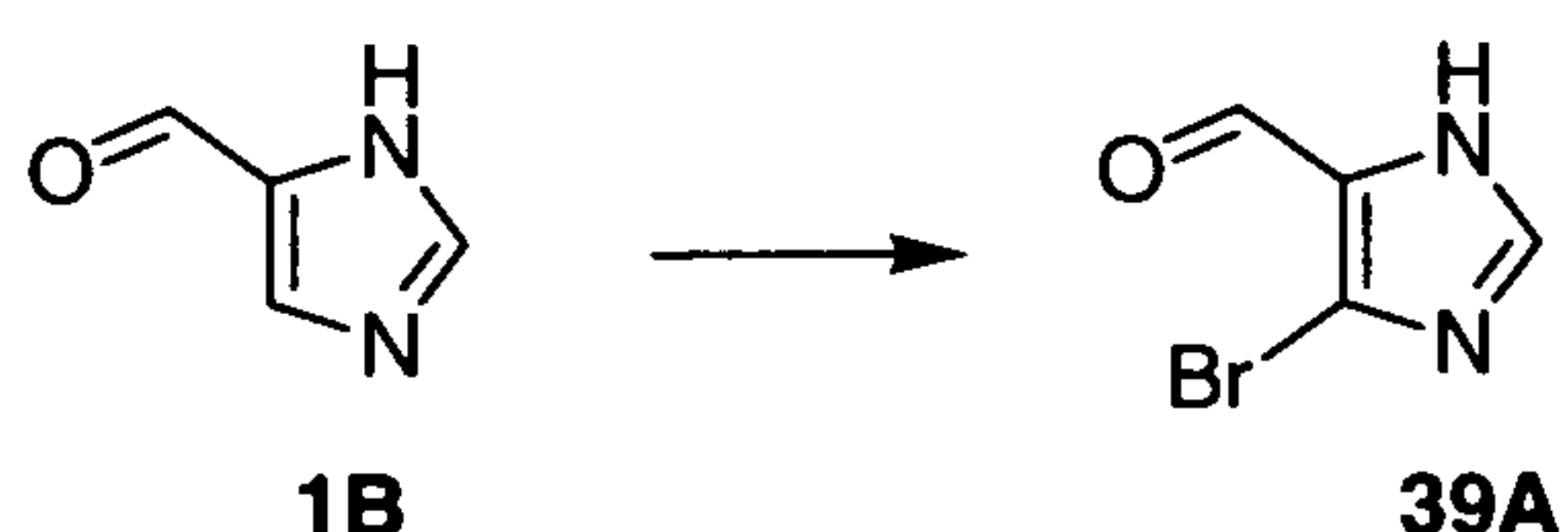
5 A solution of compound **38C** (21.65 g, 65 mmol) in of CH₂Cl₂ (300 ml) was treated with TFA (100 mL) and refluxed for 0.5 h. The reaction mixture was concentrated, treated with 20% NaOH (150mL) and extracted with CH₂Cl₂ (4X). The combined organic layers were dried with Na₂SO₄, filtered and concentrated to give a white solid (14.23 g, ~93%).

10

The crude product (16.2 g, 68.9 mmol) was combined with 4-imidazolecarboxaldehyde (**1B**, 6.6 g, 68.9 mmol) and Ti(OiPr)₄ (25 mL, 86 mmol) in CH₂Cl₂ (15 ml) and stirred at RT until the reaction mixture became clear (~1 h). Following the addition of NaBH₄ (3.3 g, 86 mmol) and EtOH (200 mL), the reaction was stirred at RT overnight and concentrated. The residue was taken up in 0.5 N NaOH and extracted with CH₂Cl₂ (4x). The combined organic layers were dried with Na₂SO₄, filtered, and concentrated. Chromatography (5-10% of 7N NH₃-MeOH in CH₂Cl₂) provided compound **38** (14.13 g, 68%) as a white solid.

15

20 PREPARATIVE EXAMPLE 39

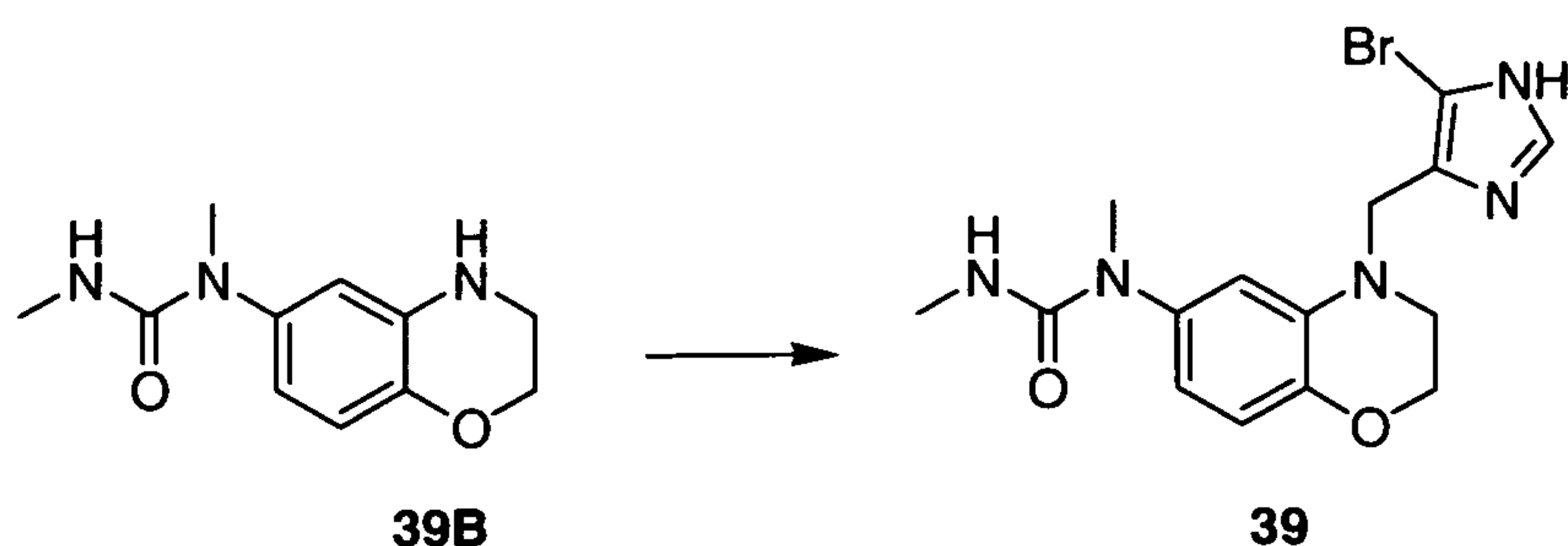


Bromine (8.0 g, 50 mmol, 2.3 eq) in anhydrous Ac₂O (40 mL) was added

25 dropwise to a solution of **1B** (2.08 g, 21.7 mmol) and NaOAc (18.7 g, 228 mmol, 10.5 eq) in anhydrous HOAc (200 mL) over a period of 1 h at RT. The resulting mixture was stirred at RT for 2.5 h and then concentrated. The residue was partitioned between Et₂O (200 mL) and water (200 mL), the layers were separated and the aqueous layer was extracted with Et₂O (200 mL). The combined organic phase was dried, concentrated and chromatographed (EtOAc) to afford 5-bromo-4-formyl imidazole **39A** (1.00 g, 26%) as white crystals.

30

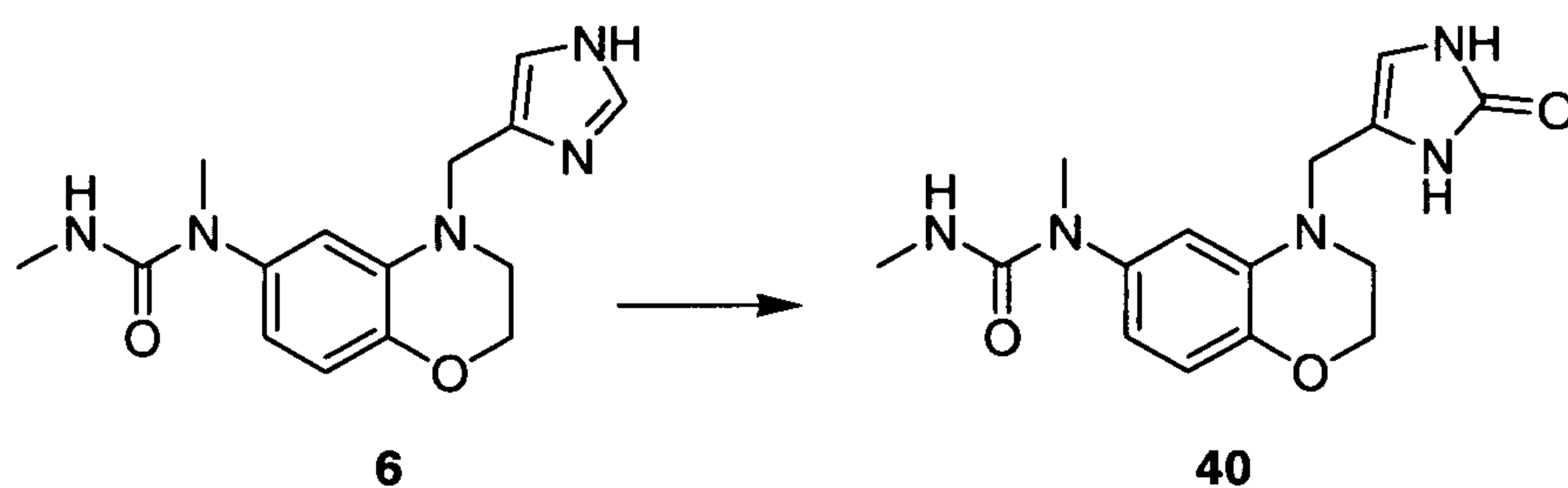
86



In a manner similar to that found in Example 1, **39A** was treated with **39B** (Example 6) to afford the title compound **39**. LCMS m/z 280 (MH^+).

5

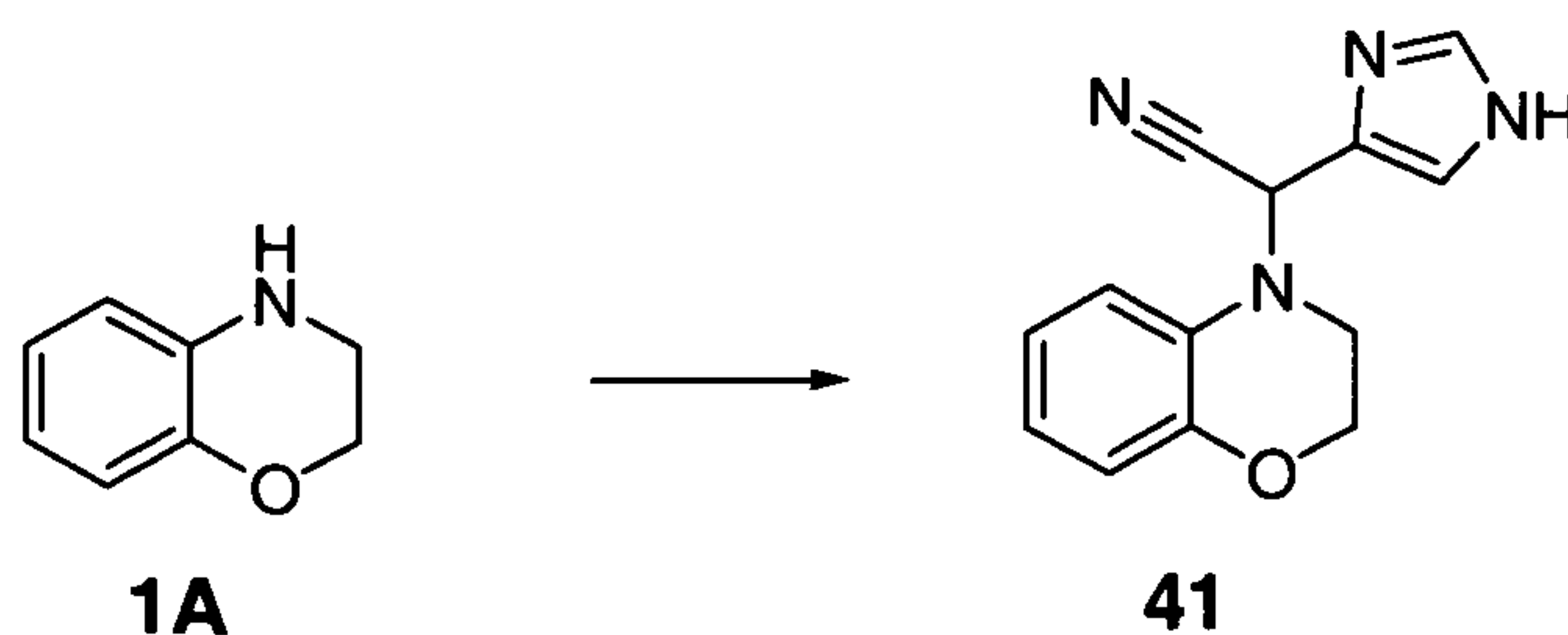
PREPARATIVE EXAMPLE 40



10 A mixture of **6** (0.25 g, 0.83 mmol) and $NaHCO_3$ (0.7g, 8.3 mmol) in 1:1 THF- H_2O (20 mL) was stirred vigorously for 10 min and then treated with phenyl chloroformate ($PhOCOCl$, 0.26 mL, 2.1 mmol). The reaction was stirred at RT for 2 h and then diluted with EtOAc. The organic layer was isolated, dried over Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH, treated with Et_3N (0.6

15 mL, 4.3 mmol) and stirred overnight. The solution was concentrated and subjected to chromatography (5-10% NH_3 -MeOH/EtOAc) to provide the title compound **40** as a light yellow foam (0.2 g, 76%).

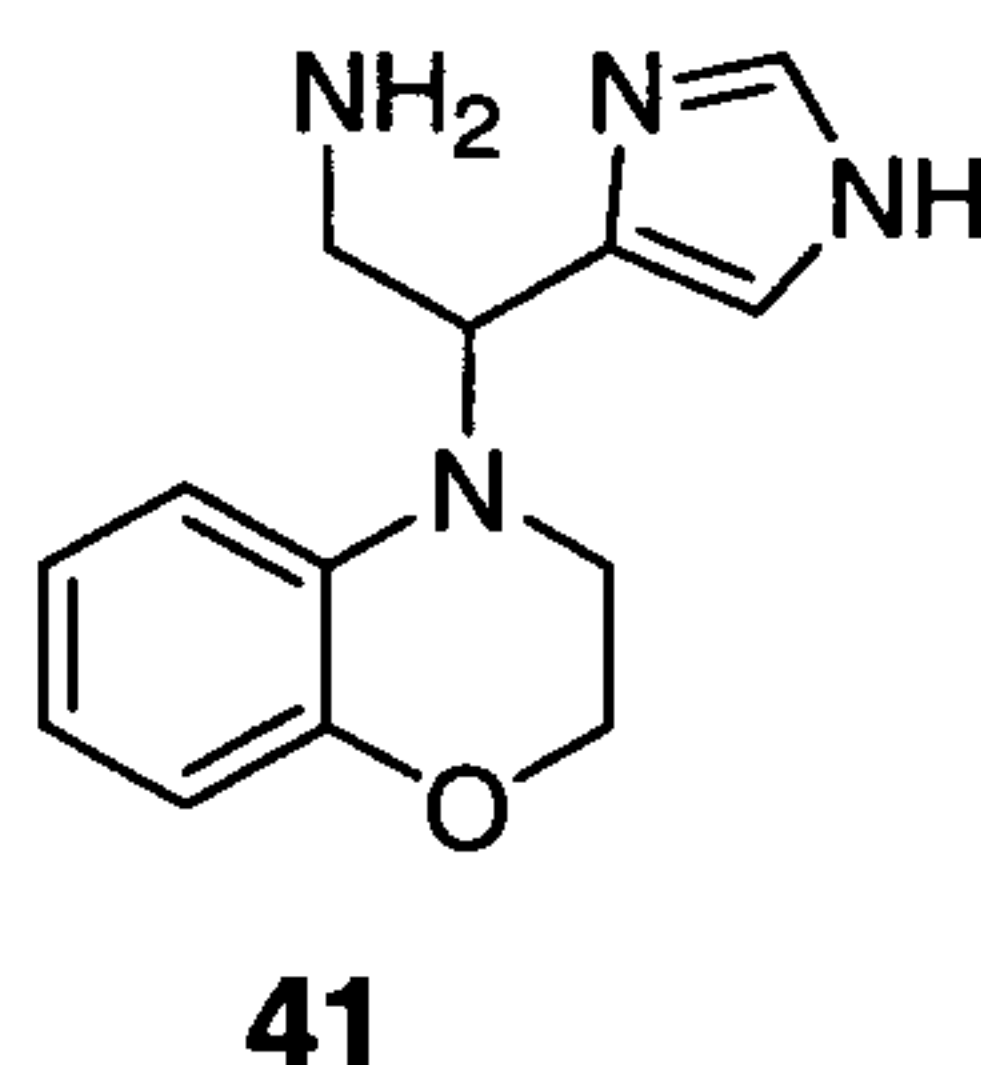
PREPARATIVE EXAMPLE 41



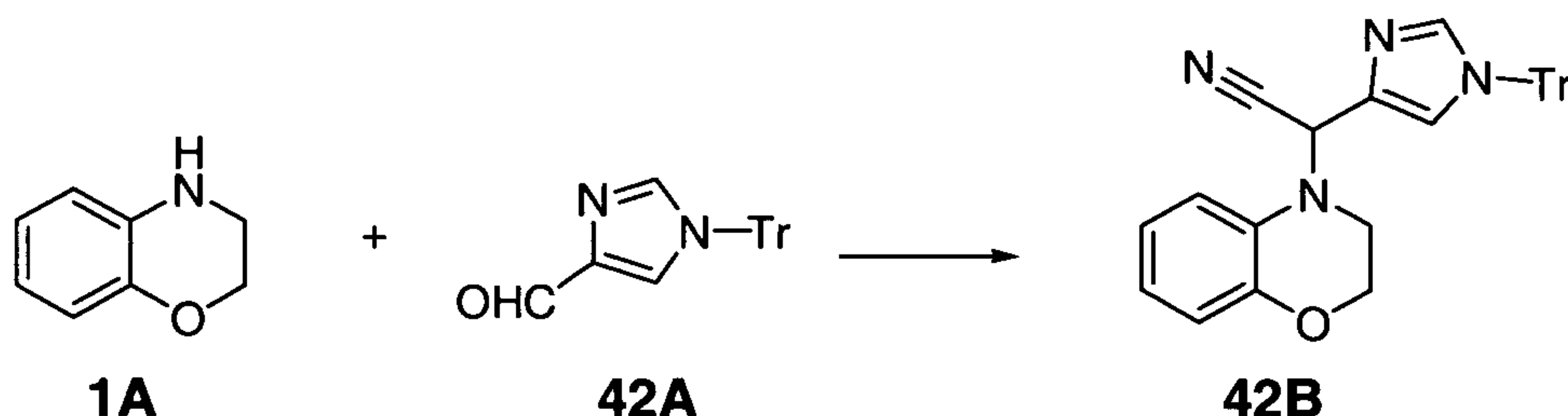
20

87

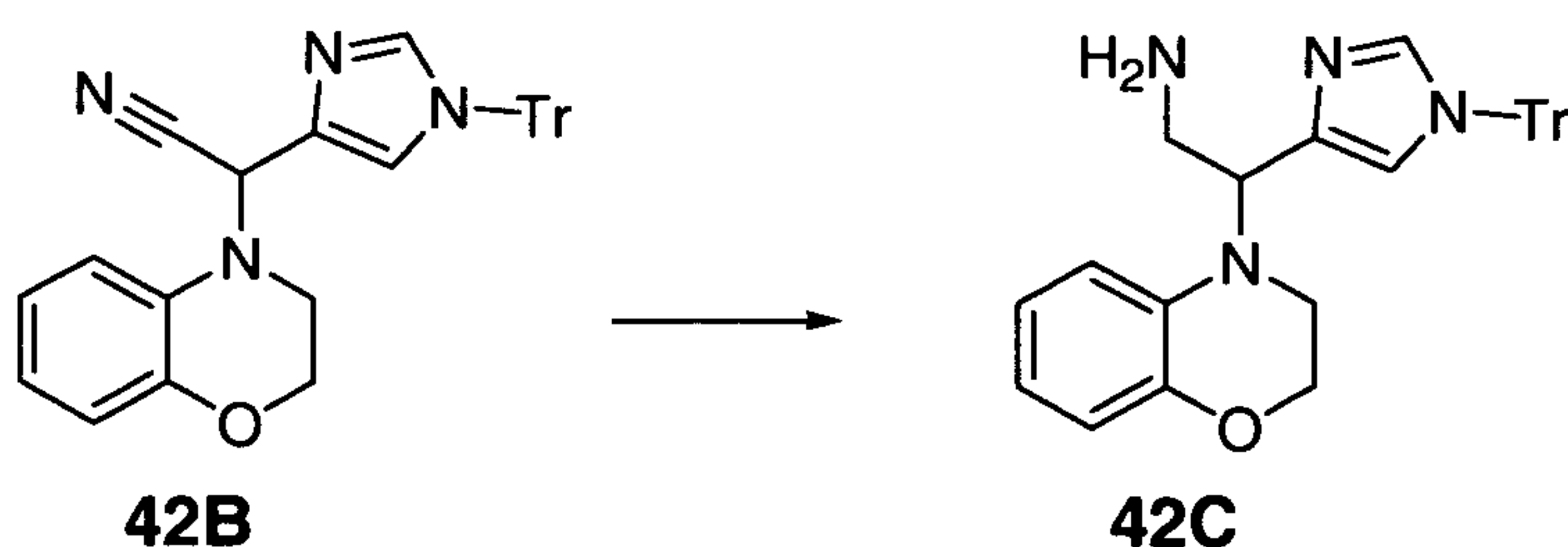
A mixture of **1A** (0.2 g, 1.5 mmol) and imidazole-4-carboxaldehyde (**1B**, 0.16 g, 1.6 mmol) in CH₂Cl₂ (5 mL) was treated with Ti(OiPr)₄ (0.55 mL, 1.88 mmol), stirred at RT overnight, and then treated with Et₂AlCN (2 mL, 1M/toluene). After 18 h, EtOAc, H₂O, and celite were added. Filtration and subsequent chromatography (0-10% of 7N NH₃-MeOH in CH₂Cl₂) provided **41** as a yellow solid (0.178 g, 50%). LCMS m/z 241 (MH⁺).

PREPARATIVE EXAMPLE 42

10

Step 1

In a manner similar to that found in Example 41, a mixture of **1A** and **42A** (Journal of Medicinal Chemistry, 1971, 14, 883) was treated sequentially with Ti(OiPr)₄ and Et₂AlCN to provide the compound **42B**.

Steps 2-3

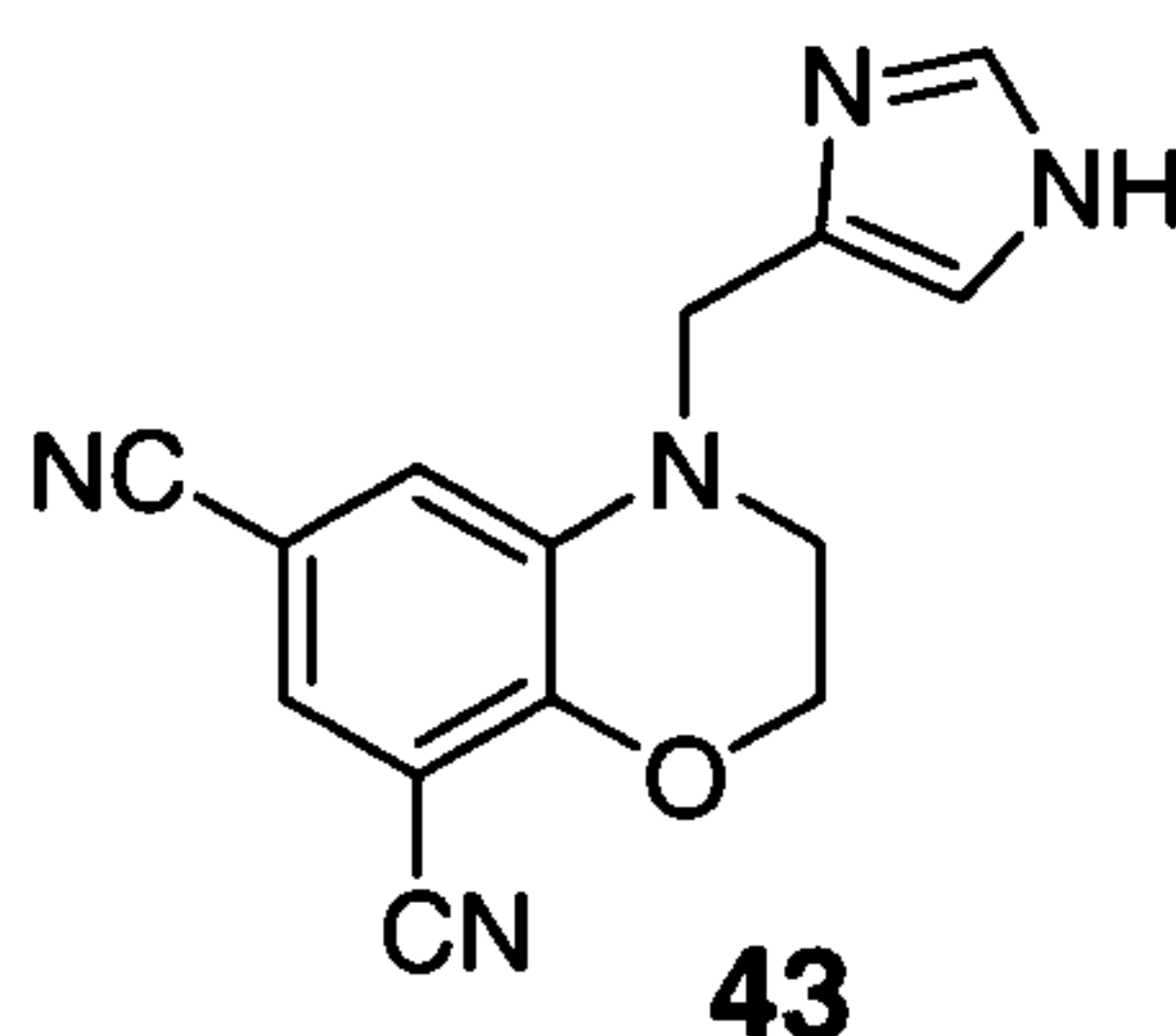
A solution of **42B** (0.2 g, 0.41 mmol) in 1N NH₃-MeOH (50 mL) was treated with Raney Ni and hydrogenated (50 psi H₂) overnight at RT. Filtration and subsequent

88

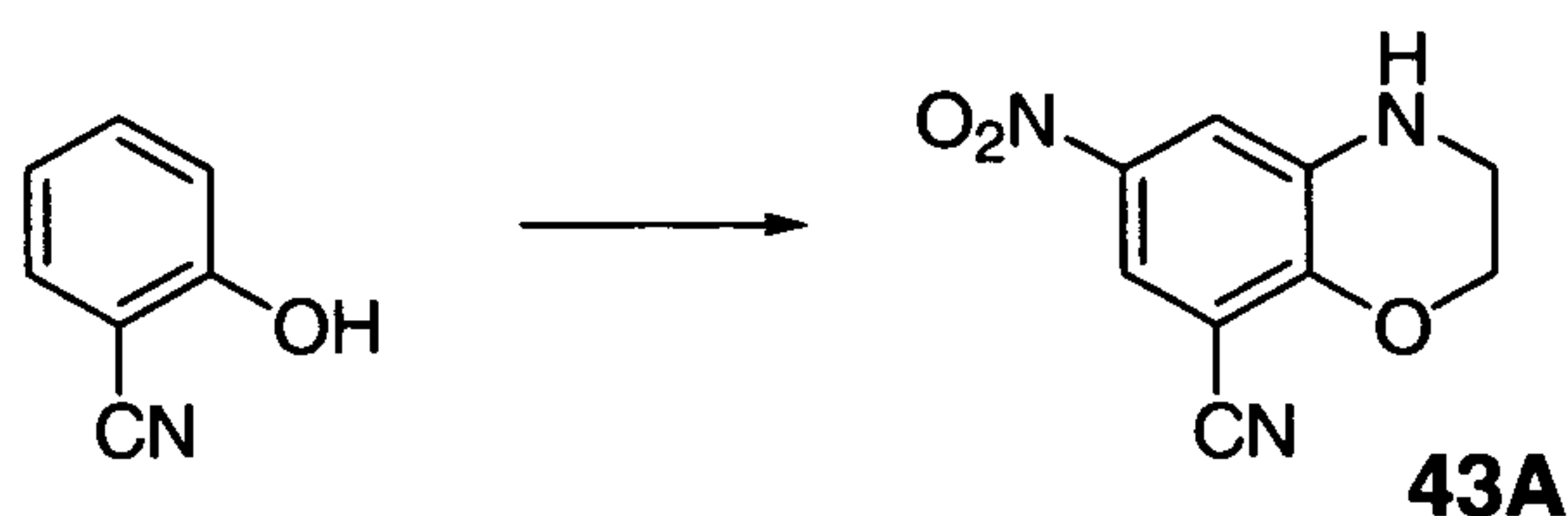
chromatography (0-7% of 7N NH_3 -MeOH in CH_2Cl_2) provided **42C** as a yellow film (0.15 g, 74%).

A mixture of **42C** (145 mg, 0.3 mmol) in CH_2Cl_2 (2 mL) was treated with TFA (0.5 mL) and Et_3SiH (0.05 mL). The reaction mixture was stirred at RT overnight and then concentrated. Chromatography (2-15% of 7 N NH_3 -MeOH in CH_2Cl_2) provided the title compound **42** (69 mg, 95%) as a yellow oil. LCMS m/z 245 (MH^+).

PREPARATIVE EXAMPLE 43

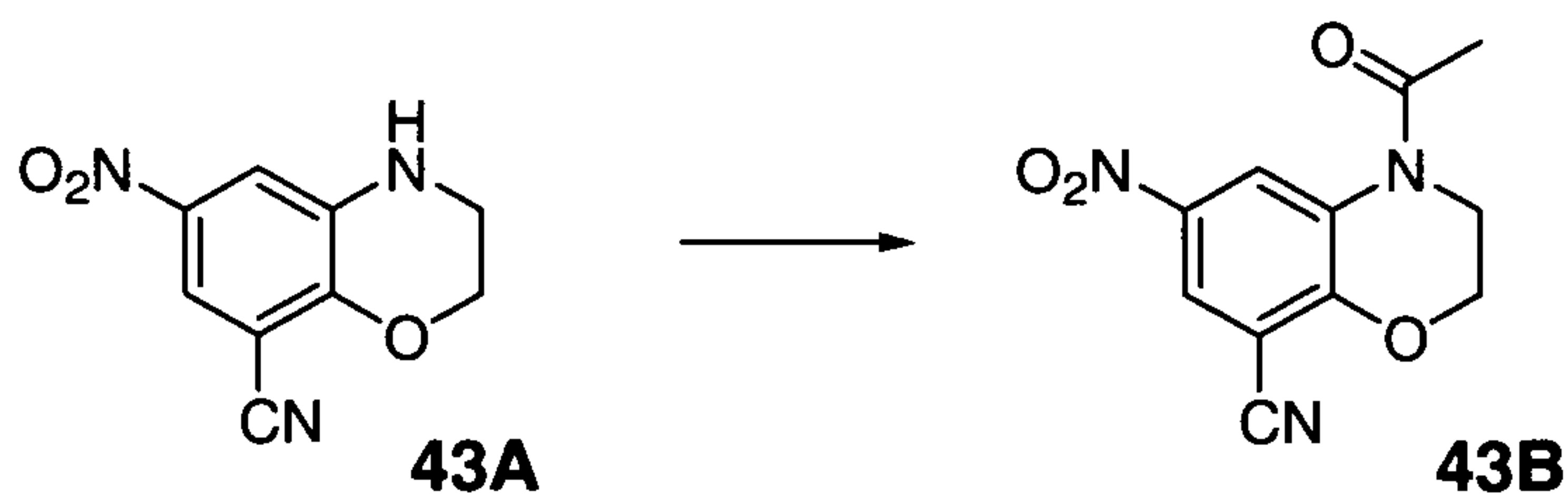


10 Steps 1-4



In a manner similar to that described in Examples 19 and 3, 2-cyanophenol was subjected to bis-nitration with HNO_3 , selective reduction with SnCl_2 , cyclization with chloroacetyl chloride, and reduction with $\text{BH}_3\text{-SMe}_2$ to provide **43A**.

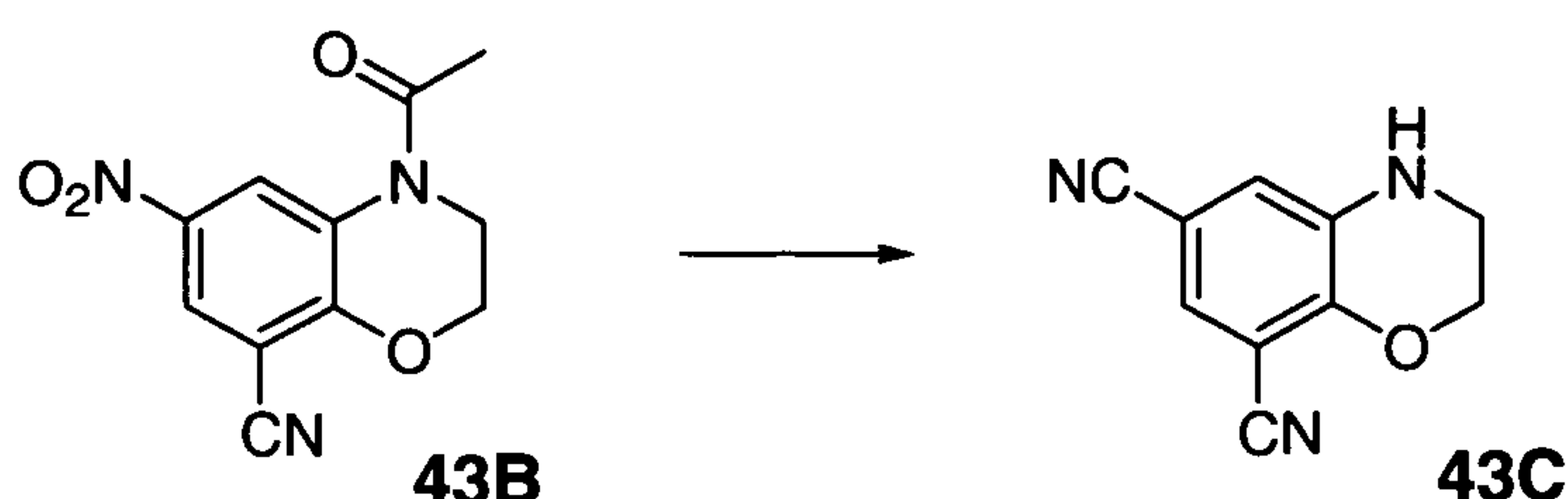
15 Step 5



A mixture of **43A** (0.65 g, 3.2 mmol) and Et_3N (0.9 mL, 6.3 mmol) in CH_2Cl_2 (60 mL) was treated with Ac_2O (6 mL) and DMAP (0.15 g) and then refluxed for 2 d. The reaction was then cooled, washed with 1N HCl (2x), washed with brine, dried over Na_2SO_4 , and concentrated. Chromatography (10-100% of EtOAc/hexanes) provided **43B** as a yellow solid (0.688 g, 88%).

Steps 5-8

89



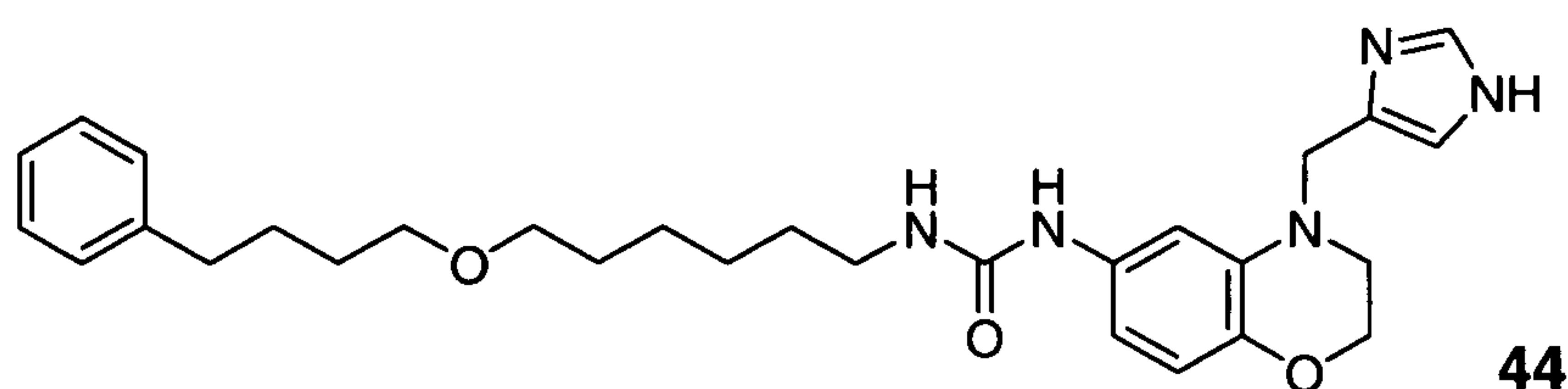
In a manner similar to that described in Example 3 (Step 4), **43B** was hydrogenated with Pd/C.

A mixture of the aniline product (0.080 g, 0.38 mmol) in 6M HCl (0.5 mL) was treated with a solution of NaNO₂ (27 mg, 0.39 mmol) at 0 °C. After 0.5 h, the solution was neutralized with sat. aq. Na₂CO₃ and then added dropwise to solution of CuCN (37 mg, 0.41 mmol) and NaCN (40 mg, 0.82 mmol). The resulting mixture was stirred at 60 °C overnight and then filtered.

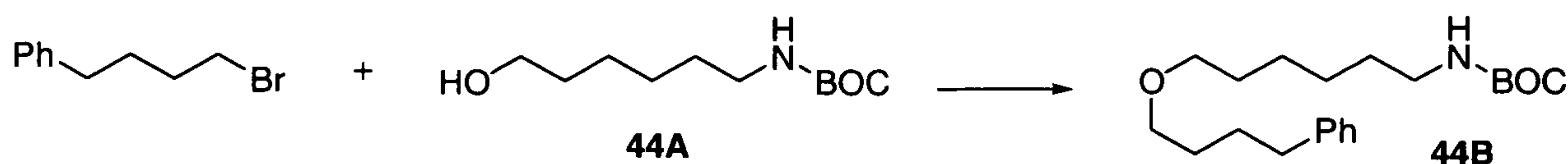
The brown precipitate (44 mg) was collected and then treated with 10% aq. NaOH (0.5 mL) for 2h at RT. The reaction was then diluted with H₂O and extracted with CH₂Cl₂ (3x). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated. Chromatography (20-100% of EtOAc/hexanes) provided **43C** as a beige solid (0.015 g).

In a manner similar to that described in Example 3 (Step 3), **43C** was converted to the title compound **43**. LCMS m/z 266 (MH⁺).

PREPARATIVE EXAMPLE 44



Step 1



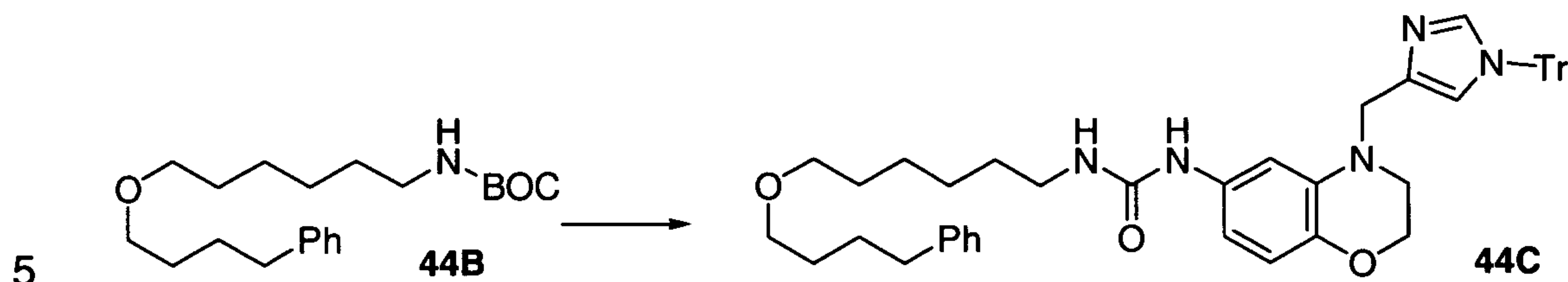
20

25

A solution of 4-phenylbutyl bromide (0.98 g, 4.6 mmol) and **44A** (1.0 g, 4.6 mmol) in 10 mL of benzene was treated sequentially with Bu₄NHSO₄ (0.16 g, 0.46 mmol) and 50% aqueous NaOH (2.4 mL, 46 mmol, added slowly). After stirring at RT under N₂ for 20 h, the solvent was removed. The reaction mixture was then diluted with H₂O, extracted with EtOAc, washed with H₂O (3x) and brine, dried over Na₂SO₄,

and filtered. The filtrate was concentrated and chromatographed (5-10% EtOAc/hexanes) to provide **44B** (0.7 g, 44%).

Steps 2-3

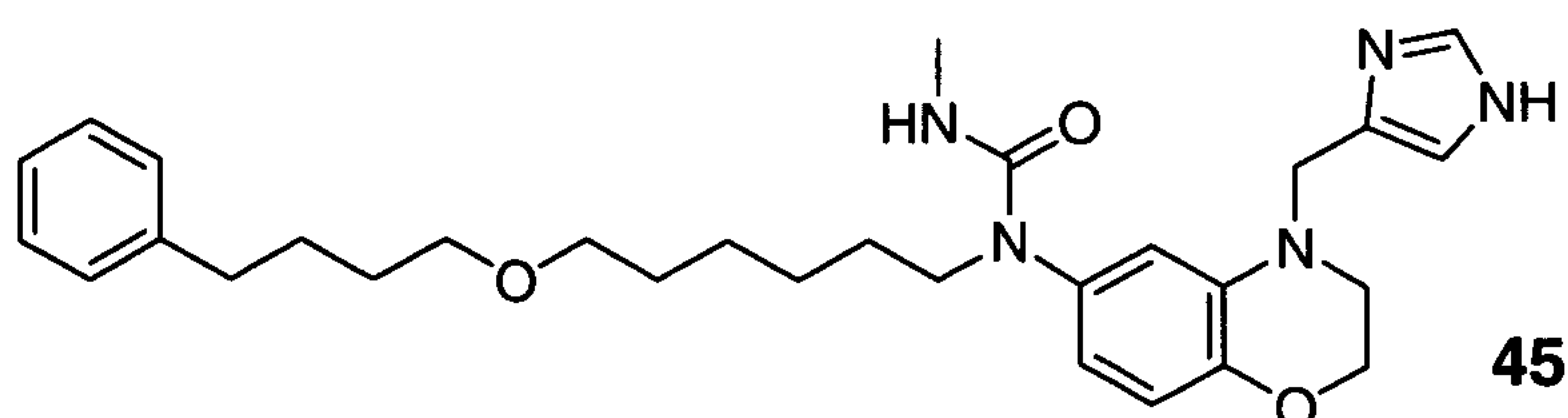


To a solution of **44B** (0.2 g, 0.57 mmol) in 5 mL of CH₂Cl₂ (5 mL) was added TFA (1.5mL). After stirring at RT for 1.5 h, the solution was cooled to 0 °C and treated with concentrated aqueous NH₃ (until pH = 10-11). The mixture was extracted with CH₂Cl₂, dried over Na₂SO₄, and filtered. The filtrate was concentrated to give an unstable amine (0.12 g, 84%) which was immediately taken up in CH₂Cl₂ (8 mL) and treated with compound **7B** (0.21g, 0.44mmol) and Et₃N (0.17 mL, 1.2mmol). After the mixture was cooled to -50 °C, triphosgene (0.04 g, 0.13 mmol) was added to the solution. The mixture was stirred at -50 °C under N₂ for 1h, then slowly warmed up to RT, and stirred under N₂ overnight. After adding 5% aqueous NaOH (10 mL), the products were extracted with CH₂Cl₂, dried over Na₂SO₄, and filtered. Chromatography (2% MeOH/EtOAc) provided **44C** (0.2 g, 67%).

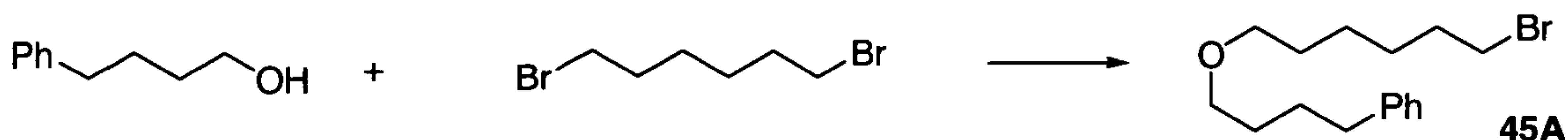
Step 4

A mixture of **44C** (0.13 g) in 3N HCl-MeOH (8 mL) was heated at 60 °C under N₂ for 1.5 h, cooled to 0 °C and neutralized with concentrated aqueous NH₃. The solution was concentrated, taken up in H₂O and extracted with CH₂Cl₂. The organic extract was dried over Na₂SO₄, filtered and chromatographed (5% NH₃-MeOH in CH₂Cl₂) to give the title compound **44** (0.05 g, 62%). LCMS m/z 506 (MH⁺).

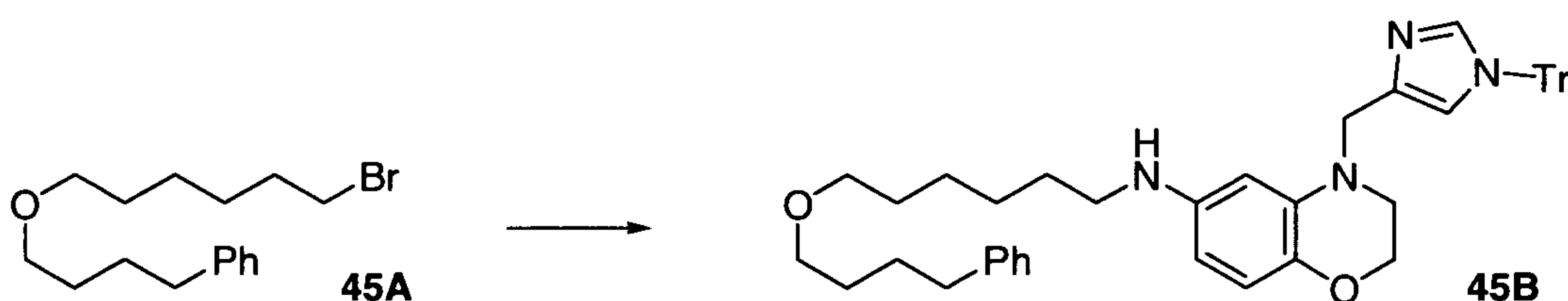
PREPARATIVE EXAMPLE 45



91

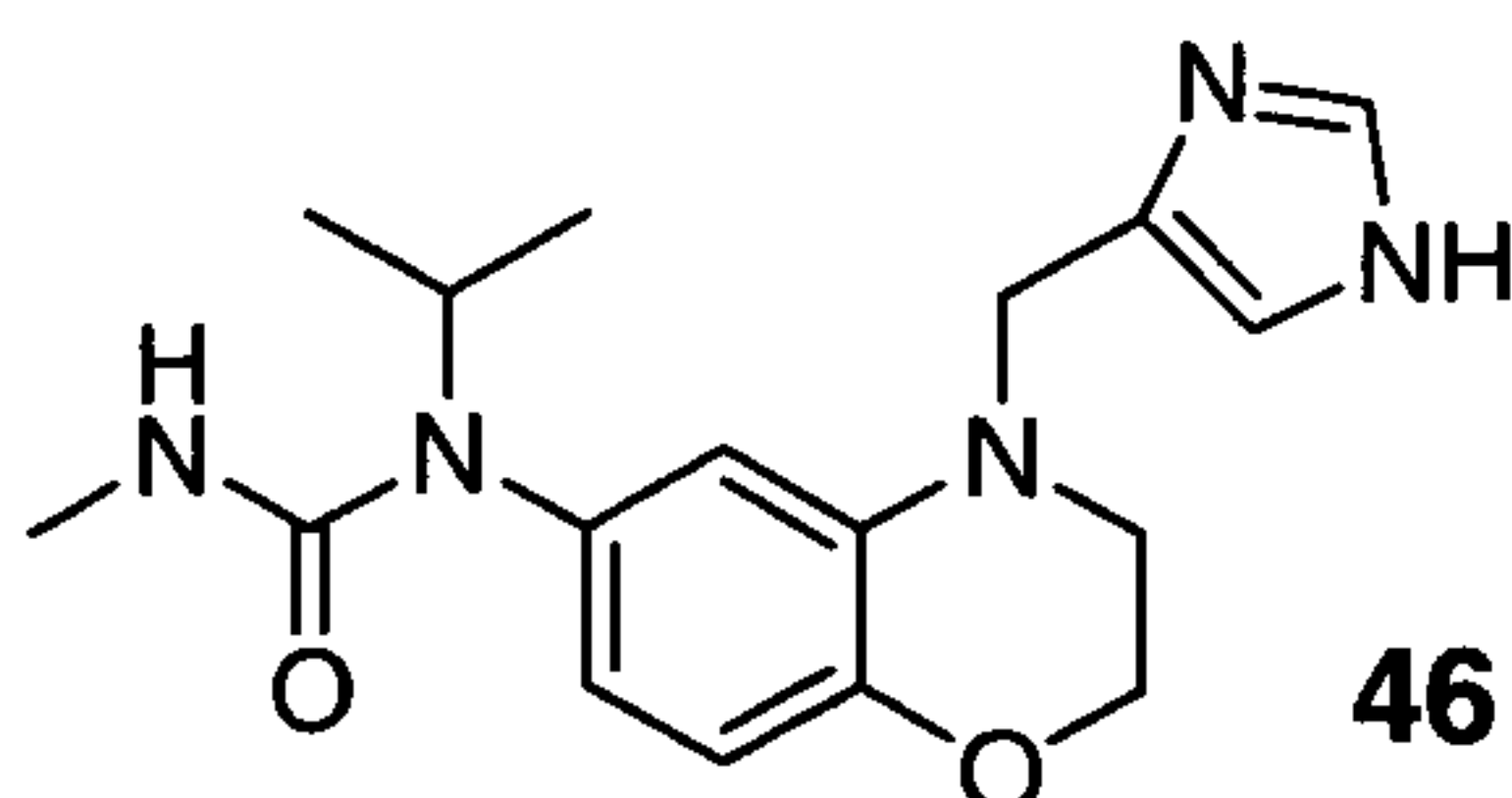
Step 1

A solution of 4-phenylbutanol (2.50 g, 16.6 mmol) and 1,6-dibromohexane (8.12 g, 33.2 mmol) in anhydrous THF (30 mL) was treated slowly with NaH (1.0 g, 24.9 mmol) at RT. After refluxing under N₂ for 20 h, the mixture was cooled to RT, and quenched with H₂O. The products were extracted with ether, washed with brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated and chromatographed (2% EtOAc/hexanes) to give **45A** (3.3 g, 63%).

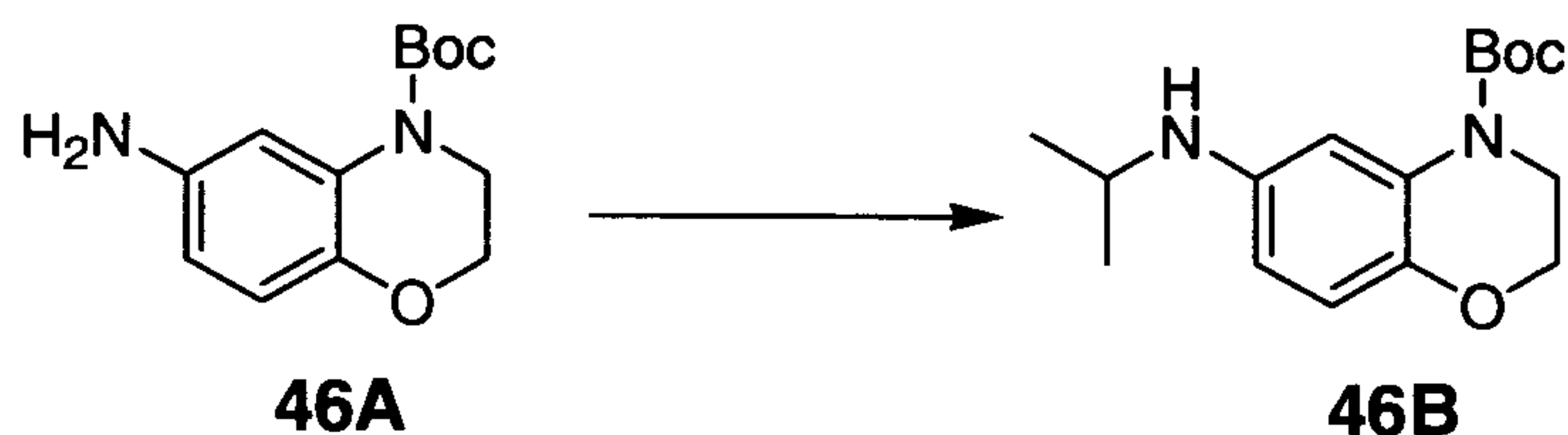
10 **Steps 2-4**

To a solution of **45A** (0.07 g, 0.21 mmol) and **7B** (0.1 g, 0.21 mmol) in toluene (3 mL) and DMF (0.5 mL) was added DIPEA (0.07 mL, 0.42 mmol) at RT. After heating at 80 °C under N₂ for 20 h, the mixture was concentrated, taken up in CH₂Cl₂, washed with H₂O (3x) and brine, dried over Na₂SO₄, and filtered. Chromatography (60% EtOAc/hexanes) provided **45B** (0.04 g, 27%).

In a manner similar to that described in Example 5 (Step 3) and Example 44 (Step 4), **45B** was sequentially treated with MeNCO and HCl to provide the title compound **45**. LCMS m/z 520 (MH⁺).

PREPARATIVE EXAMPLE 46

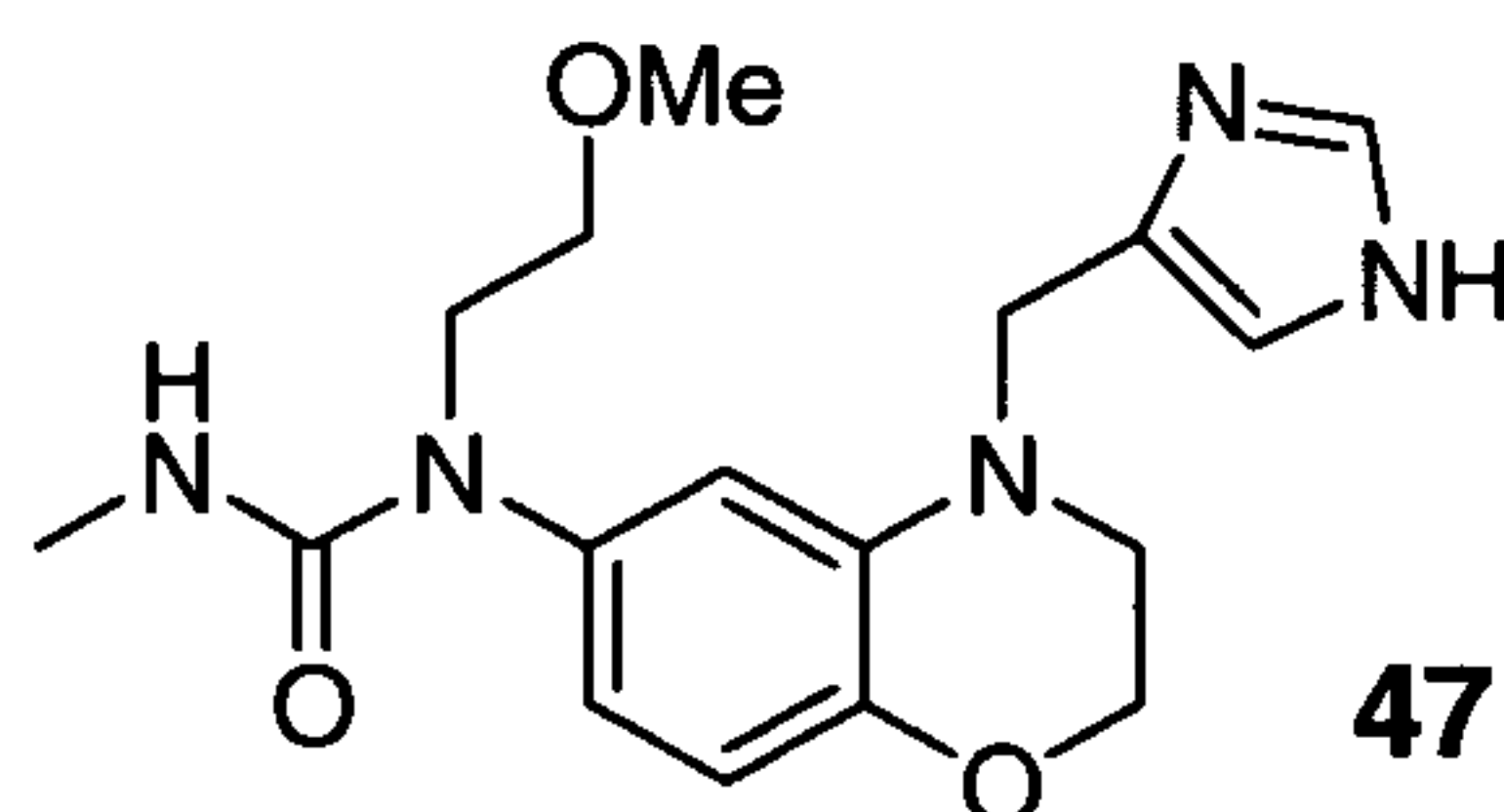
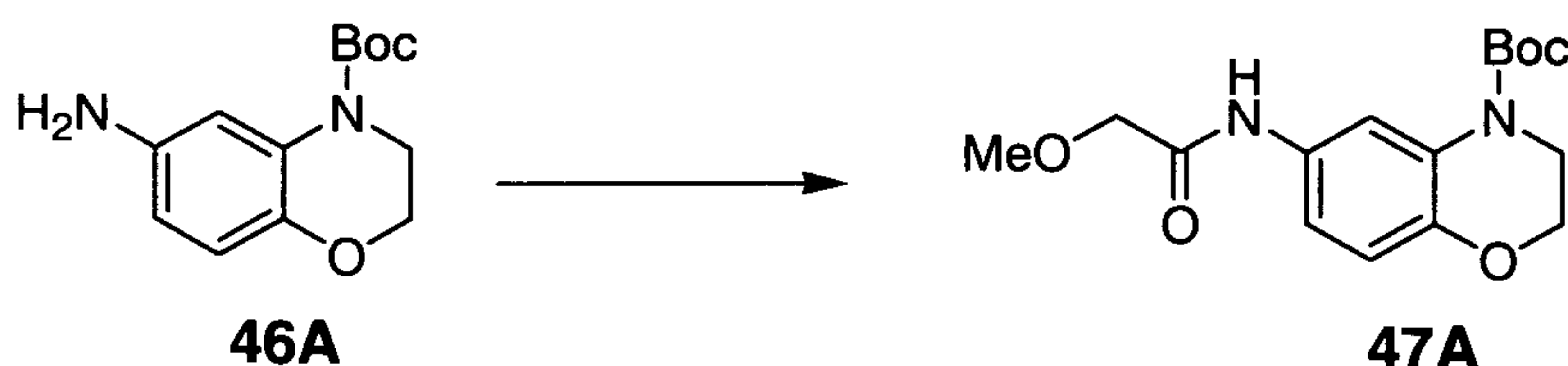
92

Steps 1-2

Compound **46A** (from Example 38, Step 2, 250 mg, 1 mmol) was taken up in DCE (10 mL) and treated sequentially with 2-methoxypropene (0.14 mL, 1.5 mmol), HOAc (0.06 mL, 1.1 mmol), and NaBH(OAc)₃ (424 mg, 2.0 mmol). The reaction mixture was stirred at RT overnight, quenched with 1.0 N NaOH and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with brine, dried, and then concentrated. Chromatography (EtOAc/hexanes) afforded **46B** (190 mg, 65%).

Steps 3-5

In a manner similar to that described in Example 38 (Steps 5-7), **46B** was sequentially treated with MeNCO, deprotected with TFA, and treated with 4-imidazolecarboxaldehyde to provide the title compound **46**. LCMS m/z 330 (MH⁺).

PREPARATIVE EXAMPLE 47**Step 1**

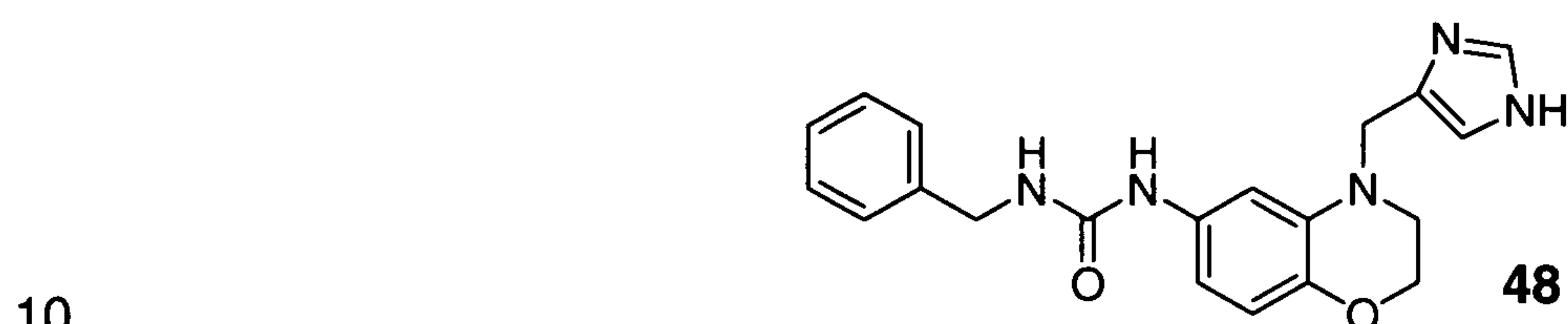
A mixture of **46A** (500 mg, 2 mmol) in CH₂Cl₂ (10 mL) was sequentially treated with methoxyacetyl chloride (0.22 mL, 2.4 mmol) and TEA (0.56 mL, 4.0 mmol). The reaction mixture was stirred at RT overnight, quenched with sat. NaHCO₃, and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were washed with

brine, dried, and concentrated. Chromatography (EtOAc/hexanes) afforded **47A** (610 mg, 95%).

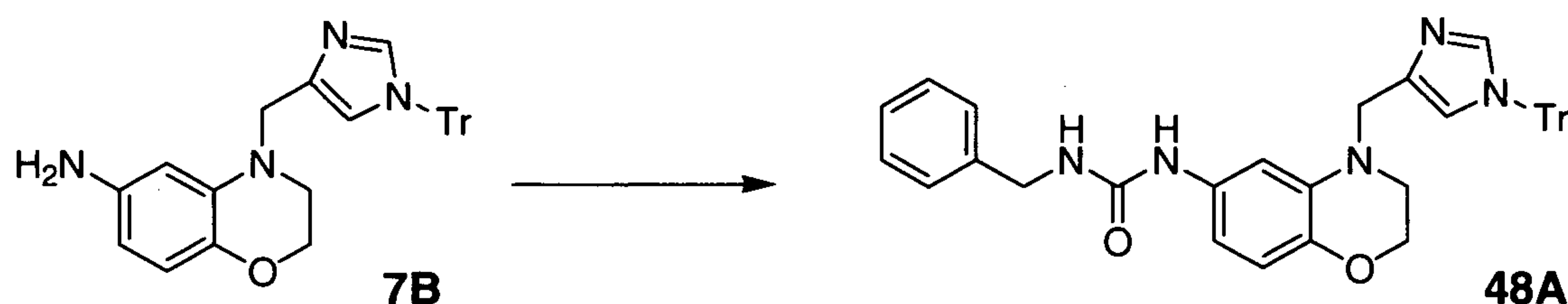
Steps 2-5

- 5 In a manner similar to that described in Example 38 (Steps 4-7), **47A** was reduced with $\text{BH}_3\text{-SMe}_e$, treated with MeNCO , deprotected with TFA, and treated with 4-imdazolecarboxaldehyde to provide the title compound **47**. LCMS m/z 346 (MH^+)

PREPARATIVE EXAMPLE 48



Steps 1-2

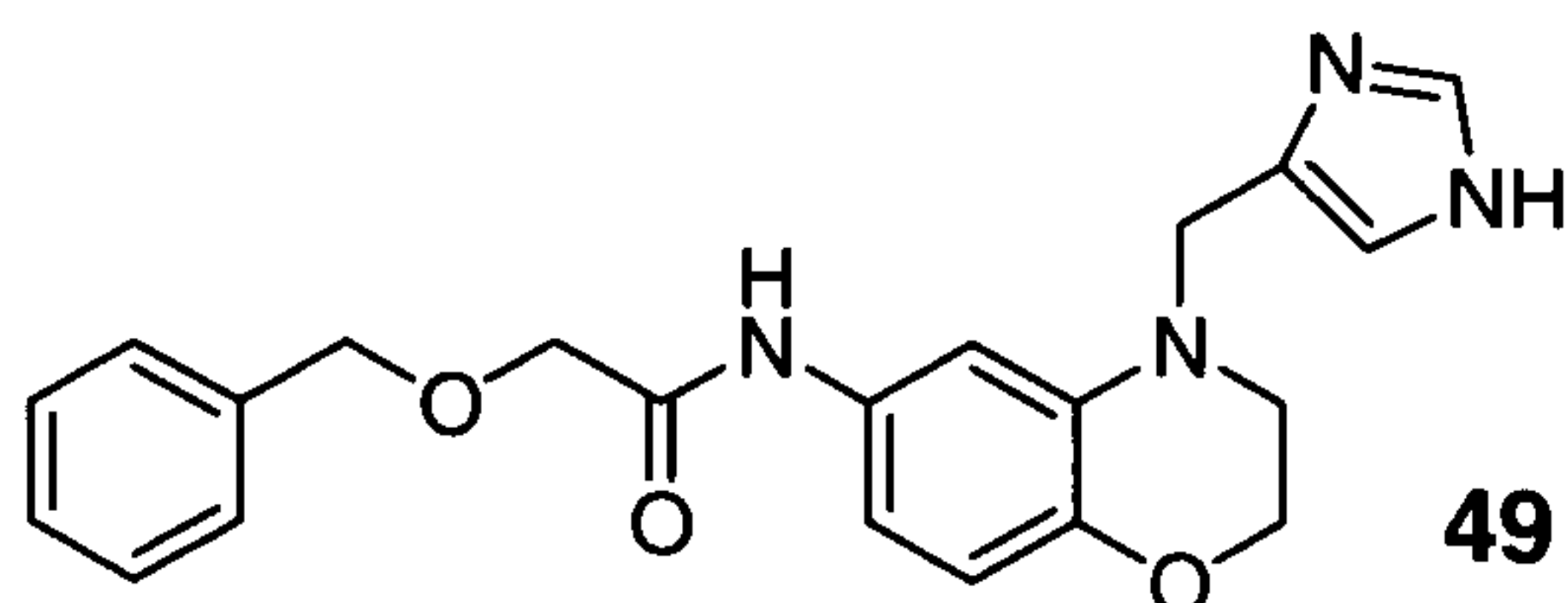


- 15 A solution of **7B** (140 mg, 0.3 mmol) in anhydrous CH_2Cl_2 (5 mL) was treated with benzyl isocyanate (48 mg, 0.36 mmol). The reaction mixture was stirred at RT overnight and then concentrated. Chromatography afforded **48A** (130 mg, 72%).

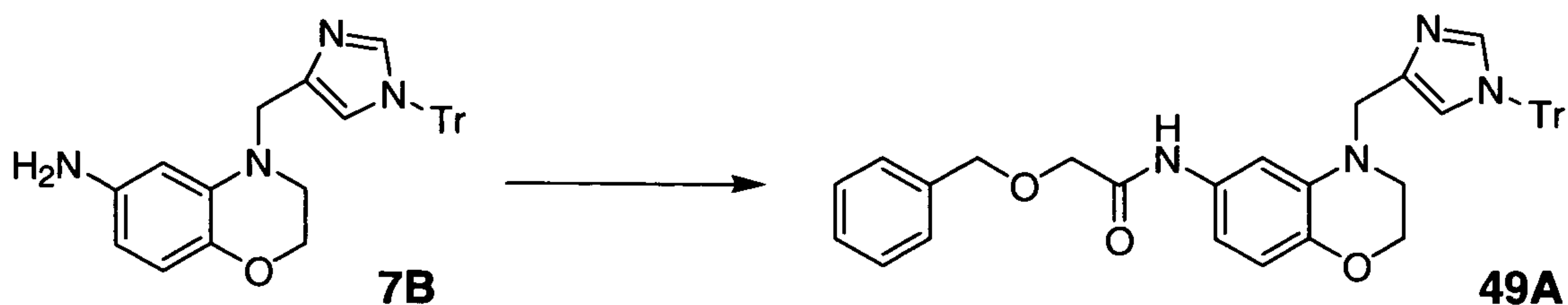
In a manner similar to that described in Example 42 (Step 3), **48A** was deprotected with TFA and Et_3SiH to provide the title compound **48**. LCMS m/z 364 (MH^+).

20

PREPARATIVE EXAMPLE 49

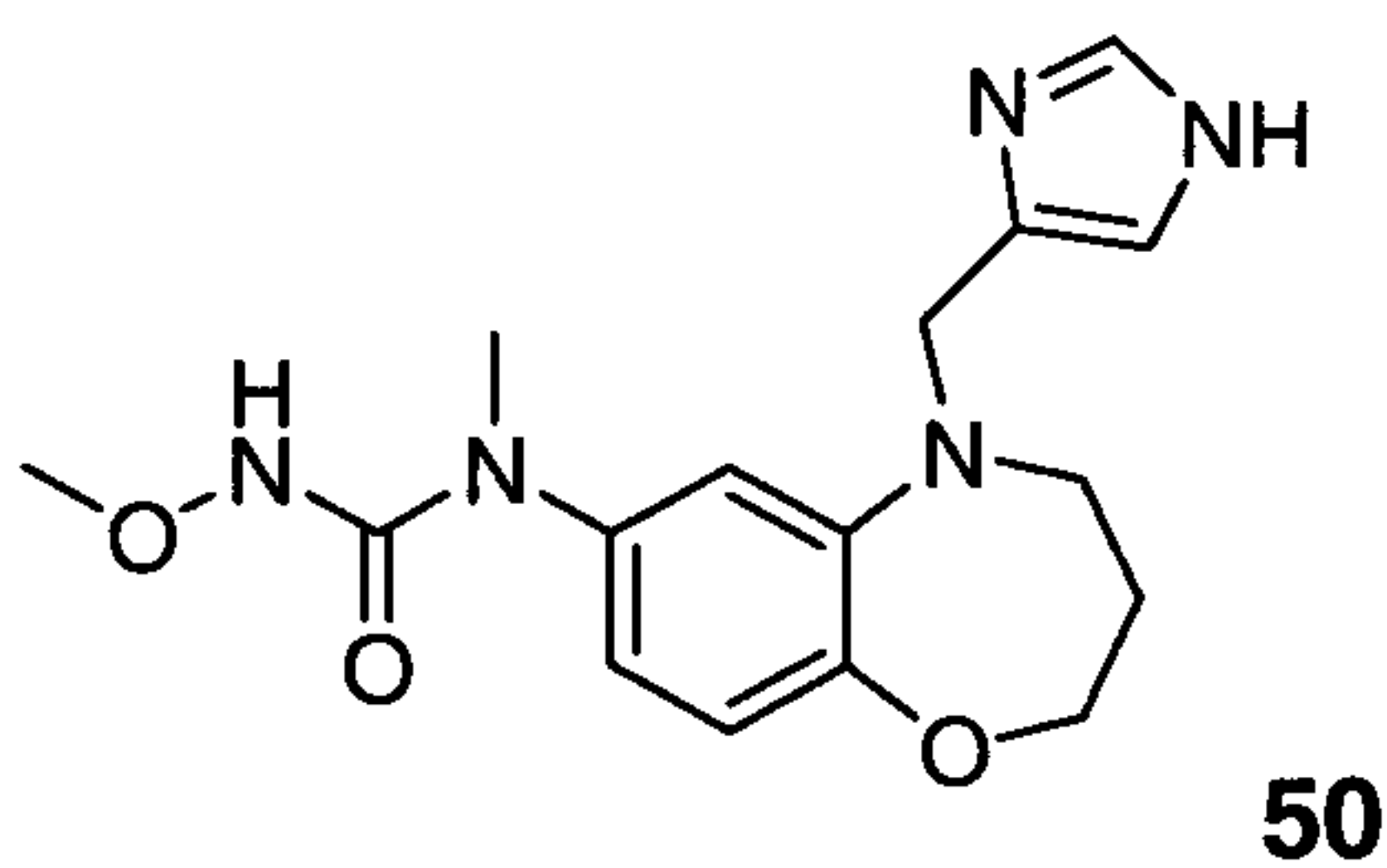
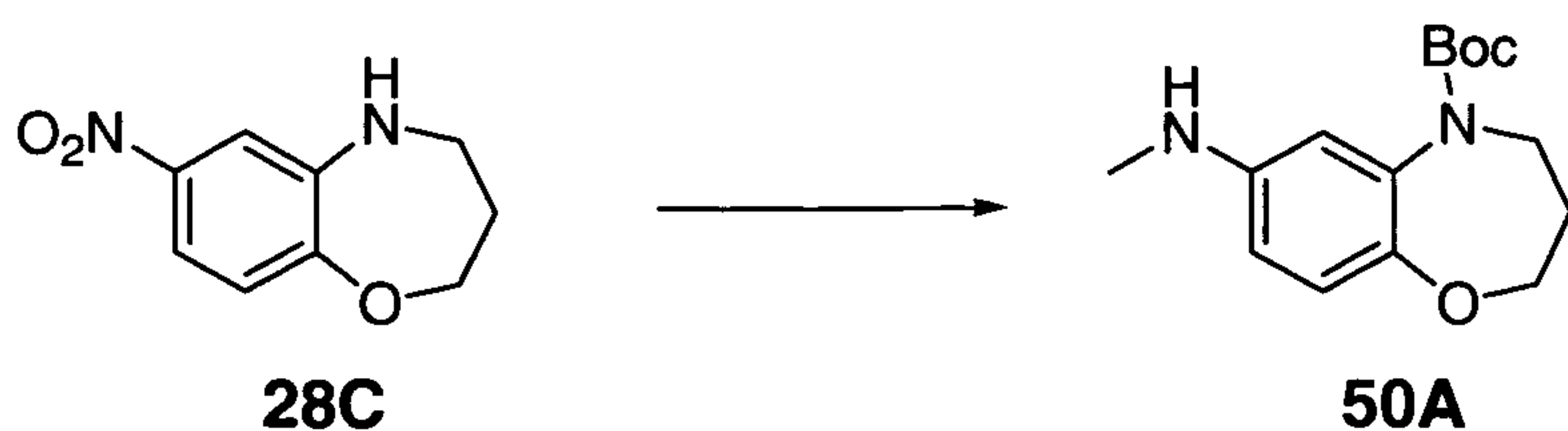


94

Steps 1-2

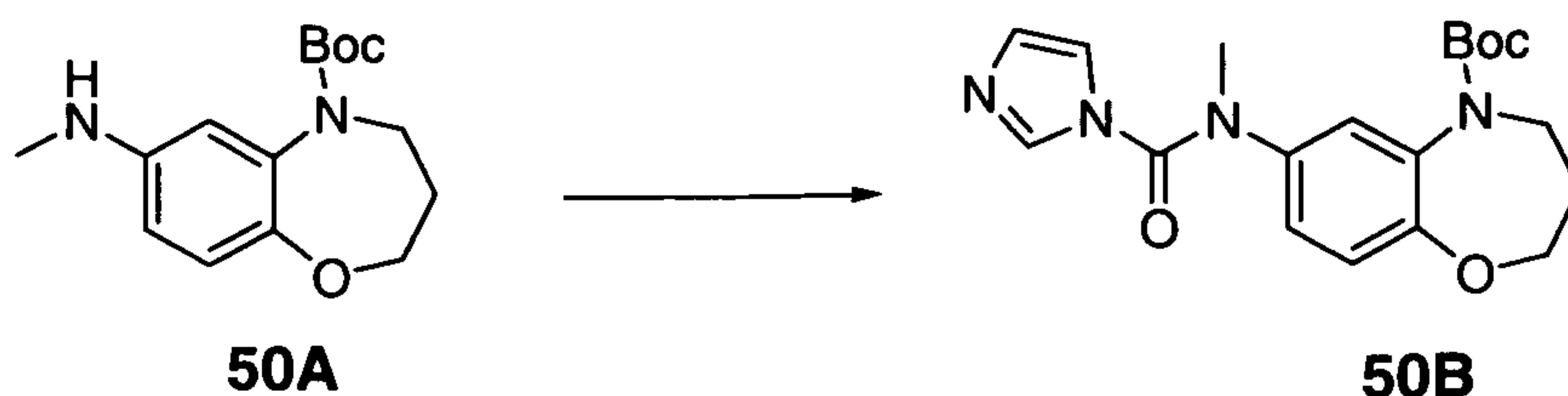
A mixture of **7B** (1.0 g, 2.12 mmol), benzyloxycarbonyl-L-proline (0.46 g, 2.75 mmol),
5 EDCI (0.61 g, 3.18 mmol) and HOBt (0.42 g, 3.18 mmol) in DMF were stirred at RT for
1 d. The reaction was quenched with 0.5 N aq. NaOH (50 mL) and extracted with
CH₂Cl₂. The combined extracts were washed with brine, dried (Na₂SO₄) and
concentrated. Preparative TLC chromatography (5% NH₃-MeOH in CH₂Cl₂) provided
49A (0.52 g).

10 In a manner similar to that described in Example 42 (Step 3), **49A** was
deprotected with TFA and Et₃SiH to provide the title compound **49**. LCMS m/z 379
(MH⁺).

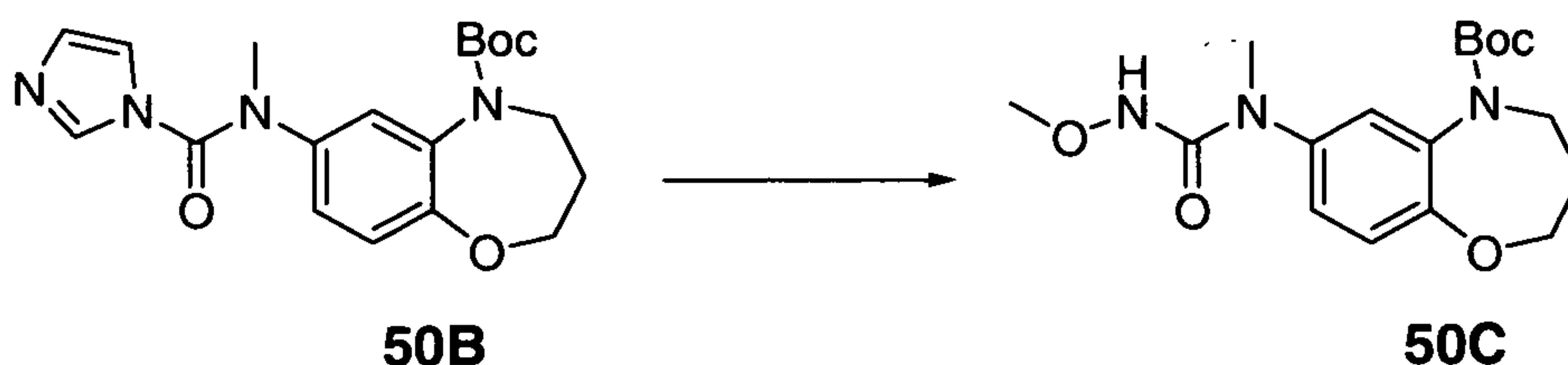
PREPARATIVE EXAMPLE 50**Steps 1-4**

20 In a manner similar to that described in Example 5 (Steps 1-2) and Example 6
(Steps 1-2), compound **28C** was converted to **50A**.

95

Step 5

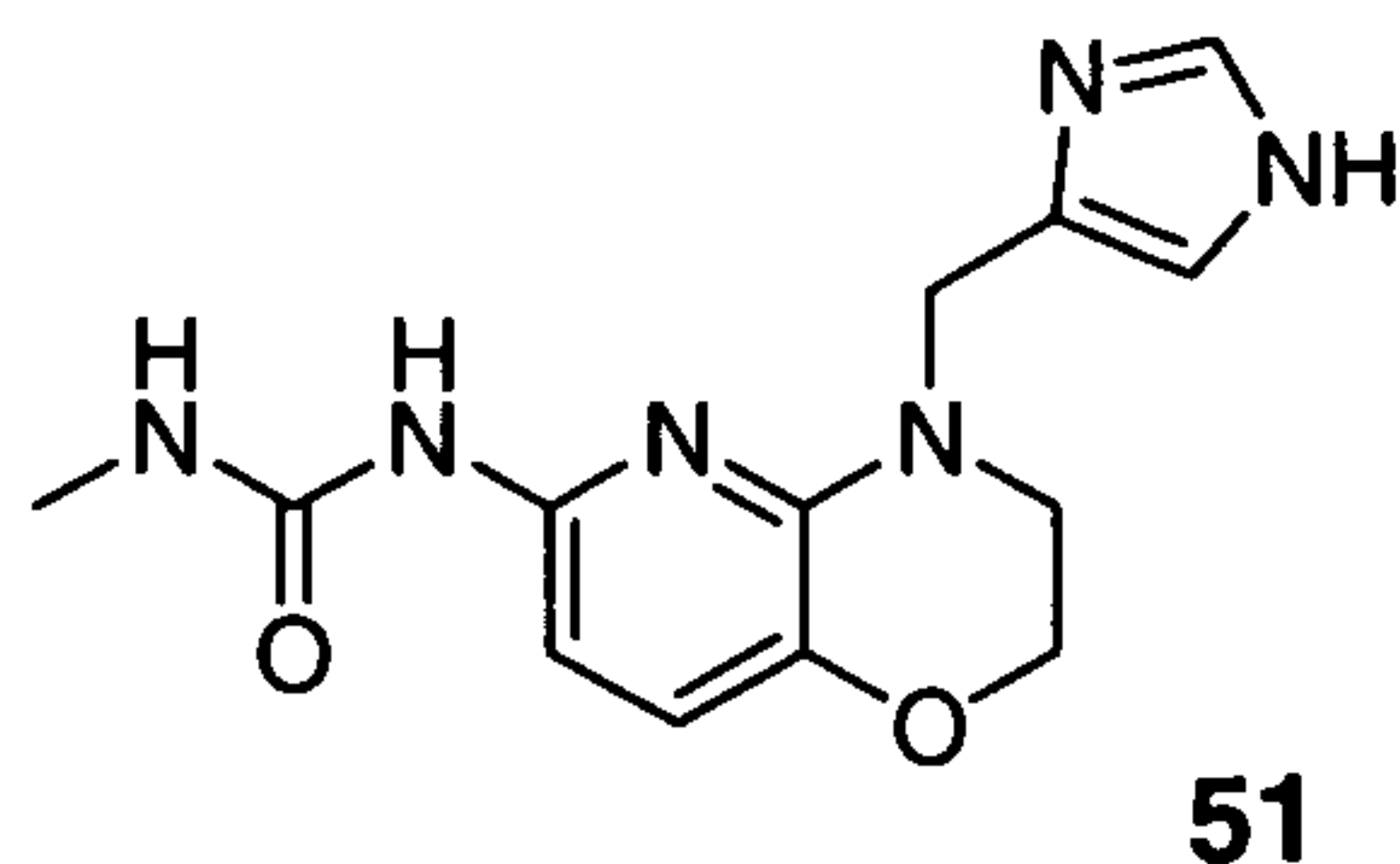
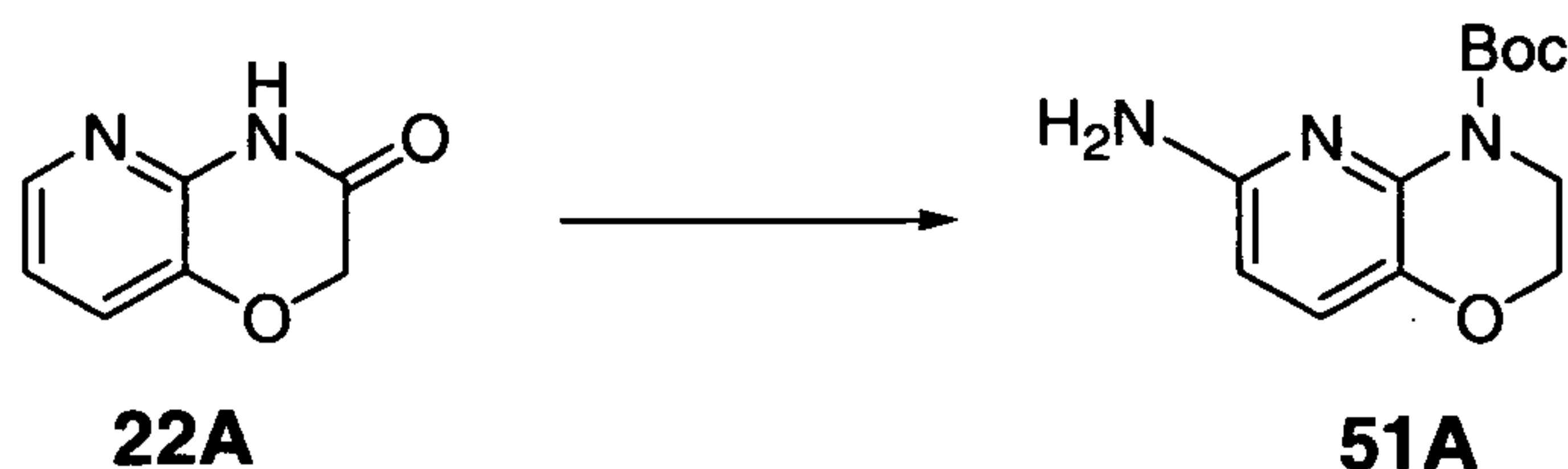
A mixture of **50A** (0.247 g, 0.99 mmol) in anhydrous DCM (5 mL) was treated with carbonyldiimidazole (0.32 g, 1.97 mmol) and Et₃N (0.28 mL, 1.97 mmol) and then stirred at RT overnight. The reaction was washed with water and extracted with DCM (3 x 10 mL). The combined organic layer was dried (MgSO₄), filtered, and concentrated under vacuum to give compound **50B**.

Steps 6-8

A solution of **50B** was in anhydrous MeCN (5 mL) in a sealed tube was treated with MeI (2 mL). The sealed reaction mixture was heated to 55 °C for 3 h, cooled to RT and concentrated. The residue was dissolved in anhydrous THF (5 mL) and then treated with MeONH₂-HCl (0.25 g, 2.97 mmol) and DIEA (0.53 mL, 2.97 mmol). After stirring at RT overnight, the reaction was quenched with saturated NH₄Cl solution and concentrated under vacuum. The residue was diluted with water and extracted with EtOAc (3 x 10 mL). The combined organic layer was dried (MgSO₄), filtered, and concentrated under vacuum to afford crude compound **50C** (279 mg, 80% for 3 steps).

In a manner similar to that found in Example 5 (Step 4) and Example 3 (Step 3), compound **50C** was deprotected and converted to the title compound **50**. MS m/z = 332 (MH⁺).

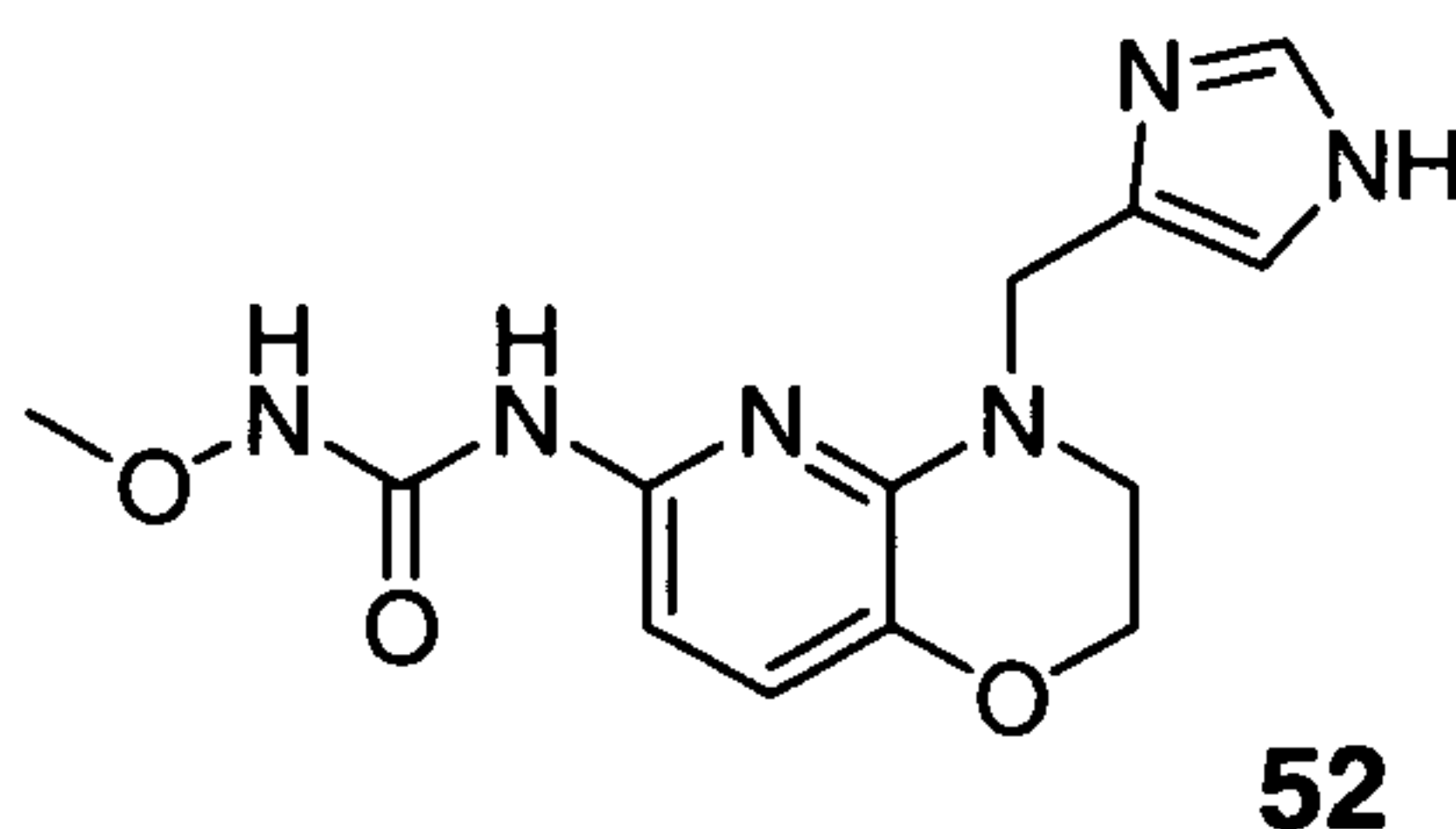
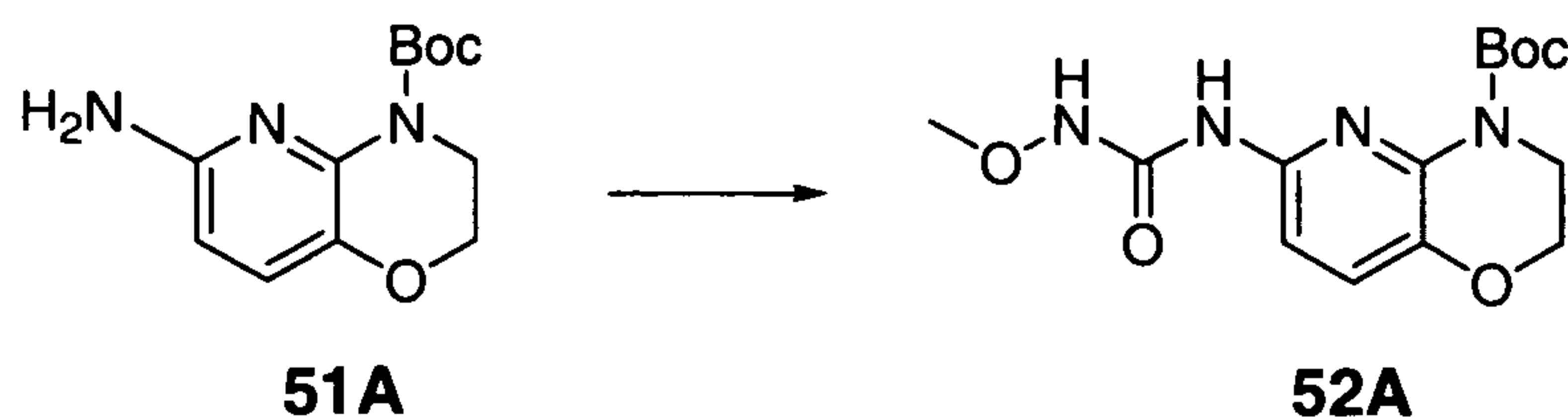
96

PREPARATIVE EXAMPLE 51**Steps 1-4**

In a manner similar to that described in Example 21 (Step 1), Example 3 (Step 2), Example 5 (Step 1) and Example 3 (Step 4), compound **22A** was sequentially nitrated, reduced with $\text{BH}_3\text{-SMe}_2$, treated with Boc_2O , and hydrogenated to yield compound **51A**.

Steps 5-7

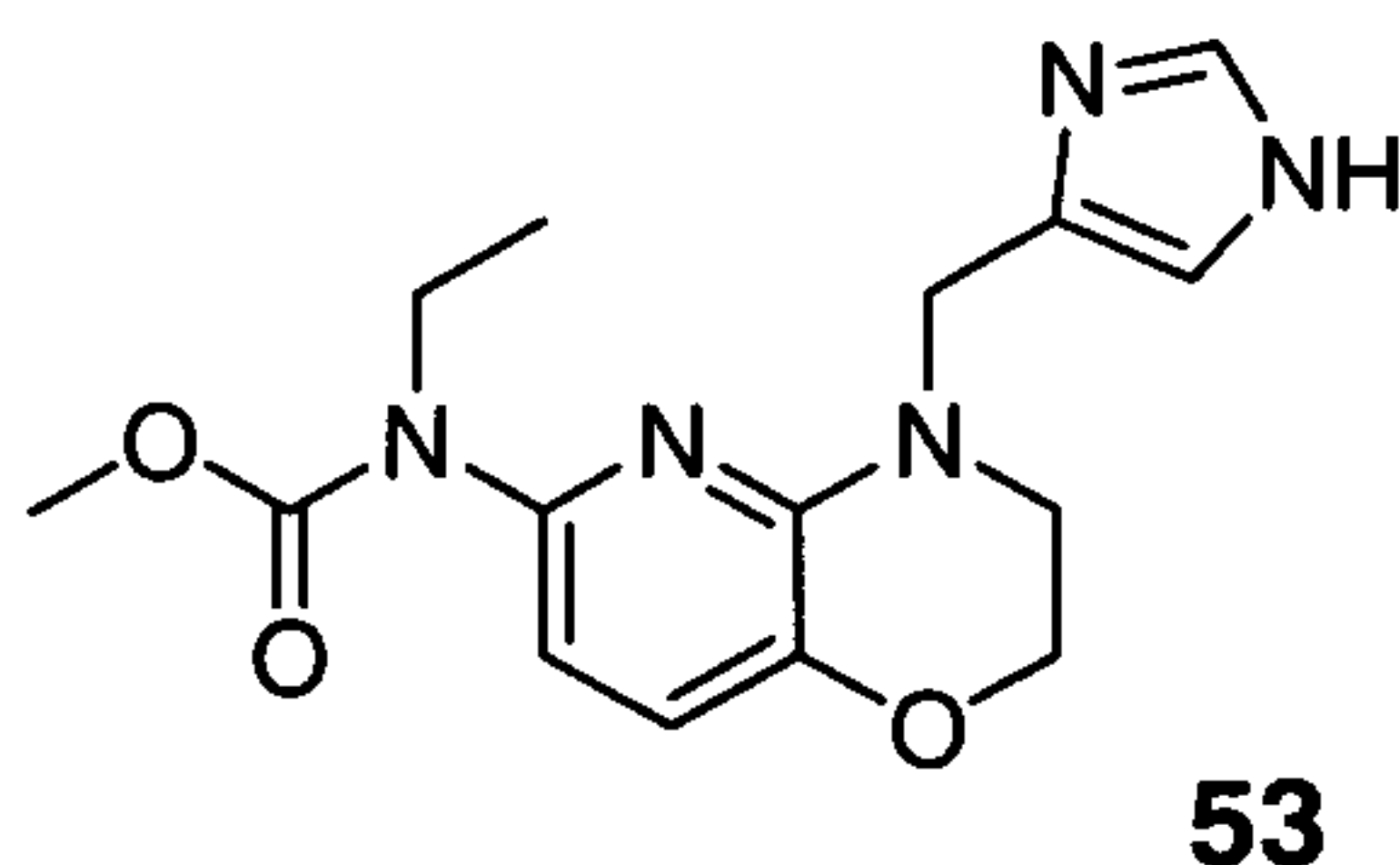
In a manner similar to that described in Example 5 (Steps 3-5), **51A** was treated with MeNCO , deprotected with TFA, and converted to the title compound **51**. MS $m/z = 289$ (MH^+).

PREPARATIVE EXAMPLE 52**Steps 1-3**

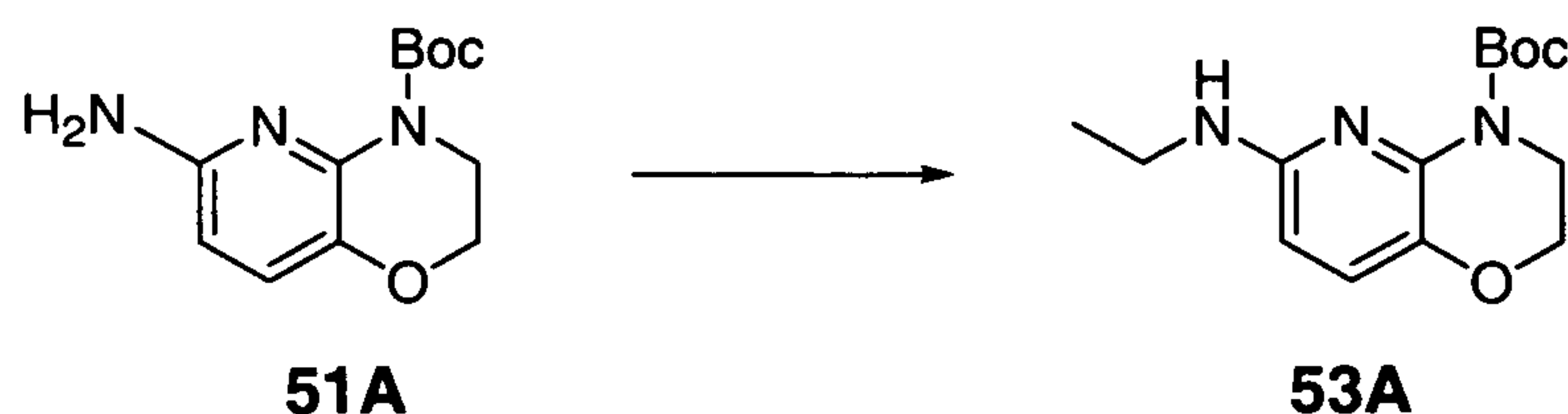
To a solution of **51A** (740 mg, 2.95 mmol) in DCM (30 ml) was added 4-nitrophenylchloroformate (891 mg, 4.42 mmol) and pyridine (0.48 ml, 5.90 mmol). After stirring overnight at RT, TLC indicated consumption of the starting material. MeONH₂-HCl salt (739 mg, 8.84 mmol) in anhydrous THF (10 ml) and DIEA (1.57 mL, 8.84 mmol) were then sequentially added. After stirring at RT overnight, the reaction was quenched by water, concentrated, diluted with water and extracted with EtOAc. The organic phase was dried (MgSO₄), filtered, and concentrated. Flash chromatography (20-50% of EtOAc/hexanes) provided **52A** (650 mg, 68%).

In a manner similar to that found in Example 5 (Step 4) and Example 3 (Step 3), **52A** was converted to **52**. MS m/z = 305 (MH⁺).

PREPARATIVE EXAMPLE 53



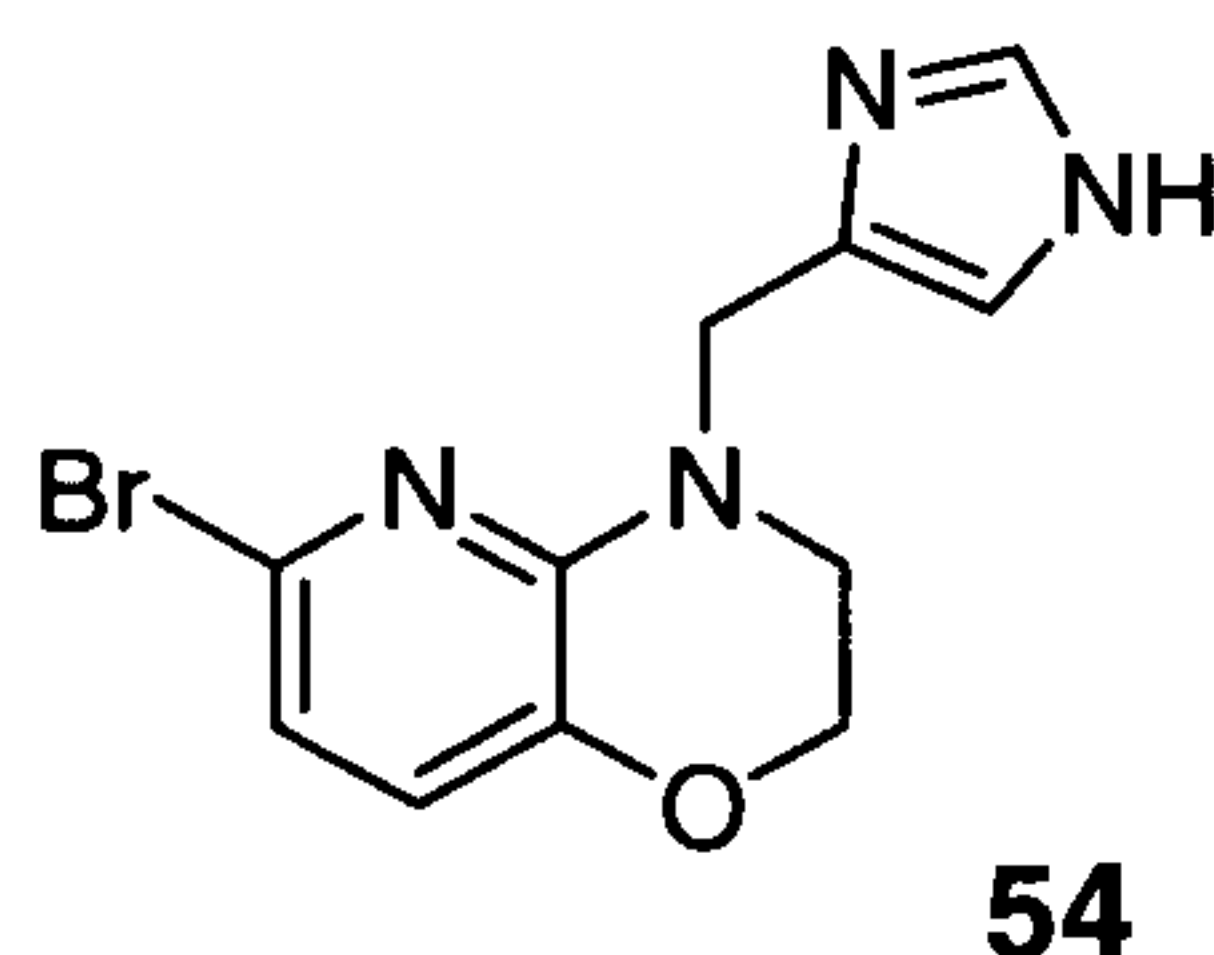
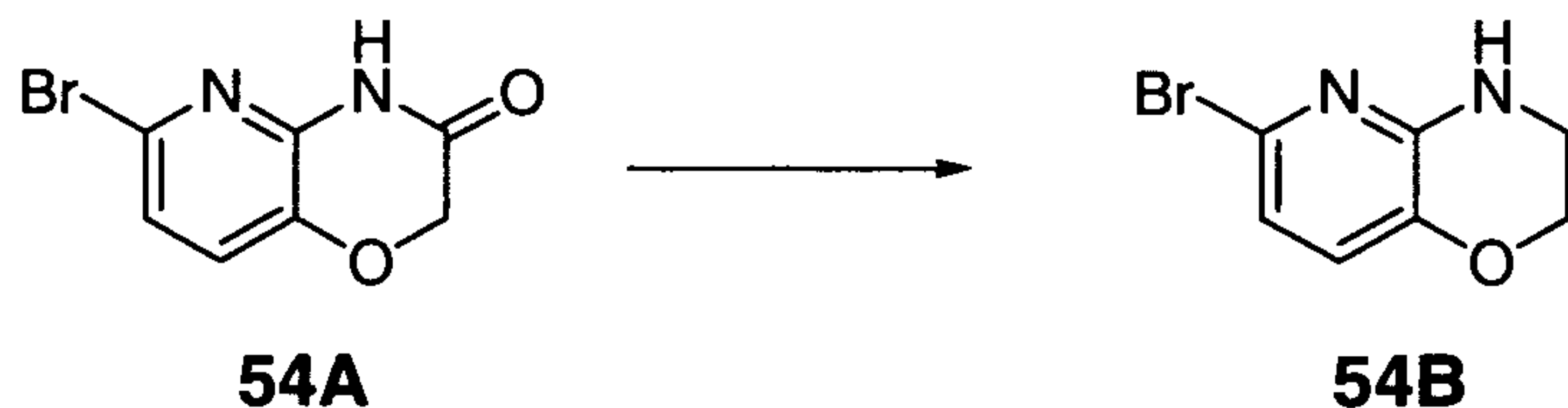
Steps 1-3



To compound **51A** (100 mg, 0.40 mmol) in DCE (5 mL) was added acetaldehyde (0.045 mL, 0.80 mmol). The mixture was stirred at RT for 1 h and then treated with MeOH (3 mL) and NaBH₄ (45.5 mg, 1.2 mmol). After stirring at RT overnight, the reaction was quenched by 2N NaOH solution, concentrated, diluted with water and extracted with EtOAc. The organic phase was dried (MgSO₄), filtered, and concentrated under vacuum to give a residue **53A** (40 mg, 36%).

In a manner similar to that found in Example 3 (Step 5), Example 5 (Step 4) and Example 3 (Step 3), **53A** was treated with ClCO₂Me/pyridine, deprotected with TFA and converted to the title compound **53**. MS m/z = 318 (MH⁺).

98

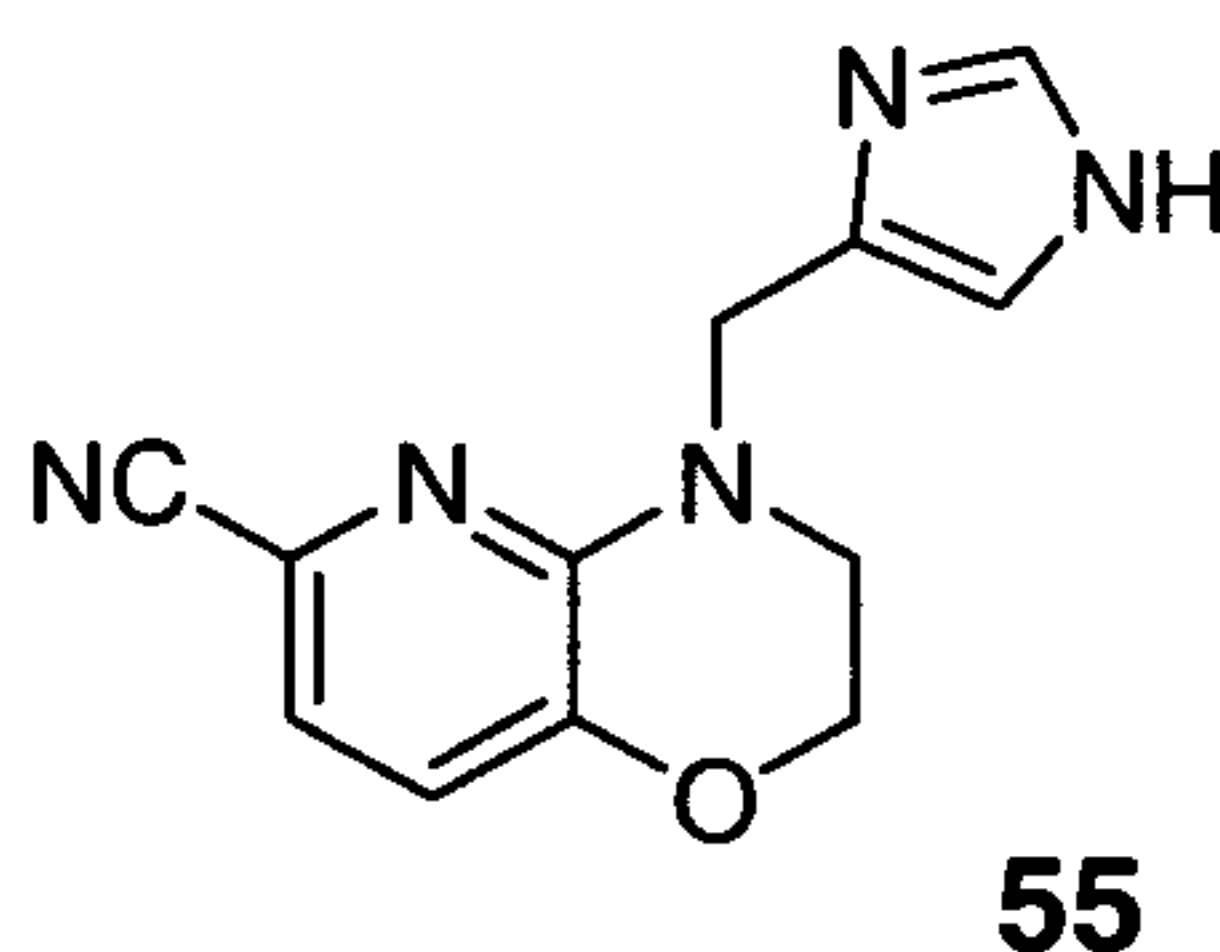
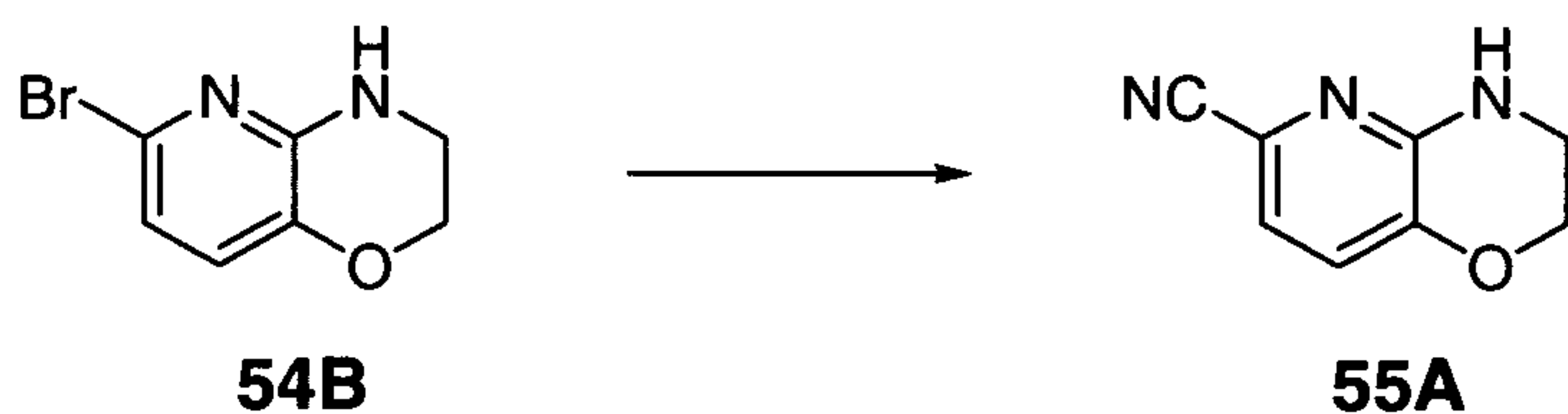
PREPARATIVE EXAMPLE 54**Steps 1-2**

5

In a manner similar to that found in Example 3 (Step 2), compound **54A** (see WO 2006/020561) was reduced with $\text{BH}_3\text{-SMe}_2$ to provide **54B**.

Compound **54B** was then elaborated into **54** (MS $m/z = 295$, MH^+) as previously described in Example 3 (Step 3).

10

PREPARATIVE EXAMPLE 55**Steps 1-2**

15

A Smith process vial was charged with a stir bar, compound **54B** (0.33 g, 1.54 mmol), CuCN (0.276 g, 3.08 mmol) and DMF (3 mL). The reaction vessel was sealed and heated to 120°C for 3 h under microwave irradiation. After cooling, the reaction mixture was transferred to a round bottom flask and concentrated under vacuum.

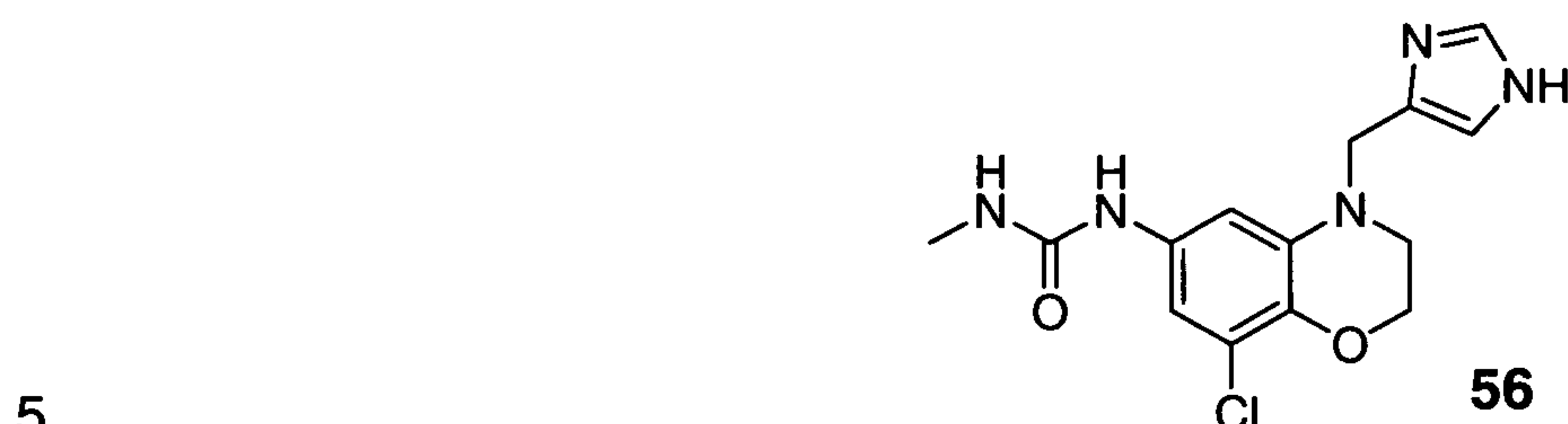
Compound **55A** was obtained quantitatively by continuous extraction with EtOAc in a Soxhlet apparatus.

20

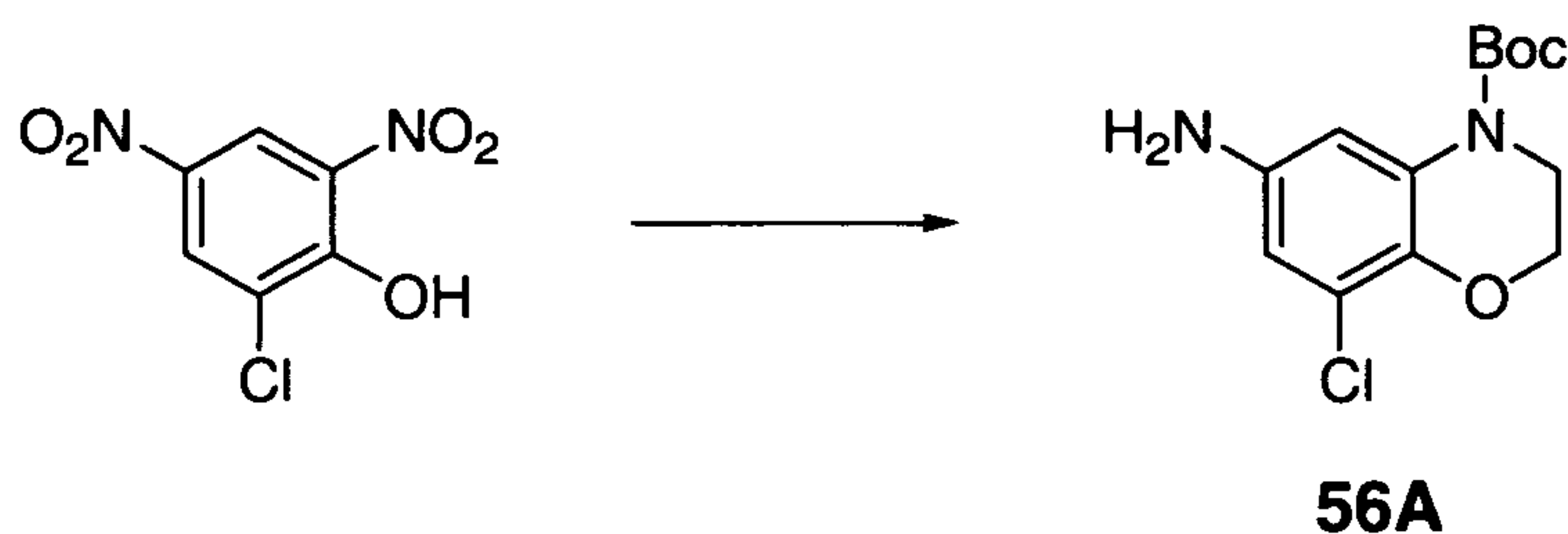
99

Compound **55A** was then elaborated into **55** (MS m/z = 242, MH^+) as previously described in Example 3 (Step 3).

PREPARATIVE EXAMPLE 56

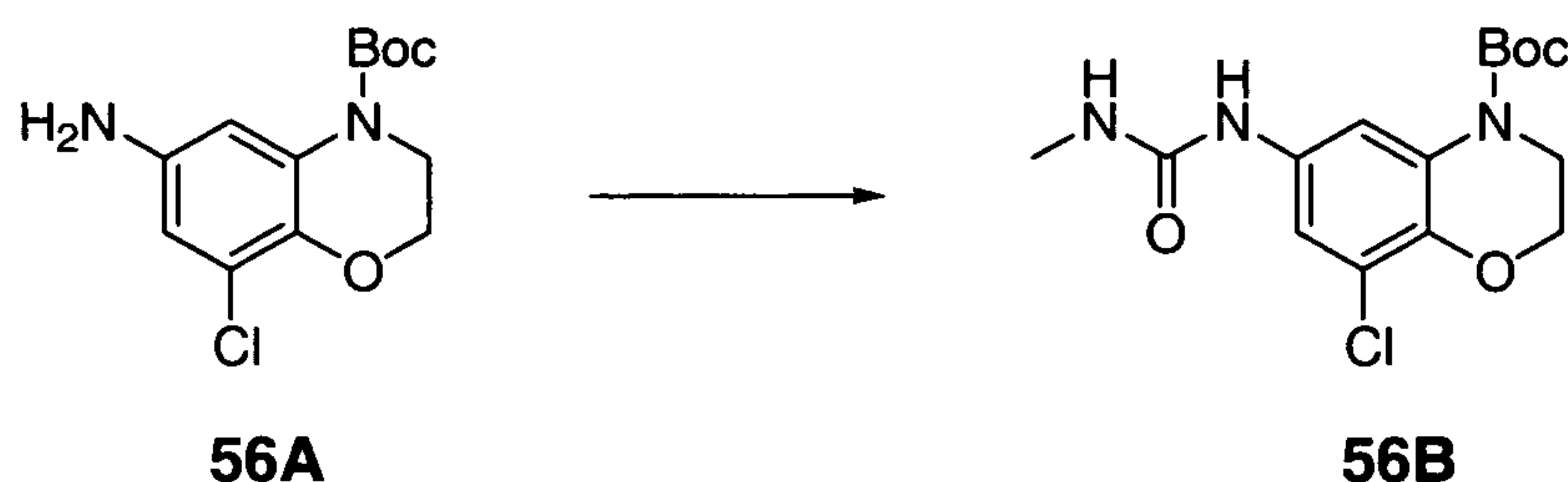


Steps 1-5



10 In a manner similar to that previously described, 2-chloro-4,6-dinitrophenol was sequentially reduced with $SnCl_2$ (Example 19, Step 2), treated with chloroacetyl chloride, reduced with BH_3-SMe_2 (Example 3, Steps 1-2), protected with Boc_2O (Example 5, Step 1), and reduced again with $SnCl_2$ to yield compound **56A**.

Steps 6-8



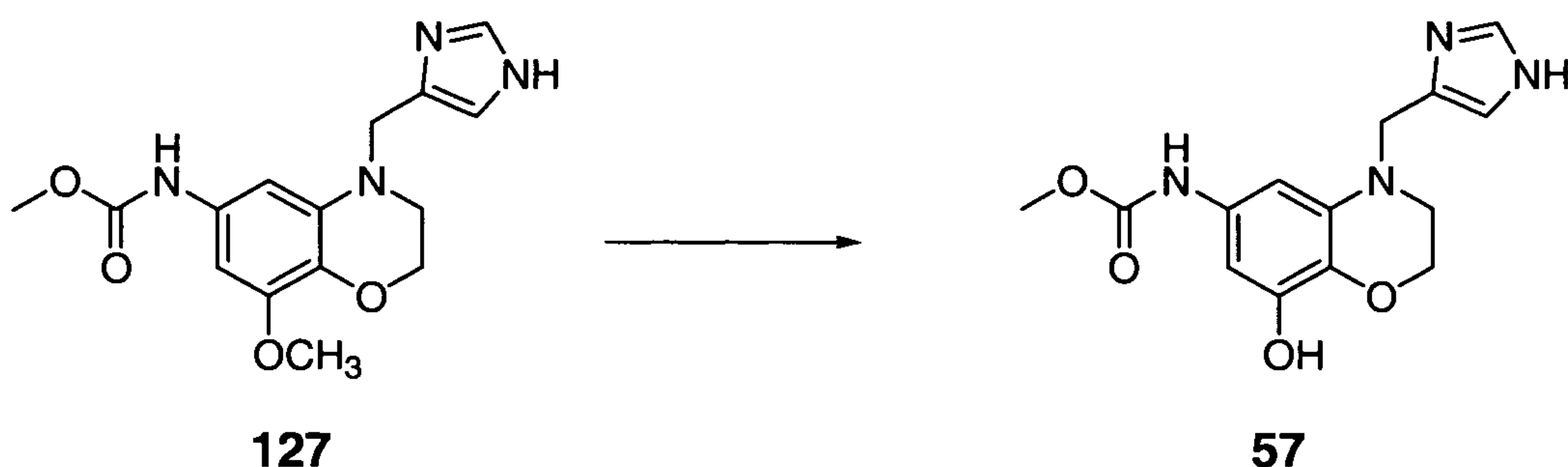
15 To a solution of compound **56A** (0.29 g, 1 mmol) in anhydrous DCM (3 ml) was added 4-nitrophenylchloroformate (0.24 g, 1.2 mmol) and pyridine (0.13 ml, 1.57 mmol). After stirring overnight at RT, the reaction was quenched with sat. NH_4Cl solution and extracted with DCM. The organic phase was then concentrated. A solution of this residue in CH_3CN (5 mL) was treated with 40% $MeNH_2$ in H_2O (20 mL) and heated in a sealed tube at 90 °C overnight. The mixture was cooled, stirred at RT overnight, and then quenched with water. The reaction was concentrated, diluted with

20

water and extracted with EtOAc. The organic phase was dried (MgSO₄), filtered, and concentrated to give **56B**.

As described previously in Example 5 (Step 4) and Example 3 (Step 3), **56B** was deprotected and converted to **56**. MS m/z = 322 (MH⁺).

PREPARATIVE EXAMPLE 57



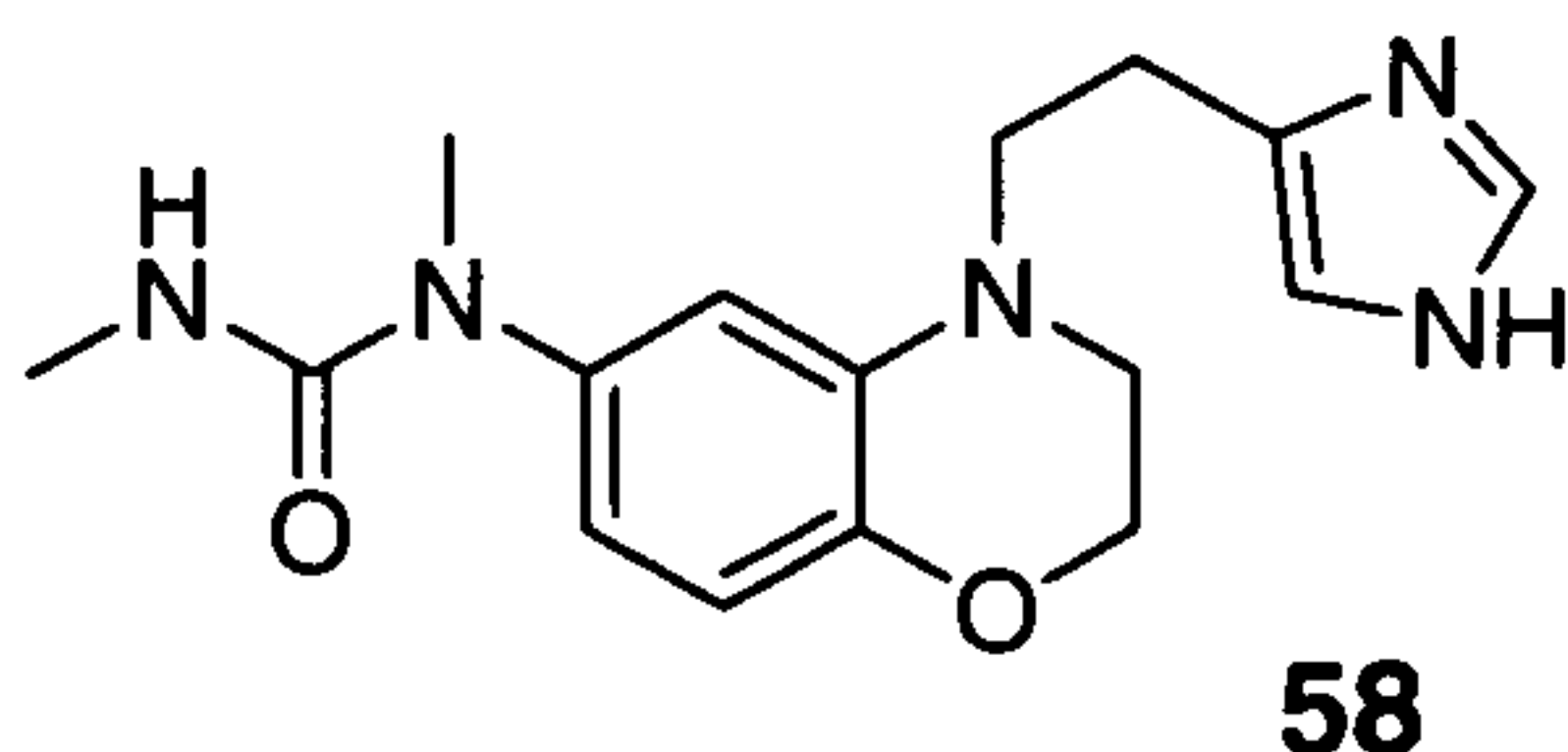
10

Compound **127** (0.388 g, 1.22 mmol) was dissolved in anhydrous DCM (10 mL) and cooled to -78 °C. To this solution was added 1.0M BBr₃ in DCM (6.1 mL) dropwise. The reaction mixture was stirred at -78 °C for 30 min and then at RT for 3 h. The reaction was quenched with water and neutralized with 2N NaOH solution.

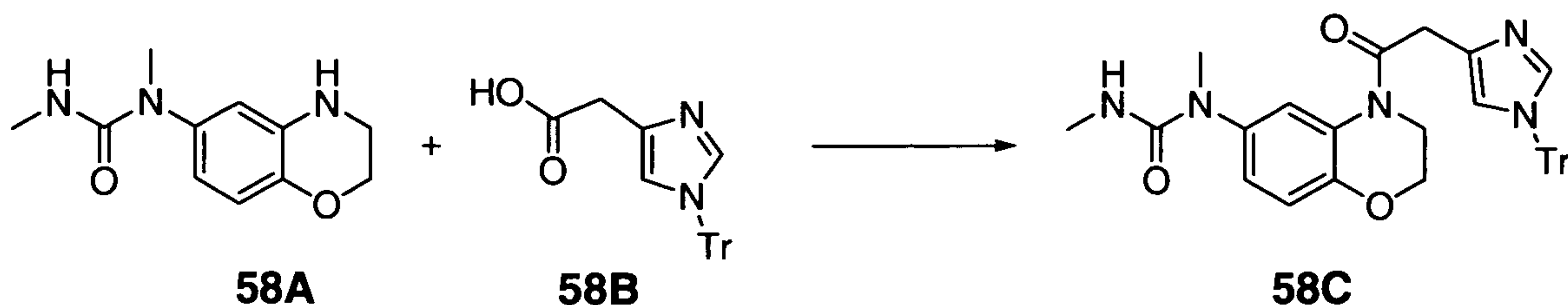
The mixture was separated and the aqueous phase was extracted with DCM (3 x 10 mL). The organic phase was dried (MgSO₄), filtered, and concentrated under vacuum. The residue was purified by flash column chromatography (DCM containing 2 to 8% of 7N NH₃ in MeOH) to afford compound **57** in 30% yield. MS m/z = 305 (MH⁺).

20

PREPARATIVE EXAMPLE 58



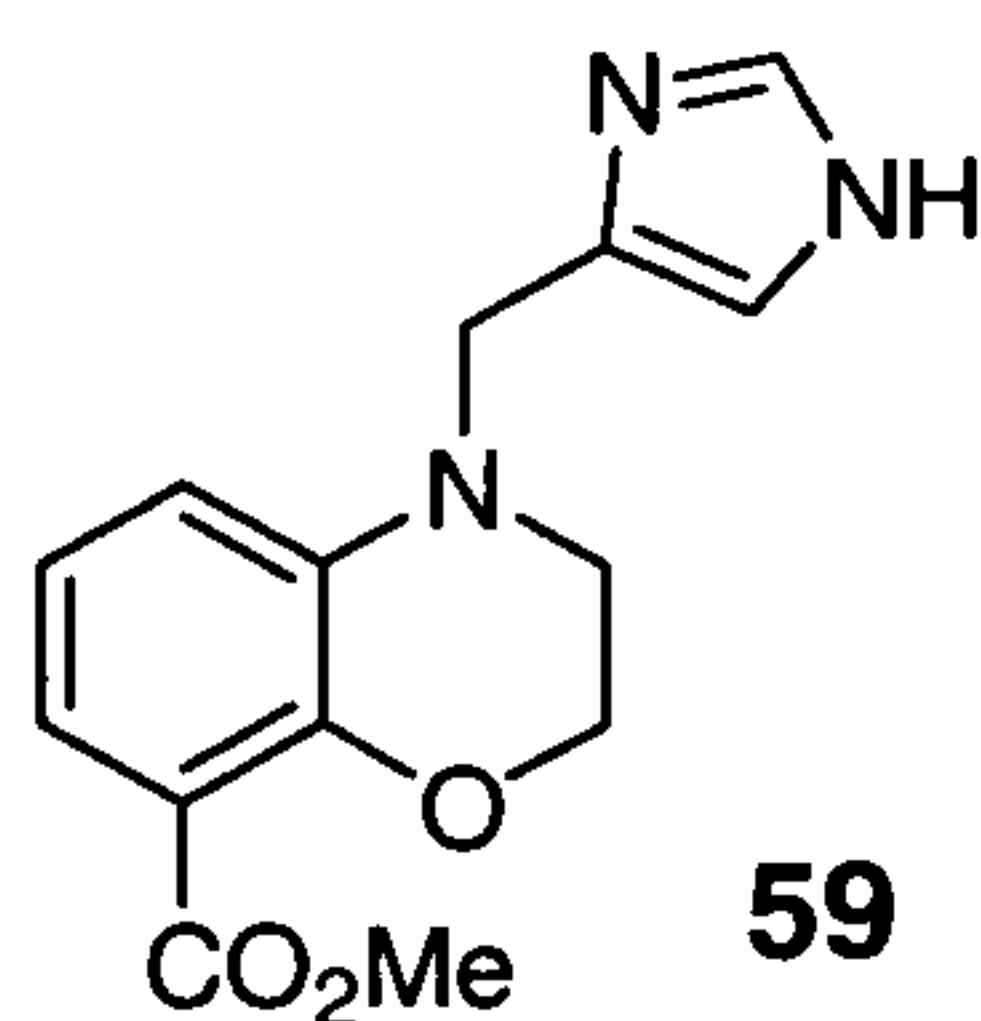
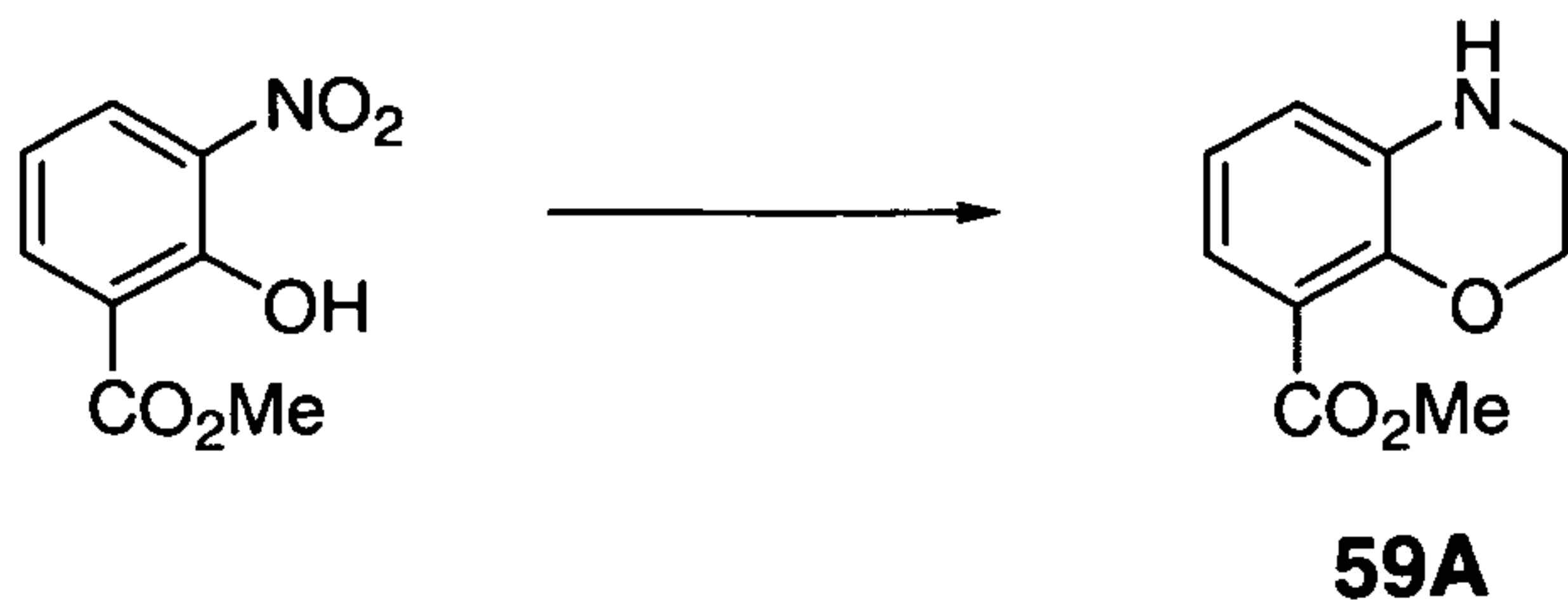
101

Step 1

In a manner similar to that described in Example 37, compound **58A** (prepared in Example 6) and **58B** (Bioconjugate Chemistry, 13, 333-350, 2002) were reacted with HATU to provide **58C**. MS m/z = 572 (MH^+)

Steps 2-3

A solution of **58C** (720 mg, 1.3 mmol) in THF (50 mL) was treated with $BH_3 \cdot SMe_2$ (5 mL, 2 M in THF) and heated at 80 °C for 12 h. After it was cooled to 25 °C, MeOH (15 mL) was added dropwise until bubbling ceased. The solvent was removed and partitioned between EtOAc and water. The organic phase was dried over Na_2SO_4 and concentrated. The crude residue was stirred in DCM/TFA (1:3, 5 mL) at 25 °C for 4 h. Solvent was removed and the residue was partitioned between EtOAc and water. The organic phase was dried and concentrated. Column chromatography and preparative TLC (DCM containing 5% of 7N $NH_3/MeOH$) gave **58**. MS m/z = 316 (MH^+).

PREPARATIVE EXAMPLE 59**Steps 1-3**

In a manner similar to that described in Example 3 (Step 4 then Steps 1-2), methyl 2-hydroxy-3-nitrobenzoate was sequentially hydrogenated, treated with chloroacetylchloride, and reduced with $\text{BH}_3\text{-SMe}_2$ to yield compound **59A**.

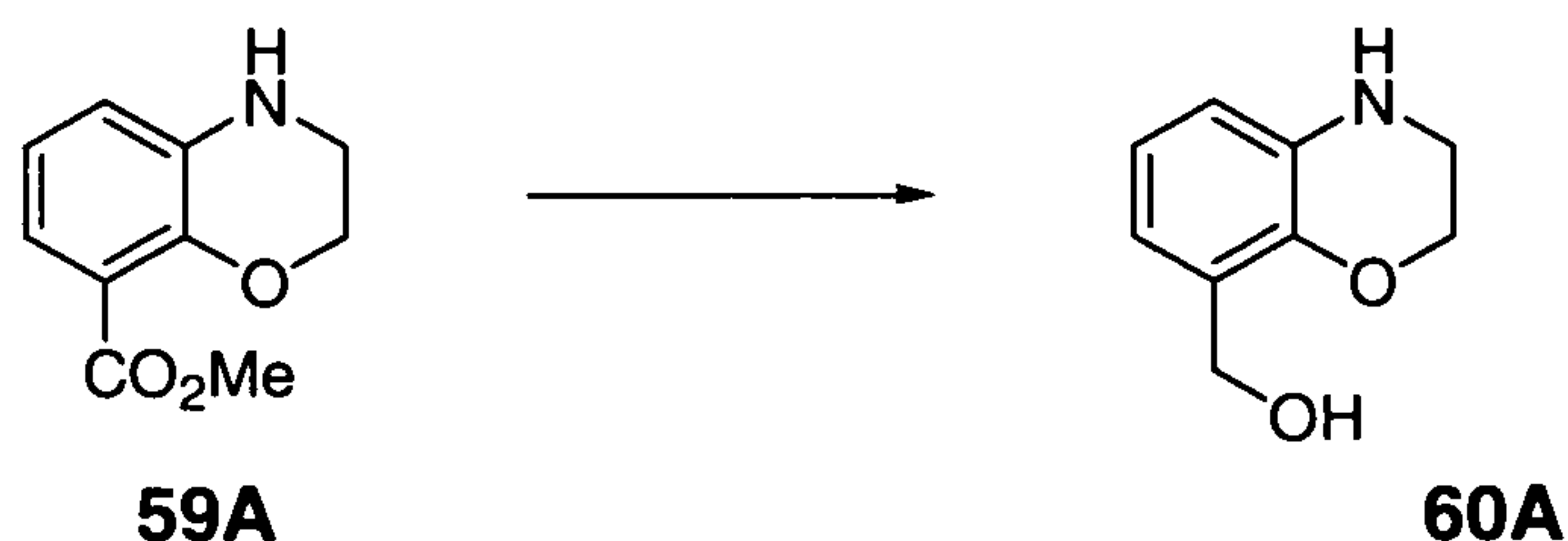
5 Step 4

Compound **59A** was treated with 4-imidazolecarboxaldehyde to afford the title compound **59** in a manner similar to that described in Example 3 (Step 3). MS m/z = 274 (MH^+).

10 PREPARATIVE EXAMPLE 60



Steps 1-2

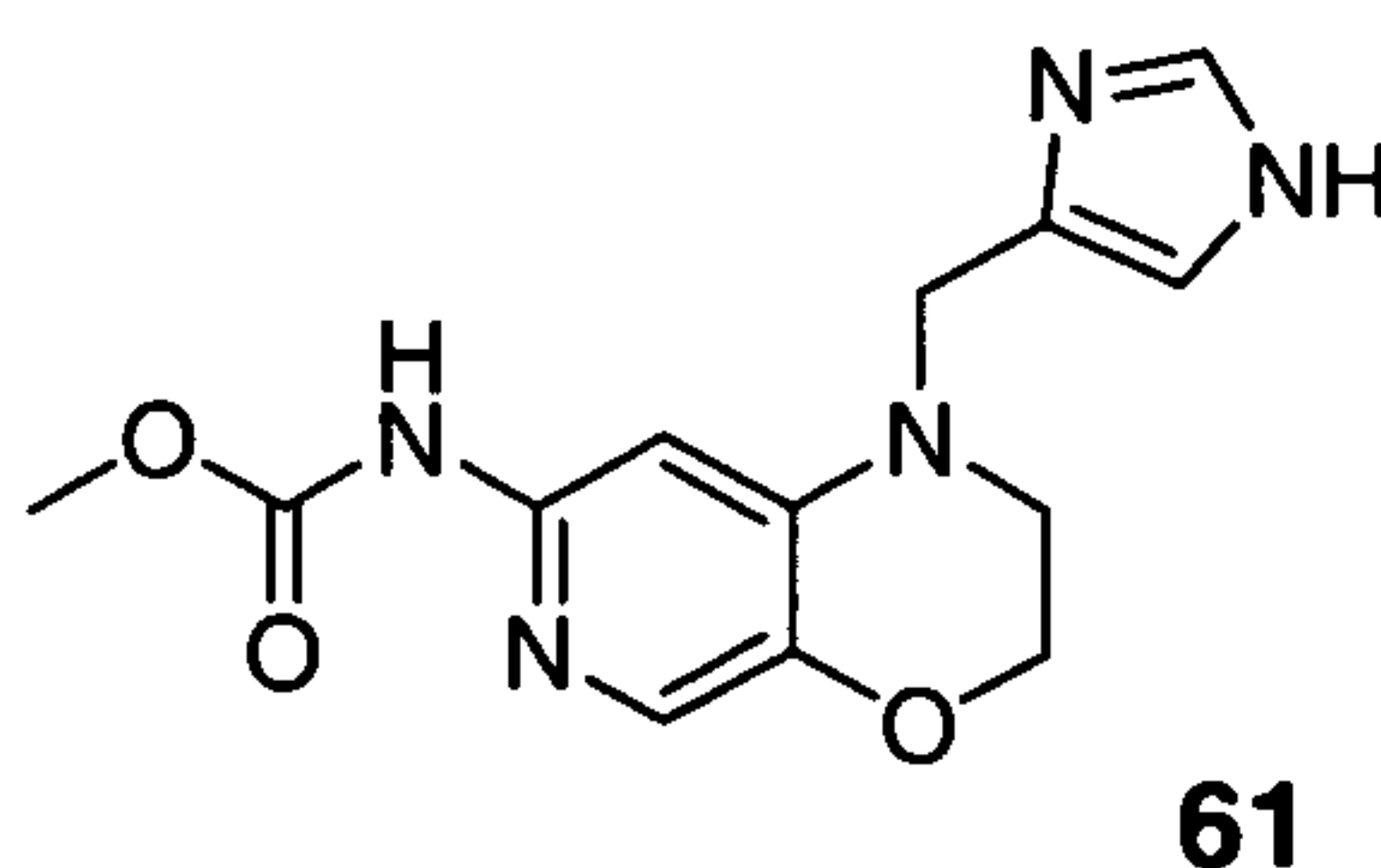


15 A mixture of LiBH_4 (44 mg, 2 mmol) and **59A** (400 mg, 2 mmol) in THF (50 mL) was stirred at RT for 4 h and then concentrated. The residue was partitioned between EtOAc and water. The organic phase was dried and concentrated to give **60A** (300 mg, 91%).

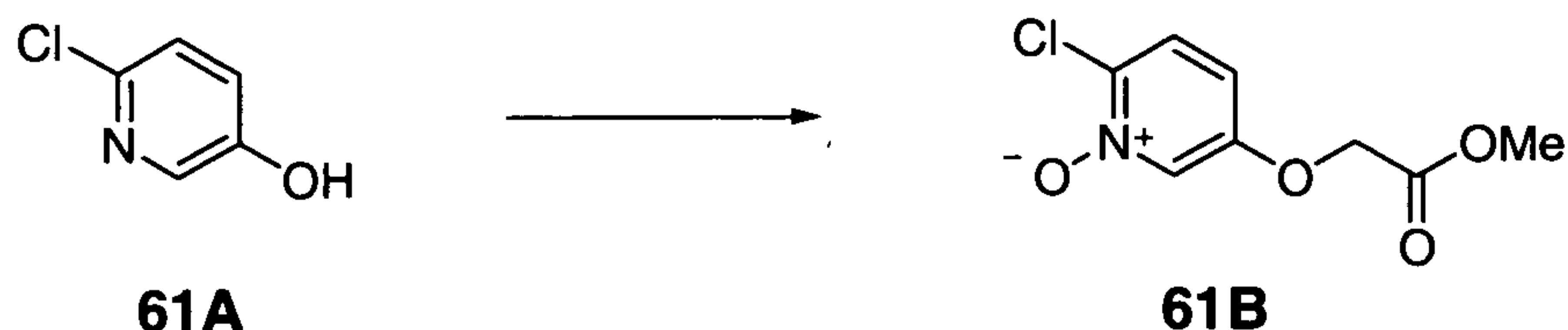
Compound **60A** was converted to **60** in a manner similar to that described in Example 3 (Step 3). MS m/z = 246 (MH^+).

20

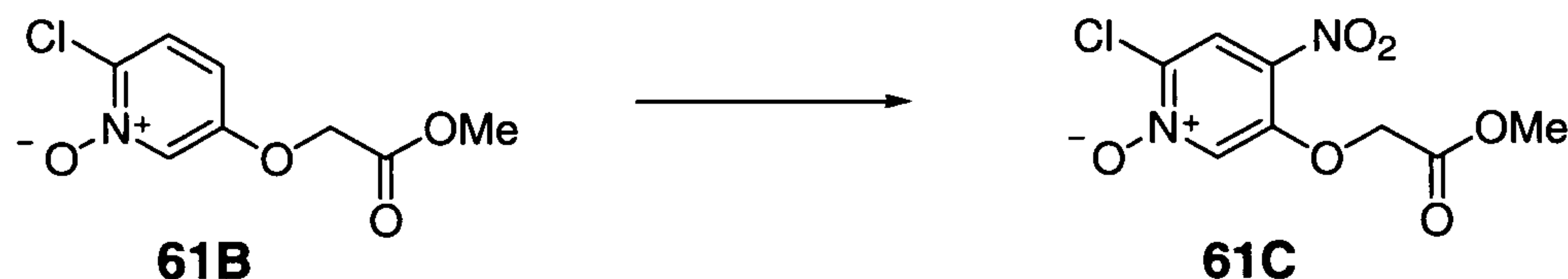
PREPARATIVE EXAMPLE 61



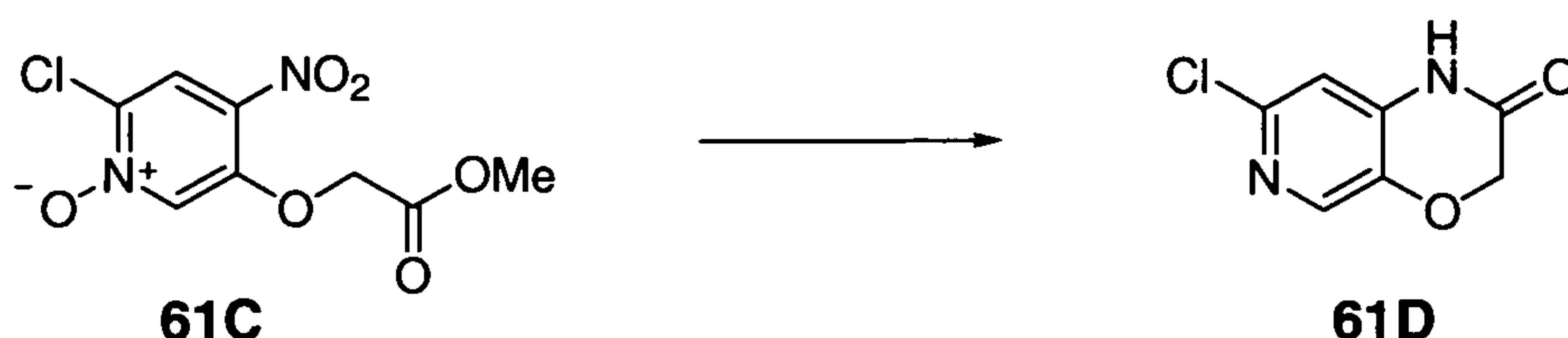
103

Steps 1-2

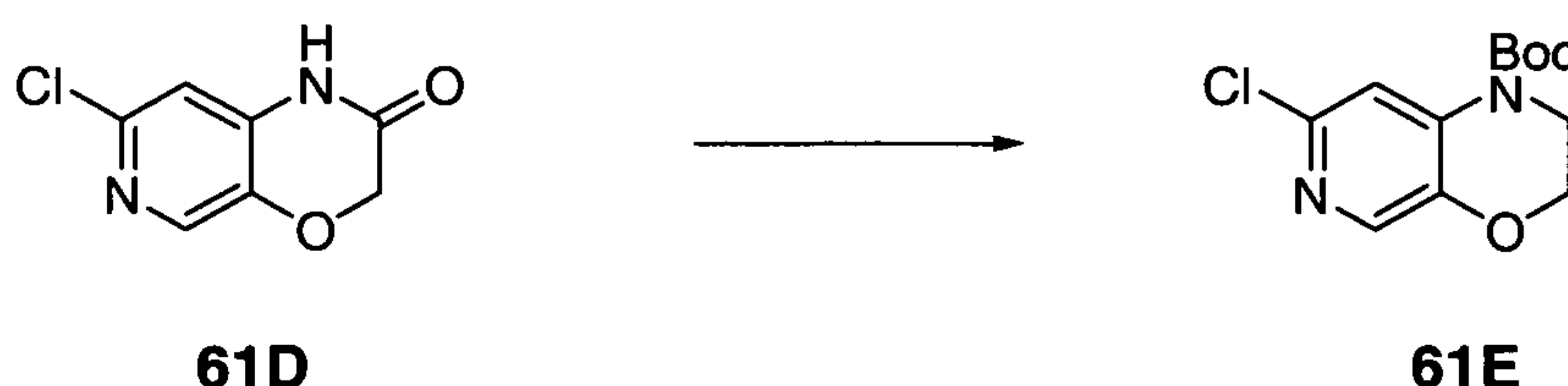
To 2-chloro-5-hydroxypyridine (**61A**) in acetone (80 mL) was added K_2CO_3 (8.96 g, 65 mmol) and methylchloroacetate (2.54 mL, 29 mmol). The mixture was heated at 60 °C for 4 h. After cooling to RT, the mixture was filtered, and the solids were washed with acetone (50 mL). The filtrate was concentrated *in vacuo* to give 4.3 g intermediate (92% yield). The intermediate (4.3 g, 21.3 mmol) was dissolved in $CHCl_3$ (75 mL) and treated with m-chloroperbenzoic acid (4.78 g, 27.7 mmol). The resulting solution was heated at 50 °C for 4 h, then stirred at RT overnight. The mixture was treated with sodium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (5%-10% MeOH in DCM) provided **61B** (3.46 g, 75%).

Steps 3-4

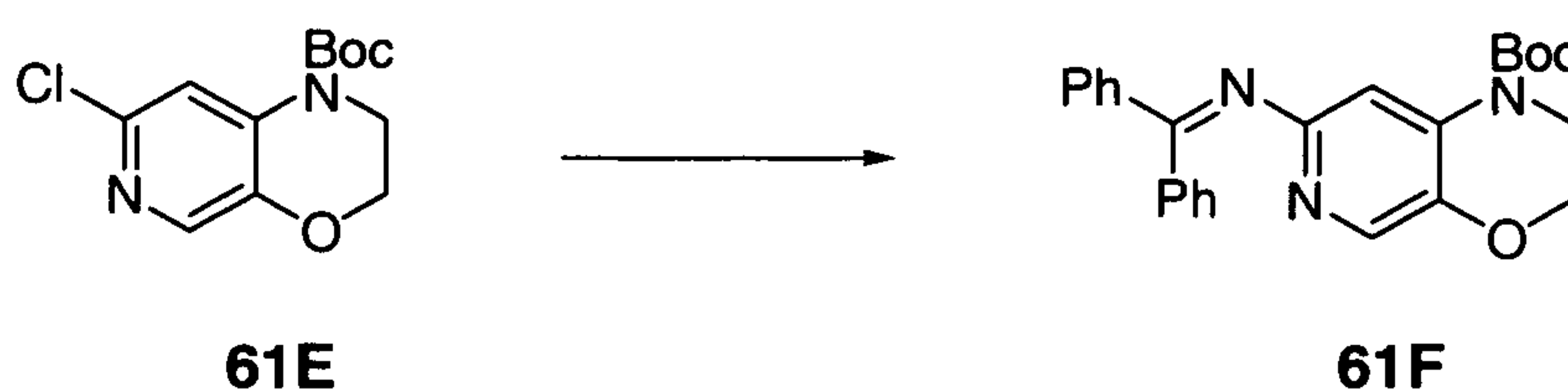
The N-oxide **61B** (1.0 g, 4.61 mmol) was dissolved in H_2SO_4 (2 mL) at 0 °C. HNO_3 (1 mL) was added slowly over several minutes. The reaction mixture was then placed in an oil bath heated to 40 °C. The temperature was slowly raised to 75 °C over 1 h and then maintained there for 2 h. The mixture was then poured over ice and adjusted to pH 9 by the addition of 50% NaOH. Water was removed *in vacuo*, and the resultant solids were washed with MeOH to yield crude nitro pyridine N-oxide intermediate (2.6 g). A portion of this intermediate (1.33 g, 5.3 mmol) was dissolved in MeOH (50 mL) and treated with H_2SO_4 (1 mL). The mixture was heated at 70 °C for 2 h and then concentrated. The residue was treated with 1N NaOH (20 mL) and EtOAc (50 mL). The solution was extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to give compound **61C** (1.4 g, 100%).

Steps 5-6

- 5 A mixture of **61C** (0.06 g, 0.23 mmol) in MeOH (2 mL) was treated with iron powder (0.09 g, 1.61 mmol) and HOAc (0.08 mL). The resulting solution was heated at 70 °C for 4 h. The hot solution was filtered through a pad of celite and concentrated. The residue was taken up in MeOH (2 mL) and treated with K₂CO₃ (0.073 g, 0.53 mmol). After heating at 65 °C for 2 h, the solvent was removed *in vacuo* and the product purified by preparative TLC (5% MeOH in DCM) to give
- 10 compound **61D** (0.032 g, 76%).

Steps 7-8

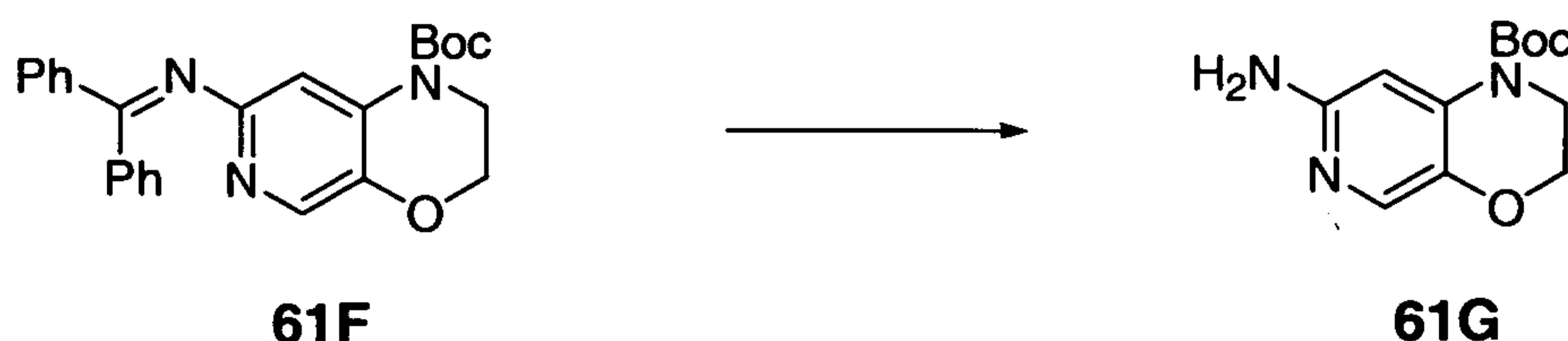
- 15 In a manner similar to that found in Example 3 (Step 2) and Example 5 (Step 1), compound **61D** was reduced and protected to give compound **61E**.

Step 9

- 20 A mixture of **61E** (0.250 g, 0.91 mmol), benzophenoneimine (0.152 mL, 0.91 mmol), tris(dibenzylideneacetone dipalladium(0) (0.004 g, 0.0045 mmol), rac-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene (0.004 g, 0.007 mmol), and NaOtBu (0.088g, 0.91 mmol) in toluene (8 mL) in a culture tube was heated in a rotating oven at 80 °C overnight. After cooling to RT, the contents were transferred to a round-

bottomed flask and treated with several scoops of silica gel. The solvent was removed *in vacuo* and the product purified by flash column chromatography (10% to 50% EtOAc-hexanes) to give **61F** (0.205 g, 54%).

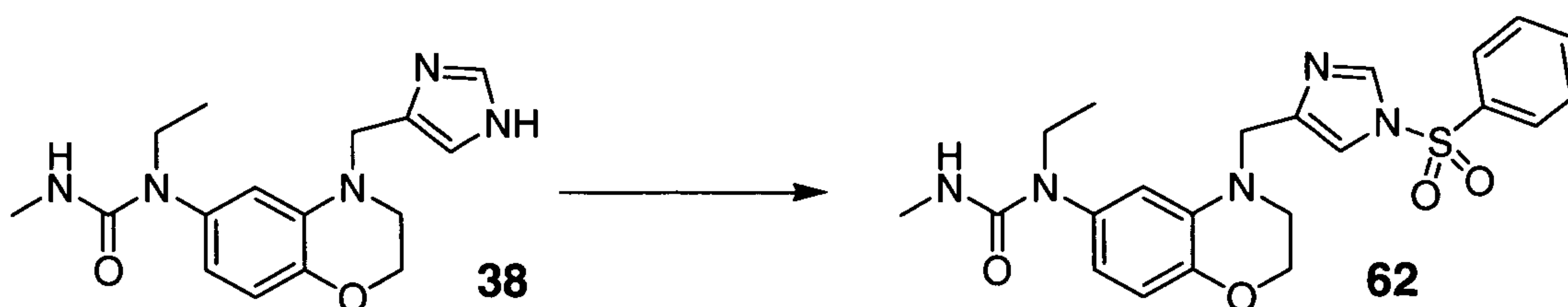
5 Steps 10-13



A mixture of **61F** (0.205 g, 0.5 mmol) in THF (4 mL) was treated with 15% aqueous citric acid solution (4 mL). The resulting solution was stirred at RT overnight. Saturated aqueous NaHCO₃ (5 mL) was added and the solution was extracted with EtOAc (2 x 25 mL). The organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The product was purified by flash column chromatography (10% to 50% EtOAc-hexanes) to give **61G** (0.114g, 91%).

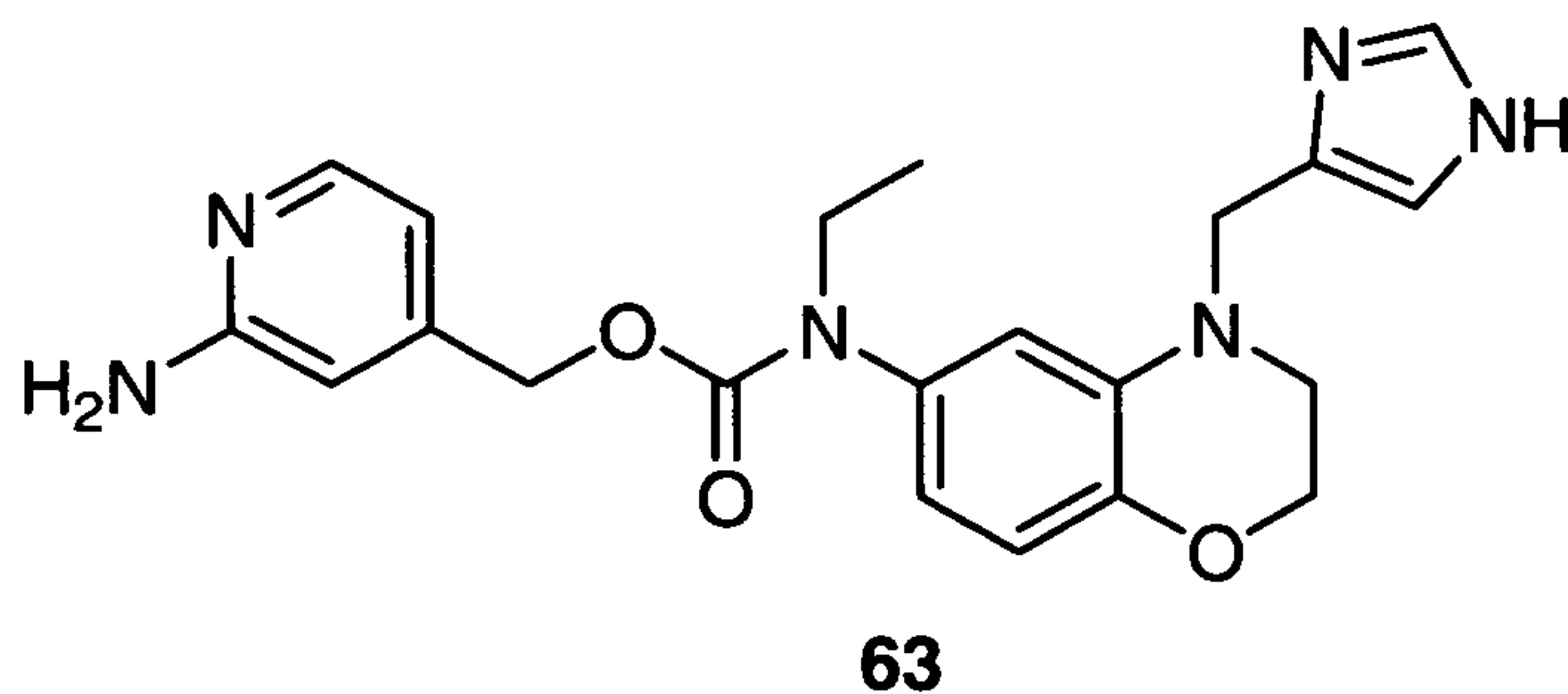
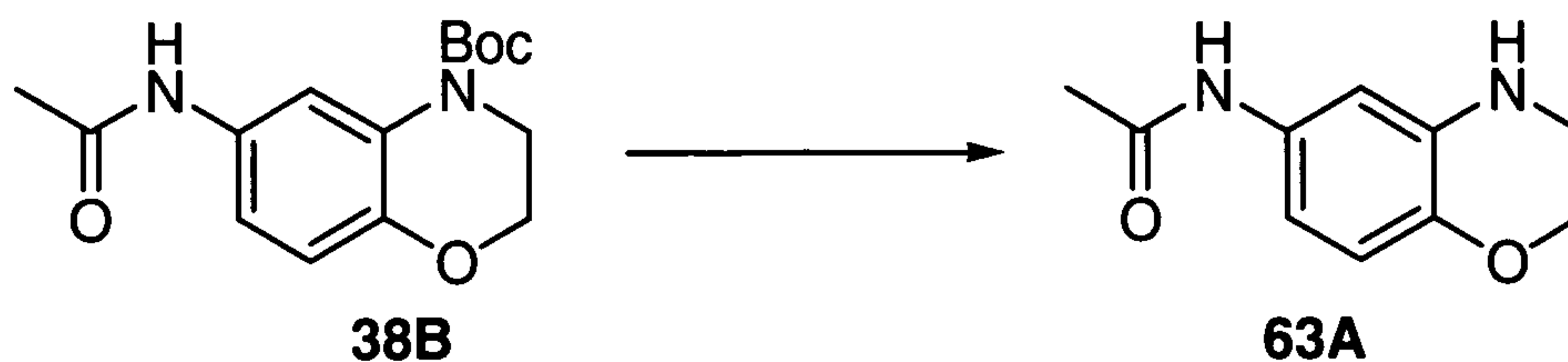
In a manner similar to that found in Example 3 (Step 5), Example 5 (Step 4) and Example 3 (Step 3), compound **61G** was sequentially treated with ClCO₂Me, deprotected and converted the title compound **61**. MS *m/z* = 290 (MH⁺).

PREPARATIVE EXAMPLE 62

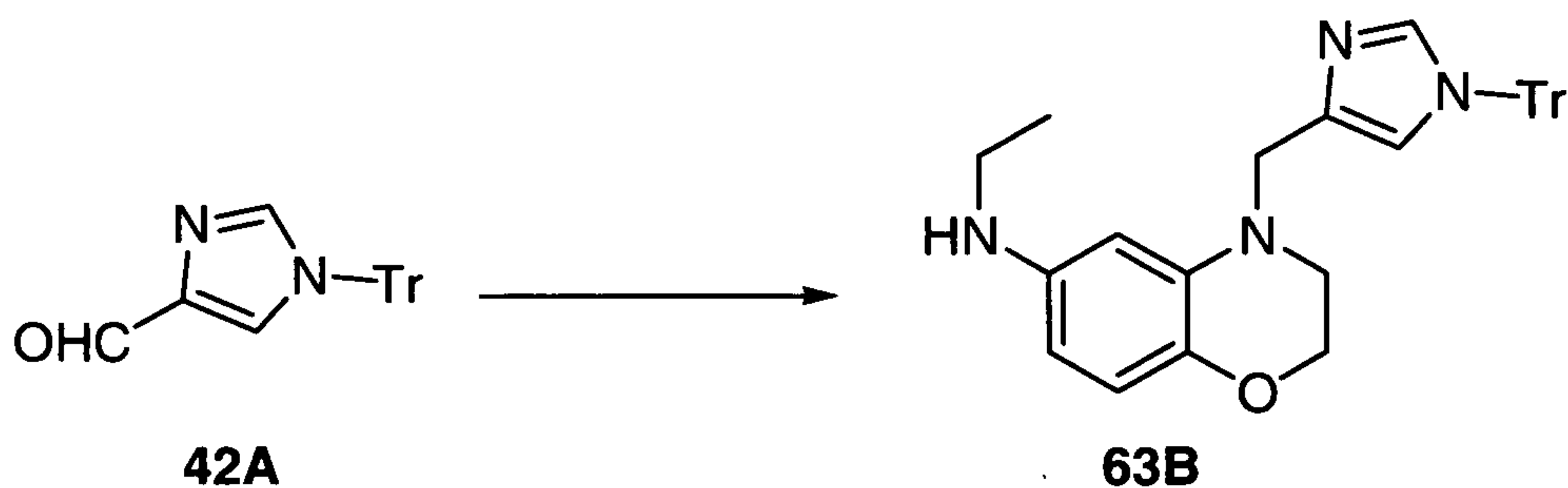


A slurry of **38** in anhydrous DCE (4 ml) and anhydrous THF (4 ml) was treated with anhydrous TEA (0.2 ml) followed by benzenesulfonyl chloride (0.070 mL). After 2 h at RT, additional benzenesulfonyl (0.2 mL) was added. The mixture was stirred for 1 h, then diluted with CH₂Cl₂, washed with brine, dried (Na₂SO₄), and concentrated. Preparative TLC chromatography (9% MeOH/CH₂Cl₂) afforded **62** (43 mg).

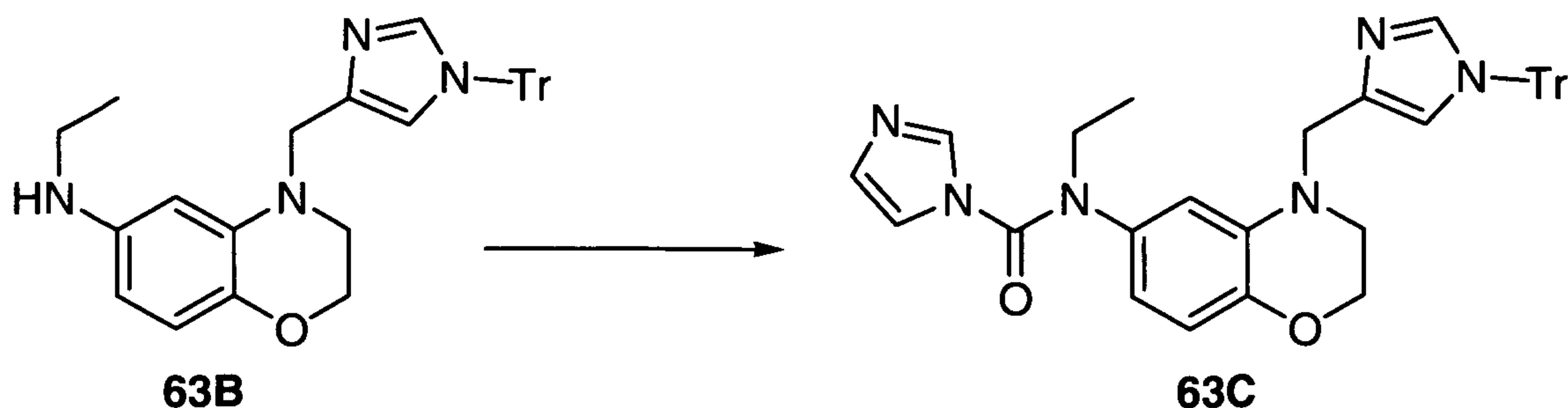
106

PREPARATIVE EXAMPLE 63**Step 1**

5 In a manner similar to that found in Example 38 (Step 6), **38B** was sequentially deprotected with TFA to provide **63A**.

Steps 2-3

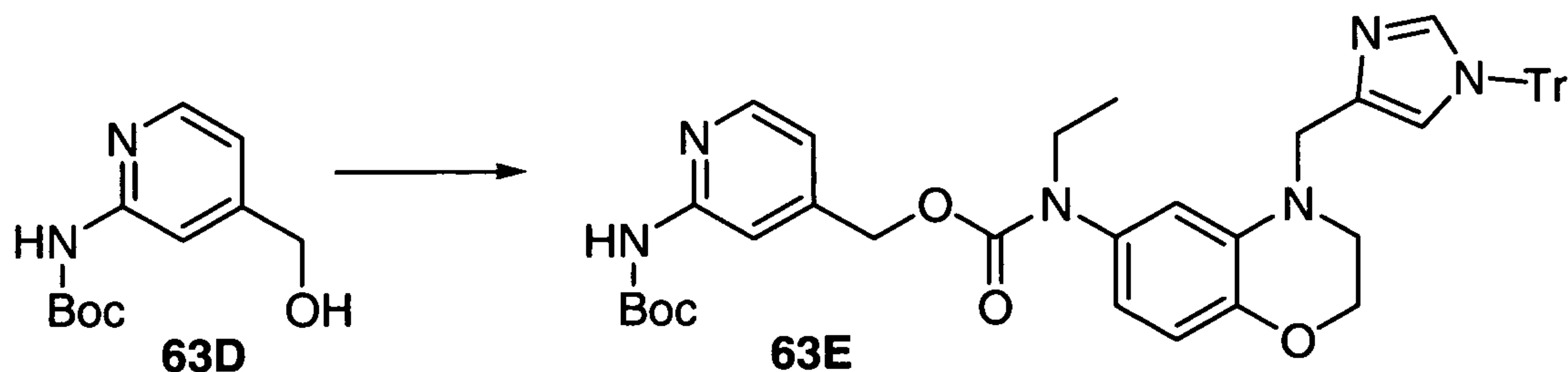
10 In a manner similar to that found in Example 3 (Step 3) and Example 26 (Step 3), **42A** (Journal of Medicinal Chemistry, **1971**, 14, 883) was sequentially treated with **63A**/ $\text{NaBH}(\text{OAc})_3$, and then reduced with LAH in THF to provide **63B**.

Step 4

15

In a manner similar to that found in Example 50 (Step 5), **63B** was reacted with carbonyldiimidazole to provide **63C**.

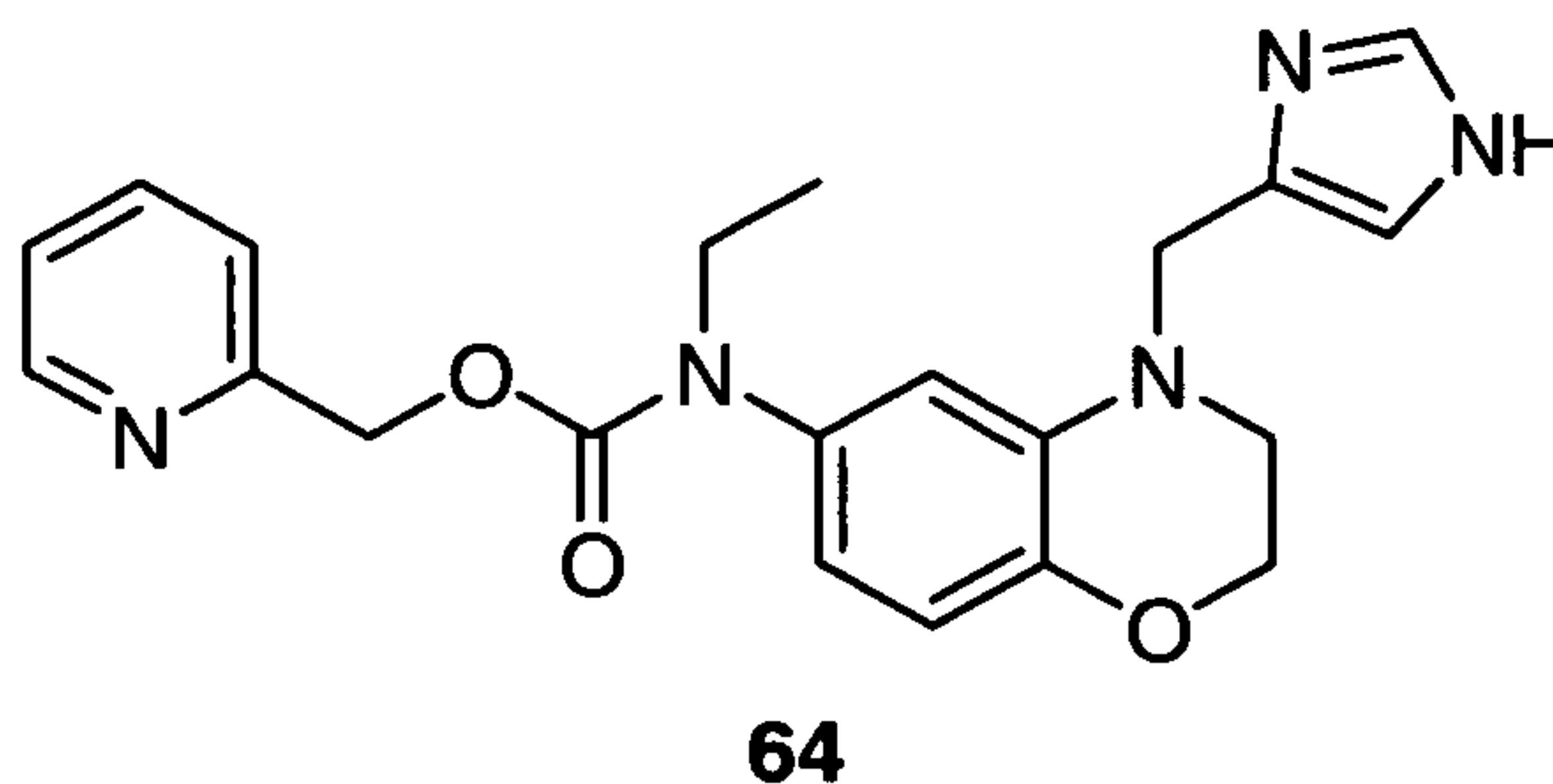
5 Steps 5-6



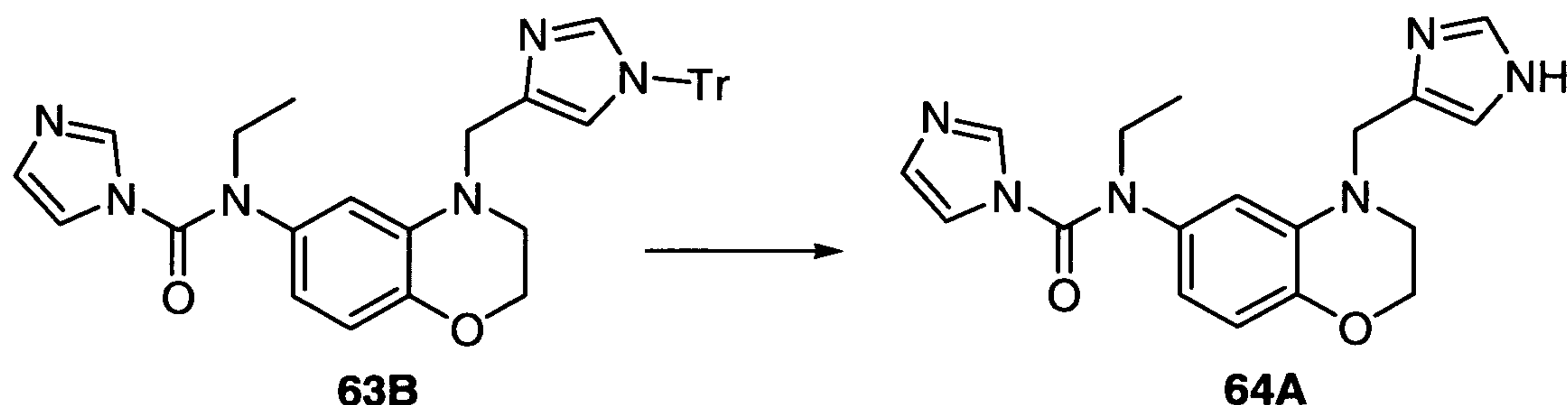
A solution of **63D** (188 mg, 0.84 mmol, PCT WO2002032893) in THF (4 mL) at 20 °C was treated with NaHMDS (340 μ L, 1.68 mmol), stirred for 1h, and then treated with **63C** (100 mg, 0.17 mmol). After stirring overnight, the solution was diluted with NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic phase was concentrated in vacuo to provide **63E**.

This product was then treated with TFA/Et₃SiH to provide the title compound **63** in a manner similar to that found in Example 42 (Step 3). LCMS m/z 409 (MH⁺).

PREPARATIVE EXAMPLE 64



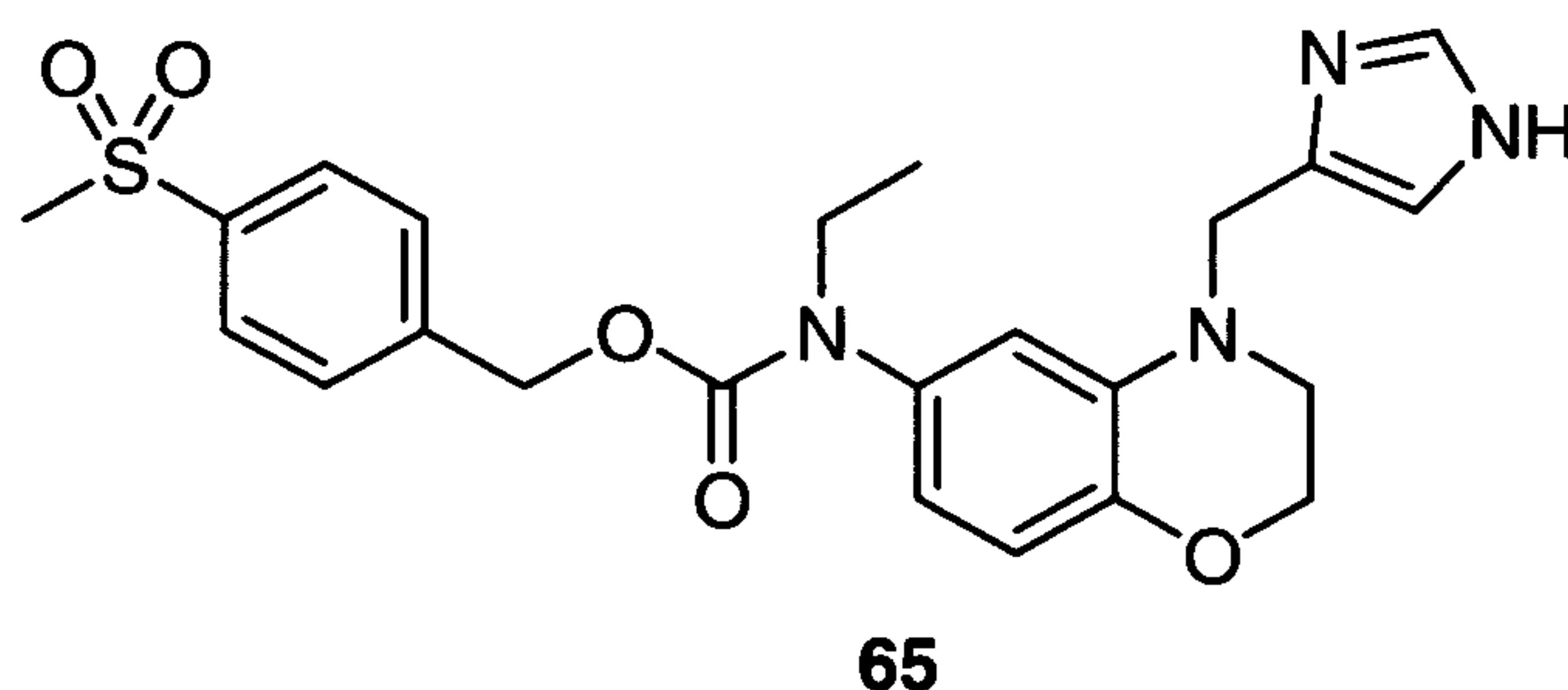
Steps 1-2



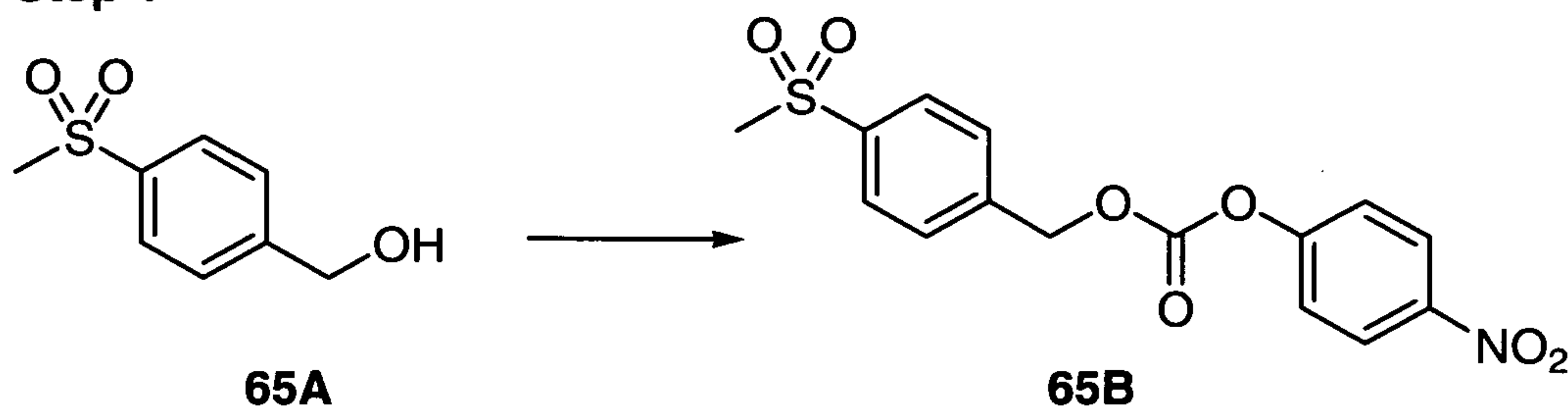
In a manner similar to that found in Example 42 (Step 3), **63C** was treated with
5 TFA/Et₃SiH to provide **64A**. LCMS m/z 353 (MH⁺).

This product was then treated with NaHMDS and pyridine-2-methanol, as described in Example 63 (Step 5) to provide the title compound **64**. LCMS m/z 394 (MH⁺).

PREPARATIVE EXAMPLE 65

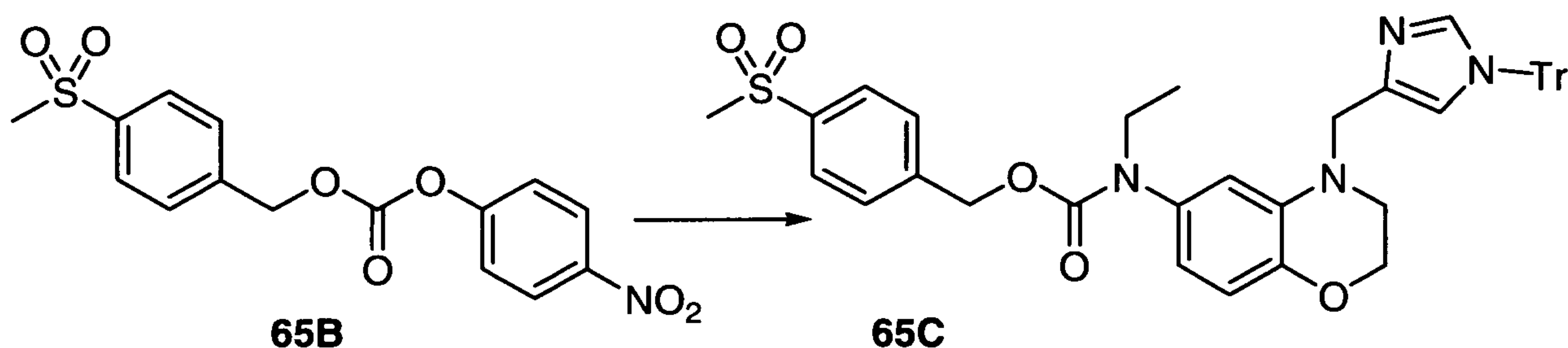


Step 1



A solution of 4-(methylsulfonyl)benzyl alcohol (**65A**, 150 mg, 0.81 mmol) in THF (3 mL) at 20 °C was treated with 4-nitrophenyl chloroformate (162 mg, 0.81 mmol) and pyridine (66 μ L, 0.81 mmol). The mixture was stirred overnight and then partitioned between EtOAc and water. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated to provide **65B**.

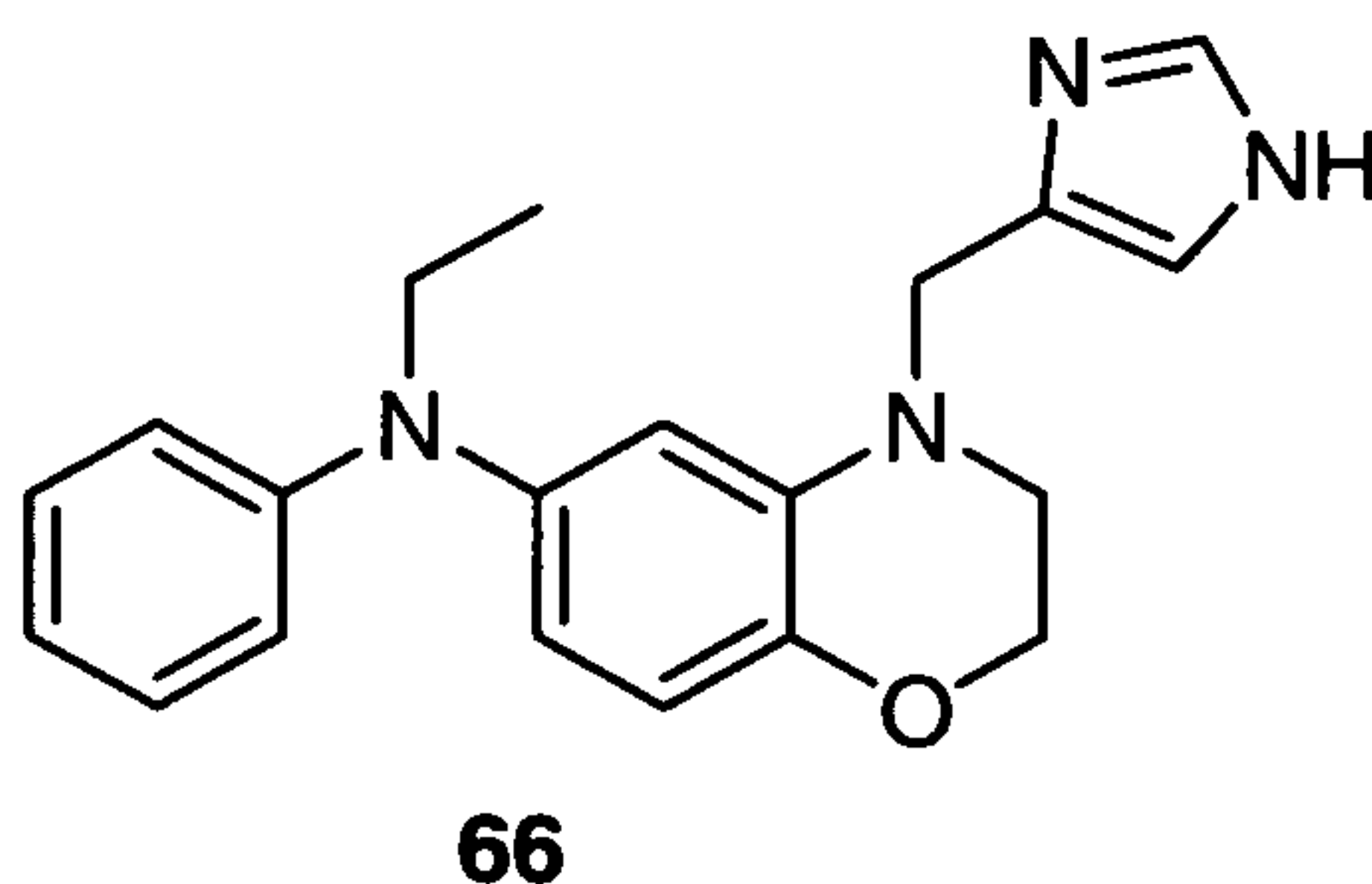
Steps 2-3



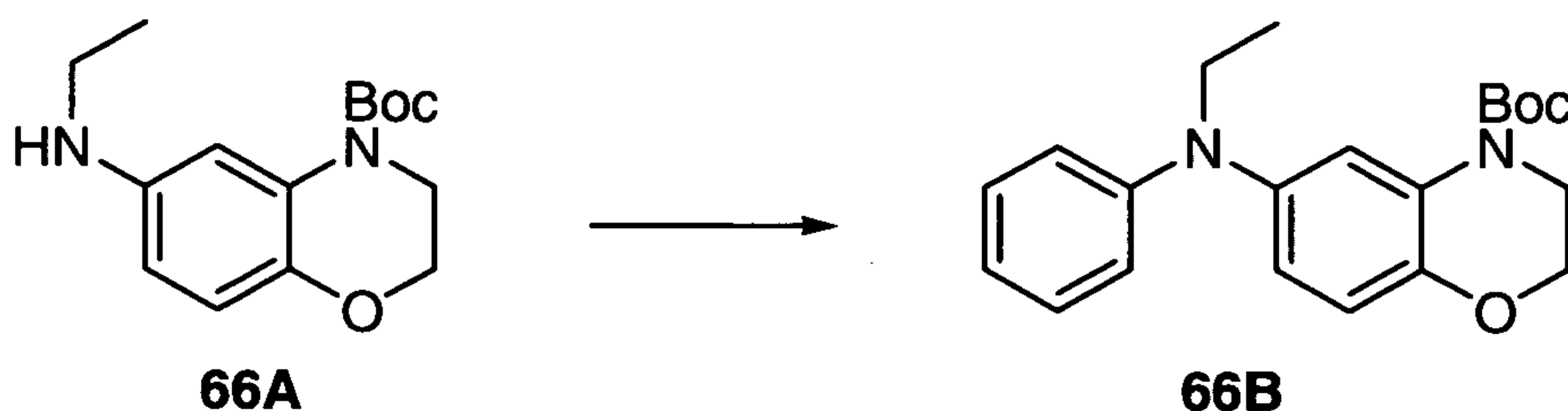
A solution of **65B** (crude material from previous step) in THF (3 mL) was treated with **63B** (160 mg, 0.34 mmol) and pyridine (66 mL, 0.81 mmol). After stirring for 2d at 20 °C, the mixture was diluted with CH₂Cl₂, washed with saturated aqueous NaHCO₃, and concentrated to provide **65C**.

This product was then deprotected with TFA to provide the title compound **65** in a manner similar to that found in Example 42 (Step 3). LCMS m/z 471 (MH⁺).

10 PREPARATIVE EXAMPLE 66



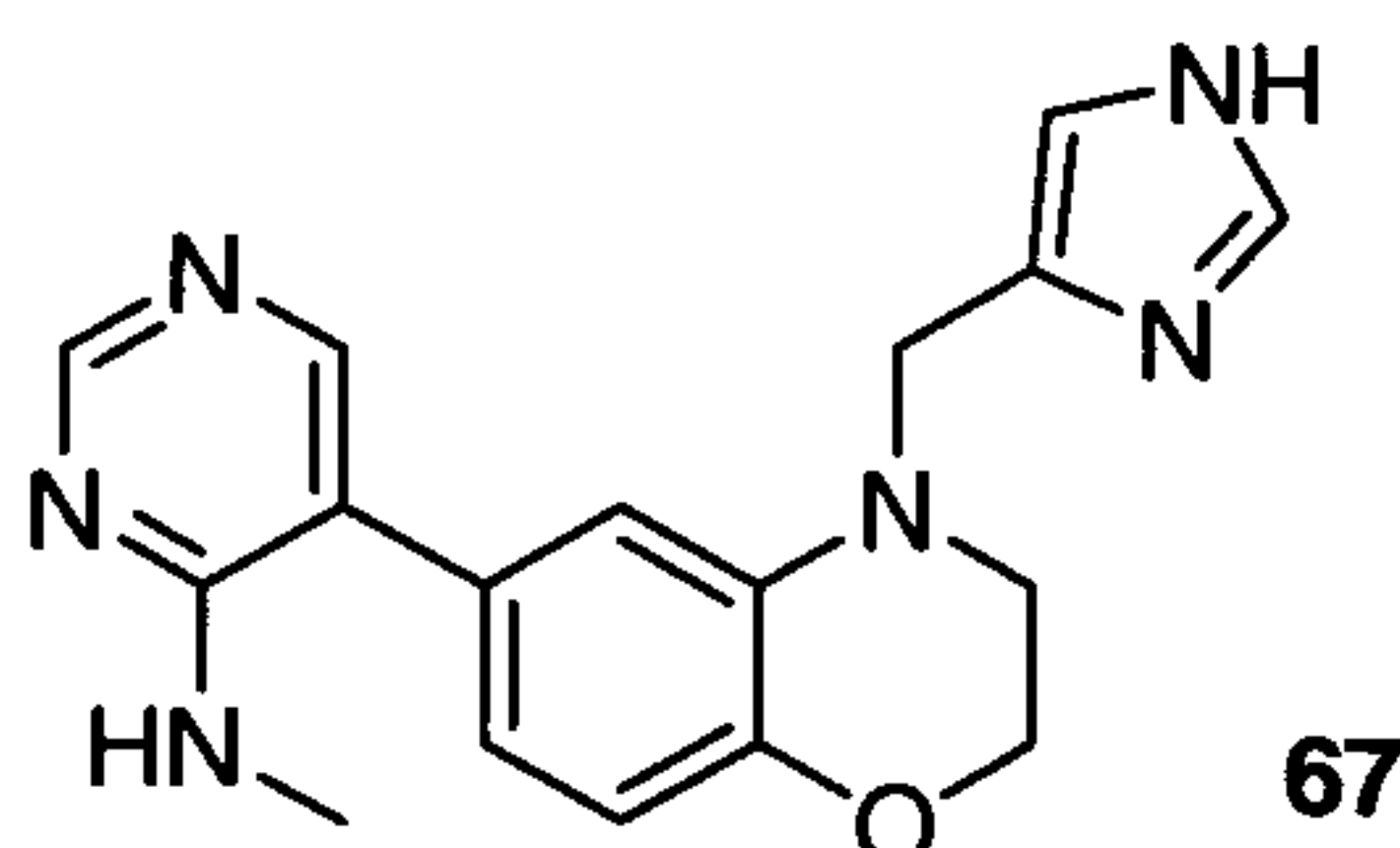
Steps 1-3



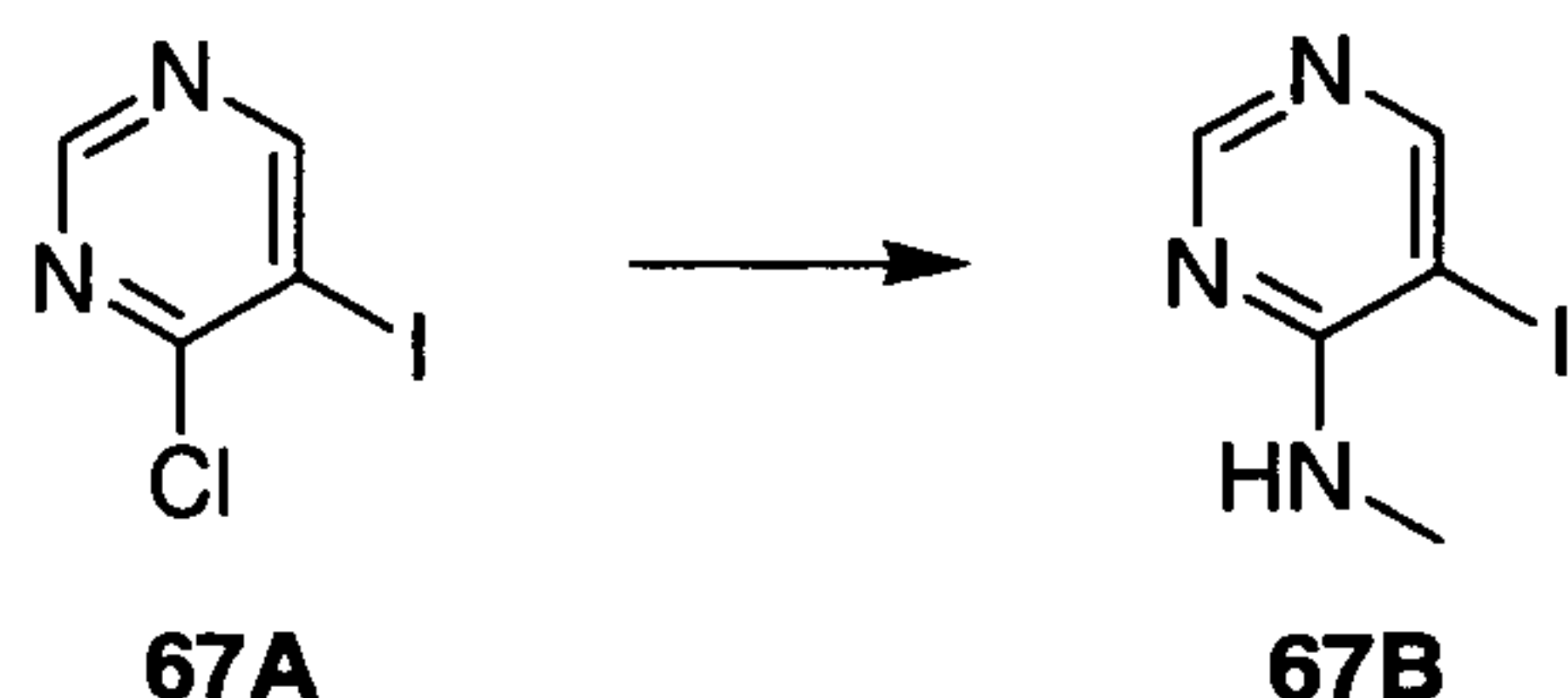
A solution of bromobenzene (135 mg, 0.863 mmol), **66A** (200 mg, 0.719 mmol, product of Example 38, Step 4) was treated with Pd₂(dba)₃ (33 mg, 0.036 mmol), Ligand S-Phos (30 mg, 0.076 mmol), and NaOtBu (90 mg, 0.934 mmol). The mixture was stirred at 100°C for 12 h under N₂, filtered. Chromatography (50% EtOAc/Hexane) afforded **66B** as an oil.

In a manner similar to that found in Example 38 (Step 6) and Example 3 (Step 3), **66B** was then deprotected with TFA and then converted to the title compound **66**. LCMS m/z 335 (MH⁺).

5 PREPARATIVE EXAMPLE 67

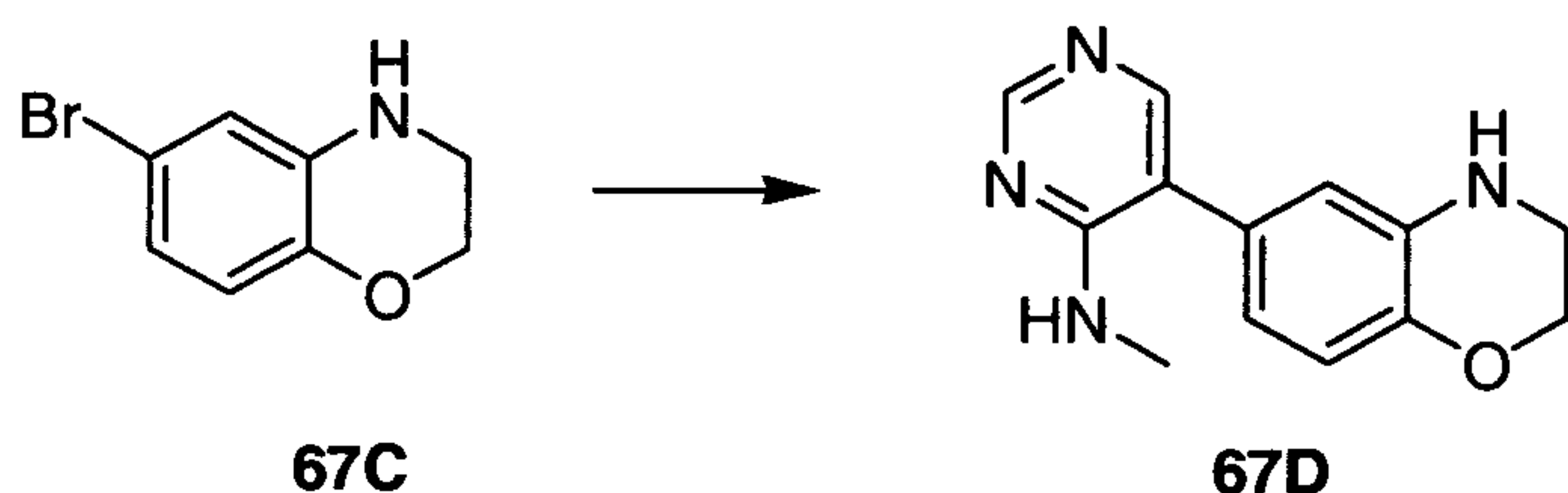


Step 1



A solution of 4-chloro-5-iodopyrimidine **67A** (2.03 g, 8.44 mmol) in 40% aqueous MeNH₂ solution was stirred at RT for 17h. The mixture was then extracted with DCM (2 x 150 ml). The combined organic phase were dried concentrated to give 5-iodo-4-methylaminopyrimidine **67B** (1.55 g, 78%) as an orange solid which was used for the next step without further purification.

Steps 2-3

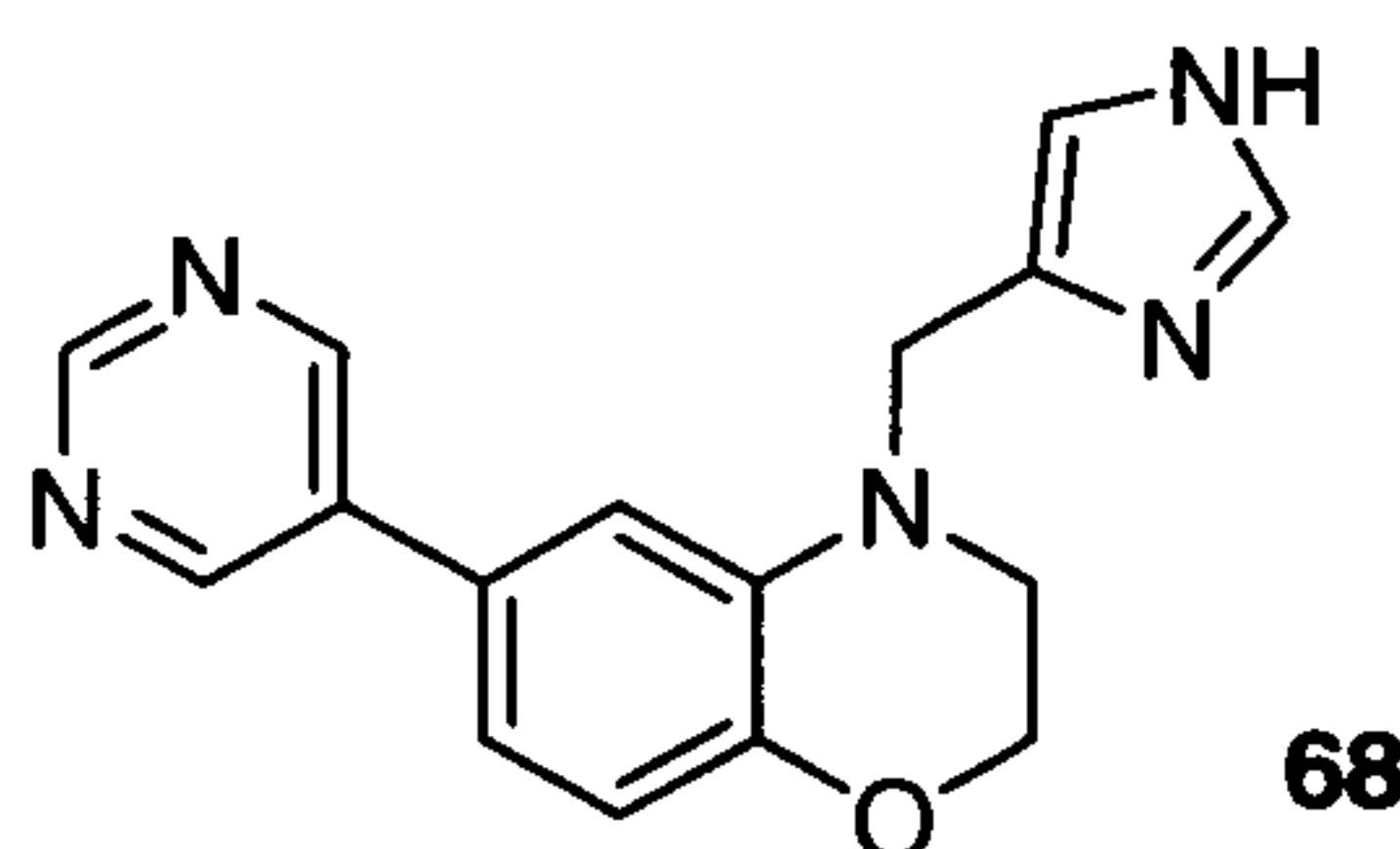


A 15 mL-sealed tube was charged with 6-bromophenyl morpholine (**67C**, 0.431 g, 2.013 mmol), bis(pinacolato)diboron (1.02 g, 4.03 mmol), KOAc (0.592 g, 6.04 mmol), Pd(dppf)Cl₂.DCM (0.164 g, 0.20 mmol) and dry 1,4-dioxane (8 ml). The resulting mixture was heated at 100 °C for 1.5h. The mixture was then cooled to RT

and treated sequentially with 5-iodo-4-methylaminopyrimidine (**67B**, 0.66 g, 4.03 mmol, 2.0 eq) and 1 M aqueous K_2CO_3 (5 mL). The resulting mixture was heated again at 100 °C for 13h, cooled to RT, diluted with water and extracted with DCM to give a brown oil. Chromatography (0-10% of (9:1 MeOH/ NH_3) in DCM) provided **67D** (0.198 g, 41%) as a pale brown foam.

In a manner similar to that described in Example 3 (Step 3), compound **67D** converted to the title compound **67**. MS m/z 323 (MH^+).

PREPARATIVE EXAMPLE 68



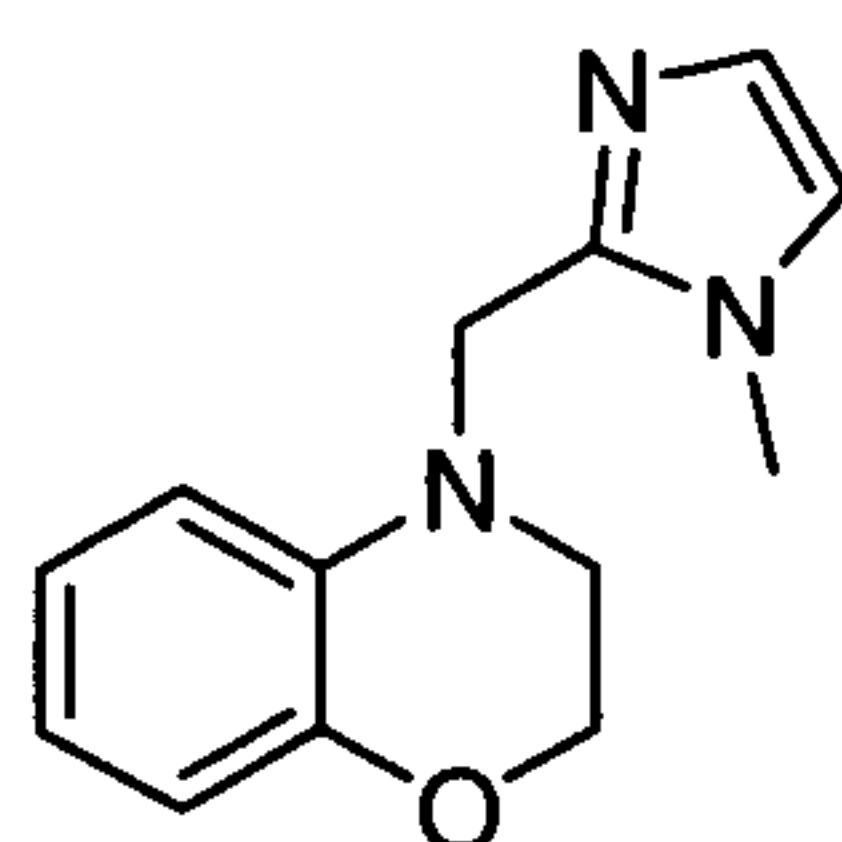
In a manner similar to those previously described (Examples 15-17, 67), 6-bromophenyl morpholine (**67C**) was treated with pyrimidine-5-boronic acid, $PdCl_2(dppf)$, and K_2CO_3 , to provide compound 6-(pyrimidin-5-yl)-benzomorpholine, which was further converted to the title compound **68**. MS m/z 294 (MH^+).

The following compounds were prepared following essentially the same procedure as described above.

Cpd	Structure	MS (MH^+)
100		230
101		230

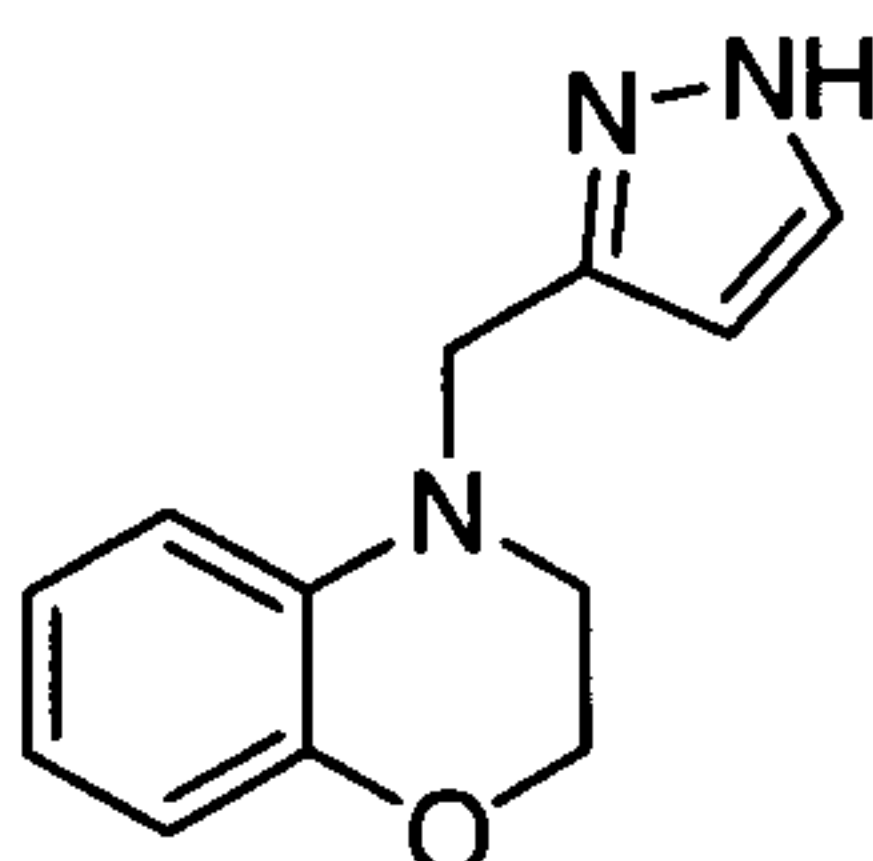
112

102



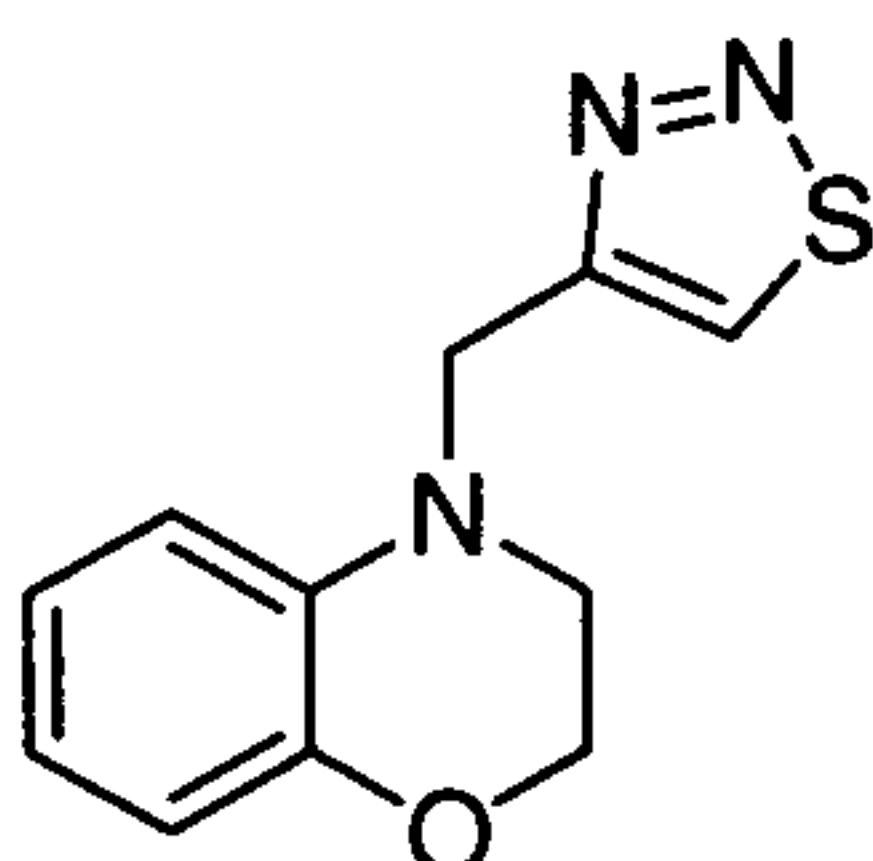
230

103



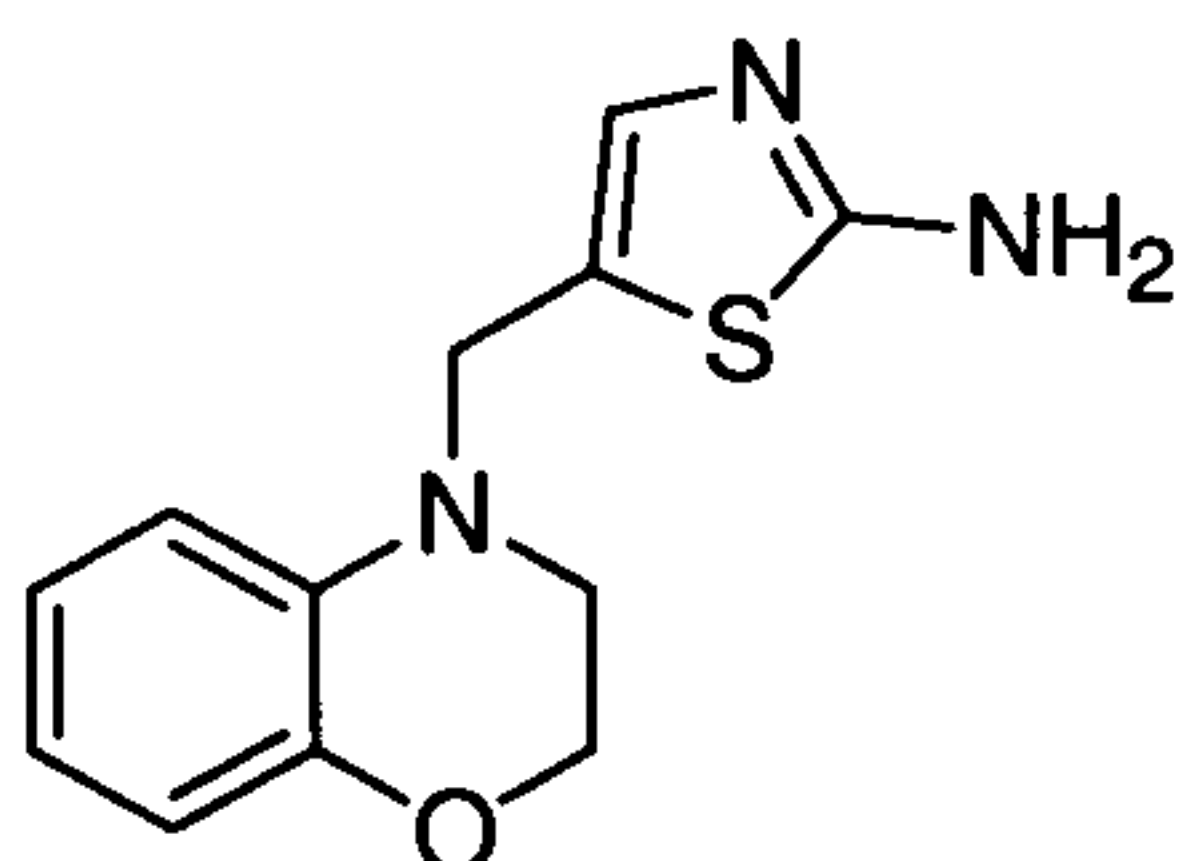
216

104



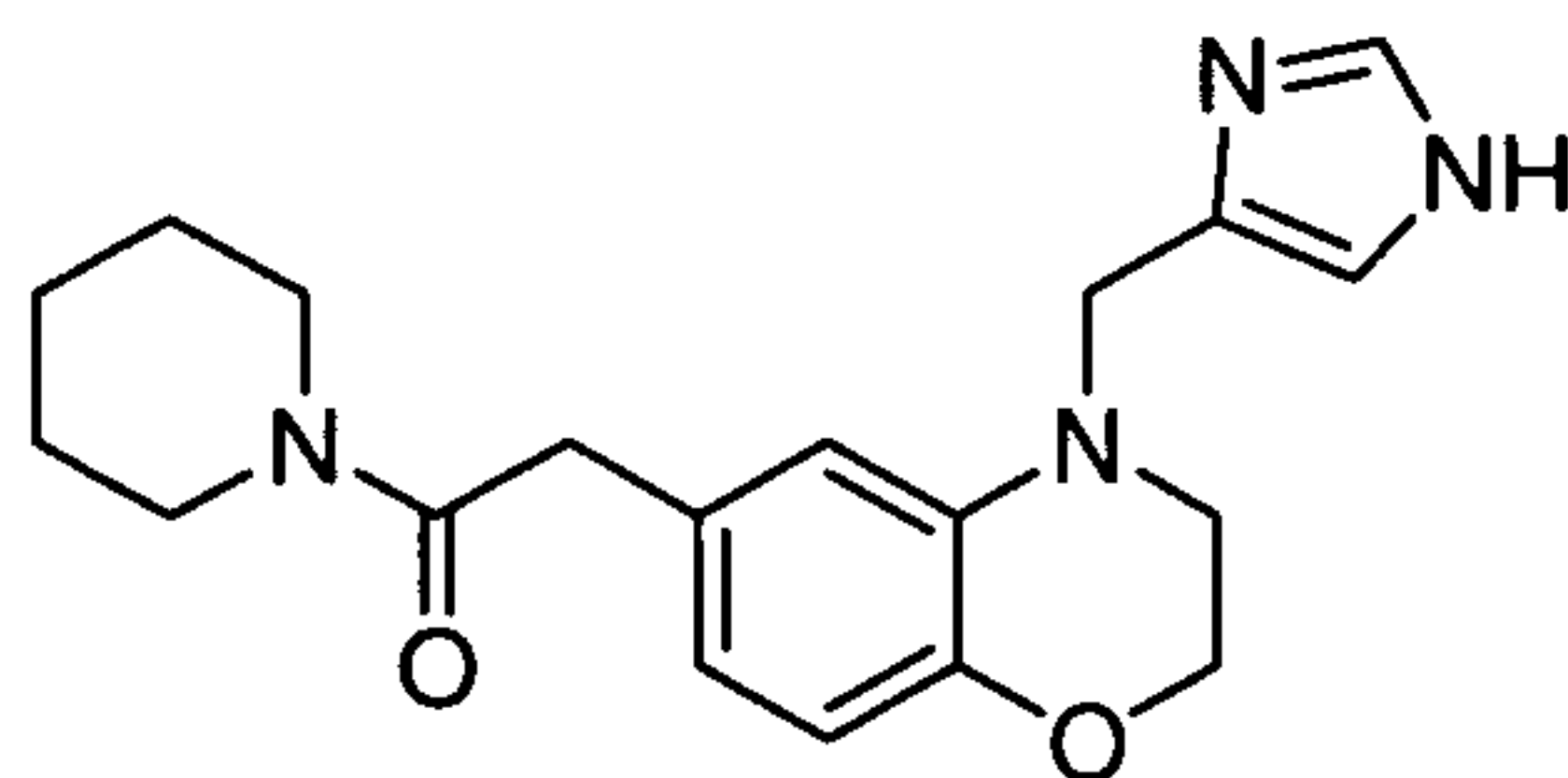
234

105



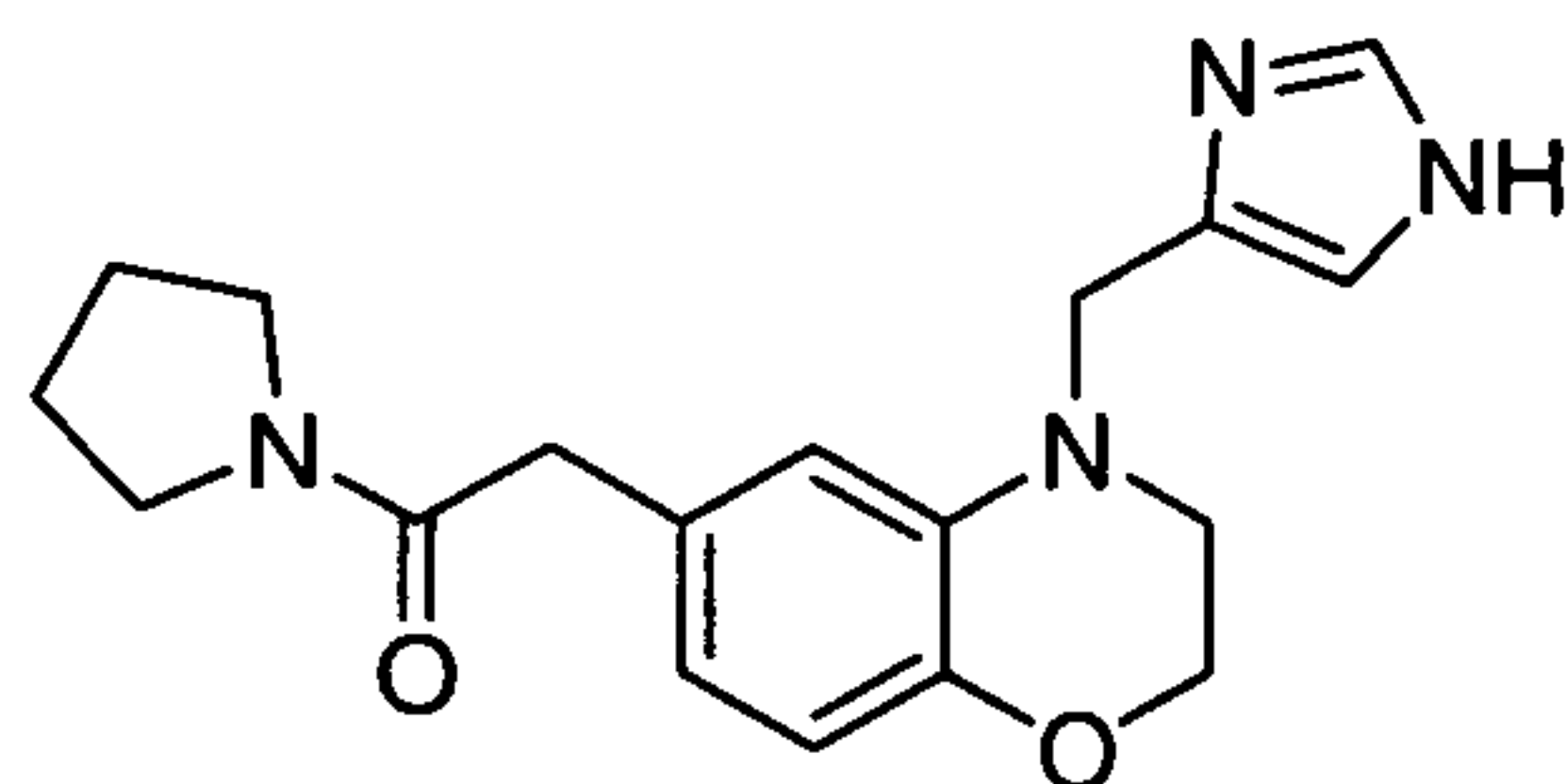
248

106



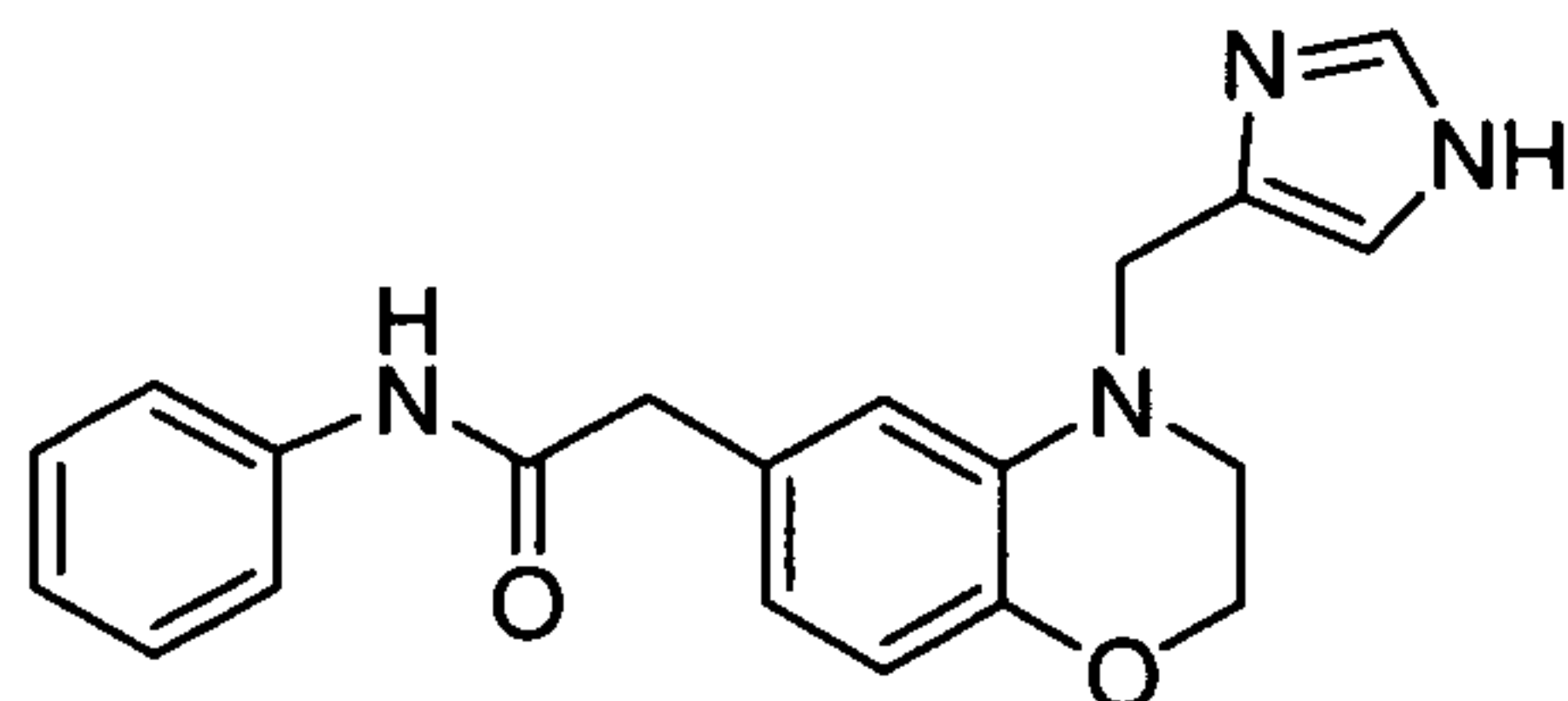
341

107



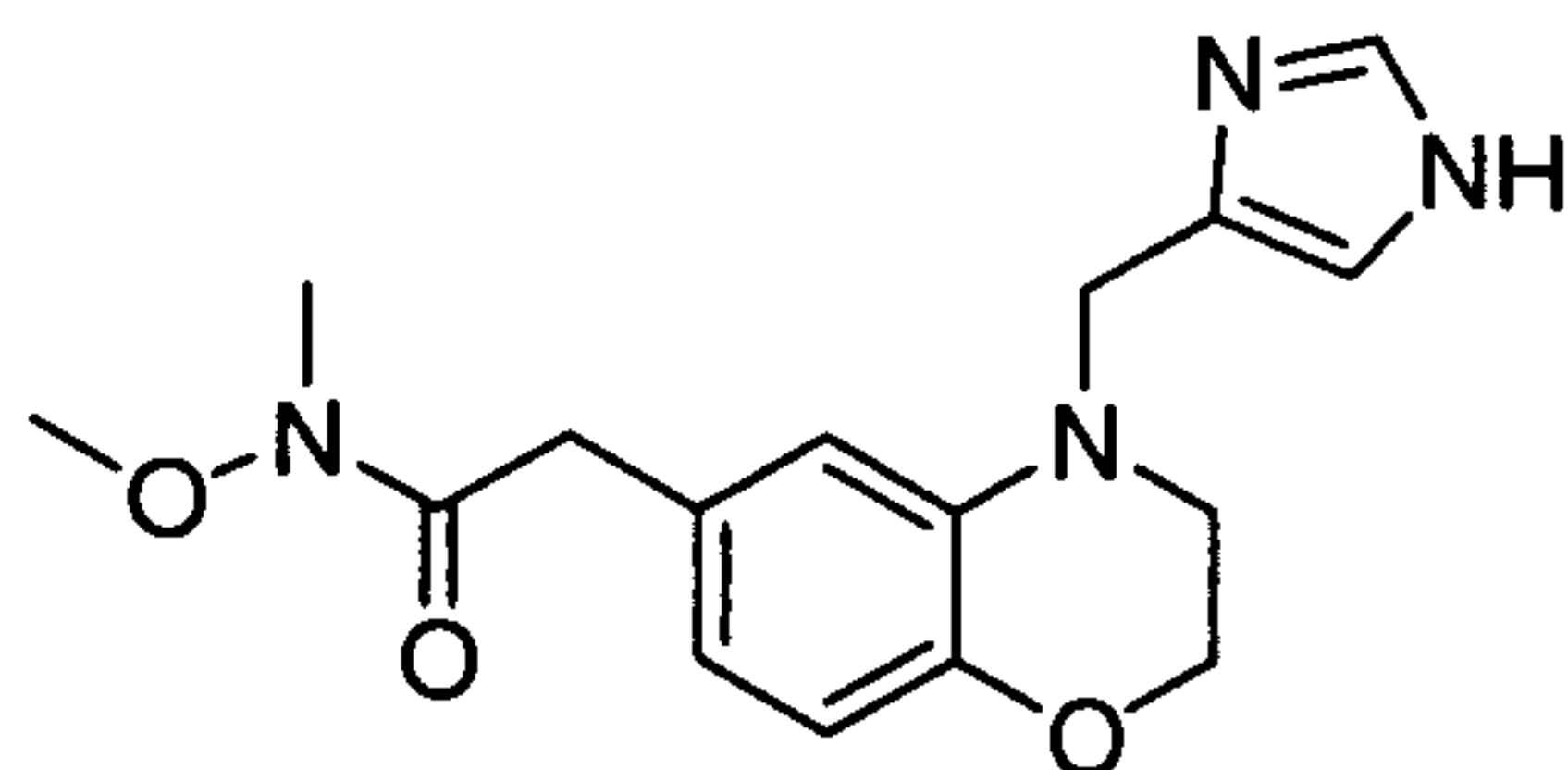
327

108



349

109

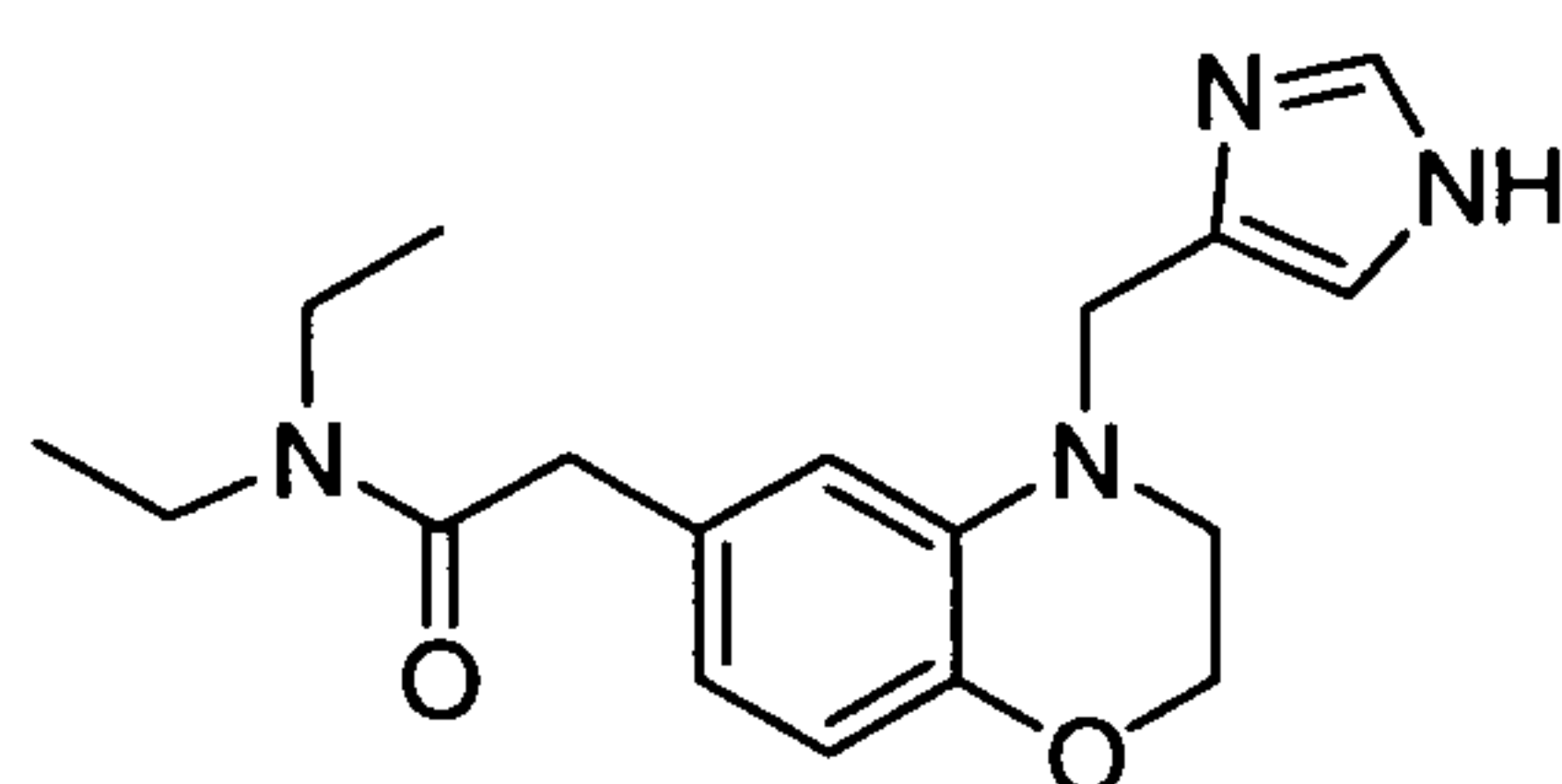


317

113

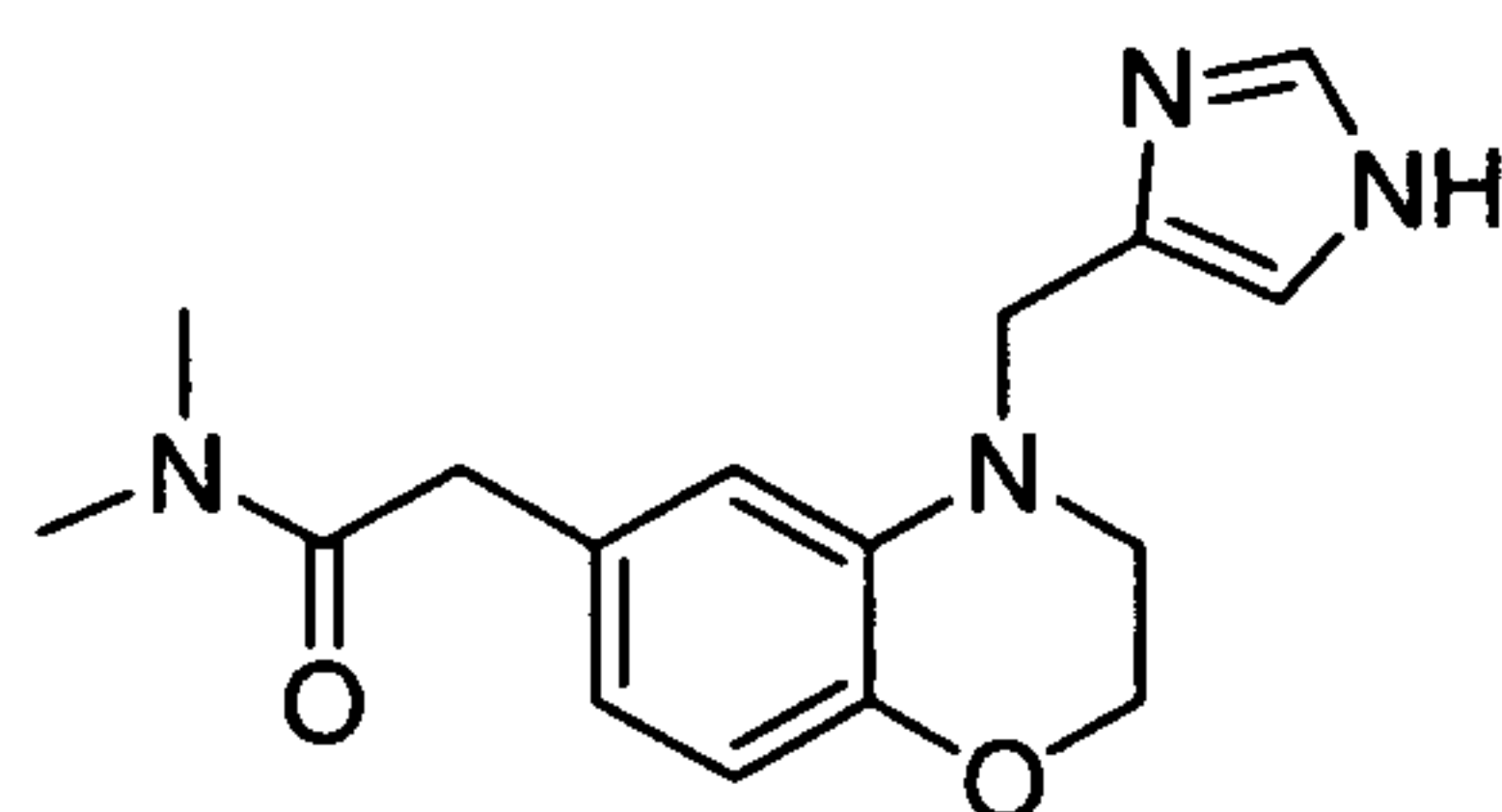
110

329



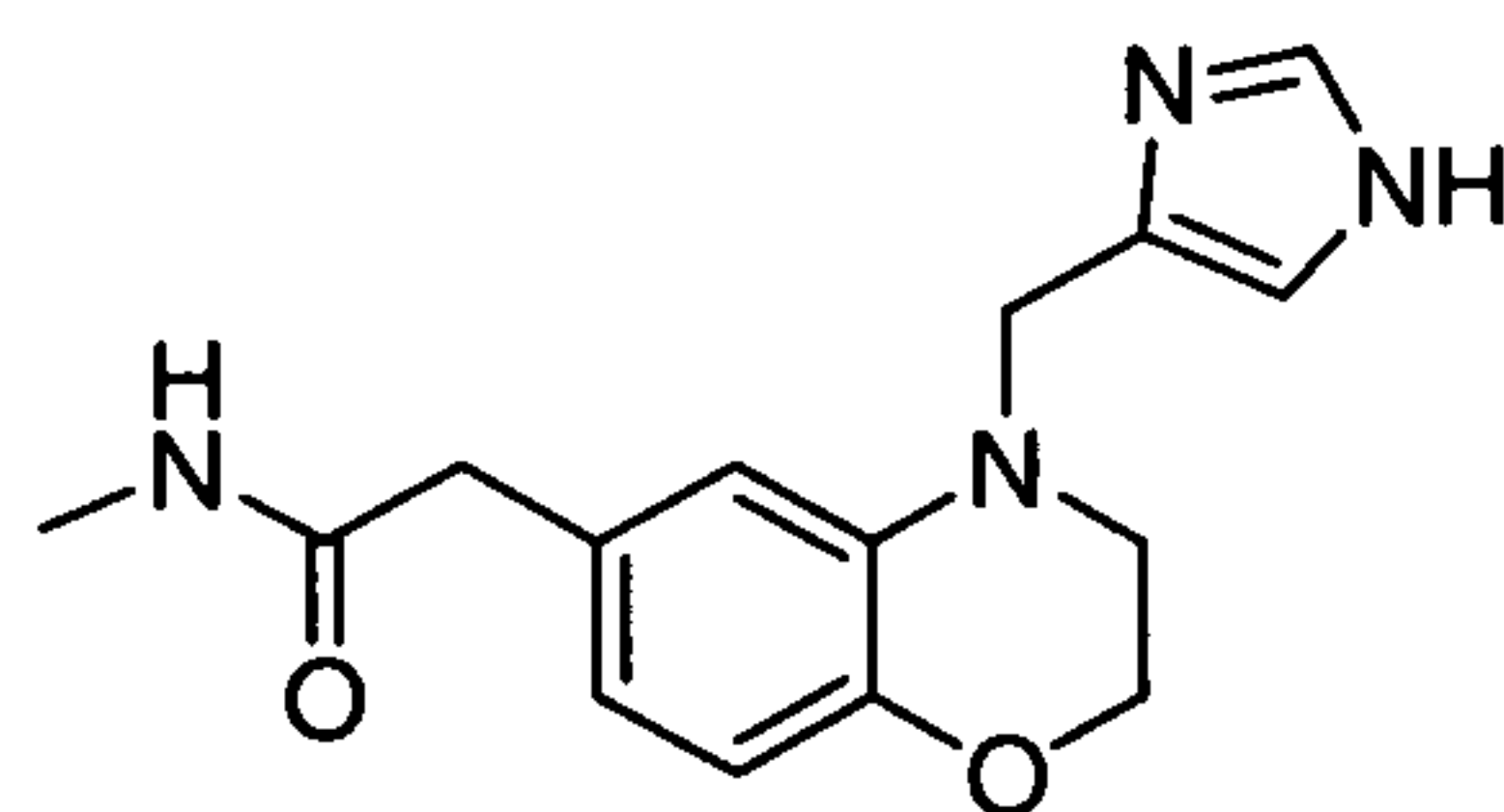
111

301



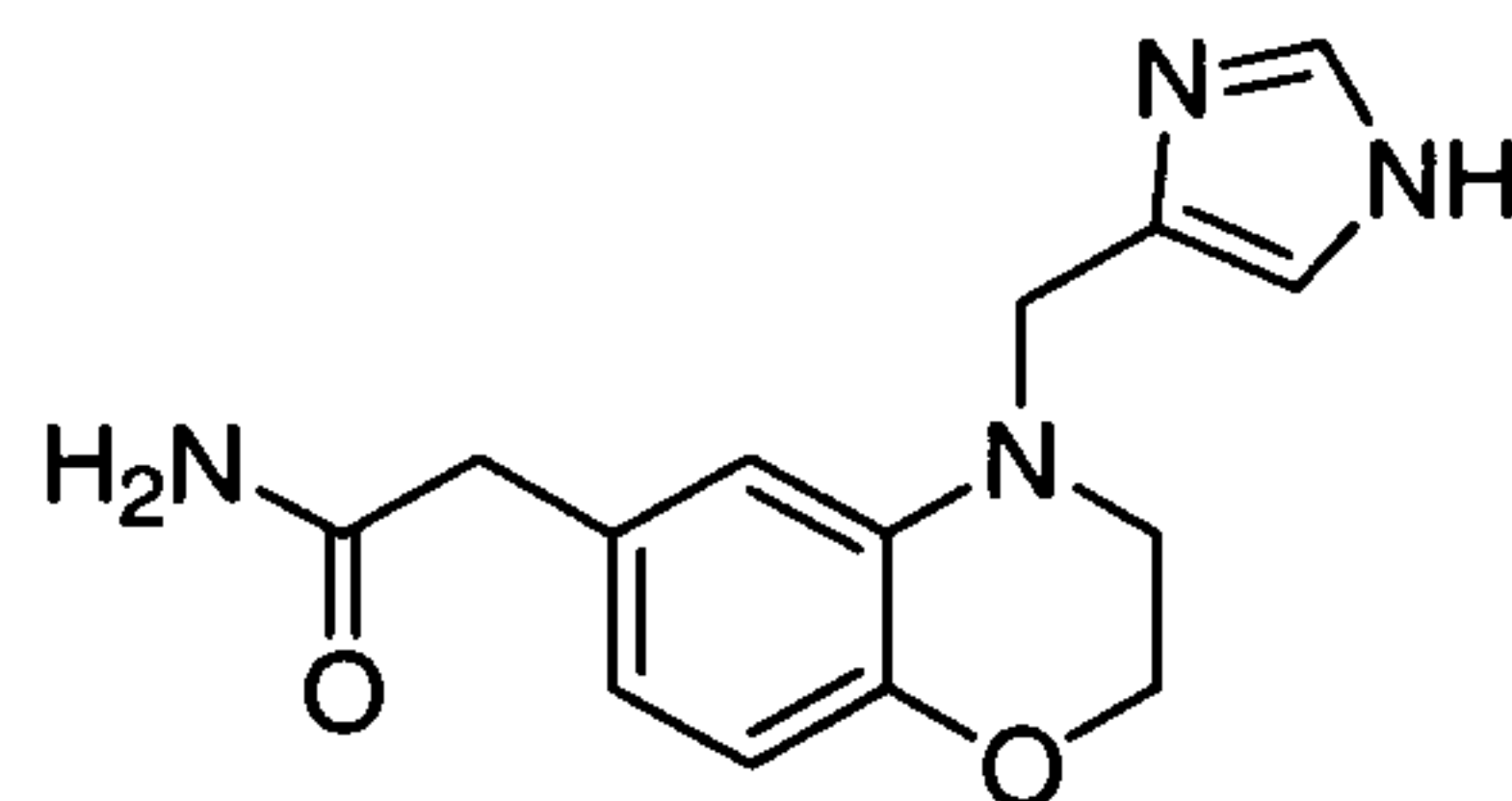
112

287



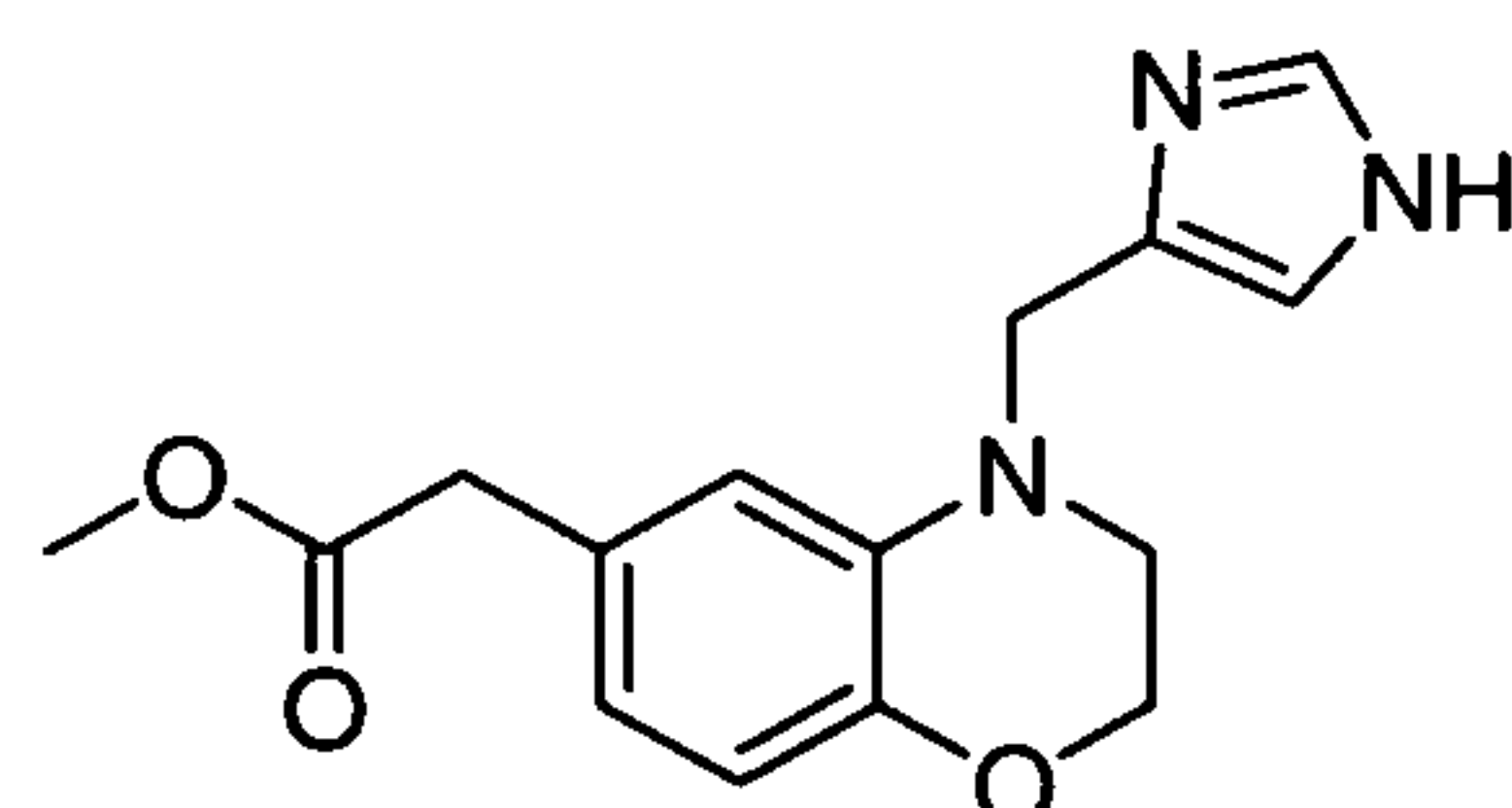
113

273



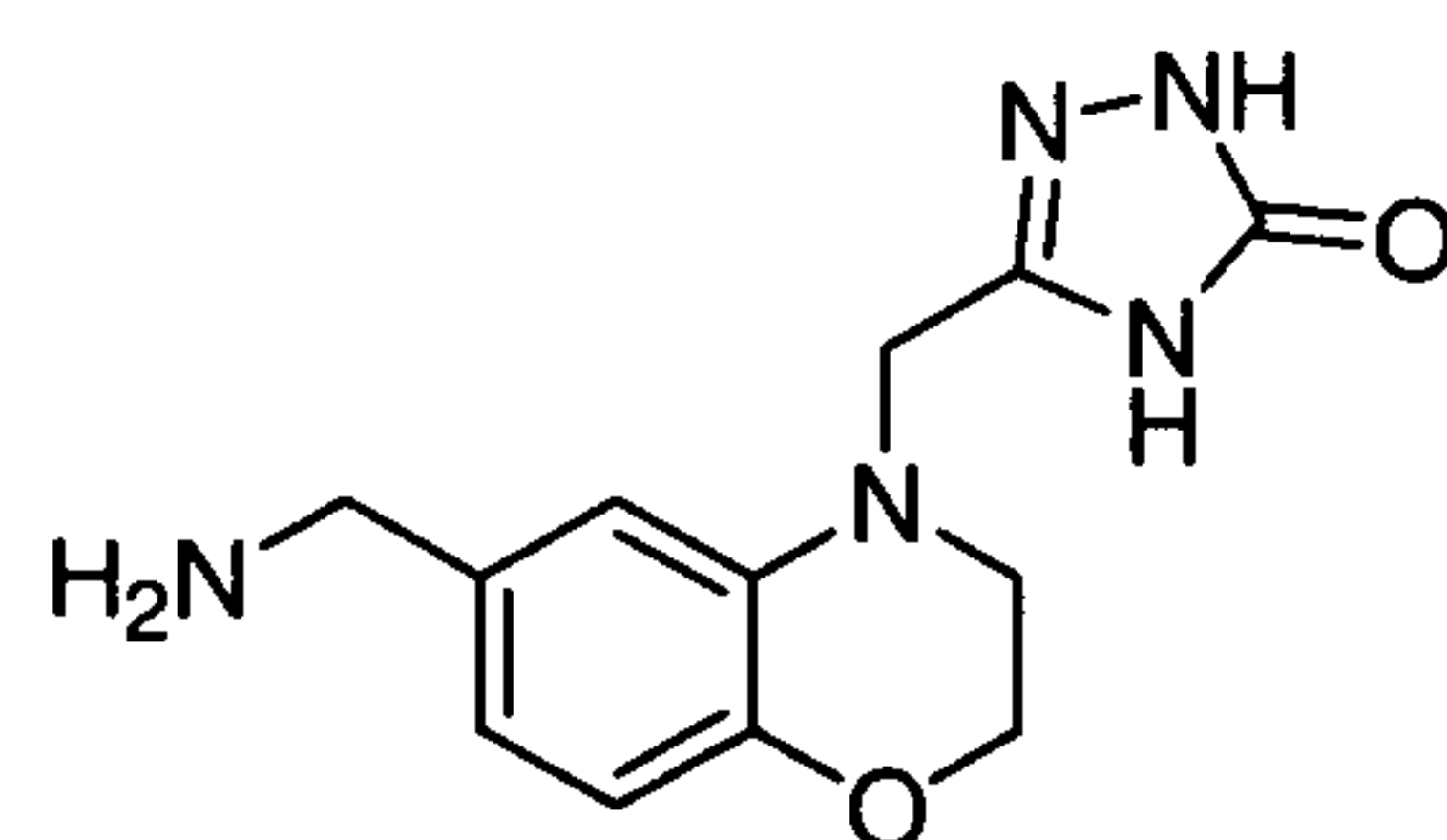
114

288



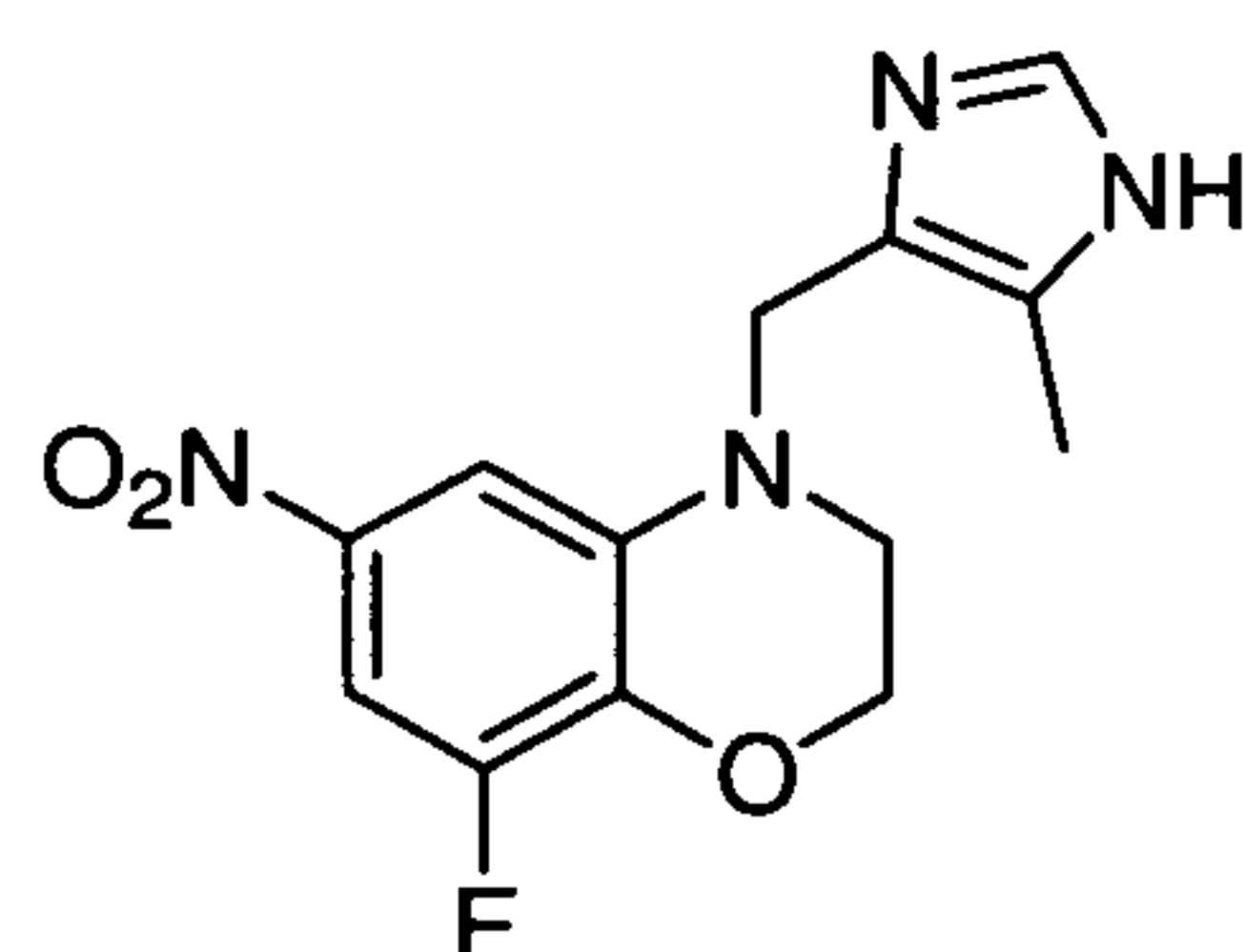
115

262



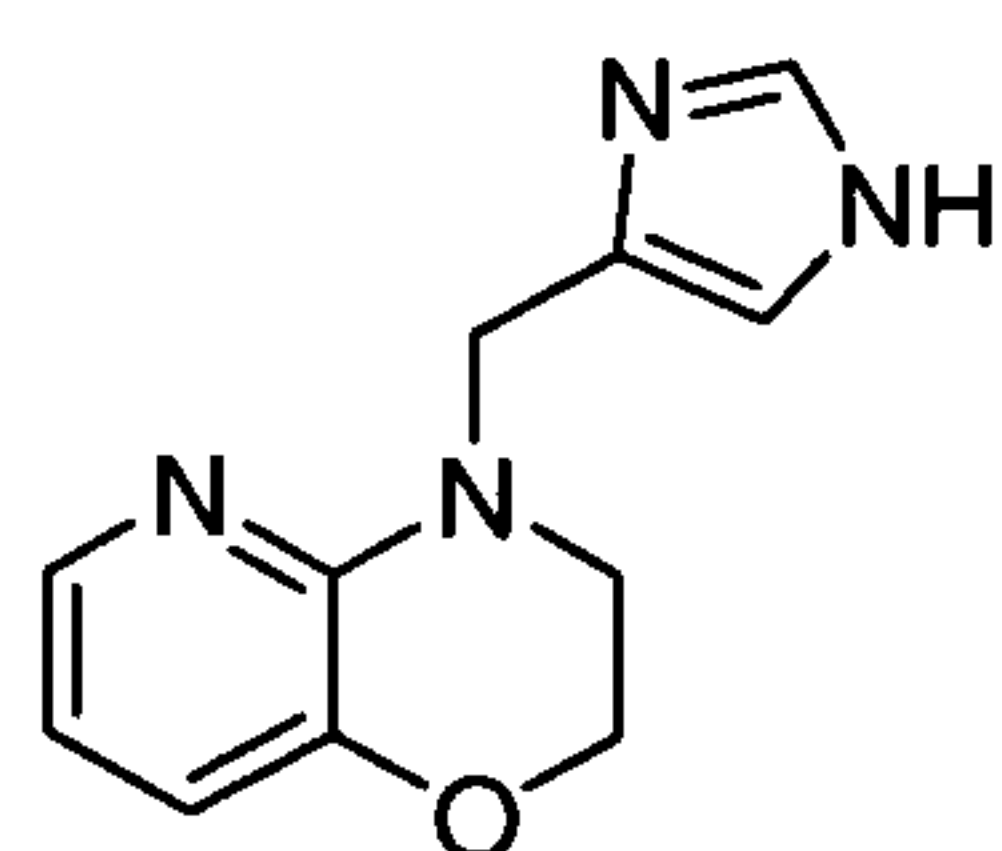
116

293



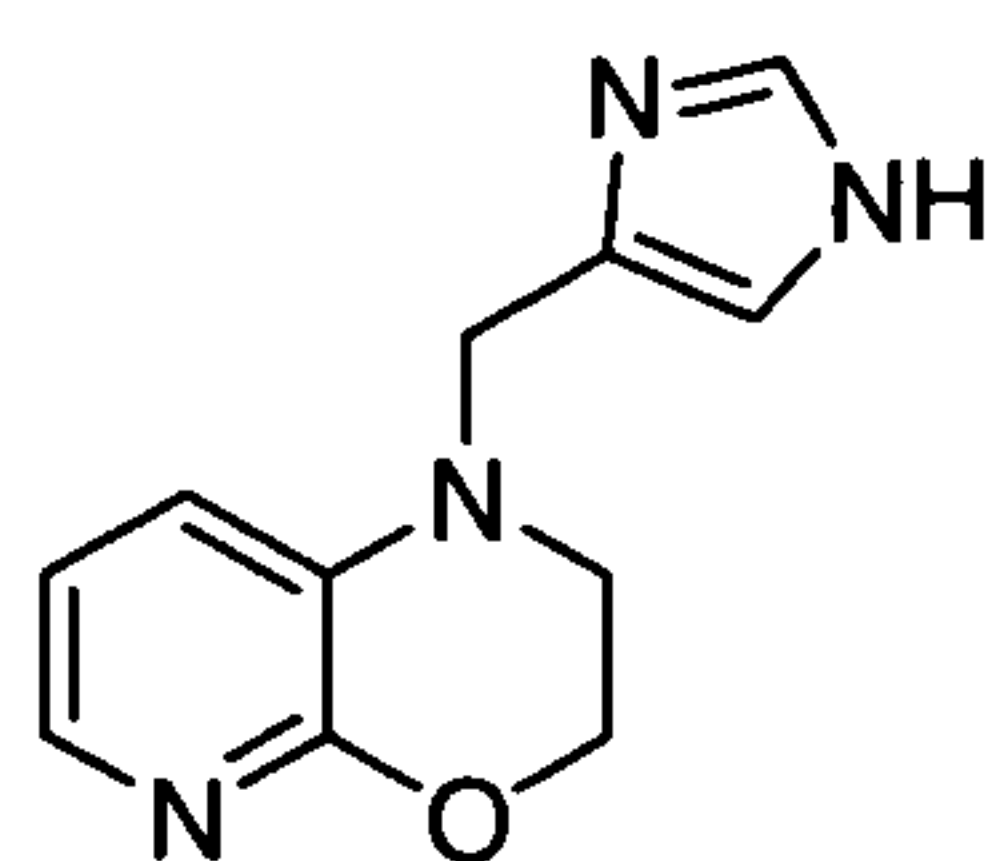
117

217



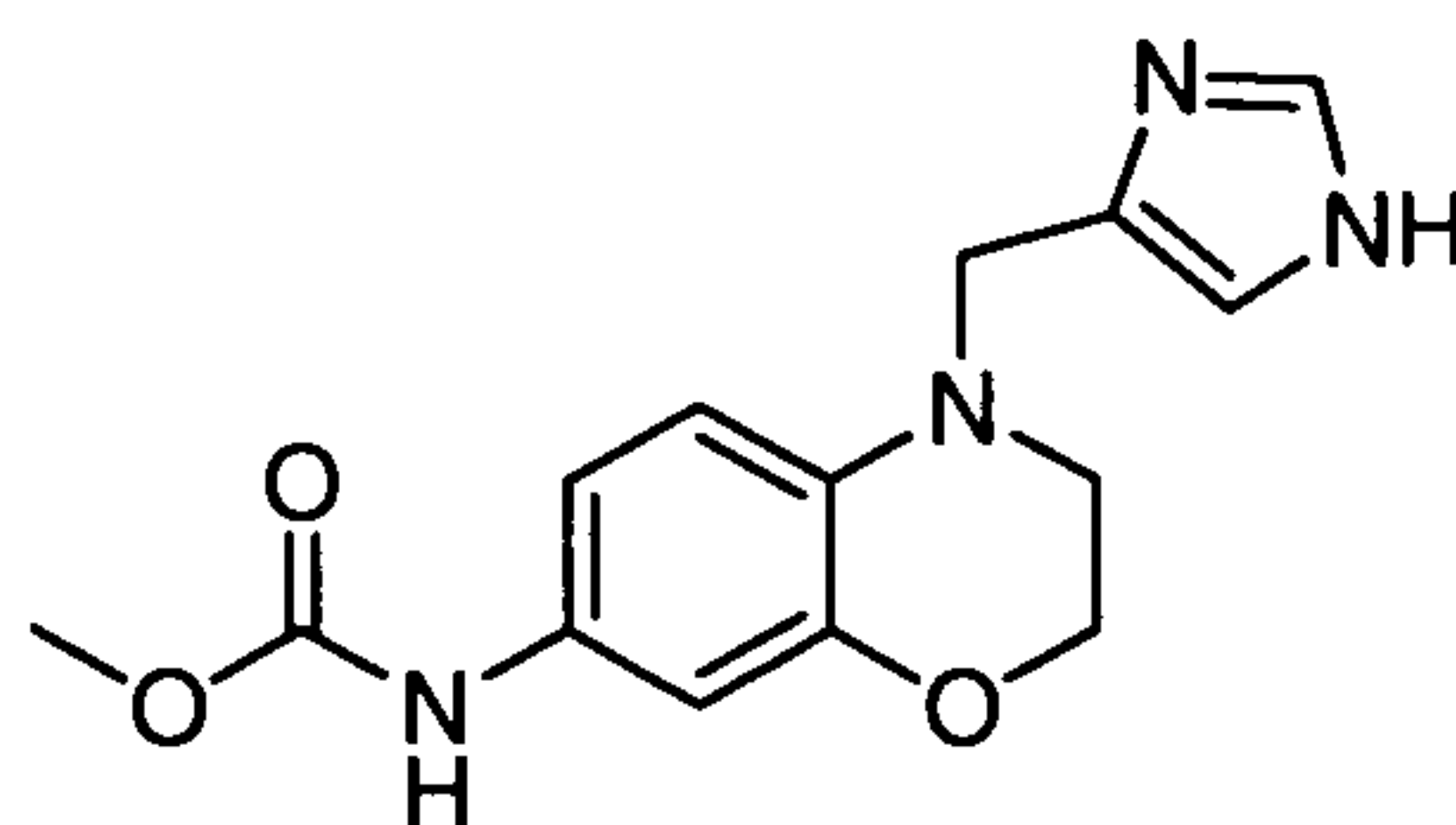
114

118



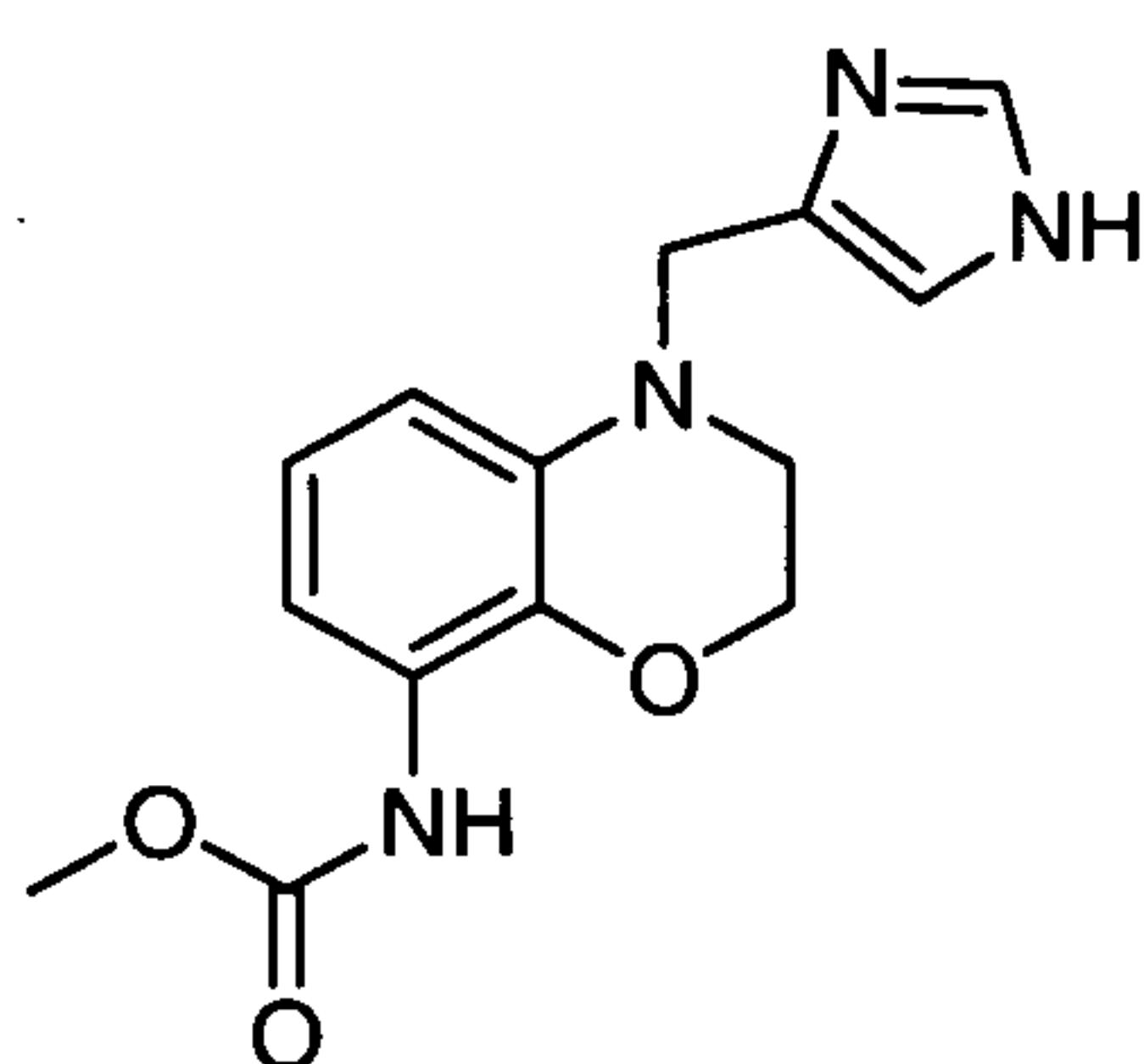
217

119



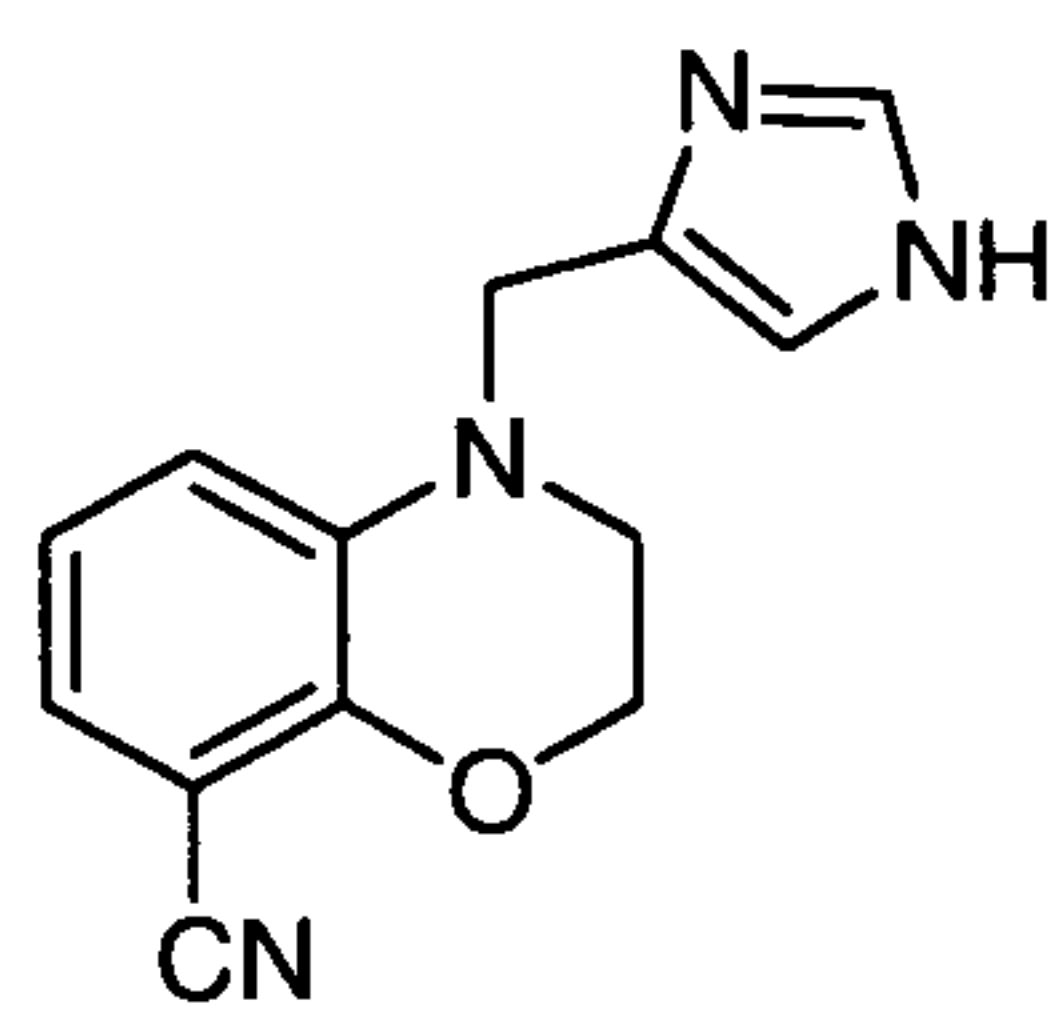
289

120



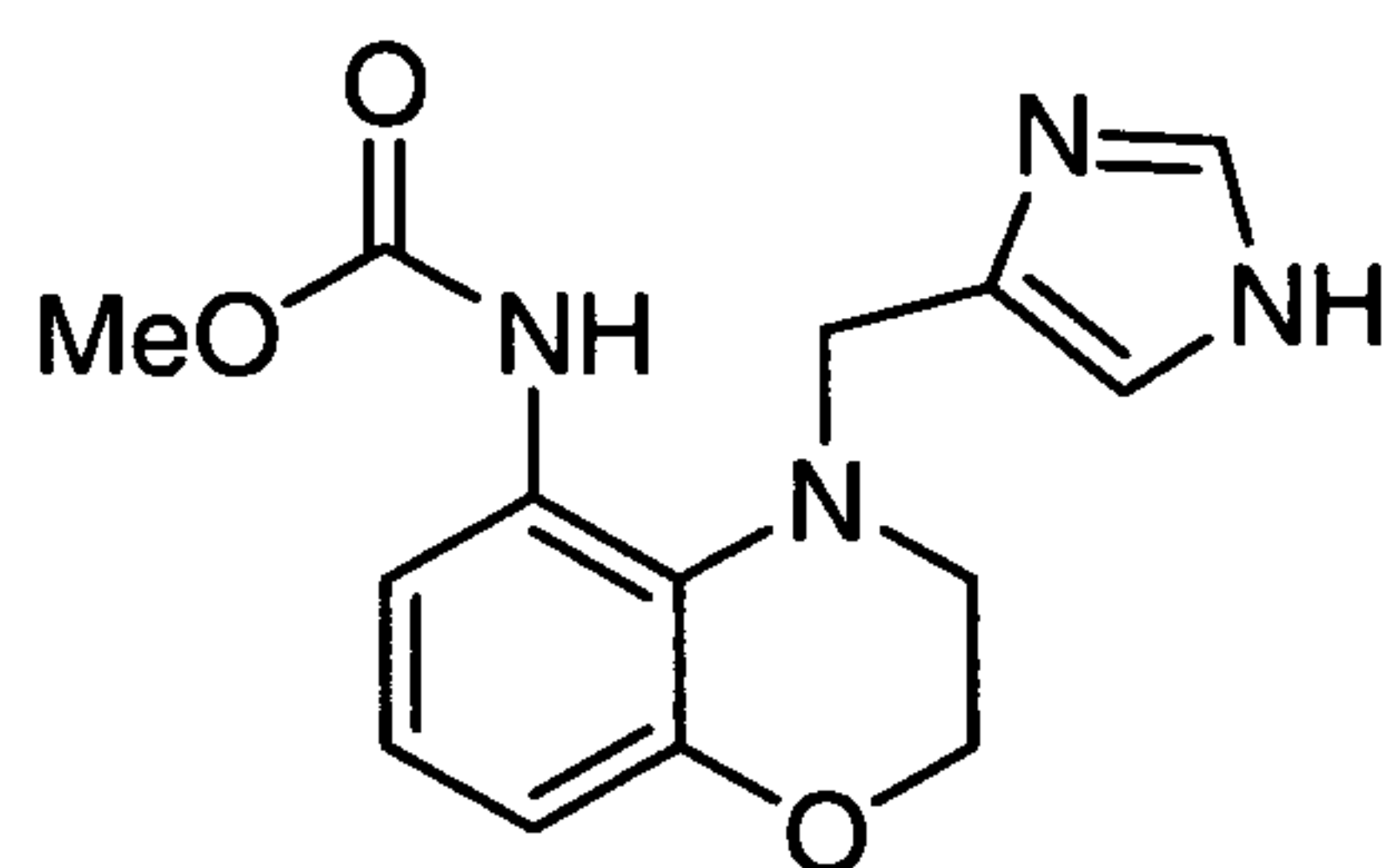
289

121



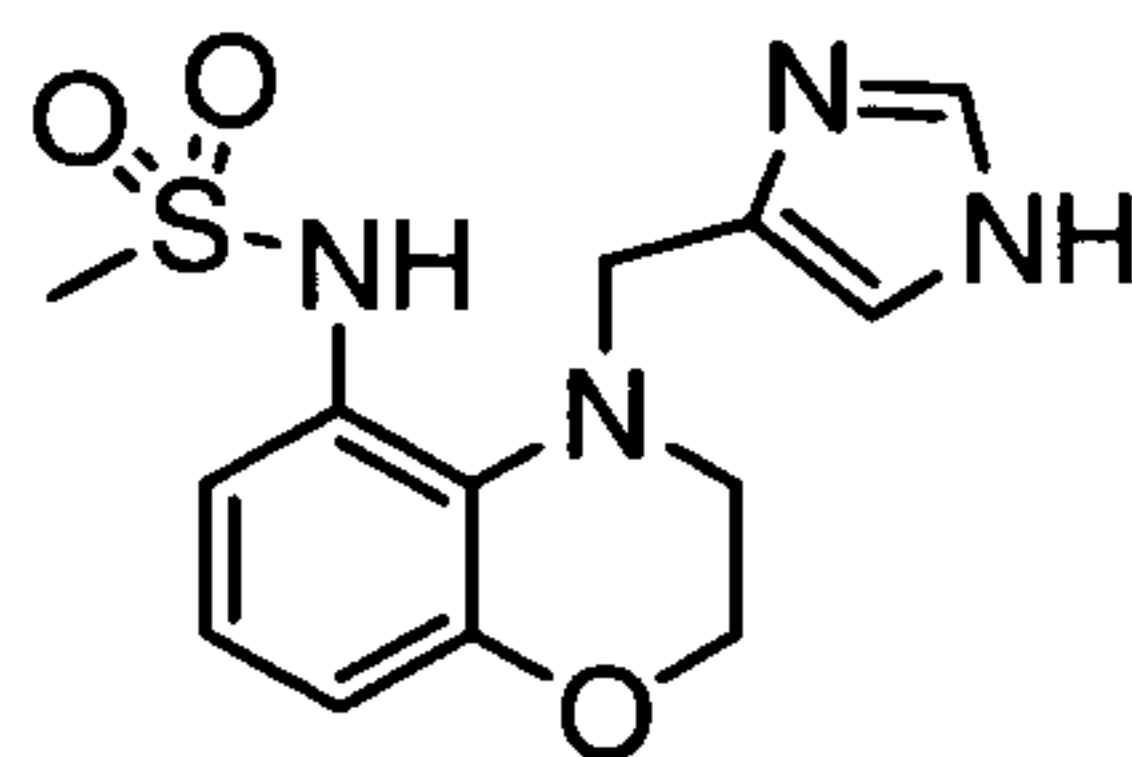
241

122



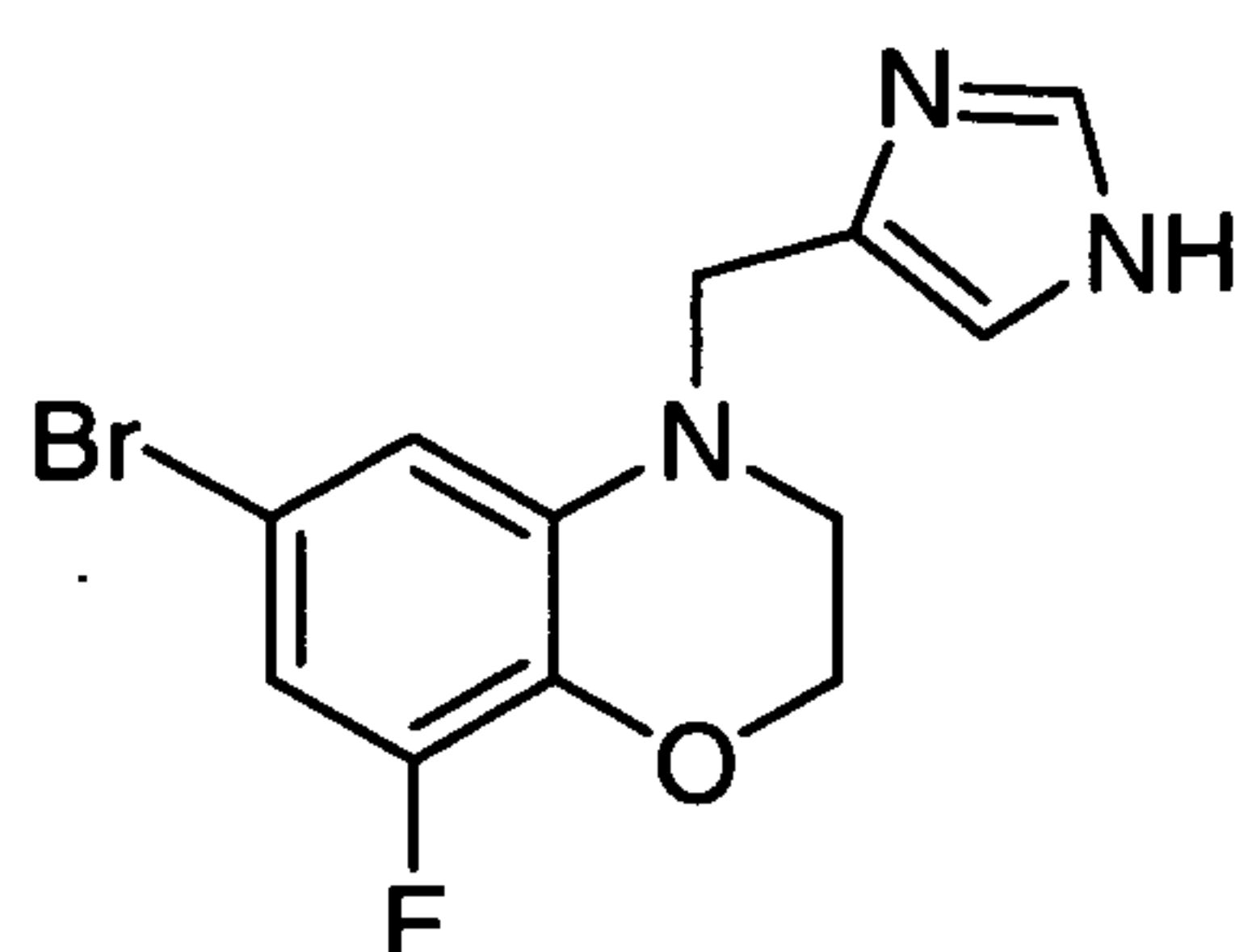
289

123



309

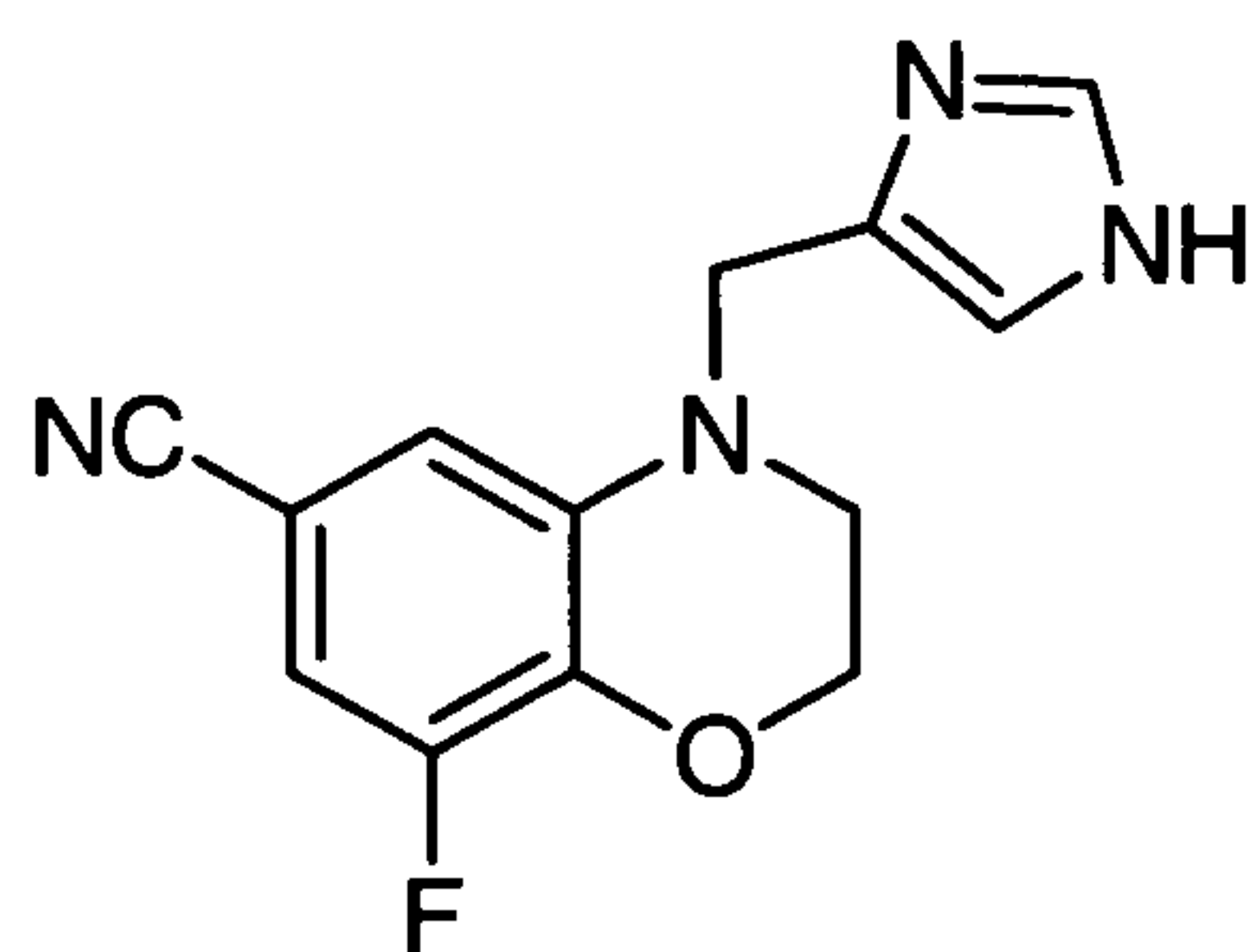
124



312

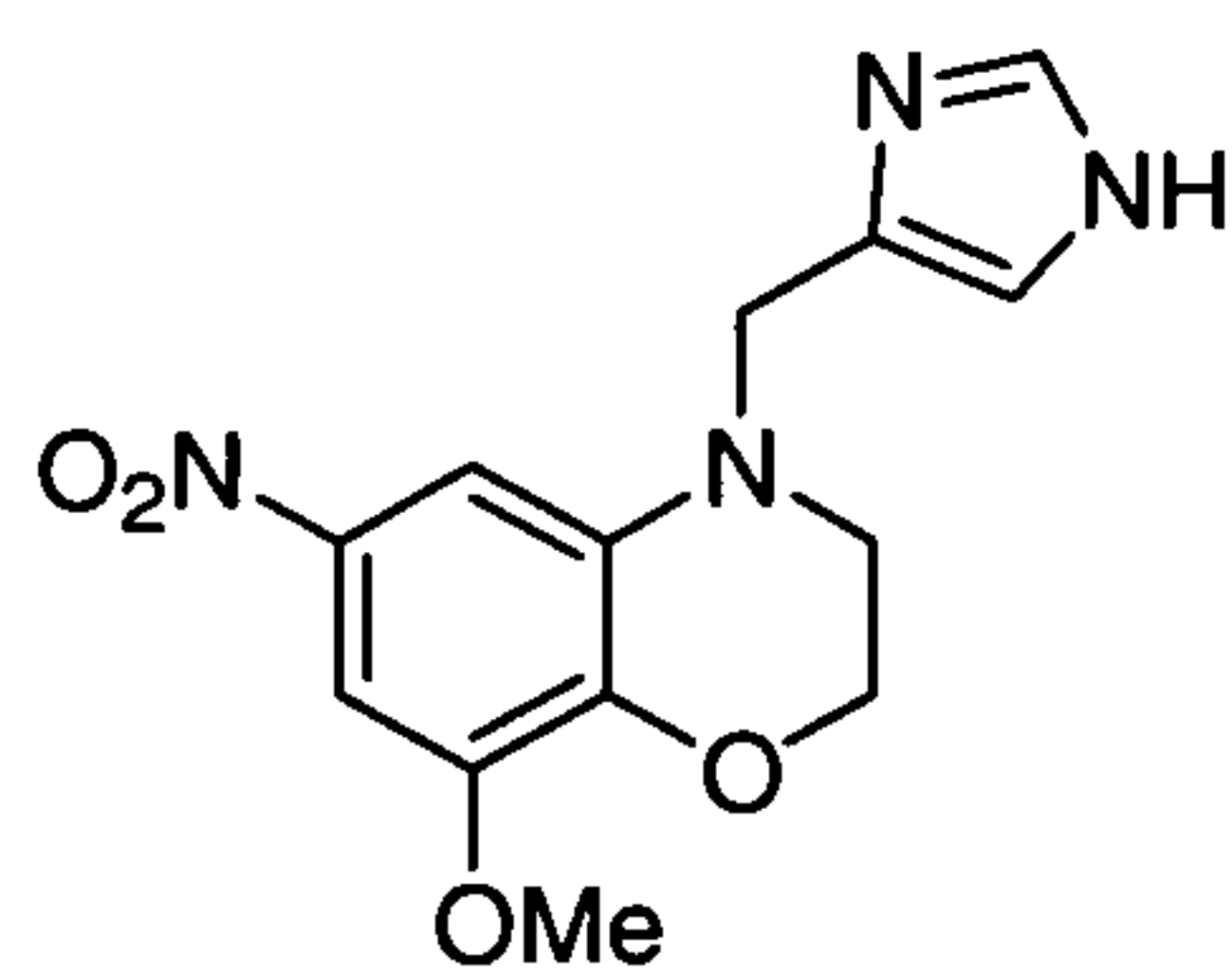
115

125



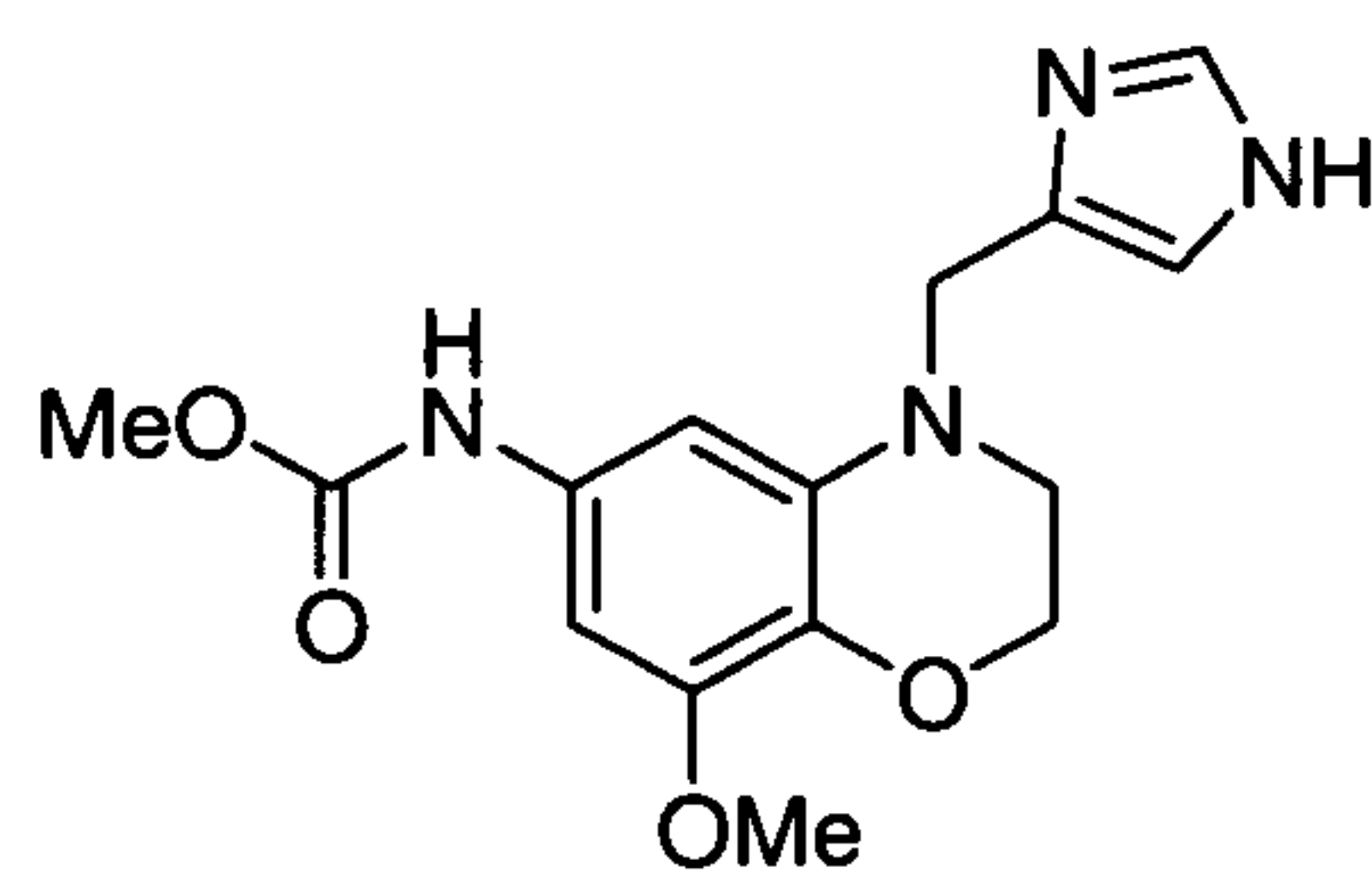
259

126



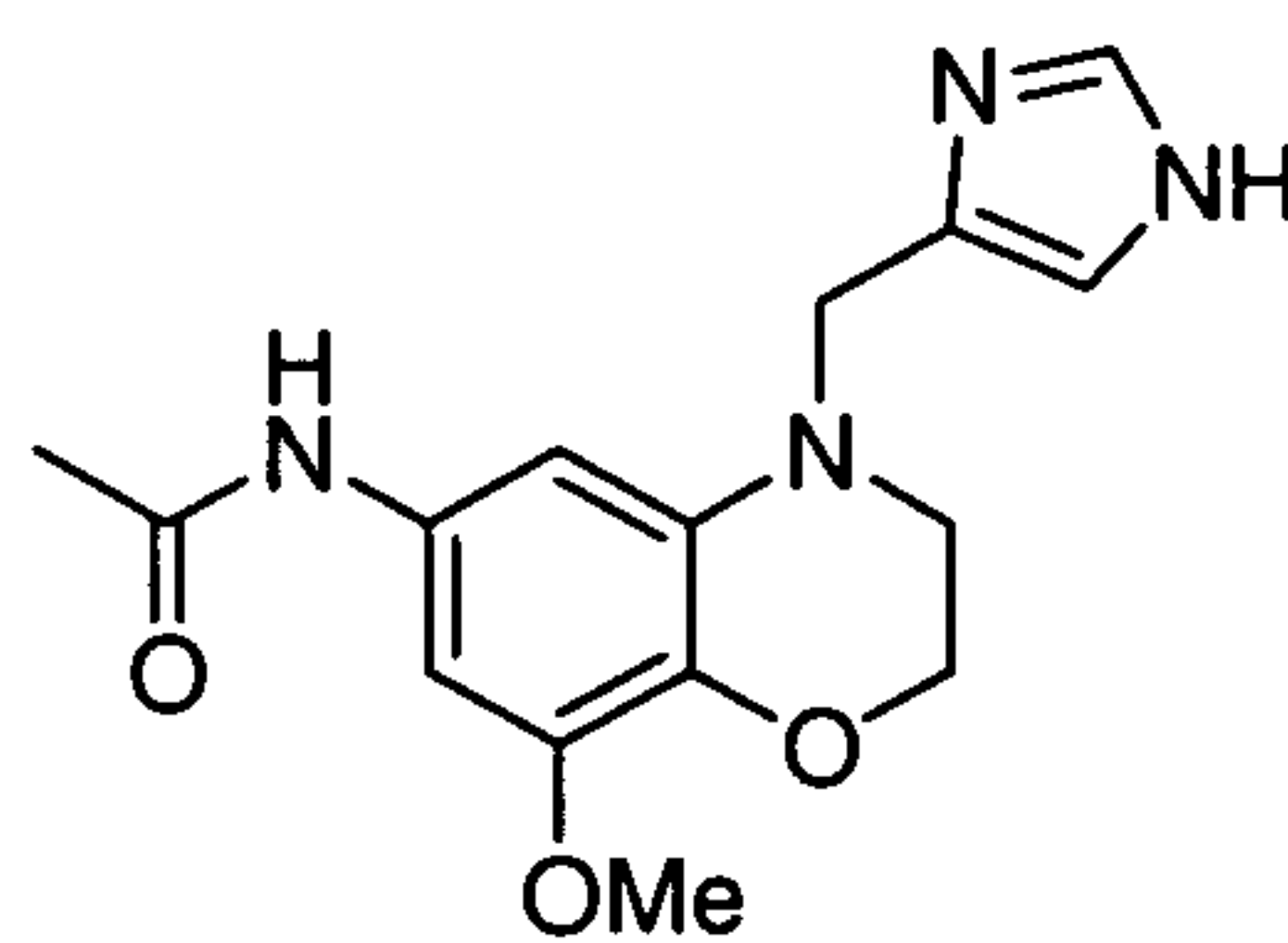
291

127



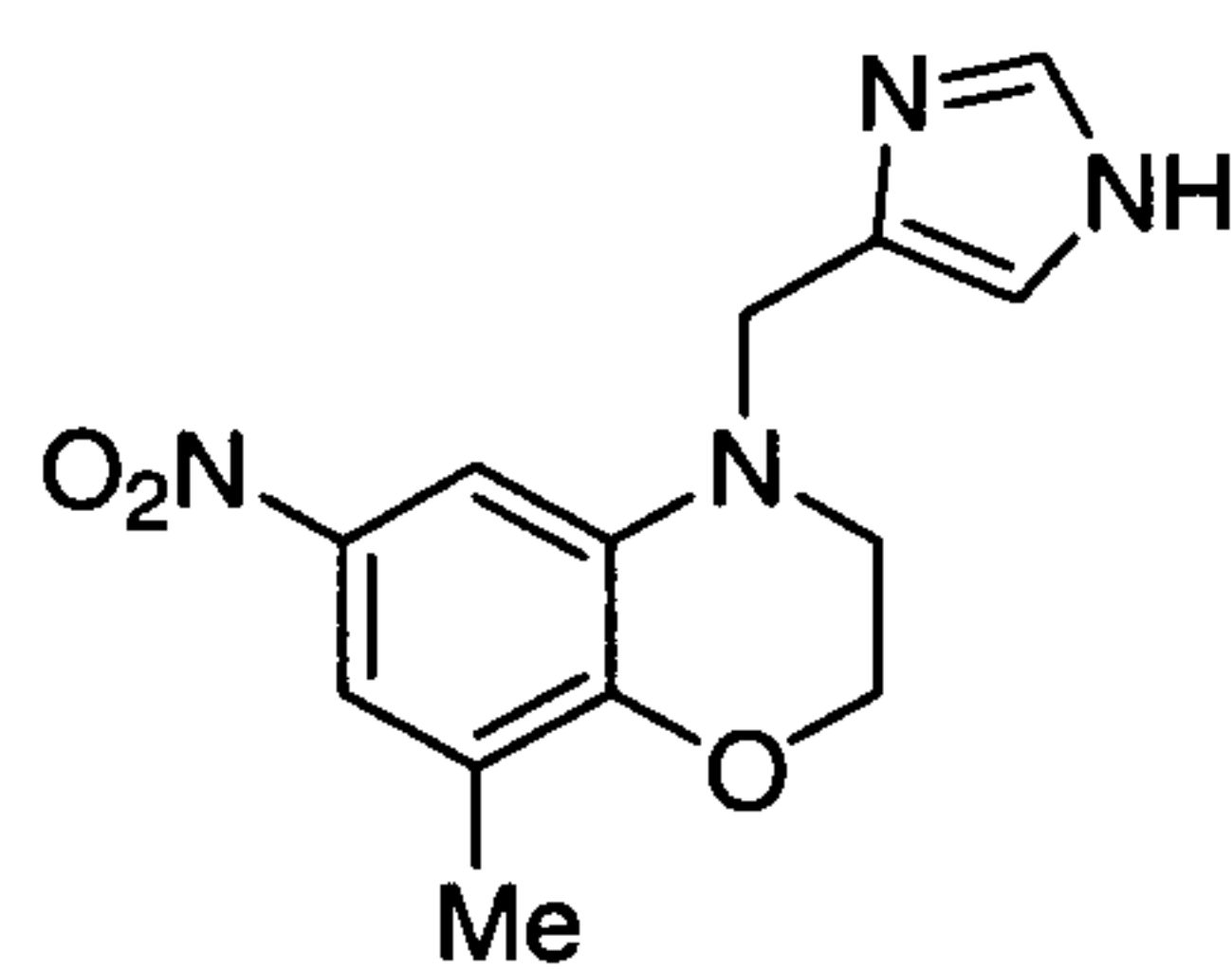
319

128



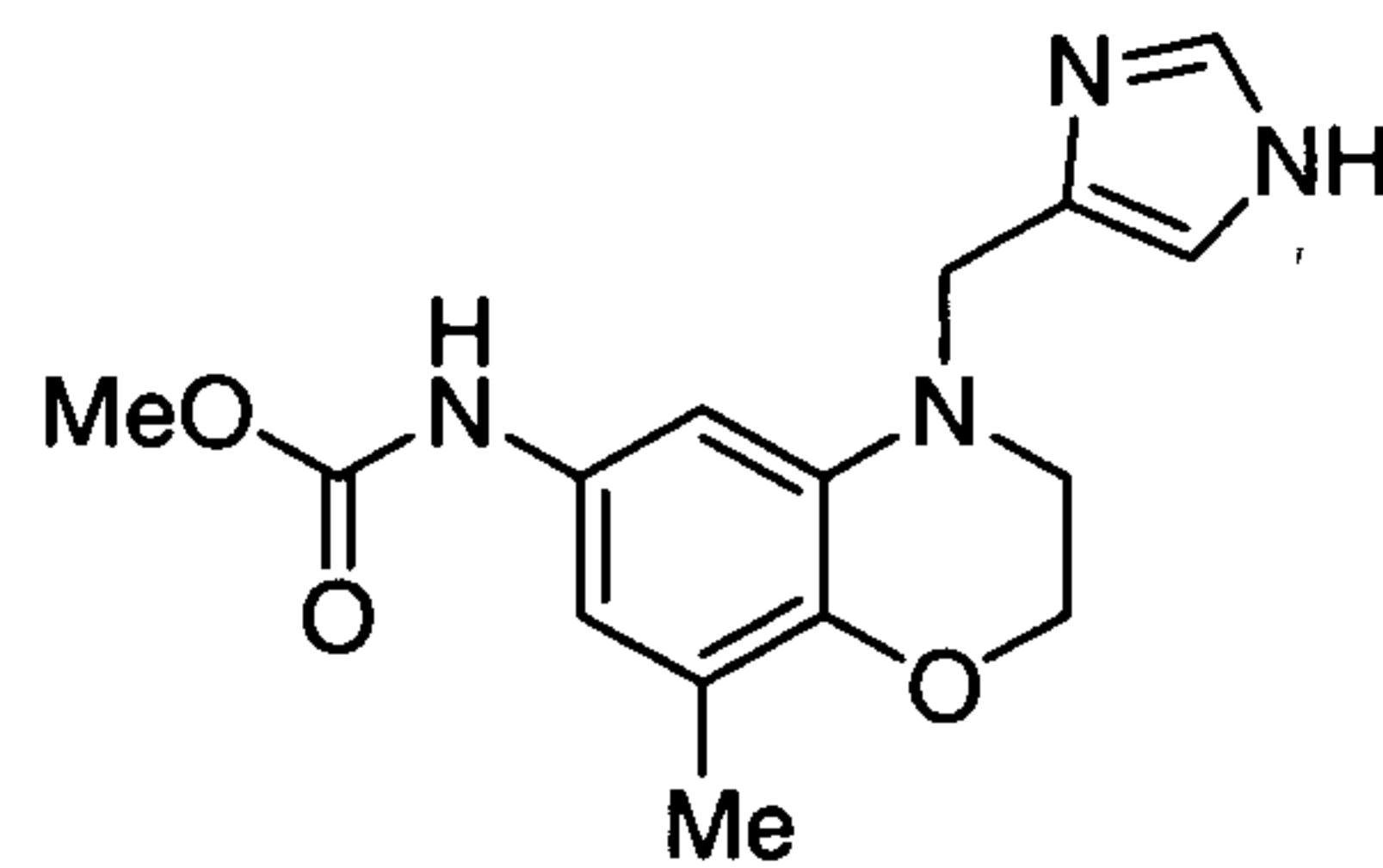
303

129



275

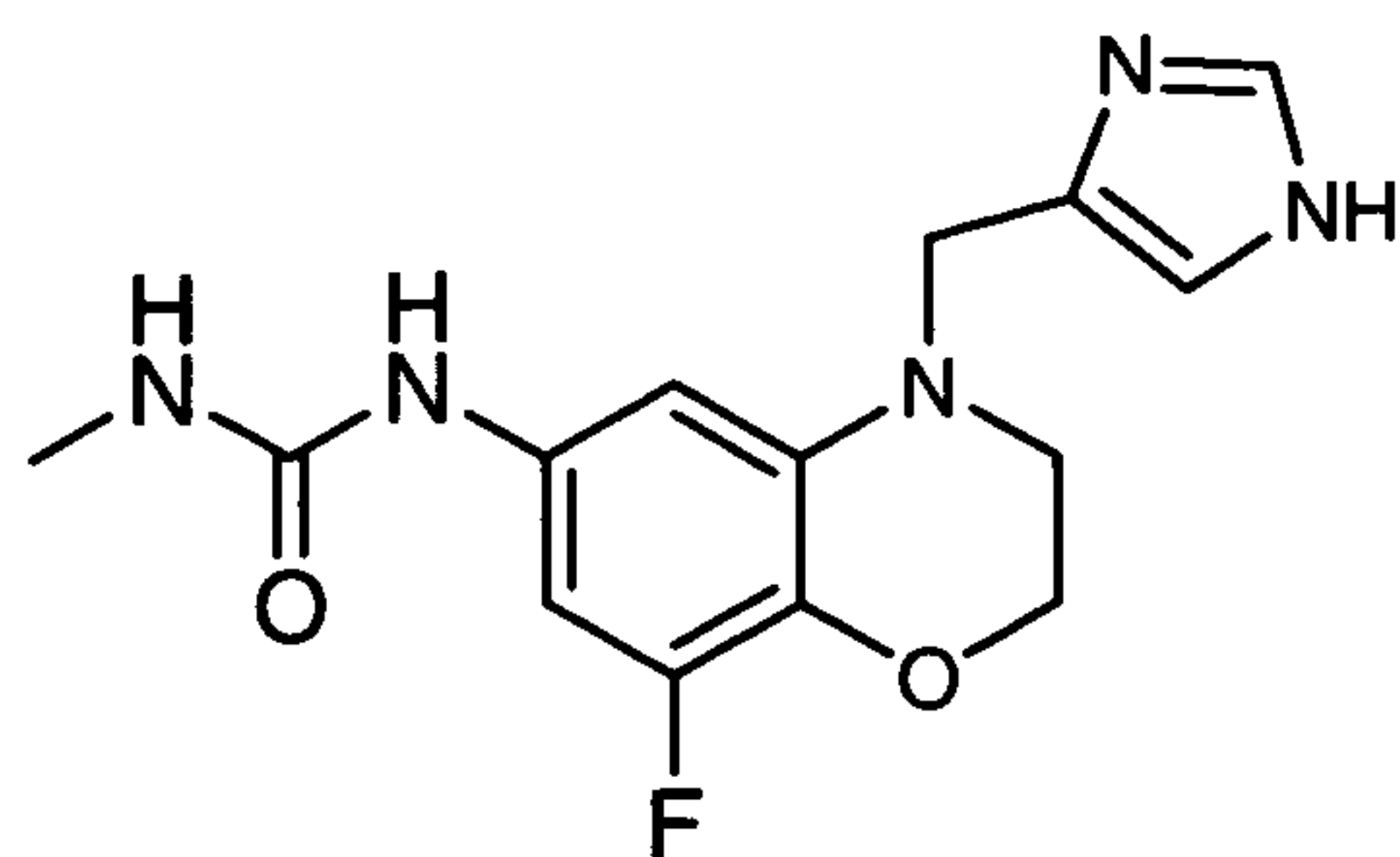
130



303

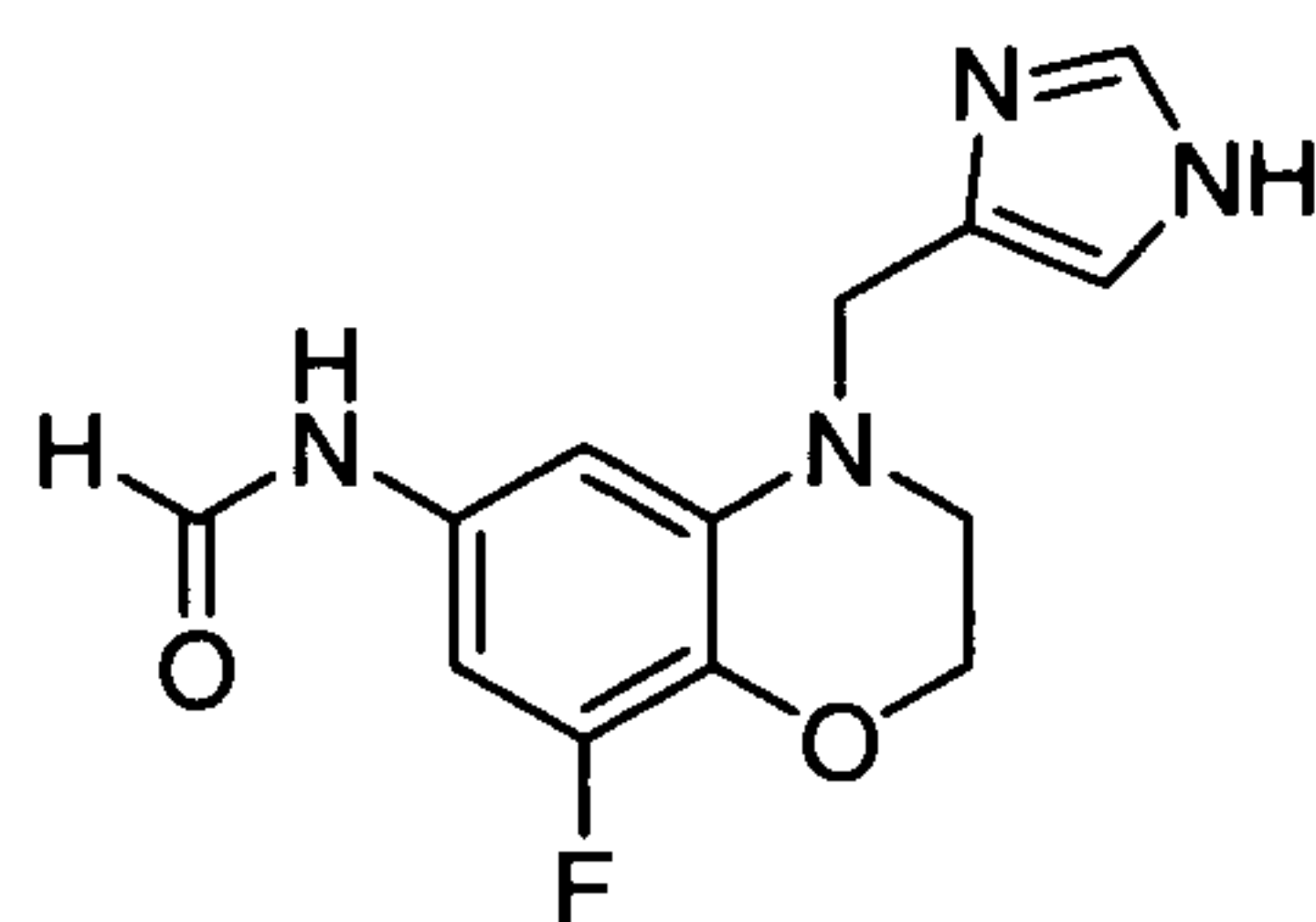
116

131



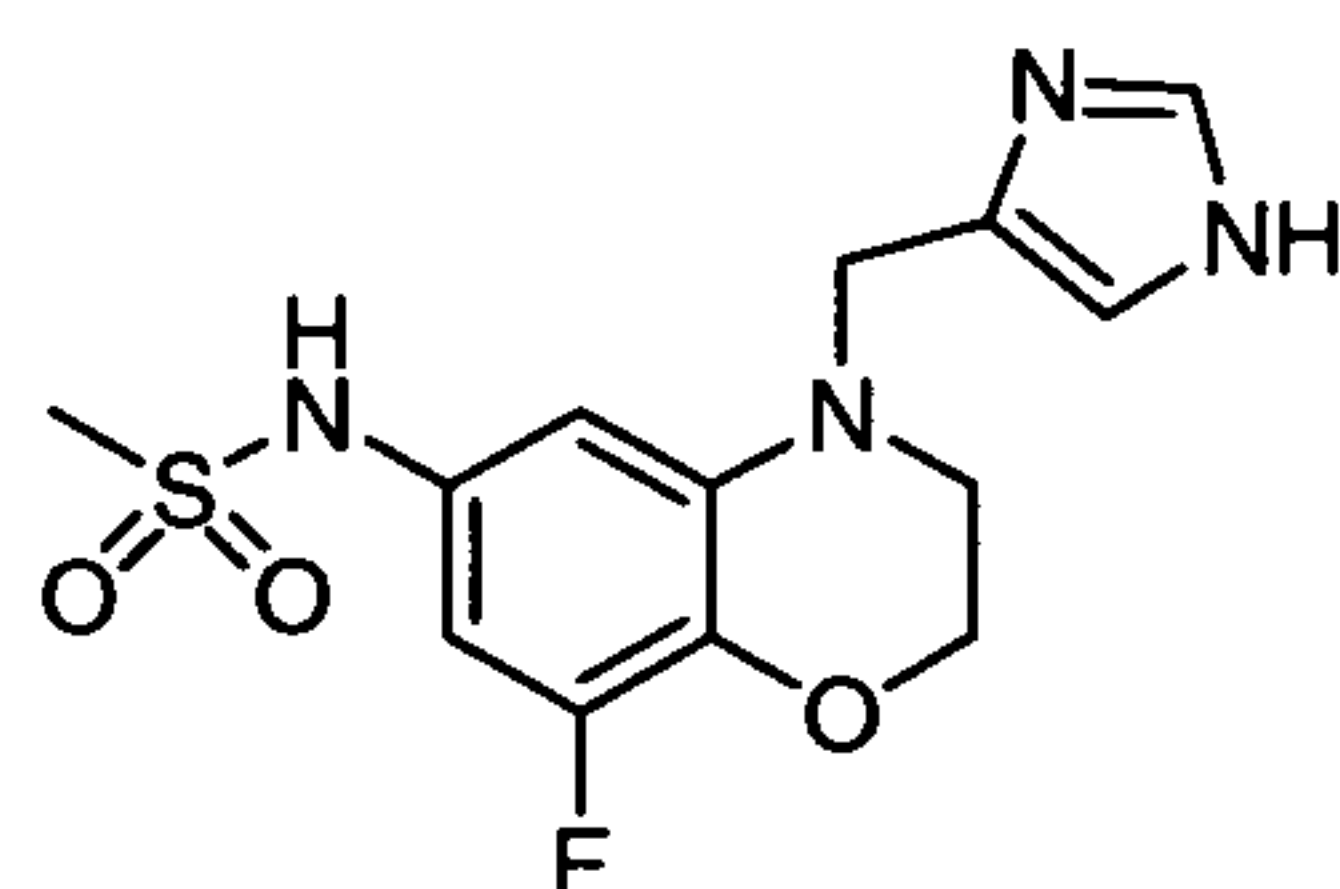
306

132



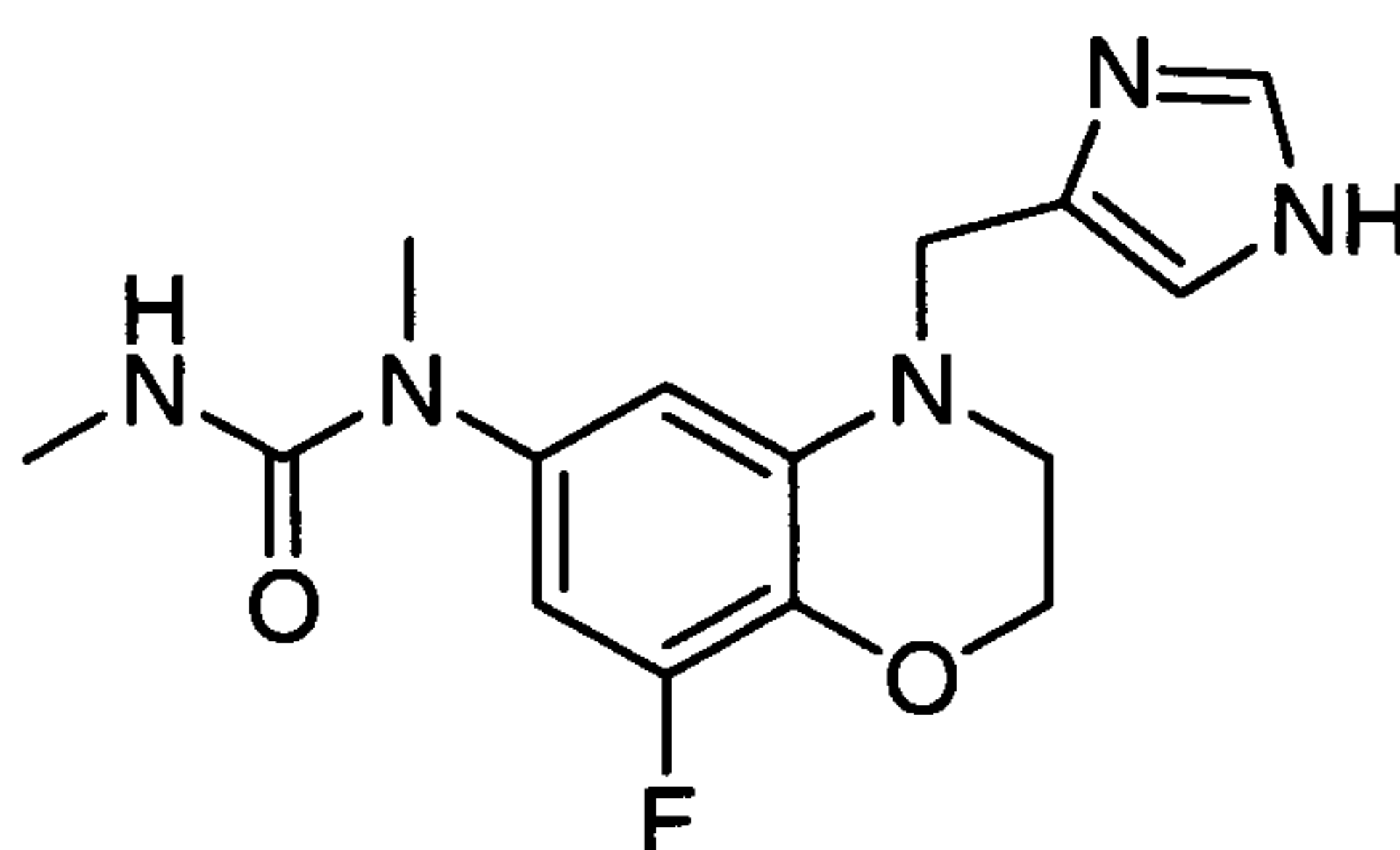
277

133



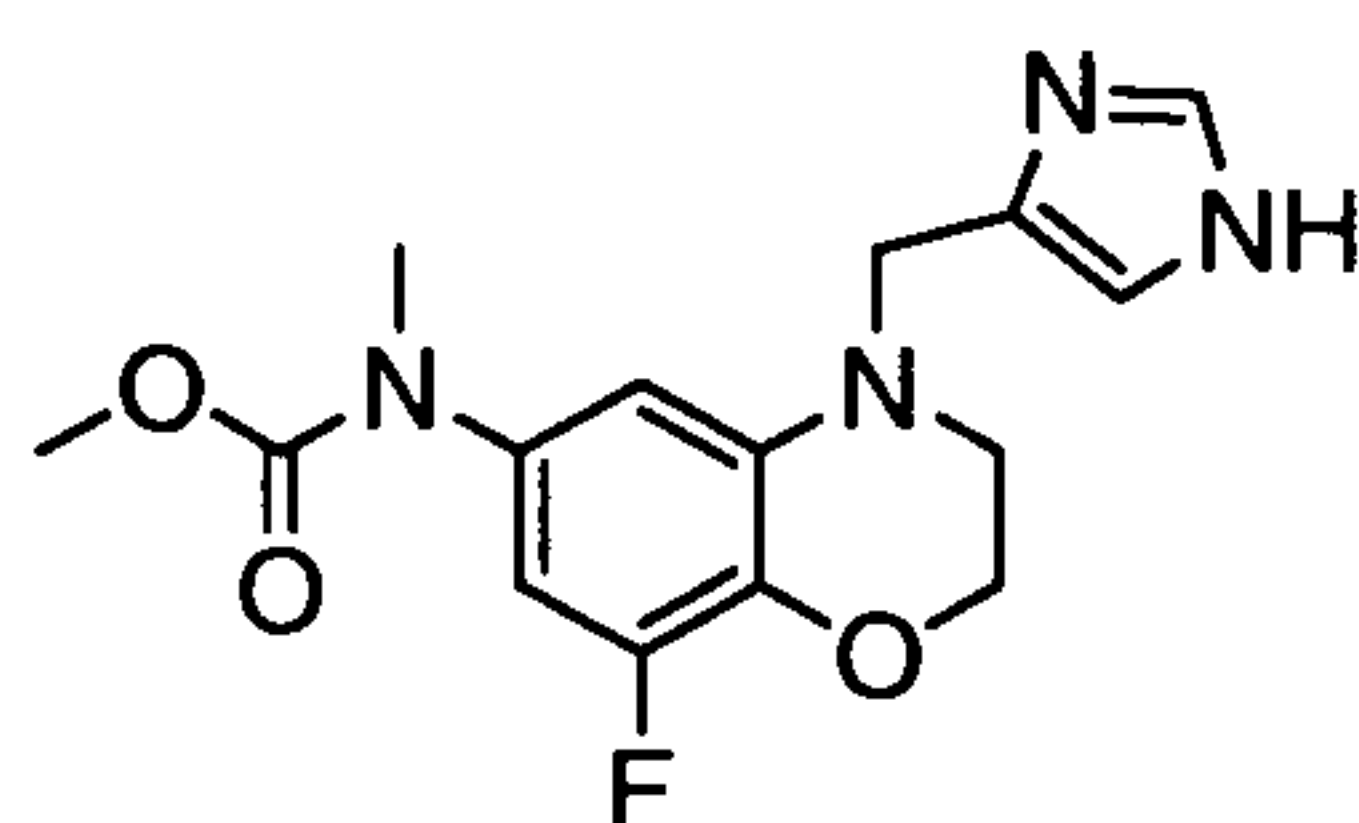
327

134



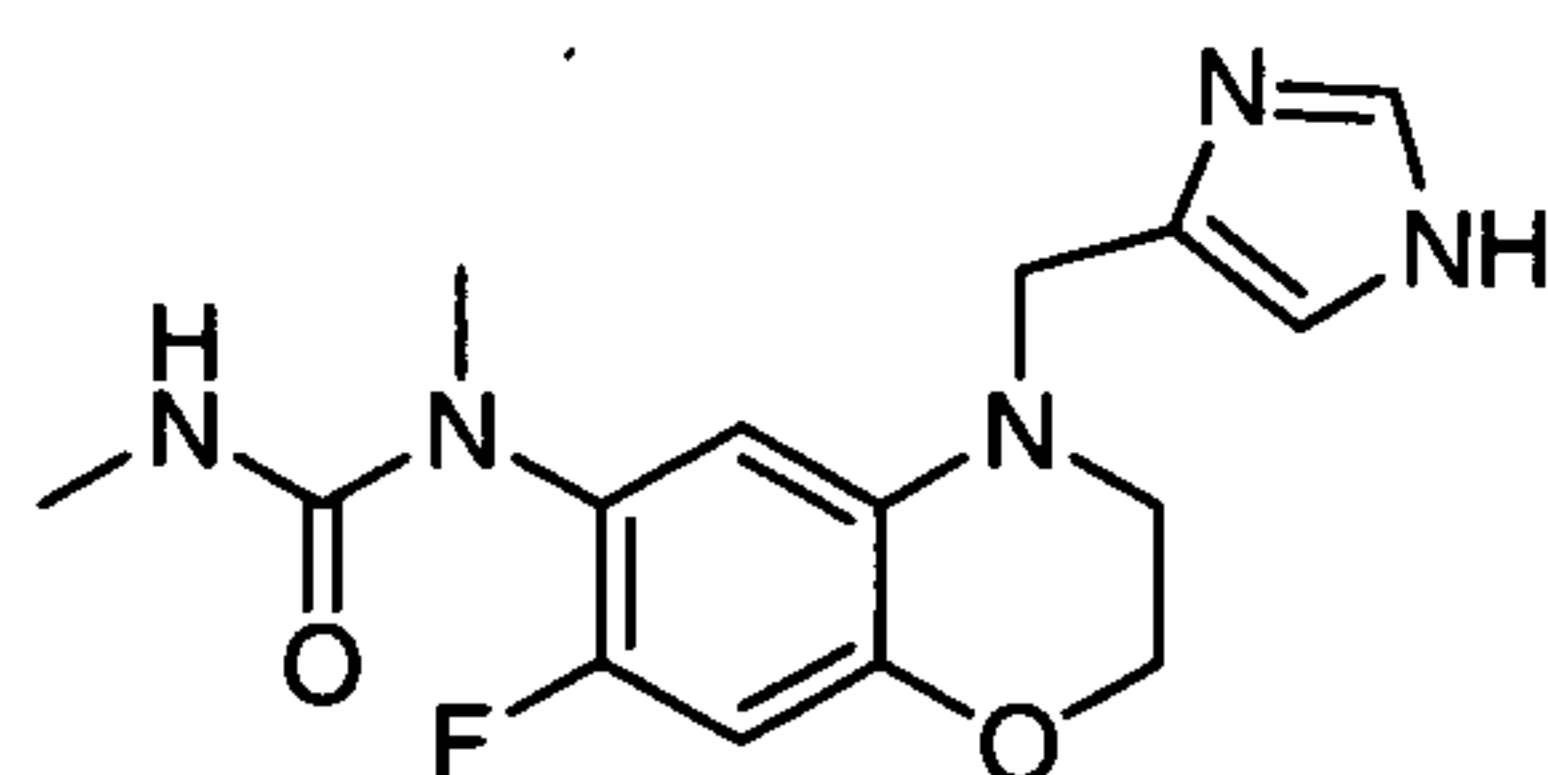
320

135



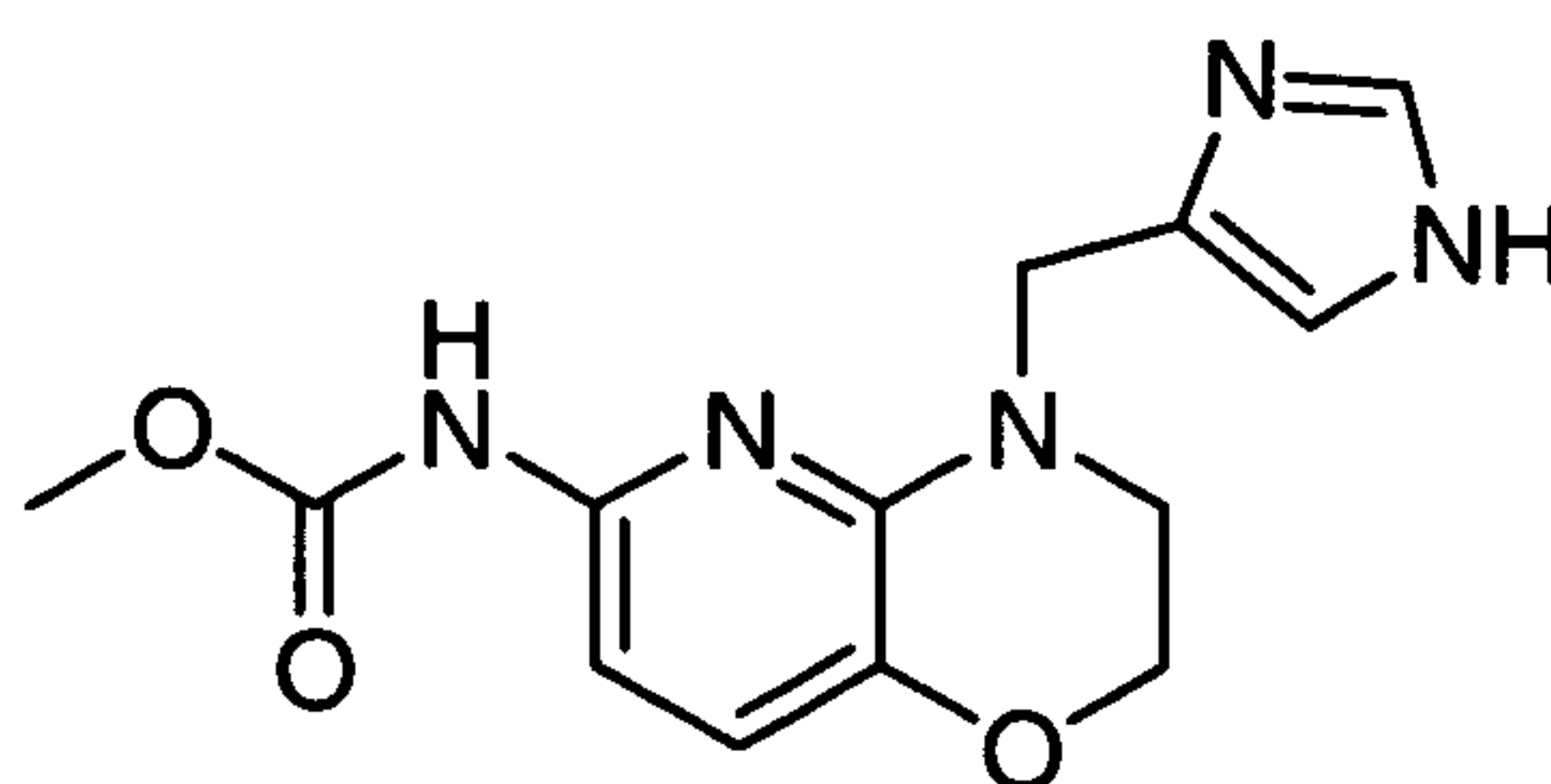
321

136



320

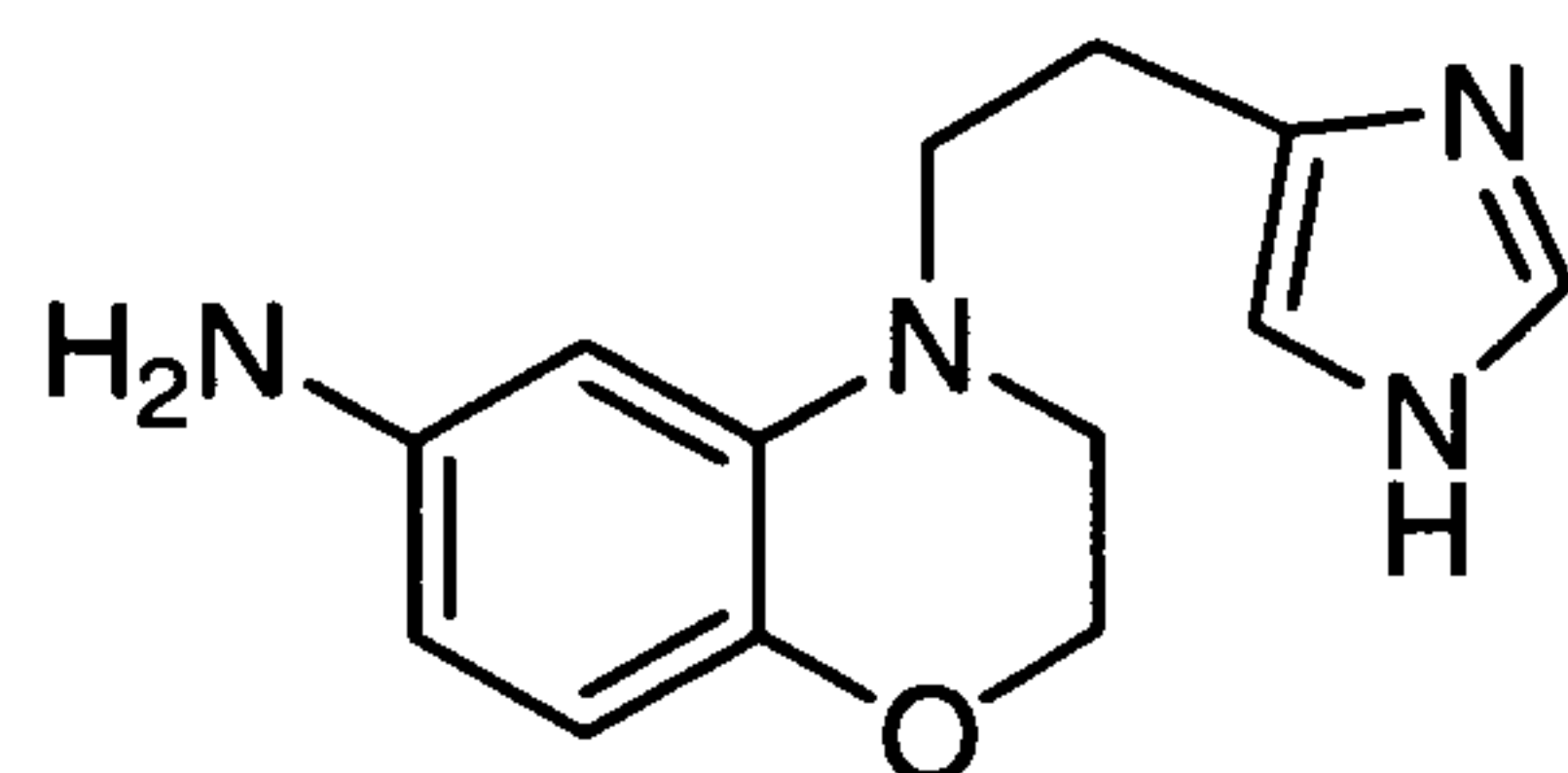
137



290

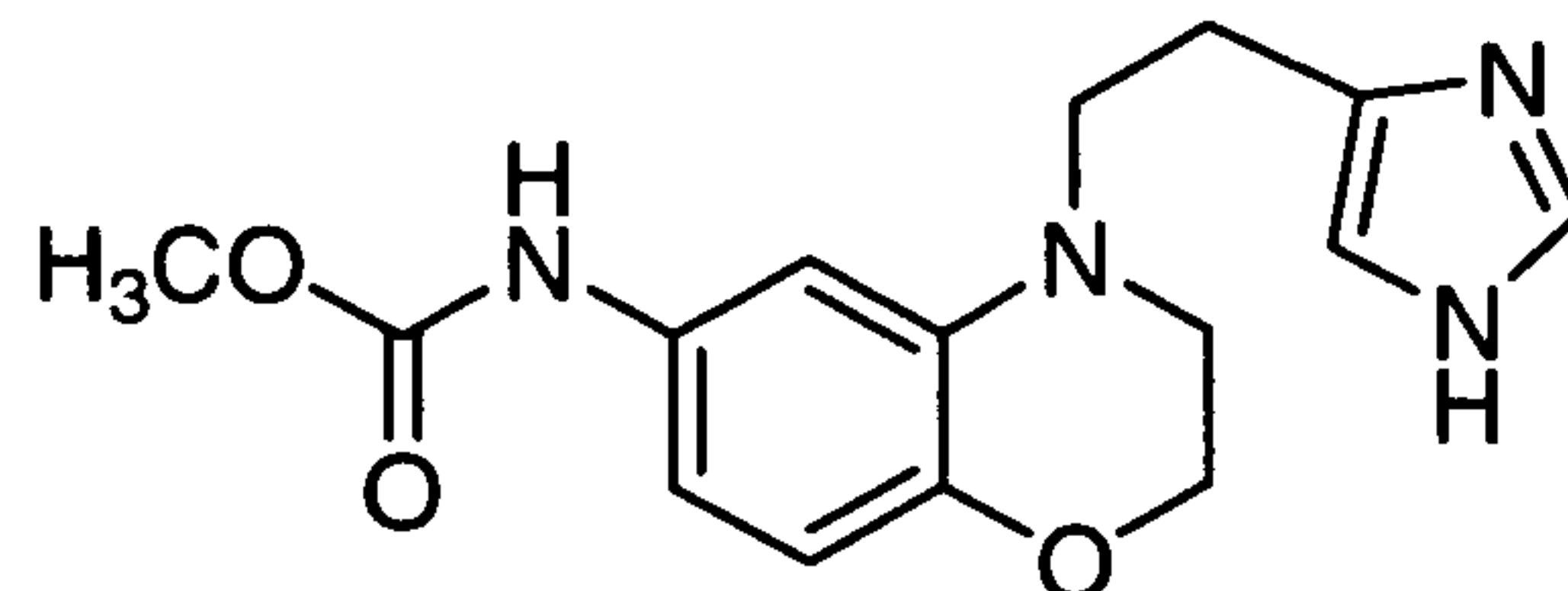
117

138



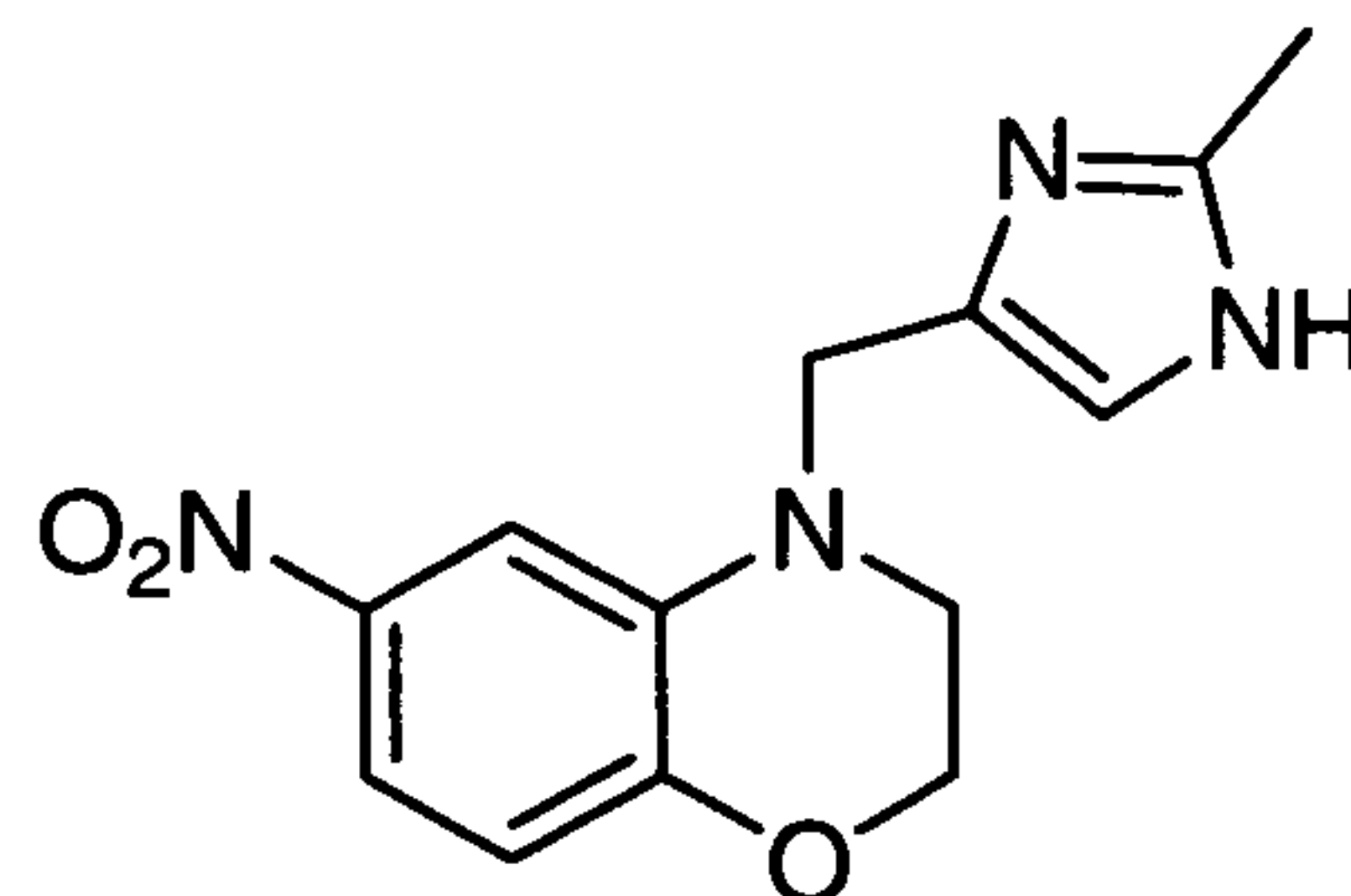
245

139



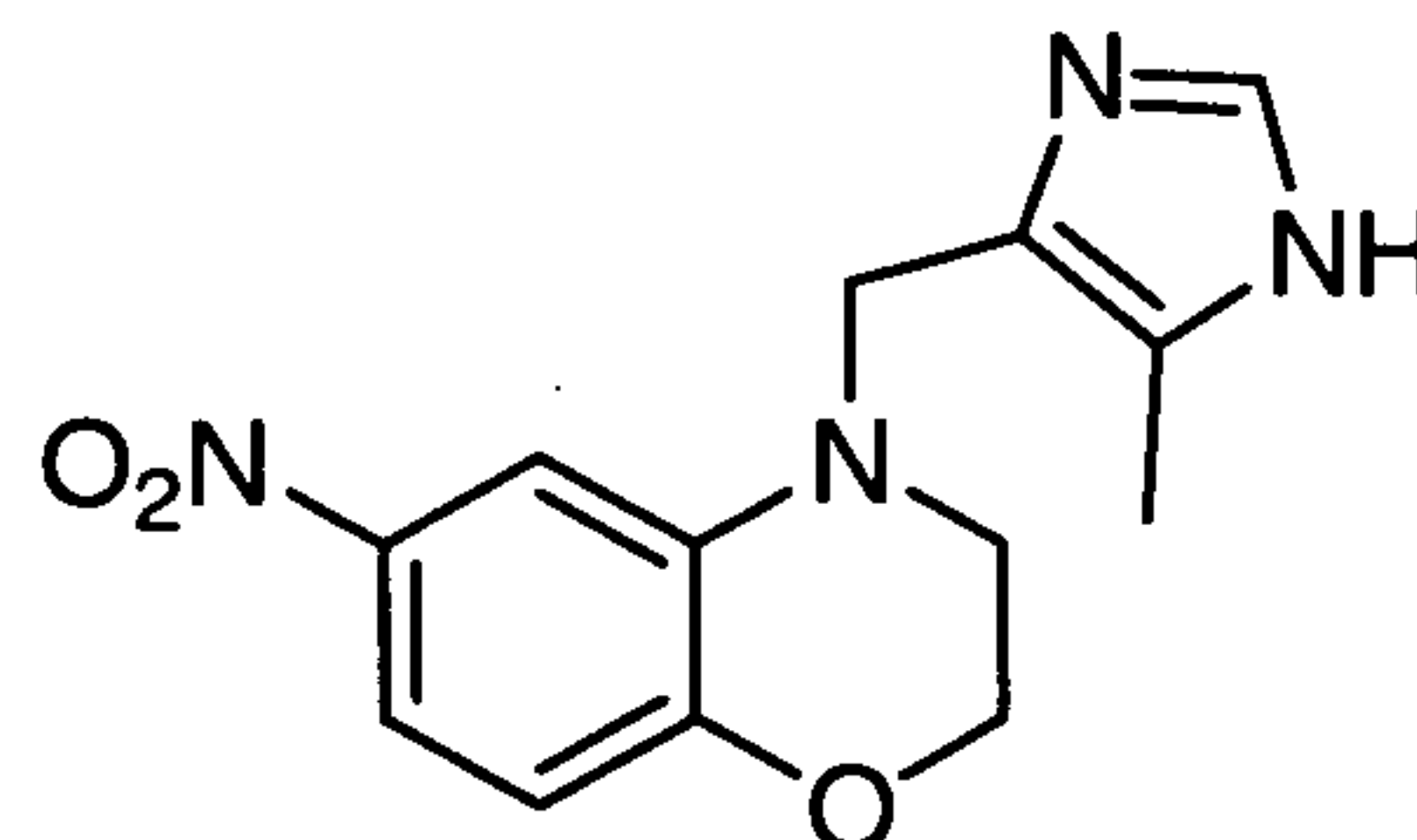
303

140



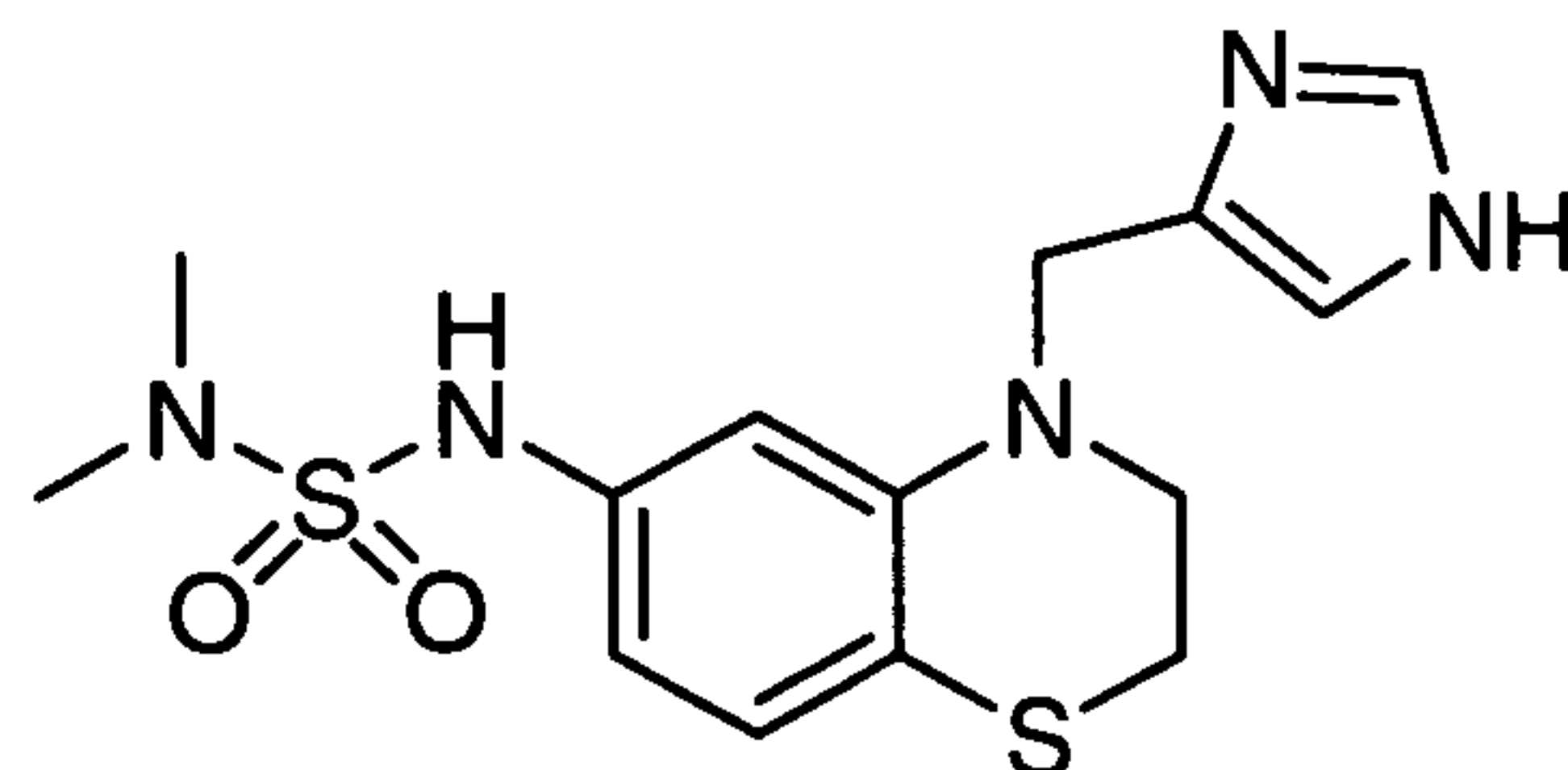
275

141



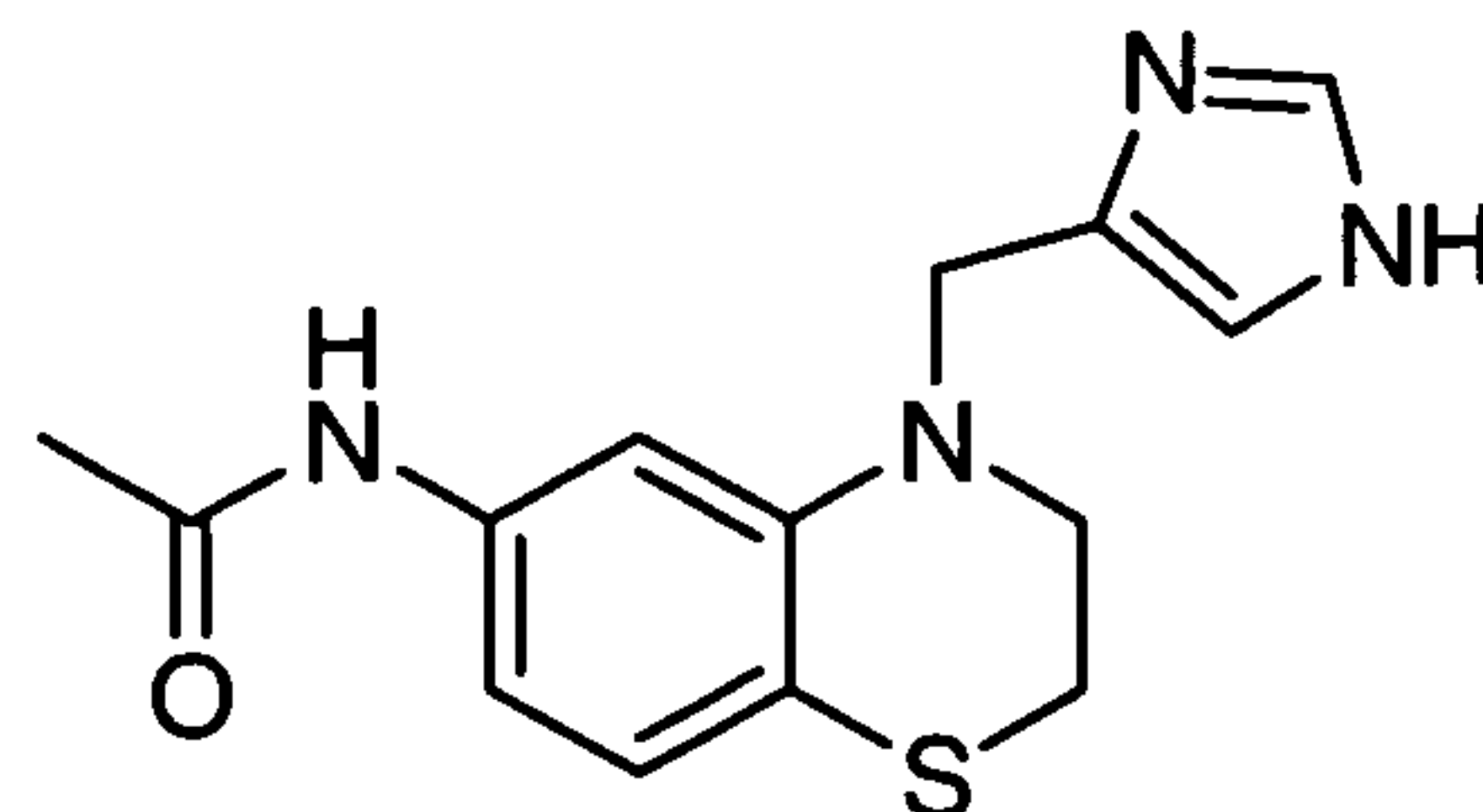
275

142



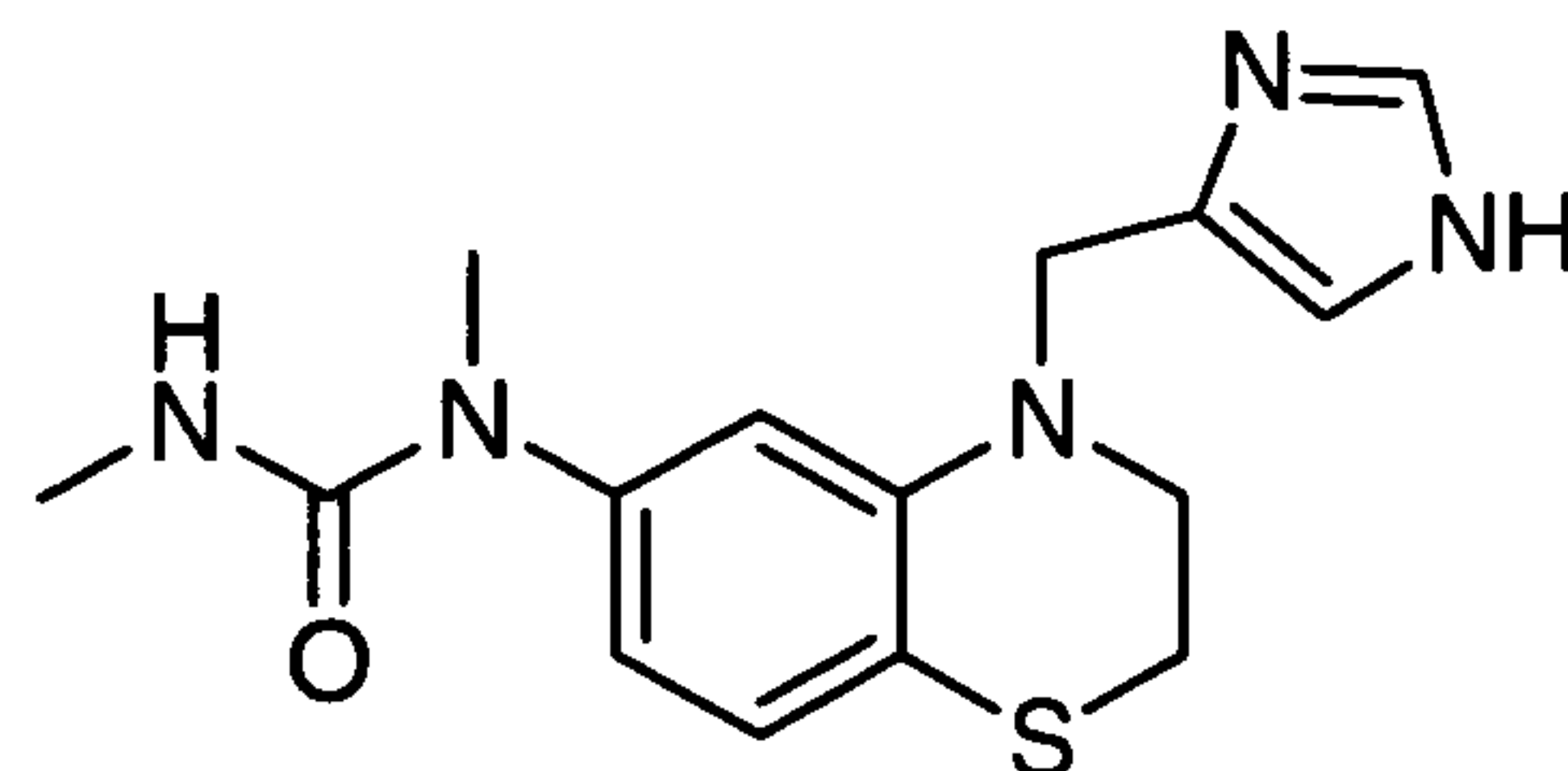
354

143



289

144

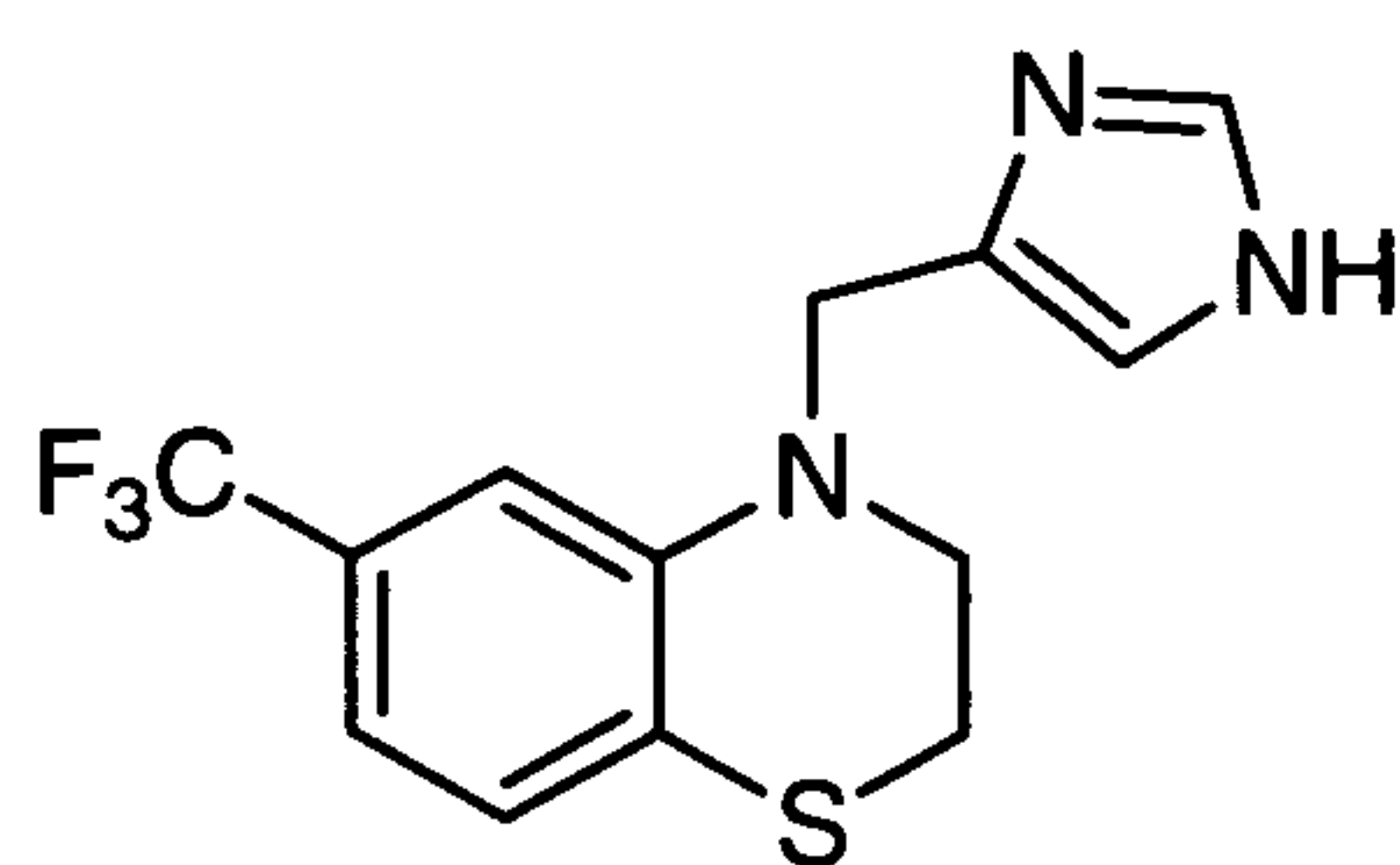


318

118

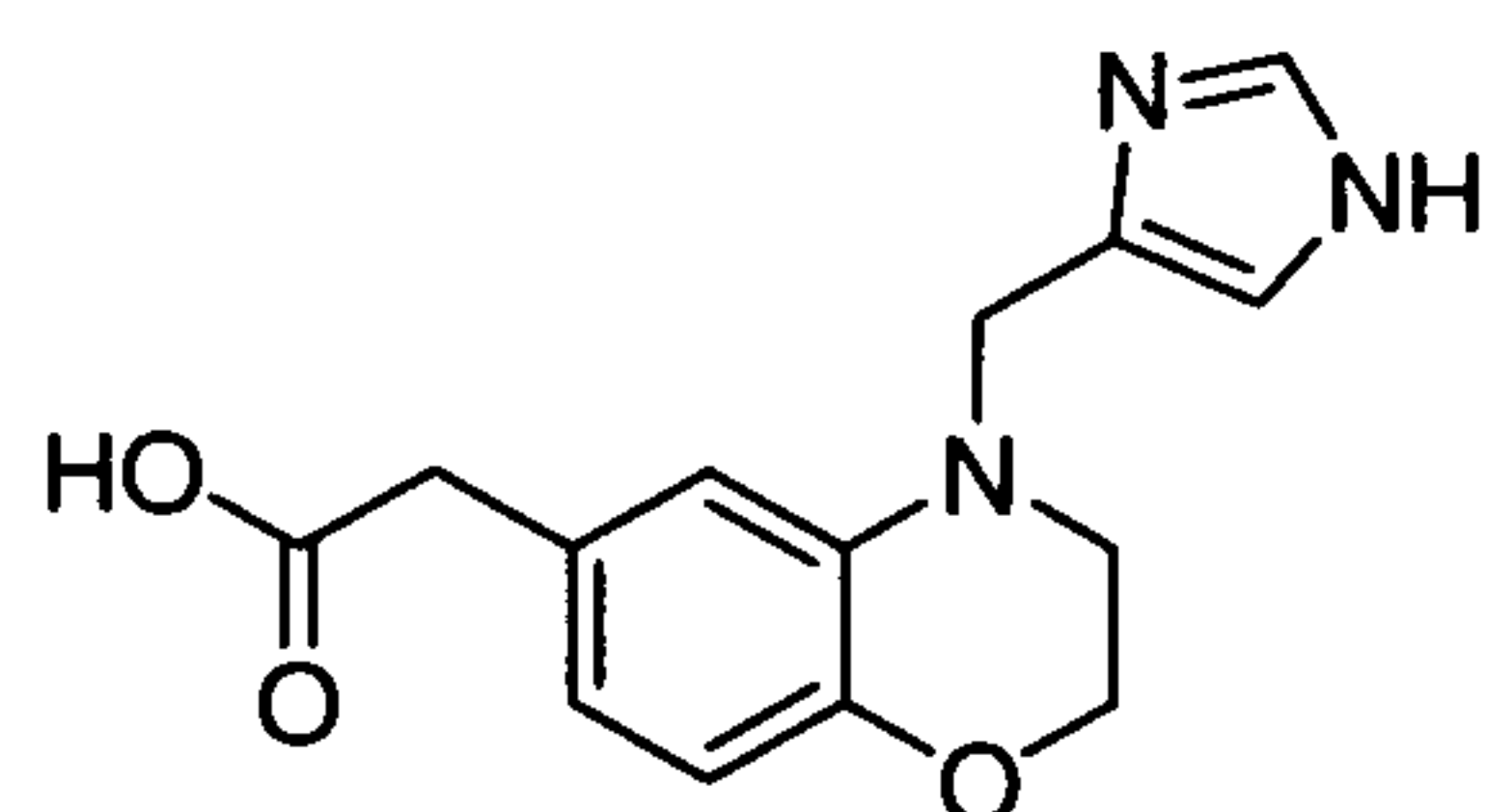
145

300



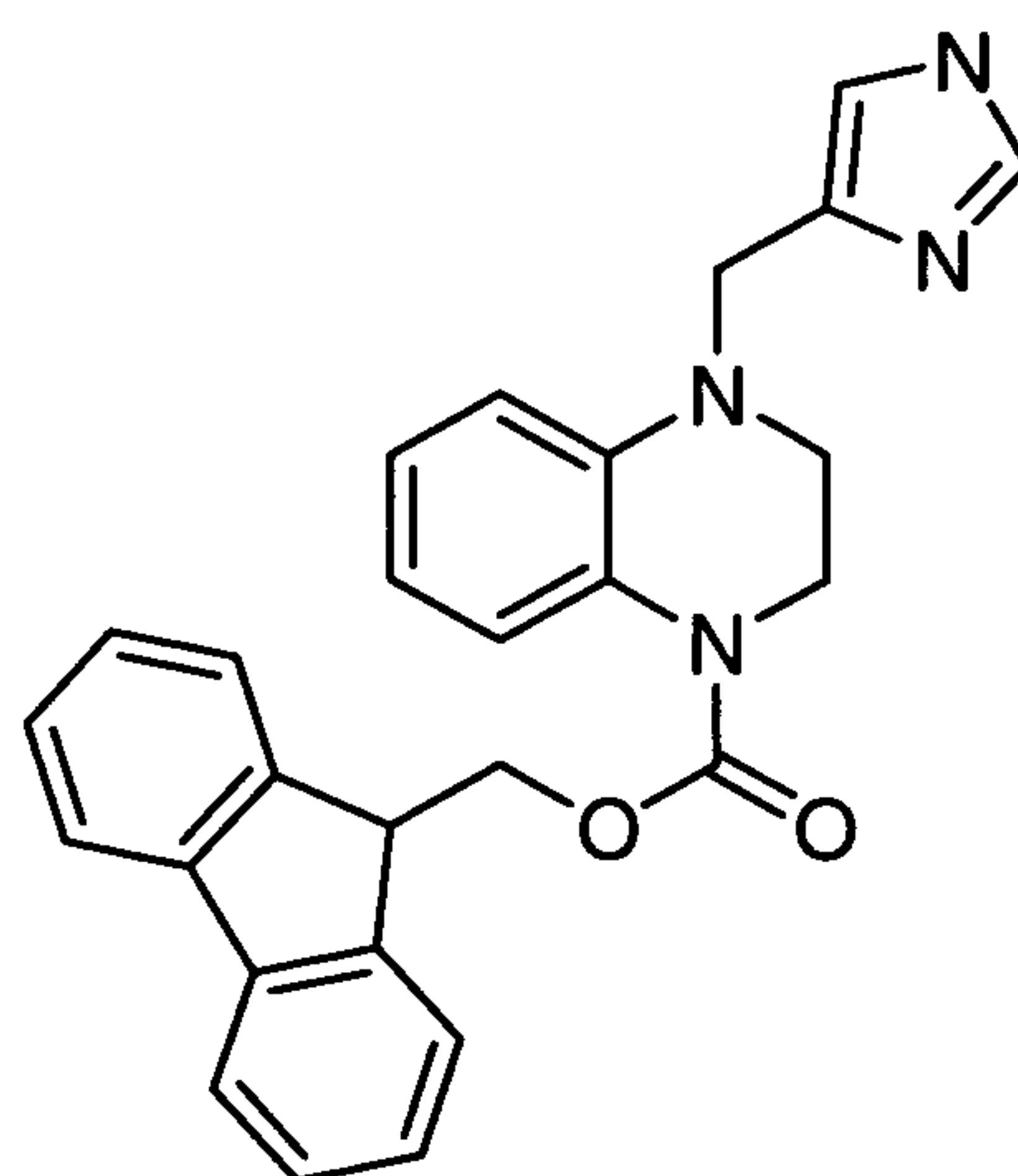
146

274



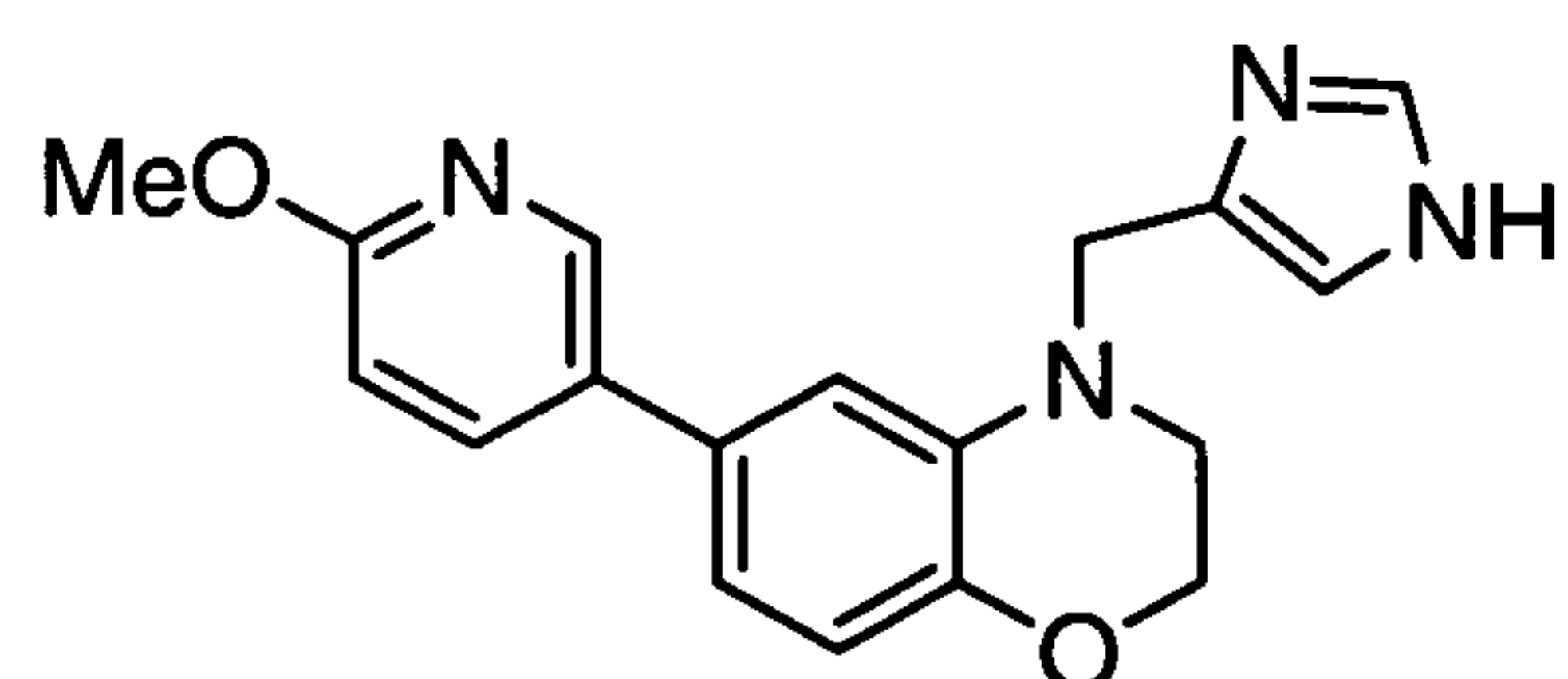
147

437



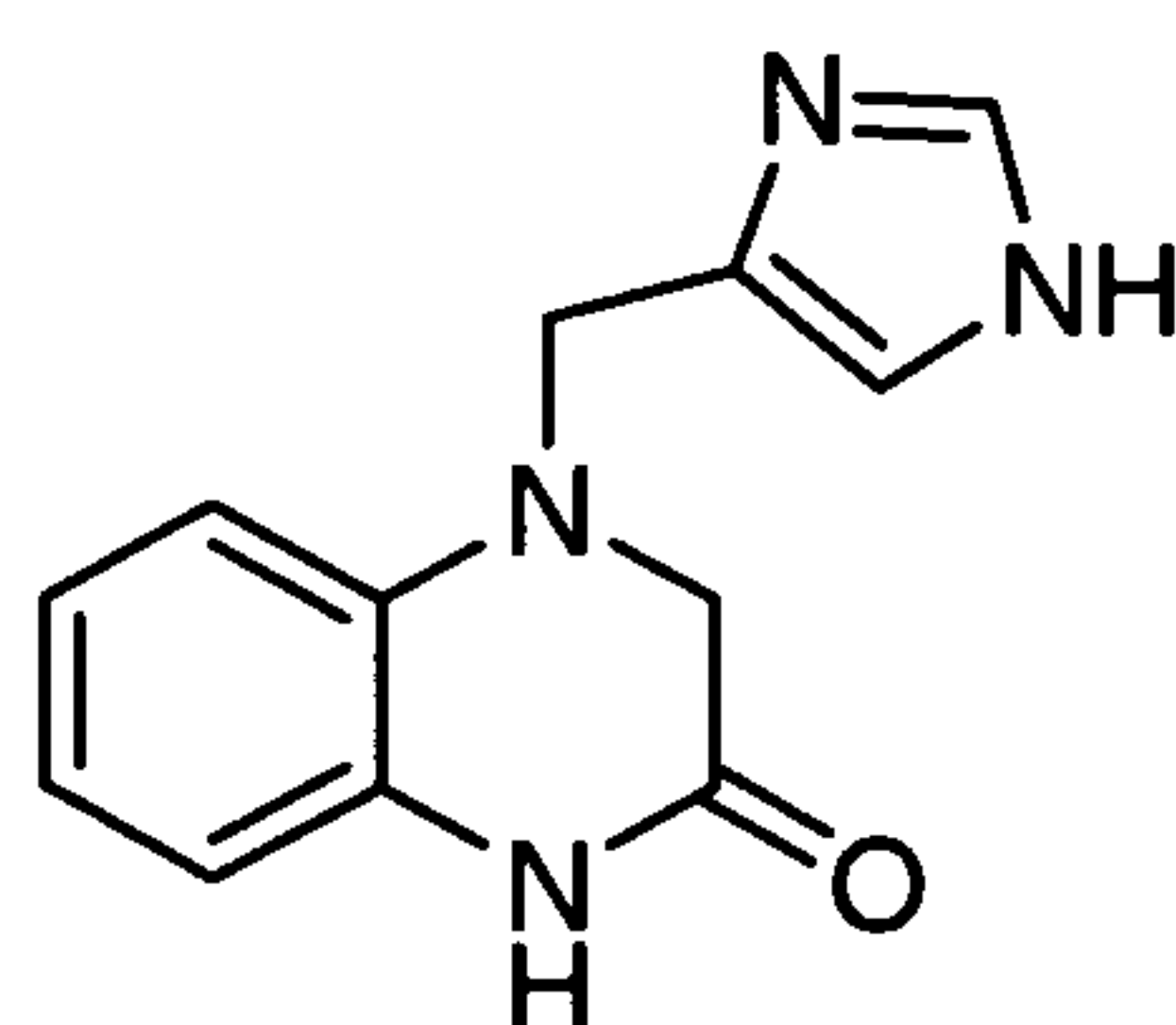
148

323



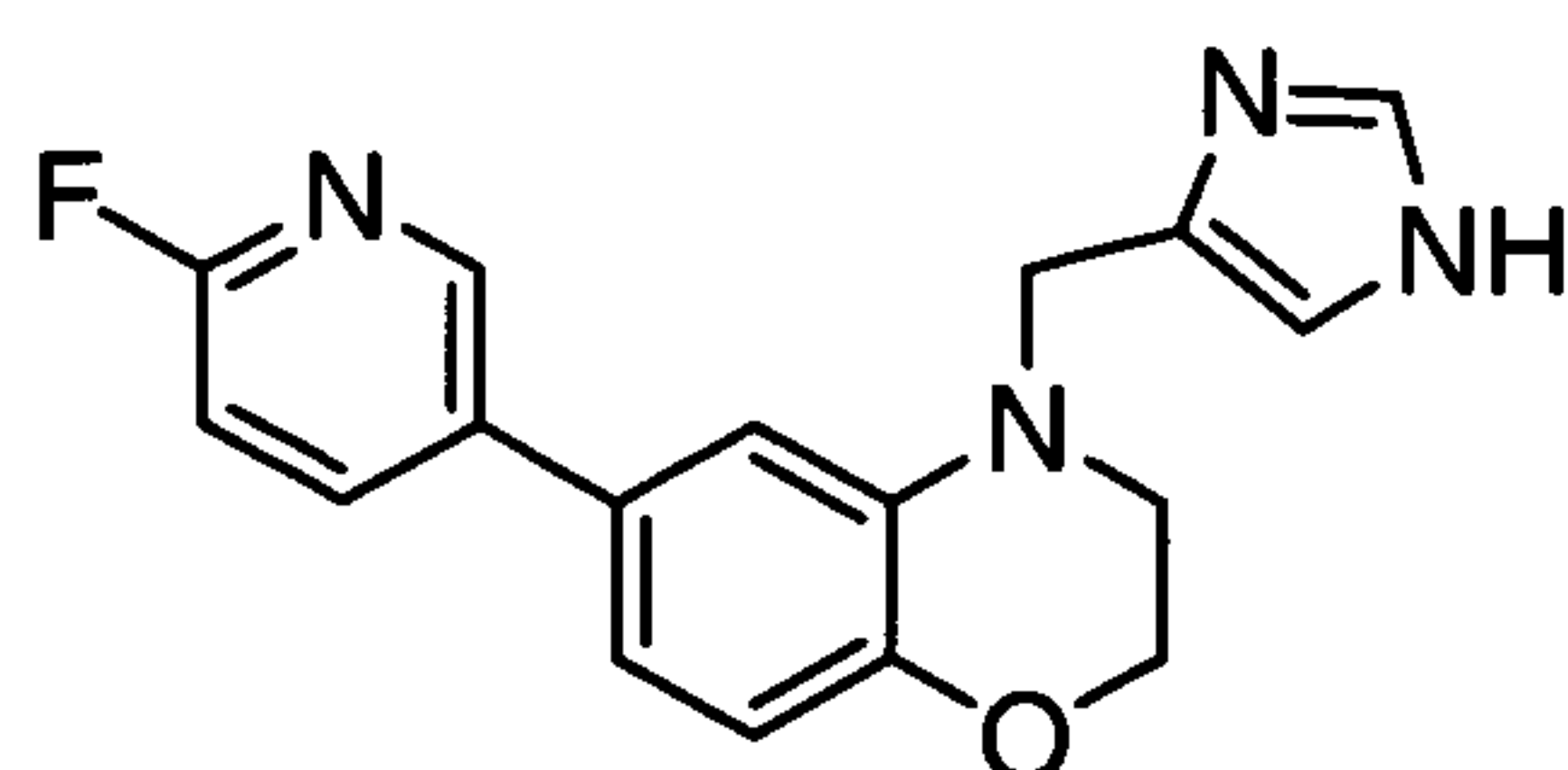
149

229



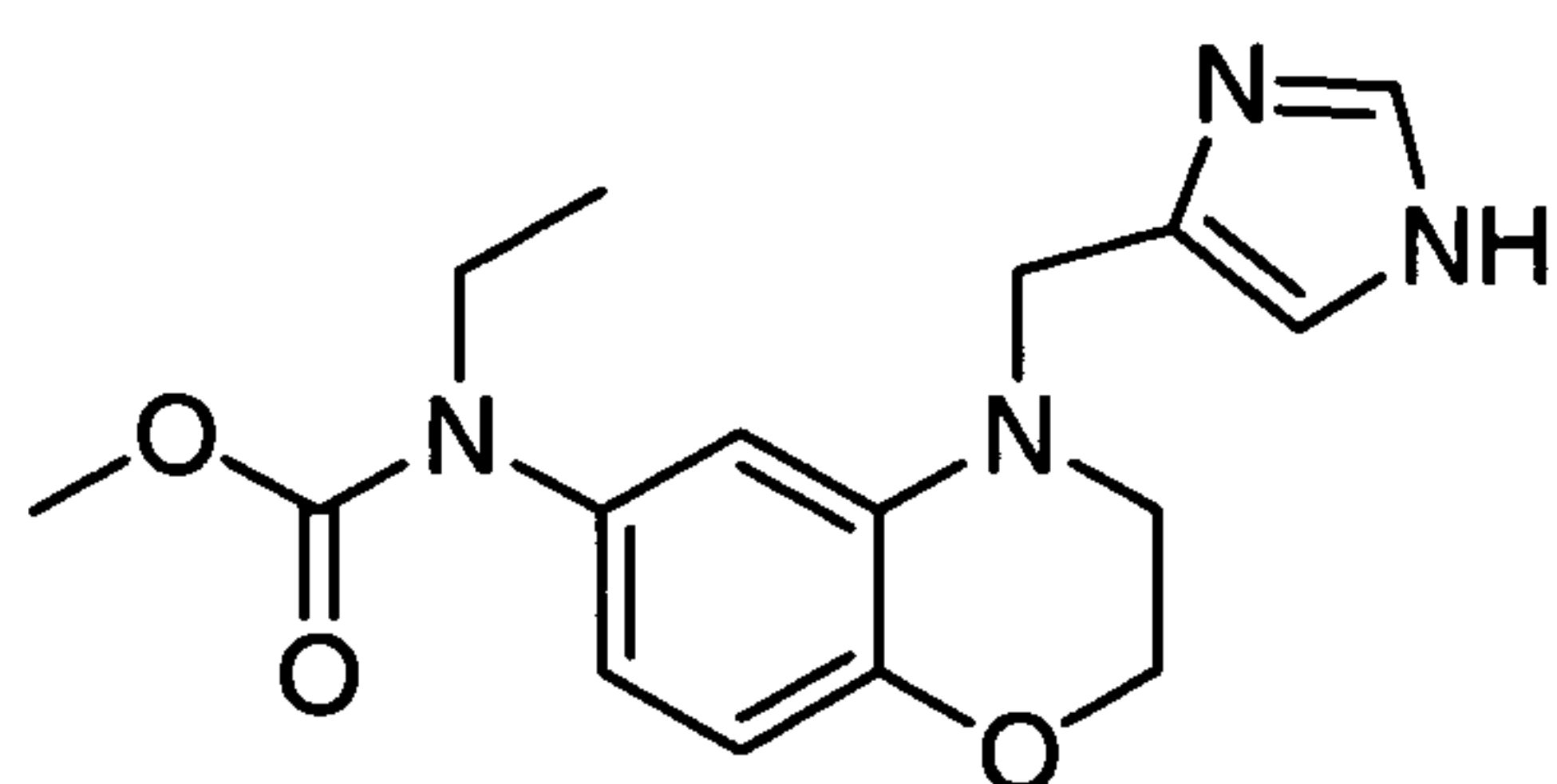
150

311



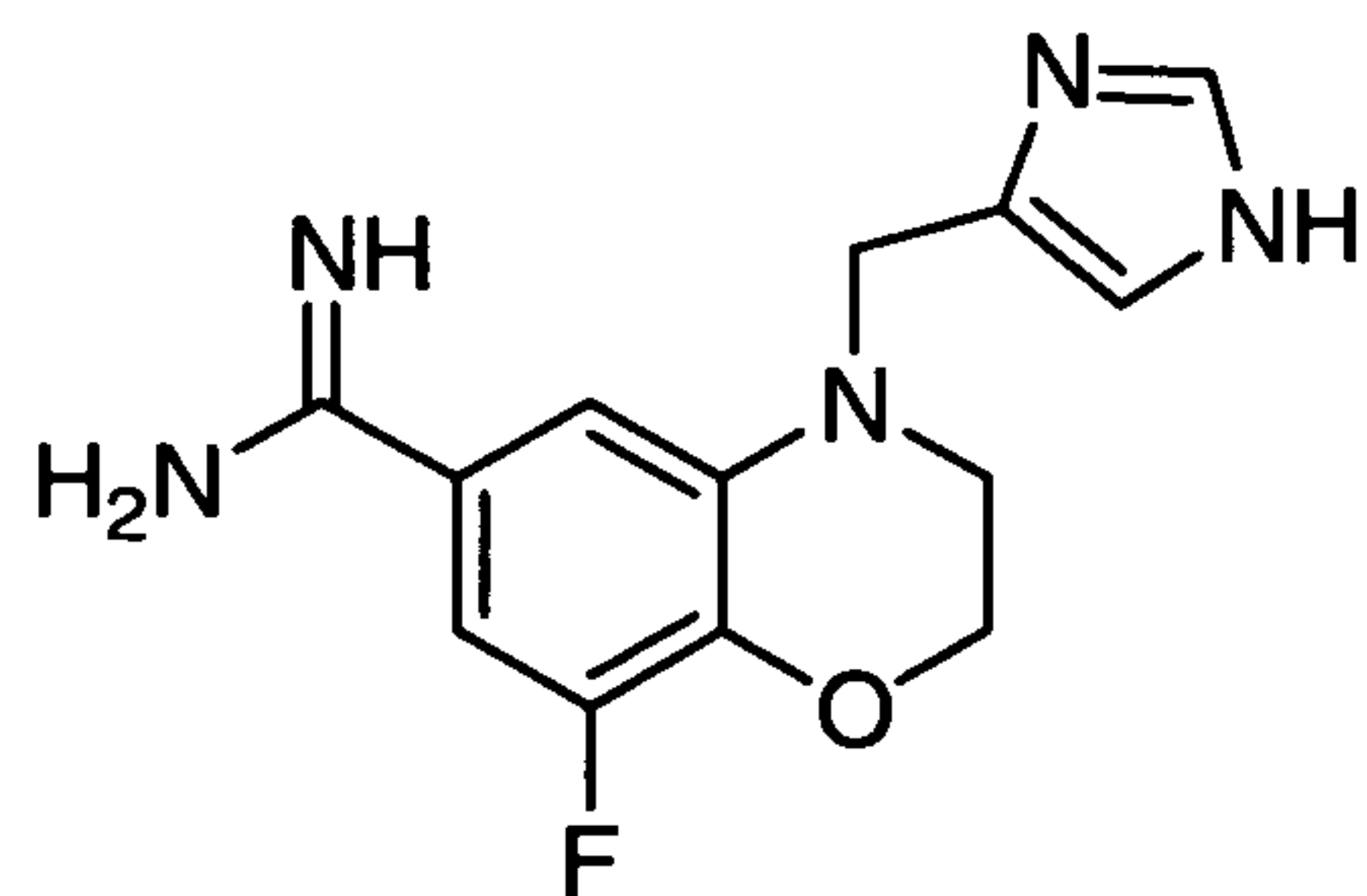
119

151



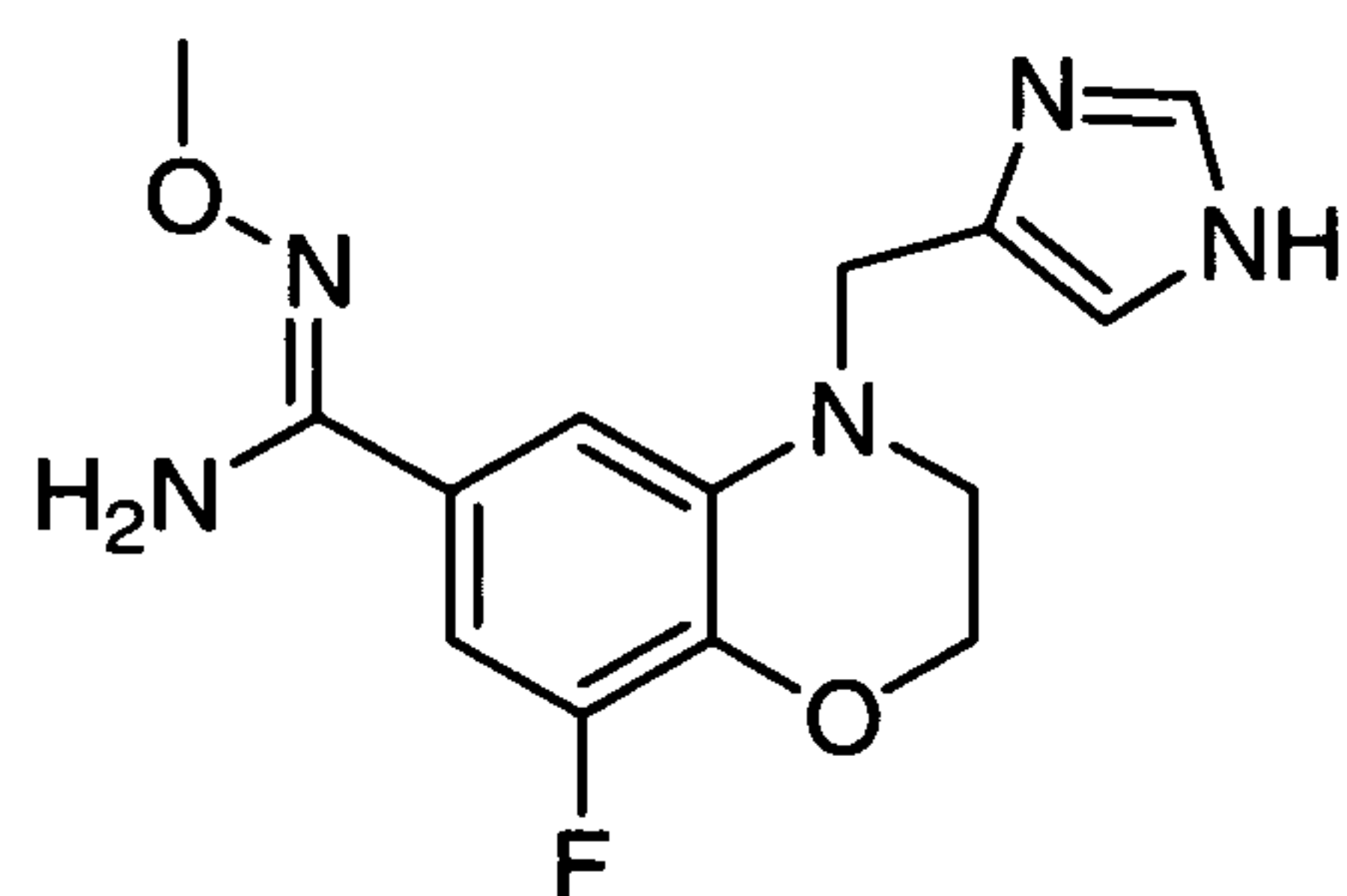
317

152



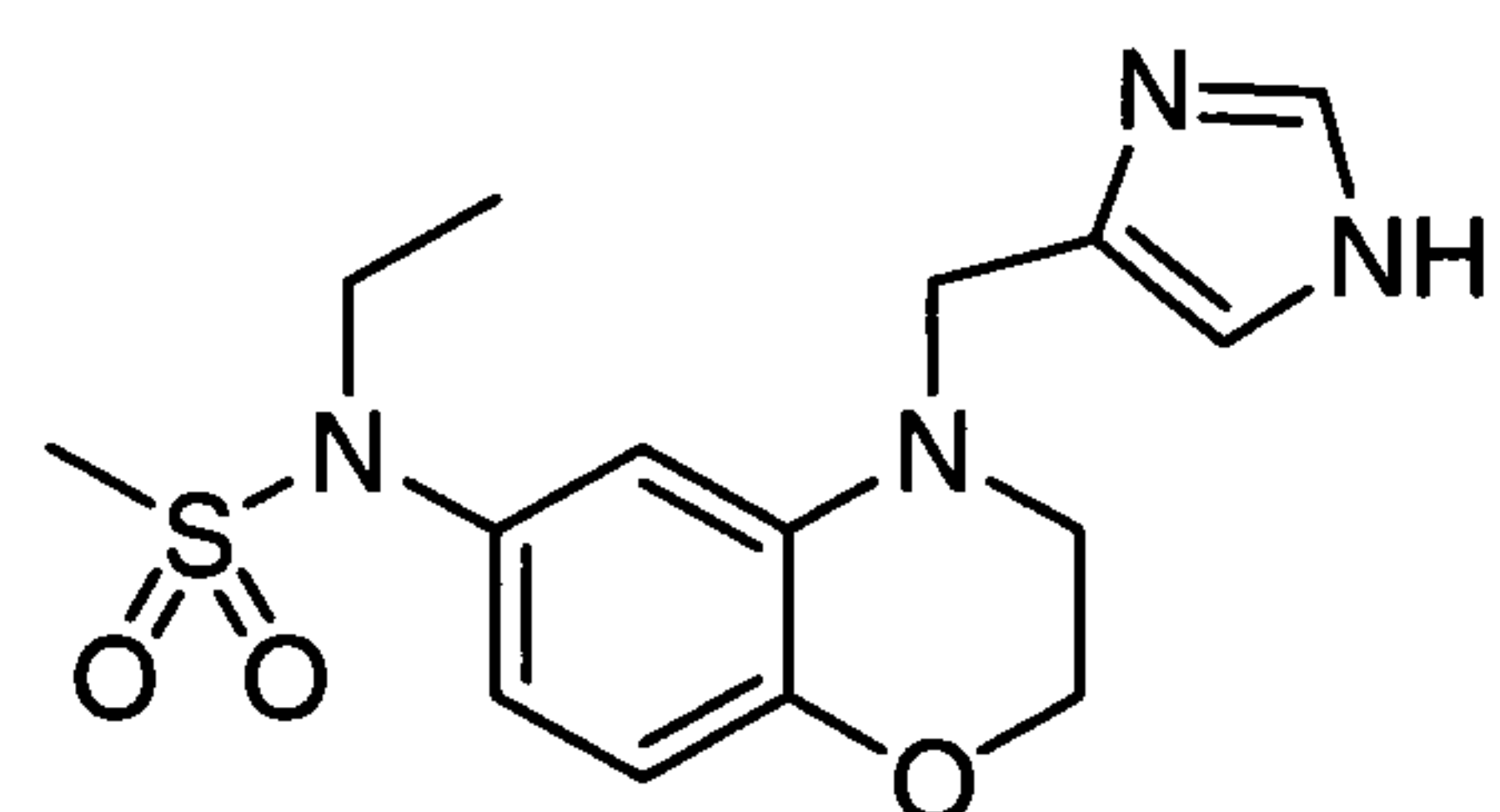
276

153



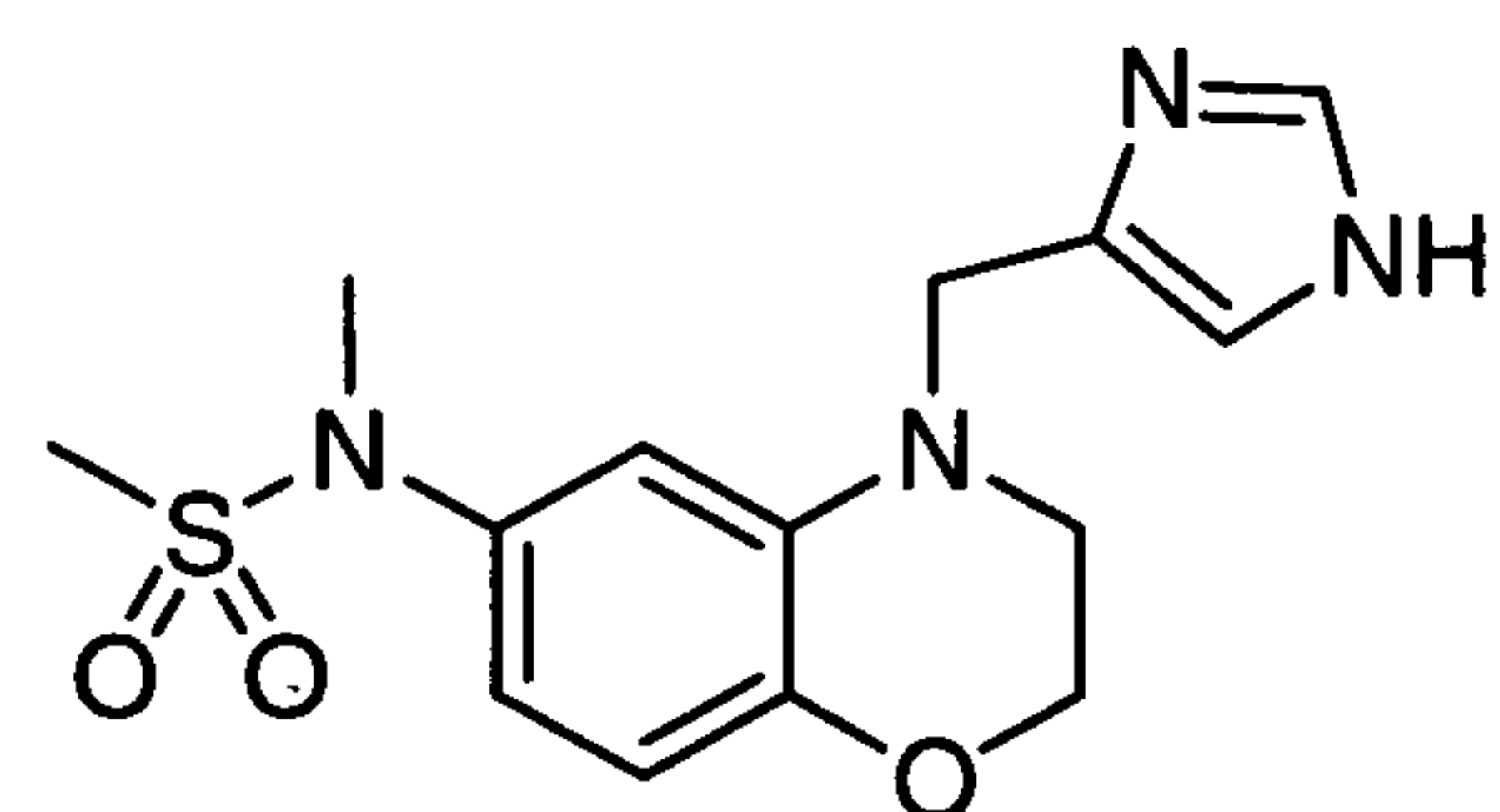
306

154



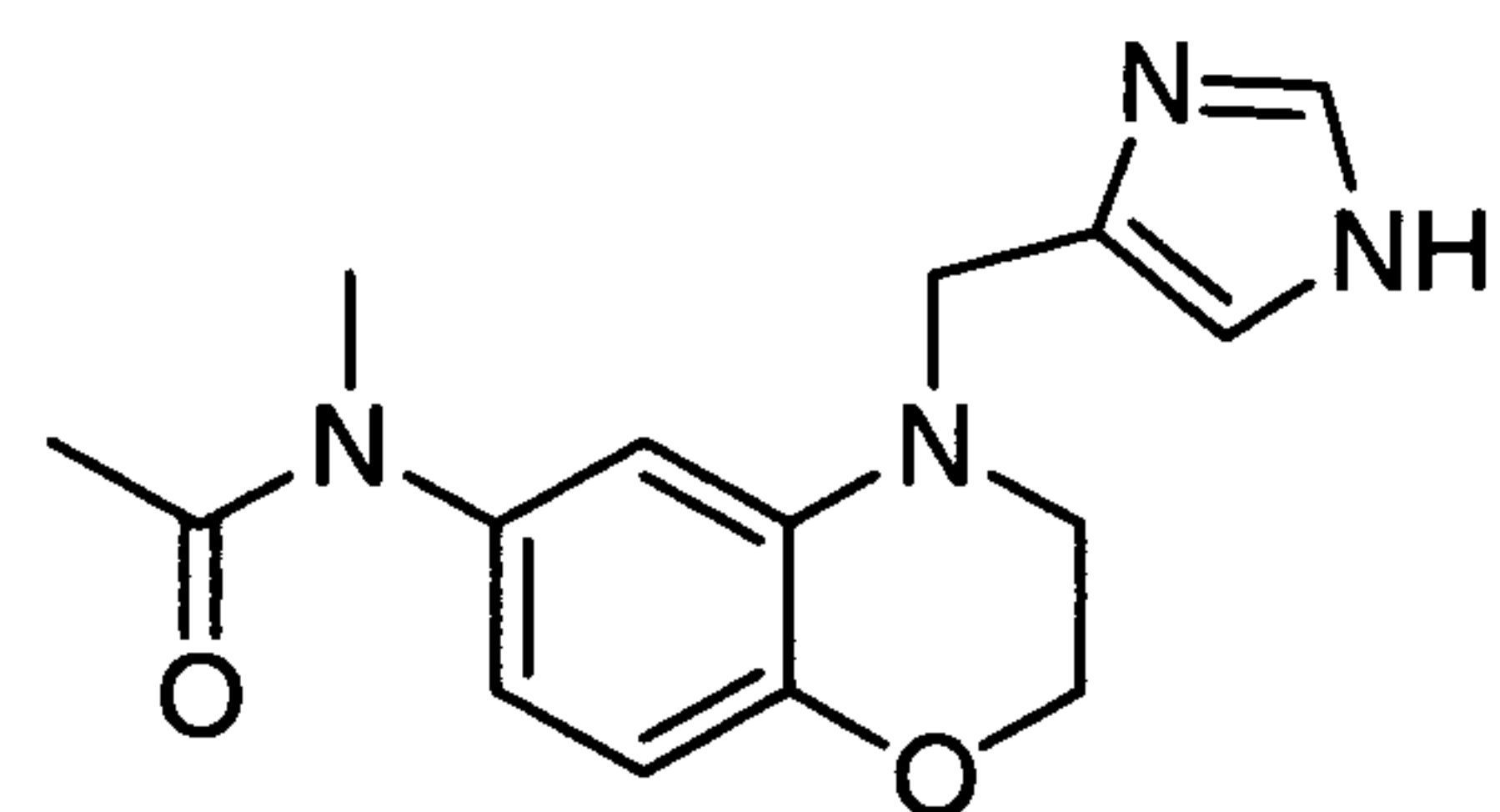
337

155



323

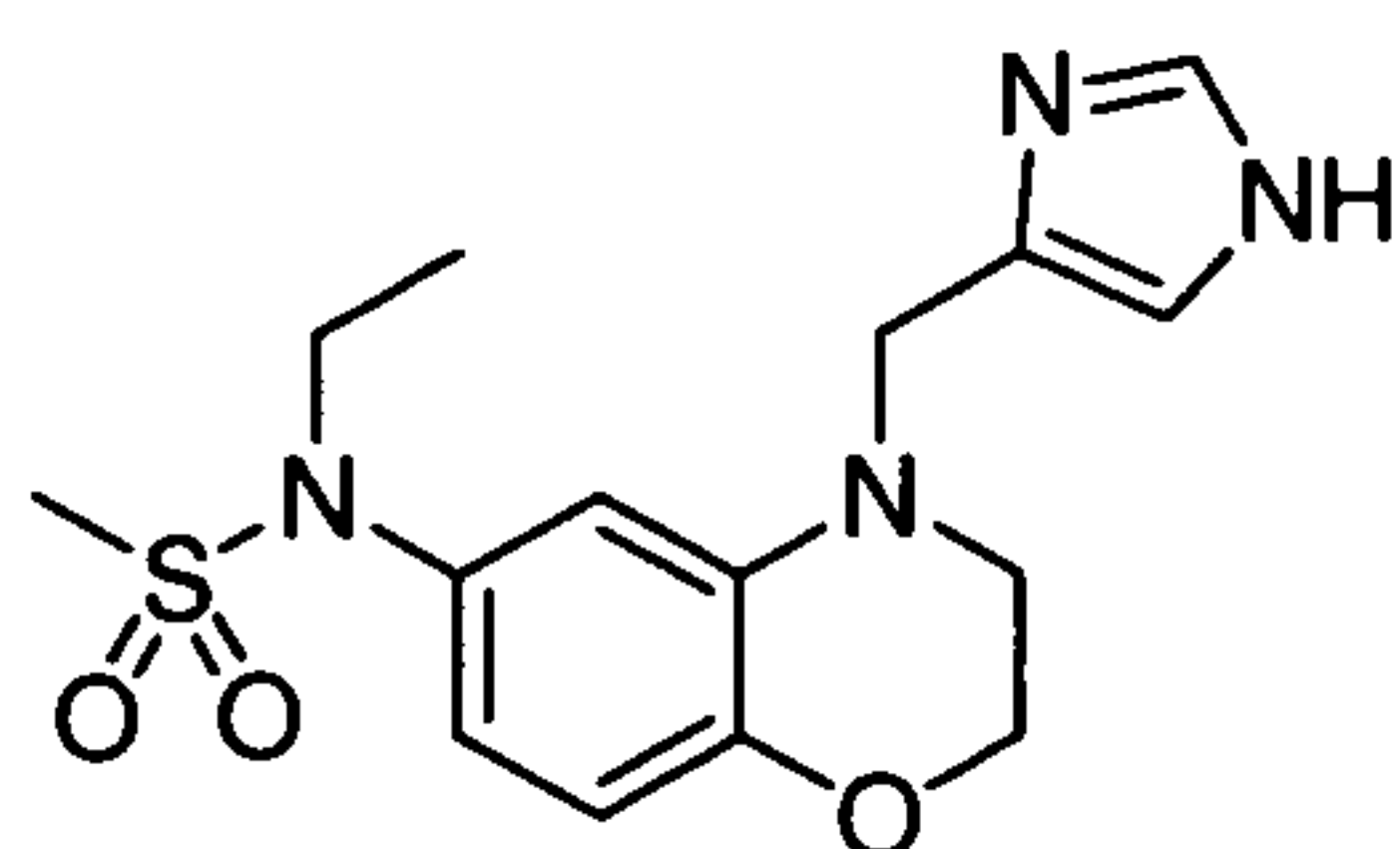
156



287

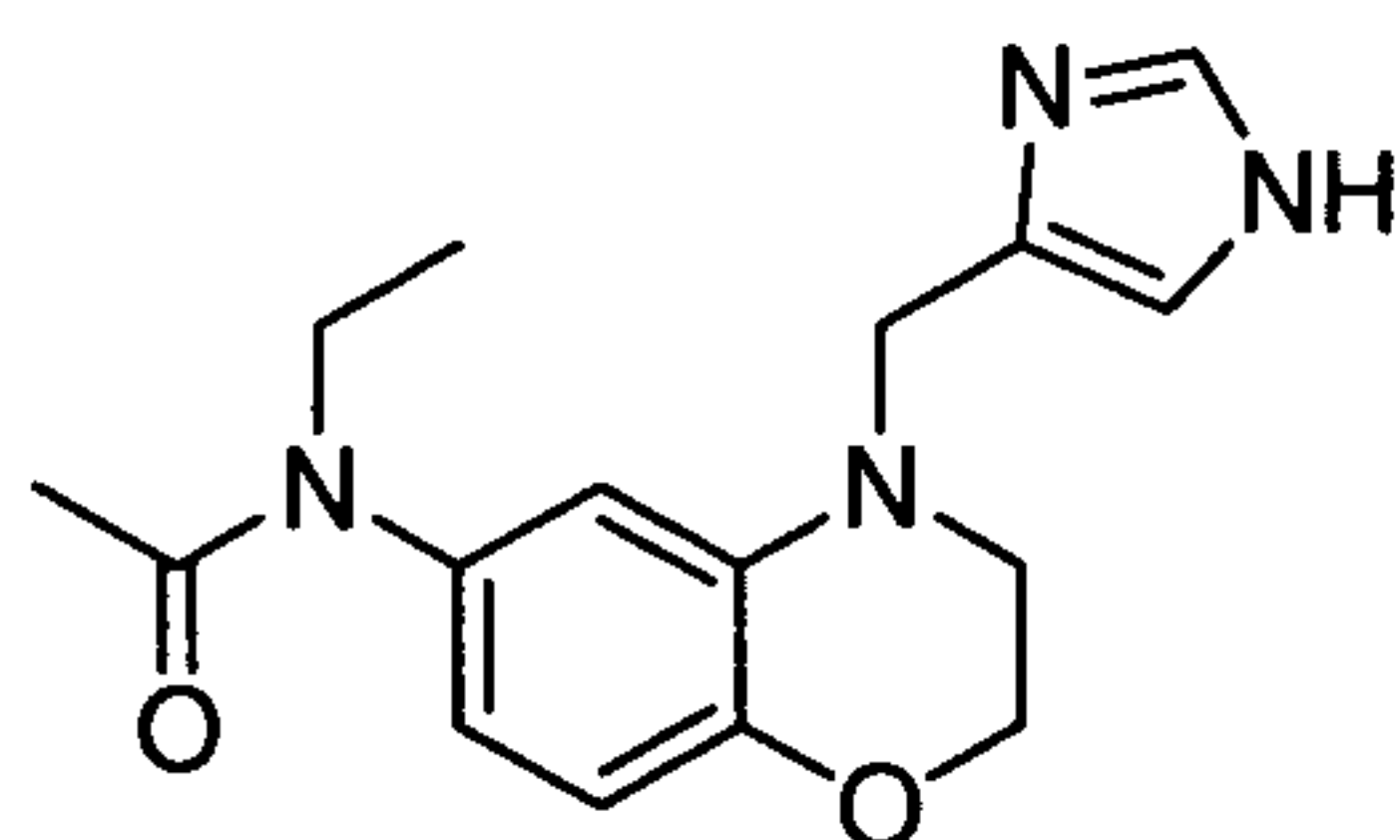
120

157



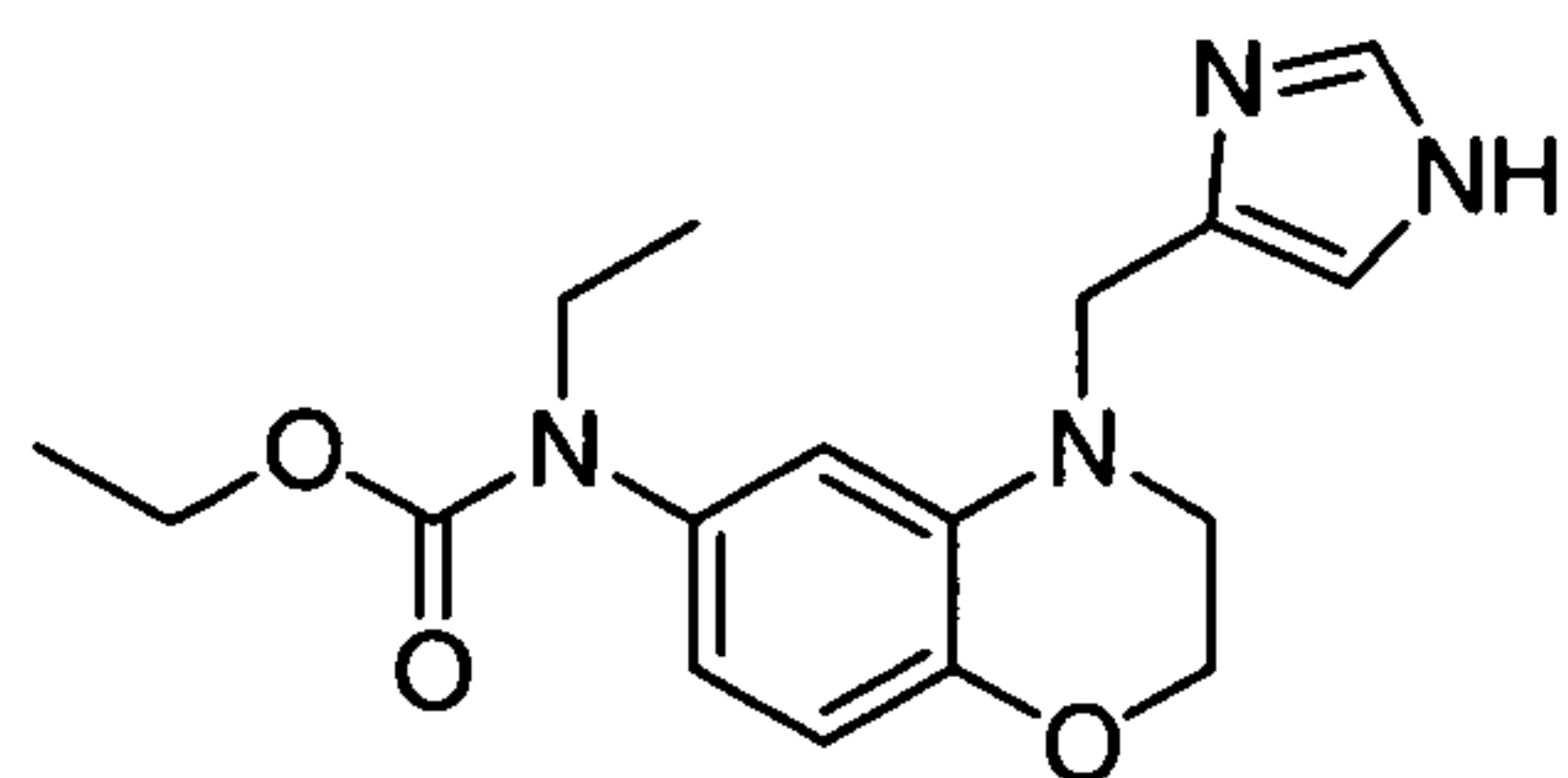
301

158



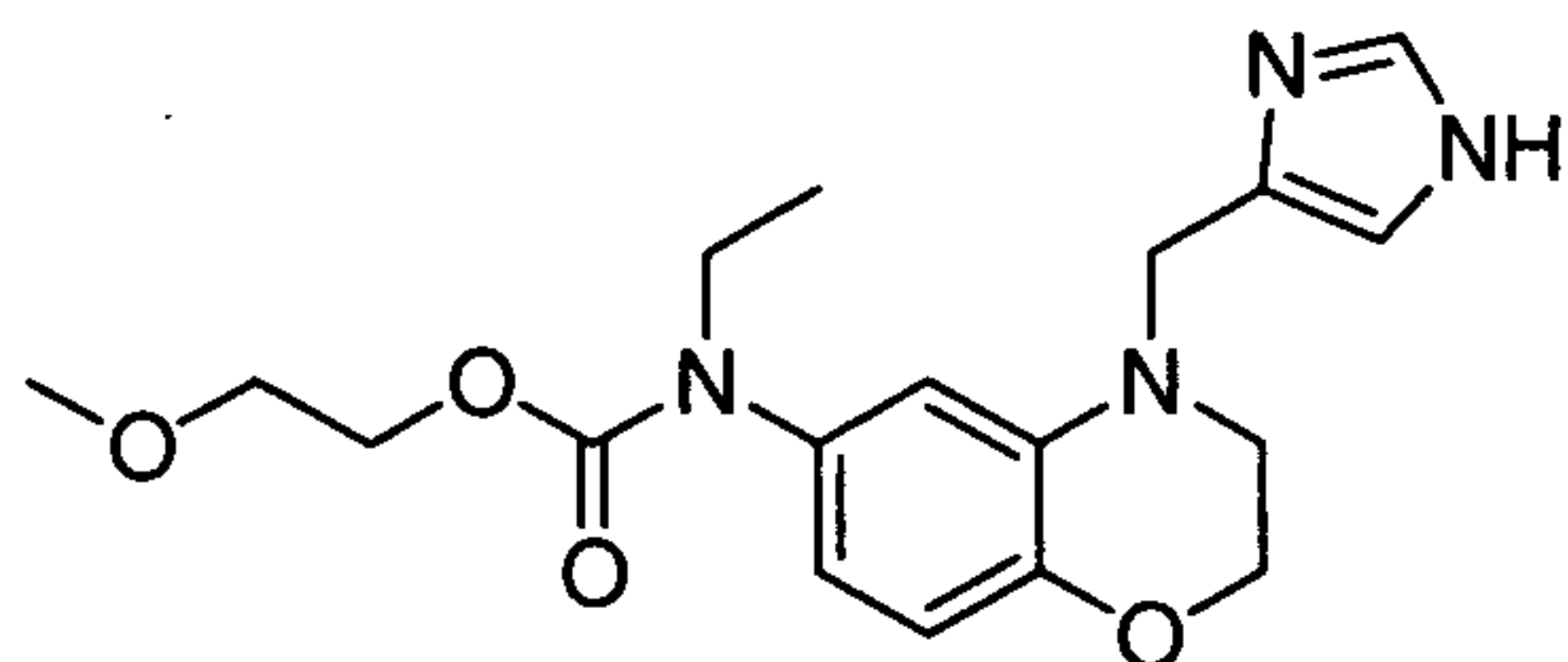
301

159



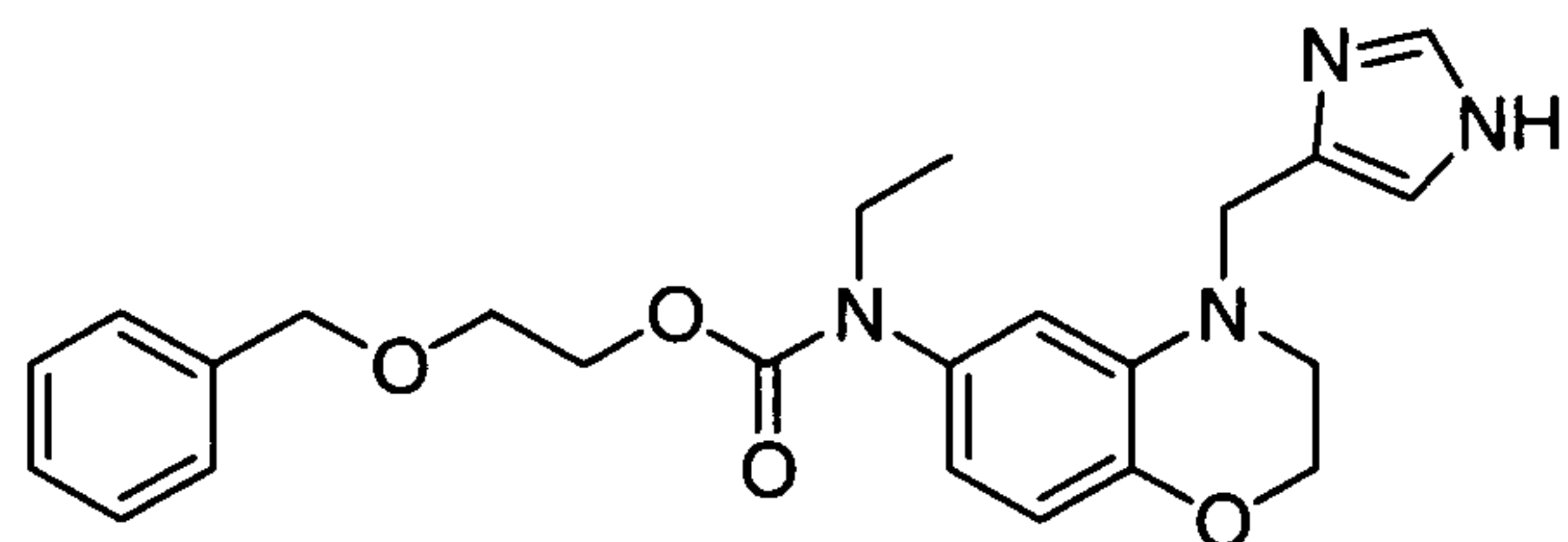
331

160



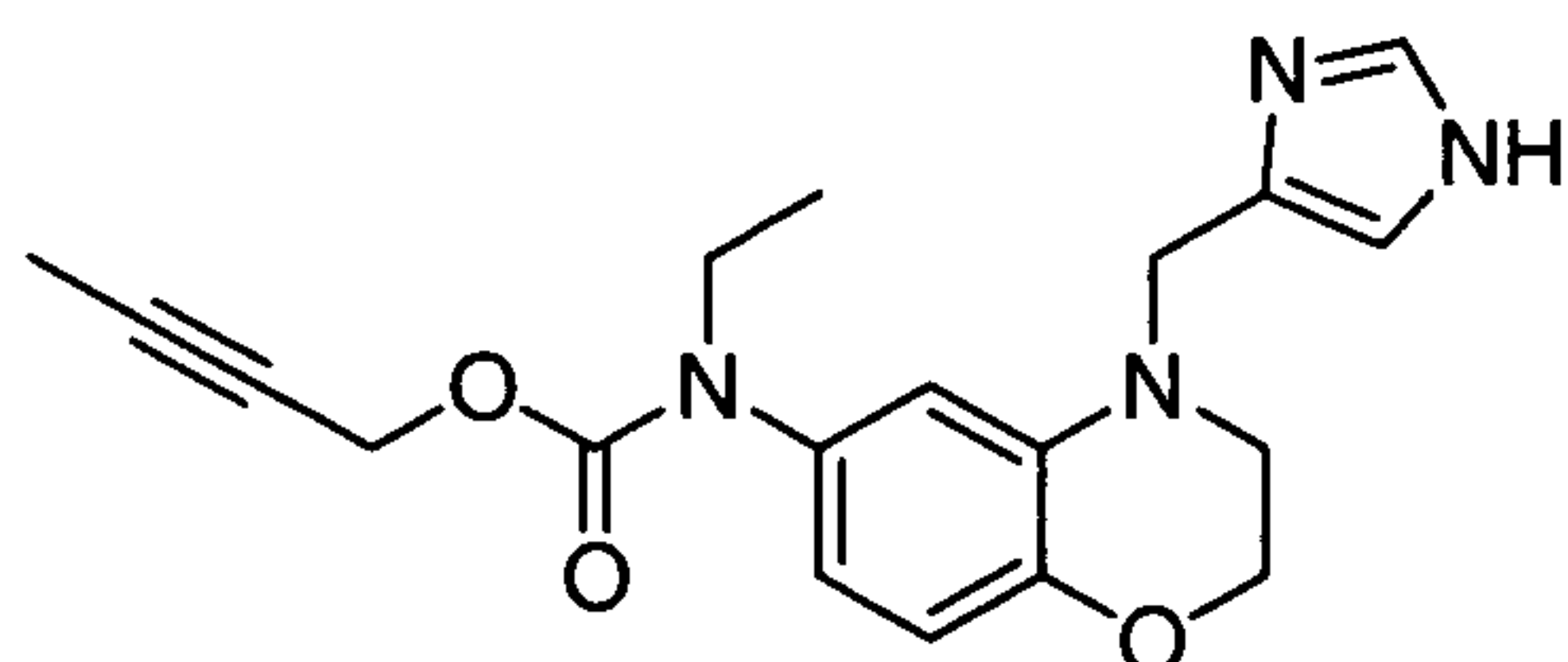
361

161



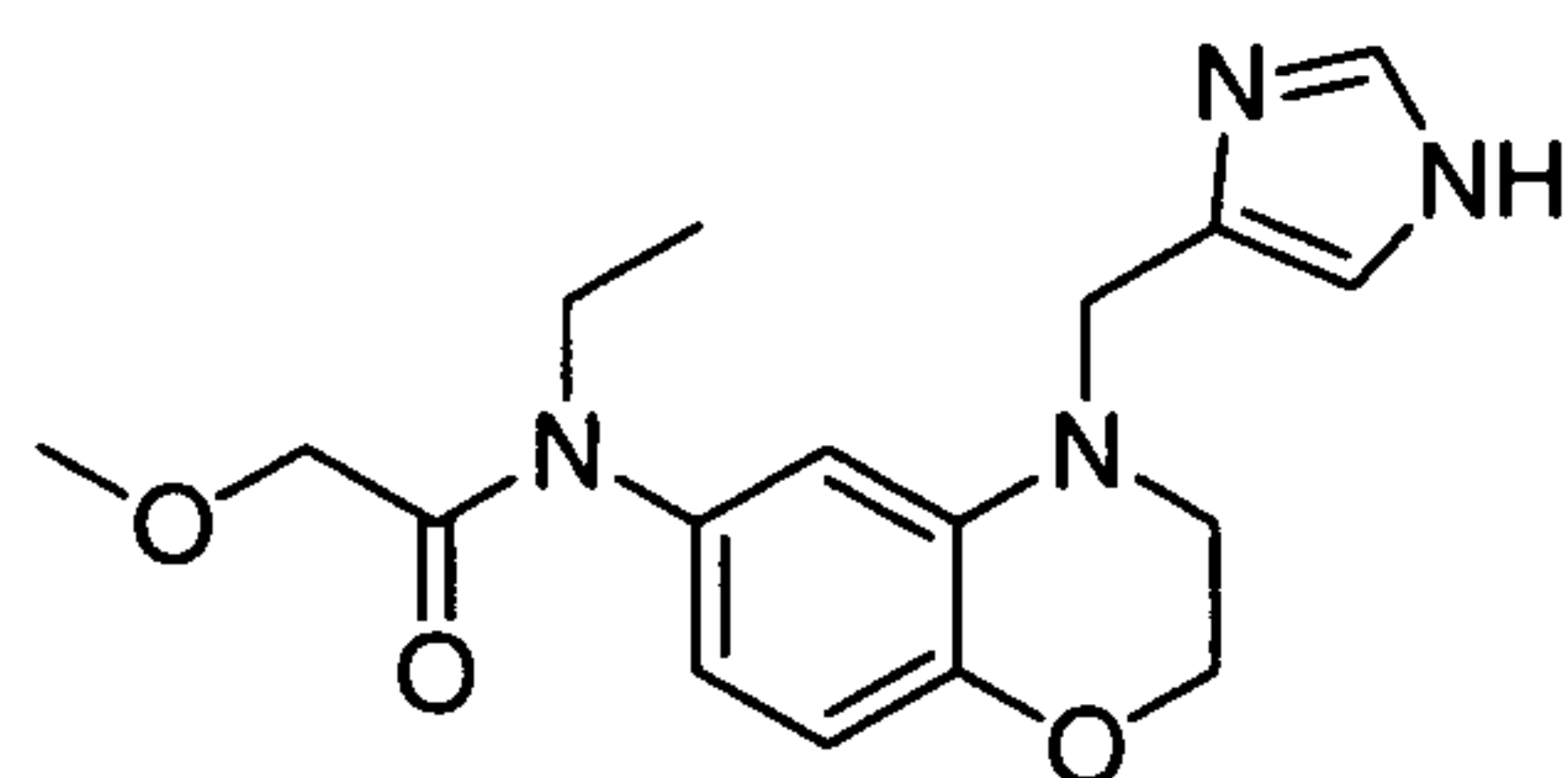
436

162



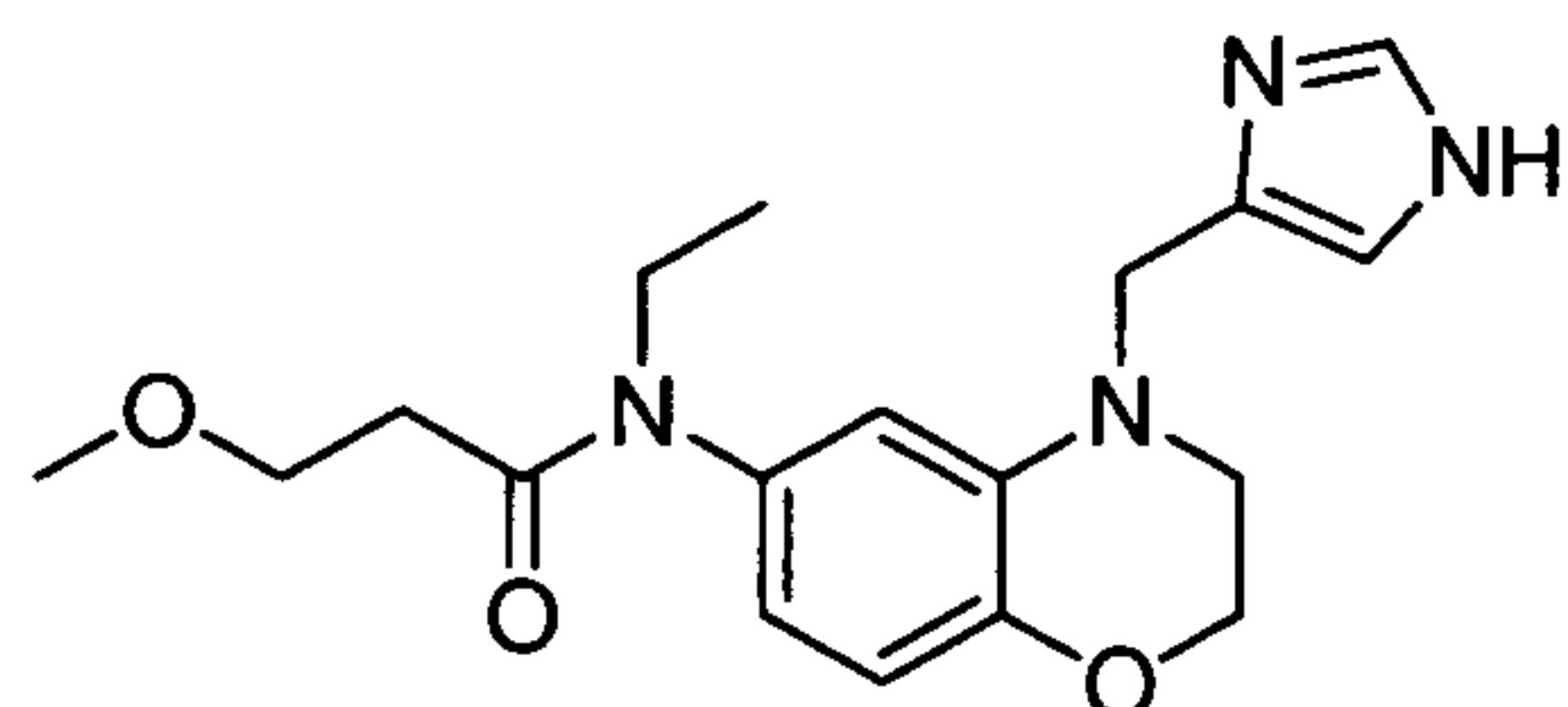
355

163



331

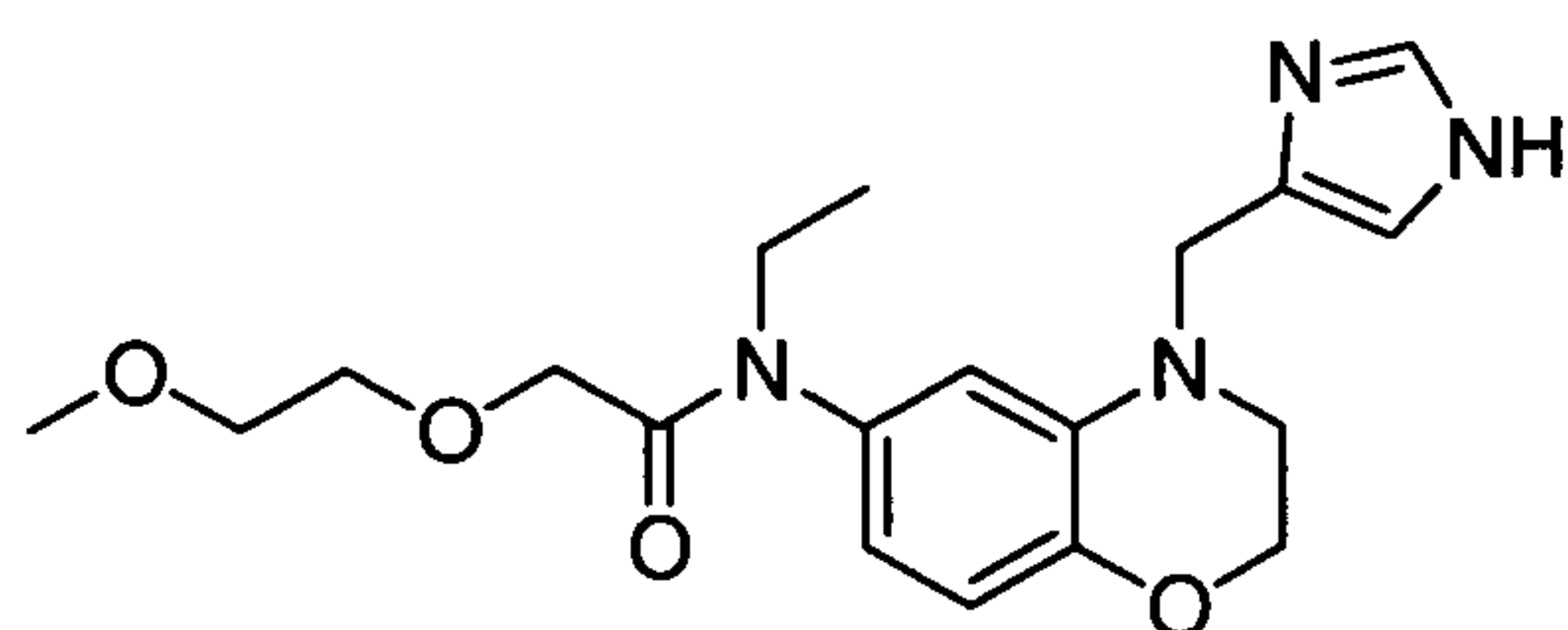
164



345

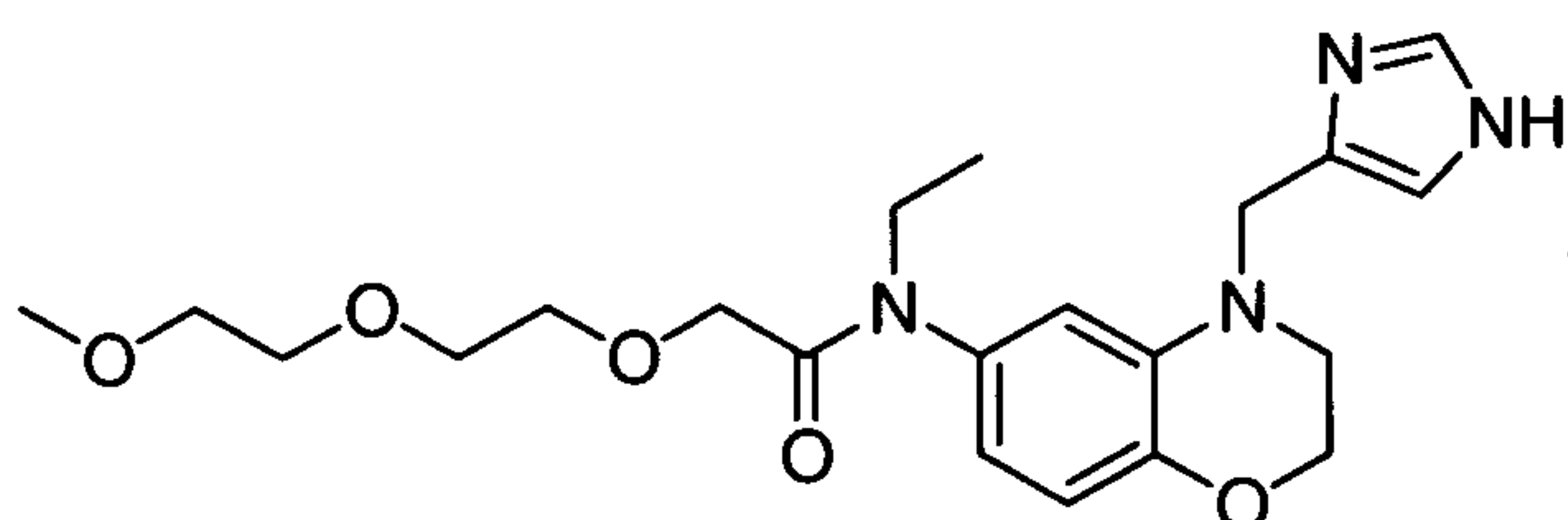
121

165



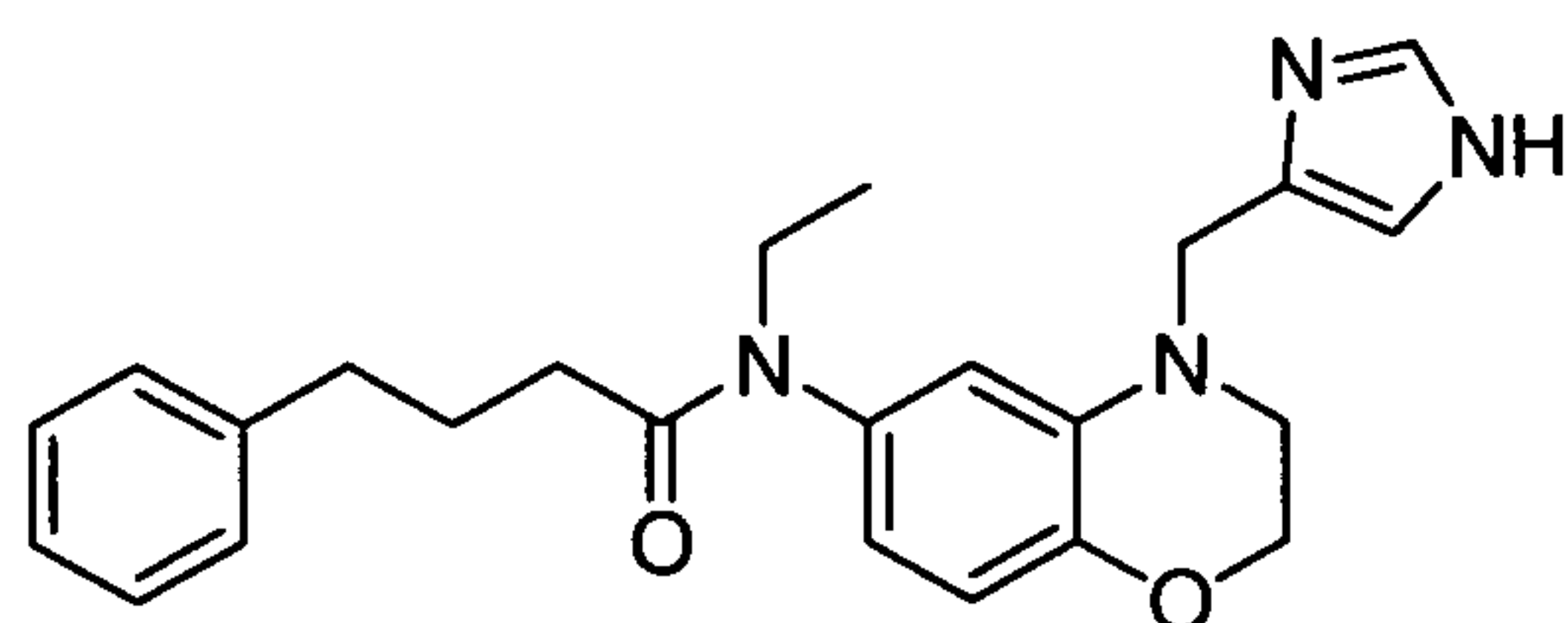
375

166



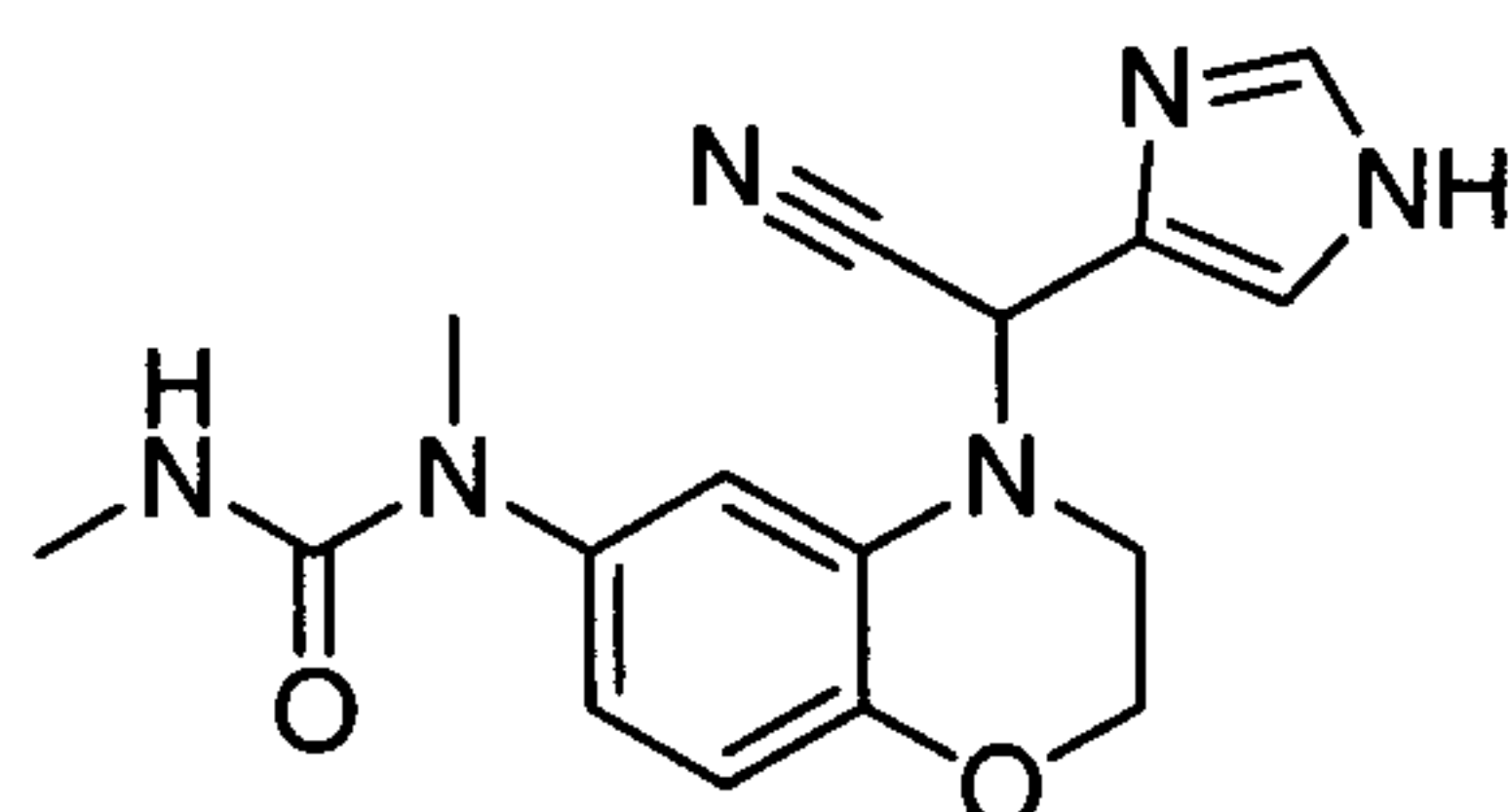
419

167



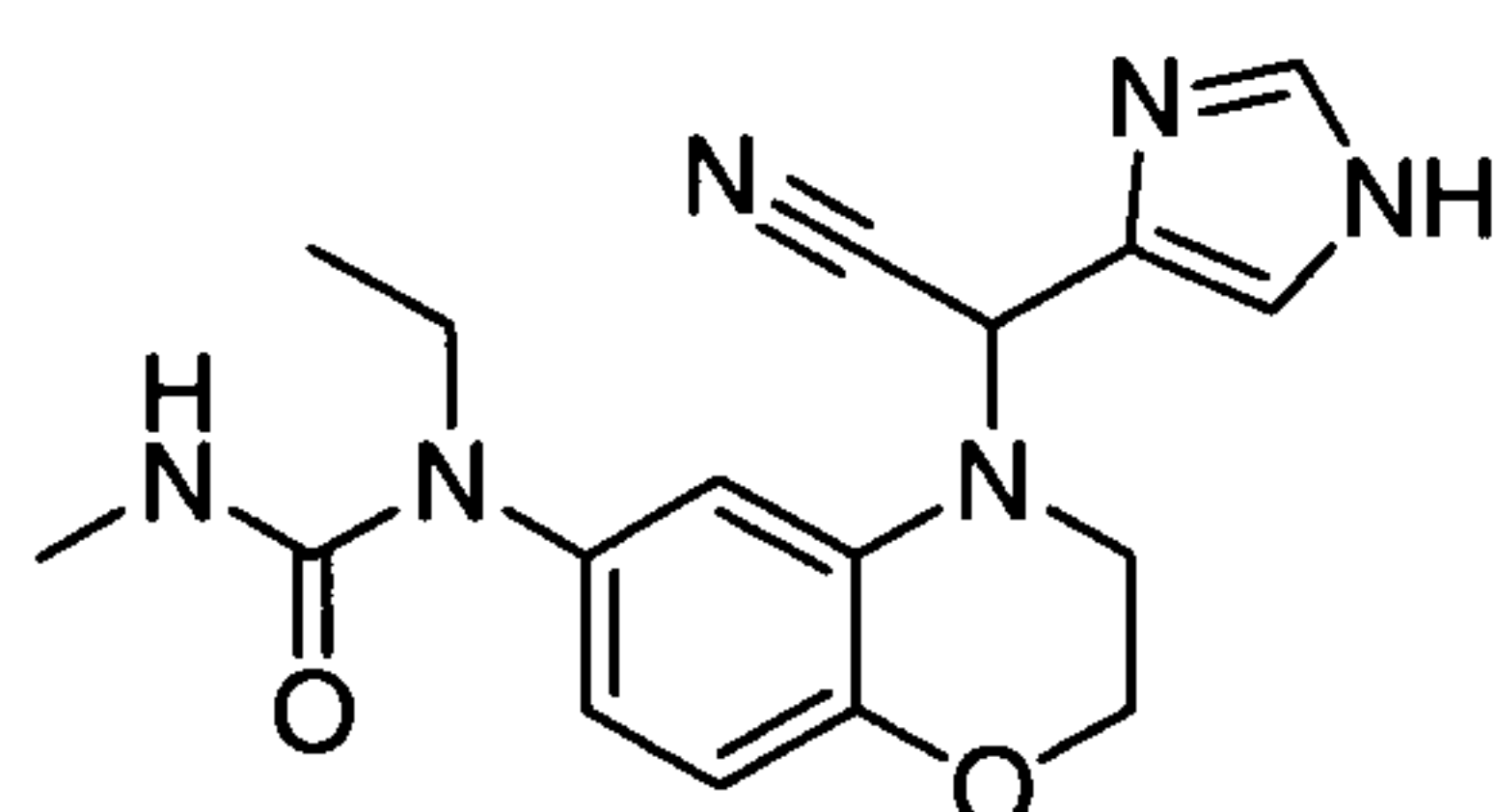
405

168



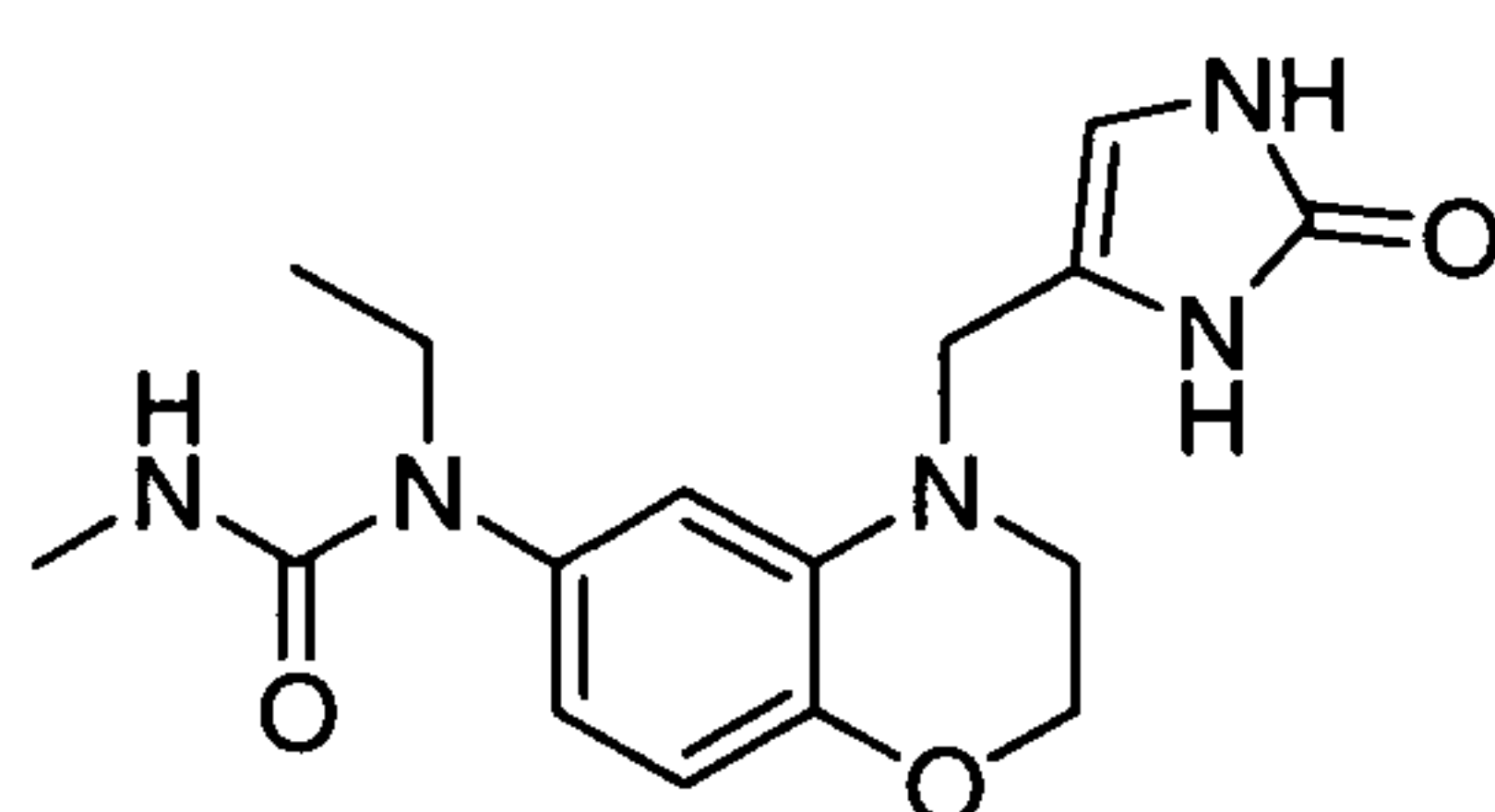
327

169



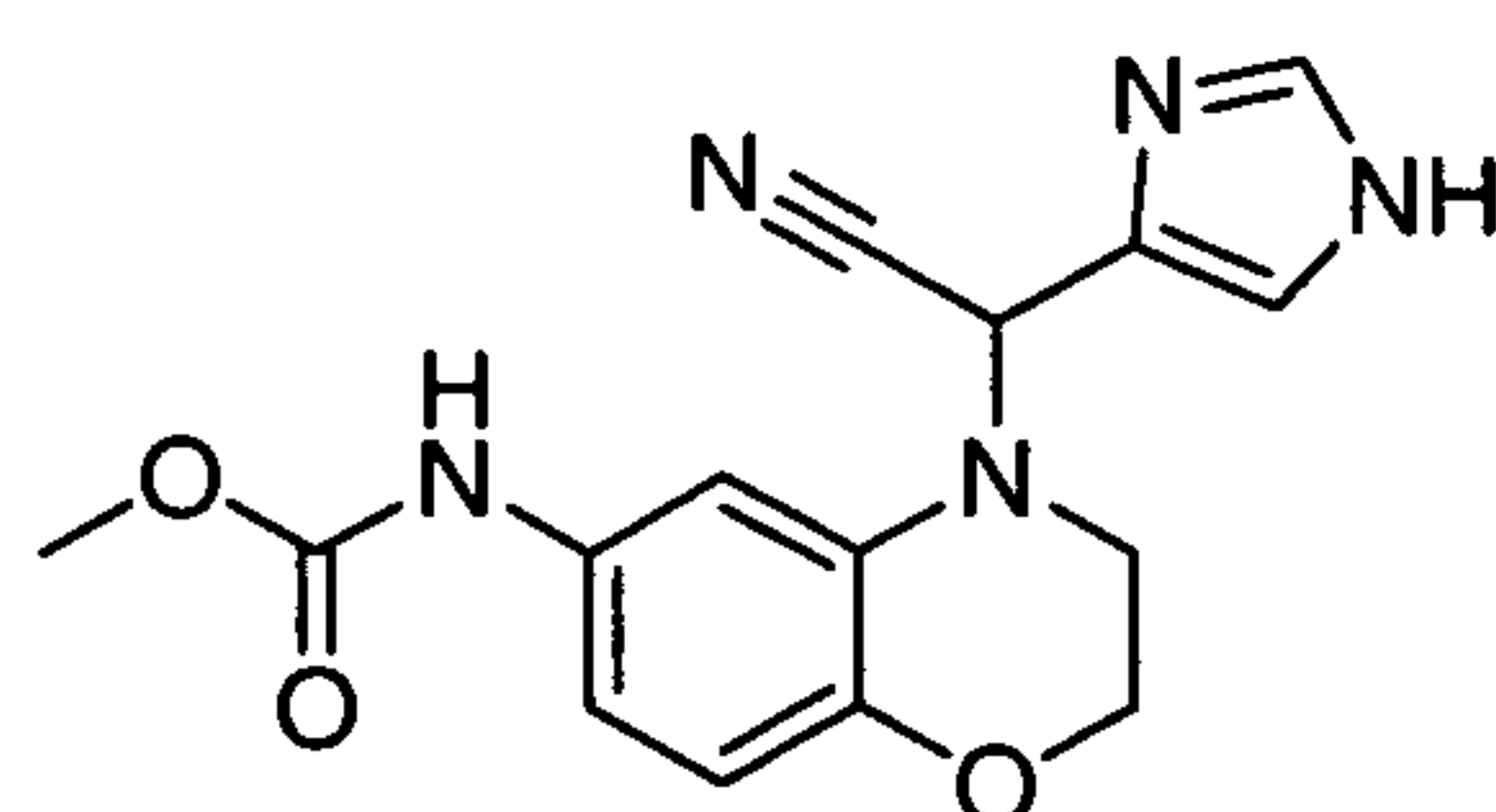
341

170



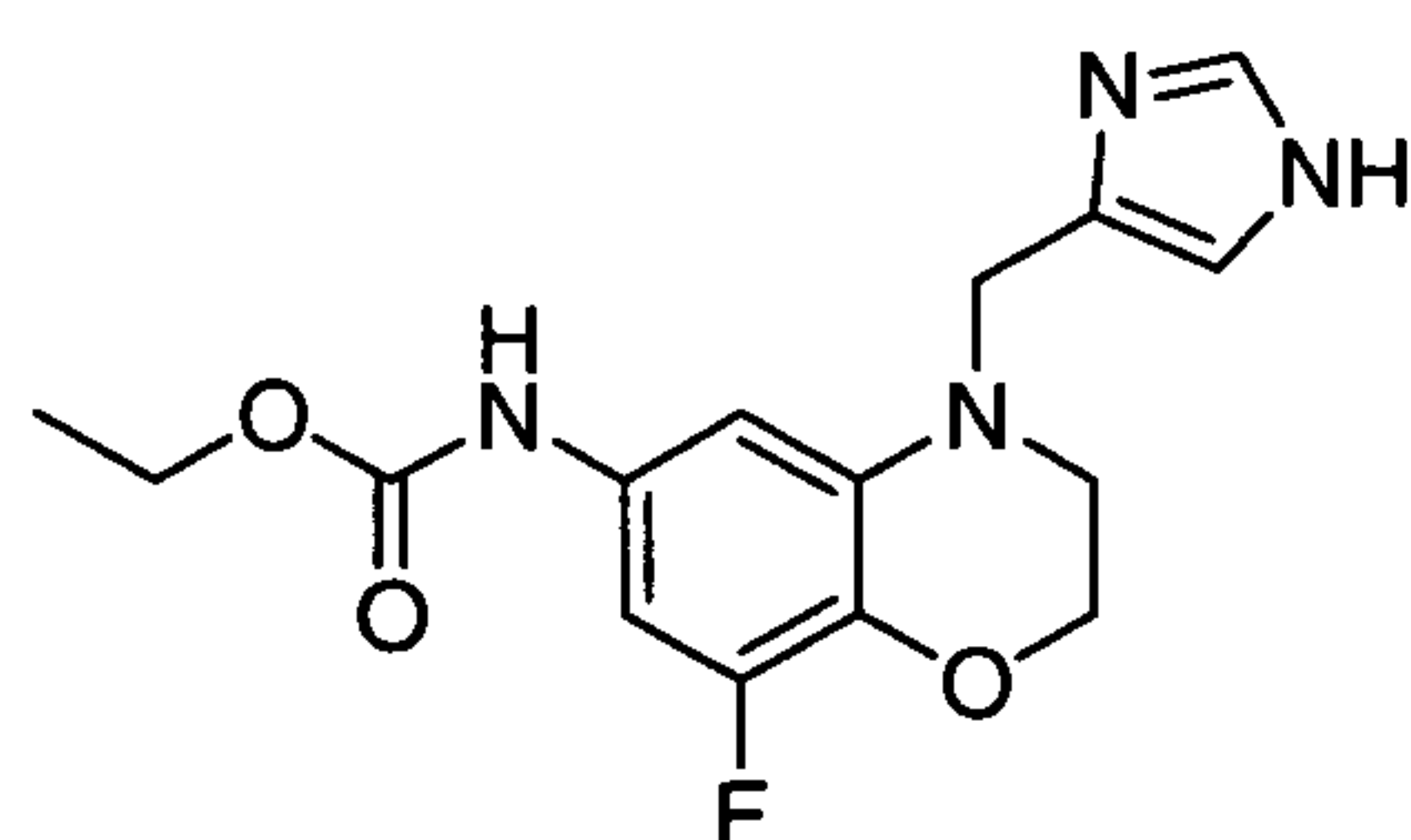
332

171



314

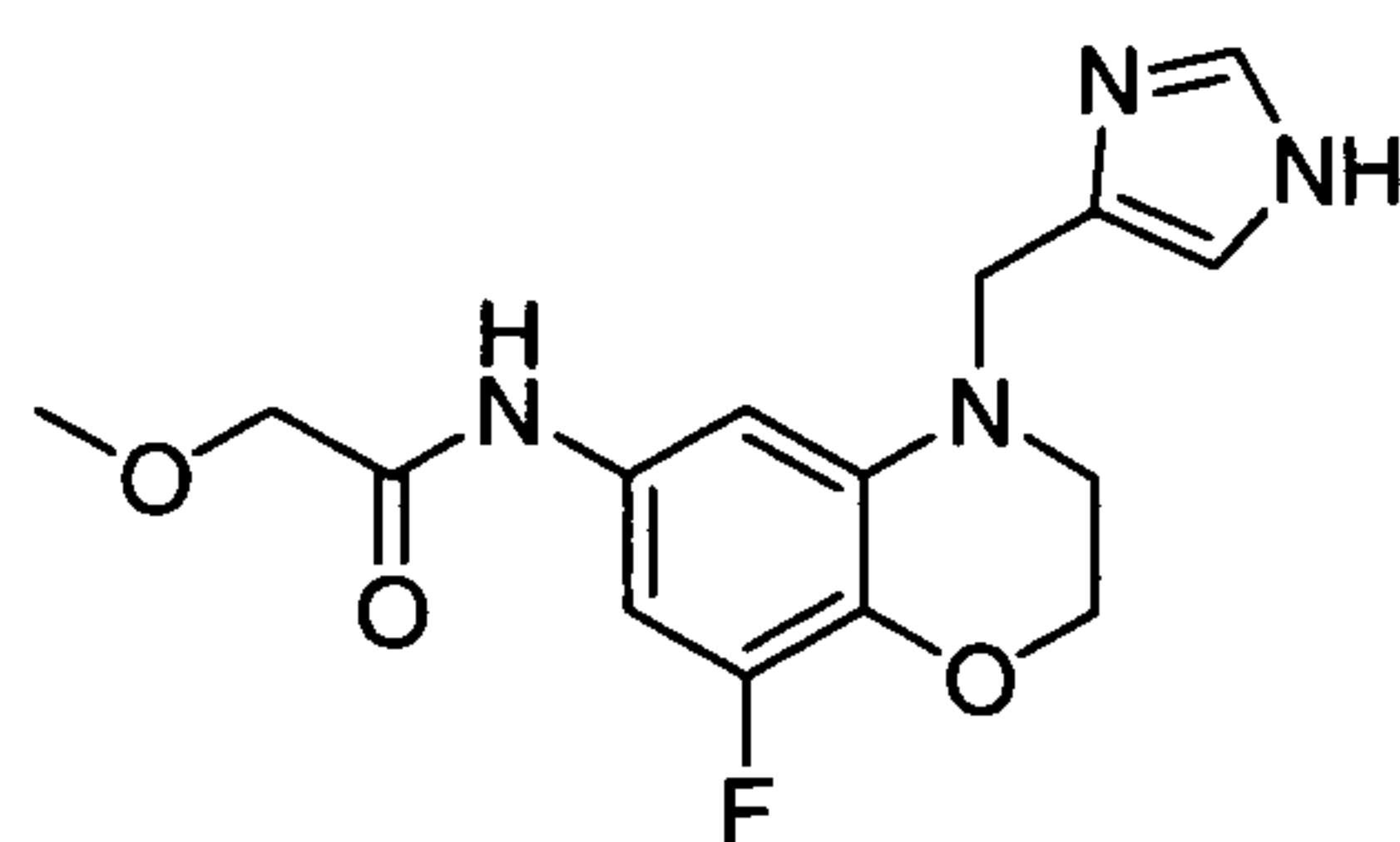
172



321

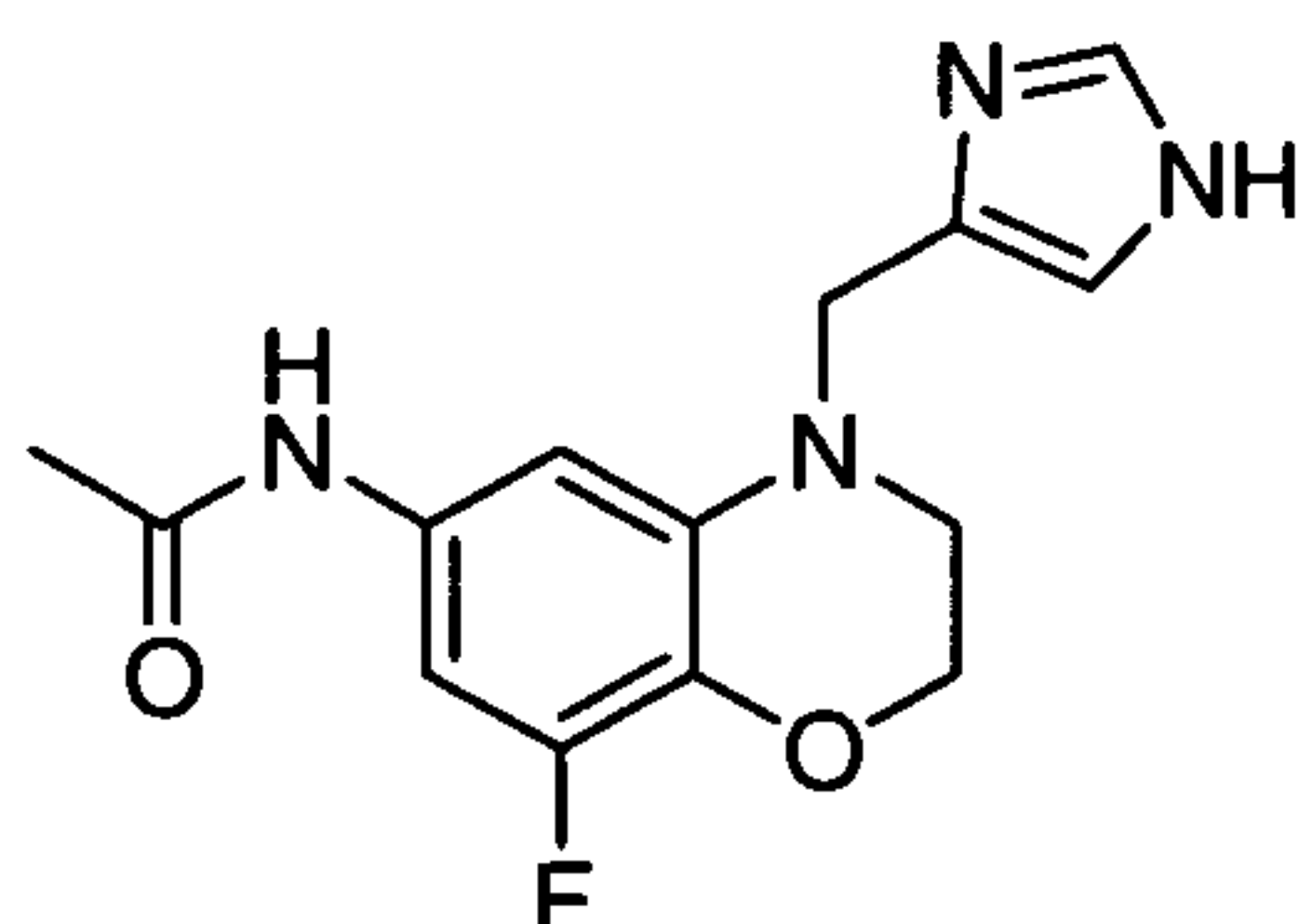
122

173



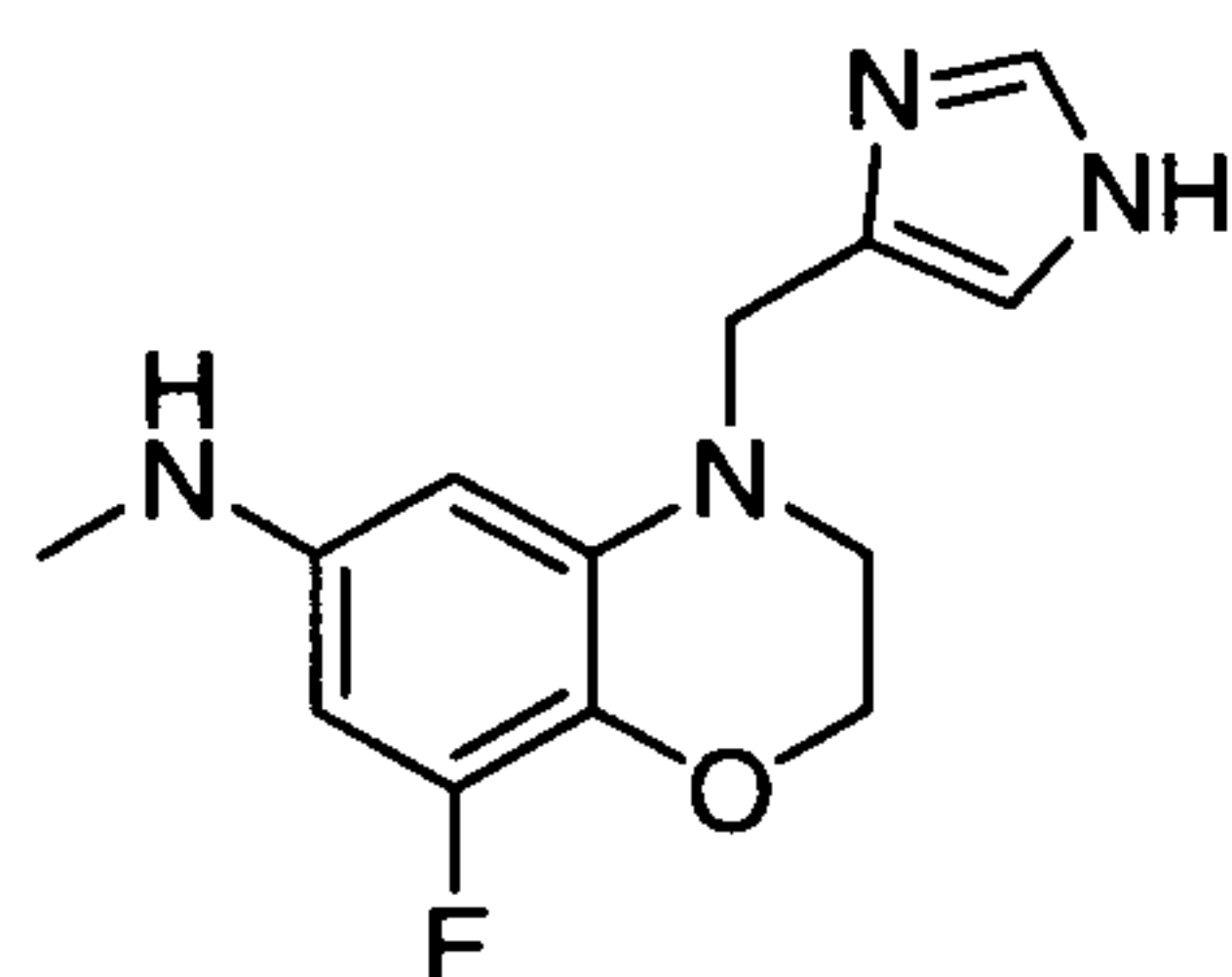
321

174



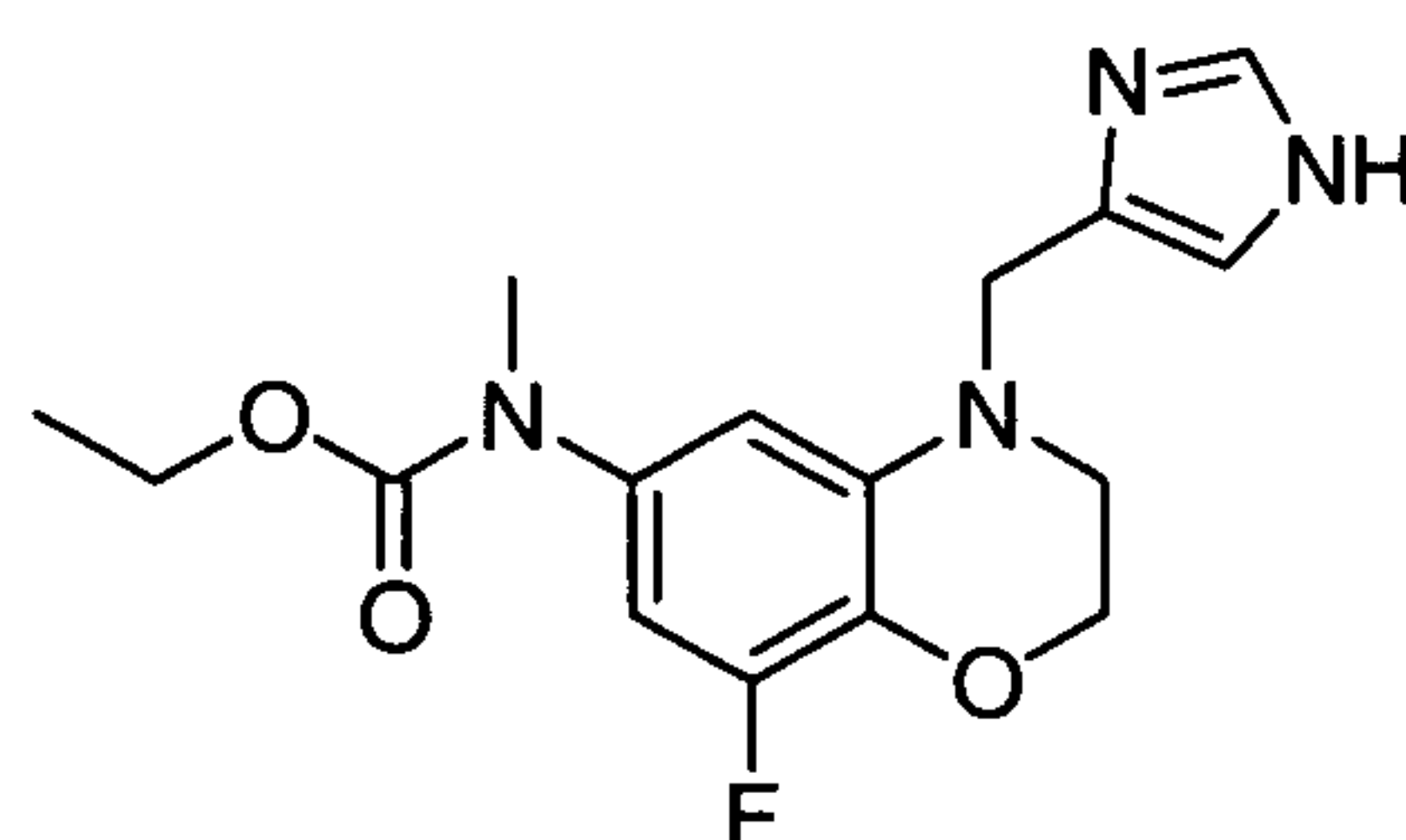
291

175



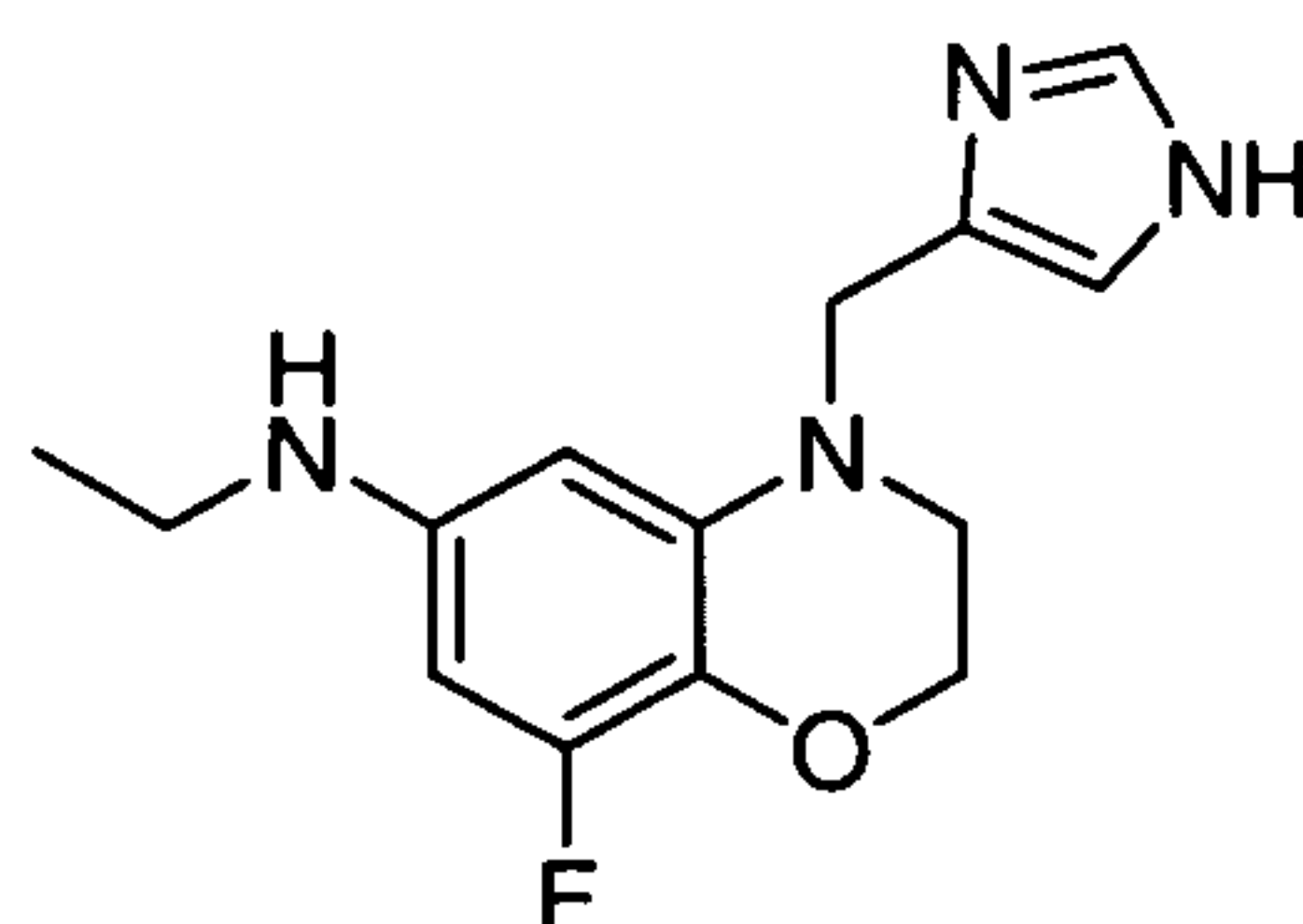
263

176



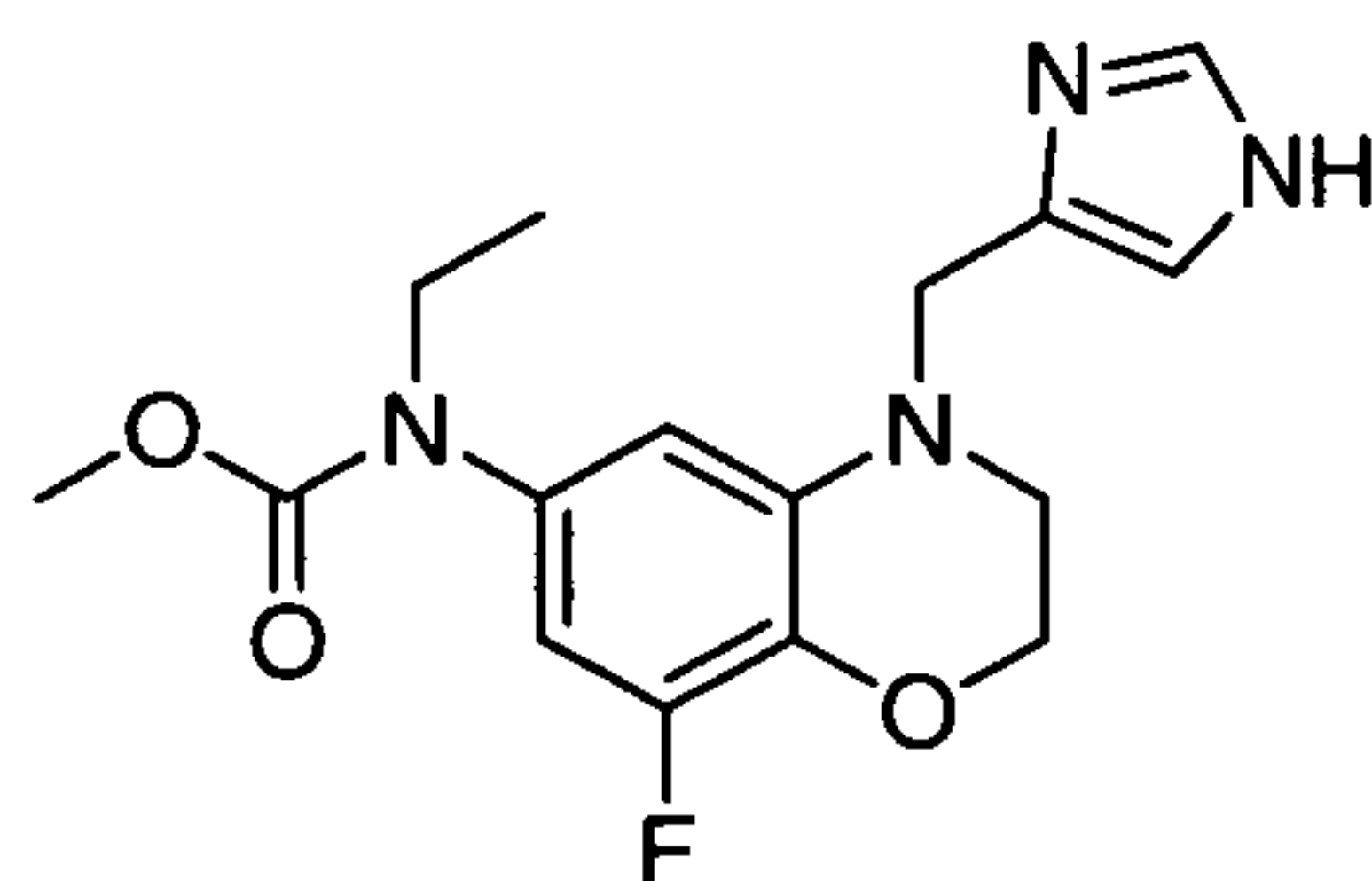
335

177



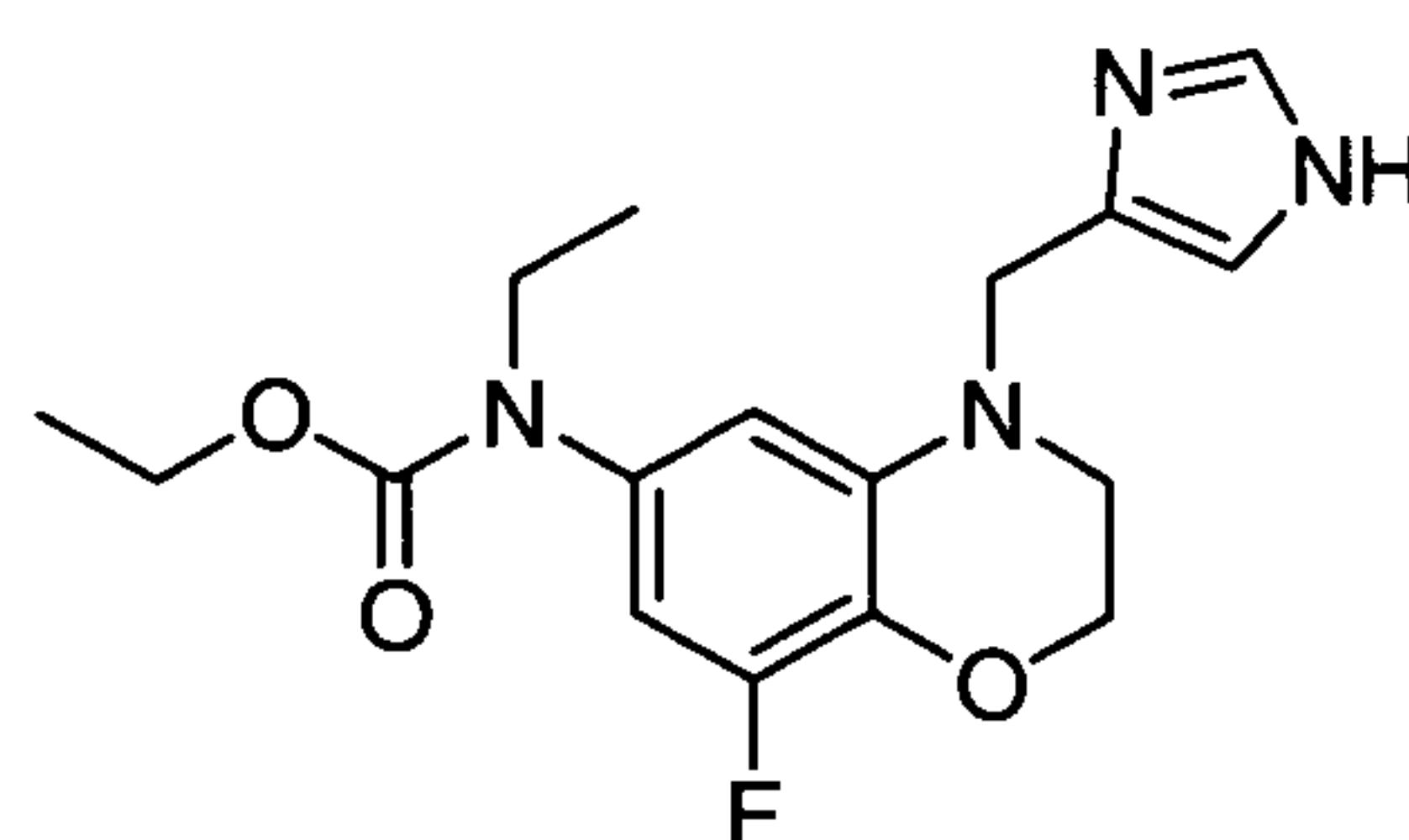
277

178



335

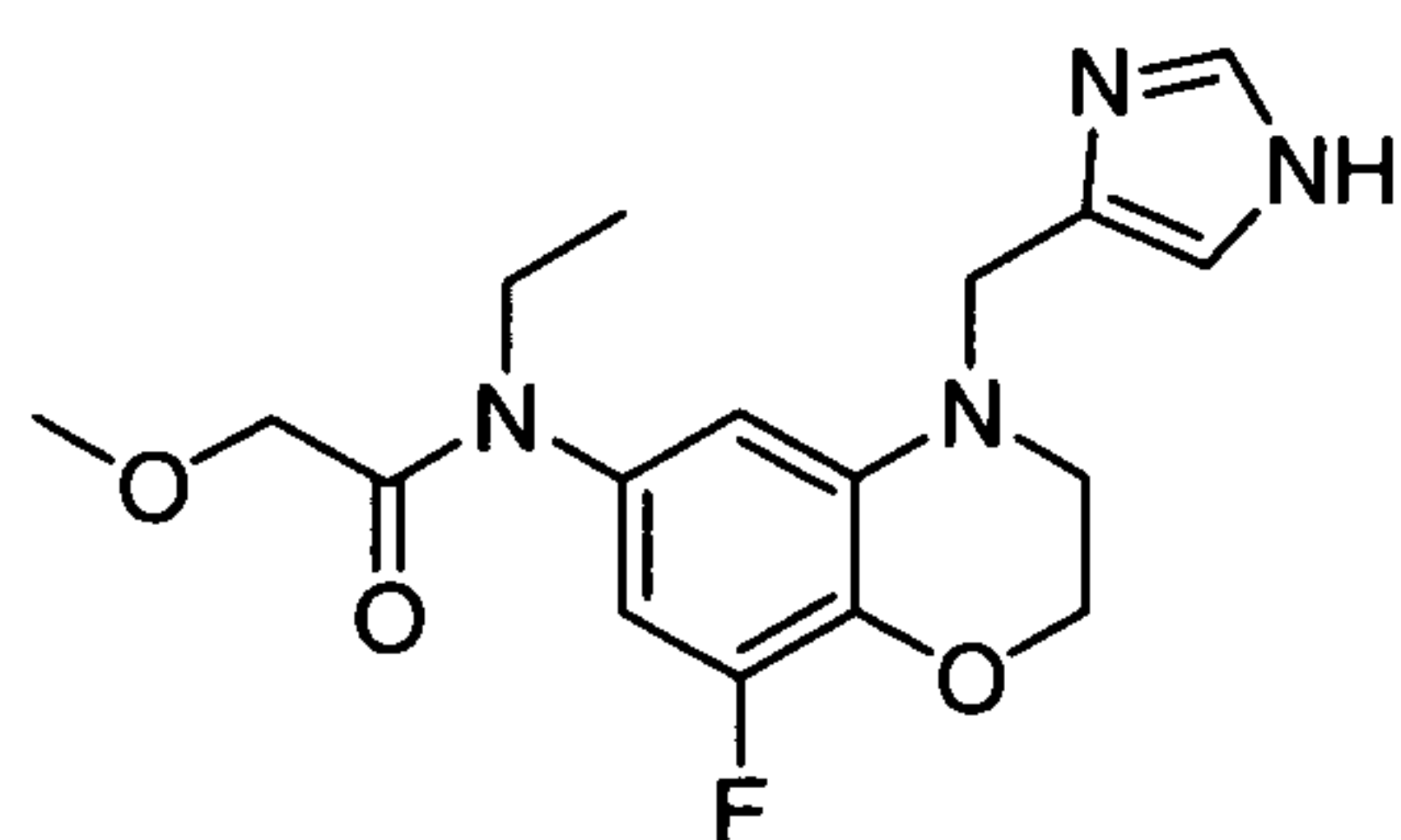
179



349

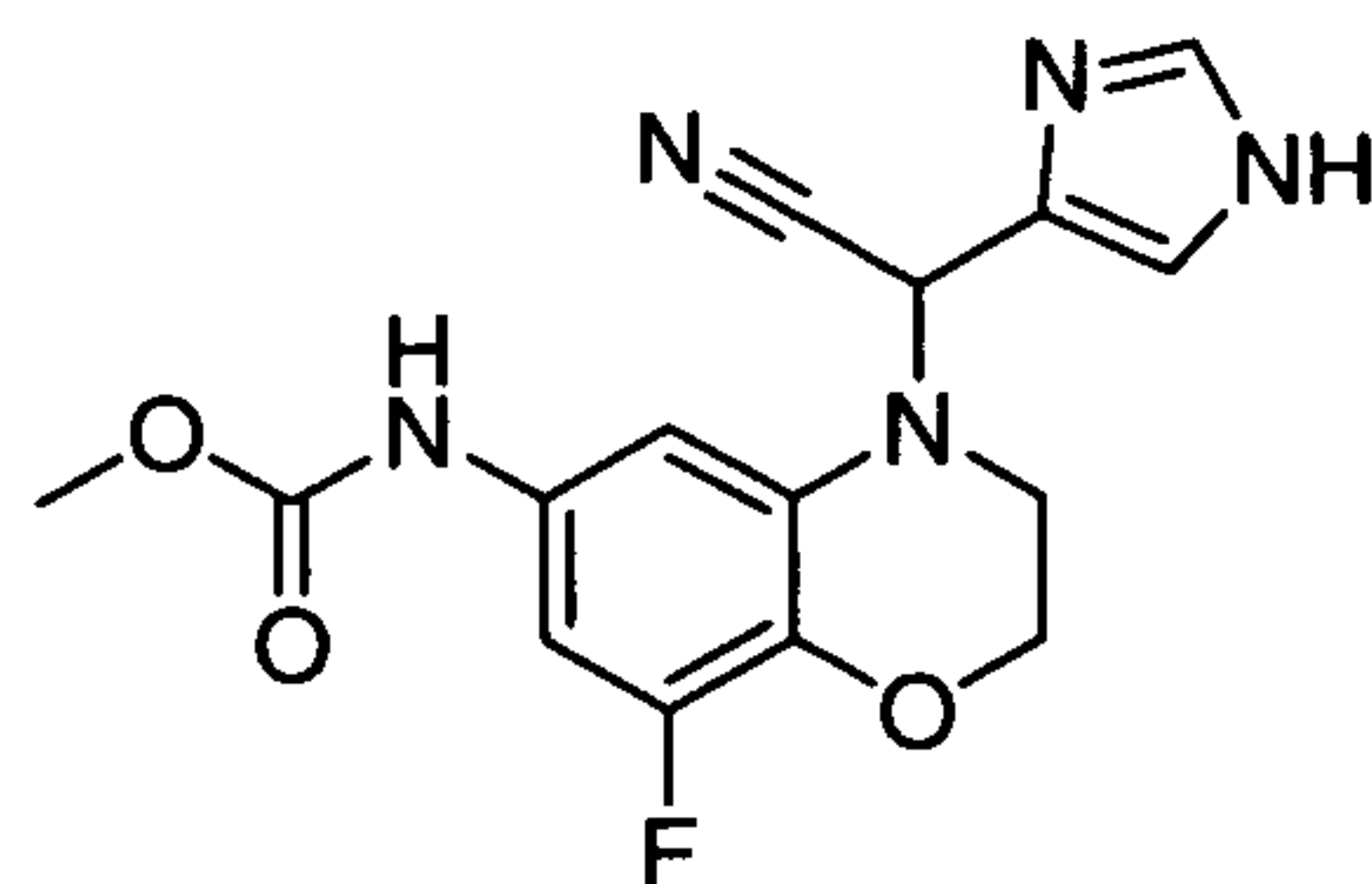
123

180



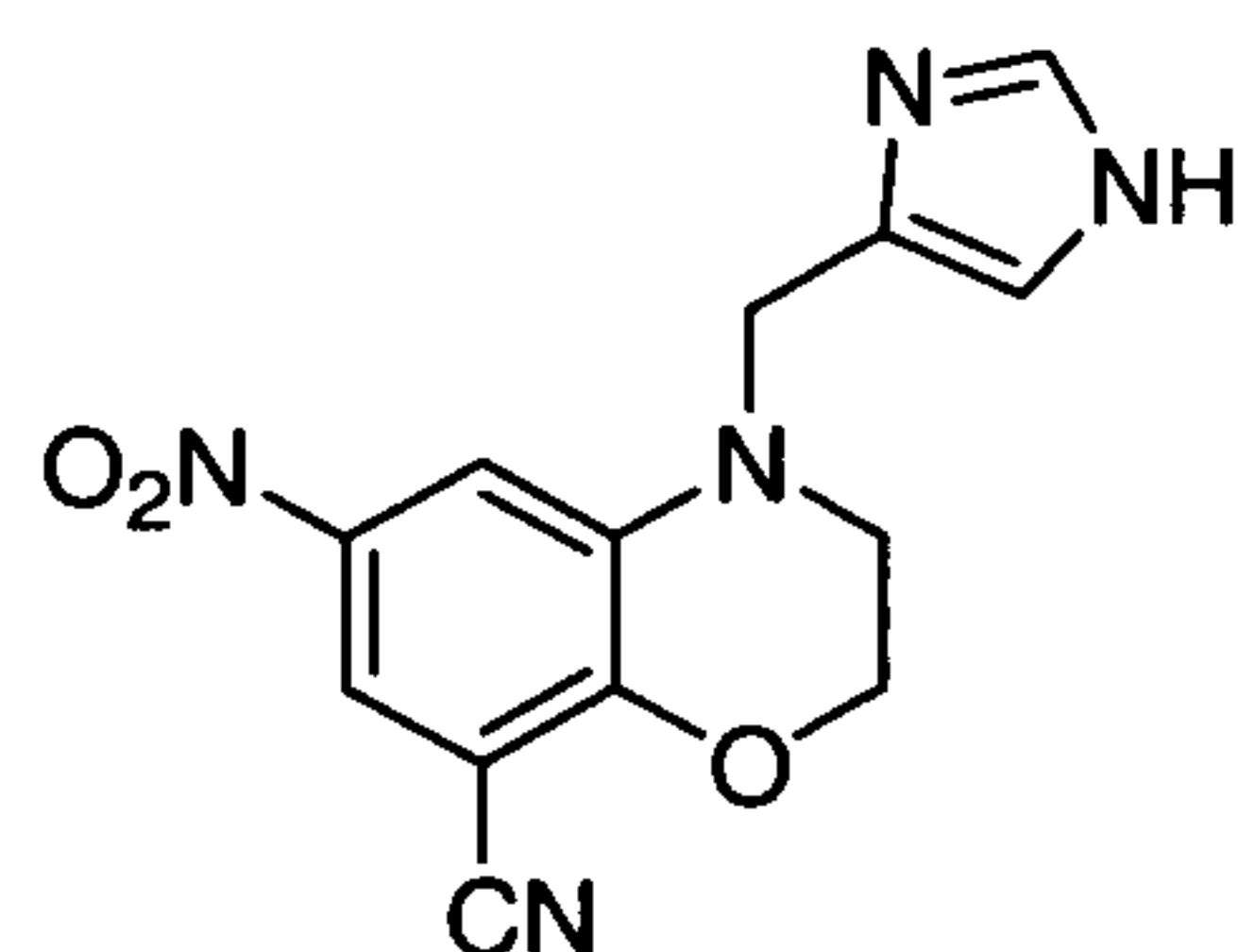
349

181



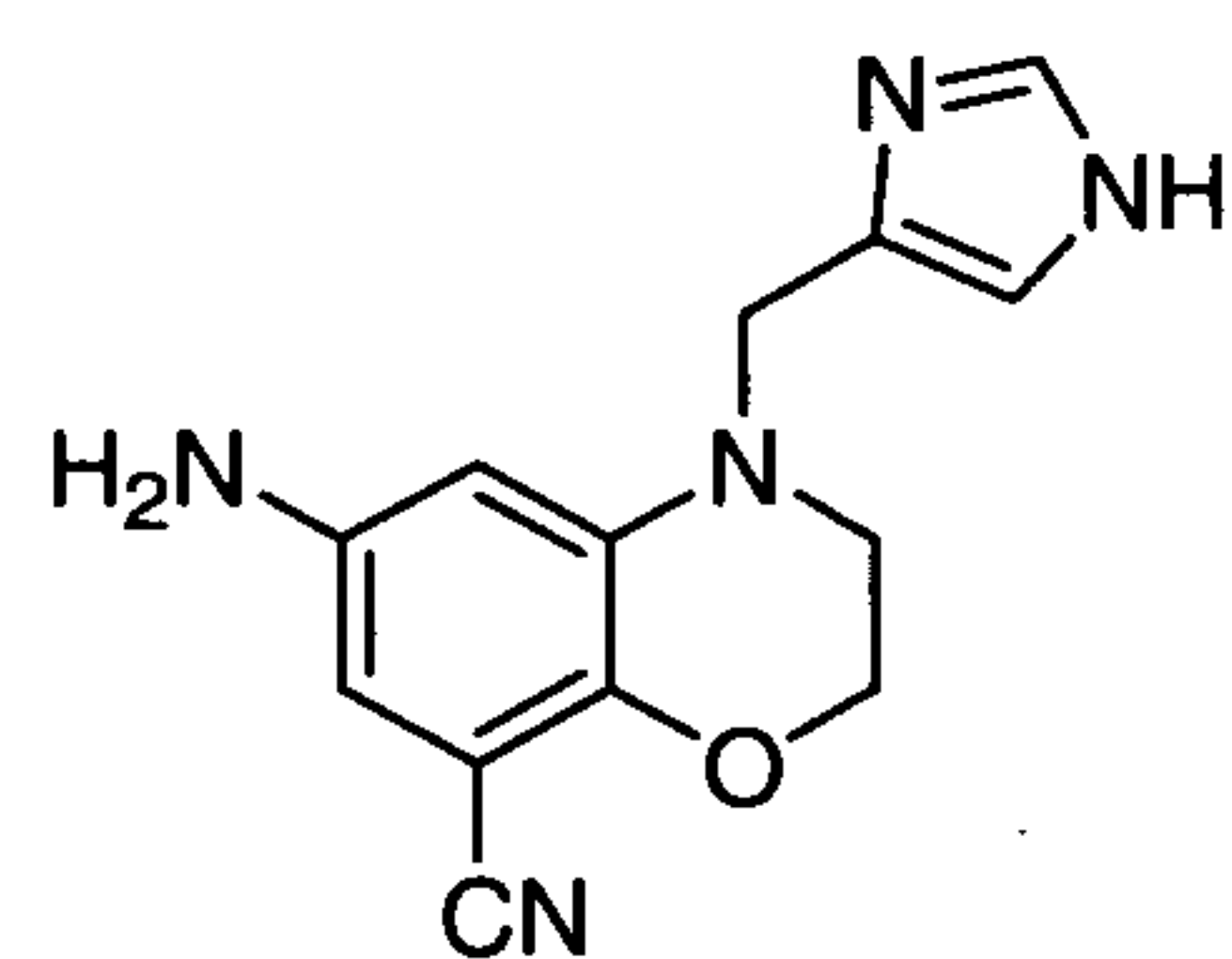
332

182



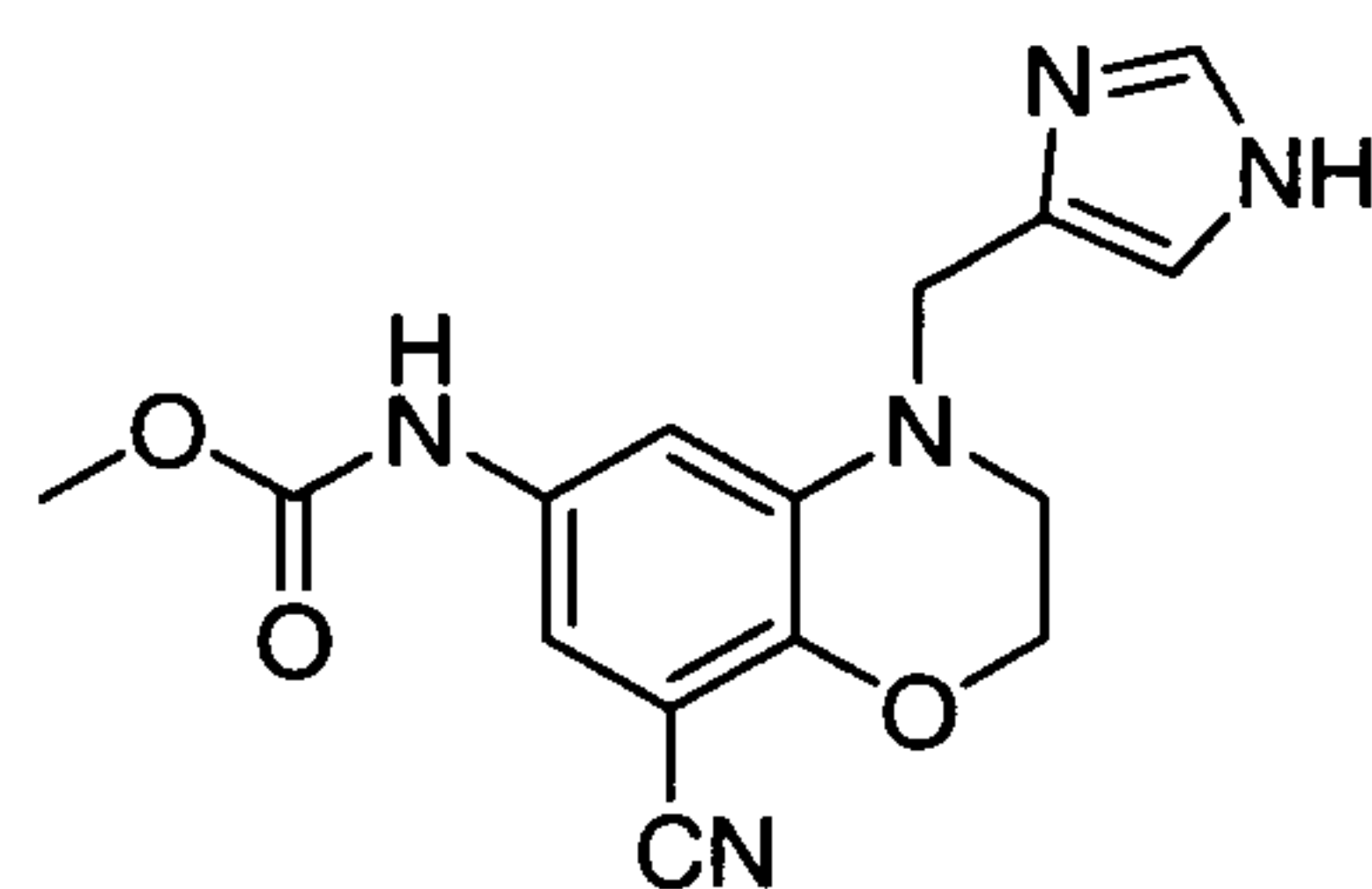
286

183



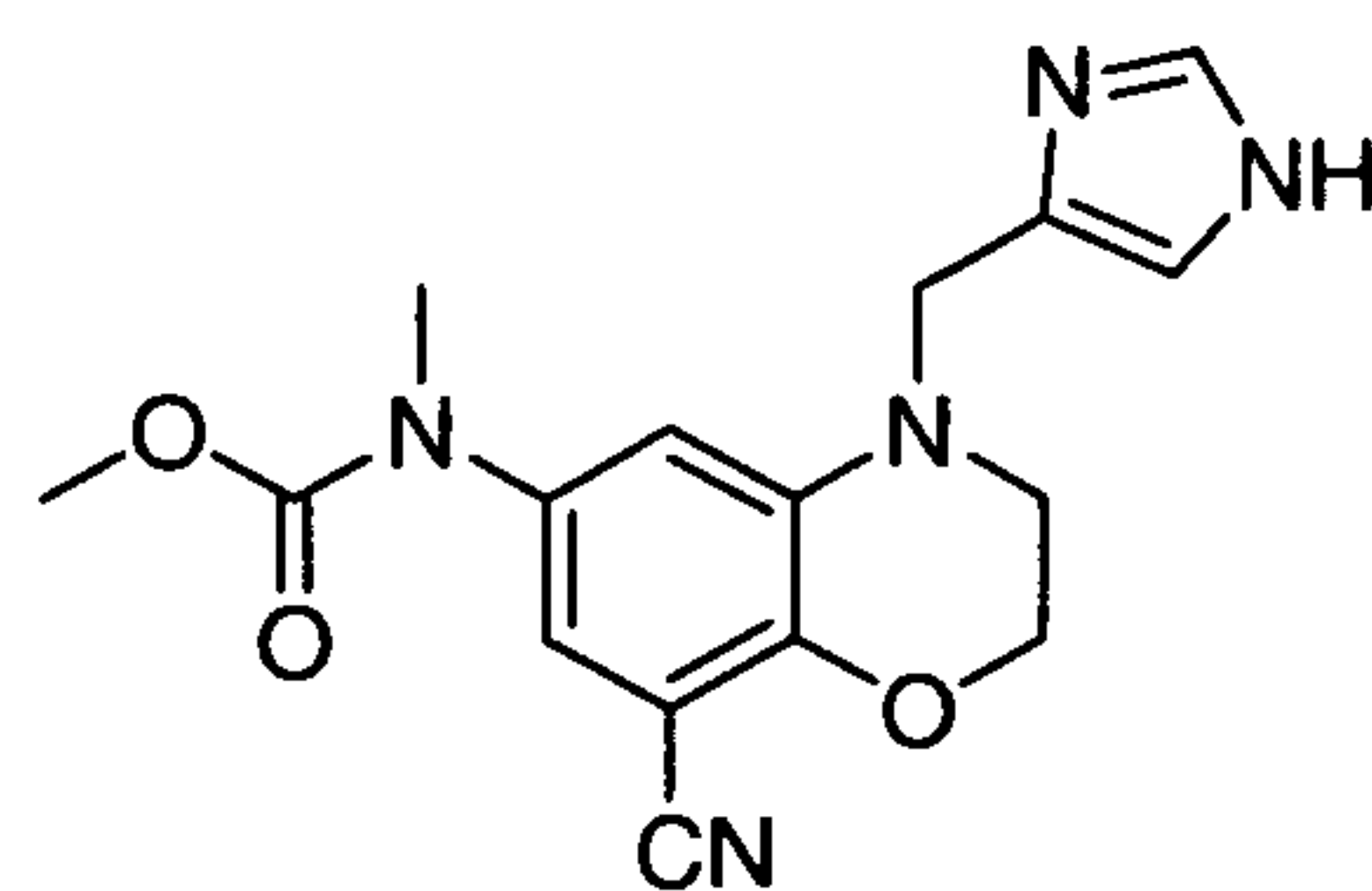
256

184



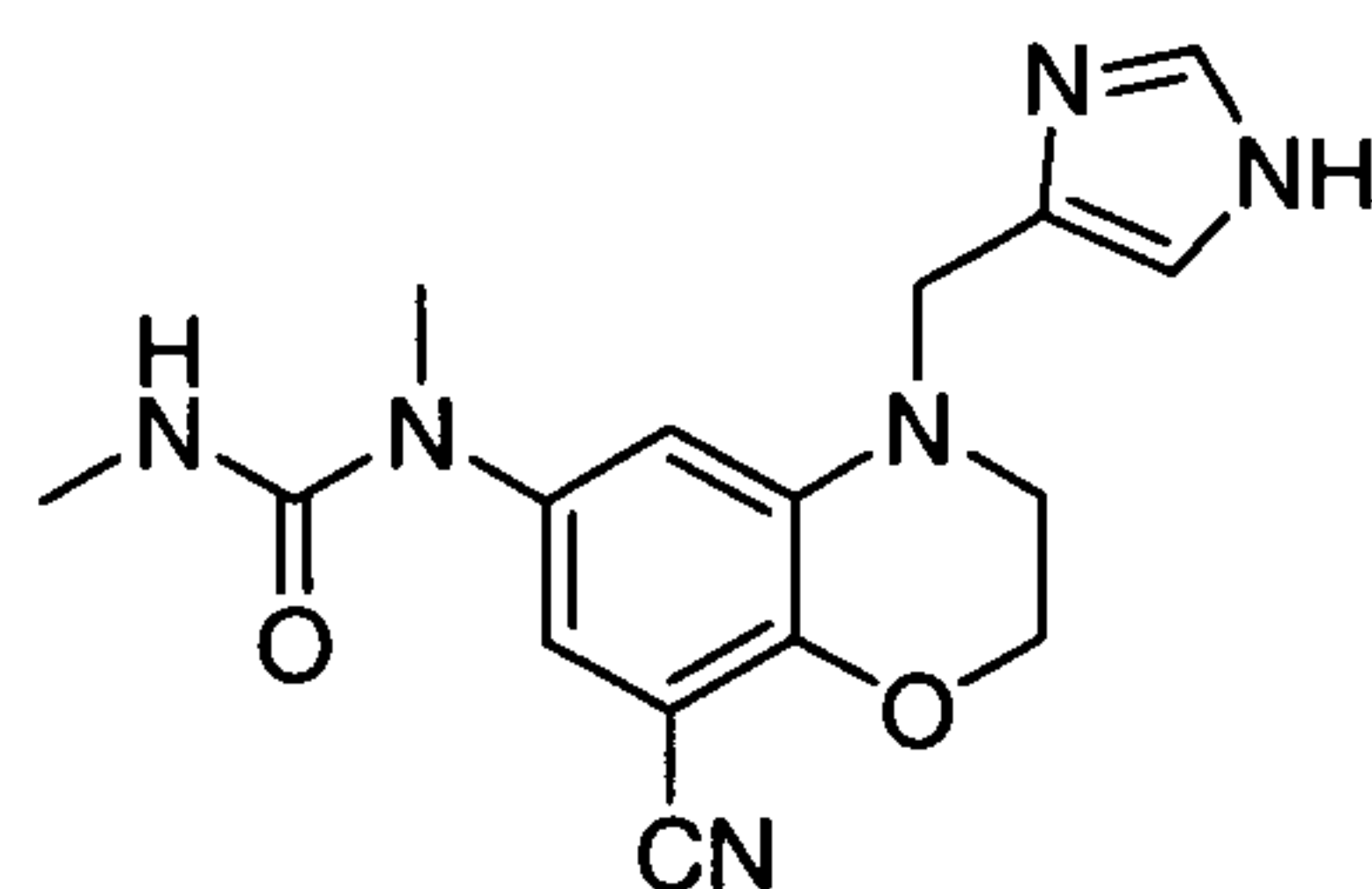
314

185



328

186

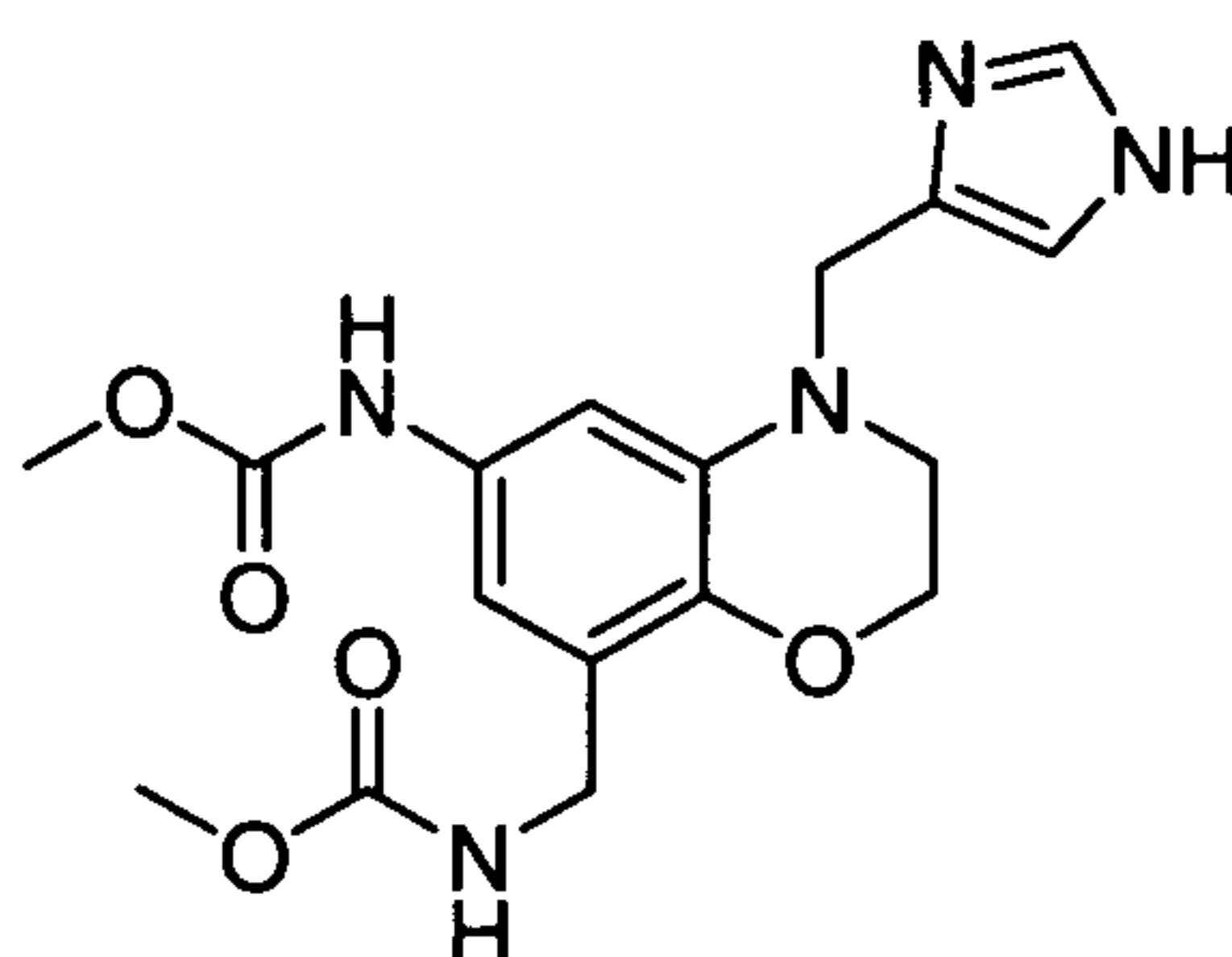


327

124

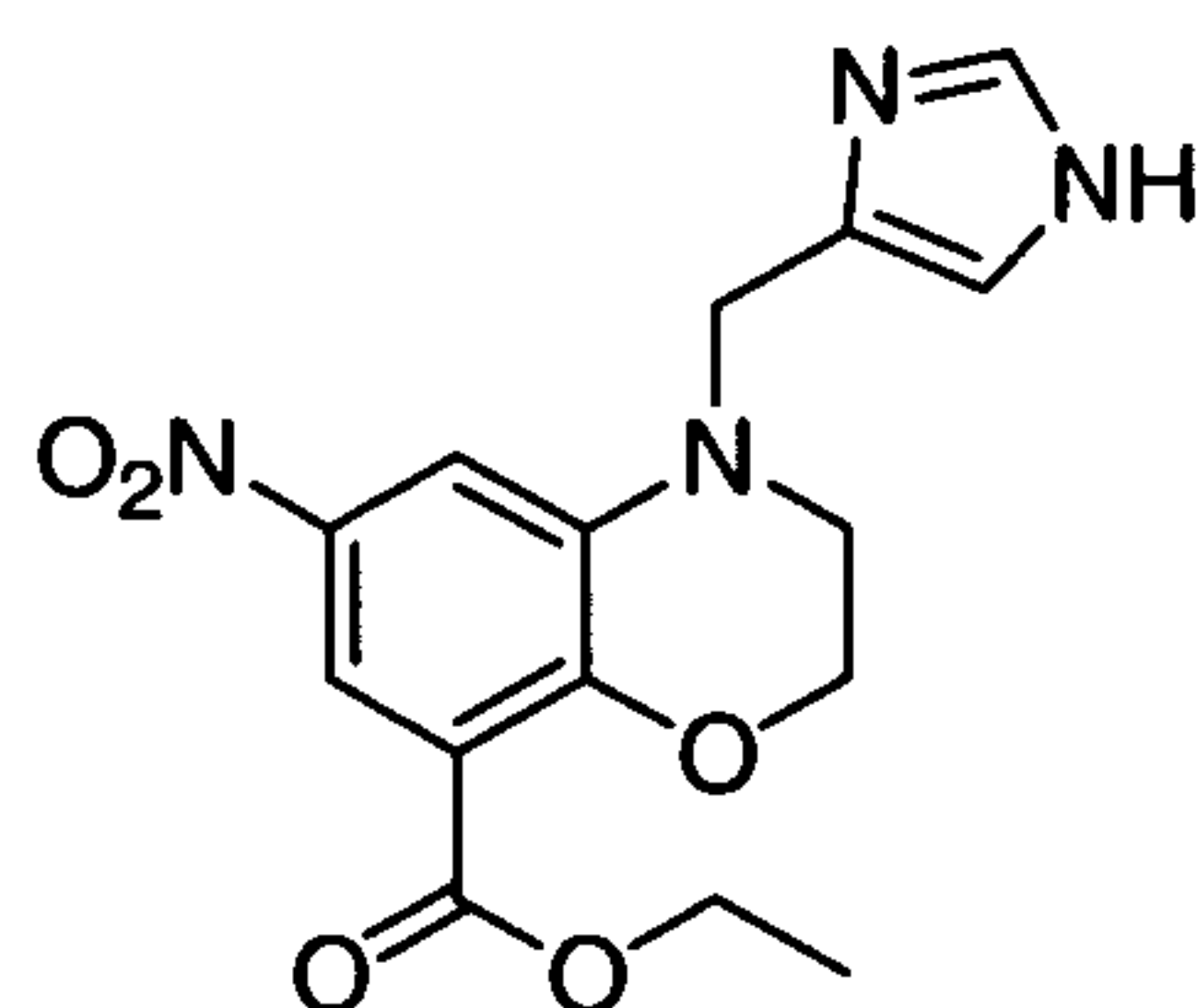
187

376



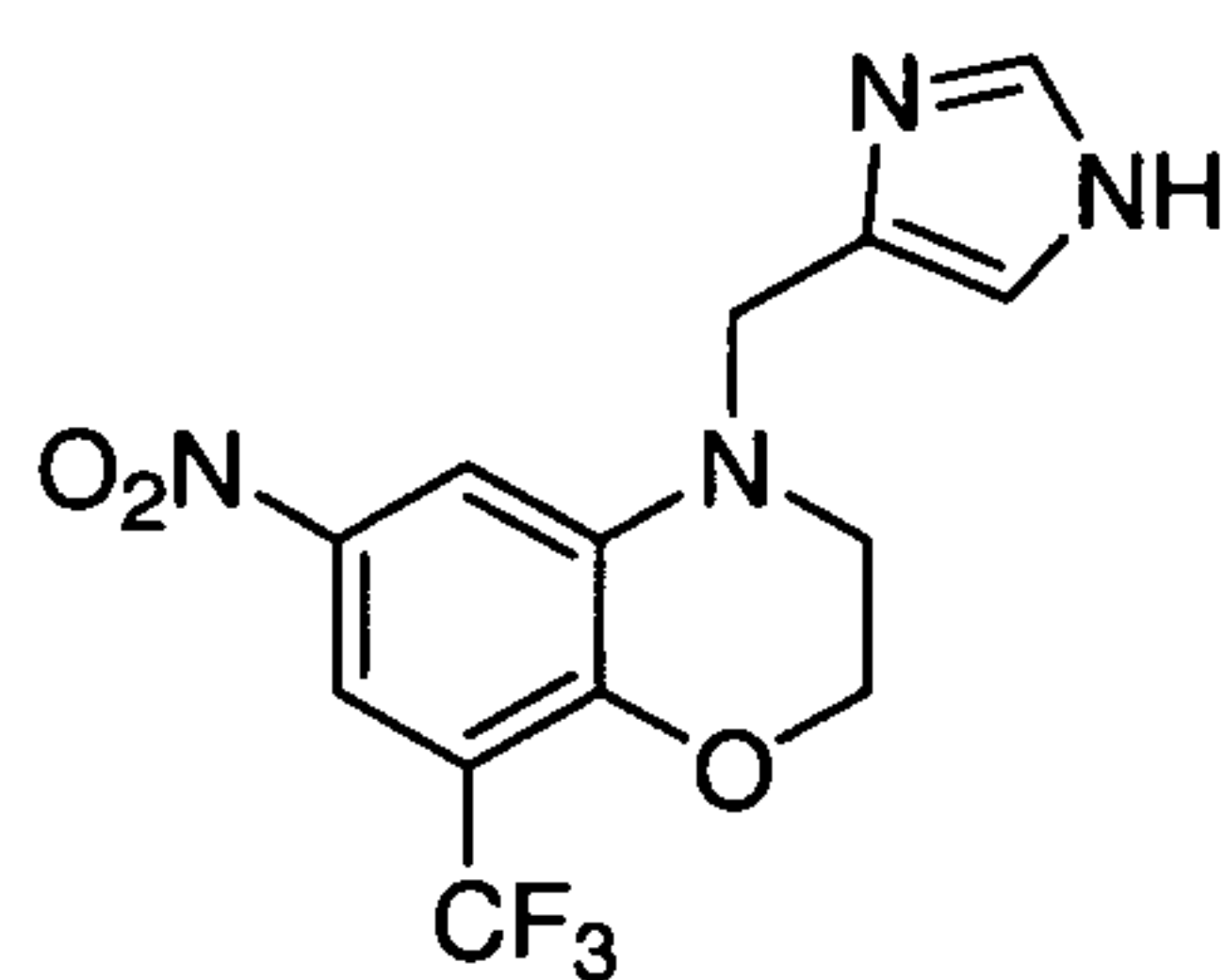
188

333



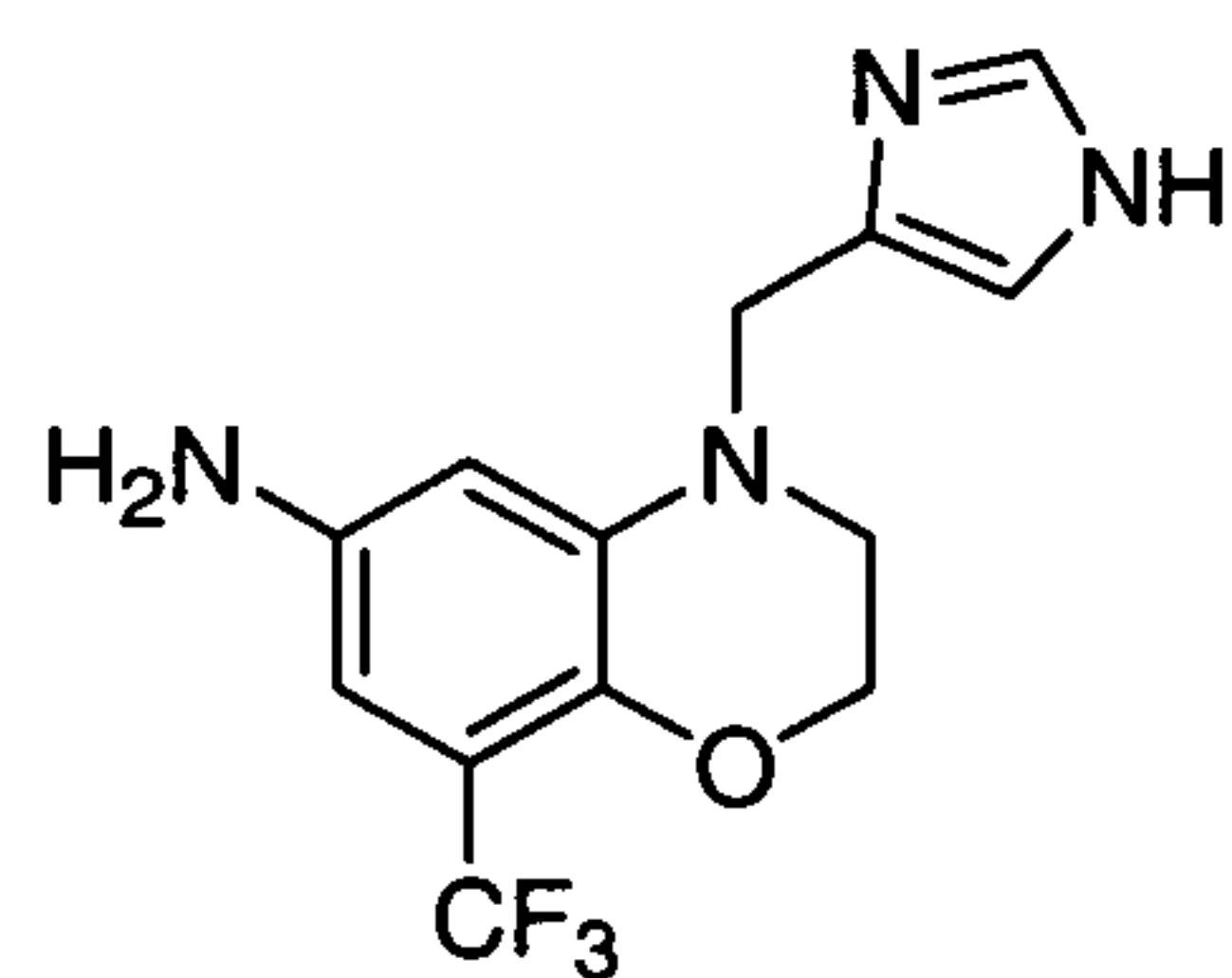
189

329



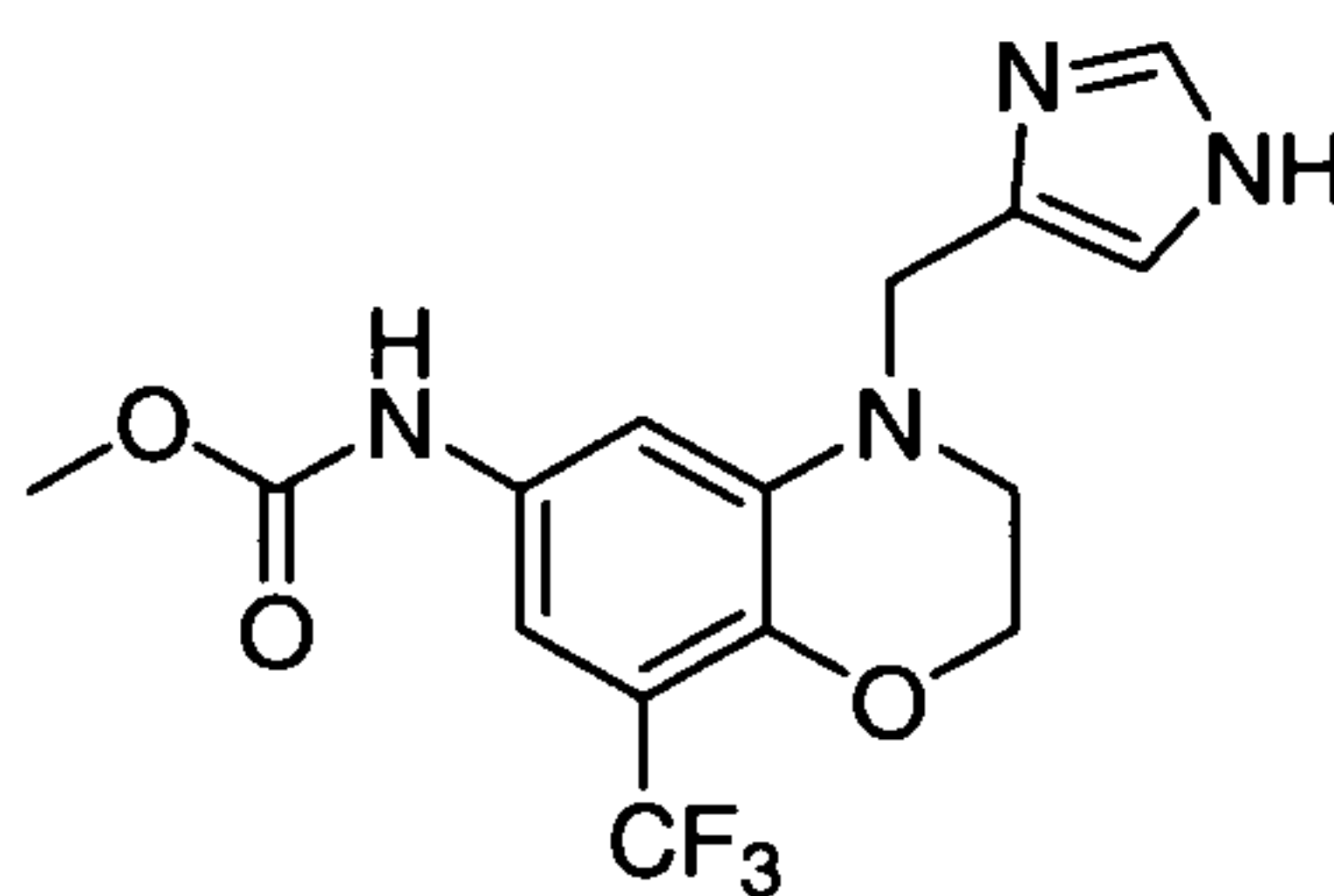
190

299



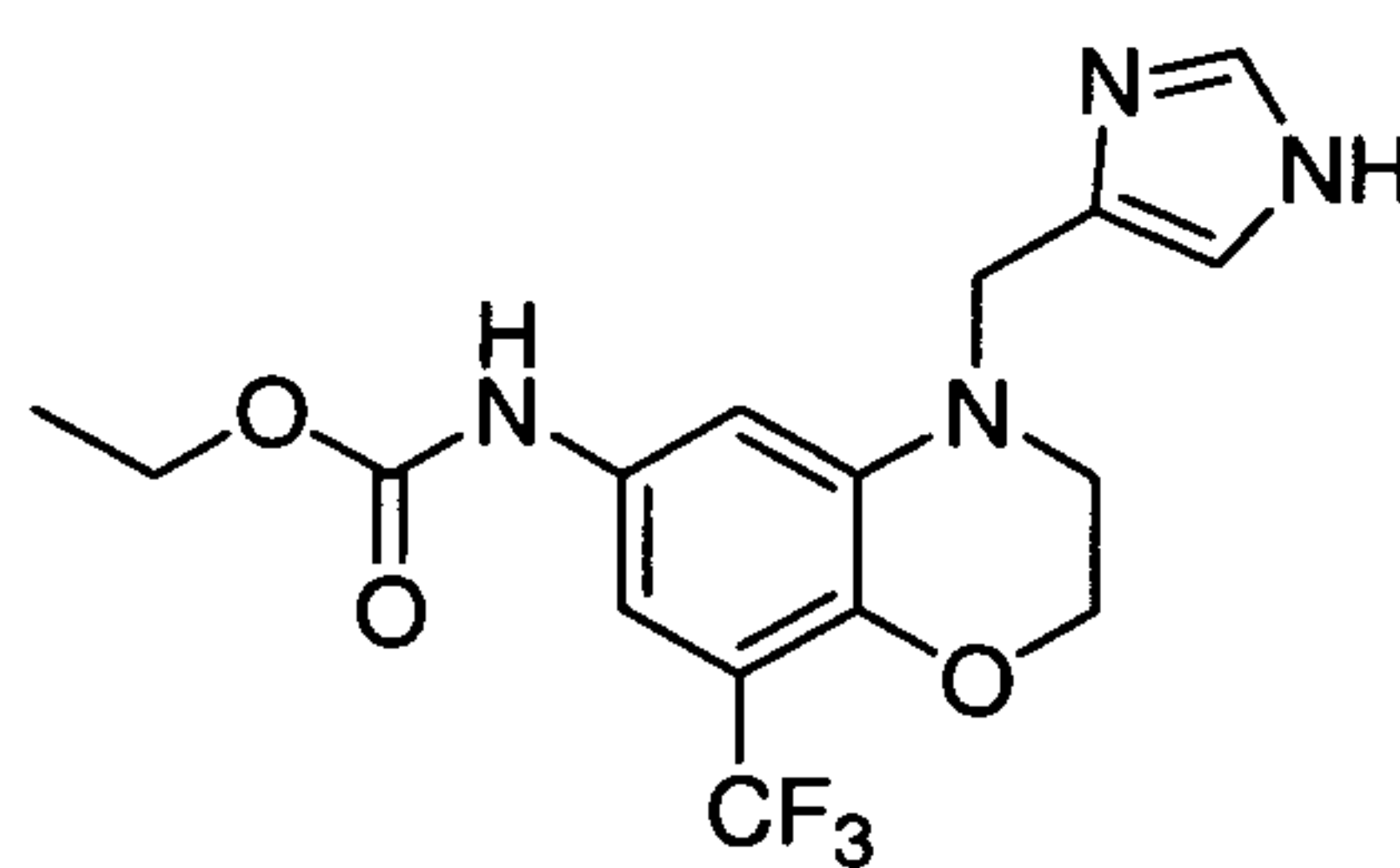
191

357



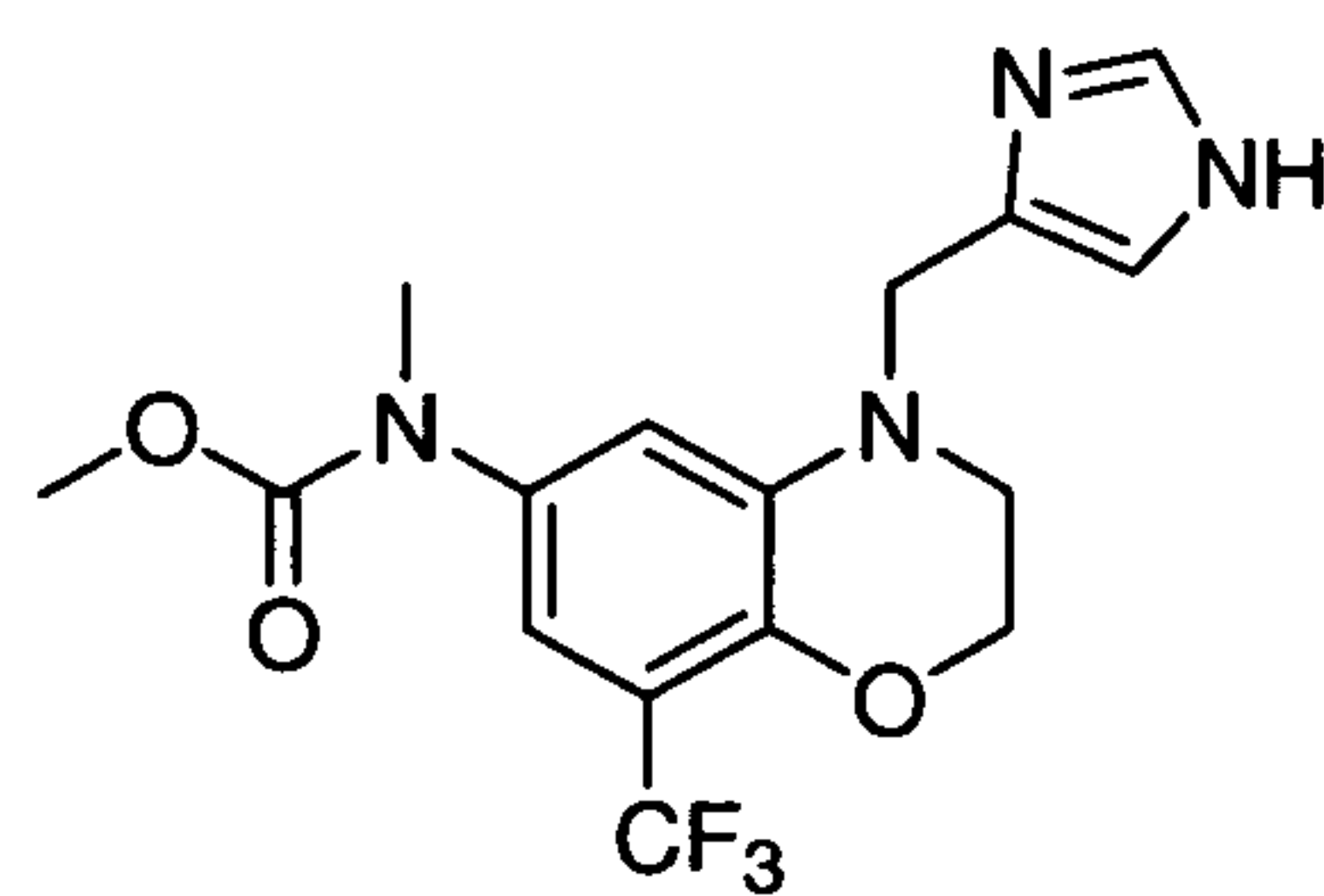
192

371



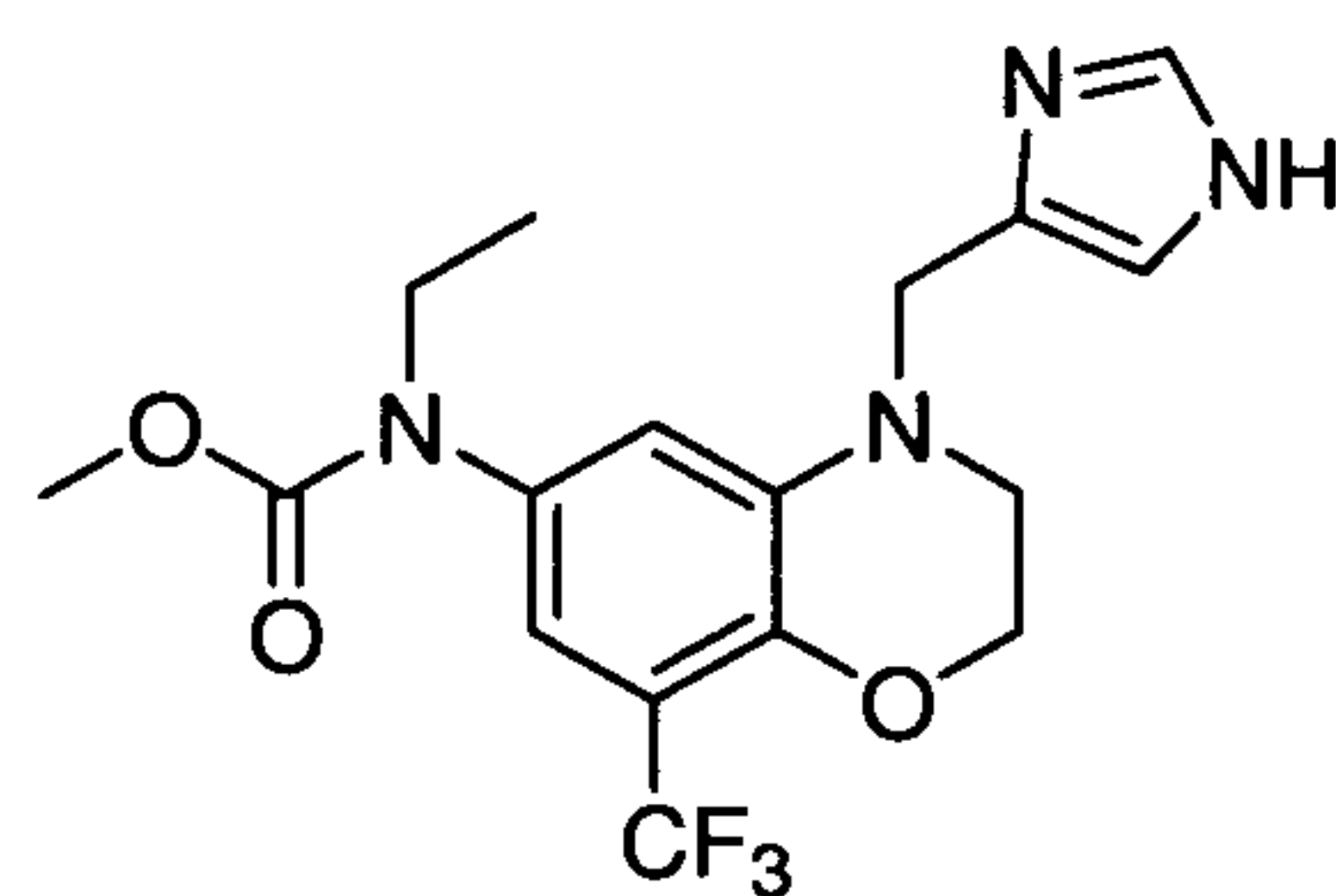
125

193



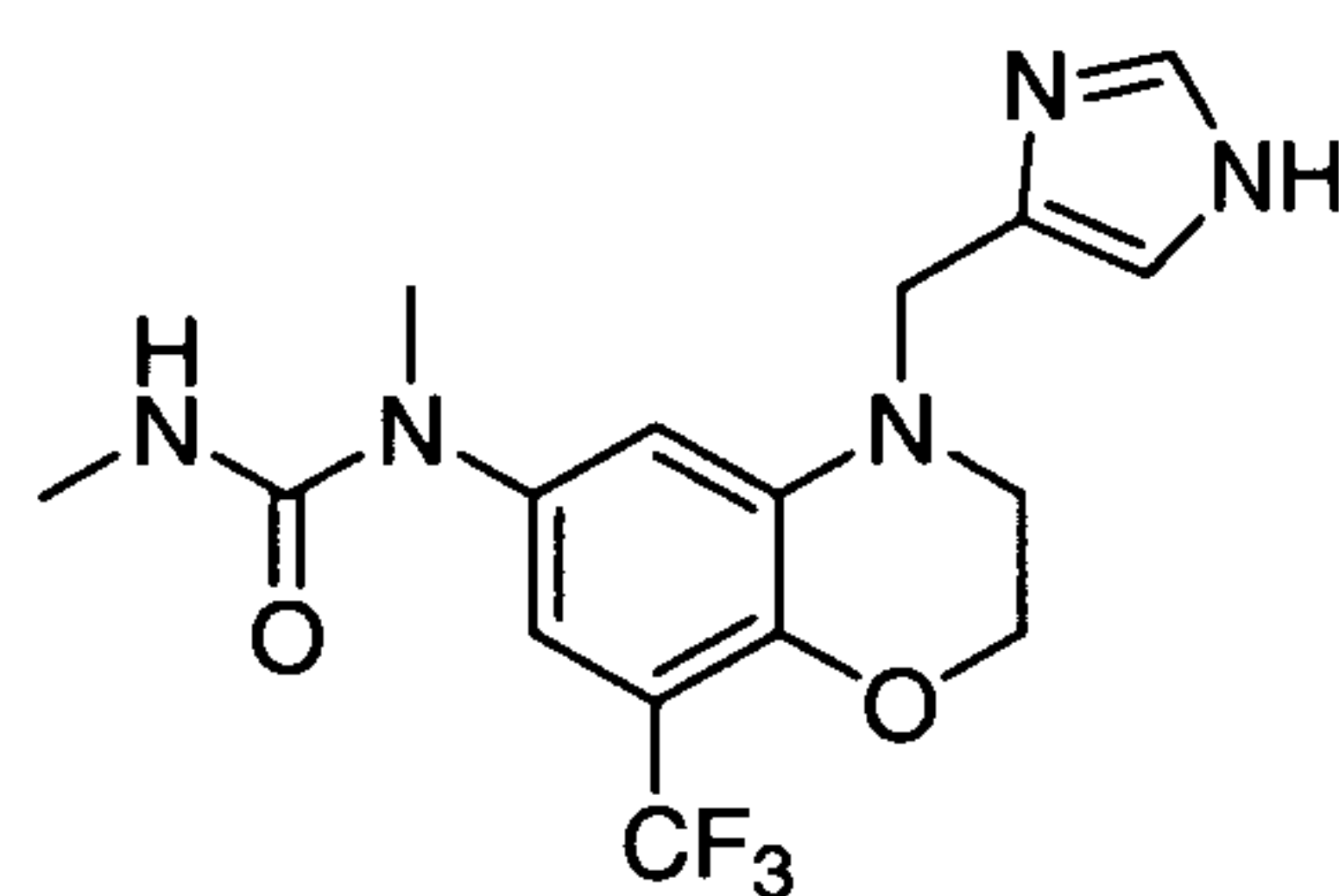
371

194



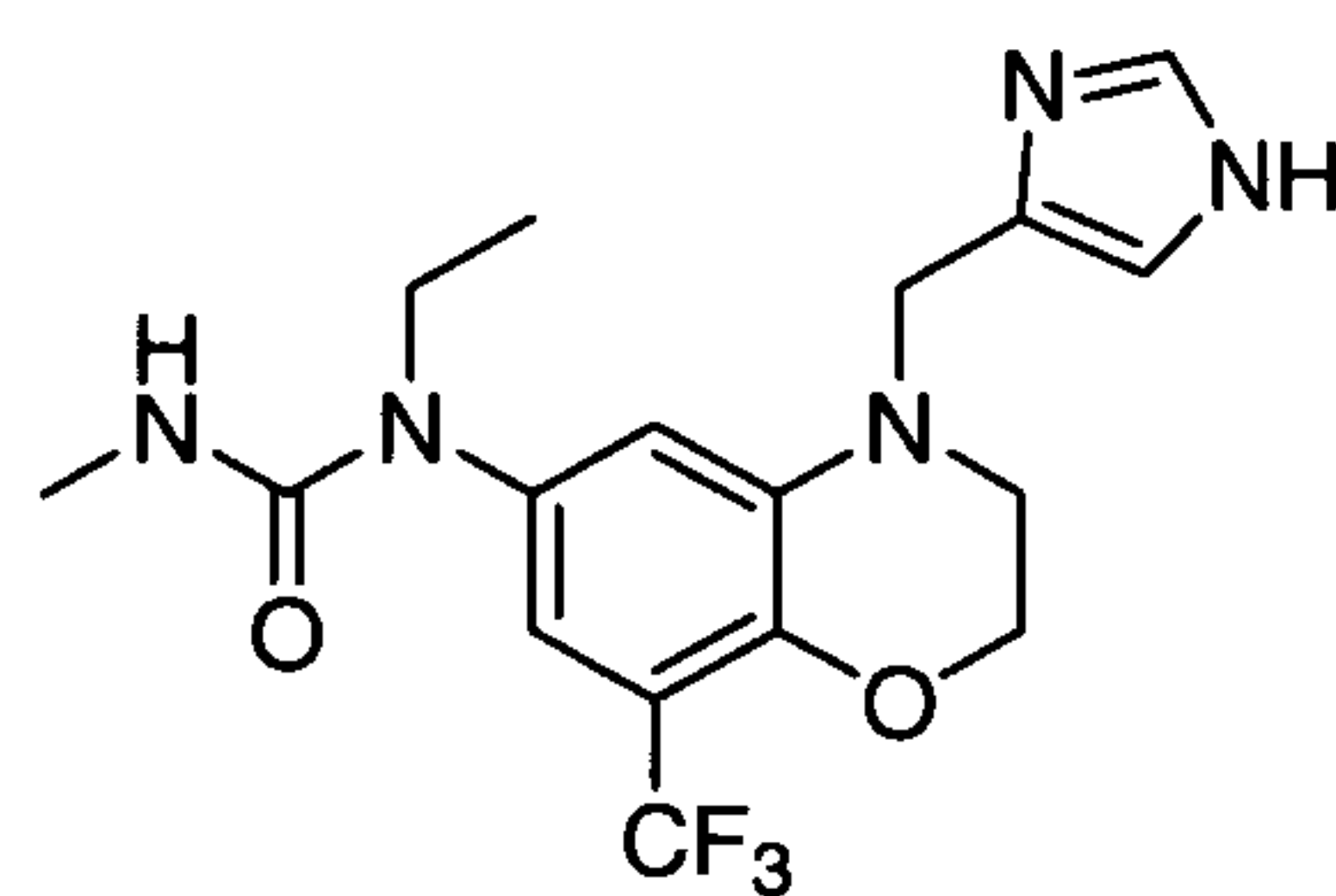
385

195



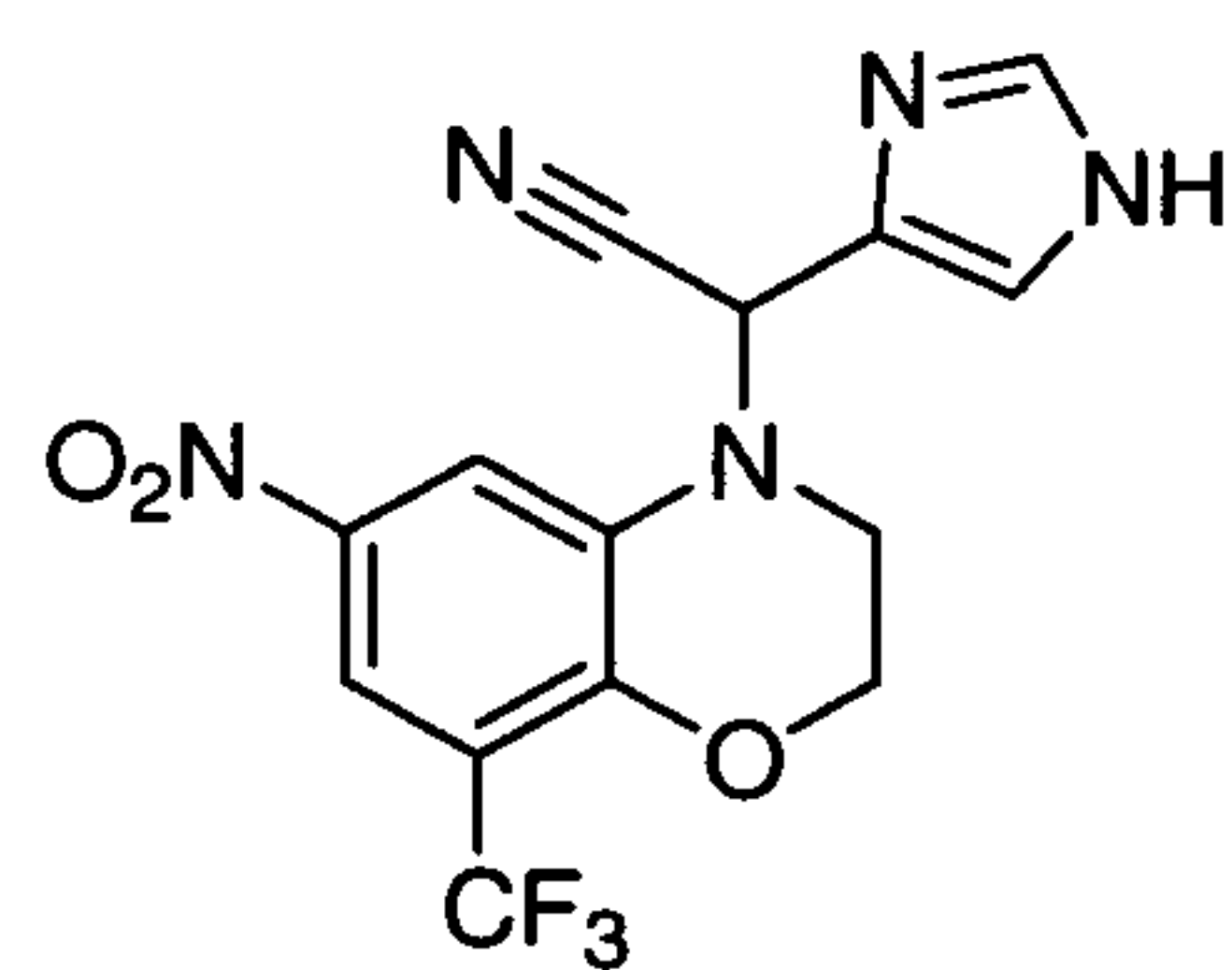
370

196



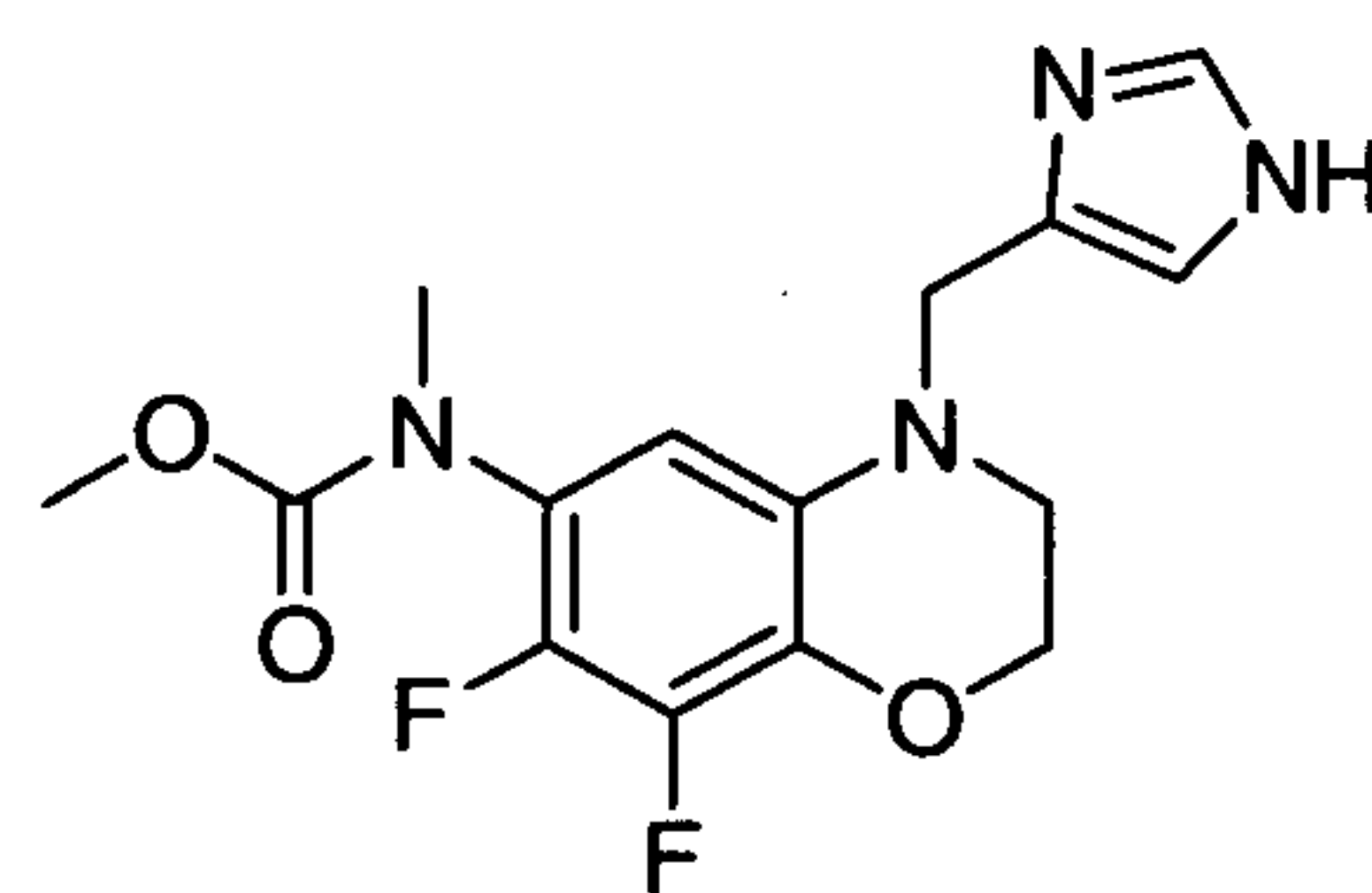
384

197



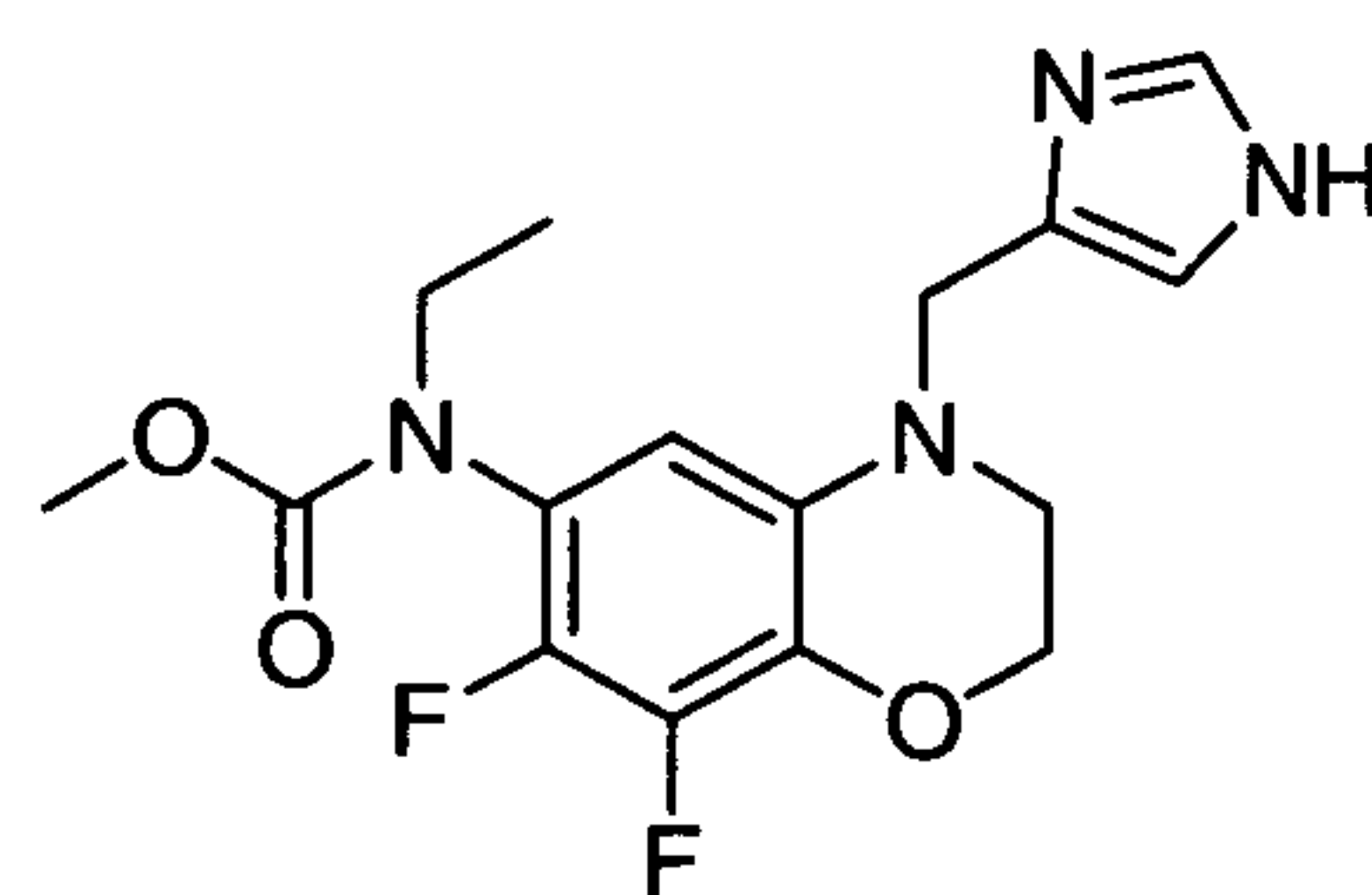
354

198



339

199

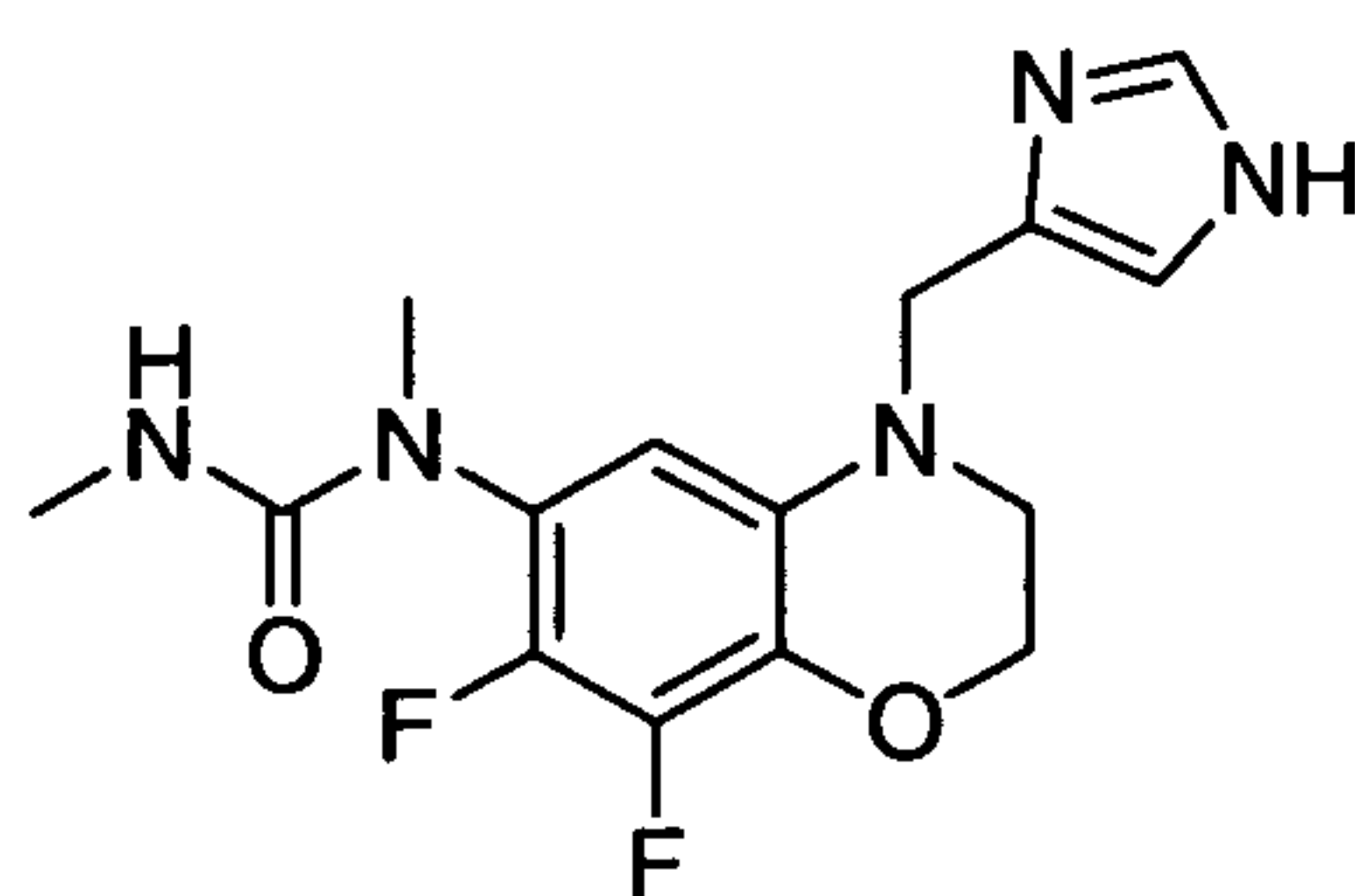


353

126

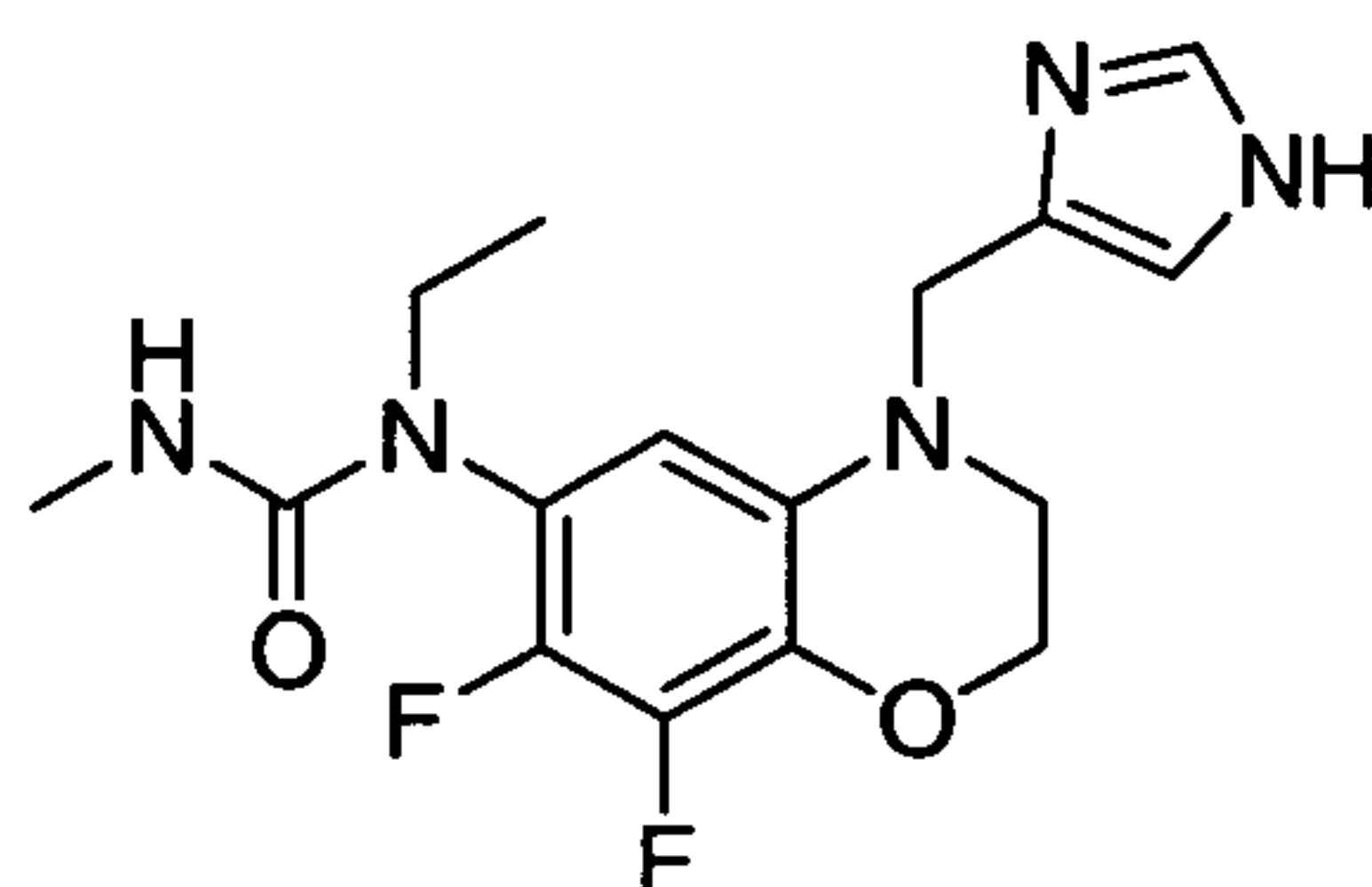
200

338



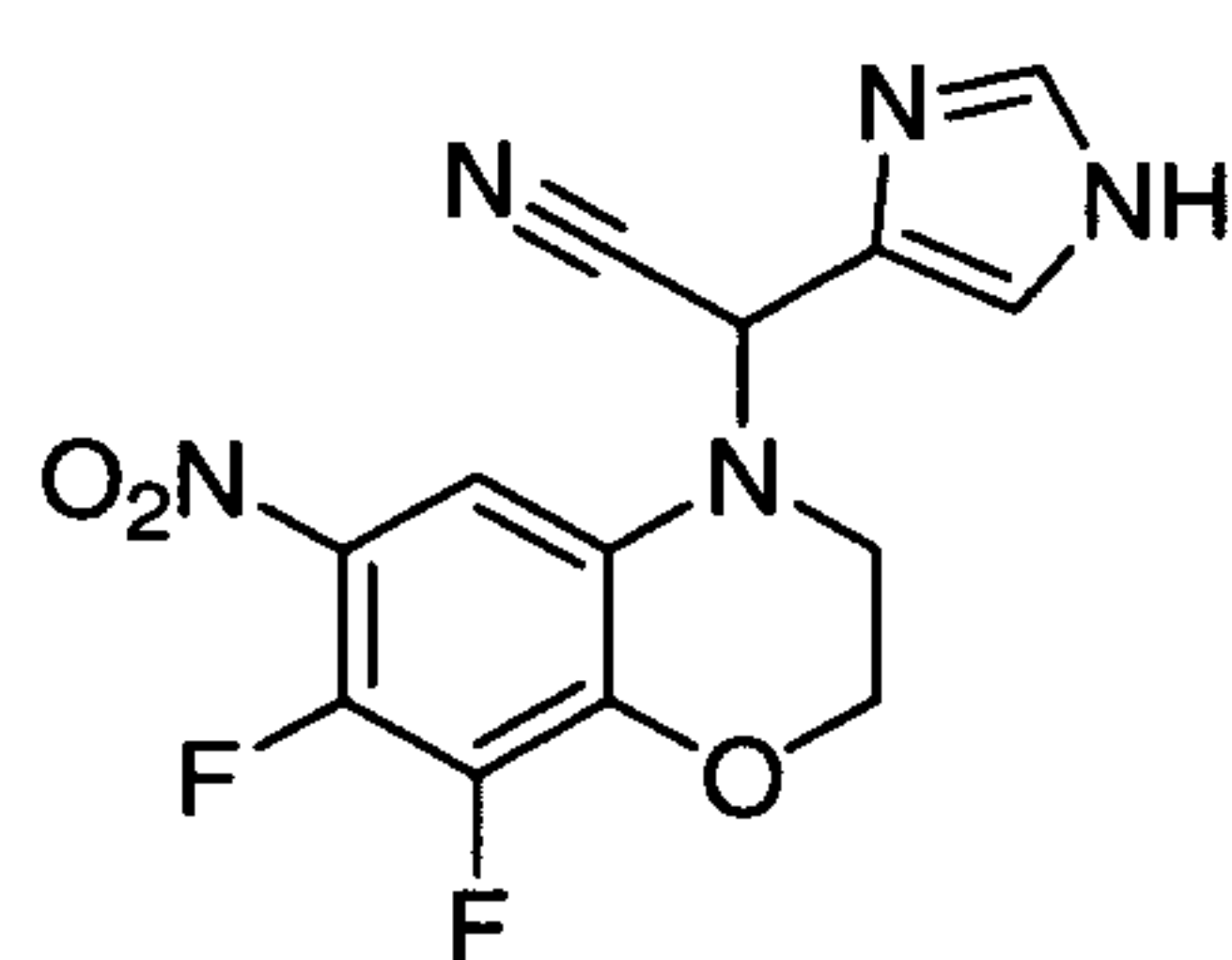
201

352



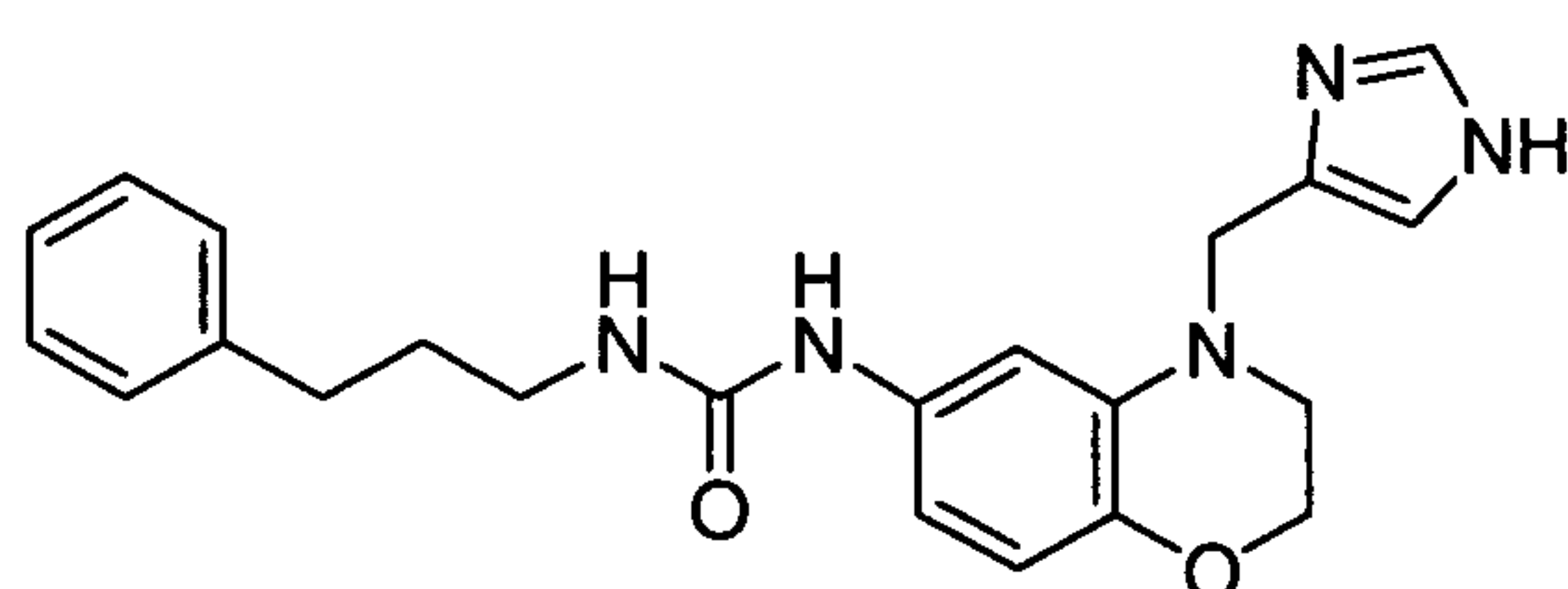
202

322



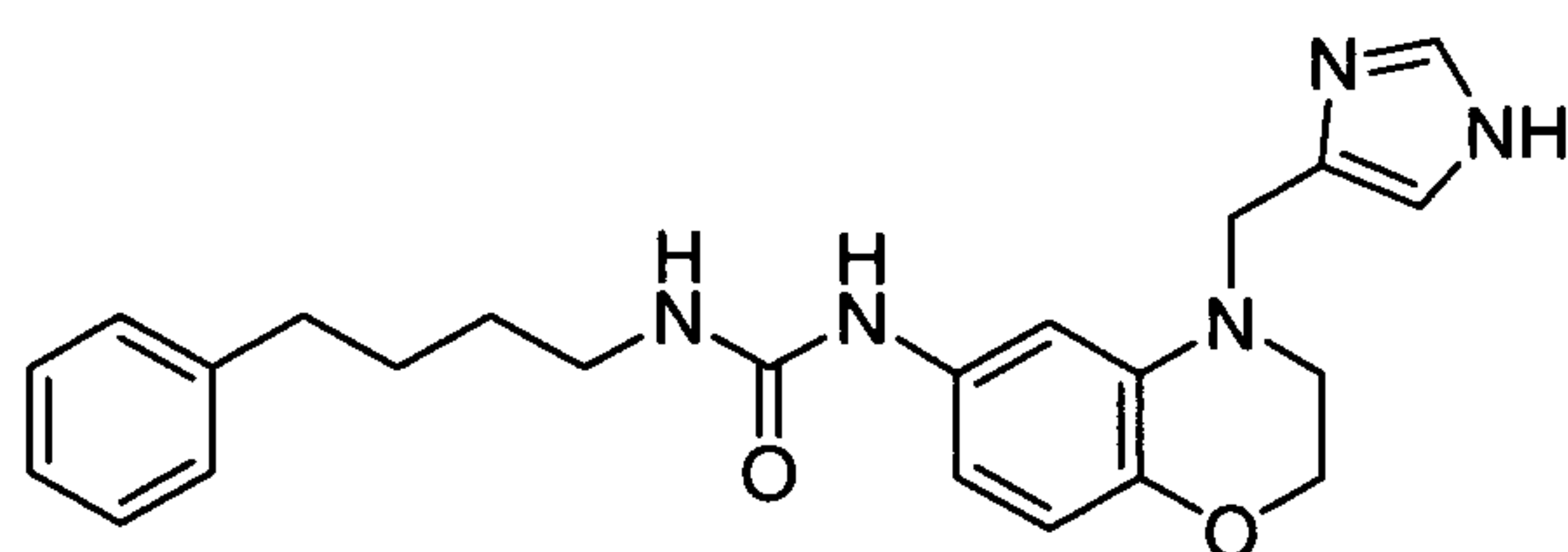
203

392



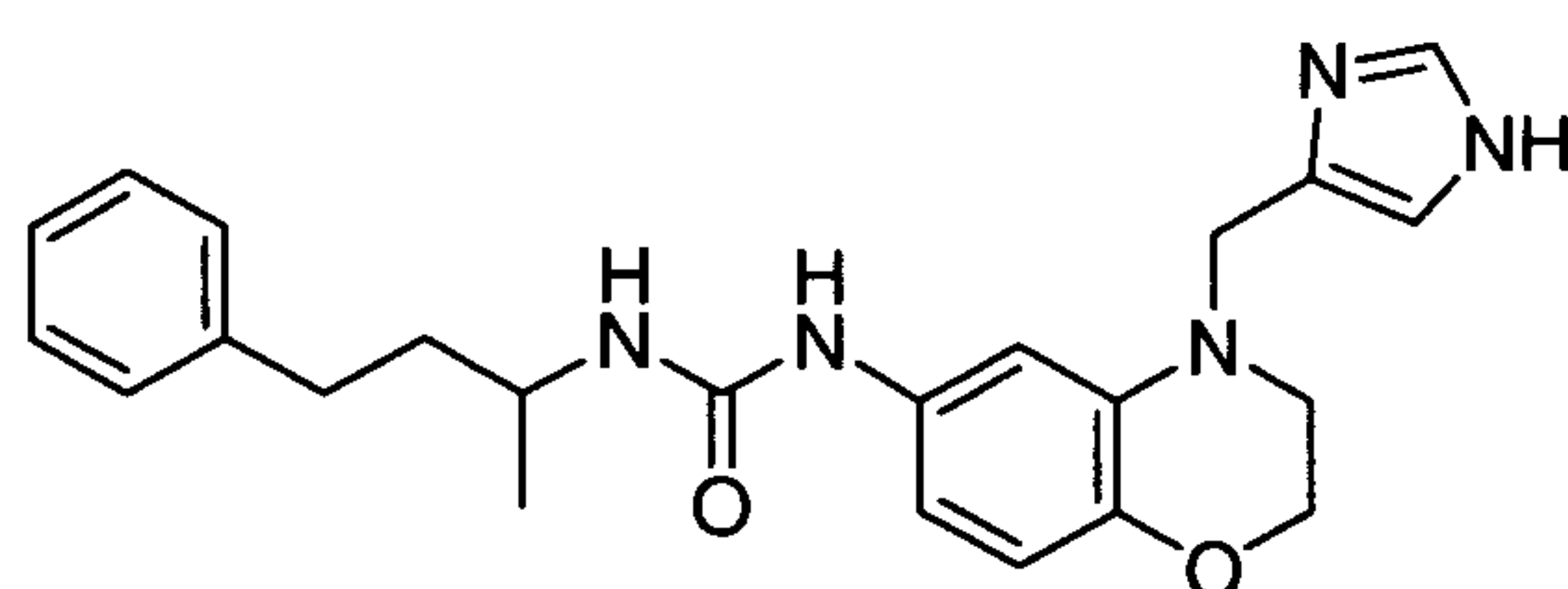
204

406



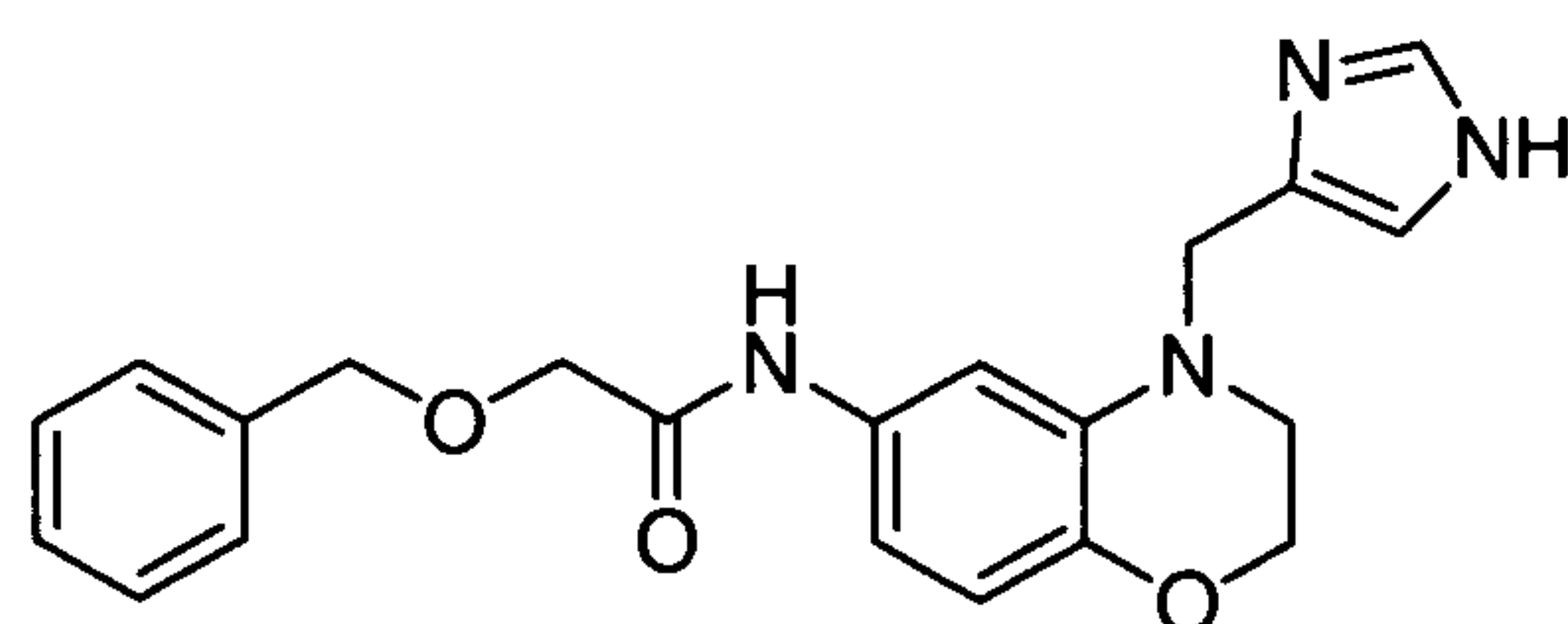
205

406



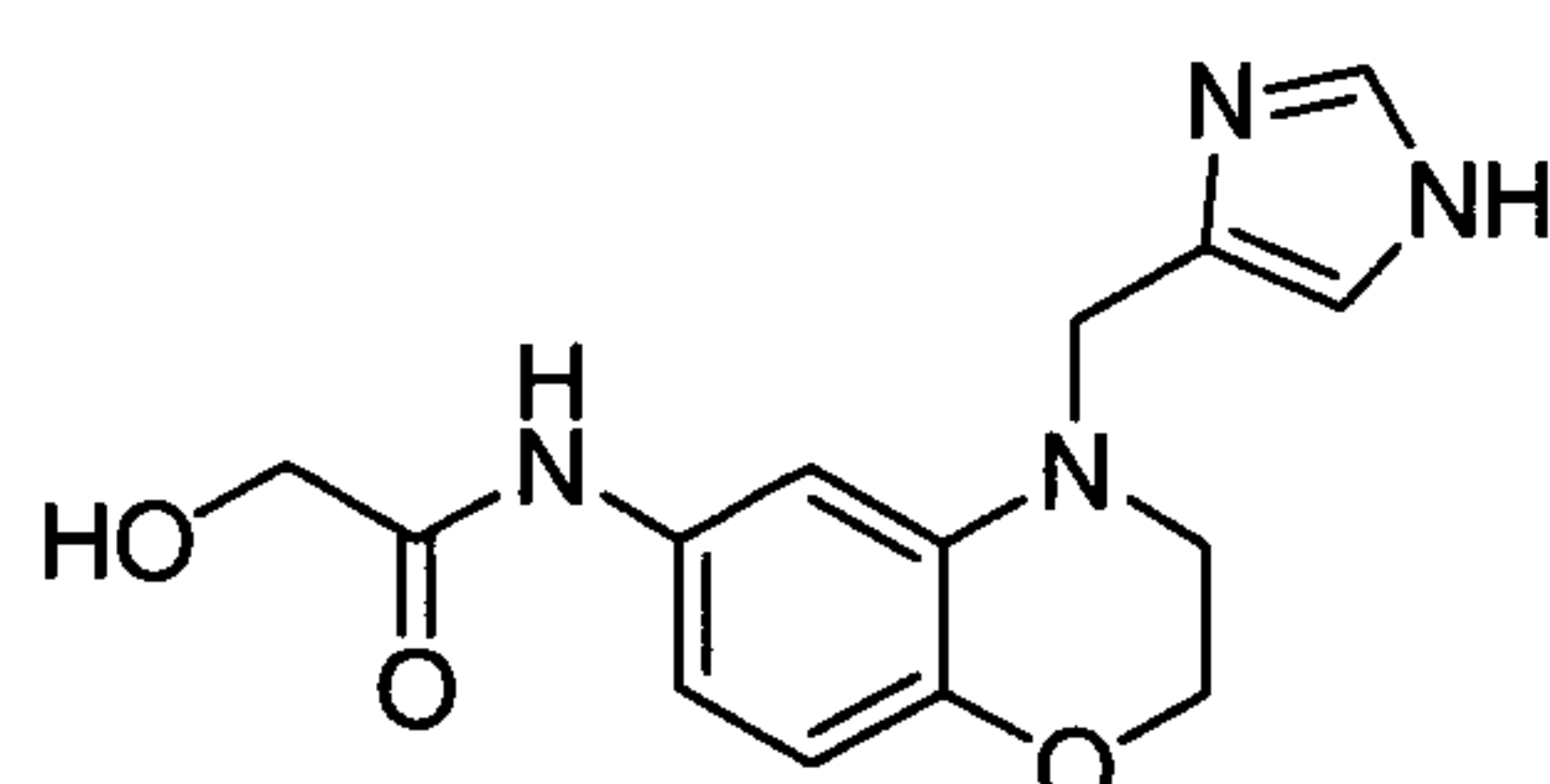
206

389



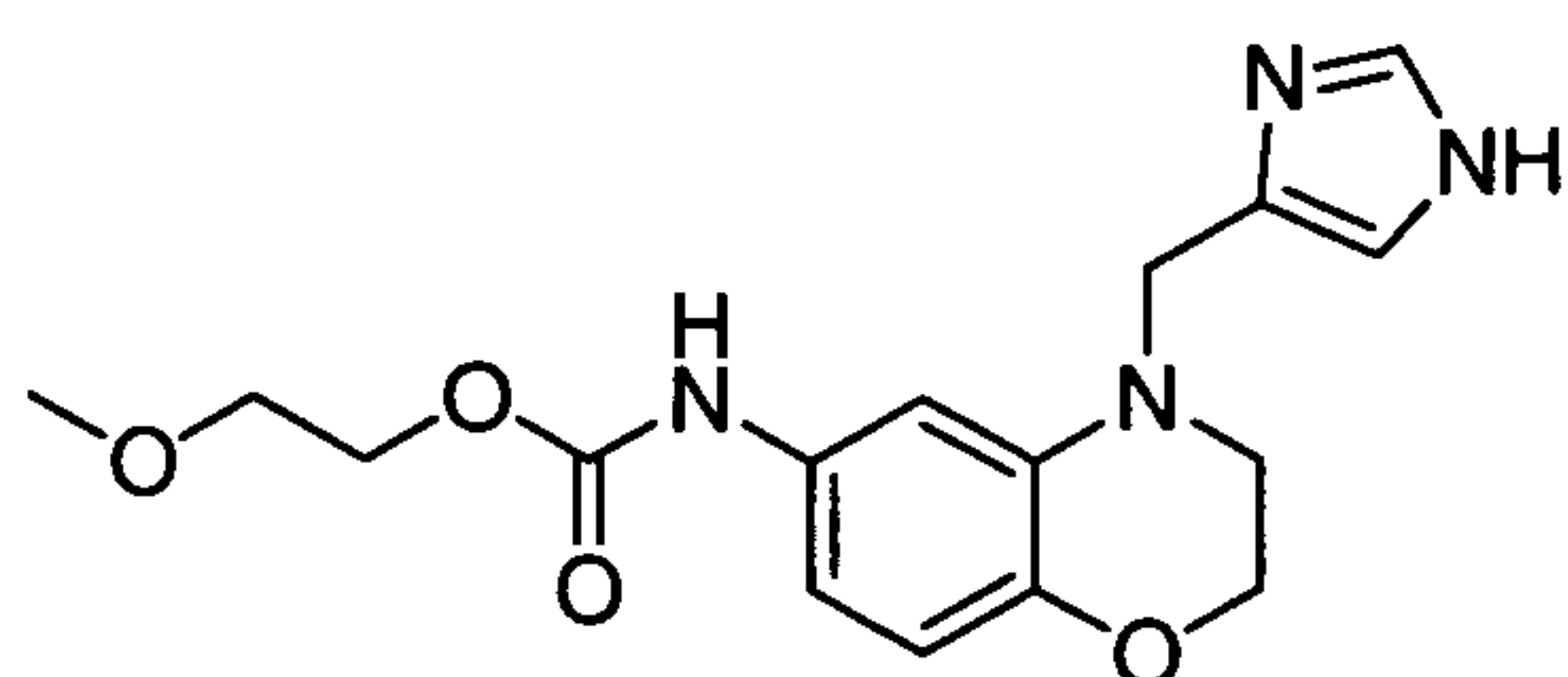
207

289



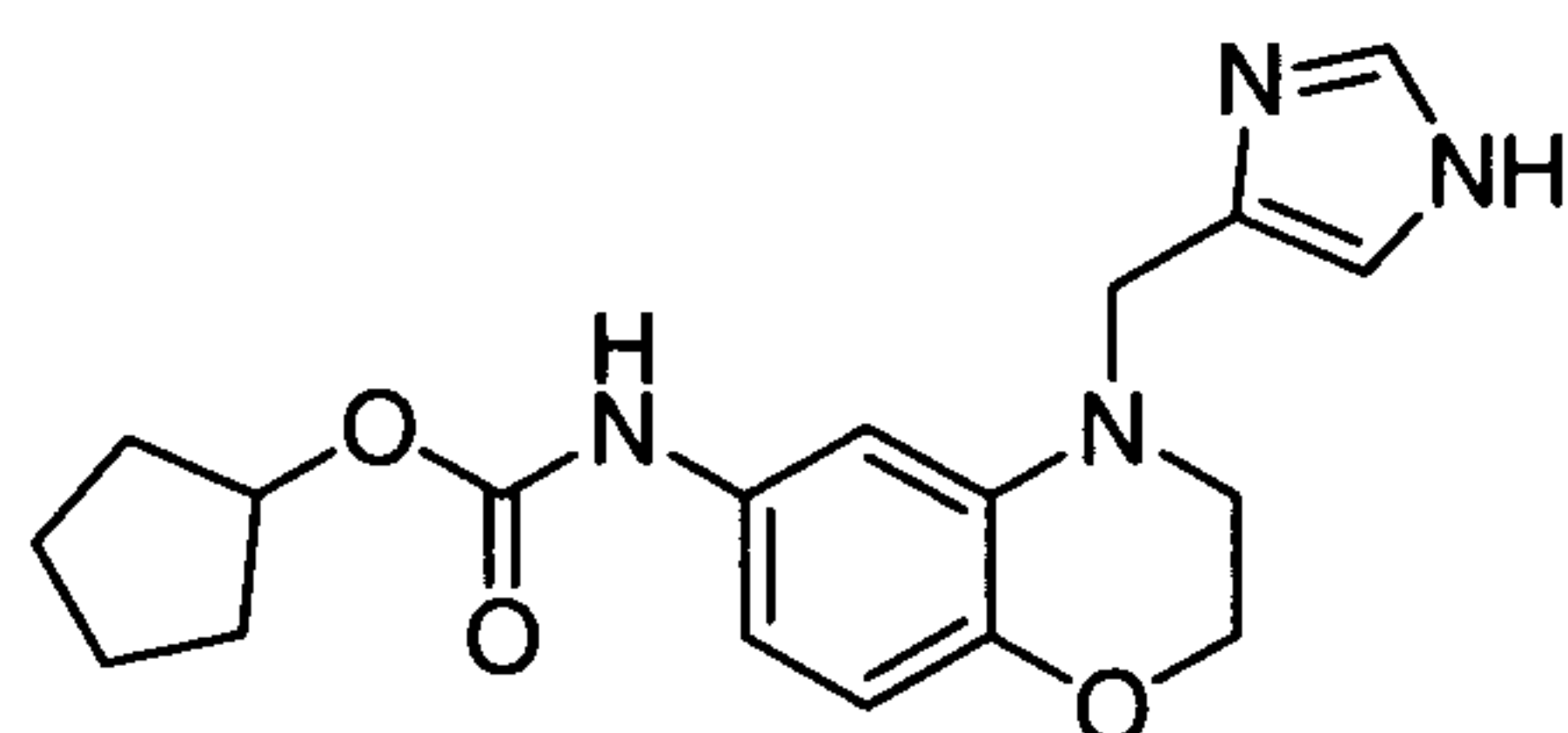
127

208



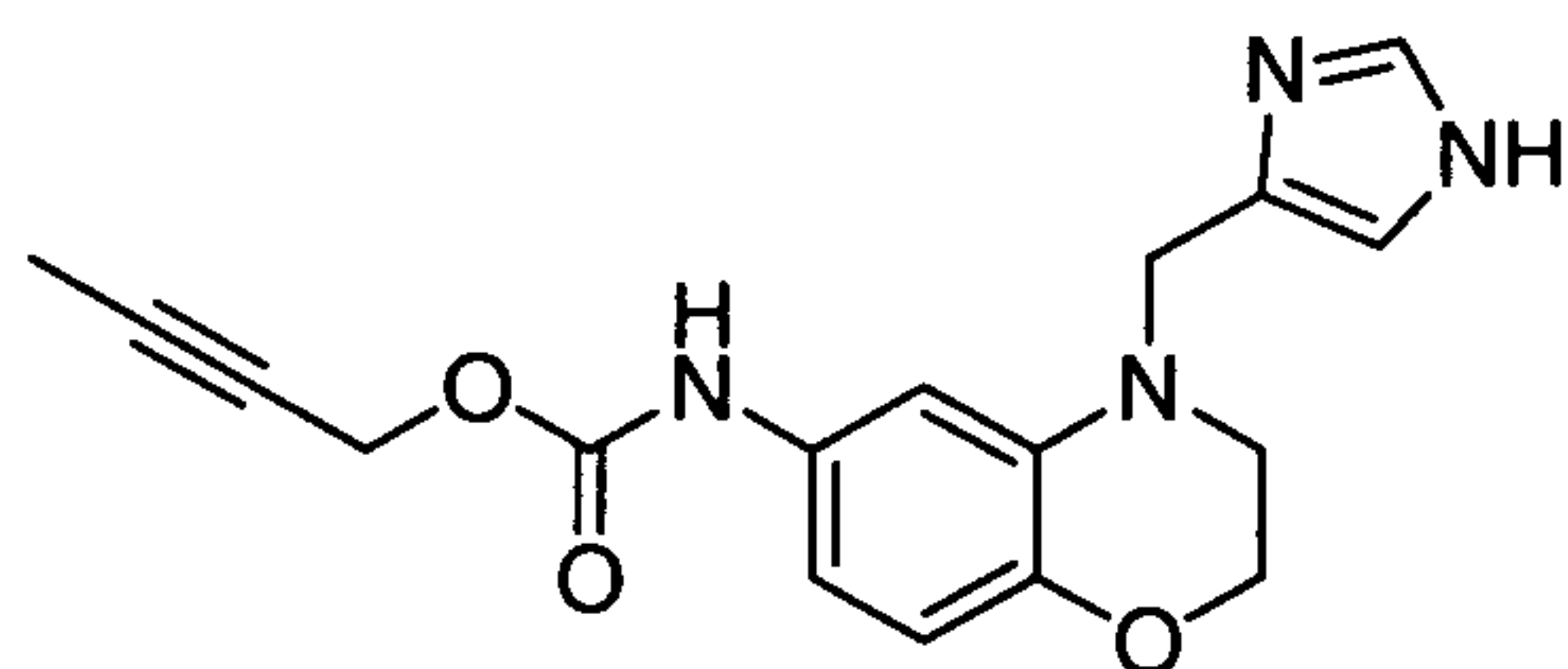
333

209



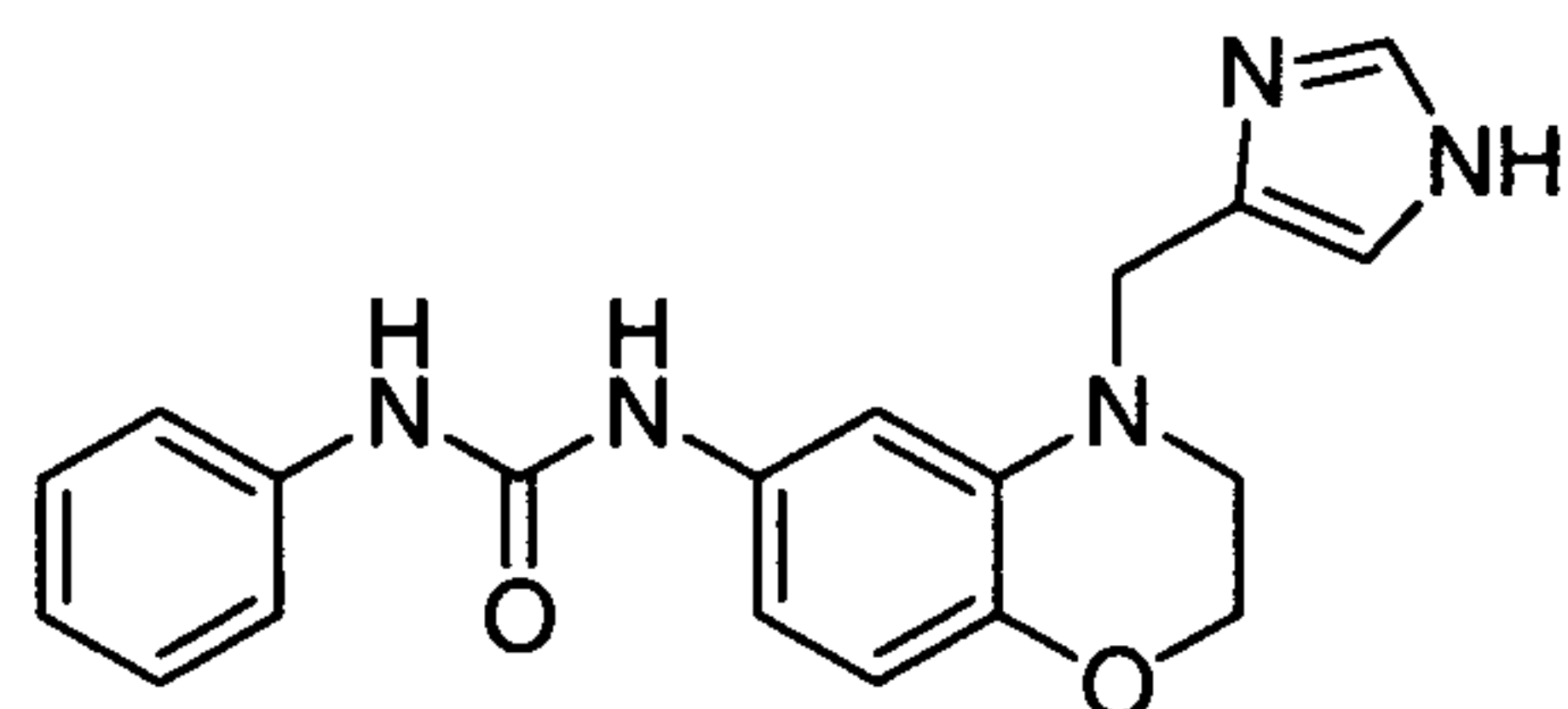
343

210



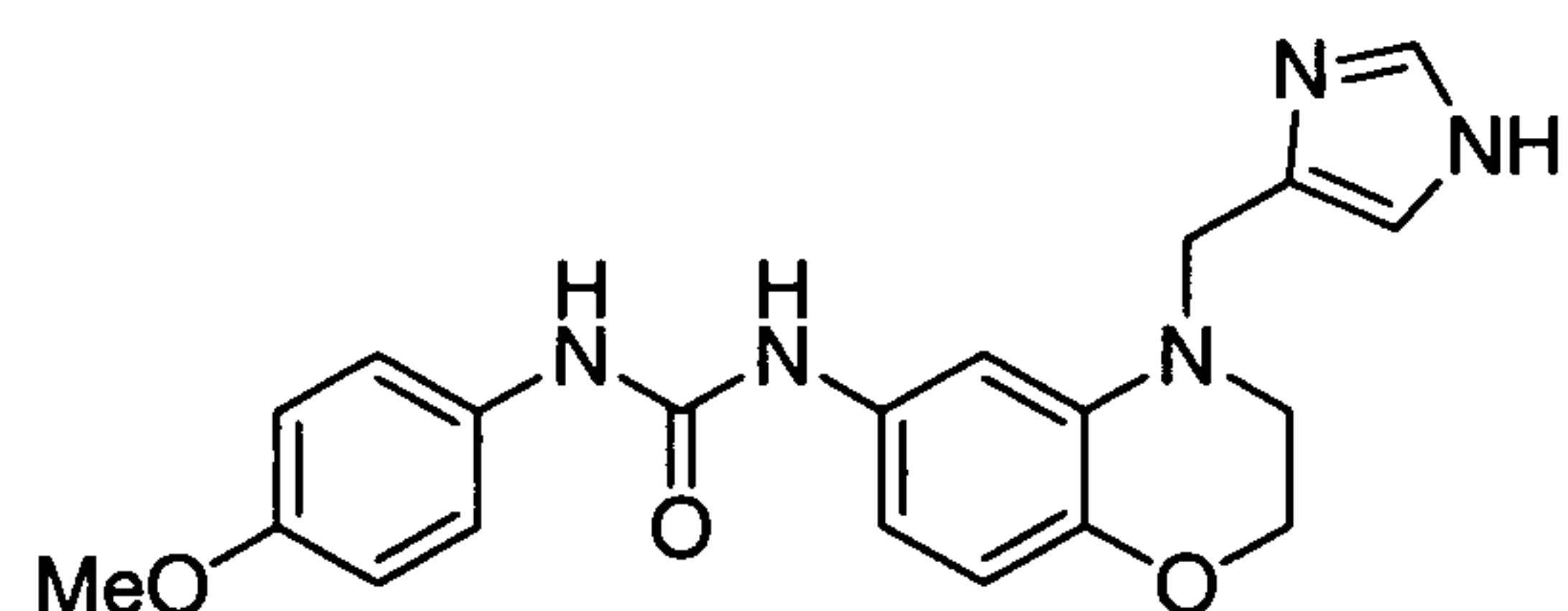
327

211



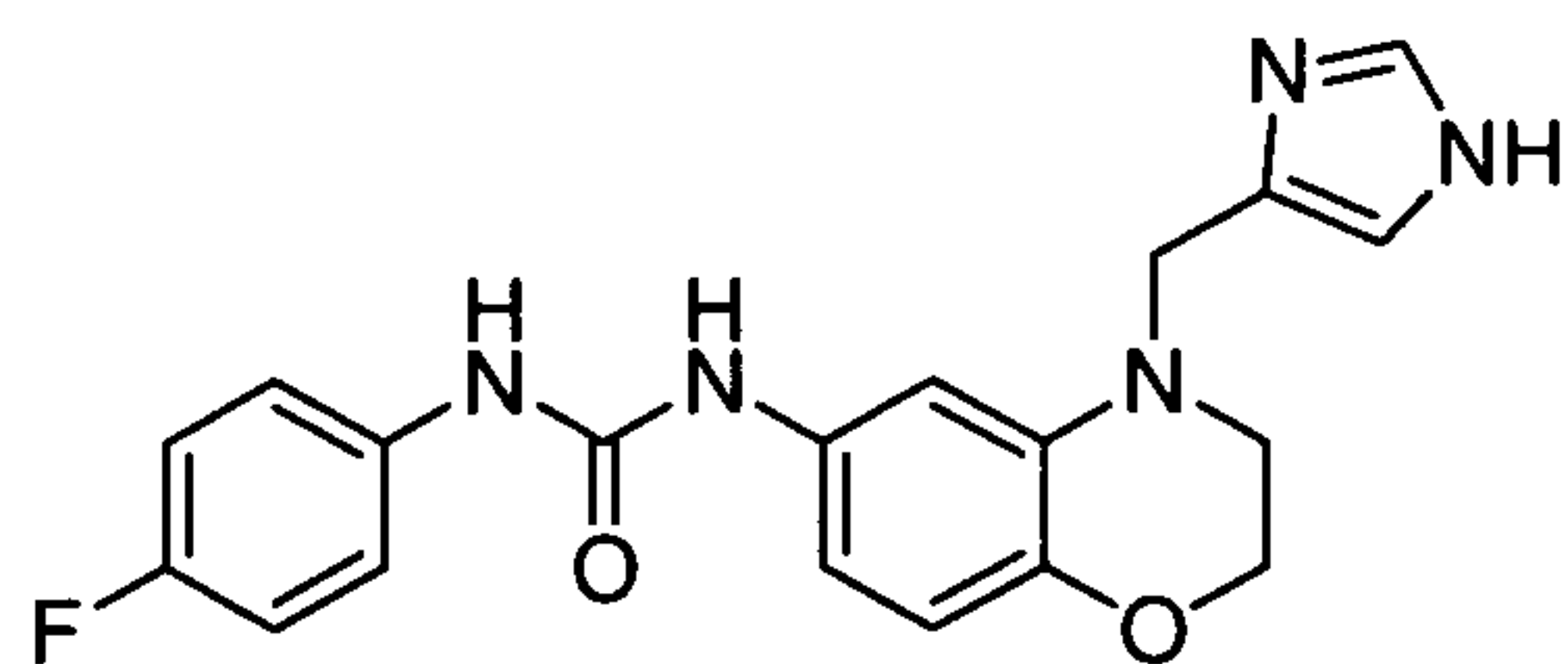
350

212



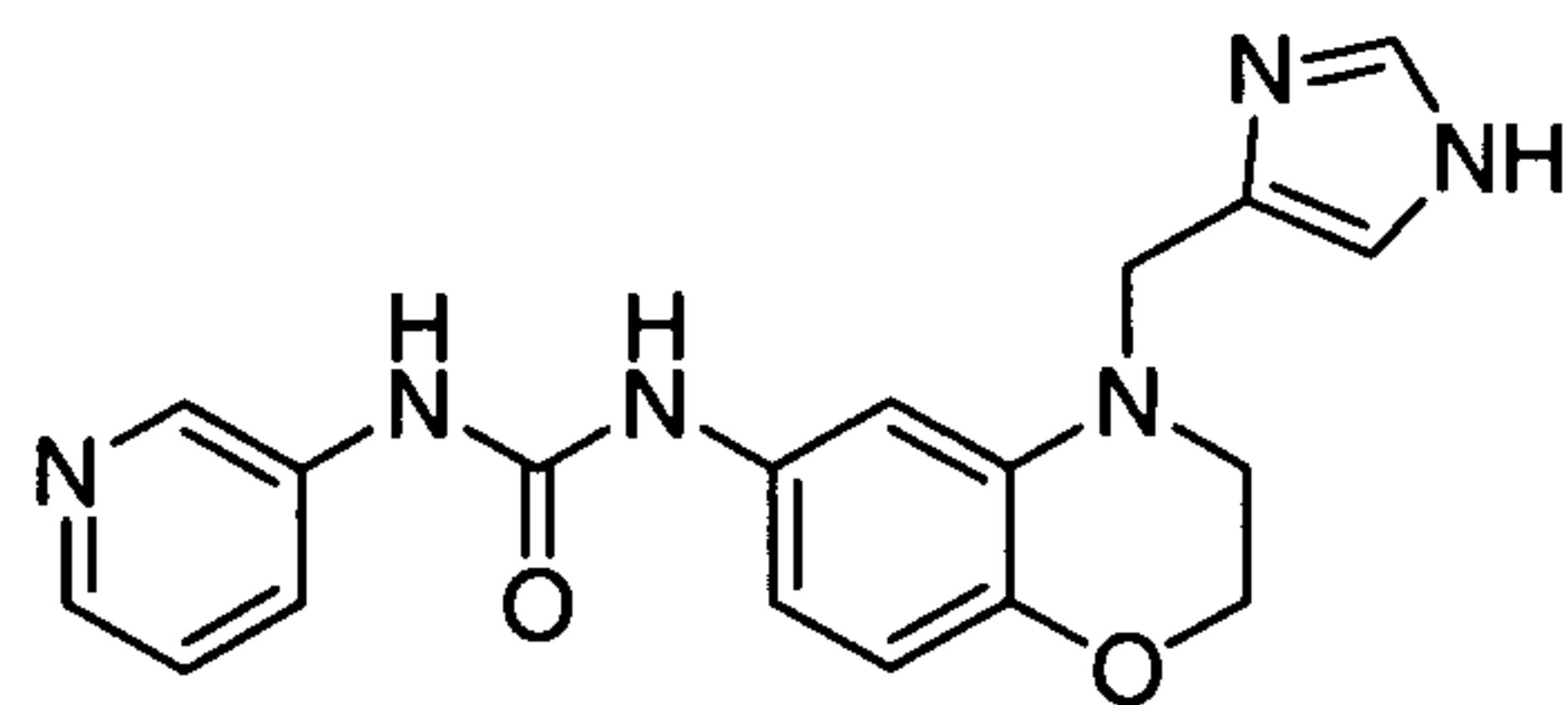
380

213



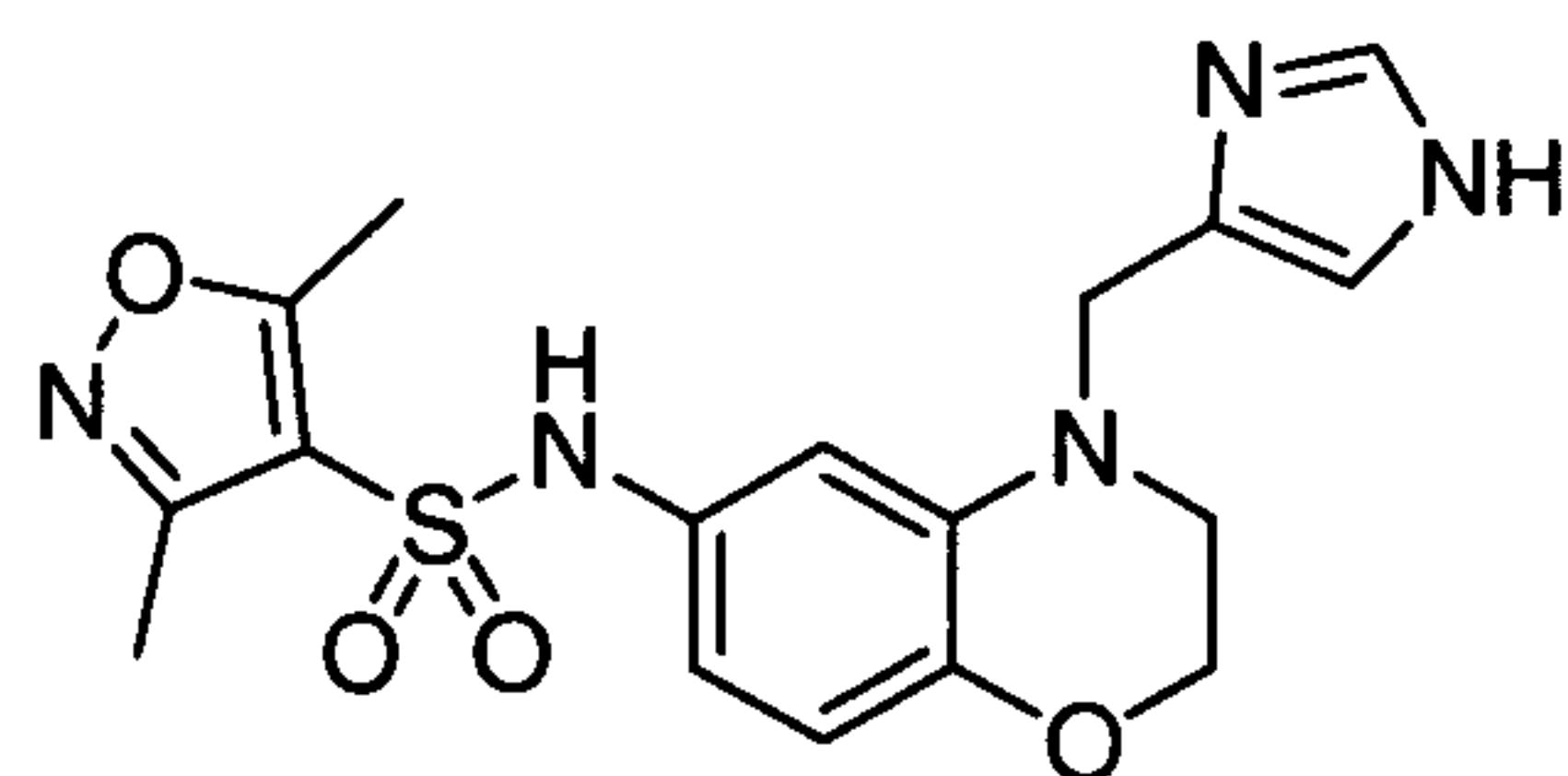
368

214



351

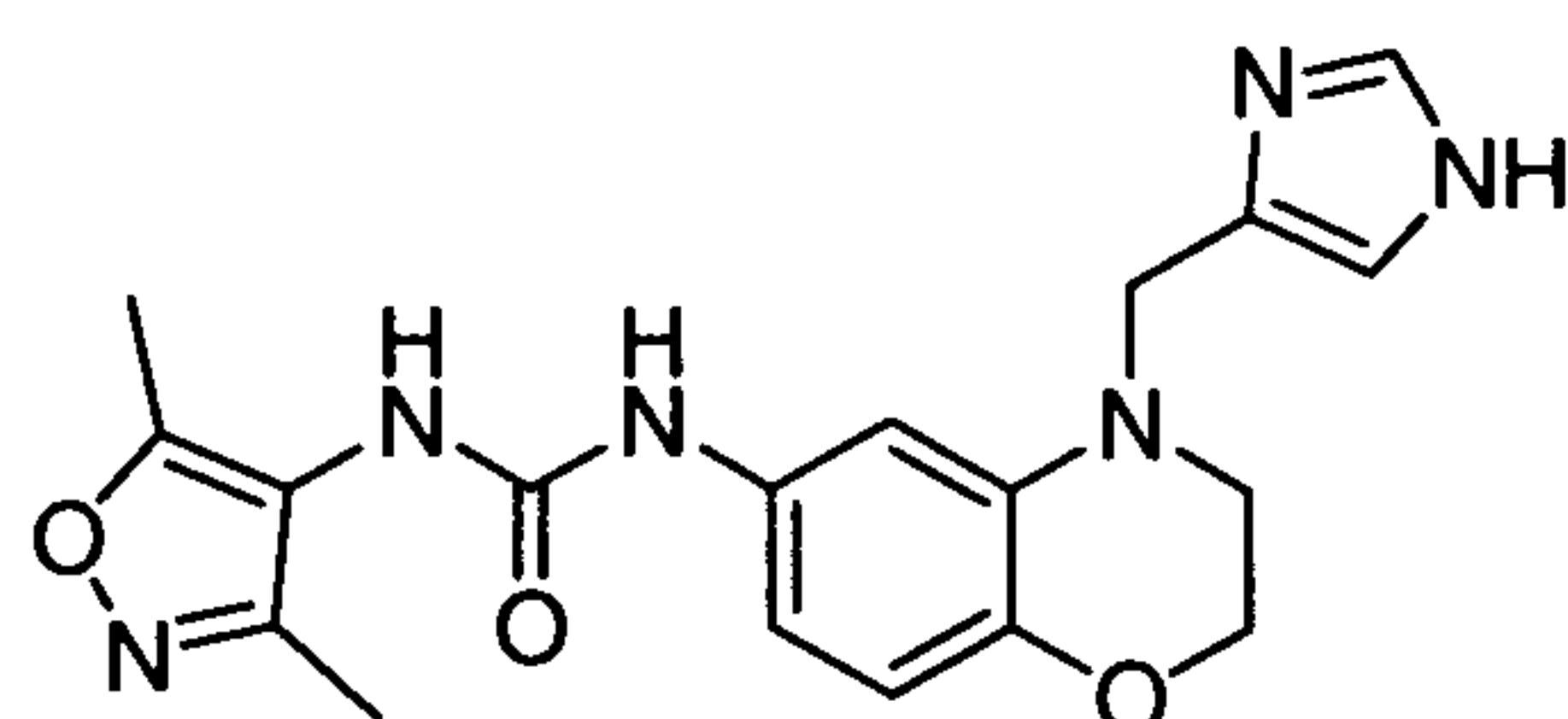
215



390

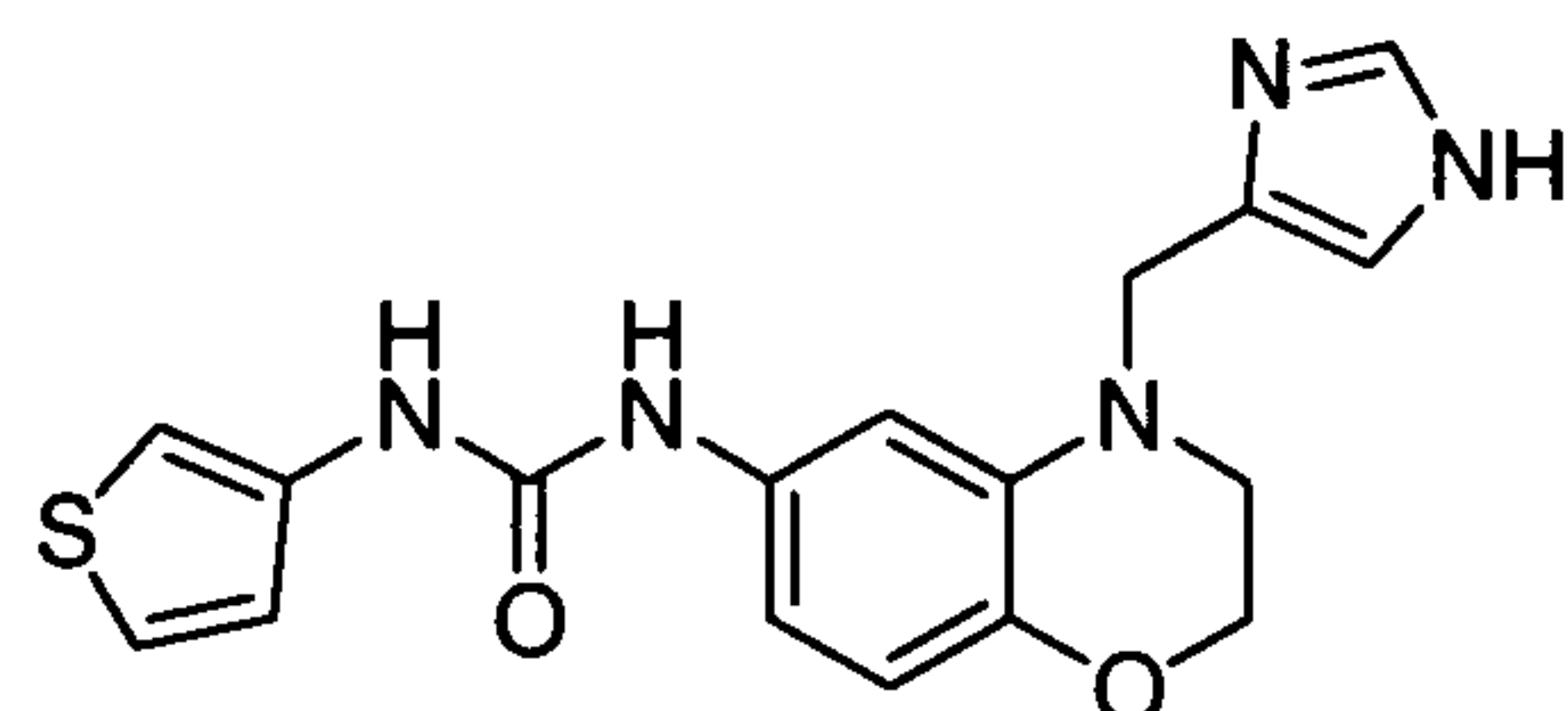
128

216



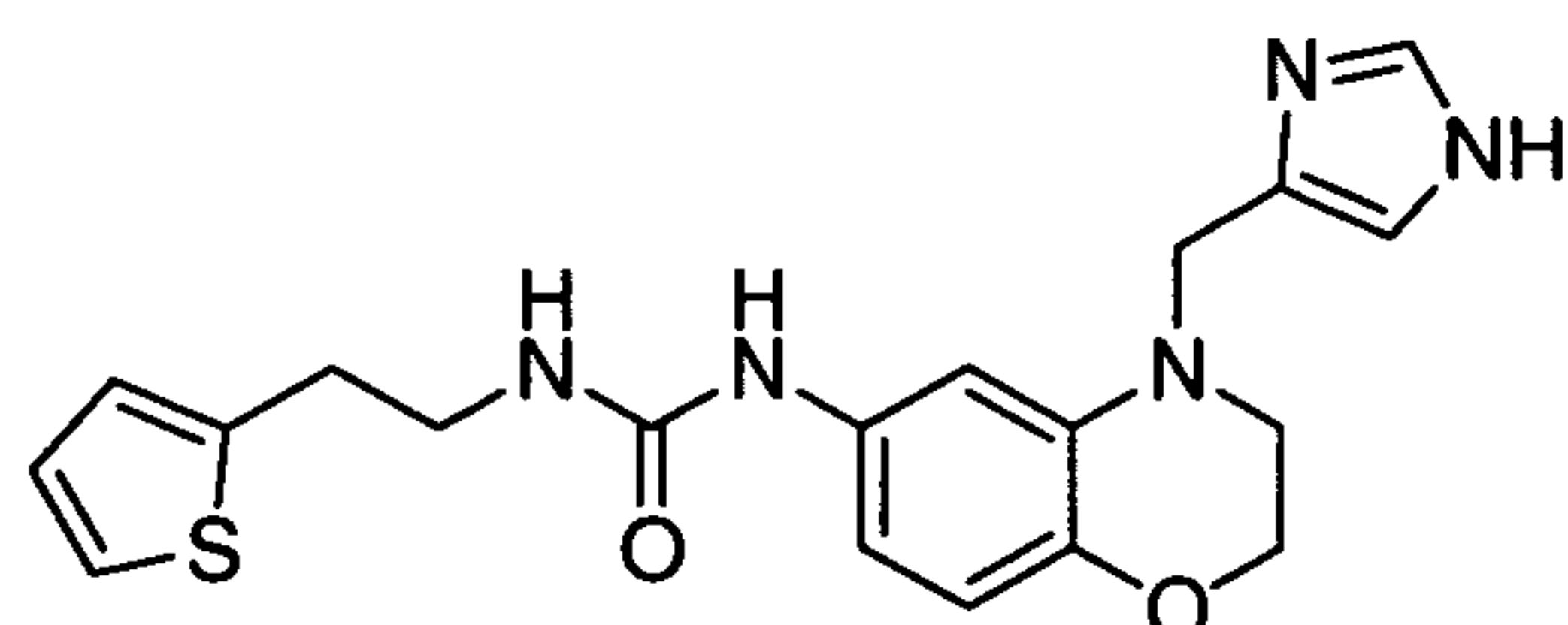
369

217



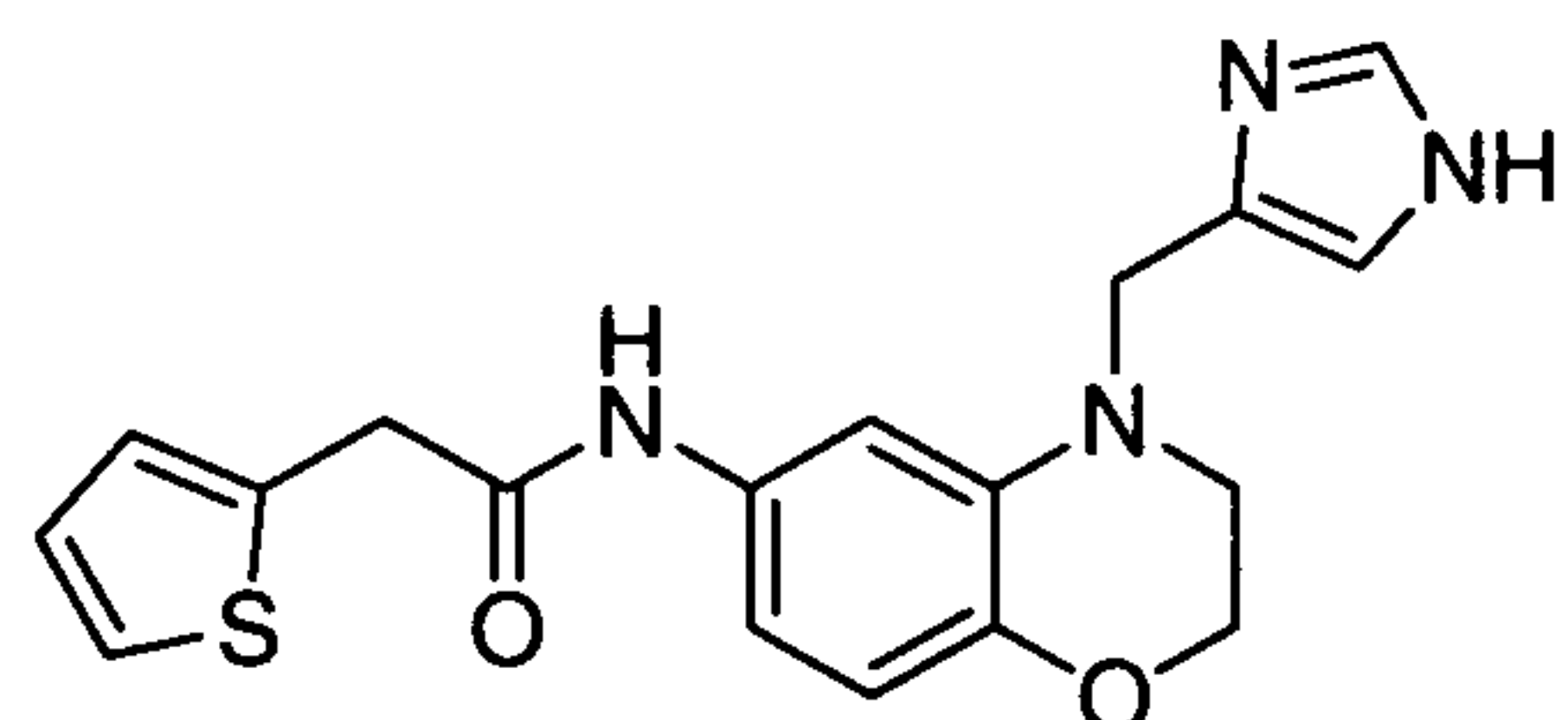
356

218



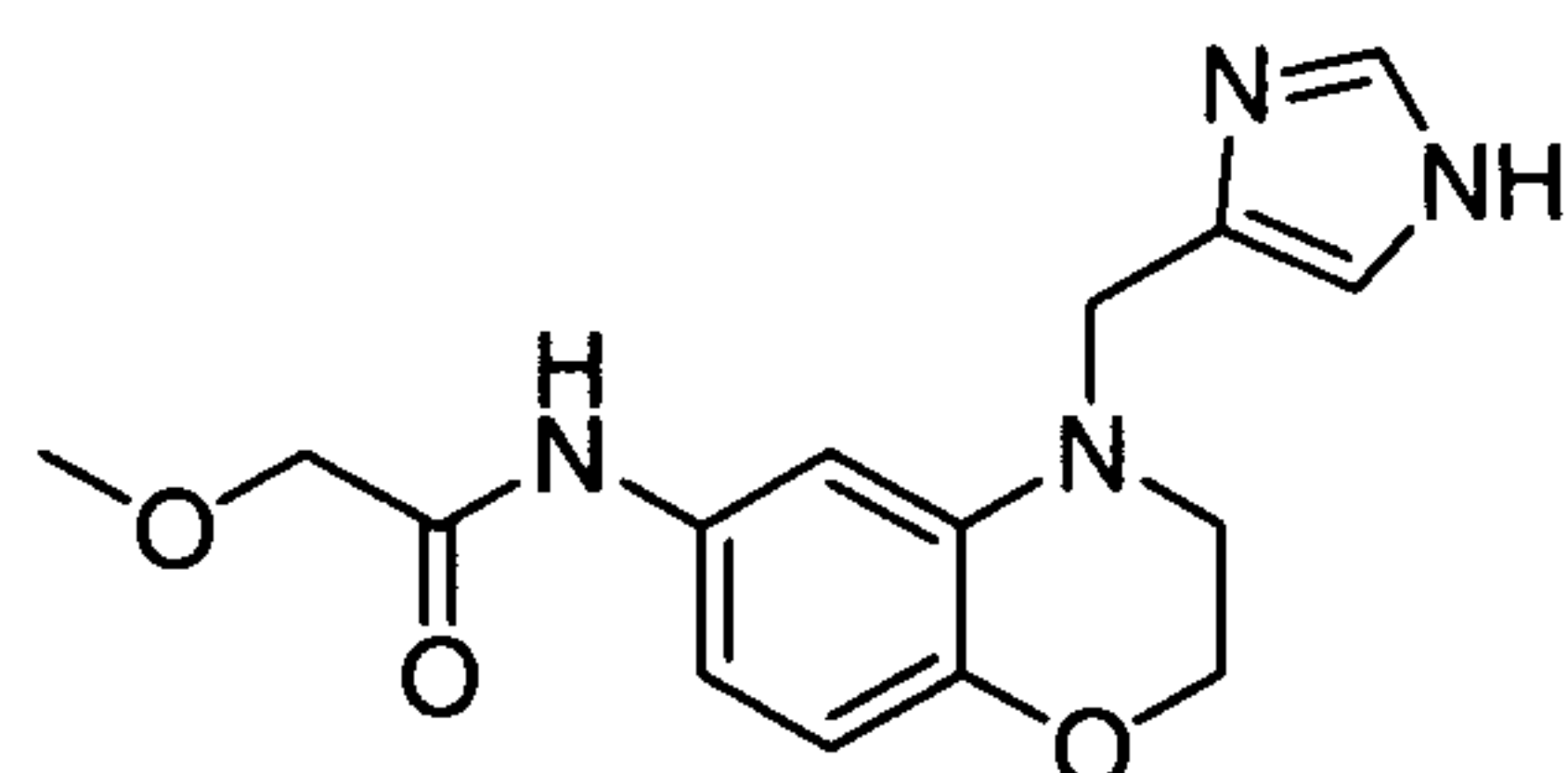
384

219



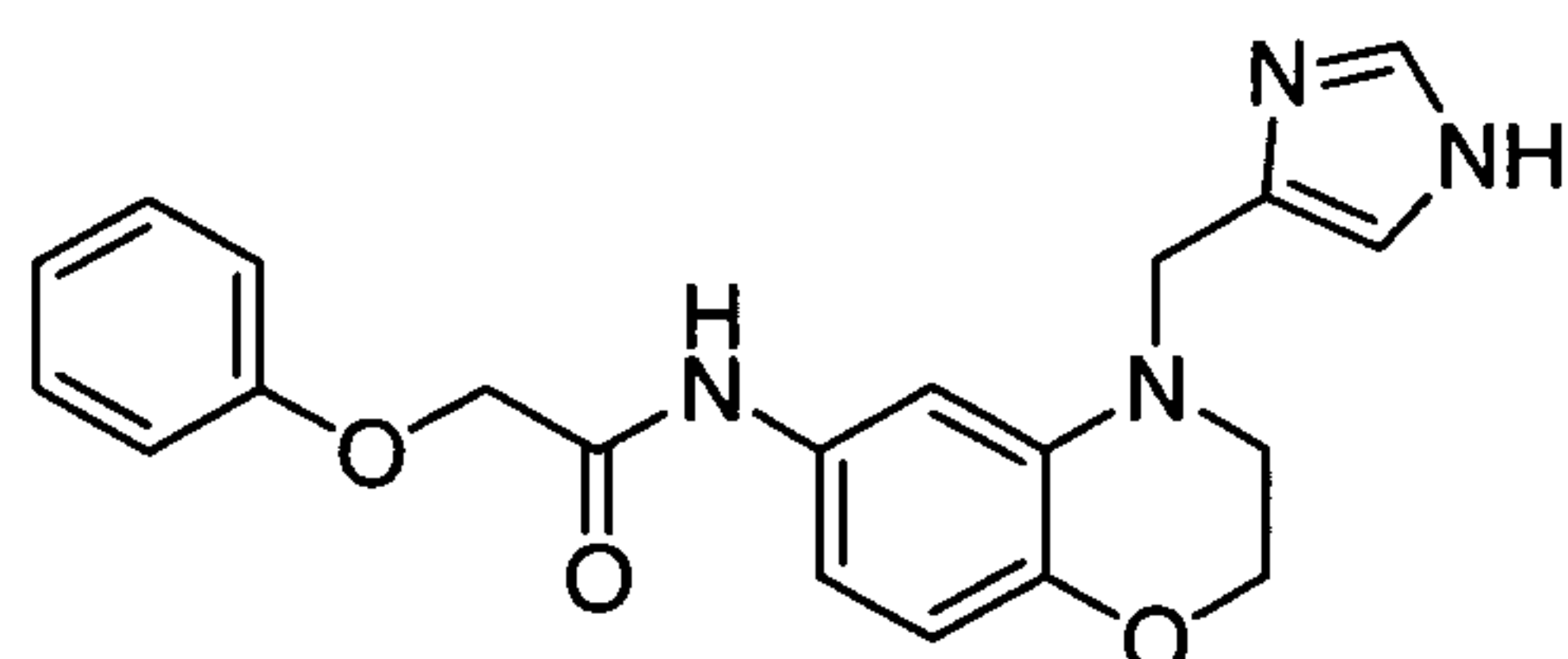
355

220



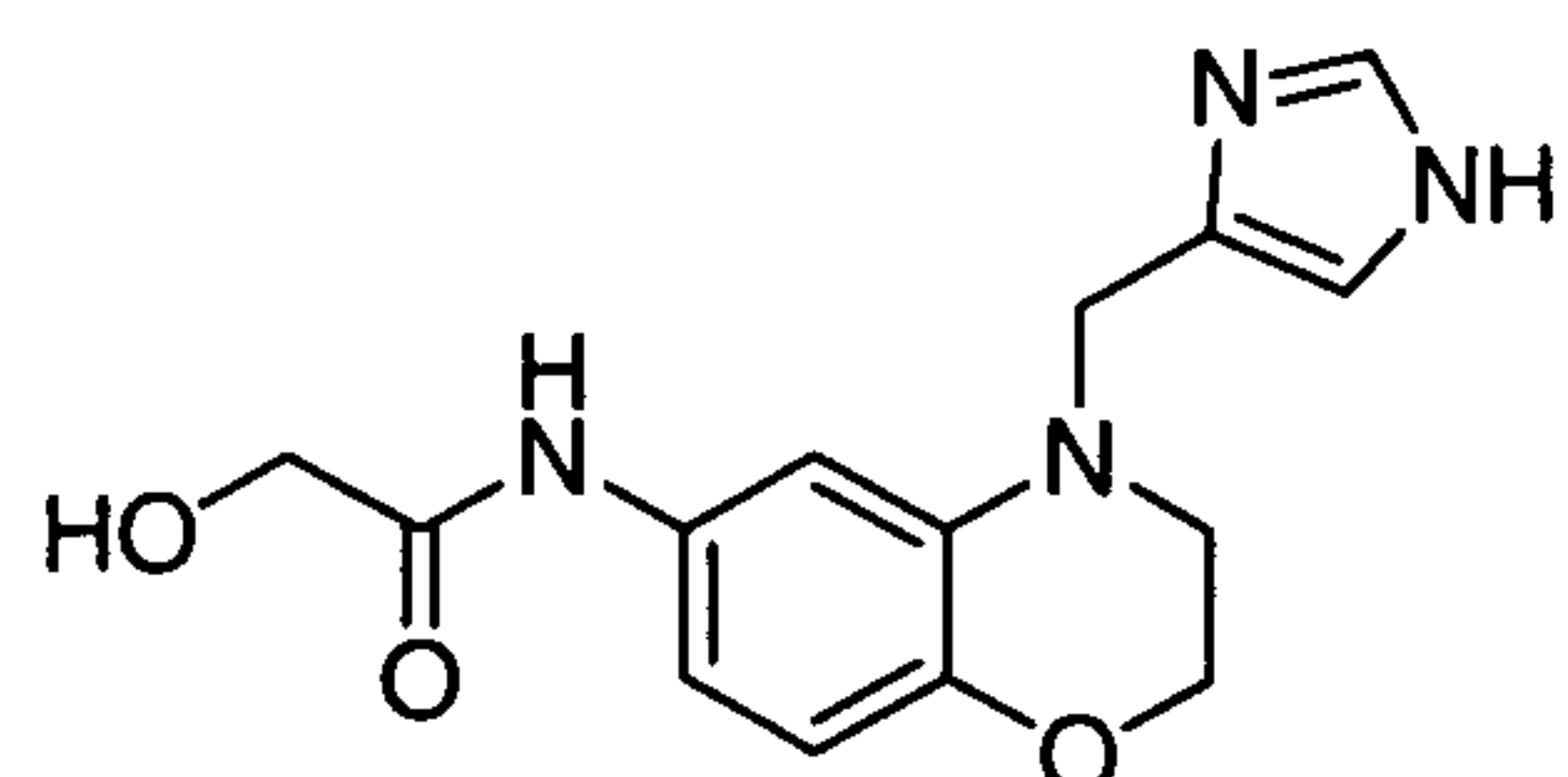
303

221



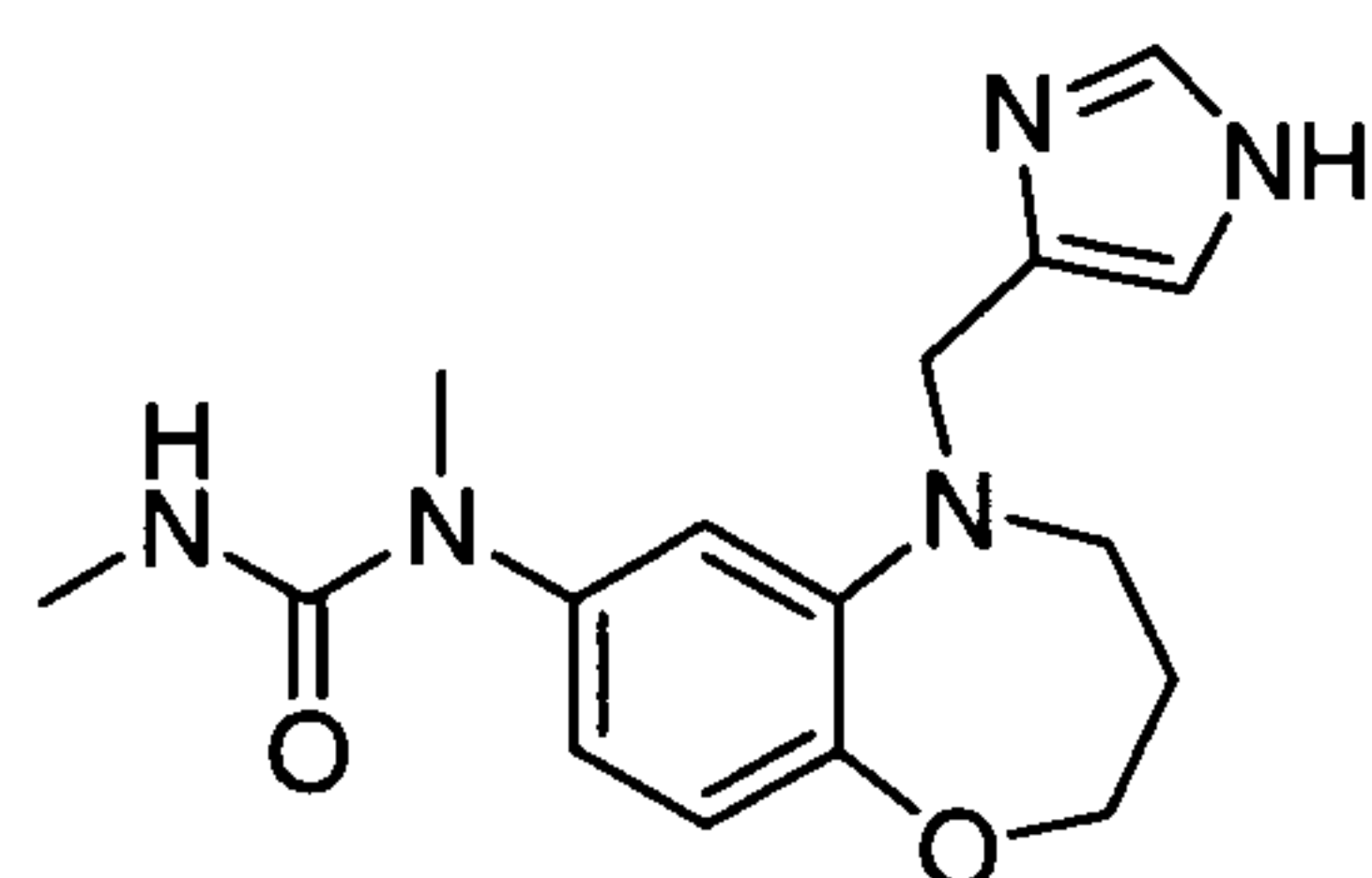
365

222



289

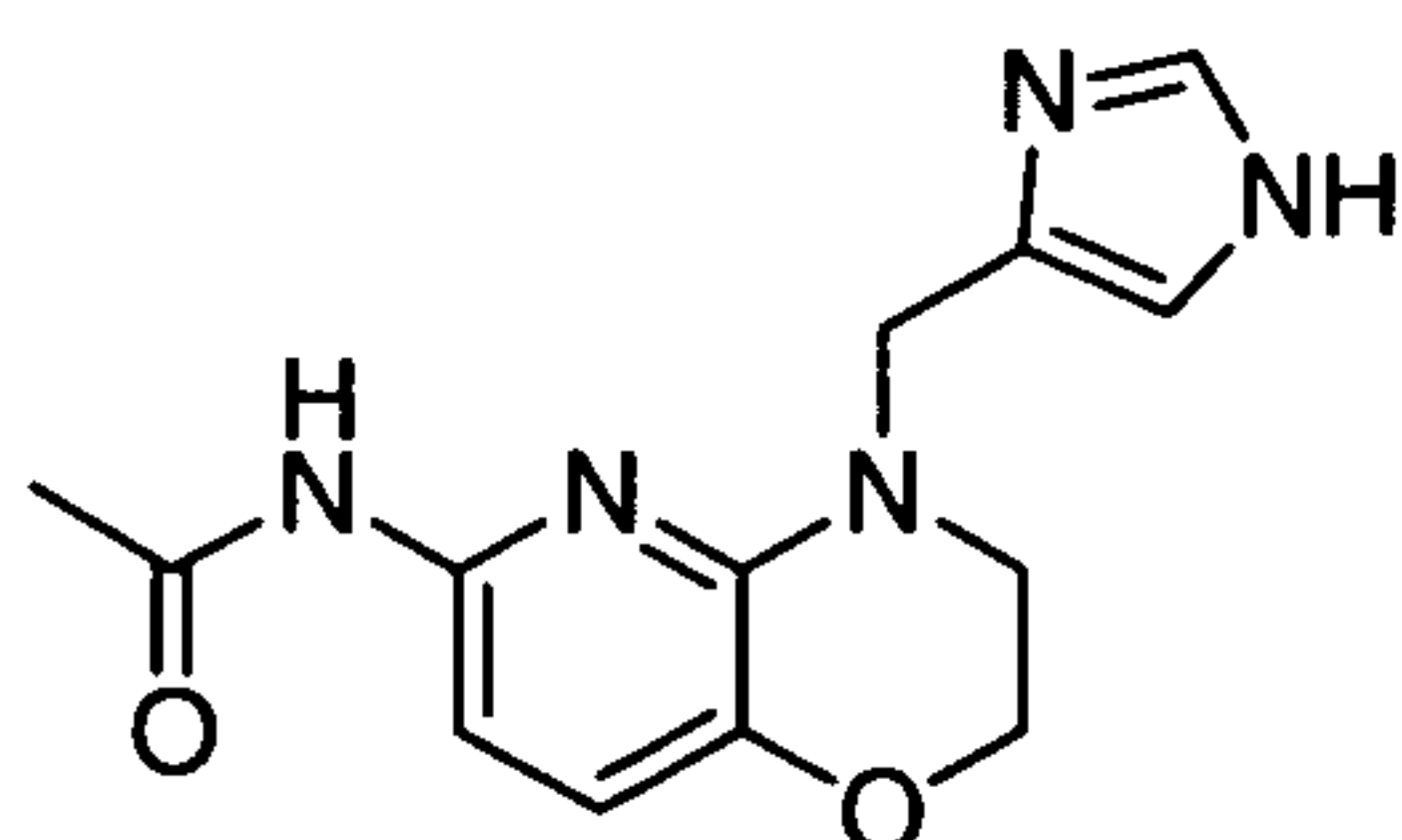
223



316

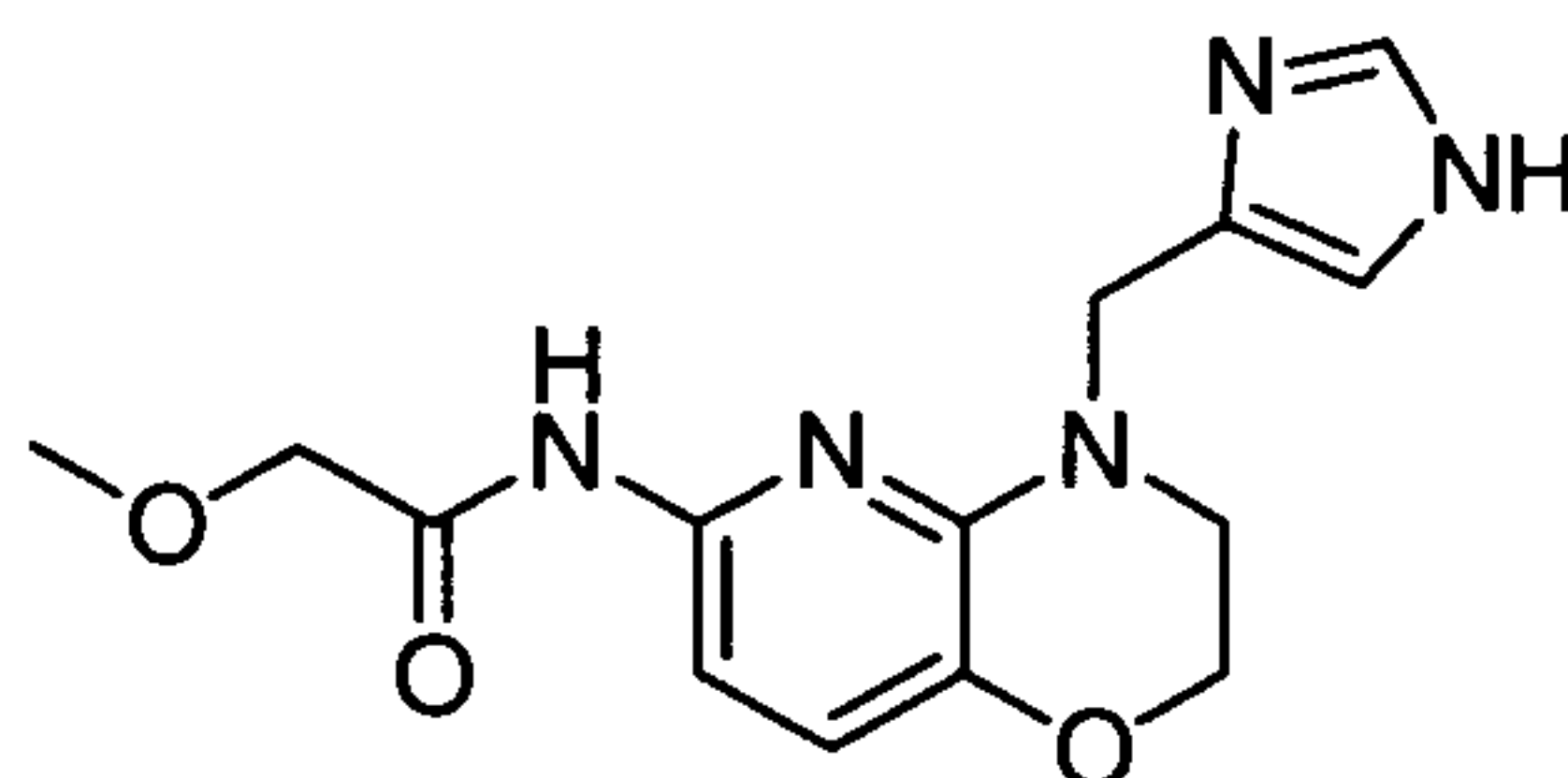
129

224



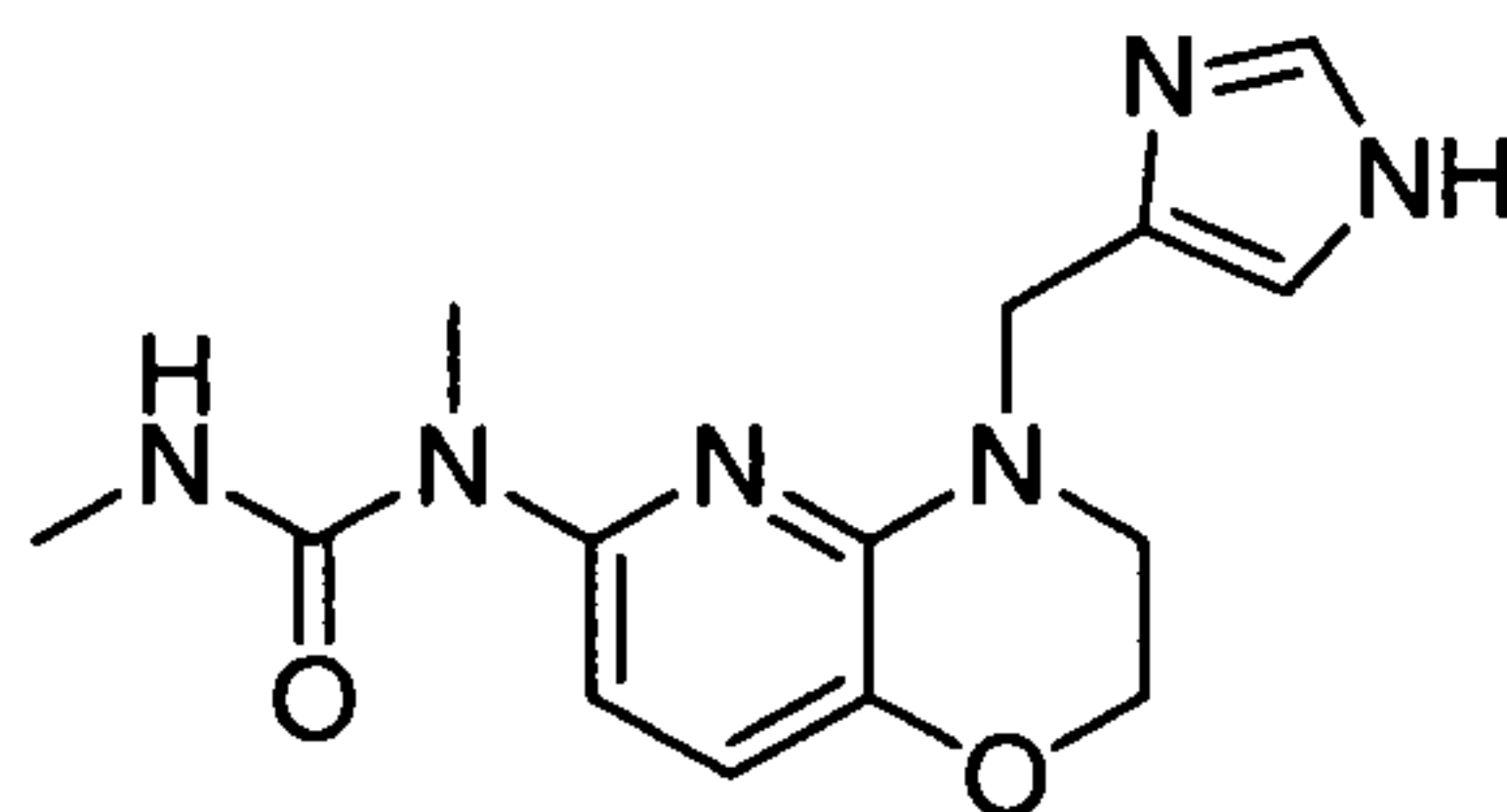
274

225



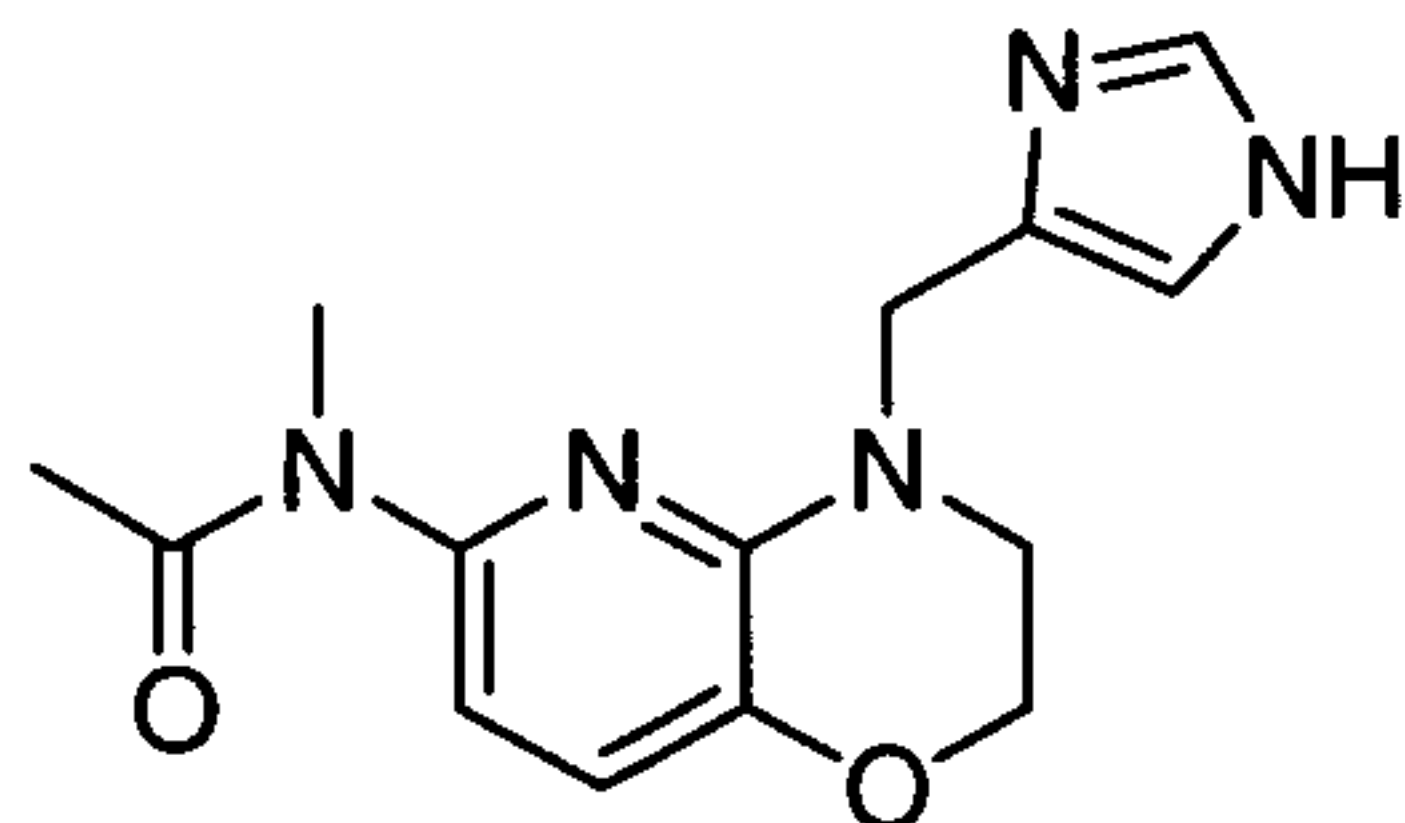
304

226



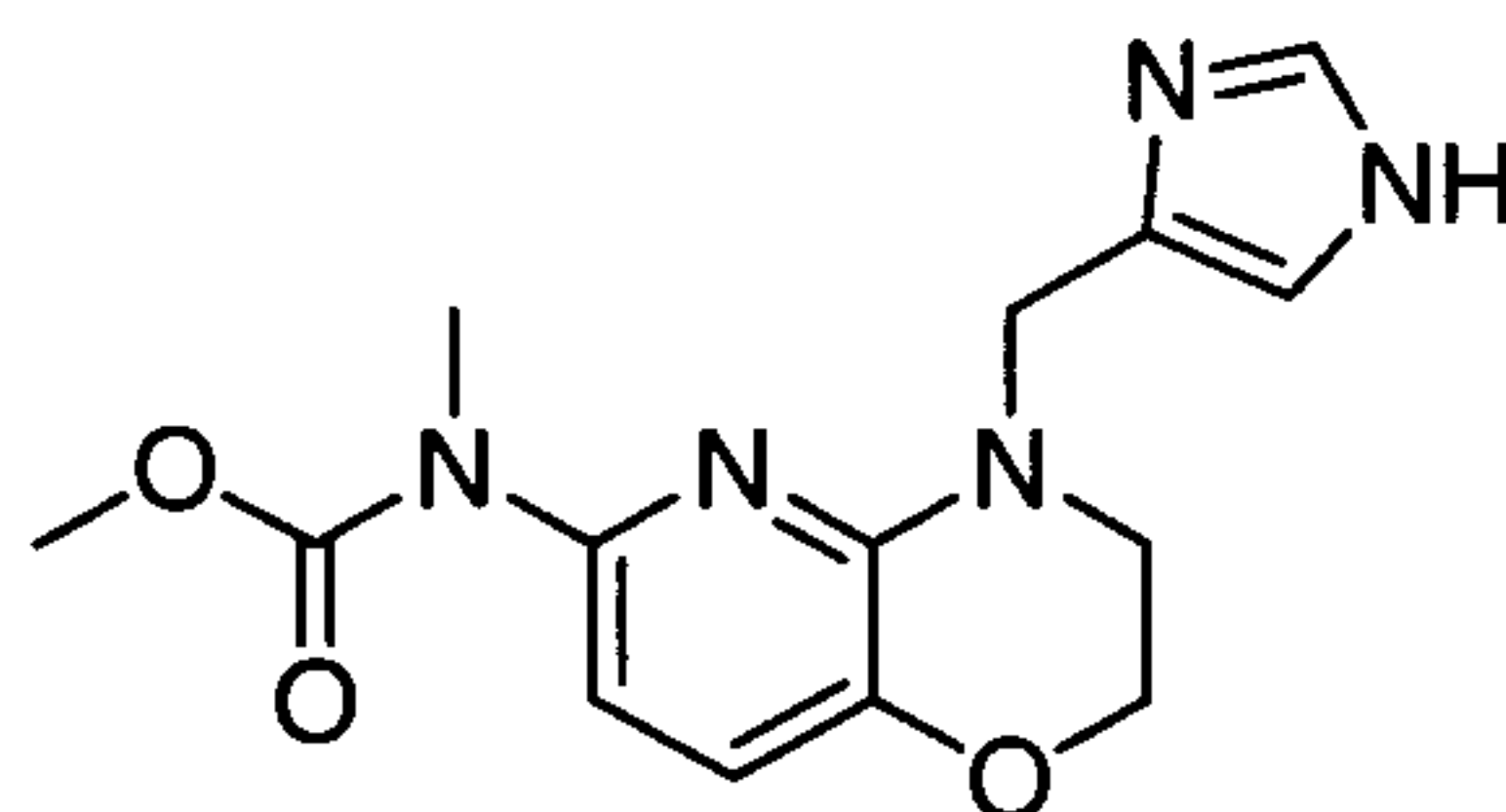
303

227



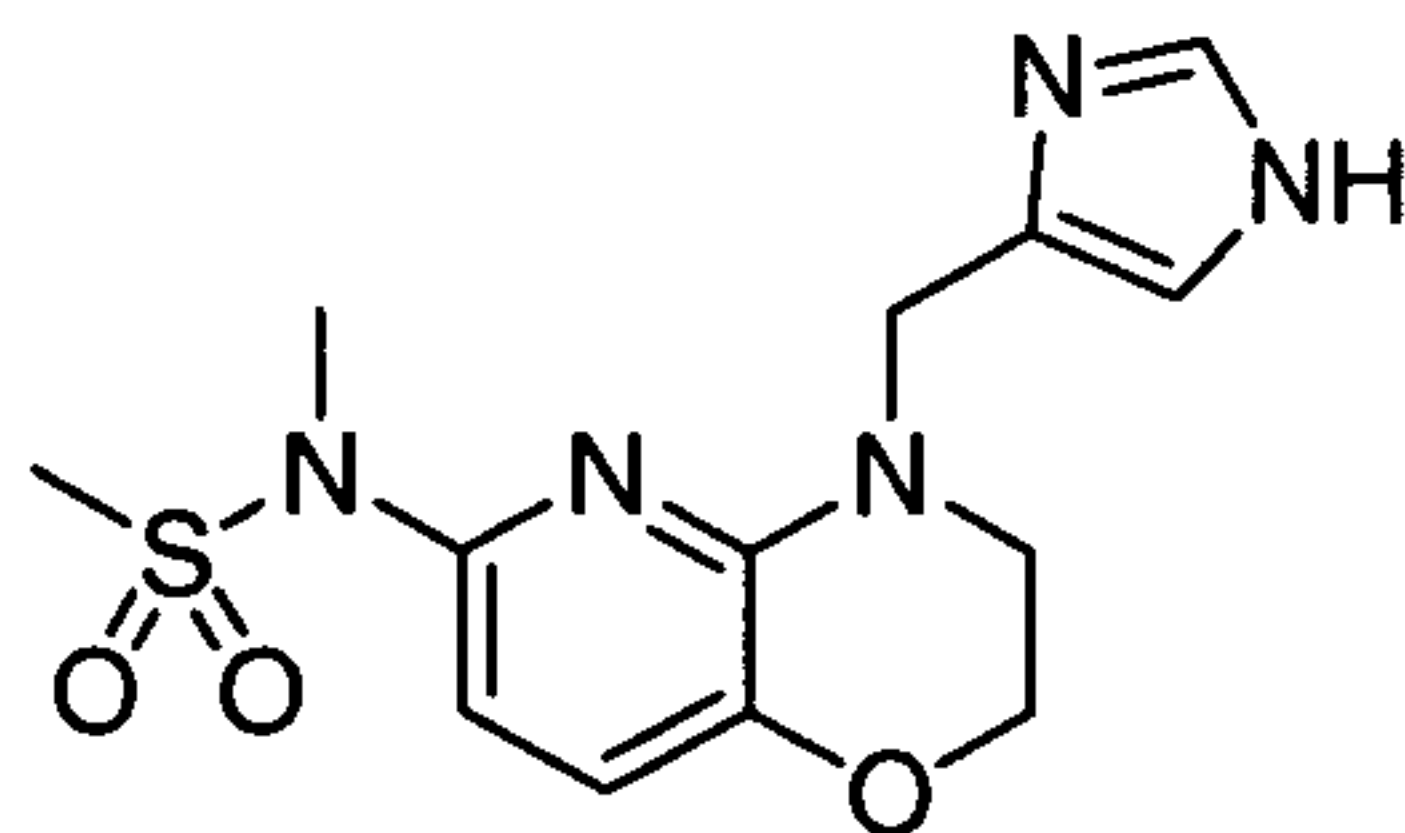
288

228



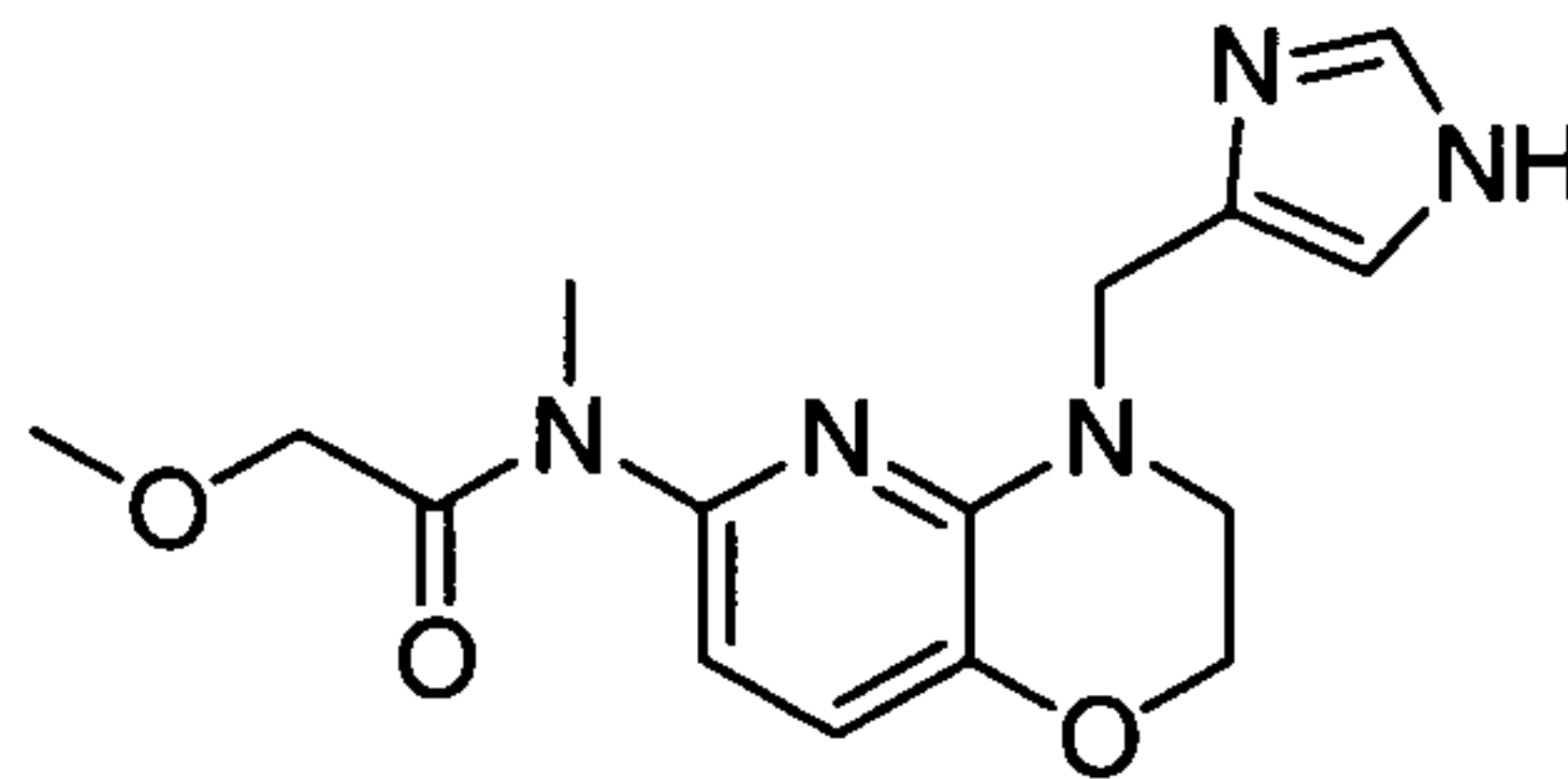
304

229



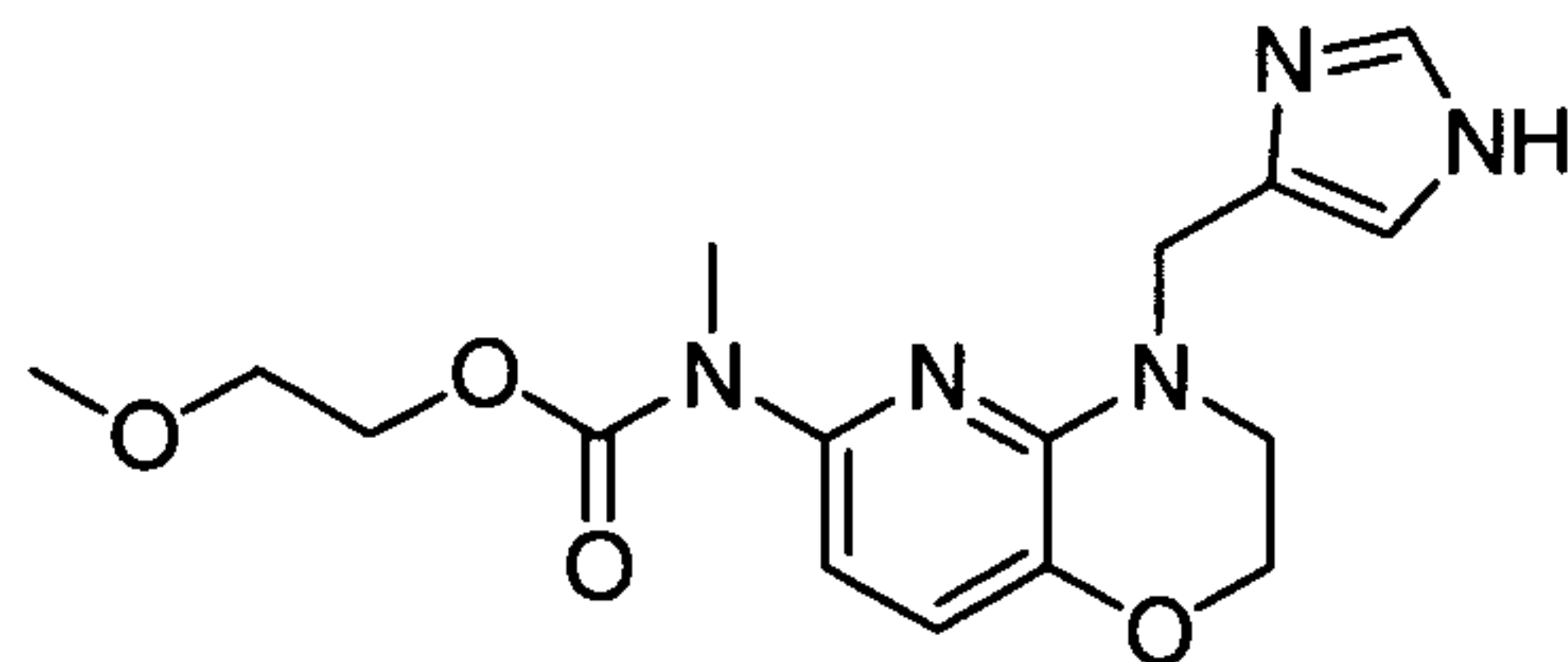
324

230



318

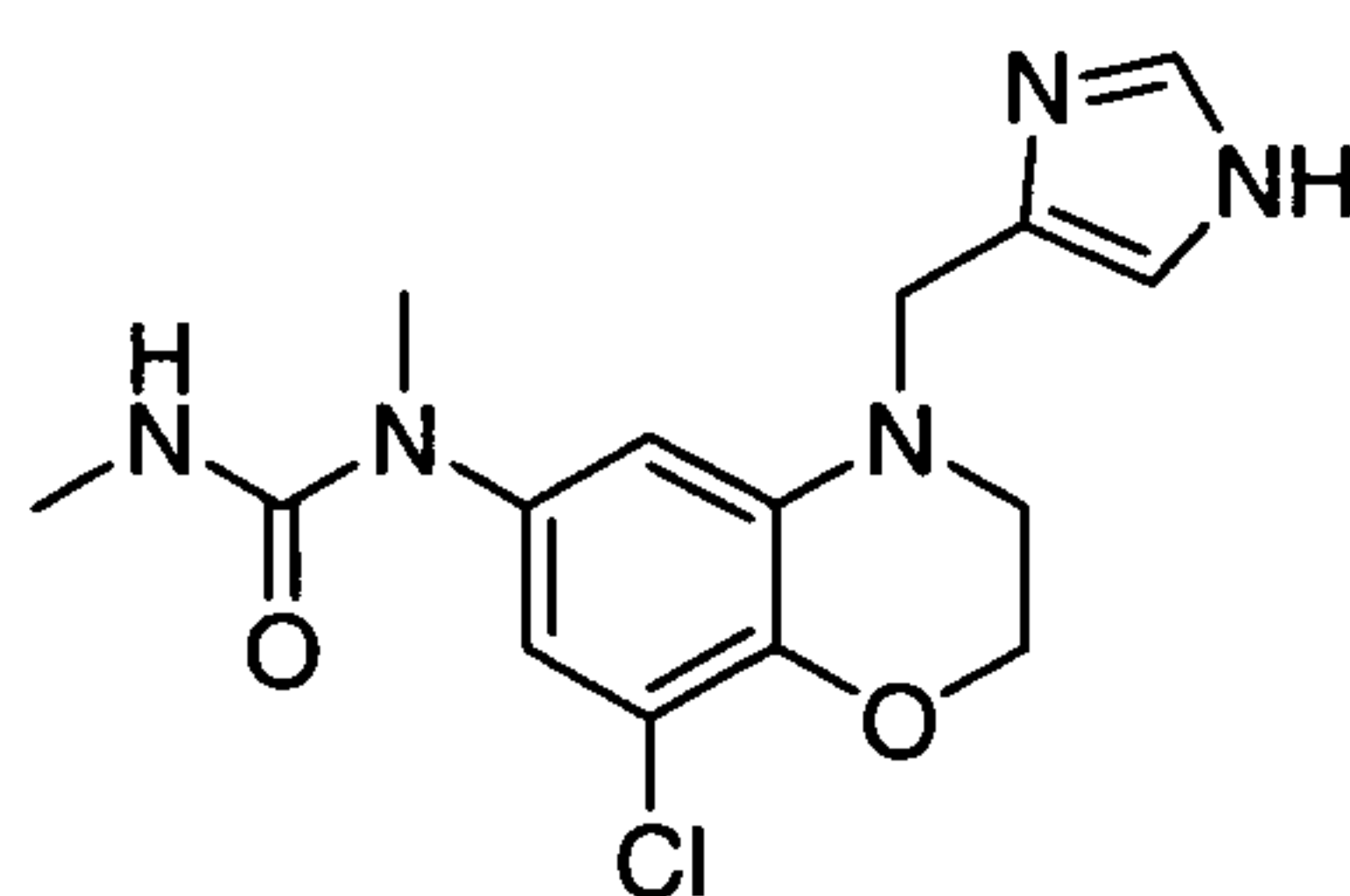
231



348

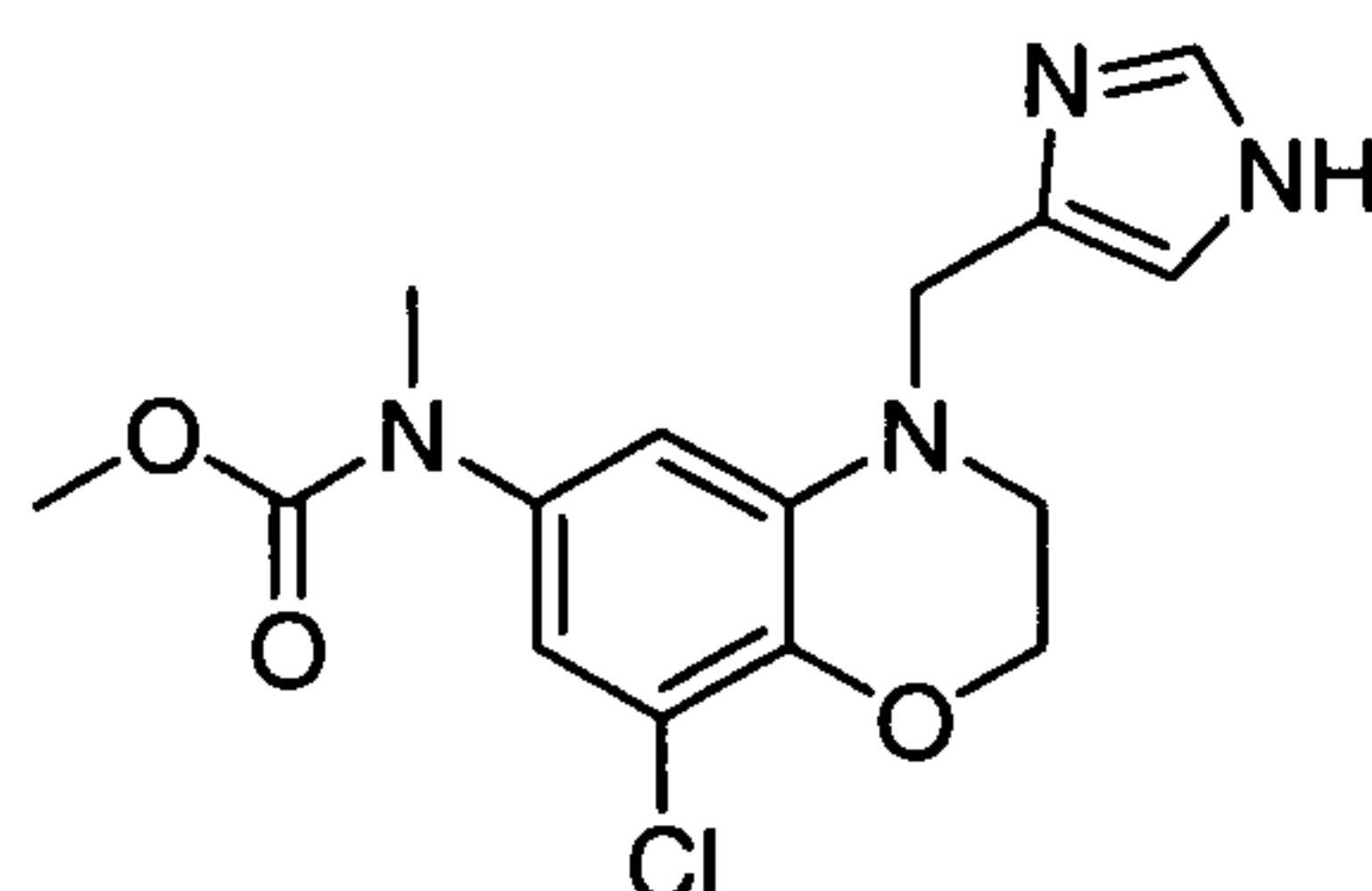
130

232



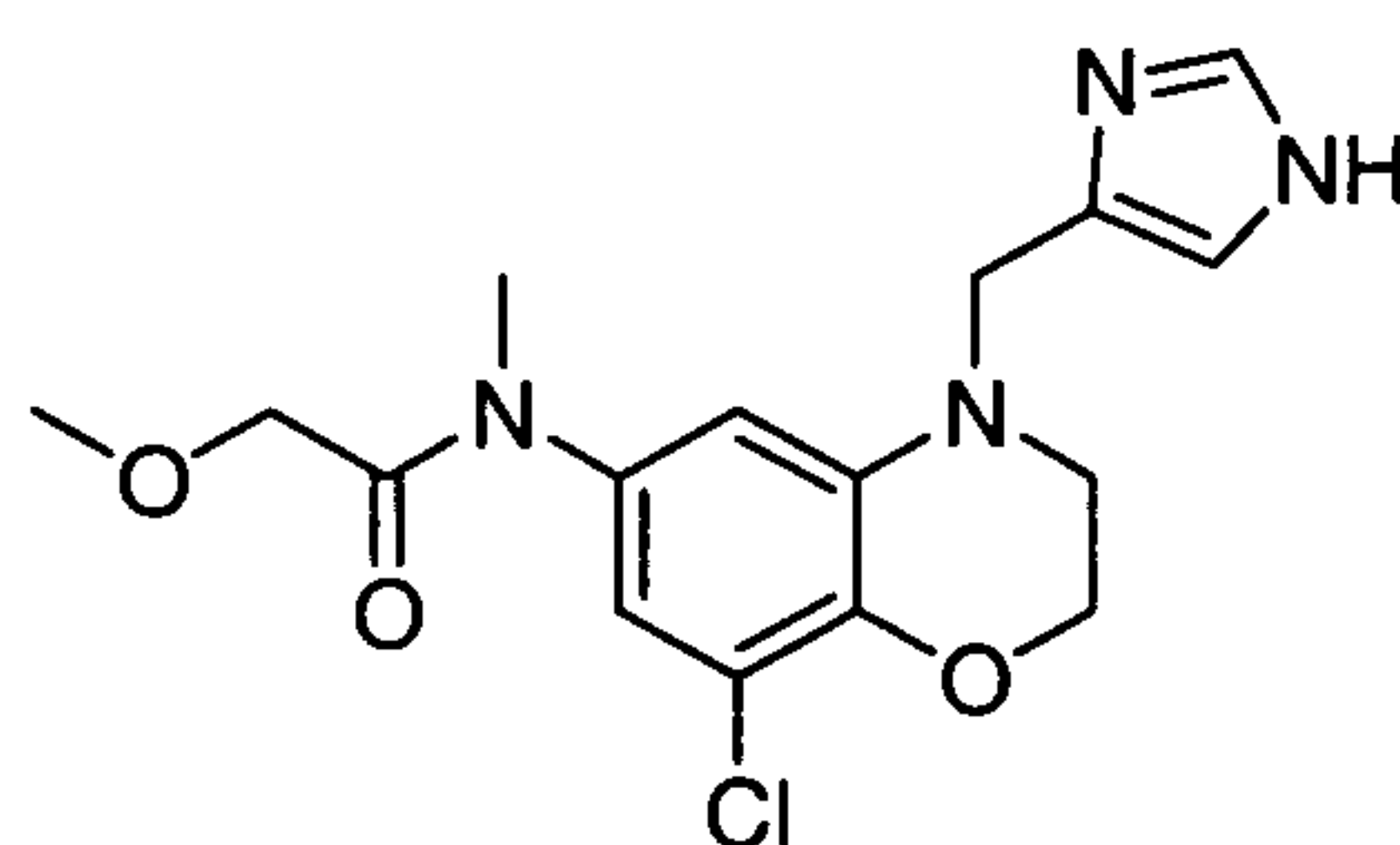
336

233



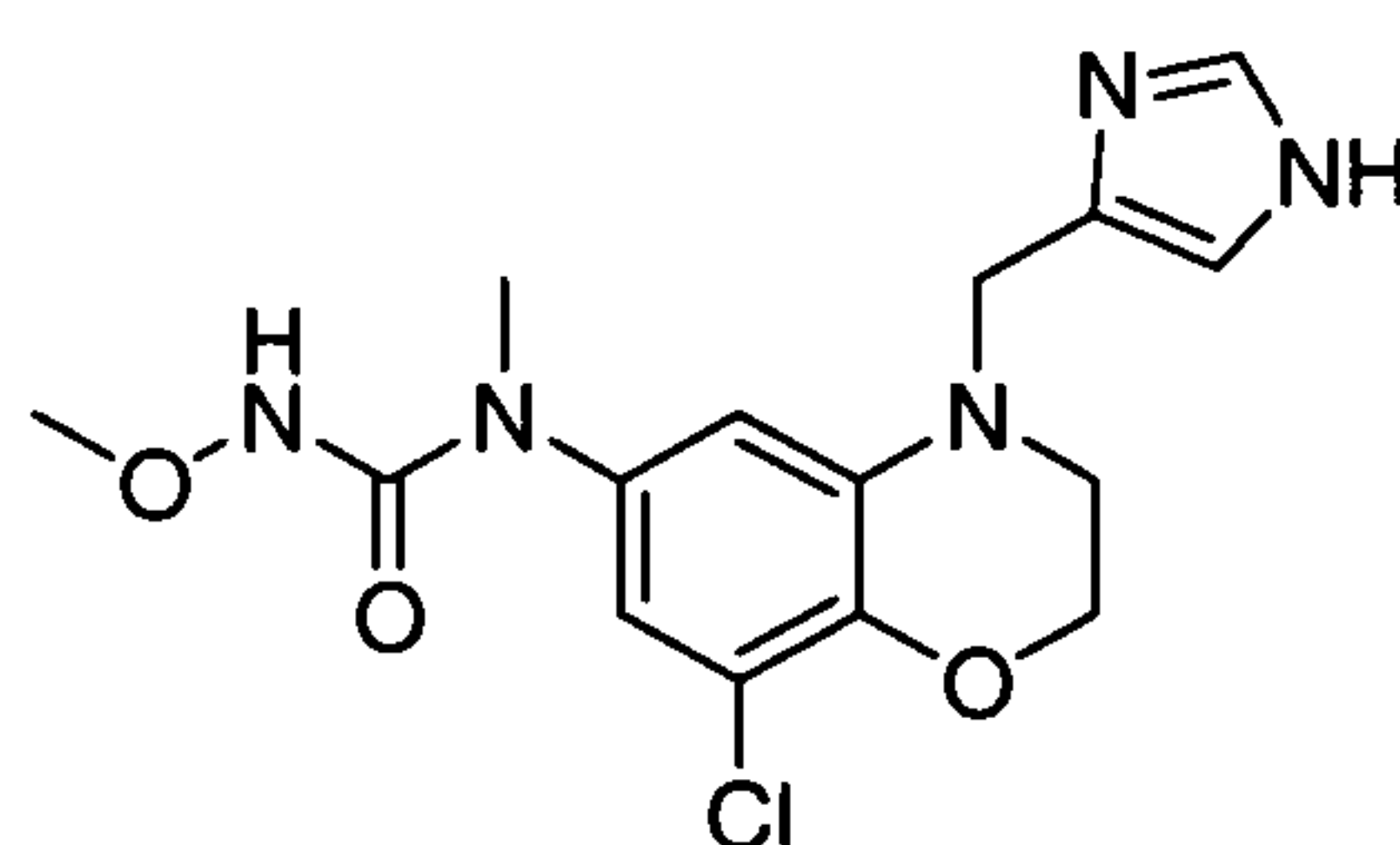
337

234



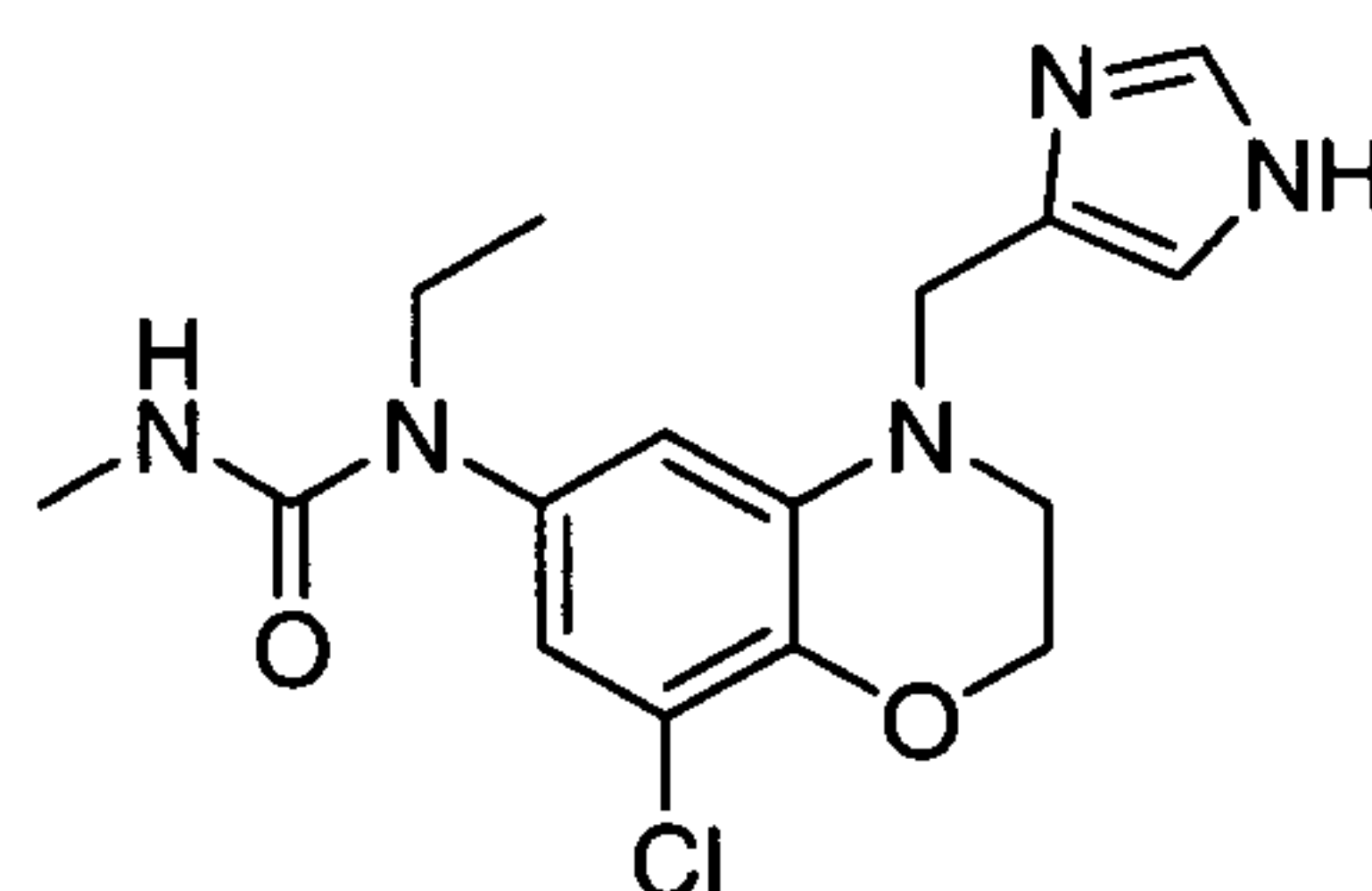
351

235



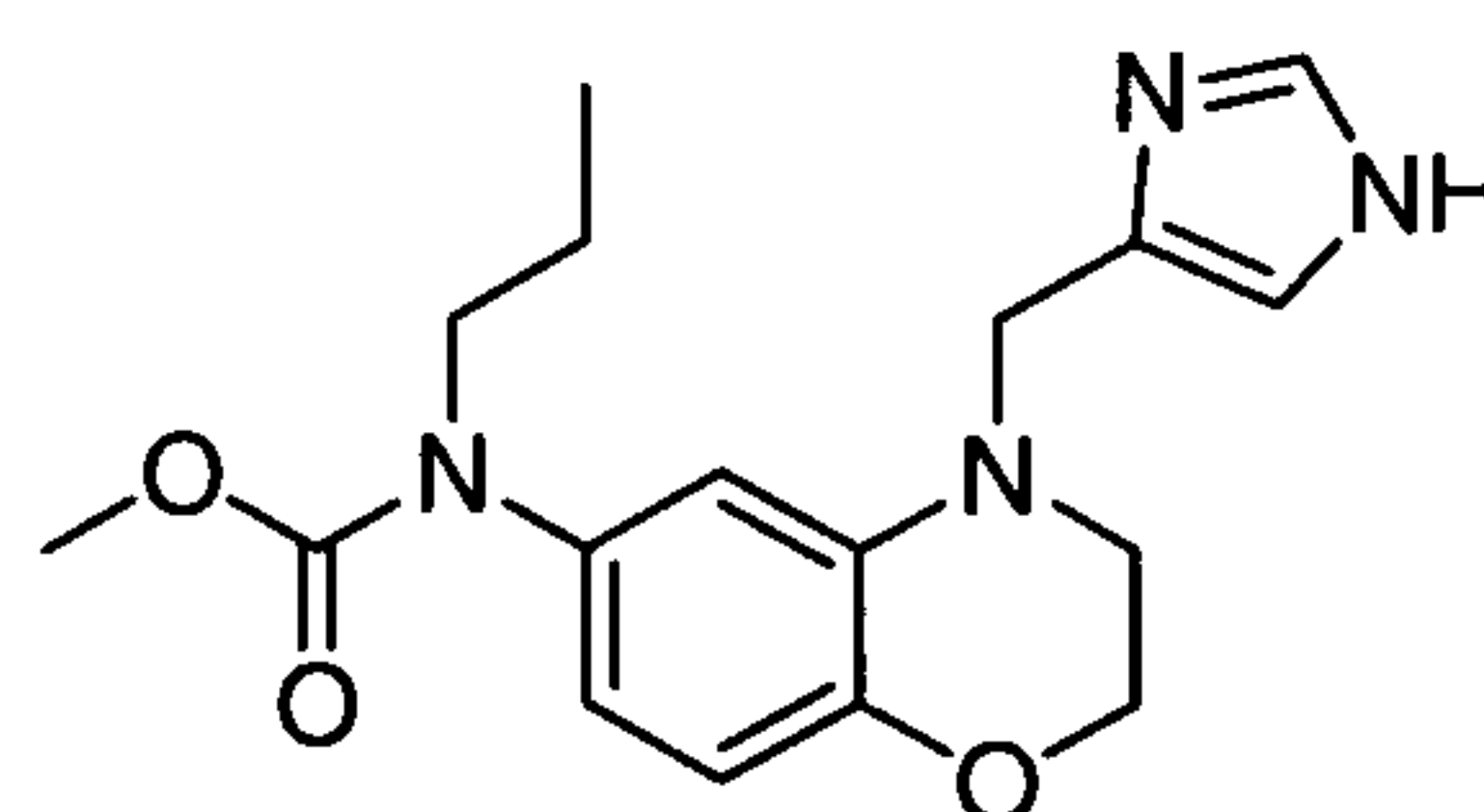
352

236



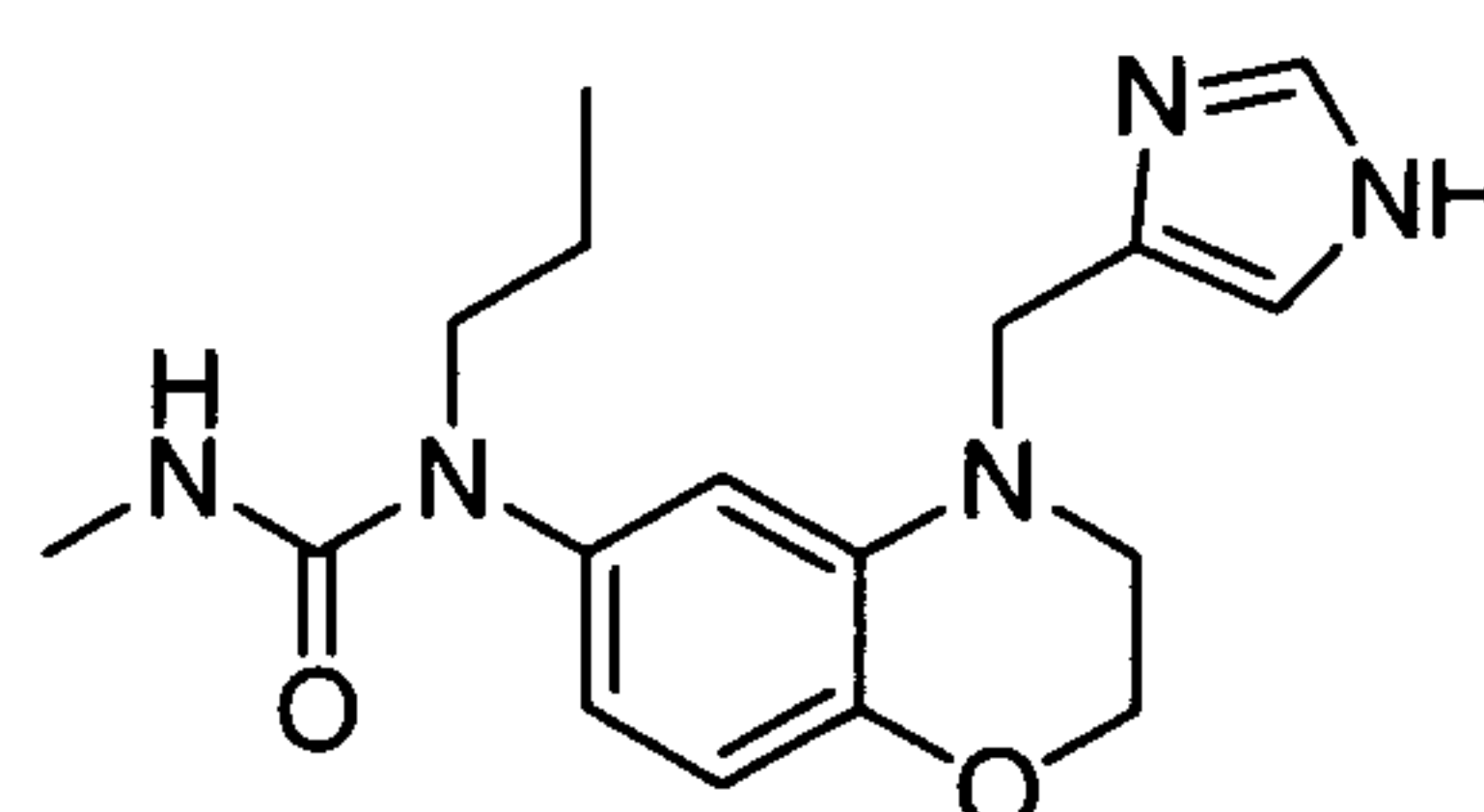
350

237



331

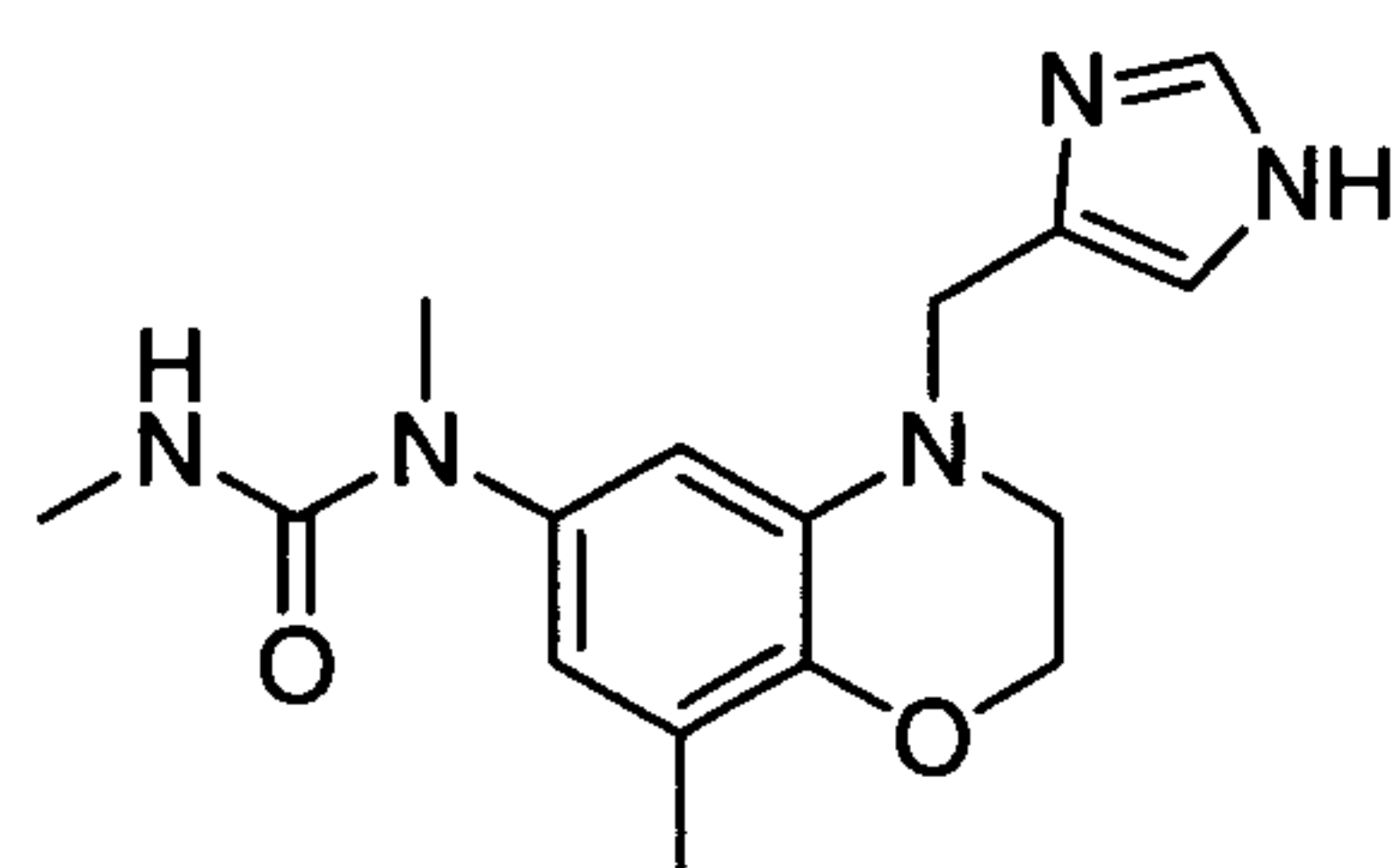
238



330

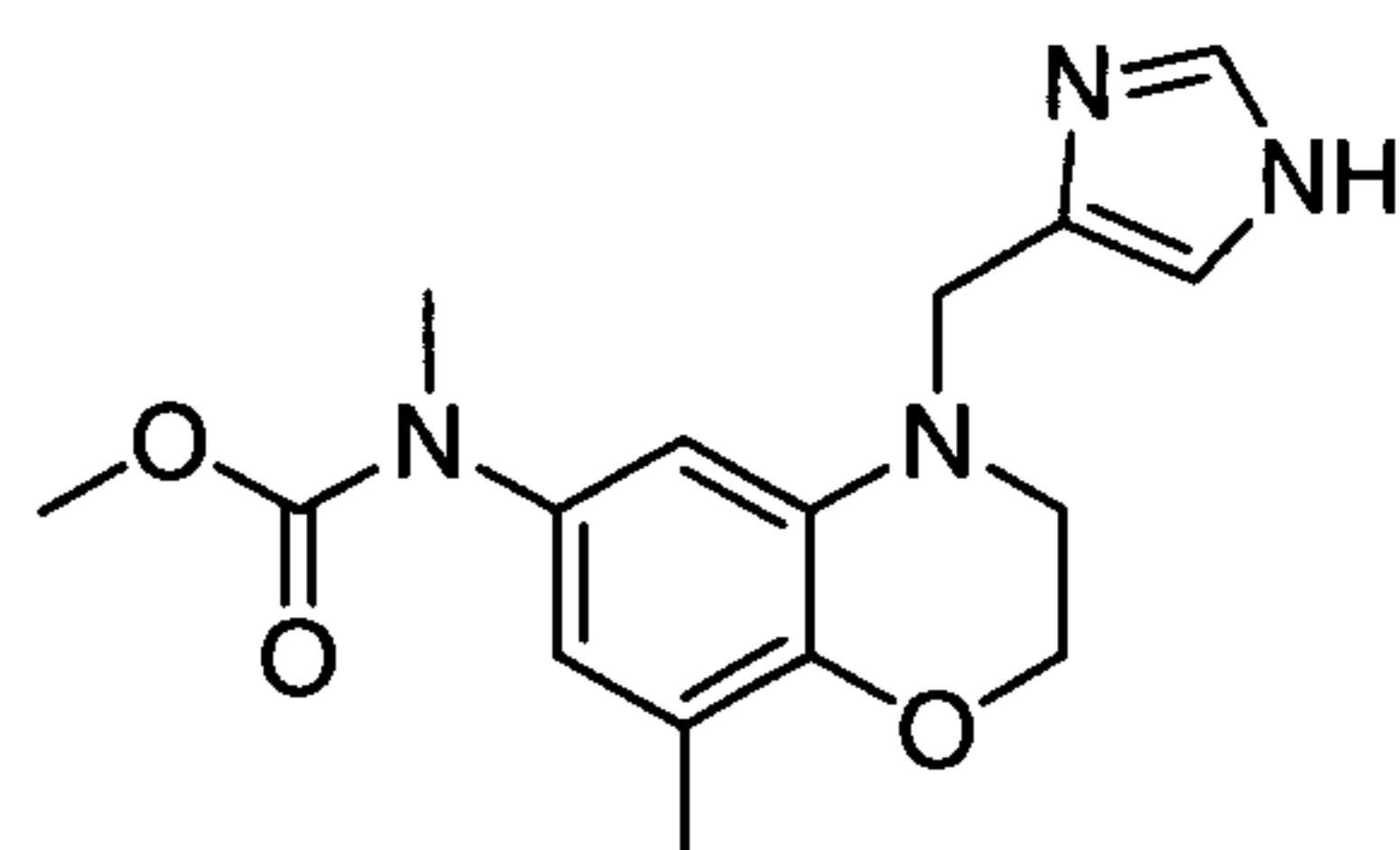
131

239



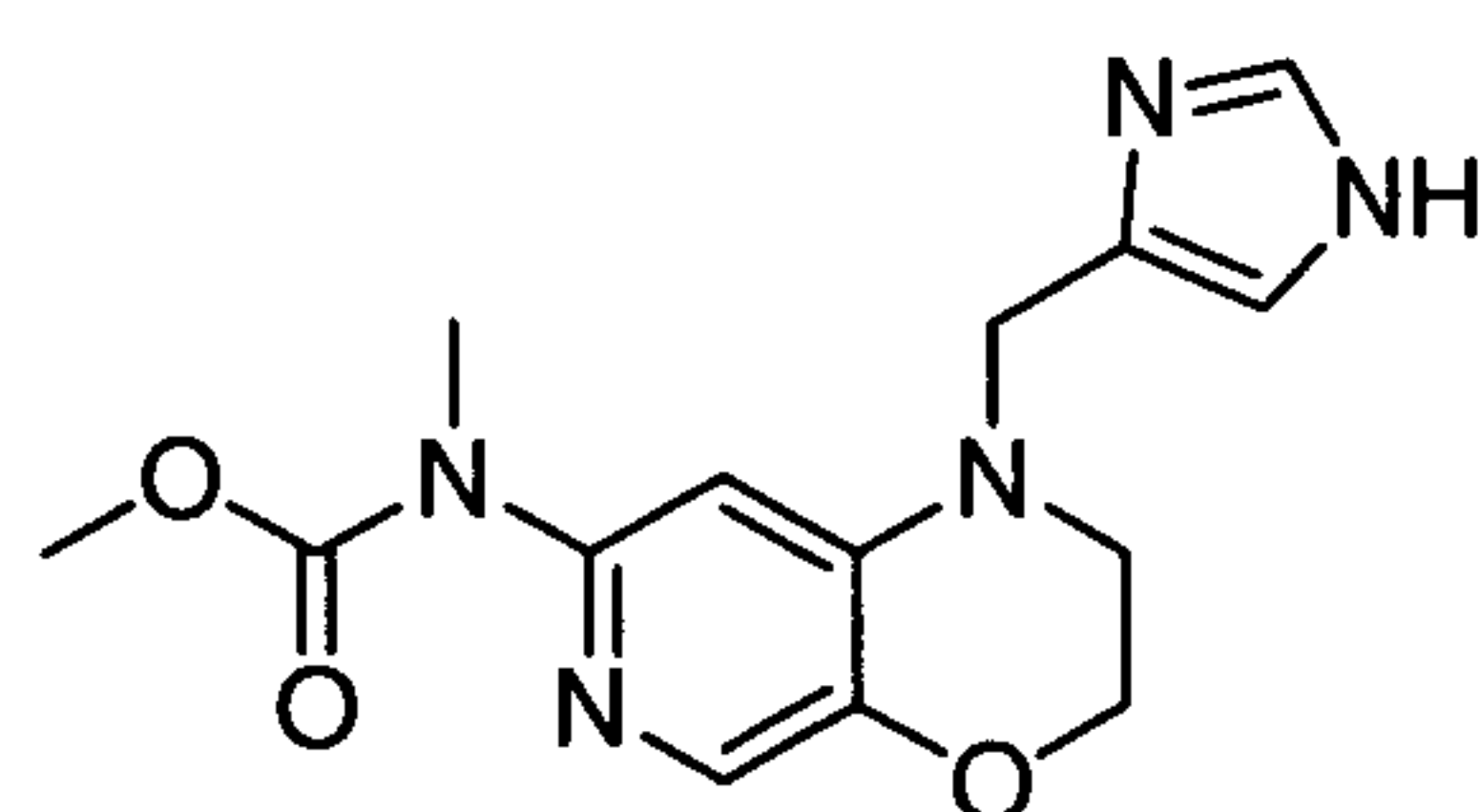
316

240



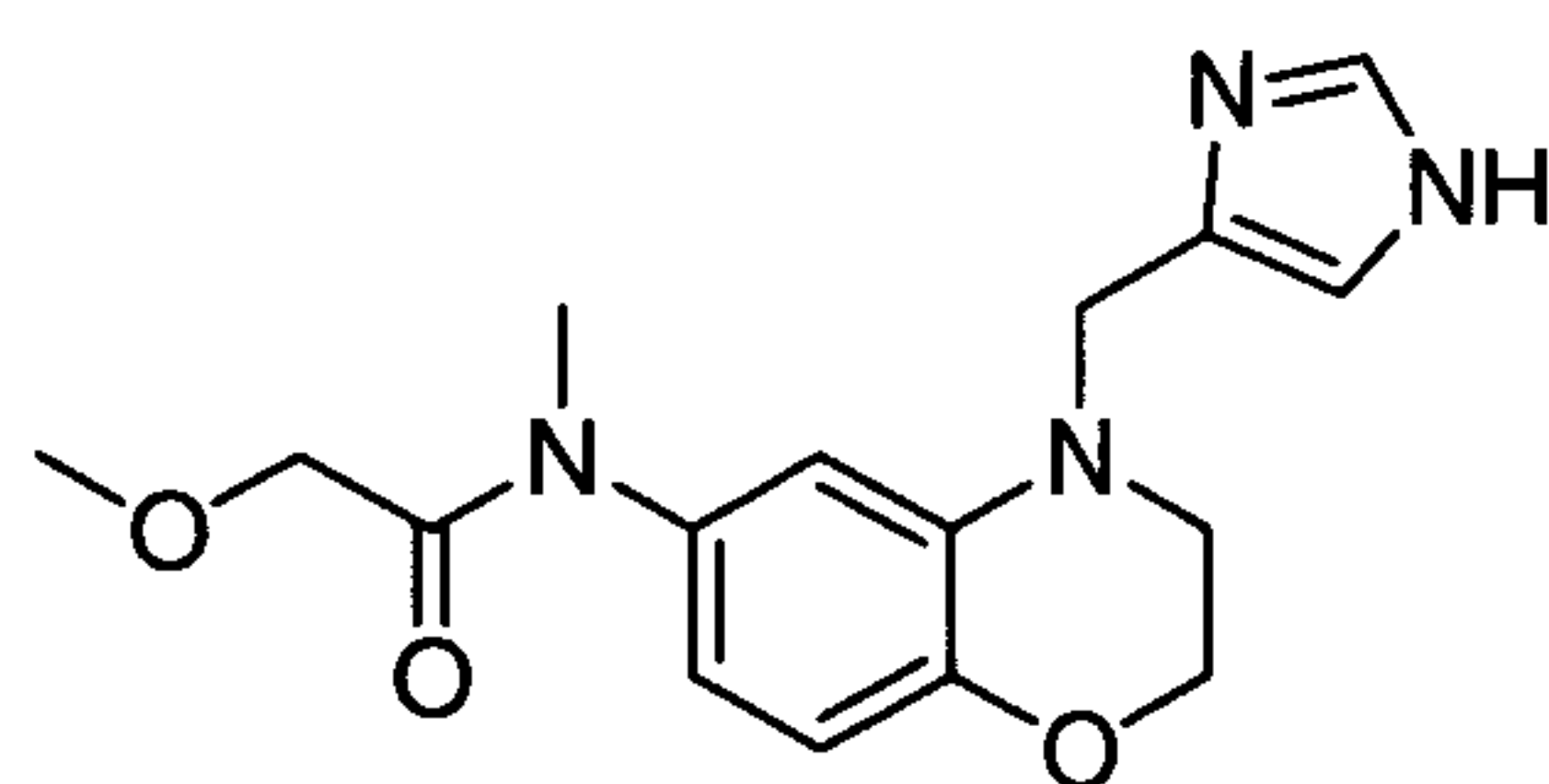
317

241



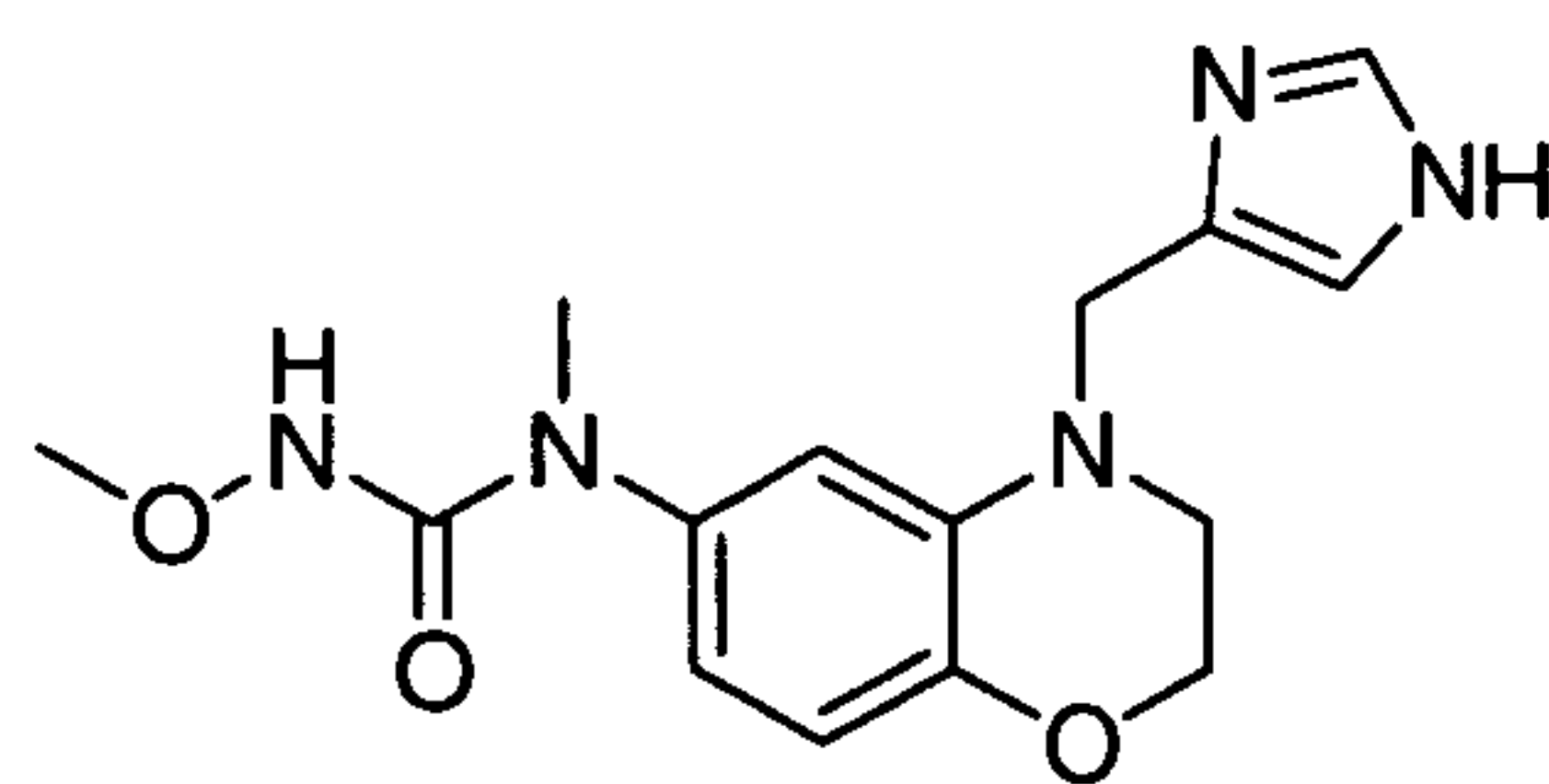
304

242



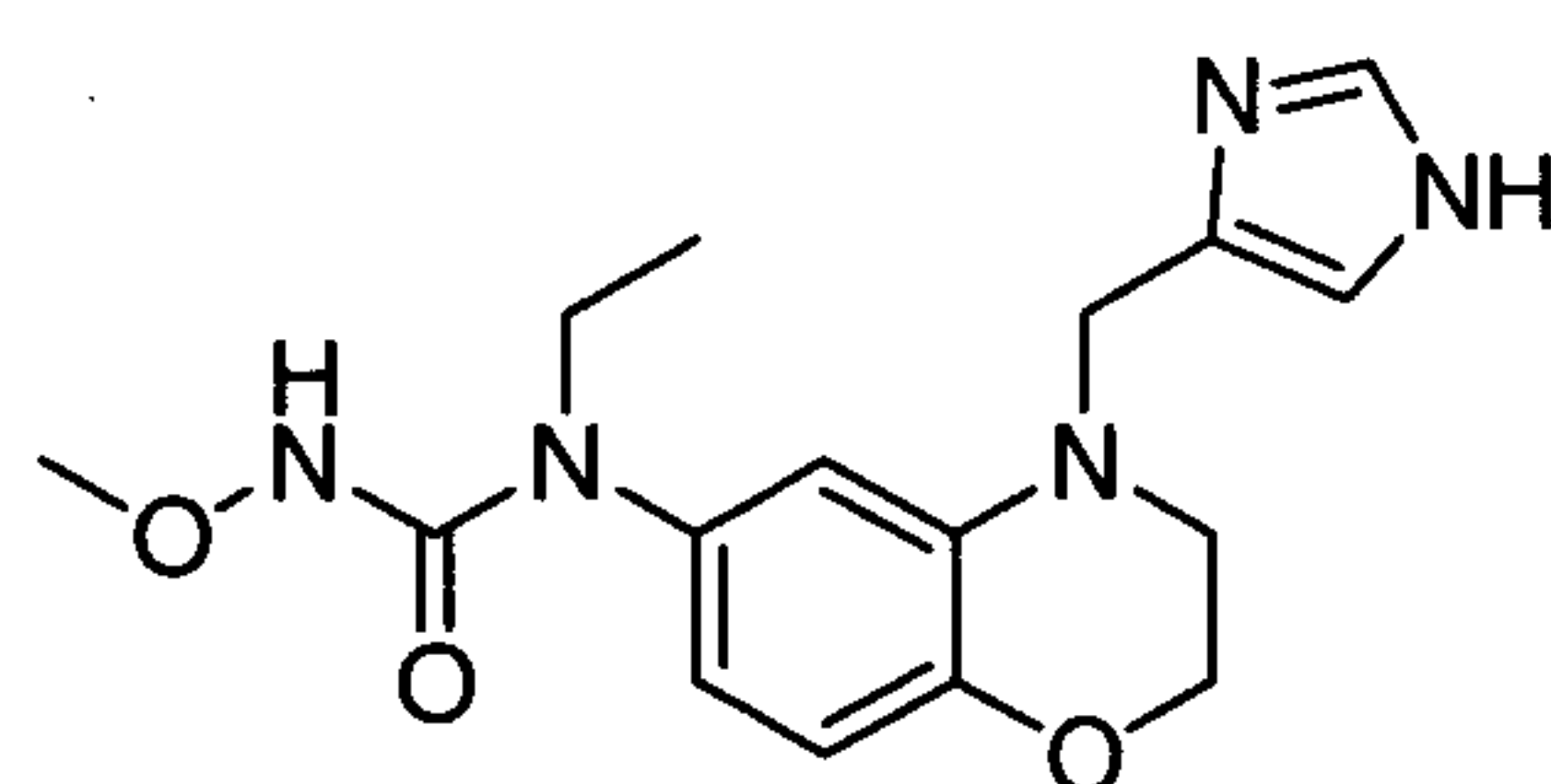
317

243



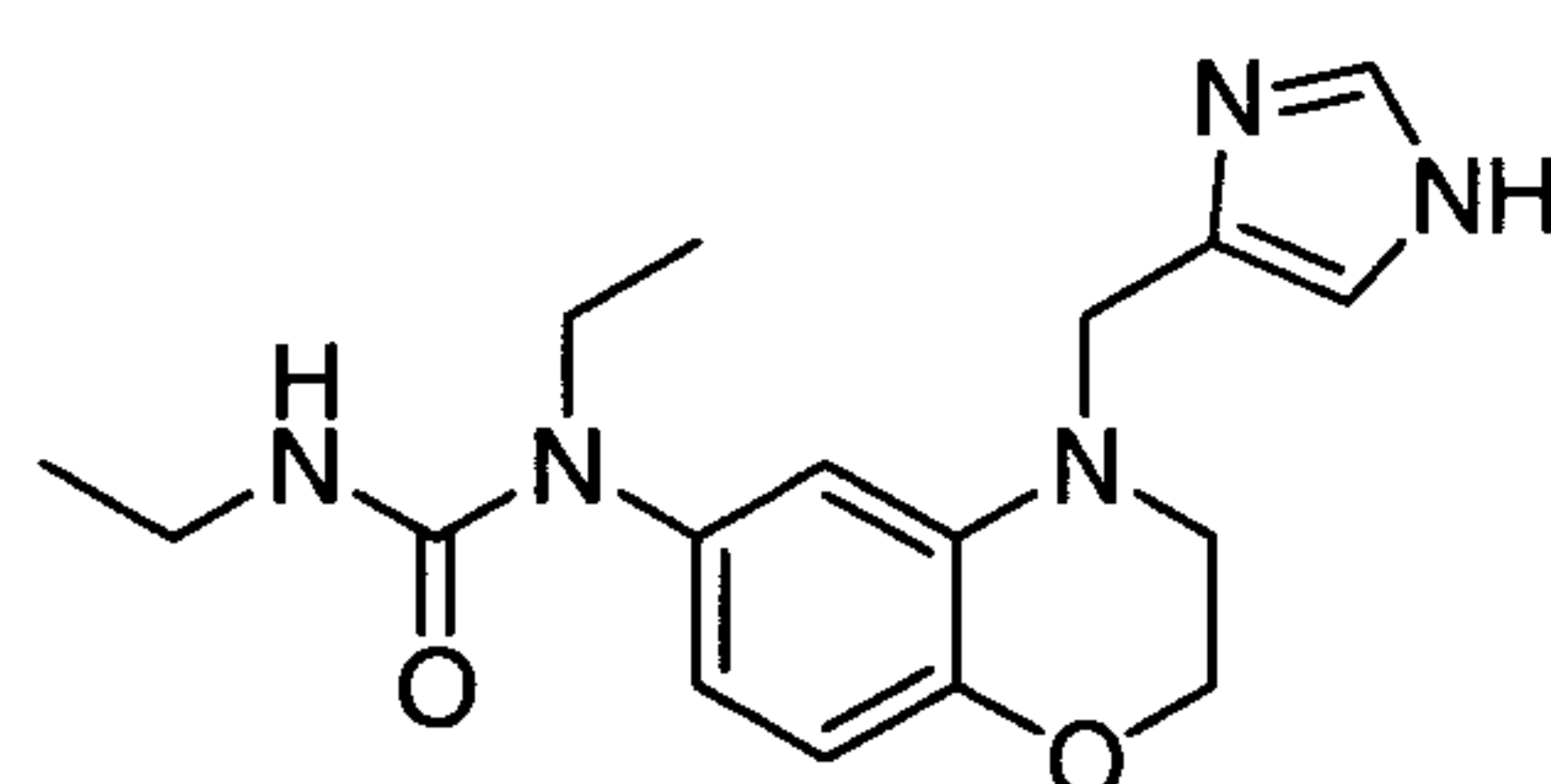
318

244



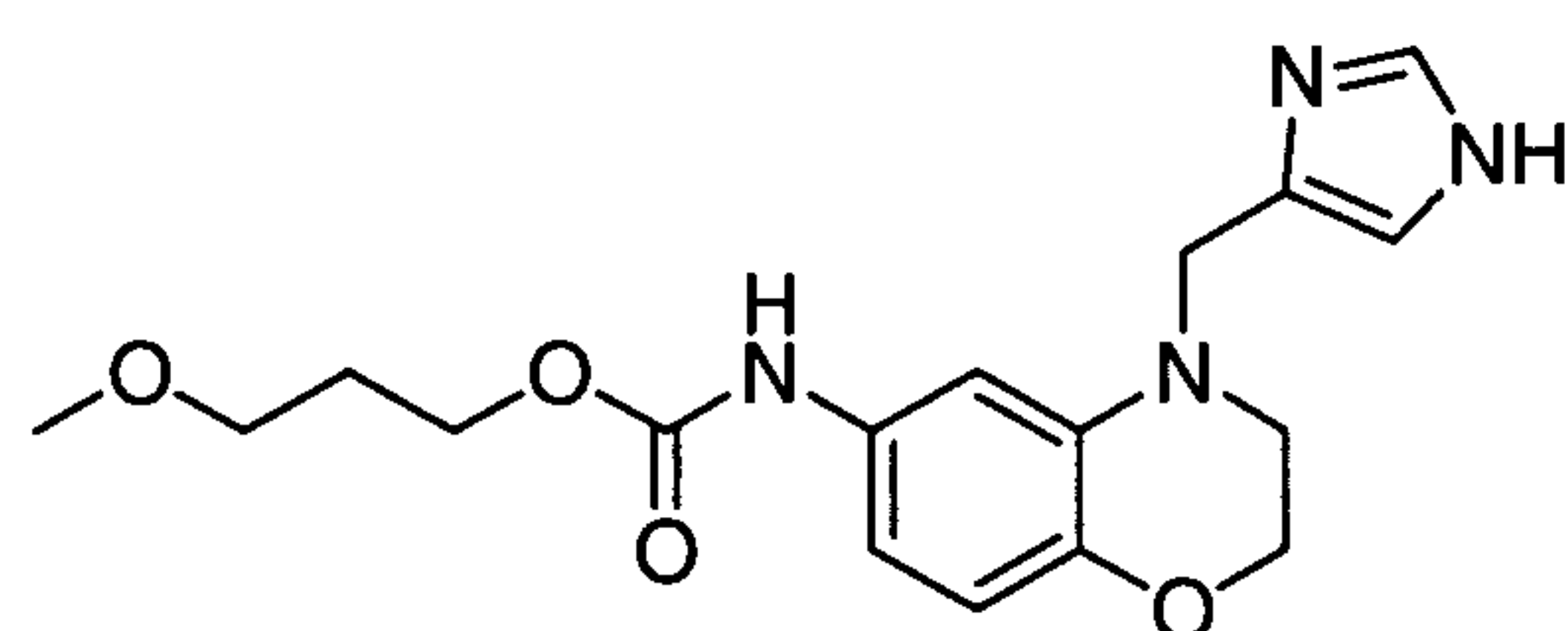
332

245



330

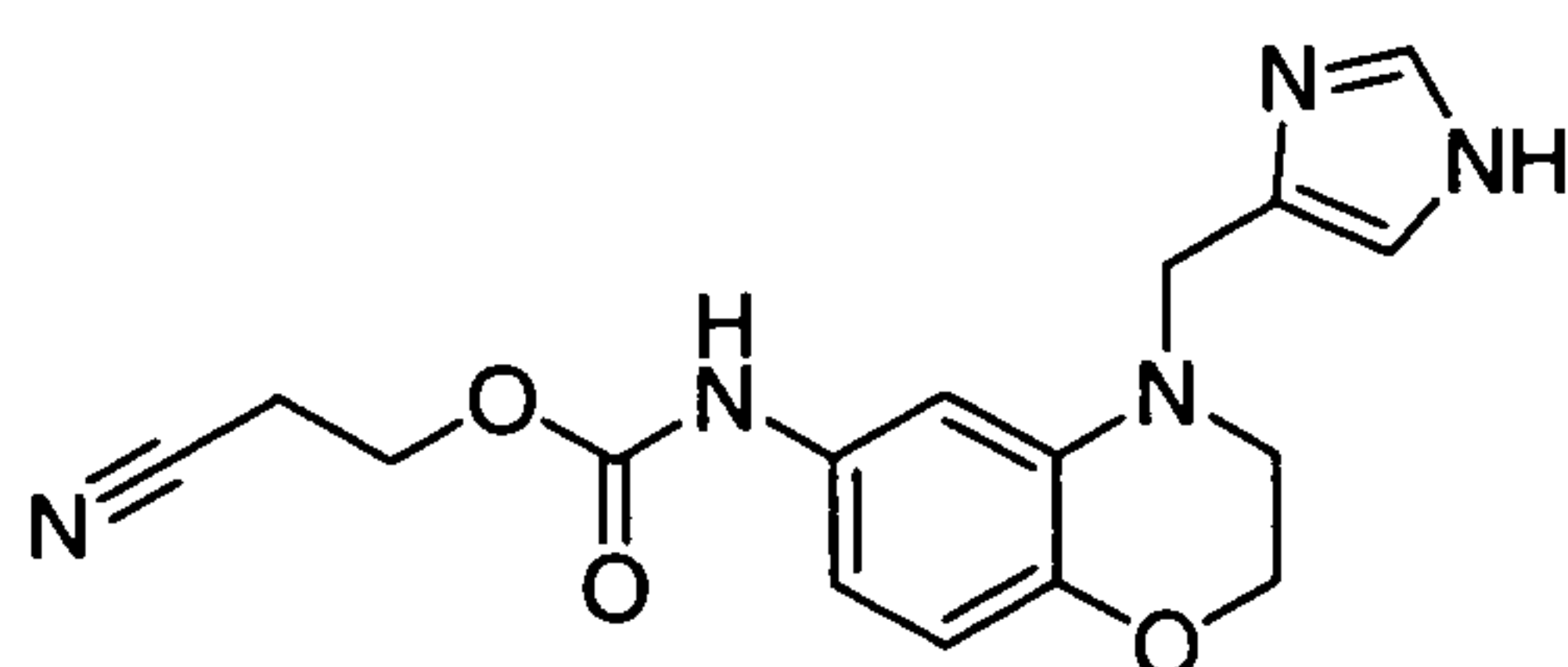
246



347

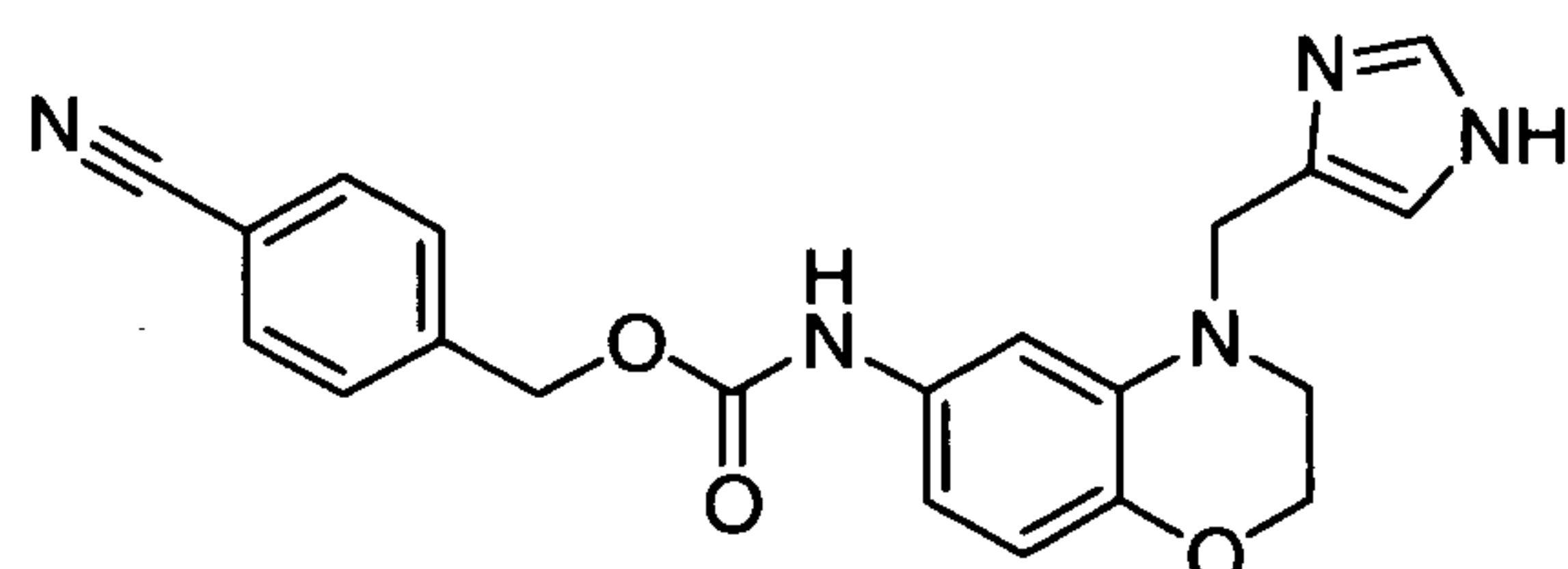
132

247



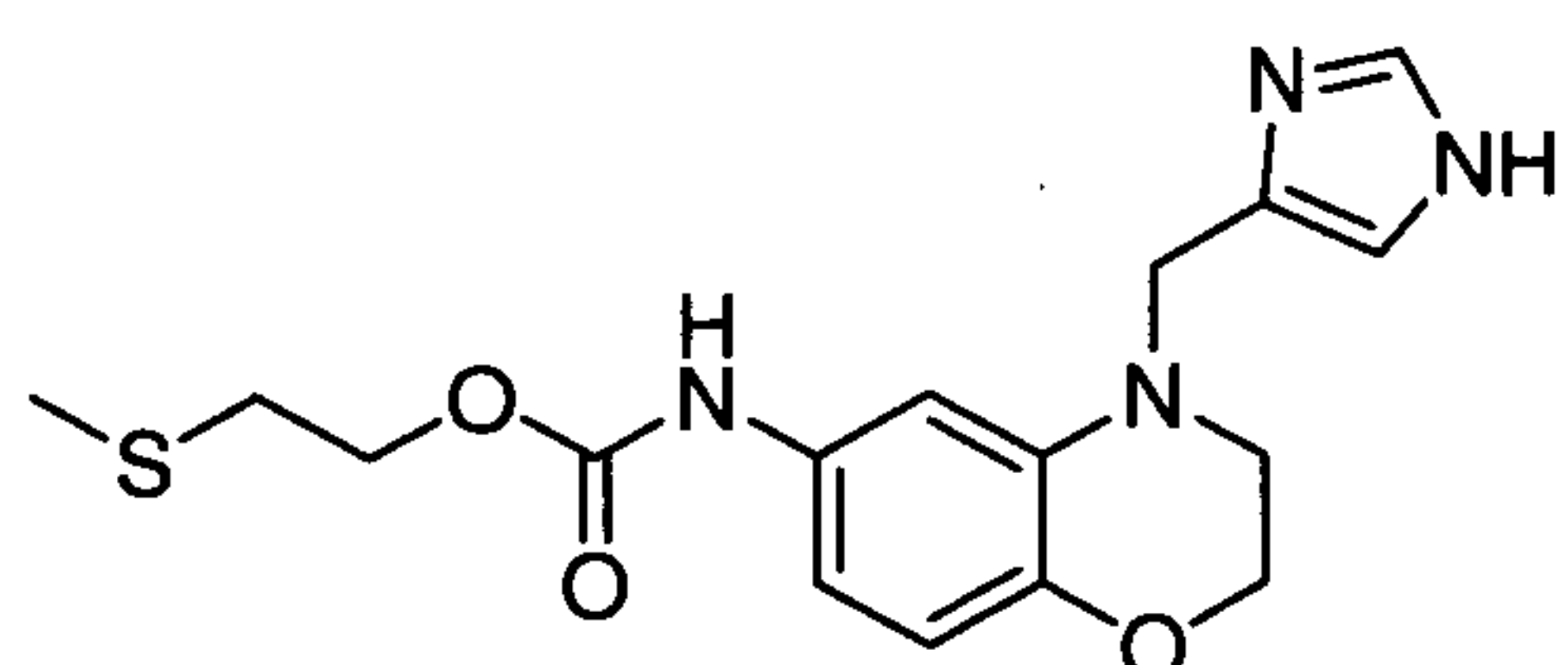
328

248



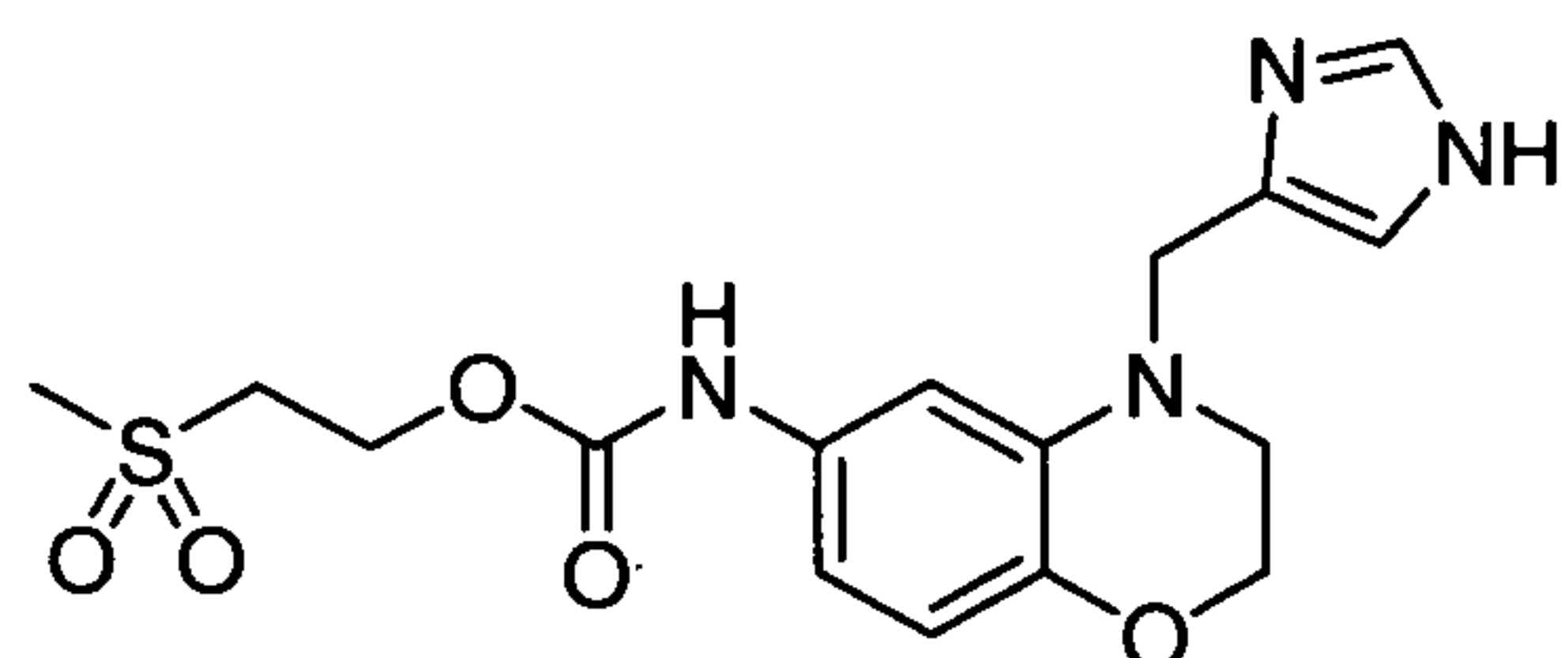
390

249



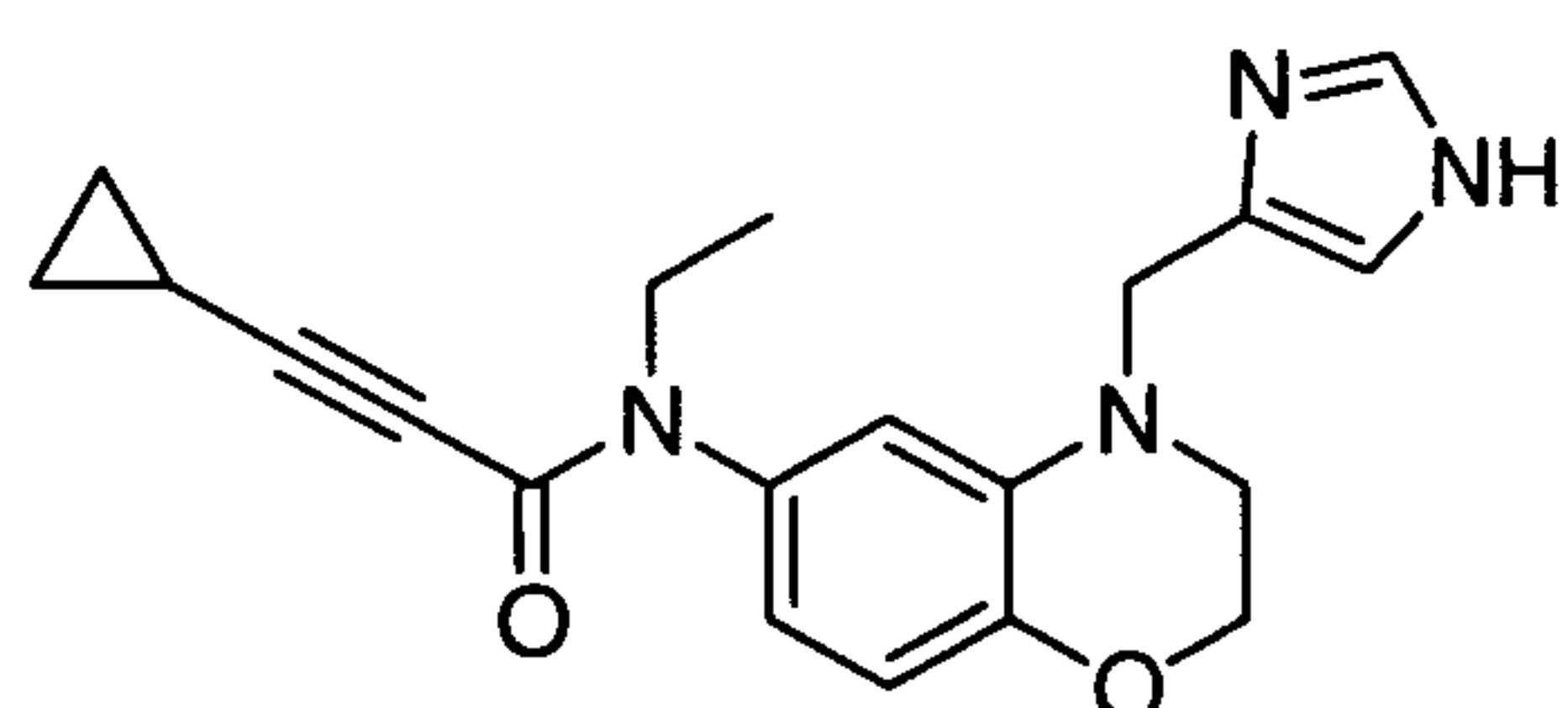
349

250



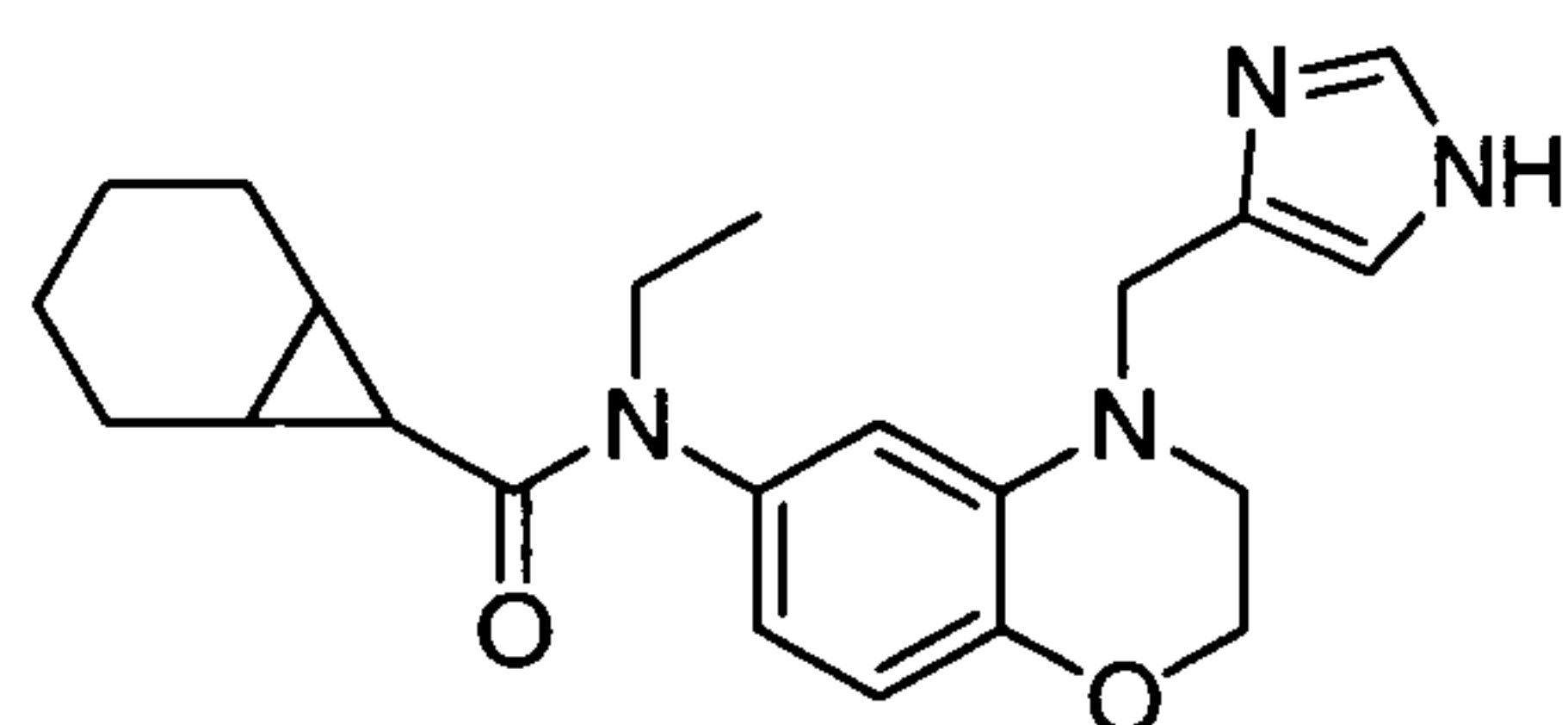
381

251



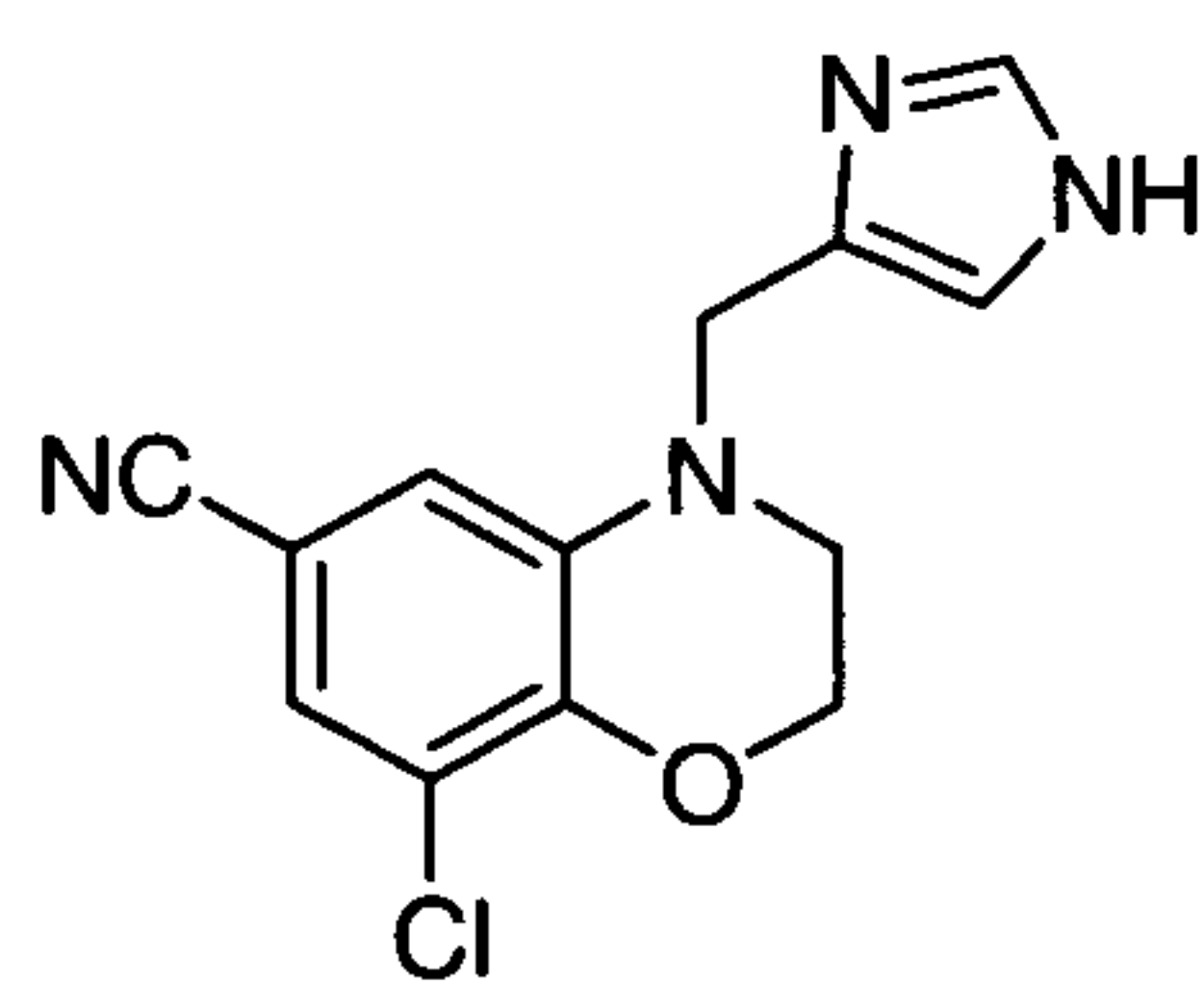
351

252



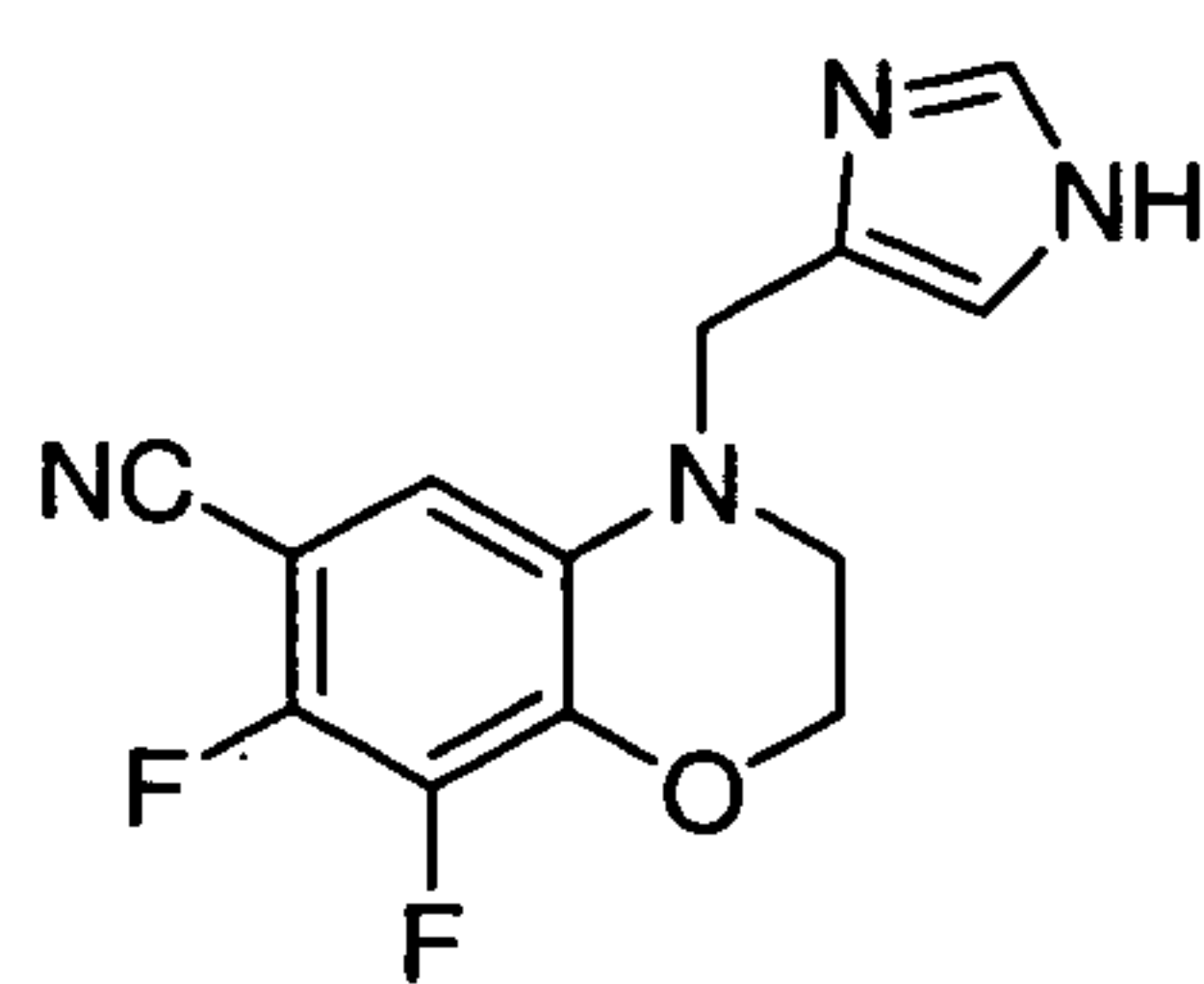
381

253



275

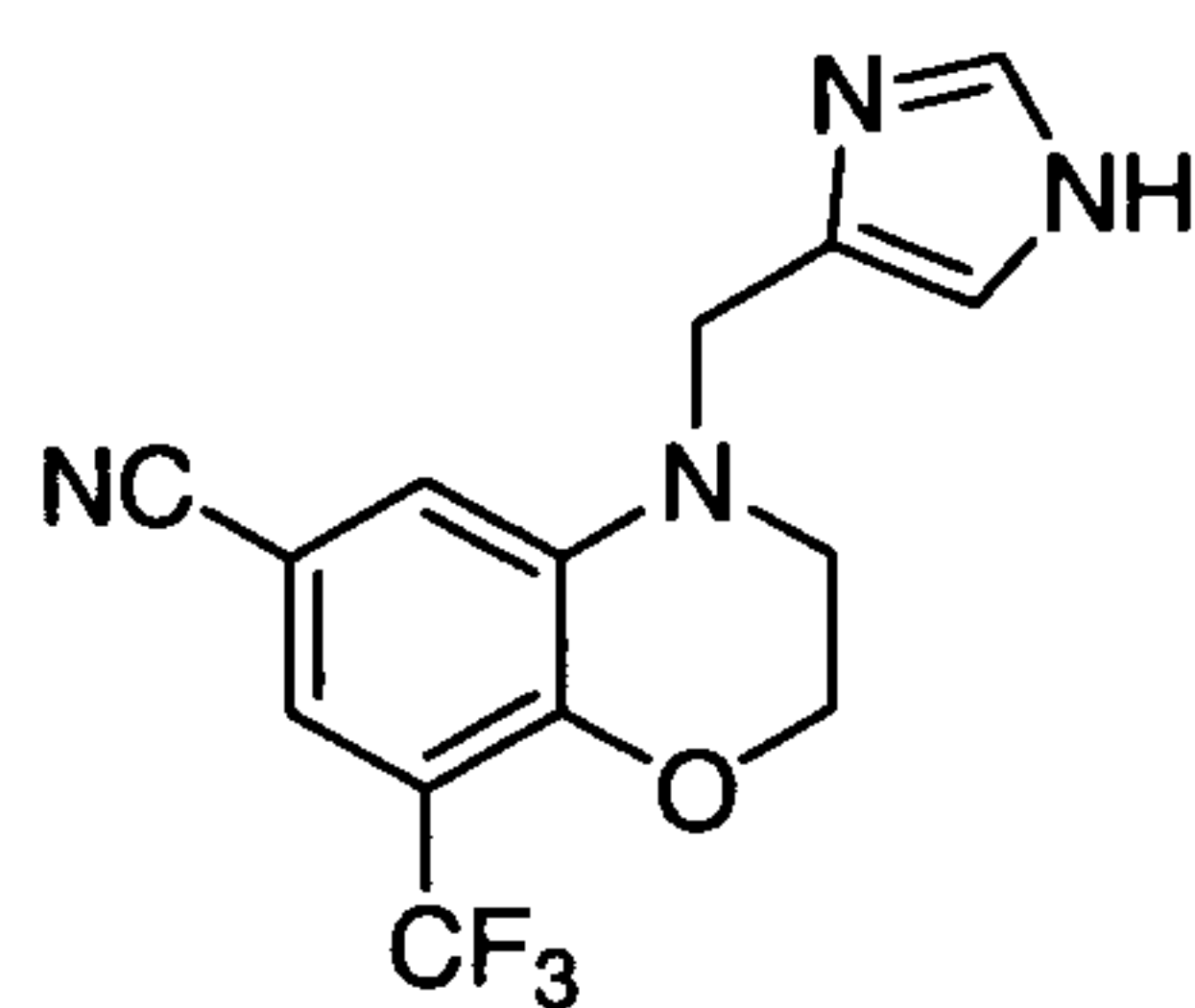
254



277

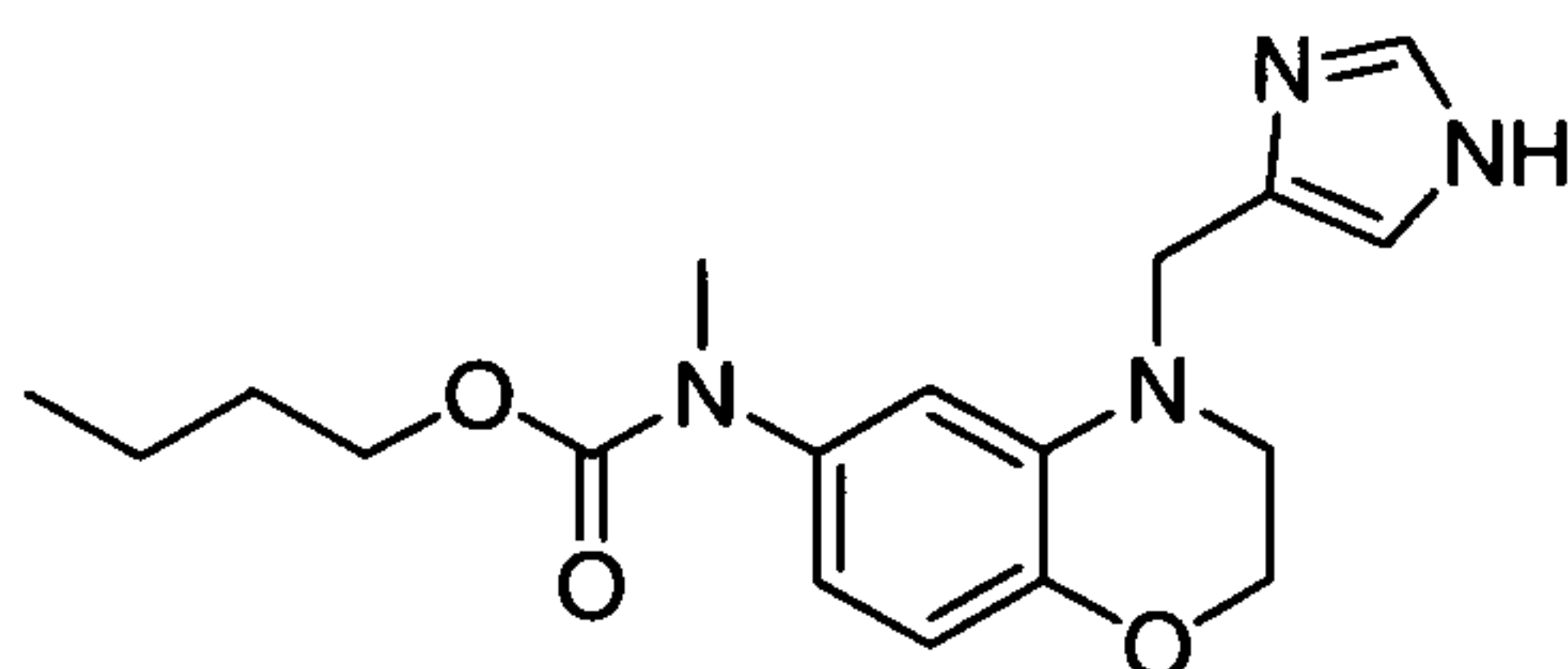
133

255



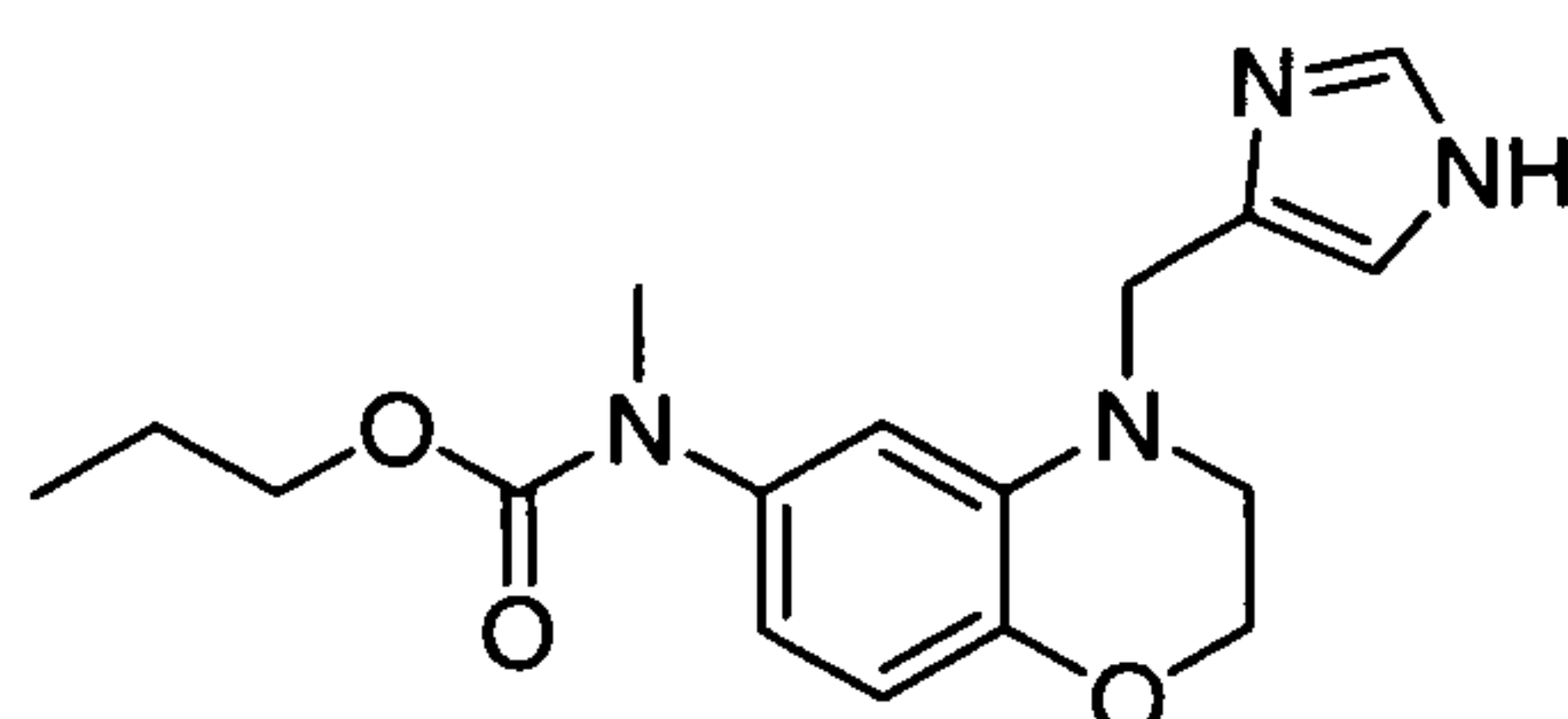
309

256



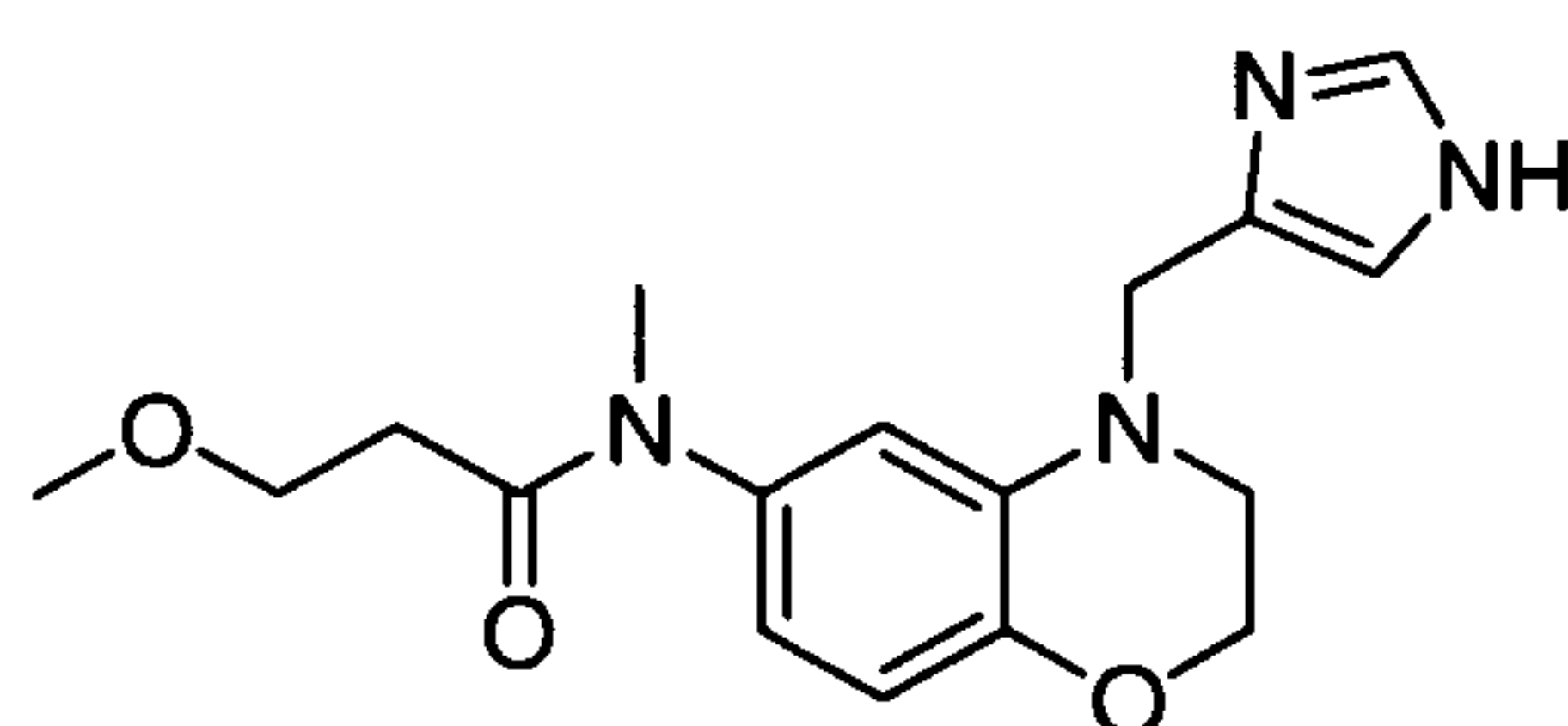
345

257



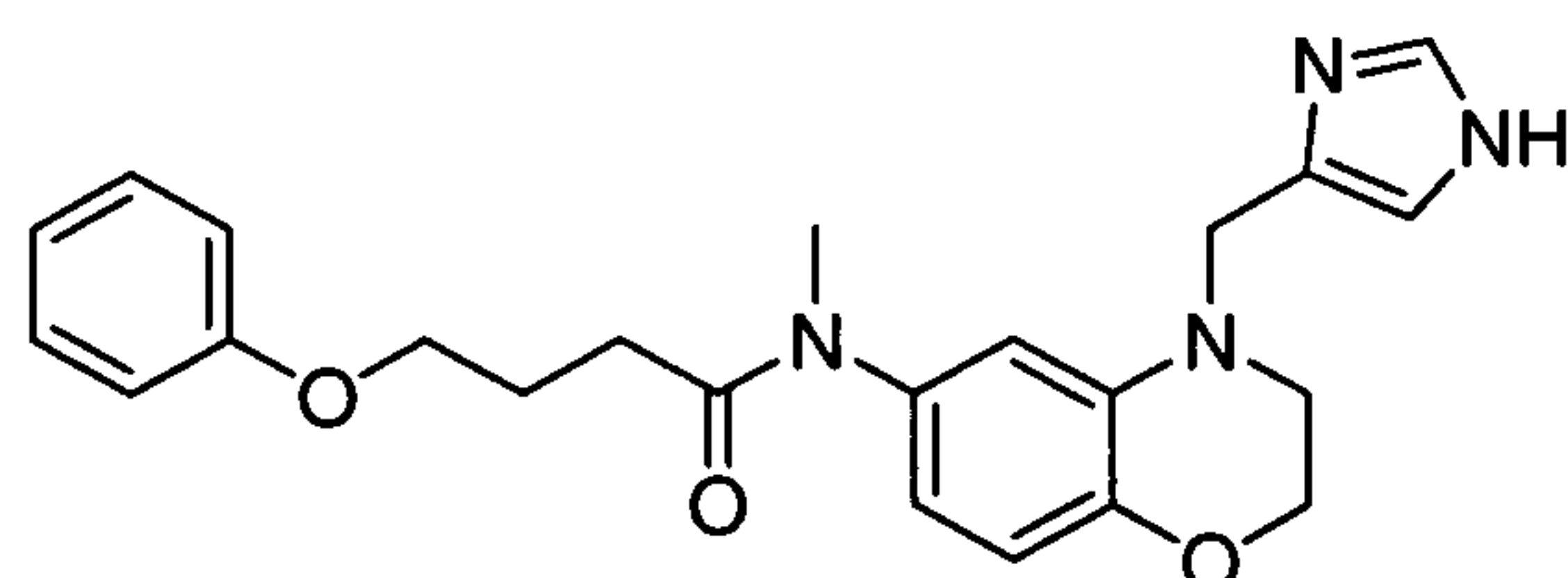
331

258



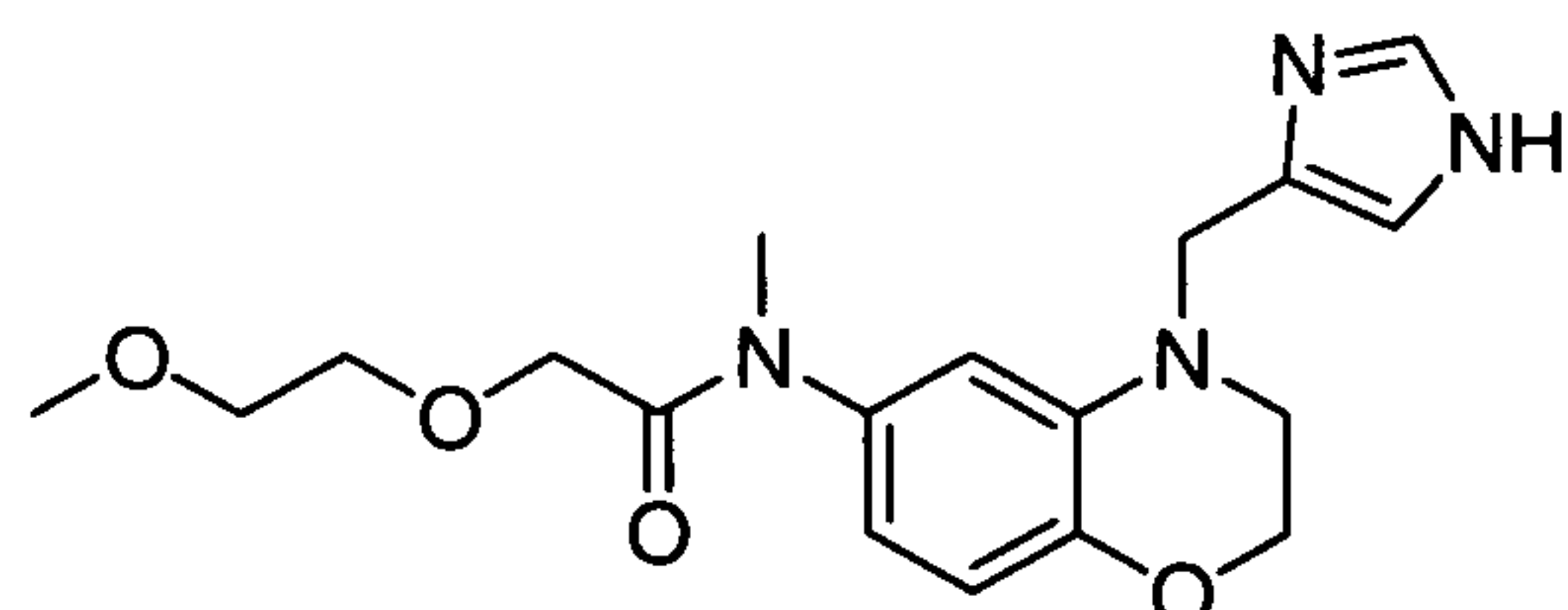
331

259



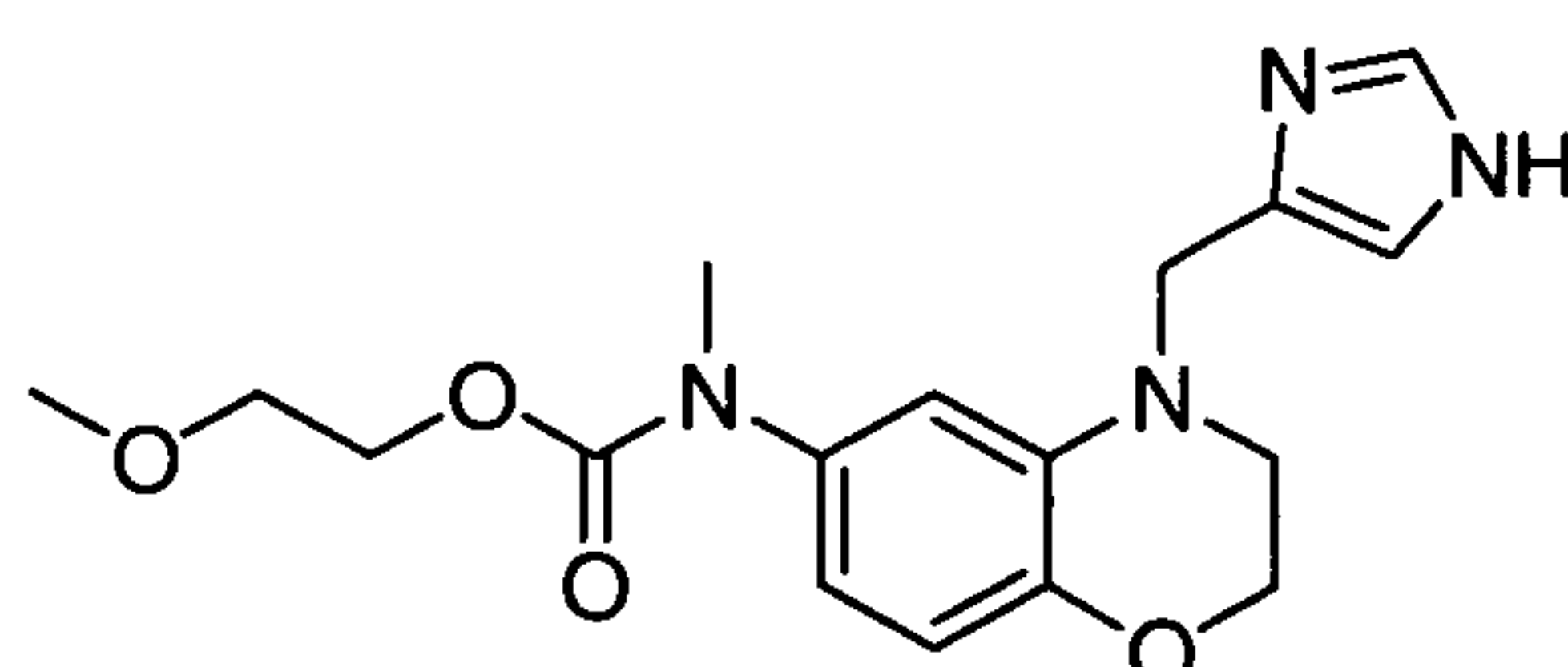
407

260



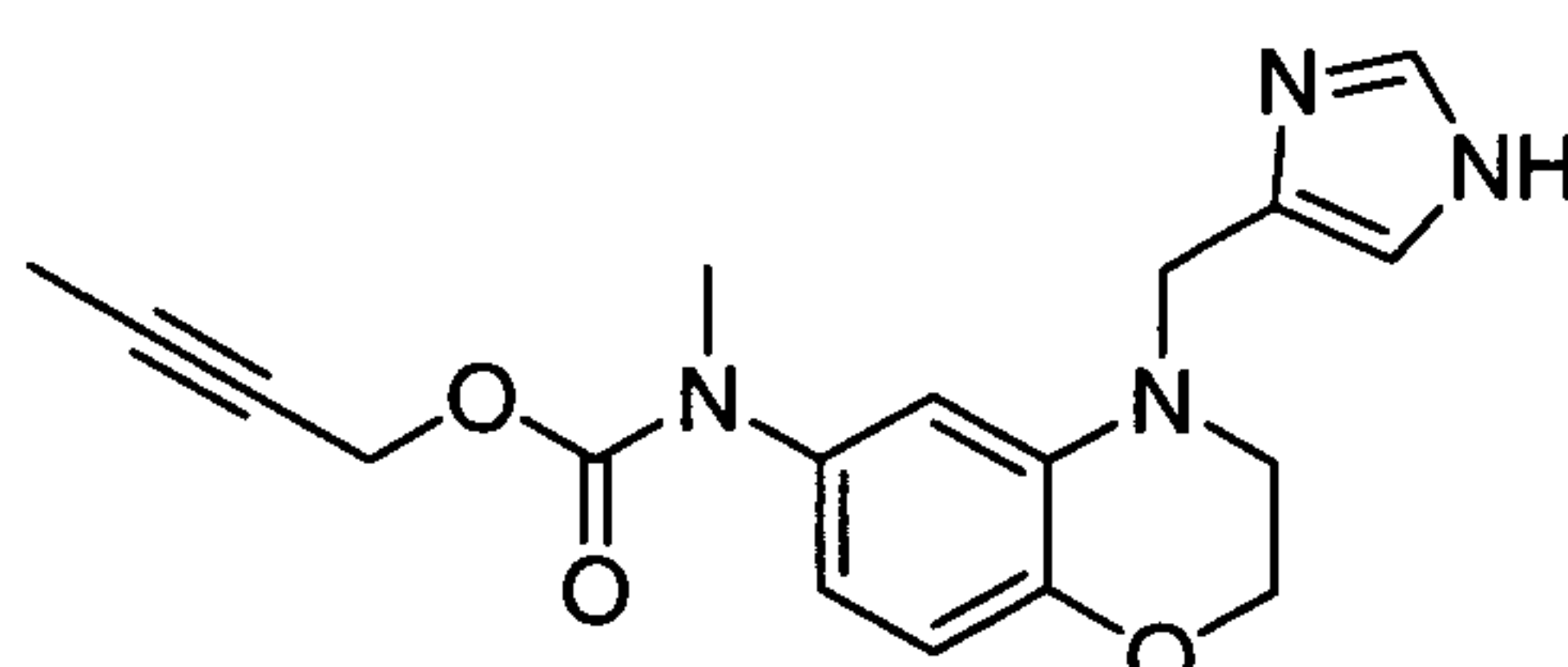
361

261



247

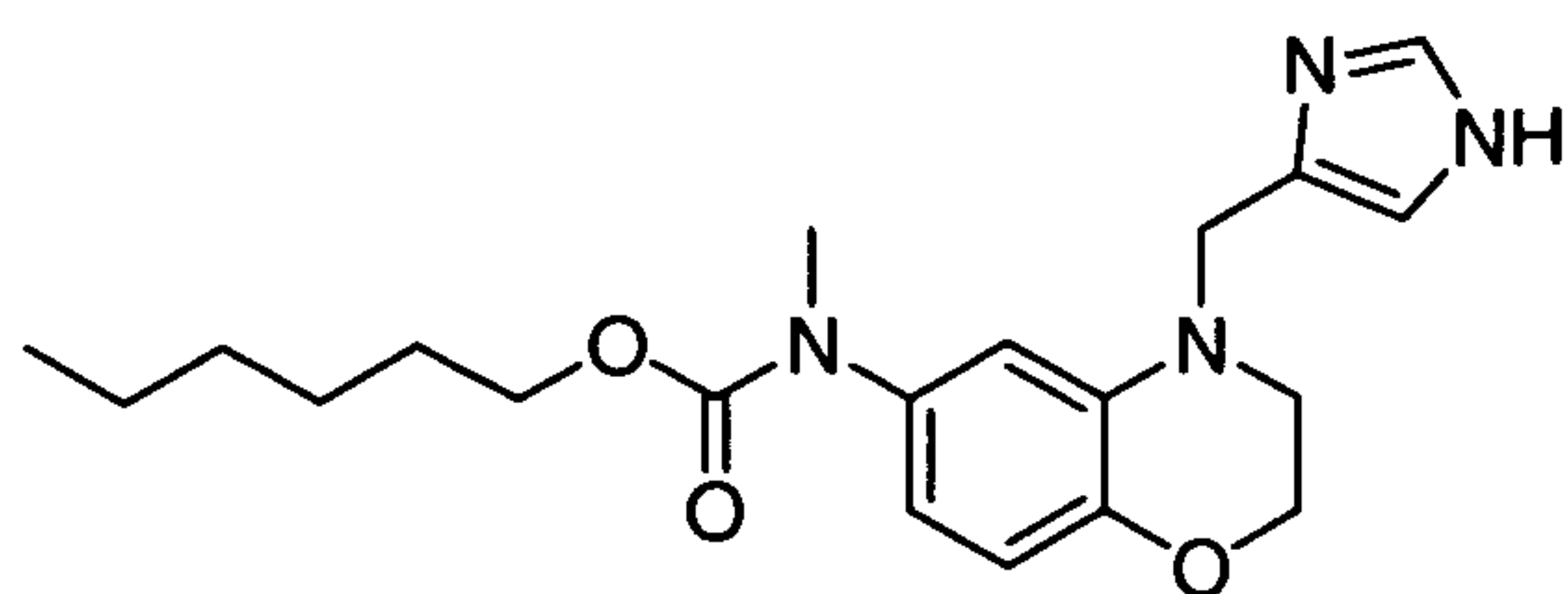
262



341

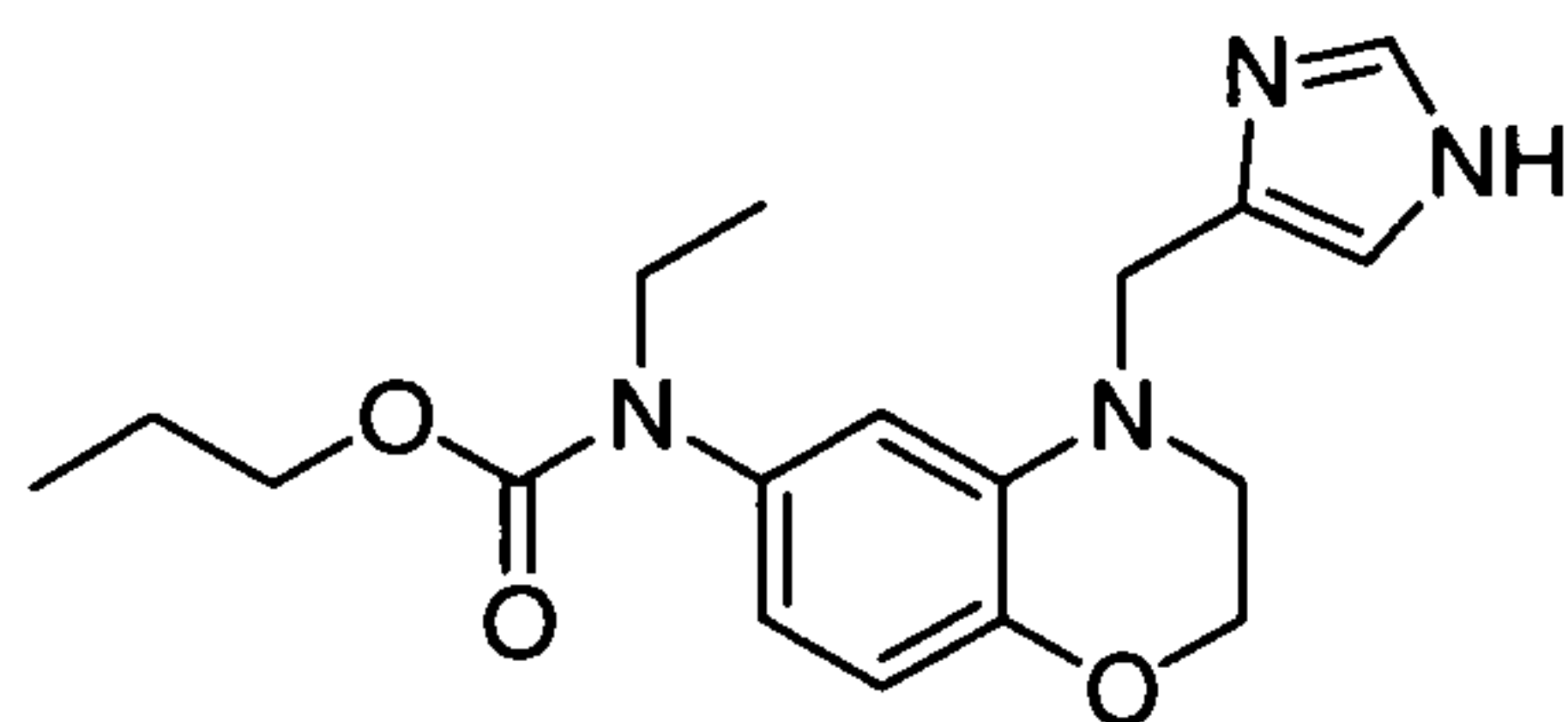
134

263



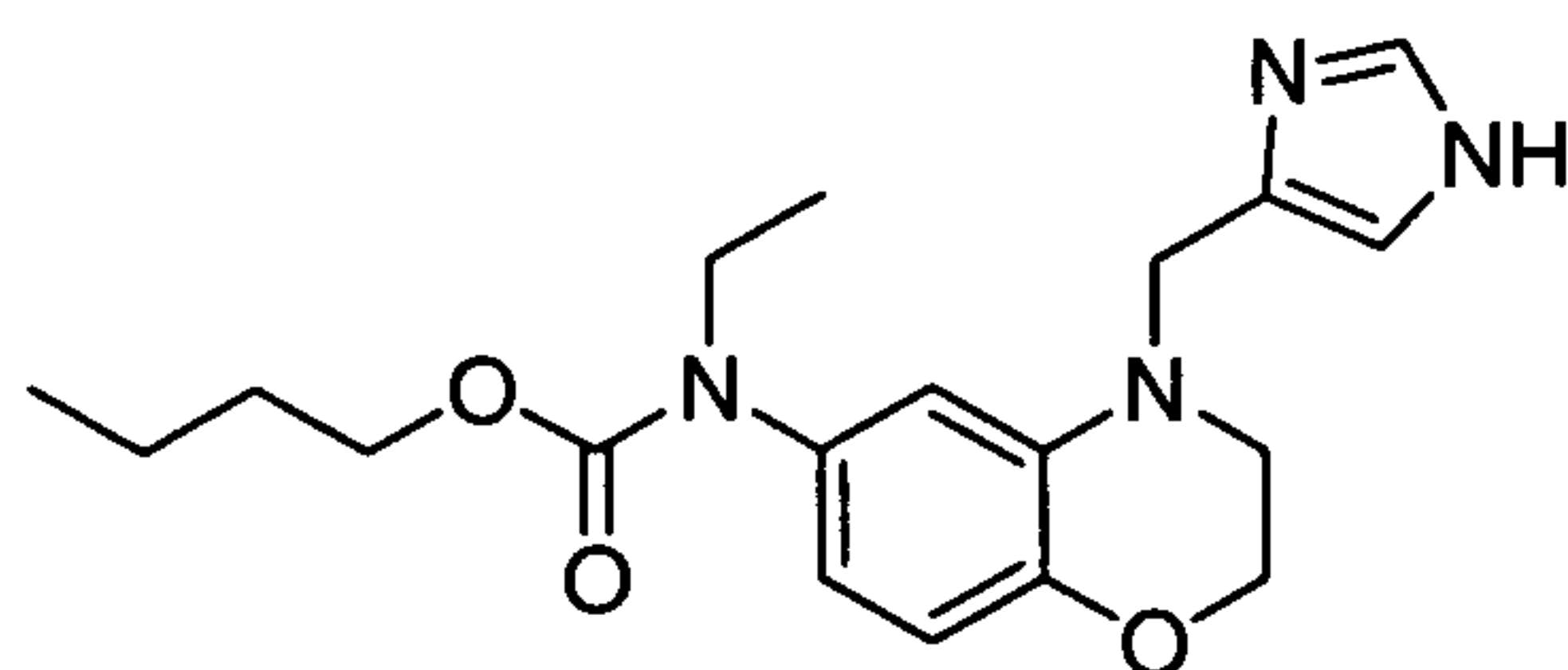
373

264



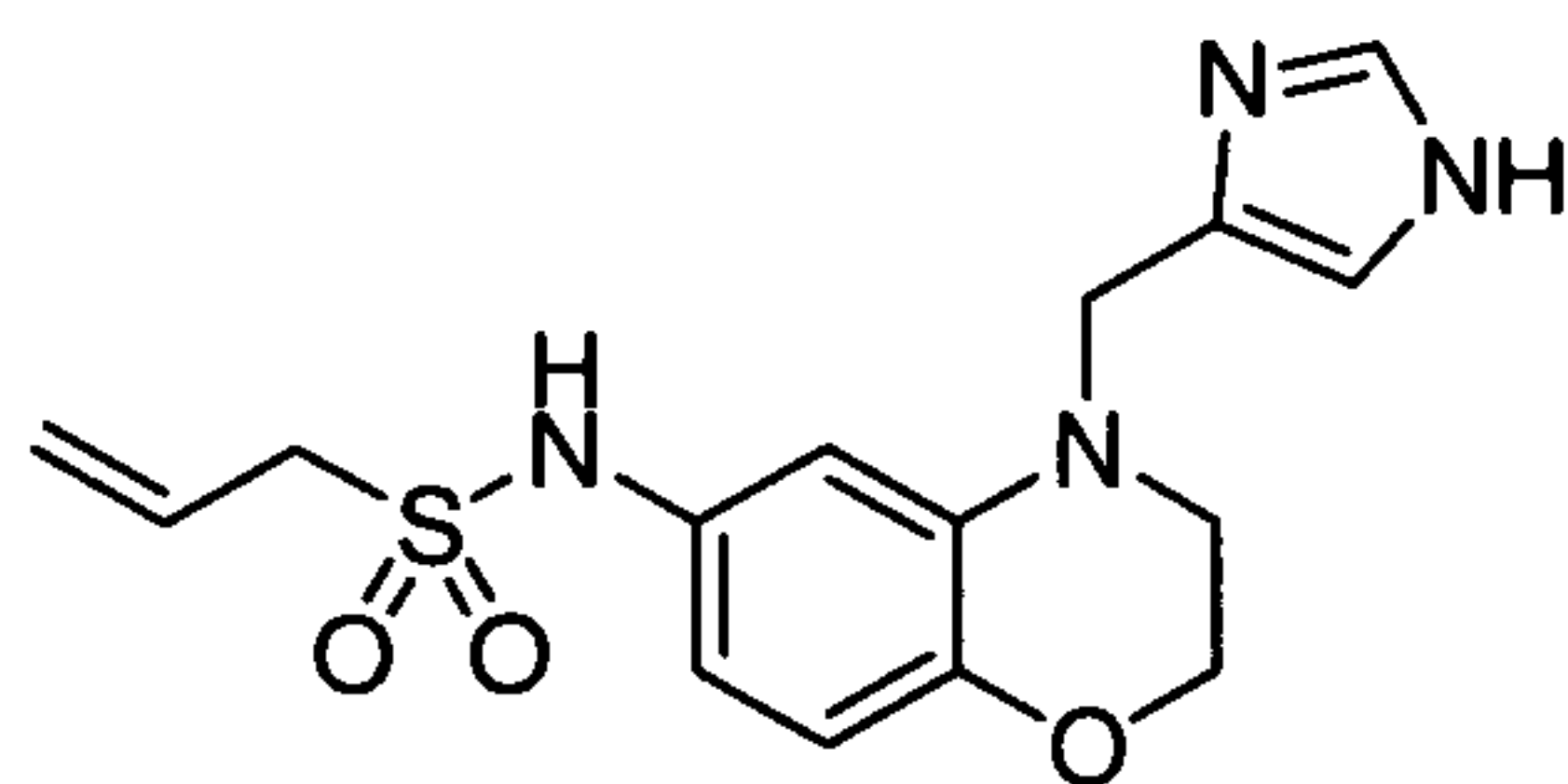
345

265



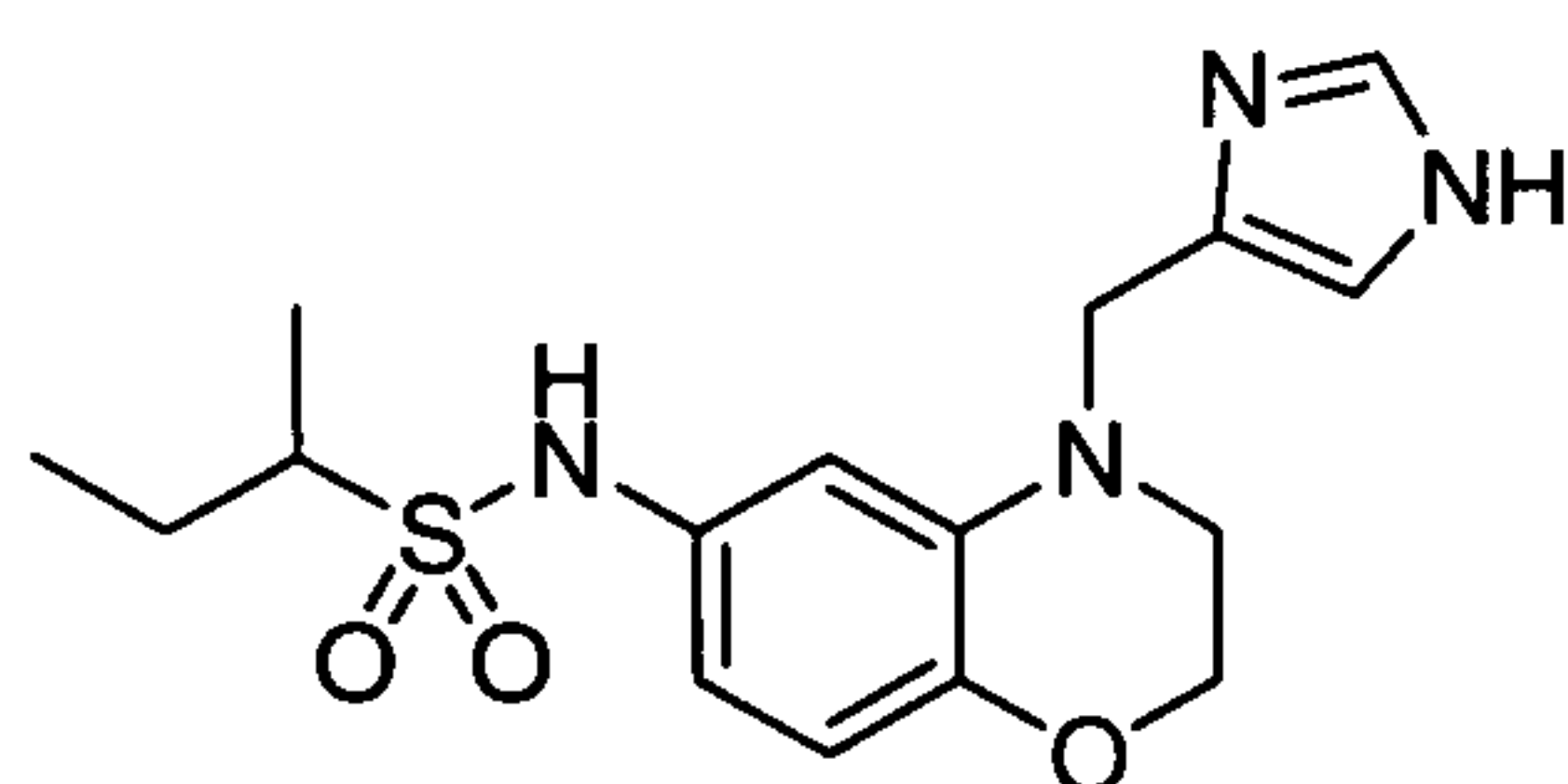
359

266



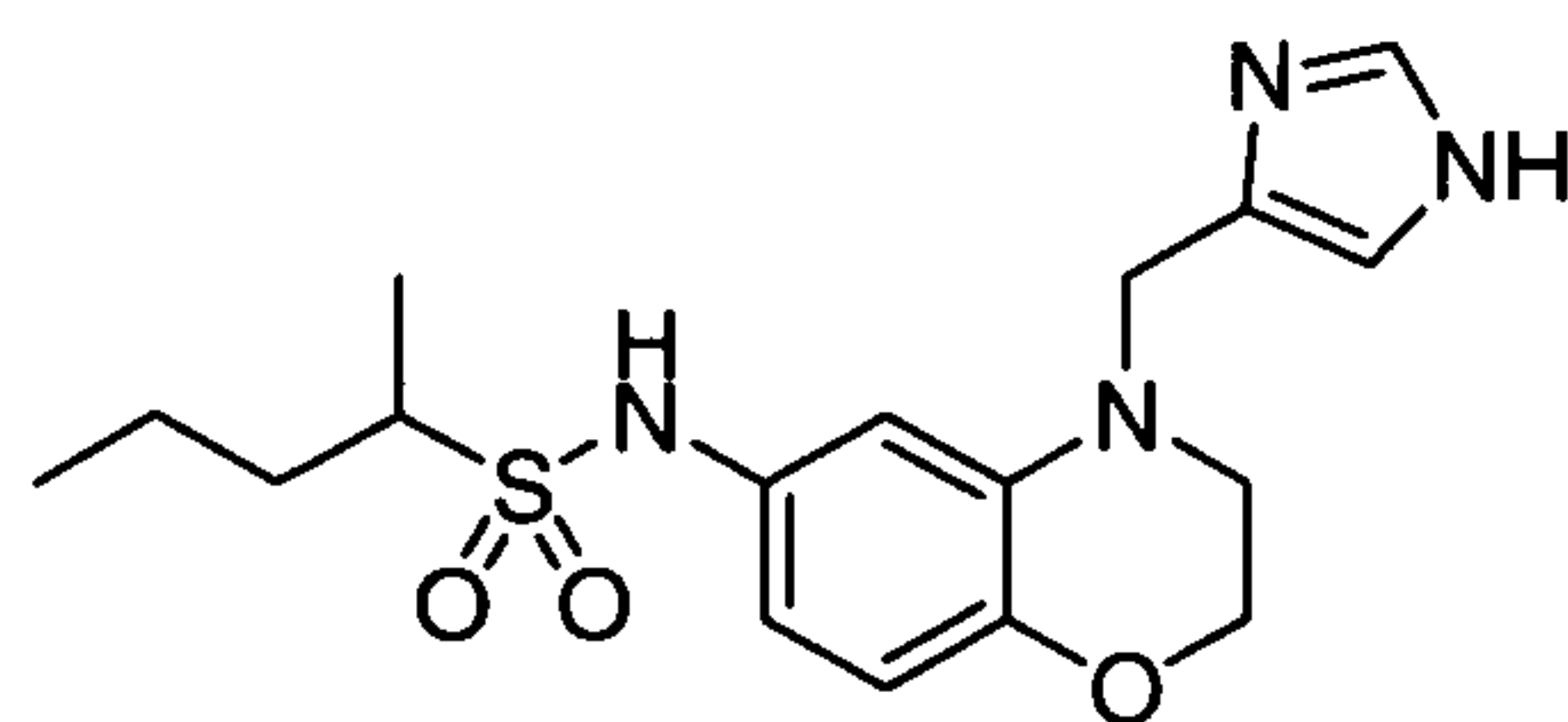
335

267



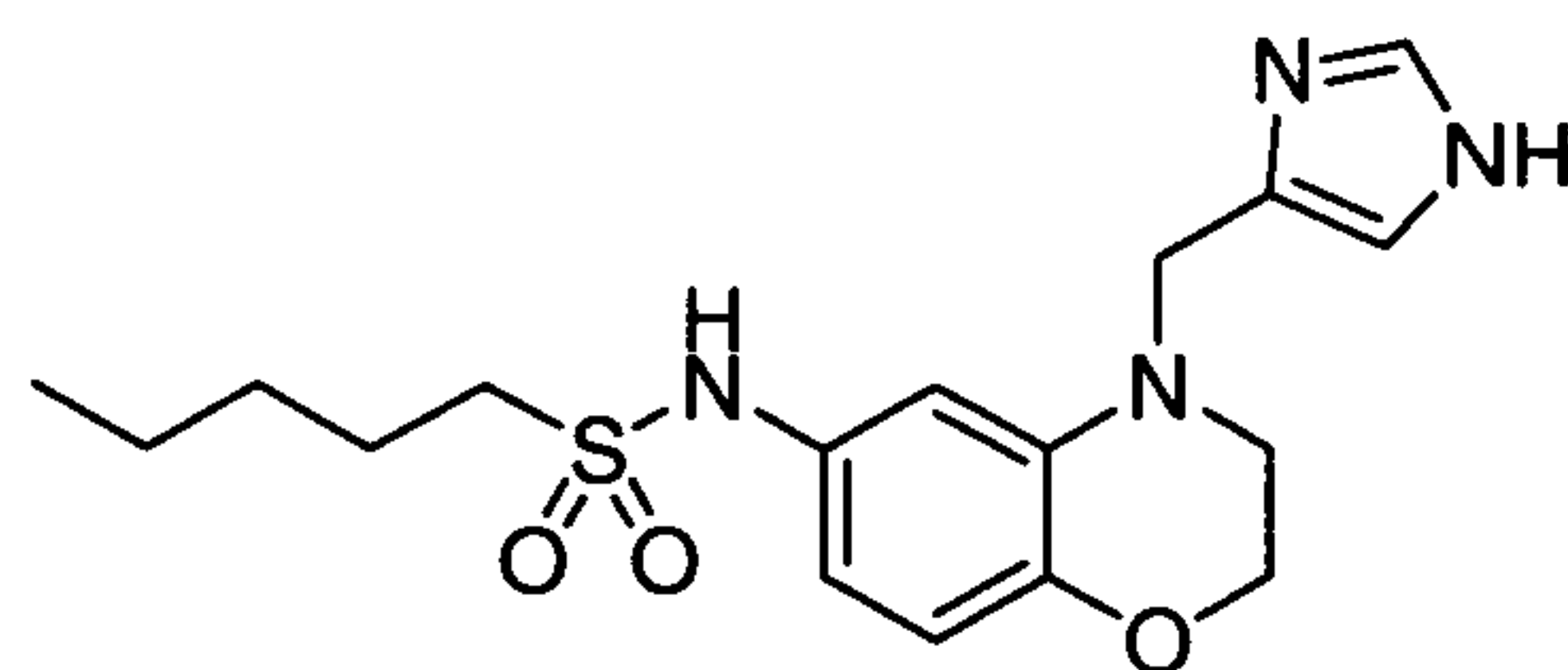
351

268



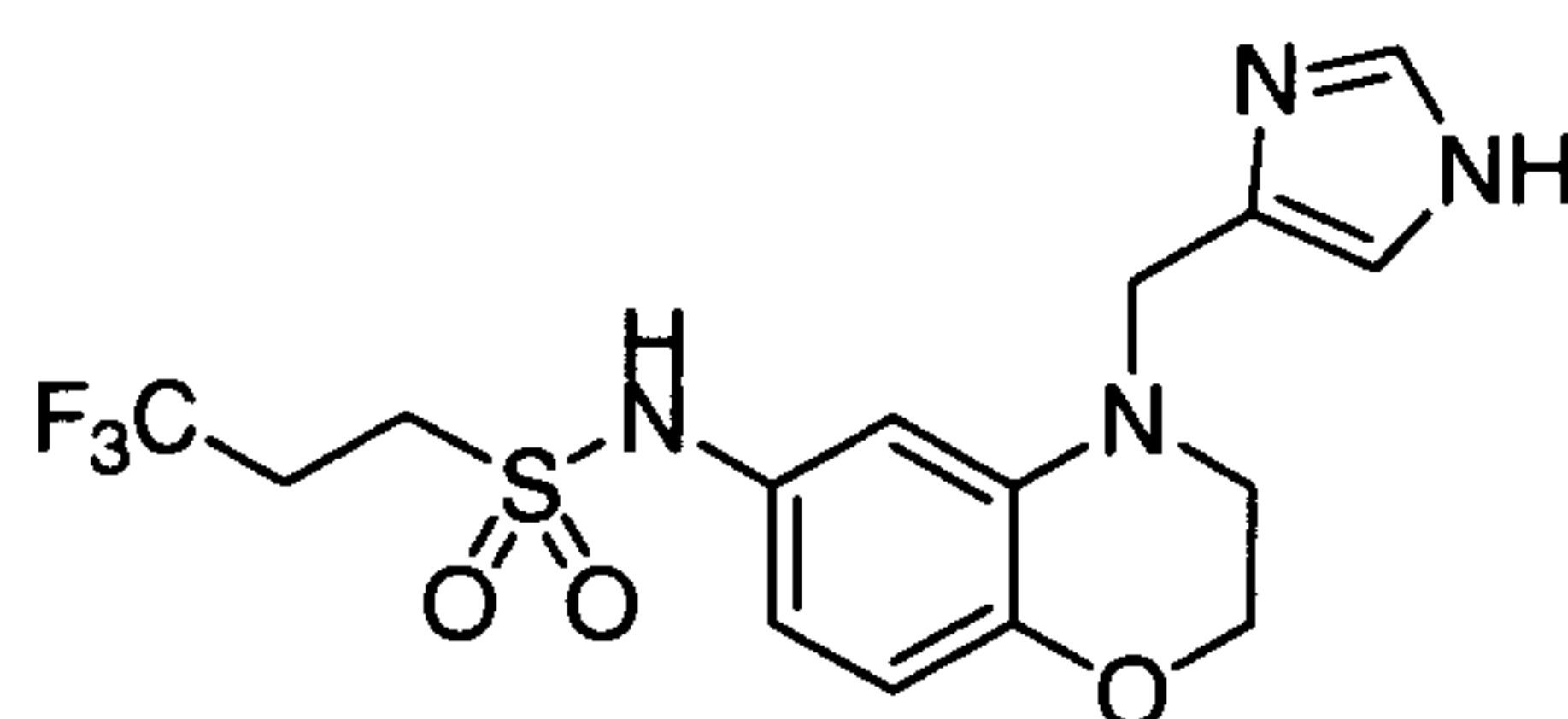
365

269



365

270

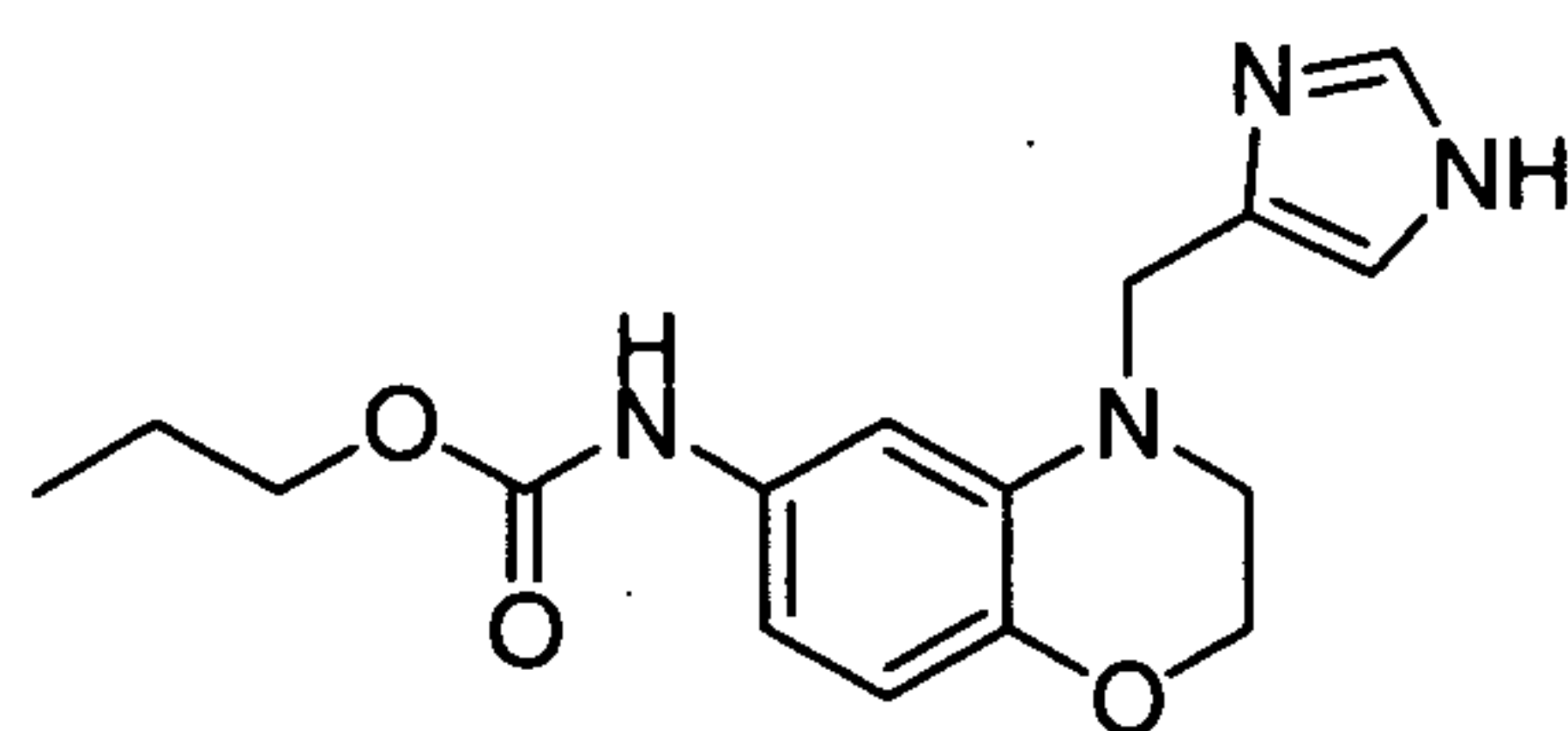


391

135

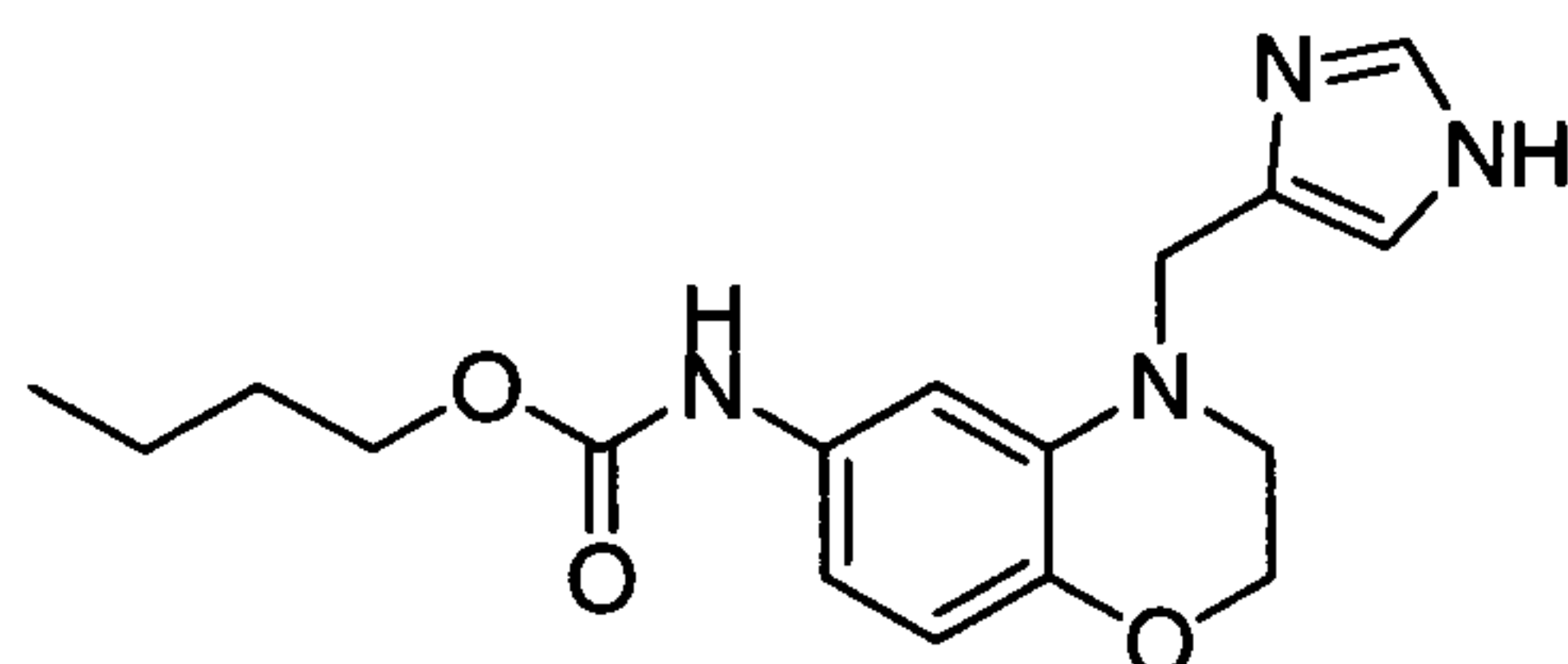
271

317



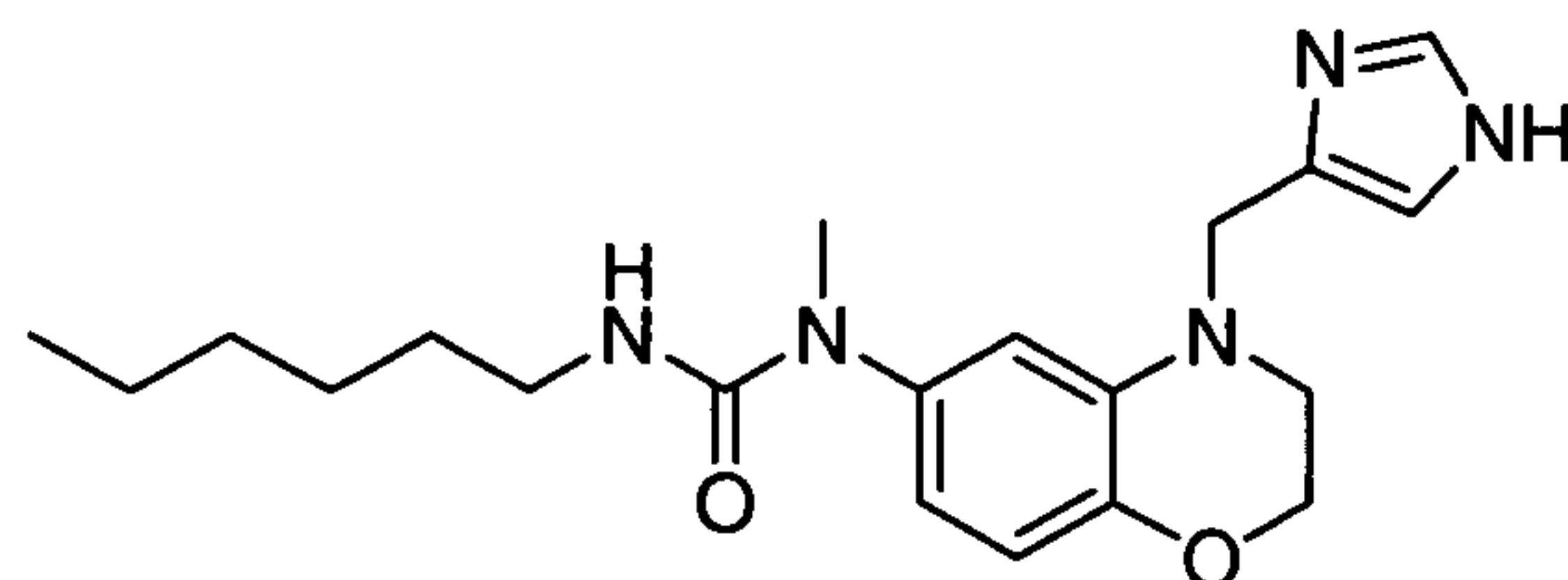
272

331



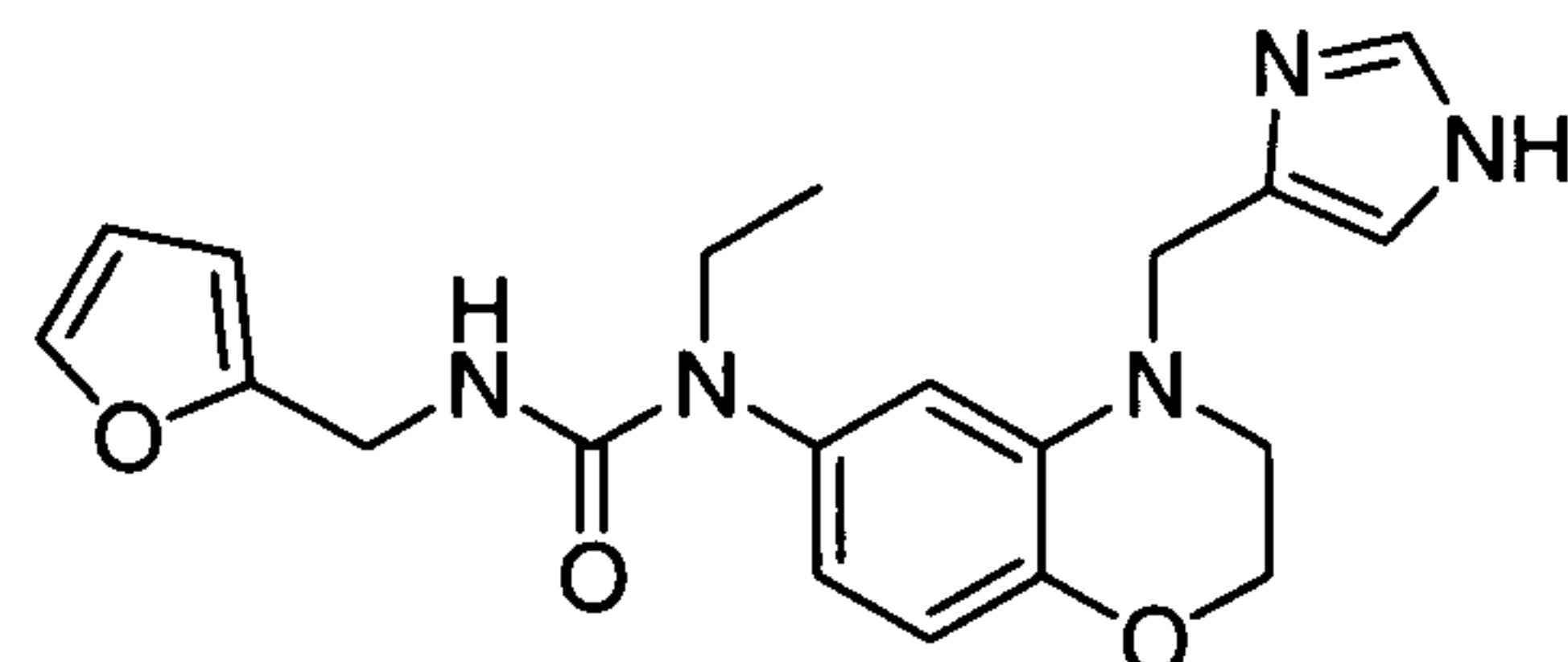
273

372



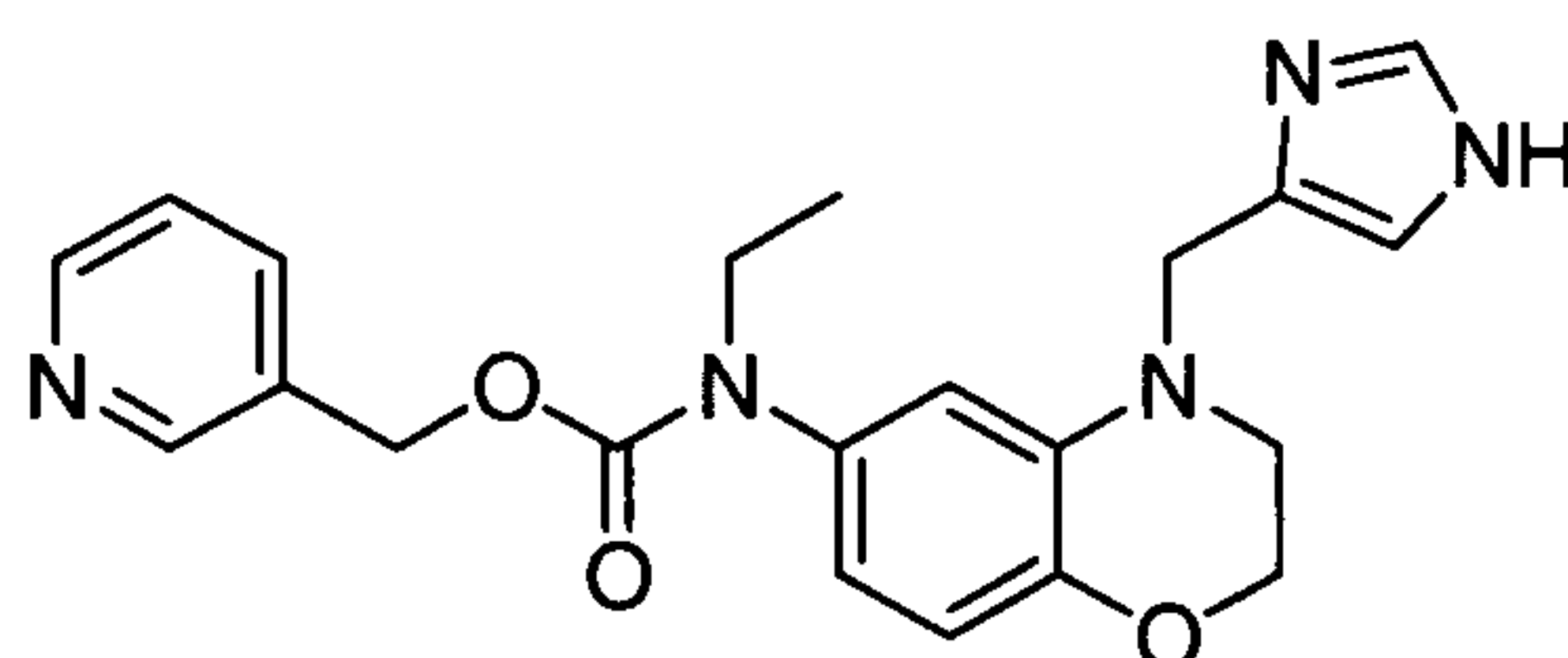
274

382



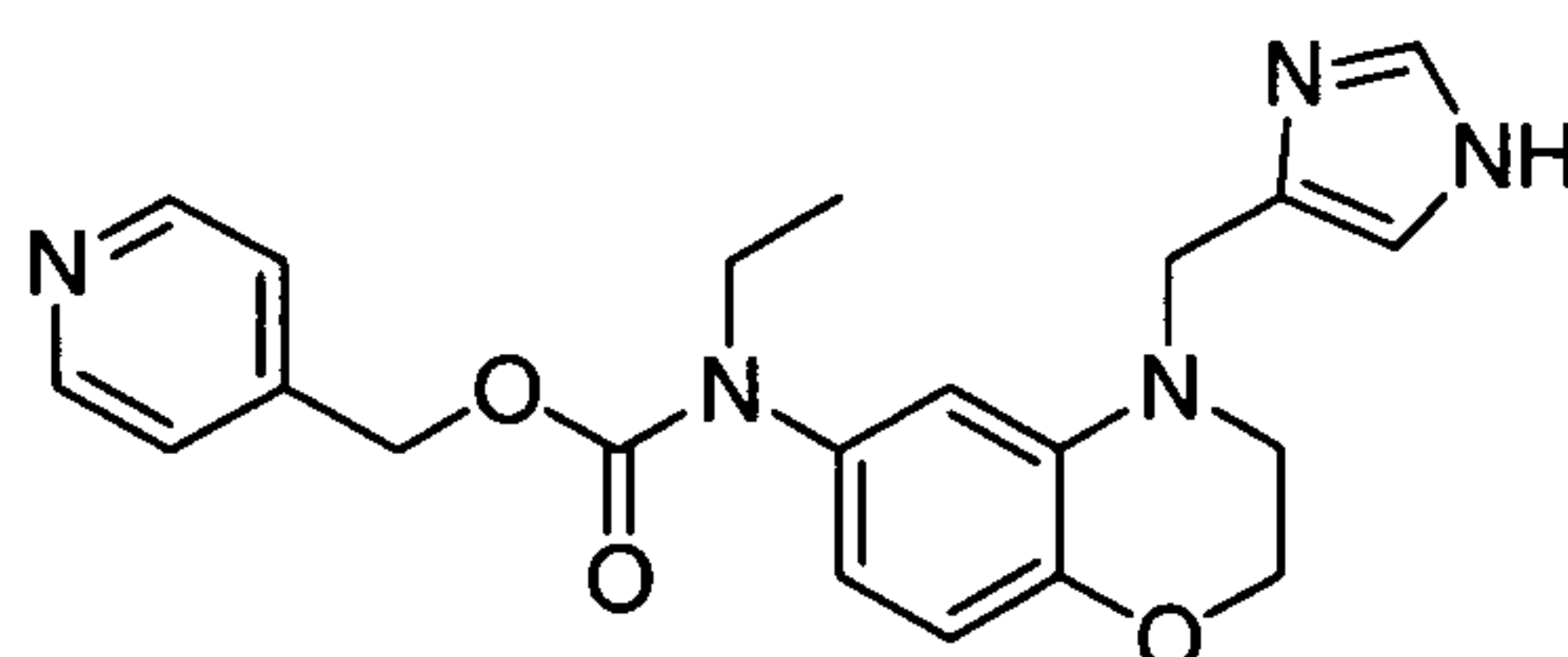
275

394



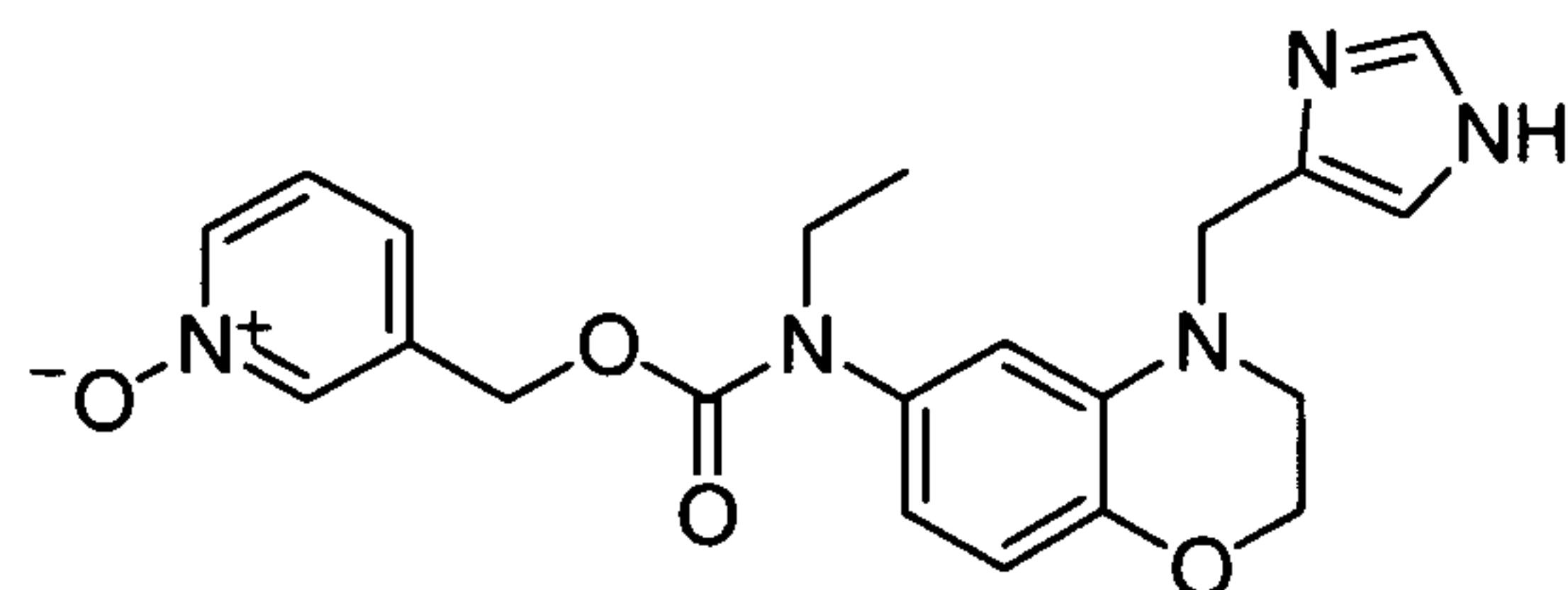
276

394



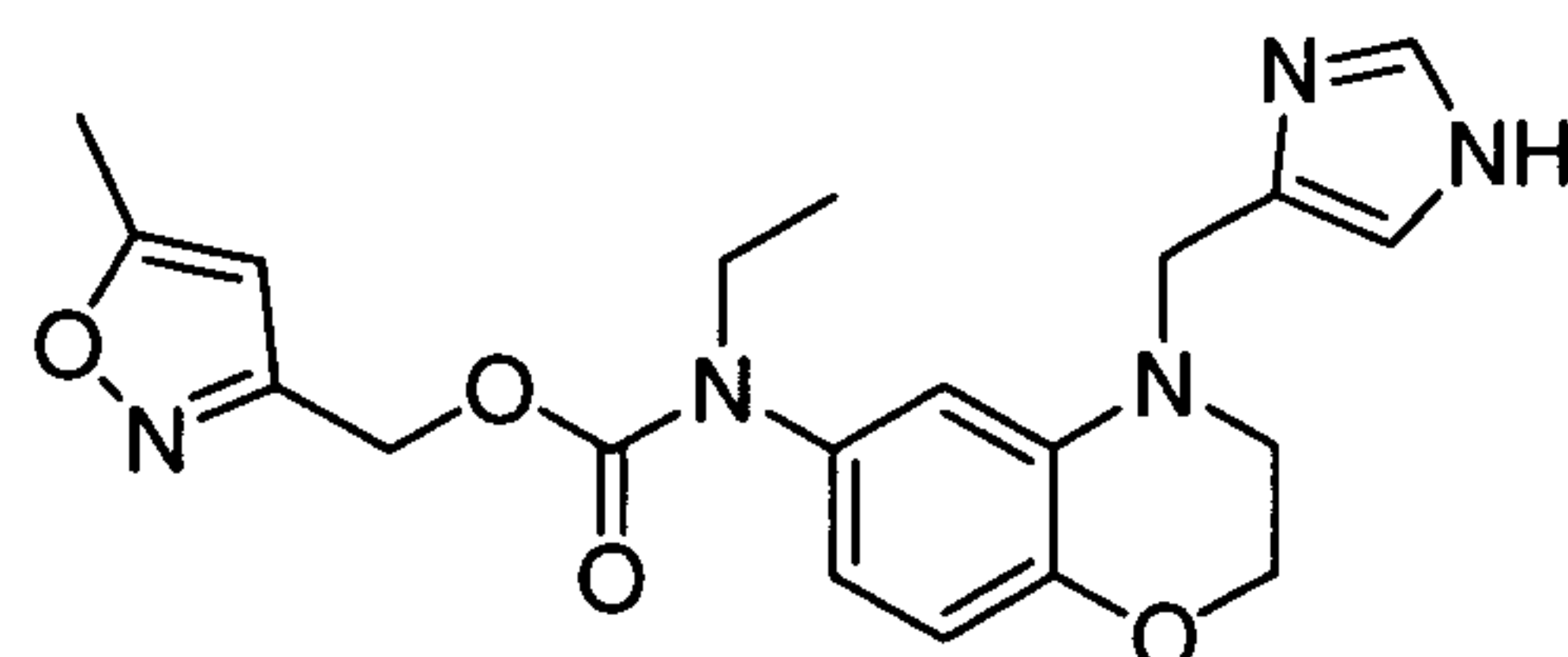
277

410



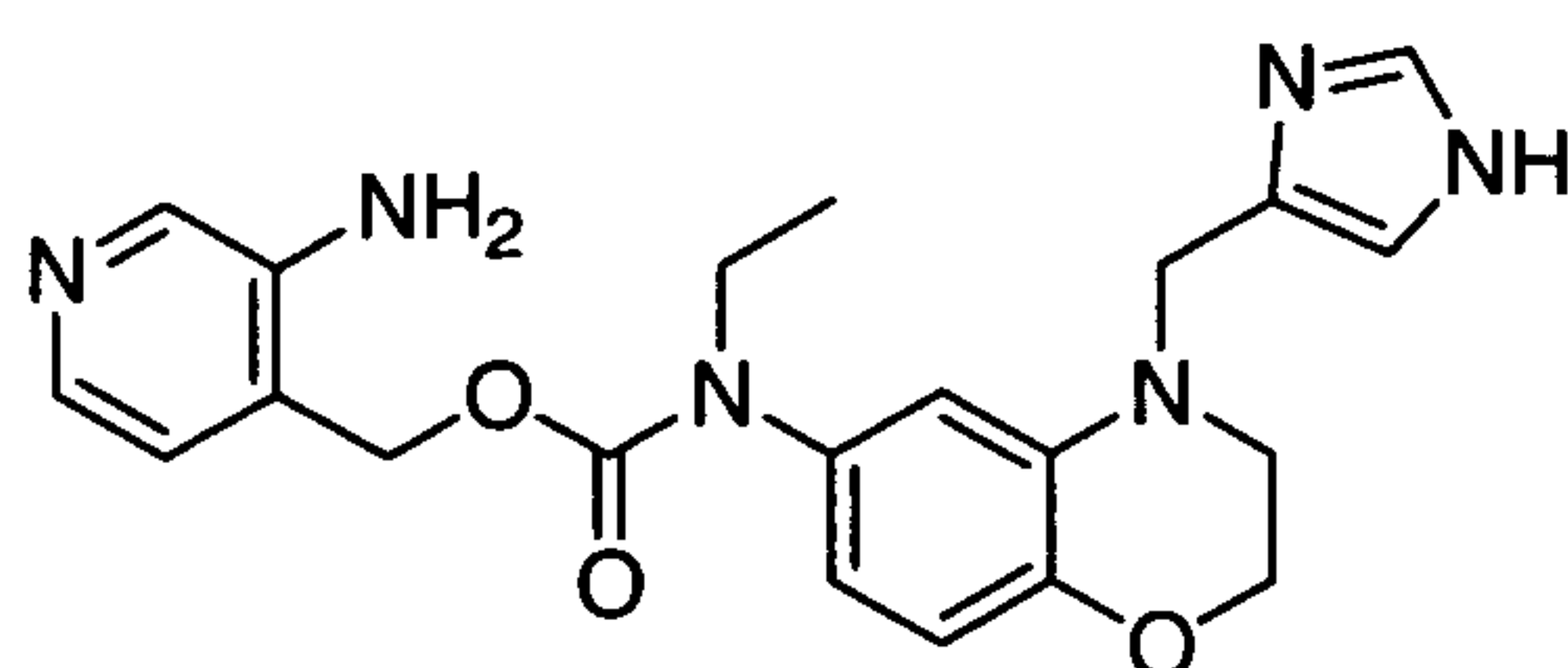
278

398



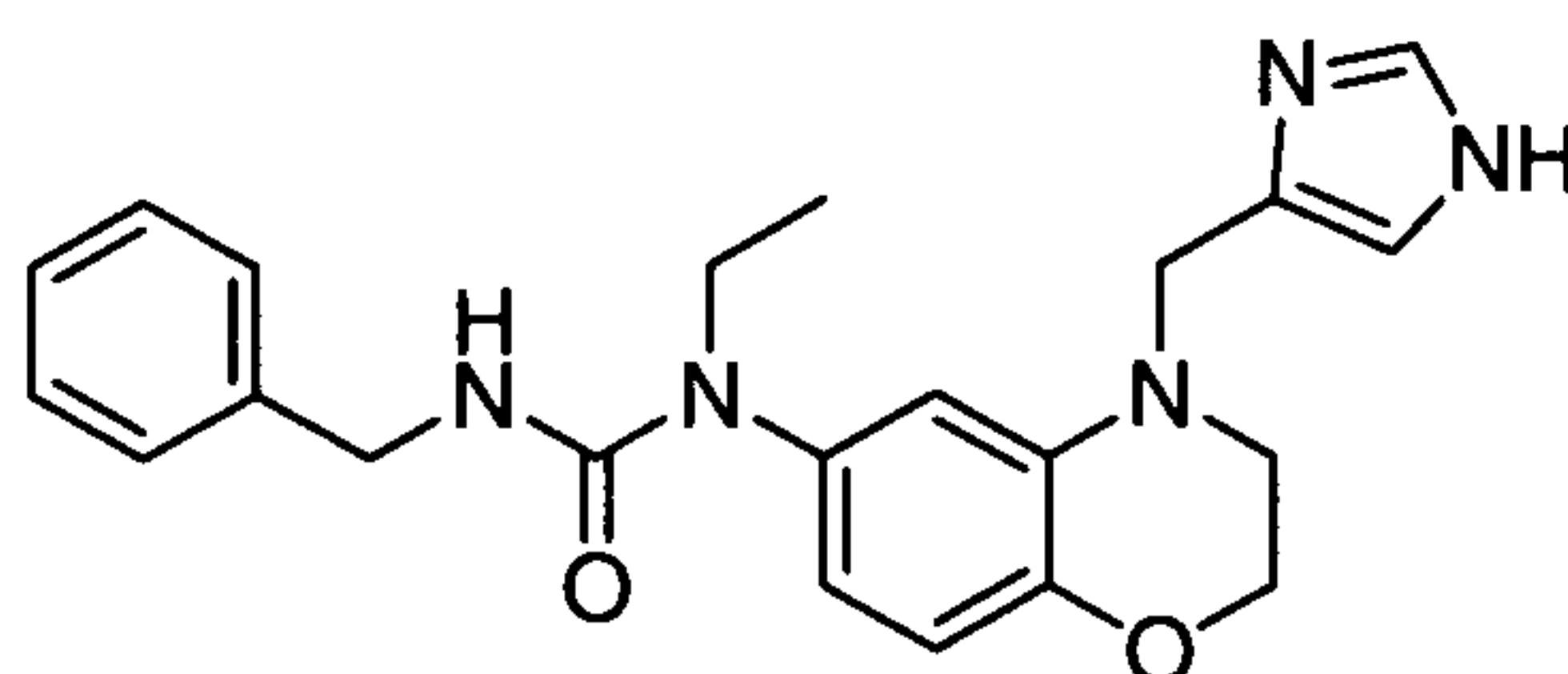
136

279



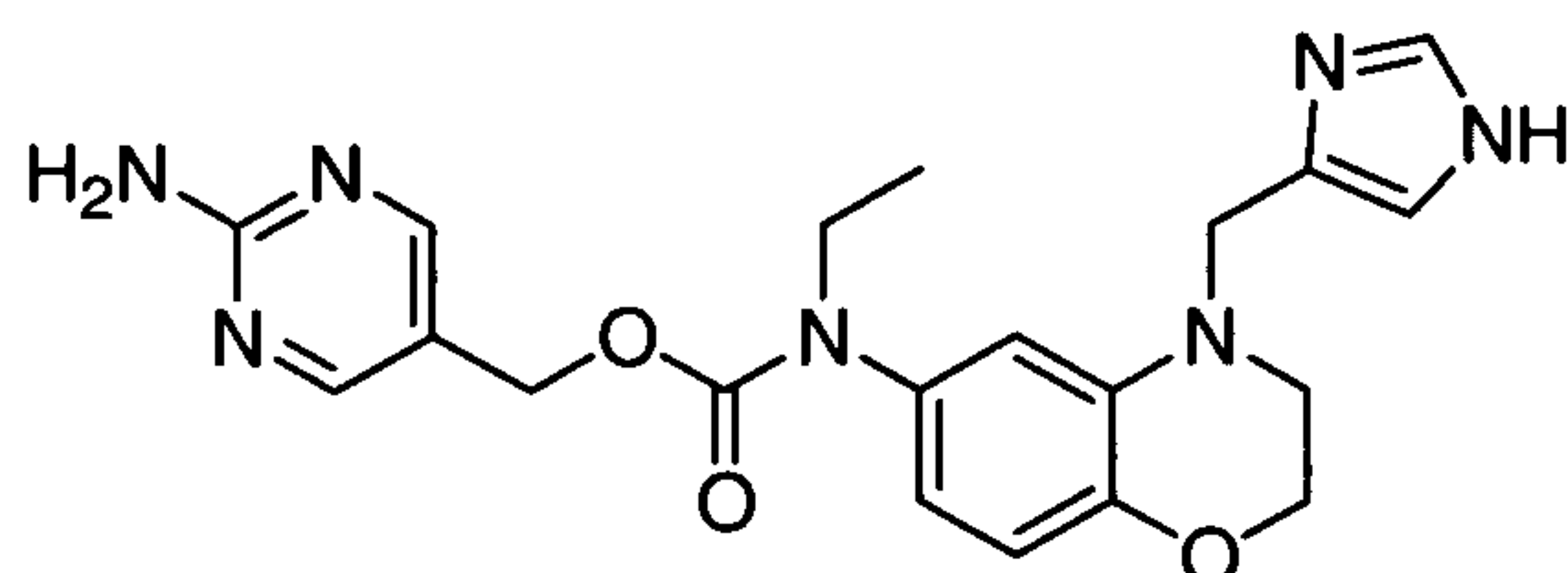
409

280



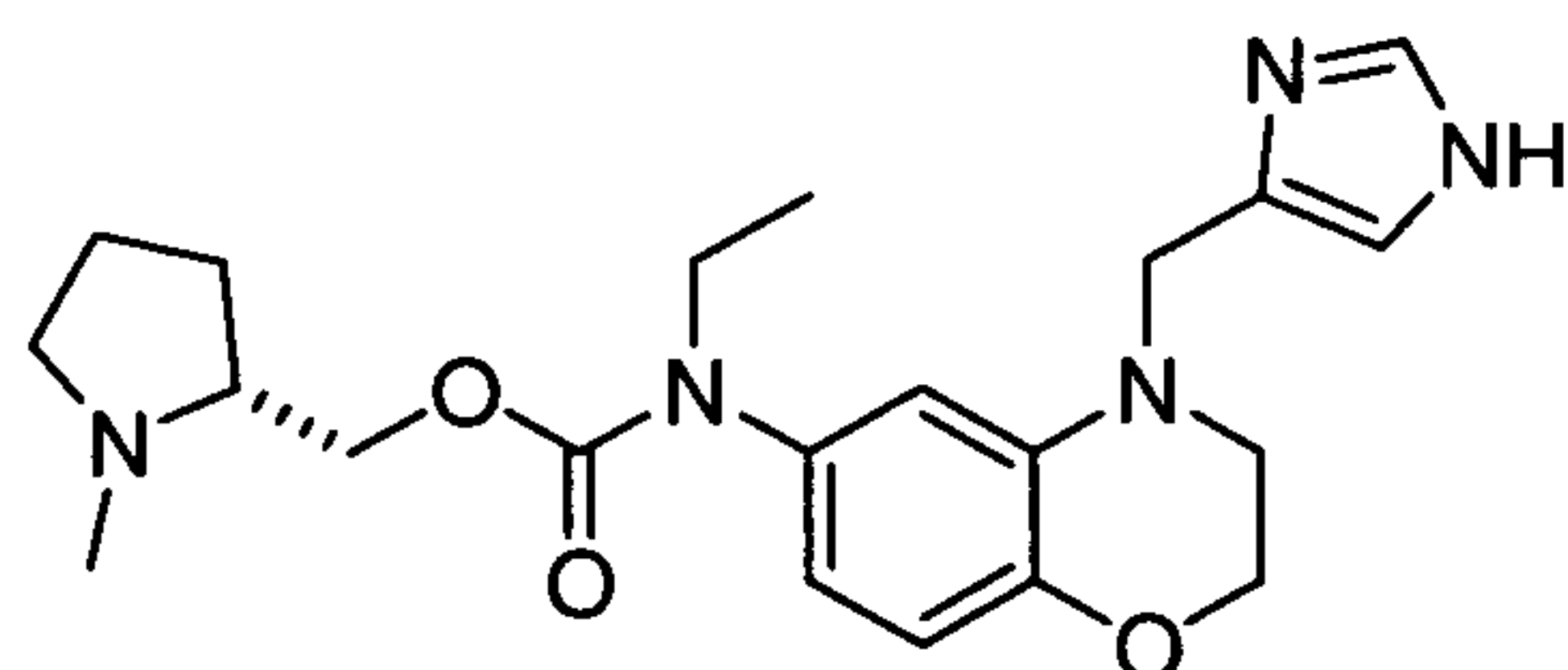
392

281



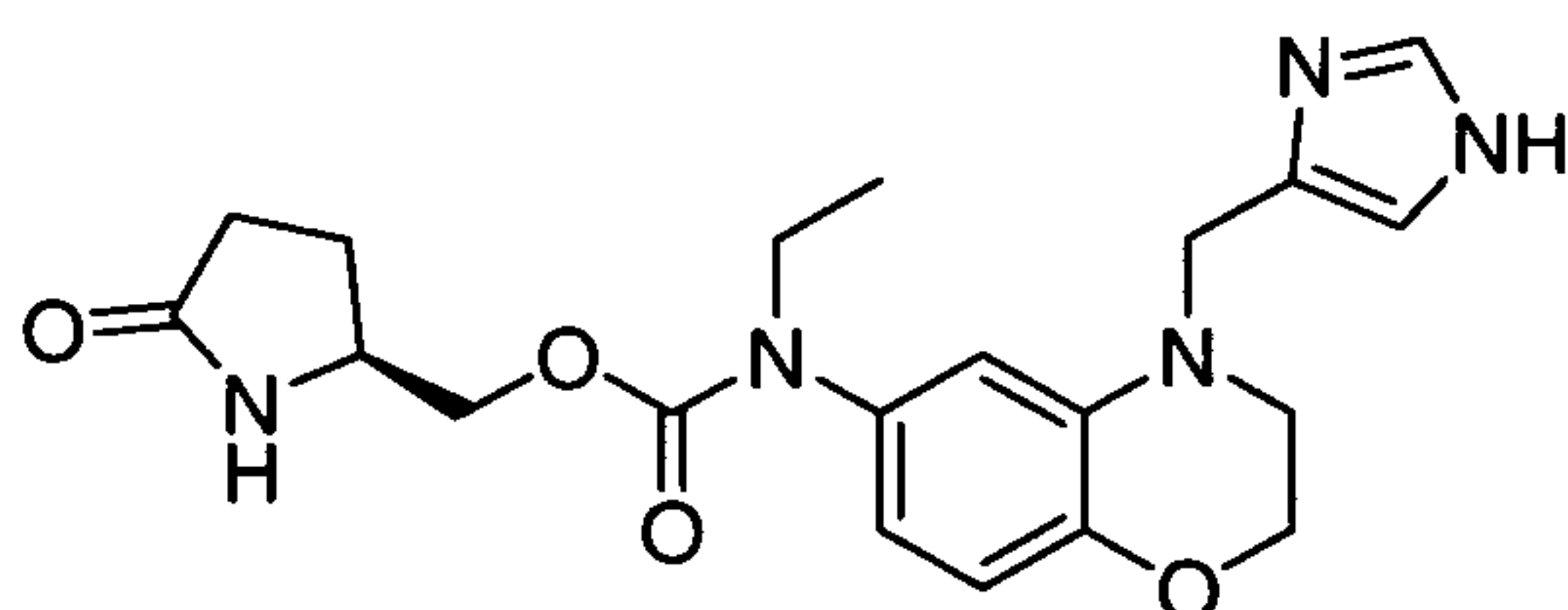
410

282



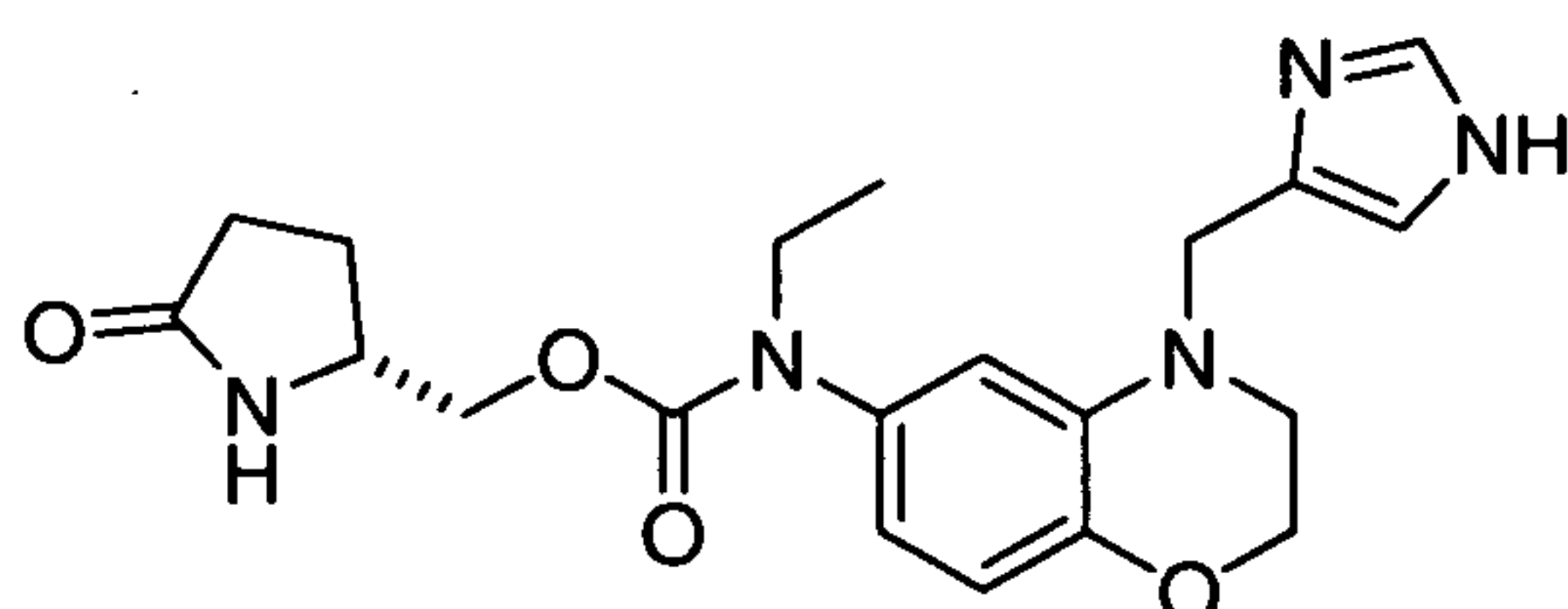
400

283



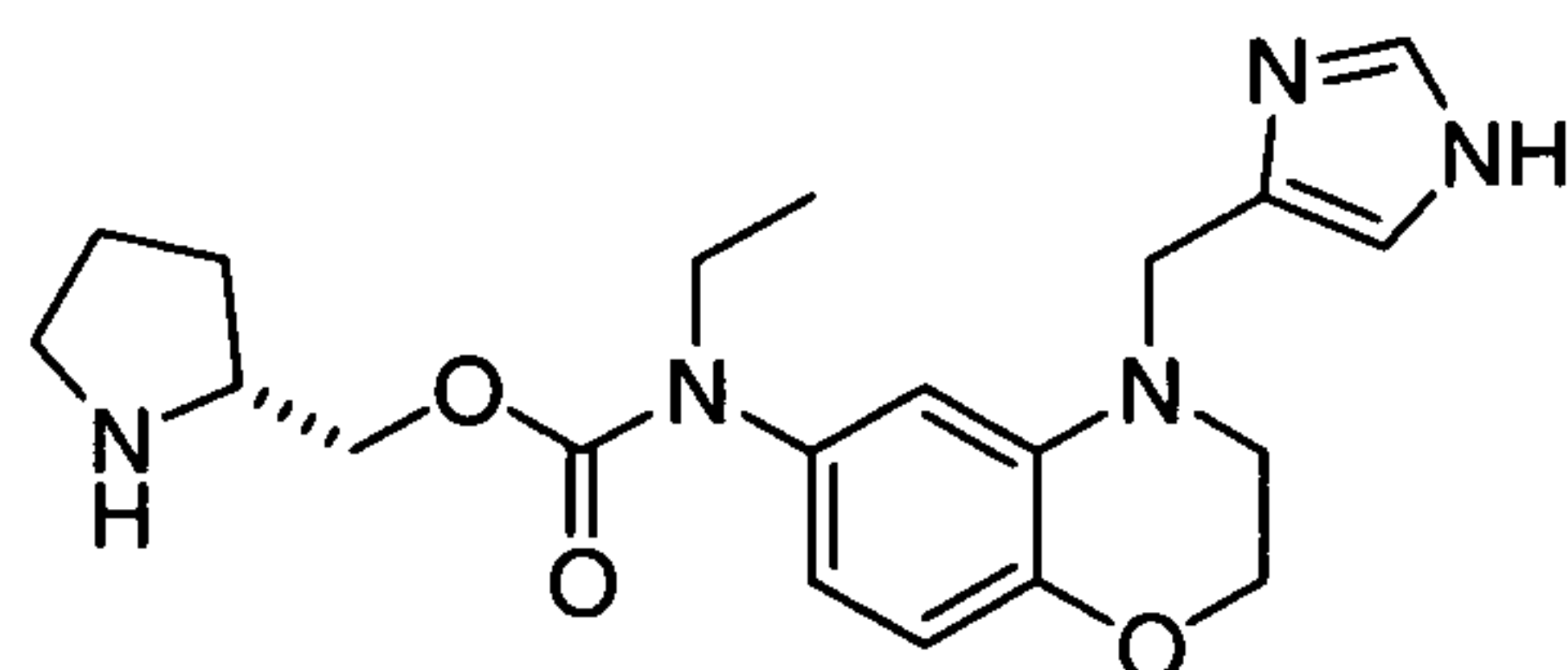
400

284



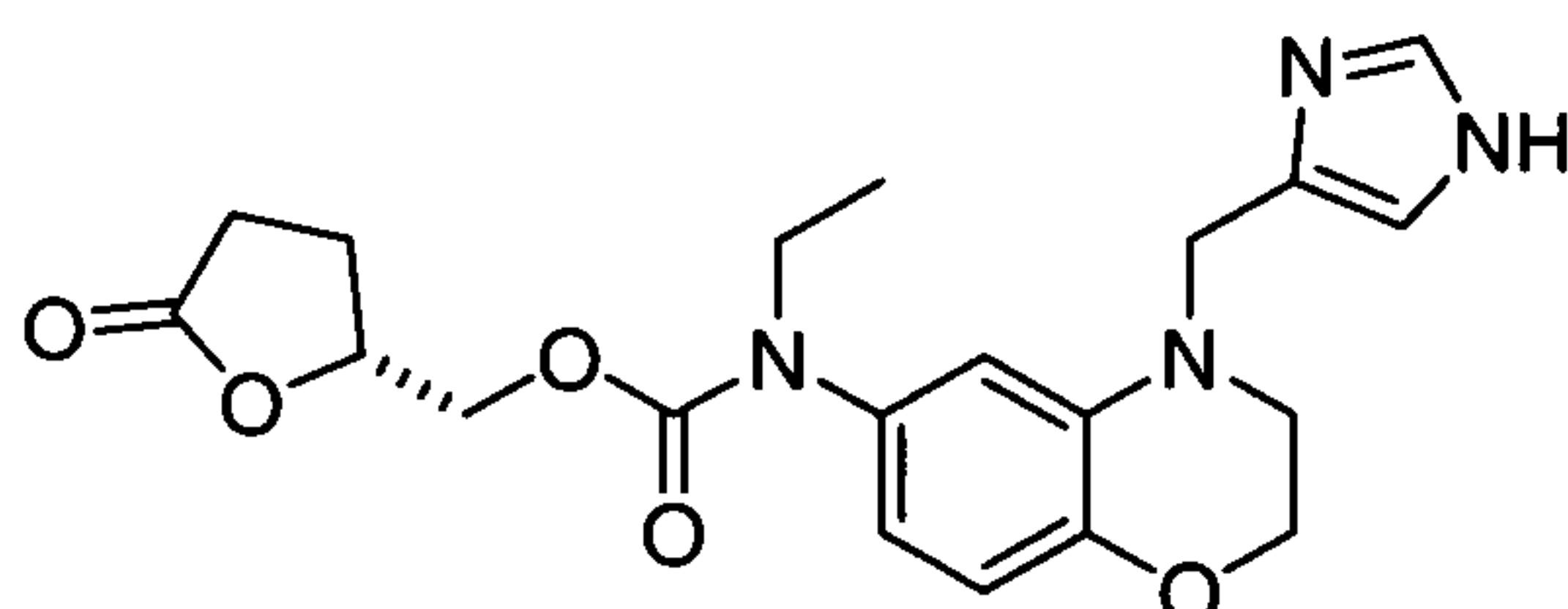
400

285



386

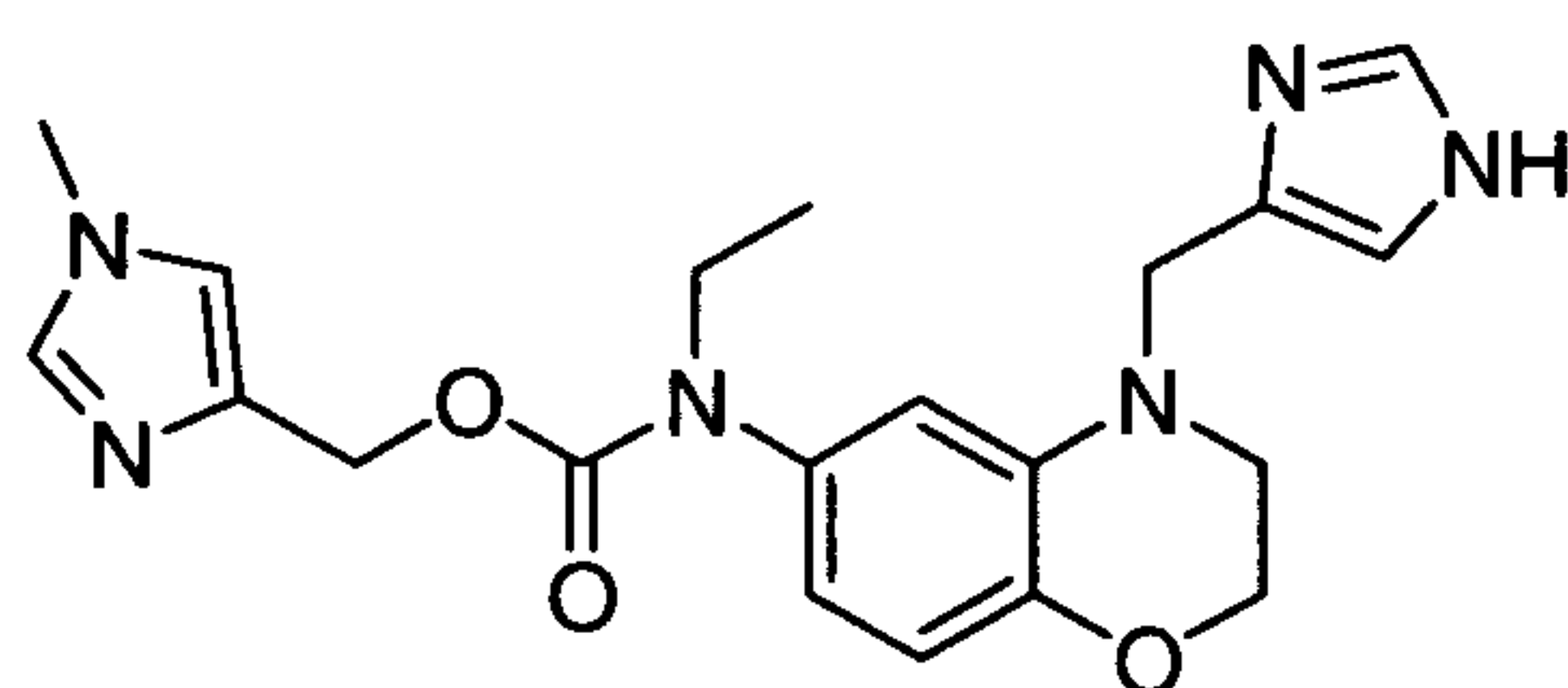
286



401

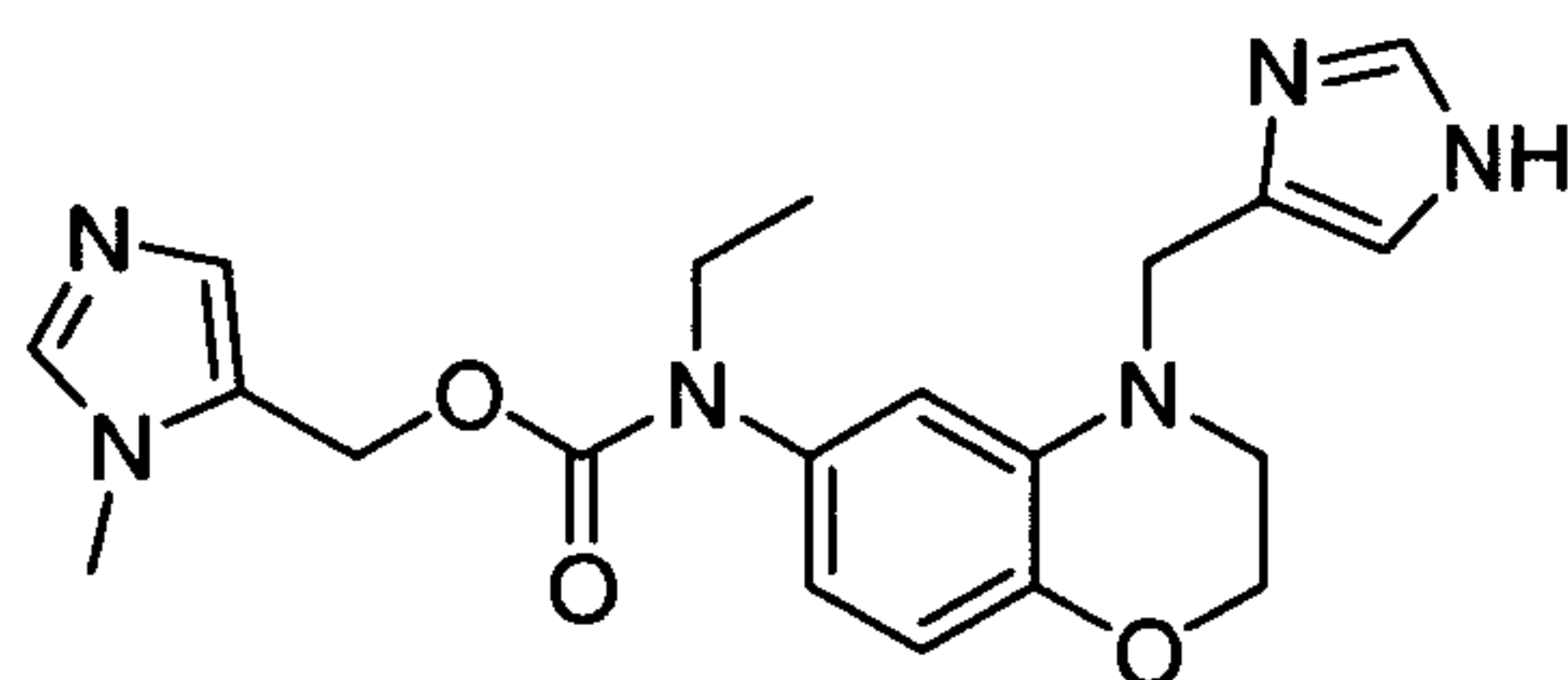
137

287



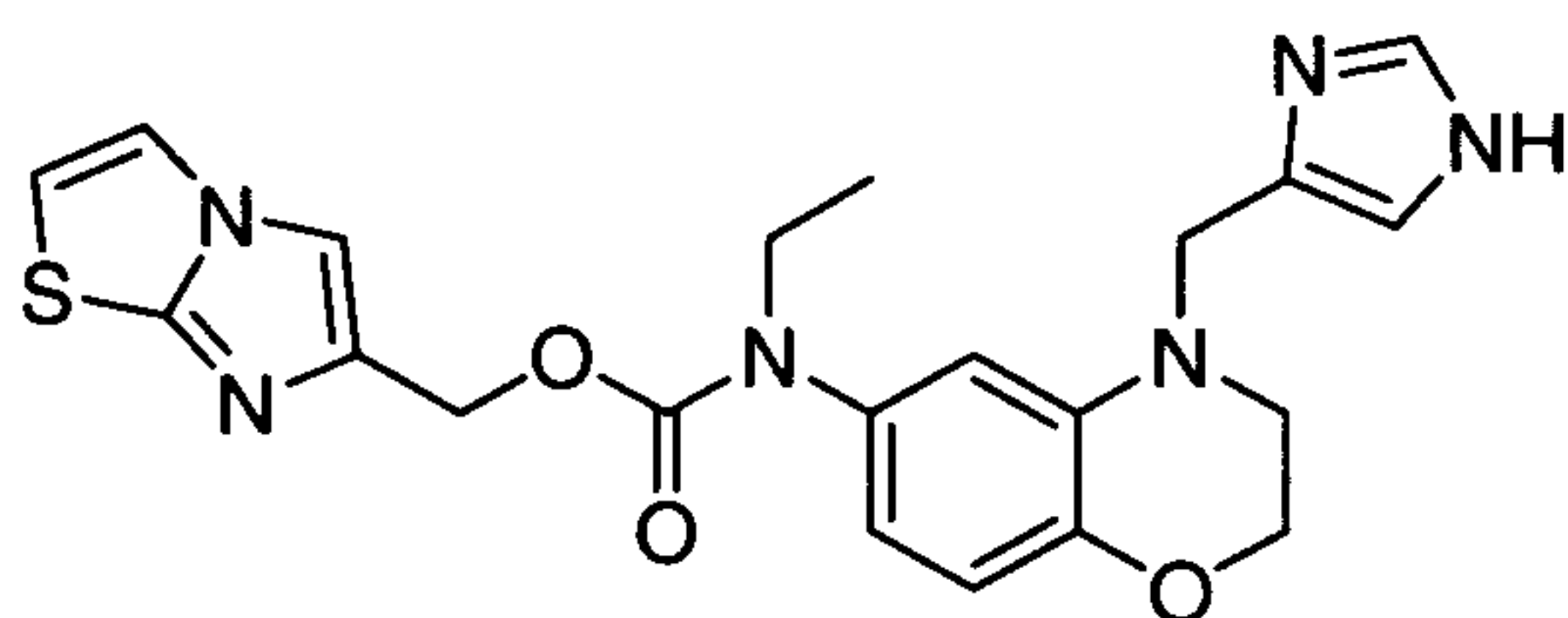
397

288



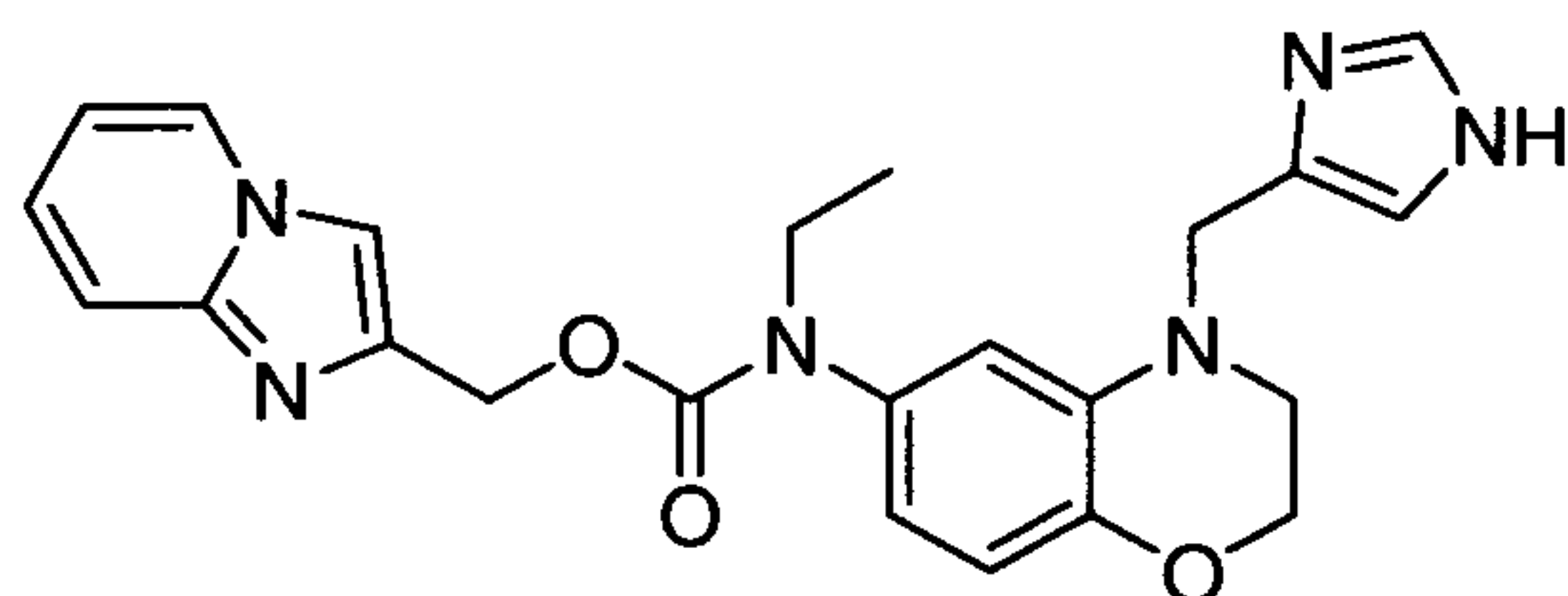
397

289



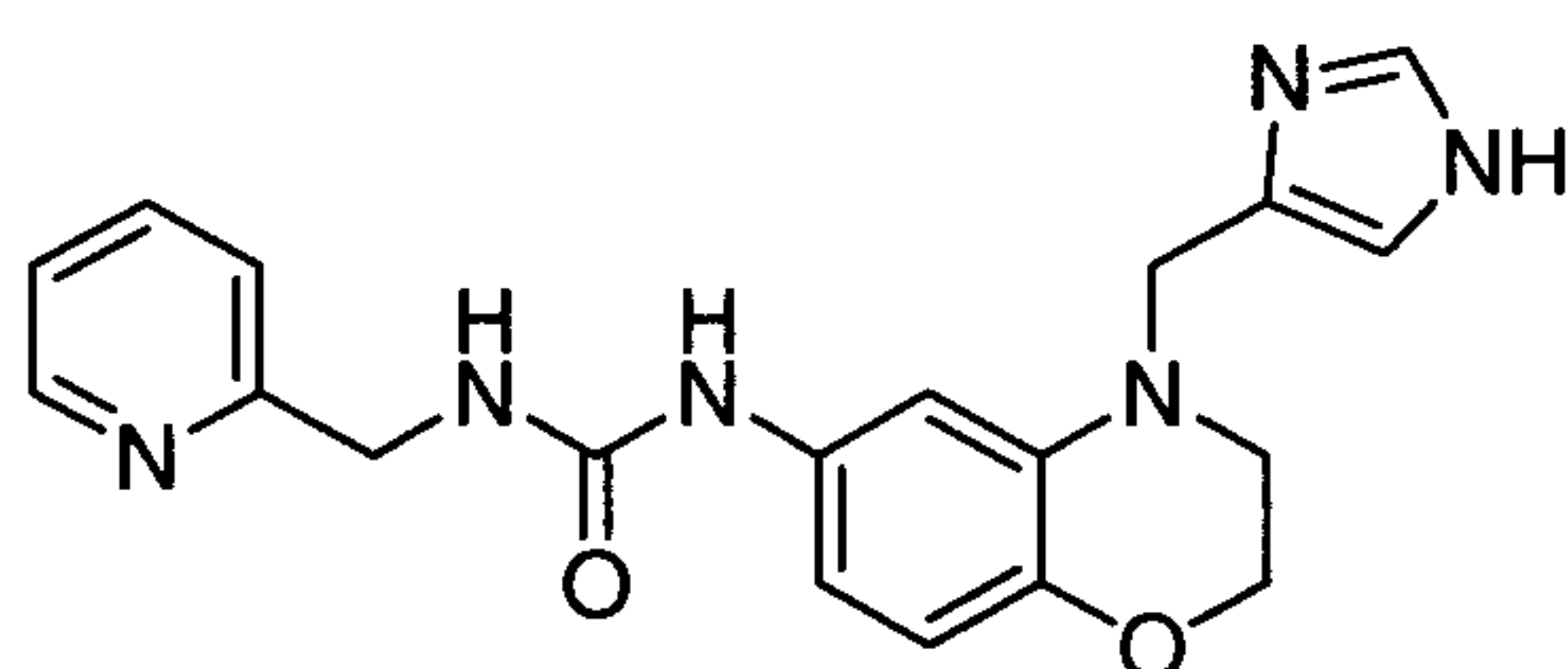
439

290



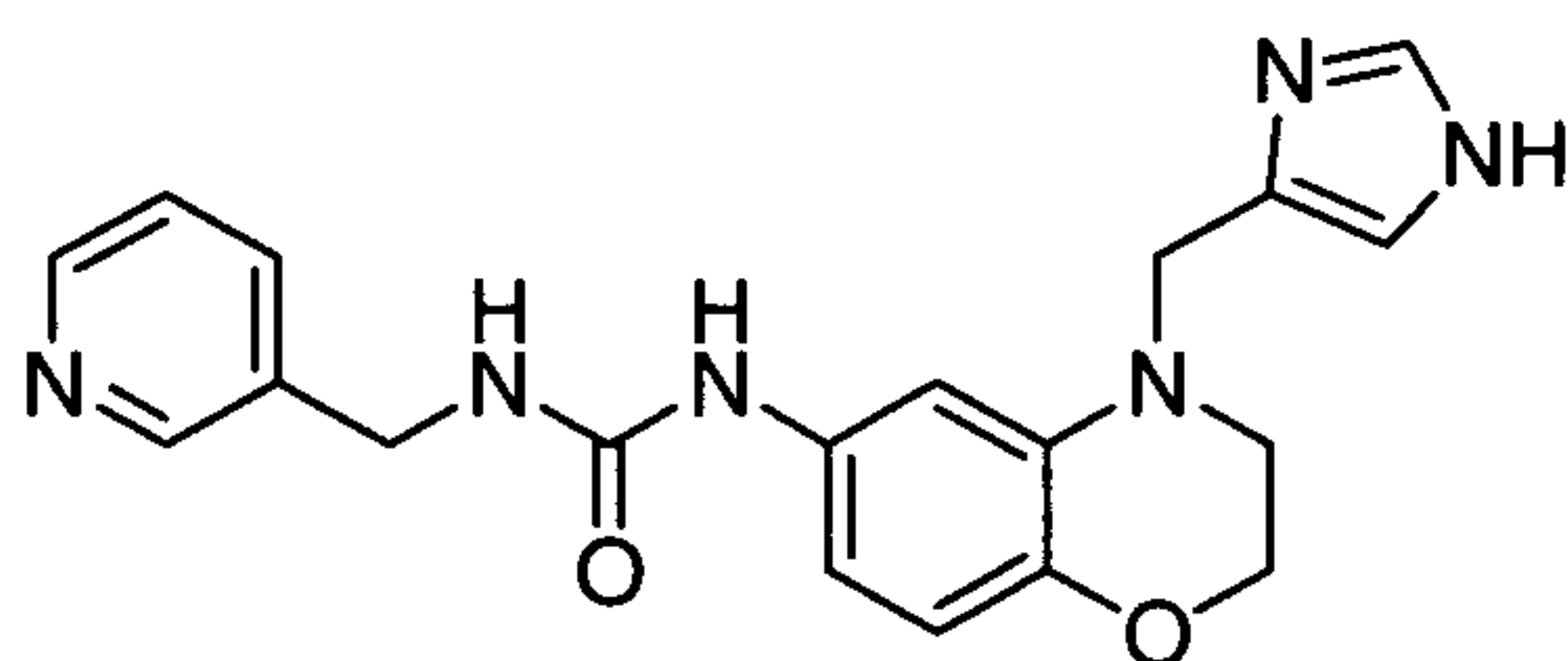
433

291



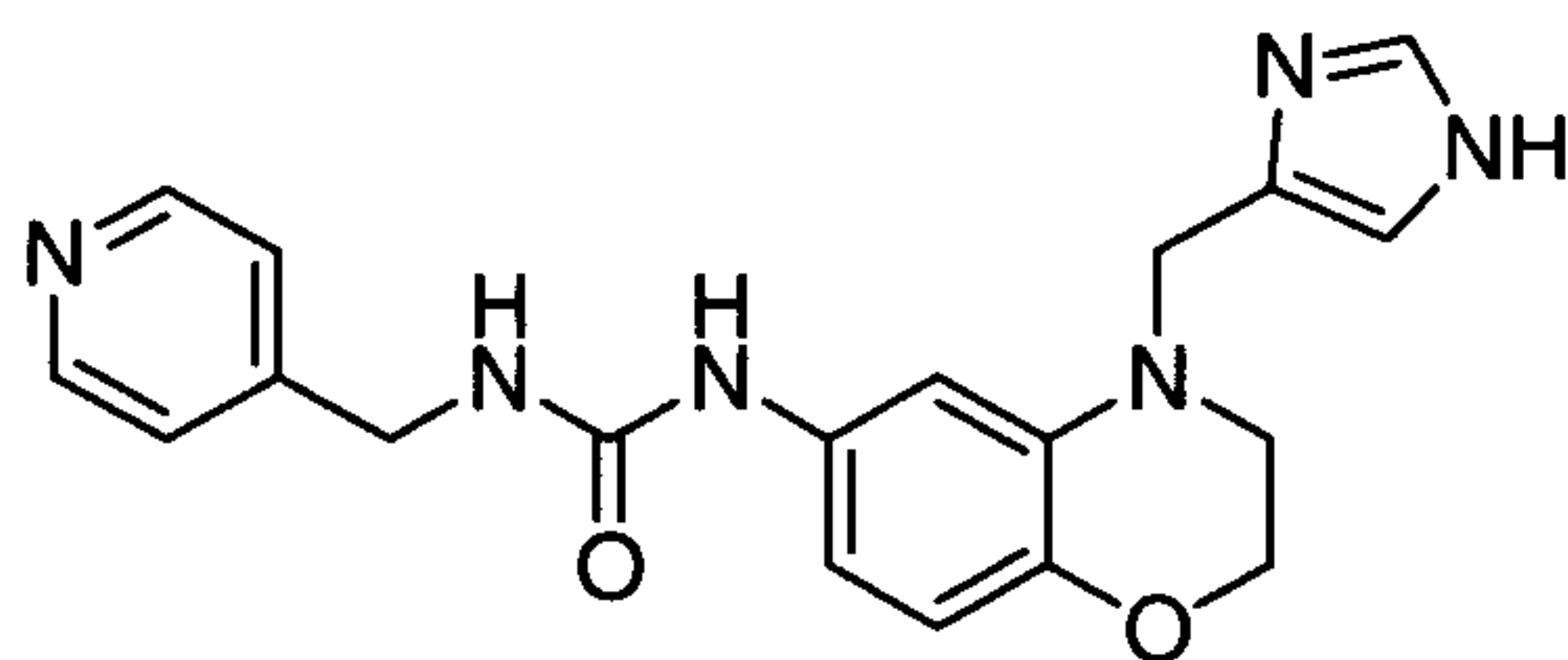
365

292



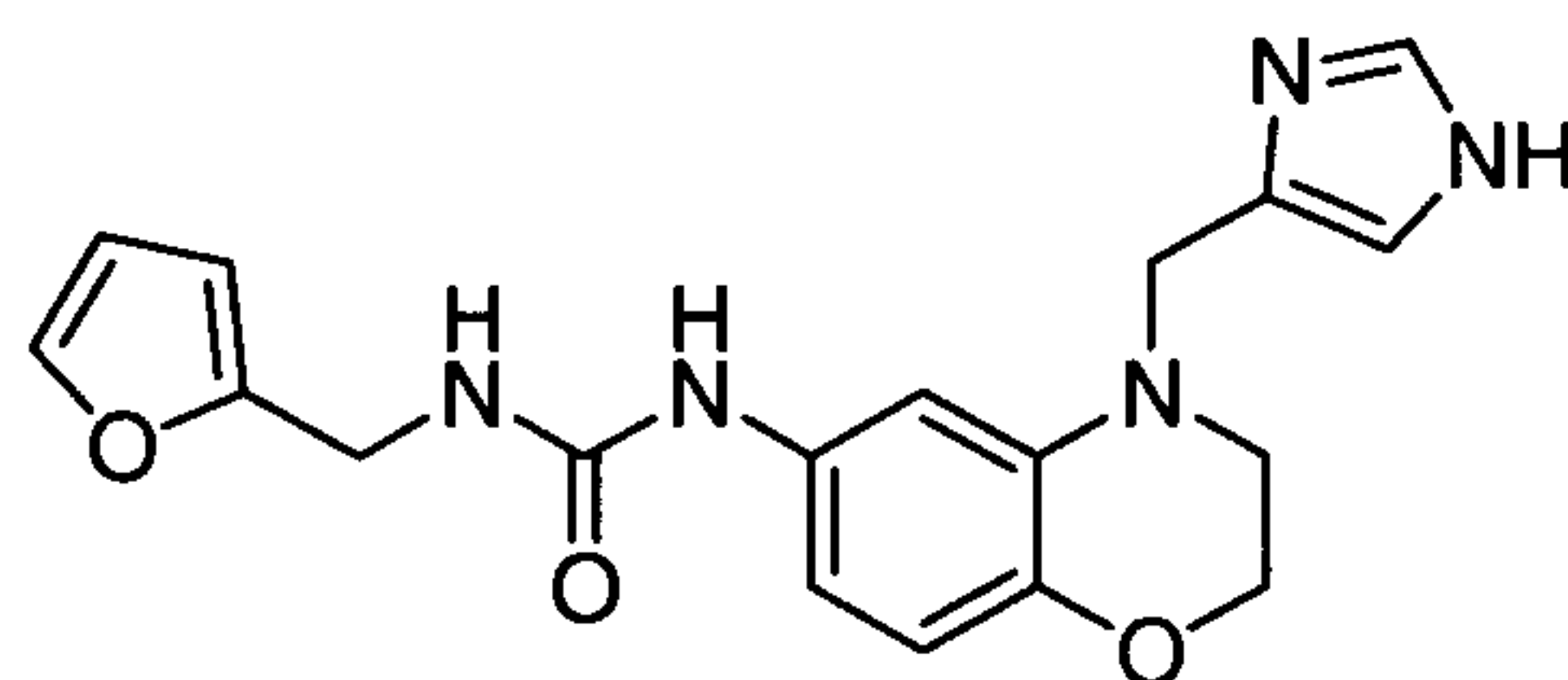
365

293



365

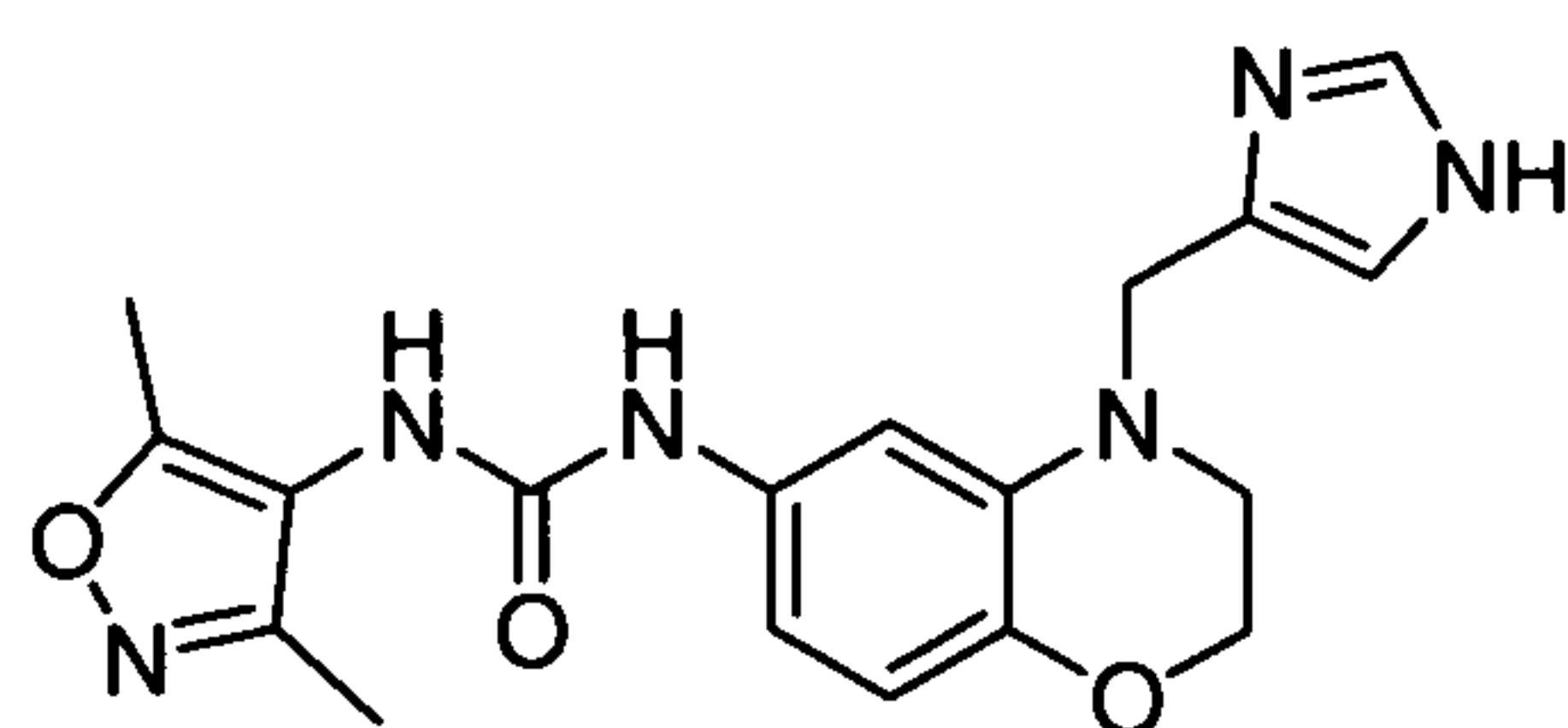
294



354

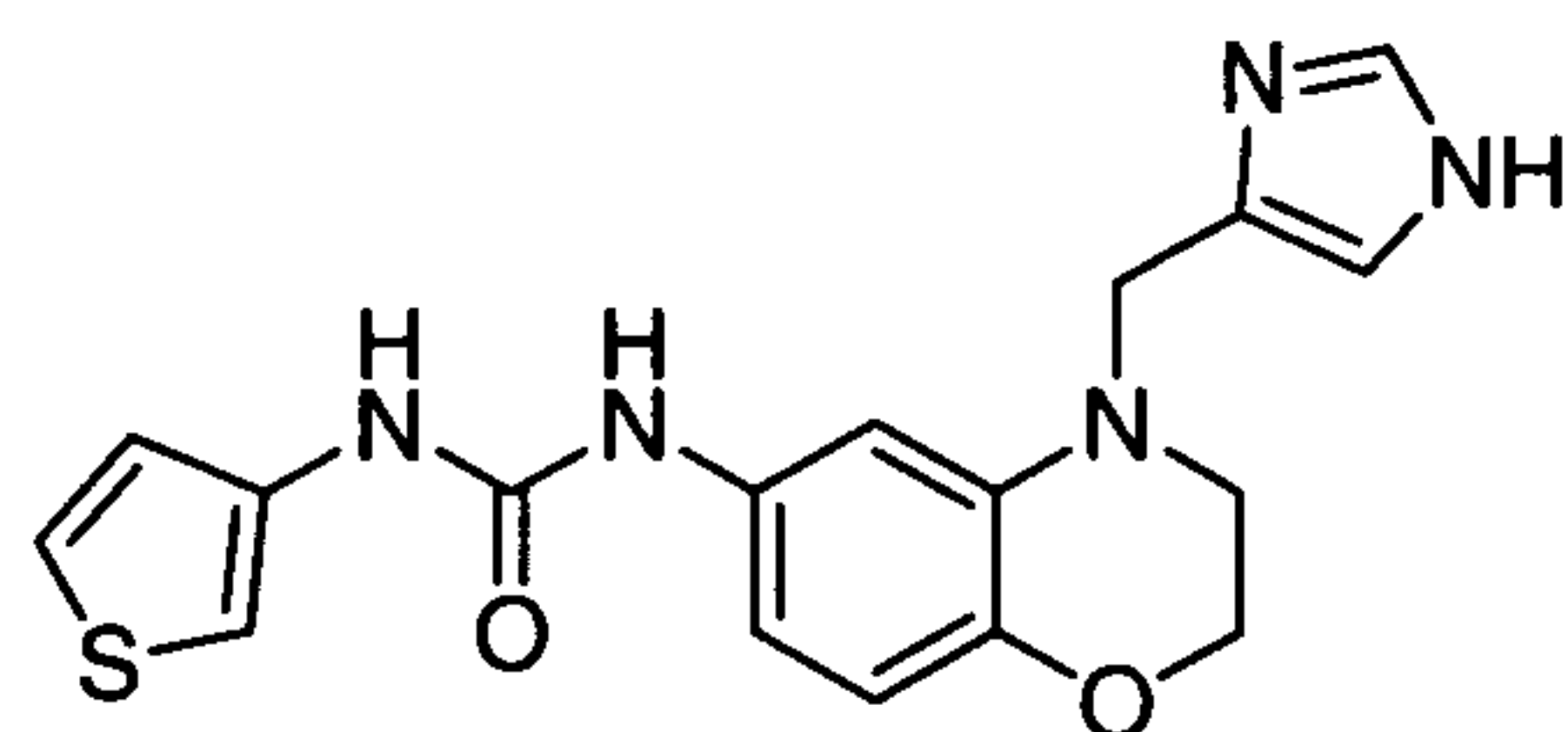
138

295



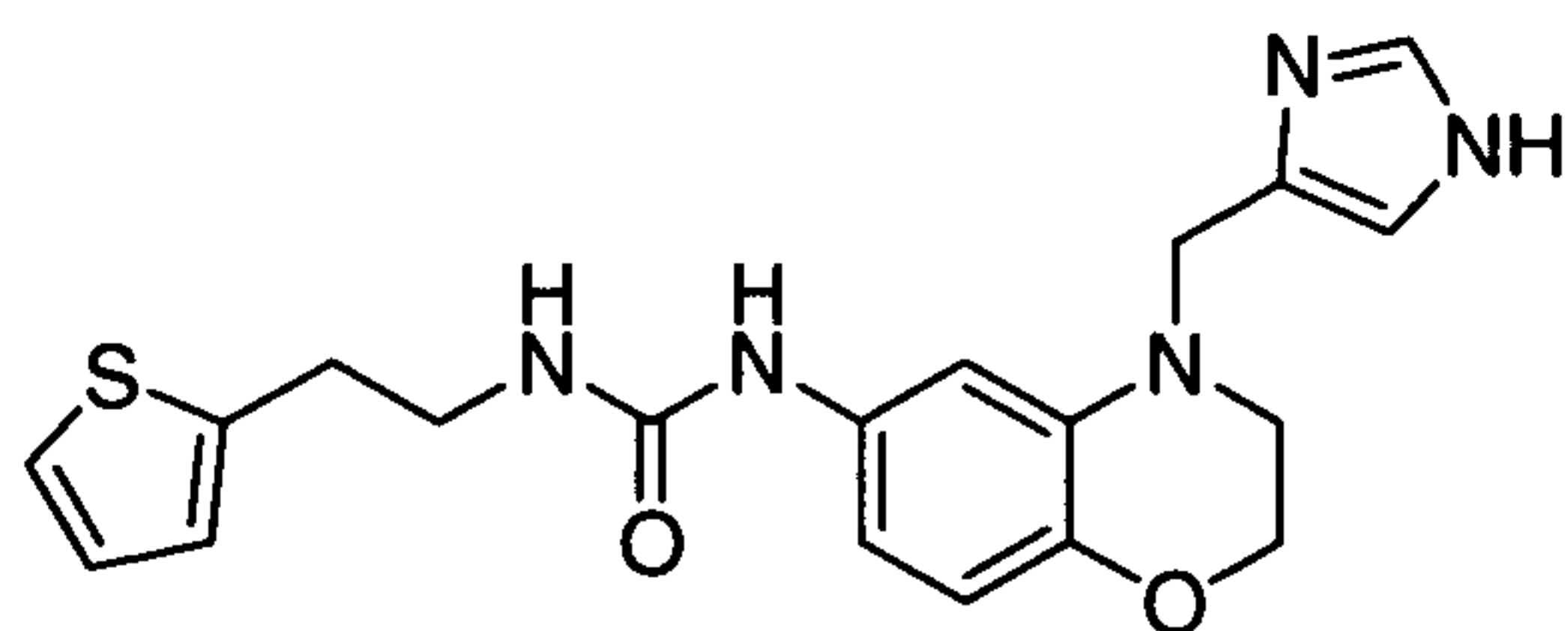
369

296



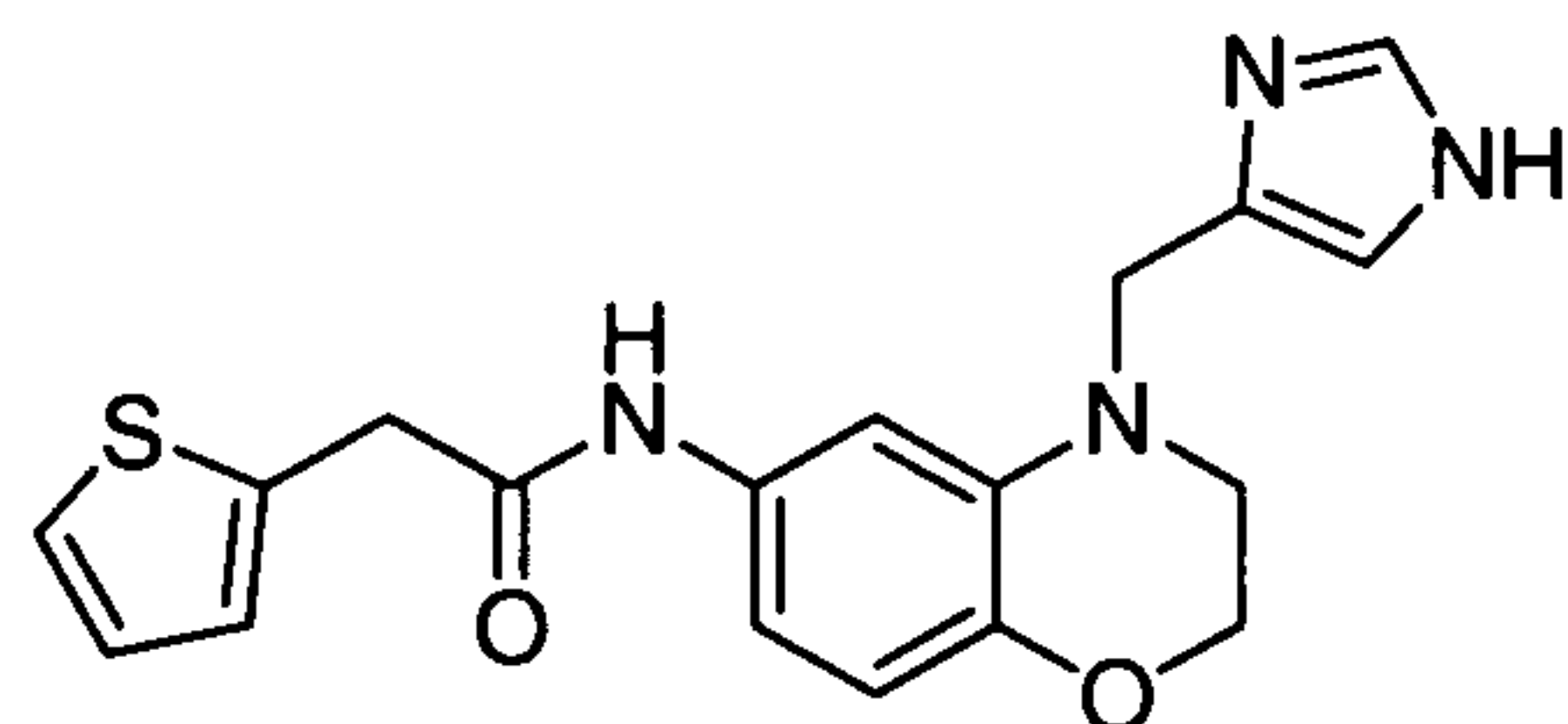
356

297



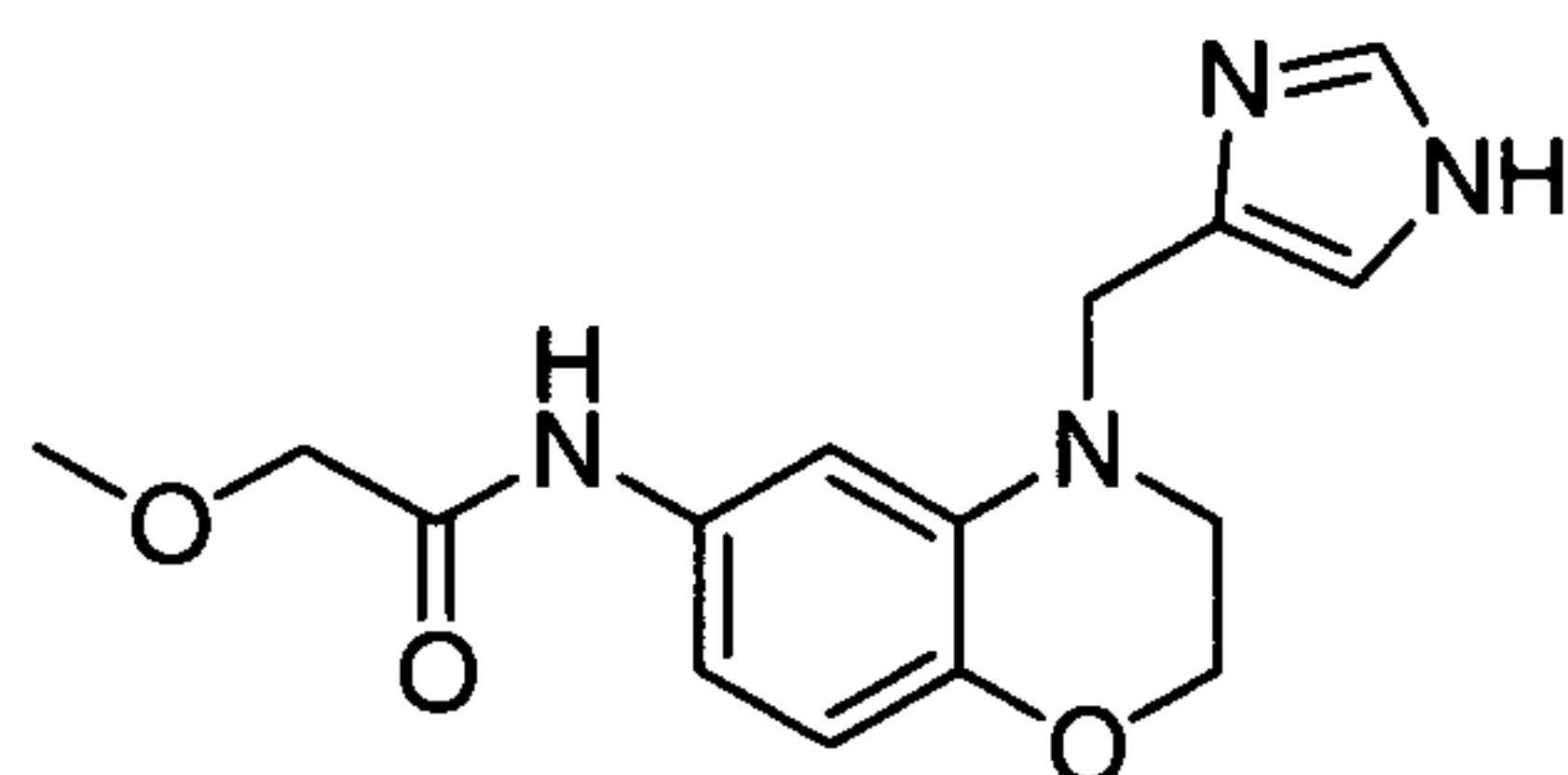
384

298



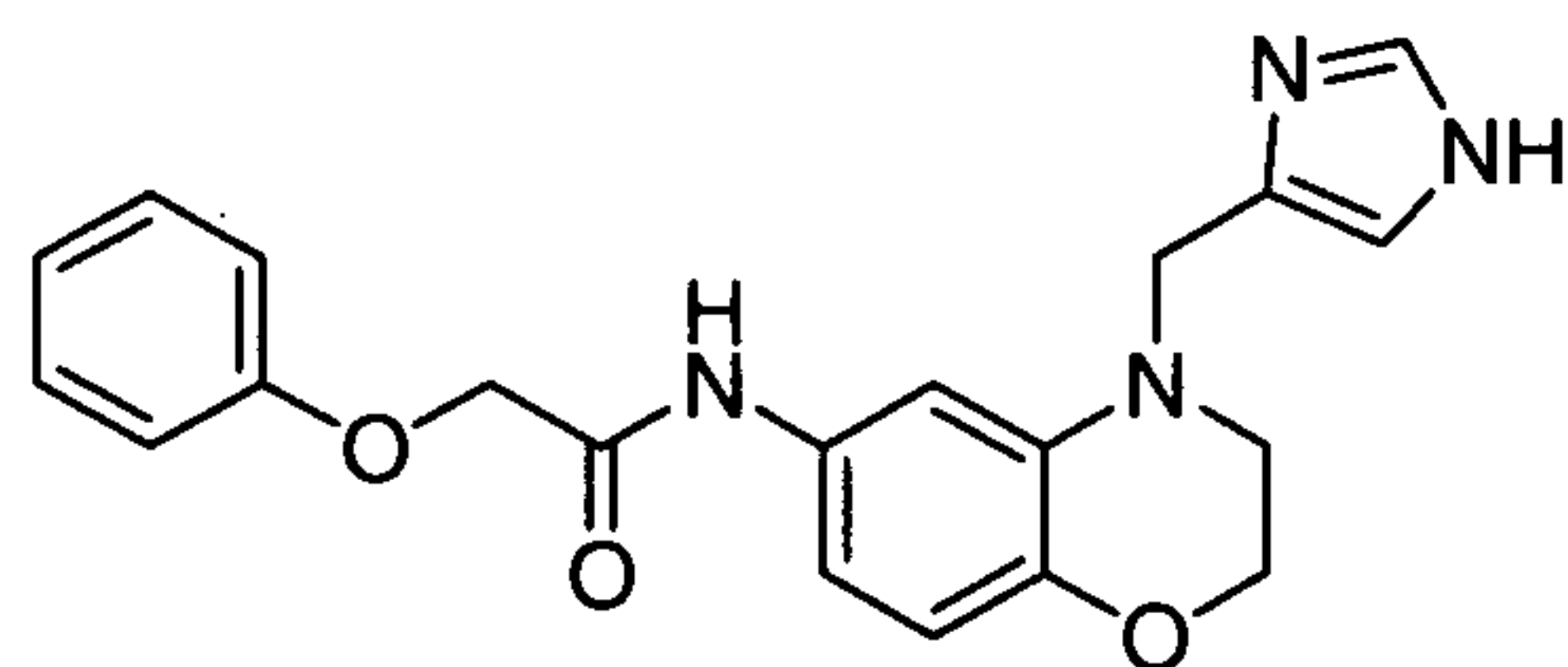
355

299



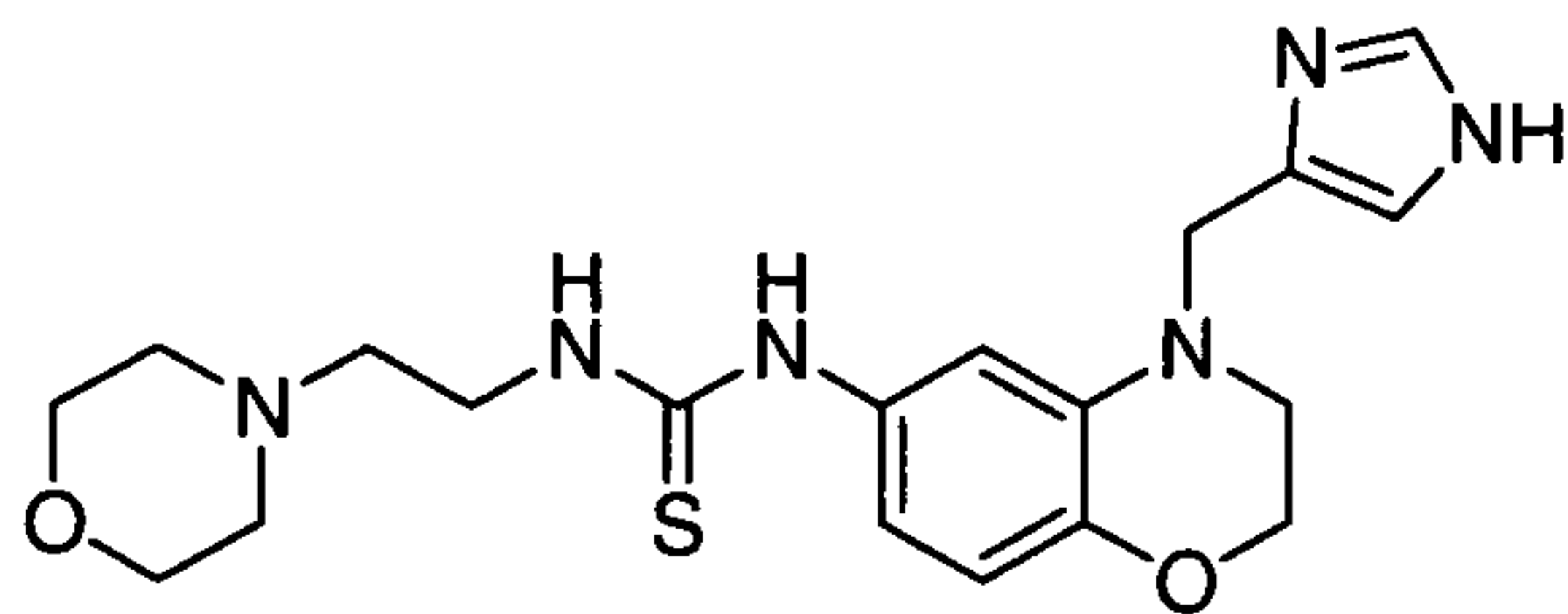
303

300



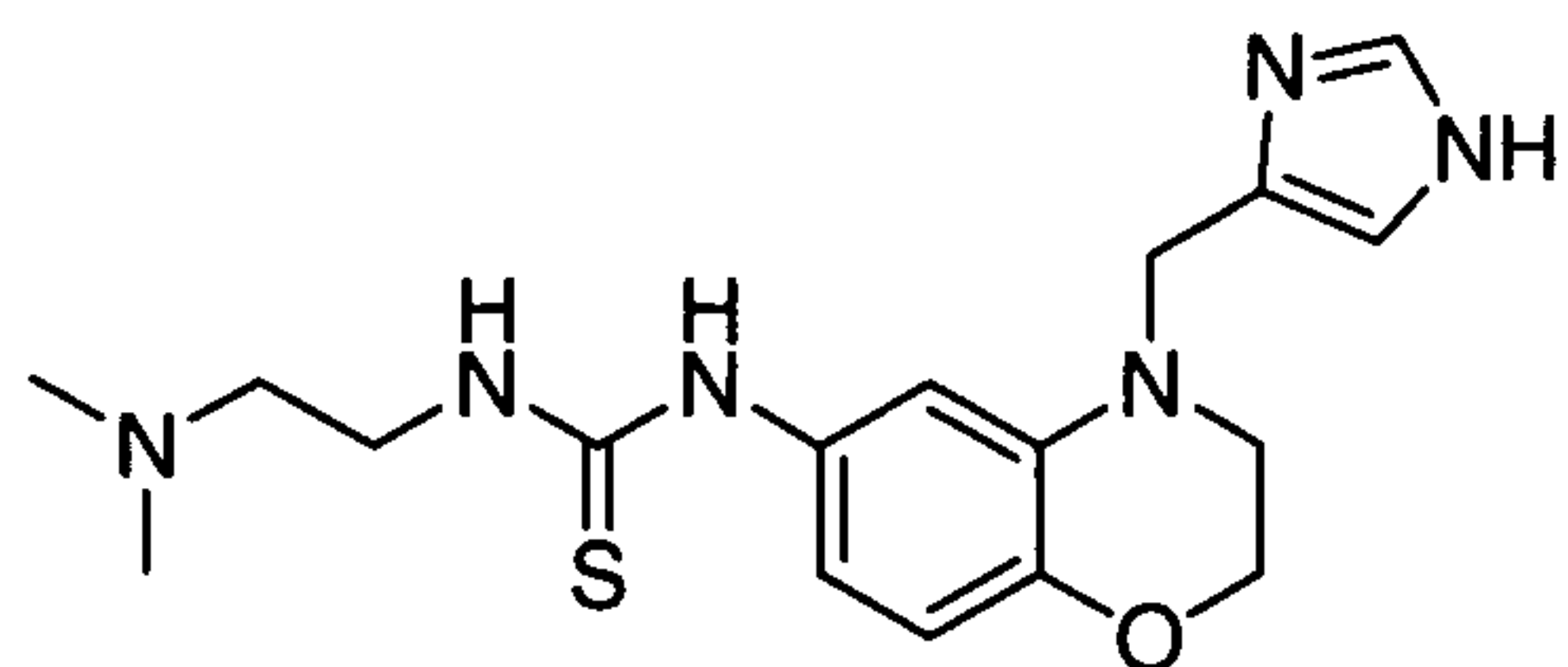
365

301



403

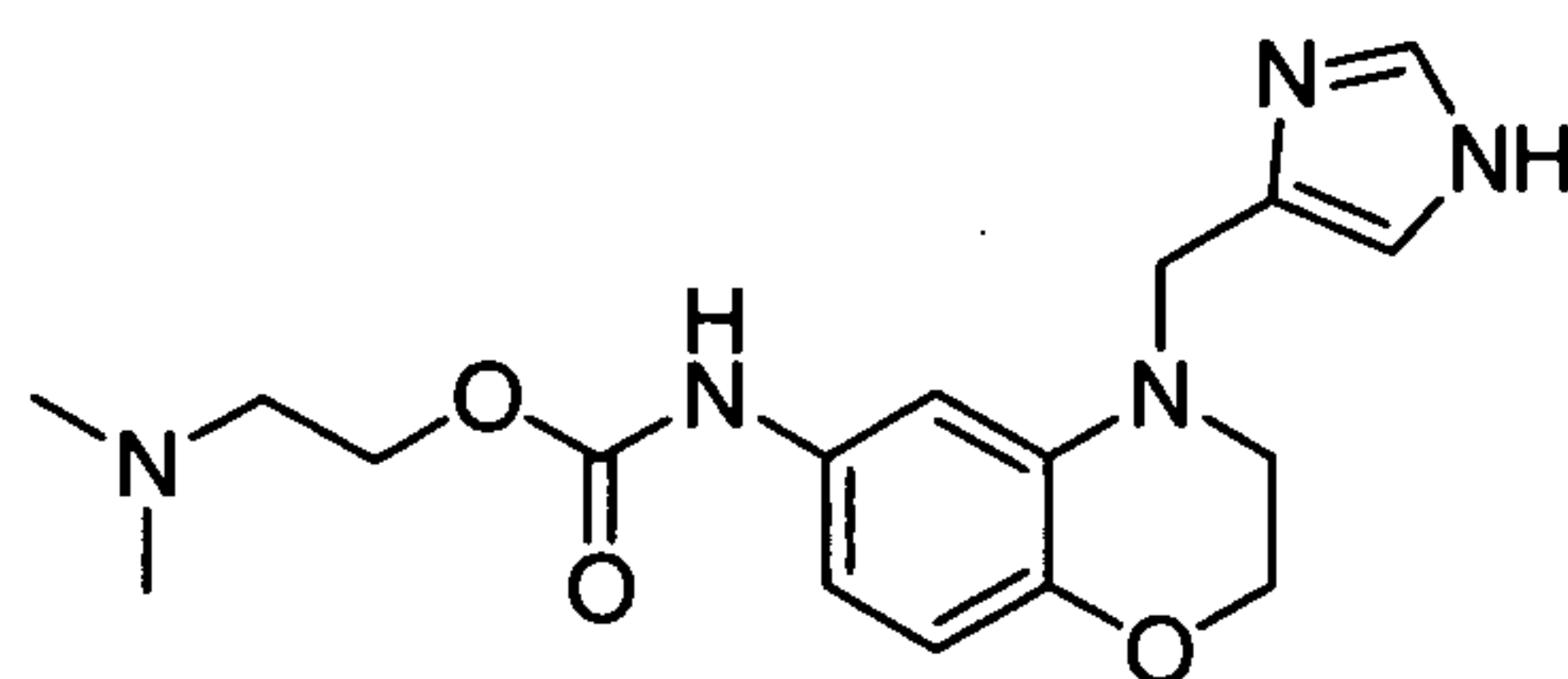
302



361

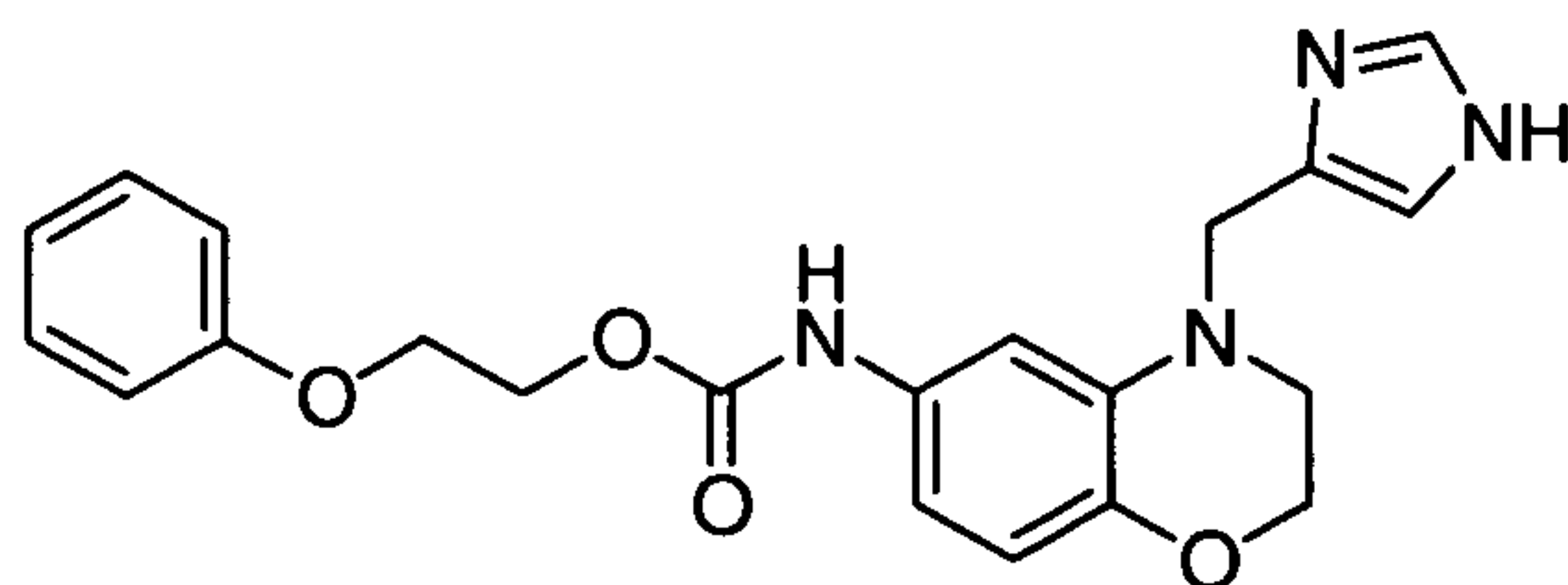
139

303



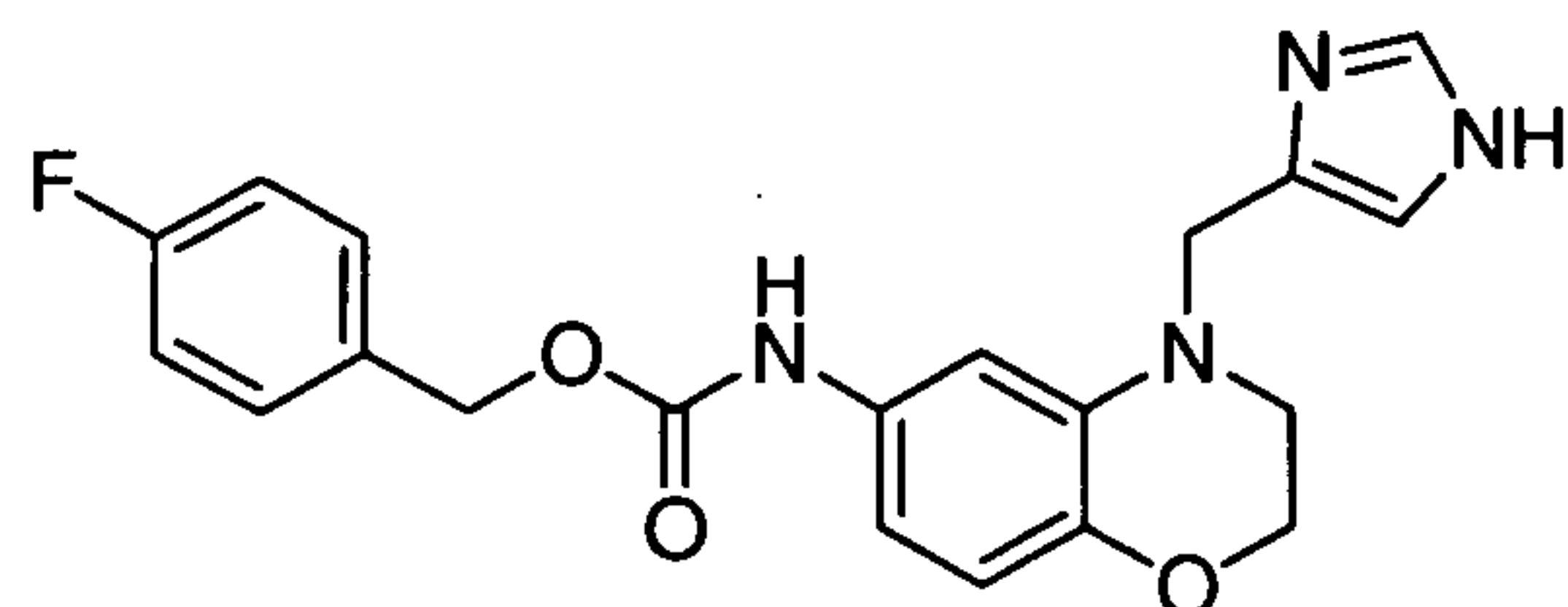
346

304



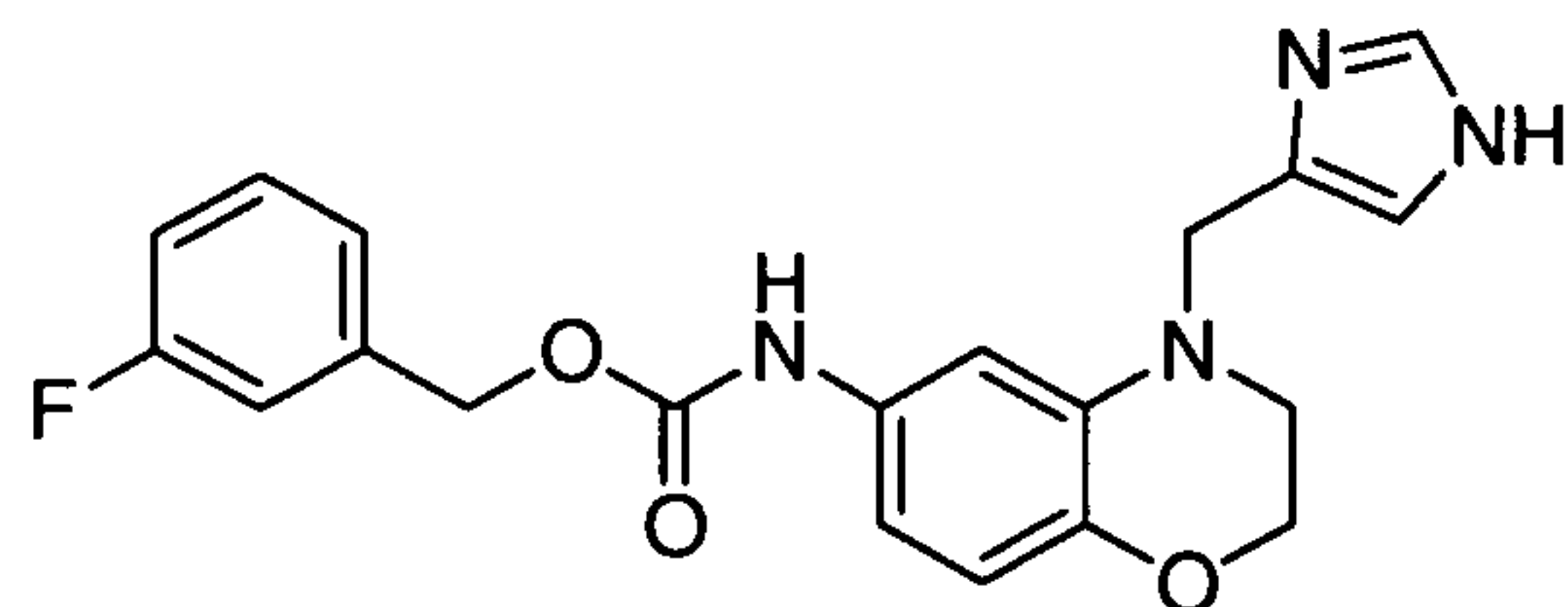
395

305



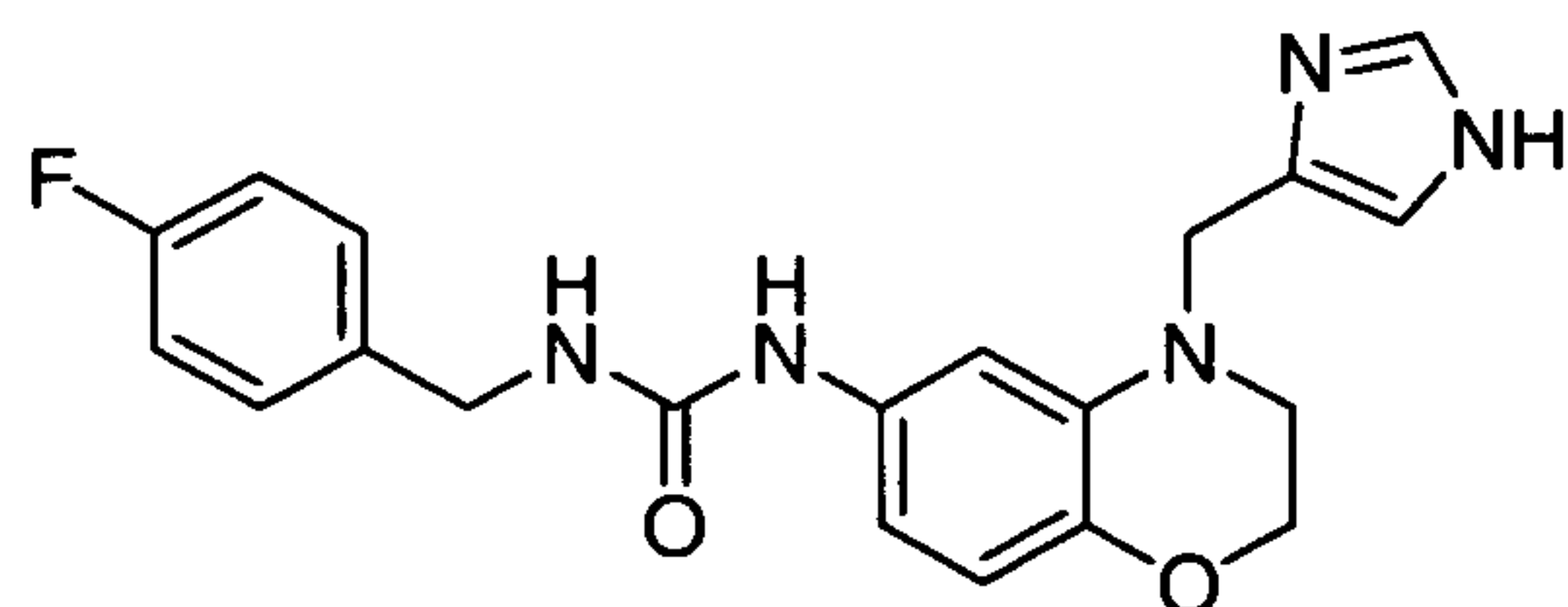
383

306



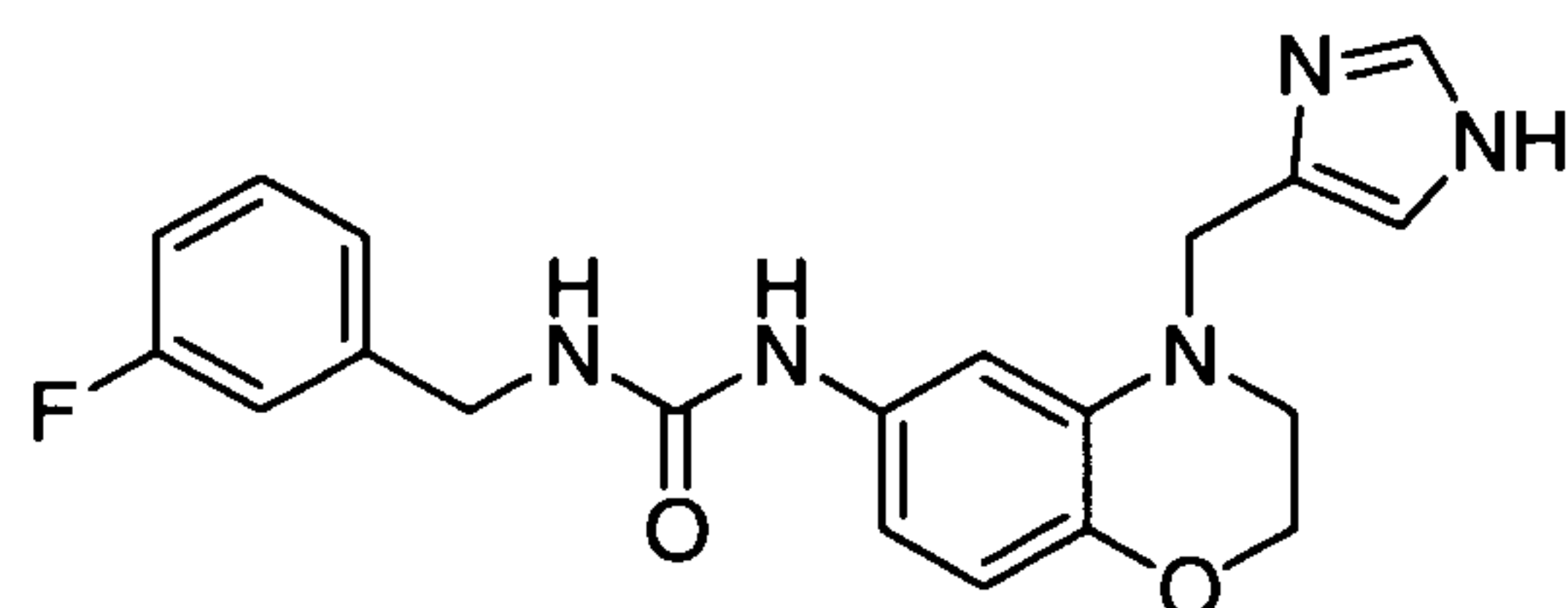
383

307



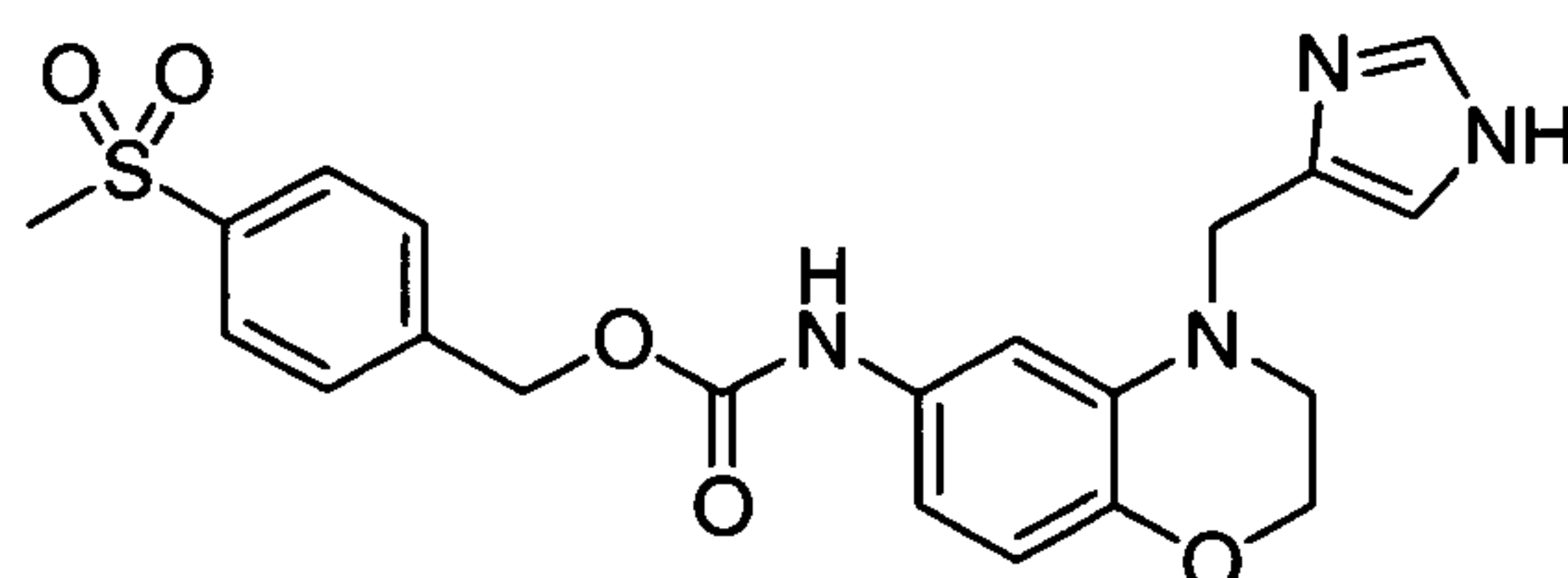
382

308



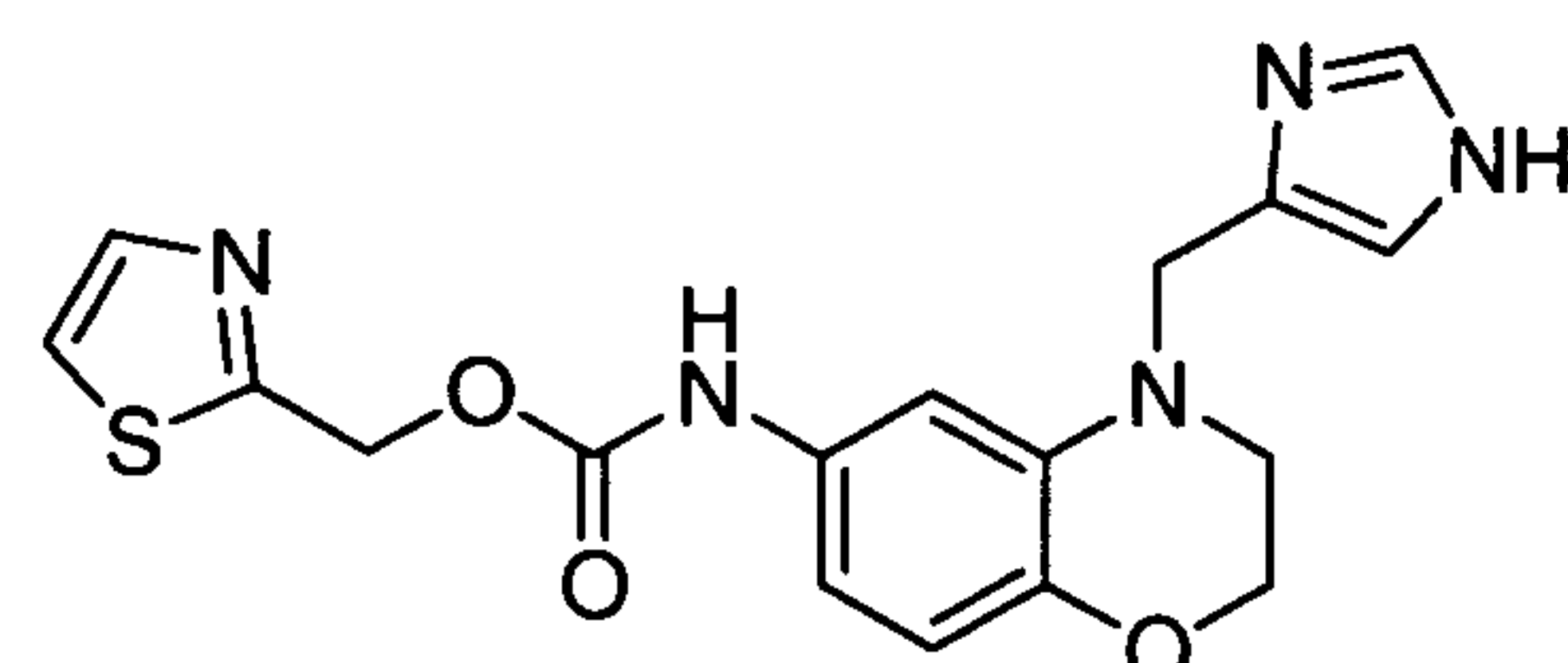
382

309



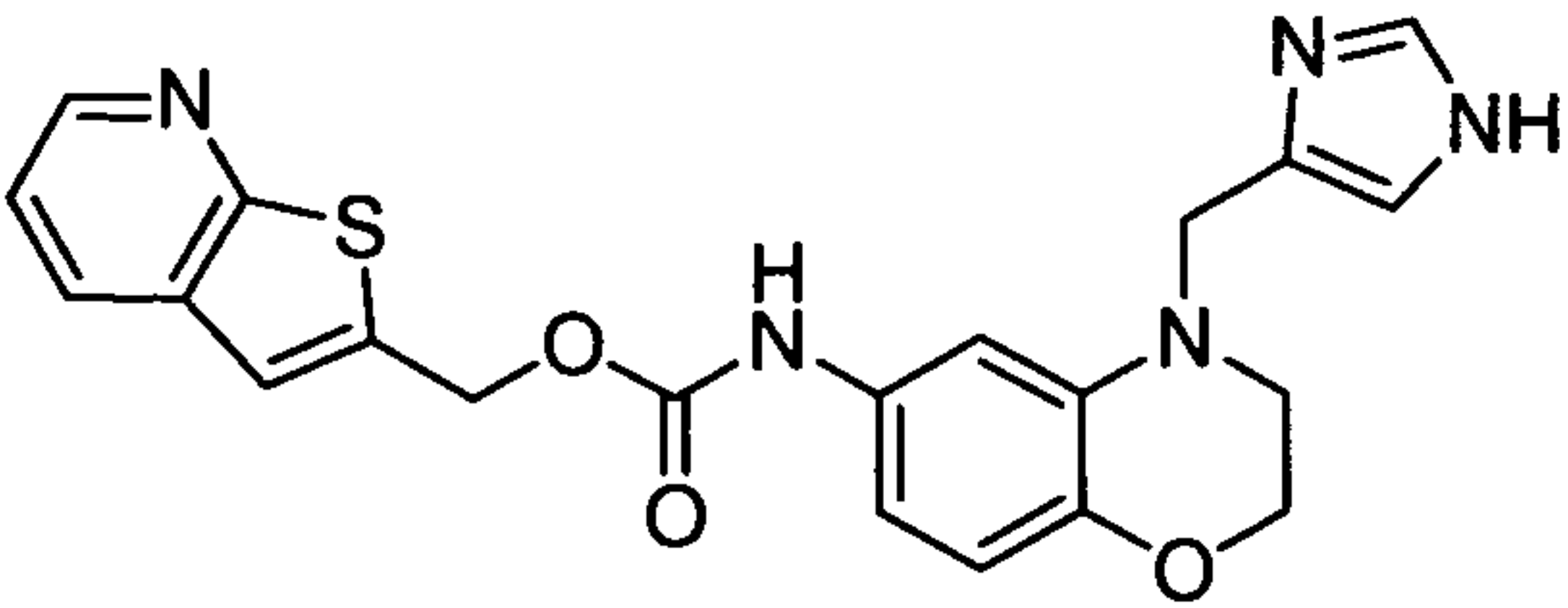
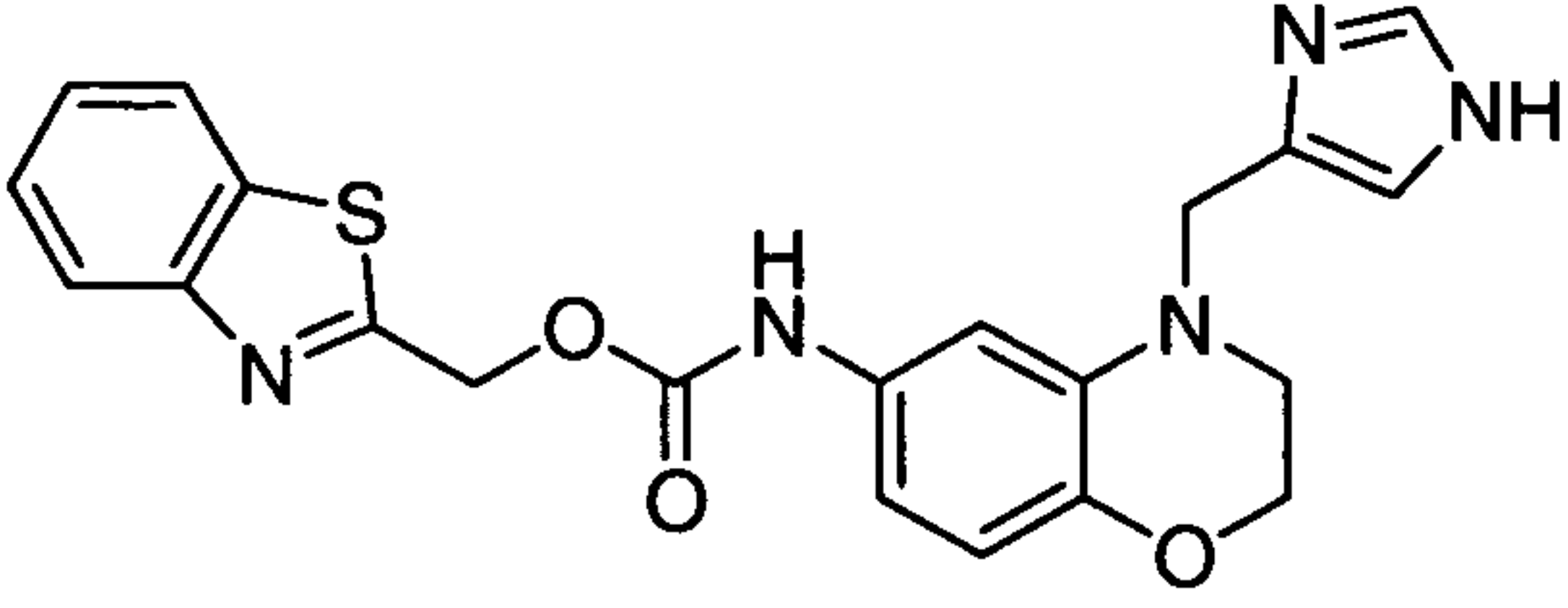
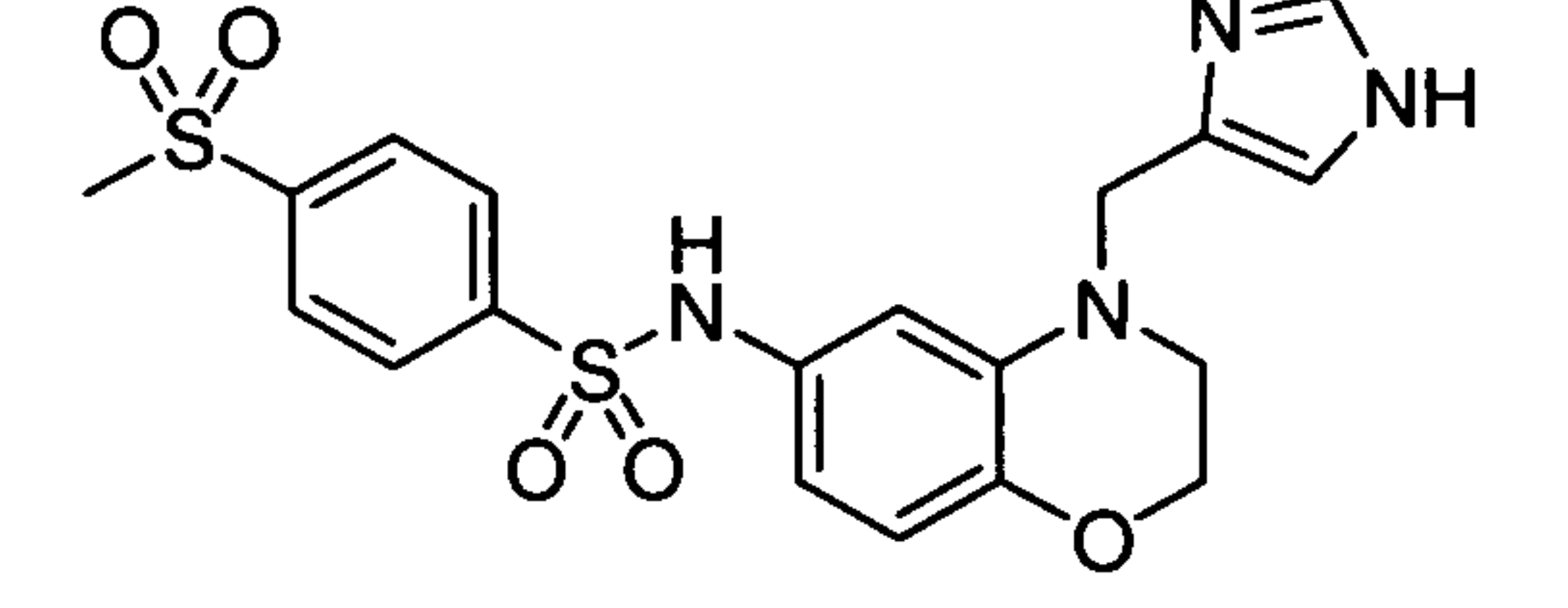
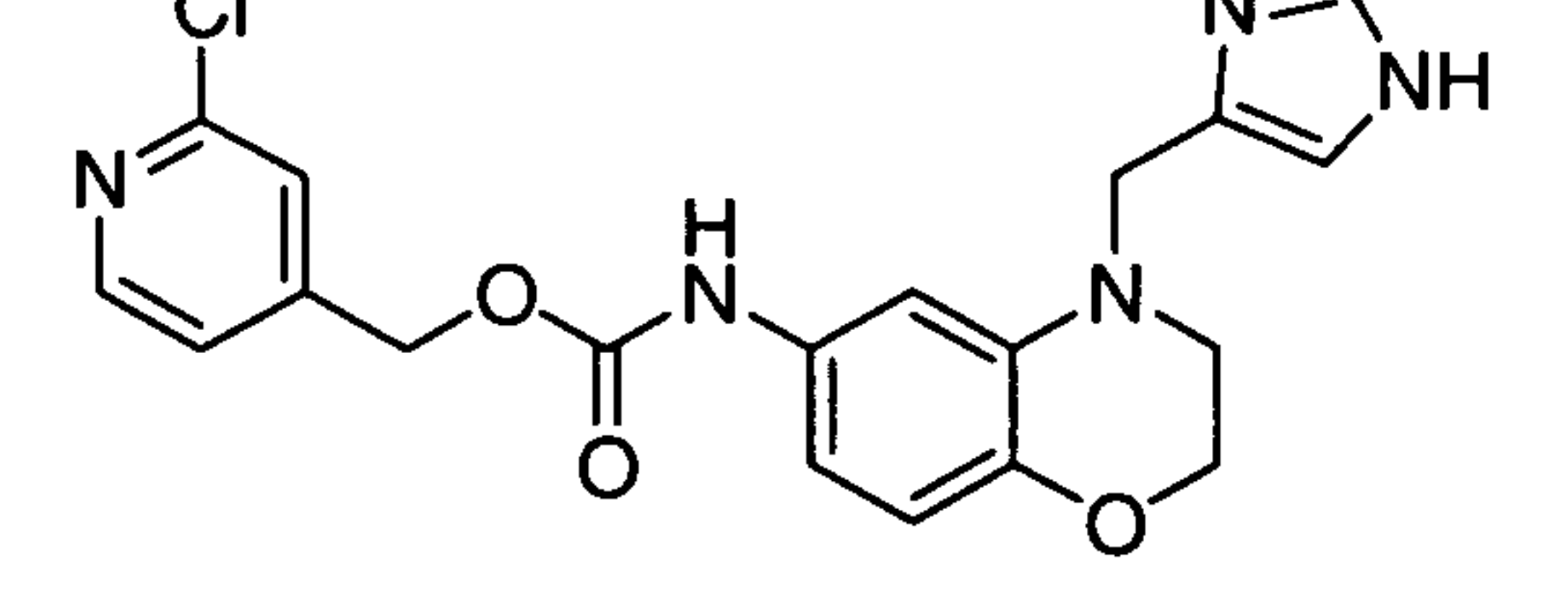
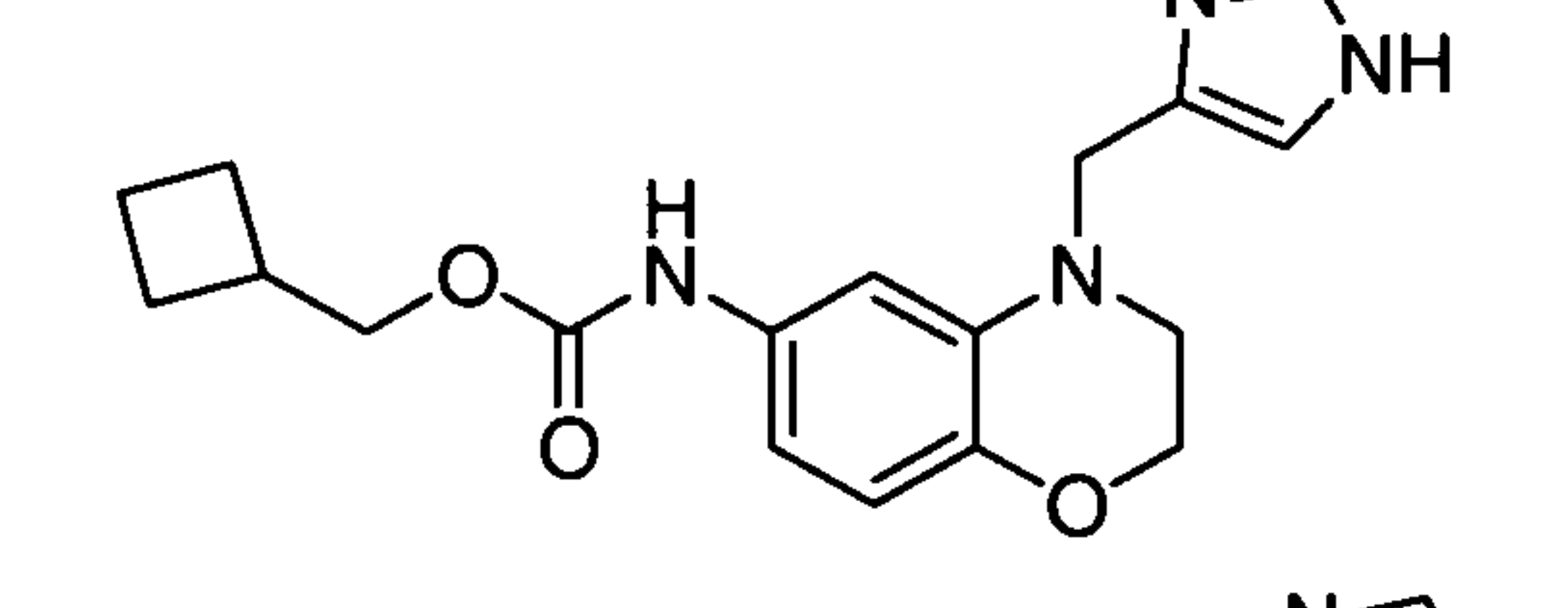
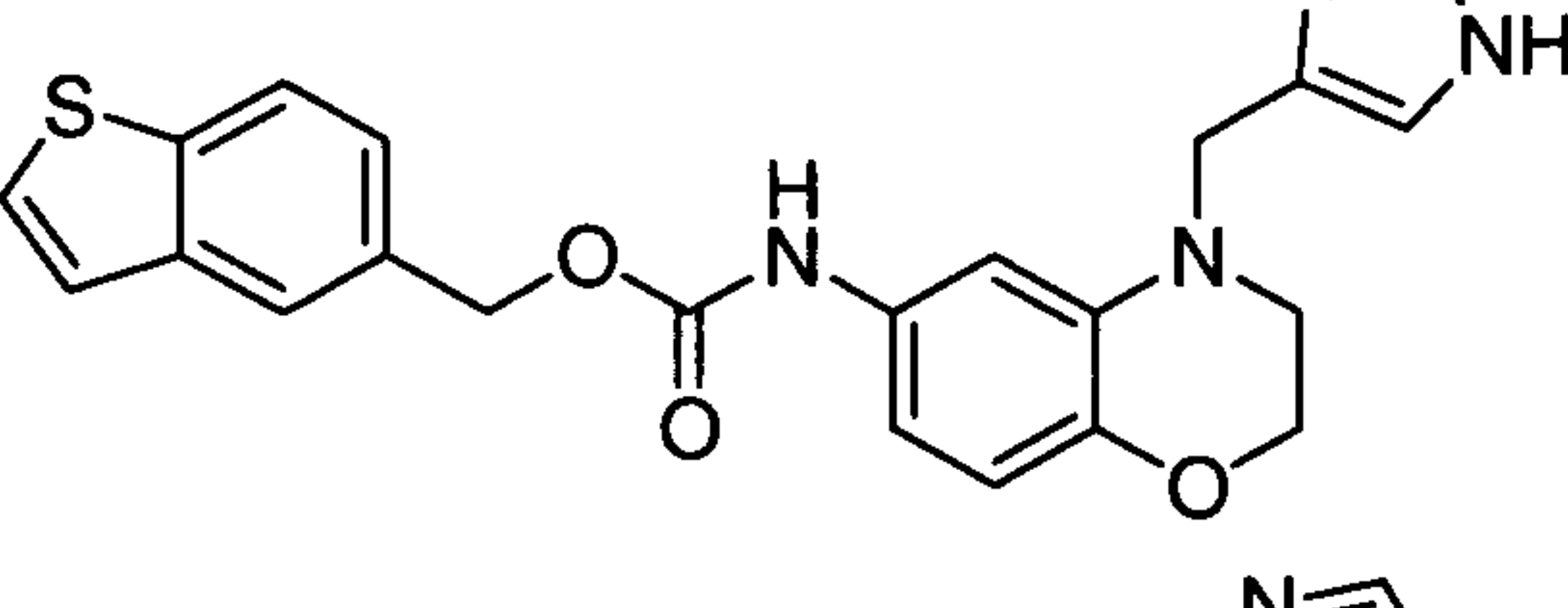
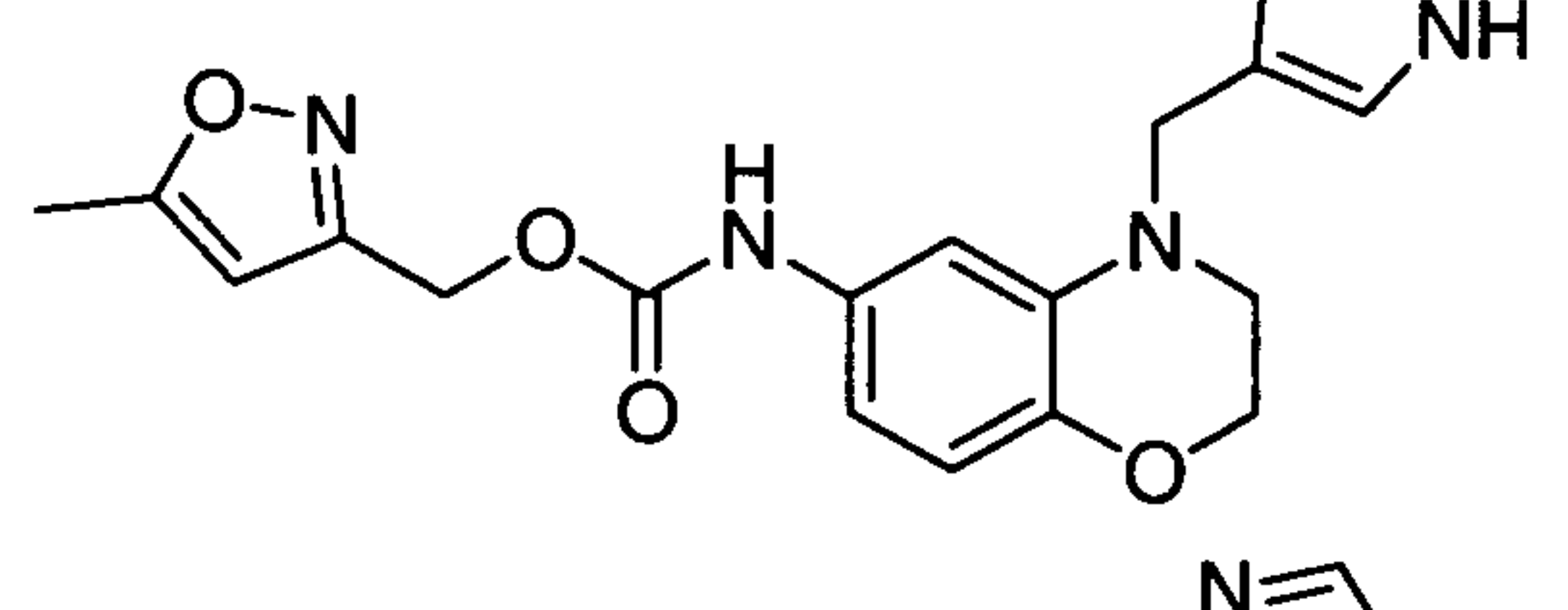
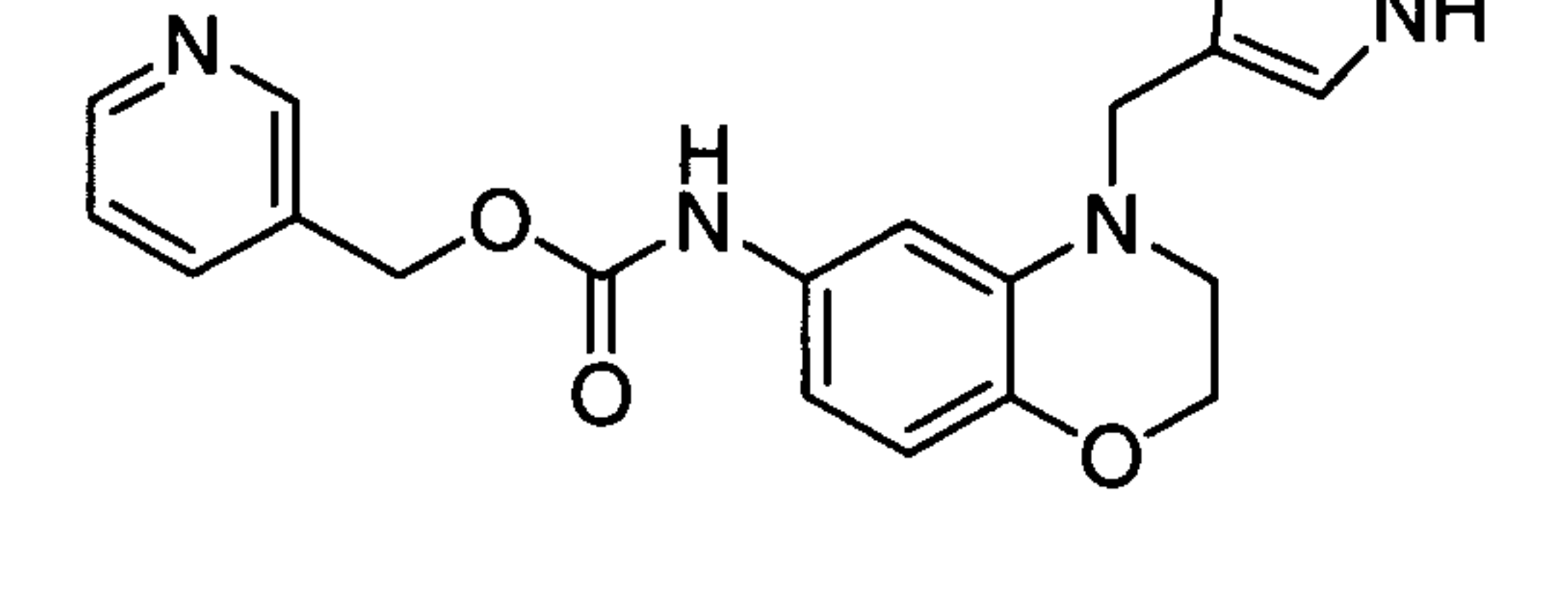
443

310



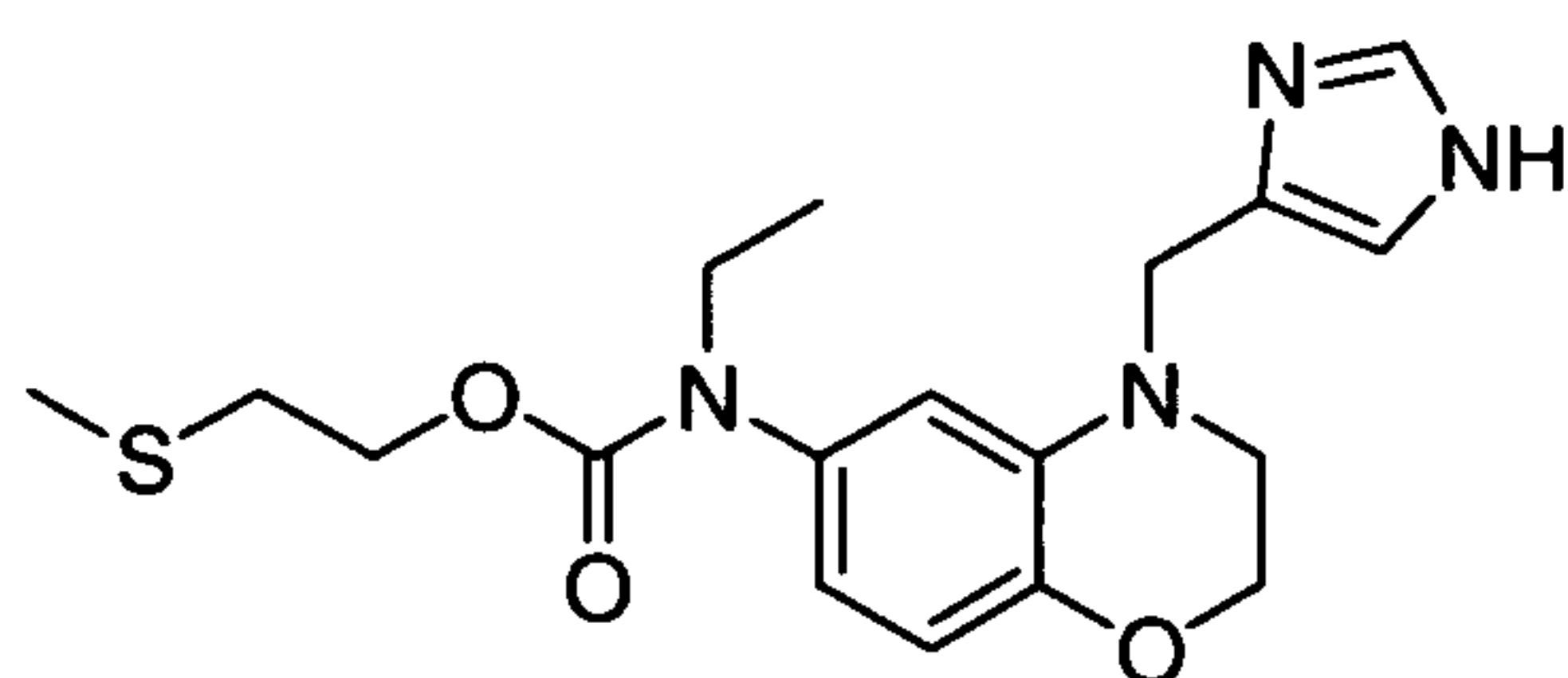
372

140

311		422
312		422
313		449
314		400
315		343
316		421
317		370
318		366

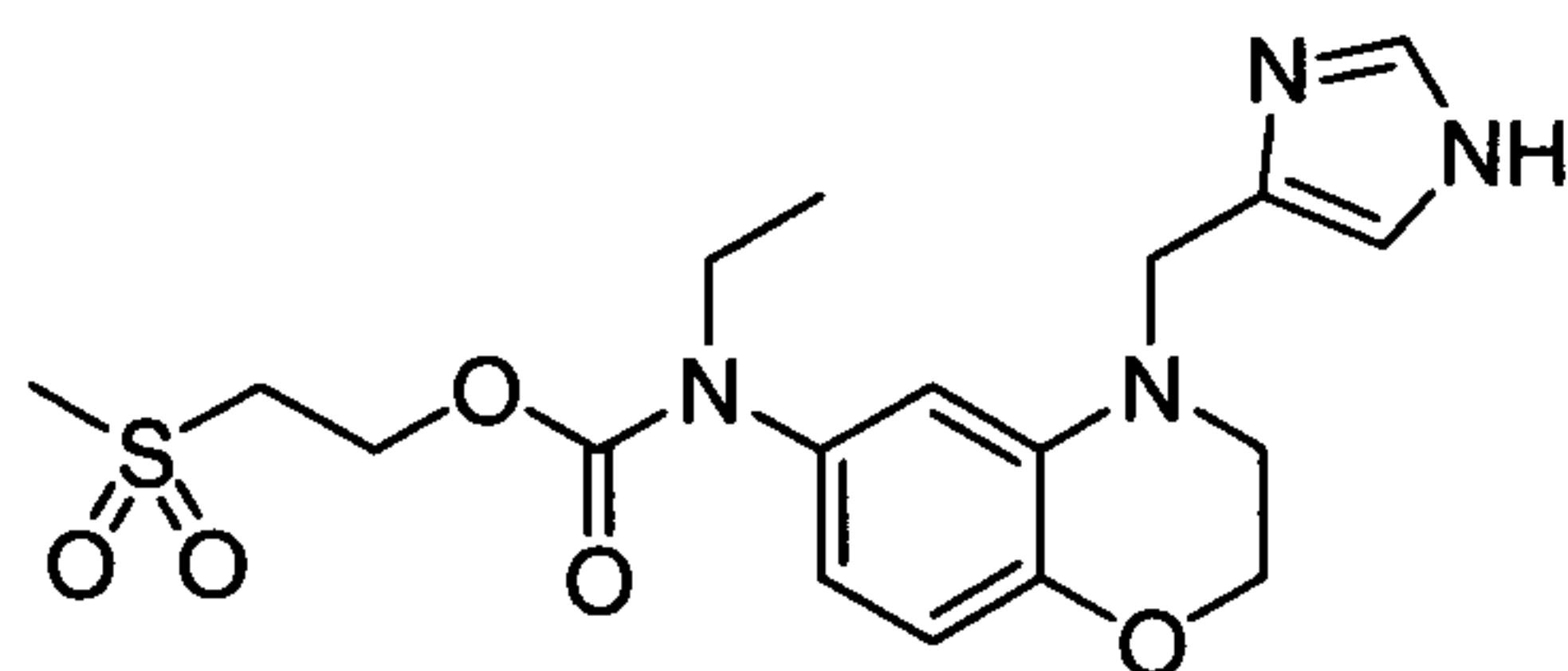
141

319



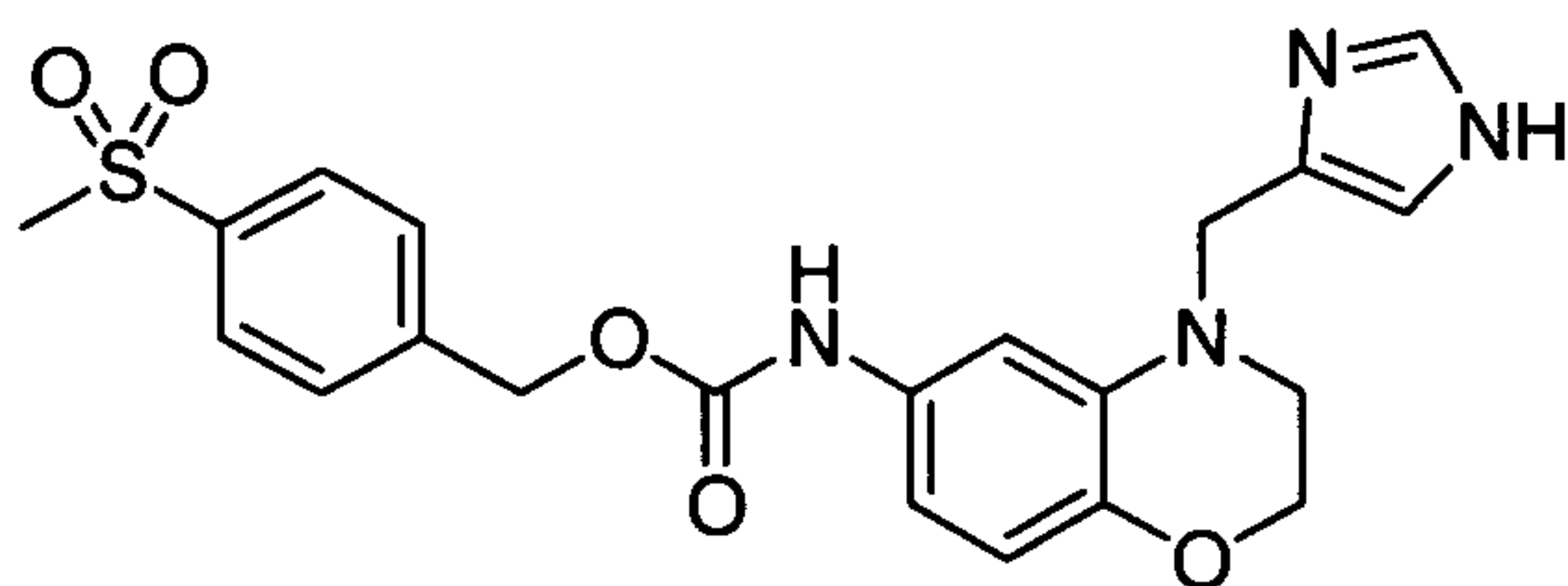
377

320



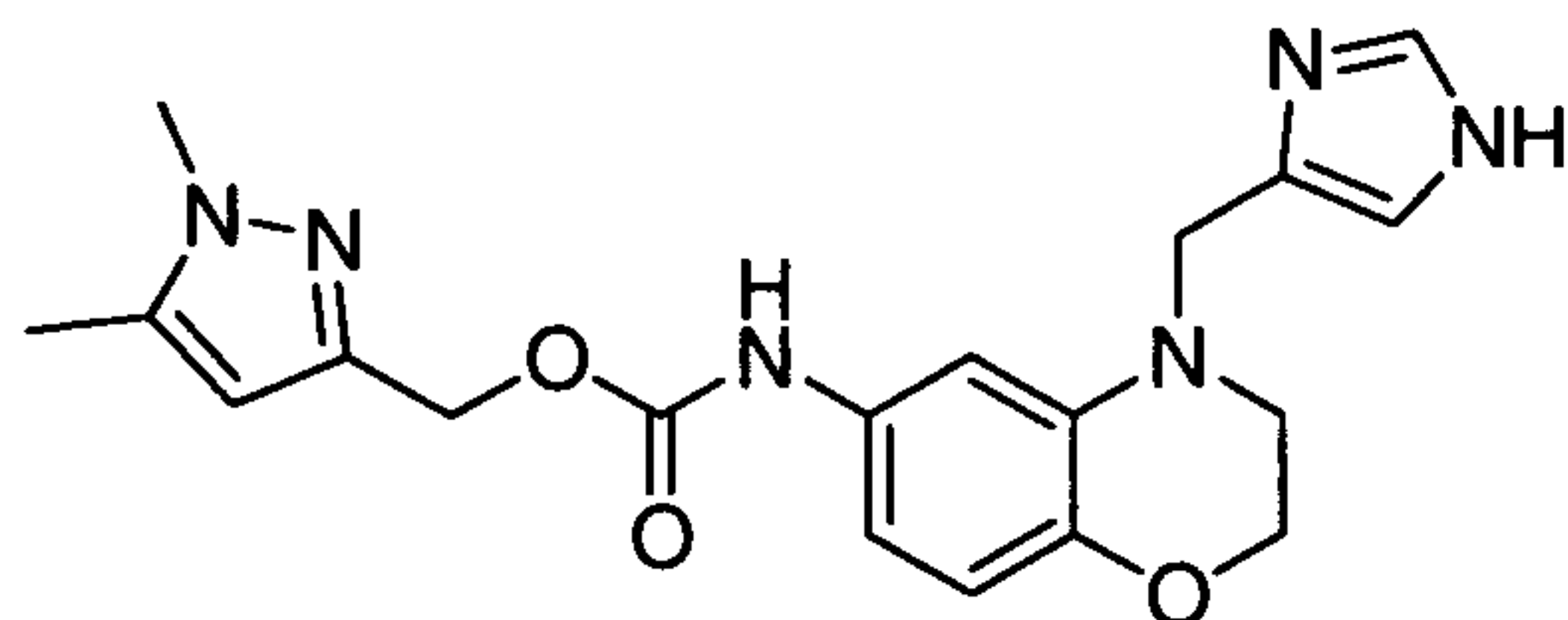
409

321



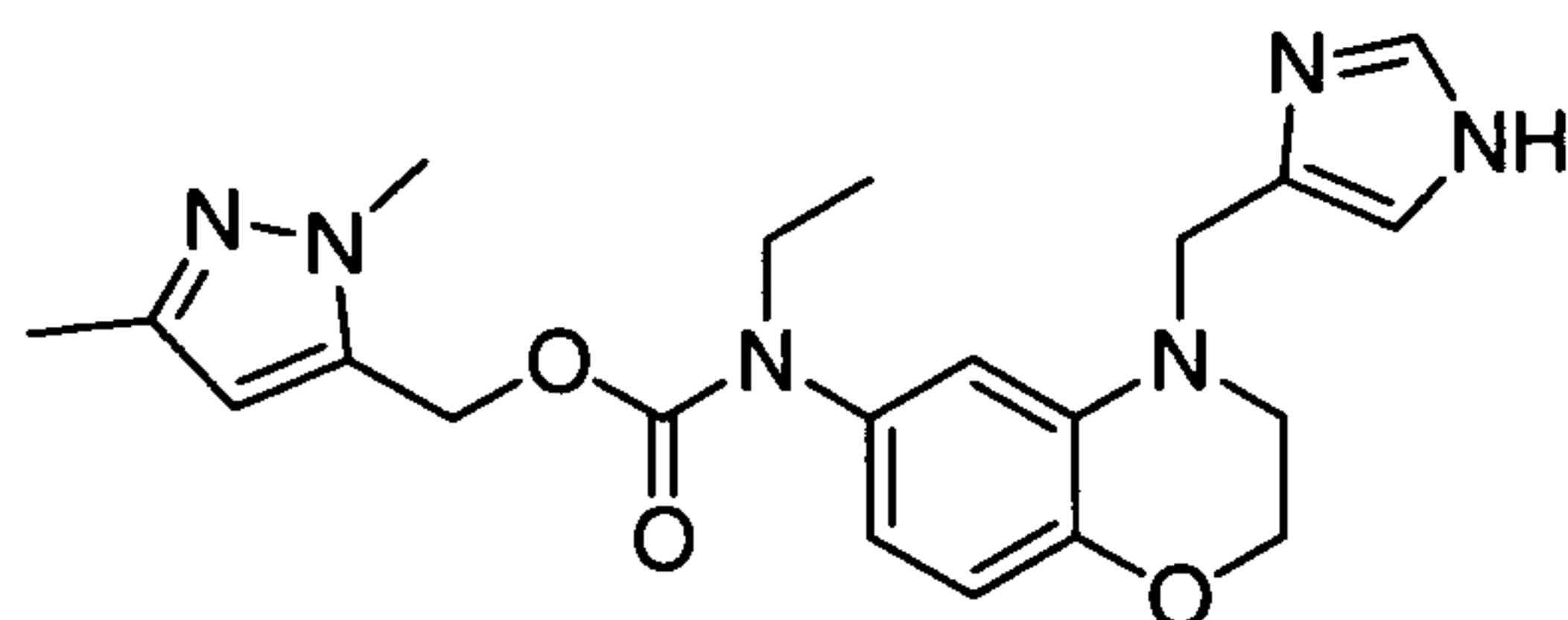
471

322



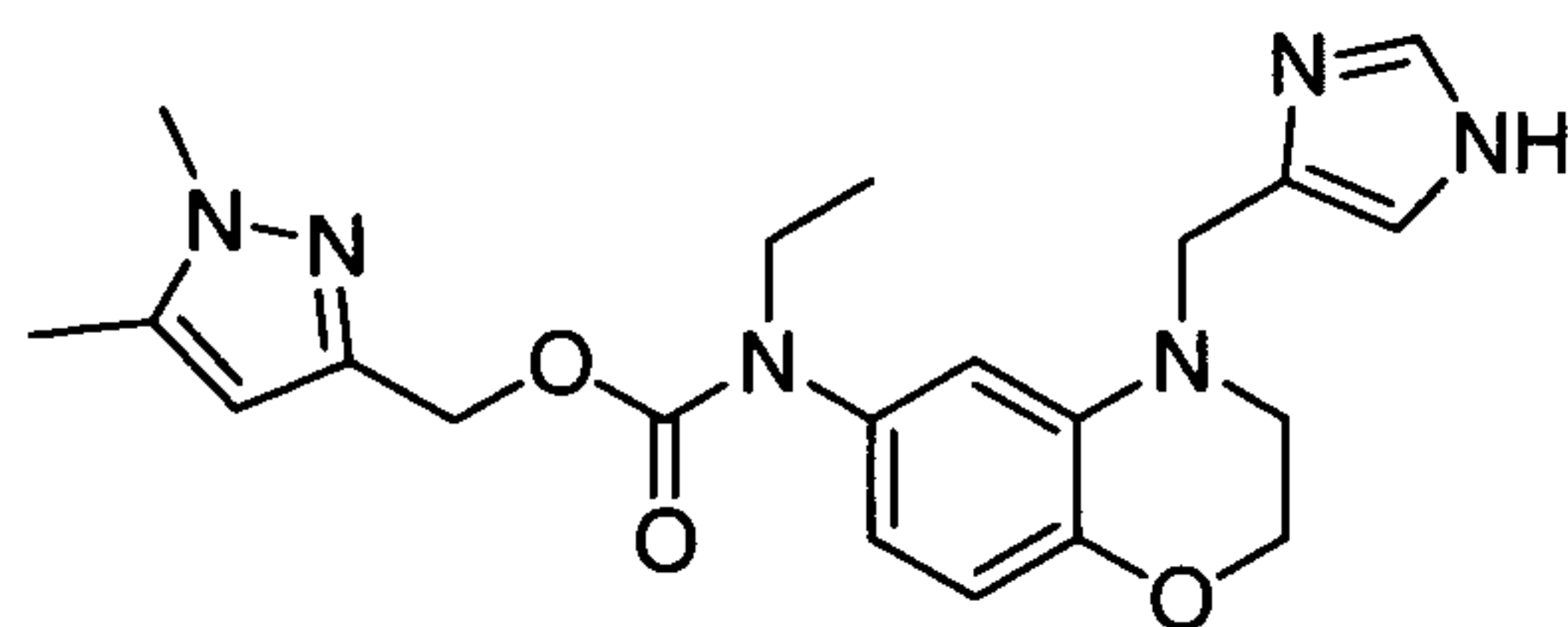
383

323



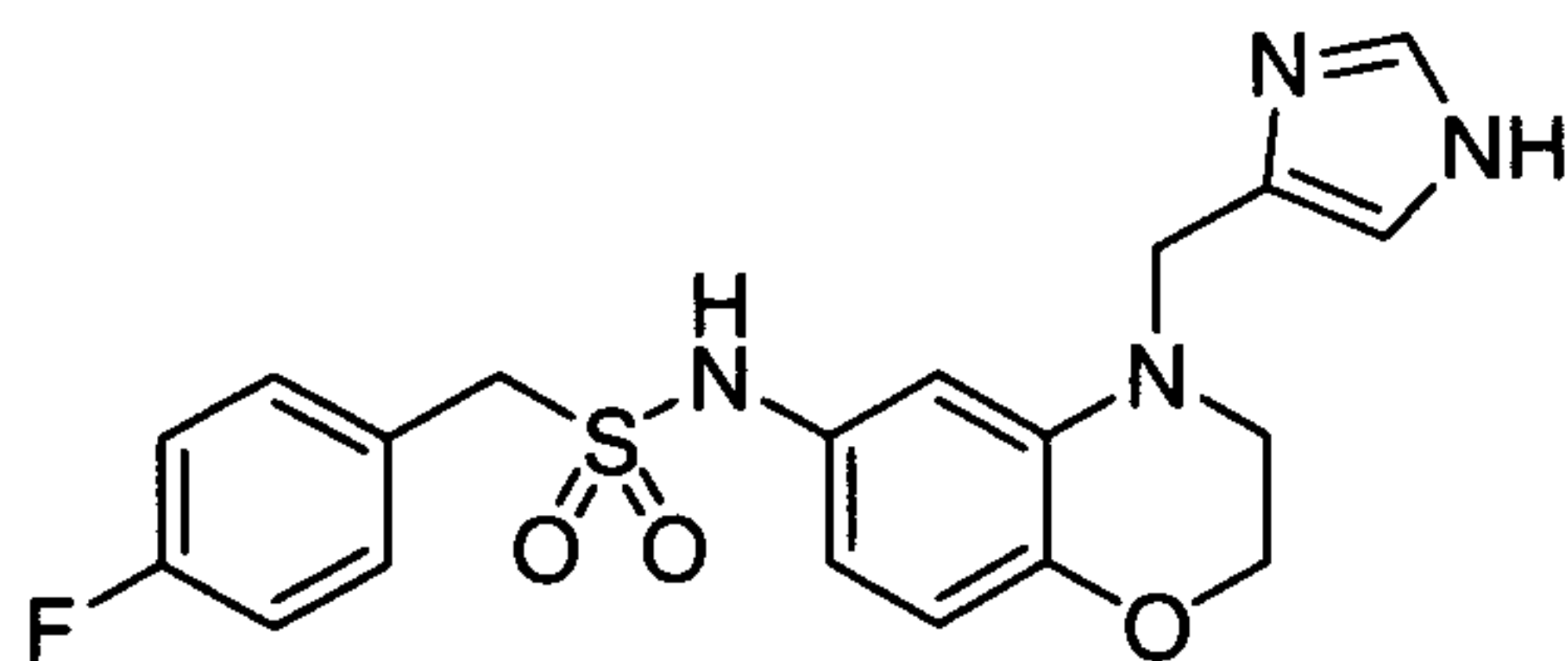
411

324



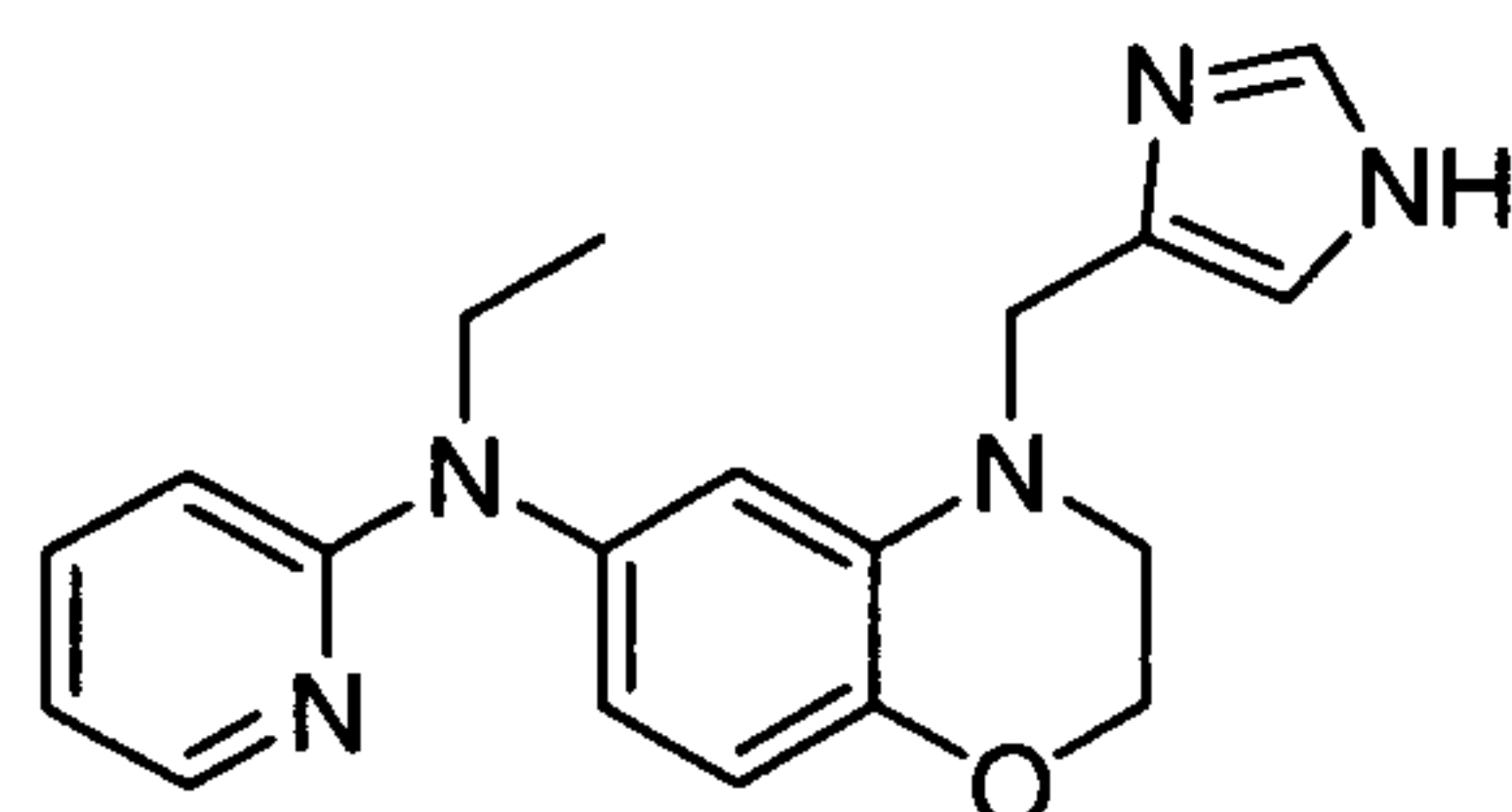
411

325



403

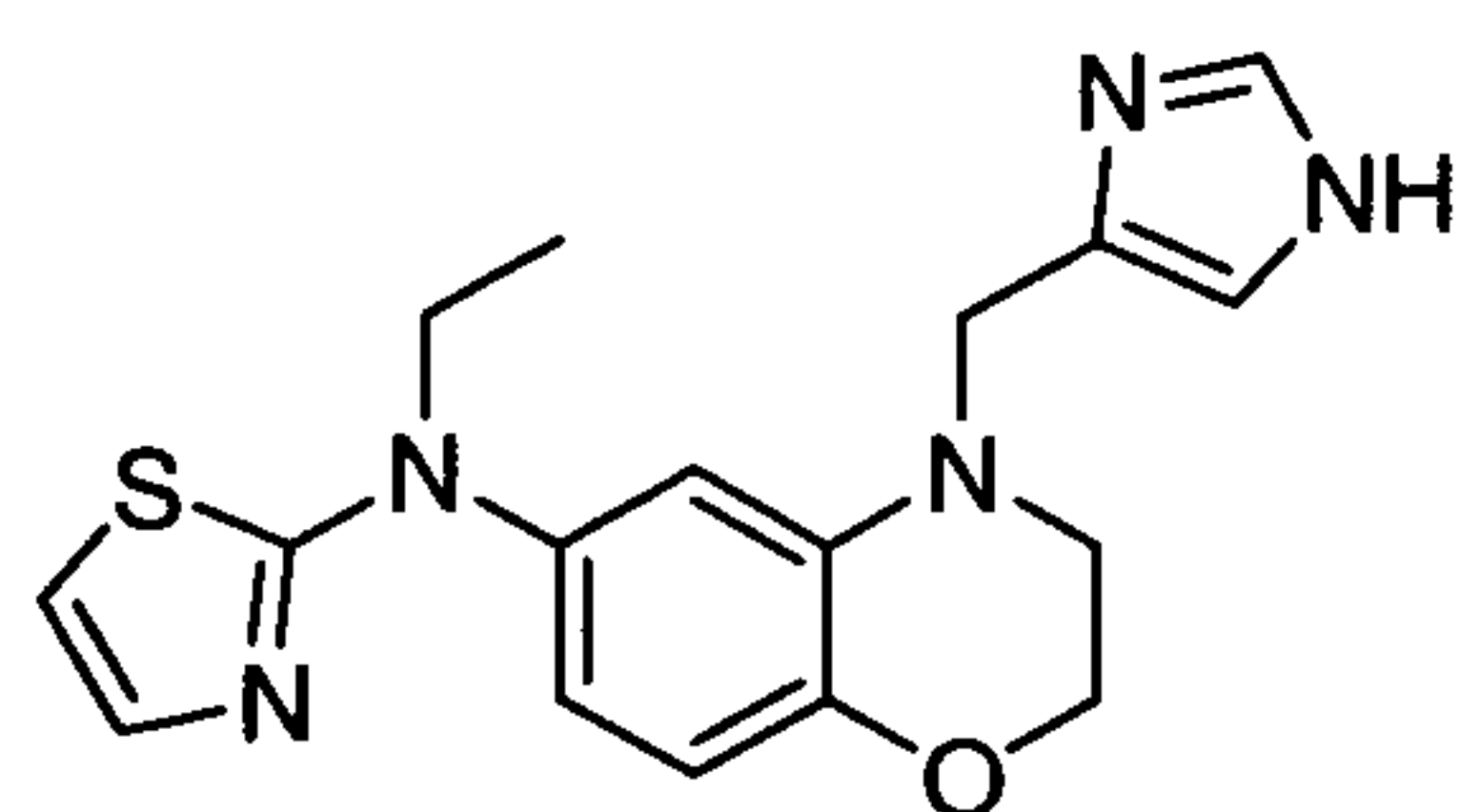
326



336

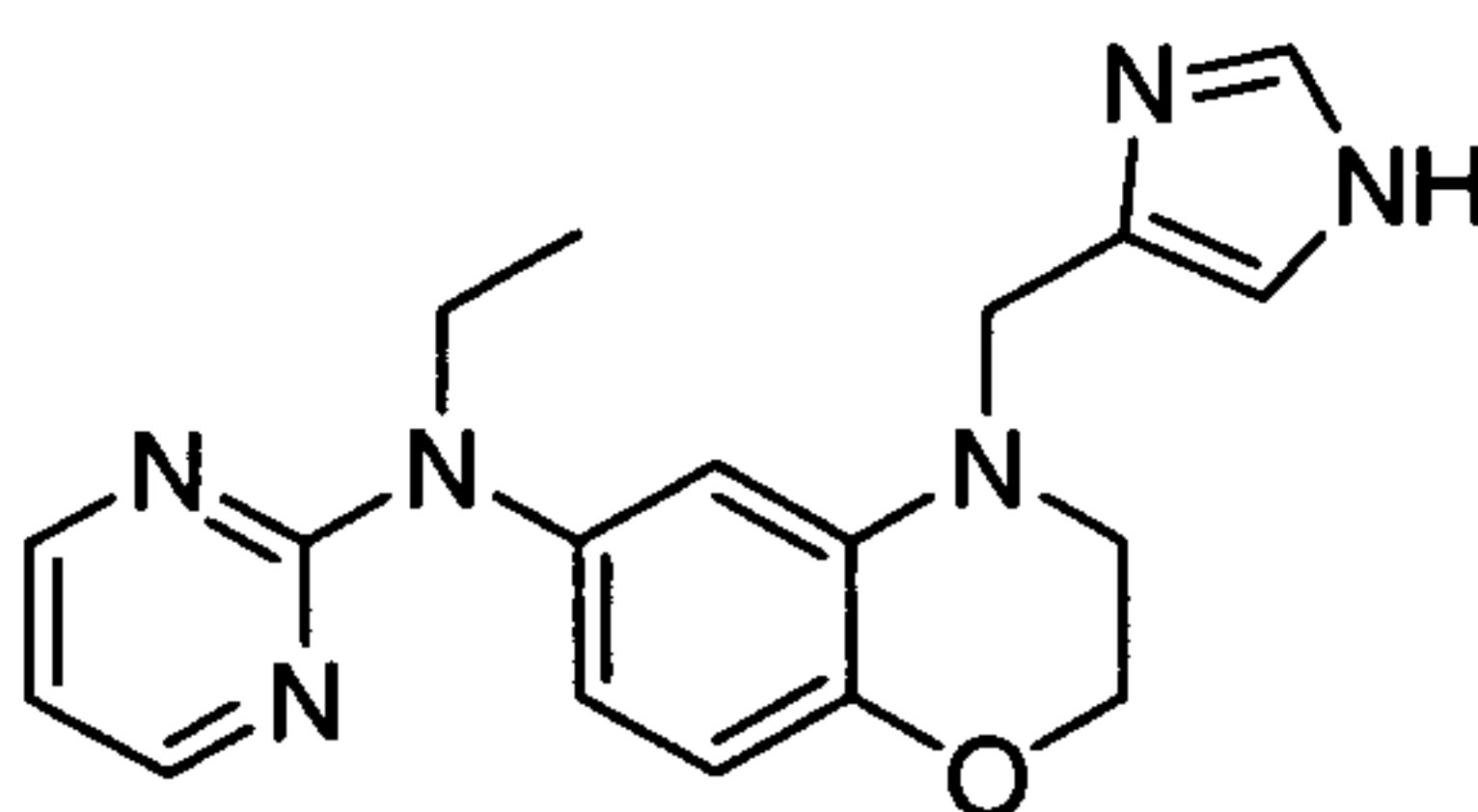
142

327



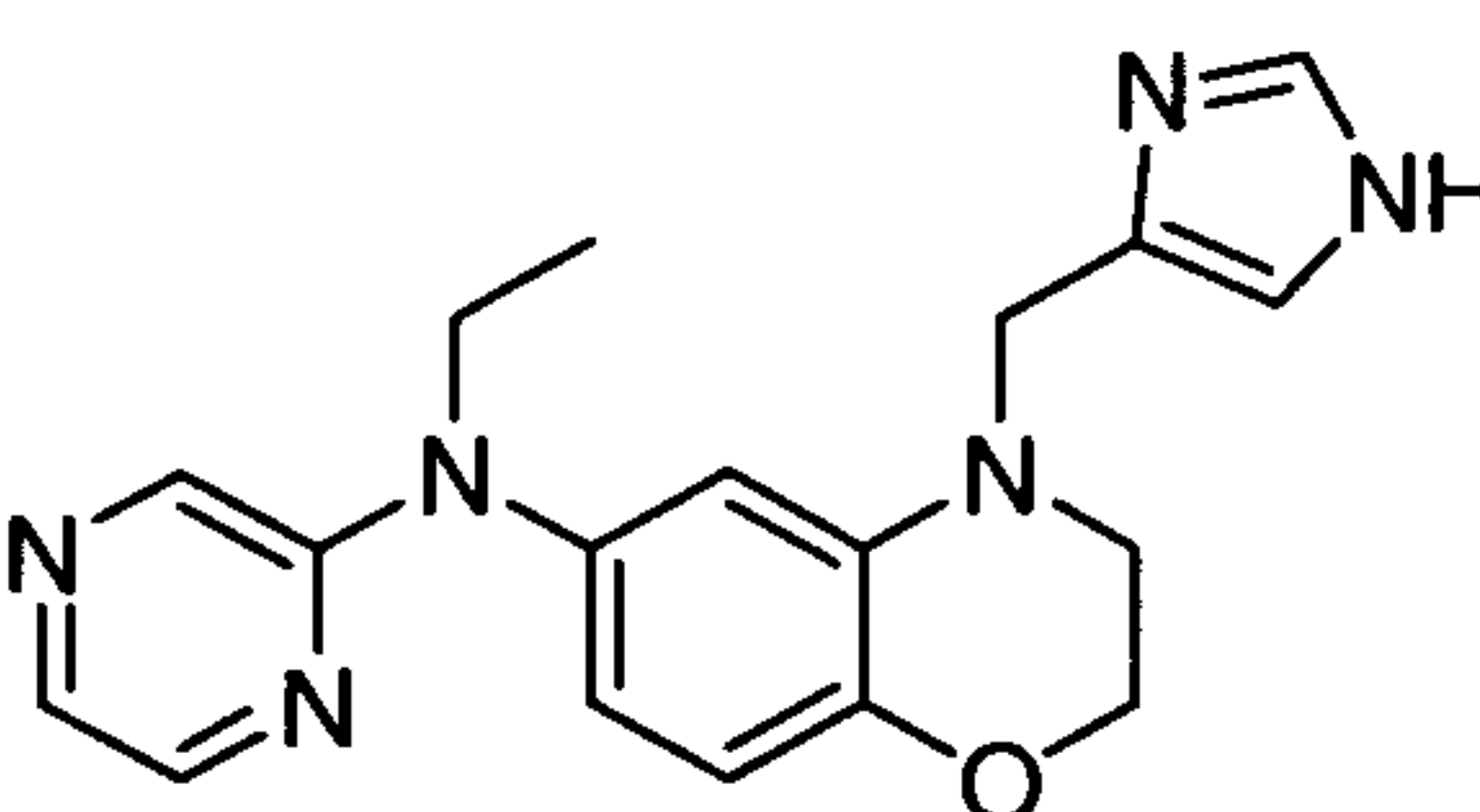
342

328



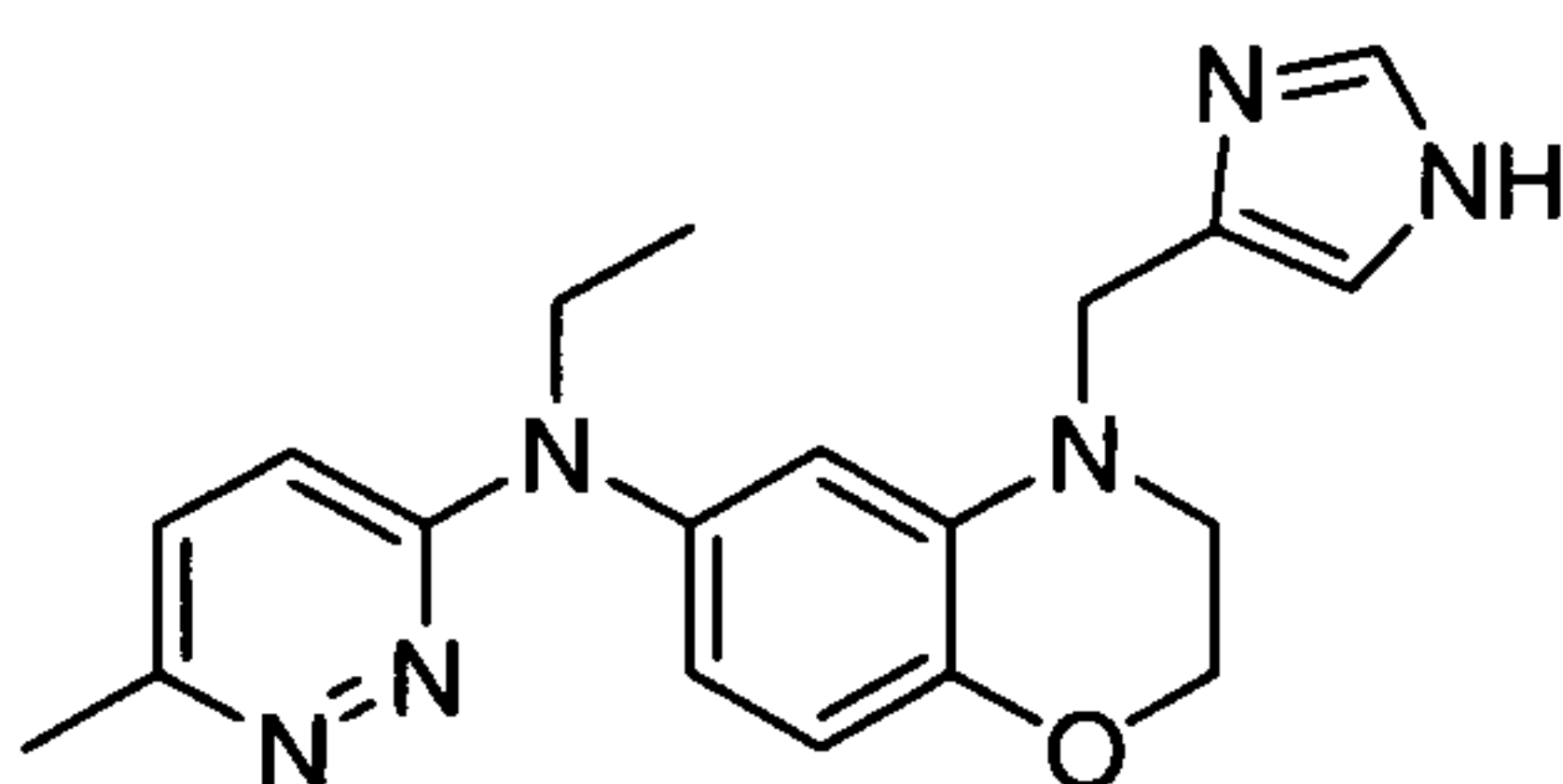
337

329



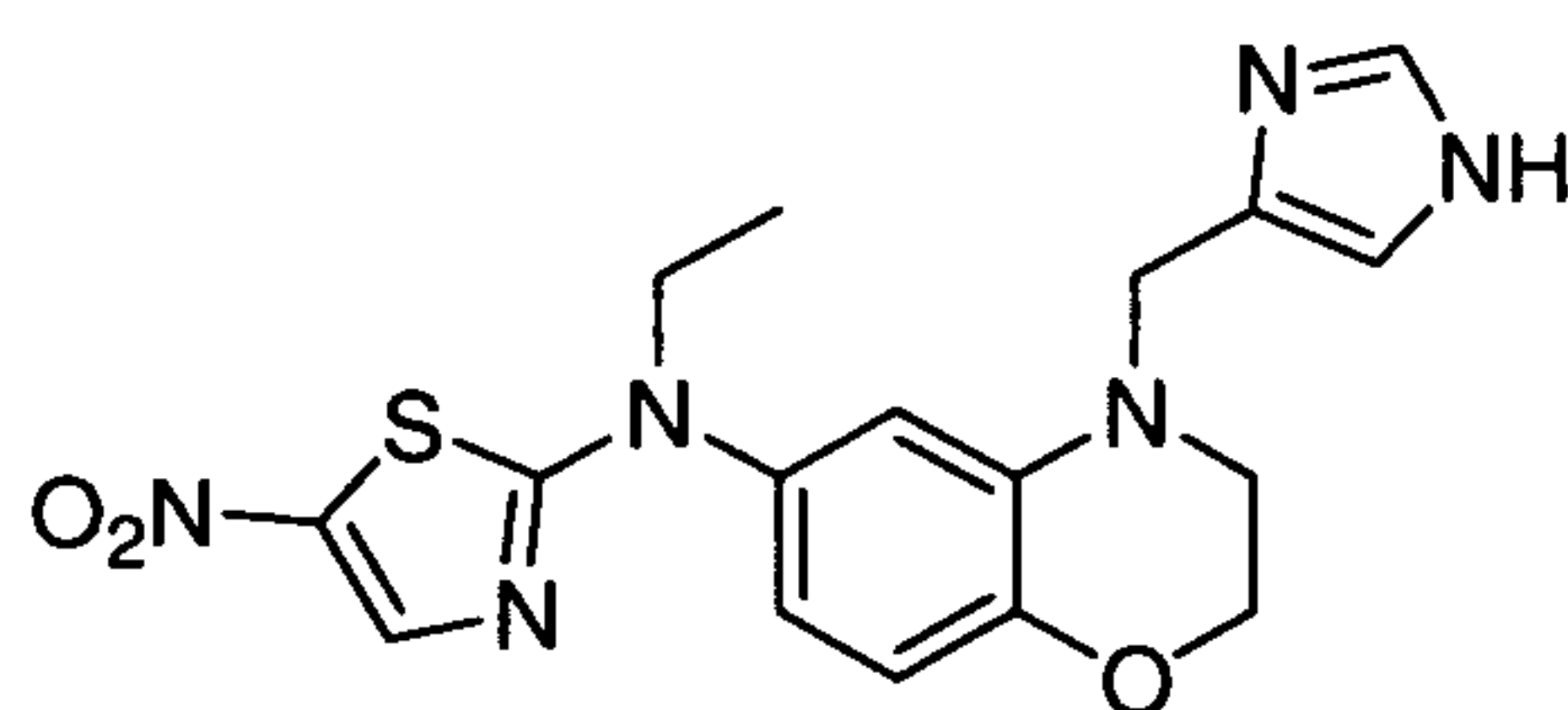
337

330



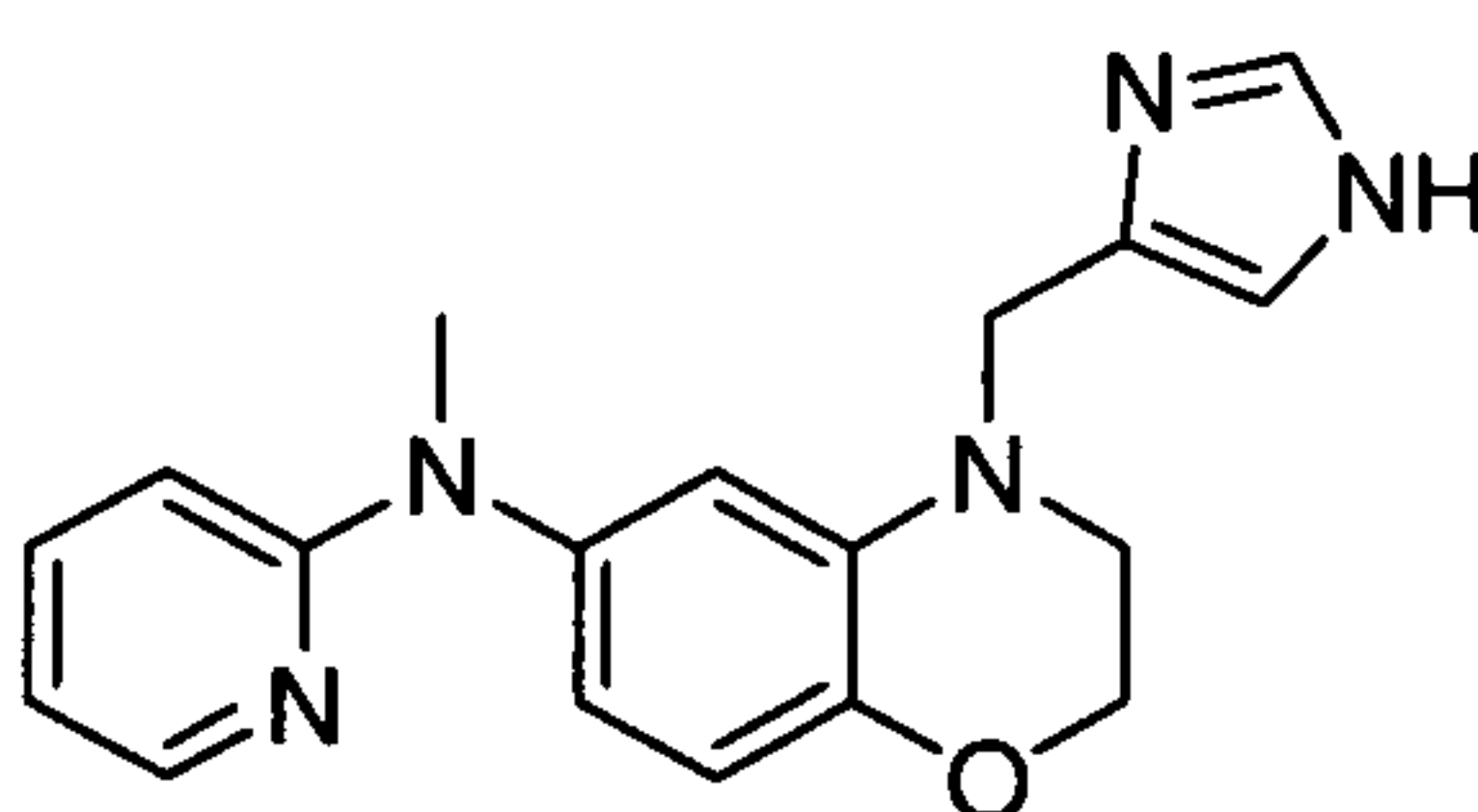
351

331



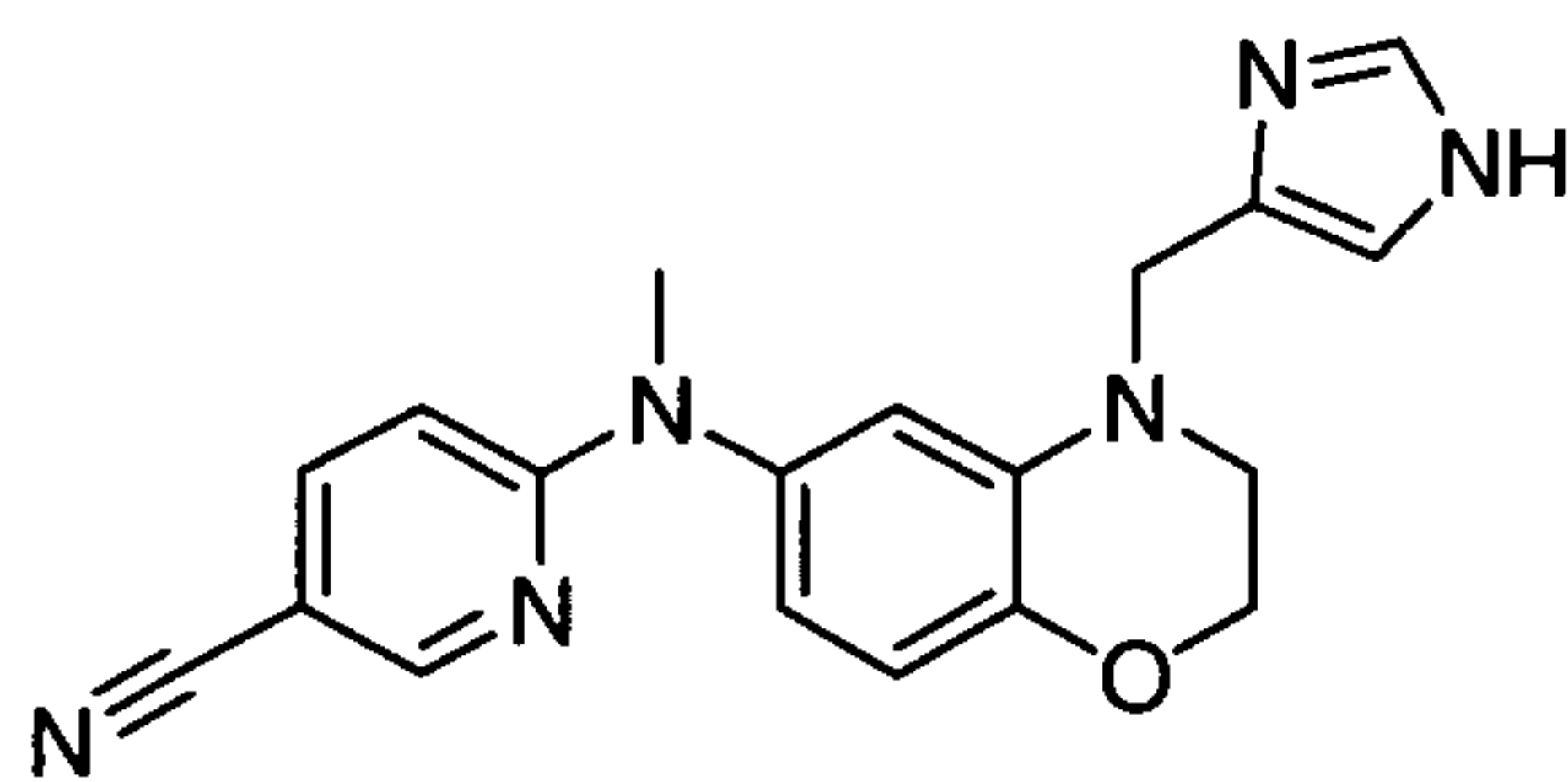
387

332



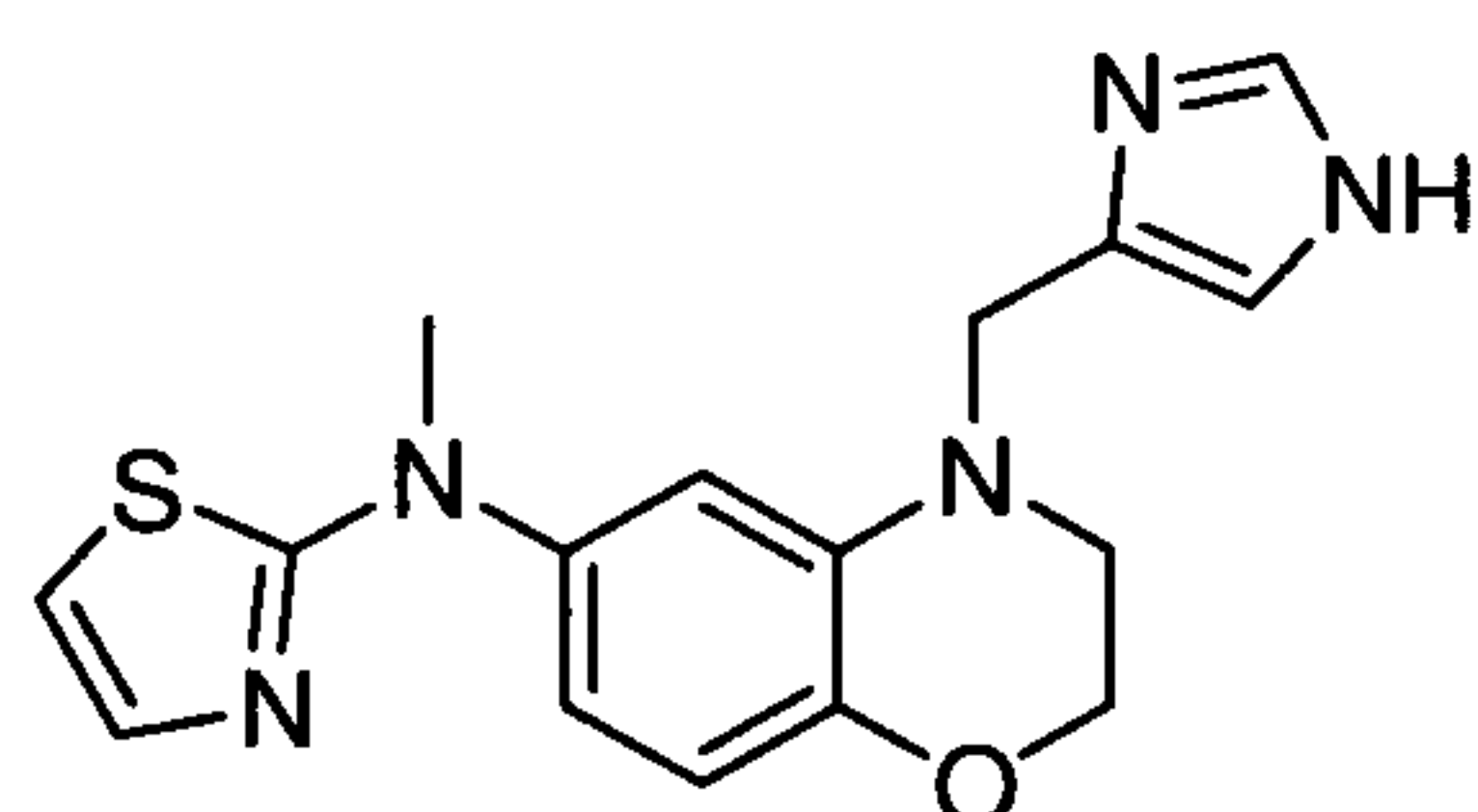
322

333



347

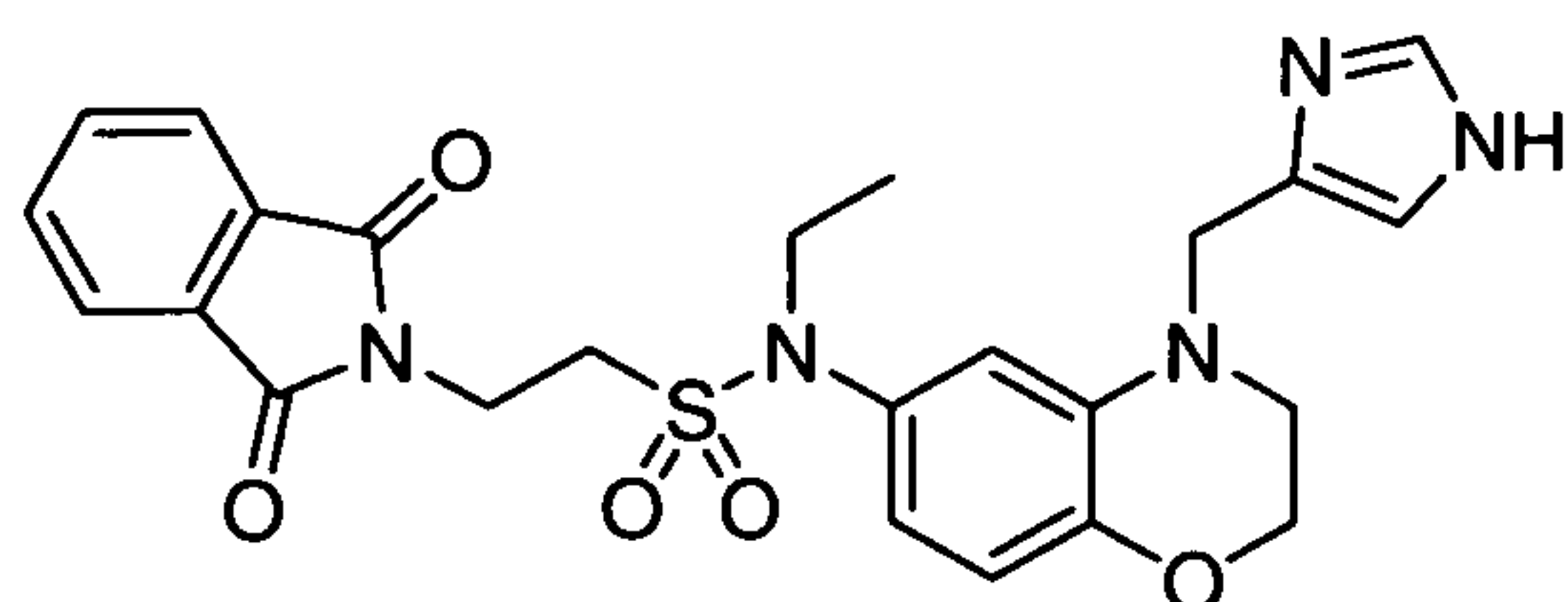
334



328

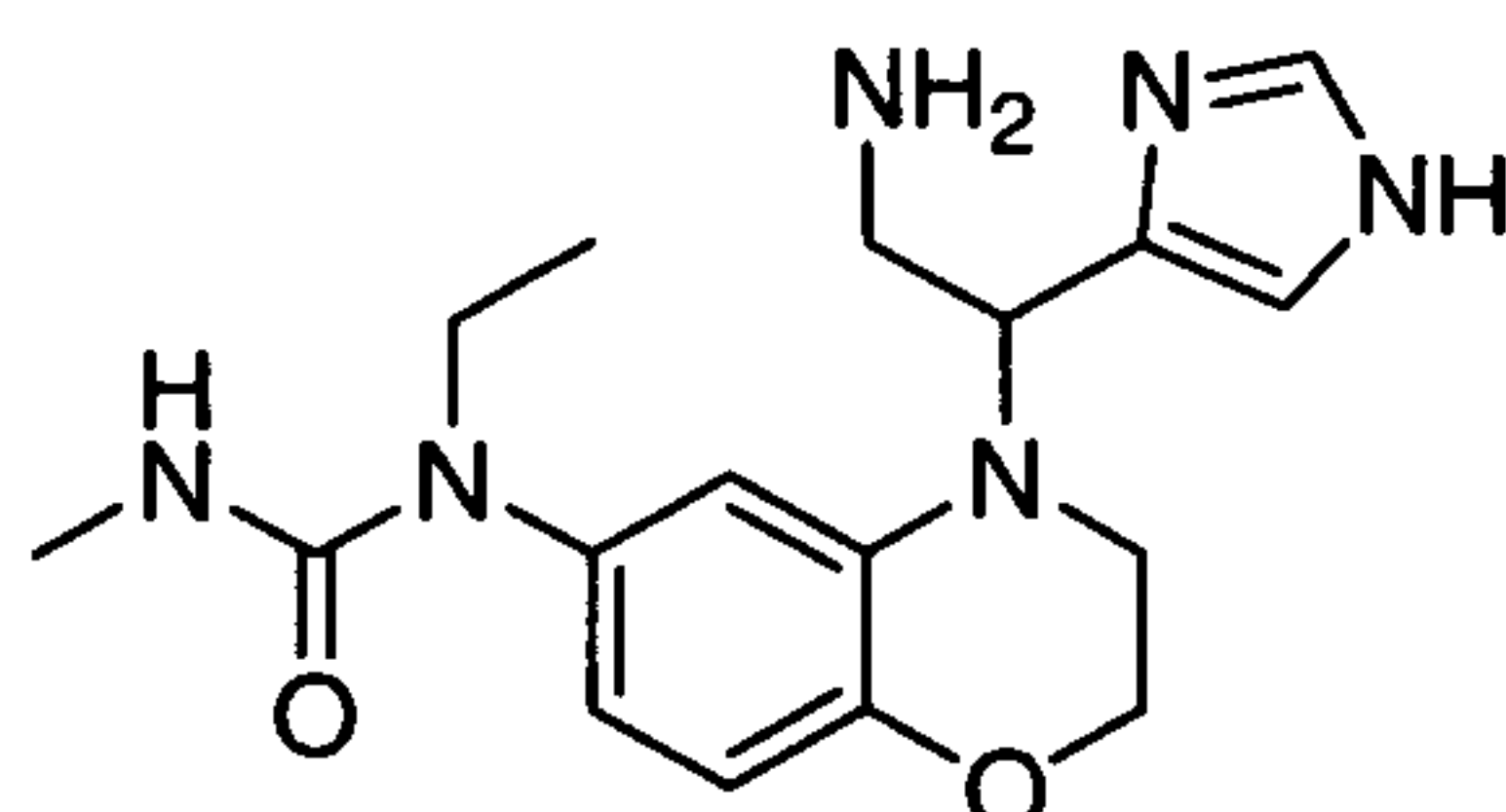
143

335



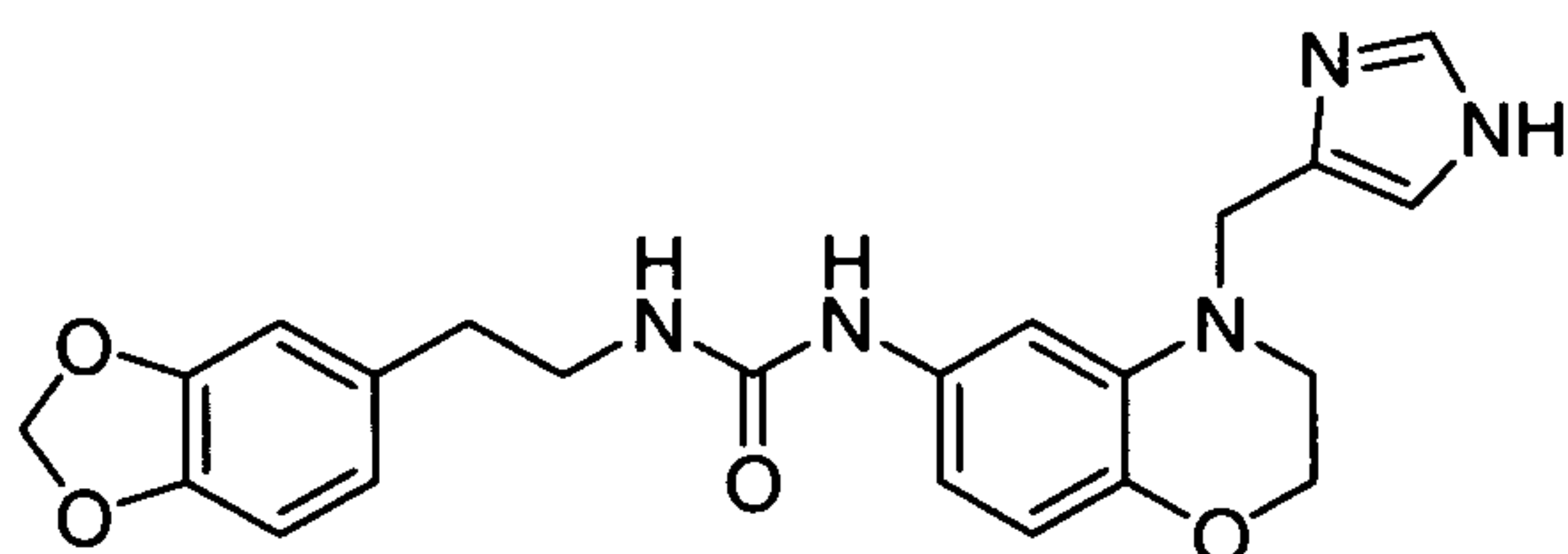
496

336



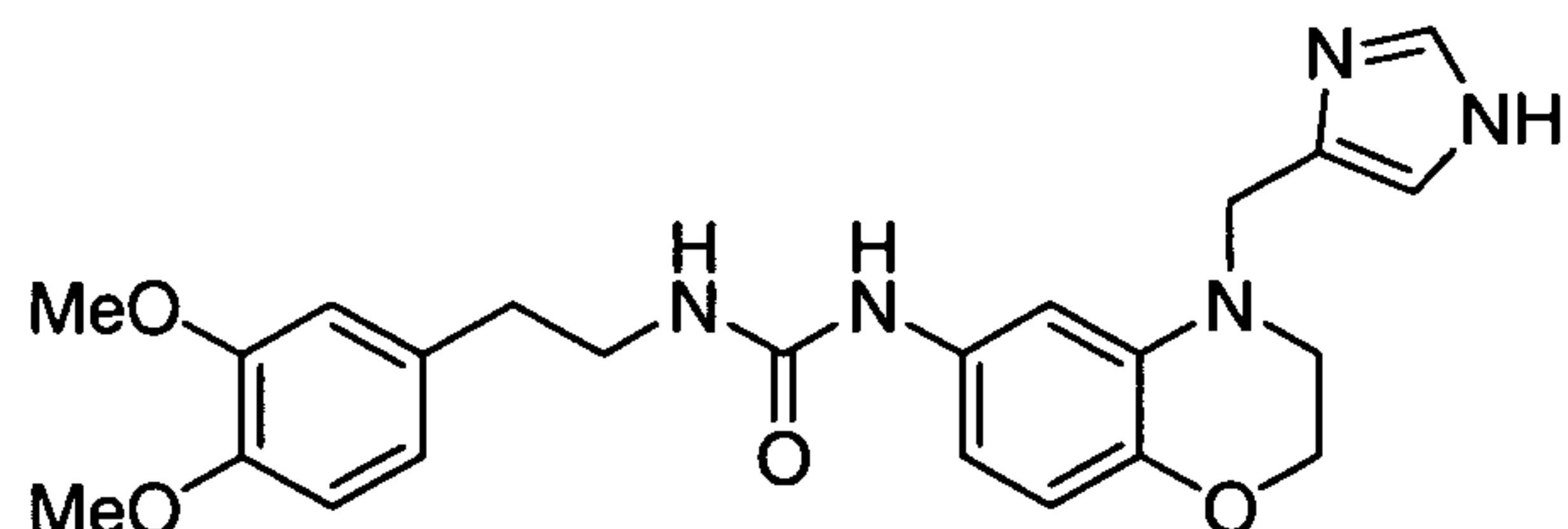
345

337



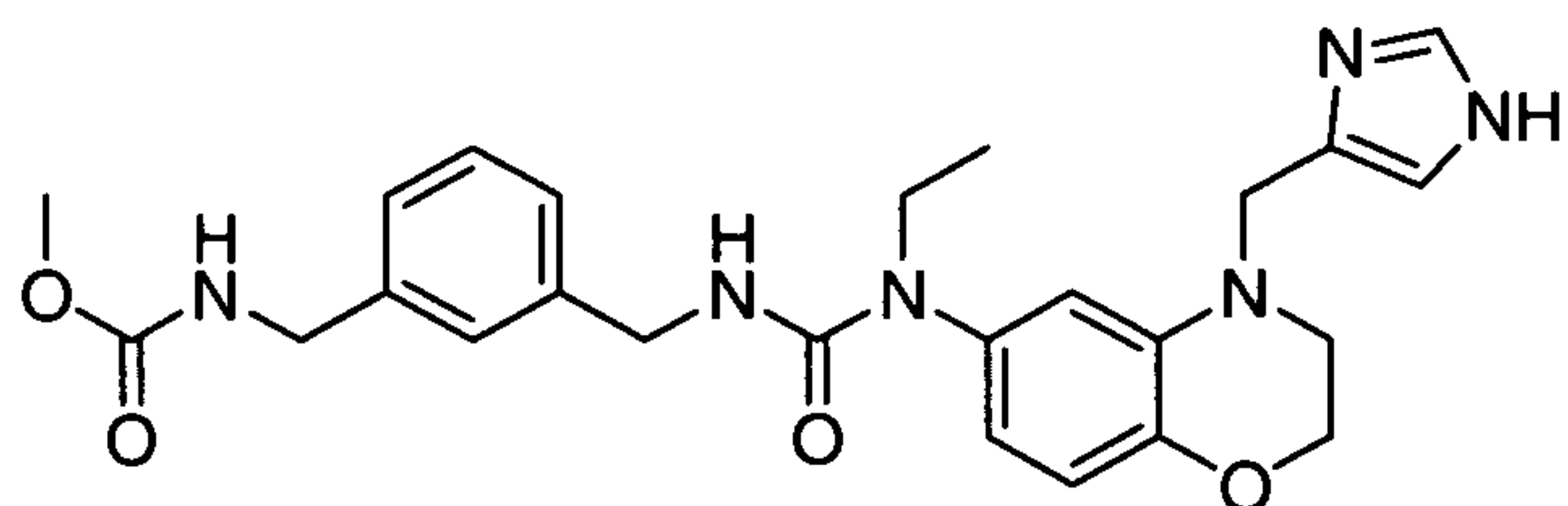
422

338



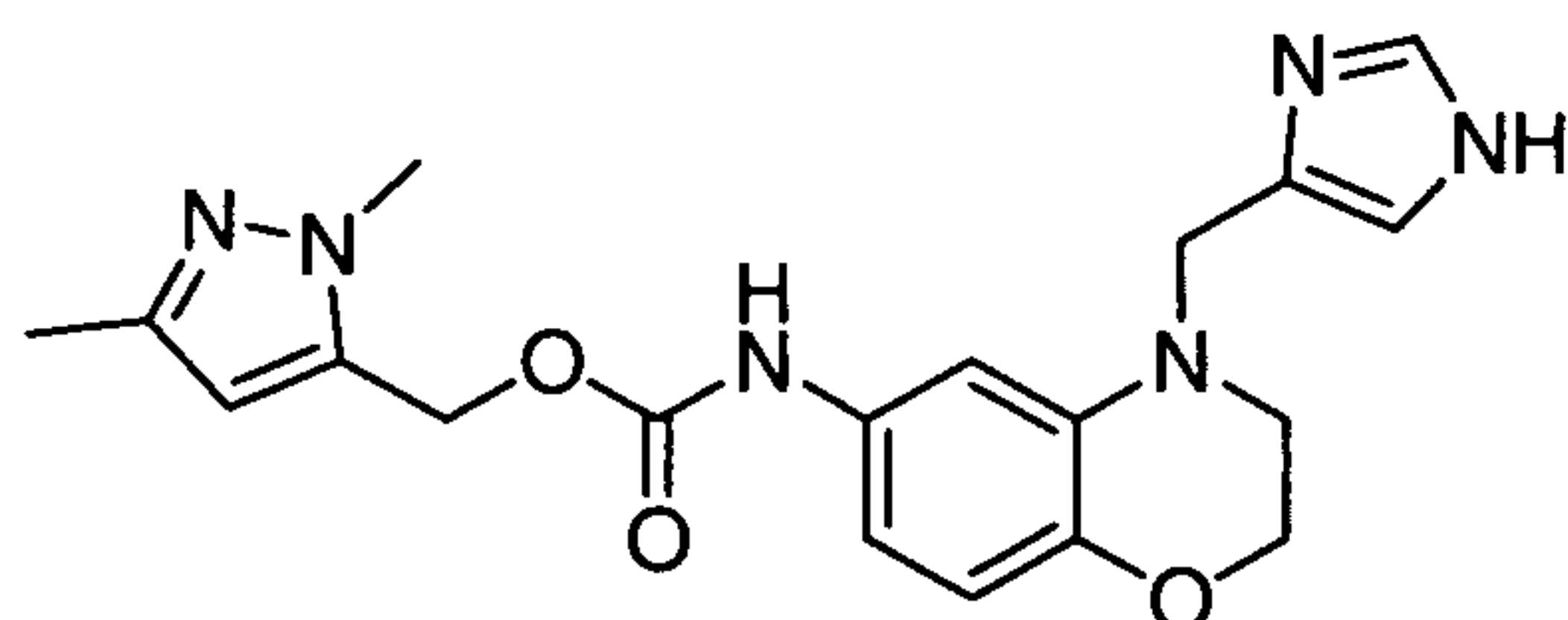
438

339



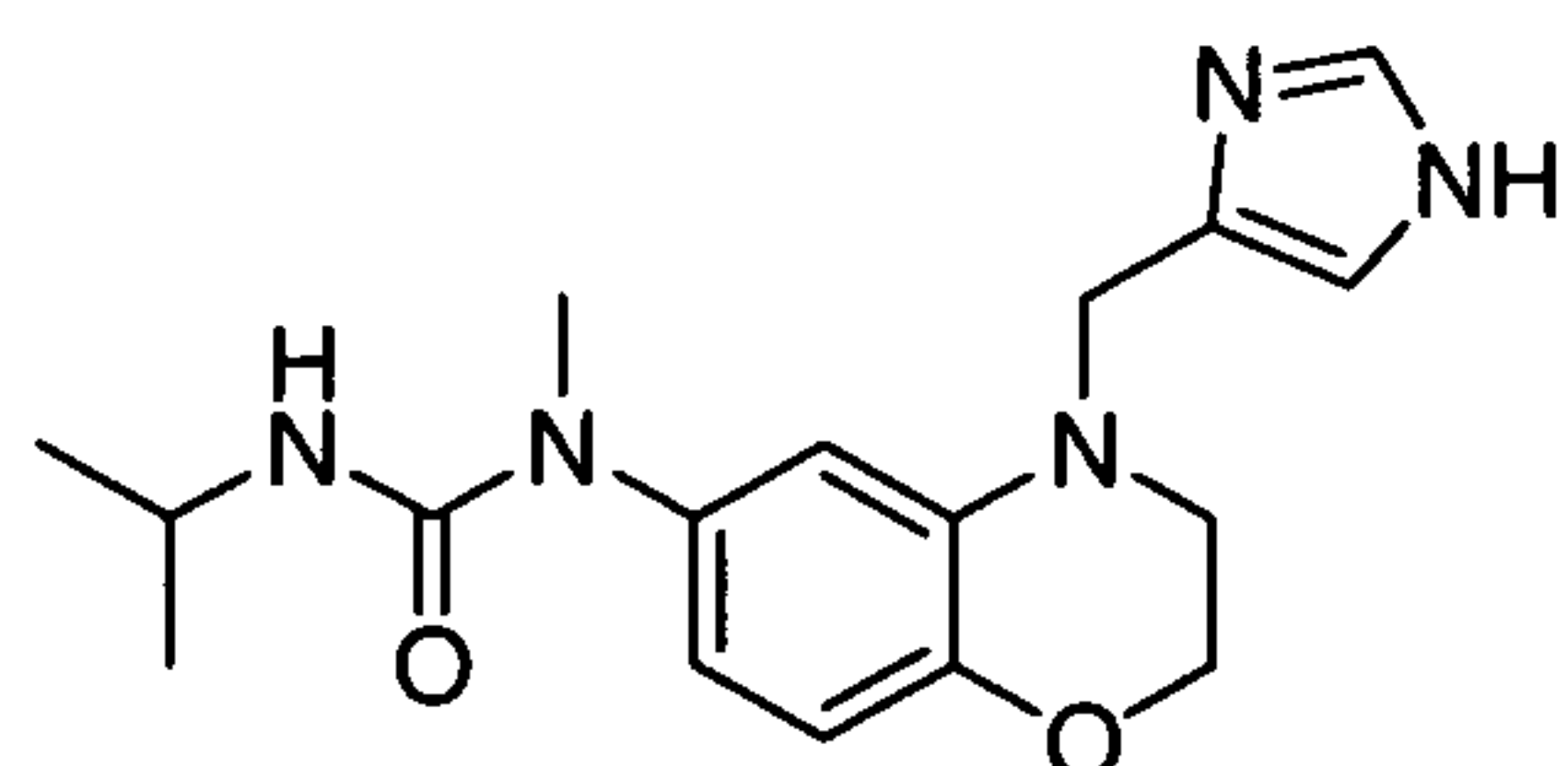
479

340



383

341



330

ASSAY:

Efficacy agonist activity values ($E_{\max}$, GTP γ S assay) for α_2C were determined by following the general procedure detailed by Umland *et. al* ("Receptor reserve analysis of the human α_{2c} -adrenoceptor using [^{35} S]GTP γ S and cAMP functional assays" European Journal of Pharmacology **2001**, 411, 211-221). For the purposes of the present invention, a compound is defined to be an active agonist of the α_2C receptor subtype if the compound's efficacy at the α_2C receptor is $\geq 30\%$ $E_{\max}$ (GTP γ S assay). A compound is a functionally selective agonist of the α_2C receptor subtype over the α_2A receptor subtype if the compound's efficacy at the α_2C receptor is $\geq 30\%$ $E_{\max}$ (GTP γ S assay) and its efficacy at the α_2A receptor is $\leq 30\%$ $E_{\max}$ (GTP γ S assay).

The following compounds were evaluated to be active or functionally selective agonists of the α_2C receptor subtype based on the previously defined definition: 1, 3, 3D, 3E, 5, 6, 6E, 7, 8, 9E, 9G, 9I, 9K, 9L, 9M, 9N, 9P, 9Q, 9R, 9S, 12, 13, 14, 14B, 15, 19, 19D, 20, 21, 22, 24, 24D, 25B, 26, 26A, 26B, 27E, 28, 28D, 29, 30, 37, 38, 46, 51, 53, 54, 55, 57, 58, 63, 64, 64A, 65, 114, 117, 124, 125, 129, 130, 132, 134, 135, 137, 139, 142, 144, 145, 148, 151, 152, 158, 159, 160, 162, 163, 164, 165, 167, 168, 169, 171, 178, 181, 218, 223, 231, 232, 235, 236, 238, 239, 240, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 253, 256, 257, 259, 260, 261, 262, 263, 264, 265, 266, 271, 272, 273, 274, 275, 276, 278, 279, 280, 281, 287, 289, 290, 291, 297, 304, 305, 306, 307, 308, 309, 310, 311, 312, 314, 315, 316, 317, 318, 319, 321, 323, 324, 326, 327, 329, 331, 332, 335, and 340.

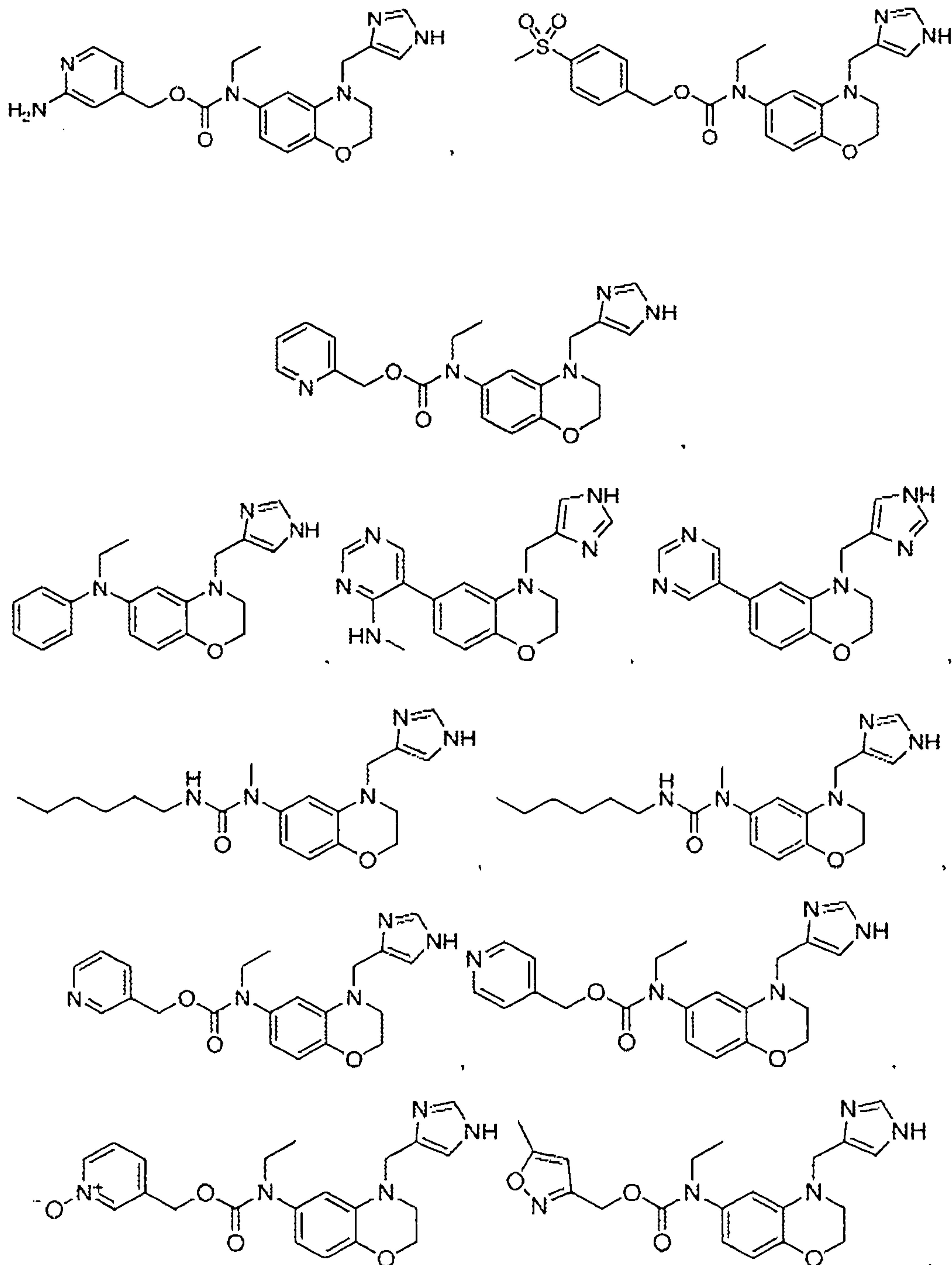
While the present invention has been described with in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

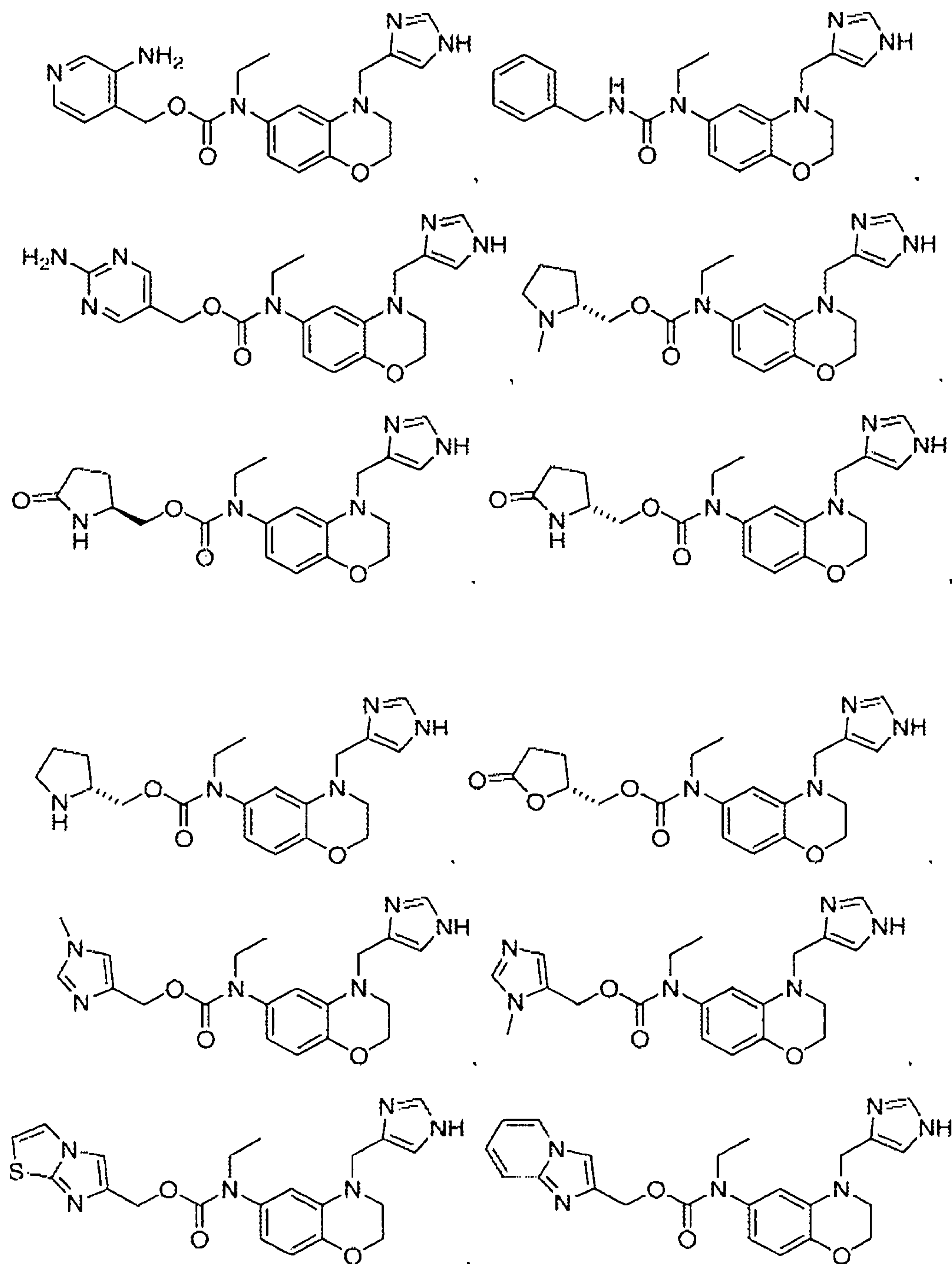
AMENDED CLAIMS

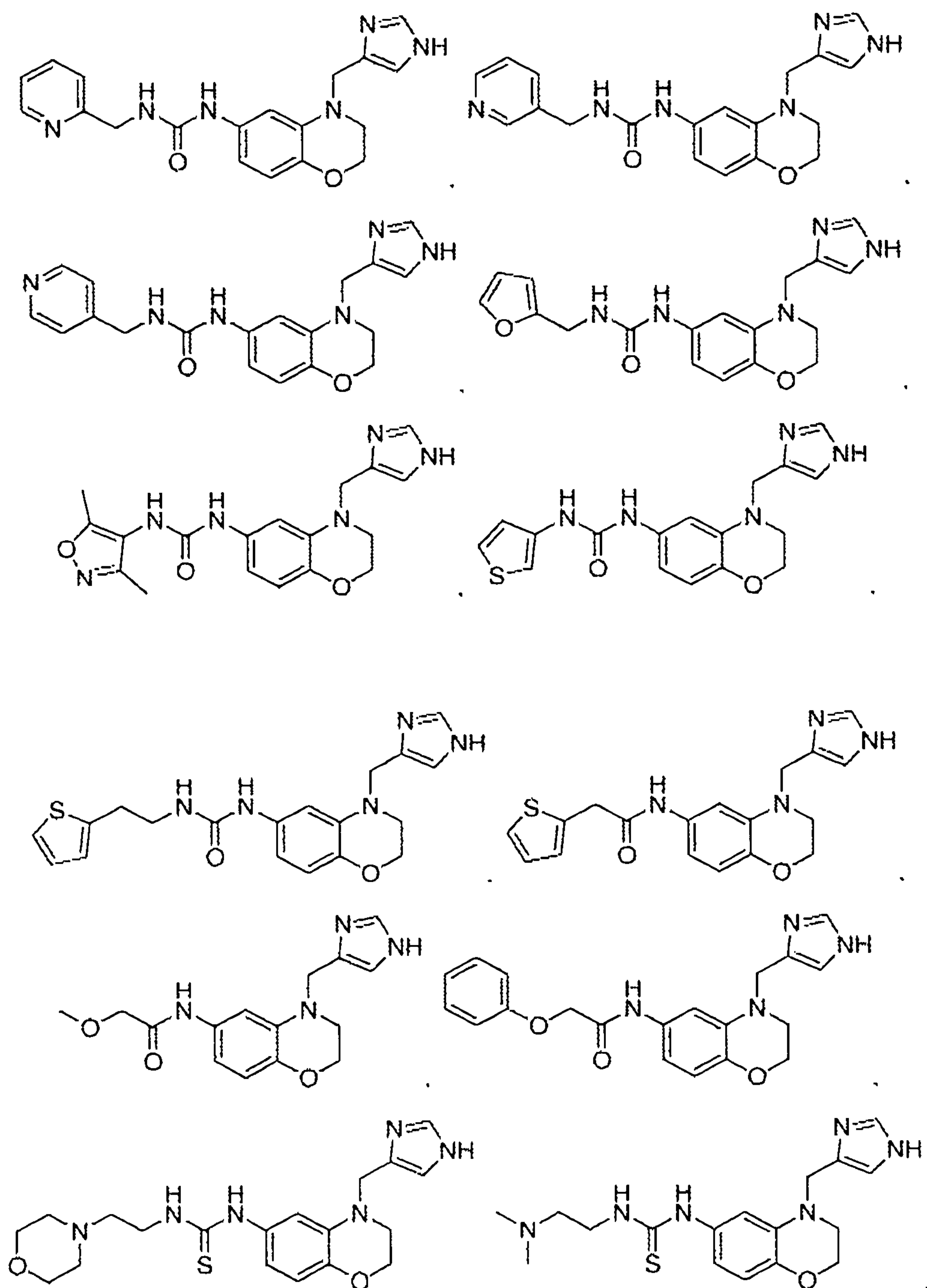
received by the International Bureau on 28 August 2008 (28.08.2008)

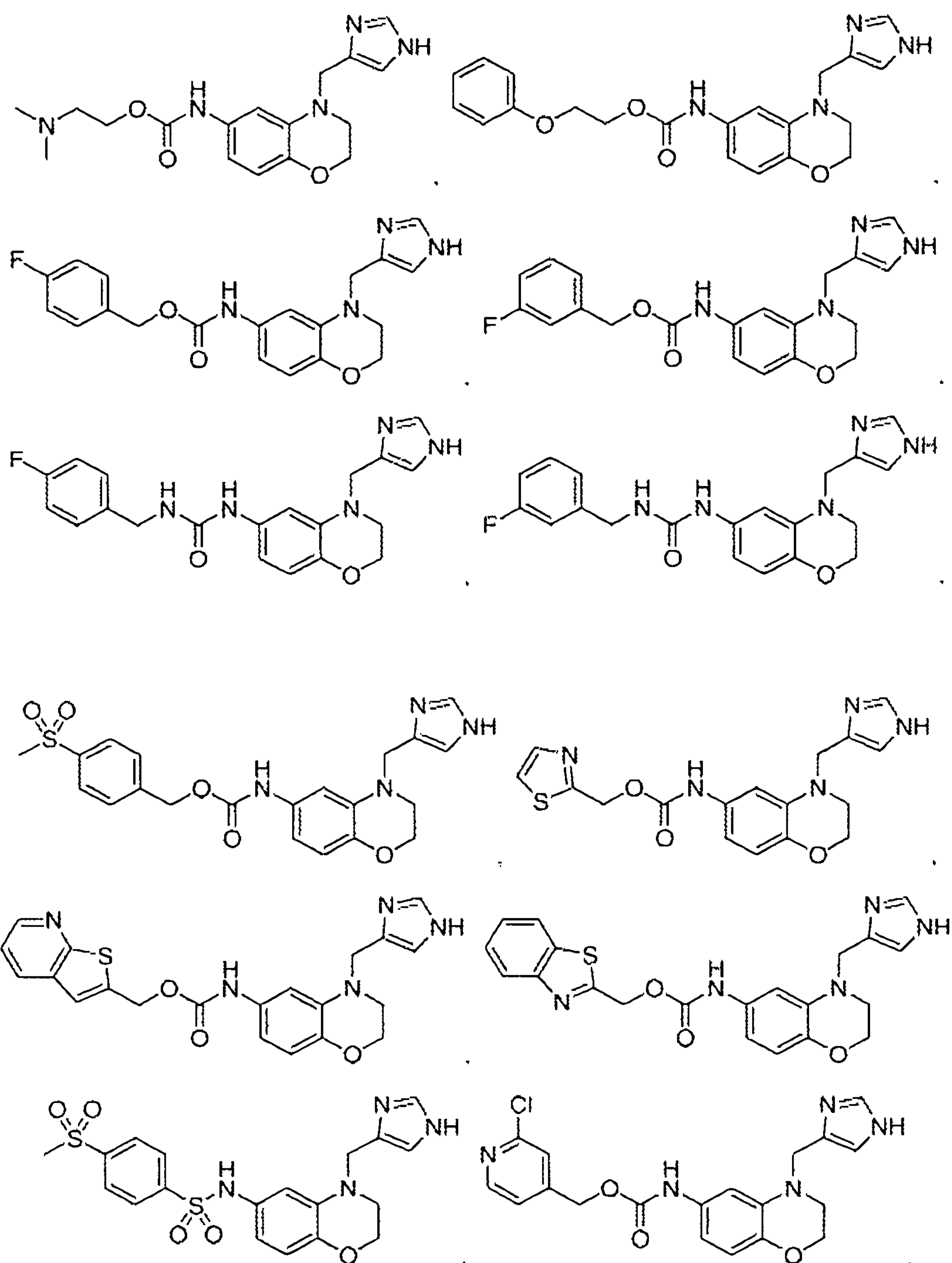
What is claimed is:

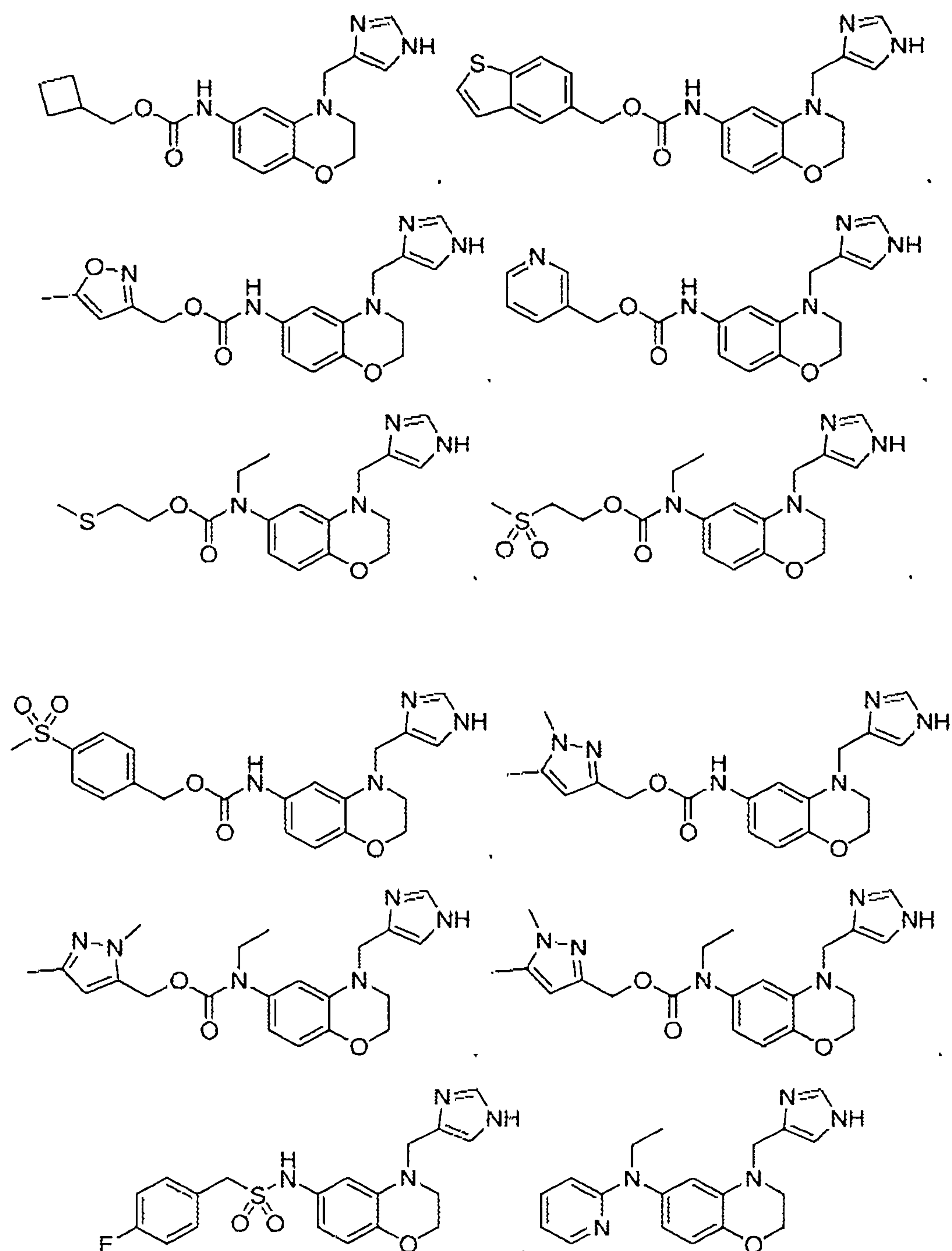
1. A compound selected from the group consisting of

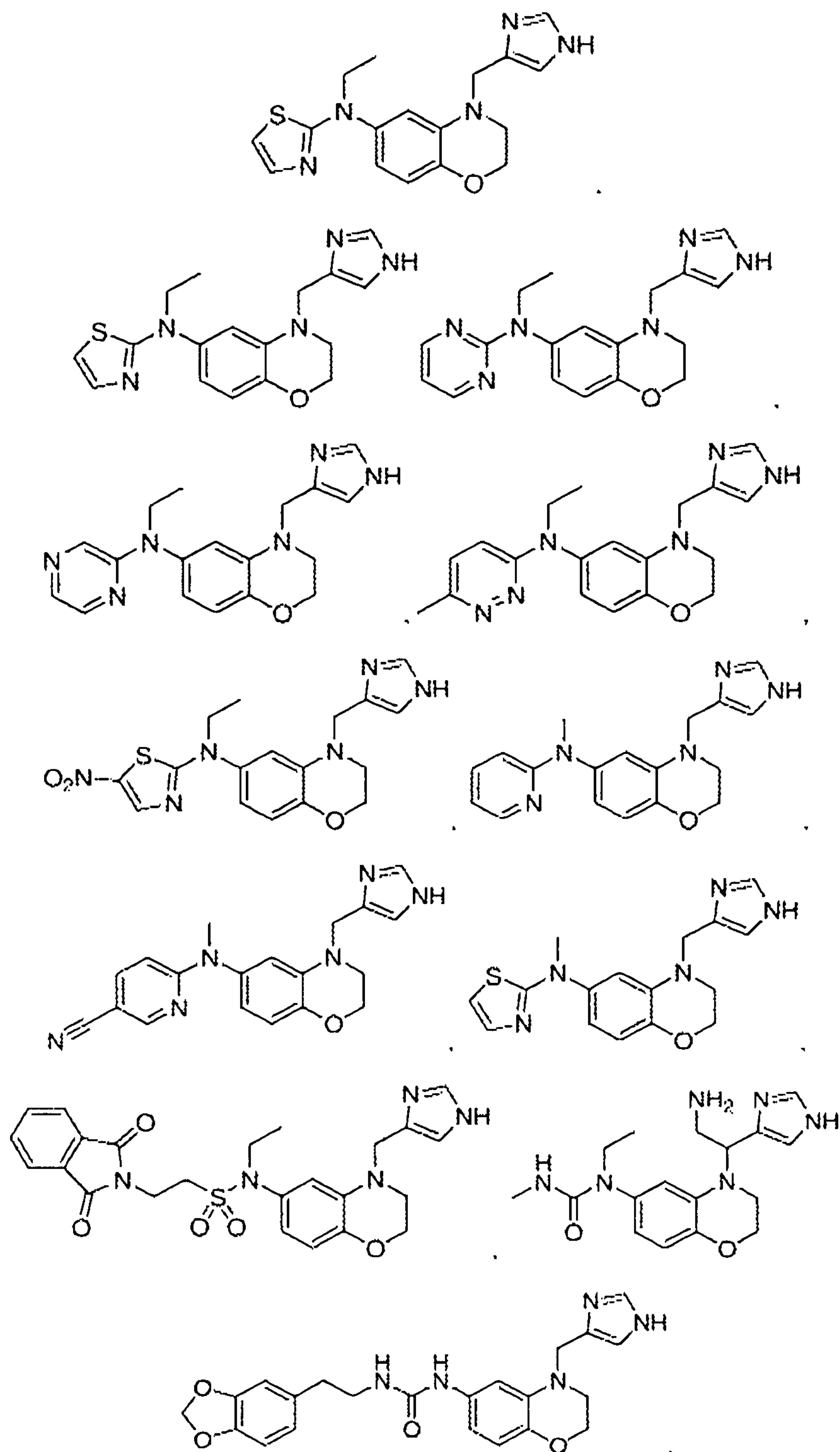


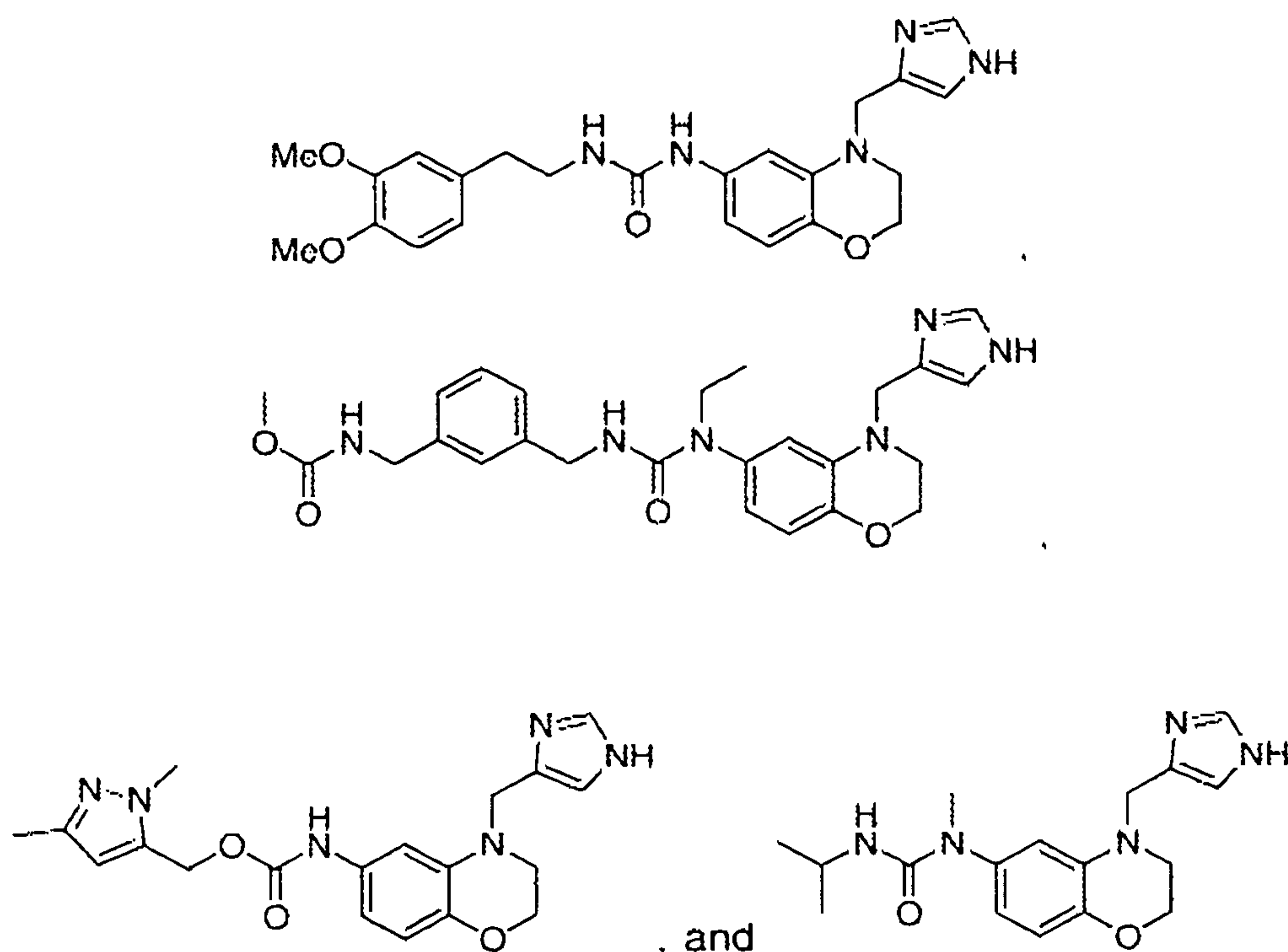












or a pharmaceutically acceptable salt or solvate thereof.

2. A pharmaceutical composition comprising at least one compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof and at least one pharmaceutically acceptable carrier, adjuvant or vehicle.
3. The pharmaceutical composition of claim 2, further comprising one or more additional therapeutic agents.
4. The pharmaceutical composition of claim 3, wherein said additional therapeutic agents are selected from the group consisting of anti-inflammatory steroids, PDE-4 inhibitors, anti-muscarinic agents, cromolyn sodium, H₁ receptor antagonists, 5-HT₁ agonists, NSAIDs, angiotensin-converting enzyme inhibitors, angiotensin II receptor agonists, β -blockers, β -agonists, leukotriene antagonists, diuretics, aldosterone antagonists, ionotropic agents, and natriuretic peptides.

5. The pharmaceutical composition of claim 3, wherein said additional therapeutic agents are selected from the group consisting of pain management agents, anti-anxiety agents, anti-migraine agents, and therapeutic agents suitable for treating heart conditions, psychotic disorders, and glaucoma.
6. A method for selectively stimulating α_2C adrenergic receptors in a cell in need thereof, comprising contacting said cell with a therapeutically effective amount of at least one compound according to claim 1 or a salt or solvate thereof.
7. A method for treating one or more conditions associated with α_2C adrenergic receptors, comprising administering to a mammal in need of such treatment at least one compound according to claim 1 or a salt or solvate thereof.
8. The method of claim 7, wherein the conditions are selected from the group consisting of allergic rhinitis, congestion, pain, diarrhea, glaucoma, congestive heart failure, cardiac ischemia, manic disorders, depression, anxiety, migraine, stress-induced urinary incontinence, neuronal damage from ischemia and schizophrenia.
9. The method of claim 8, wherein the condition is congestion.
10. The method of claim 9, wherein the congestion is associated with perennial allergic rhinitis, seasonal allergic rhinitis, non-allergic rhinitis, vasomotor rhinitis, rhinitis medicamentosa, sinusitis, acute rhinosinusitis, or chronic rhinosinusitis.
11. The method of claim 9, wherein the congestion is caused by polyps or is virally induced.

12. The method of claim 9, wherein the congestion is associated with perennial allergic rhinitis, seasonal allergic rhinitis, non-allergic rhinitis, vasomotor rhinitis, rhinitis medicamentosa, sinusitis, acute rhinosinusitis, or chronic rhinosinusitis.

13. The method of claim 8, wherein the condition is pain.

14. The method of claim 12, wherein the pain is associated with neuropathy, inflammation, arthritis or diabetes.

15. A compound of claim 1, in isolated and purified form.