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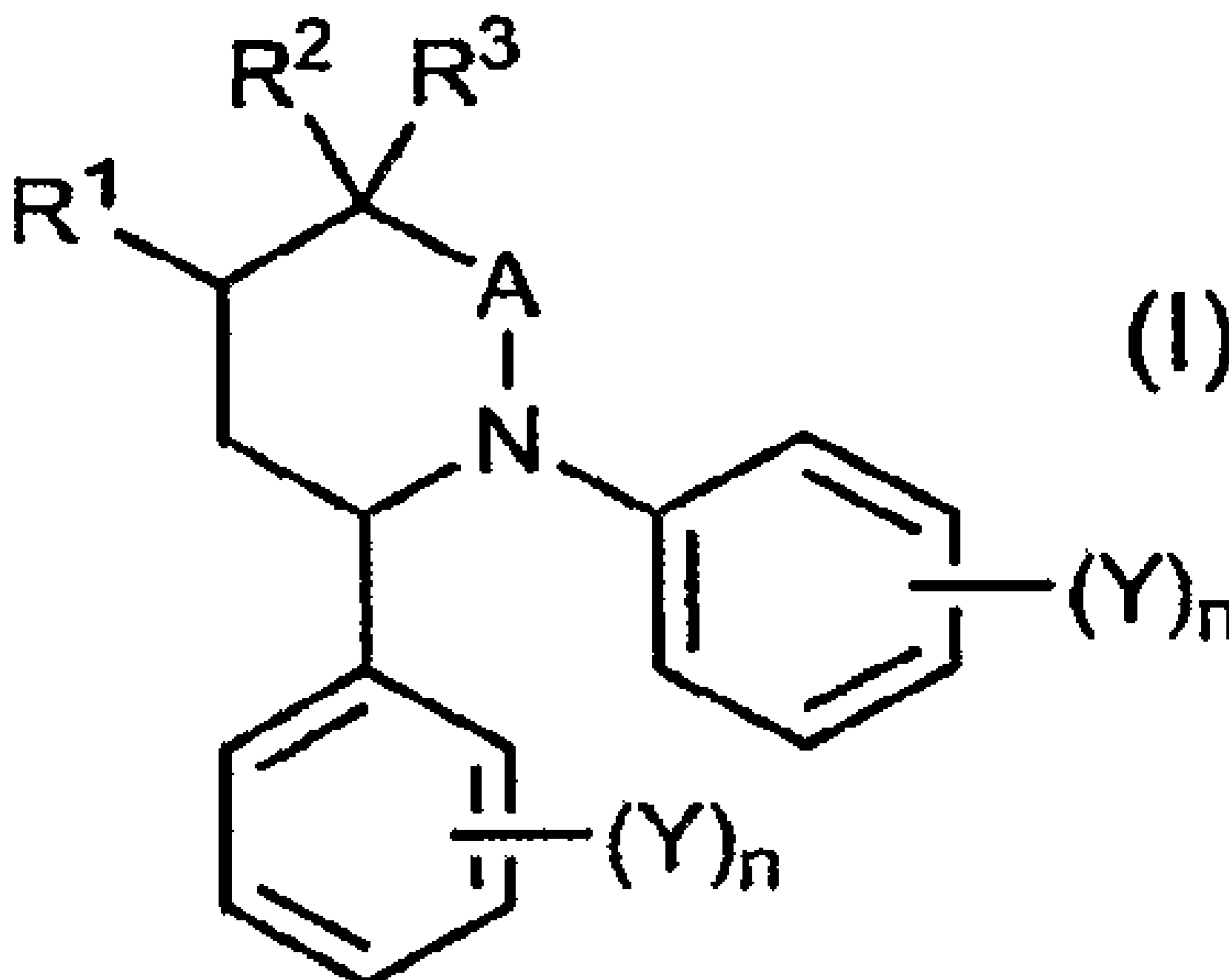
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(54) Titre : UTILISATION DE DIARYLE PIPERIDINES COMME MODULATEURS DE CB1

(54) Title: DIARYL PIPERIDINES AS CB1 MODULATORS



(57) Abrégé/Abstract:

A compound having the general structure of Formula (I): or a pharmaceutically acceptable salt, solvate, or ester thereof, are useful in treating diseases, disorders, or conditions such as metabolic syndrome (e.g., obesity, waist circumference, lipid profile, and



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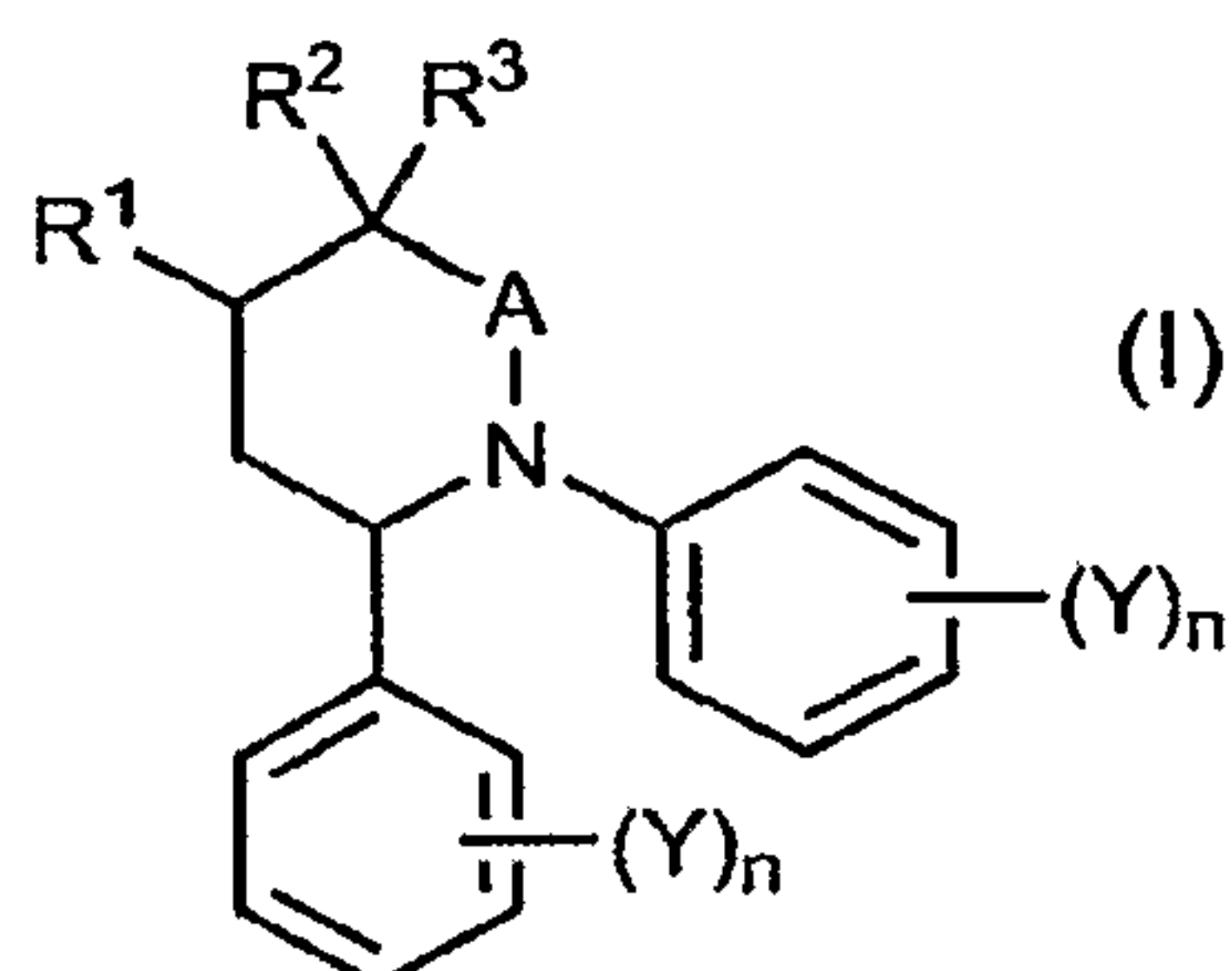
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(54) Title: DIARYL PIPERIDINES AS CB1 MODULATORS



(57) **Abstract:** A compound having the general structure of Formula (I); or a pharmaceutically acceptable salt, solvate, or ester thereof, are useful in treating diseases, disorders, or conditions such as metabolic syndrome (e.g., obesity, waist circumference, lipid profile, and insulin sensitivity), neuroinflammatory disorders, cognitive disorders, psychosis, addictive behavior, gastrointestinal disorders, and cardiovascular conditions.

DIARYL PIPERIDINES AS CB₁ MODULATORS

FIELD OF THE INVENTION

The present invention relates to diaryl piperidine compounds useful as CB₁ modulators (e.g., CB₁ antagonists, agonists or inverse agonists), pharmaceutical compositions comprising such compounds, and methods of treatment using the compounds and compositions to treat conditions such as metabolic syndrome, neuroinflammatory disorders, cognitive or psychiatric disorders, psychosis, addictive behaviors such as eating disorders, alcoholism and drug dependence, gastrointestinal disorders, cardiovascular conditions, weight reduction, lowering of waist circumference, treatment of dyslipidemia, insulin sensitivity, diabetes mellitus, hypertriglyceridemia, inflammation, migraine, nicotine dependence, Parkinson's disease, schizophrenia, sleep disorder, attention deficit hyperactivity disorder, male sexual dysfunction, premature ejaculation, premenstrual syndrome, seizure, epilepsy & convulsion, non-insulin dependent diabetes, dementia, major depressive disorder, bulimia nervosa, drug dependence, septic shock, cognitive disorder, endocrine disorders, eczema, emesis, allergy, glaucoma, hemorrhagic shock, hypertension, angina, thrombosis, atherosclerosis, restenosis, acute coronary syndrome, angina pectoris, arrhythmia, heart failure, cerebral ischemia, stroke, myocardial infarction, glomerulonephritis, thrombotic and thromboembolytic stroke, peripheral vascular diseases, neurodegenerative disease, osteoporosis, pulmonary disease, autoimmune disease, hypotension, arthropathy, cancer, demyelinating diseases, Alzheimer's disease, hypoactive sexual desire disorder, bipolar disorder, hyperlipidemia, narcotic dependence, Huntington's chorea, pain, multiple sclerosis, anxiety disorder, bone disorders such as osteoporosis, Paget's disease, rheumatoid arthritis, ulcerative colitis, irritable bowel syndrome and inflammatory bowel diseases.

BACKGROUND OF THE INVENTION

The CB₁ receptor is one of the most abundant neuromodulatory receptors in the brain, and is expressed at high levels in the hippocampus, cortex, cerebellum, and basal ganglia (e.g., Wilson et al., *Science*, **2002**, vol. 296, 678-682). Selective
5 CB₁ receptor antagonists, for example pyrazole derivatives such as rimonabant (e.g., U.S. 6,432,984), can be used to treat various conditions, such as obesity and metabolic syndrome (e.g., Bensaid et al., *Molecular Pharmacology*, **2003** vol. 63, no. 4, pp. 908-914; Trillou et al., *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2002** vol. 284, R345-R353; Kirkham, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2002** vol.
10 284, R343-R344), neuroinflammatory disorders (e.g., Adam, et al., *Expert Opin. Ther. Patents*, **2002**, vol. 12, no. 10, 1475-1489; U.S. 6,642,258), cognitive disorders and psychosis (e.g., Adam et al., *Expert Opin. Ther. Pat.*, **2002**, vol. 12, pp. 1475-1489), addiction (e.g., smoking cessation; U.S. Patent Publ. 2003/0087933), gastrointestinal disorders (e.g., Lange et al., *J. Med. Chem.* **2004**, vol. 47, 627-643)
15 and cardiovascular conditions (e.g., Porter et al., *Pharmacology and Therapeutics*, **2001** vol. 90, 45-60; Sanofi-Aventis Publication, Bear Stearns Conference, New York, September 14, 2004, pages 19-24).

However, there is still a need for improved cannabinoid agents, particularly selective CB₁ receptor antagonists, with fewer side-effects and improved efficacy. It
20 is therefore an object of the present invention to provide substituted piperazines useful in the treatment of diseases or conditions mediated by CB₁ receptors.

U.S. Patent Application Publication U.S. 2004/0167185 describes Edg-3 receptor inhibitors including substituted piperidines. U.S. Patent Application Publication U.S. 2002/0128476 and U.S. Patent Application Publication U.S.
25 2004/0180927 describe 3-piperidinone and 3-piperidinol cysteine protease inhibitors. U.S. Patent Application Publication U.S. 2001/0006972 describes aryl piperidine NK-1 receptor antagonists. U.S. Patent Application Publication U.S. 2003/0171588 describes piperidine-3-carboxamide derivatives. U.S. 5,234,895 describes 2-arylpyridone herbicides. U.S. 5,185,349 describes lactam ACAT inhibitors. U.S.
30 4,839,360 describes 1,6-diaryl-2-piperidones. U.S. 6,369,077 describes protease inhibitors. U.S. 5,332,817 describes 3-aminopiperidine derivatives. WO 03/062392 describes Edg-2, Edg-3, Edg-4, and Edg-7 antagonists. U.S. 5,580,883 describes

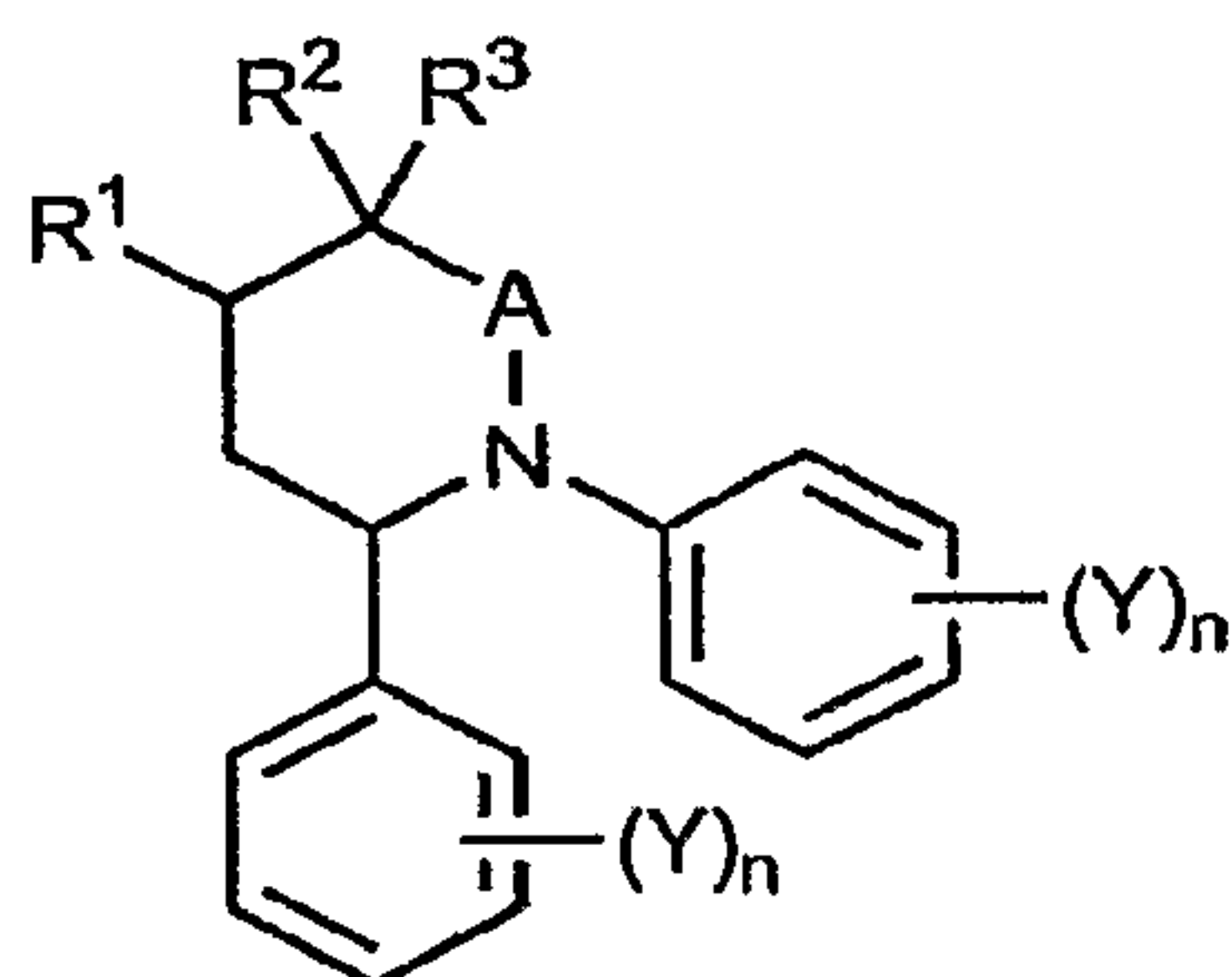
piperidine derivatives which present nerve degeneration. U.S. 6,441,001 describes piperidine derivatives as CCR3 modulators. Weis et al., Tetrahedron, 59 (2003) 1403-1411, describe the synthesis of diphenylpyralines. Josephsohn et al., J. Am. Chem. Soc., 125(2003) 4018-4019 describe methods of preparing diarylpiperidines.

5 However, the compounds disclosed in each of the above references differ substantially from the compounds of the present invention.

SUMMARY OF THE INVENTION

10 In its many embodiments, the present invention provides a novel class of substituted piperazine compounds as selective CB₁ receptor antagonists for treating various conditions including, but not limited to metabolic syndrome, neuroinflammatory disorders, cognitive or psychiatric disorders, psychosis, addictive behaviors such as eating disorders, alcoholism and drug dependence, gastrointestinal disorders, cardiovascular conditions, weight reduction, lowering of
15 waist circumference, treatment of dyslipidemia, insulin sensitivity, diabetes mellitus, hypertriglyceridemia, inflammation, migraine, nicotine dependence, Parkinson's disease, schizophrenia, sleep disorder, attention deficit hyperactivity disorder, male sexual dysfunction, premature ejaculation, premenstrual syndrome, seizure, epilepsy & convulsion, non-insulin dependent diabetes, dementia, major depressive disorder, bulimia nervosa, drug dependence, septic shock, cognitive disorder, endocrine
20 disorders, eczema, emesis, allergy, glaucoma, hemorrhagic shock, hypertension, angina, thrombosis, atherosclerosis, restenosis, acute coronary syndrome, angina pectoris, arrhythmia, heart failure, cerebral ischemia, stroke, myocardial infarction, glomerulonephritis, thrombotic and thromboembolytic stroke, peripheral vascular
25 diseases, neurodegenerative disease, osteoporosis, pulmonary disease, autoimmune disease, hypotension, arthropathy, cancer, demyelinating diseases, Alzheimer's disease, hypoactive sexual desire disorder, bipolar disorder, hyperlipidemia, narcotic dependence, Huntington's chorea, pain, multiple sclerosis, anxiety disorder, bone disorders such as osteoporosis, Paget's disease, rheumatoid
30 arthritis, ulcerative colitis, irritable bowel syndrome and inflammatory bowel diseases.

The selective CB₁ receptor antagonists of the present invention are piperazine derivatives having the structure of Formula (I):



(I)

5 or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

A is $-\text{CH}_2-$ or $-\text{C}(\text{O})-$;

R^1 is selected from the group consisting of H, $-\text{N}(\text{R}^4)(\text{R}^5)$, unsubstituted heterocyclyl, heterocyclyl substituted with one or more X groups, $-\text{N}_3$, and $-\text{O}-\text{R}^7$;

10 R^2 is selected from the group consisting of H, $-(\text{C}(\text{R}^6)_2)_p$ -aryl, cycloalkylalkyl, cycloalkylalkyl substituted with Z, $-(\text{C}(\text{R}^6)_2)_q$ -heterocyclyl, $-(\text{C}(\text{R}^6)_2)_p$ - $\text{S}(\text{O})_2$ -heterocyclyl, and $-\text{C}(\text{R}^6)_2$ - $\text{O}-\text{R}^7$,

wherein the aryl portion of said $-(\text{C}(\text{R}^6)_2)_p$ -aryl of R^2 is unsubstituted or substituted with one or more Y groups,

wherein the heterocyclyl portion of said

15 $-(\text{C}(\text{R}^6)_2)_p$ - $\text{S}(\text{O})_2$ -heterocyclyl of R^2 is unsubstituted or substituted with one or more X groups,

wherein the heterocyclyl portion of said $-(\text{C}(\text{R}^6)_2)_q$ -heterocyclyl of R^2 is unsubstituted or substituted with one or more X groups;

20 R^3 is selected from the group consisting of H, $-\text{C}(\text{R}^6)_2$ -aryl, $-\text{C}(\text{R}^6)_2$ - $\text{O}-\text{R}^7$, $-(\text{C}(\text{R}^6)_2)_q$ - $\text{C}(\text{O})-\text{N}(\text{R}^{12})_2$, $-(\text{C}(\text{R}^6)_2)_p$ - $\text{N}(\text{R}^9)-\text{C}(\text{O})-(\text{C}(\text{R}^6)_2)_q$ - R^{16} , $-(\text{C}(\text{R}^6)_2)_q$ - $\text{S}(\text{O})_2$ - $\text{N}(\text{R}^9)-(\text{C}(\text{R}^6)_2)_q$ - R^{15} , $-(\text{C}(\text{R}^6)_2)_q$ - $\text{N}(\text{R}^9)-\text{S}(\text{O})_2-(\text{C}(\text{R}^6)_2)_q$ - R^{15} and $-(\text{C}(\text{R}^6)_2)_q$ - $\text{N}(\text{R}^8)_2$,

wherein the aryl portion of said $-(\text{C}(\text{R}^6)_2)_p$ -aryl of R^3 is unsubstituted or substituted with one or more Y groups;

25 with the following independent provisos:

- (i) at least one of R^1 , R^2 , and R^3 is not H;
- (ii) when R^1 is $-\text{OH}$, at least one of R^2 and R^3 is not H; and
- (iii) when A is $-\text{C}(\text{O})-$, at least one of R^2 and R^3 is not H;

or, R^2 and R^3 together with the ring carbon atom to which they are shown attached form an unsubstituted heterocyclyl ring or a heterocyclyl ring substituted with one or more X groups;

R^4 is selected from the group consisting of H, -C(O)-alkyl, and alkyl;

5 R^5 is selected from the group consisting of $-(C(R^6)_2)_m-G$, -S(O)₂-alkyl, -S(O)₂-cycloalkyl, alkyl, -S(O)-cycloalkyl, -C(O)-cycloalkyl, -S(O)₂-aryl, -S(O)₂-(C(R⁶)₂)_m-aryl, -S(O)₂-heteroaryl, -C(O)-alkyl, -C(O)-aryl, -C(O)-O-alkyl, -C(O)-O-aryl, -C(O)-(C(R⁶)₂)_m-aryl, -C(O)-cycloalkylene-aryl, -C(O)-heteroaryl, -C(O)-heteroarylalkyl, -C(O)-(C(R⁶)₂)_m-O-aryl, -C(O)-(benzo-fused cycloalkyl), -S(O)₂-(benzo-fused heterocyclyl), -C(O)-N(R⁹)-(C(R⁶)₂)_m-aryl, 10 -C(O)-N(R⁹)-aryl, cycloalkyl, benzo-fused cycloalkyl, unsubstituted aryl, aryl substituted with one or more Y groups, unsubstituted heterocyclyl, and heterocyclyl substituted with one or more X groups, wherein the aryl or heteroaryl portion of said -S(O)₂-aryl, -S(O)₂-(C(R⁶)₂)_m-aryl, 15 -S(O)₂-heteroaryl, -C(O)-aryl, -C(O)-(C(R⁶)₂)_m-aryl, -C(O)-cycloalkylene-aryl, -C(O)-heteroaryl, -C(O)-(C(R⁶)₂)_m-O-aryl, -C(O)-N(R⁹)-(C(R⁶)₂)_m-aryl, or -C(O)-N(R⁹)-aryl of R^5 is unsubstituted or substituted with one or more Y groups;

wherein the heterocyclyl portion of -S(O)₂-(benzo-fused heterocyclyl) aryl of 20 R^5 is unsubstituted or substituted with one or more X groups;

each R^6 is independently selected from the group consisting of H and alkyl;

R^7 is selected from the group consisting of H, alkyl, unsubstituted heteroaryl and heteroaryl substituted with one or more Y groups, unsubstituted aryl, and aryl substituted with one or more Y groups;

25 each R^8 is independently selected from the group consisting of H, alkyl, arylalkyl, heteroarylalkyl, unsubstituted aryl, unsubstituted heteroaryl, -C(O)-alkyl, -C(O)-aryl, -C(O)-cycloalkyl, -C(O)N(R⁹)₂, -S(O)₂-aryl, -S(O)₂-heteroaryl, -SO₂N(R⁹)₂, -S(O)₂-cycloalkyl, aryl and heteroaryl substituted with one or more Y groups, and -S(O)₂-alkyl,

30 wherein the aryl portion of said arylalkyl, -C(O)-aryl or -S(O)₂-aryl and the heteroaryl portion of said heteroarylalkyl, -S(O)₂-heteroaryl of R^8 is unsubstituted or substituted with one or more Y groups,

6

wherein the alkyl portion of said arylalkyl and heteroarylalkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said alkyl portion is NOT Cbz or Boc;

- 5 each R^9 is independently selected from the group consisting of H, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, unsubstituted aryl and unsubstituted heteroaryl;
- each R^{12} is independently selected from the group consisting of H, alkyl, cycloalkylalkyl, $-(C(R^6)_2)_q-C(O)R^{13}$, benzoheterocyclyl, benzocycloalkyl, $-(C(R^6)_2)_q-N(R^9)-C(O)R^{13}$, $-(C(R^6)_2)_q-N(R^{14})_2$, arylalkyl, heteroarylalkyl, HO-alkyl-,
- 10 alkyl-O-, aryl-O-, Y-alkylenyl-O-, W-O-alkylenyl, heterocyclalkyl, unsubstituted cycloalkyl, cycloalkyl substituted with one or more X groups, unsubstituted heterocyclyl, heterocyclyl substituted with one or more X groups, unsubstituted heteroaryl, heteroaryl substituted with one or more Y groups, unsubstituted aryl and aryl substituted with one or more Y groups, and
- 15 wherein the aryl and heteroaryl portion of said arylalkyl and heteroarylalkyl is unsubstituted or substituted with one or more Y groups,
- wherein the alkyl portion of said cycloalkylalkyl, arylalkyl and heteroarylalkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said alkyl portion is NOT Cbz or Boc,
- 20 wherein the cycloalkyl of said cycloalkylalkyl is unsubstituted or substituted with one or more X groups,
- wherein the benzo portion of said benzoheterocyclyl can be optionally substituted with one or more Y groups and the heterocyclyl portion of benzoheterocyclyl can be optionally substituted with one or more X
- 25 groups,
- wherein the benzo portion of said benzocycloalkyl can be optionally substituted with one or more Y groups and the cycloalkyl portion of benzocycloalkyl can be optionally substituted with one or more X groups;
- with the following provisos that
- 30 for $-N(R^{14})_2$ of R^{12} , the two R^{14} groups, with the ring nitrogen atom to which they are shown attached, form an unsubstituted heterocyclyl ring or a heterocyclyl ring substituted with one or more X groups;

each R^{13} is independently selected from the group consisting of H, alkyl, cycloalkylalkyl, arylalkyl, heteroarylalkyl, HO-alkyl-, alkyl-O-, aryl-O-, unsubstituted cycloalkyl, cycloalkyl substituted with one or more X groups, unsubstituted heterocyclyl, heterocyclyl substituted with one or more X groups, unsubstituted heteroaryl, heteroaryl substituted with one or more Y groups, unsubstituted aryl and aryl substituted with one or more Y groups

wherein the aryl and heteroaryl portion of said arylalkyl and heteroarylalkyl is unsubstituted or substituted with one or more Y groups,

wherein the alkyl portion of said cycloalkylalkyl, arylalkyl and heteroarylalkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said alkyl portion is NOT Cbz or Boc,

wherein the cycloalkyl of said cycloalkylalkyl is unsubstituted or substituted with one or more X groups;

each R^{14} is independently selected from the group consisting of H, Boc,

unsubstituted alkyl, alkyl substituted with one or more X groups, unsubstituted cycloalkyl, cycloalkyl substituted with one or more Y groups, unsubstituted aryl, aryl substituted with one or more Y groups, heterocyclyl, unsubstituted heteroaryl and heteroaryl substituted with one or more Y groups;

each R^{15} is independently selected from the group consisting of H, alkyl,

$-N(R^4)(R^5)$, $(C(R^6)_2)_q-N(R^{14})_2$, alkylene- CF_3 , $-CF_3$, cycloalkylalkyl, unsubstituted cycloalkyl, cycloalkyl substituted with one or more X groups, unsubstituted heterocyclyl, heterocyclyl substituted with one or more X groups, benzoheterocyclyl, benzocycloalkyl, unsubstituted heteroaryl, heteroaryl substituted with one or more Y groups, unsubstituted aryl and aryl substituted with one or more Y groups,

wherein the alkyl portion of said cycloalkylalkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said alkyl portion is NOT Cbz or Boc,

wherein the cycloalkyl of said cycloalkylalkyl is unsubstituted or substituted with one or more X groups,

wherein the benzo portion of said benzoheterocyclyl can be optionally substituted with one or more Y groups and the heterocyclyl portion of

benzoheterocyclyl can be optionally substituted with one or more X groups,

wherein the benzo portion of said benzocycloalkyl can be optionally

substituted with one or more Y groups and the cycloalkyl portion of

5 benzocycloalkyl can be optionally substituted with one or more X groups;

each R^{16} is independently selected from the group consisting of H, alkyl,

cycloalkylalkyl, $-(C(R^6)_2)_p-C(O)R^{13}$, $-(C(R^6)_2)_p-N(R^9)-C(O)R^{13}$, $-(C(R^6)_2)_p-N(R^{14})_2$,

arylalkyl, heteroarylalkyl, HO-alkyl-, alkyl-O-, aryl-O-, unsubstituted cycloalkyl,

cycloalkyl substituted with one or more X groups, unsubstituted heterocyclyl,

10 heterocyclyl substituted with one or more X groups, unsubstituted heteroaryl,

heteroaryl substituted with one or more Y groups, unsubstituted aryl and aryl

substituted with one or more Y groups, and

wherein the aryl and heteroaryl portion of said arylalkyl and heteroarylalkyl is

unsubstituted or substituted with one or more Y groups,

15 wherein the alkyl portion of said cycloalkylalkyl, arylalkyl and heteroarylalkyl is

unsubstituted or substituted with one or more X groups with the proviso

that X substituted on said alkyl portion is NOT Cbz or Boc,

wherein the cycloalkyl of said cycloalkylalkyl is unsubstituted or substituted

with one or more X groups,

20 for $-N(R^{14})_2$, the two R^{14} groups, with the ring nitrogen atom to which they are

shown attached, form an unsubstituted heterocyclyl ring or a heterocyclyl

ring substituted with one or more X groups;

G is selected from the group consisting of H, alkyl, unsubstituted aryl, aryl

substituted with one or more Y groups, $-CN$, cycloalkyl, $-O-R^7$, $-S-R^7$,

25 unsubstituted heteroaryl, heteroaryl substituted with one or more Y groups,

$-N(R^8)_2$, unsubstituted heterocyclyl, and heterocyclyl substituted with one or more

X groups;

each W is independently selected from the group consisting of hydrogen, alkyl, aryl,

$-C(O)-alkyl$, $-C(O)-O-alkyl$, $-C(R^6)_2-N(R^6)_2$, and

30 $-C(R^6)_2-N(R^6)-S(O)_2-R^6$;

each X is independently selected from the group consisting of hydrogen, $-OH$, alkyl,

arylalkyl, heteroarylalkyl, Cbz, Boc, alkylsulfonyl, acetyl,

-C(O)-R¹², -C(O)-N(R⁹)₂, -C(O)-heteroaryl, heteroaryl, -S(O)₂-cycloalkyl,
-C(O)-alkyl, -C(O)-O-alkyl, -(C(R⁶)₂)_m-aryl and aryl

wherein the aryl and heteroaryl portion of said arylalkyl and heteroarylalkyl is
unsubstituted or substituted with one or more Y groups,

5 wherein the alkyl portion of said arylalkyl and heteroarylalkyl is unsubstituted
or substituted with one or more X groups with the proviso that X
substituted on said alkyl portion is NOT Cbz or Boc,

wherein said heteroaryl or the heteroaryl portion of said -C(O)-heteroaryl
of X is unsubstituted or substituted with one or more substituents
10 selected from the group consisting of halogen, -OH, -O-alkyl, haloalkyl,
and -CN, and

wherein said aryl or the aryl portion of said -(C(R⁶)₂)_m-aryl of X is
unsubstituted or substituted with one or more substituents selected
from the group consisting of halogen, -OH, -O-alkyl, haloalkyl, and -CN

15 wherein in a single X moiety, =O, can replace two available hydrogens on
the same carbon on a ring system;

each Y is independently selected from the group consisting of hydrogen, halogen,
alkyl, aryl, -C(O)-alkyl, -O-alkyl, -O-heteroaryl, -O-aryl, -O-R⁹, haloalkyl,
-O-haloalkyl, -CN, -C(O)-O-alkyl, -N(R⁶)₂, -C(R⁶)₂-N(R⁶)₂,
20 -S(O)₂-heterocyclyl, -S(O)₂-heteroaryl and -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶; or
two of said Y groups attached to adjacent carbon atoms form a -O-CH₂-O- or
-O-CH₂CH₂-O- group;

each Z is independently selected from the group consisting of hydrogen, alkyl,
arylalkyl, heteroarylalkyl, -C(O)-N(R⁹)₂, -C(O)-heteroaryl, heteroaryl,
25 -S(O)₂-cycloalkyl, -C(O)-alkyl, -(C(R⁶)₂)_m-aryl, -N(R⁶)-S(O)₂-R⁹ and aryl

wherein the aryl and heteroaryl portion of said arylalkyl and heteroarylalkyl is
unsubstituted or substituted with one or more Y groups,

wherein the alkyl portion of said arylalkyl and heteroarylalkyl is unsubstituted
or substituted with one or more X groups with the proviso that X
30 substituted on said alkyl portion is NOT Cbz or Boc,

wherein said heteroaryl or the heteroaryl portion of said -C(O)-heteroaryl
of Z is unsubstituted or substituted with one or more substituents

10

selected from the group consisting of halogen, -OH, -O-alkyl, haloalkyl, and -CN, and

wherein said aryl or the aryl portion of said $-(C(R^6)_2)_m$ -aryl of Z is

unsubstituted or substituted with one or more substituents selected

5 from the group consisting of halogen, -OH, -O-alkyl, haloalkyl, and -CN;

wherein in a single Z moiety, =O, can replace two available hydrogens on the same carbon on a ring system;

each n, p and q is independently an integer from 0-5; and

m is an integer from 1-5.

10 In another embodiment, the present invention is directed to a pharmaceutical composition comprising a therapeutically effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof, and at least one pharmaceutically acceptable carrier.

In another embodiment, the present invention is directed to a method of
15 treating a disease or disorder in a patient, such as metabolic syndrome, neuroinflammatory disorders, cognitive or psychiatric disorders, psychosis, addictive behaviors such as eating disorders, alcoholism and drug dependence, gastrointestinal disorders, cardiovascular conditions, weight reduction, lowering of waist circumference, treatment of dyslipidemia, insulin sensitivity, diabetes mellitus,
20 hypertriglyceridemia, inflammation, migraine, nicotine dependence, Parkinson's disease, schizophrenia, sleep disorder, attention deficit hyperactivity disorder, male sexual dysfunction, premature ejaculation, premenstrual syndrome, seizure, epilepsy & convulsion, non-insulin dependent diabetes, dementia, major depressive disorder, bulimia nervosa, drug dependence, septic shock, cognitive disorder, endocrine
25 disorders, eczema, emesis, allergy, glaucoma, hemorrhagic shock, hypertension, angina, thrombosis, atherosclerosis, restenosis, acute coronary syndrome, angina pectoris, arrhythmia, heart failure, cerebral ischemia, stroke, myocardial infarction, glomerulonephritis, thrombotic and thromboembolytic stroke, peripheral vascular diseases, neurodegenerative disease, osteoporosis, pulmonary disease,
30 autoimmune disease, hypotension, arthropathy, cancer, demyelinating diseases, Alzheimer's disease, hypoactive sexual desire disorder, bipolar disorder, hyperlipidemia, narcotic dependence, Huntington's chorea, pain, multiple sclerosis,

anxiety disorder, bone disorders such as osteoporosis, Paget's disease, rheumatoid arthritis, ulcerative colitis, irritable bowel syndrome and inflammatory bowel diseases. The method comprises administering to the patient an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof.

In another embodiment, the present invention is directed to a method of treating a disease or disorder in a patient, such as metabolic syndrome, neuroinflammatory disorders, cognitive or psychiatric disorders, psychosis, addictive behaviors such as eating disorders, alcoholism and drug dependence, gastrointestinal disorders, cardiovascular conditions, weight reduction, lowering of waist circumference, treatment of dyslipidemia, insulin sensitivity, diabetes mellitus, hypertriglyceridemia, inflammation, migraine, nicotine dependence, Parkinson's disease, schizophrenia, sleep disorder, attention deficit hyperactivity disorder, male sexual dysfunction, premature ejaculation, premenstrual syndrome, seizure, epilepsy & convulsion, non-insulin dependent diabetes, dementia, major depressive disorder, bulimia nervosa, drug dependence, septic shock, cognitive disorder, endocrine disorders, eczema, emesis, allergy, glaucoma, hemorrhagic shock, hypertension, angina, thrombosis, atherosclerosis, restenosis, acute coronary syndrome, angina pectoris, arrhythmia, heart failure, cerebral ischemia, stroke, myocardial infarction, glomerulonephritis, thrombotic and thromboembolytic stroke, peripheral vascular diseases, neurodegenerative disease, osteoporosis, pulmonary disease, autoimmune disease, hypotension, arthropathy, cancer, demyelinating diseases, Alzheimer's disease, hypoactive sexual desire disorder, bipolar disorder, hyperlipidemia, narcotic dependence, Huntington's chorea, pain, multiple sclerosis, anxiety disorder, bone disorders such as osteoporosis, Paget's disease, rheumatoid arthritis, ulcerative colitis, irritable bowel syndrome and inflammatory bowel diseases. The method comprises administering to the patient an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof, in combination with at least one other pharmaceutical compound, such as a cholesterol lowering compound.

DETAILED DESCRIPTION OF THE INVENTION

In a first embodiment, the present invention is directed to a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof, as described herein.

5 In another embodiment of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof,

A is $-\text{CH}_2-$ or $-\text{C}(\text{O})-$;

R^1 is selected from the group consisting of H, $-\text{N}(\text{R}^4)(\text{R}^5)$, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups,
10 $-\text{N}_3$, and $-\text{O}-\text{R}^7$;

R^2 is selected from the group consisting of H, $-(\text{C}(\text{R}^6)_2)_p-(\text{C}_6-\text{C}_{10})\text{aryl}$, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl substituted with Z, $-(\text{C}(\text{R}^6)_2)_q-(\text{C}_2-\text{C}_{10})\text{heterocyclyl}$, $-(\text{C}(\text{R}^6)_2)_p-\text{S}(\text{O})_2-(\text{C}_2-\text{C}_{10})\text{heterocyclyl}$, and $-\text{C}(\text{R}^6)_2-\text{O}-\text{R}^7$,

15 wherein the (C₆-C₁₀)aryl portion of said $-(\text{C}(\text{R}^6)_2)_p-(\text{C}_6-\text{C}_{10})\text{aryl}$ of R^2 is unsubstituted or substituted with one or more Y groups,

wherein the (C₂-C₁₀)heterocyclyl portion of said $-(\text{C}(\text{R}^6)_2)_p-\text{S}(\text{O})_2-(\text{C}_2-\text{C}_{10})\text{heterocyclyl}$ of R^2 is unsubstituted or substituted with one or more X groups,

20 wherein the (C₂-C₁₀)heterocyclyl portion of said $-(\text{C}(\text{R}^6)_2)_q-(\text{C}_2-\text{C}_{10})\text{heterocyclyl}$ of R^2 is unsubstituted or substituted with one or more X groups;

R^3 is selected from the group consisting of H, $-(\text{C}(\text{R}^6)_2)_p-(\text{C}_6-\text{C}_{10})\text{aryl}$, $-\text{C}(\text{R}^6)_2-\text{O}-\text{R}^7$, $-(\text{C}(\text{R}^6)_2)_q-\text{C}(\text{O})-\text{N}(\text{R}^{12})_2$, $-(\text{C}(\text{R}^6)_2)_p-\text{N}(\text{R}^9)-\text{C}(\text{O})-(\text{C}(\text{R}^6)_2)_q-\text{R}^{16}$,
25 $-(\text{C}(\text{R}^6)_2)_q-\text{S}(\text{O})_2-\text{N}(\text{R}^9)-(\text{C}(\text{R}^6)_2)_q-\text{R}^{15}$, $-(\text{C}(\text{R}^6)_2)_q-\text{N}(\text{R}^9)-\text{S}(\text{O})_2-(\text{C}(\text{R}^6)_2)_q-\text{R}^{15}$ and $-(\text{C}(\text{R}^6)_2)_q-\text{N}(\text{R}^8)_2$,

wherein the (C₆-C₁₀)aryl portion of said $-(\text{C}(\text{R}^6)_2)_p-(\text{C}_6-\text{C}_{10})\text{aryl}$ of R^3 is unsubstituted or substituted with one or more Y groups;

with the following independent provisos:

- 30 (i) at least one of R^1 , R^2 , and R^3 is not H;
(ii) when R^1 is $-\text{OH}$, at least one of R^2 and R^3 is not H; and
(iii) when A is $-\text{C}(\text{O})-$, at least one of R^2 and R^3 is not H;

or, R^2 and R^3 together with the ring carbon atom to which they are shown attached form an unsubstituted (C_2-C_{10}) heterocyclyl ring or a (C_2-C_{10}) heterocyclyl ring substituted with one or more X groups;

R^4 is selected from the group consisting of H, $-C(O)-(C_1-C_6)$ alkyl, and (C_1-C_6) alkyl;

5 R^5 is selected from the group consisting of $-(C(R^6)_2)_m-G$, $-S(O)_2-(C_1-C_6)$ alkyl, $-S(O)_2-(C_3-C_6)$ cycloalkyl, (C_1-C_6) alkyl, $-S(O)-(C_3-C_6)$ cycloalkyl, $-C(O)-(C_3-C_6)$ cycloalkyl, $-S(O)_2-(C_6-C_{10})$ aryl, $-S(O)_2-(C(R^6)_2)_m-(C_6-C_{10})$ aryl, $-S(O)_2-(C_2-C_{10})$ heteroaryl, $-C(O)-(C_1-C_6)$ alkyl, $-C(O)-(C_6-C_{10})$ aryl, $-C(O)-O-(C_1-C_6)$ alkyl, $-C(O)-O-(C_6-C_{10})$ aryl, $-C(O)-(C(R^6)_2)_m-(C_6-C_{10})$ aryl,
10 $-C(O)-(C_3-C_6)$ cycloalkylene- (C_6-C_{10}) aryl, $-C(O)-(C_2-C_{10})$ heteroaryl, $-C(O)-(C_2-C_{10})$ heteroaryl (C_1-C_6) alkyl, $-C(O)-(C(R^6)_2)_m-O-(C_6-C_{10})$ aryl, $-C(O)-(benzo-fused (C_3-C_6)cycloalkyl)$, $-S(O)_2-(benzo-fused (C_2-C_{10})heterocyclyl)$, $-C(O)-N(R^9)-(C(R^6)_2)_m-(C_6-C_{10})$ aryl, $-C(O)-N(R^9)-(C_6-C_{10})$ aryl, (C_3-C_6) cycloalkyl, benzo-fused (C_3-C_6) cycloalkyl, unsubstituted (C_6-C_{10}) aryl, (C_6-C_{10}) aryl substituted with one or more Y groups, unsubstituted (C_2-C_{10}) heterocyclyl, and
15 (C_2-C_{10}) heterocyclyl substituted with one or more X groups,

wherein the (C_6-C_{10}) aryl or (C_2-C_{10}) heteroaryl portion of said $-S(O)_2-(C_6-C_{10})$ aryl, $-S(O)_2-(C(R^6)_2)_m-(C_6-C_{10})$ aryl, $-S(O)_2-(C_2-C_{10})$ heteroaryl, $-C(O)-(C_6-C_{10})$ aryl,
20 $-C(O)-(C(R^6)_2)_m-(C_6-C_{10})$ aryl, $-C(O)-(C_3-C_6)$ cycloalkylene- (C_6-C_{10}) aryl, $-C(O)-(C_2-C_{10})$ heteroaryl, $-C(O)-(C(R^6)_2)_m-O-(C_6-C_{10})$ aryl, $-C(O)-N(R^9)-(C(R^6)_2)_m-(C_6-C_{10})$ aryl, or $-C(O)-N(R^9)-(C_6-C_{10})$ aryl of R^5 is unsubstituted or substituted with one or more Y groups;

wherein the heterocyclyl portion of $-S(O)_2-(benzo-fused (C_2-C_{10})heterocyclyl)$

25 aryl of R^5 is unsubstituted or substituted with one or more X groups;

each R^6 is independently selected from the group consisting of H and (C_1-C_6) alkyl;

R^7 is selected from the group consisting of H, (C_1-C_6) alkyl, unsubstituted (C_2-C_{10}) heteroaryl and (C_2-C_{10}) heteroaryl substituted with one or more Y groups, unsubstituted (C_6-C_{10}) aryl, and (C_6-C_{10}) aryl substituted with one or more Y
30 groups;

each R^8 is independently selected from the group consisting of H, (C_1-C_6) alkyl, (C_6-C_{10}) aryl (C_1-C_6) alkyl, (C_2-C_{10}) heteroaryl (C_1-C_6) alkyl, unsubstituted (C_6-C_{10}) aryl,

unsubstituted (C₂-C₁₀)heteroaryl,

-C(O)-(C₁-C₆)alkyl, -C(O)-(C₆-C₁₀)aryl, -C(O)-(C₃-C₆)cycloalkyl, -C(O)N(R⁹)₂,

-S(O)₂-(C₆-C₁₀)aryl, -S(O)₂-(C₂-C₁₀)heteroaryl, -SO₂N(R⁹)₂,

-S(O)₂-(C₃-C₆)cycloalkyl, (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl substituted with one
5 or more Y groups, and -S(O)₂-(C₁-C₆)alkyl,

wherein the (C₆-C₁₀)aryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl, -C(O)-(C₆-
C₁₀)aryl or -S(O)₂-(C₆-C₁₀)aryl and the (C₂-C₁₀)heteroaryl portion of said
(C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, -S(O)₂-(C₂-C₁₀)heteroaryl of R⁸ is
unsubstituted or substituted with one or more Y groups,

10 wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and
(C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or
more X groups with the proviso that X substituted on said (C₁-C₆)alkyl
portion is NOT Cbz or Boc;

each R⁹ is independently selected from the group consisting of H, (C₁-C₆)alkyl,

15 halo(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, unsubstituted (C₆-
C₁₀)aryl and unsubstituted (C₂-C₁₀)heteroaryl;

each R¹² is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-
C₆)cycloalkyl(C₁-C₆)alkyl, -(C(R⁶)₂)_q-C(O)R¹³, benzo(C₂-C₁₀)heterocyclyl,
benzocyclo(C₁-C₆)alkyl,

20 -(C(R⁶)₂)_q-N(R⁹)-C(O)R¹³, -(C(R⁶)₂)_q-N(R¹⁴)₂, (C₆-C₁₀)aryl(C₁-C₆)alkyl,
(C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-,
Y-(C₁-C₆)alkylenyl-O-, W-O-(C₁-C₆)alkylenyl, (C₂-C₁₀)heterocyclyl(C₁-C₆)alkyl,
unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X
groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with
25 one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl
substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-
C₁₀)aryl substituted with one or more Y groups, and

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-
C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or
30 substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-
C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or

15

substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups,

5 wherein the benzo portion of said benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more Y groups and the (C₂-C₁₀)heterocyclyl portion of benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more X groups,

10 wherein the benzo portion of said benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more Y groups and the (C₃-C₆)cycloalkyl portion of benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more X groups;

with the following provisos that

15 for -N(R¹⁴)₂ of R¹², the two R¹⁴ groups, with the ring nitrogen atom to which they are shown attached, form an unsubstituted (C₂-C₁₀)heterocyclyl ring or a (C₂-C₁₀)heterocyclyl ring substituted with one or more X groups;

each R¹³ is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups

25 wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

30 wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups;

each R¹⁴ is independently selected from the group consisting of H, Boc,

unsubstituted (C₁-C₆)alkyl, (C₁-C₆)alkyl substituted with one or more X groups,

5 unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl substituted with one or more Y groups, (C₂-C₁₀)heterocyclyl, unsubstituted (C₂-C₁₀)heteroaryl and (C₂-C₁₀)heteroaryl substituted with one or more Y groups;

each R¹⁵ is independently selected from the group consisting of H, (C₁-C₆)alkyl, -

10 N(R⁴)(R⁵), (C(R⁶)₂)_q-N(R¹⁴)₂, (C₁-C₆)alkylenyl-CF₃, -CF₃, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, benzo(C₂-C₁₀)heterocyclyl, benzocyclo(C₁-C₆)alkyl, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, 15 unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is

unsubstituted or substituted with one or more X groups with the proviso

20 that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is

unsubstituted or substituted with one or more X groups,

wherein the benzo portion of said benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more Y groups and the (C₂-C₁₀)heterocyclyl portion

25 of benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more X groups,

wherein the benzo portion of said benzocyclo(C₁-C₆)alkyl can be optionally

substituted with one or more Y groups and the (C₃-C₆)cycloalkyl portion of

benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more X

30 groups;

each R¹⁶ is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-

C₆)cycloalkyl(C₁-C₆)alkyl, -(C(R⁶)₂)_p-C(O)R¹³,

$-(C(R^6)_2)_p-N(R^9)-C(O)R^{13}$, $-(C(R^6)_2)_p-N(R^{14})_2$, (C_6-C_{10}) aryl (C_1-C_6) alkyl,
 (C_2-C_{10}) heteroaryl (C_1-C_6) alkyl, $HO-(C_1-C_6)$ alkyl-, (C_1-C_6) alkyl-O-, (C_6-C_{10}) aryl-O-,
 unsubstituted (C_3-C_6) cycloalkyl, (C_3-C_6) cycloalkyl substituted with one or more X
 groups, unsubstituted (C_2-C_{10}) heterocyclyl, (C_2-C_{10}) heterocyclyl substituted with
 one or more X groups, unsubstituted (C_2-C_{10}) heteroaryl, (C_2-C_{10}) heteroaryl
 substituted with one or more Y groups, unsubstituted (C_6-C_{10}) aryl and $(C_6-$
 $C_{10})$ aryl substituted with one or more Y groups, and

wherein the (C_6-C_{10}) aryl and (C_2-C_{10}) heteroaryl portion of said $(C_6-$
 $C_{10})$ aryl (C_1-C_6) alkyl and (C_2-C_{10}) heteroaryl (C_1-C_6) alkyl is unsubstituted or
 substituted with one or more Y groups,

wherein the (C_1-C_6) alkyl portion of said (C_3-C_6) cycloalkyl (C_1-C_6) alkyl, $(C_6-$
 $C_{10})$ aryl (C_1-C_6) alkyl and (C_2-C_{10}) heteroaryl (C_1-C_6) alkyl is unsubstituted or
 substituted with one or more X groups with the proviso that X substituted
 on said (C_1-C_6) alkyl portion is NOT Cbz or Boc,

wherein the (C_3-C_6) cycloalkyl of said (C_3-C_6) cycloalkyl (C_1-C_6) alkyl is
 unsubstituted or substituted with one or more X groups,

for $-N(R^{14})_2$, the two R^{14} groups, with the ring nitrogen atom to which they are
 shown attached, form an unsubstituted (C_2-C_{10}) heterocyclyl ring or a
 (C_2-C_{10}) heterocyclyl ring substituted with one or more X groups;

G is selected from the group consisting of H, (C_1-C_6) alkyl, unsubstituted (C_6-C_{10}) aryl,
 (C_6-C_{10}) aryl substituted with one or more Y groups, $-CN$, (C_3-C_6) cycloalkyl, $-O-R^7$,
 $-S-R^7$, unsubstituted (C_2-C_{10}) heteroaryl, (C_2-C_{10}) heteroaryl substituted with one or
 more Y groups, $-N(R^8)_2$, unsubstituted (C_2-C_{10}) heterocyclyl, and
 (C_2-C_{10}) heterocyclyl substituted with one or more X groups;

each W is independently selected from the group consisting of hydrogen,
 (C_1-C_6) alkyl, (C_6-C_{10}) aryl, $-C(O)-(C_1-C_6)$ alkyl, $-C(O)-O-(C_1-C_6)$ alkyl,
 $-C(R^6)_2-N(R^6)_2$, and $-C(R^6)_2-N(R^6)-S(O)_2-R^6$;

each X is independently selected from the group consisting of hydrogen, $-OH$,
 (C_1-C_6) alkyl, (C_6-C_{10}) aryl (C_1-C_6) alkyl, (C_2-C_{10}) heteroaryl (C_1-C_6) alkyl, Cbz, Boc,
 (C_1-C_6) alkylsulfonyl, acetyl, $-C(O)-R^{12}$, $-C(O)-N(R^9)_2$,
 $-C(O)-(C_2-C_{10})$ heteroaryl, (C_2-C_{10}) heteroaryl, $-S(O)_2-(C_3-C_6)$ cycloalkyl,

-C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -(C(R⁶)₂)_m-(C₆-C₁₀)aryl and (C₆-C₁₀)aryl

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said -C(O)-(C₂-C₁₀)heteroaryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN, and

wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said -(C(R⁶)₂)_m-(C₆-C₁₀)aryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN

wherein in a single X moiety, =O, can replace two available hydrogens on the same carbon on a ring system;

each Y is independently selected from the group consisting of hydrogen, halogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -O-(C₁-C₆)alkyl, -O-(C₂-C₁₀)heteroaryl, -O-(C₆-C₁₀)aryl, -O-R⁹, halo(C₁-C₆)alkyl, -O-halo(C₁-C₆)alkyl, -CN, -C(O)-O-(C₁-C₆)alkyl, -N(R⁶)₂, -C(R⁶)₂-N(R⁶)₂, -S(O)₂-(C₂-C₁₀)heterocyclyl, -S(O)₂-(C₂-C₁₀)heteroaryl and -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶; or

two of said Y groups attached to adjacent carbon atoms form a -O-CH₂-O- or -O-CH₂CH₂-O- group;

each Z is independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, -C(O)-N(R⁹)₂, -C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl, -S(O)₂-(C₃-C₆)cycloalkyl, -C(O)-(C₁-C₆)alkyl, -(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -N(R⁶)-S(O)₂-R⁹ and (C₆-C₁₀)aryl

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said -C(O)-(C₂-C₁₀)heteroaryl of Z is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN, and

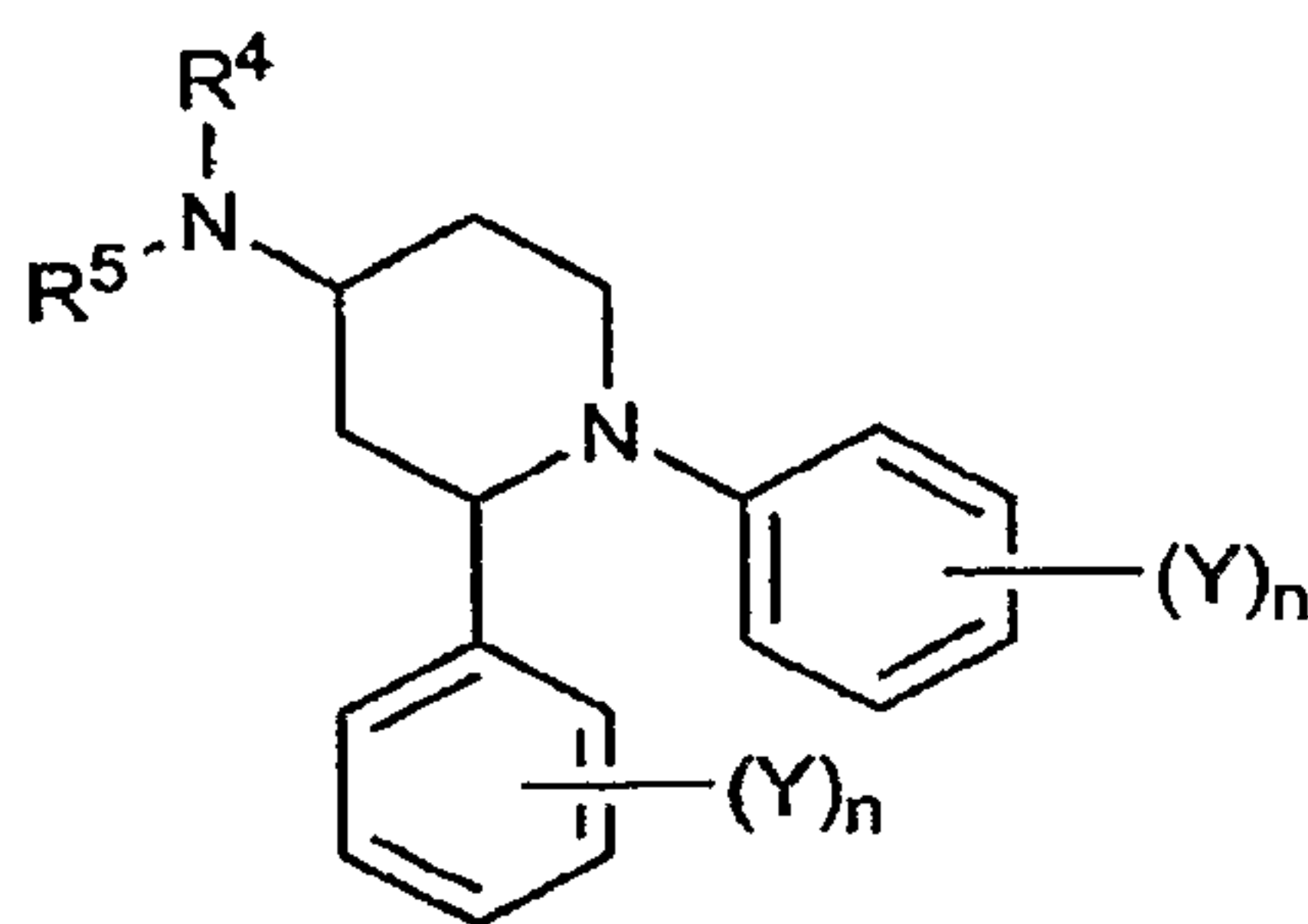
wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said -(C(R⁶)₂)_m-(C₆-C₁₀)aryl of Z is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN;

wherein in a single Z moiety, =O, can replace two available hydrogens on the same carbon on a ring system;

each n, p and q is independently an integer from 0-5; and

m is an integer from 1-5.

In another embodiment, the compound of Formula (I) is a compound having the structural Formula (IA):



(IA)

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

R⁴ is selected from the group consisting of H, -C(O)-(C₁-C₆)alkyl, and (C₁-C₆)alkyl;

R⁵ is selected from the group consisting of -(C(R⁶)₂)_m-G, -S(O)₂-(C₁-C₆)alkyl, -S(O)₂-(C₃-C₆)cycloalkyl, (C₁-C₆)alkyl, -S(O)-(C₃-C₆)cycloalkyl, -C(O)-(C₃-

20

C_6)cycloalkyl, $-S(O)_2-(C_6-C_{10})$ aryl, $-S(O)_2-(C(R^6)_2)_m-(C_6-C_{10})$ aryl,
 $-S(O)_2-(C_2-C_{10})$ heteroaryl, $-C(O)-(C_1-C_6)$ alkyl, $-C(O)-(C_6-C_{10})$ aryl,
 $-C(O)-O-(C_1-C_6)$ alkyl, $-C(O)-O-(C_6-C_{10})$ aryl, $-C(O)-(C(R^6)_2)_m-(C_6-C_{10})$ aryl,
 $-C(O)-(C_3-C_6)$ cycloalkylene- (C_6-C_{10}) aryl, $-C(O)-(C_2-C_{10})$ heteroaryl,
5 $-C(O)-(C_2-C_{10})$ heteroaryl- (C_1-C_6) alkyl, $-C(O)-(C(R^6)_2)_m-O-(C_6-C_{10})$ aryl,
 $-C(O)-(benzo-fused (C_3-C_6)cycloalkyl)$, $-S(O)_2-(benzo-fused (C_2-C_{10})heterocyclyl)$,
 $-C(O)-N(R^9)-(C(R^6)_2)_m-(C_6-C_{10})$ aryl, $-C(O)-N(R^9)-(C_6-C_{10})$ aryl, (C_3-C_6) cycloalkyl,
benzo-fused (C_3-C_6) cycloalkyl, unsubstituted (C_6-C_{10}) aryl, (C_6-C_{10}) aryl substituted
with one or more Y groups, unsubstituted (C_2-C_{10}) heterocyclyl, and
10 (C_2-C_{10}) heterocyclyl substituted with one or more X groups,

wherein the (C_6-C_{10}) aryl or heteroaryl portion of said $-S(O)_2-(C_6-C_{10})$ aryl,
 $-S(O)_2-(C(R^6)_2)_m-(C_6-C_{10})$ aryl, $-S(O)_2-(C_2-C_{10})$ heteroaryl, $-C(O)-(C_6-$
 $C_{10})$ aryl, $-C(O)-(C(R^6)_2)_m-(C_6-C_{10})$ aryl,
 $-C(O)-(C_3-C_6)$ cycloalkylene- (C_6-C_{10}) aryl, $-C(O)-(C_2-C_{10})$ heteroaryl,
15 $-C(O)-(C(R^6)_2)_m-O-(C_6-C_{10})$ aryl, $-C(O)-N(R^9)-(C(R^6)_2)_m-(C_6-C_{10})$ aryl, or
 $-C(O)-N(R^9)-(C_6-C_{10})$ aryl of R^5 is unsubstituted or substituted with one
or more Y groups;

wherein the heterocyclyl portion of $-S(O)_2-(benzo-fused (C_2-C_{10})heterocyclyl)$
 aryl of R^5 is unsubstituted or substituted with one or more X groups;

20 each R^6 is independently selected from the group consisting of H and (C_1-C_6) alkyl;
 R^7 is selected from the group consisting of H, (C_1-C_6) alkyl, unsubstituted
 (C_6-C_{10}) aryl, and (C_6-C_{10}) aryl substituted with one or more Y groups;

each R^8 is independently selected from the group consisting of H, (C_1-C_6) alkyl,
 $-C(O)-(C_6-C_{10})$ aryl, $-S(O)_2-(C_6-C_{10})$ aryl, and $-S(O)_2-(C_1-C_6)$ alkyl;

25 each R^9 is independently selected from the group consisting of H, (C_1-C_6) alkyl, $(C_3-$
 $C_6)$ cycloalkyl, unsubstituted (C_6-C_{10}) aryl, and (C_6-C_{10}) aryl substituted with one or
more Y groups;

G is selected from the group consisting of H, (C_1-C_6) alkyl, unsubstituted (C_6-C_{10}) aryl,
 (C_6-C_{10}) aryl substituted with one or more Y groups, $-CN$, (C_3-C_6) cycloalkyl, $-O-R^7$,
 30 $-S-R^7$, unsubstituted (C_2-C_{10}) heteroaryl, (C_2-C_{10}) heteroaryl substituted with one or
more Y groups, $-N(R^8)_2$, unsubstituted (C_2-C_{10}) heterocyclyl, and
 (C_2-C_{10}) heterocyclyl substituted with one or more X groups;

each X is independently selected from the group consisting of (C₁-C₆)alkyl,

-C(O)-N(R⁹)₂, -C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl,

-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, and (C₆-C₁₀)aryl,

wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said

5 -C(O)-(C₂-C₁₀)heteroaryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-alkyl, haloalkyl, and -CN, and

wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said -(C(R⁶)₂)_m-(C₆-C₁₀)aryl of X is unsubstituted or substituted with one or more

10 substituents selected from the group consisting of halogen, -OH, -O-alkyl, haloalkyl, and -CN;

each Y is independently selected from the group consisting of halogen, (C₁-C₆)alkyl,

(C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -O-R⁹, (C₁-C₆)haloalkyl, -O-(C₁-C₆)haloalkyl,

-CN, -C(O)-O-(C₁-C₆)alkyl, -N(R⁶)₂, and -C(R⁶)₂-N(R⁸)₂; or

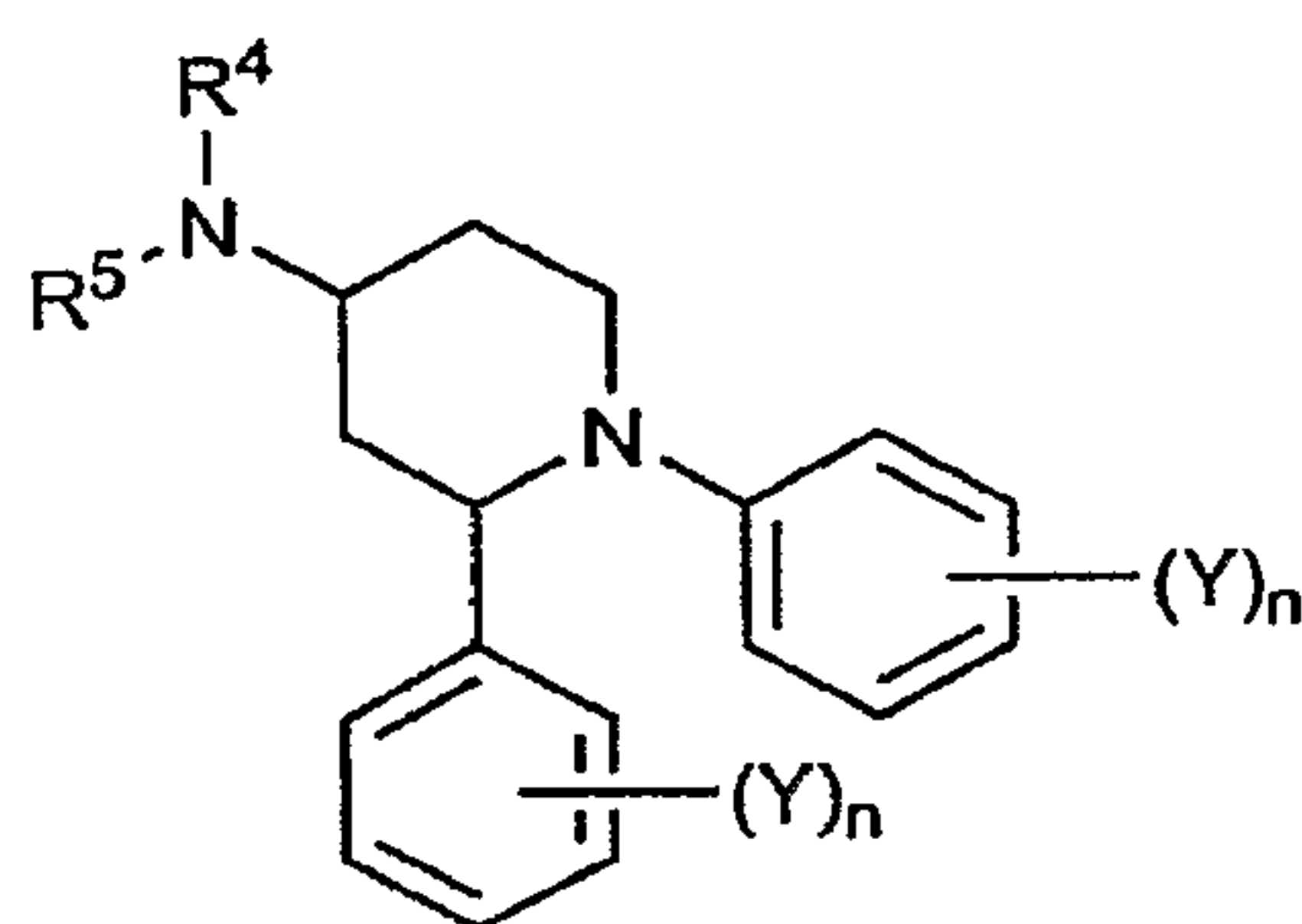
15 two of said Y groups attached to adjacent carbon atoms form a -O-CH₂-O- or -O-CH₂CH₂-O- group;

each n is independently an integer from 0-5; and

m is an integer from 1-5.

In another embodiment, the compound of Formula (I) is a compound having

20 the structural Formula (IA):



(IA)

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

R⁴ is H;

25 R⁵ is selected from the group consisting of -(C(R⁶)₂)_m-G, -S(O)₂-(C₁-C₆)alkyl, -S(O)₂-(C₃-C₆)cycloalkyl, (C₁-C₆)alkyl, -S(O)-(C₃-C₆)cycloalkyl, -C(O)-(C₃-C₆)cycloalkyl, -S(O)₂-(C₆-C₁₀)aryl, -S(O)₂-(C(R⁶)₂)_m-(C₆-C₁₀)aryl,

-S(O)₂-(C₂-C₁₀)heteroaryl, -C(O)-(C₁-C₆)alkyl, -C(O)-(C₆-C₁₀)aryl,
 -C(O)-O-(C₁-C₆)alkyl, -C(O)-O-(C₆-C₁₀)aryl, -C(O)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl,
 -C(O)-(C₃-C₆)cycloalkylene-(C₆-C₁₀)aryl, -C(O)-(C₂-C₁₀)heteroaryl,
 -C(O)-(C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, -C(O)-(C(R⁶)₂)_m-O-(C₆-C₁₀)aryl,
 5 -C(O)-(benzo-fused (C₃-C₆)cycloalkyl), -S(O)₂-(benzo-fused (C₂-C₁₀)heterocyclyl),
 -C(O)-N(R⁹)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -C(O)-N(R⁹)-(C₆-C₁₀)aryl, (C₃-C₆)cycloalkyl,
 benzo-fused (C₃-C₆)cycloalkyl, unsubstituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl substituted
 with one or more Y groups, unsubstituted (C₂-C₁₀)heterocyclyl, and
 (C₂-C₁₀)heterocyclyl substituted with one or more X groups,

10 wherein the (C₆-C₁₀)aryl or heteroaryl portion of said -S(O)₂-(C₆-C₁₀)aryl,
 -S(O)₂-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -S(O)₂-(C₂-C₁₀)heteroaryl, -C(O)-(C₆-
 C₁₀)aryl, -C(O)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl,
 -C(O)-(C₃-C₆)cycloalkylene-(C₆-C₁₀)aryl, -C(O)-(C₂-C₁₀)heteroaryl,
 -C(O)-(C(R⁶)₂)_m-O-(C₆-C₁₀)aryl, -C(O)-N(R⁹)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, or
 15 -C(O)-N(R⁹)-(C₆-C₁₀)aryl of R⁵ is unsubstituted or substituted with one
 or more Y groups;

wherein the heterocyclyl portion of -S(O)₂-(benzo-fused (C₂-C₁₀)heterocyclyl)
 aryl of R⁵ is unsubstituted or substituted with one or more X groups;

each R⁶ is independently selected from the group consisting of H and (C₁-C₆)alkyl;

20 R⁷ is selected from the group consisting of H, (C₁-C₆)alkyl, unsubstituted
 (C₆-C₁₀)aryl, and (C₆-C₁₀)aryl substituted with one or more Y groups;

each R⁸ is independently selected from the group consisting of H, (C₁-C₆)alkyl,
 -C(O)-(C₆-C₁₀)aryl, -S(O)₂-(C₆-C₁₀)aryl, and -S(O)₂-(C₁-C₆)alkyl;

25 each R⁹ is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-
 C₆)cycloalkyl, unsubstituted (C₆-C₁₀)aryl, and (C₆-C₁₀)aryl substituted with one or
 more Y groups;

G is selected from the group consisting of H, (C₁-C₆)alkyl, unsubstituted (C₆-C₁₀)aryl,
 (C₆-C₁₀)aryl substituted with one or more Y groups, -CN, (C₃-C₆)cycloalkyl, -O-R⁷,
 -S-R⁷, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or
 30 more Y groups, -N(R⁸)₂, unsubstituted (C₂-C₁₀)heterocyclyl, and
 (C₂-C₁₀)heterocyclyl substituted with one or more X groups;

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each X is independently selected from the group consisting of (C₁-C₆)alkyl,

-C(O)-N(R⁹)₂, -C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl,

-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, and (C₆-C₁₀)aryl,

wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said

5 -C(O)-(C₂-C₁₀)heteroaryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-alkyl, haloalkyl, and -CN, and

wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said -(C(R⁶)₂)_m-(C₆-C₁₀)aryl of X is unsubstituted or substituted with one or more

0 substituents selected from the group consisting of halogen, -OH, -O-alkyl, haloalkyl, and -CN;

each Y is independently selected from the group consisting of halogen, (C₁-C₆)alkyl,

(C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -O-R⁹, (C₁-C₆)haloalkyl, -O-(C₁-C₆)haloalkyl,

-CN, -C(O)-O-(C₁-C₆)alkyl, -N(R⁶)₂, and -C(R⁶)₂-N(R⁸)₂; or

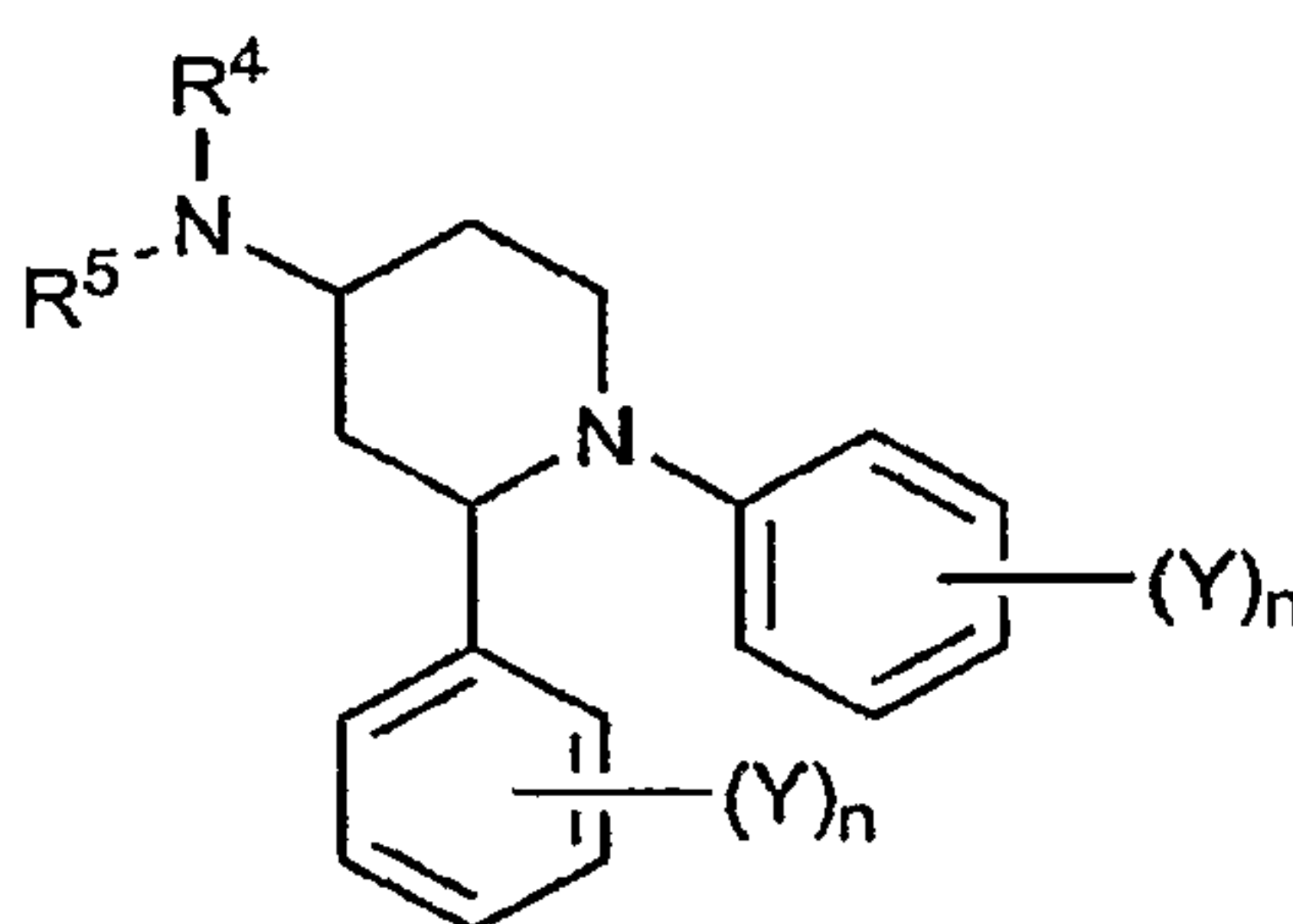
5 two of said Y groups attached to adjacent carbon atoms form a -O-CH₂-O- or -O-CH₂CH₂-O- group;

each n is independently an integer from 0-5; and

m is an integer from 1-5.

In another embodiment, the compound of Formula (I) is a compound having

10 the structural Formula (IA):



(IA)

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

R⁴ is H;

25 R⁵ is selected from the group consisting of -(C(R⁶)₂)_m-G, -S(O)₂-(C₁-C₆)alkyl,

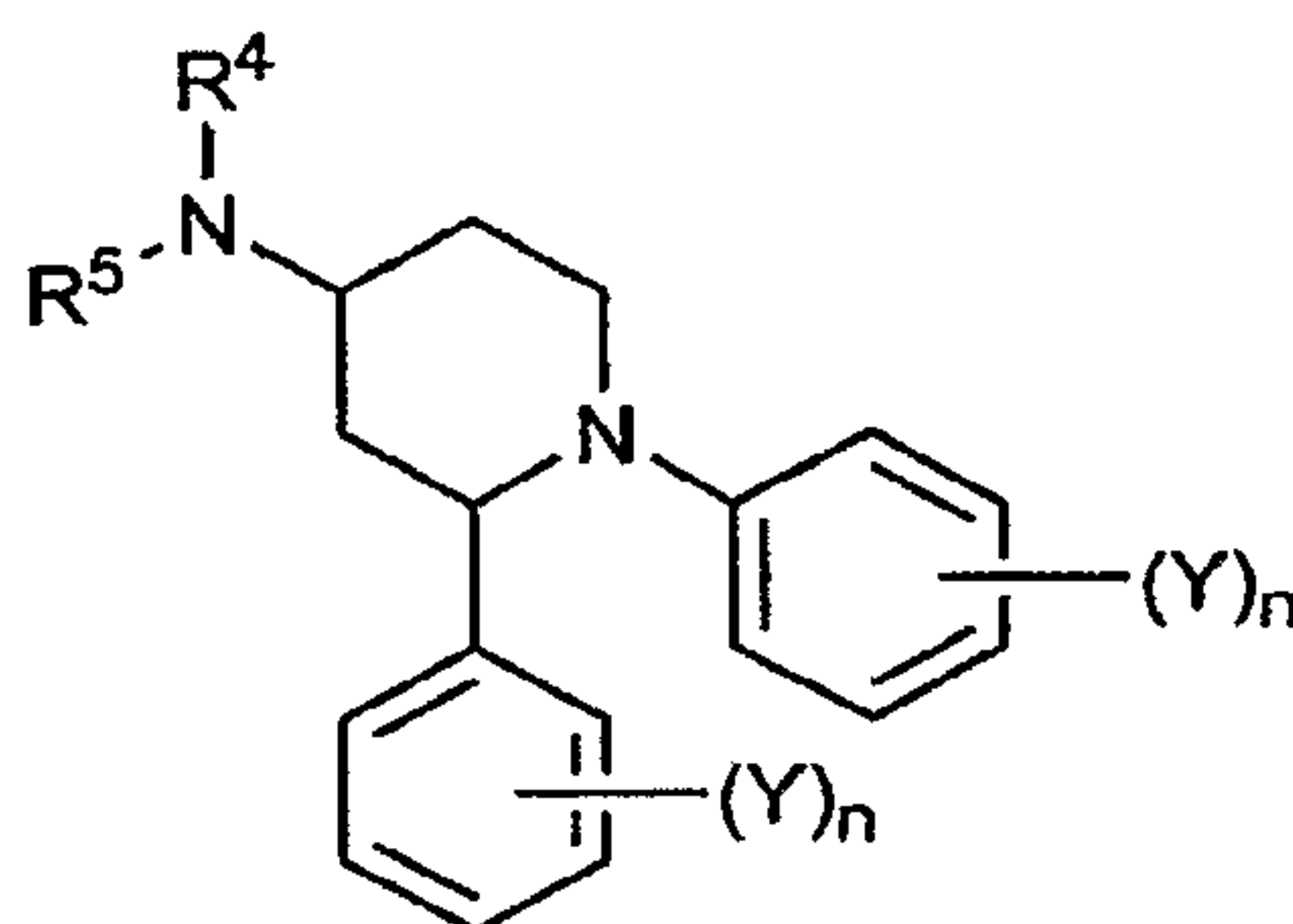
-S(O)-(C₃-C₆)cycloalkyl, -C(O)-(C₃-C₆)cycloalkyl, -S(O)₂-(C₆-C₁₀)aryl,

-S(O)₂-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -S(O)₂-(C₂-C₁₀)heteroaryl, -C(O)-(C₆-C₁₀)aryl,

- C(O)-O-(C₁-C₆)alkyl, -C(O)-O-(C₆-C₁₀)aryl, -C(O)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -C(O)-(C₃-C₆)cycloalkylene-(C₆-C₁₀)aryl, -C(O)-(C₂-C₁₀)heteroaryl, -C(O)-(C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, -C(O)-(C(R⁶)₂)_m-O-(C₆-C₁₀)aryl, -C(O)-(benzo-fused (C₃-C₆)cycloalkyl), -S(O)₂-(benzo-fused (C₂-C₁₀)heterocyclyl),
- 5 -C(O)-N(R⁹)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -C(O)-N(R⁹)-(C₆-C₁₀)aryl, (C₃-C₆)cycloalkyl, and benzo-fused (C₃-C₆)cycloalkyl;
- each R⁶ is independently selected from the group consisting of H and (C₁-C₆)alkyl; R⁷ is selected from the group consisting of H, (C₁-C₆)alkyl and unsubstituted (C₆-C₁₀)aryl;
- 10 each R⁹ is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, unsubstituted (C₆-C₁₀)aryl, and (C₆-C₁₀)aryl substituted with one or more Y groups;
- G is selected from the group consisting of H, (C₁-C₆)alkyl, unsubstituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl substituted with one or more Y groups, -CN, (C₃-C₆)cycloalkyl, -O-R⁷, -S-R⁷, unsubstituted (C₂-C₁₀)heteroaryl, unsubstituted (C₂-C₁₀)heterocyclyl, and (C₂-C₁₀)heterocyclyl substituted with one or more X groups;
- 15 each X is independently selected from the group consisting of (C₁-C₆)alkyl and (C₆-C₁₀)aryl substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-alkyl, haloalkyl, and -CN; and
- 20 each Y is independently selected from the group consisting halogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, -O-R⁹, (C₁-C₆)haloalkyl, -O-(C₁-C₆)haloalkyl, -CN, -C(O)-O-(C₁-C₆)alkyl, -C(O)-(C₁-C₆)alkyl, -N(R⁶)₂, and -C(R⁶)₂-N(R⁸)₂; or two of said Y groups attached to adjacent carbon atoms form a -O-CH₂-O- or -O-CH₂CH₂-O- group.
- 25 each n is independently an integer from 0-5; and m is an integer from 1-5.

In another embodiment, the compound of Formula (I) is a compound having the structural Formula (IA):

25



(IA)

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

R⁴ is H;

- 5 R⁵ is selected from the group consisting of $-(C(R^6)_2)_m-G$, $-S(O)_2-CH_3$, $-S(O)_2$ -phenyl, $-S(O)_2-C(R^6)_2$ -phenyl, $-S(O)_2$ -thiophenyl, $-C(O)$ -phenyl, $-C(O)-C(R^6)_2$ -phenyl, $-C(O)$ -cyclopropylene-phenyl, $-C(O)$ -(benzo-fused cyclohexyl), $-C(O)$ -furanyl, $-C(O)-C(R^6)_2-O$ -phenyl, $-C(O)-(C(R^6)_2)_2$ -phenyl, $-C(O)-N(R^9)$ -phenyl, $-C(O)-N(R^9)-C(R^6)_2$ -phenyl, cyclobutyl, cyclopentyl, cyclohexyl, and indanyl,

- 10 wherein the phenyl, thiophenyl, and furanyl portions of said $-S(O)_2$ -phenyl, $-S(O)_2-C(R^6)_2$ -phenyl, $-S(O)_2$ -thiophenyl, $-C(O)$ -phenyl, $-C(O)-C(R^6)_2$ -phenyl, $-C(O)$ -cyclopropylene-phenyl, $-C(O)$ -furanyl, $-C(O)-C(R^6)_2-O$ -phenyl, $-C(O)-(C(R^6)_2)_2$ -phenyl, $-C(O)-N(R^9)$ -phenyl, or $-C(O)-N(R^9)-C(R^6)_2$ -phenyl of R⁵ are unsubstituted or substituted with one or more Y groups;

each R⁶ is independently selected from the group consisting of H, $-CH_3$, $-CH_2CH_3$, and $-CH_2(CH_3)_2$;

R⁷ is selected from the group consisting of H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, and unsubstituted phenyl;

- 20 Each R⁹ is independently selected from the group consisting of H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, unsubstituted phenyl, and phenyl substituted with one or more Y groups;

G is selected from the group consisting of H, $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, unsubstituted phenyl, phenyl substituted with one or more Y groups, $-CN$, cyclohexyl, $-O-R^7$, $-S-R^7$, furanyl, thiophenyl, pyridinyl, benzothiophenyl, and pyrrolidinyl substituted with one or more X groups;

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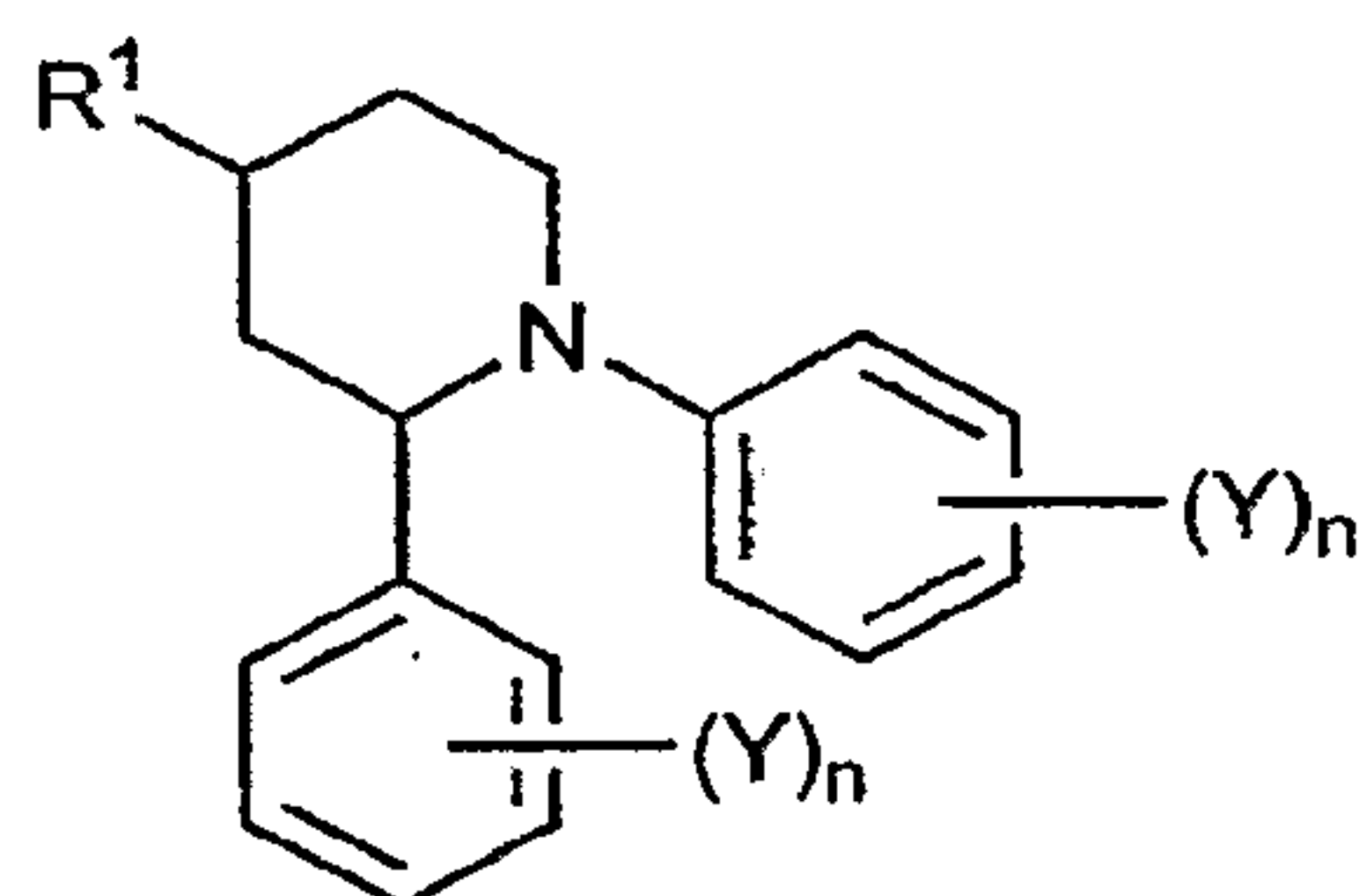
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each X is independently selected from the group consisting of $-\text{CH}_3$ and phenyl substituted with one or more Cl; and

each Y is independently selected from the group consisting of F, Cl, $-\text{OCF}_3$, $-\text{OCH}_3$, phenyl, $-\text{C}(\text{O})-\text{CH}_3$, $-\text{CH}_3$, $-\text{CN}$, $-\text{NH}_2$, and $-\text{CF}_3$; or

- 5 two of said Y groups attached to adjacent carbon atoms form a $-\text{O}-\text{CH}_2-\text{O}-$ group; each n is independently an integer from 0-5; and m is an integer from 1-5.

In another embodiment, the compound of Formula (I) is a compound having the structural Formula (IB):



(IB)

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

R^1 is selected from the group consisting of unsubstituted $(\text{C}_2-\text{C}_{10})$ heterocyclyl, $(\text{C}_2-\text{C}_{10})$ heterocyclyl substituted with one or more X groups, $-\text{N}_3$, and $-\text{OR}^7$;

- 15 with the following proviso:

(i) when R^1 is $-\text{OH}$, n is independently an integer of from 1-5;

each R^6 is independently selected from the group consisting of H and (C_1-C_6) alkyl;

R^7 is selected from the group consisting of H, (C_1-C_6) alkyl, unsubstituted $(\text{C}_6-\text{C}_{10})$ aryl, and $(\text{C}_6-\text{C}_{10})$ aryl substituted with one or more Y groups;

- 20 with the proviso that when R^7 is H, each n is independently an integer of from 1-5;

each R^8 is independently selected from the group consisting of H, (C_1-C_6) alkyl, $-\text{C}(\text{O})-(\text{C}_6-\text{C}_{10})$ aryl, $-\text{S}(\text{O})_2-(\text{C}_6-\text{C}_{10})$ aryl, and $-\text{S}(\text{O})_2-(\text{C}_1-\text{C}_6)$ alkyl;

each X is independently selected from the group consisting of (C_1-C_6) alkyl,

- 25 $-\text{C}(\text{O})-\text{N}(\text{R}^8)_2$, $-\text{C}(\text{O})-(\text{C}_2-\text{C}_{10})$ heteroaryl, $(\text{C}_2-\text{C}_{10})$ heteroaryl, $-(\text{C}(\text{R}^6)_2)-(\text{C}_6-\text{C}_{10})$ aryl, and $(\text{C}_6-\text{C}_{10})$ aryl

wherein said $(\text{C}_2-\text{C}_{10})$ heteroaryl or the $(\text{C}_2-\text{C}_{10})$ heteroaryl portion of said

$-\text{C}(\text{O})-(\text{C}_2-\text{C}_{10})$ heteroaryl of X is unsubstituted or substituted with one or

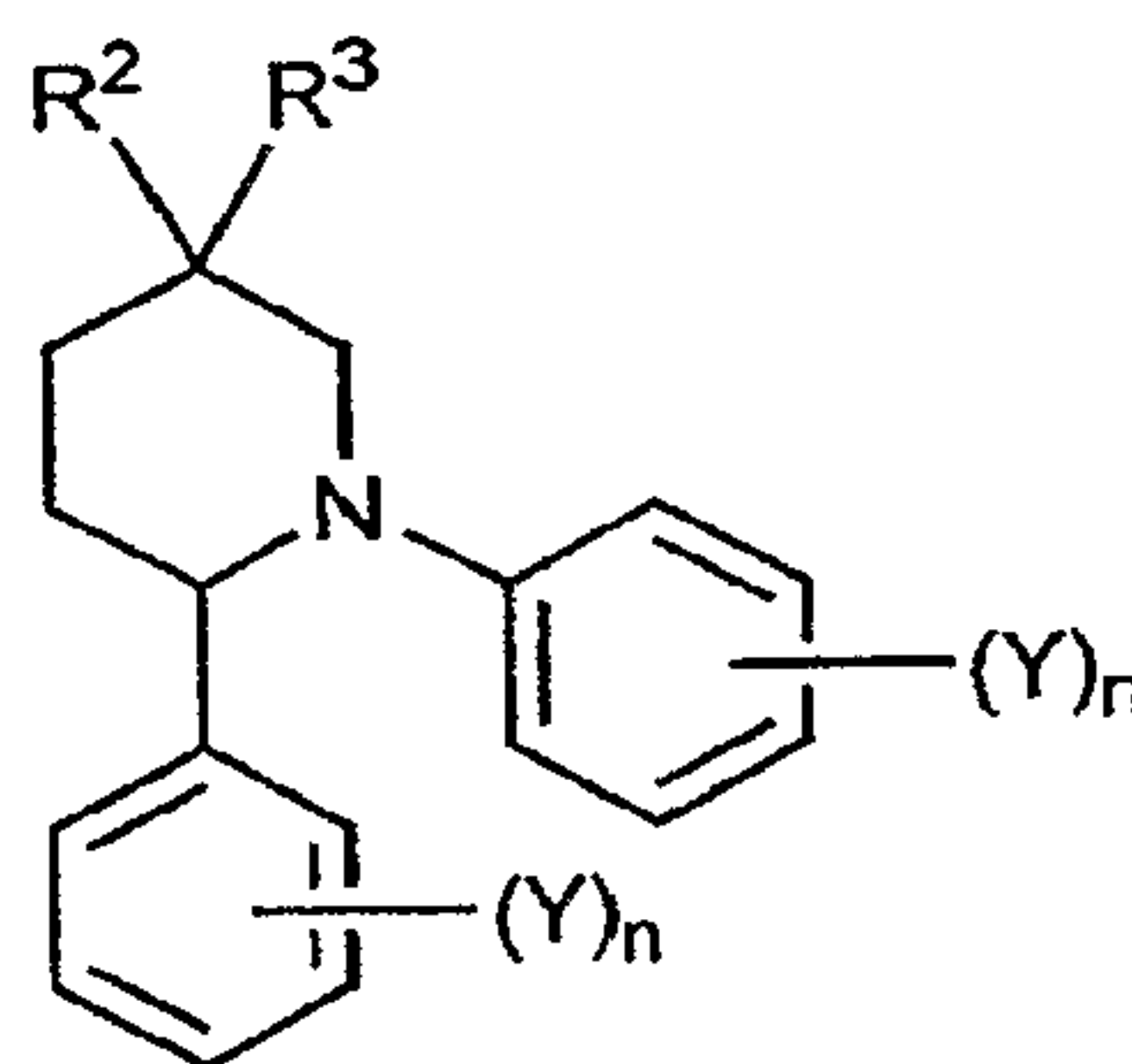
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more substituents selected from the group consisting of halogen, -OH, -O-alkyl, haloalkyl, and -CN, and

wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said -(C(R⁶)₂)-(C₆-C₁₀)aryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-alkyl, haloalkyl, and -CN; and

n is an integer from 0-5.

In another embodiment, the compound of Formula (I) is a compound having the structural Formula (IC):



(IC)

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

R² is selected from the group consisting of H, -C(R⁶)₂-(C₆-C₁₀)aryl, and -C(R⁶)₂-O-R⁷,

wherein the (C₆-C₁₀)aryl portion of said -C(R⁶)₂-(C₆-C₁₀)aryl of R² is

unsubstituted or substituted with one or more Y groups;

R³ is selected from the group consisting of H, -C(R⁶)₂-(C₆-C₁₀)aryl, -C(R⁶)₂-O-R⁷, -O-R⁷, and -C(R⁶)₂-N(R⁸)₂,

wherein the (C₆-C₁₀)aryl portion of said -C(R⁶)₂-(C₆-C₁₀)aryl of R³ is

unsubstituted or substituted with one or more Y groups; or

R² and R³ together with the ring carbon atom to which they are shown attached form an unsubstituted (C₂-C₁₀)heterocyclyl ring or a (C₂-C₁₀)heterocyclyl ring substituted with one or more X groups;

with the following proviso:

(ii) at least one of R² and R³ is not H;

each R⁶ is independently selected from the group consisting of H and (C₁-C₆)alkyl;

R⁷ is selected from the group consisting of H, (C₁-C₆)alkyl, unsubstituted

(C₆-C₁₀)aryl, and (C₆-C₁₀)aryl substituted with one or more Y groups;

each R^8 is independently selected from the group consisting of H, (C_1-C_6) alkyl, $-C(O)-(C_6-C_{10})$ aryl, $-S(O)_2-(C_6-C_{10})$ aryl, $-S(O)_2-(C_2-C_{10})$ heteroaryl, and $-S(O)_2-(C_1-C_6)$ alkyl,

wherein the (C_6-C_{10}) aryl portion of said $-C(O)-(C_6-C_{10})$ aryl or $-S(O)_2-(C_6-$

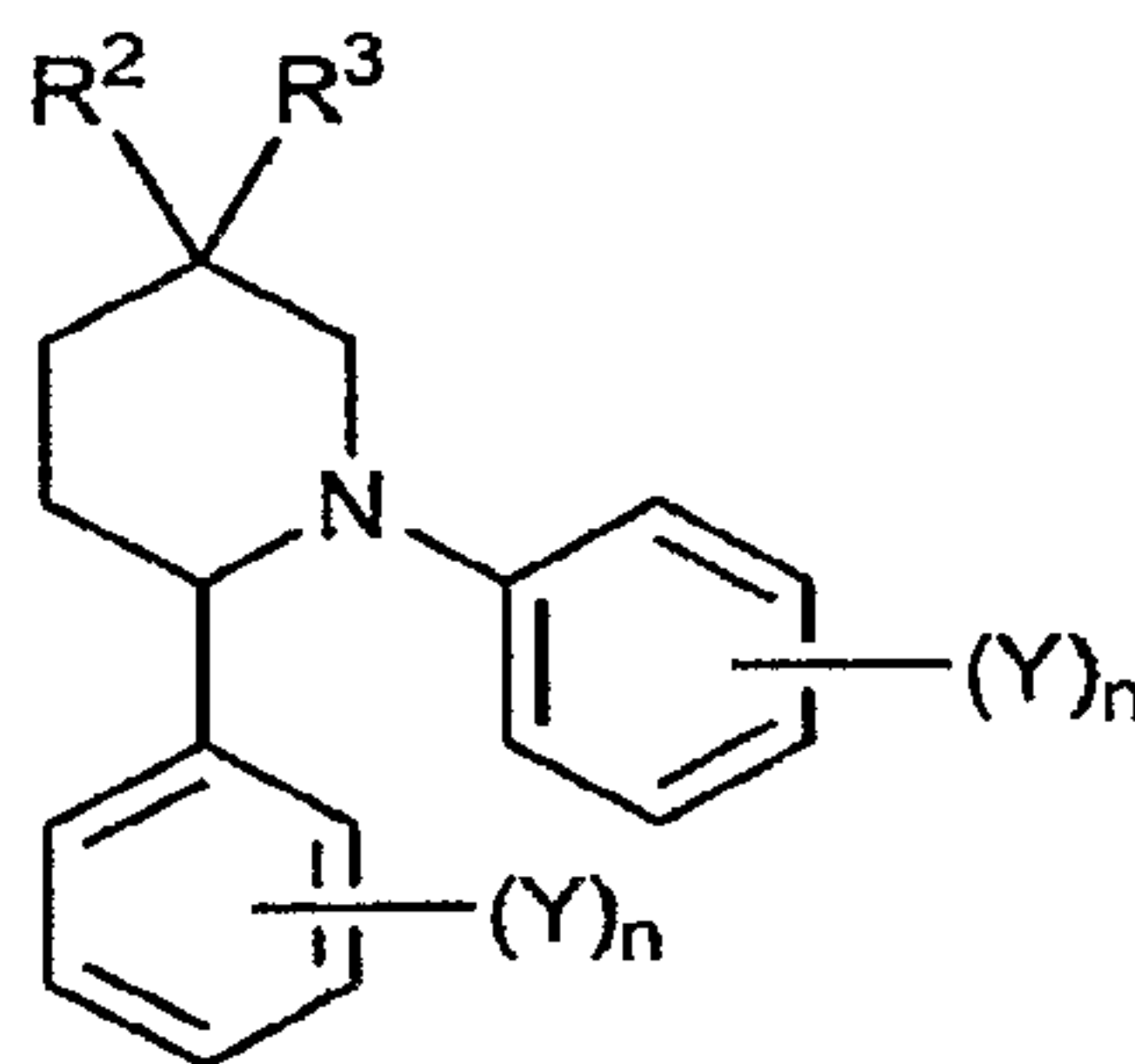
5 $C_{10})$ aryl and the (C_2-C_{10}) heteroaryl portion of said $-S(O)_2-(C_2-C_{10})$ heteroaryl of R^8 is unsubstituted or substituted with one or more Y groups;

each Y is independently selected from the group consisting of halogen, (C_1-C_6) alkyl,

10 $-C(O)-(C_1-C_6)$ alkyl, $-O-R^9$, $-O-C(R^6)_2-O-$, (C_1-C_6) haloalkyl, $-O-(C_1-C_6)$ haloalkyl, $-CN$, $-C(O)-O-(C_1-C_6)$ alkyl, $-C(R^6)_2-N(R^8)_2$, and $-C(R^6)_2-N(R^6)-S(O)_2-R^6$; and

each n is independently an integer from 0-5.

In another embodiment, the compound of Formula (I) is a compound having the structural Formula (IC):



15

(IC)

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

R^2 is H;

R^3 is selected from the group consisting of $-C(R^6)_2-(C_6-C_{10})$ aryl, $-C(R^6)_2-O-R^7$, and $-C(R^6)_2-N(R^8)_2$,

20

wherein the (C_6-C_{10}) aryl portion of said $-C(R^6)_2-(C_6-C_{10})$ aryl of R^3 is unsubstituted or substituted with one or more Y groups;

each R^6 is H;

R^7 is (C_6-C_{10}) aryl substituted with one or more Y groups;

each R^8 is independently selected from the group consisting of H,

25

$-S(O)_2-(C_6-C_{10})$ aryl, and $-S(O)_2-(C_1-C_6)$ alkyl;

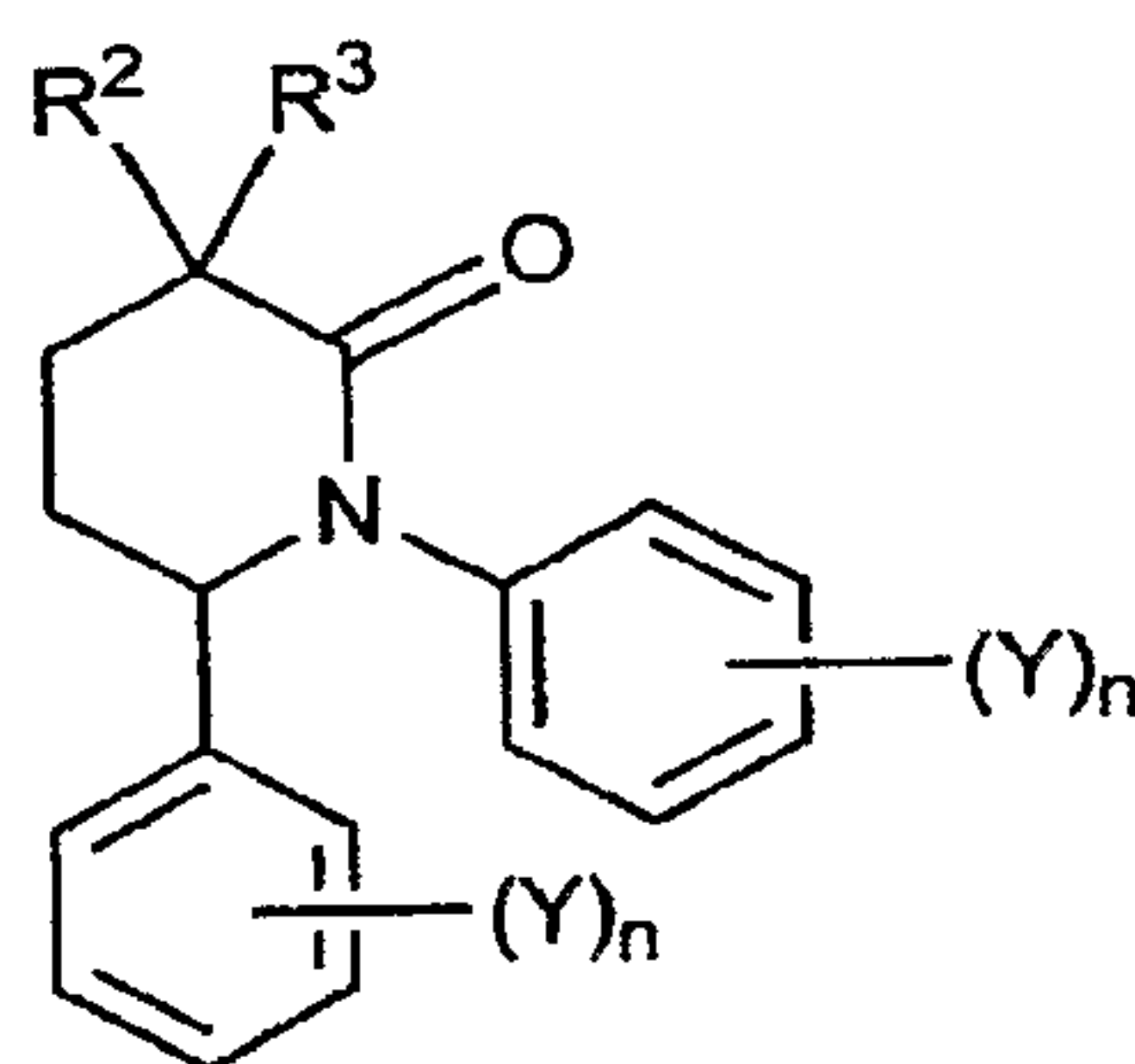
each R^9 is independently selected from the group consisting of H, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, unsubstituted (C_6-C_{10}) aryl, and (C_6-C_{10}) aryl substituted with one or more Y groups;

each Y is independently selected from the group consisting of halogen,

5 $-C(R^6)_2-N(R^8)_2$, and $-C(R^6)_2-N(R^6)-S(O)_2-R^6$; and

each n is independently an integer from 0-5.

In another embodiment, the compound of Formula (I) is a compound having the structural Formula (ID):



(ID)

10 or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

R^2 is selected from the group consisting of H, $-C(R^6)_2-(C_6-C_{10})$ aryl, and $-C(R^6)_2-O-R^7$,

wherein the (C_6-C_{10}) aryl portion of said $-C(R^6)_2-(C_6-C_{10})$ aryl of R^2 is unsubstituted or substituted with one or more Y groups;

15 R^3 is selected from the group consisting of $-C(R^6)_2-(C_6-C_{10})$ aryl, $-C(R^6)_2-O-R^7$, $-O-R^7$, and $-C(R^6)_2-N(R^8)_2$,

wherein the (C_6-C_{10}) aryl portion of said $-C(R^6)_2-(C_6-C_{10})$ aryl of R^3 is unsubstituted or substituted with one or more Y groups;

each R^6 is independently selected from the group consisting of H and (C_1-C_6) alkyl;

20 R^7 is selected from the group consisting of H, (C_1-C_6) alkyl, unsubstituted (C_6-C_{10}) aryl, and (C_6-C_{10}) aryl substituted with one or more Y groups;

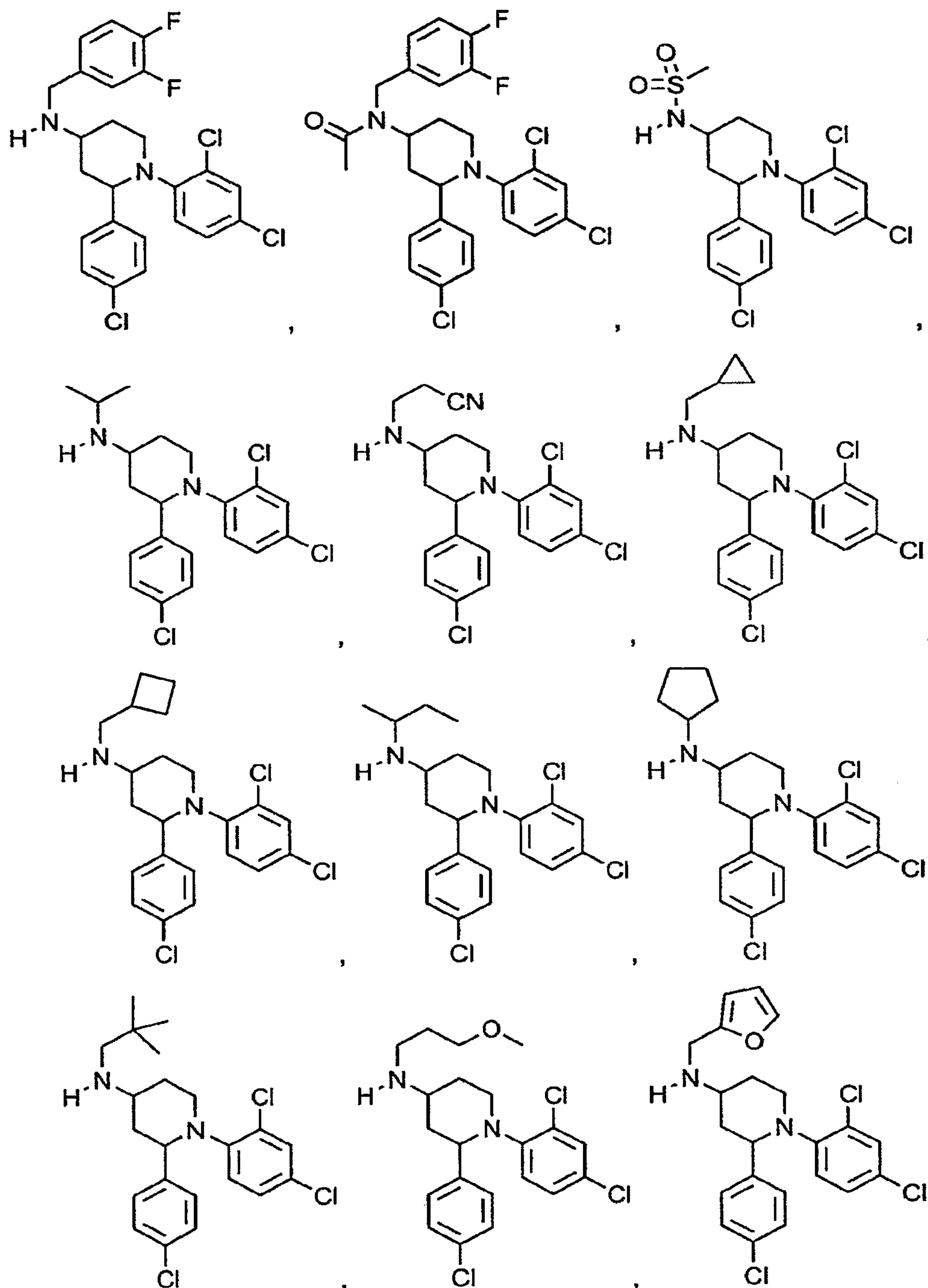
each R^8 is independently selected from the group consisting of H, (C_1-C_6) alkyl, $-C(O)-(C_6-C_{10})$ aryl, $-S(O)_2-(C_6-C_{10})$ aryl, and $-S(O)_2-(C_1-C_6)$ alkyl;

each Y is independently selected from the group consisting of halogen, (C_1-C_6) alkyl,

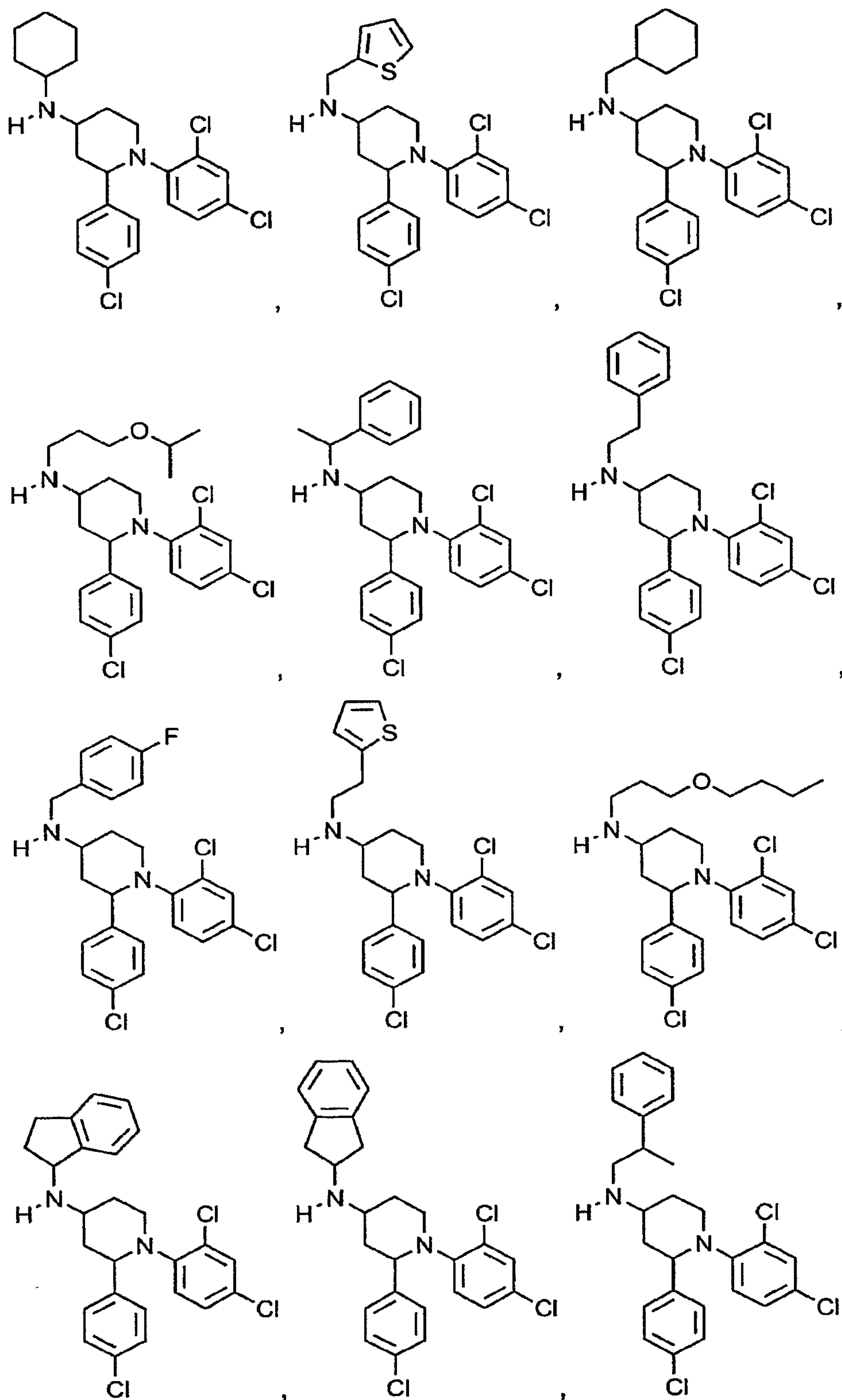
25 $-O-R^9$, $-O-C(R^6)_2-O-$, (C_1-C_6) haloalkyl, $-CN$, $-C(R^6)_2-N(R^8)_2$, and $-C(R^6)_2-N(R^6)-S(O)_2-R^6$; and

each n is independently an integer from 0-5.

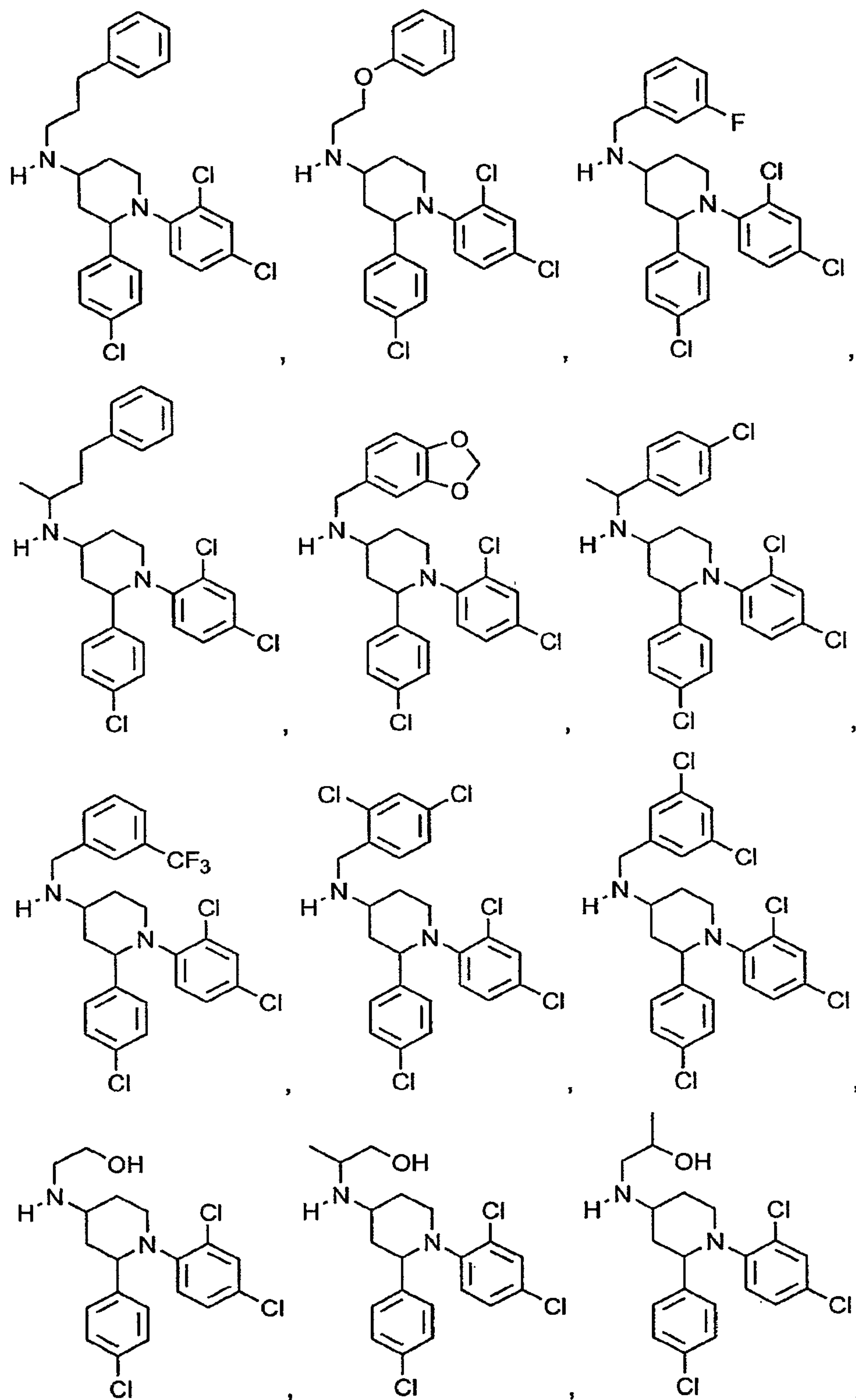
In another embodiment, the compound of Formula (I) is selected from the group consisting of:



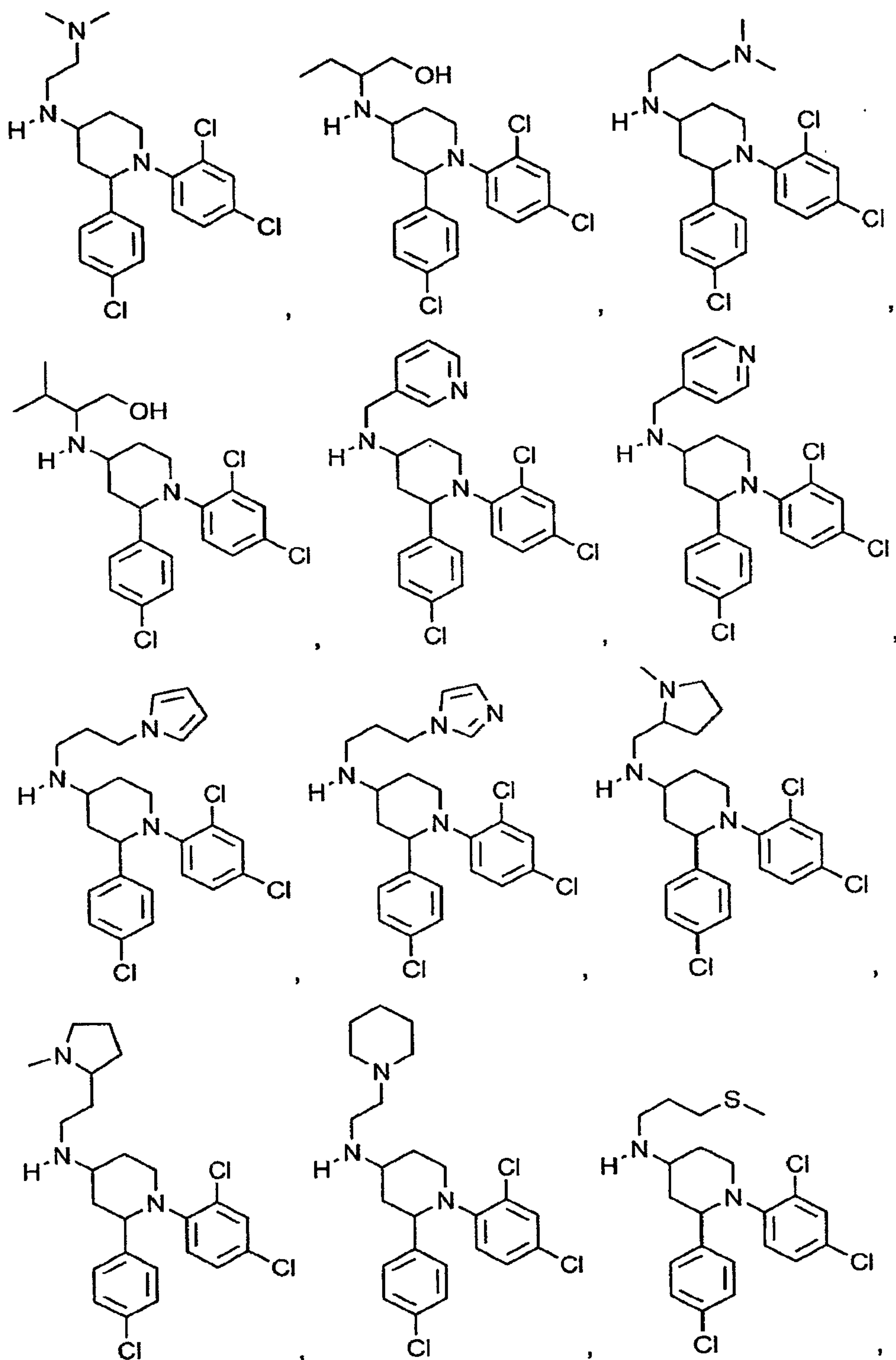
31



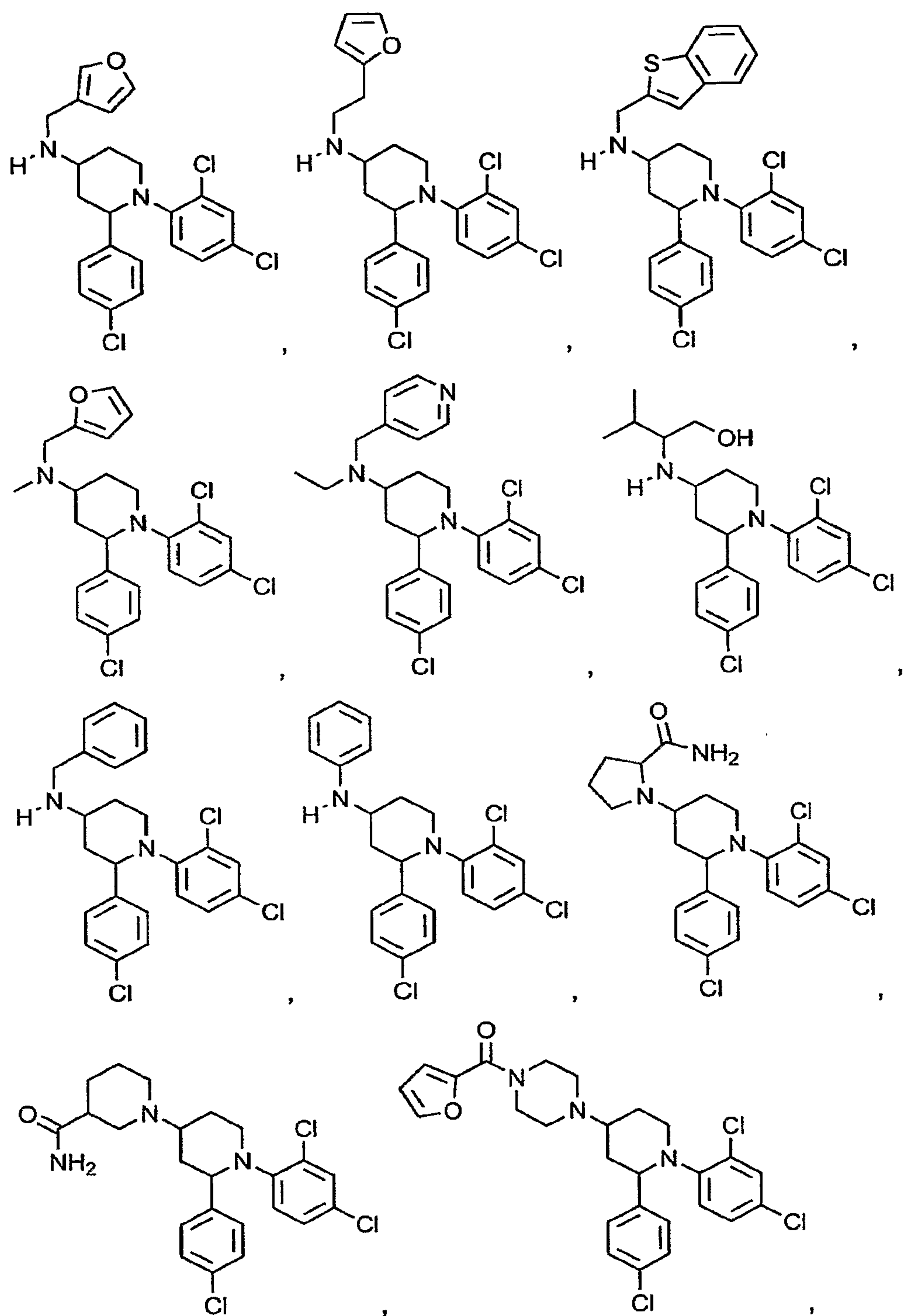
32



33

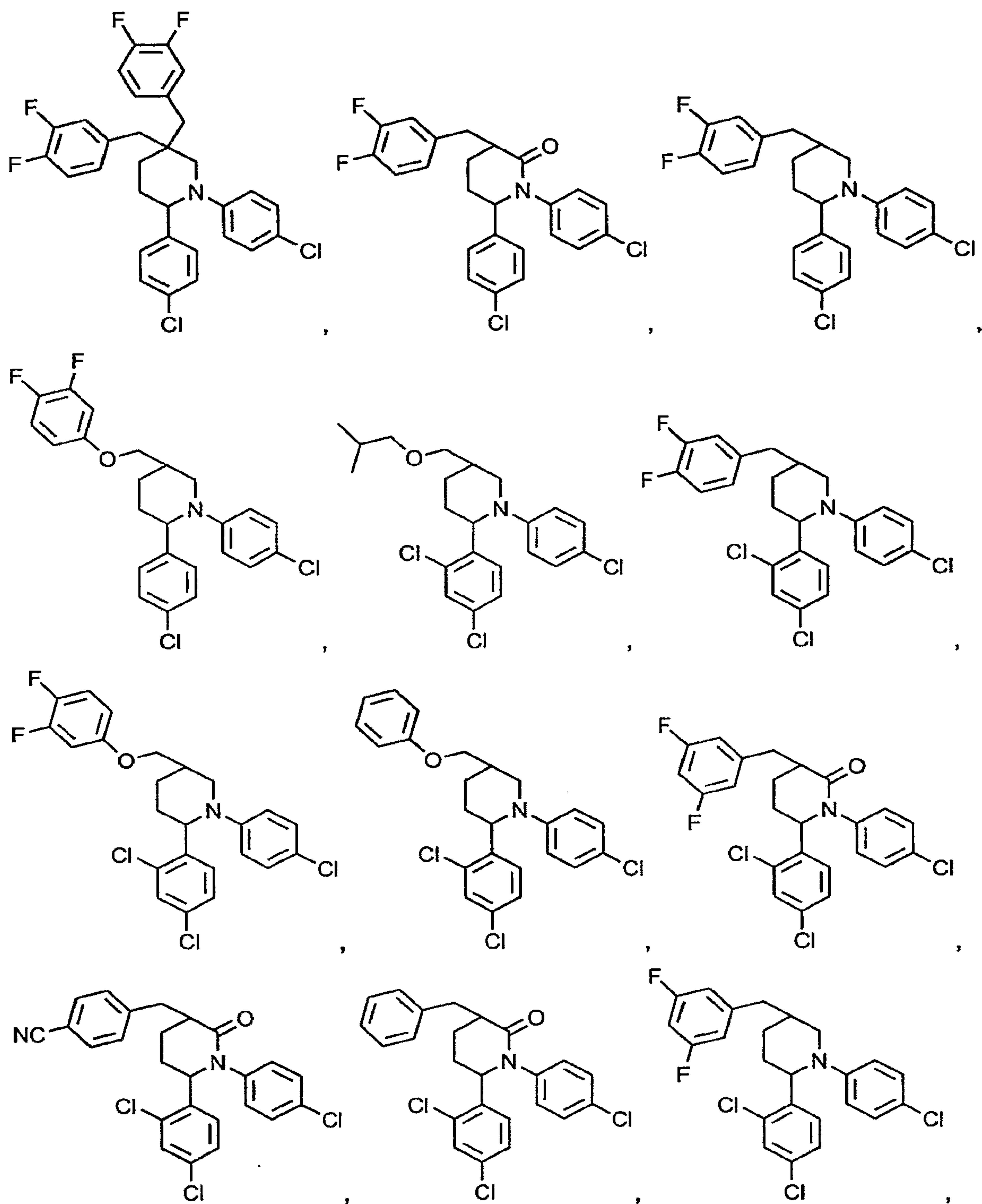


34



[illegible]

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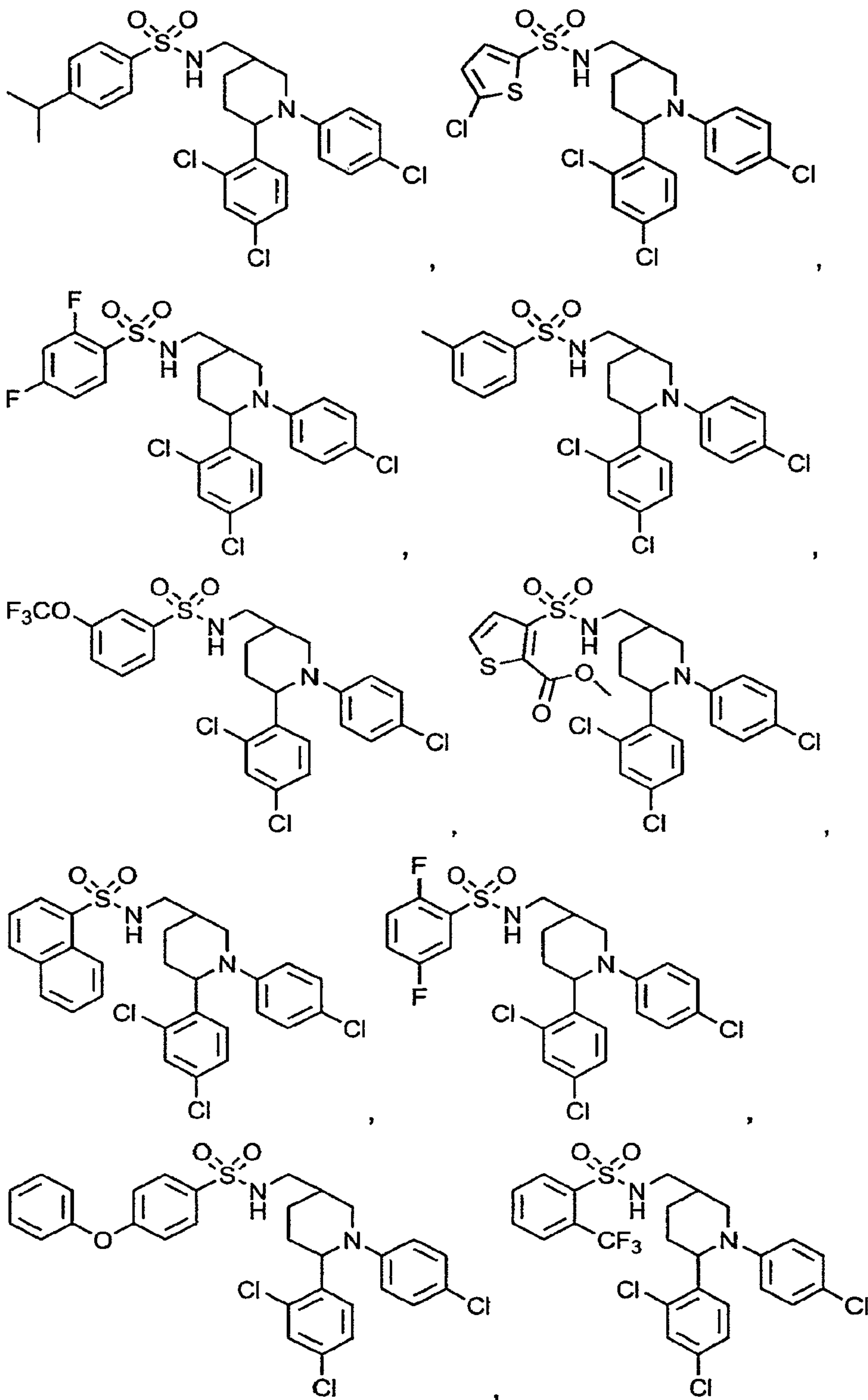


The image displays 11 chemical structures of substituted piperazine derivatives, arranged in a grid. Each structure features a central piperazine ring substituted with a 3,5-dichlorophenyl group and a 4-chlorophenyl group. The piperazine ring is further substituted with various groups at the 1 and 4 positions:

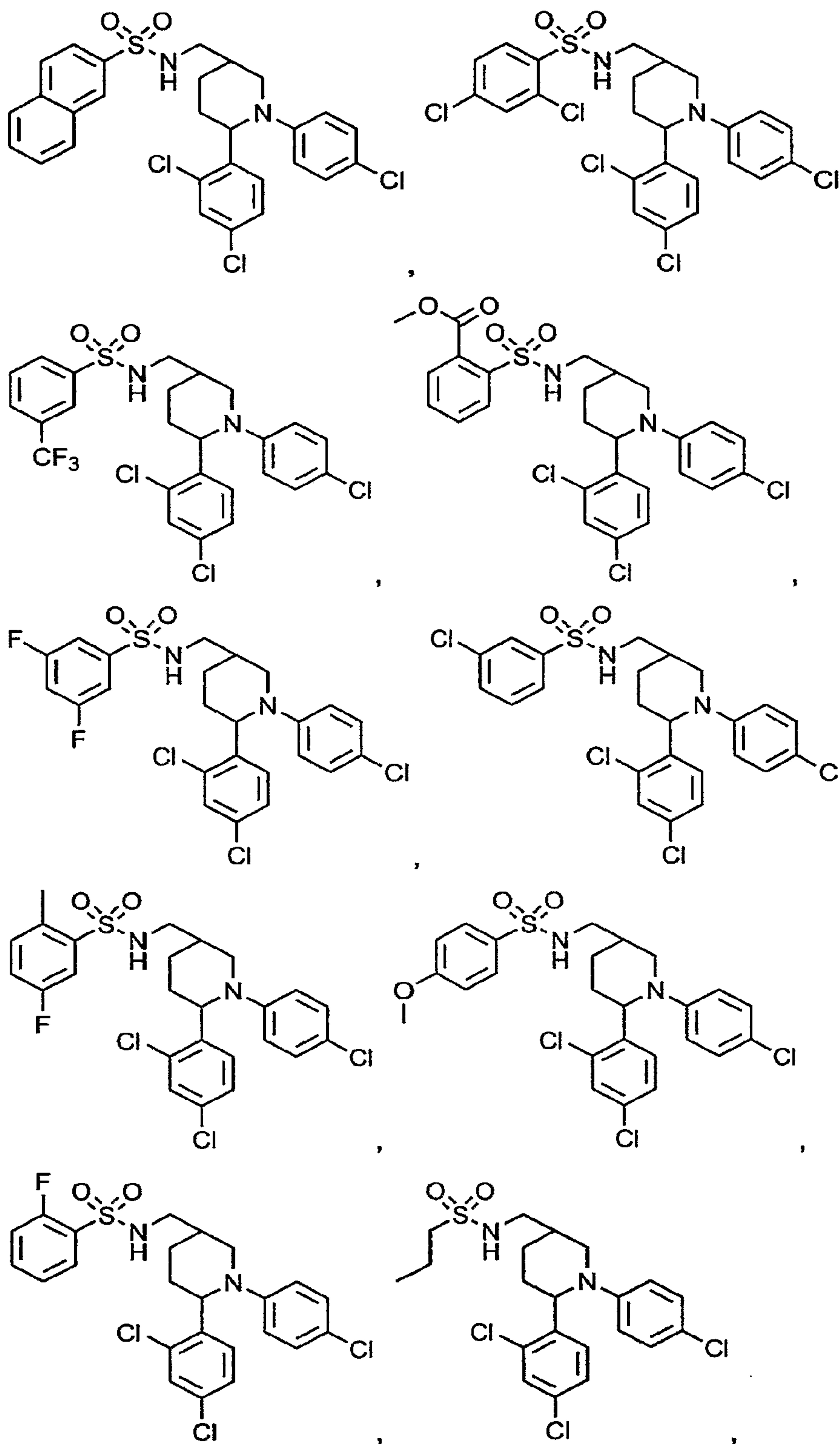
- Structure 1 (top left): 1-(4-aminophenyl)-4-(3,5-dichlorophenyl)piperazine.
- Structure 2 (top middle): 1-phenyl-4-(3,5-dichlorophenyl)piperazine.
- Structure 3 (top right): 1-(4-aminophenyl)-4-(3,5-dichlorophenyl)piperazine.
- Structure 4 (middle left): 1-(benzoylamino)-4-(3,5-dichlorophenyl)piperazine.
- Structure 5 (middle middle): 1-(benzenesulfonylamino)-4-(3,5-dichlorophenyl)piperazine.
- Structure 6 (middle right): 1-(4-(benzenesulfonylamino)phenyl)-4-(3,5-dichlorophenyl)piperazine.
- Structure 7 (bottom left): 1-(4-(benzenesulfonylamino)phenyl)-4-(3,5-dichlorophenyl)piperazine.
- Structure 8 (bottom middle): 1-(4-(benzenesulfonylamino)phenyl)-4-(3,5-dichlorophenyl)piperazine.
- Structure 9 (bottom right): 1-(4-(benzenesulfonylamino)phenyl)-4-(3,5-dichlorophenyl)piperazine.
- Structure 10 (bottom left): 1-(4-(benzenesulfonylamino)phenyl)-4-(3,5-dichlorophenyl)piperazine.
- Structure 11 (bottom right): 1-(4-(benzenesulfonylamino)phenyl)-4-(3,5-dichlorophenyl)piperazine.

Chemical structures of 10 sulfonamide derivatives of compound 1, labeled 1a through 1j, are shown. Each structure features a central piperidine ring substituted with a 3,5-dichlorophenyl group and a 4-chlorophenyl group. The piperidine nitrogen is linked via a methylene group to a sulfonamide moiety. The substituents on the sulfonamide group are: 1a: 3-chloro-4-fluorophenyl; 1b: 4-acetylphenyl; 1c: 2,6-difluorophenyl; 1d: 2-chlorophenyl; 1e: 3-fluorophenyl; 1f: 2-thienyl; 1g: 3,4-dichlorophenyl; 1h: ethyl; 1i: 1-methyl-4-chloro-1H-imidazole-5-yl; 1j: 3-chloro-4-fluorophenyl.

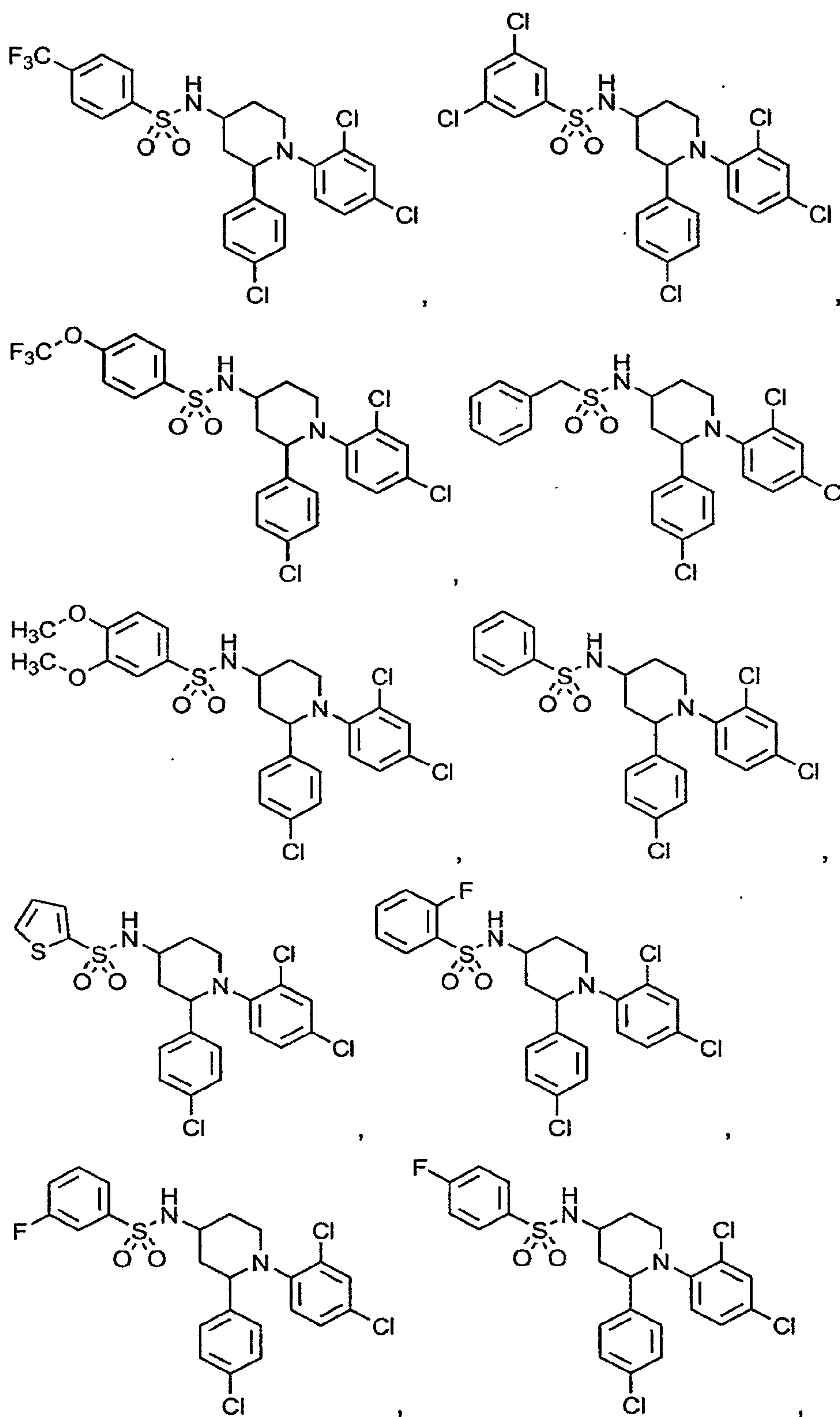
39



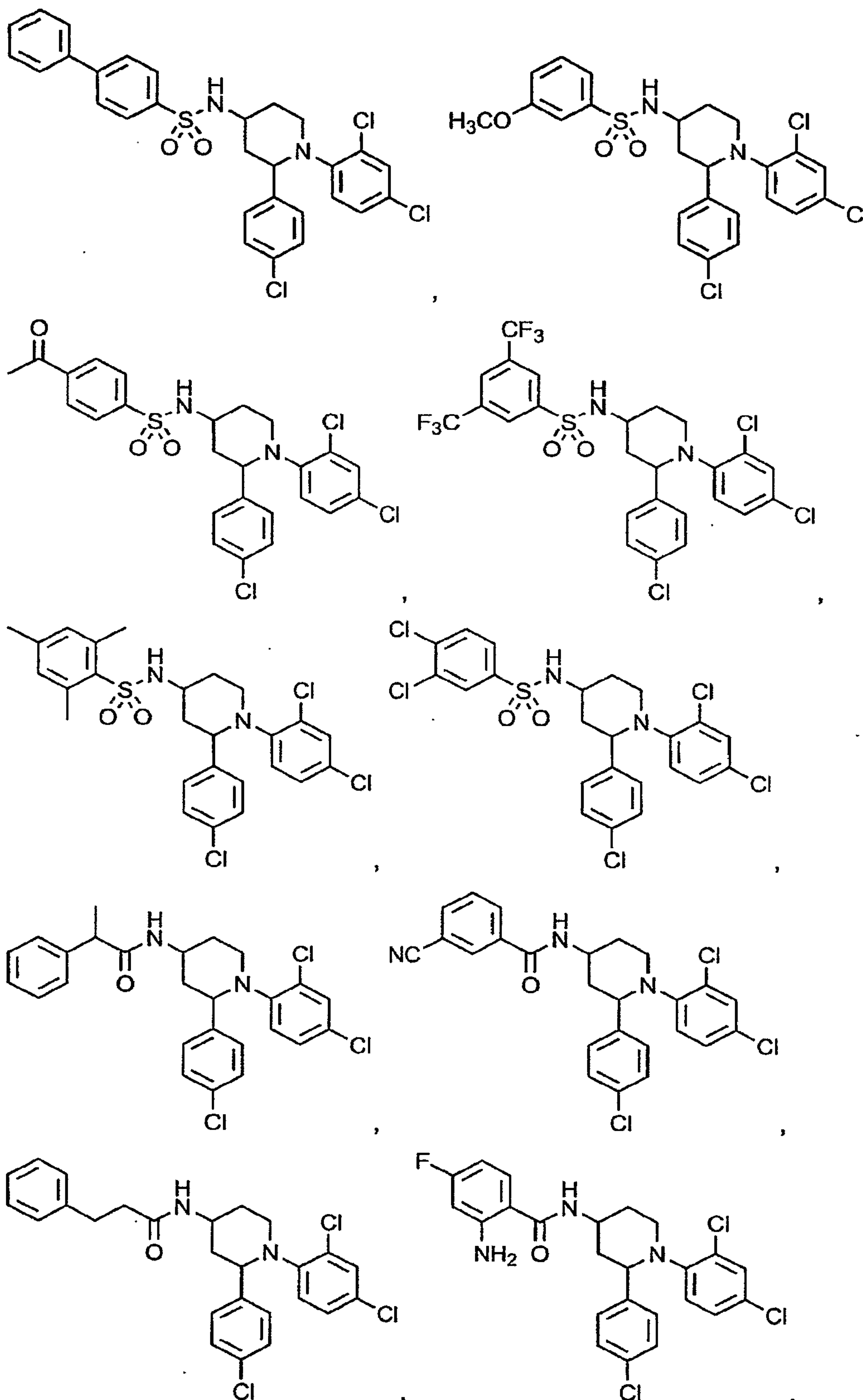
40



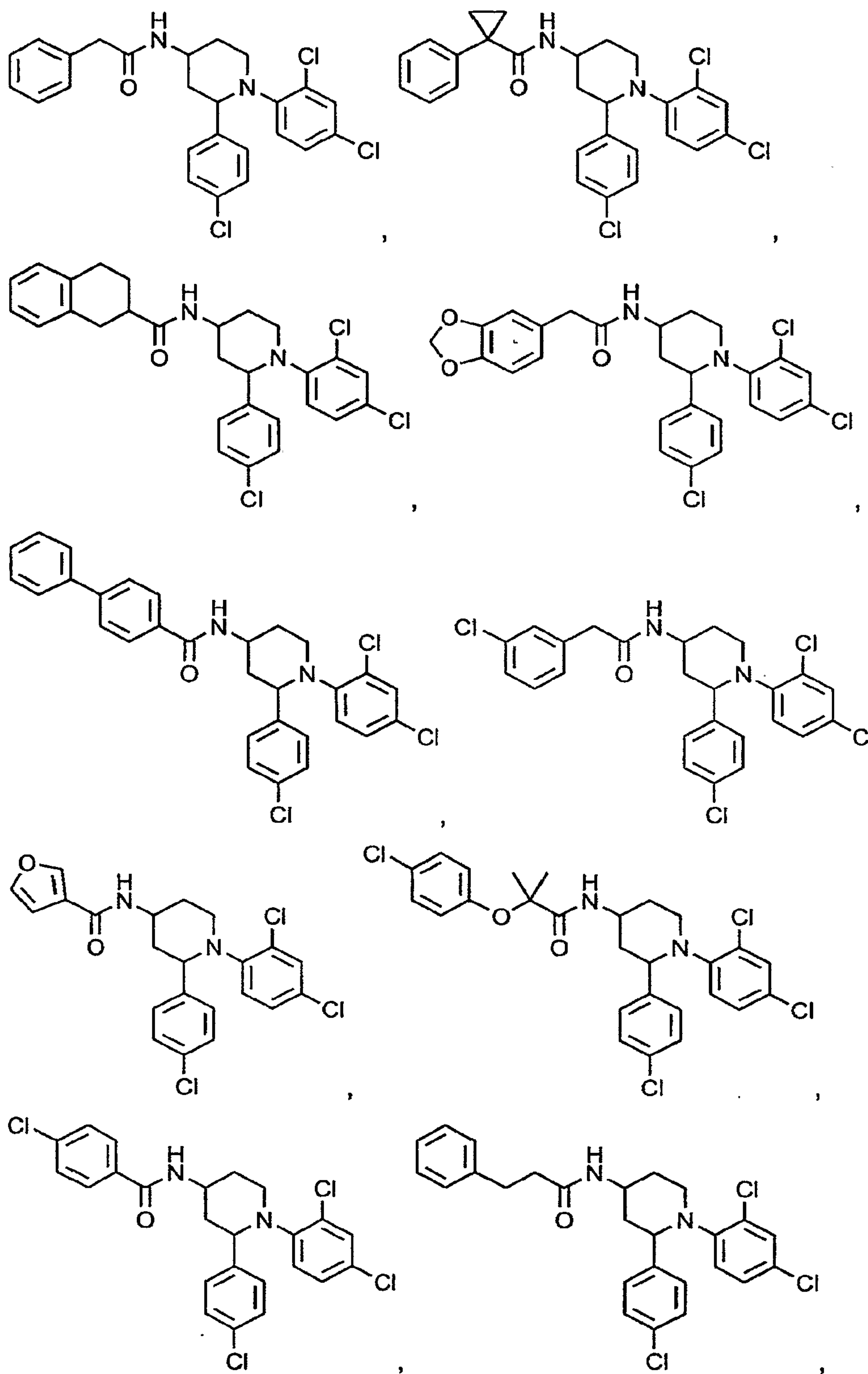
41



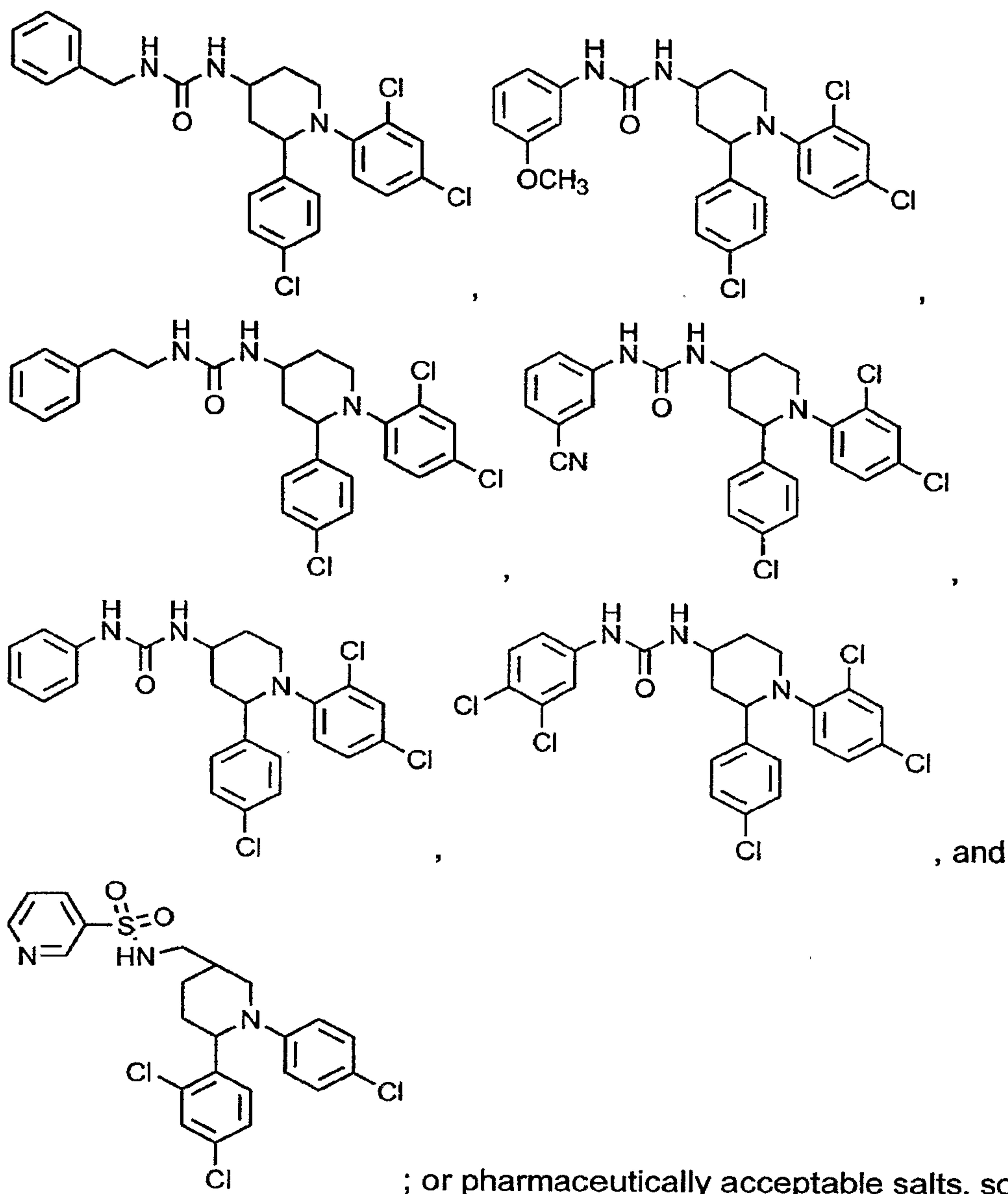
42



43

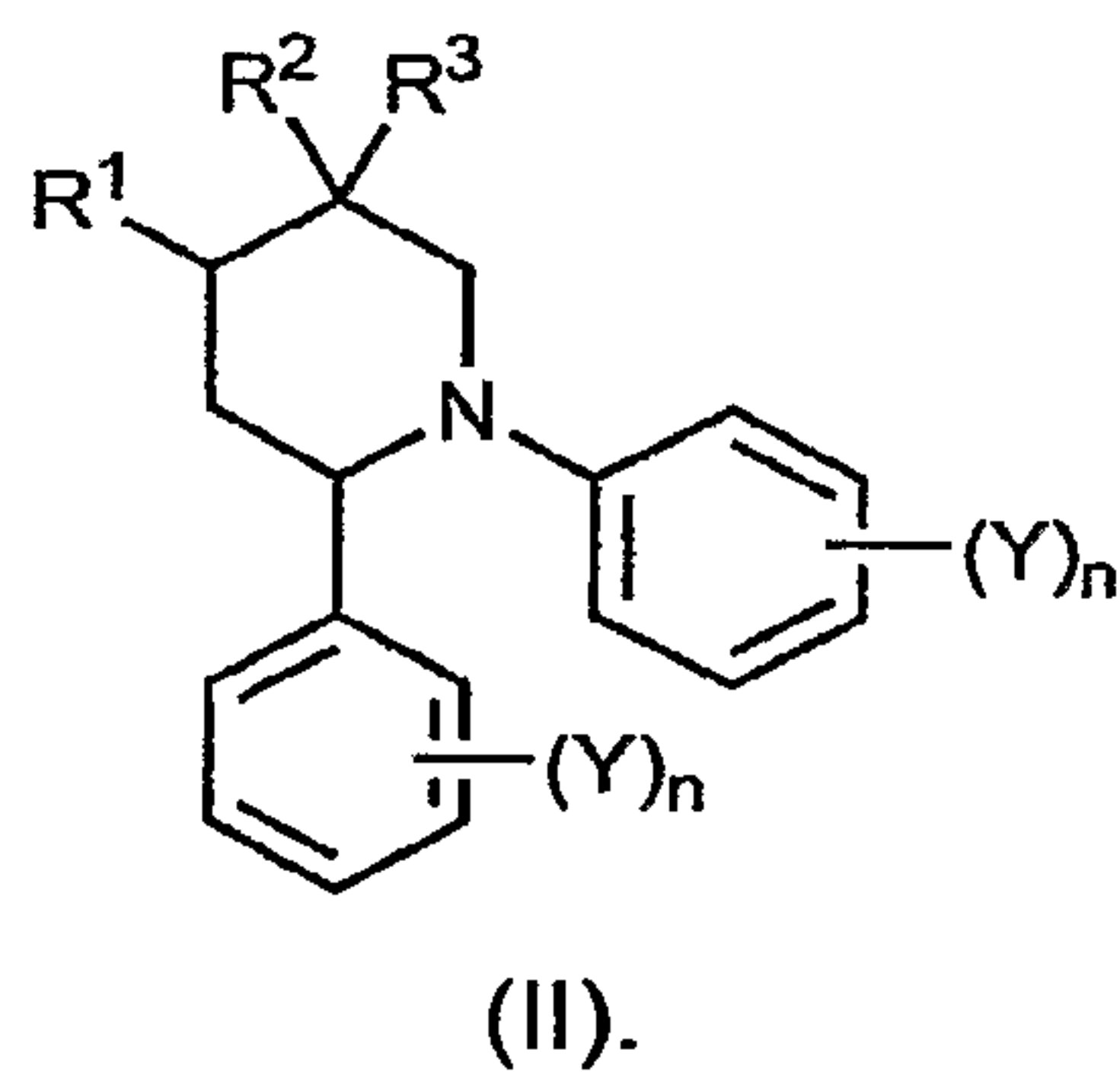


44



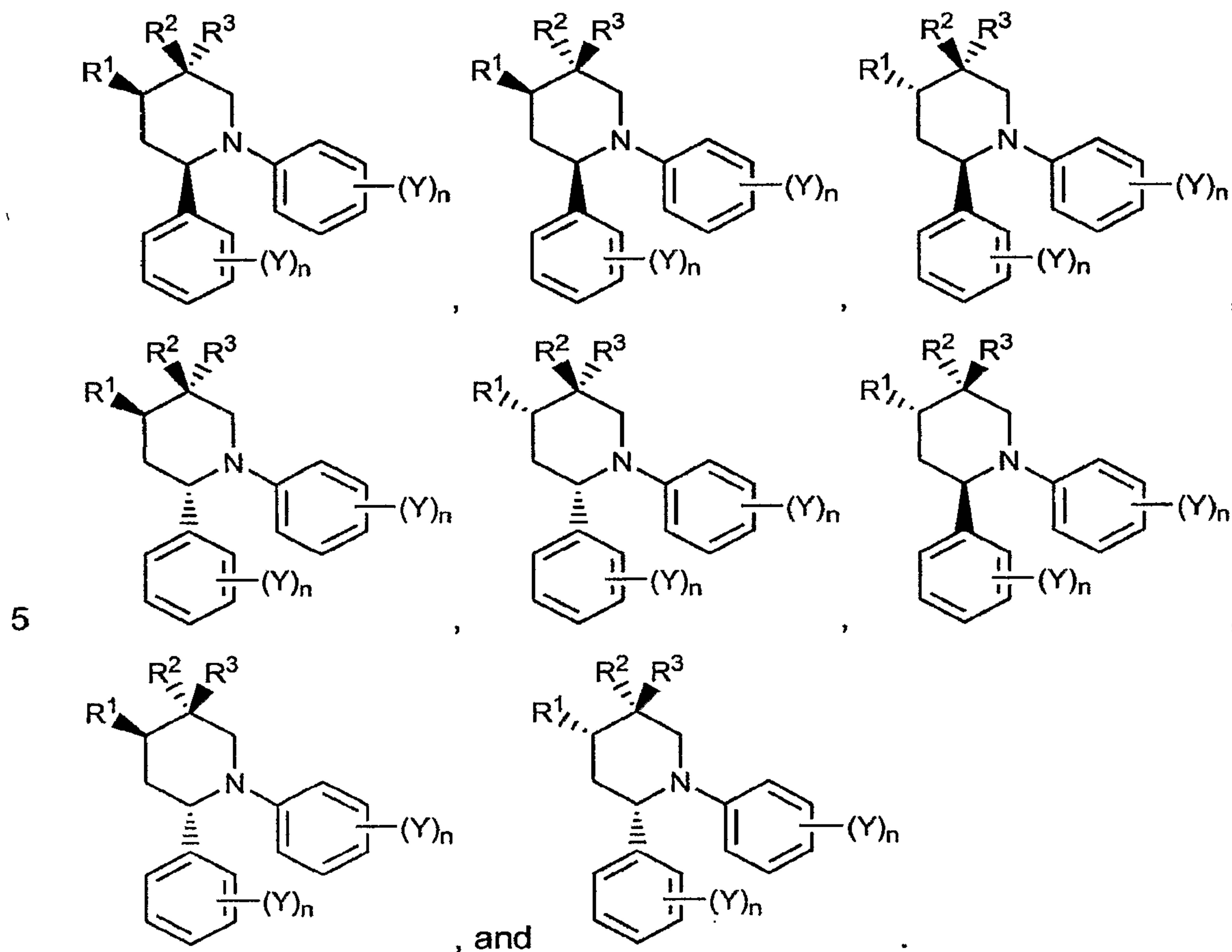
5 ; or pharmaceutically acceptable salts, solvates, or esters thereof.

When A is $-\text{CH}_2-$, the compounds of Formula (I) have the structure of Formula (II):

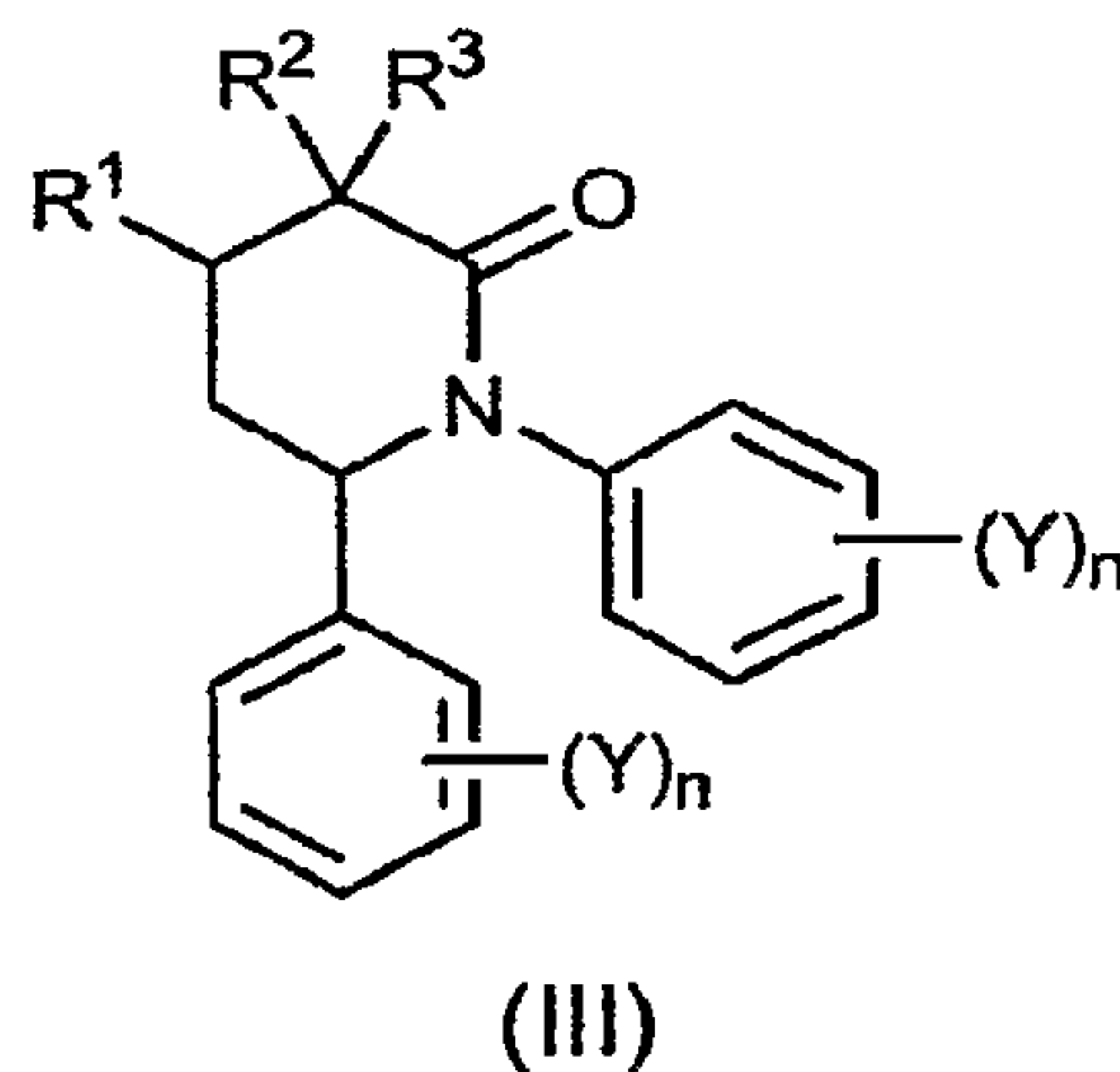


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It will be recognized by one of skill in the art that compounds of Formula (II) include all stereoisomers of such compounds. A non-limiting list of stereoisomers of Formula (II) can include:

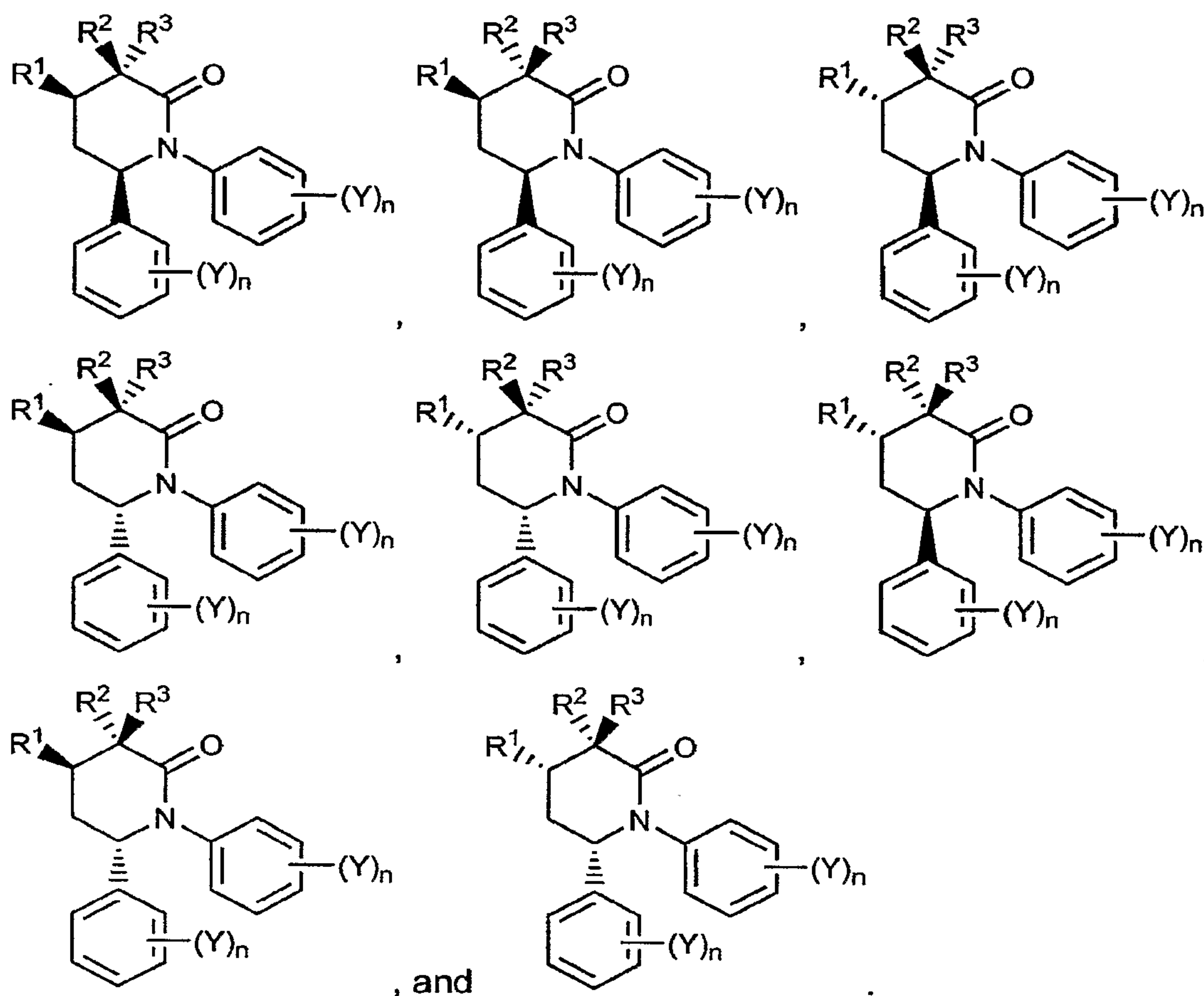


When A is $-\text{C}(\text{O})-$, the compounds of Formula (I) have the structure of Formula (III):

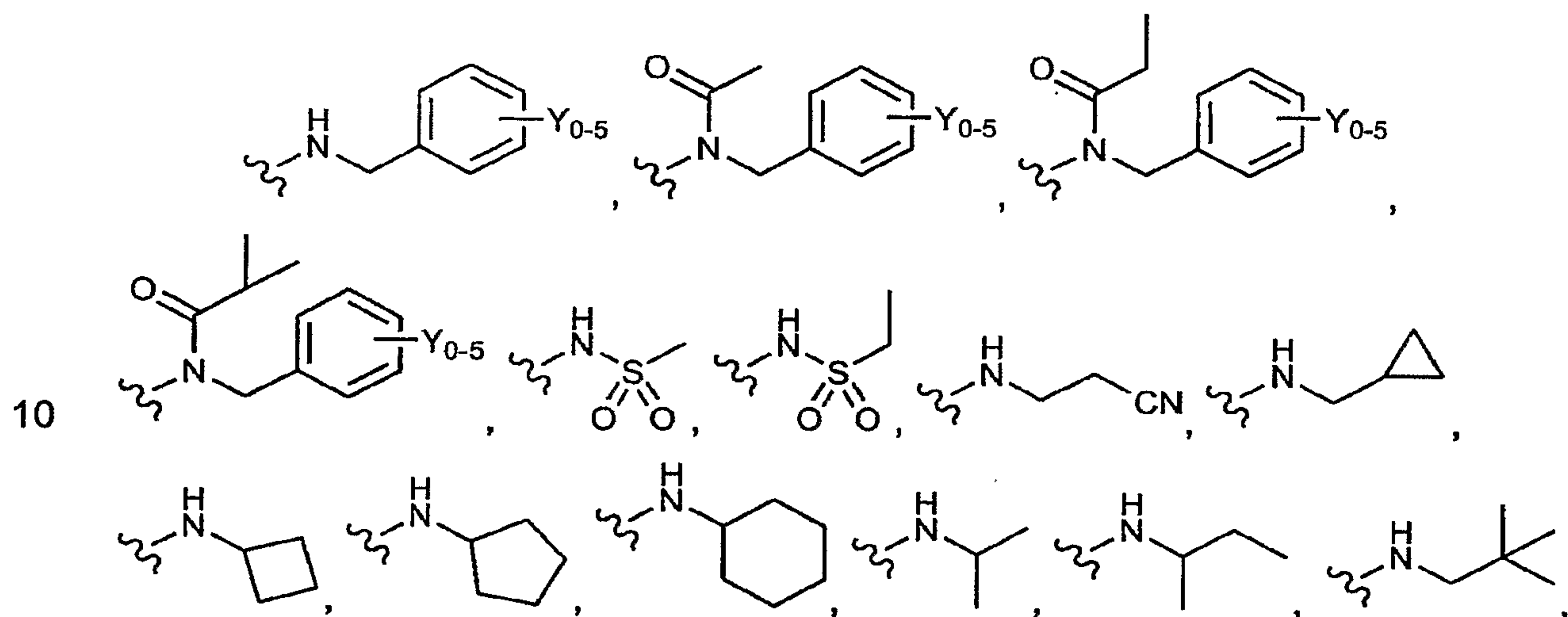


It will be recognized by one of skill in the art that compounds of Formula (III) include all stereoisomers of such compounds. A non-limiting list of stereoisomers of Formula (III) can include:

46



R^1 is selected from the group consisting of H, $-N(R^4)(R^5)$, unsubstituted
 5 heterocyclyl, heterocyclyl substituted with one or more X groups, $-N_3$, and $-O-R^7$, with
 the proviso that when R^1 is $-OH$, n is independently an integer of from 1-5. When R^1
 is $-N(R^4)(R^5)$, R^4 and R^5 are as defined herein. Non-limiting examples of $-N(R^4)(R^5)$
 of R^1 include:

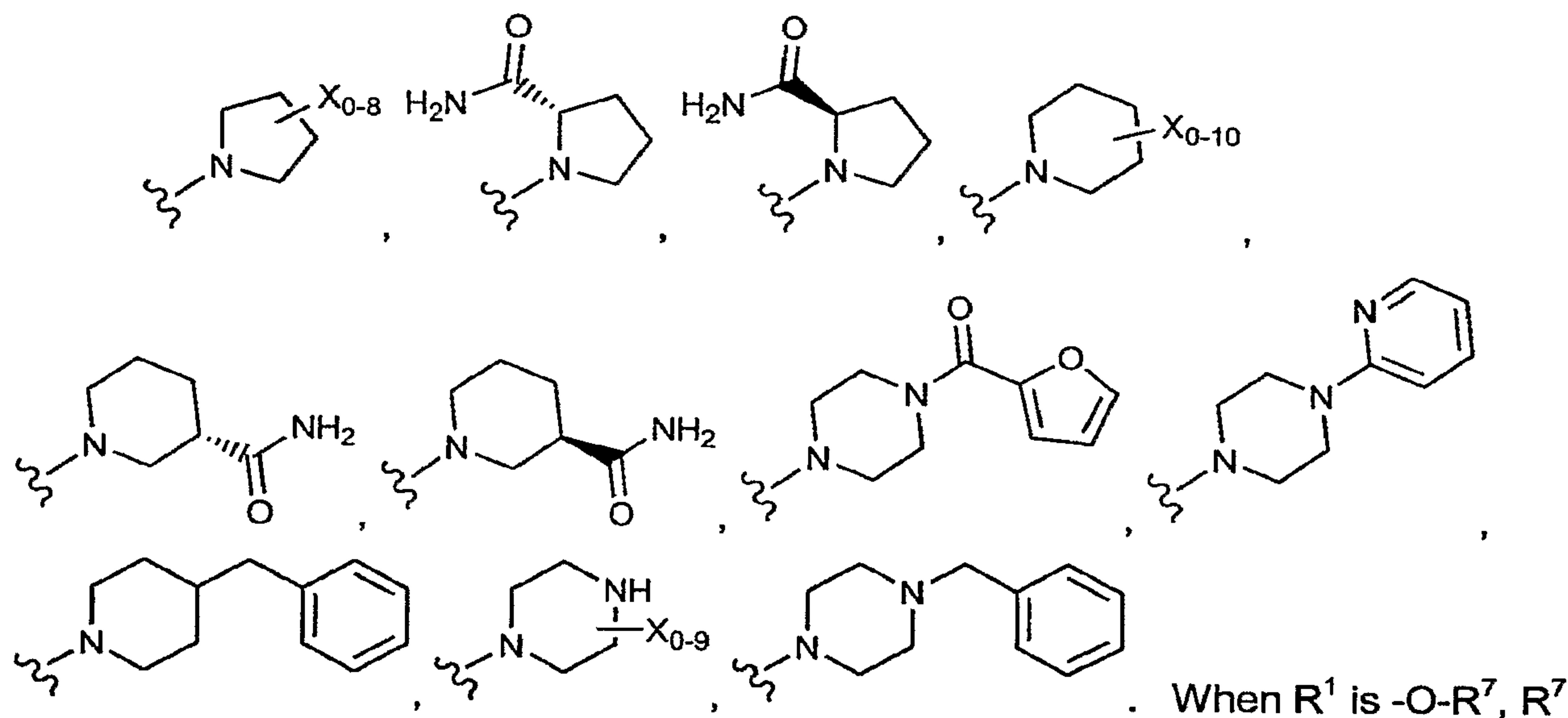


5

0

When R^1 is substituted or unsubstituted heterocyclvl, no


 When R¹ is substituted or unsubstituted heterocyclyl, non-
 5 limiting examples include:



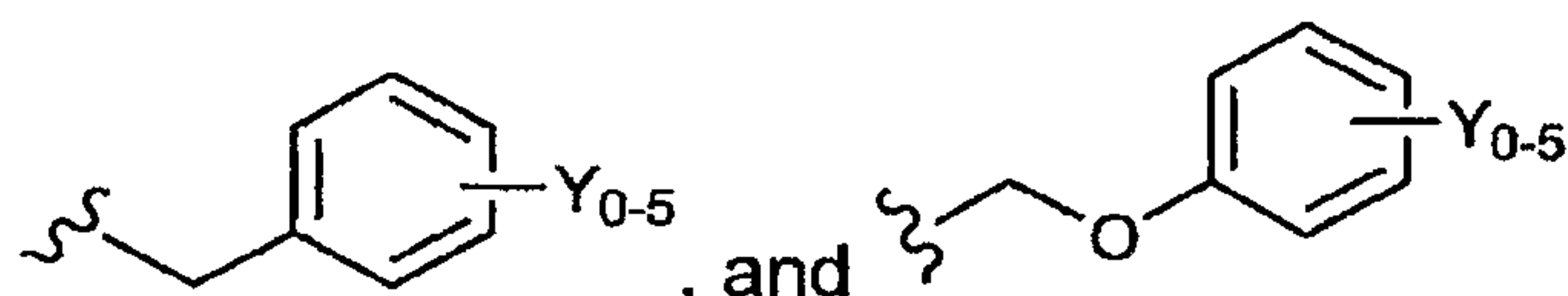
When R^1 is $-O-R^7$, R^7

is defined as described herein. Non-limiting examples of R¹ when R¹ is -O-R⁷

10 include -OH with the proviso that n is independently an integer of from 1-5, -OCH₃, -O-CH₂CH₃, -O-CH₂(CH₃)₂, -O-C(CH₃)₃, -O-CH₂CH₂CH₃, -O-CH₂CH₂CH₂CH₃, and substituted or unsubstituted -O-phenyl.

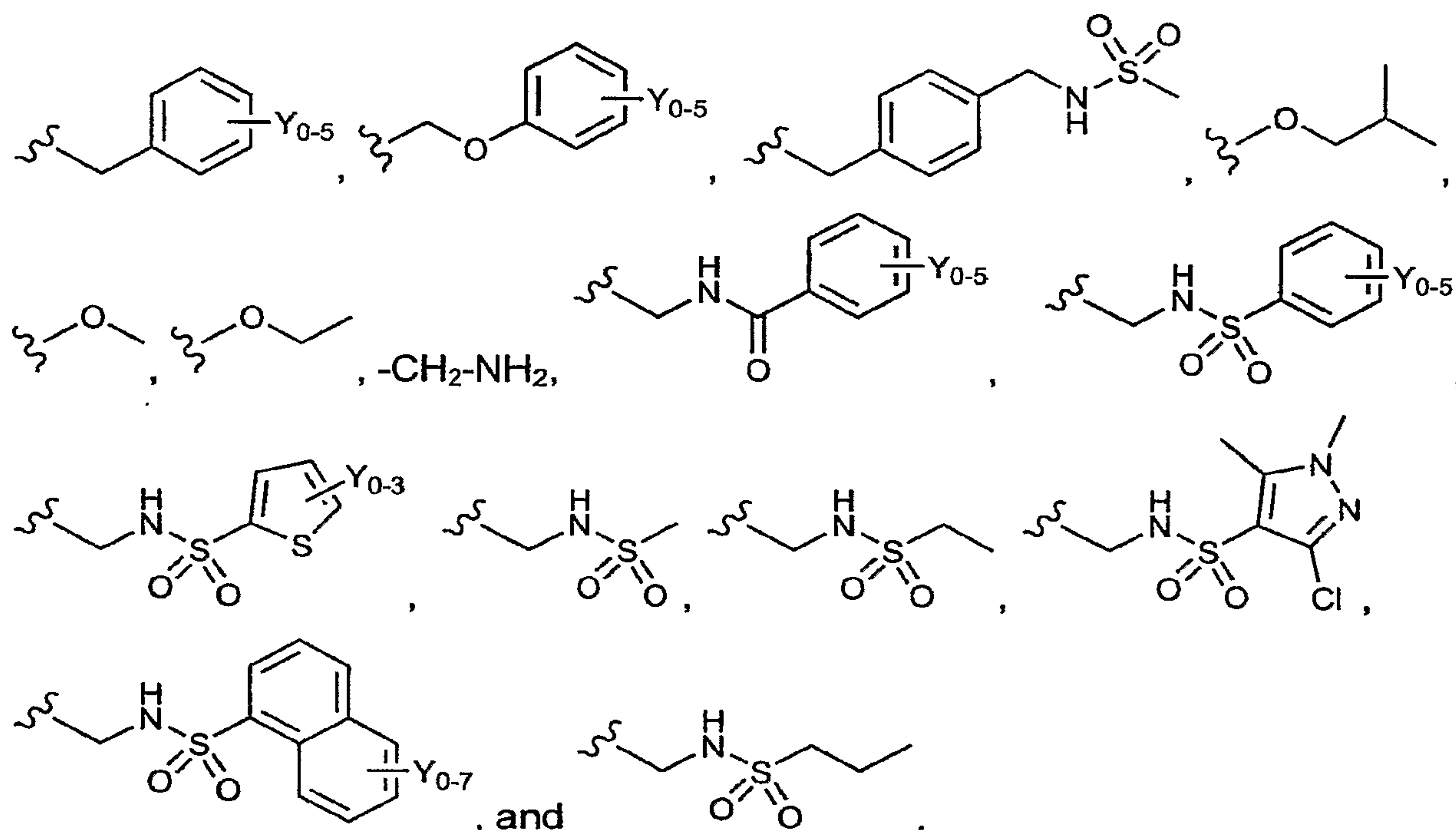
R^2 is selected from the group consisting of H, $-C(R^6)_2$ -aryl, and $-C(R^6)_2$ -O- R^7 , wherein the aryl portion of said $-C(R^6)_2$ -aryl of R^2 is unsubstituted or substituted with one or more Y groups. When R^2 is $-C(R^6)_2$ -aryl or $-C(R^6)_2$ -O- R^7 , R^6 , R^7 and aryl are as defined herein. Non-limiting examples of $-C(R^6)_2$ -aryl or $-C(R^6)_2$ -O- R^7 of R^2

5 include:



R^3 is selected from the group consisting of H, $-C(R^6)_2$ -aryl, $-C(R^6)_2$ -O- R^7 , $-O$ - R^7 , and $-C(R^6)_2$ -N(R^8)₂, wherein the aryl portion of said $-C(R^6)_2$ -aryl of R^3 is unsubstituted or substituted with one or more Y groups. When R^3 is $-C(R^6)_2$ -aryl, $-C(R^6)_2$ -O- R^7 , $-O$ - R^7 , or $-C(R^6)_2$ -N(R^8)₂, R^6 , R^7 , R^8 and aryl are as defined herein. Non-limiting examples of $-C(R^6)_2$ -aryl, $-C(R^6)_2$ -O- R^7 , $-O$ - R^7 , or $-C(R^6)_2$ -N(R^8)₂ of R^3

10



15

Alternatively, R^2 and R^3 together with the carbon atom to which they are shown attached can form a spiro-fused unsubstituted heterocyclyl ring or a heterocyclyl ring substituted with one or more X groups as defined herein. Non-limiting example of such heterocyclyl rings include piperidyl, piperidinyl, pyrrolidinyl, etc.

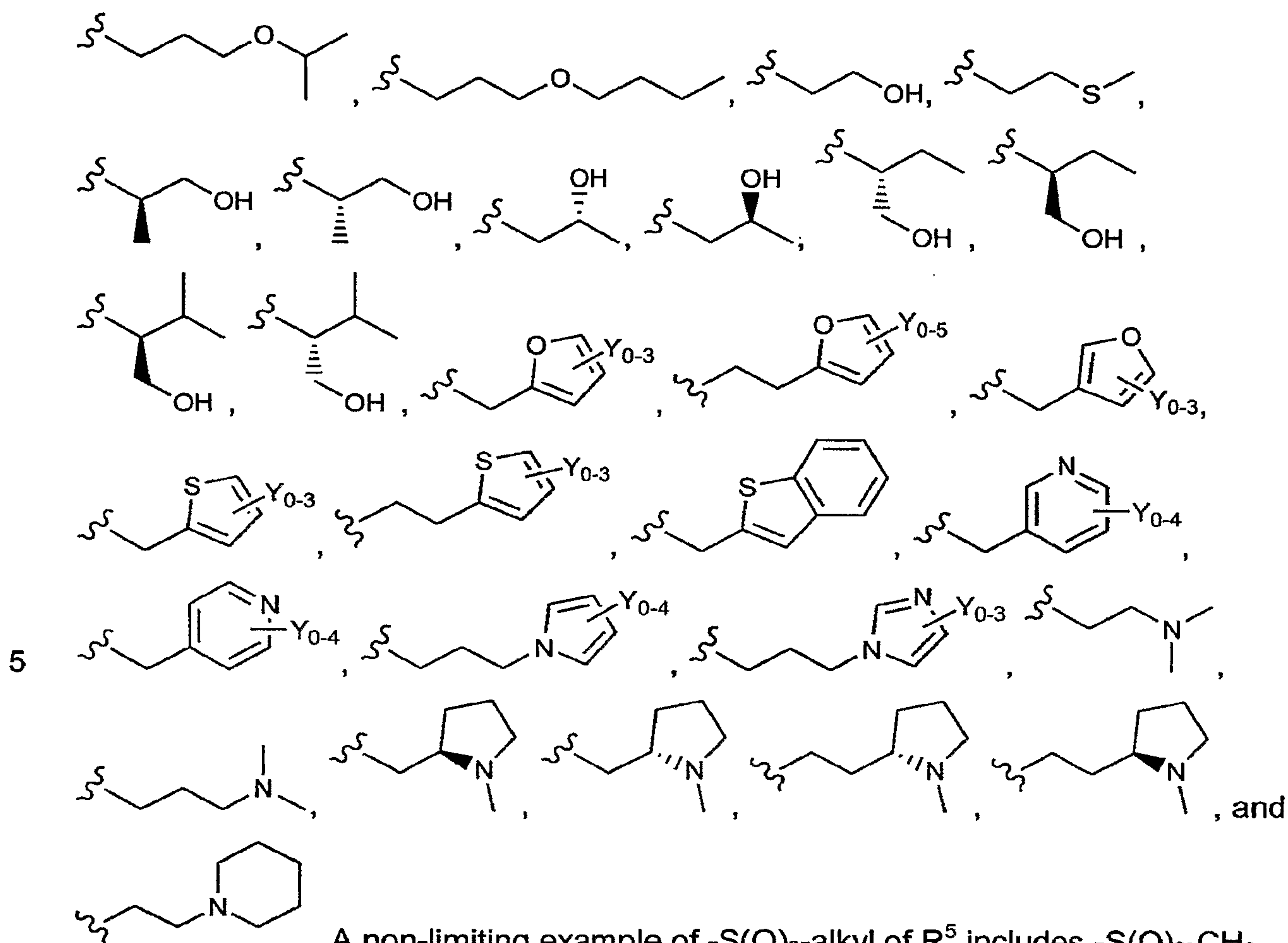
20

$-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, , , , and $-\text{C}(\text{O})-\text{CH}_3$.

15



51



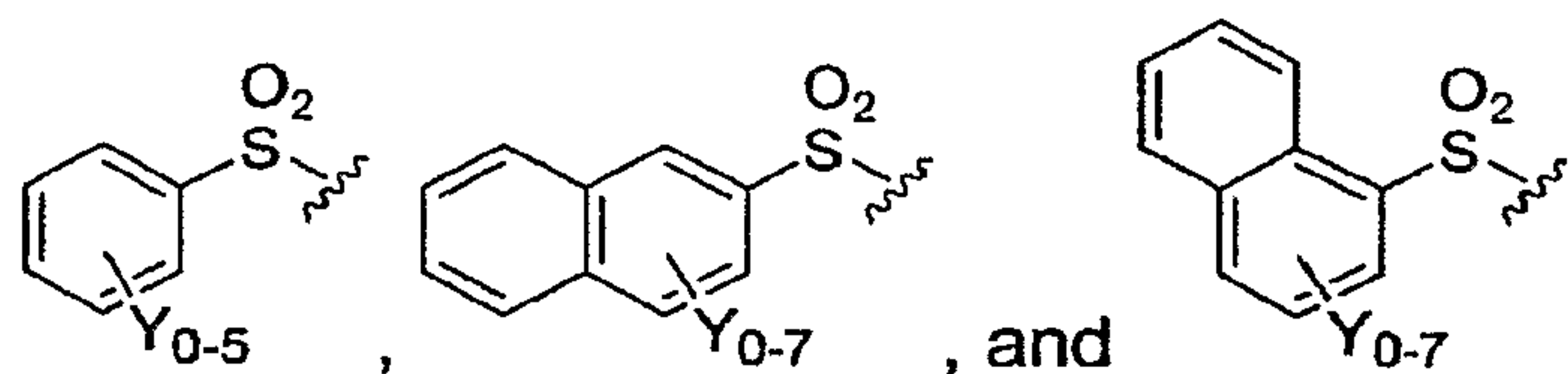
. A non-limiting example of -S(O)₂-alkyl of R⁵ includes -S(O)₂-CH₃.

Non-limiting examples of -S(O)-cycloalkyl of R⁵ include -S(O)-cyclopropyl,

-S(O)-cyclobutyl, -S(O)-cyclopentyl, -S(O)-cyclohexyl, etc. Non-limiting examples of

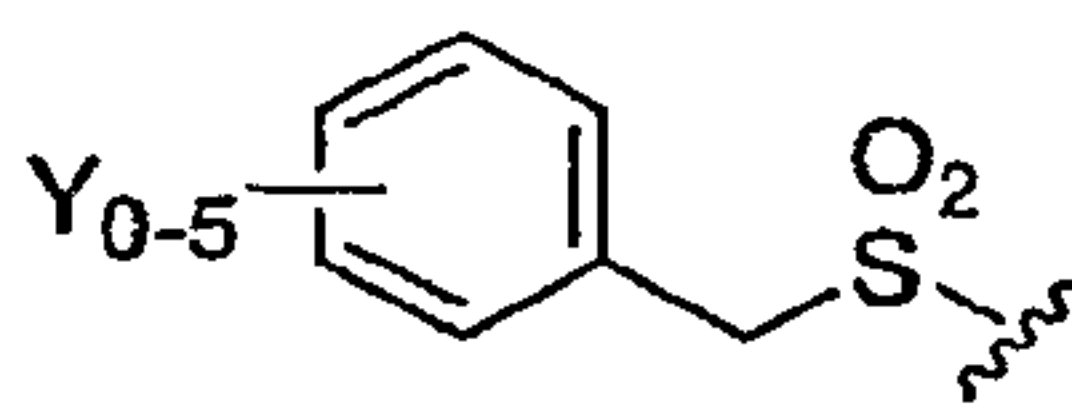
10 -C(O)-cycloalkyl of R⁵ include -C(O)-cyclopropyl, -C(O)-cyclobutyl, -C(O)-cyclopentyl, -C(O)-cyclohexyl, etc.

Non-limiting examples of -S(O)₂-aryl of R⁵ include:

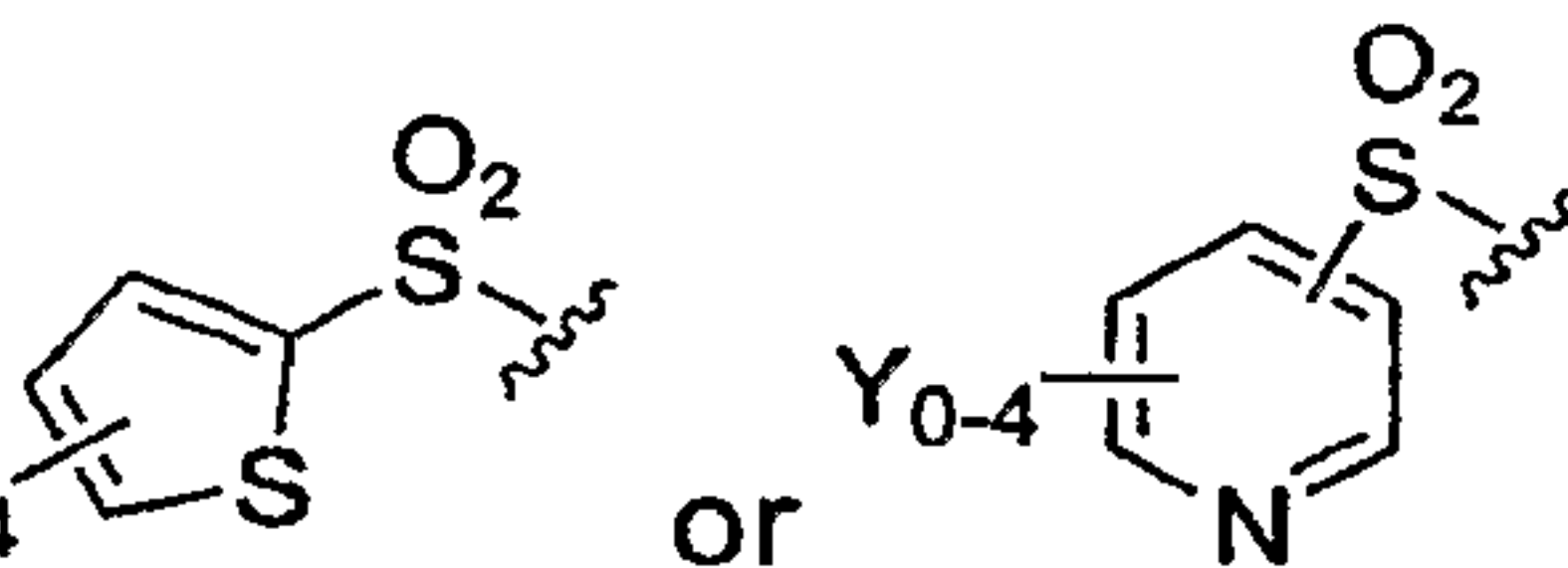


. A non-limiting example of

-S(O)₂-(C(R⁶)₂)_m-aryl of R⁵ includes

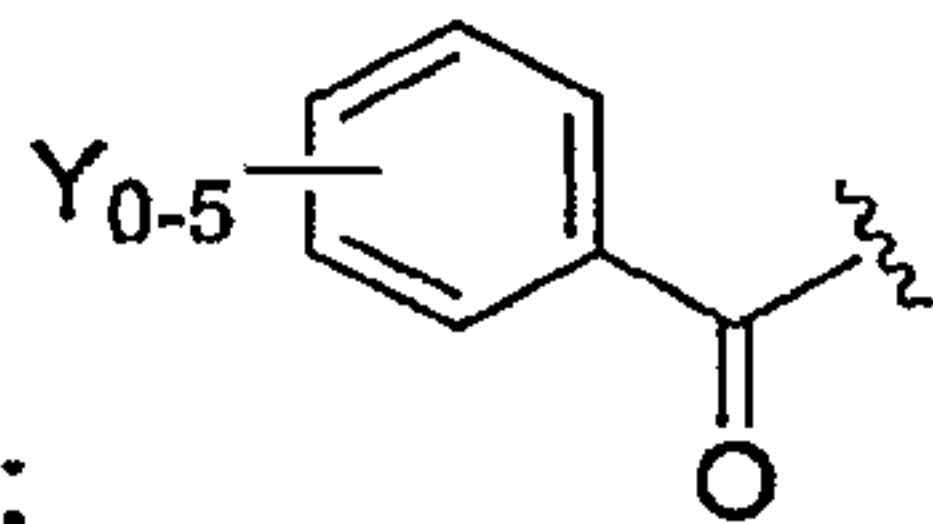


Non-limiting examples of



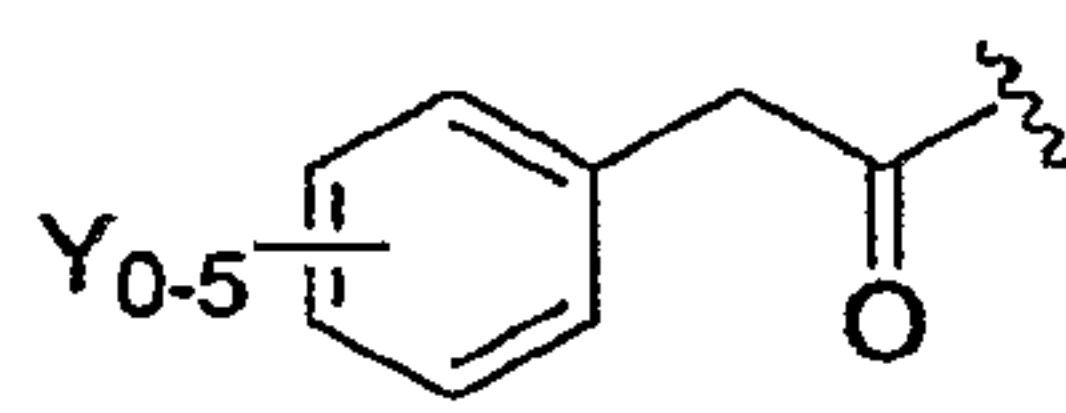
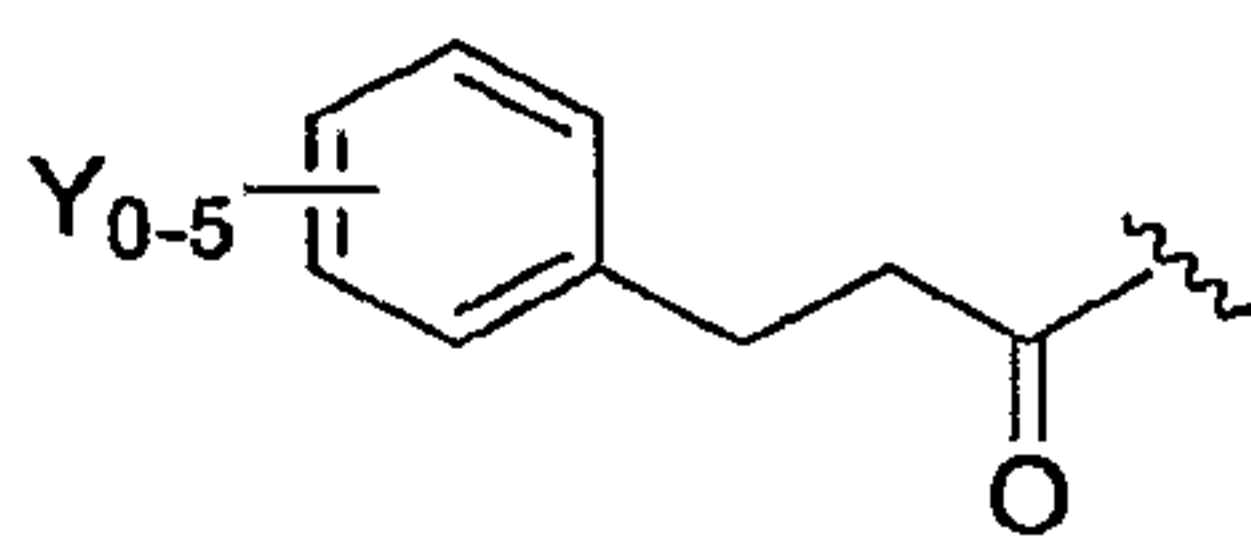
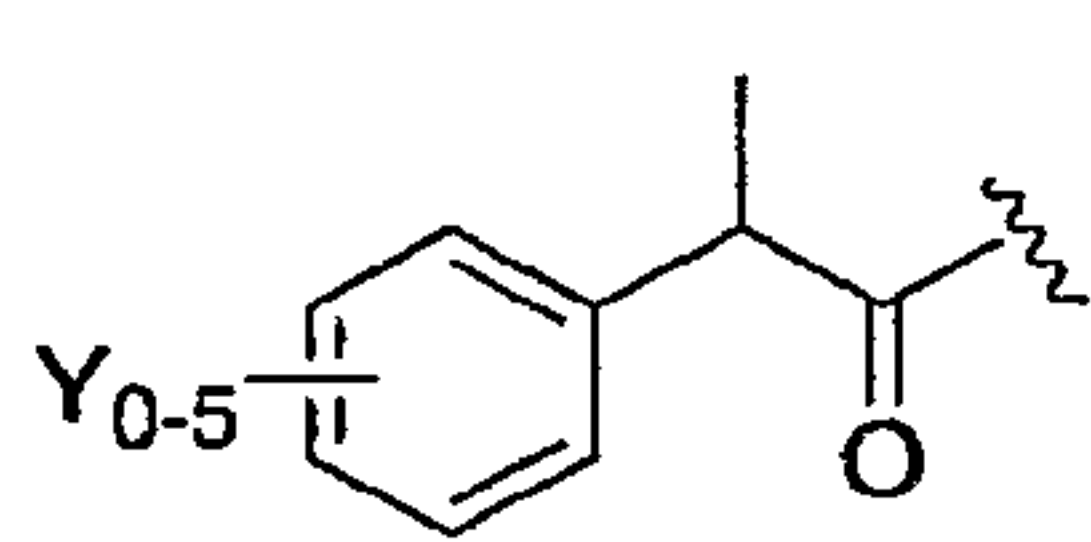
. A non-limiting

example of $-\text{C}(\text{O})$ -alkyl of R^5 includes $-\text{C}(\text{O})-\text{CH}_3$. A non-limiting example of



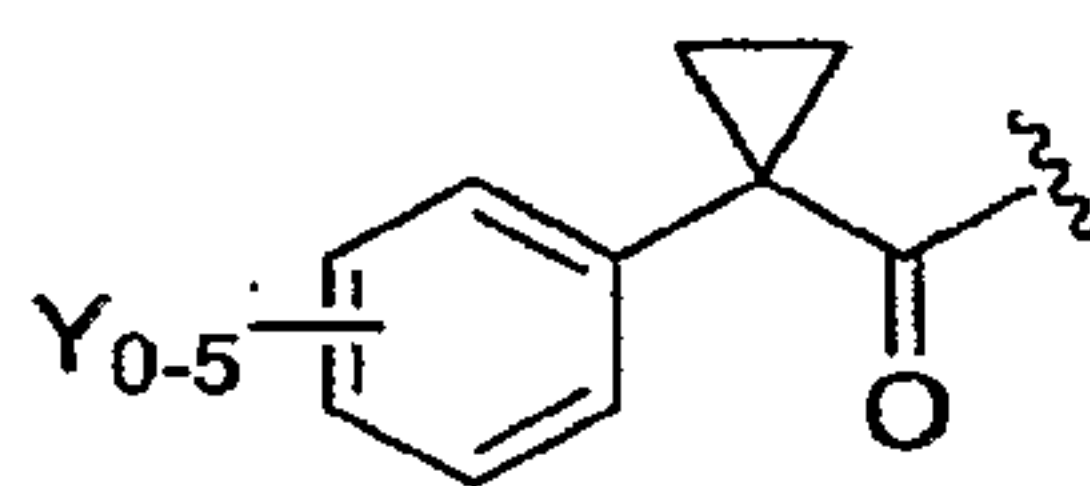
$-\text{C}(\text{O})$ -aryl of R^5 includes:

$-\text{C}(\text{O})-(\text{C}(\text{R}^6)_2)_m$ -aryl of R^5 include:



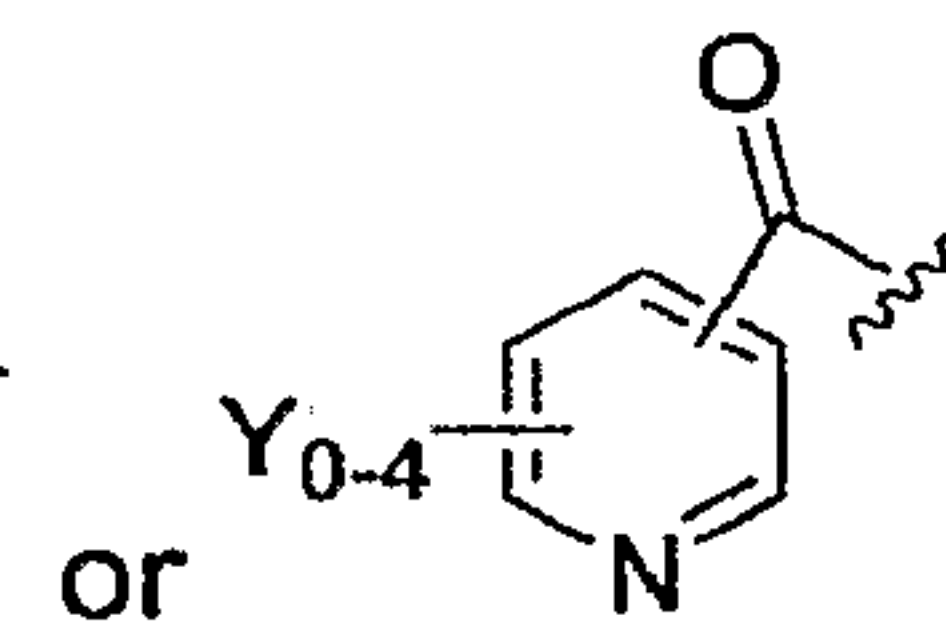
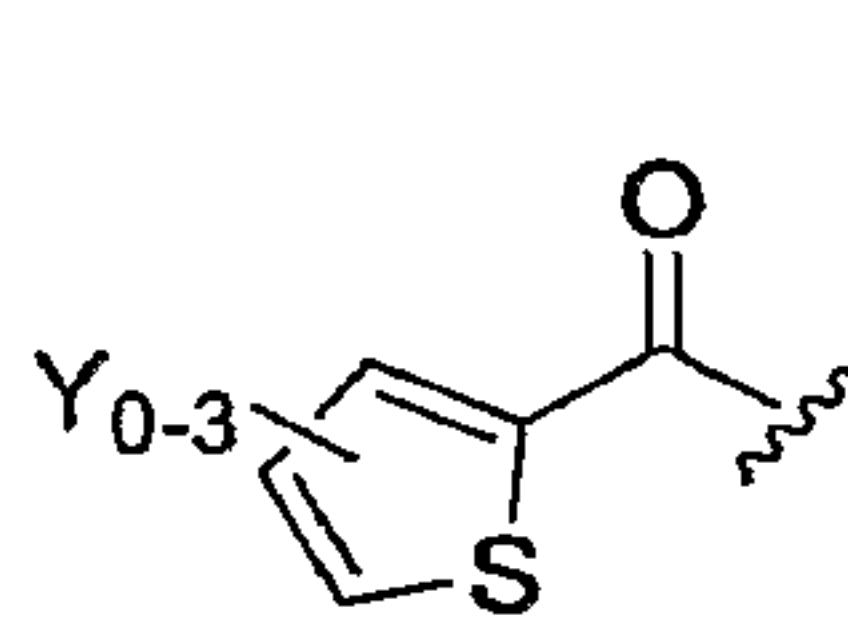
. A non-limiting

5 example of $-\text{C}(\text{O})$ -cycloalkylene-aryl of R^5 includes



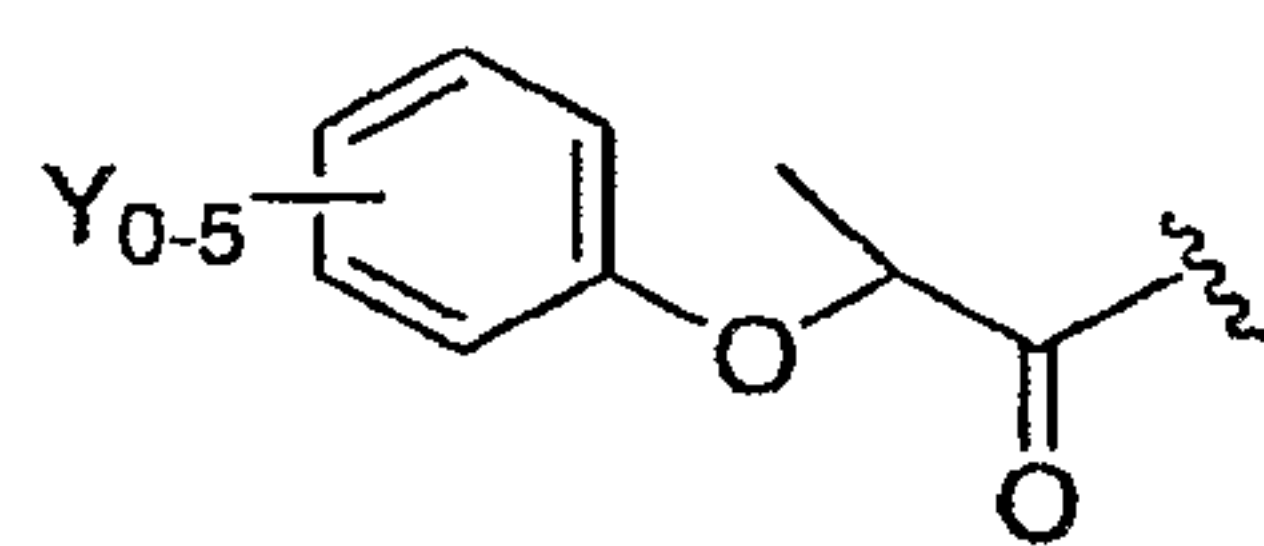
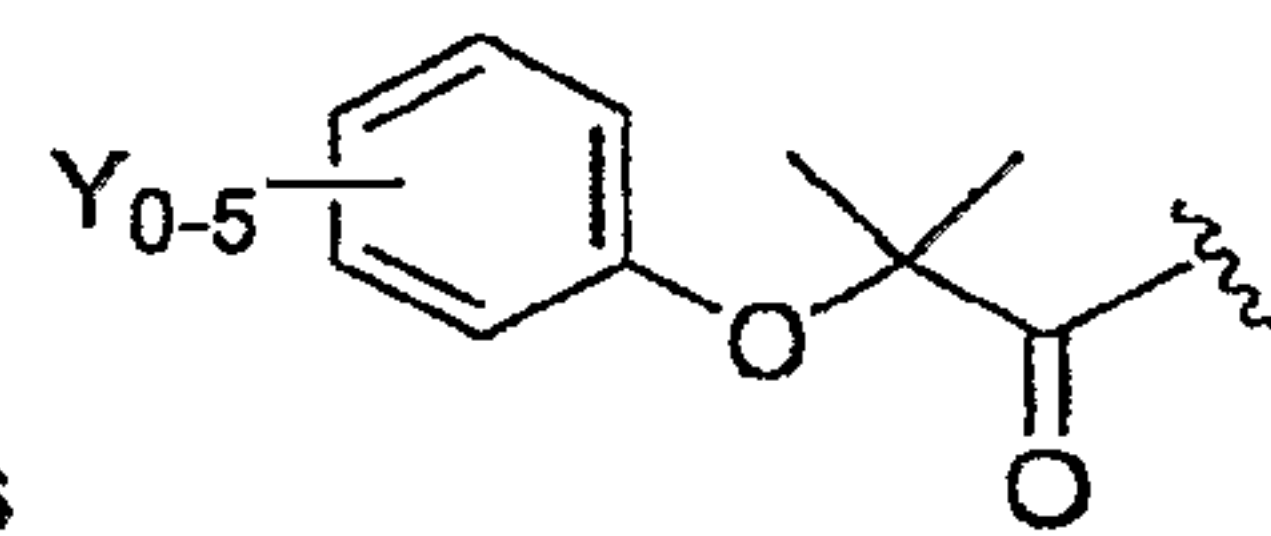
. Non-limiting

examples of $-\text{C}(\text{O})$ -heteroaryl of R^5 includes

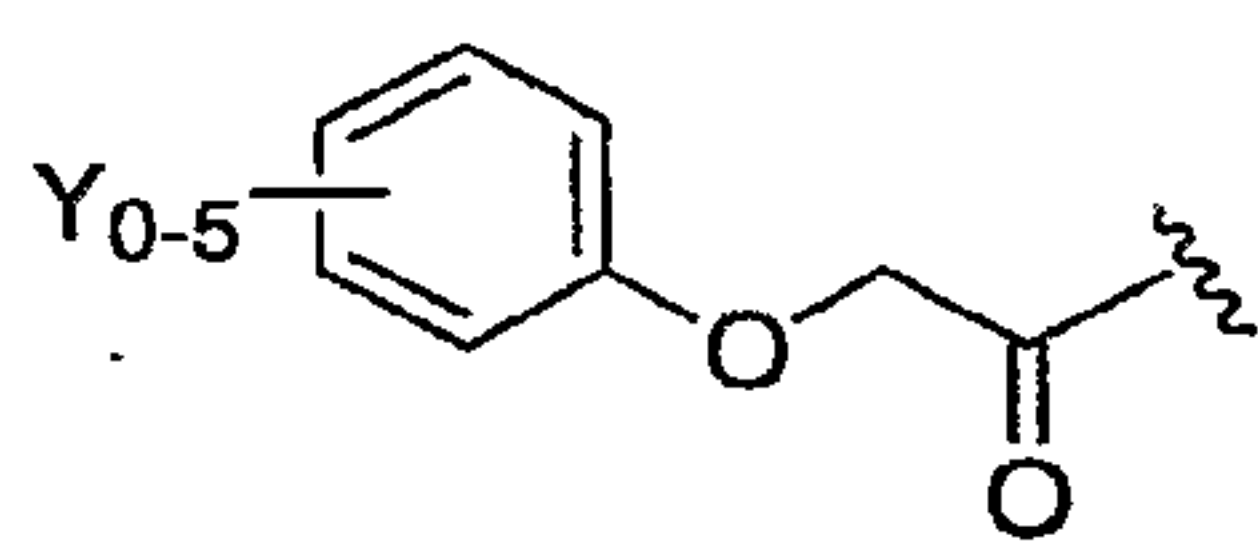


. A non-

limiting example of $-\text{C}(\text{O})-(\text{C}(\text{R}^6)_2)_m$ -O-aryl of R^5 includes

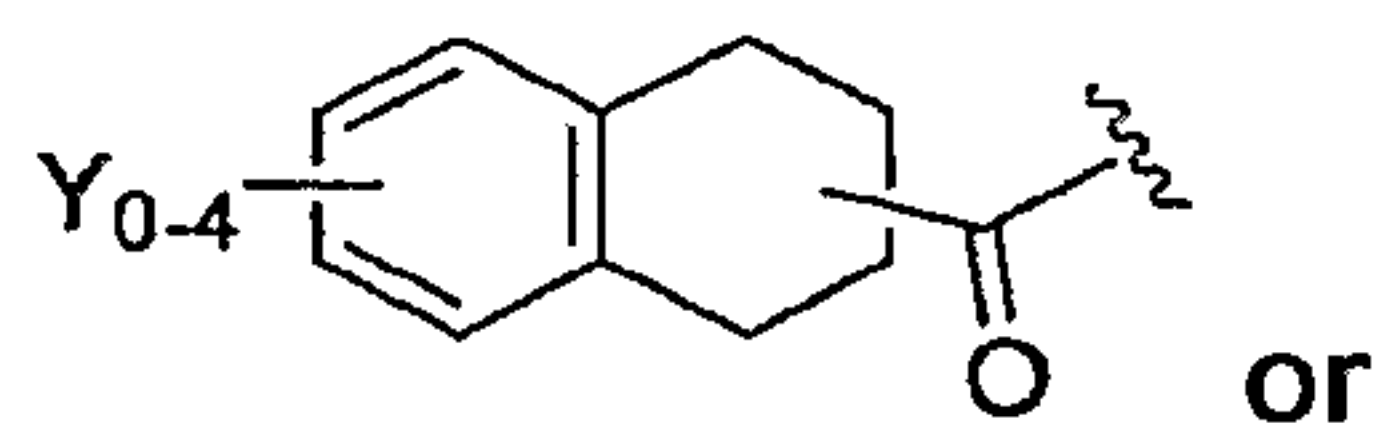


, and

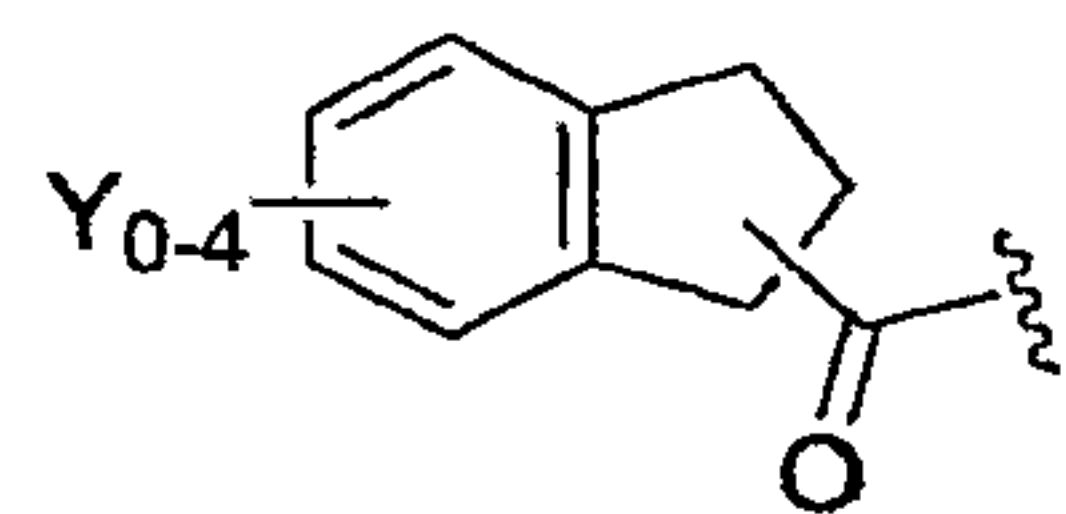


. A non-limiting example of

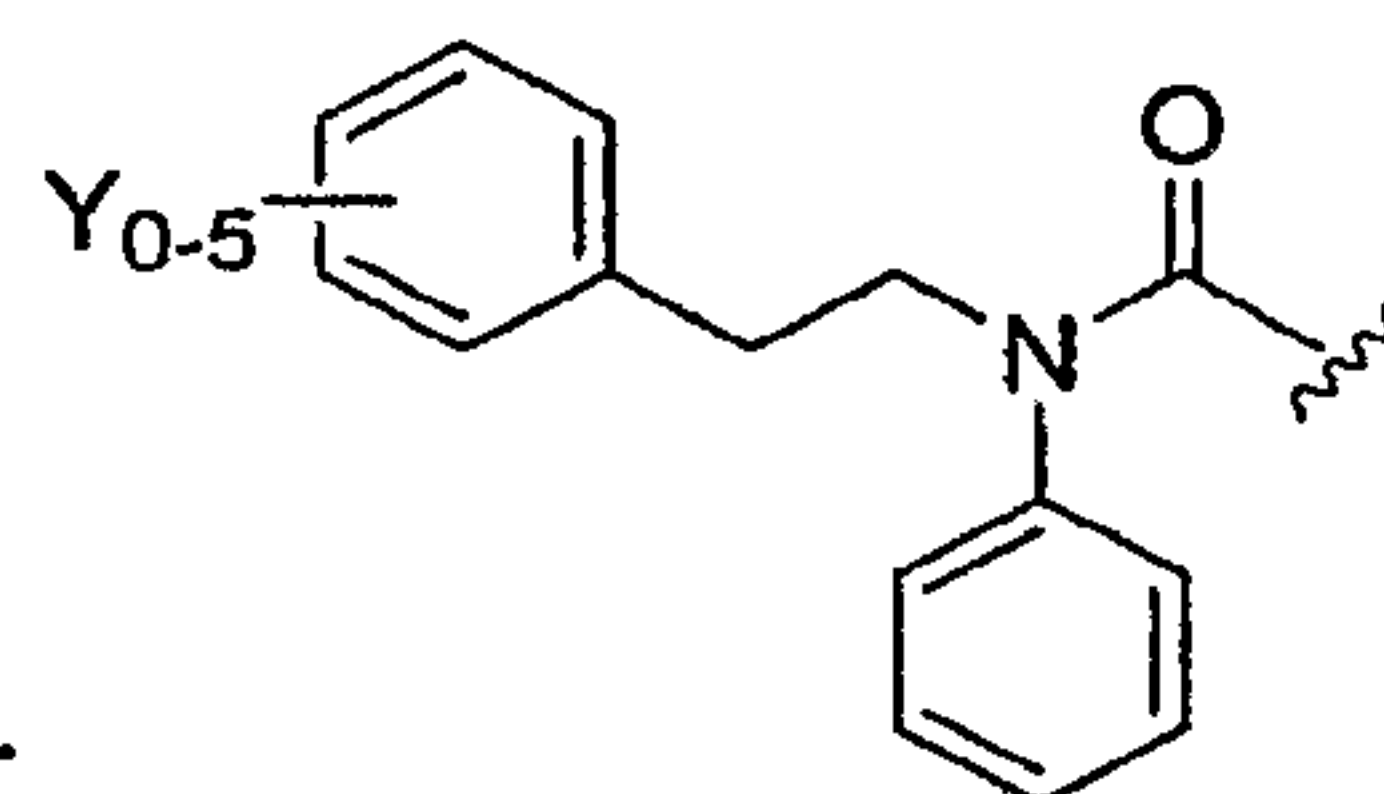
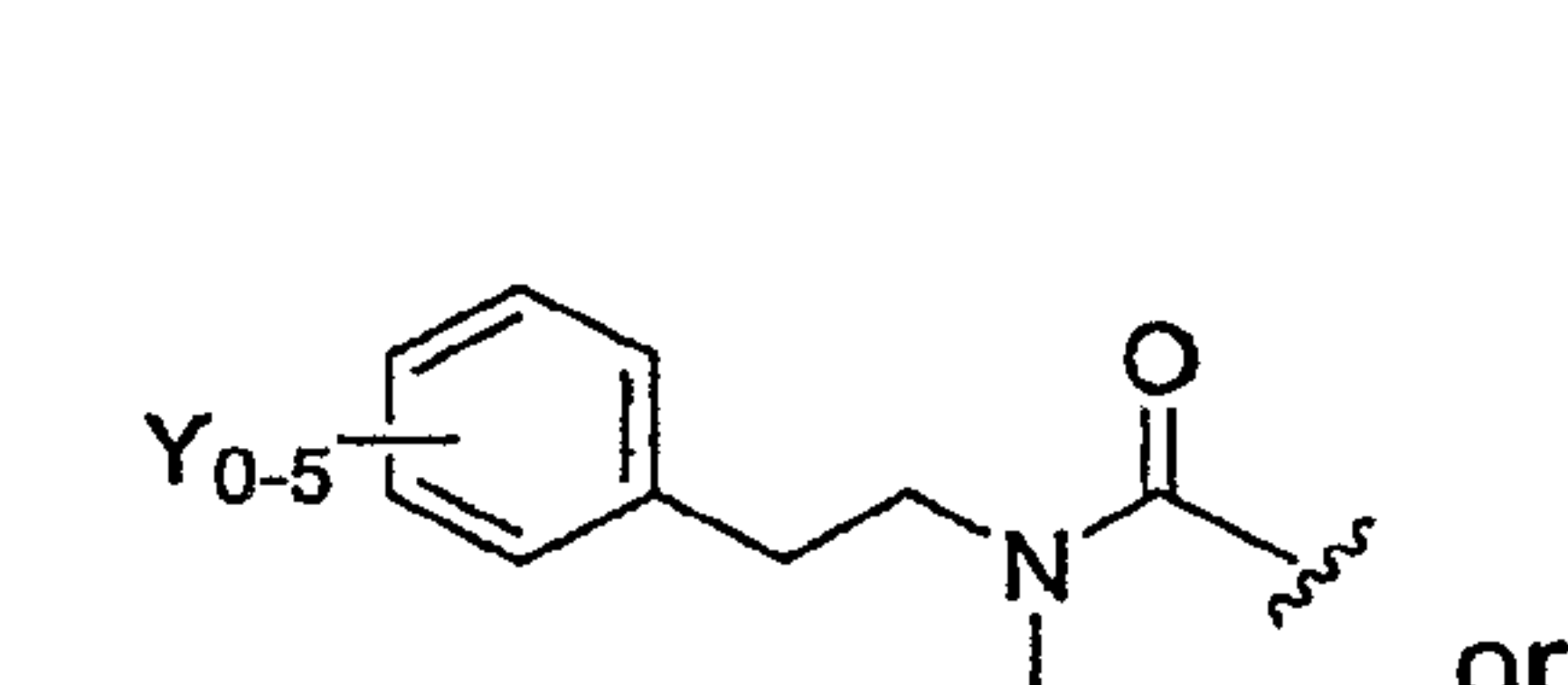
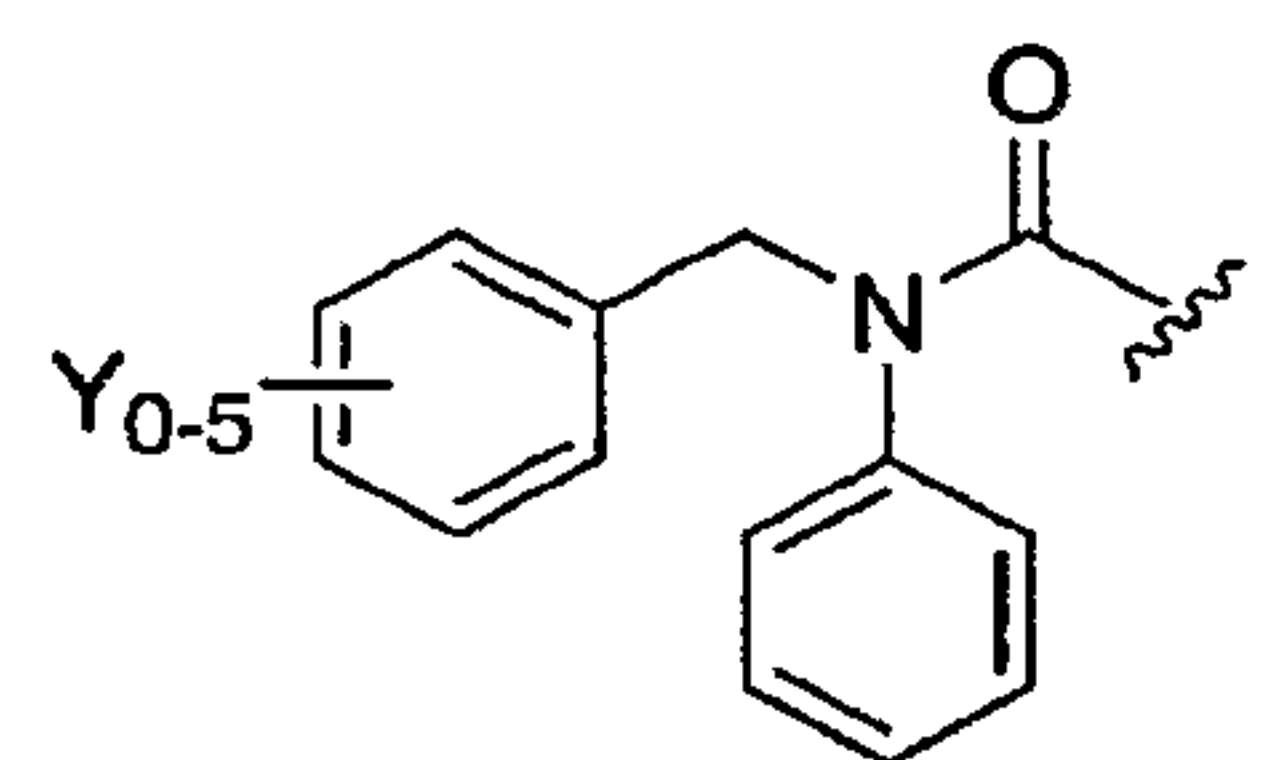
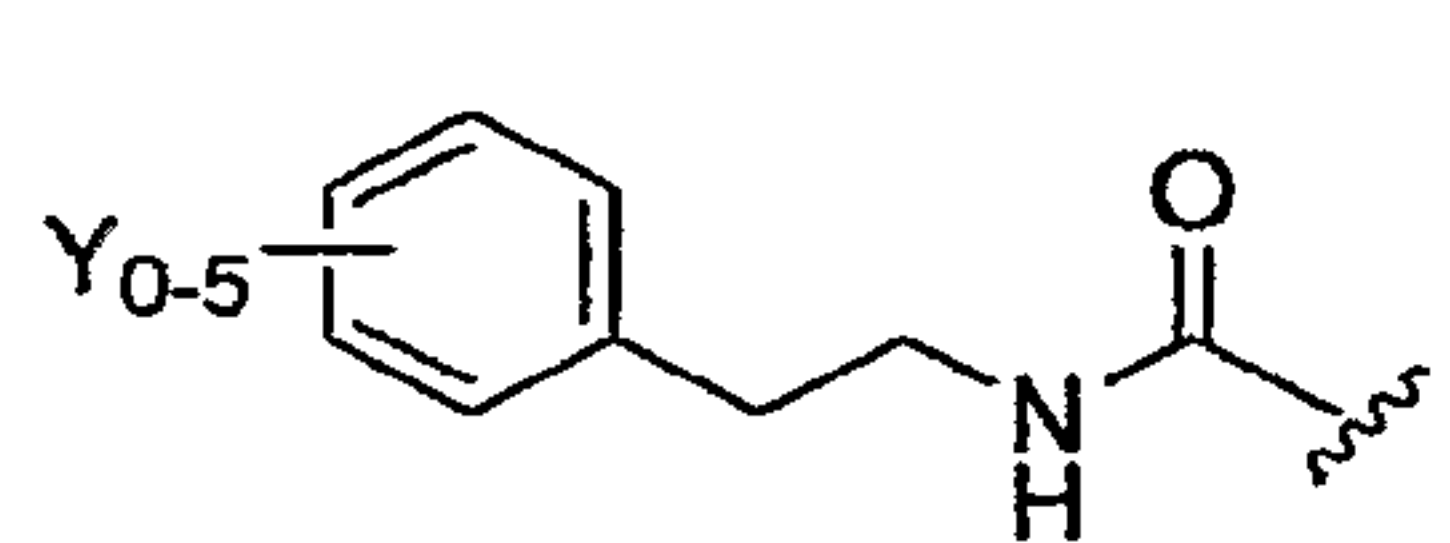
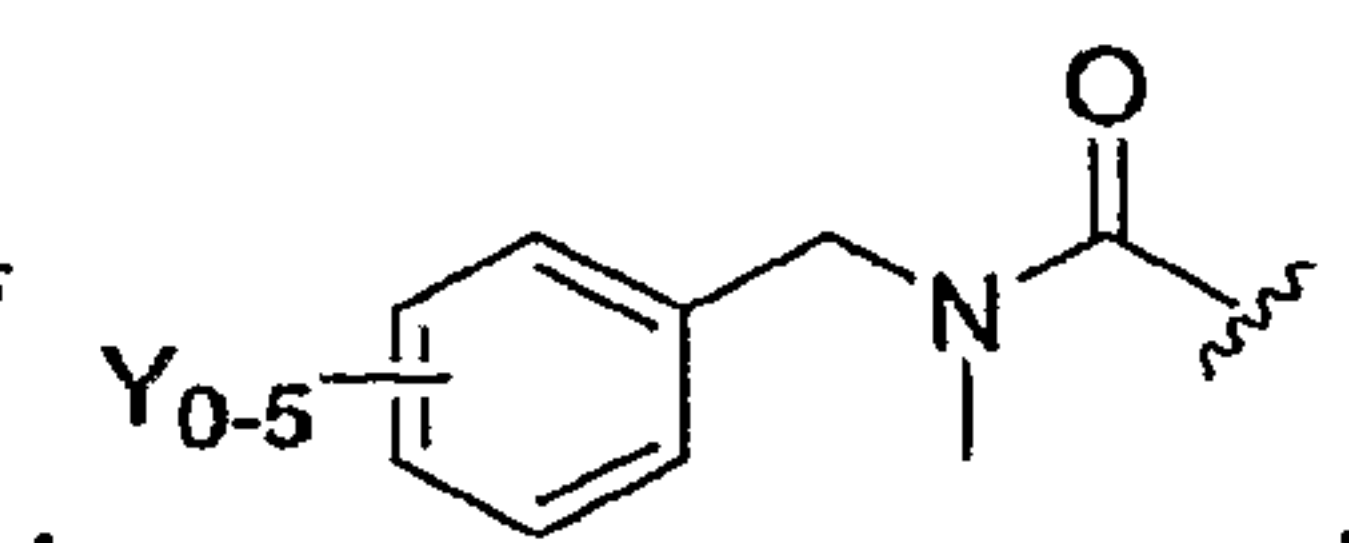
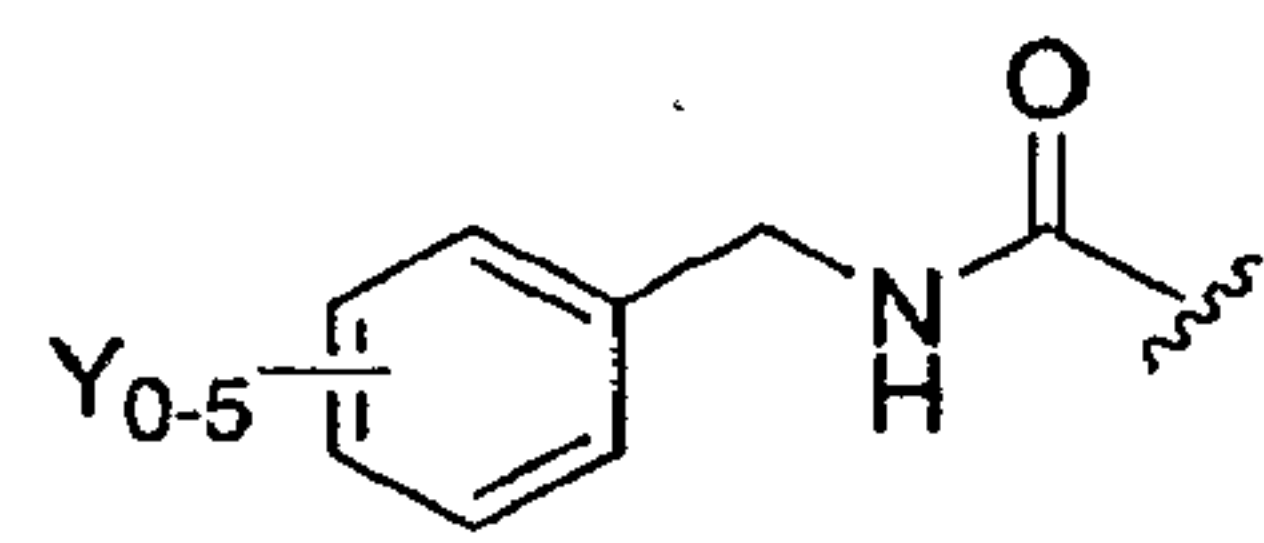
$-\text{C}(\text{O})$ -(benzo-fused cycloalkyl) of R^5 includes



or



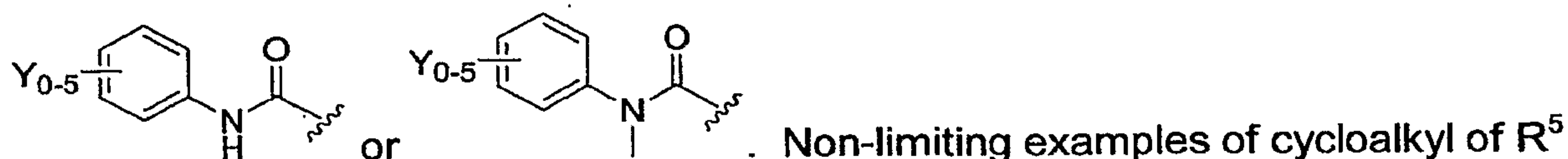
10 . Non-limiting examples of $-\text{C}(\text{O})-\text{N}(\text{R}^9)-(\text{C}(\text{R}^6)_2)_m$ -aryl of R^5 include:



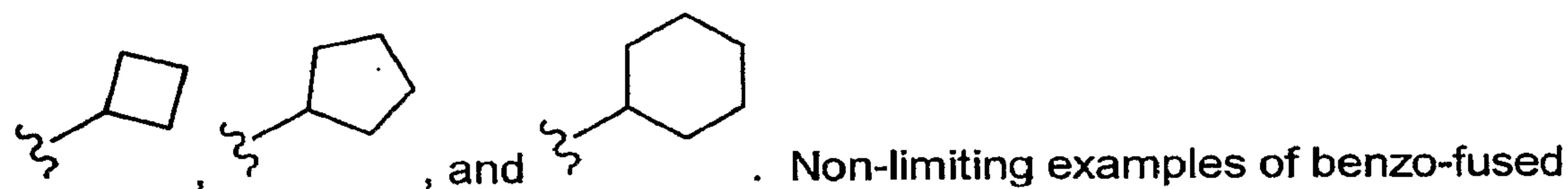
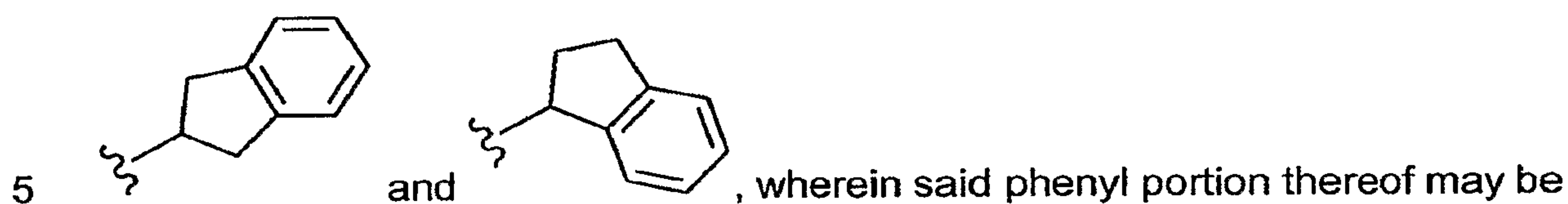
. Non-

limiting examples of $-\text{C}(\text{O})-\text{N}(\text{R}^9)$ -aryl or R^5 include:

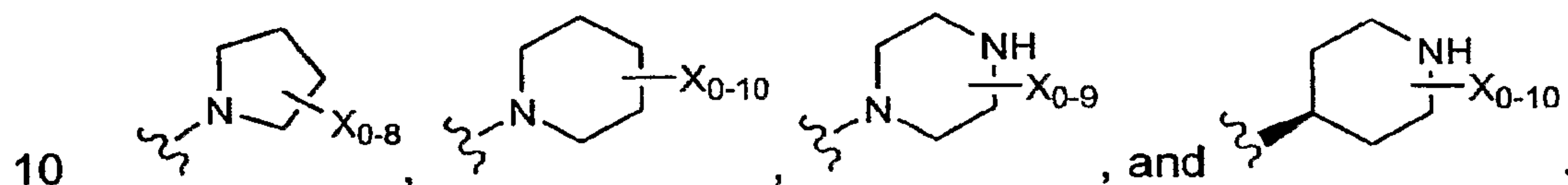
53



include:

cycloalkyl of R⁵ include:

unsubstituted or substituted with one or more Y groups as defined herein. A non-limiting example of an aryl of R⁵ includes unsubstituted phenyl or phenyl substituted with one or more Y groups as defined herein. Non-limiting examples of heterocyclyl of R⁵ include:



Each R⁶ is independently selected from the group consisting of H and alkyl. Non-limiting examples of R⁶ include H, -CH₃, -CH₂CH₃, -CH₂(CH₃)₂, -C(CH₃)₃, and -CH₂C(CH₃)₃.

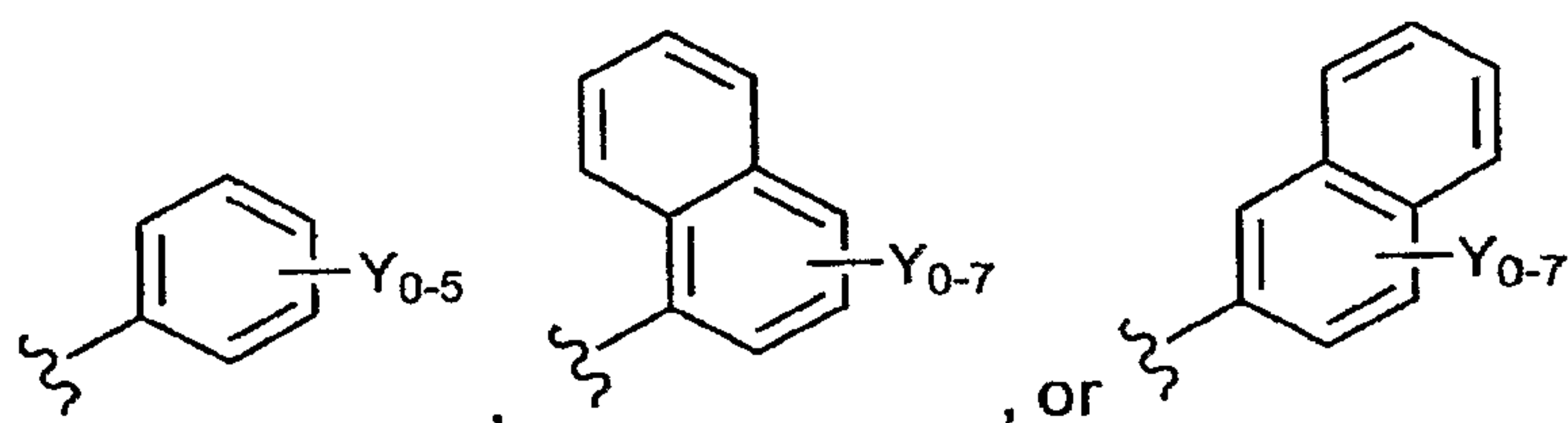
R⁷ is selected from the group consisting of H, alkyl, unsubstituted aryl, and aryl substituted with one or more Y groups. Non-limiting examples of R⁷ include H, -CH₃, -CH₂CH₃, -CH₂(CH₃)₂, -C(CH₃)₃, -CH₂CH₂CH₃, -CH₂CH₂CH₂CH₃, unsubstituted phenyl, and phenyl substituted with one or more Y groups.

Each R⁸ is independently selected from the group consisting of H, alkyl, -C(O)-aryl, -S(O)₂-aryl, and -S(O)₂-heteroaryl, -S(O)₂-alkyl. Non-limiting examples of R⁸ include H, -CH₃, -CH₂CH₃, -CH₂(CH₃)₂, -C(CH₃)₃, -CH₂CH₂CH₃, -CH₂CH₂CH₂CH₃, -C(O)-phenyl, -S(O)₂-phenyl (wherein said phenyl portion may be unsubstituted or substituted with one or more Y groups as defined herein), -S(O)₂-thiophenyl (wherein said thiophenyl portion may be unsubstituted or substituted with one or more Y groups as defined herein), -S(O)₂-imidazolyl (wherein said imidazolyl portion may be unsubstituted or substituted with one or more Y groups as defined herein),

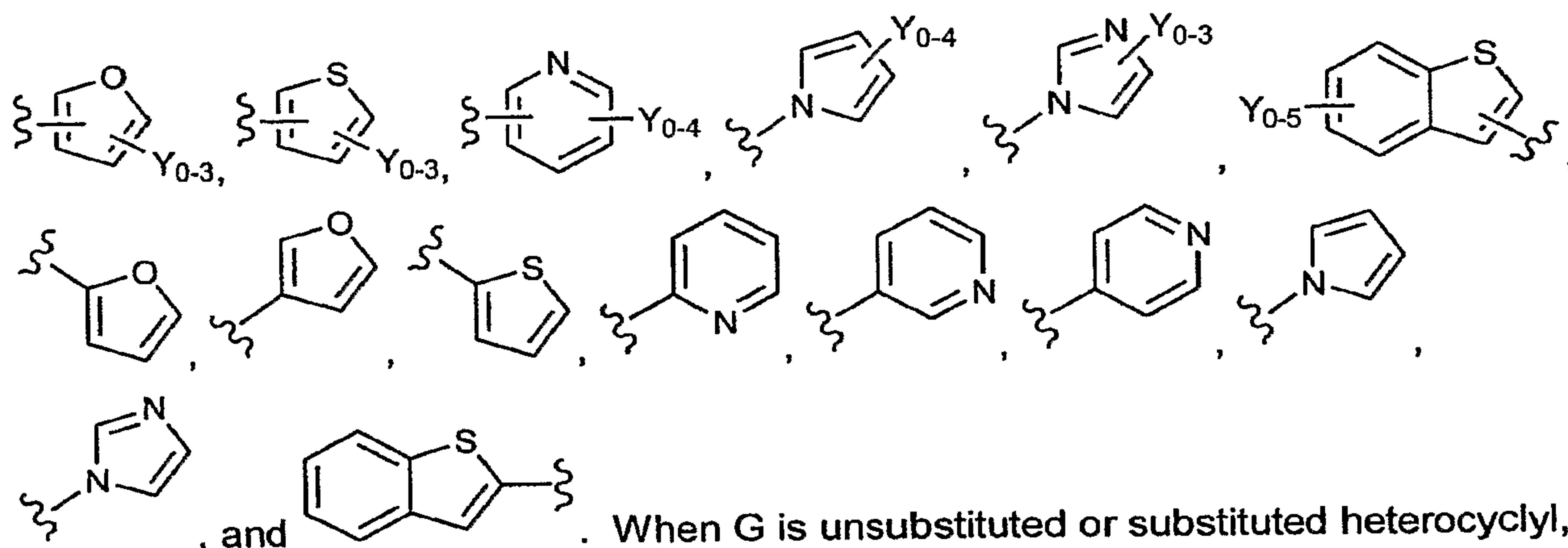
-S(O)₂-diazolyl (wherein said diazolyl portion may be unsubstituted or substituted with one or more Y groups as defined herein), -S(O)₂-triazolyl (wherein said triazolyl portion may be unsubstituted or substituted with one or more Y groups as defined herein), -S(O)₂-pyridyl (wherein said pyridyl portion may be unsubstituted or substituted with one or more Y groups as defined herein), -S(O)₂-CH₃,
 5 -S(O)₂-CH₂CH₃, and -S(O)₂-CH₂CH₂CH₃.

Each R⁹ is independently selected from the group consisting of H, alkyl, cycloalkyl, and substituted or unsubstituted aryl. Non-limiting examples of R⁹ include H, -CH₃, -CH₂CH₃, -CH₂(CH₃)₂, -C(CH₃)₃, -CH₂C(CH₃)₃, cyclopropyl, cyclobutyl,
 10 cyclopentyl, cyclohexyl, phenyl, and naphthyl.

G is selected from the group consisting of H, alkyl, unsubstituted aryl, aryl substituted with one or more Y groups, -CN, cycloalkyl, -O-R⁷, -S-R⁷, unsubstituted heteroaryl, heteroaryl substituted with one or more Y groups, -N(R⁸)₂, unsubstituted heterocyclyl, and heterocyclyl substituted with one or more X groups. When G is
 15 alkyl, non-limiting examples of G include -CH₃, -CH₂CH₃, -CH₂(CH₃)₂, -C(CH₃)₃, -CH₂CH₂CH₃, -CH₂CH₂CH₂CH₃. When G is unsubstituted aryl, non-limiting examples include phenyl and naphthyl. When G is substituted aryl, non-limiting examples include:

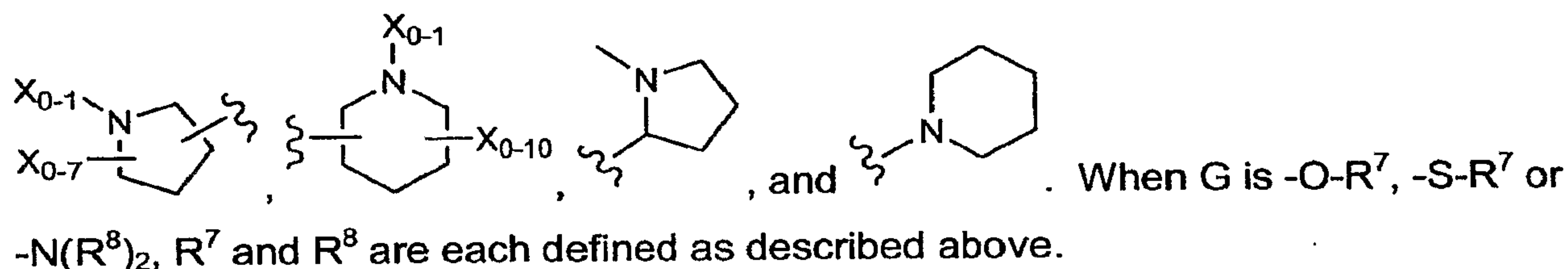


When G is cycloalkyl, non-limiting examples of G include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. When G is unsubstituted or substituted heteroaryl, non-limiting examples include:

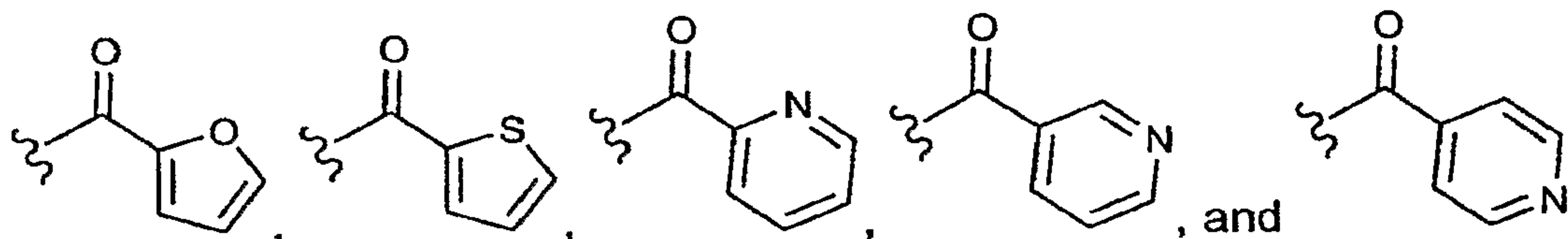


When G is unsubstituted or substituted heterocyclyl,

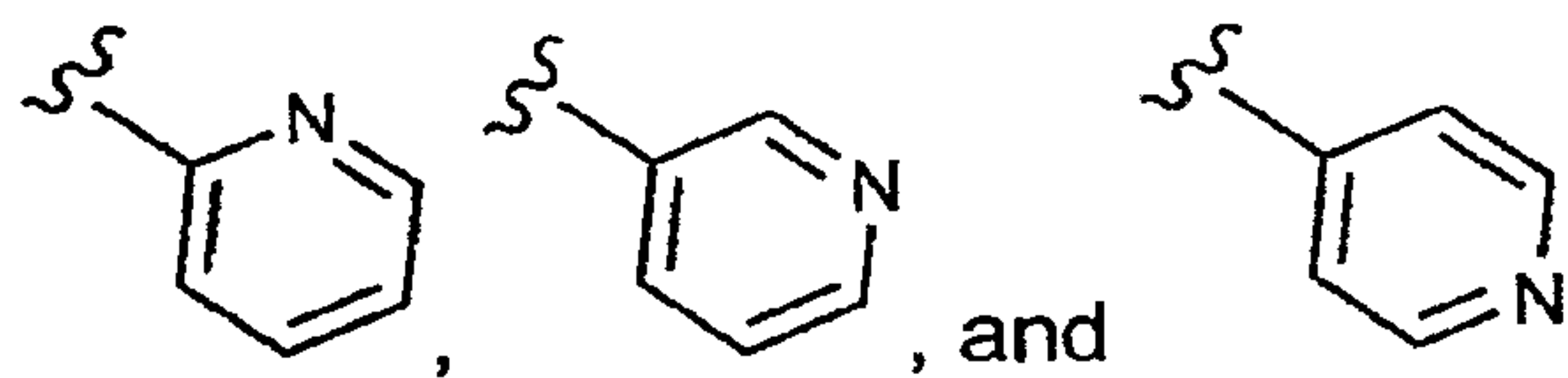
non-limiting examples include any of the unsubstituted or substituted heteroaryls described above, as well as:



- 5 Each X is independently selected from the group consisting of alkyl, $-C(O)-N(R^9)_2$, $-C(O)$ -heteroaryl (wherein said heteroaryl portion is optionally substituted with one or more halogen), heteroaryl (wherein said heteroaryl is optionally substituted with one or more halogen), $-(C(R^6)_2)_m$ -aryl (wherein said aryl portion is optionally substituted with one or more substituents selected from the
- 10 group consisting of halogen, $-OH$, $-O$ -alkyl, haloalkyl, and $-CN$), and aryl (wherein said aryl portion is optionally substituted with one or more substituents selected from the group consisting of halogen, $-OH$, $-O$ -alkyl, haloalkyl, and $-CN$). When X is alkyl, non-limiting examples of X include $-CH_3$ and $-CH_2CH_3$. When X is $-C(O)-N(R^9)_2$, each R^9 is independently defined as described above. When X is $-C(O)$ -heteroaryl,
- 15 non-limiting examples of X include:



When X is heteroaryl, non-limiting examples of X include:



- When X is $-(C(R^6)_2)_m$ -aryl, R^6 is defined as described above, non-limiting examples of said aryl portion of $-(C(R^6)_2)_m$ -aryl include phenyl, chlorophenyl, dichlorophenyl, and naphthyl; e.g., non-limiting
- 20 examples of X include benzyl, chlorobenzyl, and dichlorobenzyl. When X is aryl, non-limiting examples of X include phenyl, chlorophenyl, dichlorophenyl, and naphthyl.

- Each Y is independently selected from the group consisting of halogen, alkyl,
- 25 aryl, $-C(O)$ -alkyl, $-O-R^9$, haloalkyl, $-O$ -haloalkyl, $-CN$, and $-C(O)$ - O -alkyl, $-N(R^6)_2$, $-C(R^6)_2-N(R^6)_2$, and $-C(R^6)_2-N(R^6)-S(O)_2-R^6$; or two Y groups form a $-O-CH_2-O-$

group. When Y is halogen, non-limiting examples of Y include F, Cl, and Br. When Y is alkyl, non-limiting examples include methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, i-butyl, t-butyl, etc. When Y is aryl, non-limiting examples include phenyl or naphthyl. When Y is -C(O)-alkyl, non-limiting examples include -C(O)-CH₃,

5 -C(O)-CH₂CH₃, -C(O)-CH₂CH₂CH₃, -C(O)-CH(CH₃)₂, -C(O)-CH₂CH₂CH₂CH₃, -C(O)-CH(CH₃)CH₂CH₃, -C(O)-CH₂CH(CH₃)₂, -C(O)-C(CH₃)₃, etc. When Y is -O-R⁹, R⁹ is defined as described above. When Y is haloalkyl, non-limiting examples of Y include -CF₃, -CHF₂, -CH₂F, -CH₂CF₃, and -CF₂CF₃. When Y is -O-haloalkyl, non-limiting examples include -O-CF₃, -O-CHF₂, -O-CH₂F, -O-CH₂CF₃, and -O-CF₂CF₃.

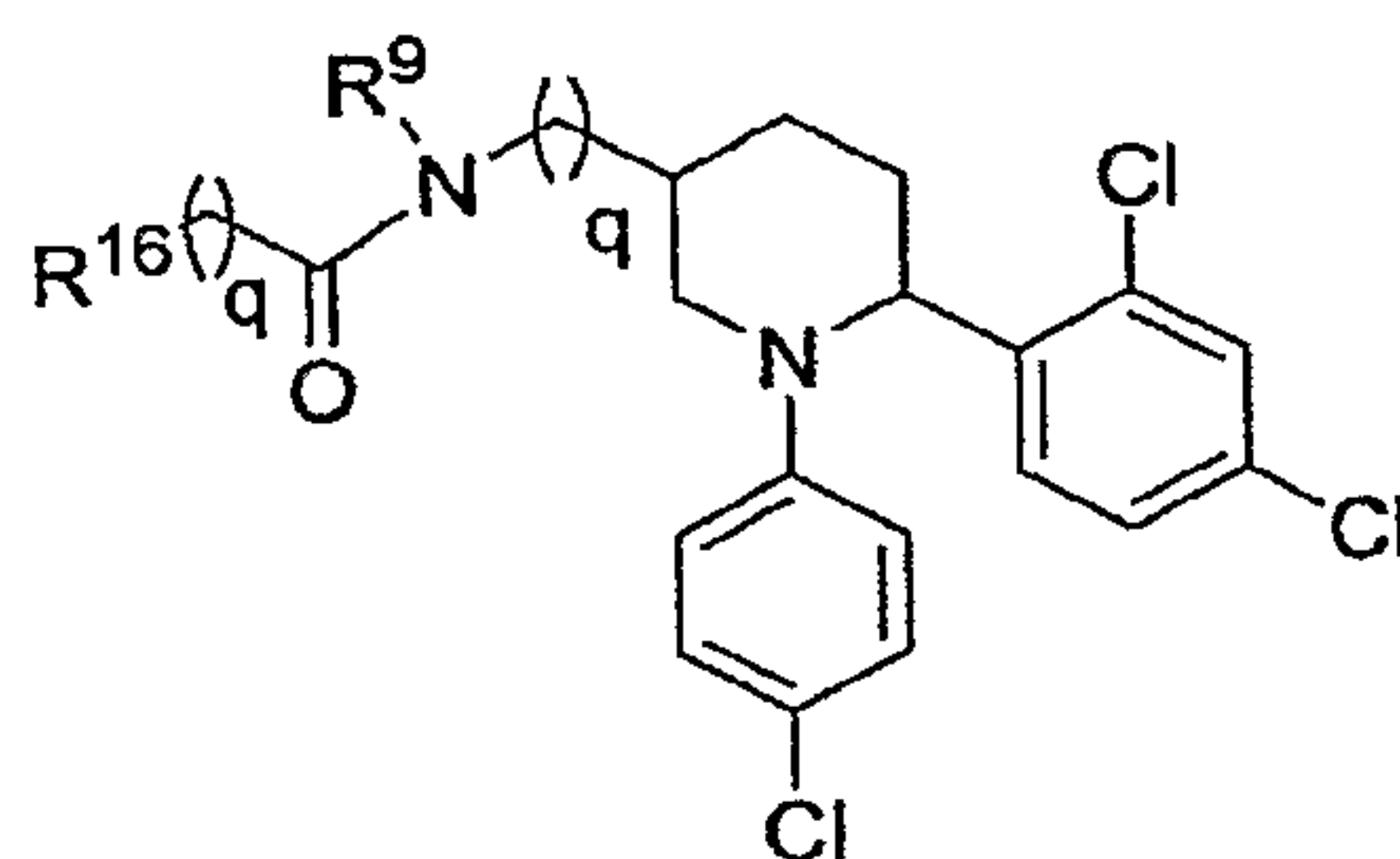
10 When Y is -C(O)-O-alkyl non-limiting examples include -C(O)-O-CH₃, -C(O)-O-CH₂CH₃, -C(O)-O-CH₂CH₂CH₃, -C(O)-O-CH(CH₃)₂, -C(O)-O-CH₂CH₂CH₂CH₃, -C(O)-O-CH(CH₃)CH₂CH₃, -C(O)-O-CH₂CH(CH₃)₂, -C(O)-O-C(CH₃)₃, etc. When Y is -N(R⁶)₂ or -C(R⁶)₂-N(R⁶)₂, each R⁶ is defined independently as described above. For example, -C(R⁶)₂-N(R⁶)₂ includes -CH₂NH₂ and -CH₂-N(H)CH₃, and -N(R⁶)₂ includes -NH₂ and -N(CH₃)₂. When Y is

15 -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶, -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶ includes -CH₂-NH-SO₂-CH₃, -CH₂-N(CH₃)-SO₂-CH₃, -CH₂-NH-SO₂-CH₂CH₃, -CH₂-N(CH₃)-SO₂-CH₂CH₃, etc.

The variable "n" can be 0, 1, 2, 3, 4, or 5, and variable "m" can be 1, 2, 3, 4, or

5.

20 In another embodiment, the compound of Formula (I) is a compound having the following structural Formula:



wherein:

25 each R⁶ is independently selected from the group consisting of H and (C₁-C₆)alkyl;
 each R⁹ is independently selected from the group consisting of H, (C₁-C₆)alkyl,
 halo(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, unsubstituted (C₆-
 C₁₀)aryl and unsubstituted (C₂-C₁₀)heteroaryl;

each R^{12} is independently selected from the group consisting of H, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, (C_1-C_6) alkyl, $-(C(R^6)_2)_q-C(O)R^{13}$, benzo (C_2-C_{10}) heterocyclyl, benzocyclo (C_1-C_6) alkyl, $-(C(R^6)_2)_q-N(R^9)-C(O)R^{13}$, $-(C(R^6)_2)_q-N(R^{14})_2$, (C_6-C_{10}) aryl (C_1-C_6) alkyl, (C_2-C_{10}) heteroaryl (C_1-C_6) alkyl, HO- (C_1-C_6) alkyl-, (C_1-C_6) alkyl-O-, (C_6-C_{10}) aryl-O-, Y- (C_1-C_6) alkylenyl-O-, W-O- (C_1-C_6) alkylenyl, (C_2-C_{10}) heterocyclyl (C_1-C_6) alkyl, unsubstituted (C_3-C_6) cycloalkyl, (C_3-C_6) cycloalkyl substituted with one or more X groups, unsubstituted (C_2-C_{10}) heterocyclyl, (C_2-C_{10}) heterocyclyl substituted with one or more X groups, unsubstituted (C_2-C_{10}) heteroaryl, (C_2-C_{10}) heteroaryl substituted with one or more Y groups, unsubstituted (C_6-C_{10}) aryl and (C_6-C_{10}) aryl substituted with one or more Y groups, and

wherein the (C_6-C_{10}) aryl and (C_2-C_{10}) heteroaryl portion of said (C_6-C_{10}) aryl (C_1-C_6) alkyl and (C_2-C_{10}) heteroaryl (C_1-C_6) alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C_1-C_6) alkyl portion of said (C_3-C_6) cycloalkyl (C_1-C_6) alkyl, (C_6-C_{10}) aryl (C_1-C_6) alkyl and (C_2-C_{10}) heteroaryl (C_1-C_6) alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C_1-C_6) alkyl portion is NOT Cbz or Boc,

wherein the (C_3-C_6) cycloalkyl of said (C_3-C_6) cycloalkyl (C_1-C_6) alkyl is unsubstituted or substituted with one or more X groups,

wherein the benzo portion of said benzo (C_2-C_{10}) heterocyclyl can be optionally substituted with one or more Y groups and the (C_2-C_{10}) heterocyclyl portion of benzo (C_2-C_{10}) heterocyclyl can be optionally substituted with one or more X groups,

wherein the benzo portion of said benzocyclo (C_1-C_6) alkyl can be optionally substituted with one or more Y groups and the (C_3-C_6) cycloalkyl portion of benzocyclo (C_1-C_6) alkyl can be optionally substituted with one or more X groups;

with the following provisos that

for $-N(R^{14})_2$ of R^{12} , the two R^{14} groups, with the ring nitrogen atom to which they are shown attached, form an unsubstituted (C_2-C_{10}) heterocyclyl ring or a (C_2-C_{10}) heterocyclyl ring substituted with one or more X groups;

each R^{13} is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-

C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups;

each R^{14} is independently selected from the group consisting of H, Boc,

unsubstituted (C₁-C₆)alkyl, (C₁-C₆)alkyl substituted with one or more X groups,

unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl substituted with one or more Y groups, (C₂-C₁₀)heterocyclyl, unsubstituted (C₂-C₁₀)heteroaryl and (C₂-C₁₀)heteroaryl substituted with one or more Y groups;

each R^{16} is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-

C₆)cycloalkyl(C₁-C₆)alkyl, $-(C(R^6)_2)_p-C(O)R^{13}$,

$-(C(R^6)_2)_p-N(R^9)-C(O)R^{13}$, $-(C(R^6)_2)_p-N(R^{14})_2$, (C₆-C₁₀)aryl(C₁-C₆)alkyl,

(C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups, and

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups,

for -N(R¹⁴)₂, the two R¹⁴ groups, with the ring nitrogen atom to which they are shown attached, form an unsubstituted (C₂-C₁₀)heterocyclyl ring or a (C₂-C₁₀)heterocyclyl ring substituted with one or more X groups;

each W is independently selected from the group consisting of hydrogen,

(C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl,

-C(R⁶)₂-N(R⁶)₂, and -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶;

each X is independently selected from the group consisting of hydrogen, -OH,

(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, Cbz, Boc,

(C₁-C₆)alkylsulfonyl, acetyl, -C(O)-R¹², -C(O)-N(R⁹)₂,

-C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl, -S(O)₂-(C₃-C₆)cycloalkyl,

-C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -(C(R⁶)₂)_m-(C₆-C₁₀)aryl and

(C₆-C₁₀)aryl

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or

substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and

(C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said

-C(O)-(C₂-C₁₀)heteroaryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH,

-O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN, and

wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said

-(C(R⁶)₂)_m-(C₆-C₁₀)aryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN

5 wherein in a single X moiety, =O, can replace two available hydrogens on the same carbon on a ring system;

each Y is independently selected from the group consisting of hydrogen, halogen,

(C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -O-(C₁-C₆)alkyl,

-O-(C₂-C₁₀)heteroaryl, -O-(C₆-C₁₀)aryl, -O-R⁹, halo(C₁-C₆)alkyl,

10 -O-halo(C₁-C₆)alkyl, -CN, -C(O)-O-(C₁-C₆)alkyl, -N(R⁶)₂, -C(R⁶)₂-N(R⁶)₂,

-S(O)₂-(C₂-C₁₀)heterocyclyl, -S(O)₂-(C₂-C₁₀)heteroaryl and

-C(R⁶)₂-N(R⁶)-S(O)₂-R⁶; or

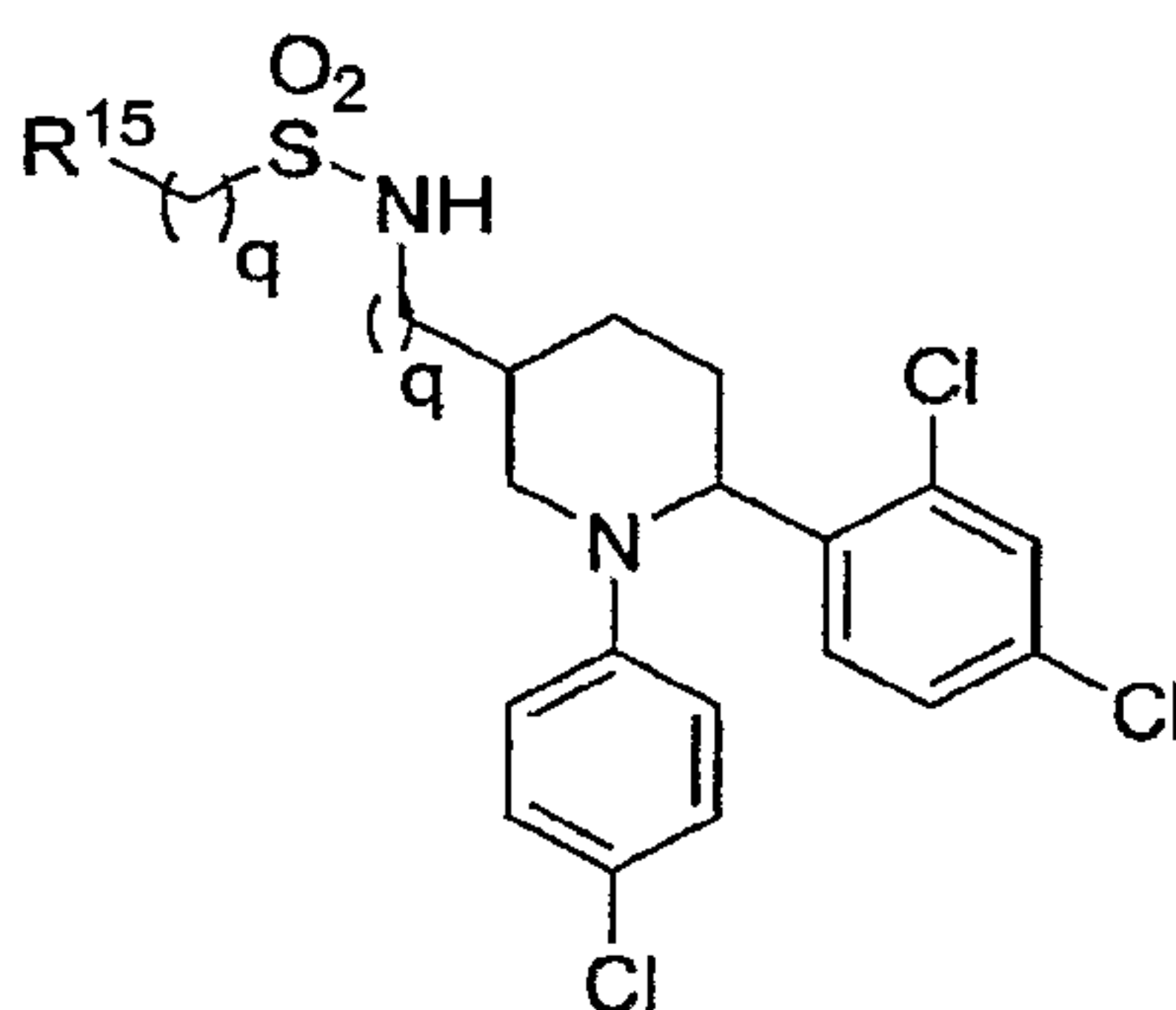
two of said Y groups attached to adjacent carbon atoms form a -O-CH₂-O- or

-O-CH₂CH₂-O- group;

15 each n, p and q is independently an integer from 0-5; and

m is an integer from 1-5.

In another embodiment, the compound of Formula (I) is a compound having the following structural Formula:



20 wherein:

R⁴ is selected from the group consisting of H, -C(O)-(C₁-C₆)alkyl, and (C₁-C₆)alkyl;

R⁵ is selected from the group consisting of -(C(R⁶)₂)_m-G, -S(O)₂-(C₁-C₆)alkyl,

-S(O)₂-(C₃-C₆)cycloalkyl, (C₁-C₆)alkyl, -S(O)-(C₃-C₆)cycloalkyl, -C(O)-(C₃-

C₆)cycloalkyl, -S(O)₂-(C₆-C₁₀)aryl, -S(O)₂-(C(R⁶)₂)_m-(C₆-C₁₀)aryl,

25 -S(O)₂-(C₂-C₁₀)heteroaryl, -C(O)-(C₁-C₆)alkyl, -C(O)-(C₆-C₁₀)aryl,

-C(O)-O-(C₁-C₆)alkyl, -C(O)-O-(C₆-C₁₀)aryl, -C(O)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl,

-C(O)-(C₃-C₆)cycloalkylene-(C₆-C₁₀)aryl, -C(O)-(C₂-C₁₀)heteroaryl,

-C(O)-(C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, -C(O)-(C(R⁶)₂)_m-O-(C₆-C₁₀)aryl, -C(O)-(benzo-fused (C₃-C₆)cycloalkyl), -S(O)₂-(benzo-fused (C₂-C₁₀)heterocyclyl), -C(O)-N(R⁹)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -C(O)-N(R⁹)-(C₆-C₁₀)aryl, (C₃-C₆)cycloalkyl, benzo-fused (C₃-C₆)cycloalkyl, unsubstituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl substituted with one or more Y groups, unsubstituted (C₂-C₁₀)heterocyclyl, and (C₂-C₁₀)heterocyclyl substituted with one or more X groups,

wherein the (C₆-C₁₀)aryl or (C₂-C₁₀)heteroaryl portion of said -S(O)₂-(C₆-C₁₀)aryl, -S(O)₂-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -S(O)₂-(C₂-C₁₀)heteroaryl, -C(O)-(C₆-C₁₀)aryl,

-C(O)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -C(O)-(C₃-C₆)cycloalkylene-(C₆-C₁₀)aryl, -C(O)-(C₂-C₁₀)heteroaryl, -C(O)-(C(R⁶)₂)_m-O-(C₆-C₁₀)aryl, -C(O)-N(R⁹)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, or -C(O)-N(R⁹)-(C₆-C₁₀)aryl of R⁵ is unsubstituted or substituted with one or more Y groups;

wherein the heterocyclyl portion of -S(O)₂-(benzo-fused (C₂-C₁₀)heterocyclyl) aryl of R⁵ is unsubstituted or substituted with one or more X groups;

each R⁶ is independently selected from the group consisting of H and (C₁-C₆)alkyl; R⁷ is selected from the group consisting of H, (C₁-C₆)alkyl, unsubstituted (C₂-C₁₀)heteroaryl and (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl, and (C₆-C₁₀)aryl substituted with one or more Y groups;

each R⁸ is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, unsubstituted (C₆-C₁₀)aryl, unsubstituted (C₂-C₁₀)heteroaryl,

-C(O)-(C₁-C₆)alkyl, -C(O)-(C₆-C₁₀)aryl, -C(O)-(C₃-C₆)cycloalkyl, -C(O)N(R⁹)₂, -S(O)₂-(C₆-C₁₀)aryl, -S(O)₂-(C₂-C₁₀)heteroaryl, -SO₂N(R⁹)₂, -S(O)₂-(C₃-C₆)cycloalkyl, (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl substituted with one or more Y groups, and -S(O)₂-(C₁-C₆)alkyl,

wherein the (C₆-C₁₀)aryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl, -C(O)-(C₆-C₁₀)aryl or -S(O)₂-(C₆-C₁₀)aryl and the (C₂-C₁₀)heteroaryl portion of said (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, -S(O)₂-(C₂-C₁₀)heteroaryl of R⁸ is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc;

5 each R⁹ is independently selected from the group consisting of H, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, unsubstituted (C₆-C₁₀)aryl and unsubstituted (C₂-C₁₀)heteroaryl;

each R¹² is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, -(C(R⁶)₂)_q-C(O)R¹³, benzo(C₂-C₁₀)heterocyclyl, benzocyclo(C₁-C₆)alkyl, -(C(R⁶)₂)_q-N(R⁹)-C(O)R¹³, -(C(R⁶)₂)_q-N(R¹⁴)₂, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, Y-(C₁-C₆)alkylenyl-O-, W-O-(C₁-C₆)alkylenyl, (C₂-C₁₀)heterocyclyl(C₁-C₆)alkyl, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups, and

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups,

wherein the benzo portion of said benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more Y groups and the (C₂-C₁₀)heterocyclyl portion of benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more X groups,

wherein the benzo portion of said benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more Y groups and the (C₃-C₆)cycloalkyl portion of benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more X groups;

5 with the following provisos that

for -N(R¹⁴)₂ of R¹², the two R¹⁴ groups, with the ring nitrogen atom to which they are shown attached, form an unsubstituted (C₂-C₁₀)heterocyclyl ring or a (C₂-C₁₀)heterocyclyl ring substituted with one or more X groups;

each R¹³ is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

20 wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups;

each R¹⁴ is independently selected from the group consisting of H, Boc, unsubstituted (C₁-C₆)alkyl, (C₁-C₆)alkyl substituted with one or more X groups, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl substituted with one or more Y groups, (C₂-C₁₀)heterocyclyl, unsubstituted (C₂-C₁₀)heteroaryl and (C₂-C₁₀)heteroaryl substituted with one or more Y groups;

each R^{15} is independently selected from the group consisting of H, (C_1-C_6) alkyl, $-N(R^4)(R^5)$, $(C(R^6)_2)_q-N(R^{14})_2$, (C_1-C_6) alkylenyl- CF_3 , $-CF_3$, (C_3-C_6) cycloalkyl (C_1-C_6) alkyl, unsubstituted (C_3-C_6) cycloalkyl, (C_3-C_6) cycloalkyl substituted with one or more X groups, unsubstituted (C_2-C_{10}) heterocyclyl, (C_2-C_{10}) heterocyclyl substituted with one or more X groups, benzo (C_2-C_{10}) heterocyclyl, benzocyclo (C_1-C_6) alkyl, unsubstituted (C_2-C_{10}) heteroaryl, (C_2-C_{10}) heteroaryl substituted with one or more Y groups, unsubstituted (C_6-C_{10}) aryl and (C_6-C_{10}) aryl substituted with one or more Y groups,

wherein the (C_1-C_6) alkyl portion of said (C_3-C_6) cycloalkyl (C_1-C_6) alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C_1-C_6) alkyl portion is NOT Cbz or Boc, wherein the (C_3-C_6) cycloalkyl of said (C_3-C_6) cycloalkyl (C_1-C_6) alkyl is unsubstituted or substituted with one or more X groups,

wherein the benzo portion of said benzo (C_2-C_{10}) heterocyclyl can be optionally substituted with one or more Y groups and the (C_2-C_{10}) heterocyclyl portion of benzo (C_2-C_{10}) heterocyclyl can be optionally substituted with one or more X groups,

wherein the benzo portion of said benzocyclo (C_1-C_6) alkyl can be optionally

substituted with one or more Y groups and the (C_3-C_6) cycloalkyl portion of benzocyclo (C_1-C_6) alkyl can be optionally substituted with one or more X groups;

G is selected from the group consisting of H, (C_1-C_6) alkyl, unsubstituted (C_6-C_{10}) aryl, (C_6-C_{10}) aryl substituted with one or more Y groups, $-CN$, (C_3-C_6) cycloalkyl, $-O-R^7$, $-S-R^7$, unsubstituted (C_2-C_{10}) heteroaryl, (C_2-C_{10}) heteroaryl substituted with one or more Y groups, $-N(R^8)_2$, unsubstituted (C_2-C_{10}) heterocyclyl, and (C_2-C_{10}) heterocyclyl substituted with one or more X groups;

each W is independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl, (C_6-C_{10}) aryl, $-C(O)-(C_1-C_6)$ alkyl, $-C(O)-O-(C_1-C_6)$ alkyl, $-C(R^6)_2-N(R^6)_2$, and $-C(R^6)_2-N(R^6)-S(O)_2-R^6$;

each X is independently selected from the group consisting of hydrogen, $-OH$, (C_1-C_6) alkyl, (C_6-C_{10}) aryl (C_1-C_6) alkyl, (C_2-C_{10}) heteroaryl (C_1-C_6) alkyl, Cbz, Boc, (C_1-C_6) alkylsulfonyl, acetyl, $-C(O)-R^{12}$, $-C(O)-N(R^9)_2$,

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-C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl, -S(O)₂-(C₃-C₆)cycloalkyl, -C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -(C(R⁶)₂)_m-(C₆-C₁₀)aryl and (C₆-C₁₀)aryl

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said -C(O)-(C₂-C₁₀)heteroaryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN, and

wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said -(C(R⁶)₂)_m-(C₆-C₁₀)aryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN

wherein in a single X moiety, =O, can replace two available hydrogens on the same carbon on a ring system;

each Y is independently selected from the group consisting of hydrogen, halogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -O-(C₁-C₆)alkyl, -O-(C₂-C₁₀)heteroaryl, -O-(C₆-C₁₀)aryl, -O-R⁹, halo(C₁-C₆)alkyl, -O-halo(C₁-C₆)alkyl, -CN, -C(O)-O-(C₁-C₆)alkyl, -N(R⁶)₂, -C(R⁶)₂-N(R⁶)₂, -S(O)₂-(C₂-C₁₀)heterocyclyl, -S(O)₂-(C₂-C₁₀)heteroaryl and -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶; or

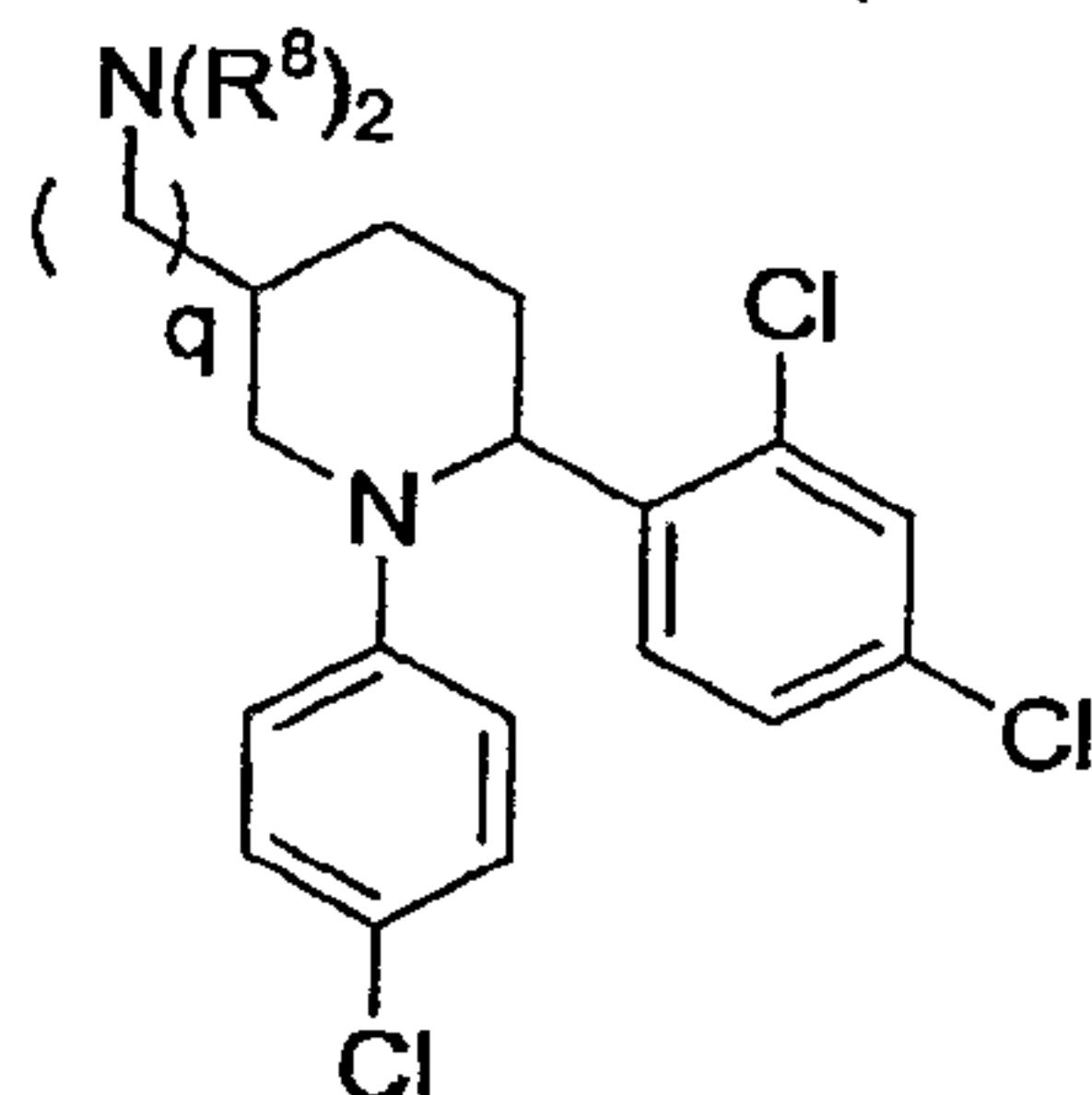
two of said Y groups attached to adjacent carbon atoms form a -O-CH₂-O- or -O-CH₂CH₂-O- group;

each n, p and q is independently an integer from 0-5; and

m is an integer from 1-5.

In another embodiment, the compound of Formula (I) is a compound having the following structural Formula:

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wherein:

each R^6 is independently selected from the group consisting of H and (C_1-C_6) alkyl;

5 each R^8 is independently selected from the group consisting of H, (C_1-C_6) alkyl, (C_6-C_{10}) aryl, (C_1-C_6) alkyl, (C_2-C_{10}) heteroaryl, unsubstituted (C_6-C_{10}) aryl, unsubstituted (C_2-C_{10}) heteroaryl,

$-C(O)-(C_1-C_6)$ alkyl, $-C(O)-(C_6-C_{10})$ aryl, $-C(O)-(C_3-C_6)$ cycloalkyl, $-C(O)N(R^9)_2$,

$-S(O)_2-(C_6-C_{10})$ aryl, $-S(O)_2-(C_2-C_{10})$ heteroaryl, $-SO_2N(R^9)_2$,

10 $-S(O)_2-(C_3-C_6)$ cycloalkyl, (C_6-C_{10}) aryl and (C_2-C_{10}) heteroaryl substituted with one or more Y groups, and $-S(O)_2-(C_1-C_6)$ alkyl,

wherein the (C_6-C_{10}) aryl portion of said (C_6-C_{10}) aryl, $-C(O)-(C_6-C_{10})$ aryl or $-S(O)_2-(C_6-C_{10})$ aryl and the (C_2-C_{10}) heteroaryl portion of said (C_2-C_{10}) heteroaryl, $-S(O)_2-(C_2-C_{10})$ heteroaryl of R^8 is

15 unsubstituted or substituted with one or more Y groups,

wherein the (C_1-C_6) alkyl portion of said (C_6-C_{10}) aryl, (C_1-C_6) alkyl and (C_2-C_{10}) heteroaryl, (C_1-C_6) alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C_1-C_6) alkyl portion is NOT Cbz or Boc;

20 each R^9 is independently selected from the group consisting of H, (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, hydroxy (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, unsubstituted (C_6-C_{10}) aryl and unsubstituted (C_2-C_{10}) heteroaryl;

each Y is independently selected from the group consisting of hydrogen, halogen,

(C_1-C_6) alkyl, (C_6-C_{10}) aryl, $-C(O)-(C_1-C_6)$ alkyl, $-O-(C_1-C_6)$ alkyl,

5 $-O-(C_2-C_{10})$ heteroaryl, $-O-(C_6-C_{10})$ aryl, $-O-R^9$, halo (C_1-C_6) alkyl,

$-O$ -halo (C_1-C_6) alkyl, $-CN$, $-C(O)-O-(C_1-C_6)$ alkyl, $-N(R^6)_2$, $-C(R^6)_2-N(R^6)_2$,

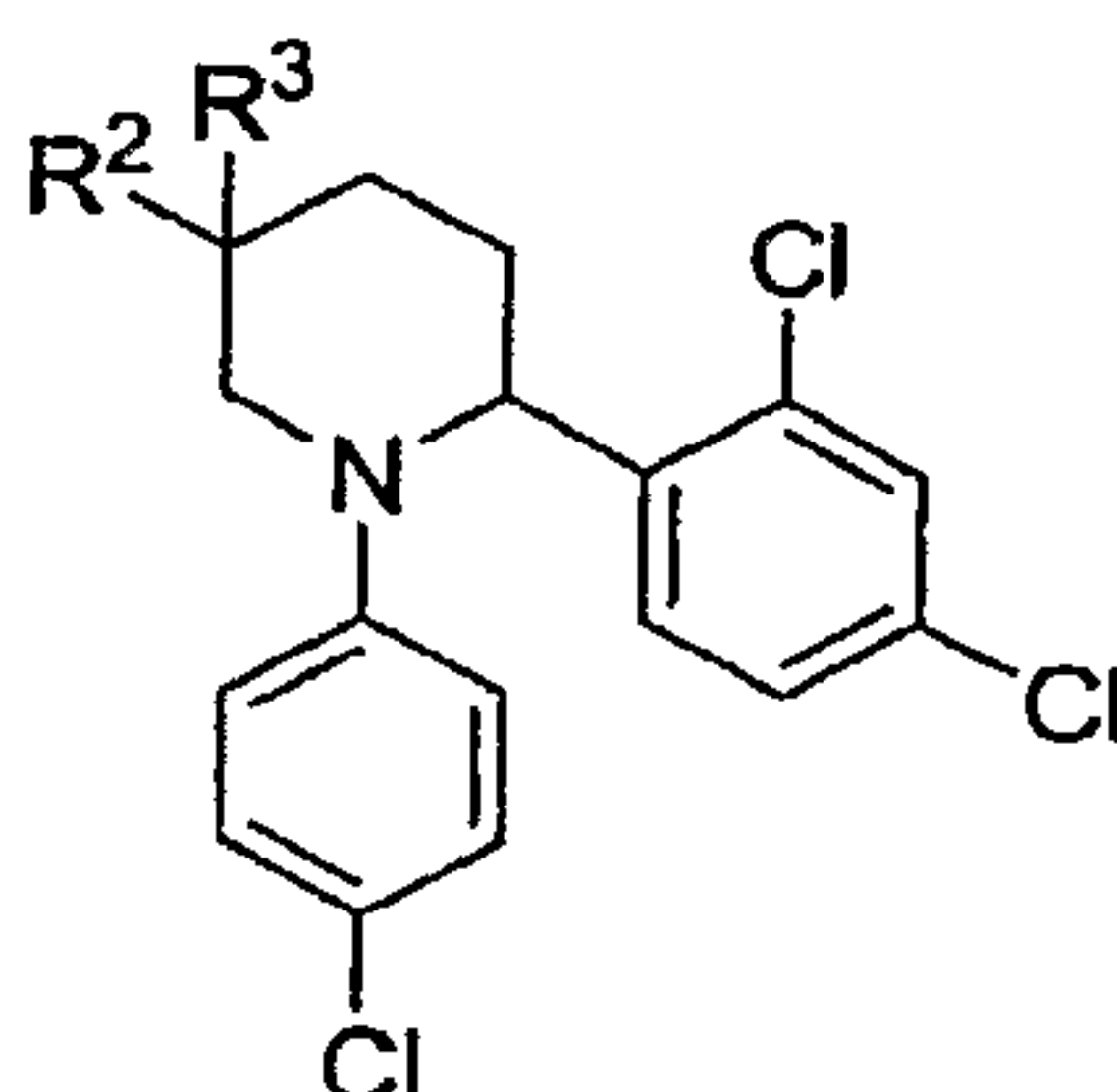
$-S(O)_2-(C_2-C_{10})$ heterocyclyl, $-S(O)_2-(C_2-C_{10})$ heteroaryl and

$-C(R^6)_2-N(R^6)-S(O)_2-R^6$; or

two of said Y groups attached to adjacent carbon atoms form a $-\text{O}-\text{CH}_2-\text{O}-$ or $-\text{O}-\text{CH}_2\text{CH}_2-\text{O}-$ group;

each q is independently an integer from 0 to 5.

In another embodiment, the compound of Formula (I) is a compound having
5 the following structural Formula:



wherein

10 R² is selected from the group consisting of H, $-(\text{C}(\text{R}^6)_2)_p-(\text{C}_6-\text{C}_{10})\text{aryl}$, $(\text{C}_3-\text{C}_6)\text{cycloalkyl}(\text{C}_1-\text{C}_6)\text{alkyl}$, $(\text{C}_3-\text{C}_6)\text{cycloalkyl}(\text{C}_1-\text{C}_6)\text{alkyl}$ substituted with Z, $-(\text{C}(\text{R}^6)_2)_q-(\text{C}_2-\text{C}_{10})\text{heterocyclyl}$, $-(\text{C}(\text{R}^6)_2)_p-\text{S}(\text{O})_2-(\text{C}_2-\text{C}_{10})\text{heterocyclyl}$, and $-\text{C}(\text{R}^6)_2-\text{O}-\text{R}^7$,

15 wherein the $(\text{C}_6-\text{C}_{10})\text{aryl}$ portion of said $-(\text{C}(\text{R}^6)_2)_p-(\text{C}_6-\text{C}_{10})\text{aryl}$ of R² is unsubstituted or substituted with one or more Y groups,

wherein the $(\text{C}_2-\text{C}_{10})\text{heterocyclyl}$ portion of said

$-(\text{C}(\text{R}^6)_2)_p-\text{S}(\text{O})_2-(\text{C}_2-\text{C}_{10})\text{heterocyclyl}$ of R² is unsubstituted or substituted with one or more X groups,

wherein the $(\text{C}_2-\text{C}_{10})\text{heterocyclyl}$ portion of said

20 $-(\text{C}(\text{R}^6)_2)_q-(\text{C}_2-\text{C}_{10})\text{heterocyclyl}$ of R² is unsubstituted or substituted with one or more X groups;

R³ is selected from the group consisting of H, $-(\text{C}(\text{R}^6)_2)_q-\text{C}(\text{O})-\text{N}(\text{R}^{12})_2$ or $-(\text{C}(\text{R}^6)_2)_q-\text{N}(\text{R}^8)_2$;

each R⁶ is independently selected from the group consisting of H and $(\text{C}_1-\text{C}_6)\text{alkyl}$;

25 R⁷ is selected from the group consisting of H, $(\text{C}_1-\text{C}_6)\text{alkyl}$, unsubstituted $(\text{C}_2-\text{C}_{10})\text{heteroaryl}$ and $(\text{C}_2-\text{C}_{10})\text{heteroaryl}$ substituted with one or more Y groups, unsubstituted $(\text{C}_6-\text{C}_{10})\text{aryl}$, and $(\text{C}_6-\text{C}_{10})\text{aryl}$ substituted with one or more Y groups;

each R^8 is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, unsubstituted (C₆-C₁₀)aryl, unsubstituted (C₂-C₁₀)heteroaryl,
 -C(O)-(C₁-C₆)alkyl, -C(O)-(C₆-C₁₀)aryl, -C(O)-(C₃-C₆)cycloalkyl, -C(O)N(R⁹)₂,
 5 -S(O)₂-(C₆-C₁₀)aryl, -S(O)₂-(C₂-C₁₀)heteroaryl, -SO₂N(R⁹)₂,
 -S(O)₂-(C₃-C₆)cycloalkyl, (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl substituted with one or more Y groups, and -S(O)₂-(C₁-C₆)alkyl,

wherein the (C₆-C₁₀)aryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl, -C(O)-(C₆-C₁₀)aryl or -S(O)₂-(C₆-C₁₀)aryl and the (C₂-C₁₀)heteroaryl portion of said
 10 (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, -S(O)₂-(C₂-C₁₀)heteroaryl of R^8 is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl
 15 portion is NOT Cbz or Boc;

each R^9 is independently selected from the group consisting of H, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, unsubstituted (C₆-C₁₀)aryl and unsubstituted (C₂-C₁₀)heteroaryl;

each R^{12} is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, -(C(R⁶)₂)_q-C(O)R¹³, benzo(C₂-C₁₀)heterocyclyl, benzocyclo(C₁-C₆)alkyl,
 20 -(C(R⁶)₂)_q-N(R⁹)-C(O)R¹³, -(C(R⁶)₂)_q-N(R¹⁴)₂, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, Y-(C₁-C₆)alkylenyl-O-, W-O-(C₁-C₆)alkylenyl, (C₂-C₁₀)heterocyclyl(C₁-C₆)alkyl,
 25 unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups, and

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

5 wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups,

wherein the benzo portion of said benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more Y groups and the (C₂-C₁₀)heterocyclyl portion of benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or
10 more X groups,

wherein the benzo portion of said benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more Y groups and the (C₃-C₆)cycloalkyl portion of benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more X groups;

15 with the following provisos that

for -N(R¹⁴)₂ of R¹², the two R¹⁴ groups, with the ring nitrogen atom to which they are shown attached, form an unsubstituted (C₂-C₁₀)heterocyclyl ring or a (C₂-C₁₀)heterocyclyl ring substituted with one or more X groups;

each R¹³ is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups
20
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wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

30 wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or

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substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc, wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups;

5 each R¹⁴ is independently selected from the group consisting of H, Boc, unsubstituted (C₁-C₆)alkyl, (C₁-C₆)alkyl substituted with one or more X groups, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl substituted with one or more Y groups, (C₂-C₁₀)heterocyclyl, unsubstituted (C₂-C₁₀)heteroaryl and
10 (C₂-C₁₀)heteroaryl substituted with one or more Y groups;

each W is independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -C(R⁶)₂-N(R⁶)₂, and -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶;

each X is independently selected from the group consisting of hydrogen, -OH,
15 (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, Cbz, Boc, (C₁-C₆)alkylsulfonyl, acetyl, -C(O)-R¹², -C(O)-N(R⁹)₂, -C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl, -S(O)₂-(C₃-C₆)cycloalkyl, -C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -(C(R⁶)₂)_m-(C₆-C₁₀)aryl and (C₆-C₁₀)aryl

20 wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or
25 more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said -C(O)-(C₂-C₁₀)heteroaryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH,
30 -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN, and

wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said -(C(R⁶)₂)_m-(C₆-C₁₀)aryl of X is unsubstituted or substituted with one or

more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN

wherein in a single X moiety, =O, can replace two available hydrogens on the same carbon on a ring system;

- 5 each Y is independently selected from the group consisting of hydrogen, halogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -O-(C₁-C₆)alkyl, -O-(C₂-C₁₀)heteroaryl, -O-(C₆-C₁₀)aryl, -O-R⁹, halo(C₁-C₆)alkyl, -O-halo(C₁-C₆)alkyl, -CN, -C(O)-O-(C₁-C₆)alkyl, -N(R⁶)₂, -C(R⁶)₂-N(R⁶)₂, -S(O)₂-(C₂-C₁₀)heterocyclyl, -S(O)₂-(C₂-C₁₀)heteroaryl and
- 10 -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶; or

two of said Y groups attached to adjacent carbon atoms form a -O-CH₂-O- or -O-CH₂CH₂-O- group;

- each Z is independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl,
- 15 -C(O)-N(R⁹)₂, -C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl, -S(O)₂-(C₃-C₆)cycloalkyl, -C(O)-(C₁-C₆)alkyl, -(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -N(R⁶)-S(O)₂-R⁹ and (C₆-C₁₀)aryl

- wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or
- 20 substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

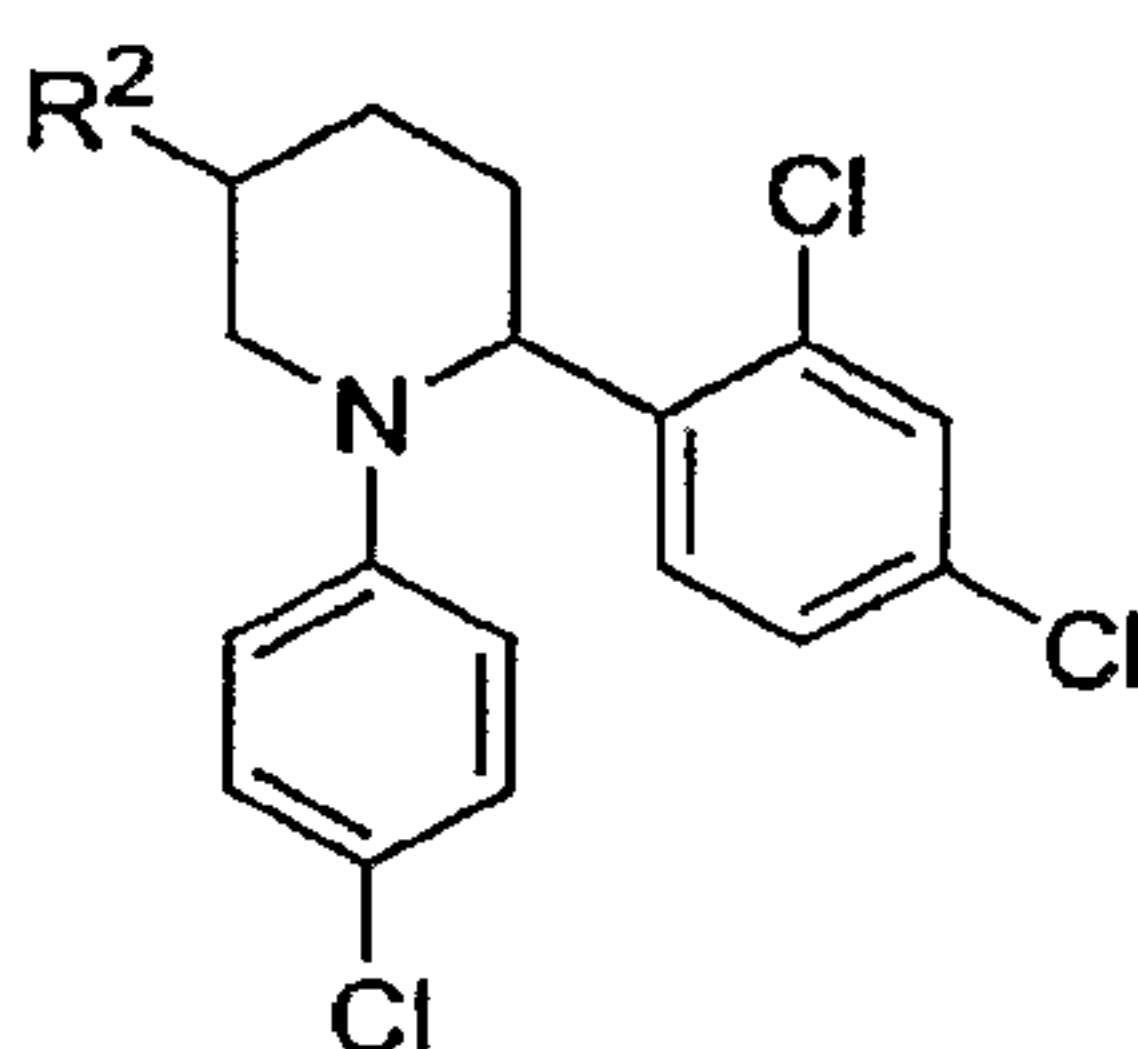
- 25 wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said -C(O)-(C₂-C₁₀)heteroaryl of Z is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN, and

- wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said
- 30 -(C(R⁶)₂)_m-(C₆-C₁₀)aryl of Z is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN;

wherein in a single Z moiety, =O, can replace two available hydrogens on the same carbon on a ring system;

each n, p and q is independently an integer from 0-5; and
m is an integer from 1-5.

- 5 In another embodiment, the compound of Formula (I) is a compound having the following structural Formula:



- 10 wherein;

R² is $-(C(R^6)_2)_q-(C_2-C_{10})\text{heterocyclyl}$;

wherein the $(C_2-C_{10})\text{heterocyclyl}$ portion of said

$-(C(R^6)_2)_q-(C_2-C_{10})\text{heterocyclyl}$ of R² is unsubstituted or substituted with one or more X groups;

- 15 each R⁶ is independently selected from the group consisting of H and $(C_1-C_6)\text{alkyl}$;

each R⁹ is independently selected from the group consisting of H, $(C_1-C_6)\text{alkyl}$, halo $(C_1-C_6)\text{alkyl}$, hydroxy $(C_1-C_6)\text{alkyl}$, $(C_3-C_6)\text{cycloalkyl}$, unsubstituted $(C_6-C_{10})\text{aryl}$ and unsubstituted $(C_2-C_{10})\text{heteroaryl}$;

each R¹² is independently selected from the group consisting of H, $(C_1-C_6)\text{alkyl}$, $(C_3-C_6)\text{cycloalkyl}$, $(C_1-C_6)\text{alkyl}$, $-(C(R^6)_2)_q-C(O)R^{13}$, benzo $(C_2-C_{10})\text{heterocyclyl}$,

- 20 benzocyclo $(C_1-C_6)\text{alkyl}$, $-(C(R^6)_2)_q-N(R^9)-C(O)R^{13}$, $-(C(R^6)_2)_q-N(R^{14})_2$, $(C_6-C_{10})\text{aryl}(C_1-C_6)\text{alkyl}$, $(C_2-C_{10})\text{heteroaryl}(C_1-C_6)\text{alkyl}$, HO- $(C_1-C_6)\text{alkyl}$ -, $(C_1-C_6)\text{alkyl-O-}$, $(C_6-C_{10})\text{aryl-O-}$, Y- $(C_1-C_6)\text{alkylenyl-O-}$, W-O- $(C_1-C_6)\text{alkylenyl}$, $(C_2-C_{10})\text{heterocyclyl}(C_1-C_6)\text{alkyl}$,

- 25 unsubstituted $(C_3-C_6)\text{cycloalkyl}$, $(C_3-C_6)\text{cycloalkyl}$ substituted with one or more X groups, unsubstituted $(C_2-C_{10})\text{heterocyclyl}$, $(C_2-C_{10})\text{heterocyclyl}$ substituted with one or more X groups, unsubstituted $(C_2-C_{10})\text{heteroaryl}$, $(C_2-C_{10})\text{heteroaryl}$ substituted with one or more Y groups, unsubstituted $(C_6-C_{10})\text{aryl}$ and $(C_6-C_{10})\text{aryl}$ substituted with one or more Y groups, and

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups,

wherein the benzo portion of said benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more Y groups and the (C₂-C₁₀)heterocyclyl portion of benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more X groups,

wherein the benzo portion of said benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more Y groups and the (C₃-C₆)cycloalkyl portion of benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more X groups;

with the following provisos that

for -N(R¹⁴)₂ of R¹², the two R¹⁴ groups, with the ring nitrogen atom to which they are shown attached, form an unsubstituted (C₂-C₁₀)heterocyclyl ring or a (C₂-C₁₀)heterocyclyl ring substituted with one or more X groups;

each R¹³ is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

5 wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups;

each R¹⁴ is independently selected from the group consisting of H, Boc,

unsubstituted (C₁-C₆)alkyl, (C₁-C₆)alkyl substituted with one or more X groups, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl substituted with one or more Y groups, (C₂-C₁₀)heterocyclyl, unsubstituted (C₂-C₁₀)heteroaryl and (C₂-C₁₀)heteroaryl substituted with one or more Y groups;

each W is independently selected from the group consisting of hydrogen,

(C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -C(R⁶)₂-N(R⁶)₂, and -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶;

each X is independently selected from the group consisting of hydrogen, -OH,

(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, Cbz, Boc, (C₁-C₆)alkylsulfonyl, acetyl, -C(O)-R¹², -C(O)-N(R⁹)₂,

-C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl, -S(O)₂-(C₃-C₆)cycloalkyl,

-C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -(C(R⁶)₂)_m-(C₆-C₁₀)aryl and (C₆-C₁₀)aryl

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-

C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

25 wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said

30 -C(O)-(C₂-C₁₀)heteroaryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN, and

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wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said

-(C(R⁶)₂)_m-(C₆-C₁₀)aryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN

5 wherein in a single X moiety, =O, can replace two available hydrogens on the same carbon on a ring system;

each Y is independently selected from the group consisting of hydrogen, halogen,

(C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -O-(C₁-C₆)alkyl,

-O-(C₂-C₁₀)heteroaryl, -O-(C₆-C₁₀)aryl, -O-R⁹, halo(C₁-C₆)alkyl,

10 -O-halo(C₁-C₆)alkyl, -CN, -C(O)-O-(C₁-C₆)alkyl, -N(R⁶)₂, -C(R⁶)₂-N(R⁶)₂,

-S(O)₂-(C₂-C₁₀)heterocyclyl, -S(O)₂-(C₂-C₁₀)heteroaryl and

-C(R⁶)₂-N(R⁶)-S(O)₂-R⁶; or

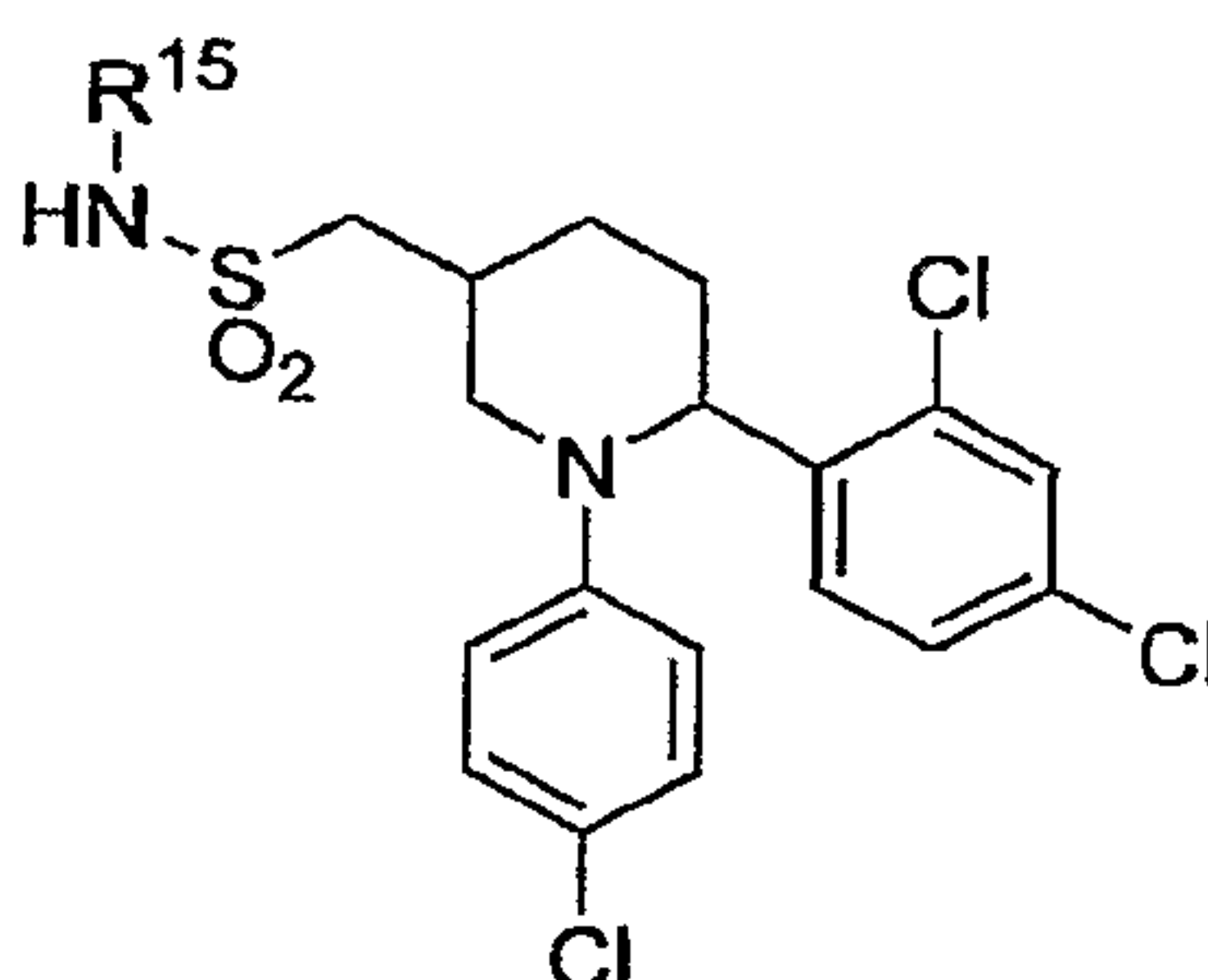
two of said Y groups attached to adjacent carbon atoms form a -O-CH₂-O- or

-O-CH₂CH₂-O- group;

15 each n, p and q is independently an integer from 0-5; and m is an integer from 1-5.

In another embodiment of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof, R³ is -C(R⁶)₂_q-N(R⁸)₂ or -C(R⁶)₂_q-(C₂-C₁₀)heterocyclyl.

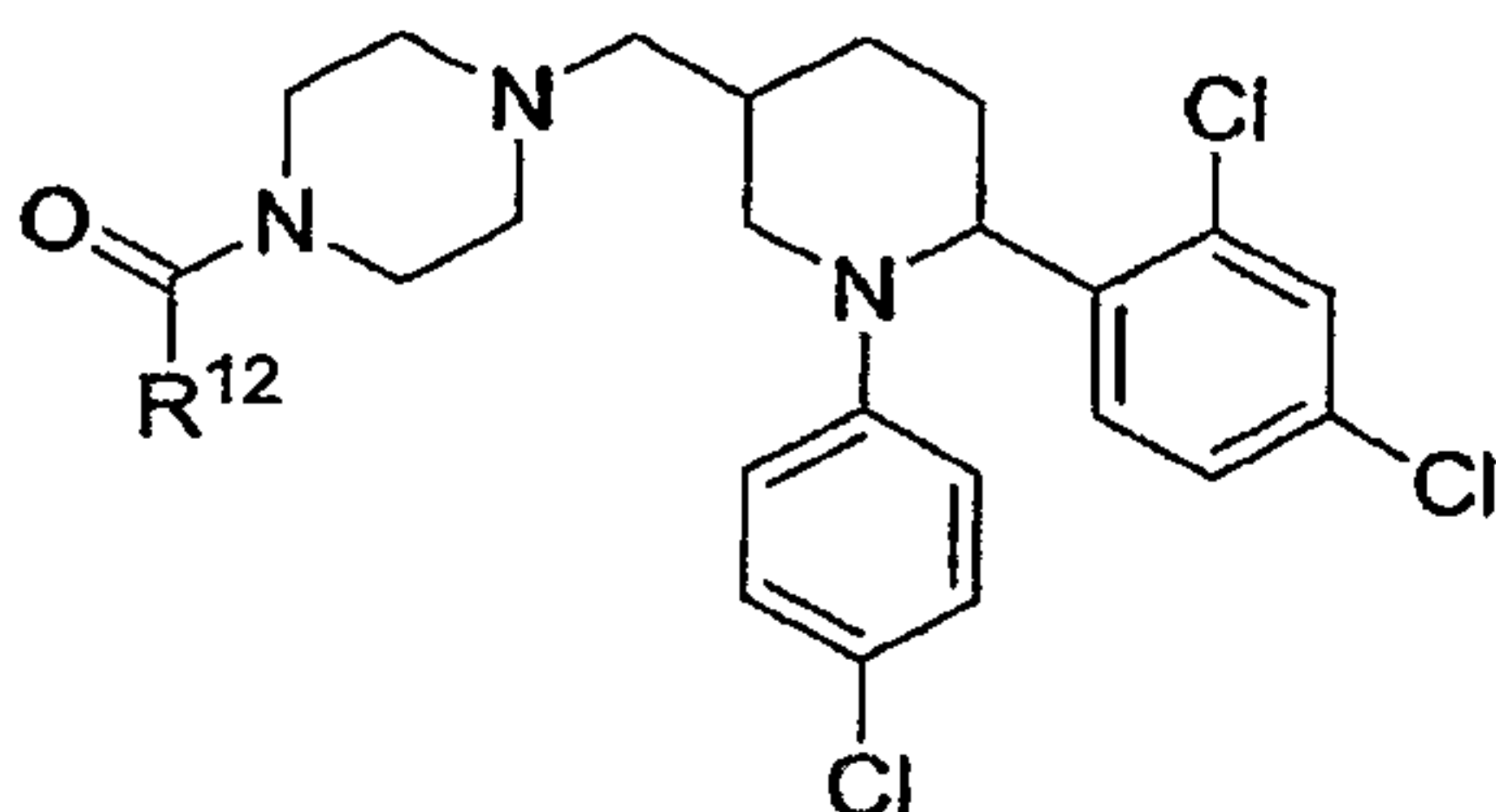
20 In another embodiment, the compound of Formula (I) is a compound having the following structural Formula:



25 or a pharmaceutically acceptable salt, solvate or ester thereof, wherein: R¹⁵ is alkyl.

In another embodiment, the compound of Formula (I) is a compound having the following structural Formula:

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or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

each R^6 is independently selected from the group consisting of H and (C_1-C_6) alkyl;

5 each R^9 is independently selected from the group consisting of H, (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, hydroxy (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, unsubstituted (C_6-C_{10}) aryl and unsubstituted (C_2-C_{10}) heteroaryl;

each R^{12} is independently selected from the group consisting of H, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl (C_1-C_6) alkyl, $-(C(R^6)_2)_q-C(O)R^{13}$, benzo (C_2-C_{10}) heterocyclyl, benzocyclo (C_1-C_6) alkyl,

10 $-(C(R^6)_2)_q-N(R^9)-C(O)R^{13}$, $-(C(R^6)_2)_q-N(R^{14})_2$, (C_6-C_{10}) aryl (C_1-C_6) alkyl, (C_2-C_{10}) heteroaryl (C_1-C_6) alkyl, HO- (C_1-C_6) alkyl-, (C_1-C_6) alkyl-O-, (C_6-C_{10}) aryl-O-, Y- (C_1-C_6) alkylenyl-O-, W-O- (C_1-C_6) alkylenyl, (C_2-C_{10}) heterocyclyl (C_1-C_6) alkyl, unsubstituted (C_3-C_6) cycloalkyl, (C_3-C_6) cycloalkyl substituted with one or more X groups, unsubstituted (C_2-C_{10}) heterocyclyl, (C_2-C_{10}) heterocyclyl substituted with one or more X groups, unsubstituted (C_2-C_{10}) heteroaryl, (C_2-C_{10}) heteroaryl substituted with one or more Y groups, unsubstituted (C_6-C_{10}) aryl and (C_6-C_{10}) aryl substituted with one or more Y groups, and

wherein the (C_6-C_{10}) aryl and (C_2-C_{10}) heteroaryl portion of said (C_6-C_{10}) aryl (C_1-C_6) alkyl and (C_2-C_{10}) heteroaryl (C_1-C_6) alkyl is unsubstituted or

20 substituted with one or more Y groups,

wherein the (C_1-C_6) alkyl portion of said (C_3-C_6) cycloalkyl (C_1-C_6) alkyl, (C_6-C_{10}) aryl (C_1-C_6) alkyl and (C_2-C_{10}) heteroaryl (C_1-C_6) alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C_1-C_6) alkyl portion is NOT Cbz or Boc,

25 wherein the (C_3-C_6) cycloalkyl of said (C_3-C_6) cycloalkyl (C_1-C_6) alkyl is unsubstituted or substituted with one or more X groups,

wherein the benzo portion of said benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more Y groups and the (C₂-C₁₀)heterocyclyl portion of benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more X groups,

5 wherein the benzo portion of said benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more Y groups and the (C₃-C₆)cycloalkyl portion of benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more X groups;

with the following provisos that

10 for -N(R¹⁴)₂ of R¹², the two R¹⁴ groups, with the ring nitrogen atom to which they are shown attached, form an unsubstituted (C₂-C₁₀)heterocyclyl ring or a (C₂-C₁₀)heterocyclyl ring substituted with one or more X groups;

each R¹³ is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, 15 HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl 20 substituted with one or more Y groups

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

25 wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups;

30 each R¹⁴ is independently selected from the group consisting of H, Boc, unsubstituted (C₁-C₆)alkyl, (C₁-C₆)alkyl substituted with one or more X groups, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more Y

groups, unsubstituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl substituted with one or more Y groups, (C₂-C₁₀)heterocyclyl, unsubstituted (C₂-C₁₀)heteroaryl and (C₂-C₁₀)heteroaryl substituted with one or more Y groups;

each W is independently selected from the group consisting of hydrogen,

5 (C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -C(R⁶)₂-N(R⁶)₂, and -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶;

each X is independently selected from the group consisting of hydrogen, -OH,

10 (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, Cbz, Boc, (C₁-C₆)alkylsulfonyl, acetyl, -C(O)-R¹², -C(O)-N(R⁹)₂, -C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl, -S(O)₂-(C₃-C₆)cycloalkyl, -C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -(C(R⁶)₂)_m-(C₆-C₁₀)aryl and (C₆-C₁₀)aryl

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-

15 C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

20 wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said -C(O)-(C₂-C₁₀)heteroaryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN, and

25 wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said -(C(R⁶)₂)_m-(C₆-C₁₀)aryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN

wherein in a single X moiety, =O, can replace two available hydrogens on the same carbon on a ring system;

30 each Y is independently selected from the group consisting of hydrogen, halogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -O-(C₁-C₆)alkyl, -O-(C₂-C₁₀)heteroaryl, -O-(C₆-C₁₀)aryl, -O-R⁹, halo(C₁-C₆)alkyl,

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-O-halo(C₁-C₆)alkyl, -CN, -C(O)-O-(C₁-C₆)alkyl, -N(R⁶)₂, -C(R⁶)₂-N(R⁶)₂,
 -S(O)₂-(C₂-C₁₀)heterocyclyl, -S(O)₂-(C₂-C₁₀)heteroaryl and
 -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶; or

two of said Y groups attached to adjacent carbon atoms form a -O-CH₂-O- or

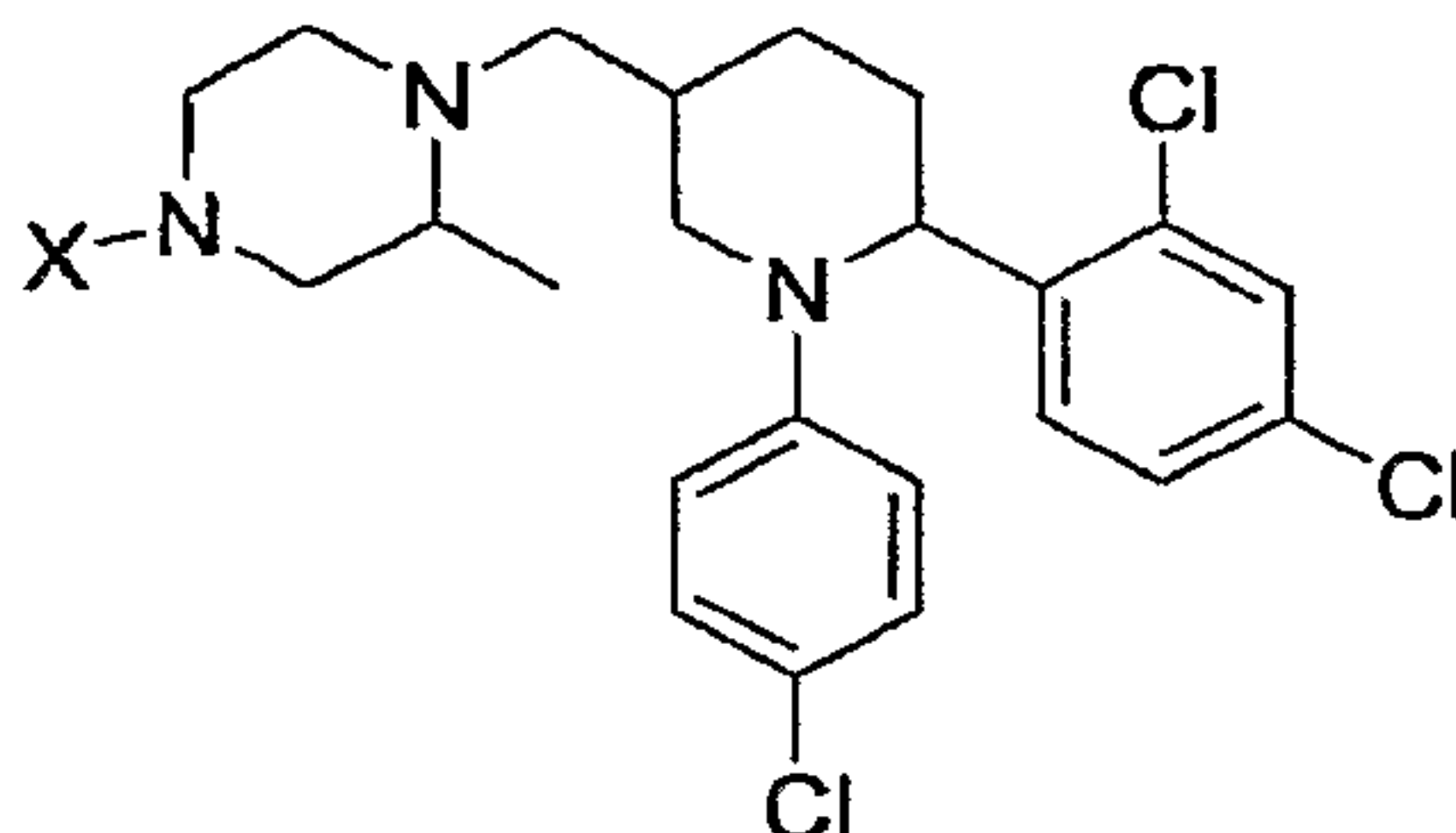
5 -O-CH₂CH₂-O- group;

each n, p and q is independently an integer from 0-5; and

m is an integer from 1-5.

In another embodiment, the compound of Formula (I) is a compound having
 the following structural Formula:

10



or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

each R⁹ is independently selected from the group consisting of H, (C₁-C₆)alkyl,

15 halo(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, unsubstituted (C₆-C₁₀)aryl and unsubstituted (C₂-C₁₀)heteroaryl;

R¹² is (C₁-C₆)alkyl;

each X is independently selected from the group consisting of hydrogen, -OH,

20 (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, Cbz, Boc, (C₁-C₆)alkylsulfonyl, acetyl, -C(O)-R¹², -C(O)-N(R⁹)₂, -C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl, -S(O)₂-(C₃-C₆)cycloalkyl, -C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -(C(R⁶)₂)_m-(C₆-C₁₀)aryl and (C₆-C₁₀)aryl

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-

25 C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and

(C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or

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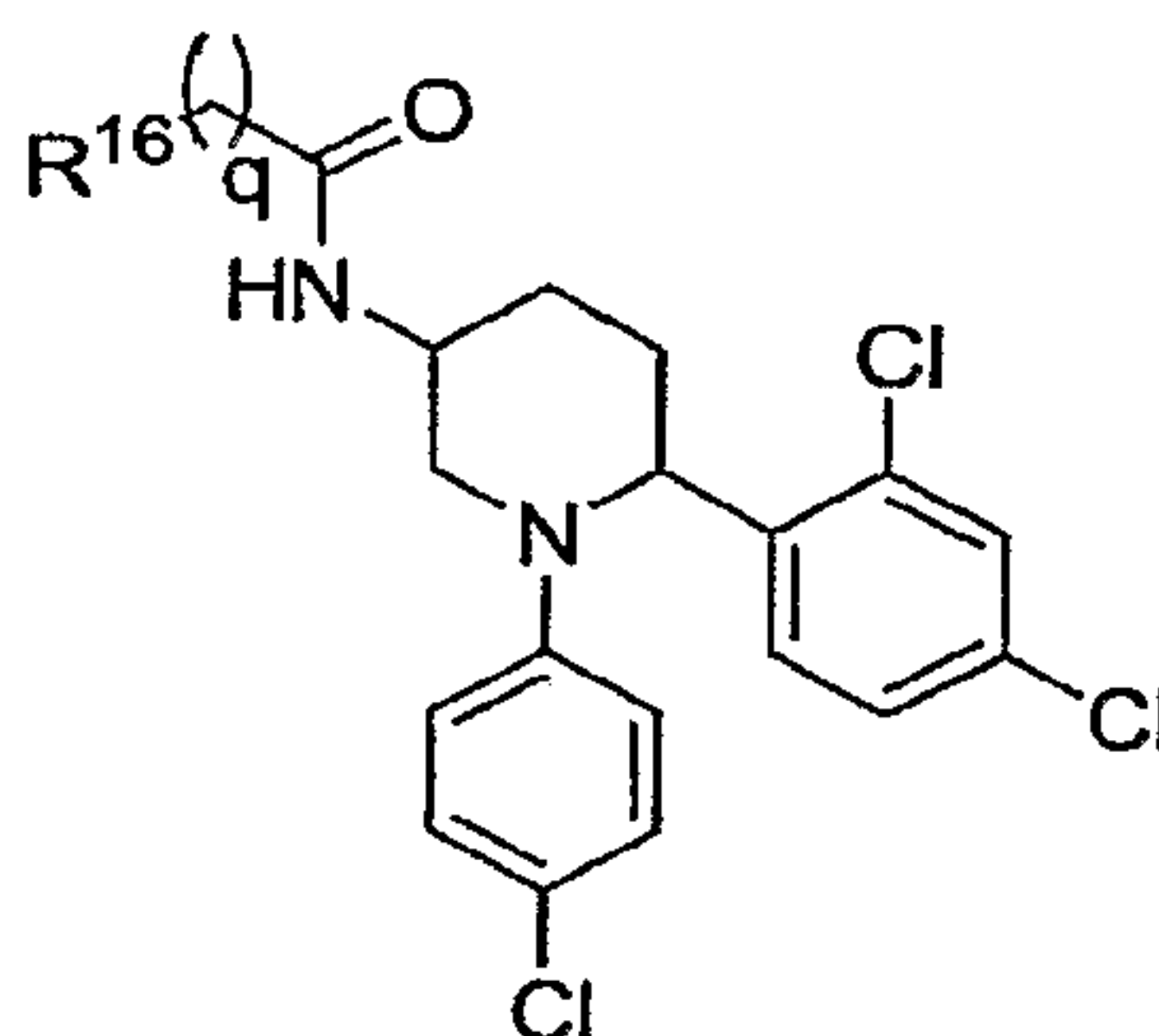
more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said -C(O)-(C₂-C₁₀)heteroaryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN, and

wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said -(C(R⁶)₂)_m-(C₆-C₁₀)aryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN

wherein in a single X moiety, =O, can replace two available hydrogens on the same carbon on a ring system.

In another embodiment, the compound of Formula (I) is a compound having the following structural Formula:



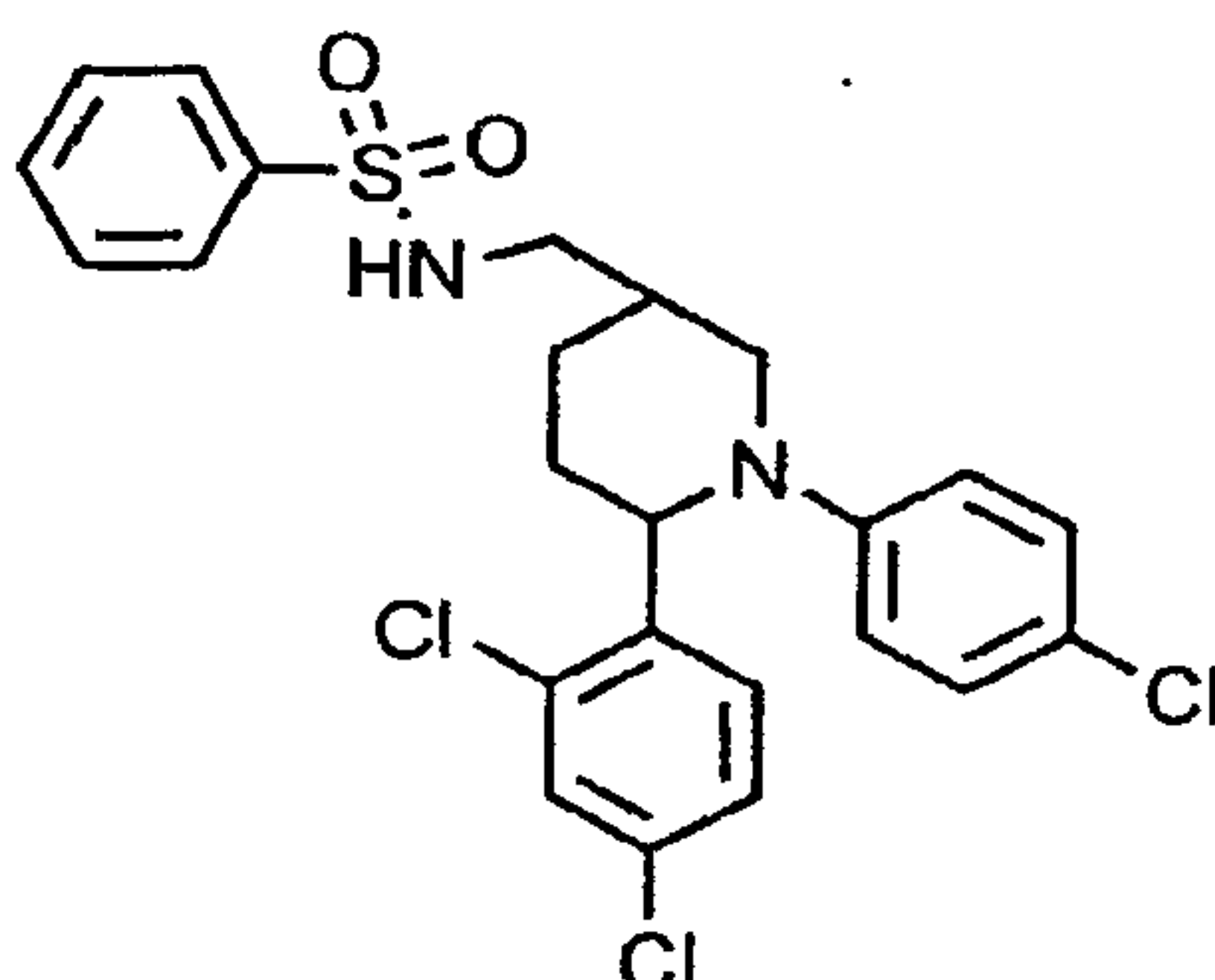
or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

R¹⁶ is -O-(C₁-C₆)alkyl or (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl

q is 1 or 2.

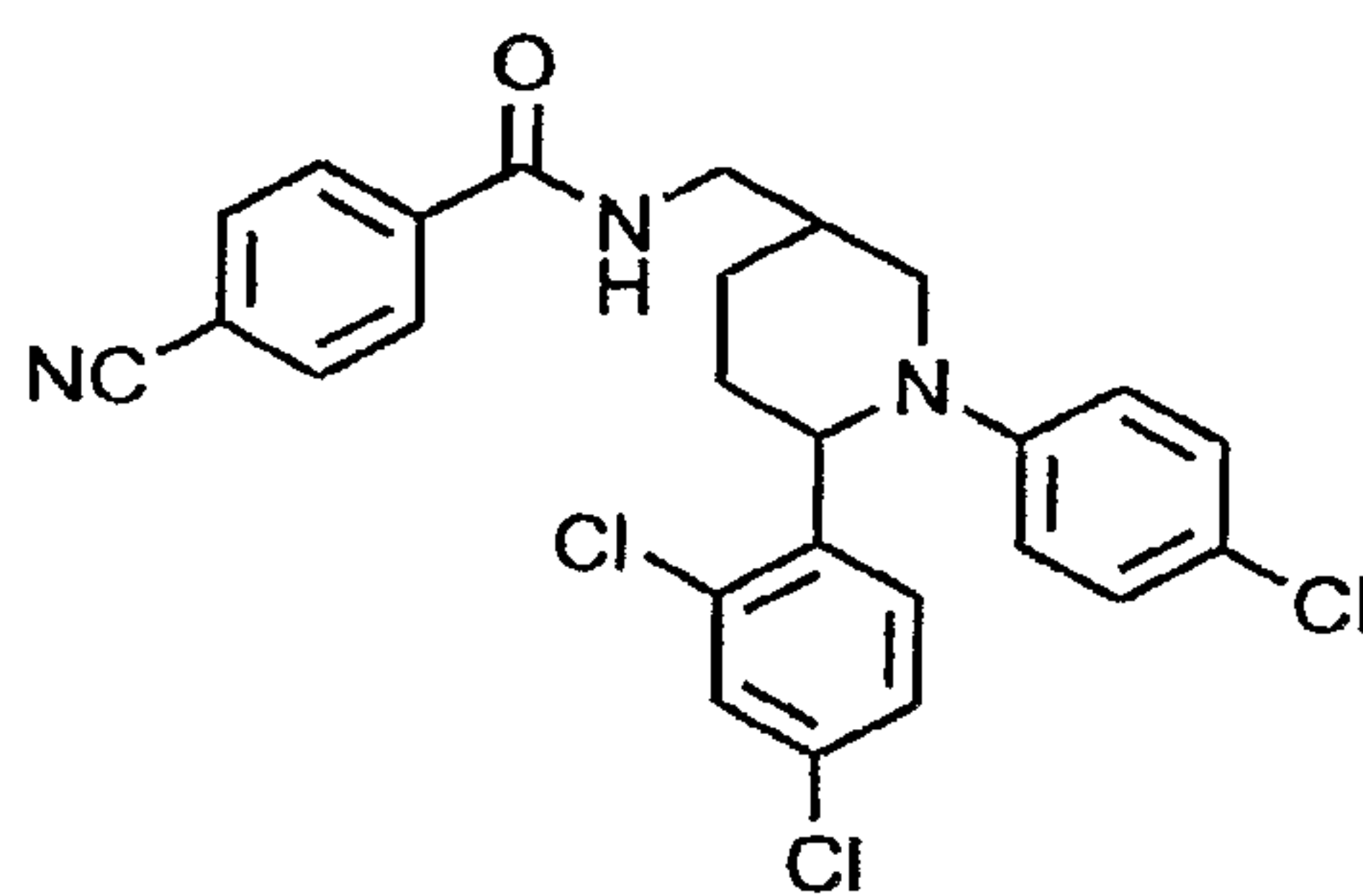
In another embodiment, the compound of Formula (I) has the following structure:

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or a pharmaceutically acceptable salt, solvate, or ester thereof.

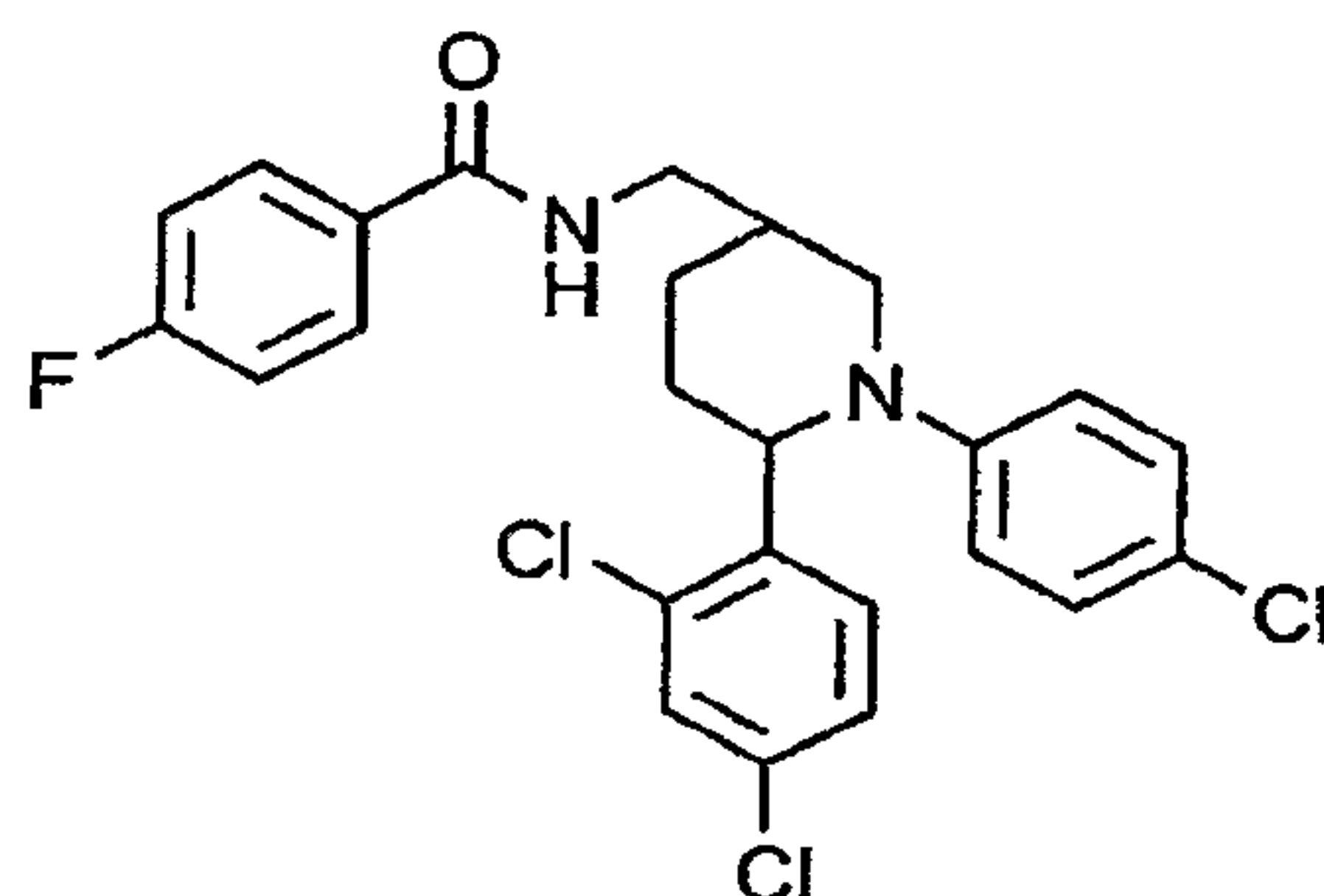
In another embodiment, the compound of Formula (I) has the following structure:



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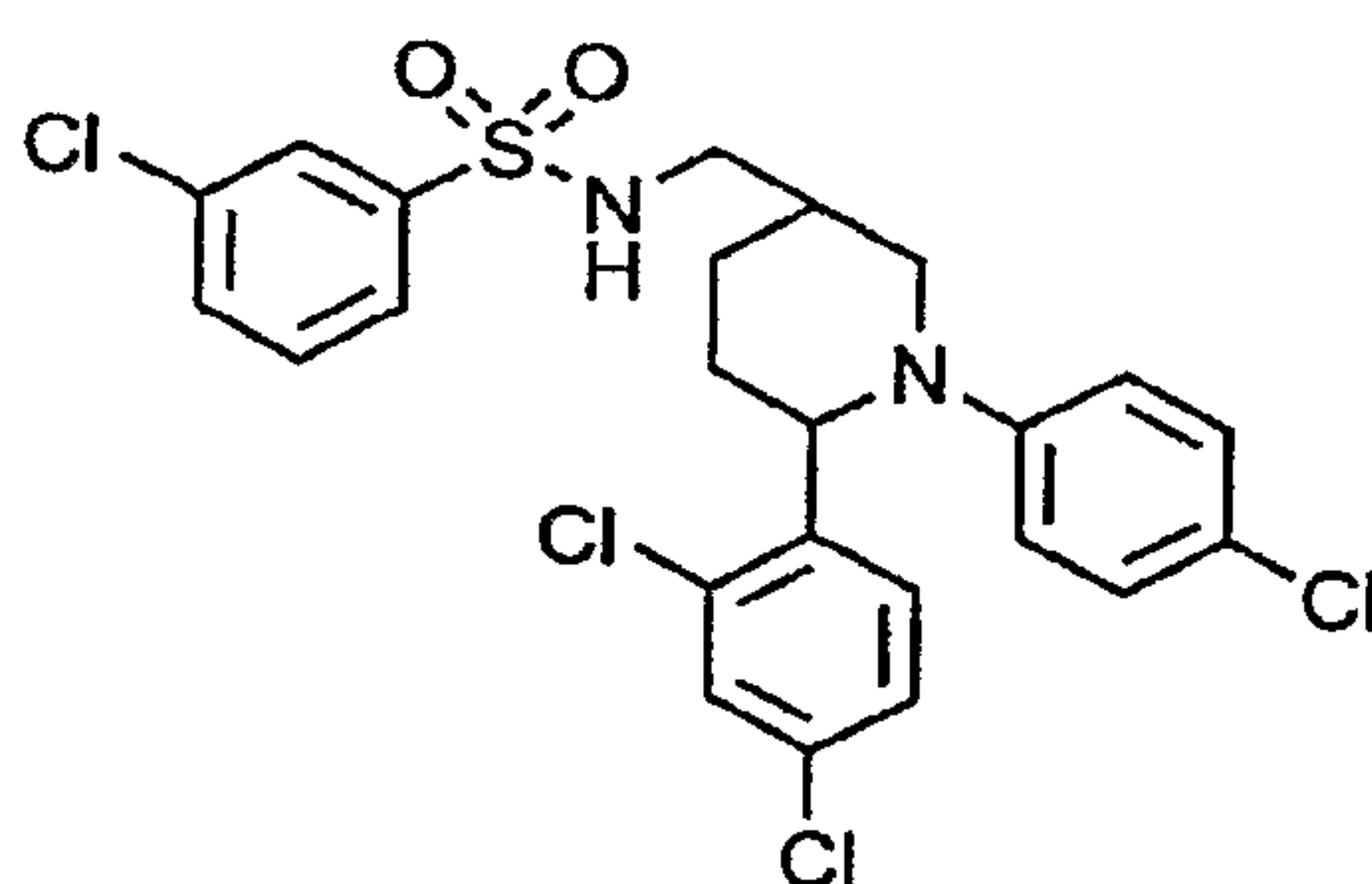
or a pharmaceutically acceptable salt, solvate, or ester thereof.

In another embodiment, the compound of Formula (I) has the following structure:



10 or a pharmaceutically acceptable salt, solvate, or ester thereof.

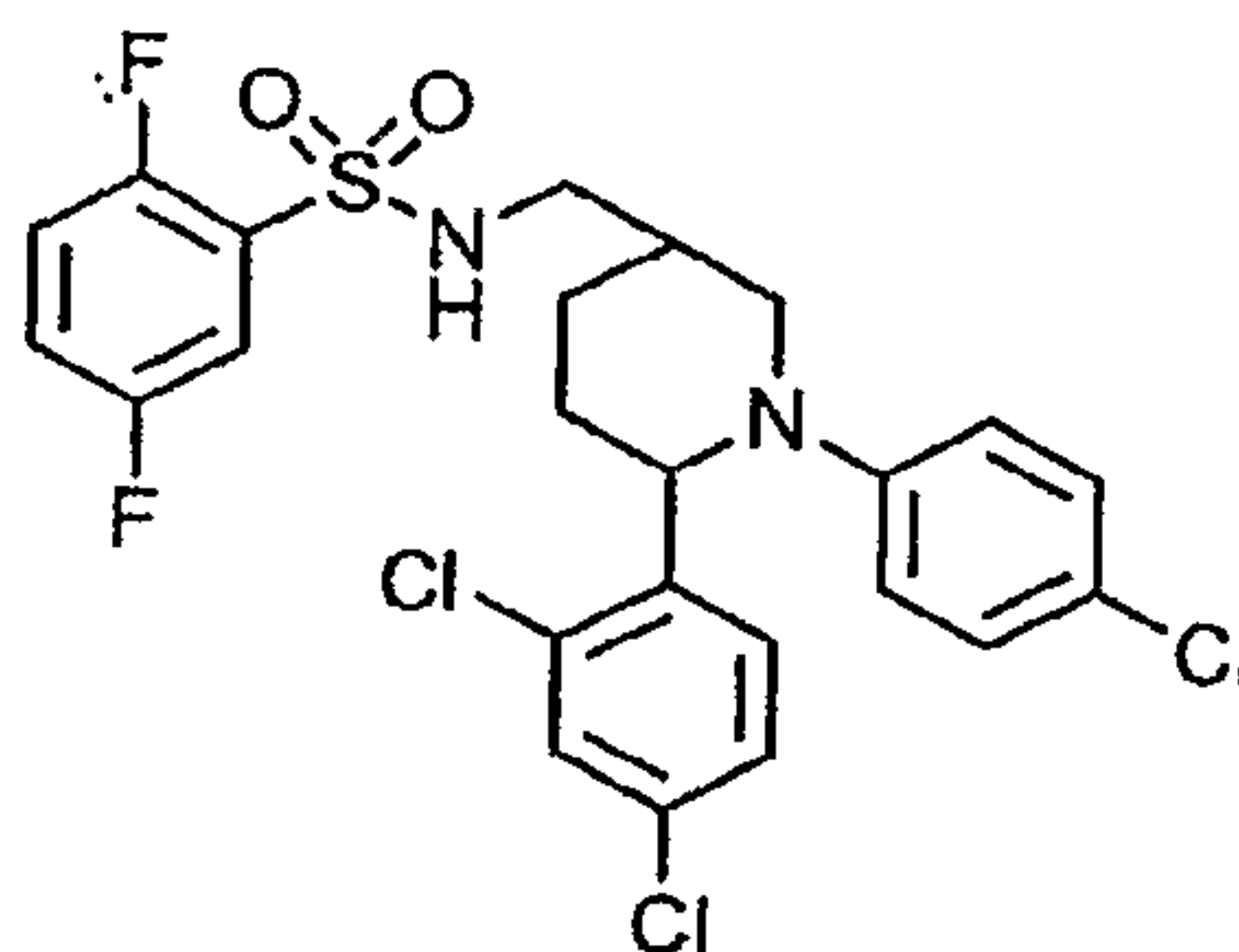
In another embodiment, the compound of Formula (I) has the following structure:



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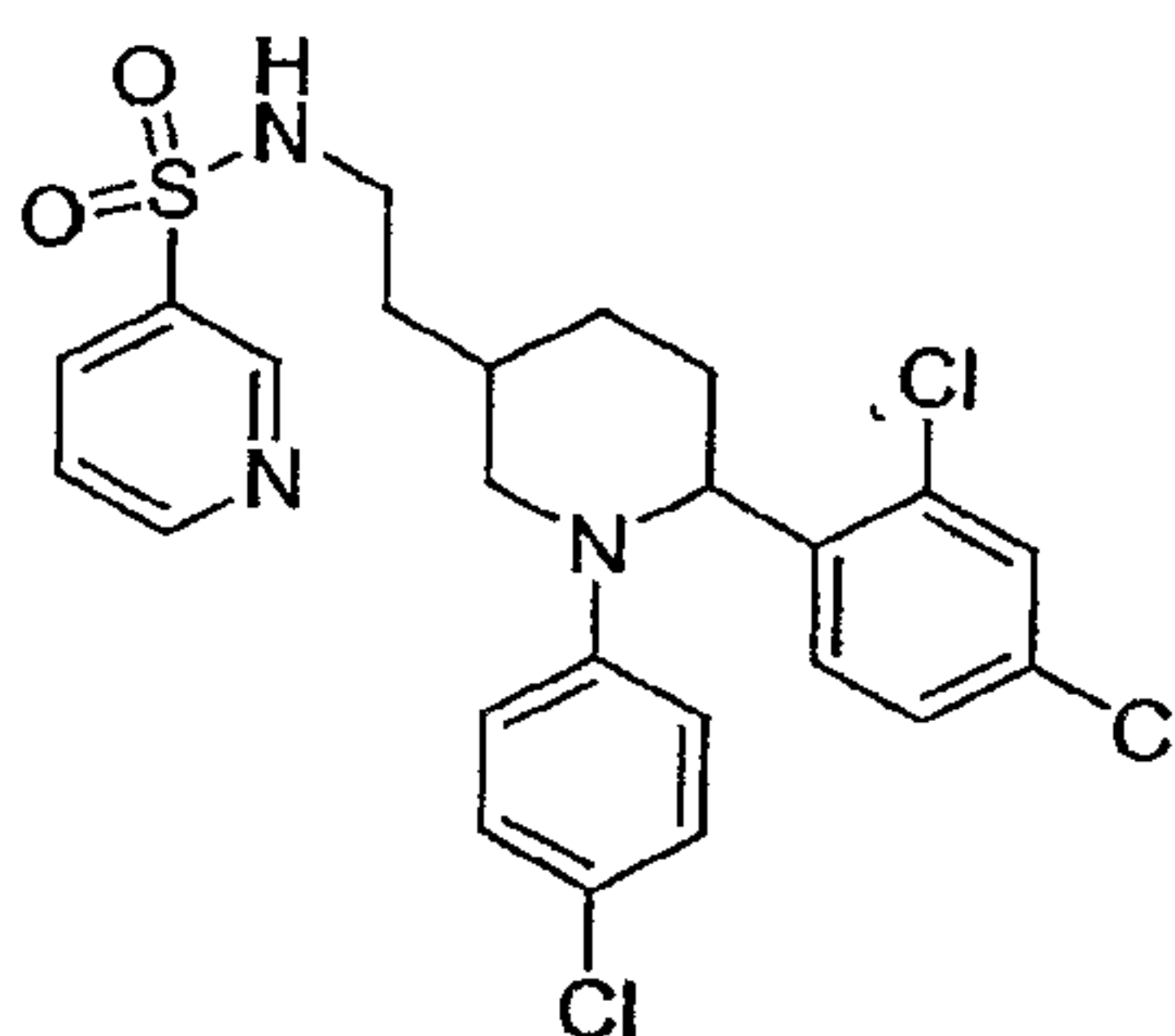
or a pharmaceutically acceptable salt, solvate, or ester thereof.

In another embodiment, the compound of Formula (I) has the following structure:



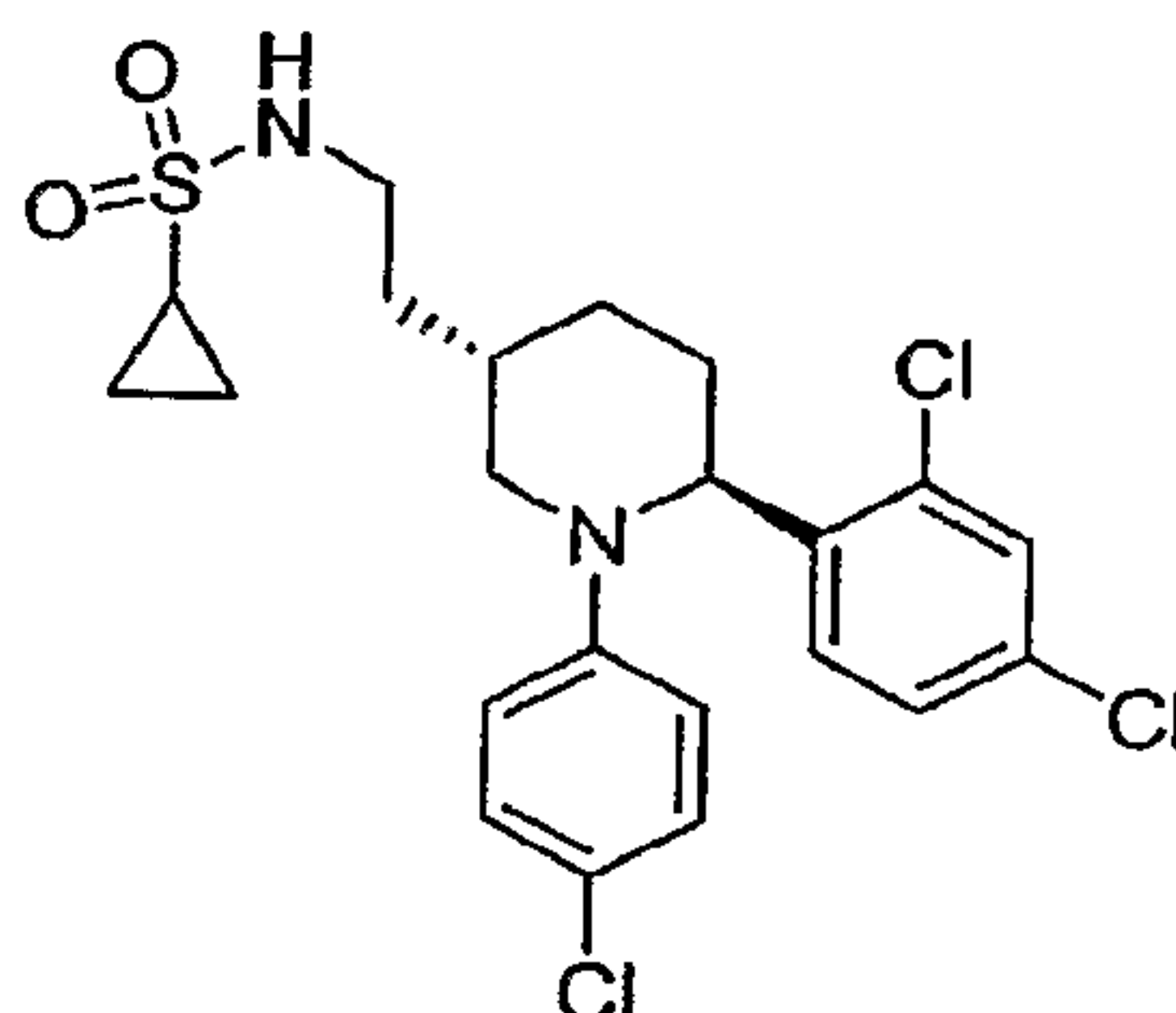
5 or a pharmaceutically acceptable salt, solvate, or ester thereof.

In another embodiment, the compound of Formula (I) has the following structure:



or a pharmaceutically acceptable salt, solvate, or ester thereof.

10 In another embodiment, the compound of Formula (I) has the following structure:



or a pharmaceutically acceptable salt, solvate, or ester thereof.

15 The compounds of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, are preferably purified to a degree suitable for use as a pharmaceutically active substance. That is, the compounds of Formula (I) can have

a purity of 95 wt% or more (excluding adjuvants such as pharmaceutically acceptable carriers, solvents, etc., which are used in formulating the compound of Formula (I) into a conventional form, such as a pill, capsule, IV solution, etc. suitable for administration into a patient). In other embodiments, the purity can be 97 wt% or more, or 99 wt% or more. A purified compound of Formula (I) includes a single isomer having a purity, as discussed above, of 95 wt% or more, 97 wt% or more, or 99 wt% or more, as discussed above. For example, the purified compound of Formula (I) can include a compound of Structure (IA), (IB), (IC), (ID), (II), or (III) (above) having a purity of 95 wt% or more, 97 wt% or more, or 99 wt% or more.

Alternatively, the purified compound of Formula (I) can include a mixture of isomers, each having a structure according to Formula (I), where the amount of impurity (i.e., compounds or other contaminants, exclusive of adjuvants as discussed above) is 5 wt% or less, 3 wt% or less, or 1 wt% or less. For example, the purified compound of Formula (I) can be an isomeric mixture of compounds of Structure (I), where the ratio of the amounts of the two isomers is approximately 1:1, and the combined amount of the two isomers is 95 wt% or more, 97 wt% or more, or 99 wt% or more.

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"DCE" means dichloroethane.

"DIAD" means diisopropylazodicarboxylate.

"DMSO" means dimethylsulfoxide.

"DPPA" means diphenylphosphoryl azide.

"EDCI" means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

"Et" means ethyl.

"EtOH" mean ethanol.

"HOBt" means 1-hydroxybenzotriazole.

"LDA" means lithium diisopropyl amide.

"Me" means methyl.

"MeOH" means methanol.

"MsCl" means mesyl chloride or methanesulfonyl chloride.

"Ms" means mesyl or methanesulfonyl.

"Mammal" means humans and other mammalian animals.

"Patient" includes both human and animals.

"PS-DIEA" means diisopropylethyl amine functionalized polystyrene.

"PS-isocyanate" means isocyanate functionalized polystyrene.

5 "PS-trisamine" means trisamine functionalized polystyrene.

"RT" means room temperature.

"TFAA" means trifluoroacetic anhydride.

"THF" means tetrahydrofuran.

"DMF" means N,N-dimethylformamide

10 "Cbz" means benzyloxycarbonyl

"Boc" means *tert*-butoxycarbonyl

"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
15 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. "Alkyl" may be unsubstituted
20 or optionally 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, -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, carboxy and -C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl,
25 ethyl, n-propyl, isopropyl and t-butyl.

"Alkylene" means a difunctional group obtained by removal of a hydrogen atom from an alkyl group that is defined above. Non-limiting examples of alkylene include methylene, ethylene and propylene.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one
30 carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 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 alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. "Alkenyl" may be unsubstituted or optionally substituted by one or more
5 substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, alkoxy and $-S(alkyl)$. Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkenylene" means a difunctional group obtained by removal of a hydrogen
10 from an alkenyl group that is defined above. Non-limiting examples of alkenylene include $-CH=CH-$, $-C(CH_3)=CH-$, and $-CH=CHCH_2-$.

"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
15 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,
20 2-butyne and 3-methylbutynyl. "Alkynyl" may be unsubstituted or optionally 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.

"Alkynylene" means a difunctional group obtained by removal of a hydrogen
25 from an alkynyl group that is defined above. Non-limiting examples of alkenylene include $-C\equiv C-$ and $-CH_2C\equiv C-$.

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

“Heteroaryl” means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, or 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. In some embodiments, 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, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxaliny, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term “heteroaryl” also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl, indazolyl, and the like, in which there is at least one aromatic ring.

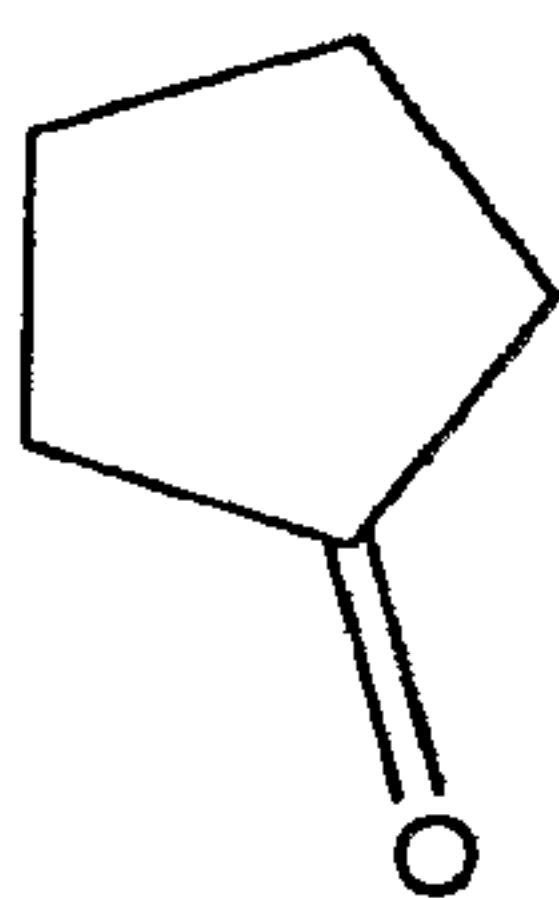
“Aralkyl”, “arylalkyl”, or “-alkylene-aryl” means an aryl-alkyl- group in which the aryl and alkyl are as previously described. In some embodiments, aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to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

“Alkylaryl” means an alkyl-aryl- group in which the alkyl and aryl are as previously described. In some embodiments, 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.

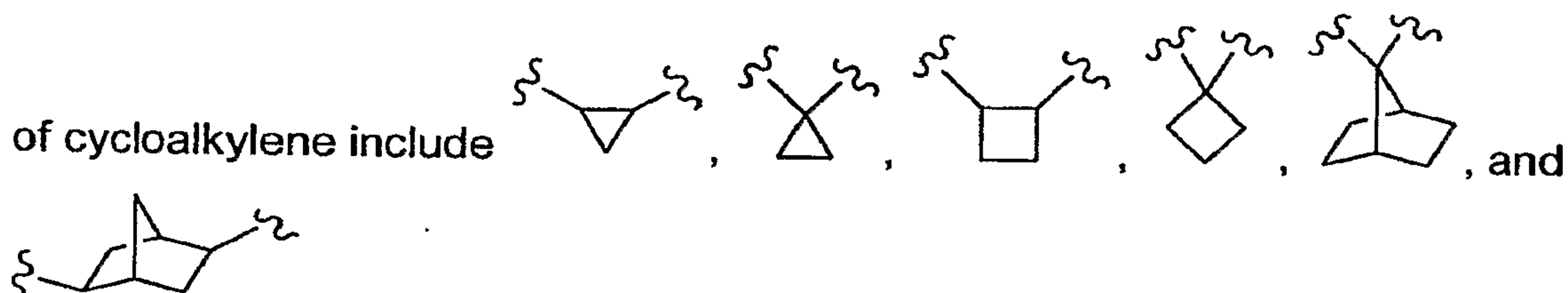
“Cycloalkyl” means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The

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, as well as partially saturated species such as, for example, indanyl, tetrahydronaphthyl and the like.

"Cycloalkyl" can also mean a cycloalkyl wherein a single moiety (e.g., carbonyl) can simultaneously replace two available hydrogens on the same carbon atom on a ring system. A non-limiting example of such moiety is:



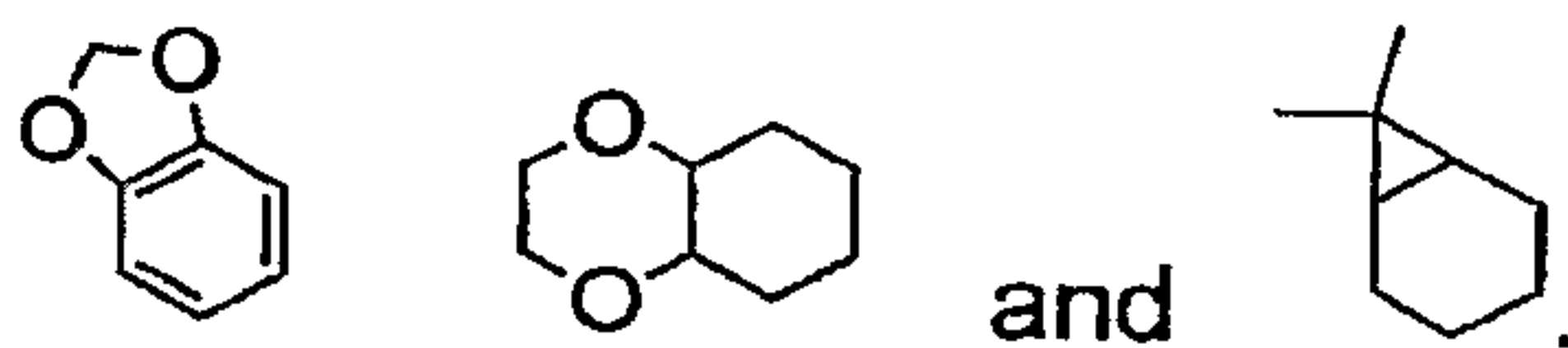
"Cycloalkylene" means a difunctional group obtained by removal of a hydrogen atom from a cycloalkyl group that is defined above. Non-limiting examples



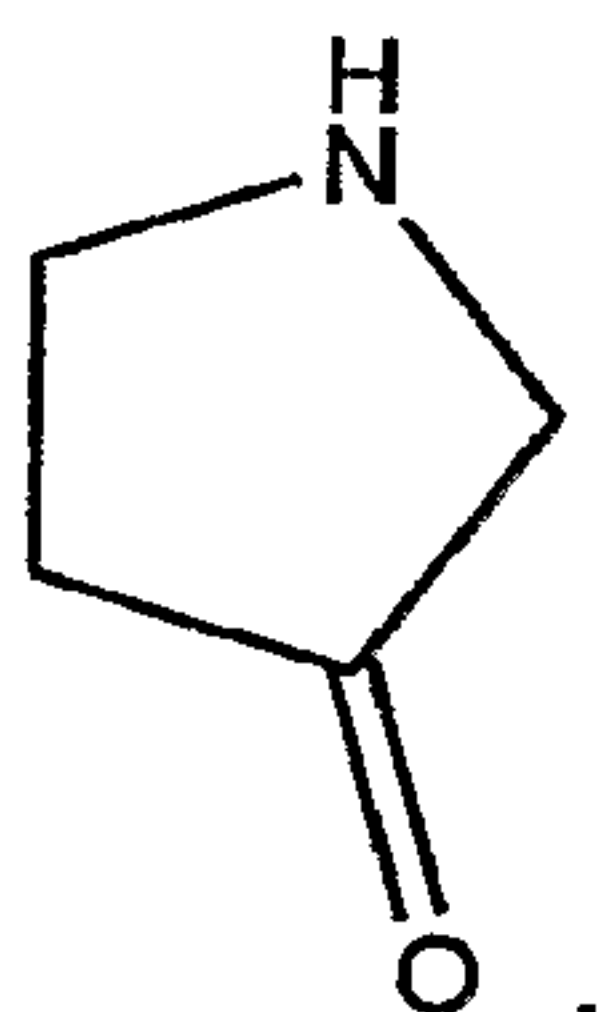
"Halogen" or "halo" means fluorine, chlorine, bromine, or iodine. In some embodiments, halogen is selected from fluorine, chlorine and bromine.

"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 alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, 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, $-C(=N-CN)-NH_2$, $-C(=NH)-NH_2$, $-C(=NH)-NH(alkyl)$, Y_1Y_2N- , $Y_1Y_2N-alkyl-$, $Y_1Y_2NC(O)-$, $Y_1Y_2NSO_2-$ and $-SO_2NY_1Y_2$,

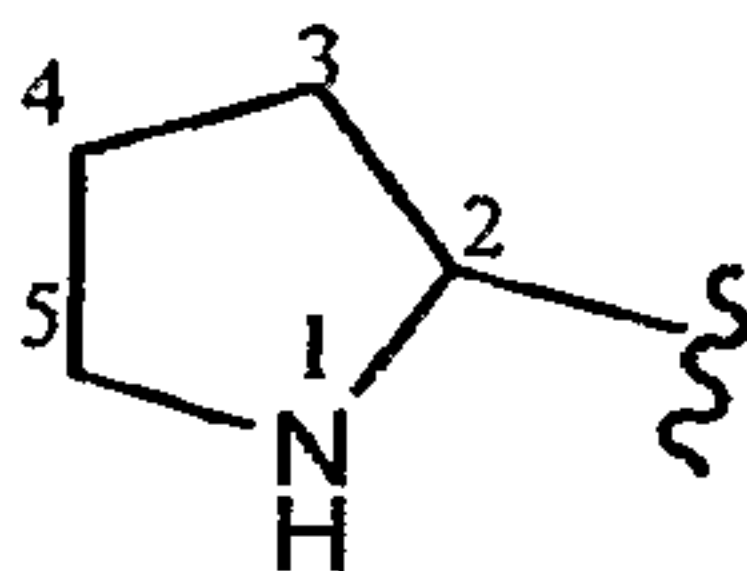
wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylenedioxy, ethylenedioxy, $-C(CH_3)_2-$ and the like which form moieties such as, for example:



"Heterocyclyl" or "Heterocycloalkyl" 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 protections 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, lactam, lactone, and the like. "Heterocyclyl" can also mean a heterocyclyl wherein a single moiety (e.g., carbonyl) can simultaneously replace two available hydrogens on the same carbon atom on a ring system. Example of such moiety is pyrrolidone:

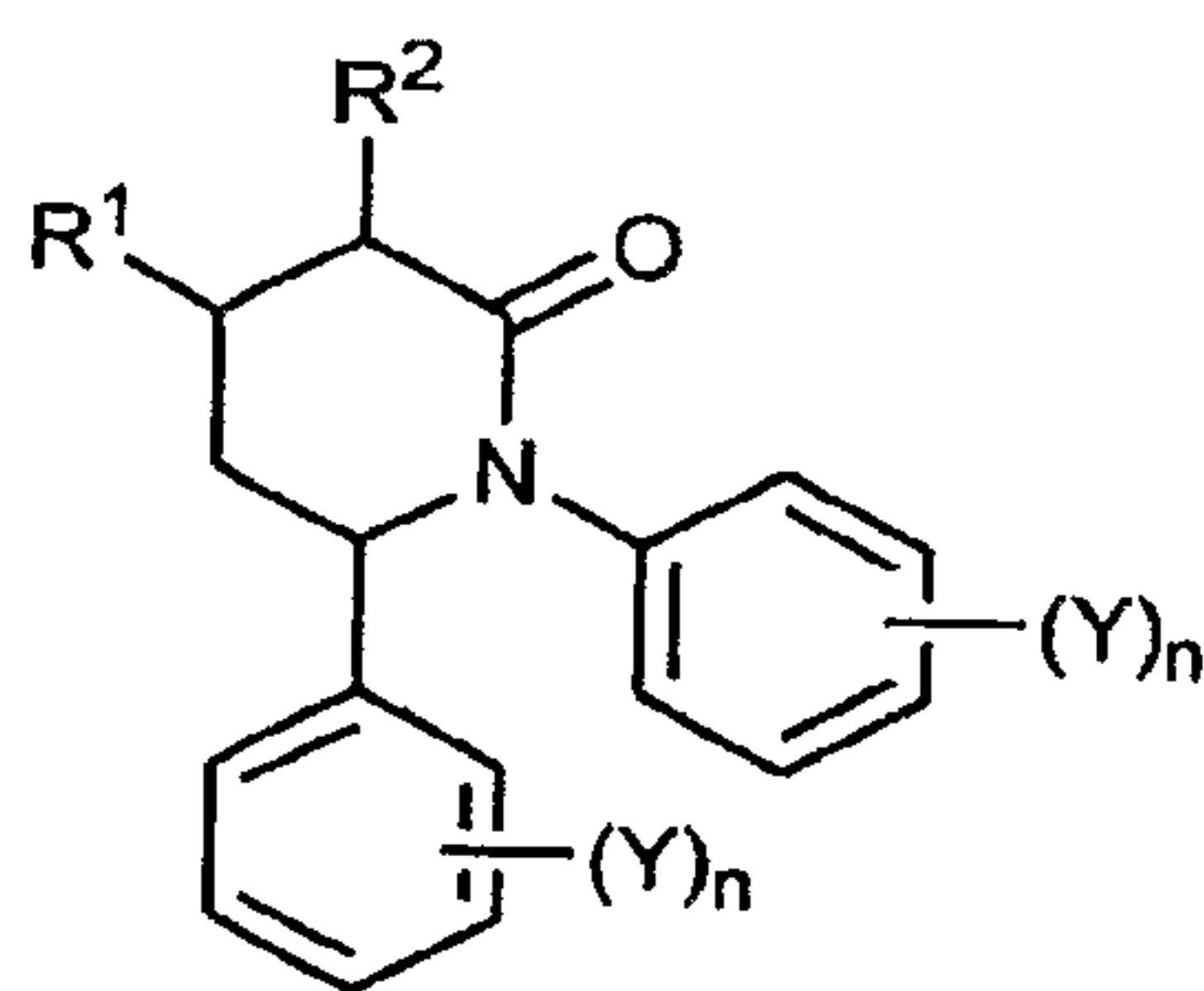


It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:

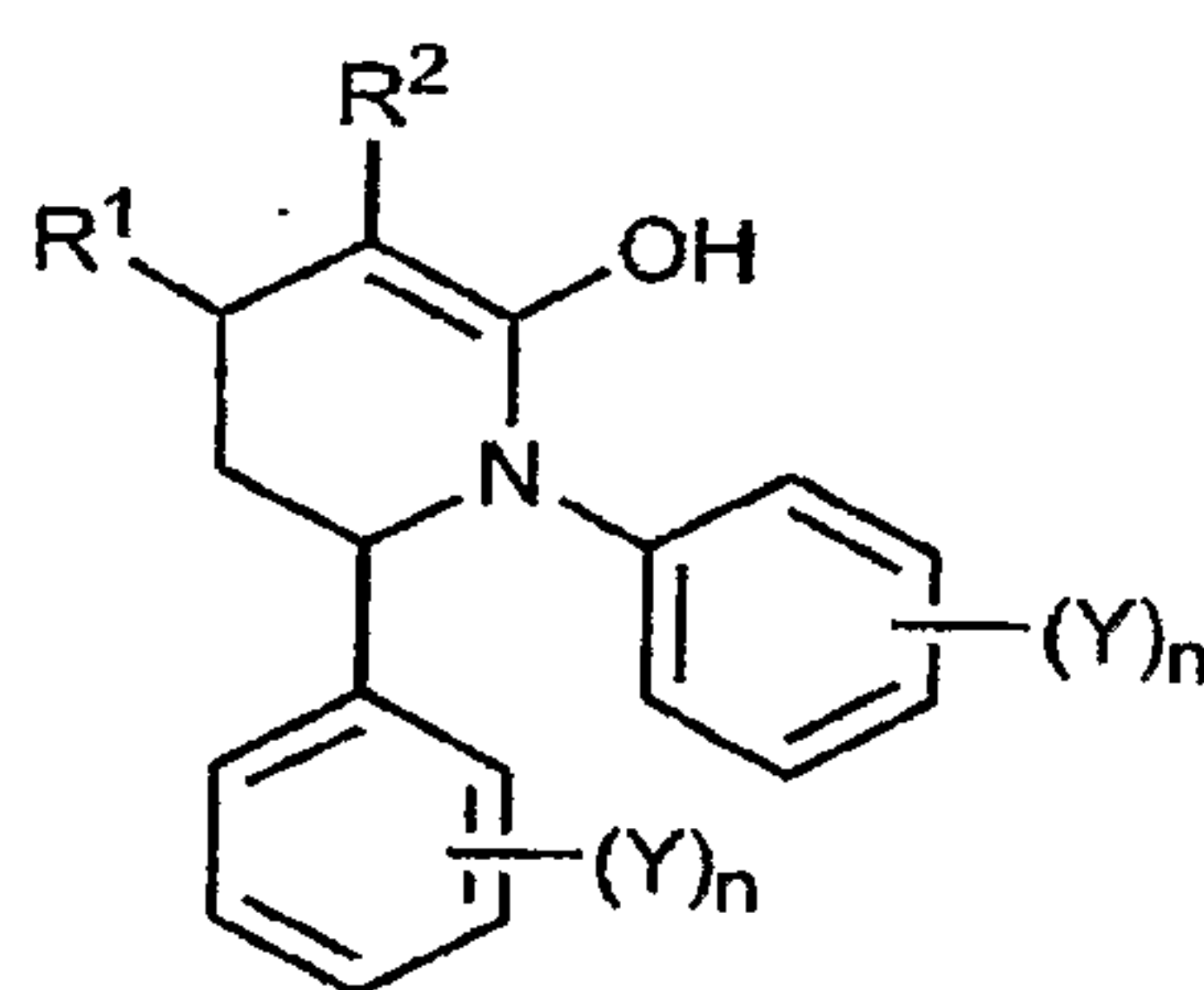


there is no -OH attached directly to carbons marked 2 and 5.

It should also be noted that tautomeric forms of the compounds of Formula (I), including salts, solvates, esters, and prodrugs thereof are also contemplated herein. For example, the moieties:



and



(e.g., when R^3 is H)

are considered equivalent in certain embodiments of this invention.

"Heterocyclalkyl" means a heterocyclalkyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heterocyclalkyls include piperidinylmethyl, piperazinylmethyl and the like.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. In some embodiments, 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.

"Heteroaralkyl", "Heteroarylalkyl" or "-alkylene-heteroaryl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. In some embodiments, 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.

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

5 "Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. In some embodiments, acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

10 "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.

15 "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.

20 "Aralkyloxy" 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.

"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.

0 "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.

“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.

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

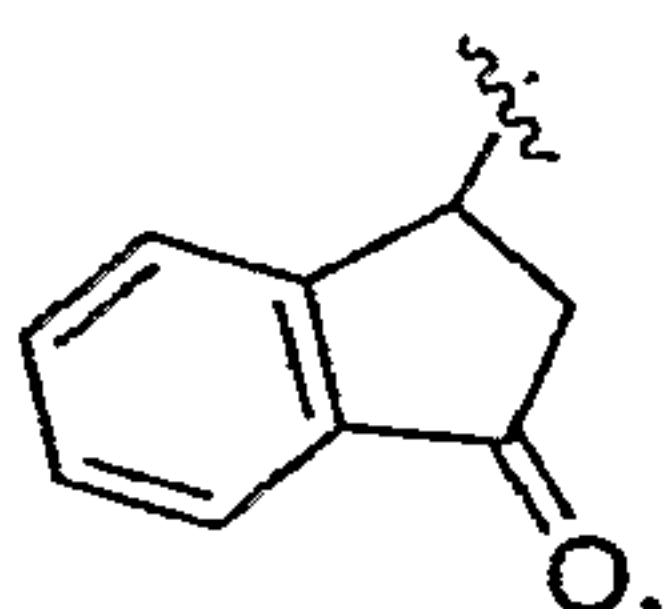
“Aralkoxycarbonyl” means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

10 “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.

15 “Benzo-fused-cycloalkyl” or “Benzocycloalkyl” means a phenyl ring fused to a cycloalkyl, as defined above, wherein said benzo-fused-cycloalkyl or benzocycloalkyl, can be optionally substituted with 1 to 3 “ring system substituents” as defined above. Non-limiting examples of suitable benzo-fused-cycloalkyl or benzocycloalkyl groups include the following:

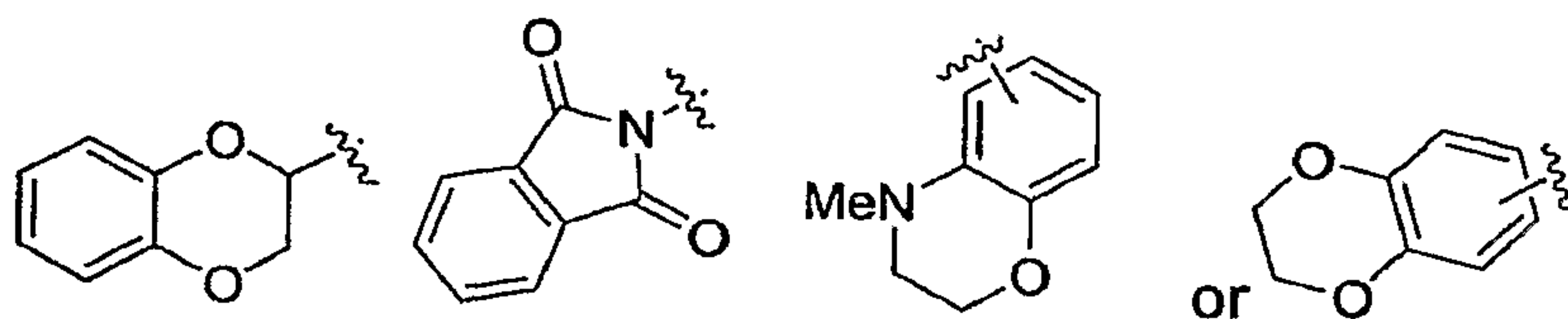
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“Benzo-fused-heterocycloalkyl”, “benzo-fused-heterocyclyl” or “benzoheterocyclyl” means a phenyl ring fused to a heterocycloalkyl or heterocyclyl ring, as defined above, wherein said benzo-fused-heterocycloalkyl, benzo-fused-heterocyclyl or benzoheterocyclyl can be optionally substituted with 1 to 3 “ring system substituents” as defined above. Non-limiting examples of suitable benzo-fused-heterocycloalkyl, benzo-fused-heterocyclyl or benzoheterocyclyl groups include the following:

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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 robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

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

The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being isolated from a synthetic process or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan, in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the sufficient number of hydrogen atom(s) 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, heterocyclyl, R^2 , etc.) occurs more than one time in any constituent or in Formula (I), its definition on each occurrence is independent of its definition at every other occurrence.

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. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 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. The term "prodrug" means a compound (e.g., a drug precursor) that is transformed *in vivo* to yield a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, 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 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 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-C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂-C₃)alkyl, and the like.

5 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-C₆)alkoxycarbonyloxymethyl, N-(C₁-C₆)alkoxycarbonylaminomethyl, succinoyl, (C₁-
10 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 carbohydrate), and the like.

15 If a compound of Formula (I) incorporates an amine functional group, 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
20 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.

25 One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In
30 certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting

examples of suitable solvates include ethanulates, methanulates, and the like.

"Hydrate" is a solvate wherein the solvent molecule is H₂O.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the above-noted diseases and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

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 I 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 P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use*. (2002) Zurich: Wiley-VCH; 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.

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 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 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.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for

example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C₁₋₄alkyl, or C₁₋₄alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4)
5 phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C₁₋₂₀ alcohol or reactive derivative thereof, or by a 2,3-di (C₆₋₂₄)acyl glycerol.

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

The compounds of Formula (I) may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of Formula (I) as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the
15 present invention embraces all geometric and positional isomers. 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.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those
20 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 diastereomeric 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
25 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.

It is also possible that the compounds of Formula (I) may exist in different
30 tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including 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, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). (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. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.).

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

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 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.

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

The compounds according to the invention have pharmacological properties; in particular, the compounds of Formula I can be CB1 modulators.

The term "pharmaceutical composition" is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage unit is an oral dosage unit such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

As used herein, the term "pharmaceutical combination" means a combination of two or more pharmaceutical compounds. Such combination can be in any form.

The term "pharmaceutical combination" is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". The bulk composition is material that has not yet been formed into individual dosage units. An illustrative

dosage unit is an oral dosage unit such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units. A pharmaceutical combination can also include two or more pharmaceutical compounds administered separately, e.g., in two or more separate dosage units.

The compounds of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, can be administered in any suitable form, e.g., alone, or in combination with a pharmaceutically acceptable carrier, excipient or diluent in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, can be administered orally or parenterally, including intravenous, intramuscular, interperitoneal, subcutaneous, rectal, or topical routes of administration.

Pharmaceutical compositions comprising at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof can be in a form suitable for oral administration, e.g., as tablets, troches, capsules, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, syrups, or elixirs. Oral compositions may be prepared by any conventional pharmaceutical method, and may also contain sweetening agents, flavoring agents, coloring agents, and preserving agents.

The amount of compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof, administered to a patient can be determined by a physician based on the age, weight, and response of the patient, as well as by the severity of the condition treated. For example, the amount of compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or ester thereof, administered to the patient can range from about 0.1 mg/kg body weight per day to about 60 mg/kg/d. In some embodiments, the dose is about 0.5 mg/kg/d to about 40 mg/kg/d.

The compounds of Formula (I) may also be used in conjunction with an additional therapeutic agent or agents for the treatment of the diseases, conditions and/or disorders described herein. Thus, in another embodiment, methods of

treatment that include administering compounds of the present invention in combination with other therapeutic agents are also provided.

Suitable other therapeutic agents that may be used in combination with compounds of Formula (I) include anti-obesity agents such as apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, 11 β -hydroxy steroid dehydrogenase-1 (11 β -HSD type 1) inhibitors, peptide YY₃₋₃₆ or analogs thereof, MCR-4 agonists, cholecystokinin-A (CCK-A) agonists, monoamine reuptake inhibitors (e.g., sibutramine), sympathomimetic agents, β 3 adrenergic receptor agonists, dopamine agonists (e.g., bromocriptine), melanocyte-stimulating hormone receptor analogs, 5HT_{2c} agonists, melanin concentrating hormone antagonists, leptin (the OB protein), leptin analogs, leptin receptor agonists, galanin antagonists, lipase inhibitors (such as tetrahydrolipstatin, i.e. orlistat), anorectic agents (such as a bombesin agonist), neuropeptide-Y antagonists (e.g., NPY Y5 receptor antagonists, such as the spiro compounds described in U.S. Patent Nos. 6,566,367; 6,649,624; 6,638,942; 6,605,720; 6,495,559; 6,462,053; 6,388,077; 6,335,345; 6,326,375, and 6,566,367; U.S. Publication Nos. 2002/0151456, 2003/036652, 2004/192705, 2003/036652, 2004/072847, and 2005/033048; and PCT Publication No. WO 03/082190), thyromimetic agents, dehydroepiandrosterone or an analog thereof, glucocorticoid receptor agonists or antagonists, orexin receptor antagonists, glucagon-like peptide-1 receptor agonists, ciliary neurotrophic factors (such as Axokine.TM. available from Regeneron Pharmaceuticals, Inc., Tarrytown, N.Y. and Procter & Gamble Company, Cincinnati, Ohio), human agouti-related proteins (AGRP), ghrelin receptor antagonists, histamine 3 receptor antagonists or inverse agonists, neuromedin U receptor agonists and the like. Other anti-obesity agents are well known or would be readily apparent to one of ordinary skill in the art.

In one embodiment, compounds of Formula (I) are combined with anti-obesity agents selected from the group consisting of orlistat, sibutramine, bromocriptine, ephedrine, leptin, pseudoephedrine, PYY₃₋₃₆ or an analog thereof, and 2-oxo-N-(5-phenylpyrazinyl)spiro-[isobenzofuran-1(3H), 4'-piperidine]-1'-carboxamide.

Representative anti-obesity agents for use in the combinations, pharmaceutical compositions, and methods of the present invention can be prepared using methods known in the art, for example, sibutramine can be prepared as

described in U.S. 4,929,629; bromocriptine can be prepared as described in U.S. 3,752,814 and U.S. 3,752,888; orlistat can be prepared as described in U.S. 5,274,143; U.S. 5,420,305; U.S. 5,540,917; and U.S. 5,643,874; PYY₃₋₃₆ (including analogs) can be prepared as described in U.S. Publication No. 2002/0141985 and

5 WO 03/027637; and the NPY Y5 receptor antagonist 2-oxo-N-(5-phenyl-pyrazinyl)spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide can be prepared as described in U.S. Publication No. 2002/0151456. Other useful NPY Y5 receptor antagonists include those described in PCT Publication No. 03/082190, such as 3-

10 oxo-N-(5-phenyl-2-pyrazinyl)-spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide; 3-oxo-N-(7-trifluoromethylpyrido[3,2-b]pyridin-2-yl)-spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide; N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro-isobenzofuran-1(3H),[4'-piperidine]-1'-carboxamide; trans-3'-

15 oxo-N-(5-phenyl-2-pyrimidinyl)]spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide; trans-3'-oxo-N-[1-(3-quinolyl)-4-imidazolyl]spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide; trans-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[4-

20 azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; trans-N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; trans-N-[5-(2-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-

25 azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; trans-N-[1-(3,5-difluorophenyl)-4-imidazolyl]-3-oxospiro[7-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; trans-3-oxo-N-(1-phenyl-4-pyrazolyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; trans-N-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; trans-3-oxo-N--

(1-phenyl-3-pyrazolyl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; trans-3-oxo-N-(2-phenyl-1,2,3-triazol-4-yl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; and pharmaceutically acceptable salts and esters thereof. All of the above recited patents and publications are incorporated herein by reference.

Other suitable therapeutic agents that may be administered in combination

0 with one or more compounds of Formula (I) include therapeutic agents designed to treat tobacco abuse (e.g., nicotine receptor partial agonists, bupropion hydrochloride (also known under the tradename ZybanTM) and nicotine replacement therapies),

agents to treat erectile dysfunction (e.g., dopaminergic agents, such as apomorphine), ADD/ADHD agents (e.g., RitalinTM, StratteraTM, ConcertaTM and AdderallTM), and agents to treat alcoholism, such as opioid antagonists (e.g., naltrexone (also known under the tradename ReViaTM) and nalmefene), disulfiram (also known under the tradename AntabuseTM), and acamprosate (also known under the tradename CampralTM)). In addition, agents for reducing alcohol withdrawal symptoms may also be co-administered, such as benzodiazepines, beta-blockers, clonidine, carbamazepine, pregabalin, and gabapentin (NeurontinTM).

Other therapeutic agents that may administered in combination with one or more compounds of Formula (I) include antihypertensive agents, anti-inflammatory agents (e.g., COX-2 inhibitors), antidepressants (e.g., fluoxetine hydrochloride (ProzacTM)), cognitive improvement agents (e.g., donepezil hydrochloride (AirceptTM) and other acetylcholinesterase inhibitors), neuroprotective agents (e.g., memantine), antipsychotic medications (e.g., ziprasidone (GeodonTM), risperidone (RisperdalTM), and olanzapine (ZyprexaTM)), insulin and insulin analogs (e.g., LysPro insulin), GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)-NH₂, sulfonylureas and analogs thereof (e.g., chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, GlypizideTM, glimepiride, repaglinide, meglitinide; biguanides: metformin, phenformin, buformin), α 2-antagonists and imidazolines (e.g., midaglizole, isaglidole, deriglidole, idazoxan, efaroxxan, fluparoxan), other insulin secretagogues (e.g., linoglitride, A-4166), glitazones (e.g., ciglitazone, ActoseTM, pioglitazone, englitazone, troglitazone, darglitazone, AvandiaTM, BRL49653), fatty acid oxidation inhibitors (e.g., clomoxir, etomoxir), α -glucosidase inhibitors (e.g., acarbose, miglitol, emiglitate, voglibose, MDL-25,637, camiglibose, MDL-73,945), β -agonists (e.g., BRL 35135, BRL 37344, RO 16-8714, ICI D7114, CL 316,243), phosphodiesterase inhibitors (e.g., L-386,398), lipid-lowering agents (e.g., benfluorex, fenfluramine), vanadate and vanadium complexes (e.g., NaglivanTM) and peroxovanadium complexes, amylin antagonists, glucagon antagonists, gluconeogenesis inhibitors, somatostatin analogs, antilipolytic agents (e.g., nicotinic acid, acipimox, WAG 994, pramlintide (SymlinTM), AC 2993, nateglinide, aldose reductase inhibitors (e.g., zopolrestat), glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, sodium-

hydrogen exchanger type 1 (NHE-1) inhibitors and/or cholesterol lowering compounds.

Non-limiting examples of cholesterol lowering compounds suitable for administration in combination with one or more compounds of Formula (I) include
5 cholesterol biosynthesis inhibitors, cholesterol absorption inhibitors, HMG-CoA reductase inhibitors, HMG-CoA synthase inhibitors, HMG-CoA reductase or synthase gene expression inhibitors, CETP inhibitors, bile acid sequesterants, fibrates, ACAT inhibitors, squalene synthetase inhibitors, squalene epoxidase inhibitors, sterol biosynthesis inhibitors, nicotinic acid derivatives, bile acid
10 sequestrants, inorganic cholesterol sequestrants, AcylCoA:Cholesterol O-acyltransferase inhibitors, cholesteryl ester transfer protein inhibitors, fish oils containing Omega 3 fatty acids, natural water soluble fibers, plant stanols and/or fatty acid esters of plant stanols, low-density lipoprotein receptor activators, anti-oxidants and niacin.

15 A non-limiting list of cholesterol lowering compounds suitable for administration with one or more compounds of Formula (I) include HMG CoA reductase inhibitor compounds such as lovastatin (for example MEVACOR® which is available from Merck & Co.), simvastatin (for example ZOCOR® which is available from Merck & Co.), pravastatin (for example PRAVACHOL® which is available from
20 Bristol Meyers Squibb), atorvastatin, fluvastatin, cerivastatin, CI-981, rivastatin (sodium 7-(4-fluorophenyl)-2,6-diisopropyl-5-methoxymethylpyridin-3-yl)-3,5-dihydroxy-6-heptanoate), rosuvastatin calcium (CRESTOR® from AstraZeneca Pharmaceuticals), pitavastatin (such as NK-104 of Negma Kowa of Japan); HMG CoA synthetase inhibitors, for example L-659,699 ((E,E)-11-[3'R-(hydroxy-methyl)-4'-oxo-2'R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid); squalene synthesis
25 inhibitors, for example squalestatin 1; squalene epoxidase inhibitors, for example, NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride); sterol biosynthesis inhibitors such as DMP-565; nicotinic acid derivatives (e.g., compounds comprising a pyridine-3-carboxylate structure or a pyrazine-2-carboxylate structure, including acid forms,
30 salts, esters, zwitterions and tautomers) such as niceritrol, nicofuranose and acipimox (5-methyl pyrazine-2-carboxylic acid 4-oxide); clofibrate; gemfibrozil; bile

acid sequestrants such as cholestyramine (a styrene-divinylbenzene copolymer containing quaternary ammonium cationic groups capable of binding bile acids, such as QUESTRAN® or QUESTRAN LIGHT® cholestyramine which are available from Bristol-Myers Squibb), colestipol (a copolymer of diethylenetriamine and 1-chloro-
5 2,3-epoxypropane, such as COLESTID® tablets which are available from Pharmacia), colesevelam hydrochloride (such as WelChol® Tablets (poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide) which are available from Sankyo), water soluble derivatives such as 3,3-ioene, N-(cycloalkyl) alkylamines and
10 poliglusam, insoluble quaternized polystyrenes, saponins and mixtures thereof; inorganic cholesterol sequestrants such as bismuth salicylate plus montmorillonite clay, aluminum hydroxide and calcium carbonate antacids; ileal bile acid transport ("IBAT") inhibitors (or apical sodium co-dependent bile acid transport ("ASBT") inhibitors) such as benzothiepine, for example the therapeutic compounds
15 comprising a 2,3,4,5-tetrahydro-1-benzothiepine 1,1-dioxide structure such as are disclosed in PCT Patent Application WO 00/38727 which is incorporated herein by reference; AcylCoA:Cholesterol O-acyltransferase ("ACAT") Inhibitors such as avasimibe ([2,4,6-tris(1-methylethyl)phenyl]acetyl)sulfamic acid, 2,6-bis(1-methylethyl)phenyl ester, formerly known as CI-1011), HL-004, lecimibide (DuP-128)
20 and CL-277082 (N-(2,4-difluorophenyl)-N-[[4-(2,2-dimethylpropyl)phenyl]methyl]-N-heptylurea), and the compounds described in P. Chang et al., "Current, New and Future Treatments in Dyslipidaemia and Atherosclerosis", Drugs 2000 Jul;60(1): 55-93, which is incorporated by reference herein; Cholesteryl Ester Transfer Protein ("CETP") Inhibitors such as those disclosed in PCT Patent Application No. WO
25 00/38721 and U.S. Patent No. 6,147,090, which are incorporated herein by reference; probucol or derivatives thereof, such as AGI-1067 and other derivatives disclosed in U.S. Patents Nos. 6,121,319 and 6,147,250, herein incorporated by reference; low-density lipoprotein (LDL) receptor activators such as HOE-402, an imidazolidinyl-pyrimidine derivative that directly stimulates LDL receptor activity,
30 described in M. Huettinger et al., "Hypolipidemic activity of HOE-402 is Mediated by Stimulation of the LDL Receptor Pathway", Arterioscler. Thromb. 1993; 13:1005-12, herein incorporated by reference; fish oils containing Omega 3 fatty acids (3-PUFA);

natural water soluble fibers, such as psyllium, guar, oat and pectin; plant stanols and/or fatty acid esters of plant stanols, such as sitostanol ester used in BENECOL® margarine; and the substituted azetidinone or substituted β -lactam sterol absorption inhibitors.

5 As used herein, "sterol absorption inhibitor" means a compound capable of inhibiting the absorption of one or more sterols, including but not limited to cholesterol, phytosterols (such as sitosterol, campesterol, stigmasterol and avenosterol), 5α -stanols (such as cholestanol, 5α -campestanol, 5α -sitostanol), and/or mixtures thereof, when administered in a therapeutically effective (sterol
10 and/or 5α -stanol absorption inhibiting) amount to a mammal or human. Particularly useful sterol absorption inhibitors include hydroxy-substituted azetidinone compounds and substituted β -lactam compounds, for example those disclosed in U.S. Patents Nos. 5,767,115, 5,624,920, 5,668,990, 5,656,624 and 5,688,787, which are herein incorporated by reference in their entirety. These patents, respectively,
15 disclose hydroxy-substituted azetidinone compounds and substituted β -lactam compounds useful for lowering cholesterol and/or in inhibiting the formation of cholesterol-containing lesions in mammalian arterial walls. U.S. Patent No. 5,756,470, U.S. Patent Application No. 2002/0137690, U.S. Patent Application No. 2002/0137689 and PCT Patent Application No. WO 2002/066464 (each of which is
20 herein incorporated by reference in its entirety) disclose sugar-substituted azetidinones and amino acid substituted azetidinones useful for preventing or treating atherosclerosis and reducing plasma cholesterol levels.

One or more compounds of Formula (I) may also be administered in combination with a naturally occurring compound that acts to lower plasma
25 cholesterol levels. Such naturally occurring compounds are commonly called nutraceuticals and include, for example, garlic extract, Hoodia plant extracts, and niacin.

The dosage of the additional therapeutic agent is generally dependent upon a number of factors including the health of the subject being treated, the extent of
30 treatment desired, the nature and kind of concurrent therapy, if any, and the frequency of treatment and the nature of the effect desired. In one embodiment the dosage range of the additional therapeutic agent is in the range of from about 0.001

mg to about 100 mg per kilogram body weight of the individual per day. In another embodiment, the dosage range of the additional therapeutic agent is from about 0.1 mg to about 10 mg per kilogram body weight of the individual per day. However, some variability in the general dosage range may also be required depending upon the age and weight of the subject being treated, the intended route of administration, the particular additional therapeutic agent being administered and the like. The determination of dosage ranges and optimal dosages for a particular patient is also well within the ability of one of ordinary skill in the art.

According to the methods of the invention, one or more compounds Formula (I), or one or more compounds of Formula (I) in combination with one or more additional therapeutic agents is administered to a subject in need of such treatment, for example in the form of a pharmaceutical composition. When one or more compounds of Formula (I) is administered with one or more additional therapeutic agents, the compound of the present invention and at least one other therapeutic agent (e.g., anti-obesity agent, nicotine receptor partial agonist, dopaminergic agent, or opioid antagonist) may be administered either separately or in the pharmaceutical composition comprising both. In one embodiment, such administration is oral. In other embodiments, such administration is parenteral or transdermal.

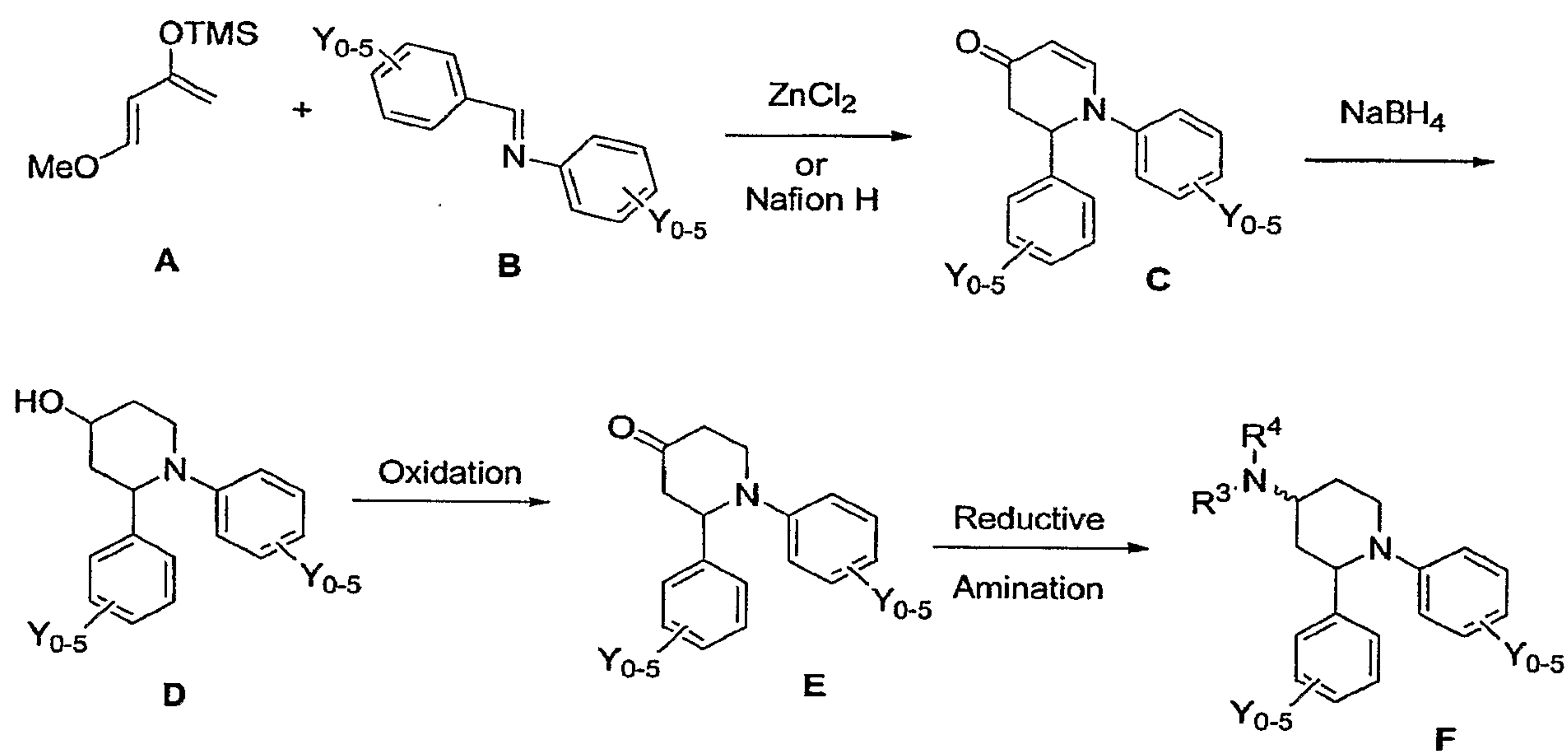
When a combination of one or more compounds of Formula (I) and at least one other therapeutic agent are administered together, such administration can be sequential in time or simultaneous. For sequential administration, one or more compounds of Formula (I) and the additional therapeutic agent can be administered in any order. In one embodiment, such administration is oral. In another embodiment, such administration is oral and simultaneous. When one or more compounds of Formula (I) and one or more additional therapeutic agents are administered sequentially, the administration of each can be by the same or by different methods.

In one embodiment, one or more compounds of Formula (I) or a combination of one or more compounds of Formula (I) and at least one additional therapeutic agent (referred to herein as a "combination") is administered in the form of a pharmaceutical composition. Accordingly, one or more compounds of Formula (I) or a combination can be administered to a patient separately or together in any

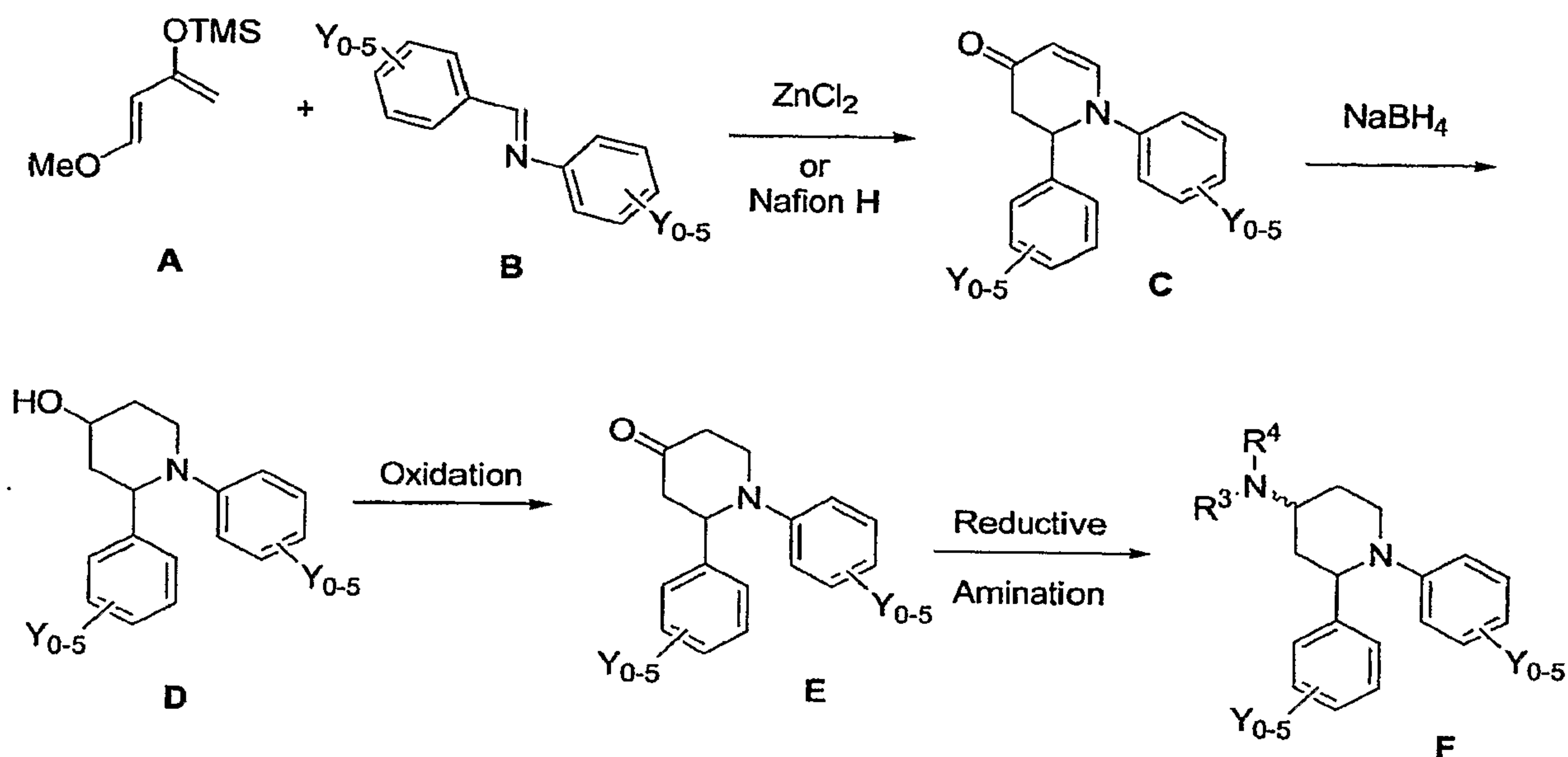
conventional oral, rectal, transdermal, parenteral, (for example, intravenous, intramuscular, or subcutaneous) intracisternal, intravaginal, intraperitoneal, intravesical, local (for example, powder, ointment or drop), or buccal, or nasal, dosage form.

5 Examples

The synthesis of 2-aryl-4-amino-N-aryl-piperidines according to structural Formula (IA) is shown in **Scheme 1**. Diene **A** and imine **B** are reacted in the presence of a promoter (e.g., ZnCl_2 or Nafion H) to furnish the enone **C**. The enone **C** can be reduced (e.g., with NaBH_4) to the alcohol **D**. The alcohol **D** can be oxidized by methods known in the art to the ketone **E**. Reductive amination of the ketone **E** with various amines furnishes the desired 4-amino-2-aryl-N-aryl-piperidines **F**.



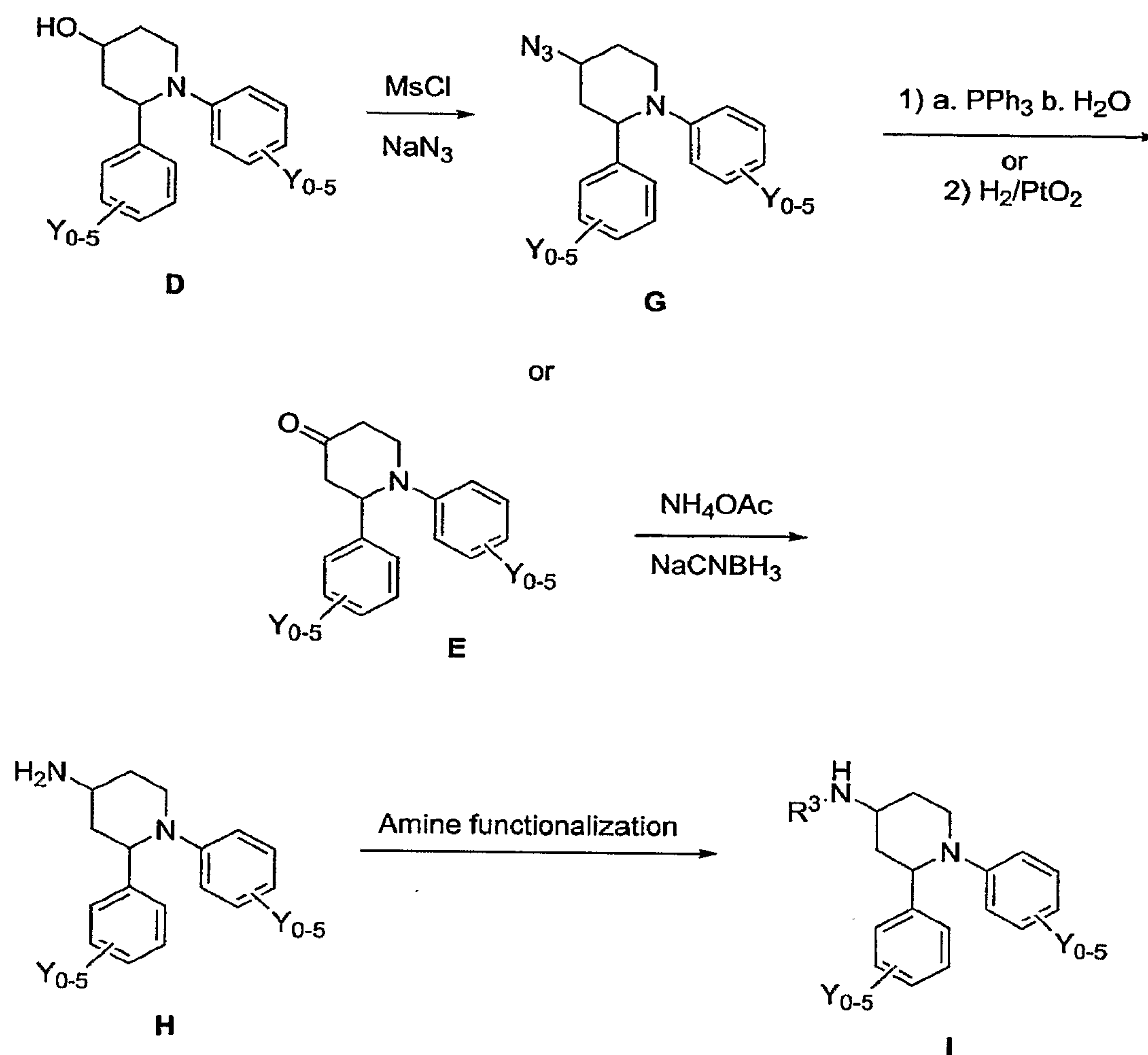
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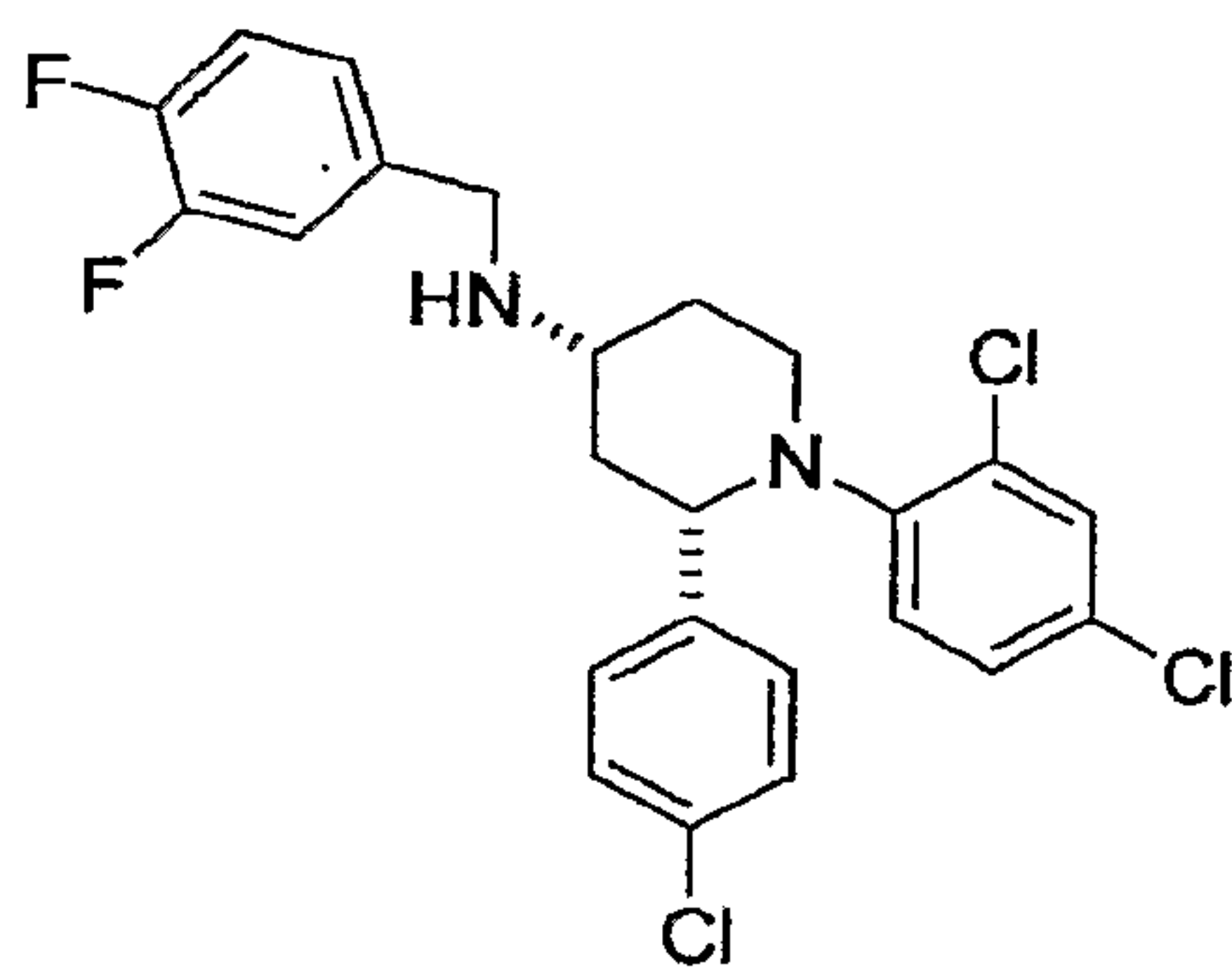
Scheme 1

Alcohol **D** can be converted into the azide **G** using conditions known in the art (e.g., MsCl and NaN_3). The azide **G** can be reduced to the primary amine **H** (e.g., step-wise with PPh_3 and H_2O , or with H_2/PtO_2). Alternatively, amine **H** can be prepared via reductive amination of ketone **E** with, e.g., $\text{NH}_4\text{OAc}/\text{NaCNBH}_3$. The primary amine in **H** can be functionalized under conditions known in the art.

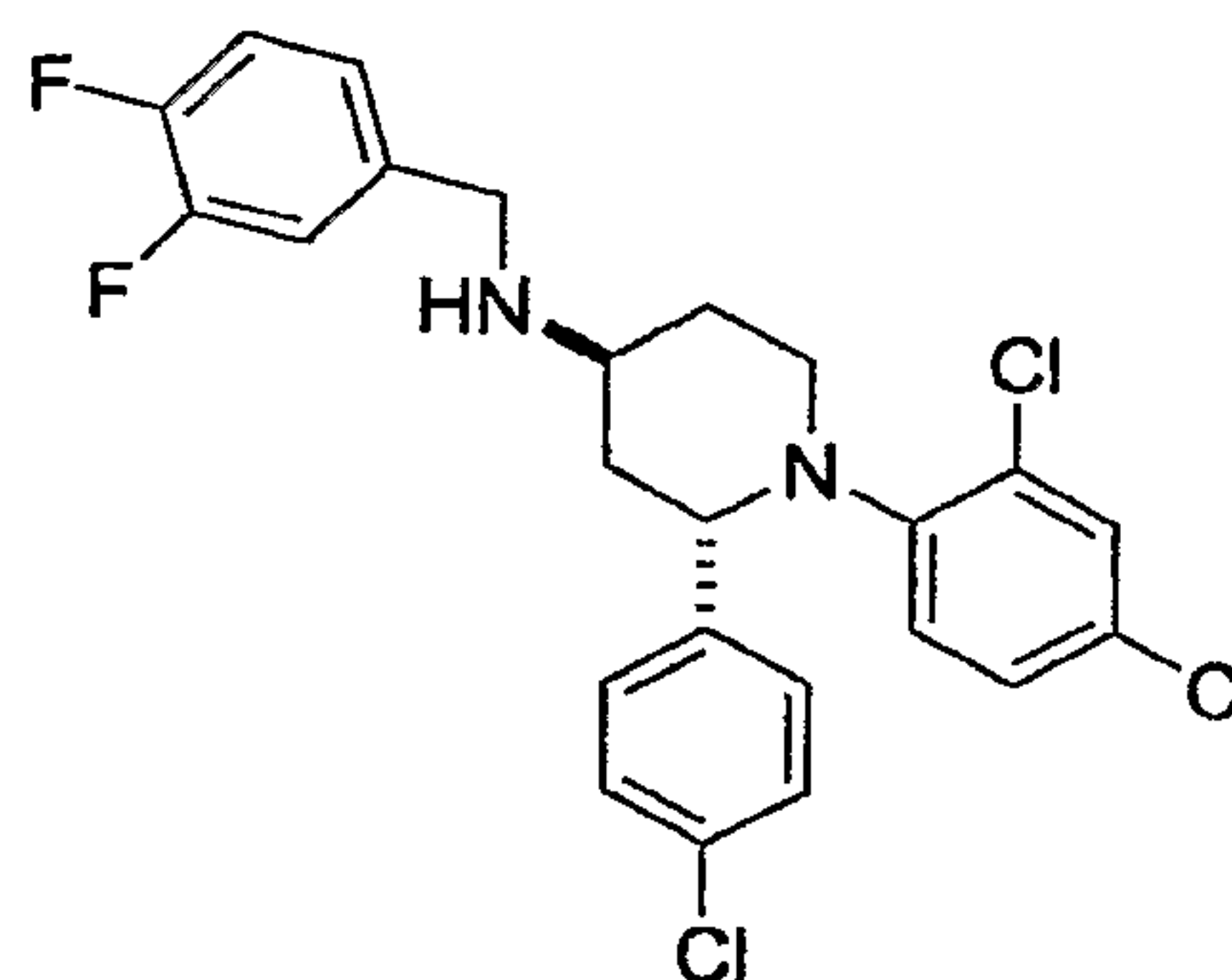
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 $\text{R}^3 = \text{e.g., } -\text{SO}_2\text{R}, \text{SO}_2\text{NR}_2, \text{C(O)R}, \text{C(O)NR}_2$

Preparation of Examples 1 and 2

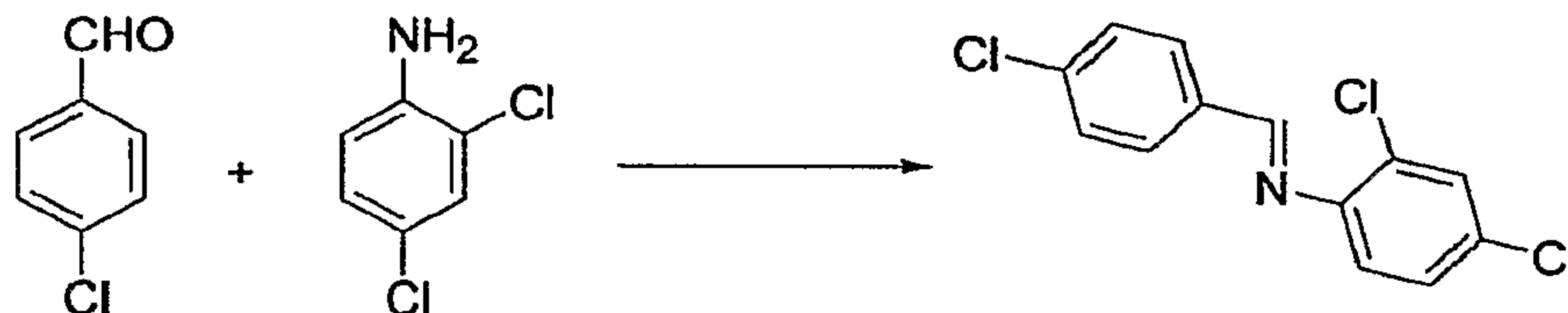


Example 1

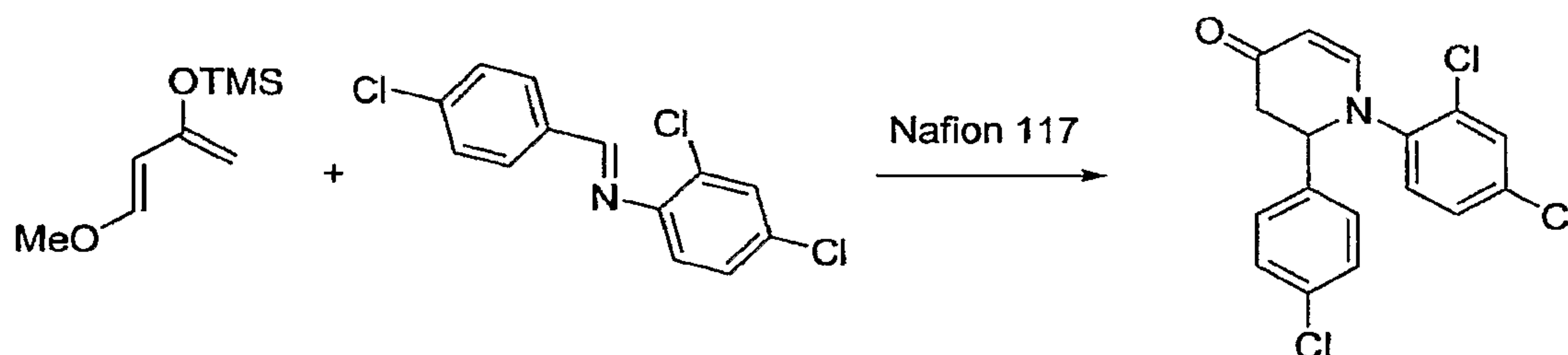


Example 2

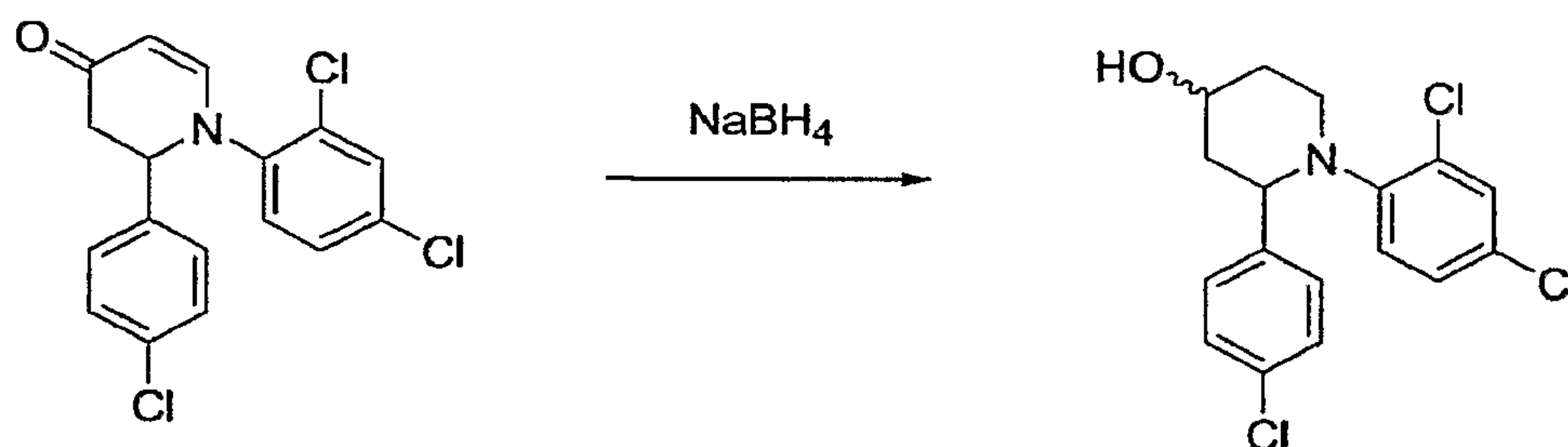
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Step 1:

A solution of 2,4-dichloroaniline (10.0g, 61.7 mmol) and 4-chlorobenzaldehyde (9.6g, 67.9 mmol) in toluene (150 mL) with a Dean-Stark trap attached was heated to reflux for 24 hr. The solution was cooled to RT and treated with activated carbon, filtered and concentrated to afford (4-chloro-benzylidene)-(2,4-dichlorophenyl) amine.

Step 2:

Nafion® 117 (33 mg), trans-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (0.15 mL), and (4-chloro-benzylidene)-(2,4-dichlorophenyl) amine (71 mg) were taken up in CH₂Cl₂ and stirred at 25°C for 16 hours. The mixture was filtered, the Nafion® 117 was washed with CH₂Cl₂, and the resulting solution was concentrated. The residue was purified via thin-layer preparative chromatography (5/2 hexanes/EtOAc, SiO₂) gave 50 mg (56 %) of the enone as a yellow oil.

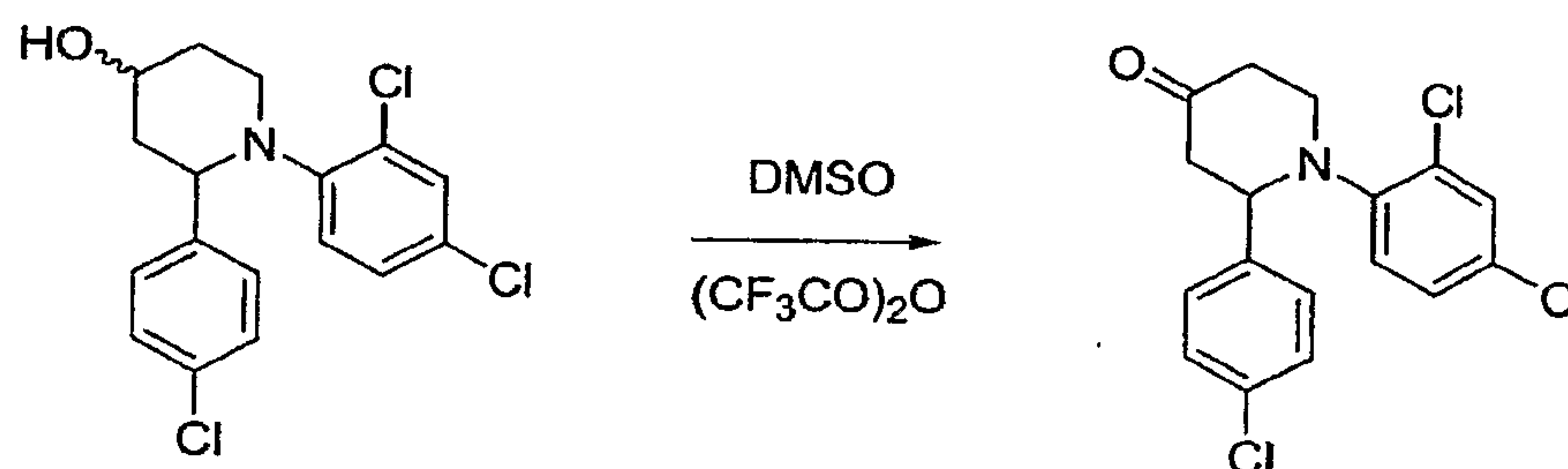
Step 3:

The enone prepared in **Step 2** (148 mg) was taken up in EtOH/THF (1/1, 2 mL), and NaBH₄ (40 mg) was added to the solution. The solution was stirred at

25°C for 16 hours. The reaction mixture was quenched with 1M HCl_(aq.) and CH₂Cl₂. After 0.5 h stirring at 25°C, the mixture was neutralized with NaHCO₃. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried (MgSO₄). Filtration and concentration gave a yellow oil.

- 5 Purification via flash chromatography (95/5 CH₂Cl₂/EtOAc, SiO₂) gave 100 mg of the alcohol (67 %) as a mixture of diastereomers.

Step 4:

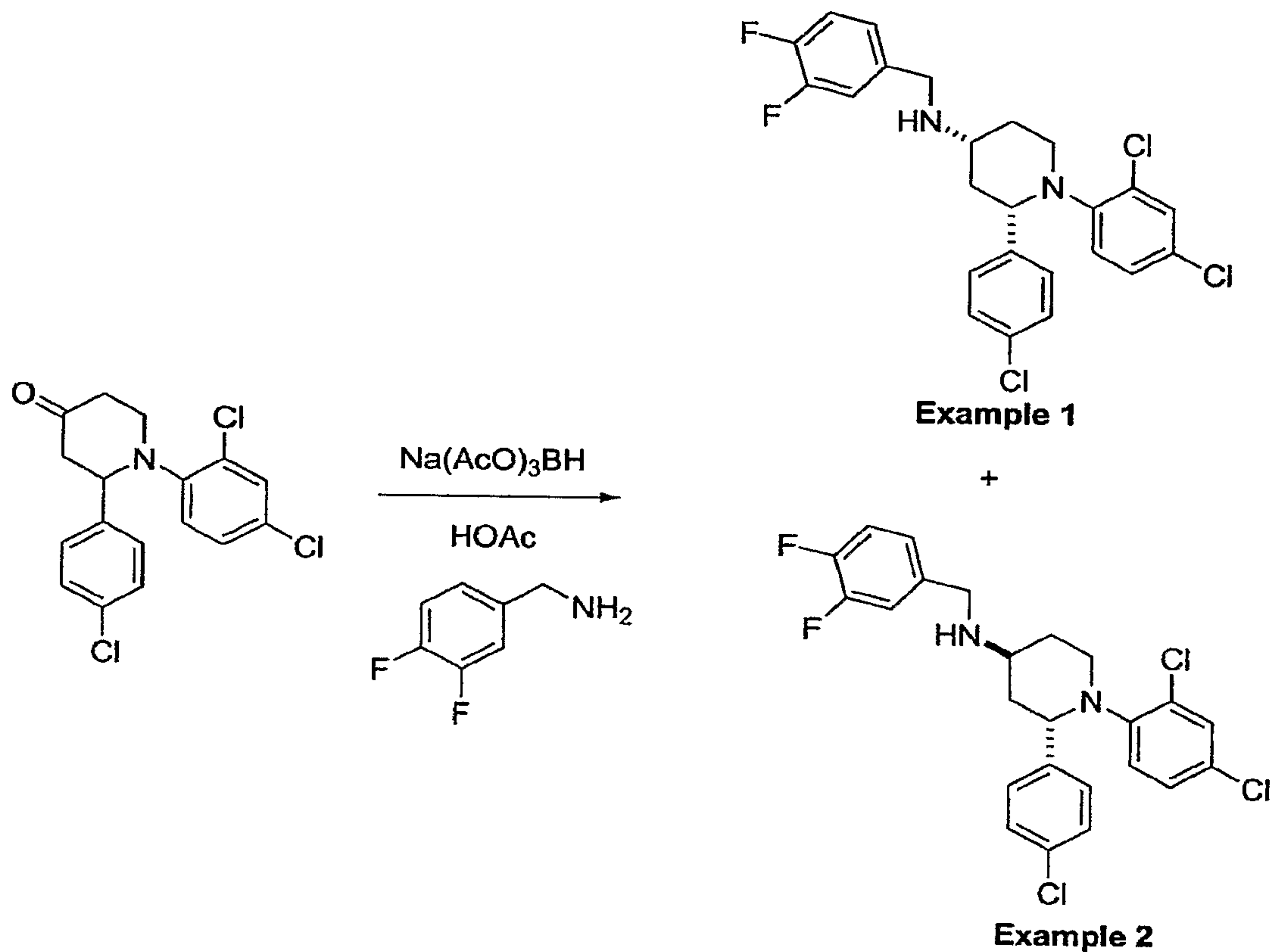


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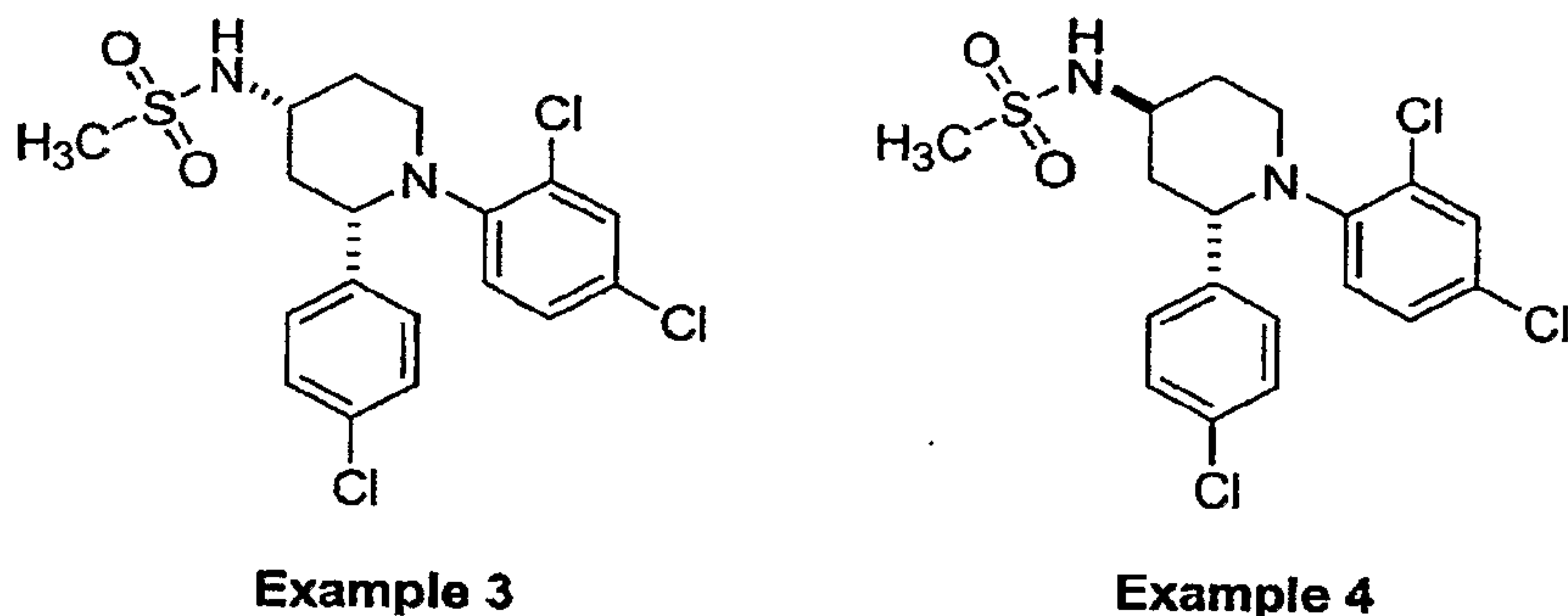
DMSO (0.89 mL) in CH₂Cl₂ (3 mL) was cooled to -60°C. After 15 minutes, TFAA (0.6 mL) was added at -60°C. After 10 minutes, a solution of the alcohol prepared in **Step 3** in CH₂Cl₂ was added. After an additional 10 minutes, Et₃N (0.9 mL) was added, and the solution was stirred at 25°C (0.5 h). The solution was

- 15 diluted with H₂O and extracted with CH₂Cl₂. The combined organic layers were dried (MgSO₄), filtered, and concentrated. Purification via thin-layer preparative chromatography (95/5 CH₂Cl₂/EtOAc, SiO₂) furnished the ketone (quant. Yield).

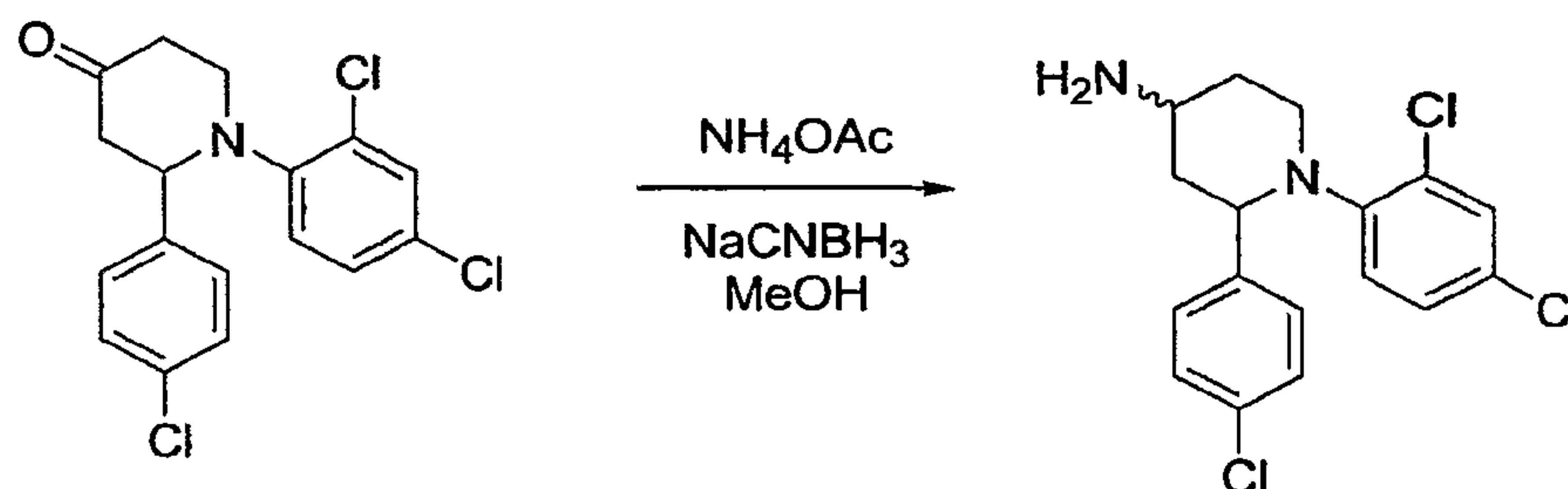
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Step 5:

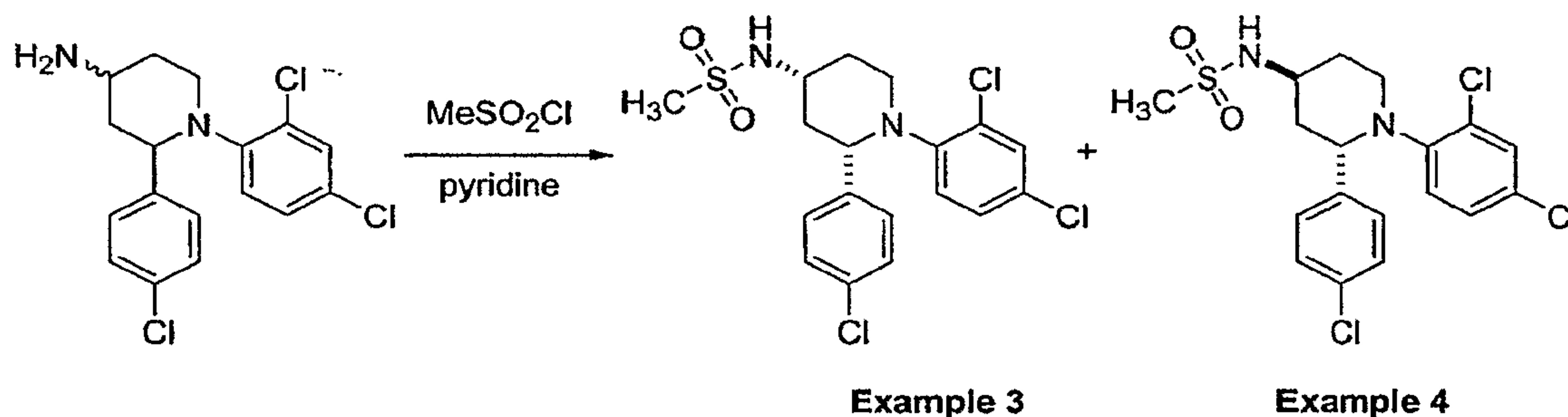
- 3,4-Difluorobenzylamine (23 mg), the ketone prepared in **Step 4** (46 mg),
 5 $\text{Na}(\text{AcO})_3\text{BH}$ (28 mg), and HOAc (60 μL) were taken up in CH_2Cl_2 and stirred at
 25°C (16 h). The solution was diluted with CH_2Cl_2 and washed with sat. NaHCO_3
 (aq.). The combined organic layers were dried (MgSO_4), filtered, and concentrated.
 Purification via thin-layer preparative chromatography (9/1 $\text{CH}_2\text{Cl}_2/\text{EtOAc}$, SiO_2)
 gave 27 mg of **Example 2** (2,4-trans). Further purification of mixed fractions
 10 (hexanes/ Et_2O , SiO_2) gave 9 mg of **Example 1** (2,4-cis).

Preparation of Examples 3 and 4

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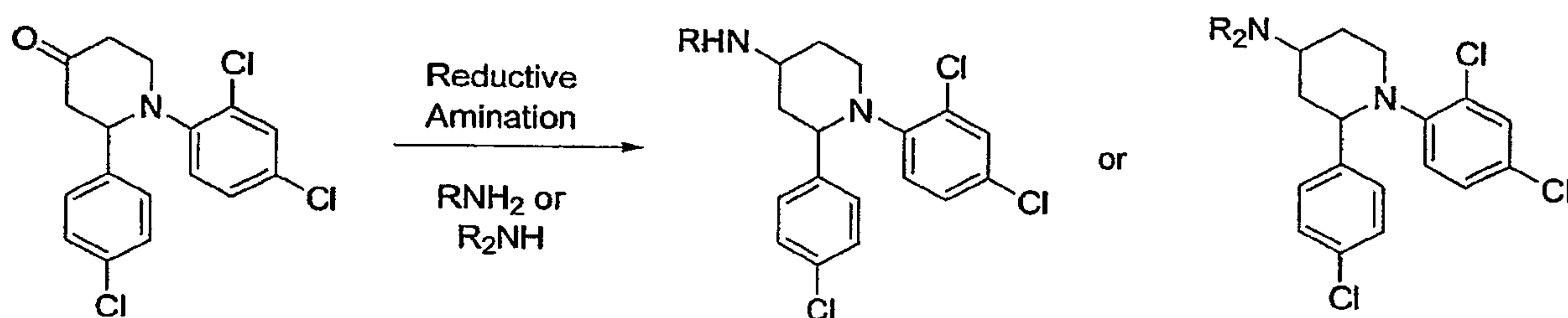
Step 1:

The ketone (60 mg) from **Step 4** of **Examples 1** and **2** (see above), NH_4OAc (13 mg), and NaCNBH_3 (25 mg) was taken up in MeOH (1.5 mL), and the solution was stirred at 25°C (24 h). The reaction was quenched with 0.01 N HCl (aq.). The reaction was concentrated and basified with sat. Na_2CO_3 (aq.). The solution was extracted with Et_2O . The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give a yellow oil. Purification via thin-layer chromatography (8/2 Et_2O /hexane, SiO_2) gave the primary amine (14 mg) as a mixture of diastereomers.

Step 2:

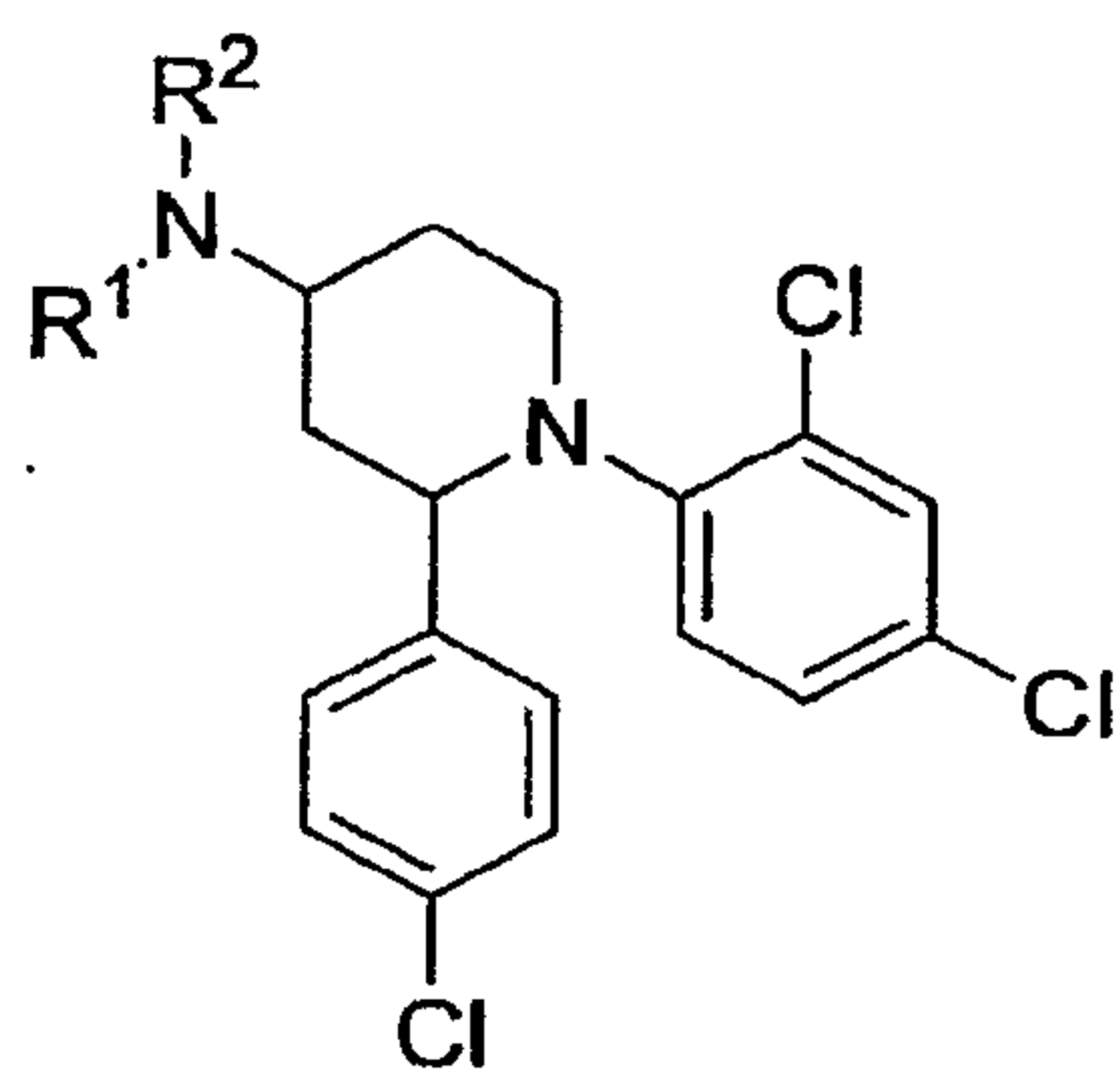
The amine (14 mg) prepared in **Step 1**, MeSO_2Cl (6 mg), and pyridine (0.2 mL) were taken up in CH_2Cl_2 and stirred at 25°C (18 h). The solution was concentrated, and the residue was taken up in CH_2Cl_2 and washed with sat Na_2CO_3 (aq.). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Purification via thin-layer preparative chromatography (Et_2O , SiO_2) gave the cis isomer **Example 3** (4 mg) and trans isomer **Example 4** (1 mg).

Reaction of ketone with an amine library to furnish 2-aryl-4-amino substituted analogs



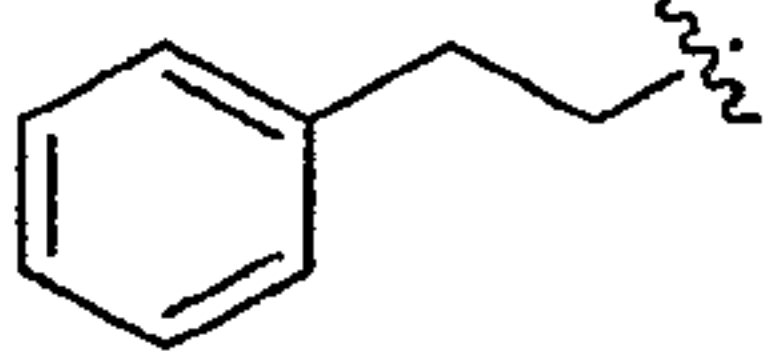
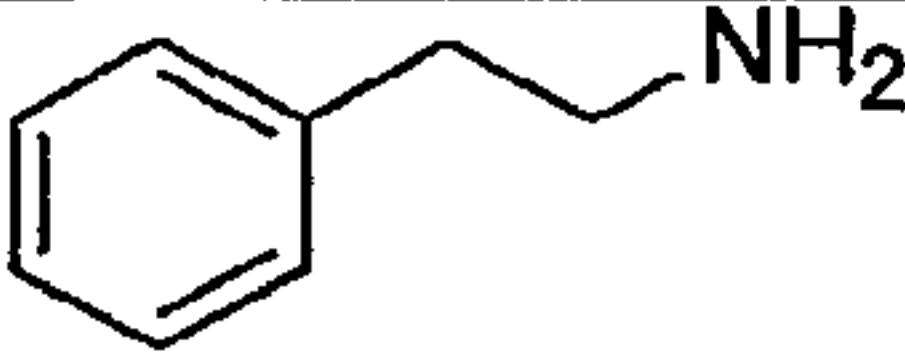
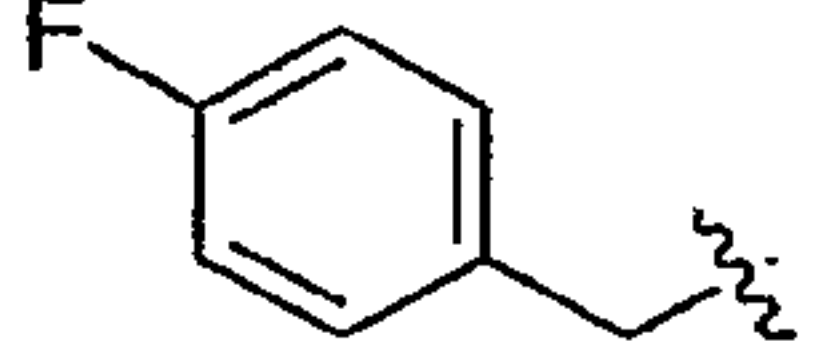
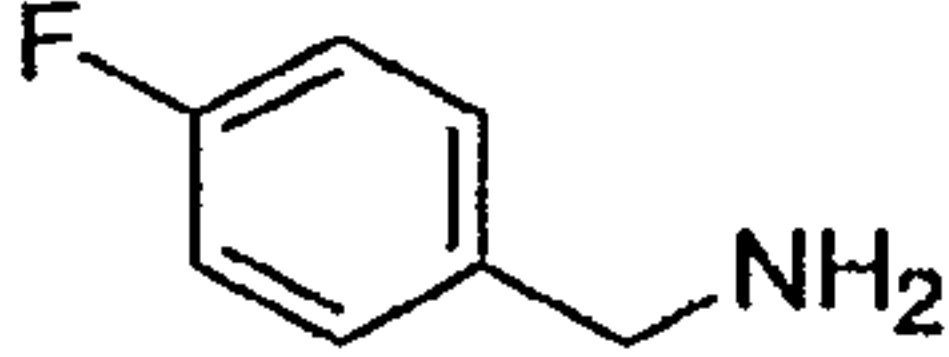
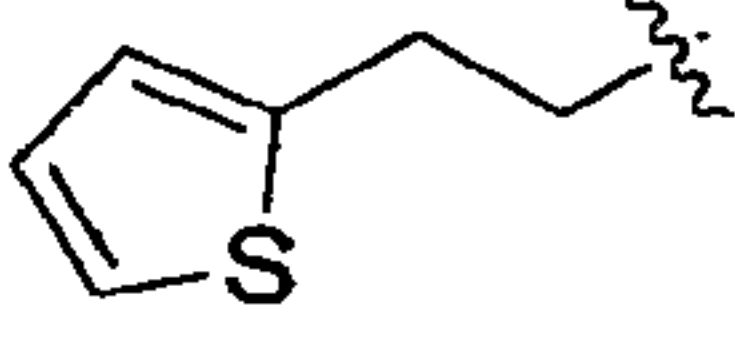
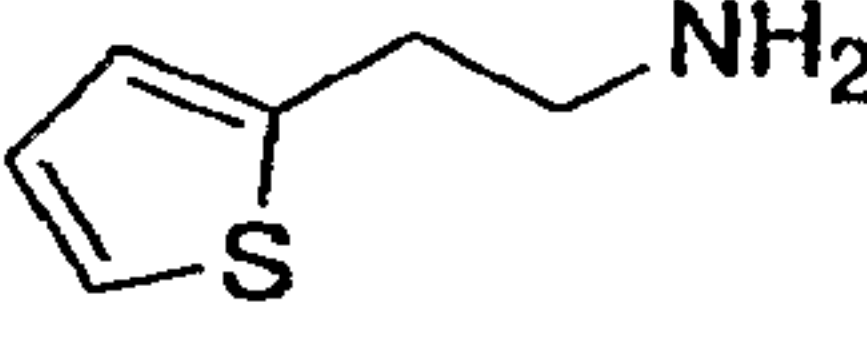
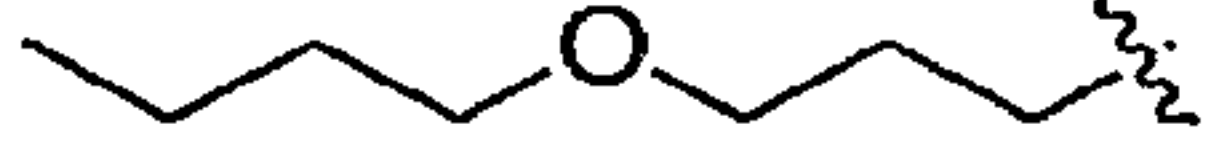
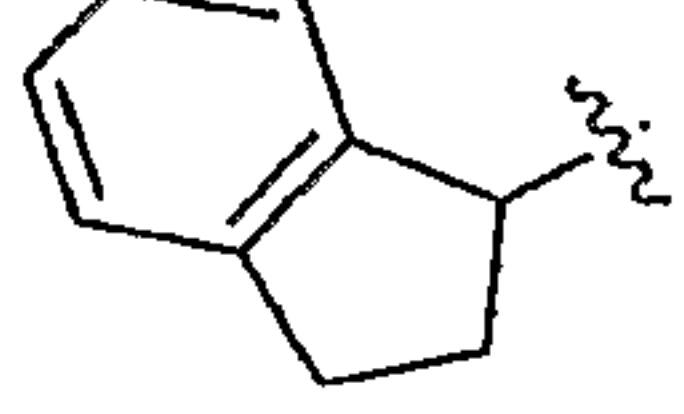
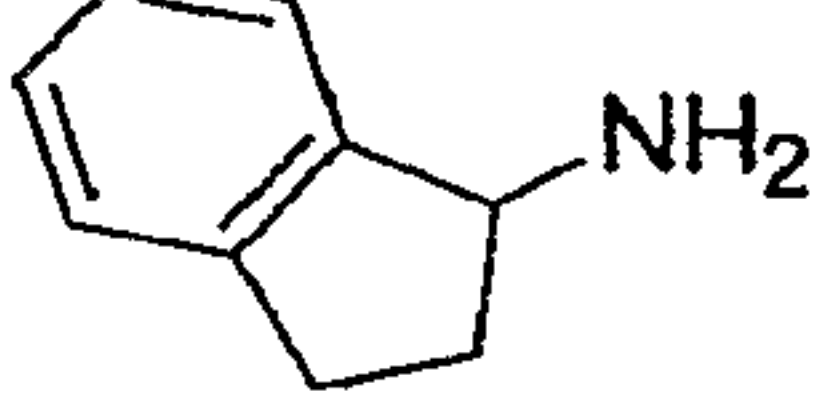
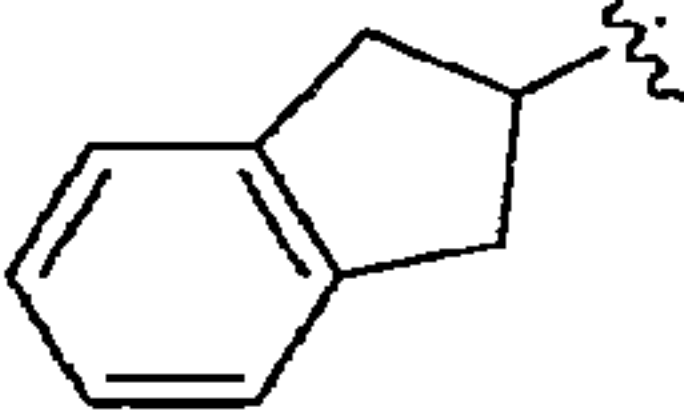
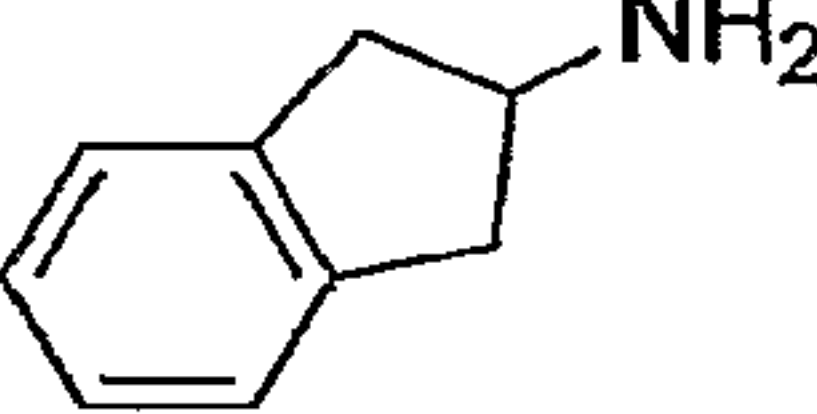
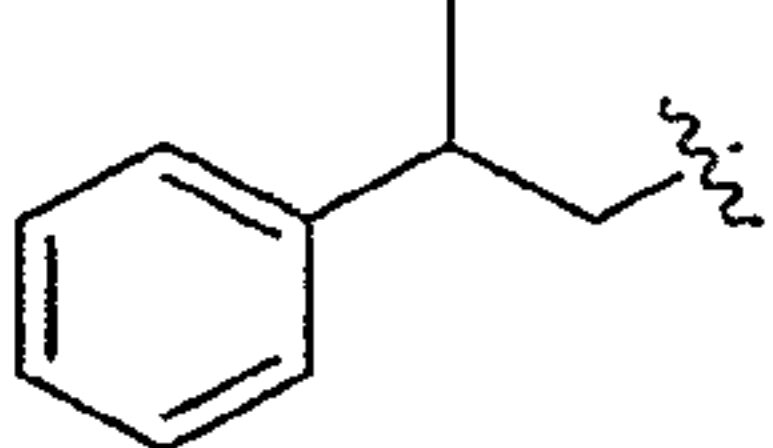
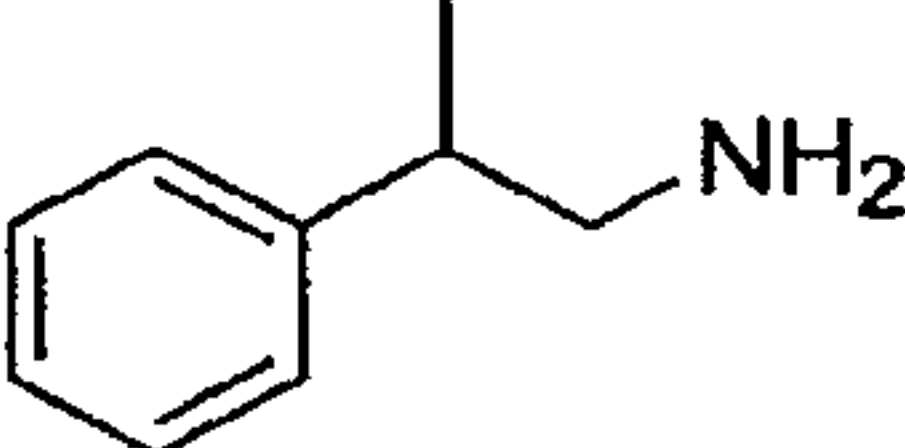
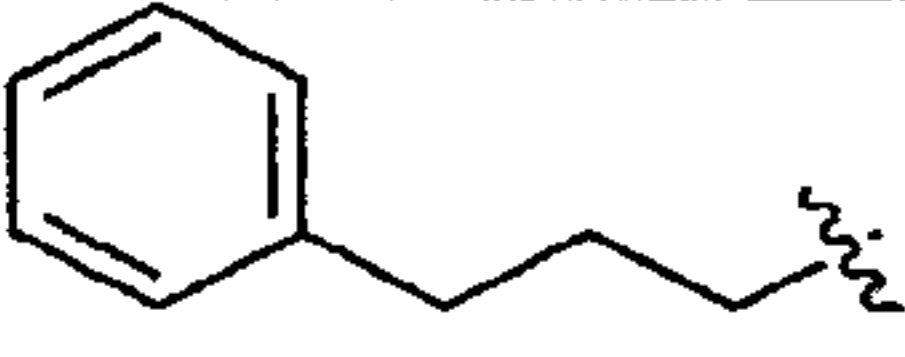
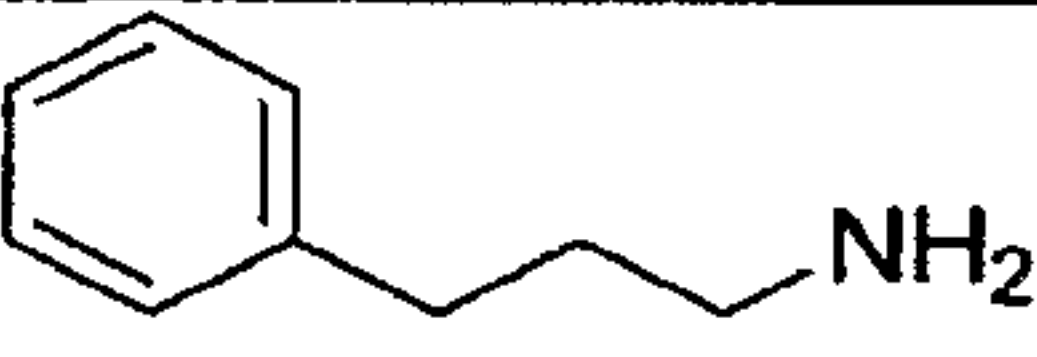
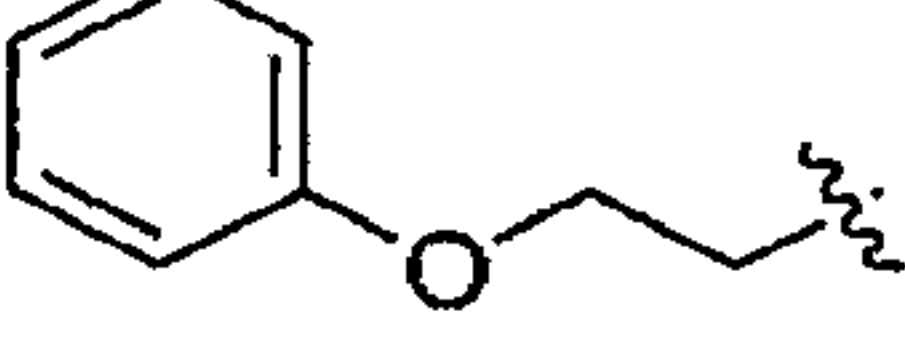
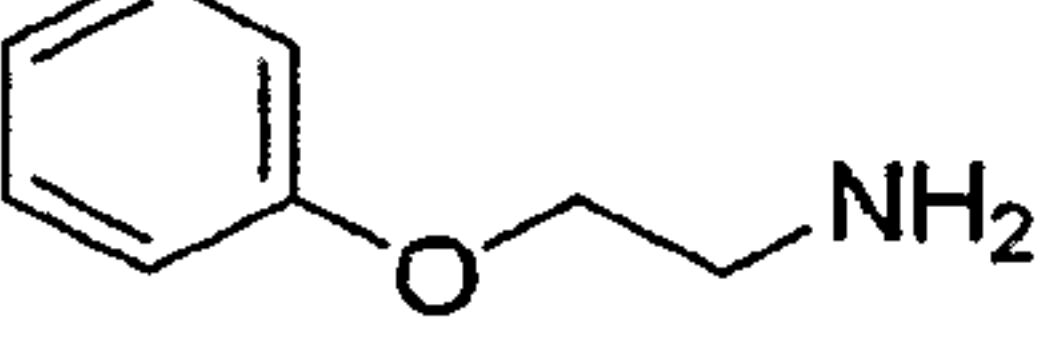
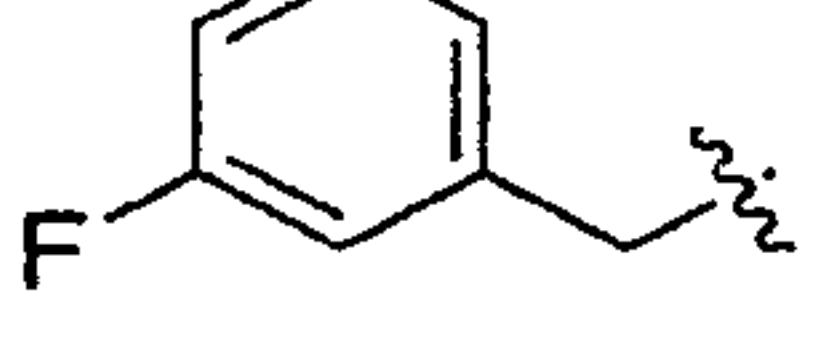
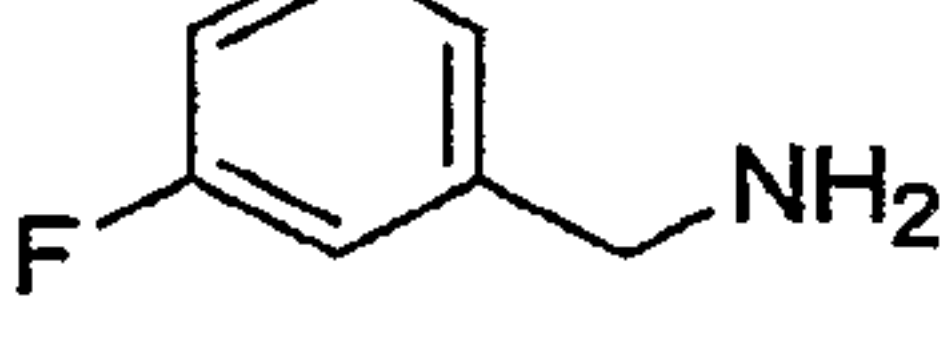
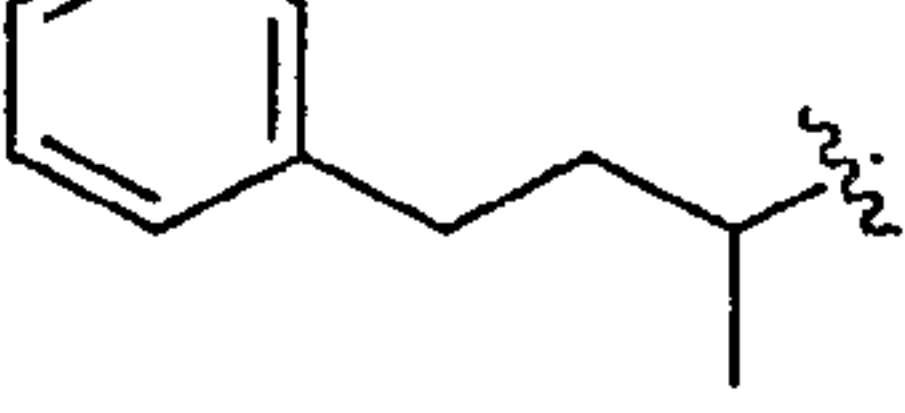
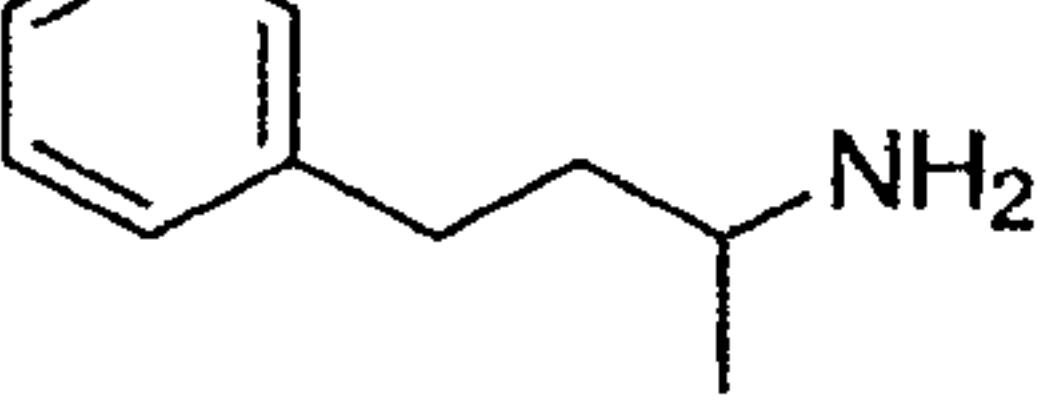
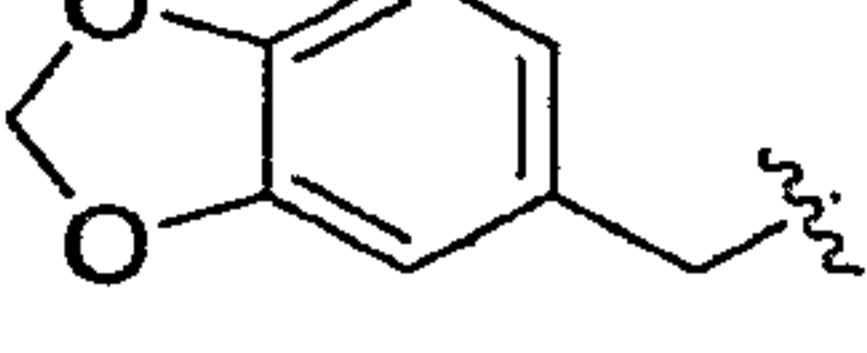
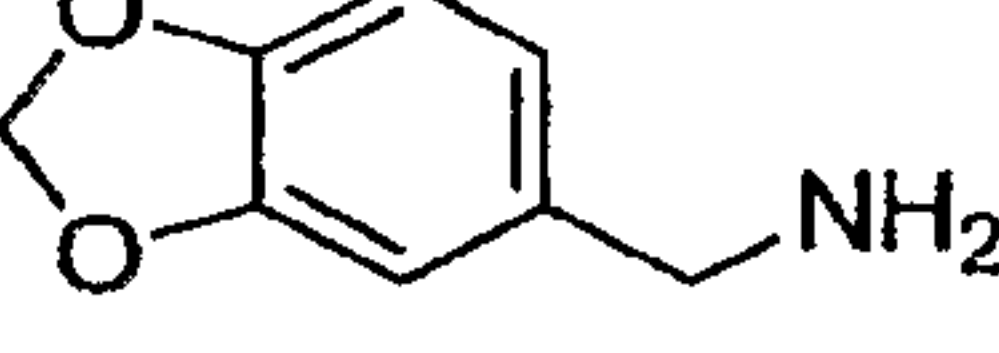
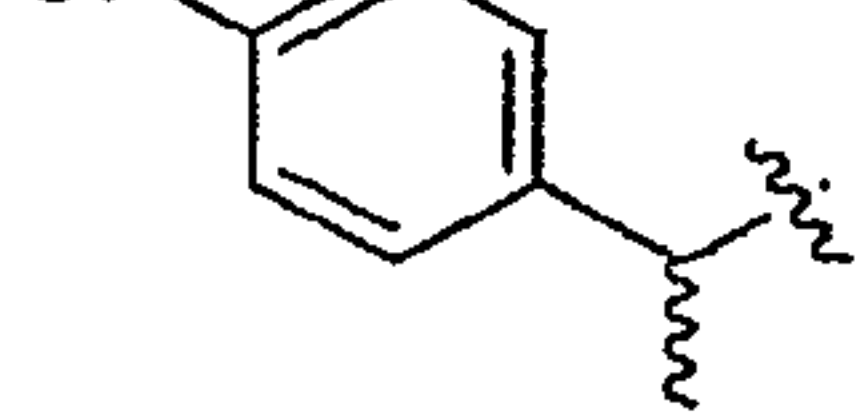
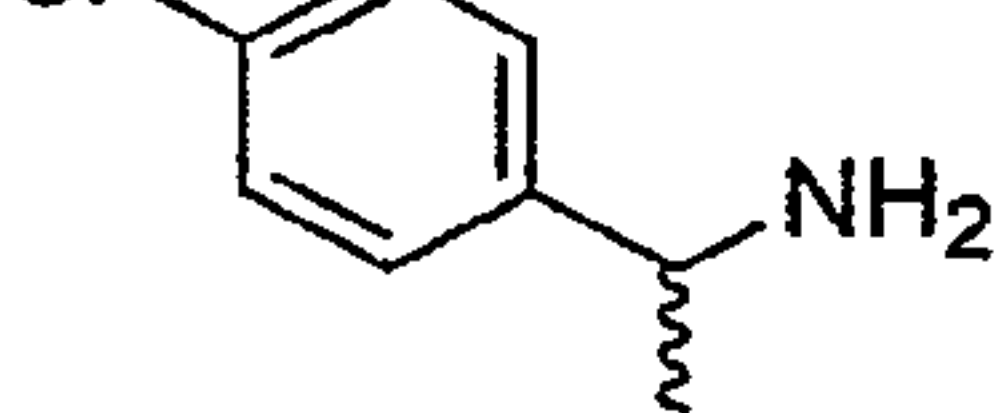
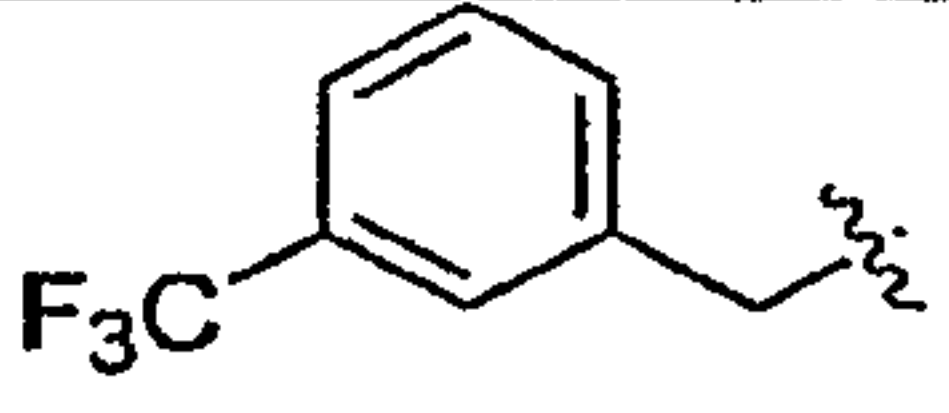
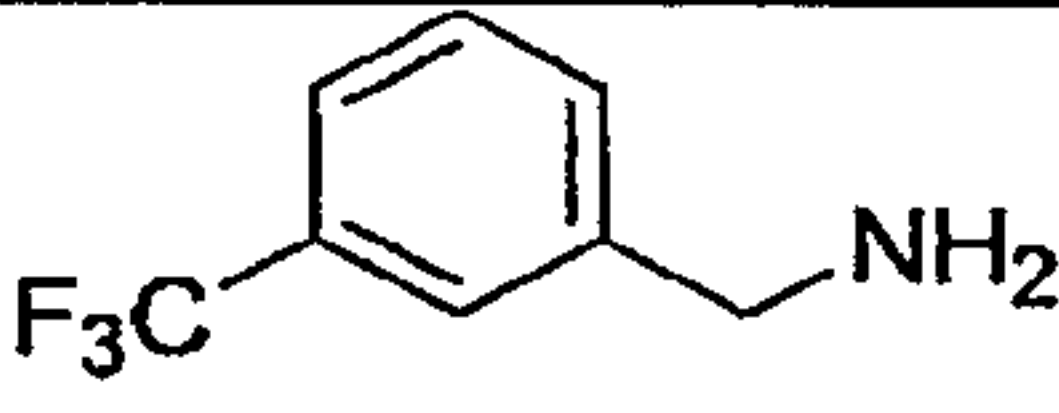
MP-Triacetoxyborohydride resin (Argonaut Technologies) (49 mg, 0.1 mmol) was added to 96-wells of a deep well polypropylene microtiter plate followed by a stock solution of the ketone (0.02 mmol) from **Step 4 of Examples 1 and 2** in DCE/MeCN (3 mL, 1/1 with 1% AcOH). A stock solution of each of the various amines (100 μ L, 0.1 mmol, 1M in DCE/MeCN, 1/1) were added to the wells; and the microtiter plate was sealed and shaken at 25°C for 20 h. For primary amines, PS-activated ketone (Aldrich) (3 mmol, 40 mg) was added to the wells and shaken an additional 20 h. For secondary amines, PS-benzaldehyde (1.5 mmol, 80 mg) was added to the wells and shaken an additional 20 h. The solutions were then filtered thru a polypropylene frit into a 2nd microtiter plate containing MP-TsOH resin (80 mg). After the top plate was washed with MeCN (0.5 mL), the plate was removed; the bottom microtiter plate was sealed and shaken at 25°C for 2h. Then the solutions were filtered thru a polypropylene frit, and the resin was washed three times each with DCM and MeOH to remove unreacted reagents. After the plate was allowed to dry for 10 min., the bottom microtiter plate was resealed, and ammonia in methanol (2N, 1 mL) was added to each well. The plate was sealed and shaken at 25°C for 1 hr. Then, the solutions were filtered thru a polypropylene frit into a 96-well collection plate. The wells of the top plate were then washed with MeOH (0.5 mL), and the plate removed. The resultant solutions in the collection plate were then transferred into 2-dram vials, and the solvents removed in vacuo via a SpeedVac concentrator. The resulting samples were evaluated by LCMS, and those that were >70% pure are listed in the table below (**Examples 5-63**).

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Ex. #	R^1	R^2	Amine
5		H	
6		H	
7		H	
8		H	
9		H	
10		H	
11		H	
12		H	
13		H	
14		H	
15		H	
16		H	
17		H	
18		H	

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Ex. #	R ¹	R ²	Amine
19		H	
20		H	
21		H	
22		H	
23		H	
24		H	
25		H	
26		H	
27		H	
28		H	
29		H	
30		H	
31		H	
32		H	

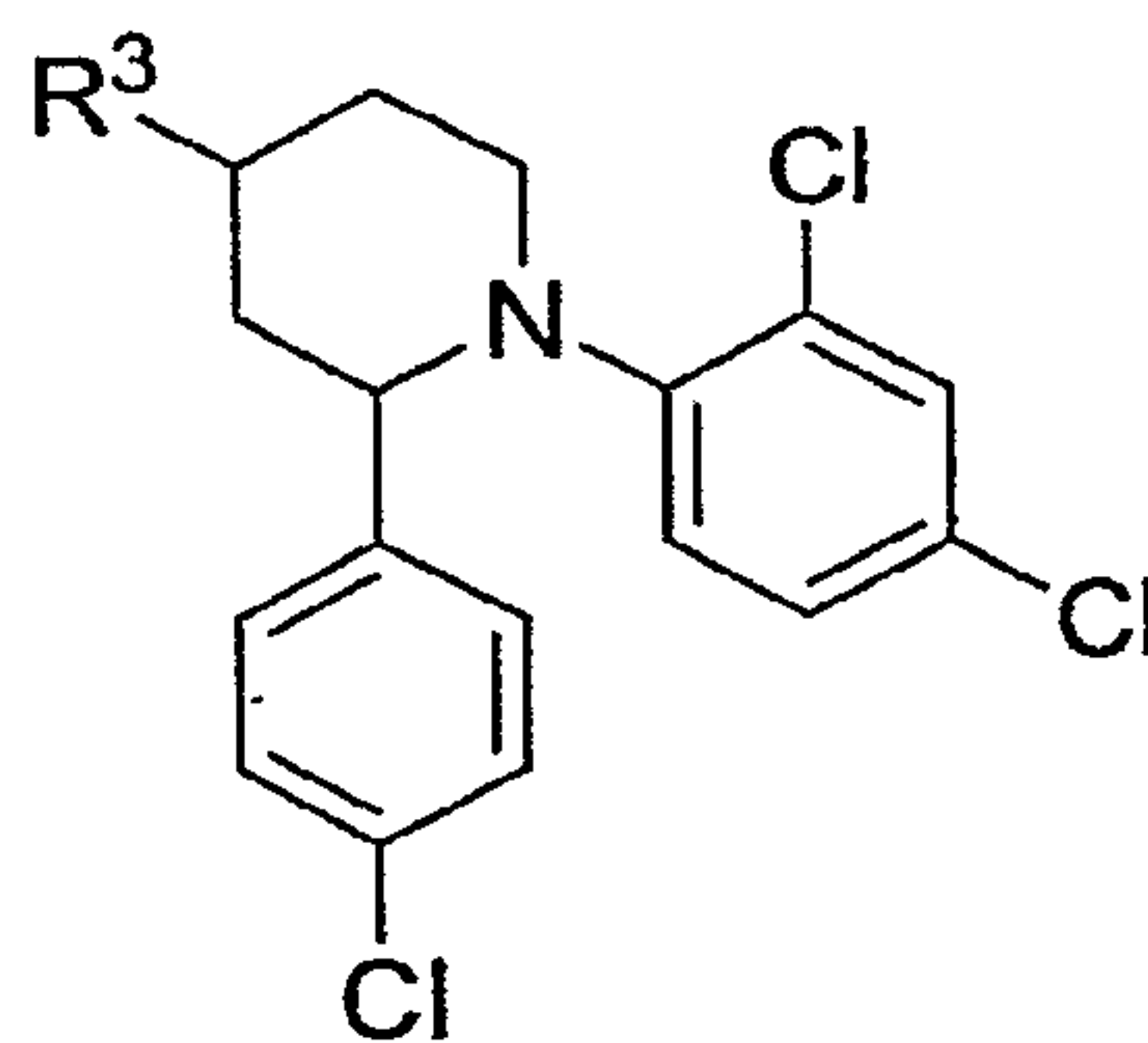
118

Ex. #	R ¹	R ²	Amine
33		H	
34		H	
35		H	
36		H	
37		H	
38		H	
39		H	
40		H	
41		H	
42		H	
43		H	
44		H	
45		H	
46		H	
47		H	

119

Ex. #	R ¹	R ²	Amine
48		H	
49		H	
50		H	
51		H	
52		H	
53		CH ₃	
54		CH ₃ CH ₂	
55		H	
56		H	
57		H	

Compounds were tested as a 3/2 mixture of cis/trans.



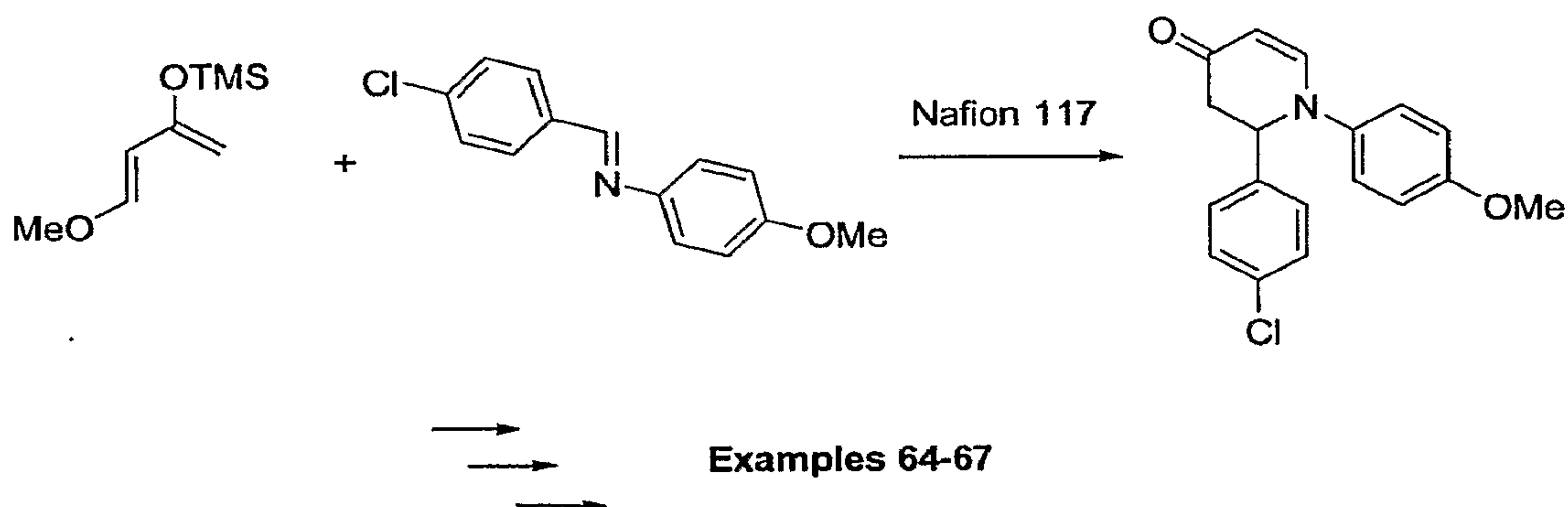
Ex. #	R ³	Amine
58		

120

Ex. #	R ³	Amine
59		
60		
61		
62		
63		

Compounds were tested as a 3/2 mixture of cis/trans.

Preparation of Examples 64-67

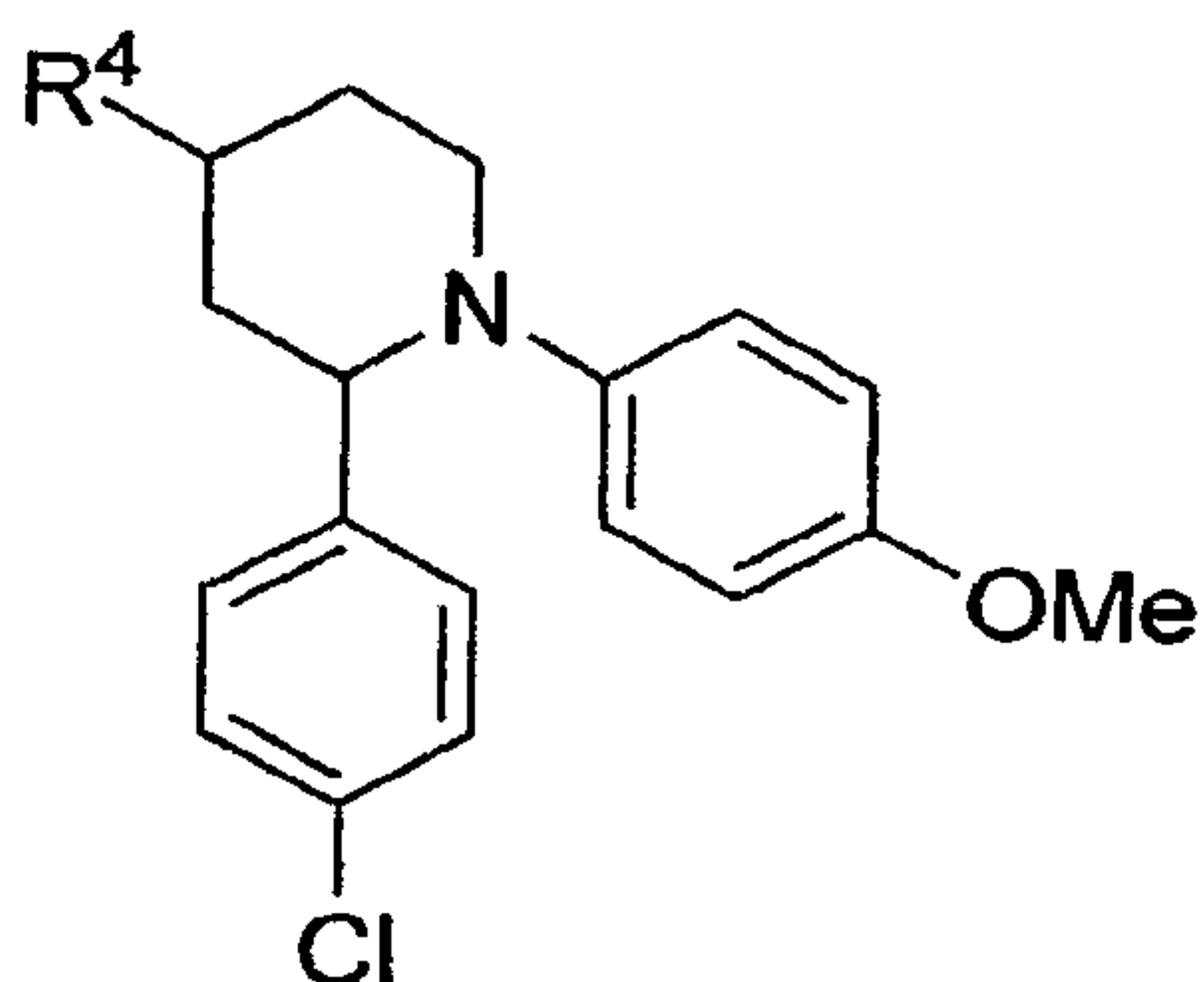


5

Example 64-67 were prepared in a manner similar to that described above for Examples 1 and 2, except that (4-chloro-benzylidene)-(4-methoxyphenyl) amine was used instead of (4-chloro-benzylidene)-(2,4-dichlorophenyl) amine. The resulting enone was reduced to the corresponding alcohol (i.e., **Example 64**), or the alcohol was subsequently oxidized and then reacted with the appropriate amine.

10

121



Ex. #	R ⁴
64	OH
65	
66	
67	

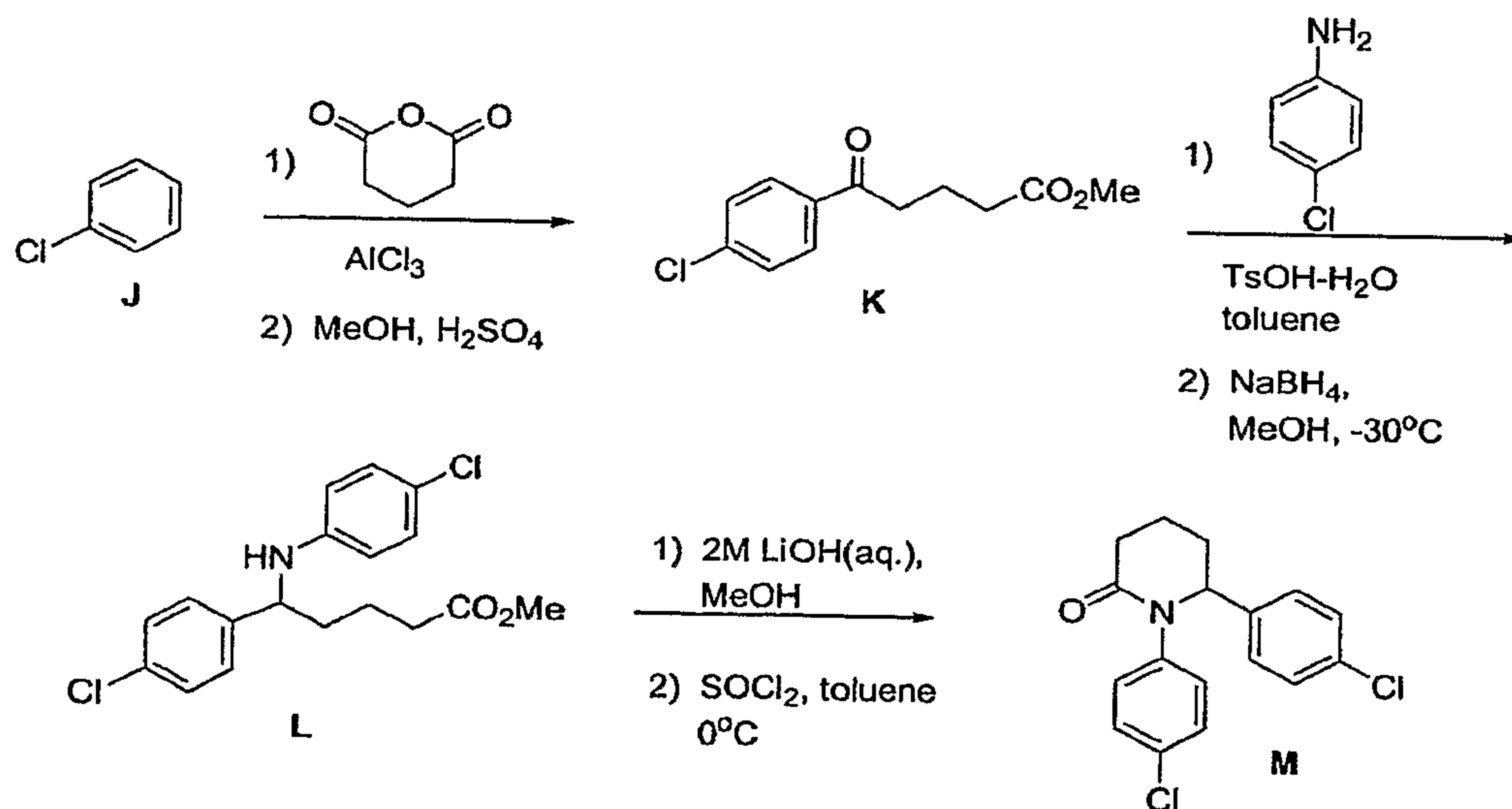
a – 2,4-cis isomer

b- 2,4-trans isomer

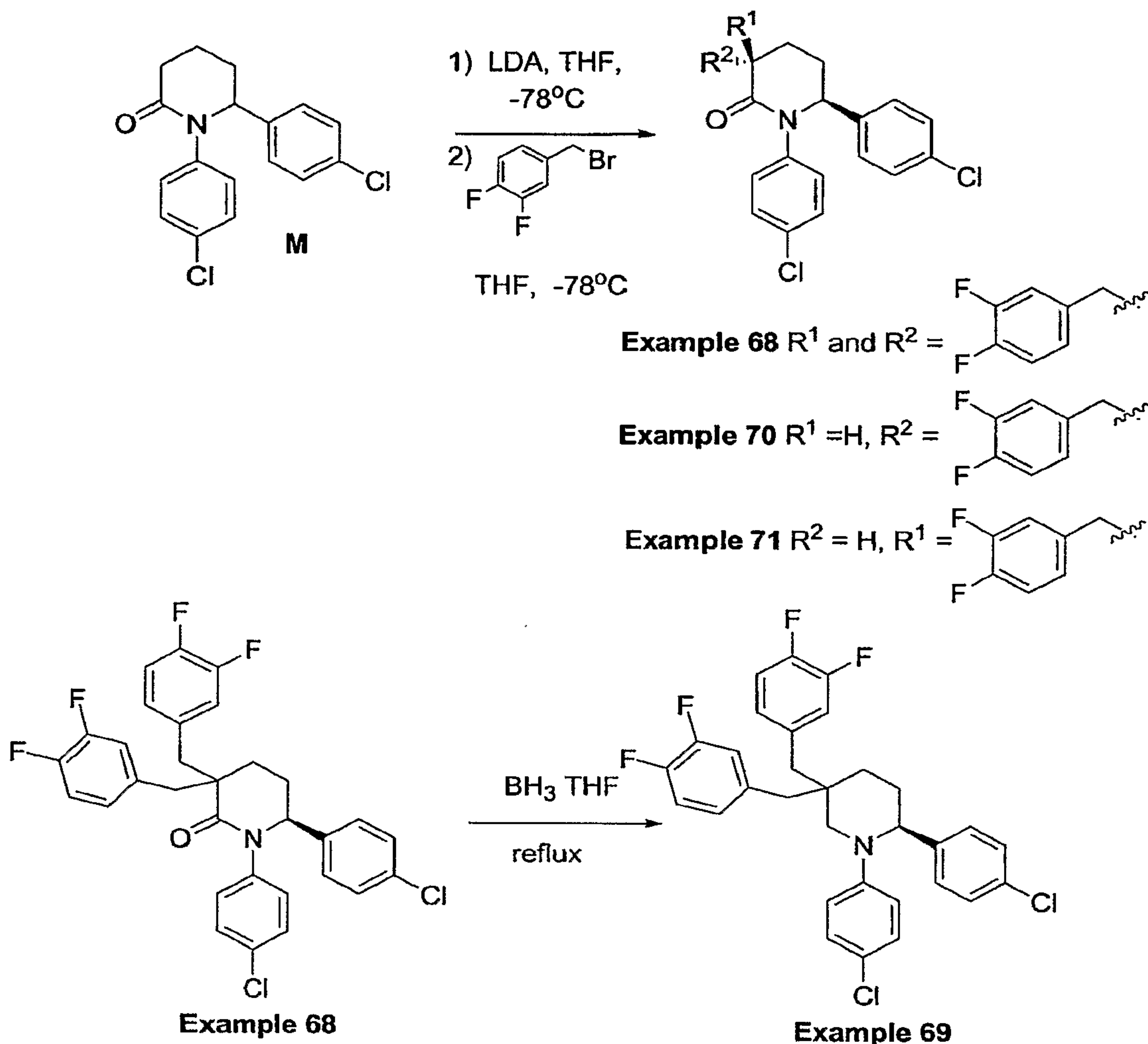
If not specified, compounds were tested as a 3/2 mixture of cis/trans

5

Preparation of Examples 68-71



122

**Step 1:**

To a solution of glutaric anhydride (21.3g, 114 mmol) in chlorobenzene (158 g, 1.40 mol) was added AlCl_3 (50.0 g, 375 mmol). The mixture was stirred at RT using a mechanical stirrer for 1.5 days. The reaction mixture was slowly poured into ice cold concentrated HCl. The mixture was stirred at 0°C for 1h. The solid was removed by filtration, and the solid was then washed with water and dried on a filter for 2 h. The solid was then dried under vacuum overnight to afford a keto acid (25 g) as a tan solid.

To a solution of the keto acid (13.8 g, 61 mmol) in MeOH (200 mL) was added conc. H_2SO_4 (0.5 mL). The solution was heated to 75°C for 2.5h. The solution was concentrated, and partitioned between EtOAc and NaHCO_3 (aq.). The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed

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with brine, dried over Na_2SO_4 , filtered and concentrated to afford **K** (8.1g) as a yellow solid.

Step 2:

To a solution of **K** (8.0g, 33.3 mmol) in toluene (100 mL) was added 4-chloroaniline (5.93g, 46.6 mmol) and p-toluenesulfonic acid monohydrate (253 mg, 1.33 mmol). The solution was heated to reflux for 1.5 d with a Dean-Stark trap attached. The solution was cooled and concentrated. To the resultant oil was added MeOH (100 mL) followed by NaHCO_3 (1.0 g). The solution was cooled to -30°C and NaBH_4 (2.4 g) was added over 1 hour in portions; the solution was then stirred at -30°C for an additional 1h. The solution was warmed to room temperature and water was added. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated to afford **L**. The material was used without purification.

Step 3:

To a solution of **L** (8.6g, 24.5 mmol) in MeOH (150 mL) was added 2M LiOH (aq.) (37 mL, 73.4 mmol). The solution was stirred at RT for 4 h. The solution was adjusted to pH 6 with the addition of 4M HCl (aq.). The solution was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated to afford an orange oil. This oil was taken up in dry toluene (200 mL) and cooled to 0°C . Pyridine (5.05, 63.9 mmol) was added followed by the addition (over 1 h) of a solution of thionyl chloride (3.03g, 26 mmol) in dry toluene (10 mL). The resultant solution was stirred for an additional 1h at 0°C . The solution was poured into H_2O and extracted with EtOAc. The organic layer was washed with 1M HCl, followed by saturated aqueous NaHCO_3 and brine. The organic layer was dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by flash chromatography gradient elution (SiO_2 : 100:0 to 40:60 hexanes: ethyl acetate) to afford **M** (5.3g) as an orange crystalline solid.

Examples 68, 70 and 71:

To a solution of LDA (3.2 mmol) in dry THF (20 mL) at -78°C was added **M** (510 mg, 1.6 mmol) in dry THF (5 mL). This solution was allowed to stir at -78°C for 1 h. To this solution was added 3,4-difluorobenzyl bromide (364 mg, 1.76 mmol) and the solution was stirred at -78°C for 4 h. Water was added and the solution was

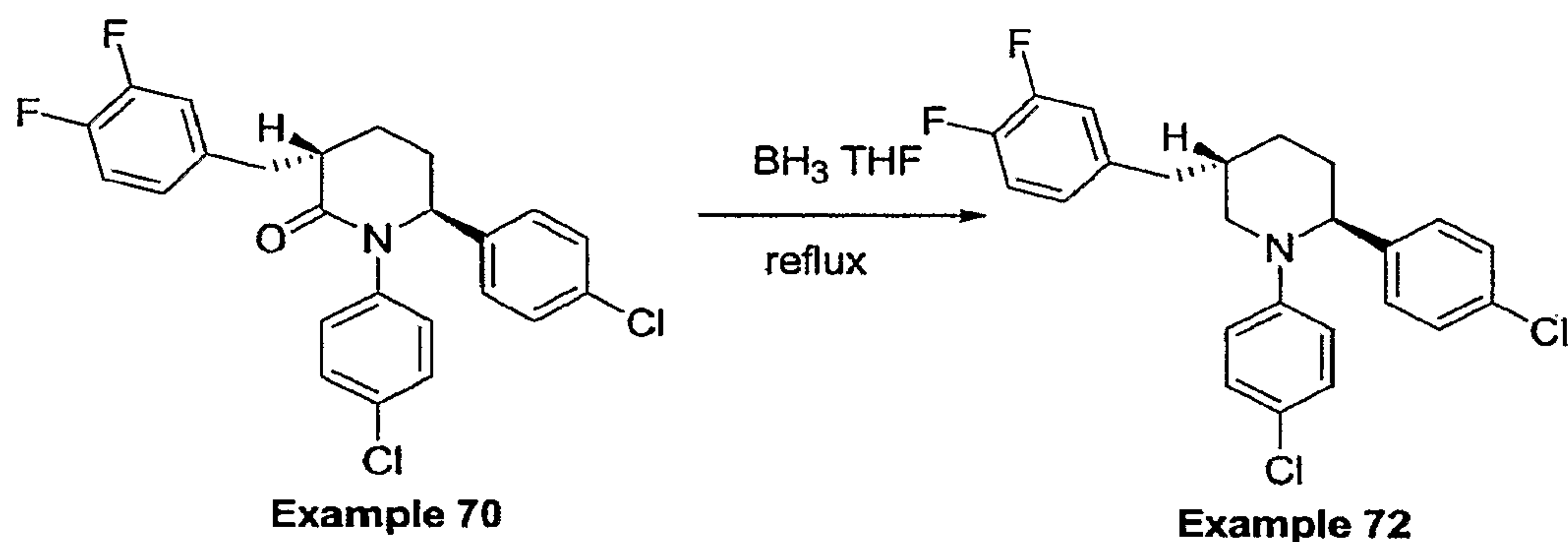
allowed to warm to RT. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were then washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash chromatography using gradient elution (SiO₂: 100:0 to 1:1 hexanes/EtOAc) to afford **68** (105 mg), **70** (30 mg) and **71** (41 mg).

Preparation of Example 69

To a solution of **68** (63 mg, 0.11 mmol) in THF (4 mL) was added borane THF complex (1M solution in THF, 0.33 mmol). The solution was heated to reflux for 4 h. The solution was cooled to RT and water was added. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by prep TLC (SiO₂: 4:1 hexanes/EtOAc) to afford **69** (6 mg).

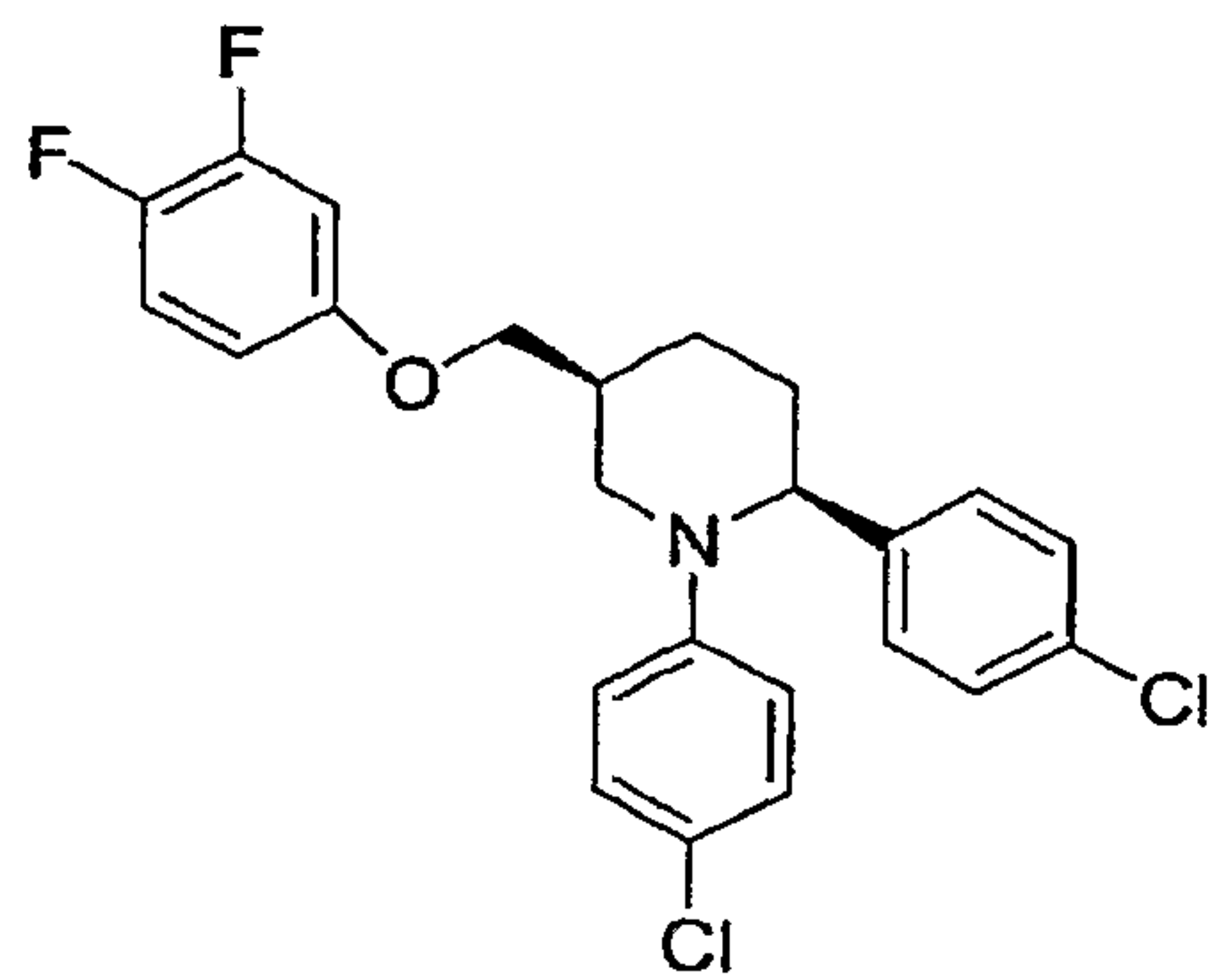
Preparation of Example 72

Example 72 was prepared in a manner similar to that of **Example 69**, except that **Example 70** was the starting material instead of **Example 68**.

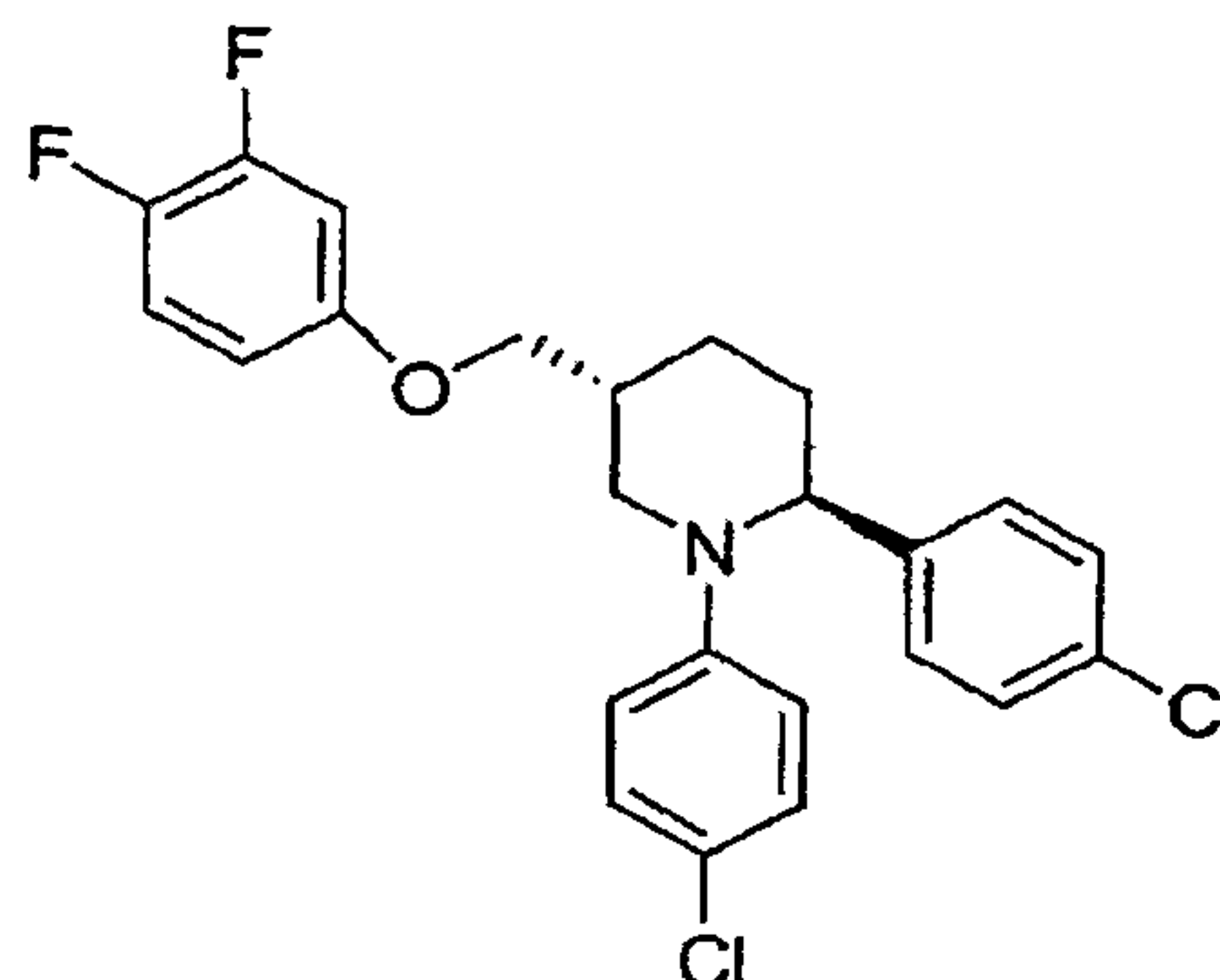


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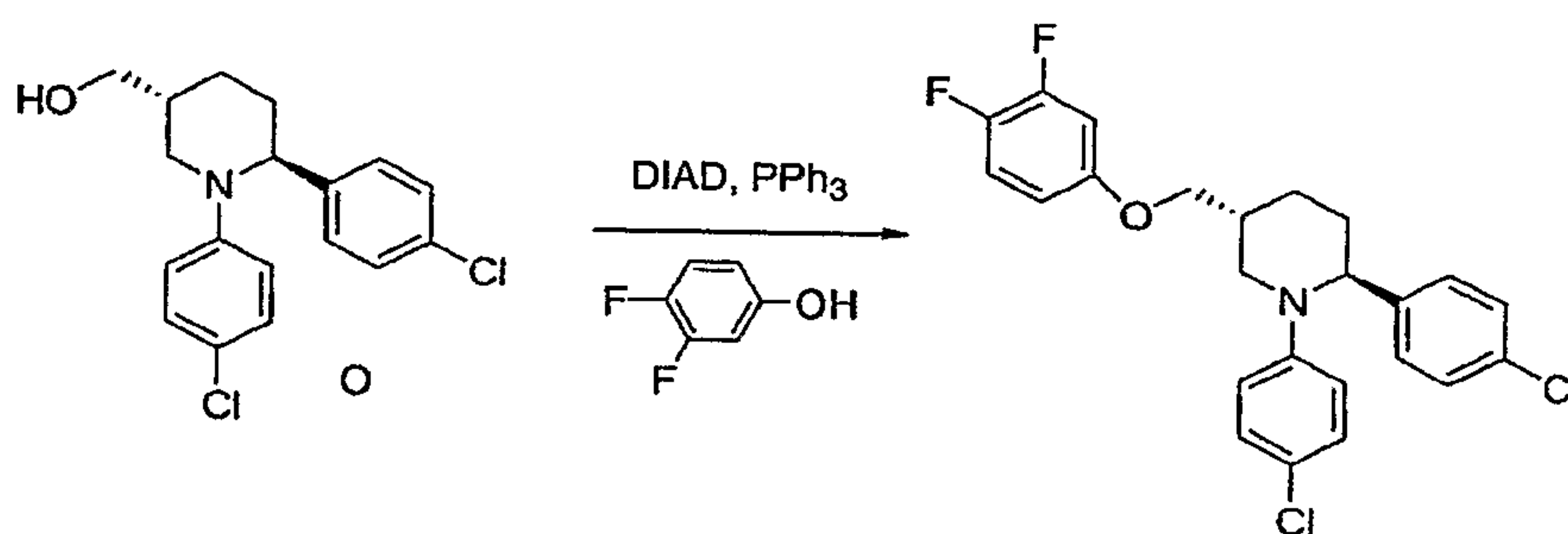
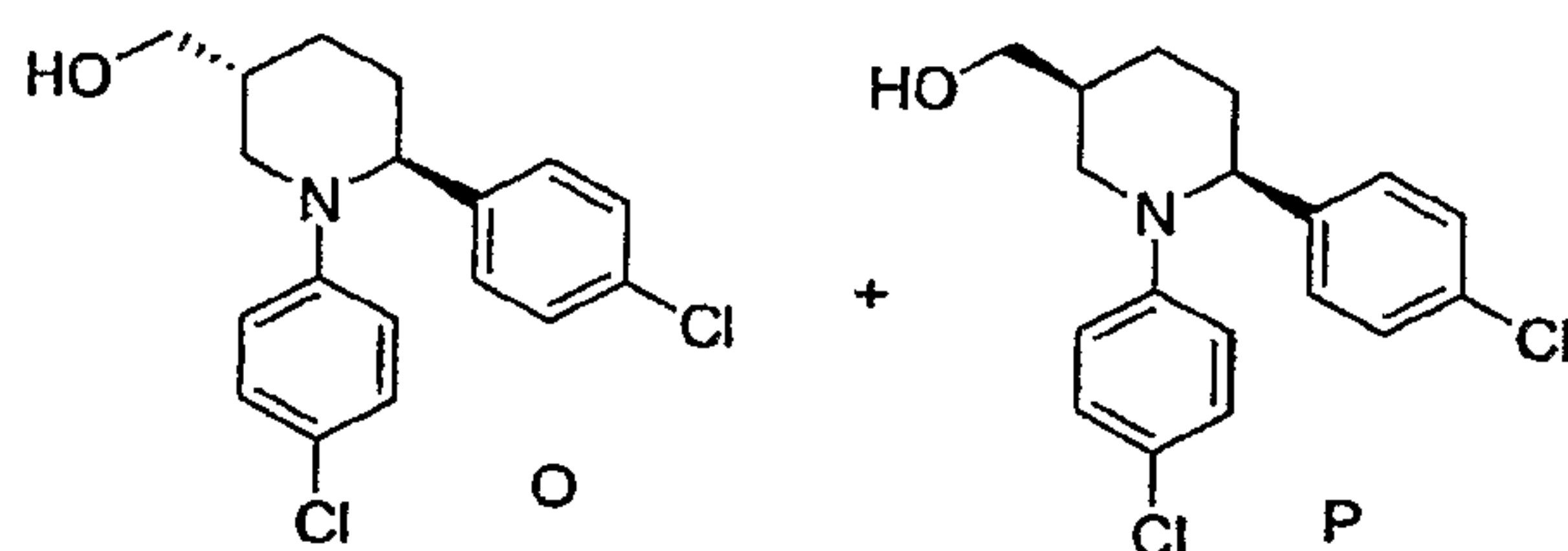
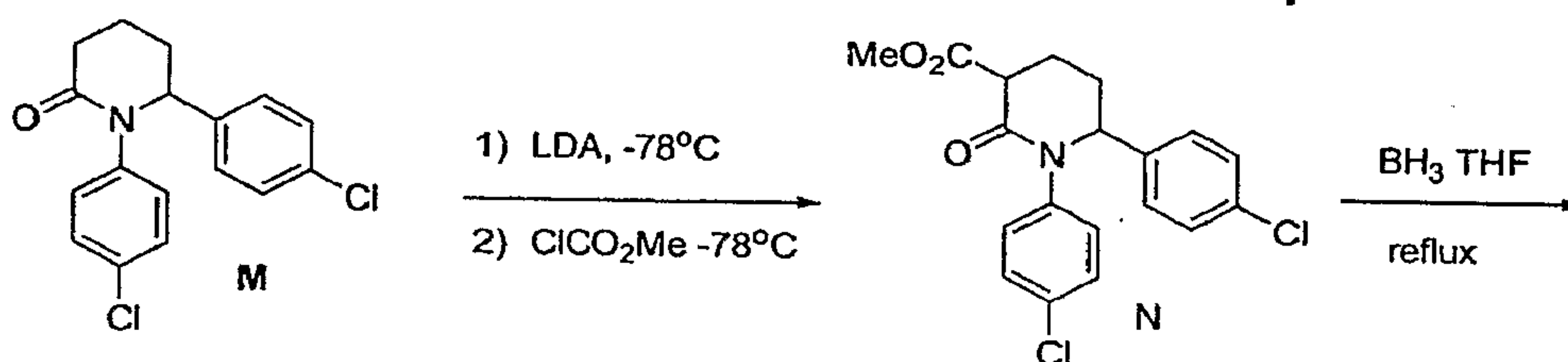
Preparation of Examples 73 and 74



Example 73



Example 74



Example 74

Step 1:

- 5 To a solution of LDA (6.1 mmol) in anhydrous THF (10 mL) at -78°C was added **Compound M** (1.3g, 4.1 mmol) in anhydrous THF (5 mL). The solution was allowed to stir at -78°C for 1h. To this solution was added methyl chloroformate (9.4 mmol). The solution was stirred at -78°C for 1.5 h and warmed to RT and allowed to stir for an additional 1 h. The reaction was quenched with saturated NH₄Cl (aq.) and

allowed to stir at RT overnight. The mixture was concentrated and partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash chromatography using gradient elution (SiO₂: 100:0 to 30:70 hexanes/EtOAc) to afford **Compound N** (480 mg) as a mixture of diastereomers.

Step 2:

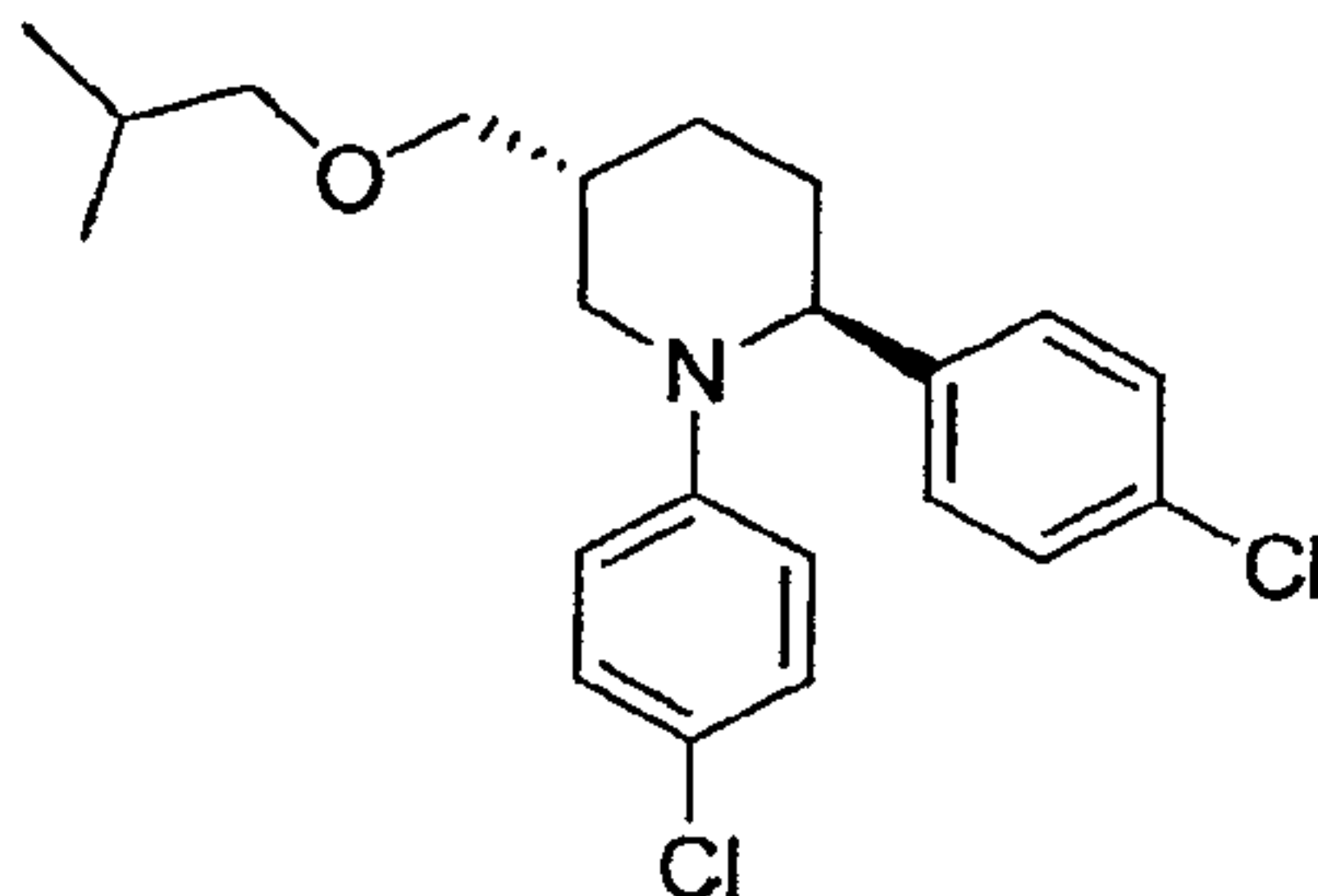
To a solution of **N** (500 mg, 1.3 mmol) in THF was added borane THF complex (1M solution in THF, 3.9 mmol). The solution was heated to reflux for 2 h. The solution was cooled to RT and excess MeOH was added. The solution was concentrated. The product was partitioned between CH₂Cl₂ and NaHSO₄ (aq.). The aqueous layer was extracted with CH₂Cl₂ (3x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash chromatography using gradient elution (SiO₂: 100:0 to 70:30 hexanes/EtOAc) to afford the trans diastereomer **O** (110 mg) and the cis diastereomer **P** (170 mg).

Step 3:

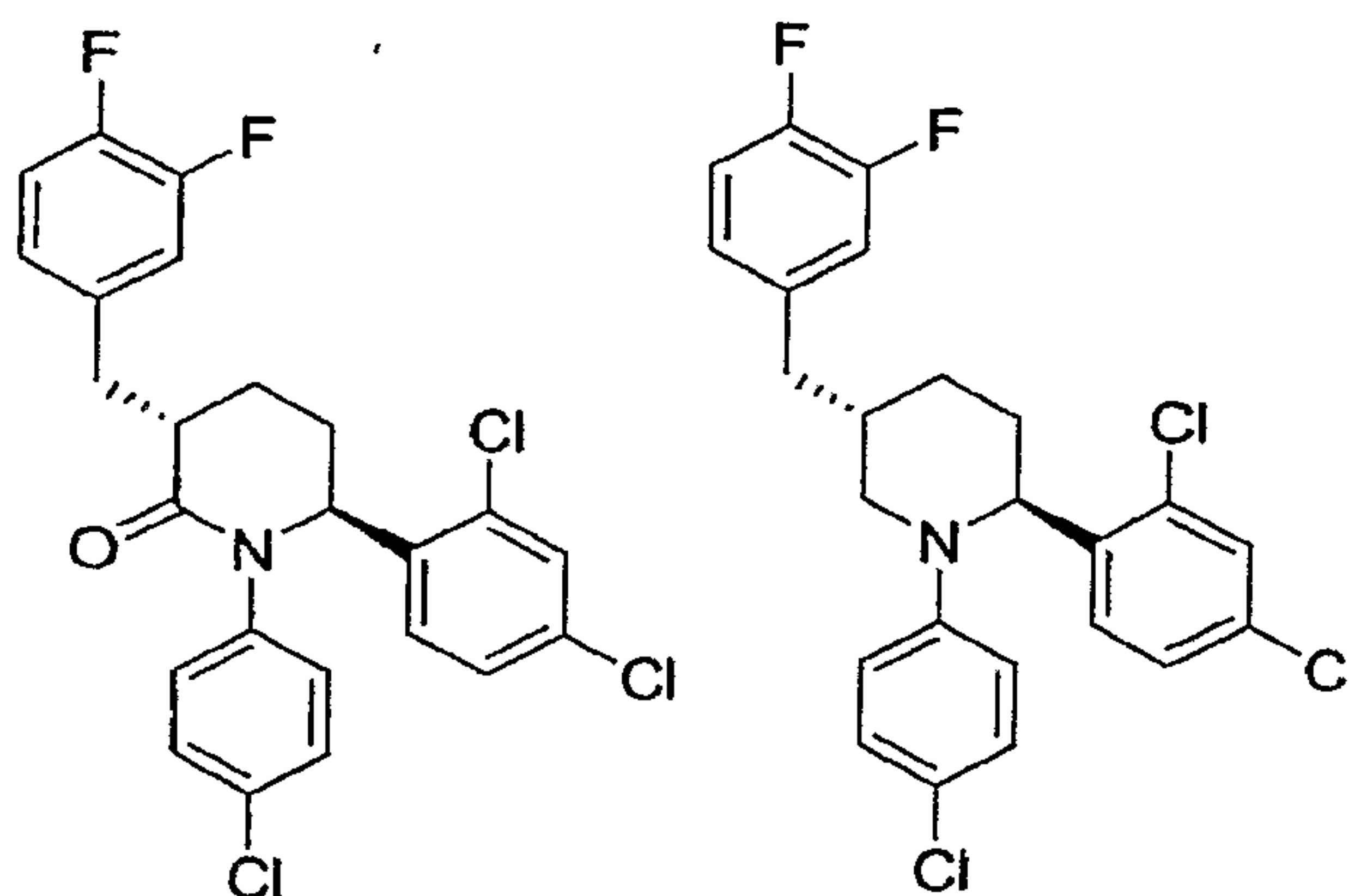
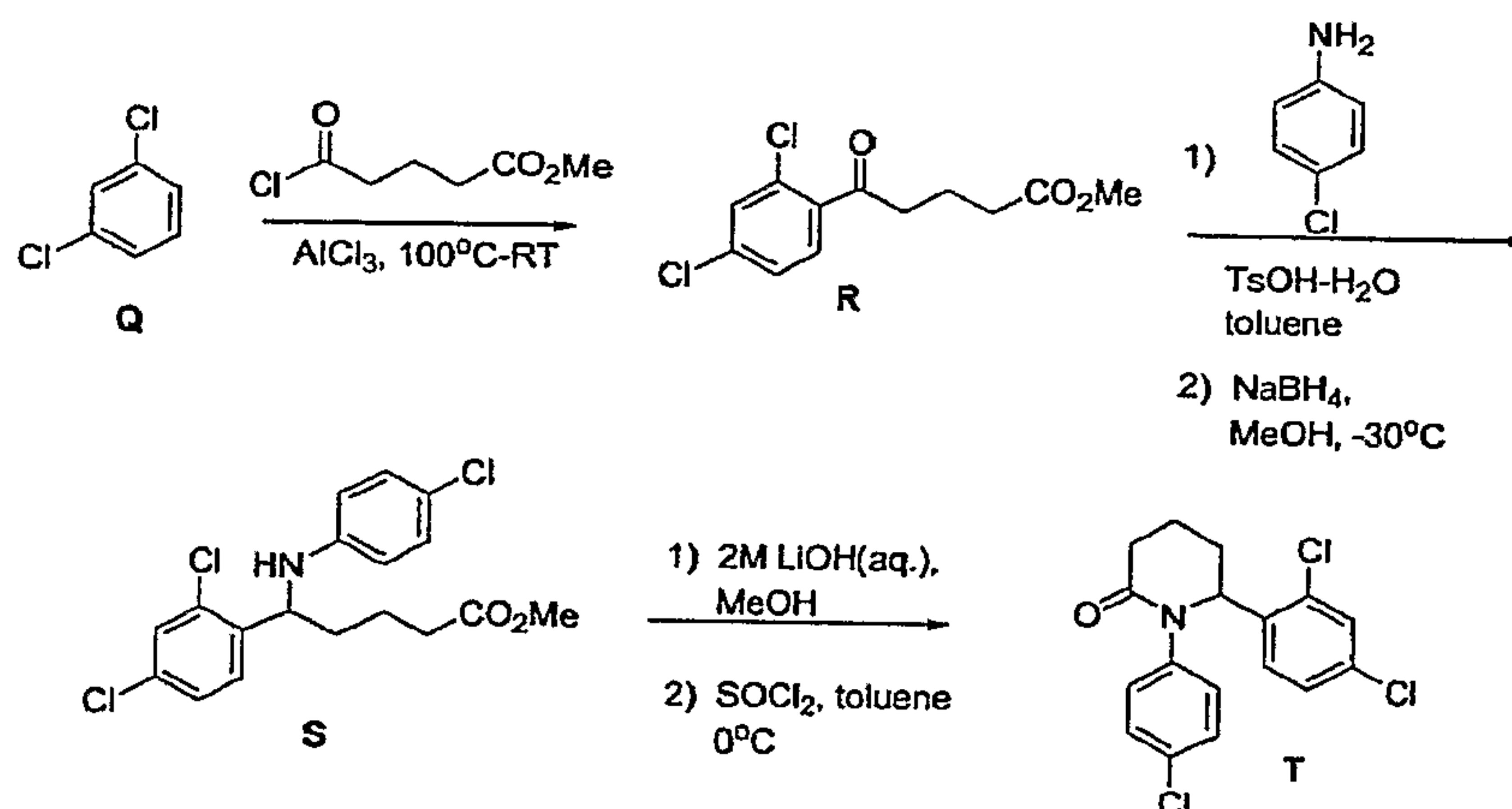
To a solution of the trans diastereomer **O** (60 mg, 0.2 mmol) in THF (3 mL) at 0°C was added DIAD (diisopropylazodicarboxylate) (43 mg, 0.21 mmol) and this solution was stirred at 0°C for 15 min. To this solution was added PPh₃ (61 mg, 0.23 mmol) and 3,4-difluorophenol (30 mg, 0.23 mmol). The solution was allowed to warm up to RT overnight. The solution was concentrated and partitioned between EtOAc and 1N NaOH. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude material was purified by repeated preparative TLC (SiO₂: 20% EtOAc/hexanes) to afford **Example 74** (10 mg).

Example 73 was prepared according to Step 3, above, except that cis diastereomer **P** was used instead of trans diastereomer **O**.

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Preparation of Example 75**Example 75**

To a suspension of KOH (26 mg, 0.47 mmol) in DMSO (1 mL) was added a solution of **O** (30 mg, 0.1 mmol) followed by 1-bromo-2-methylpropane (16 mg, 0.12 mmol). The solution was allowed to stir at RT overnight. Water and brine was added and the mixture was extracted with EtOAc (3x). Dried combined organic layers over Na₂SO₄, filtered and concentrated. The crude material was purified by preparative TLC (SiO₂: 23% EtOAc/hexanes) to afford **Example 75** (4 mg).

Preparation of Examples 76 and 77**Example 76****Example 77**

Step 1:

To a stirred suspension of AlCl_3 (19.2 g, 144 mmol) in 1,3-dichlorobenzene (**Q**) (43.2g, 294 mmol) was added glutaric acid monomethyl ester chloride (12g, 72 mmol). The resultant mixture was heated to 100°C for 4 hours. The solution was
5 allowed to slowly cool to room temperature and was stirred overnight at this temperature. To the solution was slowly added ice water followed by 1N HCl (aq.). The aqueous layer was extracted with CH_2Cl_2 . The organic layer was dried over Na_2SO_4 , filtered, and concentrated. The crude material was purified by flash chromatography using gradient elution (SiO_2 : 100:0 to 85:15 hexanes:ethyl acetate)
10 to afford ketone **R** (9.9 g, 50% yield) as a light yellow oil.

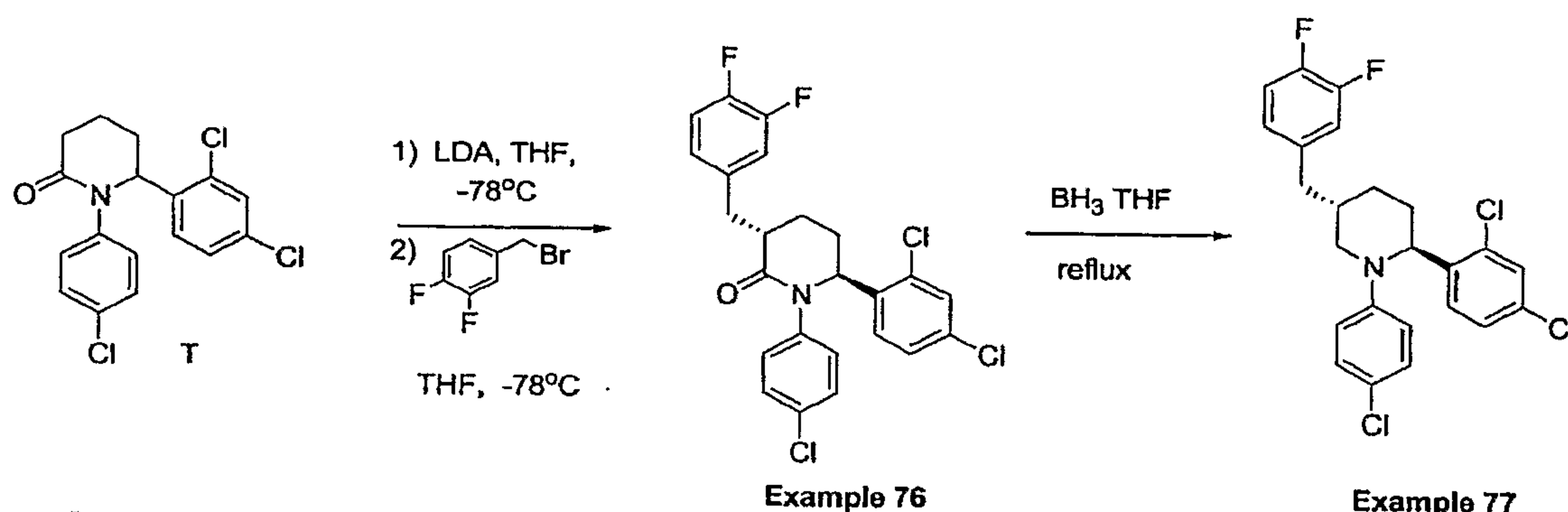
Step 2:

To a solution of the ketone **R** (10.5 g, 38.2 mmol) in toluene (150 mL) was added 4-chloroaniline (5.6 g, 43.9 mmol) and p-toluenesulfonic acid monohydrate (290 mg, 1.5 mmol). The solution was heated to reflux overnight with a Dean-Stark
15 trap attached. The solution was cooled to room temperature and concentrated. To the resultant oil was added MeOH (150 mL) followed by NaHCO_3 (1.3 g). The solution was cooled to -30°C and NaBH_4 (3.5 g) was added over 1 hour in portions. The solution was then stirred at -30°C for an additional 30 min. The solution was warmed to room temperature and water was added. The aqueous layer was
20 extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated to afford amino ester **S**. The material was used without purification.

Step 3:

To a solution of the crude amino ester **S** (35 mmol) in methanol (150 mL) was
25 added 2M LiOH (aq.) (57 mL, 115 mmol). The solution was stirred at room temperature for 4 h. The pH was adjusted to approx 6 using 4N HCl (aq.) The solution was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated. To the crude product was added anhydrous toluene (100 mL) and pyridine (8.3 g, 105 mmol). The resultant
30 solution was cooled to 0°C. To this solution was added dropwise a solution of SOCl_2 (3.1 mL, 42 mmol) in toluene (15 mL). After the addition was complete the solution was stirred for an additional 1 h. To the solution was added 1 M HCl (aq.). The

aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude material was purified by flash chromatography using gradient elution (SiO₂: 100:0 to 1:1 hexanes:ethyl acetate) to afford lactam **T** (3.4g, 25% yield over 4 steps) as a white solid.



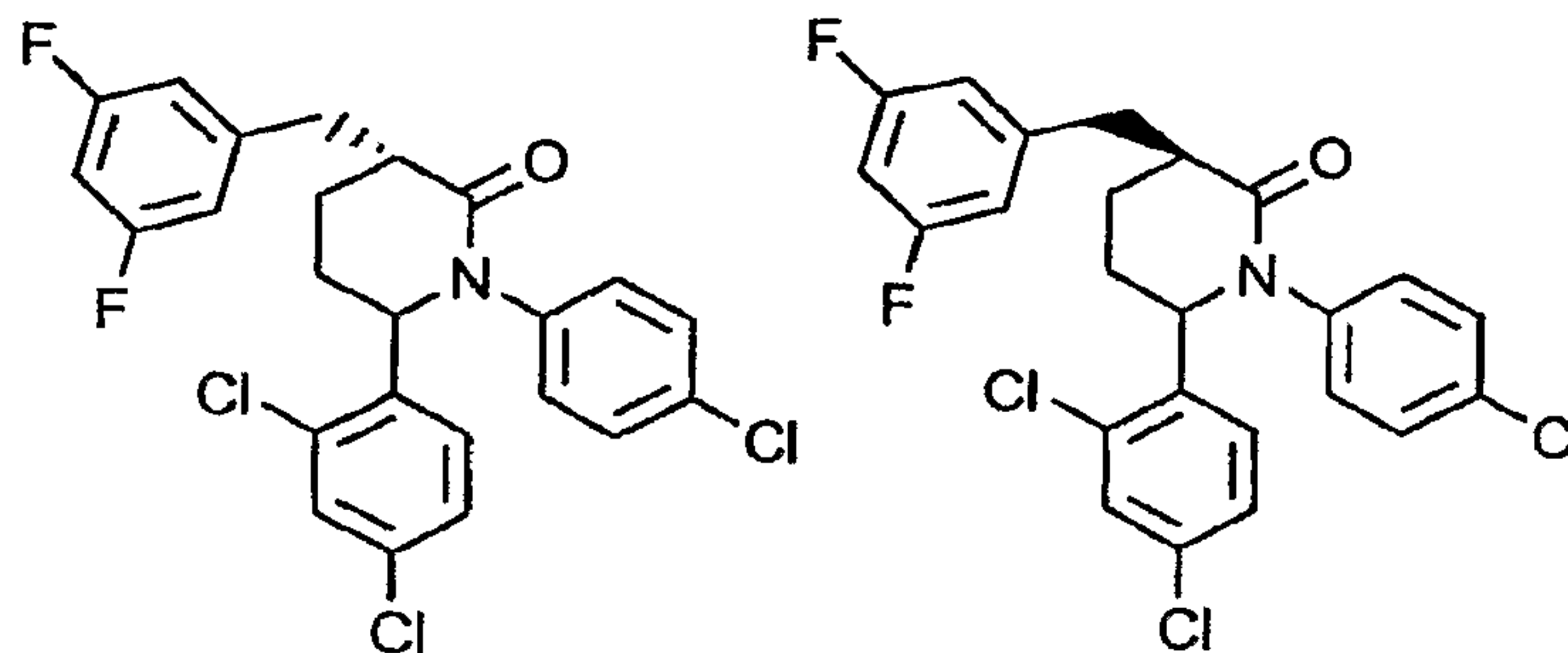
Example 76:

To a solution of LDA (2.52 mmol) in anhydrous THF (10 mL) at -78°C was added a solution of the lactam **T** (600 mg, 1.68 mmol) in anhydrous THF (2 mL). The solution was stirred at -78°C for 1 h. 3,4-difluorobenzyl bromide (2.52 mmol) was added slowly. After TLC confirmed the absence of lactam **T** (approx 30 min) the reaction was quenched with sat. NH₄Cl (aq.). The mixture was then extracted with EtOAc (3x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude material was purified by flash chromatography using gradient elution (SiO₂: 100:0 to 70:30 hexanes:ethyl acetate) to afford 210 mg **Example 76** (26% yield).

Example 77:

To a solution of **Example 76** in THF was added a solution of BH₃•THF complex (1 M solution in THF, 1.3 mL). The solution was heated to reflux for 2h. To this solution was added MeOH and the solution was concentrated. The crude product was partitioned between CH₂Cl₂ and H₂O. The aqueous layer was extracted with CH₂Cl₂ (3x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude material was purified by flash chromatography using gradient elution (SiO₂: 100:0 to 96:4 hexanes:ethyl acetate) to afford 170 mg of **Example 77** (83% yield).

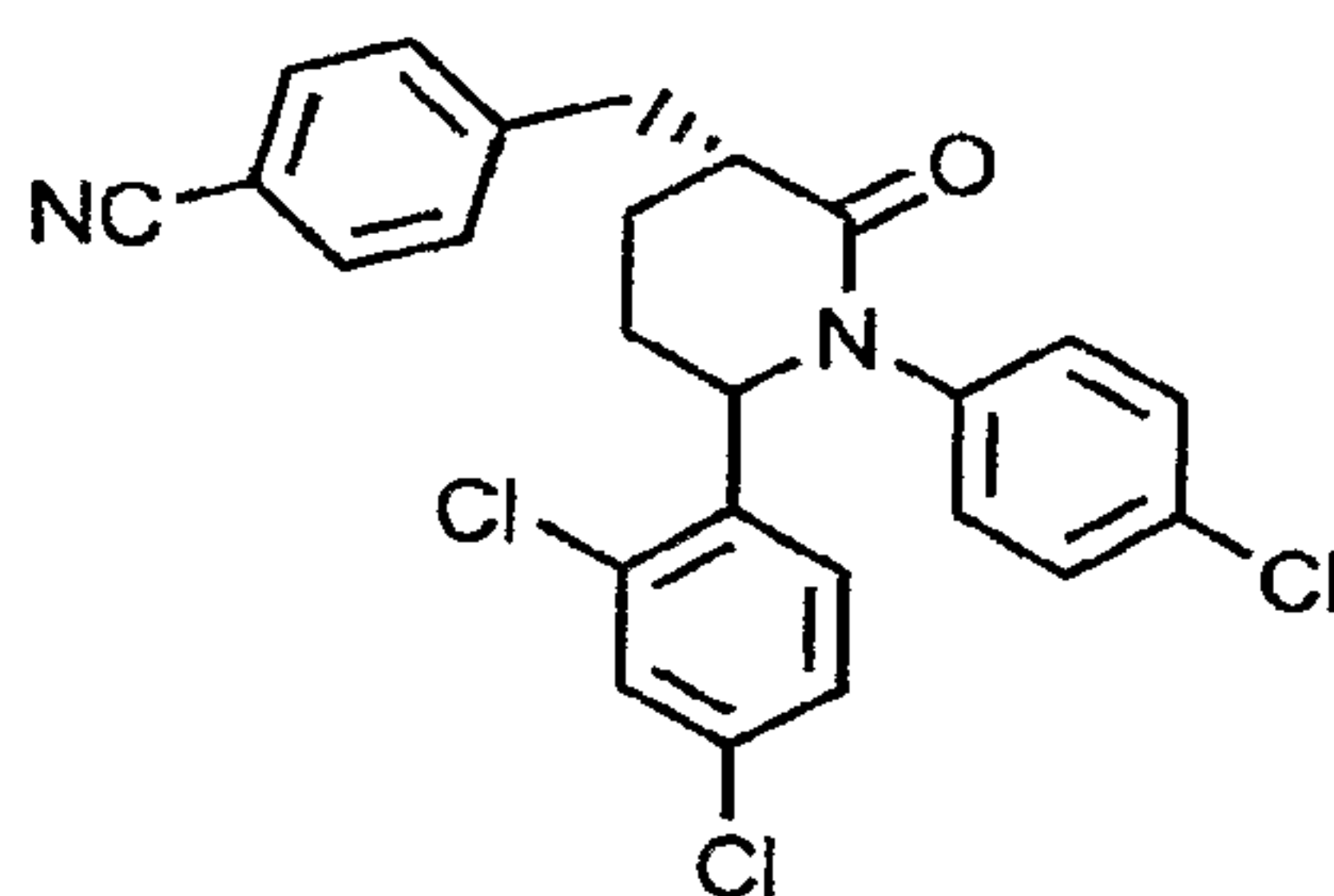
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Preparation of Examples 78 and 79

Example 78

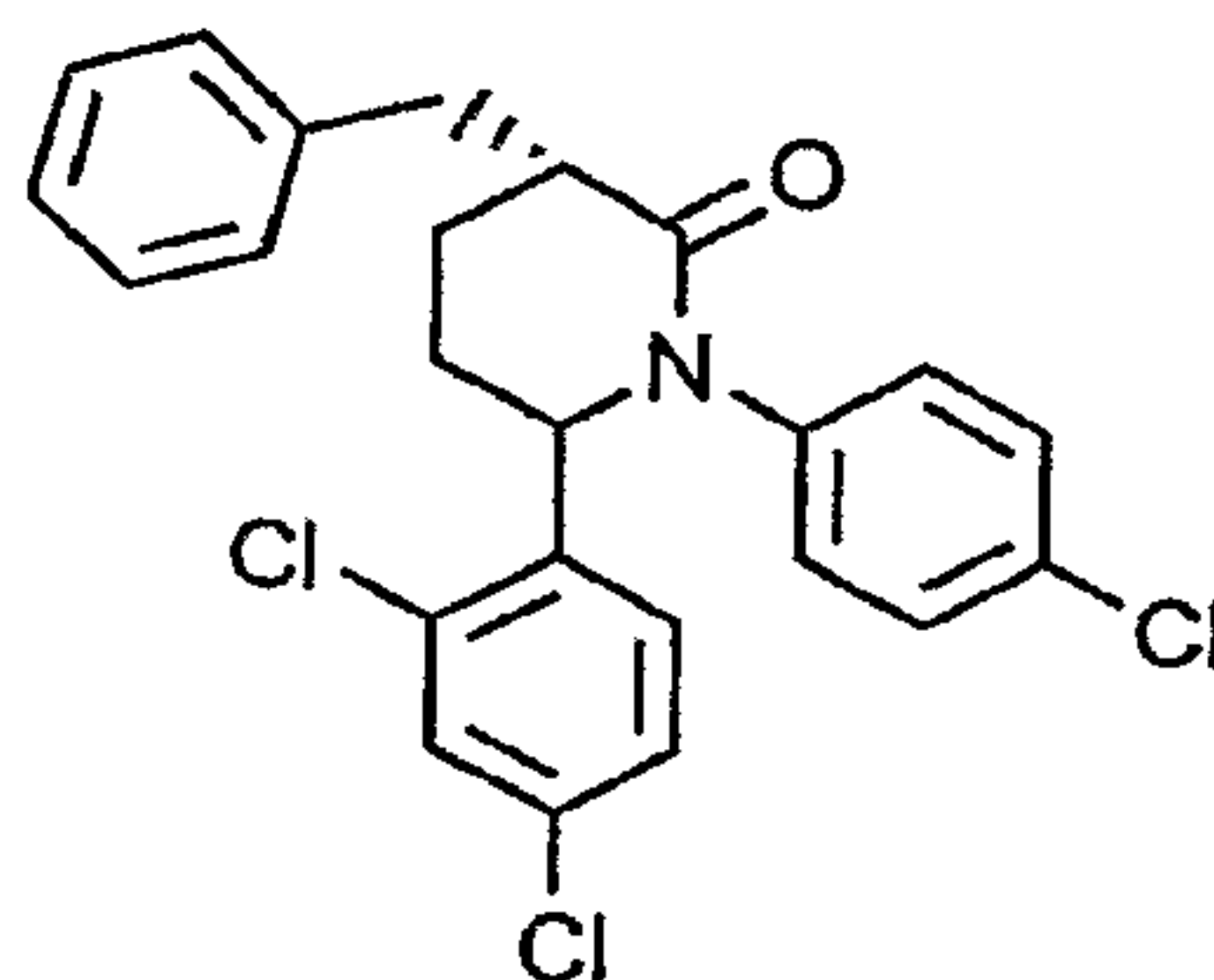
Example 79

Examples 78 and 79 were prepared using procedures similar to those described above for **Example 76**, except that 3,5-difluorobenzyl bromide was used instead of 3,4-difluorobenzyl bromide.

Preparation of Example 80

Example 80

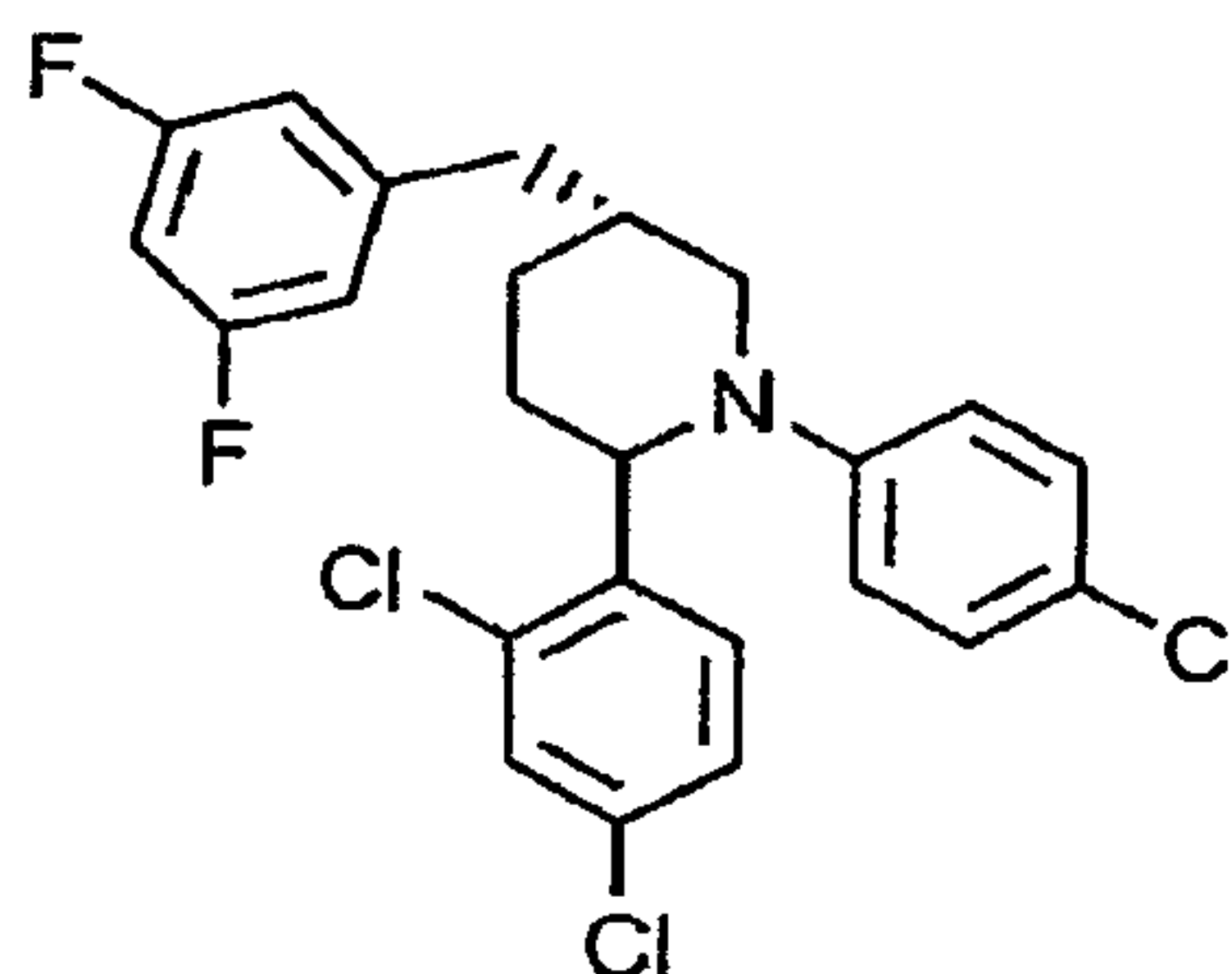
Example 80 was prepared using a procedure similar to that described above for **Example 76**, except that 4-cyanobenzyl bromide was used instead of 1-bromo-2-methylpropane.

Preparation of Example 81

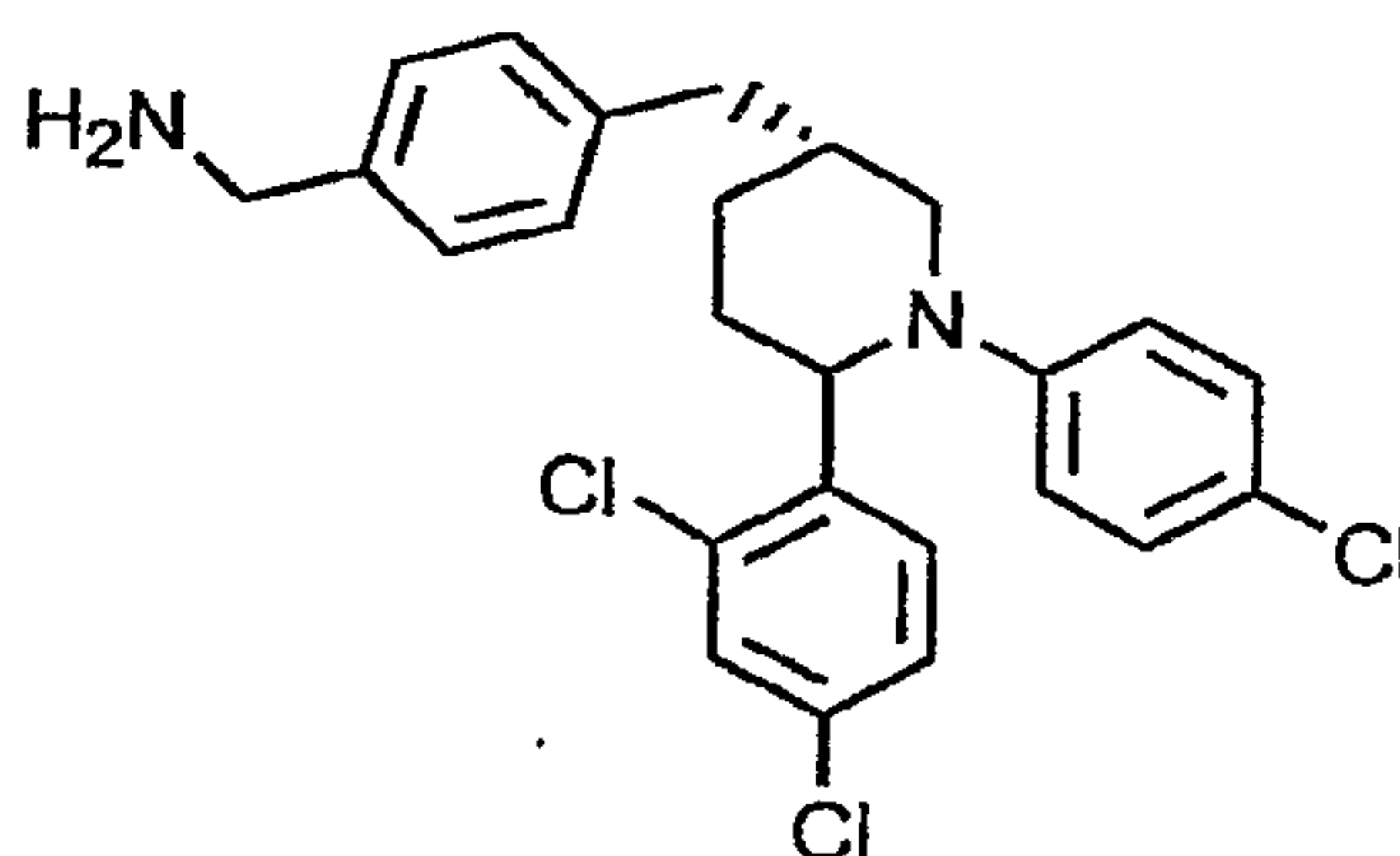
Example 81

Example 81 was prepared using a procedure similar to that described above for **Example 76**, except that benzyl bromide was used instead of 1-bromo-2-methylpropane.

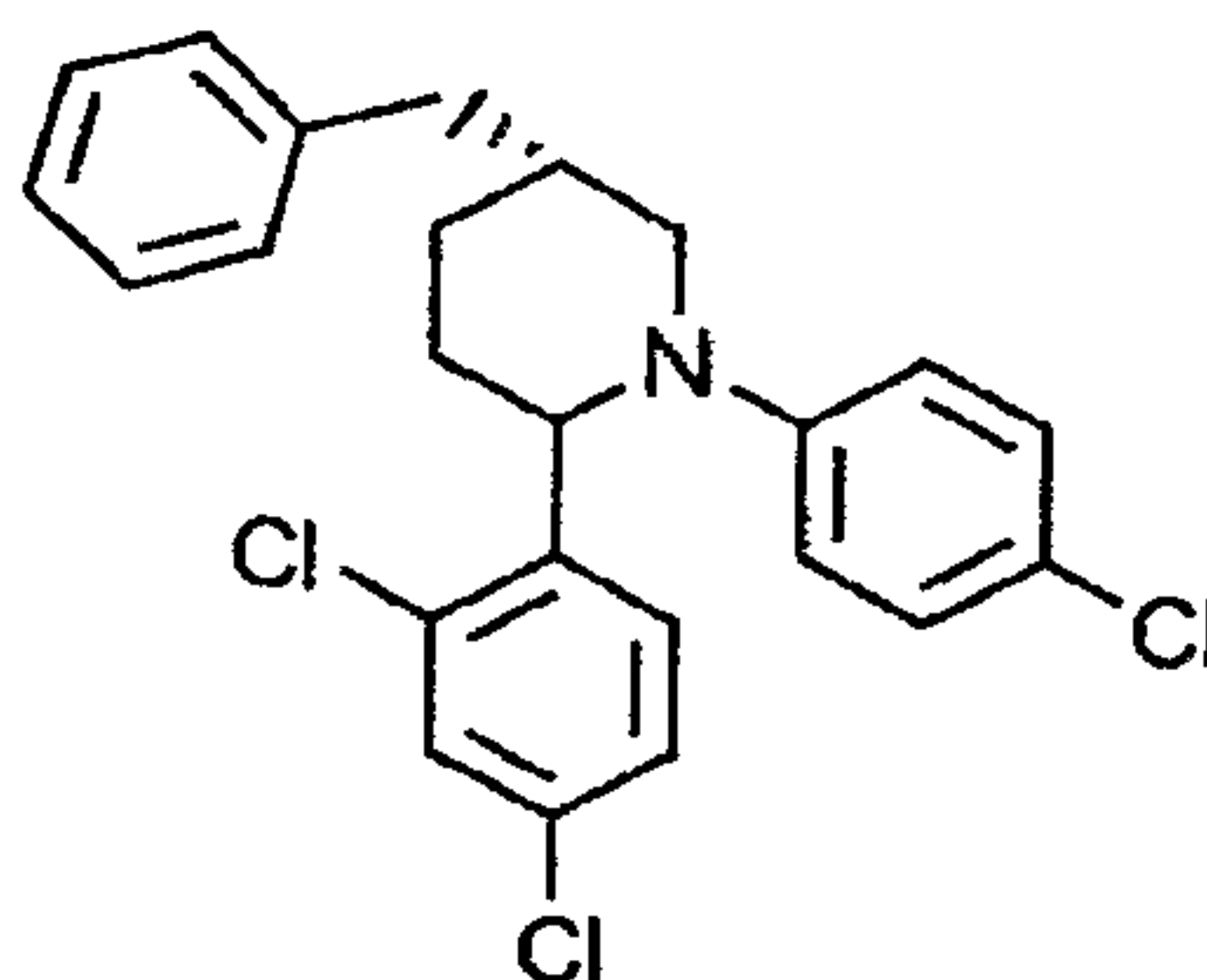
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Preparation of Example 82**Example 82**

Example 82 was prepared using a procedure similar to that described above for **Example 77**, except that **Example 78** was used as the starting material instead of **Example 76**.

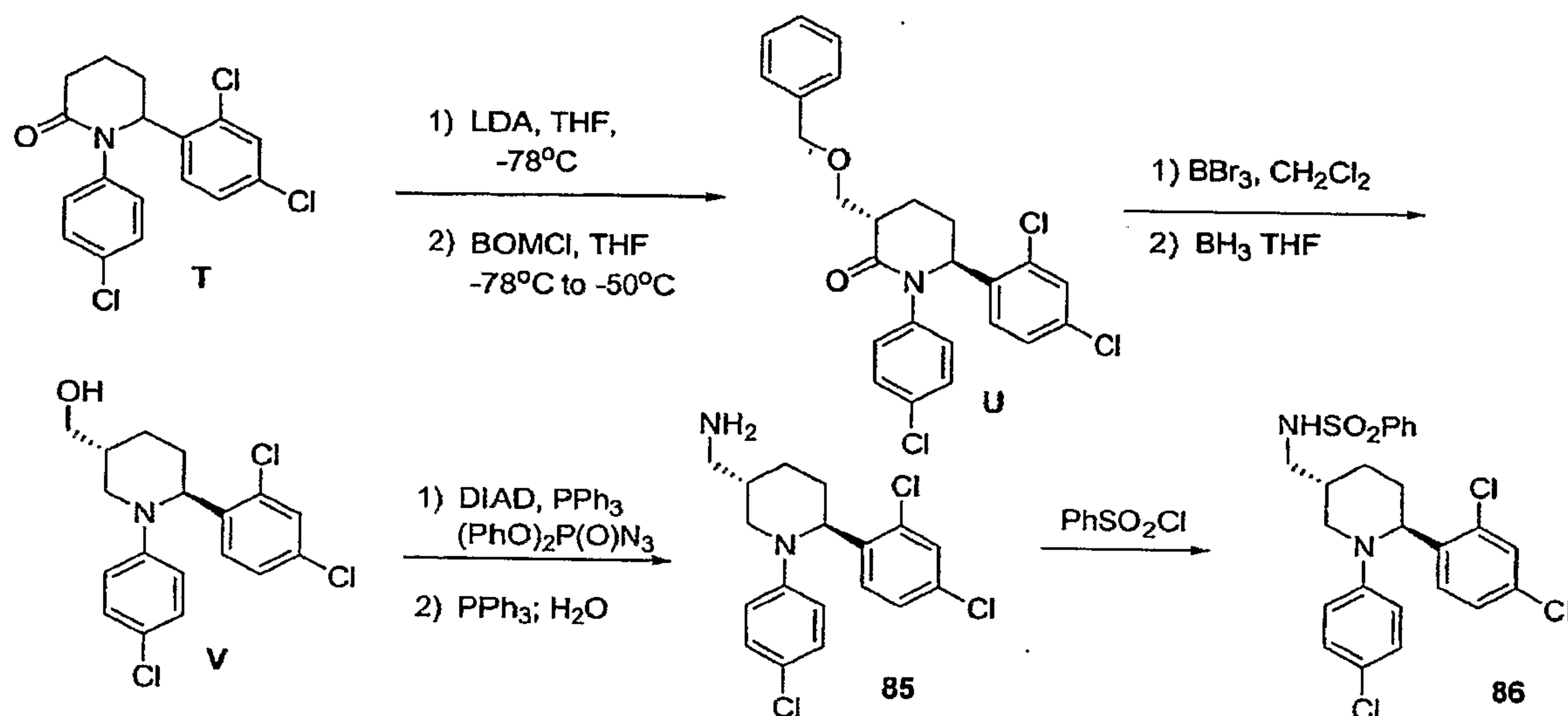
Preparation of Example 83**Example 83**

To a solution of **Example 80** (160 mg, 0.33 mmol) in THF (2 mL) was added $\text{BH}_3 \cdot \text{THF}$ complex (1 M solution in THF, 1.0 mL). The solution was heated to reflux for 2h. To this solution was added MeOH and the solution was concentrated. The crude product was partitioned between CH_2Cl_2 and H_2O . The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by prep TLC (SiO_2 : 4:1 hexanes:EtOAc) to afford **Example 83** (18 mg).

Preparation of Example 84**Example 84**

Example 84 was prepared using a procedure similar to that described above for **Example 77**, except that **Example 81** was used as the starting material instead of **Example 76**.

Preparation of Examples 85 and 86



Step 1:

To a solution of LDA (4.23 mmol) in anhydrous THF at -78°C was added a solution of the lactam **T** (1.0 g, 2.82 mmol) in anhydrous THF (2 mL). The solution was stirred at -78°C for 1 h. To this solution was added benzyl chloromethyl ether (530 mg, 3.4 mmol). The solution was warmed to -50°C and allowed to stir at this temperature for 1h. Saturated NH₄Cl was added and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude material was purified by flash chromatography using gradient elution (SiO₂: 100:0 to 75:25 hexanes:ethyl acetate) to afford 567 mg ether **U** (42% yield).

Step 2:

To a solution of ether **U** (567 mg, 1.25 mmol) in anhydrous CH₂Cl₂ at 0°C was added BBr₃ (1 M solution in hexanes, 1.87 mmol). The solution was warmed to RT and allowed to stir at this temperature for 2h. To this solution was added NaHCO₃ (aq.). The mixture was extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude material was purified by flash chromatography using gradient elution (100:0 to 1:9 hexanes:ethyl acetate) to afford 400 mg product (83% yield). The product was dissolved in anhydrous THF (5 mL).

To this solution was added borane THF complex (1M in THF, 3.1 mL). The solution was heated to reflux for 2h. The solution was cooled to RT and 1M HCl was slowly added. The resultant mixture was stirred at RT for 30 min. The solution was basified by the addition of NaHCO₃ (aq.) and extracted with CH₂Cl₂ (3x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude material was purified by flash chromatography using gradient elution (100:0 to 65:35 hexanes:ethyl acetate) to afford 310 mg of alcohol **V** (67% yield for the 2 steps).

Example 85:

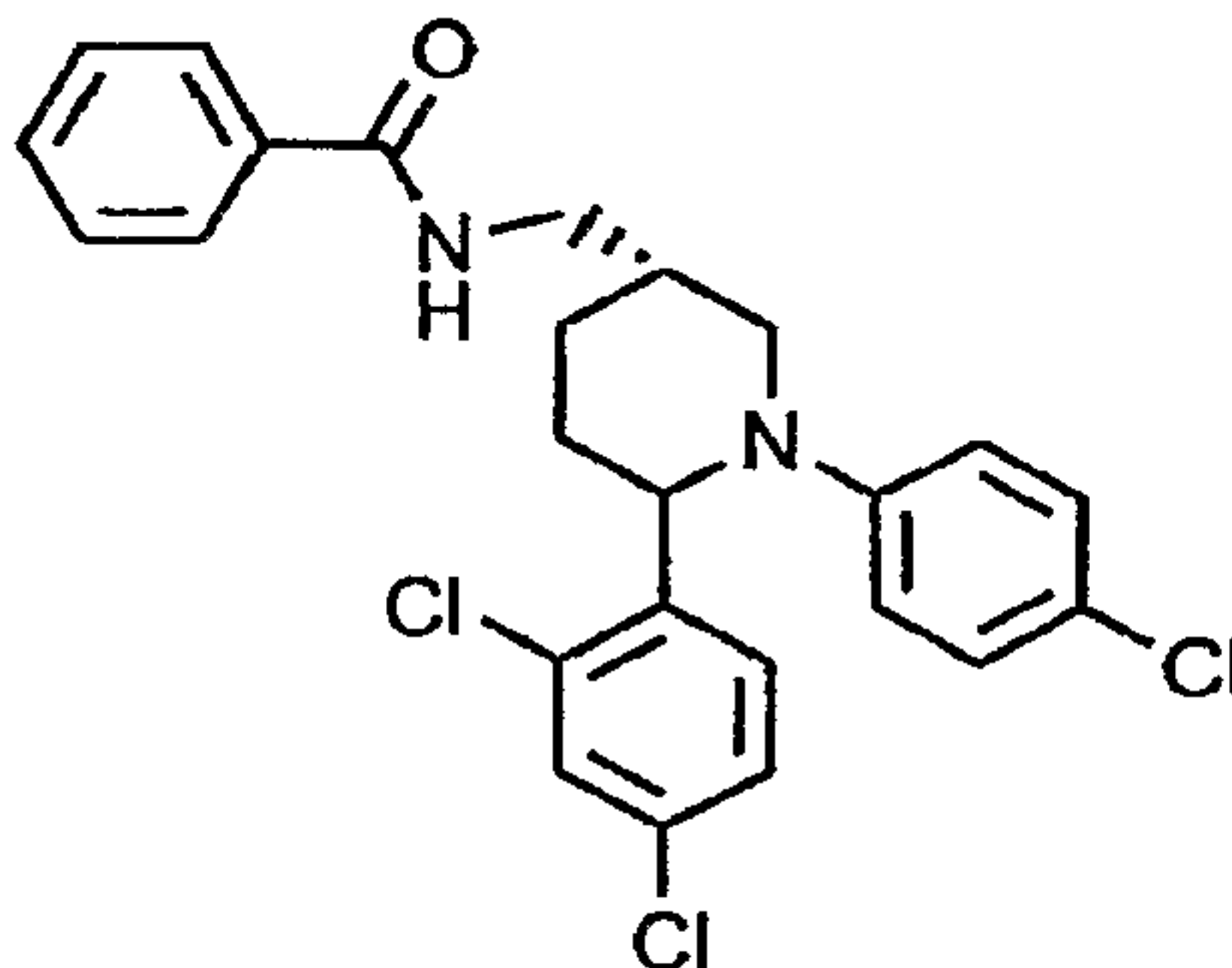
To a solution of the alcohol **V** (320 mg, 0.88 mmol) in THF (3 mL) at 0°C was added PPh₃ (460 mg, 1.76 mmol) followed by the addition of DIAD (356 mg, 1.76 mmol). After the formation of a white precipitate (ca. 2 min) DPPA (484 mg, 1.76 mmol) was added. The mixture was warmed to RT and allowed to stir an additional 1.5 h. Water (3 drops) was added to the reaction mixture and the solution was concentrated. The crude material was purified by flash chromatography using gradient elution (SiO₂: 100:0 to 95:5 hexanes: EtOAc) to afford the azide (270 mg).

To a solution of the azide (70 mg, 0.18 mmol) stirred at RT for 1 h followed by an additional 1.5 h at 60°C, water (0.094 mL) was added and the mixture was stirred at 45°C for 2.5 days. To this mixture was added Na₂SO₄ (ca. 50 mg) and the mixture was stirred at RT for several minutes. The mixture was filtered and concentrated. The crude material was purified by preparative TLC (SiO₂: 90:9.3:0.7 CH₂Cl₂:MeOH:conc. NH₄OH(aq.)) to afford **Example 85** (53mg).

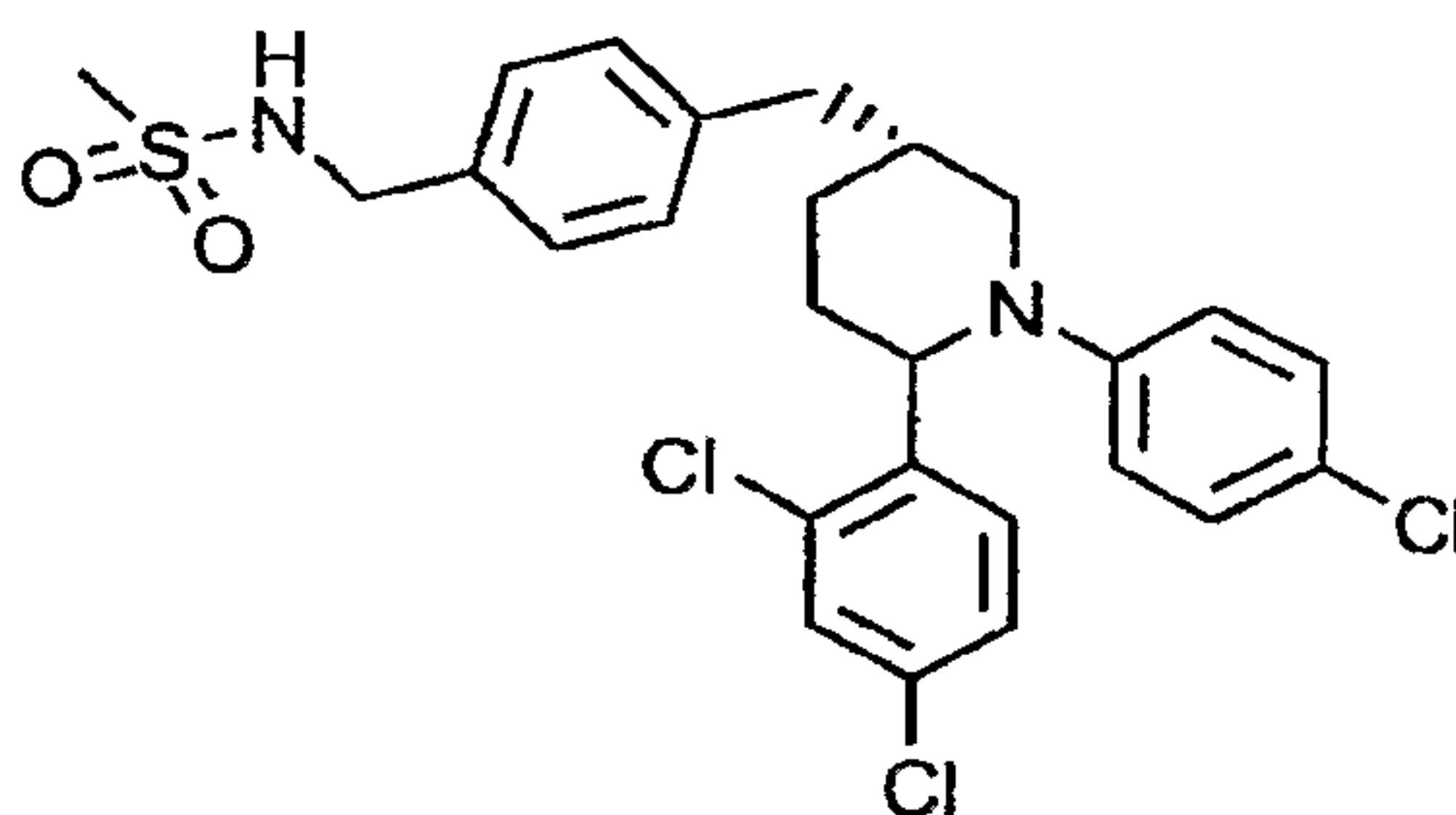
Example 86:

To a solution of **Example 85** (53 mg, 0.14 mmol) in CH₂Cl₂ (2 mL) was added Et₃N (10 drops) followed by benzene sulfonyl chloride (76 mg, 0.43 mmol). The solution was stirred at RT overnight and concentrated. The crude product was purified by prep TLC (SiO₂: 3:1 hexanes: EtOAc) to afford **Example 86** (53 mg, 74% yield).

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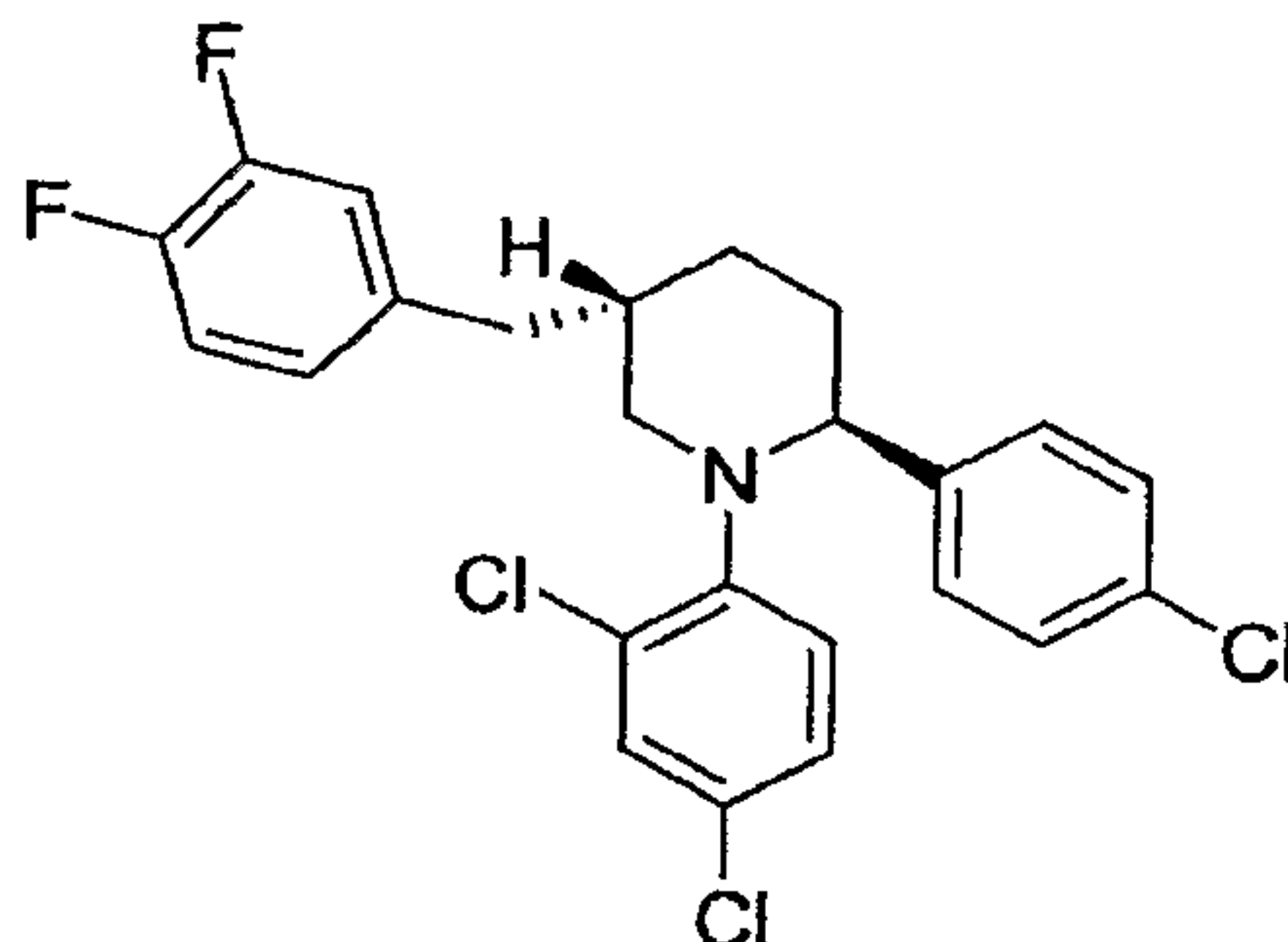
Preparation of Example 87**Example 87**

Example 87 was prepared using procedures similar to those for preparing **Example 86**, except that benzoyl chloride was the reagent used instead of benzene sulfonyl chloride.

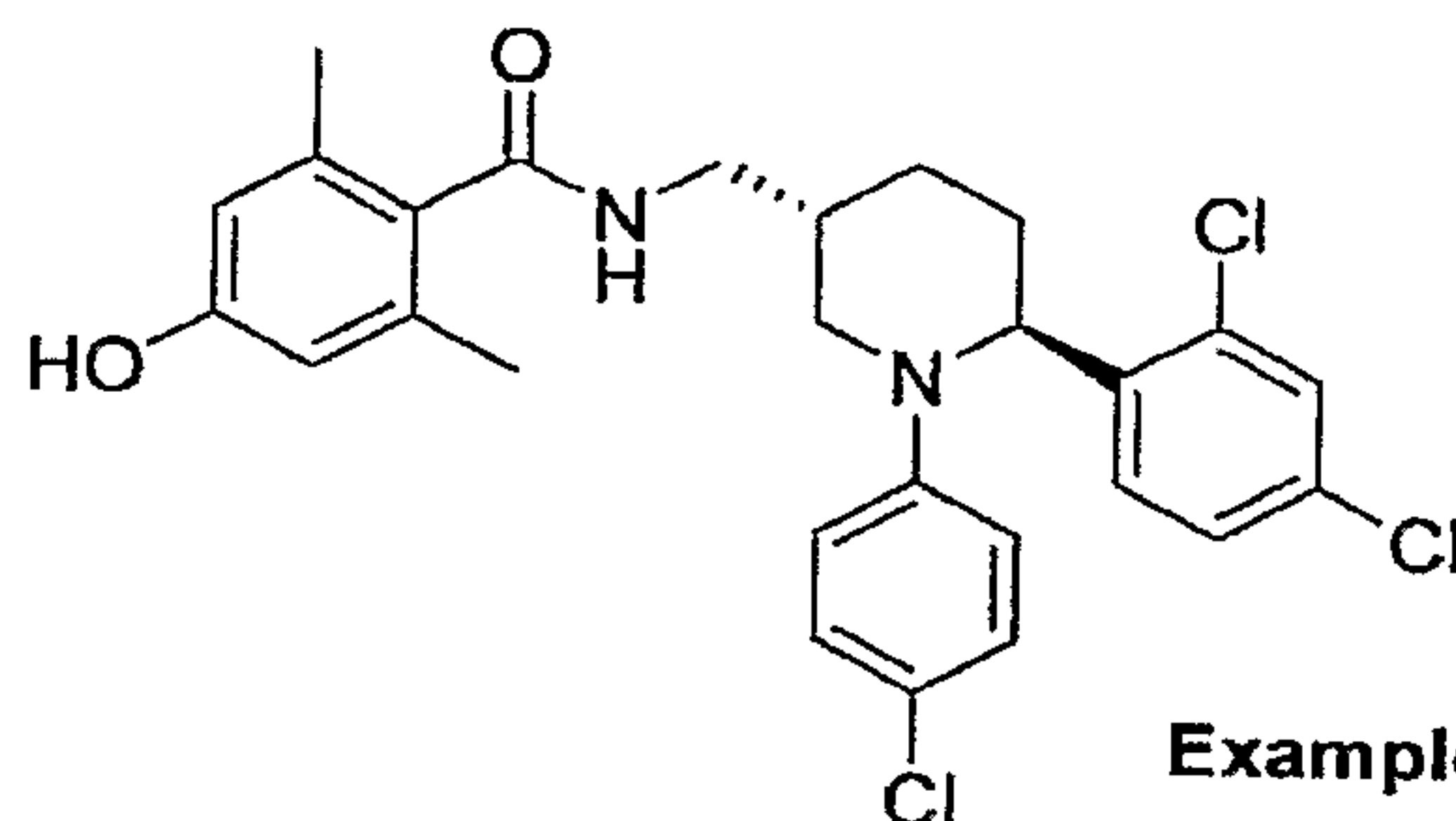
Preparation of Example 88**Example 88**

To a solution of **Example 83** (15 mg, 0.033 mmol) in CH_2Cl_2 (1 mL) was added pyridine (3 drops) and methane sulfonyl chloride (7 mg, 0.66 mmol). The solution was heated to reflux and stirred overnight. The solution was then concentrated and partitioned between EtOAc and NaHCO_3 (aq.). The aqueous layer was extracted with EtOAc. The organic layer was dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by prep TLC (SiO_2 : 3:1 hexanes: EtOAc) to afford **88** (10 mg).

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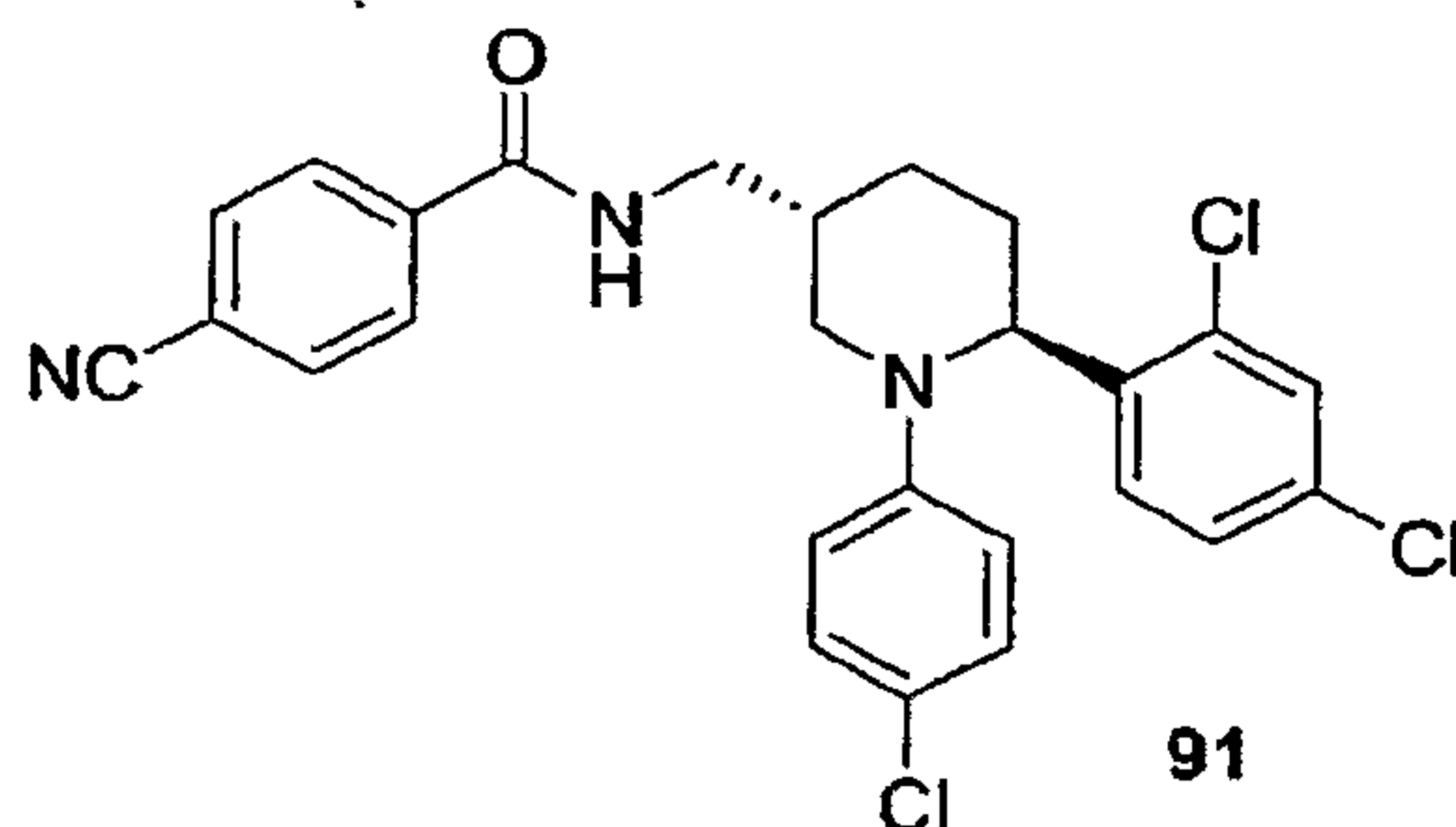
Preparation of Example 89**Example 89**

To a solution of **Example 72** (50 mg, 0.116 mmol) in CH_2Cl_2 (3 mL) was added in portions over 2 h sulfuryl chloride (42 mg, 0.318 mmol). The solution was allowed to stir at RT for an additional 1 h. Water was added and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by repeated prep TLC (SiO_2 ; 4:1 and 8:1 hexanes:EtOAc) to afford **Example 89** (1 mg).

Preparation of Example 90**Example 90**

To a solution of **Example 85** (35 mg, 0.095 mmol) in MeCN (1.5 mL) was added EDCI (27 mg, 0.14 mmol), HOBt (20 mg, 0.14 mmol), $i\text{Pr}_2\text{NEt}$ (61 mg, 0.48 mmol) and 4-hydroxy-2,6-dimethyl benzoic acid (31 mg, 0.19 mmol). 4-hydroxy-2,6-dimethyl benzoic acid was prepared by the method described in U.S. Patent 6391865B1, which is herein incorporated by reference. The solution was allowed to stir at RT overnight. The solution was concentrated and partitioned between water and CH_2Cl_2 . The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by preparative TLC (1:1 EtOAc: hexanes) to afford 37 mg of **Example 90**.

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Preparation of Example 91

Example 91 was prepared using procedures similar to those used to prepare **Example 90**, except 4-cyanobenzoic acid was used instead of 4-hydroxy-2,6-dimethyl benzoic acid.

Preparation of Example 92

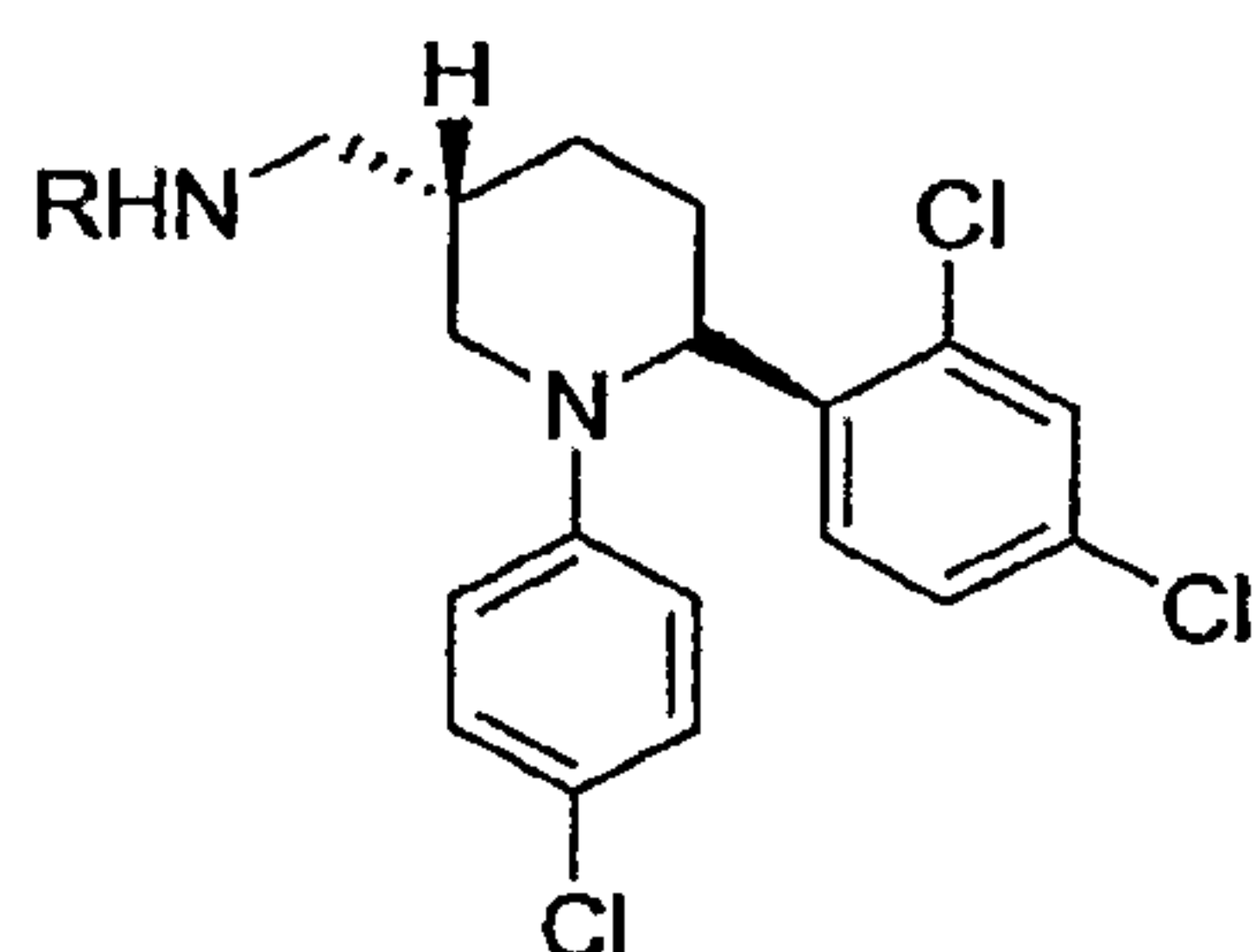
Example 92 was prepared using procedures similar to those used to prepare **Example 90**, except 4-fluorobenzoic acid was used instead of 4-hydroxy-2,6-dimethyl benzoic acid.

Examples 93 through 124

Sulfonamide analogs were prepared by the reaction of **Example 85** with a sulfonyl chloride library as indicated below.

PS-DIEA (33 mg, 0.11 mmol) (Argonaut Technologies) was added to a 96-well microtiter plate followed by a stock solution of **Example 85** (0.022 mmol) in dioxane/THF (1 mL 7:3 dioxane/THF). A stock solution of one of the various sulfonyl chlorides listed in the table below (0.088 mmol, 0.5M in THF) was added to each well of the microtiter plate and the plate was sealed and shaken overnight. PS-isocyanate (44 mg, 0.066 mmol) (Argonaut Technologies), PS-trisamine (32 mg, 0.13 mmol) (Argonaut Technologies) and MeCN (0.5 mL) were added to each well. The plate was resealed and shaken overnight. The solutions were filtered through a polypropylene frit into a 96 well collection plate and the resin was washed with MeCN (3x 0.5 mL). The resultant solutions were transferred into 2-dram vials and the solvents were removed in vacuo via a SpeedVac concentrator. The resulting samples were evaluated by LCMS and those that were >70% pure are listed in the table below:

137



Ex.	R	Sulfonyl chloride
93		
94		
95		
96		
97		
98		
99		
100		
101		

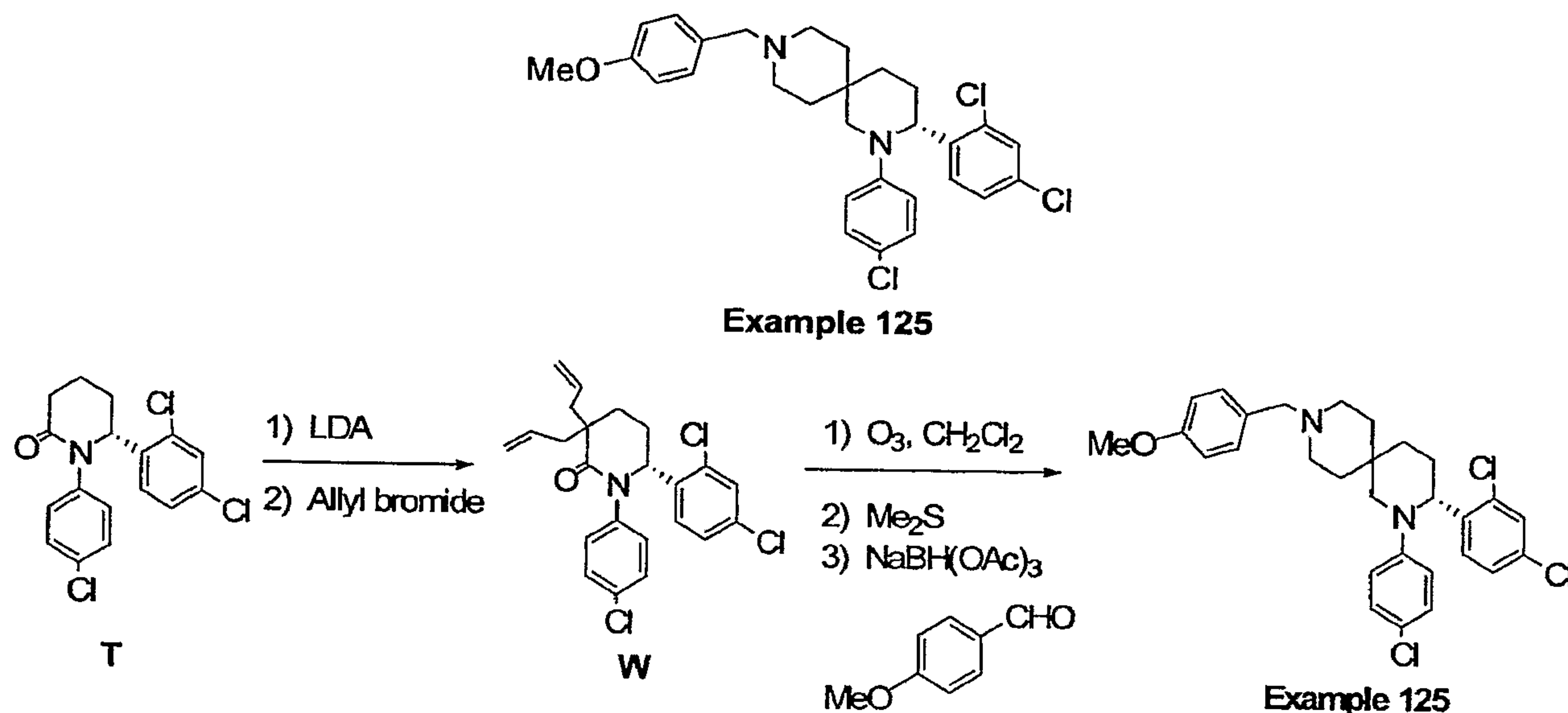
138

Ex.	R	Sulfonyl chloride
102		
103		
104		
105		
106		
107		
108		
109		
110		
111		
112		
113		

139

Ex.	R	Sulfonyl chloride
114		
115		
116		
117		
118		
119		
120		
121		
122		
123		
124		

140

Preparation of Example 125**5 Step 1:**

A solution of lactam **T** (940 mg, 2.65 mmol) in THF (20 mL) at -78°C was added to a solution of LDA (7.95 mmol) in THF (20 mL). The resultant solution was stirred at -78°C for 30 min. Allyl bromide (737 mg, 6.09 mmol) was added and the solution was stirred at -78°C for 30 min. The reaction was quenched with pH 6.0 buffer and the mixture was allowed to warm to RT. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by flash chromatography (SiO_2 : gradient elution 100:0 to 80:20 hexanes:EtOAc) to afford 540 mg **W**.

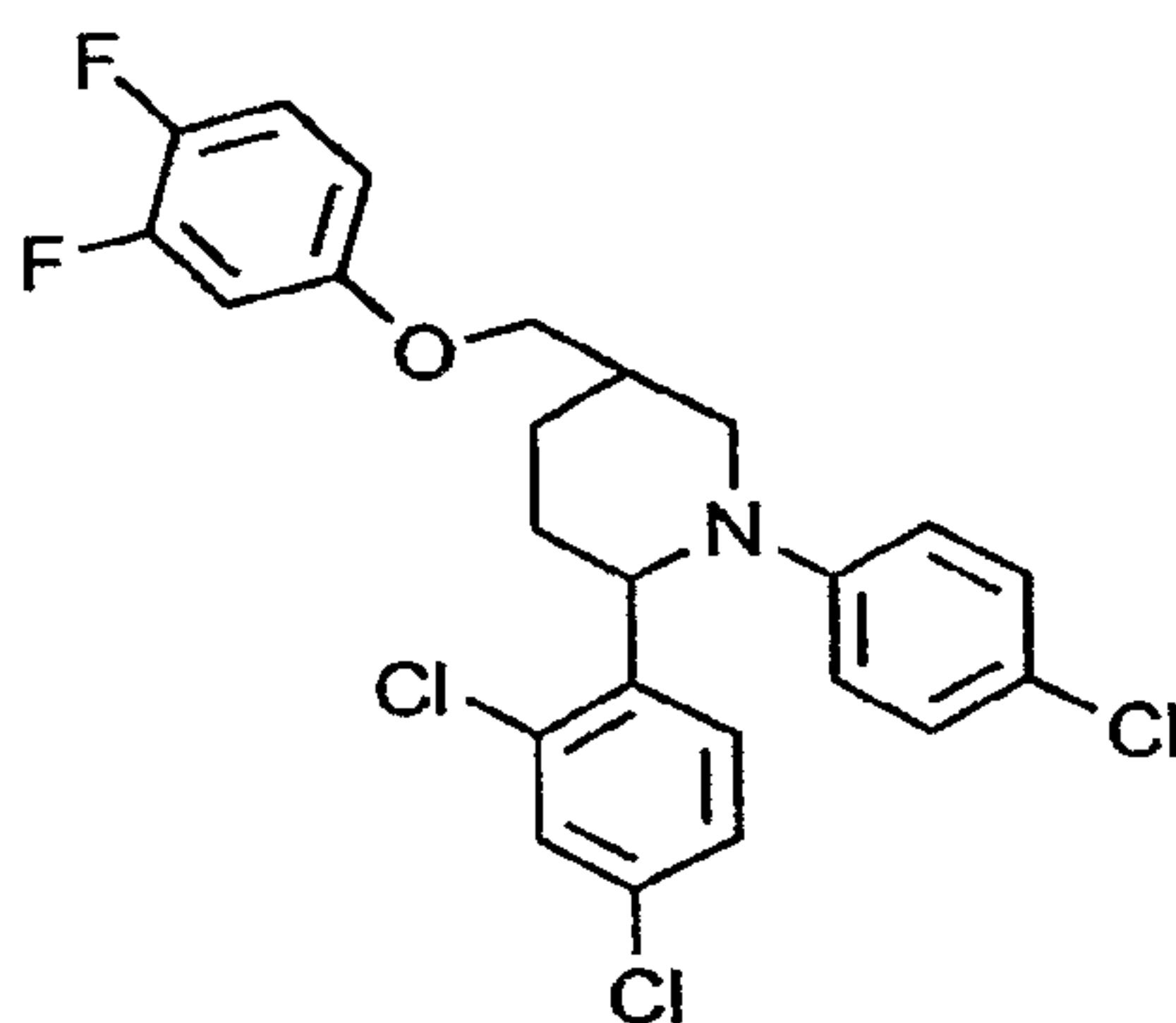
15 Step 2:

To a solution of **W** (640 mg, 1.47 mmol) in CH_2Cl_2 at -78°C was bubbled O_3 until the solution turned blue. The solution was then degassed with N_2 and excess Me_2S was added. The solution was warmed to RT and stirred overnight. The solution was concentrated and partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was redissolved in 1,2-dichloroethane (20 mL). To this solution was added 4-methoxybenzylamine (303 mg, 2.2 mmol) and $\text{NaBH}(\text{OAc})_3$ (934 mg, 4.4 mmol). The resultant mixture was

141

stirred at RT for 96 h. The solution was diluted with CH₂Cl₂ and the organic layer was washed with 1 M NaOH. The aqueous layer was extracted with CH₂Cl₂ (2x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by preparative TLC (1:1 Acetone: hexanes) to afford 140 mg **Example 125**.

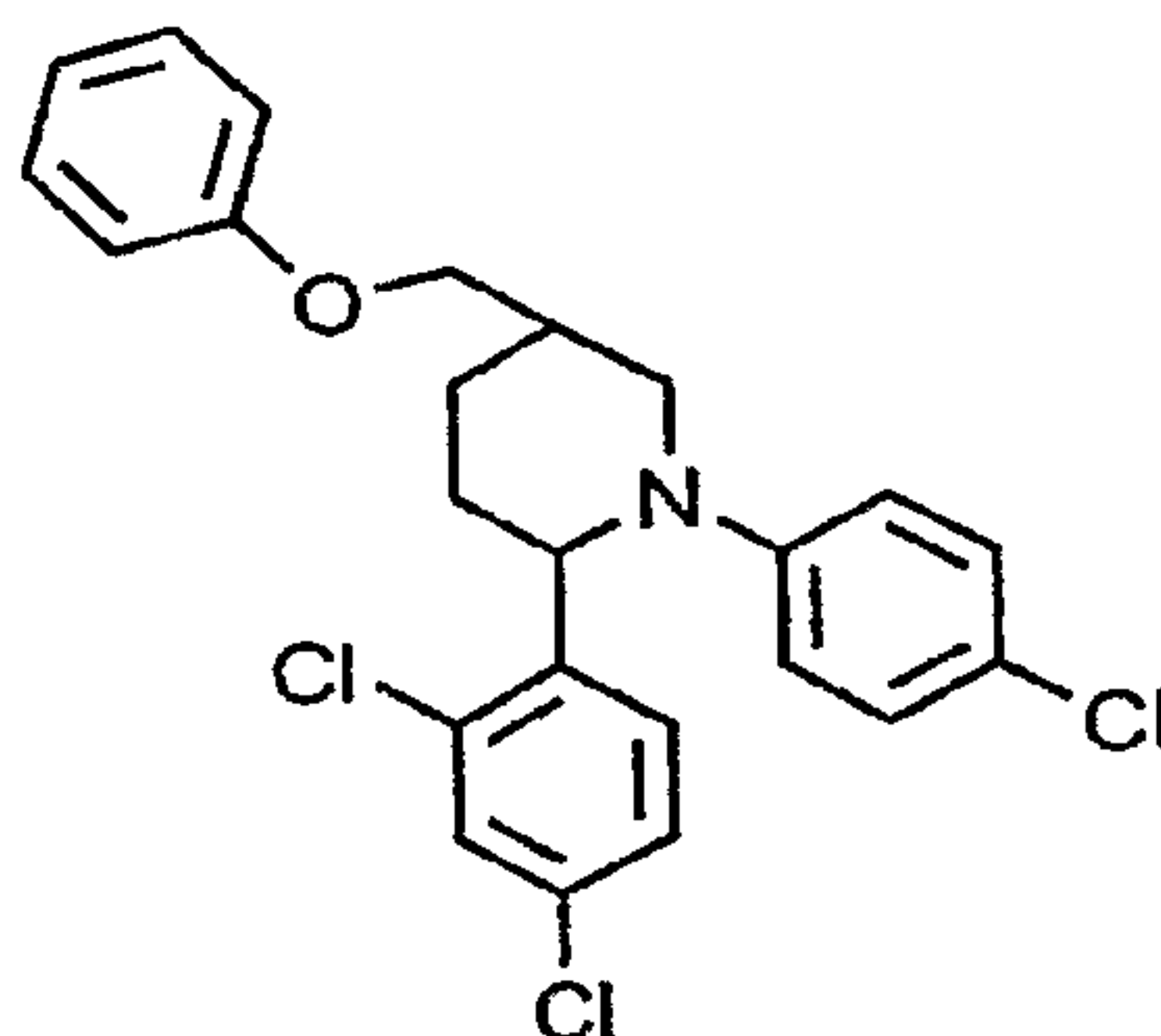
Preparation of Example 126



Example 126

Example 126 was prepared using procedures similar to those used to prepare **Example 74**, except alcohol **V** was used instead of alcohol **O** in Step 3.

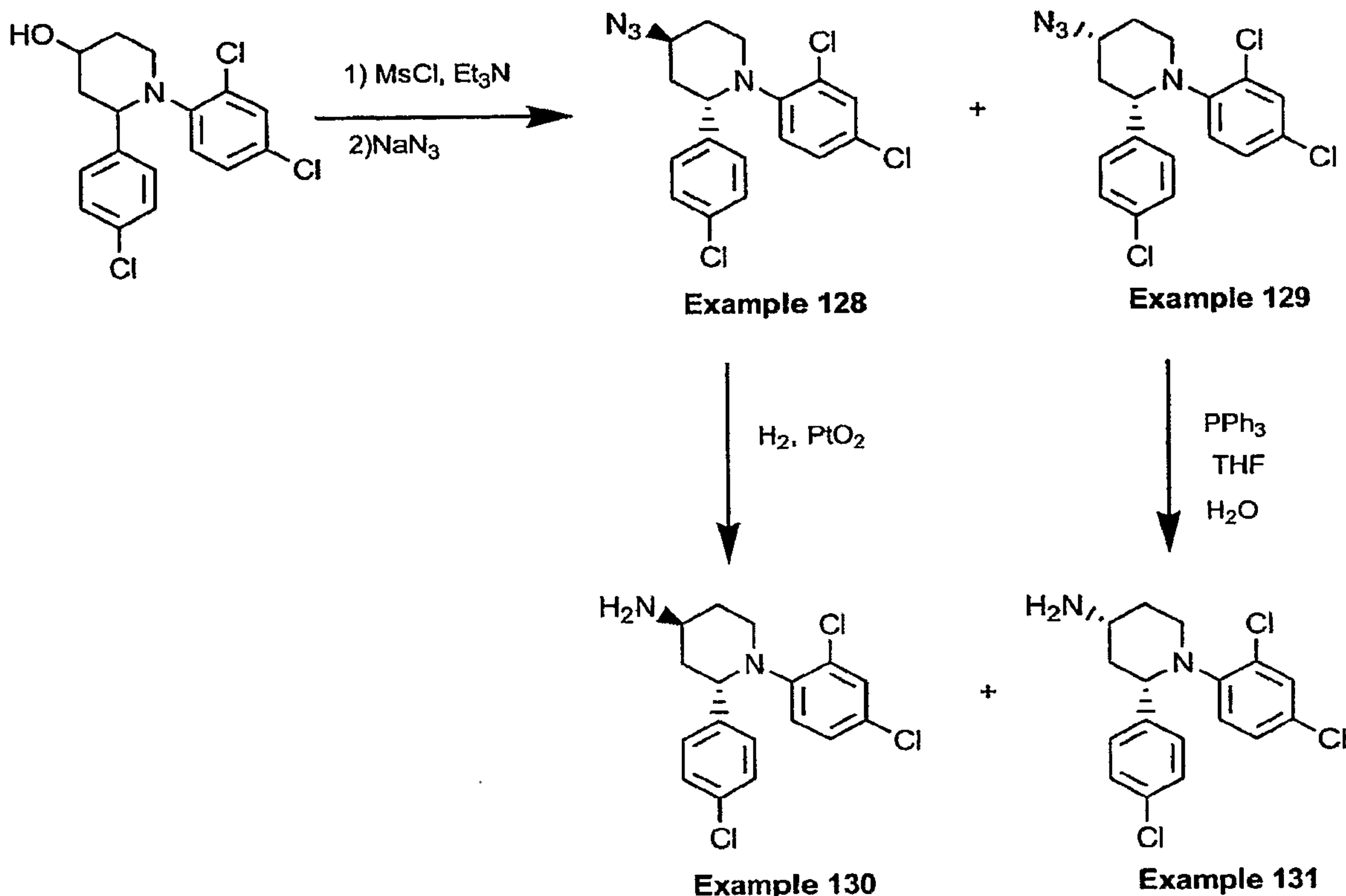
Preparation of Example 127



Example 127

Example 127 was prepared using procedures similar to those used to prepare **Example 126**, except phenol was used instead of 3,4-difluorophenol.

142

Preparation of Examples 128-131**Step 1:**

To a solution of the alcohol from Step 2 of **Examples 1 and 2** (43 mg, 0.12 mmol) in CH_2Cl_2 (0.7 mL) at 0°C was added Et_3N (31 mg, 0.30 mmol) and methane sulfonyl chloride (18 mg, 0.16 mmol). The mixture was stirred at 0°C for 1 hour followed by an additional 1 hr at RT. Water was added and the aqueous layer was extracted with CH_2Cl_2 . The organic layer was dried over Na_2SO_4 , filtered and concentrated.

Step 2:

To a solution of the mesylate from step 1 (38 mg, 0.088 mmol) in DMF (0.4 mL) was added sodium azide (12 mg, 0.17 mmol). The solution was heated to 83°C for 6 hr. The solution was concentrated. The material was partitioned between water and CH_2Cl_2 . The organic layer was dried over Na_2SO_4 , filtered and concentrated. The crude material was purified by prep TLC (SiO_2 , 7:3 hexanes: Et_2O) to afford 6 mg of **Example 128** and 6 mg of **Example 129**.

143

Step 3:

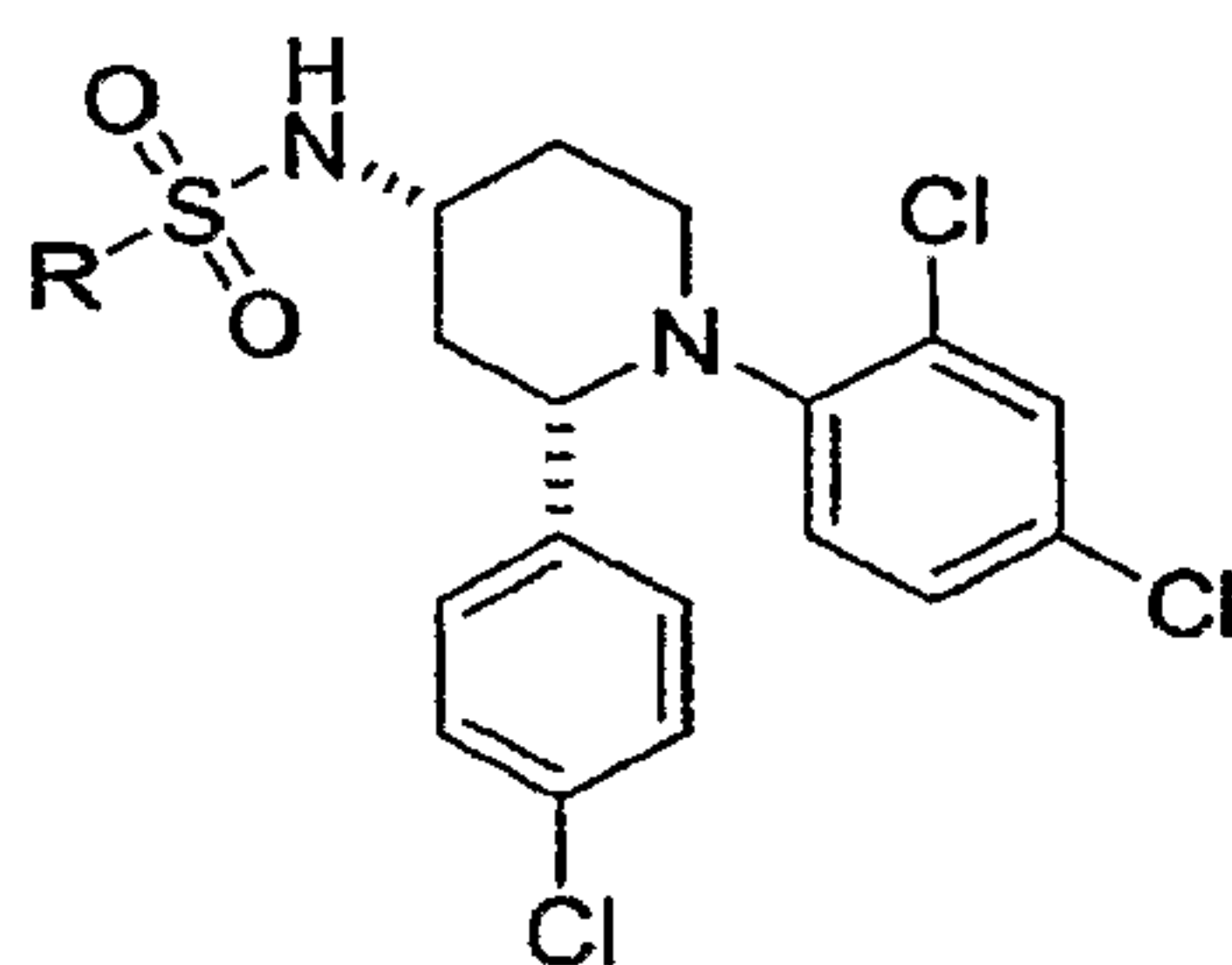
To a solution of **Example 128** (4.8 mg) in MeOH (0.15 mL) was added PtO₂ (1.6 mg) in a round bottom flask and the flask was sealed with a septum. A balloon filled with H₂ was attached to the flask. The mixture was stirred at RT for 2 hr. The catalyst was removed via filtration and the solution was concentrated. The crude product was purified by prep TLC (SiO₂; 95:5:0.1 CH₂Cl₂: MeOH: 7N NH₃/MeOH) to afford 3 mg amine **Example 130**.

Step 4:

To a solution of **Example 129** (0.48 g, 1.26 mmol) in THF (8 mL) was added triphenylphosphine (2 g). The solution was heated to reflux until the starting material was consumed. Water (0.5 mL) was added and the solution was stirred until the intermediate was consumed at which point the mixture was concentrated. The crude product was purified by flash chromatography (100:0 to 0:100 hexanes:Et₂O followed by 95:5:0.1 CH₂Cl₂: MeOH: 7N NH₃/MeOH) to afford **Example 131** (448 mg).

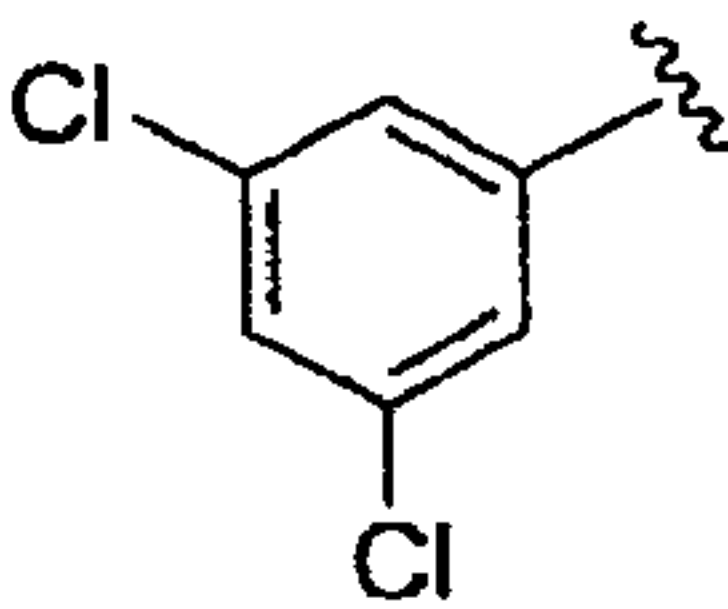
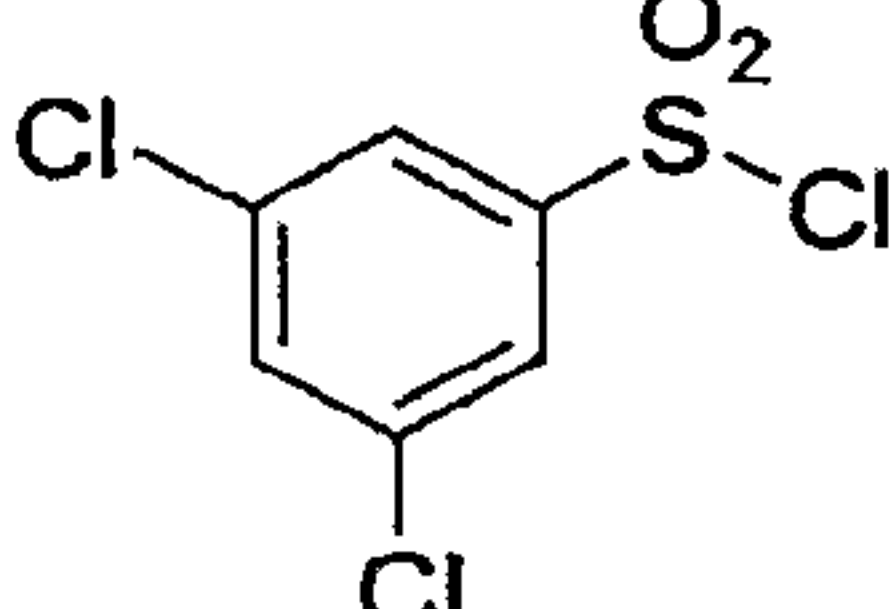
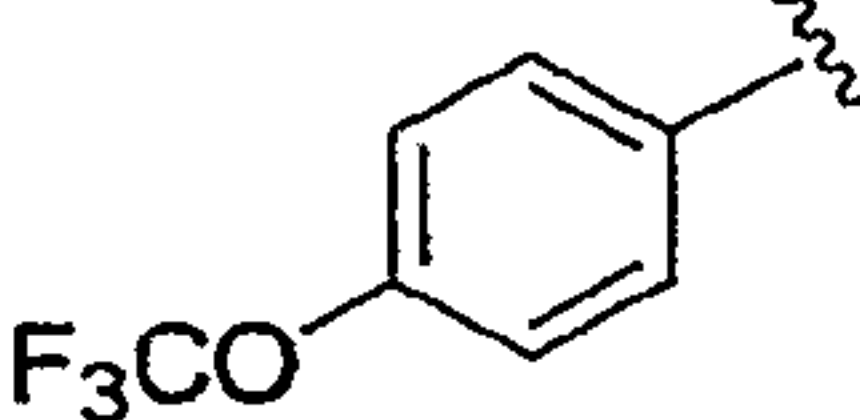
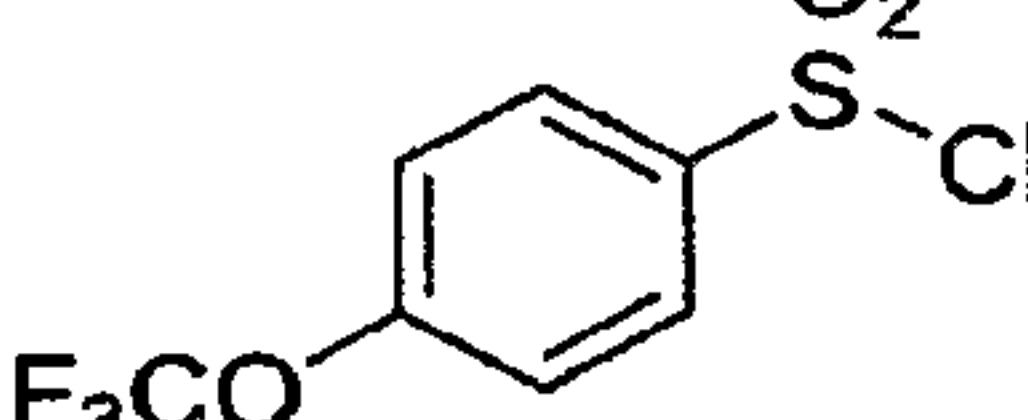
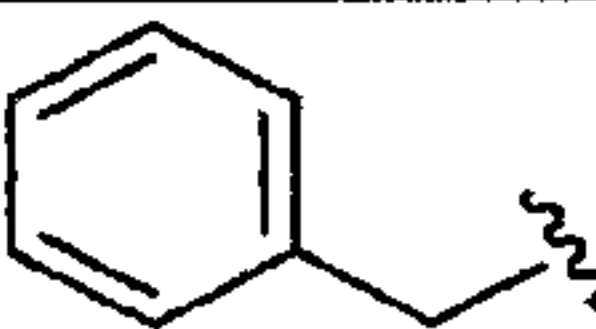
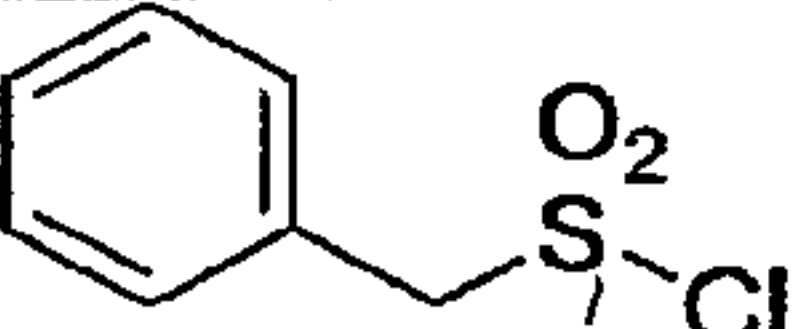
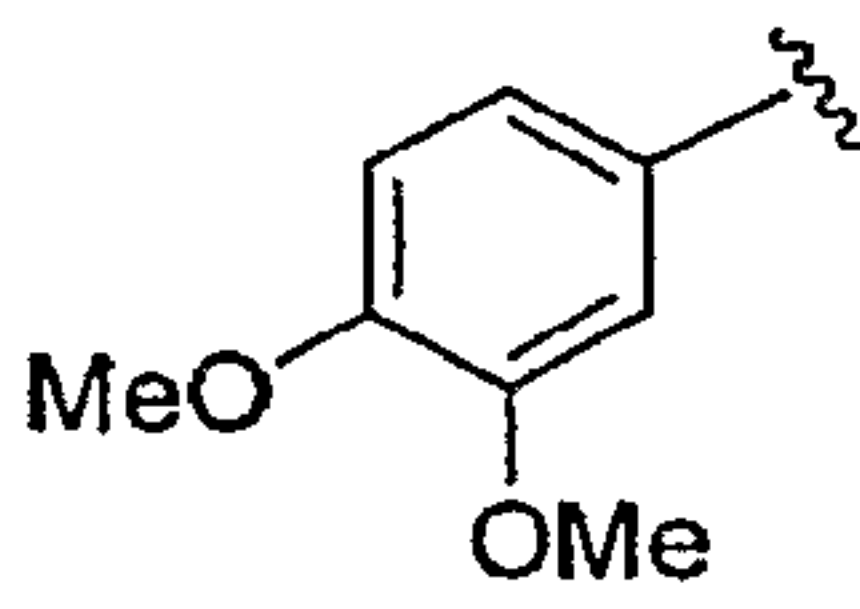
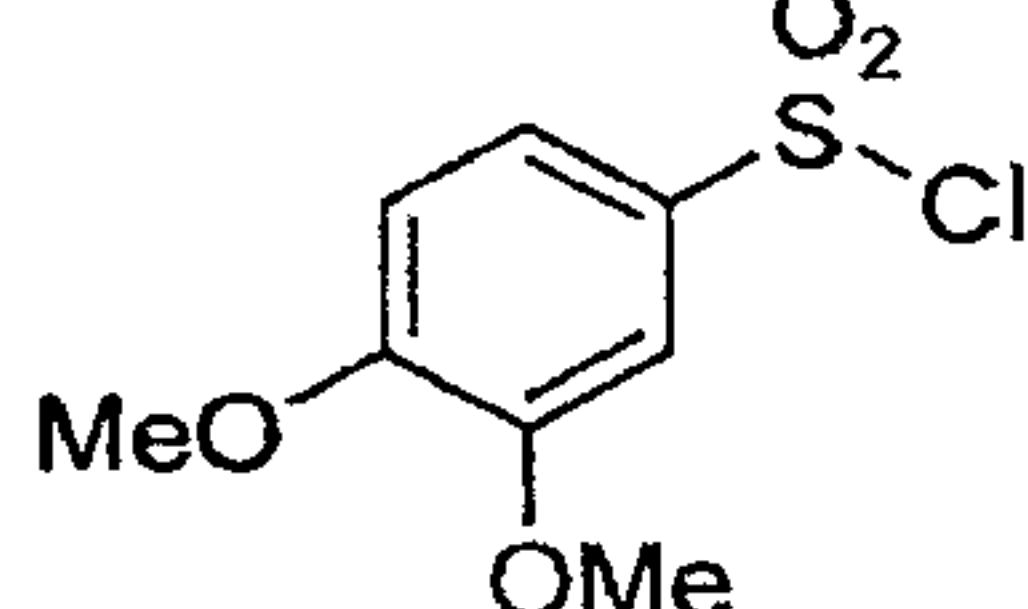
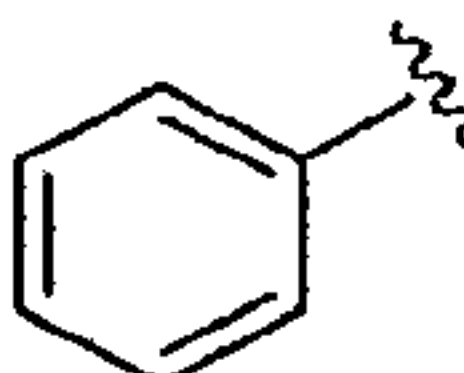
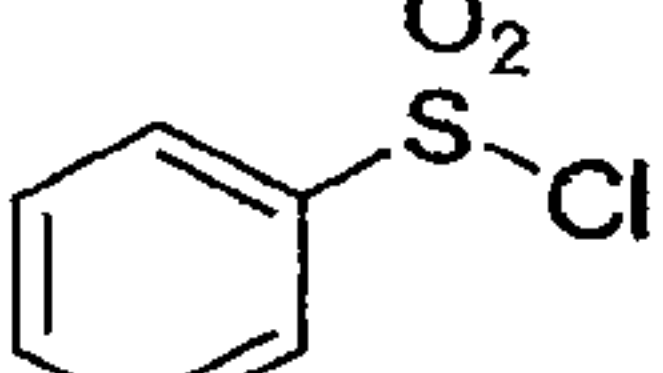
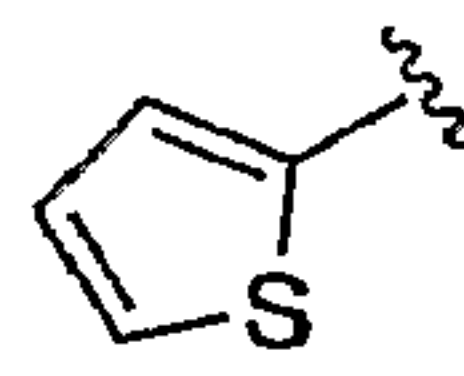
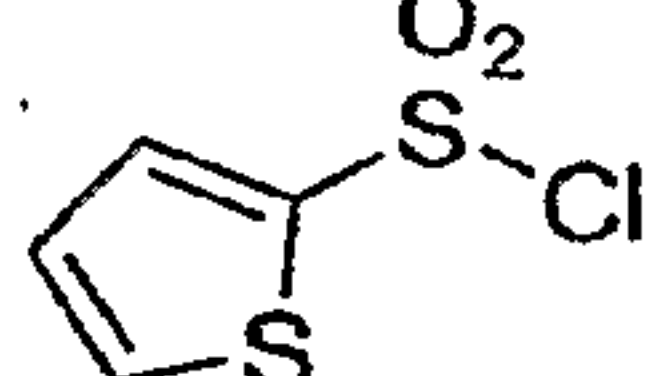
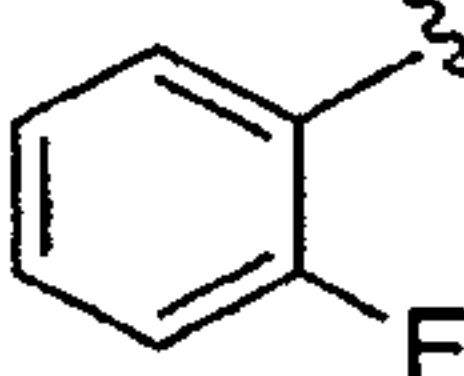
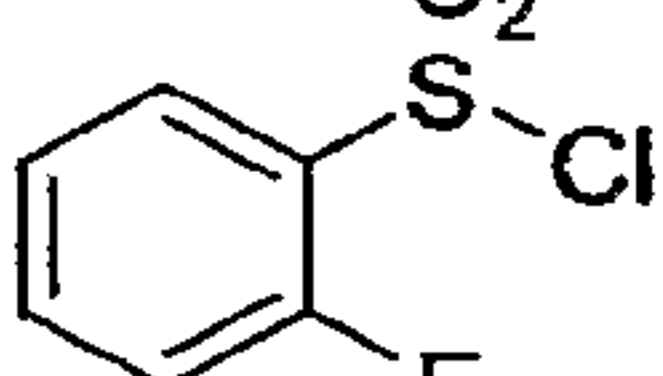
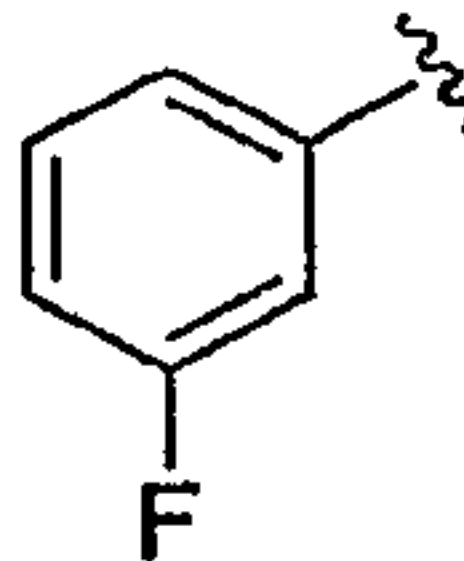
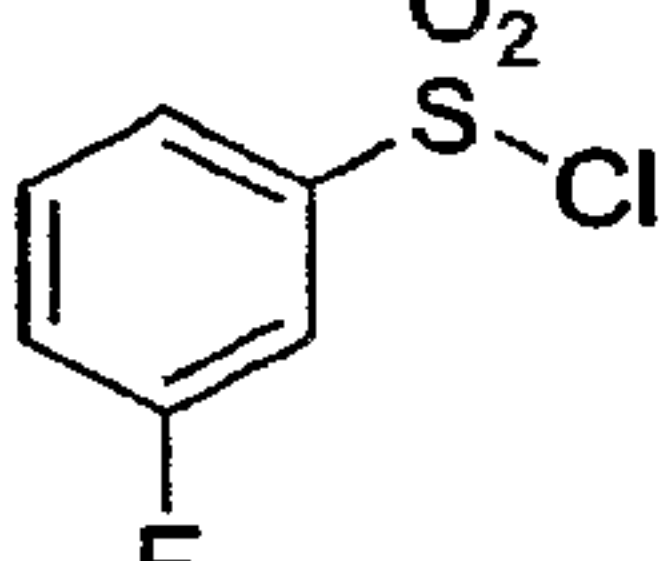
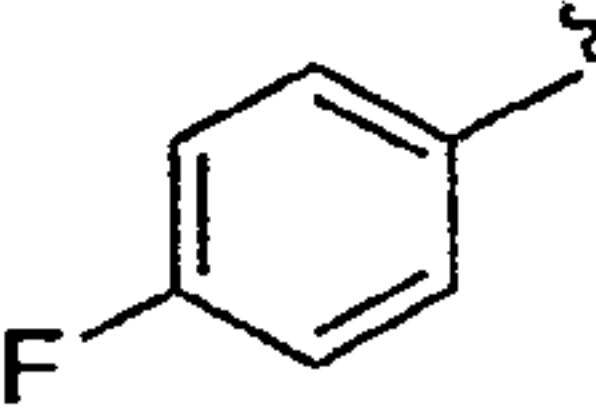
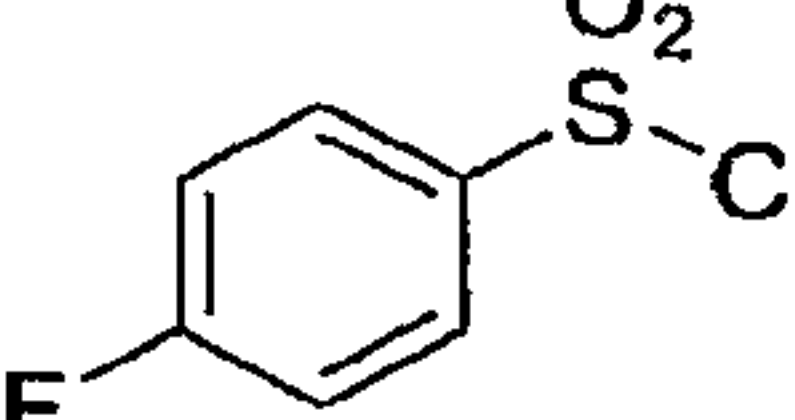
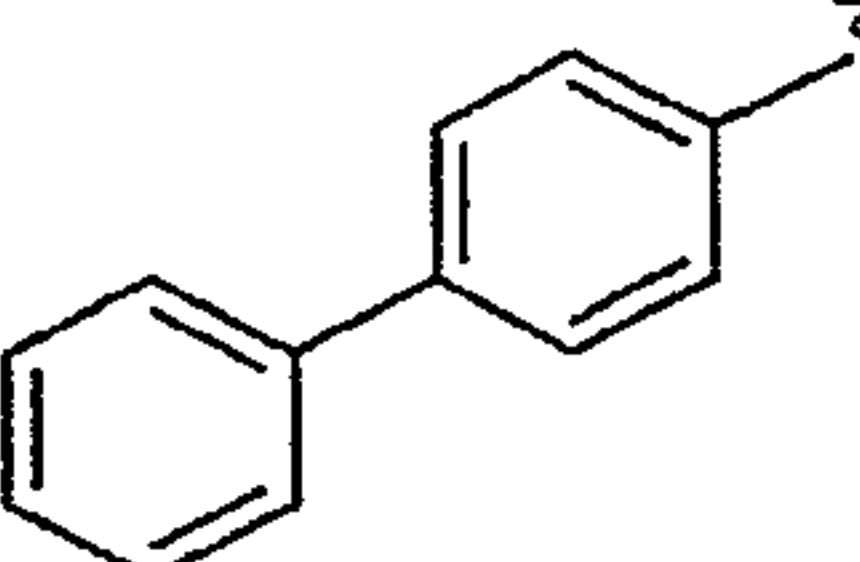
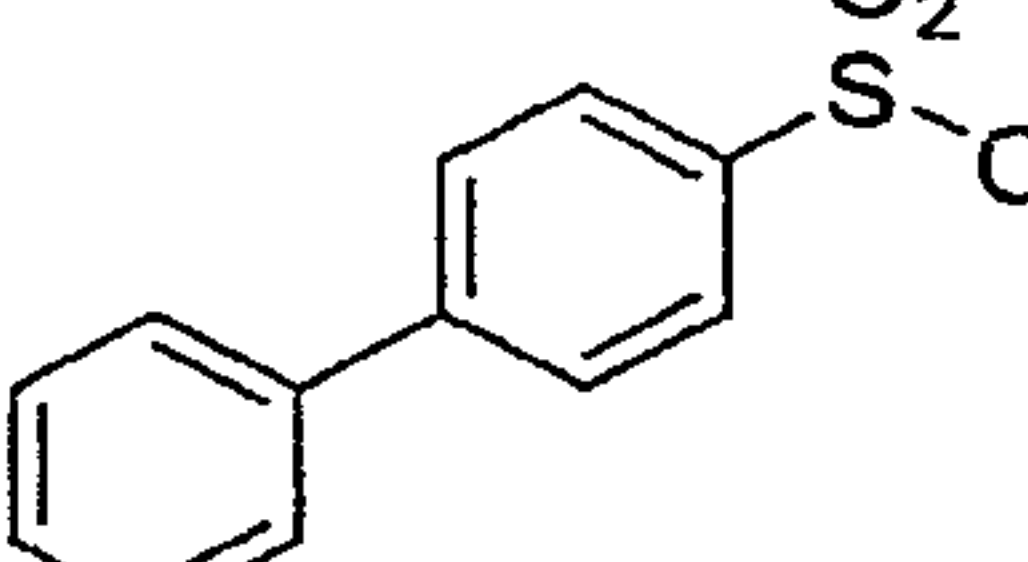
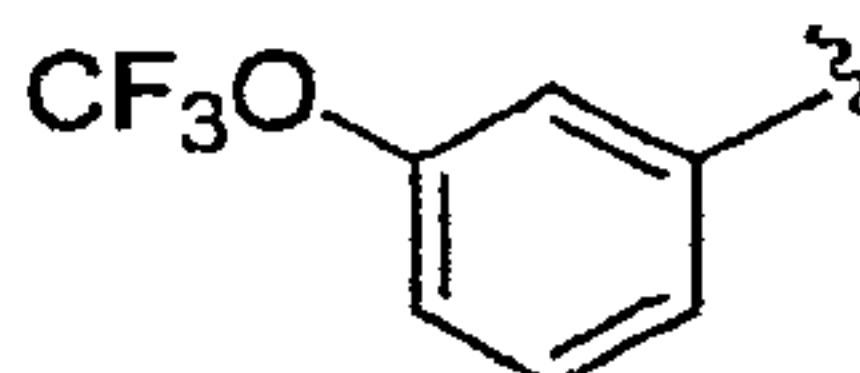
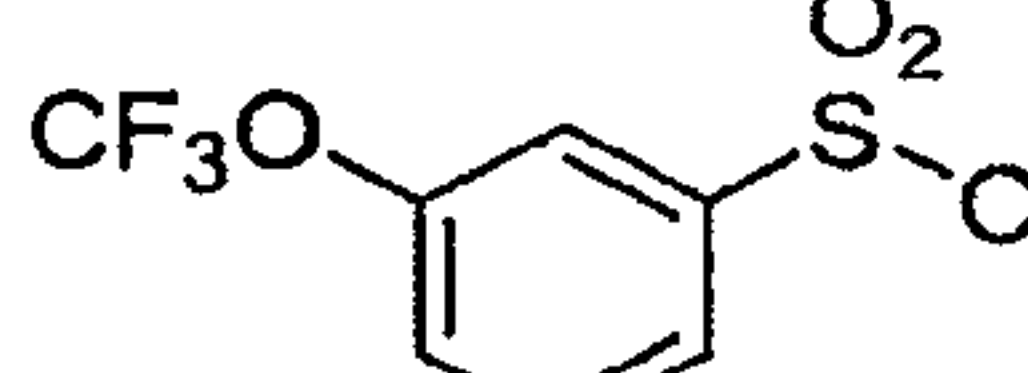
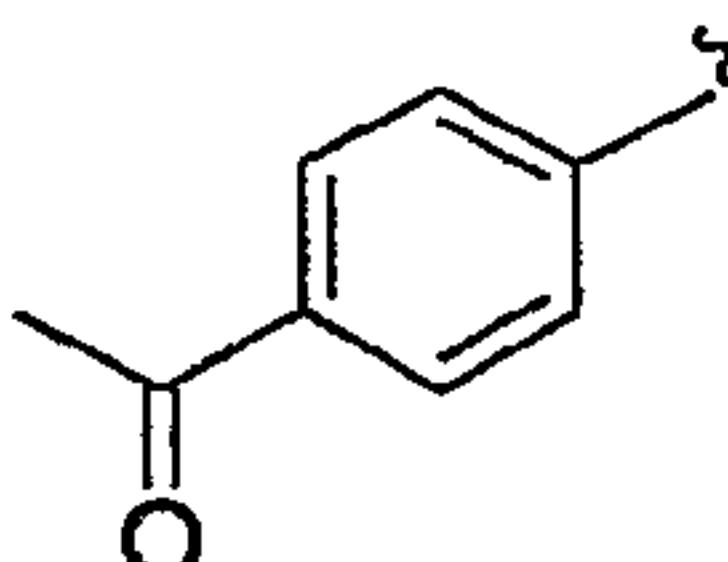
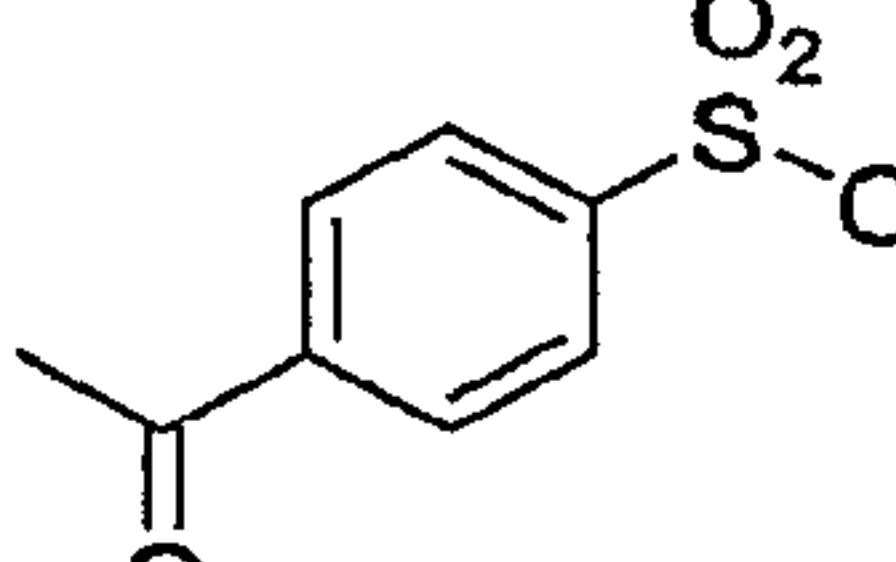
Preparation of Examples 132-148

Sulfonamide analogs were prepared in a manner similar to the procedures described in **Examples 93-124**, except that the indicated sulfonyl chloride was reacted with either **Example 130** or **131** prepared in Steps 3 or 4 above.



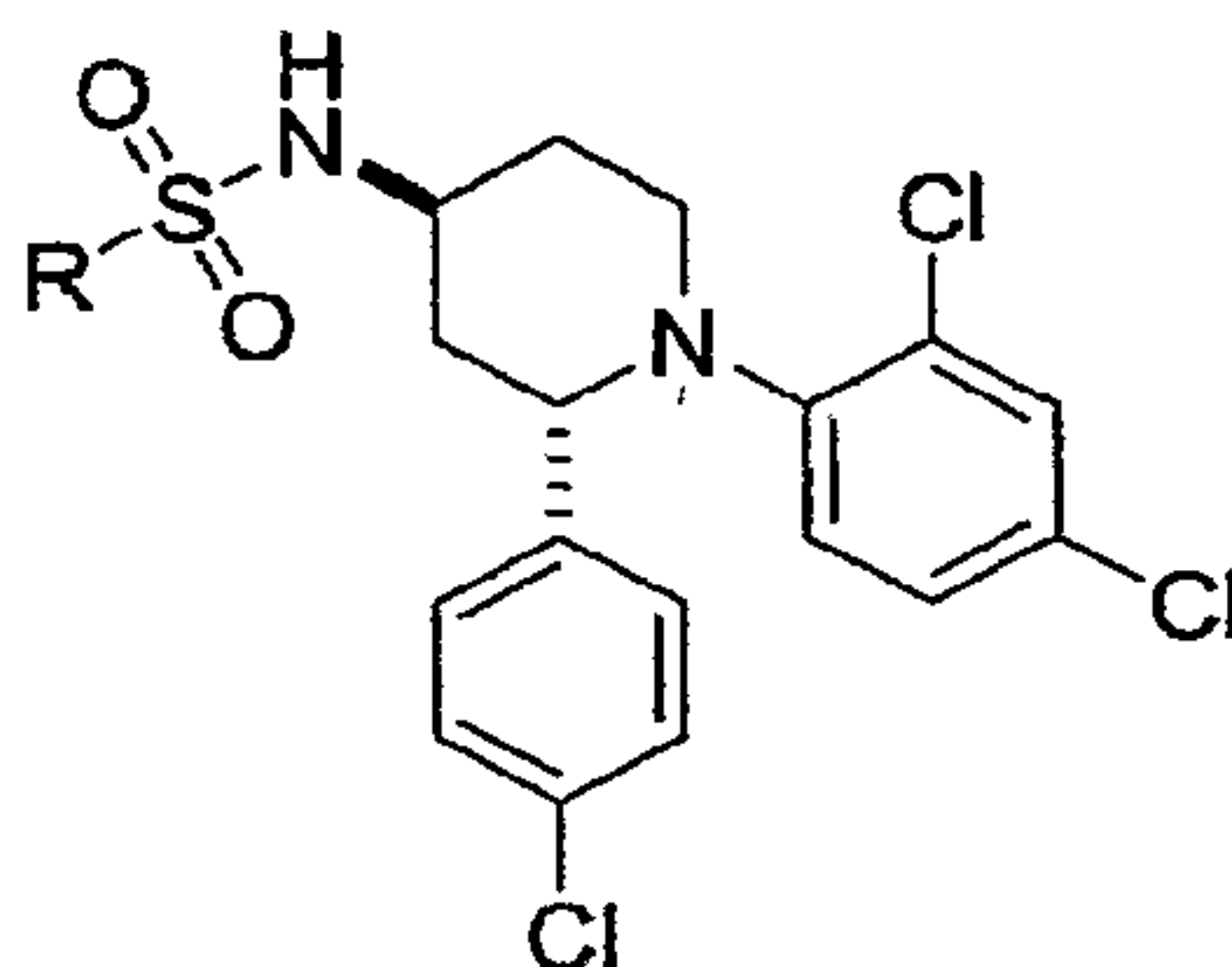
Ex.	R	Sulfonyl Chloride
132		

144

Ex.	R	Sulfonyl Chloride
133		
134		
135		
136		
137		
138		
139		
140		
141		
142		
143		
144		

145

Ex.	R	Sulfonyl Chloride
145		
146		
147		



5

Ex.	R	Sulfonyl Chloride
148		

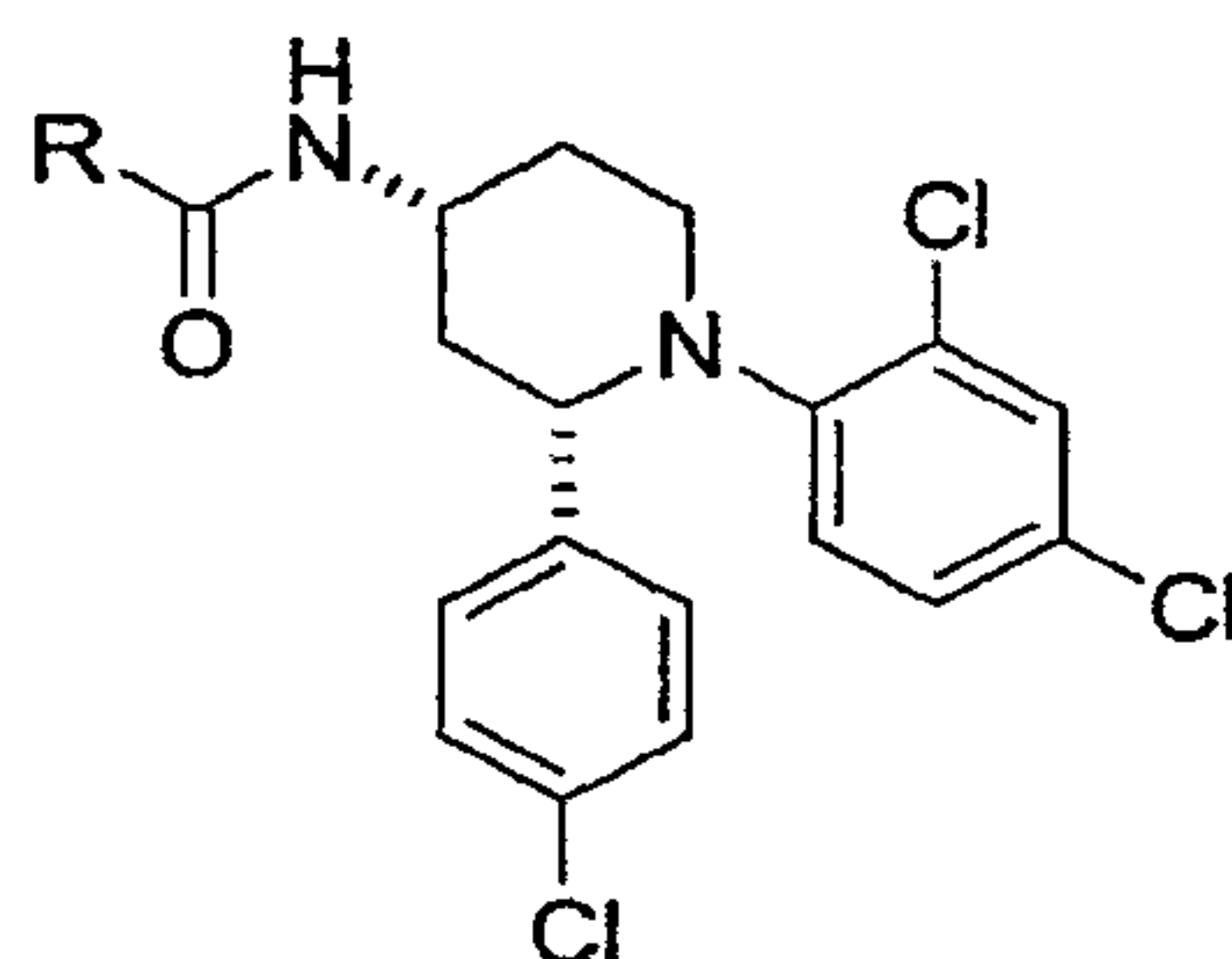
Preparation of Examples 149-162

Amide analogs were prepared by the reaction of either **Example 130** or **131** prepared in Steps 3 or 4, above, with a carboxylic acid library as indicated in the table below.

PS-EDC resin (Polymer Laboratories) (48 mg, 0.068 mmol) was added to each well of a 96 deep well polypropylene microtiter plate followed by a stock solution of one of the amines prepared in Step 1 of **Examples 3** and **4** (6.0 mg, 0.0169 mmol) in MeCN/THF (3/2, 1 mL) and HOBt (5 mg, 0.025 mmol). To this solution was added a 1 M stock solution of the appropriate carboxylic acid (0.025 mmol). The wells were sealed and the plate was shaken at RT overnight. The

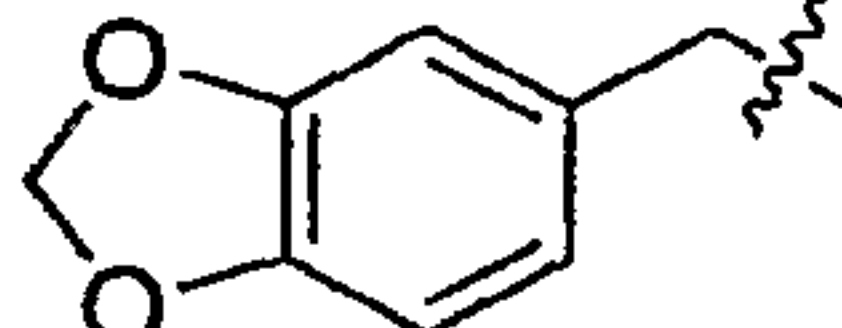
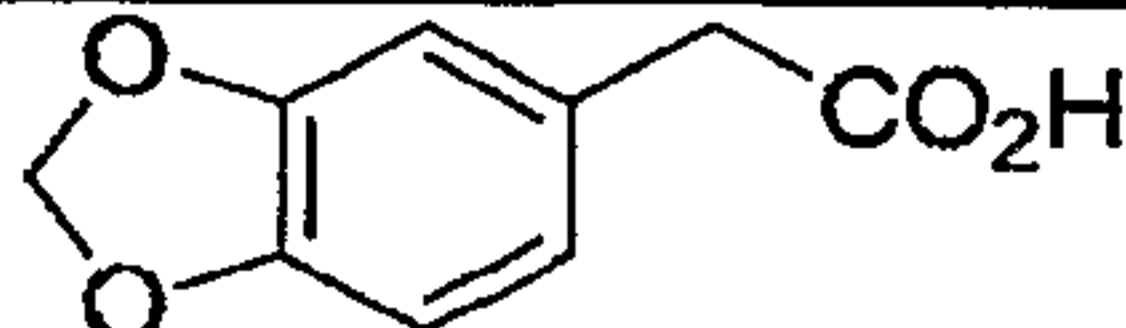
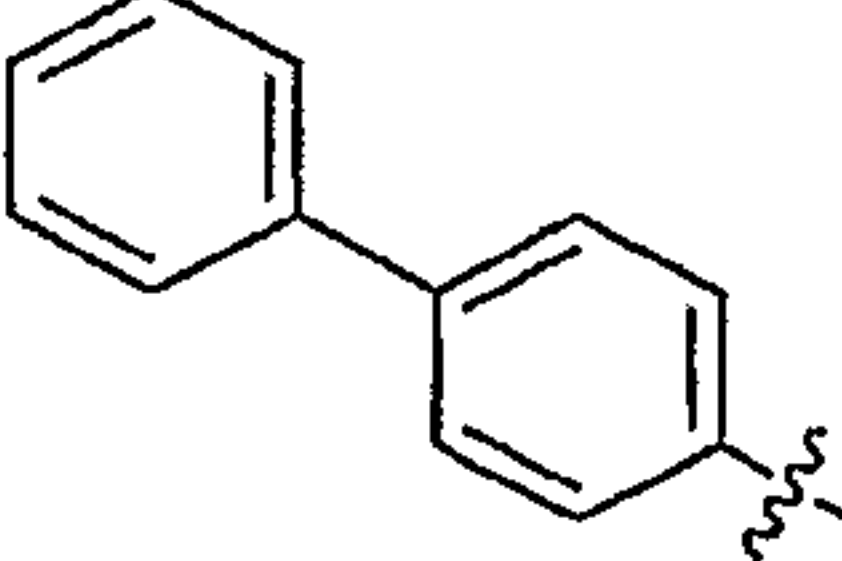
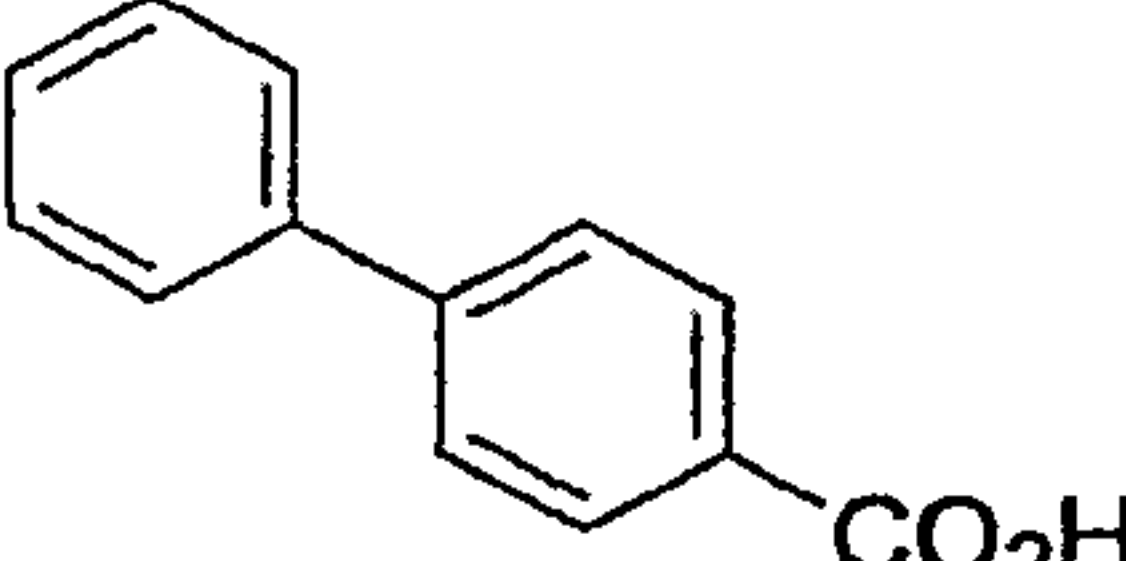
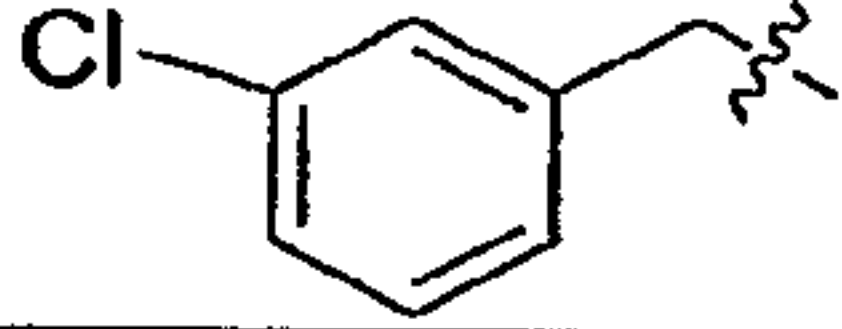
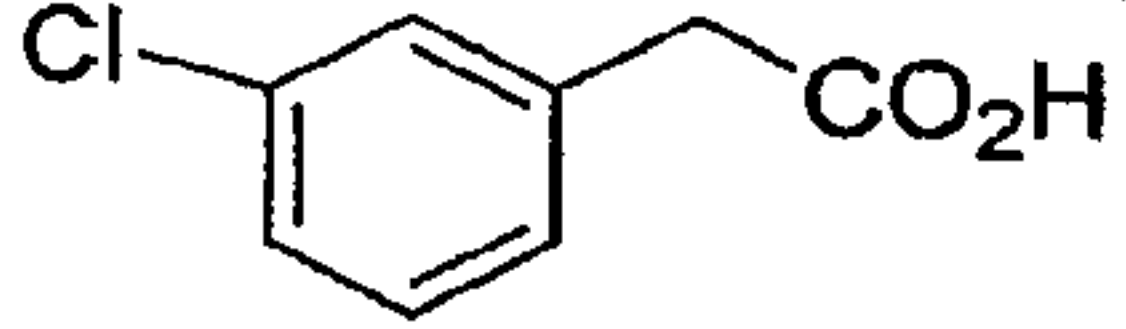
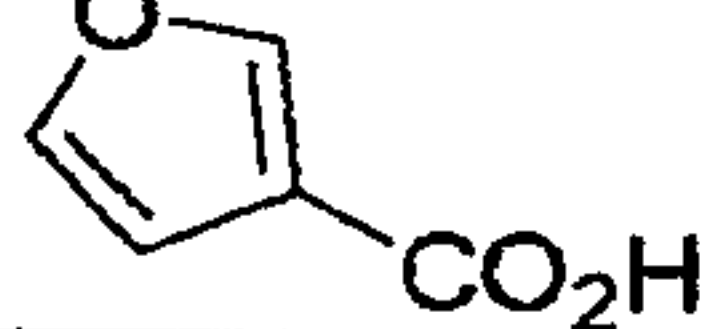
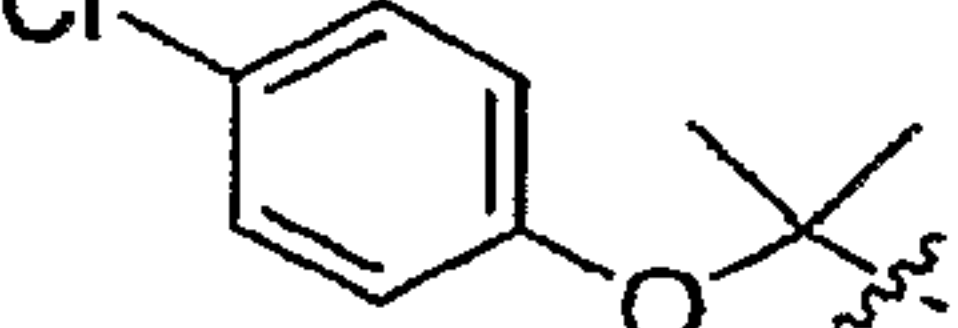
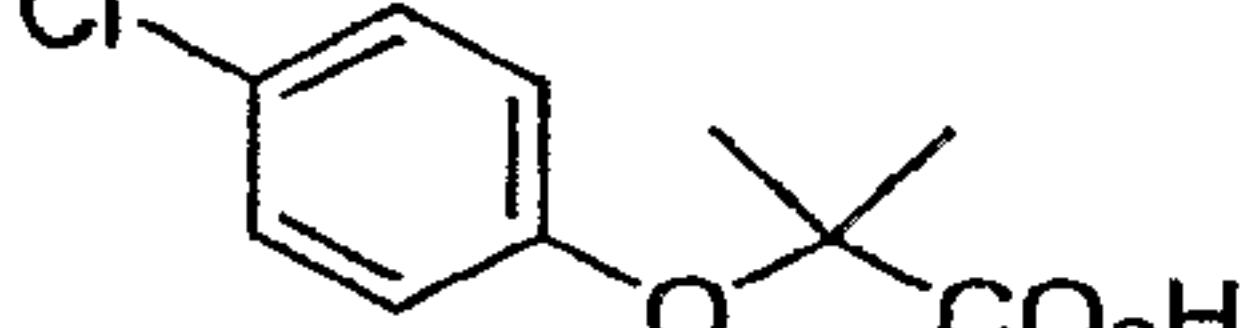
146

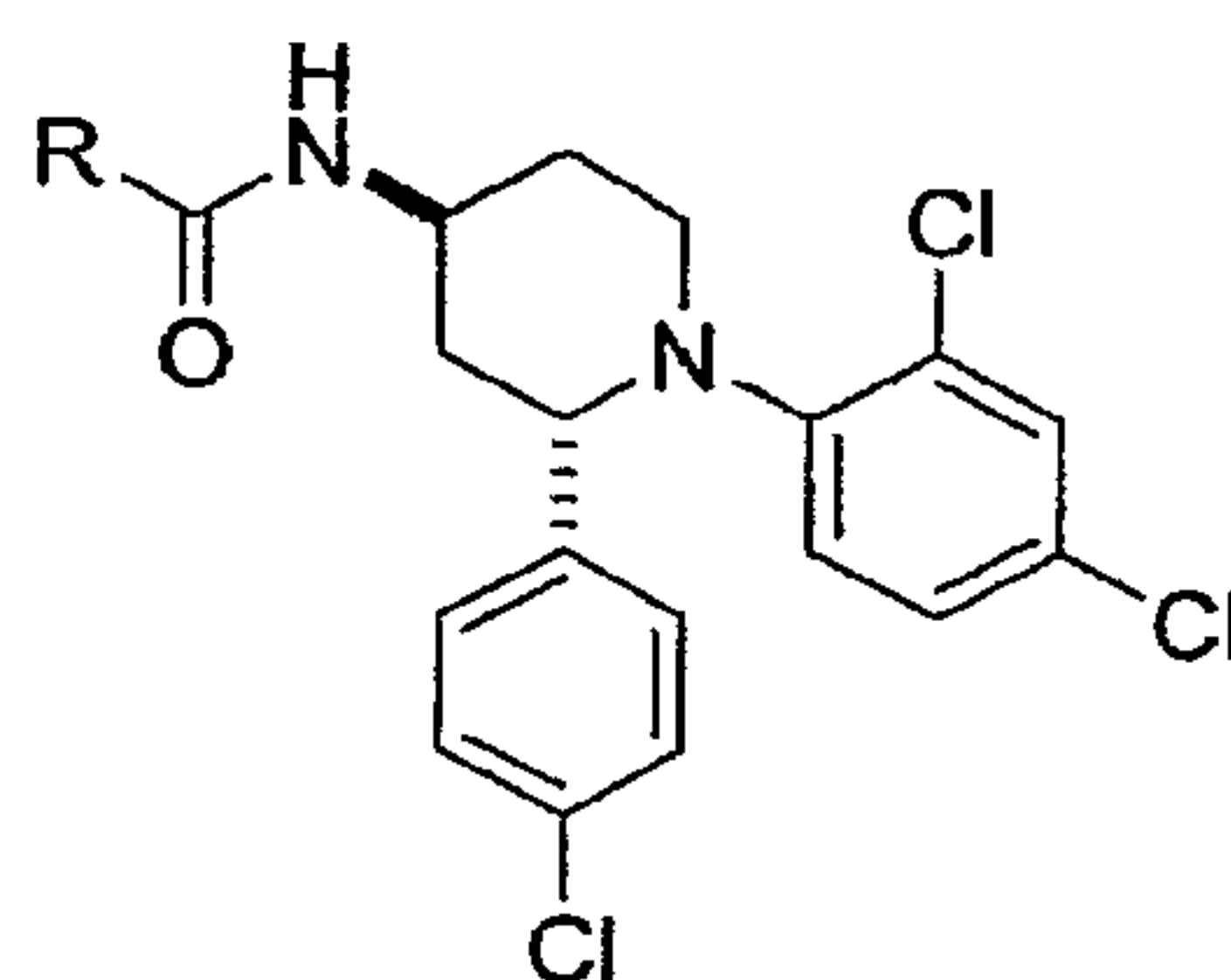
solutions were filtered through a polypropylene frit into a second microtiter plate containing PS-Isocyanate resin (Argonaut Technologies) (0.051 mmol) and PS-trisamine (Argonaut Technologies) (0.135 mmol). The top plate was rinsed with MeCN (0.5 mL/well). The bottom plate was sealed and shaken at RT overnight. The solutions were filtered through a polypropylene frit into a 96 well collection plate. The wells of the top plate were washed with MeCN (0.5 mL/well). The resultant solutions in the collection plate were transferred into vials and the solvent was removed *in vacuo* using a Speedvac. The resulting samples were evaluated by LCMS and those that were >70% pure are shown below:

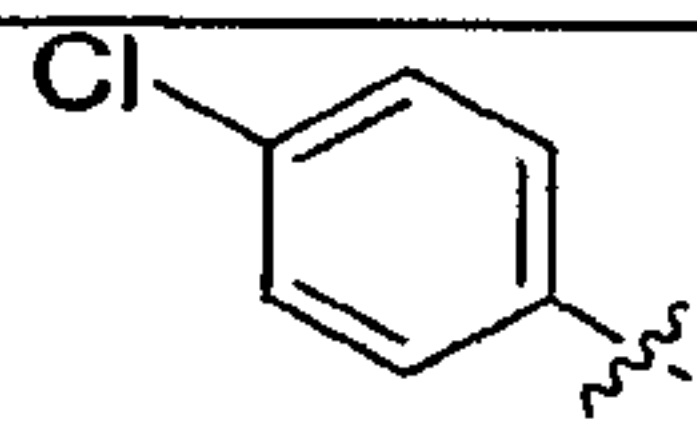
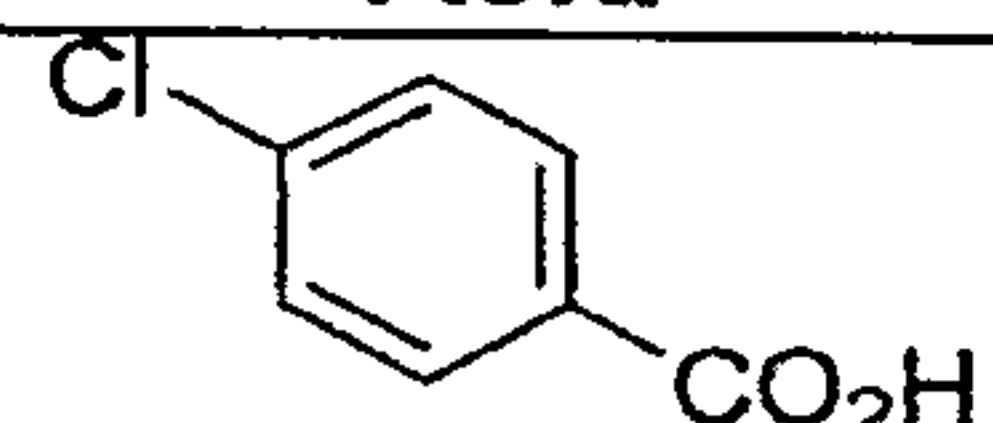
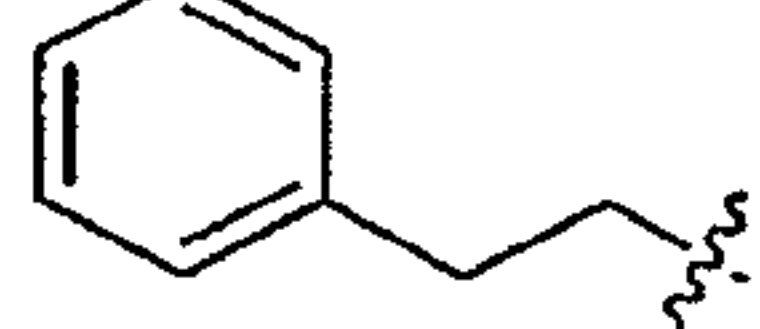
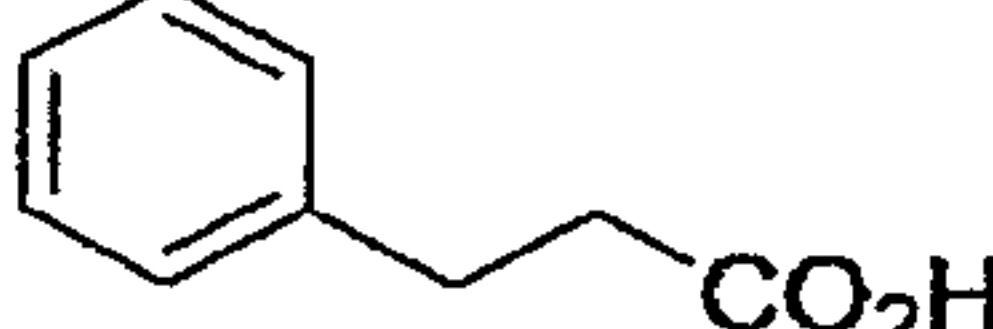


Ex.	R	Carboxylic Acid
149		
150		
151		
152		
153		
154		
155		

147

Ex.	R	Carboxylic Acid
156		
157		
158		
159		
160		



Ex.	R	Carboxylic Acid
161		
162		

5

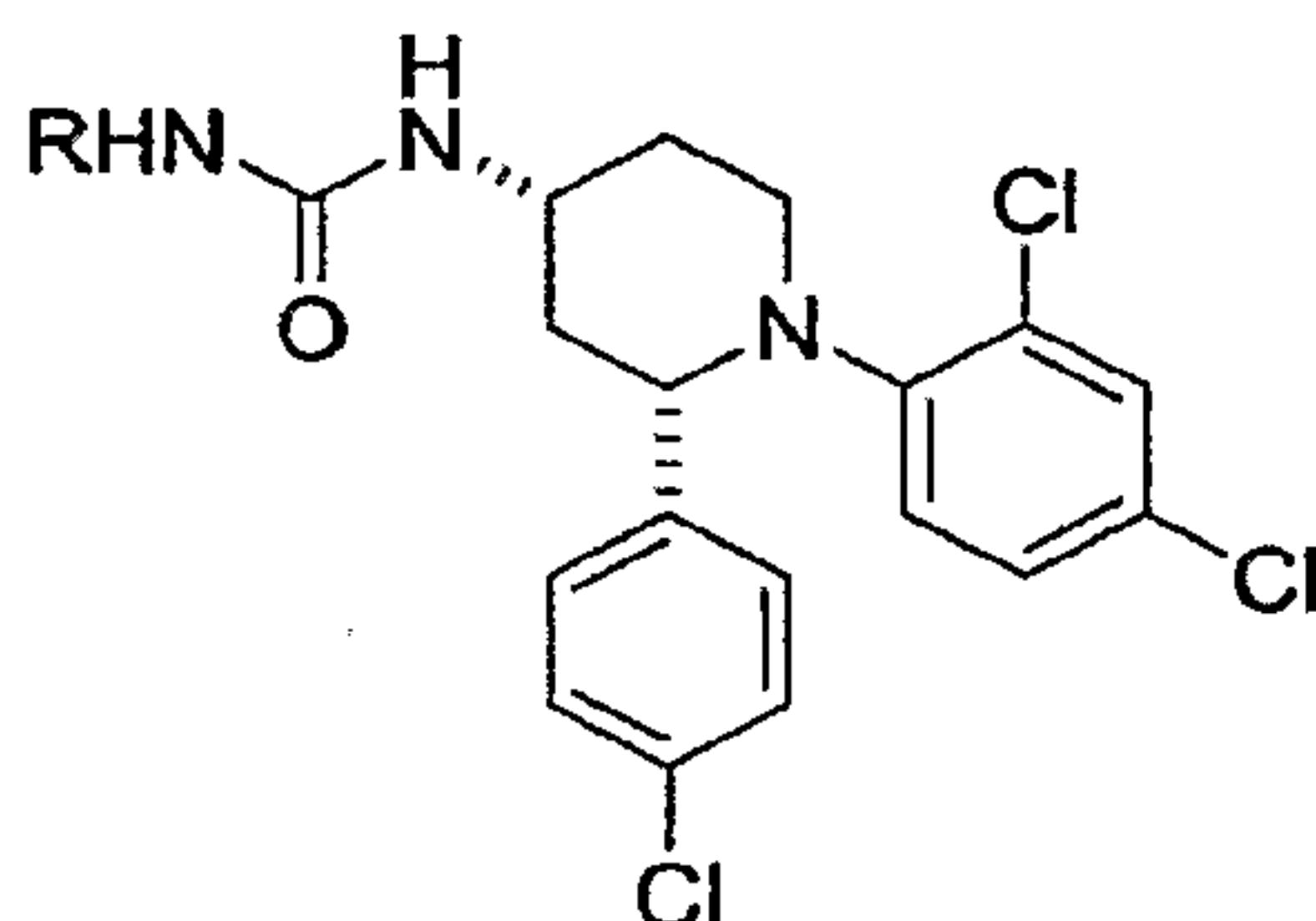
Preparation of Examples 163-167

Urea analogs were prepared by the reaction of **Example 131** prepared in Steps 3 above with an isocyanate library as indicated in the table below.

10 A solution of **Example 130** (0.0169 mmol) in dichloroethane:acetonitrile (1:1, 1 mL) was added to 16 wells of a deep well polypropylene microtiter plate. To these wells were added a 0.5 M solution of the appropriate isocyanate (0.051 mmol) in dichloromethane. The plate was sealed and shaken at RT overnight. The solutions were filtered through a polypropylene frit into a second microtiter plate containing PS-Isocyanate resin (Argonaut Technologies) (0.051 mmol) and PS-trisamine

148

(Argonaut Technologies) (0.135 mmol). The top plate was rinsed with MeCN (0.5 mL/well). The bottom plate was sealed and shaken at RT overnight. The solutions were filtered through a polypropylene frit into a 96 well collection plate. The wells of the top plate were washed with MeCN (0.5 mL/well). The resultant solutions in the
 5 collection plate were transferred into vials and the solvent was removed *in vacuo* using a Speedvac. The resulting samples were evaluated by LCMS and those that were >70% pure are shown below.



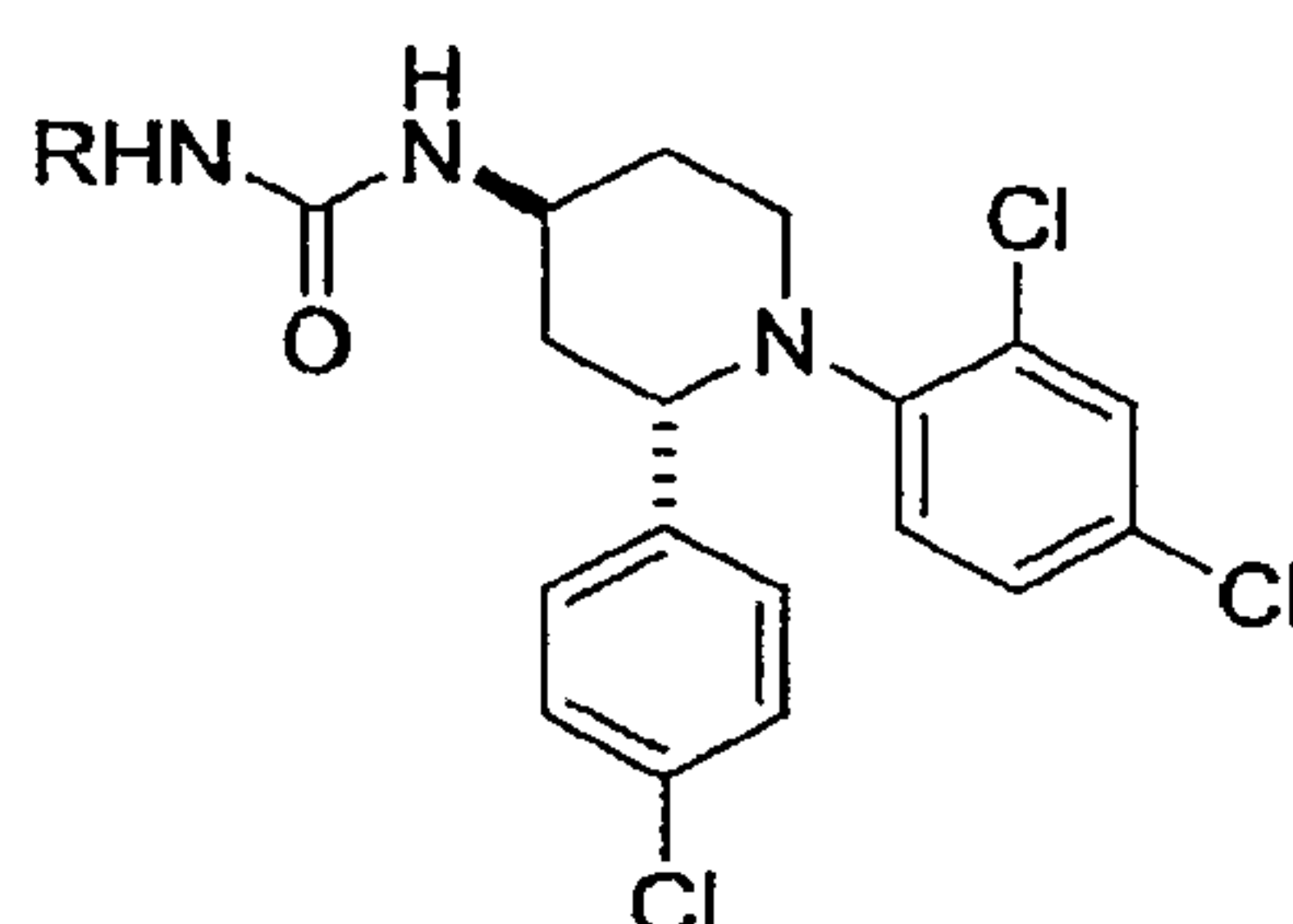
10

Ex.	R	Isocyanate
163		
164		
165		
166		
167		

Preparation of Examples 168-169

15 The urea analogs were prepared in the same method as **Examples 163-167** except **Example 131** was used as the starting material.

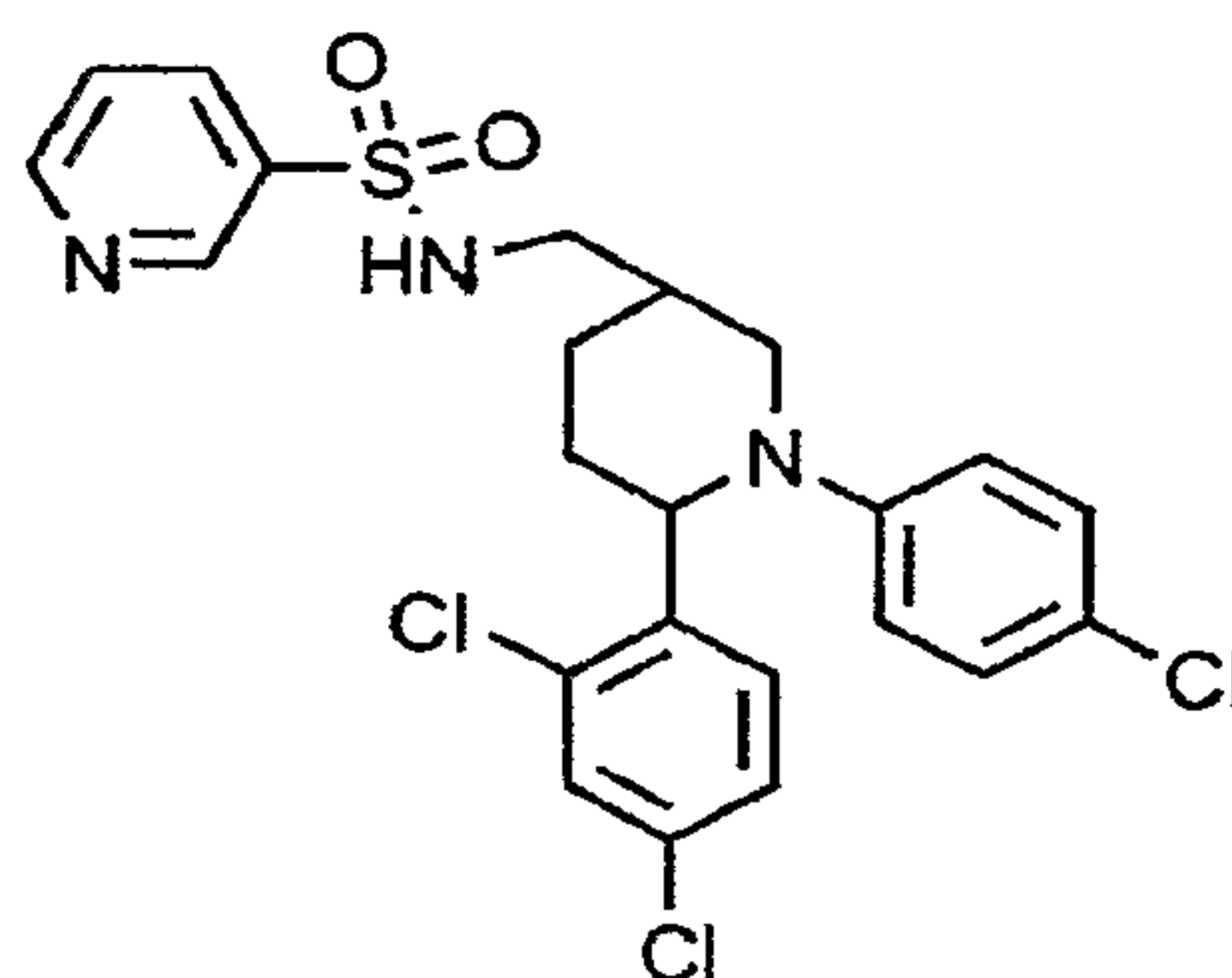
149



Ex.	R	Isocyanate
168		
169		

5

Preparation of Example 170

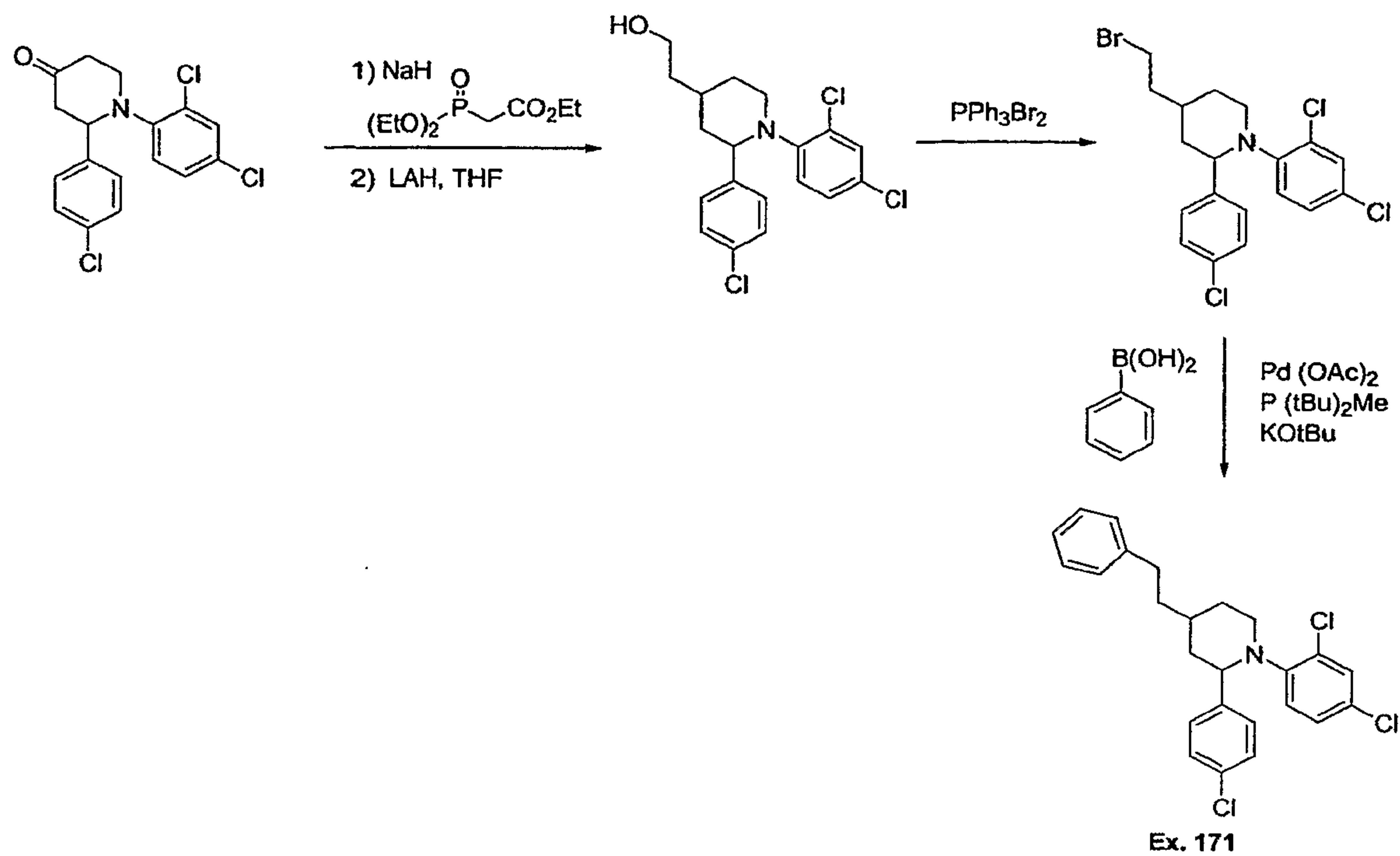


Example 170

Example 170 was prepared using the procedure for preparing **Example 86**, except that 3-pyridine sulfonyl chloride hydrochloride salt (Chemical Synthesis Services) was used instead of benzene sulfonyl chloride.

10

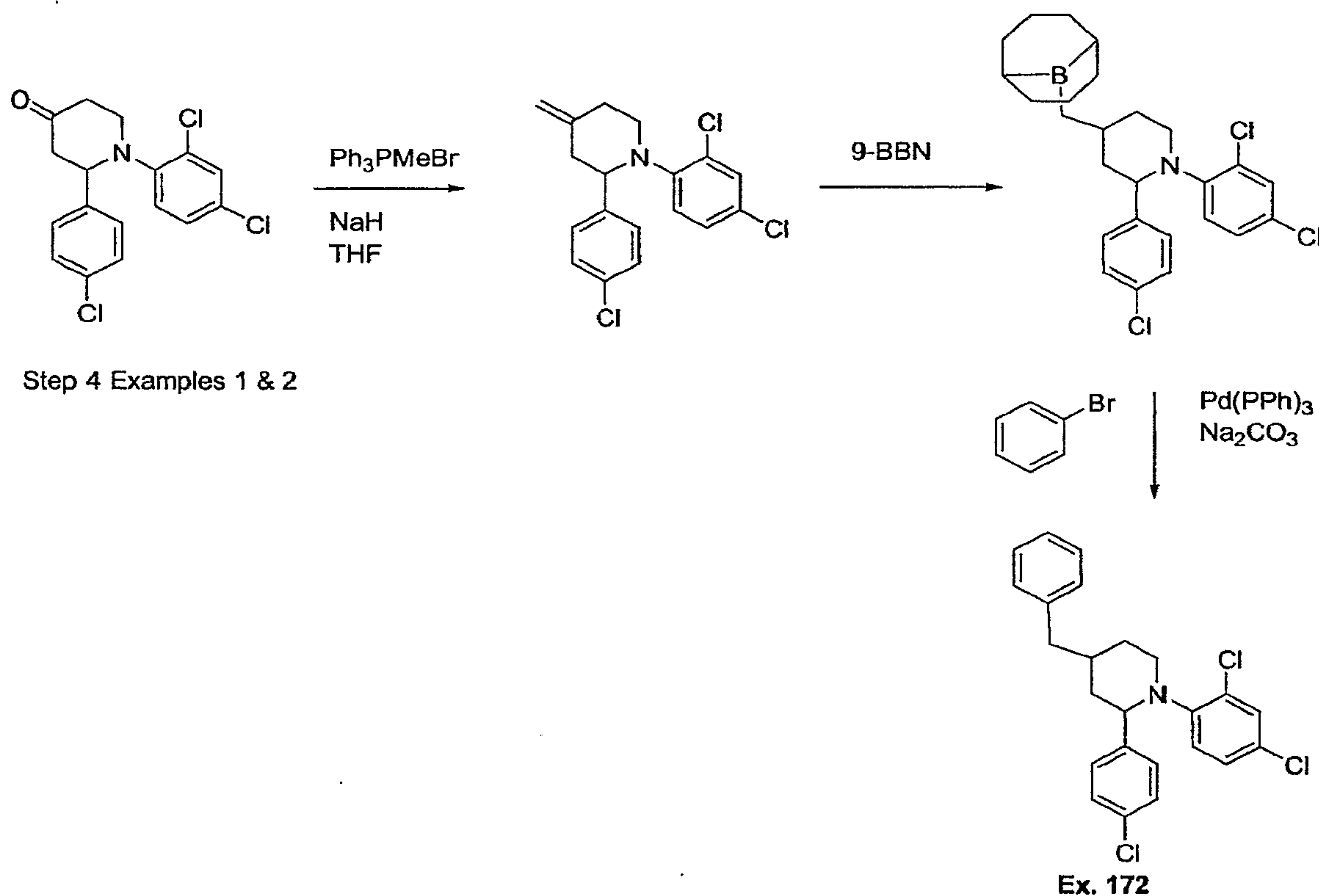
150

Preparation of Example 171

151

The ketone prepared by the method of Step 4 of Examples 1 & 2 can be converted to 2-[2-(4-chloro-phenyl)-1-(2,4-dichloro-phenyl)-piperidin-4-yl]-ethanol, for example, using the procedure described in J. Med. Chem. (2001), 2707-2718. 2-[2-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-piperidin-4-yl]-ethanol can then be converted to 4-(2-bromo-ethyl)-2-(4-chloro-phenyl)-1-(2,4-dichloro-phenyl)-piperidine with $P(Ph)_3Br_2$ using conventional methods. 4-(2-Bromo-ethyl)-2-(4-chloro-phenyl)-1-(2,4-dichloro-phenyl)-piperidine can then be converted to **Example 171**, for example using the procedure described in J. Am. Chem. Soc. (2002), 13662-13663.

Preparation of Example 172



The ketone prepared by the method of Step 4 of Examples 1 & 2 can then be converted to 2-(4-chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-methylene-piperidine using Wittig reaction conditions. 2-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-methylene-piperidine can then be reacted with 9-BBN to form 4-(9-Bora-bicyclo[3.3.1]non-9-ylmethyl)-2-(4-chloro-phenyl)-1-(2,4-dichloro-phenyl)-piperidine, which can then be reacted with bromobenzene to provide **Example 172**.

Preparation of Examples 173-224

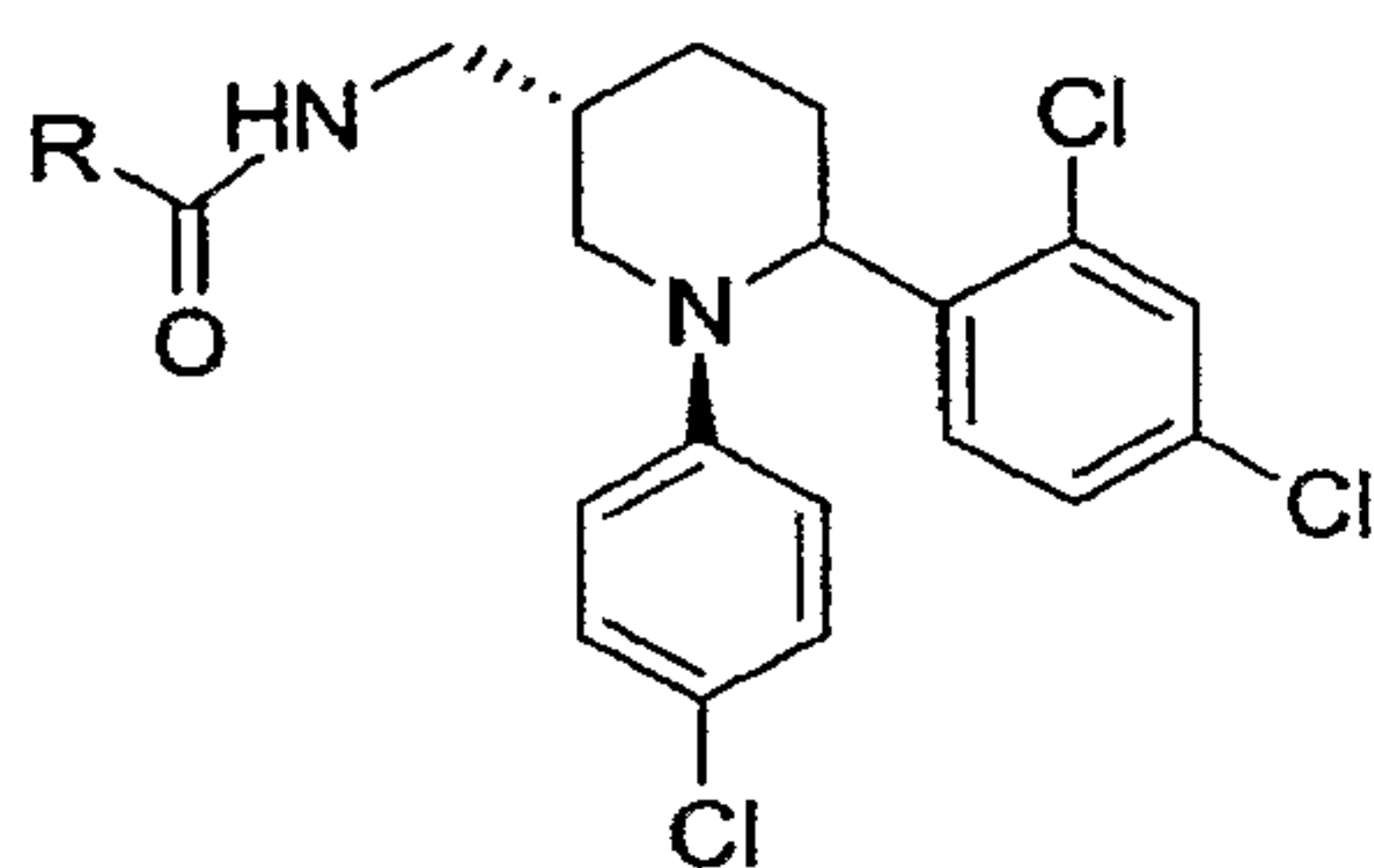
152

Examples 173-224 were prepared using a procedure similar to that described above for **Examples 149-162**, except that **Example 85** was used as the starting material instead of **Examples 130 or 131**.

5

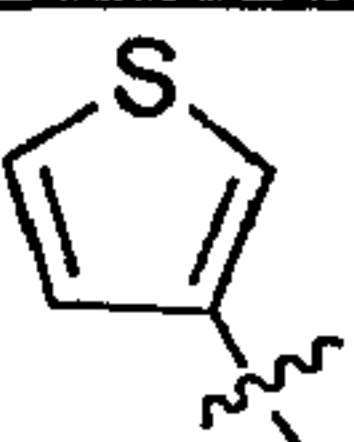
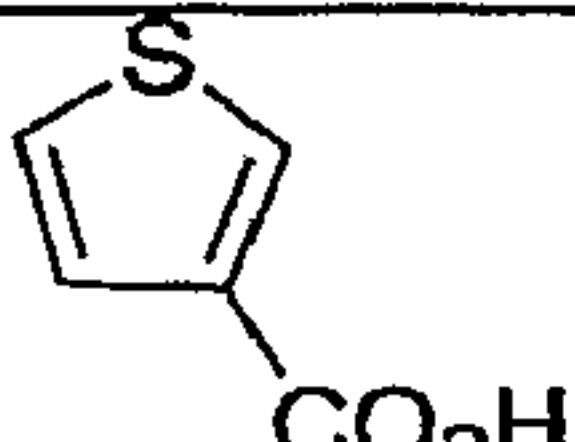
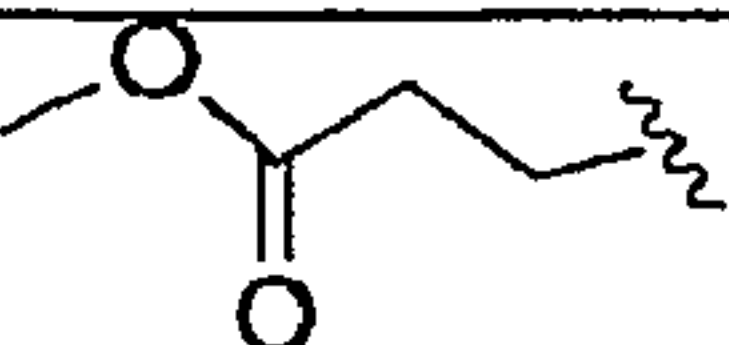
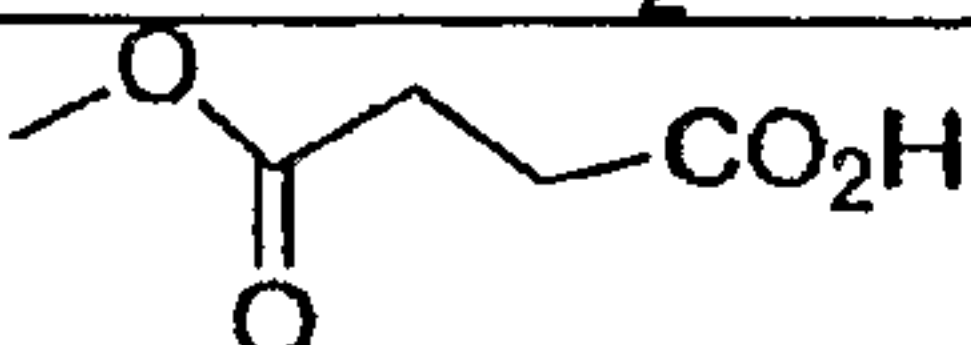
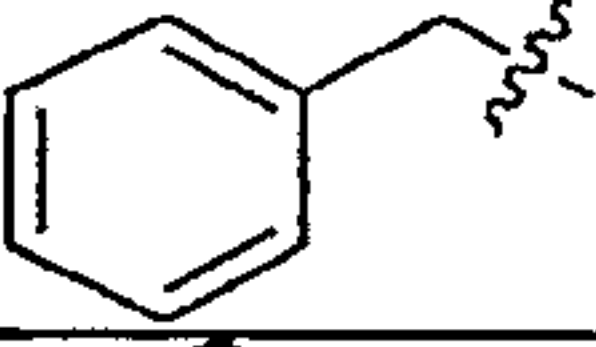
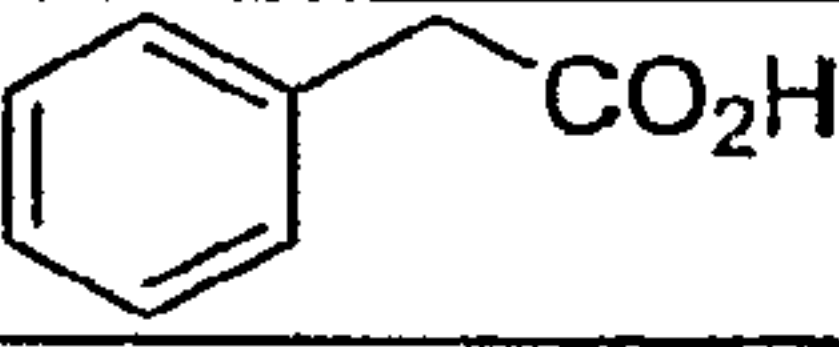
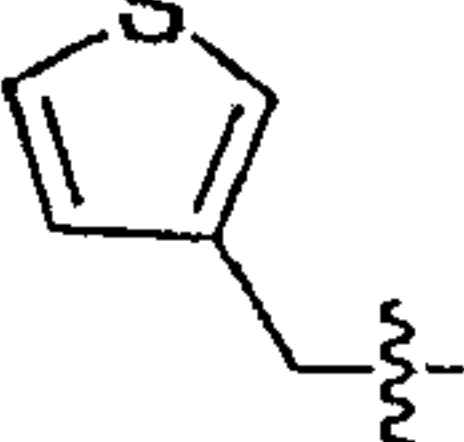
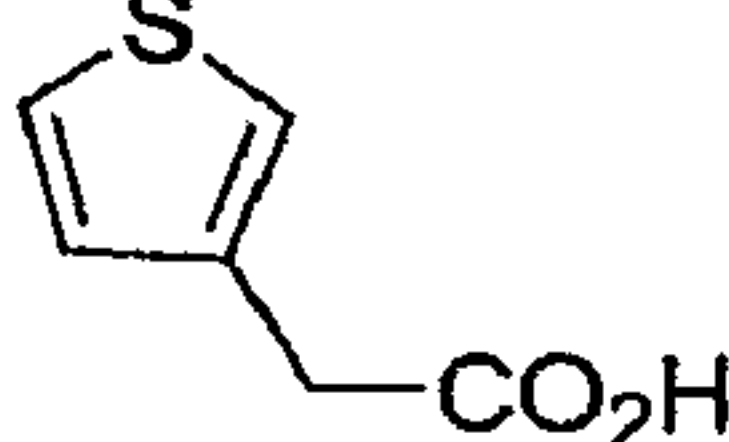
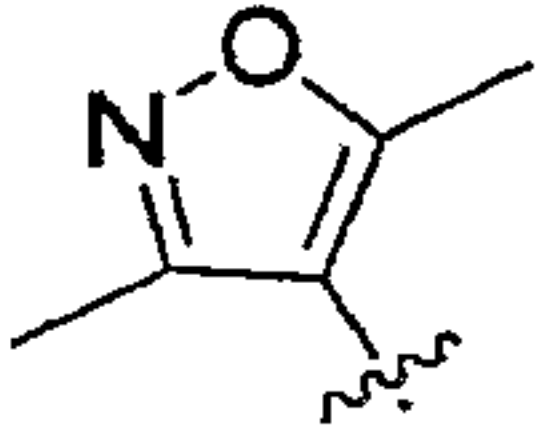
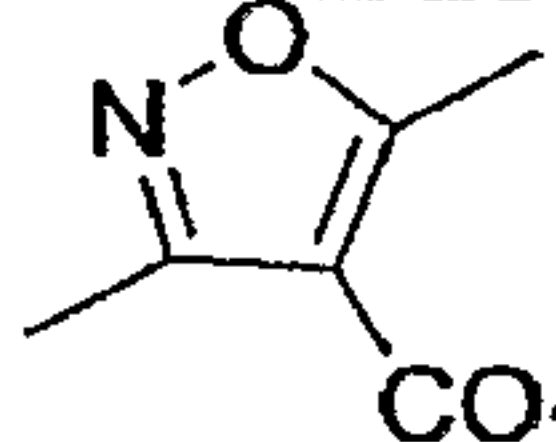
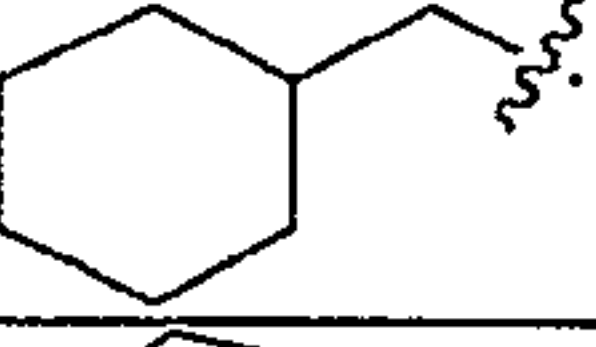
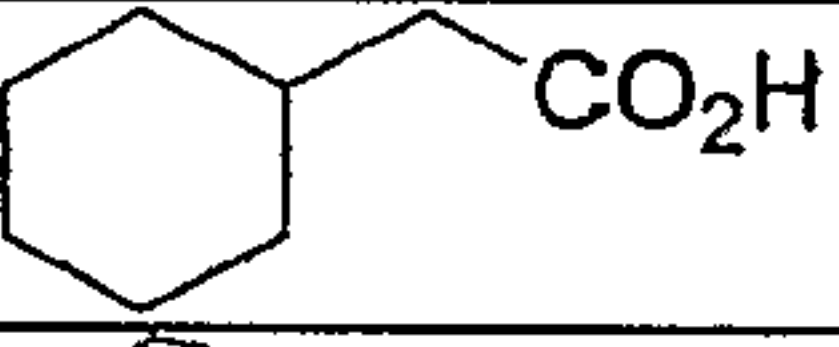
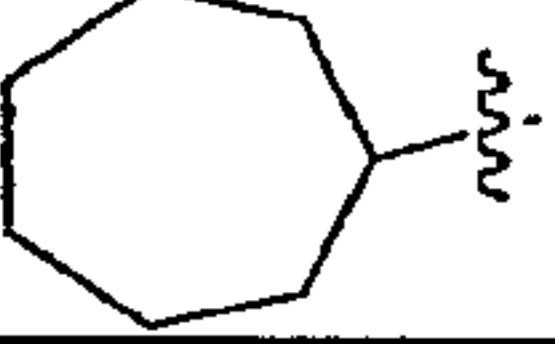
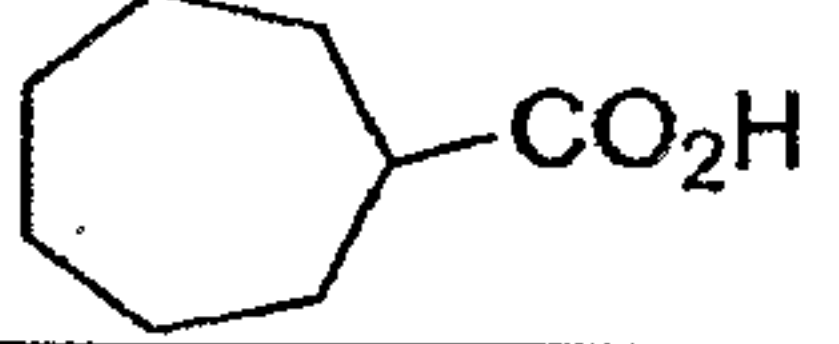
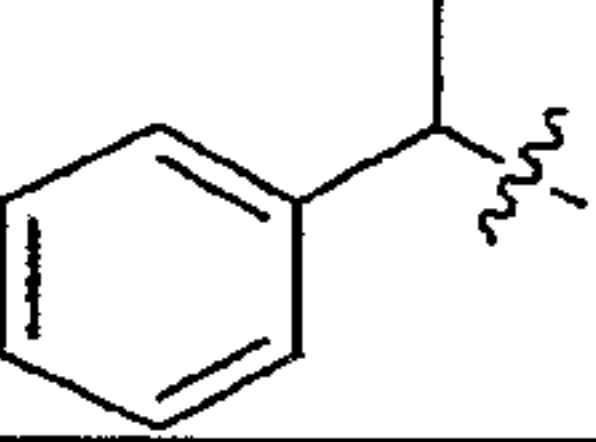
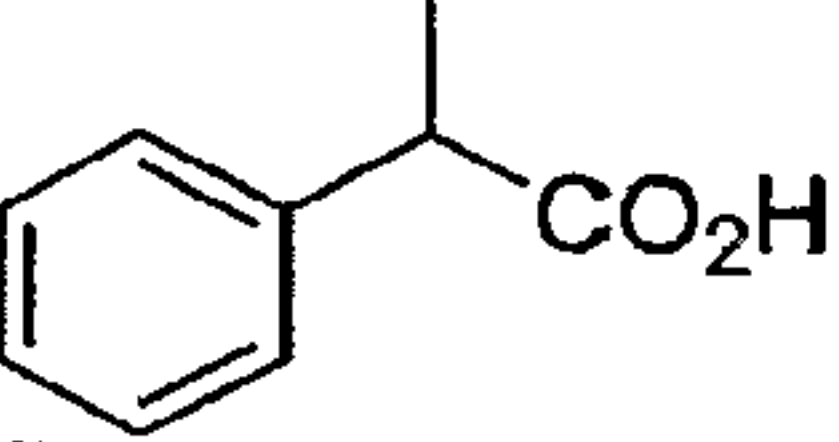
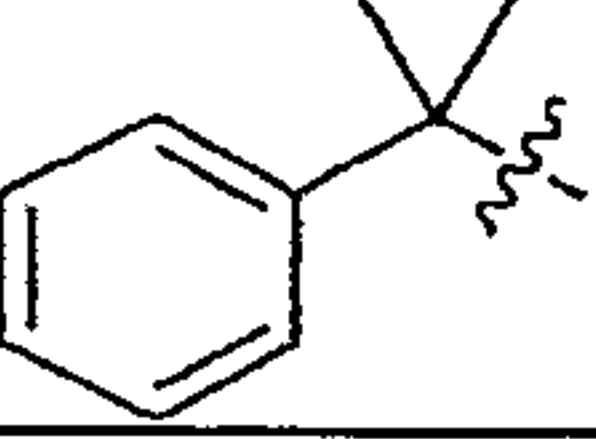
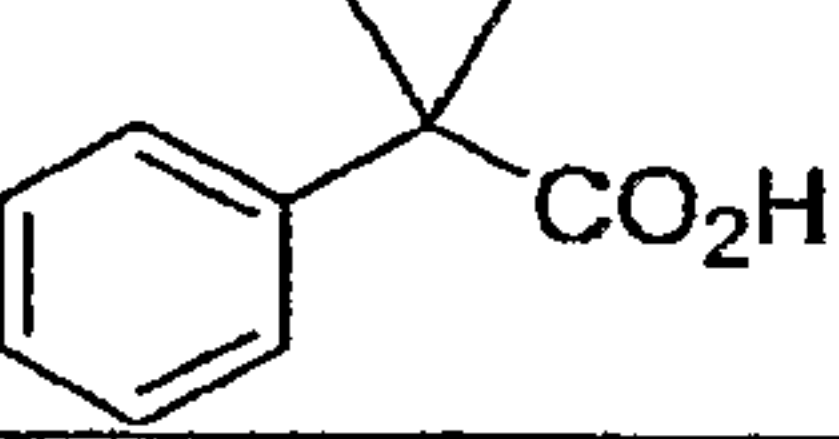
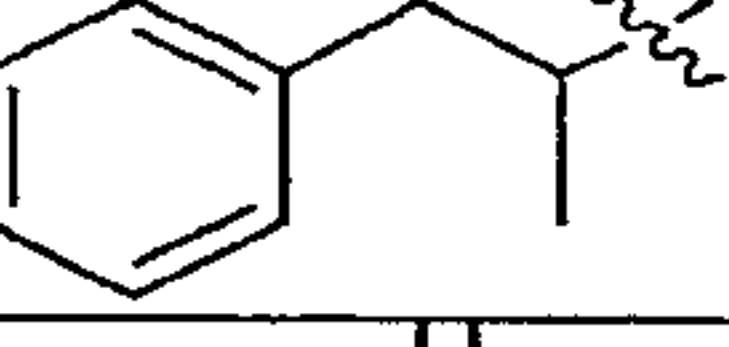
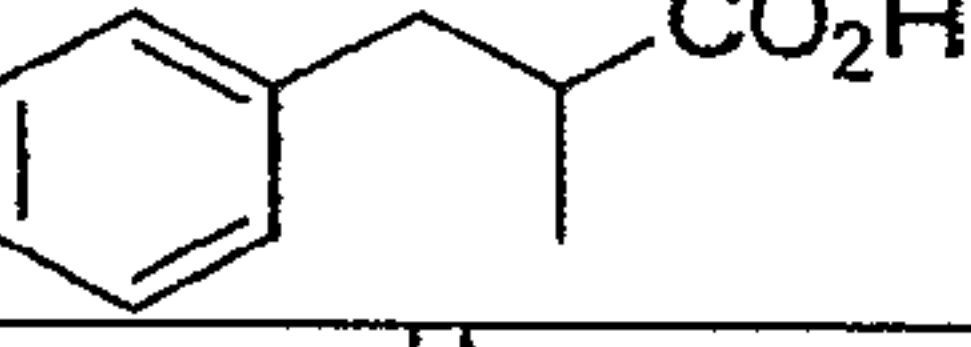
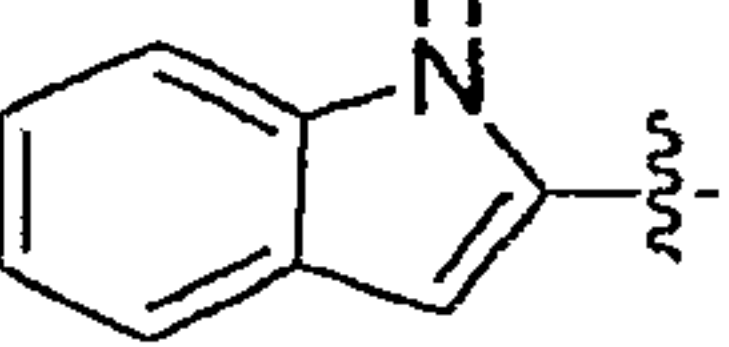
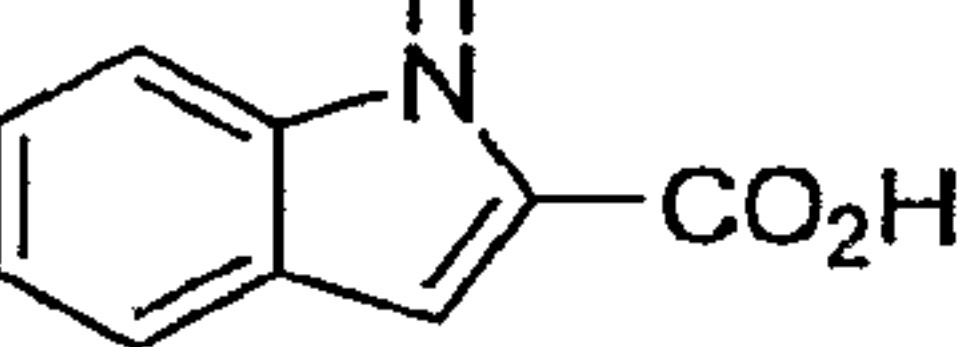
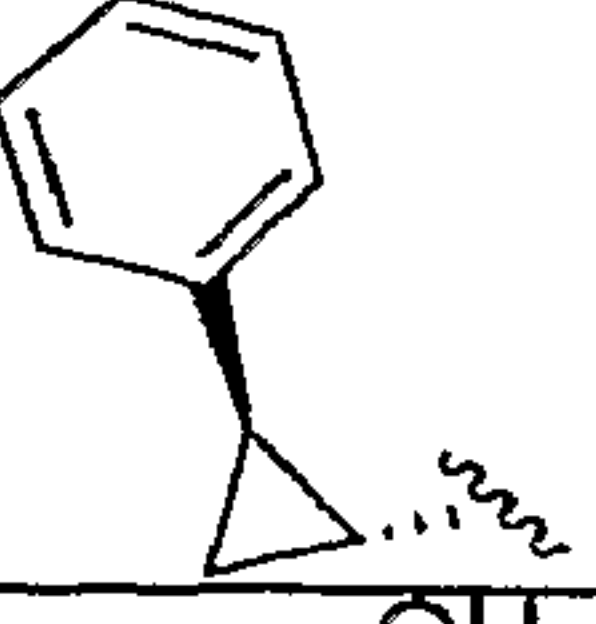
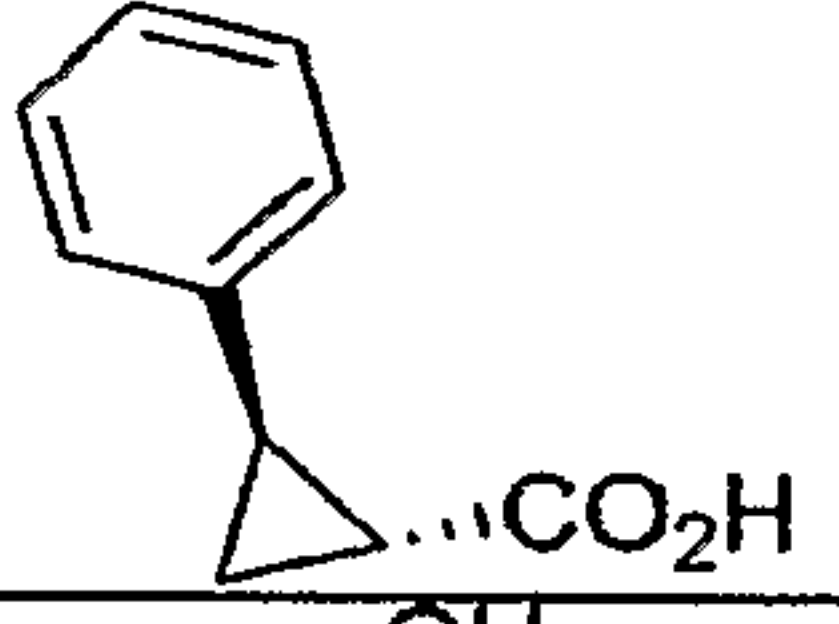
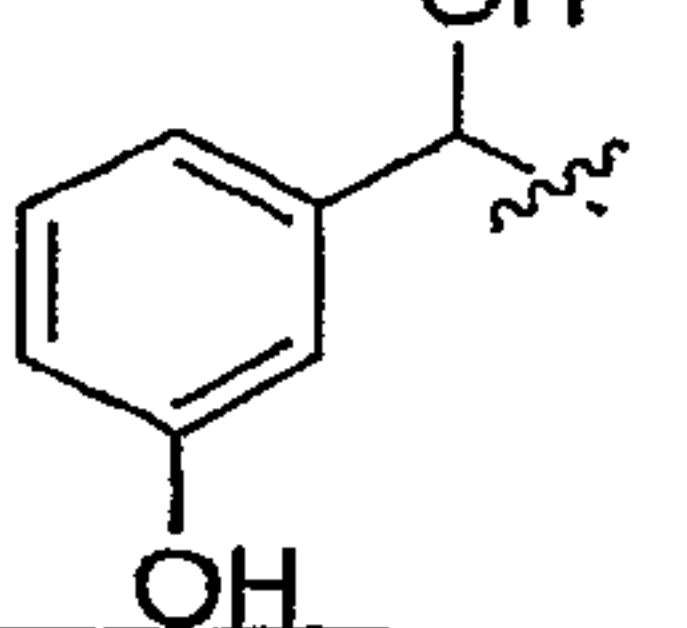
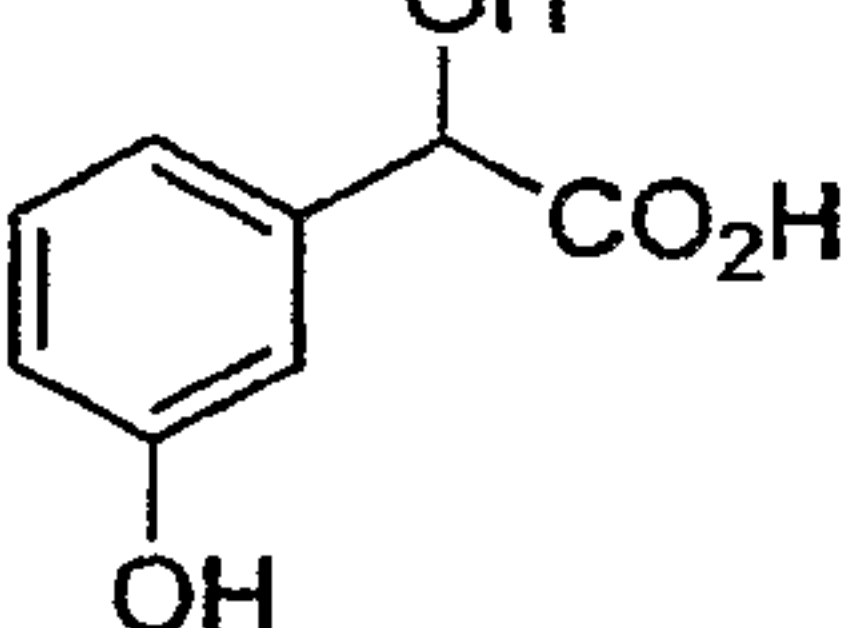
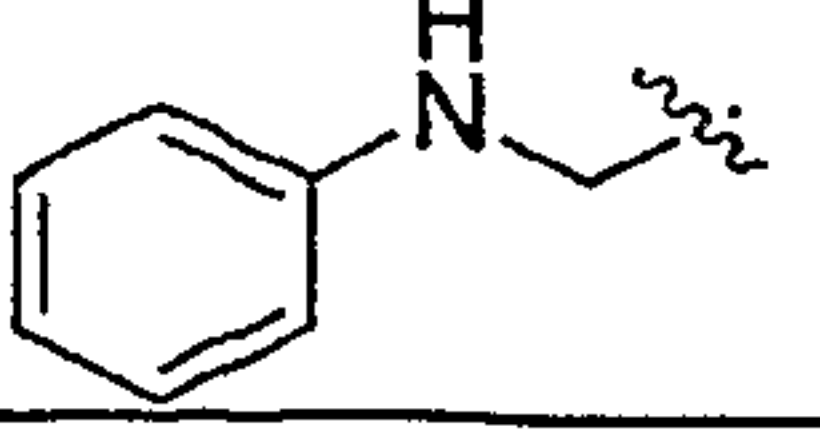
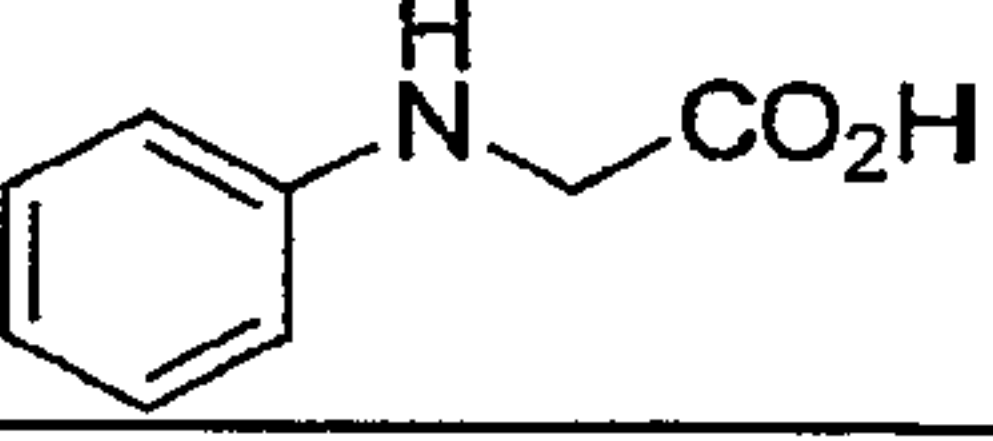
Preparation of Example 225

Example 225 was prepared using a procedure similar to that described above for **Examples 149-162** except the *tert*-butoxy carbonyl group was removed by the treatment of the intermediate with MP-TsOH in MeOH.



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Ex.	R	Carboxylic Acid
173		
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183		

Ex.	R	Carboxylic Acid
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185		
186		
187		
188		
189		
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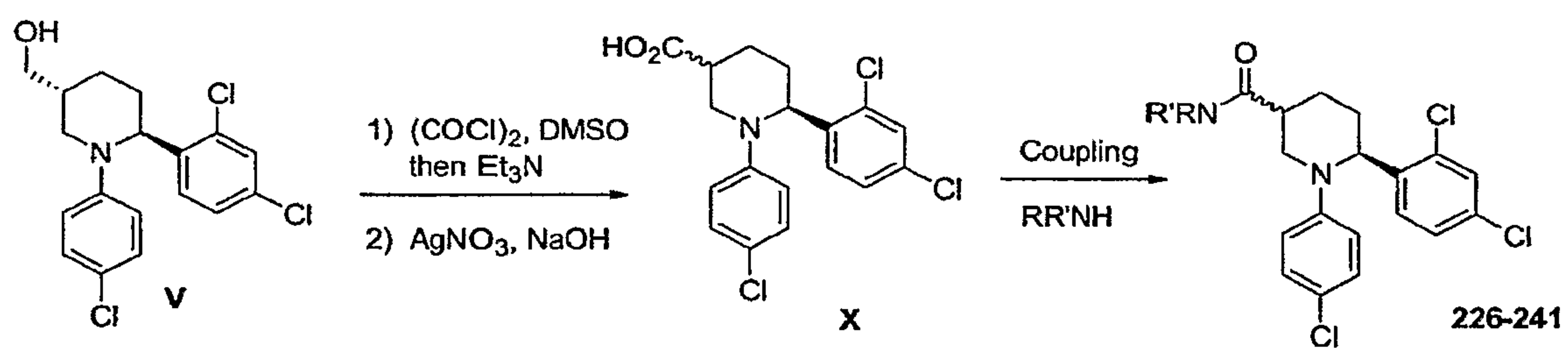
154

Ex.	R	Carboxylic Acid
199		
200		
201		
202		
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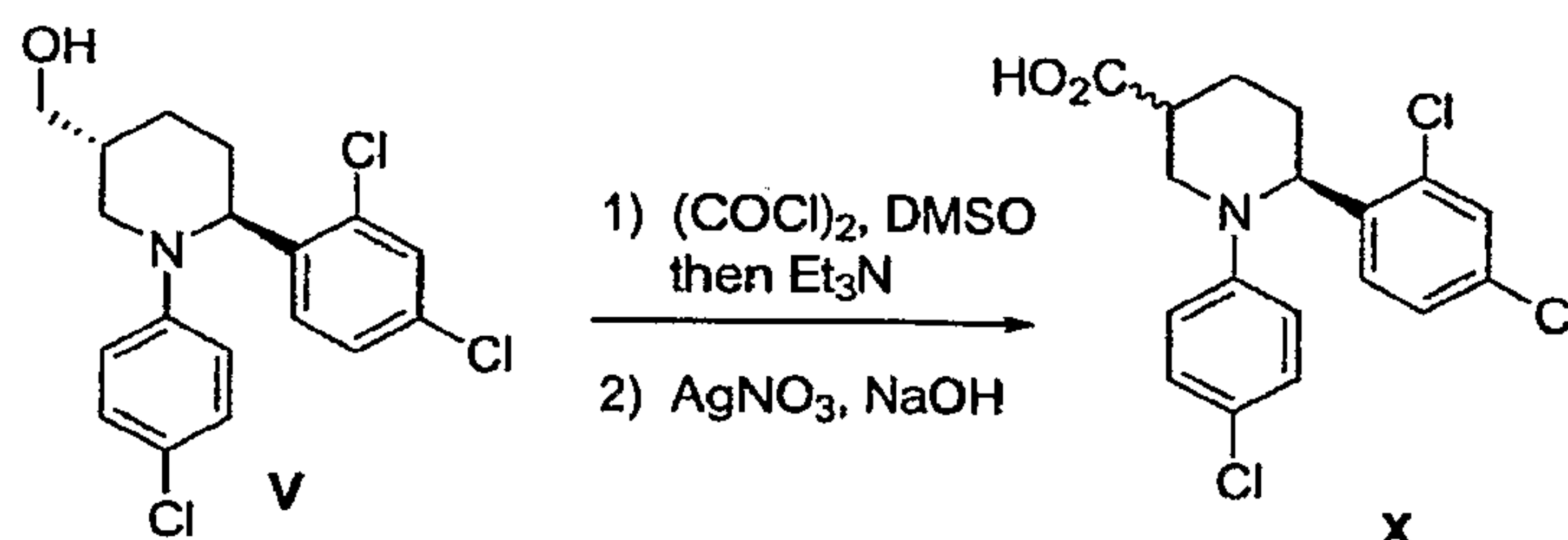
155

Ex.	R	Carboxylic Acid
216		
217		
218		
219		
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221		
222		
223		
224		
225		

Preparation of Examples 226-241



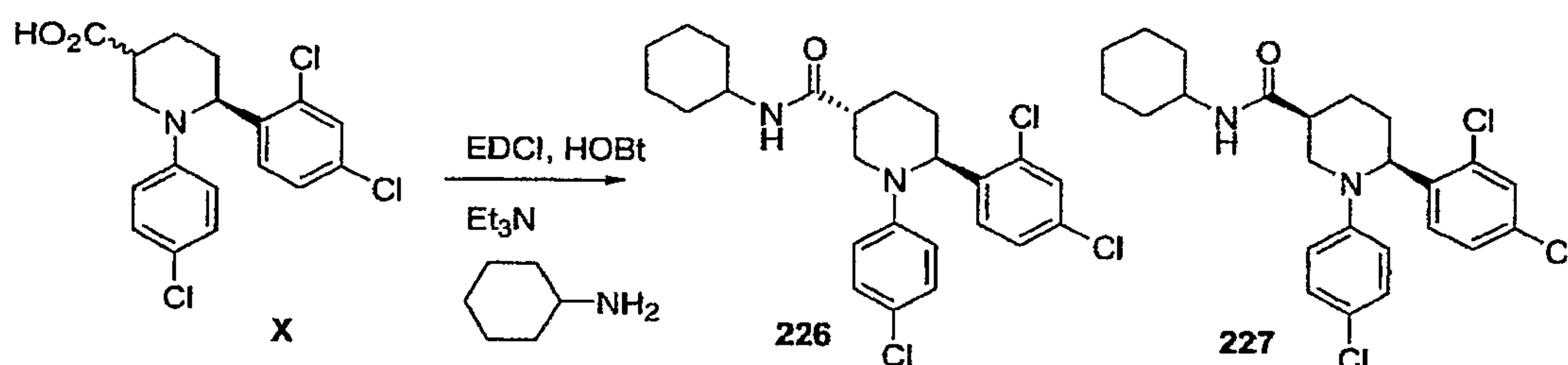
156

Step 1:

5 A solution of DMSO (29 μ L, 0.34 mmol) in CH_2Cl_2 (0.5 mL) was added to a
 solution of oxalyl chloride (48 μ L, 0.67 mmol) in CH_2Cl_2 (0.5 mL) at -78°C under
 nitrogen and stirred for 20 min. A solution of **V** (from **Examples 85 and 86**) (50 mg,
 0.14 mmol) in CH_2Cl_2 (1.5 mL) was added at -78°C and stirred for 30 min. A
 solution of Et_3N (190 μ L, 1.4 mmol) in CH_2Cl_2 (2 mL) was added at -78°C and stirred
 for 30 min at -78°C and 15 min at RT. The solution was diluted with CH_2Cl_2 ,
 10 washed with water, dried and concentrated to afford the intermediate aldehyde
 product (46 mg, 92%).

AgNO_3 (129 mg, 0.76 mmol) was added to a solution of NaOH (61 mg, 1.5
 mmol) in H_2O (1 mL) at RT under nitrogen and stirred for 15 min. A solution of the
 above aldehyde product (140 mg, 0.38 mmol) in ethanol (2.8 mL) was added at 0°C
 15 and stirred for 60 min. The mixture was filtered through celite. The filtrate was
 concentrated. The residue was dissolved in water, acidified with 3M HCl , and
 extracted with ether. The organic layer was dried and concentrated to afford **X** (110
 mg, 75%).

20 **Step 2:**

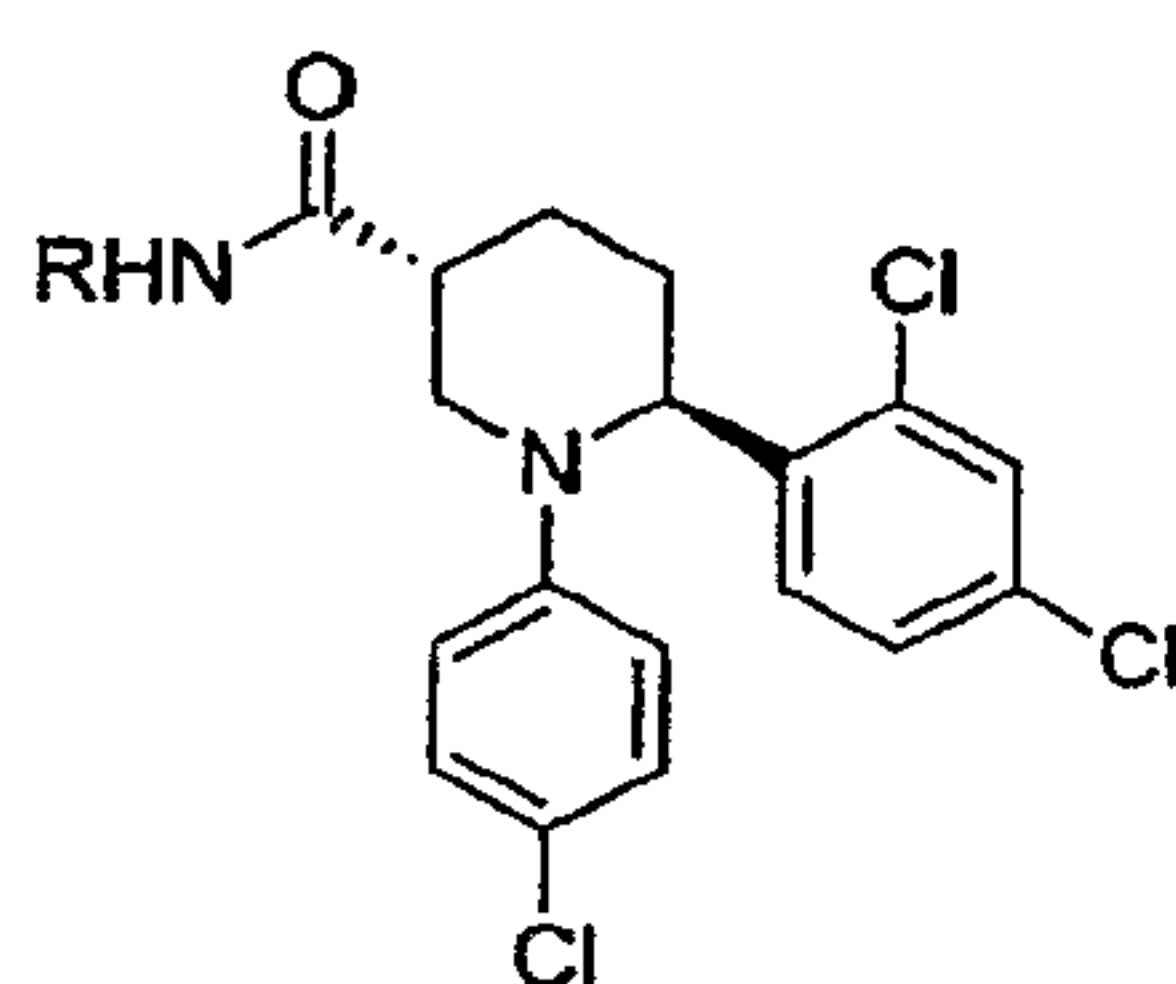


Cyclohexylamine (100 μ L, 0.34 mmol) was added to a solution of the acid **X**
 (35 mg, 0.09 mmol) in DMF (0.9 mL) at RT followed by Et_3N (190 μ L, 1.4 mmol),
 25 EDCI (173 mg, 0.90 mmol), and HOBT (62 mg, 0.45 mmol). The mixture was stirred
 at RT for 2 h. The mixture was concentrated. The residue was dissolved in water

157

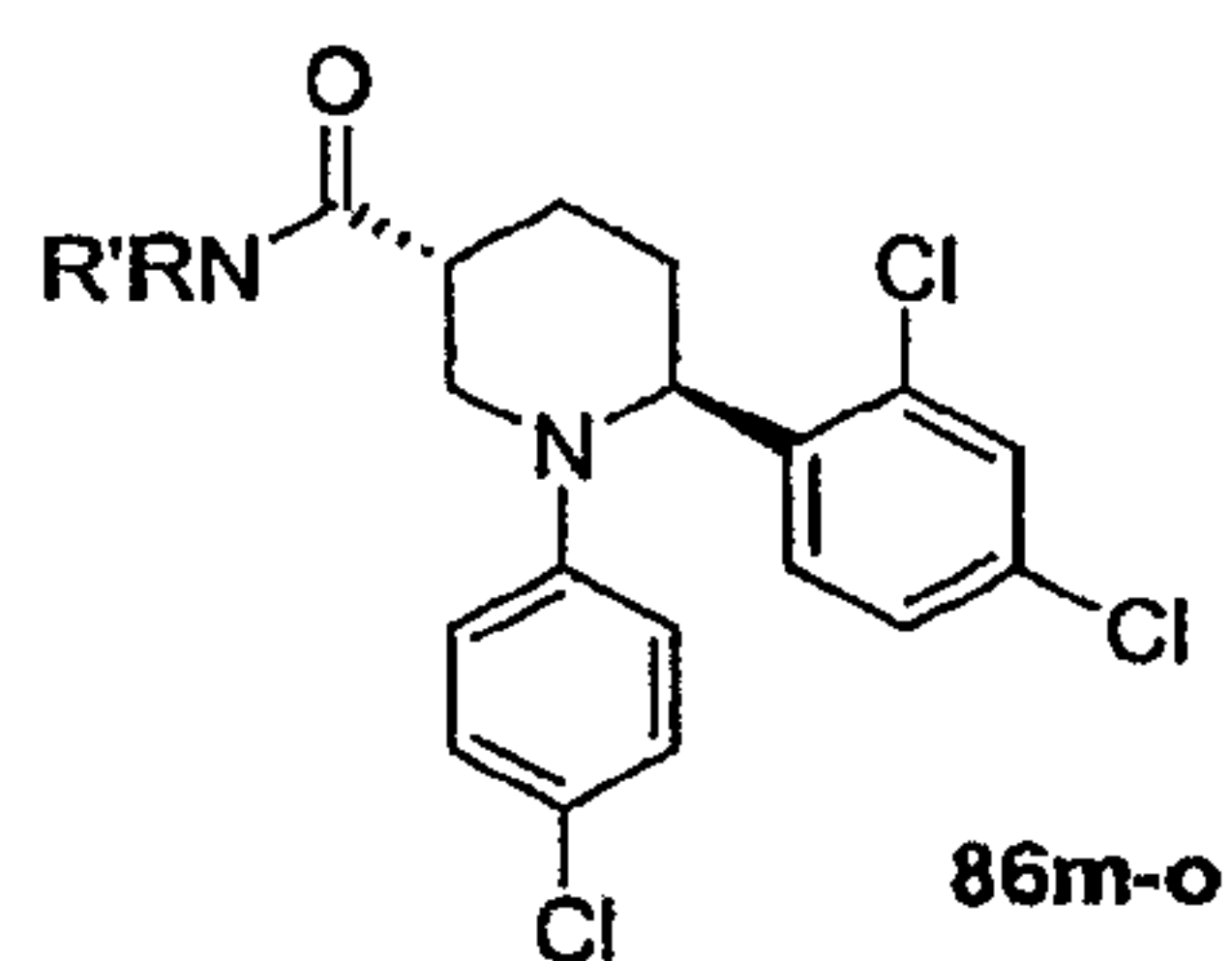
and extracted with ether. The organic layer was dried and concentrated. Separation of the residue via flash chromatography (50/50 hexanes/EtOAc, SiO₂) gave **226** (25 mg, 60%) and **227** (6 mg, 14%).

- 5 The following amides **228-241** were prepared similarly using the acid **X** and the appropriate amines.



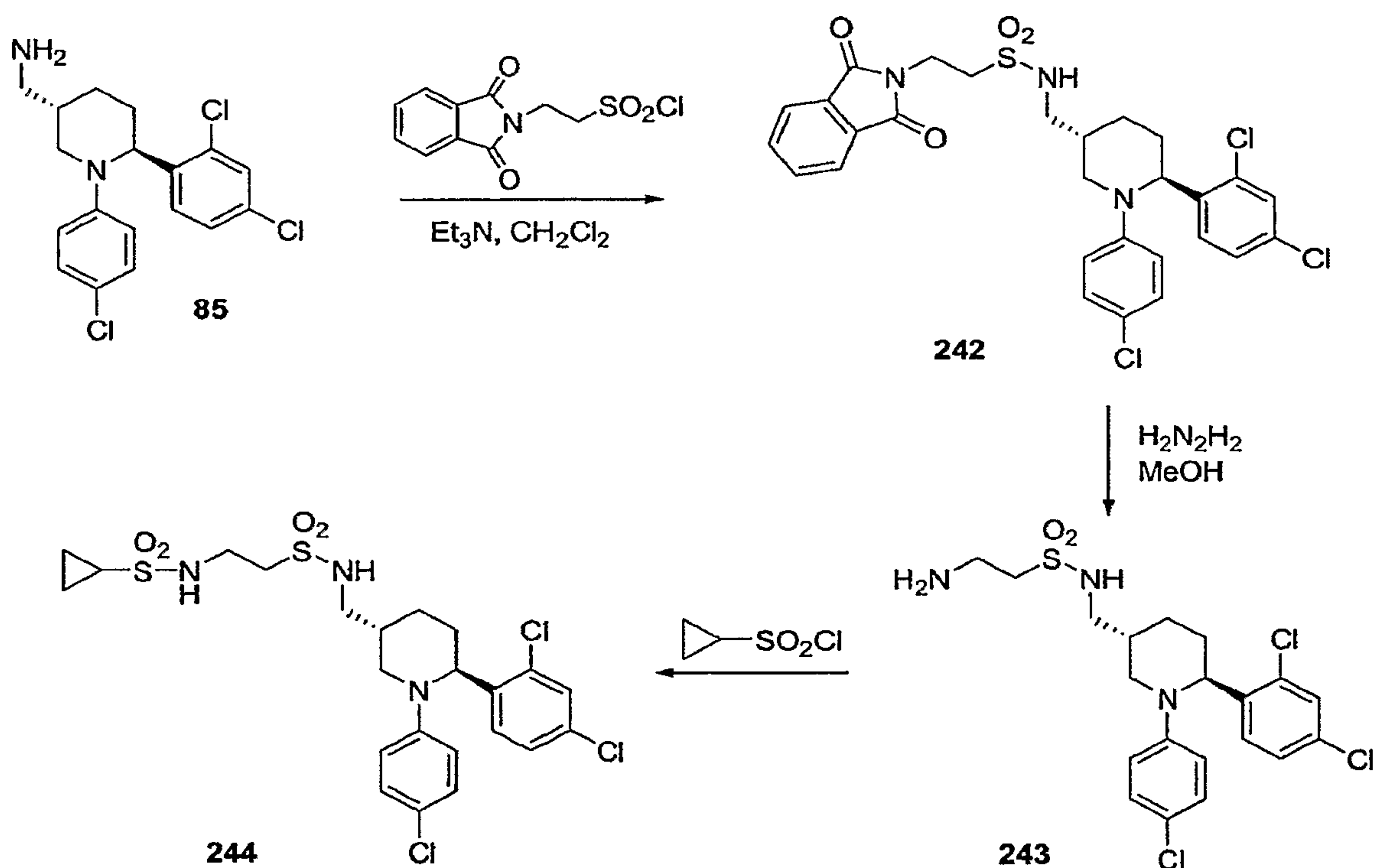
Ex. #	R	Amine
228		
229		
230		
231		
232		
233		
234		
235		
236		
237		
238		

158



Ex. #	NRR'	Amine
239		
240		
241		

5



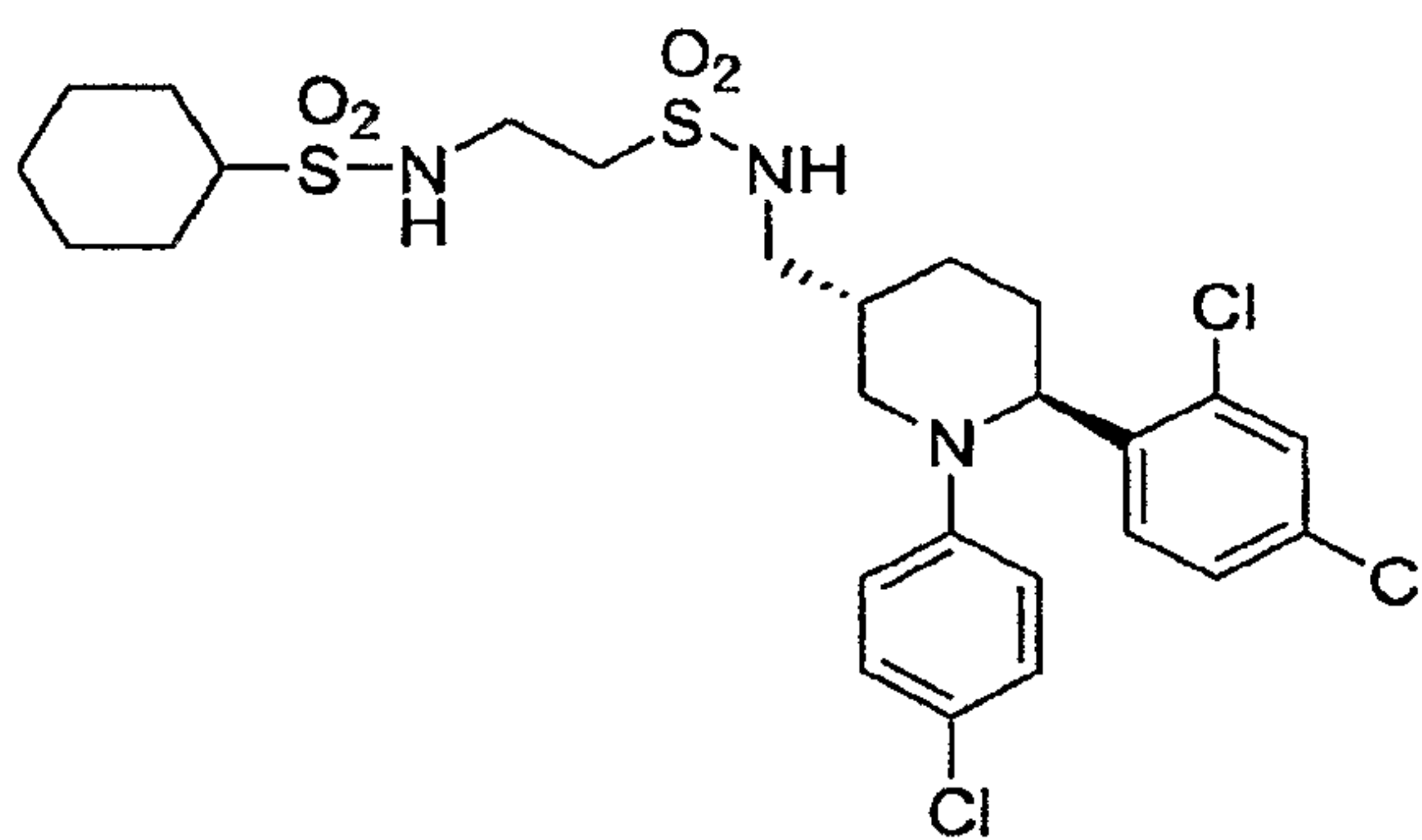
To a solution of **Example 85** (200mg, 0.54 mmol) in CH₂Cl₂ (2 mL) was added Et₃N (10 drops) and 2-phthalimidoethane sulfonyl chloride (Astatech). The

159

solution was stirred at RT overnight. The solution was diluted with CH_2Cl_2 . The solution was washed with H_2O . The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by flash chromatography (SiO_2 : gradient 1:0 to 1:1 hexanes:EtOAc) to afford 300 mg **Example 242**.

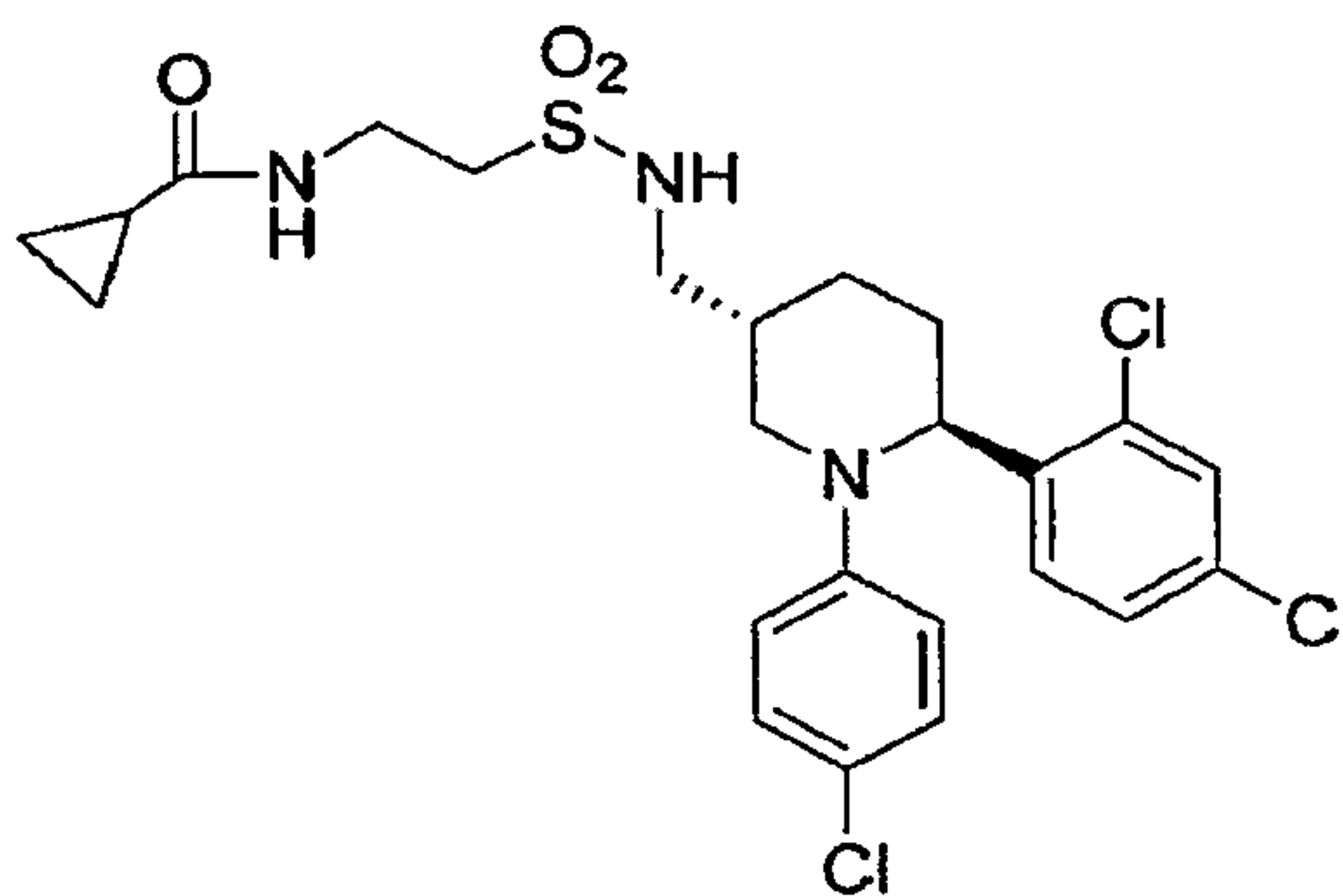
To a solution of **Example 242** (300 mg, 0.50 mmol) in MeOH was added hydrazine (48 mg, 1.5 mmol). The resultant solution was heated to reflux for 3 h at which time additional hydrazine (20 mg) was added and the solution was heated to reflux for an additional 1 h. The solution was then concentrated. To the crude material was added EtOAc and the white precipitate was removed by filtration. The solution was concentrated and the crude product was purified by flash chromatography [SiO_2 : gradient 1:0:0 to 95:7:0.7 CH_2Cl_2 :MeOH:7N NH_3 (in MeOH)] to afford **Example 243** (135 mg).

To a solution of **Example 243** (40 mg, 0.084 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (10 drops) and cyclopropyl sulfonyl chloride (Array) (18 mg, 0.13 mmol). The solution was stirred at RT followed by an additional 24 h at reflux. The crude product was purified by preparative TLC [SiO_2 : 95:5:0.5 CH_2Cl_2 :MeOH: ammonium hydroxide]. to afford **Example 244**.

**Example 245**

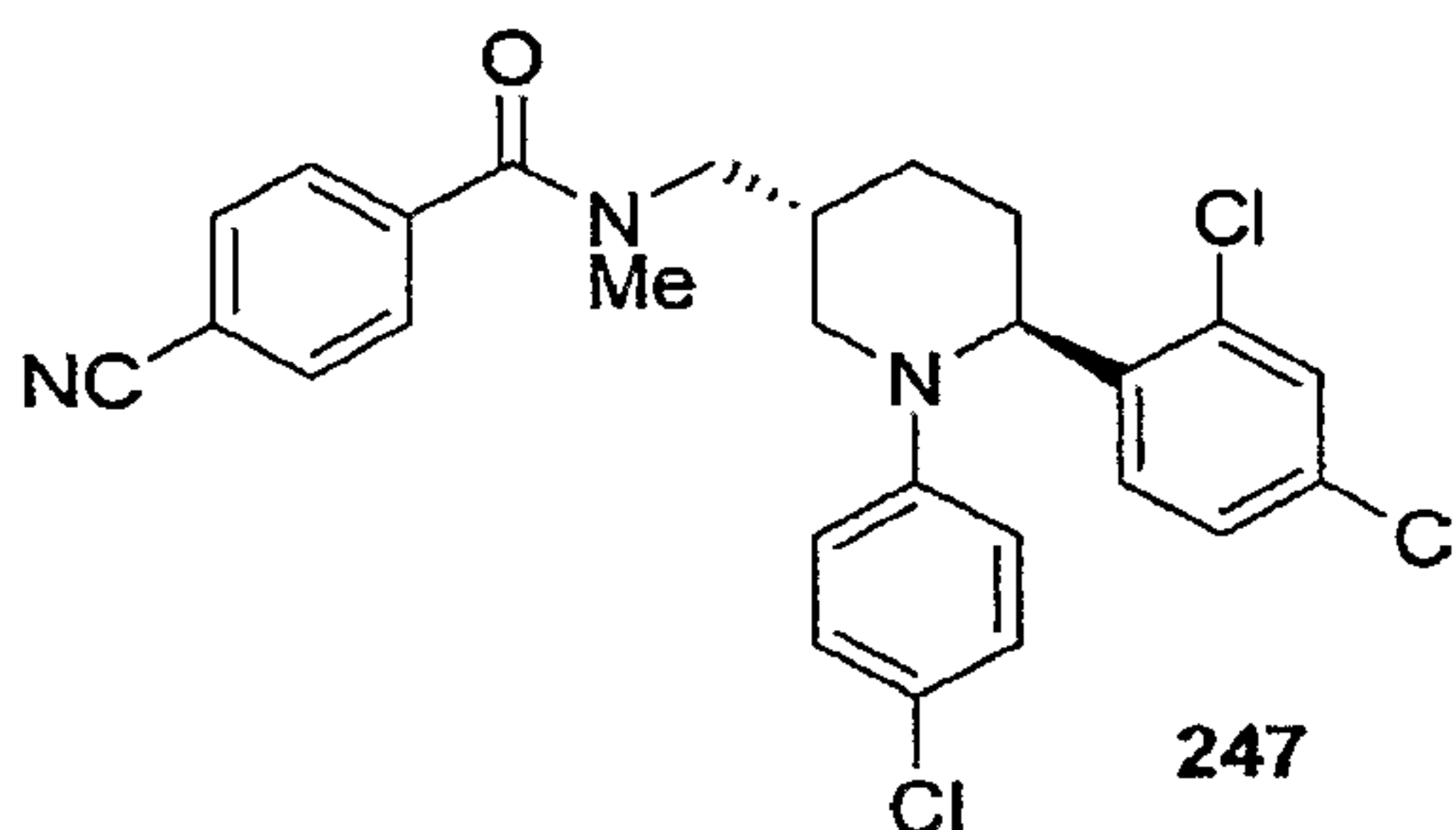
Example 245 was prepared using a procedure similar to that described above for **Example 244**, except cyclohexyl sulfonyl chloride (Array) was used instead of cyclopropyl sulfonylchloride.

160

**Example 246**

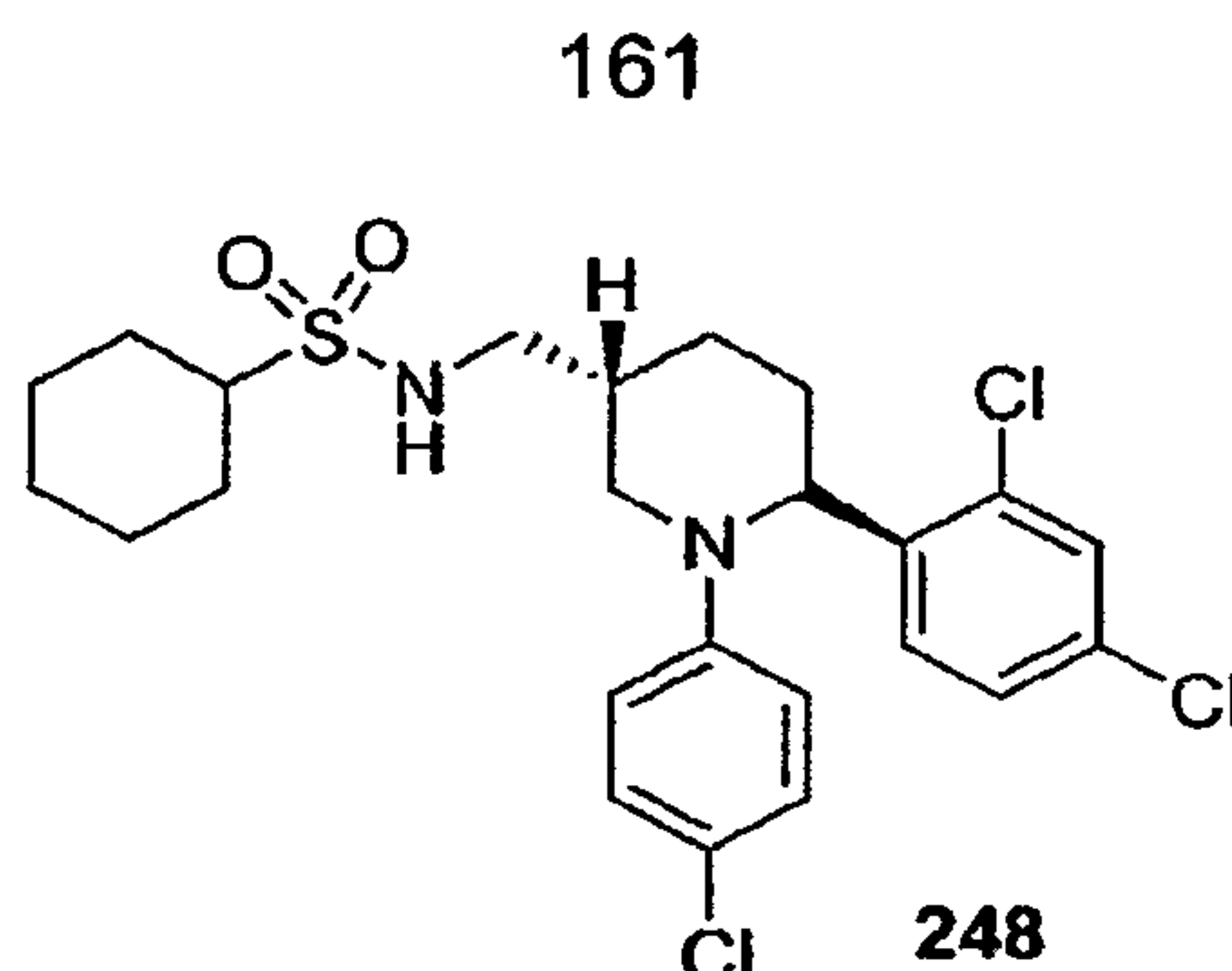
Example 246 was prepared using a procedure similar to that described above for **Example 244**, except cyclopropanecarbonyl chloride was used instead of cyclopropyl sulfonylchloride.

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Preparation of Example 247**247**

To a solution of **Example 91** (81 mg, 0.16 mmol) in DMF was added NaH (4.8 mg, 0.20 mmol) followed by methyl iodide (28 mg, 0.2 mmol). The solution was stirred overnight. The solution was diluted with EtOAc and washed with water. The water layer was extracted with EtOAc (2x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash chromatography (SiO₂: gradient 1:0 to 1:1 hexanes:EtOAc) to afford 46 mg of **Example 247**.

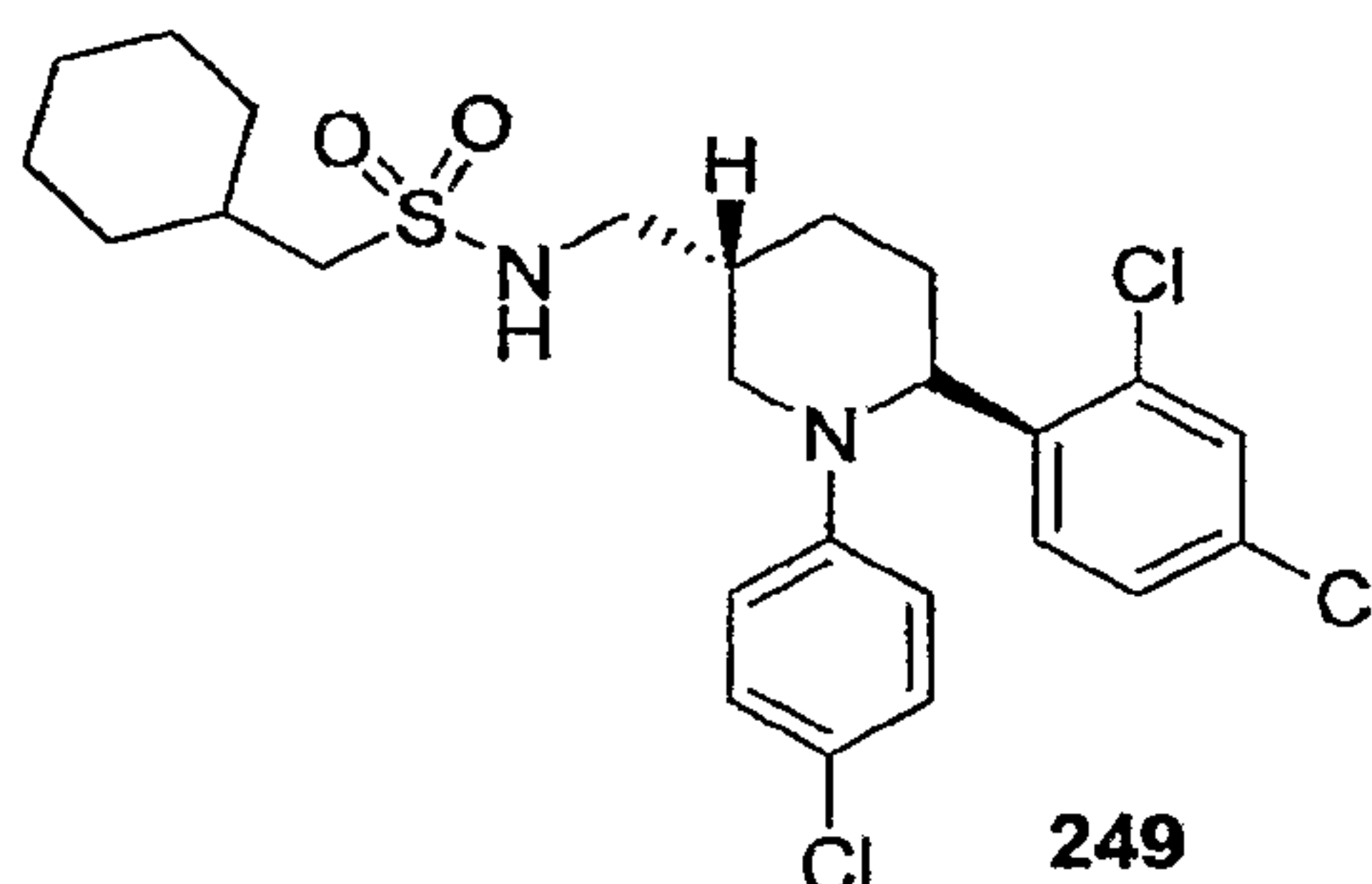
Preparation of Example 248



Example 248 was prepared using a procedure similar to that described above for **Example 86**, except cyclohexanesulfonyl chloride was used instead of benzene sulfonyl chloride.

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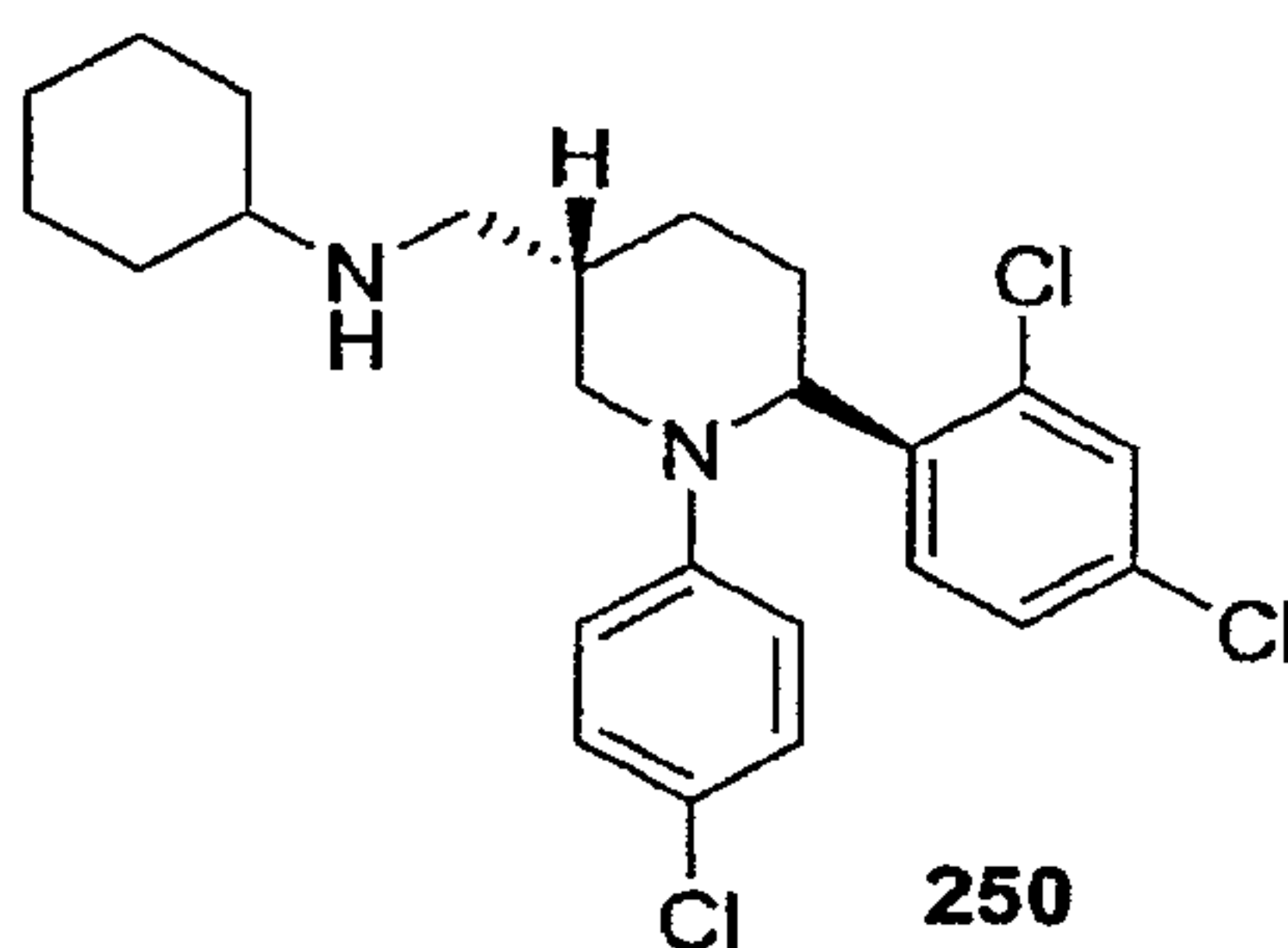
Preparation of Example 249



Example 249 was prepared using a procedure similar to that described above for **Example 86**, except cyclohexylmethanesulfonyl chloride was used instead of benzene sulfonyl chloride.

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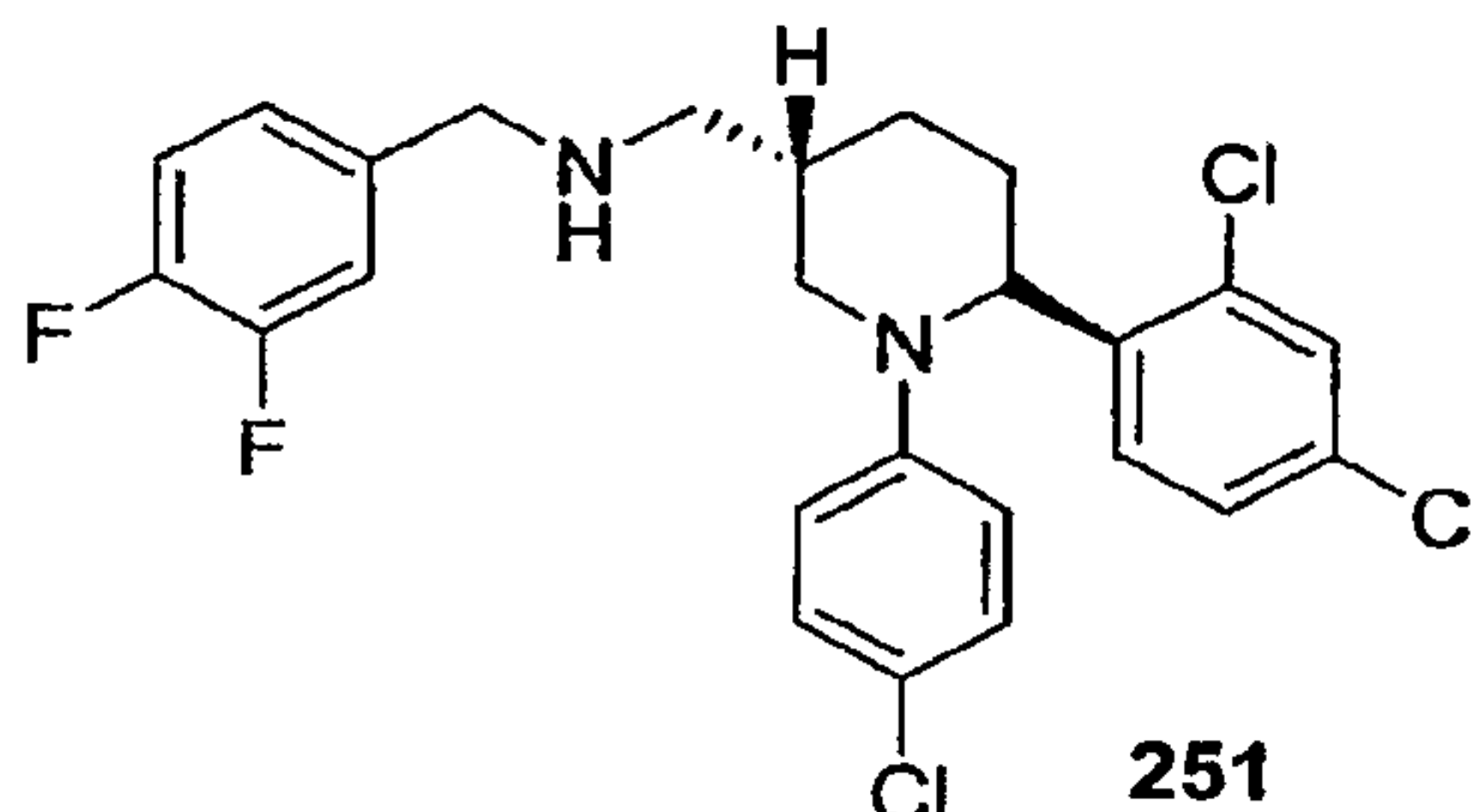
Preparation of Example 250



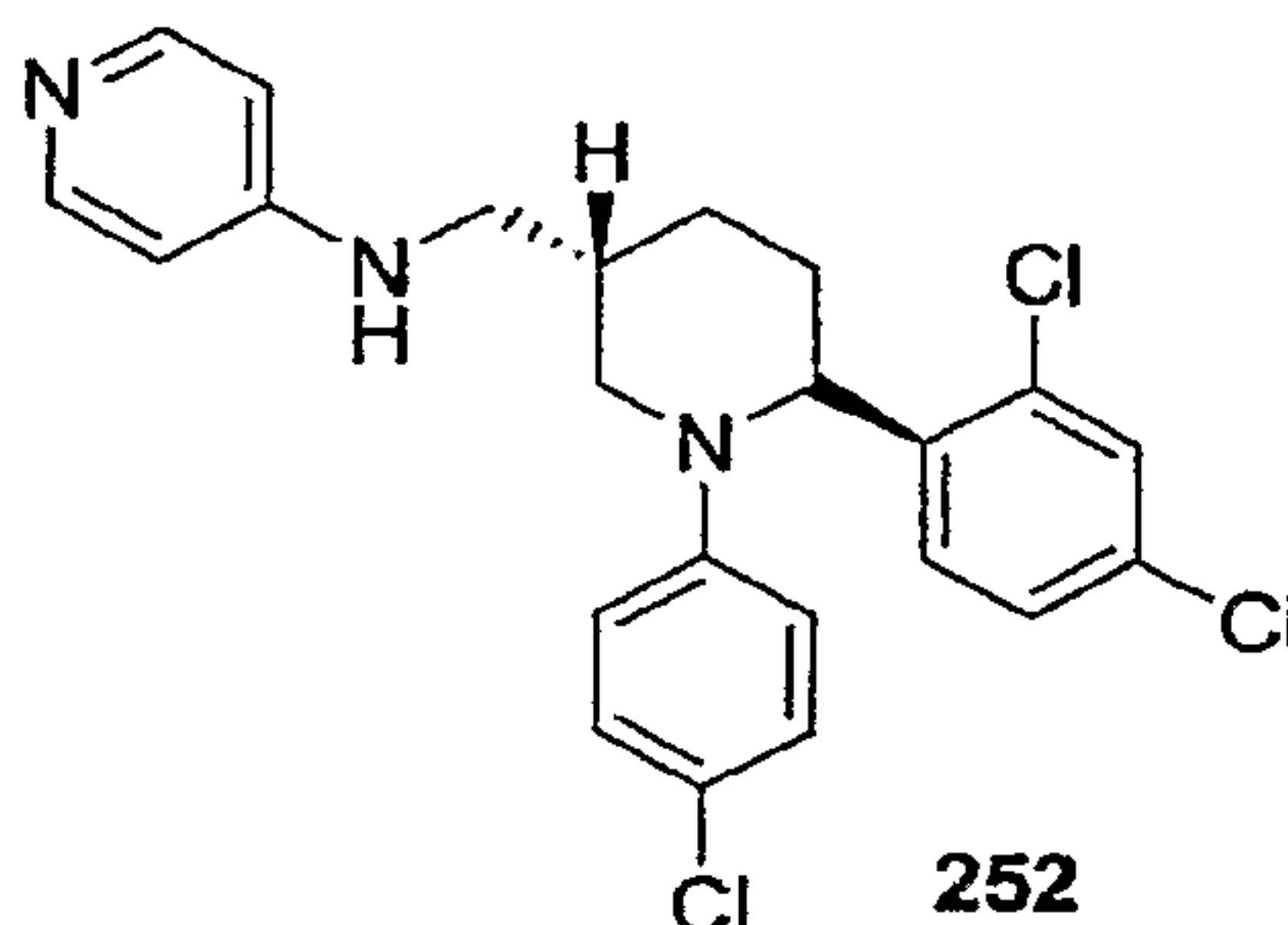
15

To a solution of **Example 85** (50 mg, 0.14 mmol) in CH_2Cl_2 (1 mL) was added cyclohexanone (14 μL , 0.14 mmol) followed by sodium triacetoxyborohydride (34 mg, 0.16 mmol) and acetic acid (2 drops). The solution was stirred at RT overnight. The solution was diluted with NaHCO_3 (aq.) and extracted with EtOAc. The organic layer was dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by preparative TLC [SiO_2 : 95:5:0.5 CH_2Cl_2 :MeOH:ammonium hydroxide] to afford 33 mg **Example 250**.

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Preparation of Example 251

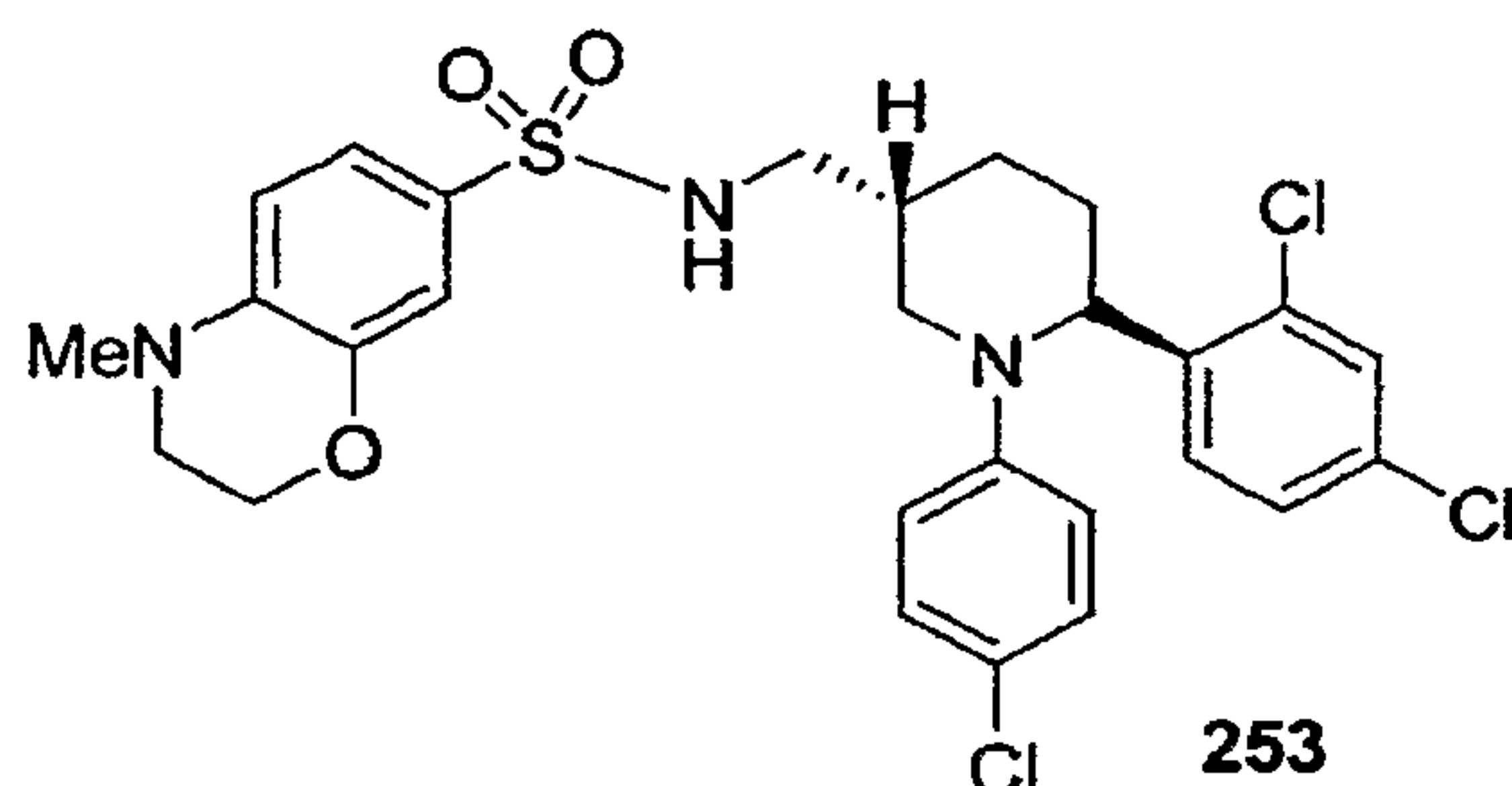
To a solution of **Example 85** (50 mg, 0.14 mmol) in CHCl_3 was added MgSO_4 (50 mg) and 3,4 difluorobenzaldehyde (15 μL , 0.14 mmol). The mixture was stirred at RT for 70 h. The mixture was filtered and concentrated. Methanol was added followed by NaBH_4 (6.6 mg, 0.18 mmol). The mixture was stirred at RT for 2 h. The material was partitioned between H_2O and EtOAc. The organic layer was dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by flash chromatography (SiO_2 : gradient 1:0 to 1:1 hexanes:EtOAc) to afford 50 mg of **Example 251**.

Preparation of Example 252

A mixture of **Example 85** (50 mg, 0.14 mmol), 4-bromopyridine hydrochloride (31 mg, 0.16 mmol), NaOtBu (26 mg, 0.27 mmol), $\text{Pd}(\text{OAc})_2$ (1.6 mg, 0.006 mmol) and BINAP (2.4 mg, 0.006 mmol) in toluene (1.5 mL) was heated at 70°C for 2 days. The mixture was filtered and concentrated. The crude product was purified by semi-preparative HPLC (C_{18} : 100:0:1 to 0:100:1 H_2O : MeCN: formic acid) to afford **Example 252** (7 mg).

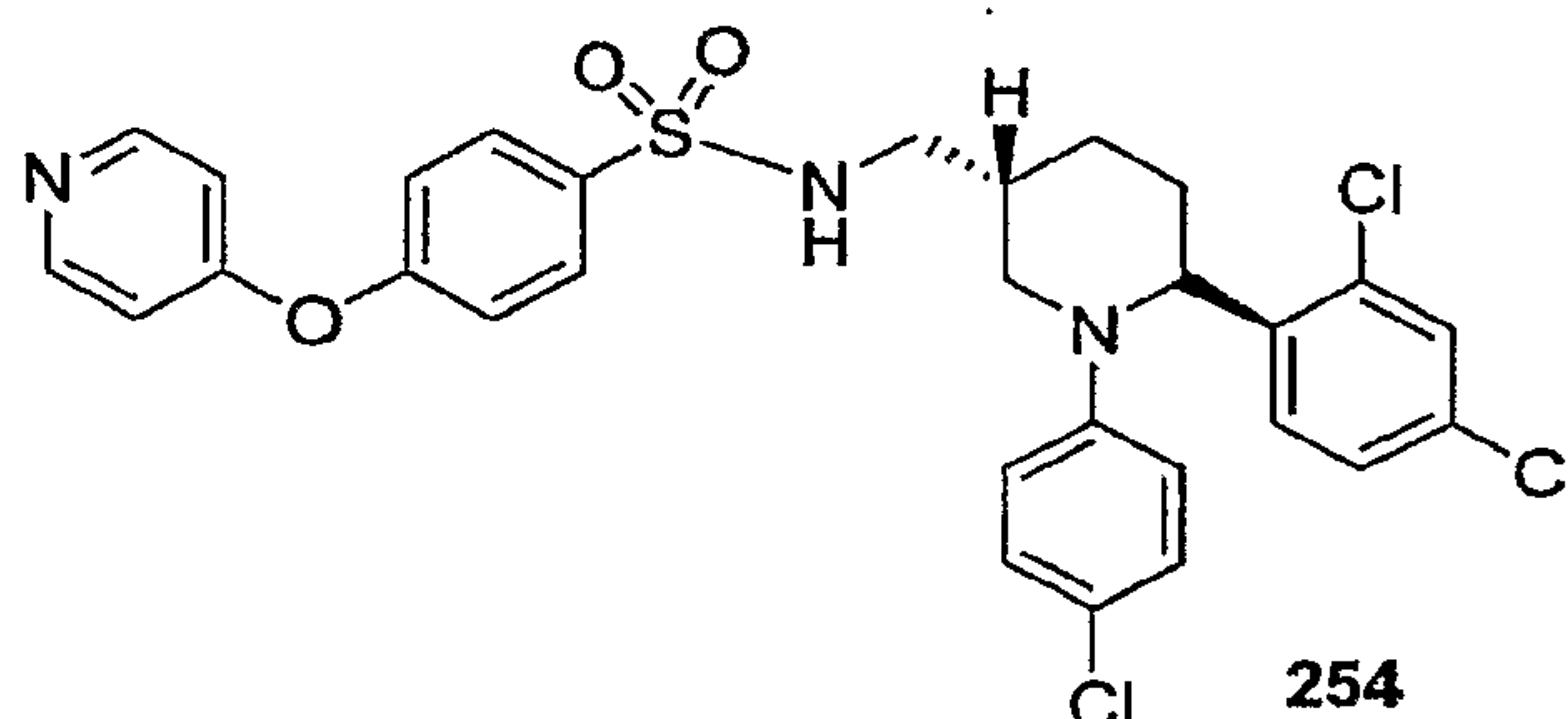
Preparation of Example 253

163



To a solution of **Example 85** (50 mg, 0.14 mmol) in CH_2Cl_2 was added 4-methyl-3,4-dihydro-2H-1,4-benzoxazine-7-sulfonyl chloride (Maybridge) (40 mg, 0.16 mmol) and Et_3N (10 drops). The solution was heated to reflux overnight. The solution was concentrated and the crude product was purified by preparative TLC chromatography (SiO_2 : 1:1 hexanes:EtOAc) to afford **Example 253**.

Preparation of Example 254

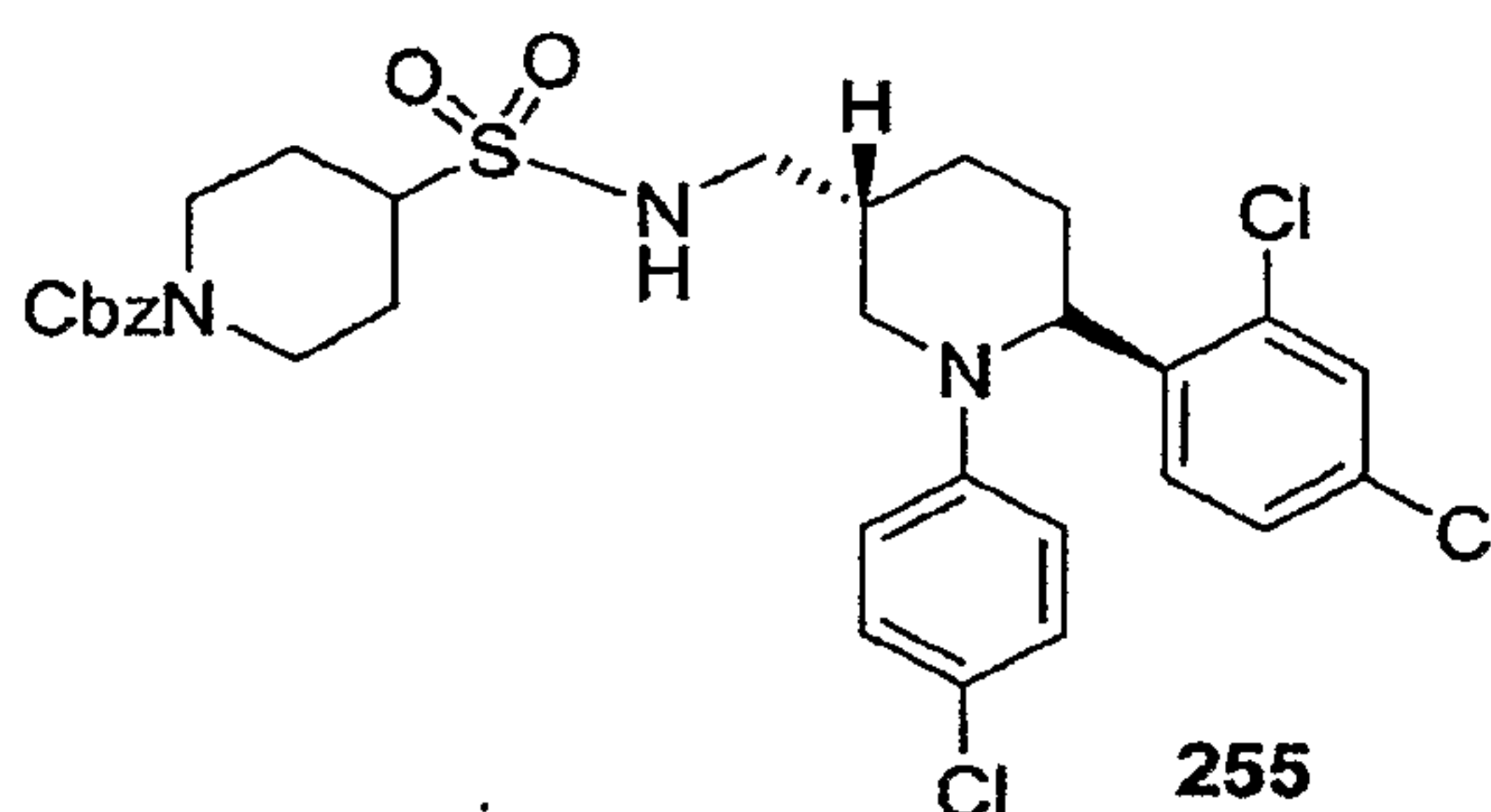


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Example 254 was prepared using a procedure similar to that described above for **Example 253**, except (4-(4-pyridyloxy)phenyl)sulfonyl chloride hydrochloride was used instead of 4-methyl-3,4-dihydro-2H-1,4-benzoxazine-7-sulfonyl chloride.

15

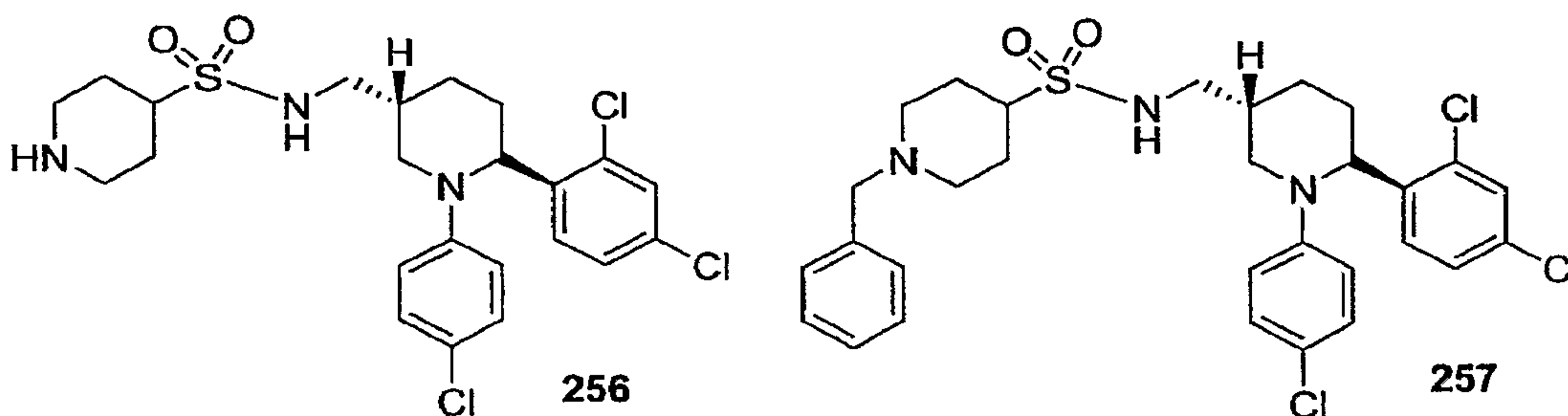
Preparation of Example 255



Example 255 was prepared using the procedure for **Example 253**, except 1-piperidine carboxylic acid, 4-(chlorosulfonyl)-,phenylmethyl ester (Magical Scientific; Oklahoma City, OK) was used instead of 4-methyl-3,4-dihydro-2H-1,4-benzoxazine-7-sulfonyl chloride.

5

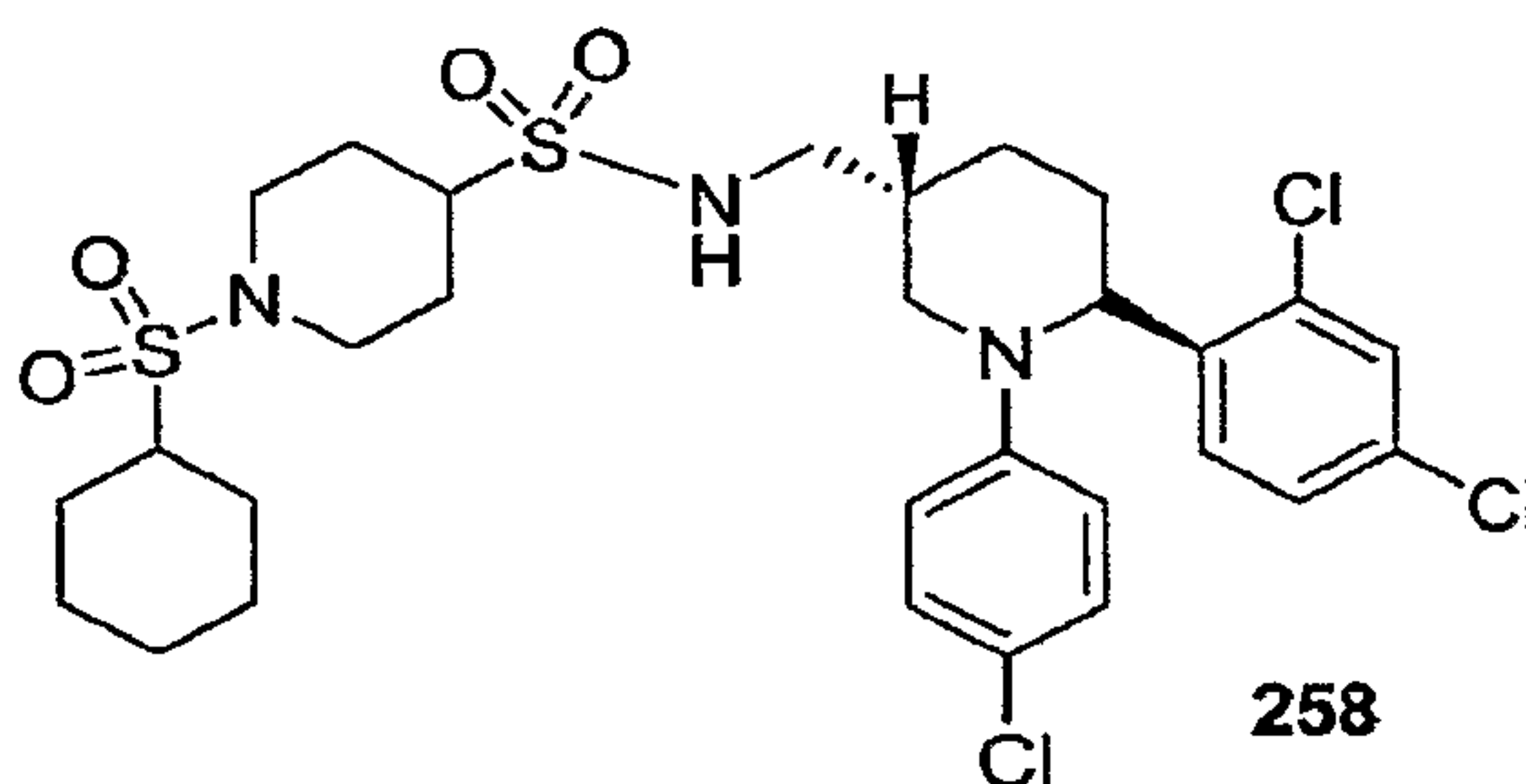
Preparation of Examples 256 and 257



To a solution of **Example 255** (135 mg, 0.21 mmol) in CH_2Cl_2 (15 mL) at 0°C was added boron tribromide (156 mg, 0.6 mmol). The solution was allowed to warm to RT and stirred for 50 min. To this solution was added NaHCO_3 (aq.). The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. . The crude product was purified by flash chromatography (SiO_2 : gradient 1:0:0 to 90:11:0.75 CH_2Cl_2 : MeOH: ammonium hydroxide) to afford 20 mg of **Example 256** and 100 mg **Example 257**.

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Preparation of Example 258

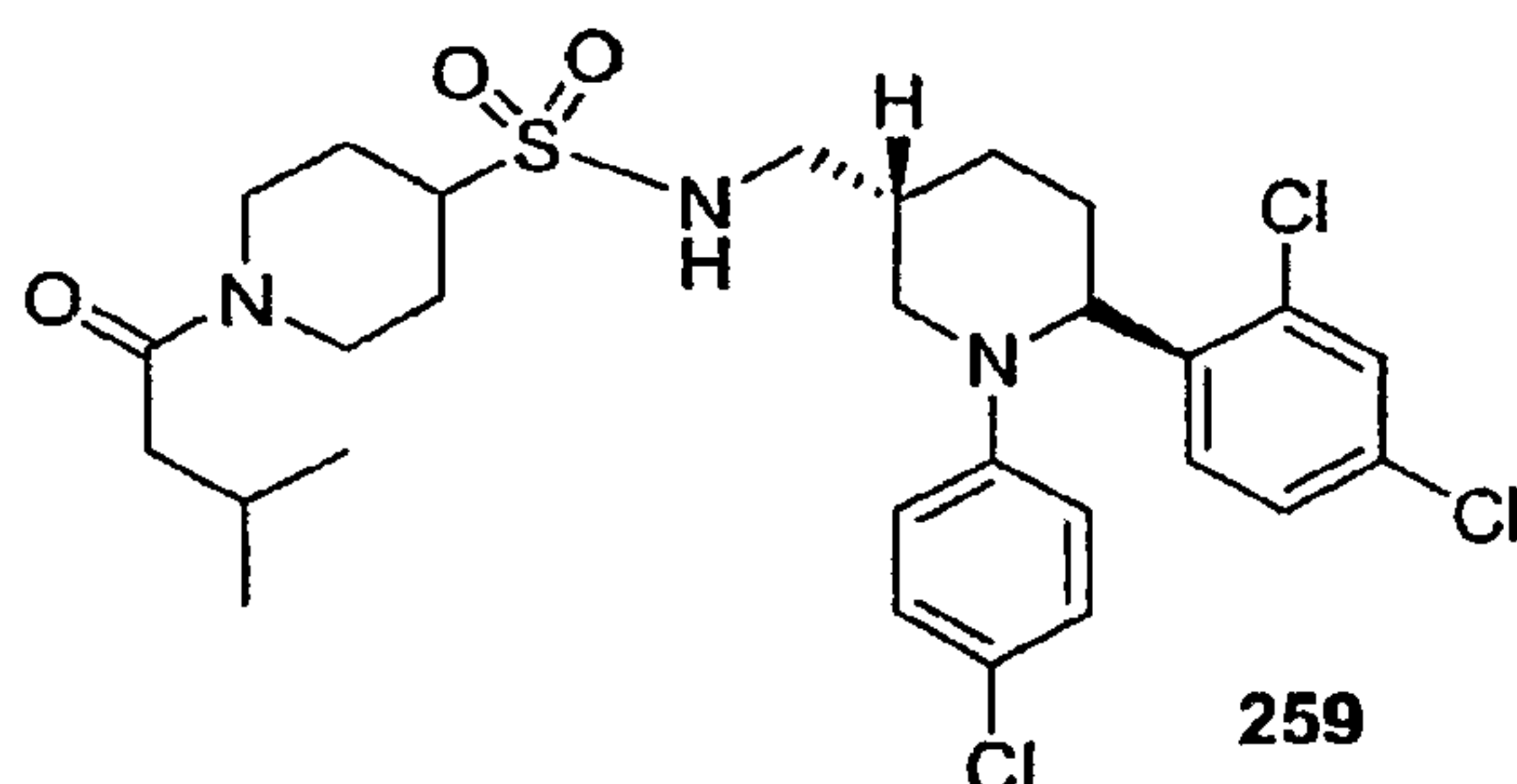


To a solution of **Example 256** (30 mg, 0.06 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (10 drops) followed by cyclohexyl sulfonyl chloride (17 mg, 0.09 mmol). The solution was stirred at RT overnight. Additional cyclohexyl sulfonyl chloride (90 mg) was added and the solution was heated to reflux for an additional 24h. The solution was concentrated. The crude product was purified by preparative TLC chromatography (SiO_2 : 6:4 hexanes:EtOAc) to afford 33mg **Example 258**.

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Preparation of Example 259

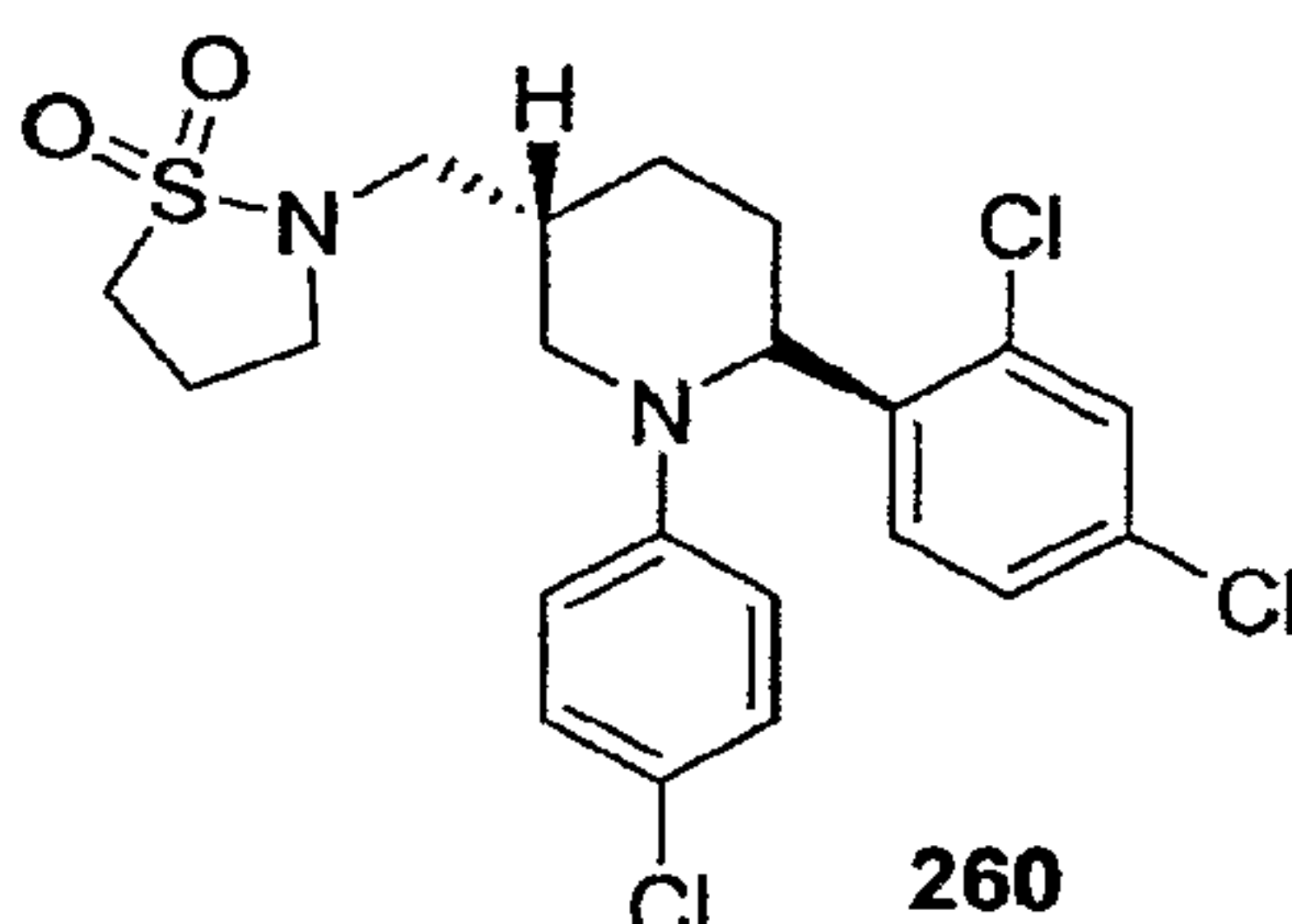
165



To a solution of **Example 256** (30 mg, 0.06 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (10 drops) followed by 3-methyl butyryl chloride (10 mg, 0.09 mmol). The solution was stirred at RT overnight. The solution was concentrated.

- 5 The crude product was purified by preparative TLC chromatography (SiO_2 : 1:1 hexanes:EtOAc) to afford 4 mg **Example 259**.

Preparation of Example 260

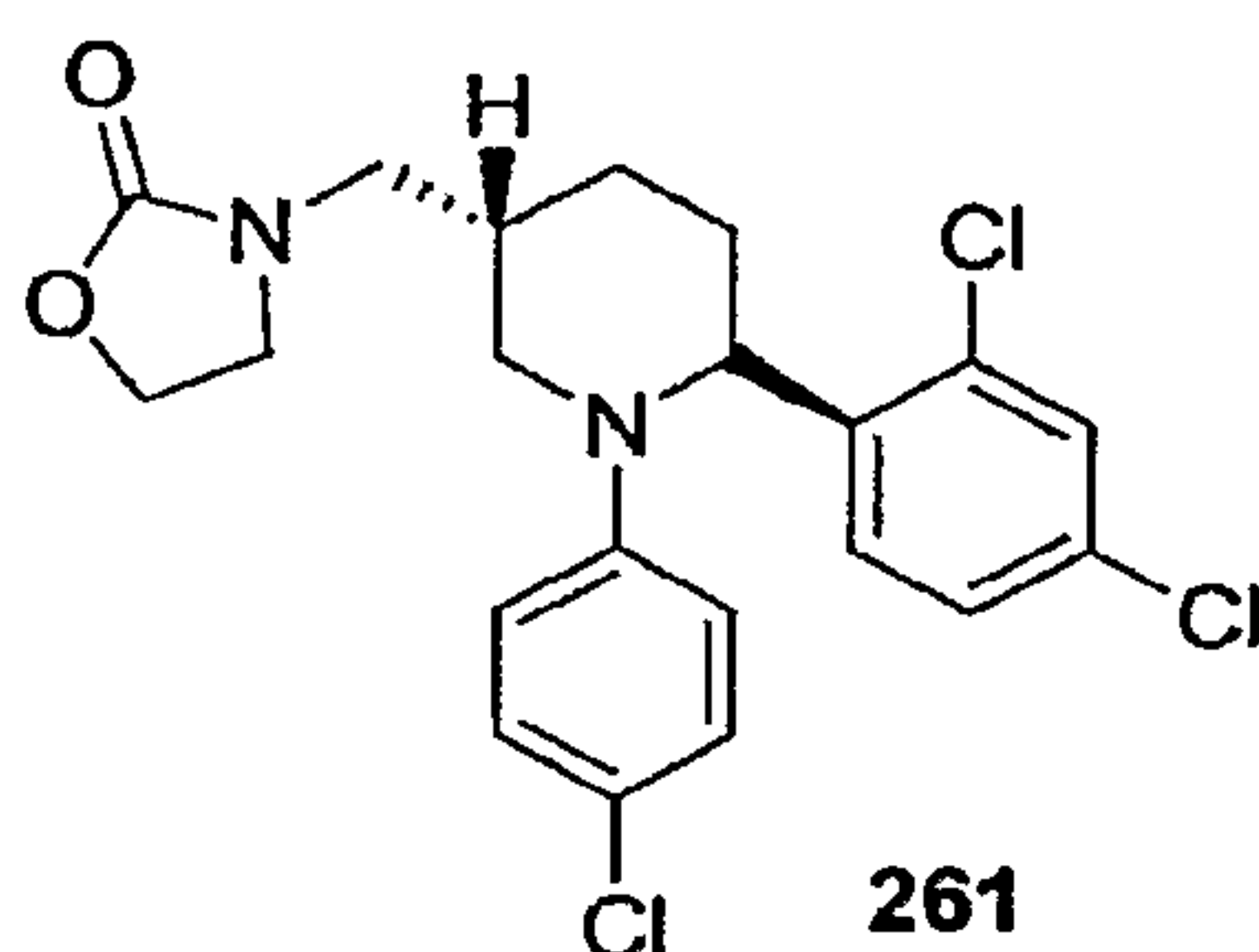


10 To a solution of **Example 85** (30 mg, 0.084 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (10 drops) followed by 3-chloropropyl sulfonyl chloride (22 mg, 0.13 mmol). The solution was stirred at RT overnight. Additional 3-chloropropyl sulfonyl chloride (90 mg) was added and the solution was heated to reflux for another 24h. The solution was concentrated. The crude product was purified by preparative TLC chromatography (SiO_2 : 6:4 hexanes:EtOAc). This product was dissolved in THF (2 mL) and potassium t-butoxide (7 mg, 0.06 mmol) was added. The mixture was heated to reflux for 3 h. The mixture was concentrated. The crude product was purified by preparative TLC chromatography (SiO_2 : 65:35 hexanes:EtOAc) to afford 17 mg **Example 260**.

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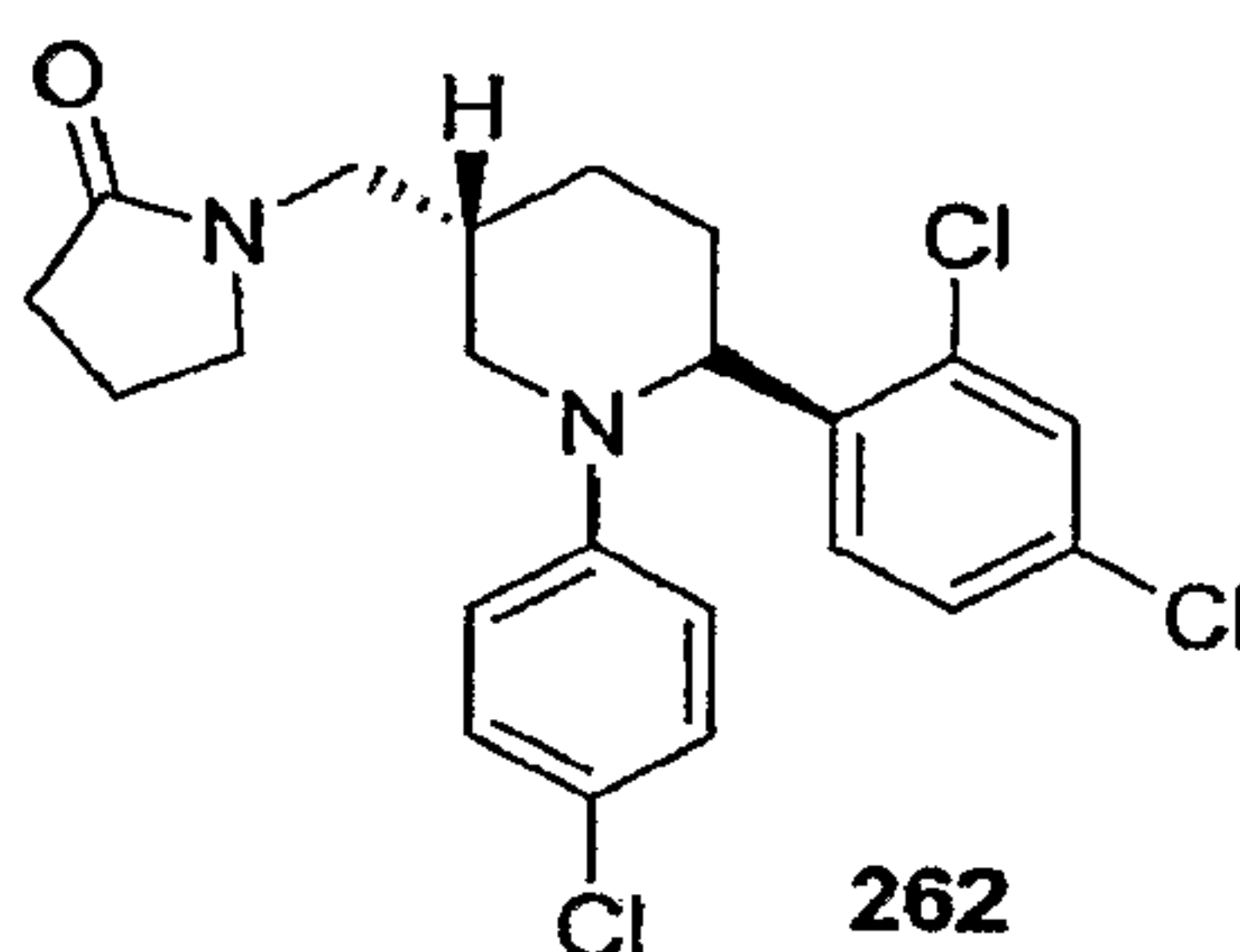
Preparation of Example 261

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To a solution of **Example 85** (26 mg, 0.070 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (8.5 mg, 0.084 mmol) followed by 2-chloroethyl chloroformate (12 mg, 0.084 mmol). The solution was stirred at RT for 48 h. The solution was concentrated. The material was redissolved in CH_2Cl_2 and washed with NaHCO_3 (aq.). The aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was dissolved in THF (2 mL) and NaH (6 mg, 0.14 mmol) was added. The solution was heated to reflux for 2h. Water was added and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by preparative TLC chromatography (SiO_2 : 1:1 hexanes:EtOAc) to afford 22 mg **Example 261**.

Preparation of Example 262



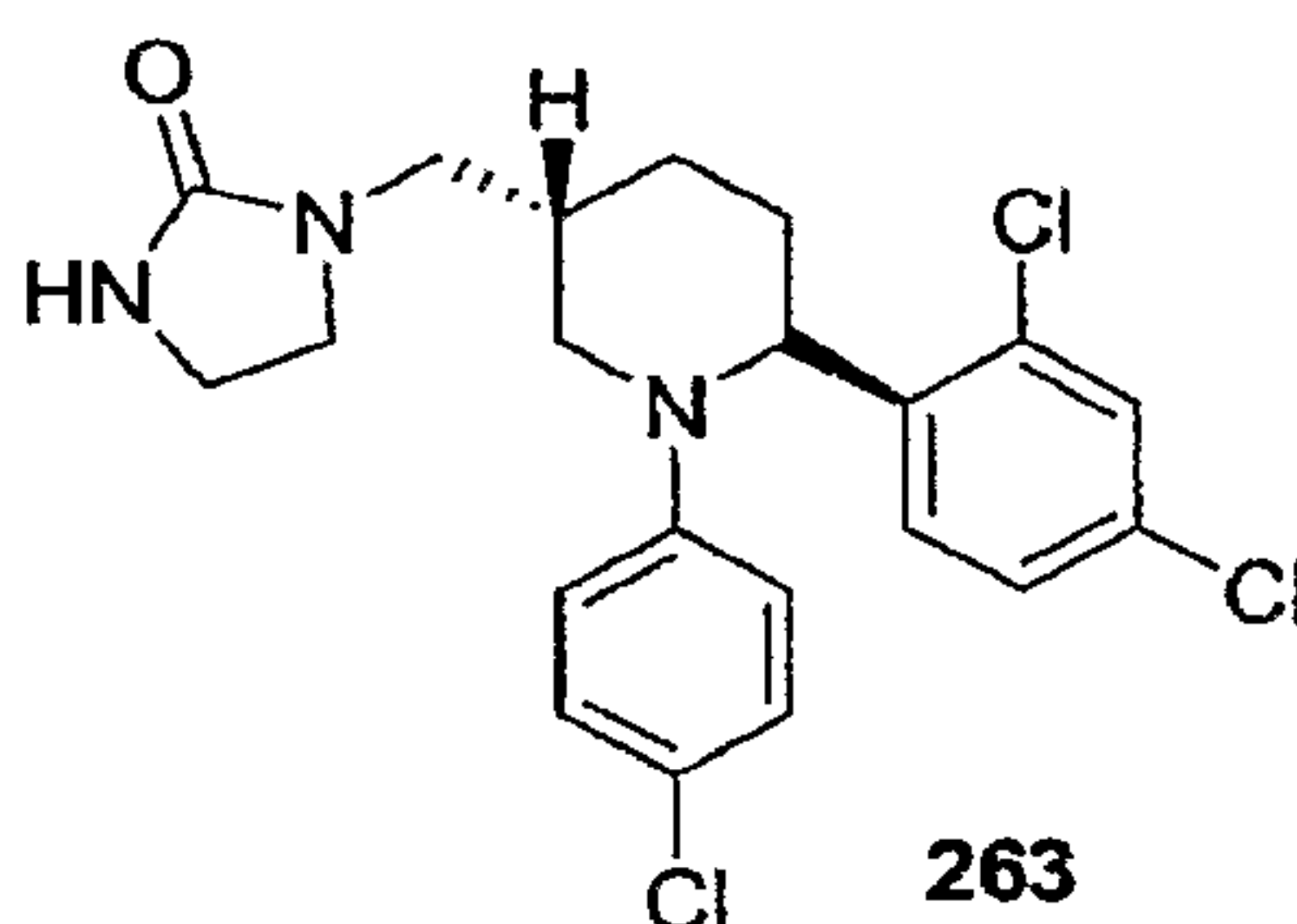
To a solution of **Example 85** (30 mg, 0.081 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (8.5 mg, 0.084 mmol) followed by 4-chlorobutryl chloride (14 mg, 0.097 mmol). The solution was stirred at RT for 48 h. The solution was concentrated. The material was redissolved with CH_2Cl_2 and washed with NaHCO_3 (aq.). The aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were dried over

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Na₂SO₄, filtered and concentrated. The crude product was dissolved in THF (2 mL) and NaH (7 mg, 0.16 mmol) was added. The solution was heated to reflux for 2h. Water was added and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated.

- 5 The crude product was purified by preparative TLC chromatography (SiO₂: 1:1 hexanes:EtOAc) to afford 20 mg **Example 262**.

Preparation of Example 263

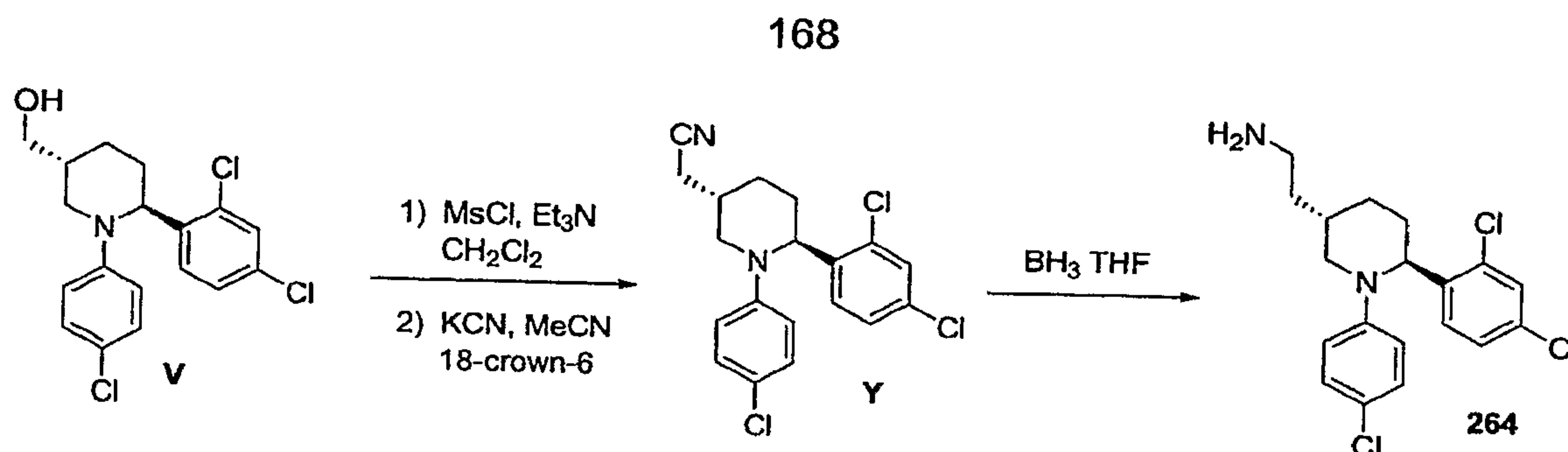


10

- To a solution of **Example 85** (54 mg, 0.15 mmol) in CH₂Cl₂ (2 mL) was added Et₃N (17 mg, 0.17 mmol) followed by 2-chloroethyl isocyanate (18 mg, 0.17 mmol). The solution was stirred at RT for 3 h. The solution was concentrated. The solution
- 15 was diluted with CH₂Cl₂ and washed with NaHCO₃ (aq.). The aqueous layer was extracted with CH₂Cl₂ (2x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was dissolved in THF (2 mL) and NaH (12 mg, 0.30 mmol) was added. The solution was stirred at RT for 48h. Water was added and the mixture was extracted with EtOAc (3x). The combined organic layers
- 20 were washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by preparative TLC chromatography (SiO₂: 1:2 hexanes:EtOAc) to afford 38 mg **Example 263**.

Preparation of Example 264

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**Step 1:**

To a solution of **V** (see **Example 85**) (2.0 g, 5.4 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (820 mg, 8.1 mmol) followed by methanesulfonyl chloride (680 mg, 5.9 mmol). The solution was stirred at RT overnight. Additional methanesulfonyl chloride (90 mg) was added and the solution was heated to reflux for 24 h. The solution was washed with NaHCO_3 (aq.) dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by flash chromatography (SiO_2 : gradient elution 1:0 to 3:1 hexanes:EtOAc) to afford 2.36 g mesylate.

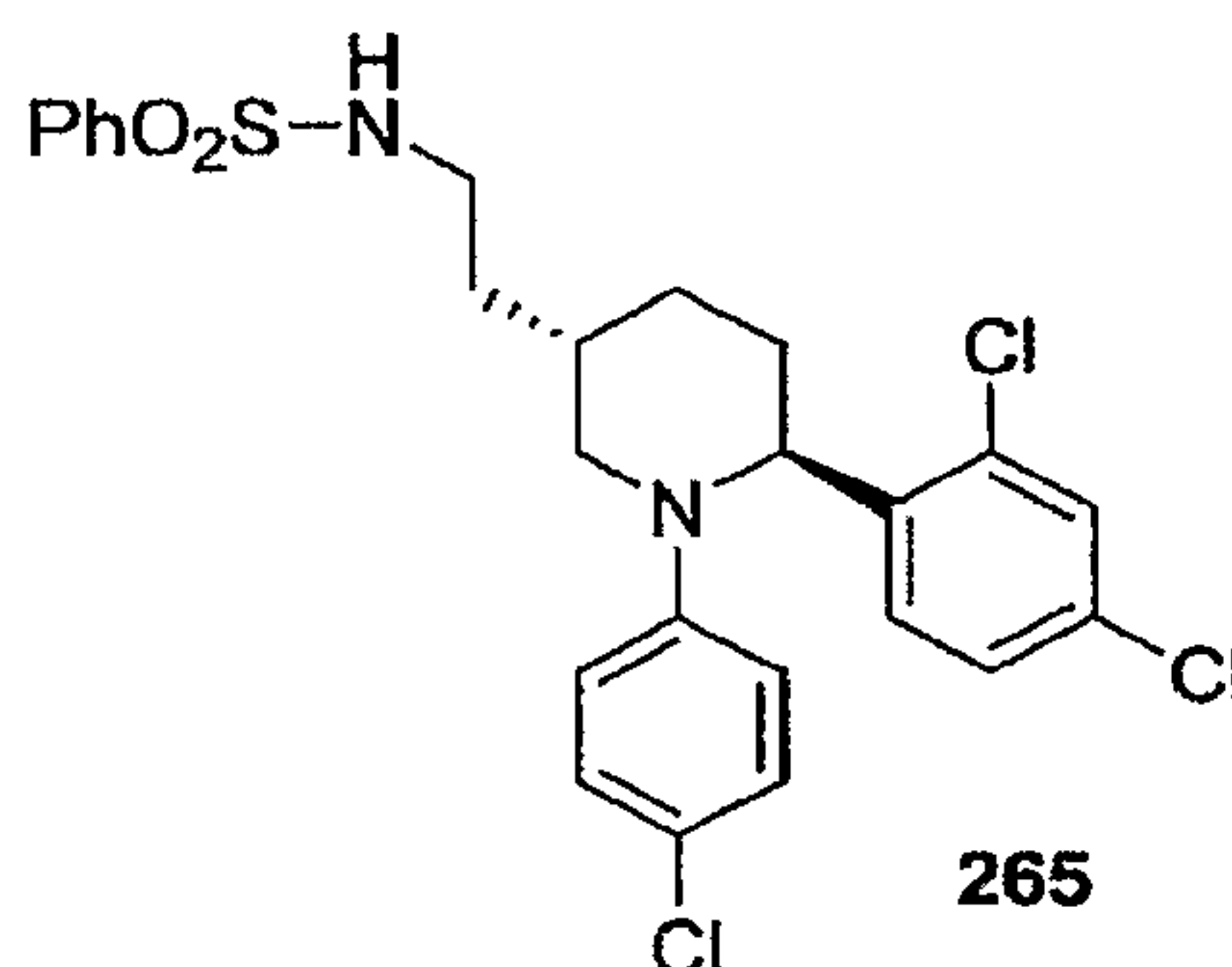
Step 2:

To a portion of the mesylate (1.76 g, 3.9 mmol) in MeCN (10 mL) was added potassium cyanide (970 mg, 14.9 mmol) and 18-crown-6 (120 mg). The solution was heated to reflux for 30 h. To the solution was added 1 N NaOH (aq.) and the mixture was extracted with CH_2Cl_2 . The organic layer was washed with H_2O (2x). The organic layer was dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by flash chromatography (SiO_2 : gradient elution 1:0 to 3:1 hexanes:EtOAc) to afford 1.36 g **Y**.

Step 3:

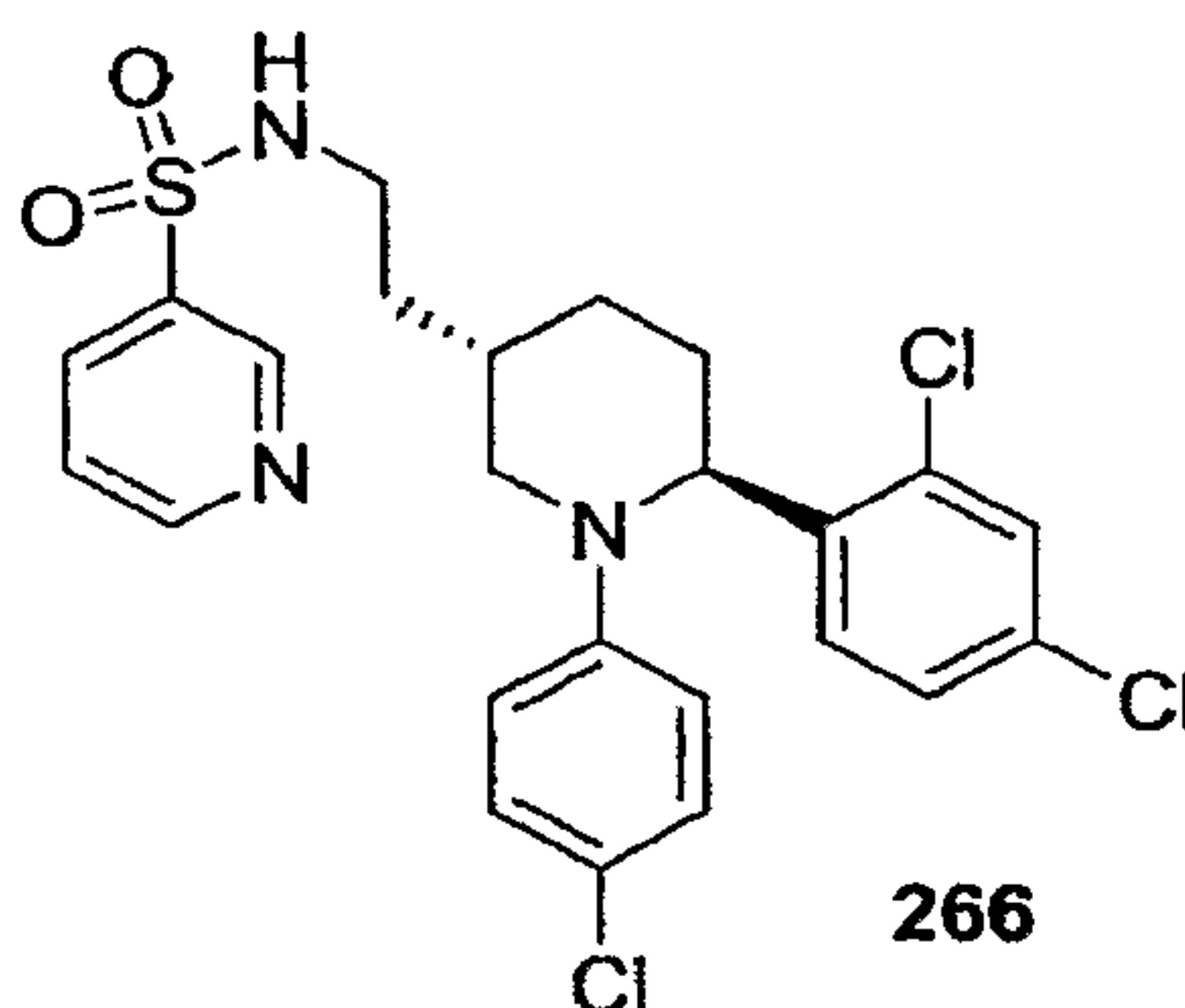
To a solution of **Y** (350 mg, 0.92 mmol) in THF (25 mL) was added borane-THF complex (1M in THF) (2.77 mL, 2.77 mmol). The solution was heated to reflux for 2 h. The solution was cooled to RT and 1 M HCl (aq.) (3 mL) was added slowly. The mixture was stirred at RT for 30 min. The mixture was washed with H_2O . To the organic layer was added NaHCO_3 (aq.) and the mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by flash chromatography (SiO_2 : gradient elution 1:0:0 to 95:7:0.5 CH_2Cl_2 : MeOH: ammonium hydroxide)) to afford 243 mg **Example 264**.

169

Preparation of Example 265**265**

5 To a solution of **Example 264** (40 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (10 drops) followed by benzenesulfonyl chloride (28 mg, 0.16 mmol). The solution was stirred at RT for 48 h. The solution was concentrated. The crude product was purified by preparative TLC chromatography (SiO_2 : 3:1hexanes:EtOAc) to afford 60 mg **Example 265**.

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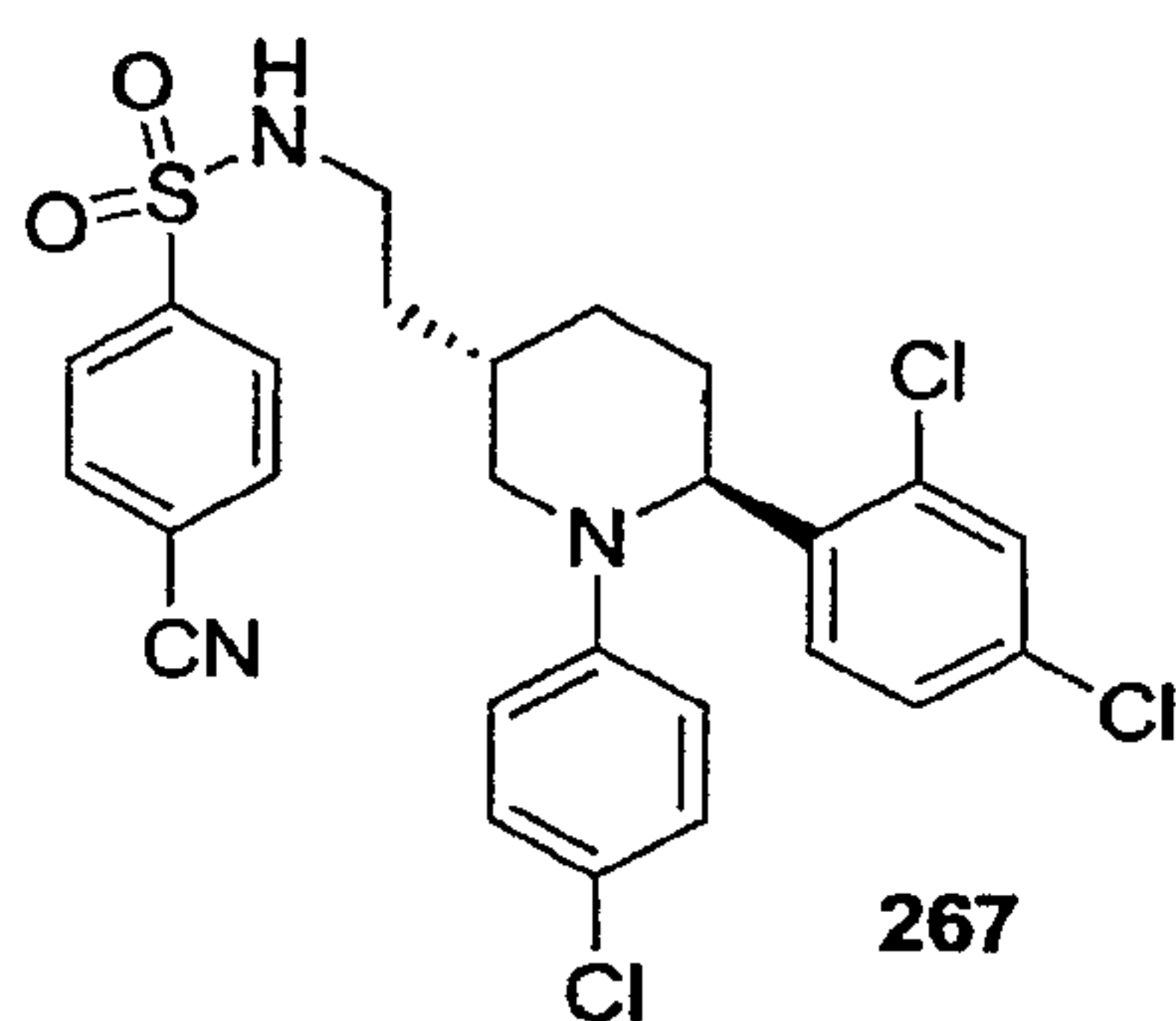
Preparation of Example 266**266**

15 **Example 266** was prepared using a procedure similar to that described above for **Example 265**, except 3-pyridylsulfonyl chloride was used instead of benzene sulfonyl chloride.

Preparation of Example 267

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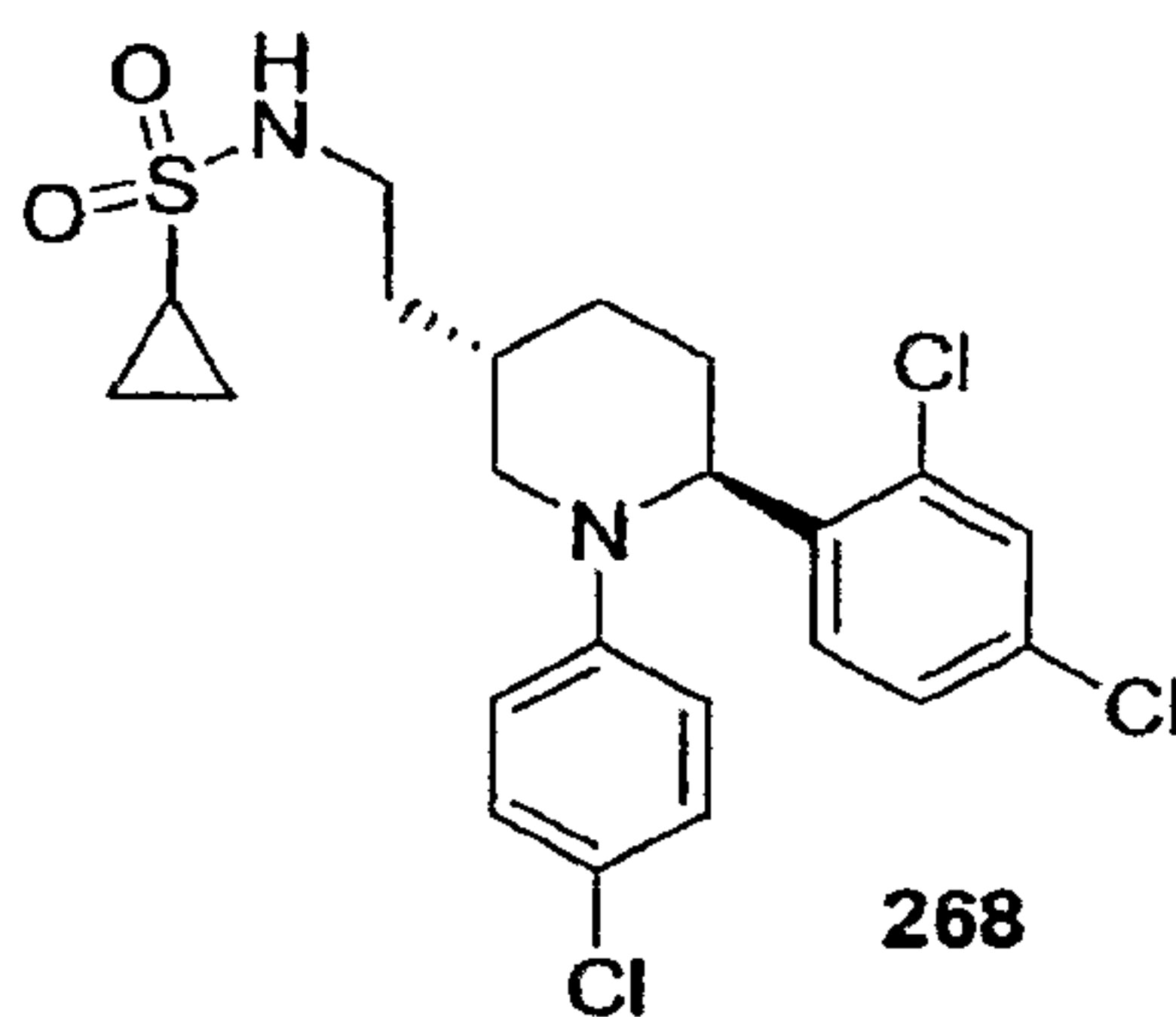
170



Example 267 was prepared using a procedure similar to that described above for **Example 265**, except 4-cyanobenzene sulfonyl chloride was used instead of benzene sulfonyl chloride.

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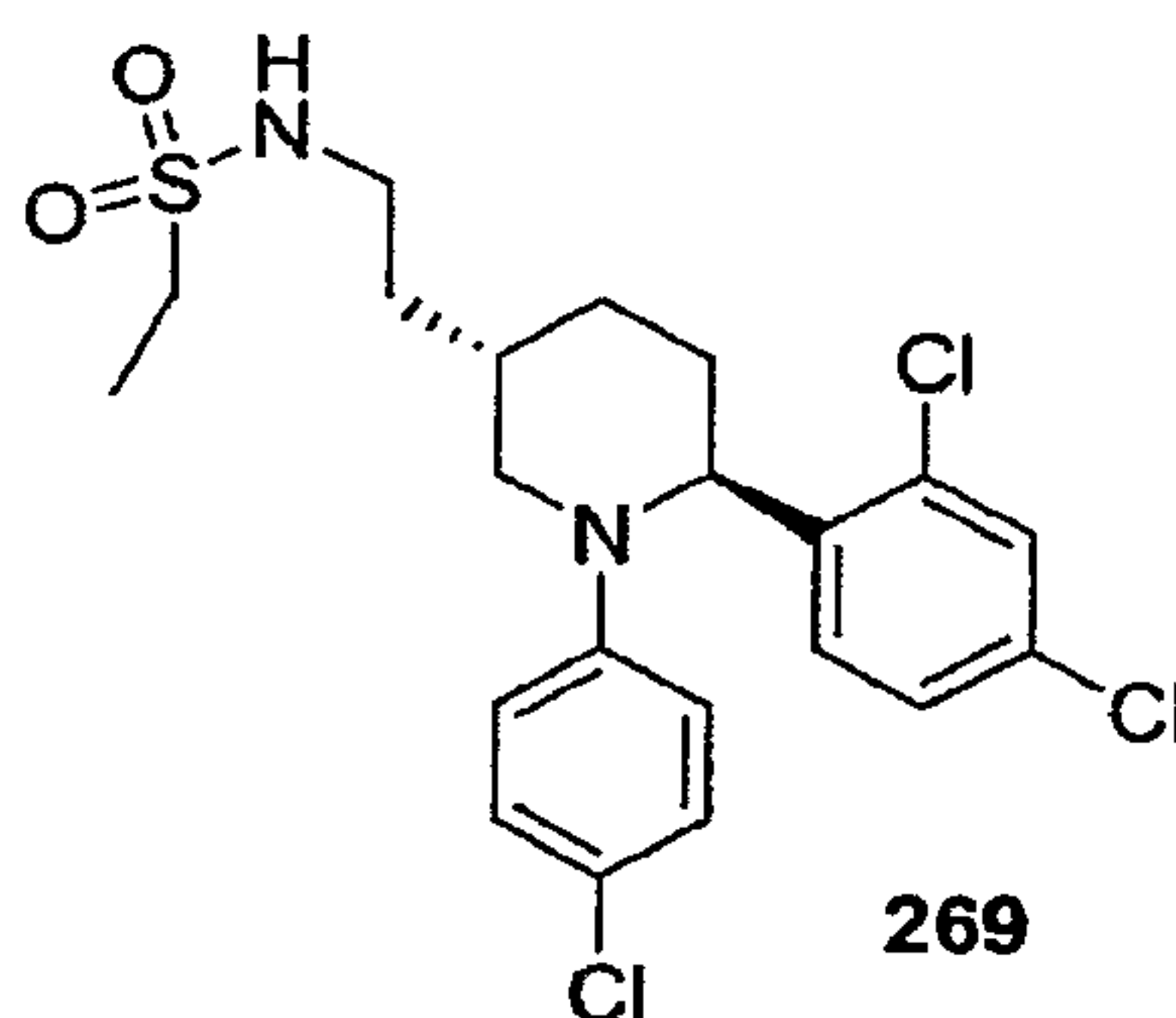
Preparation of Example 268



Example 268 was prepared using a procedure similar to that described above for **Example 265**, except cyclopropane sulfonyl chloride was used instead of benzene sulfonyl chloride.

10

Preparation of Example 269



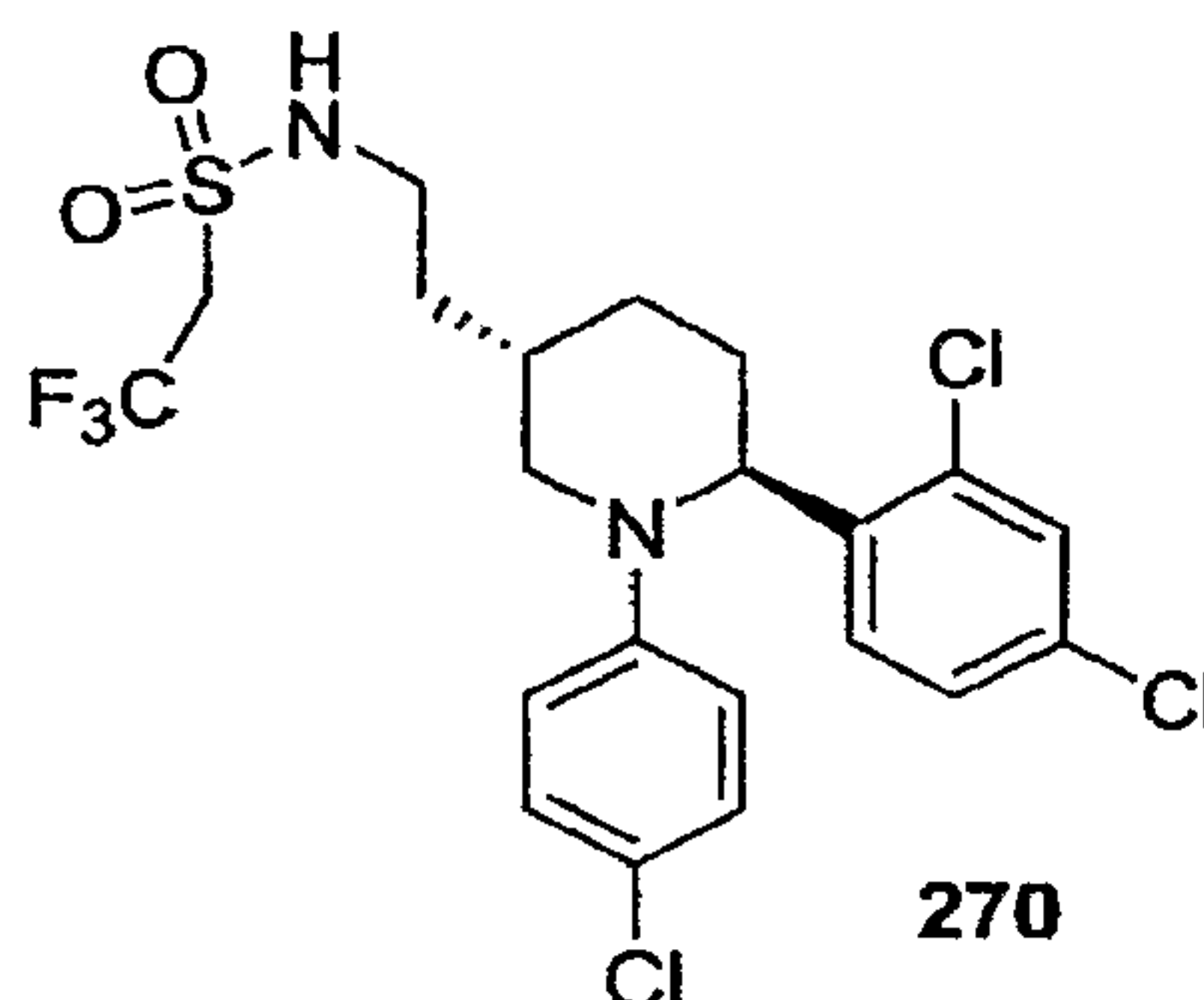
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171

Example 269 was prepared using a procedure similar to that described above for **Example 265**, except ethane sulfonyl chloride was used instead of benzene sulfonyl chloride.

Preparation of Example 270

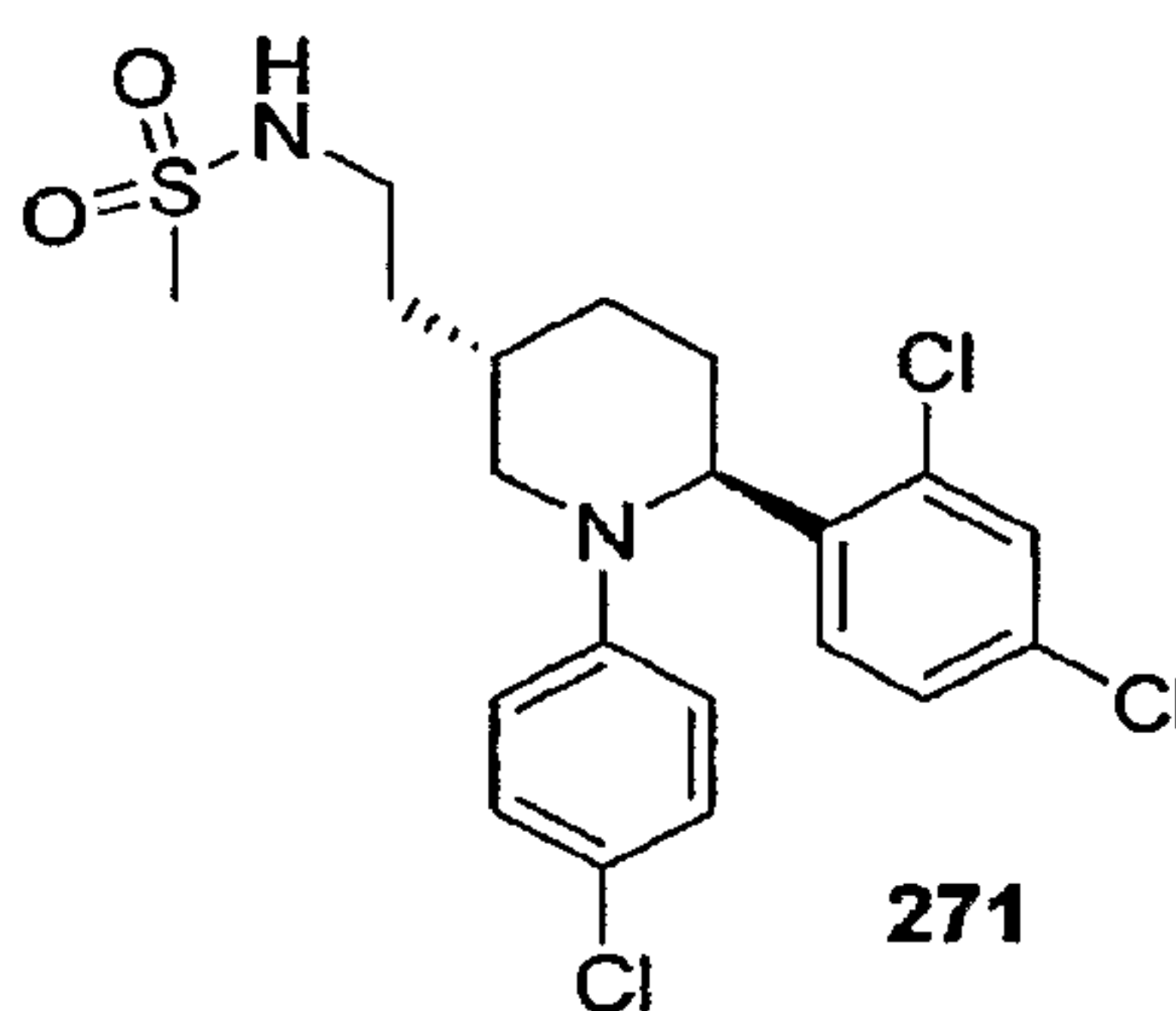
5



Example 270 was prepared using a procedure similar to that described above for **Example 265**, except 2,2,2-trifluoroethane sulfonyl chloride was used instead of benzene sulfonyl chloride.

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Preparation of Example 271

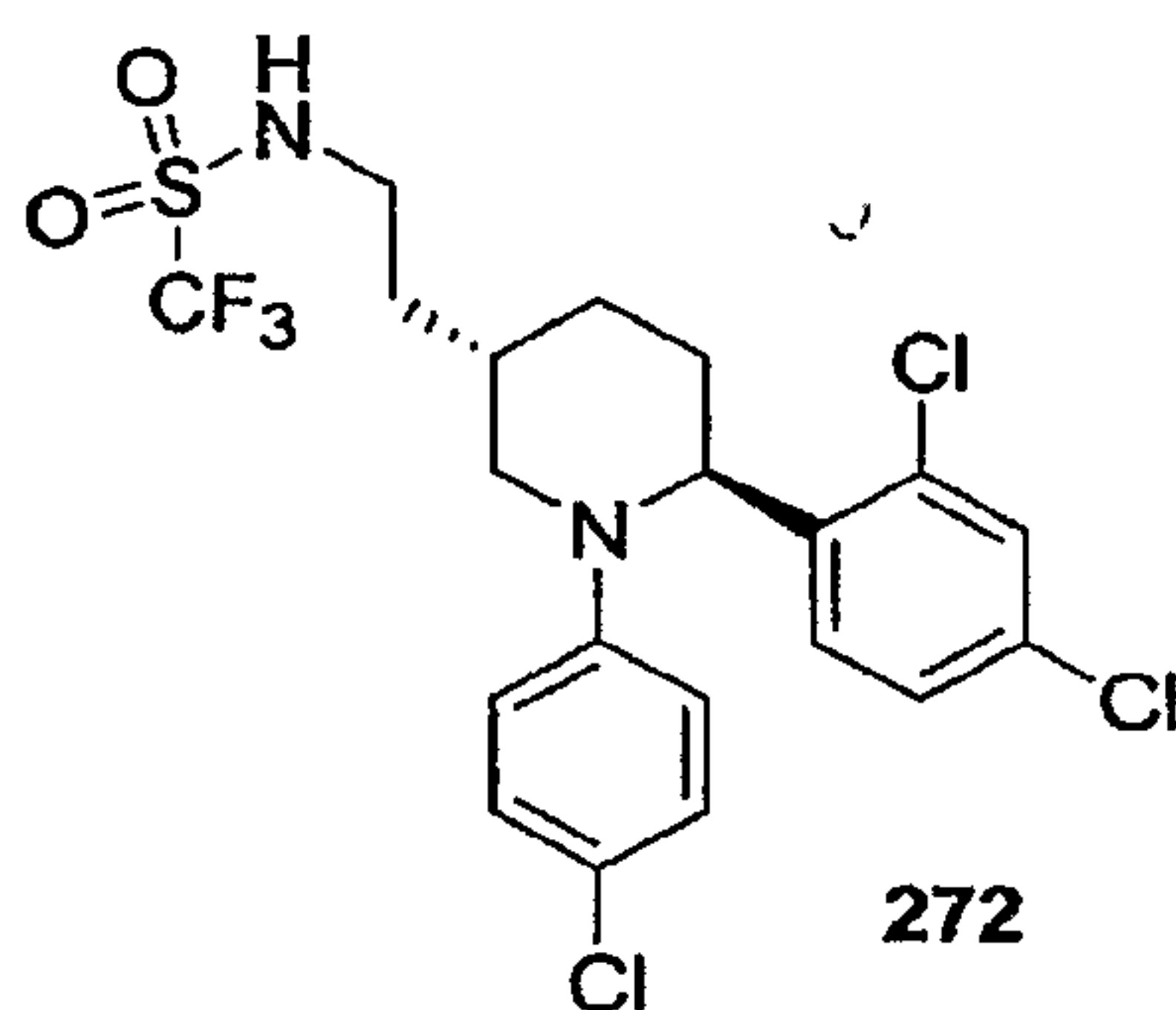


Example 271 was prepared using a procedure similar to that described above for **Example 265**, except methanesulfonyl chloride was used instead of benzene sulfonyl chloride.

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Preparation of Example 272

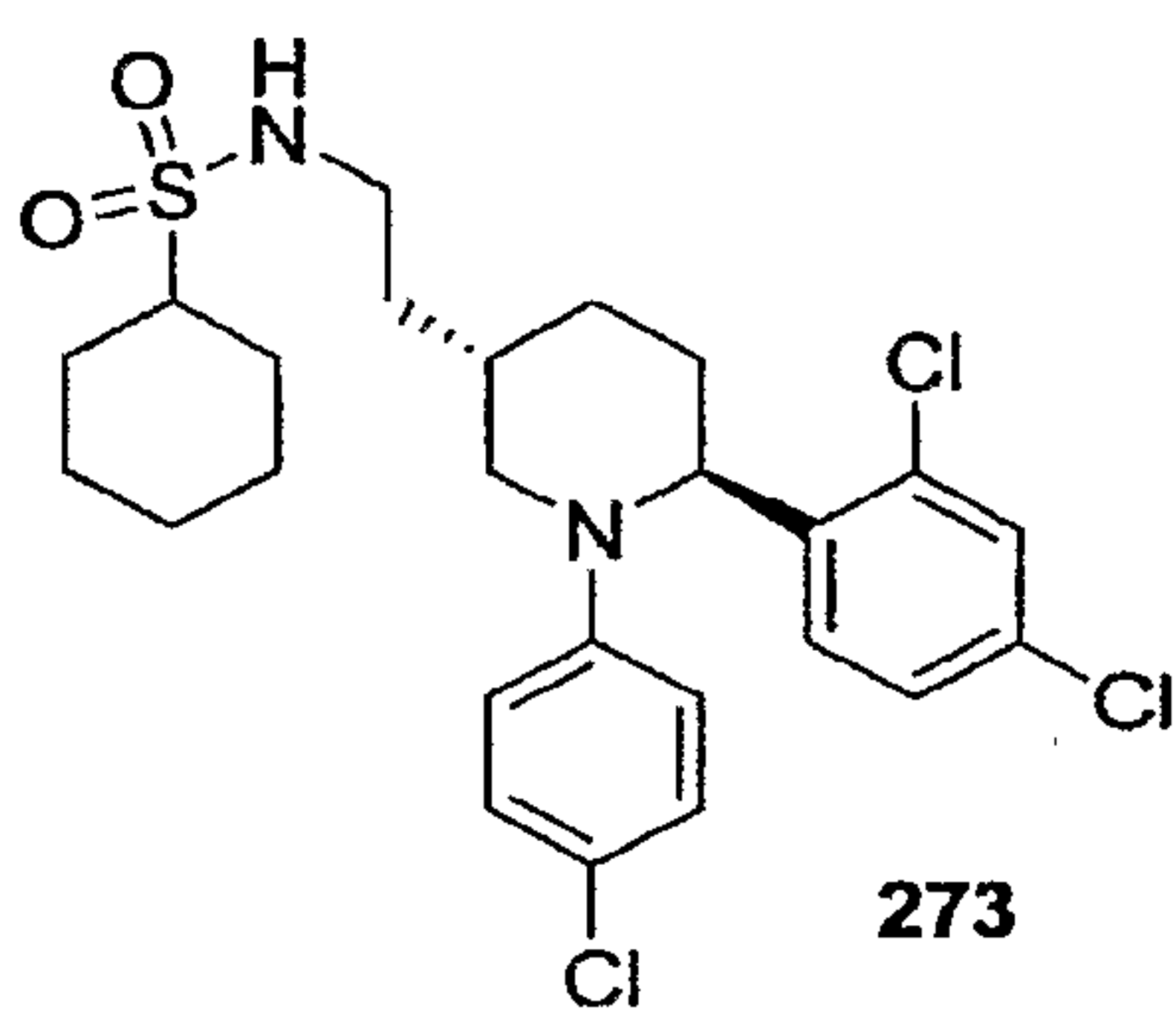
172



Example 272 was prepared using a procedure similar to that described above for **Example 265**, except trifluoromethanesulfonyl anhydride was used instead of benzene sulfonyl chloride.

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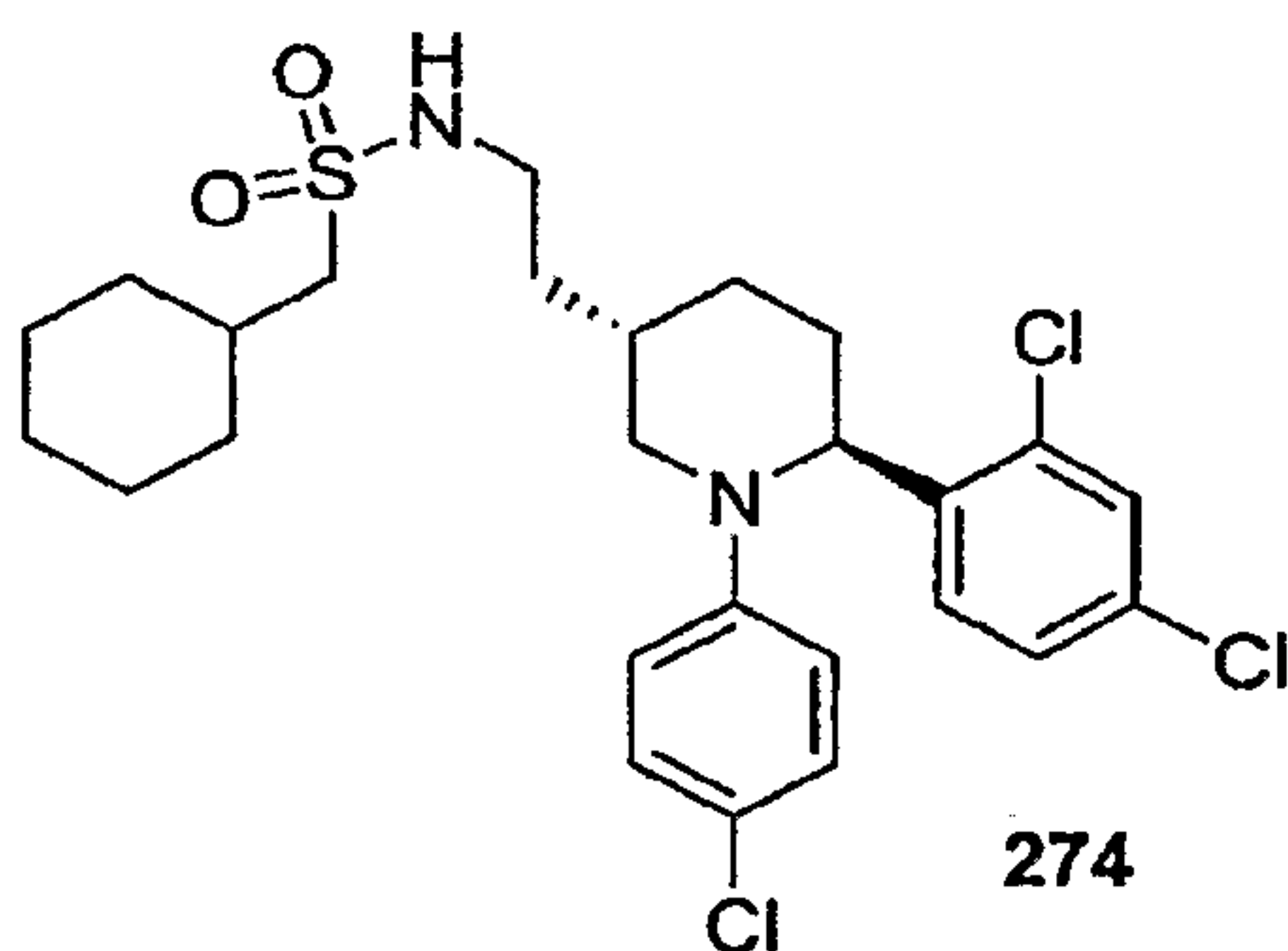
Preparation of Example 273



Example 273 was prepared using a procedure similar to that described above for **Example 265**, except cyclohexanesulfonyl chloride was used instead of benzene sulfonyl chloride.

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Preparation of Example 274



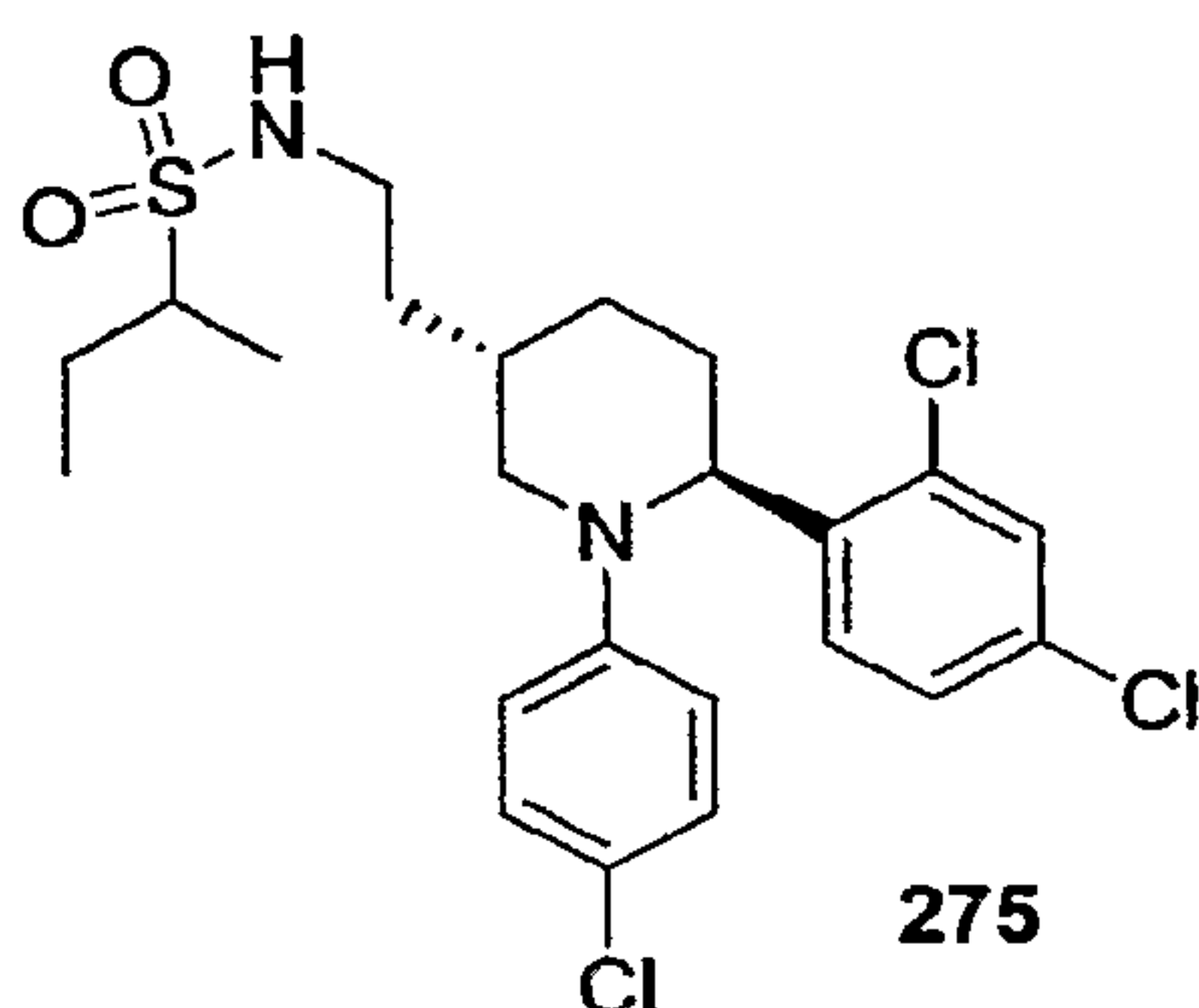
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173

Example 274 was prepared using a procedure similar to that described above for **Example 265**, except cyclohexylmethanesulfonyl chloride was used instead of benzene sulfonyl chloride.

Preparation of Example 275

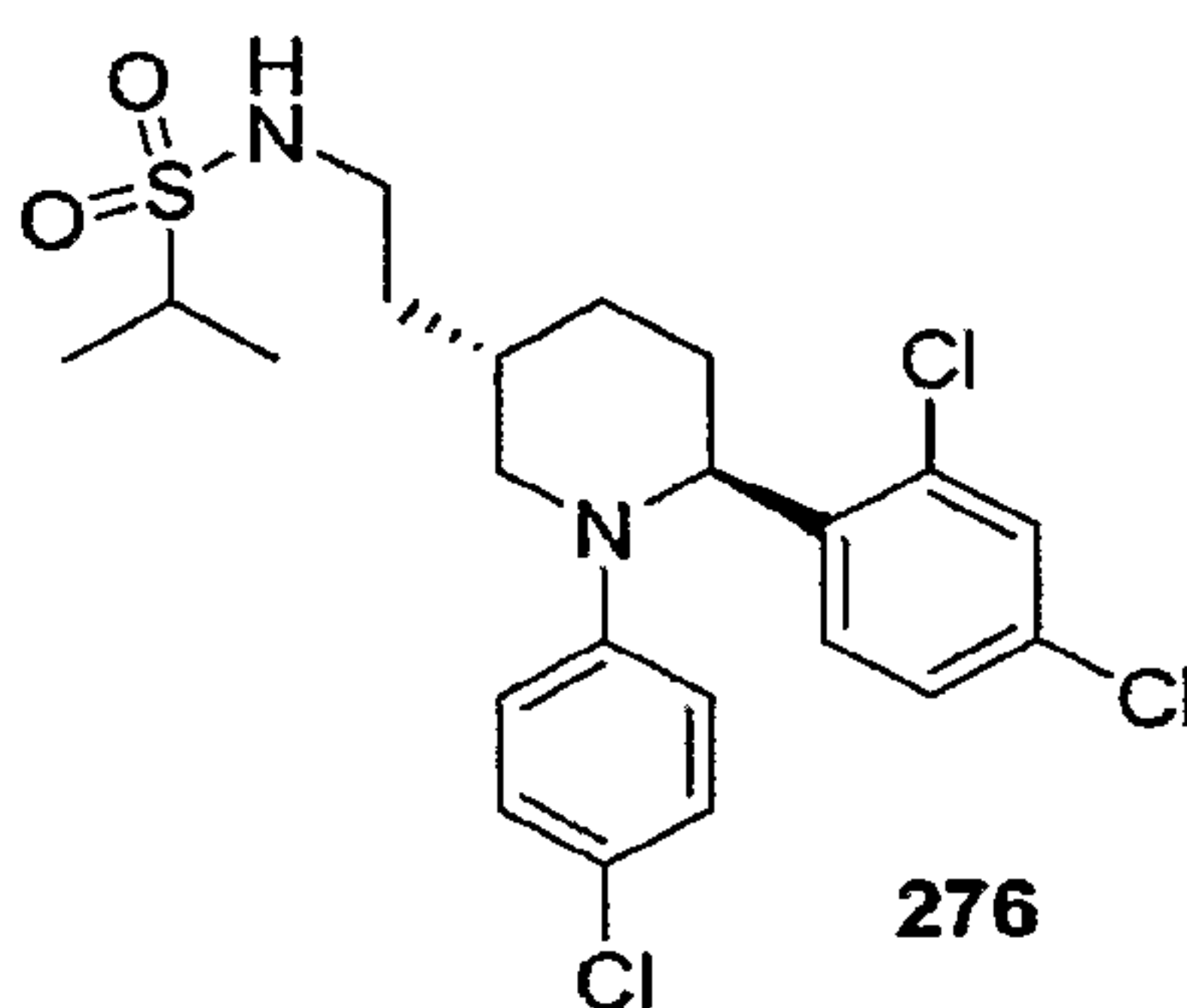
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Example 275 was prepared using a procedure similar to that described above for **Example 265**, except butane-2-sulfonyl chloride was used instead of benzene sulfonyl chloride.

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Preparation of Example 276



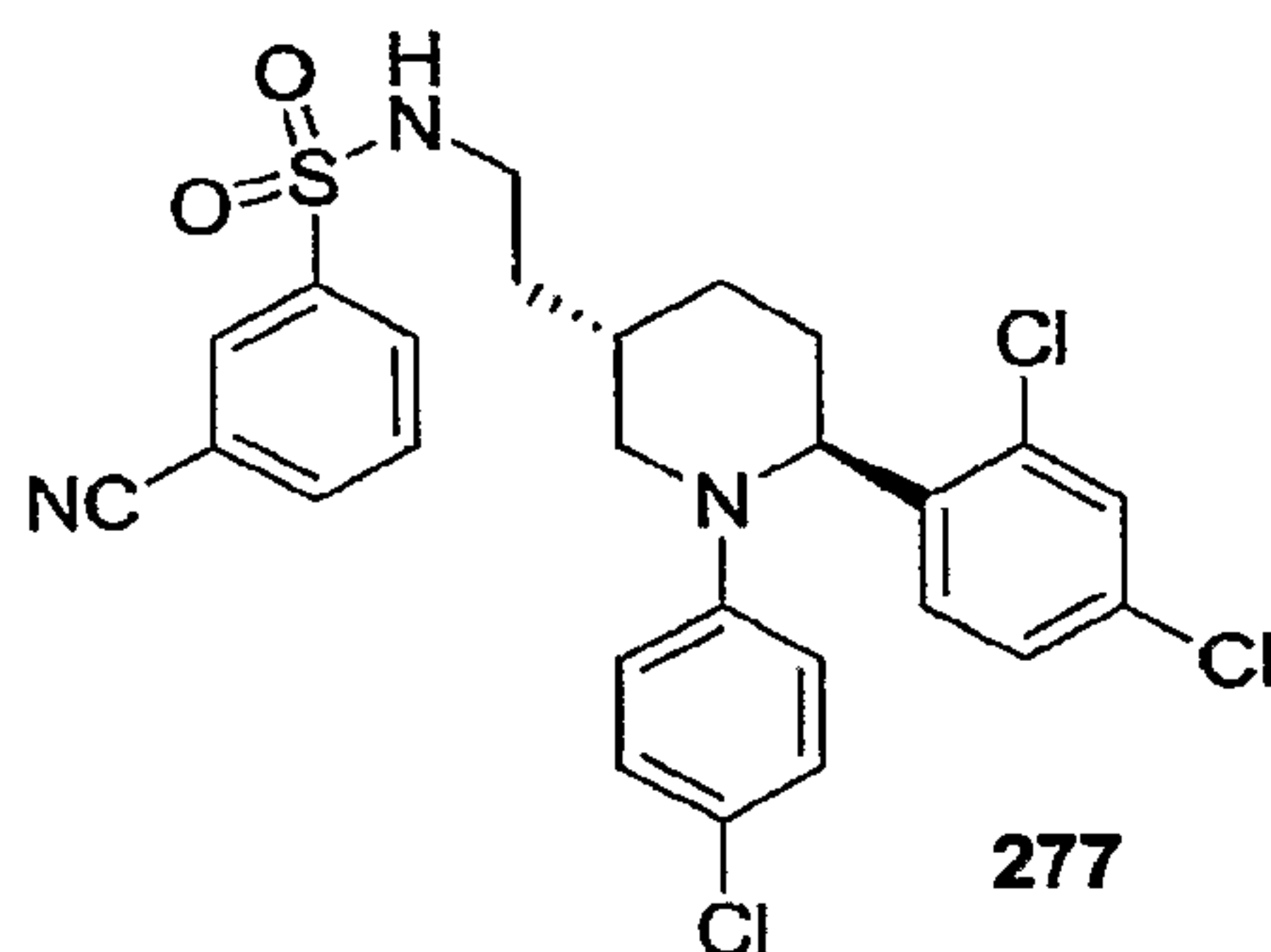
Example 276 was prepared using a procedure similar to that described above for **Example 265**, except 2-propylsulfonyl chloride was used instead of benzene sulfonyl chloride.

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Preparation of Example 277

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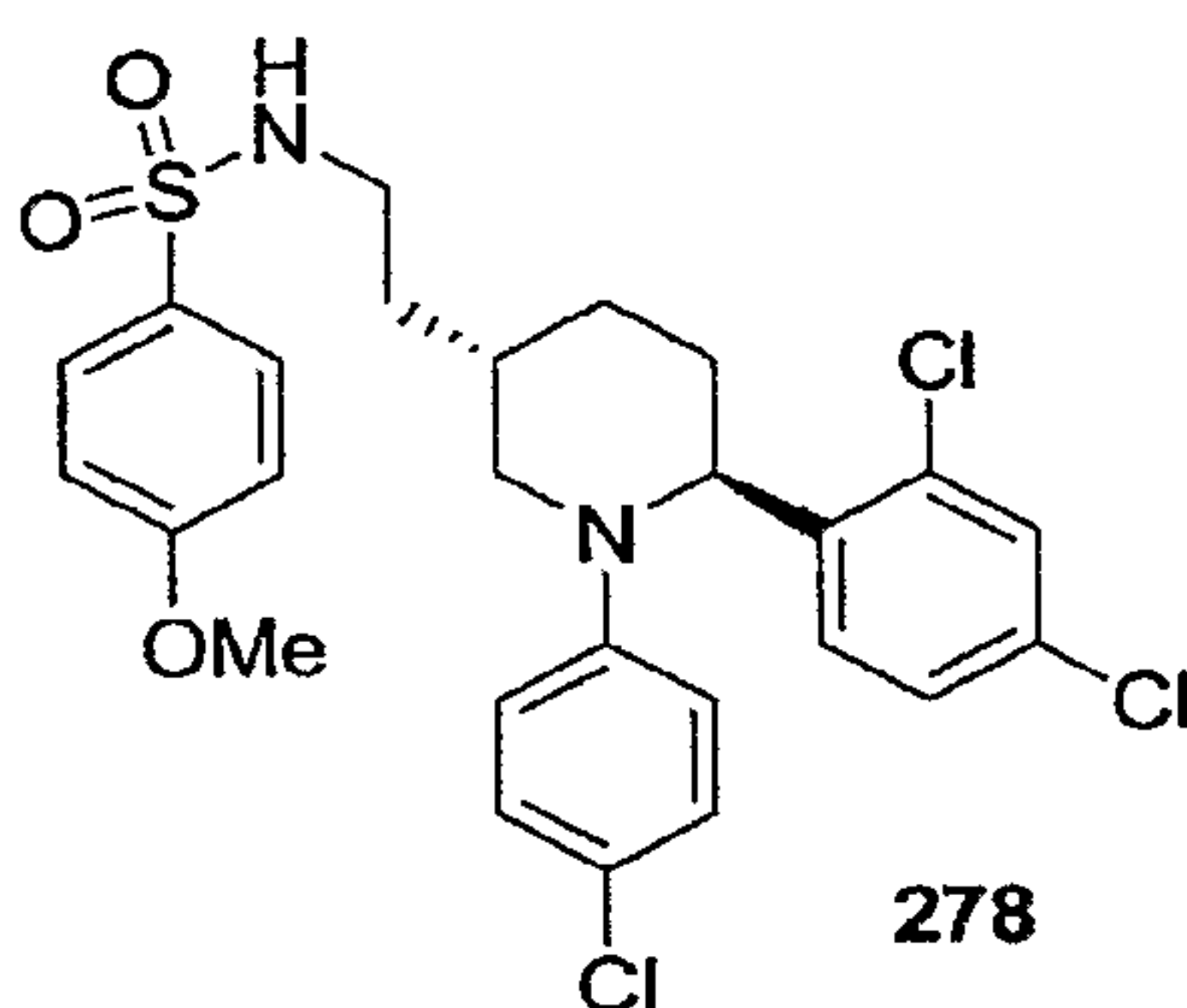
174



Example 277 was prepared using a procedure similar to that described above for **Example 265**, except 3-cyanobenzene sulfonyl chloride was used instead of benzene sulfonyl chloride.

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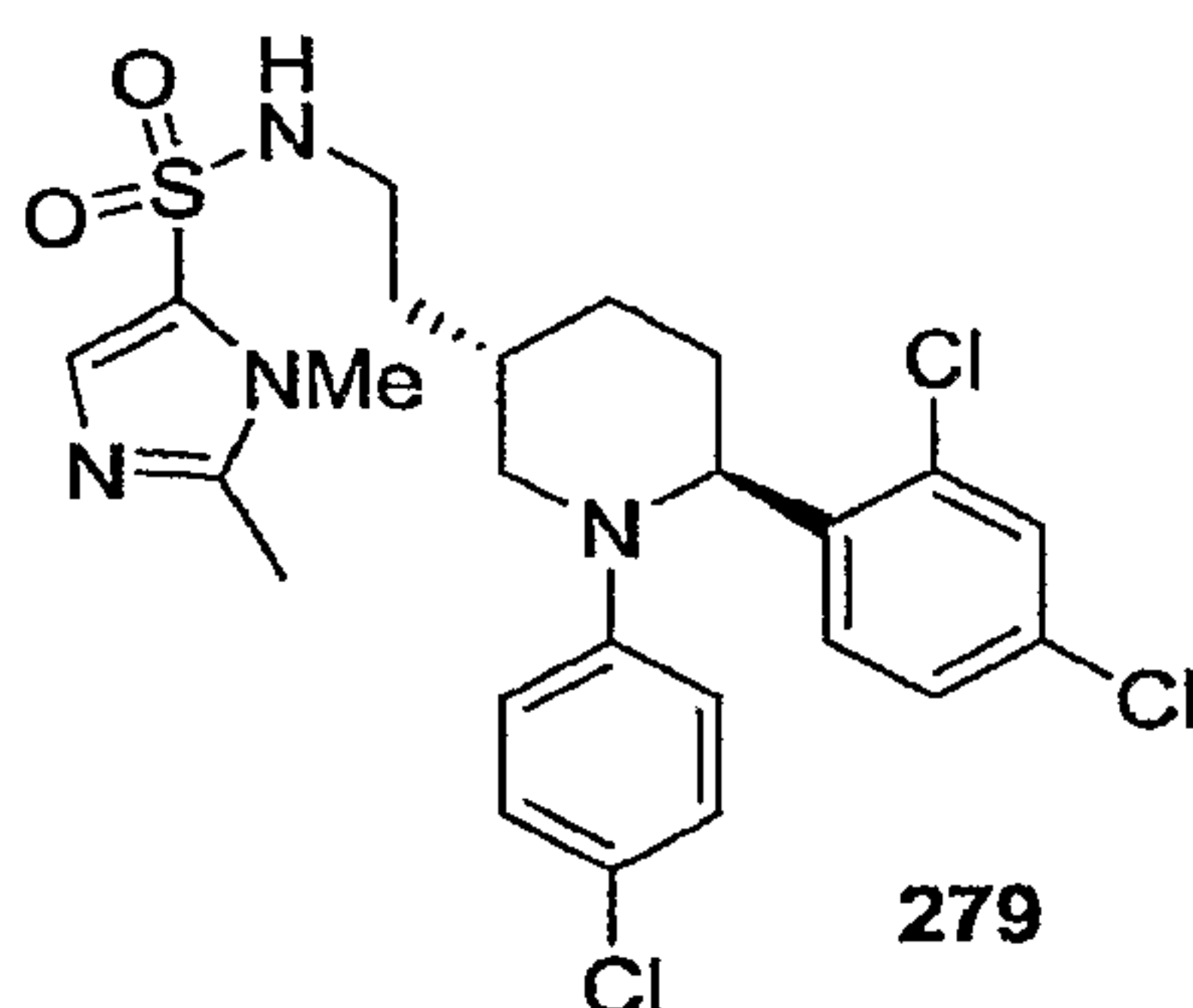
Preparation of Example 278



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Example 278 was prepared using a procedure similar to that described above for **Example 265**, except 4-methoxybenzene sulfonyl chloride was used instead of benzene sulfonyl chloride.

Preparation of Example 279



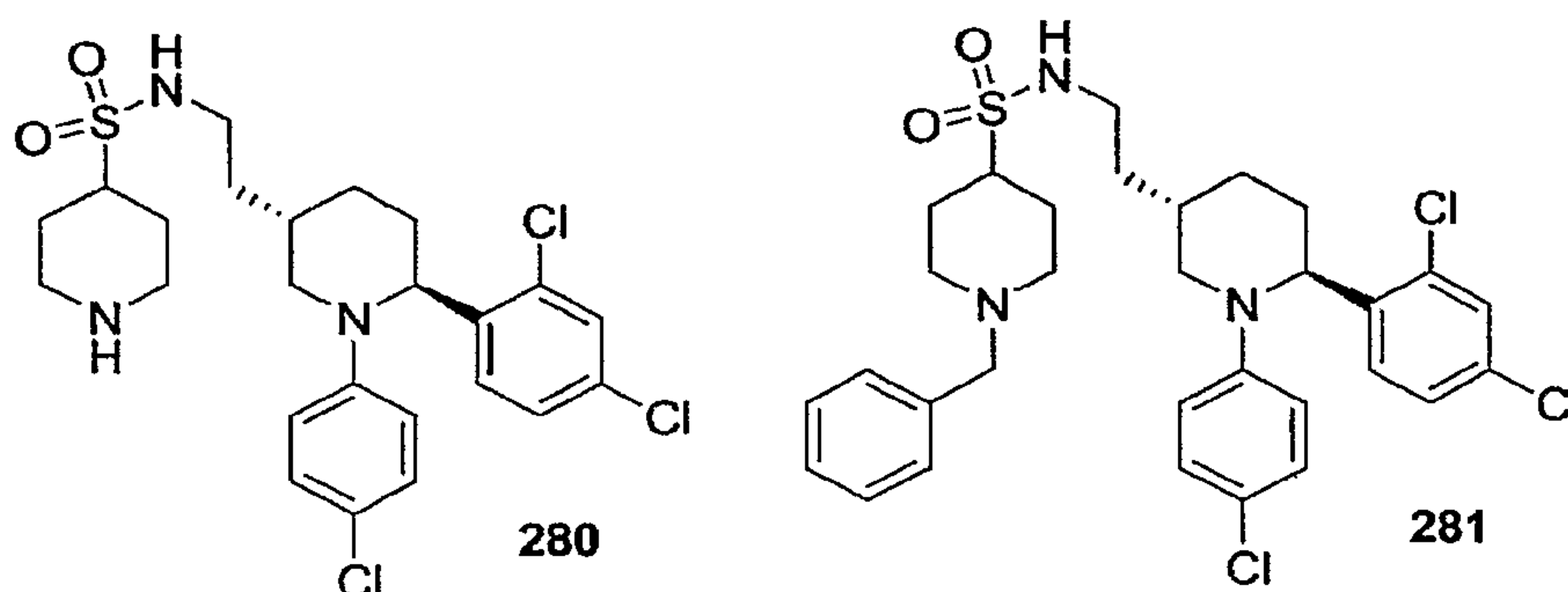
15

175

Example 279 was prepared using a procedure similar to that described above for **Example 265**, except 2,3-dimethyl-3H-imidazole-4-sulfonyl chloride was used instead of benzene sulfonyl chloride.

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Preparation of Examples 280 and 281

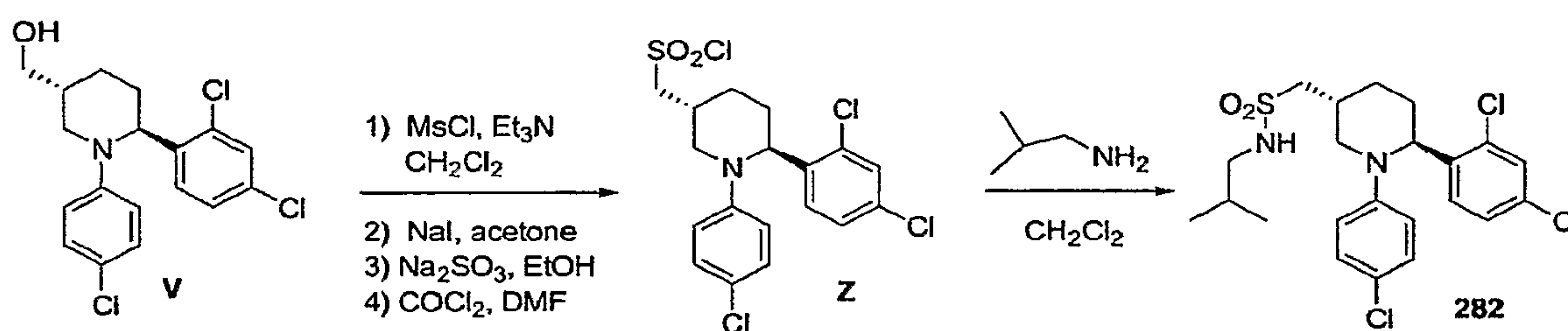


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Examples 280 and **281** were prepared using procedures similar to those used above for **Examples 255-257**, except **Example 254** was used instead of **Example 85**.

Preparation of Example 282

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Step 1:

20

To a solution of **V** (2.0 g, 5.4 mmol) in CH₂Cl₂ (20 mL) was added Et₃N (820 mg, 8.1 mmol) followed by methanesulfonyl chloride (680 mg, 5.9 mmol). The solution was stirred at RT overnight. Additional methanesulfonyl chloride (90 mg) was added and the solution was heated to reflux for 24 h. The solution was washed with NaHCO₃ (aq.) dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash chromatography (SiO₂: gradient elution 1:0 to 3:1 hexanes:EtOAc) to afford 2.36 g mesylate.

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Step 2:

To a solution of the mesylate from Step 1 (200 mg, 0.45 mmol) in acetone (5 mL) was added sodium iodide (80 mg, 0.53 mmol). The mixture was heated to reflux overnight. To the mixture was added H₂O. The aqueous layer was
5 extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by preparative TLC (SiO₂: 98:2 hexanes:EtOAc) to afford 175 mg iodide.

Step 3:

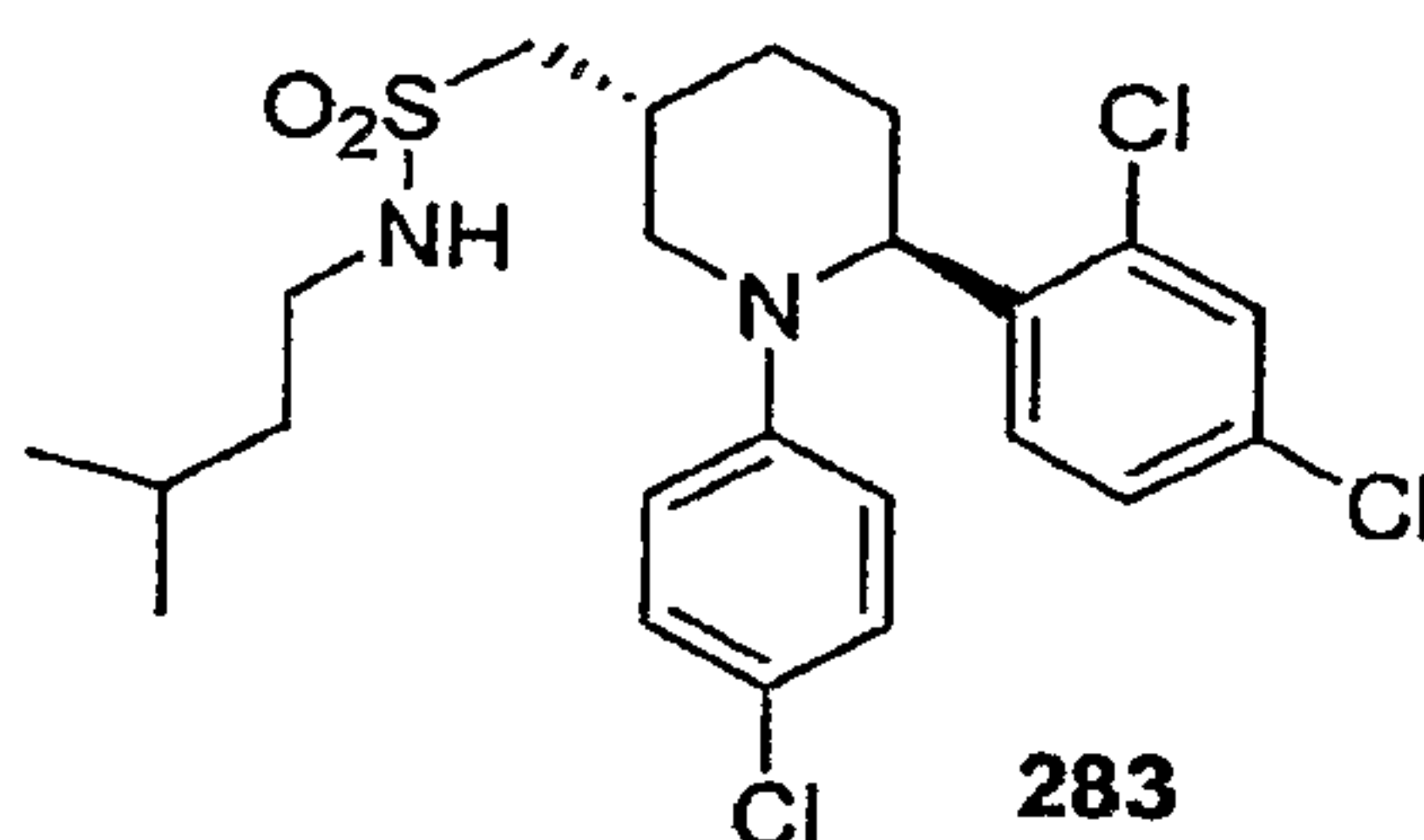
To a mixture of the iodide from step 2 (256 mg, 0.54 mmol) in EtOH/H₂O (1:1
10 4 mL) in a pressure tube was added sodium sulfite (100 mg, 0.79 mmol). The tube was sealed and heated to 100°C for 4 days. The mixture was concentrated and the crude product was treated with toluene and re-evaporated twice to afford the crude product (ca. 256 mg) that was used without any further purification.

Step 4:

To a mixture of the product from step 3 (256 mg, 0.54 mmol) in CH₂Cl₂ (2 mL)
15 was added a solution of phosgene (1.9 M in toluene) (0.56 mL) followed by DMF (0.05 mL). The mixture was stirred at RT for 1 h. The mixture was concentrated and used without purification.

Step 5:

To the crude product from step 4 (0.27 mmol) in a vial was added excess
20 isobutyl amine. The solution was stirred at RT overnight. Water was added and the mixture was extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by preparative TLC (77:23 hexanes:EtOAc) to afford **Example 282** (46 mg).

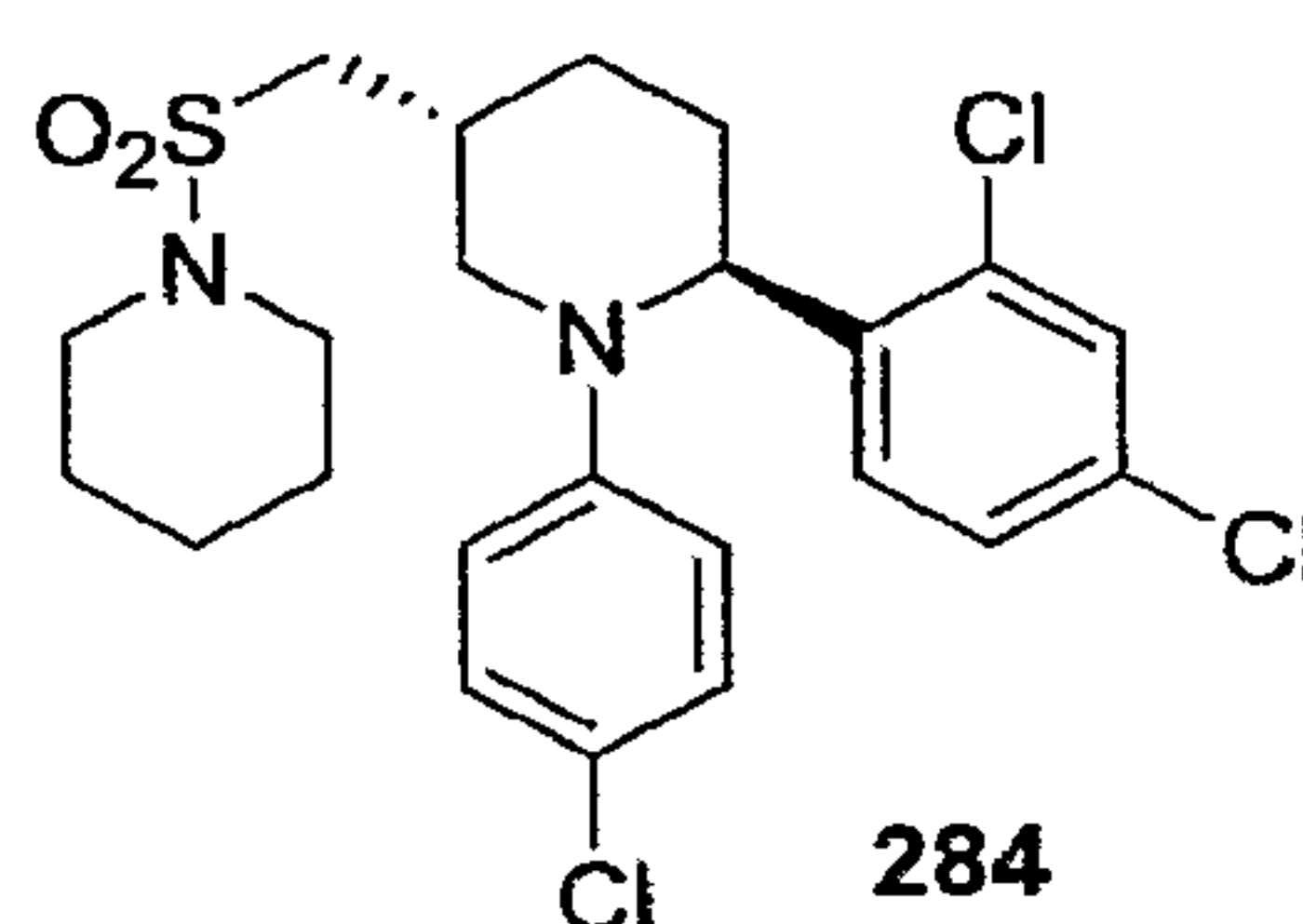
Preparation of Example 283

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Example 283 was prepared using a procedure similar to that described above for **Example 282** step 5, except 3-methyl butyl amine was used instead of isobutylamine.

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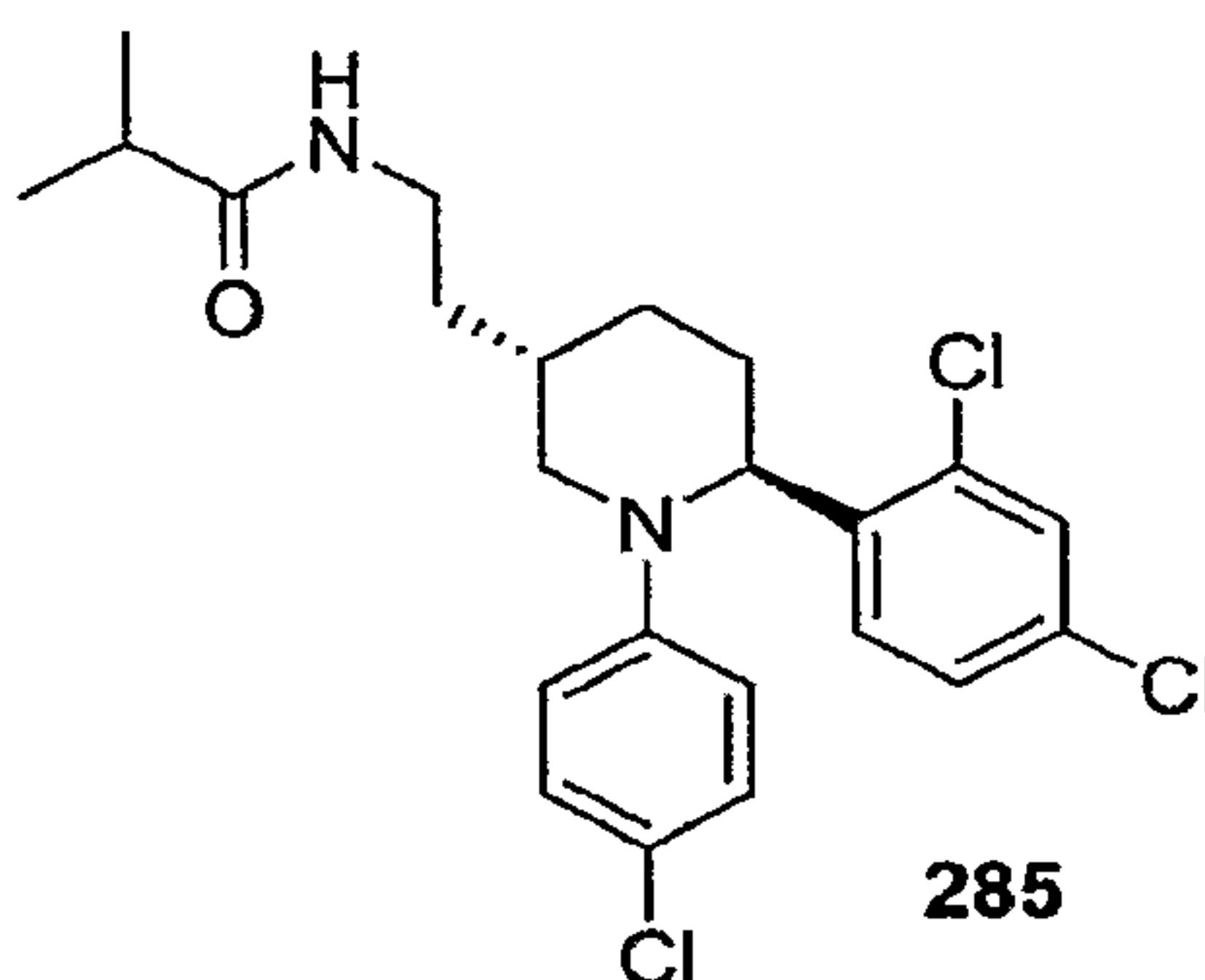
Preparation of Example 284



Example 284 was prepared using a procedure similar to that described above for **Example 282** step 5, except piperidine was used instead of isobutylamine.

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Preparation of Example 285

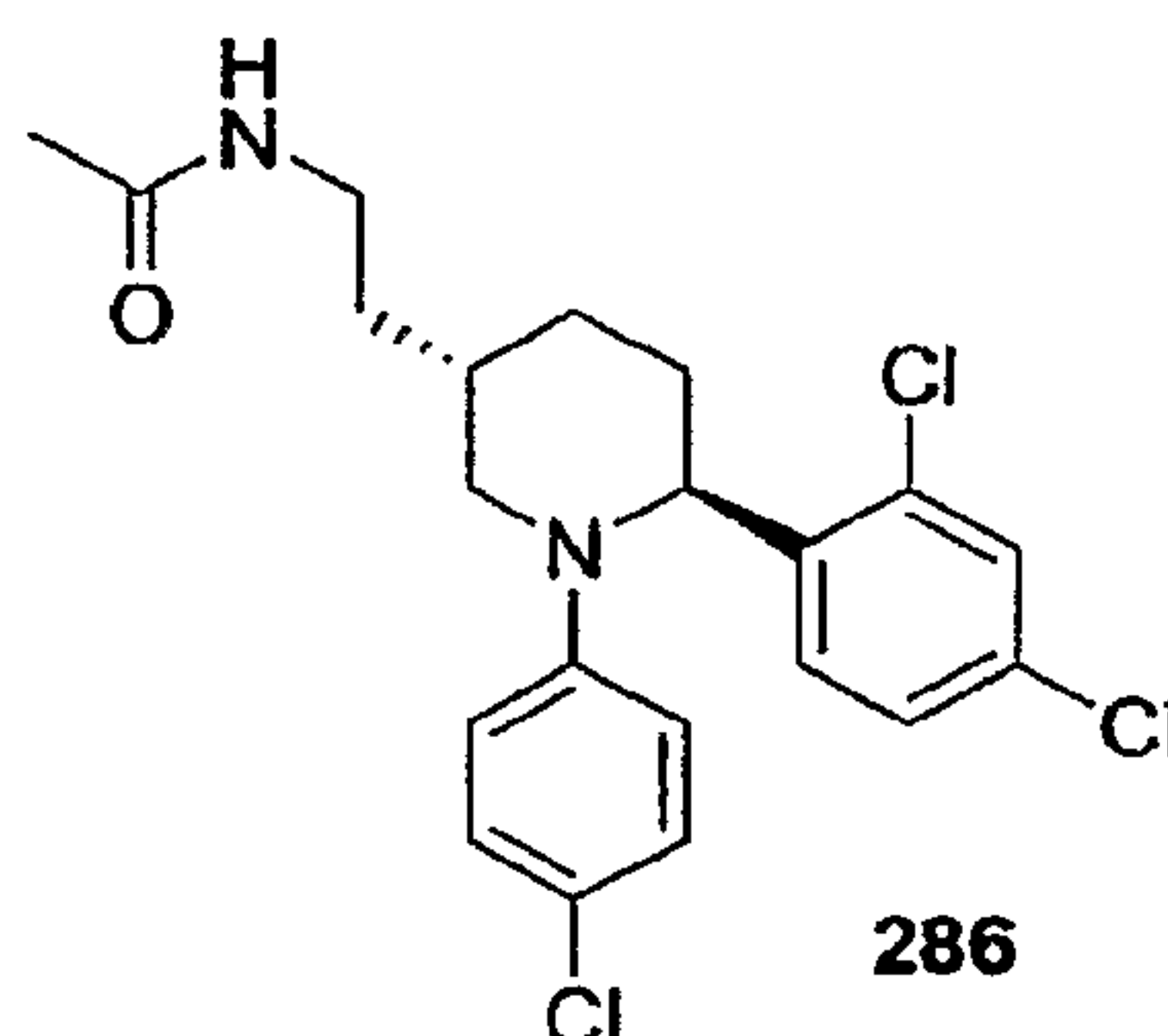


To a solution of **Example 264** (40 mg, 0.10 mmol) in MeCN (1.5 mL) was added EDCI (29 mg, 0.15 mmol), HOBt (20 mg, 0.15 mmol), iPr₂NEt (122 mg, 0.96 mmol) and isopropyl carboxylic acid (18 mg, 0.20 mmol). The mixture was stirred at RT overnight. The mixture was concentrated, partitioned between 1 N NaOH (aq.) and EtOAc. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by preparative TLC (7:3 hexanes:EtOAc) to afford **Example 285** which was converted to the HCl salt (59 mg) via the addition of 2 N HCl in Et₂O to a solution of the free base in CH₂Cl₂ followed by removal of the solvent.

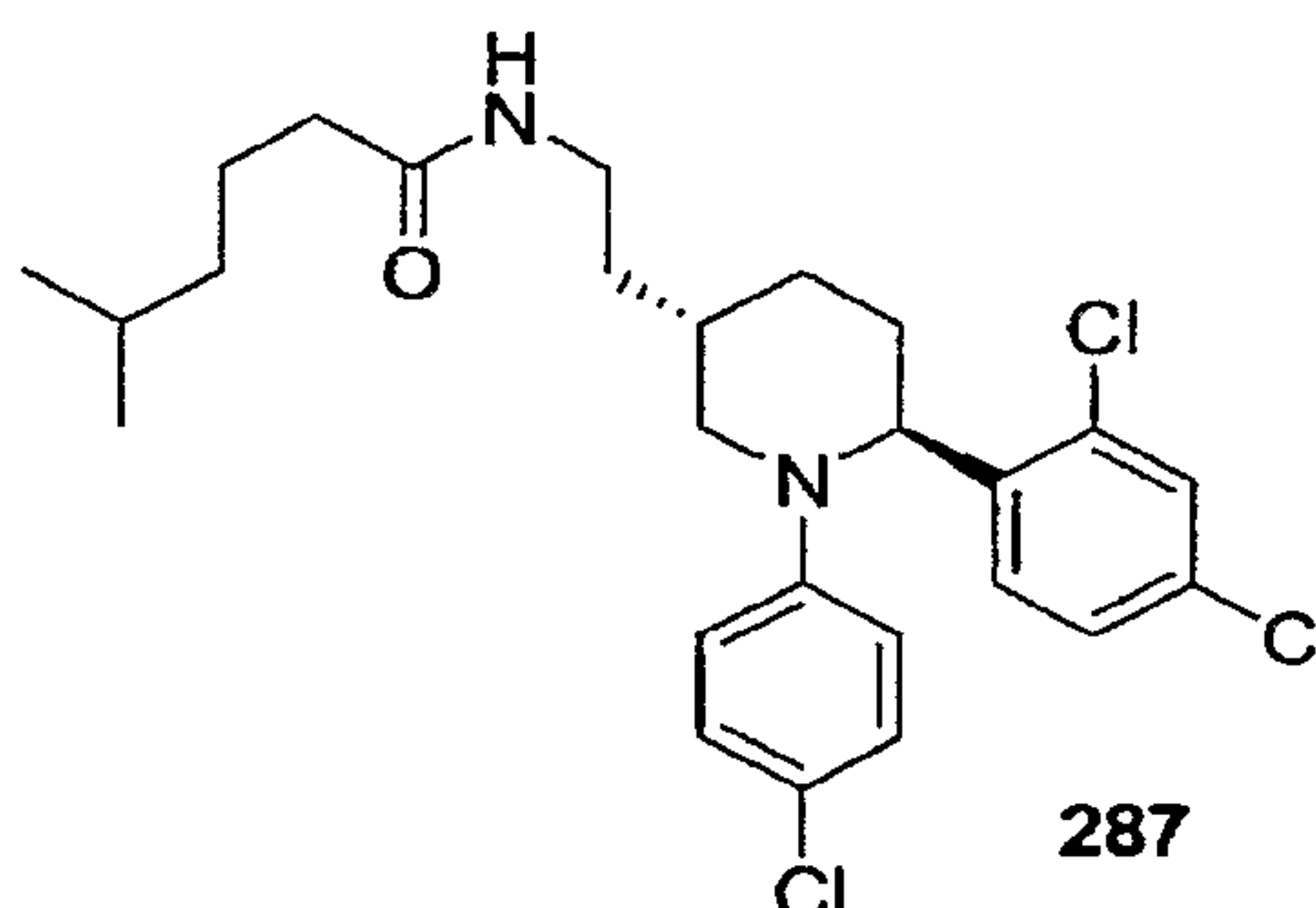
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Preparation of Example 286

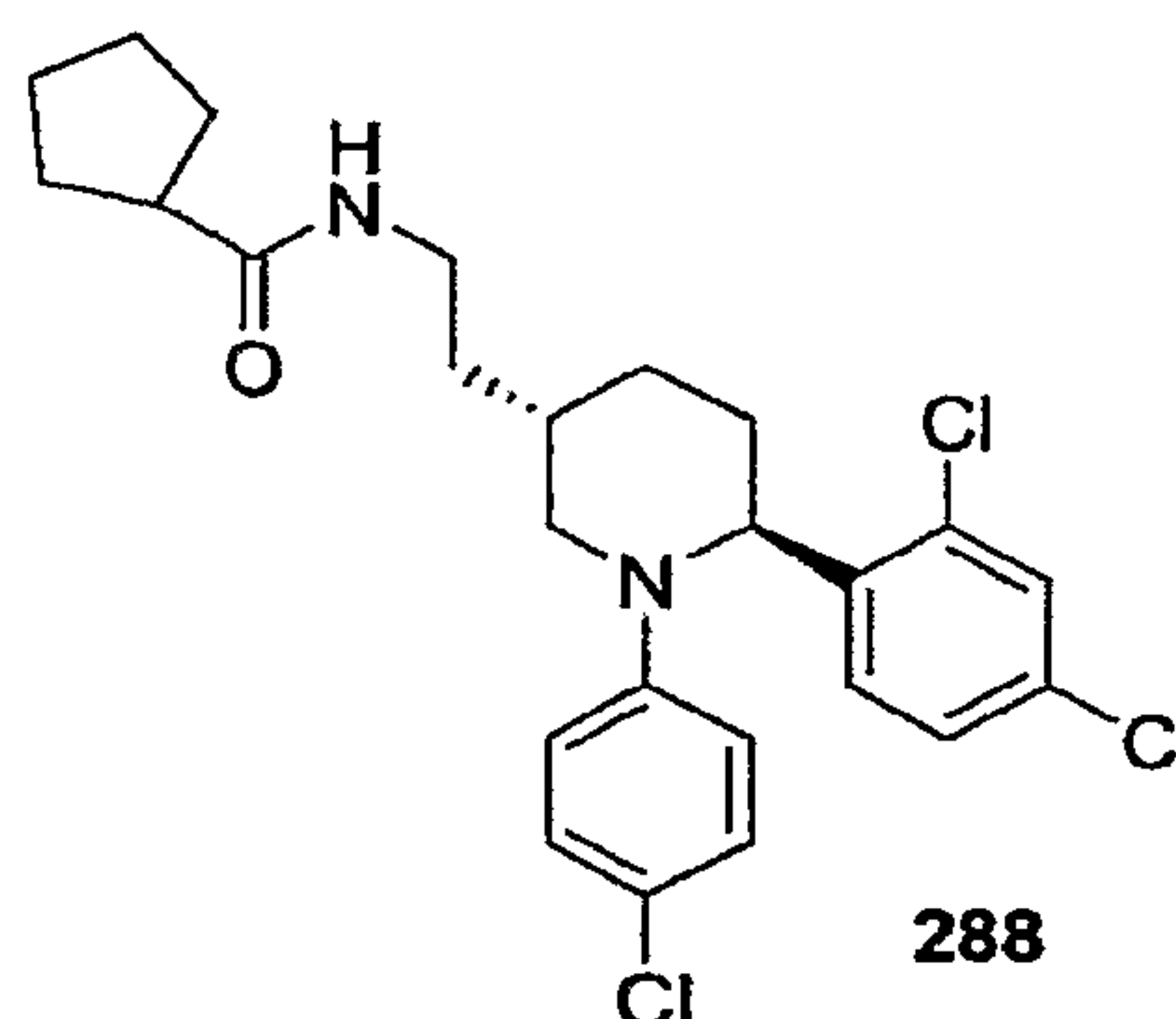
Example 286 was prepared using a procedure similar to that described above
5 for Example 285, except acetic acid was used instead of isopropyl carboxylic acid.

Preparation of Example 287

10 Example 287 was prepared using a procedure similar to that described above
for Example 285, except 5-methyl hexanoic acid was used instead of isopropyl
carboxylic acid.

Preparation of Example 288

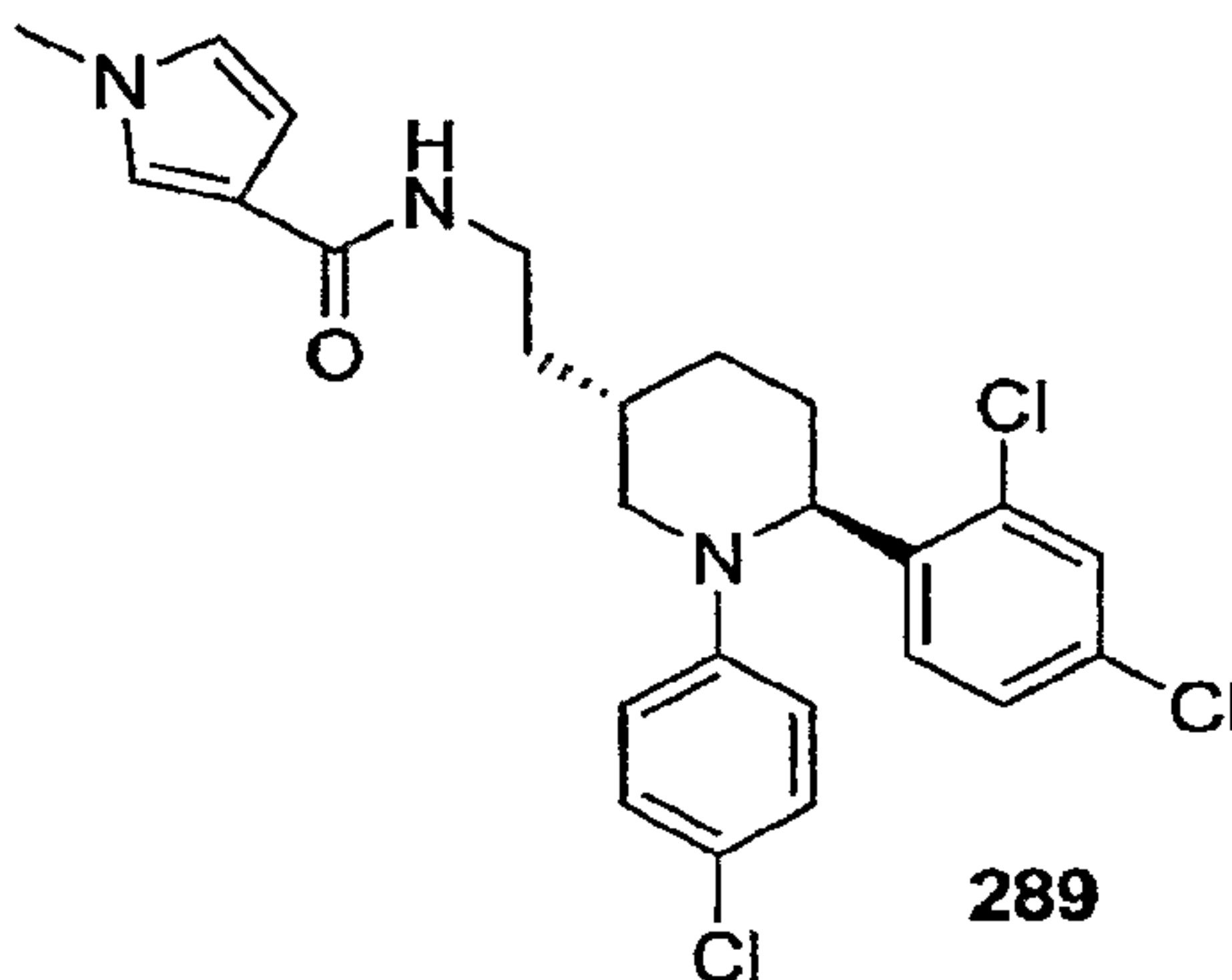
15



179

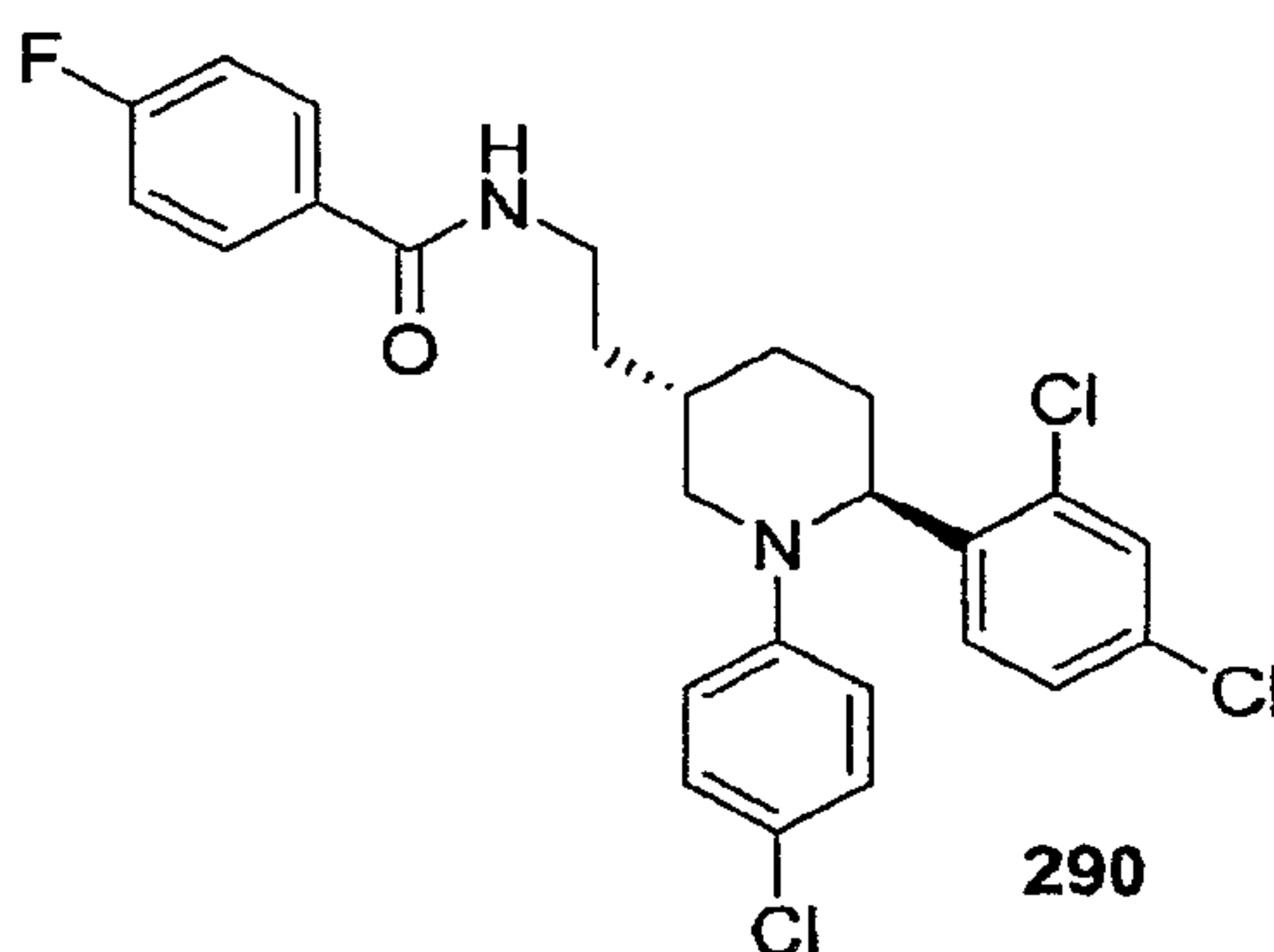
Example 288 was prepared using a procedure similar to that described above for **Example 285**, except cyclopentyl carboxylic acid was used instead of isopropyl carboxylic acid.

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Preparation of Example 289

Example 289 was prepared using a procedure similar to that described above for **Example 285**, except N-Methylpyrrole-3-carboxylic acid was used instead of isopropyl carboxylic acid.

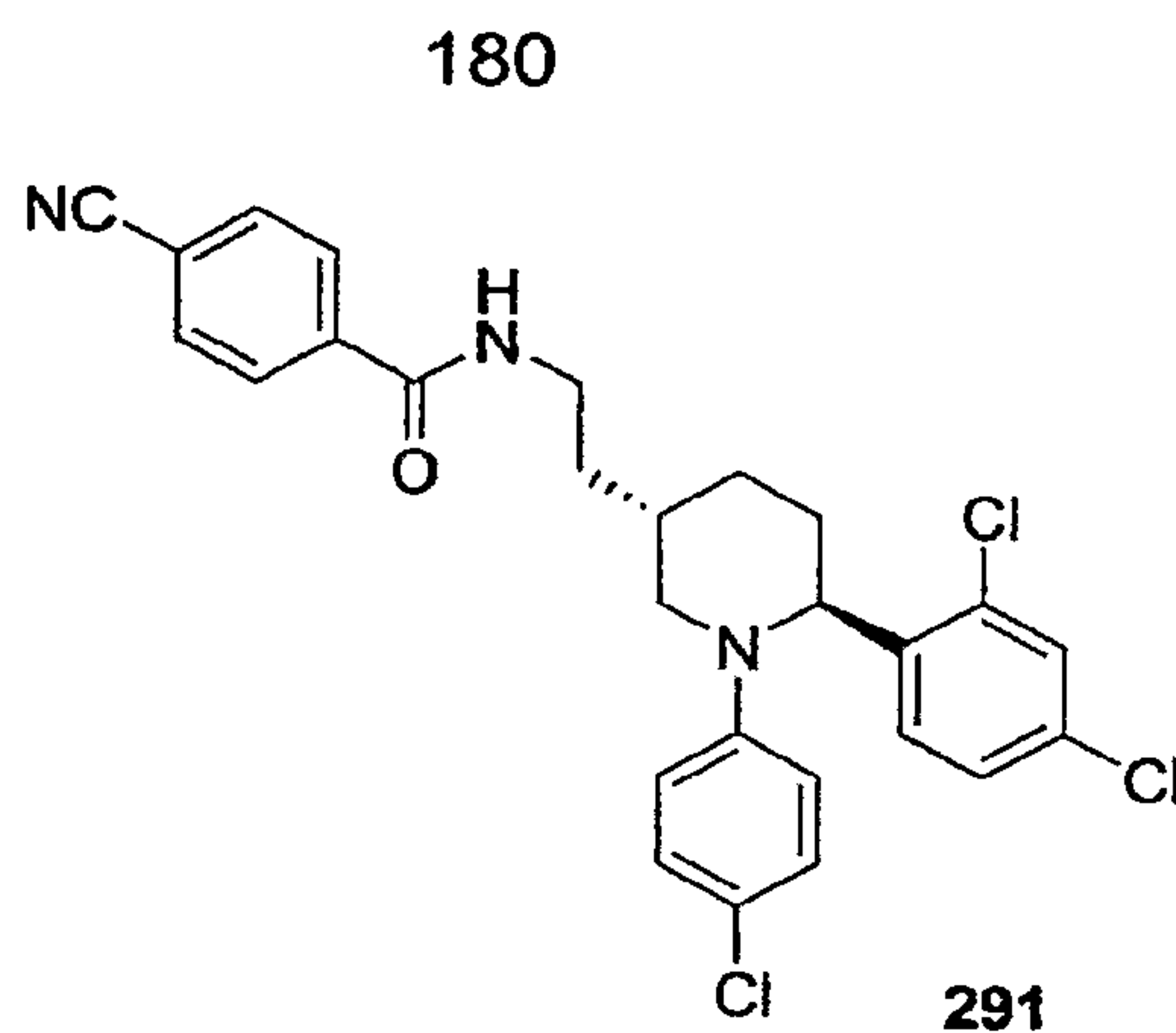
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Preparation of Example 290

Example 290 was prepared using a procedure similar to that described above for **Example 285**, except 4-fluorobenzoic acid was used instead of isopropyl carboxylic acid.

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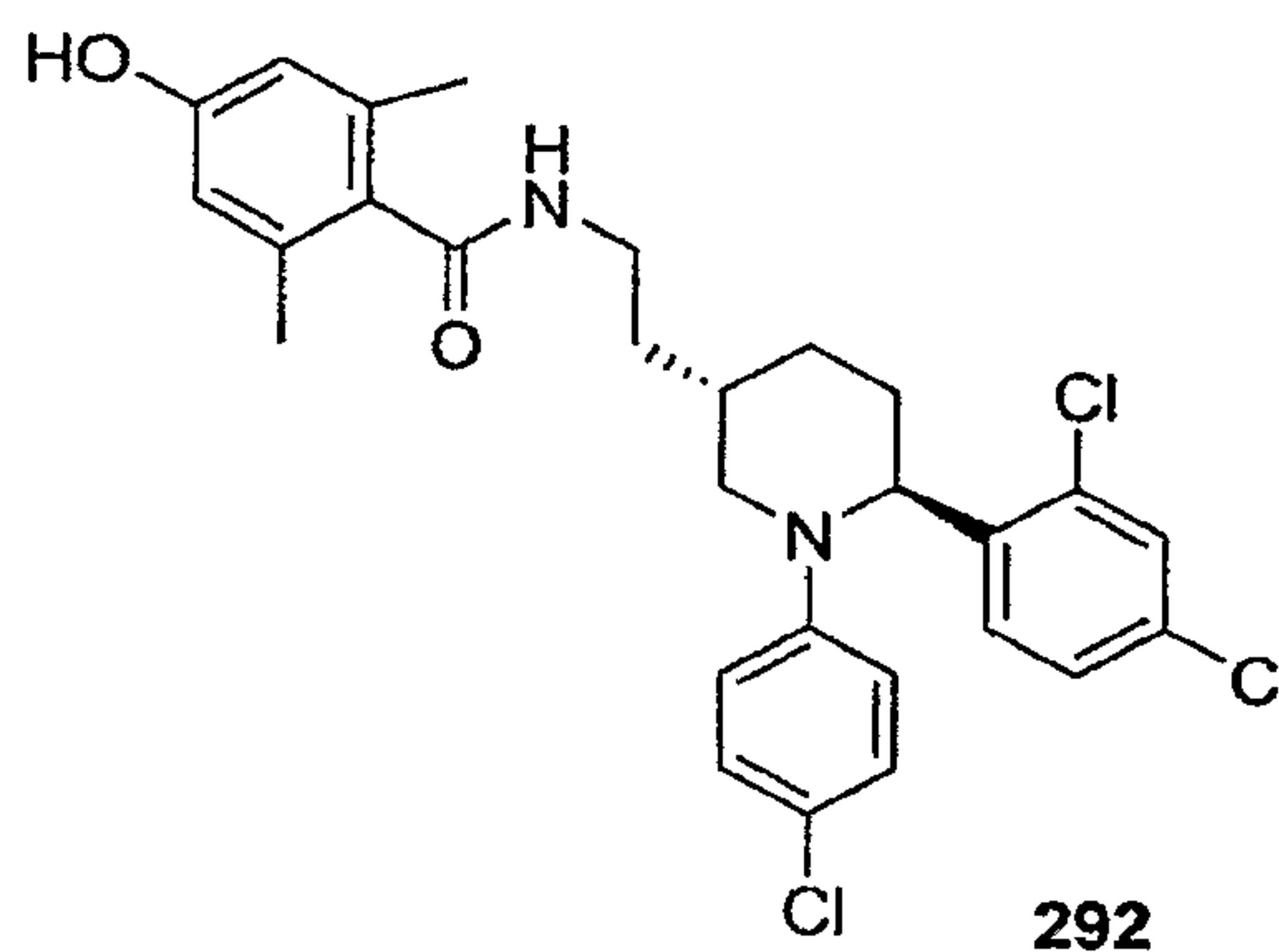
Preparation of Example 291



Example 291 was prepared using a procedure similar to that described above for **Example 285**, except 4-cyanobenzoic acid was used instead of isopropyl carboxylic acid.

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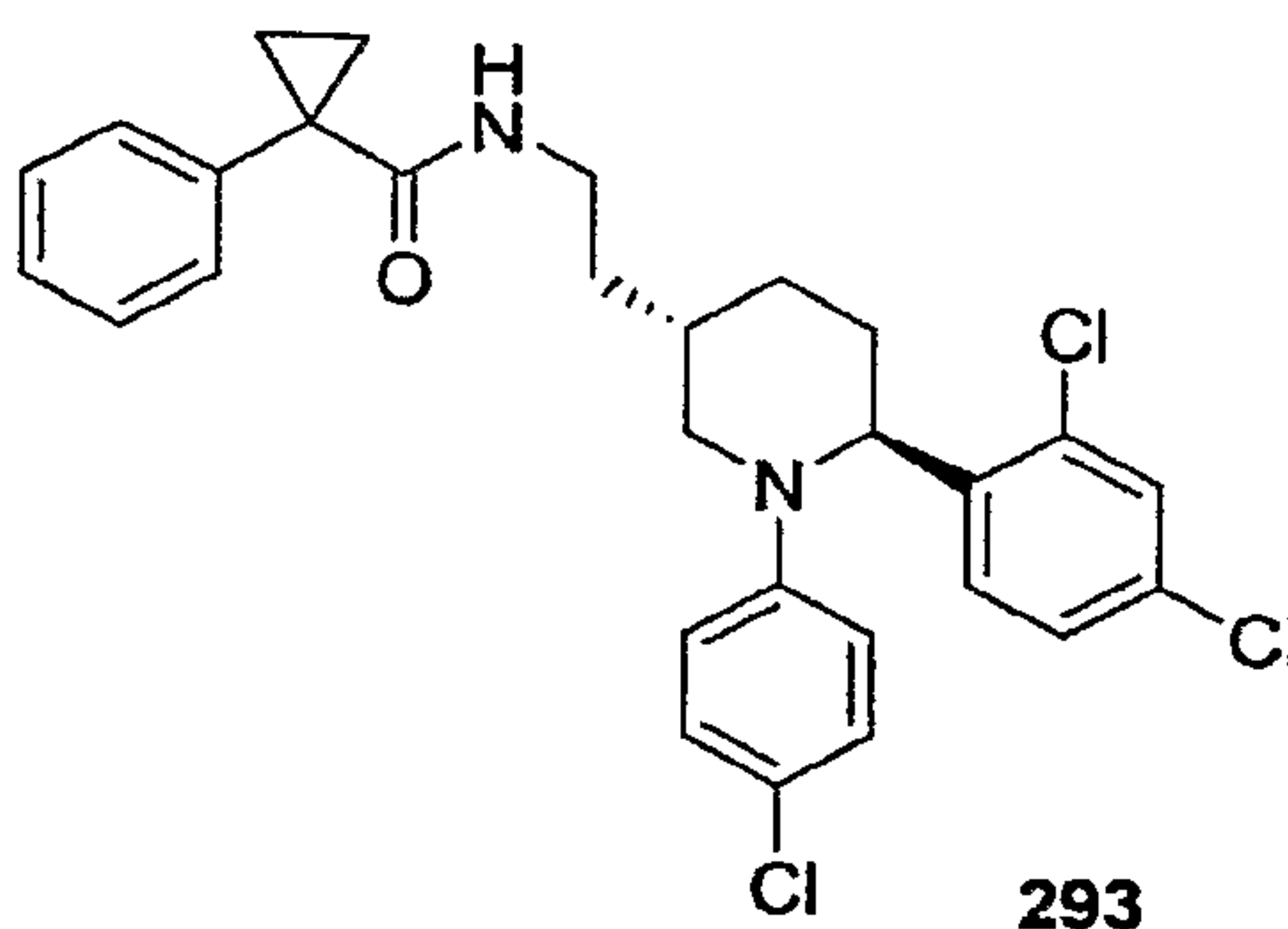
Preparation of Example 292



Example 292 was prepared using a procedure similar to that described above for **Example 285**, except 4-hydroxy-2,6-dimethylbenzoic acid was used instead of isopropyl carboxylic acid.

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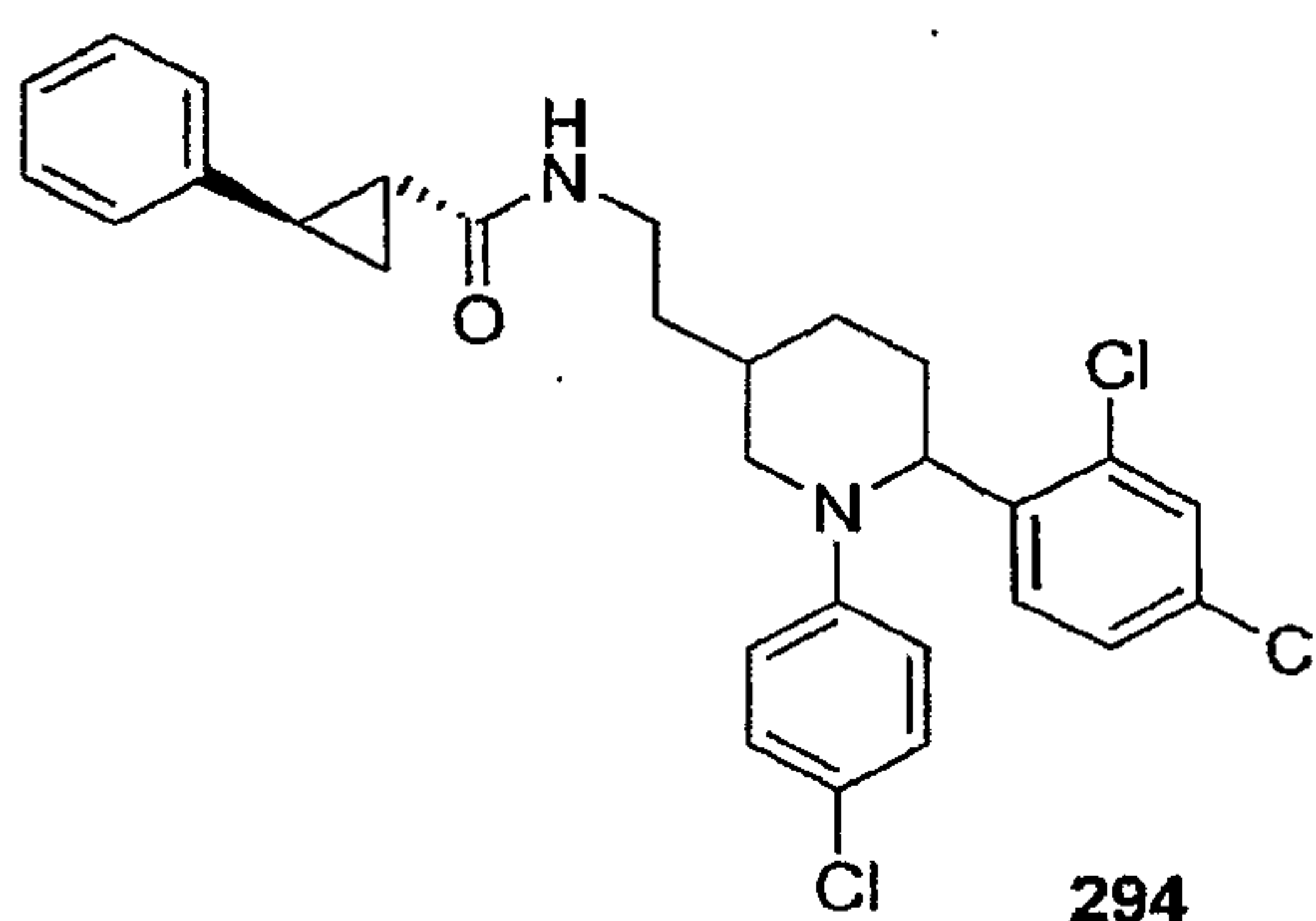
Preparation of Example 293



Example 293 was prepared using a procedure similar to that described above for **Example 285**, except 1-phenyl-cyclopropanecarboxylic acid was used instead of isopropyl carboxylic acid.

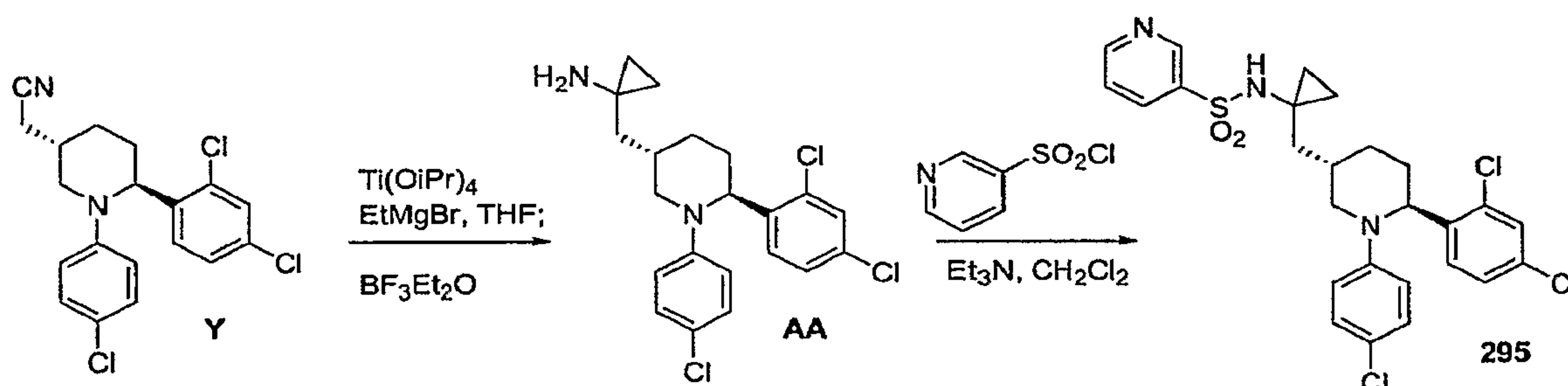
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Preparation of Example 294



Example 294 was prepared using a procedure similar to that described above for **Example 285**, except 2-phenyl-cyclopropanecarboxylic acid was used instead of isopropyl carboxylic acid.

Preparation of Example 295



15 Step 1:

To a solution of **Y** (200 mg, 0.53 mmol) in anhydrous THF was added titanium(IV)isopropoxide (0.17 mL, 0.58 mmol). To this solution was added a dropwise solution of ethyl magnesium bromide (1 M in Et₂O)(1.1 mL, 1.05 mmol). The solution was stirred at RT for 3 h. To the solution was added borontrifluoride etherate (0.13 mL, 1.05 mmol). The solution was stirred at RT for 1 h. To the solution was added 1 M NaOH (aq.) and the aqueous layer was extracted with

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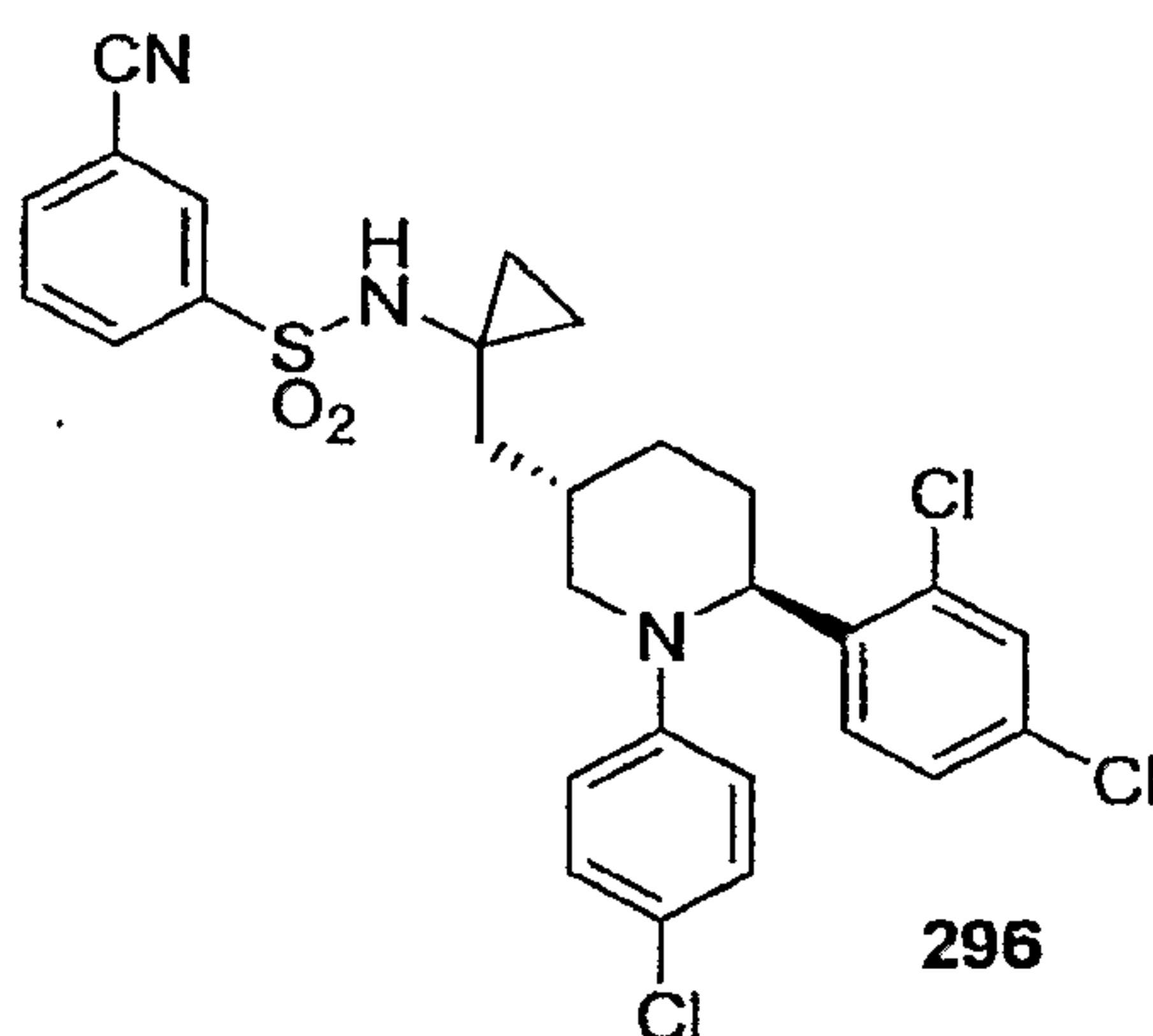
182

EtOAc. The organic layer was dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by flash chromatography (SiO_2 : gradient elution 100:0 to 75:25 hexanes: EtOAc to elute unreacted **Y** changing to 95:5:0.5 CH_2Cl_2 :MeOH:ammonium hydroxide to elute **AA**) to afford 100 mg **AA**.

5 Step 2:

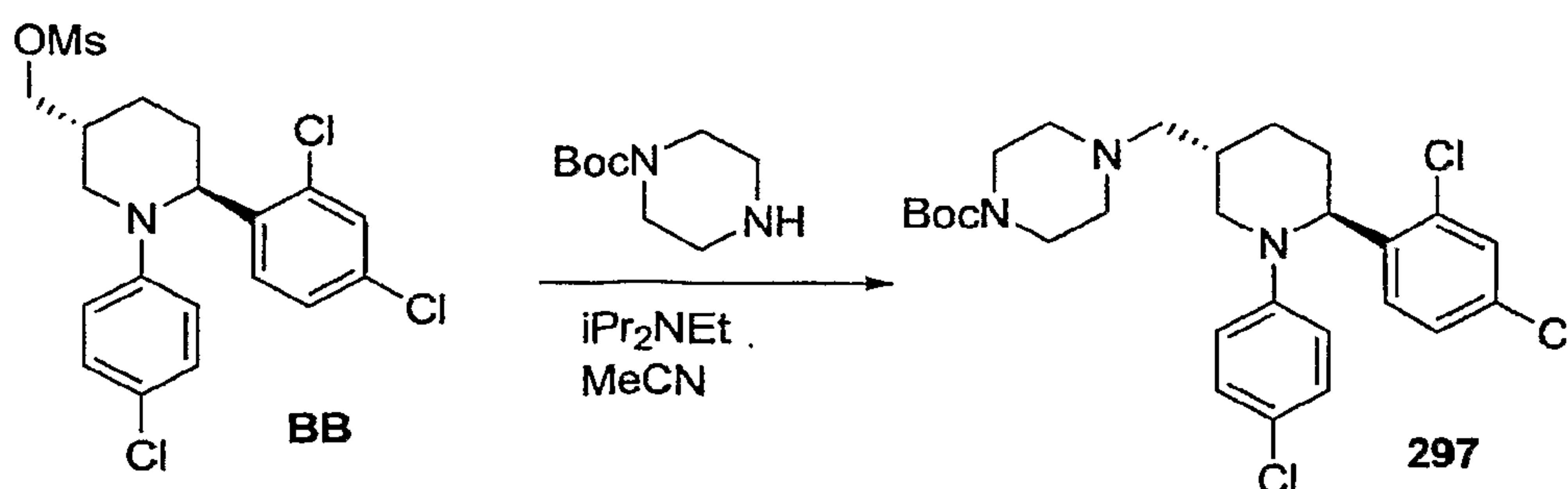
To a solution of **AA** (30 mg, 0.07 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (23 mg, 0.32 mmol) followed by 3-pyridine sulfonyl chloride (21 mg, 0.12 mmol). The solution was stirred at RT overnight followed by 4 hours at reflux. The crude material was purified by preparative TLC (SiO_2 : 65:35 hexanes:EtOAc) to afford **Example**
 10 **295**, which was converted to the HCl salt using a procedure similar to that described above for **Example 285** (20 mg).

Preparation of Example 296



Example 296 was prepared using a procedure similar to that described above for **Example 295**, step 2, except 3-cyano-benzenesulfonyl chloride was used instead of 3-pyridine sulfonyl chloride.

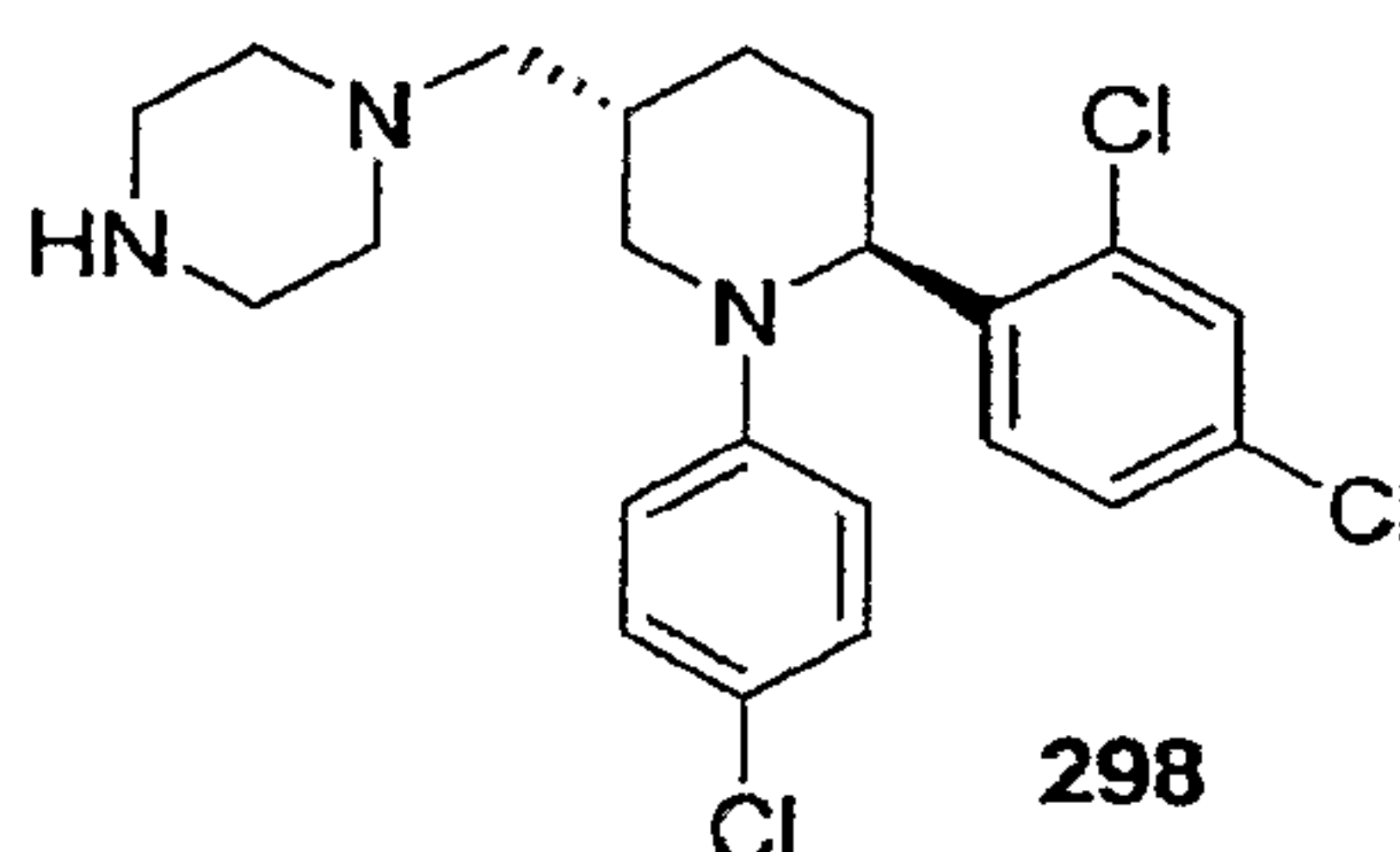
Preparation of Example 297



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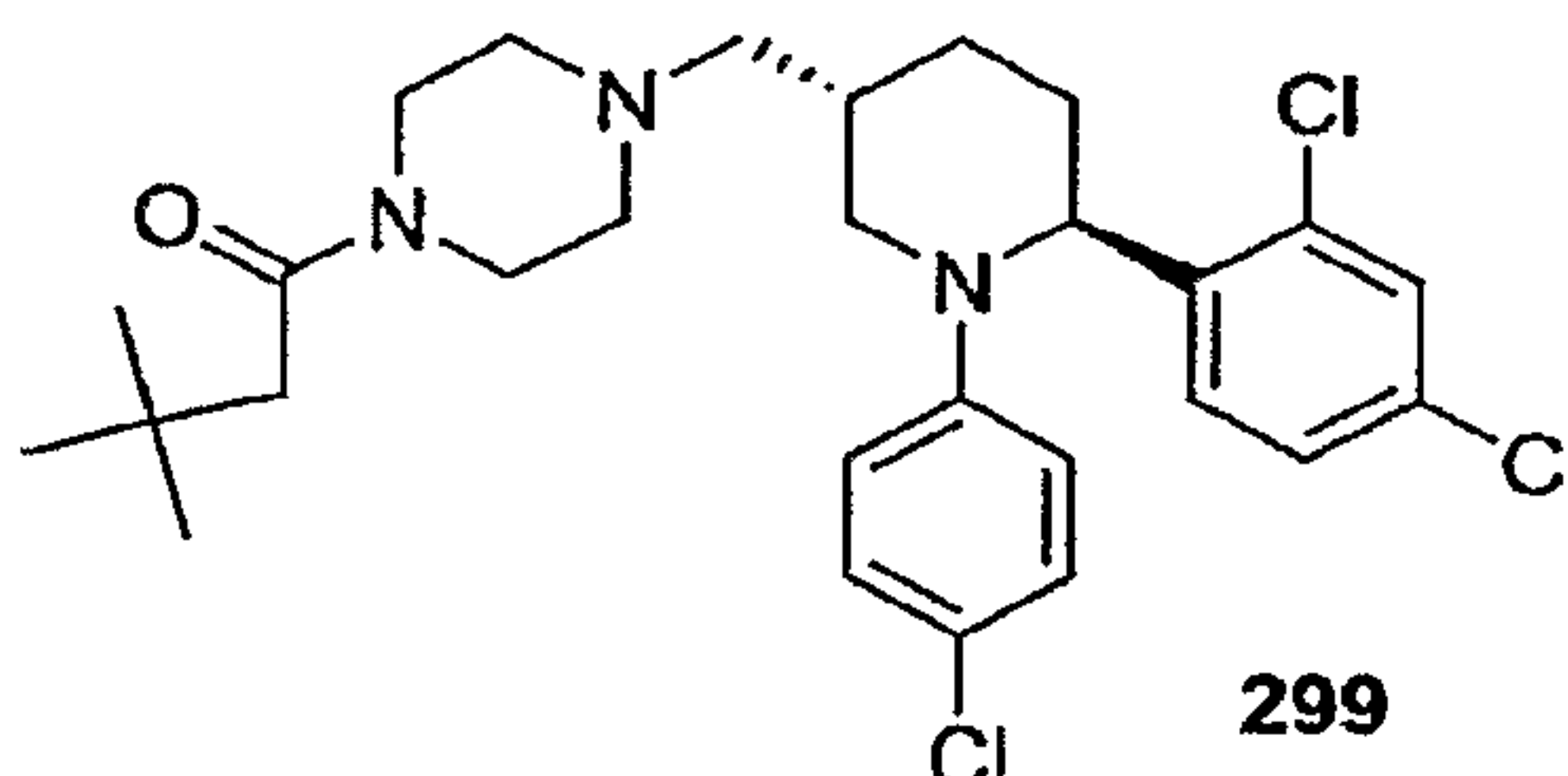
To a solution of **BB** (See Step 1, **Example 282**) (1.0 g, 2.2 mmol) in MeCN (15 mL) was added N-Boc piperazine (466 mg, 2.5 mmol) and $i\text{Pr}_2\text{NEt}$ (341 mg, 2.64 mmol). The solution was heated to reflux for 24 h. The solution was concentrated and the crude product was partitioned between CH_2Cl_2 and NaHCO_3 (aq.). The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by flash chromatography (SiO_2 : gradient elution 100:0 to 65:35 hexanes:EtOAc) to afford 475 mg **Example 297**.

Preparation of Example 298



To a solution of **Example 297** (475 mg) in MeOH (20 mL) was added 4 N HCl (in dioxane) (5 mL). The solution was stirred at RT for 2 h. The solution was concentrated and the crude material was partitioned between CH_2Cl_2 and NaHCO_3 (aq.). The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by flash chromatography [SiO_2 : gradient elution 100:0:0 to 92:8:1 CH_2Cl_2 :MeOH: 7N NH_3 (in MeOH)] to afford 320 mg **Example 298**.

Preparation of Example 299



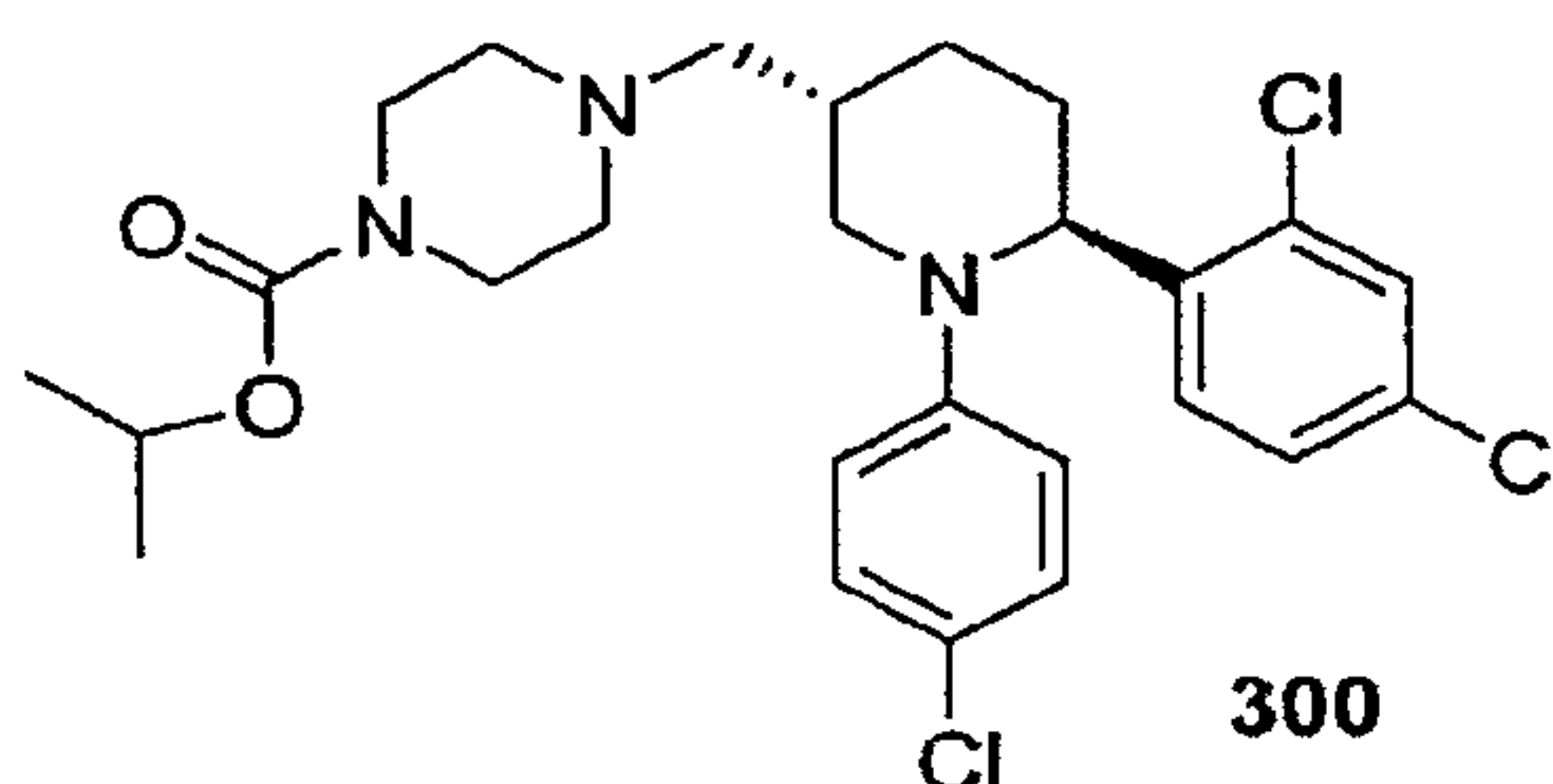
To a solution of **Example 298** (41 mg, 0.093 mmol) in MeCN (1 mL) was added EDCI (17 mg, 0.112 mmol), HOBt (15 mg, 0.112 mmol) (13 mg, 0.112 mmol) 3,3 dimethyl butyric Acid and $i\text{Pr}_2\text{NEt}$ (14 mg, 0.112 mmol). The solution was stirred at RT overnight. The solution was concentrated and the crude product was

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partitioned between 1 M NaOH (aq.) and EtOAc. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by preparative TLC (SiO₂: 3:1 hexanes:EtOAc) to afford 42 mg **Example 299**.

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Preparation of Example 300

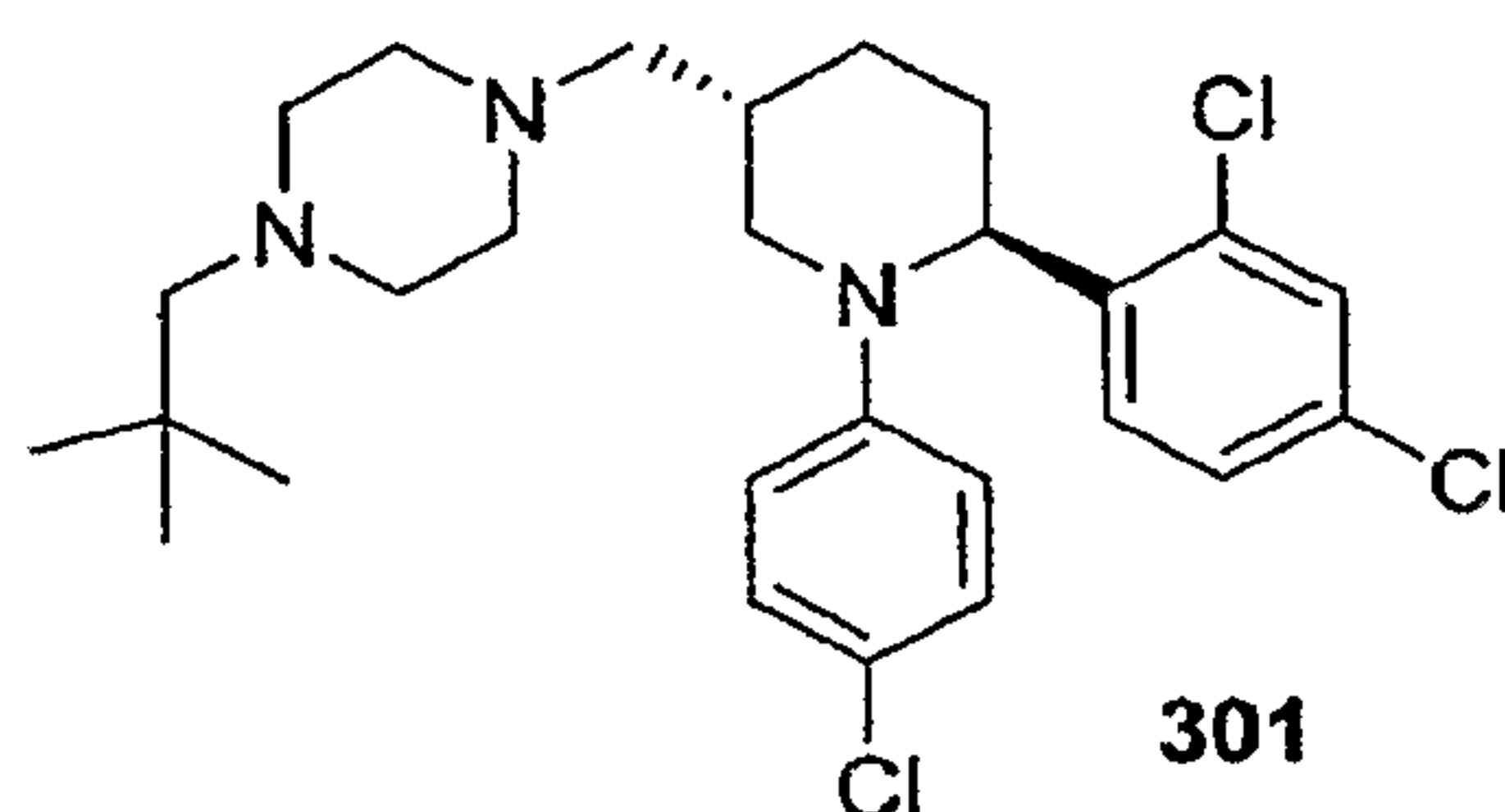


300

To a solution of **Example 298** (29 mg, 0.066 mmol) in CH₂Cl₂ (2 mL) was added isopropyl chloroformate (1M solution in toluene; 80uL, 0.080 mmol) and Et₃N (8.7 mg, 0.080 mmol). The solution was stirred at RT overnight. The solution was diluted with CH₂Cl₂. The organic layer was washed with NaHCO₃ (aq.). The aqueous layer was back extracted with CH₂Cl₂ (2x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by preparative TLC (SiO₂: 3:1 hexanes:EtOAc) to afford 30 mg **Example 300**.

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Preparation of Example 301

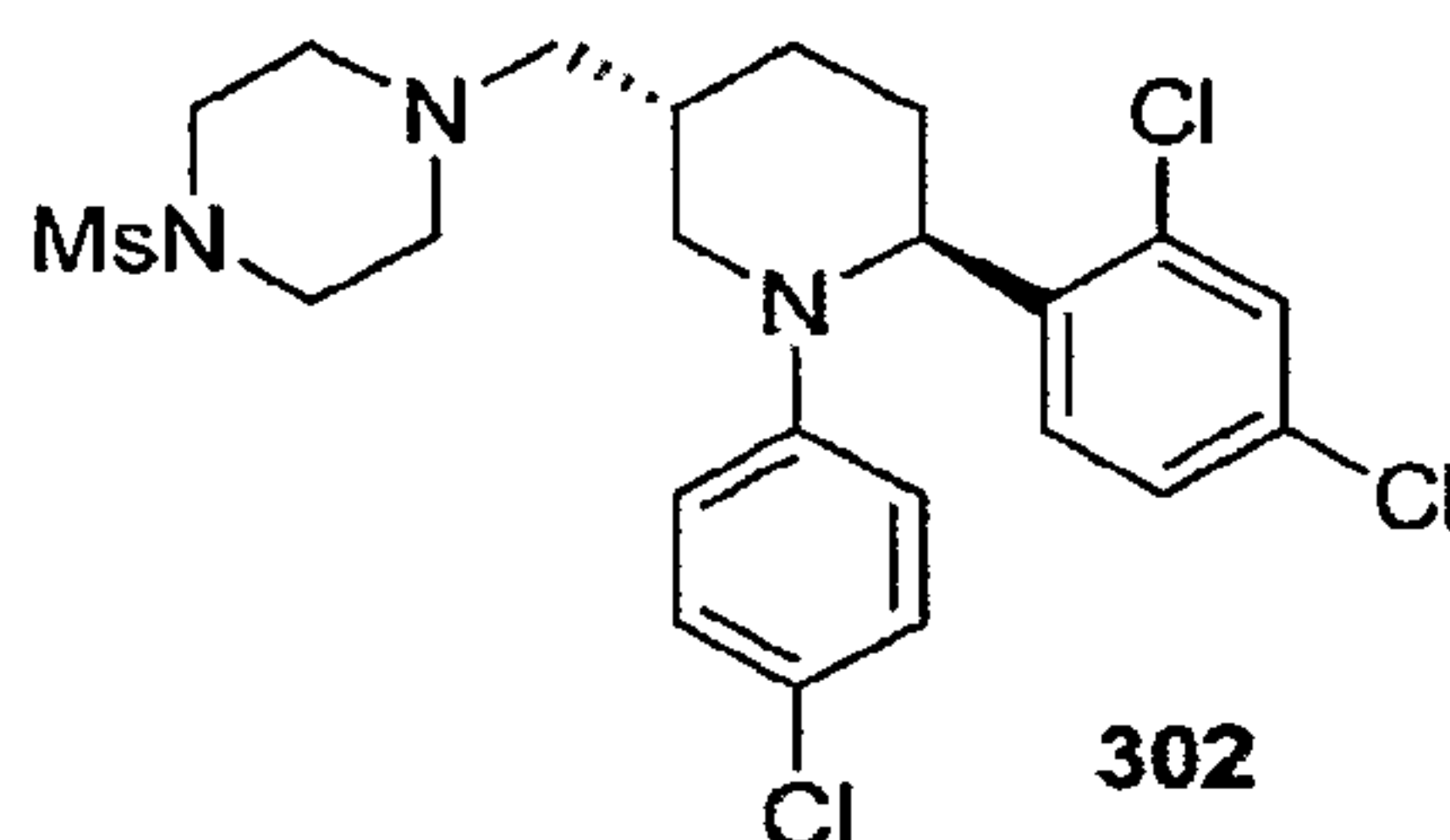


301

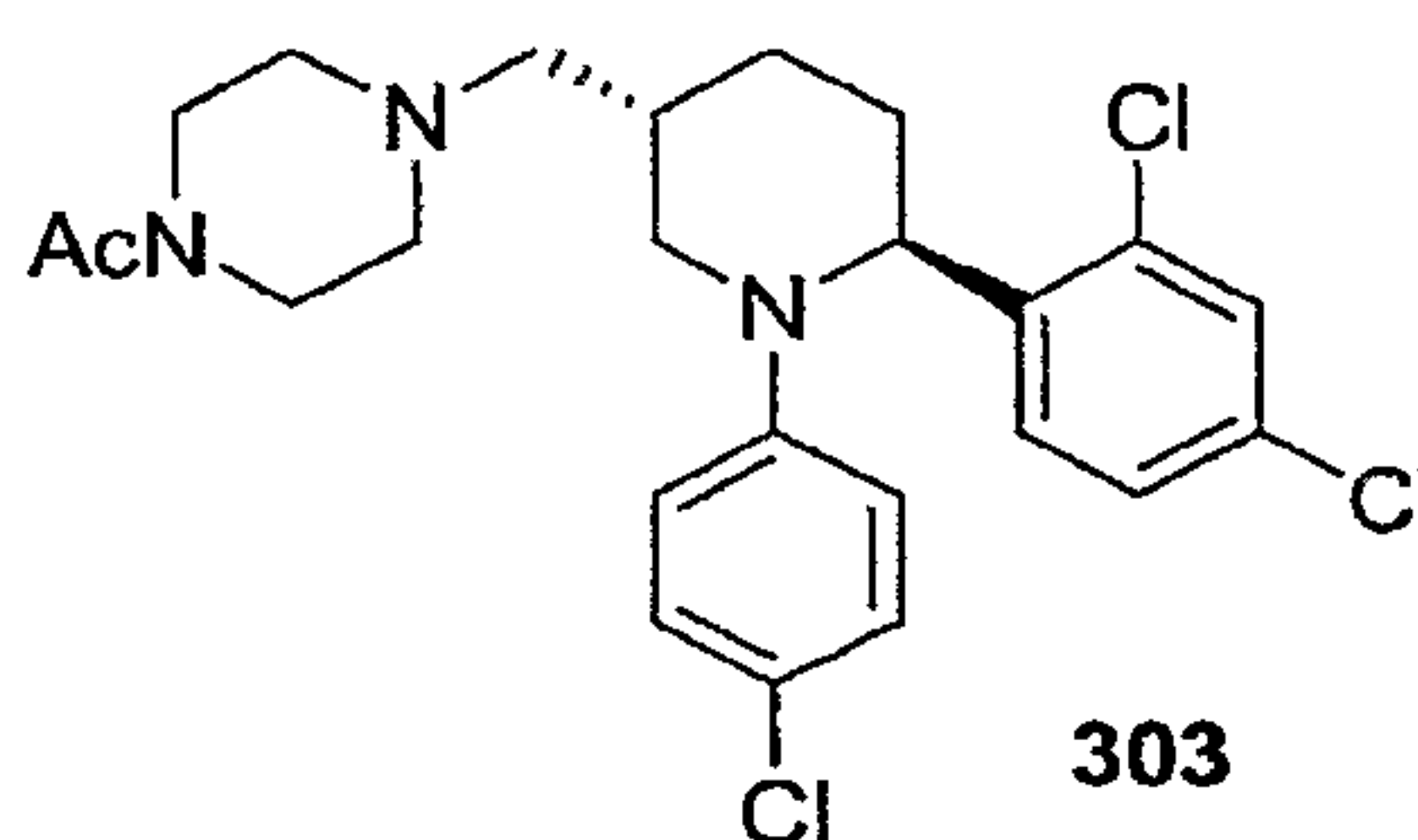
To a solution of **Example 298** (25 mg, 0.057 mmol) in 1,2-dichloroethane (1 mL) was added 3,3-dimethyl butyraldehyde (7 mg, 0.068 mmol) followed by NaBH(OAc)₃ (14 mg, 0.068 mmol). The solution was stirred at RT overnight. The solution was diluted with CH₂Cl₂. The organic layer was washed with 1 M NaOH (aq.). The aqueous layer was back extracted with CH₂Cl₂ (2x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by preparative TLC (SiO₂: 1:2 hexanes:EtOAc) to afford **Example 301**.

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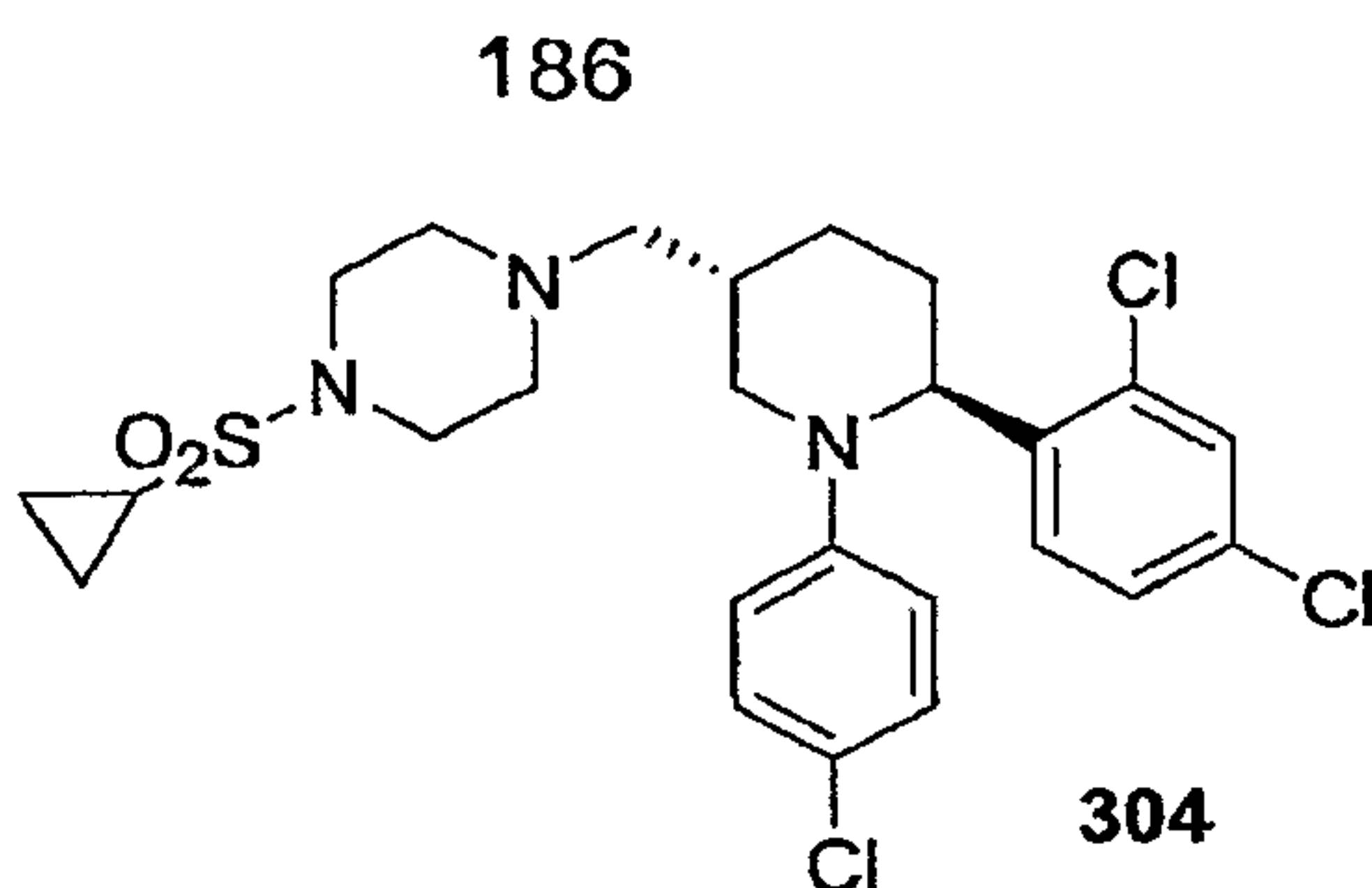
Preparation of Example 302

5 To a solution of **Example 298** (29 mg, 0.066 mmol) in CH₂Cl₂ (2 mL) was added methanesulfonyl chloride (9 mg, 0.079 mmol) followed by Et₃N (10 mg, 0.099 mmol). The solution was stirred at RT for 2.5 days. The solution was diluted with CH₂Cl₂. The organic layer was washed with 1 NaHCO₃ (aq.). The aqueous layer was back extracted with CH₂Cl₂ (2x). The combined organic layers were dried
10 over Na₂SO₄, filtered and concentrated. The crude product was purified by preparative TLC (SiO₂: 2:1 hexanes:EtOAc) to afford 20 mg **Example 302**.

Preparation of Example 303

15 To a solution of **Example 298** (21 mg, 0.048 mmol) in CH₂Cl₂ (2 mL) was added acetic anhydride (6 mg, 0.058 mmol) followed by Et₃N (7 mg, 0.072 mmol). The solution was stirred at RT for 2.5 days. The solution was diluted with CH₂Cl₂. The organic layer was washed with 1 NaHCO₃ (aq.). The aqueous layer was back
20 extracted with CH₂Cl₂ (2x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by preparative TLC (SiO₂: 1:1 hexanes:EtOAc) to afford 18 mg **Example 303**.

Preparation of Example 304



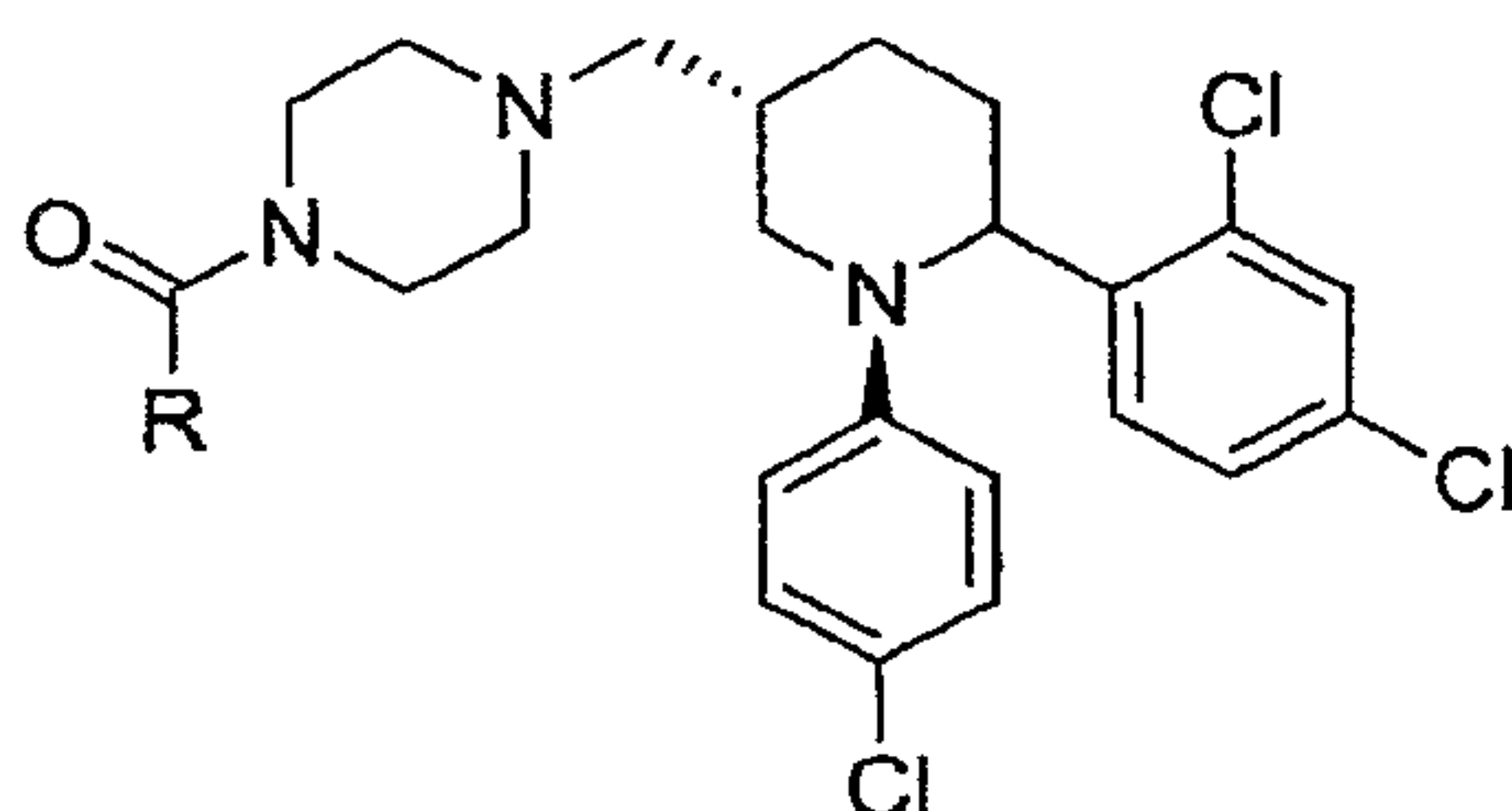
Example 304 was prepared using a procedure similar to that described above for **Example 302**, except cyclopropanesulfonyl chloride was used instead of methanesulfonyl chloride.

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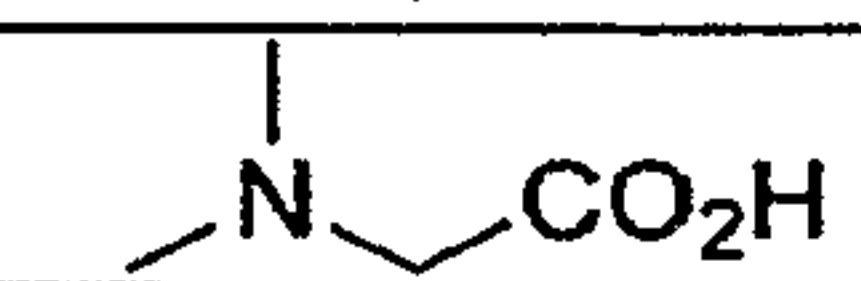
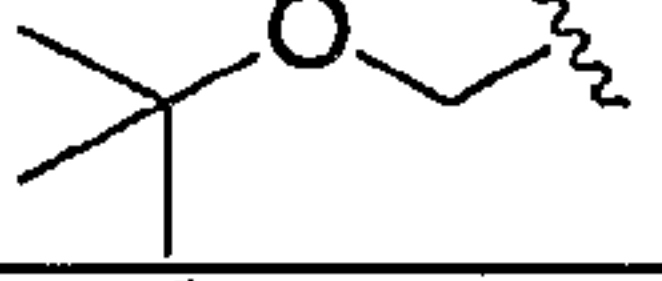
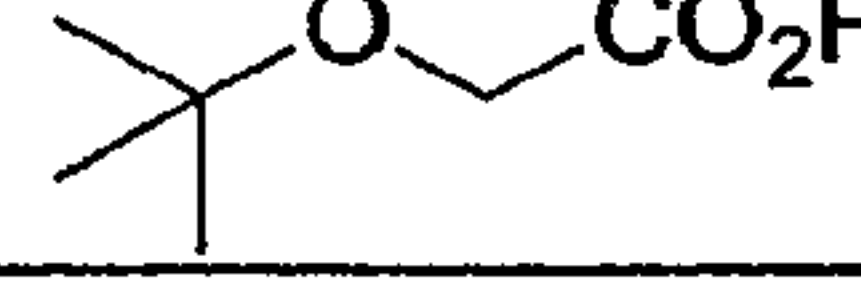
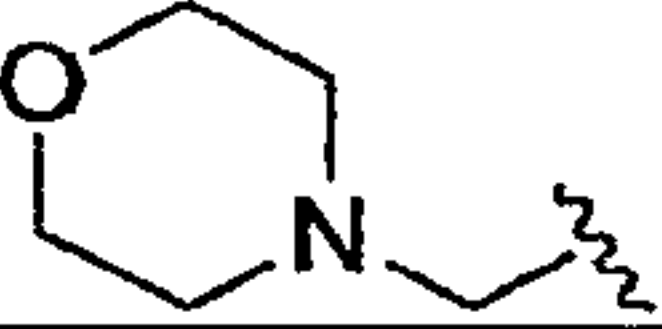
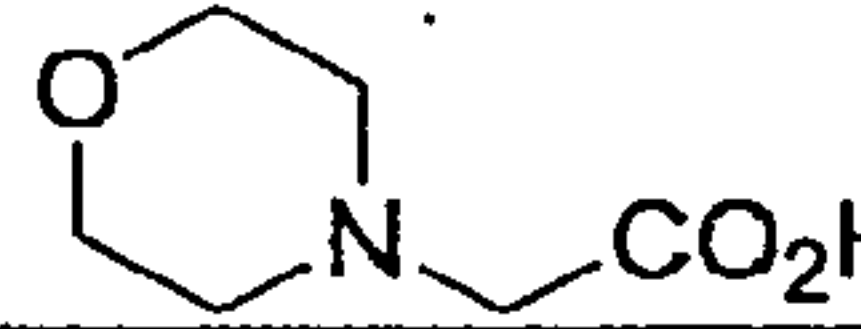
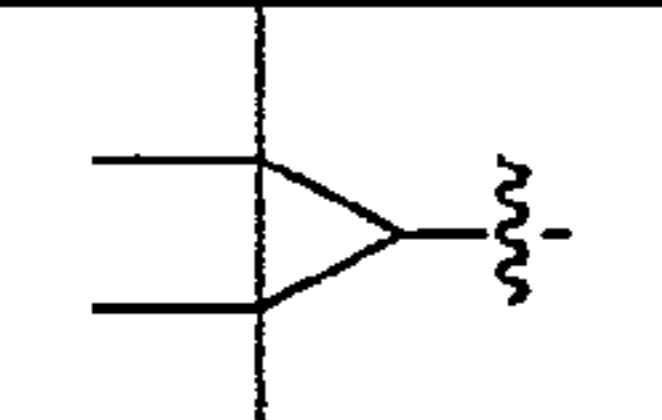
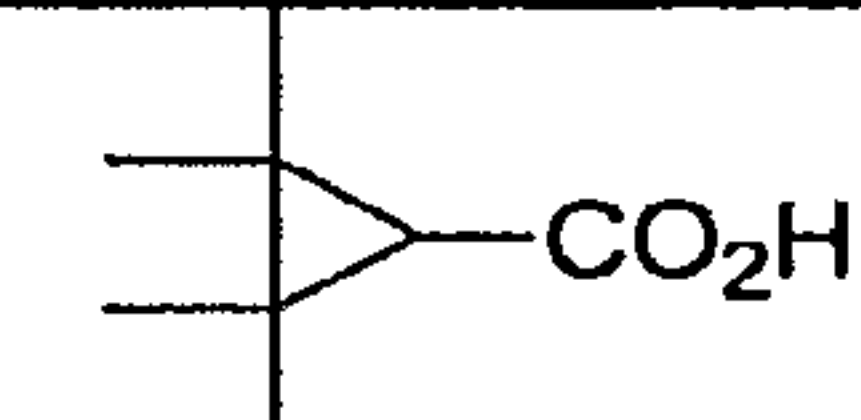
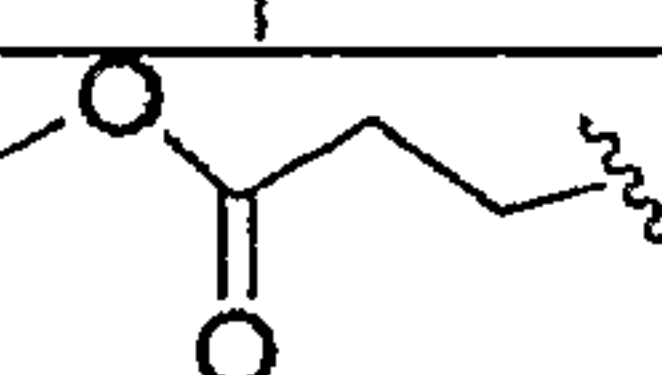
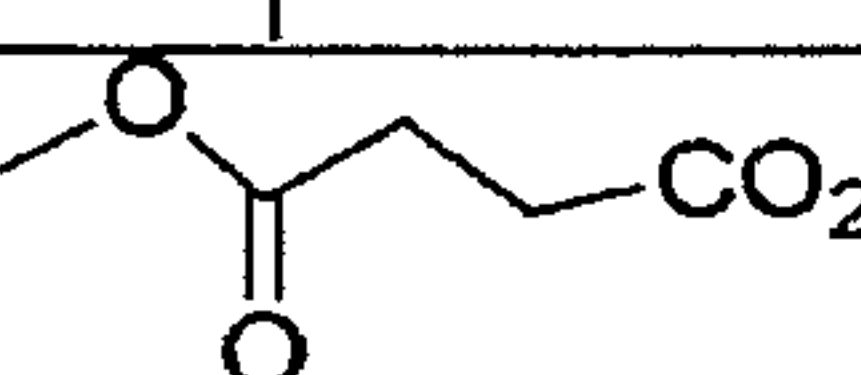
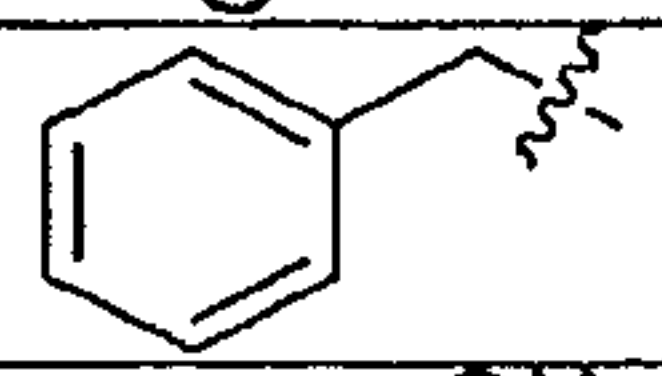
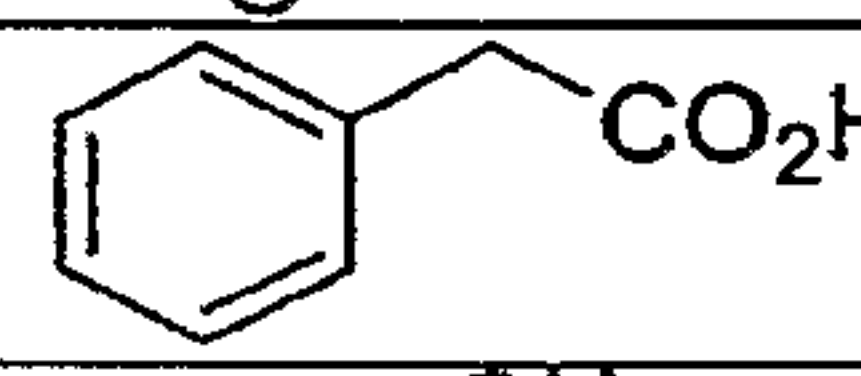
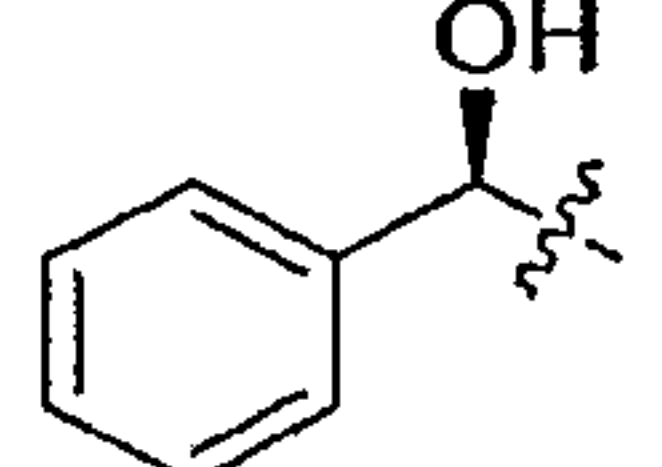
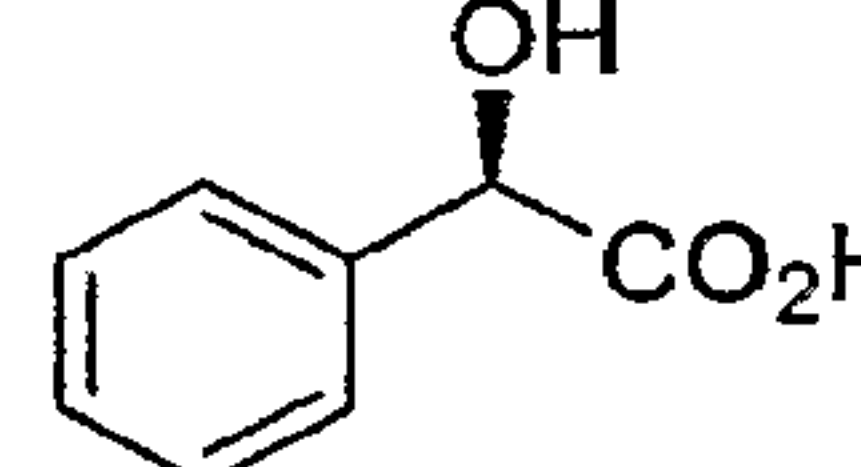
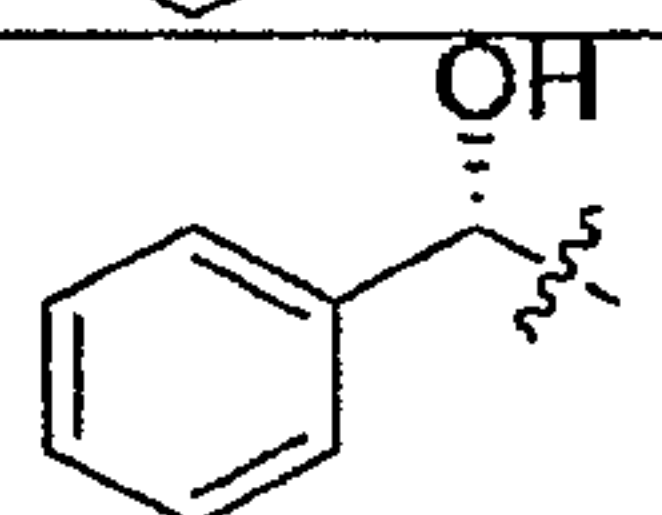
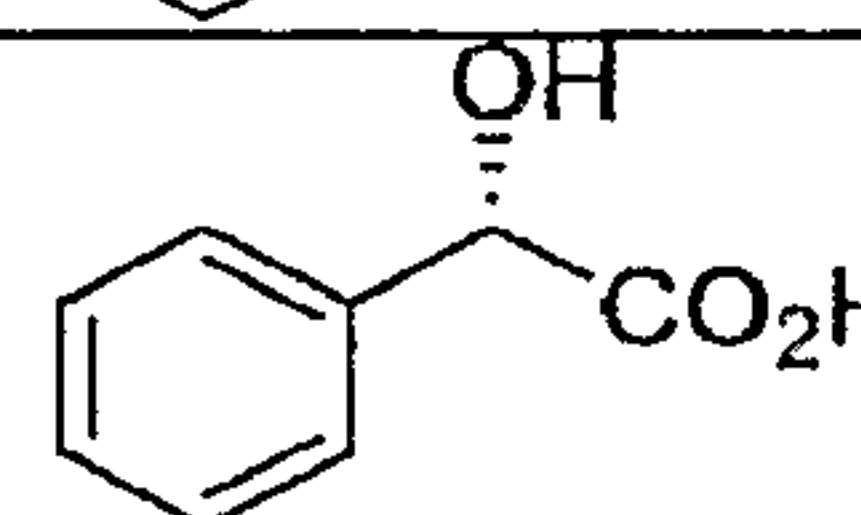
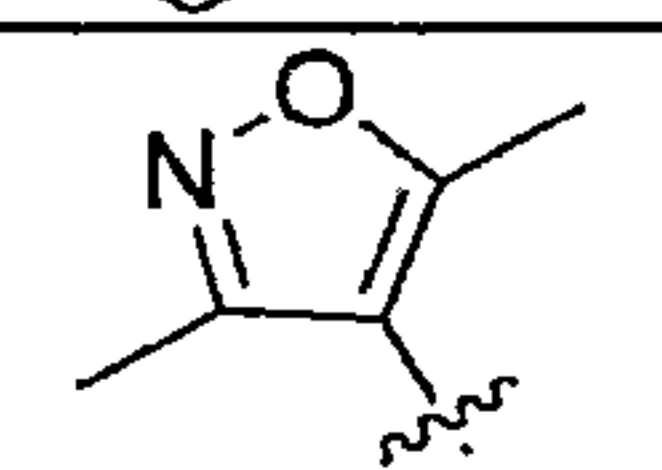
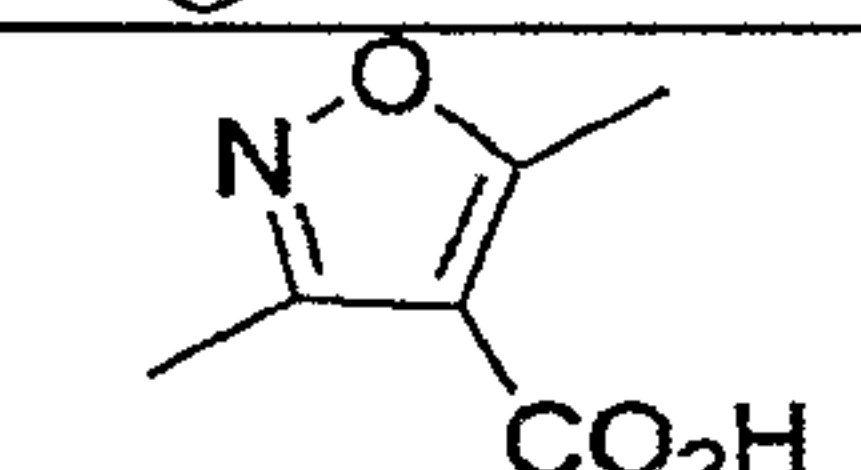
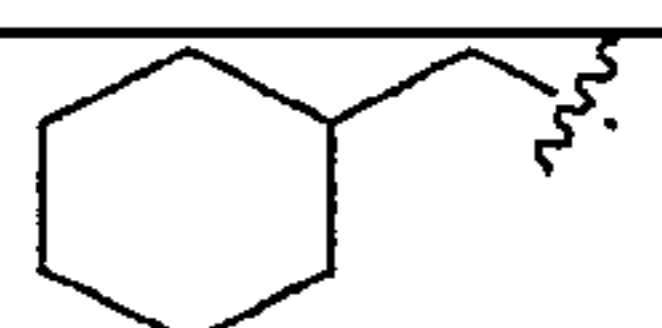
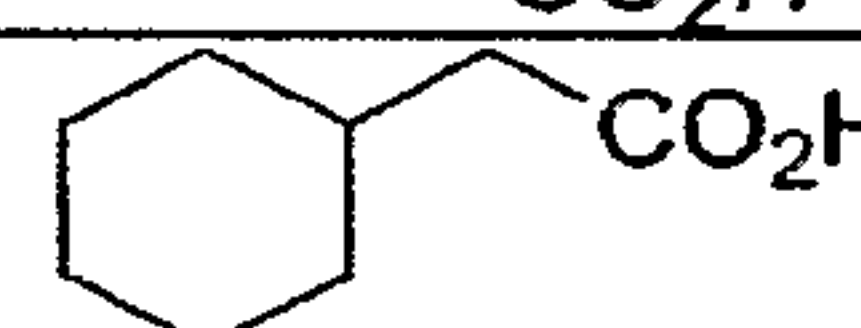
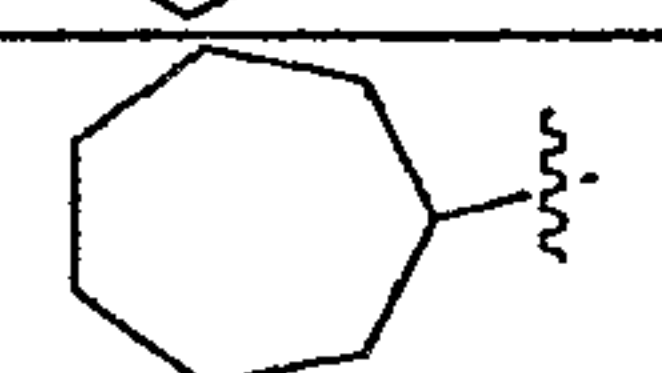
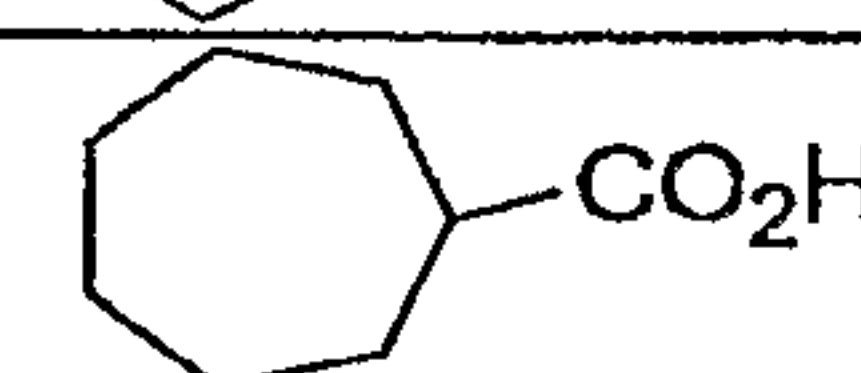
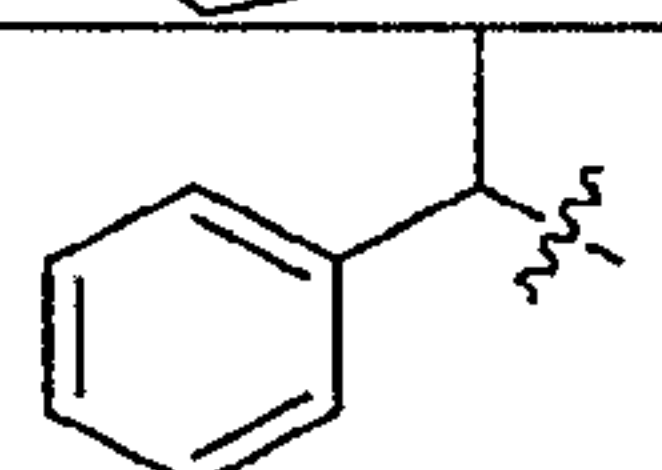
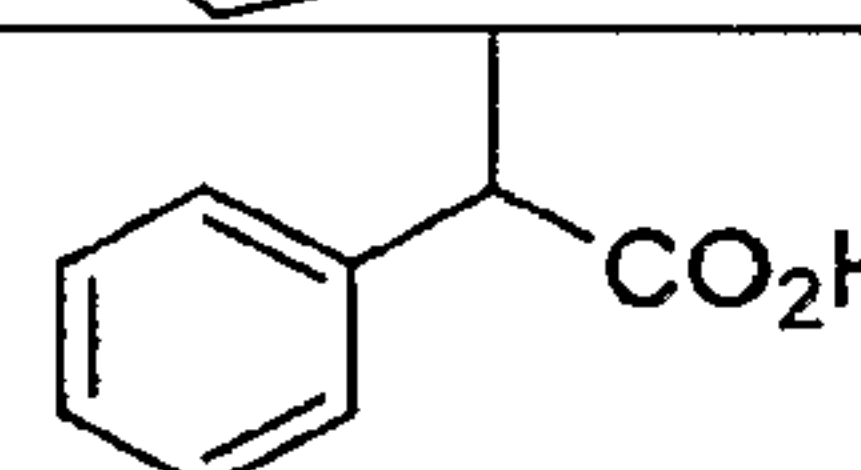
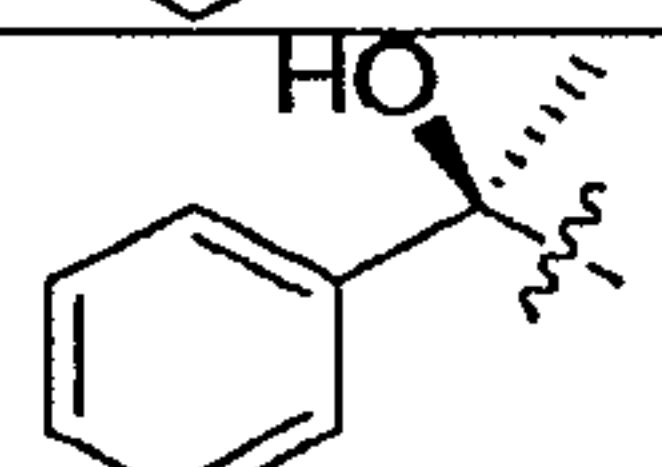
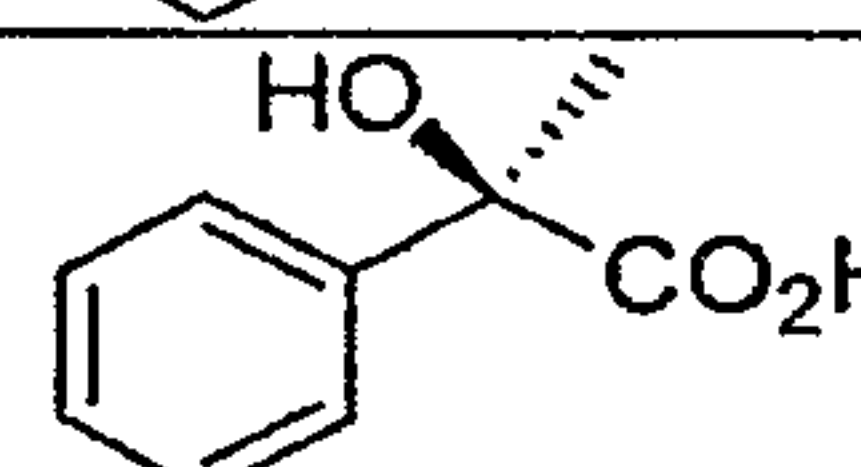
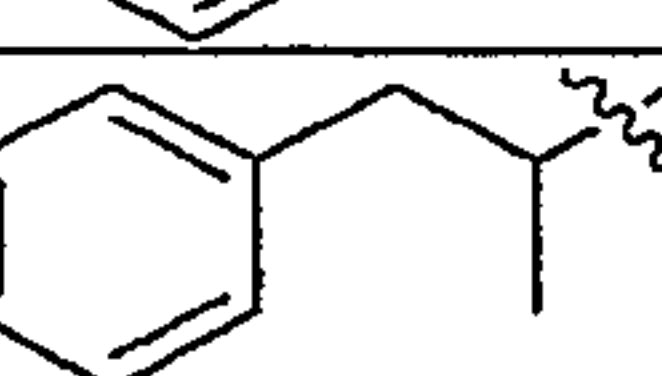
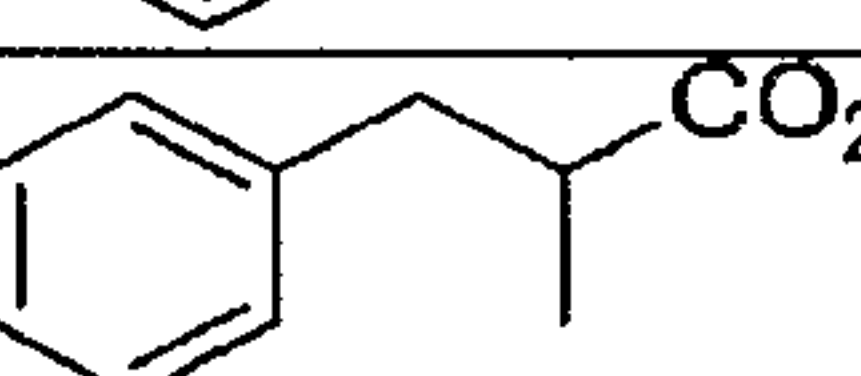
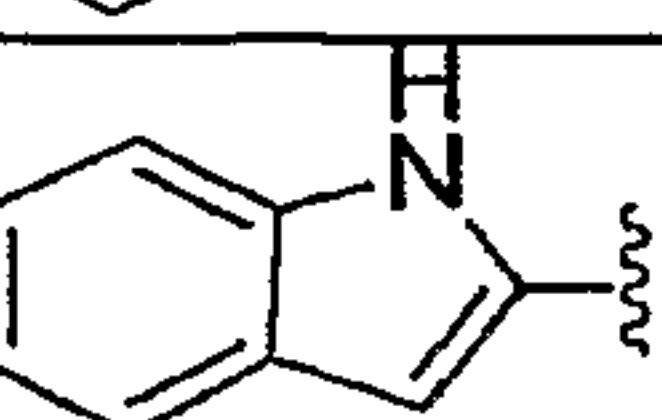
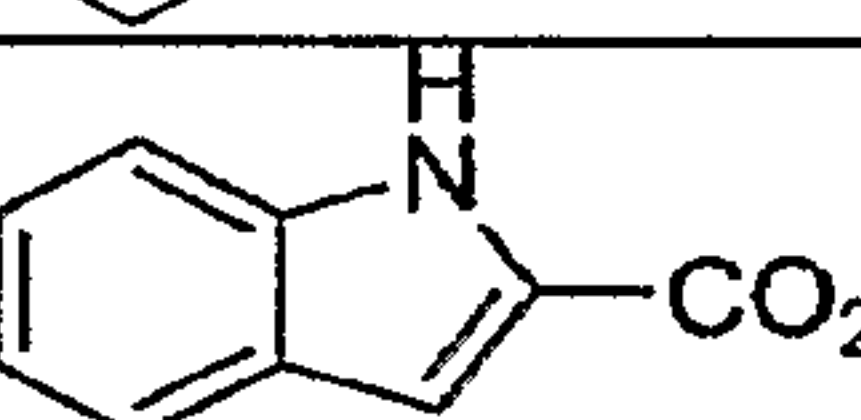
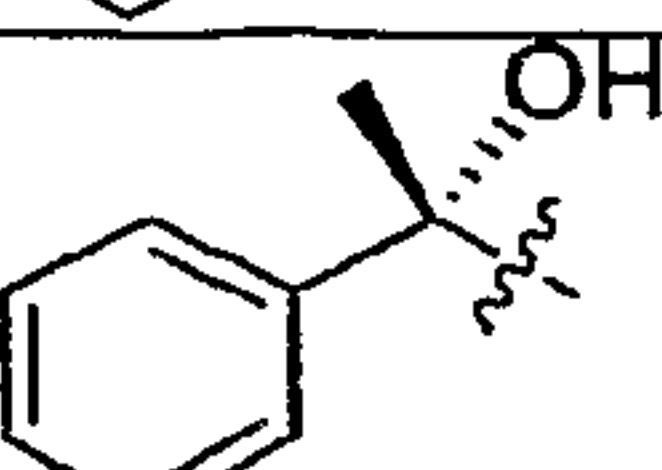
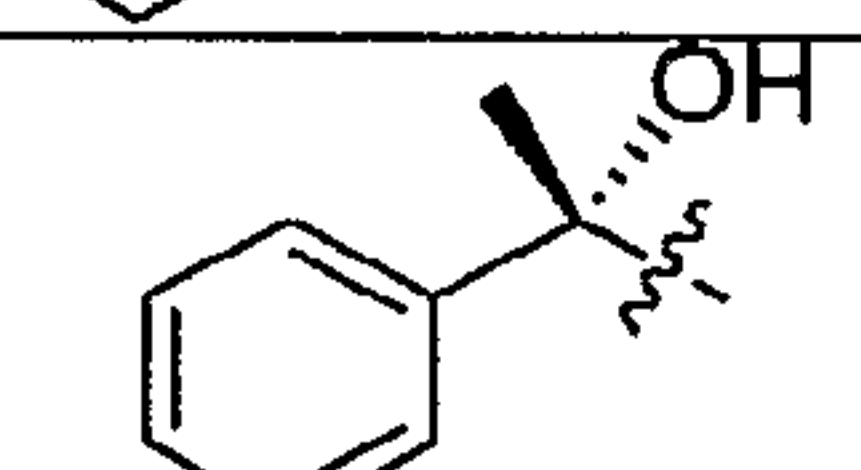
Preparation of Examples 305-352

Examples 305-352 were prepared using a procedure similar to that described above for preparing **Examples 149-162**, except that **Example 298** was used as the starting material instead of **Examples 130 or 131**.

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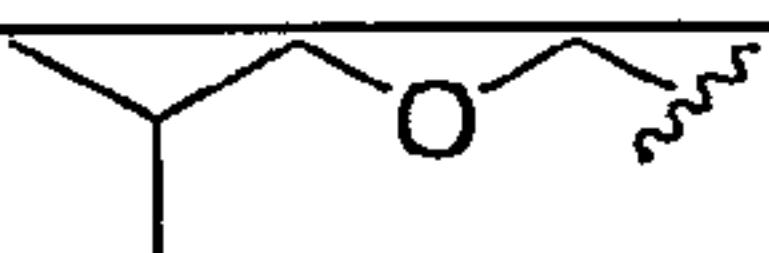
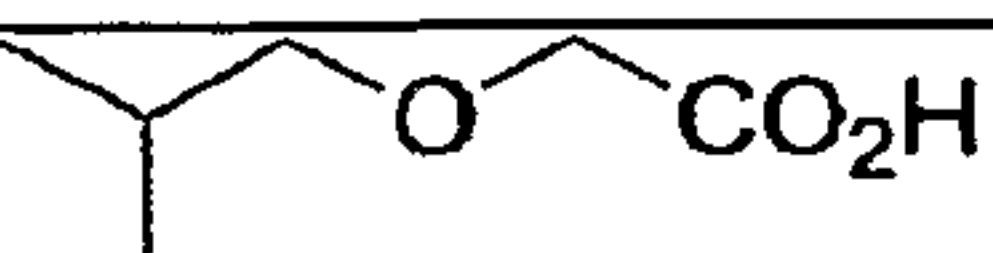
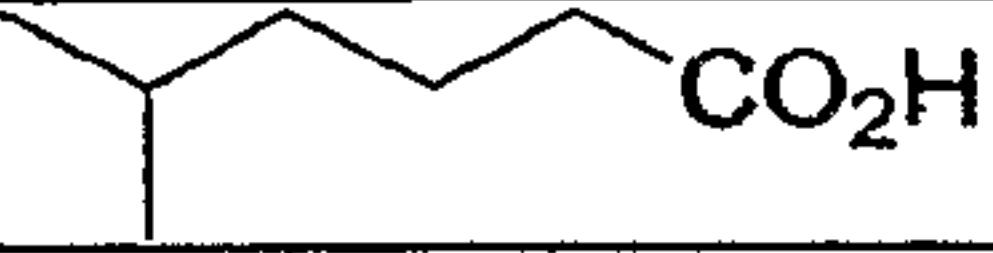
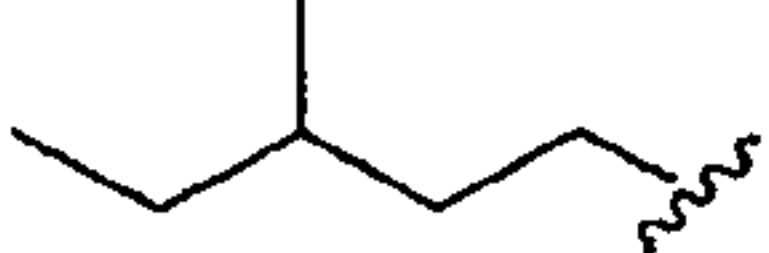
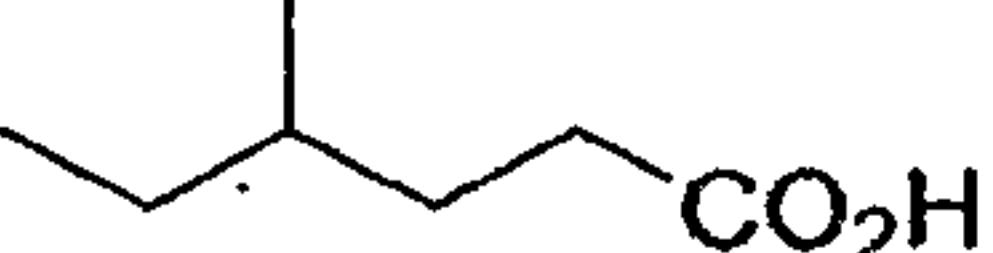
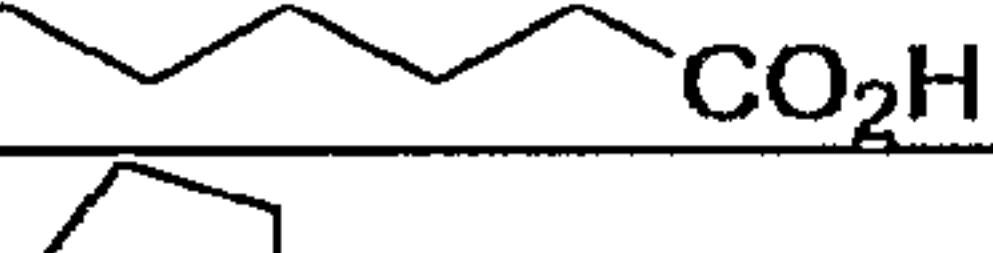
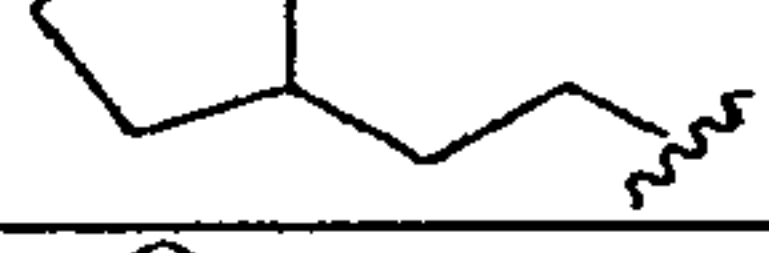
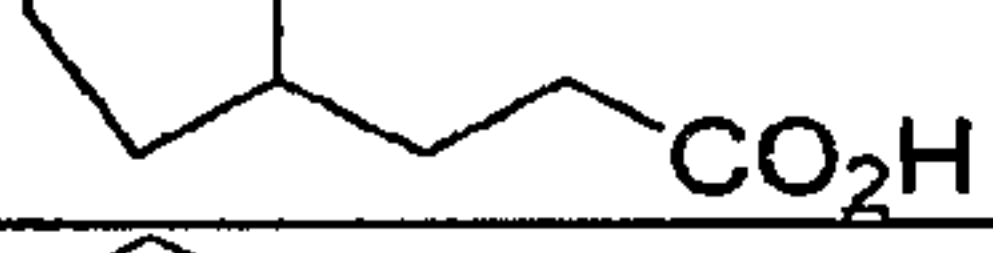
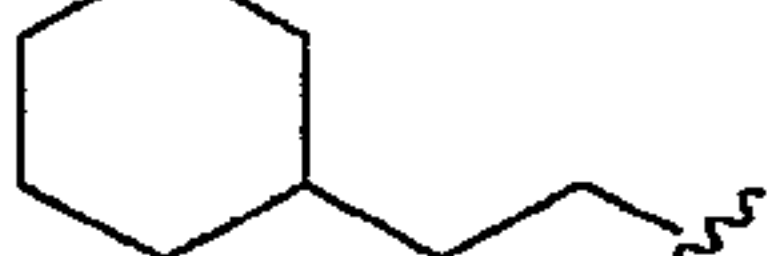
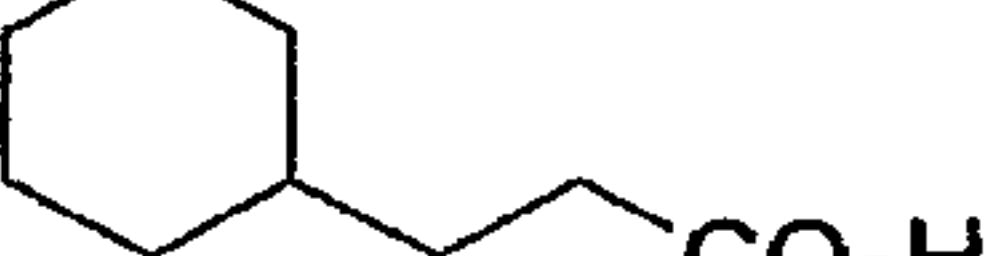
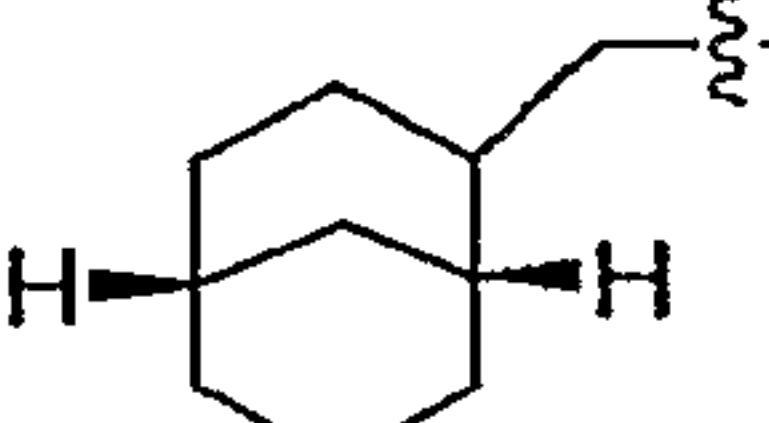
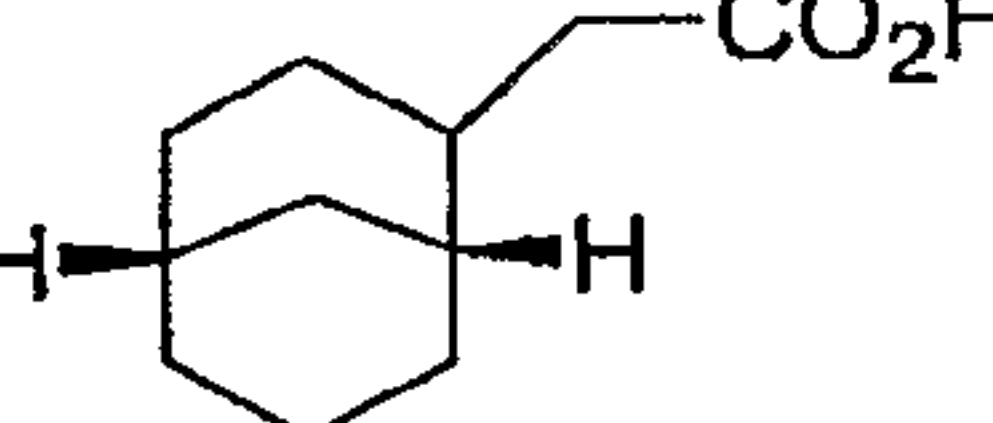


Ex.	R	Carboxylic Acid
305		
306		
307		
308		
309		
310		
311		

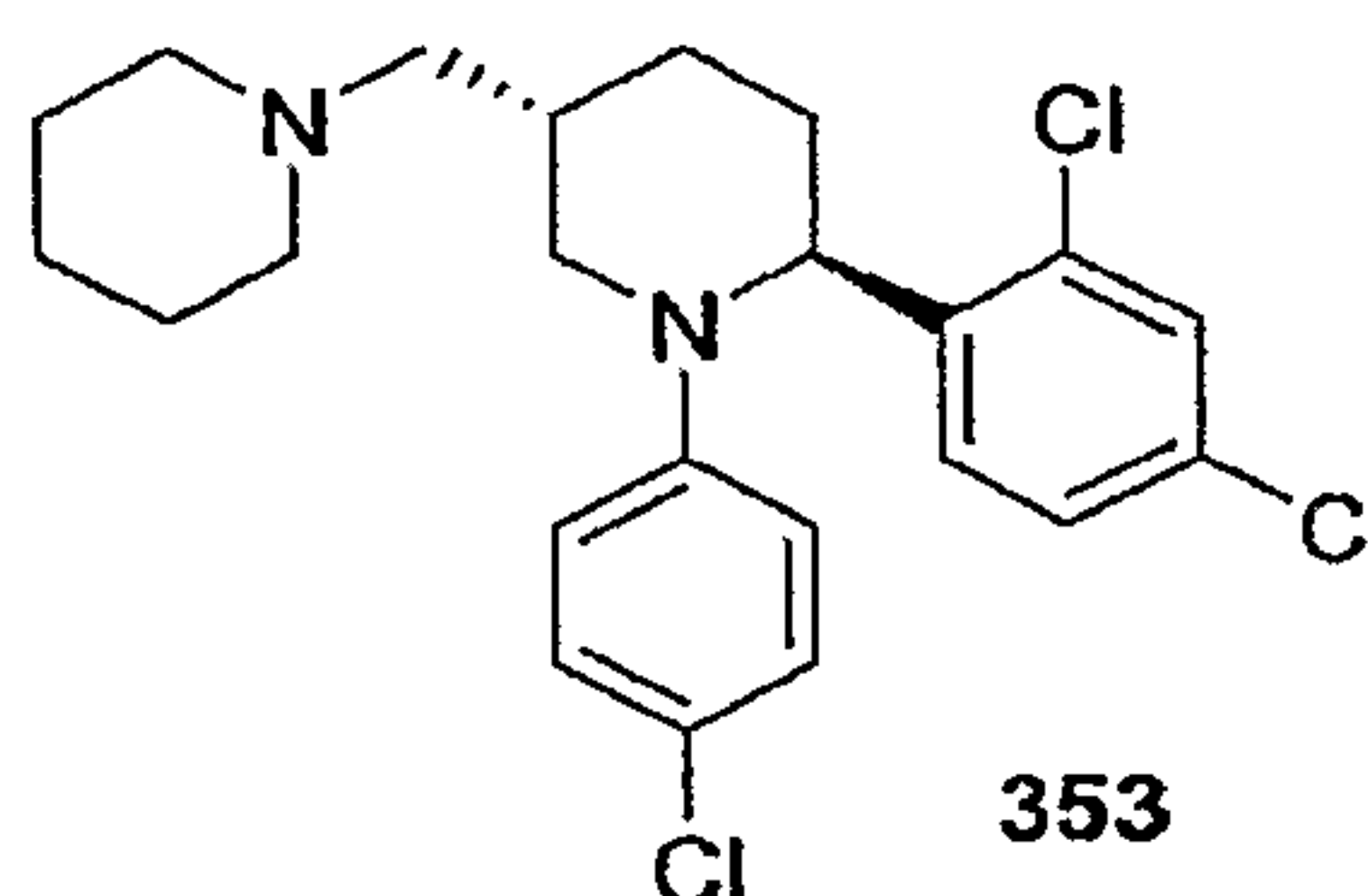
Ex.	R	Carboxylic Acid
312		
313		
314		
315		
316		
317		
318		
319		
320		
321		
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323		
324		
325		
326		
327		
328		

Ex.	R	Carboxylic Acid
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330		
331		
332		
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335		
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189

Ex.	R	Carboxylic Acid
347		
219		
348		
349		
350		
351		
352		

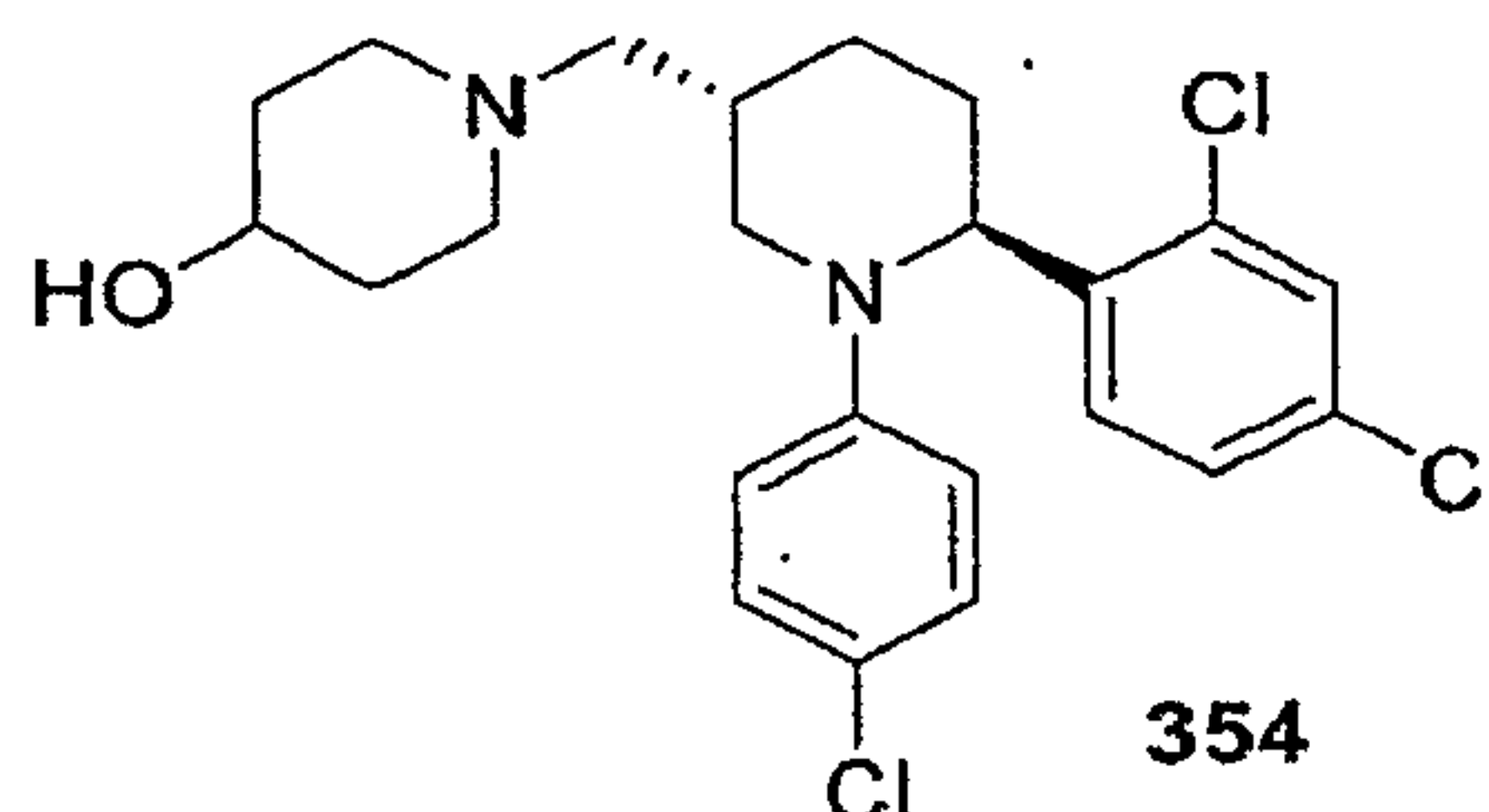
190

Preparation of Example 353

5 To a solution of **BB** (Step 1 **Example 297**) (35 mg, 0.078 mmol) in MeCN (15 mL) in a pressure tube was added piperidine (8 mg, 0.094 mmol) and $i\text{Pr}_2\text{NEt}$ (12 mg, 0.094 mmol). The tube was sealed and the solution was heated to 90°C for 16 h. The solution was concentrated. The crude product was partitioned between CH_2Cl_2 and NaHCO_3 (aq.). The aqueous layer was extracted with CH_2Cl_2 (3x). The
10 combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by preparative TLC [SiO_2 : 95:5:0.1 CH_2Cl_2 : MeOH: 7 N NH_3 (in MeOH)] to afford **Example 353**.

Preparation of Example 354

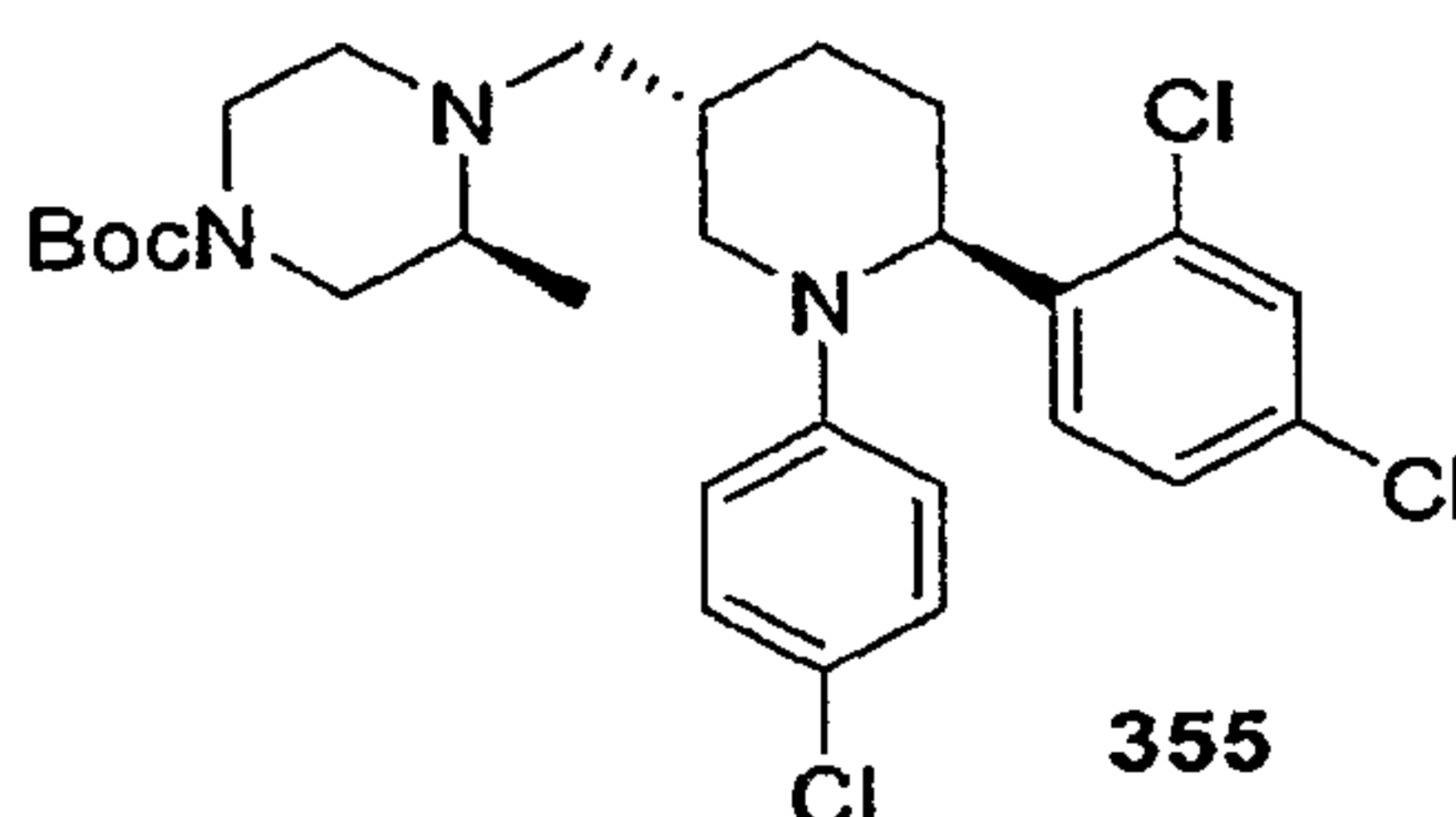
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Example 354 was prepared using a procedure similar to that described above for **Example 353**, except 4-hydroxypiperidine was used instead of piperidine.

Preparation of Example 355

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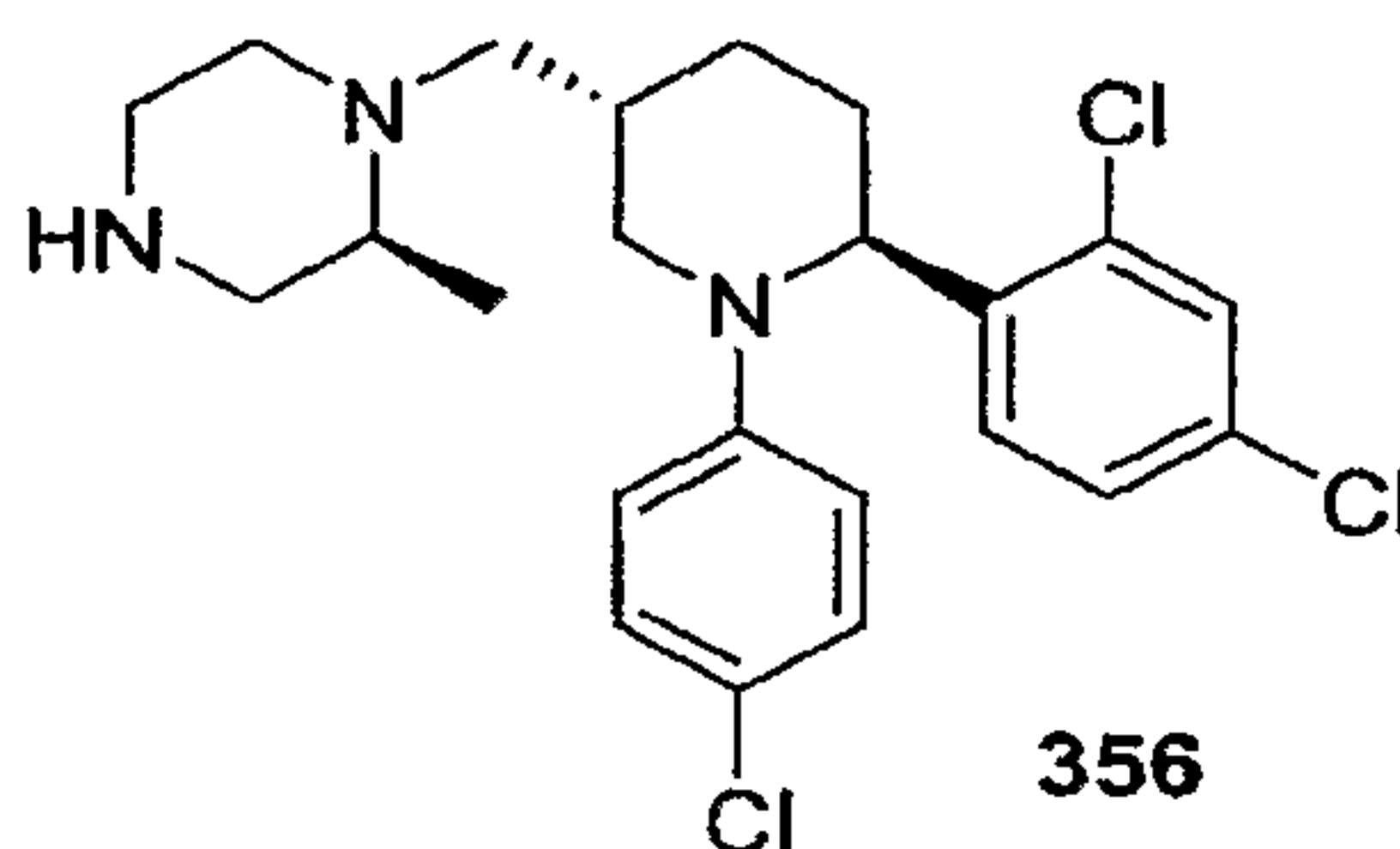


191

Example 355 was prepared using a procedure similar to that described above for **Example 297**, except 3-(S)-methyl-1N-Boc-piperazine (WO2003084942) was used instead of N-Boc-piperazine.

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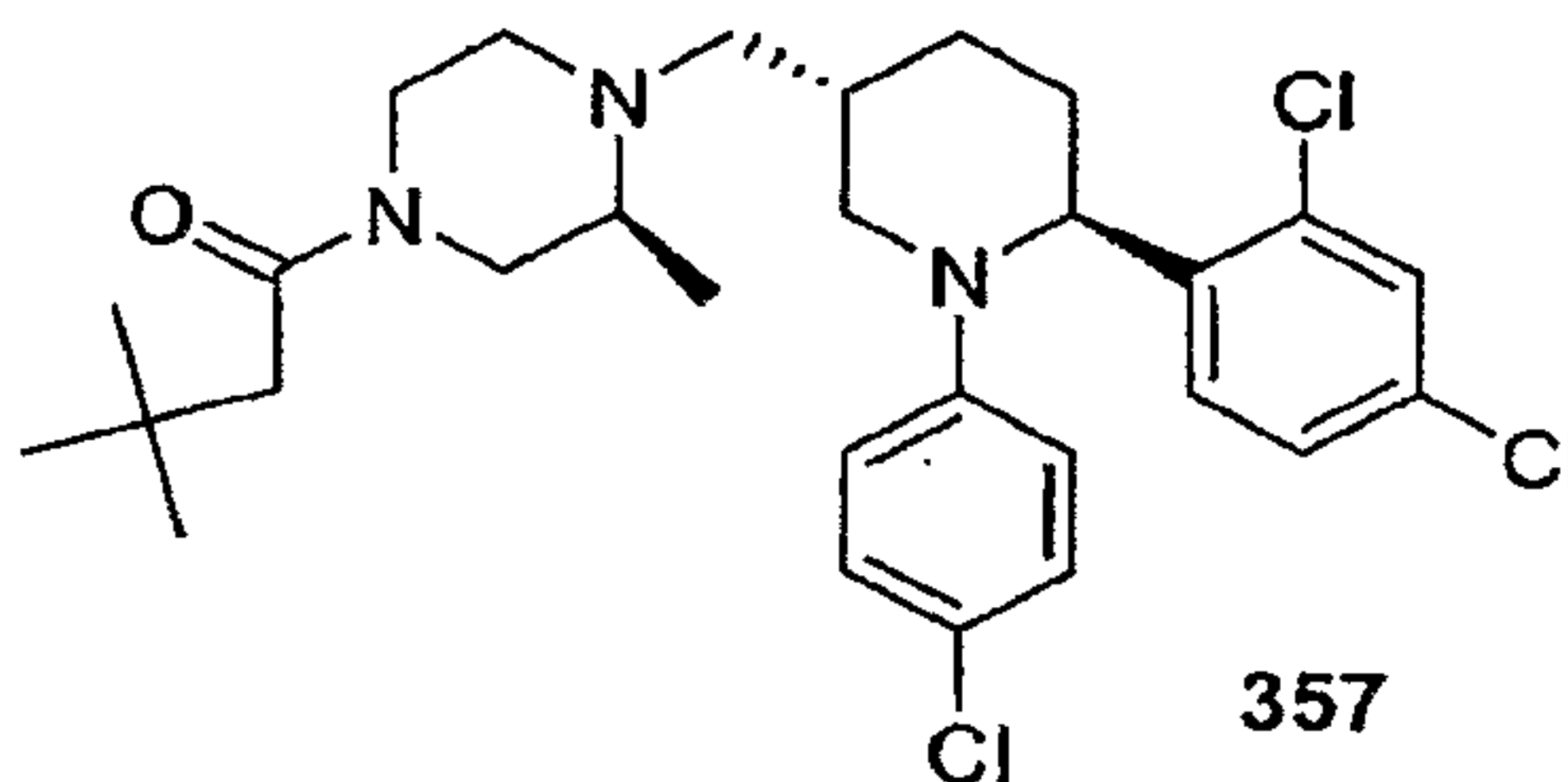
Preparation of Example 356



Example 356 was prepared using a procedure similar to that described above for **Example 298**, except **Example 355** was used instead of **Example 297**.

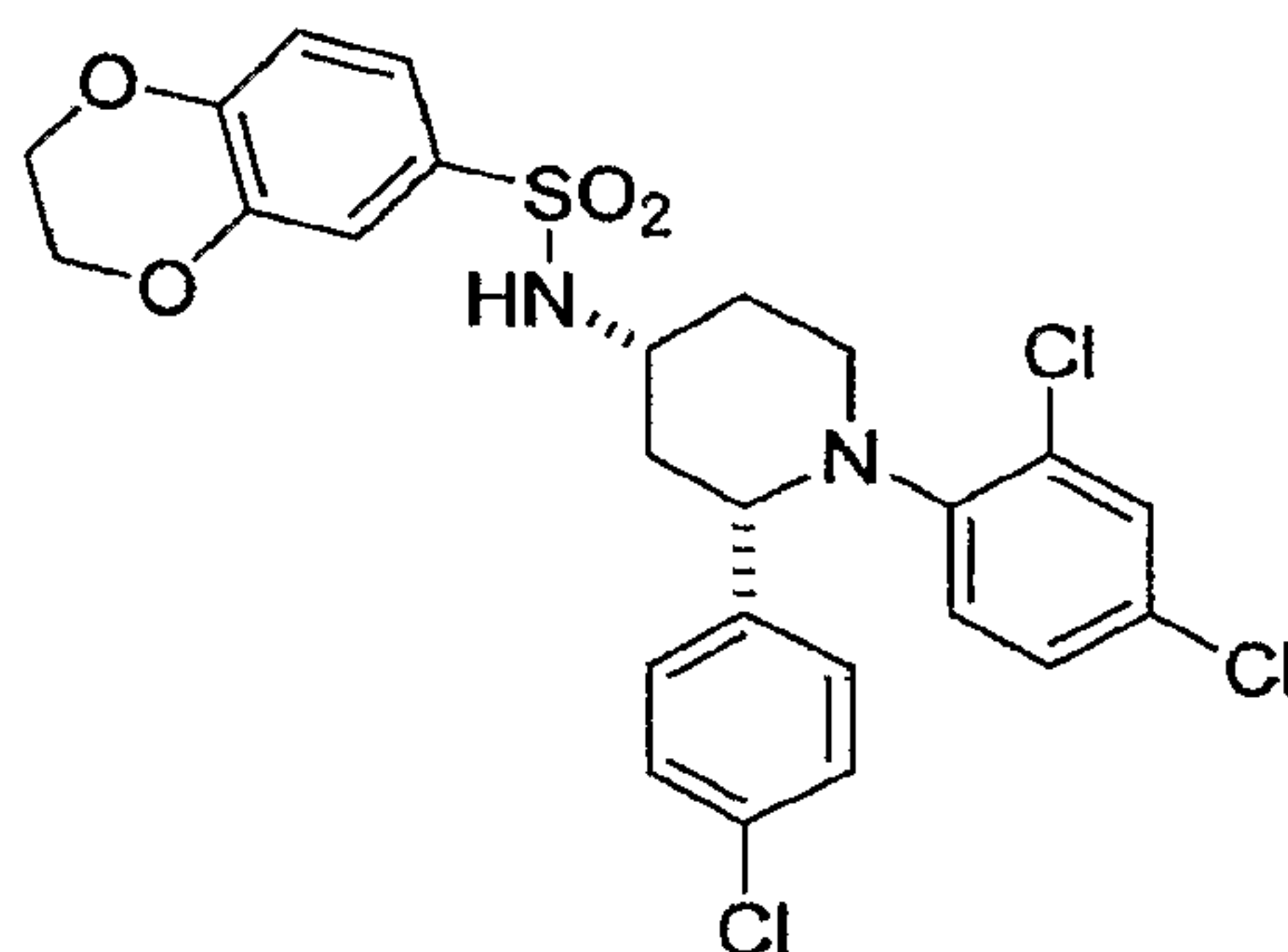
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Preparation of Example 357

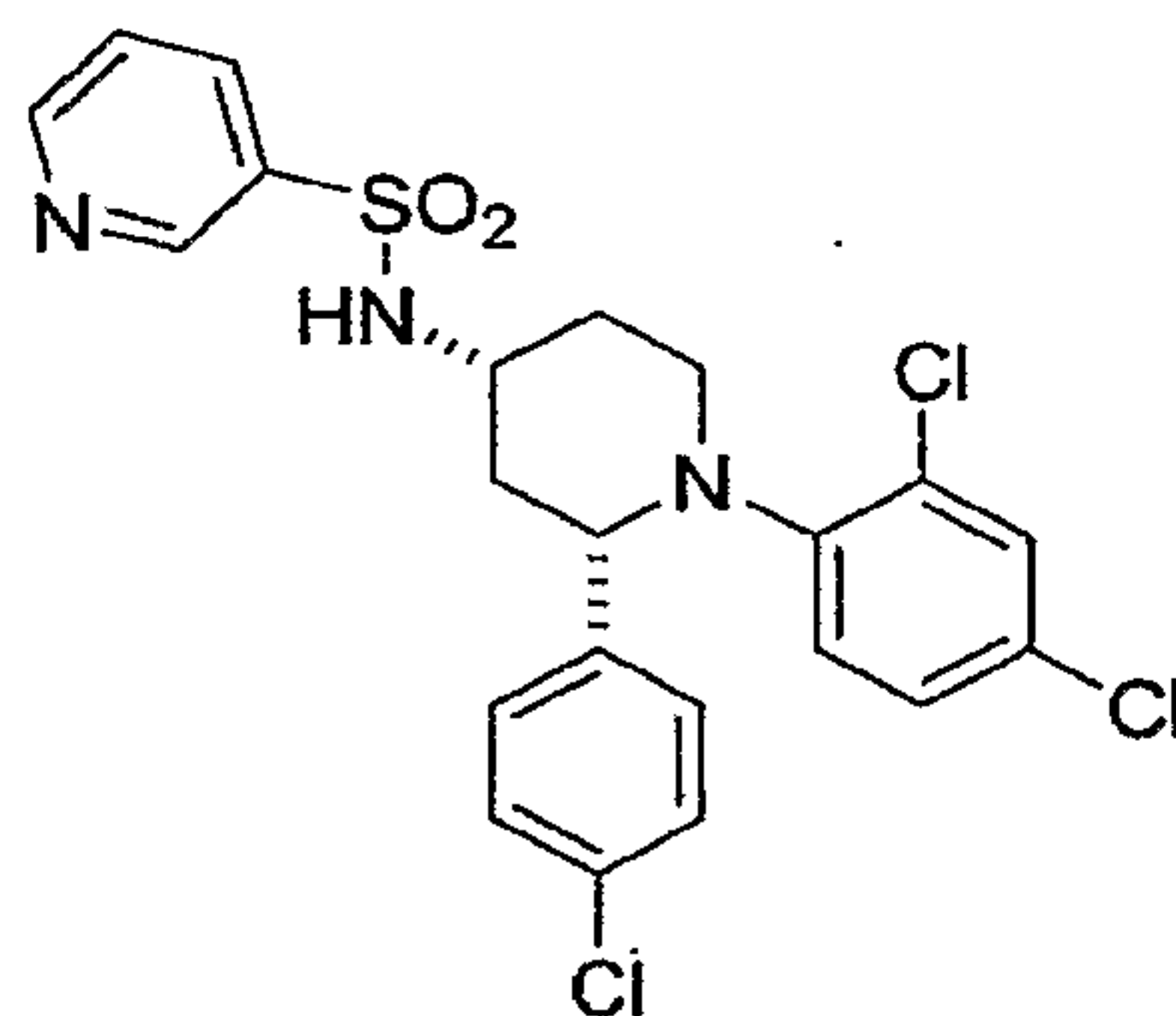


Example 357 was prepared using a procedure similar to that described above for **Example 299**, except **Example 356** was used instead of **Example 298**.

192

Preparation of Example 358**Example 358**

To a solution of **Example 131** (10 mg, 0.028 mmol) in 1,2-dichloroethane (0.1 mL) was added $i\text{Pr}_2\text{NEt}$ (35 μL) followed by 2,3-dihydro-1,4-benzodioxane-8-sulfonyl chloride (Maybridge) (22 mg). The solution was stirred at RT overnight. The solution was concentrated and the crude product was purified by preparative TLC (SiO_2 : 99:1 CH_2Cl_2 : MeOH) to afford **Example 358**.

Preparation of Example 359**Example 359**

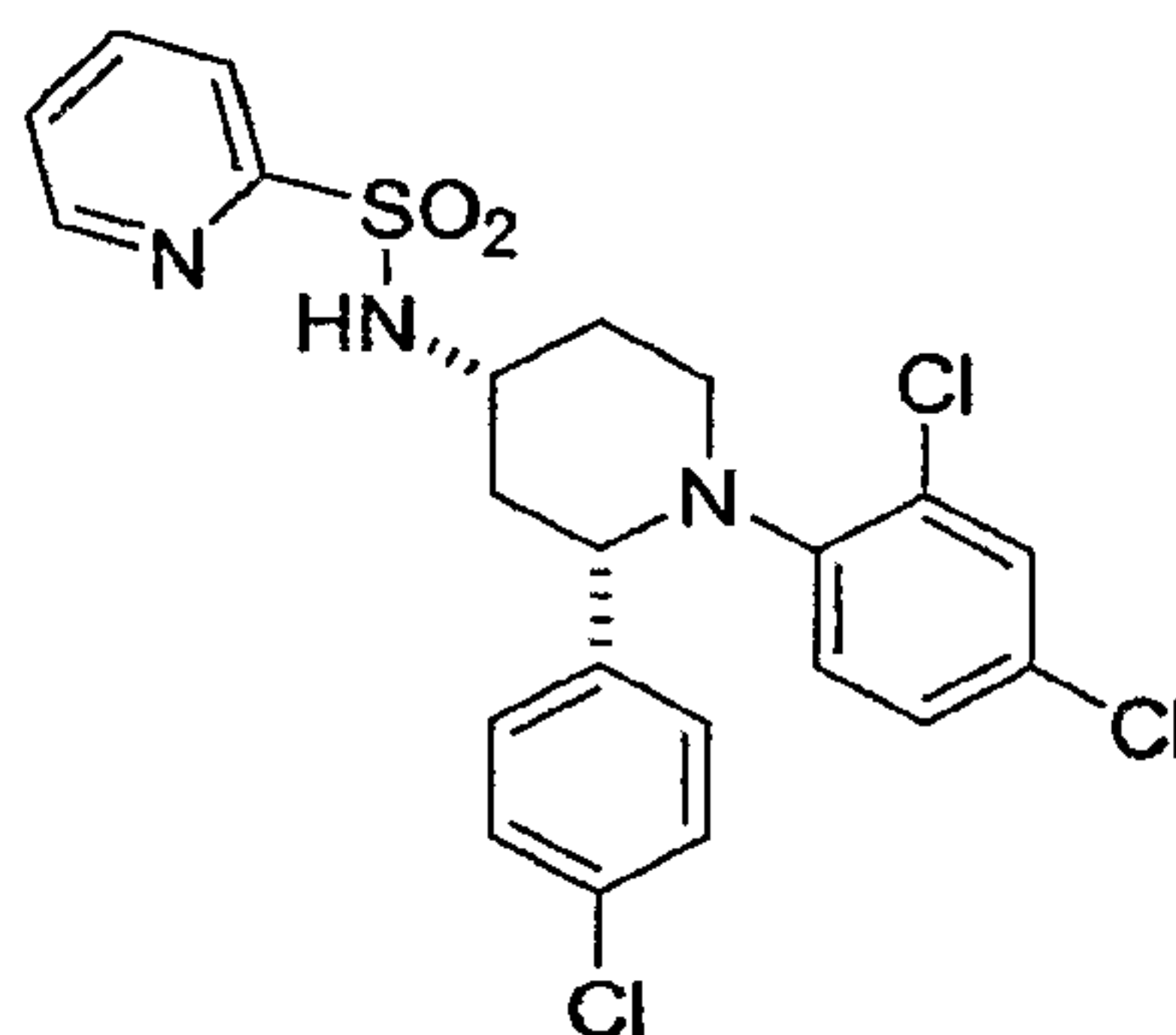
Example 359 was prepared using a procedure similar to that described above for **Example 358**, except 3-pyridyl sulfonyl chloride was used instead of 2,3-dihydro-1,4-benzodioxane-8-sulfonyl chloride.

Preparation of Example 360

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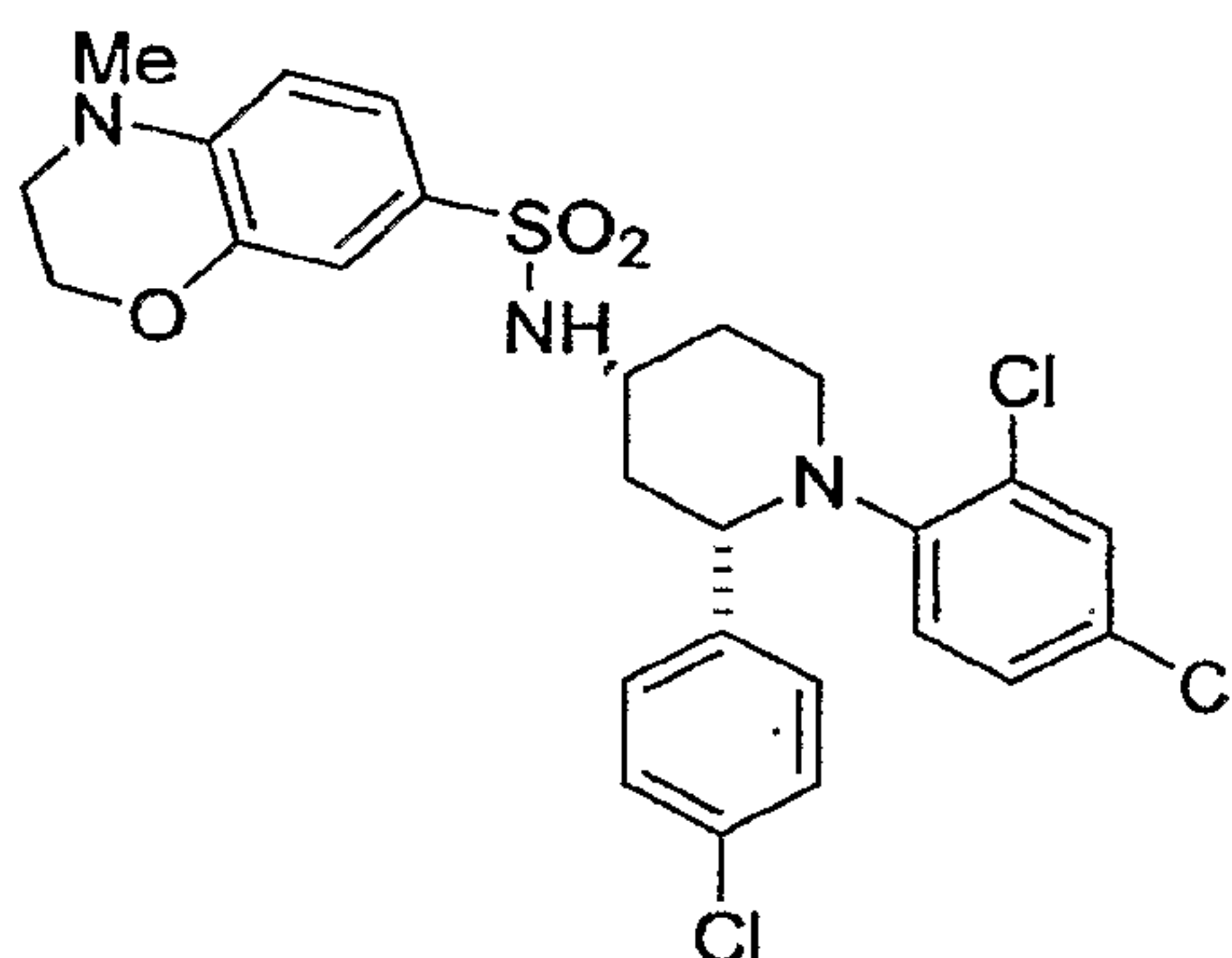
15

193

**Example 360**

Example 360 was prepared using a procedure similar to that described above for **Example 358**, except 2-pyridyl sulfonyl chloride was used instead of 2,3-dihydro-1,4-benzodioxane-8-sulfonyl chloride.

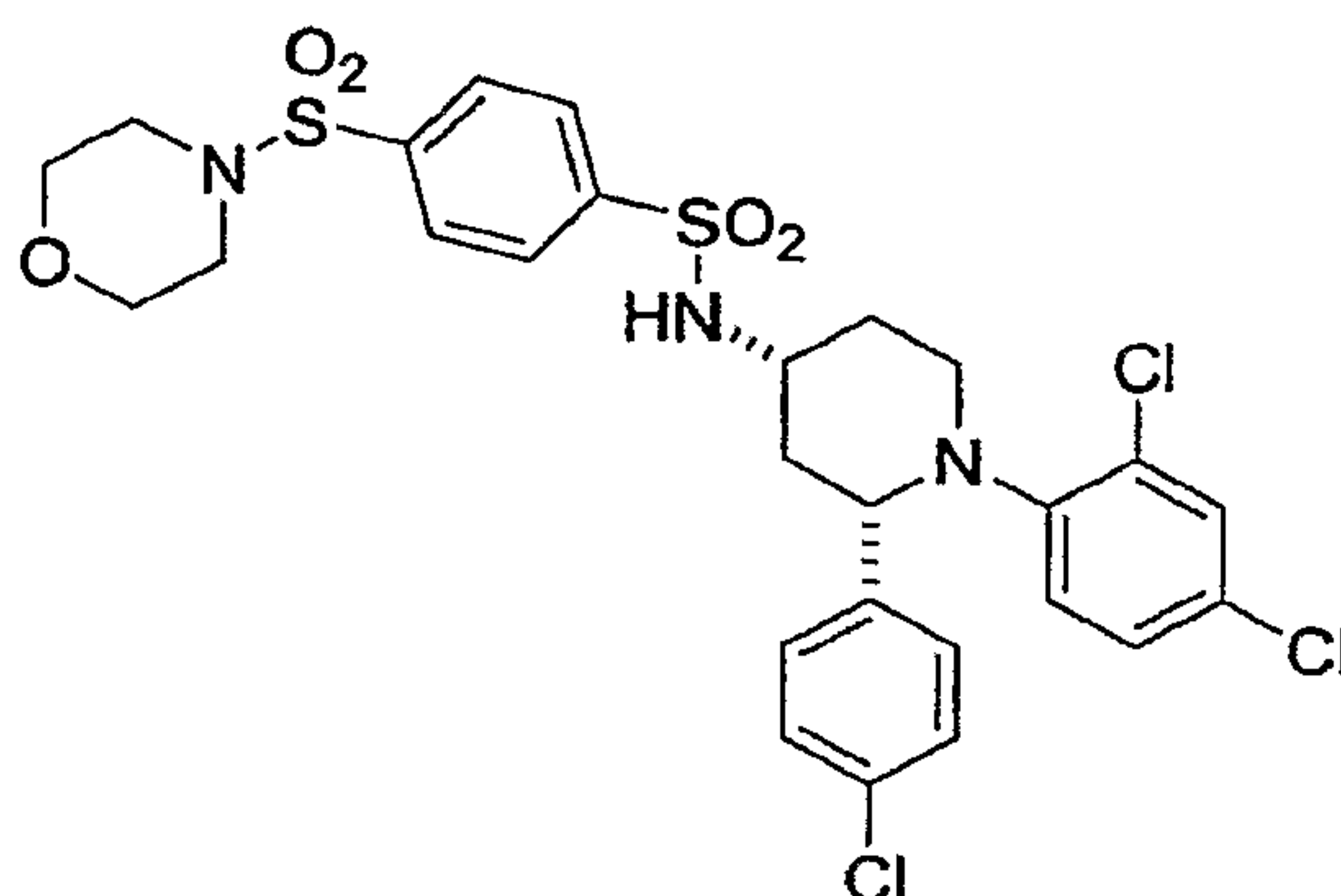
Preparation of Example 361

**Example 361**

Example 361 was prepared using a procedure similar to that described above for **Example 358**, except 4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-sulfonyl chloride (Maybridge) was used instead of 2,3-dihydro-1,4-benzodioxane-8-sulfonyl chloride.

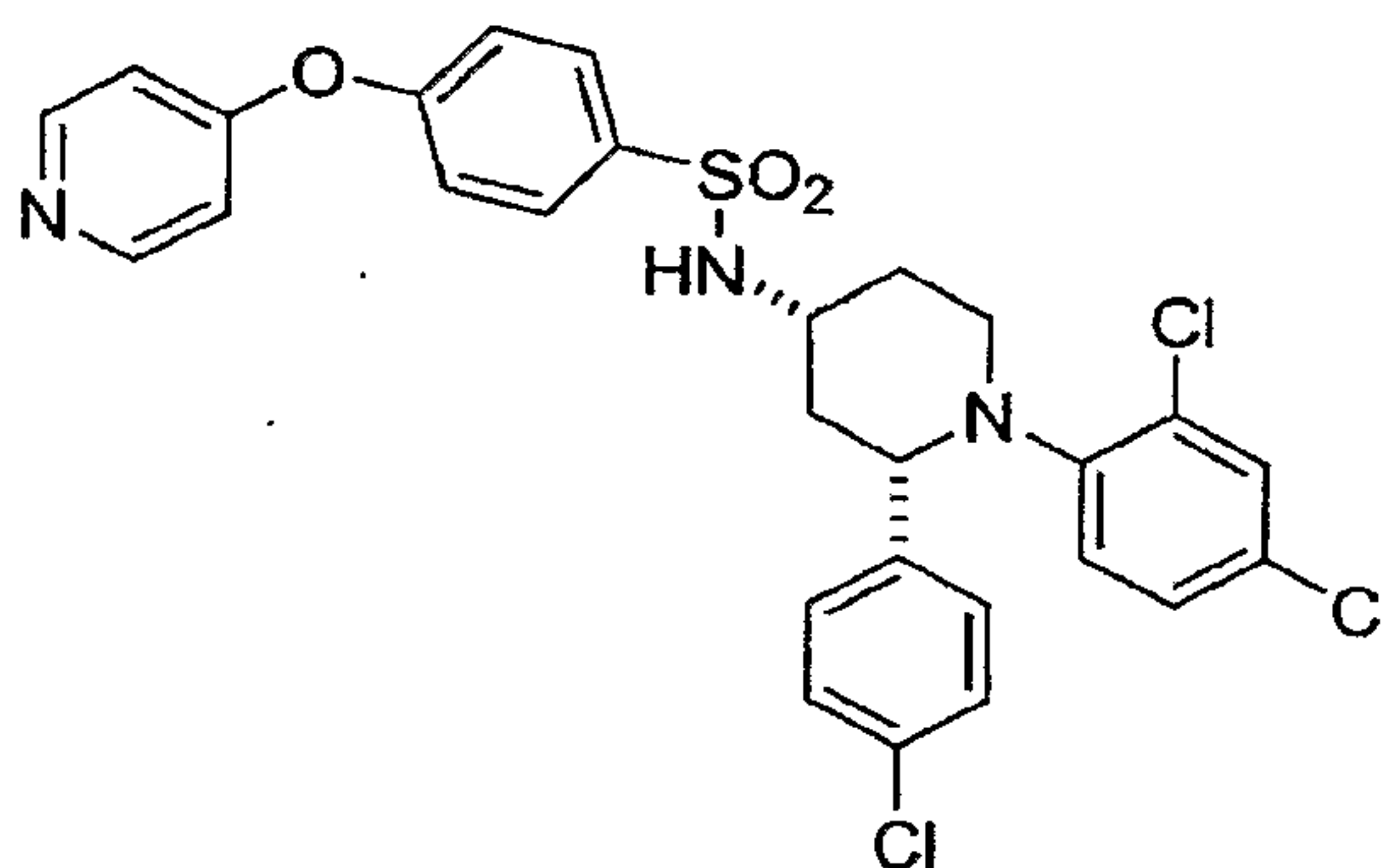
Preparation of Example 362

194

**Example 362**

Example 362 was prepared using a procedure similar to that described above for **Example 358**, except 4-(morpholine-4-sulfonyl)-benzenesulfonyl chloride (Maybridge) was used instead of 2,3-dihydro-1,4-benzodioxane-8-sulfonyl chloride.

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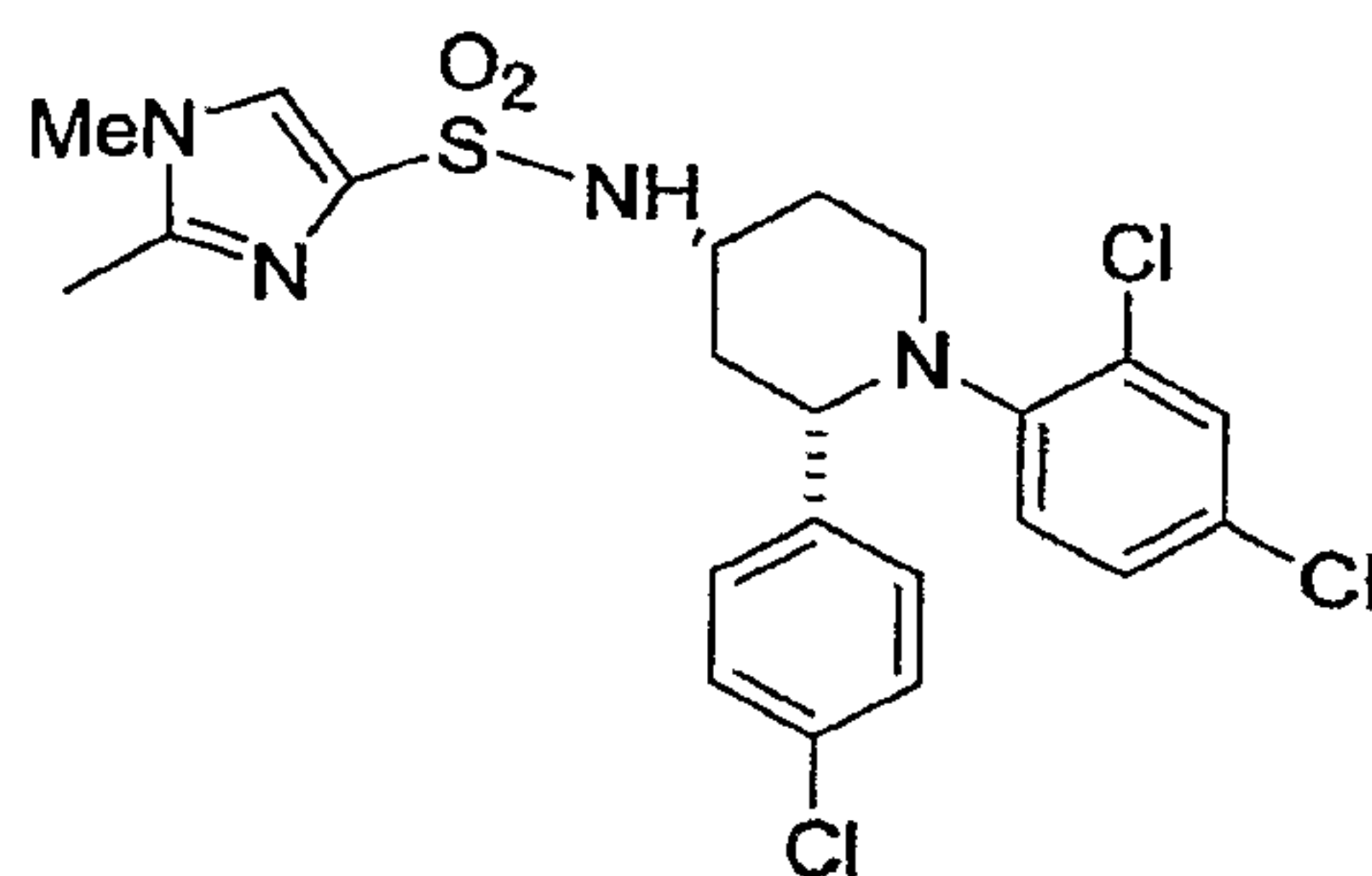
Preparation of Example 363**Example 363**

Example 363 was prepared using a procedure similar to that described above for **Example 358**, except 4-(pyridine-4-yloxy)-benzenesulfonyl chloride (Array Biopharma) was used instead of 2,3-dihydro-1,4-benzodioxane-8-sulfonyl chloride.

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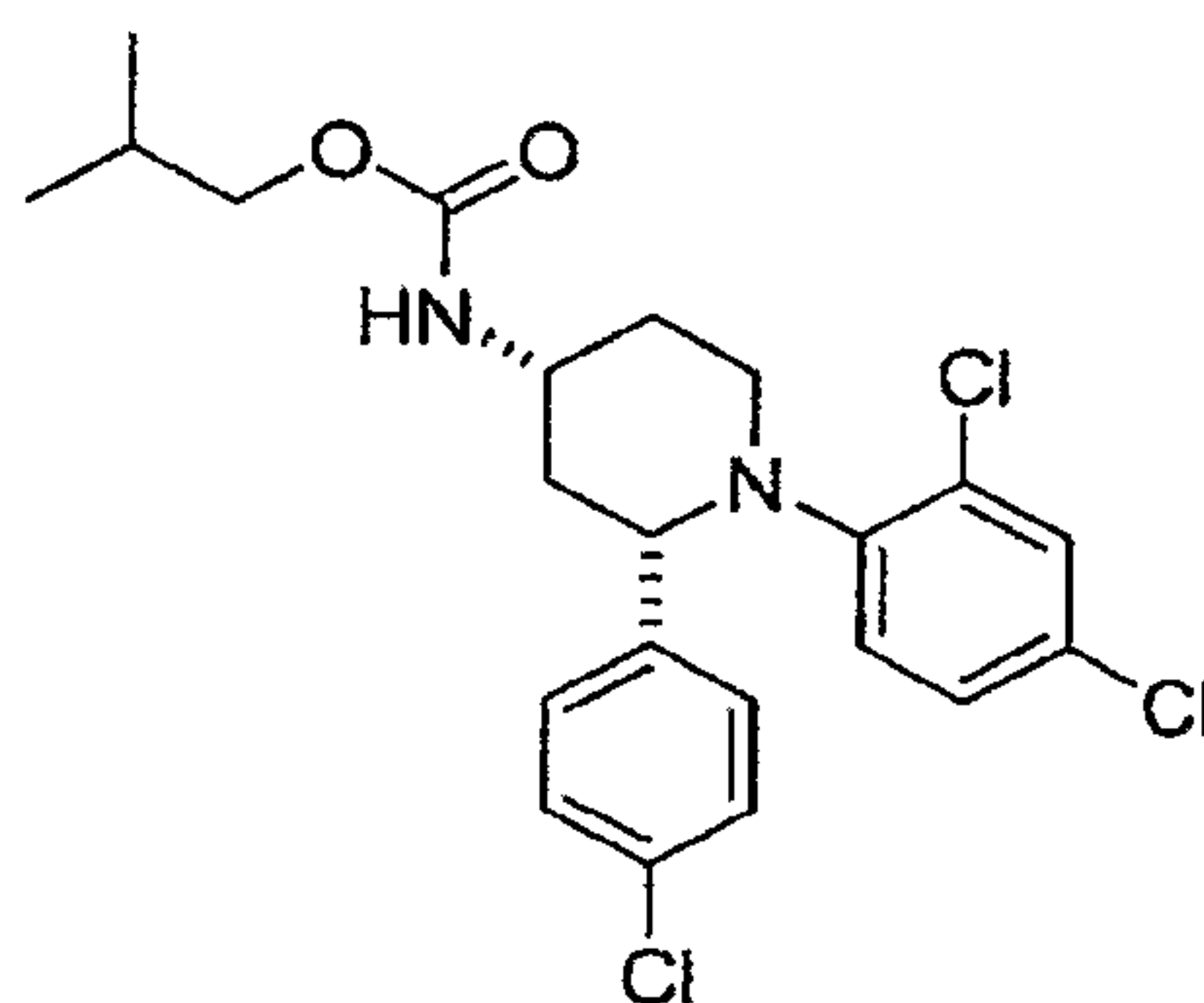
Preparation of Example 364

195

**Example 364**

Example 364 was prepared using a procedure similar to that described above for **Example 358**, except 1,2-Dimethyl-1H-imidazole-4-sulfonyl chloride (Maybridge) was used instead of 2,3-dihydro-1,4-benzodioxane-8-sulfonyl chloride.

Preparation of Example 365

**Example 365**

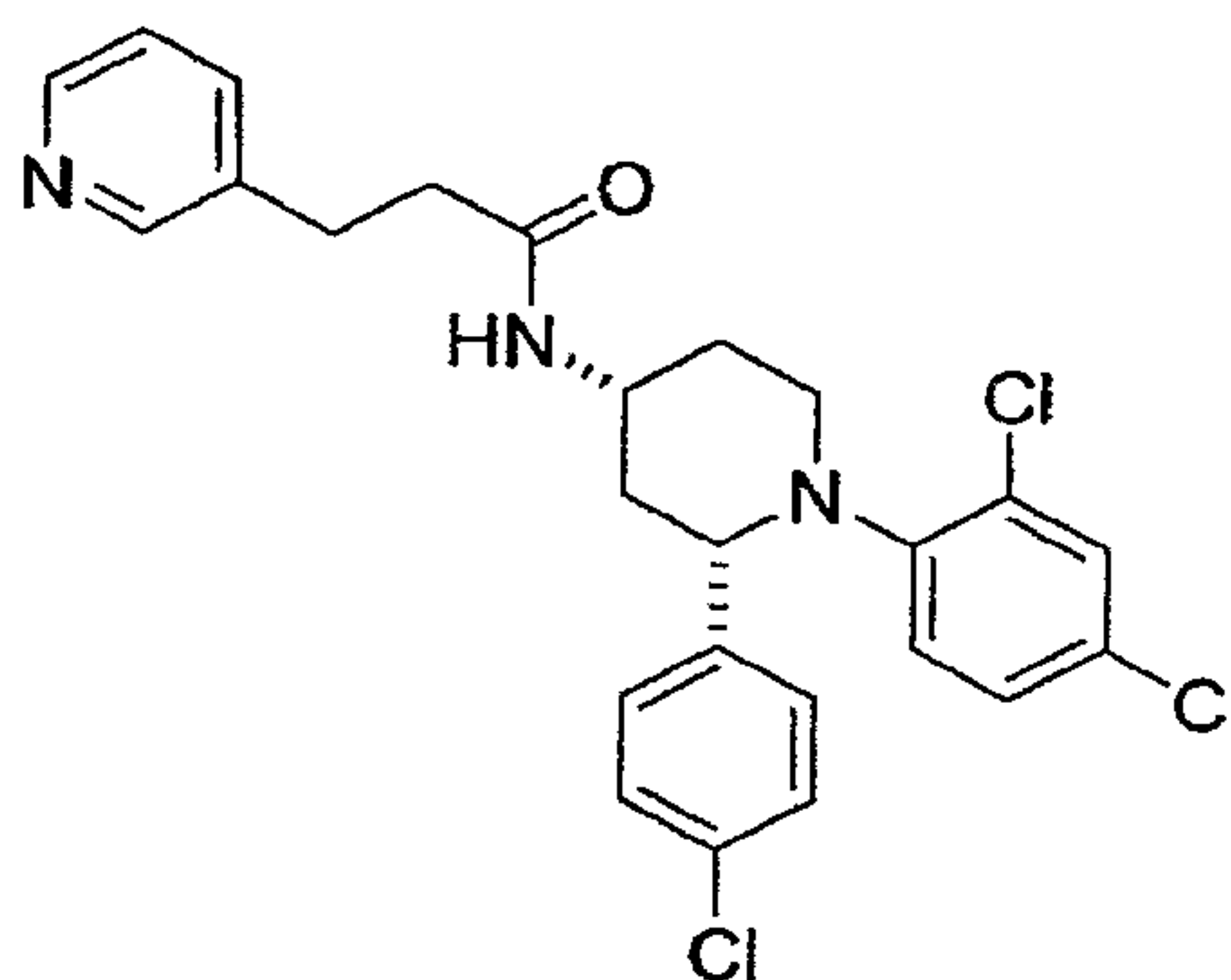
196

To a solution of **Example 131** (5 mg, 0.014 mmol) in 1,2 dichloroethane (0.1 mL) at 4°C was added Et₃N (5.7 mg, 0.056 mmol) followed by isobutyl chloroformate (3.8 mg, 0.028 mmol). The solution was stirred and allowed to slowly warm to RT overnight. The solution was diluted with CH₂Cl₂ and washed with NaHCO₃ (aq.).

5 The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by preparative TLC (SiO₂: 1:1 Et₂O: hexanes) to afford 3.8 mg **Example 365**.

Preparation of Example 366

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Example 366

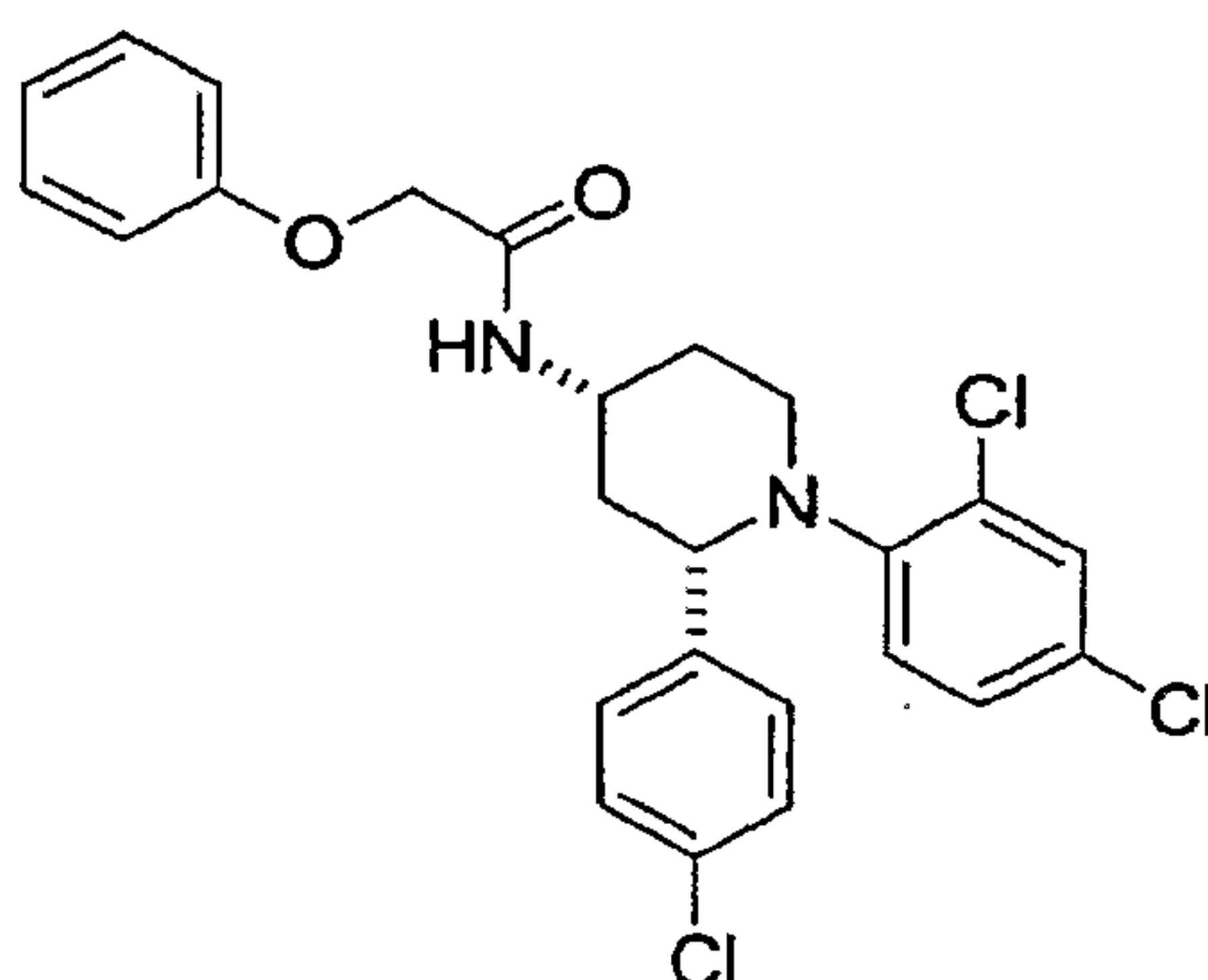
To a solution of **Example 131** (5mg, 0.014 mmol) in DMF (0.075 mL) was added N-methylmorpholine (3.6 mg, 0.035 mmol), HOBt (2.9 mg, 0.021 mmol), 3(3-pyridyl)propionic acid (4.3 mg, 0.028 mmol) followed by dicyclohexylcarbodiimide

15 (8.0 mg, 0.042 mmol). The reaction mixture was stirred at RT overnight. The solution was concentrated and placed under vacuum for 3 days. The crude material was dissolved in CH₂Cl₂ and washed with NaHCO₃ (aq.) (2x). The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by preparative TLC (SiO₂: 80:1 CH₂Cl₂: MeOH) to afford 5.5 mg **Example 366**.

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Preparation of Example 367

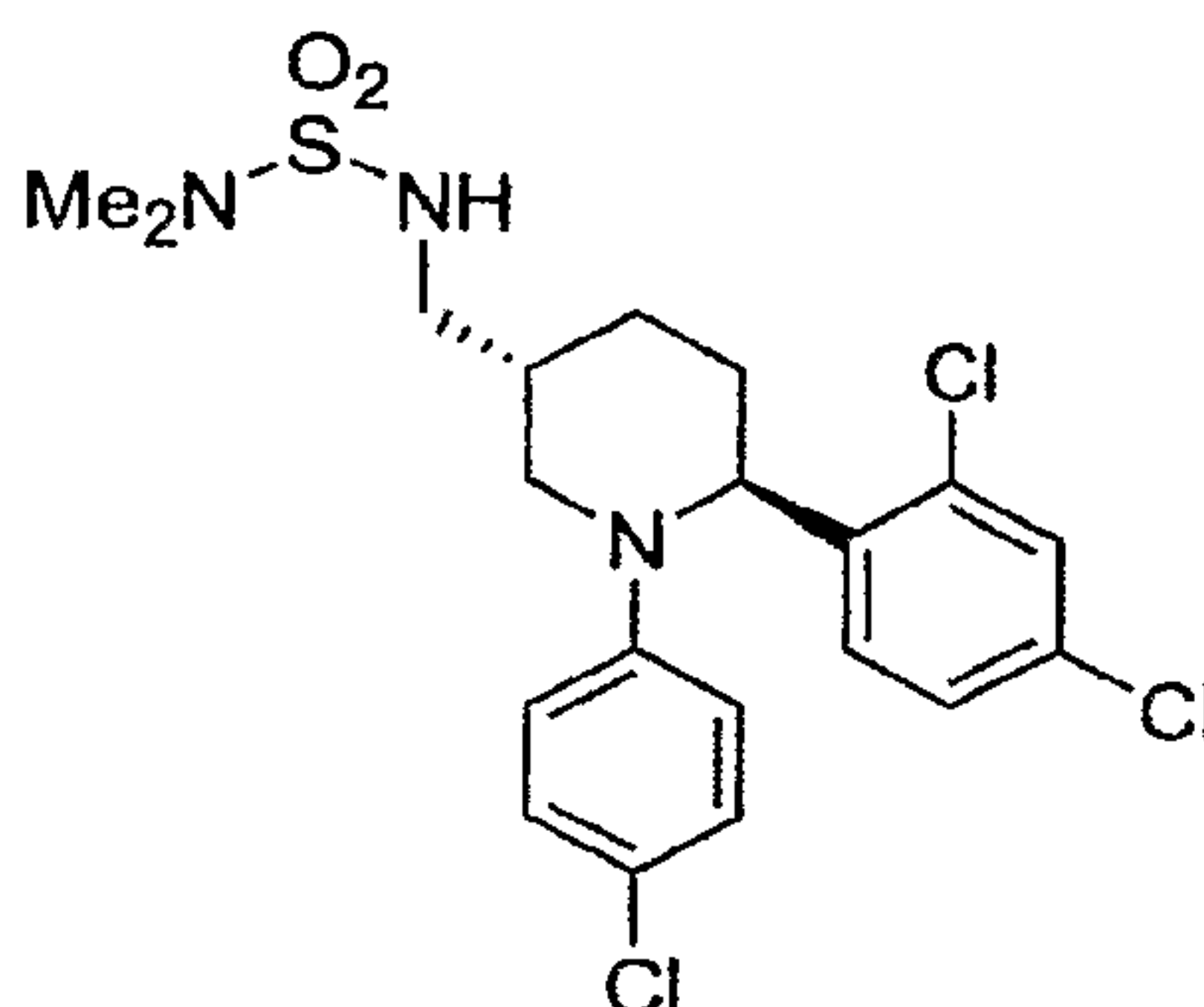
197

**Example 367**

Example 367 was prepared using a procedure similar to that described above for **Example 366**, except phenoxyacetic acid was used instead of 3(3-pyridyl)propionic acid.

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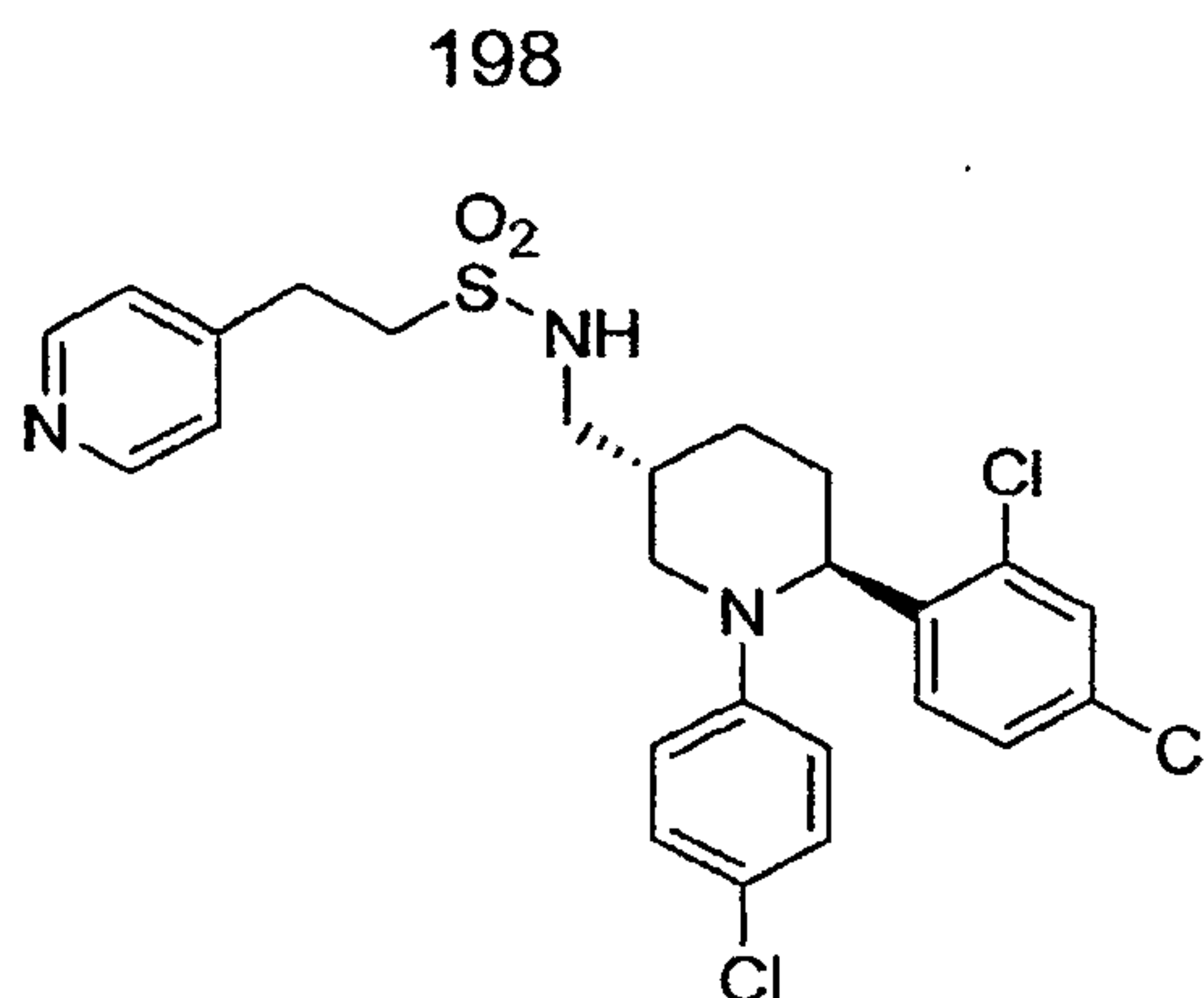
Preparation of Example 368

**Example 368**

To a solution of **Example 85** (26 mg, 0.070 mmol) in CH_2Cl_2 (1 mL) was added $i\text{Pr}_2\text{NEt}$ (11 mg, 0.084 mmol) and N,N -dimethylamino-sulfonyl chloride (12 mg, 0.084 mmol). The solution was stirred at RT for 3 days. The solution was diluted with NaHCO_3 (aq.). The aqueous layer was back extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by preparative TLC (SiO_2 : 2:1 hexanes: EtOAc) to afford 20 mg **Example 368**.

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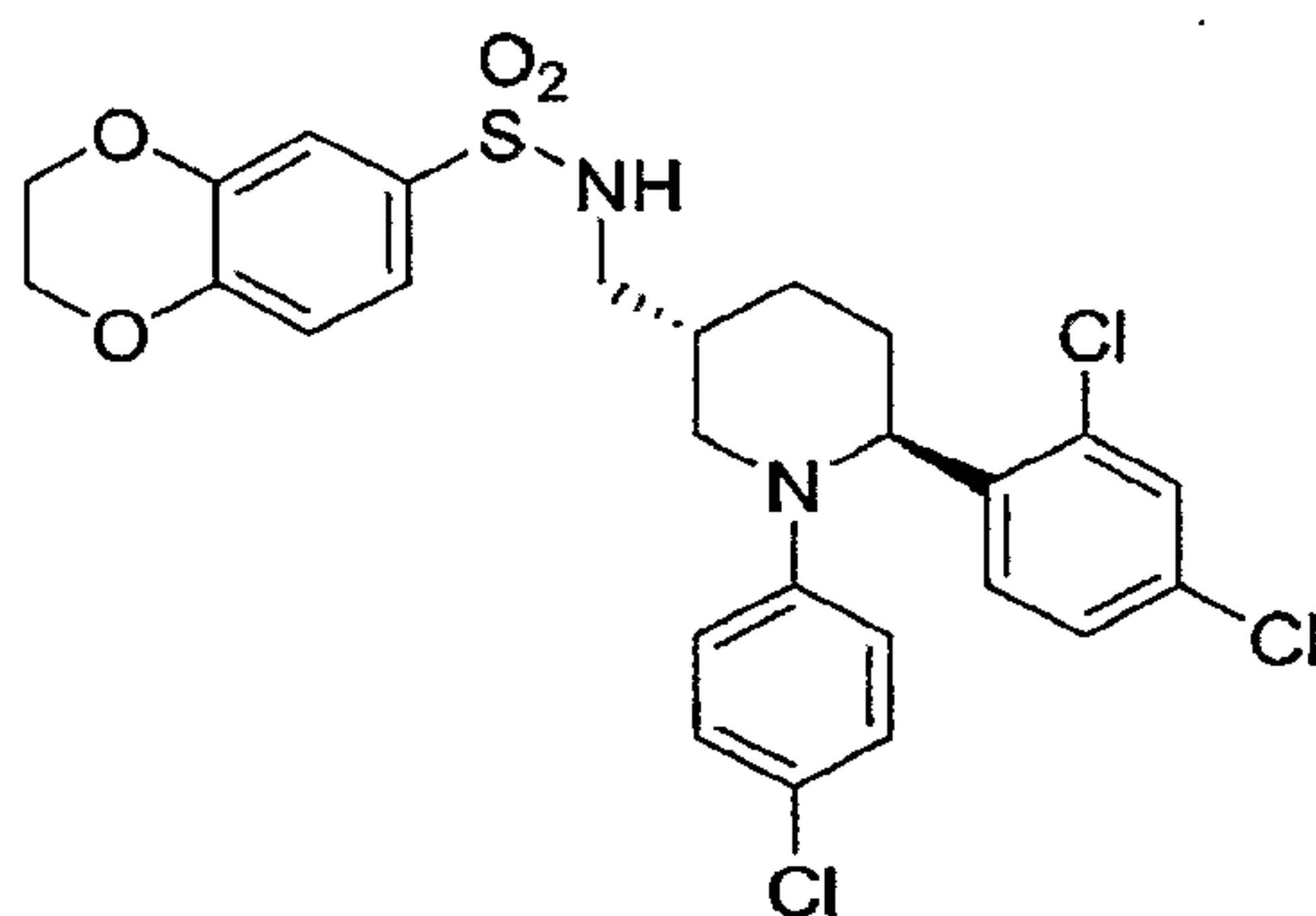
Preparation of Example 369



Example 369

Example 369 was prepared using a procedure similar to that described above for **Example 253**, except 4-pyridylethanesulfonyl chloride hydrochloride (Chemical Synthesis Services: Graigavon, Northern Ireland) was used instead of 4-methyl-3,4-dihydro-2H-1,4-benzoxazine-7-sulfonyl chloride.

Preparation of Example 370

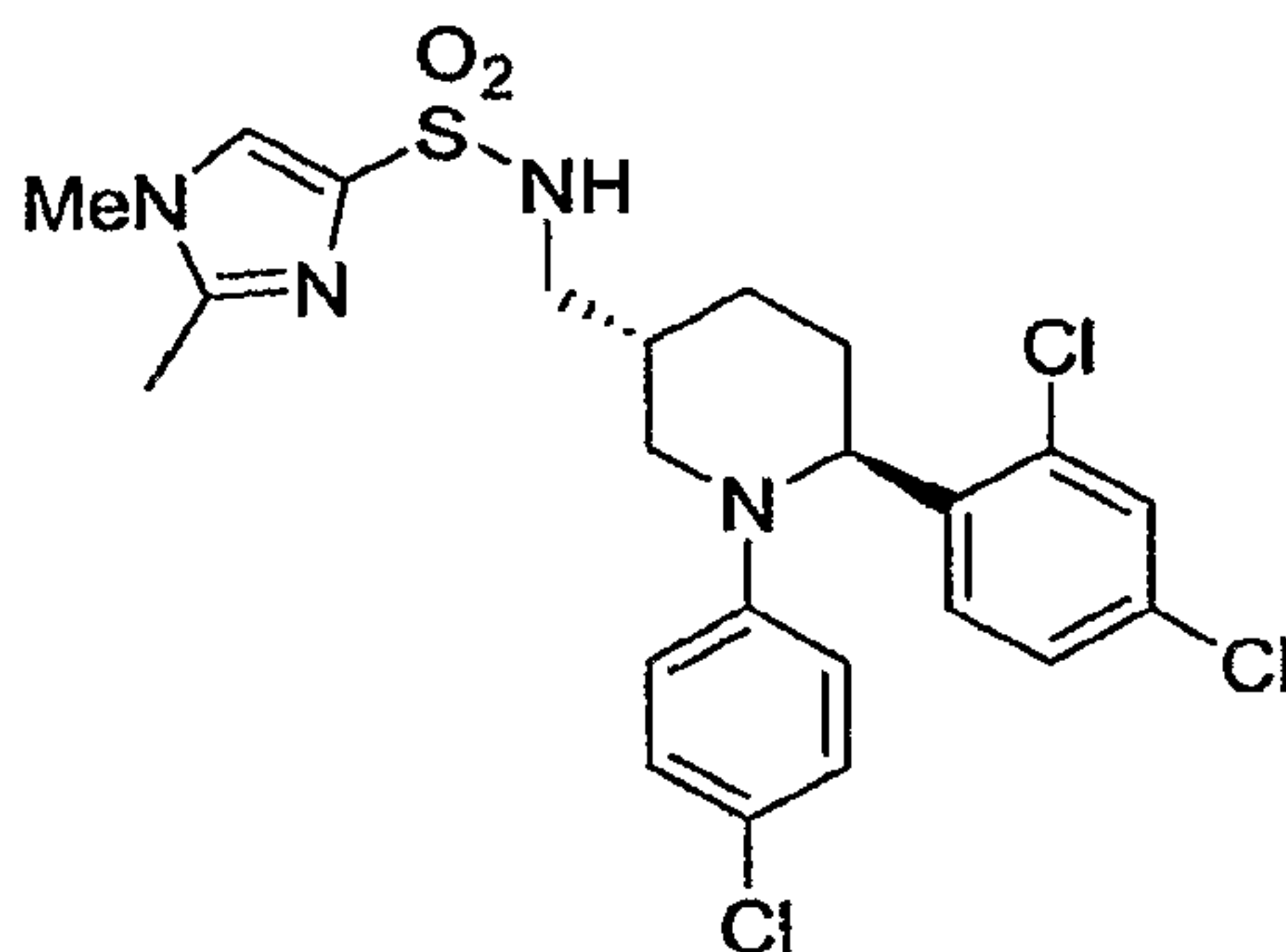


Example 370

Example 370 was prepared using a procedure similar to that described above for **Example 253**, except 2,3-Dihydro-benzo[1,4]dioxine-6-sulfonyl chloride was used instead of 4-methyl-3,4-dihydro-2H-1,4-benzoxazine-7-sulfonyl chloride.

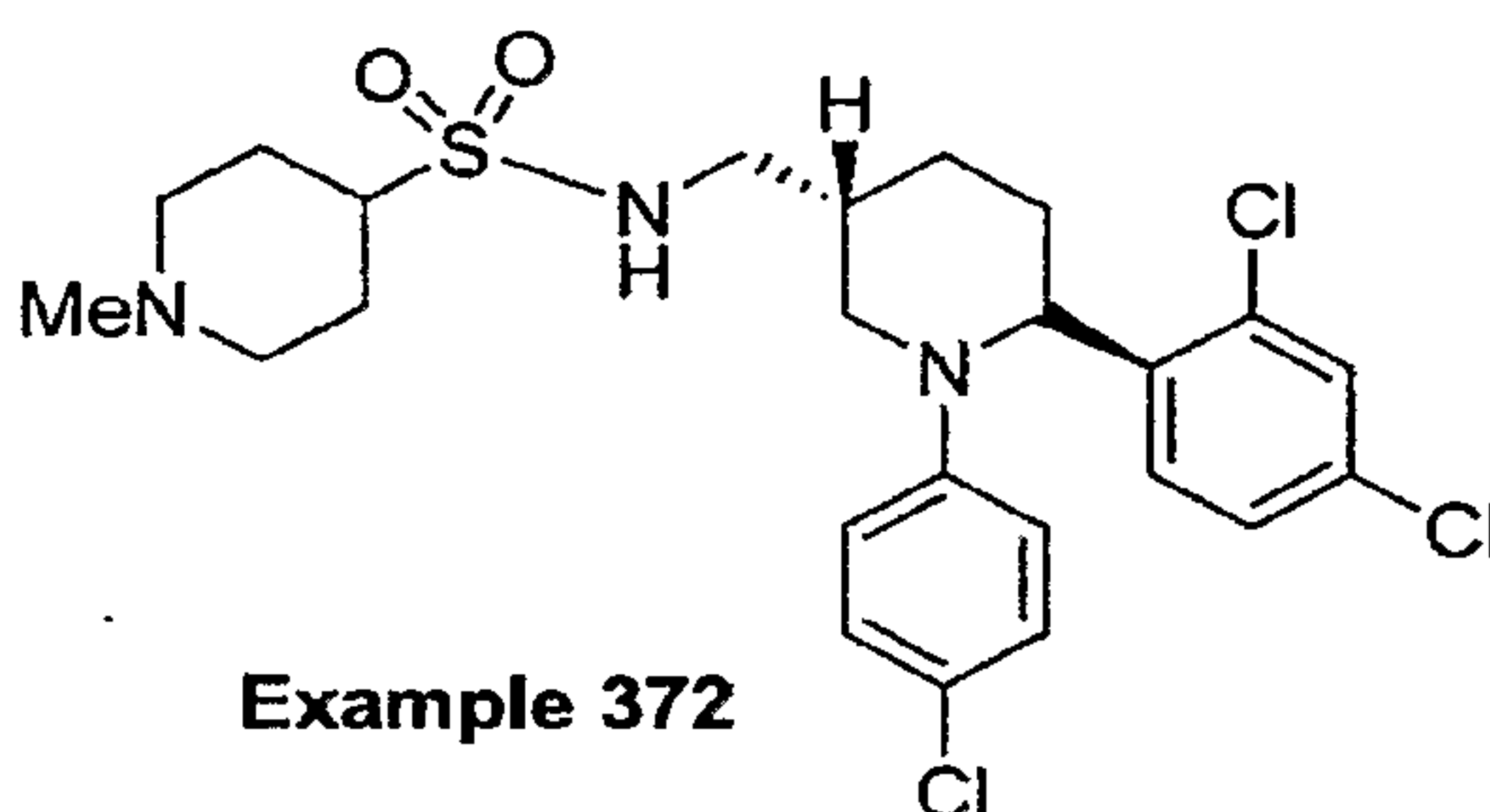
Preparation of Example 371

199

**Example 371**

Example 371 was prepared using a procedure similar to that described above for **Example 253**, except 1,2-Dimethyl-1H-imidazole-4-sulfonyl chloride was used instead of 4-methyl-3,4-dihydro-2H-1,4-benzoxazine-7-sulfonyl chloride.

5

Preparation of Example 372**Example 372**

To a solution of **Example 256** (50 mg, 0.10 mmol) in formic acid was added formalin (150 μ L). The solution was heated to 98°C for 2 h. The solution was basified with sat Na_2CO_3 (aq.). Water was added and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by flash chromatography (SiO_2 : 95:7:0.5 CH_2Cl_2 : MeOH: ammonium hydroxide) to afford **Example 372**.

15 **ASSAY**

Method for evaluating Cannabinoid CB_1 and CB_2 affinity

Competition binding assays for cannabinoid CB_1 and CB_2 affinity were performed by incubating commercially purchased membranes prepared from cells expressing each receptor subtype (8 μ g pro) with 0.5 nM ^3H -CP55,940, a non-selective cannabinoid agonist, along with concentrations of drug ranging from 0.0001-3 μ M in Buffer A (5 mM MgCl_2 , 2.5 mM EDTA and 0.13% BSA). Non-specific

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200

binding was defined in the presence of 10 μ M CP55,940. For saturation studies, concentrations of ^{3} H-CP55,940 ranging from 0.1-5 nM were incubated with membranes in the presence and absence of 10 μ M CP55,940. Assays were terminated after incubation for 1 ½ hours by rapid filtration onto 0.3 %

5 polyethylenamine treated GF/C filterplates using a BRANDEL cell harvester. The plates were dried and MICROSCINT scintillation cocktail was added, after which the bound radioactivity was quantified using a TOPCOUNT scintillation counter.

The dissociation constant (K_d) of ^{3} H-CP55,940 at the CB₁ and CB₂ receptor were determined by plotting specific binding at each concentration of radioligand, and analysis by non-linear regression. For competition studies, the concentration of each drug that inhibited 50 percent of ^{3} H-CP55,940 binding (IC_{50}) was determined by non-linear regression analysis of the radioligand displacement curves. Affinity constants (K_i) were calculated using the equation derived by Cheng and Prusoff (1973), defined as: $IC_{50}/1+[conc. ligand / K_d]$.

15 GTPyS Binding Protocol

The functional efficacy of compounds to activate second messengers within the cell was determined utilizing the GTPyS binding assay. Guanine nucleotides are phosphorylated within the plasma membrane of the cell following binding and activation by agonists. A radiolabelled derivative of guanine triphosphate (GTP) is utilized in this assay as it cannot be dephosphorylated and therefore accumulates following agonist binding. The simultaneous presence of an antagonist into this system will shift the agonist concentration curve to the right, with increasing concentrations of antagonist producing a greater rightward shift in the dose-response curve of the agonist.

25 Commercially purchased membranes were incubated with 10 mM GDP to allow sufficient substrate for phosphorylation in the presence of agonist. The membranes were then pre-incubated with increasing concentrations of test compound for 30 minutes to determine if they were capable of stimulating phosphorylation alone. Increasing concentrations of the non-selective cannabinoid agonist WIN55,122 were then added in the presence or absence of each concentration of test compound. The assay was then incubated for 1 hour at room temperature. To complete the assay, ^{35} S-GTPyS was added and the assay incubated for another 30 minutes.

Assays were terminated by rapid filtration onto 10 mM sodium phosphate-treated GF/C filterplates using a BRANDEL cell harvester. The plates were dried and Microscint scintillation cocktail was added, after which the bound radioactivity was quantified using a TOPCOUNT scintillation counter.

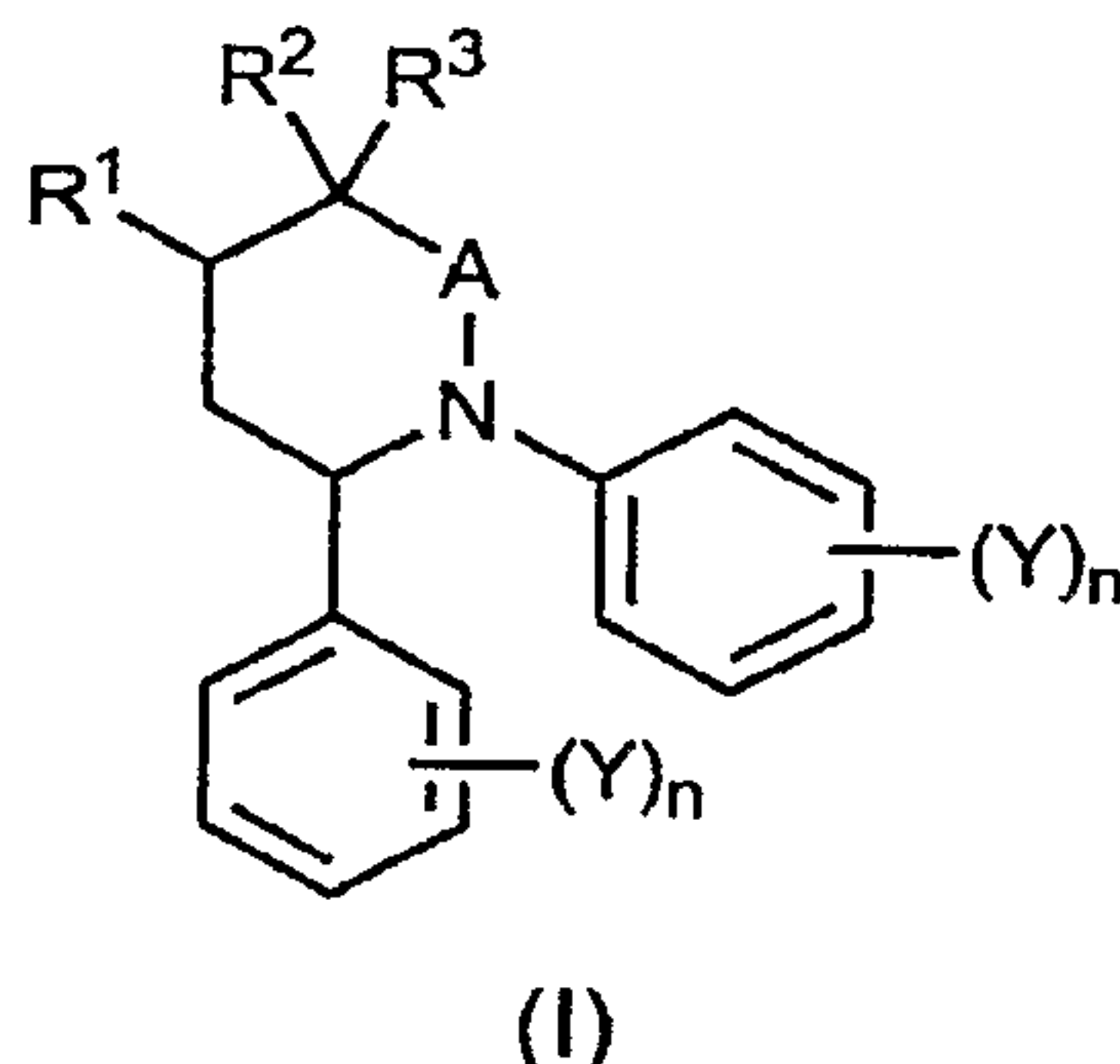
- 5 The stimulation of ^{35}S -GTPyS binding as a function of the concentration of the agonist WIN55,122, in the absence and presence of test compound, was plotted and the EC_{50} determined by nonlinear regression analysis using GraphPad Prism software. A Schild analysis of the rightward shift in the dose response curve of WIN55,122 in the presence of test compound was determined by plotting the
- 10 concentration of test compound against the negative log of the dose ratio $[1 - (\text{EC}_{50} \text{ agonist} + \text{test compound} / \text{EC}_{50} \text{ of agonist alone})]$. A linear regression analysis yields the K_b , defined as the X-intercept of the linear equation.

- In one embodiment, the compounds of Formula (I) of the present invention, and salts, solvates, or esters thereof, have K_i values of about 800 nM or less. In
- 15 another embodiment, the compounds of Formula (I) of the present invention, and salts, solvates, or esters thereof, have K_i values of about 100 nM or less. In another embodiment, the compounds of Formula (I) of the present invention, and salts, solvates, or esters thereof, have K_i values of about 50 nM or less. In another embodiment, the compounds of Formula (I) of the present invention, and salts,
- 20 solvates, or esters thereof, have K_i values of about 20 nM or less. In another embodiment, the compounds of Formula (I) of the present invention, and salts, solvates, or esters thereof, have K_i values of 10 nM or less. Examples 9, 14, 18, 29, 31, 33, 51, 52, 86, 90-92, 95, 97-99, 101, 107-109, 111, 112, 114, 116, 117, 119-121, 123, 131-137, 140, 147, 149, 162 have K_i values of 10 nm or less. Examples
- 25 86, 91, 92, 112, and 120, respectively, have K_i values of approximately 9, 4, 7, 2, and 2 nM.

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WE CLAIM:

1. A compound of Formula (I):



5 or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

A is $-\text{CH}_2-$ or $-\text{C}(\text{O})-$;

R^1 is selected from the group consisting of H, $-\text{N}(\text{R}^4)(\text{R}^5)$, unsubstituted heterocyclyl, heterocyclyl substituted with one or more X groups, $-\text{N}_3$, and $-\text{O}-\text{R}^7$;

10 R^2 is selected from the group consisting of H, $-(\text{C}(\text{R}^6)_2)_p$ -aryl, cycloalkylalkyl, cycloalkylalkyl substituted with Z, $-(\text{C}(\text{R}^6)_2)_q$ -heterocyclyl, $-(\text{C}(\text{R}^6)_2)_p$ - $\text{S}(\text{O})_2$ -heterocyclyl, and $-\text{C}(\text{R}^6)_2$ - $\text{O}-\text{R}^7$,

wherein the aryl portion of said $-(\text{C}(\text{R}^6)_2)_p$ -aryl of R^2 is unsubstituted or substituted with one or more Y groups,

wherein the heterocyclyl portion of said

15 $-(\text{C}(\text{R}^6)_2)_p$ - $\text{S}(\text{O})_2$ -heterocyclyl of R^2 is unsubstituted or substituted with one or more X groups,

wherein the heterocyclyl portion of said $-(\text{C}(\text{R}^6)_2)_q$ -heterocyclyl of R^2 is unsubstituted or substituted with one or more X groups;

20 R^3 is selected from the group consisting of H, $-(\text{C}(\text{R}^6)_2)_p$ -aryl, $-(\text{C}(\text{R}^6)_2)_p$ - $\text{O}-\text{R}^7$, $-(\text{C}(\text{R}^6)_2)_q$ - $\text{C}(\text{O})-\text{N}(\text{R}^{12})_2$, $-(\text{C}(\text{R}^6)_2)_p$ - $\text{N}(\text{R}^9)-\text{C}(\text{O})-(\text{C}(\text{R}^6)_2)_q$ - R^{16} , $-(\text{C}(\text{R}^6)_2)_q$ - $\text{S}(\text{O})_2$ - $\text{N}(\text{R}^9)-(\text{C}(\text{R}^6)_2)_q$ - R^{15} , $-(\text{C}(\text{R}^6)_2)_q$ - $\text{N}(\text{R}^9)-\text{S}(\text{O})_2-(\text{C}(\text{R}^6)_2)_q$ - R^{15} and $-(\text{C}(\text{R}^6)_2)_q$ - $\text{N}(\text{R}^8)_2$,

wherein the aryl portion of said $-(\text{C}(\text{R}^6)_2)_p$ -aryl of R^3 is unsubstituted or substituted with one or more Y groups;

25 with the following independent provisos:

- (i) at least one of R^1 , R^2 , and R^3 is not H;
- (ii) when R^1 is $-\text{OH}$, at least one of R^2 and R^3 is not H; and
- (iii) when A is $-\text{C}(\text{O})-$, at least one of R^2 and R^3 is not H;

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or, R^2 and R^3 together with the ring carbon atom to which they are shown attached form an unsubstituted heterocyclyl ring or a heterocyclyl ring substituted with one or more X groups;

R^4 is selected from the group consisting of H, -C(O)-alkyl, and alkyl;

5 R^5 is selected from the group consisting of $-(C(R^6)_2)_m-G$, $-S(O)_2$ -alkyl, $-S(O)_2$ -cycloalkyl, alkyl, $-S(O)$ -cycloalkyl, $-C(O)$ -cycloalkyl, $-S(O)_2$ -aryl, $-S(O)_2-(C(R^6)_2)_m$ -aryl, $-S(O)_2$ -heteroaryl, $-C(O)$ -alkyl, $-C(O)$ -aryl, $-C(O)$ -O-alkyl, $-C(O)$ -O-aryl, $-C(O)-(C(R^6)_2)_m$ -aryl, $-C(O)$ -cycloalkylene-aryl, $-C(O)$ -heteroaryl, $-C(O)$ -heteroarylalkyl, $-C(O)-(C(R^6)_2)_m$ -O-aryl, $-C(O)$ -(benzo-fused cycloalkyl), $-S(O)_2$ -(benzo-fused heterocyclyl), $-C(O)-N(R^9)-(C(R^6)_2)_m$ -aryl, $-C(O)-N(R^9)$ -aryl, cycloalkyl, benzo-fused cycloalkyl, unsubstituted aryl, aryl substituted with one or more Y groups, unsubstituted heterocyclyl, and heterocyclyl substituted with one or more X groups,

15 wherein the aryl or heteroaryl portion of said $-S(O)_2$ -aryl, $-S(O)_2-(C(R^6)_2)_m$ -aryl, $-S(O)_2$ -heteroaryl, $-C(O)$ -aryl, $-C(O)-(C(R^6)_2)_m$ -aryl, $-C(O)$ -cycloalkylene-aryl, $-C(O)$ -heteroaryl, $-C(O)-(C(R^6)_2)_m$ -O-aryl, $-C(O)-N(R^9)-(C(R^6)_2)_m$ -aryl, or $-C(O)-N(R^9)$ -aryl of R^5 is unsubstituted or substituted with one or more Y groups;

20 wherein the heterocyclyl portion of $-S(O)_2$ -(benzo-fused heterocyclyl) aryl of R^5 is unsubstituted or substituted with one or more X groups;

each R^6 is independently selected from the group consisting of H and alkyl;

R^7 is selected from the group consisting of H, alkyl, unsubstituted heteroaryl and heteroaryl substituted with one or more Y groups, unsubstituted aryl, and aryl substituted with one or more Y groups;

25 each R^8 is independently selected from the group consisting of H, alkyl, arylalkyl, heteroarylalkyl, unsubstituted aryl, unsubstituted heteroaryl, $-C(O)$ -alkyl, $-C(O)$ -aryl, $-C(O)$ -cycloalkyl, $-C(O)N(R^9)_2$, $-S(O)_2$ -aryl, $-S(O)_2$ -heteroaryl, $-SO_2N(R^9)_2$, $-S(O)_2$ -cycloalkyl, aryl and heteroaryl substituted with one or more Y groups, and $-S(O)_2$ -alkyl,

30 wherein the aryl portion of said arylalkyl, $-C(O)$ -aryl or $-S(O)_2$ -aryl and the heteroaryl portion of said heteroarylalkyl, $-S(O)_2$ -heteroaryl of R^8 is unsubstituted or substituted with one or more Y groups,

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wherein the alkyl portion of said arylalkyl and heteroarylalkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said alkyl portion is NOT Cbz or Boc;

each R^9 is independently selected from the group consisting of H, alkyl, haloalkyl,

5 hydroxyalkyl, cycloalkyl, unsubstituted aryl and unsubstituted heteroaryl;

each R^{12} is independently selected from the group consisting of H, alkyl,

cycloalkylalkyl, $-(C(R^6)_2)_q-C(O)R^{13}$, benzoheterocyclyl, benzocycloalkyl,

$-(C(R^6)_2)_q-N(R^9)-C(O)R^{13}$, $-(C(R^6)_2)_q-N(R^{14})_2$, arylalkyl, heteroarylalkyl, HO-alkyl-,

alkyl-O-, aryl-O-, Y-alkylenyl-O-, W-O-alkylenyl, heterocyclylalkyl, unsubstituted

10 cycloalkyl, cycloalkyl substituted with one or more X groups, unsubstituted heterocyclyl, heterocyclyl substituted with one or more X groups, unsubstituted heteroaryl, heteroaryl substituted with one or more Y groups, unsubstituted aryl and aryl substituted with one or more Y groups, and

wherein the aryl and heteroaryl portion of said arylalkyl and heteroarylalkyl is

15 unsubstituted or substituted with one or more Y groups,

wherein the alkyl portion of said cycloalkylalkyl, arylalkyl and heteroarylalkyl is

unsubstituted or substituted with one or more X groups with the proviso

that X substituted on said alkyl portion is NOT Cbz or Boc,

wherein the cycloalkyl of said cycloalkylalkyl is unsubstituted or substituted

20 with one or more X groups,

wherein the benzo portion of said benzoheterocyclyl can be optionally

substituted with one or more Y groups and the heterocyclyl portion of

benzoheterocyclyl can be optionally substituted with one or more X

groups,

25 wherein the benzo portion of said benzocycloalkyl can be optionally

substituted with one or more Y groups and the cycloalkyl portion of

benzocycloalkyl can be optionally substituted with one or more X groups;

with the following provisos that

for $-N(R^{14})_2$ of R^{12} , the two R^{14} groups, with the ring nitrogen atom to which

30 they are shown attached, form an unsubstituted heterocyclyl ring or a

heterocyclyl ring substituted with one or more X groups;

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each R^{13} is independently selected from the group consisting of H, alkyl, cycloalkylalkyl, arylalkyl, heteroarylalkyl, HO-alkyl-, alkyl-O-, aryl-O-, unsubstituted cycloalkyl, cycloalkyl substituted with one or more X groups, unsubstituted heterocyclyl, heterocyclyl substituted with one or more X groups, unsubstituted heteroaryl, heteroaryl substituted with one or more Y groups, unsubstituted aryl and aryl substituted with one or more Y groups

wherein the aryl and heteroaryl portion of said arylalkyl and heteroarylalkyl is unsubstituted or substituted with one or more Y groups,

wherein the alkyl portion of said cycloalkylalkyl, arylalkyl and heteroarylalkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said alkyl portion is NOT Cbz or Boc,

wherein the cycloalkyl of said cycloalkylalkyl is unsubstituted or substituted with one or more X groups;

each R^{14} is independently selected from the group consisting of H, Boc, unsubstituted alkyl, alkyl substituted with one or more X groups, unsubstituted cycloalkyl, cycloalkyl substituted with one or more Y groups, unsubstituted aryl, aryl substituted with one or more Y groups, heterocyclyl, unsubstituted heteroaryl and heteroaryl substituted with one or more Y groups;

each R^{15} is independently selected from the group consisting of H, alkyl, $-N(R^4)(R^5)$, $(C(R^6)_2)_q-N(R^{14})_2$, alkylenyl- CF_3 , $-CF_3$, cycloalkylalkyl, unsubstituted cycloalkyl, cycloalkyl substituted with one or more X groups, unsubstituted heterocyclyl, heterocyclyl substituted with one or more X groups, benzoheterocyclyl, benzocycloalkyl, unsubstituted heteroaryl, heteroaryl substituted with one or more Y groups, unsubstituted aryl and aryl substituted with one or more Y groups,

wherein the alkyl portion of said cycloalkylalkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said alkyl portion is NOT Cbz or Boc,

wherein the cycloalkyl of said cycloalkylalkyl is unsubstituted or substituted with one or more X groups,

wherein the benzo portion of said benzoheterocyclyl can be optionally substituted with one or more Y groups and the heterocyclyl portion of

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benzoheterocyclyl can be optionally substituted with one or more X groups,

wherein the benzo portion of said benzocycloalkyl can be optionally

substituted with one or more Y groups and the cycloalkyl portion of

5 benzocycloalkyl can be optionally substituted with one or more X groups;

each R^{16} is independently selected from the group consisting of H, alkyl,

cycloalkylalkyl, $-(C(R^6)_2)_p-C(O)R^{13}$, $-(C(R^6)_2)_p-N(R^9)-C(O)R^{13}$, $-(C(R^6)_2)_p-N(R^{14})_2$,

arylalkyl, heteroarylalkyl, HO-alkyl-, alkyl-O-, aryl-O-, unsubstituted cycloalkyl,

cycloalkyl substituted with one or more X groups, unsubstituted heterocyclyl,

10 heterocyclyl substituted with one or more X groups, unsubstituted heteroaryl,

heteroaryl substituted with one or more Y groups, unsubstituted aryl and aryl

substituted with one or more Y groups, and

wherein the aryl and heteroaryl portion of said arylalkyl and heteroarylalkyl is

unsubstituted or substituted with one or more Y groups,

15 wherein the alkyl portion of said cycloalkylalkyl, arylalkyl and heteroarylalkyl is

unsubstituted or substituted with one or more X groups with the proviso

that X substituted on said alkyl portion is NOT Cbz or Boc,

wherein the cycloalkyl of said cycloalkylalkyl is unsubstituted or substituted

with one or more X groups,

20 for $-N(R^{14})_2$, the two R^{14} groups, with the ring nitrogen atom to which they are

shown attached, form an unsubstituted heterocyclyl ring or a heterocyclyl

ring substituted with one or more X groups;

G is selected from the group consisting of H, alkyl, unsubstituted aryl, aryl

substituted with one or more Y groups, $-CN$, cycloalkyl, $-O-R^7$, $-S-R^7$,

25 unsubstituted heteroaryl, heteroaryl substituted with one or more Y groups,

$-N(R^8)_2$, unsubstituted heterocyclyl, and heterocyclyl substituted with one or more

X groups;

each W is independently selected from the group consisting of hydrogen, alkyl, aryl,

$-C(O)-alkyl$, $-C(O)-O-alkyl$, $-C(R^6)_2-N(R^6)_2$, and

30 $-C(R^6)_2-N(R^6)-S(O)_2-R^6$;

each X is independently selected from the group consisting of hydrogen, $-OH$, alkyl,

arylalkyl, heteroarylalkyl, Cbz, Boc, alkylsulfonyl, acetyl,

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-C(O)-R¹², -C(O)-N(R⁹)₂, -C(O)-heteroaryl, heteroaryl, -S(O)₂-cycloalkyl,
-C(O)-alkyl, -C(O)-O-alkyl, -(C(R⁶)₂)_m-aryl and aryl

wherein the aryl and heteroaryl portion of said arylalkyl and heteroarylalkyl is
unsubstituted or substituted with one or more Y groups,

5 wherein the alkyl portion of said arylalkyl and heteroarylalkyl is unsubstituted
or substituted with one or more X groups with the proviso that X
substituted on said alkyl portion is NOT Cbz or Boc,

wherein said heteroaryl or the heteroaryl portion of said -C(O)-heteroaryl
of X is unsubstituted or substituted with one or more substituents
10 selected from the group consisting of halogen, -OH, -O-alkyl, haloalkyl,
and -CN, and

wherein said aryl or the aryl portion of said -(C(R⁶)₂)_m-aryl of X is
unsubstituted or substituted with one or more substituents selected
from the group consisting of halogen, -OH, -O-alkyl, haloalkyl, and -CN

15 wherein in a single X moiety, =O, can replace two available hydrogens on
the same carbon on a ring system;

each Y is independently selected from the group consisting of hydrogen, halogen,
alkyl, aryl, -C(O)-alkyl, -O-alkyl, -O-heteroaryl, -O-aryl, -O-R⁹, haloalkyl,
-O-haloalkyl, -CN, -C(O)-O-alkyl, -N(R⁶)₂, -C(R⁶)₂-N(R⁶)₂,
20 -S(O)₂-heterocyclyl, -S(O)₂-heteroaryl and -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶; or
two of said Y groups attached to adjacent carbon atoms form a -O-CH₂-O- or
-O-CH₂CH₂-O- group;

each Z is independently selected from the group consisting of hydrogen, alkyl,
arylalkyl, heteroarylalkyl, -C(O)-N(R⁹)₂, -C(O)-heteroaryl, heteroaryl,

25 -S(O)₂-cycloalkyl, -C(O)-alkyl, -(C(R⁶)₂)_m-aryl, -N(R⁶)-S(O)₂-R⁹ and aryl

wherein the aryl and heteroaryl portion of said arylalkyl and heteroarylalkyl is
unsubstituted or substituted with one or more Y groups,

wherein the alkyl portion of said arylalkyl and heteroarylalkyl is unsubstituted
or substituted with one or more X groups with the proviso that X
30 substituted on said alkyl portion is NOT Cbz or Boc,

wherein said heteroaryl or the heteroaryl portion of said -C(O)-heteroaryl
of Z is unsubstituted or substituted with one or more substituents

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selected from the group consisting of halogen, -OH, -O-alkyl, haloalkyl, and -CN, and

wherein said aryl or the aryl portion of said $-(C(R^6)_2)_m$ -aryl of Z is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-alkyl, haloalkyl, and -CN; wherein in a single Z moiety, =O, can replace two available hydrogens on the same carbon on a ring system;

each n, p and q is independently an integer from 0-5; and m is an integer from 1-5.

2. The compound of Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

A is $-CH_2-$ or $-C(O)-$;

R^1 is selected from the group consisting of H, $-N(R^4)(R^5)$, unsubstituted (C_2-C_{10}) heterocyclyl, (C_2-C_{10}) heterocyclyl substituted with one or more X groups, $-N_3$, and $-O-R^7$;

R^2 is selected from the group consisting of H, $-(C(R^6)_2)_p-(C_6-C_{10})$ aryl, (C_3-C_6) cycloalkyl (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl (C_1-C_6) alkyl substituted with Z, $-(C(R^6)_2)_q-(C_2-C_{10})$ heterocyclyl, $-(C(R^6)_2)_p-S(O)_2-(C_2-C_{10})$ heterocyclyl, and $-C(R^6)_2-O-R^7$,

wherein the (C_6-C_{10}) aryl portion of said $-C(R^6)_2-(C_6-C_{10})$ aryl of R^2 is unsubstituted or substituted with one or more Y groups,

wherein the (C_2-C_{10}) heterocyclyl portion of said $-(C(R^6)_2)_p-S(O)_2-(C_2-C_{10})$ heterocyclyl of R^2 is unsubstituted or substituted with one or more X groups,

wherein the (C_2-C_{10}) heterocyclyl portion of said $-(C(R^6)_2)_q-(C_2-C_{10})$ heterocyclyl of R^2 is unsubstituted or substituted with one or more X groups;

R^3 is selected from the group consisting of H, $-C(R^6)_2-(C_6-C_{10})$ aryl, $-C(R^6)_2-O-R^7$, $-(C(R^6)_2)_q-C(O)-N(R^{12})_2$, $-(C(R^6)_2)_p-N(R^9)-C(O)-(C(R^6)_2)_q-R^{16}$, $-(C(R^6)_2)_q-S(O)_2-N(R^9)-(C(R^6)_2)_q-R^{15}$, $-(C(R^6)_2)_q-N(R^9)-S(O)_2-(C(R^6)_2)_q-R^{15}$ and $-(C(R^6)_2)_q-N(R^8)_2$,

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wherein the (C₆-C₁₀)aryl portion of said -C(R⁶)₂-(C₆-C₁₀)aryl of R³ is unsubstituted or substituted with one or more Y groups;

with the following independent provisos:

- (i) at least one of R¹, R², and R³ is not H;
- (ii) when R¹ is -OH, at least one of R² and R³ is not H; and
- (iii) when A is -C(O)-, at least one of R² and R³ is not H;

or, R² and R³ together with the ring carbon atom to which they are shown attached form an unsubstituted (C₂-C₁₀)heterocyclyl ring or a (C₂-C₁₀)heterocyclyl ring substituted with one or more X groups;

R⁴ is selected from the group consisting of H, -C(O)-(C₁-C₆)alkyl, and (C₁-C₆)alkyl;

R⁵ is selected from the group consisting of -(C(R⁶)₂)_m-G, -S(O)₂-(C₁-C₆)alkyl, -S(O)₂-(C₃-C₆)cycloalkyl, (C₁-C₆)alkyl, -S(O)-(C₃-C₆)cycloalkyl, -C(O)-(C₃-C₆)cycloalkyl, -S(O)₂-(C₆-C₁₀)aryl, -S(O)₂-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -S(O)₂-(C₂-C₁₀)heteroaryl, -C(O)-(C₁-C₆)alkyl, -C(O)-(C₆-C₁₀)aryl, -C(O)-O-(C₁-C₆)alkyl, -C(O)-O-(C₆-C₁₀)aryl, -C(O)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -C(O)-(C₃-C₆)cycloalkylene-(C₆-C₁₀)aryl, -C(O)-(C₂-C₁₀)heteroaryl, -C(O)-(C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, -C(O)-(C(R⁶)₂)_m-O-(C₆-C₁₀)aryl, -C(O)-(benzo-fused (C₃-C₆)cycloalkyl), -S(O)₂-(benzo-fused (C₂-C₁₀)heterocyclyl), -C(O)-N(R⁹)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -C(O)-N(R⁹)-(C₆-C₁₀)aryl, (C₃-C₆)cycloalkyl, benzo-fused (C₃-C₆)cycloalkyl, unsubstituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl substituted with one or more Y groups, unsubstituted (C₂-C₁₀)heterocyclyl, and (C₂-C₁₀)heterocyclyl substituted with one or more X groups,

wherein the (C₆-C₁₀)aryl or (C₂-C₁₀)heteroaryl portion of said -S(O)₂-(C₆-C₁₀)aryl, -S(O)₂-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -S(O)₂-(C₂-C₁₀)heteroaryl, -C(O)-(C₆-C₁₀)aryl, -C(O)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -C(O)-(C₃-C₆)cycloalkylene-(C₆-C₁₀)aryl, -C(O)-(C₂-C₁₀)heteroaryl, -C(O)-(C(R⁶)₂)_m-O-(C₆-C₁₀)aryl, -C(O)-N(R⁹)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, or -C(O)-N(R⁹)-(C₆-C₁₀)aryl of R⁵ is unsubstituted or substituted with one or more Y groups;

wherein the heterocyclyl portion of -S(O)₂-(benzo-fused (C₂-C₁₀)heterocyclyl) aryl of R⁵ is unsubstituted or substituted with one or more X groups;

each R⁶ is independently selected from the group consisting of H and (C₁-C₆)alkyl;

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R^7 is selected from the group consisting of H, (C₁-C₆)alkyl, unsubstituted (C₂-C₁₀)heteroaryl and (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl, and (C₆-C₁₀)aryl substituted with one or more Y groups;

5 each R^8 is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, unsubstituted (C₆-C₁₀)aryl, unsubstituted (C₂-C₁₀)heteroaryl,

-C(O)-(C₁-C₆)alkyl, -C(O)-(C₆-C₁₀)aryl, -C(O)-(C₃-C₆)cycloalkyl, -C(O)N(R⁹)₂,
-S(O)₂-(C₆-C₁₀)aryl, -S(O)₂-(C₂-C₁₀)heteroaryl, -SO₂N(R⁹)₂,

10 -S(O)₂-(C₃-C₆)cycloalkyl, (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl substituted with one or more Y groups, and -S(O)₂-(C₁-C₆)alkyl,

wherein the (C₆-C₁₀)aryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl, -C(O)-(C₆-C₁₀)aryl or -S(O)₂-(C₆-C₁₀)aryl and the (C₂-C₁₀)heteroaryl portion of said (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, -S(O)₂-(C₂-C₁₀)heteroaryl of R^8 is

15 unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc;

20 each R^9 is independently selected from the group consisting of H, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, unsubstituted (C₆-C₁₀)aryl and unsubstituted (C₂-C₁₀)heteroaryl;

each R^{12} is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, -(C(R⁶)₂)_q-C(O)R¹³, benzo(C₂-C₁₀)heterocyclyl, benzocyclo(C₁-C₆)alkyl,

15 -(C(R⁶)₂)_q-N(R⁹)-C(O)R¹³, -(C(R⁶)₂)_q-N(R¹⁴)₂, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, Y-(C₁-C₆)alkylenyl-O-, W-O-(C₁-C₆)alkylenyl, (C₂-C₁₀)heterocyclyl(C₁-C₆)alkyl,

0 unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl

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substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups, and

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups,

wherein the benzo portion of said benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more Y groups and the (C₂-C₁₀)heterocyclyl portion of benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more X groups,

wherein the benzo portion of said benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more Y groups and the (C₃-C₆)cycloalkyl portion of benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more X groups;

with the following provisos that

for -N(R¹⁴)₂ of R¹², the two R¹⁴ groups, with the ring nitrogen atom to which they are shown attached, form an unsubstituted (C₂-C₁₀)heterocyclyl ring or a (C₂-C₁₀)heterocyclyl ring substituted with one or more X groups;

each R¹³ is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups

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wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups;

each R¹⁴ is independently selected from the group consisting of H, Boc, unsubstituted (C₁-C₆)alkyl, (C₁-C₆)alkyl substituted with one or more X groups, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl substituted with one or more Y groups, (C₂-C₁₀)heterocyclyl, unsubstituted (C₂-C₁₀)heteroaryl and (C₂-C₁₀)heteroaryl substituted with one or more Y groups;

each R¹⁵ is independently selected from the group consisting of H, (C₁-C₆)alkyl, -N(R⁴)(R⁵), (C(R⁶)₂)_q-N(R¹⁴)₂, (C₁-C₆)alkylenyl-CF₃, -CF₃, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, benzo(C₂-C₁₀)heterocyclyl, benzocyclo(C₁-C₆)alkyl, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc, wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups,

wherein the benzo portion of said benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more Y groups and the (C₂-C₁₀)heterocyclyl portion

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of benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more X groups,

wherein the benzo portion of said benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more Y groups and the (C₃-C₆)cycloalkyl portion of benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more X groups;

each R¹⁶ is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, -(C(R⁶)₂)_p-C(O)R¹³, -(C(R⁶)₂)_p-N(R⁹)-C(O)R¹³, -(C(R⁶)₂)_p-N(R¹⁴)₂, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups, and

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups,

for -N(R¹⁴)₂, the two R¹⁴ groups, with the ring nitrogen atom to which they are shown attached, form an unsubstituted (C₂-C₁₀)heterocyclyl ring or a (C₂-C₁₀)heterocyclyl ring substituted with one or more X groups;

G is selected from the group consisting of H, (C₁-C₆)alkyl, unsubstituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl substituted with one or more Y groups, -CN, (C₃-C₆)cycloalkyl, -O-R⁷, -S-R⁷, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, -N(R⁸)₂, unsubstituted (C₂-C₁₀)heterocyclyl, and (C₂-C₁₀)heterocyclyl substituted with one or more X groups;

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each W is independently selected from the group consisting of hydrogen,
 (C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl,
 -C(R⁶)₂-N(R⁶)₂, and -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶;

each X is independently selected from the group consisting of hydrogen, -OH,

5 (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, Cbz, Boc,
 (C₁-C₆)alkylsulfonyl, acetyl, -C(O)-R¹², -C(O)-N(R⁹)₂,
 -C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl, -S(O)₂-(C₃-C₆)cycloalkyl,
 -C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -(C(R⁶)₂)_m-(C₆-C₁₀)aryl and
 (C₆-C₁₀)aryl

10 wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-
 C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or
 substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and
 (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or
 15 more X groups with the proviso that X substituted on said (C₁-C₆)alkyl
 portion is NOT Cbz or Boc,

wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said
 -C(O)-(C₂-C₁₀)heteroaryl of X is unsubstituted or substituted with one or
 more substituents selected from the group consisting of halogen, -OH,
 20 -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN, and

wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said
 -(C(R⁶)₂)_m-(C₆-C₁₀)aryl of X is unsubstituted or substituted with one or
 more substituents selected from the group consisting of halogen, -OH,
 -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN

25 wherein in a single X moiety, =O, can replace two available hydrogens on
 the same carbon on a ring system;

each Y is independently selected from the group consisting of hydrogen, halogen,
 (C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -O-(C₁-C₆)alkyl,
 -O-(C₂-C₁₀)heteroaryl, -O-(C₆-C₁₀)aryl, -O-R⁹, halo(C₁-C₆)alkyl,
 30 -O-halo(C₁-C₆)alkyl, -CN, -C(O)-O-(C₁-C₆)alkyl, -N(R⁶)₂, -C(R⁶)₂-N(R⁶)₂,
 -S(O)₂-(C₂-C₁₀)heterocyclyl, -S(O)₂-(C₂-C₁₀)heteroaryl and
 -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶; or

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two of said Y groups attached to adjacent carbon atoms form a $-\text{O}-\text{CH}_2-\text{O}-$ or $-\text{O}-\text{CH}_2\text{CH}_2-\text{O}-$ group;

each Z is independently selected from the group consisting of hydrogen,

(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl,

5 -C(O)-N(R⁹)₂, -C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl,

-S(O)₂-(C₃-C₆)cycloalkyl, -C(O)-(C₁-C₆)alkyl,

-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -N(R⁶)-S(O)₂-R⁹ and (C₆-C₁₀)aryl

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-

C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or

10 substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and

(C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or

more X groups with the proviso that X substituted on said (C₁-C₆)alkyl

portion is NOT Cbz or Boc,

15 wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said

-C(O)-(C₂-C₁₀)heteroaryl of Z is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH,

-O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN, and

wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said

20 -(C(R⁶)₂)_m-(C₆-C₁₀)aryl of Z is unsubstituted or substituted with one or

more substituents selected from the group consisting of halogen, -OH,

-O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN;

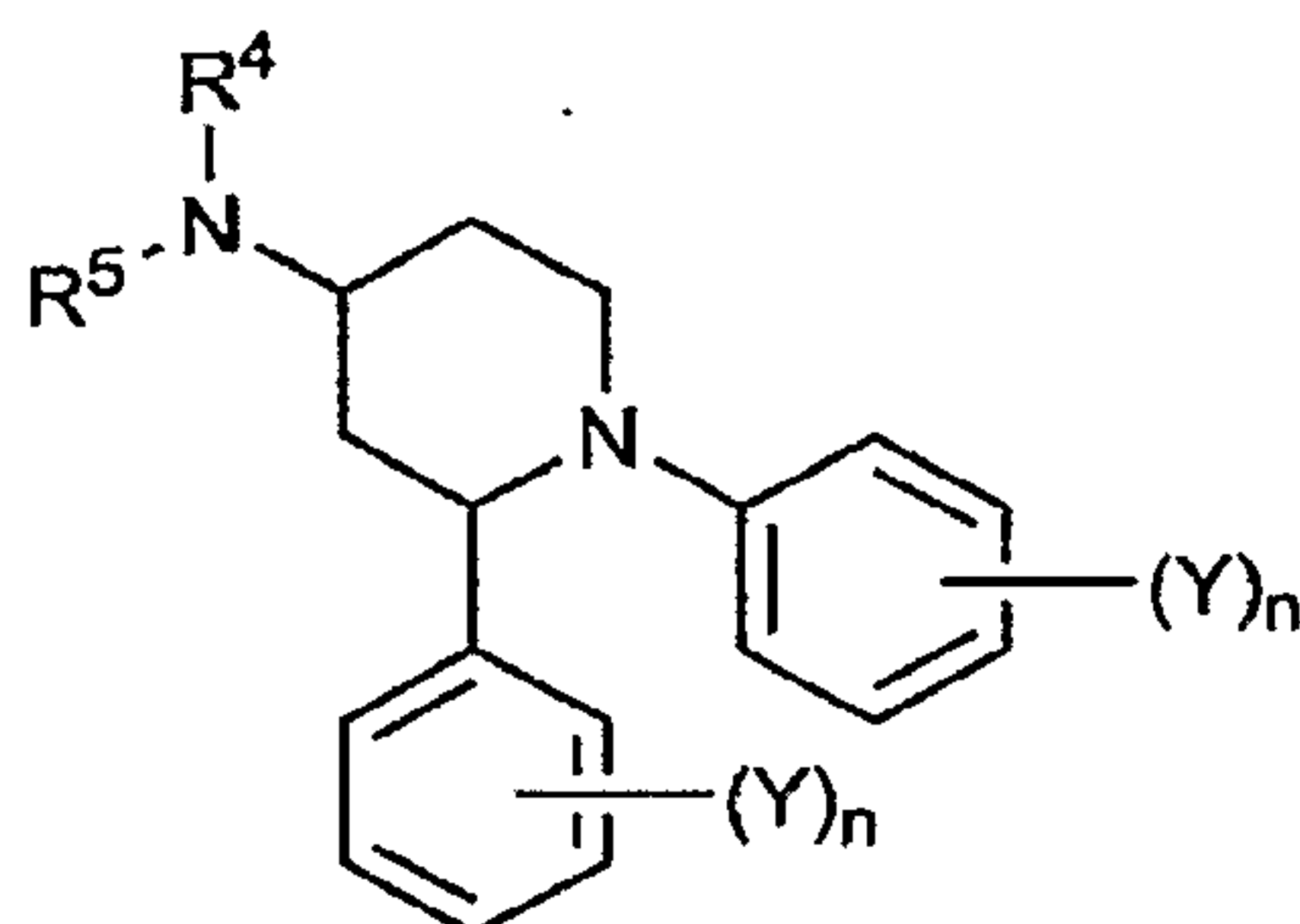
wherein in a single Z moiety, =O, can replace two available hydrogens on the same carbon on a ring system;

25 each n, p and q is independently an integer from 0-5; and

m is an integer from 1-5.

3. The compound of Claim 1 having the structural Formula (IA):

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(IA)

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

R⁴ is selected from the group consisting of H, -C(O)-(C₁-C₆)alkyl, and (C₁-C₆)alkyl;

- 5 R⁵ is selected from the group consisting of -(C(R⁶)₂)_m-G, -S(O)₂-(C₁-C₆)alkyl, -S(O)-(C₃-C₆)cycloalkyl, -C(O)-(C₃-C₆)cycloalkyl, -S(O)₂-(C₆-C₁₀)aryl, -S(O)₂-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -S(O)₂-(C₂-C₁₀)heteroaryl, -C(O)-(C₁-C₆)alkyl, -C(O)-(C₆-C₁₀)aryl, -C(O)-O-(C₁-C₆)alkyl, -C(O)-O-(C₆-C₁₀)aryl, -C(O)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -C(O)-(C₃-C₆)cycloalkylene-(C₆-C₁₀)aryl, -C(O)-(C₂-C₁₀)heteroaryl, -C(O)-(C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, -C(O)-(C(R⁶)₂)_m-O-(C₆-C₁₀)aryl, -C(O)-(benzo-fused (C₃-C₆)cycloalkyl), -S(O)₂-(benzo-fused (C₂-C₁₀)heterocyclyl), -C(O)-N(R⁹)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -C(O)-N(R⁹)-(C₆-C₁₀)aryl, (C₃-C₆)cycloalkyl, benzo-fused (C₃-C₆)cycloalkyl, unsubstituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl substituted with one or more Y groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups,

wherein the (C₆-C₁₀)aryl or heteroaryl portion of said -S(O)₂-(C₆-C₁₀)aryl,

-S(O)₂-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -S(O)₂-(C₂-C₁₀)heteroaryl, -C(O)-(C₆-C₁₀)aryl, -C(O)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl,

-C(O)-(C₃-C₆)cycloalkylene-(C₆-C₁₀)aryl, -C(O)-(C₂-C₁₀)heteroaryl,

-C(O)-(C(R⁶)₂)_m-O-(C₆-C₁₀)aryl, -C(O)-N(R⁹)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, or -C(O)-N(R⁹)-(C₆-C₁₀)aryl of R⁵ is unsubstituted or substituted with one or more Y groups;

wherein the heterocyclyl portion of -S(O)₂-(benzo-fused (C₂-C₁₀)heterocyclyl)

aryl of R⁵ is unsubstituted or substituted with one or more X groups;

each R⁶ is independently selected from the group consisting of H and (C₁-C₆)alkyl;

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R^7 is selected from the group consisting of H, (C_1-C_6) alkyl, unsubstituted (C_6-C_{10}) aryl, and (C_6-C_{10}) aryl substituted with one or more Y groups;

each R^8 is independently selected from the group consisting of H, (C_1-C_6) alkyl, $-C(O)-(C_6-C_{10})$ aryl, $-S(O)_2-(C_6-C_{10})$ aryl, and $-S(O)_2-(C_1-C_6)$ alkyl;

5 each R^9 is independently selected from the group consisting of H, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl and unsubstituted (C_6-C_{10}) aryl;

G is selected from the group consisting of H, (C_1-C_6) alkyl, unsubstituted (C_6-C_{10}) aryl, (C_6-C_{10}) aryl substituted with one or more Y groups, $-CN$, (C_3-C_6) cycloalkyl, $-O-R^7$, $-S-R^7$, unsubstituted (C_2-C_{10}) heteroaryl, (C_2-C_{10}) heteroaryl substituted with one or
10 more Y groups, $-N(R^8)_2$, unsubstituted (C_2-C_{10}) heterocyclyl, and (C_2-C_{10}) heterocyclyl substituted with one or more X groups;

each X is independently selected from the group consisting of (C_1-C_6) alkyl, $-C(O)-N(R^9)_2$, $-C(O)-(C_2-C_{10})$ heteroaryl, (C_2-C_{10}) heteroaryl, $-(C(R^6)_2)_m-(C_6-C_{10})$ aryl, and (C_6-C_{10}) aryl,

15 wherein said (C_2-C_{10}) heteroaryl or the (C_2-C_{10}) heteroaryl portion of said $-C(O)-(C_2-C_{10})$ heteroaryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, $-OH$, $-O$ -alkyl, haloalkyl, and $-CN$, and

20 wherein said (C_6-C_{10}) aryl or the (C_6-C_{10}) aryl portion of said $-(C(R^6)_2)_m-(C_6-C_{10})$ aryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, $-OH$, $-O$ -alkyl, haloalkyl, and $-CN$;

each Y is independently selected from the group consisting of halogen, (C_1-C_6) alkyl, (C_6-C_{10}) aryl, $-C(O)-(C_1-C_6)$ alkyl, $-O-R^9$, (C_1-C_6) haloalkyl, $-O-(C_1-C_6)$ haloalkyl,
25 $-CN$, $-C(O)-O-(C_1-C_6)$ alkyl, $-N(R^6)_2$, and $-C(R^6)_2-N(R^6)_2$; or

two of said Y groups attached to adjacent carbon atoms form a $-O-CH_2-O-$ or $-O-CH_2CH_2-O-$ group;

each n is independently an integer from 0-5; and

m is an integer from 1-5.

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4. The compound of Claim 3, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

R^4 is H.

5. The compound of Claim 4, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

- 5 R^5 is selected from the group consisting of $-(C(R^6)_2)_m-G$, $-S(O)_2-(C_1-C_6)alkyl$,
 $-S(O)-(C_3-C_6)cycloalkyl$, $-C(O)-(C_3-C_6)cycloalkyl$, $-S(O)_2-(C_6-C_{10})aryl$,
 $-S(O)_2-(C(R^6)_2)_m-(C_6-C_{10})aryl$, $-S(O)_2-(C_2-C_{10})heteroaryl$, $-C(O)-(C_6-C_{10})aryl$,
 $-C(O)-O-(C_1-C_6)alkyl$, $-C(O)-O-(C_6-C_{10})aryl$,
 $-C(O)-(C(R^6)_2)_m-(C_6-C_{10})aryl$, $-C(O)-(C_3-C_6)cycloalkylene-(C_6-C_{10})aryl$,
10 $-C(O)-(C_2-C_{10})heteroaryl$, $-C(O)-(C_2-C_{10})heteroaryl(C_1-C_6)alkyl$,
 $-C(O)-(C(R^6)_2)_m-O-(C_6-C_{10})aryl$, $-C(O)-(benzo-fused (C_3-C_6)cycloalkyl)$,
 $-S(O)_2-(benzo-fused (C_2-C_{10})heterocyclyl)$, $-C(O)-N(R^9)-(C(R^6)_2)_m-(C_6-C_{10})aryl$,
 $-C(O)-N(R^9)-(C_6-C_{10})aryl$, $(C_3-C_6)cycloalkyl$, and benzo-fused $(C_3-C_6)cycloalkyl$;
each R^6 is independently selected from the group consisting of H and $(C_1-C_6)alkyl$;
15 R^7 is selected from the group consisting of H, $(C_1-C_6)alkyl$ and unsubstituted
 $(C_6-C_{10})aryl$;
each R^9 is independently selected from the group consisting of H, $(C_1-C_6)alkyl$,
 $(C_3-C_6)cycloalkyl$ and unsubstituted $(C_6-C_{10})aryl$;
G is selected from the group consisting of H, $(C_1-C_6)alkyl$, unsubstituted $(C_6-C_{10})aryl$,
20 $(C_6-C_{10})aryl$ substituted with one or more Y groups, $-CN$, $(C_3-C_6)cycloalkyl$, $-O-R^7$,
 $-S-R^7$, unsubstituted $(C_2-C_{10})heteroaryl$, unsubstituted $(C_2-C_{10})heterocyclyl$, and
 $(C_2-C_{10})heterocyclyl$ substituted with one or more X groups;
each X is independently selected from the group consisting of $(C_1-C_6)alkyl$ and
 $(C_6-C_{10})aryl$ substituted with one or more halogen; and
25 each Y is independently selected from the group consisting halogen, $(C_1-C_6)alkyl$,
 $(C_6-C_{10})aryl$, $-O-R^9$, $(C_1-C_6)haloalkyl$, $-O-(C_1-C_6)haloalkyl$, $-CN$,
 $-C(O)-O-(C_1-C_6)alkyl$, $-C(O)-(C_1-C_6)alkyl$, $-N(R^6)_2$, and $-C(R^6)_2-N(R^6)_2$; or
two of said Y groups attached to adjacent carbon atoms form a $-O-CH_2-O-$ or
 $-O-CH_2CH_2-O-$ group.

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6. The compound of Claim 5, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

R^5 is selected from the group consisting of $-(C(R^6)_2)_m-G$, $-S(O)_2-CH_3$, $-S(O)_2$ -phenyl, $-S(O)_2-C(R^6)_2$ -phenyl, $-S(O)_2$ -thiophenyl, $-C(O)$ -phenyl, $-C(O)-C(R^6)_2$ -phenyl, $-C(O)$ -cyclopropylene-phenyl, $-C(O)$ -(benzo-fused cyclohexyl), $-C(O)$ -furanyl, $-C(O)-C(R^6)_2-O$ -phenyl, $-C(O)-(C(R^6)_2)_2$ -phenyl, $-C(O)-N(R^9)$ -phenyl,

5 $-C(O)-N(R^9)-C(R^6)_2$ -phenyl, cyclobutyl, cyclopentyl, cyclohexyl, and indanyl, wherein the phenyl, thiophenyl, and furanyl portions of said $-S(O)_2$ -phenyl, $-S(O)_2-C(R^6)_2$ -phenyl, $-S(O)_2$ -thiophenyl, $-C(O)$ -phenyl, $-C(O)-C(R^6)_2$ -phenyl, $-C(O)$ -cyclopropylene-phenyl, $-C(O)$ -furanyl, $-C(O)-C(R^6)_2-O$ -phenyl, $-C(O)-(C(R^6)_2)_2$ -phenyl, $-C(O)-N(R^9)$ -phenyl, or

10 $-C(O)-N(R^9)-C(R^6)_2$ -phenyl of R^5 are unsubstituted or substituted with one or more Y groups;

each R^6 is independently selected from the group consisting of H, $-CH_3$, $-CH_2CH_3$, and $-CH_2(CH_3)_2$;

R^7 is selected from the group consisting of H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, and unsubstituted phenyl;

15 each R^9 is independently selected from the group consisting of H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, and unsubstituted phenyl;

G is selected from the group consisting of H, $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, unsubstituted phenyl, phenyl substituted with one or more Y groups, $-CN$, cyclohexyl, $-O-R^7$, $-S-R^7$, furanyl, thiophenyl, pyridinyl, benzothiophenyl, and pyrrolidinyl substituted with one or more X groups;

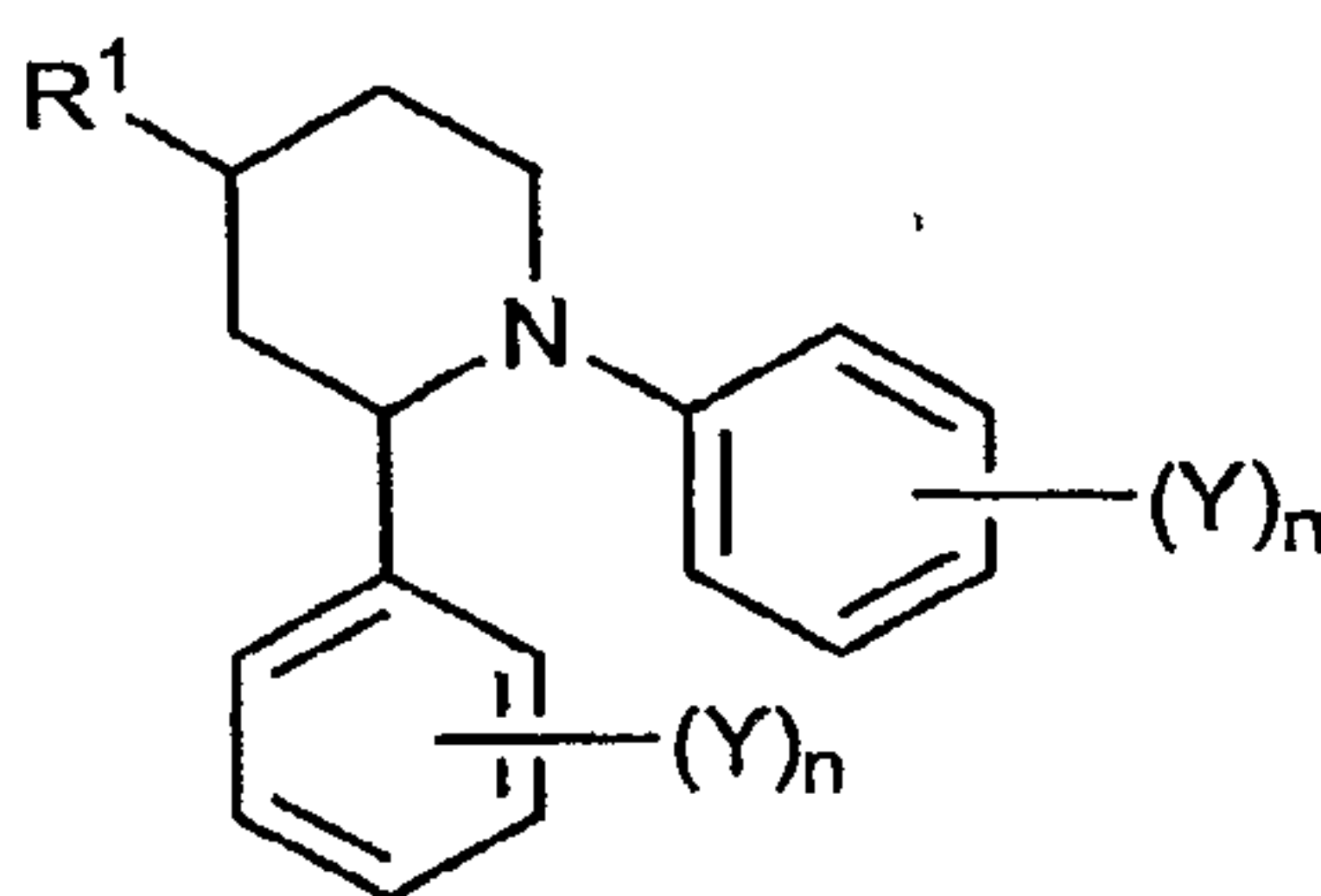
20 each X is independently selected from the group consisting of $-CH_3$ and phenyl substituted with one or more Cl; and

each Y is independently selected from the group consisting of F, Cl, $-OCF_3$, $-OCH_3$, phenyl, $-C(O)-CH_3$, $-CH_3$, $-CN$, $-NH_2$, and $-CF_3$; or

25 two of said Y groups attached to adjacent carbon atoms form a $-O-CH_2-O-$ group.

7. The compound of Claim 1 having the structural Formula (IB):

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(IB)

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

R¹ is selected from the group consisting of unsubstituted (C₂-C₁₀)heterocyclyl,

5 (C₂-C₁₀)heterocyclyl substituted with one or more X groups, -N₃, and -OR⁷;

each R⁶ is independently selected from the group consisting of H and (C₁-C₆)alkyl;

R⁷ is selected from the group consisting of (C₁-C₆)alkyl, unsubstituted (C₆-C₁₀)aryl, and (C₆-C₁₀)aryl substituted with one or more Y groups;

each R⁸ is independently selected from the group consisting of H, (C₁-C₆)alkyl,

10 -C(O)-(C₆-C₁₀)aryl, -S(O)₂-(C₆-C₁₀)aryl, and -S(O)₂-(C₁-C₆)alkyl;

each X is independently selected from the group consisting of (C₁-C₆)alkyl,

-C(O)-N(R⁸)₂, -C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl, -(C(R⁶)₂)-(C₆-C₁₀)aryl, and (C₆-C₁₀)aryl

wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said

15 -C(O)-(C₂-C₁₀)heteroaryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-alkyl, haloalkyl, and -CN, and

wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said -(C(R⁶)₂)-(C₆-

20 C₁₀)aryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-alkyl, haloalkyl, and -CN; and

n is an integer from 0-5.

8. The compound of Claim 1 having the structural Formula (IC):

-S(O)₂-(C₂-C₁₀)heteroaryl of R⁸ is unsubstituted or substituted with one or more Y groups;

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each Y is independently selected from the group consisting of halogen, (C₁-C₆)alkyl, -C(O)-(C₁-C₆)alkyl, -O-R⁹, -O-C(R⁶)₂-O-, (C₁-C₆)haloalkyl, -O-(C₁-C₆)haloalkyl, -CN, -C(O)-O-(C₁-C₆)alkyl, -C(R⁶)₂-N(R⁶)₂, and -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶; and each n is independently an integer from 0-5.

5

9. The compound of Claim 8, or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

R² is H

R³ is selected from the group consisting of -C(R⁶)₂-(C₆-C₁₀)aryl, -C(R⁶)₂-O-R⁷, and

10 -C(R⁶)₂-N(R⁸)₂,

wherein the (C₆-C₁₀)aryl portion of said -C(R⁶)₂-(C₆-C₁₀)aryl of R³ is unsubstituted or substituted with one or more Y groups;

each R⁶ is H;

R⁷ is (C₆-C₁₀)aryl substituted with one or more Y groups;

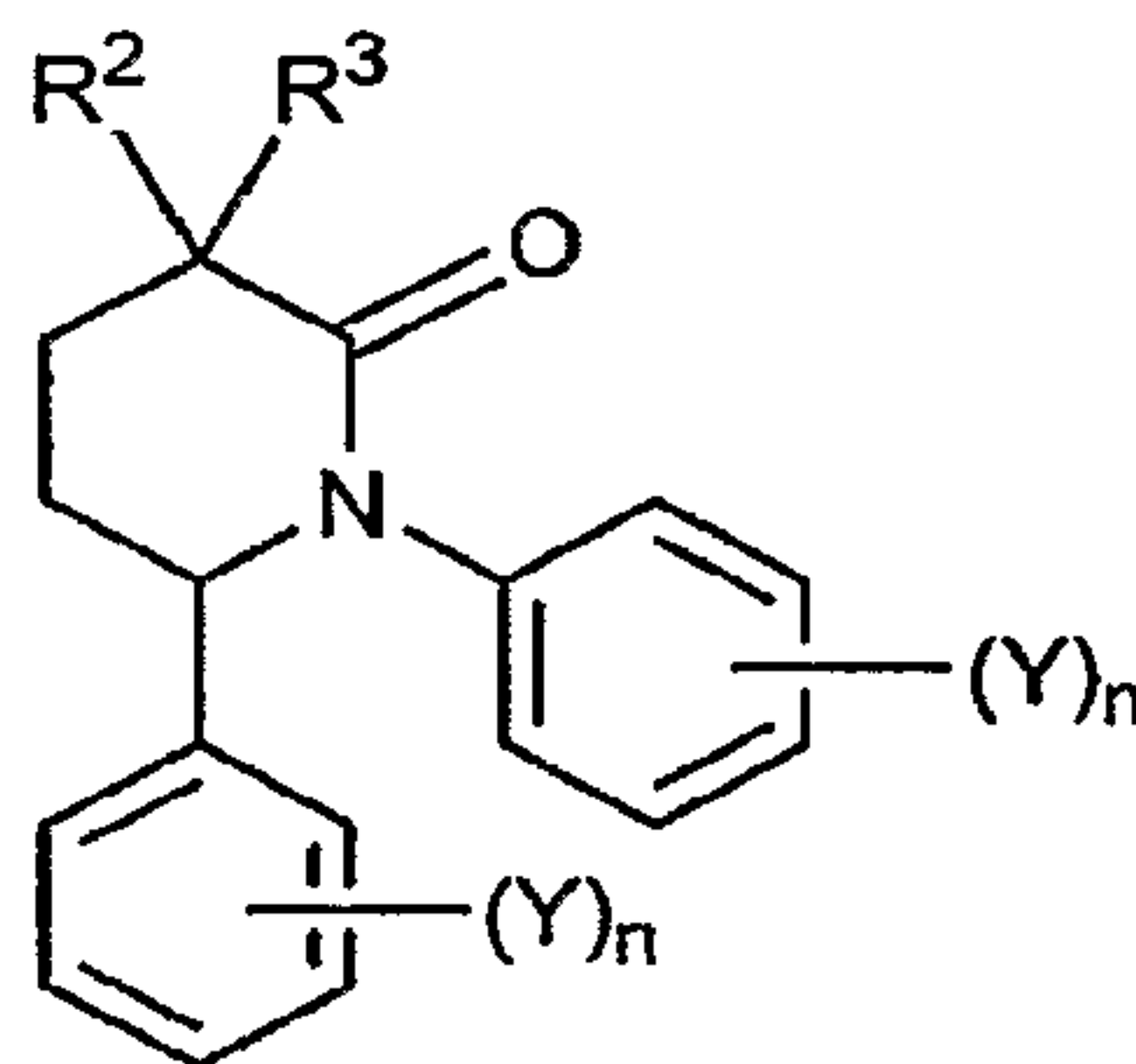
15 each R⁸ is independently selected from the group consisting of H, -S(O)₂-(C₆-C₁₀)aryl, and -S(O)₂-(C₁-C₆)alkyl;

each R⁹ is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl and unsubstituted (C₆-C₁₀)aryl;

each Y is independently selected from the group consisting of halogen,

20 -C(R⁶)₂-N(R⁶)₂, and -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶.

10. The compound of Claim 1 having the structural Formula (ID):



(ID)

25 or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

R² is selected from the group consisting of H, -C(R⁶)₂-(C₆-C₁₀)aryl, and -C(R⁶)₂-O-R⁷,

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wherein the (C₆-C₁₀)aryl portion of said -C(R⁶)₂-(C₆-C₁₀)aryl of R² is unsubstituted or substituted with one or more Y groups;

R³ is selected from the group consisting of -C(R⁶)₂-(C₆-C₁₀)aryl, -C(R⁶)₂-O-R⁷, and -C(R⁶)₂-N(R⁸)₂,

5 wherein the (C₆-C₁₀)aryl portion of said -C(R⁶)₂-(C₆-C₁₀)aryl of R³ is unsubstituted or substituted with one or more Y groups; with the following proviso:

(i) at least one of R² and R³ is not H;

each R⁶ is independently selected from the group consisting of H and (C₁-C₆)alkyl;

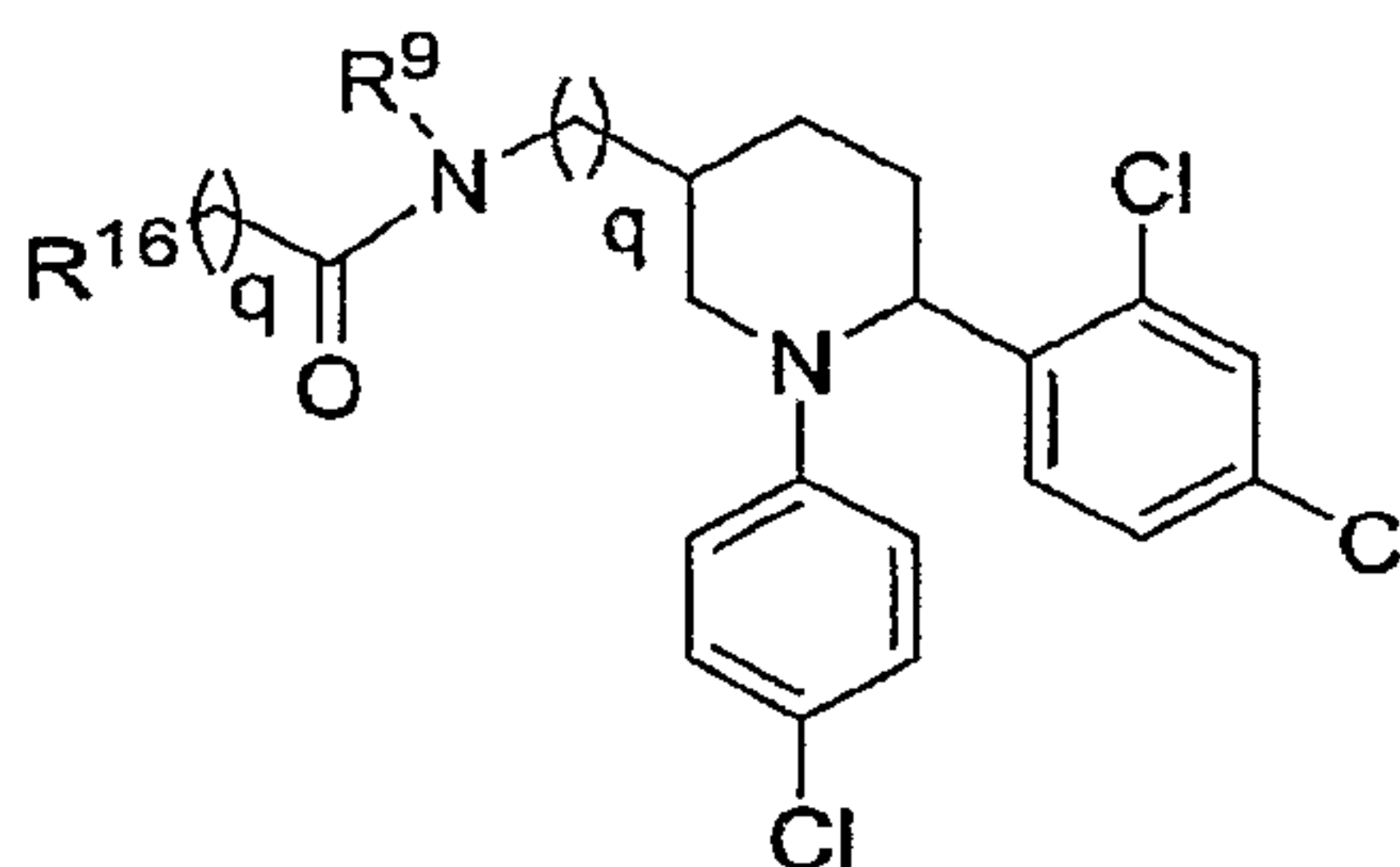
10 R⁷ is selected from the group consisting of H, (C₁-C₆)alkyl, unsubstituted (C₆-C₁₀)aryl, and (C₆-C₁₀)aryl substituted with one or more Y groups;

each R⁸ is independently selected from the group consisting of H, (C₁-C₆)alkyl, -C(O)-(C₆-C₁₀)aryl, -S(O)₂-(C₆-C₁₀)aryl, and -S(O)₂-(C₁-C₆)alkyl;

15 each Y is independently selected from the group consisting of halogen, (C₁-C₆)alkyl, -O-R⁹, -O-C(R⁶)₂-O-, (C₁-C₆)haloalkyl, -CN, -C(R⁶)₂-N(R⁶)₂, and -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶; and

each n is independently an integer from 0-5.

11. The compound of Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, with the following structural formula



wherein:

each R⁶ is independently selected from the group consisting of H and (C₁-C₆)alkyl;

25 each R⁹ is independently selected from the group consisting of H, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, unsubstituted (C₆-C₁₀)aryl and unsubstituted (C₂-C₁₀)heteroaryl;

each R^{12} is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, $-(C(R^6)_2)_q-C(O)R^{13}$, benzo(C₂-C₁₀)heterocyclyl, benzocyclo(C₁-C₆)alkyl, $-(C(R^6)_2)_q-N(R^9)-C(O)R^{13}$, $-(C(R^6)_2)_q-N(R^{14})_2$, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, Y-(C₁-C₆)alkylenyl-O-, W-O-(C₁-C₆)alkylenyl, (C₂-C₁₀)heterocyclyl(C₁-C₆)alkyl, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups, and

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups,

wherein the benzo portion of said benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more Y groups and the (C₂-C₁₀)heterocyclyl portion of benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more X groups,

wherein the benzo portion of said benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more Y groups and the (C₃-C₆)cycloalkyl portion of benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more X groups;

with the following provisos that

for $-N(R^{14})_2$ of R^{12} , the two R^{14} groups, with the ring nitrogen atom to which they are shown attached, form an unsubstituted (C₂-C₁₀)heterocyclyl ring or a (C₂-C₁₀)heterocyclyl ring substituted with one or more X groups;

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each R^{13} is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups;

each R^{14} is independently selected from the group consisting of H, Boc,

unsubstituted (C₁-C₆)alkyl, (C₁-C₆)alkyl substituted with one or more X groups, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl substituted with one or more Y groups, (C₂-C₁₀)heterocyclyl, unsubstituted (C₂-C₁₀)heteroaryl and (C₂-C₁₀)heteroaryl substituted with one or more Y groups;

each R^{16} is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, -(C(R⁶)₂)_p-C(O)R¹³,

-(C(R⁶)₂)_p-N(R⁹)-C(O)R¹³, -(C(R⁶)₂)_p-N(R¹⁴)₂, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups, and

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups,

for -N(R¹⁴)₂, the two R¹⁴ groups, with the ring nitrogen atom to which they are shown attached, form an unsubstituted (C₂-C₁₀)heterocyclyl ring or a (C₂-C₁₀)heterocyclyl ring substituted with one or more X groups;

each W is independently selected from the group consisting of hydrogen,

(C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl,

-C(R⁶)₂-N(R⁶)₂, and -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶;

each X is independently selected from the group consisting of hydrogen, -OH,

(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, Cbz, Boc,

(C₁-C₆)alkylsulfonyl, acetyl, -C(O)-R¹², -C(O)-N(R⁹)₂,

-C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl, -S(O)₂-(C₃-C₆)cycloalkyl,

-C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -(C(R⁶)₂)_m-(C₆-C₁₀)aryl and

(C₆-C₁₀)aryl

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said

-C(O)-(C₂-C₁₀)heteroaryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN, and

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wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said

-(C(R⁶)₂)_m-(C₆-C₁₀)aryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN

5 wherein in a single X moiety, =O, can replace two available hydrogens on the same carbon on a ring system;

each Y is independently selected from the group consisting of hydrogen, halogen,

(C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -O-(C₁-C₆)alkyl,

-O-(C₂-C₁₀)heteroaryl, -O-(C₆-C₁₀)aryl, -O-R⁹, halo(C₁-C₆)alkyl,

10 -O-halo(C₁-C₆)alkyl, -CN, -C(O)-O-(C₁-C₆)alkyl, -N(R⁶)₂, -C(R⁶)₂-N(R⁶)₂,

-S(O)₂-(C₂-C₁₀)heterocyclyl, -S(O)₂-(C₂-C₁₀)heteroaryl and

-C(R⁶)₂-N(R⁶)-S(O)₂-R⁶; or

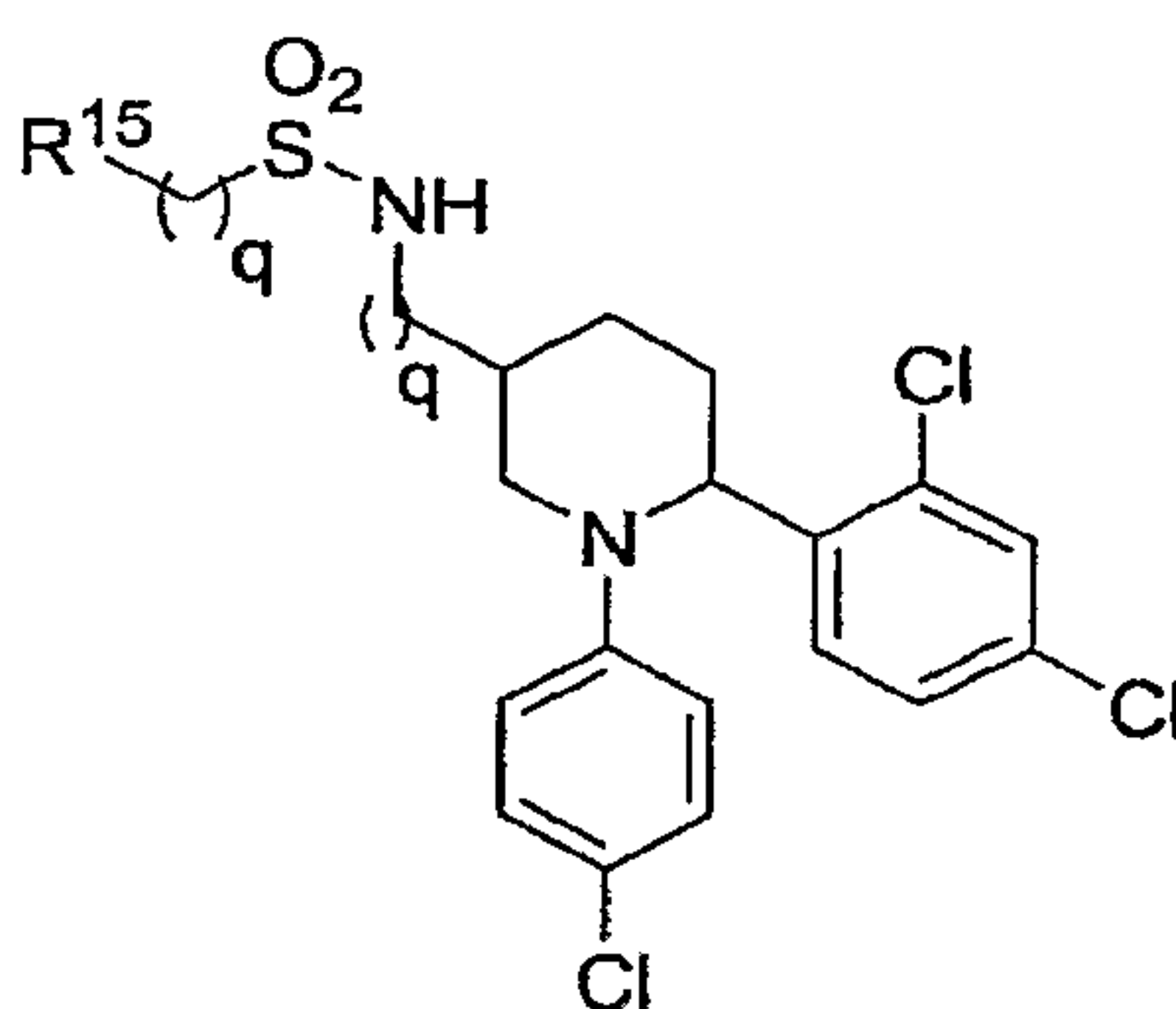
two of said Y groups attached to adjacent carbon atoms form a -O-CH₂-O- or

-O-CH₂CH₂-O- group;

15 each n, p and q is independently an integer from 0-5; and

m is an integer from 1-5.

12. The compound of Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, with the following structural formula



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wherein:

R⁴ is selected from the group consisting of H, -C(O)-(C₁-C₆)alkyl, and (C₁-C₆)alkyl;

R⁵ is selected from the group consisting of -(C(R⁶)₂)_m-G, -S(O)₂-(C₁-C₆)alkyl,

-S(O)₂-(C₃-C₆)cycloalkyl, (C₁-C₆)alkyl, -S(O)-(C₃-C₆)cycloalkyl, -C(O)-(C₃-

25 C₆)cycloalkyl, -S(O)₂-(C₆-C₁₀)aryl, -S(O)₂-(C(R⁶)₂)_m-(C₆-C₁₀)aryl,

-S(O)₂-(C₂-C₁₀)heteroaryl, -C(O)-(C₁-C₆)alkyl, -C(O)-(C₆-C₁₀)aryl,

-C(O)-O-(C₁-C₆)alkyl, -C(O)-O-(C₆-C₁₀)aryl, -C(O)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl,

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-C(O)-(C₃-C₆)cycloalkylene-(C₆-C₁₀)aryl, -C(O)-(C₂-C₁₀)heteroaryl,
 -C(O)-(C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, -C(O)-(C(R⁶)₂)_m-O-(C₆-C₁₀)aryl,
 -C(O)-(benzo-fused (C₃-C₆)cycloalkyl), -S(O)₂-(benzo-fused (C₂-C₁₀)heterocyclyl),
 -C(O)-N(R⁹)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -C(O)-N(R⁹)-(C₆-C₁₀)aryl, (C₃-C₆)cycloalkyl,
 5 benzo-fused (C₃-C₆)cycloalkyl, unsubstituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl substituted
 with one or more Y groups, unsubstituted (C₂-C₁₀)heterocyclyl, and
 (C₂-C₁₀)heterocyclyl substituted with one or more X groups,

wherein the (C₆-C₁₀)aryl or (C₂-C₁₀)heteroaryl portion of said -S(O)₂-(C₆-
 C₁₀)aryl, -S(O)₂-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -S(O)₂-(C₂-C₁₀)heteroaryl, -C(O)-
 10 (C₆-C₁₀)aryl,

-C(O)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -C(O)-(C₃-C₆)cycloalkylene-(C₆-C₁₀)aryl,
 -C(O)-(C₂-C₁₀)heteroaryl, -C(O)-(C(R⁶)₂)_m-O-(C₆-C₁₀)aryl,
 -C(O)-N(R⁹)-(C(R⁶)₂)_m-(C₆-C₁₀)aryl, or -C(O)-N(R⁹)-(C₆-C₁₀)aryl of R⁵ is
 unsubstituted or substituted with one or more Y groups;

15 wherein the heterocyclyl portion of -S(O)₂-(benzo-fused (C₂-C₁₀)heterocyclyl)
 aryl of R⁵ is unsubstituted or substituted with one or more X groups;

each R⁶ is independently selected from the group consisting of H and (C₁-C₆)alkyl;

R⁷ is selected from the group consisting of H, (C₁-C₆)alkyl, unsubstituted
 (C₂-C₁₀)heteroaryl and (C₂-C₁₀)heteroaryl substituted with one or more Y groups,
 20 unsubstituted (C₆-C₁₀)aryl, and (C₆-C₁₀)aryl substituted with one or more Y
 groups;

each R⁸ is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₆-
 C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, unsubstituted (C₆-C₁₀)aryl,
 unsubstituted (C₂-C₁₀)heteroaryl,

25 -C(O)-(C₁-C₆)alkyl, -C(O)-(C₆-C₁₀)aryl, -C(O)-(C₃-C₆)cycloalkyl, -C(O)N(R⁹)₂,
 -S(O)₂-(C₆-C₁₀)aryl, -S(O)₂-(C₂-C₁₀)heteroaryl, -SO₂N(R⁹)₂,

-S(O)₂-(C₃-C₆)cycloalkyl, (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl substituted with one
 or more Y groups, and -S(O)₂-(C₁-C₆)alkyl,

wherein the (C₆-C₁₀)aryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl, -C(O)-(C₆-
 30 C₁₀)aryl or -S(O)₂-(C₆-C₁₀)aryl and the (C₂-C₁₀)heteroaryl portion of said
 (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, -S(O)₂-(C₂-C₁₀)heteroaryl of R⁸ is
 unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc;

5 each R⁹ is independently selected from the group consisting of H, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, unsubstituted (C₆-C₁₀)aryl and unsubstituted (C₂-C₁₀)heteroaryl;

each R¹² is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, -(C(R⁶)₂)_q-C(O)R¹³, benzo(C₂-C₁₀)heterocyclyl, benzocyclo(C₁-C₆)alkyl, 10 -(C(R⁶)₂)_q-N(R⁹)-C(O)R¹³, -(C(R⁶)₂)_q-N(R¹⁴)₂, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, Y-(C₁-C₆)alkylenyl-O-, W-O-(C₁-C₆)alkylenyl, (C₂-C₁₀)heterocyclyl(C₁-C₆)alkyl, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, 15 unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups, and

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-

20 C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted 25 on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups,

wherein the benzo portion of said benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more Y groups and the (C₂-C₁₀)heterocyclyl portion 30 of benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more X groups,

wherein the benzo portion of said benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more Y groups and the (C₃-C₆)cycloalkyl portion of benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more X groups;

5 with the following provisos that

for -N(R¹⁴)₂ of R¹², the two R¹⁴ groups, with the ring nitrogen atom to which they are shown attached, form an unsubstituted (C₂-C₁₀)heterocyclyl ring or a (C₂-C₁₀)heterocyclyl ring substituted with one or more X groups;

each R¹³ is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

20 wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups;

each R¹⁴ is independently selected from the group consisting of H, Boc, unsubstituted (C₁-C₆)alkyl, (C₁-C₆)alkyl substituted with one or more X groups, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl substituted with one or more Y groups, (C₂-C₁₀)heterocyclyl, unsubstituted (C₂-C₁₀)heteroaryl and (C₂-C₁₀)heteroaryl substituted with one or more Y groups;

each R^{15} is independently selected from the group consisting of H, (C_1-C_6) alkyl, -
 $N(R^4)(R^5)$, $(C(R^6)_2)_q-N(R^{14})_2$, (C_1-C_6) alkylenyl- CF_3 , $-CF_3$, $(C_3-$
 $C_6)$ cycloalkyl (C_1-C_6) alkyl, unsubstituted (C_3-C_6) cycloalkyl, (C_3-C_6) cycloalkyl
substituted with one or more X groups, unsubstituted (C_2-C_{10}) heterocyclyl,
5 (C_2-C_{10}) heterocyclyl substituted with one or more X groups,
benzo (C_2-C_{10}) heterocyclyl, benzocyclo (C_1-C_6) alkyl, unsubstituted
 (C_2-C_{10}) heteroaryl, (C_2-C_{10}) heteroaryl substituted with one or more Y groups,
unsubstituted (C_6-C_{10}) aryl and (C_6-C_{10}) aryl substituted with one or more Y
groups,

10 wherein the (C_1-C_6) alkyl portion of said (C_3-C_6) cycloalkyl (C_1-C_6) alkyl is
unsubstituted or substituted with one or more X groups with the proviso
that X substituted on said (C_1-C_6) alkyl portion is NOT Cbz or Boc,
wherein the (C_3-C_6) cycloalkyl of said (C_3-C_6) cycloalkyl (C_1-C_6) alkyl is
unsubstituted or substituted with one or more X groups,

15 wherein the benzo portion of said benzo (C_2-C_{10}) heterocyclyl can be optionally
substituted with one or more Y groups and the (C_2-C_{10}) heterocyclyl portion
of benzo (C_2-C_{10}) heterocyclyl can be optionally substituted with one or
more X groups,

wherein the benzo portion of said benzocyclo (C_1-C_6) alkyl can be optionally

20 substituted with one or more Y groups and the (C_3-C_6) cycloalkyl portion of
benzocyclo (C_1-C_6) alkyl can be optionally substituted with one or more X groups;

G is selected from the group consisting of H, (C_1-C_6) alkyl, unsubstituted (C_6-C_{10}) aryl,
 (C_6-C_{10}) aryl substituted with one or more Y groups, $-CN$, (C_3-C_6) cycloalkyl, $-O-R^7$,
 $-S-R^7$, unsubstituted (C_2-C_{10}) heteroaryl, (C_2-C_{10}) heteroaryl substituted with one or
25 more Y groups, $-N(R^8)_2$, unsubstituted (C_2-C_{10}) heterocyclyl, and
 (C_2-C_{10}) heterocyclyl substituted with one or more X groups;

each W is independently selected from the group consisting of hydrogen,

(C_1-C_6) alkyl, (C_6-C_{10}) aryl, $-C(O)-(C_1-C_6)$ alkyl, $-C(O)-O-(C_1-C_6)$ alkyl,
 $-C(R^6)_2-N(R^6)_2$, and $-C(R^6)_2-N(R^6)-S(O)_2-R^6$;

30 each X is independently selected from the group consisting of hydrogen, $-OH$,
 (C_1-C_6) alkyl, (C_6-C_{10}) aryl (C_1-C_6) alkyl, (C_2-C_{10}) heteroaryl (C_1-C_6) alkyl, Cbz, Boc,
 (C_1-C_6) alkylsulfonyl, acetyl, $-C(O)-R^{12}$, $-C(O)-N(R^9)_2$,

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-C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl, -S(O)₂-(C₃-C₆)cycloalkyl,
 -C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -(C(R⁶)₂)_m-(C₆-C₁₀)aryl and
 (C₆-C₁₀)aryl

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-
 5 (C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or
 substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and
 (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or
 more X groups with the proviso that X substituted on said (C₁-C₆)alkyl
 10 portion is NOT Cbz or Boc,

wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said
 -C(O)-(C₂-C₁₀)heteroaryl of X is unsubstituted or substituted with one or
 more substituents selected from the group consisting of halogen, -OH,
 -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN, and

15 wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said
 -(C(R⁶)₂)_m-(C₆-C₁₀)aryl of X is unsubstituted or substituted with one or
 more substituents selected from the group consisting of halogen, -OH,
 -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN

wherein in a single X moiety, =O, can replace two available hydrogens on
 20 the same carbon on a ring system;

each Y is independently selected from the group consisting of hydrogen, halogen,
 (C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -O-(C₁-C₆)alkyl,
 -O-(C₂-C₁₀)heteroaryl, -O-(C₆-C₁₀)aryl, -O-R⁹, halo(C₁-C₆)alkyl,
 -O-halo(C₁-C₆)alkyl, -CN, -C(O)-O-(C₁-C₆)alkyl, -N(R⁶)₂, -C(R⁶)₂-N(R⁶)₂,
 25 -S(O)₂-(C₂-C₁₀)heterocyclyl, -S(O)₂-(C₂-C₁₀)heteroaryl and
 -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶; or

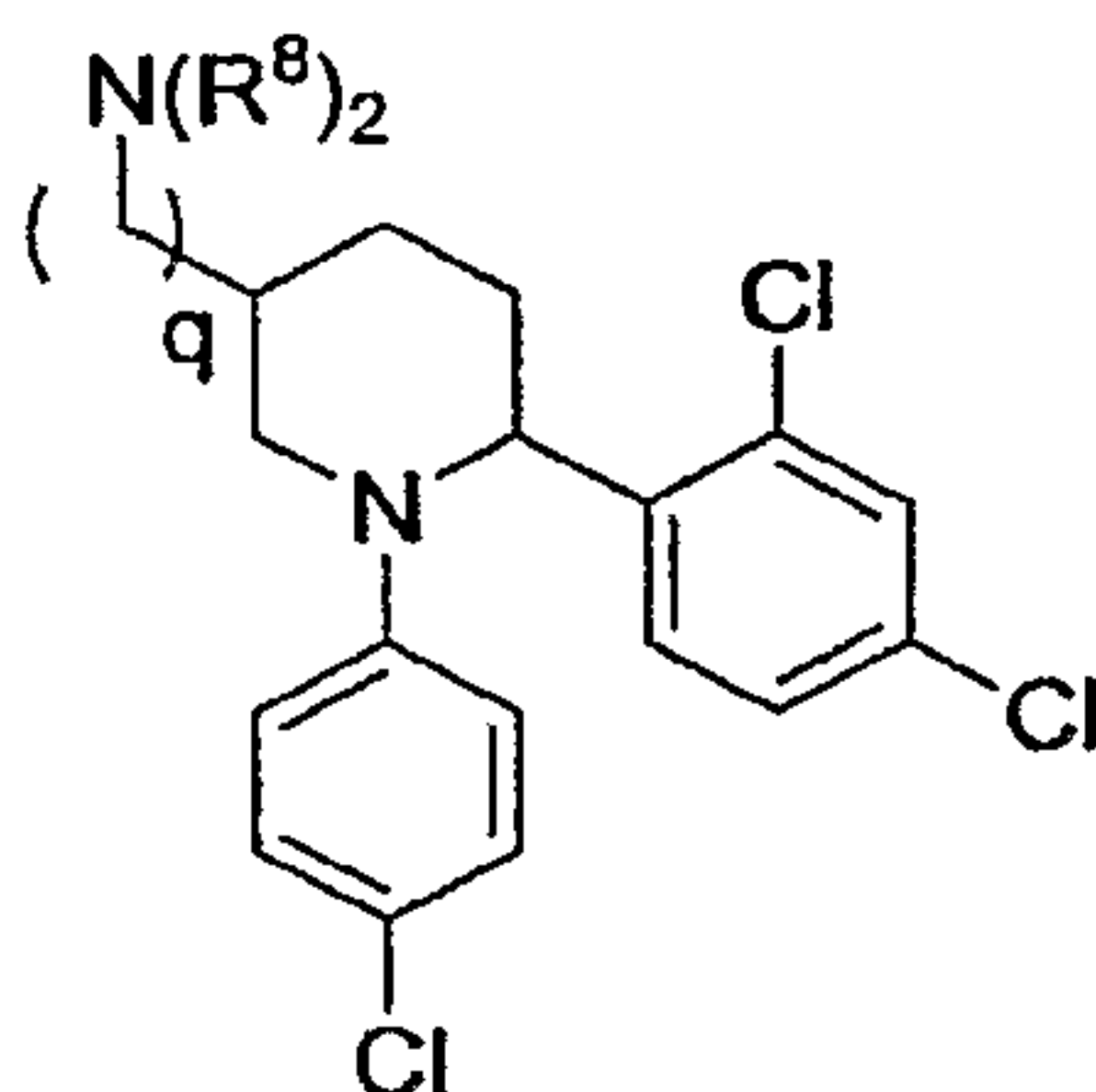
two of said Y groups attached to adjacent carbon atoms form a -O-CH₂-O- or
 -O-CH₂CH₂-O- group;

each n, p and q is independently an integer from 0-5; and

30 m is an integer from 1-5.

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13. The compound of Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, with the following structural formula



5 wherein:

each R^6 is independently selected from the group consisting of H and (C_1-C_6) alkyl;

each R^8 is independently selected from the group consisting of H, (C_1-C_6) alkyl, (C_6-C_{10}) aryl, (C_1-C_6) alkyl, (C_2-C_{10}) heteroaryl, unsubstituted (C_6-C_{10}) aryl, unsubstituted (C_2-C_{10}) heteroaryl,

10 $-C(O)-(C_1-C_6)$ alkyl, $-C(O)-(C_6-C_{10})$ aryl, $-C(O)-(C_3-C_6)$ cycloalkyl, $-C(O)N(R^9)_2$, $-S(O)_2-(C_6-C_{10})$ aryl, $-S(O)_2-(C_2-C_{10})$ heteroaryl, $-SO_2N(R^9)_2$, $-S(O)_2-(C_3-C_6)$ cycloalkyl, (C_6-C_{10}) aryl and (C_2-C_{10}) heteroaryl substituted with one or more Y groups, and $-S(O)_2-(C_1-C_6)$ alkyl,

15 wherein the (C_6-C_{10}) aryl portion of said (C_6-C_{10}) aryl, $-C(O)-(C_6-C_{10})$ aryl or $-S(O)_2-(C_6-C_{10})$ aryl and the (C_2-C_{10}) heteroaryl portion of said (C_2-C_{10}) heteroaryl, $-S(O)_2-(C_2-C_{10})$ heteroaryl of R^8 is unsubstituted or substituted with one or more Y groups,

20 wherein the (C_1-C_6) alkyl portion of said (C_6-C_{10}) aryl, (C_1-C_6) alkyl and (C_2-C_{10}) heteroaryl, (C_1-C_6) alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C_1-C_6) alkyl portion is NOT Cbz or Boc;

each R^9 is independently selected from the group consisting of H, (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, hydroxy (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, unsubstituted (C_6-C_{10}) aryl and unsubstituted (C_2-C_{10}) heteroaryl;

25 each Y is independently selected from the group consisting of hydrogen, halogen, (C_1-C_6) alkyl, (C_6-C_{10}) aryl, $-C(O)-(C_1-C_6)$ alkyl, $-O-(C_1-C_6)$ alkyl, $-O-(C_2-C_{10})$ heteroaryl, $-O-(C_6-C_{10})$ aryl, $-O-R^9$, halo (C_1-C_6) alkyl, $-O$ -halo (C_1-C_6) alkyl, $-CN$, $-C(O)-O-(C_1-C_6)$ alkyl, $-N(R^6)_2$, $-C(R^6)_2-N(R^6)_2$,

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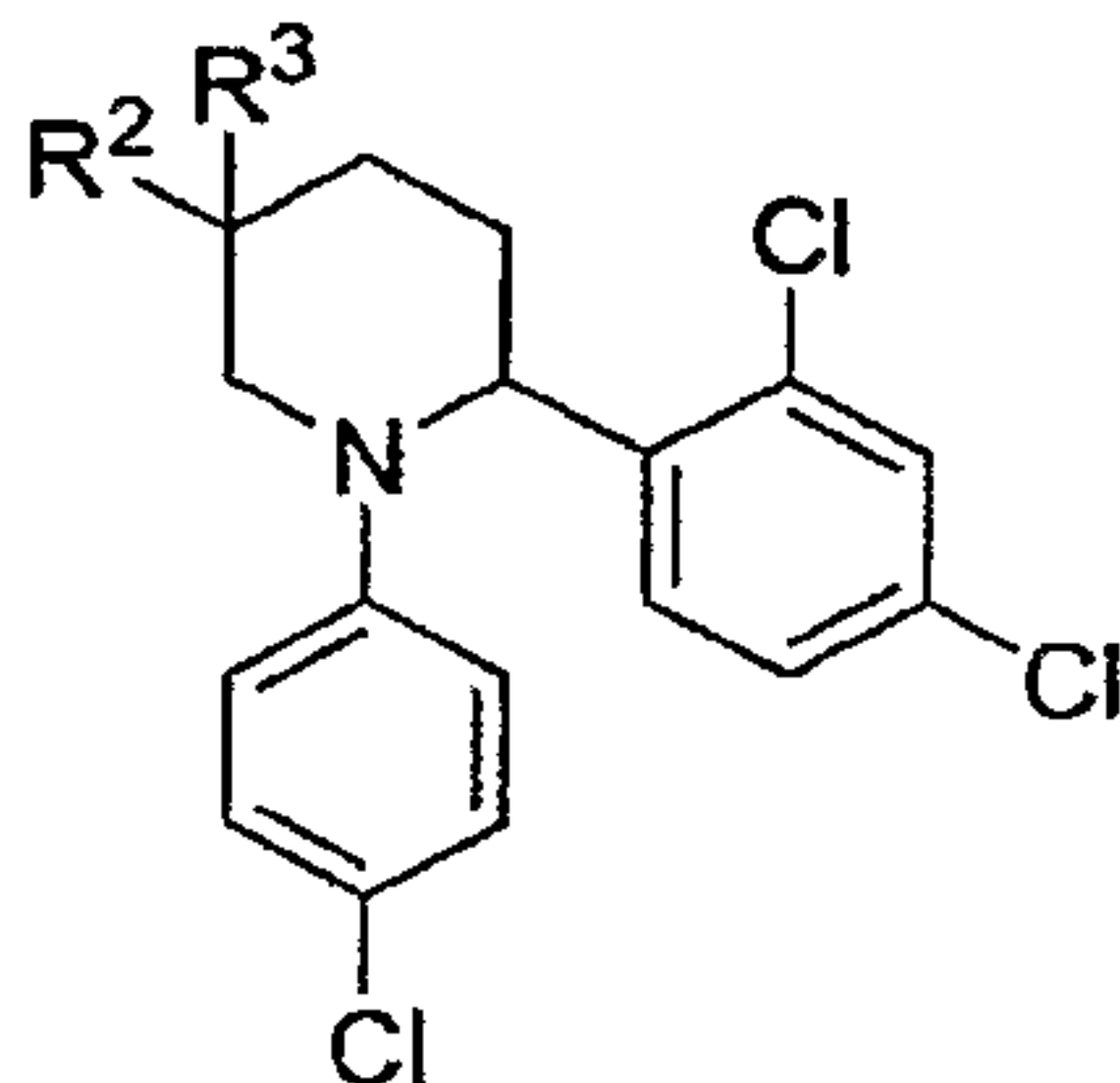
-S(O)₂-(C₂-C₁₀)heterocyclyl, -S(O)₂-(C₂-C₁₀)heteroaryl and
 -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶; or

two of said Y groups attached to adjacent carbon atoms form a -O-CH₂-O- or
 -O-CH₂CH₂-O- group;

5 each q is independently an integer from 0 to 5.

14. The compound of Claim 1, or a pharmaceutically acceptable salt, solvate or
 ester thereof, with the following structural formula

10



wherein

R² is selected from the group consisting of H, -(C(R⁶)₂)_p-(C₆-C₁₀)aryl, (C₃-
 C₆)cycloalkyl(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl substituted with Z,
 15 -(C(R⁶)₂)_q-(C₂-C₁₀)heterocyclyl, -(C(R⁶)₂)_p-S(O)₂-(C₂-C₁₀)heterocyclyl, and -
 C(R⁶)₂-O-R⁷,

wherein the (C₆-C₁₀)aryl portion of said -(C(R⁶)₂)_p-(C₆-C₁₀)aryl of R² is
 unsubstituted or substituted with one or more Y groups,

wherein the (C₂-C₁₀)heterocyclyl portion of said

20

-(C(R⁶)₂)_p-S(O)₂-(C₂-C₁₀)heterocyclyl of R² is unsubstituted or
 substituted with one or more X groups,

wherein the (C₂-C₁₀)heterocyclyl portion of said

-(C(R⁶)₂)_q-(C₂-C₁₀)heterocyclyl of R² is unsubstituted or substituted with
 one or more X groups;

25

R³ is selected from the group consisting of H, -(C(R⁶)₂)_q-C(O)-N(R¹²)₂ or
 -(C(R⁶)₂)_q-N(R⁸)₂;

each R⁶ is independently selected from the group consisting of H and (C₁-C₆)alkyl;

R^7 is selected from the group consisting of H, (C₁-C₆)alkyl, unsubstituted (C₂-C₁₀)heteroaryl and (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl, and (C₆-C₁₀)aryl substituted with one or more Y groups;

- 5 each R^8 is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, unsubstituted (C₆-C₁₀)aryl, unsubstituted (C₂-C₁₀)heteroaryl, -C(O)-(C₁-C₆)alkyl, -C(O)-(C₆-C₁₀)aryl, -C(O)-(C₃-C₆)cycloalkyl, -C(O)N(R⁹)₂, -S(O)₂-(C₆-C₁₀)aryl, -S(O)₂-(C₂-C₁₀)heteroaryl, -SO₂N(R⁹)₂,
 10 -S(O)₂-(C₃-C₆)cycloalkyl, (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl substituted with one or more Y groups, and -S(O)₂-(C₁-C₆)alkyl,

wherein the (C₆-C₁₀)aryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl, -C(O)-(C₆-C₁₀)aryl or -S(O)₂-(C₆-C₁₀)aryl and the (C₂-C₁₀)heteroaryl portion of said (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, -S(O)₂-(C₂-C₁₀)heteroaryl of R^8 is
 15 unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc;

- 20 each R^9 is independently selected from the group consisting of H, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, unsubstituted (C₆-C₁₀)aryl and unsubstituted (C₂-C₁₀)heteroaryl;

each R^{12} is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, -(C(R⁶)₂)_q-C(O)R¹³, benzo(C₂-C₁₀)heterocyclyl, benzocyclo(C₁-C₆)alkyl,
 25 -(C(R⁶)₂)_q-N(R⁹)-C(O)R¹³, -(C(R⁶)₂)_q-N(R¹⁴)₂, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, Y-(C₁-C₆)alkylenyl-O-, W-O-(C₁-C₆)alkylenyl, (C₂-C₁₀)heterocyclyl(C₁-C₆)alkyl, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with
 30 one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl

substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups, and

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups,

wherein the benzo portion of said benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more Y groups and the (C₂-C₁₀)heterocyclyl portion of benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more X groups,

wherein the benzo portion of said benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more Y groups and the (C₃-C₆)cycloalkyl portion of benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more X groups;

with the following provisos that

for -N(R¹⁴)₂ of R¹², the two R¹⁴ groups, with the ring nitrogen atom to which they are shown attached, form an unsubstituted (C₂-C₁₀)heterocyclyl ring or a (C₂-C₁₀)heterocyclyl ring substituted with one or more X groups;

each R¹³ is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups

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wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups;

each R¹⁴ is independently selected from the group consisting of H, Boc, unsubstituted (C₁-C₆)alkyl, (C₁-C₆)alkyl substituted with one or more X groups, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl substituted with one or more Y groups, (C₂-C₁₀)heterocyclyl, unsubstituted (C₂-C₁₀)heteroaryl and (C₂-C₁₀)heteroaryl substituted with one or more Y groups;

each W is independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -C(R⁶)₂-N(R⁶)₂, and -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶;

each X is independently selected from the group consisting of hydrogen, -OH,

(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, Cbz, Boc, (C₁-C₆)alkylsulfonyl, acetyl, -C(O)-R¹², -C(O)-N(R⁹)₂, -C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl, -S(O)₂-(C₃-C₆)cycloalkyl, -C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -(C(R⁶)₂)_m-(C₆-C₁₀)aryl and (C₆-C₁₀)aryl

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

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wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said
 -C(O)-(C₂-C₁₀)heteroaryl of X is unsubstituted or substituted with one or
 more substituents selected from the group consisting of halogen, -OH,
 -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN, and

5 wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said
 -(C(R⁶)₂)_m-(C₆-C₁₀)aryl of X is unsubstituted or substituted with one or
 more substituents selected from the group consisting of halogen, -OH,
 -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN

10 wherein in a single X moiety, =O, can replace two available hydrogens on
 the same carbon on a ring system;

each Y is independently selected from the group consisting of hydrogen, halogen,
 (C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -O-(C₁-C₆)alkyl,
 -O-(C₂-C₁₀)heteroaryl, -O-(C₆-C₁₀)aryl, -O-R⁹, halo(C₁-C₆)alkyl,
 -O-halo(C₁-C₆)alkyl, -CN, -C(O)-O-(C₁-C₆)alkyl, -N(R⁶)₂, -C(R⁶)₂-N(R⁶)₂,
 15 -S(O)₂-(C₂-C₁₀)heterocyclyl, -S(O)₂-(C₂-C₁₀)heteroaryl and
 -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶; or

two of said Y groups attached to adjacent carbon atoms form a -O-CH₂-O- or
 -O-CH₂CH₂-O- group;

20 each Z is independently selected from the group consisting of hydrogen,
 (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl,
 -C(O)-N(R⁹)₂, -C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl,
 -S(O)₂-(C₃-C₆)cycloalkyl, -C(O)-(C₁-C₆)alkyl,
 -(C(R⁶)₂)_m-(C₆-C₁₀)aryl, -N(R⁶)-S(O)₂-R⁹ and (C₆-C₁₀)aryl

25 wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-
 C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or
 substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and
 (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or
 more X groups with the proviso that X substituted on said (C₁-C₆)alkyl
 30 portion is NOT Cbz or Boc,

wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said
 -C(O)-(C₂-C₁₀)heteroaryl of Z is unsubstituted or substituted with one or

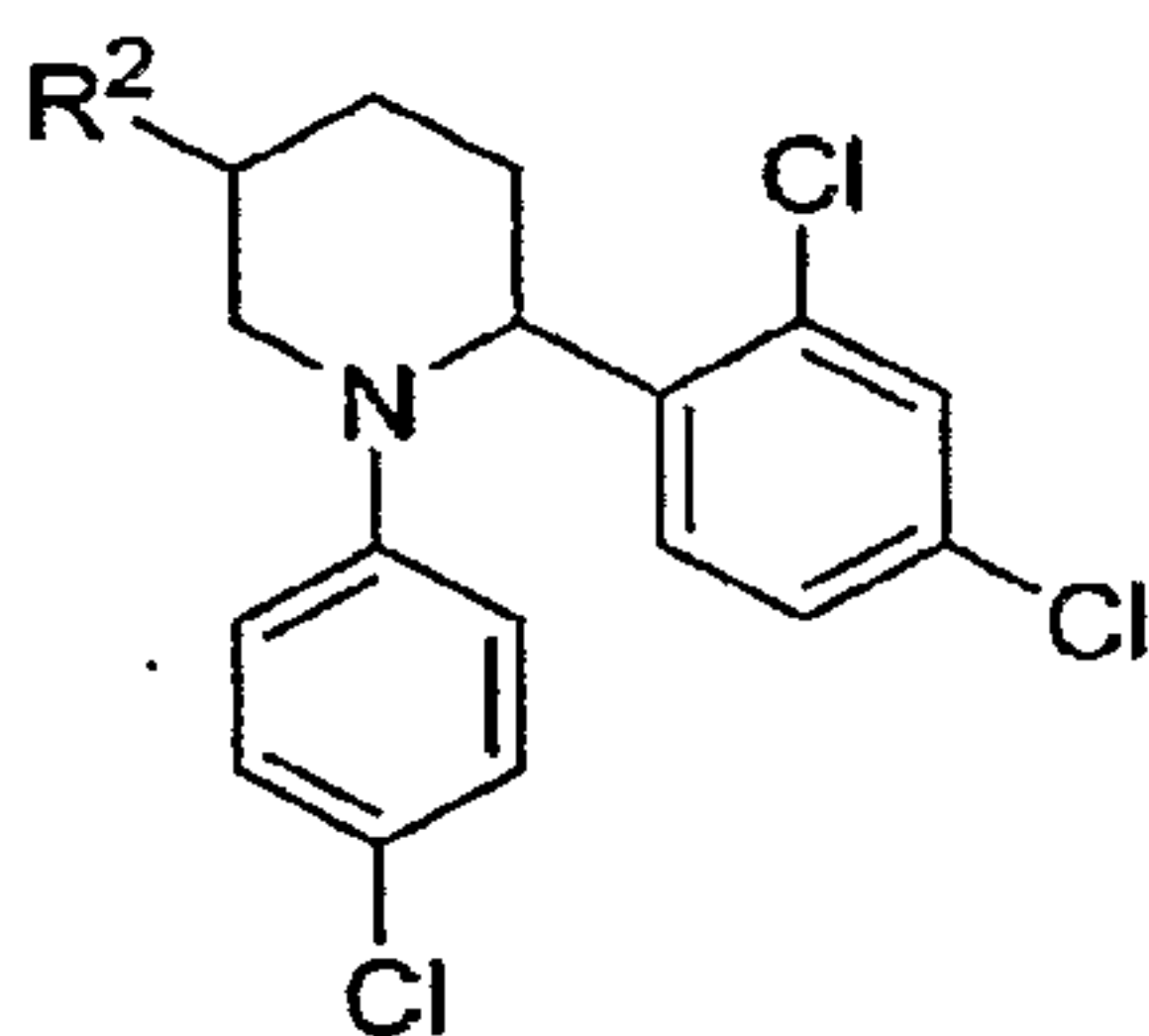
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more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN, and wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said -(C(R⁶)₂)_m-(C₆-C₁₀)aryl of Z is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN; wherein in a single Z moiety, =O, can replace two available hydrogens on the same carbon on a ring system;

each n, p and q is independently an integer from 0-5; and

m is an integer from 1-5.

15. The compound of Claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof, with the following structural formula



wherein;

R² is -(C(R⁶)₂)_q-(C₂-C₁₀)heterocyclyl;

wherein the (C₂-C₁₀)heterocyclyl portion of said

-(C(R⁶)₂)_q-(C₂-C₁₀)heterocyclyl of R² is unsubstituted or substituted with one or more X groups;

each R⁶ is independently selected from the group consisting of H and (C₁-C₆)alkyl;

each R⁹ is independently selected from the group consisting of H, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, unsubstituted (C₆-C₁₀)aryl and unsubstituted (C₂-C₁₀)heteroaryl;

each R¹² is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, -(C(R⁶)₂)_q-C(O)R¹³, benzo(C₂-C₁₀)heterocyclyl, benzocyclo(C₁-C₆)alkyl, -(C(R⁶)₂)_q-N(R⁹)-C(O)R¹³, -(C(R⁶)₂)_q-N(R¹⁴)₂, (C₆-C₁₀)aryl(C₁-C₆)alkyl,

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(C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, Y-(C₁-C₆)alkylenyl-O-, W-O-(C₁-C₆)alkylenyl, (C₂-C₁₀)heterocyclyl(C₁-C₆)alkyl, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups, and

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups,

wherein the benzo portion of said benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more Y groups and the (C₂-C₁₀)heterocyclyl portion of benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more X groups,

wherein the benzo portion of said benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more Y groups and the (C₃-C₆)cycloalkyl portion of benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more X groups;

with the following provisos that

for -N(R¹⁴)₂ of R¹², the two R¹⁴ groups, with the ring nitrogen atom to which they are shown attached, form an unsubstituted (C₂-C₁₀)heterocyclyl ring or a (C₂-C₁₀)heterocyclyl ring substituted with one or more X groups;

each R¹³ is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups,

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unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups

5 wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

10 wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups;

each R¹⁴ is independently selected from the group consisting of H, Boc,

15 unsubstituted (C₁-C₆)alkyl, (C₁-C₆)alkyl substituted with one or more X groups, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl substituted with one or more Y groups, (C₂-C₁₀)heterocyclyl, unsubstituted (C₂-C₁₀)heteroaryl and (C₂-C₁₀)heteroaryl substituted with one or more Y groups;

20 each W is independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -C(R⁶)₂-N(R⁶)₂, and -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶;

each X is independently selected from the group consisting of hydrogen, -OH,

25 (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, Cbz, Boc, (C₁-C₆)alkylsulfonyl, acetyl, -C(O)-R¹², -C(O)-N(R⁹)₂, -C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl, -S(O)₂-(C₃-C₆)cycloalkyl, -C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -(C(R⁶)₂)_m-(C₆-C₁₀)aryl and (C₆-C₁₀)aryl

30 wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

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wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

5 wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said -C(O)-(C₂-C₁₀)heteroaryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN, and

10 wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said -(C(R⁶)₂)_m-(C₆-C₁₀)aryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN

wherein in a single X moiety, =O, can replace two available hydrogens on the same carbon on a ring system;

15 each Y is independently selected from the group consisting of hydrogen, halogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -O-(C₁-C₆)alkyl, -O-(C₂-C₁₀)heteroaryl, -O-(C₆-C₁₀)aryl, -O-R⁹, halo(C₁-C₆)alkyl, -O-halo(C₁-C₆)alkyl, -CN, -C(O)-O-(C₁-C₆)alkyl, -N(R⁶)₂, -C(R⁶)₂-N(R⁶)₂, -S(O)₂-(C₂-C₁₀)heterocyclyl, -S(O)₂-(C₂-C₁₀)heteroaryl and
20 -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶; or

two of said Y groups attached to adjacent carbon atoms form a -O-CH₂-O- or -O-CH₂CH₂-O- group;

each n, p and q is independently an integer from 0-5; and

m is an integer from 1-5.

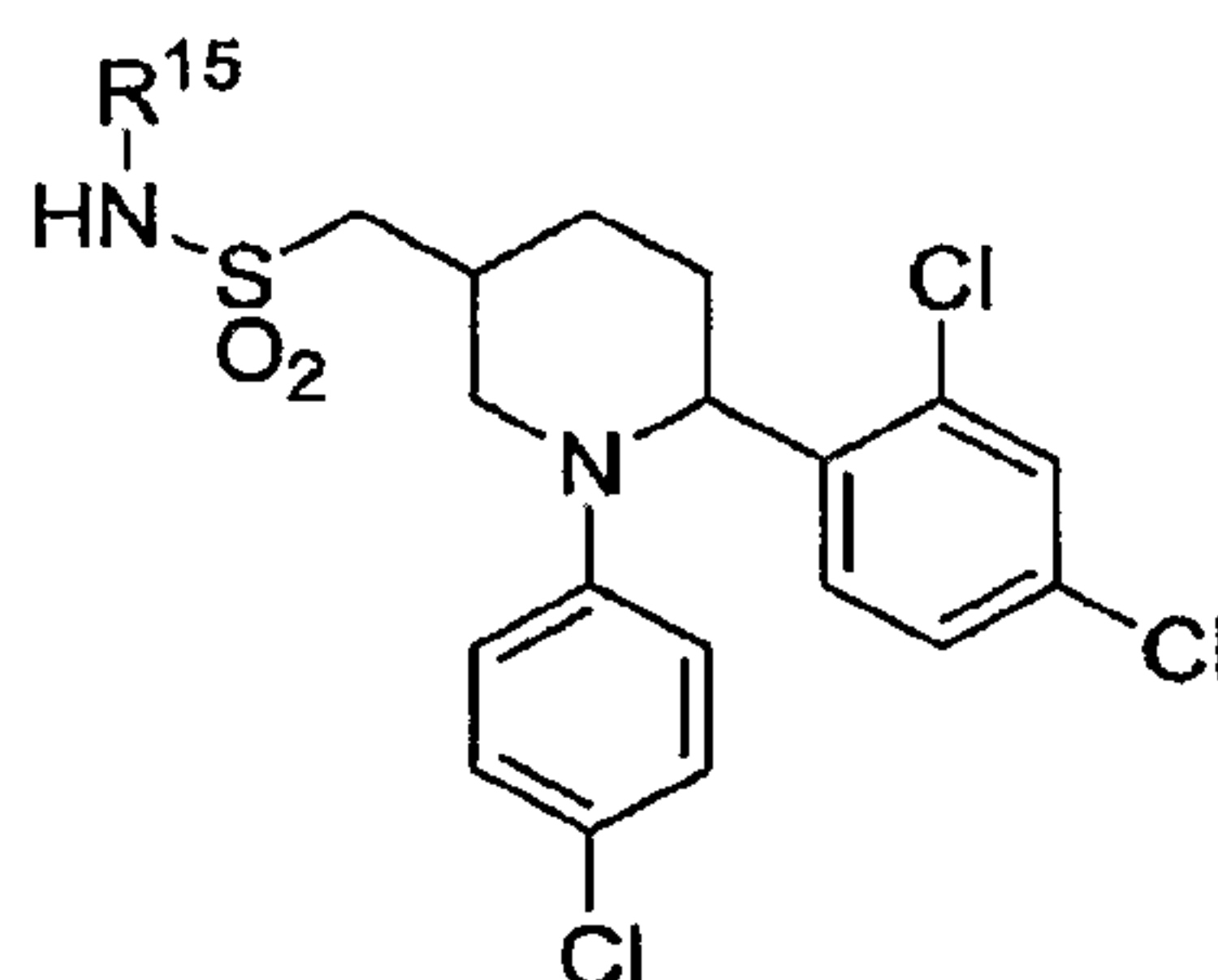
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16. The compound of claim 15 wherein R³ is -C(R⁶)₂)_q-N(R⁸)₂ or -C(R⁶)₂)_q-(C₂-C₁₀)heterocyclyl.

17. The compound of Claim 1 having the structural formula:

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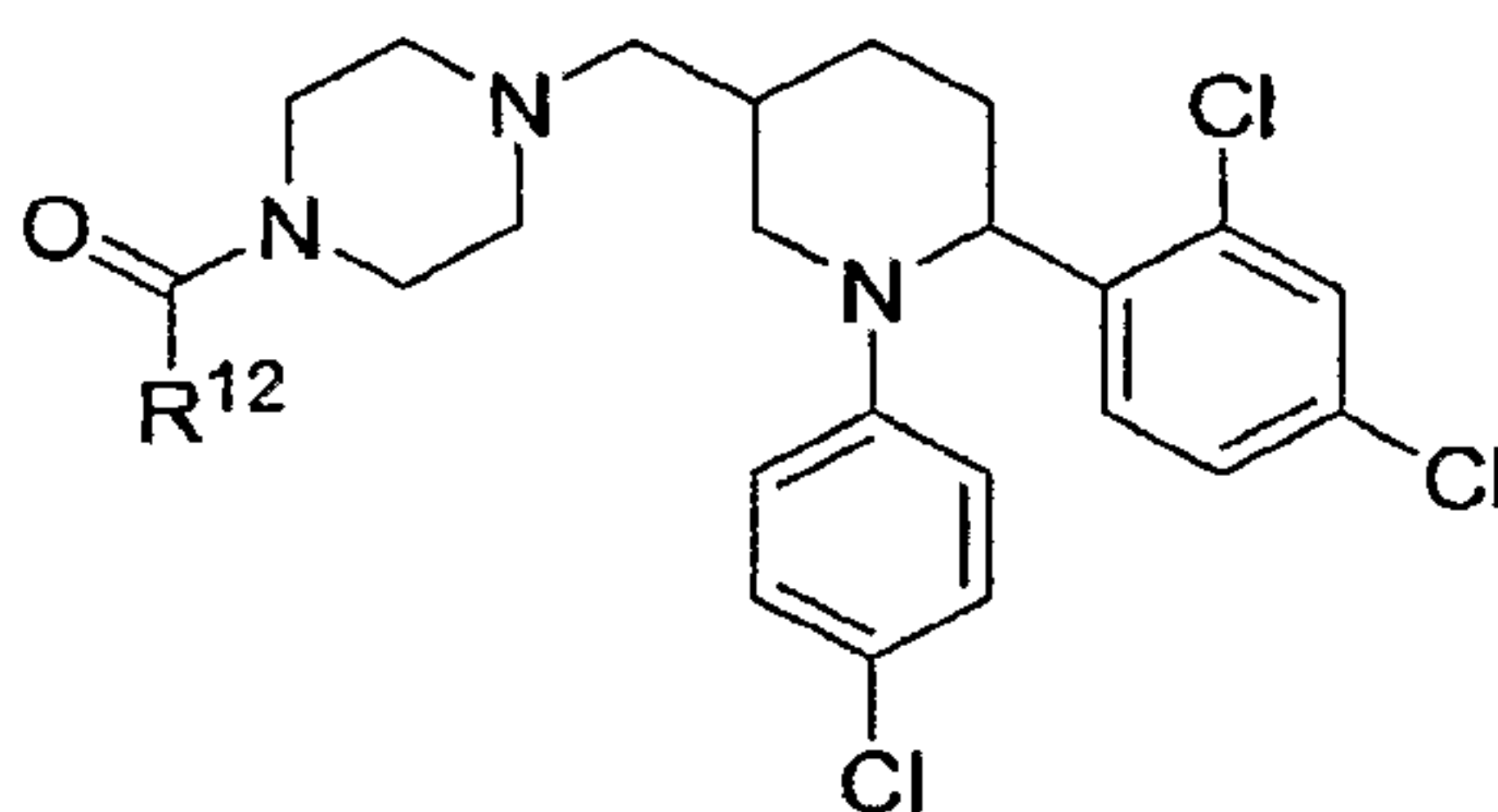
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or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

R^{15} is alkyl.

- 5 18. The compound of Claim 1 having the structural formula



or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

each R^6 is independently selected from the group consisting of H and (C_1-C_6) alkyl;

- 10 each R^9 is independently selected from the group consisting of H, (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, hydroxy (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, unsubstituted (C_6-C_{10}) aryl and unsubstituted (C_2-C_{10}) heteroaryl;

each R^{12} is independently selected from the group consisting of H, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, (C_1-C_6) alkyl, $-(C(R^6)_2)_q-C(O)R^{13}$, benzo (C_2-C_{10}) heterocyclyl,

- 15 benzocyclo (C_1-C_6) alkyl, $-(C(R^6)_2)_q-N(R^9)-C(O)R^{13}$, $-(C(R^6)_2)_q-N(R^{14})_2$, (C_6-C_{10}) aryl (C_1-C_6) alkyl, (C_2-C_{10}) heteroaryl (C_1-C_6) alkyl, HO- (C_1-C_6) alkyl-, (C_1-C_6) alkyl-O-, (C_6-C_{10}) aryl-O-, Y- (C_1-C_6) alkylenyl-O-, W-O- (C_1-C_6) alkylenyl, (C_2-C_{10}) heterocyclyl (C_1-C_6) alkyl, unsubstituted (C_3-C_6) cycloalkyl, (C_3-C_6) cycloalkyl substituted with one or more X groups, unsubstituted (C_2-C_{10}) heterocyclyl, (C_2-C_{10}) heterocyclyl substituted with one or more X groups, unsubstituted (C_2-C_{10}) heteroaryl, (C_2-C_{10}) heteroaryl substituted with one or more Y groups, unsubstituted (C_6-C_{10}) aryl and (C_6-C_{10}) aryl substituted with one or more Y groups, and
- 20

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups,

wherein the benzo portion of said benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more Y groups and the (C₂-C₁₀)heterocyclyl portion of benzo(C₂-C₁₀)heterocyclyl can be optionally substituted with one or more X groups,

wherein the benzo portion of said benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more Y groups and the (C₃-C₆)cycloalkyl portion of benzocyclo(C₁-C₆)alkyl can be optionally substituted with one or more X groups;

with the following provisos that

for -N(R¹⁴)₂ of R¹², the two R¹⁴ groups, with the ring nitrogen atom to which they are shown attached, form an unsubstituted (C₂-C₁₀)heterocyclyl ring or a (C₂-C₁₀)heterocyclyl ring substituted with one or more X groups;

each R¹³ is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, HO-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-, (C₆-C₁₀)aryl-O-, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heterocyclyl, (C₂-C₁₀)heterocyclyl substituted with one or more X groups, unsubstituted (C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl and (C₆-C₁₀)aryl substituted with one or more Y groups

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

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wherein the (C₁-C₆)alkyl portion of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

5 wherein the (C₃-C₆)cycloalkyl of said (C₃-C₆)cycloalkyl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups;

each R¹⁴ is independently selected from the group consisting of H, Boc,

unsubstituted (C₁-C₆)alkyl, (C₁-C₆)alkyl substituted with one or more X groups, unsubstituted (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl substituted with one or more Y groups, unsubstituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl substituted with one or more Y groups, (C₂-C₁₀)heterocyclyl, unsubstituted (C₂-C₁₀)heteroaryl and (C₂-C₁₀)heteroaryl substituted with one or more Y groups;

each W is independently selected from the group consisting of hydrogen,

15 (C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -C(R⁶)₂-N(R⁶)₂, and -C(R⁶)₂-N(R⁶)-S(O)₂-R⁶;

each X is independently selected from the group consisting of hydrogen, -OH,

(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, Cbz, Boc, (C₁-C₆)alkylsulfonyl, acetyl, -C(O)-R¹², -C(O)-N(R⁹)₂, -C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl, -S(O)₂-(C₃-C₆)cycloalkyl, -C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -(C(R⁶)₂)_m-(C₆-C₁₀)aryl and (C₆-C₁₀)aryl

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

25 wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl portion is NOT Cbz or Boc,

wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said -C(O)-(C₂-C₁₀)heteroaryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN, and

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wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said

-(C(R⁶)₂)_m-(C₆-C₁₀)aryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN

5 wherein in a single X moiety, =O, can replace two available hydrogens on the same carbon on a ring system;

each Y is independently selected from the group consisting of hydrogen, halogen,

(C₁-C₆)alkyl, (C₆-C₁₀)aryl, -C(O)-(C₁-C₆)alkyl, -O-(C₁-C₆)alkyl,

-O-(C₂-C₁₀)heteroaryl, -O-(C₆-C₁₀)aryl, -O-R⁹, halo(C₁-C₆)alkyl,

10 -O-halo(C₁-C₆)alkyl, -CN, -C(O)-O-(C₁-C₆)alkyl, -N(R⁶)₂, -C(R⁶)₂-N(R⁶)₂,

-S(O)₂-(C₂-C₁₀)heterocyclyl, -S(O)₂-(C₂-C₁₀)heteroaryl and

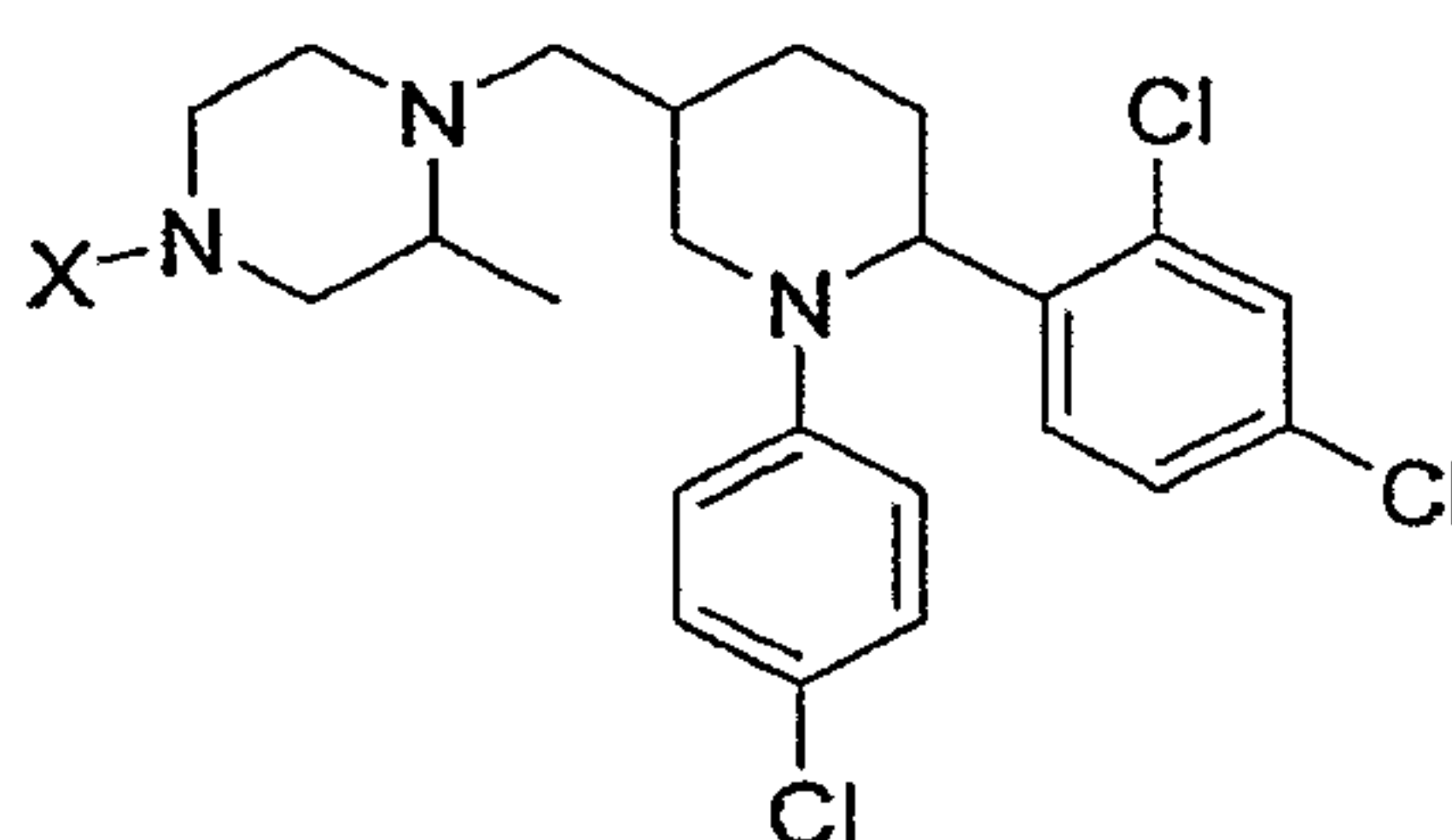
-C(R⁶)₂-N(R⁶)-S(O)₂-R⁶; or

two of said Y groups attached to adjacent carbon atoms form a -O-CH₂-O- or

-O-CH₂CH₂-O- group;

15 each n, p and q is independently an integer from 0-5; and m is an integer from 1-5.

19. The compound of Claim 1 having the structural formula



20

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

each R⁹ is independently selected from the group consisting of H, (C₁-C₆)alkyl,

halo(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, unsubstituted (C₆-C₁₀)aryl and unsubstituted (C₂-C₁₀)heteroaryl;

25 R¹² is (C₁-C₆)alkyl;

each X is independently selected from the group consisting of hydrogen, -OH,

(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl, Cbz, Boc, (C₁-C₆)alkylsulfonyl, acetyl, -C(O)-R¹², -C(O)-N(R⁹)₂,

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-C(O)-(C₂-C₁₀)heteroaryl, (C₂-C₁₀)heteroaryl, -S(O)₂-(C₃-C₆)cycloalkyl, -C(O)-(C₁-C₆)alkyl, -C(O)-O-(C₁-C₆)alkyl, -(C(R⁶)₂)_m-(C₆-C₁₀)aryl and (C₆-C₁₀)aryl

wherein the (C₆-C₁₀)aryl and (C₂-C₁₀)heteroaryl portion of said (C₆-

5 C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more Y groups,

wherein the (C₁-C₆)alkyl portion of said (C₆-C₁₀)aryl(C₁-C₆)alkyl and

(C₂-C₁₀)heteroaryl(C₁-C₆)alkyl is unsubstituted or substituted with one or more X groups with the proviso that X substituted on said (C₁-C₆)alkyl

10 portion is NOT Cbz or Boc,

wherein said (C₂-C₁₀)heteroaryl or the (C₂-C₁₀)heteroaryl portion of said

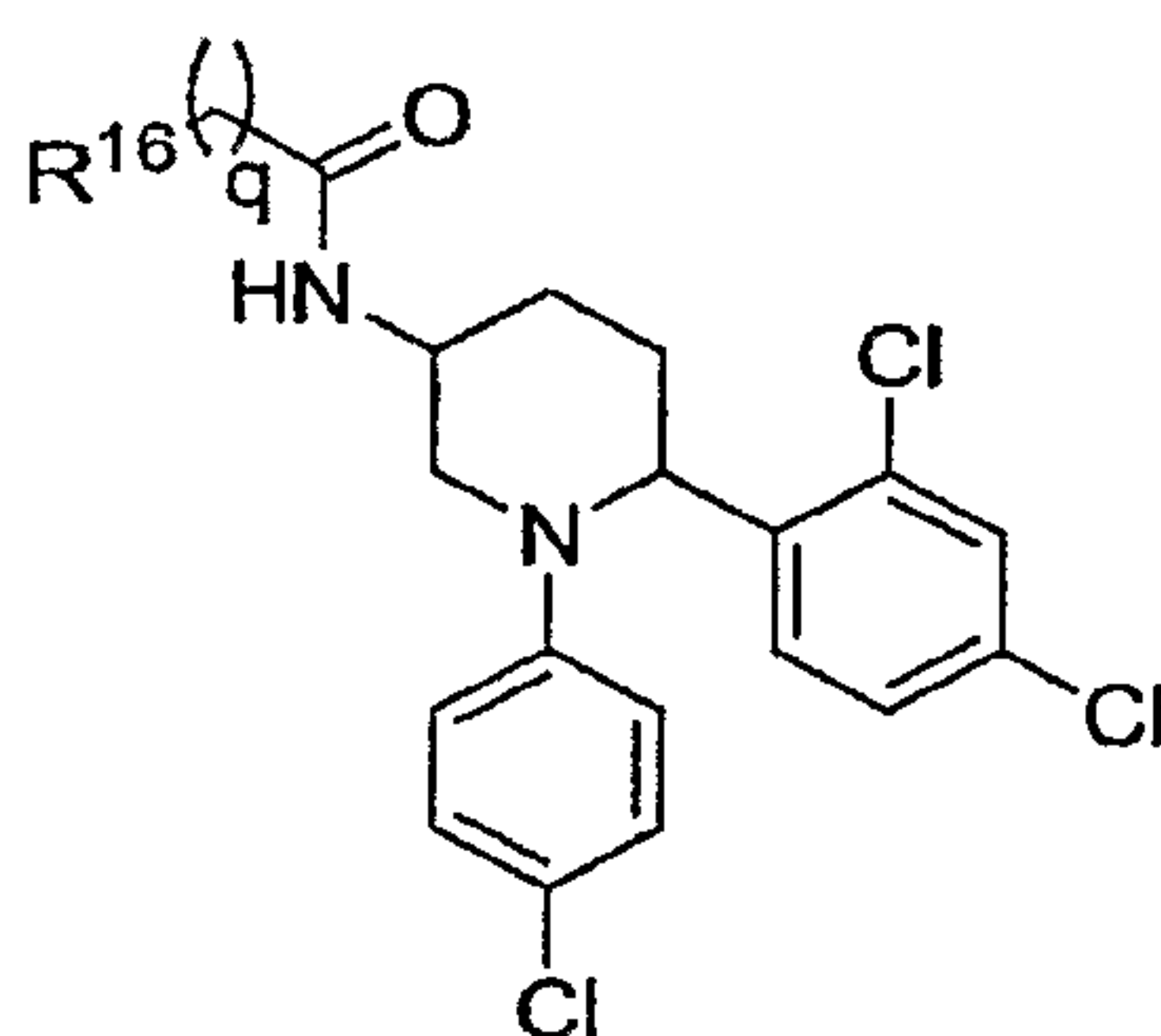
-C(O)-(C₂-C₁₀)heteroaryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN, and

15 wherein said (C₆-C₁₀)aryl or the (C₆-C₁₀)aryl portion of said

-(C(R⁶)₂)_m-(C₆-C₁₀)aryl of X is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, and -CN

wherein in a single X moiety, =O, can replace two available hydrogens on
20 the same carbon on a ring system.

20. The compound of claim 1 having the structural formula:



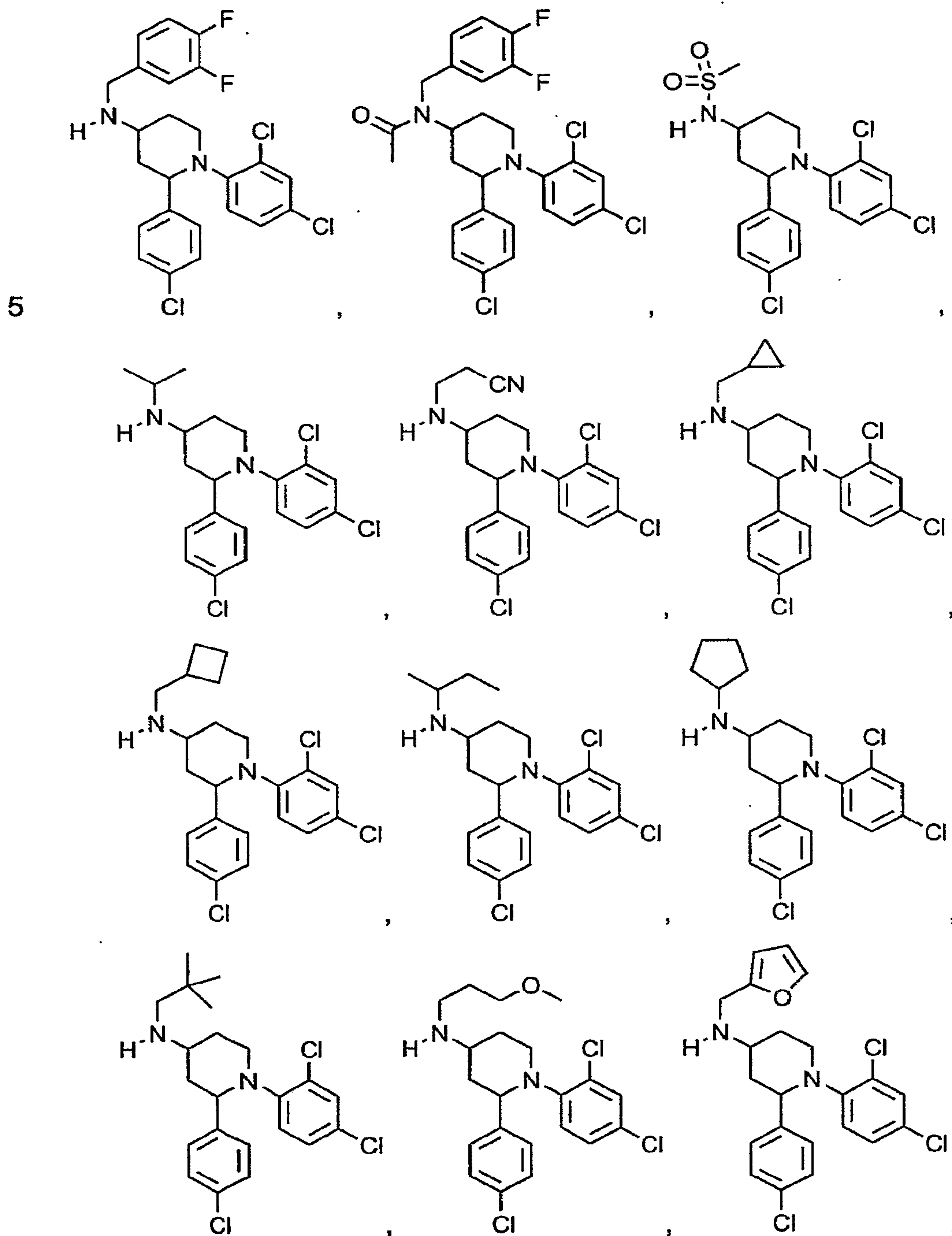
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or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

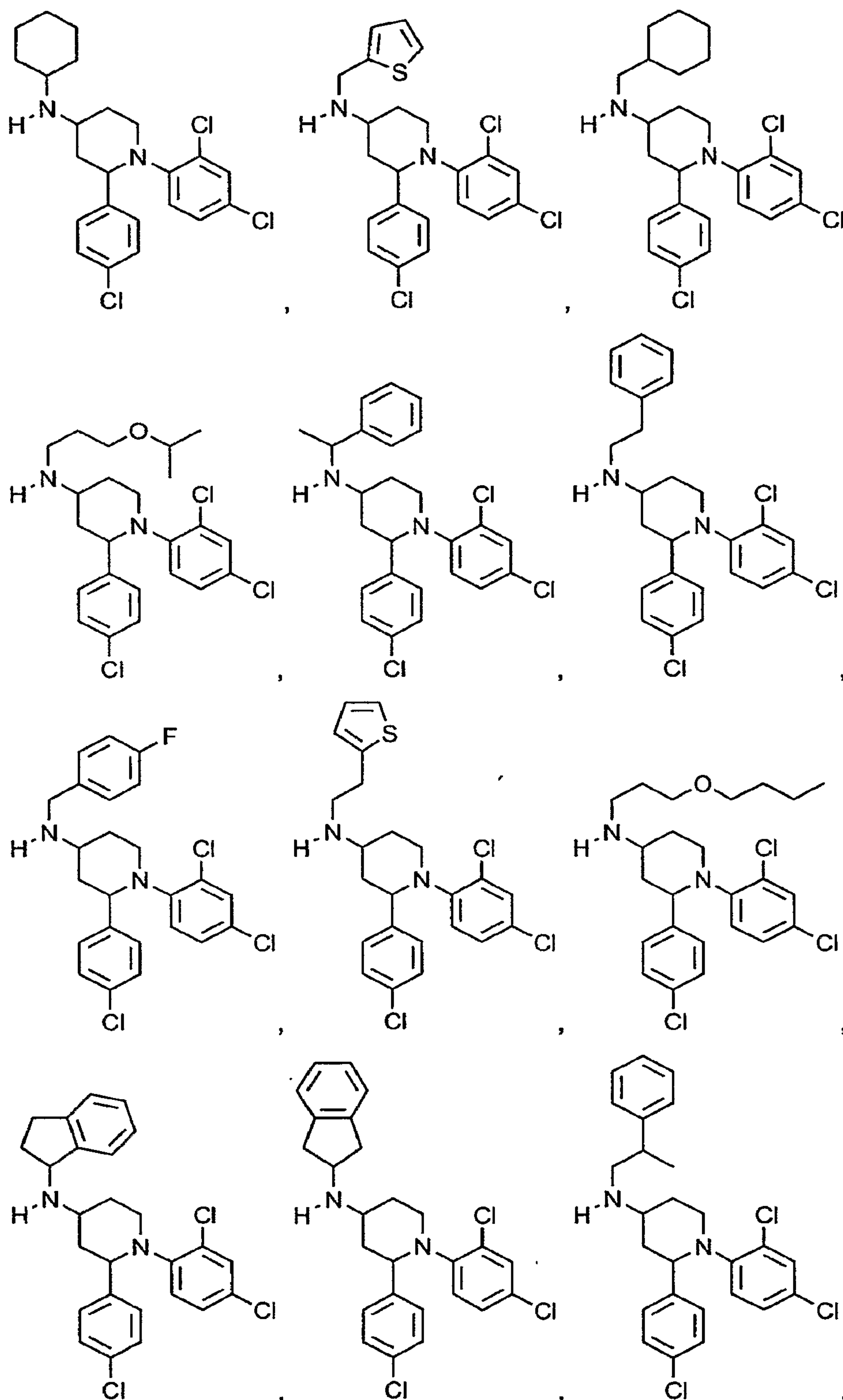
R¹⁶ is -O-(C₁-C₆)alkyl or (C₂-C₁₀)heteroaryl(C₁-C₆)alkyl

q is 1 or 2.

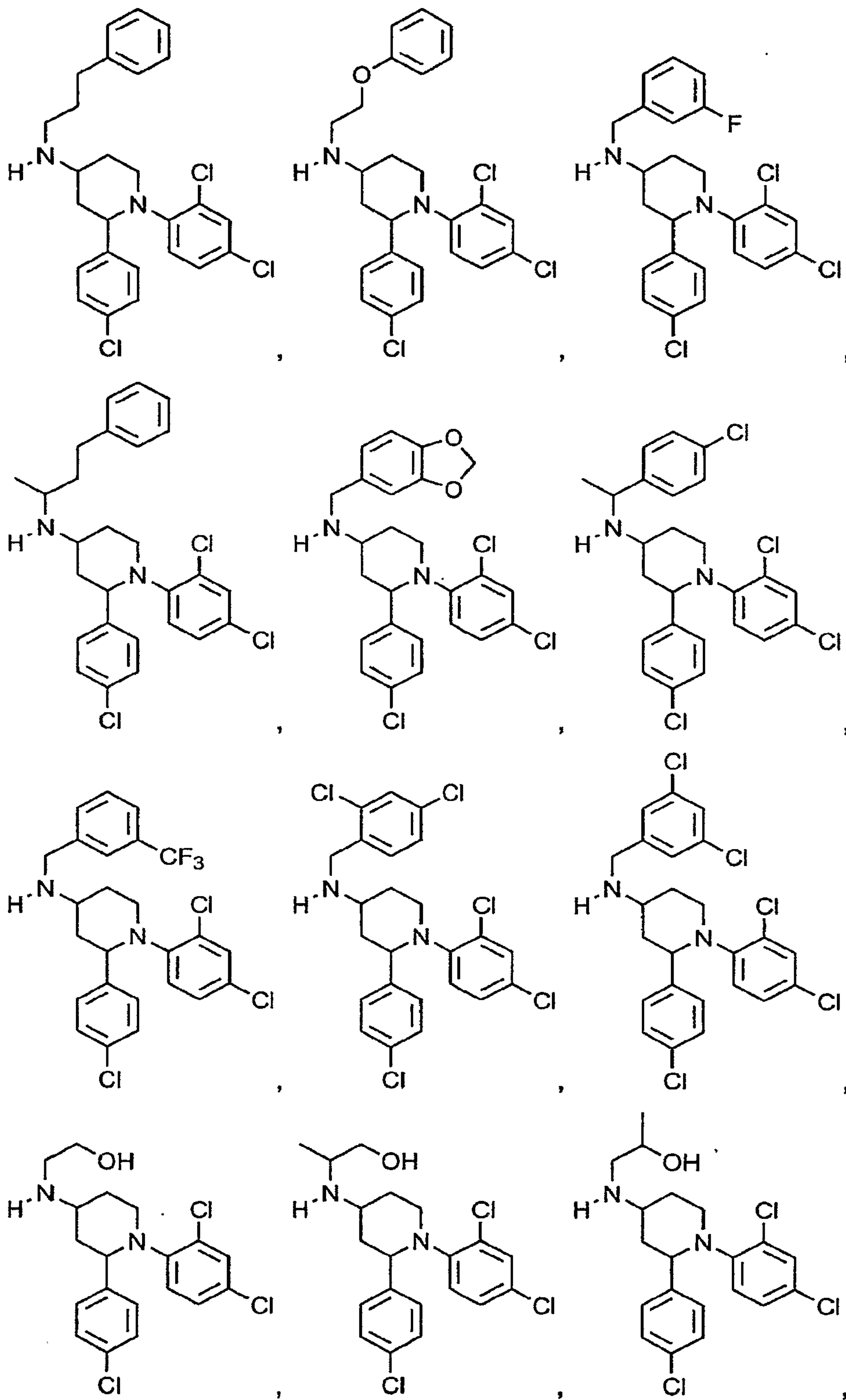
21. The compound of Claim 1, a pharmaceutically acceptable salt, solvate or ester thereof having a structure selected from the group consisting of:



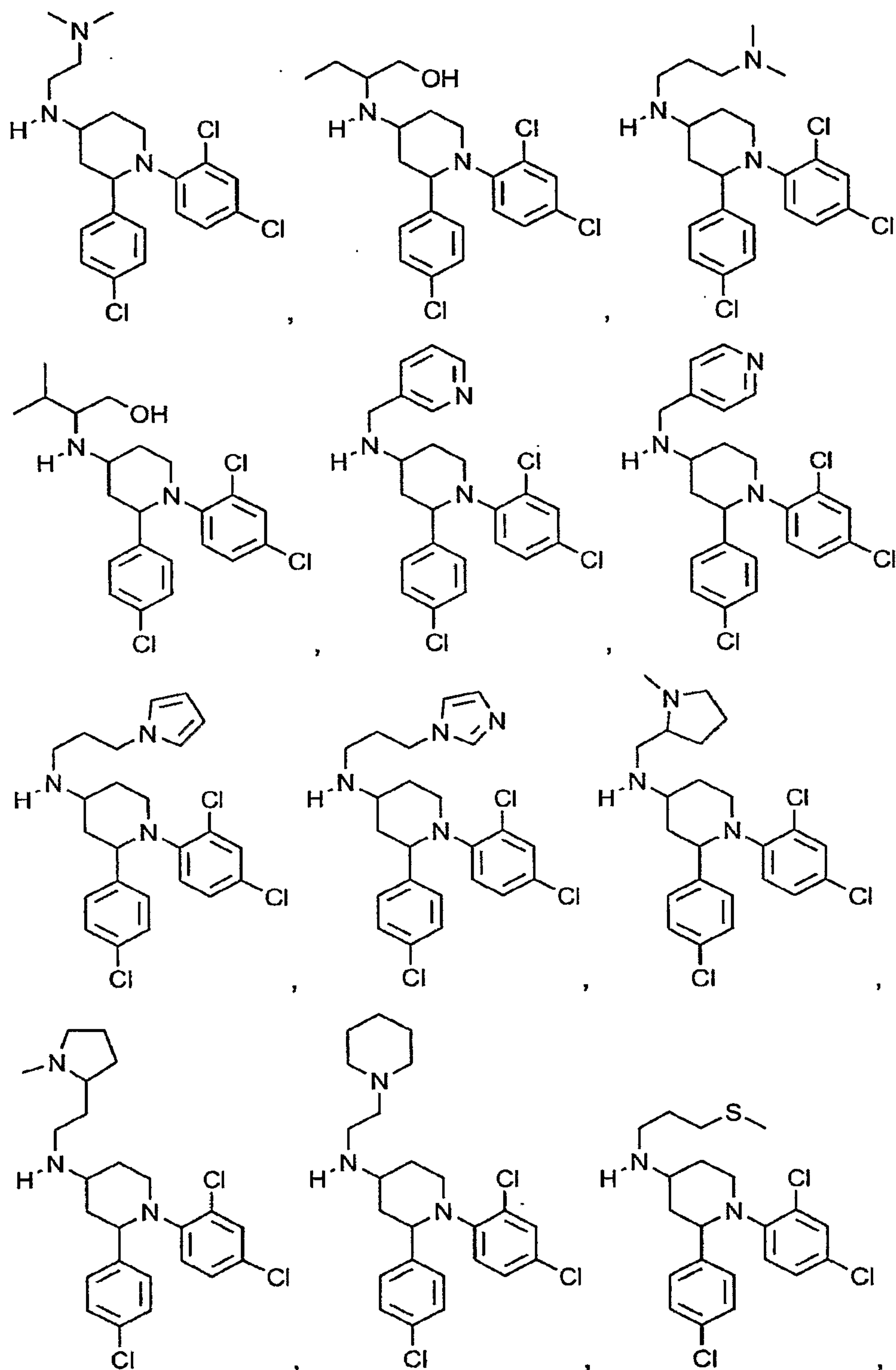
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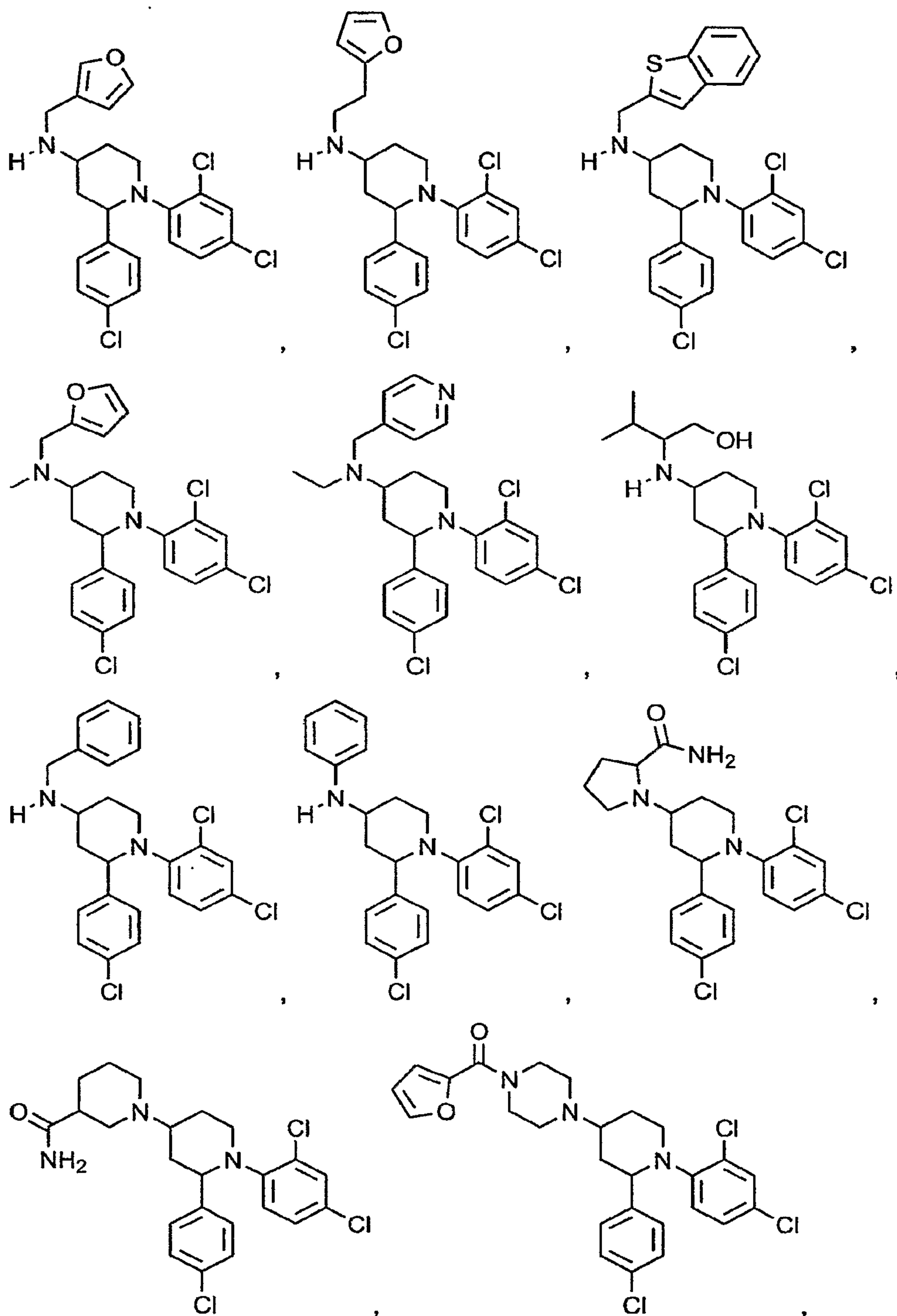
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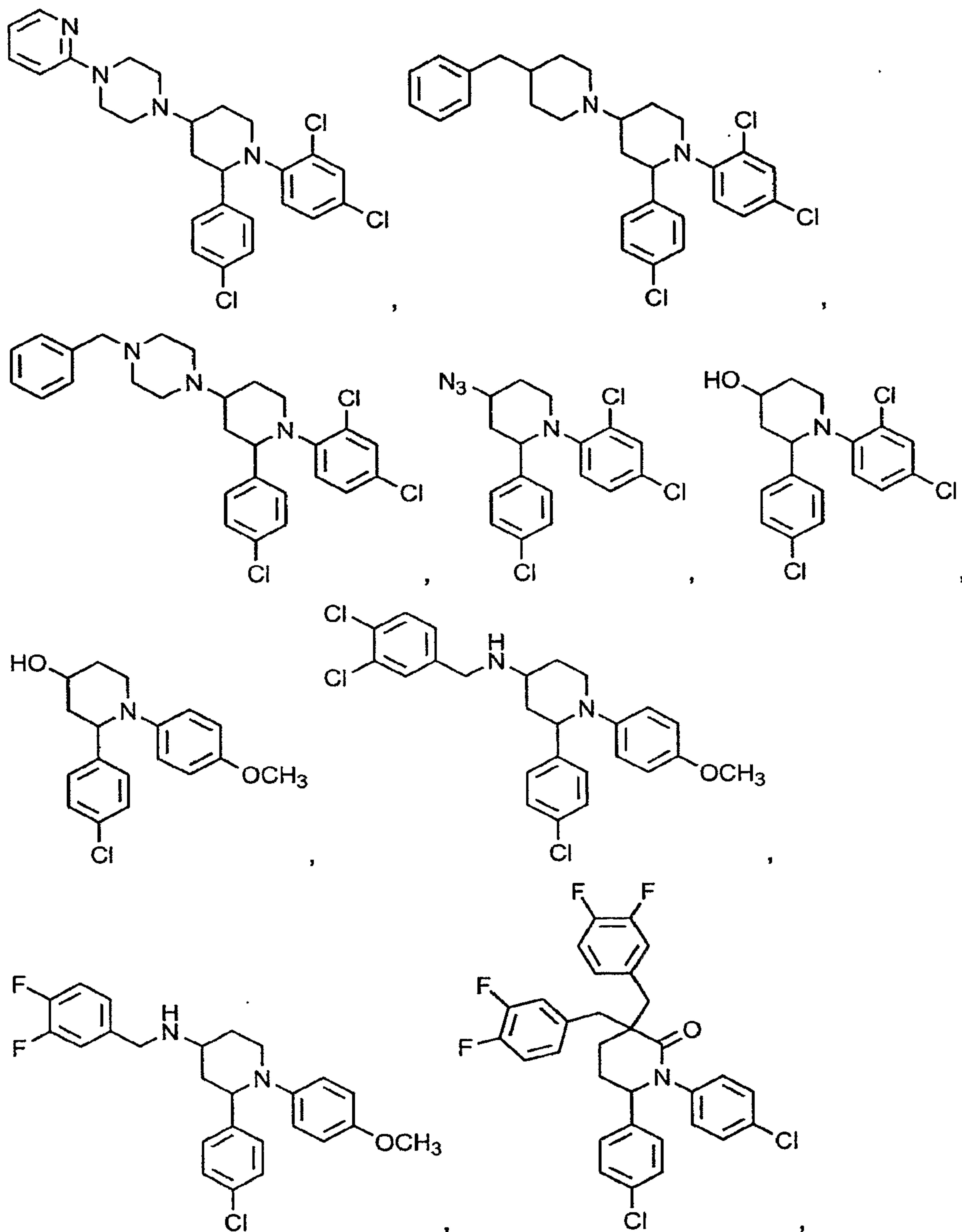
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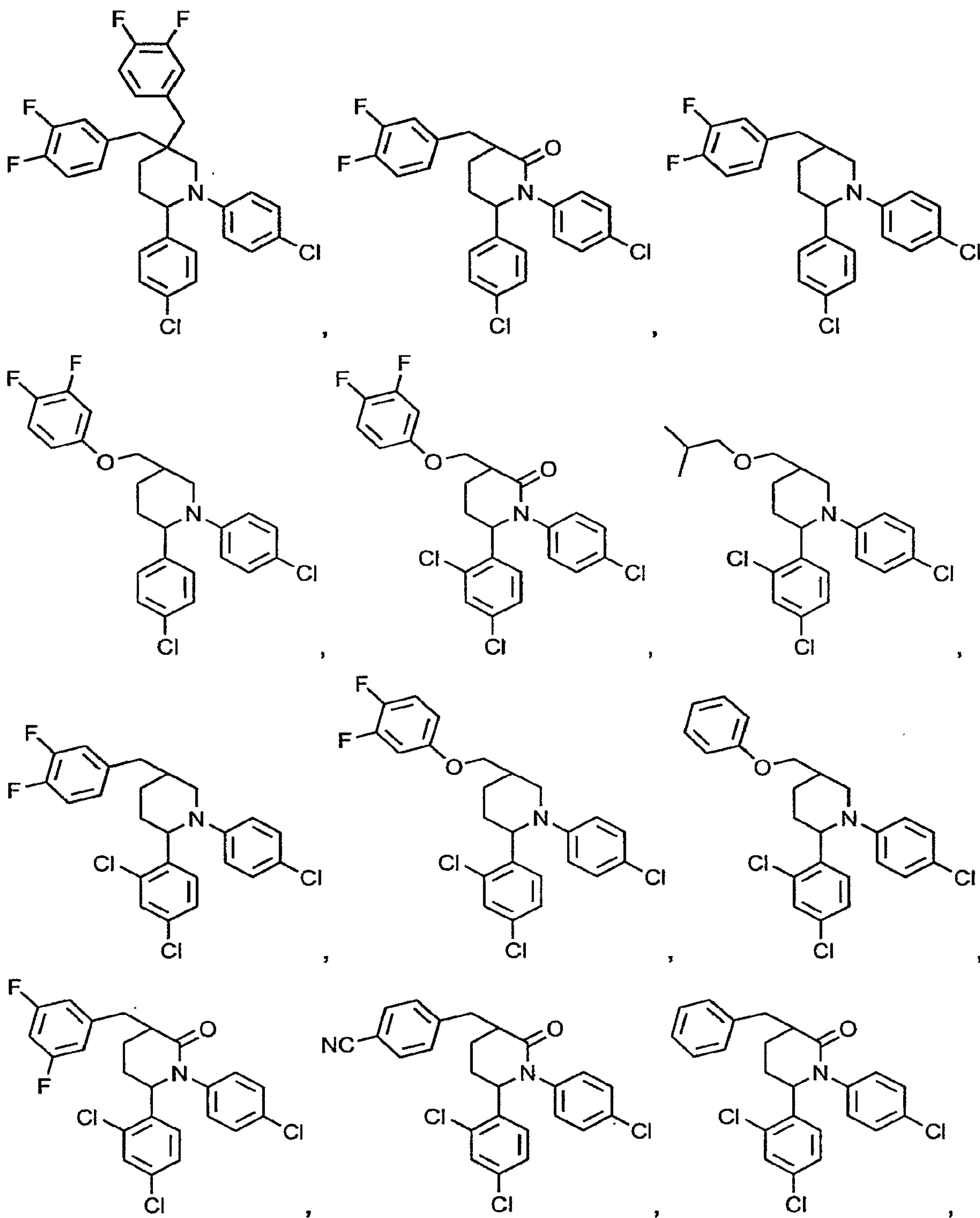
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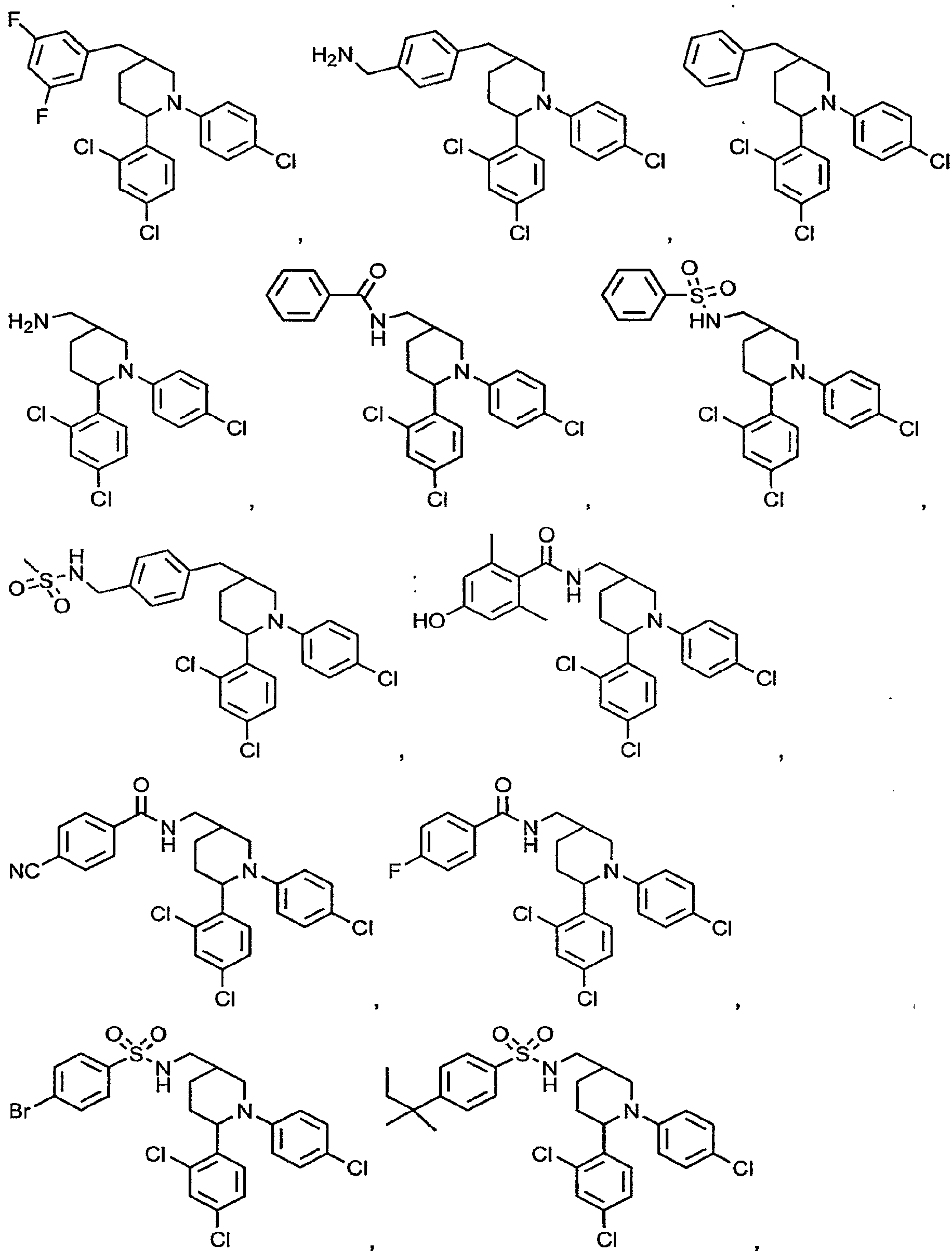
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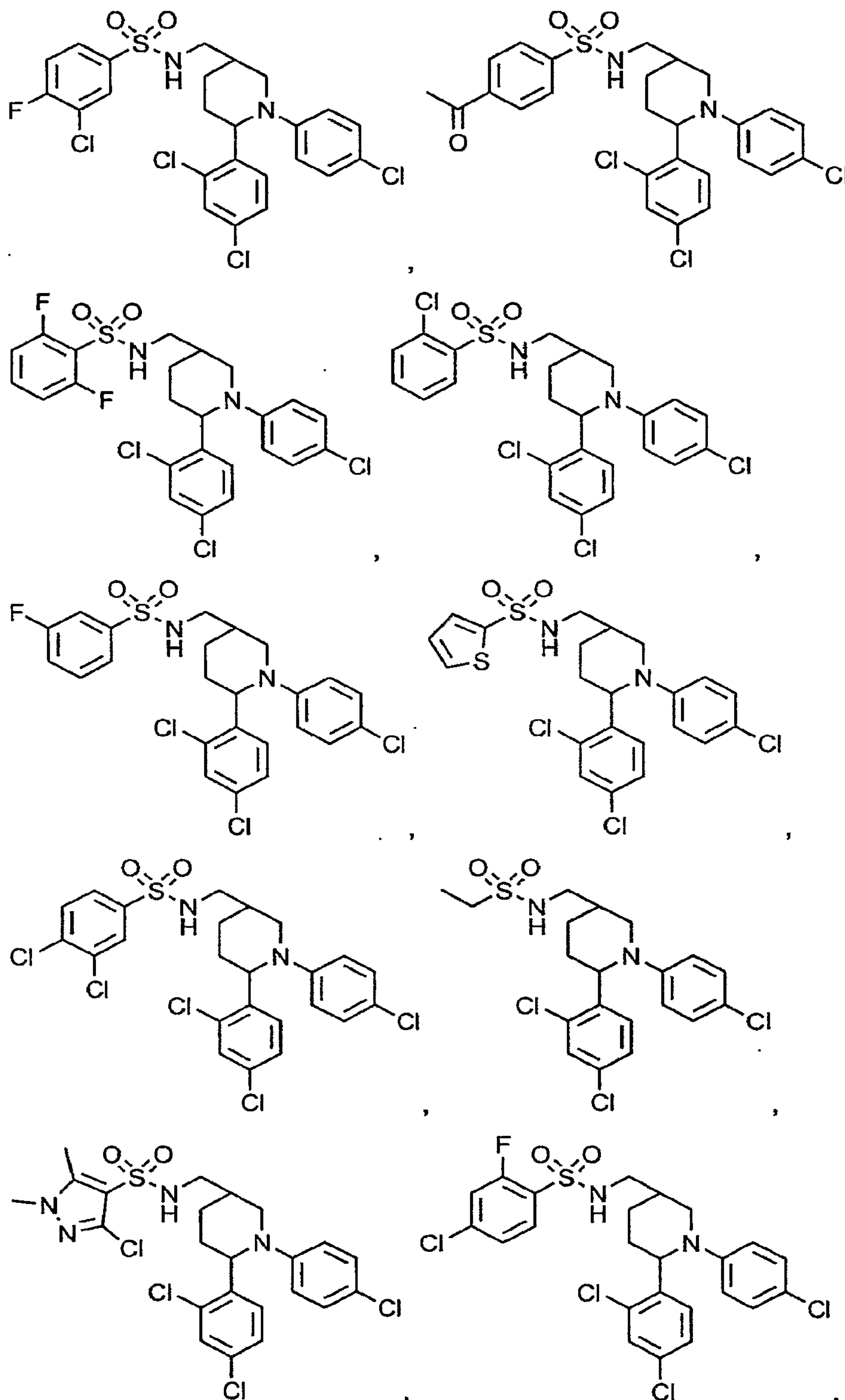
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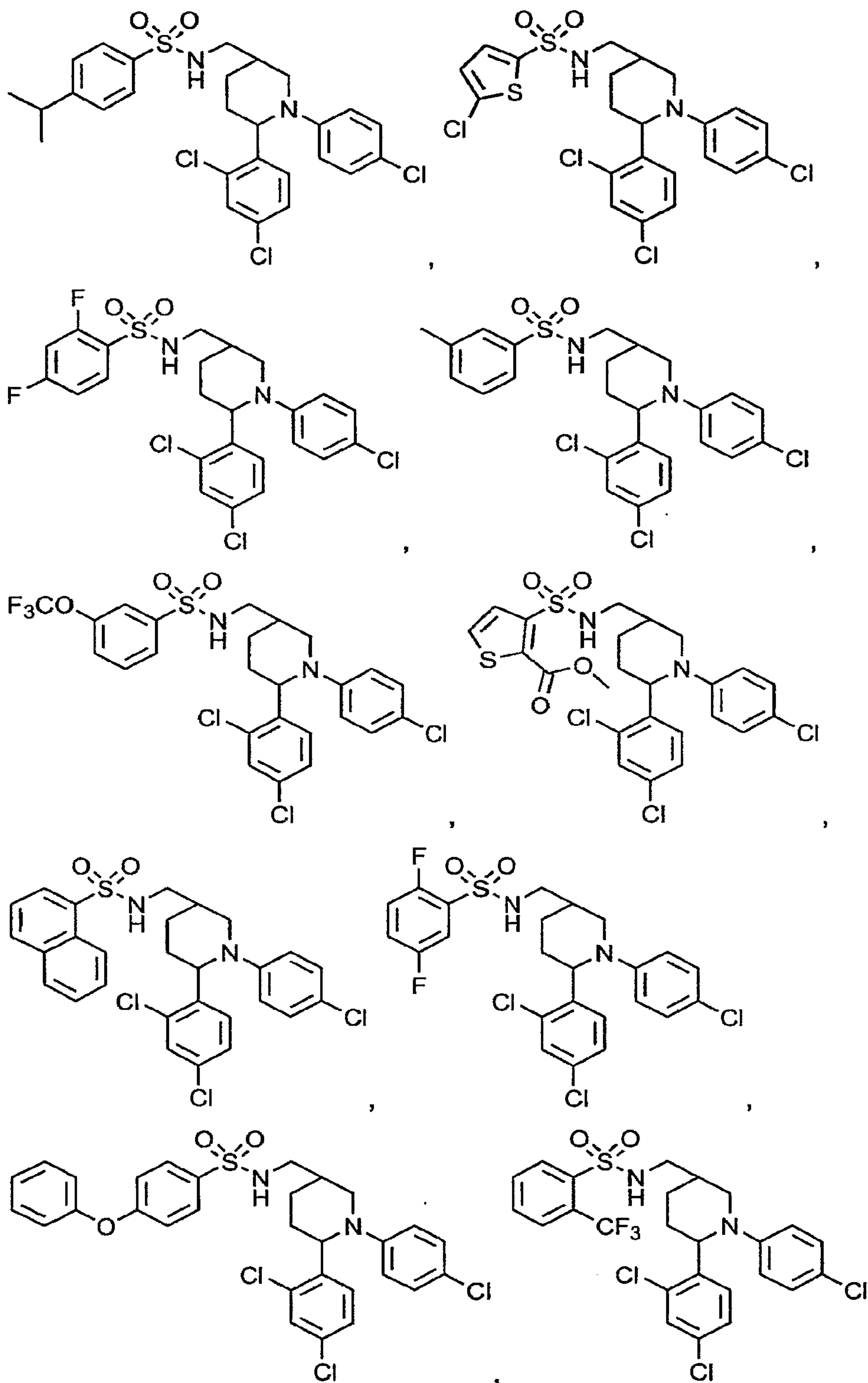
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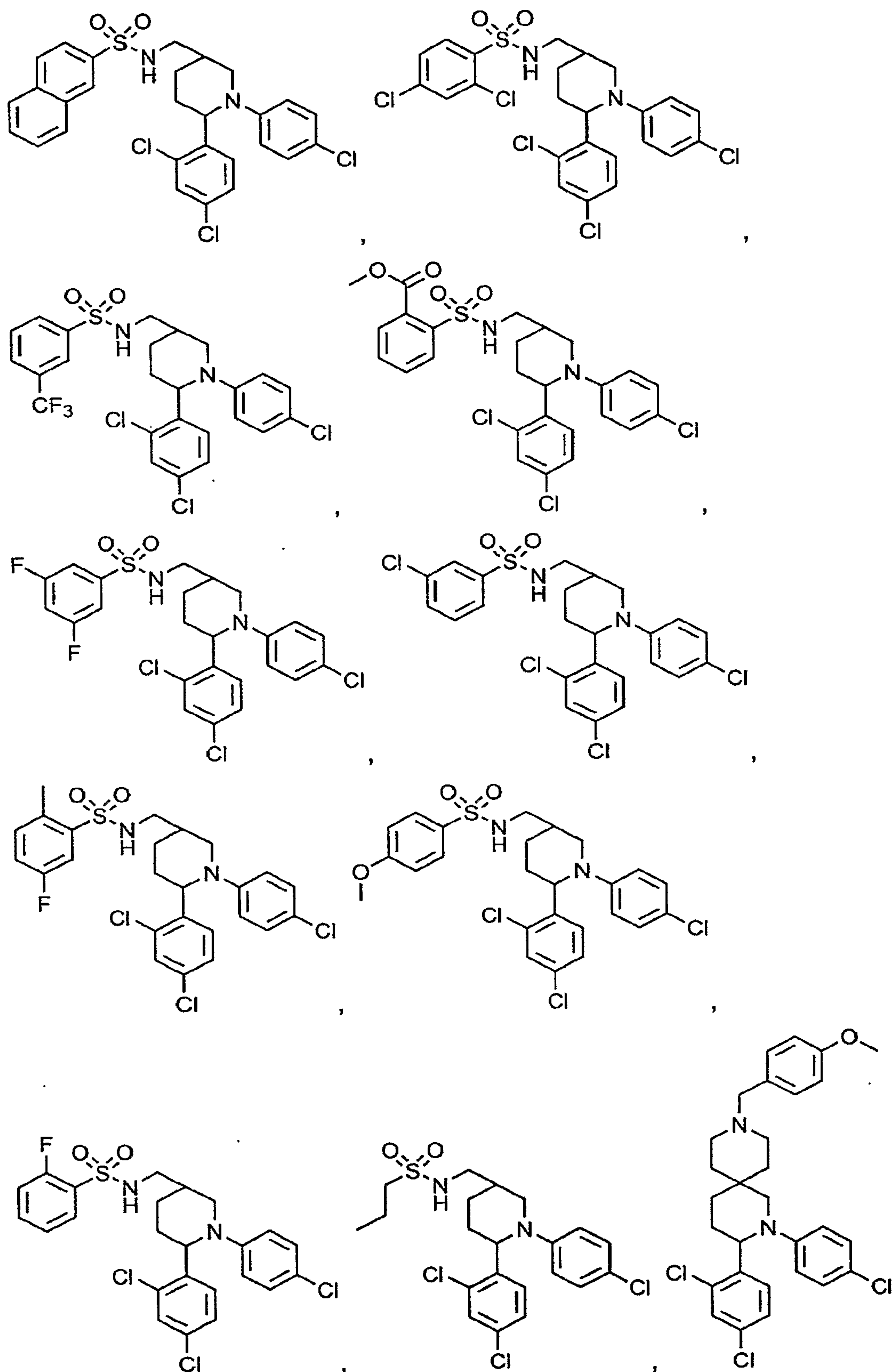
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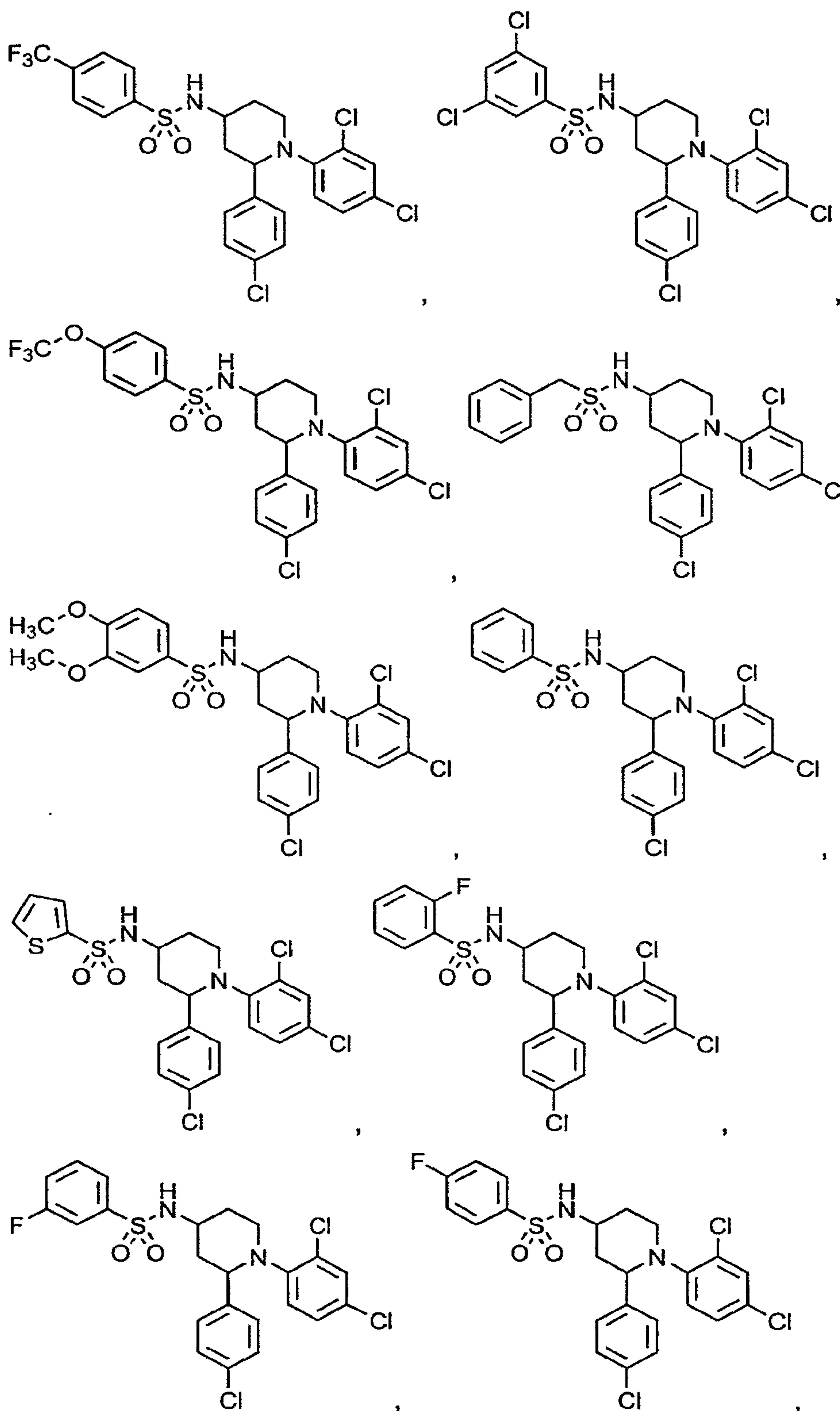
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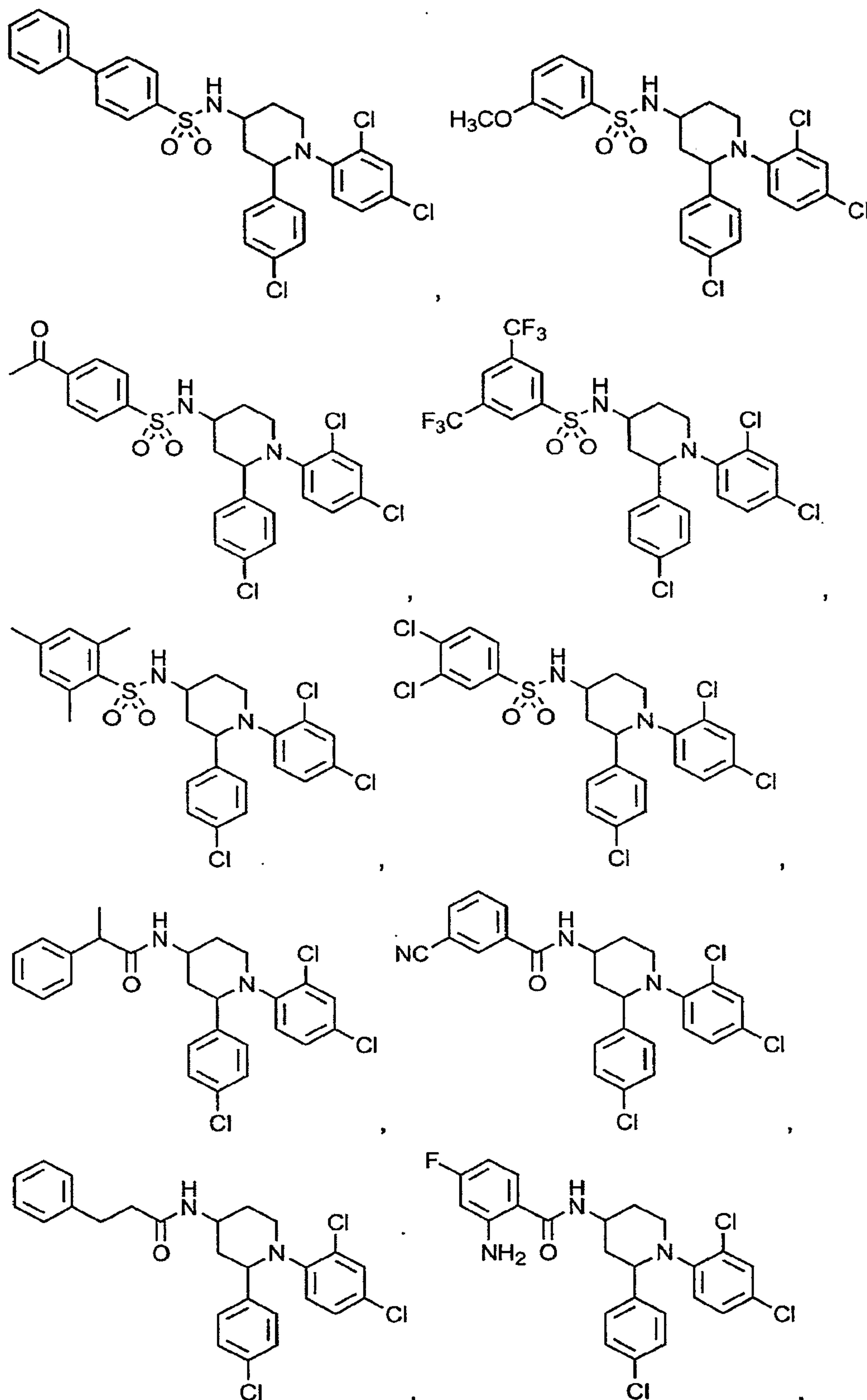
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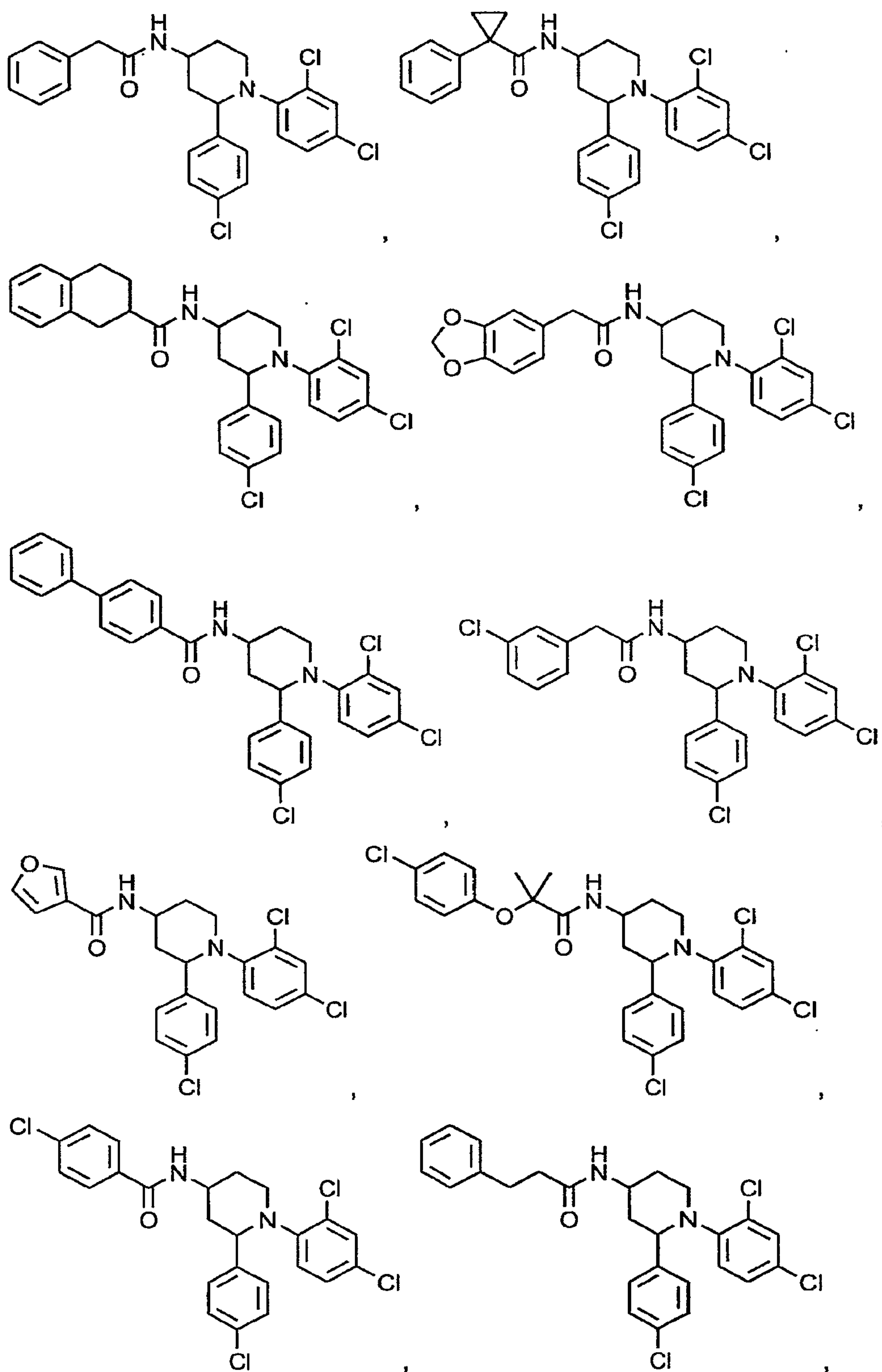
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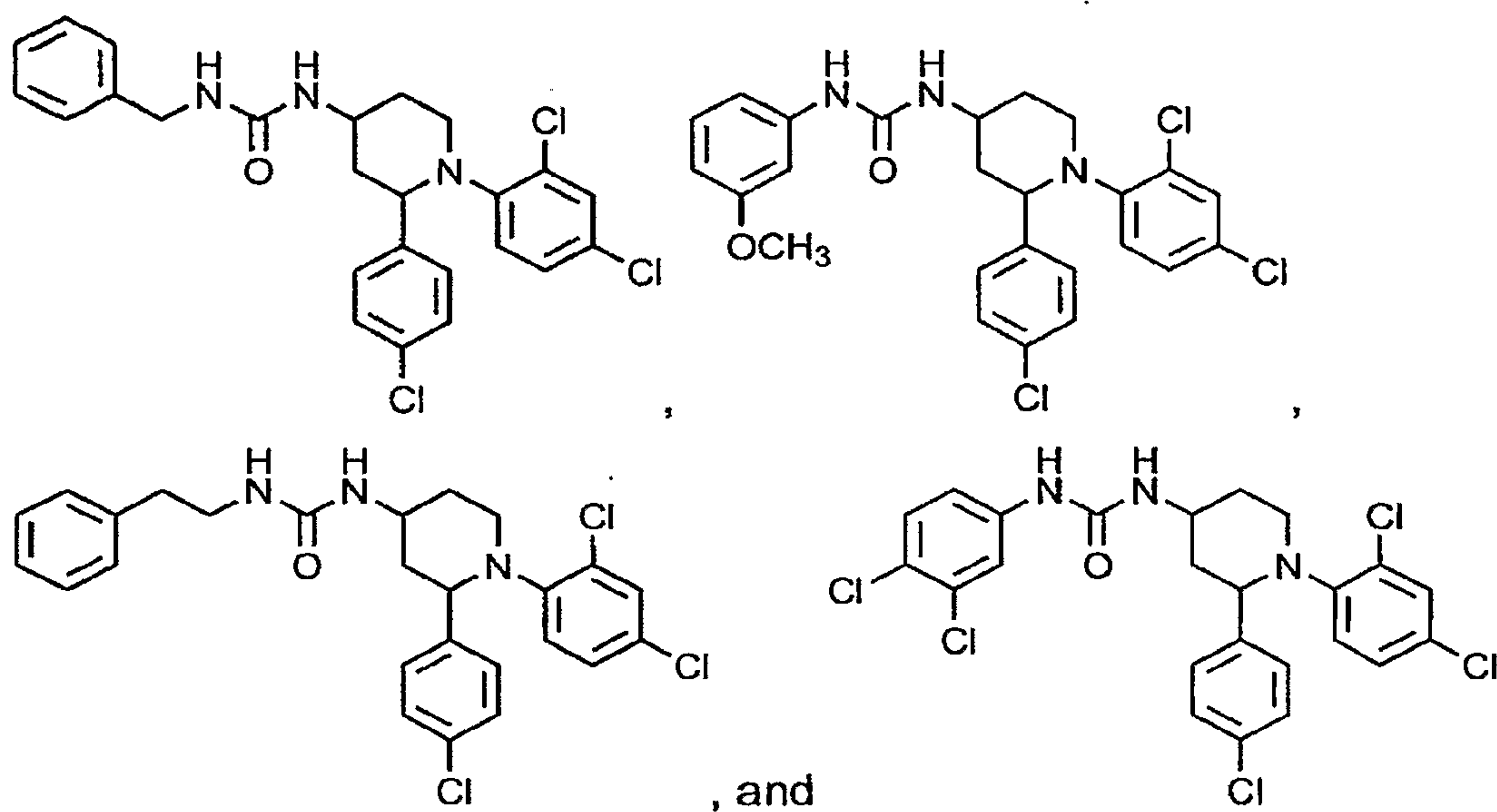
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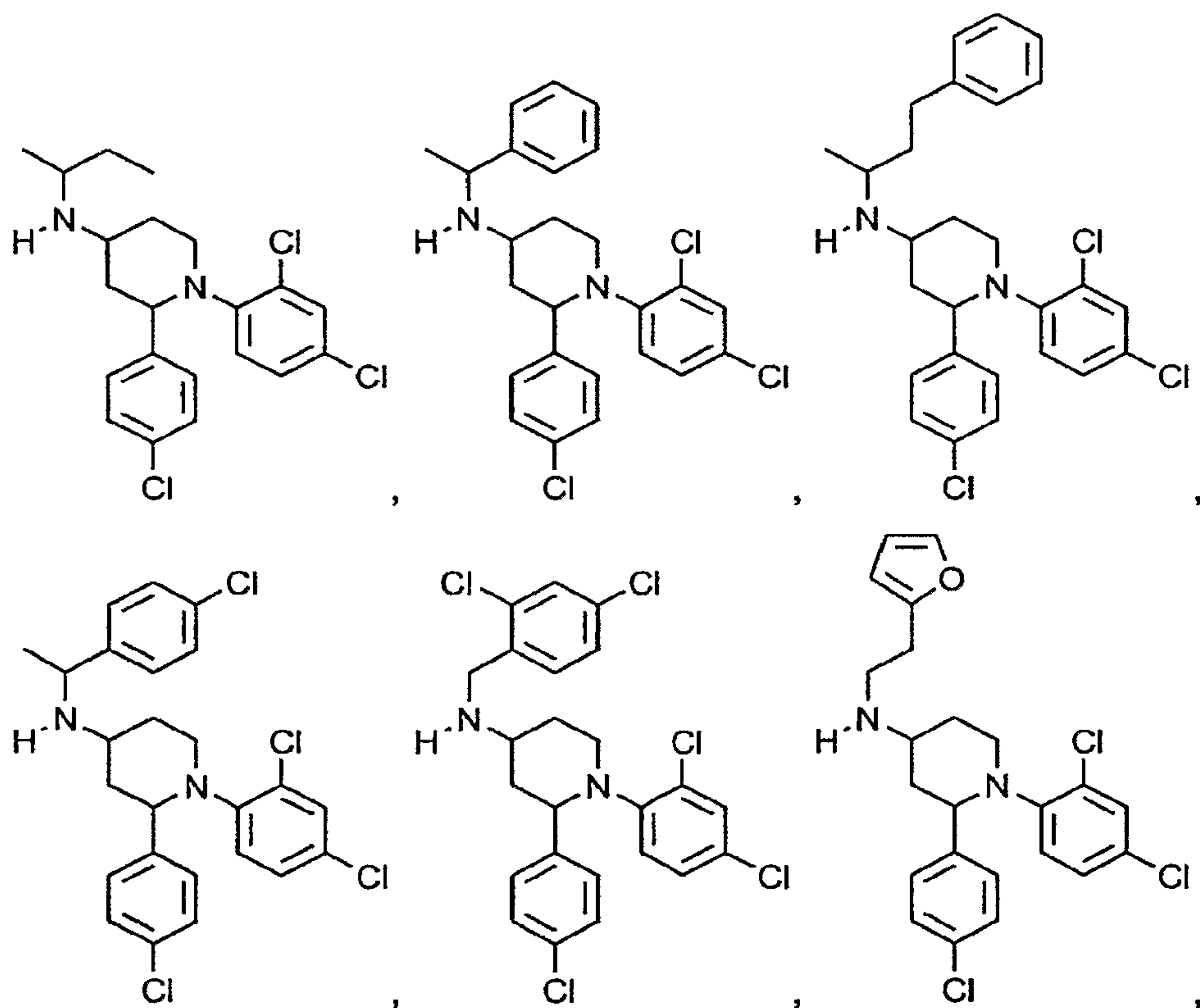
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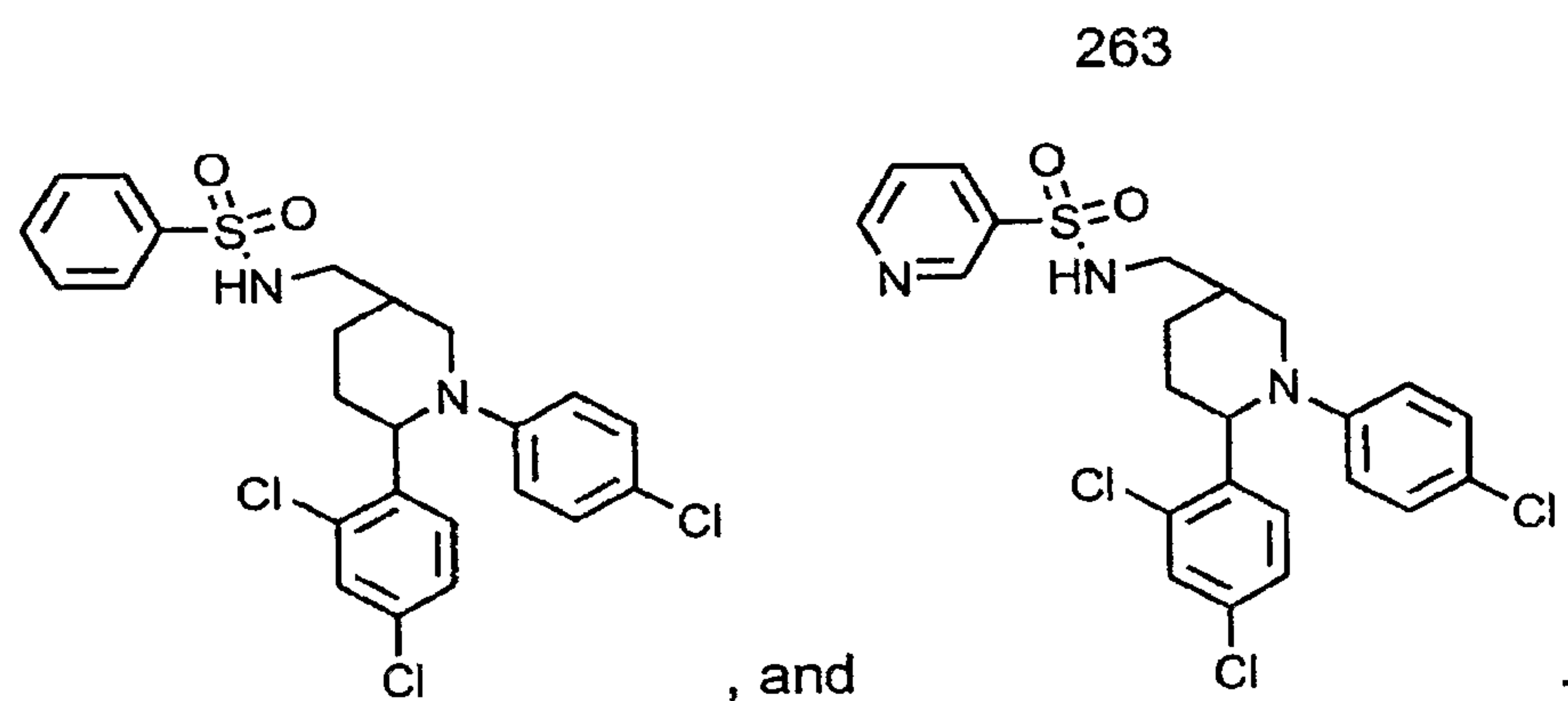


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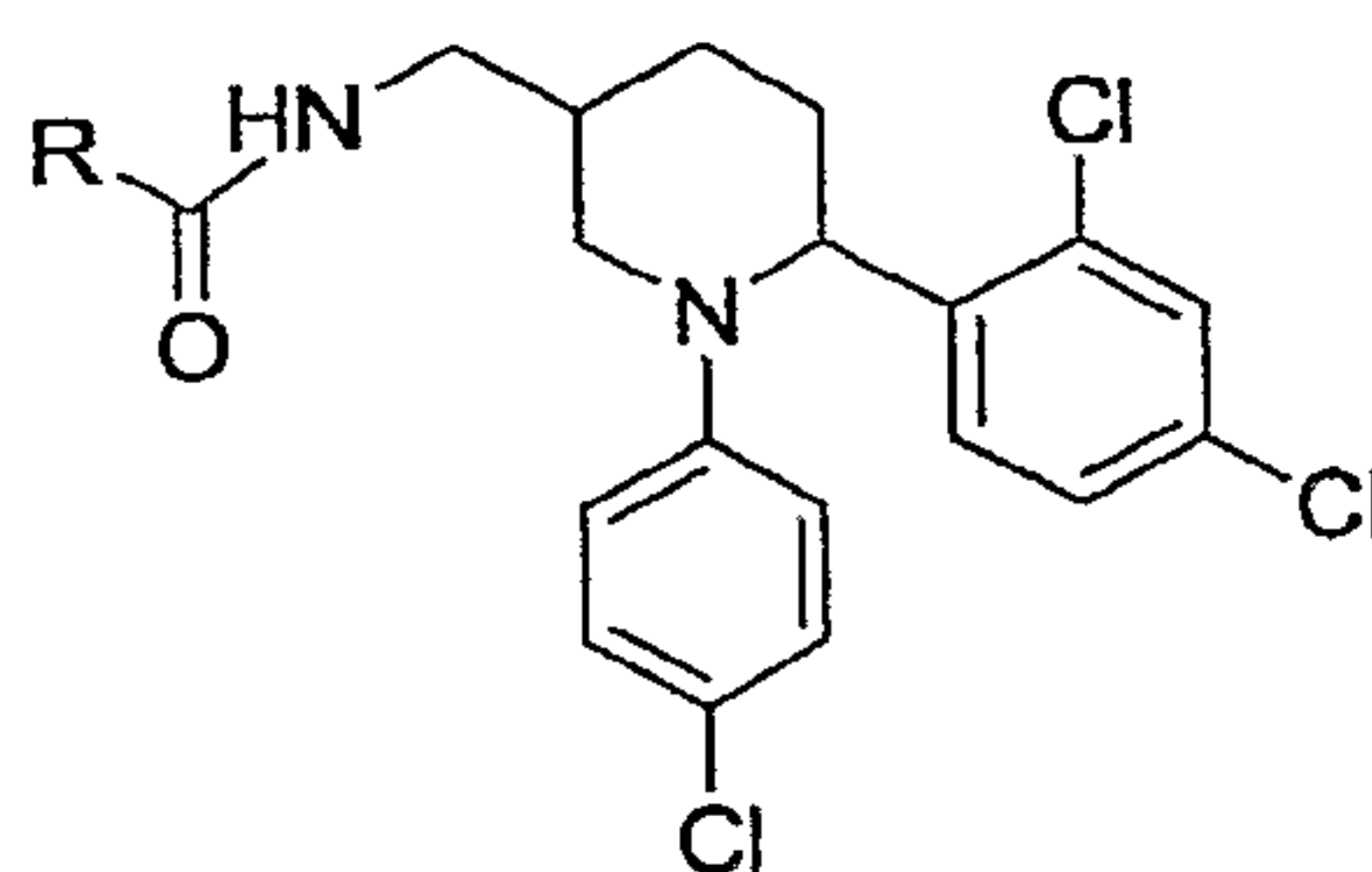
22. The compound of Claim 1, a pharmaceutically acceptable salt, solvate or ester thereof having a structure selected from the group consisting of:





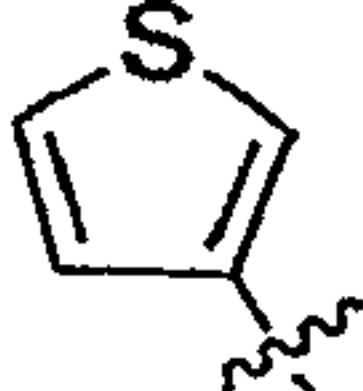
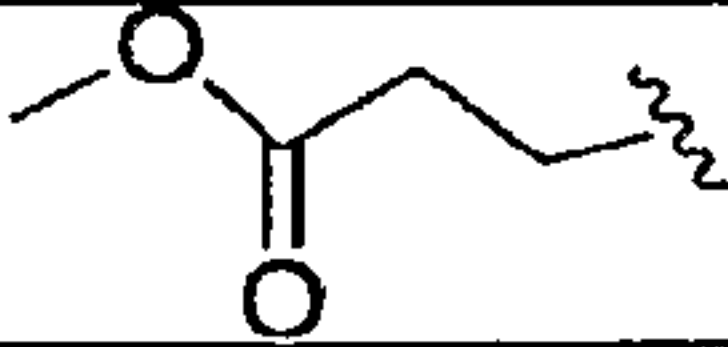
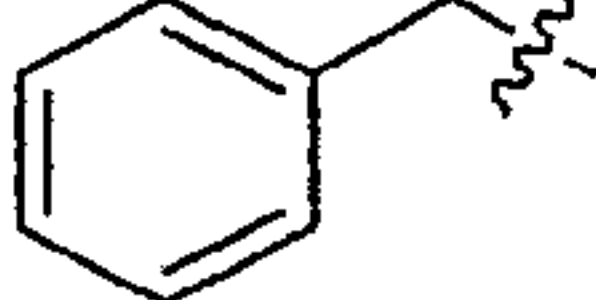
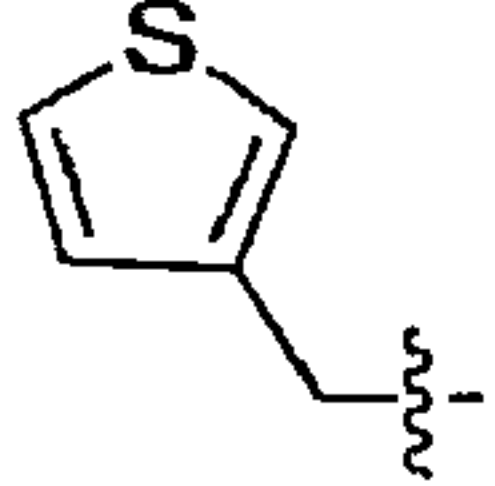
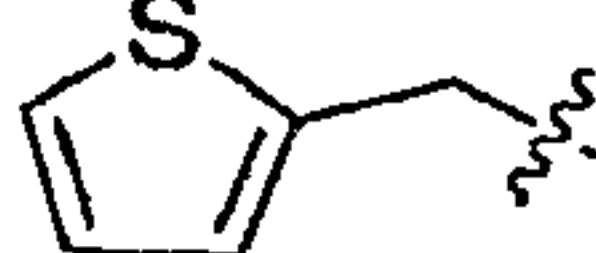
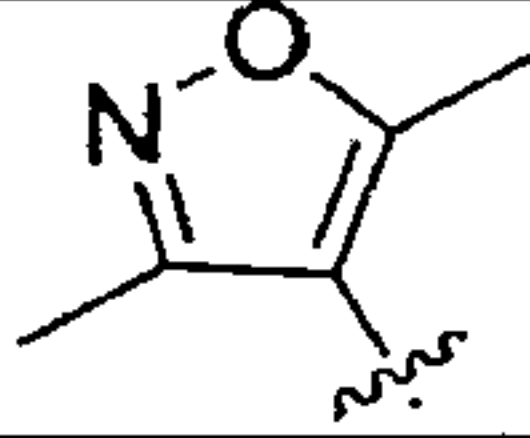
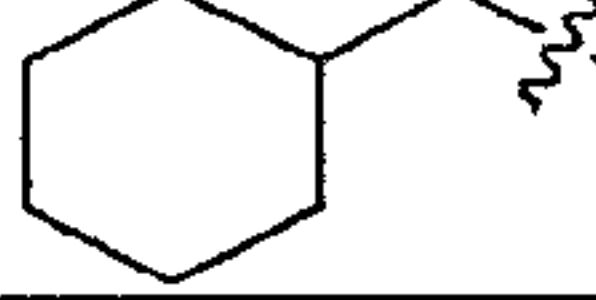
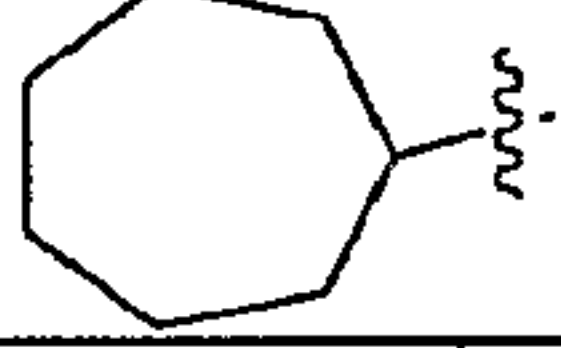
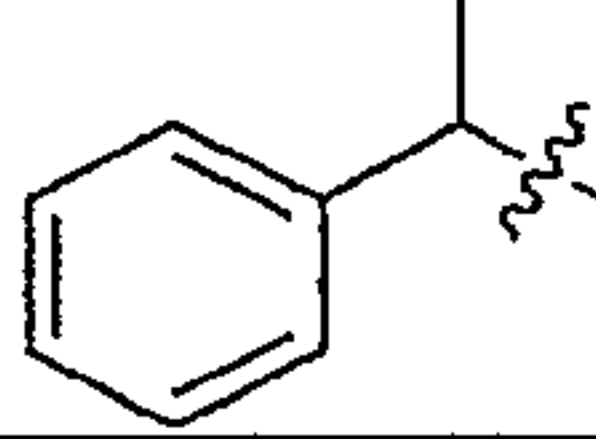
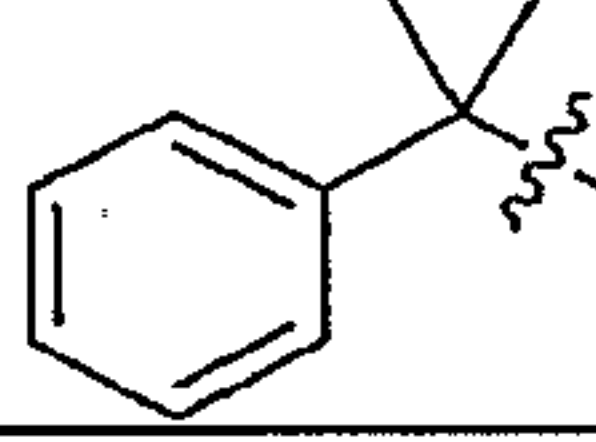
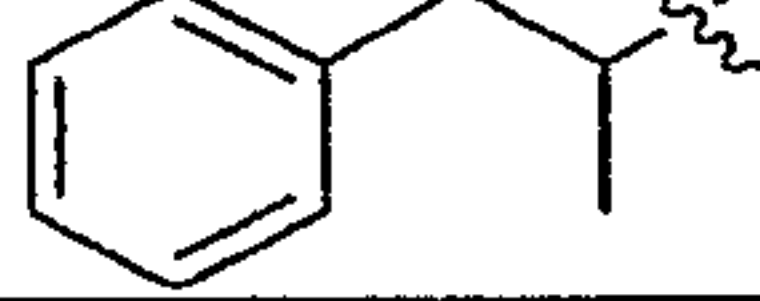
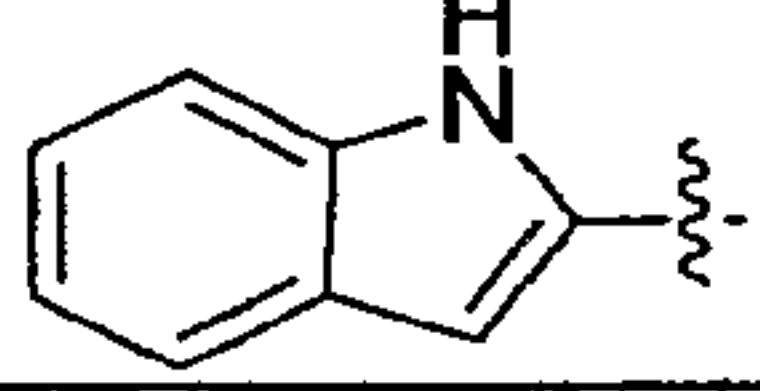
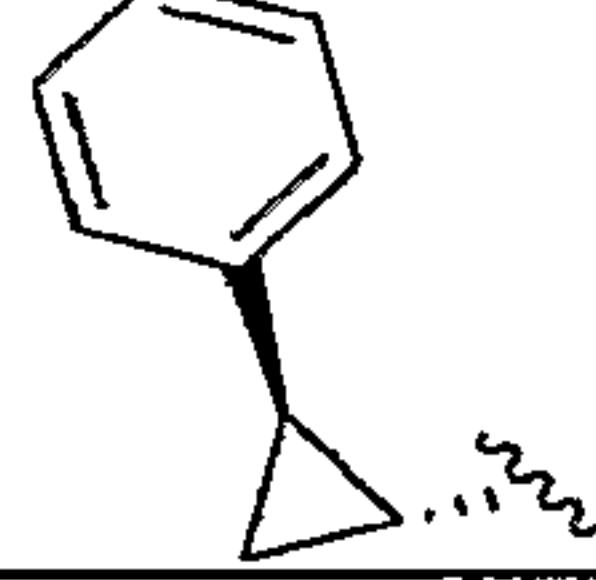
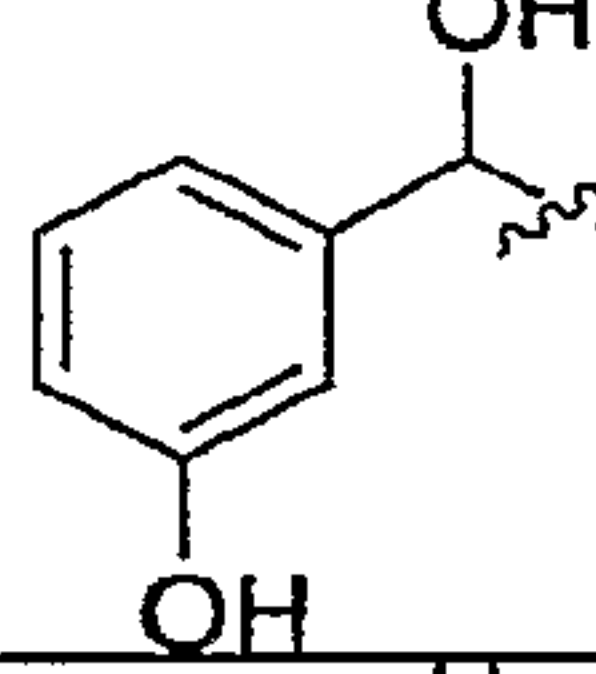
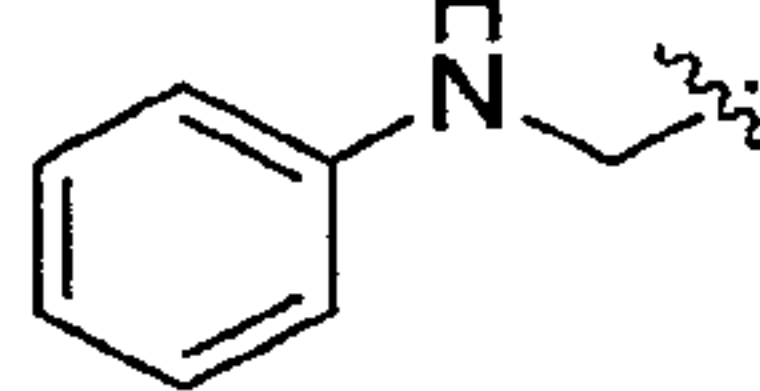
23. The compound of Claim 1, a pharmaceutically acceptable salt, solvate or ester thereof having a structure selected from the group consisting of:

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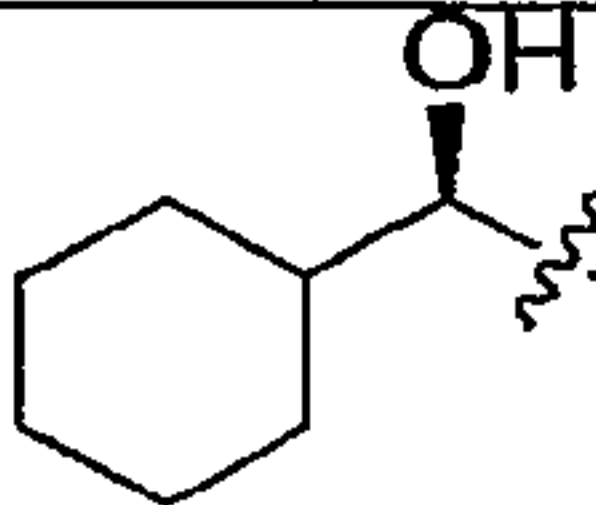
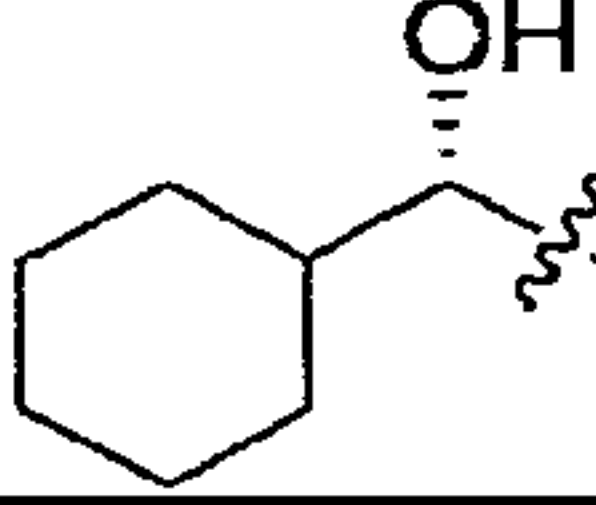


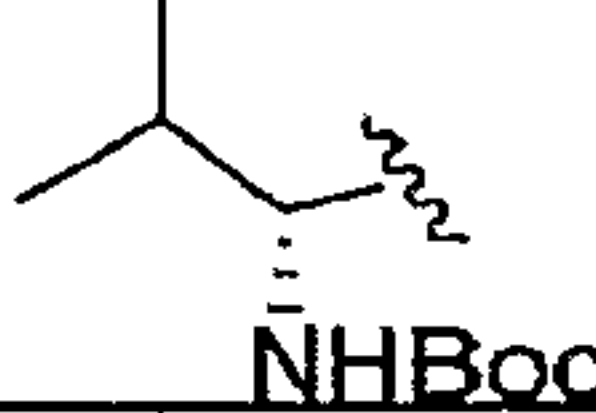
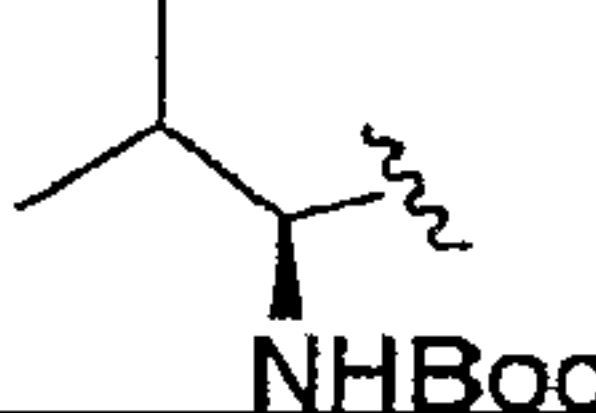
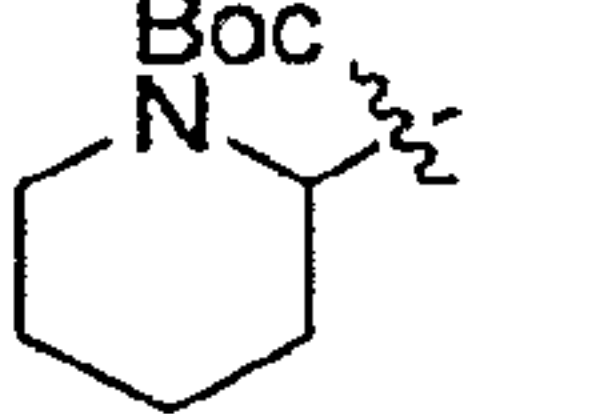
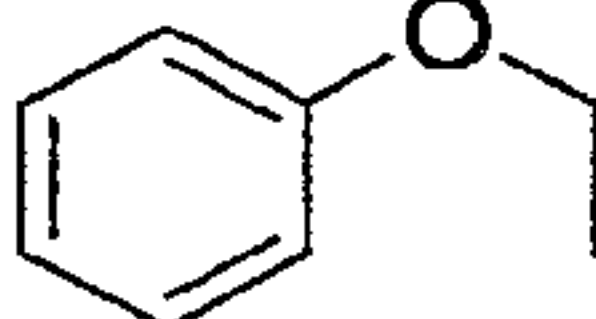
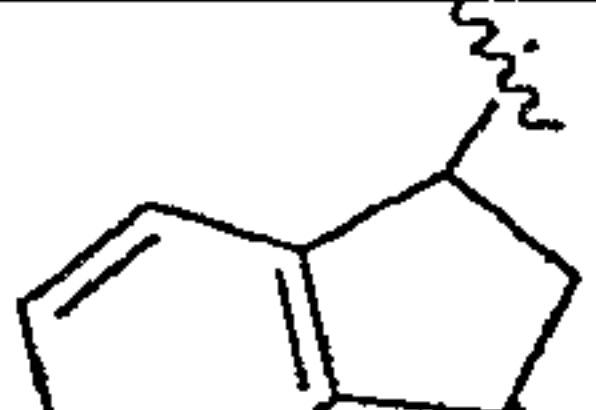
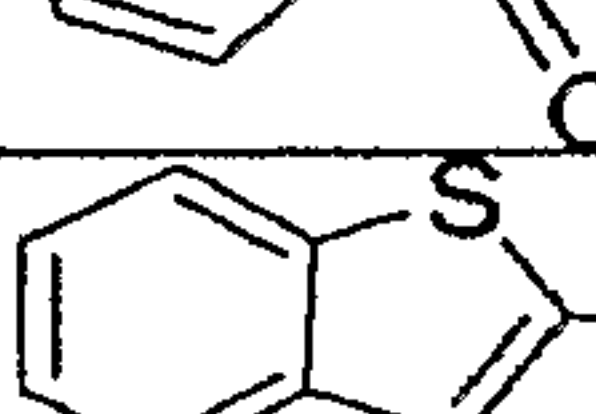
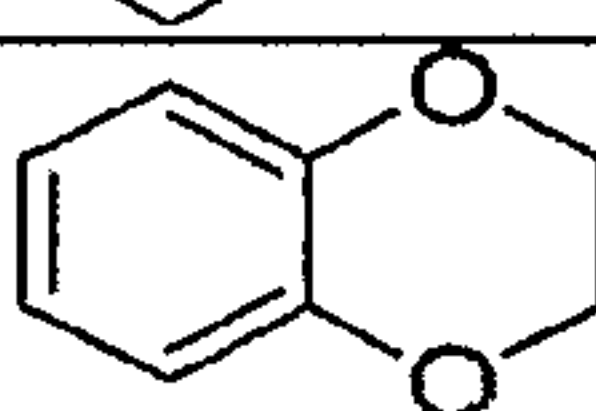
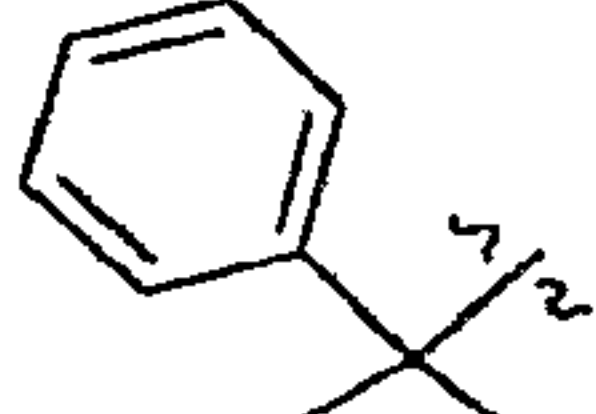
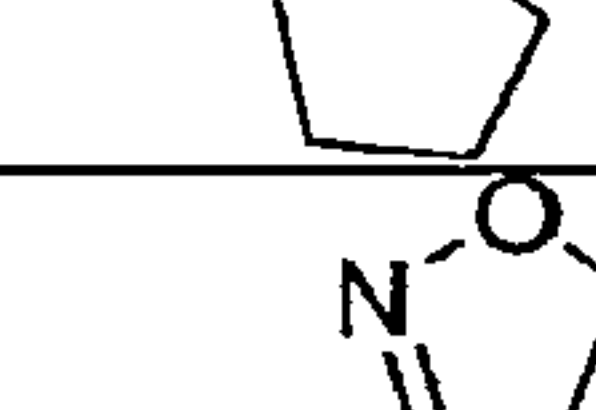
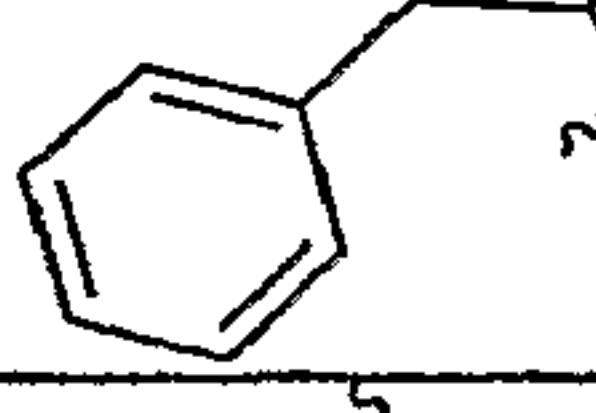
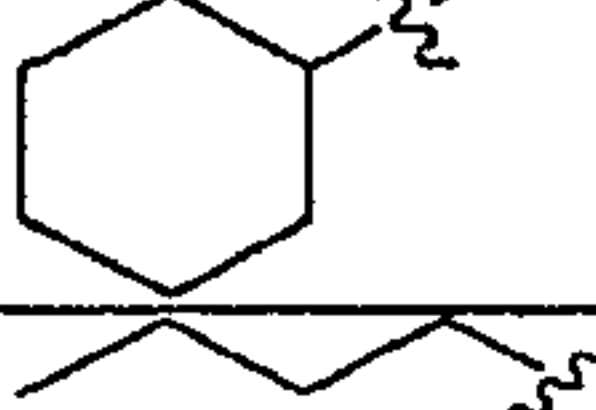
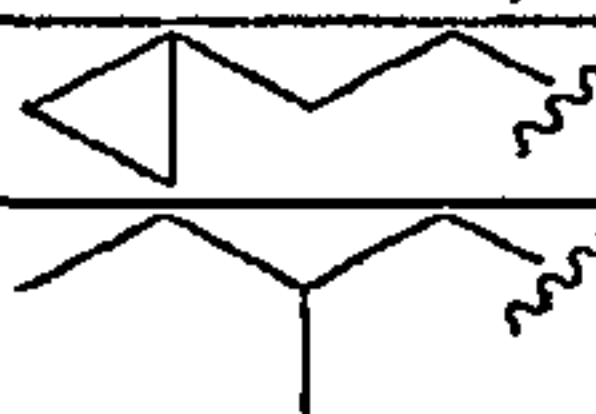
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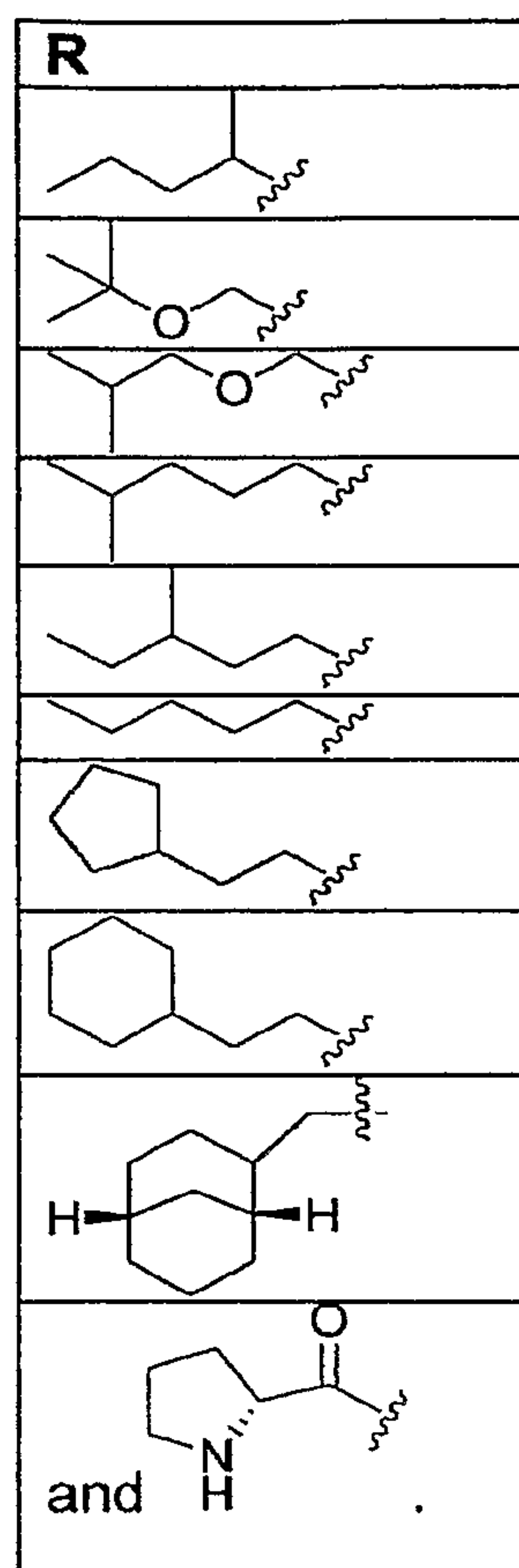
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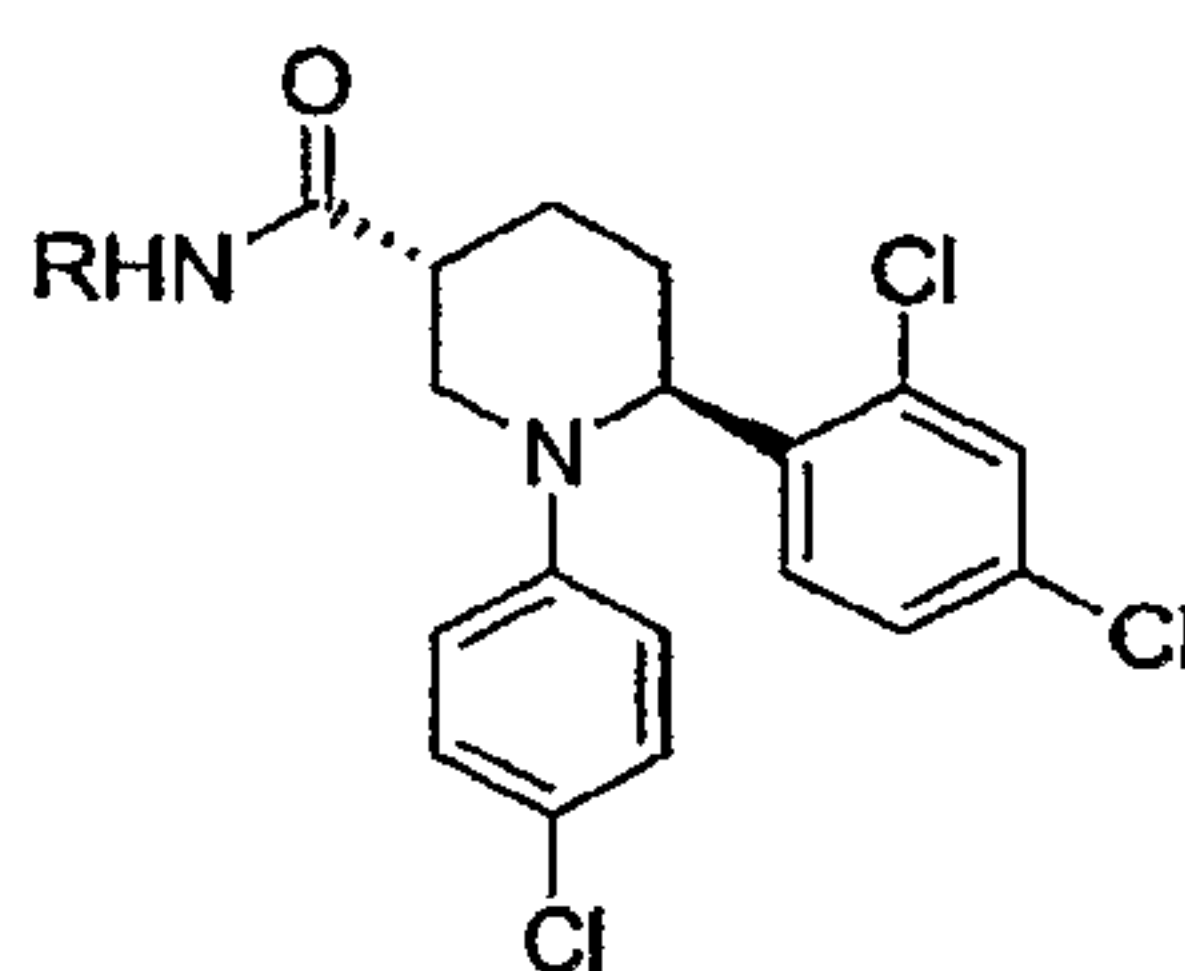
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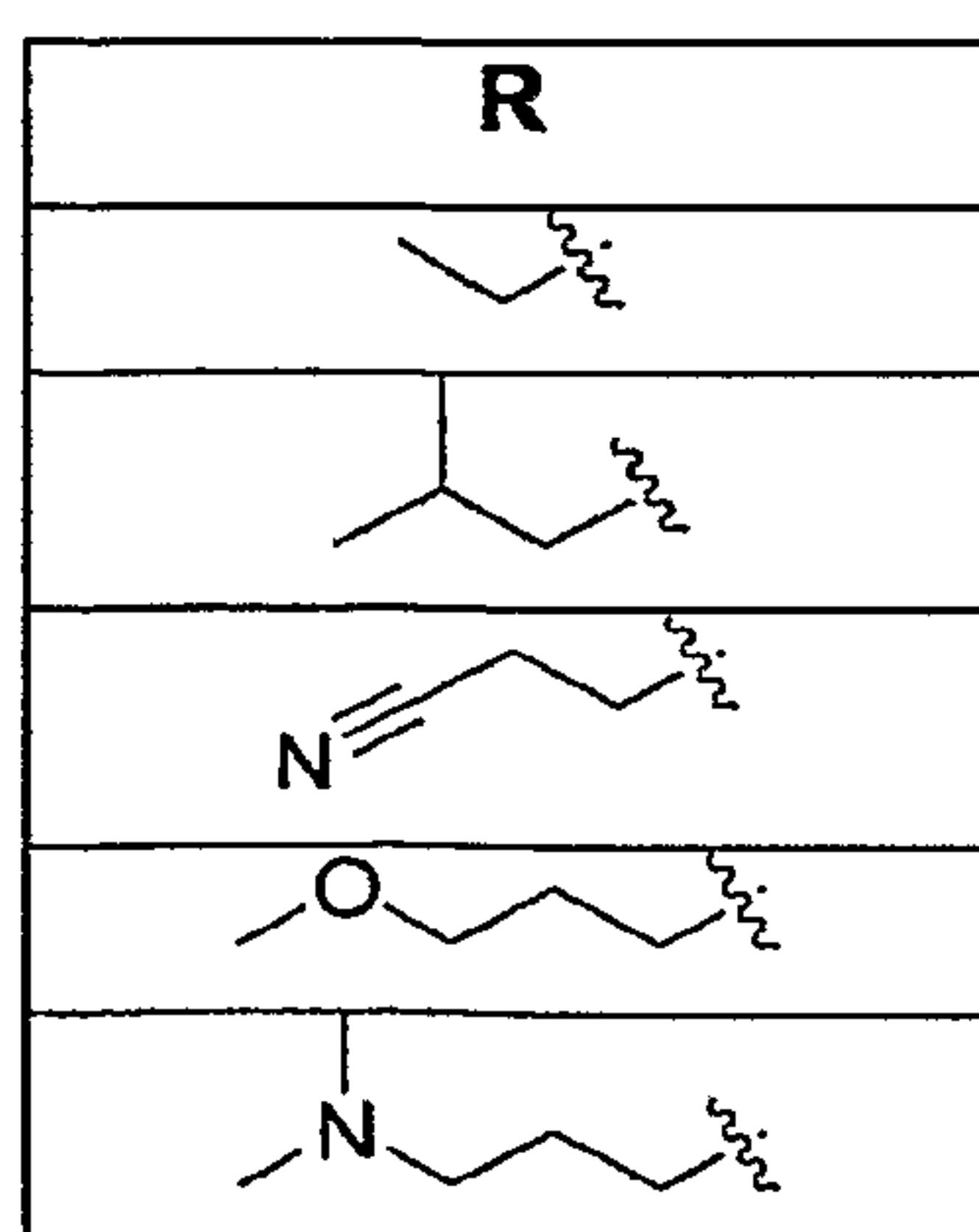
266



24. The compound of Claim 1, a pharmaceutically acceptable salt, solvate or ester thereof having a structure selected from the group consisting of:

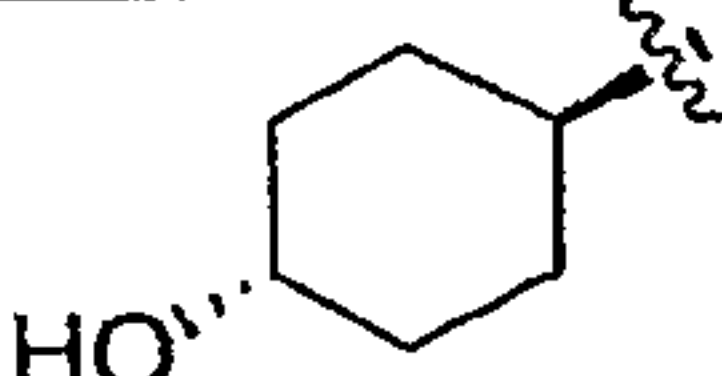
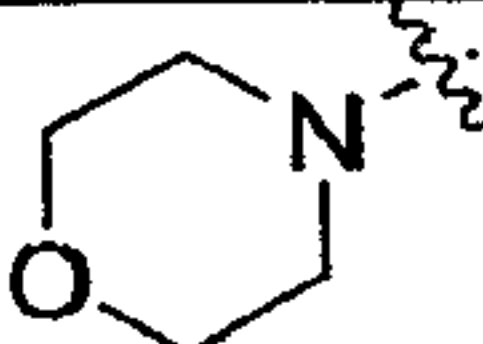
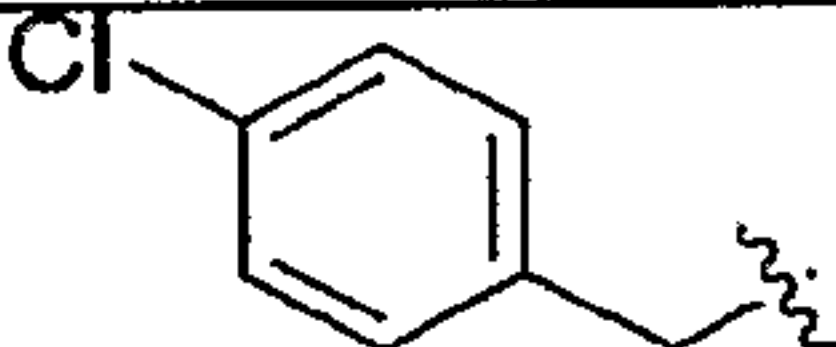
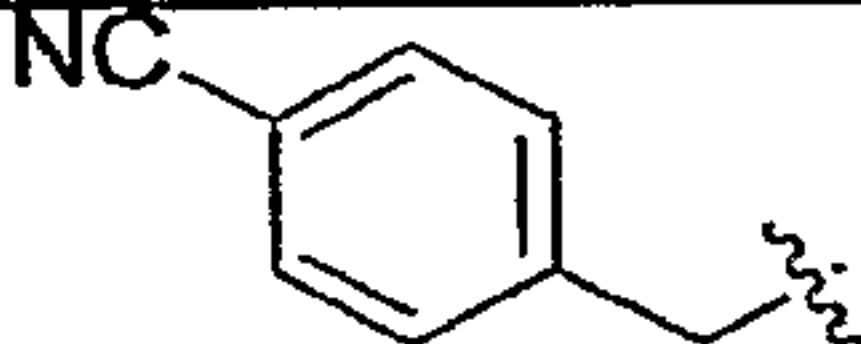
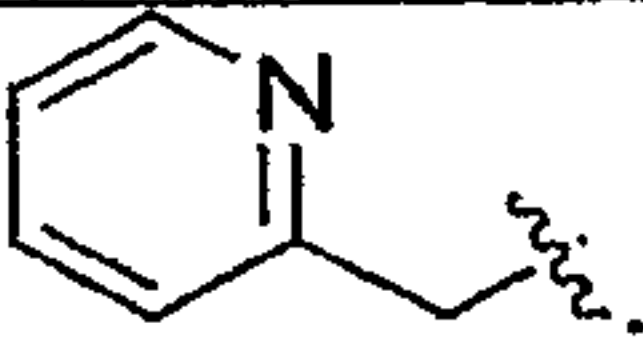


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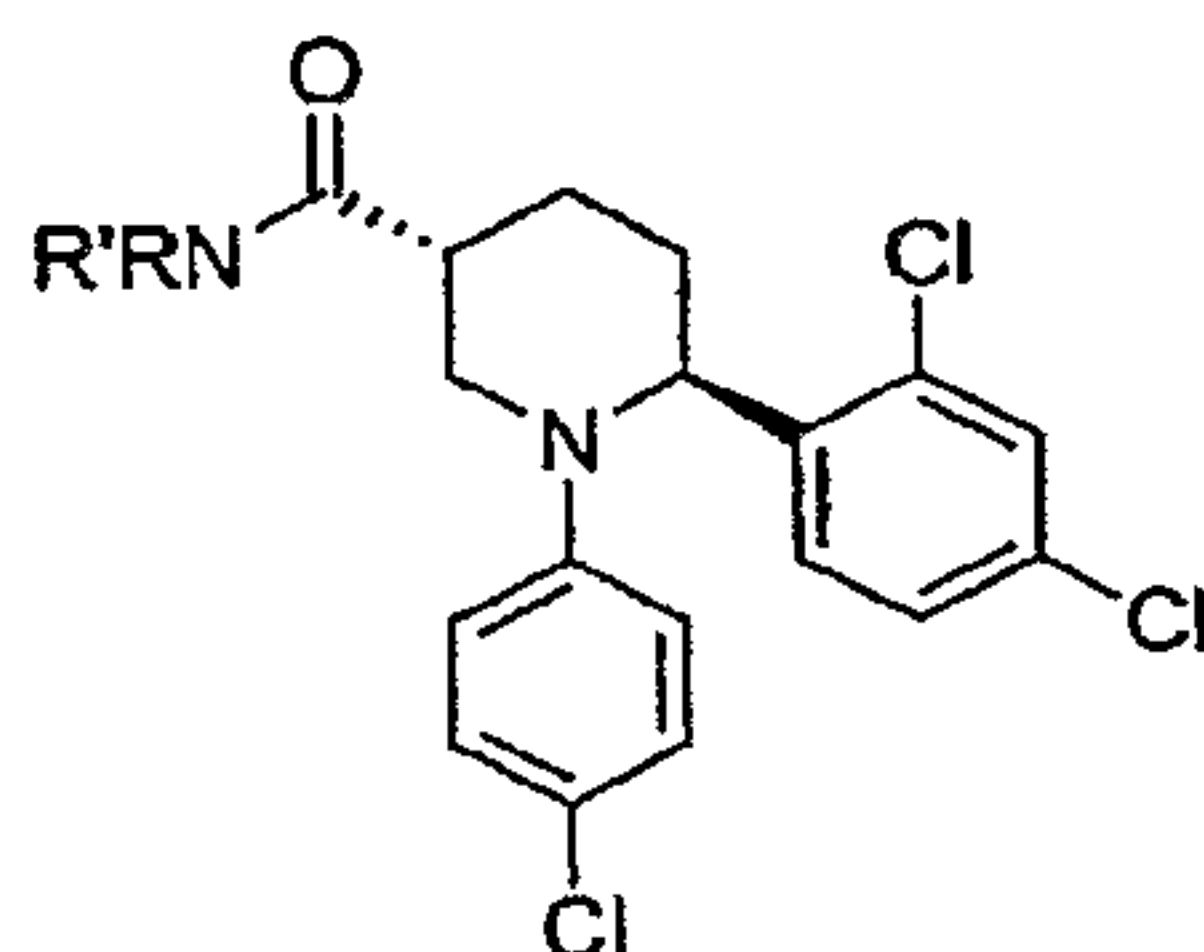


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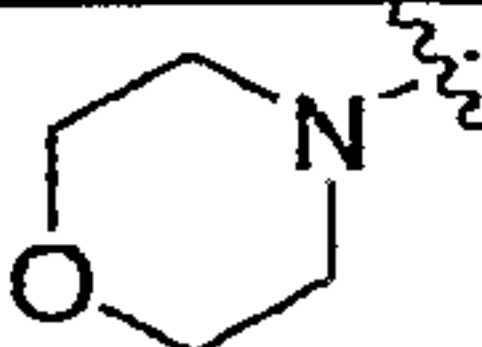
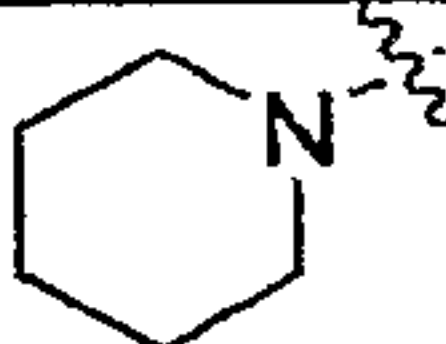
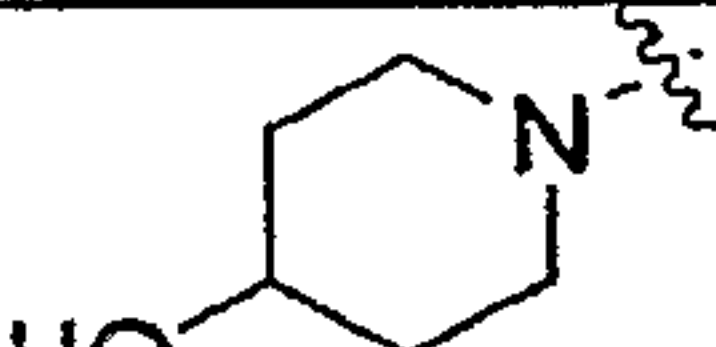
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and 

25. The compound of Claim 1, a pharmaceutically acceptable salt, solvate or ester thereof having a structure selected from the group consisting of:

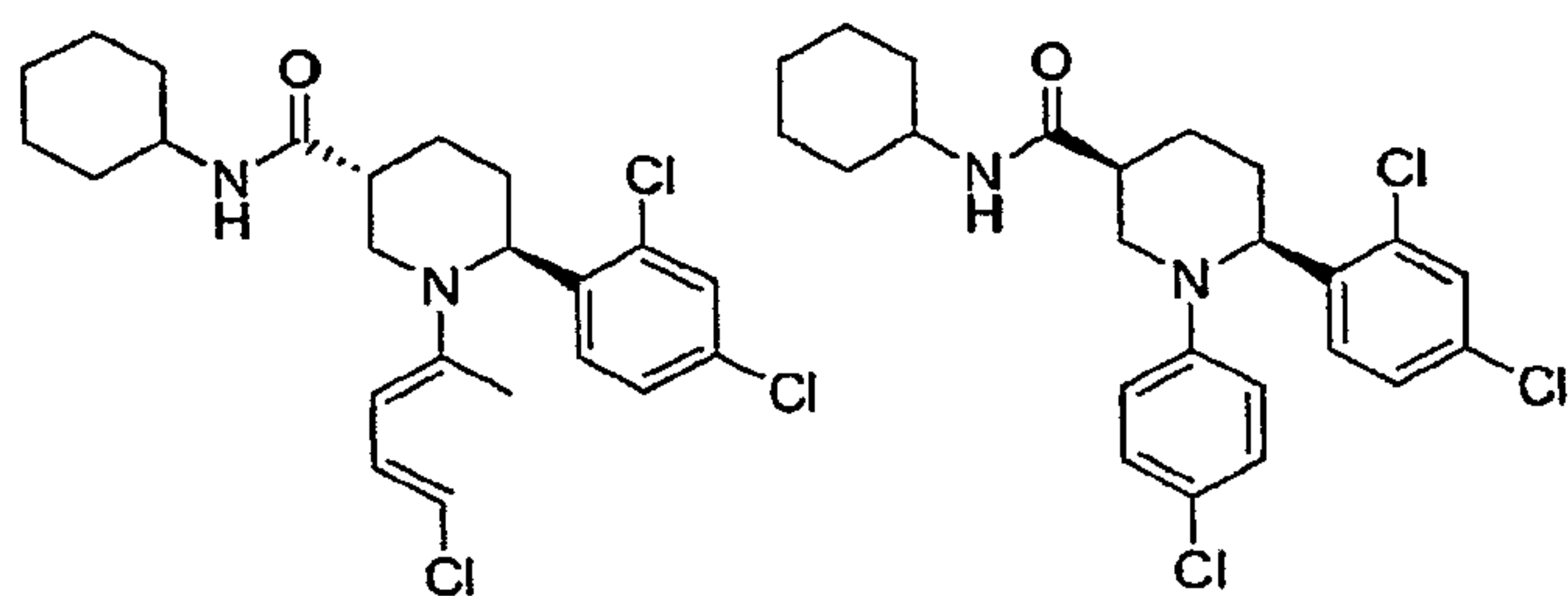


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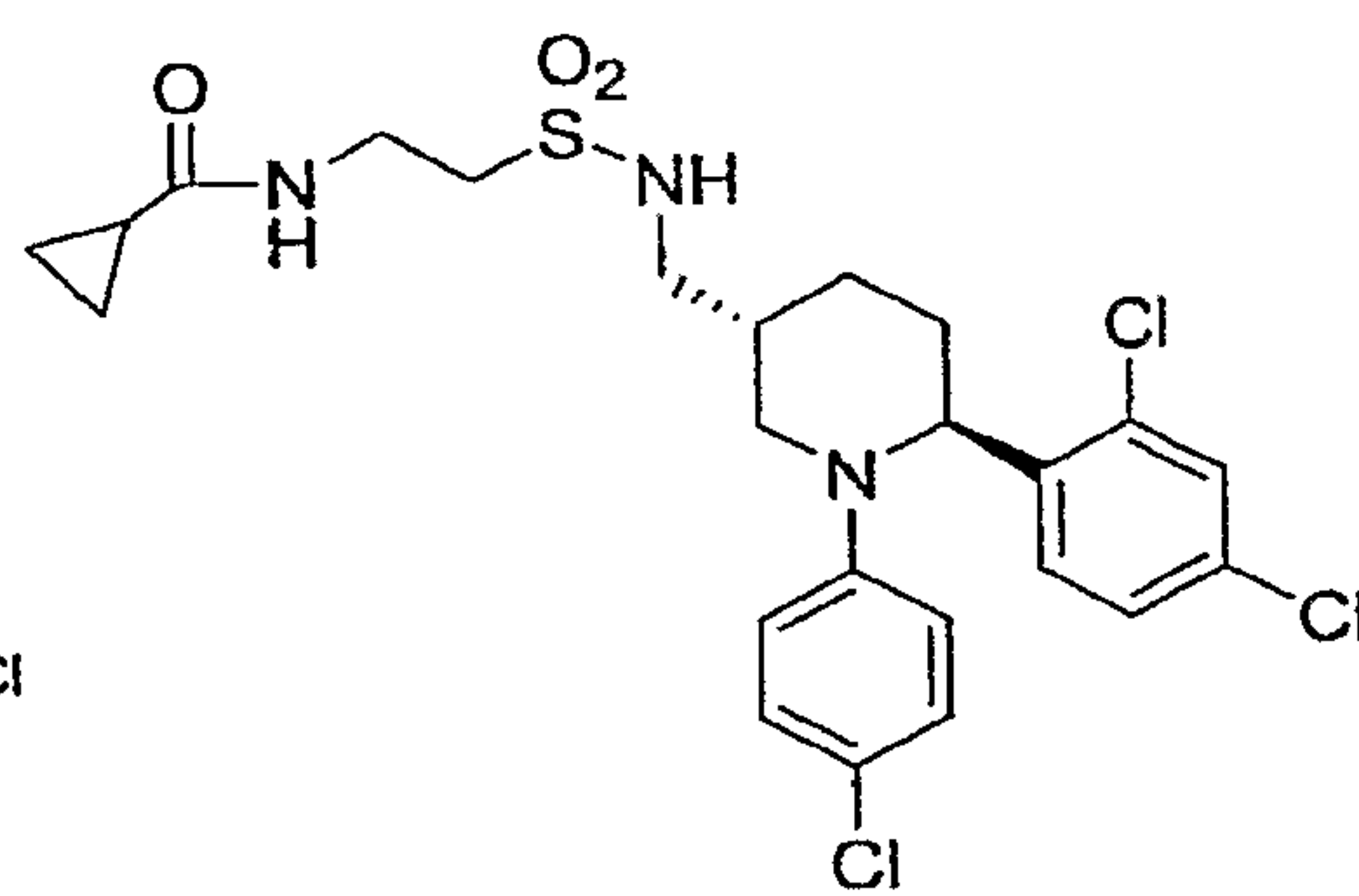
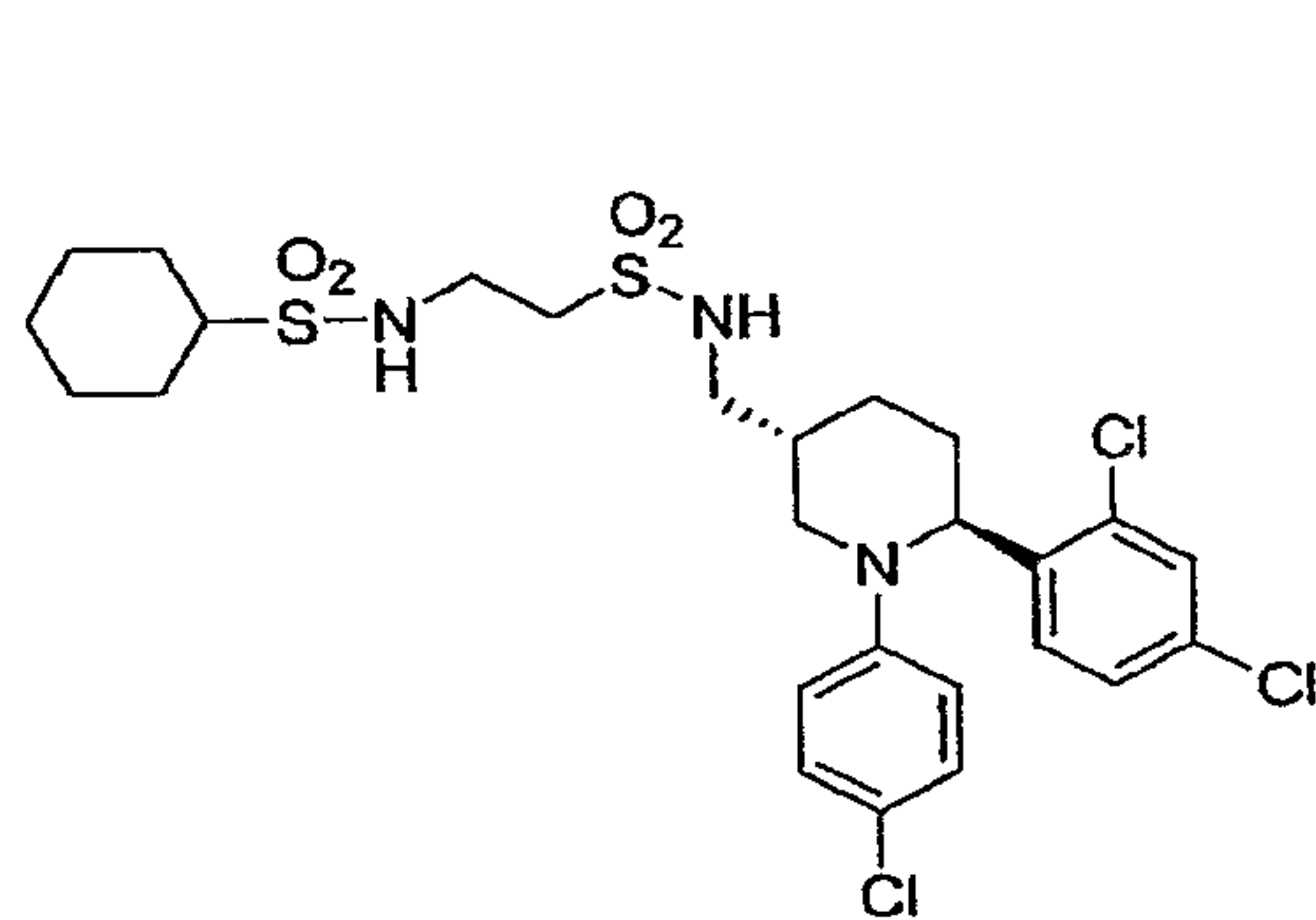
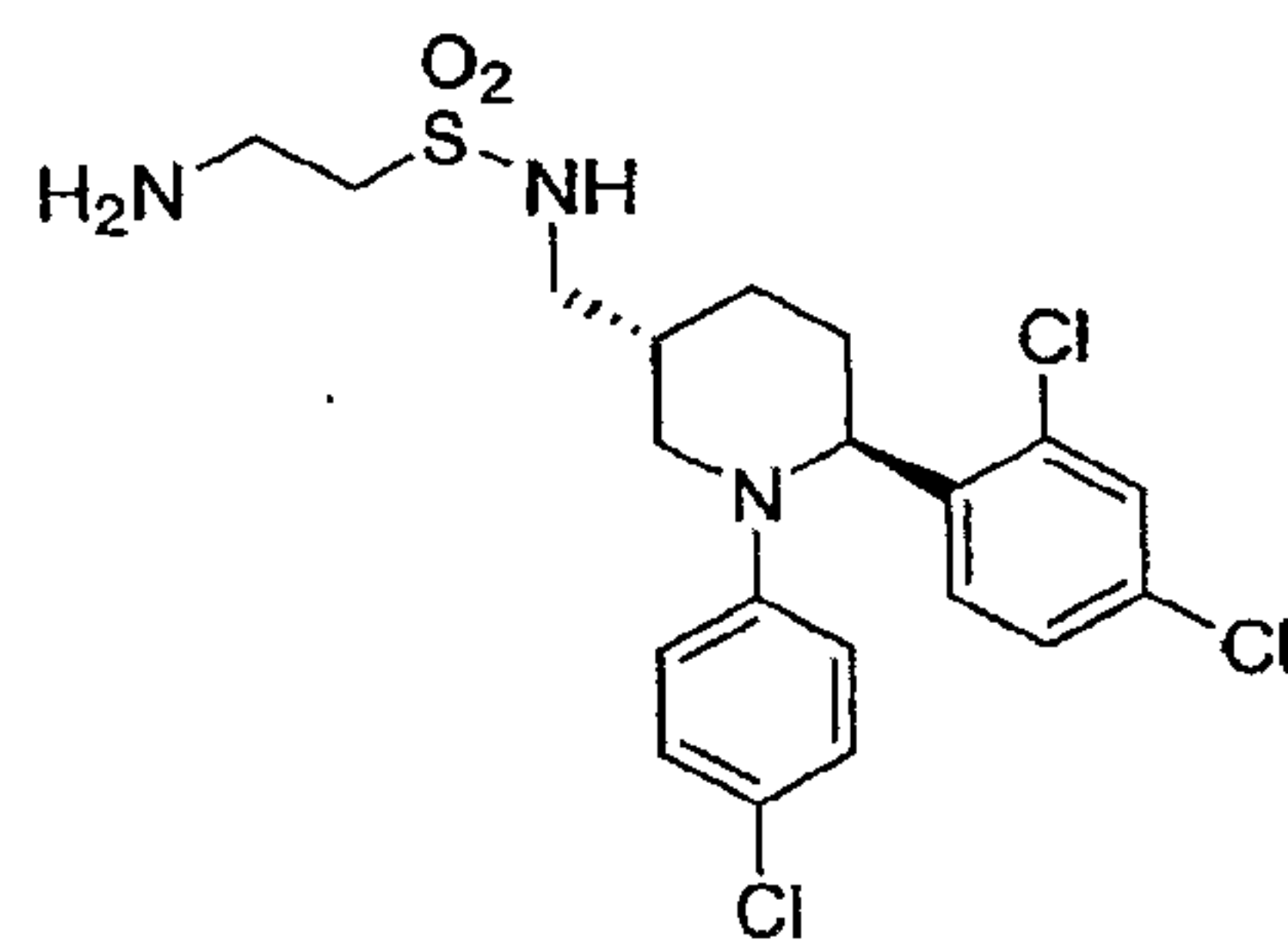
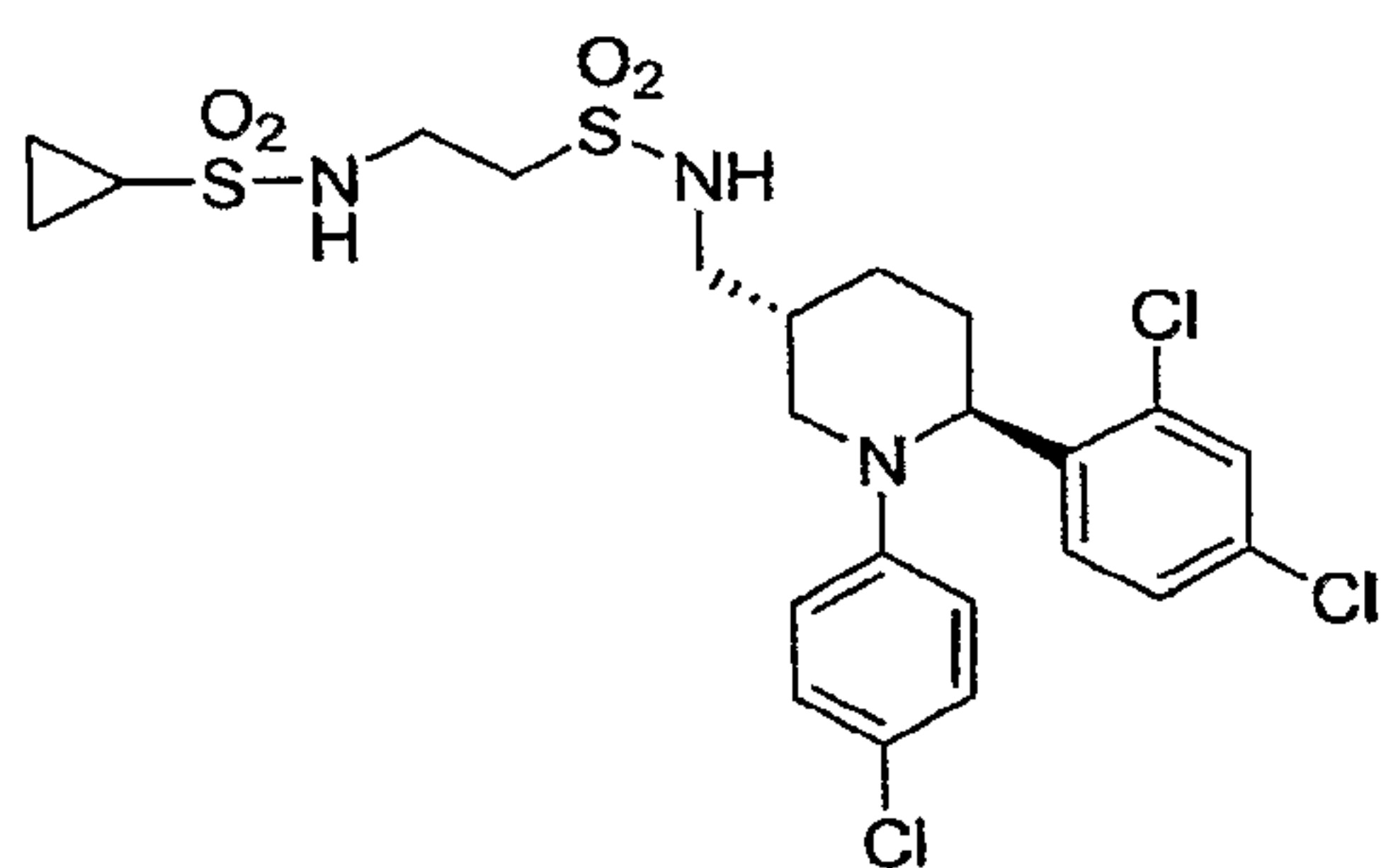
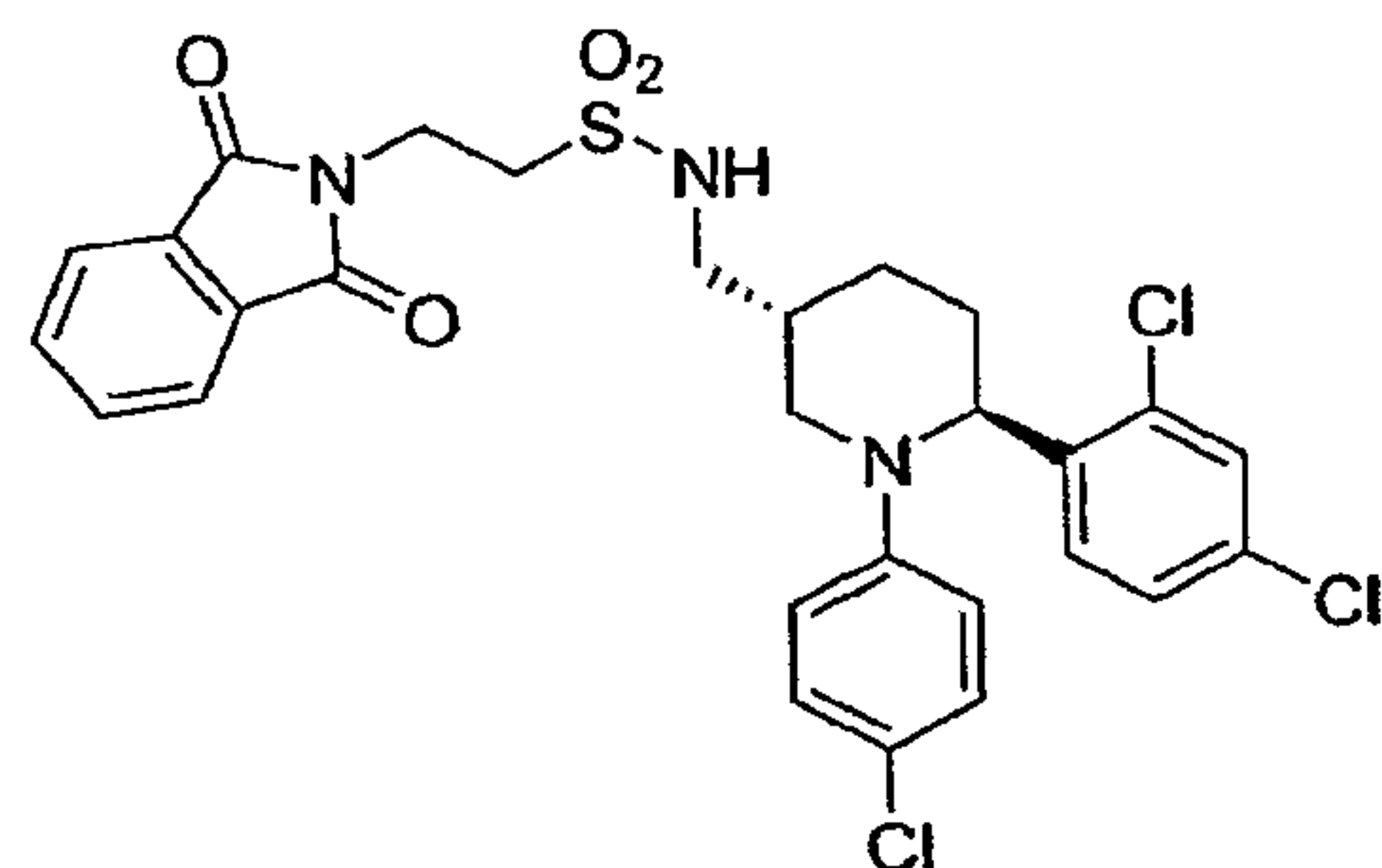
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26. The compound of Claim 1, a pharmaceutically acceptable salt, solvate or ester thereof having a structure selected from the group consisting of:

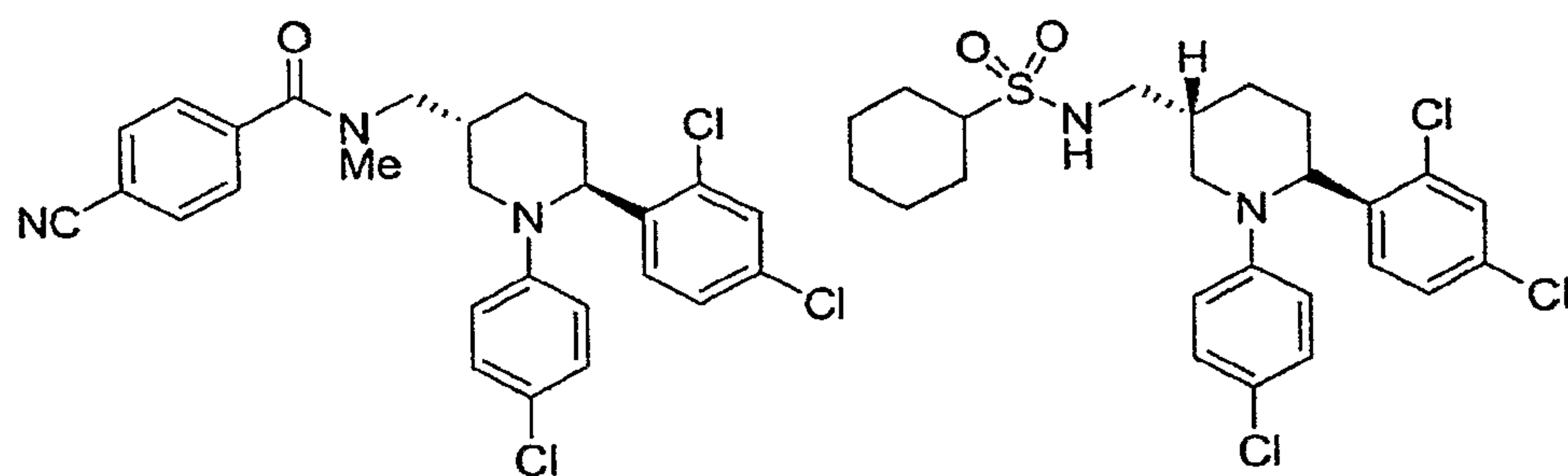
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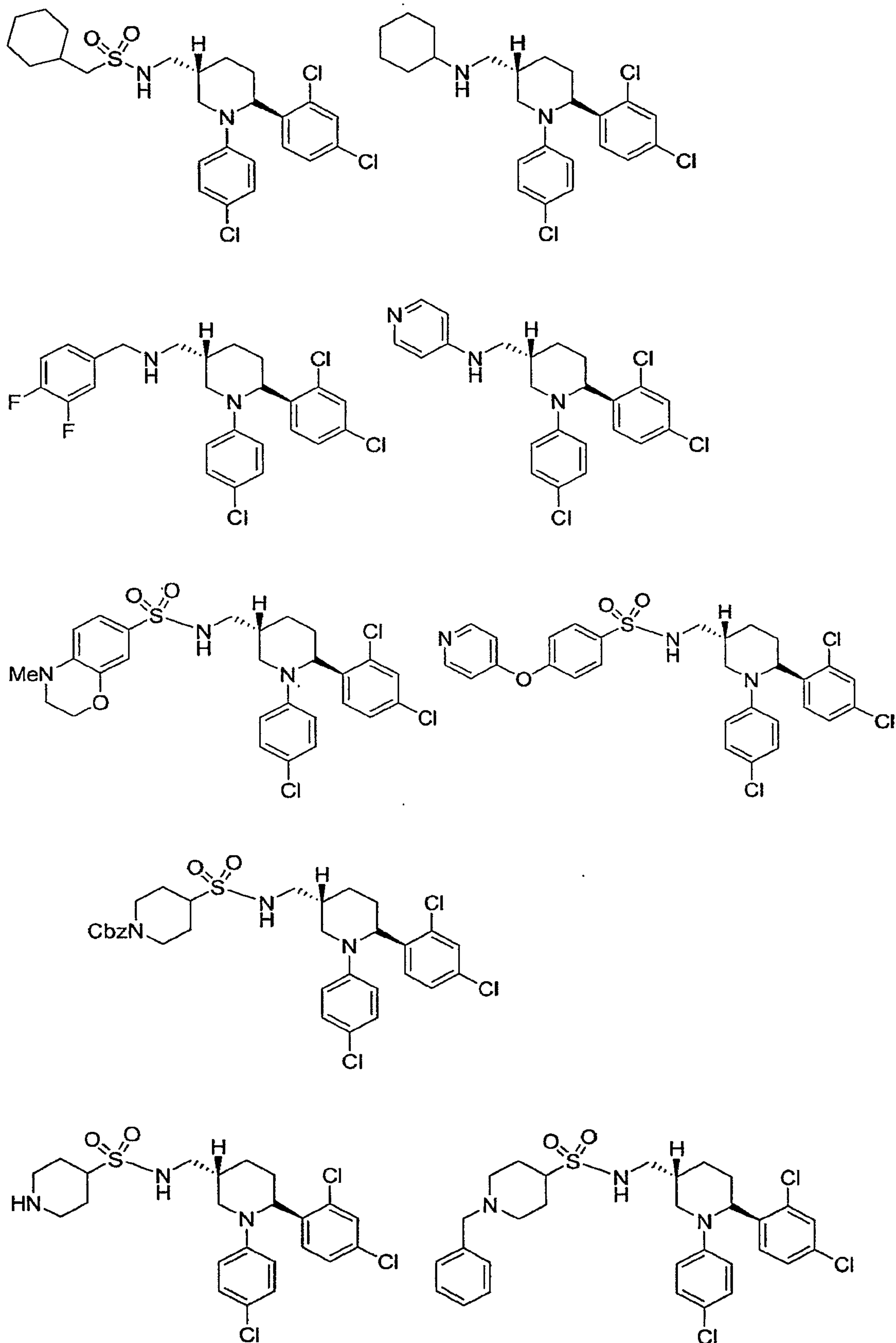
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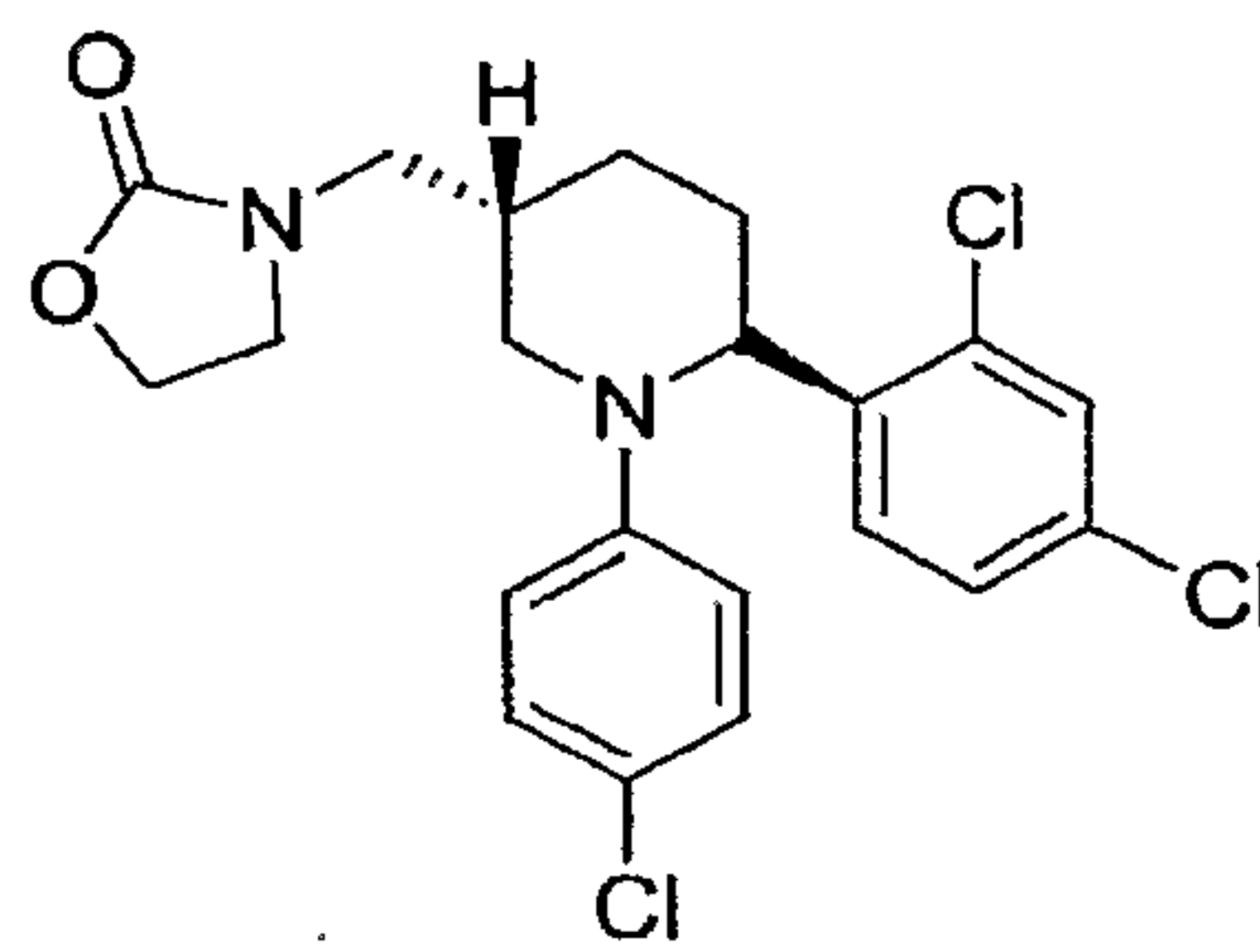
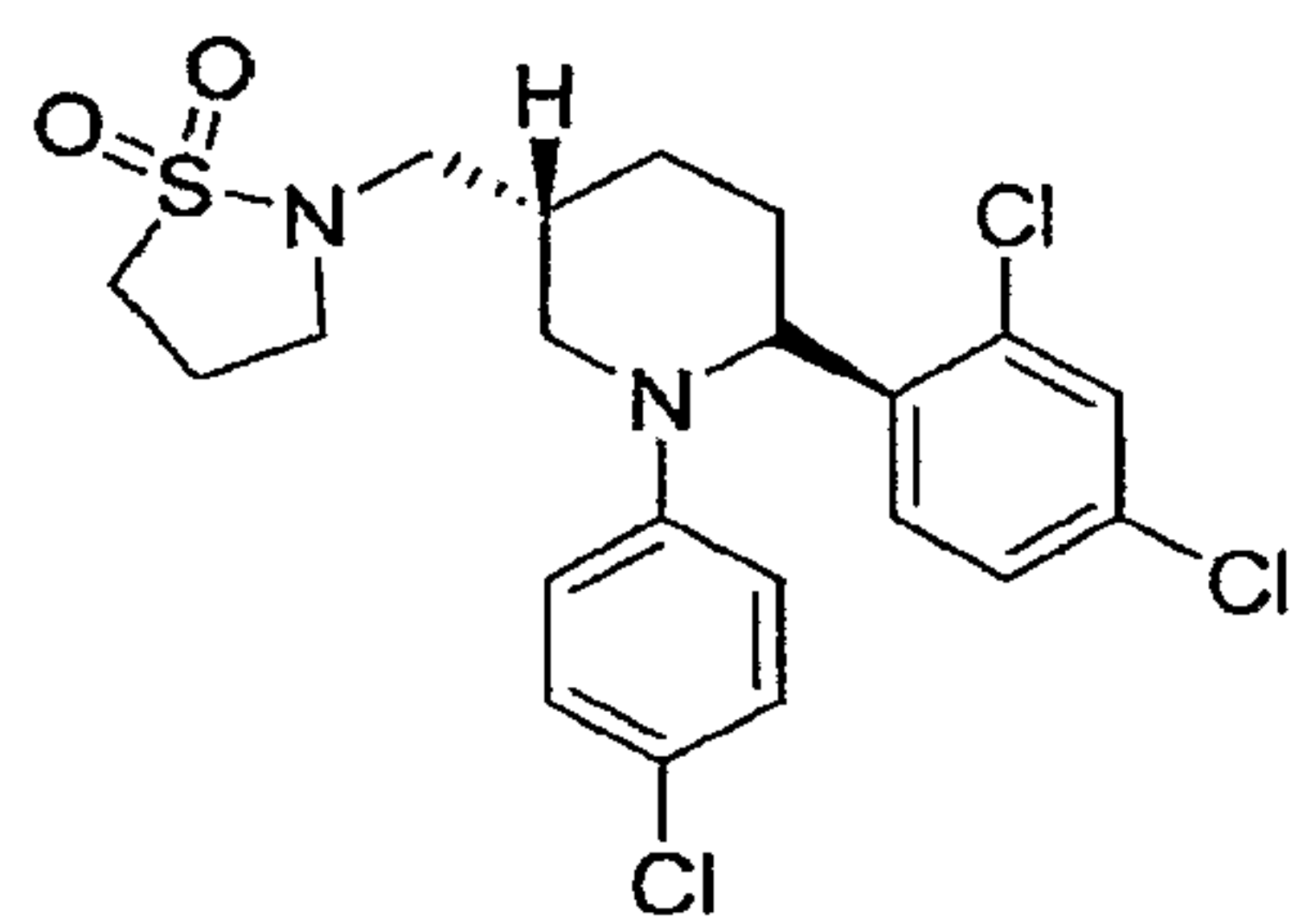
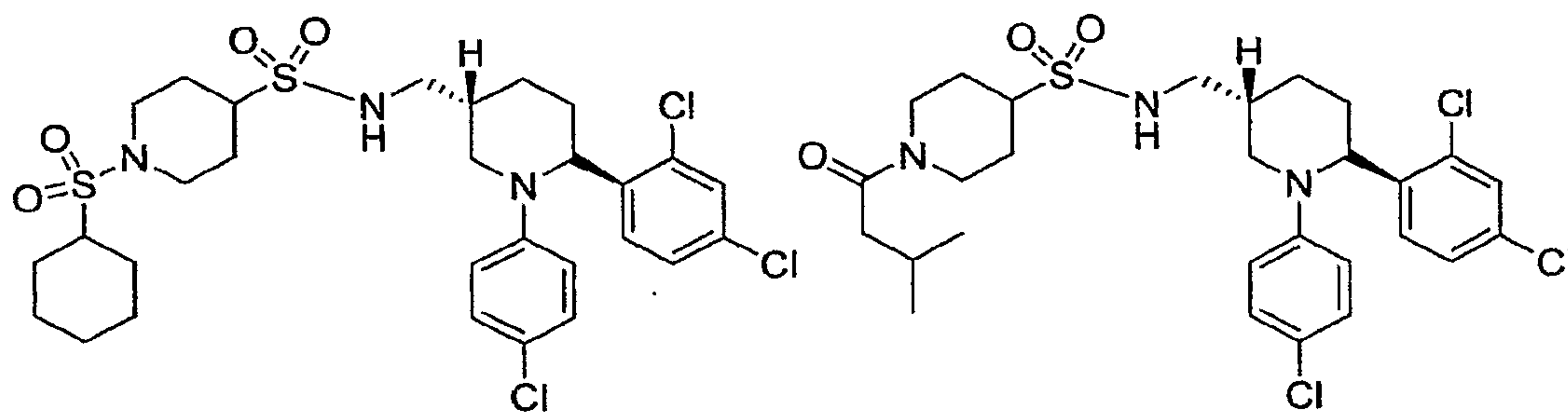
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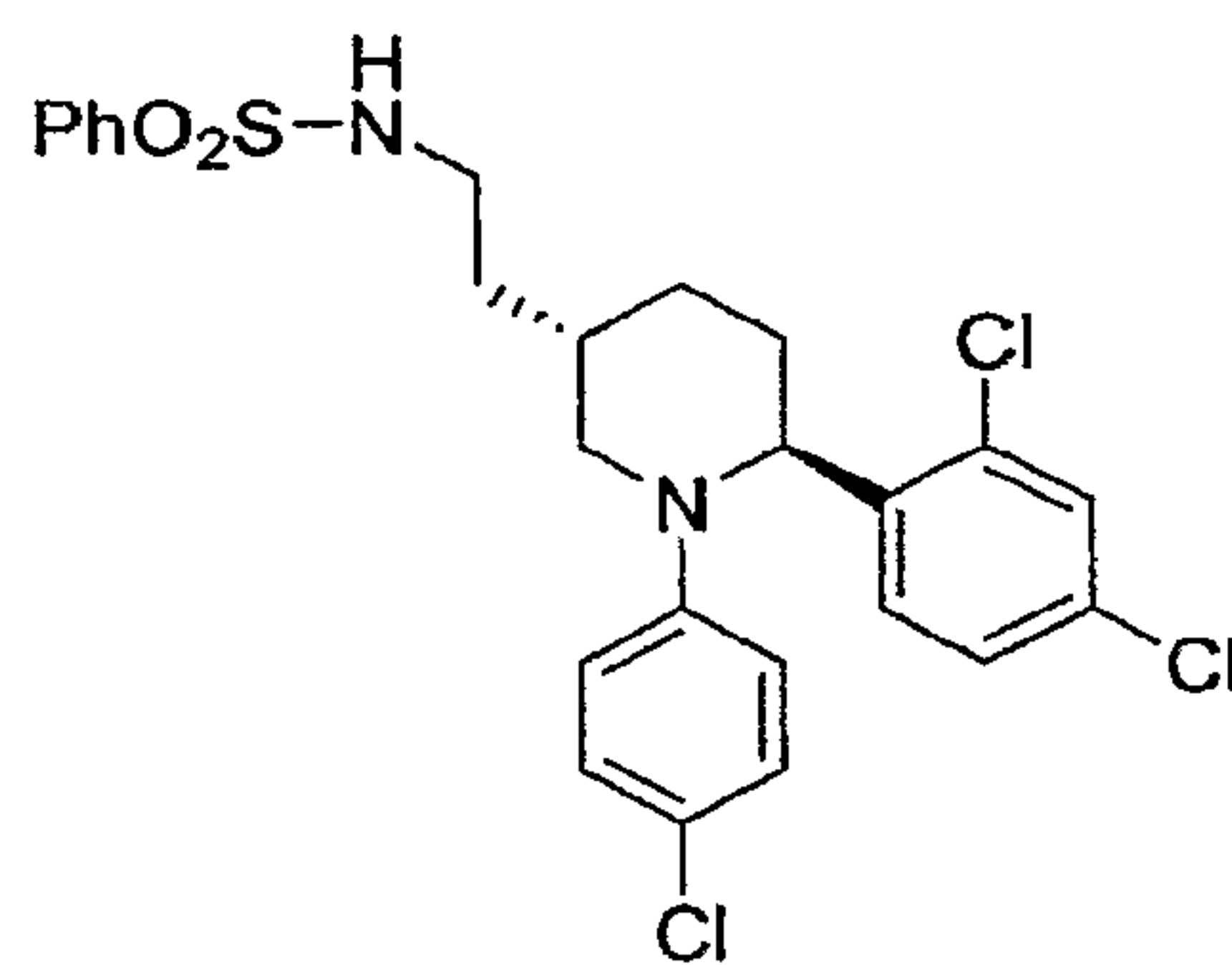
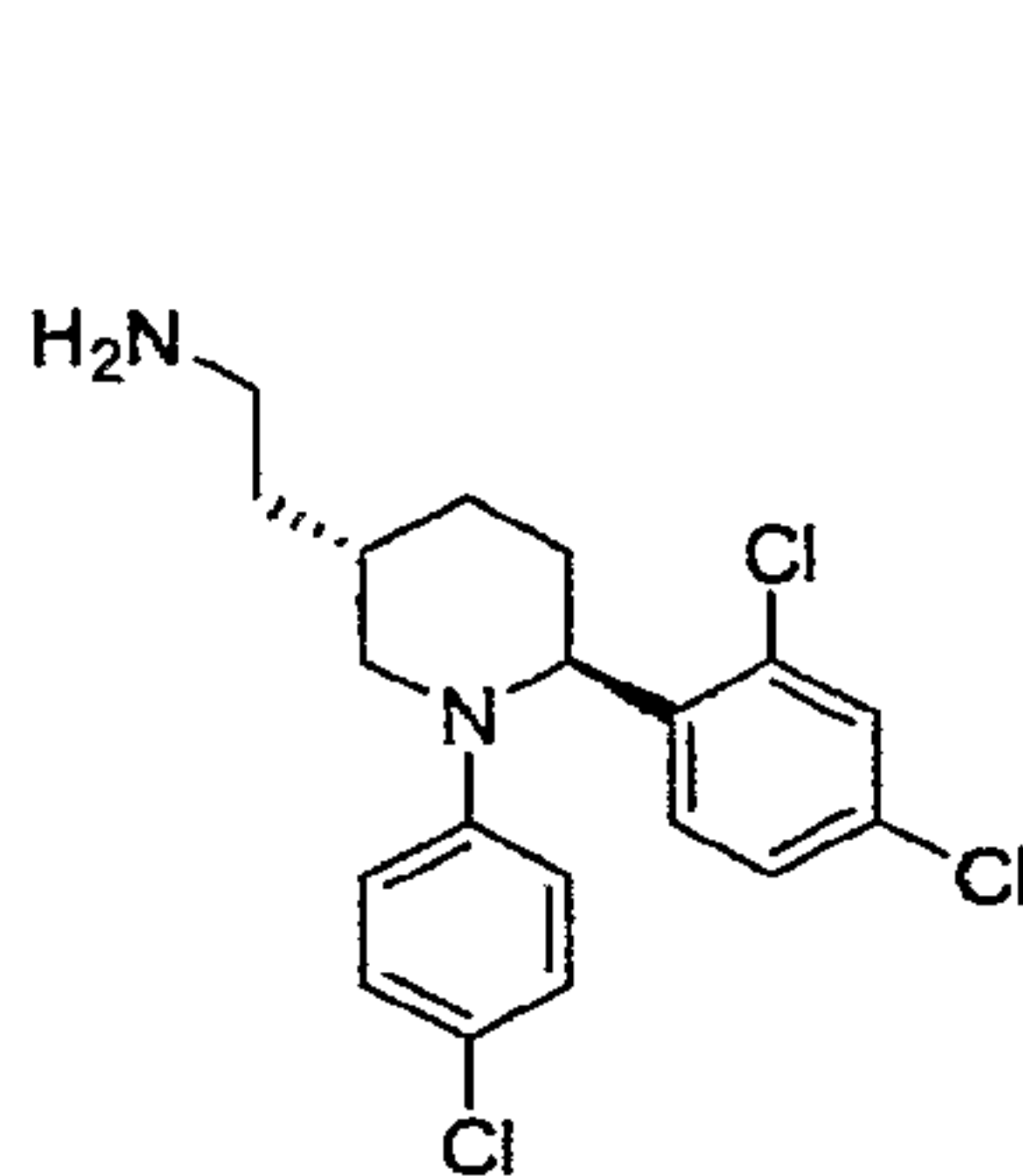
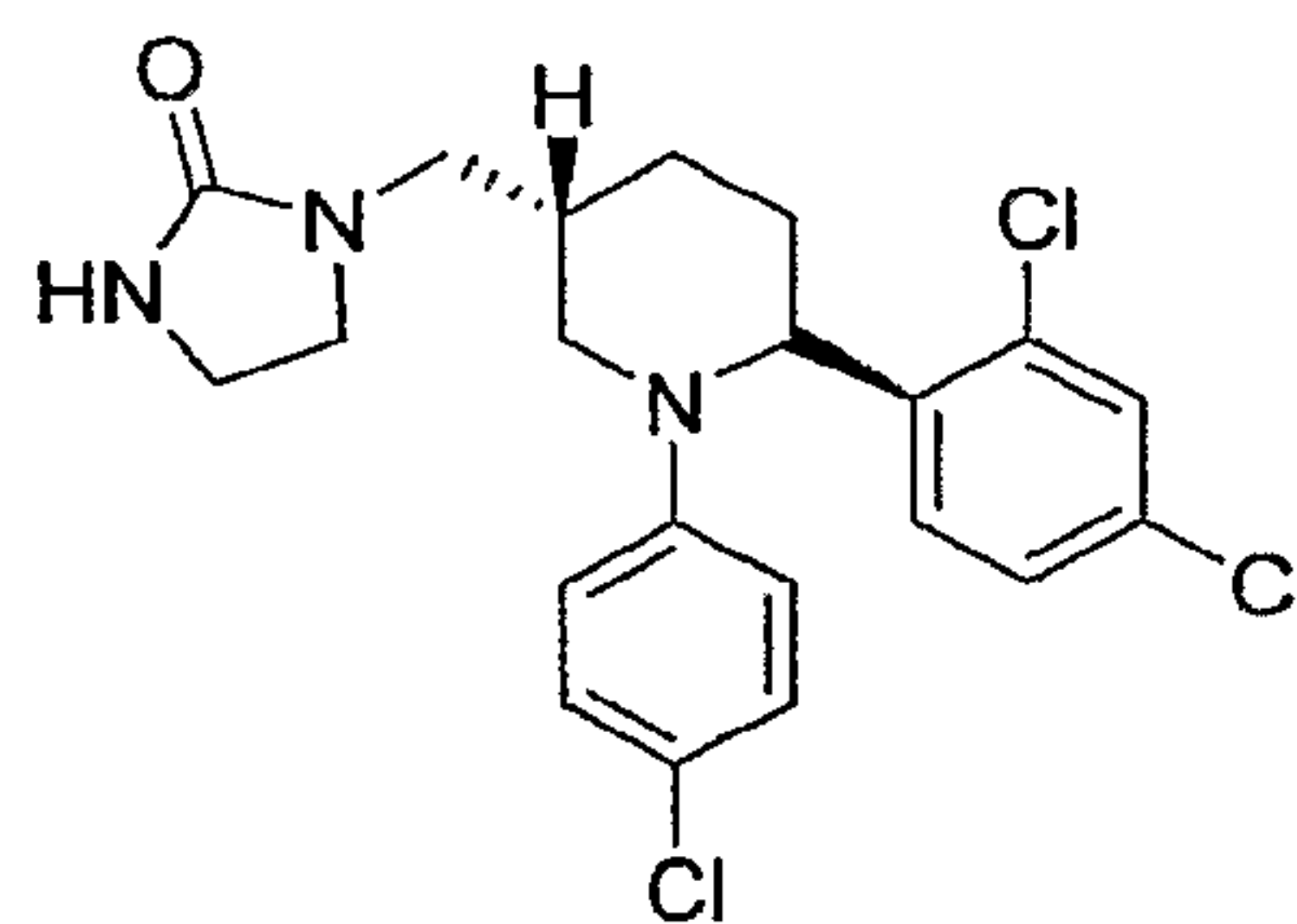
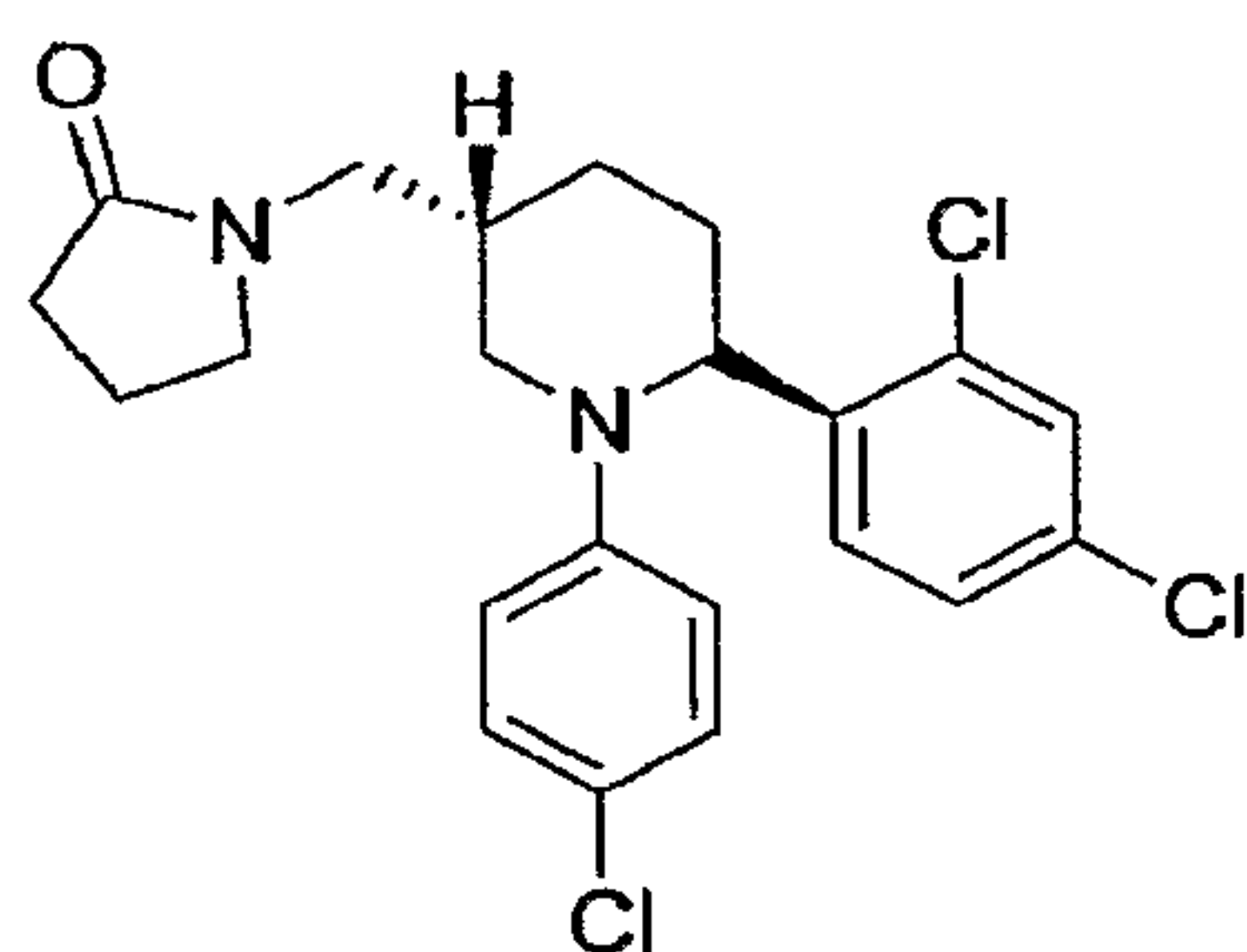
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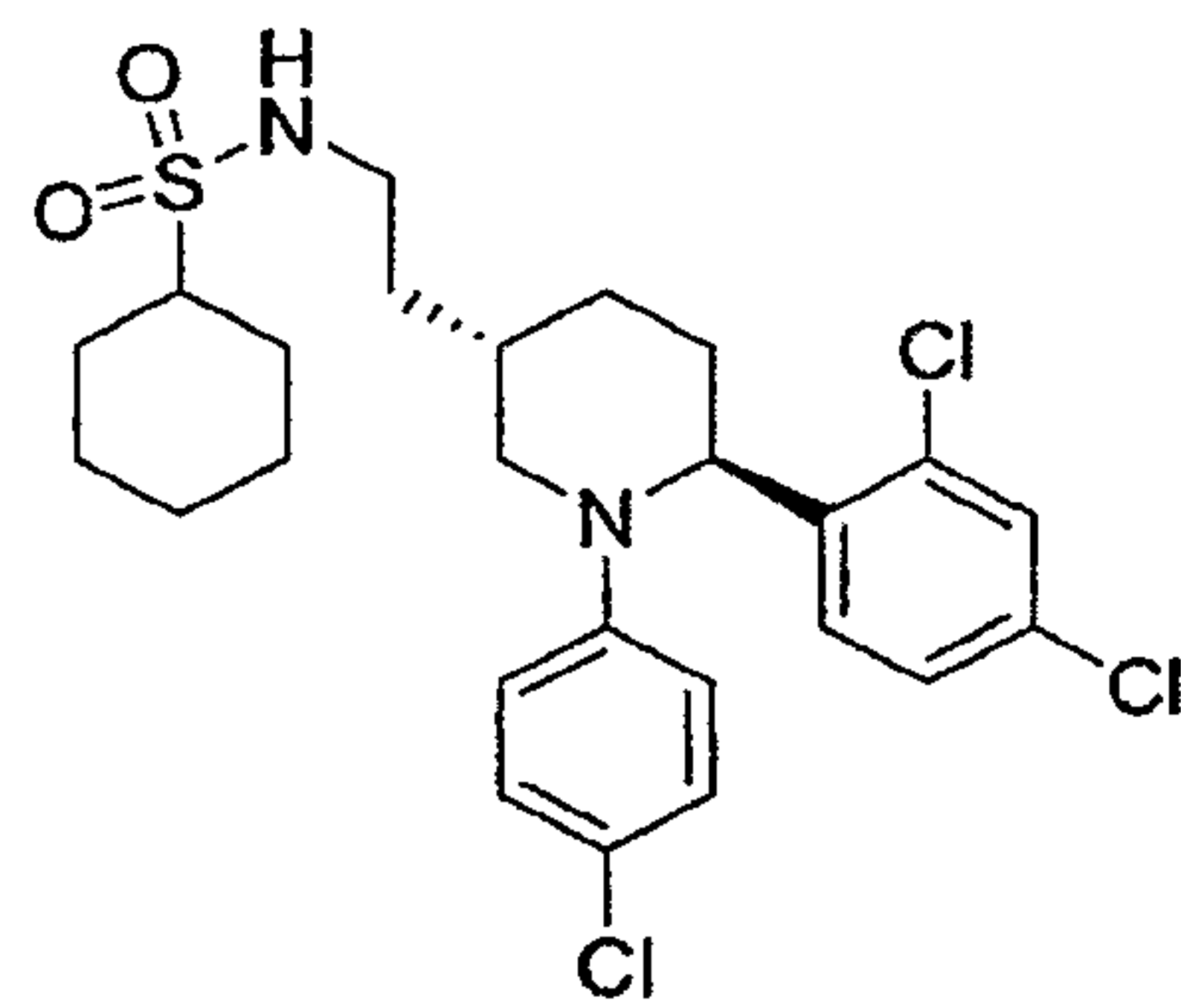
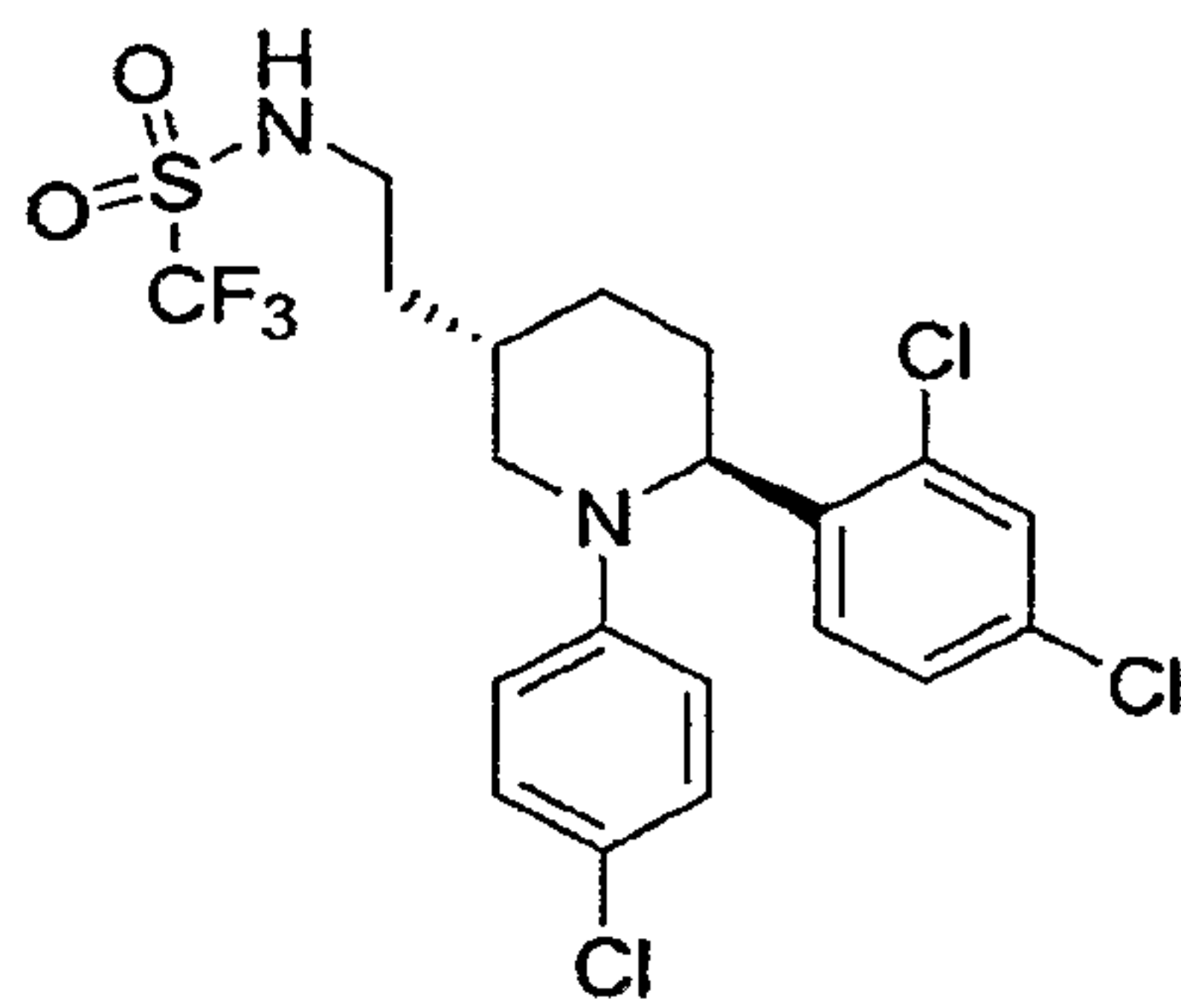
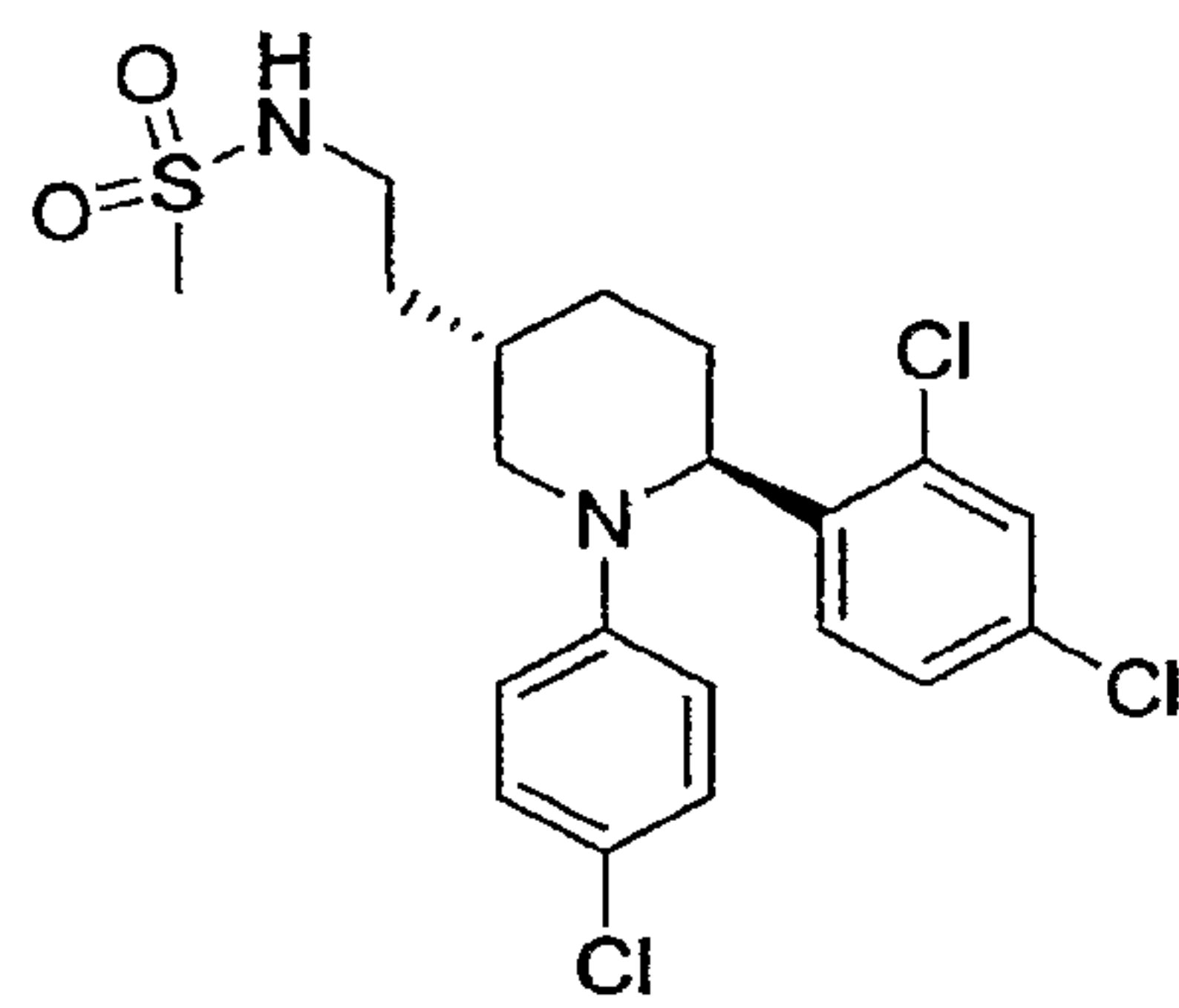
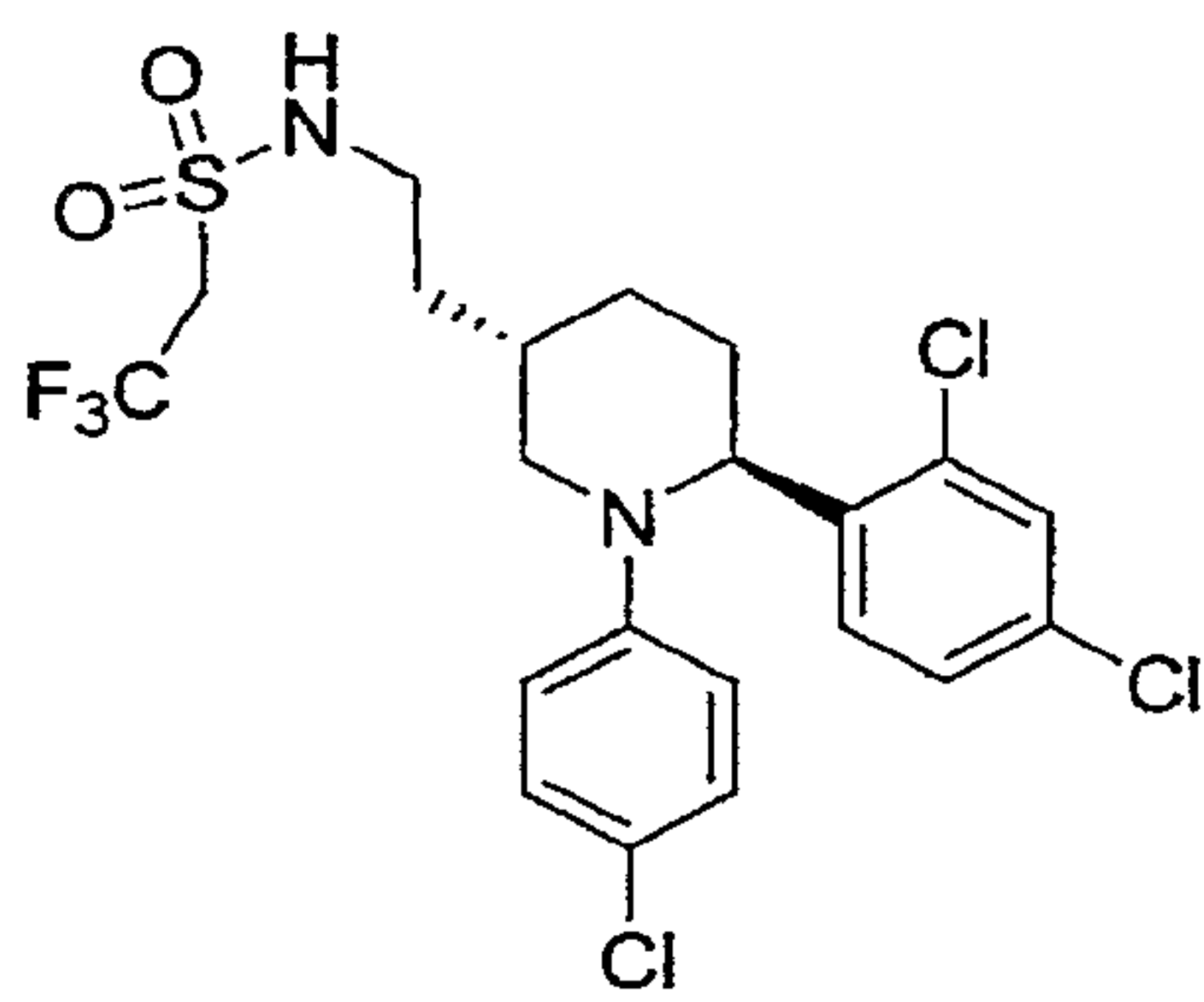
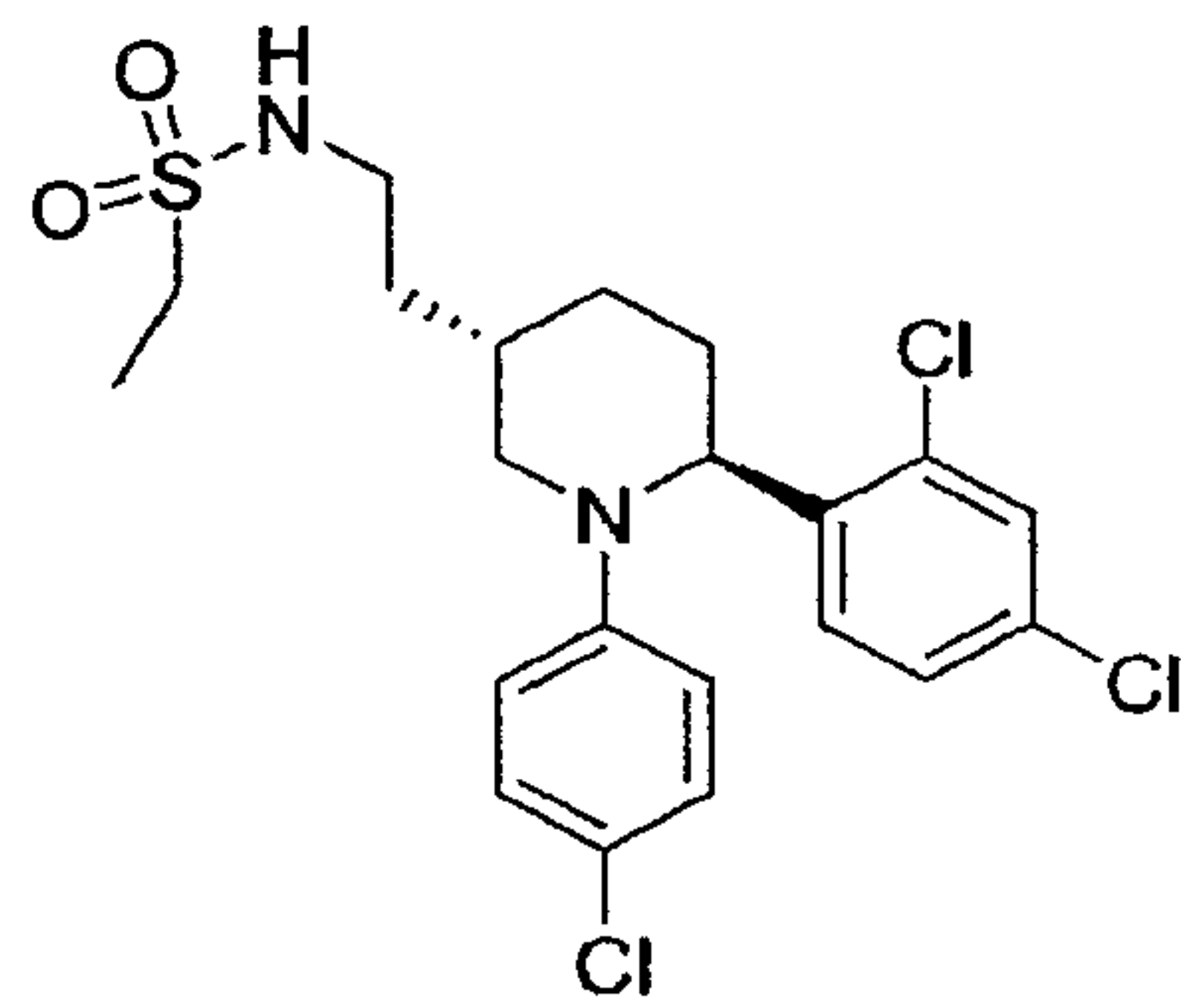
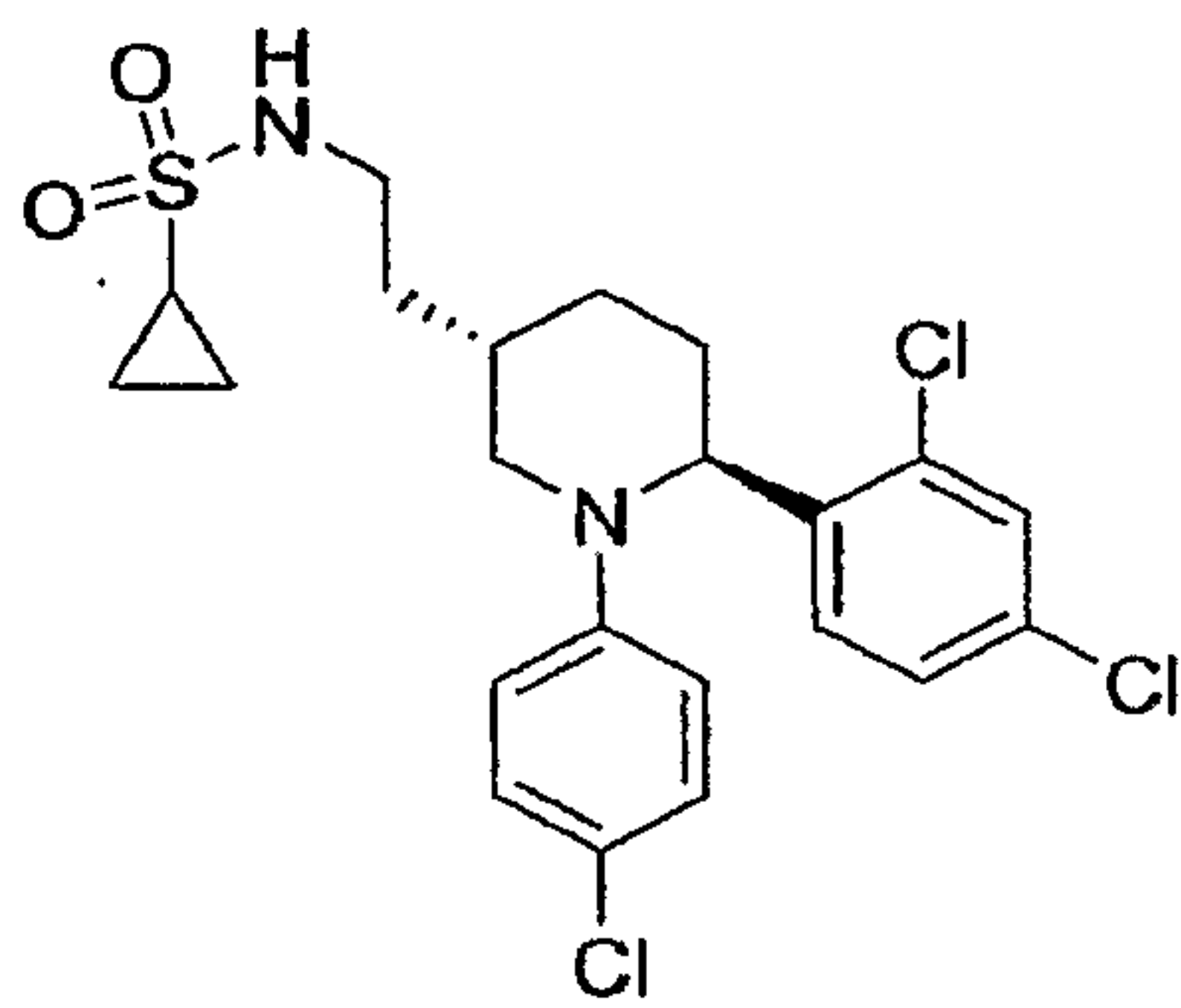
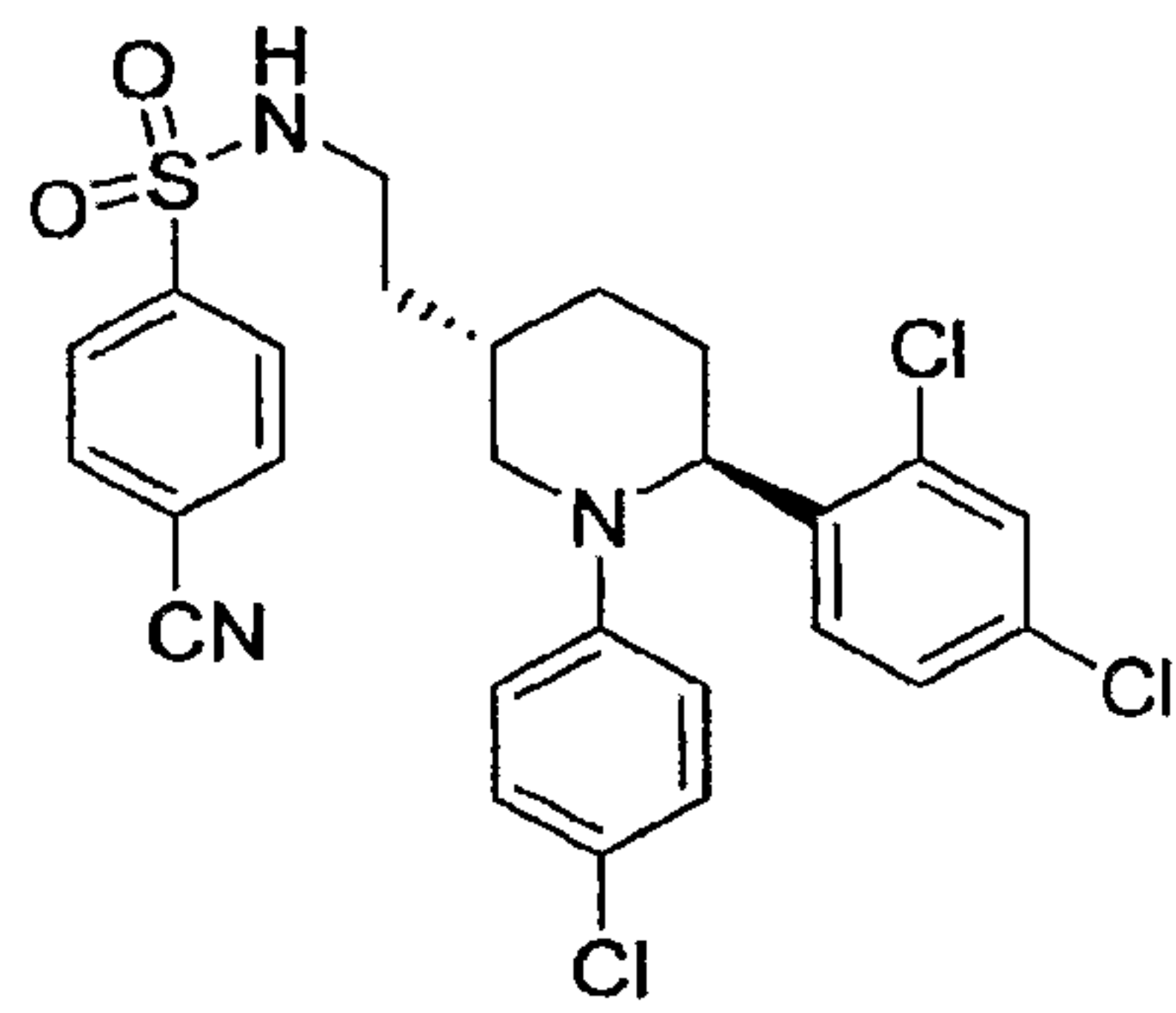
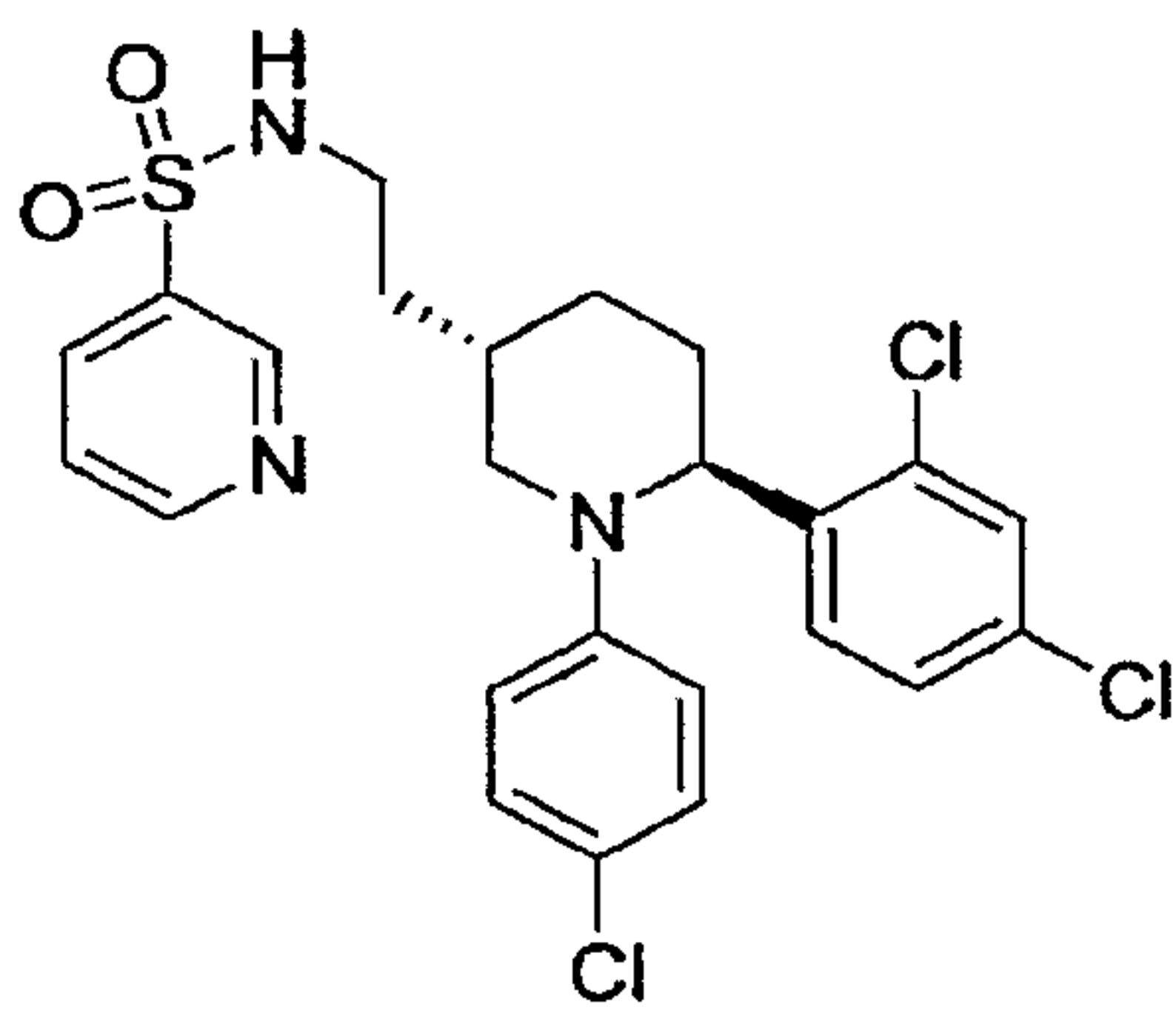
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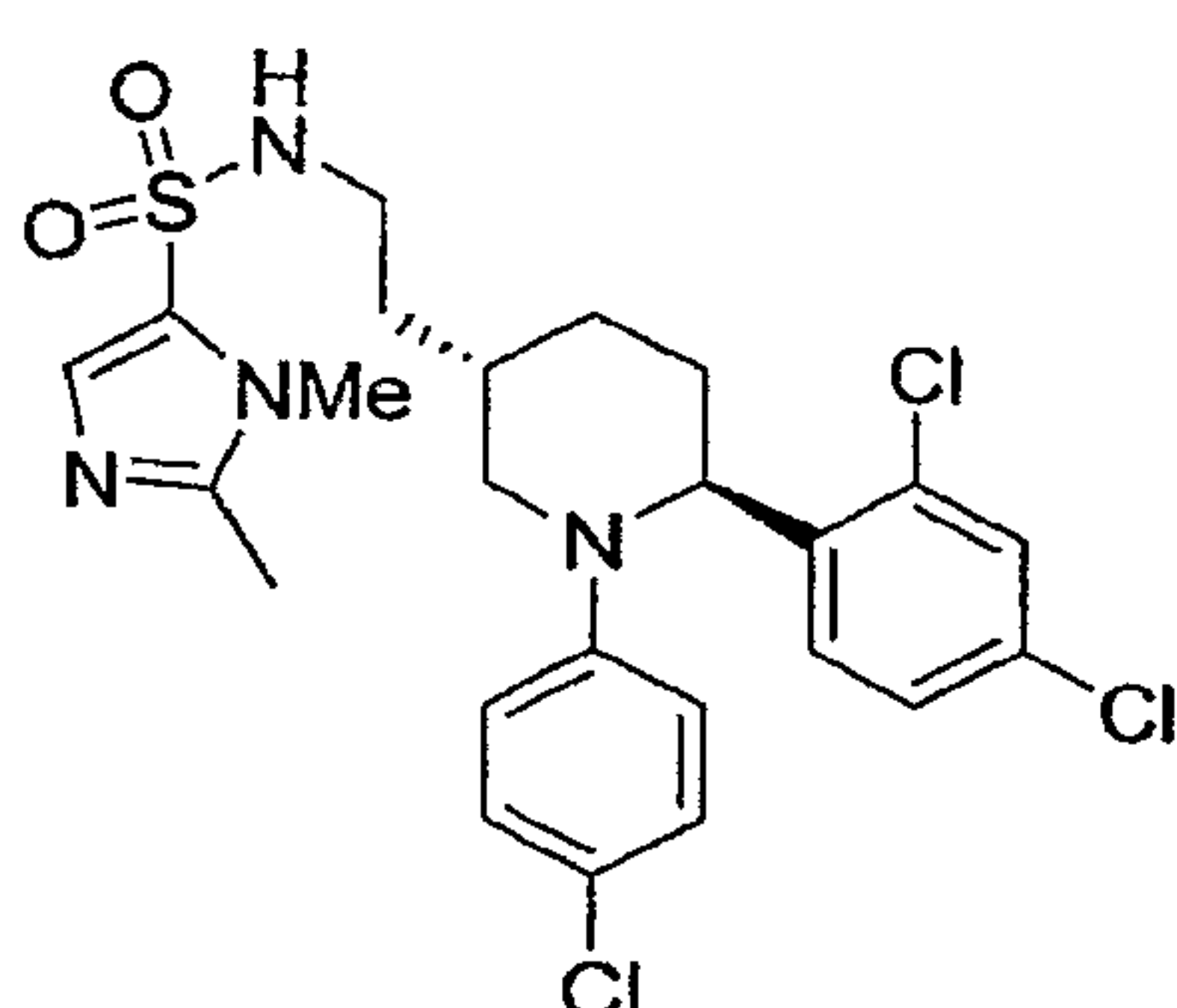
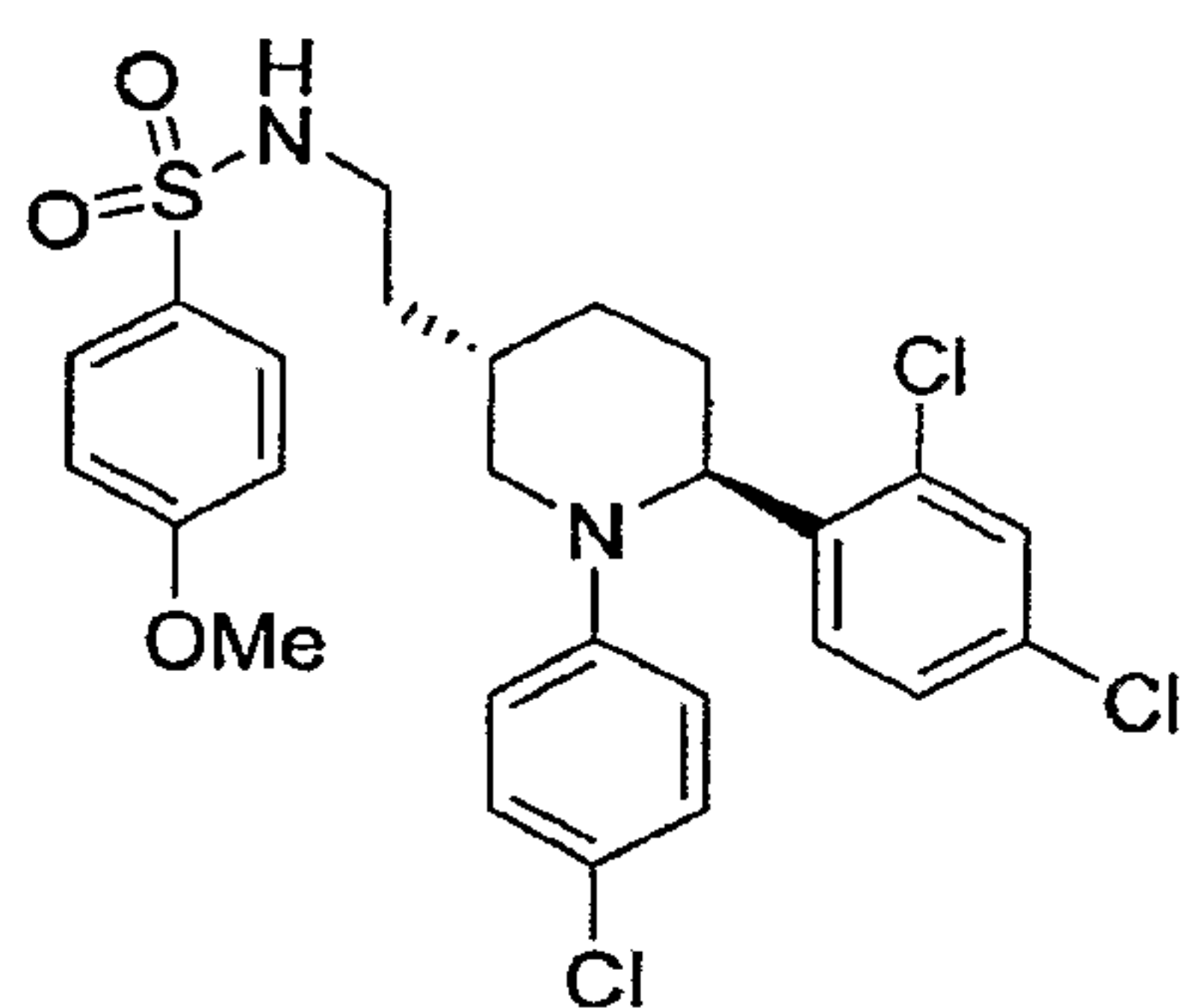
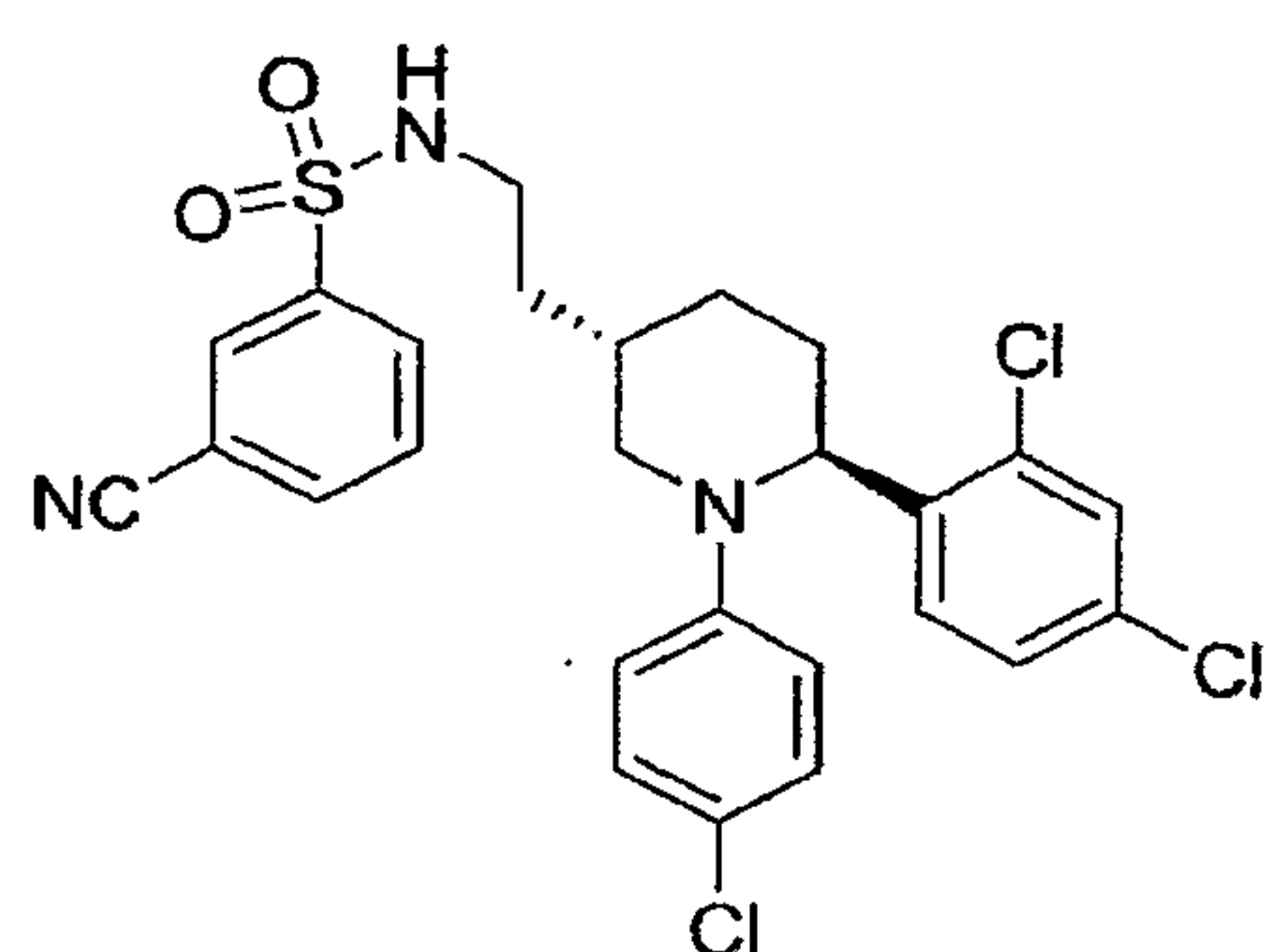
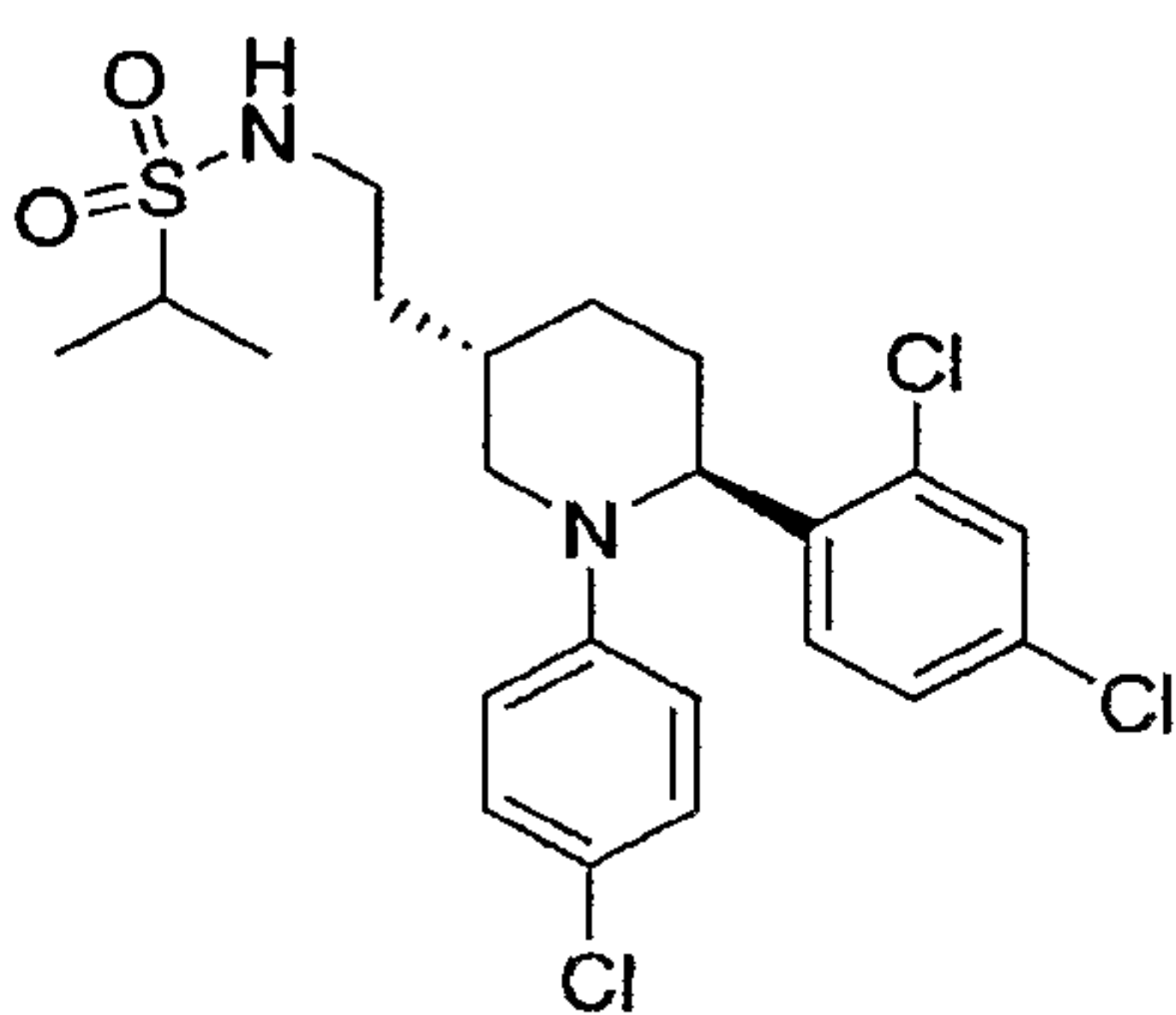
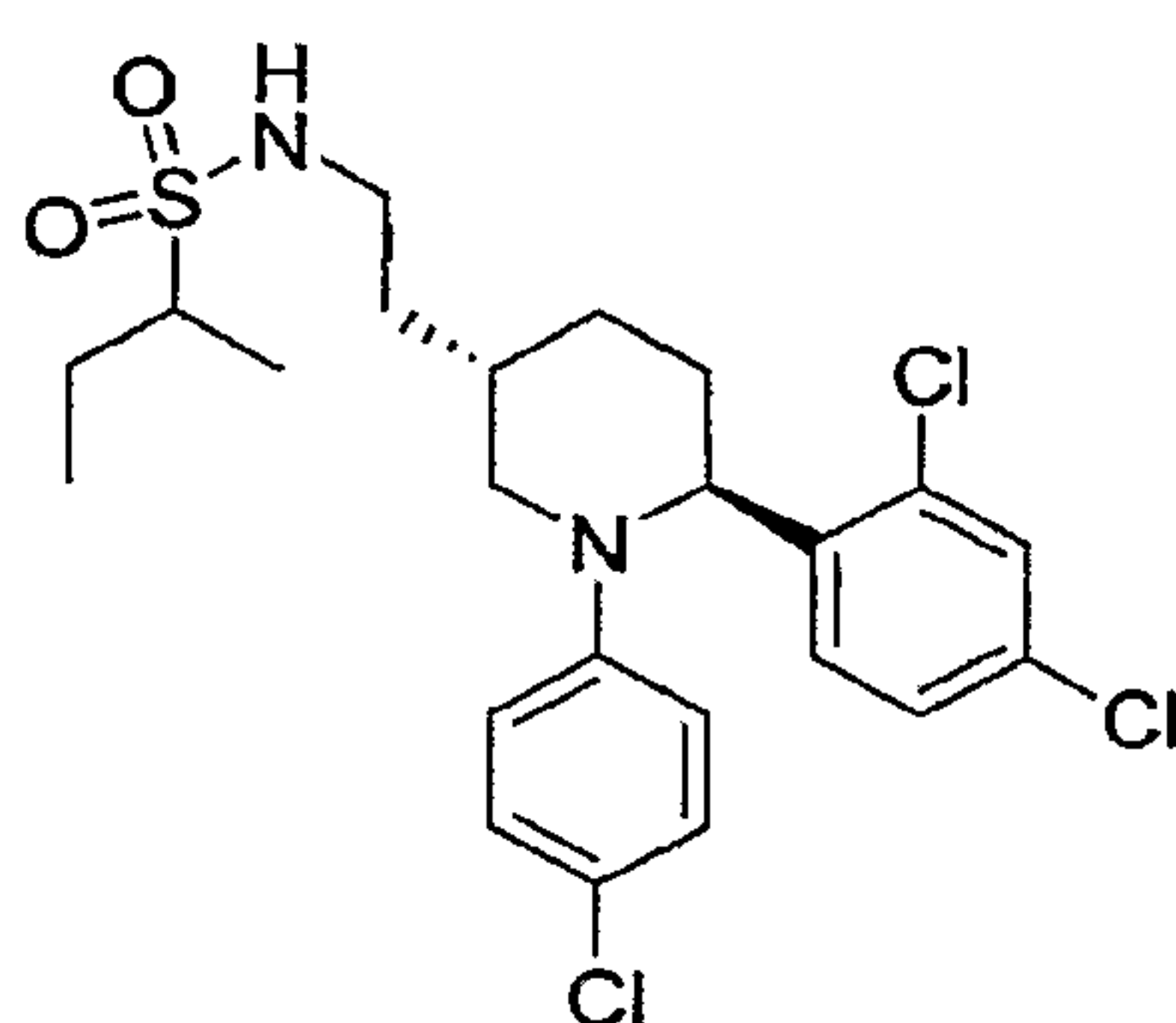
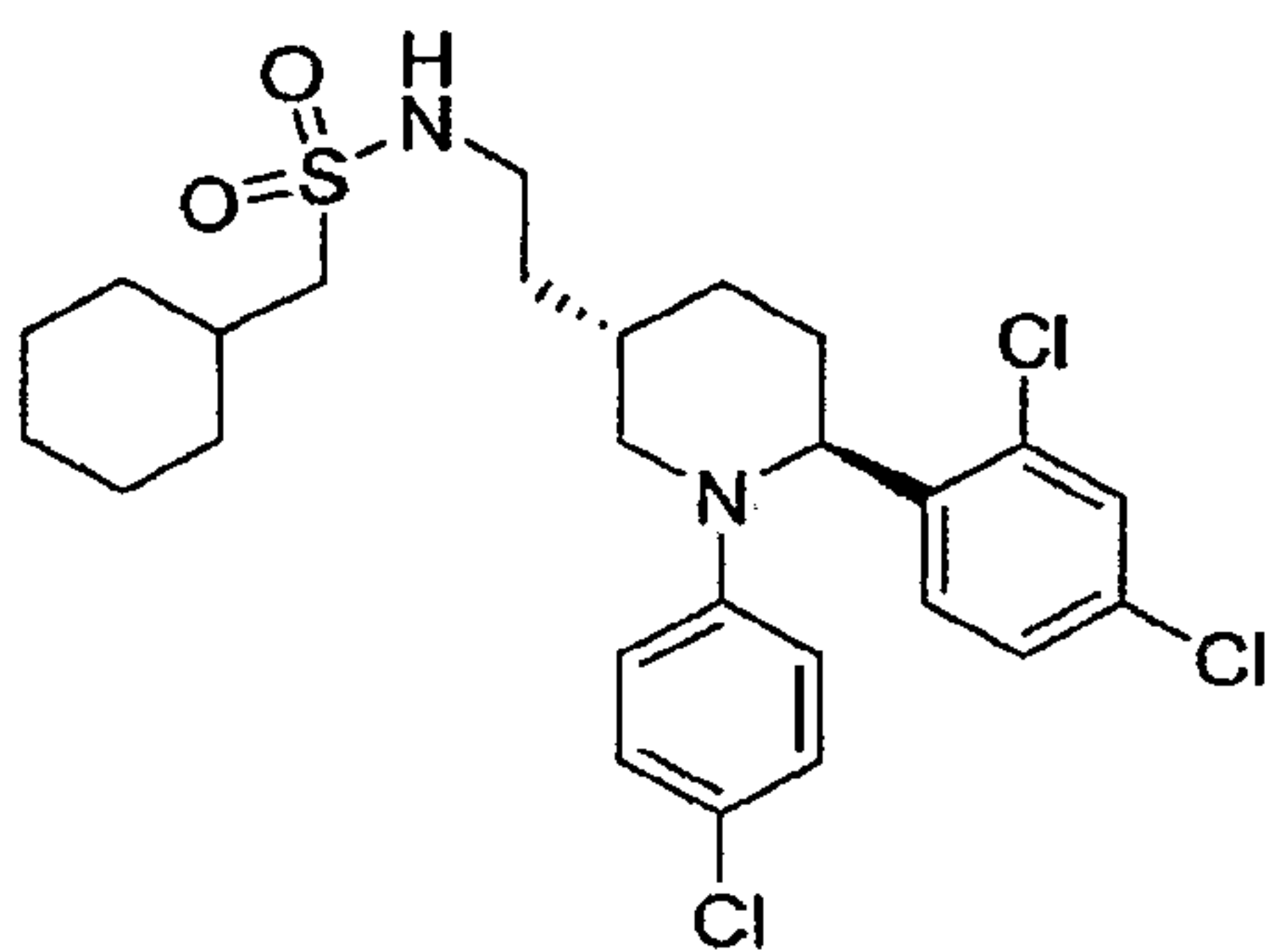
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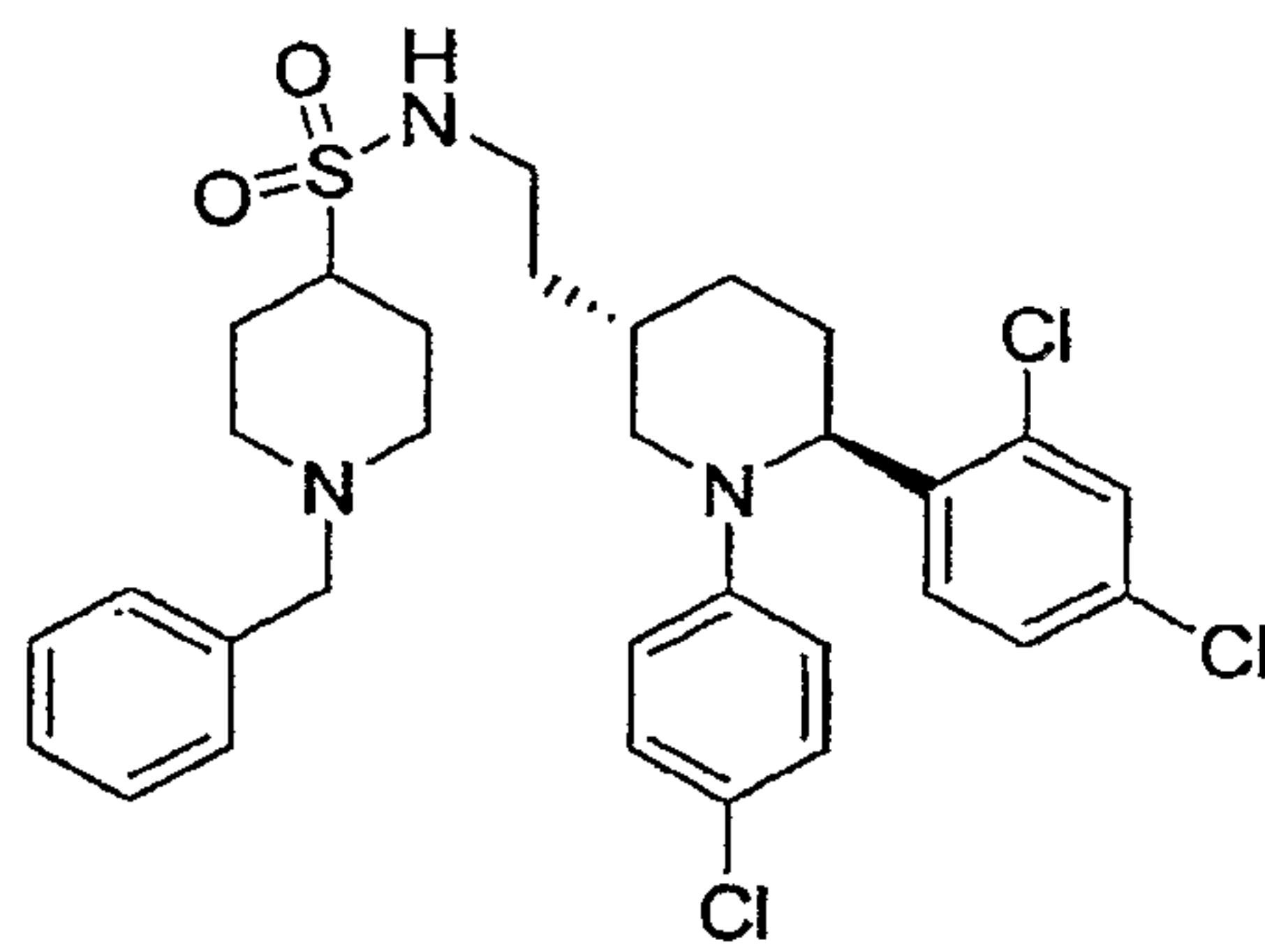
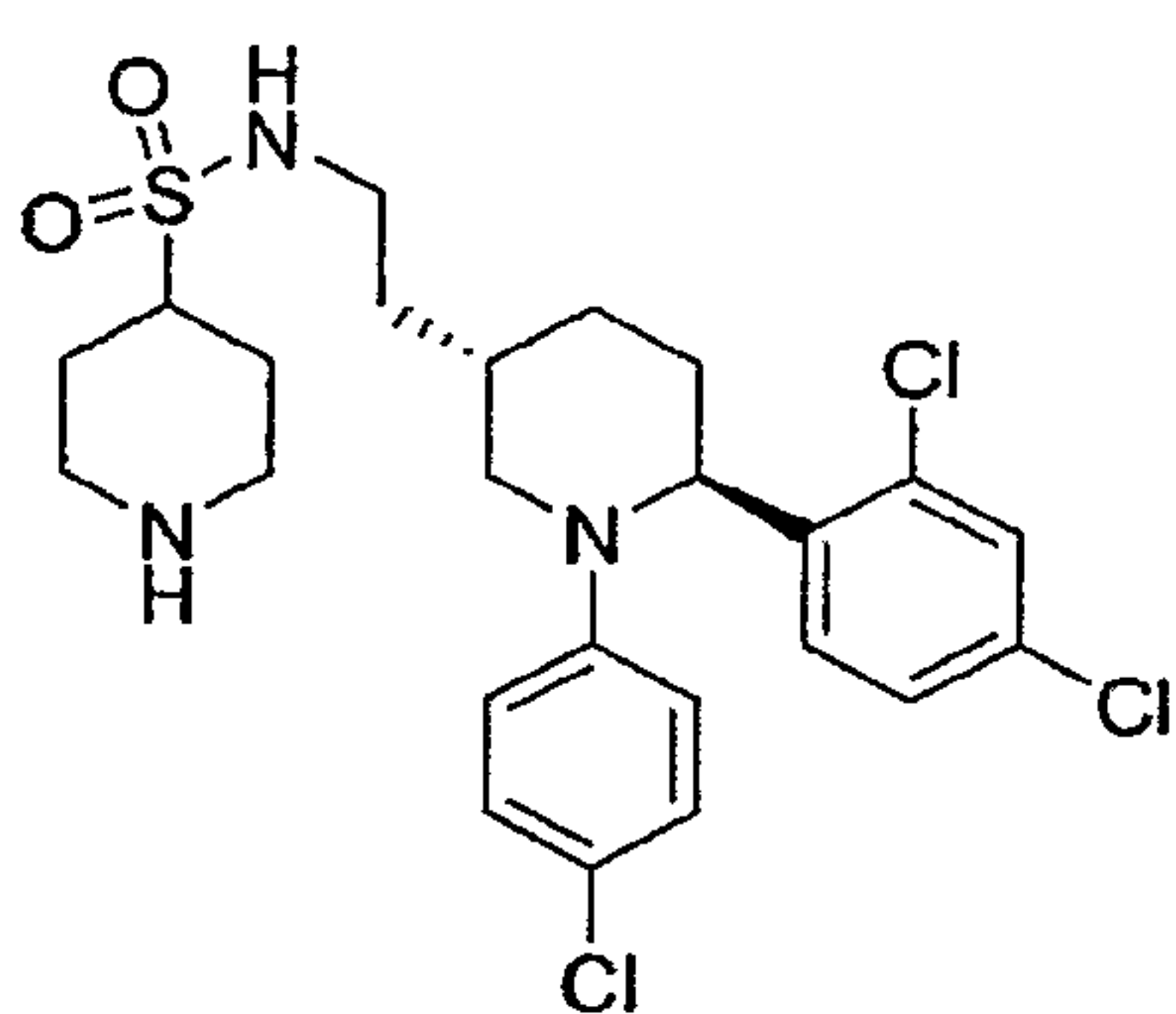
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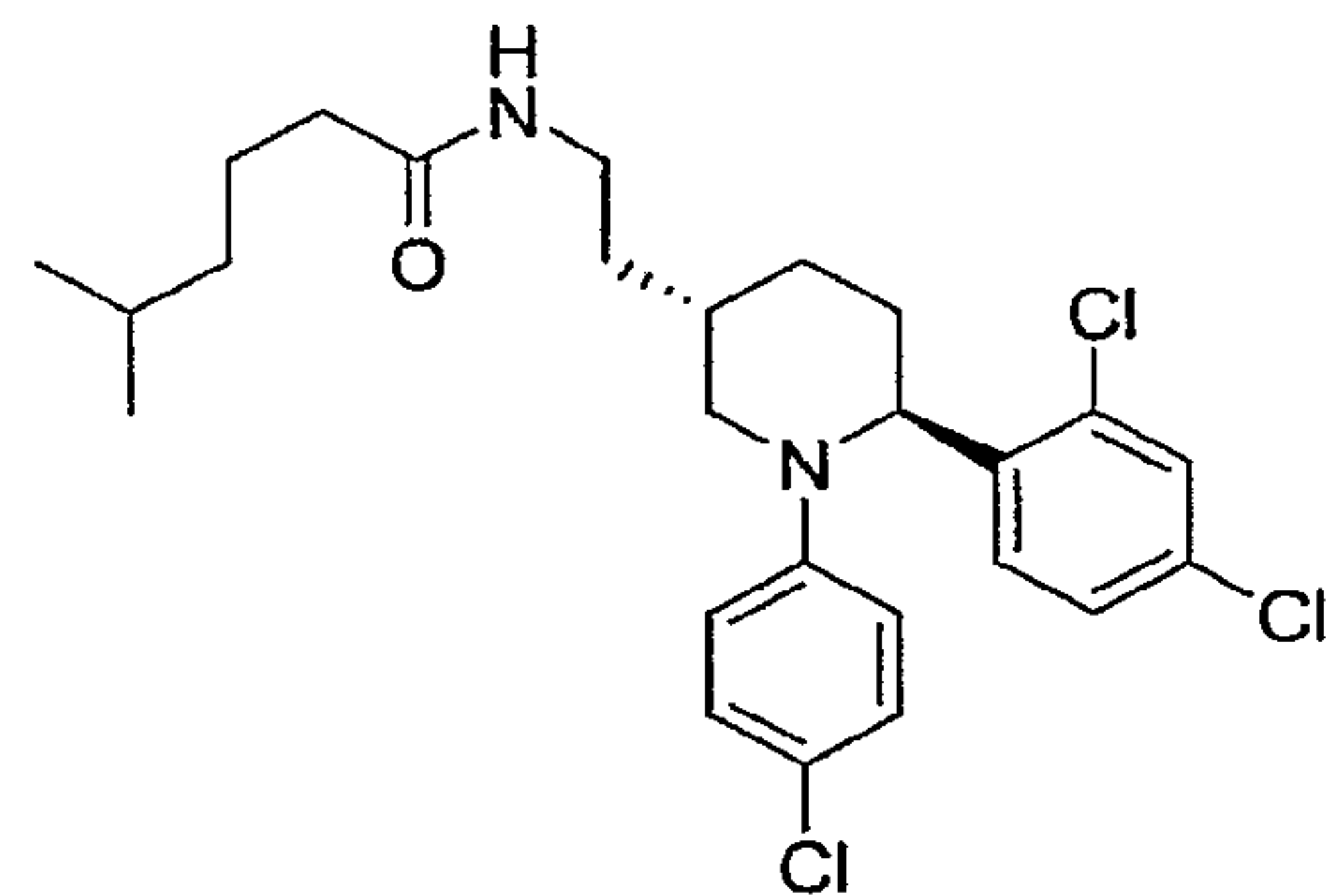
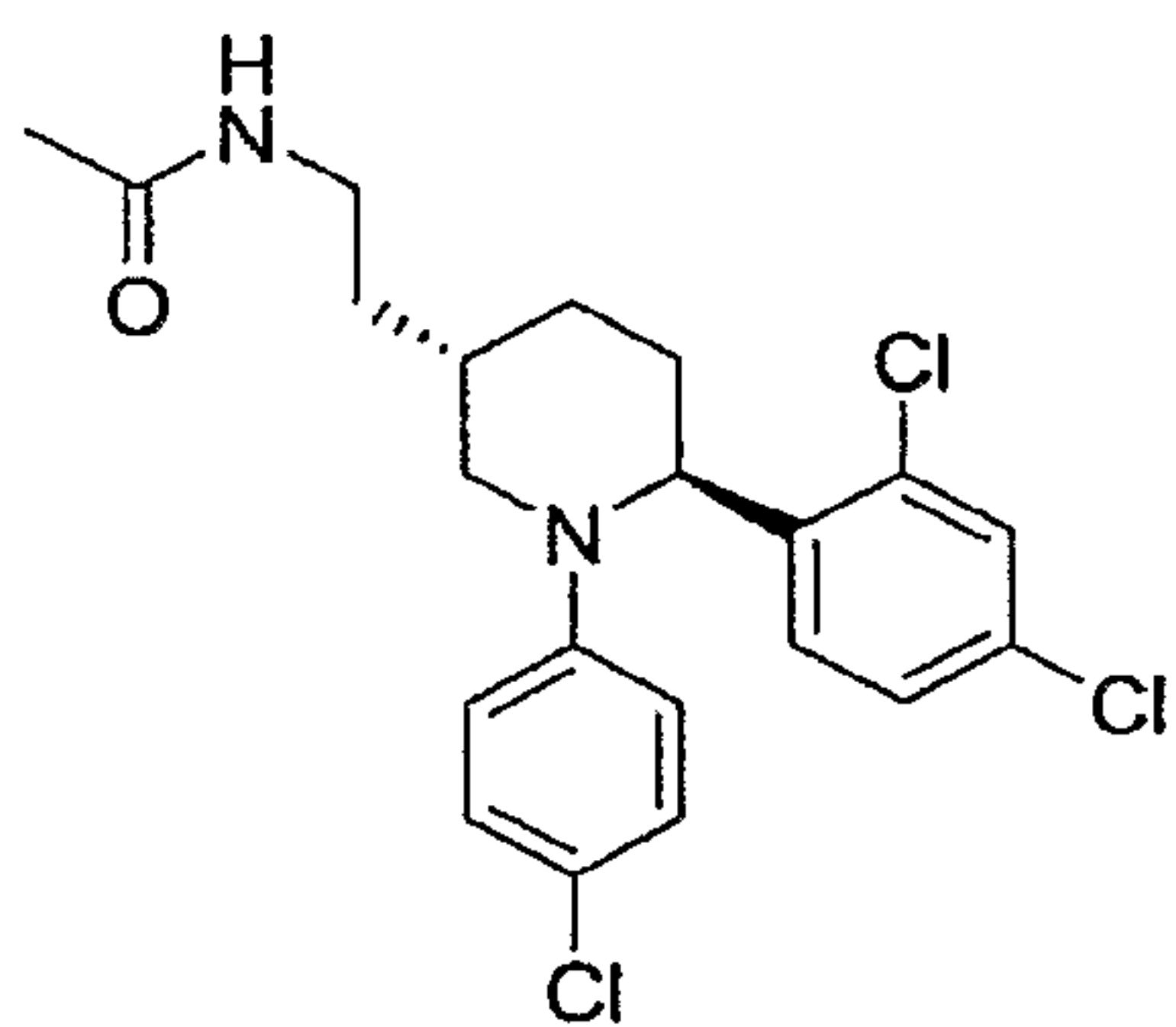
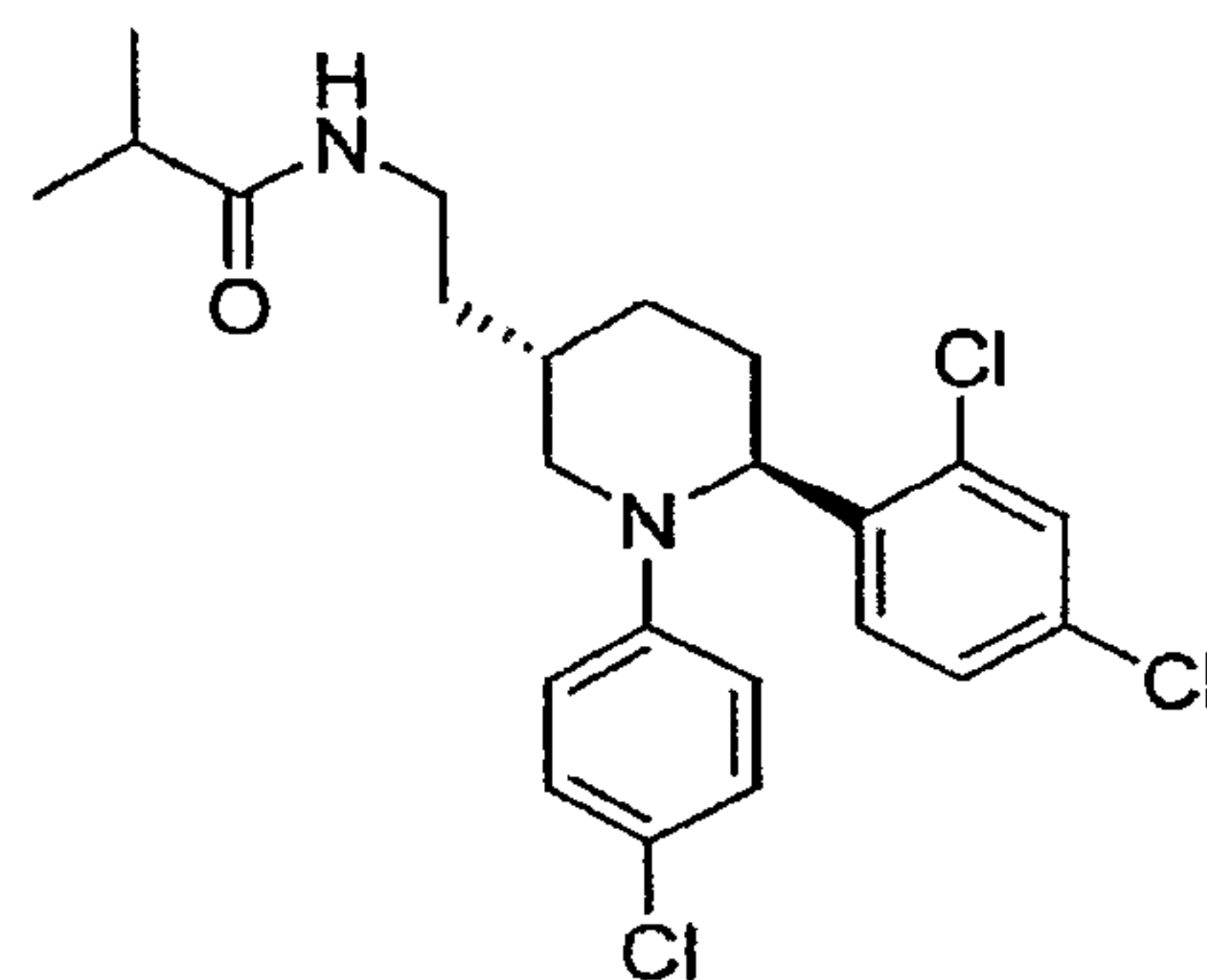
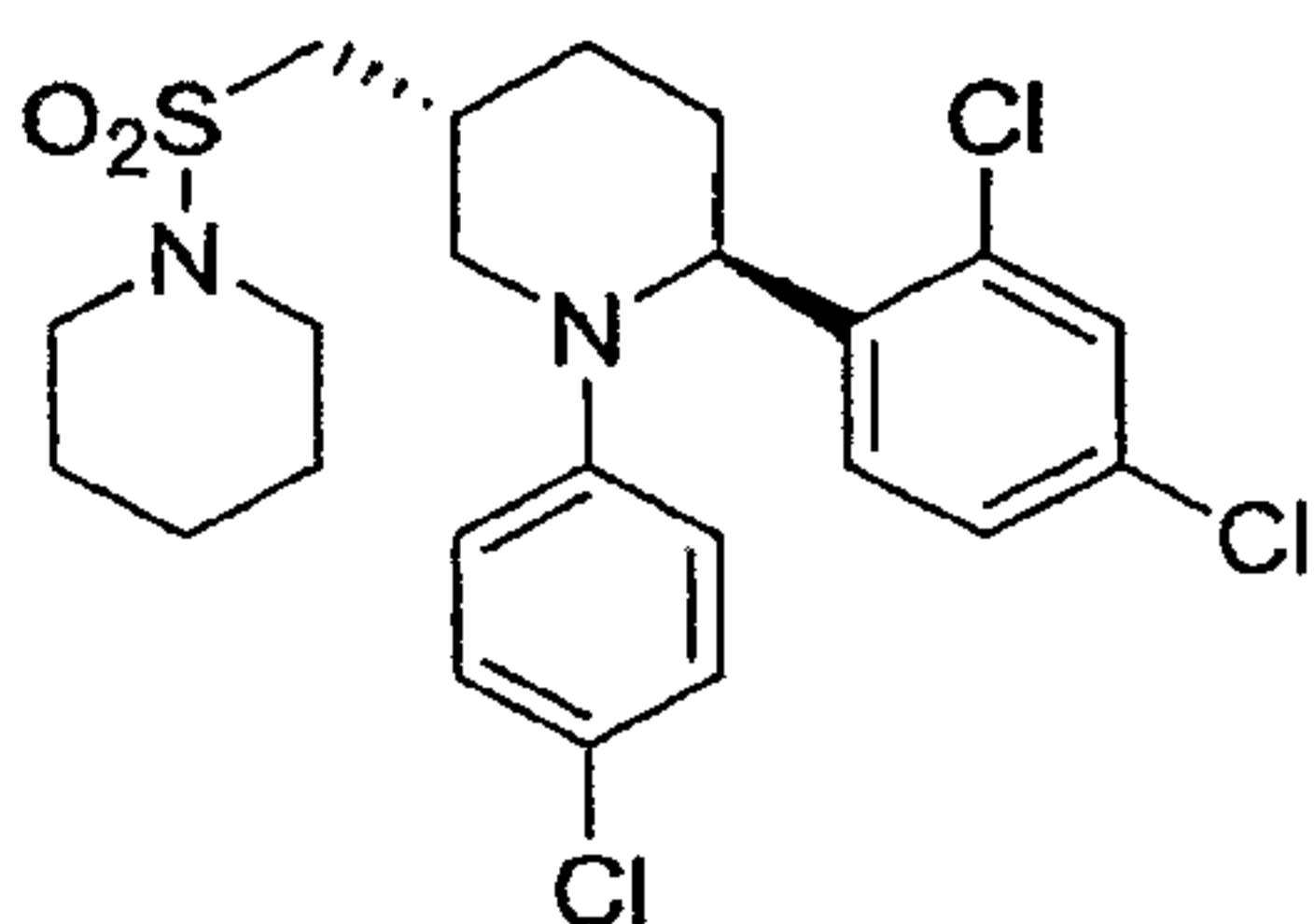
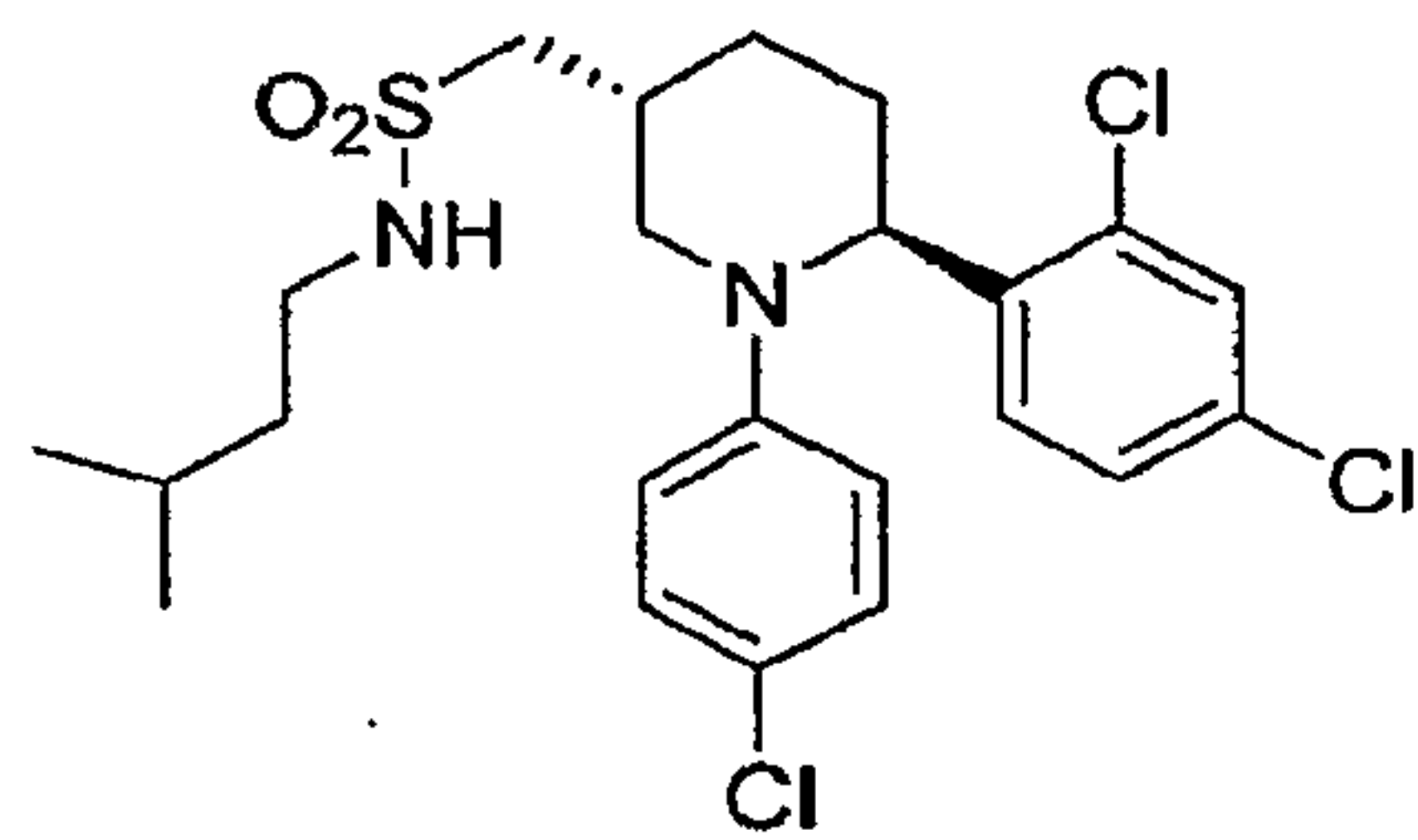
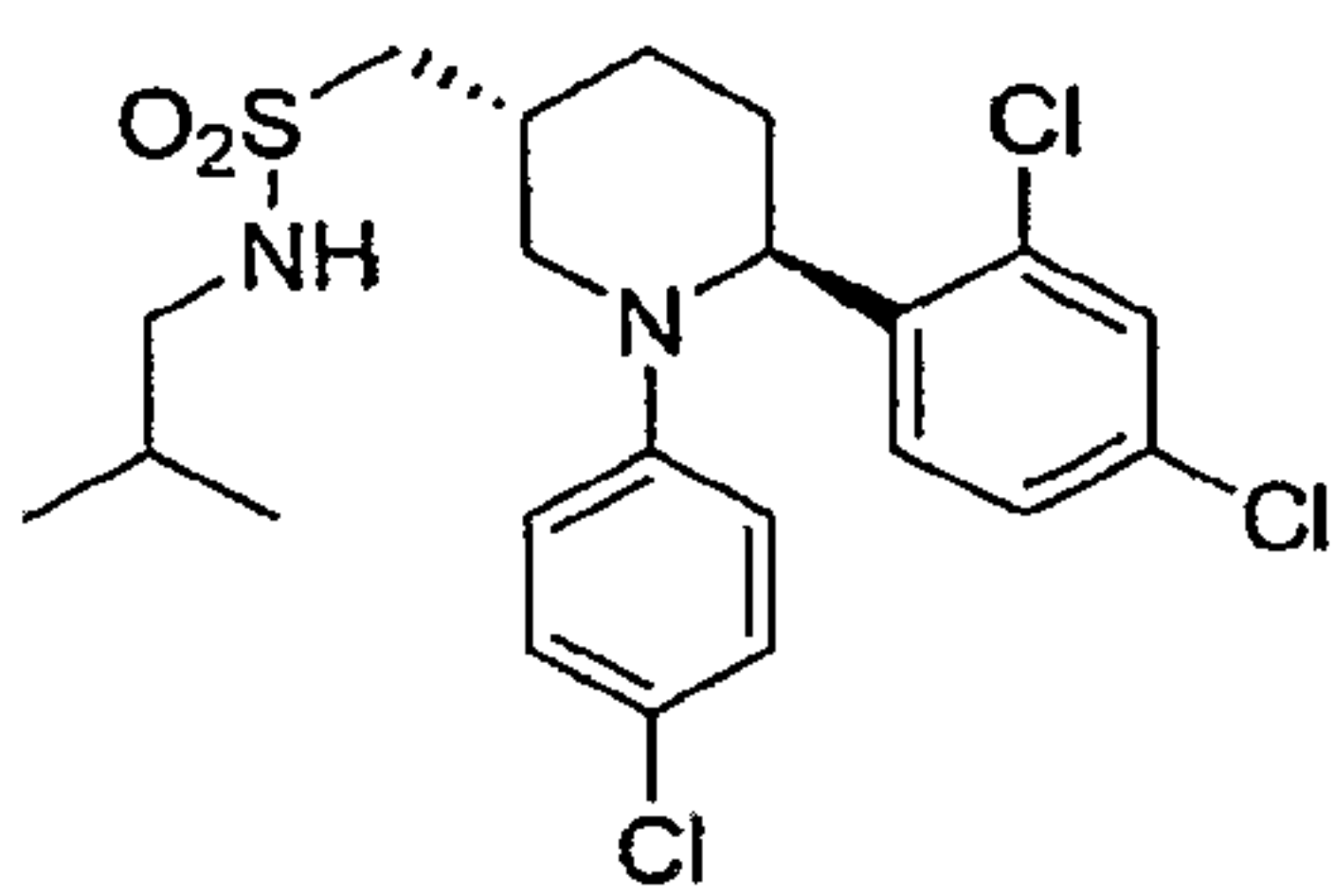
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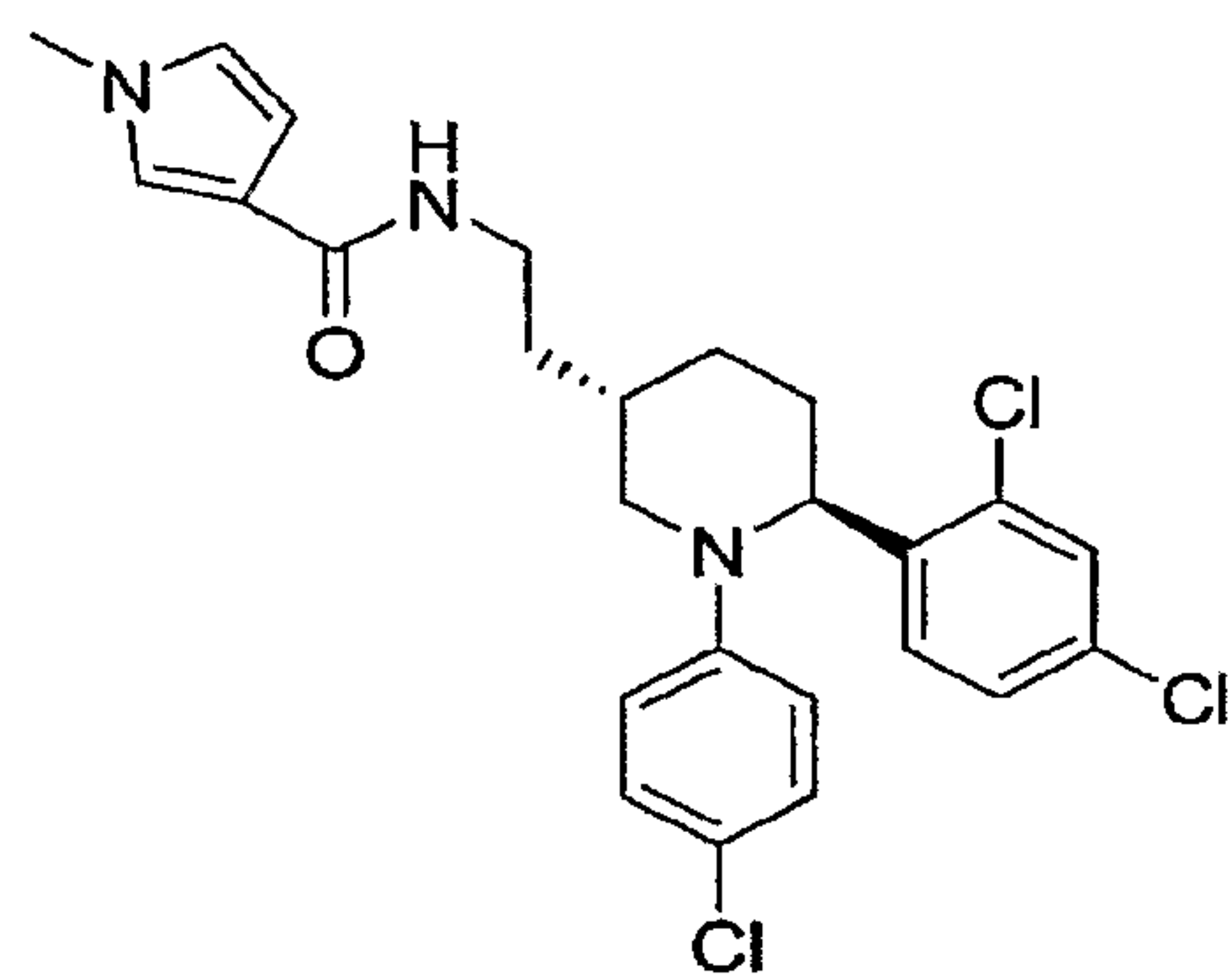
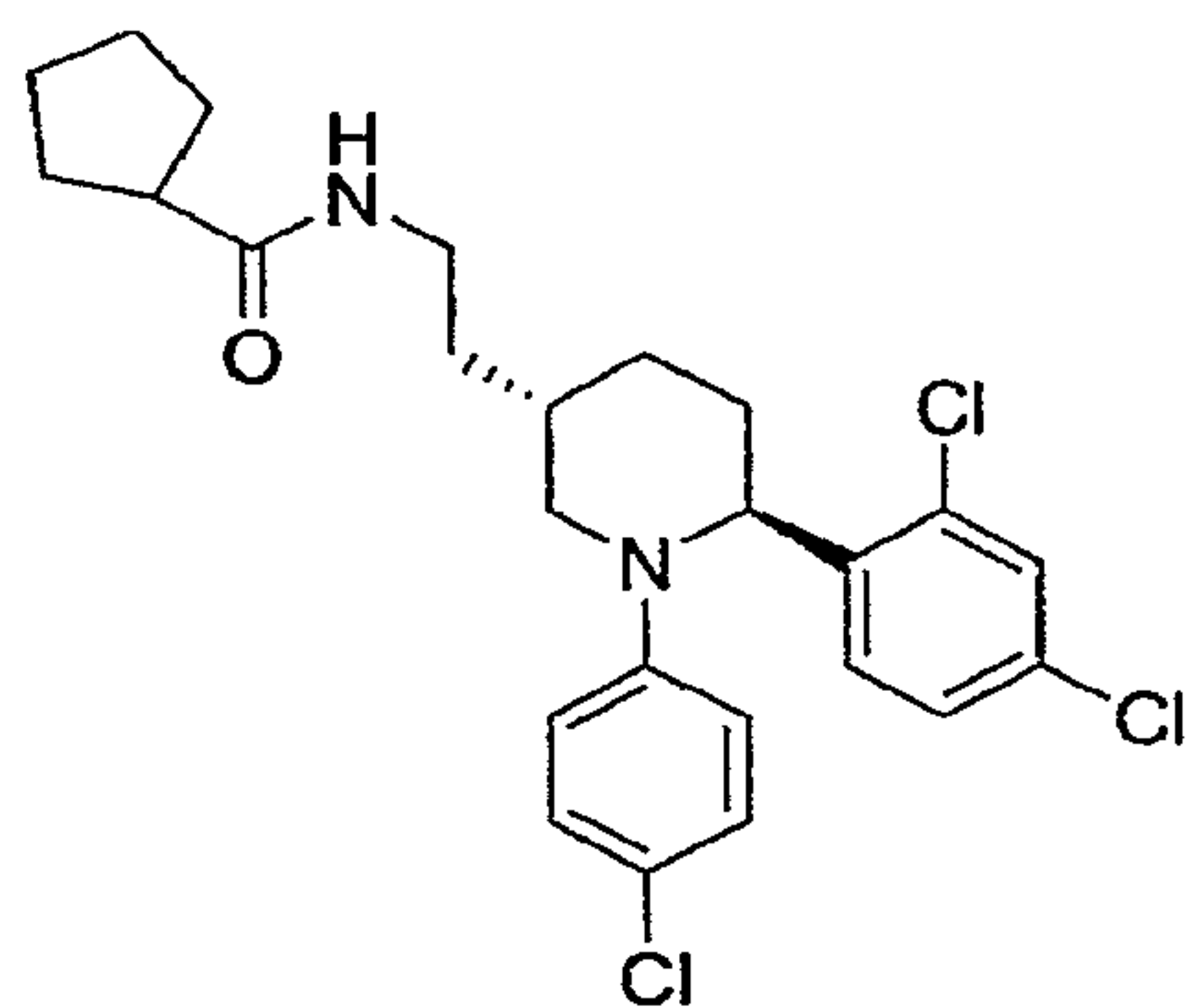
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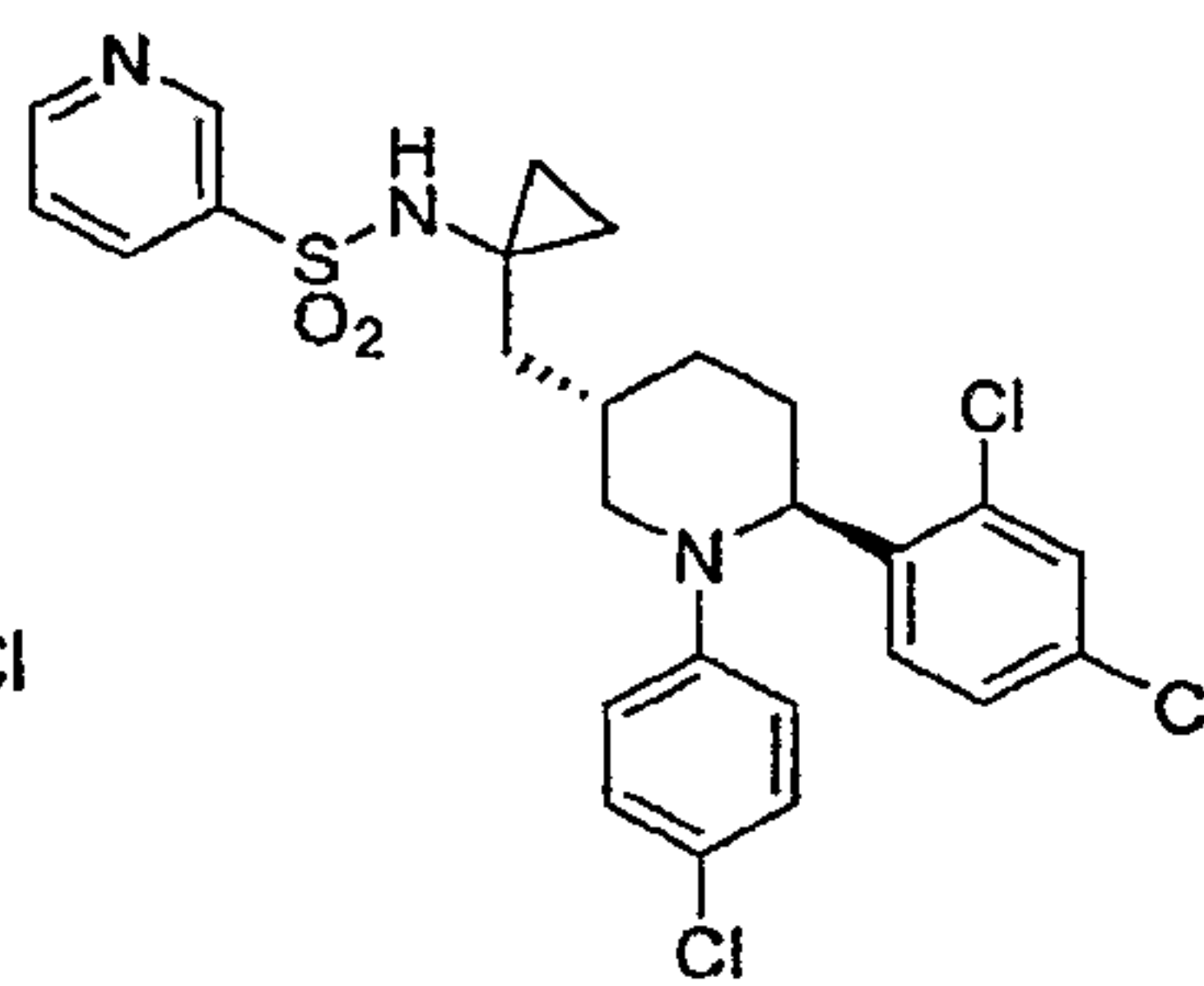
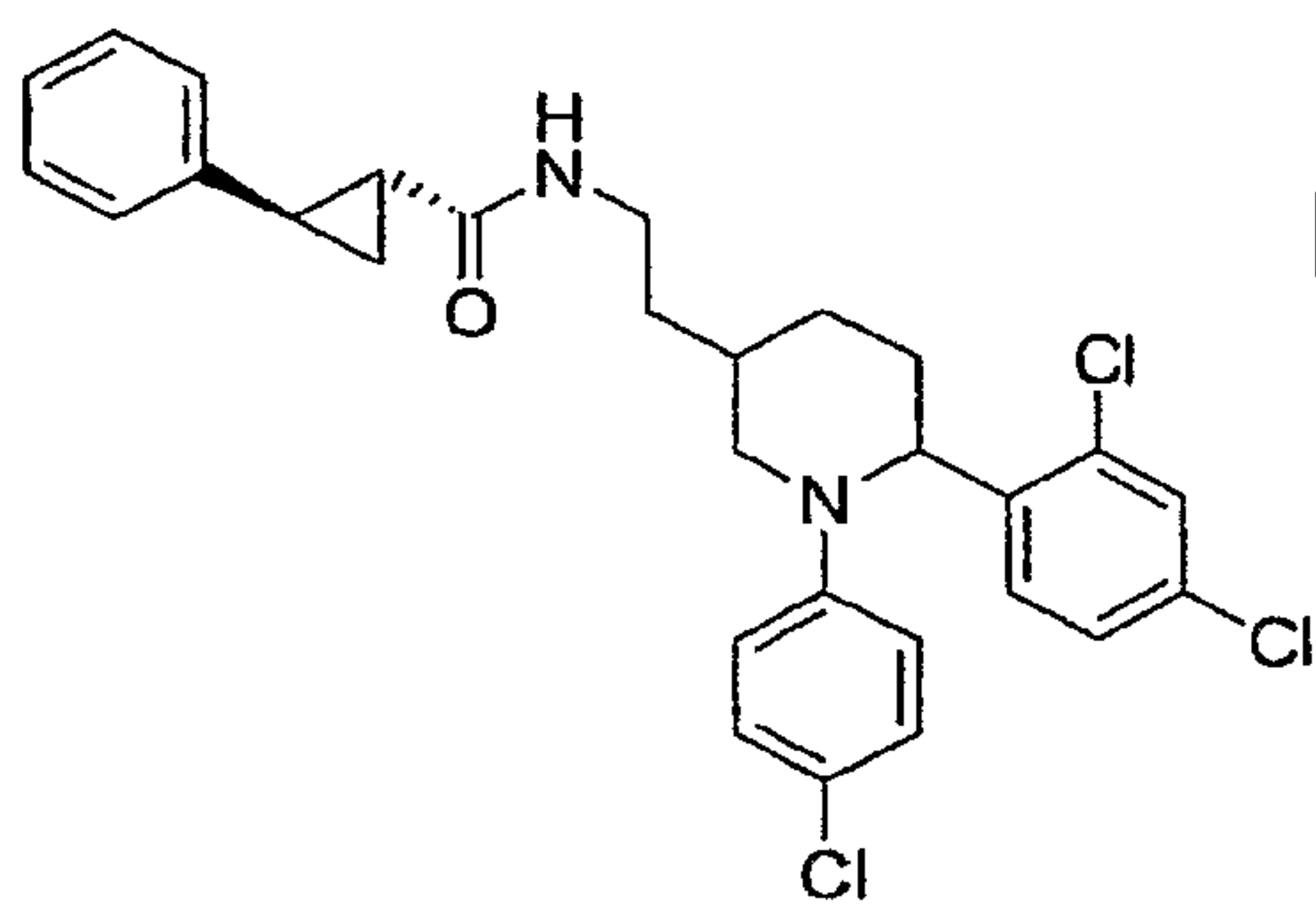
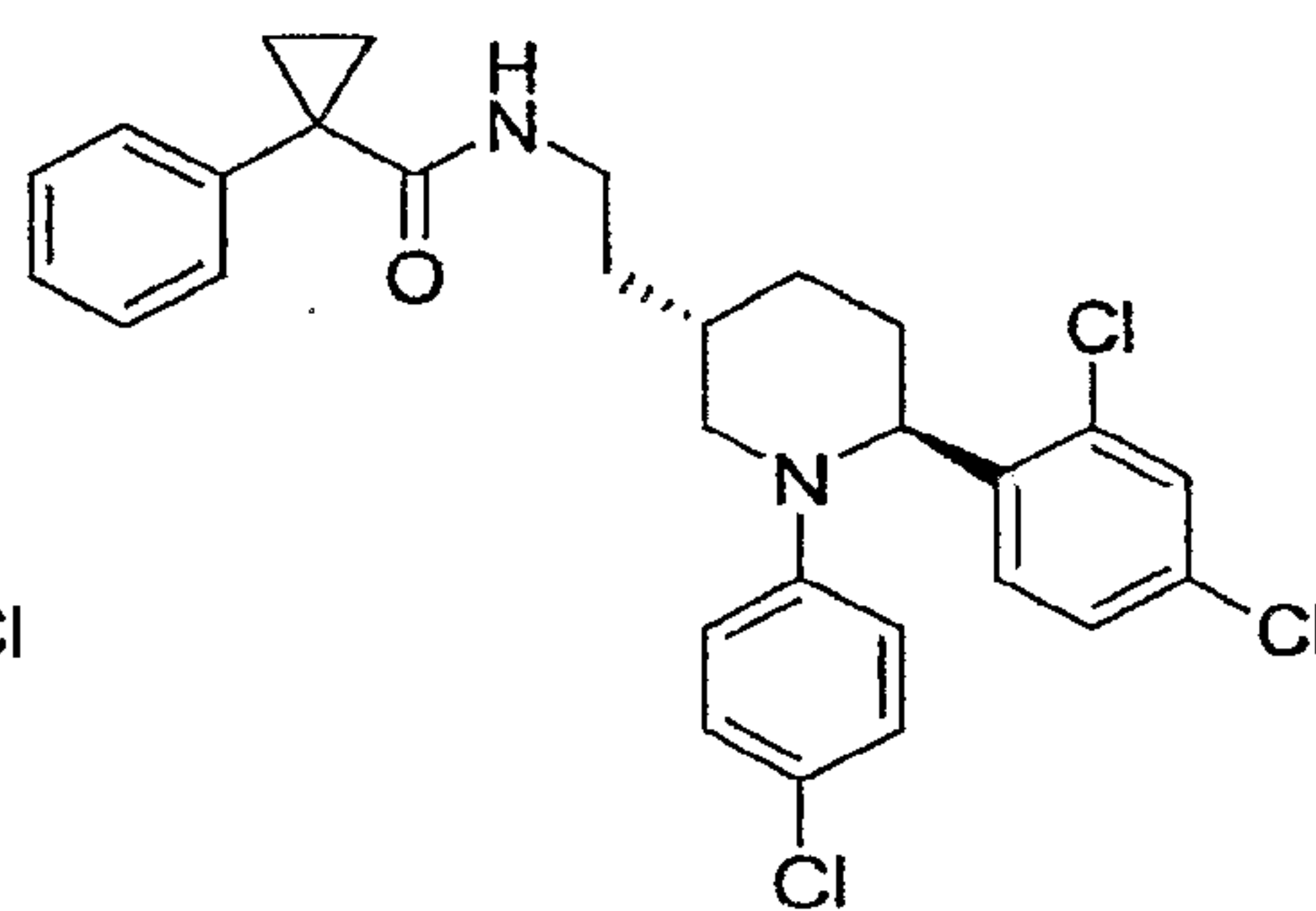
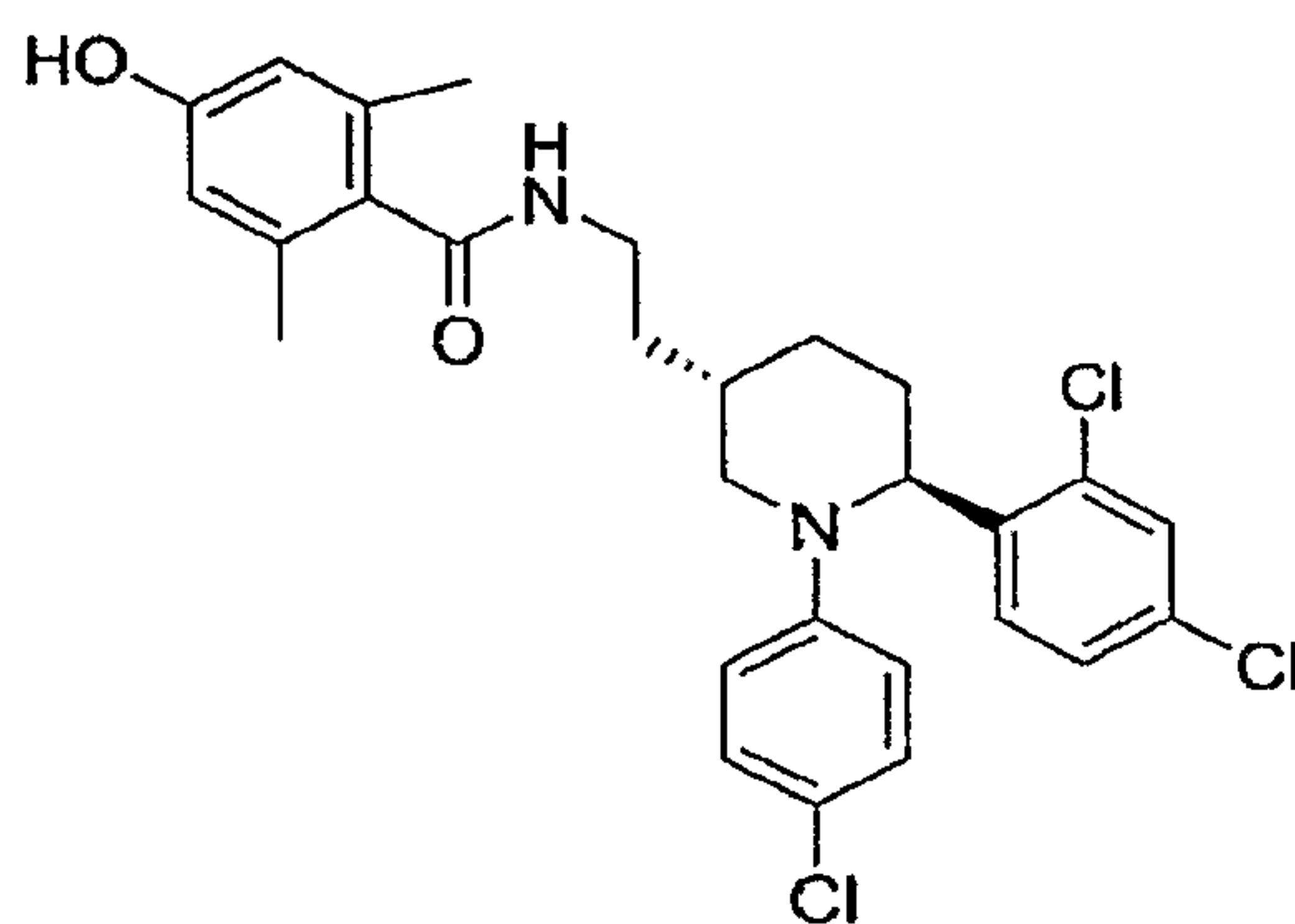
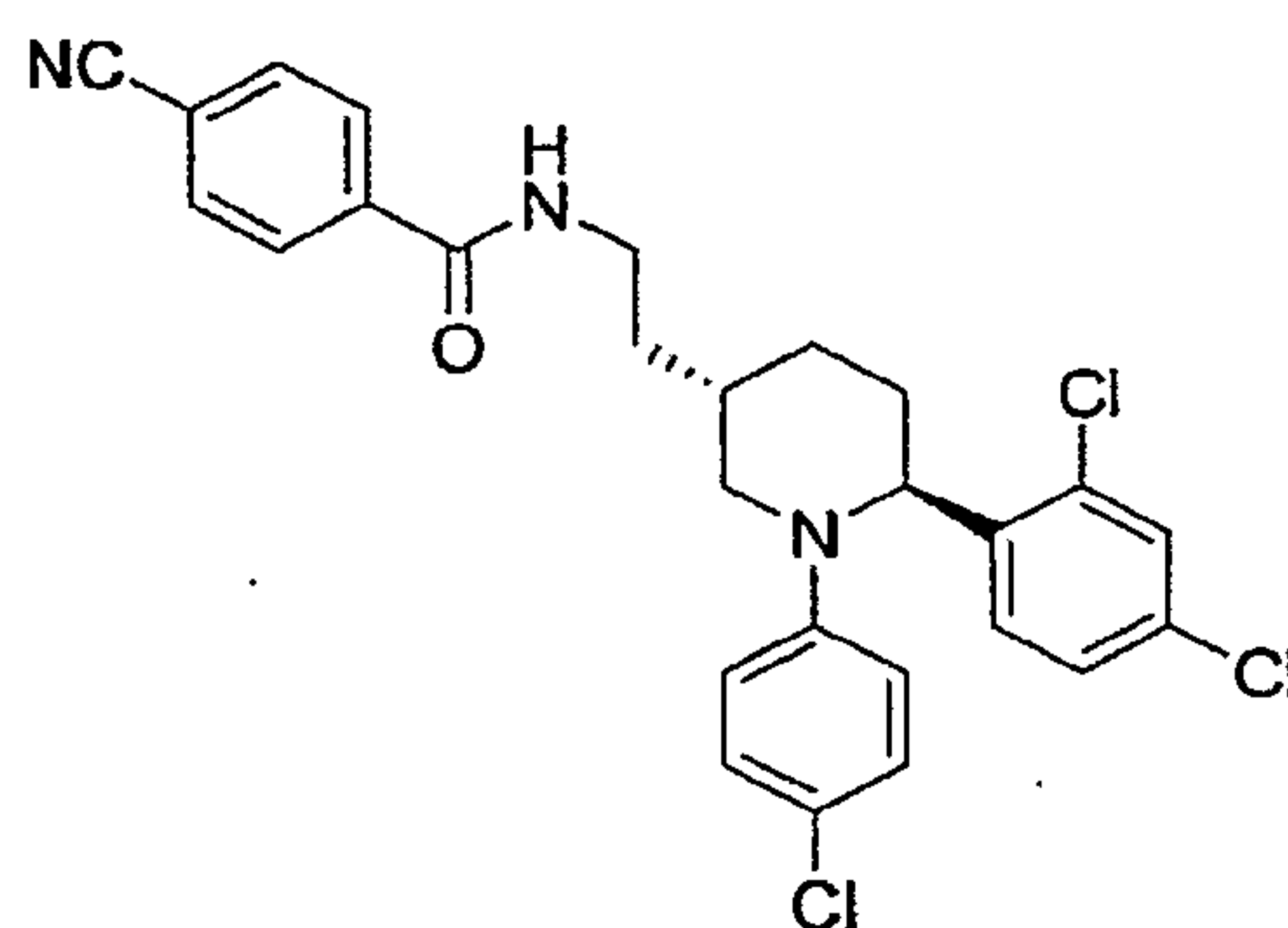
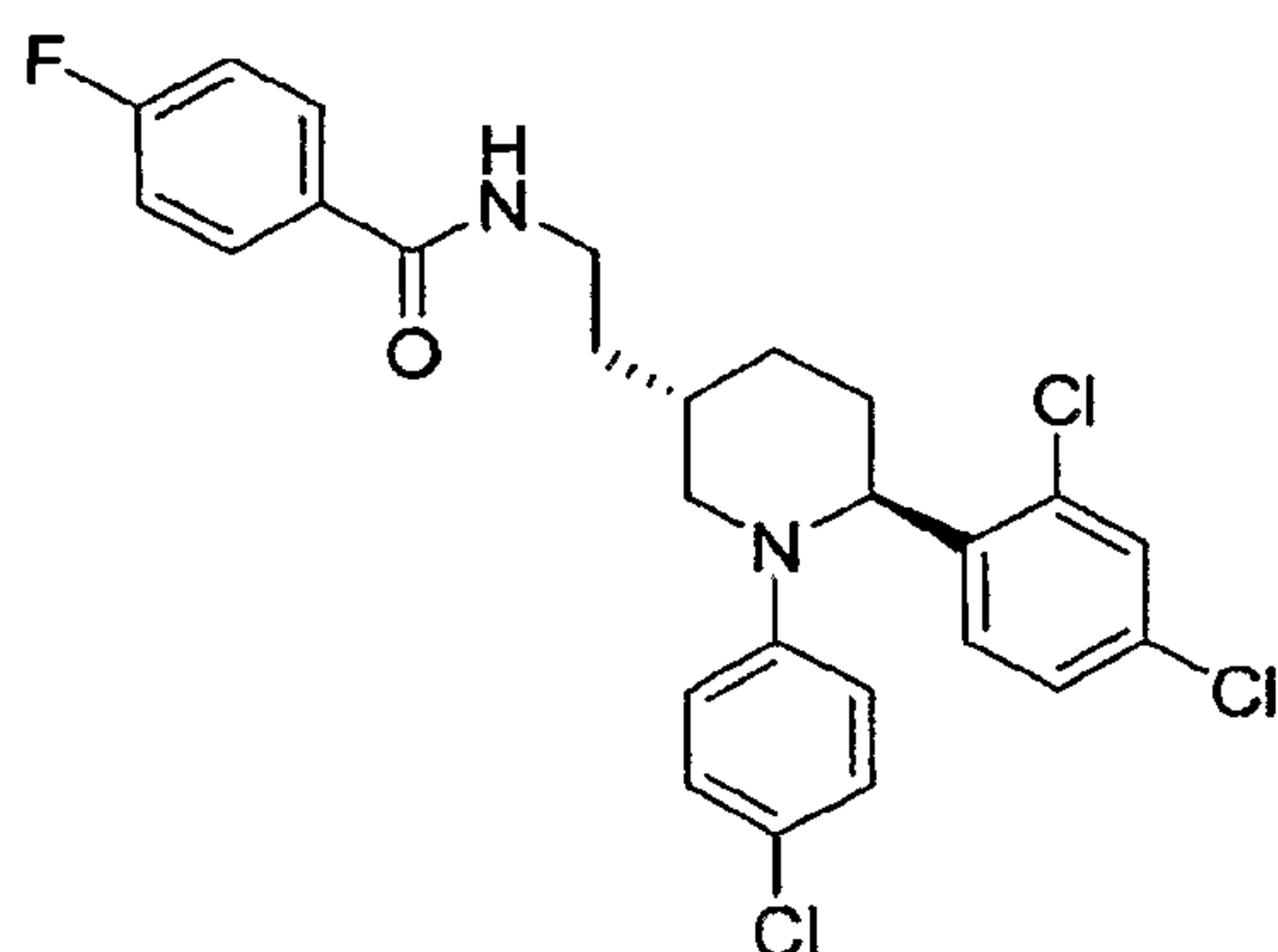
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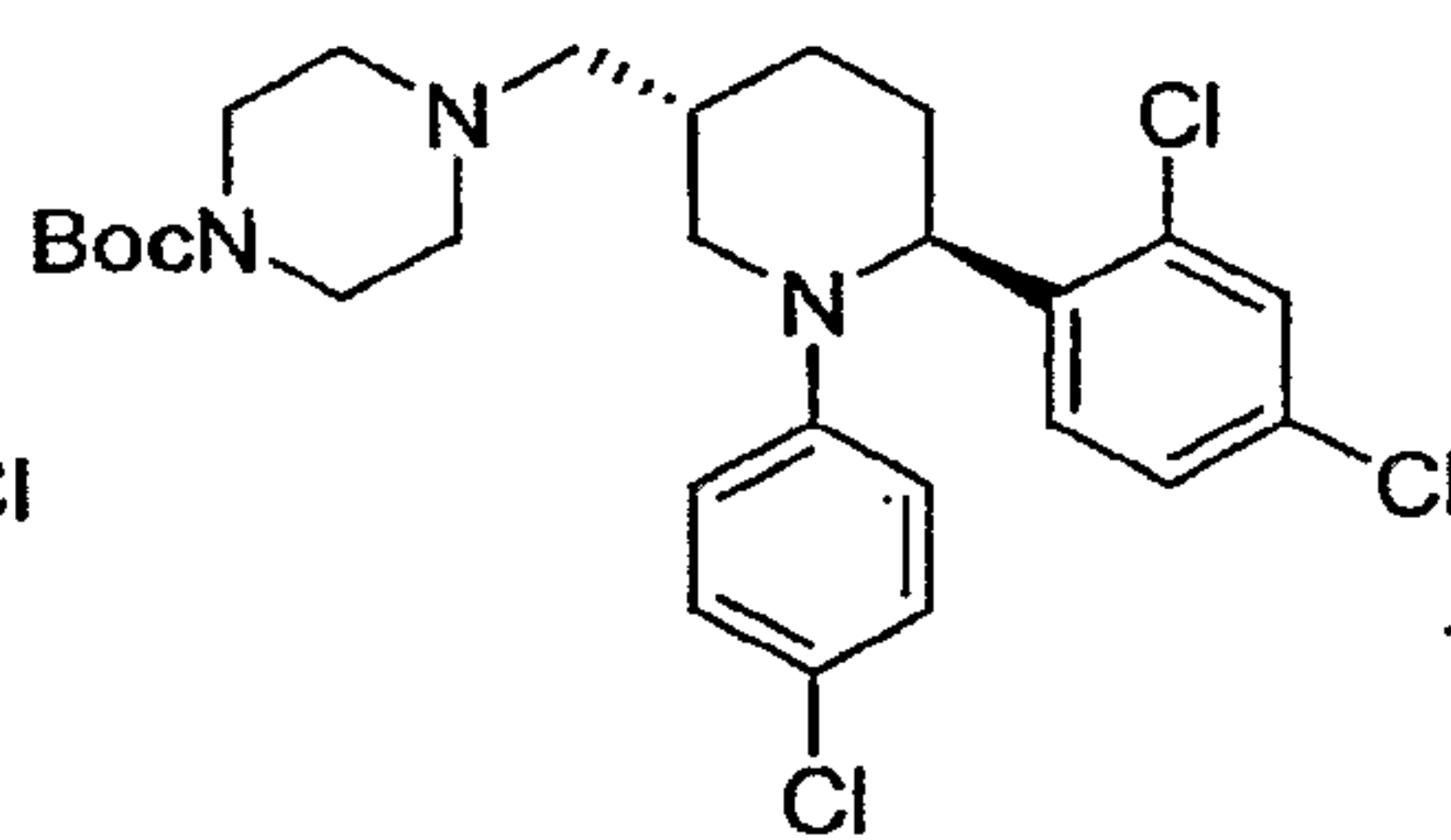
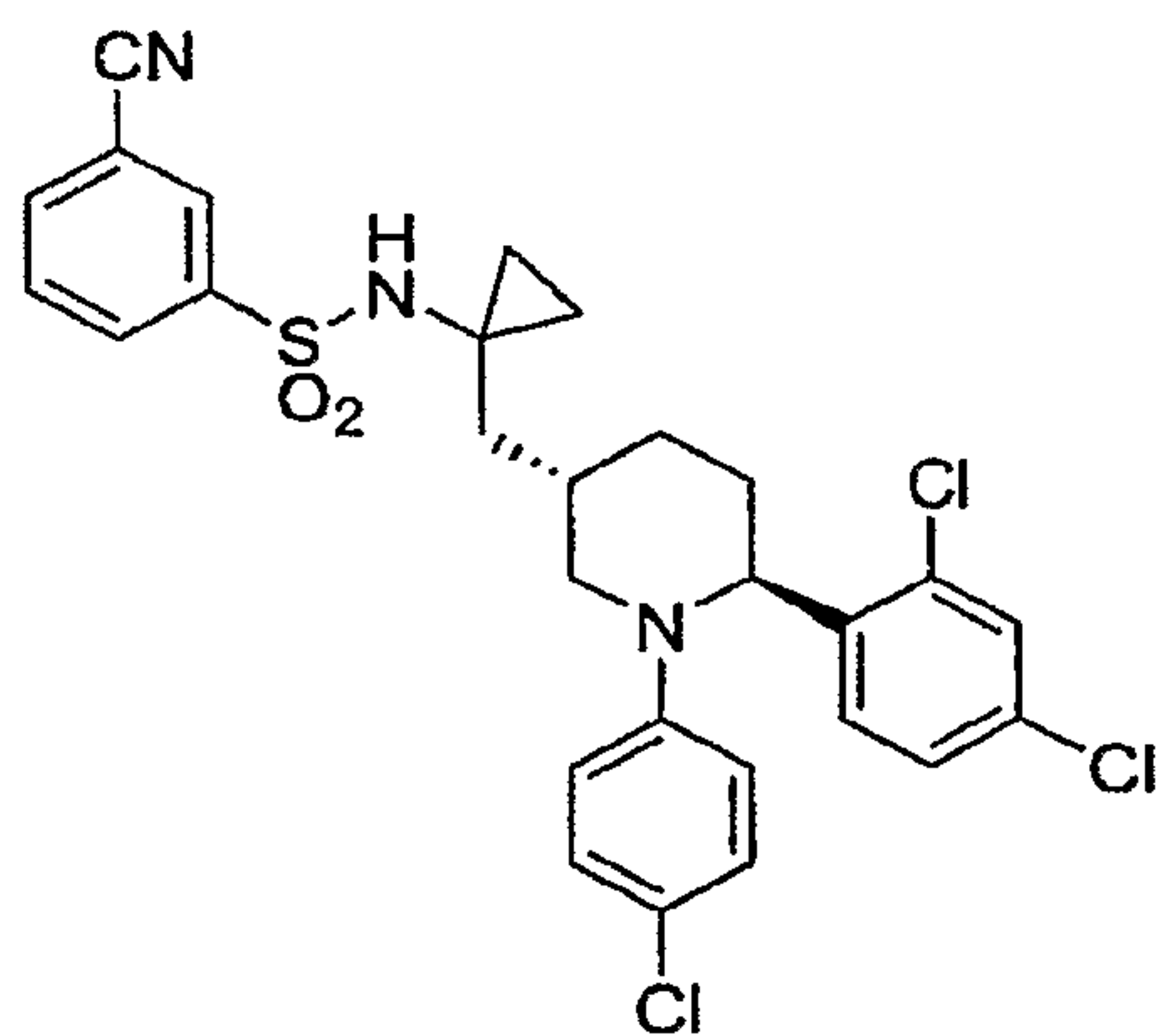
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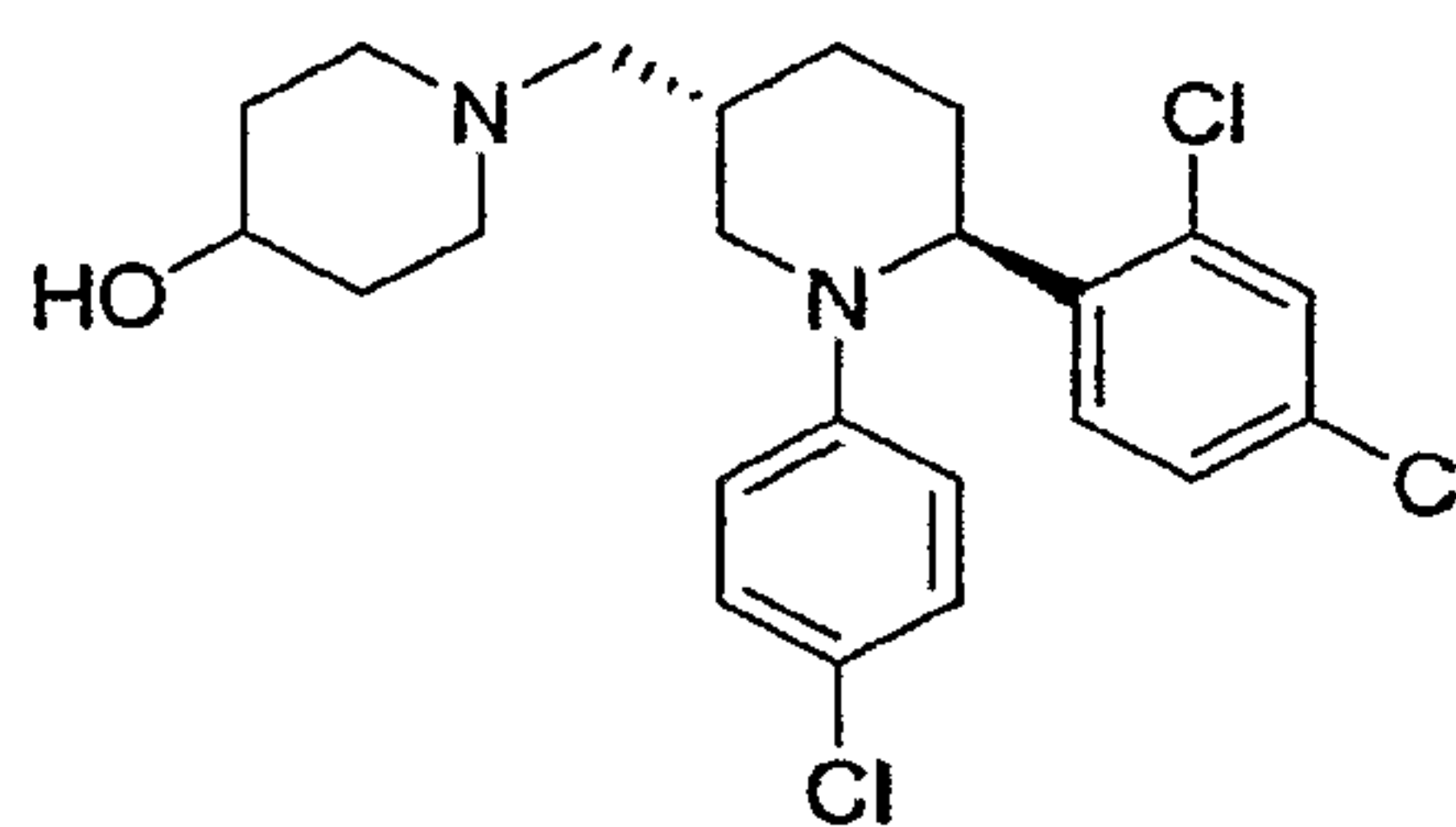
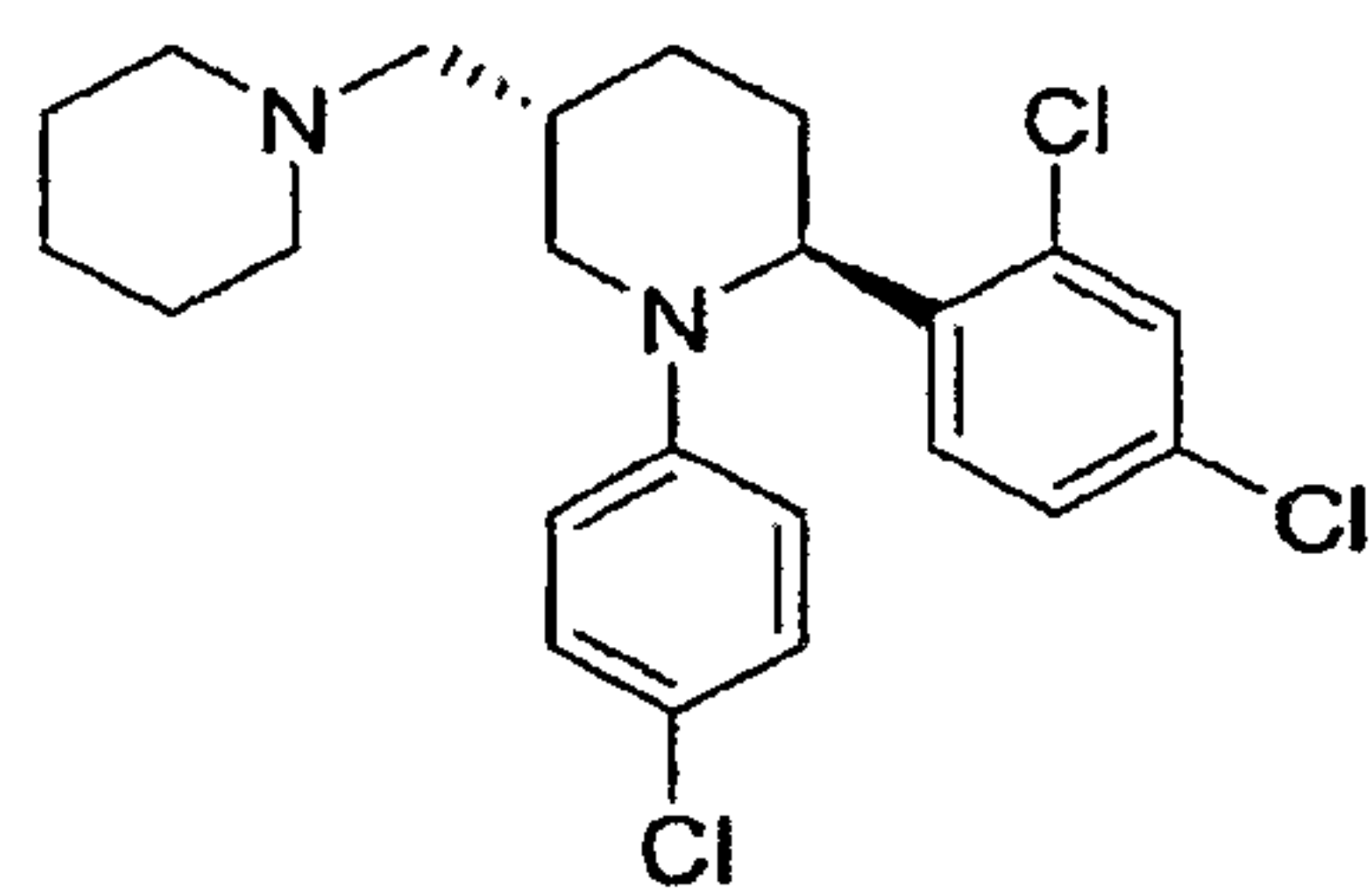
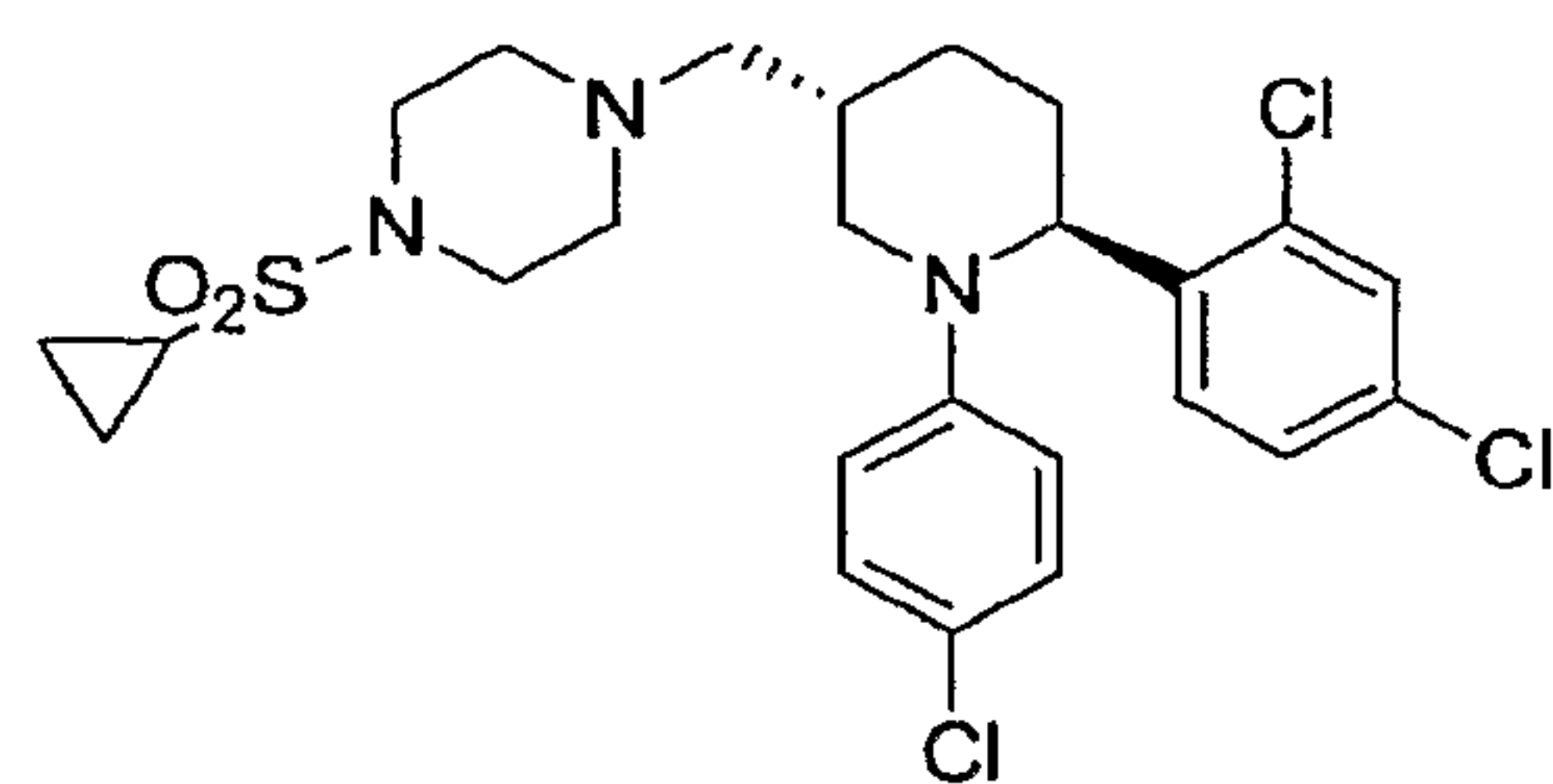
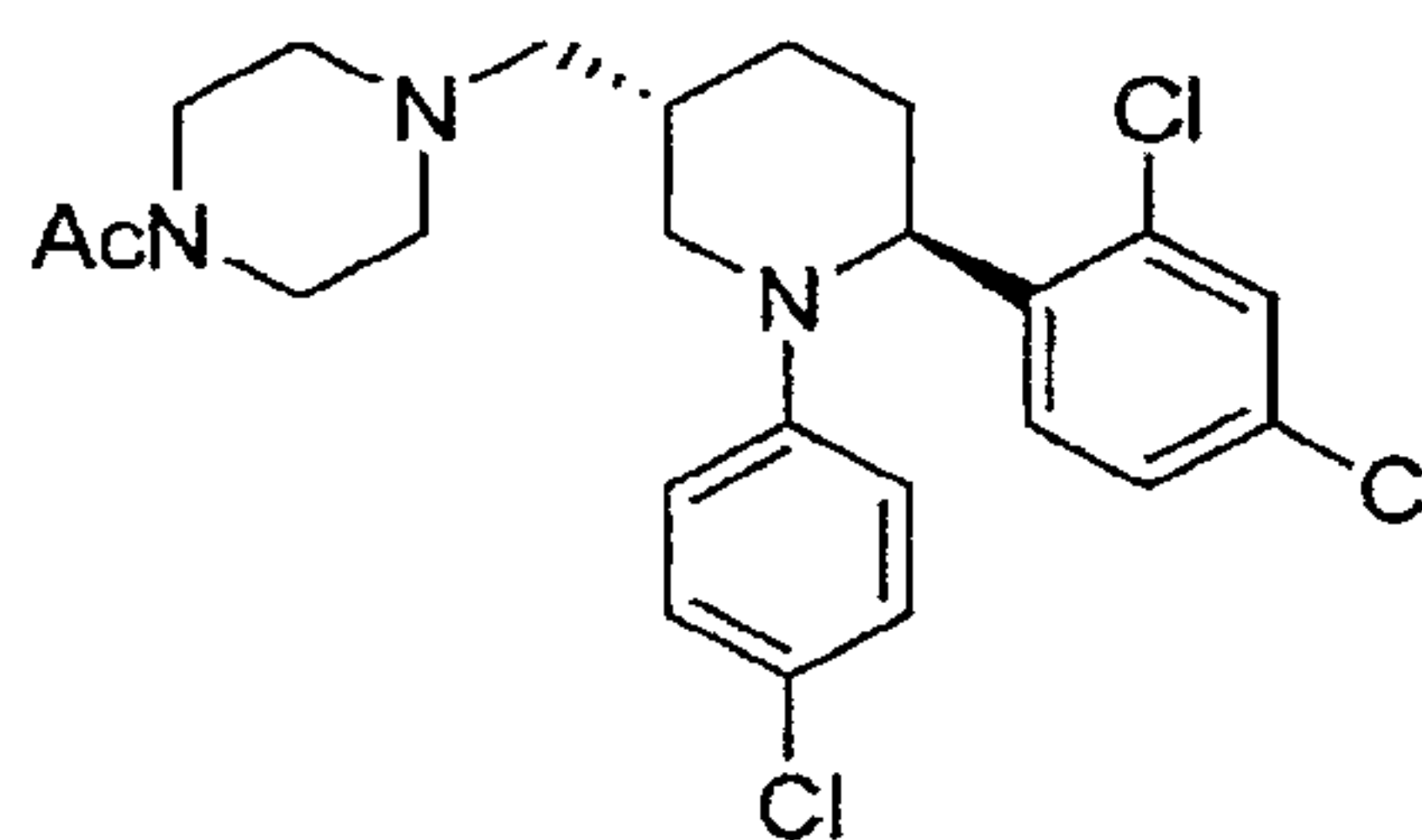
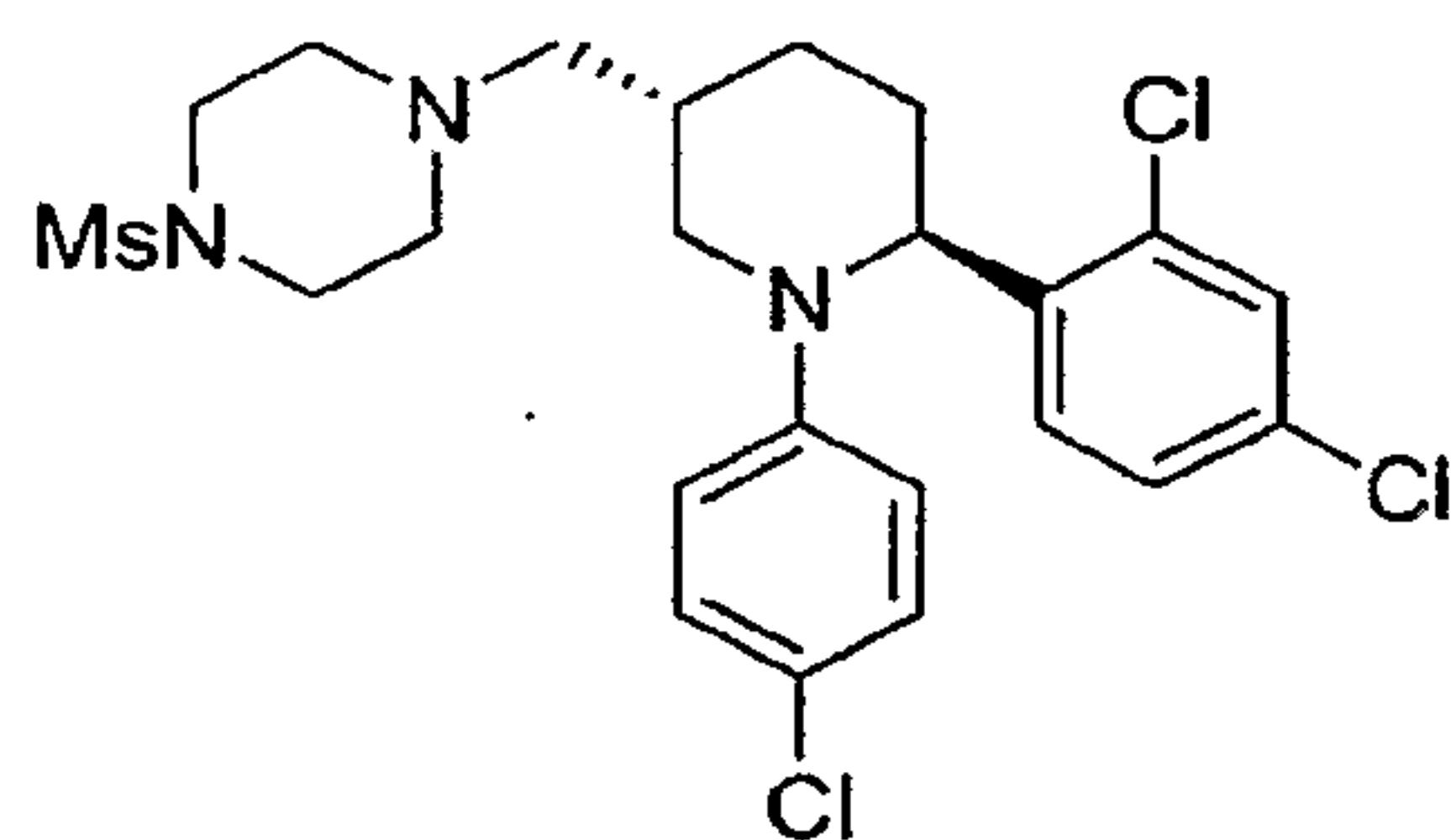
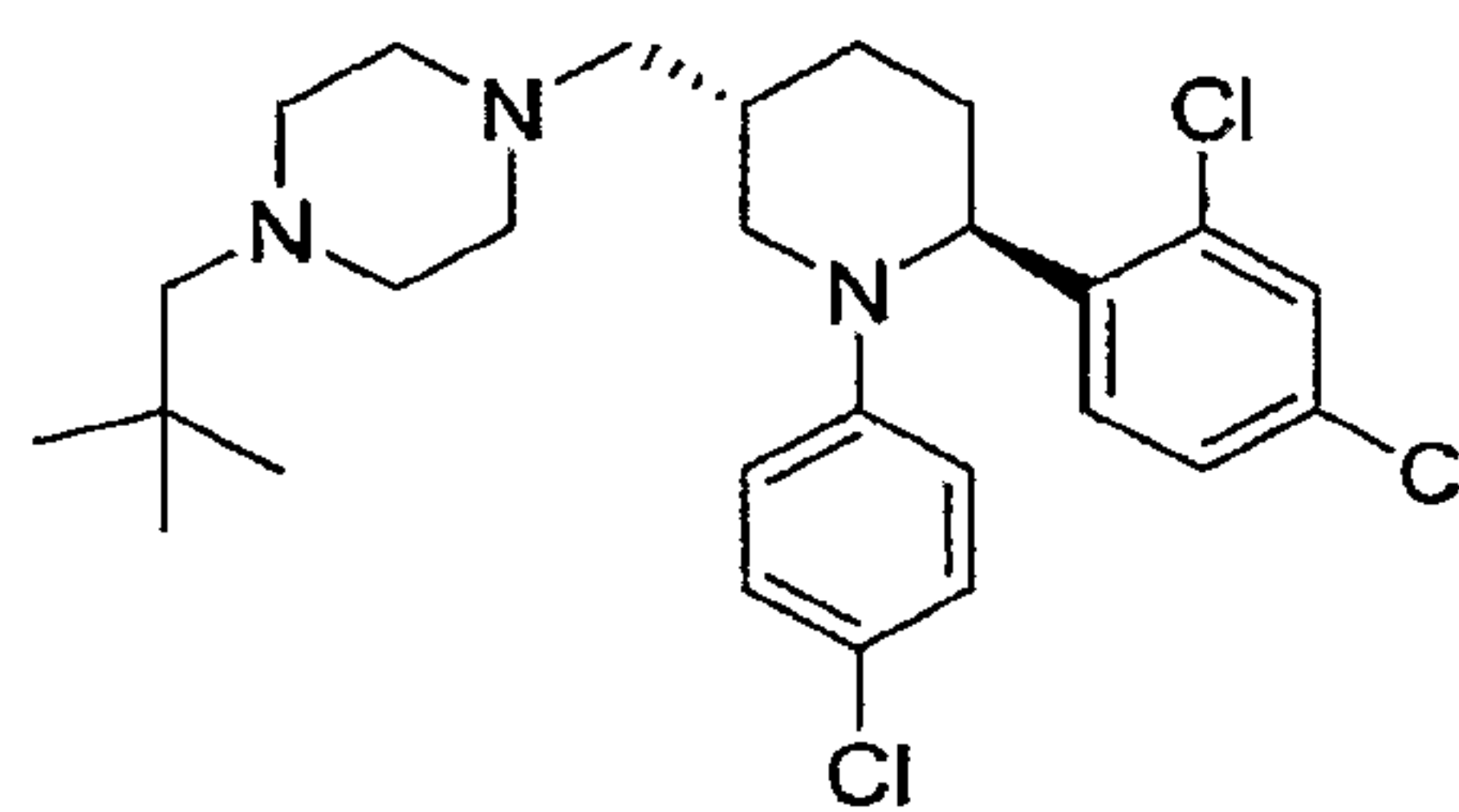
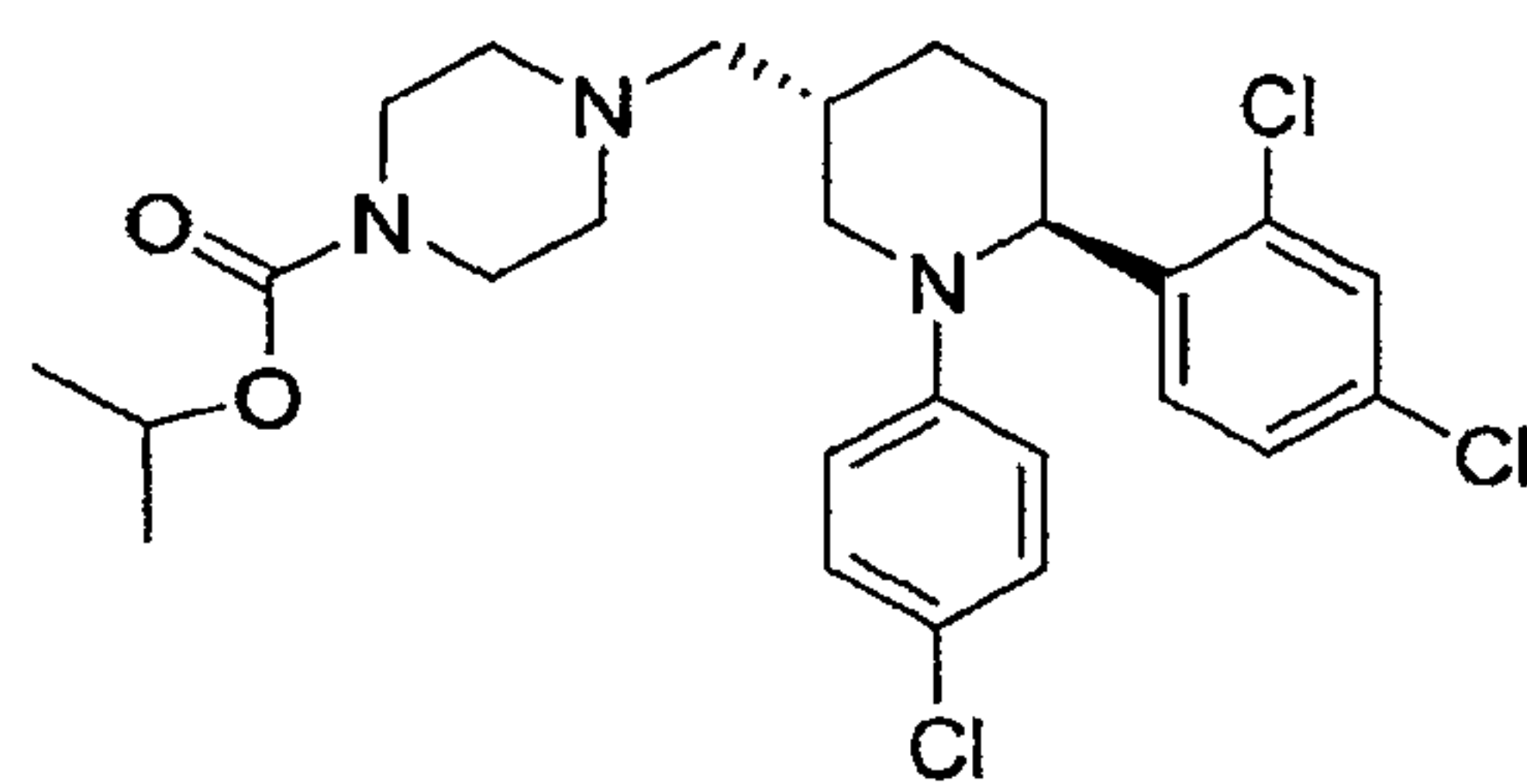
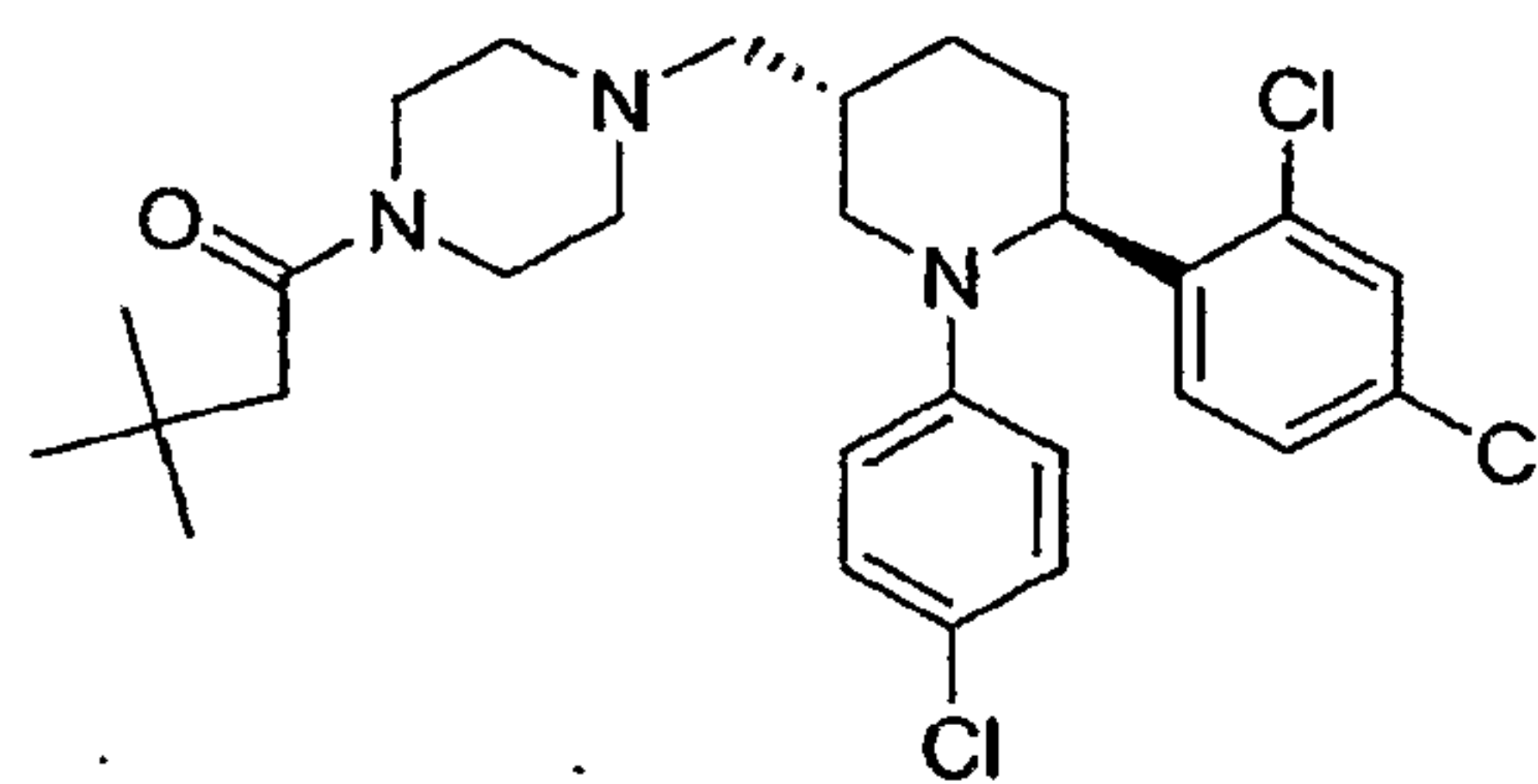
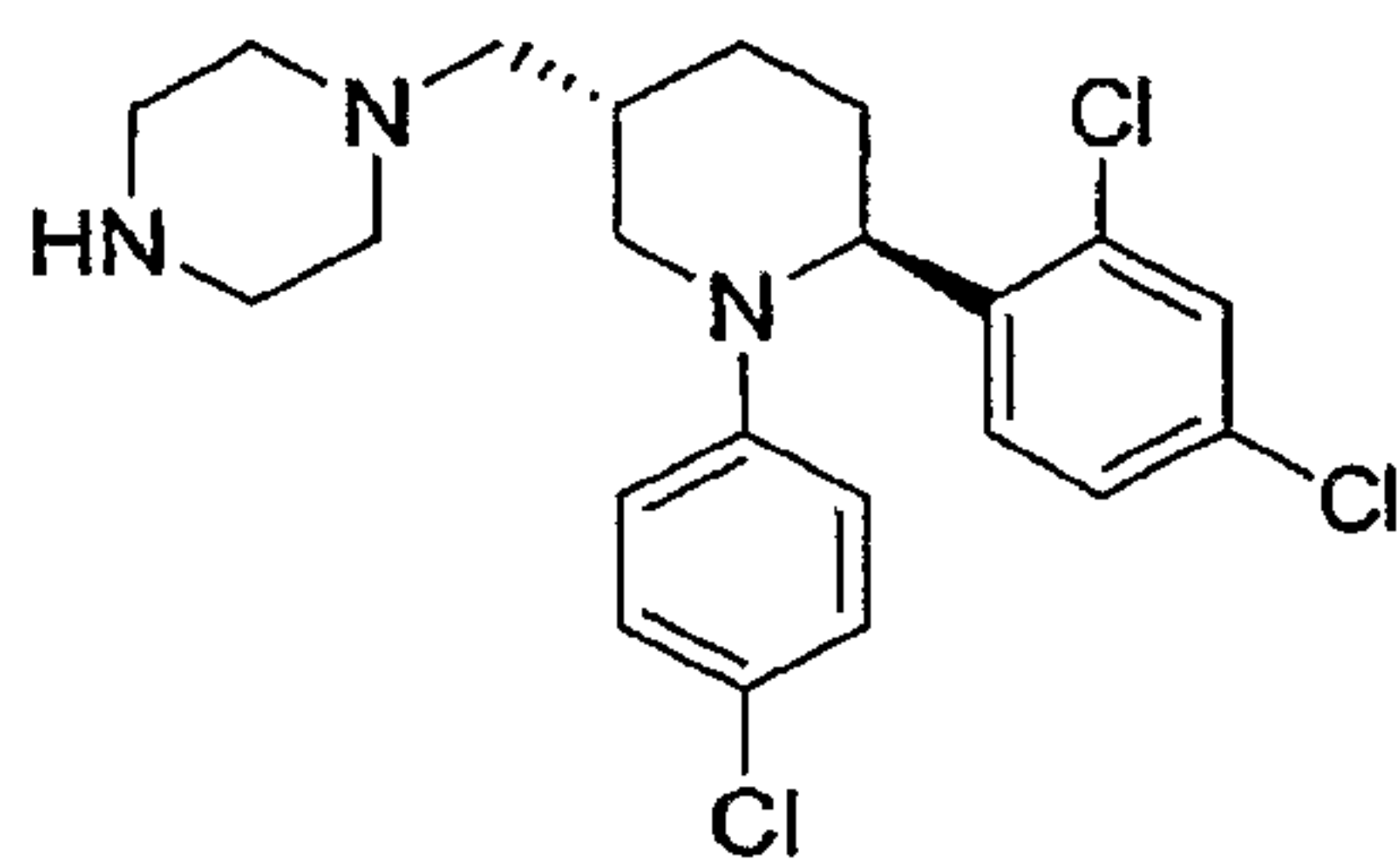
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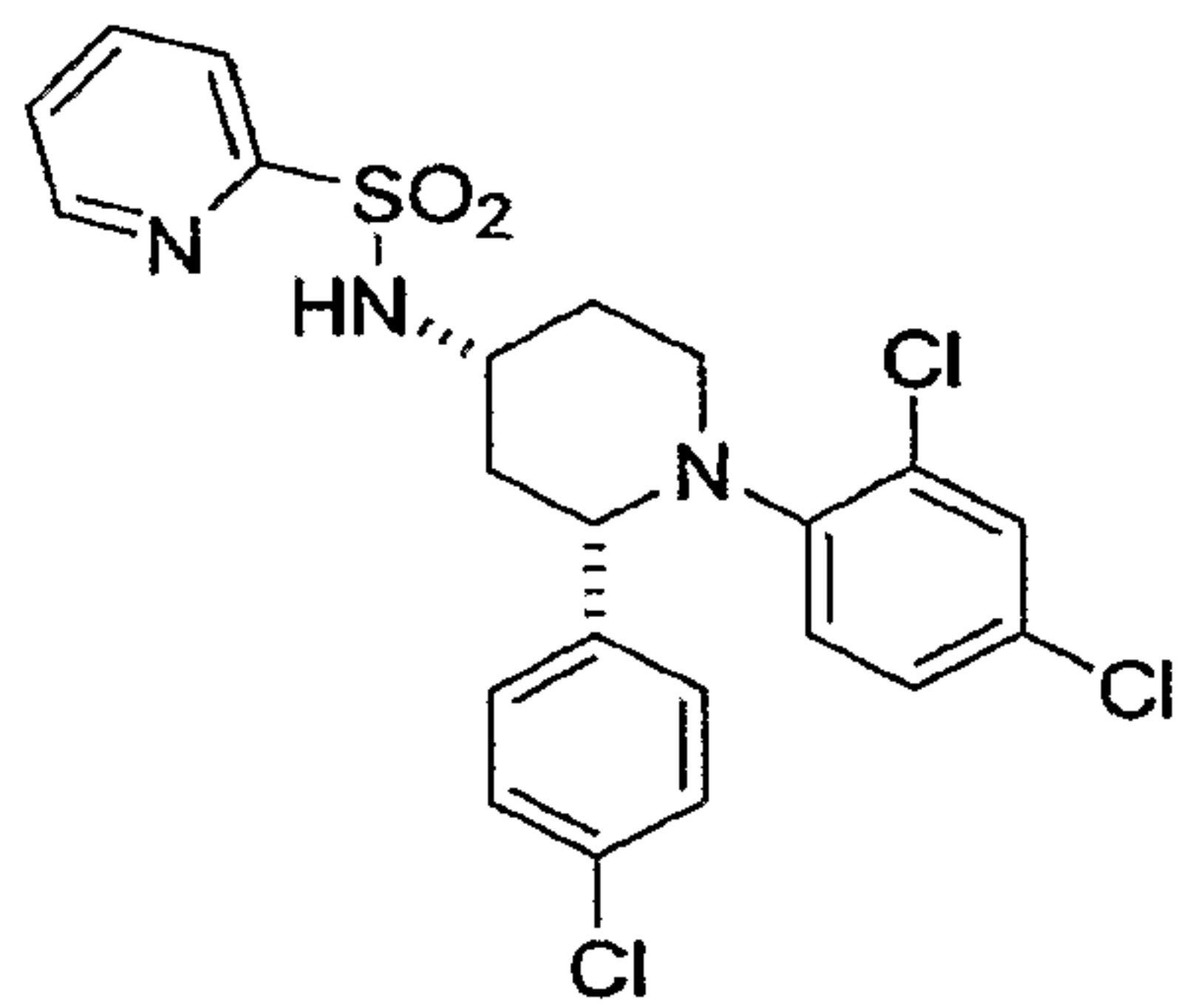
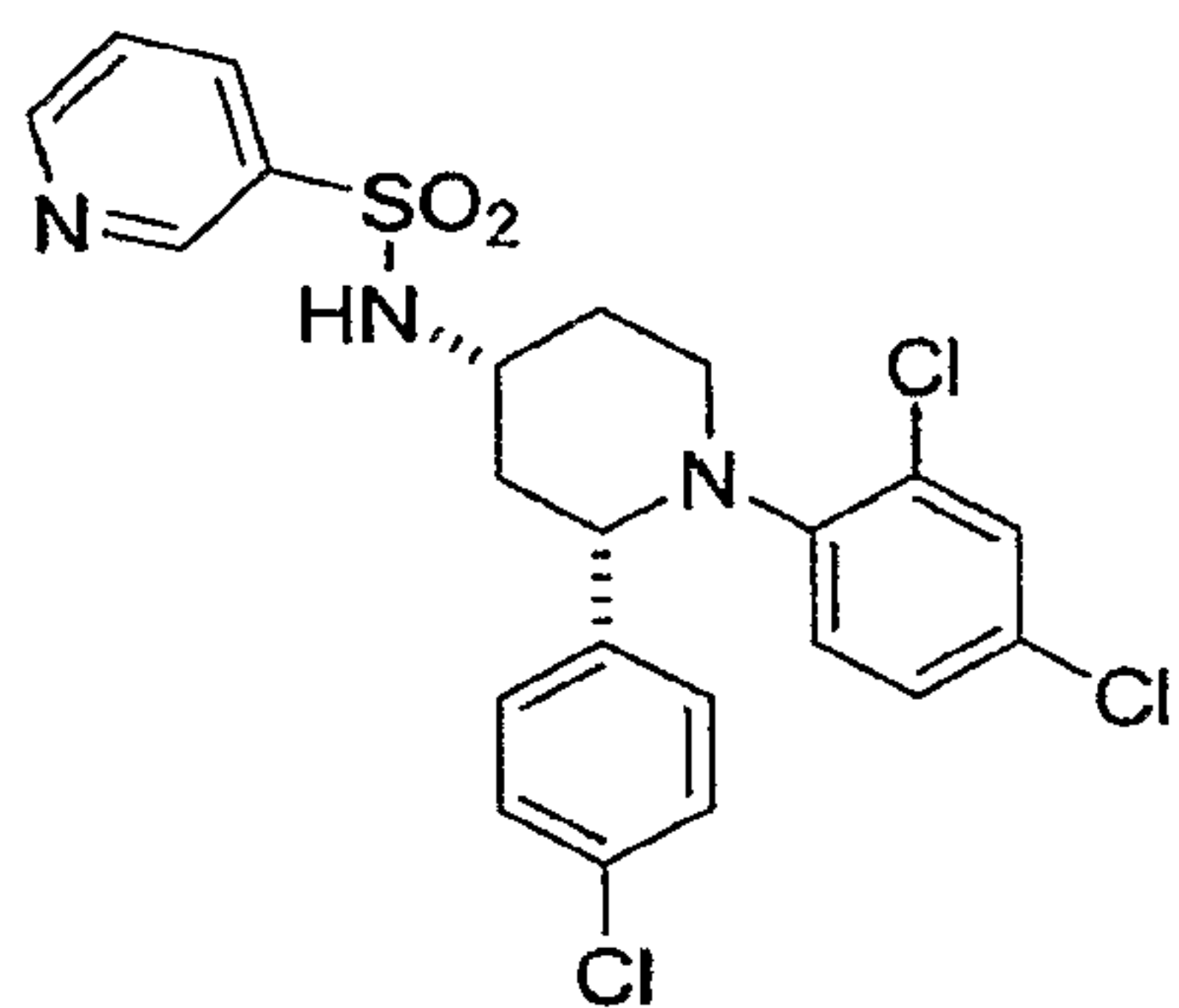
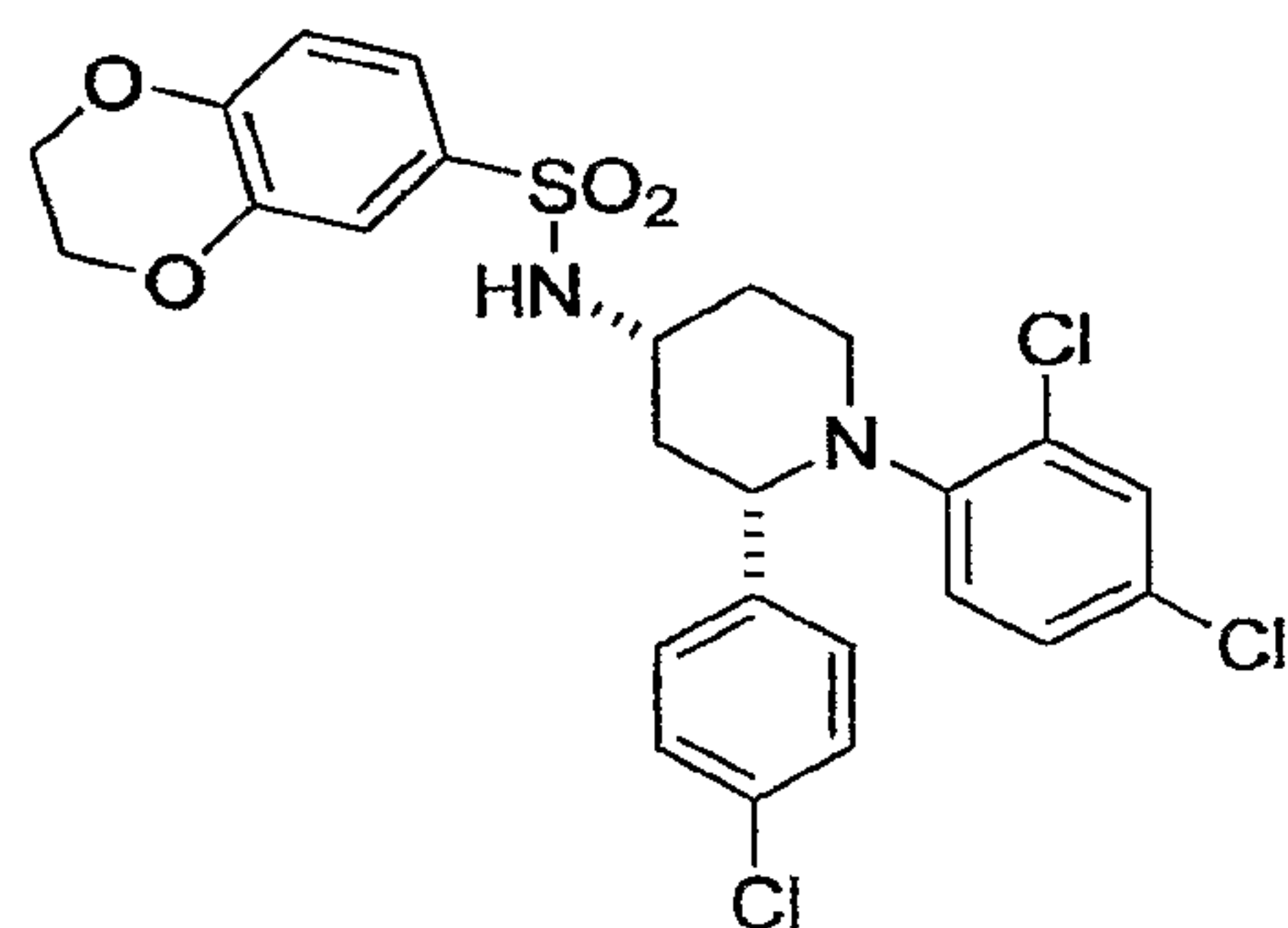
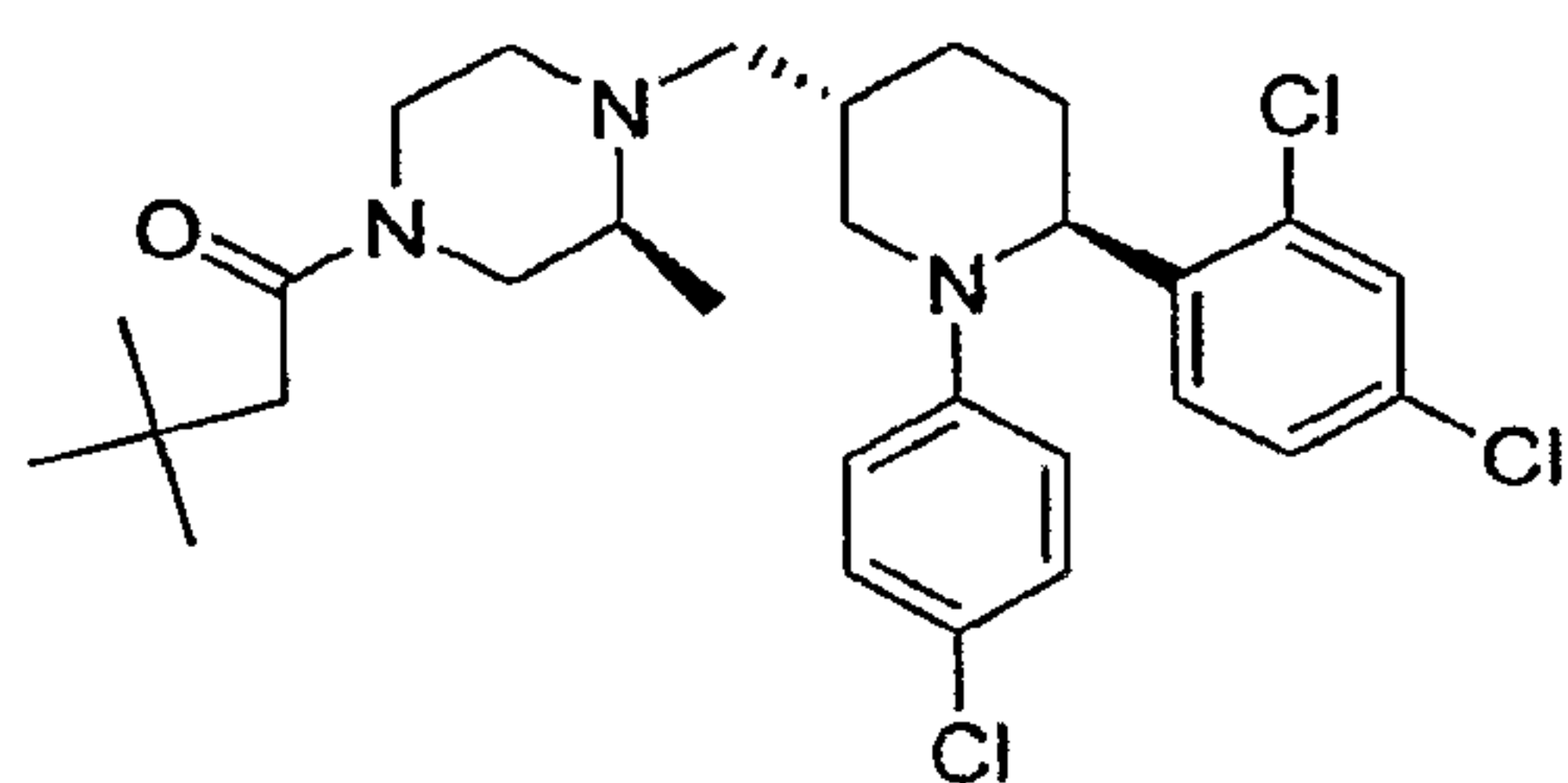
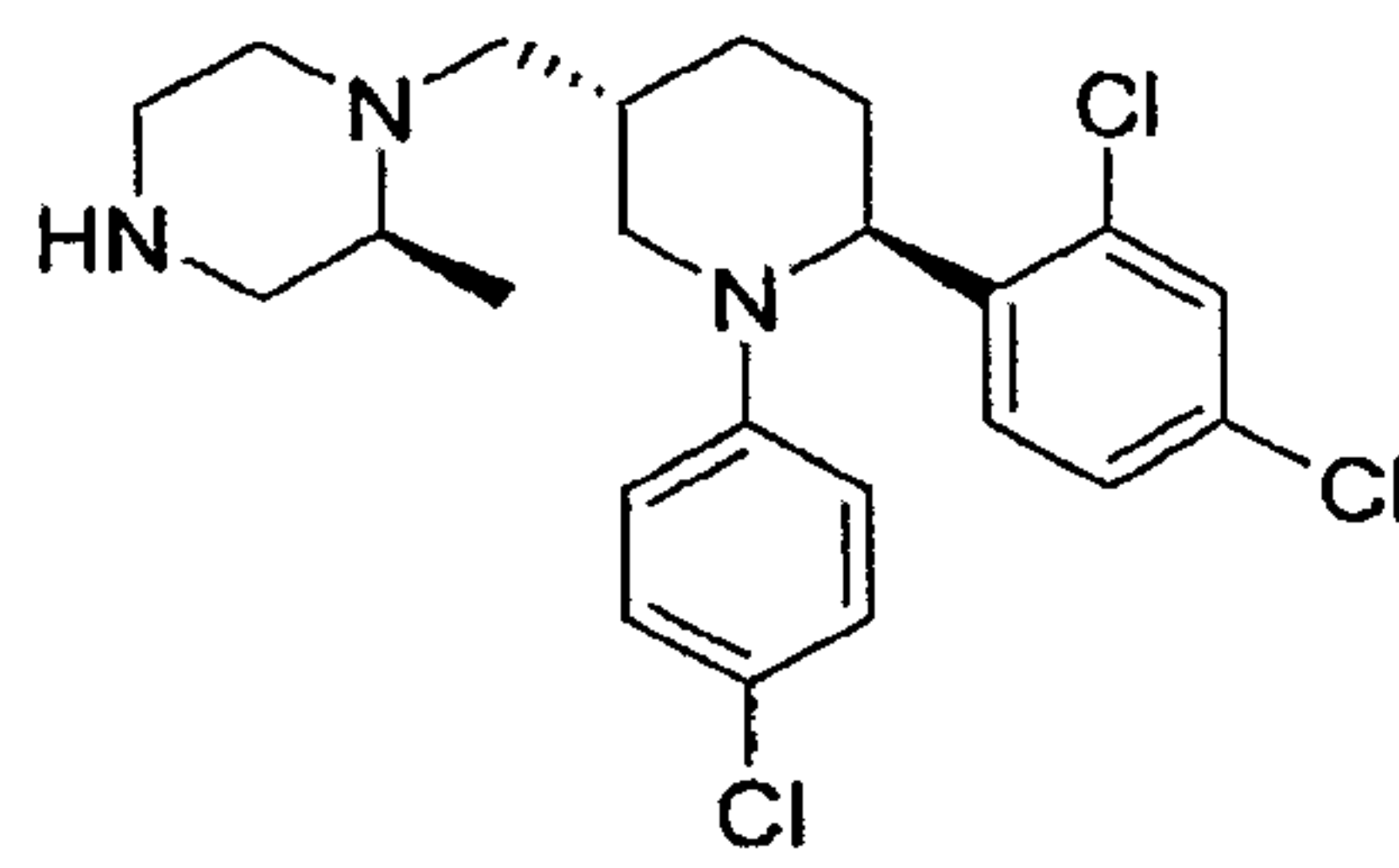
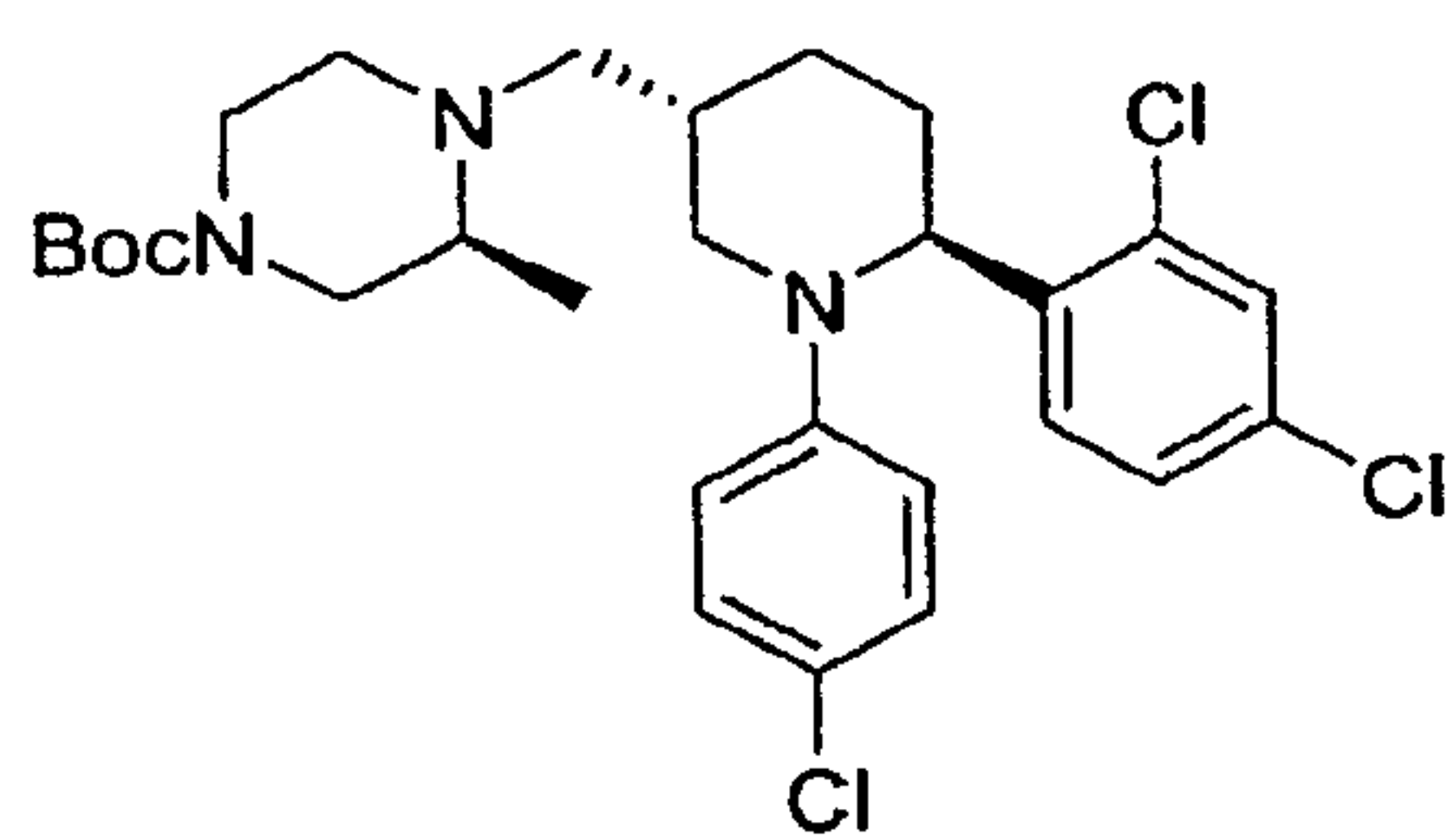
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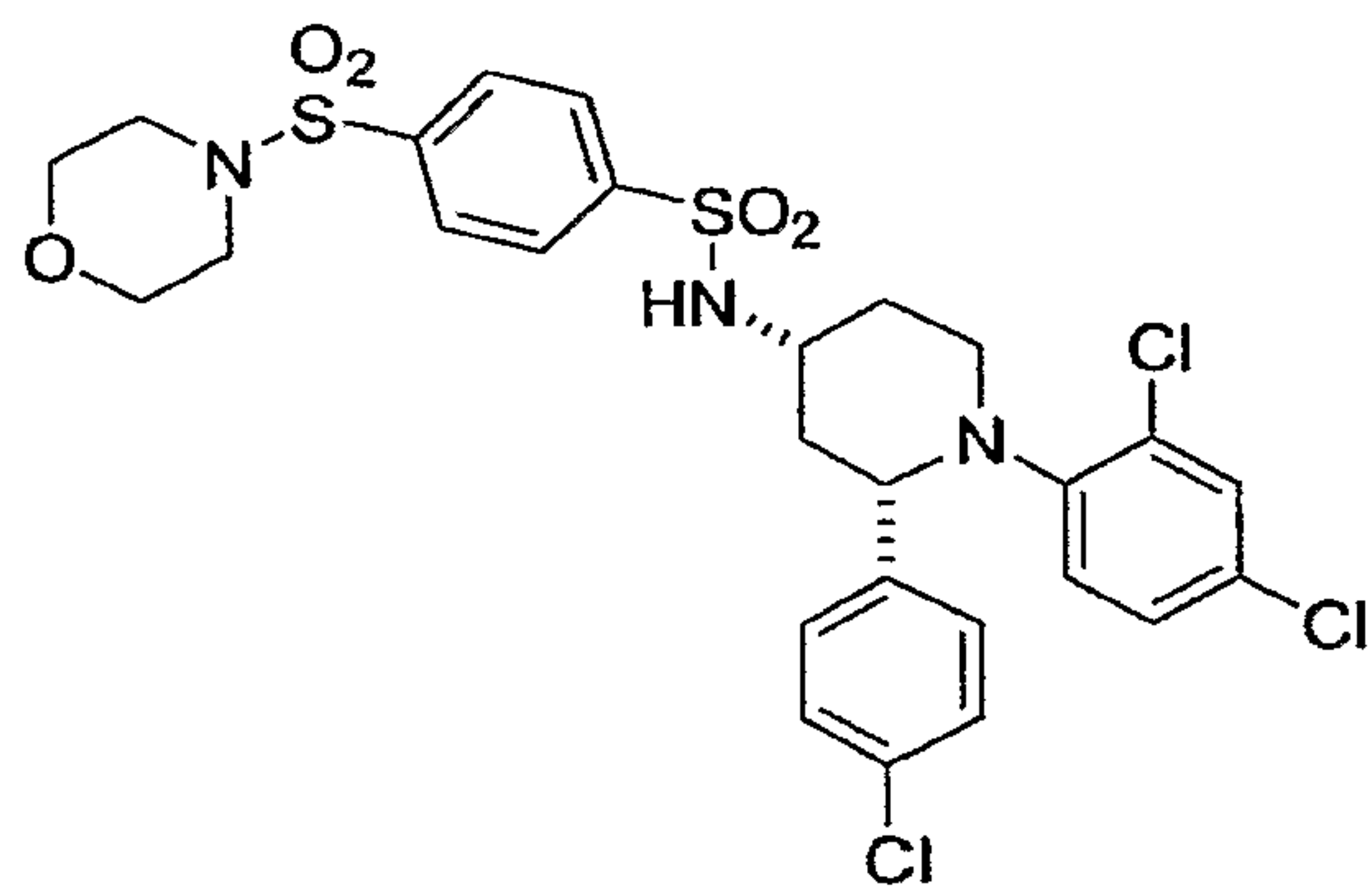
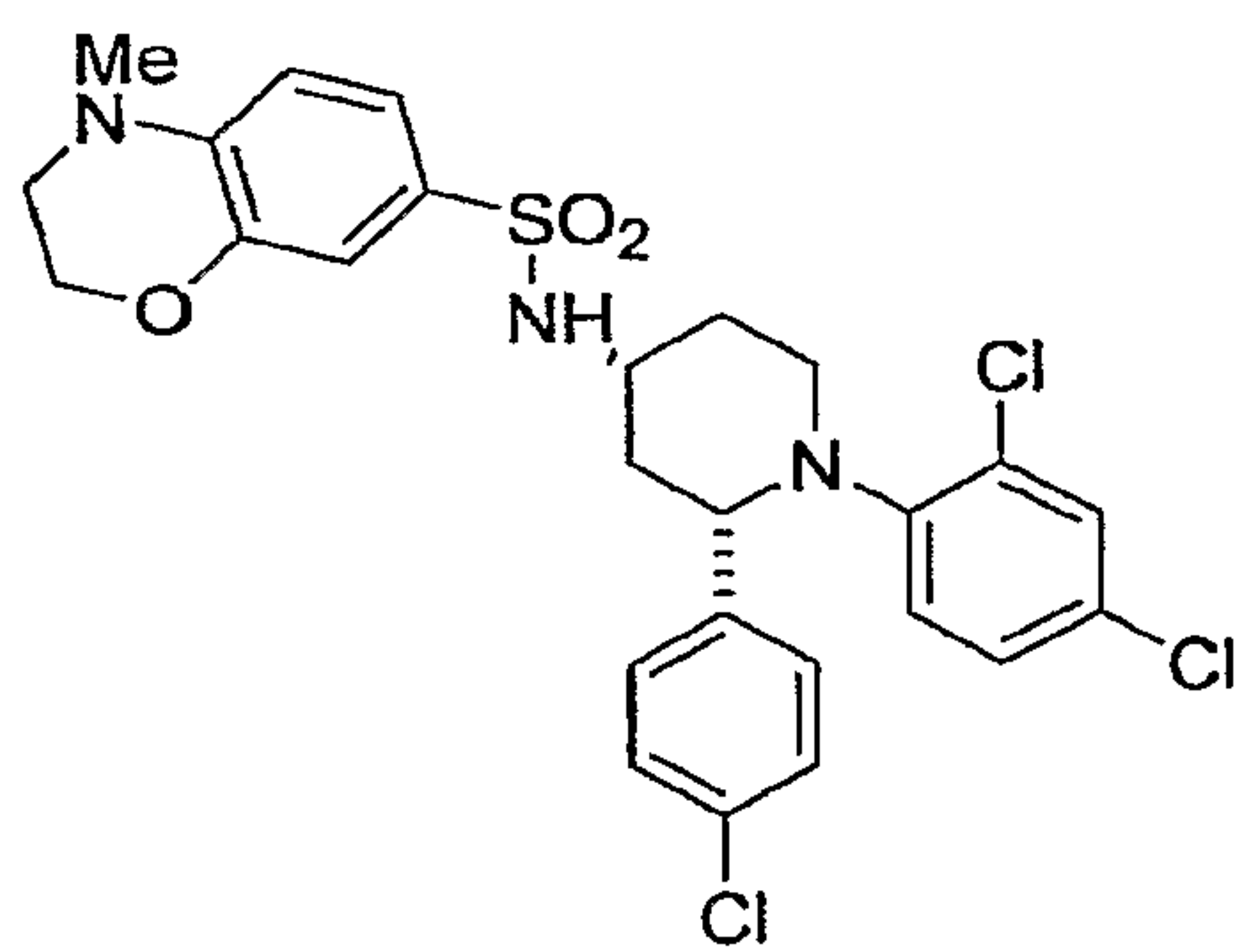
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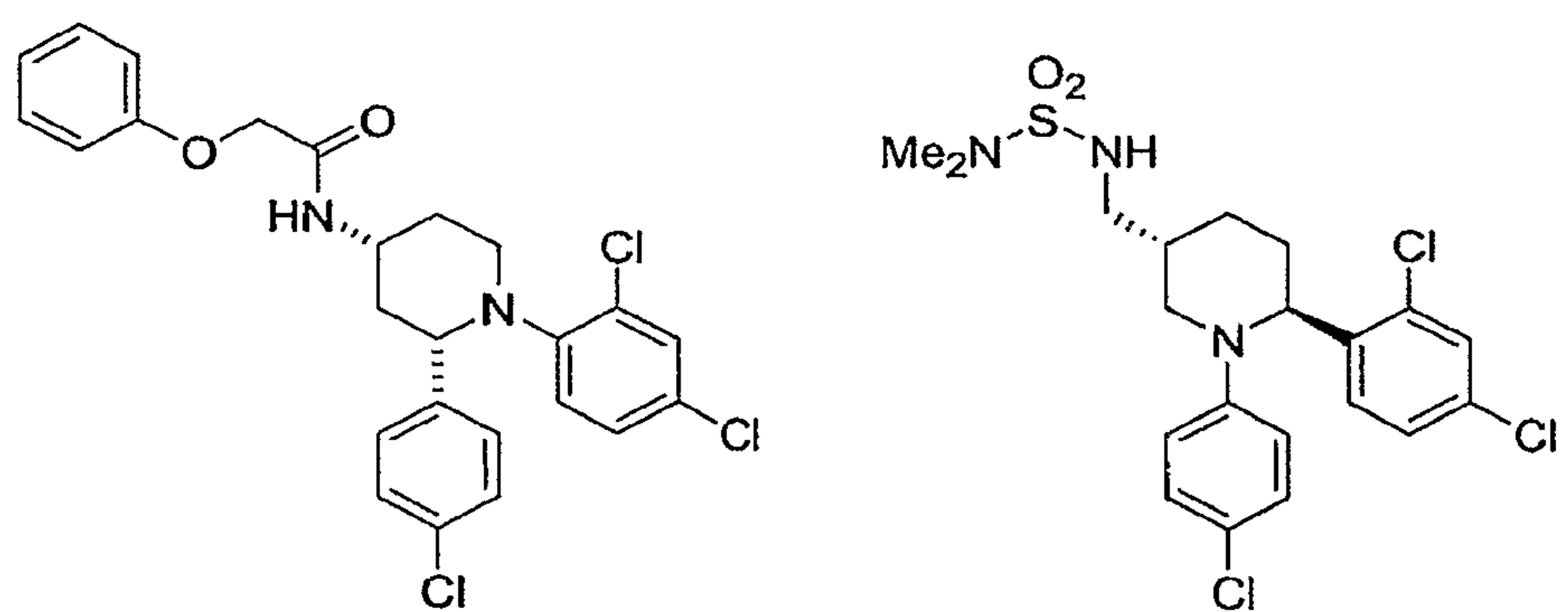
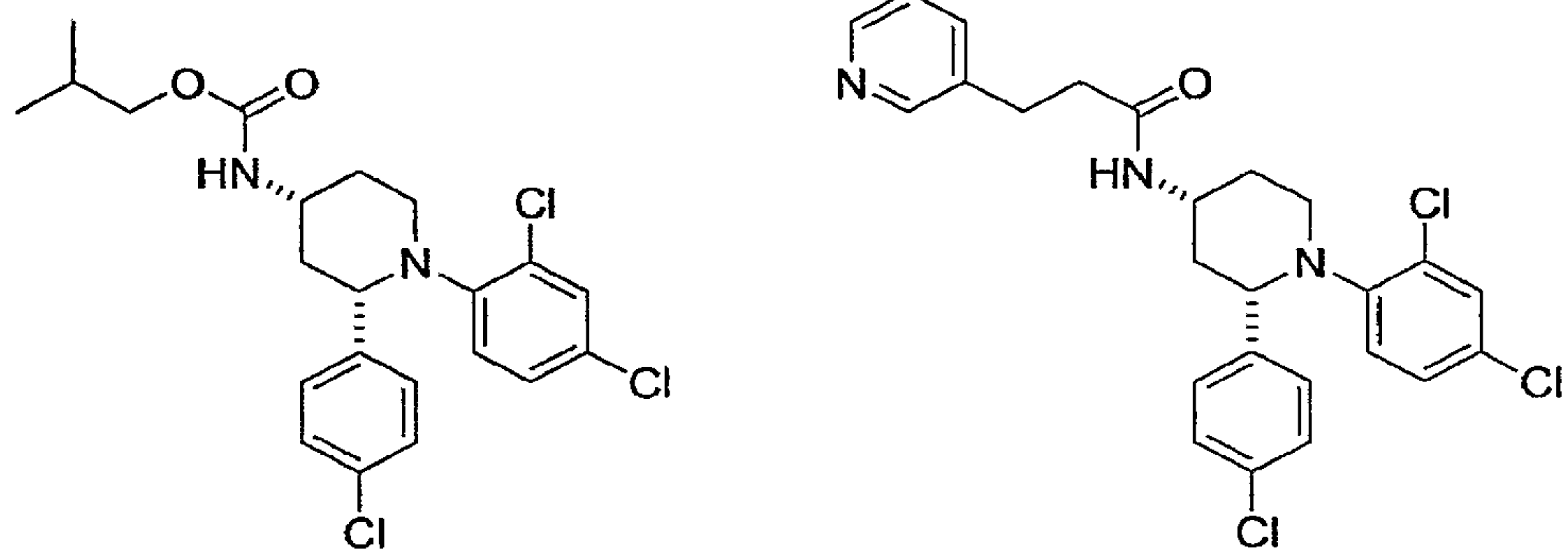
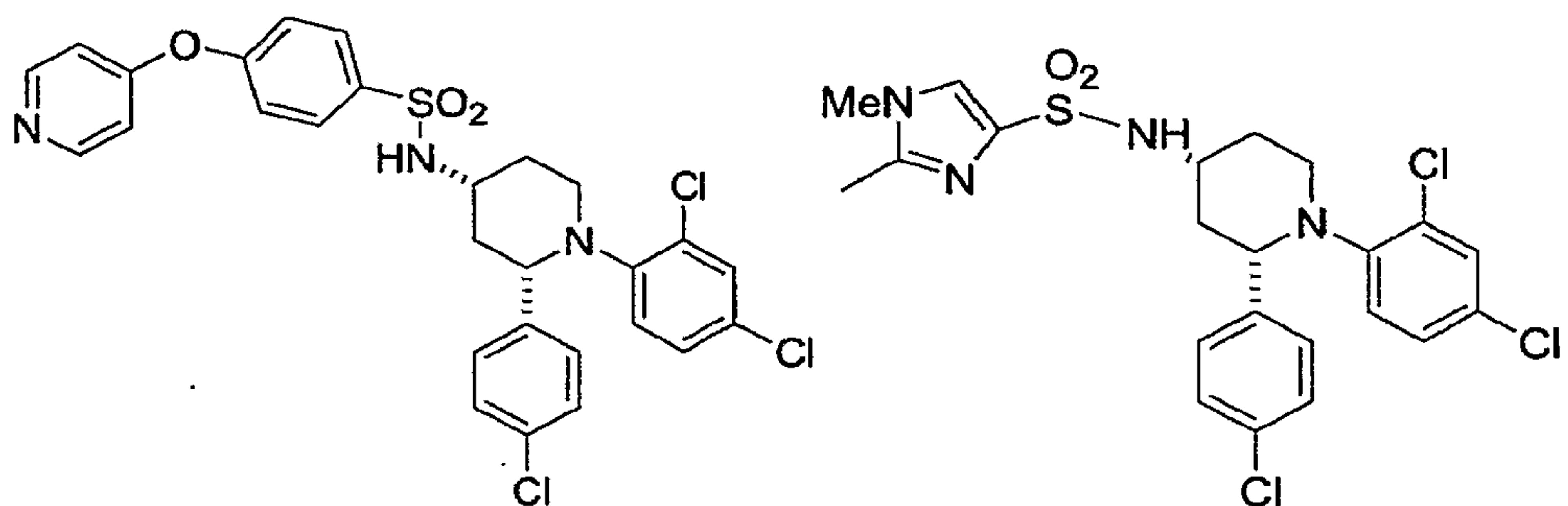
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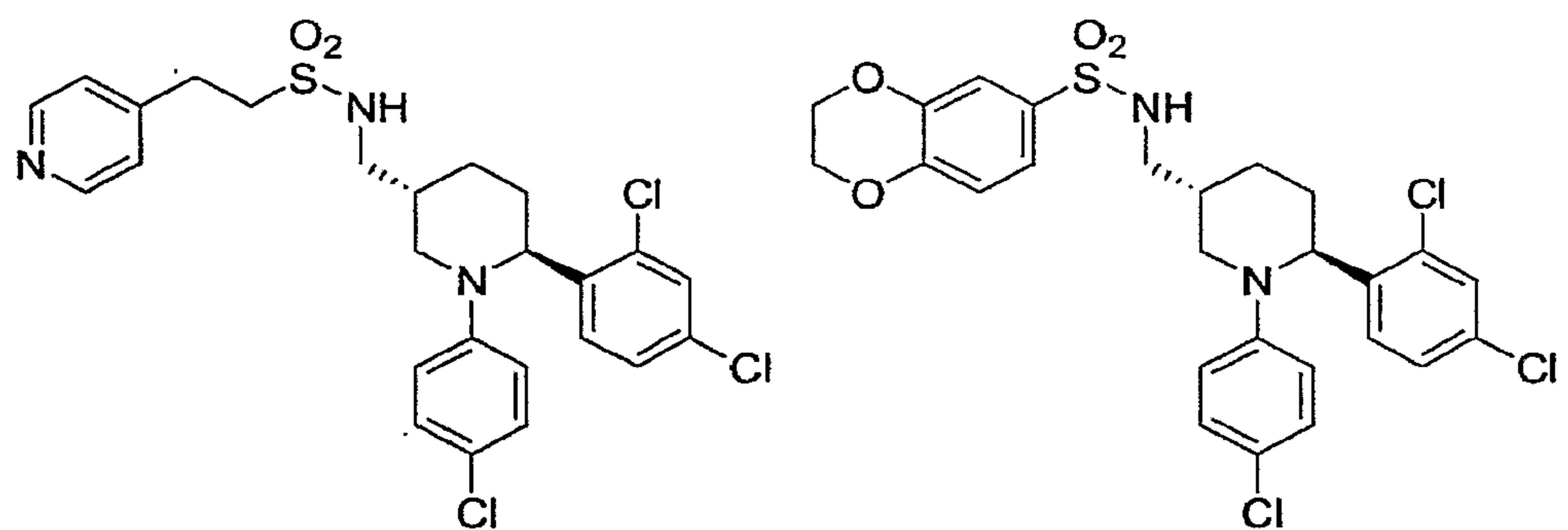
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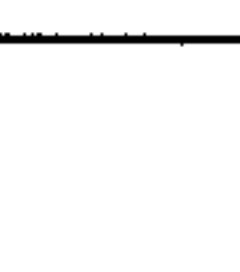


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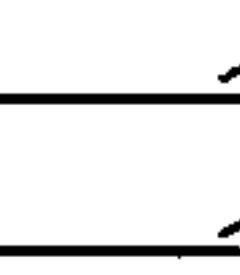
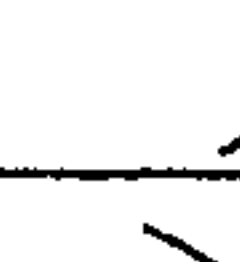
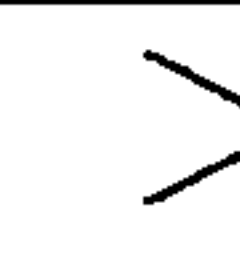
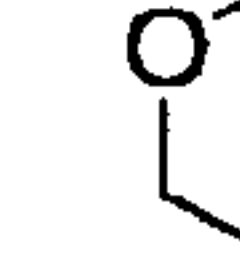




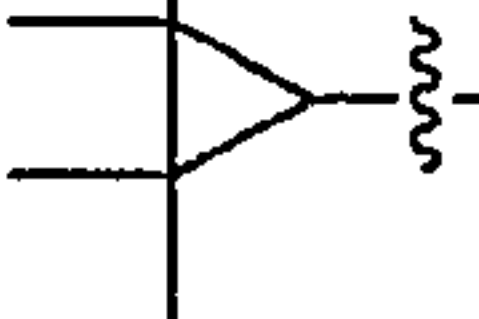
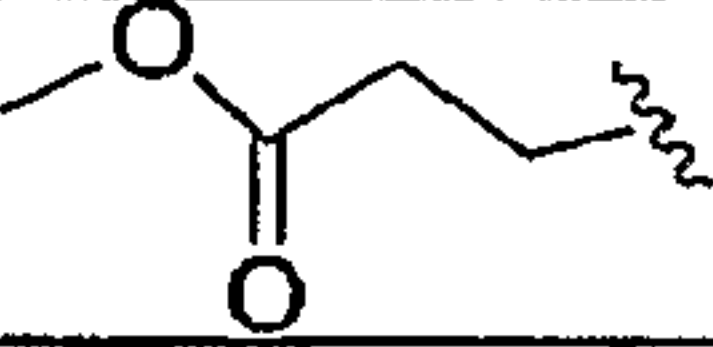
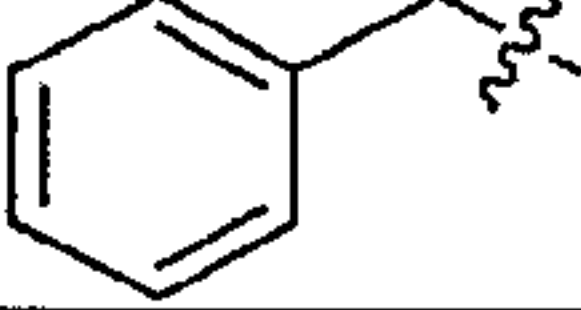
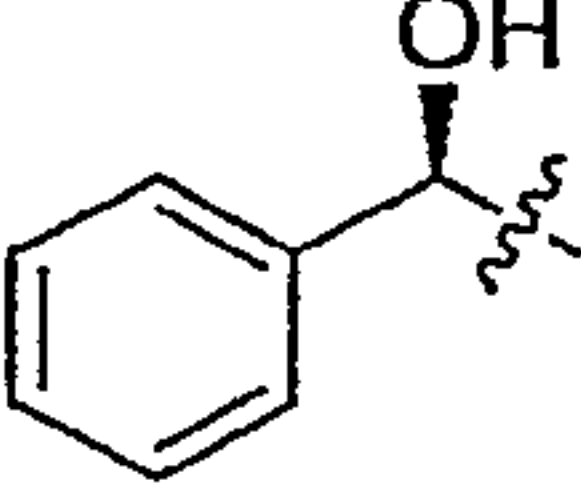
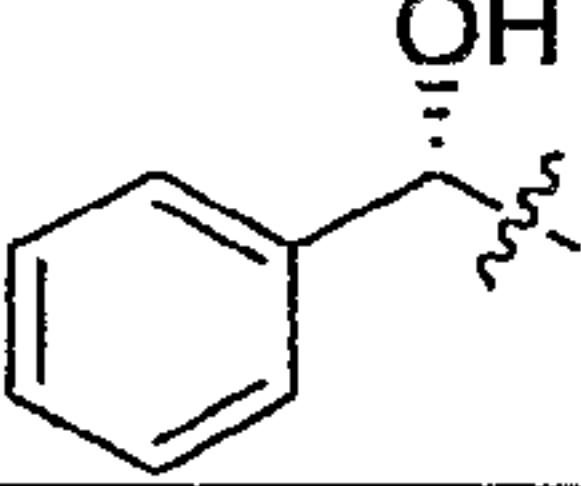
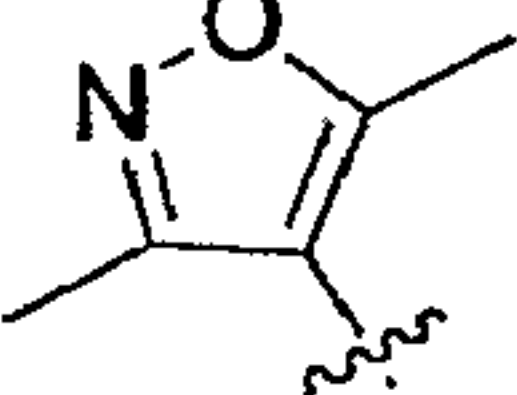
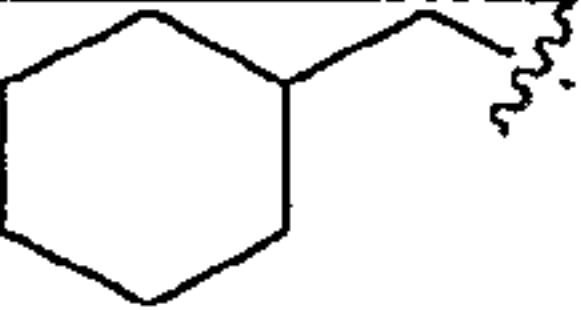
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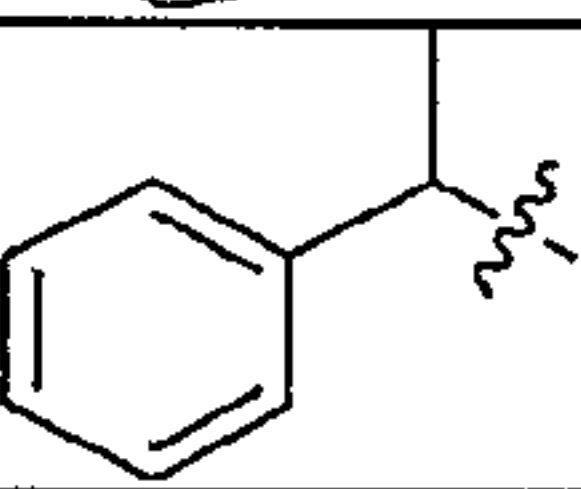
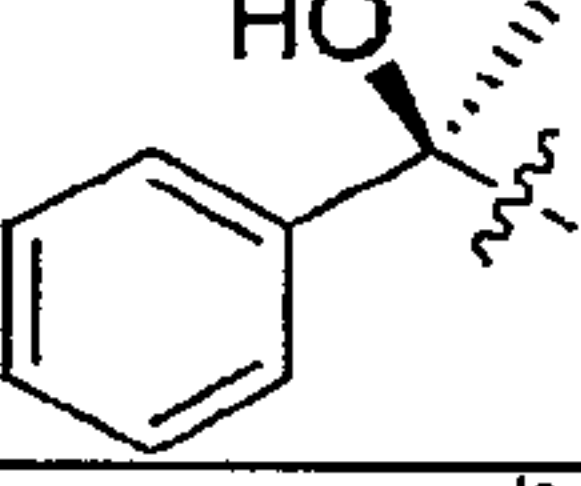
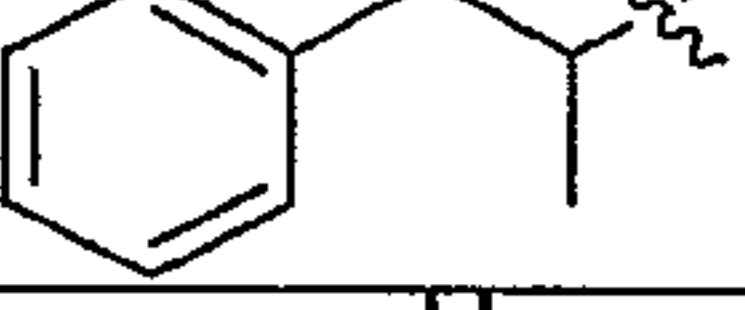
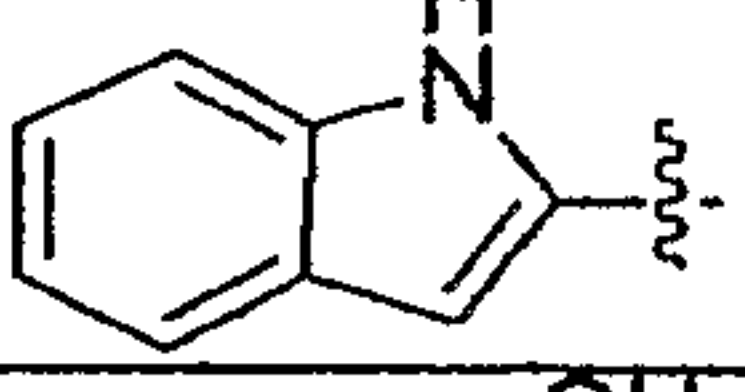
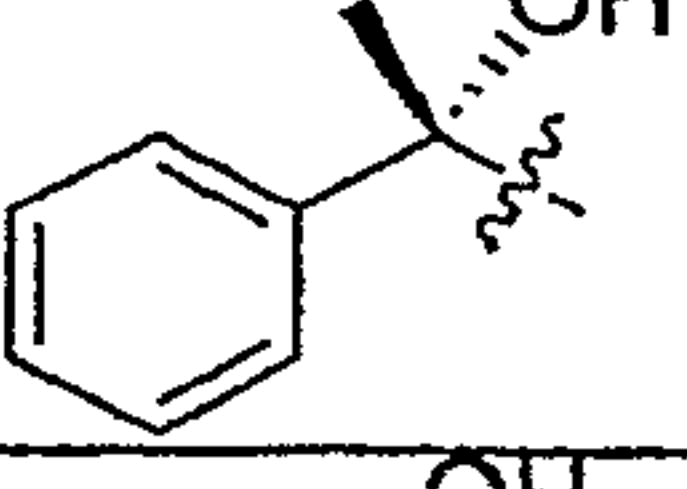
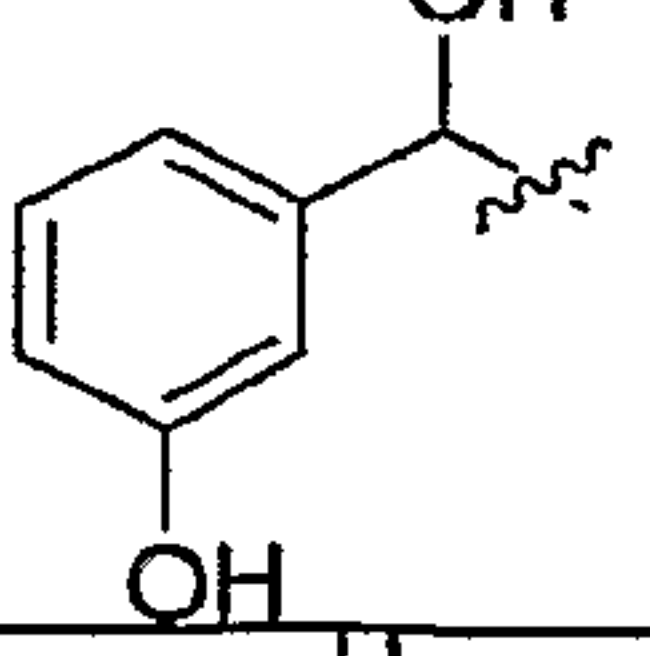
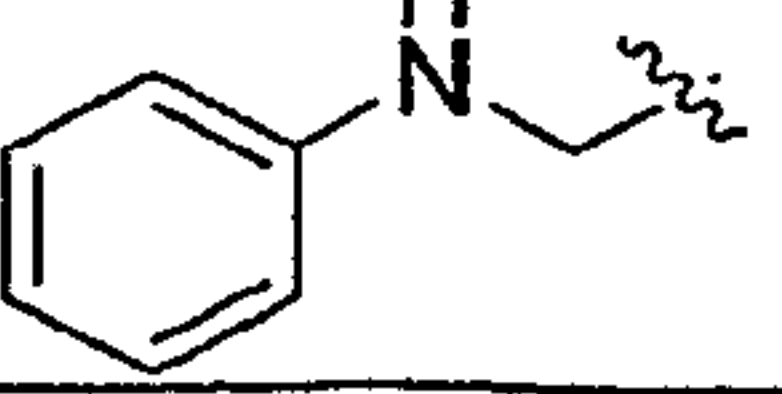





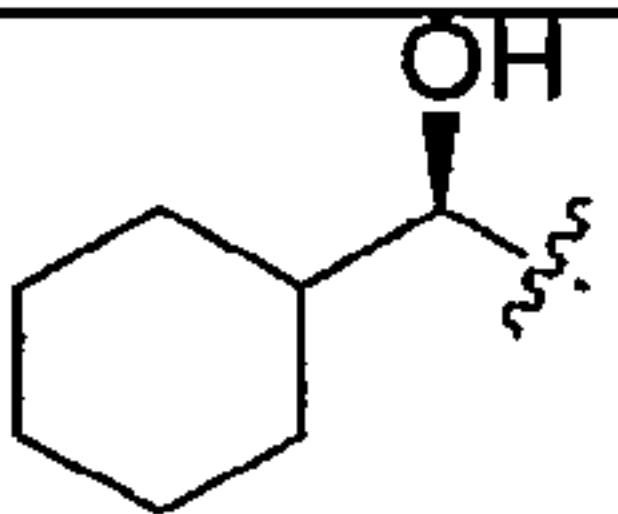
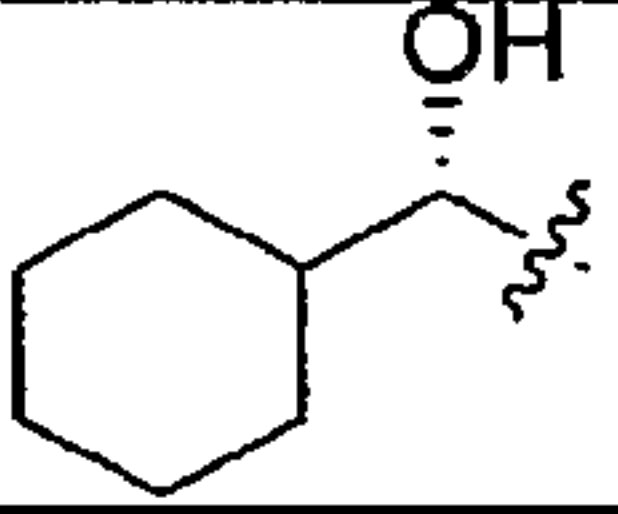





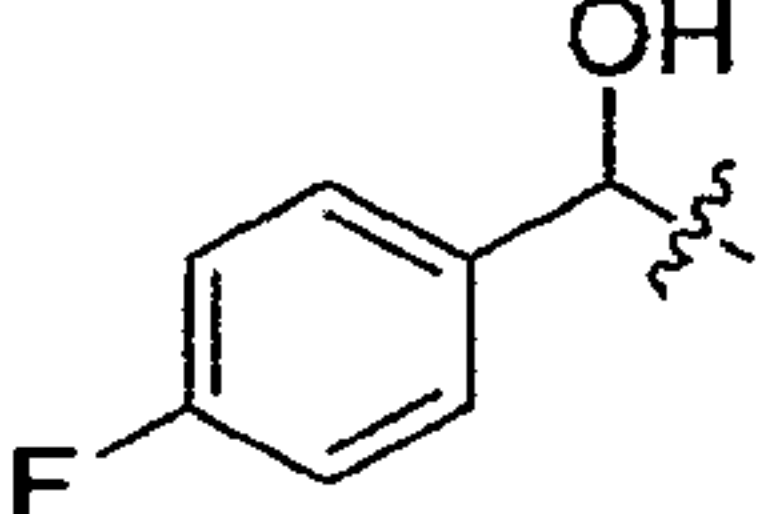
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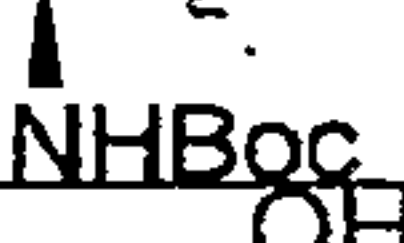
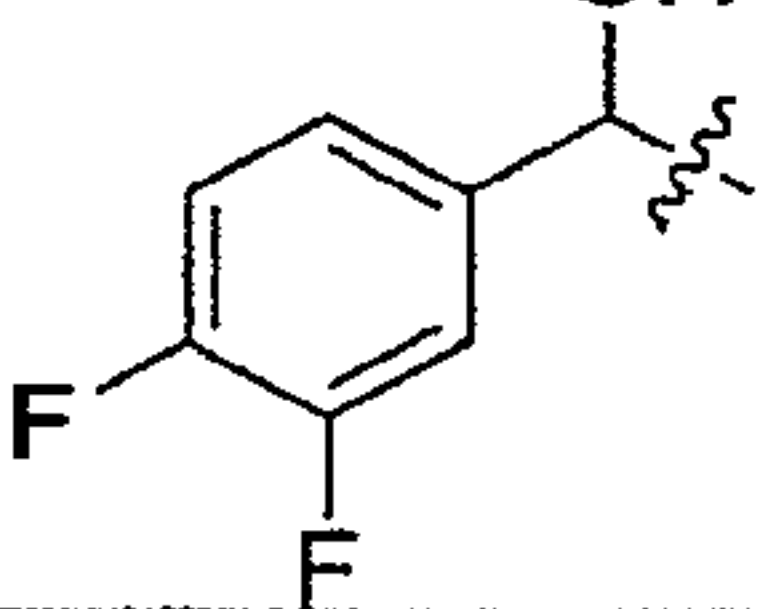
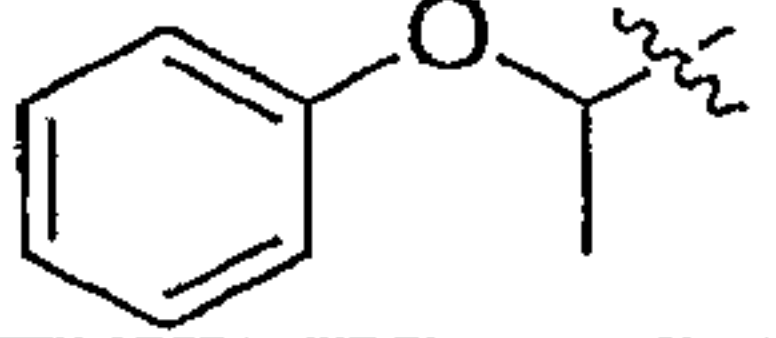
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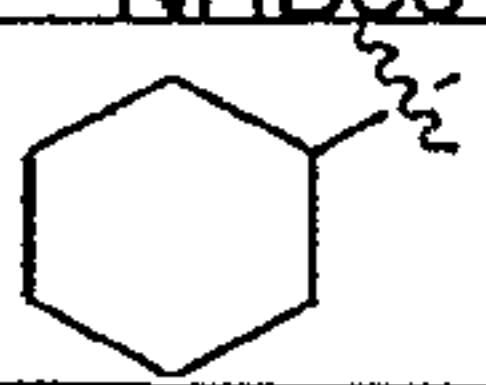








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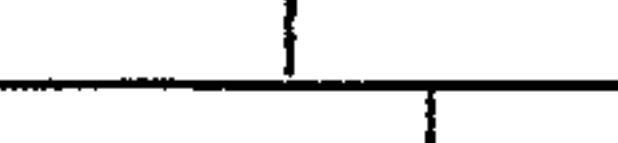
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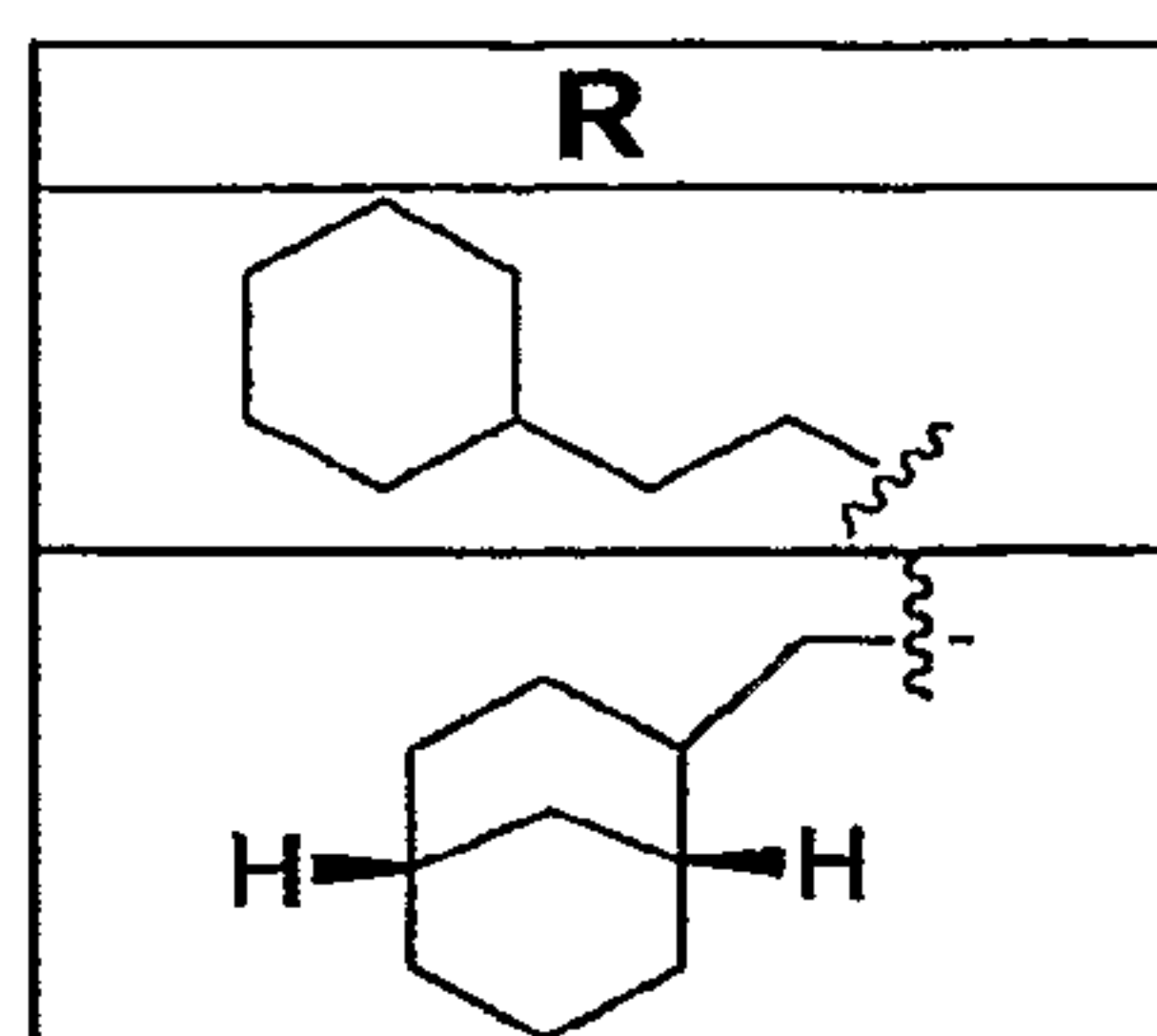






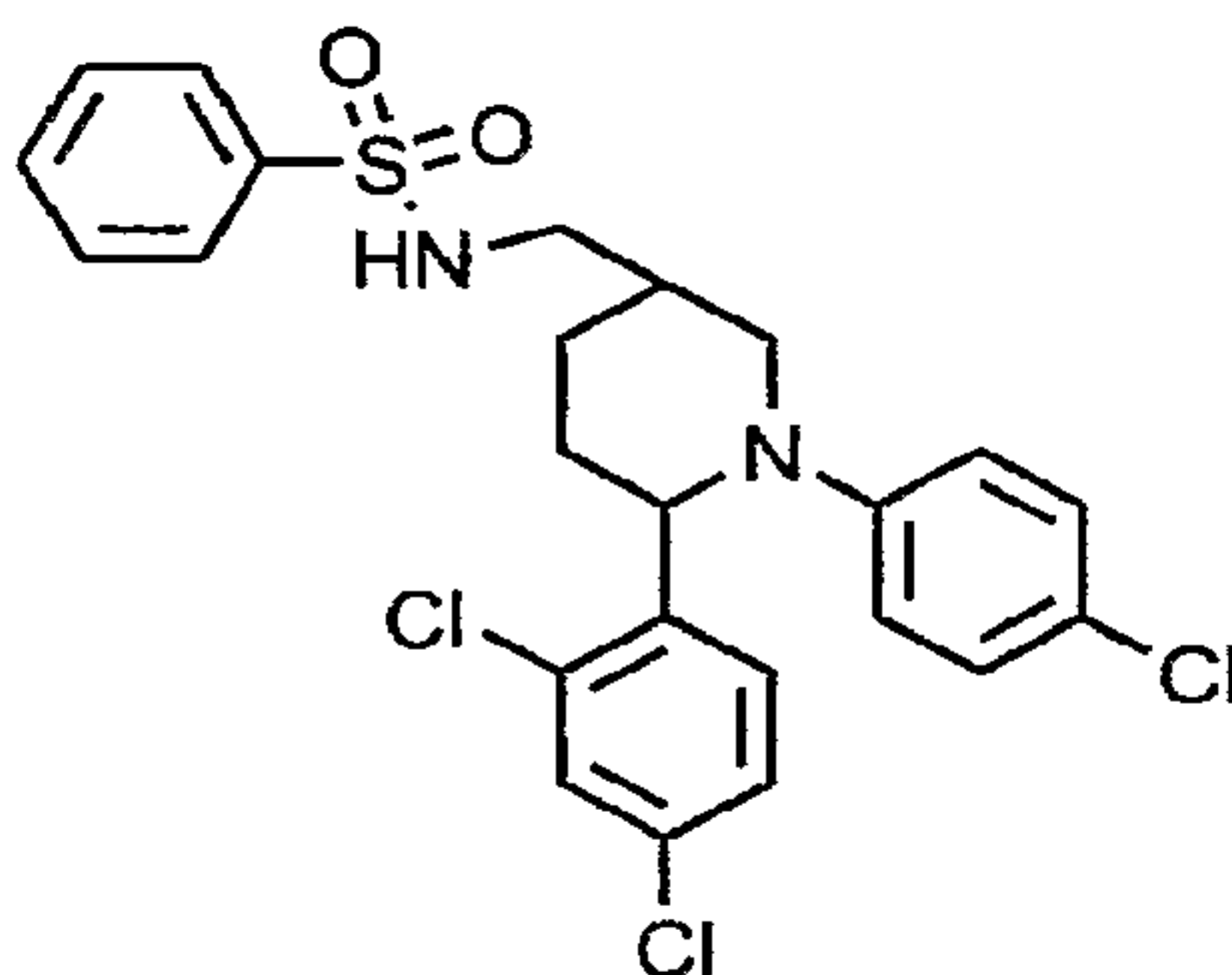



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28. A purified compound of Claim 1.

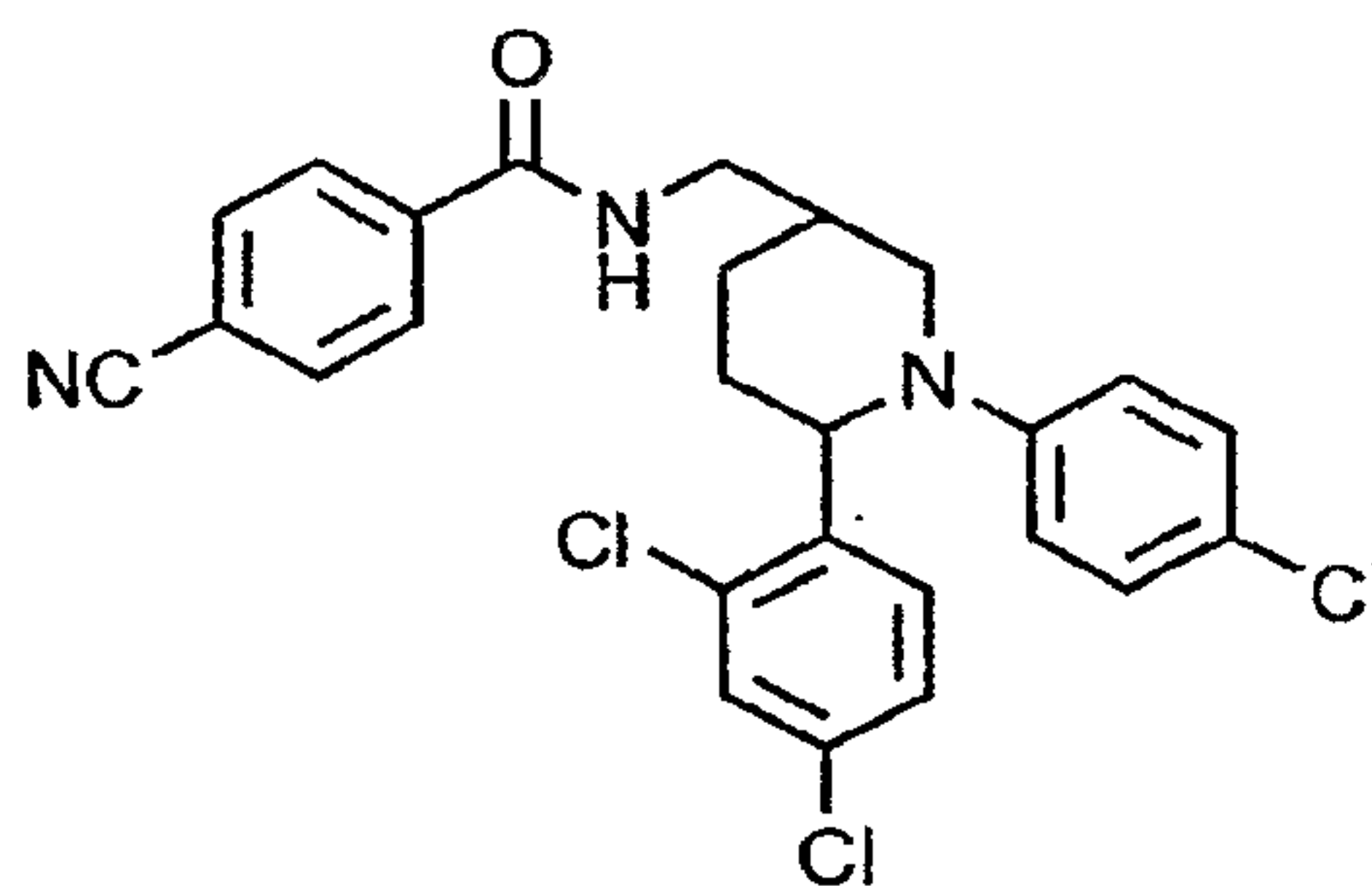
29. A compound having the following structural formula:



5

or a pharmaceutically acceptable salt, solvate, or ester thereof.

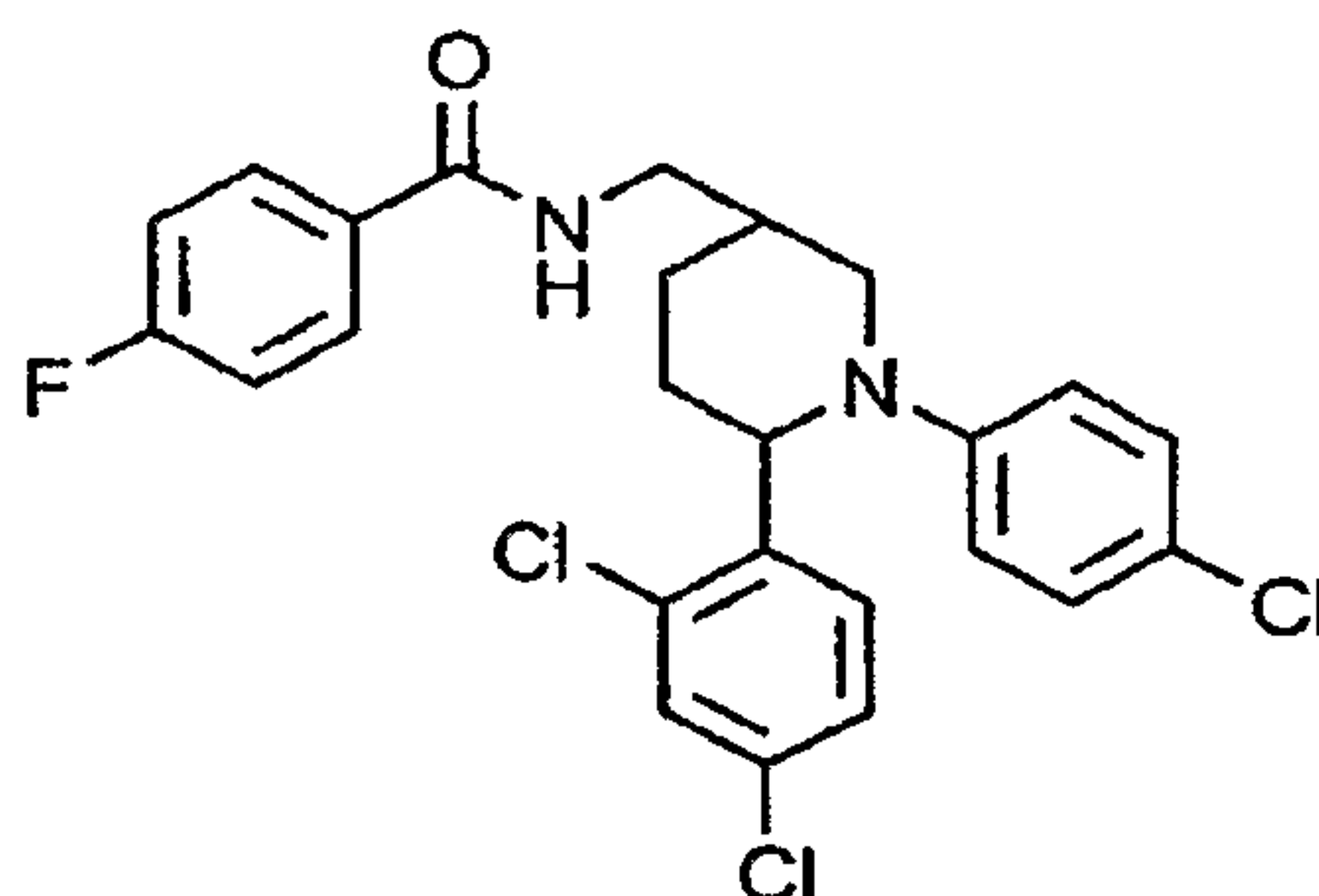
30. A compound having the following structural formula:



10

or a pharmaceutically acceptable salt, solvate, or ester thereof.

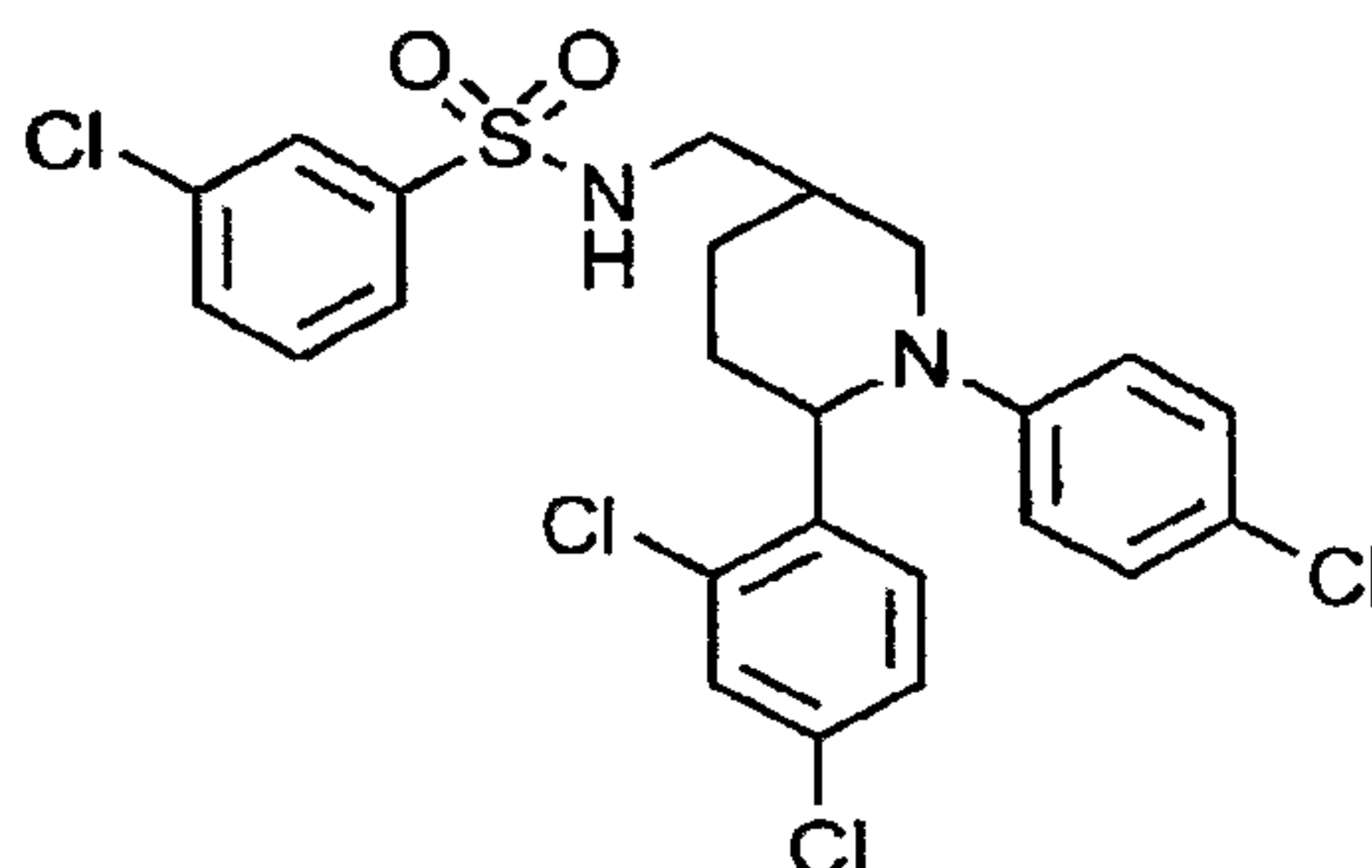
31. A compound having the following structural formula:



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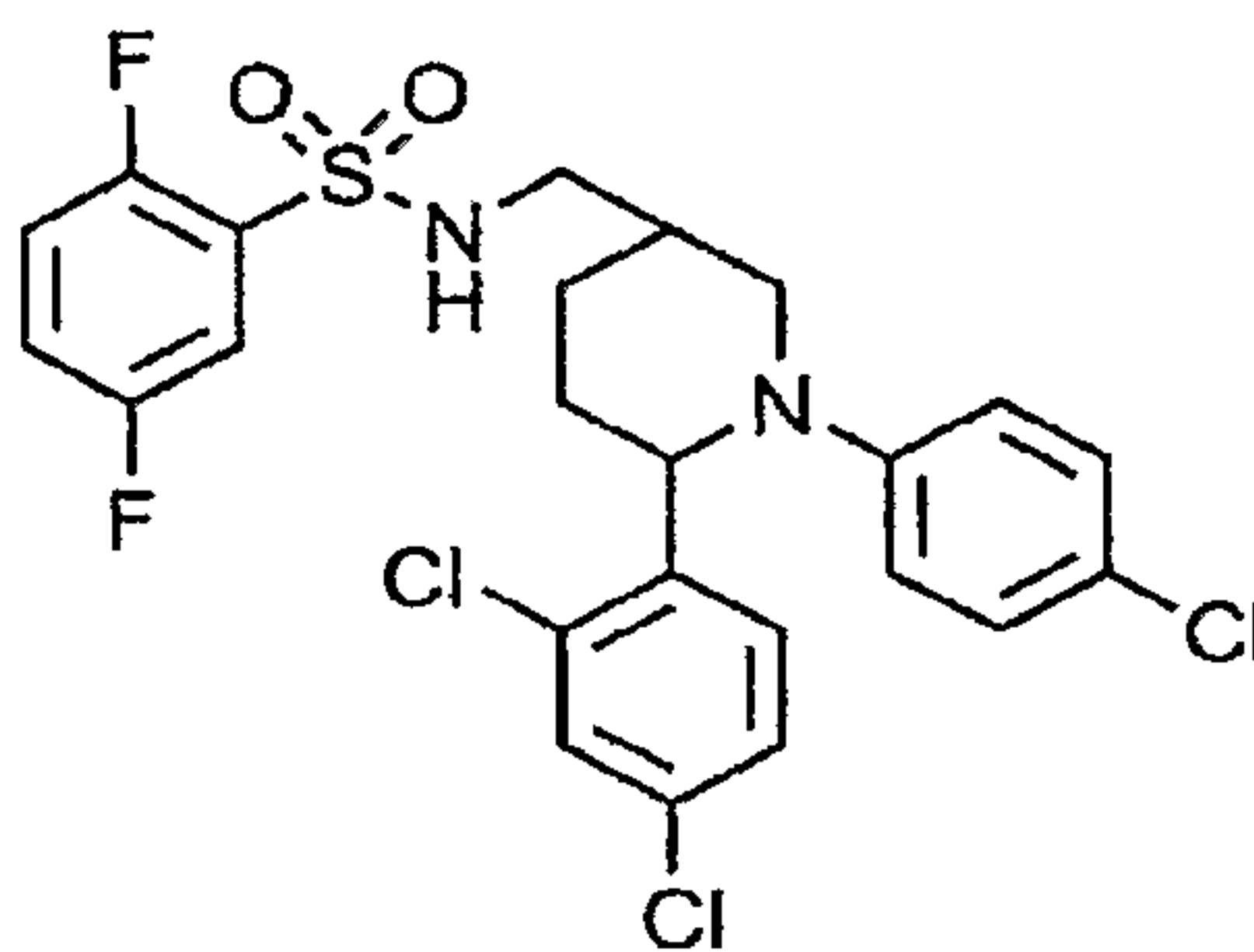
or a pharmaceutically acceptable salt, solvate, or ester thereof.

32. A compound having the following structural formula:



5 or a pharmaceutically acceptable salt, solvate, or ester thereof.

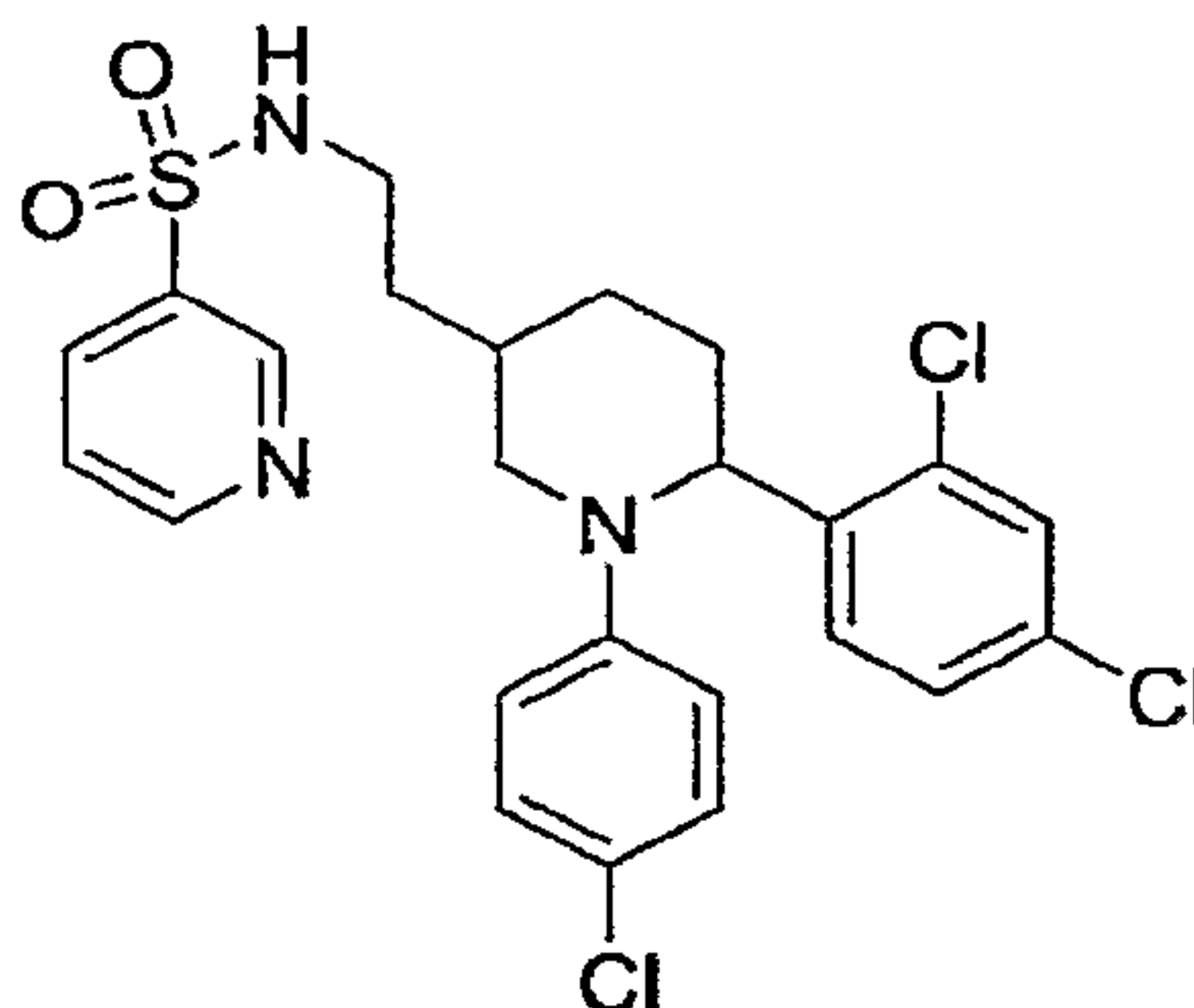
33. A compound having the following structural formula:



or a pharmaceutically acceptable salt, solvate, or ester thereof.

10

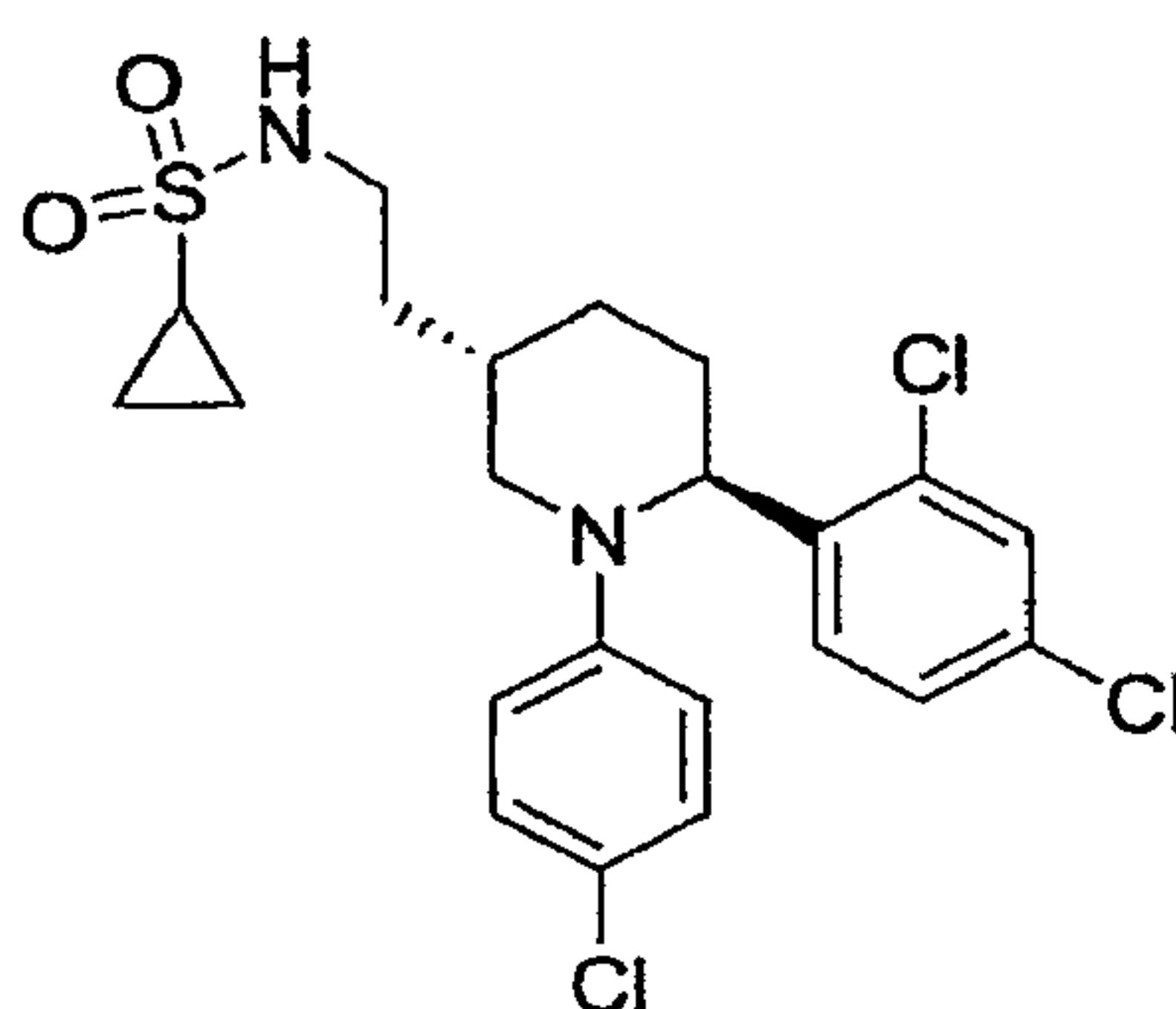
34. A compound having the following structural formula:



or a pharmaceutically acceptable salt, solvate, or ester thereof.

15 35. A compound having the following structural formula:

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or a pharmaceutically acceptable salt, solvate, or ester thereof.

36. A composition comprising:

- 5 a compound of Claim 1, or a pharmaceutically acceptable salt, solvate, or ester thereof; and
at least one pharmaceutically acceptable carrier.

10 37. A pharmaceutical composition comprising a compound of Claim 1, or a pharmaceutically acceptable salt, solvate, or ester thereof, in combination with at least one additional therapeutic agent.

15 38. The pharmaceutical composition of Claim 37, wherein said additional therapeutic agent comprises an antiobesity agent, an antidiabetic agent, or lipid lowering agent.

39. The pharmaceutical composition of Claim 38, wherein:
said antiobesity agent is selected from the group consisting of rimonabant, orlistat, sibutramine, bromocriptine, ephedrine, leptin, pseudoephedrine, and PYY₃₋₃₆;
20 said antidiabetic agent is selected from the group consisting of PPAR_γ agonist, PPAR_{α/γ} dual agonist, biguanidine, sulfonylurea, meglitinide, insulin, insulin secretagogue, and a dipeptidyl peptidase IV inhibitor; and
said lipid lowering agent is selected from the group consisting of a bile acid sequesterant, an HMG-CoA reductase inhibitor, a cholesterol absorption inhibitor,
25 an ACAT inhibitor, a CETP inhibitor, a PPAR_α agonist, niacin and a niacin receptor agonist.

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40. A method of treating a disease, disorder, or condition comprising:
administering to a patient in need thereof a therapeutically effective amount of at
least one compound of Claim 1, or a pharmaceutically acceptable salt, solvate, or
ester thereof;
- 5 wherein said disease, disorder, or condition is selected from the group consisting of
metabolic syndrome, neuroinflammatory disorders, cognitive disorders,
psychosis, addictive behavior, gastrointestinal disorders, and cardiovascular
conditions.
- 10 41. The method of Claim 40, wherein said disease, disorder, or condition is
metabolic syndrome.
42. The method of Claim 41, further comprising administering at least one
additional therapeutic agent selected from the group consisting of an antiobesity
15 agent, an antidiabetic agent, or lipid lowering agent.
43. The method of Claim 42, wherein:
said antiobesity agent is selected from the group consisting of rimonabant, orlistat,
sibutramine, bromocriptine, ephedrine, leptin, pseudoephedrine, and PYY₃₋₃₆;
20 said antidiabetic agent is selected from the group consisting of PPAR_γ agonist, dual
agonist, biguanidine, sulfonylurea, meglitinide, insulin, insulin secretagogue, and
a dipeptidyl peptidase IV inhibitor; and
said lipid lowering agent is selected from the group consisting of a bile acid
sequesterant, an HMG-CoA reductase inhibitor, a cholesterol absorption inhibitor,
25 an ACAT inhibitor, a CETP inhibitor, a PPAR_α agonist, niacin and a niacin
receptor agonist.

