Description

Benzylamine Derivative

Technical Field

[0001]

The present invention relates to a novel benzylamine derivative or a salt thereof which exhibits excellent antagonistic activity against substance P receptor (NK-1 receptor) or neurokinin A receptor (NK-2 receptor).

Background Art

[0002]

Tachykinins, which form a group of peptidergic neurotransmitters, play an important role in nociception functioning as a biowarning system, as well as the emotion cycle. Desctruction of such a biowarning system readily causes a variety of diseases and disorders inculuding irritable bowel syndrome (IBS), pain, anxiety, obstructive bronchial diseases, headache, and vomiting. In mammals, substance P, neurokinin A, and neurokinin B are known tachykinins, and these tachykinin species have high affinity with respect to NK-1 receptor, NK-2 receptor, and NK-3 receptor, respectively.

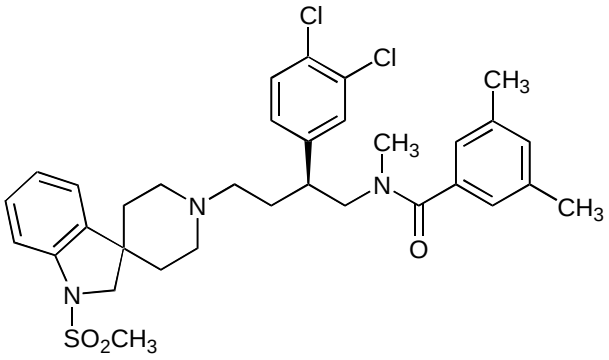
[0003]

Tachykinin receptor antagonists have been used as drugs for treating various diseases caused by destruction of the

biowarning system. For example, the following compounds (A), (B) and (C) are low-molecular weight non-peptidergic compounds known to exhibit antagonistic activity against both NK-1 receptor and NK-2 receptor (Patent Documents 1 to 3).

[0004]

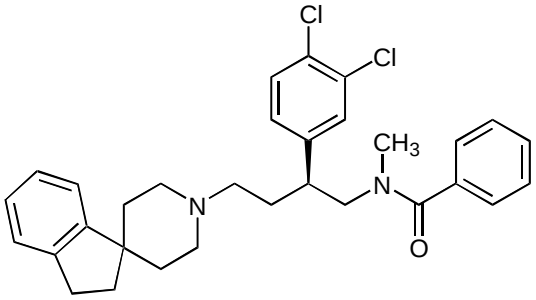
[F1]



(A)

[0005]

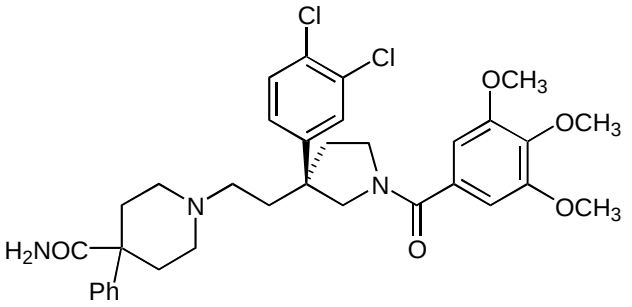
[F2]



(B)

[0006]

[F3]



(C)

[0007]

However, actually, compound (B) in vitro exhibits antagonistic activity only to NK-2 receptor. When any of compounds (A) to (C) are perorally administered, satisfatory antagonistic activity is not always attained (Patent Documents 4 and 5).

[0008]

Meanwhile, the aforementioned optically active sulfoxide derivative (D) is known to exhibit excellent antagonistic activity against both NK-1 receptor and NK-2 receptor (see Patent Document 4). However, there are only a limited number of reports on low-molecular-weight compounds exhibiting antagonistic activity against NK-1 receptor or NK-2 receptor.

Patent Document 1: International Patent Publication WO94/29309 pamphlet)

Patent Document 2: International Patent Publication WO94/17045 pamphlet)

Patent Document 3: International Patent Publication WO94/26735 pamphlet)

Patent Document 4: International Patent Publication

WO94/17045 pamphlet

Patent Document 5: Japanese Patent Application Laid-Open (*kokai*) No. 11-43490

Disclosure of the Invention

Problems to be Solved by the Invention

[0009]

Thus, an object of the present invention is to provide a compound which exhibits excellent peroral absorbability and excellent antagonistic activity against NK-1 receptor or NK-2 receptor and which is useful as a drug for preventing and/or treating diseases such as irritable bowel syndrome (IBS).

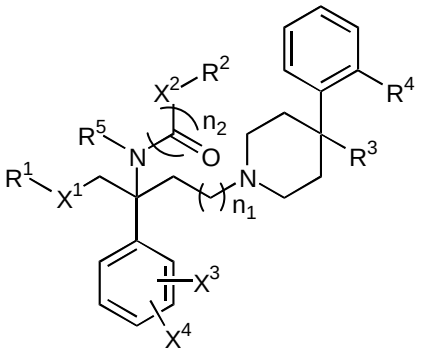
[0010]

The present inventors have conducted extensive research over years on synthesis of derivatives having tachykinin antagonistic activity (particularly, substance P antagonistic activity and antagonistic activity against neurokinin A and neurokinin B) and pharmacological activity thereof, and have found that a novel benzylamine derivative and a salt thereof exhibit excellent peroral absorbability and remarkably excellent antagonistic activity against NK-1 receptor or NK-2 receptor. The present invention has been accomplished on the basis of this finding.

[0011]

Accordingly, the present invention provides a benzylamine derivative represented by formula (1):

[F4]



(1)

[0012]

[wherein X^1 represents $-N(CH_3)-$, -NH-, or -O-;

X^2 represents a single bond, -NH-, an amido bond, an ester bond, -O-, -S-, or -CO-;

each of X^3 and X^4 represents a hydrogen atom or a halogen atom;

R^1 represents a hydrogen atom; a lower alkyl group; a phenyl group which may be substituted by 1 to 3 halogen atoms or cyano groups; a benzyl group which may be substituted by 1 to 3 lower alkyl groups, cyano groups, halogeno(lower alkyl) groups, or lower alkoxy groups; a benzoyl group which may be substituted by 1 to 3 lower alkyl groups, hydroxyl groups, halogeno(lower alkyl) groups, or lower alkoxy groups; a lower alkanoyl group which may be substituted by 1 to 5 halogen atoms, amino groups, or carbamoyl groups; a hydroxyl group; a carbamoyl group; a lower alkylsulfonyl group; a lower alkoxycarbonyl-lower alkyl group; a thienylcarbonyl group; a pyridylcarbonyl group; a lower alkylcarbonyl group; or a phenoxycarbonyl group;

R^2 represents a hydrogen atom, a lower alkyl group, a lower alkenyl group, a lower alkylsulfonyl group, a C3-C7

cycloalkyl group, a C6-C14 cycloalkyl-alkyl group, a C6-C14 aryl group, a C6-C14 aryloxy group, a C6-C14 aryloxy-lower alkyl group, C6-C14 arylthio-lower alkyl group, a C7-C16 aralkyl group, a lower alkoxycarbonyl-lower alkyl group, a lower alkoxy-lower alkyl group, an amino-lower alkyl group, a C7-C16 aralkyl group substituted by a C3-C7 cycloalkyl group, a halogeno(lower alkyl)carbonyl group, an indanyl group, a 1,2,3,4-tetrahydronaphthalenyl group, a xanthenyl group, a piperidinyl group, a pyrrolidinyl group, a morpholino group, a tetrahydroisoquinolyl group, an indolyl group, a chromenyl group, an isobenzofuranyl group, a tetrahydropyranyl group, a benzothienyl group, an adamantyl group, an adamantyl(lower alkyl) group, a fluorenyl group, a fluorenyl(lower alkyl) group, a pyridyl(lower alkyl) group, or an amino group which may be substututed by a phenyl group or a lower alkyl group (wherein a ring hydrogen of these group may be substituted by 1 to 5 atoms or groups selected from among a halogen atom, a lower alkyl group, a lower alkoxy group, a nitro group, an oxo group, a halogeno(lower alkyl) group, a C6-C14 aryl group, and a lower alkylamino group);

when R^3 represents a (lower alkanoyl)amino group, an amino(lower alkanoyl) group, an amino(lower alkanoyl)amino group, a di(lower alkyl)carbamoylamino group, or a C7-C16 aralkyloxy(lower alkyl) group, R^4 represents a hydrogen atom; or R^3 and R^4 may together form $-SOCH_2-$, $-SO_2CH_2-$, $-NHCOCH_2-$, $-CH(OH)CH_2-$, $-OCH_2-$, or $-C(=NOH)CH_2-$; R^5 represents a hydrogen atom or a lower alkyl group; n_1 is 1 or 2; and n_2 is 0 or 1]

or a salt thereof.

[0013]

The present invention also provides a drug containing, as an active ingredient, a benzylamine derivative represented by formula (1) or a salt thereof.

[0014]

The present invention also provides a pharmaceutical composition containing a benzylamine derivative represented by formula (1) or a salt thereof, and a phramaceutically acceptable carrier therefor.

[0015]

The present invention also provides use of a benzylamine derivative represented by formula (1) or a salt thereof for producing a drug.

[0016]

The present invention also provides a method for treating irritable bowel syndrome, pain, anxiety, obstructive bronchial diseases, headache, or vomiting, characterized in that the method comprises administerring, in an effective amount, a benzylamine derivative represented by formula (1) or a salt thereof.

[0017]

The benzylamine derivative of the present invention or a salt thereof exhibits remarkably excellent antagonistic activity against NK-1 receptor or NK-2 receptor. Thus, the drug of the present invention containing as an active ingredient the derivative or a salt thereof is a useful drug

for preventing and/or treating various diseases and disorders such as disorders inculduing irritable bowel syndrome (IBS), pain, anxiety, and obstructive bronchial diseases.

Best Mode for Carrying Out the Invention

[0018]

In the above formula (1), X^1 represents $-N(CH_3)-$, -NH-, or -O-, preferably $-N(CH_3)-$ or -O-. X^2 represents a single bond, -NH-, an amido bond, an ester bond, -O-, -S-, or -CO-. As used herein, the amido bond is -NHCO- or -CONH-, and the ester bond is -OCO- or -COO-. X^2 is preferably a single bond, -NH-, an amido bond, an ester bond, -O-, or -CO-, more preferably a single bond or -NH-.

[0019]

X^3 and X^4 each represent a halogen atom. Examples of the "halogen atom" include F, Cl, Br, and I. Preferably, both X^3 and X^4 are Cl, and the positions of the X^3 and X^4 are preferably the 3- and 4-positions.

[0020]

Next, R^1 will be described.

[0021]

The "lower alkyl group" is a C1-C6 linear, C1-C6 branched, or C3-C6 cyclic alkyl group, and specific examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, sec-pentyl, tert-pentyl, neopentyl, cyclopropyl, cyclopentyl, cyclohexyl. Among them, methyl, ethyl, propyl, and isopropyl are preferred, and methyl is more preferred.

[0022]

The "phenyl group which may be substituted by 1 to 3 halogen atoms or cyano groups" is a non-substituted phenyl group, and a phenyl group which has been substituted by the above halogen atom or a cyano group. When the phenyl group has been substituted by a plurality of groups, the groups may be identical to or different from one another.

[0023]

Specific examples of the phenyl group which has been substituted by a halogen atom include fluorophenyl, chlorophenyl, and bromophenyl, with chlorophenyl being preferred. Examples of the phenyl group which has been substituted by a cyano group include cyanophenyl.

[0024]

The "benzyl group which may be substituted by a lower alkyl group, a cyano group, a halogeno(lower alkyl) group, or a lower alkoxy group" is a non-substituted benzyl group, or a substituted benzyl group derived from substitution of hydrogen on phenyl with a lower alkoxy group, a cyano group, a halogeno(lower alkyl) group, or a lower alkoxy group. The number of the substituents is preferably 2 or 3, more preferably 3.

[0025]

As used herein, examples of the lower alkyl group include those described above. Examples of the "halogeno(lower alkyl) group" include trifluoromethyl, trichloromethyl, difluorochloromethyl, dichlorofluoromethyl,

difluoromethyl, dichloromethyl, monofluoromethyl, monochloromethyl, 2,2,2-trifluoroethyl, and 3,3,3-trifluoropropyl. Examples of the "lower alkoxy group" include C1-C6 linear, C1-C6 branched, and C3-C6 cyclic alkoxy groups, such as methoxy, ethoxy, n-propoxy, isopropyloxy, n-butoxy, isobutyloxy, sec-butyloxy, tert-butyloxy, cyclopentyloxy, and cyclohexyloxy. Of these, methoxy, ethoxy, and n-propoxy are preferred, with methoxy being more preferred.

[0026]

Specific examples of the benzyl group which has been substituted by a lower alkyl group include methylbenzyl, ethylbenzyl, and n-propylbenzyl.

Specific examples of the benzyl group which has been substituted by a cyano group include cyanobenzyl.

Specific examples of the benzyl group which has been substituted by a halogeno(lower alkyl) group include trifluoromethylbenzyl and bis(trifluoromethyl)benzyl.

Specific examples of the benzyl group which has been substituted by a lower alkoxy group include methoxybenzyl, dimethoxybenzyl, and 3,4,5-trimethoxybenzyl.

[0027]

The "benzoyl group which may be substituted by 1 to 3 lower alkyl groups, hydroxyl groups, halogeno(lower alkyl) groups, or lower alkoxy groups" is a non-substituted benzoyl group, or a benzoyl group which has been substituted by the above lower alkyl group, a hydroxyl group, the above

halogeno(lower alkyl) group, or the above lower alkoxy group. The number of the substituents is preferably 2 or 3. When the benzoyl group has been substituted by a plurality of groups, the groups may be identical to or different from one another.

[0028]

Examples of the benzoyl group which has been substituted by a lower alkyl group or lower alkyl groups include methylbenzoyl, ethylbenzoyl, and n-propylbenzoyl. Examples of the benzoyl group which has been substituted by a lower alkoxy group or lower alkoxy groups include methoxybenzoyl, dimethoxybenzoyl and trimethoxybenzoyl. Examples of the benzoyl group which has been substituted by a halogeno(lower alkyl) group or halogeno(lower alkyl) groups include trifluoromethylbenzoyl and bis(trifluoromethyl)benzoyl. Examples of the benzoyl group which has been substituted by a hydroxyl group (or hydroxyl groups) or a lower alkoxy group (or lower alkoxy groups) include hydroxy(dimethoxy)benzoyl.

[0029]

The "lower alkanoyl group which may be substituted by 1 to 5 of halogen atoms, amino groups, or carbamoyl groups" is a non-substituted lower alkanoyl group, or a lower alkanoyl group which has been substituted by 1 to 5 of the above halogen atoms, an amino group, and the carbamoyl groups described below. When the lower alkanoyl group has been substituted by a plurality of groups, the groups may be

identical to or different from one another.

[0030]

As used herein, the "lower alkanoyl group" is a C1-C8 alkanoyl group. Examples include formyl, acetyl, n-propionyl, n-butyryl, isobutyryl, and pivaloyl. Of these, acetyl, n-propionyl, isobutyryl, and pivaloyl are preferred, with isobutyryl being more preferred.

[0031]

Examples of the alkanoyl group which has been substituted by the above halogen atom(s) include alkanoyl groups which have been substituted by 1 to 5 of F and Cl. Specific examples include fluoroacetyl, chloroacetyl, difluoroacetyl, dichloroacetyl, difluorochloroacetyl, trifluoroacetyl, trichloroacetyl, dichlorofluoroacetyl, 3,3,3-trifluoropropionyl, 3,3,3-trichloropropionyl, 4,4,4-trifluorobutyryl, and 4,4,4-trichlorobutyryl. Of these, trifluoroacetyl, difluoroacetyl, 2,2-difluoro-2-chloroacetyl, 3,3,3-trifluoropropionyl, and 4,4,4-trifluorobutyryl are preferred, with trifluoroacetyl and 3,3,3-trifluoropropionyl being more preferred.

[0032]

Examples of the alkanoyl group which has been substituted by an amino group include aminoacetyl and 3-aminopropionyl. Examples of the alkanoyl group which has been substituted by a carbamoyl group include (chlorophenylcarbamoyl)formyl. The alkanoyl group may be substituted by a phenyl group which may have a substituent

(e.g., the above alkoxy group, phenyl). Examples of the alkanoyl group include trimethoxyphenylacetyl and phenylacetyl.

[0033]

The "carbamoyl group" is a non-substituted carbamoyl group, or a carbamoyl group which has been substituted by 1 to 2 groups such as the above lower alkyl groups, the above halogen atoms, a phenyl group, and a benzyl group. Examples of the substituted carbamoyl group include methylcarbamoyl, ethylcarbamoyl, n-propylcarbamoyl, isopropylcarbamoyl, n-butylcarbamoyl, sec-butylcarbamoyl, tert-butylcarbamoyl, n-pentylcarbamoyl, n-hexylcarbamoyl, cyclopropylcarbamoyl, cyclobutylcarbamoyl, cyclopentylcarbamoyl, cyclohexylcarbamoyl, cyclopropylmethylcarbamoyl, cyclopentylmethylcarbamoyl, dimethylcarbamoyl, methylethylcarbamoyl, diethylcarbamoyl, methylpropylcarbamoyl, methylisopropylcarbamoyl, methylcyclopropylcarbamoyl, methylcyclopropylmethylcarbamoyl, chlorobenzylaminocarbamoyl, fluorobenzylaminocarbamoyl, phenylmethylcarbamoyl, and diphenylmethylcarbamoyl.

[0034]

The "lower alkylsulfonyl group" is a sulfonyl group which has been substituted by the above lower alkyl group. Specific examples include methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, n-butylsulfonyl, and tert-butylsulfonyl, with methylsulfonyl being preferred.

[0035]

The "(lower alkoxy)carbonyl(lower alkyl) group" is a group corresponding to the above lower alkyl group which has been substituted by a (lower alkoxy)carbonyl, which is formed of a lower alkoxy group as mentioned above and a carbonyl group. Specific examples include methoxycarbonylmethyl, ethoxycarbonylmethyl, 2-methoxycarbonylethyl, and 2-ethoxycarbonylethyl, with ethoxycarbonylmethyl being preferred.

[0036]

The "(lower alkyl)carbonyl group" is a group which is formed of the above lower alkyl group and a carbonyl group. Examples include cyclopropylcarbonyl, cyclobutylcarbonyl, and cyclohexylcarbonyl.

[0037]

Next, R^2 will be described. The ring-hydrogen(s) of the group represented by R^2 may be substituted by 1 to 5 groups selected from among halogen atoms, the above lower alkyl group, the above lower alkoxy group, a nitro group, an oxo group, the above halogeno(lower alkyl) group, the aryl group described later, and the (lower alkyl)amino group described later.

[0038]

In the definition of R^2, the "lower alkyl group" is a C1-C8 linear or branched alkyl groups, and does not include the cyclic alkyl groups described later. Specific examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, sec-pentyl, tert-

pentyl, neopentyl, n-hexyl, n-heptyl, and n-octyl.

[0039]

The "lower alkenyl group" is a C2-C7 linear or branched alkenyl group. Examples include ethenyl (vinyl), 2-propenyl, 1-propenyl, 2-butenyl, 1,3-butadienyl, and isopropenyl.

[0040]

The "lower alkylsulfonyl group" is similar to those listed above in relation to R^1.

[0041]

Examples of the "C3-C7 cycloalkyl group" include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. The cycloalkyl group may further be substituted by a phenyl group. Examples include phenylcyclopentyl. The branched alkyl group, which is formed of a cycloalkyl group and a linear alkyl group, will be described later in relation to the cycloalkyl-alkyl group.

[0042]

The "C6-C14 cycloalkyl-alkyl group" is a group corresponding to the above lower alkyl group which has been substituted by a C3-C7 cycloalkyl group. As used herein, "the above lower alkyl group" is a lower alkyl group defined in relation to R^1. Specific examples include cyclopentylmethyl, cyclohexylmethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, dicyclopentylmethyl, 2,2-dicyclopentylethyl, dicyclohexylmethyl, 2,2-dicyclohexylethyl.

[0043]

Specific examples of the "C6-C14 aryl group" include

phenyl and naphthyl, with phenyl being preferred.

[0044]

Examples of the aryl group which has been substituted by a halogen atom or the like include chlorophenyl, fluorophenyl, bromophenyl, dichlorophenyl, difluorophenyl, dibromophenyl, methylphenyl, dimethylphenyl, methoxyphenyl, dimethoxyphenyl, trifluoromethylphenyl, bis(trifluoromethyl)phenyl, methylchlorophenyl, methoxychlorophenyl, methoxy(trifluoromethyl)phenyl, dichloromethylphenyl, chlorodimethylphenyl, dimethoxychlorophenyl, trifluorophenyl, trichlorophenyl, tribromophenyl, methoxyfluorochlorophenyl, methoxytrifluorophenyl, trifluoromethoxyphenyl, trimethoxyphenyl, phenylphenyl, dimethylaminophenyl, and nitrophenyl. Of these, trifluoromethylphenyl is preferred.

[0045]

Examples of the "C6-C14 aryloxy group" include phenoxy.

[0046]

Examples of the "C6-C14 aryloxy(lower alkyl) group" include phenoxymethyl.

[0047]

Examples of the "C6-C14 arylthio(lower alkyl) group" include phenylthiomethyl.

[0048]

The "C7-C16 aralkyl group" is a group formed of the above lower alkyl group and the above aryl group. Specific examples include benzyl, 1-phenylethyl, phenethyl, and

naphthylmethyl.

[0049]

The methylene group of the benzyl group may be substituted by a phenyl group which may have a substituent (examples of the substituent including the above lower alkyl group, halogen atoms, and the above lower alkoxy group). In addition, a group such as cyclopentane or cyclohexane may be spiro-bonded to the methylene group. The methylene group at the α- or β- position of the phenethyl group may be substituted by a phenyl group which may have a substituent (examples of the substituent including the above lower alkyl group, halogen atoms, and the above lower alkoxy group). Examples of the benzyl group which has been substituted by such a phenyl group include α-phenylbenzyl, α-methylbenzyl, α-methoxyphenylbenzyl, α-chlorophenylbenzyl, α-fluorophenylbenzyl, α-methoxyphenylbenzyl, α-methoxyphenyl-methoxybenzyl, α-methyl-α-phenylbenzyl, α-phenyl-chlorobenzyl, α-chlorophenyl-chlorobenzyl, α-cyclopropylbenzyl, α-cyclobutylbenzyl, α-cyclopentylbenzyl, α-cyclohexylbenzyl, and α-dimethylaminophenylbenzyl, with α-phenylbenzyl being preferred. Examples of the phenethyl group which has been substituted by a phenyl group include α,α-diphenylethyl, α,β-diphenylethyl, and β,β-diphenylethyl, with β,β-diphenylethyl being preferred.

[0050]

Specific examples of the benzyl group derived from substitution of ring-hydrogen with a halogen atom or the like

include chlorobenzyl, fluorobenzyl, bromobenzyl, dichlorobenzyl, difluorobenzyl, dibromobenzyl, methylbenzyl, dimethylbenzyl, trimethylbenzyl, methoxybenzyl, dimethoxybenzyl, trimethoxybenzyl, trifluoromethylbenzyl, and nitrobenzyl.

[0051]

The "(lower alkoxy)carbonyl(lower alkyl) group" is similar to those listed above in relation to R^1. Ethoxycarbonylmethyl is preferred.

[0052]

The "(lower alkoxy)(lower alkyl) group" is a group corresponding to the above lower alkyl group which has been substituted by the above lower alkoxy group. Examples include methoxymethyl, ethoxymethyl, n-propoxymethyl, ethoxymethyl, ethoxyethyl, and ethoxypropyl.

[0053]

The "amino(lower alkyl) group" is, for example, a group corresponding to the above lower alkyl group which has been substituted by an amino group. The amino group may be substituted by the above aryl group or the above aralkyl group. Examples include phenylaminomethyl, phenylaminoethyl, benzylaminomethyl, and benzylaminoethyl.

[0054]

The "C7-C16 aralkyl group which has been substituted by a C3-C7 cycloalkyl group" is a C7-C16 aralkyl group which has been substituted by the above C3-C7 cycloalkyl group. Examples include groups derived from a benzyl group whose

methylene group has been substituted by a cyclopentyl group, a cyclohexyl group, a cycloheptyl group, or a similar group. Cyclopropylbenzyl, cyclobutylbenzyl, cyclopentylbenzyl, and cyclohexylbenzyl are preferred, among others.

[0055]

The "halogeno(lower alkyl)carbonyl group" is a group formed of the above halogeno(lower alkyl) group and a carbonyl group. Examples include chloromethylcarbonyl, dichloromethylcarbonyl, fluoromethylcarbonyl, difluoromethylcarbonyl, chloroethylcarbonyl, 2,2-dichloroethylcarbonyl, fluoroethylcarbonyl, and 2,2-difluoroethylcarbonyl.

[0056]

The "amino group which may be substituted by a phenyl group or a lower alkyl group" is a non-substituted amino group, or an amino group which has been substituted by a phenyl group or the above lower alkyl group (an amino group which has been substituted by the above lower alkyl group is referred to as "(lower alkyl)amino group"). The ring-hydrogen on phenyl may be substituted by any of the above substituents. Specific examples of the amino group which has been substituted by a phenyl group include phenylamino, N,N-diphenylamino, and tolylamino (p-methylphenylamino). Specific examples of the (lower alkyl)amino group include methylamino, dimethylamino, ethylamino, diethylamino, and n-propylamino. Specific examples of the amino group which has been substituted by the phenyl group and the (lower

alkyl)amino group include N-phenyl-N-methylamino, N-cyclohexyl-N-methylamino, N-cyclohexyl-N-phenylamino, N-tolyl-N-methylamino, and N-phenyl-N-ethylamino.

[0057]

Other examples of the group represented by R^2 include fluorenyl, indanyl, 1,2,3,4-tetrahydronaphthalenyl, xanthenyl, piperidinyl, pyrrolidinyl, morpholino, tetrahydroisoquinolyl, indolyl, chromenyl, isobenzofuranyl, tetrahydropyranyl, benzothienyl, adamantyl, fluorenyl(lower alkyl), adamantyl(lower alkyl), and pyridyl(lower alkyl). The "fluorenyl(lower alkyl) group" is a group corresponding to the above lower alkyl group which has been substituted by a fluorenyl group, and examples include fluorenylmethyl. The "adamantyl(lower alkyl) group" is a group corresponding to the above lower alkyl group which has been substituted by an adamantyl group, and examples include adamantylmethyl. The "pyridyl(lower alkyl) group" is a group corresponding to the above lower alkyl group which has been substituted by a pyridyl group, and examples include pyridylmethyl. These groups may be substituted by any of the above substituents (1 to 5 atoms or groups selected from among halogen atoms, the above lower alkyl group, the above lower alkoxy group, nitro group, oxo group, the above halogeno(lower alkyl) group, the above aryl group, the above lower alkylamino group). Examples include methylindolyl and oxochromenyl.

[0058]

Among these R^2, a C7-C16 aralkyl group, a lower alkyl

group, a C6-C14 aryl group, a C3-C7 cycloalkyl group, and an amino group which may be substituted by a phenyl group or a lower alkyl group are preferred.

[0059]

When R^3 represents a (lower alkanoyl)amino group, amino(lower alkanoyl) group, amino(lower alkanoyl)amino group, di(lower alkyl)carbamoylamino group, or aralkyloxy(lower alkyl) group, R^4 represents a hydrogen atom, or R^3 and R^4 together form $-SOCH_2-$, $-SO_2CH_2-$, $-NHCOCH_2-$, $-C(=NOH)CH_2-$, $-CH(OH)CH_2-$, or $-OCH_2-$. Preferably, R^3 and R^4 together form $-SOCH_2-$, $-SO_2CH_2-$, $-NHCOCH_2-$, $-CH(OH)CH_2-$, $-OCH_2-$, or $-C(=NOH)CH_2-$.

[0060]

As used herein, the "(lower alkanoyl)amino group" is an amino group which has been substituted by the above lower alkanoyl group. Specific examples include acetylamino, propionylamino, butyrylamino, and pivaloylamino. The "amino(lower alkanoyl) group" is a group corresponding to the above alkanoyl group which has been substituted by an amino group. Specific examples include aminoacetyl, aminopropionyl, and aminobutyryl. The "amino(lower alkanoyl)amino group" is a group corresponding to the above (lower alkanoyl)amino group which has been substituted by an amino group. Specific examples include aminoacetylamino, aminopropionylamino, aminobutyrylamino, and aminopivaloylamino. The "di(lower alkyl)carbamoylamino group" is an amino group which has been substituted by a carbamoyl group which has been substituted

by two of the above lower alkyl groups. Examples include dimethylcarbamoylamino and diethylcarbamoylamino. The "aralkyloxy(lower alkyl) group" is a group corresponding to the above lower alkyl group which has been substituted by an aralkyloxy group having the above aralkyl group. Examples include benzyloxymethyl.

[0061]

Examples of the lower alkyl group represented by R^5 include those listed above, with methyl being preferred.

[0062]

n_1 denotes 1 or 2, with 1 being preferred. n_2 denotes 0 or 1, with 1 being preferred.

[0063]

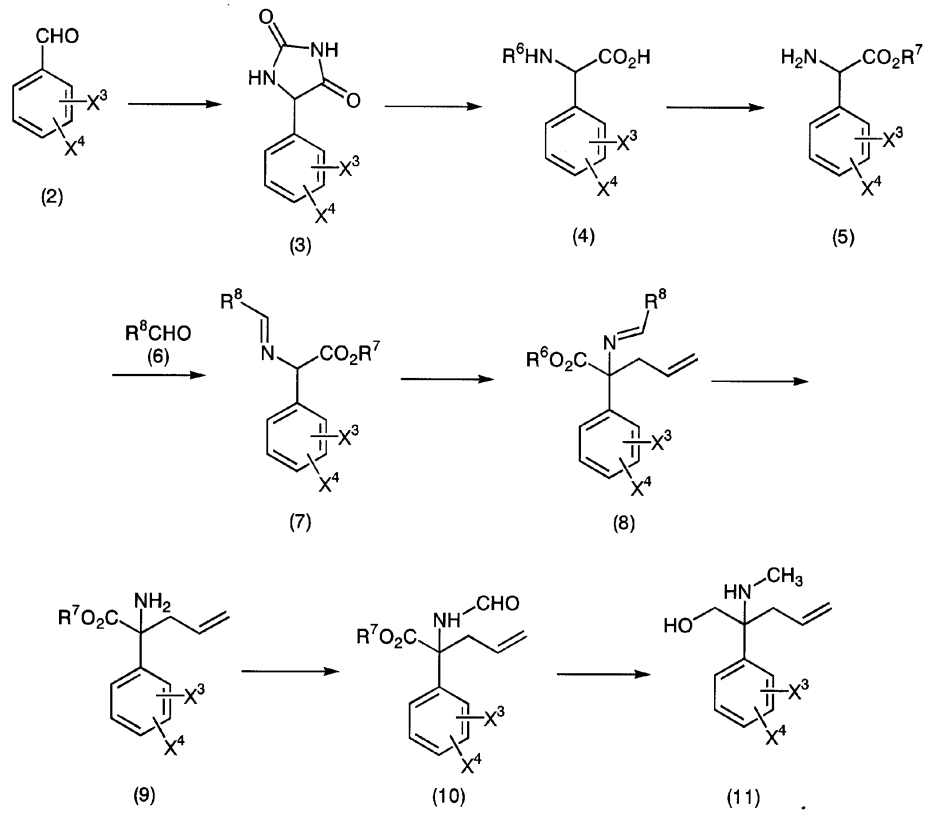
No particular limitation is imposed on the salt of the present invention and a salt thereof, so long as the salt is pharmaceutically acceptable. Examples of the salt include acid-addition salts such as hydrochlorides, sulfates, nitrates, hydrobromides, p-toluenesulfonates, methanesulfonates, fumarates, succinates, and lactates. Of these, hydrochlorides are preferred. The compound of the present invention and a salt thereof also encompass solvates thereof. The compound of the present invention includes optically active species attributable to an asymmetric carbon atom or other structural features. These optically active species and mixtures thereof also fall within the scope of the present invention.

[0064]

The compound of the present invention or a salt thereof may be produced via an intermediate, for example, a 2-methylaminopentenol derivative (11). Specifically, compound (11) can be produced through the following scheme:

[0065]

[F5]



[0066]

[wherein X^3 and X^4 have the same meanings as defined above; R^6 represents a protective group for an amino group; R^7 represents the aforementioned lower alkyl group; and R^8 represents a tert-butyl group or a phenyl group].

[0067]

Specifically, commercial benzaldehyde (2) is dissolved

in a solvent such as ethanol-water in the presence of ammonium carbonate, followed by reacting with potassium cyanate, to thereby form compound (3). The imidazolidine ring of the compound (3) is opened with a base, and amino groups are protected with an appropriate protective group, to thereby form compound (4). Examples of the base employed for opening the imidazolidine ring include sodium hydroxide, potassium hydroxide, and barium hydroxide. Among them, sodium hydroxide is preferred. Examples of the protective group include a benzyloxycarbonyl group (Z group), a trifluoroacetyl group, and a tert-butoxycarbonyl group (Boc group). Of these, a Boc group is preferred. Alternatively, benzaldehyde (2) can be produced through a known production method.

[0068]

Subsequently, compound (4) is reacted with an acid source (i.e., reagent generating acid in the reaction system) in a solvent such as alcohol, whereby deprotection of amino groups and esterification can be performed. The thus-formed ester compound (5) is reacted with aldehyde (6) in the presence of a base in a solvent such as acetonitrile, to thereby form compound (7). Examples of the acid source employed in esterification include thionyl chloride, hydrochloric acid, sulfuric acid, nitric acid, hydrofluoric acid, hydrobromic acid, hydroiodic acid, p-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid, trichloroacetic acid, acetic acid, and formic acid. Of these

thionyl chloride is preferred. The aldehyde (6) is preferably benzaldehyde.

[0069]

Compound (8) can be produced by dissolving compound (7) in an estric solvent such as ethyl acetate, in a halogen-containing solvent such as chloromethylene (preferably ethyl acetate) and treating the solution with allyl bromide in the presence of a base and a phase transfer catalyst. Examples of the base include potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, potassium tert-butoxide. Examples of the phase transfer catalyst include n-tetrabutylammonium bromide, n-tetrabutylammonium chloride, and n-tetrabutylammonium sulfate.

[0070]

The compound (8) is treated with acid to form compound (9), and subsequently, formic acid and acetic anhydride are reacted with compound (9), to thereby produce compound (10). The compound (10) is reduced, to thereby form an intermediate (11) for producing the compound of the present invention. Examples of the acid employed in treating of compound (8) include hydrochloric acid, sulfiruc acid, nitric acid, hydrofluoric acid, hydrobromic acid, and hydroiodic acid. Of these hydrochloric acid is preferred. Preferably, the compound (10) is reduced by use of a reducing agent such as aluminum lithium hydride, sodium borohydride, boroacetic acid (in situ preparation from sodium borohydride and acetic acid), diisobutylaluinum hydride, or sodium bis(2-

methoxyethoxy)aluminum hydride (Red-Al).

[0071]

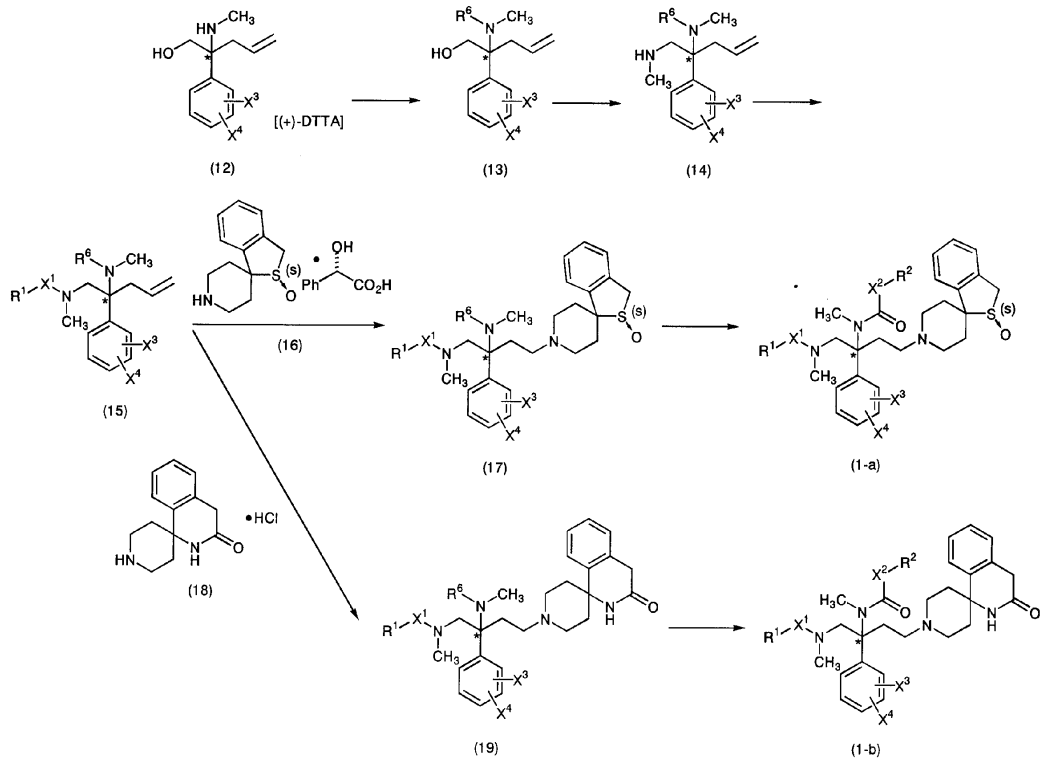
Compound (11), which is a mixture of diastereomers, can be derived to an optically active species through routine optical resolution. For example, compound (11) is reacted with (+)-di-p-toluoyl-D-tartaric acid (hereinafter referred to as "(+)-DTTA"), to thereby form a diastereomer salt mixture containing a racemic mixture of compound (11) and an optical resolution agent. Subsequently, a diastereomer salt of interest is separated through precipitation or a similar technique, followed by optional recrystallization, and the thus-separated diastereomer salt is treated with alkali. The diesteromer salt not treated with alkali may also be used. Preferably, an optical active species of compound (11) is employed as an intermediate in production of the compound of the present invention.

[0072]

The compound of the present invention or a salt thereof may be produced through the following scheme:

[0073]

[F6]



[0074]

[wherein R^1, R^2, R^6, X^1, X^2, X^3 and X^4 have the same meanigs as defined above].

[0075]

The amino group of the optical active species (12) of compound (11), produced through the above method, is protected in a routine manner, to thereby form compound (13). The compound (13) is sequentially oxidized and methylaminated, to thereby produce compound (14). The oxidation may be performed by dissolving copound (13) in a solvent such as dimethyl sulfoxide, and treating the solution with sulfur trioxide-pyridine in the presence of a base such as triethylamine, or treating the solution with tetrapropylammonium perruthenate in the presence of N-

methylmorpholine-N-oxide. Methylamination may be performed by dissolving aldehyde of compound (13) in a solvent such as methanol, adding methylamine to the solution, refluxing the mixture to thereby form an imine (Schiff base), and refluxing the imine with a reducing agent such as sodium borocyanohydride or sodium borohydride.

[0076]

In order to produce compound (15) by introducing R^1 group in formula (1) into the amino group of compound (14), the compiund (14) is dissolved in a solvent such as acetonitrile, and acid chloride (R^1-Cl) is reacted with the solution in the presence of a base such as triethylamine. When acid chlorides, trifluoropropionyl chloride, pivaloyl chloride, and propionyl chloride, are used, compounds Nos. 1, 2, and 5, respectively, described later in the Examples can be produced. The acid chloride may be prepared from the corresponding carboxylic acid in a routine manner. In this case, reaction is preferably performed under cooling with ice. Alternatively, instead of acid chloride, anhydride of trifluoroacetic acid, chlorodifluoroacetic acid, etc. may also be employed for introducing R^1 group, whereby compounds Nos. 3 and 4 described later in the Examples can be produced.

[0077]

Subsequently, the vinyl group of compound (15) is treated with osmium tetraoxide, to thereby form a diol species, which is oxidized by sodium periodate, to thereby form an aldehyde. The aldehyde is reacted with separately

prepared spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide/(S)-(+)-mandelate (16), to thereby form the corresponding imine. This imine is reduced, to thereby produce compound (17). Examples of the reducing agent include sodium cyanoborohydride.

[0078]

When the aldehyde obtained from compound (15) is reacted with spiro[isoquinoline-1(2H),4'-piperidine]-3(4H) monohydrochloride (18) instead of compound (16), followed by reacting a reducing agent, compound (19) can be produced.

[0079]

Through reaction with the corresponding piperidine species, the invention compounds in which R^3 and R^4 together form $-SO_2CH_2-$ or $-CH(OH)CH_2-$ can be produced in a similar manner as described above.

[0080]

Conversion of compound (17) to the compound of the present invention (1-a) may be carried out by deprotecting the amino group of compound (17) with trifluoroacetic acid or a similar reagent and reacting the deprotected species with an acid chloride(R^2-X^2-COCl) in a solvent such as acetonitrile in the presence of a base. For example, when 3,3-diphenylpropionyl chloride is used as an acid chloride, hydrochloride of compound No. 1 described later in the Examples can be produced. In this case, reaction is preferably performed under cooling with ice.

[0081]

Conversion of compound (19) to the compound of the present invention (1-b) may be carried out by deprotecting compound (17) in a manner that employed in conversion to compound (1-a), and reacting the deprotected species with an isocyanate (R^2-NCO) in an inert solvent such as tetrahydrofuran. For example, when diphenylmethyl isosyanate is used as an isocyanate, hydrochlorides of compounds Nos. 3 and 4 described later in the Examples can be produced.

[0082]

Compounds according to the present invention in which X^2 is -NHCO- or -OCO- can be produced in a similar manner as described above.

[0083]

The compound of the present invention and a salt thereof exhibited excellent antagonistic activity against NK-1 receptor and/or NK-2 receptor as mentioned in the test Examples described later. Particularly, the following compounds and salts falling within the scope of the present invention exhibited remarkably excellent NK-2 receptor antagonistic activity, and antagonistic activity against NK-1 and NK-2 receptors.

(I) Compounds and salts exhibiting NK-2 receptor antagonistic activity;

(1-1) Compounds and salts in which X^2 is a single bond.

(1-2) The above compounds and salts (1-1) in which R^3 and R^4 together form -NHCOCH$_3$- are more preferred.

(1-3) The above compounds and salts (1-2) in which R^2

represents a C6-C14 aryl group or a C7-C16 aralkyl group are particularly preferred. A ring hydrogen atom of these groups may be substituted by 1 to 5 atoms and groups selected from among a halogen atom, a lower alkyl group, a lower alkoxy group, a nitro group, an oxo group, a halogeno(lower alkyl) group, a C6-C14 aryl group, and a lower alkylamino group. Examples of the aryl group and aralkyl group include phenyl and trifluoromethylphenyl.

(II) Compounds and salts exhibiting NK-1 and NK-2 receptors antagonistic activity;

(2-1) Compounds and salts in which R^2 represents a C6-C14 aryl group, or an amino group which may be substituted with a phenyl group. A ring hydrogen atom of these groups may be substituted by 1 to 5 atoms or groups selected from among a halogen atom, a lower alkyl group, a lower alkoxy group, a nitro group, an oxo group, a halogeno(lower alkyl) group, a C6-C14 aryl group, and a lower alkylamino group. Examples of the aryl group and amino group include α-phenylbenzyl, α-chlorophenylbenzyl, α-dimethylaminophenylbenzyl, α,α-diphenylethyl, β,β-diphenylethyl, and N,N-diphenylamino.

(2-2) The above compounds and salts (2-1) in which X^1 represents NH or a single bond are more preferred.

(2-3) The above compounds and salts (2-2) in which R^3 represents $-SOCH_2-$ or $-NHCOCH_2-$ are further more preferred.

(2-4) The above compounds and salts (2-3) in which R^1 represents a lower alkanoyl group which may be substituted by 1 to 5 halogen atoms are particularly preferred.

[0084]

Accordingly, the compound of the present invention or a salt thereof is an effective ingredient as a drug, particularly as a drug for preventing and/or treating diseases related to tachykinin.

Examples of the diseases related to tachykinin include those related to the central nervous system, including anxiety, depression, psycopathy, and shizophrenia; nerve degeneration diseases including AIDS-associated dementia, senile dementia of Alzheimer type, Alzheimer's disease, Down's syndrome, demyelinating disease, amyotrophic lateral sclerosis, neuropathy, peripheral neuropathy, and neuralgia; respiratory diseases including chronic obstructive pulmonary disease, bronchitis, pneumonia, bronchoconstriction, asthma, cough; inflammatory diseases including Inflammatory Bowel Diesease (IBD), psoriasis, fibrositis, osteoarthritis, degenerative arthritis, and articular rheumatism; eczema; and allergic diseases including rhinitis; irritable diseases including those caused by vine plants; irritable bowel syndrome (IBS); ophthalmological diseases including conjunctivitis, vernal conjunctivitis, spring catarrh, destruction of the blood-aqueous humor barrier associated with various inflammatory ophthalmological diseases, elevation of inside pressure of the ocular chamber, miosis; skin diseases including contact dermatitis, atopic dermatitis, hives, and other skin diseases including eczema-like dermatitis; addictions including alcohol dependence;

physically expressed pathological condition caused by stress; reflex sympathetic dystrophy including shoulder-hand syndrome; dysthymia; immunoenhancement- or immunosuppression-related diseases including undesired immunoreactions (such as rejection of grafts) and systemic lupus erythematosus; digestive diseases including diseases caused by abnormality of the nerve controlling the internal organs, colitis, ulcerative colitis, Crohn's disease; emesises induced by X-ray irradiation, chemotherapeutic agents, poisons, toxins, pregnancy, vestibular disorder, postoperative disease, gastrointestinal obstruction, reduction of gastrointestinal motility, visceral pain, migraine, increase in intracranial pressure, decrease in intracranial pressure, and an emesis as a side effect caused by administration of various drugs; bladder function disorders including cystitis and urinary incontinence; collagen disease, scleroderma, and eosinophilia caused by fascila hepatica; diseases caused by anomalous blood flow by vasodilatation or vasoconstriction, including angina, migraine, and Raynaud's disease; pains involving the pain-nociceptor, including migraine, headache, and toothache.

[0085]

The compound of the present invention or a salt thereof may be administered perorally or parenterally. Examples of the peroral form include tablets, capsules, granules, powder, and syrup. Examples of the parenteral form include injections and suppositories.

Such drug preparations may be produced through any

suitable known method by use of a variety of additives: excipients (e.g., sugar derivatives such as lactose, sucrose, glucose, mannite, and sorbit; starch derivatives such as corn starch, potato starch, α-starch, dextrin, and carboxymethylstarch; cellulose derivatives such as crystalline cellulose, low-substituted hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, carboxymethylcellulose calcium, and internal-cross-linked carboxymethylcellulose sodium; organic excipients such as acacia, dextran, and pullulan; silicate derivatives such as light anhydrous silicic acid, synthetic aluminum silicate, and magnesium metasilicate aluminate; and inorganic excipients such as phosphates (e.g, calcium phosphate), carbonates (e.g., calcium carbonate), and sulfates (e.g., calcium sulfate)); lubricants (e.g., metal stearates such as stearic acid, calcium stearate, and magnesium stearate; talc; colloidal silica; waxes such as veegum and spermaceti; boric acid; adipic acid; sulfates such as sodium sulfate; glycol; fumaric acid; sodium benzoate; DL-leucine; fatty acid sodium salts; lauryl sulfates such as sodium lauryl sulfate and magnesium lauryl sulfate; silicates such as silicic acid anhydrate and silicic acid hydrate; and the aforementioned starch derivatives); binders (e.g., poly(vinylpyrrolidone), macrogol, and the same compounds as mentioned in relation to above excipients); disintegrants (e.g., the same compounds as mentioned in relation to the above excipients and chemically modified starch/cellulose species such as sodium

croscarmellose, sodium carboxymethylstarch, and cross-linked poly(vinylpyrrolidone)), stabilizers (e.g., paraoxybenzoates such as methylparaben and propylparaben; alcohols such as chlorobutanol, benzyl alcohol, and phenylethyl alcohol; benzalkonium chloride; phenols such as phenol and cresol; thimerosal; dehydroacetic acid; and sorbic acid); sweetening and flavoring agents (e.g., generally employed sweeteners, sour agents, flavors), and diluents.

[0086]

When the compound of the present invention or a salt thereof is employed as a drug, the dose to humans varies in accordance with the condition, age, sex, administration method, and other factors of patients. For example, in peroral administration, preferably 0.01 to 100 mg/kg-body weight, more preferably 0.1 to 50 mg/kg-body weight, is administered at a time, and in intravenous diministration, preferably 0.01 to 100 mg/kg-body weight, more preferably 0.05 to 50 mg/kg-body weight, is administered at a time. The drug is preferably administered once to several times per day, depending on the condition.

Examples

[0087]

The present invention will next be described in more detail by way of Examples, which should not be construed as limiting the invention thereto. In the following Examples, all the optically active species were derived through resolution by use of (+)-DTTA.

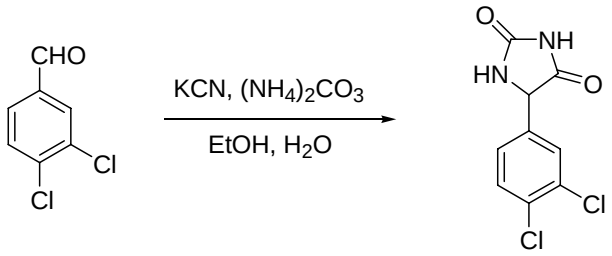
[0088]

Example 1(a)

Synthesis of 5-(3,4-dichlorophenyl)-imidazolidine-2,4-dione

[0089]

[F7]



[0090]

3,4-Dichlorobenzaldehyde (500 g), potassium cyanide (279 g), and ammonium carbonate (824 g) were dissolved in a solvent mixture of ethanol (1.25 L) and water (1.25 L), followed by stirring at an internal temperature of 60 to 65°C for 1 hour. The reaction mixture was left to cool to room temperature, and ethanol was evaporated under reduced pressure. Water was added to the residue, followed by filtration and drying, to thereby give the title compound (900 g). The title compound was used in the next step without further purification.

[0091]

mp. 223.0-225.0°C

MS (EI) m/z 244 (M^+)

^{1}H-NMR (270MHz, DMSO-d_6)δ ppm:5.26 (1H, s),7.35 (1H, dd, J=2.0, 8.5Hz),7.60 (1H, d, J=2.0Hz),7.69 (1H, d, J=8.0Hz),8.46 (1H, s),10.90 (1H, br).

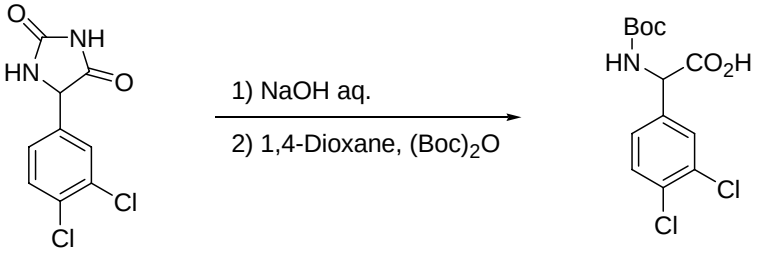
[0092]

Example 1(b)

Synthesis of tert-butoxycarbonylamino-(3,4-dichlorophenyl)-acetic acid

[0093]

[F8]



[0094]

5-(3,4-Dichlorophenyl)-imidazolidine-2,4-dione (900 g) was dissolved in 25% aqueous sodium hydroxide solution (3.66 L), followed by refluxing for 3 hours. The resultant mixture was cooled with ice to an internal temperature of 20°C or lower. 1,4-Dioxane (1.83 L) and di-tert-butoxydicarbonate (936 g) were added to the mixture, and the mixture was stired at an internal temperature of 15 to 25°C for one hour. Concentrated hydrochloric acid (2.4 L) and 1N aqueous potassium hydrogensulfate (1.7 L) were sequentially added to the mixture to adjust the pH to 4. The insoluble matter was passed through Celite, followed by washing with ethyl acetate. The filtrate was subjected to partitioning and then extraction with ethyl acetate. The organic layer was washed with saturated brine (1 L), dried over sodium sulfate anhydrate, and concentrated under reduced pressure, to thereby give the title compound (900 g). The title compound was used in the next step without further purification.

[0095]

MS (EI) m/z 319 (M^+)

^{1}H-NMR (270MHz, DMSO-d_6, 60°C)δ ppm:1.37 (9H, s),5.05 (1H, d, J=7.5Hz),7.19-7.51 (1H, br),7.37 (1H, dd, J=2.0, 8.5Hz),7.56 (1H, d, J=8.5Hz),7.62 (1H, d, J=2.0Hz).

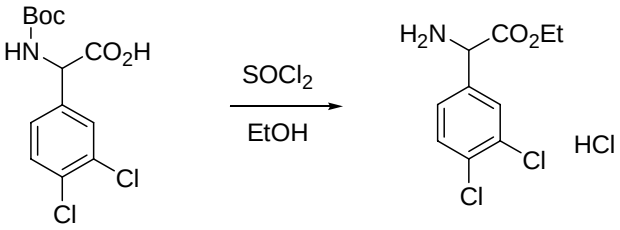
[0096]

Example 1(c)

Synthesis of ethyl amino-(3,4-dichlorophenyl)-acetate hydrochloride

[0097]

[F9]



[0098]

tert-Butoxycarbonylamino-(3,4-dichlorophenyl)-acetic acid (900 g) was dissolved in ethanol (4.5 L). Thionyl chloride (417 mL) was added to the resultant solution, followed by refluxing for one hour. The reaction mixture was left to cool to room temperature. The solvent was evaporated under reduced pressure. Ethyl acetate was added to the residue, followed by filtration and drying, to thereby give the title compound (286 g, 35%, 3 steps).

[0099]

mp. 171.0-174.0°C

MS (EI) m/z 247 (M^+)

^{1}H-NMR (270MHz, DMSO-d_6)δ ppm:1.15 (3H, t, J=7.0Hz),4.10-4.30 (2H, m),5.37 (1H, s),7.55 (1H, dd, J=2.0, 8.5Hz),7.75 (1H, d, J=8.5Hz),7.91 (1H,s),9.35 (3H, br).

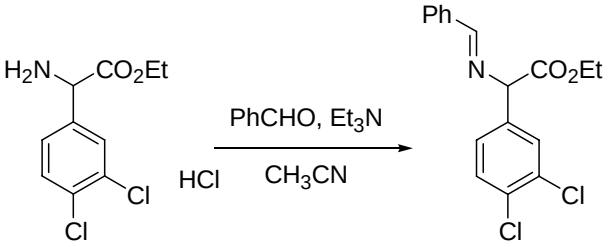
[0100]

Example 1(d)

Synthesis of ethyl (benzylidene-amino)-(3,4-dichlorophenyl) acetate

[0101]

[F10]



[0102]

Triethylamine (170 mL) and benzaldehyde (130 mL) were added to a suspension of ethyl amino-(3,4-dichlorophenyl)-acetate hydrochloride (350 g) in acetonitrile (1.5 L), followed by stirring at room temperature overnight. The insoluble matter was removed through Celite, followed by washing with ethyl acetate. The filtrate was subjected to partitioning with water and then extraction with ethyl acetate. The thus-obtained organic layer was washed with saturated brine, and then dried over sodium sulfate anhydrate. The solvent was removed under reduced pressure, to thereby give the title compound (425 g). The title compound was used in the next step without further purification.

[0103]

MS (EI) m/z 335 (M^+)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.24 (3H, t, J=7.0Hz),4.20 (2H, q, J=7.0Hz),5.10 (1H, s),7.36-7.60 (5H, m),7.66 (1H, s),7.81-7.97 (2H, m),8.36 (1H, s).

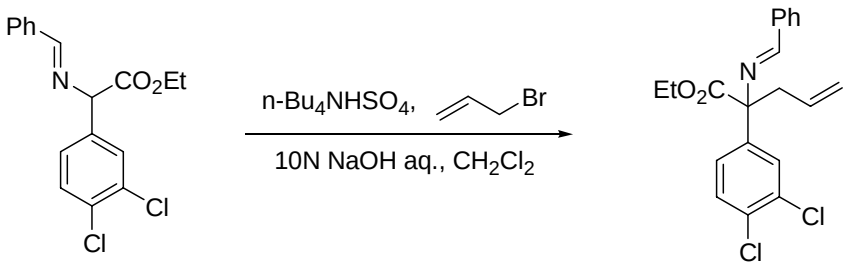
[0104]

Example 1(e1)

Synthesis of ethyl 2-(benzylidene-amino)-2-(3,4-dichlorophenyl)-4-pentenoate

[0105]

[F11]



[0106]

Ethyl (benzylidene-amino)-(3,4-dichlorophenyl) acetate (425 g) was dissolved in methylene chloride (1.8 L). 10N Aqueous sodium hydroxide (1.2 L), allyl bromide (158 mL), and tetrabutylammonium sulfate (41 g) were added to the resultant solution, followed by stirring at room temperature for one hour. The reaction mixture was subjected to partitioning. Water (1 L) was added to the aqueous layer, and then the mixture was extracted with methylene chloride. The thus-obtained organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure, to thereby give the title compound (518 g). The

title compound was used in the next step without further purification.

[0107]

MS (EI) m/z 375 (M^+)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.20 (3H, t, J=7.0Hz),2.90 (1H, dd, J=7.0, 14Hz),3.05 (1H, dd, J=7.0, 14Hz),4.21 (2H, q, J=7.0Hz),4.92-5.10 (2H, m),5.61-5.81 (1H, m),7.30-7.60 (5H, m),7.72 (1H, s),7.80-7.93 (2H, m),8.22 (1H, s).

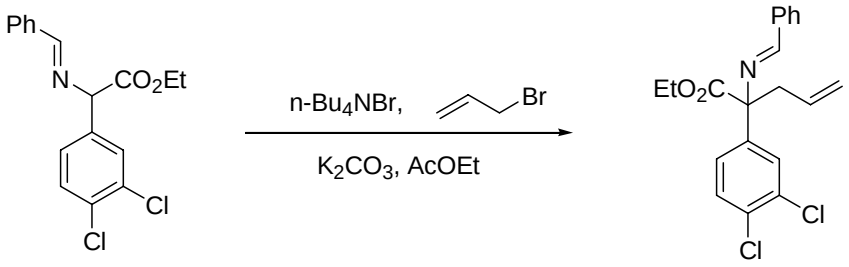
[0108]

Example 1(e2)

Synthesis of ethyl 2-(benzylidene-amino)-2-(3,4-dichlorophenyl)-4-pentenoate (alternative method)

[0109]

[F12]



[0110]

Ethyl (benzylidene-amino)-(3,4-dichlorophenyl)-acetate (1.41 mol) was dissolved in ethyl acetate (2.3 L). Allyl bromide (341 g), potassium carbonate (390 g), and tetrabutylammonium bromide (45 g) were added to the resultant mixture, followed by refluxing for 2.5 hours. The reaction mixture was left to cool to room temperature. The mixture was sequentially washed with water and saturated brine, dried

over sodium sulfate anhydrate, and concentrated under reduced pressure, to thereby give the title compound (500 g, 94%).

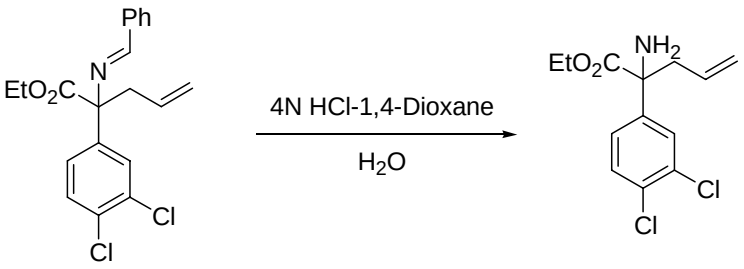
[0111]

Example 1(f)

Synthesis of ethyl 2-amino-2-(3,4-dichlorophenyl)-4-pentenoate

[0112]

[F13]



[0113]

4N HCl-1,4-dioxane (308 mL) and water (65 mL) were added to ethyl 2-(benzylidene-amino)-2-(3,4-dichlorophenyl)-4-pentenoate (518 g), followed by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. Water (1 L) and 1N aqueous hydrochloric acid (500 mL) were added to the residue, and the mixture was washed with diisopropyl ether (500 mL) three times. 25% Aqueous sodium hydroxide (250 mL) was added to the aqueous layer to adjust the pH to 9. The resultant mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate anhydrate. The solvent was removed under reduced pressure, to thereby give the title compound (231 g). The title

compound was used in the next step without further purification.

MS (EI) m/z 287 (M^+)

[0114]

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.26 (3H, t, J=7.0Hz),1.75-2.05 (2H, br),2.59 (1H, dd, J=8.0, 14.0Hz),2.94 (1H, dd, J=6.5, 14.0Hz),4.19 (2H, q, J=7.0Hz),5.16 (1H, s),5.21 (1H, d, J=4.0Hz),5.58-5.80 (1H, m),7.41 (2H, s),7.72 (1H, s).

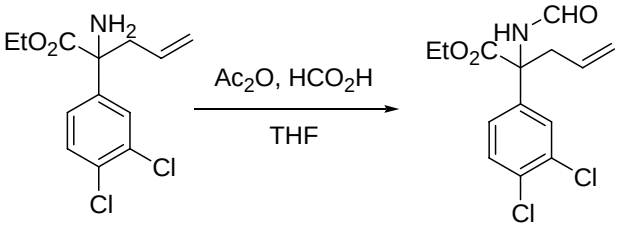
[0115]

Example 1(g)

Synthesis of ethyl 2-(3,4-dichlorophenyl)-2-formylamino-4-pentenoate

[0116]

[F14]



[0117]

Under cooling on ice, formic acid (140 mL) was added to acetic anhydride (255 mL), followed by stirring at 50°C for 30 minutes. The reaction mixture was cooled with ice. Subsequently, ethyl 2-amino-2-(3,4-dichlorophenyl)-4-pentenoate (298 g) in tetrahydrofuran (1.5 L) was added to the mixture, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure. The residue was neutaralized with

saturated aqueous sodium bicarbonate. The resultant mixture was subjected to extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate anhydrate. The solvent was removed under reduced pressure, to thereby give the title compound (334 g). The title compound was used in the next step without further purification.

[0118]

MS (EI) m/z 315 (M^+)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.20 (3H, t, J=7.0Hz),3.15 (1H, dd, J=7.5, 13.5Hz),3.60 (1H, dd, J=7.0, 13.5Hz),4.06-4.31 (2H, m),5.13-5.32 (2H, m),5.54-5.72 (1H, m),7.09 (1H, s),7.28 (1H, dd, J=2.5, 8.5Hz),7.42 (1H, d, J=8.5Hz),7.53 (1H, d, J=2.5Hz),8.20 (1H, s).

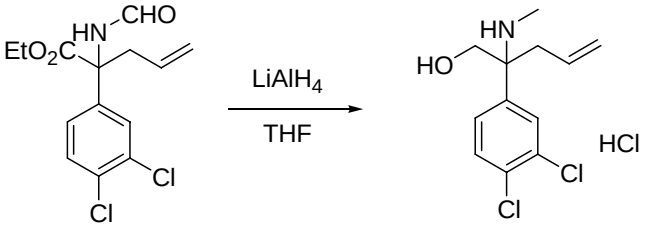
[0119]

Example 1(h)

Synthesis of 2-(3,4-dichlorophenyl)-2-methylamino-4-pentenol hydrochloride

[0120]

[F15]



[0121]

Under argon flow, lithium aluminum hydride (78 g) was suspended in dehydrated tetrahydrofuran (1 L). Ethyl 2-(3,4-

dichlorophenyl)-2-formylamino-4-pentenoate (334 g) in dehydrated tetrahydrofuran (1 L) was added to the suspension at room temperature, followed by refluxing for 15 minutes. After the mixture was cooled with ice, water (78 mL), 15% aqueous sodium hydroxide (78 mL), and then water (234 mL) were added to the mixture, and the resultant mixture was stirred at room temperature for one hour. The insoluble matter was passed through Celite, followed by washing with ethyl acetate. The filtrate was dried over magnesium sulfate anhydrate and concentrated under reduced pressure until the volume of the solution was decreased to 1 L. 4N HCl-1,4-dioxane (260 mL) was added to the residue, and the mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue, followed by filtration and drying, to thereby give the title compound (260 g, 69%, 5 steps).

[0122]

mp. 225.5-232.5°C

MS (EI) m/z 259 (M^+)

^{1}H-NMR (270MHz, DMSO-d_6)δ ppm:2.38 (3H, s),2.83 (2H, d, J=7.0Hz),3.94 (1H, d, J=12.0Hz),4.00 (1H, d, J=12.0Hz),5.00-5.20 (2H, m),5.35-5.57 (1H,m),5.98 (1H, br),7.63 (1H, dd, J=1.5, 8.5Hz),7.71 (1H, d, J=8.5Hz),7.94(1H, d, J=1.5Hz),9.31 (1H, br),9.62 (1H, br).

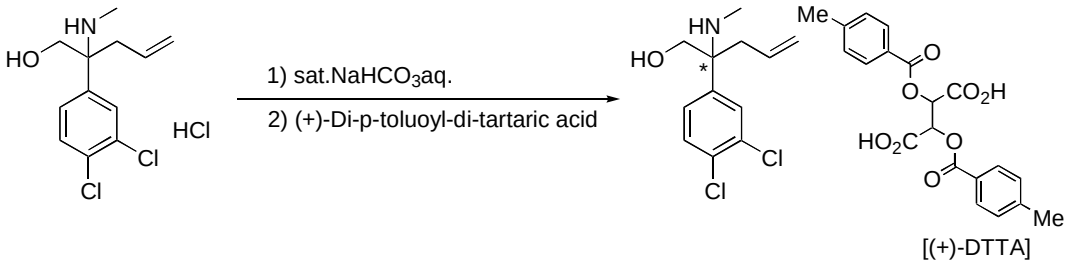
[0123]

Example 1(i)

Optical resolution of 2-(3,4-dichlorophenyl)-2-methylamino-4-pentenol (synthesis of (+)-di-p-toluoyl-D-tartrate)

[0124]

[F16]



[0125]

Ethyl acetate (2 L) and saturated aqueous sodium bicarbonate (2 L) were added to 2-(3,4-dichlorophenyl)-2-methylamino-4-pentenol hydrochloride (260 g). The mixture was stirred until the solid was completely dissolved, and the solution was subjected to partitioning. Ethyl acetate layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure until the volume of the mixture was reduced to 1 L. (+)-Di-p-toluoyl-D-tartaric acid (283 g) was added and dissolved in the residue under heat, followed by stirring at room temperature overnight. The crystals that precipitated was collected through filtration with suction and dried, to thereby give crude crystals (296 g). The crude crystals were recrystallized from ethyl acetate (1.5 L), to thereby give crystals (238 g). The crystals were recrystallized from ethyl acetate (6 L), to thereby give the title compound (194 g, 34%, 99.7%ee).

[0126]

mp. 74.0-74.5°C

MS (FAB) m/z 646 (M^+H)

^{1}H-NMR (270MHz, DMSO-d_6)δ ppm:2.26 (3H, s),2.36 (6H, s),2.66 (2H, d, J=7.0Hz),3.79 (1H, d, J=12.0Hz),3.84 (1H, d, J=12.0Hz),4.97-5.12 (2H, m),5.35-5.57 (1H, m),5.67 (2H, s),7.31 (4H, d, J=8.0Hz),7.45 (1H, dd, J=2.0,8.5Hz),7.63 (1H, d, J=8.5Hz),7.72 (1H, d, J=2.0Hz),7.84 (4H, d, J=8.0Hz).

$[\alpha]_D^{27}$ = +87.7°(c=0.508, MeOH)

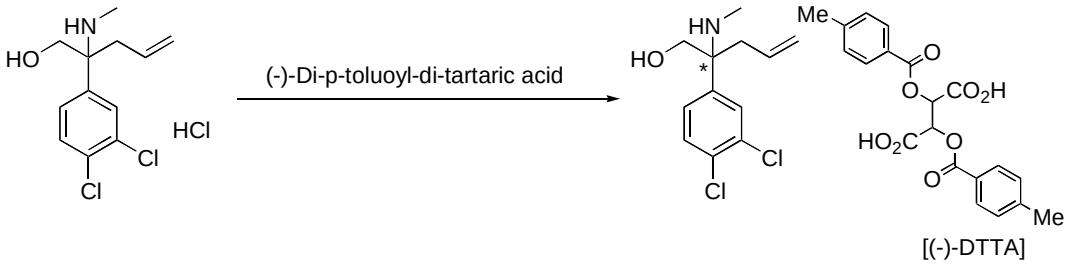
[0127]

Example 1(j)

Optical resolution of 2-(3,4-dichlorophenyl)-2-methylamino-4-pentenol (synthesis of (-)-di-p-toluoyl-L-tartrate)

[0128]

[F17]



[0129]

2-(3,4-Dichlorophenyl)-2-methylamino-4-pentenol (10 g) was dissolved in ethyl acetate (25 mL), and (-)-di-p-toluoyl-L-tartaric acid (14.8 g) was added to and dissolved in the solution with heat, followed by stirring overnight at room temperature. The crystals that precipitated was collected through filtration with suction and dried, to thereby give crude crystals (11.7 g). The crude crystals were recrystallized from ethyl acetate (200 mL), to thereby give

the title compound (8.3 g, 33%, 94.8%ee).

[0130]

mp. 78.0-78.5°C

^{1}H-NMR: coincide with (+)-form

$[\alpha]_D^{27}$ =-90.9°(c=0.507, MeOH)

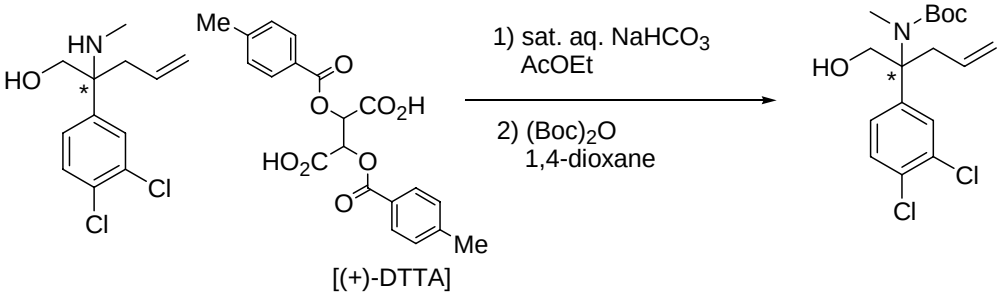
[0131]

Example 2

Synthesis of tert-butyl [1-(3,4-dichlorophenyl)-1-hydroxymethyl-3-butenyl]methylcarbamate

[0132]

[F18]



[0133]

Ethyl acetate (500 mL) and saturated aqueous sodium bicarbonate (650 mL) were added to 2-(3,4-dichlorophenyl)-2-methylamino-4-pentenol (+)-di-p-toluoyl-D-tartrate (84.8 g). The insoluble matter was passed through Celite, followed by washing with ethyl acetate. The filtrate was partitioned. The ethyl acetate layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure. The residue was dissolved in 1,4-dioxane (250 mL). Di-tert-butoxydicarbonate (30.5 g) was added to the resultant solution, followed by stirring at 100°C

overnight. The reaction mixture was concentrated under reduced pressure and the residue was purified through silica gel column chromatography (n-hexan:ethyl acetate=8:1 to 3:1), to thereby give the title compound (45.3g, 99%).

[0134]

MS (EI) m/z 359 (M^+)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.38 (9H, s),2.75 (3H, s),2.70-2.98 (2H, m),3.68-3.82 (1H, m),4.02-4.18 (1H, m),5.10-5.25 (2H, m),5.75-5.97 (1H, m),7.12 (1H, dd, J=2.5, 8.5Hz), 7.36 (1H, d, J=2.5Hz),7.41 (1H, d, J=8.5Hz).

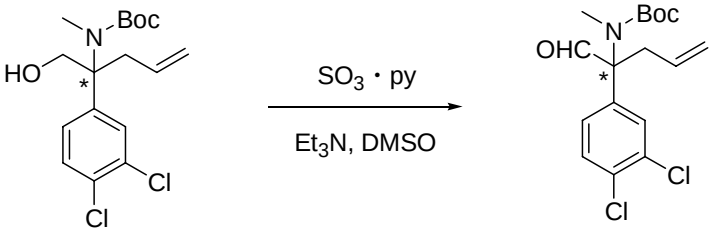
[0135]

Example 3

Synthesis of tert-butyl [1-(3,4-dichlorophenyl)-1-formyl-3-butenyl]methylcarbamate

[0136]

[F19]



[0137]

tert-Butyl [1-(3,4-dichlorophenyl)-1-hydroxymethyl-3-butenyl]methylcarbamate (45 g) was dissolved in anhydrous dimethyl sulfoxide (320 mL), and triethylamine (87 mL) was added thereto. Under cooling with ice, sulfur trioxide-pyridine (31.7 g) was added, and the resultant mixture was stirred for 1 hour at room temperature. Ice-water (650 mL)

was added to the reaction mixture, followed by extraction with ethyl acetate (500 mL). The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (n-hexane : ethyl acetate=10:1), to thereby give the title compound (35.5 g, 77%).

[0138]

MS (EI) m/z 357 (M^+)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.47 (9H, s),2.53-2.77 (4H, m),3.32-3.50 (1H, m),5.05-5.25 (2H, m),5.83-6.07 (1H, m),7.22 (1H, dd, J=2.5, 8.5Hz),7.46 (1H, d, J=2.5Hz),7.49 (1H, d, J=8.5Hz),9.36 (1H, s).

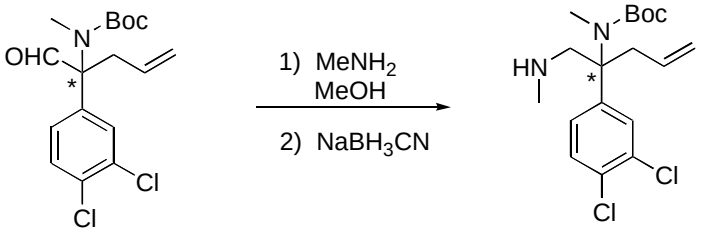
[0139]

Example 4

Synthesis of tert-butyl [1-(3,4-dichlorophenyl)-1-methylaminomethyl-3-butenyl]methylcarbamate

[0140]

[F20]



[0141]

tert-Butyl [1-(3,4-dichlorophenyl)-1-formyl-3-butenyl]methylcarbamate (35 g) was dissolved in methanol (350 mL), and 40% methylamine-methanol solution (44 mL) was added

thereto, followed by refluxing for 15 hours. The reaction mixture was cooled to room temperature, and sodium cyanoborohydride (12.5 g) was added thereto, followed by refluxing for 7 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified through silica gel column chromatography (sequentially through use of n-hexane : ethyl acetate=2:1 and chloroform : methanol=10:1 to 5:1), to thereby give the title compound (24.8 g, 70%).

[0142]

MS (EI) m/z 372 (M^+)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.19 (9H, s),2.33 (3H, s),2.72-3.03 (4H, m),3.10 (3H, s),3.06-3.22 (1H, m),5.08-5.20 (2H, m),5.58-5.77 (1H, m),7.08 (1H, dd, J=2.5, 8.5Hz),7.30-7.40 (2H, m).

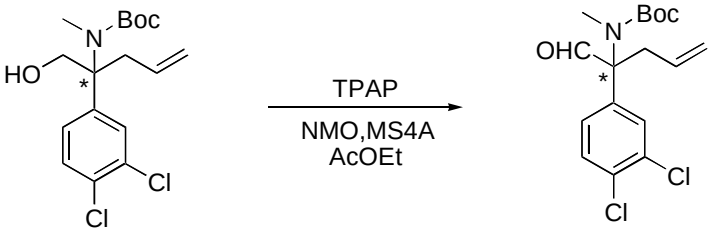
[0143]

Example 3-1

Synthesis of tert-butyl [1-(3,4-dichlorophenyl)-1-formyl-3-butenyl]methylcarbamate (alternative method)

[0144]

[F21]



[0145]

Ethyl acetate (100 mL) was added to tert-butyl [1-(3,4-dichlorophenyl)-1-formyl-3-butenyl]methylcarbamate (5.0 g),

N-methylmorpholine-N-oxide (2.5 g), and molecular sieve 4A (powder), and the mixture was stirred for 20 minutes at room temperature. Tetrapropylammonium perruthenate (251 mg) was added to the mixture, and the resultant mixture was stirred for 1 hour at room temperature. The insoluble matter was removed by filtration through Celite, and the filtrate was sequentially washed with aqueous sodium sulfite, saturated brine, and saturated aqueous cupper sulfate, dried over sodium sulfate anhydrate, and concentrated under reduced pressure, to thereby give the title compound (4.63 g, 93%). The title compound was used in the next step without further purification.

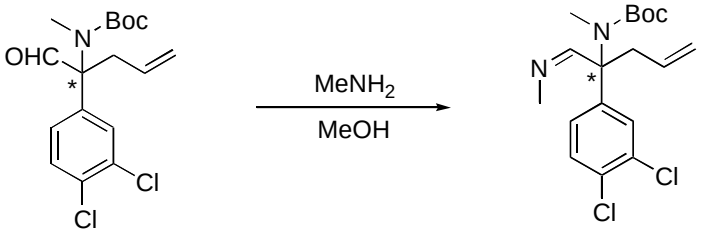
[0146]

Example 3-2

Synthesis of tert-butyl [1-(3,4-dichlorophenyl)-1-methyliminomethyl-3-butenyl]methylcarbamate

[0147]

[F22]



[0148]

40% Methylamine-methanol solution (17.3 mL) was added to tert-butyl [1-(3,4-dichlorophenyl)-1-methyliminomethyl-3-butenyl]methylcarbamate (4.0 g), and the mixture was refluxed for 13 hours. The reaction mixture was concentrated under

reduced pressure, and water was added to the residue, followed by extraction with toluene. The organic layer was sequentially washed with water and saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure, to thereby give the title compound (3.70 g, 89%). The title compound was used in the next step without further purification.

[0149]

MS(EI)m/z 370(M^+)

^{1}H-NMR(270MHz,$CDCl_3$)δppm:

1.35(9H,s), 2.76(3H,s),2.80-2.93(1H,m), 3.25(3H,d,J=2.0Hz), 3.30-3.42(1H,m), 5.01-5.18(2H,m), 5.80-6.00(1H,m), 7.15(1H,dd,J=2.0,8.5Hz), 7.35-7.46(2H,m), 7.78(1H,s).

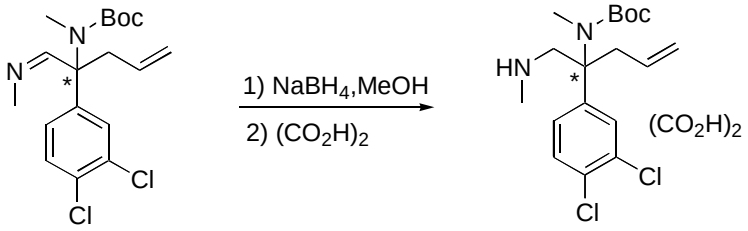
[0150]

Example 3-3

Synthesis of tert-butyl [1-(3,4-dichlorophenyl)-1-methylaminomethyl-3-butenyl]methylcarbamate oxalate

[0151]

[F23]



[0152]

tert-Butyl [1-(3,4-dichlorophenyl)-1-methylaminomethyl-3-butenyl]methylcarbamate (1.7 g) was dissolved in methanol, and sodium boron hydride (174 mg) was added thereto, followed

by stirring for 30 minutes at 50°C. Sodium boron hydride (173 mg) was added to the reaction mixture five times at intervals of 30 minutes, and the resultant mixture was stirred for 1.5 hours at 50°C. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate, washing with saturated brine, and drying over sodium sulfate anhydrate. The drying agent was removed through filtration, and oxalic acid (425 mg) in ethyl acetate was added to the filtrate. The mixture was concentrated under reduced pressure, and isopropyl ether was added to the residue, followed by filtration with suction and drying, to thereby give the title compound (1.4 g, 66%).

[0153]

$[\alpha]_D^{27}$=+2.7°(c=0.50,MeOH)

mp. 152.0-153.0°C

MS(EI)m/z 372(M^+)

^{1}H-NMR(270MHz,DMSO-d_6)δppm:1.12(9H,s), 2.60(3H,s), 2.81(1H,dd,J=6.5,13.5Hz), 2.91-3.14(4H,m), 3.54-3.75(2H,m), 5.00-5.15(2H,m), 5.30-5.50(1H,m), 7.19(1H,dd,J=2.0,8.5Hz), 7.40(1H,d,J=2.0Hz), 7.62(1H,d,J=8.5Hz), 8.00-8.80(2H,br).

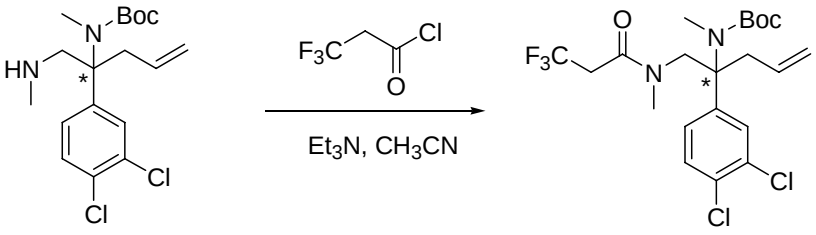
[0154]

Example 5(a)

Synthesis of tert-butyl (1-(3,4-dichlorophenyl)-1-{[methyl-(3,3,3-trifluoro-propionyl)-amino]-methyl-3-butenyl}-methyl-carbamate

[0155]

[F24]



[0156]

tert-Butyl [1-(3,4-dichlorophenyl)-1-methylaminomethyl-3-butenyl]methylcarbamate (3.0 g) was dissolved in acetonitrile (30 mL), and triethylamine (1.7 mL) and 3,3,3,-trifluoropropionyl chloride (2.36 g) was added thereto under cooling with ice, followed by stirring for 1 hour under cooling with ice. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (n-hexane : ethyl acetate=2:1), to thereby give the title compound (2.83 g, 73%).

[0157]

MS (FAB) m/z 483 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.22 (9H, brs),2.57 (1H, dd, J=6.5, 7.5Hz),2.74-2.90 (1H, m),2.85 (3H, s),3.07 (3H, s),3.27-3.38 (2H, m),4.0-4.20 (1H, m),4.25-4.42 (1H, m),4.85-5.04 (2H, m),5.64-5.85 (1H, m),7.00 (1H, dd, J=2.5, 8.5Hz),7.25 (1H, d, J=2.5Hz),7.37 (1H, d, J=8.5Hz).

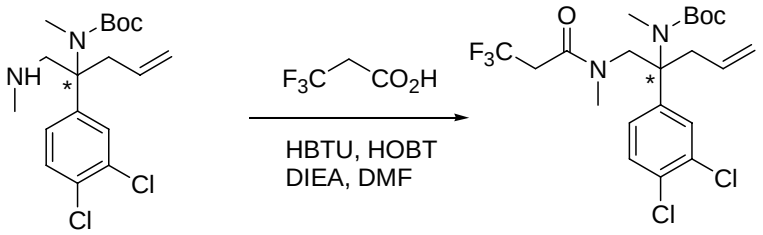
[0158]

Example 5(a1)

Synthesis of tert-butyl (1-(3,4-dichlorophenyl)-1-{[methyl-(3,3,3-trifluoro-propionyl)-amino]-methyl}-3-butenyl)-methyl-carbamate (alternative method)

[0159]

[F25]



[0160]

tert-Butyl [1-(3,4-dichlorophenyl)-1-methylaminomethyl-3-butenyl]methylcarbamate (5.0 g) was dissolved in N,N-dimethylformamide (50 mL), and, at room temperature, 3,3,3-trifluoropropionic acid (1.3 mL), [2-(1H)-benzotriazole-1-yl]-1,1,3,3-tetramethyluronium hexafluorophosphate (5.6 g), 1-hydroxybenzotriazole monohydrate (2.0 g), and N,N-diisopropylethylamine (3.5 mL) were added thereto, followed by stirring for 2 hours at room temperature. 3,3,3-Trifluoropropionic acid (0.6 mL), [2-(1H)-benzotriazole-1-yl]-1,1,3,3-tetramethyluronium hexafluorophosphate (2.5 g), 1-hydroxybenzotriazole monohydrate (1.0 g), and N,N-diisopropylethylamine (1.75 mL) were added to the reaction mixture, and the resultant mixture was stirred for 1 hour at room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was sequentially washed with water and

saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (n-hexane : ethyl acetate=2:1), to thereby give the title compound (3.38 g, 52%).

[0161]

MS (FAB) m/z 483 ((M+H) $^{+}$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.22 (9H, brs),2.57 (1H, dd, J=6.5, 7.5Hz),2.74-2.90 (1H, m),2.85 (3H, s),3.07 (3H, s),3.27-3.38 (2H, m),4.05-4.20 (1H, m),4.25-4.42 (1H, m),4.85-5.04 (2H, m),5.64-5.85 (1H, m),7.00 (1H, dd, J=2.5, 8.5Hz),7.25 (1H, d, J=2.5Hz),7.37 (1H, d, J=8.5Hz).

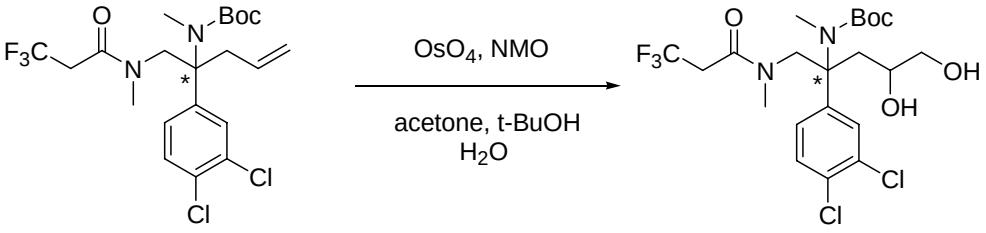
[0162]

Example 5(b)

Synthesis of tert-butyl (1-(3,4-dichlorophenyl)-3,4-dihydroxy-1-{[methyl-(3,3,3-trifluoro-propionyl)-amino]-methyl}-butyl)-methyl-carbamate

[0163]

[F26]



[0164]

tert-Butyl (1-(3,4-dichlorophenyl)-1-{[methyl-(3,3,3-trifluoro-propionyl)-amino]-methyl}-3-butenyl)-methyl-carbamate (2.0 g) was dissolved in a solvent mixture of

acetone (5 mL), 2-methyl-2-propanol (2.5 mL), and water (2.5 mL). Osmium tetraoxide (2.5% 2-methyl-2-propanol solution) (561 μL) and N-methylmorpholine N-oxide (971 mg) were added thereto, and the mixture was stirred overnight at room temperature. Aqueous sodium thiosulfate was added to the reaction mixture, and the mixture was stirred for 30 minutes at room temperature. The insoluble matter was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with methylene chloride. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure, to thereby give the title compound (1.95 g, 91%). The compound was used in the next step without further purification.

[0165]

MS (FAB) m/z 518 $((M+H)^+)$

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.20 (9H, brs),1.93-2.53 (4H, m),3.09 (3H, s),3.00-3.62 (6H, m),3.68-3.80 (2H, m),4.68-5.38 (2H, m),7.00-7.10 (1H, m),7.20-7.32 (1H, m),7.37-7.46 (1H, m).

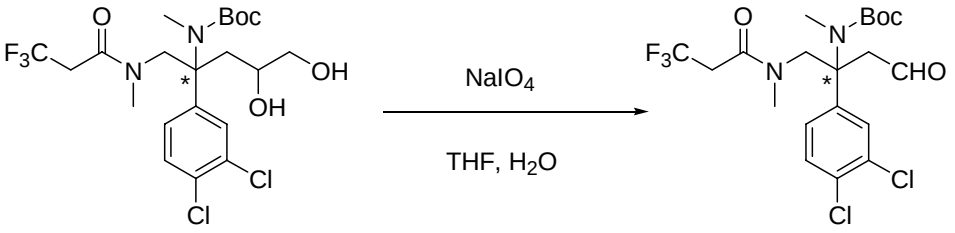
[0166]

Example 5(c)

Synthesis of tert-butyl (1-(3,4-dichlorophenyl)-1-{[methyl-(3,3,3-trifluoro-propionyl)-amino]-methyl}-3-oxo-propyl)-methyl-carbamate

[0167]

[F27]



[0168]

tert-Butyl (1-(3,4-dichlorophenyl)-3,4-dihydroxy-1-{[methyl-(3,3,3-trifluoro-propionyl)-amino]-methyl}-butyl)-methyl-carbamate (1.95 g) was dissolved in a mixture solvent of tetrahydrofuran (20 mL) and water (10 mL). Sodium periodate (1.61 g) was added thereto, and the mixture was stirred for 1 hours at room temperature. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure, to thereby give the title compound (1.79 g, 98%). The compound was used in the next step without further purification.

[0169]

MS (FAB) m/z 485 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.26 (9H, brs),2.78 (3H, s),2.94-3.14 (1H,m),3.07 (3H, s),3.18-3.37 (3H, m),4.24 (1H, d, J=13.5Hz),4.52 (1H, d,J=13.5Hz),7.10 (1H, dd, J=2.0, 8.5Hz),7.33 (1H, d, J=2.0Hz),7.43 (1H, d,J=8.5Hz),9.67 (1H, t, J=2.0Hz).

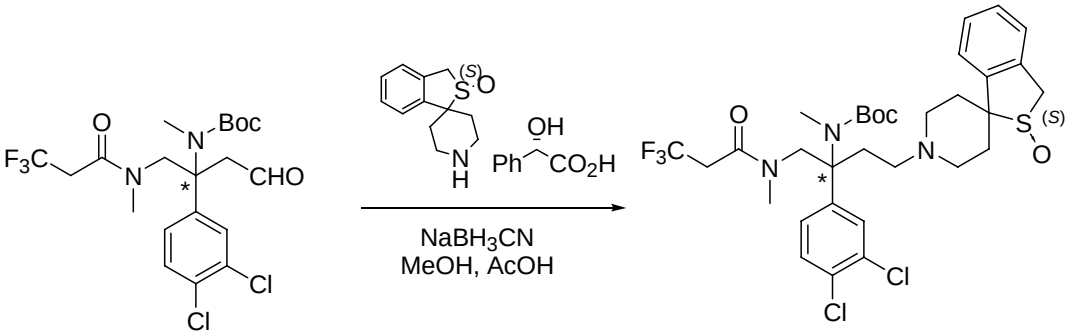
[0170]

Example 5(d)

Synthesis of tert-butyl {1-(3,4-dichlorophenyl)-1-{[methyl-(3,3,3-trifluoro-propionyl)-amino]-methyl}-3-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-propyl}-methyl-carbamate

[0171]

[F28]



[0172]

tert-Butyl (1-(3,4-dichlorophenyl)-1-{[methyl-(3,3,3-trifluoro-propionyl)-amino]-methyl}-3-oxo-propyl)-methyl-carbamate (1.0 g) was dissolved in methanol (20 mL). Spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide/(S)-(+)-mandelic acid salt (1.08 g) and sodium cyanoborohydride (191 mg) were added thereto. Acetic acid (0.3 mL) was added to the mixture to adjust the pH to 4, and the resultant mixture was stirred for 30 minutes at room temperature. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, followed by extraction with chloroform. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (sequentially through use of

n-hexane : ethyl acetate=1:2 and chloroform : methanol=20:1 to 5:1), to thereby give the title compound (1.38 g, 97%).

[0173]

MS (FAB) m/z 690 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.23 (9H, s),1.51 (1H, d, J=13Hz), 1.82-2.08 (2H, m),2.15-2.68 (7H, m),2.72-3.05 (2H, m),2.89 (3H, s),3.10 (3H, s),3.20-3.42 (2H, m),3.92-4.65 (2H, m),3.97 (1H, d, J=17Hz),4.30 (1H, d, J=17Hz),7.05 (1H, dd, J=2.0, 8.5Hz),7.22-7.48 (6H, m).

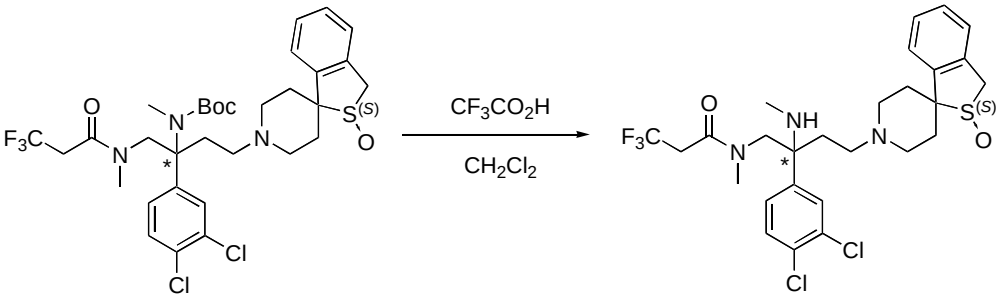
[0174]

Example 5(e)

Synthesis of N-{2-(3,4-dichlorophenyl)-2-methylamino-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl}-3,3,3-trifluoro-N-methyl-propionamide

[0175]

[F29]



[0176]

tert-Butyl {1-(3,4-dichlorophenyl)-1-{[methyl-(3,3,3-trifluoro-propionyl)-amino]-methyl}-3-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-propyl}-methyl-carbamate (1.38 g) was dissolved in methylene chloride (20 mL), and trifluoroacetic acid (10 mL)

was added thereto, followed by stirring for 30 minutes at room temperature. The reaction mixture was neutralized with saturated aqueous sodium bicarbonate, and the mixture was extracted with methylene chloride. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure, to thereby give the title compound (1.09 g, 92%). The compound was used in the next step without further purification.

[0177]

MS (FAB) m/z 590 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.95-2.68 (10H, m),2.26 (3H, s),2.54 (3H, s),2.92-3.28 (4H, m),3.42 (1H, d, J=13Hz),3.93-4.12 (2H, m),4.34 (1H,d, J=17Hz),7.25-7.42 (5H, m),7.44 (1H, d, J=8.5Hz),7.63 (1H, d, J=2.0Hz).

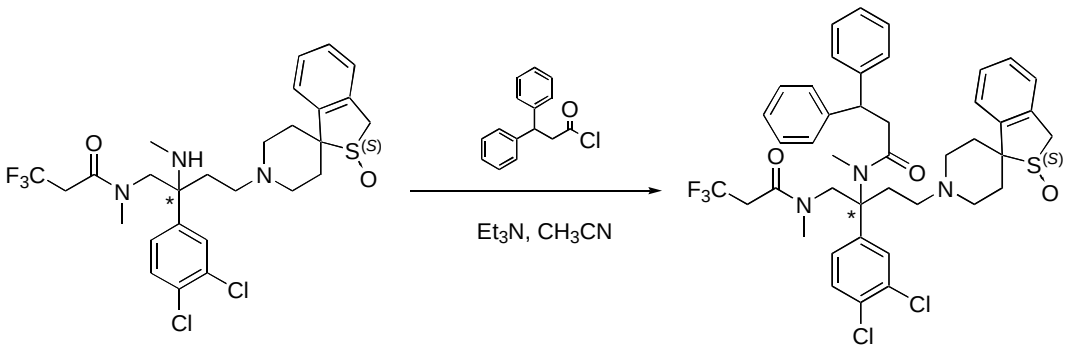
[0178]

Example 5(f)

Synthesis of N-{2-(3,4-dichlorophenyl)-2-[(3,3-diphenylpropionyl)-methylamino]-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl}-3,3,3-trifluoro-N-methyl-propionamide

[0179]

[F30]



[0180]

N-{2-(3,4-Dichlorophenyl)-2-methylamino-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl}-3,3,3-trifluoro-N-methyl-propionamide (300 mg) was dissolved in acetonitrile (5 mL). Under cooling with ice, triethylamine (212 μL) and 3,3-diphenylpropionyl chloride (373 mg) were added thereto. Under cooling with ice, the mixture was stirred for 1 hour. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (sequentially through use of ethyl acetate and ethyl acetate : methanol=20:1 to 5:1), to thereby give the title compound (350 mg, 86%).

[0181]

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:

1.44-1.58(1H,m),1.77-1.92(1H,m),1.97-2.47(7H,m),2.56(3H,s),2.65-2.85(2H,m),2.97-3.27(8H,m),3.97(1H,d,J=16.5Hz),4.05-

4.18(1H,m),4.29(1H,d,J=16.5Hz),4.22-4.42(1H,m),4.61(1H,t,J=7.5Hz),6.72(1H,d,J=8.0Hz),7.10-7.37(16H,m).

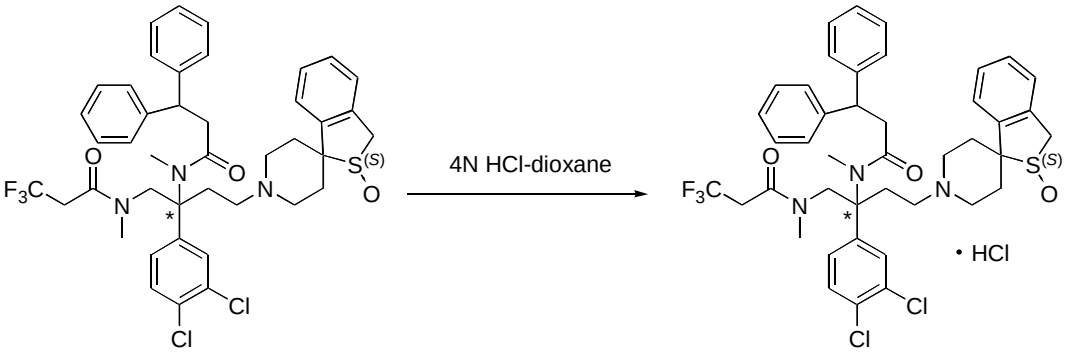
[0182]

Example 5(g)

Synthesis of N-{2-(3,4-dichlorophenyl)-2-[(3,3-diphenylpropionyl)-methylamino]-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl}-3,3,3-trifluoro-N-methyl-propionamide hydrochloride (Compound No. 1)

[0183]

[F31]



[0184]

N-{2-(3,4-Dichlorophenyl)-2-[(3,3-diphenylpropionyl)-methylamino]-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl}-3,3,3-trifluoro-N-methyl-propionamide (350 mg) was dissolved in methylene chloride (2 mL). 4N HCl-1,4-dioxane (1 mL) was added thereto, and the mixutre was concentrated under reduced pressure. Ether was added to the residue, followed by filtration and drying, to thereby give the title compound (307 mg, 84%).

[0185]

$[\alpha]_D^{27}$=-14.1°(c=0.21,MeOH)

MS (FAB) m/z 798 ((M+H) $^+$)

^{1}H-NMR (270MHz, DMSO-d_6)δ ppm:1.88-2.02 (1H, m),2.15-2.60 (6H, m),2.68-2.86 (1H, m),2.90-3.10 (3H, m),3.20 (3H, s),3.15-3.50 (6H, m),3.52-3.95 (3H, m),4.08 (1H, d, J=17Hz),4.23 (1H, d, J=12Hz),4.36 (2H, t,J=7.5Hz),4.69 (1H, d, J=17Hz),7.03-7.48 (17H, m), 10.45 (1H, br).

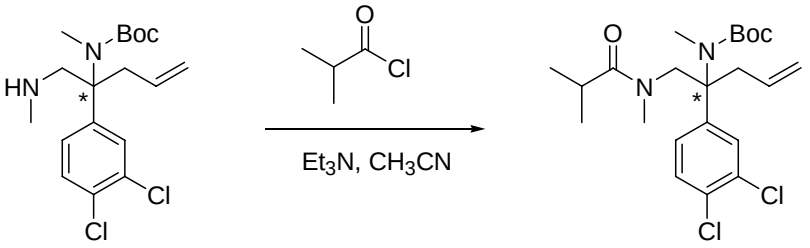
[0186]

Example 6(a)

Synthesis of tert-butyl {1-(3,4-dichlorophenyl)-1-[(isobutyryl-methylamino)-methyl]-3-butenyl}-methyl-carbamate

[0187]

[F32]



[0188]

tert-Butyl [1-(3,4-dichlorophenyl)-1-methylaminomethyl-3-butenyl]methylcarbamate (2.0 g) produced in Example 4 was dissolved in acetonitrile (40 mL). Under cooling with ice, triethylamine (1.49 mL) and isobutyryl chloride (1.12 mL) was added thereto. Under cooling with ice, the mixture was stirred for 1 hour. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate. The organic layer

was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (n-hexane : ethyl acetate=3:1), to thereby give the title compound (1.53 g, 64%).

[0189]

MS (FAB) m/z 443 ((M+H) $^{+}$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.14 (6H, d, J=7.0Hz),1.23 (9H, s),2.55 (1H,dd, J=7.0, 13.5Hz),2.78 (3H, s),2.78-2.85 (2H, m),3.09 (3H, s),4.08-4.16(2H, m),4.86-4.99 (2H, m),5.85-5.87 (1H, m),7.02 (1H, dd, J=2.5, 8.5Hz),7.25 (1H, d, J=2.5Hz),7.36 (1H, d, J=8.5Hz).

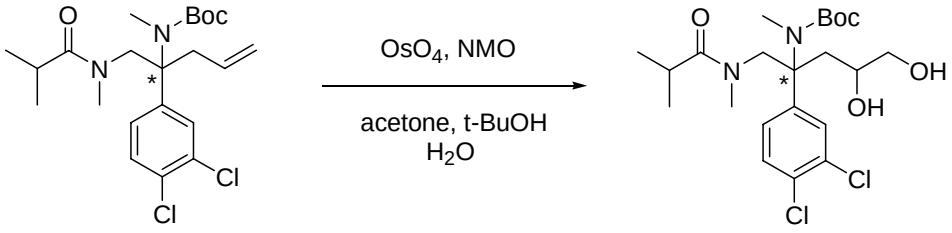
[0190]

Example 6(b)

Synthesis of tert-butyl {1-(3,4-dichlorophenyl)-3,4-dihydroxy-1-[(isobutyryl-methylamino)-methyl]-butyl}-methyl-carbamate

[0191]

[F33]



[0192]

tert-Butyl {1-(3,4-dichlorophenyl)-1-[(isobutyryl-methylamino)-methyl]-3-butenyl}-methyl-carbamate (1.12 g) was dissolved in a mixture solvent of acetone (3 mL), 2-methyl-2-

propanol (1.5 mL), and water (1.5 mL). Osmium tetraoxide (2.5% 2-methyl-2-propanol solution) (302 μL) and N-methylmorpholine N-oxide (592 mg) were added thereto, and the mixture was stirred for 2.5 days at room temperature. Aqueous sodium thiosulfate was added to the reaction mixture, and the resultant mixture was stirred for 10 minutes at room temperature. The insoluble matter was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with methylene chloride. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure, to thereby give the title compound (1.13 g, 94%). The compound was used in the next step without further purification.

[0193]

MS (FAB) m/z 477 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.04-1.20 (15H, m),1.90-2.23 (2H, m),2.41 (1H, t, J=4.5Hz),2.65-3.65 (9H, m),3.72 (2H, t, J=5.0Hz),5.02-5.28 (1H, m),5.52-5.78 (1H, m),7.00-7.15 (1H, m),7.18-7.35 (1H, m),7.40 (1H, d, J=8.5Hz).

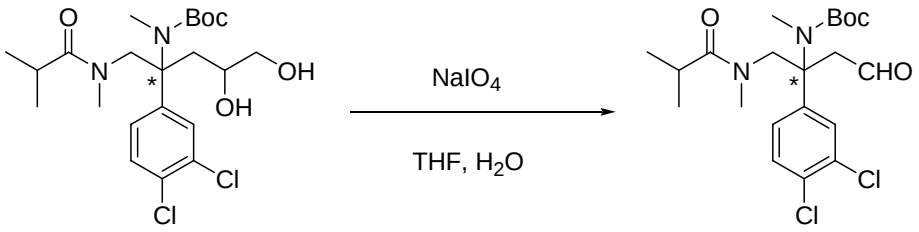
[0194]

Example 6(c)

Synthesis of tert-butyl {1-(3,4-dichlorophenyl)-1-[(isobutyryl-methylamino)-methyl]-3-oxo-propyl}-methyl-carbamate

[0195]

[F34]



[0196]

tert-Butyl {1-(3,4-dichlorophenyl)-3,4-dihydroxy-1-[(isobutyryl-methylamino)-methyl]-butyl}-methyl-carbamate (1.41 g) was dissolved in a mixture solvent of tetrahydrofuran (8 mL) and water (8 mL). Sodium periodate (1.3 g) was added thereto, and the mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure, to thereby give the title compound (1.33 g, quantative amount). The compound was used in the next step without further purification.

[0197]

MS (FAB) m/z 445 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.13 (6H, dd, J=3.0, 7.0Hz),1.23-1.29 (9H, m),2.73 (3H, s),2.76-2.84 (1H, m),2.90 (1H, d, J=16Hz),3.11 (3H, s),3.16(1H, d, J=16Hz),4.10-4.18 (1H, m),4.45 (1H, d, J=13Hz),7.10 (1H, dd, J=2.5, 8.5Hz),7.33 (1H, d, J=2.5Hz),7.41 (1H, dd, J=2.5, 8.5Hz),9.71 (1H, t,J=2.0Hz).

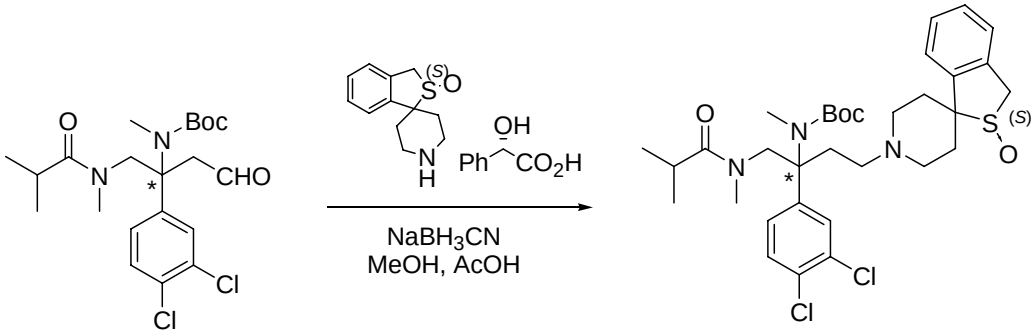
[0198]

Example 6(d)

Synthesis of tert-butyl {1-(3,4-dichlorophenyl)-1-[(isobutyryl-methylamino)-methyl]-3-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-propyl}-methyl-carbamate

[0199]

[F35]



[0200]

tert-Butyl {1-(3,4-dichlorophenyl)-1-[(isobutyryl-methylamino)-methyl]-3-oxo-propyl}-methyl-carbamate (1.33 g) was dissolved in methanol (15 mL). Spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide/(S)-(+)-mandelate (1.45 g) and sodium cyanoborohydride (257 mg) were added thereto. Acetic acid was added to the mixture to adjust the pH to 4, and the resultant mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography

(sequentially through use of ethyl acetate and chloroform : methanol=20:1), to thereby give the title compound (1.85 g, 95%).

[0201]

MS (FAB) m/z 650 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.16 (6H, dd, J=4.0, 6.5Hz),1.20-1.29 (9H, m),1.50 (1H, d, J=15Hz),1.79-2.01 (2H, m),2.17-2.52 (7H, m),2.58-2.79 (2H, m),2.82-2.87 (5H, m),3.13 (3H, s),3.97 (1H, d, J=17Hz),4.07-4.19 (1H,m),4.29 (1H, d, J=17Hz),7.06 (1H, dd, J=2.0, 8.5Hz),7.19-7.33 (5H, m),7.39 (1H, d, J=8.5Hz).

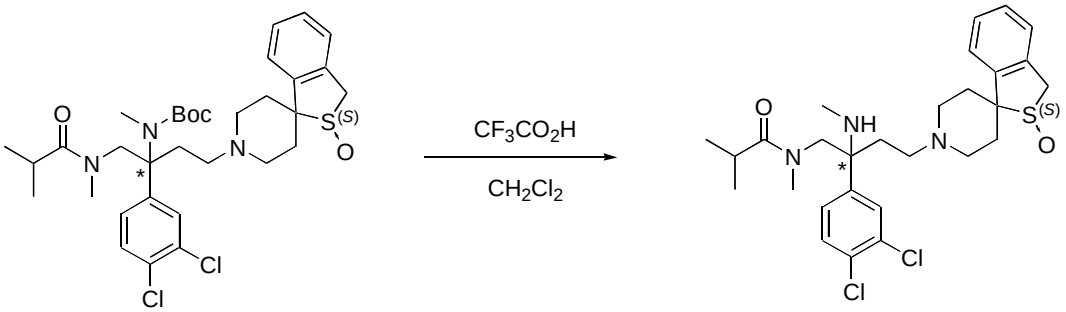
[0202]

Example 6(e)

Synthesis of N-[2-(3,4-dichlorophenyl)-2-methylamino-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl]-N-methyl-isobutyrylamide

[0203]

[F36]



[0204]

tert-Butyl {1-(3,4-dichlorophenyl)-1-[(isobutyryl-methylamino)-methyl]-3-{spiro[benzo(c)thiophene-1(3H),4'-

piperidine]-(2S)-oxide}-1'-yl-propyl}-methyl-carbamate (1.85 g) was dissolved in methylene chloride (10 mL). Trifluoroacetic acid (5 mL) was added thereto, and the mixture was stirred for 2 hours at room temperature. The reaction mixture was neutralized with saturated aqueous sodium bicarbonate, and the mixture was extracted with methylene chloride. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure, to thereby give the title compound (1.35 g, 86%). The compound was used in the next step without further purification.

[0205]

MS (FAB) m/z 550 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.02 (3H, d, J=6.5Hz),1.09 (3H, d, J=7.0Hz),1.57-1.66 (4H, m),2.05-2.17 (2H, m),2.25 (3H, s),2.31-2.45 (4H, m),2.53 (3H, s),2.64-2.79 (2H, m),2.97-3.09 (2H, m),3.34-3.39 (1H, m),3.83-4.00 (1H, m),4.02 (1H, d, J=17Hz),4.35 (1H, d, J=17Hz),7.25-7.40 (5H, m),7.43(1H, d, J=8.5Hz),7.58-7.65 (1H, m).

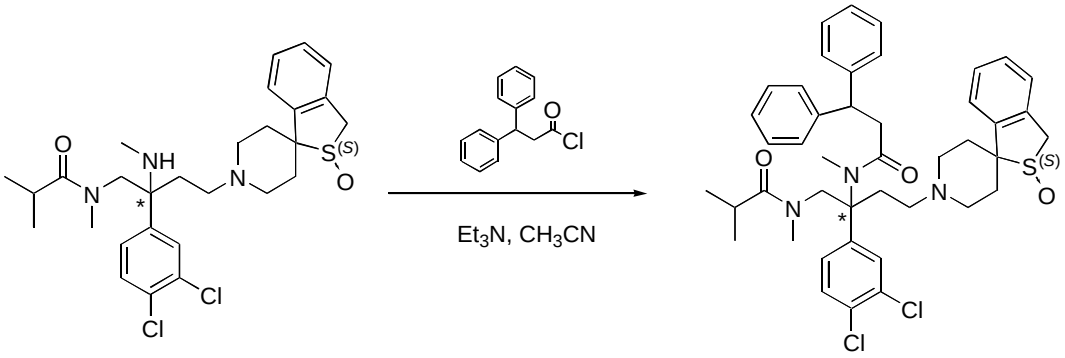
[0206]

Example 6(f)

Synthesis of N-{2-(3,4-dichlorophenyl)-2-[(3,3-diphenylpropionyl)-methylamino]-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl}-N-methyl-isobutylamide

[0207]

[F37]



[0208]

N-[2-(3,4-dichlorophenyl)-2-methylamino-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl]-N-methyl-isobutylamide (1.0 g) was dissolved in acetonitrile (20 mL). Under cooling with ice, triethylamine (761 μL) and 3,3-diphenylpropionyl chloride (1.34 g) were added thereto, and the mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (sequentially through use of ethyl acetate, ethyl acetate : methanol=20:1, and chloroform : methanol=20:1).

[0209]

MS (FAB) m/z 758 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.07(3H,s),1.09(3H,s),1.42-1.55(1H,m),1.76-1.90(1H,m),1.94-2.06(1H,m),2.10-2.47(7H,m),2.54(3H,s),2.63-2.88(3H,m),3.00-3.18(5H,m),3.90-4.10(2H,m),4.23-

4.36(2H,m),4.62(1H,t,J=7.5Hz),6.72(1H,d,J=8.5Hz),7.12-7.35(16H,m).

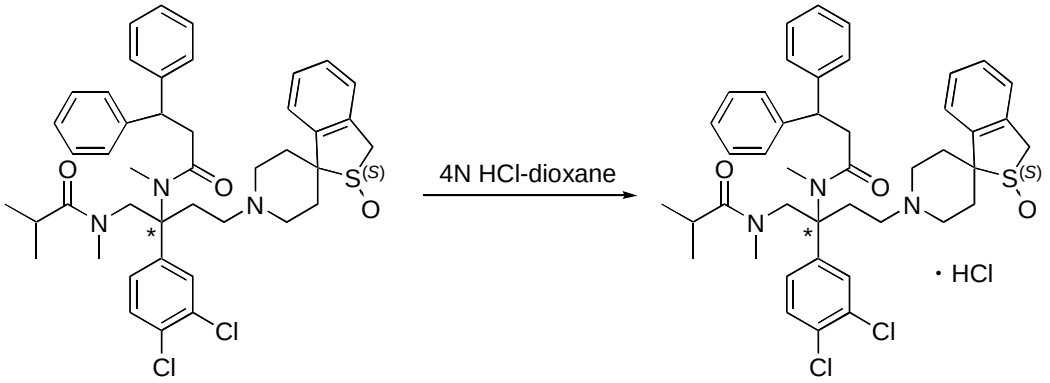
[0210]

Example 6(g)

Synthesis of N-{2-(3,4-dichlorophenyl)-2-[(3,3-diphenylpropionyl)-methylamino]-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl}-N-methyl-isobutylamide hydrochloride (Compound No. 2)

[0211]

[F38]



[0212]

N-{2-(3,4-Dichlorophenyl)-2-[(3,3-diphenylpropionyl)-methylamino]-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl}-N-methyl-isobutylamide was dissolved in methylene chloride. 4N HCl-1,4-dioxane was added thereto, and the mixture was concentrated under reduced pressure. Ether was added to the residue, followed by filtration and drying, to thereby give the title compound (1.15 g, 80%).

[0213]

MS (FAB) m/z 758 ($(M+H)^+$)

^{1}H-NMR (270MHz, DMSO-d_6)δ ppm:0.98 (6H, dd, J=3.0, 6.5Hz),2.00 (1H, d, J=14.5Hz),2.09-2.29 (3H, m),2.33-2.47 (2H, m),2.64-2.79 (3H, m),3.00-3.03 (3H, m),3.20 (3H, s),3.23-3.50 (6H, m),3.60-3.90 (1H, m),4.09 (1H, d, J=17Hz),4.22 (1H, d, J=10Hz),4.36 (1H, t, J=7.0Hz),4.70 (1H, d, J=17Hz),7.06-7.17 (3H, m),7.22-7.33 (10H, m),7.33-7.45 (4H, m),10.33 (1H, br).

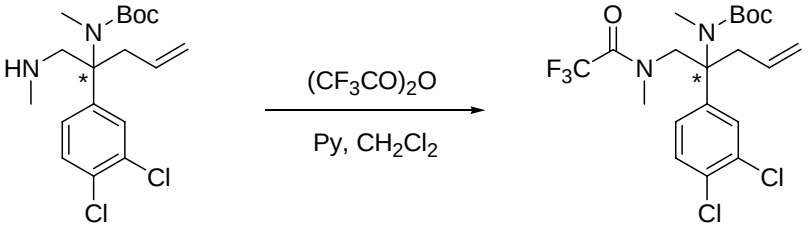
[0214]

Example 7(a)

Synthesis of tert-butyl (1-(3,4-dichlorophenyl)-1-{[methyl-(2,2,2-trifluoroacetyl)-amino]-methyl}-3-butenyl)-methyl-carbamate

[0215]

[F39]



[0216]

tert-Butyl [1-(3,4-dichlorophenyl)-1-methylaminomethyl-3-butenyl]methylcarbamate (240 mg) produced in Example 4 was dissolved in methylene chloride (5 mL). Under cooling with ice, pyridine (107 μL) and trifluoroacetic acid anhydride (186 μL) were added thereto. Under cooling with ice, the mixture was stirred for 40 minutes. Water was added to the reaction mixture, and the mixture was extracted with methylene chloride. The organic layer was washed with

saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (n-hexane : ethyl acetate=5:1), to thereby give the title compound (250 mg, 77%).

[0217]

MS (FAB) m/z 469 ((M+H) $^{+}$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.26 (9H, s),2.58 (1H, dd, J=7.0, 13.5Hz),2.77 (1H, dd, J=7.0, 13.5Hz),3.02 (3H, s),3.07 (3H, s),4.07-4.28 (1H, m),4.43 (1H, d, J=13.5Hz),4.86-5.06 (2H, m),5.55-5.75 (1H, m),6.99 (1H, dd, J=2.5, 8.5Hz),7.24 (1H, d, J=2.5Hz),7.39 (1H, d, J=8.5Hz).

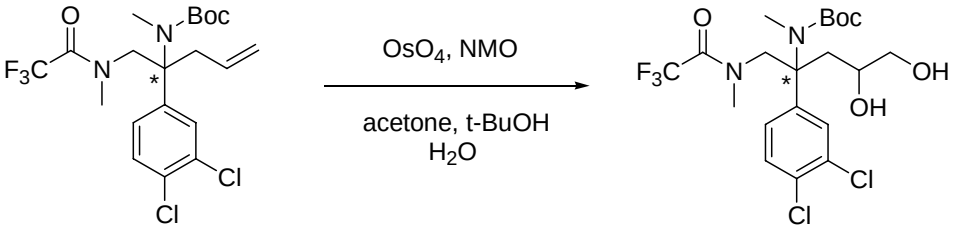
[0218]

Example 7(b)

Synthesis of tert-butyl {1-(3,4-dichlorophenyl)-3,4-dihydroxy-1-{[methyl-(2,2,2-trifluoroacetyl)-amino]-methyl}-butyl}-methyl-carbamate

[0219]

[F40]



[0220]

tert-Butyl (1-(3,4-dichlorophenyl)-1-{[methyl-(2,2,2-trifluoroacetyl)-amino]-methyl}-3-butenyl)-methyl-carbamate (659 mg) was dissolved in a mixture solvent of acetone (4 mL),

2-methyl-2-propanol (2 mL), and water (2 mL). Osmium tetraoxide (2.5% 2-methyl-2-propanol solution) (338 μL) and N-methylmorpholine N-oxide (329 mg) were added thereto, and the mixture was stirred overnight at room temperature. Aqueous sodium thiosulfate was added to the reaction mixture, and the resultant mixture was stirred for 30 minutes at room temperature. The insoluble matter was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with methylene chloride. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure,to thereby give the title compound (701 mg, quantative amount). The compound was used in the next step without further purification.

[0221]

MS (FAB) m/z 503 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.24 (9H, brs),1.76-1.88 (1H, m),1.94-2.20 (2H, m),2.26-2.50 (1H, m),3.00-3.30 (6H, m),3.38-3.63 (2H, m),3.70-3.82 (1H, m),3.90-4.20 (1H, m),4.95-5.25 (1H, m),7.00-7.15 (1H, m),7.22-7.32 (1H, m),7.40-7.50 (1H, m).

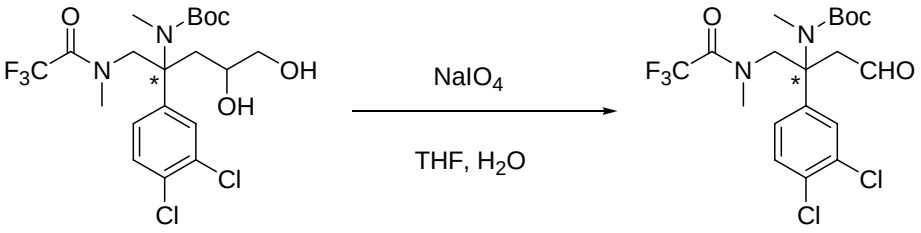
[0222]

Example 7(c)

Synthesis of tert-butyl (1-(3,4-dichlorophenyl)-1-{methyl-(2,2,2-trifluoroacetyl)-amino}-methyl)-3-oxo-propyl)-methyl-carbamate

[0223]

[F41]



[0224]

tert-Butyl (1-(3,4-dichlorophenyl)-3,4-dihydroxy-1-{[methyl-(2,2,2-trifluoroacetyl)-amino]-methyl}-butyl)-methyl-carbamate (701 mg) was dissolved in a mixture solvent of tetrahydrofuran (4 mL) and water (4 mL). Sodium periodate (596 mg) was added thereto, and the mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure, to thereby give the title compound (633 mg, 97%). The compound was used in the next step without further purification.

[0225]

MS (FAB) m/z 471 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.29 (9H, s),2.95 (3H, s),2.90-3.10 (1H, m),3.04 (3H, s),3.23 (1H, d, J=16Hz),4.37 (1H, d, J=13.5Hz),4.53 (1H, d, J=13.5Hz),7.11 (1H, dd, J=2.5, 8.5Hz),7.34 (1H, d, J=2.5Hz),7.44 (1H, d, J=8.5Hz),9.62 (1H, t, J=2.0Hz).

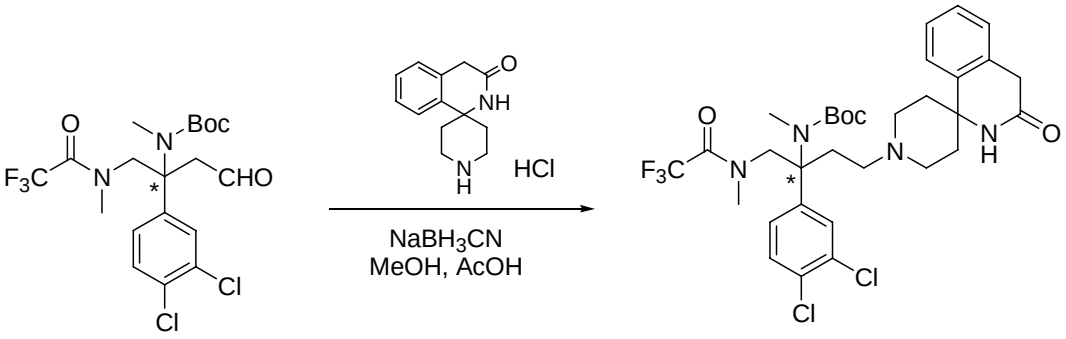
[0226]

Example 7(d)

Synthesis of tert-butyl {1-(3,4-dichlorophenyl)-1-{[methyl-(2,2,2-trifluoroacetyl)-amino]-methyl}-3-{spiro[isoquinoline-1(2H),4'-piperidine]-3(4H)-one}-1'-yl-propyl}-methyl-carbamate

[0227]

[F42]



[0228]

tert-Butyl (1-(3,4-dichlorophenyl)-1-{[methyl-(2,2,2-trifluoroacetyl)-amino]-methyl}-3-oxo-propyl)-methyl-carbamate (300 mg) was dissolved in methanol (5 mL). Spiro[isoquinoline-1(2H),4'-piperidine]-3(4H)-one hydrochloride (225 mg) and sodium cyanoborohydride (59 mg) were added thereto. Acetic acid (0.2 mL) was added to the mixture to adjust the pH to 4, and the mixutre was stirred for 30 minutes at room temperature. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, followed by extraction with chloroform. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced

pressure. The residue was purified through silica gel column chromatography (sequentially through use of n-hexane : ethyl acetate=1:2 and chloroform : methanol=20:1), to thereby give the title compound (323 mg, 76%).

MS (FAB) m/z 671 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.25 (9H, brs),1.63-1.80 (2H, m),1.90-2.30 (7H, m),2.45-2.60 (1H, m),2.71 (1H, d, J=10Hz),2.81 (1H, d, J=10Hz),3.0 5(3H, s),3.12 (3H, s),3.61 (2H, s),4.05-4.28 (1H, m),4.45-4.68 (1H, m),6.29 (1H, s),7.04 (1H, dd, J=2.5, 8.5Hz),7.10-7.38 (5H, m),7.43 (1H, d, J=8.5Hz).

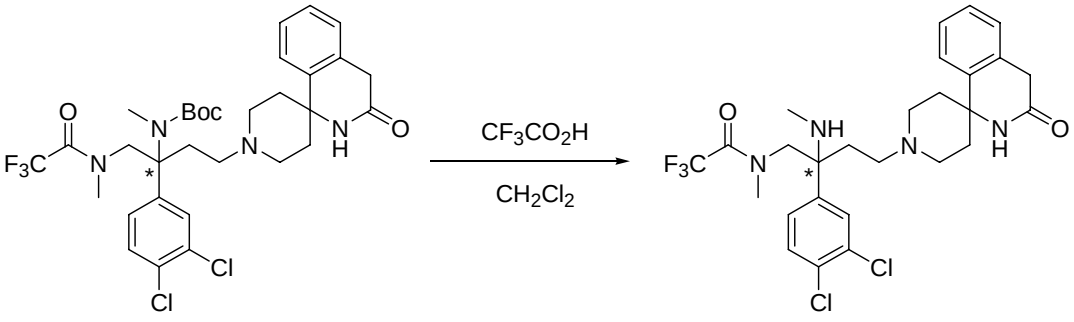
[0229]

Example 7(e)

Synthesis of N-{2-(3,4-dichlorophenyl)-2-methylamino-4-{spiro[isoquinoline-1(2H),4'-piperidine]-3(4H)-one}-1'-yl-butyl}-2,2,2-trifluoro-N-methyl-acetamide

[0230]

[F43]



[0231]

tert-Butyl {1-(3,4-dichlorophenyl)-1-{[methyl-(2,2,2-trifluoroacetyl)-amino]-methyl}-3-{spiro[isoquinoline-1(2H),4'-piperidine]-3(4H)-one}-1'-yl-propyl}-methyl-

carbamate (323 mg) was dissolved in methylene chloride (4 mL). Trifluoroacetic acid (2 mL) was added thereto, and the mixture was stirred for 30 minutes at room temperature. The reaction mixture was neutralized with saturated aqueous sodium bicarbonate, and the mixture was extracted with methylene chloride. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure, to thereby give the title compound (264 mg, 96%). The compound was used in the next step without further purification.

[0232]

MS (FAB) m/z 571 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.73-1.88 (2H, m),1.95-2.60 (9H, m),2.28 (3H, s),2.72 (3H, s),2.88-3.03 (2H, m),3.48 (1H, d, J=14Hz),3.64 (2H, s),3.93 (1H, d, J=14Hz),6.36 (1H, s),7.17 (1H, dd, J=2.5, 8.5Hz),7.23-7.42 (4H, m),7.45 (1H, d, J=8.5Hz),7.63 (1H, d, J=2.5Hz).

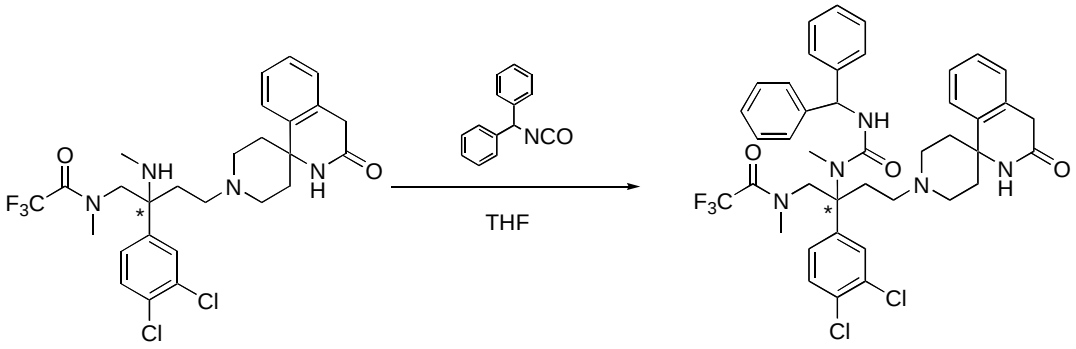
[0233]

Synthesis of Example 7(f)

N-{2-(3-benzhydryl-1-methylureido)-2-(3,4-dihydrodichlorophenyl)-4-{spiro[isoquinoline-1(2H),4'-piperidine]-3(4H)-one}-1'-yl-butyl}-2,2,2-trifluoro-N-methyl-acetamide

[0234]

[F44]



[0235]

N-{2-(3,4-Dichlorophenyl)-2-methylamino-4-{spiro[isoquinoline-1(2H),4'-piperidine]-3(4H)-one}-1'-yl-butyl}-2,2,2-trifluoro-N-methyl-acetamide (264 mg) was dissolved in tetrahydrofuran (5 mL). Diphenylmethyl isocyanate (175 μL) was added thereto, and the mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was purified through silica gel column chromatography (sequentially through use of n-hexane : ethyl acetate=1:2 and chloroform : methanol=20:1).

[0236]

MS (FAB) m/z 780 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.55-1.80(2H,m),1.93-2.27(7H,m),2.41-2.57(1H,m),2.68-2.85(2H,m),2.89(3H,s),3.12(3H,s),3.61(2H,s),4.34(1H,d,J=13.5Hz),4.49(1H,d,J=13.5Hz),5.07(1H,d,J=7.0Hz),5.99(1H,d,J=7.0Hz),6.24(1H,s),7.03(1H,dd,J=2.0,8.5Hz),7.10-7.43(16H,m).

[0237]

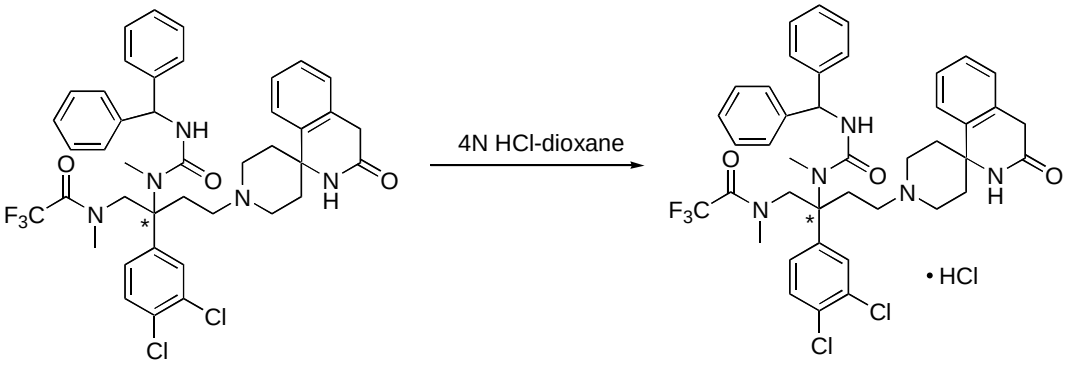
Example 7(g)

Synthesis of N-{2-(3-benzhydryl-1-methylureido)-2-(3,4-

dihydrodichlorophenyl)-4-{spiro[isoquinoline-1(2H),4'-piperidine]-3(4H)-one}-1'-yl-butyl}-2,2,2-trifluoro-N-methyl-acetamide hydrochloride (Compound No. 3)

[0238]

[F45]



[0239]

N-{2-(3-Benzhydryl-1-methylureido)-2-(3,4-dihydrodichlorophenyl)-4-{spiro[isoquinoline-1(2H),4'-piperidine]-3(4H)-one}-1'-yl-butyl}-2,2,2-trifluoro-N-methyl-acetamide was dissolved in methylene chloride. 4N HCl-1,4-dioxane was added thereto, and the mixture was concentrated under reduced pressure. Ether was added to the residue, followed by filtration and drying, to thereby give the title compound (319 mg, 85%).

[0240]

MS (FAB) m/z 780 ($(M+H)^+$)

^{1}H-NMR (270MHz, DMSO-d_6)δ ppm:1.82-1.99 (2H, m),2.75 (3H, s),2.79-3.12 (2H, m),3.07 (3H, s),3.22-3.50 (8H, m),3.53-3.65 (1H, m),3.61 (2H, s),4.18 (1H, d, J=13.5Hz),4.36 (1H, d, J=13.5Hz),5.85 (1H, d, J=7.5Hz),7.15-7.42 (15H, m),7.52-7.62 (2H, m),8.29 (1H, s),10.77 (1H, br).

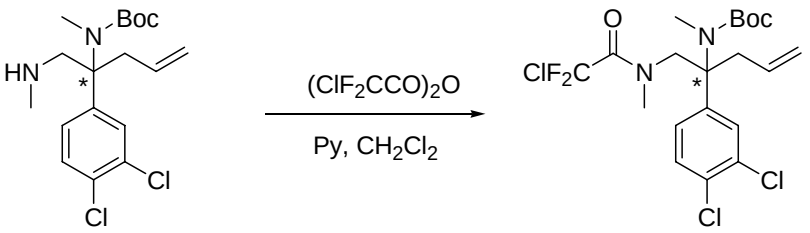
[0241]

Example 8(a)

Synthesis of tert-butyl [1-{[(2-chloro-2,2-difluoroacetyl)-methylamino]-methyl}-1-(3,4-dichlorophenyl)-3-butenyl]methylcarbamate

[0242]

[F46]



[0243]

tert-Butyl [1-(3,4-dichlorophenyl)-1-methylaminomethyl-3-butenyl]methylcarbamate (500 mg) produced in Example 4 was dissolved in methylene chloride (10 mL). Under cooling with ice, pyridine (163 μL) and chlorodifluoroacetic acid anhydride (350 μL) were added thereto. Under cooling with ice, the mixture was stirred for 50 minutes. Saturated aqueous sodium bicarbonate was added to the reaction mixture, and the resultant mixture was extracted with methylene chloride. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (n-hexane : ethyl acetate=4:1), to thereby give the title compound (300 mg, 46%).

[0244]

MS (FAB) m/z 487 ($(M+3H)^+$), 485 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.26 (9H, s),2.59 (1H, dd, J=7.0, 14Hz),2.78 (1H, dd, J=7.0, 14Hz),3.05 (3H, s),3.09 (3H, s),4.07-4.30 (1H, m),4.40(1H, d, J=12.5Hz),4.89-5.01 (2H, m),5.60-5.75 (1H, m),7.00 (1H, dd, J=2.5, 8.5Hz),7.24 (1H, d, J=2.5Hz),7.38 (1H, d, J=8.5Hz).

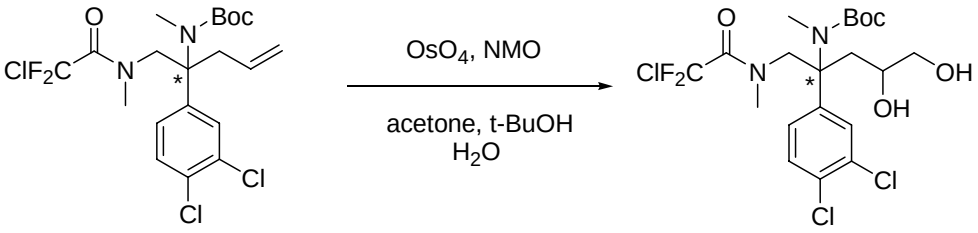
[0245]

Example 8(b)

Synthesis of tert-butyl [1-{[(2-chloro-2,2-difluoroacetyl)-methylamino]-methyl}-1-(3,4-dichlorophenyl)-3,4-dihydroxybutyl]methylcarbamate

[0246]

[F47]



[0247]

tert-Butyl [1-{[(2-chloro-2,2-difluoroacetyl)-methylamino]-methyl}-1-(3,4-dichlorophenyl)-3-butenyl]methylcarbamate (300 mg) was dissolved in a mixture solvent of acetone (10 mL), 2-methyl-2-propanol (5 mL), and water (5 mL). Osmium tetraoxide (2.5% 2-methyl-2-propanol solution) (148 μL) and N-methylmorpholine N-oxide (218 mg) were added thereto, and the mixture was stirred overnight at room temperature. Aqueous sodium thiosulfate was added to the reaction mixture, and the resultant mixture was stirred for 30 minutes at room temperature. The insoluble matter was

removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with methylene chloride. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure, to thereby give the title compound (323 mg, quantative amount). The compound was used in the next step without further purification.

[0248]

MS (FAB) m/z 521 ($(M+3H)^+$), 519 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.26 (9H, brs),1.78-1.90(1H,m),2.00-2.18 (2H, m),2.41 (1H, t, J=4.5Hz),3.11 (3H, s),3.20 (3H, s),3.39-3.68 (1H, m),3.72 (2H, t, J=4.5Hz),3.90-4.40 (1H, m),4.90-5.44 (1H, m),7.08 (1H, dd, J=2.0, 8.0Hz),7.29 (1H, d, J=2.0Hz),7.43 (1H, dd, J=4.5, 8.0Hz).

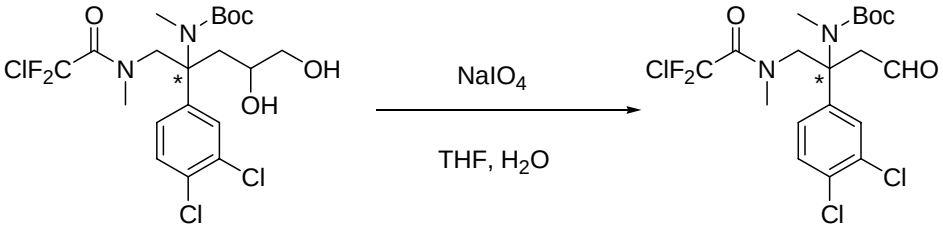
[0249]

Example 8(c)

Synthesis of tert-butyl [1-{[(2-chloro-2,2-difluoroacetyl)-methylamino]-methyl}-1-(3,4-dichlorophenyl)-3-oxo-propyl]methylcarbamate

[0250]

[F48]



[0251]

tert-Butyl [1-{[(2-chloro-2,2-difluoroacetyl)-methylamino]-methyl}-1-(3,4-dichlorophenyl)-3,4-dihydroxybutyl]methylcarbamate (323 mg) was dissolved in a mixture solvent of tetrahydrofuran (3 mL) and water (3 mL). Sodium periodate (266 mg) was added thereto, and the mixture was stirred for 1.5 hours at room temperature. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure, to thereby give the title compound (291 mg, 96%). The compound was used in the next step without further purification.

[0252]

MS (FAB) m/z 489 ($(M+3H)^+$), 487 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.28 (9H, s),2.97 (3H, s),3.04 (1H, d, J=16.5Hz),3.07 (3H, s),3.22 (1H, d, J=16.5Hz),4.36 (1H, d, J=13.5Hz),4.55 (1H,d, J=13.5Hz),7.12 (1H, dd, J=2.5, 8.5Hz),7.33 (1H, dd, J=2.5, 5.5Hz),7.43 (1H, dd, J=5.5, 8.5Hz),9.64 (1H, t, J=1.5Hz).

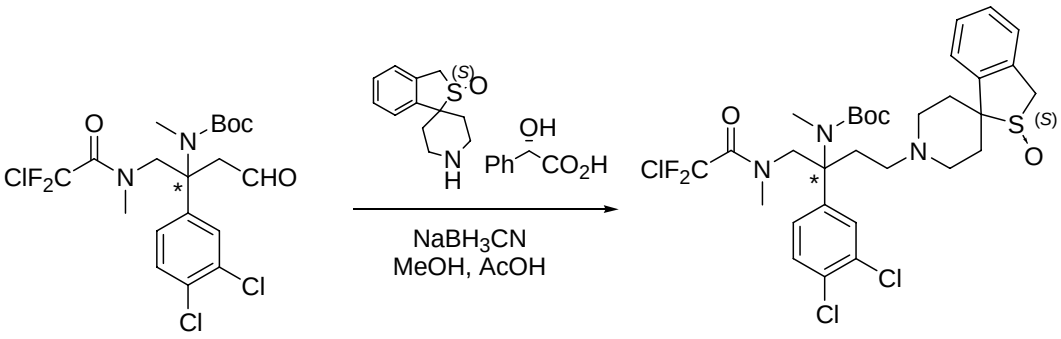
[0253]

Example 8(d)

Synthesis of tert-butyl {1-{[(2-chloro-2,2-difluoroacetyl)-methylamino]-methyl}-1-(3,4-dichlorophenyl)-3-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-propyl}-methyl-carbamate

[0254]

[F49]



[0255]

tert-Butyl [1-{[(2-chloro-2,2-difluoroacetyl)-methylamino]-methyl}-1-(3,4-dichlorophenyl)-3-oxo-propyl]methylcarbamate (956 mg) was dissolved in methanol (10 mL). Spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide/(S)-(+)-mandelate (878 mg) and sodium cyanoborohydride (156 mg) were added thereto. Acetic acid (0.3 mL) was added to the mixture to adjust the pH to 4, and the resultant mixture was stirred for 30 minutes at room temperature. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (sequentially through use of n-hexane : ethyl acetate=1:2 and chloroform : methanol=20:1), to thereby give the title compound (1.31 g, 96%).

[0256]

MS (FAB) m/z 694 ($(M+3H)^+$), 692 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.26 (9H, s),1.51 (1H, d,

J=15Hz),1.81-1.98 (1H, m),2.01-2.44 (7H, m),2.53-2.57 (1H, m),2.74 (1H, d, J=12Hz),2.88(1H, d, J=12Hz),3.06 (3H, s),3.11 (3H, s),3.98 (1H, d, J=17Hz),4.10-4.27(1H, m),4.30 (1H, d, J=17Hz),4.40-4.70 (1H, m),7.05 (1H, dd, J=2.5, 8.5Hz),7.20-7.38 (5H, m),7.42 (1H, d, J=8.5Hz).

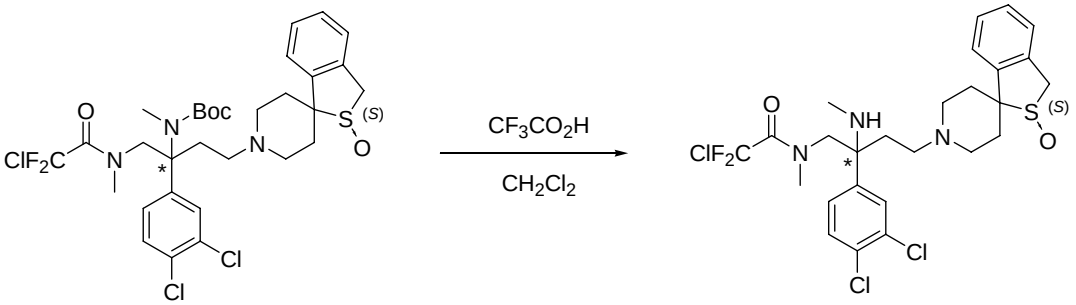
[0257]

Example 8(e)

Synthesis of 2-chloro-N-{2-(3,4-dichlorophenyl)-2-methylamino-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl}-2,2-difluoro-N-methyl-acetamide

[0258]

[F50]



[0259]

tert-Butyl {1-{[(2-chloro-2,2-difluoroacetyl)-methylamino]-methyl}-1-(3,4-dichlorophenyl)-3-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-propyl}-methyl-carbamate (1.31 g) was dissolved in methylene chloride (10 mL). Trifluoroacetic acid (5 mL) was added thereto, and the mixture was stirred for 45 minutes at room temperature. The reaction mixture was neutralized with saturated aqueous sodium bicarbonate, and the mixture was extracted with methylene chloride. The organic layer was

washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure, to thereby give the title compound (970 mg, 87%). The compound was used in the next step without further purification.

[0260]

MS (FAB) m/z 594 ((M+3H) $^{+}$), 592 ((M+H) $^{+}$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.57-1.65 (2H, m),1.96-2.22 (3H, m),2.28 (3H, s),2.35-2.52 (6H, m),2.75 (3H, t, J=2.0Hz),2.95 (1H, d, J=12Hz),3.06 (1H, d, J=10Hz),3.49 (1H, d, J=14Hz),3.91 (1H, d, J=14Hz),4.02 (1H, d, J=17Hz),4.34 (1H, d, J=17Hz),7.28-7.37 (5H, m),7.45 (1H, d, J=8.5Hz),7.66(1H, d, J=2.5Hz).

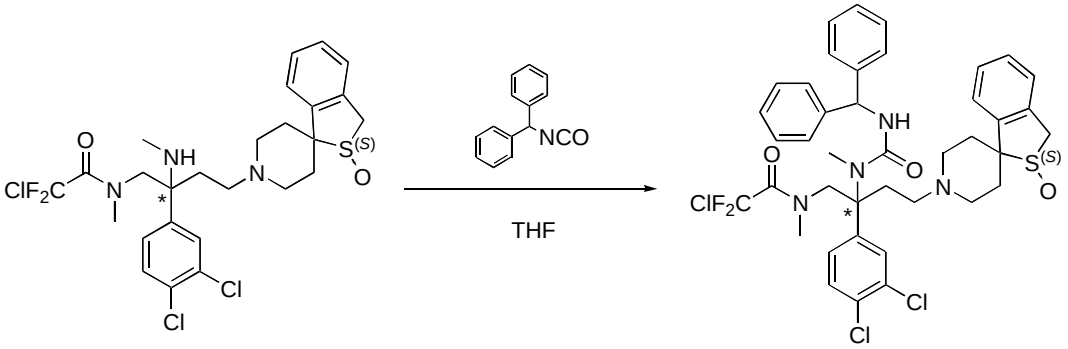
[0261]

Example 8(f)

Synthesis of N-{2-(3-benzohydryl-1-methylureido)-2-(3,4-dichlorophenyl)-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl}-2-chloro-2,2-difluoro-N-methyl-acetamide

[0262]

[F51]



[0263]

2-Chloro-N-{2-(3,4-dichlorophenyl)-2-methylamino-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl}-2,2-difluoro-N-methyl-acetamide (85 mg) was dissolved in tetrahydrofuran (2 mL). Diphenylmethyl isocyanate (90 mg) was added thereto, and the mixture was stirred for 2 hours at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was purified through silica gel column chromatography (sequentially through use of n-hexane : ethyl acetate=1:2 and chloroform : methanol=20:1).

[0264]

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.45-1.63(1H,m),1.78-1.93(1H,m),2.01-2.58(8H,m),2.70-2.95(5H,m),3.10(3H,s),3.98(1H,d,J=16.5Hz),4.30(1H,d,J=16.5Hz),4.42(2H,br),5.06(1H,d,J=7.0Hz),6.00(1H,d,J=7.0Hz),7.06(1H,dd,J=2.5,8.5Hz),7.10-7.33(16H,m).

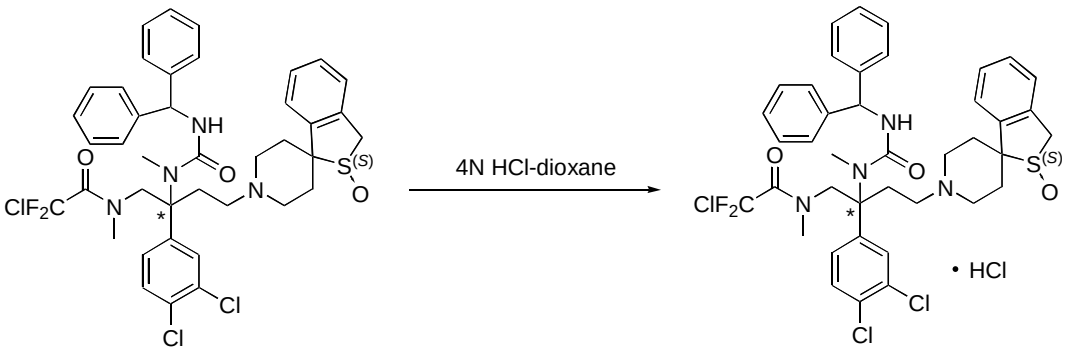
[0265]

Example 8(g)

Synthesis of N-{2-(3-benzohydryl-1-methylureido)-2-(3,4-dichlorophenyl)-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl}-2-chloro-2,2-difluoro-N-methyl-acetamide hydrochloride (Compound No. 4)

[0266]

[F52]



[0267]

N-{2-(3-benzohydryl-1-methylureido)-2-(3,4-dichlorophenyl)-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl}-2-chloro-2,2-difluoro-N-methyl-acetamide was dissolved in methylene chloride. 4N HCl-1,4-dioxane was added thereto, and the mixture was concentrated under reduced pressure. Ether was added to the residue, followed by filtration and drying, to thereby give the title compound (104 mg, 88%).

[0268]

MS(FAB) m/z:803 ($(M+3H)^+$), 801 ($(M+H)^+$)

^{1}H-NMR (270MHz, DMSO-d_6)δ ppm:1.99 (1H, d, J=15Hz),2.26 (2H, d, J=13Hz),2.40-2.62 (1H, m),2.70-2.88 (4H, m),2.90-3.18 (7H, m),3.20-3.43 (2H, m),3.55 (2H, d, J=9.0Hz),4.08 (1H, d, J=17Hz),4.22-4.28 (2H, m),4.68 (1H, d,J=17Hz),5.84 (1H, d, J=7.5Hz),7.22-7.40 (15H, m),7.55 (2H, d, J=8.5Hz),10.78 (1H, br).

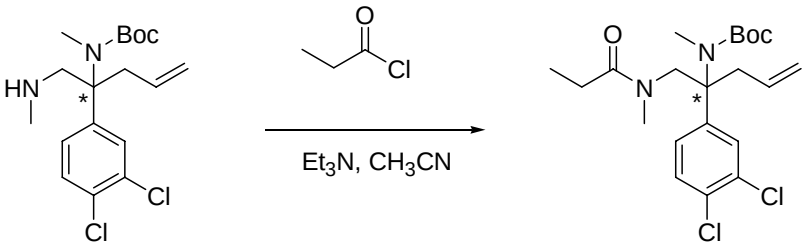
[0269]

Example 9(a)

Synthesis of tert-butyl {1-(3,4-dichlorophenyl)-1-[(methylpropionylamino)-methyl]-3-butenyl-methyl-carbamate

[0270]

[F53]



[0271]

tert-Butyl [1-(3,4-dichlorophenyl)-1-methylaminomethyl-3-butenyl]methylcarbamate (2.0 g) produced in Example 4 was dissolved in acetonitrile (40 mL). Under cooling with ice, triethylamine (1.49 mL) and propionyl chloride (932 μL) were added thereto. Under cooling with ice, the mixture was stirred for 1 hour. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (n-hexane : ethyl acetate=2:1), to thereby give the title compound (1.44 g, 63%).

[0272]

MS (FAB) m/z 429 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.16 (3H, t, J=7.5Hz),1.19 (9H, brs),2.35 (2H, q, J=7.5Hz),2.57 (1H, dd, J=7.5, 13.5Hz),2.75 (3H, s),2.67-2.88 (1Hm),3.08 (3H, s),3.97-4.32 (2H, m),4.82-5.03 (2H, m),5.72-5.93 (1H, m),7.01 (1H, dd, J=2.5, 8.5Hz),7.26 (1H, d, J=2.5Hz),7.36 (1H, d, J=8.5Hz).

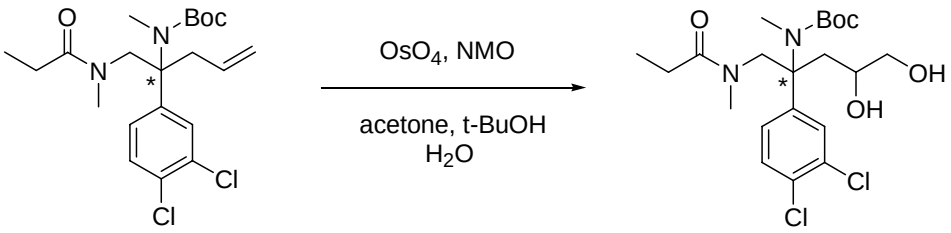
[0273]

Example 9(b)

Synthesis of tert-butyl {1-(3,4-dichlorophenyl)-3,4-dihydroxy-1-[(methylpropionylamino)-methyl]-butyl}-methyl-carbamate

[0274]

[F54]



[0275]

tert-Butyl {1-(3,4-dichlorophenyl)-1-[(methylpropionylamino)-methyl]-3-butenyl}-methyl-carbamate (1.0 g) was dissolved in a mixture solvent of acetone (3 mL), 2-methyl-2-propanol (1.5 mL), and water (1.5 mL). Osmium tetraoxide(2.5% 2-methyl-2-propanol solution) (278 μL) and N-methylmorpholine N-oxide (546 mg) were added thereto, and the mixture was stirred overnight at room temperature. Aqueous sodium thiosulfate was added to the reaction mixture, and the resultant mixture was stirred for 10 minutes at room temperature. The insoluble matter was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with methylene chloride. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure,

to thereby give the title compound (1.09 g, quantative amount). The compound was used in the next step without further purification.

[0276]

MS (FAB) m/z 463 ((M+H) $^{+}$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:0.93-1.45 (12H, m),1.98-2.50 (7H, m),2.80-3.80 (8H, m),5.00-5.28 (1H, m),5.50-5.75 (1H, m),7.00-7.16 (1H, m),7.20-7.32 (1H, m),7.40 (1H, d, J=8.5Hz).

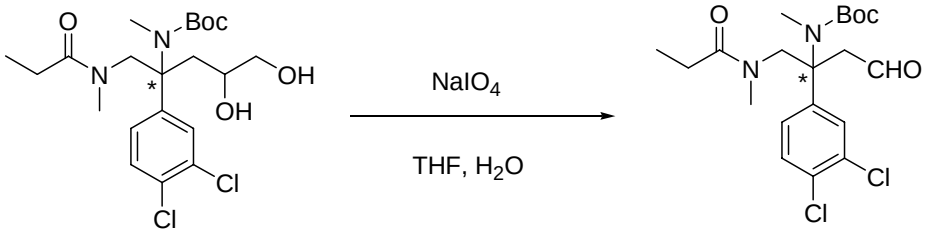
[0277]

Example 9(c)

Synthesis of tert-butyl {1-(3,4-dichlorophenyl)-1-[(methylpropionylamino)-methyl]-3-oxo-propyl}-methyl-carbamate

[0278]

[F55]



[0279]

tert-Butyl {1-(3,4-dichlorophenyl)-3,4-dihydroxy-1-[(methylpropionylamino)-methyl]-butyl}-methyl-carbamate (1.09 g) was dissolved in a mixture solvent of tetrahydrofuran (8 mL) and water (8 mL). Sodium periodate (1.0 g) was added thereto, and the mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated under reduced pressure, and water was added to the residue,

followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure, to thereby give the title compound (1.05 g, quantative amount). The compound was used in the next step without further purification.

[0280]

MS (FAB) m/z 431 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.15 (3H, t, J=7.5Hz),1.24 (9H, s),2.35 (2H,q, J=7.5Hz),2.69 (3H, s),2.95 (1H, d, J=14.5Hz),3.09 (3H, s),3.20 (1H, d,J=14.5Hz),4.17 (1H, d, J=13.5Hz), 4.44 (1H, d, J=13.5Hz),7.11 (1H, dd,J=2.5, 8.5Hz),7.33 (1H, d, J=2.5Hz),7.42 (1H, d, J=8.5Hz),9.71 (1H, t, J=2.0Hz).

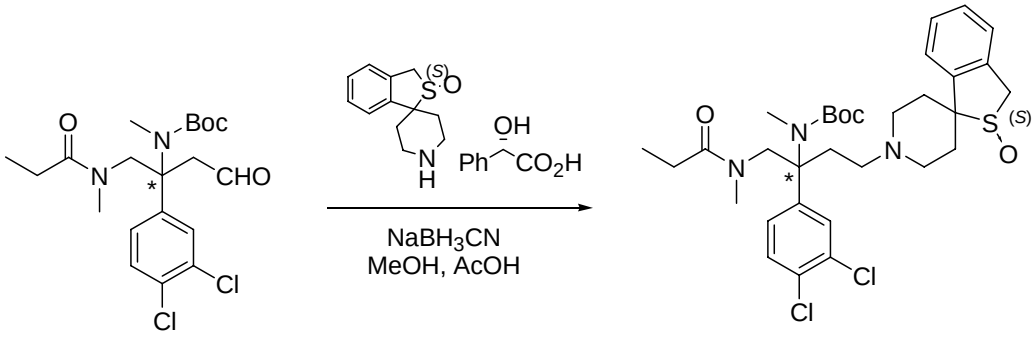
[0281]

Example 9(d)

Synthesis of tert-butyl {1-(3,4-dichlorophenyl)-1-[(methylpropionylamino)-methyl]-3-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-propyl}-methyl-carbamate

[0282]

[F56]



[0283]

tert-Butyl {1-(3,4-dichlorophenyl)-1-[(methylpropionylamino)-methyl]-3-oxo-propyl}-methyl-carbamate (300 mg) was dissolved in methanol (5 mL). Spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide/(S)-(+)-mandelate (363 mg) and sodium cyanoborohydride (65 mg) was added thereto. Acetic acid was added to the mixture to adjust the pH to 4, and the mixture was stirred for 30 minutes at room temperature. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, followed by extraction with chloroform. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (sequentially through use of n-hexane : ethyl acetate=1:4 and chloroform : methanol=10:1), to thereby give the title compound (504 mg, 68%).

[0284]

MS (FAB) m/z 636 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.18 (3H, t, J=7.5Hz),1.25 (9H, brs),1.65-2.15 (6H, m),2.20-3.25 (13H, m),3.15 (3H, s),4.00-

4.25 (1H, m),4.35-4.52 (1H, m),7.12 (1H, d, J=8.5Hz),7.18-7.55 (6H, m).

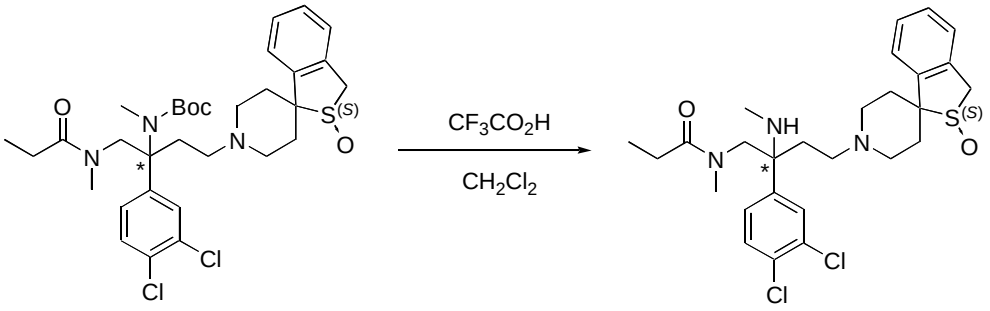
[0285]

Example 9(e)

Synthesis of N-[2-(3,4-dichlorophenyl)-2-methylamino-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl]-N-methyl-propionamide

[0286]

[F57]



[0287]

tert-Butyl {1-(3,4-dichlorophenyl)-1-[(isobutyrylmethylamino)-methyl]-3-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-propyl}-methyl-carbamate (504 mg) was dissolved in methylene chloride (10 mL). Trifluoroacetic acid (5 mL) was added thereto, and the mixture was stirred for 30 minutes at room temperature. The reaction mixture was neutralized with saturated aqueous sodium bicarbonate, and the mixture was extracted with methylene chloride. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure, to thereby give the title compound (418 mg, 98%). The compound was used in the

next step without further purification.

[0288]

MS (FAB) m/z 536 ($(M-H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:0.78-0.93 (1H, m),1.12 (3H, t, J=7.5Hz),1.06-1.18 (1H, m),1.58-1.92 (3H, m),2.10-2.66 (8H, m),2.21 (3H, s),2.29 (2H,q, J=7.5Hz),2.44 (3H, s),3.96-4.14 (2H, m),4.30-4.50 (2H, m),7.13-7.58(7H, m).

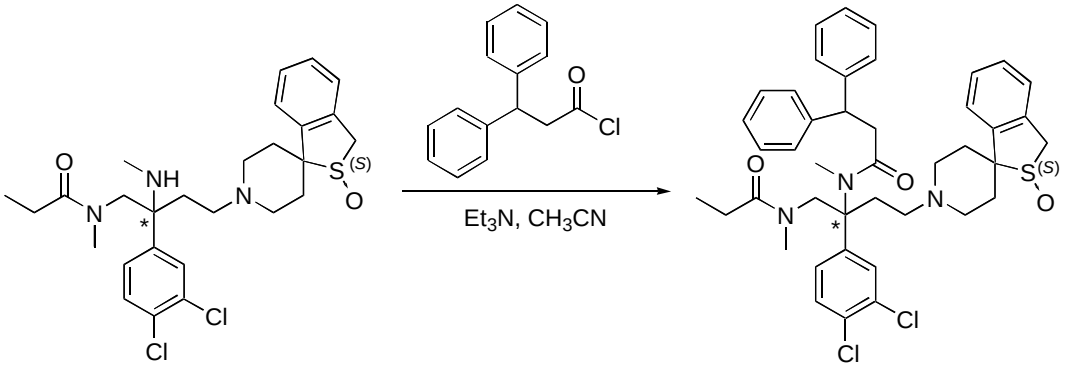
[0289]

Example 9(f)

Synthesis of N-{2-(3,4-dichlorophenyl)-2-[(3,3-diphenylpropionyl)-methylamino]-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl}-N-methyl-propionamide

[0290]

[F58]



[0291]

N-[2-(3,4-Dichlorophenyl)-2-methylamino-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl]-N-methyl-propionamide (418 mg) was dissolved in acetonitrile (10 mL). Under cooling with ice, triethylamine (217 μL) and 3,3 –diphenylpropionyl chloride (381 mg) were

added thereto. Under cooling with ice, the mixture was stirred for 1 hour. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (sequentially through use of n-hexane : ethyl acetate=1:4, ethyl acetate : methanol=10:1, and chloroform : methanol=10:1).

[0292]

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm:1.10(3H,t,J=7.5Hz),1.43-1.57(1H,m),1.77-1.92(1H,m),1.96-2.08(1H,m),2.10-2.50(9H,m),2.47(3H,s),2.66-2.90(2H,m),3.00-3.20(5H,m),3.90-4.08(2H,m),4.22-4.38(2H,m),4.62(1H,t,J=7.5Hz),6.74(1H,d,J=8.5Hz),7.10-7.35(16H,m).

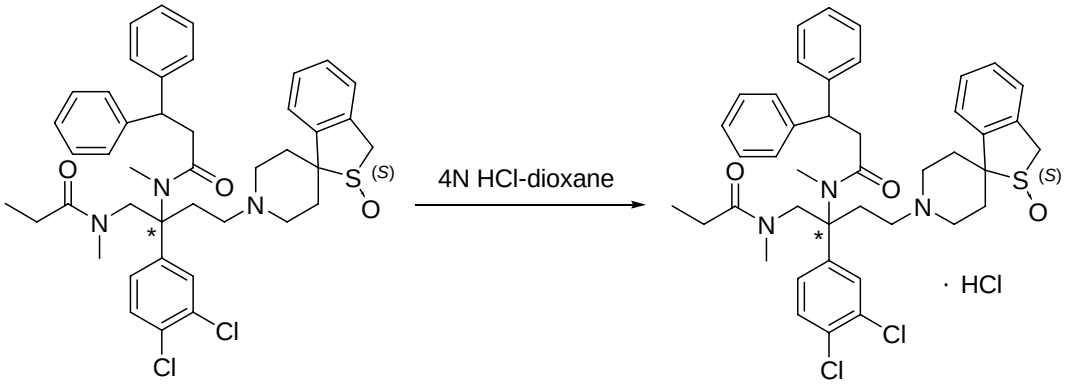
[0293]

Example 9(g)

Synthesis of N-{2-(3,4-dichlorophenyl)-2-[(3,3-diphenylpropionyl)-methylamino]-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl}-N-methyl-propionamide hydrochloride (Compound No. 5)

[0294]

[F59]



[0295]

N-{2-(3,4-Dichlorophenyl)-2-[(3,3-diphenylpropionyl)-methylamino]-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxide}-1'-yl-butyl}-N-methyl-propionamide was dissolved in methylene chloride. 4N HCl-1,4-dioxane was added thereto, and the mixture was concentrated under reduced pressure. Ether was added to the residue, followed by filtration and drying, to thereby give the title compound (388 mg, 64%).

[0296]

MS (FAB) m/z 744 ($(M+H)^+$)

^{1}H-NMR (270MHz, DMSO-d_6)δ ppm:0.97 (3H, t, J=7.5Hz),1.96 (1H, d, J=14.5Hz),2.15-2.60 (13H, m),2.88-3.52 (11H, m),3.20 (3H, s),3.41 (3H, s),3.70-3.90 (1H, m),4.08 (1H, d, J=17Hz),4.18 (1H, d, J=12.5Hz),4.36 (1H, t, J=7.0Hz),4.68 (1H, d, J=17Hz),7.00-7.50 (17H, m),10.89 (1H, br).

[0297]

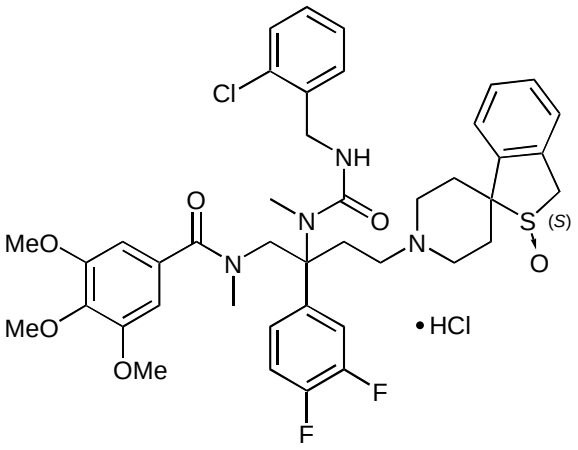
Example 10

N-{2-[3-(2-Chloro-benzyl)-1-methyl-ureido]-2-(3,4-difluoro-phenyl)-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxido}-1'-yl-butyl}-3,4,5-trimethoxy-N-methyl-benzamide

hydrochloride (Compound No. 6)

[0298]

[F60]



[0299]

Racemic compound

MS(FAB)m/z 809 ($(M+H)^+$)

^{1}H-NMR(270MHz, DMSO-d_6)δppm:1.92-2.10(1H,m), 2.18-2.32(2H,m), 2.40-2.88(4H,m), 3.06(3H,s), 3.00-3.30(5H,m), 3.43-3.82(12H,m), 3.90-4.13(2H,m), 4.20-4.30(2H,m), 4.43-4.57(1H,m), 4.67(1H,d,J=17Hz), 6.63(2H,s), 7.10-7.60(12H,m), 10.6(1H,br).

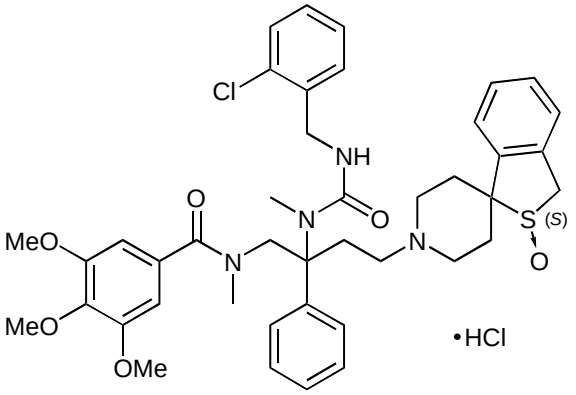
[0300]

Example 11

N-{2-[3-(2-Chloro-benzyl)-1-methyl-ureido]-2-phenyl-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxido}-1'-yl-butyl}-3,4,5-trimethoxy-N-methyl-benzamide hydrochloride (Compound No. 7)

[0301]

[F61]



[0302]

Racemic compound

MS(FAB)m/z 773 ($(M+H)^+$)

^{1}H-NMR(270MHz, DMSO-d_6)δppm:1.92-2.08(1H,m), 2.20-2.40(4H,m), 2.58-2.90(3H,m), 2.94(3H,s), 3.00-3.30(5H,m), 3.47-3.97(12H,m), 4.07(1H,d,J=17Hz), 4.22-4.34(2H,m), 4.60-4.78(2H,m), 6.59(2H,s), 7.03-7.14(1H,m), 7.20-7.52(13H,m),10.6(1H,br).

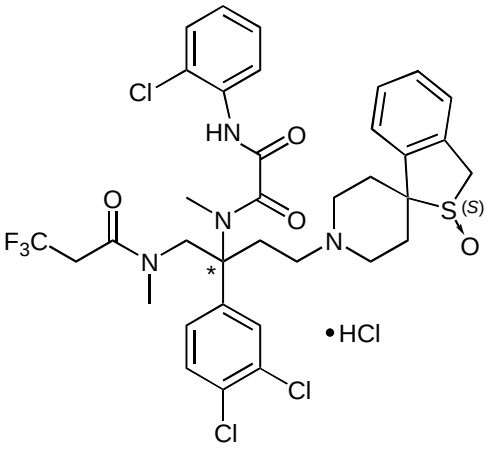
[0303]

Example 13

N-(2-Chloro-phenyl)-N'-{1-(3,4-dichloro-phenyl)-1-{[methyl-(3,3,3-trifluoro-propionyl)-amino]-methyl}-3-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxido}-1'-yl-propyl}-N'-methyl-oxalamide hydrochloride (Compound No. 9)

[0304]

[F62]



[0305]

MS(FAB)m/z 772 ($(M+H)^+$)

^{1}H-NMR(270MHz, DMSO-d_6)δppm:1.92-2.10(1H,m), 2.20-2.40(2H,m), 2.52-2.94(5H,m), 3.00-3.42(7H,m), 3.50-3.80(5H,m), 3.92-4.10(1H,m), 4.09(1H,d,J=17Hz), 4.54(1H,d,J=13.5Hz), 4.70(1H,d,J=17Hz), 7.25-7.40(7H,m), 7.53-7.70(4H,m), 10.34(1H,s), 10.72(1H,br).

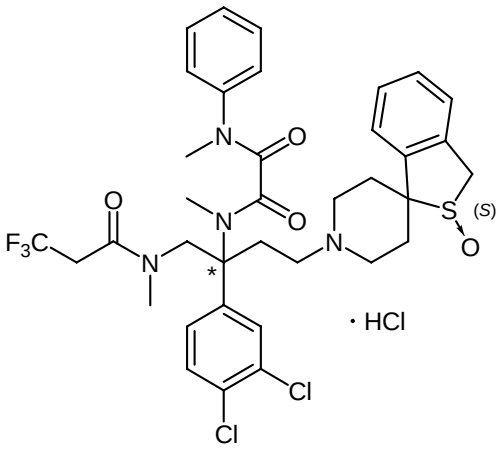
[0306]

Example 14

N-{1-(3,4-Dichloro-phenyl)-1-{[methyl-(3,3,3-trifluoro-propionyl)-amino]-methyl}-3-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxido}-1'-yl-propyl}-N,N'-dimethyl-N'-phenyl-oxalamide hydlochloride (Compound No. 10)

[0307]

[F63]



[0308]

MS(FAB)m/z 751 ($(M+H)^+$)

^{1}H-NMR(270MHz, DMSO-d_6)δppm:1.92-2.12(1H,m), 2.20-2.65(5H,m), 2.73-3.83(18H,m), 3.90-4.28(2H,m), 4.69(1H,d,J=17Hz), 6.64(1H,br), 7.26-7.60(11H,m), 10.68(1H,br).

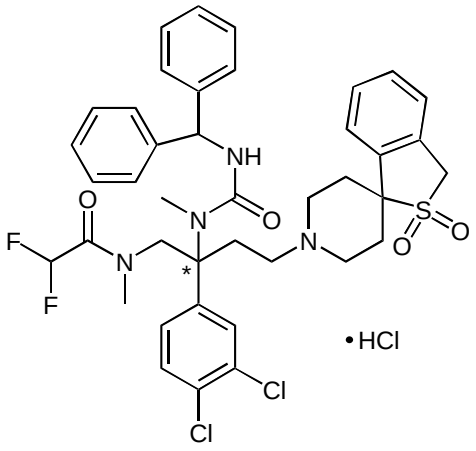
[0309]

Example 15

N-[2-(3-Benzhydryl-1-methyl-ureido)-2-(3,4-dichloro-phenyl)-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-2,2-dioxido}-1'-yl-butyl]-2,2-difluoro-N-methyl-acetamide hydrochloride (Compound No. 11)

[0310]

[F64]



[0311]

MS(FAB)m/z 783 ($(M+H)^+$)

^{1}H-NMR(270MHz, DMSO-d_6)δppm:2.35-2.80(9H,m), 2.90-3.80(10H,m), 4.05-4.20(1H,m), 4.26(1H,d,J=13.5Hz), 4.76(2H,s), 5.83(1H,d,J=7.5Hz), 6.66(1H,t,J=52.5Hz), 7.20-7.65(17H,m), 10.99(1H,br).

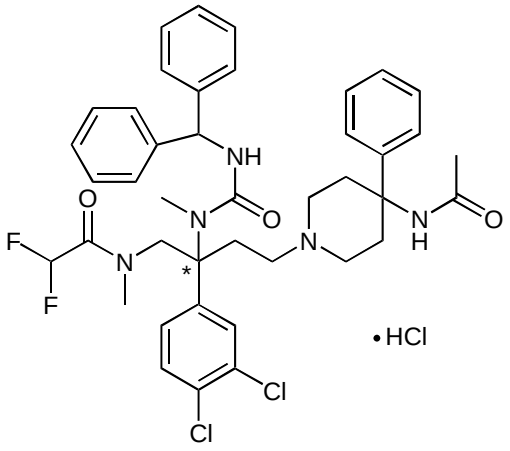
[0312]

Example 16

N-[4-(4-Acetylamino-4-phenyl-piperidine-1'-yl)-2-(3-benzhydryl-1-methyl-ureido)-2-(3,4-dichlorophenyl)-butyl]-2,2-difluoro-N-methyl-acetamide hydrochloride (Compound No. 12)

[0313]

[F65]



[0314]

MS(FAB)m/z 764 ($(M+H)^+$)

^{1}H-NMR(270MHz, DMSO-d_6)δppm:1.93(3H,s), 2.13-2.75(8H,m), 2.85-3.80(11H,m), 4.05-4.20(1H,m), 4.27(1H,d,J=13.5Hz), 5.83(1H,d,J=7.5Hz), 6.68(1H,t,J=52.5Hz), 7.18-7.45(16H,m), 7.50-7.62(2H,m), 8.19(1H,s), 10.11(1H,br).

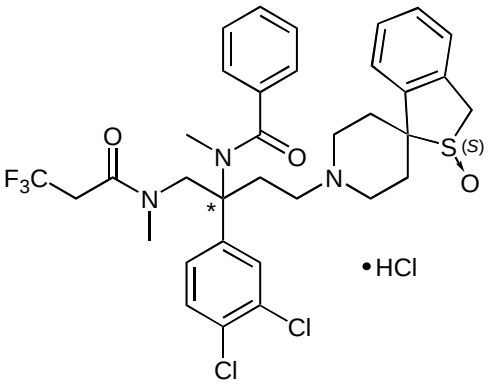
[0315]

Example 17

N-{1-(3,4-Dichloro-phenyl)-1-{[methyl-(3,3,3-trifluoro-propionyl)-amino]-methyl}-3-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxido}-1'-yl-propyl}-N-methyl-benzamide hydrochloride (Compound No. 13)

[0316]

[F66]



[0317]

MS(FAB)m/z 694 ((M+H) $^{+}$)

^{1}H-NMR(270MHz, DMSO-d_6)δppm:2.02(1H,d,J=16Hz), 2.20-2.40(2H,m), 2.52-2.90(6H,m), 3.00-3.80(11H,m), 4.02-4.18(2H,m), 4.50(1H,d,J=13.5Hz), 4.70(1H,d,J=17.5Hz), 7.26-7.65(11H,m), 7.75(1H,s), 10.57(1H,br).

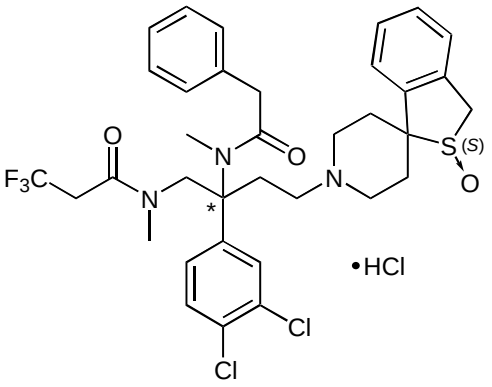
[0318]

Example 18

N-[2-(3,4-Dichloro-phenyl)-2-(methyl-phenylacetyl-amino)-4-{spiro[benzo(c)thiophene-1(3H),4'-piperidine]-(2S)-oxido}-1'-yl-butyl]-3,3,3-trifluoro-N-methyl-propionamide hydrochloride (Compound No. 14)

[0319]

[F67]



[0320]

MS(FAB)m/z 708 ((M+H) $^{+}$)

^{1}H-NMR(270MHz, DMSO-d_6)δppm:1.99(1H,d,J=15Hz), 2.20-2.90(8H,m), 2.94-3.20(7H,m), 3.46-3.80(7H,m), 3.85-4.00(1H,m), 4.08(1H,d,J=17Hz), 4.33(1H,d,J=14Hz), 4.70(1H,d,J=17Hz), 7.10-7.58(12H,m), 10.6(1H,br).

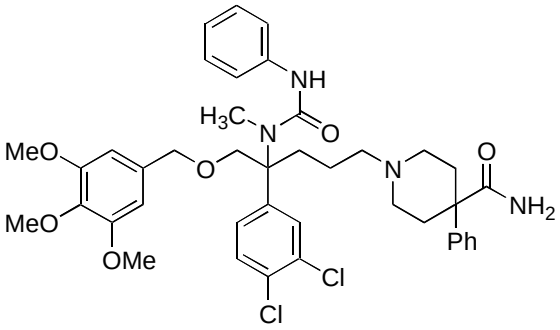
[0321]

Example 19

1-[4-(3,4-Dichloro-phenyl)-4-(1-methyl-3-phenyl-ureido)-5-(3,4,5-trimethoxy-benzyloxy)-pentyl]-4-phenyl-piperidine-4-carboxylic acid amide (Compound No. 15)

[0322]

[F68]



[0323]

Racemic compound

MS(FAB)m/z 763 ((M+H) $^{+}$)

^{1}H-NMR(270MHz, $CDCl_3$)δppm:1.20-1.38(2H,m), 1.95-2.10(4H,m), 2.16-2.40(6H,m), 2.42-2.58(2H,m), 3.05(3H,s), 3.77(6H,s), 3.83(3H,s), 4.00(1H,d,J=10Hz), 4.09(1H,d,J=10Hz), 4.48(2H,s), 5.18(2H,br), 6.44(2H,s), 6.86-7.00(3H,m), 7.18-7.40(10H,m), 7.45(1H,d,J=2.0Hz).

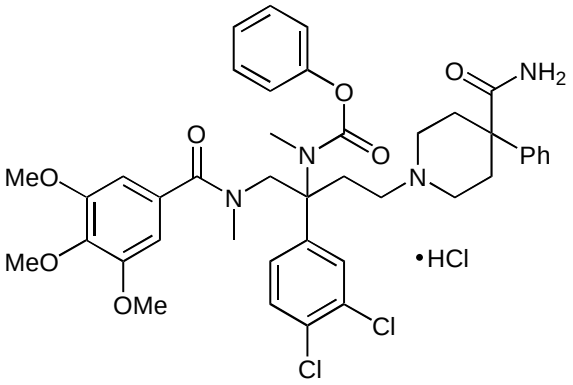
[0324]

Example 20

(3-(4-Carbamoyl-4-phenyl-piperidine-1-yl)-1-(3,4-dichloro-phenyl)-1-{[methyl-(3,4,5-trimethoxy-benzoyl)-amino]-methyl}-propyl)-methyl-carbamic acid phenyl ester hydrochloride (Compound No. 16)

[0325]

[F69]



[0326]

Racemic compound

MS(FAB)m/z 777 ((M+H) $^{+}$)

^{1}H-NMR(270MHz, DMSO-d_6)δppm:2.00-2.20(2H,m), 2.52-3.40(16H,m), 3.50-3.82(2H,m), 3.68(3H,s), 3.80(6H,s), 3.90-4.10(1H,m),

4.57-4.72(1H,m), 6.66(2H,s), 6.93-7.60(11H,m),7.67(1H,d,J=8.0Hz), 7.78(1H,brs), 10.70(1H,br).

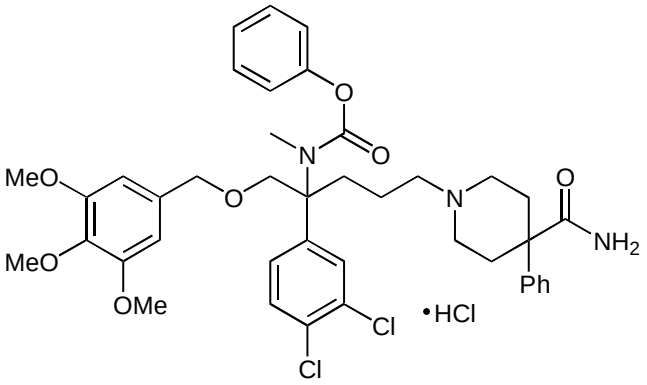
[0327]

Example 21

[4-(4-Carbamoyl-4-phenyl-piperidine-1-yl)-1-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzyloxymethyl)-butyl]-methyl-carbamic acid phenyl ester hydrochloride (Compound No. 17)

[0328]

[F70]



[0329]

Racemic compound

MS(FAB)m/z 764 ($(M+H)^+$)

^{1}H-NMR(270MHz, $CDCl_3$)δppm:2.24-2.80(8H,m), 2.86-3.15(4H,m), 3.31(3H,s),3.38-3.52(2H,m), 3.82(9H,s), 3.90-4.10(2H,m), 4.44(2H,s), 5.22-5.38(2H,m), 6.45(2H,s), 6.80-7.08(2H,m), 7.10-7.48(11H,m), 12.18(1H,br).

[0330]

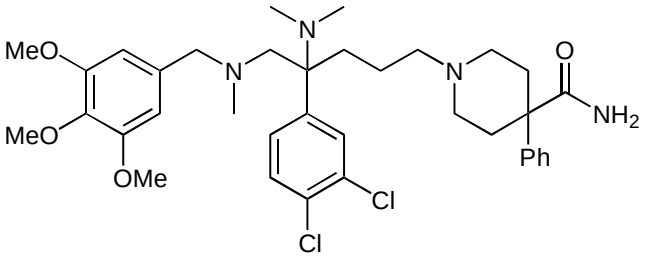
Example 22

1-{4-(3,4-Dichloro-phenyl)-4-dimethylamino-5-[methyl-(3,4,5-trimethoxy-benzyl)-amino]-pentyl}-4-phenyl-piperidine-4-

carboxylic acid amide (Compound No. 18)

[0331]

[F71]



[0332]

Racemic compound

MS(FAB)m/z 671 ($(M+H)^+$)

^{1}H-NMR(270MHz, $CDCl_3$)δppm:1.30-1.48(2H,m), 1.95-2.45(19H,m), 2.50-2.65(2H,m), 2.79(1H,d,J=14Hz), 2.98(1H,d,J=14Hz), 3.33(1H,d,J=13Hz), 3.53(1H,d,J=13Hz), 3.82(3H,s), 3.83(6H,s), 5.19(2H,br), 6.48(2H,s), 7.20-7.45(7H,m), 7.64(1H,s).

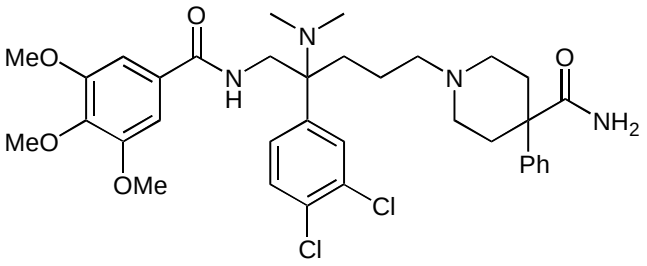
[0333]

Example 23

1-[4-(3,4-Dichloro-phenyl)-4-dimethylamino-5-(3,4,5-trimethoxy-benzoylamino)-pentyl]-4-phenyl-piperidine-4-carboxylic acid amide (Compound No. 19)

[0334]

[F72]



[0335]

Racemic compound

MS(FAB)m/z 671 ($(M+H)^+$)

^{1}H-NMR(270MHz, $CDCl_3$)δppm:1.33-1.56(2H,m), 1.72-1.88(1H,m), 1.94-2.10(3H,m), 2.20-2.40(12H,m), 2.44-2.58(2H,m), 3.67-3.78(1H,m), 3.82-4.00(10H,m), 5.15(2H,br), 6.50-6.58(1H,m), 6.92(2H,s), 7.20-7.38(6H,m), 7.44(1H,d,J=8.5Hz), 7.52(1H,d,J=2.0Hz).

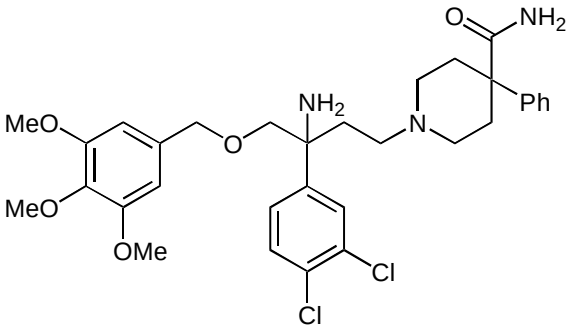
[0336]

Example 24

1-[3-Amino-3-(3,4-dichloro-phenyl)-4-(3,4,5-trimethoxy-benzyloxy)-butyl]-4-phenyl-piperidine-4-carboxylic acid amide (Compound No. 20)

[0337]

[F73]



[0338]

Racemic compound

MS(FAB)m/z 616 ($(M+H)^+$)

^{1}H-NMR(270MHz, $CDCl_3$)δppm:1.78-2.70(14H,m), 3.52(2H,dd,J=9.0, 25.5Hz), 3.80(6H,s), 3.83(3H,s), 4.41(2H,dd,J=12, 26.5Hz), 5.25(2H,br), 6.41(2H,s), 7.25-7.39(7H,m), 7.59(1H,d,J=2.0Hz).

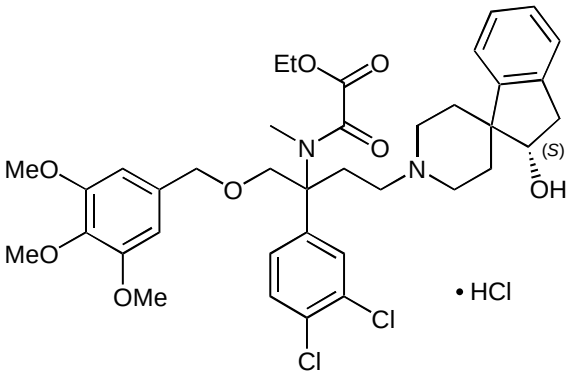
[0339]

Example 25

N-[1-(3,4-Dichloro-phenyl)-3-{spiro[((2S)-hydroxy)indan-1,4'-piperidine]}-1'-yl-1-(3,4,5-trimethoxy-benzyloxymethyl)-propyl]-N-methyl-oxamic acid ethyl ester hydrochloride (Compound No. 21)

[0340]

[F74]



[0341]

Racemic compound

MS(FAB)m/z 729 ($(M+H)^+$)

^{1}H-NMR(270MHz, DMSO-d_6)δppm:1.09(3H,t,J=7.0Hz) 1.56-1.67(1H,m), 1.88-2.34(4H,m), 2.60-3.00(5H,m), 3.08-3.78(14H,m), 3.92-4.10(2H,m), 4.31(2H,q,J=7.0Hz), 4.27-4.50(3H,m), 5.05(1H,br), 6.50(2H,s), 6.54(2H,br), 7.05-7.50(5H,m), 7.63(1H,s), 7.65(1H,d,J=8.5Hz), 10.16(1H,br).

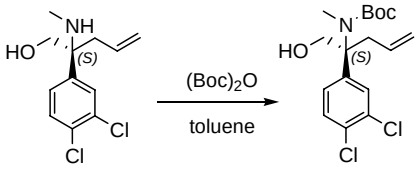
[0342]

Example 26(a)

Synthesis of tert-butyl [2-(S)-(3,4-dichlorophenyl)-1-hydroxy(4-pentene)-2-yl]-methylcarbamate

[0343]

[F75]



[0344]

2-(S)-(3,4-Dichlorophenyl)-2-methylamino-4-pentenol (271.5 g) was dissolved in absolute toluene (1.0 L). At room temperature, a solution of di-tert-butylcarbonate (341.6 g) in absolute toluene (0.36 L) was added thereto, and the mixture was refluxed for 3 hours. Under cooling with ice, 28% aqueous ammonia (76 mL) was added to the reaction mixture, and the resultant mixture was stirred for 30 minutes. n-Hexane (0.8 L) was added to the reaction mixture. The organic layer was sequentially washed with water, 1.5% hydrochloric acid, water, saturated aqueous sodium bicarbonate, water, and saturated brine, and then dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, to thereby give the title compound (383 g). The compound was used in the next step without further purification.

[0345]

MS (EI) m/z 359 (M^+)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.38 (9H, s), 2.75 (3H, s), 2.70—2.98 (2H, m), 3.68—3.82 (1H, m), 4.02—4.18 (1H, m), 5.10—5.25 (2H, m), 5.75—5.97 (1H, m), 7.12 (1H, dd, J = 2.5, 8.5Hz), 7.36 (1H, d, J = 2.5Hz), 7.41 (1H, d, J = 8.5Hz).

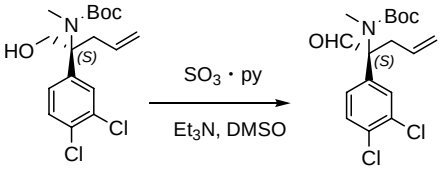
[0346]

Example 26(b)

Synthesis of tert-butyl [1-(S)-(3,4-dichlorophenyl)-1-formyl(3-butenyl)]methylcarbamate

[0347]

[F76]



[0348]

tert-Butyl [2-(S)-(3,4-dichlorophenyl)-1-hydroxy(4-pentene)-2-yl]-methylcarbamate (383 g) was dissolved in anhydrous dimethyl sulfoxide (1.92 L). At room temperature, triethylamine (636 g) was added thereto. Under cooling with ice, pyridine sulfur trioxide complex (499 g) was added to the mixture, and the resultant mixture was stirred for 3 hours at room temperature. The reaction mixture was poured into ice-water and then extracted with ethyl acetate. The organic layer was sequentially washed with saturated aqueous sodium bicarbonate, water, and saturated brine, and then dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, to thereby give the title compound (417.8 g). The compound was used in the next step without further purification.

[0349]

MS (EI) m/z 357 (M^+)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.47 (9H, s), 2.53–2.77 (4H, m),

3.32—3.50 (1H, m), 5.05—5.25 (2H, m), 5.83—6.07 (1H, m), 7.22 (1H, dd, J = 2.5, 8.5 Hz), 7.46 (1H, d, J = 2.5 Hz), 7.49 (1H, d, J = 8.5 Hz), 9.36 (1H, s).

[0350]

Example 26(c)

Synthesis of tert-butyl [2-(S)-(3,4-dichlorophenyl)-1-methylimino(4-penten-2-yl)]methylcarbamate

[0351]

[F77]



[0352]

At room temperature, 40% methylamine-methanol solution (1,230 mL) was added to acetic acid (529 g), and the mixture was stirred for 20 minutes. A solution of tert-butyl [1-(S)-(3,4-dichlorophenyl)-1-formyl(3-butenyl)]methylcarbamate (330.1 g) in methanol (600 mL) was added to the reaction mixture, and the resultant mixture was refluxed for 1 hour. 40% Methylamine-methanol solution (137 mL) was further added to the mixture, and the resultant mixture was refluxed for another 15 minutes. The reaction mixture was poured into saturated aqueous sodium bicarbonate, extracted with ethyl acetate, sequentially washed with water and saturated brine, and dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, to thereby give the title compound (324.5 g). The compound was used in the next

step without further purification.

[0353]

MS (EI) m/z 370 (M^+)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.35 (9H, s), 2.76 (3H, s), 2.80—2.93 (1H, m), 3.25 (3H, d, J = 2.0 Hz), 3.30—3.42 (1H, m), 5.01—5.18 (2H, m), 5.80—6.00 (1H, m), 7.15 (1H, dd, J = 2.0, 8.5 Hz), 7.35—7.46 (2H, m), 7.78 (1H, s).

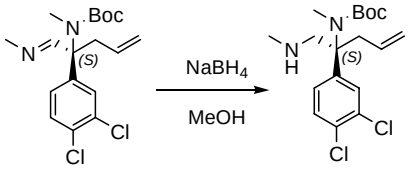
[0354]

Example 26(d)

Synthesis of tert-butyl [2-(S)-(3,4-dichlorophenyl)-1-methylamino(4-penten-2-yl)]methylcarbamate

[0355]

[F78]



[0356]

tert-Butyl [2-(S)-(3,4-dichlorophenyl)-1-methylimino(4-penten-2-yl)]methylcarbamate (314.5 g) was dissolved in methanol (2 L). Under cooling with ice, sodium boron hydride (38.5 g) was added thereto, and the mixture was stirred for 3 hours. Acetone (177 g) was added to the reaction mixture and then stirred for 30 minutes. The reaction mixture was poured into water, and the resultant mixture was extracted with ethyl acetate. The organic layer was sequentially washed with water and saturated brine and dried over sodium sulfate anhydrate. The solvent was concentrated under reduced

pressure, and the residue was dissolved in methanol (2 L). Under cooling with ice, sodium boron hydride (16.0 g) was added thereto, and the mixture was stirred for 30 minutes. Acetone (49.2 g) was added to the reaction mixture, and the resultant mixture was stirred for 30 minutes. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The organic layer was sequentially washed with water and saturated brine and dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, to thereby give the title compound (318.8 g). The compound was used in the next step without further purification.

[0357]

MS (EI) m/z 372 (M^+)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.19 (9H, s), 2.33 (3H, s), 2.72—3.03 (4H, m), 3.10 (3H, s), 3.06—3.22 (1H, m), 5.08—5.20 (2H, m), 5.58—5.77 (1H, m), 7.08 (1H, dd, J = 2.5, 8.5 Hz), 7.30—7.40 (2H, m).

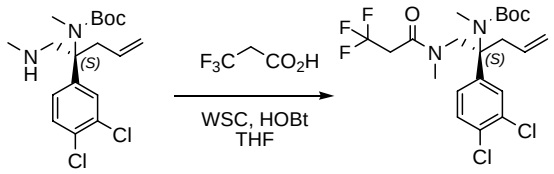
[0358]

Example 26(e)

Synthesis of tert-butyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)(4-penten-2-yl)]methylcarbamate

[0359]

[F79]



[0360]

1-Hydroxybenzotriazole monohydrate (11.5 g) was dissolved in anhydrous tetrahydrofuran (0.8 L). At room temperature, 3,3,3-trifluoropropionic acid (120.3 g) was added thereto. Under cooling with ice, 1-[3-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (180.0 g) was added to the mixture, and the resultant mixture was stirred for 10 minutes at the same temperature. A solution of tert-butyl [2-(S)-(3,4-dichlorophenyl)-1-methylamino(4-penten-2-yl)]methylcarbamate (318.8 g) in anhydrous tetrahydrofuran (0.9 L) was added thereto, and the mixture was stirred for 2 hours at room temperature. The reaction mixture was poured into water, extracted with ethyl acetate, sequentially washed with water, aqueous citric acid, saturated aqueous sodium bicarbonate, and saturated brine, and dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, and the residue was purified through silica gel column chromatography (n-hexane : ethyl acetate=6:1 to 5:1 to 2:1 to 1:1), to thereby give the title compound (275.7g, 69.7%, 5 steps).

[0361]

MS (FAB) m/z 483 $((M+H)^+)$

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.22 (9H, brs), 2.57 (1H, dd, J = 6.5, 7.5 Hz), 2.74—2.90 (1H, m), 2.85 (3H, s), 3.07 (3H, s),

3.27—3.38 (2H, m), 4.05—4.20 (1H, m), 4.25—4.42 (1H, m), 4.85—5.04 (2H, m), 5.64—5.85 (1H, m), 7.00 (1H, dd, J = 2.5, 8.5 Hz), 7.25 (1H, d, J = 2.5 Hz), 7.37 (1H, d, J = 8.5 Hz).

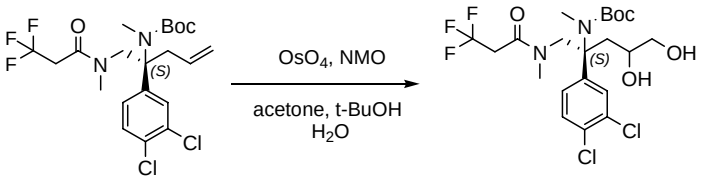
[0362]

Example 26(f)

Synthesis of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(3,3,3-trifluoro-N-methylpropanamido)-4,5-dihydroxy]pentan-2-yl}methylcarbamate

[0363]

[F80]



[0364]

tert-Butyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)(4-penten-2-yl)]methylcarbamate (275.7 g) was dissolved in acetone (690 mL), and t-butyl alcohol (345 mL) and water (345 mL) were added thereto. At room temperature, N-methylmorpholine-N-oxide (103.3 g) and osmium tetraoxide (2.5% t-butyl alcohol solution) (58.0 mL) were added to the mixture, and the resultant mixture was stirred for 14 hours at the same temperature. Under cooling with ice, an aqueous solution (2 L) of sodium thiosulfate pentahydrate (276 g) was added to the reaction mixture, and then stirred for 15 minutes at the same temperature. Water was added to the reaction mixture, and the resultant mixture was extracted with ethyl acetate. The organic layer was

sequentially washed with aqueous citric acid, water, saturated aqueous sodium bicarbonate, and saturated brine, and dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, to thereby give the title compound (297.8 g). The compound was used in the next step without further purification.

[0365]

MS (FAB) m/z 518 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.20 (9H, brs), 1.93–2.53 (4H, m), 3.09 (3H, s), 3.00–3.62 (6H, m), 3.68–3.80 (2H, m), 4.68–5.38 (2H, m), 7.00–7.10 (1H, m), 7.20–7.32 (1H, m), 7.37–7.46 (1H, m).

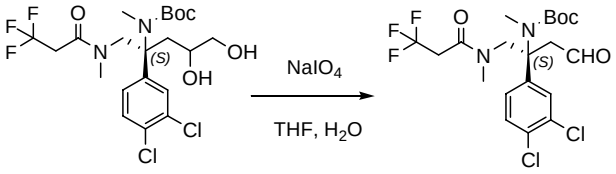
[0366]

Example 26(g)

Synthesis of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(3,3,3-trifluoro-N-methylpropanamido)-4-oxo]butan-2-yl}methylcarbamate

[0367]

[F81]



[0368]

tert-Butyl {[2-(S)-(3,4-dichlorophenyl)-1-(3,3,3-trifluoro-N-methylpropanamido)-4,5-dihydroxy]pentan-2-yl}methylcarbamate (297.8 g) was dissolved in tetrahydrofuran (2.4 L). A solution of sodium periodate (246.0 g) in water

(1.2 L) was added thereto, and the mixture was stirred for 30 minutes at room temperature. The reaction mixture was poured into water, extracted with ethyl acetate, sequentially washed with water and saturated brine, and dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, to thereby give the title compound (277.7 g). The compound was used in the next step without further purification.

[0369]

MS (FAB) m/z 485 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.26 (9H, brs), 2.78 (3H, s), 2.94—3.14 (1H, m), 3.07 (3H, s), 3.18—3.37 (3H, m), 4.24 (1H, d, J = 13.5 Hz), 4.52 (1H, d, J = 13.5 Hz), 7.10 (1H, dd, J = 2.0, 8.5 Hz), 7.33 (1H, d, J = 2.0 Hz), 7.43 (1H, d, J = 8.5 Hz), 9.67 (1H, t, J = 2.0 Hz).

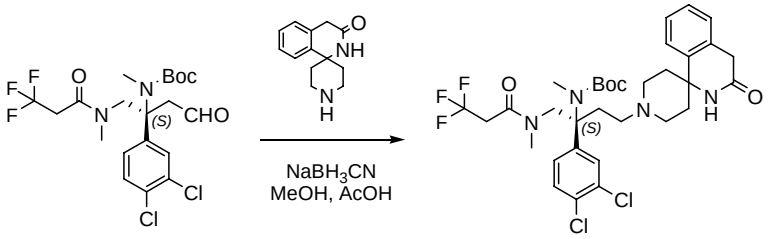
[0370]

Example 26(h)

Synthesis of tert-butyl {[1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate

[0371]

[F82]



[0372]

tert-Butyl {[2-(S)-(3,4-dichlorophenyl)-1-(3,3,3-trifluoro-N-methylpropanamido)-4-oxo]butan-2-yl}methylcarbamate (3.0 g) was dissolved in methanol (15 mL). Under cooling with ice, sodium cyanoborohydride (450 mg) and 3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidine) (1.47 g) were added thereto, and thereafter acetic acid (0.6 mL) was added thereto, followed by stirring for 30 minutes at room temperature. The reaction mixture was poured into saturated aqueous sodium bicarbonate, extracted with ethyl acetate, sequentially washed with water and saturated brine, and dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, to thereby give the title compound (4.23 g, 99.8%). The compound was used in the next step without further purification.

[0373]

MS (FAB) m/z 685 $((M+H)^+)$

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.24 (9H, s), 1.65—1.78 (2H, m), 1.87—2.30 (7H, m), 2.50—3.02 (6H, m), 3.12 (3H, s), 3.16—3.40 (2H, m), 3.61 (2H, s), 4.00—4.22 (1H, m), 4.45—4.67 (1H, m), 6.30 (1H, br), 7.02—7.07 (1H, m), 7.12—7.16 (1H, m), 7.22—7.44 (5H, m).

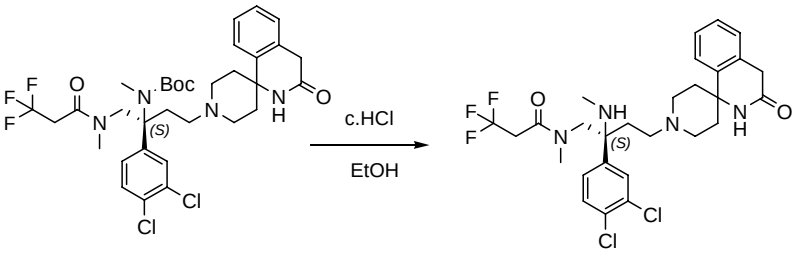
[0374]

Example 26(i)

Synthesis of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-3,3,3-trifluoro-N-methylpropanamido

[0375]

[F83]



[0376]

tert-Butyl {[1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate (4.22 g) was dissolved in ethanol (20 mL). Under cooling with ice, concentrated hydrochloric acid (20 mL) was added dropwise thereto, and the mixture was stirred for 1.5 hours at room temperature. The reaction mixture was poured into saturated aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The organic layer was sequentially washed with water and saturated brine, and then dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, to thereby give the title compound (3.55 g, 98.4%).

[0377]

MS (FAB) m/z 585 $((M+H)^+)$

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.80 (2H, d, J = 12.5 Hz), 1.93–2.40 (11H, m), 2.47–2.60 (4H, m), 2.90–3.00 (2H, m), 3.18–3.20 (2H, m), 3.44 (1H, d, J = 14 Hz), 3.64 (2H, s), 3.95 (1H, d, J = 14 Hz), 6.37 (1H, br), 7.14–7.18 (1H, m), 7.24–7.40 (4H, m), 7.44 (1H, d, J = 8.5 Hz), 7.62 (1H, d, J =

2.0 Hz).

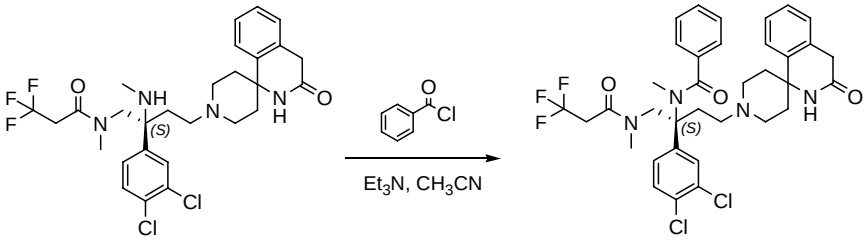
[0378]

Example 26(j)

Synthesis of N-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N-methylbenzamide

[0379]

[F84]



[0380]

N-{2-(S)-(3,4-Dichlorophenyl)-2-methylamino-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-3,3,3-trifluoro-N-methylpropanamide (440 mg) was dissolved in acetonitrile (5 mL). Under cooling with ice, triethylamine (314 μL) and benzoyl chloride (174 μL) were added thereto, and the mixture was stirred for 1 hour at the same temperature. Water was added to the reaction mixture, and the resultant mixture was extracted with ethyl acetate, sequentially washed with 0.5N aqueous hydrochloric acid, water, saturated aqueous sodium bicarbonate, and saturated brine, and dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, and the residue was purified through silica gel column chromatography (n-hexane :

ethyl acetate=1:1 → ethyl acetate → ethyl acetate : methanol=10:1), to thereby give the title compound (442 mg, 85.5%) as white powder.

[0381]

MS (FAB) m/z 689 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.69—1.80 (2H, m), 2.06—2.34 (6H, m), 2.42—2.54 (1H, m), 2.60—2.71 (1H, m), 2.77 (1H, d, J = 11 Hz), 2.87 (1H, d, J = 11 Hz), 3.02 (3H, s), 3.14 (3H, s), 3.18—3.39 (2H, m), 3.62 (2H, s), 4.45—4.60 (2H, m), 6.31 (1H, br), 7.12—7.16 (1H, m), 7.20—7.35 (4H, m), 7.37—7.48 (7H, m).

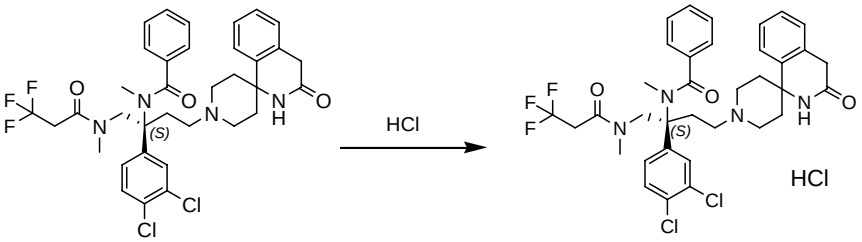
[0382]

Example 26(k)

Synthesis of N-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N-methylbenzamide hydrochloride (Compound No. 22)

[0383]

[F85]



[0384]

N-{1-(3,3,3-Trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N-methylbenzamide (442 mg) was dissolved in chloroform, and 4N HCl-1,4-dioxane (160 μL)

was added thereto. The solvent was concentrated under reduced pressure. Ether was added to the residue, followed by filtration and drying, to thereby give the title compound (391 mg, 84.0%) as white powder.

[0385]

MS (FAB) m/z 689 ($(M+H)^+$) (free form)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.93 (2H, d , J = 13 Hz), 2.48—2.62 (3H, m), 2.70—2.80 (4H, m), 2.88—3.14 (4H, m), 3.18—3.28 (1H, m), 3.33—3.53 (3H, m), 3.62 (2H, s), 3.72 (2H, q, J = 11 Hz), 4.05—4.20 (1H, m), 4.53 (1H, d, J = 14 Hz), 7.18—7.68 (11H, m), 7.77 (1H, d, J = 2.0 Hz), 8.36 (1H, s), 10.56 (1H, br).

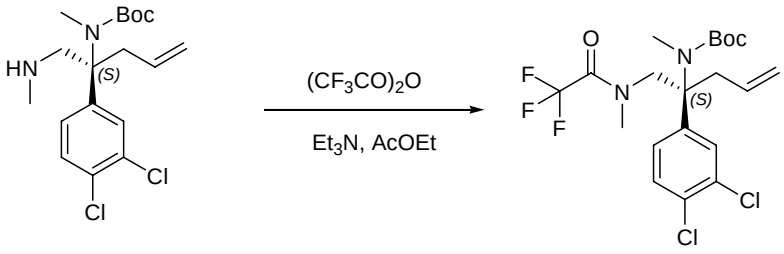
[0386]

Example 27(a)

Synthesis of tert-butyl [1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)(4-penten-2-yl)]methylcarbamate

[0387]

[F86]



[0388]

tert-Butyl [2-(S)-(3,4-dichlorophenyl)-1-methylamino(4-penten-2-yl)]methylcarbamate (3.55 g) synthesized in Example

26(d) was dissolved in ethyl acetate (20 mL). Under cooling with ice, triethylamine (2.65 mL) and trifluoroacetic acid anhydride (1.88 mL) were added thereto. At room temperature, the mixture was stirred for 45 minutes. The reaction mixture was neutralized with saturated aqueous sodium bicarbonate, extracted with ethyl acetate, sequentially washed with aqueous citric acid, saturated aqueous sodium bicarbonate, and saturated brine, and dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, and the residue was purified through silica gel column chromatography (n-hexane : ethyl acetate=10:1 to 2:1), to thereby give the title compound (4.22 g, 94.7%).

[0389]

MS (FAB) m/z 469 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.26 (9H, s), 2.58 (1H, dd, J = 7.0, 13.5 Hz), 2.77 (1H, dd, J = 7.0, 13.5 Hz), 3.02 (3H, s), 3.07 (3H, s), 4.07—4.28 (1H, m), 4.43 (1H, d, J = 13.5 Hz), 4.86—5.06 (2H, m), 5.55—5.75 (1H, m), 6.99 (1H, dd, J = 2.5, 8.5 Hz), 7.24 (1H, d, J = 2.5 Hz), 7.39 (1H, d, J = 8.5 Hz).

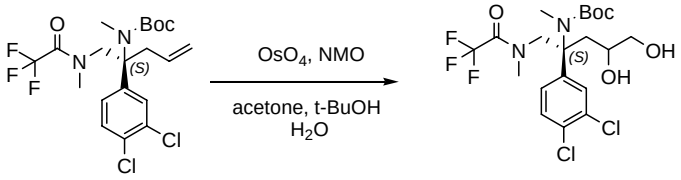
[0390]

Example 27(b)

Synthesis of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(2,2,2-trifluoro-N-methylacetamide)-4,5-dihydroxy]pentan-2-yl}methylcarbamate

[0391]

[F87]



[0392]

Similar to Example 26(f), the title compound was obtained (4.56g, 98.9%) by use of tert-butyl [1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)(4-penten-2-yl)]methylcarbamate (4.3 g).

[0393]

MS (FAB) m/z 503 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.24 (9H, brs), 1.76–1.88 (1H, m), 1.94–2.20 (2H, m), 2.26–2.50 (1H, m), 3.00–3.30 (6H, m), 3.38–3.63 (2H, m), 3.70–3.82 (1H, m), 3.90–4.20 (1H, m), 4.95–5.25 (1H, m), 7.00–7.15 (1H, m), 7.22–7.32 (1H, m), 7.40–7.50 (1H, m).

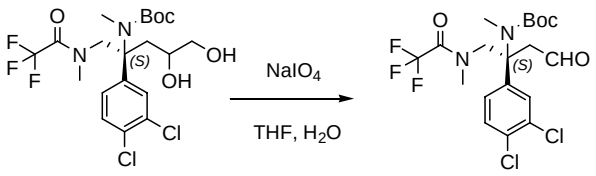
[0394]

Example 27(c)

Synthesis of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(2,2,2-trifluoro-N-methylacetamide)-4 -oxo]butan-2-yl)methylcarbamate

[0395]

[F88]



[0396]

Similar to Example 26(g), the title compound was

obtained (4.17 g, 99.0%) by use of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(2,2,2-trifluoro-N-methylacetamide)-4,5-dihydroxy]pentan-2-yl}methylcarbamate (4.5 g).

[0397]

MS (FAB) m/z 471 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.29 (9H, s), 2.95 (3H, s), 2.90–3.10 (1H, m), 3.04 (3H, s), 3.23 (1H, d, J = 16 Hz), 4.37 (1H, d, J = 13.5 Hz), 4.53 (1H, d, J = 13.5 Hz), 7.11 (1H, dd, J = 2.5, 8.5 Hz), 7.34 (1H, d, J = 2.5 Hz), 7.44 (1H, d, J = 8.5 Hz), 9.62 (1H, t, J = 2.0 Hz).

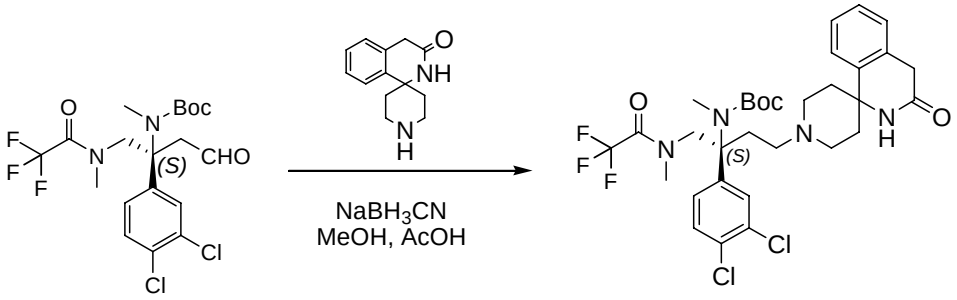
[0398]

Example 27(d)

Synthesis of tert-butyl {[1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate

[0399]

[F89]



[0400]

Similar to Example 26(h), the title compound was obtained (2.65 g, 94.9%) by use of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(2,2,2-trifluoro-N-methylacetamide)-4-

oxo]butan-2-yl}methylcarbamate (1.96 g).

[0401]

MS (FAB) m/z 671 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.25 (9H, brs), 1.63–1.80 (2H, m), 1.90–2.30 (7H, m), 2.45–2.60 (1H, m), 2.71 (1H, d, J = 10 Hz), 2.81 (1H, d, J = 10 Hz), 3.05 (3H, s), 3.12 (3H, s), 3.61 (2H, s), 4.05–4.28 (1H, m), 4.45–4.68 (1H, m), 6.29 (1H, s), 7.04 (1H, dd, J = 2.5, 8.5 Hz), 7.10–7.38 (5H, m), 7.43 (1H, d, J = 8.5 Hz).

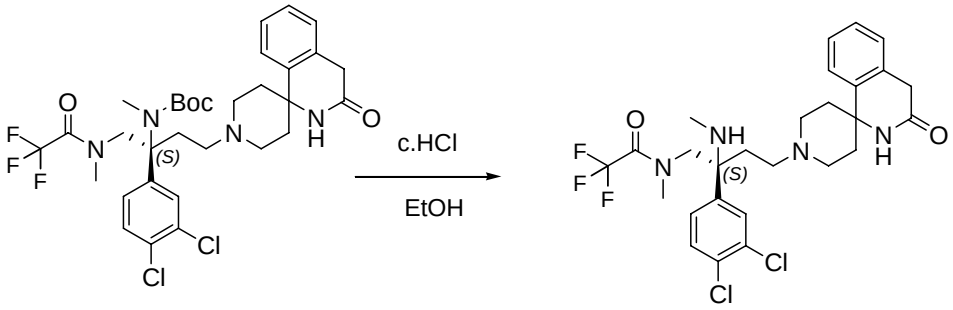
[0402]

Example 27(e)

Synthesis of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-2,2,2-trifluoro-N-methylacetamide

[0403]

[F90]



[0404]

Similar to Example 26(i), the title compound was obtained (2.30 g, quant.) by use of tert-butyl {[1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate (2.65 g).

[0405]

MS (FAB) m/z 571 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.73–1.88 (2H, m), 1.95–2.60 (9H, m), 2.28 (3H, s), 2.72 (3H, s), 2.88–3.03 (2H, m), 3.48 (1H, d, J = 14 Hz), 3.64 (2H, s), 3.93 (1H, d, J = 14 Hz), 6.36 (1H, s), 7.17 (1H, dd, J = 2.5, 8.5 Hz), 7.23–7.42 (4H, m), 7.45 (1H, d, J = 8.5 Hz), 7.63 (1H, d, J = 2.5 Hz).

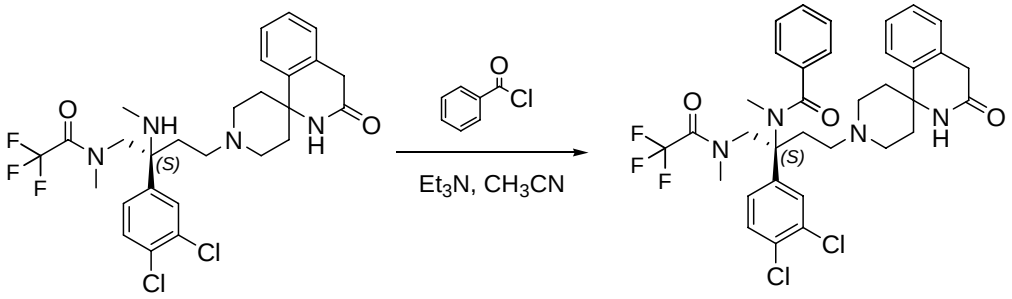
[0406]

Example 27(f)

Synthesis of N-{1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N-methylbenzamide

[0407]

[F91]



[0408]

Similar to Example 26(j), the title compound was obtained as white powder (1.48 g, 64.2%) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-2,2,2-trifluoro-N-methylacetamide (1.95 g).

[0409]

MS (FAB) m/z 675 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.70—1.80 (2H, m), 2.06—2.32 (6H, m), 2.36—2.46 (1H, m), 2.62—2.72 (1H, m), 2.79 (1H, d, J = 12 Hz), 2.87 (1H, d, J = 12 Hz), 3.14 (3H, s), 3.16 (3H, s), 3.63 (2H, s), 4.56—4.67 (2H, m), 6.30 (1H, br), 7.13—7.17 (1H, m), 7.19—7.35 (4H, m), 7.38—7.47 (7H, m).

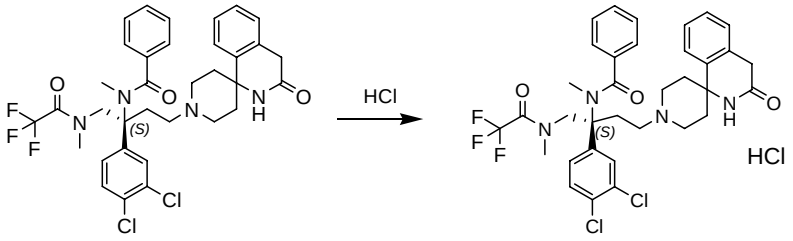
[0410]

Example 27(g)

Synthesis of N-{1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N-methylbenzamide hydrochloride (Compound No. 23)

[0411]

[F92]



[0412]

Similar to Example 26(k), the title compound was obtained as white powder (350 mg, 94.9%) by use of N-{1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N-methylbenzamide (350 mg).

[0413]

MS(FAB)m/z 675 ($(M+H)^+$) (free form)

^{1}H-NMR (270MHz, DMSO-d_6)δ ppm : 1.90—2.08 (2H, m), 2.42—2.87

(4H, m), 2.97 (3H, s), 3.04 (3H, s), 3.12—3.70 (8H, m), 4.25 (1H, d , J = 14.5 Hz), 4.69 (1H, d , J = 14.5 Hz), 7.15—7.77 (11H, m), 7.81 (1H, d , J = 2.0 Hz), 8.26 (1H, s), 10.7 (1H, br).

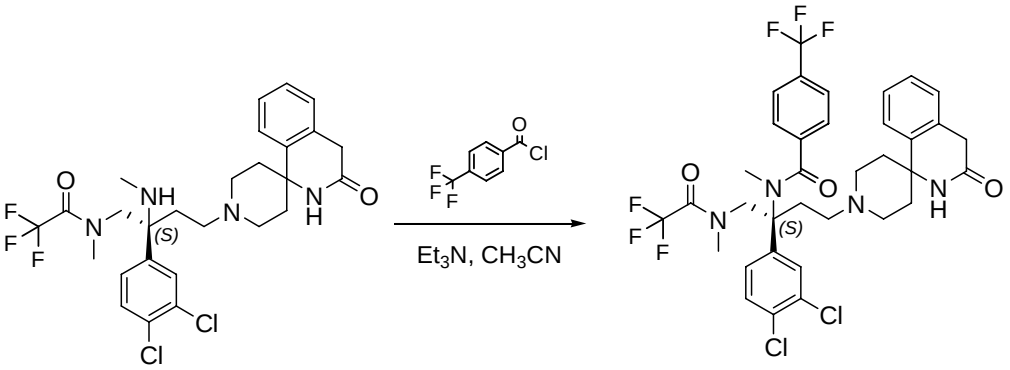
[0414]

Example 28(a)

Synthesis of N-{1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N-methyl-4-trifluoromethyl-benzamide

[0415]

[F93]



[0416]

Similar to Example 26(j), the title compound was obtained as pale yellow powder (172 mg, 66.1%) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-2,2,2-trifluoro-N-methylacetamide (200 mg) synthesized in Example 27(e) and 4-trifluoromethylbenzoyl chloride (156 μL).

[0417]

MS (FAB) m/z 743 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.71—1.81 (2H, m), 2.06—2.32 (6H, m), 2.40—2.50 (1H, m), 2.58—2.68 (1H, m), 2.80 (1H, d, J = 12 Hz), 2.87 (1H, d, J = 12 Hz), 3.11 (3H, s), 3.13 (3H, s), 3.63 (2H, s), 4.49 (1H, d, J = 13.5 Hz), 4.68 (1H, d, J = 13.5 Hz), 6.29 (1H, br), 7.13—7.35 (5H, m), 7.44—7.48 (2H, m), 7.51 (2H, d, J = 8.0 Hz), 7.71 (2H, d, J = 8.0 Hz).

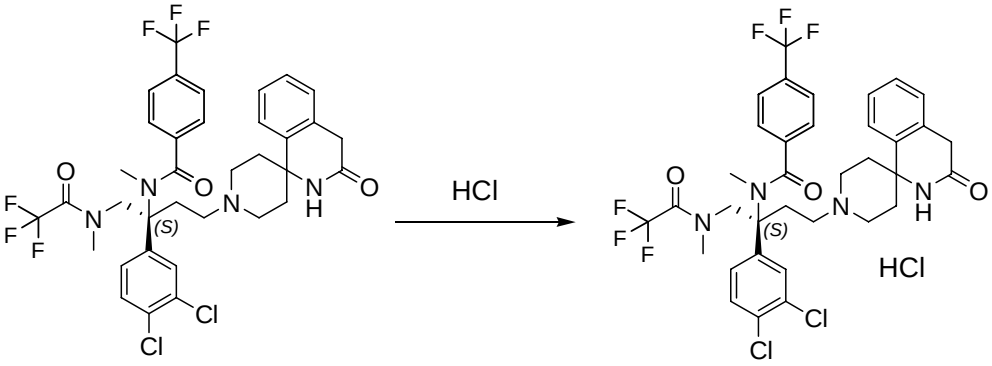
[0418]

Example 28(b)

Synthesis of N-{1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N-methyl-4-trifluoromethyl-benzamide hydrochloride (Compound No. 24)

[0419]

[F94]



[0420]

Similar to Example 26(k), the title compound was obtained as white powder (137 mg, 76.0%) by use of N-{1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N-methyl-4-trifluoromethyl-

benzamide (172 mg).

[0421]

MS (FAB) m/z 743 ($(M+H)^+$) (free form)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.92—2.02 (2H, m), 2.47—2.63 (1H, m), 2.65—2.83 (2H, m), 2.90—3.08 (8H, m), 3.12—3.52 (3H, m), 3.55—3.65 (3H, m), 4.21 (1H, d, J = 13.5 Hz), 4.76 (1H, d, J = 13.5 Hz), 7.20—7.24 (1H, m), 7.27—7.40 (4H, m), 7.58—7.75 (4H, m), 7.82—7.90 (3H, m), 8.25 (1H, s), 10.76 (1H, br).

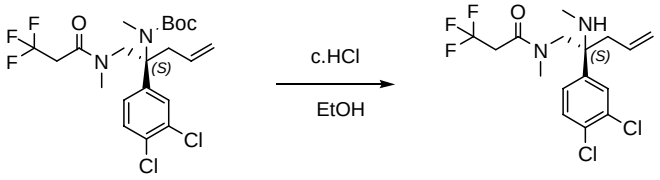
[0422]

Example 29(a)

Synthesis of N-[2-(S)-(3,4-dichlorophenyl)-2-(methylamino)-4-pentenyl]-3,3,3-trifluoro-N-methylpropanamido

[0423]

[F95]



[0424]

tert-Butyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)(4-penten-2-yl)]methylcarbamate (2.42 g) synthesized in Example 26(e) was dissolved in ethanol (15.4 mL). Under cooling with ice, concentrated hydrochloric acid (15.4 mL) was added thereto, and the mixture was stirred for 1.5 hours at room temperature. The reaction mixture was neutralized with saturated aqueous sodium bicarbonate, extracted with ethyl acetate, sequentially washed with water

and saturated brine, and dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, to thereby give the title compound (2.10 g). The compound was used in the next step without further purification.

[0425]

MS (FAB) m/z 383 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.52—1.72 (1H, br), 2.20 (3H, s), 2.56 (3H, s), 2.65 (2H, d, J = 7.0 Hz), 3.11 (2H, dq, J = 2.0, 10 Hz), 3.49 (1H, d, J = 14 Hz), 3.76 (1H, d, J = 14 Hz), 5.17—5.32 (2H, m), 5.78—5.90 (1H, m), 7.33 (1H, dd, J = 2.0, 8.5 Hz), 7.42 (1H, d, J = 8.5 Hz), 7.63 (1H, d, J = 2.0 Hz).

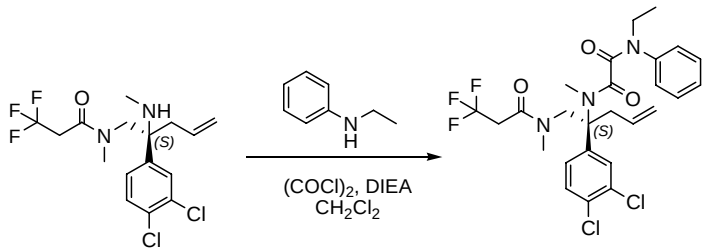
[0426]

Example 29(b)

Synthesis of N^1-[1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)(4-penten-2-yl)]-N^2-ethyl-N^1-methyl-N^2-phenyloxalamide

[0427]

[F96]



[0428]

N-[2-(S)-(3,4-Dichlorophenyl)-2-(methylamino)-4-pentenyl]-3,3,3-trifluoro-N-methylpropanamide (200 mg) was dissolved in anhydrous methylene chloride (1 mL). Under

cooling with ice, N,N-diisopropylethylamine (109 μL) and oxalyl chloride (109 μL) were added thereto, and the mixture was stirred for 30 minuites. A solution of N-ethylaniline (127 mg) in anhydrous methylene chloride (1 mL) was added to the reaction mixture, and the resultant mixture was stirred for 1 hour at room temperature. Water was added to the reaction mixture, extracted with methylene chloride, washed with saturated brine, and dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, and the residue was purified through silica gel column chromatography (n-hexane : ethyl acetate=3:1 to 1:1), to thereby give the title compound (221 mg, 75.8%).

[0429]

MS (FAB) m/z 558 $((M+H)^+)$

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.17 (3H, t, J = 7.0 Hz), 2.42—2.50 (1H, m), 2.73—2.92 (4H, m), 2.99 (3H, s), 3.13—3.35 (2H, m), 3.72—3.86 (2H, m), 4.07—4.28 (2H, m), 4.75—4.92 (2H, m), 5.28—5.41 (1H, m), 6.10 (1H, br), 6.92 (1H, d, J = 2.0 Hz), 7.02 (1H, d, J = 8.5 Hz), 7.23—7.30 (2H, m), 7.45—7.52 (3H, m).

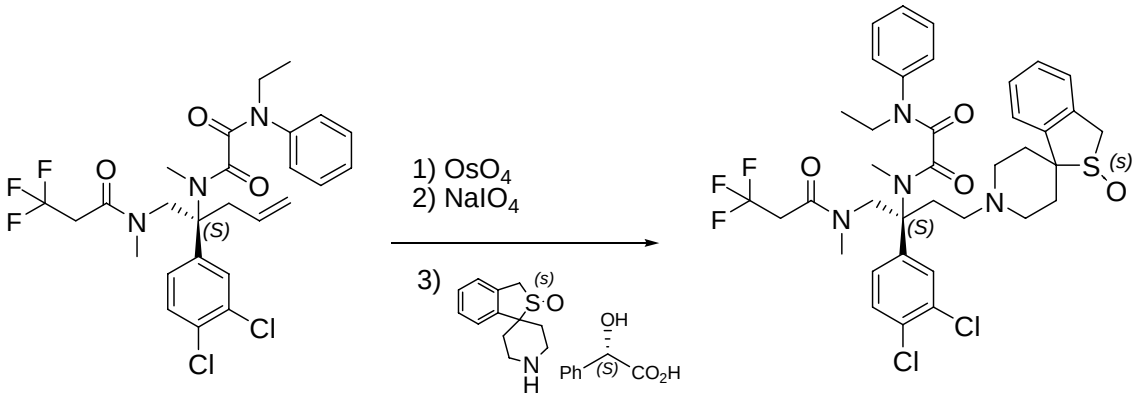
[0430]

Example 29(c)

Synthesis of N^1-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl-N^2-ethyl-N^2-phenyloxalamide

[0431]

[F97]



[0432]

Similar to Example 26(f), N^1-{2-(S)-(3,4-dichlorophenyl)-1-(3,3,3-trifluoro-N-methylpropanamido)-4,5-dihydroxy}pentan-2-yl}-N^2-ethyl-N^1-methyl-N^2-phenyloxalamide was obtained (889 mg) by use of N^1-[1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)(4-penten-2-yl)]-N^2-ethyl-N^1-methyl-N^2-phenyloxalamide (850 mg). Subsequently, similar to Example 26(g), N^1-{2-(S)-(3,4-dichlorophenyl)-1-(3,3,3-trifluoro-N-methylpropanamido)-4-oxo}butan-2-yl}-N^2-ethyl-N^1-methyl-N^2-phenyloxalamide was obtained (857 mg) by use of N^1-{2-(S)-(3,4-dichlorophenyl)-1-(3,3,3-trifluoro-N-methylpropanamido)-4,5-dihydroxy}pentan-2-yl}-N^2-ethyl-N^1-methyl-N^2-phenyloxalamide (889 mg). Thereafter, similar to Example 26(h), the title compound was obtained as white powder (736 mg, 63.2%, 3 steps) by use of N^1-{2-(S)-(3,4-dichlorophenyl)-1-(3,3,3-trifluoro-N-methylpropanamido)-4-oxo}butan-2-yl}-N^2-ethyl-N^1-methyl-N^2-phenyloxalamide (857 mg) and spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidine)/(S)-(+)-mandelate (616 mg).

[0433]

MS (FAB) m/z 765 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.17 (3H, t, J = 7.0 Hz), 1.49 (1H, d, J = 13.5 Hz), 1.77–2.02 (3H, m), 2.12–2.22 (2H, m), 2.29–2.46 (4H, m), 2.63–2.73 (2H, m), 2.84 (3H, s), 3.04 (3H, s), 3.13–3.38 (2H, m), 3.70–3.90 (2H, m), 3.97 (1H, d, J = 17 Hz), 4.10–4.18 (1H, m), 4.25–4.40 (2H, m), 6.20 (1H, br), 6.98–7.08 (2H, m), 7.24–7.35 (6H, m), 7.43–7.54 (3H, m).

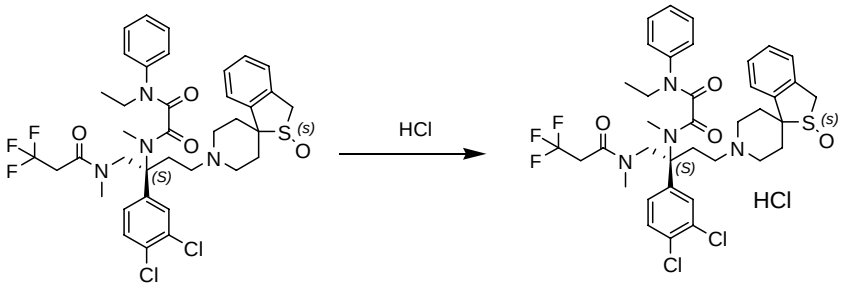
[0434]

Example 29(d)

Synthesis of N^1-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl-N^2-ethyl-N^2-phenyloxalamide hydrochloride (Compound No. 25)

[0435]

[F98]



[0436]

Similar to Example 26(k), the title compound was obtained as white powder (611 mg, 83.1%) by use of N^1-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl-N^2-ethyl-N^2-

phenyloxalamide (736 mg).

[0437]

$[\alpha]_D^{28}$= -27.7°(c 0.501, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.04 (3H, t, J = 7.0 Hz), 1.92—2.07 (1H, m), 2.20—2.40 (5H, m), 2.70—3.12 (5H, m), 3.14 (3H, s), 3.25—3.45 (4H, m), 3.60—3.80 (4H, m), 3.86—4.00 (1H, m), 4.04—4.18 (2H, m), 4.68 (1H, d, J = 17Hz), 6.63 (1H, br), 7.22—7.58 (11H, m), 10.70 (1H, br).

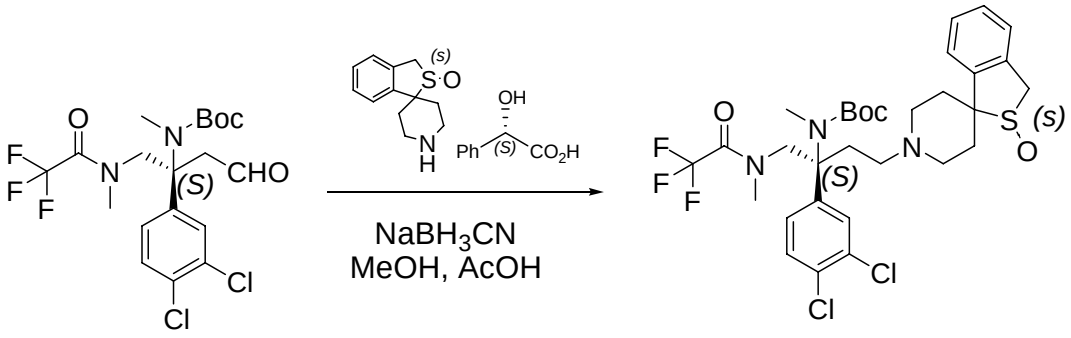
[0438]

Example 30(a)

Synthesis of tert-butyl {[1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate

[0439]

[F99]



[0440]

Similar to Example 26(h), the title compound was obtained (1.34 g, 93.4%) by use of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(2,2,2-trifluoro-N-methylacetamide)-4-oxo]butan-2-yl}methylcarbamate (1.0 g) synthesized in Example

25(c) and spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidine)/(S)-(+)-mandelate (871 mg).

[0441]

MS (FAB) m/z 676 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.25 (9H, brs), 1.82—1.93 (1H, m), 1.96—2.08 (2H, m), 2.14—2.44 (6H, m), 2.48—2.60 (1H, m), 2.70—2.80 (1H, m), 2.83—2.92 (1H, m), 3.02 (3H, s), 3.10 (3H, s), 3.98 (1H, d, J = 16.5 Hz), 4.07—4.33 (1H, m), 4.30 (1H, d, J = 16.5 Hz), 4.43—4.60 (1H, m), 7.03—7.07 (1H, m), 7.25—7.35 (5H, m), 7.42 (1H, d, J = 8.5 Hz).

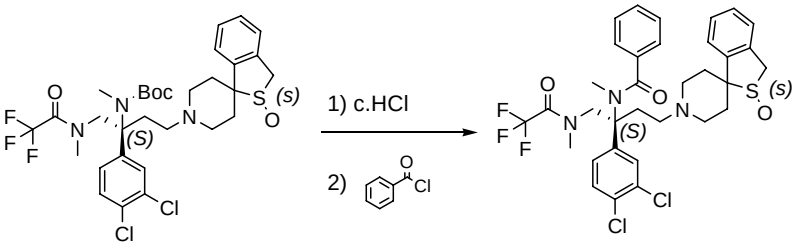
[0442]

Example 30(b)

Synthesis of N-{1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N-methylbenzamide

[0443]

[F100]



[0444]

Similar to Example 26(i), N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-2,2,2-trifluoro-N-methylacetamide was obtained (1.22 g, 92.2%) by use of tert-butyl {[1-(2,2,2-trifluoro-N-methylacetamide)-2-

(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate (1.30 g). Subsequently, similar to Example 36(j), the title compound was obtained as white powder (77 mg, 65.4%) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-2,2,2-trifluoro-N-methylacetamide (100 mg).

[0445]

MS (FAB) m/z 680 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.50—1.60 (1H, m), 1.83—1.96 (1H, m), 2.05—2.50 (7H, m), 2.63—2.75 (1H, m), 2.81 (1H, d, J = 12 Hz), 2.94 (1H, d, J = 12 Hz), 3.12 (3H, s), 3.13 (3H, s), 3.99 (1H, d, J = 16.5 Hz), 4.31 (1H, d, J = 16.5 Hz), 4.55 (1H, d, J = 13.5 Hz), 4.67 (1H, d, J = 13.5 Hz), 7.22 (1H, dd, J = 2.5, 8.0 Hz), 7.27—7.36 (4H, m), 7.38—7.47 (7H, m).

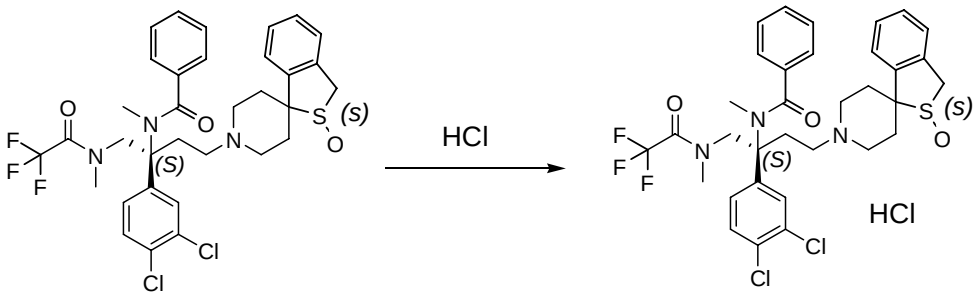
[0446]

Example 30(c)

Synthesis of N-{1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N-methylbenzamide hydrochloride (Compound No. 26)

[0447]

[F101]



[0448]

Similar to Example 26(k), the title compound was obtained as pale yellow powder (63 mg, 77.7%) by use of N-{1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N-methylbenzamide (77 mg).

[0449]

$[\alpha]_D^{28}$= + 9.2°(c 0.509, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 2.07 (1H, d , J = 16 Hz), 2.18—2.35 (2H,m), 2.60—2.82 (3H, m), 2.94 (3H, s), 3.05 (3H, s), 3.06—3.30 (4H, m), 3.60—3.78 (2H, m), 4.09 (1H, d, J = 17 Hz), 4.18—4.28 (1H, m), 4.63 (1H, d, J = 17 Hz), 4.70 (1H, d, J = 17 Hz), 7.31 (1H, d, J = 7.0 Hz), 7.35—7.58 (9H, m), 7.64 (1H, d, J = 8.5 Hz), 7.79 (1H, s), 10.46 (1H, br).

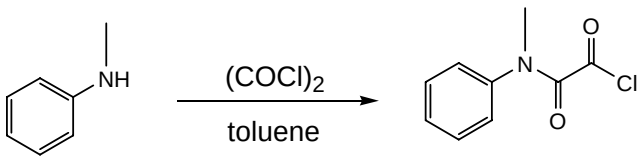
[0450]

Referential Example 1

Synthesis of (methylphenylamino)-oxo-acetyl chloride

[0451]

[F102]



[0452]

N-methylaniline (1.0 g) was dissolved in toluene (10 mL). Under cooling with ice, oxalyl chloride (4.07 mL) was added thereto, and the temperature of the mixture was lowered to room temperature, followed by stirring for 1 hour. The reaction mixture was concentrated under reduced pressure, to thereby give the title compound (1.06 g, 86.8%) as a brown oil. The compound was used without further purification.

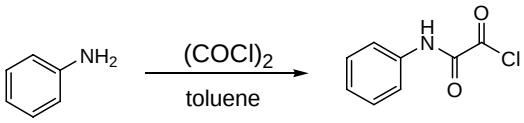
[0453]

Referential Example 2

Synthesis of oxo-phenylamino-acetyl chloride

[0454]

[F103]



[0455]

Similar to Referential Example 1, aniline hydrochloride (3.0 g) was dissolved in benzen (10 mL), and oxalyl chloride (10 mL) was added thereto under cooling with ice. The temperature of the mixture was then returned to room temperature, and the mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure, to thereby give the title compound (3.26 g, 76.6%) as a brown oil.

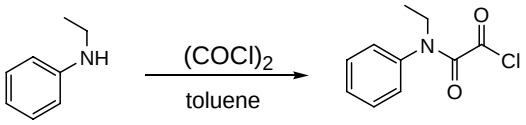
[0456]

Referential Example 3

Synthesis of (ethylphenylamino)-oxo-acetyl chloride

[0457]

[F104]



[0458]

Similar to Referential Example 1, N-ethylaniline (1.0 g) was dissolved in toluene (10 mL), and oxalyl chloride (4.0 mL) was added thereto under cooling with ice. The temperature of the mixture was then returned to room temperature, and the mixture was stirred for 1 hour. The reaction mixture was concentrated under reduced pressure, to thereby give the title compound (2.05 g) as a brown oil. The compound was used without further purification.

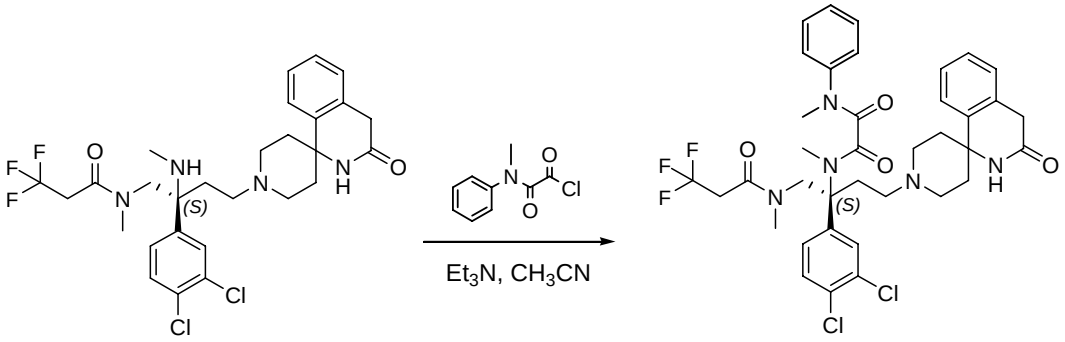
[0459]

Example 31(a)

Synthesis of N^1-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N^1,N^2-dimethyl-N^2-phenyloxalamide

[0460]

[F105]



[0461]

Similar to Example 26(j), the title compound was obtained (105 mg, 82.2%) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-3,3,3-trifluoro-N-methylpropanamide (100 mg) and (methylphenylamino)-oxo-acetyl chloride (68 mg) synthesized in Referential Example 1.

[0462]

MS (FAB) m/z 746 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.64—1.74 (2H, m), 1.80—1.96 (2H, m), 2.00—2.24 (5H, m), 2.35—2.47 (1H, m), 2.60—2.73 (2H, m), 2.83 (3H, s), 3.03 (3H, s), 3.12—3.39 (5H, m), 3.61 (2H, s), 4.09—4.20 (1H, m), 4.27—4.40 (1H, m), 6.18—6.32 (2H, m), 6.97—7.01 (1H, m), 7.07 (1H, d, J = 8.5 Hz), 7.12—7.16 (1H, m), 7.22—7.34 (5H, m), 7.42—7.53 (3H, m).

[0463]

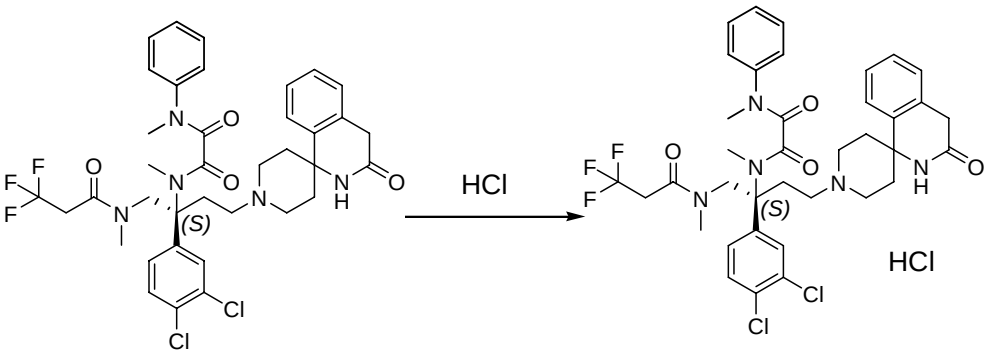
Example 31(b)

Synthesis of N^1-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N^1,N^2-

dimethyl-N^2-phenyloxalamide hydrochloride (Compound No. 27)

[0464]

[F106]



[0465]

Similar to Example 26(k), the title compound was obtained as pale yellow powder (81 mg, 73.4%) by use of N^1-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N^1,N^2-dimethyl-N^2-phenyloxalamide (105 mg).

[0466]

$[\alpha]_D^{28}$= -55.4°(c 0.505, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.84—1.97 (2H, m), 2.28—2.75 (5H, m), 2.82—2.96 (1H, m), 3.11 (3H, s), 3.15—3.48 (10H, m), 3.61 (2H, s), 3.65—3.77 (2H, m), 3.83—3.98 (1H, m), 4.12—4.25 (1H, m), 6.65 (1H, s), 7.18—7.80 (11H, m), 8.35 (1H, s), 10.44 (1H, br).

[0467]

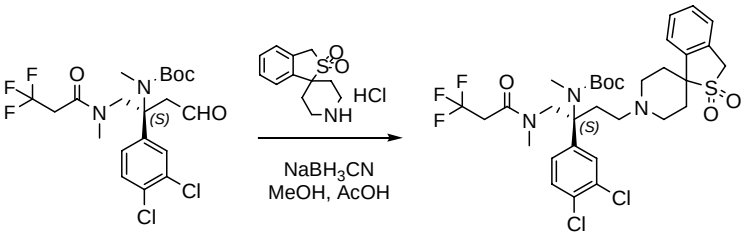
Example 32(a)

Synthesis of tert-butyl {[1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-

[spiro(benzo(c)thiophene-2,2-dioxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate

[0468]

[F107]



[0469]

Similar to Example 26(h), the title compound was obtained (398 mg, 69.9%) by use of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(3,3,3-trifluoro-N-methylpropanamido)-4-oxo]butan-2-yl}methylcarbamate (390 mg) and spiro(benzo(c)thiophene-2,2-dioxido-1(3H),4'-piperidine) (242 mg).

[0470]

MS (FAB) m/z 706 $((M+H)^+)$

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.24 (9H, s), 1.93—2.38 (7H, m), 2.47—2.77 (5H, m), 2.92 (3H, s), 3.11 (3H, s), 3.18—3.40 (2H, m), 3.90—4.17 (1H, m), 4.29 (2H, s), 4.40—4.66 (1H, m), 7.04 (1H, dd, J = 2.0, 8.5 Hz), 7.21—7.43 (6H, m).

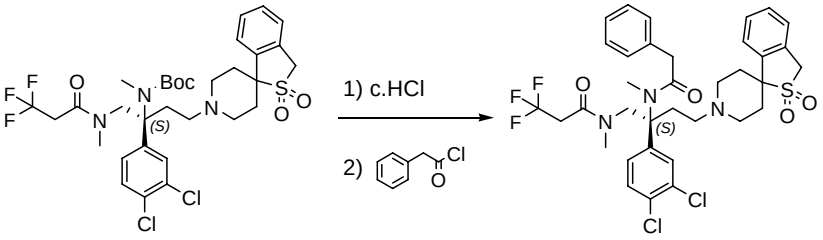
[0471]

Example 32(b)

Synthesis of N-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-2,2-dioxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N-methyl-phenylacetamide

[0472]

[F108]



[0473]

Similar to Example 26(i), N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[spiro(benzo(c)thiophene-2,2-dioxido-1(3H),4'-piperidin)-1'-yl]}butyl}-3,3,3-trifluoro-N-methylpropanamide was obtained (326 mg, 95.3%) by use of tert-butyl {[1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-2,2-dioxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate (398 mg). Subsequently, similar to Example 26(j), the title compound was obtained as white powder (546 mg, quant.) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[spiro(benzo(c)thiophene-2,2-dioxido-1(3H),4'-piperidin)-1'-yl]}butyl}-3,3,3-trifluoro-N-methylpropanamide (450 mg) and phenylacetyl chloride (196 μL).

[0474]

MS (FAB) m/z 724 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.93–2.20 (4H, m), 2.26–2.40 (3H, m), 2.43–2.74 (5H, m), 2.76 (3H, s), 3.09 (3H, s), 3.11–3.28 (2H, m), 3.69 (2H, s), 4.22–4.34 (3H, m), 4.40 (1H, d, J = 14 Hz), 6.94–6.98 (1H, m), 7.17–7.39 (11H, m).

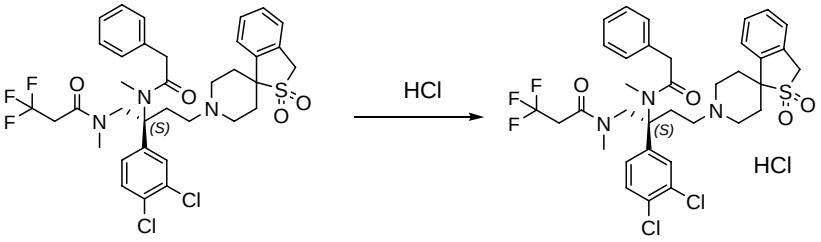
[0475]

Example 32(c)

Synthesis of N-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-2,2-dioxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N-methyl-phenylacetamide hydrochloride (Compound No. 28)

[0476]

[F109]



[0477]

Similar to Example 26(k), the title compound was obtained as white powder (476 mg, 84.6%) by use of N-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-2,2-dioxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N-methyl-phenylacetamide (546 mg).

[0478]

$[\alpha]_D^{28}$= -30.4°(c 0.509, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 2.30—2.55 (4H, m), 2.60—2.78 (3H, m), 3.05—3.28 (6H, m), 3.34 (3H, s), 3.47—3.80 (6H, m), 3.83—3.98 (1H, m), 4.30—4.40 (1H, m), 4.75 (2H, s), 7.10—7.60 (12H, m), 10.95 (1H, br).

[0479]

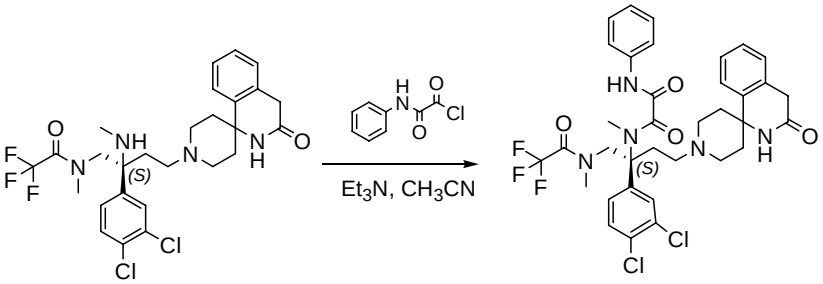
Example 33(a)

Synthesis of N^1-{1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-

(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl- N^2-phenyloxalamide

[0480]

[F110]



[0481]

Similar to Example 26(j), the title compound was obtained (433 mg, 50.6%) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-2,2,2-trifluoro-N-methylacetamide (680 mg) synthesized in Example 27(e) and oxo-phenylamino-acetyl chloride (653 mg) synthesized in Referential Example 2.

[0482]

MS (FAB) m/z 718 $((M+H)^+)$

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.67—1.78 (2H, m), 2.00—2.30 (6H, m), 2.34—2.46 (1H, m), 2.52—2.62 (1H, m), 2.73—2.87 (2H, m), 3.01 (3H, s), 3.48 (3H, s), 3.61 (2H, s), 4.08—4.24 (1H, m), 4.75 (1H, d, J = 14 Hz), 6.36 (1H, br), 7.11—7.40 (9H, m), 7.45 (1H, d, J = 8.5 Hz), 7.56 (2H, d, J = 8.0 Hz), 8.84 (1H, br).

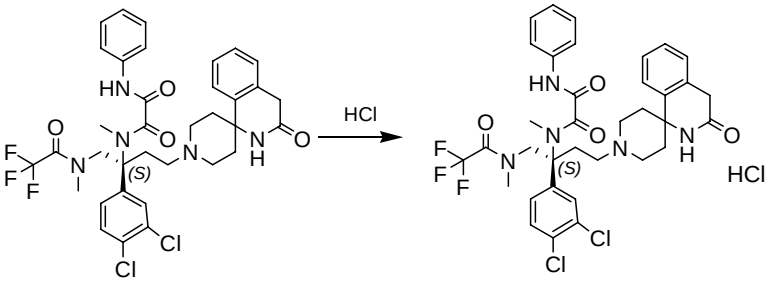
[0483]

Example 33(b)

Synthesis of N^1-{1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl- N^2-phenyloxalamide hydrochloride (Compound No. 29)

[0484]

[F111]



[0485]

Similar to Example 26(k), the title compound was obtained as yellow powder (350 mg, 94.9%) by use of N^1-{1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl- N^2-phenyloxalamide (350 mg).

[0486]

$[\alpha]_D^{28}$= -32.9°(c 0.515, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.93—2.06 (2H, m), 2.37—2.78 (9H, m), 3.16 (3H, s), 3.18—3.27 (1H, m), 3.46—3.72 (5H, m), 4.15 (1H, d, J = 15 Hz), 4.58 (1H, d, J = 15 Hz), 7.10—7.55 (9H, m), 7.68—7.71 (2H, m), 7.77 (1H, s), 8.37 (1H, s), 10.35 (1H, br), 10.86 (1H, s).

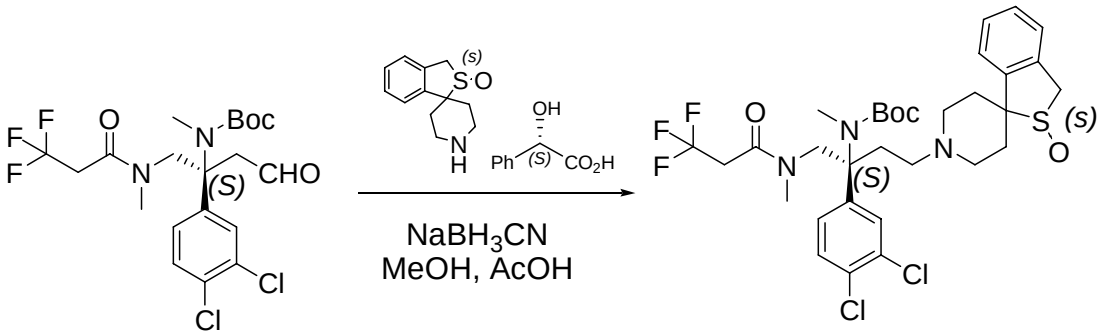
[0487]

Example 34(a)

Synthesis of tert-butyl {[1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate

[0488]

[F112]



[0489]

Similar to Example 26(h), the title compound was obtained (1.45 g, quant.) by use of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(3,3,3-trifluoro-N-methylpropanamido)-4-oxo]butan-2-yl}methylcarbamate (1.0 g) and spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidine)/(S)-(+)-mandelate (846 mg).

[0490]

MS (FAB) m/z 690 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.23 (9H, s), 1.51 (1H, d, J = 13 Hz), 1.82—2.08 (2H, m), 2.15—2.68 (7H, m), 2.72—3.05 (2H, m), 2.89 (3H, s), 3.10 (3H, s), 3.20—3.42 (2H, m), 3.92—4.65 (2H, m), 3.97 (1H, d, J = 17 Hz), 4.30 (1H, d, J = 17 Hz), 7.05 (1H, dd, J = 2.0, 8.5 Hz), 7.22—7.48 (6H, m).

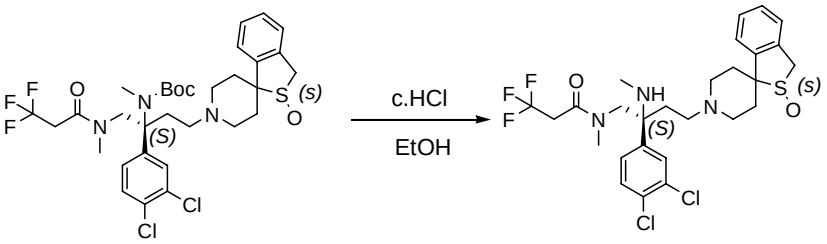
[0491]

Example 34(b)

Synthesis of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butyl}-3,3,3-trifluoro-N-methylpropanamido

[0492]

[F113]



[0493]

Similar to Example 26(i), the title compound was obtained (1.02 g, 92.2%) by use of tert-butyl {[1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate (1.33 g).

[0494]

MS (FAB) m/z 590 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.95—2.68 (10H, m), 2.26 (3H, s), 2.54 (3H, s), 2.92—3.28 (4H, m), 3.42 (1H, d, J = 13 Hz), 3.93—4.12 (2H, m), 4.34 (1H, d, J = 17 Hz), 7.25—7.42 (5H, m), 7.44 (1H, d, J = 8.5 Hz), 7.63 (1H, d, J = 2.0 Hz).

[0495]

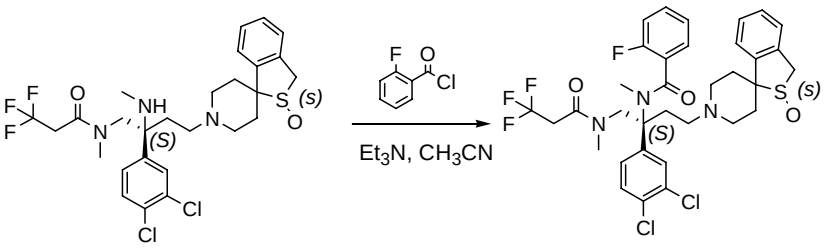
Example 34(c)

Synthesis of N-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-

oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N-methyl-2-fluorobenzamide

[0496]

[F114]



[0497]

Similar to Example 26(j), the title compound was obtained (682 mg, quant.) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butyl}-3,3,3-trifluoro-N-methylpropanamide (550 mg) and 2-fluorobenzoyl chloride (278 μL).

[0498]

MS (FAB) m/z 712 $((M+H)^+)$

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.54–1.65 (1H, m), 2.02–2.16 (1H, m), 2.23–2.68 (9H, m), 2.75–2.86 (1H, m), 2.93 (3H, s), 3.05 (3H, s), 3.20–3.40 (2H, m), 4.01 (1H, d, J = 17 Hz), 4.25–4.45 (2H, m), 4.63–4.73 (1H, m), 7.05–7.50 (11H, m).

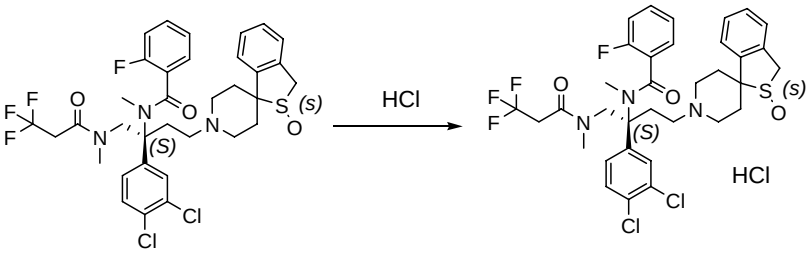
[0499]

Example 34(d)

Synthesis of N-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N-methyl-2-fluorobenzamide hydrochloride (Compound No. 30)

[0500]

[F115]



[0501]

Similar to Example 26(k), the title compound was obtained as white powder (594 mg, 85.2%) by use of N-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N-methyl-2-fluorobenzamide (682 mg).

[0502]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 2.00 (1H, d , J = 15 Hz), 2.22—2.40 (2H, m), 2.52—2.95 (6H, m), 3.03—3.43 (8H, m), 3.54—3.64 (1H, m), 3.67—3.78 (2H, m), 4.03—4.20 (2H, m), 4.44—4.56 (1H, m), 4.70 (1H, d, J = 17 Hz), 7.28—7.54 (9H, m), 7.63 (1H, d, J = 8.5 Hz), 7.69 (1H, s), 10.85 (1H, br)

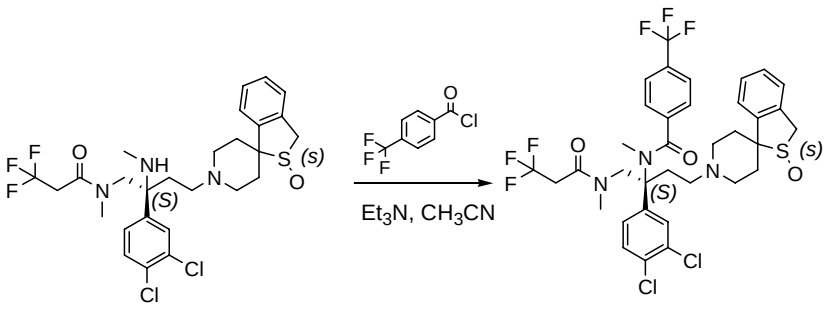
[0503]

Example 35(a)

Synthesis of N-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N-methyl-4-trifluoromethylbenzamide

[0504]

[F116]



[0505]

Similar to Example 26(j), the title compound was obtained (466 mg, 65.6%) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butyl}-3,3,3-trifluoro-N-methylpropanamide (550 mg) synthesized in Example 34(b) and 4-trifluoromethylbenzoyl chloride (483 μL).

[0506]

MS (FAB) m/z 762 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.58—1.68 (1H, m), 2.08—2.21 (1H, m), 2.33—2.73 (7H, m), 2.80—3.10 (9H, m), 3.20—3.37 (2H, m), 4.03 (1H, d, J = 17 Hz), 4.20—4.47 (2H, m), 4.75 (1H, d, J = 14 Hz), 7.20—7.35 (5H, m), 7.42—7.54 (4H, m), 7.65—7.72 (2H, m).

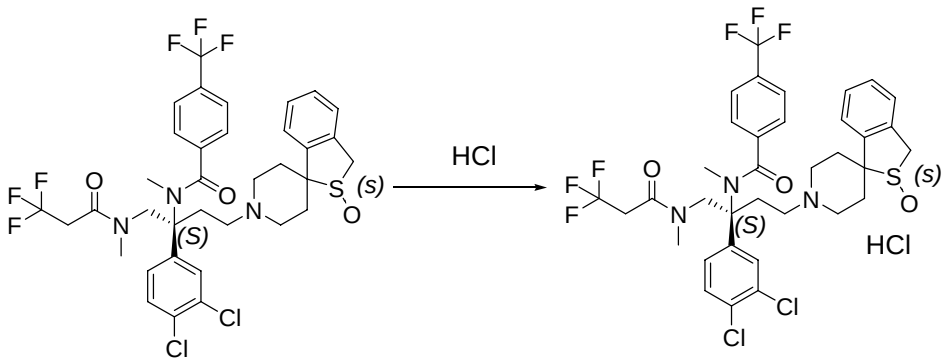
[0507]

Example 35(b)

Synthesis of N-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N-methyl-4-trifluoromethylbenzamide hydrochloride (Compound No. 31)

[0508]

[F117]



[0509]

Similar to Example 26(k), the title compound was obtained as pale yellow powder (376 mg, 77.0%) by use of N-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N-methyl-4-trifluoromethylbenzamide (466 mg).

[0510]

$[\alpha]_D^{28}$= + 6.1°(c 0.502, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 2.01 (1H, d , J = 14.5 Hz), 2.20—2.40 (2H, m), 2.54—2.90 (5H, m), 3.00—3.20 (2H, m), 3.07 (3H, s), 3.23—3.42 (2H, m), 3.57—3.75 (5H, m), 4.03—4.13 (2H, m), 4.57 (1H, d, J = 13 Hz), 4.70 (1H, d, J = 17 Hz), 7.27—7.47 (3H, m), 7.55 (1H, d, J = 8.5 Hz), 7.61 (1H, d, J = 8.5 Hz), 7.70 (2H, d, J = 8.0 Hz), 7.77 (1H, s), 7.84—7.90 (2H, m), 8.14 (1H, d, J = 8.0 Hz), 10.82 (1H, br).

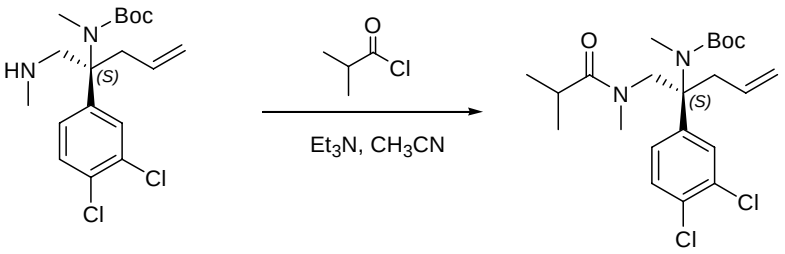
[0511]

Example 36(a)

Synthesis of tert-butyl [1-(N-methylisobutylamide)-2-(S)-(3,4-dichlorophenyl)(4-penten-2-yl)]methylcarbamate

[0512]

[F118]



[0513]

tert-Butyl [2-(S)-(3,4-dichlorophenyl)-1-methylamino(4-penten-2-yl)]methylcarbamate (2.0 g) synthesized in Example 26(d) was dissolved in acetonitrile (40 mL). Under cooling with ice, triethylamine (1.49 mL) and isobutyryl chloride (1.12 mL) were added thereto. Under cooling with ice, the mixture was stirred for 1 hour. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate anhydrate, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (n-hexane : ethyl acetate=3:1), to thereby give the title compound (1.53 g, 64.0%).

[0514]

MS (FAB) m/z 443 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.14 (6H, d, J = 7.0 Hz), 1.23 (9H, s), 2.55 (1H, dd, J = 7.0, 13.5 Hz), 2.78 (3H, s), 2.78—2.85 (2H, m), 3.09 (3H, s), 4.08—4.16 (2H, m), 4.86—4.99 (2H, m), 5.85—5.87 (1H, m), 7.02 (1H, dd, J = 2.5, 8.5 Hz), 7.25 (1H, d, J = 2.5 Hz), 7.36 (1H, d, J = 8.5 Hz).

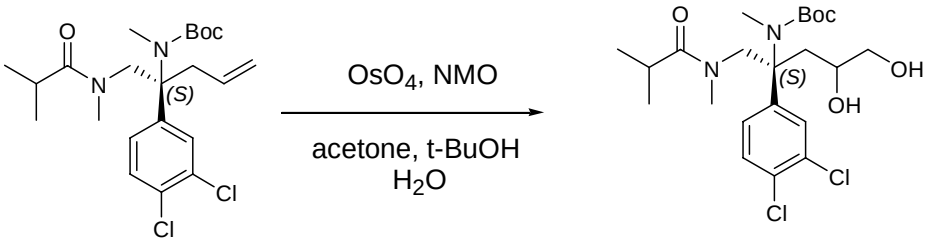
[0515]

Example 36(b)

Synthesis of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(N-methylisobutylamide)-4,5-dihydroxy]pentan-2-yl}methylcarbamate

[0516]

[F119]



[0517]

Similar to Example 26(f), the title compound was obtained (1.13 g, 94%) by use of tert-butyl [1-(N-methylisobutylamide)-2-(S)-(3,4-dichlorophenyl)(4-penten-2-yl)]methylcarbamate (1.12 g).

[0518]

MS (FAB) m/z 477 $((M+H)^+)$

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.04—1.20 (15H, m), 1.90—2.23 (2H, m), 2.41 (1H, t, J = 4.5 Hz), 2.65—3.65 (8H, m), 3.72 (2H, t, J = 5.0 Hz), 5.02—5.28 (1H, m), 5.52—5.78 (1H, m), 7.00—7.15 (1H, m), 7.18—7.35 (1H, m), 7.40 (1H, d, J = 8.5 Hz).

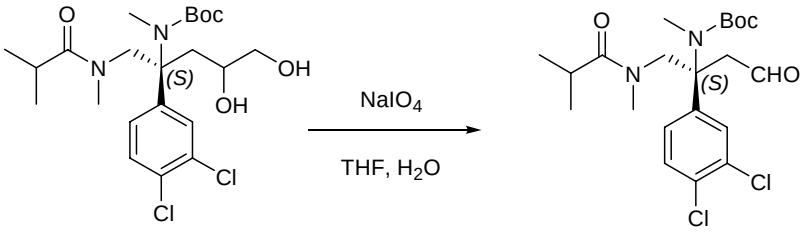
[0519]

Example 36(c)

Synthesis of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(N-methylisobutylamide)-4-oxo]butan-2-yl}methylcarbamate

[0520]

[F120]



[0521]

Similar to Example 26(g), the title compound was obtained (4.17 g, 99.0%) by use of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(N-methylisobutylamide)-4,5-dihydroxy]pentan-2-yl}methylcarbamate (4.5 g).

[0522]

MS (FAB) m/z 445 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.13 (6H, dd, J = 3.0, 7.0 Hz), 1.23—1.29 (9H, m), 2.73 (3H, s), 2.76—2.84 (1H, m), 2.90 (1H, d, J = 16 Hz), 3.11 (3H, s), 3.16 (1H, d, J = 16 Hz), 4.10—4.18 (1H, m), 4.45 (1H, d, J = 13 Hz), 7.10 (1H, dd, J = 2.5, 8.5 Hz), 7.33 (1H, d, J = 2.5 Hz), 7.41 (1H, dd, J = 2.5, 8.5 Hz), 9.71 (1H, t, J = 2.0 Hz).

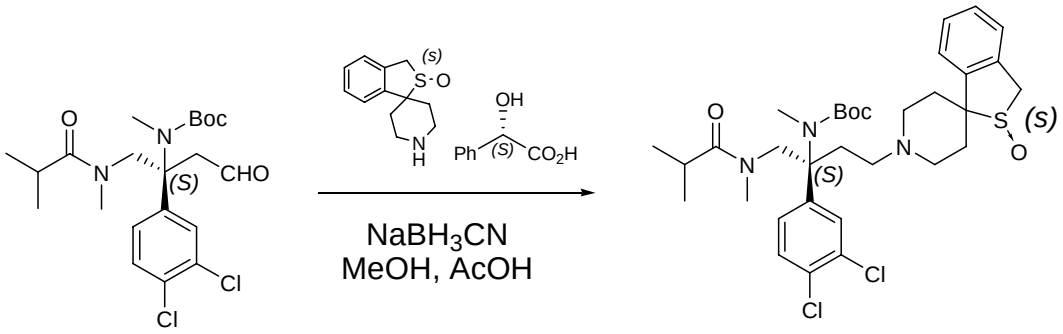
[0523]

Example 36(d)

Synthesis of tert-butyl {[1-(N-methylisobutylamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate

[0524]

[F121]



[0525]

Similar to Example 26(h), the title compound was obtained (1.85 g, 95%) by use of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(N-methylisobutylamide)-4-oxo]butan-2-yl}methylcarbamate (1.33 g) and spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidine)/(S)-(+)-mandelate (1.45 g).

[0526]

MS (FAB) m/z 650 $((M+H)^+)$

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.16 (6H, dd, J = 4.0, 6.5 Hz), 1.20—1.29 (9H, m), 1.50 (1H, d, J = 15 Hz), 1.79—2.01 (2H, m), 2.17—2.52 (7H, m), 2.58—2.79 (2H, m), 2.82—2.87 (5H, m), 3.13 (3H, s), 3.97 (1H, d, J = 17 Hz), 4.07—4.19 (1H, m), 4.29 (1H, d, J = 17 Hz), 7.06 (1H, dd, J = 2.0, 8.5 Hz), 7.19—7.33 (5H, m), 7.39 (1H, d, J = 8.5 Hz).

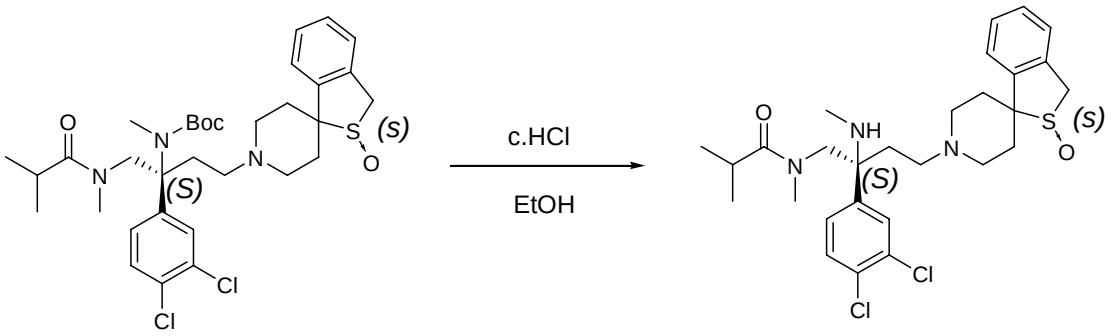
[0527]

Example 36(e)

Synthesis of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butyl}-N-methylisobutylamide

[0528]

[F122]



[0529]

Similar to Example 26(i), the title compound was obtained (1.35 g, 86%) by use of tert-butyl {[1-(N-methylisobutylamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate (1.85 g).

[0530]

MS (FAB) m/z 550 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.02 (3H, d, J = 6.5 Hz), 1.09 (3H, d, J = 7.0 Hz), 1.57—1.66 (4H, m), 2.05—2.17 (2H, m), 2.25 (3H, s), 2.31—2.45 (4H, m), 2.53 (3H, s), 2.64—2.79 (2H, m), 2.97—3.09 (2H, m), 3.34—3.39 (1H, m), 3.83—4.00 (1H, m), 4.02 (1H, d, J = 17 Hz), 4.35 (1H, d, J = 17 Hz), 7.25—7.40 (5H, m), 7.43 (1H, d, J = 8.5 Hz), 7.58—7.65 (1H, m).

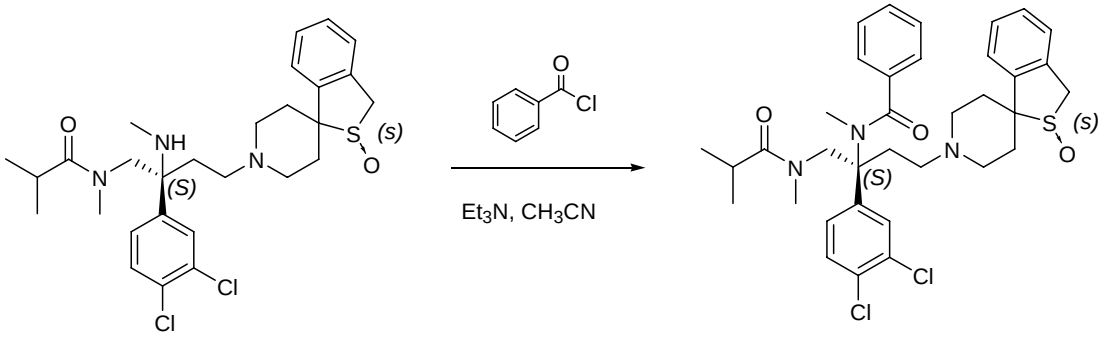
[0531]

Example 36(f)

Synthesis of N-{1-(N-methylisobutylamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N-methylbenzamide

[0532]

[F123]



[0533]

Similar to Example 26(j), the title compound was obtained as white powder (100 mg, 83.9%) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butyl}-N-methylisobutylamide (100 mg).

[0534]

MS (FAB) m/z 654 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.10—1.17 (6H, m), 1.49—1.60 (1H, m), 1.82—1.93 (1H, m), 2.08—2.53 (8H, m), 2.68—2.90 (3H, m), 2.96 (3H, s), 3.15 (3H, s), 3.98 (1H, d, J = 17 Hz), 4.31 (1H, d, J = 17 Hz), 4.38—4.53 (2H, m), 7.21—7.36 (5H, m), 7.39—7.48 (7H, m).

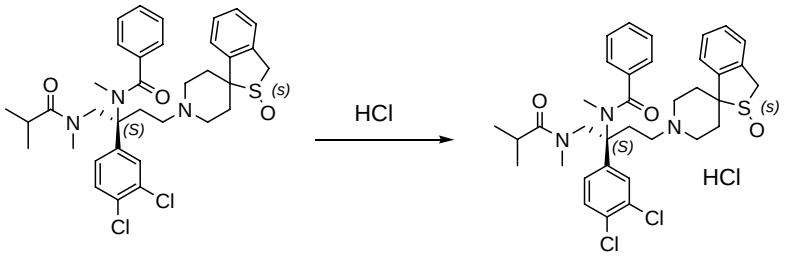
[0535]

Example 36(g)

Synthesis of N-{1-(N-methylisobutylamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N-methylbenzamide hydrochloride (Compound No. 32)

[0536]

[F124]



[0537]

Similar to Example 26(k), the title compound was obtained as white powder (84 mg, 79.4%) by use of N-{1-(N-methylisobutylamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N-methylbenzamide (100 mg).

[0538]

$[\alpha]_D^{28}$= -4.2°(c 0.511, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.00—1.04 (6H, m), 2.03 (1H, d, J = 15.5 Hz), 2.22—2.45 (2H, m), 2.52—2.60 (1H, m), 2.65—2.95 (5H, m), 3.05—3.25 (2H, m), 3.10 (3H, s), 3.57 (3H, s), 3.57—3.75 (2H, m), 3.98—4.13 (2H, m), 4.40—4.50 (1H, m), 4.70 (1H, d, J = 17 Hz), 7.28—7.65 (11H, m), 7.74 (1H, s), 10.96 (1H, br).

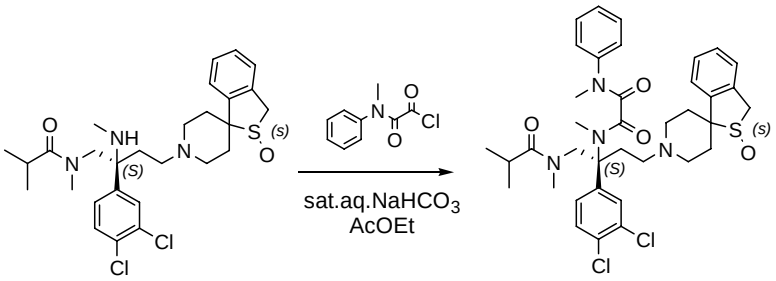
[0539]

Example 37(a)

Synthesis of N^1-{1-(N-methylisobutylamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N^1,N^2-dimethyl-N^2-phenyloxalamide

[0540]

[F125]



[0541]

N-{2-(S)-(3,4-Dichlorophenyl)-2-methylamino-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butyl}-N-methylisobutylamide (100 mg) synthesized in Example 36(e) was dissolved in ethyl acetate (1 mL). At room temperature, saturated aqueous sodium bicarbonate (1 mL) and (methylphenylamino)-oxo-acetyl chloride (107 mg) synthesized in Referential Example 1 were added thereto, and the mixture was stirred for 1 hour at the same temperature. The reaction mixture was subjected to partitioning, extracted with ethyl acetate, washed with saturated brine, and dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, and the residue was purified through silica gel column chromatography (n-hexane : ethyl acetate=1:1 → ethyl acetate → ethyl acetate : methanol=20:1), to thereby give the title compound (115 mg, 88.8%) as white powder.

[0542]

MS (FAB) m/z 711 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.09 (3H, d, J = 6.5 Hz), 1.10 (3H, d, J = 6.5 Hz), 1.45—1.52 (1H, m), 1.75—1.92 (2H, m), 2.02—2.48 (8H, m), 2.62—2.84 (5H, m), 3.02 (3H, s), 3.33 (3H, s), 4.29 (1H, d, J = 17 Hz), 4.05—4.26 (2H, m), 4.29 (1H, d,

J = 17 Hz), 6.30 (1H, br), 7.03 (1H, d, J = 2.0 Hz), 7.08 (1H, d, J = 8.5 Hz), 7.25—7.35 (6H, m), 7.44—7.50 (3H, m).

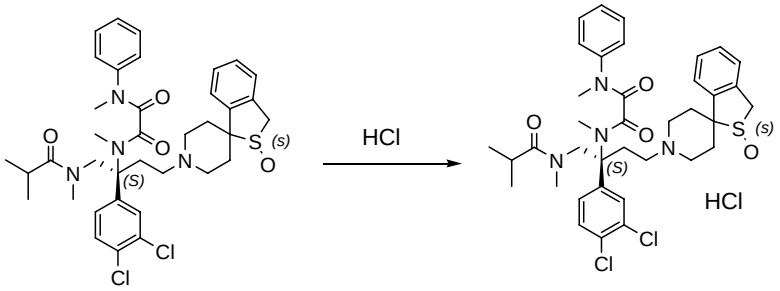
[0543]

Example 37(b)

Synthesis of N^1-{1-(N-methylisobutylamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N^1,N^2-dimethyl-N^2-phenyloxalamide hydrochloride (Compound No. 33)

[0544]

[F126]



[0545]

Similar to Example 26(k), the title compound was obtained as white powder (102 mg, 84.2%) by use of N^1-{1-(N-methylisobutylamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N^1,N^2-dimethyl-N^2-phenyloxalamide (115 mg).

[0546]

$[\alpha]_D^{29}$= -42.0°(c 0.437, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 0.95—1.00 (6H, m), 2.01 (1H, d, J = 18.5 Hz), 2.22—2.36 (3H, m), 2.40—2.50 (2H, m), 2.60—2.90 (3H, m), 2.92—3.05 (2H, m), 3.09 (3H, s), 3.24 (3H, s), 3.30—3.50 (4H, m), 3.70—3.90 (1H, m), 4.09 (1H, d, J = 17

Hz), 4.10—4.25 (1H, m), 4.69 (1H, d, J = 17 Hz), 6.65 (1H, br), 7.30—7.47 (9H, m), 7.50—7.60 (3H, m), 10.79 (1H, br).

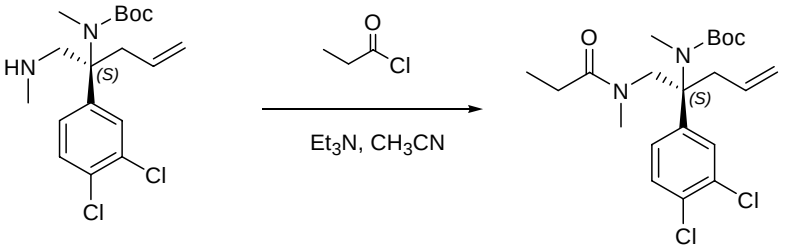
[0547]

Example 38(a)

Synthesis of tert-butyl [1-(N-methyl-propionamide)-2-(S)-(3,4-dichlorophenyl)(4-penten-2-yl)]methylcarbamate

[0548]

[F127]



[0549]

Similar to Example 36(a), the title compound was obtained (1.12 g, 65.2%) by use of tert-butyl [2-(S)-(3,4-dichlorophenyl)-1-methylamino(4-penten-2-yl)]methylcarbamate (1.49 g) synthesized in Example 26(d) and propionyl chloride (417 μL).

[0550]

MS (FAB) m/z 429 $((M+H)^+)$

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.16 (3H, t, J = 7.5 Hz), 1.19 (9H, brs), 2.35 (2H, q, J = 7.5 Hz), 2.57 (1H, dd, J = 7.5, 13.5 Hz), 2.75 (3H, s), 2.67—2.88 (1H, m), 3.08 (3H, s), 3.97—4.32 (2H, m), 4.82—5.03 (2H, m), 5.72—5.93 (1H, m), 7.01 (1H, dd, J = 2.5, 8.5 Hz), 7.26 (1H, d, J = 2.5 Hz), 7.36 (1H, d, J = 8.5 Hz).

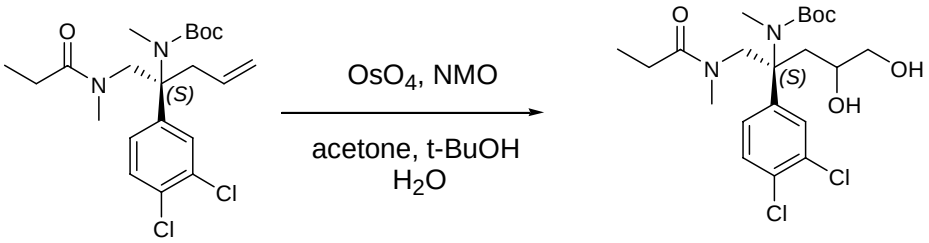
[0551]

Example 38(b)

Synthesis of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(N-methyl-propionamide)-4,5-dihydroxy]pentan-2-yl}methylcarbamate

[0552]

[F128]



[0553]

Similar to Example 26(f), the title compound was obtained (1.09 g, quant) by use of tert-butyl [1-(N-methyl-propionamide)-2-(S)-(3,4-dichlorophenyl)(4-penten-2-yl)]methylcarbamate (1.0 g).

[0554]

MS (FAB) m/z 463 $((M+H)^+)$

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 0.93—1.45 (12H, m), 1.98—2.50 (7H, m), 2.80—3.80 (8H, m), 5.00—5.28 (1H, m), 5.50—5.75 (1H, m), 7.00—7.16 (1H, m), 7.20—7.32 (1H, m), 7.40 (1H, d, J = 8.5 Hz).

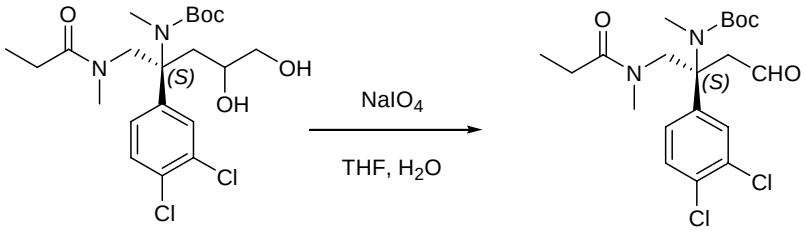
[0555]

Example 38(c)

Synthesis of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(N-methyl-propionamide)-4-oxo]butan-2-yl}methylcarbamate

[0556]

[F129]



[0557]

Similar to Example 26(g), the title compound was obtained (1.05 g, 99.0%) by use of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(N-methyl-propionamide)-4,5-dihydroxy]pentan-2-yl}methylcarbamate (1.09 g).

[0558]

MS (FAB) m/z 431 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.15 (3H, t, J = 7.5 Hz), 1.24 (9H, s), 2.35 (2H, q, J = 7.5 Hz), 2.69 (3H, s), 2.95 (1H, d, J = 14.5 Hz), 3.09 (3H, s), 3.20 (1H, d, J = 14.5 Hz), 4.17 (1H, d, J = 13.5 Hz), 4.44 (1H, d, J = 13.5 Hz), 7.11 (1H, dd, J = 2.5, 8.5 Hz), 7.33 (1H, d, J = 2.5 Hz), 7.42 (1H, d, J = 8.5 Hz), 9.71 (1H, t, J = 2.0 Hz).

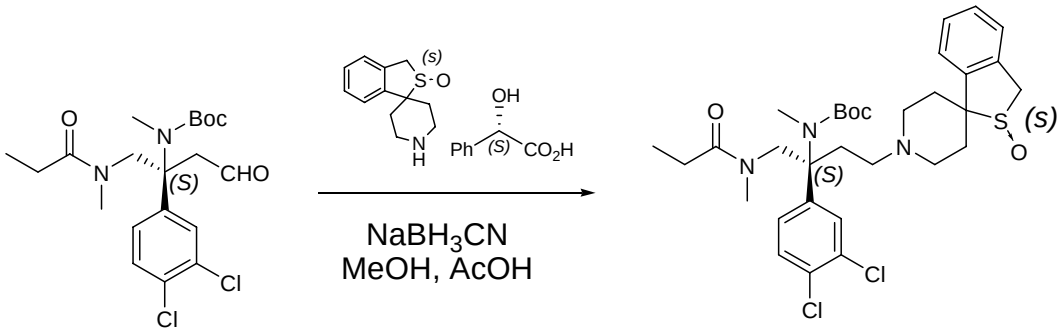
[0559]

Example 38(d)

Synthesis of tert-butyl {[1-(N-methyl-propionamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate

[0560]

[F130]



[0561]

Similar to Example 26(h), the title compound was obtained (504 mg, 68%) by use of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(N-methyl-propionamide)-4-oxo]butan-2-yl}methylcarbamate (300 mg) and spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidine)/(S)-(+)-mandelate (363 mg).

[0562]

MS (FAB) m/z 636 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.18 (3H, t, J = 7.5 Hz), 1.25 (9H, brs), 1.65—2.15 (6H, m), 2.20—3.25 (13H, m), 3.15 (3H, s), 4.00—4.25 (1H, m), 4.35—4.52 (1H, m), 7.12 (1H, d, J = 8.5 Hz), 7.18—7.55 (6H, m).

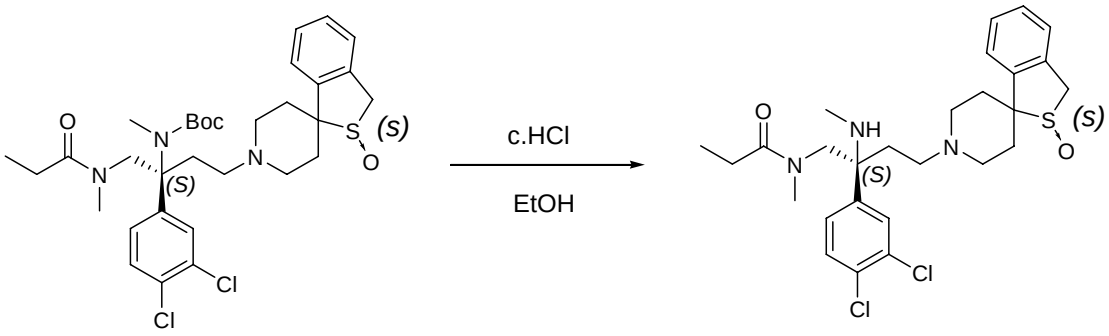
[0563]

Example 38(e)

Synthesis of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butyl}-N-methyl-propionamide

[0564]

[F131]



[0565]

Similar to Example 26(i), the title compound was obtained (418 mg, 98%) by use of tert-butyl {[1-(N-methyl-propionamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate (504 mg).

[0566]

MS (FAB) m/z 536 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 0.78—0.93 (1H, m), 1.12 (3H, t, J = 7.5 Hz), 1.06—1.18 (1H, m), 1.58—1.92 (3H, m), 2.10—2.66 (8H, m), 2.21 (3H, s), 2.29 (2H, q, J = 7.5 Hz), 2.44 (3H, s), 3.96—4.14 (2H, m), 4.30—4.50 (2H, m), 7.13—7.58 (7H, m).

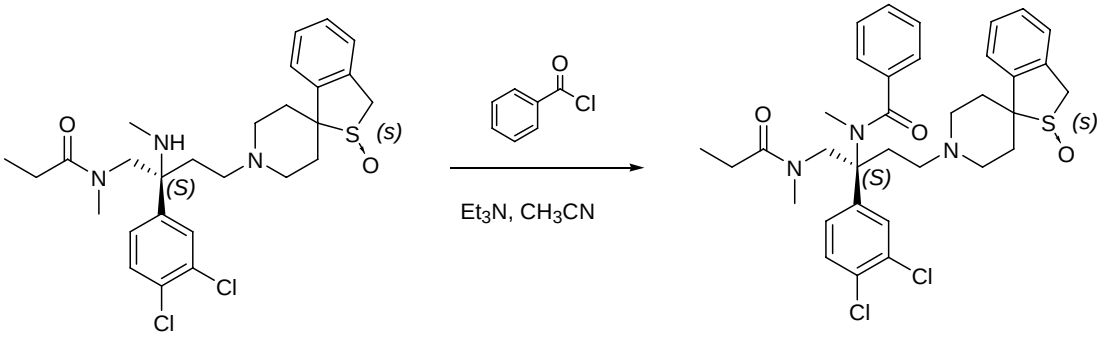
[0567]

Example 38(f)

Synthesis of N-{1-(N-methyl-propionamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N-methylbenzamide

[0568]

[F132]



[0569]

Similar to Example 26(j), the title compound was obtained as white powder (543 mg, 82.3%) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butyl}-N-methyl-propionamide (550 mg).

[0570]

MS (FAB) m/z 640 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.15 (3H, t, J = 7.0 Hz), 1.50—1.60 (1H, m), 1.85—1.97 (1H, m), 2.12—2.58 (9H, m), 2.70—3.03 (6H, m), 3.13 (3H, s), 3.98 (1H, d, J = 17 Hz), 4.31 (1H, d, J = 17 Hz), 4.33—4.54 (2H, m), 7.20—7.35 (5H, m), 7.39—7.48 (7H, m).

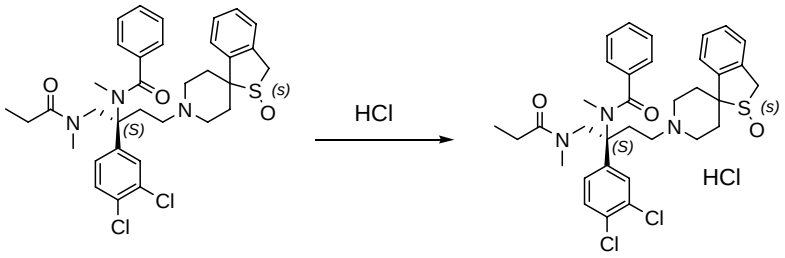
[0571]

Example 38(g)

Synthesis of N-{1-(N-methyl-propionamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N-methylbenzamide hydrochloride (Compound No. 34)

[0572]

[F133]



[0573]

Similar to Example 26(k), the title compound was obtained as white powder (473 mg, 82.4%) by use of N-{1-(N-methyl-propionamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N-methylbenzamide (543 mg).

[0574]

$[\alpha]_D^{28}$= + 24.1°(c 0.508, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.02 (3H, t, J = 7.5 Hz), 2.04 (1H, d, J = 15.5 Hz), 2.23—2.40 (4H, m), 2.50—2.62 (1H, m), 2.71 (3H, s), 2.78—2.92 (1H, m), 3.03—3.25 (6H, m), 3.27—3.42 (1H, m), 3.60—3.70 (2H, m), 4.03—4.15 (2H, m), 4.38—4.47 (1H, m), 4.69 (1H, d, J = 17 Hz), 7.27—7.65 (12H, m), 7.74 (1H, s), 10.67 (1H, br).

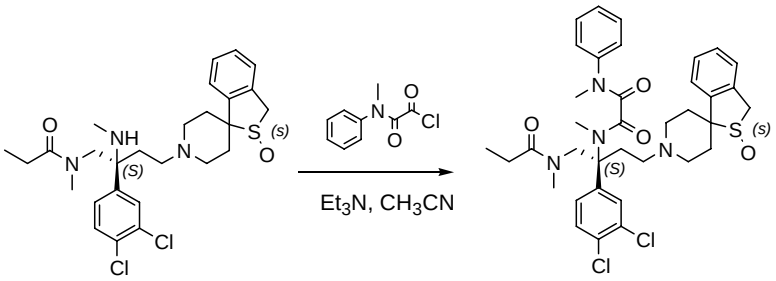
[0575]

Example 39(a)

Synthesis of N^1-{1-(N-methyl-propionamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N^1,N^2-dimethyl-N^2-phenyloxalamide

[0576]

[F134]



[0577]

Similar to Example 26(j), the title compound was obtained (490 mg, 68.2%) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butyl}-N-methyl-propionamide (550 mg) synthesized in Example 38(e) and (methylphenylamino)-oxo-acetyl chloride (407 mg) synthesized in Referential Example 1.

[0578]

MS (FAB) m/z 697 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.14 (3H, t, J = 7.0 Hz), 1.45—1.53 (1H, m), 1.78—1.95 (2H, m), 2.03—2.48 (10H, m), 2.65—2.80 (4H, m), 3.01 (3H, s), 3.33 (3H, s), 3.98 (1H, d, J = 17 Hz), 4.10—4.20 (2H, m), 4.29 (1H, d, J = 17 Hz), 6.33 (1H, br), 7.03 (1H, d, J = 2.0 Hz), 7.09 (1H, d, J = 8.5 Hz), 7.22—7.35 (6H, m), 7.44—7.51 (3H, m).

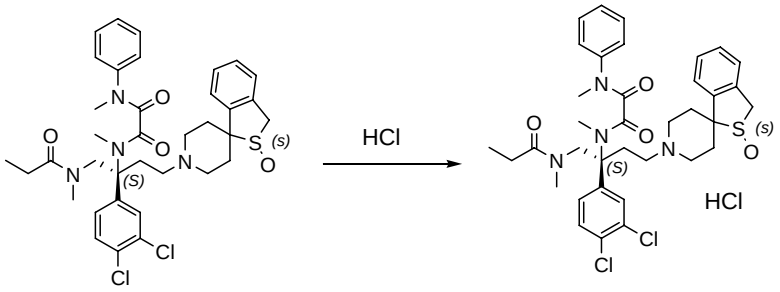
[0579]

Example 39(b)

Synthesis of N^1-{1-(N-methyl-propionamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N^1,N^2-dimethyl-N^2-phenyloxalamide hydrochloride (Compound No. 35)

[0580]

[F135]



[0581]

Similar to Example 26(k), the title compound was obtained as white powder (404 mg, 78.4%) by use of N^1-{1-(N-methyl-propionamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N^1,N^2-dimethyl-N^2-phenyloxalamide (490 mg).

[0582]

$[\alpha]_D^{28}$= -37.6°(c 0.501, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.09 (3H, t, J = 7.0 Hz), 1.97—2.07 (1H, m), 2.18—2.45 (7H, m), 2.60—2.85 (2H, m), 2.90—3.07 (3H, m), 3.11 (3H, s), 3.23 (3H, s), 3.27—3.53 (4H, m), 3.72—3.88 (1H, m), 4.05—4.20 (2H, m), 4.69 (1H, d, J = 17 Hz), 6.64 (1H, br), 7.25—7.55 (11H, m), 10.42 (1H, br).

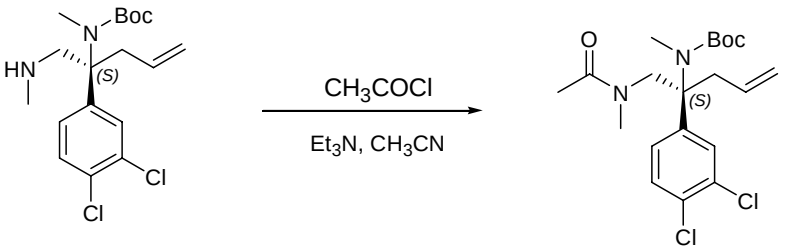
[0583]

Example 40(a)

Synthesis of tert-butyl [1-(N-methyl-acetamide)-2-(S)-(3,4-dichlorophenyl)(4-penten-2-yl)]methylcarbamate

[0584]

[F136]



[0585]

Similar to Example 36(a), the title compound was obtained (936 mg) by use of tert-butyl [2-(S)-(3,4-dichlorophenyl)-1-methylamino(4-penten-2-yl)]methylcarbamate (679 mg) synthesized in Example 26(d) and acetyl chloride (500 μL).

[0586]

MS (FAB) m/z 415 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.20 (9H, brs), 2.12 (3H, s), 2.50–2.90 (5H, m), 3.09 (3H, s), 3.96–4.32 (2H, m), 4.82–5.02 (2H, m), 5.65–5.88 (1H, m), 7.01 (1H, dd, J = 2.5, 8.5 Hz), 7.26 (1H, d, J = 2.5 Hz), 7.36 (1H, d, J = 8.5 Hz).

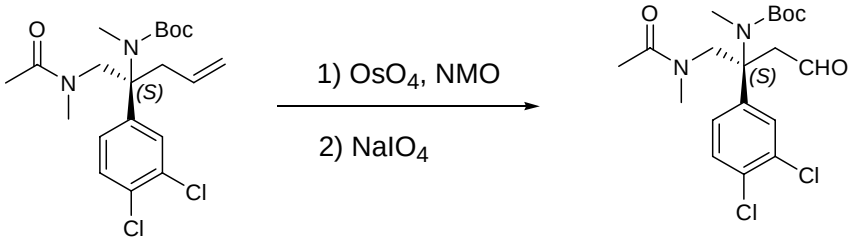
[0587]

Example 40(b)

Synthesis of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(N-methyl-acetamide)-4-oxo]butan-2-yl}methylcarbamate

[0588]

[F137]



[0589]

Similar to Example 26(f), tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(N-methyl-acetamide)-4,5-dihydroxy]pentan-2-yl}methylcarbamate was obtained (995 mg) by use of tert-butyl [1-(N-methyl-acetamide)-2-(S)-(3,4-dichlorophenyl)(4-penten-2-yl)]methylcarbamate (936 mg). Subsequently, similar to Example 26(g), the title compound was obtained (792 mg) by use of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(N-methyl-acetamide)-4,5-dihydroxy]pentan-2-yl}methylcarbamate (995 mg).

[0590]

MS (FAB) m/z 417 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.26 (9H, s), 2.11 (3H, s), 2.72 (3H, s), 2.96 (1H, d, J = 16 Hz), 3.09 (3H, s), 3.20 (1H, d, J = 16 Hz), 4.08—4.25 (1H, m), 4.45—4.50 (1H, m), 7.08—7.15 (1H, m), 7.25—7.47 (2H, m), 9.68 (1H, br).

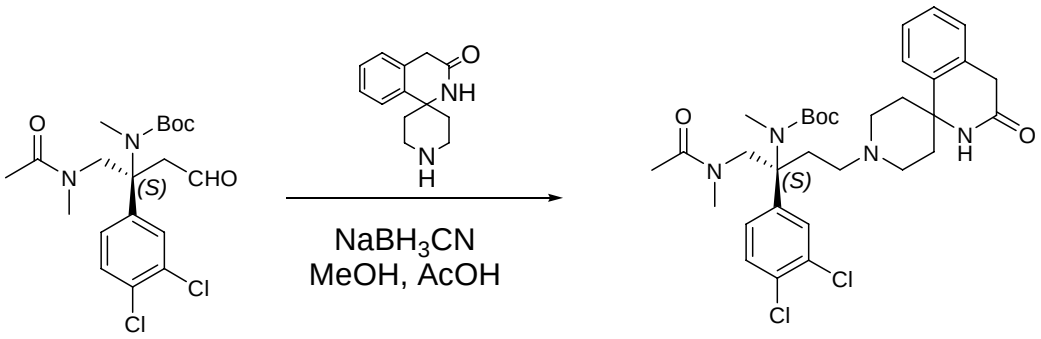
[0591]

Example 40(c)

Synthesis of tert-butyl {[1-(N-methyl-acetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate

[0592]

[F138]



[0593]

Similar to Example 26(h), the title compound was obtained (519 mg, 46.2%, 4 steps) by use of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(N-methyl-acetamide)-4-oxo]butan-2-yl}methylcarbamate (792 mg).

[0594]

MS (FAB) m/z 617 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.20 (9H, brs), 1.66–1.80 (2H, m), 1.90–2.35 (11H, m), 2.50–2.98 (5H, m), 3.13 (3H, s), 3.61 (2H, s), 4.07–4.20 (2H, m), 6.28 (1H, br), 7.03–7.20 (2H, m), 7.23–7.48 (5H, m).

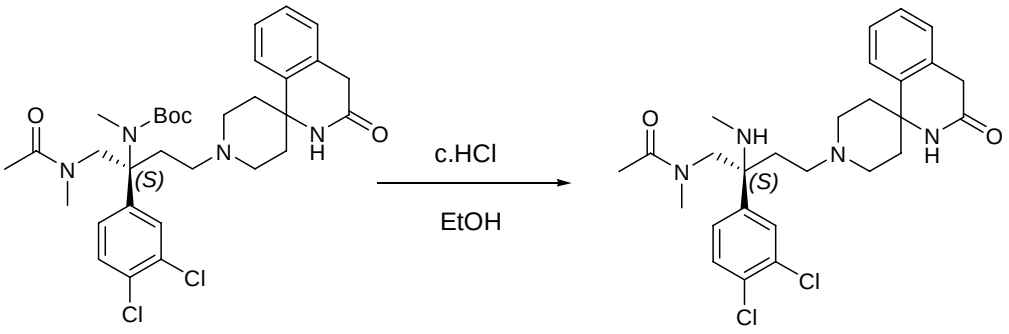
[0595]

Example 40(d)

Synthesis of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-N-methyl-acetamide

[0596]

[F139]



[0597]

Similar to Example 26(i), the title compound was obtained (397 mg, 91.3%) by use of tert-butyl {[1-(N-methyl-

acetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate (519 mg).

[0598]

MS (FAB) m/z 517 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.76—1.86 (2H, m), 1.93—2.42 (13H, m), 2.46 (3H, s), 2.53—2.65 (1H, m), 2.92—3.02 (2H, m), 3.33 (1H, d, J = 14 Hz), 3.42—3.60 (1H, m), 3.64 (2H, s), 3.94 (1H, d, J = 14 Hz), 6.33 (1H, br), 7.14—7.19 (1H, m), 7.24—7.47 (5H, m), 7.60—7.64 (1H, m).

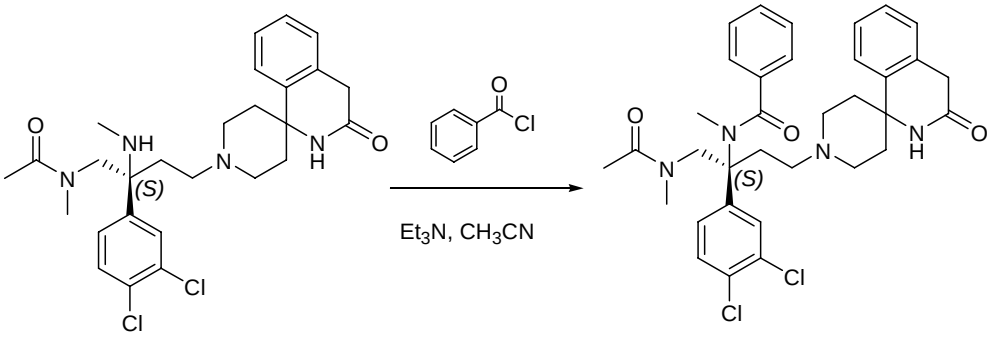
[0599]

Example 40(e)

Synthesis of N-{1-(N-methyl-acetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N-methylbenzamide

[0600]

[F140]



[0601]

Similar to Example 26(j), the title compound was obtained as white powder (190 mg, 79.4%) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[3-oxo-3,4-dihydro-2H-

spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-N-methyl-acetamide (199 mg).

[0602]

MS (FAB) m/z 621 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.92—2.22 (7H, m), 2.32—2.47 (3H, m), 2.50—2.60 (3H, m), 2.67—2.74 (1H, m), 2.80—2.88 (1H, m), 2.94 (3H, s), 3.13 (3H, s), 3.81 (2H, s), 4.36—4.50 (2H, m), 7.18 (1H, dd, J = 2.0, 8.5 Hz), 7.23—7.63 (12H, m).

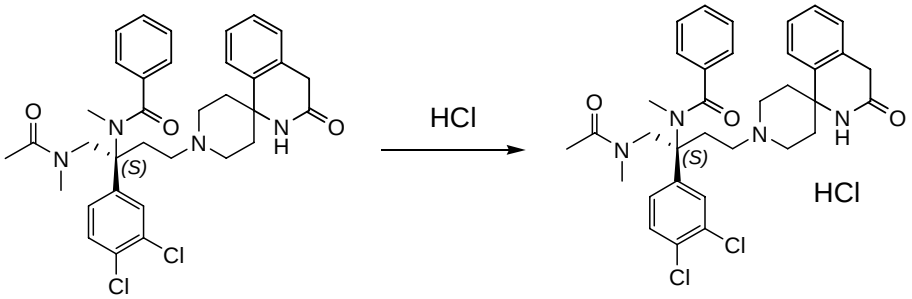
[0603]

Example 40(f)

Synthesis of N-{1-(N-methyl-acetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N-methylbenzamide hydrochloride (Compound No. 36)

[0604]

[F141]



[0605]

Similar to Example 26(k), the title compound was obtained as white powder (350 mg, 94.9%) by use of N-{1-(N-methyl-acetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N-methylbenzamide (350 mg).

[0606]

$[\alpha]_D^{28}$= + 6.1°(c 0.313, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.96 (2H, d, J = 14.5 Hz), 2.07 (3H, s), 2.42–2.58 (1H, m), 2.65–2.78 (4H, m), 2.85–3.03 (2H, m), 3.11 (3H, s), 3.21–3.48 (6H, m), 3.62 (2H, s), 4.02–4.17 (1H, m), 4.42 (1H, d, J = 14 Hz), 7.20–7.24 (1H, m), 7.27–7.39 (3H, m), 7.47 (5H, s), 7.54 (1H, dd, J = 2.0, 8.5 Hz), 7.63 (1H, d, J = 8.5 Hz), 7.77 (1H, d, J = 2.0 Hz), 8.30 (1H, s), 10.24 (1H, br).

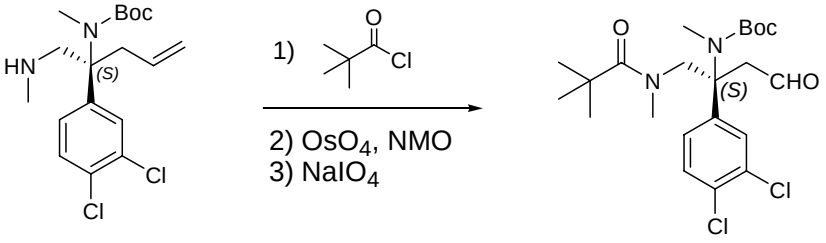
[0607]

Example 41(a)

Synthesis of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(N-methyl-trimethylacetamide)-4-oxo]butan-2-yl}methylcarbamate

[0608]

[F142]



[0609]

Similar to Example 36(a), tert-butyl [1-(N-methyl-trimethylacetamide)-2-(S)-(3,4-dichlorophenyl)(4-penten-2-yl)]methylcarbamate was obtained (1.60 g) by use of tert-butyl [2-(S)-(3,4-dichlorophenyl)-1-methylamino(4-penten-2-yl)]methylcarbamate (1.23 g) synthesized in Example 26(d) and pivaloyl chloride (0.49 mL). Subsequently, similar to Example 26(f), tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(N-

methyl-trimethylacetamide)-4,5-dihydroxy]pentan-2-yl}methylcarbamate (1.62 g) was obtained by use of tert-butyl [1-(N-methyl-trimethylacetamide)-2-(S)-(3,4-dichlorophenyl)(4-penten-2-yl)]methylcarbamate (1.60 g). Thereafter, similar to Example 26(g), tert-butyl {[1-(S)-(3,4-dichlorophenyl)-1-(N-methyl-trimethylacetamide)-3,4-dihydroxy]butyl}methylcarbamate (1.62 g) was obtained by use of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(N-methyl-trimethylacetamide)-4,5-dihydroxy]pentan-2-yl}methylcarbamate (1.60 g). Thereafter, similar to Example 26(g), the title compound was obtained (1.40 g, 92.6%, 3 steps) by use of tert-butyl {[1-(S)-(3,4-dichlorophenyl)-1-(N-methyl-trimethylacetamide)-3,4-dihydroxy]butyl}methylcarbamate (1.60 g).

[0610]

MS (FAB) m/z 459 $((M+H)^+)$

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.23 (9H, brs), 1.28 (9H, s), 2.82 (3H, s), 2.80—2.92 (1H, m), 3.07—3.18 (4H, m), 4.15—4.28 (1H, m), 4.36—4.48 (1H, m), 7.10 (1H, dd, J = 2.5, 8.5 Hz), 7.33 (1H, d, J = 2.5 Hz), 7.41 (1H, d, J = 8.5 Hz), 9.69 (1H, t, J = 2.0 Hz).

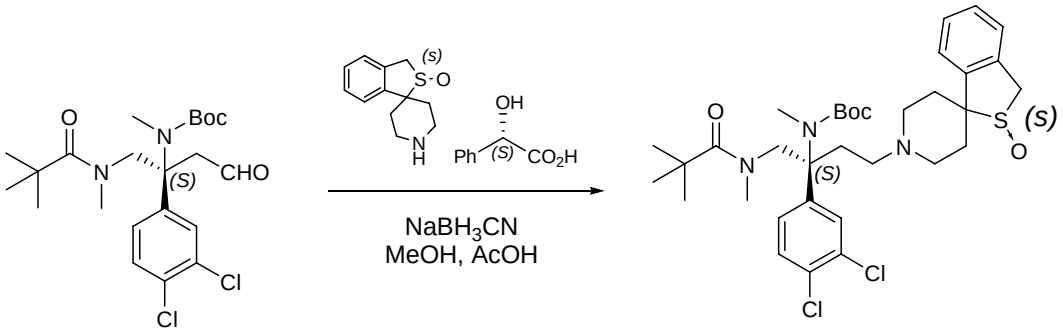
[0611]

Example 41(b)

Synthesis of tert-butyl {[1-(N-methyl-trimethylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate

[0612]

[F143]



[0613]

Similar to Example 26(h), the title compound was obtained (748 mg) by use of tert-butyl {[2-(S)-(3,4-dichlorophenyl)-1-(N-methyl-trimethylacetamide)-4-oxo]butan-2-yl}methylcarbamate (500 mg) and spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidine)/(S)-(+)-mandelate (448 mg).

[0614]

MS (FAB) m/z 664 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.20 (9H, brs), 1.30 (9H, s), 1.45—1.55 (1H, m), 1.80—1.98 (2H, m), 2.13—2.28 (3H, m), 2.32—2.47 (3H, m), 2.50—2.62 (1H, m), 2.68—2.78 (1H, m), 2.82—3.00 (4H, m), 3.13 (3H, s), 3.97 (1H, d, J = 17 Hz), 3.90—4.20 (1H, m), 4.29 (1H, d, J = 17 Hz), 4.47—4.70 (1H, m), 7.05—7.09 (1H, m), 7.25—7.33 (5H, m), 7.38 (1H, d, J = 8.5 Hz).

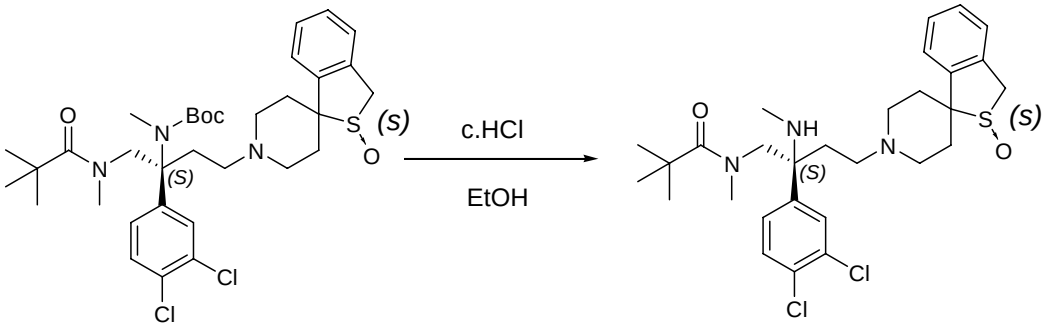
[0615]

Example 41(c)

Synthesis of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butyl}-N-methyl-trimethylacetamide

[0616]

[F144]



[0617]

Similar to Example 26(i), the title compound was obtained (532 mg, 86.4%, 2 steps) by use of tert-butyl {[1-(N-methyl-trimethylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate (730 mg).

[0618]

MS (FAB) m/z 564 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.20 (9H, s), 1.52–1.75 (2H, m), 1.95–2.20 (3H, m), 2.23 (3H, s), 2.32–2.58 (6H, m), 2.61 (3H, s), 2.90–3.15 (2H, m), 3.23–3.33 (1H, m), 3.92–4.07 (2H, m), 4.34 (1H, d, J = 17 Hz), 7.29–7.38 (5H, m), 7.42 (1H, d, J = 8.5 Hz), 7.62 (1H, br).

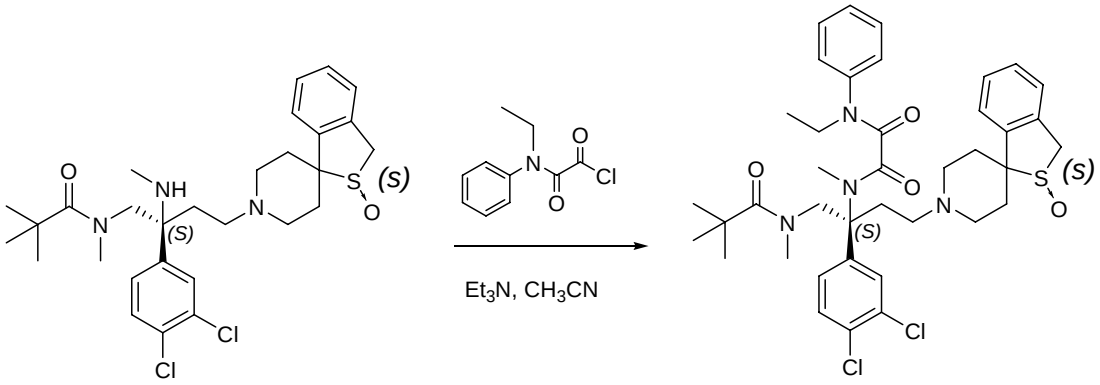
[0619]

Example 41(d)

Synthesis of N^1-{1-(N-methyl-trimethylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl-N^2-ethyl-N^2-phenyloxalamide

[0620]

[F145]



[0621]

Similar to Example 26(j), the title compound was obtained (111 mg, 82.4%) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butyl}-N-methyl-trimethylacetamide (60 mg).

[0622]

MS (FAB) m/z 739 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.25 (9H, s), 1.25 (3H, t, J = 7.0 Hz), 1.44–1.52 (1H, m), 1.78–1.92 (2H, m), 1.98–2.10 (1H, m), 2.13–2.27 (2H, m), 2.30–2.43 (4H, m), 2.64–2.78 (2H, m), 2.86 (3H, s), 3.05 (3H, s), 3.72–3.88 (2H, m), 3.97 (1H, d, J = 17 Hz), 4.05–4.35 (3H, m), 6.25 (1H, br), 7.02–7.07 (2H, m), 7.25–7.35 (6H, m), 7.45–7.52 (3H, m).

[0623]

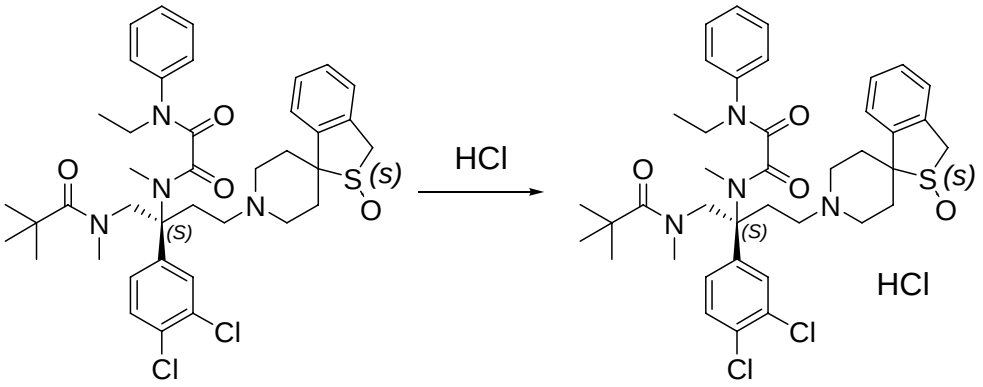
Example 41(e)

Synthesis of N^1-{1-(N-methyl-trimethylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-

1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl-N^2-ethyl-N^2-phenyloxalamide hydrochloride (Compound No. 37)

[0624]

[F146]



[0625]

Similar to Example 26(k), the title compound was obtained as white powder (88 mg, 75.6%) by use of N^1-{1-(N-methyl-trimethylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl-N^2-ethyl-N^2-phenyloxalamide (111 mg).

[0626]

$[\alpha]_D^{28}$= -38.4°(c 0.513, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.05 (3H, t, J = 7.0 Hz), 1.16 (9H, s), 1.98—2.57 (6H, m), 2.73—2.87 (2H, m), 2.92—3.18 (5H, m), 3.25—3.62 (6H, m), 3.68—3.78 (2H, m), 4.10 (1H, d, J = 17 Hz), 4.15—4.32 (1H, m), 4.70 (1H, d, J = 17 Hz), 7.22—7.60 (12H, m), 10.47 (1H, br).

[0627]

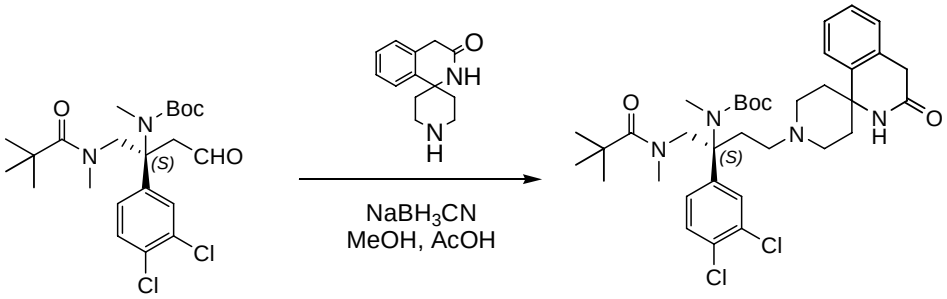
Example 42(a)

Synthesis of tert-butyl {[1-(N-methyl-trimethylacetamide)-2-

(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate

[0628]

[F147]



[0629]

Similar to Example 26(h), the title compound was obtained (723 mg) by use of tert-butyl {[1-(S)-(3,4-dichlorophenyl)-1-(N-methyl-trimethylacetamide)-3-oxo]propyl}methylcarbamate (500 mg) synthesized in Example 41(a).

[0630]

MS (FAB) m/z 659 $((M+H)^+)$

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.18 (9H, brs), 1.30 (9H, s), 1.63–1.77 (2H, m), 1.82–1.93 (1H, m), 2.02–2.30 (6H, m), 2.50–2.62 (1H, m), 2.68–2.78 (1H, m), 2.80–3.02 (4H, m), 3.14 (3H, s), 3.62 (2H, s), 3.85–4.12 (1H, m), 4.30–4.68 (1H, m), 6.31 (1H, br), 7.06 (1H, dd, J = 2.0, 8.5 Hz), 7.12–7.15 (1H, m), 7.22–7.36 (4H, m), 7.39 (1H, d, J = 8.5 Hz).

[0631]

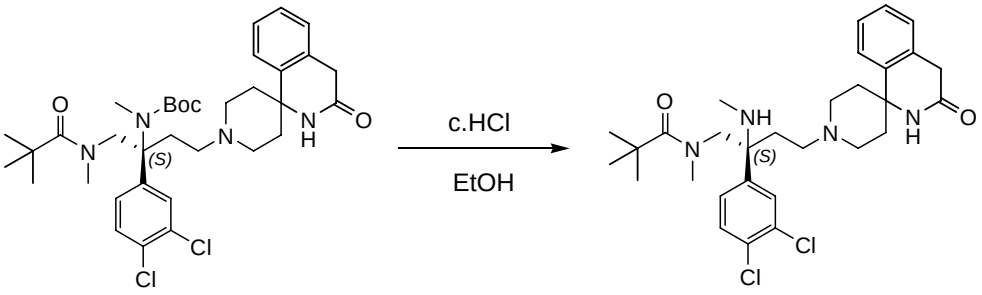
Example 42(b)

Synthesis of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-

[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-N-methyl-trimethylacetamide

[0632]

[F148]



[0633]

Similar to Example 26(i), the title compound was obtained (528 mg, 89.0%, 2 steps) by use of tert-butyl {[1-(N-methyl-trimethylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate (700 mg).

[0634]

MS (FAB) m/z 559 $((M+H)^+)$

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.20 (9H, s), 1.60—1.88 (3H, m), 1.95—2.58 (11
H, m), 2.61 (3H, s), 2.90—3.04 (2H, m), 3.32 (1H, d, J = 14 Hz), 3.64 (2H, s), 3.93 (1H, d, J = 14 Hz), 6.42 (1H, br), 7.16 (1H, d, J = 7.0 Hz), 7.24—7.45 (5H, m), 7.62 (1H, s).

[0635]

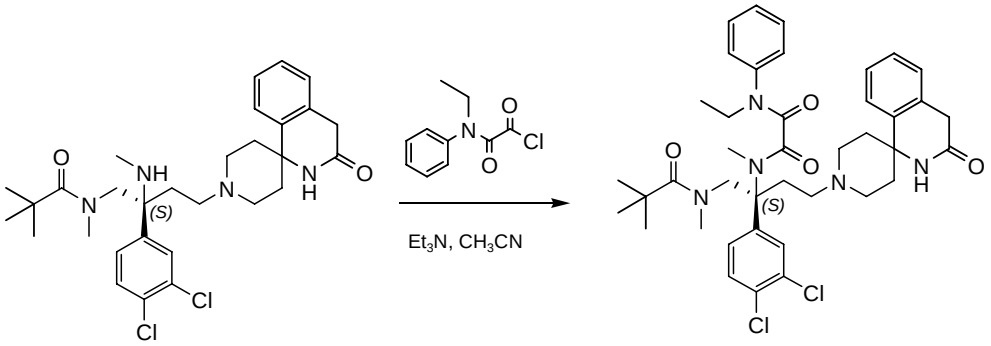
Example 42(c)

Synthesis of N^1-{1-(N-methyl-trimethylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl-N^2-ethyl-N^2-

phenyloxalamide

[0636]

[F149]



[0637]

Similar to Example 26(j), the title compound was obtained (114 mg, 85.2%) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-N-methyl-trimethylacetamide and (ethylphenylamino)-oxo-acetyl chloride (53 mg) synthesized in Referential Example 3.

[0638]

MS (FAB) m/z 734 $((M+H)^+)$

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.16 (3H, t, J = 7.0 Hz), 1.26 (9H, s), 1.60—1.73 (2H, m), 1.77—1.89 (1H, m), 1.95—2.23 (6H, m), 2.32—2.45 (1H, m), 2.62—2.74 (2H, m), 2.83 (3H, s), 3.07 (3H, s), 3.62 (2H, s), 3.70—3.89 (2H, m), 4.05—4.29 (2H, m), 6.17—6.35 (2H, m), 7.00—7.07 (2H, m), 7.11—7.16 (1H, m), 7.21—7.30 (4H, m), 7.30—7.37 (1H, m), 7.42—7.54 (3H, m).

[0639]

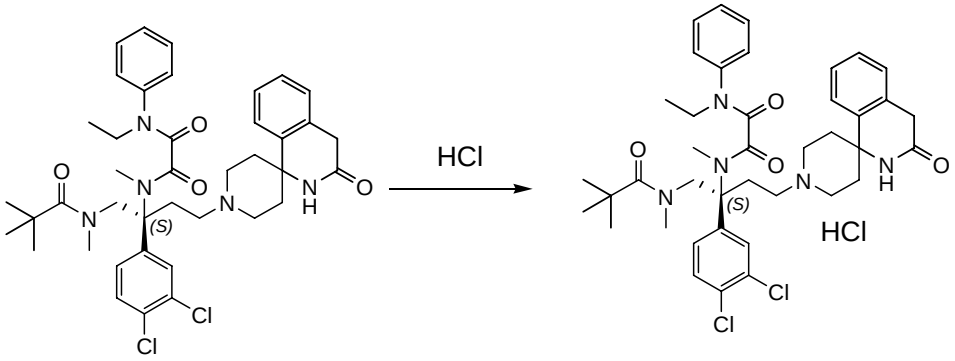
Example 42(d)

Synthesis of N^1-{1-(N-methyl-trimethylacetamide)-2-(S)-(3,4-

dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl-N^2-ethyl-N^2-phenyloxalamide hydrochloride (Compound No. 38)

[0640]

[F150]



[0641]

Similar to Example 26(k), the title compound was obtained as white powder (75 mg, 62.7%) by use of N^1-{1-(N-methyl-trimethylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl-N^2-ethyl-N^2-phenyloxalamide (114 mg).

[0642]

$[\alpha]_D^{28}$= -64.9°(c 0.505, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.05 (3H, t, J = 7.0 Hz), 1.18 (9H, s), 1.90—2.00 (2H, m), 2.18—2.90 (8H, m), 3.10 (3H, s), 3.16—3.53 (6H, m), 3.60—3.78 (4H, m), 4.22—4.38 (1H, m), 6.52 (1H, br), 7.20—7.60 (11H, m), 8.37 (1H, s), 10.53 (1H, br).

[0643]

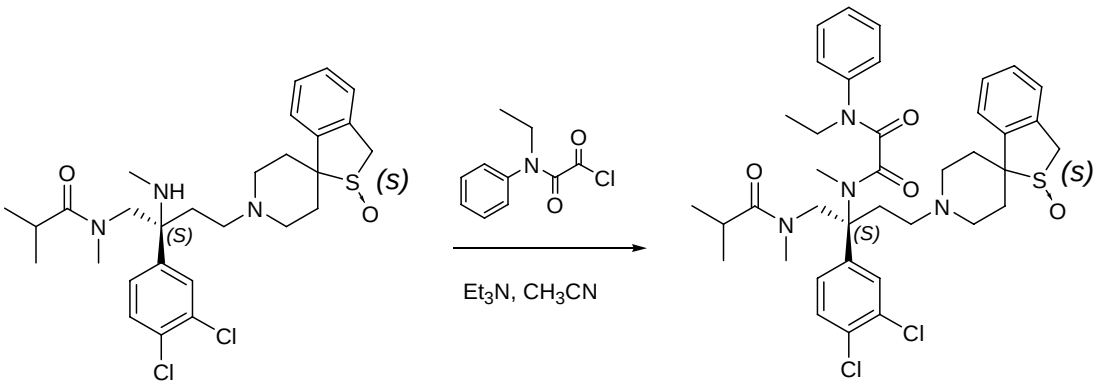
Example 43(a)

Synthesis of N^1-{1-(N-methylisobutylamide)-2-(S)-(3,4-

dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl-N^2-ethyl-N^2-phenyloxalamide

[0644]

[F151]



[0645]

Similar to Example 26(j), the title compound was obtained (92 mg, 69.6%) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butyl}-N-methylisobutylamide (100 mg) synthesized in Example 36(e) and (ethylphenylamino)-oxo-acetyl chloride (77 mg) synthesized in Referential Example 3.

[0646]

MS (FAB) m/z 725 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.09 (3H, d, J = 6.5 Hz), 1.11 (3H, d, J = 6.5 Hz), 1.17 (3H, t, J = 7.0 Hz), 1.44–1.52 (1H, m), 1.77–1.92 (2H, m), 2.00–2.10 (1H, m), 2.13–2.23 (2H, m), 2.28–2.45 (4H, m), 2.63–2.86 (6H, m), 3.05 (3H, s), 3.70–3.90 (2H, m), 3.97 (1H, d, J = 17 Hz), 4.03–4.33 (2H, m), 4.29 (1H,

d, J = 17 Hz), 6.25 (1H, br), 7.01—7.08 (2H, m), 7.25—7.35 (6H, m), 7.43—7.54 (3H, m).

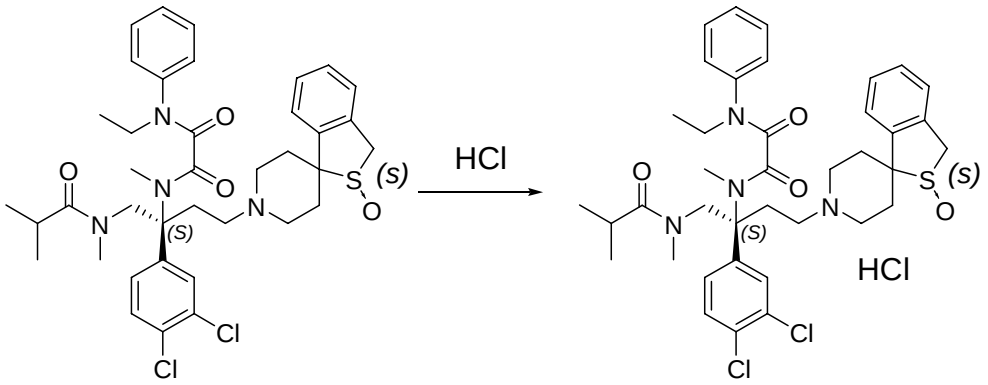
[0647]

Example 43(b)

Synthesis of N^1-{1-(N-methylisobutylamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl-N^2-ethyl-N^2-phenyloxalamide hydrochloride (Compound No. 39)

[0648]

[F152]



[0649]

Similar to Example 26(k), the title compound was obtained as white powder (65 mg, 67.1%) by use of N^1-{1-(N-methylisobutylamide)-2-(S)-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl-N^2-ethyl-N^2-phenyloxalamide (92 mg).

[0650]

$[\alpha]_D^{28}$= -44.3°(c 0.508, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 0.98 (6H, t, J = 7.0 Hz), 1.05 (3H, t, J = 7.0 Hz), 1.98—2.07 (1H, m), 2.22—2.58 (6H,

m), 2.73—2.86 (3H, m), 2.95—3.10 (2H, m), 3.12 (3H, s), 3.30—3.53 (4H, m), 3.67—3.78 (3H, m), 4.05—4.20 (2H, m), 4.70 (1H, d, J = 17 Hz), 7.25—7.58 (12H, m), 10.52 (1H, br).

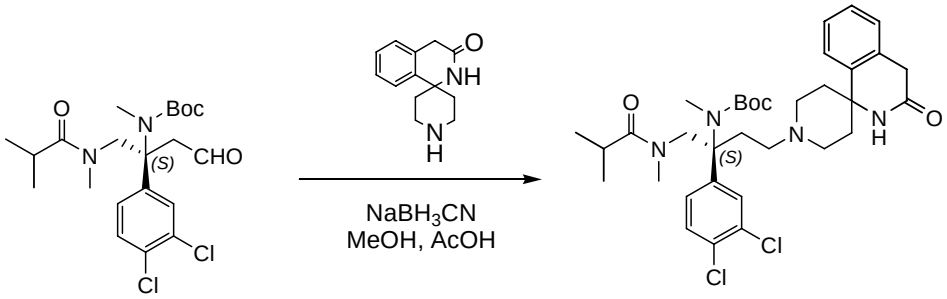
[0651]

Example 44(a)

Synthesis of tert-butyl {[1-(N-methylisobutylamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate

[0652]

[F153]



[0653]

Similar to Example 26(h), the title compound was obtained (1.30 g, 91.5%) by use of tert-butyl {[1-(S)-(3,4-dichlorophenyl)-1-(N-methylisobutylamide)-3-oxo]propyl}methylcarbamate (1.0 g) synthesized in Example 36(c).

[0654]

MS (FAB) m/z 645 ($(M+H)^+$)

^{1}H-NMR (270MHz, $CDCl_3$)δ ppm : 1.10—1.40 (15H, m), 1.62—2.00 (2H, m), 2.07—2.40 (5H, m), 2.58—2.68 (1H, m), 2.69 (3H, s), 2.79—3.06 (3H, m), , 3.13 (3H, s), 3.62 (3H, s), 3.62—3.72

(1H, m), 3.85—4.15 (1H, m), 4.30—4.70 (2H, m), 6.30—6.40 (2H, m), 7.05—7.58 (6H, m).

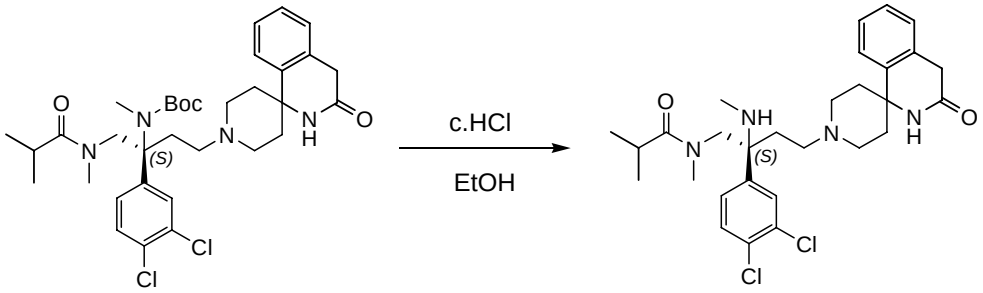
[0655]

Example 44(b)

Synthesis of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-N-methylisobutylamide

[0656]

[F154]



[0657]

Similar to Example 26(i), the title compound was obtained (950 mg, 86.6%) by use of tert-butyl {[1-(N-methylisobutylamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl]methylcarbamate (1.30 g).

[0658]

MS (FAB) m/z 545 $((M+H)^+)$

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.02 (3H, d, J = 6.5 Hz), 1.08 (3H, d, J = 6.5 Hz), 1.75—1.87 (3H, m), 1.95—2.45 (7H, m), 2.53 (3H, s), 2.50—2.77 (2H, m), 2.87—3.07 (3H, m), 3.36 (1H, d, J = 13 Hz), 3.61 (1H, d, J = 10 Hz), 3.64 (3H, s), 3.92 (1H, d, J = 13 Hz), 6.36 (1H, br), 7.13—7.18 (1H, m),

7.24—7.47 (5H, m), 7.61 (1H, d, J = 2.0 Hz).

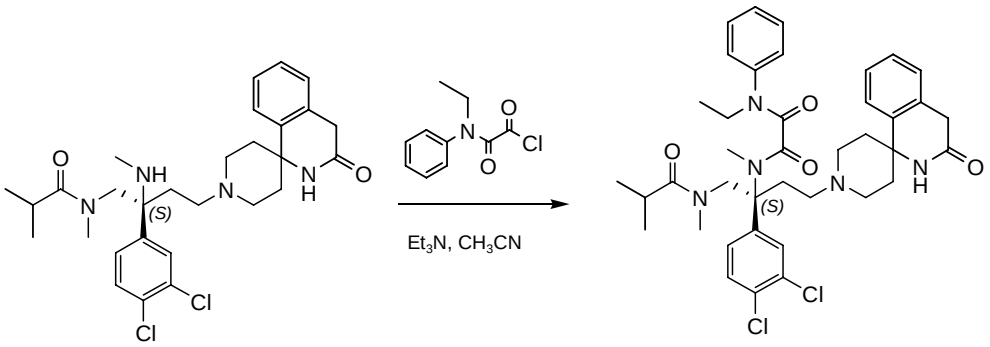
[0659]

Example 44(c)

Synthesis of N^1-{1-(N-methylisobutylamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl-N^2-ethyl-N^2-phenyloxalamide

[0660]

[F155]



[0661]

Similar to Example 26(j), the title compound was obtained as white powder (80 mg, 60.7%) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-N-methylisobutylamide (100 mg) and (ethylphenylamino)-oxo-acetyl chloride (77 mg) synthesized in Referential Example 3.

[0662]

MS (FAB) m/z 720 $((M+H)^+)$

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.09 (3H, d, J = 7.0 Hz), 1.10 (3H, d, J = 7.0 Hz), 1.15 (3H, t, J = 7.0 Hz), 1.63—1.73 (1H, m), 1.77—1.87 (1H, m), 1.96—2.25 (7H, m), 2.37—2.48 (1H, m),

2.60—2.87 (6H, m), 3.07 (3H, s), 3.61 (2H, s), 3.70—3.90 (2H, m), 4.02—4.30 (2H, m), 6.19—6.32 (2H, m), 7.00—7.08 (2H, m), 7.11—7.16 (1H, m), 7.21—7.35 (5H, m), 7.43—7.54 (3H, m).

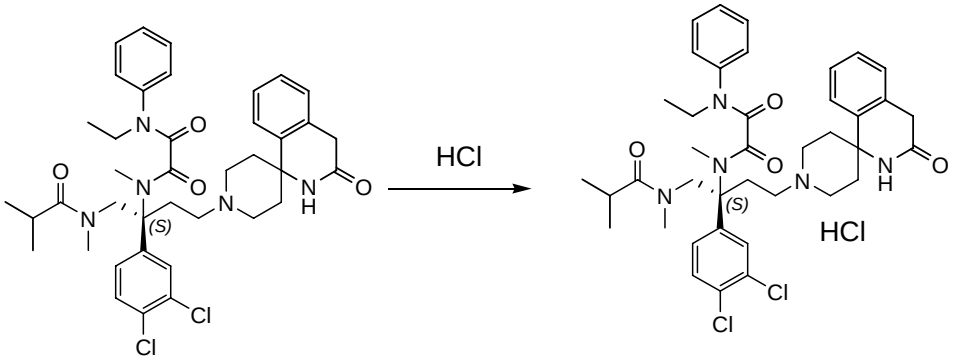
[0663]

Example 44(d)

Synthesis of N^1-{1-(N-methylisobutylamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl-N^2-ethyl-N^2-phenyloxalamide hydrochloride (Compound No. 40)

[0664]

[F156]



[0665]

Similar to Example 26(k), the title compound was obtained as white powder (55 mg, 65.4%) by use of N^1-{1-(N-methylisobutylamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl-N^2-ethyl-N^2-phenyloxalamide (80 mg).

[0666]

$[\alpha]_D^{28}$= -72.5°(c 0.434, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 0.99 (6H, t, J = 7.0 Hz), 1.05 (3H, t, J = 7.0 Hz), 1.99—2.00 (2H, m), 2.18—2.95 (9H,

m), 3.10 (3H, s), 3.15—3.50 (5H, m), 3.62 (2H, s), 3.68—3.78 (3H, m), 4.15—4.27 (1H, m), 6.59 (1H, br), 7.20—7.60 (11H, m), 8.38 (1H, s), 10.68 (1H, br).

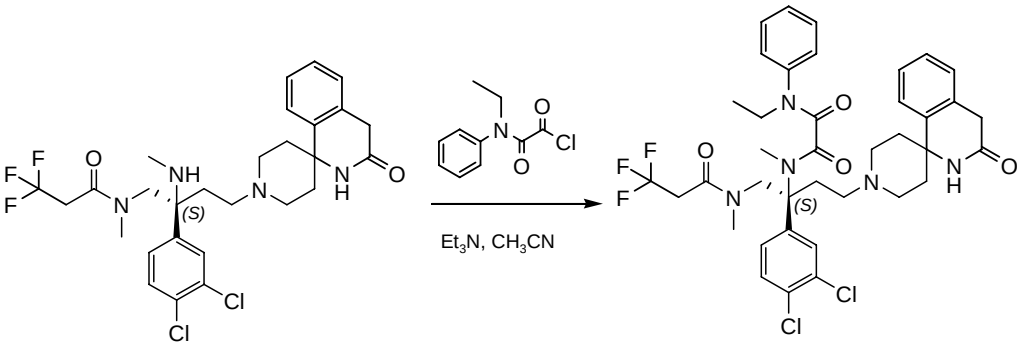
[0667]

Example 45(a)

Synthesis of N^1-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl-N^2-ethyl-N^2-phenyloxalamide

[0668]

[F157]



[0669]

Similar to Example 35(i), the title compound was obtained as white powder (197 mg, 76.2%) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-3,3,3-trifluoro-N-methylpropanamide (200 mg) synthesized in Example 26(i) and (ethylphenylamino)-oxo-acetyl chloride (143 mg) synthesized in Referential Example 3.

[0670]

MS (FAB) m/z 760 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.17 (3H, t, J = 7.0 Hz), 1.62—1.72 (2H, m), 1.78—1.93 (2H, m), 1.98—2.22 (5H, m), 2.32—2.44 (1H, m), 2.60—2.73 (2H, m), 2.83 (3H, s), 3.06 (3H, s), 3.12—3.38 (2H, m), 3.61 (2H, s), 3.70—3.90 (2H, m), 4.07—4.18 (1H, m), 4.28—4.38 (1H, m), 6.14—6.29 (2H, m), 6.97—7.08 (2H, m), 7.12—7.16 (1H, m), 7.21—7.37 (5H, m), 7.43—7.54 (3H, m).

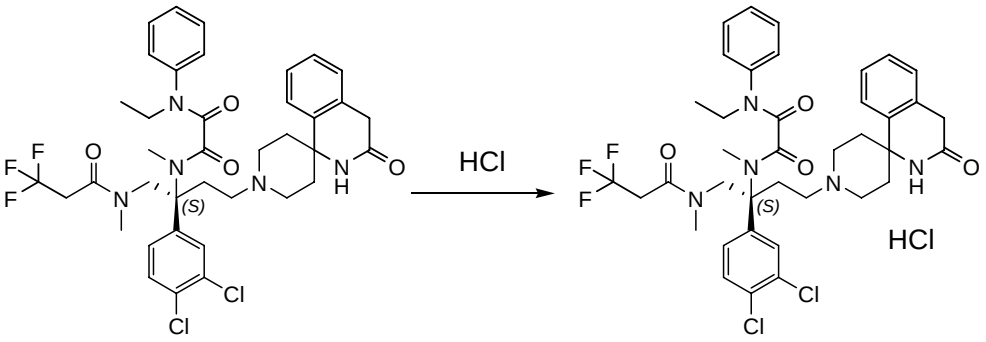
[0671]

Example 45(b)

Synthesis of N^1-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl-N^2-ethyl-N^2-phenyloxalamide hydrochloride (Compound No. 41)

[0672]

[F158]



[0673]

Similar to Example 26(k), the title compound was obtained as white powder (172 mg, 83.3%) by use of N^1-{1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-

1,4'-piperidin)-1'-yl]butan-2-yl}-N^1-methyl-N^2-ethyl-N^2-phenyloxalamide (197 mg).

[0674]

$[\alpha]_D^{28}$= -56.4°(c 0.509, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.19 (3H, t, J = 7.0 Hz), 1.85—1.98 (2H, m), 2.25—2.60 (5H, m), 2.65—2.97 (2H, m), 3.13 (3H, s), 3.15—3.50 (5H, m), 3.61 (3H, s), 3.63—3.78 (4H, m), 3.80—3.97 (1H, m), 4.10—4.23 (1H, m), 6.61 (1H, br), 7.18—7.58 (11H, m), 8.38 (1H, br), 10.25 (1H, br).

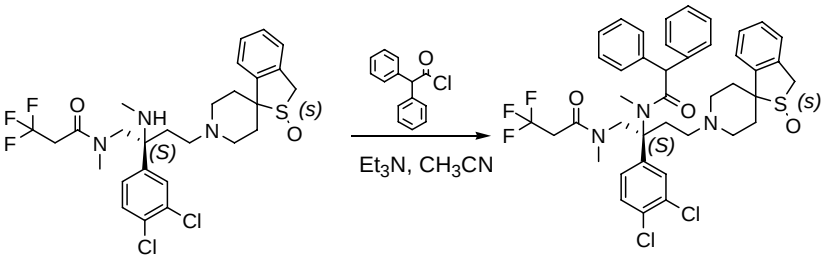
[0675]

Example 46(a)

Synthesis of N-{2-(S)-(N-methyl-2,2-diphenylacetamide)-2-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butyl}-3,3,3-trifluoro-N-methylpropanamido

[0676]

[F159]



[0677]

Similar to Example 26(j), the title compound was obtained (500 mg, 47.5%) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butyl}-3,3,3-trifluoro-

N-methylpropanamide (790 mg) synthesized in Example 34(b) and diphenylacetyl chloride (1.55 g).

[0678]

MS (FAB) m/z 784 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.43—1.58 (1H, m), 1.80—2.10 (2H, m), 2.16—2.60 (7H, m), 2.66—2.93 (5H, m), 3.02—3.30 (5H, m), 3.97 (1H, d, J = 17 Hz), 4.10—4.40 (2H, m), 4.45—4.58 (1H, m), 5.21 (1H, br), 6.97 (1H, dd, J = 2.0, 8.5 Hz), 7.10—7.40 (16H, m).

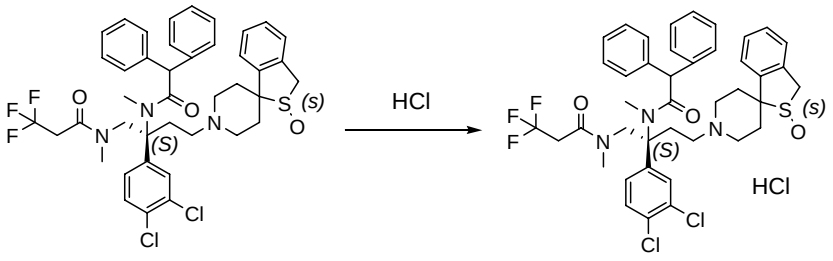
[0679]

Example 46(b)

Synthesis of N-{2-(S)-(N-methyl-2,2-diphenylacetamide)-2-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butyl}-3,3,3-trifluoro-N-methylpropanamido hydrochloride (Compound No. 42)

[0680]

[F160]



[0681]

Similar to Example 26(k), the title compound was obtained as pale yellow powder (434 mg, 85.2%) by use of N-{2-(S)-(N-methyl-2,2-diphenylacetamide)-2-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-

1(3H),4'-piperidin)-1'-yl]butyl}-3,3,3-trifluoro-N-methylpropanamide (500 mg).

[0682]

$[\alpha]_D^{28}$= -7.7°(c 0.506, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.92—2.02 (1H, m), 2.18—2.47 (4H, m), 2.57—2.86 (3H, m), 2.95—3.22 (8H, m), 3.48—3.73 (5H, m), 4.09 (1H, d, J = 17 Hz), 4.21—4.35 (1H, m), 4.71 (1H, d, J = 17 Hz), 5.57 (1H, s), 7.10—7.50 (17H, m), 10.60 (1H, br).

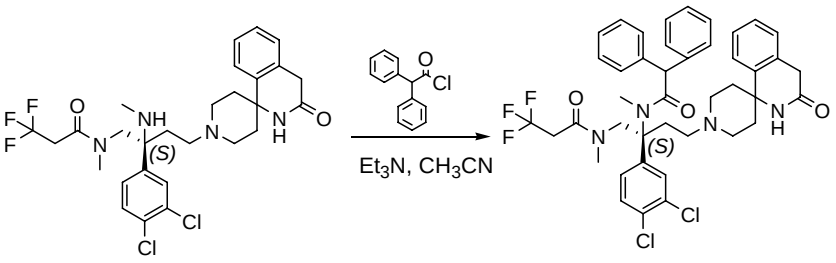
[0683]

Example 47(a)

Synthesis of N-{2-(S)-(N-methyl-2,2-diphenylacetamide)-2-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-3,3,3-trifluoro-N-methylpropanamido

[0684]

[F161]



[0685]

Similar to Example 26(j), the title compound was obtained (190 mg, 26.6%) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-3,3,3-trifluoro-N-methylpropanamide (536 mg) synthesized in Example

26(i) and diphenylacetyl chloride (1.06 g).

[0686]

MS (FAB) m/z 779 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.60—1.76 (2H, m), 1.87—2.40 (7H, m), 2.44—2.58 (1H, m), 2.63—2.72 (5H, m), 3.03—3.32 (5H, m), 3.61 (2H, s), 4.20—4.35 (1H, m), 4.38—4.50 (1H, m), 5.22 (1H, s), 6.27 (1H, br), 6.97 (1H, dd, J = 2.0, 8.5 Hz), 7.10—7.40 (16H, m).

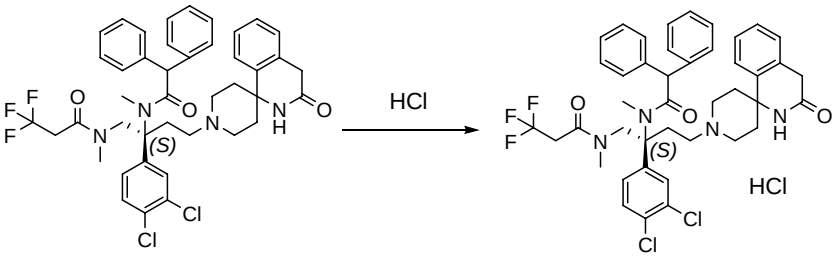
[0687]

Example 47(b)

Synthesis of N-{2-(S)-(N-methyl-2,2-diphenylacetamide)-2-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-3,3,3-trifluoro-N-methylpropanamido hydrochloride (Compound No. 43)

[0688]

[F162]



[0689]

Similar to Example 26(k), the title compound was obtained as white powder (136 mg, 68.3%) by use of N-{2-(S)-(N-methyl-2,2-diphenylacetamide)-2-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-3,3,3-trifluoro-N-methylpropanamide (190 mg).

[0690]

$[\alpha]_D^{28}$= -11.7°(c 0.512, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.89 (2H, d, J = 14.5 Hz), 2.31—2.70 (5H, m), 2.98—3.10 (1H, m), 3.18 (3H, s), 3.20—3.53 (6H, m), 3.58—3.75 (5H, m), 3.88—4.06 (1H, m), 4.26—4.37 (1H, m), 5.58 (1H, s), 7.11—7.38 (15H, m), 7.46 (1H, d, J = 2.0 Hz), 7.58 (1H, d, J = 8.5 Hz), 8.36 (1H, s), 10.41 (1H, br).

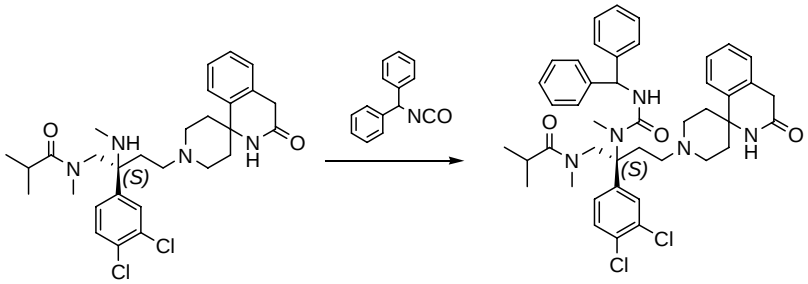
[0691]

Example 48(a)

Synthesis of 1-{1-(N-methyl-isobutylamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-3-benzhydryl-1-methylurea

[0692]

[F163]



[0693]

N-{2-(S)-(3,4-Dichlorophenyl)-2-methylamino-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-N-methylisobutylamide (157 mg) synthesized in Example 44(b) was dissolved in tetrahydrofuran (2 mL). Diphenylmethyl isocyanate (109 μL) was added thereto at room temperature, and the mixture was stirred for 30 minutes at the same temperature. The reaction mixture was concentrated

under reduced pressure, and the residue was purified through silica gel column chromatography (n-hexane : ethyl acetate=1:4 → chloroform : methanol=10:1), to thereby give the title compound (205 mg, 94.3%).

[0694]

MS (FAB) m/z 754 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.10 (3H, d, J = 7.0 Hz), 1.11 (3H, d, J = 7.0 Hz), 1.62—1.75 (2H, m), 1.93—2.30 (7H, m), 2.46—2.60 (1H, m), 2.65—2.90 (6H, m), 3.16 (3H, s), 3.62 (2H, s), 4.07—4.20 (1H, m), 4.24—4.40 (1H, m), 4.92 (1H, d, J = 7.0 Hz), 5.99 (1H, d, J = 7.0 Hz), 6.27 (1H, br), 7.02—7.16 (6H, m), 7.20—7.38 (11H, m).

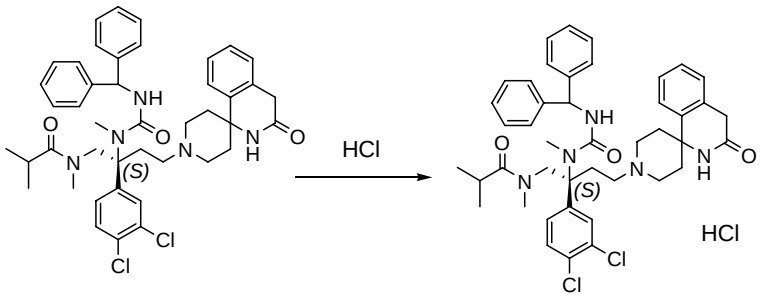
[0695]

Example 48(b)

Synthesis of 1-{1-(N-methyl-isobutylamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-3-benzhydryl-1-methylureahydrochloride (Compound No. 44)

[0696]

[F164]



[0697]

Similar to Example 26(k), the title compound was

obtained as white powder (178 mg, 82.7%) by use of 1-{1-(N-methyl-isobutylamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-3-benzhydryl-1-methylurea (205 mg).

[0698]

$[\alpha]_D^{28}$= -22.2°(c 0.503, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.01 (6H, d, J = 7.0 Hz), 1.85—1.97 (2H, m), 2.20—2.60 (6H, m), 2.72—3.18 (7H, m), 3.25—3.50 (5H, m), 3.73 (2H, s), 3.80—4.00 (1H, m), 4.20—4.32 (1H, m), 5.82 (1H, d, J = 8.0 Hz), 7.13—7.38 (15H, m), 7.48—7.60 (2H, m), 8.35 (1H, s), 10.20 (1H, br).

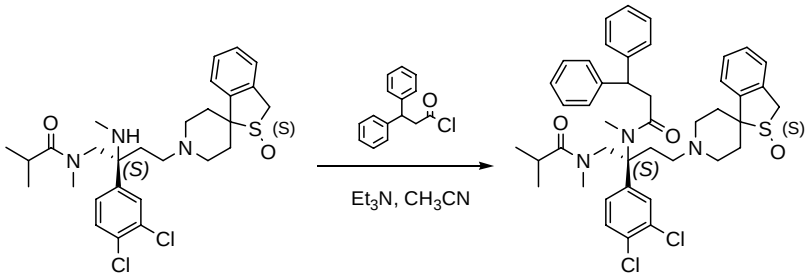
[0699]

Example 49(a)

Synthesis of N-{2-(S)-(N-methyl-3,3-diphenylpropanamido)-2-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butyl}-N-methyl-isobutylamide

[0700]

[F165]



[0701]

Similar to Example 26(j), the title compound was obtained (417 mg, 74.3%) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[spiro(benzo(c)thiophene-

(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butyl}-N-methylisobutylamide (408 mg) synthesized in Example 46(e) and 3,3-diphenylpropionyl chloride (544 mg).

[0702]

MS (FAB) m/z 758 ($(M+H)^+$)

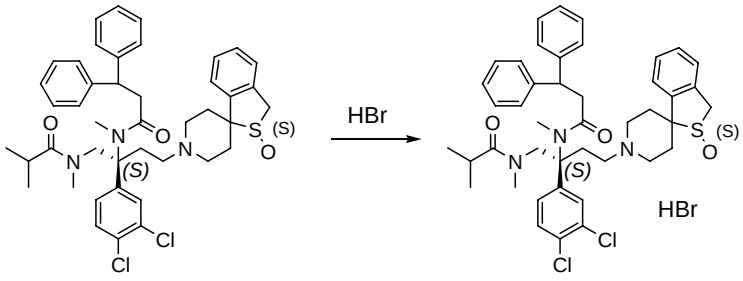
^{1}H-NMR (270MHz, CDCl3)δ ppm : 1.07 (3H, s), 1.09 (3H, s), 1.42—1.55 (1H, m), 1.76—1.90 (1H, m), 1.94—2.06 (1H, m), 2.10—2.47 (7H, m), 2.54 (3H, s), 2.63—2.88 (3H, m), 3.00—3.18 (5H, m), 3.90—4.10 (2H, m), 4.23—4.36 (2H, m), 4.62 (1H, t, J = 7.5 Hz), 6.72 (1H, d, J = 8.5 Hz), 7.12—7.35 (16H, m).

[0703]

Example 49(b)

Synthesis of N-{2-(S)-(N-methyl-3,3-diphenylpropanamido)-2-(3,4-dichlorophenyl)-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butyl}-N-methyl-isobutylamide hydrobromide (Compound No. 45)

[0704]



[0705]

N-{2-(S)-(3,4-Dichlorophenyl)-2-methylamino-4-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]butyl}-N-methylisobutylamide (11.0 g) was dissolved in ethanol (50 mL). An aqueous solution (50 mL) of 48%

hydrobromic acid (2.45 g) was added thereto at 55°C. The temperature of the mixture was lowered to room temperature, and 50% aqueous ethanol (100 mL) was added to the mixture. The crystals were collected through filtration and dried, to thereby give the title compound (8.5 g, 83%) as pale yellow crystals.

[0706]

Mp:172.4–173.8°C(dec.)

$[\alpha]_D^{27}$= -23.3°(c 0.207, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 0.98 (3H, d, J = 6.0 Hz), 0.99 (3H, d, J = 6.0 Hz), 2.00–2.19 (2H, m), 2.22–2.34 (2H, m), 2.37–2.45 (2H, m), 2.60–2.81 (2H, m), 2.98–3.43 (11H, m), 3.47–3.57 (2H, m), 3.64–3.76 (1H, m), 4.10 (1H, d, J = 17 Hz), 4.17–4.28 (1H, m), 4.36 (1H, t, J = 7.5 Hz), 4.71 (1H, d, J = 17 Hz), 7.06–7.18 (3H, m), 7.22–7.32 (9H, m), 7.36–7.43 (5H, m), 9.55 (1H, br).

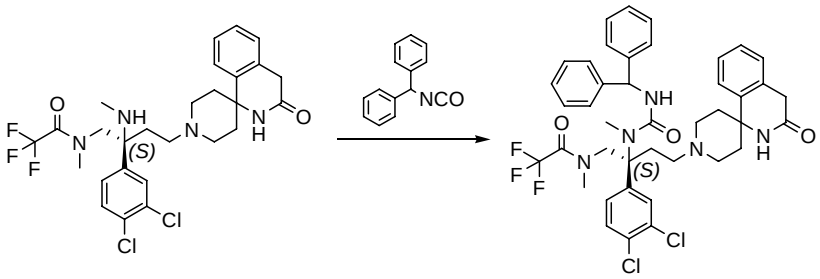
[0707]

Example 50(a)

Synthesis of 1-{1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-3-benzhydryl-1-methylurea

[0708]

[F167]



[0709]

Similar to Example 48(a), the title compound was obtained (355 mg, 98.4%) by use of N-{2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butyl}-2,2,2-trifluoro-N-methylacetamide (264 mg) synthesized in Example 27(e).

[0710]

MS (FAB) m/z 780 ($(M+H)^+$)

^{1}H-NMR (270MHz, CDCl3)δ ppm : 1.55—1.80 (2H, m), 1.93—2.27 (7H, m), 2.41—2.57 (1H, m), 2.68—2.85 (2H, m), 2.89 (3H, s), 3.12 (3H, s), 3.61 (2H, s), 4.34 (1H, d, J = 13.5 Hz), 4.49 (1H, d, J = 13.5 Hz), 5.07 (1H, d, J = 7.0 Hz), 5.99 (1H, d, J = 7.0 Hz), 6.24 (1H, s), 7.03 (1H, dd, J = 2.0, 8.5 Hz), 7.10—7.43 (16H, m).

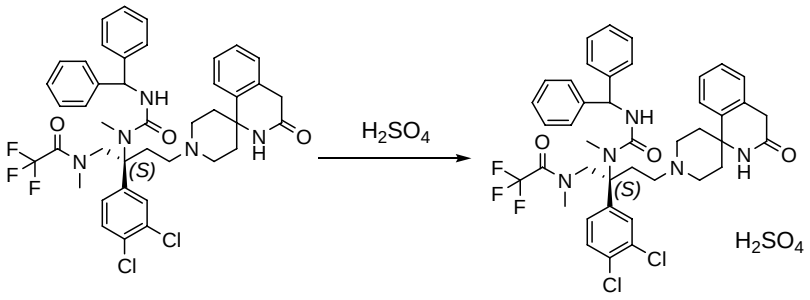
[0711]

Example 50(b)

Synthesis of 1-{1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-3-benzhydryl-1-methylurea sulfate (Compound No. 46)

[0712]

[F168]



[0713]

1-{1-(2,2,2-Trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-[3-oxo-3,4-dihydro-2H-spiro(isoquinoline-1,4'-piperidin)-1'-yl]butan-2-yl}-3-benzhydryl-1-methylurea (8.2 g) was dissolved in ethanol (30 mL). At an internal temperature of 30°C, a solution of concentrated sulfuric acid (1.07 g) in ethanol (10 mL) was added thereto. The temperature of the mixture was lowered to room temperature, and ethanol:isopropyl ether (5:2) mixture solution (30 mL) was added to the mixture. The crystals were collected through filtration and dried, to thereby give the title compound (8.12 g, 88.0%) as white crystals.

[0714]

Mp:185.9–186.0°C(dec.)

$[\alpha]_D^{28}$ = -5.9°(c 0.209, MeOH)

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.96 (2H, d, J = 14 Hz), 2.24–2.38 (2H, m), 2.41–2.56 (2H, m), 2.73 (3H, s), 2.85–2.98 (1H, m), 3.03–3.16 (4H, m), 3.27–3.53 (4H, m), 3.63 (2H, s), 4.09–4.22 (1H, m), 4.38 (1H, d, J = 13.5 Hz), 5.85 (1H, d, J = 7.5 Hz), 7.20–7.37 (16H, m), 7.56 (1H, d, J = 2 .0 Hz), 7.59 (1H, d, J = 8.5 Hz), 8.27 (1H, s), 9.18 (2H, br).

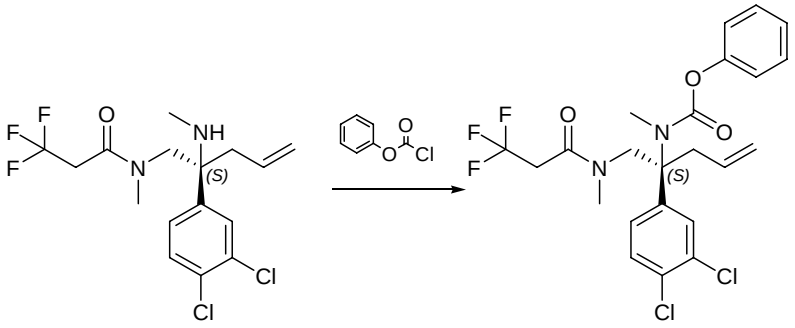
[0715]

Example 51(a)

Synthesis of phenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate

[0716]

[F169]



[0717]

N-[2-(S)-(3,4-Dichlorophenyl)-2-methylamino-4-pentene-1'-yl]-3,3,3-trifluoro-N-methylpropanamide (400 mg) synthesized in Example 29(a) was dissolved in ethyl acetate (4 mL). At room temperature, saturated aqueous sodium bicarbonate (4 mL) and phenyl chloroformate (0.26 mL) were added thereto, and the mixture was stirred for 2 hours at the same temperature. Subsequently, phenyl chloroformate (0.26 mL) was added to the reaction mixture, and the resultant mixture was stirred for another 2 hours. The reaction mixture was extracted with ethyl acetate, sequentially washed with water and saturated brine, and dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, and the residue was purified through silica gel column chromatography (n-hexane : ethyl acetate=2:1), to

thereby give the title compound (498 mg, 94.8%).

[0718]

MS (FAB) m/z 503 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 2.73 (1H, dd, J = 6.5, 13.5 Hz), 2.87 (3H, s), 2.92–3.06 (1H, m), 3.12–3.36 (2H, m), 3.18 (3H, s), 3.98–4.17 (1H, m), 4.44–4.62 (1H, m), 5.04 (1H, d, J = 17.0 Hz), 5.08 (1H, d, J = 10.5 Hz), 5.75–5.89 (1H, m), 6.90–7.07 (2H, m), 7.11 (1H, dd, J = 2.5, 8.5 Hz), 7.13–7.19 (1H, m), 7.25–7.38 (3H, m), 7.41 (1H, d, J = 8.5 Hz).

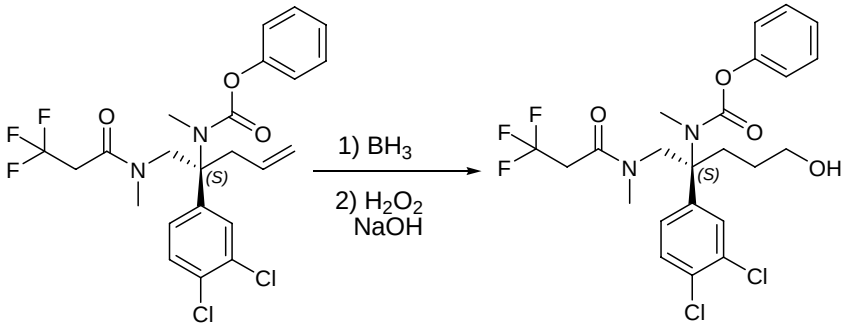
[0719]

Example 51(b)

Synthesis of phenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate

[0720]

[F170]



[0721]

Under argon, phenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate (410 mg) was dissolved in anhydrous tetrahydrofuran (4 mL). Under cooling with ice, a 1.06M

solution (0.80 mL) of borane tetrahydrofuran complex in tetrahydrofuran was added thereto, and the mixture was stirred for 1 hour. Water (0.3 mL), 3N aqueous sodium hydroxide (0.9 mL), and 30% aqueous hydrogen peroxide (0.9 mL) were added to the reaction mixture, and the resultant mixture was stirred for 1 hour at room temperature. The reaction mixture was extracted with ethyl acetate, sequentially washed with water and saturated brine, and dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, and the residue was purified through silica gel column chromatography (n-hexane : ethyl acetate=1:2), to thereby give the title compound (311 mg, 70.0%).

[0722]

MS (FAB) m/z 521 $((M+H)^+)$

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.05—1.21 (1H, m), 1.64—1.78 (1H, m), 1.85—1.97 (2H, m), 2.17—2.30 (1H, m), 2.97 (3H, s), 3.20—3.41 (2H, m), 3.28 (3H, s), 3.48—3.59 (1H, m), 3.60—3.69 (1H, m), 4.23—4.57 (2H, m), 6.88—7.04 (2H, m), 7.10 (1H, dd, J = 2.0, 8.5 Hz), 7.13—7.20 (1H, m), 7.25—7.38 (3H, m), 7.41 (1H, d, J = 8.5 Hz).

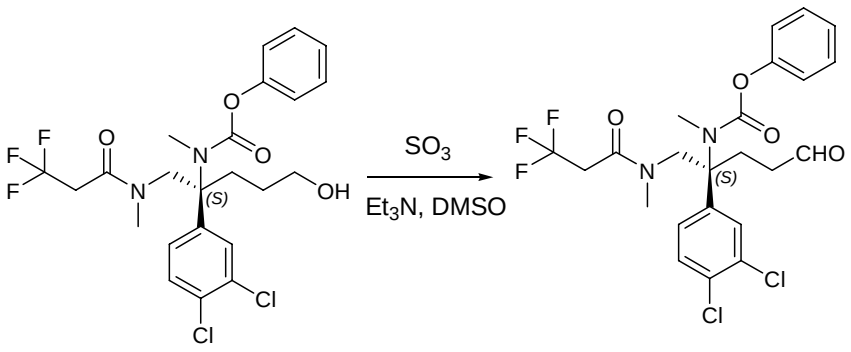
[0723]

Example 51(c)

Synthesis of phenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate

[0724]

[F171]



[0725]

Under argon, phenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate (100 mg) was dissolved in anhydrous dimethyl sulfoxide (1.0 mL). At room temperature, triethylamine (0.16 mL) and pyridine sulfur trioxide complex (94 mg) were added thereto, and the mixture was stirred for 4 hours at room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was sequentially washed with water and saturated brine and dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, to thereby give the title compound (115 mg).

[0726]

MS (FAB) m/z 519 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 2.07—2.23 (2H, m), 2.28—2.40 (1H, m), 2.78—2.90 (1H, m), 2.96 (3H, s), 3.18—3.39 (2H, m), 3.29 (3H, s), 4.20—4.53 (2H, m), 6.81—7.05 (2H, m), 7.11 (1H, dd, J = 2.0, 8.5 Hz), 7.17 (1H, t, J = 7.5 Hz), 7.24—7.37 (3H, m), 7.43 (1H, d, J = 8.5 Hz), 9.65 (1H, s).

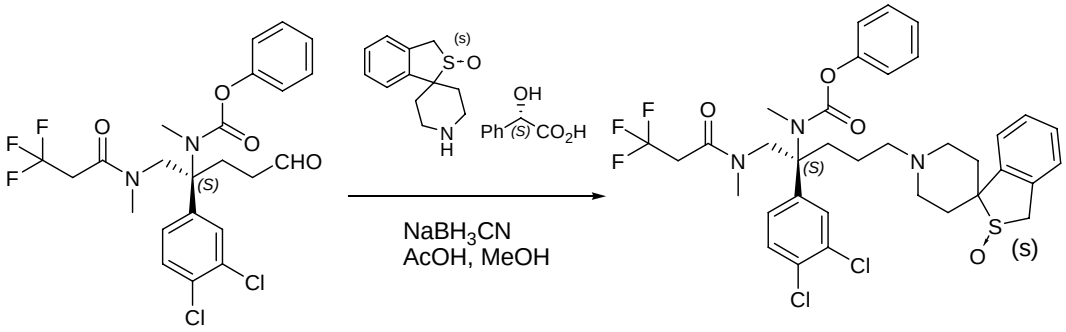
[0727]

Example 51(d)

Synthesis of phenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate

[0728]

[F172]



[0729]

Phenyl {[1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate (115 mg) was dissolved in methanol (1 mL). Under cooling with ice, sodium cyanoborohydride (14 mg) and spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidine)/(S)-(+)-mandelate (79 mg) were added thereto, and then acetic acid (19 μL) was added thereto. The temperature of the mixture was then returned to room temperature, and the mixture was stirred for 30 minutes. The reaction mixture was poured into saturated aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate, washed with saturated brine, and dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, and the residue was purified through silica gel column chromatography (ethyl acetate → ethyl acetate :

methanol=10:1), to thereby give the title compound (97 mg, 69.7%, two steps).

[0730]

MS (FAB) m/z 724 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 0.97—1.17 (1H, m), 1.51—1.77 (2H, m), 1.82—2.09 (3H, m), 2.25—2.49 (6H, m), 2.80—2.98 (2H, m), 3.02 (3H, s), 3.17—3.47 (2H, m), 3.28 (3H, s), 3.99 (1H, d, J = 16.5 Hz), 4.18—4.38 (2H, m), 4.43—4.55 (1H, m), 6.87—7.06 (1H, m), 7.08—7.19 (2H, m), 7.25—7.43 (9H, m).

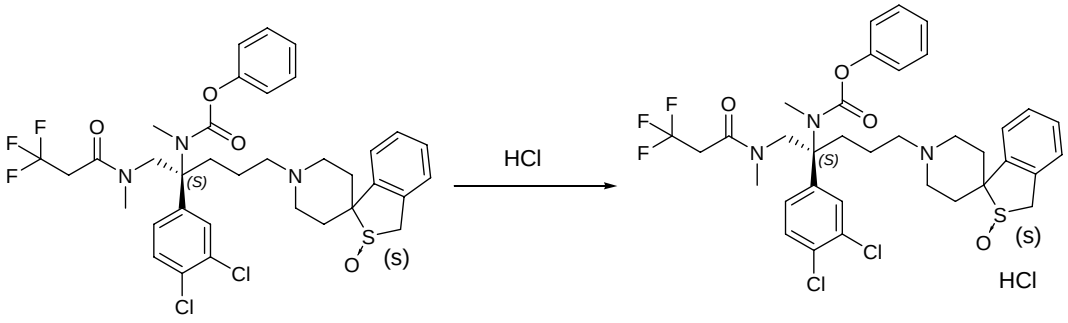
[0731]

Example 51(e)

Synthesis of phenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate hydrochloride (Compound No. 591)

[0732]

[F173]



[0733]

Phenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate (97 mg)

was dissolved in ethyl acetate. 4N HCl-1,4-dioxane (0.1 mL) was added thereto, and the solvent was concentrated under reduced pressure. Ether was added to the residue, followed by filtration and drying, to thereby give the title compound (70 mg, 68.6%) as white powder.

[0734]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.15—1.43 (1H, m), 1.75—1.93 (1H, m), 1.95—2.20 (3H, m), 2.25 (1H, d, J = 14.0 Hz), 2.34—2.48 (1H, m), 2.73—3.19 (8H, m), 3.27 (3H, s), 3.47—3.57 (1H, m), 3.59—3.88 (3H, m), 4.08 (1H, d, J = 17.0 Hz), 4.13—4.42 (2H, m), 4.68 (1H, d, J = 17.0 Hz), 6.40—6.67 (1H, m), 6.93—7.10 (1H, m), 7.11—7.22 (1H, m), 7.25—7.46 (7H, m), 7.52—7.69 (2H, m), 10.70 (1H, br).

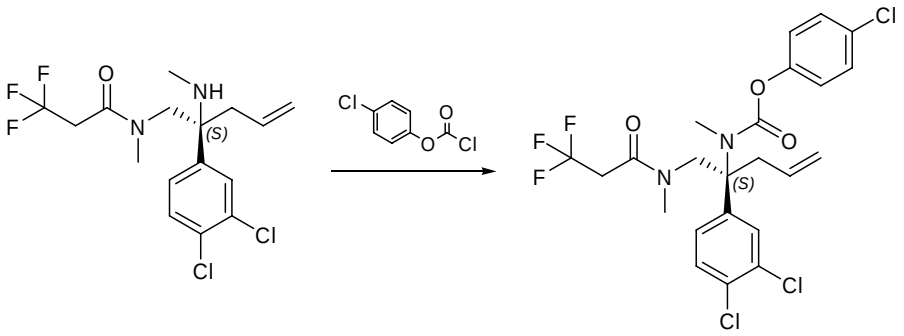
[0735]

Example 52(a)

Synthesis of 4-chlorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate

[0736]

[F174]



[0737]

Similar to Example 51(a), the title compound was obtained (303 mg, >100%) by use of N-[2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-pentene-1'-yl]-3,3,3-trifluoro-N-methylpropanamide (200 mg) synthesized in Example 4(a) and 4-chlorophenyl chloroformate (0.29 mL).

[0738]

MS (FAB) m/z 537 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 2.74 (1H, dd, J = 6.0, 13.5 Hz), 2.85 (3H, s), 2.92—3.33 (3H, m), 3.15 (3H, s), 3.84—4.06 (1H, m), 4.50—4.73 (1H, m), 4.98—5.12 (2H, m), 5.71—5.88 (1H, m), 6.87—7.06 (2H, m), 7.10 (1H, dd, J = 2.5, 8.5 Hz), 7.21—7.32 (2H, m), 7.34 (1H, d, J = 2.5 Hz), 7.42 (1H, d, J = 8.5 Hz).

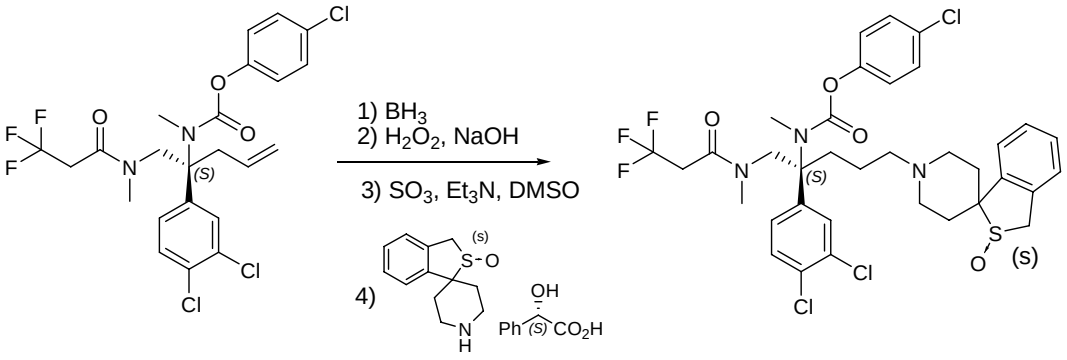
[0739]

Example 52(b)

Synthesis of 4-chlorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate

[0740]

[F175]



[0741]

Similar to Example 51(b), 4-chlorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate (180 mg) was obtained by use of 4-chlorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate (296 mg). Subsequently, similar to Example 51(c), 4-chlorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate (167 mg) was obtained by use of 4-chlorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate (174 mg). Thereafter, similar to Example 51(d), the title compound was obtained as white powder (136 mg, 36.3%, 4 steps) by use of 4-chlorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate (167 mg).

[0742]

MS (FAB) m/z 760 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.00—1.17 (1H, m), 1.52—1.71 (2H, m), 1.82—2.08 (3H, m), 2.25—2.47 (6H, m), 2.82—3.09 (2H, m), 2.98 (3H, s), 3.17—3.43 (2H, m), 3.25 (3H, s), 3.99 (1H, d, J = 16.5 Hz), 4.20—4.52 (3H, m), 6.83—7.02 (1H, br), 7.10 (1H, dd, J = 2.0, 8.5 Hz), 7.20—7.36 (8H, m), 7.40 (1H, d, J = 8.5 Hz).

[0743]

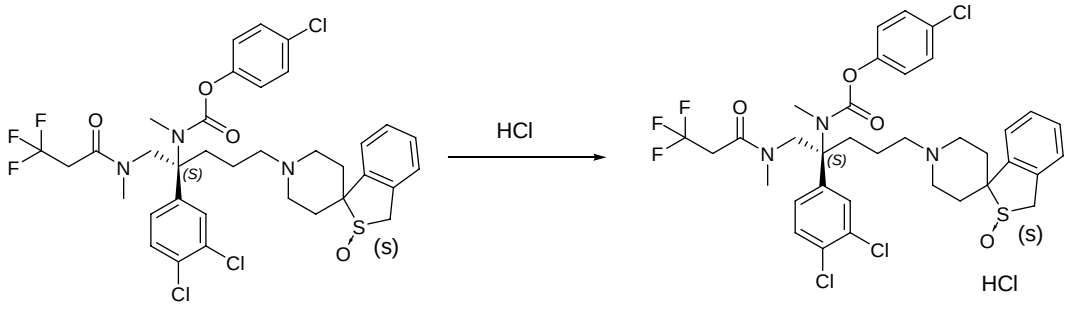
Example 52(c)

Synthesis of 4-chlorophenyl {1-(3,3,3-trifluoro-N-

methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate hydrochloride (Compound No. 633)

[0744]

[F176]



[0745]

Similar to Example 51(e), the title compound was obtained as white powder (80 mg, 56.2%) by use of 4-chlorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate (136 mg).

[0746]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.21—1.47 (1H, m), 1.76—1.91 (1H, m), 1.94—2.19 (3H, m), 2.25 (1H, d, J = 14.0 Hz), 2.35—2.48 (1H, m), 2.77—3.18 (8H, m), 3.25 (3H, s), 3.47—3.55 (1H, m), 3.59—3.87 (3H, m), 4.04—4.53 (3H, m), 4.68 (1H, d, J = 17.0 Hz), 6.51—6.73 (1H, m), 7.03—7.17 (1H, m), 7.29—7.46 (7H, m), 7.55—7.67 (2H, m), 10.73 (1H, br).

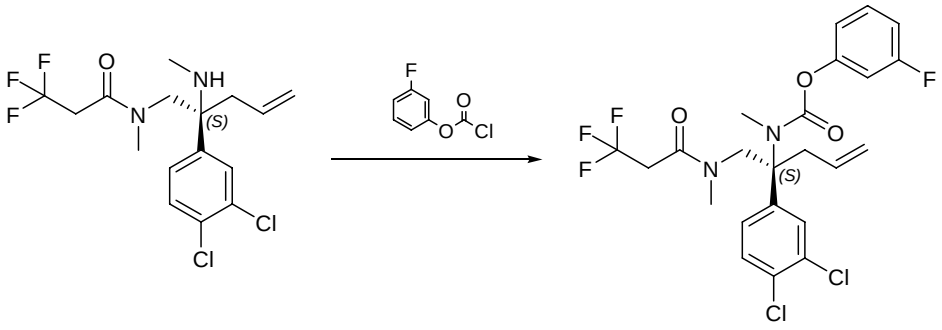
[0747]

Example 53(a)

Synthesis of 3-fluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate

[0748]

[F177]



[0749]

Similar to Example 51(a), the title compound was obtained (256 mg, 94.1%) by use of N-[2-(S)-(3,4-dichlorophenyl)-2-(methylamino)-4-pentene-1'-yl]-3,3,3-trifluoro-N-methylpropanamide (200 mg) synthesized in Example 4(a) and 3-fluorophenyl chloro formate (873 mg).

[0750]

MS (FAB) m/z 521 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 2.75 (1H, dd, J = 6.0, 13.5 Hz), 2.85 (3H, s), 2.92–3.05 (1H, m), 3.09–3.32 (2H, m), 3.16 (3H, s), 3.90–4.07 (1H, m), 4.52–4.72 (1H, m), 5.05 (1H, d, J = 17.0 Hz), 5.09 (1H, d, J = 10.0 Hz), 5.72–5.89 (1H, m), 6.68–6.95 (3H, m), 7.11 (1H, dd, J = 2.5, 8.5 Hz), 7.22–7.31 (1H, m), 7.35 (1H, d, J = 2.5 Hz), 7.42 (1H, d, J = 8.5 Hz).

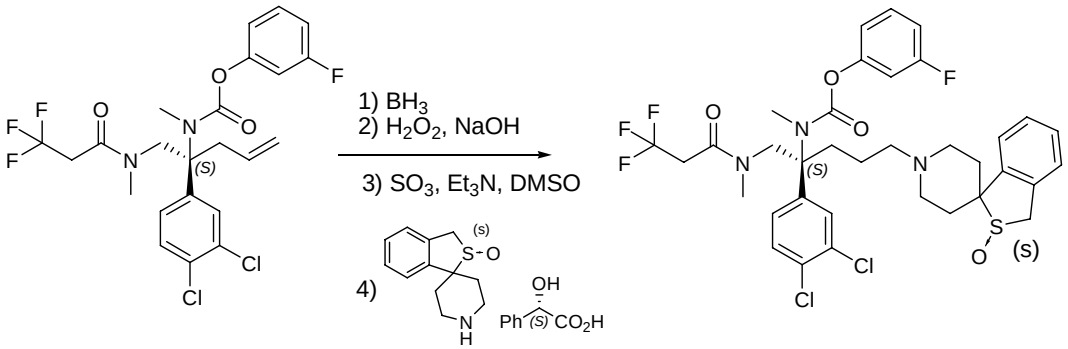
[0751]

Example 53(b)

Synthesis of 3-fluorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate

[0752]

[F178]



[0753]

Similar to Example 51(b), 3-fluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate was obtained (110 mg) by use of 3-fluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)(4-penten-2-yl)]methylcarbamate (236 mg). Subsequently, similar to Example 51(c), 3-fluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate was obtained (117 mg) by use of 3-fluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate (105 mg). Thereafter, similar to Example 51(d), the title compound was obtained as white powder (102 mg, 36.6%, 4 steps) by use of 3-fluorophenyl [1-(3,3,3-trifluoro-N-

methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate (114 mg).

[0754]

MS (FAB) m/z 742 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 0.97—1.18 (1H, m), 1.53—2.09 (5H, m), 2.25—2.48 (6H, m), 2.80—3.09 (2H, m), 2.99 (3H, s), 3.14—3.44 (2H, m), 3.26 (3H, s), 3.99 (1H, d, J = 16.5 Hz), 4.20—4.57 (3H, m), 6.66—6.92 (2H, m), 7.10 (1H, dd, J = 2.0, 8.5 Hz), 7.20—7.37 (7H, m), 7.41 (1H, d, J = 8.5 Hz).

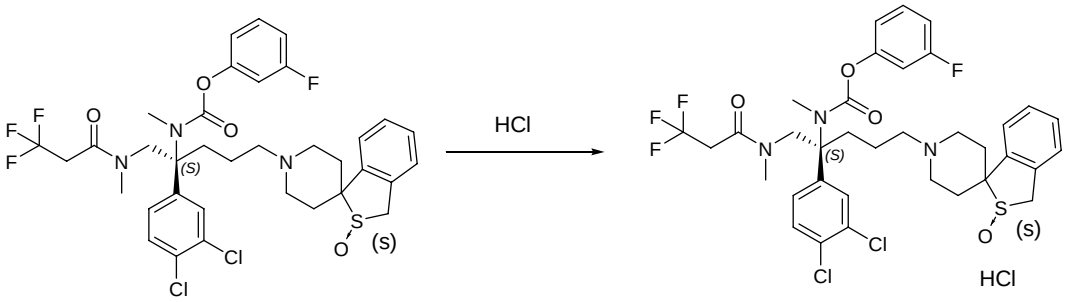
[0755]

Example 53(c)

Synthesis of 3-fluorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate hydrochloride (Compound No. 634)

[0756]

[F179]



[0757]

Similar to Example 51(e), the title compound was obtained as white powder (84 mg, 78.7%) by use of 3-fluorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-

(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate (102 mg).

[0758]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.21—1.44 (1H, m), 1.76—1.91 (1H, m), 1.93—2.20 (3H, m), 2.25 (1H, d, J = 14.0 Hz), 2.34—2.47 (1H, m), 2.78—3.18 (8H, m), 3.25 (3H, s), 3.47—3.89 (4H, m), 4.03—4.50 (3H, m), 4.68 (1H, d, J = 17.0 Hz), 6.38—6.64 (1H, m), 6.86—7.11 (2H, m), 7.28—7.47 (6H, m), 7.53—7.69 (2H, m), 10.72 (1H, br).

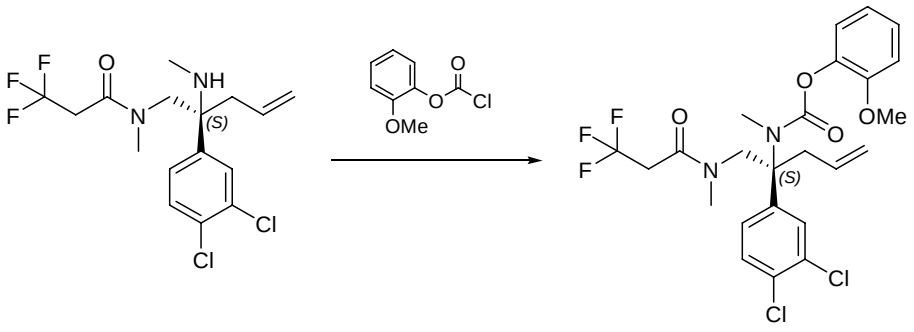
[0759]

Example 54(a)

Synthesis of 2-methoxyphenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate

[0760]

[F180]



[0761]

Similar to Example 51(a), the title compound was obtained (264 mg, 94.8%) by use of N-[2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-pentene-1'-yl]-3,3,3-

trifluoro-N-methylpropanamide (200 mg) synthesized in Example 29(a) and 2-methoxyphenyl chloroformate (933 mg).

[0762]

MS (FAB) m/z 533 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 2.68 (1H, dd, J = 7.0, 13.5 Hz), 2.90 (1H, dd, J = 7.0, 13.5 Hz), 2.97 (3H, s), 3.18—3.39 (2H, m), 3.25 (3H, s), 3.78 (3H, s), 4.24—4.47 (2H, m), 4.98 (1H, d, J = 17.0 Hz), 5.03 (1H, d, J = 10.0 Hz), 5.72—5.86 (1H, m), 6.82—6.99 (3H, m), 7.07—7.17 (2H, m), 7.35 (1H, d, J = 2.0 Hz), 7.38 (1H, d, J = 8.5 Hz).

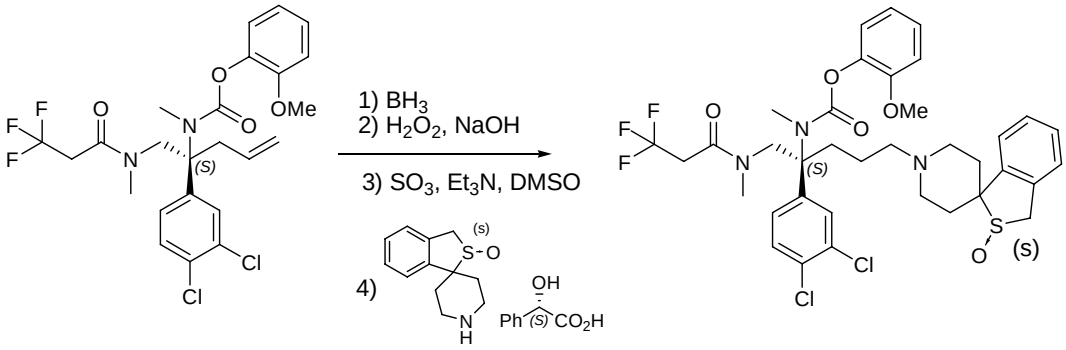
[0763]

Example 54(b)

Synthesis of 2-methoxyphenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate

[0764]

[F181]



[0765]

Similar to Example 51(b), 2-methoxyphenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-

hydroxy-pentan-2-yl]methylcarbamate was obtained (178 mg) by use of 2-methoxyphenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate (258 mg). Subsequently, similar to Example 51(c), 2-methoxyphenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate was obtained (193 mg) by use of 2-methoxyphenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate (170 mg). Thereafter, similar to Example 51(d), the title compound was obtained as white powder (179 mg, 51.6%, 4 steps) by use of 2-methoxyphenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate (193 mg).

[0766]

MS (FAB) m/z 754 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 0.89—1.12 (1H, m), 1.58 (1H, dd, J = 1.5, 15.0 Hz), 1.64—1.80 (1H, m), 1.82—2.02 (3H, m), 2.24—2.49 (6H, m), 2.82—2.98 (2H, m), 3.08 (3H, s), 3.31 (3H, s), 3.18—3.49 (2H, m), 3.76 (3H, s), 3.98 (1H, d, J = 16.5 Hz), 4.07—4.22 (1H, m), 4.31 (1H, d, J = 16.5 Hz), 4.53—4.78 (1H, m), 6.81—6.92 (2H, m), 7.07—7.16 (2H, m), 7.25—7.40 (7H, m).

[0767]

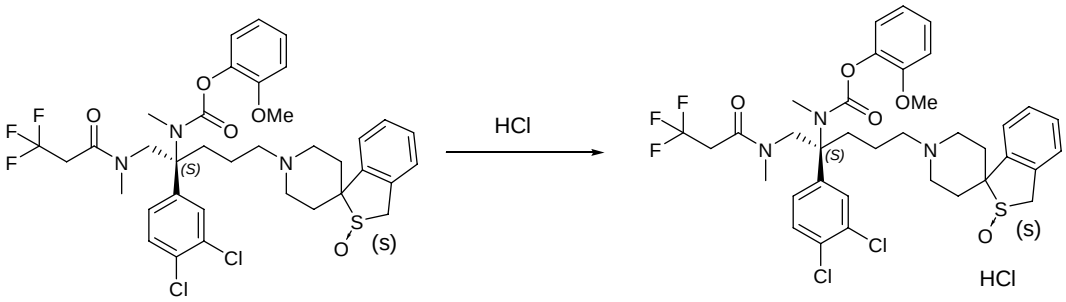
Example 54(c)

Synthesis of 2-methoxyphenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-

[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate hydrochloride (Compound No. 636)

[0768]

[F182]



[0769]

Similar to Example 51(e), the title compound was obtained as white powder (114 mg, 60.8%) by use of 2-methoxyphenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate (179 mg).

[0770]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.13—1.44 (1H, m), 1.78—2.16 (4H, m), 2.24 (1H, d, J = 14.0 Hz), 2.34—2.48 (1H, m), 2.80—3.18 (8H, m), 3.30 (3H, s), 3.45—3.55 (1H, m), 3.57 (3H, s), 3.60—3.92 (3H, m), 3.97—4.17 (2H, m), 4.31—4.49 (1H, m), 4.68 (1H, d, J = 17.0 Hz), 6.79—7.09 (3H, m), 7.11—7.20 (1H, m), 7.29—7.46 (5H, m), 7.52—7.66 (2H, m), 10.55 (1H, br).

[0771]

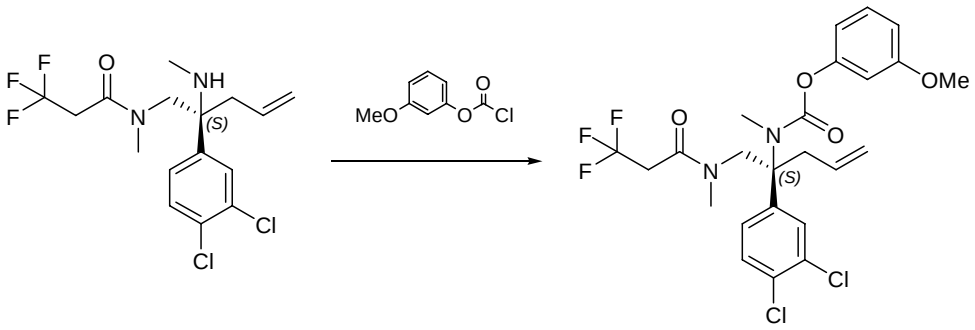
Example 55(a)

Synthesis of 3-methoxyphenyl [1-(3,3,3-trifluoro-N-

methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate

[0772]

[F183]



[0773]

Similar to Example 51(a), the title compound was obtained (263 mg, 94.5%) by use of N-[2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-pentene-1'-yl]-3,3,3-trifluoro-N-methylpropanamide (200 mg) synthesized in Example 4(a) and 3-methoxyphenyl chloroformate (933 mg).

[0774]

MS (FAB) m/z 533 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 2.66—2.79 (1H, m), 2.89 (3H, s), 2.92—3.05 (1H, m), 3.10—3.37 (2H, m), 3.18 (3H, s), 3.75 (3H, s), 3.96—4.19 (1H, m), 4.40—4.69 (1H, m), 5.04 (1H, d, J = 17.0 Hz), 5.08 (1H, d, J = 10.5 Hz), 5.72—5.88 (1H, m), 6.45—6.67 (2H, m), 6.71 (1H, d, J = 7.5 Hz), 7.11 (1H, dd, J = 2.0, 8.5 Hz), 7.15—7.25 (1H, m), 7.33—7.39 (1H, m), 7.41 (1H, d, J = 8.5 Hz).

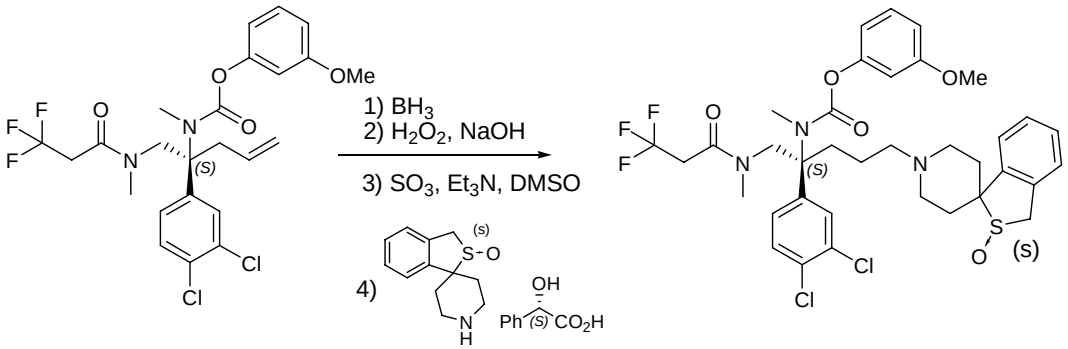
[0775]

Example 55(b)

Synthesis of 3-methoxyphenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate

[0776]

[F184]



[0777]

Similar to Example 51(b), 3-methoxyphenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate (167 mg) was obtained by use of 3-methoxyphenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)(4-penten-2-yl)]methylcarbamate (256 mg). Subsequently, similar to Example 51(c), 3-methoxyphenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate (135 mg) was obtained by use of 3-methoxyphenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate (160 mg). Thereafter, similar to Example 51(d), the title compound was obtained as white powder (84 mg, 24.3%, 4 steps) by use of 3-methoxyphenyl [1-(3,3,3-trifluoro-N-

methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate (135 mg).

[0778]

MS (FAB) m/z 754 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 0.94–1.14 (1H, m), 1.58 (1H, dd, J = 2.0, 15.0 Hz), 1.63–1.76 (1H, m), 1.83–2.06 (3H, m), 2.23–2.47 (6H, m), 2.82–2.97 (2H, m), 3.02 (3H, s), 3.15–3.46 (2H, m), 3.27 (3H, s), 3.73 (3H, s), 3.99 (1H, d, J = 16.5 Hz), 4.20–4.37 (2H, m), 4.40–4.63 (1H, m), 6.46–6.62 (1H, m), 6.67–6.74 (1H, m), 7.11 (1H, dd, J = 2.0, 8.5 Hz), 7.14–7.23 (1H, m), 7.25–7.38 (6H, m), 7.41 (1H, d, J = 8.5 Hz).

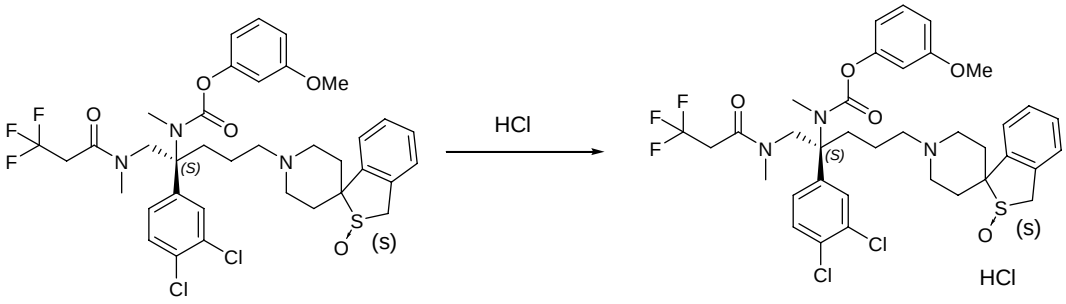
[0779]

Example 55(c)

Synthesis of 3-methoxyphenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate hydrochloride (Compound No. 637)

[0780]

[F185]



[0781]

Similar to Example 51(e), the title compound was

obtained as white powder (70 mg, 79.7%) by use of 3-methoxyphenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate (84 mg).

[0782]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.17—1.43 (1H, m), 1.77—2.19 (4H, m), 2.25 (1H, d, J = 14.0 Hz), 2.32—2.47 (1H, m), 2.78—3.18 (8H, m), 3.25 (3H, s), 3.46—3.88 (7H, m), 4.02—4.45 (3H, m), 4.68 (1H, d, J = 17.0 Hz), 6.12—6.33 (1H, m), 6.51—6.82 (2H, m), 7.13—7.26 (1H, m), 7.38—7.46 (5H, m), 7.53—7.73 (2H, m), 10.61 (1H, br).

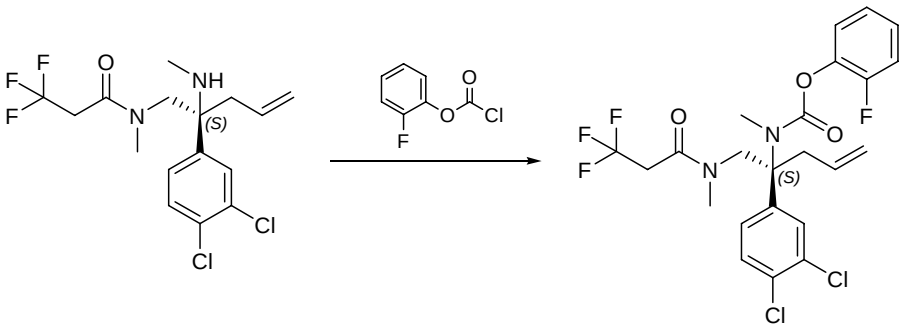
[0783]

Example 56(a)

Synthesis of 2-fluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate

[0784]

[F186]



[0785]

Similar to Example 51(a), the title compound was obtained (286 mg, >100%) by use of N-[2-(S)-(3,4-

dichlorophenyl)-2-(methylamino)-4-pentene-1'-yl]-3,3,3-trifluoro-N-methylpropanamide (200 mg) synthesized in Example 4(a) and 2-fluorophenyl chloroformate (873 mg).

[0786]

MS (FAB) m/z 521 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 2.72 (1H, dd, J = 6.5, 13.5 Hz), 2.87—3.04 (1H, m), 2.93 (3H, s), 3.10—3.40 (2H, m), 3.22 (3H, s), 4.16—4.50 (2H, m), 5.00 (1H, dd, J = 1.5, 17.0 Hz), 5.05 (1H, dd, J = 1.5, 10.5 Hz), 5.69—5.84 (1H, m), 7.01—7.19 (5H, m), 7.33 (1H, d, J = 2.0 Hz), 7.40 (1H, d, J = 8.5 Hz).

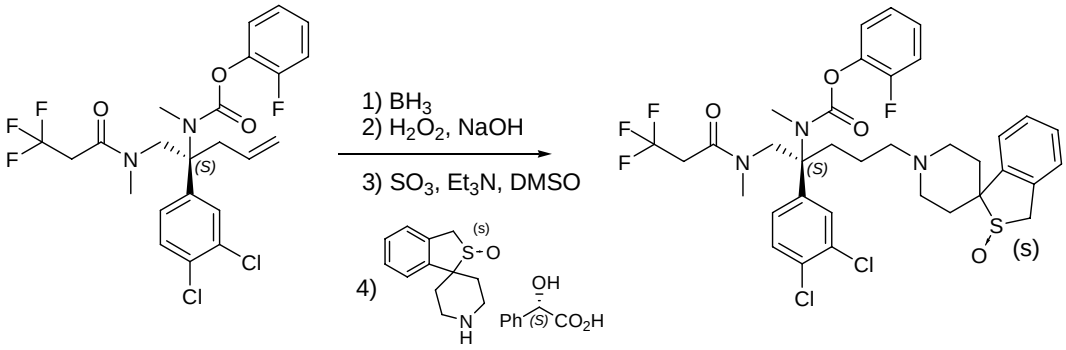
[0787]

Example 56(b)

Synthesis of 2-fluorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate

[0788]

[F187]



[0789]

Similar to Example 51(b), 2-fluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-

hydroxy-pentan-2-yl]methylcarbamate was obtained (130 mg) by use of 2-fluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate (278 mg). Subsequently, similar to Example 51(c), 2-fluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate (122 mg) was obtained by use of 2-fluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate (123 mg). Thereafter, similar to Example 51(d), the title compound was obtained as white powder (101 mg, 26.1%, 4 steps) by use of 2-fluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate (122 mg).

[0790]

MS (FAB) m/z 742 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 0.92—1.11 (1H, m), 1.52—1.77 (2H, m), 1.82—2.06 (3H, m), 2.24—2.49 (6H, m), 2.82—2.97 (2H, m), 3.05 (3H, s), 3.17—3.48 (2H, m), 3.31 (3H, s), 3.98 (1H, d, J = 16.5 Hz), 4.08—4.25 (1H, m), 4.31 (1H, d, J = 16.5 Hz), 4.52—4.70 (1H, m), 7.01—7.20 (4H, m), 7.25—7.36 (6H, m), 7.39 (1H, d, J = 8.5 Hz).

[0791]

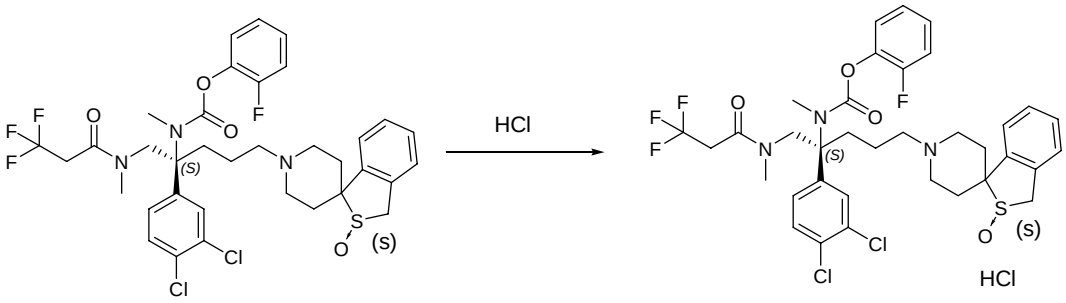
Example 56(c)

Synthesis of 2-fluorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-

yl]pentan-2-yl}methylcarbamate hydrochloride (Compound No. 638)

[0792]

[F188]



[0793]

Similar to Example 51(e), the title compound was obtained as white powder (73 mg, 68.9%) by use of 2-fluorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate (101 mg).

[0794]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.16—1.40 (1H, m), 1.78—1.92 (1H, m), 1.96—2.19 (3H, m), 2.25 (1H, d, J = 14.5 Hz), 2.33—2.47 (1H, m), 2.78—3.19 (8H, m), 3.32 (3H, s), 3.46—3.91 (4H, m), 4.02—4.40 (3H, m), 4.69 (1H, d, J = 17.0 Hz), 7.07—7.45 (9H, m), 7.53—7.67 (2H, m), 10.58 (1H, br).

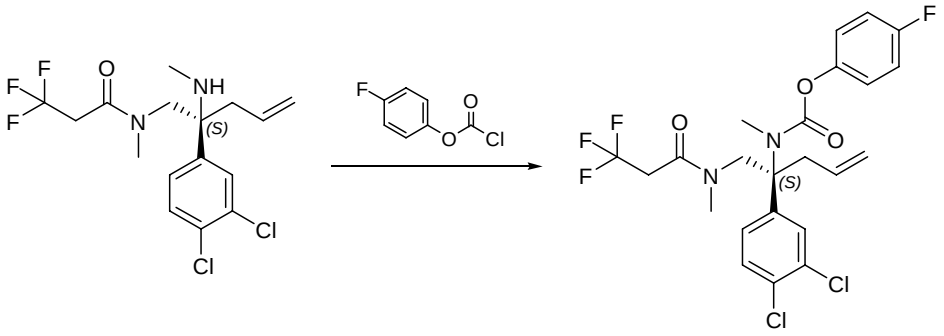
[0795]

Example 57(a)

Synthesis of 4-fluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate

[0796]

[F189]



[0797]

Similar to Example 51(a), the title compound was obtained (271 mg, 99.6%) by use of N-[2-(S)-(3,4-dichlorophenyl)-2-(methylamino)-4-pentene-1'-yl]-3,3,3-trifluoro-N-methylpropanamide (200 mg) synthesized in Example 29(a) and 4-fluorophenyl chloroformate (873 mg).

[0798]

MS (FAB) m/z 521 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 2.74 (1H, dd, J = 6.5, 13.5 Hz), 2.85 (3H, s), 2.93—3.05 (1H, m), 3.09—3.33 (2H, m), 3.16 (3H, s), 3.88—4.08 (1H, m), 4.49—4.70 (1H, m), 5.04 (1H, d, J = 17.0 Hz), 5.09 (1H, d, J = 10.5 Hz), 5.72—5.87 (1H, m), 6.90—7.06 (4H, m), 7.11 (1H, dd, J = 2.5, 8.5 Hz), 7.34 (1H, d, J = 2.5 Hz), 7.42 (1H, d, J = 8.5 Hz).

[0799]

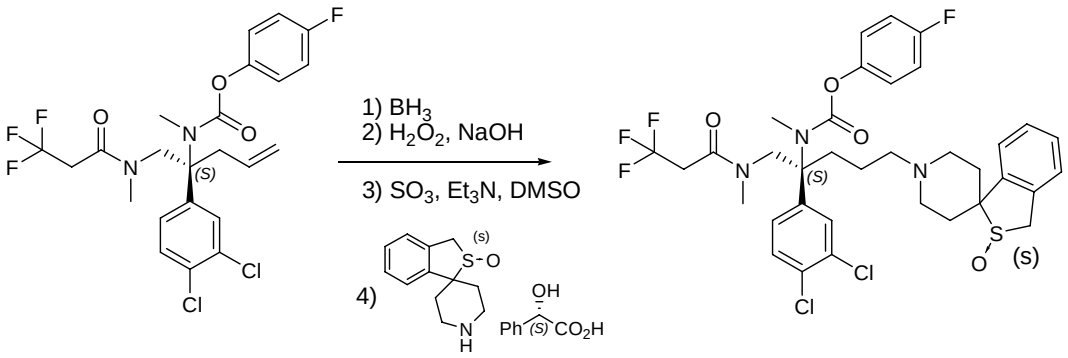
Example 57(b)

Synthesis of 4-fluorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-

yl]pentan-2-yl}methylcarbamate

[0800]

[F190]



[0801]

Similar to Example 51(b), 4-fluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate was obtained (91 mg) by use of 4-fluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate (238 mg). Subsequently, similar to Example 51(c), 4-fluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate was obtained (96 mg) by use of 4-fluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate (85 mg). Thereafter, similar to Example 51(d), the title compound was obtained as white powder (58 mg, 16.6%, 4 steps) by use of 4-fluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate (96 mg).

[0802]

MS (FAB) m/z 742 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 0.98—1.18 (1H, m), 1.52—1.76 (2H, m), 1.83—2.08 (3H, m), 2.26—2.48 (6H, m), 2.82—3.11 (2H, m), 2.99 (3H, s), 3.16—3.47 (2H, m), 3.26 (3H, s), 3.99 (1H, d, J = 16.5 Hz), 4.23—4.56 (3H, m), 6.90—7.03 (3H, m), 7.10 (1H, dd, J = 2.0, 8.5 Hz), 7.25—7.36 (6H, m), 7.40 (1H, d, J = 8.5 Hz).

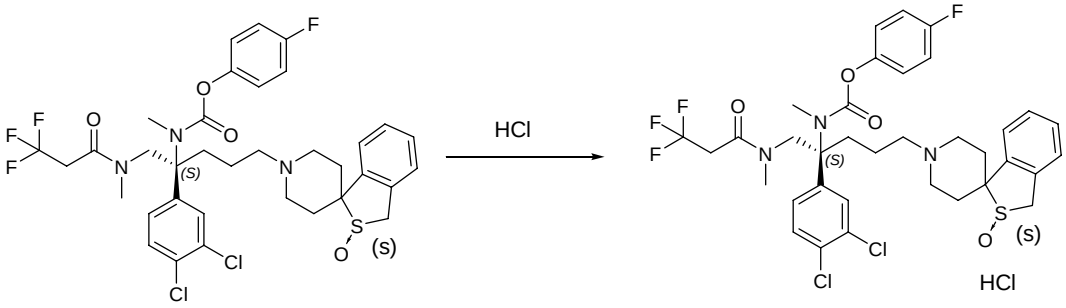
[0803]

Example 57(c)

Synthesis of 4-fluorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate hydrochloride (Compound No. 639)

[0804]

[F191]



[0805]

Similar to Example 51(c), the title compound was obtained as white powder (41 mg, 67.5%) by use of 4-fluorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate (58 mg).

[0806]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.18–1.42 (1H, m), 1.76–1.90 (1H, m), 1.95–2.17 (3H, m), 2.25 (1H, d, J = 14.0 Hz), 2.31–2.46 (1H, m), 2.79–3.18 (8H, m), 3.26 (3H, s), 3.48–3.88 (4H, m), 4.03–4.42 (3H, m), 4.68 (1H, d, J = 17.0 Hz), 6.48–6.69 (1H, m), 7.01–7.22 (3H, m), 7.26 (1H, d, J = 6.5 Hz), 7.29–7.45 (4H, m), 7.53–7.67 (2H, m), 10.59 (1H, br).

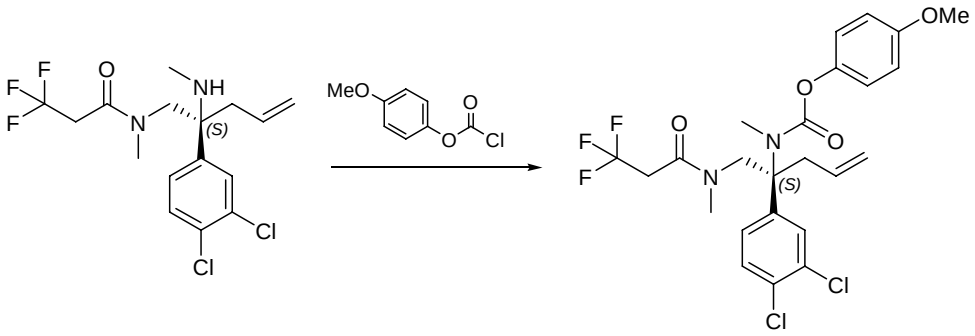
[0807]

Example 58(a)

Synthesis of 4-methoxyphenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate

[0808]

[F192]



[0809]

Similar to Example 51(a), the title compound was obtained (190 mg, 68.2%) by use of N-[2-(S)-(3,4-dichlorophenyl)-2-(methylamino)-4-pentene-1'-yl]-3,3,3-trifluoro-N-methylpropanamide (200 mg) synthesized in Example 4(a) and 4-methoxyphenyl chloroformate (0.31 mL).

[0810]

MS (FAB) m/z 533 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 2.72 (1H, dd, J = 6.5, 13.5 Hz), 2.86 (3H, s), 2.92—3.04 (1H, m), 3.08—3.36 (2H, m), 3.17 (3H, s), 3.75 (3H, s), 3.97—4.18 (1H, m), 4.40—4.64 (1H, m), 5.02 (1H, d, J = 17.0 Hz), 5.07 (1H, d, J = 10.5 Hz), 5.72—5.89 (1H, m), 6.69—6.99 (4H, m), 7.10 (1H, dd, J = 2.0, 8.5 Hz), 7.34 (1H, d, J = 2.0 Hz), 7.41 (1H, d, J = 8.5 Hz).

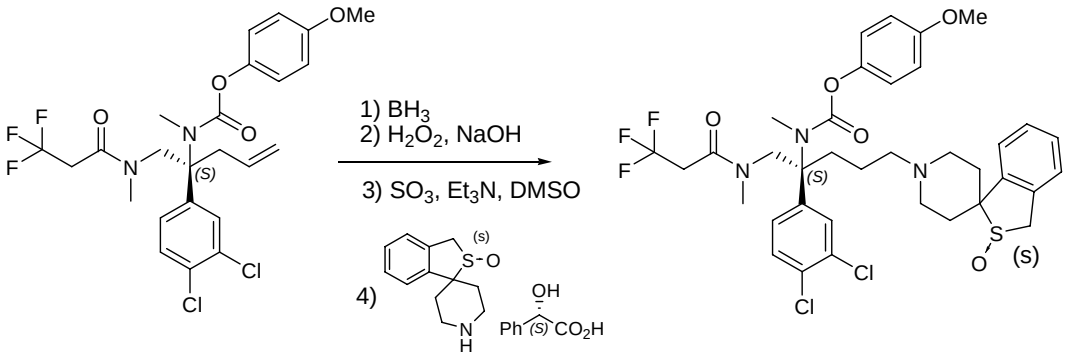
[0811]

Example 58(b)

Synthesis of 4-methoxyphenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate

[0812]

[F193]



[0813]

Similar to Example 51(b), 4-methoxyphenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate was obtained (109 mg) by use of 4-methoxyphenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-

yl]methylcarbamate (190 mg). Subsequently, similar to Example 51(c), 4-methoxyphenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate was obtained (150 mg) by use of 4-methoxyphenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate (106 mg). Thereafter, similar to Example 51(d), the title compound was obtained as white powder (105 mg, 39.8%, 4 steps) by use of 4-methoxyphenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate (150 mg).

[0814]

MS (FAB) m/z 754 $((M+H)^+)$

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 0.96—1.18 (1H, m), 1.53—1.79 (2H, m), 1.83—2.08 (3H, m), 2.24—2.48 (6H, m), 2.82—3.08 (2H, m), 3.01 (3H, s), 3.16—3.46 (2H, m), 3.26 (3H, s), 3.75 (3H, s), 3.99 (1H, d, J = 16.5 Hz), 4.17—4.37 (2H, m), 4.41—4.51 (1H, m), 6.74—6.98 (3H, m), 7.10 (1H, dd, J = 2.0, 8.5 Hz), 7.25—7.37 (6H, m), 7.40 (1H, d, J = 8.5 Hz).

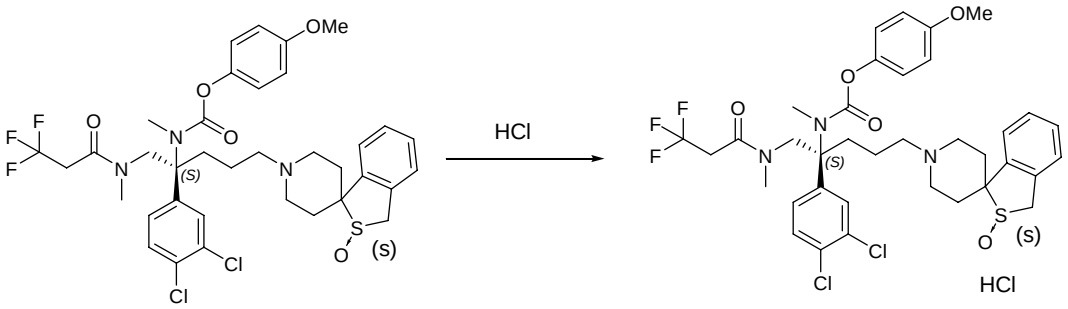
[0815]

Example 58(c)

Synthesis of 4-methoxyphenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate hydrochloride (Compound No. 640)

[0816]

[F194]



[0817]

Similar to Example 51(e), the title compound was obtained as white powder (62 mg, 56.4%) by use of 4-methoxyphenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate (105 mg).

[0818]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.15—1.47 (1H, m), 1.77—1.92 (1H, m), 1.94—2.20 (3H, m), 2.25 (1H, d, J = 13.0 Hz), 2.39—2.48 (1H, m), 2.78—3.16 (8H, m), 3.26 (3H, s), 3.45—3.55 (1H, m), 3.61—3.89 (3H, m), 3.70 (3H, s), 4.04—4.38 (3H, m), 4.68 (1H, d, J = 17.0 Hz), 6.32—6.60 (1H, m), 6.74—7.08 (3H, m), 7.28—7.46 (5H, m), 7.51—7.68 (2H, m), 10.88 (1H, br).

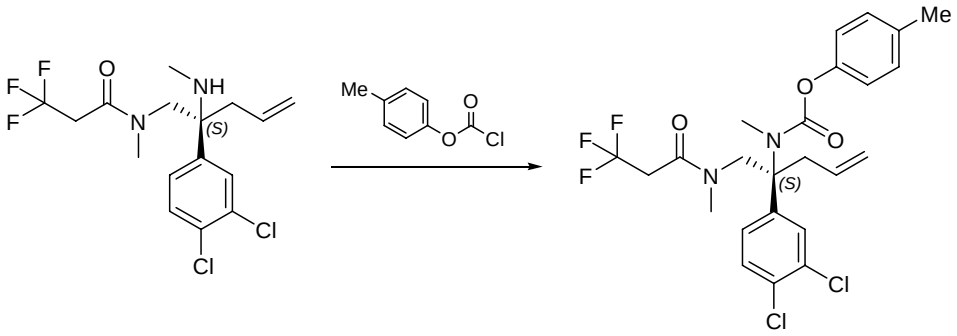
[0819]

Example 59(a)

Synthesis of 4-tolyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate

[0820]

[F195]



[0821]

Similar to Example 51(a), the title compound was obtained (260 mg, 96.3%) by use of N-[2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-pentene-1'-yl]-3,3,3-trifluoro-N-methylpropanamide (200 mg) synthesized in Example 4(a) and 4-tolyl chloroformate (174 mg).

[0822]

MS (FAB) m/z 517 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 2.29 (3H, s), 2.72 (1H, dd, J = 6.5, 13.5 Hz), 2.87 (3H, s), 2.91—3.04 (1H, m), 3.08—3.36 (2H, m), 3.17 (3H, s), 3.98—4.22 (1H, m), 4.38—4.62 (1H, m), 4.97—5.10 (2H, m), 5.73—5.88 (1H, m), 6.76—6.98 (2H, m), 7.04—7.16 (3H, m), 7.34 (1H, d, J = 2.0 Hz), 7.40 (1H, d, J = 8.5 Hz).

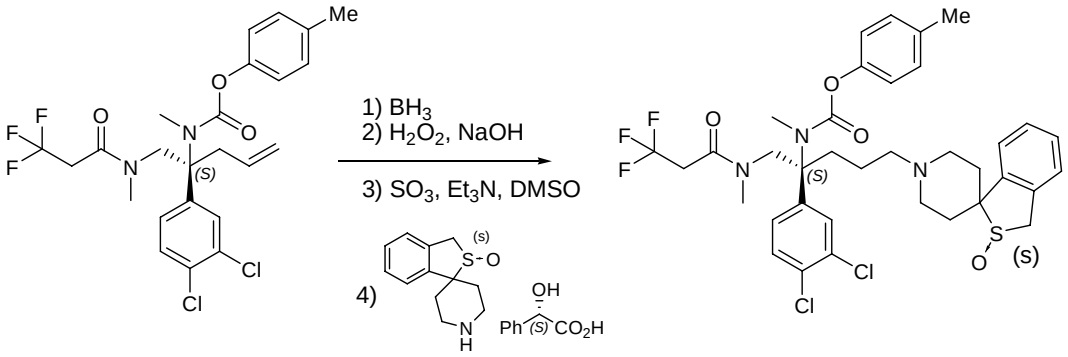
[0823]

Example 59(b)

Synthesis of 4-tolyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate

[0824]

[F196]



[0825]

Similar to Example 51(b), 4-tolyl {[1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy]pentan-2-yl}methylcarbamate was obtained (160 mg) by use of 4-tolyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate (250 mg). Subsequently, similar to Example 51(c), 4-tolyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate was obtained (185 mg) by use of (4-tolyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate (154 mg). Thereafter, similar to Example 51(d), the title compound was obtained as white powder (131 mg, 36.9%, 4 steps) by use of 4-tolyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate (185 mg).

[0826]

MS (FAB) m/z 738 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 0.95—1.13 (1H, m), 1.54—1.76 (2H, m), 1.82—2.06 (3H, m), 2.22—2.48 (6H, m), 2.28 (3H, s),

2.80—2.97 (2H, m), 3.01 (3H, s), 3.15—3.45 (2H, m), 3.27 (3H, s), 3.99 (1H, d, J = 16.5 Hz), 4.16—4.37 (2H, m), 4.42—4.61 (1H, br), 6.73—6.93 (1H, m), 7.03—7.14 (3H, m), 7.25—7.36 (6H, m), 7.39 (1H, d, J = 8.5 Hz).

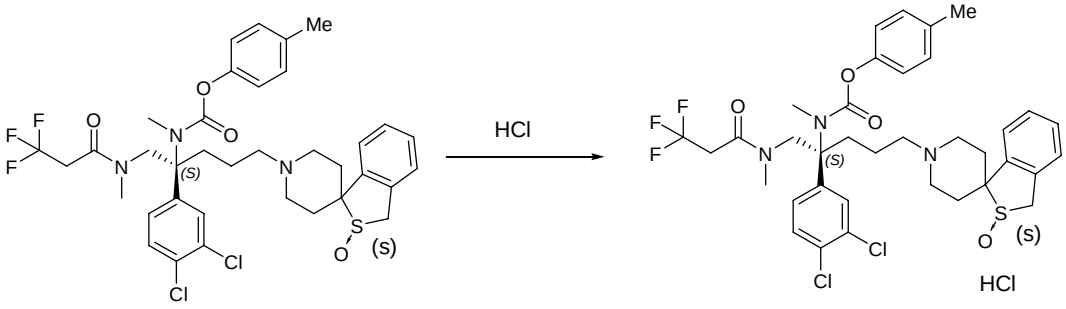
[0827]

Example 59(c)

Synthesis of 4-tolyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate hydrochloride (Compound No. 652)

[0828]

[F197]



[0829]

Similar to Example 51(e), the title compound was obtained as white powder (77 mg, 56.1%) by use of 4-tolyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate (131 mg).

[0830]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.16—1.42 (1H, m), 1.76—2.30

(5H, m), 2.24 (3H, s), 2.35–2.48 (1H, m), 2.77–3.18 (8H, m), 3.26 (3H, s), 3.46–3.89 (4H, m), 4.08 (1H, d, J = 17.0 Hz), 4.14–4.36 (2H, m), 4.68 (1H, d, J = 17.0 Hz), 6.31–6.55 (1H, m), 6.83–6.99 (1H, m), 7.02–7.19 (2H, m), 7.30–7.45 (5H, m), 7.53–7.67 (2H, m), 10.69 (1H, br).

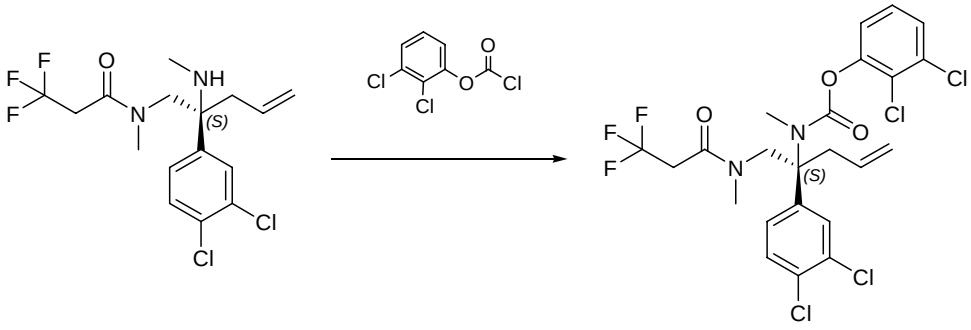
[0831]

Example 60(a)

Synthesis of 2,3-dichlorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate

[0832]

[F198]



[0833]

Similar to Example 51(a), the title compound was obtained (300 mg, 100%) by use of N-[2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-pentene-1'-yl]-3,3,3-trifluoro-N-methylpropanamide (200 mg) synthesized in Example 29(a) and 2,3-dichlorophenyl chloroformate (588 mg).

[0834]

MS (FAB) m/z 571 $((M+H)^+)$

^{1}H-NMR (400MHz, $CDCl_3$)

δ ppm : 2.73 (1H, dd, J = 6.5, 14.0 Hz), 2.88 (3H, s), 2.90 (1H, dd, J = 7.5, 14.0 Hz), 3.15–3.46 (2H, m), 3.23 (3H, s), 4.03–4.17 (1H, m), 4.50 (1H, d, J = 13.5 Hz), 4.99–5.12 (2H, m), 5.74–5.89 (1H, m), 6.97–7.07 (1H, m), 7.11 (1H, dd, J = 2.0, 8.5 Hz), 7.14–7.22 (1H, m), 7.31 (1H, d, J = 8.0 Hz), 7.36 (1H, d, J = 2.0 Hz), 7.41 (1H, d, J = 8.5 Hz).

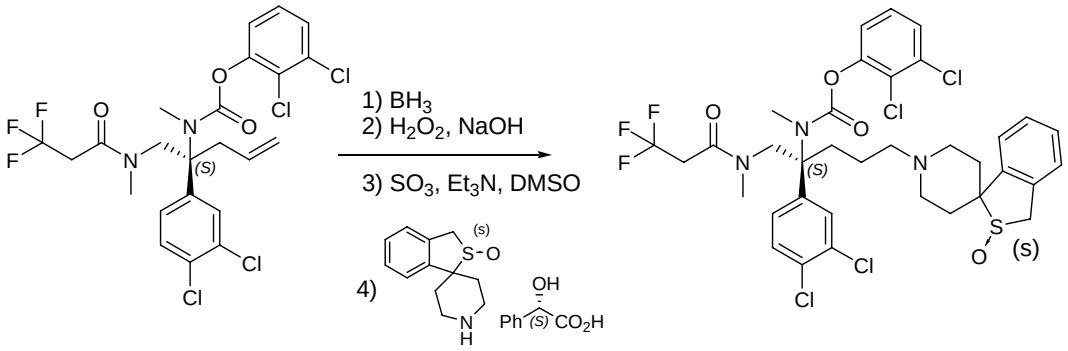
[0835]

Example 60(b)

Synthesis of 2,3-dichlorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate

[0836]

[F199]



[0837]

Similar to Example 51(b), 2,3-dichlorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate was obtained (130 mg) by use of 2,3-dichlorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate (290 mg). Subsequently, similar to

Example 51(c), 2,3-dichlorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate was obtained (126 mg) by use of 2,3-dichlorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate (123 mg). Thereafter, similar to Example 51(d), the title compound was obtained as white powder (124 mg, 32.6%, 4 steps) by use of 2,3-dichlorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate (126 mg).

[0838]

MS (FAB) m/z 792 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.01—1.20 (1H, m), 1.53—1.75 (2H, m), 1.82—2.07 (3H, m), 2.25—2.48 (6H, m), 2.82—3.07 (2H, m), 3.00 (3H, s), 3.16—3.43 (2H, m), 3.32 (3H, s), 3.99 (1H, d, J = 16.5 Hz), 4.18—4.58 (3H, m), 6.92—7.04 (1H, m), 7.08—7.21 (2H, m), 7.25—7.43 (7H, m).

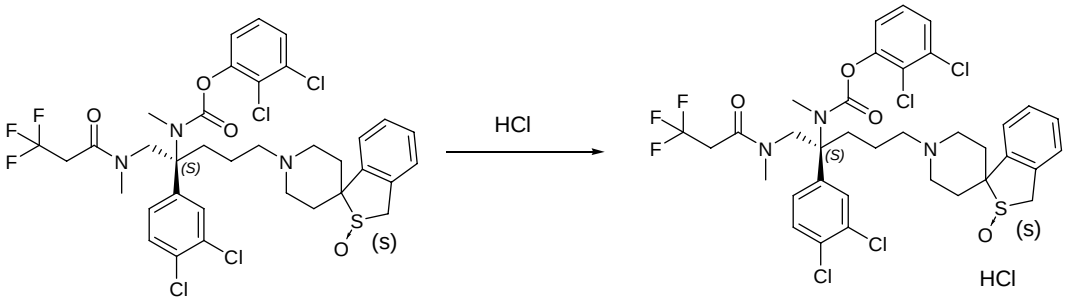
[0839]

Example 60(c)

Synthesis of 2,3-dichlorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate hydrochloride (Compound No. 653)

[0840]

[F200]



[0841]

Similar to Example 51(e), the title compound was obtained as white powder (89 mg, 56.1%) by use of 2,3-dichlorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate (124 mg).

[0842]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.25—1.48 (1H, m), 1.78—2.32 (5H, m), 2.40—2.49 (1H, m), 2.76—3.17 (8H, m), 3.24—3.55 (4H, m), 3.62—3.88 (3H, m), 4.04—4.40 (3H, m), 4.69 (1H, d, J = 17.0 Hz), 7.24—7.45 (7H, m), 7.47—7.66 (3H, m), 10.84 (1H, br).

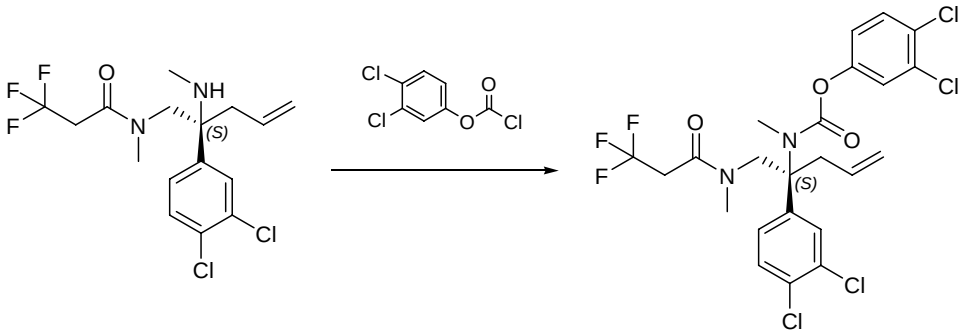
[0843]

Example 61(a)

Synthesis of 3,4-dichlorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate

[0844]

[F201]



[0845]

Similar to Example 51(a), the title compound was obtained (271 mg, 90.7%) by use of N-[2-(S)-(3,4-dichlorophenyl)-2-(methylamino)-4-pentene-1'-yl]-3,3,3-trifluoro-N-methylpropanamide (200 mg) synthesized in Example 29(a) and 3,4-dichlorophenyl chloroformate (588 mg).

[0846]

MS (FAB) m/z 571 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 2.70—2.81 (1H, m), 2.84 (3H, s), 2.92—3.33 (3H, m), 3.12 (3H, s), 3.77—3.96 (1H, m), 4.60—4.79 (1H, m), 5.06 (1H, d, J = 17.0 Hz), 5.10 (1H, d, J = 10.5 Hz), 5.69—5.88 (1H, m), 6.85—7.00 (1H, m), 7.10 (1H, dd, J = 2.5, 8.5 Hz), 7.14—7.25 (1H, m), 7.32—7.46 (3H, m).

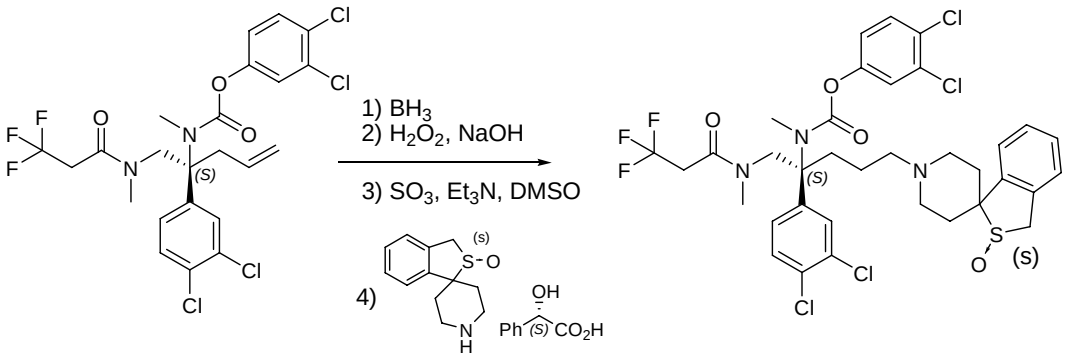
[0847]

Example 61(b)

Synthesis of 3,4-dichlorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate

[0848]

[F202]



[0849]

Similar to Example 51(b), 3,4-dichlorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate was obtained (102 mg) by use of 3,4-dichlorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate (260 mg). Subsequently, similar to Example 51(c), 3,4-dichlorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate was obtained (99 mg) by use of 3,4-dichlorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate (96 mg). Thereafter, similar to Example 51(d), the title compound was obtained as white powder (99 mg, 29.2%, 4 steps) by use of 3,4-dichlorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate (99 mg).

[0850]

MS (FAB) m/z 792 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.02—1.19 (1H, m), 1.52—1.75 (2H, m), 1.83—2.10 (3H, m), 2.27—2.48 (6H, m), 2.79—3.07 (2H,

m), 2.98 (3H, s), 3.14—3.42 (2H, m), 3.23 (3H, s), 3.99 (1H, d, J = 16.5 Hz), 4.22—4.48 (3H, m), 6.82—6.96 (1H, m), 7.06—7.20 (2H, m), 7.24—7.45 (7H, m).

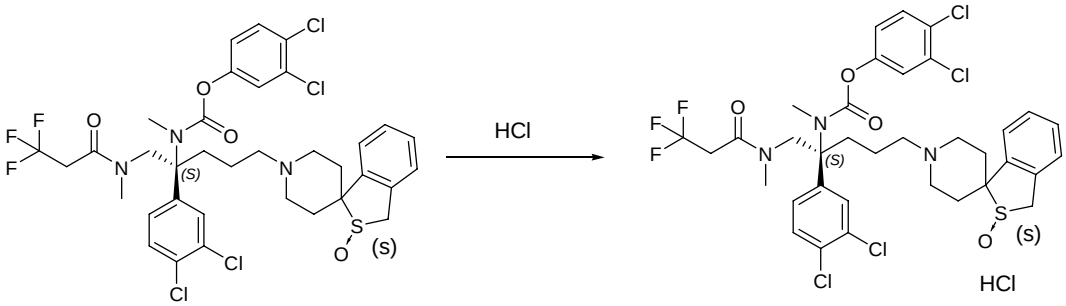
[0851]

Example 61(c)

Synthesis of 3,4-dichlorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate hydrochloride (Compound No. 654)

[0852]

[F203]



[0853]

Similar to Example 51(c), the title compound was obtained as white powder (62 mg, 59.9%) by use of 3,4-dichlorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate (99 mg).

[0854]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.27—1.47 (1H, m), 1.75—1.90 (1H, m), 1.95—2.20 (3H, m), 2.26 (1H, d, J = 13.5 Hz),

2.39—2.50 (1H, m), 2.80—3.18 (8H, m), 3.24 (3H, s), 3.46—3.55 (1H, m), 3.60—3.88 (3H, m), 3.97—4.14 (2H, m), 4.40—4.57 (1H, m), 4.68 (1H, d, J = 17.0 Hz), 7.07—7.21 (1H, m), 7.30—7.69 (9H, m), 10.97 (1H, br).

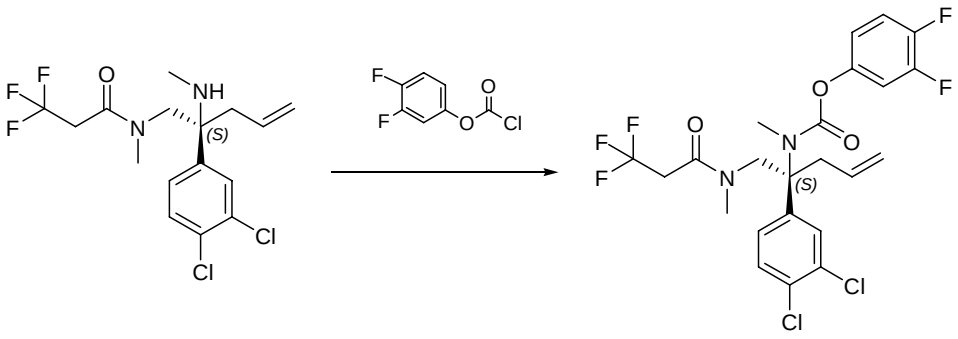
[0855]

Example 62(a)

Synthesis of 3,4-difluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate

[0856]

[F204]



[0857]

Similar to Example 51(a), the title compound was obtained (267 mg, 94.9%) by use of N-[2-(S)-(3,4-dichlorophenyl)-2-(methylamino)-4-pentene-1'-yl]-3,3,3-trifluoro-N-methylpropanamide (200 mg) synthesized in Example 4(a) and 3,4-difluorophenyl chloroformate (502 mg).

[0858]

MS (FAB) m/z 539 $((M+H)^+)$

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 2.68—2.81 (1H, m), 2.85 (3H, s), 2.91—3.34 (3H, m), 3.13 (3H, s), 3.76—3.96 (1H, m), 4.60—4.80

(1H, m), 5.06 (1H, d, J = 17.0 Hz), 5.10 (1H, d, J = 10.5 Hz), 5.70—5.86 (1H, m), 6.70—6.99 (2H, m), 7.03—7.15 (2H, m), 7.34 (1H, d, J = 2.0 Hz), 7.42 (1H, d, J = 8.5 Hz).

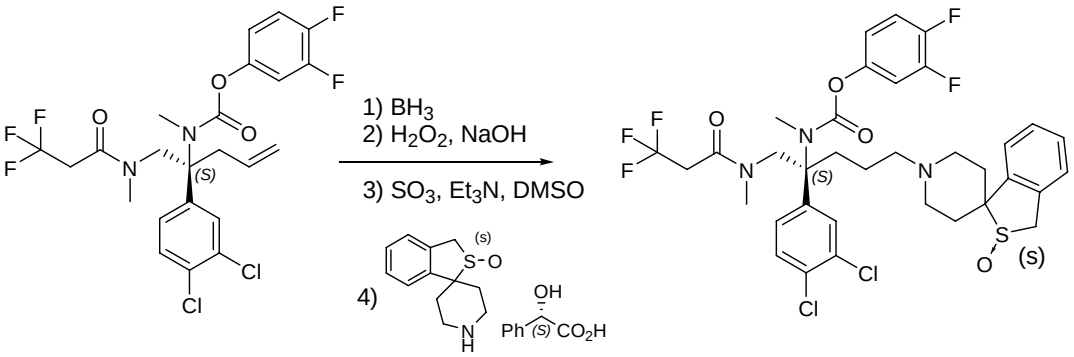
[0859]

Example 62(b)

Synthesis of 3,4-difluorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]-pentan-2-yl}methylcarbamate

[0860]

[F205]



[0861]

Similar to Example 51(b), 3,4-difluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate was obtained (119 mg) by use of 3,4-difluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate (255 mg). Subsequently, similar to Example 51(c), 3,4-difluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate was obtained (113 mg) by use of 3,4-

difluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate (110 mg). Thereafter, similar to Example 51(d), the title compound was obtained as white powder (128 mg, 38.5%, 4 steps) by use of 3,4-difluorophenyl [1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate (113 mg).

[0862]

MS (FAB) m/z 760 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.02—1.17 (1H, m), 1.52—1.69 (2H, m), 1.84—2.10 (3H, m), 2.27—2.47 (6H, m), 2.82—3.05 (2H, m), 2.98 (3H, s), 3.15—3.43 (2H, m), 3.24 (3H, s), 3.99 (1H, d, J = 16.5 Hz), 4.23—4.46 (3H, m), 6.70—6.96 (2H, m), 7.03—7.14 (2H, m), 7.25—7.36 (5H, m), 7.41 (1H, d, J = 8.5 Hz).

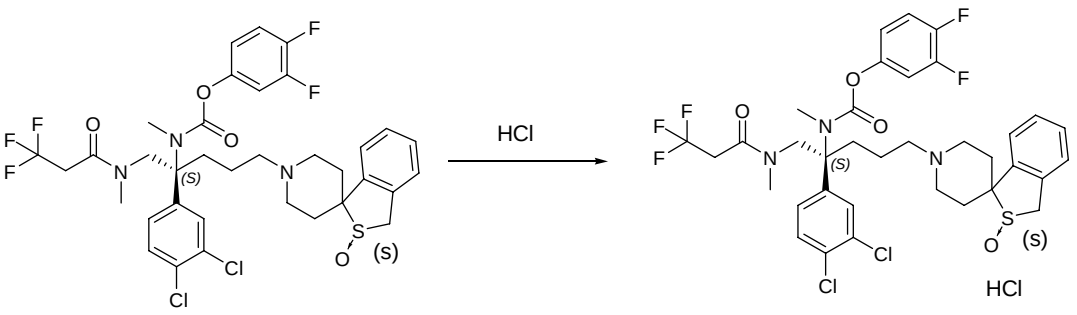
[0863]

Example 62(c)

Synthesis of 3,4-difluorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate hydrochloride (655)

[0864]

[F206]



[0865]

Similar to Example 51(e), the title compound was obtained as white powder (78 mg, 58.2%) by use of 3,4-difluorophenyl {1-(3,3,3-trifluoro-N-methylpropanamido)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate (128 mg).

[0866]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.23—1.47 (1H, m), 1.77—1.90 (1H, m), 1.95—2.21 (3H, m), 2.26 (1H, d, J = 13.5 Hz), 2.39—2.50 (1H, m), 2.81—3.17 (8H, m), 3.24 (3H, s), 3.45—3.86 (4H, m), 4.00—4.14 (2H, m), 4.36—4.55 (1H, m), 4.69 (1H, d, J = 17.0 Hz), 6.90—7.02 (1H, m), 7.27—7.47 (7H, m), 7.52—7.69 (2H, m), 10.93 (1H, br).

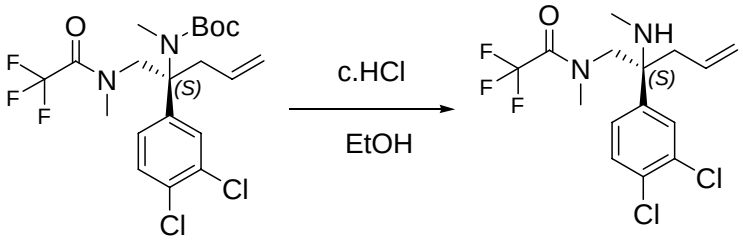
[0867]

Example 63(a)

Synthesis of N-[2-(S)-(3,4-dichlorophenyl)-2-(methylamino)-4-pentenyl]-2,2,2-trifluoro-N-methylacetamide

[0868]

[F207]



[0869]

Similar to Example 29(a), the title compound was obtained (3.59 g, 90.9%) by use of tert-butyl [1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate (5.0 g) synthesized in Example 27 (a).

[0870]

MS (FAB) m/z 369 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 2.22 (3H, s), 2.62—2.74 (2H, m), 2.72 (3H, s), 3.51 (1H, d, J = 14.0 Hz), 3.74 (1H, d, J = 14.0 Hz), 5.19—5.28 (2H, m), 5.73—5.86 (1H, m), 7.34 (1H, dd, J = 2.0, 8.5 Hz), 7.43 (1H, d, J = 8.5 Hz), 7.63 (1H, d, J = 2.0 Hz).

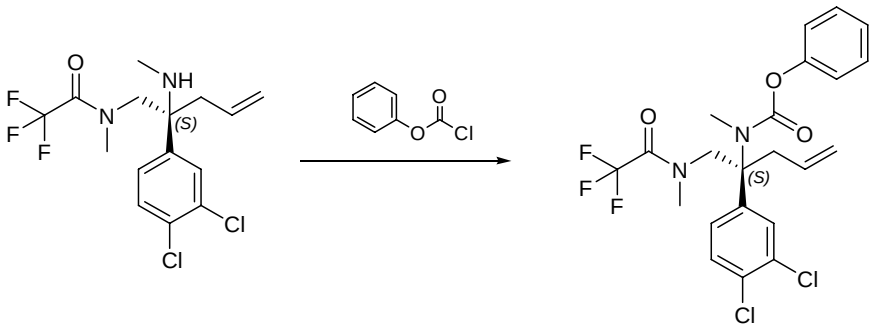
[0871]

Example 63(b)

Synthesis of phenyl [1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate

[0872]

[F208]



[0873]

Similar to Example 51(a), the title compound was obtained (303 mg, >100%) by use of N-[2-(S)-(3,4-dichlorophenyl)-2-(methylamino)-4-pentene-1'-yl]-2,2,2-trifluoro-N-methylacetamide (200 mg) and phenyl chloroformate (0.29 mL).

[0874]

MS (FAB) m/z 537 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 2.75 (1H, dd, J = 6.5, 14.0 Hz), 2.94 (1H, dd, J = 7.5, 14.0 Hz), 3.02 (3H, s), 3.20 (3H, s), 4.13—4.28 (1H, m), 4.46—4.67 (1H, m), 5.02—5.16 (2H, m), 5.67—5.80 (1H, m), 6.93—7.08 (2H, m), 7.10 (1H, dd, J = 2.5, 8.5 Hz), 7.14—7.20 (1H, m), 7.27—7.37 (3H, m), 7.42 (1H, d, J = 8.5 Hz).

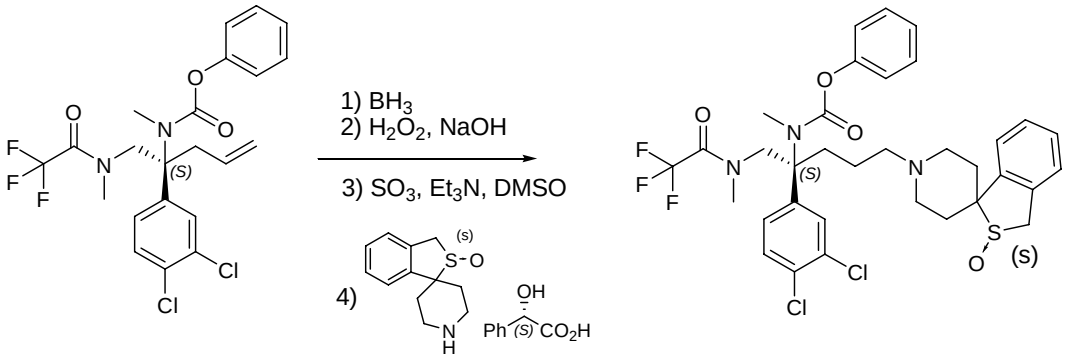
[0875]

Example 63(c)

Synthesis of phenyl {1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate

[0876]

[F209]



[0877]

Similar to Example 51(b), phenyl [1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate was obtained (180 mg) by use of phenyl [1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl] methylcarbamate (296 mg). Subsequently, similar to Example 51(c), phenyl [1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate was obtained (167 mg) by use of phenyl [1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate (174 mg). Thereafter, similar to Example 51(d), the title compound was obtained as white powder (136 mg, 36.3%, 4 steps) by use of phenyl [1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate (167 mg).

[0878]

MS (FAB) m/z 710 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 0.97—1.14 (1H, m), 1.53—1.76 (2H, m), 1.87—2.02 (3H, m), 2.25—2.48 (6H, m), 2.80—2.98 (2H, m), 3.14 (3H, s), 3.30 (3H, s), 4.00 (1H, d, J = 16.5 Hz),

4.25—4.42 (2H, m), 4.47—4.61 (1H, m), 6.86—7.03 (1H, m), 7.10 (1H, dd, J = 2.0, 8.5 Hz), 7.18 (1H, t, J = 7.5 Hz), 7.25—7.37 (8H, m), 7.41 (1H, d, J = 8.5 Hz).

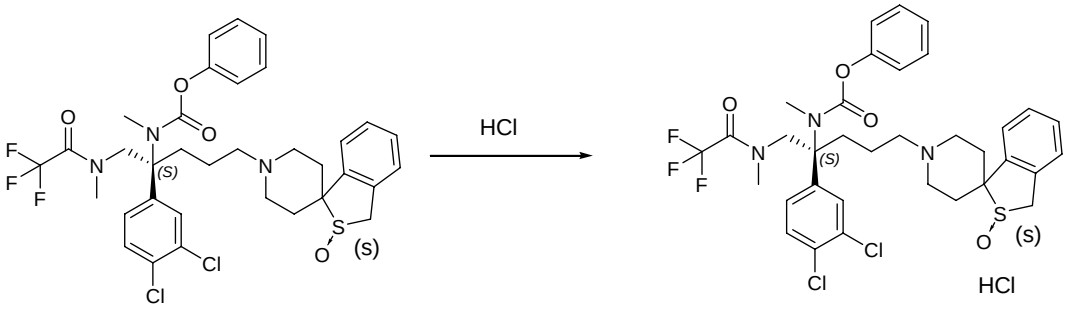
[0879]

Example 63(d)

Synthesis of phenyl {1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate hydrochloride (Compound No. 642)

[0880]

[F210]



[0881]

Similar to Example 51(e), the title compound was obtained as white powder (80 mg, 56.2%) by use of phenyl{1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate (136 mg).

[0882]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.22—1.48 (1H, m), 1.70—1.90 (1H, m), 1.95—2.22 (3H, m), 2.26 (1H, d, J = 14.5 Hz), 2.34—2.47 (1H, m), 2.83—3.20 (8H, m), 3.24 (3H, s), 3.47—3.68

(2H, m), 4.08 (1H, d, J = 17.0 Hz), 4.22—4.57 (2H, m), 4.68 (1H, d, J = 17.0 Hz), 6.44—6.74 (1H, m), 6.95—7.23 (2H, m), 7.26—7.47 (7H, m), 7.56—7.72 (2H, m), 10.77 (1H, br).

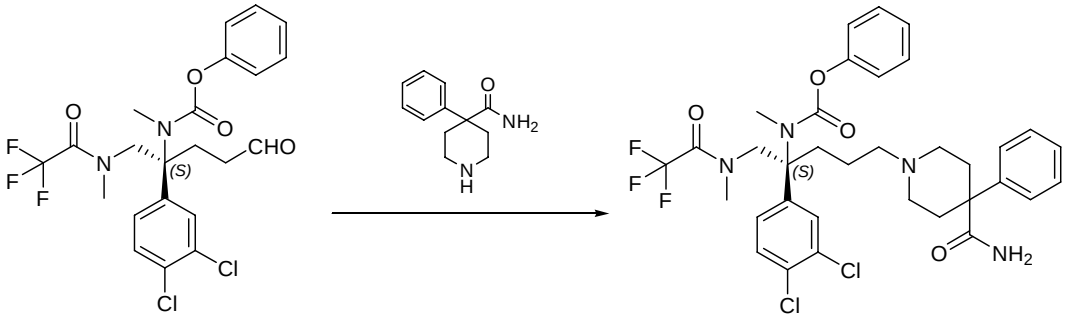
[0883]

Example 64(a)

Synthesis of phenyl [1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-5-(4-carbamoyl-4-phenylpiperidine-1'-yl)pentan-2-yl]methylcarbamate

[0884]

[F211]



[0885]

Subsequently, similar to Example 26(h), the title compound was obtained as white powder (70 mg, 67.8%) by use of phenyl [1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate (120 mg) synthesized in Example 63(c) and 4-phenylpiperidine-4-carboxamide (62 mg).

[0886]

MS (FAB) m/z 693 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 0.95—1.10 (1H, m), 1.50—1.65 (1H, m), 1.85—2.10 (4H, m), 2.25—2.58 (8H, m), 3.12 (3H, s),

3.25 (3H, s), 4.22—4.58 (2H, m), 5.25 (2H, br), 6.91—7.43 (13H, m).

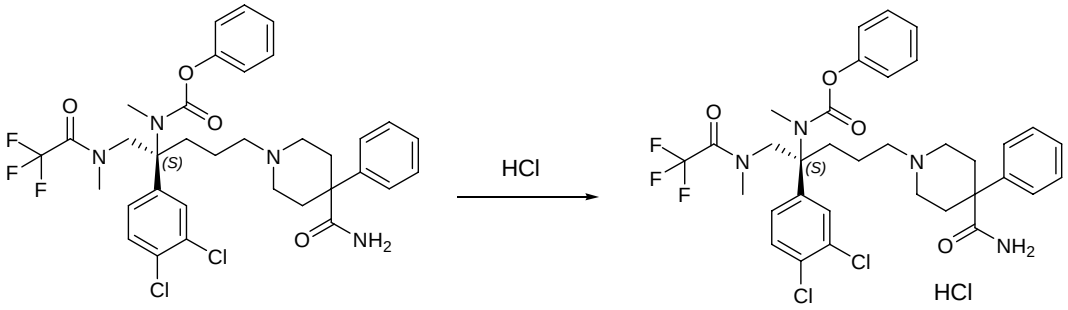
[0887]

Example 64(b)

Synthesis of phenyl [1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-5-(4-carbamoyl-4-phenylpiperidine-1'-yl)pentan-2-yl]methylcarbamate hydrochloride (Compound No. 578)

[0888]

[F212]



[0889]

Similar to Example 26(k), the title compound was obtained as white powder (80 mg, 56.2%) by use of phenyl [1-(2,2,2-trifluoro-N-methylacetamide)-2-(S)-(3,4-dichlorophenyl)-5-(4-carbamoyl-4-phenylpiperidine-1'-yl)pentan-2-yl]methylcarbamate (136 mg).

[0890]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.25—1.37 (1H, m), 1.60—1.82 (1H, m), 1.95—2.13 (3H, m), 2.58—3.13 (9H, m), 3.21 (3H, s), 3.36 (3H, s), 3.45—3.58 (1H, m), 4.05—4.57 (3H, m), 6.90—7.50 (11H, m), 7.58—7.70 (2H, m), 9.95 (1H, br).

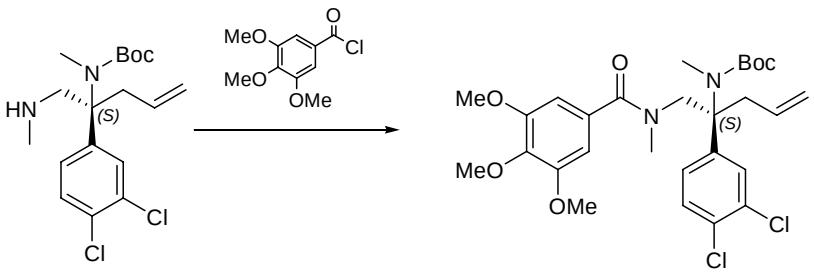
[0891]

Example 65(a)

Synthesis of tert-butyl [1-(3,4,5-trimethoxy-N-methylbenzamide)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate

[0892]

[F213]



[0893]

tert-Butyl [1-methylamino-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate (500 mg) synthesized in Example 26(d) was dissolved in ethyl acetate (5 mL). Under cooling with ice, sodium hydrogencarbonate (225 mg) and water (2.5 mL) were added thereto, and thereafter 3,4,5-trimethoxybenzoyl chloride (309 mg) was added to the mixture, followed by stirring for 30 minutes at the same temperature. Saturated aqueous sodium bicarbonate was added to the reaction mixture, and the resultant mixture was extracted with ethyl acetate, washed with saturated brine, and dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, and the residue was purified through silica gel column chromatography (n-hexane : ethyl acetate=7:1 to 4:1 to 2:1 to 1:1), to thereby give the title compound (715 mg, 93.8%).

[0894]

MS (FAB) m/z 567 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.22 (9H, s), 2.65—2.80 (4H, m), 2.95—3.05 (1H, m), 3.17 (3H, s), 3.86 (3H, s), 3.88 (6H, s), 4.20—4.48 (2H, m), 4.97—5.10 (2H, m), 5.80—5.94 (1H, m), 6.60 (2H, s), 7.10—7.18 (1H, m), 7.34—7.44 (2H, m).

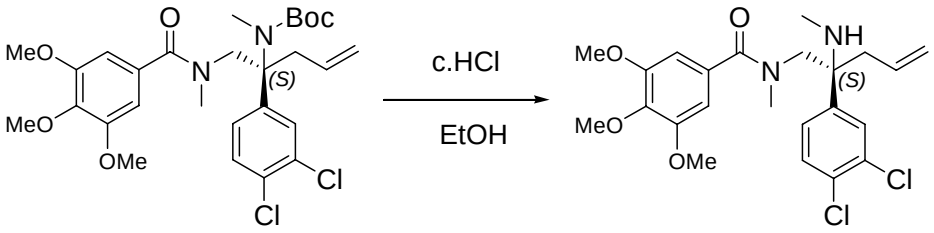
[0895]

Example 65(b)

Synthesis of N-[2-(S)-(3,4-dichlorophenyl)-2-(methylamino)-4-pentene-1'-yl]-3,4,5-trimethoxy-N-methylbenzamide

[0896]

[F214]



[0897]

Similar to Example 29(a), the title compound was obtained (171 mg, 89.5%) by use of tert-butyl [1-(3,4,5-trimethoxy-N-methylbenzamide)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate (232 mg).

[0898]

MS (FAB) m/z 467 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.71 (1H, br), 2.28 (3H, s), 2.60 (3H, s), 2.68—2.82 (2H, m), 3.68 (1H, d, J = 14.5 Hz), 3.83 (3H, s), 3.84 (6H, s), 3.80—3.90 (1H, m), 5.18—5.28 (2H, m), 5.77—5.90 (1H, m), 6.37 (2H, s), 7.40—7.48 (2H, m),

7.75–7.82 (1H, m).

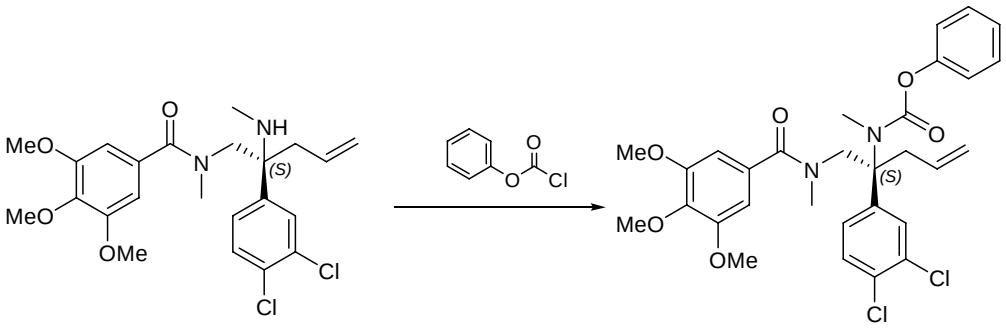
[0899]

Example 65(c)

Synthesis of phenyl [1-(3,4,5-trimethoxy-N-methylbenzamide)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate

[0900]

[F215]



[0901]

Similar to Example 51(a), the title compound was obtained (170 mg, 78.2%) by use of N-[2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-pentene-1'-yl]-3,4,5-trimethoxy-N-methylbenzamide (171 mg) and phenyl chloroformate (174 mg).

[0902]

MS (FAB) m/z 587 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 2.80–2.98 (4H, m), 3.14 (3H, s), 3.28–3.40 (1H, m), 3.77 (6H, s), 3.86 (3H, s), 3.95–4.09 (1H, m), 4.68–4.82 (1H, m), 5.05–5.17 (2H, m), 5.70–5.88 (1H, m), 6.61 (2H, s), 6.87–7.03 (1H, m), 7.13–7.18 (1H, m), 7.22–7.33 (4H, m), 7.43–7.52 (2H, m).

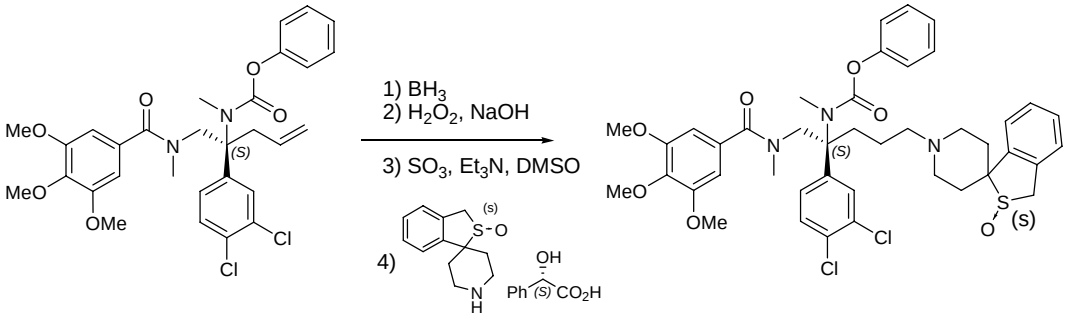
[0903]

Example 65(d)

Synthesis of phenyl {1-(3,4,5-trimethoxy-N-methylbenzamide)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate

[0904]

[F216]



[0905]

Similar to Example 51(b), phenyl [1-(3,4,5-trimethoxy-N-methylbenzamide)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate was obtained (77 mg) by use of phenyl [1-(3,4,5-trimethoxy-N-methylbenzamide)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate (170 mg). Subsequently, similar to Example 51(c), phenyl [1-(3,4,5-trimethoxy-N-methylbenzamide)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate was obtained (87 mg) by use of phenyl [1-(3,4,5-trimethoxy-N-methylbenzamide)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate (77 mg). Thereafter, similar to Example 51(d), the title compound was obtained as white powder (70 mg, 29.8%, 4 steps) by use of phenyl [1-(3,4,5-trimethoxy-N-methylbenzamide)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate (87 mg).

[0906]

MS (FAB) m/z 808 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.27–1.30 (1H, m), 1.51–1.60 (1H, m), 1.65–1.82 (1H, m), 1.87–2.12 (2H, m), 2.25–2.47 (7H, m), 2.80–3.00 (5H, m), 3.26 (3H, s), 3.81 (6H, s), 3.86 (3H, s), 3.98 (1H, d, J = 16.5 Hz), 4.07–4.17 (1H, m), 4.30 (1H, d, J = 16.5 Hz), 4.36–4.58 (1H, m), 6.64 (2H, s), 6.85–7.05 (2H, m), 7.13–7.19 (1H, m), 7.21–7.35 (7H, m), 7.43–7.48 (2H, m).

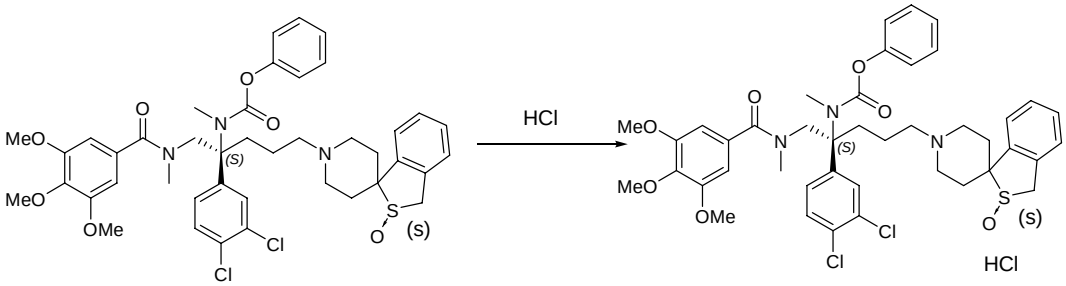
[0907]

Example 65(e)

Synthesis of phenyl{1-(3,4,5-trimethoxy-N-methylbenzamide)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate hydrochloride (Compound No. 589)

[0908]

[F217]



[0909]

Similar to Example 26(k), the title compound was obtained as white powder (50 mg, 68.4%) by use of phenyl {1-(3,4,5-trimethoxy-N-methylbenzamide)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl-]pentan-2-yl}methylcarbamate (70

mg).

[0910]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.80—2.00 (2H, m), 2.13—2.27 (2H, m), 2.32—2.48 (2H, m), 2.58—2.97 (3H, m), 3.01—3.20 (4H, m), 3.28—3.42 (6H, m), 3.54—3.72 (4H, m), 3.81 (6H, s), 4.06 (1H, d, J = 17.0 Hz), 4.12—4.60 (2H, m), 4.65 (1H, d, J = 17.0 Hz), 6.73 (2H, s), 6.90—7.85 (12H, m), 10.58 (1H, br).

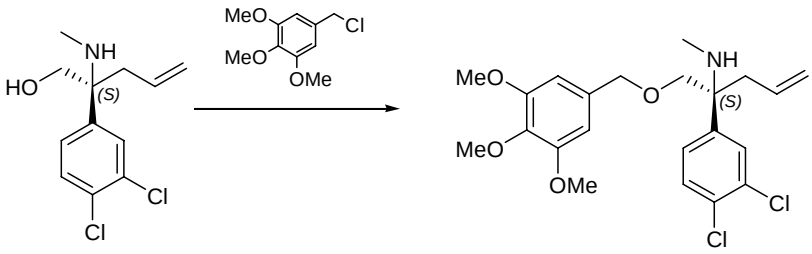
[0911]

Example 66(a)

Synthesis of 1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-2-(N-methylamino)-4-pentene

[0912]

[F218]



[0913]

Under argon, a solution of 2-(S)-(3,4-dichlorophenyl)-2-methylamino-4-penten-1-ol (8.5 g) in anhydrous N,N-dimethylformamide (50 mL) was added to a suspension of sodium hydride (1.5 g) in anhydrous N,N-dimethylformamide (50 mL) under cooling with ice, and the mixture was stirred for 1 hour at room temperature. A solution of 3,4,5-trimethoxybenzyl chloride (7.8 g) in anhydrous N,N-dimethylformamide (30 mL) was added to the reaction mixture

under cooling with ice, and the resultant mixture was stirred overnight at room temperature. The reaction mixture was poured into ice-water, extracted with ether, sequentially washed with water and saturated brine, and dried over sodium sulfate anhydrate. The solvent was concentrated under reduced pressure, and the residue was purified through silica gel column chromatography (n-hexane : ethyl acetate=5:1 to 2:1 → ethyl acetate), to thereby give the title compound (11.8 g, 81.8%).

[0914]

MS (FAB) m/z 440 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.58 (1H, br), 2.17 (3H, s), 2.45–2.62 (2H, m), 3.59 (1H, d, J = 17.0 Hz), 3.61 (1H, d, J = 17.0. Hz), 3.83 (6H, s), 3.84 (3H, s), 4.43 (1H, d, J = 18.0 Hz), 4.46 (1H, d, J = 18.0 Hz), 5.01–5.09 (2H, m), 5.53–5.66 (1H, m), 6.47 (2H, s), 7.26 (1H, dd, J = 2.0, 8.5 Hz), 7.39 (1H, d, J = 8.5 Hz), 7.53 (1H, d, J = 2.0 Hz).

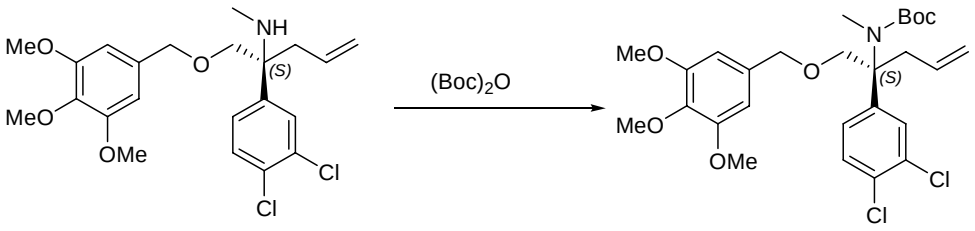
[0915]

Example 66(b)

Synthesis of tert-butyl [1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate

[0916]

[F219]



[0917]

Similar to Example 26(a), the title compound was obtained (9.98 g, 69.2%) by use of 1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-2-(N-methylamino)-4-pentene (11.8 g).

[0918]

MS (FAB) m/z 540 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.18 (9H, brs), 2.78 (1H, dd, J = 7.0, 13.0 Hz), 3.10 (3H, s), 3.16 (1H, dd, J = 7.0, 13.0 Hz), 3.72—3.87 (2H, m), 3.80 (6H, s), 3.83 (3H, s), 4.33 (1H, d, J = 12.0 Hz), 4.38 (1H, d, J = 12.0 Hz), 5.07—5.15 (2H, m), 5.63—5.76 (1H, m), 6.35 (2H, s), 7.09 (1H, dd, J = 2.0, 8.5 Hz), 7.32—7.37 (2H, m).

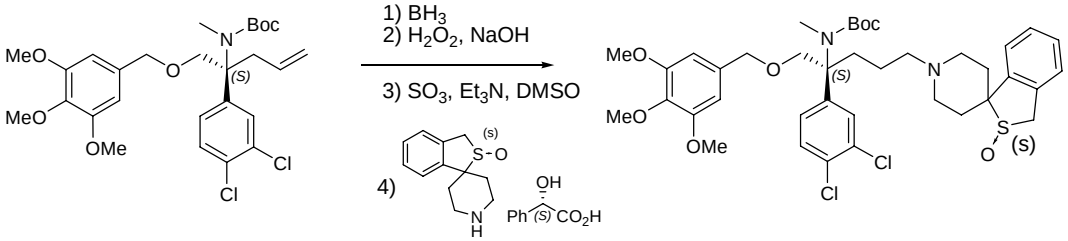
[0919]

Example 66(c)

Synthesis of tert-butyl {1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate

[0920]

[F220]



[0921]

Similar to Example 51(b), tert-butyl [1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-

pentan-2-yl]methylcarbamate was obtained (1.25 g, 56.0%) by use of tert-butyl [1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-4-penten-2-yl]methylcarbamate (2.17 g). Subsequently, similar to Example 51(c), tert-butyl [1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate was obtained (1.0 g, 78.1%) by use of tert-butyl [1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-hydroxy-pentan-2-yl]methylcarbamate (1.25 g). Thereafter, similar to Example 51(d), the title compound was obtained (1.62 g, >100%) by use of tert-butyl [1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-oxo-pentan-2-yl]methylcarbamate (1.0 g).

[0922]

MS (FAB) m/z 761 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.90 (9H, brs), 1.60—1.72 (4H, m), 1.92—2.08 (2H, m), 2.30—2.50 (6H, m), 2.82—2.90 (1H, m), 2.95—3.02 (1H, m), 3.13 (3H, s), 3.81 (6H, s), 3.82 (3H, s), 3.83—3.90 (2H, m), 4.01 (1H, d, J = 17.0 Hz), 4.33 (1H, d, J = 17.0 Hz), 4.35—4.38 (2H, m), 6.37 (2H, s), 7.10 (1H, dd, J = 2.0, 8.5 Hz), 7.25—7.37 (6H, m).

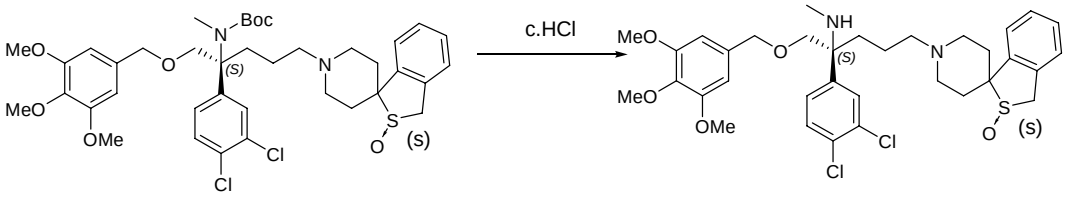
[0923]

Example 66(d)

Synthesis of 1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-2-(N-methylamino)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentane

[0924]

[F221]



[0925]

Similar to Example 26(i), the title compound was obtained (1.14 g, 95.7%) by use of tert-butyl {1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}methylcarbamate (1.62 g).

[0926]

MS (FAB) m/z 661 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.32–1.83 (6H, m), 1.90–2.02 (1H, m), 2.19 (3H, s), 2.27–2.46 (6H, m), 2.76–2.98 (2H, m), 3.59–3.69 (2H, m), 3.83 (6H, s), 3.84 (3H, s), 4.00 (1H, d, J = 17.0 Hz), 4.32 (1H, d, J = 17.0 Hz), 4.44 (1H, d, J = 12.0 Hz), 4.48 (1H, d, J = 12.0 Hz), 6.46 (2H, s), 7.24–7.36 (5H, m), 7.39 (1H, d, J = 8.5 Hz), 7.54 (1H, d, J = 2.0 Hz).

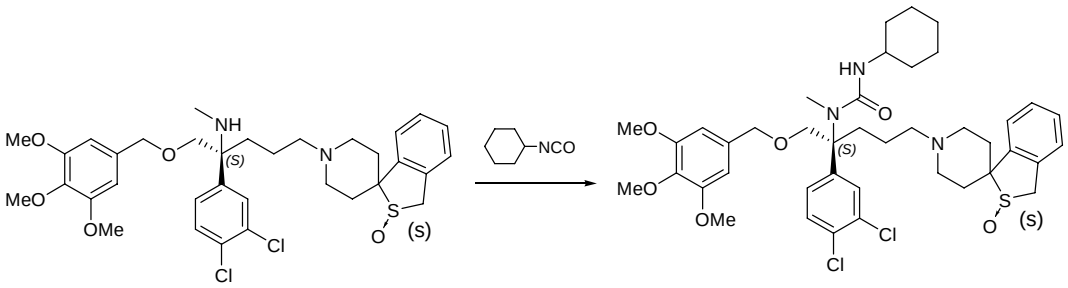
[0927]

Example 66(e)

Synthesis of 1-{1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}-3-cyclohexyl-1-methylurea

[0928]

[F222]



[0929]

Similar to Example 48(a), the title compound was obtained (55 mg, 92.5%) by use of 1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-2-(N-methylamino)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentane (50 mg) and cyclohexyl isocyanate (50 μL).

[0930]

MS (FAB) m/z 786 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 0.78—0.94 (2H, m), 1.02—1.44 (4H, m), 1.47—1.78 (5H, m), 1.88—2.12 (3H, m), 2.15—2.24 (1H, m), 2.28—2.45 (6H, m), 2.78—2.86 (1H, m), 2.90—2.98 (4H, m), 3.42—3.52 (2H, m), 3.82 (6H, s), 3.82 (3H, s), 3.94—4.04 (3H, m), 4.30—4.44 (3H, m), 4.58 (1H, d, J = 7.5 Hz), 6.39 (2H, s), 7.17 (1H, dd, J = 2.0, 8.0 Hz), 7.27—7.35 (4H, m), 7.37 (1H, d, J = 8.5 Hz), 7.42 (1H, d, J = 2.0 Hz).

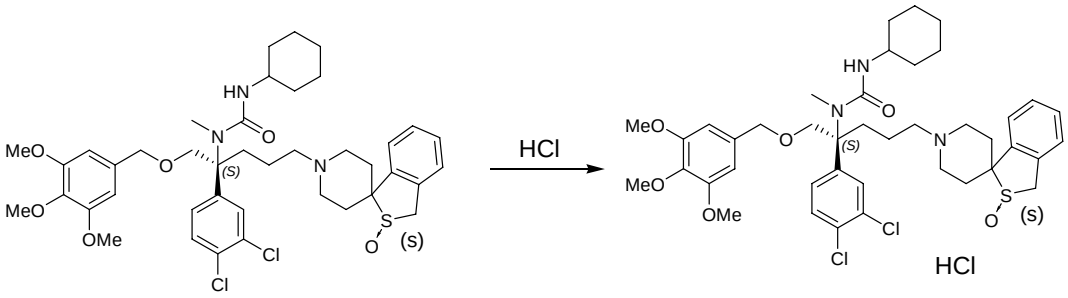
[0931]

Example 66(f)

Synthesis of 1-{1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}-3-cyclohexyl-1-methylurea hydrochloride (Compound No. 599)

[0932]

[F223]



[0933]

Similar to Example 26(k), the title compound was obtained as white powder (45 mg, 78.1%) by use of 1-{1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}-3-cyclohexyl-1-methylurea (55 mg).

[0934]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 0.98—1.32 (7H, m), 1.47—1.80 (7H, m), 1.92—2.02 (1H, m), 2.08—2.42 (4H, m), 2.81—2.93 (1H, m), 2.97 (3H, s), 3.02—3.40 (5H, m), 3.60 (3H, s), 3.71 (6H, s), 3.84 (1H, d, J = 10.0 Hz), 3.96 (1H, d, J = 10.0 Hz), 4.09 (1H, d, J = 17.0 Hz), 4.32—4.42 (2H, m), 4.66 (1H, d , J = 17.0 Hz), 6.00—6.10 (1H, m), 6.45 (2H, s), 7.24 (1H, dd, J = 2.0, 8.5 Hz), 7.30—7.50 (5H, m), 7.53 (1H, d, J = 8.5 Hz), 10.78 (1H, br).

[0935]

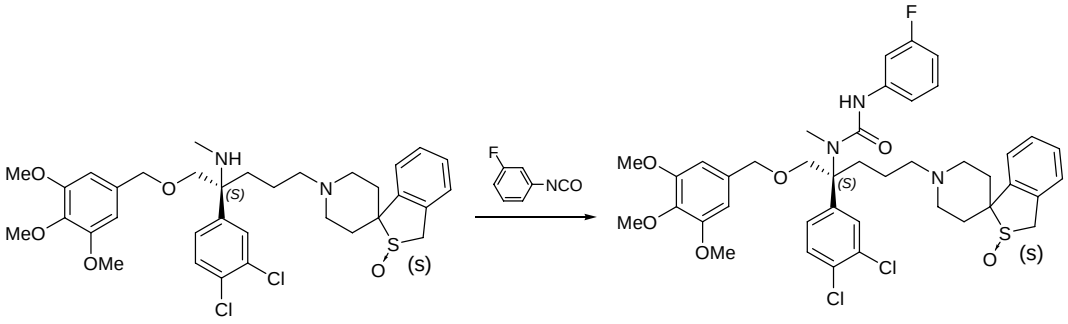
Example 67(a)

Synthesis of 1-{1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}-3-(3-fluorophenyl)-1-

methylurea

[0936]

[F224]



[0937]

Similar to Example 48(a), the title compound was obtained (50 mg, 82.8%) by use of 1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-2-(N-methylamino)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentane (50 mg) and 3-fluorophenyl isocyanate (50 μL).

[0938]

MS (FAB) m/z 798 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.20–1.42 (2H, m), 1.52–1.62 (1H, m), 1.88–1.98 (1H, m), 2.03–2.12 (2H, m), 2.25–2.44 (6H, m), 2.71–2.79 (1H, m), 2.86–2.94 (1H, m), 3.08 (3H, s), 3.78 (6H, s), 3.83 (3H, s), 3.99 (1H, d, J = 6.5 Hz), 4.00 (1H, d, J = 17.0 Hz), 4.08–4.17 (1H, m), 4.32 (1H, d, J = 17.0 Hz), 4.52 (2H, s), 6.47 (2H, s), 6.50 (1H, dd, J = 1.5, 8.0 Hz), 6.59 (1H, dt, J = 1.5, 8.0 Hz), 6.92 (1H, dt, J = 1.5, 8.0 Hz), 6.99–7.06 (1H, m), 7.20 (1H, dd, J = 2.0, 8.5 Hz), 7.24–7.36 (5H, m), 7.46 (1H, d, J = 2.0 Hz), 7.49–7.51 (1H,

m).

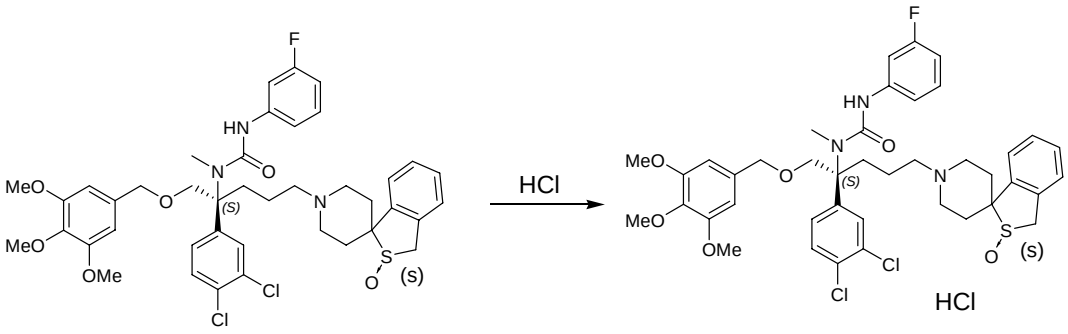
[0939]

Example 67(b)

Synthesis of 1-{1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}-3-(3-fluorophenyl)-1-methylurea hydrochloride (Compound No. 615)

[0940]

[F225]



[0941]

Similar to Example 26(k), the title compound was obtained as white powder (40 mg, 76.5%) by use of 1-{1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}-3-(3-fluorophenyl)-1-methylurea (50 mg).

[0942]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.62—1.87 (2H, m), 1.93—2.02 (1H, m), 2.17—2.48 (4H, m), 2.77—2.89 (1H, m), 3.00—3.24 (7H, m), 3.50—3.67 (5H, m), 3.70 (6H, s), 3.92 (1H, d, J = 10.0 Hz), 4.05 (1H, d, J = 10.0 Hz), 4.09 (1H, d, J = 17.0 Hz), 4.38 (1H, d, J = 12.0 Hz), 4.42 (1H, d, J = 12.0 Hz), 4.66

(1H, d, J = 17.0 Hz), 6.46 (2H, s), 6.66—6.76 (1H, m), 7.11—7.45 (8H, m), 7.52—7.61 (2H, m), 8.73 (1H, s), 10.62 (1H, br).

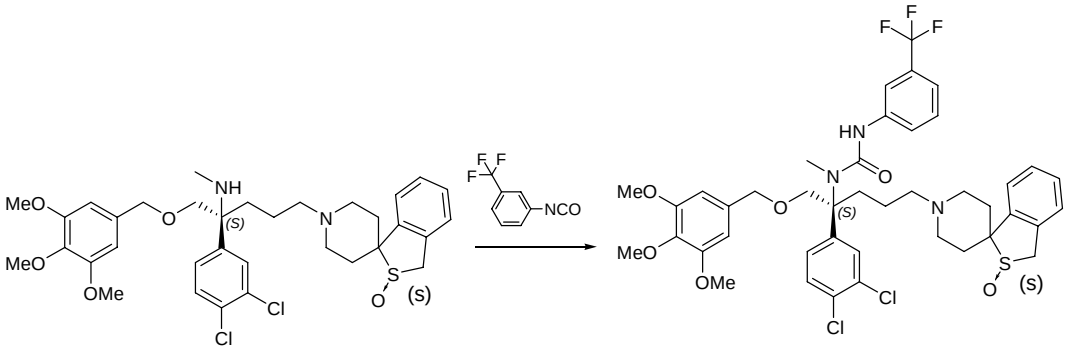
[0943]

Example 68(a)

Synthesis of 1-{1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}-3-[3-(trifluoromethyl)phenyl]-1-methylurea

[0944]

[F226]



[0945]

Similar to Example 48(a), the title compound was obtained (60 mg, 93.5%) by use of 1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-2-(N-methylamino)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentane (50 mg) and 3-trifluoromethylphenyl isocyanate (50 μL).

[0946]

MS (FAB) m/z 848 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.20—1.42 (2H, m), 1.52—1.60

(1H, m), 1.88–1.98 (1H, m), 2.03–2.10 (2H, m), 2.23–2.44 (7H, m), 2.70–2.78 (1H, m), 2.85–2.92 (1H, m), 3.09 (3H, s), 3.78 (6H, s), 3.83 (3H, s), 3.97–4.03 (2H, m), 4.08–4.17 (1H, m), 4.32 (1H, d, J = 17.0 Hz), 4.54 (2H, s), 6.47 (2H, s), 6.98–7.02 (1H, m), 7.12–7.23 (3H, m), 7.24–7.36 (5H, m), 7.45 (1H, d, J = 2.0 Hz), 7.61 (1H, br).

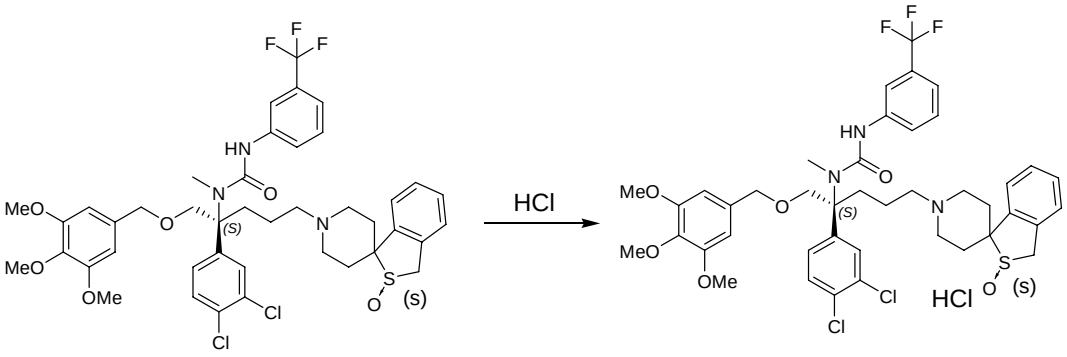
[0947]

Example 68(b)

Synthesis of 1-{1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}-3-[3-(trifluoromethyl)phenyl]-1-methylurea hydrochloride (Compound No. 616)

[0948]

[F227]



[0949]

Similar to Example 26(k), the title compound was obtained as white powder (53 mg, 84.7%) by use of 1-{1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}-3-[3-(trifluoromethyl)phenyl]-1-methylurea

(60 mg).

[0950]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.63–1.87 (2H, m), 1.97 (1H, d, J = 15.0 Hz), 2.18–2.47 (4H, m), 2.77–2.88 (1H, m), 3.03–3.25 (7H, m), 3.50–3.58 (6H, m), 3.70 (6H, s), 3.93 (1H, d, J = 10.0 Hz), 4.06 (1H, d, J = 10.0 Hz), 4.09 (1H, d, J = 17.0 Hz), 4.38 (1H, d, J = 12.0 Hz), 4.43 (1H, d, J = 12.0 Hz), 4.66 (1H, d, J = 17.0 Hz), 6.46 (2H, s), 7.24 (1H, d, J = 7.5 Hz), 7.28–7.46 (5H, m), 7.52–7.58 (2H, m), 7.65 (1H, d, J = 8.0 Hz), 7.82 (1H, s), 8.87 (1H, s), 10.60 (1H, br).

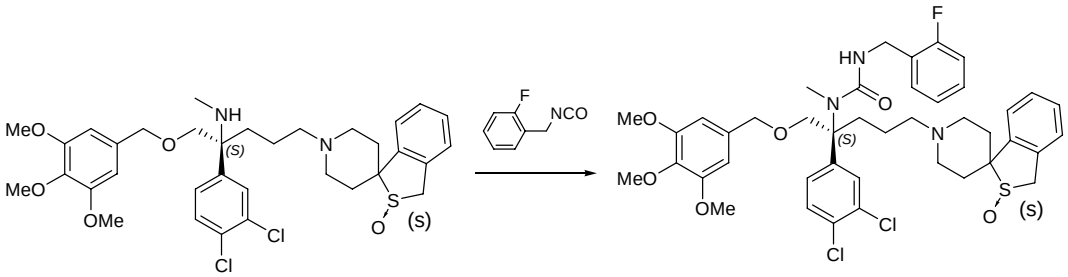
[0951]

Example 69(a)

Synthesis of 1-{1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}-3-(2-fluorobenzyl)-1-methylurea

[0952]

[F228]



[0953]

Similar to Example 48(a), the title compound was obtained (50 mg, 81.4%) by use of 1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-2-(N-

methylamino)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentane (50 mg) and 2-fluorobenzyl isocyanate (50 μL).

[0954]

MS (FAB) m/z 812 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.30—1.40 (2H, m), 1.52—1.60 (1H, m), 1.88—2.10 (2H, m), 2.14—2.45 (7H, m), 2.74—2.82 (1H, m), 2.88—2.94 (1H, m), 3.01 (3H, s), 3.80 (6H, s), 3.82 (3H, s), 3.84—4.04 (3H, m), 4.21—4.39 (5H, m), 5.13 (1H, t, J = 6.0 Hz), 6.37 (2H, s), 6.93—7.06 (2H, m), 7.09—7.24 (3H, m), 7.25—7.38 (6H, m).

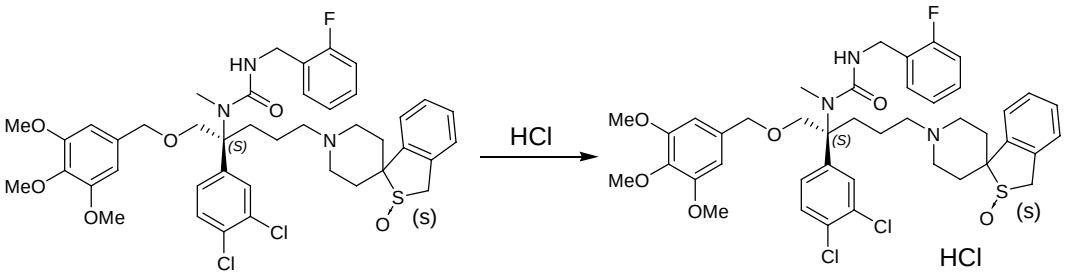
[0955]

Example 69(b)

Synthesis of 1-{1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}-3-(2-fluorobenzyl)-1-methylurea hydrochloride (Compound No. 617)

[0956]

[F229]



[0957]

Similar to Example 26(k), the title compound was obtained as white powder (40 mg, 76.6%) by use of 1-{1-

(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}-3-(2-fluorobenzyl)-1-methylurea (50 mg).

[0958]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.59 (1H, br), 1.78 (1H, br), 1.96 (1H, d, J = 15.0 Hz), 2.10—2.28 (2H, m), 2.32—2.46 (2H, m), 2.82—2.92 (1H, m), 2.98—3.28 (7H, m), 3.44—3.53 (6H, m), 3.71 (6H, s), 3.85 (1H, d, J = 10.0 Hz), 3.97 (1H, d, J = 10.0 Hz), 4.10 (1H, d, J = 17.0 Hz), 4.17—4.22 (2H, m), 4.35 (1H, d, J = 12.0 Hz), 4.39 (1H, d, J = 12.0 Hz), 4.67 (1H, d J = 17.0 Hz), 6.45 (2H, s), 7.03—7.13 (3H, m), 7.20—7.55 (8H, m), 10.79 (1H, br).

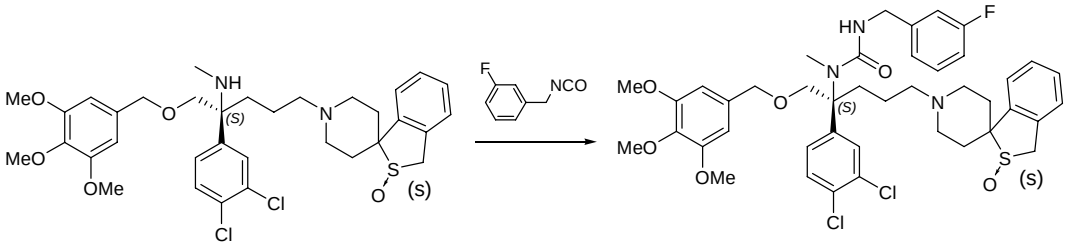
[0959]

Example 70(a)

Synthesis of 1-{1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}-3-(3-fluorobenzyl)-1-methylurea

[0960]

[F230]



[0961]

Similar to Example 48(a), the title compound was obtained (60 mg, 97.6%) by use of 1-(3,4,5-

trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-2-(N-methylamino)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentane (50 mg) and 3-fluorobenzyl isocyanate (50 μL).

[0962]

MS (FAB) m/z 812 ($(M+H)^+$)

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.34–1.43 (2H, m), 1.57 (1H, dd, J = 2.0, 15.0 Hz), 1.78 (1H, br), 1.90–2.00 (1H, m), 2.02–2.12 (1H, m), 2.17–2.46 (7H, m), 2.77–2.84 (1H, m), 2.90–2.97 (1H, m), 3.03 (3H, s), 3.80 (6H, s), 3.82 (3H, s), 3.95–4.04 (3H, m), 4.23 (1H, dq, J = 5.5, 15.0 Hz), 4.33 (1H, d, J = 17.0 Hz), 4.37 (1H, d, J = 12.0 Hz), 4.40 (1H, d, J = 12.0 Hz), 5.12 (1H, t, J = 5.5 Hz), 6.37 (2H, s), 6.76–6.93 (3H, m), 7.15 (1H, dd, J = 2.0, 8.5 Hz), 7.18–7.37 (6H, m), 7.39 (1H, d, J = 2.0 Hz).

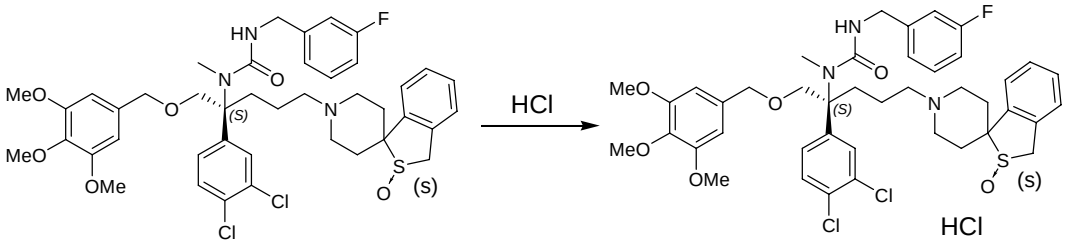
[0963]

Example 70(b)

Synthesis of 1-{1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}-3-(3-fluorobenzyl)-1-methylurea hydrochloride (Compound No. 618)

[0964]

[F231]



[0965]

Similar to Example 26(k), the title compound was obtained as white powder (50 mg, 80.0%) by use of 1-{1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}-3-(3-fluorobenzyl)-1-methylurea (60 mg).

[0966]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.57 (1H, br), 1.77 (1H, br), 1.96 (1H, d, J = 14.5 Hz), 2.10—2.46 (4H, m), 2.74—2.87 (1H, m), 2.98—3.20 (7H, m), 3.45—3.63 (6H, m), 3.71 (6H, s), 3.86 (1H, d, J = 10.0 Hz), 3.97 (1H, d, J = 10.0 Hz), 4.05—4.23 (3H, m), 4.35 (1H, d, J = 12.0 Hz), 4.39 (1H, d, J = 12.0 Hz), 4.67 (1H, d, J = 17.0 Hz), 6.45 (2H, s), 6.93—7.05 (3H, m), 7.10—7.18 (1H, m), 7.23—7.48 (6H, m), 7.51 (1H, d, J = 8.5 Hz), 10.51 (1H, br).

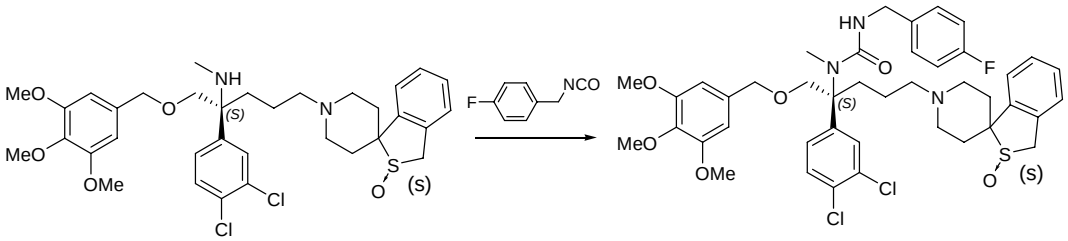
[0967]

Example 71(a)

Synthesis of 1-{1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}-3-(4-fluorobenzyl)-1-methylurea

[0968]

[F232]



[0969]

Similar to Example 48(a), the title compound was obtained (55 mg, 89.5%) by use of 1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-2-(N-methylamino)-5-[spiro(benzo(c)thiophene-(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentane (50 mg) and 4-fluorobenzyl isocyanate (50 μL).

[0970]

MS (FAB) m/z 812 $((M+H)^+)$

^{1}H-NMR (400MHz, $CDCl_3$)δ ppm : 1.32—1.43 (2H, m), 1.53—1.60 (1H, m), 1.90—2.10 (2H, m), 2.17—2.45 (7H, m), 2.75—2.83 (1H, m), 2.90—2.97 (1H, m), 3.02 (3H, s), 3.80 (6H, s), 3.83 (3H, s), 3.93—4.04 (3H, m), 4.11—4.25 (2H, m), 4.33 (1H, d, J = 17.0 Hz), 4.38 (2H, s), 5.03 (1H, t, J = 5.5 Hz), 6.36 (2H, s), 6.90—6.96 (2H, m), 6.99—7.04 (2H, m), 7.14 (1H, dd, J = 2.0, 8.5 Hz), 7.25—7.36 (5H, m), 7.38 (1H, d, J = 2.0 Hz).

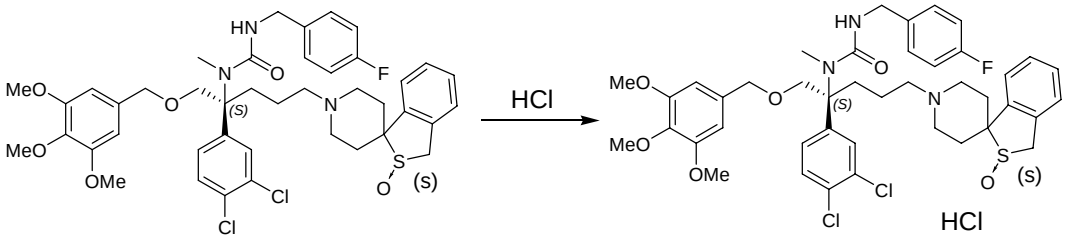
[0971]

Example 71(b)

Synthesis of 1-{1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}-3-(4-fluorobenzyl)-1-methylurea hydrochloride (Compound No. 621)

[0972]

[F233]



[0973]

Similar to Example 26(k), the title compound was obtained as white powder (40 mg, 69.6%) by use of 1-{1-(3,4,5-trimethoxybenzyloxy)-2-(S)-(3,4-dichlorophenyl)-5-[spiro(benzo(c)thiophene(2S)-oxido-1(3H),4'-piperidin)-1'-yl]pentan-2-yl}-3-(4-fluorobenzyl)-1-methylurea (55 mg).

[0974]

^{1}H-NMR (400MHz, DMSO-d_6)δ ppm : 1.52–1.65 (1H, m), 1.73–1.86 (1H, m), 1.92–2.00 (1H, m), 2.12–2.28 (2H, m), 2.34–2.47 (2H, m), 2.83–2.97 (1H, m), 2.99–3.18 (6H, m), 3.45–3.64 (7H, m), 3.71 (6H, s), 3.85 (1H, d, J = 10.0 Hz), 3.98 (1H, d, J = 10.0 Hz), 4.06–4.16 (3H, m), 4.34 (1H, d, J = 12.0 Hz), 4.39 (1H, d, J = 12.0 Hz), 4.66 (1H, d, J = 17.0 Hz), 6.44 (2H, s), 7.04–7.13 (3H, m), 7.17–7.27 (3H, m), 7.31–7.45 (3H, m), 7.46 (1H, d, J = 2.0 Hz), 7.53 (1H, d, J = 8.5 Hz), 10.91 (1H, br).

[0975]

Table 1 shows other compounds and salts of the present invention produced in accordance with any of the production processes described above.

[0976]

[Table 1]

Compound No.	R^1	R^2	R^3	R_4	Spiro	R^5	X^1	X^2	X^3	X^4	n1	n2	Salt	Quaternary carbon	Form
47	Propionyl	Diphenylmethyl	-$SOCH_2$-		S	CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
48	Methyl	3,4,5-Trimethoxyphenyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
49	isobutyryl	2,2-Diphenylethyl	-$NHCOCH_2$-			CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
50	iso-Butyryl	Diphenylmethyl	-$SOCH_2$-		S	CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
51	iso-Butyryl	2,2-Diphenylethyl	-SO_2CH_2-			CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
52	iso-Butyryl	Diphenylmethyl	-SO_2CH_2-			CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
53	iso-Butyryl	2,2-Diphenylethyl	-$SOCH_2$-		S	CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	HCl	R	Amorphous
54	Difluoroacetyl	2,2-Diphenylethyl	-$SOCH_2$-		S	CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
55	Benzyl	H	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	0	Free	racemic	Amorphous
56	Acetyl	Diphenylmethyl	-$SOCH_2$-		S	CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
57	Acetyl	2,2-Diphenylethyl	-$SOCH_2$-		S	CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
58	4-Cyanophenyl	3,4,5-Trimethoxyphenyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
59	4-Cyanobenzyl	3,4,5-Trimethoxyphenyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
60	3,4,5-Trimethoxyphenylacetyl	3,4,5-Trimethoxyphenyl	NHAc	H		CH_3	O	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
61	3,4,5-Trimethoxybenzyl	1-Methyl-1H-indol-3-yl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
62	3,4,5-Trimethoxybenzyl	4-Oxo-4H-chromen-2-yl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous

63	3,4,5-Trimethoxybenzyl	2-Benzofuranyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
64	3,4,5-Trimethoxybenzyl	3-Benzothienyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
65	3,4,5-Trimethoxybenzyl	Methyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
66	3,4,5-Trimethoxybenzyl	H	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
67	3,4,5-Trimethoxybenzyl	Methyl	NHAc	H		CH_3	O	Single bond	3-Cl	4-Cl	1	0	Free	racemic	Amorphous
68	3,4,5-Trimethoxybenzyl	H	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	0	Free	racemic	Amorphous
69	3,4,5-Trimethoxybenzyl	Methyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	0	Free	racemic	Amorphous
70	3,4,5-Trimethoxybenzyl	n-Propyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
71	3,4,5-Trimethoxybenzyl	3,4,5-Trimethoxyphenyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
72	3,4,5-Trimethoxybenzyl	3,4,5-Trimethoxybenzyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
73	3,4,5-Trimethoxybenzyl	Cyclopropyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
74	3,4,5-Trimethoxybenzyl	Cyclobutyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
75	3,4,5-Trimethoxybenzyl	Cyclopentyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
76	3,4,5-Trimethoxybenzyl	Ethoxycarbonylmethyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
77	3,4,5-Trimethoxybenzyl	Ethyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	0	HCl	racemic	Amorphous
78	3,4,5-Trimethoxybenzyl	Ethoxymethyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
79	3,4,5-Trimethoxybenzyl	Methansulphonyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	0	Free	racemic	Amorphous
80	3,4,5-Trimethoxybenzyl	Phenylthiomethyl	$-SOCH_2-$		S	CH_3	O	Single bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
81	3,4,5-Trimethoxybenzyl	3,4,5-Trimethoxyphenyl	$-SOCH_2-$		S	CH_3	O	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
82	3,4,5-Trimethoxybenzyl	3,4,5-Trimethoxyphenyl	$-SOCH_2-$		S	CH_3	O	Single bond	3-Cl	4-Cl	1	1	HCl	R	Amorphous

83	3,4,5-Trimethoxybenzoyl	Cyclohexyl	$CONH_2$	H		CH_2CH_3	O	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
84	3,4,5-Trimethoxybenzoyl	H	$CONH_2$	H		CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	0	Free	racemic	Amorphous
85	3,4,5-Trimethoxybenzoyl	2,2-Dimethylpropyl	$CONH_2$	H		CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
86	3,4,5-Trimethoxybenzoyl	3,4,5-Trimethoxyphenyl	$CONH_2$	H		CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
87	3,4,5-Trimethoxybenzoyl	3,4,5-Trimethoxybenzyl	$CONH_2$	H		CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
88	3,4,5-Trimethoxybenzoyl	Phenyl	$CONH_2$	H		CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
89	3,4,5-Trimethoxybenzoyl	Cyclohexyl	$CONH_2$	H		CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
90	3,4,5-Trimethoxybenzoyl	Benzyl	$CONH_2$	H		CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
91	3,4,5-Trimethoxybenzoyl	H	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	1	0	Free	racemic	Amorphous
92	3,4,5-Trimethoxybenzoyl	Benzylaminomethyl	$-SOCH_2-$		S	CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	2HCl	racemic	Amorphous
93	3,4,5-Trimethoxybenzoyl	1-Pipelidyl	$-SOCH_2-$		S	CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
94	3,4,5-Trimethoxybenzoyl	1-Pyrrolidin y l	$-SOCH_2-$		S	CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
95	3,4,5-Trimethoxybenzoyl	Phenylaminomethyl	$-SOCH_2-$		S	CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
96	3,4,5-Trimethoxybenzoyl	H	$-SOCH_2-$		S	CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	0	2HCl	S	Amorphous
97	3,4,5-Trimethoxybenzoyl	H	$-SOCH_2-$		S	CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	0	2HCl	R	Amorphous
98	3,4,5-Trimethoxybenzoyl	3,4,5-Trimethoxyphenyl	$-SOCH_2-$		S	CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
99	3,4,5-Trimethoxybenzoyl	3,4,5-Trimethoxyphenyl	$-SOCH_2-$		S	CH_3	NCH_3	Single bond	3-Cl	4-Cl	1	1	HCl	R	Amorphous
100	3,3,3-Trifluoropropionyl	2,2-Diphenylethyl	$-NHCOCH_2-$			CH_3	NCH	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous

							3								
101	3,3,3-Trifluoropropionyl	2,2-Diphenylethyl	-SO_2CH_2-			CH_3	NCH 3	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
102	3,3,3-Trifluoropropionyl	Diphenylmethyl	-SO_2CH_2-			CH_3	NCH 3	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
103	3,3,3-Trifluoropropionyl	2,2-Diphenylethyl	-$SOCH_2$-		S	CH_3	NCH 3	Single bond	3-Cl	4-Cl	1	1	HCl	R	Amorphous
104	2-Chlorobenzylaminocarbonyl	H	-$SOCH_2$-		S	CH_3	NCH 3	Single bond	3-Cl	4-Cl	1	0	2HCl	R	Amorphous
105	2-Chloro-2-difluoroacetyl	2,2-Diphenylethyl	-$SOCH_2$-		S	CH_3	NCH 3	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
106	Thiophene-2-carbonyl	Cyclopentyl	-$SOCH_2$-		S	CH_3	NCH 3	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
107	Pyridin-2-carbonyl	Cyclopentyl	-$SOCH_2$-		S	CH_3	NCH 3	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
108	Phenylacetyl	Cyclopentyl	-$SOCH_2$-		S	CH_3	NCH 3	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
109	Phenoxycarbonyl	Cyclopentyl	-$SOCH_2$-		S	CH_3	NCH 3	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
110	Cyclohexylcarbonyl	Cyclopentyl	-$SOCH_2$-		S	CH_3	NCH 3	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
111	Benzyl	Ethyl	-$NHCOCH_2$-			CH_3	O	Ester bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
112	Benzyl	Ethyl	-$SOCH_2$-		S	CH_3	O	Ester bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
113	Benzyl	iso-Propyl	-$SOCH_2$-		S	CH_3	O	Ester bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
114	Benzyl	iso-Propyl	-$NHCOCH_2$-			CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
115	Benzoyl	Cyclopentyl	-$SOCH_2$-		S	CH_3	NCH 3	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
116	4-Methoxybenzoyl	Cyclopentyl	-$SOCH_2$-		S	CH_3	NCH 3	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
117	3,5-Dimethoxybenzoyl	Cyclopentyl	-$SOCH_2$-		S	CH_3	NCH 3	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous

118	3,5-Bis(trifluromethyl)benzoyl	Cyclopentyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
119	3,4,5-Trimethoxybenzyl	2-Indanyl	-SOCH$_2$-		S	CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
120	3,4,5-Trimethoxybenzyl	H	$CONH_2$	H		CH_3	O	Ester bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
121	3,4,5-Trimethoxybenzyl	Ethyl	$CONH_2$	H		CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
122	3,4,5-Trimethoxybenzyl	Methyl	$CONH_2$	H		CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
123	3,4,5-Trimethoxybenzyl	Ethyl	NHAc	H		CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
124	3,4,5-Trimethoxybenzyl	Ethyl	-NHCOCH$_2$-			CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
125	3,4,5-Trimethoxybenzyl	Ethyl	-SOCH$_2$-		S	CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
126	3,4,5-Trimethoxybenzyl	n-Propyl	$CONH_2$	H		CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
127	3,4,5-Trimethoxybenzyl	Benzyl	$CONH_2$	H		CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
128	3,4,5-Trimethoxybenzyl	Cyclopropyl	$CONH_2$	H		CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
129	3,4,5-Trimethoxybenzyl	Cyclohexyl	$CONH_2$	H		CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
130	3,4,5-Trimethoxybenzyl	Phenyl	$CONH_2$	H		CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
131	3,4,5-Trimethoxybenzyl	Ethyl	-C(=NOH)CH$_2$-			CH_3	O	Ester bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
132	3,4,5-Trimethoxybenzyl	Ethyl	$NHCONMe_2$	H		CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
133	3,4,5-Trimethoxybenzyl	Ethyl	-COCH$_2$-			CH_3	O	Ester bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
134	3,4,5-Trimethoxybenzyl	Ethyl	$CONH_2$	H		H	O	Ester bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
135	3,4,5-Trimethoxybenzyl	Cyclopentyl	$CONH_2$	H		CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
136	3,4,5-Trimethoxybenzyl	iso-Butyl	$CONH_2$	H		CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
137	3,4,5-Trimethoxybenzyl	Ethyl	-NHCOCH$_2$-			CH_3	O	Ester bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous

138	3,4,5-Trimethoxybenzyl	Ethyl	-SOCH$_2$-		S	CH_3	O	Ester bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
139	3,4,5-Trimethoxybenzyl	iso-Propyl	-NHCOCH$_2$-			CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
140	3,4,5-Trimethoxybenzyl	iso-Propyl	-SOCH$_2$-		S	CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
141	3,4,5-Trimethoxybenzyl	iso-Propyl	$CONH_2$	H		CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
142	3,4,5-Trimethoxybenzyl	Ethyl	$CONH_2$	H		$CH_2CH_2CH_3$	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
143	3,4,5-Trimethoxybenzyl	Cyclopentylmethyl	-NHCOCH$_2$-			CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
144	3,4,5-Trimethoxybenzyl	Cyclohexyl	-SOCH$_2$-		S	CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
145	3,4,5-Trimethoxybenzyl	Cyclohexyl	-NHCOCH$_2$-			CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
146	3,4,5-Trimethoxybenzyl	Cyclopentyl	-SOCH$_2$-		S	CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
147	3,4,5-Trimethoxybenzyl	Cyclopentyl	-SOCH$_2$-		S	CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
148	3,4,5-Trimethoxybenzyl	Cyclopentyl	-SOCH$_2$-		S	CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	R	Amorphous
149	3,4,5-Trimethoxybenzoyl	2-Indanyl	-SOCH$_2$-		S	CH_3	NCH_3	Ester bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
150	3,4,5-Trimethoxybenzoyl	Ethyl	$CONH_2$	H		CH_3	O	Ester bond	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
151	3,4,5-Trimethoxybenzoyl	Cyclopentyl	-SOCH$_2$-		S	CH_3	NCH_3	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
152	3,4,5-Trimethoxybenzoyl	Cyclopentyl	-SOCH$_2$-		S	CH_3	NCH_3	Ester bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
153	3,4,5-Trimethoxybenzoyl	Cyclopentyl	-SOCH$_2$-		S	CH_3	NCH_3	Ester bond	3-Cl	4-Cl	1	1	HCl	R	Amorphous
154	3,4,5-Trimethoxybenzoyl	Cyclohexyl	-SOCH$_2$-		S	CH_3	NCH_3	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
155	3,4,5-Trimethoxybenzoyl	iso-Propyl	-SOCH$_2$-		S	CH_3	NCH_3	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
156	3,4,5-Trimethoxybenzoyl	Cyclopentyl	-SOCH$_2$-		S	CH_3	NH	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous

157	3,4,5-Trimethoxybenzoyl	Cyclohexyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Ester bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
158	3,4,5-Trimethoxybenzoyl	iso-Propyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Ester bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
159	3,4,5-Trimethoxybenzoyl	Cyclopentyl	-SOCH$_2$-		S	CH_3	O	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
160	3,4,5-Trimethoxybenzoyl	4-Tetrahydro-2H-pyranyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
161	3,4,5-Trimethoxybenzoyl	2-Chlorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Ester bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
162	2-Methoxybenzoyl	Cyclopentyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Ester bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
163	Acetyl	Diphenylmethyl	-SOCH$_2$-		S	CH_3	NH	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
164	3,4,5-Trimethoxybenzyl	Phenyl	$CONH_2$	H		CH_3	O	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
165	3,4,5-Trimethoxybenzyl	Cyclohexyl	$CONH_2$	H		CH_3	O	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
166	3,4,5-Trimethoxybenzyl	Phenyl	-SOCH$_2$-		S	CH_3	O	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
167	3,4,5-Trimethoxybenzyl	Cyclohexyl	-SOCH$_2$-		S	CH_3	O	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
168	3,4,5-Trimethoxybenzyl	Phenyl	-SOCH$_2$-		S	CH_3	O	Amide bond	3-Cl	4-Cl	1	1	HCl	R	Amorphous
169	3,4,5-Trimethoxybenzyl	Cyclohexyl	-SOCH$_2$-		S	CH_3	O	Amide bond	3-Cl	4-Cl	1	1	HCl	R	Amorphous
170	3,4,5-Trimethoxybenzyl	Phenyl	-SOCH$_2$-		S	CH_3	O	Amide bond	3-Cl	4-Cl	1	1	HCl	R	Amorphous
171	3,4,5-Trimethoxybenzyl	Cyclohexyl	-SOCH$_2$-		S	CH_3	O	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
172	3,4,5-Trimethoxybenzyl	3-Chlorophenyl	-SOCH$_2$-		S	CH_3	O	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
173	3,4,5-Trimethoxybenzyl	2-Chlorophenyl	-SOCH$_2$-		S	CH_3	O	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
174	3,4,5-Trimethoxybenzyl	3-Methoxy-5-trifluoromethylphenyl	-SOCH$_2$-		S	CH_3	O	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
175	3,4,5-Trimethoxybenzyl	3,5-Difluorophenyl	-SOCH$_2$-		S	CH_3	O	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous

176	3,4,5-Trimethoxybenzyl	3-Methoxyphenyl	-SOCH$_2$-		S	CH_3	O	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
177	3,4,5-Trimethoxybenzyl	3-Fluorophenyl	-SOCH$_2$-		S	CH_3	O	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
178	3,4,5-Trimethoxybenzyl	3-Trifluoromethylphenyl	-SOCH$_2$-		S	CH_3	O	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
179	3,4,5-Trimethoxybenzyl	3,5-Difluorophenyl	-SOCH$_2$-		S	CH_3	O	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
180	3,4,5-Trimethoxybenzyl	3-Fluorophenyl	-SOCH$_2$-		S	CH_3	O	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
181	3,4,5-Trimethoxybenzyl	2-Chloro-3,5-dimethyl	-SOCH$_2$-		S	CH_3	O	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
182	3,4,5-Trimethoxybenzoyl	Diphenylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
183	3,4,5-Trimethoxybenzoyl	1-Naphthyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
184	3,4,5-Trimethoxybenzoyl	8-Tetrahydronaphthyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
185	3,4,5-Trimethoxybenzoyl	1-Naphthyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
186	3,4,5-Trimethoxybenzoyl	Dicyclohexylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
187	3,4,5-Trimethoxybenzoyl	Cyclohexyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
188	3,4,5-Trimethoxybenzoyl	Phenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
189	3,4,5-Trimethoxybenzoyl	n-Hexyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
190	3,4,5-Trimethoxybenzoyl	Cyclopentyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
191	3,4,5-Trimethoxybenzoyl	Benzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
192	3,4,5-Trimethoxybenzoyl	3-Tolyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
193	3,4,5-Trimethoxybenzoyl	2-Chlorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous

194	3,4,5-Trimethoxybenzoyl	3-Methoxyphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
195	3,4,5-Trimethoxybenzoyl	2-Chlorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
196	3,4,5-Trimethoxybenzoyl	tert-Butyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
197	3,4,5-Trimethoxybenzoyl	2-Fluorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
198	3,4,5-Trimethoxybenzoyl	3-Fluorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
199	3,4,5-Trimethoxybenzoyl	4-Fluorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
200	3,4,5-Trimethoxybenzoyl	3,4-Difluorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
201	3,4,5-Trimethoxybenzoyl	3-Trifluoromethylphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
202	3,4,5-Trimethoxybenzoyl	2-Methoxyphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
203	3,4,5-Trimethoxybenzoyl	4-Tolyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
204	3,4,5-Trimethoxybenzoyl	2-Phenylphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
205	3,4,5-Trimethoxybenzoyl	2-Trifluoromethylphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
206	3,4,5-Trimethoxybenzoyl	3-Trifluoromethoxyphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
207	3,4,5-Trimethoxybenzoyl	2,3-Difluorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
208	3,4,5-Trimethoxybenzoyl	2,4-Difluorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
209	3,4,5-Trimethoxybenzoyl	2,5-Difluorobenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
210	3,4,5-Trimethoxybenzoyl	2,6-Difluorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous

211	3,4,5-Trimethoxybenzoyl	2-Trifluoromethoxyphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
212	3,4,5-Trimethoxybenzoyl	4-Trifluoromethylphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
213	3,4,5-Trimethoxybenzoyl	2-Methoxy-5-trifluorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
214	3,4,5-Trimethoxybenzoyl	4-Trifluoromethylphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
215	3,4,5-Trimethoxybenzoyl	3-Methoxy-5-trifluoromethylphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
216	3,4,5-Trimethoxybenzoyl	3,5-Difluorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
217	3,4,5-Trimethoxybenzoyl	2-Tolyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
218	3,4,5-Trimethoxybenzoyl	3-Methoxyphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
219	3,4,5-Trimethoxybenzoyl	Cyclohexyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
220	3,4,5-Trimethoxybenzoyl	Cyclohexyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	R	Amorphous
221	3,4,5-Trimethoxybenzoyl	3-Methoxyphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	R	Amorphous
222	3,4,5-Trimethoxybenzoyl	2-Chlorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	R	Amorphous
223	3,4,5-Trimethoxybenzoyl	3-Fluorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	R	Amorphous
224	3,4,5-Trimethoxybenzoyl	3,5-Difluorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	R	Amorphous
225	3,4,5-Trimethoxybenzoyl	3-Methoxy-5-trifluoromethylphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
226	3,4,5-Trimethoxybenzoyl	3-Fluorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
227	3,4,5-Trimethoxybenzoyl	3,5-Difluorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous

228	3,4,5-Trimethoxybenzoyl	3-Trifluoromethylphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
229	3,4,5-Trimethoxybenzoyl	2-Tolyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
230	3,4,5-Trimethoxybenzoyl	2-Chlorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
231	3,4,5-Trimethoxybenzoyl	3-Chlorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
232	3,4,5-Trimethoxybenzoyl	3,5-Difluorobenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
233	3,4,5-Trimethoxybenzoyl	3,5-Dimethoxyphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
234	3,4,5-Trimethoxybenzoyl	3,5-Difluorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
235	3,4,5-Trimethoxybenzoyl	2,3-Difluorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
236	3,4,5-Trimethoxybenzoyl	2,3-Dichlorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
237	3,4,5-Trimethoxybenzoyl	2,5-Dichlorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
238	3,4,5-Trimethoxybenzoyl	2,5-Dichlorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
239	3,4,5-Trimethoxybenzoyl	2,6-Dichloro-3-methylphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
240	3,4,5-Trimethoxybenzoyl	2-Chloro-5-methylphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
241	3,4,5-Trimethoxybenzoyl	2,3,5-Trichlorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
242	3,4,5-Trimethoxybenzoyl	2-Chloro-5-methoxyphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
243	3,4,5-Trimethoxybenzoyl	2-Chloro-3-methoxyphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
244	3,4,5-Trimethoxybenzoyl	2-Chloro-3,5-dimethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous

245	3,4,5-Trimethoxybenzoyl	2-Chloro-3-fluoro-5-methoxyphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
246	3,4,5-Trimethoxybenzoyl	2-Chloro-3-fluoro-5-methoxyphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
247	3,4,5-Trimethoxybenzoyl	3-(Dimethylamino)phenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
248	3,4,5-Trimethoxybenzoyl	2-Chlorophenyl	-SO$_2$CH$_2$-			CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
249	3,4,5-Trimethoxybenzoyl	2-Chlorophenyl	-SO$_2$CH$_2$-			CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	R	Amorphous
250	3,4,5-Trimethoxybenzoyl	2-Chlorophenyl	-SOCH$_2$-		R	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	R	Amorphous
251	3,4,5-Trimethoxybenzoyl	2-Chlorophenyl	-SCH$_2$-			CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	R	Amorphous
252	3,4,5-Trimethoxybenzoyl	2-Chlorophenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	R	Amorphous
253	3,4,5-Trimethoxybenzoyl	2-Chlorophenyl	-SOCH$_2$-		R	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
254	3,4,5-Trimethoxybenzoyl	2-Chlorophenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
255	3,4,5-Trimethoxybenzoyl	2-Chlorophenyl	-SCH$_2$-			CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
256	Trifluoroacetyl	Benzyl	-NHCOCH$_2$-			CH_3	NCH$_3$	O	3-Cl	4-Cl	1	1	HCl	S	Amorphous
257	Methyl	Benzyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
258	Methyl	Phenyl	-SOCH$_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	S	Amorphous
259	Benzyl	Benzyl	-SOCH$_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
260	Benzoyl	tert-Butyl	$CONH_2$	H		CH_3	NCH$_3$	O	3-Cl	4-Cl	1	1	free	racemic	Amorphous
261	Acetyl	Benzyl	$CONH_2$	H		CH_3	NH	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
262	4-Cyanobenzyl	tert-Butyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous

263	4-Cyanobenzyl	Benzyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
264	3,5-Bis(trifluromethyl)benzyl	Phenyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	1	1	HCl	S	Amorphous
265	3,4,5-Trimethoxybenzyl	9H-Fluoren-9-yl-methyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
266	3,4,5-Trimethoxybenzyl	2-Indanyl	$-SOCH_2-$		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	R	Amorphous
267	3,4,5-Trimethoxybenzyl	tert-Butyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
268	3,4,5-Trimethoxybenzyl	Ethyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
269	3,4,5-Trimethoxybenzyl	tert-Butyl	$CONH_2$	H		H	O	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
270	3,4,5-Trimethoxybenzyl	n-Pentyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
271	3,4,5-Trimethoxybenzyl	Benzyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
272	3,4,5-Trimethoxybenzyl	Methyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
273	3,4,5-Trimethoxybenzyl	n-Propyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
274	3,4,5-Trimethoxybenzyl	Allyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
275	3,4,5-Trimethoxybenzyl	Cyclohexylmethyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
276	3,4,5-Trimethoxybenzyl	iso-Propyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
277	3,4,5-Trimethoxybenzyl	Cyclohexylmethyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
278	3,4,5-Trimethoxybenzyl	Cyclohexyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
279	3,4,5-Trimethoxybenzyl	Cyclopentyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
280	3,4,5-Trimethoxybenzyl	Benzyl	$-SOCH_2-$		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
281	3,4,5-Trimethoxybenzyl	iso-Butyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
282	3,4,5-Trimethoxybenzyl	Benzyl	$-NHCOCH_2-$			CH_3	O	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous

283	3,4,5-Trimethoxybenzyl	4-Nitrophenyl	-$SOCH_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
284	3,4,5-Trimethoxybenzyl	3-Nitrobenzyl	-$SOCH_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
285	3,4,5-Trimethoxybenzyl	2-Methylbenzyl	-$SOCH_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
286	3,4,5-Trimethoxybenzyl	4-Nitrobenzyl	-$SOCH_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
287	3,4,5-Trimethoxybenzyl	4-Methoxybenzyl	-$SOCH_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
288	3,4,5-Trimethoxybenzyl	3-Methylbenzyl	-$SOCH_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
289	3,4,5-Trimethoxybenzyl	4-Chlorobenzyl	-$SOCH_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
290	3,4,5-Trimethoxybenzyl	2-Methylbenzyl	-$SOCH_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
291	3,4,5-Trimethoxybenzyl	2-Chlorophenyl	-$SOCH_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
292	3,4,5-Trimethoxybenzyl	2-Chlorobenzyl	-$SOCH_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
293	3,4,5-Trimethoxybenzyl	4-Bromobenzyl	-$SOCH_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
294	3,4,5-Trimethoxybenzyl	Benzyl	-$SOCH_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	S	Amorphous
295	3,4,5-Trimethoxybenzyl	Benzyl	-$SOCH_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	R	Amorphous
296	3,4,5-Trimethoxybenzyl	2-Chlorobenzyl	-$SOCH_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	R	Amorphous
297	3,4,5-Trimethoxybenzyl	2-Methylbenzyl	-$SOCH_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	R	Amorphous
298	3,4,5-Trimethoxybenzyl	3-Methylbenzyl	-$SOCH_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	R	Amorphous
299	3,4,5-Trimethoxybenzyl	4-Methoxybenzyl	-$SOCH_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	R	Amorphous
300	3,4,5-Trimethoxybenzyl	3-Chlorobenzyl	-$SOCH_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	R	Amorphous
301	3,4,5-Trimethoxybenzyl	Phenyl	-$SOCH_2$-		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	S	Amorphous
302	3,4,5-Trimethoxybenzyl	Phenyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	1	1	HCl	S	Amorphous

303	3,4,5-Trimethoxybenzoyl	tert-Butyl	$CONH_2$	H		CH_3	NCH_3	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
304	3,4,5-Trimethoxybenzoyl	Benzyl	$CONH_2$	H		CH_3	NCH_3	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
305	3,4,5-Trimethoxybenzoyl	tert-Butyl	$-SOCH_2-$		S	CH_3	NCH_3	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
306	3,4,5-Trimethoxybenzoyl	Benzyl	$-SOCH_2-$		S	CH_3	NCH_3	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
307	3,4,5-Trimethoxybenzoyl	tert-Butyl	$-SOCH_2-$		S	CH_3	O	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
308	3,4,5-Trimethoxybenzoyl	Benzyl	$-SOCH_2-$		S	CH_3	NCH_3	O	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
309	3,4,5-Trimethoxybenzoyl	tert-Butyl	$-SOCH_2-$		S	CH_3	NH	O	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
310	3,4,5-Trimethoxybenzoyl	Benzyl	$-SOCH_2-$		S	CH_3	NCH_3	O	3-Cl	4-Cl	1	1	HCl	R	Amorphous
311	3,4,5-Trimethoxybenzoyl	Cyclopentyl	$-SOCH_2-$		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	R	Amorphous
312	3,4,5-Trimethoxybenzoyl	3-Chlorobenzyl	$-SOCH_2-$		S	CH_3	NCH_3	O	3-Cl	4-Cl	1	1	HCl	R	Amorphous
313	3,4,5-Trimethoxybenzoyl	Phenyl	$CONH_2$	H		CH_3	NCH_3	O	3-Cl	4-Cl	1	1	HCl	S	Amorphous
314	3,4,5-Trimethoxybenzoyl	Phenyl	$-SOCH_2-$		S	CH_3	O	O	3-Cl	4-Cl	1	1	HCl	S	Amorphous
315	3,4,5-Trimethoxybenzoyl	Phenyl	$CONH_2$	H		CH_3	NCH_3	O	3-Cl	4-Cl	1	1	HCl	R	Amorphous
316	Trifluoroacetyl	Diphenylmethyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
317	Trifluoroacetyl	Diphenylmethyl	$-SO_2CH_2-$			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
318	Trifluoroacetyl	Diphenylmethyl	$-C(OH)CH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
319	Trifluoroacetyl	Diphenylmethyl	$CONH_2$	H		CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
320	Trifluoroacetyl	Diphenylmethyl	NHAc	H		CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous

321	Trifluoroacetyl	Diphenylmethyl	-OCH_2-			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
322	Trifluoroacetyl	9H-Fluoren-9-yl	-$NHCOCH_2$-			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
323	Trifluoroacetyl	1-(1-Phenyl)cyclopentyl	-$NHCOCH_2$-			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
324	Trifluoroacetyl	Cyclopentyl(phenyl)methyl	-$NHCOCH_2$-			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
325	Trifluoroacetyl	9H-Xanthen-9-yl	-$NHCOCH_2$-			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
326	Trifluoroacetyl	Dicyclohexylmethyl	-$NHCOCH_2$-			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
327	Trifluoroacetyl	Bis(4-chlorophenyl)methyl	-$NHCOCH_2$-			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
328	Trifluoroacetyl	Bis(4-methoxyphenyl)methyl	-$NHCOCH_2$-			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
329	Trifluoroacetyl	Diphenylmethyl	-$NHCOCH_2$-			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
330	Trifluoroacetyl	Benzyl	-$NHCOCH_2$-			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
331	Trifluoroacetyl	2-Chlorobenzyl	-$NHCOCH_2$-			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
332	Trifluoroacetyl	2-Methylbenzyl	-$NHCOCH_2$-			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
333	Trifluoroacetyl	2-Fluorobenzyl	-$NHCOCH_2$-			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
334	Trifluoroacetyl	4-Chlorobenzyl	-$NHCOCH_2$-			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
335	Trifluoroacetyl	2-Trifluoromethylbenzyl	-$NHCOCH_2$-			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
336	Trifluoroacetyl	3-Chlorophenyl	-$NHCOCH_2$-			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
337	Trifluoroacetyl	Phenoxy	-$NHCOCH_2$-			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous

338	Trifluoroacetyl	2-Phenethyl	-NHCOCH$_2$-			CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
339	Propionyl	Diphenylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
340	Propionyl	1-(1-Phenyl)cyclopentyl	-NHCOCH$_2$-			CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
341	Propionyl	Diphenylmethyl	-NHCOCH$_2$-			CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
342	Pivaloyl	Dipnehylmethyl	-NHCOCH$_2$-			CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
343	Methyl	Diphenylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
344	Methyl	Diphenylmethyl	-SOCH$_2$-		S	CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
345	Methyl	Diphenylmethyl	$CONH_2$	H		CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
346	Methyl	(S)-1-Indanyl	-SOCH$_2$-		S	CH_3	NH	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
347	Methansulphonyl	Diphenylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
348	iso-Butyryl	Diphenylmethyl	-SO_2CH_2-			CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
349	iso-Butyryl	1-(1-Phenyl)cyclopentyl	-NHCOCH$_2$-			CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
350	H	Diphenylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	2HCl	R	Amorphous
351	H	Diphenylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	2HCl	S	Amorphous
352	H	Diphenylmethyl	-SOCH$_2$-		S	CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
353	H	Cyclopenyl(p h e n yl)methyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
354	H	1-(1-Phenyl)cyclopentyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	2HCl	S	Amorphous
355	H	Cyclopentyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	2HCl	S	Amorphous

356	H	n-Propyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
357	H	2-Chlorobenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	2HCl	S	Amorphous
358	H	1-Phenethyl(SorR)	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	2HCl	S	Amorphous
359	H	1-Phenethyl(SorR)	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	2HCl	S	Amorphous
360	Ethoxycarbonylmethyl	Diphenylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	2HCl	S	Amorphous
361	Diphenylmethylcarbamoyl	Diphenylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
362	Difluoroacetyl	1-Phenylcyclopentyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
363	Chloroacetyl	Diphenylmethyl	-NHCOCH$_2$-			CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
364	Carbamoyl	Diphenylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
365	Carbamoyl	Diphenylmethyl	-NHCOCH$_2$-			CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
366	Benzyl	Phenyl	$CONH_2$	H		CH_3	O	NH	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
367	Acetyl	Diphenylmethyl	-SOCH$_2$-		S	CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
368	Acetyl	Diphenylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
369	Acetyl	Diphenylmethyl	-SO$_2$CH$_2$-			CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
370	Acetyl	Diphenylmethyl	-NHCOCH$_2$-			CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
371	Acetyl	Dipnehylamino	-NHCOCH$_2$-			CH_3	NH	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
372	Acetyl	2-Chlorobenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
373	Acetyl	Phenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous

374	Acetyl	n-Propyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
375	Acetyl	Benzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
376	Acetyl	Cyclopentyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
377	4-Hydroxy-3,5-Dimethoybenzoyl	(S)-1-Indanyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
378	4-Cyanobenzyl	Phenyl	CONH$_2$	H		CH_3	O	NH	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
379	4,4,4-Trifluorobutyryl	Diphenylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
380	4,4,4-Trifluorobutyryl	Diphenylmethyl	-NHCOCH$_2$-			CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
381	3,5-Dimethoxybenzyl	Benzyl	CONH$_2$	H		CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
382	3,5-Dimethoxybenzyl	Benzyl	-SOCH$_2$-		S	CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
383	3,5-Dimethoxybenzoyl	(S)-1-Indanyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
384	3,5-Bis(trifluromethyl)benzyl	Benzyl	-SOCH$_2$-		S	CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
385	3,5-Bis(trifluromethyl)benzoyl	Benzyl	CONH$_2$	H		CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
386	3,4-Dimethoxybenzoyl	(S)-1-Indanyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
387	3,4,5-Trimethoxybenzyl	1-Naphthyl	CONH$_2$	H		CH_3	O	NH	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
388	3,4,5-Trimethoxybenzyl	Diphenylmethyl	-SOCH$_2$-		S	CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
389	3,4,5-Trimethoxybenzyl	Phenyl	CONH$_2$	H		CH_3	O	NH	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
390	3,4,5-Trimethoxybenzyl	n-Propyl	CONH$_2$	H		CH_3	O	NH	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
391	3,4,5-Trimethoxybenzyl	iso-Propyl	CONH$_2$	H		CH_3	O	NH	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
392	3,4,5-Trimethoxybenzyl	Cyclohexyl	CONH$_2$	H		CH_3	O	NH	3-Cl	4-Cl	1	1	Free	racemic	Amorphou

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393	3,4,5-Trimethoxybenzyl	Benzyl	$CONH_2$	H		CH_3	O	NH	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
394	3,4,5-Trimethoxybenzyl	Cyclopentyl	$CONH_2$	H		CH_3	O	NH	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
395	3,4,5-Trimethoxybenzyl	3,4,5-Trimethoxyphenyl	$CONH_2$	H		CH_3	O	NH	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
396	3,4,5-Trimethoxybenzyl	4-Trifluoromethylphenyl	$CONH_2$	H		CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
397	3,4,5-Trimethoxybenzyl	Benzyl	$-SOCH_2-$		S	CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
398	3,4,5-Trimethoxybenzyl	Cyclopentyl	$-SOCH_2-$		S	CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
399	3,4,5-Trimethoxybenzyl	2-Chlorobenzyl	$-SOCH_2-$		S	CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
400	3,4,5-Trimethoxybenzyl	Cyclopentyl	$-SOCH_2-$		S	CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
401	3,4,5-Trimethoxybenzyl	Benzyl	$CONH_2$	H		CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
402	3,4,5-Trimethoxybenzyl	Cyclopentyl	$-SOCH_2-$		S	CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
403	3,4,5-Trimethoxybenzyl	n-Propyl	$-SOCH_2-$		S	CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
404	3,4,5-Trimethoxybenzyl	Phenyl	$-SOCH_2-$		S	CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
405	3,4,5-Trimethoxybenzyl	2-Phenethyl	$-SOCH_2-$		S	CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
406	3,4,5-Trimethoxybenzoyl	Diphenylmethyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
407	3,4,5-Trimethoxybenzoyl	9H-Fluoren-9-yl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
408	3,4,5-Trimethoxybenzoyl	Diphenylmethyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
409	3,4,5-Trimethoxybenzoyl	Diphenylmethyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
410	3,4,5-Trimethoxybenzoyl	1-Naphthylmethyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
411	3,4,5-Trimethoxybenzoyl	9H-Fluoren-9-yl	$-SOCH_2-$		S	CH_3	NCH	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphou

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412	3,4,5-Trimethoxybenzoyl	1,2,3,4-Tetrahydronaphthalen-1-yl	-SOCH$_2$-		S	CH_3	NCH 3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
413	3,4,5-Trimethoxybenzoyl	2-Tetrahydronaphthyl	-SOCH$_2$-		S	CH_3	NCH 3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
414	3,4,5-Trimethoxybenzoyl	(R)-1-Indanyl	-SOCH$_2$-		S	CH_3	NCH 3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
415	3,4,5-Trimethoxybenzoyl	(S)-1-Indanyl	-SOCH$_2$-		S	CH_3	NCH 3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
416	3,4,5-Trimethoxybenzoyl	Cyclopentyl(phenyl)methyl	-SOCH$_2$-		S	CH_3	NCH 3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
417	3,4,5-Trimethoxybenzoyl	1-(1-Phenyl)cyclopentyl	-SOCH$_2$-		S	CH_3	NCH 3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
418	3,4,5-Trimethoxybenzoyl	Bis(4-chlorophenyl)methyl	-SOCH$_2$-		S	CH_3	NCH 3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
419	3,4,5-Trimethoxybenzoyl	9H-Xanthen-9-yl	-SOCH$_2$-		S	CH_3	NCH 3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
420	3,4,5-Trimethoxybenzoyl	1,1-Diphenylethyl	-SOCH$_2$-		S	CH_3	NCH 3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
421	3,4,5-Trimethoxybenzoyl	4-Chlorophenyl(phenyl)methyl	-SOCH$_2$-		S	CH_3	NCH 3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
422	3,4,5-Trimethoxybenzoyl	Cyclohexyl(phenyl)methyl	-SOCH$_2$-		S	CH_3	NCH 3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
423	3,4,5-Trimethoxybenzoyl	Diphenylmethyl	-SOCH$_2$-		R	CH_3	NCH 3	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
424	3,4,5-Trimethoxybenzoyl	Diphenylmethyl	-NHCOCH$_2$-			CH_3	NCH 3	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
425	3,4,5-Trimethoxybenzoyl	Diphenylmethyl	-SOCH$_2$-		R	CH_3	NCH 3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
426	3,4,5-Trimethoxybenzoyl	Diphenylmethyl	-NHCOCH$_2$-			CH_3	NCH 3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
427	3,4,5-Trimethoxybenzoyl	Diphenylmethyl	-SCH2-			CH_3	NCH 3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
428	3,4,5-Trimethoxybenzoyl	1-Naphthylmethyl	-SOCH$_2$-		S	CH_3	NCH 3	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous

429	3,4,5-Trimethoxybenzoyl	2-Indanyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
430	3,4,5-Trimethoxybenzoyl	(R)-1-Indanyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
431	3,4,5-Trimethoxybenzoyl	(S)-1-Indanyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
432	3,4,5-Trimethoxybenzoyl	Bis(4-methoxyphenyl)methyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
433	3,4,5-Trimethoxybenzoyl	1-(1-Phenyl)cyclopentyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
434	3,4,5-Trimethoxybenzoyl	(4-Dimethylaminophenyl)(phenyl)methyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
435	3,4,5-Trimethoxybenzoyl	Diphenylmethyl	-SO$_2$CH$_2$-			CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
436	3,4,5-Trimethoxybenzoyl	(S)-1-Indanyl	-SO$_2$CH$_2$-			CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
437	3,4,5-Trimethoxybenzoyl	(S)-1-Indanyl	-SO$_2$CH$_2$-			CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
438	3,4,5-Trimethoxybenzoyl	(S)-1-Indanyl	-NHCOCH$_2$-			CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
439	3,4,5-Trimethoxybenzoyl	(S)-1-Indanyl	-SOCH$_2$-		R	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
440	3,4,5-Trimethoxybenzoyl	(S)-1-Indanyl	-NHCOCH$_2$-			CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
441	3,4,5-Trimethoxybenzoyl	(S)-1-Indanyl	-SCH2-			CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
442	3,4,5-Trimethoxybenzoyl	Benzyl	CONH$_2$	H		CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
443	3,4,5-Trimethoxybenzoyl	Phenyl	CONH$_2$	H		CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
444	3,4,5-Trimethoxybenzoyl	Cyclohexyl	CONH$_2$	H		CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
445	3,4,5-Trimethoxybenzoyl	Cyclopentyl	CONH$_2$	H		CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	Free	racemic	Amorphous

446	3,4,5-Trimethoxybenzoyl	3,4,5-Trimethoxyphenyl	$CONH_2$	H		CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
447	3,4,5-Trimethoxybenzoyl	3,4-Dichlorophenyl	$CONH_2$	H		CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
448	3,4,5-Trimethoxybenzoyl	3,4-Dichlorophenyl	$CONH_2$	H		CH_3	O	NH	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
449	3,4,5-Trimethoxybenzoyl	n-Propyl	$CONH_2$	H		CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
450	3,4,5-Trimethoxybenzoyl	Cyclopentyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
451	3,4,5-Trimethoxybenzoyl	Benzyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
452	3,4,5-Trimethoxybenzoyl	n-Propyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
453	3,4,5-Trimethoxybenzoyl	iso-Propyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
454	3,4,5-Trimethoxybenzoyl	tert-Butyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
455	3,4,5-Trimethoxybenzoyl	n-Octyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
456	3,4,5-Trimethoxybenzoyl	Cyclohexyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
457	3,4,5-Trimethoxybenzoyl	Phenyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
458	3,4,5-Trimethoxybenzoyl	4-Trifluoromethoxyphenyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
459	3,4,5-Trimethoxybenzoyl	Benzoyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
460	3,4,5-Trimethoxybenzoyl	4-Bromobenzyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
461	3,4,5-Trimethoxybenzoyl	4-Fluorobenzyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
462	3,4,5-Trimethoxybenzoyl	4-Methylbenzyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
463	3,4,5-Trimethoxybenzoyl	4-Methoxybenzyl	$-SOCH_2-$		S	CH_3	NCH	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphou

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464	3,4,5-Trimethoxybenzoyl	2-Fluorobenzyl	-$SOCH_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
465	3,4,5-Trimethoxybenzoyl	2-Methylbenzyl	-$SOCH_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
466	3,4,5-Trimethoxybenzoyl	3-Methylbenzyl	-$SOCH_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
467	3,4,5-Trimethoxybenzoyl	2,4-Difluorophenyl	-$SOCH_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
468	3,4,5-Trimethoxybenzoyl	3,4-Dichlorobenzyl	-$SOCH_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
469	3,4,5-Trimethoxybenzoyl	2-Phenylethyl	-$SOCH_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
470	3,4,5-Trimethoxybenzoyl	Allyl	-$SOCH_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
471	3,4,5-Trimethoxybenzoyl	Chloromethylcarbonyl	-$SOCH_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
472	3,4,5-Trimethoxybenzoyl	4-Chlorophenyl	-$SOCH_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
473	3,4,5-Trimethoxybenzoyl	2-Chlorobenzyl	-$SOCH_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
474	3,4,5-Trimethoxybenzoyl	3-Fluorobenzyl	-$SOCH_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
475	3,4,5-Trimethoxybenzoyl	2,4-Difluorophenyl	-$SOCH_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
476	3,4,5-Trimethoxybenzoyl	2,5-Difluorobenzyl	-$SOCH_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
477	3,4,5-Trimethoxybenzoyl	2,6-Difluorobenzyl	-$SOCH_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
478	3,4,5-Trimethoxybenzoyl	3,4-Difluorobenzyl	-$SOCH_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
479	3,4,5-Trimethoxybenzoyl	3,5-Difluorobenzyl	-$SOCH_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
480	3,4,5-Trimethoxybenzoyl	Cyclohexylmethyl	-$SOCH_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous

481	3,4,5-Trimethoxybenzoyl	3-Pyridylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
482	3,4,5-Trimethoxybenzoyl	4-Trifluoromethoxybenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
483	3,4,5-Trimethoxybenzoyl	2-Trifluoromethylbenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
484	3,4,5-Trimethoxybenzoyl	3-Trifluorobenzyl	-NHCOCH$_2$-			CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
485	3,4,5-Trimethoxybenzoyl	4-Trifluoromethylbenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
486	3,4,5-Trimethoxybenzoyl	2,3-Dimethoxybenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
487	3,4,5-Trimethoxybenzoyl	2,4-Dimethoxybenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
488	3,4,5-Trimethoxybenzoyl	3,4-Dimethoxybenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
489	3,4,5-Trimethoxybenzoyl	3,5-Dimethoxybenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
490	3,4,5-Trimethoxybenzoyl	2-Chlorobenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	H	4-F	1	1	HCl	racemic	Amorphous
491	3,4,5-Trimethoxybenzoyl	2-Chlorobenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
492	3,4,5-Trimethoxybenzoyl	Benzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
493	3,4,5-Trimethoxybenzoyl	2-Methylbenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
494	3,4,5-Trimethoxybenzoyl	3-Fluorobenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
495	3,4,5-Trimethoxybenzoyl	3,5-Difluorobenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
496	3,4,5-Trimethoxybenzoyl	2-Trifluoromethylbenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
497	3,4,5-Trimethoxybenzoyl	3-Trifluorobenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous

498	3,4,5-Trimethoxybenzoyl	Cyclohexylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
499	3,4,5-Trimethoxybenzoyl	2-Chlorobenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
500	3,4,5-Trimethoxybenzoyl	2-Methylbenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
501	3,4,5-Trimethoxybenzoyl	2-Chlorobenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	H	4-Cl	1	1	HCl	racemic	Amorphous
502	3,4,5-Trimethoxybenzoyl	Bis(trifluoromethyl)phenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
503	3,4,5-Trimethoxybenzoyl	Adamantyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
504	3,4,5-Trimethoxybenzoyl	1-Phenethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
505	3,4,5-Trimethoxybenzoyl	Adamantylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
506	3,4,5-Trimethoxybenzoyl	n-Propyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
507	3,4,5-Trimethoxybenzoyl	Ethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
508	3,4,5-Trimethoxybenzoyl	2-Fluorobenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
509	3,4,5-Trimethoxybenzoyl	2-Fluorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
510	3,4,5-Trimethoxybenzoyl	2-Trifluoromethylbenzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
511	3,4,5-Trimethoxybenzoyl	Cyclohexylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
512	3,4,5-Trimethoxybenzoyl	Benzyl	CONH$_2$	H		CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	R	Amorphous
513	3,3,3-Trifluoropropionyl	Diphenylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
514	3,3,3-Trifluoropropionyl	Diphenylmethyl	-NHCOCH$_2$-			CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous

515	3,3,3-Trifluoropropionyl	Diphenylmethyl	NHAc	H		CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl		Amorphous
516	3,3,3-Trifluoropropionyl	Diphenylmethyl	$-C(OH)CH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
517	3,3,3-Trifluoropropionyl	Diphenylmethyl	$-SO_2CH_2-$			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
518	3,3,3-Trifluoropropionyl	9H-Fluoren-9-yl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
519	3,3,3-Trifluoropropionyl	1-(1-Phenyl)cyclopentyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
520	3,3,3-Trifluoropropionyl	2-Chlorobenzyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
521	2-Difluoroacetyl	Diphenylmethyl	$-NHCOCH_2-$			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
522	2-Difluoroacetyl	Diphenylmethyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
523	2-Chloro-2,2-difluoroacetyl	Diphenylmethyl	$-NHCOCH_2-$			CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
524	2-Chloro-2,2-difluoroacetyl	9H-Fluoren-9-yl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
525	2-Chloro-2,2-difluoroacetyl	Cyclopentyl(phenyl)methyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
526	2-Chloro-2,2-difluoroacetyl	9H-Xanthen-9-yl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
527	2-Chloro-2,2-difluoroacetyl	Benzyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
528	2-Chloro-2,2-difluoroacetyl	2-Chlorobenzyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
529	2-Chloro-2,2-difluoroacetyl	1-(1-Phenyl)cyclopentyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
530	2-Aminoacetyl	Diphenylmethyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	2HCl	S	Amorphous
531	(2-Chlorophenylcarbamoyl)formyl	Diphenylmethyl	$-SOCH_2-$		S	CH_3	NCH_3	NH	3-Cl	4-Cl	1	1	2HCl	S	Amorphous

532	3,5-Bis(trifluromethyl)benzyl	Phenyl	$CONH_2$	H		CH_3	O	CO	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
533	3,4,5-Trimethoxybenzyl	Methyl	$CONH_2$	H		CH_3	O	CO	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
534	3,4,5-Trimethoxybenzoyl	N,N-Diphenylamino	$-SOCH_2-$		S	CH_3	NCH_3	CO	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
535	3,4,5-Trimethoxybenzoyl	Phenyl	$CONH_2$	H		CH_3	NCH_3	CO	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
536	3,4,5-Trimethoxybenzoyl	N-Methyl-N-phenylamino	$-SOCH_2-$		S	CH_3	NCH_3	CO	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
537	3,4,5-Trimethoxybenzoyl	1-Piperidyl	$-SOCH_2-$		S	CH_3	NCH_3	CO	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
538	3,4,5-Trimethoxybenzoyl	4-Morpholinyl	$-SOCH_2-$		S	CH_3	NCH_3	CO	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
539	3,4,5-Trimethoxybenzoyl	N-Methyl-N-phenylamino	$-SOCH_2-$		S	CH_3	NCH_3	CO	3-Cl	4-Cl	1	1	HCl	S	Amorphous
540	3,4,5-Trimethoxybenzoyl	N-Cyclohexyl-N-methylamino	$-SOCH_2-$		S	CH_3	NCH_3	CO	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
541	3,4,5-Trimethoxybenzoyl	N-Methyl-N-phenylamino	$-SOCH_2-$		S	CH_3	NCH_3	CO	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
542	3,4,5-Trimethoxybenzoyl	N-Methyl-N-(2-tolyl)amino	$-SOCH_2-$		S	CH_3	NCH_3	CO	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
543	3,4,5-Trimethoxybenzoyl	N-Methyl-N-(2-tolyl)amino	$-SOCH_2-$		S	CH_3	NCH_3	CO	3-Cl	4-Cl	1	1	HCl	R	Amorphous
544	3,4,5-Trimethoxybenzoyl	2-Tetrahydroqunoliyl	$-SOCH_2-$		S	CH_3	NCH_3	CO	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
545	3,4,5-Trimethoxybenzoyl	N-Methyl-N-2-chlorophenylamino	$-SOCH_2-$		S	CH_3	NCH_3	CO	3-Cl	4-Cl	1	1	HCl	racemic	Amorphous
546	3,3,3-Trifluoropropionyl	Diphenylamino	$-SOCH_2-$		S	CH_3	NCH_3	CO	3-Cl	4-Cl	1	1	HCl	S	Amorphous
547	3,3,3-Trifluoropropionyl	1-Indoliyl	$-SOCH_2-$		S	CH_3	NCH_3	CO	3-Cl	4-Cl	1	1	HCl	S	Amorphous
548	3,3,3-Trifluoropropionyl	2-Tetrahydroqunoliyl	$-SOCH_2-$		S	CH_3	NCH_3	CO	3-Cl	4-Cl	1	1	HCl	S	Amorphous
549	Methyl	3,4,5-Trimethoxyphenyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	2	1	Free	racemic	Amorphous

550	4-Cyanobenzyl	3,4,5-Trimethoxyphenyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
551	3,4,5-Trimethoxybenzyl	Methyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	2	0	Free	racemic	Amorphous
552	3,4,5-Trimethoxybenzyl	Methyl	$-SOCH_2-$		S	CH_3	O	Single bond	3-Cl	4-Cl	2	0	Free	racemic	Amorphous
553	3,4,5-Trimethoxybenzyl	Methyl	$-SOCH_2-$		S	CH_3	O	Single bond	3-Cl	4-Cl	2	0	Free	S	Amorphous
554	3,4,5-Trimethoxybenzyl	Methyl	$-SOCH_2-$		S	CH_3	O	Single bond	3-Cl	4-Cl	2	0	Free	R or S	Amorphous
555	3,4,5-Trimethoxybenzyl	H	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	2	0	Free	racemic	Amorphous
556	3,4,5-Trimethoxybenzyl	n-Propyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
557	3,4,5-Trimethoxybenzyl	Benzyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
558	3,4,5-Trimethoxybenzyl	2,2-Dimethylpropyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
559	3,4,5-Trimethoxybenzyl	Methyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
560	3,4,5-Trimethoxybenzyl	3,4,5-Trimethoxyphenyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
561	3,4,5-Trimethoxybenzyl	3,4,5-Trimethoxybenzyl	$CONH_2$	H		CH_3	O	Single bond	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
562	3,4,5-Trimethoxybenzoyl	Methyl	$CONH_2$	H		CH_3	NCH_3	Single bond	3-Cl	4-Cl	2	0	Free	racemic	Amorphous
563	3,4,5-Trimethoxybenzoyl	H	$CONH_2$	H		CH_3	NCH_3	Single bond	3-Cl	4-Cl	2	0	Free	racemic	Amorphous
564	3,4,5-Trimethoxybenzoyl	2,2-Dimethylpropyl	$CONH_2$	H		CH_3	NCH_3	Single bond	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
565	3,4,5-Trimethoxybenzoyl	Benzyl	$CONH_2$	H		CH_3	NCH_3	Single bond	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
566	3,4,5-Trimethoxybenzyl	Ethyl	$CONH_2$	H		CH_3	O	Ester bond	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
567	3,4,5-Trimethoxybenzyl	Cyclopentyl	$-SOCH_2-$		S	CH_3	O	Ester bond	3-Cl	4-Cl	2	1	HCl	racemic	Amorphous
568	Methyl	Phenyl	$CONH_2$	H		CH_3	O	NH	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
569	iso-Butyryl	Diphenylmethyl	$-NHCOCH_2-$			CH_3	NCH	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphou

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570	Benzyl	Phenyl	$CONH_2$	H		CH_3	O	NH	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
571	3,4,5-Trimethoxybenzoyl	Benzyl	$CONH_2$	H		CH_3	NCH 3	NH	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
572	3,4,5-Trimethoxybenzoyl	Phenyl	$CONH_2$	H		CH_3	NCH 3	NH	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
573	3,4,5-Trimethoxybenzoyl	Cyclohexyl	$CONH_2$	H		CH_3	NCH 3	NH	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
574	3,4,5-Trimethoxybenzoyl	Benzyl	$CONH_2$	H		CH_3	NCH 3	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
575	3,4,5-Trimethoxybenzoyl	Benzyl	$CONH_2$	H		CH_3	NCH 3	NH	3-Cl	4-Cl	2	1	HCl	R	Amorphous
576	3,4,5-Trimethoxybenzoyl	Benzyl	$-SOCH_2-$		S	CH_3	NCH 3	NH	3-Cl	4-Cl	2	1	HCl	R	Amorphous
577	3,4,5-Trimethoxybenzoyl	Benzyl	$-SOCH_2-$		S	CH_3	NCH 3	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
579	3,5-Bis(trifluromethyl)benzoyl	Phenyl	$CONH_2$	H		CH_3	NCH 3	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
580	3,4,5-Trimethoxybenzyl	tert-Butyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
581	3,4,5-Trimethoxybenzyl	Benzyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
582	3,4,5-Trimethoxybenzyl	Phenyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	2	1	HCl	racemic	Amorphous
583	3,4,5-Trimethoxybenzyl	Phenyl	$CONH_2$	H		CH_3	O	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
584	3,4,5-Trimethoxybenzyl	Phenyl	$-SOCH_2-$		S	CH_3	O	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
585	3,4,5-Trimethoxybenzyl	Phenyl	$-SOCH_2-$		S	CH_3	O	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
586	3,4,5-Trimethoxybenzoyl	tert-Butyl	$CONH_2$	H		CH_3	NCH 3	O	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
587	3,4,5-Trimethoxybenzoyl	Phenyl	$CONH_2$	H		CH_3	NCH 3	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
588	3,4,5-Trimethoxybenzoyl	Phenyl	$CONH_2$	H		CH_3	NCH	O	3-Cl	4-Cl	2	1	HCl	R	Amorphous

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590	3,3,3-Trifluoropropionyl	Benzyl	-SOCH2-		S	CH3	NCH3	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
592	3,3,3-Trifluoropropionyl	2-Phenethyl	-SOCH2-		S	CH3	NCH3	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
593	4-Cyanobenzyl	Phenyl	CONH2	H		CH3	O	NH	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
594	3,5-Bis(trifluromethyl)benzyl	Benzyl	CONH2	H		CH3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
595	3,5-Bis(trifluromethyl)benzyl	Benzyl	-SOCH2-		S	CH3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
596	3,4,5-Trimethoxybenzyl	Methyl	CONH2	H		CH3	O	NH	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
597	3,4,5-Trimethoxybenzyl	iso-Propyl	CONH2	H		CH3	O	NH	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
598	3,4,5-Trimethoxybenzyl	1-Naphthyl	CONH2	H		CH3	O	NH	3-Cl	4-Cl	2	1	Free	racemic	Amorphous
600	3,4,5-Trimethoxybenzyl	n-Propyl	CONH2	H		CH3	O	NH	3-Cl	4-Cl	2	1	HCl	racemic	Amorphous
601	3,4,5-Trimethoxybenzyl	n-Octyl	-SOCH2-		S	CH3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
602	3,4,5-Trimethoxybenzyl	Cyclopentyl	CONH2	H		CH3	O	NH	3-Cl	4-Cl	2	1	HCl	racemic	Amorphous
603	3,4,5-Trimethoxybenzyl	Phenyl	-SOCH2-		S	CH3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
604	3,4,5-Trimethoxybenzyl	Benzyl	CONH2	H		CH3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
605	3,4,5-Trimethoxybenzyl	Benzyl	-SOCH2-		S	CH3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
606	3,4,5-Trimethoxybenzyl	Benzyl	CONH2	H		CH3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
607	3,4,5-Trimethoxybenzyl	Benzyl	-SOCH2-		S	CH3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
608	3,4,5-Trimethoxybenzyl	Cyclopentyl	-SOCH2-		S	CH3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
609	3,4,5-Trimethoxybenzyl	n-Propyl	-SOCH2-		S	CH3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
610	3,4,5-Trimethoxybenzyl	Phenyl	-SOCH2-		S	CH3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous

611	3,4,5-Trimethoxybenzyl	2-Phenethyl	-SOCH$_2$-		S	CH_3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
612	3,4,5-Trimethoxybenzyl	Benzyl	NHAc	H		CH_3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
613	3,4,5-Trimethoxybenzyl	Benzyl	CH_2OCH_2Ph	H		CH_3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
614	3,4,5-Trimethoxybenzyl	Cyclohexyl	-SOCH$_2$-		S	CH_3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
619	3,4,5-Trimethoxybenzyl	iso-Propyl	-SOCH$_2$-		S	CH_3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
620	3,4,5-Trimethoxybenzyl	tert-Butyl	-SOCH$_2$-		S	CH_3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
622	3,4,5-Trimethoxybenzyl	4-Trifluoromethoxyphenyl	-SOCH$_2$-		S	CH_3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
623	3,4,5-Trimethoxybenzyl	3,5-Bis(trifluromethyl)phenyl	-SOCH$_2$-		S	CH_3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
624	3,4,5-Trimethoxybenzyl	Benzyl	-NHCOCH$_2$-			CH_3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
625	3,4,5-Trimethoxybenzyl	Benzyl	-OCH$_2$-			CH_3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
626	3,4,5-Trimethoxybenzyl	Benzyl	-OCO-			CH_3	O	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
627	3,3,3-Trifluoropropionyl	4-Methylbenzyl	-SOCH$_2$-		S	CH_3	NCH_3	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
628	3,3,3-Trifluoropropionyl	4-Chlorobenzyl	-SOCH$_2$-		S	CH_3	NCH_3	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
629	3,3,3-Trifluoropropionyl	Cyclopentylmethyl	-SOCH$_2$-		S	CH_3	NCH_3	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
630	3,3,3-Trifluoropropionyl	n-Propyl	-SOCH$_2$-		S	CH_3	NCH_3	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
631	3,3,3-Trifluoropropionyl	n-Hexyl	-SOCH$_2$-		S	CH_3	NCH_3	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
632	3,3,3-Trifluoropropionyl	iso-Butyl	-SOCH$_2$-		S	CH_3	NCH_3	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
635	3,3,3-Trifluoropropionyl	tert-Butyl	-SOCH$_2$-		S	CH_3	NCH_3	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
641	3,3,3-Trifluoropropionyl	4-Trifluoromethylphenyl	-SOCH$_2$-		S	CH_3	NCH_3	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous

643	3,3,3-Trifluoropropionyl	Phenoxymethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	2	1	HCl	S	Amorphous
644	Trifluoroacetyl	Benzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
645	3,3,3-Trifluoropropionyl	Benzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	2	1	HCl	S	Amorphous
646	3,3,3-Trifluoropropionyl	2-Phenethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	2	1	HCl	S	Amorphous
647	3,3,3-Trifluoropropionyl	2,2-Diphenylethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	2	1	HCl	S	Amorphous
648	3,3,3-Trifluoropropionyl	Phenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
649	3,3,3-Trifluoropropionyl	Benzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
650	3,3,3-Trifluoropropionyl	Diphenylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	2	1	HCl	S	Amorphous
651	3,3,3-Trifluoropropionyl	Diphenylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	2	1	HCl	S	Amorphous
656	Trifluoroacetyl	Benzyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
657	Trifluoroacetyl	Benzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
658	Trifluoroacetyl	2-Phenethyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
659	Trifluoroacetyl	Phenyl	-SO$_2$CH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
660	Trifluoroacetyl	2-Trifluoromethylphenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
661	Trifluoroacetyl	3-Fluorophenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	2HCl	S	Amorphous
662	Trifluoroacetyl	2-Fluorophenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
663	Trifluoroacetyl	3-Fluorophenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous

664	Trifluoroacetyl	4-Fluorophenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
665	Trifluoroacetyl	2,4-Difluorophenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
666	Trifluoroacetyl	3,4-Difluorophenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
667	Trifluoroacetyl	2,6-Difluorophenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
668	Propionyl	Phenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
669	Pivaloyl	Phenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
670	Pivaloyl	Benzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
671	Pivaloyl	Phenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
672	Pivaloyl	Benzyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
673	iso-Butyryl	Benzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
674	iso-Butyryl	Phenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
675	iso-Butyryl	Benzyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
676	Acetyl	Phenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
677	Acetyl	n-Propyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
678	Acetyl	Benzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
679	Acetyl	Cyclopentyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
680	Acetyl	2,2,2-Trifluoroethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous

681	3,3,3-Trifluoropropionyl	2-Phenethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
682	3,3,3-Trifluoropropionyl	Benzyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
683	3,3,3-Trifluoropropionyl	Cyclohexyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
684	3,3,3-Trifluoropropionyl	2-Methylpropyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
685	3,3,3-Trifluoropropionyl	Phenyl	-SO$_2$CH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
686	3,3,3-Trifluoropropionyl	2,2-Dimethylpropyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
687	3,3,3-Trifluoropropionyl	4-Tolyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
688	3,3,3-Trifluoropropionyl	4-Fluorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
689	3,3,3-Trifluoropropionyl	Cyclohexylmethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
690	3,3,3-Trifluoropropionyl	3-Fluorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
691	3,3,3-Trifluoropropionyl	4-Chlorophenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
692	3,3,3-Trifluoropropionyl	4-Methoxyphenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
693	3,3,3-Trifluoropropionyl	Phenyl	-OCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
694	3,3,3-Trifluoropropionyl	Phenyl	-OCO-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
695	3,3,3-Trifluoropropionyl	Phenyl	NHAc	H		CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
696	3,3,3-Trifluoropropionyl	Phenyl	CH_2OCH_2Ph	H		CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
697	3,3,3-Trifluoropropionyl	Phenyl	$CONH_2$	H		CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous

698	3,3,3-Trifluoropropionyl	2-Fluorophenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
699	3,3,3-Trifluoropropionyl	3-Fluorophenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
700	3,3,3-Trifluoropropionyl	4-Fluorophenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
701	3,3,3-Trifluoropropionyl	4-Trifluoromethylphenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
702	3,3,3-Trifluoropropionyl	2-Trifluoromethylphenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
703	3,3,3-Trifluoropropionyl	3-Trifluoromethylphenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
704	3,3,3-Trifluoropropionyl	2,4-Difluorophenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
705	3,3,3-Trifluoropropionyl	2,6-Difluorophenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
706	3,3,3-Trifluoropropionyl	3,4-Difluorophenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
707	2-Chloro-2,2-difluoroacetyl	2-Phenethyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Single bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
708	Trifluoroacetyl	3,5-Difluorophenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
709	Trifluoroacetyl	2-Chlorophenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
710	Trifluoroacetyl	3-Methoxy-5-trifluoromethylphenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
711	Trifluoroacetyl	Phenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
712	Pivaloyl	Phenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
713	Pivaloyl	Phenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
714	iso-Butyryl	Phenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous

715	iso-Butyryl	Phenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
716	Acetyl	Phenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
717	Acetyl	Benzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
718	Acetyl	Cyclopentyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
719	Acetyl	n-Propyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
720	3,3,3-Trifluoropropionyl	Phenyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
721	3,3,3-Trifluoropropionyl	n-Propyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
722	3,3,3-Trifluoropropionyl	Cyclopentyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
723	3,3,3-Trifluoropropionyl	Benzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
724	3,3,3-Trifluoropropionyl	Phenyl	-SO$_2$CH$_2$-			CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
725	3,3,3-Trifluoropropionyl	Phenyl	-NHCOCH$_2$-			CH_3	NCH$_3$	Amide bond	3-Cl	4-Cl	1	1	HCl	S	Amorphous
726	Methyl	Phenyl	CONH$_2$	H		CH_3	O	NH	3-Cl	4-Cl	1	1	Free	racemic	Amorphous
727	Methyl	iso-Propyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	2HCl	S	Amorphous
728	Methyl	Benzyl	-SOCH$_2$-		S	CH_3	NCH$_3$	NH	3-Cl	4-Cl	1	1	2HCl	S	Amorphous
729	Methyl	Benzyl	-SOCH$_2$-		S	CH_3	O	NH	3-Cl	4-Cl	1	1	HCl	S	Amorphous
730	Trifluoroacetyl	N-Methyl-N-phenylamino	-NHCOCH$_2$-			CH_3	NCH$_3$	CO	3-Cl	4-Cl	1	1	HCl	S	Amorphous
731	Trifluoroacetyl	N-Methyl-N-phenylamino	-SOCH$_2$-		S	CH_3	NCH$_3$	CO	3-Cl	4-Cl	1	1	HCl	S	Amorphous
732	Propionyl	N-Methyl-N-phenylamino	-NHCOCH$_2$-			CH_3	NCH	CO	3-Cl	4-Cl	1	1	HCl	S	Amorphous

							3								
733	Pivaloyl	N-Methyl-N-phenylamino	-SOCH$_2$-		S	CH$_3$	NCH$_3$	CO	3-Cl	4-Cl	1	1	HCl	S	Amorphous
734	Pivaloyl	N-Methyl-N-phenylamino	-NHCOCH$_2$-			CH$_3$	NCH$_3$	CO	3-Cl	4-Cl	1	1	HCl	S	Amorphous
735	iso-Butyryl	N-Methyl-N-phenylamino	-NHCOCH$_2$-			CH$_3$	NCH$_3$	CO	3-Cl	4-Cl	1	1	HCl	S	Amorphous
736	Acetyl	N-Methyl-N-phenylamino	-SOCH$_2$-		S	CH$_3$	NCH$_3$	CO	3-Cl	4-Cl	1	1	HCl	S	Amorphous
737	Acetyl	N-Methyl-N-phenylamino	-NHCOCH$_2$-			CH$_3$	NCH$_3$	CO	3-Cl	4-Cl	1	1	HCl	S	Amorphous
738	3,3,3-Trifluoropropionyl	N-Methyl-N-phenylamino	-SO$_2$CH$_2$-			CH$_3$	NCH$_3$	CO	3-Cl	4-Cl	1	1	HCl	S	Amorphous
739	3,3,3-Trifluoropropionyl	N-Cyclohexyl-N-phenylamino	-SOCH$_2$-		S	CH$_3$	NCH$_3$	CO	3-Cl	4-Cl	1	1	HCl	S	Amorphous
740	3,3,3-Trifluoropropionyl	N-Cyclohexyl-N-methylamino	-SOCH$_2$-		S	CH$_3$	NCH$_3$	CO	3-Cl	4-Cl	1	1	HCl	S	Amorphous
741	3,3,3-Trifluoropropionyl	N-Methyl-N-phenylamino	-OCH$_2$-			CH$_3$	NCH$_3$	CO	3-Cl	4-Cl	1	1	HCl	S	Amorphous
742	3,3,3-Trifluoropropionyl	N-Methyl-N-phenylamino	NHAc	H	CH$_3$	CH$_3$	NCH$_3$	CO	3-Cl	4-Cl	1	1	HCl	S	Amorphous
743	3,3,3-Trifluoropropionyl	2,3-Dichlorophenyl	-SOCH$_2$-		CH$_3$	CH$_3$	NCH$_3$	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
745	3,3,3-Trifluoropropionyl	3,4-Dichlorophenyl	-SOCH$_2$-		CH$_3$	CH$_3$	NCH$_3$	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
746	3,3,3-Trifluoropropionyl	3,4-Difluorophenyl	-SOCH$_2$-		CH$_3$	CH$_3$	NCH$_3$	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
747	3,3,3-Trifluoropropionyl	2,3-Difluorophenyl	-SOCH$_2$-		CH$_3$	CH$_3$	NCH$_3$	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
748	3,3,3-Trifluoropropionyl	2,4-Difluorophenyl	-SOCH$_2$-		CH$_3$	CH$_3$	NCH$_3$	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
749	3,3,3-Trifluoropropionyl	2,5-Difluorophenyl	-SOCH$_2$-		CH$_3$	CH$_3$	NCH$_3$	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
750	3,3,3-Trifluoropropionyl	2,3-Dimethoxyphenyl	-SOCH$_2$-		CH$_3$	CH$_3$	NCH$_3$	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous

751	3,3,3-Trifluoropropionyl	3,4-Dimethoxyphenyl	-SOCH$_2$-		CH_3	CH_3	NCH$_3$	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
752	3,3,3-Trifluoropropionyl	3,5-Dimethoxyphenyl	-SOCH$_2$-		CH_3	CH_3	NCH$_3$	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous
753	3,3,3-Trifluoropropionyl	3,5-Difluorophenyl	-SOCH$_2$-		CH_3	CH_3	NCH$_3$	O	3-Cl	4-Cl	2	1	HCl	S	Amorphous

[0977]

Test example 1

1. NK-1 receptor-binding test

1) Preparation of human NK-1 receptor expression cells

FuGene 6 transfection reagent (Boegringer Mannheim) (3 μL) was diluted in an F-12 culture broth (97 μL), and pCR3.1 plasmid to which human NK-1 receptor cDNA had been introduced (Invitrogen) (10 μL) was added thereto. The mixture was mixed and incubated for 15 minutes (transfection reagent). CHO-K1 cells (ATCC: CCL-61) were cultured for 24 hours, and the whole reagent prepared above was added to the cultured CHO-K1 cells (2×10^{-5} cells). Subsequently, culture was performed in the presence of G418 (Stratagene), and the resistant cells were employed as cells into which human NK-1 receptor gene was introduced (hNK1-CHO).

2) Subcultivation of hNK1-CHO cells

The hNK1-CHO cells were treated with trypsin-EDTA and subcultivated in an F-12 culture broth (containing 10% fetal bovine serum, 10mM HEPES, 100 U/mL, penicillin, 100 μg/mL streptmycin, 400 μg/mL G418) in a 75-cm^2 flask (FALCON). Cells to be employed in the receptor-binding experiment were added to a 24-well plate (IWAKI) at 1×10^5 cells/well, and subcultured for 48 hours at 37°C under 95% O_2 and 5% CO_2.

3) Receptor-binding experiment

When the hNK1-CHO cells became subconfluent on the 24-well plate, an F-12 culture broth (containing 10mM HEPES and 0.1% fetal bovine serum) (450 μL), [^{3}H]-Substance P (Amersham,

final concentration 0.5 nM), and a test compound were added to the cells, and the mixture was incubated for 40 minutes at 37°C. For the measurement of non-specific binding, L703606 (Sigma) was added instead of the test compound. After completion of incubation, the mixture was washed with ice-cooled phosphate buffered saline containing 0.1% fetal bovine serum, and the cells were lysed with 1N NaOH (0.5 mL). The lysate was transfered to a plastic vial containing UltimaGold MV (5 mL), and the radioactivity was determined by means of a liquid liquid scintillation counter (Packard, 2000CA).

[0978]

2. NK-2 receptor-binding experiment

Cloned Neurokinin Receptor Subtype 2 Human (CHO cells, Biosignal Packard), [^{3}H]-SR48968 (Amersham, final concentration 0.85 nM), and a test compound were mixed with 20mM HEPES buffer, and the mixture was incubated for 50 minutes at 27°C. After completion of incubation, membrane components were collected by means of an automatic filtration apparatus (Brandel) onto a GF/C glass fiber filter (Whatman).

Before use, in order to prevent non-specific binding, the glass fiber filter had been pre-treated with 0.1% polyethylene imine solution for about 4 hours.

The filter employed to collect the membrane components was transferred to a plastic vial containing UltimaGold MV (5 mL), and measured by means of a liquid scintillation counter (Packard, 2000CA) in terms of the radioactivity.

[0979]

3. Data analysis

Percent radioactive ligand-receptor binding inhibition of each test compound was calculated by use of the following equation, and IC_{50} (nM) was determined through pseudo-Hill analysis.

[0980]

Percent inhibition (%)= [1-(C-A)/(B-A)]×100

A: Radioactivity attributed to non-specific binding

B: Radioactivity without test compound

C: Radioactivity with test compound

[0981]

Tables 2 to 4 shows the results obtained from the compounds of the present invention which exhibit particularly excellent antagonism effect to NK-1 receptor, to NK-2 receptor, and to NK-1 and NK-2 receptors, respectively.

[0982]

Table 2

Compound No.	NK-1(nM)	Compound No.	NK-1(nM)
15	0.9	633	8.3
16	3.5	634	2.0
17	1.5	636	0.9
578	9.5	637	1.7
589	0.53	638	6.0
591	6.9	639	4.0
599	0.73	640	6.0
615	0.58	642	3.7
617	0.54	652	2.7
616	2.0	653	1.6
618	1.2	654	3.0
621	0.94	655	1.3

[0983]

Table 3

Compound No.	NK-2(nM)	Compound No.	NK-2(nM)
3	1.7	29	4.0
9	7.2	30	1.2
10	4.1	31	0.75
11	8.1	32	1.0
13	2.6	33	0.65
14	0.34	34	0.96
21	8.7	35	4.6
22	0.95	36	0.85
23	1.7	37	1.8
24	2.9	38	1.9
25	0.58	39	1.0
26	0.85	40	0.73
27	6.7	41	0.84
28	2.6		

[0984]

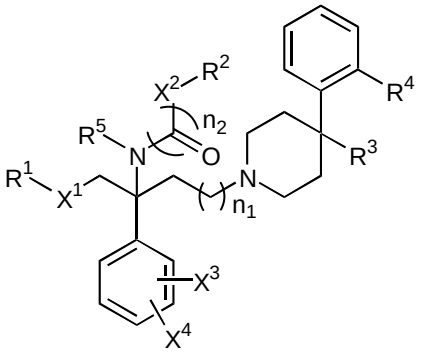
Table 4

Compound No.	NK-1(nM)	NK-2(nM)
1	1.2	1.6
2	4.3	2.1
4	3.4	1.5
5	6.3	1.9
12	11.0	6.1
42	2.1	4.0
43	7.7	2.1
44	11.0	2.4
45	4.9	2.8
46	10.1	1.8

Claims

1. A benzylamine derivative represented by formula (1):

[F1]



(1)

[wherein X^1 represents $-N(CH_3)-$, -NH-, or -O-;

X^2 represents a single bond, -NH-, an amido bond, an ester bond, -O-, -S-, or -CO-;

each of X^3 and X^4 represents a hydrogen atom or a halogen atom;

R^1 represents a hydrogen atom; a lower alkyl group; a phenyl group which may be substituted by 1 to 3 halogen atoms or cyano groups; a benzyl group which may be substituted by 1 to 3 lower alkyl groups, cyano groups, halogeno(lower alkyl) groups, or lower alkoxy groups; a benzoyl group which may be substituted by 1 to 3 lower alkyl groups, hydroxyl groups, halogeno(lower alkyl) groups, or lower alkoxy groups; a lower alkanoyl group which may be substituted by 1 to 5 halogen atoms, amino groups, or carbamoyl groups; a hydroxyl group; a carbamoyl group; a lower alkylsulfonyl group; a lower alkoxycarbonyl-lower alkyl group; a thienylcarbonyl group; a pyridylcarbonyl group; a lower alkylcarbonyl group; or a

phenoxycarbonyl group);

R^2 represents a hydrogen atom, a lower alkyl group, a lower alkenyl group, a lower alkylsulfonyl group, a C3-C7 cycloalkyl group, a C6-C14 cycloalkyl-alkyl group, a C6-C14 aryl group, a C6-C14 aryloxy group, a C6-C14 aryloxy-lower alkyl group, C6-C14 arylthio-lower alkyl group, a C7-C16 aralkyl group, a lower alkoxycarbonyl-lower alkyl group, a lower alkoxy-lower alkyl group, an amino-lower alkyl group, a C7-C16 aralkyl group substituted by a C3-C7 cycloalkyl group, a halogeno(lower alkyl)carbonyl group, an indanyl group, a 1,2,3,4-tetrahydronaphthalenyl group, a xanthenyl group, a piperidinyl group, a pyrrolidinyl group, a morpholino group, a tetrahydroisoquinolyl group, an indolyl group, a chromenyl group, an isobenzofuranyl group, a tetrahydropyranyl group, a benzothienyl group, an adamantyl group, an adamantyl(lower alkyl) group, a fluorenyl group, a fluorenyl(lower alkyl) group, a pyridyl(lower alkyl) group, or an amino group which may be substututed by a phenyl group or a lower alkyl group (wherein a ring hydrogen of these group may be substituted by 1 to 5 atoms or groups selected from among a halogen atom, a lower alkyl group, a lower alkoxy group, a nitro group, an oxo group, a halogeno(lower alkyl) group, a C6-C14 aryl group, and a lower alkylamino group;

when R^3 represents a (lower alkanoyl)amino group, an amino(lower alkanoyl) group, an amino(lower alkanoyl)amino group, a di(lower alkyl)carbamoylamino group, or a C7-C16 aralkyloxy(lower alkyl) group, R^4 represents a hydrogen atom;

or R^3 and R^4 may together form $-SOCH_2-$, $-SO_2CH_2-$, $-NHCOCH_2-$, $-CH(OH)CH_2-$, $-OCH_2-$, or $-C(=NOH)CH_2-$; R^5 represents a hydrogen atom or a lower alkyl group; n_1 is 1 or 2; and n_2 is 0 or 1] or a salt thereof.

2. A benzylamine derivative as described in claim 1 or a salt thereof, wherein R^3 and R^4 together form $-SOCH_2-$, $-SO_2CH_2-$, $-NHCOCH_2-$, $-CH(OH)CH_2-$, $-OCH_2-$, or $-C(=NOH)CH_2-$.

3. A benzylamine derivative as described in claim 1 or 2 or a salt thereof, wherein X^1 is $-N(CH_3)-$ or $-O-$.

4. A benzylamine derivative as described in any one of claims 1 to 3 or a salt thereof, wherein X^2 is a single bond, -NH-, an amido bond, an ester bond, -O-, or -CO-.

5. A benzylamine derivative as described in any one of claims 1 to 4 or a salt thereof, wherein R^2 is a C7-C16 aralkyl group, a lower alkyl group, a C6-C14 aryl group, a C3-C7 cycloalkyl group, or an amino group which may be substututed by a phenyl group or a lower alkyl group

6. A drug containing, as an active ingredient, a benzylamine derivative as recited in any one of claims 1 to 5 or a salt thereof.

7. A pharmaceutical composition containing a benzylamine derivative as recited in any one of claims 1 to 5 or a salt thereof, and a phramaceutically acceptable carrier therefor.

8. Use, for producing a drug, of a benzylamine derivative as recited in any one of claims 1 to 5 or a salt thereof.

9. A method for treating irritable bowel syndrome, pain, anxiety, obstructive bronchial diseases, headache, or vomiting, characterized in that the method comprises administerring, in an effective amount, a benzylamine derivative as recited in any one of claims 1 to 5 or a salt thereof.