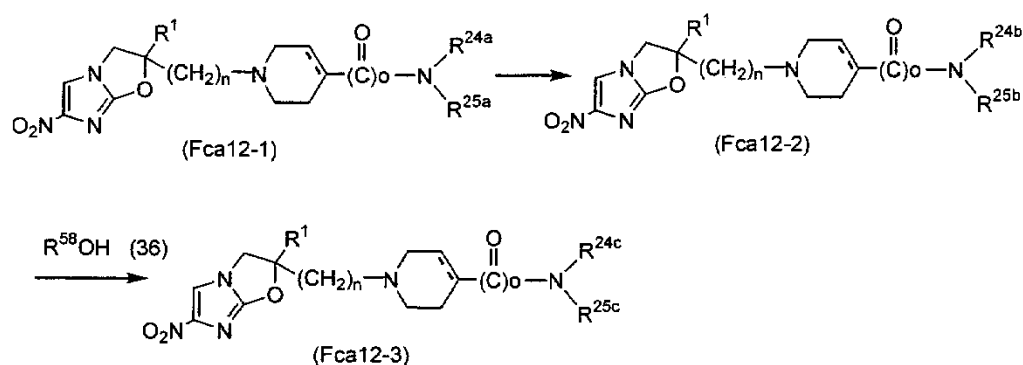


condensing agent used herein. Each of the compound
 (32) and the condensing agent is used to the compound
 (E14-2) at a molar ratio of at least equal to 1 : 1,
 and preferably between 1 : 1 and 2 : 1. This reaction
 5 is carried out generally at 0°C to 150°C, and preferably
 at 0°C to 100°C, approximately for 1 to 30 hours.

Reaction scheme 26



wherein R¹, n and o are the same as above,
 10 R^{24a} and R^{25a} form a piperazine ring through a
 nitrogen atom adjacent thereto, and the piperazine
 ring, which R^{24a} and R^{25a} form, may have, as a
 substituent, at least one substituent described as
 above, for the substituents of the 5 to 6-membered
 15 saturated heterocycle that R²⁴ and R²⁵ form through
 nitrogen atoms adjacent thereto, and the piperazine
 ring that R^{24a} and R^{25a} form has a C1-C6 alkoxy carbonyl
 group on the nitrogen atom on the piperazine ring,
 R⁵⁸ represents a phenyl group (wherein, on the
 20 phenyl ring, at least one group selected from a group

consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent),

- 5 R^{24b} and R^{25b} form a piperazine ring through a nitrogen atom adjacent thereto, and the piperazine ring, which R^{24b} and R^{25b} form, may have, as a substituent at least one substituent described as above, for the substituent of the 5 to 6-membered saturated
- 10 heterocycle that R^{24} and R^{25} form through nitrogen atoms adjacent thereto, and the piperazine ring that R^{24b} and R^{25b} form has a hydrogen atom on the nitrogen atom on the piperazine ring, and

- R^{24c} and R^{25c} form a piperazine ring through a
- 15 nitrogen atom adjacent thereto, and the piperazine ring, which R^{24c} and R^{25c} form, may have, as a substituent, at least one substituent described as above, for the substituents of the 5 to 6-membered saturated heterocycle that R^{24} and R^{25} form through
- 20 nitrogen atoms adjacent thereto, and the piperazine ring that R^{24c} and R^{25c} form has a phenyl C1-C6 alkoxy carbonyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted
- 25 C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent) on the nitrogen atom on the piperazine ring.

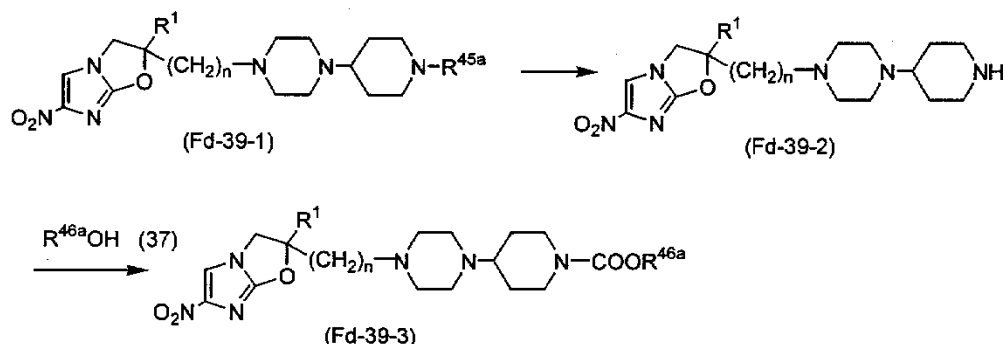
The reaction to lead the compound (Fca 12-1) into the compound (Fca 12-2) can be carried out under the same conditions for the reaction to lead the compound (E-1) into the compound (E-2) represented by

5 the above reaction scheme 16.

The reaction of the compound (Fca 12-2) with the compound (36) can be carried out under the same conditions for the reaction of the compound (E14-2) with the compound (32) represented by the above

10 reaction scheme 25.

Reaction scheme 27



wherein R^1 and n are the same as above,
 R^{45a} represents a C1-C6 alkoxy carbonyl group,

15 and

R^{46a} represents a phenyl group (wherein, on the phenyl ring, at least one group selected from a group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen

20 substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent).

The reaction to lead the compound (Fd-39-1)

into the compound (Fd-39-2) can be carried out under the same conditions for the reaction to lead the compound (E-1) into the compound (E-2) represented by the above reaction scheme 16.

5 The reaction of the compound (Fd-39-2) with the compound (37) can be carried out under the same conditions for the reaction of the compound (E14-2) with the compound (32) represented by the above reaction scheme 25.

10 The compound of the present invention includes a pharmaceutically acceptable salt. Examples of such a salt include inorganic salts such as hydrochloride, hydrobromide, nitrate, sulfate or phosphate, and organic salts such as methanesulfonate, p-
15 toluenesulfonate, acetate, citrate, tartrate, maleate, fumarate, malate or lactate.

Next, a medical preparation containing the compound of the present invention as an active ingredient will be explained.

20 The above medical preparation is obtained by preparing the compound of the present invention in the form of a common medical preparation. It is prepared using commonly used diluents or excipients such as a filler, expander, binder, wetting agent, disintegrator,
25 surfactant or lubricant.

Such a medical preparation can be selected from among various forms, depending on therapeutic purposes. Typical examples of a preparation form

include a tablet, pill, powder, liquid, suspension, emulsion, granule, capsule, suppository, and injection (liquid, suspension, etc.)

Known carriers can be widely used in making the medical preparation in a tablet form. Examples of such a carrier include excipients such as lactose, sucrose, sodium chloride, glucose, urea, starch, calcium carbonate, kaoline or crystalline cellulose; binders such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethylcellulose, shellac, methylcellulose, potassium phosphate or polyvinylpyrrolidone; disintegrators such as dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogen-carbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, monoglyceride stearate, starch or lactose; disintegration controllers such as sucrose, stearin, cacao butter or hydrogenated oil; absorption enhancers such as quaternary ammonium base or sodium lauryl sulfate, humectants such as glycerin or starch, adsorbents such as starch, lactose, kaoline, bentonite or colloidal silica, and lubricants such as purified talc, stearate, boric acid powder or polyethylene glycol.

Moreover, such tablets can be prepared as tablets with common tablet coating, such as a sugar coated tablet, gelatin coated tablet, enteric coated tablet, film coated tablet, double coated tablet, or

multi-coated tablet.

Known carriers can be widely used in making the medical preparation in a pill form. Examples of such a carrier include excipients such as glucose, lactose, starch, cacao butter, hydrogenated vegetable oil, kaoline or talc, binders such as gum arabic powder, tragacanth powder, gelatin or ethanol, and disintegrators such as laminaran or agar.

Known carriers can be widely used in making the medical preparation in a suppository form. Examples of such a carrier include polyethylene glycol, cacao butter, higher alcohol, higher alcohol esters, gelatin, and semisynthetic glyceride.

In a case where the medical preparation is prepared as an injection such as a liquid, emulsion or suspension, these solutions are preferably sterilized and prepared to be isotonic to blood. Known diluents can be widely used in making the medical preparation in such a liquid, emulsion or suspension form. Examples of such a diluent include water, ethanol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, and polyoxyethylene sorbitan fatty acid esters. Moreover, in the case of using the medical preparation as an injection, a certain amount of common salts, glucose or glycerin that is sufficient to prepare an isotonic solution may be added to the medical preparation. Otherwise, a common solubilizing agent, buffer, soothing agent or the like may also be

added to the medical preparation. Further, a coloring agent, preservative, perfume, flavor, sweetening agent or other pharmaceuticals may also be added thereto, if necessary.

5 The amount of the compound of the present invention contained in the medical preparation is not particularly limited, but it can be appropriately selected from a wide range. Generally, 1 to 70% by weight of the compound of the present invention is
10 preferably contained in the medical preparation.

 The method of administering the medical preparation of the present invention is not particularly limited. It is administered depending on various preparation forms, patients' age, sex, conditions of
15 disease, or other conditions. For example, where the medical preparation adopts a tablet, pill, liquid, suspension, emulsion, granule or capsule form, it is administered orally. In the case of an injection, it can be administered intravenously, singly or in
20 combination with a common auxiliary fluid such as glucose or amino acid. Moreover, if necessary, it can be singly administered intramuscularly, intradermally, subcutaneously or intraperitoneally. In the case of a suppository, it can be administered intrarectally.

25 The dose of the above medical preparation may be appropriately selected depending on usage, patients' age, sex, level of disease, or other conditions. Generally 0.01 to 100 mg, preferably 0.1 to 50 mg per

kg of body weight of the medical preparation is administered once or divided into several times per day.

Since the above dose is altered depending on various conditions, the dose smaller than the above range may be sufficient in some cases, or the dose greater than the above range may be required in other cases.

The compound of the present invention has a specific effect against *Mycobacterium tuberculosis* such as acid-fast bacteria (*Mycobacterium*, atypical acid-fast bacteria). The compound of the present invention has an excellent effect against multi-drug-resistant *Mycobacterium tuberculosis*. The compound of the present invention has an antimicrobial action against anaerobic bacteria.

The compound of the present invention does not only show the above described activities in vitro, but it also expresses the above activities in oral administration.

The compound of the present invention does not induce diarrhea, which is induced by known antimicrobial agents having a wide spectrum for common bacteria such as Gram-positive bacteria or Gram-negative bacteria. In addition, it has lesser adverse reactions than existing agents. Accordingly, it can be a medical preparation, which can be administered for a long time.

The compound of the present invention can be distributed well in the tissues of the lung, the main organ that is infected by acid-fast bacteria, and it has properties such as sustained efficacy or excellent
5 safety. Accordingly, a high therapeutic effect can be expected from the compound.

When compared with existing antitubercular agents, the compound of the present invention shows a strong bactericidal action even towards cytozoic
10 bacteria such as Mycobacterium tuberculosis present in a human macrophage. Accordingly, it enables a reduction of reoccurrence rate of tuberculosis and the realization of a short-term chemotherapy. It is therefore expected that the compound of the present
15 invention will also be used as a main preventive agent administered for a mixed infection by HIV and tuberculosis, which is considered to be a serious problem.

EXAMPLES

20 Formulation Example, Reference Examples, Examples and Test Examples will be described below.

Formulation Example 1

100 g of a compound of the invention, 40 g of Avicel (trade name, manufactured by Asahi Kasei
25 Corporation), 30 g of corn starch and 2 g of magnesium stearate were mixed and ground, and then formed into tablets with a pestle of sugarcoat R10 mm.

A film coating agent containing 10 g of TC-5

(trade name, hydroxypropyl methylcellulose, manufactured by Shin-Etsu Chemical Co., Ltd.), 3 g of polyethylene glycol-6000, 40 g of castor oil and an appropriate amount of ethanol was used to coat the
5 obtained tablets, producing a film-coated tablet having the composition described above.

Reference Example 1

Preparation of benzyl 4-(2-oxopropyl)piperazine-1-carboxylate

10 Potassium carbonate (1.27 g, 9.22 mmol), N-ethyl-diisopropylamine (0.80 ml, 4.61 mmol), and chloroacetone (1.22 ml, 13.83 mmol) were added to a solution of benzyl piperazine-1-carboxylate (2.03 g, 9.022 mmol) in acetonitrile (20 ml), and the mixture was heated
15 under reflux for 2 hours. The insoluble substances were removed by filtration and washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol =
20 100/1) to afford benzyl 4-(2-oxopropyl)piperazine-1-carboxylate (2.24 g, yield 88%) as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

2.15 (3H, s), 2.35 - 2.50 (4H, m), 3.21 (2H, s), 3.50 - 3.62 (4H, m), 5.13 (2H, s), 7.27 - 7.42 (5H, m).

25 Reference Example 2

Preparation of tert-butyl 4-(3-oxobutyl)piperazine-1-carboxylate

A solution of tert-butyl piperazine-1-

carboxylate (6 g, 32.3 mmol) in THF (50 ml) was gradually added dropwise to a solution of methyl vinyl ketone (2.3 g, 32.9 mmol) in THF (25 ml) while cooling in an ice-bath, and the mixture was stirred at room
5 temperature for 3 days. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to afford tert-butyl 4-(3-oxobutyl) piperazine-1-carboxylate (7.2 g,
10 yield 87%) as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.46 (9H, s), 2.17 (3H, s), 2.30 - 2.42 (4H, m), 2.53 - 2.70 (4H, m), 3.33 - 3.47 (4H, m).

Using corresponding starting materials,
15 compounds of Reference Examples 3 to 10 were prepared in the same manner as described in Reference Example 1.

Reference Example 3

1-[4-(4-trifluoromethylphenyl) piperazin-1-yl]propan-2-one

20 yield 99%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

2.18 (3H, s), 2.63 - 2.68 (4H, m), 3.27 (2H, s), 3.30 - 3.45 (4H, m), 6.92 (2H, d, $J = 8.7$ Hz), 7.48 (2H, d, $J = 8.7$ Hz).

25 Reference Example 4

1-(4-phenylpiperazin-1-yl)propan-2-one

yield 95%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

2.19 (3H, s), 2.65 - 2.70 (4H, m), 3.27 - 3.32 (6H, m),
6.97 - 7.01 (2H, m), 7.24 - 7.31 (1H, m), 7.37 - 7.43
(2H, m).

Reference Example 5

5 1-[4-(4-chlorophenyl)piperazin-1-yl]propan-2-one
yield 99%

¹H-NMR (CDCl₃) δppm:

2.17 (3H, s), 2.63 - 2.67 (4H, m), 3.18 - 3.23 (4H, m),
3.26 (2H, s), 6.80 - 6.87 (2H, m), 7.17 - 7.23 (2H, m).

10 Reference Example 6

1-[4-(4-trifluoromethoxyphenyl)piperazin-1-yl]propan-2-one

yield 100%

¹H-NMR (CDCl₃) δppm:

15 2.18 (3H, s), 2.63 - 2.68 (4H, m), 3.20 - 3.25 (4H, m),
3.26 (2H, s), 6.85 - 6.92 (2H, m), 7.09 - 7.13 (2H, m).

Reference Example 7

1-[4-(2-pyridyl)piperazin-1-yl]propan-2-one

yield 97%

20 ¹H-NMR (CDCl₃) δppm:

2.19 (3H, s), 2.58 - 2.63 (4H, m), 3.25 (2H, s), 3.57 -
3.62 (4H, m), 6.60 - 6.66 (2H, m), 7.44 - 7.51 (1H, m),
8.17 - 8.20 (1H, m).

Reference Example 8

25 1-[4-(2-pyrimidyl)piperazin-1-yl]propan-2-one
yield 88%

¹H-NMR (CDCl₃) δppm:

2.19 (3H, s), 2.53 - 2.57 (4H, m), 3.25 (2H, s), 3.86 -

3.90 (4H, m), 6.49 (1H, t, $J = 4.8$ Hz), 8.30 (2H, d, $J = 4.8$ Hz).

Reference Example 9

tert-butyl N-methyl-[1-(2-oxopropyl)piperidin-4-yl]

5 carbamate

yield 79%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.46 (9H, s), 1.57 - 1.63 (2H, m), 1.70 - 1.91 (2H, m),
2.04 - 2.18 (2H, m), 2.14 (3H, s), 2.71 - 2.74 (1H, m),
10 2.74 (3H, s), 2.90 - 2.95 (2H, m), 3.19 (2H, s).

Reference Example 10

tert-butyl 4-(2-oxopropyl)homopiperazine-1-carboxylate

yield 58%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

15 1.46 (9H, s), 1.75 - 1.93 (2H, m), 2.14 (3H, s), 2.64 -
2.76 (4H, m), 3.32 (2H, s), 3.38 - 3.58 (4H, m).

Reference Example 11

Preparation of 1-(4-trifluoromethylbenzoyl)-4-
hydroxypiperidine

20 4-(Trifluoromethyl)benzoyl chloride (1.5 ml,
9.89 mmol) was added to a solution of 4-hydroxy-
piperidine (1 g, 9.89 mmol) and triethylamine (1.7 ml,
11.9 mmol) in methylene chloride (20 ml) while cooling
in an ice-bath, and the mixture was stirred at room
25 temperature for 30 minutes. The reaction mixture was
washed with water, saturated sodium bicarbonate aqueous
solution and brine, and dried over magnesium sulfate.
After filtration, the filtrate was concentrated under

reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/acetone = 2/1) to afford 1-(4-trifluoromethylbenzoyl)-4-hydroxypiperidine (2.07 g, yield 77%) as a colorless crystalline powder.

5 ^1H -NMR (CDCl_3) δ ppm:

1.36 - 2.07 (4H, m), 3.07 - 3.70 (3H, m), 3.91 - 4.32 (2H, m), 7.51 (2H, d, $J = 8.0$ Hz), 7.68 (2H, d, $J = 8.0$ Hz).

Using a corresponding starting material, a
10 compound of Reference Example 12 was prepared in the same manner as described in Reference Example 11.

Reference Example 12

1-(4-trifluoromethoxybenzoyl)-4-hydroxypiperidine
a colorless crystalline powder, yield 100%

15 ^1H -NMR (CDCl_3) δ ppm:

1.34 - 2.07 (4H, m), 3.09 - 3.80 (3H, m), 3.91 - 4.32 (2H, m), 7.25 (2H, d, $J = 7.9$ Hz), 7.45 (2H, d, $J = 7.9$ Hz).

Reference Example 13

20 Preparation of 1-[2-(tetrahydropyran-2-yloxy)ethyl]-4-(4-trifluoromethylphenoxy)piperidine

A mixture of 4-(4-trifluoromethylphenoxy)-piperidine (1.87 g, 7.63 mmol), 2-(2-bromoethoxy)-tetrahydropyran (1.75 g, 8.4 mmol), potassium carbonate
25 (1.16 g, 8.38 mmol), sodium iodide (1.2 g, 8.01 mmol) in DMF (30 ml) was stirred at 100°C for 1 hour. The reaction mixture was allowed to return to room temperature, poured into water and extracted with ethyl

acetate twice. The extract was washed with water twice and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel

- 5 column chromatography (methylene chloride/methanol = 50/1) to afford 1-[2-(tetrahydropyran-2-yloxy)ethyl]-4-(4-trifluoromethylphenoxy)piperidine (1.69 g, yield 59%) as a colorless oil.

^1H -NMR (CDCl_3) δ ppm:

- 10 1.39 - 2.12 (10H, m), 2.36 - 2.53 (2H, m), 2.68 (2H, t, $J = 6.1$ Hz), 2.71 - 2.92 (2H, m), 3.43 - 3.63 (2H, m), 3.78 - 3.94 (2H, m), 4.31 - 4.47 (1H, m), 4.57 - 4.67 (1H, m), 6.96 (2H, d, $J = 8.7$ Hz), 7.52 (2H, d, $J = 8.7$ Hz).

15 Reference Example 14

Preparation of 2-[4-(4-trifluoromethylphenoxy)piperidin-1-yl]ethanol

- A mixture of 1-[2-(tetrahydropyran-2-yloxy)ethyl]-4-(4-trifluoromethylphenoxy)piperidine
20 (1.69 g, 4.53 mmol) prepared in Reference Example 13 and pyridinium p-toluenesulfonate (114 mg, 0.45 mmol) in ethanol (50 ml) was stirred at 60 to 70°C for 6 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced
25 pressure. To the residue, 10% sodium hydroxide aqueous solution was added, and the mixture was extracted with methylene chloride. The extract was washed with brine and dried over magnesium sulfate. After filtration,

the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford 2-[4-(4-trifluoromethylphenoxy)piperidin-1-yl]ethanol (1.19 g, yield 91%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

1.73 - 2.10 (4H, m), 2.31 - 2.47 (2H, m), 2.58 (2H, t, J = 5.5 Hz), 2.69 - 3.00 (3H, m), 3.63 (2H, t, J = 5.5 Hz), 4.33 - 4.48 (1H, m), 6.95 (2H, d, J = 8.6 Hz), 7.53 (2H, d, J = 8.6 Hz).

Reference Example 15

Preparation of 2-[2-(4-trifluoromethylphenoxy)ethoxy]-tetrahydropyran

A mixture of 4-hydroxybenzotrifluoride (2.08 g, 12.83 mmol), 2-(2-bromoethoxy)tetrahydropyran (3 g, 14.11 mmol), potassium carbonate (1.95 g, 14.11 mmol), and sodium iodide (2 g, 13.47 mmol) in DMF (15 ml) was stirred at 100°C for 3 hours. The reaction mixture was allowed to return to room temperature, poured into water, and extracted with ethyl acetate twice. The extract was washed with water twice and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/1) to afford 2-[2-(4-trifluoromethylphenoxy)ethoxy]tetrahydropyran (2.47 g, yield 66%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

1.41 - 1.90 (6H, m), 3.45 - 3.66 (1H, m), 3.76 - 3.96 (2H, m), 4.02 - 4.24 (3H, m), 4.63 - 4.76 (1H, m), 6.98 (2H, d, $J = 8.6$ Hz), 7.53 (2H, d, $J = 8.6$ Hz).

Reference Example 16

5 Preparation of 2-(4-trifluoromethylphenoxy)ethanol

Using 2-[2-(4-trifluoromethylphenoxy)ethoxy]-tetrahydropyran (2.47 g, 8.51 mmol) prepared in Reference Example 15, 2-(4-trifluoromethylphenoxy)-ethanol (1.32 g, yield 79%) as a colorless crystalline
10 powder was prepared in the same manner as described in Reference Example 14.

$^1\text{H-NMR}$ (CDCl_3) δppm :

3.88 - 4.14 (4H, m), 6.98 (2H, d, $J = 8.6$ Hz), 7.55 (2H, d, $J = 8.6$ Hz).

15 Reference Example 17

Preparation of 1-[2-(tetrahydropyran-2-yloxy)ethyl]-4-(4-trifluoromethoxyphenyl)-1,2,3,6-tetrahydropyridine

Using 4-(4-trifluoromethoxyphenyl)-1,2,3,6-tetrahydropyridine monohydrochloride (680 mg, 2.43
20 mmol) and 2-(2-bromoethoxy)tetrahydropyran (610 mg, 2.92 mmol), 1-[2-(tetrahydropyran-2-yloxy)ethyl]-4-(4-trifluoromethoxyphenyl)-1,2,3,6-tetrahydropyridine (425 mg, yield 47%) as a pale brown oil was prepared in the same manner as described in Reference Example 15.

25 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.41 - 1.92 (6H, m), 2.45 - 2.59 (2H, m), 2.67 - 2.86 (4H, m), 3.18 - 3.31 (2H, m), 3.43 - 3.65 (2H, m), 3.80 - 4.00 (2H, m), 4.55 - 4.65 (1H, m), 5.98 - 6.10 (1H,

m), 7.15 (2H, dd, $J = 2.1$ Hz, 8.8 Hz), 7.38 (2H, dd, $J = 2.1$ Hz, 8.8 Hz).

Reference Example 18

Preparation of 2-[4-(4-trifluoromethoxyphenyl)-1,2,3,6-tetrahydropyridin-1-yl]ethanol

Using 1-[2-(tetrahydropyran-2-yloxy)ethyl]-4-(4-trifluoromethoxyphenyl)-1,2,3,6-tetrahydropyridine (425 mg, 1.14 mmol) prepared in Reference Example 17, 2-[4-(4-trifluoromethoxyphenyl)-1,2,3,6-tetrahydropyridin-1-yl]ethanol (222 mg, yield 68%) as a pale brown oil was prepared in the same manner as described in Reference Example 14.

$^1\text{H-NMR}$ (CDCl_3) δppm :

2.47 - 2.59 (2H, m), 2.68 (2H, t, $J = 5.5$ Hz), 2.79 (2H, t, $J = 5.5$ Hz), 3.16 - 3.25 (2H, m), 3.70 (2H, t, $J = 5.5$ Hz), 6.00 - 6.10 (1H, m), 7.17 (2H, dd, $J = 2.1$ Hz, 6.7 Hz), 7.40 (2H, dd, $J = 2.1$ Hz, 6.7 Hz).

Reference Example 19

Preparation of 3-(4-trifluoromethylphenyl)-2-propyn-1-ol

A mixture of 4-bromobenzotrifluoride (6.5 g, 28.89 mmol), propargyl alcohol (2.35 ml, 40.45 mmol), triethylamine (5.64 ml, 40.45 mmol), triphenylphosphine (230 mg, 0.87 mmol), cuprous iodide (110 mg, 0.58 mmol), and dichlorobis (triphenylphosphine) palladium (210 mg, 0.29 mmol) in toluene (100 ml) was stirred at 100°C under a nitrogen atmosphere for 2 hours. The reaction mixture was allowed to return to room

temperature and filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford 3-(4-trifluoromethylphenyl)-2-propyn-1-ol (3.47 g, yield 60%) as a pale brown oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

4.52 (2H, d, $J = 6.2$ Hz), 7.53 (2H, d, $J = 8.7$ Hz), 7.58 (2H, d, $J = 8.7$ Hz).

10 Reference Example 20

Preparation of 2-[N-methyl-(4-trifluoromethoxyphenyl)-amino]ethanol

A mixture of N-methyl-(4-trifluoromethoxyphenyl)amine (4.83 g, 24.24 mmol), 2-(2-bromoethoxy)-tetrahydropyran (6.1 g, 29.03 mmol), and potassium carbonate (3.84 g, 27.76 mmol) in DMF (20 ml) was stirred at 100°C for 5 hours. The reaction mixture was allowed to return to room temperature, poured into water, and extracted with ethyl acetate twice. The extract was washed with water twice and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 20/1) to afford 2-[N-methyl-(4-trifluoromethoxyphenyl)-amino]ethanol (3.1 g, yield 53%) as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

2.96 (3H, s), 3.46 (2H, t, $J = 5.7$ Hz), 3.81 (2H, q, J

= 5.7 Hz), 6.74 (2H, d, $J = 8.7$ Hz), 7.08 (2H, d, $J = 8.7$ Hz).

Reference Example 21

Preparation of 8-(4-trifluoromethoxyphenyl)-1,4-dioxaspiro[4.5]decane

5 8-azaspiro[4.5]decane

A mixture of 1-bromo-4-(trifluoromethoxy)benzene (6.3 g, 26.14 mmol), 1,4-dioxaspiro[4.5]decane (3.35 ml, 26.14 mmol), palladium acetate (60 mg, 0.26 mmol), (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) (244 mg, 0.39 mmol), and sodium tert-butoxide (3.77 g, 39.23 mmol) in toluene (50 ml) was stirred at 80°C for 1 hour. The reaction mixture was allowed to return to room temperature, to which ethyl acetate (50 ml) was added, and the resulting mixture was then filtered. The filtrate was washed with water and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford 8-(4-trifluoromethoxyphenyl)-1,4-dioxaspiro[4.5]decane (6.54 g, yield 83%) as a pale yellow powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.83 (4H, t, $J = 5.8$ Hz), 3.31 (4H, t, $J = 5.8$ Hz),
25 3.99 (4H, s), 6.90 (2H, d, $J = 8.8$ Hz), 7.09 (2H, d, $J = 8.8$ Hz).

Reference Example 22

Preparation of 1-(4-trifluoromethoxyphenyl)piperidin-4-

one

A mixture of 8-(4-trifluoromethoxyphenyl)-1,4-dioxo-8-azaspiro[4.5]decane (1.23 g, 4.06 mmol) prepared in Reference Example 21, concentrated
5 hydrochloric acid (5 ml), water (10 ml), and ethanol (30 ml) was heated under reflux for 5 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, 10% sodium hydroxide aqueous solution
10 was added, and the mixture was extracted with methylene chloride. The extract was washed with water and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column
15 chromatography (n-hexane/ethyl acetate = 3/1) to afford 1-(4-trifluoromethoxyphenyl)piperidin-4-one (848 mg, yield 81%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

2.56 (4H, t, $J = 6.2$ Hz), 3.59 (4H, t, $J = 6.2$ Hz),
20 6.94 (2H, d, $J = 8.5$ Hz), 7.14 (2H, d, $J = 8.5$ Hz).

Reference Example 23

Preparation of 1-(4-trifluoromethoxyphenyl)piperidin-4-ol

Sodium borohydride (324 mg, 8.56 mmol) was
25 added to a solution of 1-(4-trifluoromethoxyphenyl)piperidin-4-one (1.11 g, 4.28 mmol) prepared in Reference Example 22 in methanol (30 ml) while cooling in an ice-bath, and the mixture was stirred for 30

minutes. To which 10% hydrochloric acid was added, and the resulting mixture was concentrated under reduced pressure. To the residue saturated sodium bicarbonate aqueous solution was added, and the mixture was
5 extracted with methylene chloride. The extract was washed with water and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-
10 hexane/ethyl acetate = 3/1) to afford 1-(4-trifluoromethoxyphenyl)piperidin-4-ol (1.08 g, yield 97%) as a white powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.59 - 1.76 (2H, m), 1.90 - 2.06 (2H, m), 2.82 - 2.98
15 (2H, m), 3.43 - 3.57 (2H, m), 3.75 - 3.91 (1H, m), 6.89 (2H, d, $J = 7.1$ Hz), 7.09 (2H, d, $J = 7.1$ Hz).

Compounds of Reference Examples 24 and 25 were prepared in the same manner as described in Example 23.

20 Reference Example 24

1-(4-trifluoromethylphenyl)piperidin-4-ol
a white powder, yield 76%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.53 - 1.71 (2H, m), 1.89 - 2.04 (2H, m), 2.91 - 3.11
25 (2H, m), 3.56 - 3.71 (2H, m), 3.80 - 4.00 (1H, m), 6.93 (2H, d, $J = 8.7$ Hz), 7.46 (2H, d, $J = 8.7$ Hz).

Reference Example 25

1-(4-methoxyphenyl)piperidin-4-ol

a white powder, yield 5%

^1H -NMR (CDCl_3) δ ppm:

1.64 - 1.79 (2H, m), 1.92 - 2.08 (2H, m), 2.74 - 2.88
(2H, m), 3.32 - 3.47 (2H, m), 3.70 - 3.85 (4H, m), 6.84
5 (2H, dd, $J = 2.4$ Hz, 6.8 Hz), 6.93 (2H, dd, $J = 2.4$ Hz,
6.8 Hz).

Reference Example 26

Preparation of 1-(4-chlorophenyl)piperidin-4-ol

A mixture of 8-(4-chlorophenyl)-1,4-dioxo-8-
10 azaspiro[4.5]decane (2.6 g, 10.25 mmol), concentrated
hydrochloric acid (12 ml), water (10 ml), and ethanol
(50 ml) was heated under reflux for 5 hours. The
reaction mixture was allowed to return to room
temperature and concentrated under reduced pressure.
15 To the residue 10% sodium hydroxide aqueous solution
was added, and the mixture was extracted with methylene
chloride. The extract was washed with water and brine,
and dried over magnesium sulfate. After filtration,
the filtrate was concentrated under reduced pressure.
20 The residue was dissolved in methanol (50 ml), to which
sodium borohydride (388 mg, 10.25 mmol) was added while
cooling in an ice-bath, and the mixture was stirred for
30 minutes. To the reaction mixture, 10% hydrochloric
acid was added, and the mixture was concentrated under
25 reduced pressure. Saturated sodium bicarbonate aqueous
solution was added to the residue, and the mixture was
extracted with methylene chloride. The extract was
washed with water and brine, and was dried over

magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 3/1) to afford 1-(4-

5 chlorophenyl)piperidin-4-ol (1.73 g, yield 80%) as a pale yellow crystalline powder.

^1H -NMR (CDCl_3) δ ppm:

1.55 - 1.74 (2H, m), 1.89 - 2.08 (2H, m), 2.79 - 3.00 (2H, m), 3.43 - 3.57 (2H, m), 3.75 - 3.92 (1H, br),
10 6.89 (2H, d, $J = 7.1$ Hz), 7.09 (2H, d, $J = 7.1$ Hz).

Using a corresponding starting material, a compound of Reference Example 27 was prepared in the same manner as described in Reference Example 26.

Reference Example 27

15 1-(4-fluorophenyl)piperidin-4-ol
a white powder, yield 66%

^1H -NMR (CDCl_3) δ ppm:

1.57 - 1.79 (2H, m), 1.92 - 2.08 (2H, m), 2.75 - 2.92 (2H, m), 3.36 - 3.50 (2H, m), 3.74 - 3.89 (1H, m), 6.77
20 - 7.00 (4H, m).

Reference Example 28

Preparation of 4-[4-(tert-butyltrimethylsiloxy)piperidin-1-yl]benzonitrile

A mixture of 4-bromobenzonitrile (2.76 g,
25 15.16 mmol), 4-(tert-butyltrimethylsiloxy)piperidine (2.9 g, 13.79 mmol), palladium acetate (62 mg, 0.28 mmol), (S)-(-)-2,2'-bis (diphenylphosphino)-1,1'-binaphthyl (BINAP) (258 mg, 0.41 mmol), and sodium

tert-butoxide (1.99 g, 20.68 mmol) in toluene (60 ml) was stirred at 80°C for 1 hour. The reaction mixture was allowed to return to room temperature, to which ethyl acetate (60 ml) was added, and the mixture was
5 filtered. The filtration was washed with water and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/methylene chloride =
10 1/1) to afford 4-[4-(tert-butyl-
butyldimethylsiloxy)piperidin-1-yl]benzonitrile (2.8 g, yield 66%) as a pale yellow crystalline powder.

¹H-NMR (CDCl₃) δppm:

0.90 (9H, s), 1.50 - 1.69 (8H, m), 1.73 - 1.90 (2H, m), 3.18 - 3.31 (2H, m), 3.50 - 3.65 (2H, m), 3.90 -
15 4.04 (1H, m), 6.85 (2H, d, J = 7.0 Hz), 7.47 (2H, d, J = 7.0 Hz).

Reference Example 29

Preparation of 4-(4-hydroxypiperidin-1-yl)benzonitrile
20 Tetra-n-butylammonium fluoride (1M) THF
solution (10.6 ml, 10.2 mmol) was added to a mixture of 4-[4-(tert-butyl-
butyldimethylsiloxy)piperidin-1-yl]benzonitrile (2.8 g, 8.85 mmol) prepared in
Reference Example 28 in THF (30 ml) while cooling in an
25 ice-bath, and the mixture was stirred at room
temperature for 16 hours. The reaction mixture was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with

ethyl acetate twice. The extract was washed with water and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel

5 column chromatography (n-hexane/ethyl acetate = 1/2) to afford 4-(4-hydroxypiperidin-1-yl)benzonitrile (1.52 g, yield 85%) as a colorless crystalline powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.50 - 1.73 (2H, m), 1.90 - 2.04 (2H, m), 3.00 - 3.20
10 (2H, m), 3.59 - 3.76 (2H, m), 3.84 - 4.04 (1H, m), 6.86
(2H, dd, $J = 2.0$ Hz, 7.1 Hz), 7.48 (2H, dd, $J = 2.0$ Hz, 7.1 Hz).

Reference Example 30

Preparation of ethyl 1-(4-trifluoromethylphenyl)-
15 piperidine-4-carboxylate

Using 4-bromobenzotrifluoride (3.15 g, 13.99 mmol) and ethyl isonipecotate (2.2 g, 13.99 mmol), ethyl 1-(4-trifluoromethylphenyl)piperidine-4-carboxylate (3.18 g, yield 74%) as a pale brown
20 crystalline powder was prepared in the same manner as described in Reference Example 21.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.27 (3H, t, $J = 7.2$ Hz), 1.71 - 2.10 (4H, m), 2.41 -
2.55 (1H, m), 2.82 - 2.98 (2H, m), 3.65 - 3.80 (2H, m),
25 4.16 (2H, q, $J = 7.2$ Hz), 6.92 (2H, d, $J = 6.9$ Hz),
7.63 (2H, d, $J = 6.9$ Hz).

Reference Example 31

Preparation of [1-(4-trifluoromethylphenyl)piperidin-4-

yl]methanol

Lithium aluminum hydride (1.58 g, 41.64 mmol) was suspended in THF (30 ml), to which a solution of ethyl 1-(4-trifluoromethylphenyl)piperidine-4-
5 carboxylate prepared in Reference Example 30 (3.18 g, 10.41 mmol) in THF (10 ml) was added dropwise therein while cooling in an ice-bath under a nitrogen atmosphere. The mixture was stirred for 30 minutes. Water and 10% sodium hydroxide aqueous solution were
10 added to the reaction mixture, which was filtered through Celite. The filtrate was extracted with ethyl acetate twice. The extract was washed with water and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced
15 pressure to afford [1-(4-trifluoromethylphenyl)-piperidin-4-yl]methanol (2.64 g, yield 98%) as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.31 - 1.47 (2H, m), 1.61 - 1.90 (3H, m), 2.74 - 2.90
20 (2H, m), 3.45 - 3.61 (2H, m), 3.83 (2H, d, $J = 12.6$ Hz), 6.92 (2H, d, $J = 8.8$ Hz), 7.46 (2H, d, $J = 8.8$ Hz).

Reference Example 32

Preparation of 1-(4-trifluoromethoxybenzyl)piperidin-4-
25 ol

Sodium triacetoxyborohydride (1.67 g, 7.89 mmol) was added to a solution of 4-(trifluoromethoxy)-benzaldehyde (1 g, 5.26 mmol) and 4-hydroxy piperidine

(798 mg, 7.89 mmol) in acetonitrile (2 ml) while cooling in an ice-bath, and the mixture was stirred for 30 minutes, and then at room temperature overnight.

The reaction mixture was poured into 7.5% sodium

5 bicarbonate aqueous solution and extracted with ethyl acetate twice. The extract was washed with water and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel
10 column chromatography (methylene chloride/methanol = 10/1) to afford 1-(4-trifluoromethoxybenzyl)piperidin-4-ol (1.21 g, yield 84%) as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.50 - 1.74 (2H, m), 1.80 - 1.98 (2H, m), 2.08 - 2.24
15 (2H, m), 2.63 - 2.84 (2H, m), 3.49 (2H, s), 3.61 - 3.80 (1H, m), 7.15 (2H, d, $J = 8.5$ Hz), 7.34 (2H, d, $J = 8.5$ Hz).

Compounds of Reference Examples 33 and 34 were prepared in the same manner as described in
20 Reference Example 32.

Reference Example 33

1-(4-chlorobenzyl) piperidin-4-ol
a white powder, yield 87%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

25 1.48 - 1.63 (2H, m), 1.76 - 1.91 (2H, m), 2.04 - 2.20 (2H, m), 2.61 - 2.76 (2H, m), 3.45 (2H, s), 3.57 - 3.72 (1H, m), 7.24 (2H, d, $J = 8.8$ Hz), 7.28 (2H, d, $J = 8.8$ Hz).

Reference Example 34

1-(4-trifluoromethylbenzyl) piperidin-4-ol

a white powder, yield 83%

¹H-NMR (CDCl₃) δppm:

- 5 1.43 - 1.67 (2H, m), 1.80 - 1.94 (2H, m), 2.06 - 2.24
(2H, m), 2.63 - 2.78 (2H, m), 3.67 (2H, s), 3.61 - 3.72
(1H, m), 7.44 (2H, d, J = 8.0 Hz), 7.57 (2H, d, J = 8.0
Hz).

Reference Example 35

- 10 Preparation of tert-butyl(4-benzylpiperazin-1-yl)carbamate

4-Benzylpiperazin-1-yl-amine (36.03 g, 188 mmol) was dissolved in methanol (260 ml) and the solution was cooled in an ice-bath, to which a solution
15 of di-tert-butyl dicarbonate (61.66 g, 283 mmol) in methanol (100 ml) was added dropwise over 20 minutes. The mixture was allowed to return to room temperature and stirred overnight. The reaction mixture was concentrated under reduced pressure, and the residue
20 was purified by silica gel column chromatography (n-hexane/acetone = 3/1). Isopropyl ether (IPE) (60 ml) and n-hexane (20 ml) were added to thus obtained solid, and the mixture was stirred and then filtered to afford primary crystals. The filtrate was concentrated under
25 reduced pressure, isopropyl ether (10 ml) and n-hexane (10 ml) were added to the residue, and the mixture was stirred and then filtered to afford secondary crystals. These crystals were combined and dried under reduced

pressure to afford tert-butyl(4-benzylpiperazin-1-yl)carbamate (42.22 g, yield 77%) as a colorless crystalline powder.

¹H-NMR (CDCl₃) δppm:

5 1.45 (9H, s), 2.55 - 2.58 (4H, m), 2.80 (4H, br), 3.51 (2H, s), 5.35 (1H, br), 7.24 - 7.31 (5H, m).

Reference Example 36

Preparation of tert-butyl piperazin-1-yl-carbamate

Tert-butyl(4-benzylpiperazin-1-yl)carbamate
10 (42.22 g, 145 mmol) prepared in Reference Example 35 was dissolved in ethanol (300 ml). To which 20% palladium hydroxide/carbon (6.0 g) was added, and the mixture was stirred at room temperature under an atmospheric pressure of hydrogen for 20 minutes, and
15 then at 50°C for 30 minutes. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. Thus obtained solid was washed with IPE, collected by filtration, and dried under reduced pressure to afford tert-butyl piperazin-1-yl-carbamate
20 (28.9 g, yield 99%) as a colorless crystalline powder.

¹H-NMR (CDCl₃) δppm:

1.46 (9H, s), 2.74 - 2.77 (4H, m), 2.95 - 2.99 (4H, m), 5.45 (1H, br).

Reference Example 37

25 Preparation of tert-butyl 4-(4-trifluoromethyl phenoxy)piperidine-1-carboxylate

Tert-butyl 4-hydroxypiperidine-1-carboxylate (2.22 g, 10.0 mmol), 4-hydroxybenzotrifluoride (1.21 g,

7.45 mmol), tri-n-butylphosphine (2.26 g, 11.2 mmol) and 1,1'-(azodicarbonyl) dipiperidine (2.82 g, 11.2 mmol) were dissolved in benzene (20 ml), and the mixture was stirred at room temperature for 2 days. To which water was added, and the mixture was extracted with ethyl acetate. The extract was dried over magnesium sulfate and thereafter filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 5/1) to afford tert-butyl 4-(4-trifluoromethylphenoxy)piperidine-1-carboxylate (1.13 g, yield 44%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.48 (9H, s), 1.65 - 1.82 (2H, m), 1.87 - 1.97 (2H, m), 3.34 - 3.44 (2H, m), 3.63 - 3.74 (2H, m), 4.47 - 4.58 (1H, m), 6.89 - 6.97 (2H, m), 7.47 - 7.55 (2H, m).

Reference Example 38

Preparation of 4-(4-trifluoromethylphenoxy)piperidine

Tert-butyl 4-(4-trifluoromethylphenoxy)piperidine-1-carboxylate (1.13 g, 3.27 mmol) prepared in Reference Example 37 was dissolved in methylene chloride (10 ml). To which trifluoroacetic acid (10 ml) was added dropwise and the mixture was stirred at room temperature for 5 hours. After the reaction mixture was concentrated under reduced pressure, the residue was again dissolved in methylene chloride. The solution was neutralized with a sodium hydroxide aqueous solution, and the mixture was extracted with

methylene chloride. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to afford 4-(4-trifluoromethylphenoxy)piperidine (727 mg, 5 yield 91%) as a white powder.

¹H-NMR (CDCl₃) δppm:

1.63 - 1.75 (2H, m), 1.97 - 2.06 (2H, m), 2.69 - 2.80 (2H, m), 3.10 - 3.20 (2H, m), 4.38 - 4.49 (1H, m), 6.94 - 6.98 (2H, m), 7.50 - 7.55 (2H, m).

10 Using corresponding starting materials, compounds of Reference Examples 39 to 43 were prepared in the same manner as described in Reference Example 38.

Reference Example 39

15 4-(4-fluorophenoxy)piperidine
a white powder, yield 76%

¹H-NMR (CDCl₃) δppm:

1.61 - 1.74 (2H, m), 1.96 - 2.06 (2H, m), 2.50 (1H, bs), 2.70 - 2.80 (2H, m), 3.11 - 3.20 (2H, m), 4.23 - 20 4.33 (1H, m), 6.80 - 6.89 (2H, m), 6.91 - 7.00 (2H, m).

Reference Example 40

4-(3-trifluoromethylphenoxy)piperidine
a white powder, yield 48%

¹H-NMR (CDCl₃) δppm:

25 1.62 - 1.76 (2H, m), 1.80 (1H, bs), 1.97 - 2.08 (2H, m), 2.71 - 2.81 (2H, m), 3.11 - 3.20 (2H, m), 4.37 - 4.47 (1H, m), 7.05 - 7.20 (3H, m), 7.34 - 7.41 (1H, m).

Reference Example 41

4-(4-trifluoromethoxyphenoxy)piperidine

a white powder, yield 88%

¹H-NMR (CDCl₃) δppm:

1.59 - 1.73 (3H, m), 1.97 - 2.04 (2H, m), 2.68 - 2.78
5 (2H, m), 3.10 - 3.19 (2H, m), 4.29 - 4.36 (1H, m), 6.85
- 6.92 (2H, m), 7.10 - 7.14 (2H, m).

Reference Example 42

4-(4-cyanophenoxy)piperidine

a white powder, yield 83%

10 ¹H-NMR (CDCl₃) δppm:

1.63 - 1.77 (3H, m), 1.98 - 2.08 (2H, m), 2.72 - 2.82
(2H, m), 3.12 - 3.21 (2H, m), 4.42 - 4.51 (1H, m), 6.92
- 6.98 (2H, m), 7.55 - 7.61 (2H, m).

Reference Example 43

15 4-(4-chlorophenoxy)piperidine

a white powder, yield 62%

¹H-NMR (CDCl₃) δppm:

1.50 (1H, bs), 1.56 - 1.71 (2H, m), 1.94 - 2.04 (2H,
m), 2.66 - 2.76 (2H, m), 3.08 - 3.18 (2H, m), 4.25 -
20 4.35 (1H, m), 6.80 - 6.86 (2H, m), 7.18 - 7.25 (2H, m).

Reference Example 44

Preparation of 1-ethyl-5-(3-methyl-3-butenyl)-1H-
tetrazole

n-Butyl lithium (1.53 M) hexane solution (6.5
25 ml, 9.98 mmol) was added dropwise to a solution of 1-
ethyl-5-methyl-1H-tetrazole (0.80 g, 7.13 mmol) in THF
(15 ml) while stirring at -70°C, and the mixture was
further stirred for 1.5 hours. A solution of 3-chloro-

2-methyl-1-propene (0.77 ml, 7.84 mmol) in THF (5 ml) was added to the mixture, and the resulting mixture was stirred for 2 hours. Water was added to the reaction mixture, the resulting mixture was extracted with ethyl acetate, and the extract was dried over magnesium sulfate, and then concentrated under reduced pressure to afford 1-ethyl-5-(3-methyl-3-butenyl)-1H-tetrazole (0.95 g, yield 80%) as a brown oil.

¹H-NMR (CDCl₃) δppm:

10 1.56 (3H, t, J = 7.3 Hz), 1.80 (3H, s), 2.44 - 2.67 (2H, m), 2.90 - 3.06 (2H, m), 4.32 (2H, q, J = 7.3 Hz), 4.65 - 4.77 (1H, m), 4.77 - 4.87 (1H, m).

Using corresponding starting materials, compounds of Reference Examples 45 and 46 were prepared in the same manner as described in Reference Example 44.

Reference Example 45

1-phenyl-5-(3-methyl-3-butenyl)-1H-tetrazole
a white powder, yield 45%

20 ¹H-NMR (CDCl₃) δppm:

1.67 (3H, s), 2.49 (2H, t, J = 8.1 Hz), 3.04 (2H, t, J = 8.1 Hz), 4.58 - 4.65 (1H, m), 4.71 - 4.77 (1H, m), 7.43 - 7.47 (2H, m), 7.59 - 7.62 (3H, m).

Reference Example 46

25 1-(4-chlorophenyl)-5-(3-methyl-3-butenyl)-1H-tetrazole
a white powder, yield 55%

¹H-NMR (CDCl₃) δppm:

1.68 (3H, s), 2.50 (2H, t, J = 8.1 Hz), 3.03 (2H, t, J

= 8.1 Hz), 4.58 - 4.63 (1H, m), 4.71 - 4.77 (1H, m),
7.38 - 7.44 (2H, m), 7.56 - 7.62 (2H, m).

Reference Example 47

Preparation of 3-(4-methyl-4-pentenyl)-3H-benzoxazol-2-
5 one

Potassium tert-butoxide (3.5 g, 31.2 mmol)
was gradually added to a mixture of methyltriphenyl-
phosphonium bromide (11 g, 30.8 mmol) in THF (100 ml)
while cooling in an ice-bath, and the mixture was
10 stirred for 20 minutes. To which a solution of 3-(4-
oxopentyl)-3H-benzoxazol-2-one (5.6 g, 25.6 mmol) in
THF (10 ml) was gradually added dropwise. The
resulting mixture was stirred at room temperature for 2
hours. The reaction mixture was poured into ice water,
15 and extracted with ethyl acetate twice. The extract
was washed with water and brine, and dried over sodium
sulfate. After filtration, the filtrate was
concentrated under reduced pressure. The residue was
purified by silica gel column chromatography (n-
20 hexane/ethyl acetate = 3/1) to afford 3-(4-methyl-4-
pentenyl)-3H-benzoxazol-2-one (3.4 g, yield 61%) as a
colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.73 (3H, s), 1.84 - 2.16 (4H, m), 3.83 (2H, t, $J = 7.3$
25 Hz), 4.75 (2H, d, $J = 12.7$ Hz), 6.97 (1H, d, $J = 8.2$
Hz), 7.02 - 7.28 (3H, m).

Reference Example 48

Preparation of 3-(5-methyl-5-hexenyl)-3H-benzoxazol-2-

one

Using 3-(5-oxohexyl)-3H-benzoxazol-2-one (1.4 g, 6 mmol), 3-(5-methyl-5-hexenyl)-3H-benzoxazol-2-one (1.1 g, yield 79%) as a colorless oil was prepared in the same manner as described in Reference Example 47.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.42 - 1.60 (2H, m), 1.65 - 1.83 (5H, m), 2.00 - 2.16 (2H, m), 3.84 (2H, t, $J = 6.9$ Hz), 4.69 (2H, d, $J = 11.7$ Hz), 6.97 (1H, d, $J = 7.9$ Hz), 7.02 - 7.23 (3H, m).

Reference Example 49

Preparation of 5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one

Triethylamine (3.52 ml, 25.28 mmol) and 1,1'-carbonyldiimidazole (4.84 g, 29.87 mmol) were added to a solution of 4-trifluoromethoxybenzoic hydrazide (5.06 g, 22.98 mmol) in THF (150 ml) while cooling in an ice-bath and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, to which water was added. The mixture was extracted with ethyl acetate, and the extract was dried over magnesium sulfate and then concentrated under reduced pressure to afford 5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one (5.34 g, yield 94%) as a colorless crystalline powder.

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm:

7.01 (1H, s), 7.47 - 7.59 (2H, m), 7.86 - 7.98 (2H, m).

Using corresponding starting materials,

compounds of Reference Examples 50 to 61 were prepared in the same manner as described in Reference Example 49.

Reference Example 50

- 5 5-(4-trifluoromethylphenyl)-3H-[1,3,4]oxadiazol-2-one
a white powder, yield 97%

$^1\text{H-NMR}$ (DMSO-d_6) δppm :

7.90 (2H, d, $J = 8.5$ Hz), 7.99 (2H, d, $J = 8.5$ Hz).

Reference Example 51

- 10 5-(4-biphenylyl)-3H-[1,3,4]oxadiazol-2-one
a white powder, yield 97%

$^1\text{H-NMR}$ (DMSO-d_6) δppm :

7.35 - 7.52 (3H, m), 7.68 - 7.73 (2H, m), 7.76 - 7.87 (4H, m).

- 15 Reference Example 52

5-phenyl-3H-[1,3,4]oxadiazol-2-one
a white powder, yield 92%

$^1\text{H-NMR}$ (CDCl_3) δppm :

7.40 - 7.58 (3H, m), 7.77 - 7.91 (2H, m).

- 20 Reference Example 53

5-(4-chlorophenyl)-3H-[1,3,4]oxadiazol-2-one
a white powder, yield 80%

$^1\text{H-NMR}$ (DMSO-d_6) δppm :

- 7.61 (2H, dd, $J = 1.9$ Hz, 6.6 Hz), 7.80 (2H, dd, $J =$
25 1.9 Hz, 6.6 Hz).

Reference Example 54

5-(4-fluorophenyl)-3H-[1,3,4]oxadiazol-2-one
a white powder, yield 74%

¹H-NMR (DMSO-d₆) δppm:

7.30 - 7.49 (2H, m), 7.78 - 7.92 (2H, m).

Reference Example 55

5-(4-bromophenyl)-3H-[1,3,4]oxadiazol-2-one

5 a white powder, yield 87%

¹H-NMR (DMSO-d₆) δppm:

7.65 - 7.78 (4H, m).

Reference Example 56

5-(4-chlorobenzyl)-3H-[1,3,4]oxadiazol-2-one

10 a white powder, yield 83%

¹H-NMR (DMSO-d₆) δppm:

3.94 (2H, s), 7.31 (2H, dd, J = 2.1 Hz, 6.4 Hz), 7.41
(2H, dd, J = 2.1 Hz, 6.4 Hz).

Reference Example 57

15 5-[2-(4-chlorophenyl) ethyl]-3H-[1,3,4]oxadiazol-2-one

a white powder, yield 78%

¹H-NMR (DMSO-d₆) δppm:

2.76 - 3.00 (4H, m), 7.27 (2H, d, J = 8.5 Hz), 7.35
(2H, d, J = 8.5 Hz), 12.03 (1H, s).

20 Reference Example 58

5-(4-chlorostyryl)-3H-[1,3,4]oxadiazol-2-one

a white powder, yield 88%

¹H-NMR (DMSO-d₆) δppm:

6.99 (1H, d, J = 16.5 Hz), 7.32 (1H, d, J = 16.5 Hz),
25 7.47 (2H, d, J = 8.6 Hz), 7.75 (2H, d, J = 8.6 Hz),
12.06 (1H, s).

Reference Example 59

5-(4-chlorophenoxymethyl)-3H-[1,3,4]oxadiazol-2-one

a white powder, yield 68%

¹H-NMR (DMSO-d₆) δppm:

5.07 (2H, s), 7.07 (2H, d, J = 6.8 Hz), 7.37 (2H, d, J = 6.8 Hz), 12.41 (1H, br).

5 Reference Example 60

5-(4-pyridyl)-3H-[1,3,4]oxadiazol-2-one

a white powder, yield 40%

¹H-NMR (DMSO-d₆) δppm:

7.72 (2H, dd, J = 1.6 Hz, 4.6 Hz), 8.76 (2H, dd, J =
10 1.6 Hz, 4.6 Hz), 12.90 (1H, s).

Reference Example 61

5-(2-pyrimidyl)-3H-[1,3,4]oxadiazol-2-one

a white powder, yield 70%

¹H-NMR (DMSO-d₆) δppm:

15 8.68 - 8.86 (2H, m), 9.12 (1H, d, J = 1.4 Hz), 12.97
(1H, s).

Reference Example 62

Preparation of tert-butyl(S)-2-(4-trifluoromethoxy-
phenoxymethyl)pyrrolidine-1-carboxylate

20 A mixture of 4-(trifluoromethoxy)phenol (2.1
g, 11.8 mmol), tert-butyl (S)-2-hydroxymethyl
pyrrolidine-1-carboxylate (2 g, 9.8 mmol), diethyl
azodicarboxylate (2.3 ml, 14.7 mmol), and triphenyl-
phosphine (3.86 g, 14.7 mmol) in THF (30 ml) was heated
25 under reflux for 1 hour. The reaction mixture was
allowed to return to room temperature and concentrated
under reduced pressure. The residue was purified by
silica gel column chromatography (n-hexane/ethyl

acetate = 10/1) to afford tert-butyl(S)-2-(4-trifluoromethoxyphenoxyethyl)pyrrolidine-1-carboxylate (2.96 g, yield 65%) as a pale yellow oil.

¹H-NMR (CDCl₃) δppm:

5 1.48 (9H, s), 1.78 - 2.10 (4H, m), 3.27 - 3.49 (2H, m),
3.73 - 3.98 (1H, m), 4.04 - 4.20 (2H, m), 6.90 (2H, dd,
J = 2.2 Hz, 7.0 Hz), 7.12 (2H, dd, J = 2.2 Hz, 7.0 Hz).

Reference Example 63

Preparation of (S)-2-(4-trifluoromethoxyphenoxyethyl)-
10 pyrrolidine

A mixture of tert-butyl(S)-2-(4-trifluoromethoxyphenoxyethyl)pyrrolidine-1-carboxylate (2.31 g, 6.39 mmol) prepared in Reference Example 62, trifluoroacetic acid (20 ml), and methylene chloride
15 (20 ml) was stirred at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure. The residue was neutralized with 10% sodium hydroxide aqueous solution and the mixture was
extracted with methylene chloride, and the extract was
20 dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford (S)-2-(4-trifluoromethoxyphenoxyethyl)-pyrrolidine (1.65 g, yield 99%) as a pale brown oil.

¹H-NMR (CDCl₃) δppm:

25 1.45 - 1.63 (1H, m), 1.65 - 2.04 (3H, m), 2.70 (1H, bs), 2.88 - 3.08 (2H, m), 3.43 - 3.59 (1H, m), 3.78 - 3.96 (2H, m), 6.88 (2H, dd, J = 2.3 Hz, 8.4 Hz), 7.11 (2H, dd, J = 2.3 Hz, 8.4 Hz).

Reference Example 64

Preparation of tert-butyl 3-oxo-4-(4-trifluoromethylbenzyl)piperazine-1-carboxylate

Sodium hydride (840 mg, 24.5 mmol) was
5 gradually added to a solution of tert-butyl 3-oxopiperazine-1-carboxylate (4.1 g, 20.4 mmol) in DMF (30 ml) while cooling in an ice-bath, and the mixture was stirred at room temperature for 30 minutes. A solution of 4-trifluoromethylbenzyl chloride (5 g, 20.9
10 mmol) in DMF (5 ml) was added dropwise to the mixture while cooling in an ice-bath, which was stirred at room temperature for 2 hours. The reaction mixture was poured into ice water, and extracted with ethyl acetate twice. The extract was washed with water twice and
15 brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride) to afford tert-butyl 3-oxo-4-(4-trifluoromethylbenzyl)piperazine-
20 1-carboxylate (6.7 g, yield 91%) as a colorless crystalline powder.

^1H -NMR (CDCl_3) δ ppm:

1.47 (9H, s), 3.27 (2H, t, $J = 5.7$ Hz), 3.62 (2H, t, $J = 5.7$ Hz), 4.18 (2H, s), 4.67 (2H, s), 7.39 (2H, d, $J =$
25 8.1 Hz), 7.61 (2H, d, $J = 8.1$ Hz).

Reference Example 65

Preparation of 1-(4-trifluoromethylbenzyl)piperazin-2-one

Using tert-butyl 3-oxo-4-(4-trifluoromethylbenzyl)piperazine-1-carboxylate (6.7 g, 18.7 mmol) prepared in Reference Example 64, 1-(4-trifluoromethylbenzyl)piperazin-2-one (4.5 g, yield 5 93%) as a pale yellow powder was prepared in the same manner as described in Reference Example 63.

¹H-NMR (CDCl₃) δppm:

3.06 (2H, t, J = 5.2 Hz), 3.24 (2H, t, J = 5.2 Hz),
3.62 (2H, s), 4.60 (2H, s), 7.39 (2H, d, J = 8.1 Hz),
10 7.59 (2H, d, J = 8.1 Hz).

Reference Example 66

Preparation of 4'-trifluoromethoxybiphenyl-4-carbaldehyde

A mixture of 1-bromo-4-(trifluoromethoxy)-
15 benzene (1.53 g, 6.35 mmol), 4-formylbenzeneboronic acid (1 g, 6.67 mmol), tetrakis(triphenylphosphine)-palladium (147 mg, 0.13 mmol), and potassium phosphate (2.02 g, 9.53 mmol) in DMF (10 ml) was stirred at 100°C for 5 hours. The reaction mixture was poured into
20 water, and extracted with ethyl acetate, and the extract was washed with water three times and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column
25 chromatography (n-hexane/methylene chloride = 3/1) to afford 4'-trifluoromethoxybiphenyl-4-carbaldehyde (1.56 g, yield 92%) as a white powder.

¹H-NMR (CDCl₃) δppm:

7.33 (2H, d, $J = 8.8$ Hz), 7.60 - 7.80 (4H, m), 7.97 (2H, d, $J = 8.2$ Hz), 10.07 (1H, s).

Compounds of Reference Examples 67 to 73 were prepared from corresponding iodobenzene or bromobenzene compounds and formylbenzeneboronic acids in the same manner as described in Reference Example 66.

Reference Example 67

4'-trifluoromethylbiphenyl-4-carbaldehyde

a colorless crystalline powder, yield 27%

10 ^1H -NMR (CDCl_3) δ ppm:

7.68 - 7.81 (6H, m), 7.99 (2H, dd, $J = 1.7$ Hz, 6.5 Hz), 10.09 (1H, s).

Reference Example 68

4'-trifluoromethylbiphenyl-3-carbaldehyde

15 a yellow oil, yield 83%

^1H -NMR (CDCl_3) δ ppm:

7.33 (2H, d, $J = 8.8$ Hz), 7.60 - 7.80 (4H, m), 7.97 (2H, d, $J = 8.2$ Hz), 10.07 (1H, s).

Reference Example 69

20 4'-dimethylaminobiphenyl-4-carbaldehyde

a yellow powder, yield 46%

^1H -NMR (CDCl_3) δ ppm:

3.03 (6H, s), 6.81 (2H, dd, $J = 2.1$ Hz, 6.8 Hz), 7.58 (2H, dd, $J = 2.1$ Hz, 6.8 Hz), 7.71 (2H, dd, $J = 1.8$ Hz, 6.6 Hz), 7.90 (2H, dd, $J = 1.8$ Hz, 6.6 Hz), 10.00 (1H, s).

Reference Example 70

4'-chlorobiphenyl-4-carbaldehyde

a pale yellow crystalline powder, yield 47%

$^1\text{H-NMR}$ (CDCl_3) δppm :

- 7.45 (2H, d, $J = 8.6$ Hz), 7.57 (2H, d, $J = 8.6$ Hz),
7.73 (2H, d, $J = 8.4$ Hz), 7.96 (2H, d, $J = 8.4$ Hz),
5 10.06 (1H, s).

Reference Example 71

2'-chlorobiphenyl-4-carbaldehyde

A colorless crystalline powder, yield 46%

$^1\text{H-NMR}$ (CDCl_3) δppm :

- 10 7.30 - 7.40 (3H, m), 7.38 - 7.58 (1H, m), 7.63 (2H, d,
 $J = 8.1$ Hz), 7.96 (2H, d, $J = 8.1$ Hz), 10.08 (1H, s).

Reference Example 72

3',4'-dichlorobiphenyl-4-carbaldehyde

A colorless crystalline powder, yield 24%

15 $^1\text{H-NMR}$ (CDCl_3) δppm :

- 7.46 (1H, dd, $J = 2.1$ Hz, 8.4 Hz), 7.56 (1H, d, $J = 8.4$
Hz), 7.70 - 7.80 (3H, m), 7.97 (2H, dd, $J = 1.8$ Hz, 6.6
Hz), 10.07 (1H, s).

Reference Example 73

20 4'-methoxybiphenyl-4-carbaldehyde

A colorless crystalline powder, yield 45%

$^1\text{H-NMR}$ (CDCl_3) δppm :

- 3.87 (3H, s), 7.01 (2H, d, $J = 6.8$ Hz), 7.59 (2H, d, J
 $= 6.8$ Hz), 7.72 (2H, d, $J = 8.3$ Hz), 7.93 (2H, d, $J =$
25 8.3 Hz), 10.04 (1H, s).

Reference Example 74

Preparation of 4-(pyridin-3-yl)benzaldehyde

A mixture of 4-bromobenzaldehyde (2 g, 10.8

mmol), diethyl(3-pyridyl)borane (1.75 g, 11.9 mmol), tetrakis(triphenylphosphine)palladium (375 mg, 0.32 mmol), and 2N sodium carbonate aqueous solution (10.8 ml, 21.6 mmol) in toluene (40 ml) was heated under
5 reflux under a nitrogen atmosphere overnight. The reaction mixture was allowed to return to room temperature and diluted with ethyl acetate. The mixture was washed with water and brine, and dried over sodium sulfate. After filtration, the filtrate was
10 concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/1) to afford 4-(pyridin-3-yl)benzaldehyde (1.43 g, yield 72%) as a pale yellow crystalline powder.
15 ¹H-NMR (CDCl₃) δppm:
7.33 - 7.50 (1H, m), 7.76 (2H, dd, J = 1.8 Hz, 6.6 Hz),
7.89 - 8.06 (3H, m), 8.56 - 8.69 (1H, m), 8.90 (1H, dd, J = 0.7 Hz, 1.7 Hz), 10.09 (1H, s).

Reference Example 75

20 Preparation of 4-(imidazol-1-yl)benzaldehyde

A mixture of 4-fluorobenzaldehyde (4.96 g, 40 mmol), imidazole (2.86 g, 42 mmol), and potassium carbonate (6.08 g, 44 mmol) in DMSO (40 ml) was stirred at 110°C overnight. The reaction mixture was allowed to
25 return to room temperature, and poured into ice water (100 ml). The resulting precipitates were collected by filtration and washed with water and then with ethyl acetate to afford 4-(imidazol-1-yl)benzaldehyde (2.33

g, yield 34%) as a pale yellow crystalline powder.

¹H-NMR (CDCl₃) δppm:

7.20 - 7.30 (1H, m), 7.38 (1H, dd, J = 1.3 Hz, 1.4 Hz),
7.58 (2H, dd, J = 1.8 Hz, 6.8 Hz), 7.98 - 8.10 (3H, m),
5 10.05 (1H, s).

Using a corresponding starting material, a compound of Reference Example 76 was prepared in the same manner as described in Reference Example 75.

Reference Example 76

10 4-(piperidin-1-yl)benzaldehyde

a yellow crystalline powder, yield 46%

¹H-NMR (CDCl₃) δppm:

1.58 - 1.75 (6H, m), 3.33 - 3.50 (4H, m), 6.89 (2H, dd,
J = 1.9 Hz, 7.0 Hz), 7.73 (2H, dd, J = 1.9 Hz, 7.0 Hz),
15 9.75 (1H, s).

Reference Example 77

Preparation of tert-butyl 4-(4-trifluoromethylphenyl)-
piperazine-1-carboxylate

A mixture of 4-bromobenzotrifluoride (3.0 g,
20 13.3 mmol), tert-butyl piperazine-1-carboxylate (2.9 g,
15.3 mmol), bis (dibenzylideneacetone) palladium (306
mg, 0.53 mmol), tri-o-tolylphosphine (162 mg, 0.53
mmol), and sodium tert-butoxide (2.2 g, 22.7 mmol) in
toluene (60 ml) was refluxed under a nitrogen
25 atmosphere for 4 hours. Ethyl acetate and water were
added to the reaction mixture, which was stirred for a
while, and the insoluble substances were removed by
filtration through Celite, and the filtrate was then

extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel
5 column chromatography (n-hexane/methylene chloride = 2/1) to afford tert-butyl 4-(4-trifluoromethylphenyl)-piperazine-1-carboxylate (3.8 g, yield 87%) as a white powder.

¹H-NMR (CDCl₃) δppm:

10 1.49 (9H, s), 3.21 - 3.26 (4H, m), 3.56 - 3.61 (4H, m),
6.90 - 6.93 (2H, m), 7.47 - 7.51 (2H, m).

Using corresponding starting materials, compounds of Reference Examples 78 to 84 were prepared in the same manner as described in Reference Example
15 77.

Reference Example 78

tert-butyl 4-(4-trifluoromethoxyphenyl)piperazine-1-carboxylate

a white powder, yield 95%

20 ¹H-NMR (CDCl₃) δppm:

1.48 (9H, s), 3.09 - 3.13 (4H, m), 3.55 - 3.60 (4H, m),
6.87 - 6.91 (2H, m), 7.10 - 7.14 (2H, m).

Reference Example 79

tert-butyl 4-(4-biphenyllyl)piperazine-1-carboxylate

25 a white powder, yield 95%

¹H-NMR (CDCl₃) δppm:

1.49 (9H, s), 3.16 - 3.21 (4H, m), 3.58 - 3.62 (4H, m),
6.97 - 7.01 (2H, m), 7.27 - 7.32 (1H, m), 7.37 - 7.44

(2H, m), 7.50 - 7.58 (4H, m).

Reference Example 80

tert-butyl 4-(4-dimethylaminophenyl)piperazine-1-carboxylate

5 a white powder, yield 79%

¹H-NMR (CDCl₃) δppm:

1.48 (9H, s), 2.87 (6H, s), 2.96 - 3.00 (4H, m), 3.54 - 3.59 (4H, m), 6.72 - 6.77 (2H, m), 6.87 - 6.92 (2H, m).

Reference Example 81

10 tert-butyl 4-(3-pyridyl)piperazine-1-carboxylate

a white powder, yield 99%

¹H-NMR (CDCl₃) δppm:

1.49 (9H, s), 3.14 - 3.19 (4H, m), 3.57 - 3.62 (4H, m), 7.17 - 7.19 (2H, m), 8.12 - 8.14 (1H, m), 8.31 - 8.33

15 (1H, m).

Reference Example 82

tert-butyl 4-(4-ethoxycarbonylphenyl)piperazine-1-carboxylate

a white powder, yield 42%

20 ¹H-NMR (CDCl₃) δppm:

1.37 (3H, t, J = 7.1 Hz), 1.48 (9H, s), 3.27 - 3.32 (4H, m), 3.56 - 3.60 (4H, m), 4.33 (2H, q, J = 7.1 Hz), 6.84 - 6.88 (2H, m), 7.92 - 7.96 (2H, m).

Reference Example 83

25 tert-butyl 4-(4-methylphenyl)piperazine-1-carboxylate

a white powder, yield 55%

¹H-NMR (CDCl₃) δppm:

1.48 (9H, s), 2.27 (3H, s), 3.04 - 3.09 (4H, m), 3.55 -

3.59 (4H, m), 6.82 - 6.87 (2H, m), 7.06 - 7.10 (2H, m).

Reference Example 84

tert-butyl 4-(4-cyanophenyl)piperazine-1-carboxylate

a white powder, yield 86%

5 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.49 (9H, s), 3.28 - 3.33 (4H, m), 3.56 - 3.60 (4H, m),
6.83 - 6.87 (2H, m), 7.49 - 7.53 (2H, m).

Reference Example 85

Preparation of 1-(4-trifluoromethylphenyl)piperazine

10 Tert-butyl 4-(4-trifluoromethylphenyl)-
piperazine-1-carboxylate (3.8 g, 11.5 mmol) prepared in
Reference Example 77 was dissolved in methylene
chloride (40 ml), to which trifluoroacetic acid (10 ml)
was added dropwise, and the mixture was stirred at room
15 temperature overnight. The reaction mixture was
concentrated under reduced pressure, and the residue
was neutralized with saturated sodium hydrogencarbonate
aqueous solution and the mixture was extracted with
methylene chloride. The extract was dried over
20 magnesium sulfate, and then filtered. The filtrate was
concentrated under reduced pressure to afford 1-(4-
trifluoromethylphenyl)piperazine (2.5 g, yield 96%) as
a white powder.

$^1\text{H-NMR}$ (CDCl_3) δppm :

25 3.01 - 3.06 (4H, m), 3.21 - 3.26 (4H, m), 6.92 (2H, d,
 $J = 8.6 \text{ Hz}$), 7.48 (2H, d, $J = 8.6 \text{ Hz}$).

Using corresponding starting materials,
compounds of Reference Examples 86 to 89 were prepared

in the same manner as described in Reference Example 85.

Reference Example 86

1-(4-trifluoromethoxyphenyl)piperazine

5 a white powder, yield 100%

¹H-NMR (CDCl₃) δppm:

1.61 (1H, s), 3.00 - 3.05 (4H, m), 3.10 - 3.15 (4H, m),
6.85 - 6.92 (2H, m), 7.08 - 7.13 (2H, m).

Reference Example 87

10 1-(4-dimethylaminophenyl)piperazine

a white powder, yield 99%

¹H-NMR (CDCl₃) δppm:

1.60 (1H, br), 2.86 (6H, s), 3.01 (8H, br), 6.71 - 6.78
(2H, m), 6.87 - 6.92 (2H, m).

15 Reference Example 88

1-(3-pyridyl)piperazine

a white powder, yield 100%

¹H-NMR (CDCl₃) δppm:

2.09 (1H, s), 3.03 - 3.09 (4H, m), 3.14 - 3.20 (4H, m),
20 7.16 - 7.18 (2H, m), 8.09 - 8.11 (1H, m), 8.31 (1H, s).

Reference Example 89

1-(4-ethoxycarbonylphenyl)piperazine

a white powder, yield 95%

¹H-NMR (CDCl₃) δppm:

25 1.37 (3H, t, J = 7.1 Hz), 1.84 (1H, s), 3.00 - 3.04.
(4H, m), 3.26 - 3.31 (4H, m), 4.33 (2H, q, J = 7.1 Hz),
6.83 - 6.89 (2H, m), 7.89 - 7.96 (2H, m).

Reference Example 90

Preparation of tert-butyl 4-(piperazin-1-yl)benzoate

A mixture of tert-butyl 4-bromobenzoate (4.8 g, 18.8 mmol), piperazine (9.7 g, 0.11 mol), palladium acetate (85 mg, 0.38 mmol), (S)-(-)-BINAP (352 mg, 0.57 mmol), and sodium tert-butoxide (2.7 g, 28.2 mmol) in toluene (50 ml) was refluxed under a nitrogen atmosphere for 2 hours. Ethyl acetate and water were added to the reaction mixture and the insoluble substances were removed by filtration through Celite, and the filtrate was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 5/1) to afford tert-butyl 4-(piperazin-1-yl) benzoate (3.8 g, yield 77%) as a gray powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.57 (9H, s), 3.00 - 3.04 (4H, m), 3.24 - 3.29 (4H, m), 6.83 - 6.87 (2H, m), 7.85 - 7.89 (2H, m).

Reference Example 91

Preparation of 4-trifluoromethoxybenzyl piperazine-1-carboxylate

To a solution of 4-trifluoromethoxybenzyl alcohol (25 g, 130.11 mmol) and phenyl chloroformate (20.37 g, 130.11 mmol) in ethyl acetate (125 ml), a solution of pyridine (11.6 ml, 143.12 mmol) in ethyl acetate (50 ml) was added dropwise below 15°C over 35

minutes. The mixture was stirred for 30 minutes. The reaction mixture was washed with water, 3 N hydrochloric acid, 10% potassium carbonate aqueous solution and brine, and dried over sodium sulfate. After
5 filtration, the filtrate was concentrated under reduced pressure to afford a carbonate compound as a colorless oil. To a solution of piperazine (33.62 g, 390.34 mmol) in methanol (125 ml), a solution of the carbonate compound in ethyl acetate (50 ml) was added dropwise
10 below 10°C over 25 minutes. The resulting mixture was stirred for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 10/1) to afford 4-
15 trifluoromethoxybenzyl piperazine-1-carboxylate (35.33 g, yield 89%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

2.57 - 2.96 (4H, m), 3.42 - 3.63 (4H, m), 5.13 (2H, s),
7.21 (2H, d, J = 8.5 Hz), 7.39 (2H, d, J = 8.5 Hz).

20 Reference Example 92

Preparation of 3-(4-trifluoromethylphenyl)-2-propenyl piperazine-1-carboxylate

A solution of pyridine (0.5 ml, 6.18 mmol) in ethyl acetate (2 ml) was gradually added dropwise to a
25 solution of 3-(4-trifluoromethylphenyl)-2-propen-1-ol (1 g, 4.95 mmol) and phenyl chloroformate (0.72 ml, 5.69 mmol) in ethyl acetate (5 ml) while cooling in an ice-bath. The mixture was stirred at room temperature

for 1 hour. The reaction mixture was washed with water, 3 N hydrochloric acid, 10% potassium carbonate aqueous solution and brine in this order, and dried over sodium sulfate. After filtration, the filtrate
5 was concentrated under reduced pressure to afford a carbonate compound as a colorless oil. To a solution of piperazine (1.28 g, 14.84 mmol) in methanol (5 ml), a solution of the carbonate compound in ethyl acetate (5 ml) was gradually added dropwise while cooling in an
10 ice-bath. The mixture was stirred at room temperature for 2.5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 10/1) to afford 3-(4-
15 trifluoromethylphenyl)-2-propenyl piperazine-1-carboxylate (1.4 g, yield 90%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

2.75 - 2.95 (4H, m), 3.43 - 3.57 (4H, m), 4.78 (2H, dd, $J = 1.2$ Hz, 6.0 Hz), 6.33 - 6.43 (1H, m), 6.66 (1H, d, 20 16.0 Hz), 7.48 (2H, d, $J = 8.4$ Hz), 7.57 (2H, d, $J = 8.4$ Hz).

Using a corresponding starting material, a compound of Reference Example 93 was prepared in the same manner as described in Reference Example 92.

25 Reference Example 93

3-(4-Trifluoromethoxyphenyl)-2-propenyl piperazine-1-carboxylate

a colorless oil, yield 90%

¹H-NMR (CDCl₃) δppm:

2.75 - 2.88 (4H, m), 3.44 - 3.52 (4H, m), 4.75 (2H, dd,
J = 1.3 Hz, 6.2 Hz), 6.29 (1H, dt, J = 6.2 Hz, 15.9
Hz), 6.62 (1H, d, J = 15.9 Hz), 7.15 - 7.18 (2H, m),
5 7.38 - 7.42 (2H, m).

Reference Example 94

Preparation of 4-(4-chlorophenyl)-1,2,3,6-tetrahydro-
pyridine-1-carbonylchloride

A mixture of 4-(4-chlorophenyl)-1,2,3,6-
10 tetrahydropyridine hydrochloride (1 g, 4.3 mmol),
pyridine (680 mg, 8.6 mmol), and triphosgene (430 mg,
1.45 mmol) in toluene (20 ml) was heated under reflux
for 3 hours. The reaction mixture was allowed to
return to room temperature and diluted with diethyl
15 ether. The mixture was washed with 10% hydrochloric
acid, water and brine in this order, and dried over
magnesium sulfate. After filtration, the filtrate was
concentrated under reduced pressure to afford 4-(4-
chlorophenyl)-1,2,3,6-tetrahydropyridine-1-
20 carbonylchloride (1 g, yield 90%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

2.51 - 2.72 (2H, m), 3.81 - 4.00 (2H, m), 4.26 - 4.40
(2H, m), 5.93 - 6.09 (1H, m), 7.16 - 7.35 (4H, m).

Reference Example 95

25 Preparation of 1-benzyl-4-(4-trifluoromethylphenyl)-
piperidin-4-ol

4-Bromobenzotrifluoride (1 g, 4.44 mmol) was
dissolved in THF (15 ml), to which n-butyllithium (1.5

M) hexane solution (3.1 ml, 4.67 mmol) was added dropwise at -70°C . Then a solution of 1-benzyl-4-piperidone in THF (15 ml) was added dropwise to the mixture, and the resulting mixture was stirred for 2
5 hours and then at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate, washed with water and brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica
10 gel column chromatography (n-hexane/acetone = 2/1) to afford 1-benzyl-4-(4-trifluoromethylphenyl)piperidin-4-ol (692 mg, yield 46%) as a colorless crystalline powder.

^1H -NMR (CDCl_3) δ ppm:

15 1.60 - 1.78 (2H, m), 2.07 - 2.25 (2H, m), 2.38 - 2.54 (2H, m), 2.74 - 2.87 (2H, m), 3.59 (2H, s), 7.20 - 7.38 (5H, m), 7.51 - 7.67 (4H, m).

Reference Example 96

Preparation of 1-benzyl-4-(4-trifluoromethylphenyl)-
20 1,2,3,6-tetrahydropyridine

A mixture of 1-benzyl-4-(4-trifluoromethylphenyl)piperidin-4-ol (692 mg, 2.06 mmol) prepared in Reference Example 95, concentrated hydrochloric acid (4.5 ml) and acetic acid (10 ml) was heated under
25 reflux overnight. The reaction mixture was allowed to return to room temperature, and diluted with methylene chloride. The mixture was washed with water, 10% sodium hydroxide aqueous solution and brine, and dried

over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/acetone = 4/1) to afford 1-benzyl-4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine (528 mg, yield 80%) as a pale yellow crystalline powder.

¹H-NMR (CDCl₃) δppm:

2.50 - 2.60 (2H, m), 2.62 - 2.76 (2H, m), 3.11 - 3.22 (2H, m), 3.65 (2H, s), 6.10 - 6.20 (1H, m), 7.20 - 7.54 (9H, m).

Reference Example 97

Preparation of 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine hydrochloride

1-Benzyl-4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine (2 g, 6.3 mmol) prepared in Reference Example 96 was dissolved in methylene chloride (20 ml), to which 2-chloroethyl chloroformate (1.67 g, 11.68 mmol) was added dropwise under a nitrogen atmosphere while cooling in an ice-bath, and the mixture was stirred at the same temperature for 3 hours. Methanol (20 ml) was added to the mixture, which was heated under reflux for 1 hour. The reaction mixture was allowed to return to room temperature, to which diethyl ether was added, and the resulting precipitates were collected by filtration to afford 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine hydrochloride (1.44 g, yield 87%) as a colorless crystalline powder.

¹H-NMR (DMSO-d₆) δppm:

2.64 - 2.80 (2H, m), 3.18 - 3.34 (2H, m), 3.68 - 3.80 (2H, m), 6.25 - 6.39 (1H, m), 7.61 - 7.80 (4H, m).

Reference Example 98

- 5 Preparation of 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carbonylchloride

Using 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine hydrochloride (300 mg, 1.14 mmol) prepared in Reference Example 97, pyridine (0.18 ml, 10 2.28 mmol) and triphosgene (112 mg, 0.38 mmol), 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carbonylchloride (220 mg, yield 67%) as a yellow oil was prepared in the same manner as described in Reference Example 94.

- 15 ¹H-NMR (CDCl₃) δppm:

2.57 - 2.75 (2H, m), 3.82 - 4.00 (2H, m), 4.25 - 4.40 (2H, m), 6.05 - 6.16 (1H, m), 7.47 (2H, d, J = 8.2 Hz), 7.59 (2H, d, J = 8.2 Hz).

Reference Example 99

- 20 Preparation of 4-(4-chlorophenyl)piperidine hydrochloride

A mixture of 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (2 g, 8.7 mmol) and platinum oxide (100 mg) in ethanol (100 ml) was stirred 25 at room temperature under an atmospheric pressure of hydrogen. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The resulting precipitates by treating the

residue with diethyl ether were collected by filtration to afford 4-(4-chlorophenyl) piperidine hydrochloride (1.9 g, yield 94%) as a pale gray powder.

^1H -NMR (DMSO- d_6) δ ppm:

- 5 1.75 - 1.95 (4H, m), 2.74 - 3.05 (3H, m), 3.25 - 3.44 (2H, m), 7.25 (2H, d, $J = 8.5$ Hz), 7.38 (2H, d, $J = 8.5$ Hz).

Reference Example 100

Preparation of 4-(4-trifluoromethylphenyl)piperidine

- 10 A mixture of 1-benzyl-4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine (528 mg, 1.66 mmol) prepared in Reference Example 96 and 10% palladium/carbon (50 mg) in acetic acid (5 ml) was stirred at room temperature under an atmospheric
- 15 pressure of hydrogen. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in methylene chloride, and the mixture was washed with water, 10% sodium hydroxide aqueous
- 20 solution and brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford 4-(4-trifluoromethylphenyl)piperidine (400 mg, quantitative) as a yellow oil.

25 ^1H -NMR (CDCl_3) δ ppm:

- 1.72 - 2.00 (4H, m), 2.61 - 2.84 (3H, m), 3.07 - 3.27 (2H, m), 7.32 (2H, d, $J = 8.2$ Hz), 7.56 (2H, d, $J = 8.2$ Hz).

Reference Example 101

Preparation of 4-(4-trifluoromethylphenyl)piperidine-1-carbonylchloride

Using 4-(4-trifluoromethylphenyl)piperidine
5 (760 mg, 3.32 mmol) prepared in Reference Example 100, 4-(4-trifluoromethylphenyl)piperidine-1-carbonylchloride (crude product) a pale brown oil was prepared in the same manner as described in Reference Example 94.

10 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.65 - 1.84 (2H, m), 1.86 - 2.02 (2H, m), 2.77 - 3.28 (3H, m), 4.42 - 4.60 (2H, m), 7.32 (2H, d, $J = 8.1$ Hz), 7.59 (2H, d, $J = 8.1$ Hz).

Reference Example 102

15 Preparation of 2-[3-(4-trifluoromethylphenyl)-2-propenyl]phthalimide

4-(Trifluoromethyl)cinnamyl alcohol (3 g, 14.84 mmol) was dissolved in THF (60 ml), and phthalimide (2.84 g, 19.29 mmol) and triphenylphosphine
20 (5.84 g, 22.26 mmol) were added to the solution, to which a solution of diethyl azodicarboxylate (3.87 g, 22.26 mmol) in THF (20 ml) was gradually added dropwise. The mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated
25 under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/methylene chloride = 1/1) to afford 2-[3-(4-trifluoro-methylphenyl)-2-propenyl]phthalimide (4.57 g, yield

93%) as a white powder.

^1H -NMR (CDCl_3) δ ppm:

4.47 (2H, dd, $J = 1.2$ Hz, 6.3 Hz), 6.27 - 6.41 (1H, m),
6.68 (1H, d, $J = 15.9$ Hz), 7.44 (2H, d, $J = 8.4$ Hz),
5 7.54 (2H, d, $J = 8.4$ Hz), 7.74 (2H, dd, $J = 2.0$ Hz, 7.0
Hz), 7.85 (2H, dd, $J = 2.0$ Hz, 7.0 Hz).

Reference Example 103

Preparation of 3-(4-trifluoromethylphenyl)-2-propenylamine

10 A mixture of 2-[3-(4-trifluoromethylphenyl)-
2-propenyl]phthalimide (4.57 g, 13.79 mmol) prepared in
Reference Example 102 and hydrazine hydrate (897 mg,
17.93 mmol) in ethanol (80 ml) was heated under reflux
for 3 hours. The reaction mixture was allowed to
15 return to room temperature and filtered, and the
filtrate was concentrated under reduced pressure. To
the residue, ethyl acetate was added, and the resulting
mixture was washed with 1 N sodium hydroxide aqueous
solution and brine, and dried over magnesium sulfate.
20 After filtration, the filtrate was concentrated under
reduced pressure to afford 3-(4-
trifluoromethylphenyl)-2-propenylamine (2.78 g,
quantitative) as a pale brown crystalline powder.

^1H -NMR (CDCl_3) δ ppm:

25 3.51 (2H, d, $J = 4.7$ Hz), 6.31 - 6.47 (1H, m), 6.55
(1H, d, $J = 16.0$ Hz), 7.45 (2H, d, $J = 8.3$ Hz), 7.55
(2H, d, $J = 8.3$ Hz).

Reference Example 104

Preparation of piperazin-1-yl-(5-chlorobenzofuran-2-yl methylene)amine

1-Aminopiperazine (29 g, 287 mmol) was dissolved in isopropyl alcohol (173 ml), to which 5-chlorobenzofuran-2-aldehyde (34.52 g, 191 mmol) was added, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to afford piperazin-1-yl-(5-chlorobenzofuran-2-yl methylene)amine (49.49 g, yield 98%) as a yellow crystalline powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

2.95 - 3.10 (4H, m), 3.17 - 3.29 (4H, m), 6.70 (1H, s), 7.20 (1H, dd, $J = 2.1 \text{ Hz}, 8.7 \text{ Hz}$), 7.38 - 7.52 (3H, m).

Reference Example 105

Preparation of piperazin-1-yl-(4-trifluoromethyl benzylidene)amine

Tert-butyl piperazin-1-yl-carbamate (403 mg, 2.0 mmol) was suspended in methylene chloride (4 ml), to which trifluoroacetic acid (1.6 ml) was added, and the mixture was stirred at room temperature for 5 minutes. To which 4-(trifluoromethyl)benzaldehyde (0.3 ml, 2.2 mmol) was added, and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into sodium hydrogencarbonate aqueous solution, and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and then concentrated under reduced pressure.

The residue was purified by silica gel column chromatography (methylene chloride/methanol = 9/1) to afford piperazin-1-yl-(4-trifluoromethylbenzylidene)-amine (432 mg, yield 84%) as a colorless crystalline powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

3.00 - 3.29 (8H, m), 7.43 - 7.62 (3H, m), 7.68 (2H, d, $J = 8.2$ Hz).

Reference Example 106

10 Preparation of piperazin-1-yl-(4-trifluoromethoxybenzylidene)amine

To a solution of 4-benzylpiperazin-1-yl-amine (43.18 g, 225 mmol) in ethanol (400 ml), a suspension of 20% palladium hydroxide/carbon (6.50 g) in ethanol (30 ml) was added, and the mixture was stirred at room temperature under an atmospheric pressure of hydrogen for 3 hours and then at 50°C for 2 hours. The reaction mixture was filtered through Celite, 4-(trifluoromethoxy)benzaldehyde (42.92 g, 225 mmol) was added to the filtrate, and the mixture was stirred at room temperature for 1.5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 10/1) to afford piperazin-1-yl-(4-trifluoromethoxybenzylidene)amine (56.88 g, yield 93%) as a pale yellow crystalline powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

3.00 - 3.23 (8H, m), 7.18 (2H, d, $J = 8.7$ Hz), 7.58 (1H, s), 7.62 (2H, d, $J = 8.7$ Hz).

Using a corresponding starting material, a compound of Reference Example 107 was prepared in the same manner as described in Reference Example 106.

Reference Example 107

piperazin-1-yl-(5-trifluoromethylbenzofuran-2-yl methylene)amine

a pale yellow crystalline powder, yield 77%

¹H-NMR (CDCl₃) δppm:

3.00 - 3.14 (4H, m), 3.23 - 3.32 (4H, m), 6.79 (1H, s), 7.41 - 7.59 (3H, m), 7.82 (1H, s).

Reference Example 108

Preparation of (4-benzylpiperazin-1-yl)-(4-trifluoromethylphenyl)amine

A mixture of 4-bromobenzotrifluoride (3.00 g, 13.3 mmol), 4-benzylpiperazin-1-yl-amine (3.06 g, 16.0 mmol), palladium acetate (60 mg, 0.267 mmol), (S)-(-)-BINAP (174 mg, 0.280 mmol) and sodium tert-butoxide (1.92 g, 20.0 mmol) in toluene (60 ml) was refluxed under a nitrogen atmosphere for 7 hours. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was then purified by silica gel column chromatography (n-hexane/acetone = 4/1) to afford (4-benzylpiperazin-1-yl)-(4-

trifluoromethylphenyl)amine (2.666 g, yield 59%) as a pale yellow oil.

^1H -NMR (CDCl_3) δ ppm:

2.58 (4H, br), 2.76 (4H, br), 3.55 (2H, s), 4.65 (1H, br), 6.90 (2H, d, $J = 8.6$ Hz), 7.23 - 7.35 (5H, m), 7.41 (2H, d, $J = 8.6$ Hz).

Reference Example 109

Preparation of piperazin-1-yl-(4-trifluoromethylphenyl)amine

10 A mixture of (4-benzylpiperazin-1-yl)-(4-trifluoromethylphenyl)amine prepared in Reference Example 108 and 10% palladium/carbon (0.53 g) in ethanol (50 ml) was stirred at room temperature under an atmospheric pressure of hydrogen for 6 hours, and
15 then at 60°C for 10 hours. After the catalyst was removed by filtration through Celite, 10% palladium/carbon (0.53 g) was added to the filtrate, and the mixture was stirred at 60°C under an atmospheric pressure of hydrogen for 8 hours. After the catalyst
20 was removed by filtration through Celite, the filtrate was concentrated under reduced pressure. The resulting solid was dried *in vacuo* to afford piperazin-1-yl-(4-trifluoromethylphenyl)amine (1.76 g, yield 90%) as a colorless crystalline powder.

25 ^1H -NMR (CDCl_3) δ ppm:

2.71 (4H, br), 3.00 (4H, t, $J = 4.8$ Hz), 4.71 (1H, br), 6.92 (2H, d, $J = 8.5$ Hz), 7.42 (2H, d, $J = 8.5$ Hz).

Reference Example 110

Preparation of tert-butyl 4-(3-phenyl-2-propenyloxy)-
piperidine-1-carboxylate

Tert-butyl 4-hydroxypiperidine-1-carboxylate
(0.396 g, 1.97 mmol) was dissolved in DMF (5 ml), to
5 which sodium hydride (0.086 g, 2.16 mmol) was added,
and the mixture was stirred at room temperature for 1
hour. Cinnamyl chloride (0.300 g, 1.97 mmol) was added
to the mixture while cooling in an ice-bath, and the
resulting mixture was stirred overnight. The reaction
10 mixture was diluted with ethyl acetate, and the mixture
was washed with water and brine. The organic layer was
dried over magnesium sulfate, and then filtered, and
the filtrate was concentrated under reduced pressure.
The residue was purified by silica gel column
15 chromatography (n-hexane/ethyl acetate = 6/1) to afford
tert-butyl 4-(3-phenyl-2-propenyloxy)piperidine-1-
carboxylate (0.314 g, yield 50%) as a yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.46 (9H, s), 1.48 - 1.59 (2H, m), 1.81 - 1.93 (2H, m),
20 3.01 - 3.15 (2H, m), 3.50 - 3.61 (1H, m), 3.74 - 3.87
(2H, m), 4.19 (2H, d, $J = 5.9$ Hz), 6.29 (1H, ddd, $J =$
5.9 Hz, 5.9 Hz, 15.9 Hz), 6.61 (1H, d, $J = 15.9$ Hz),
7.18 - 7.43 (5H, m).

Reference Example 111

25 Preparation of 4-(3-phenyl-2-propenyloxy)piperidine

Tert-butyl 4-(3-phenyl-2-propenyloxy)-
piperidine-1-carboxylate (0.314 g, 0.989 mmol) prepared
in Reference Example 110 was dissolved in ethanol (10

ml), to which 6N hydrochloric acid aqueous solution (3 ml, 18 mmol) was added, and the mixture was stirred at 60°C for 1 hour. The reaction mixture was neutralized with sodium hydroxide aqueous solution, and the mixture
5 was extracted with methylene chloride. The extract was washed with brine, dried over sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was dried *in vacuo* to afford 4-(3-phenyl-2-propenyloxy)piperidine (0.198 g, yield
10 92%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.40 - 1.57 (2H, m), 1.91 - 2.02 (2H, m), 2.56 - 2.70 (2H, m), 3.12 (2H, ddd, J = 4.2 Hz, 4.2 Hz, 12.8 Hz), 3.42 - 3.52 (1H, m), 4.19 (2H, d, J = 5.9 Hz), 6.30
15 (1H, ddd, J = 5.9 Hz, 5.9 Hz, 15.9 Hz), 6.57 (1H, d, J = 15.9 Hz), 7.20 - 7.43 (5H, m).

Reference Example 112

Preparation of tert-butyl 4-[3-(4-chlorophenyl)-2-propenyloxy]piperidine-1-carboxylate

20 Tert-butyl 4-hydroxypiperidine-1-carboxylate (3.58 g, 17.8 mmol) was dissolved in DMF (30 ml), to which sodium hydride (0.71 g, 17.8 mmol) was added, and the mixture was stirred at room temperature for 2 hours.

25 On the other hand, 4-chlorocinnamyl alcohol (3.00 g, 17.8 mmol) was dissolved in methylene chloride (60 ml), to which triethyl amine (5 ml, 35.6 mmol) and methanesulfonyl chloride (2.1 ml, 26.7 mmol) were added

dropwise while cooling in an ice-bath, the mixture was stirred at room temperature for 1.5 hours. Water was added to the mixture, which was extracted with methylene chloride, and the extract was washed with dilute hydrochloric acid solution, sodium bicarbonate aqueous solution and brine. The organic layer was dried over magnesium sulfate, and then filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in DMF (10 ml).

Both the DMF solutions were combined while cooling in an ice-bath, and the mixture was stirred overnight. After the reaction mixture was diluted with ethyl acetate, the mixture was washed with water and brine. The organic layer was dried over sodium sulfate, and then filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 6/1) to afford tert-butyl 4-[3-(4-chlorophenyl)-2-propenyloxy]piperidine-1-carboxylate (0.759 g, yield 12%) as a yellow oil.

^1H -NMR (CDCl_3) δ ppm:

1.46 (9H, s), 1.50 - 1.62 (2H, m), 1.83 - 1.94 (2H, m), 3.03 - 3.14 (2H, m), 3.53 - 3.58 (1H, m), 3.77 - 3.83 (2H, m), 4.17 (1H, d, $J = 5.7$ Hz), 4.18 (1H, d, $J = 5.7$ Hz), 6.27 (1H, ddd, $J = 5.7$ Hz, 5.7 Hz, 15.9 Hz), 6.57 (1H, d, $J = 15.9$ Hz), 7.20 - 7.33 (4H, m).

Reference Example 113

Preparation of 4-[3-(4-chlorophenyl)-2-propenyloxy]-

piperidine

Using tert-butyl 4-[3-(4-chlorophenyl)-2-propenyloxy]piperidine-1-carboxylate (0.350 g, 0.995 mmol) prepared in Reference Example 112, 4-[3-(4-chlorophenyl)-2-propenyloxy]piperidine (0.291 g, quantitative) as a brown oil was prepared in the same manner as described in Reference Example 111.

¹H-NMR (CDCl₃) δppm:

1.38 - 1.56 (2H, m), 1.91 - 2.01 (2H, m), 2.55 - 2.69 (2H, m), 3.11 (2H, ddd, J = 4.0 Hz, 4.0 Hz, 13.0 Hz), 3.39 - 3.51 (1H, m), 4.18 (2H, d, J = 5.8 Hz), 6.28 (1H, ddd, J = 5.8 Hz, 5.8 Hz, 15.9 Hz), 6.57 (1H, d, J = 15.9 Hz), 7.25 - 7.35 (4H, m).

Reference Example 114

Preparation of tert-butyl 4-[3-(4-chlorophenyl)propoxy]piperidine-1-carboxylate

A mixture of tert-butyl 4-[3-(4-chlorophenyl)-2-propenyloxy]piperidine-1-carboxylate (0.37 g, 1.05 mmol) prepared in Reference example 112 and platinum oxide (37 mg) in ethanol (10 ml), was stirred at room temperature under atmospheric pressure of hydrogen. The reaction mixture was filtered through Celite, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 4/1) to afford tert-butyl 4-[3-(4-chlorophenyl)propoxy]piperidine-1-carboxylate (0.151 g, yield 40%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.40 - 1.51 (2H, m), 1.46 (9H, s), 1.77 - 1.90 (4H, m),
2.67 (2H, t, J = 7.9 Hz), 3.02 - 3.12 (2H, m), 3.38 -
3.45 (3H, m), 3.73 - 3.79 (2H, m), 7.11 (2H, d, J = 8.4
5 Hz), 7.24 (1H, d, J = 8.4 Hz).

Reference Example 115

Preparation of 4-[3-(4-chlorophenyl) propoxy]piperidine

Tert-butyl 4-[3-(4-chlorophenyl) propoxy]-
piperidine-1-carboxylate (0.151 g, 0.427 mmol) prepared
10 in Reference example 114 was dissolved in methylene
chloride (4 ml), to which trifluoroacetic acid was
added, and the mixture was stirred at room temperature
overnight. The reaction mixture was neutralized with
sodium hydroxide aqueous solution, and the mixture was
15 extracted with methylene chloride twice. The extracts
were combined and washed with brine. The organic layer
was dried over sodium sulfate, and then filtered. The
filtrate was concentrated under reduced pressure, and
the residue was dried *in vacuo* to afford 4-[3-(4-
20 chlorophenyl) propoxy]piperidine (0.109 g, yield 92%)
as a brown oil.

¹H-NMR (CDCl₃) δppm:

1.35 - 1.51 (2H, m), 1.83 - 1.94 (4H, m), 2.54 - 2.70
(4H, m), 3.03 - 3.14 (2H, m), 3.22 - 3.38 (1H, m), 3.43
25 (2H, t, J = 6.3 Hz), 7.12 (2H, d, J = 8.4 Hz), 7.25
(2H, d, J = 8.4 Hz).

Reference Example 116

Preparation of tert-butyl 4-[2-(4-chlorophenyl)

ethoxy]piperidine-1-carboxylate

(4-Chlorobenzyl)triphenyl phosphonium chloride (1.191 g, 2.81 mmol) was dissolved in DMSO (20 ml), to which sodium hydride (0.118 g, 2.95 mmol) was
5 added while cooling in an ice-bath, and the mixture was stirred at room temperature for 1 hour. Tert-butyl 4-formyloxypiperidine-1-carboxylate (0.500 g, 2.34 mmol) was added to the mixture, and the resulting mixture was stirred at room temperature overnight. After the
10 reaction mixture was diluted with ethyl acetate, the mixture was washed with water and brine. The organic layer was dried over sodium sulfate, and then filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel
15 column chromatography (methylene chloride/hexane = 9/1) to afford a colorless oil.

Using thus obtained oil, tert-butyl 4-[2-(4-chlorophenyl) ethoxy]piperidine-1-carboxylate (0.127 g, yield 16%) as a colorless oil was prepared in the same
20 manner as described in Reference Example 114.

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.40-1.51 (2H, m), 1.45 (9H, s), 1.71 - 1.79 (2H, m),
2.83 (2H, t, $J = 6.9$ Hz), 3.02 - 3.13 (2H, m), 3.38 -
3.44 (1H, m), 3.62 - 3.75 (4H, m), 7.15 (2H, d, $J = 8.5$
25 Hz), 7.25 (2H, d, $J = 8.5$ Hz).

Reference Example 117

Preparation of 4-[2-(4-chlorophenyl) ethoxy]piperidine

Using tert-butyl 4-[2-(4-chlorophenyl)

ethoxy]piperidine-1-carboxylate (0.127 g, 0.374 mmol) prepared in Reference Example 116, 4-[2-(4-chlorophenyl)ethoxy]piperidine (0.080 g, yield 89%) as a colorless oil was prepared in the same manner as described in Reference Example 115.

¹H-NMR (CDCl₃) δppm:

1.37 - 1.48 (2H, m), 1.84 - 1.91 (2H, m), 2.53 - 2.63 (2H, m), 2.83 (2H, t, J = 7.0 Hz), 3.01 - 3.09 (2H, m), 3.25 - 3.41 (1H, m), 3.64 (2H, t, J = 7.0 Hz), 7.15 (2H, d, J = 8.4 Hz), 7.25 (2H, d, J = 8.4 Hz).

Reference Example 118

Preparation of 1-(2-nitrovinyl)-4-trifluoromethylbenzene

4-Trifluoromethylbenzaldehyde (3.00 g, 17.2 mmol) was dissolved in nitromethane (10 ml), to which ammonium acetate (1.341 g, 17.4 mmol) was added, and the mixture was heated under reflux for 2 hours. Water was added to the mixture, which was extracted with methylene chloride twice, and the extracts were combined and washed with brine, and dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 9/1) to afford 1-(2-nitrovinyl)-4-trifluoromethylbenzene (1.596 g, yield 43%) as a pale yellow crystalline powder.

¹H-NMR (CDCl₃) δppm:

7.58 - 7.74 (5H, m), 8.02 (1H, d, J = 13.8 Hz).

Reference Example 119

Preparation of 2-(4-trifluoromethylphenyl) ethylamine

Lithium aluminum hydride (0.558 g, 14.7 mmol) was suspended in THF (10 ml), to which a solution of 1-(2-nitrovinyl)-4-trifluoromethylbenzene (1.596 g, 7.35 mmol) prepared in Reference Example 118 in THF (10 ml) was added dropwise while cooling in an ice-bath, and the mixture was heated under reflux for 2 hours. Methanol was slowly added to the mixture until it no longer foamed. Water (0.6 ml), 15% sodium hydroxide aqueous solution (0.6 ml) and water (1.8 ml) were added in this order, and the insoluble substances were removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel with an amine-treated surface (Fuji Silysia ; NH-DM1020, solvent ; methylene chloride/n-hexane = 4/1) to afford 2-(4-trifluoromethylphenyl) ethylamine (0.431 g, yield 31%) as an orange-colored oil.

$^1\text{H-NMR}$ (CDCl_3) δppm :

2.81 (2H, t, $J = 6.9$ Hz), 3.03 (2H, t, $J = 6.9$ Hz),
7.32 (2H, d, $J = 8.0$ Hz), 7.56 (2H, d, $J = 8.0$ Hz).

Reference Example 120

Preparation of tert-butyl N-(1-benzylpiperidin-4-yl)-N-[2-(4-trifluoromethylphenyl) ethyl]carbamate

2-(4-Trifluoromethylphenyl)ethylamine (0.431 g, 2.28 mmol) prepared in Reference Example 119 and 1-benzyl-4-piperidone (0.517 g, 2.73 mmol) were dissolved

in methanol (15 ml), to which sodium cyanoborohydride (0.429 g, 6.83 mmol) and acetic acid (0.52 ml, 9.11 mmol) were added, and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate. The mixture was washed with saturated sodium bicarbonate aqueous solution and brine. The organic layer was dried over sodium sulfate, and then filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in methanol (5 ml), to which di-tert-butyl dicarbonate (0.597 g, 2.74 mmol) was added, and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate, and the mixture was washed with brine. The organic layer was dried over sodium sulfate, and then filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 3/1) to afford tert-butyl N-(1-benzylpiperidin-4-yl)-N-[2-(4-trifluoromethylphenyl)ethyl]carbamate (0.437 g, yield 41%) as a colorless oil.

^1H -NMR (CDCl_3) δ ppm:

1.55 (9H, s), 1.59 - 1.73 (4H, m), 1.90 - 2.10 (2H, m), 2.82 - 2.96 (4H, m), 3.24 - 3.28 (2H, m), 3.49 (2H, s), 4.00 (1H, bs), 7.26 - 7.31 (7H, m), 7.54 (2H, d, J = 8.0 Hz).

Reference Example 121

Preparation of tert-butyl N-(piperidin-4-yl)-N-[2-(4-trifluoromethylphenyl) ethyl]carbamate

A mixture of tert-butyl N-(1-benzylpiperidin-4-yl)-N-[2-(4-trifluoromethylphenyl)ethyl]carbamate
5 (0.437 g, 0.944 mmol) prepared in Reference Example 120 and 20% palladium hydroxide/carbon (100 mg) in ethanol (20 ml) was stirred at room temperature under an atmospheric pressure of hydrogen. The reaction mixture was filtered through Celite, and the filtrate was
10 concentrated under reduced pressure to afford tert-butyl N-(piperidin-4-yl)-N-[2-(4-trifluoromethylphenyl)ethyl]carbamate (0.332 g, yield 94%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

15 1.49 (9H, s), 1.51 - 1.80 (4H, m), 2.62 - 3.49 (9H, m), 7.28 - 7.31 (2H, m), 7.54 (2H, d, $J = 8.0$ Hz).

Reference Example 122

Preparation of tert-butyl 4-(4-trifluoromethylbenzyloxy)piperidine-1-carboxylate

20 Tert-butyl 4-hydroxypiperidine-1-carboxylate (1.88 g, 9.34 mmol) was dissolved in THF (20 ml). Sodium hydride (411 mg, 10.3 mmol) was added to this solution while cooling in an ice-bath, and the mixture was stirred for 1 hour. 4-(Trifluoromethyl)
25 benzylbromide (2.23 g, 9.34 mmol) was added to the mixture, which was stirred at room temperature for 2 hours. Water was added to the reaction mixture, which was extracted with methylene chloride. The extract was

dried over magnesium sulfate, and then filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to afford tert-butyl 4-(4-trifluoromethylbenzyloxy)piperidine-1-carboxylate (2.56 g, yield 76%) as a pale yellow oil.

¹H-NMR (CDCl₃) δppm:

1.46 (9H, s), 1.51 - 1.67 (2H, m), 1.83 - 1.91 (2H, m),
10 3.07 - 3.18 (2H, m), 3.52 - 3.63 (1H, m), 3.73 - 3.83 (2H, m), 4.61 (2H, m), 7.46 (2H, d, J = 8.2 Hz), 7.60 (2H, d, J = 8.2 Hz).

Using a corresponding starting material, a compound of Reference Example 123 was prepared in the same manner as described in Reference Example 122.

Reference Example 123

tert-butyl 4-(4-trifluoromethoxybenzyloxy)piperidine-1-carboxylate

a pale yellow oil, yield 74%

20 ¹H-NMR (CDCl₃) δppm:

1.46 (9H, s), 1.51 - 1.65 (2H, m), 1.82 - 1.90 (2H, m),
3.06 - 3.17 (2H, m), 3.52 - 3.62 (1H, m), 3.73 - 3.83 (2H, m), 4.54 (2H, s), 7.17 - 7.20 (2H, m), 7.35 - 7.38 (2H, m).

25 Reference Example 124

Preparation of 4-(4-trifluoromethylbenzyloxy)piperidine

Tert-butyl 4-(4-trifluoromethylbenzyloxy)-piperidine-1-carboxylate (2.56 g, 7.12 mmol) prepared

in Reference Example 122 was dissolved in methylene chloride (20 ml), to which trifluoroacetic acid (10 ml) was added dropwise, and the mixture was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was then dissolved in methylene chloride. This solution was neutralized with sodium hydroxide aqueous solution and the mixture was extracted with methylene chloride. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to afford 4-(4-trifluoromethylbenzyloxy)piperidine (1.85 g, yield 99%) as a white powder.

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.46 - 1.60 (2H, m), 1.87 (1H, s), 1.93 - 2.01 (2H, m), 2.58 - 2.69 (2H, m), 3.07 - 3.16 (2H, m), 3.43 - 3.54 (1H, m), 4.61 (2H, s), 7.44 - 7.48 (2H, m), 7.57 - 7.61 (2H, m).

Using corresponding starting materials, compounds of Reference Examples 125 to 128 were prepared in the same manner as described in Reference Example 124.

Reference Example 125

4-(4-trifluoromethoxybenzyloxy)piperidine

a white powder, yield 74%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.45 - 1.60 (2H, m), 1.92 - 2.02 (2H, m), 2.11 (1H, s), 2.59 - 2.70 (2H, m), 3.07 - 3.17 (2H, m), 3.43 - 3.54

(1H, m), 4.55 (2H, s), 7.17 - 7.20 (2H, m), 7.35 - 7.40 (2H, m).

Reference Example 126

4-(4-chlorobenzyloxy)piperidine

5 a white powder, yield 94%

¹H-NMR (CDCl₃) δppm:

1.39 - 1.56 (3H, m), 1.90 - 1.99 (2H, m), 2.55 - 2.66 (2H, m), 3.06 - 3.11 (2H, m), 3.39 - 3.51 (1H, m), 4.52 (2H, s), 7.25 - 7.33 (4H, m).

10 Reference Example 127

4-(3,4-dichlorobenzyloxy)piperidine

a white powder, yield 99%

¹H-NMR (CDCl₃) δppm:

1.45 - 1.60 (2H, m), 1.91 - 2.01 (2H, m), 2.19 (1H, s),
 15 2.59 - 2.70 (2H, m), 3.07 - 3.16 (2H, m), 3.42 - 3.52 (1H, m), 4.50 (2H, s), 7.17 (1H, dd, J = 1.9 Hz, 8.2 Hz), 7.40 (1H, d, J = 8.2 Hz), 7.45 (1H, d, J = 1.9 Hz).

Reference Example 128

20 4-(4-phenylbenzyloxy)piperidine

a white powder, yield 16%

¹H-NMR (CDCl₃) δppm:

1.45 - 1.60 (2H, m), 1.72 (1H, s), 1.95 - 2.02 (2H, m),
 2.57 - 2.68 (2H, m), 3.07 - 3.16 (2H, m), 3.45 - 3.56 (1H, m), 4.60 (2H, s), 7.25 - 7.60 (9H, m).

Reference Example 129

Preparation of (1-benzylpiperidin-4-yl)-(4-trifluoromethoxyphenyl)amine

A mixture of 1-bromo-4-trifluoromethoxybenzene (2.0 g, 8.3 mmol), 4-amino-1-benzylpiperidine (1.73 g, 9.13 mmol), palladium acetate (37 mg, 0.17 mmol), (R)-(+)-BINAP (155 mg, 0.25 mmol) and sodium tert-butoxide (1.2 g, 11.6 mmol) in toluene (30 ml) was refluxed under a nitrogen atmosphere for 5 hours. Ethyl acetate and water were added to the reaction mixture while stirring, the insoluble substances were removed by filtration through Celite, and the filtrate was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to afford (1-benzylpiperidin-4-yl)-(4-trifluoromethoxyphenyl)amine (3.0 g, yield 99%) as a dark oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.39 - 1.55 (2H, m), 1.98 - 2.05 (2H, m), 2.09 - 2.20 (2H, m), 2.80 - 2.89 (2H, m), 3.21 - 3.28 (1H, m), 3.52 (2H, s), 3.52 - 3.59 (1H, m), 6.48 - 6.55 (2H, m), 6.98 - 7.02 (2H, m), 7.22 - 7.33 (5H, m).

Reference Example 130

Preparation of piperidin-4-yl-(4-trifluoromethoxyphenyl)amine

A mixture of (1-benzylpiperidin-4-yl)-(4-trifluoromethoxyphenyl)amine (3.0 g, 8.3 mmol) prepared in Reference Example 129 and a catalytic amount of 10%

palladium/carbon in ethanol (30 ml) was refluxed under an atmospheric pressure of hydrogen for 20 hours. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The
5 residue was purified by silica gel column chromatography (methylene chloride/methanol = 10/1) to afford piperidin-4-yl-(4-trifluoromethoxyphenyl)amine (2.02 g, yield 94%) as a colorless crystalline powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

10 1.24 - 1.39 (2H, m), 2.03 - 2.08 (2H, m), 2.65 - 2.77 (2H, m), 3.08 - 3.16 (2H, m), 3.24 - 3.41 (1H, m), 3.59 (1H, br), 6.50 - 6.58 (2H, m), 6.99 - 7.03 (2H, m).

Reference Example 131

Preparation of tert-butyl 4-(4-chlorophenylamino)-
15 piperidine-1-carboxylate

A mixture of p-bromochlorobenzene (1.91 g, 9.99 mmol), tert-butyl 4-aminopiperidine-1-carboxylate (2.0 g, 9.99 mmol), palladium acetate (45 mg, 0.2 mmol), (R)-(+)-BINAP (187 mg, 0.3 mmol) and sodium
20 tert-butoxide (1.35 g, 14.0 mmol) in toluene (20 ml) was refluxed under a nitrogen atmosphere for 1 hour. Ethyl acetate and water were added to the reaction mixture while stirring, the insoluble substances were removed by filtration through Celite, and the filtrate
25 was then extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by

silica gel column chromatography (methylene chloride/methanol = 100/1) to afford tert-butyl 4-(4-chlorophenylamino)piperidine-1-carboxylate (2.67 g, yield 86%) as a yellow powder.

5 ^1H -NMR (CDCl_3) δ ppm:

1.21 - 1.54 (2H, m) 1.46 (9H, s), 1.99 - 2.05 (2H, m),
2.85 - 2.97 (2H, m), 3.37 (1H, br), 3.51 (1H, br), 4.01
- 4.07 (2H, m), 6.48 - 6.54 (2H, m), 7.07 - 7.14 (2H,
m).

10 Using corresponding starting materials,
compounds of Reference Examples 132 to 133 were
prepared in the same manner as described in Reference
Example 131.

Reference Example 132

15 tert-butyl 4-(4-trifluoromethylphenylamino)piperidine-
1-carboxylate

a yellow powder, yield 93%

^1H -NMR (CDCl_3) δ ppm:

1.21 - 1.58 (2H, m), 1.47 (9H, s), 2.00 - 2.06 (2H, m),
20 2.88 - 2.99 (2H, m), 3.47 (1H, br), 3.88 (1H, bs), 4.03
- 4.09 (1H, m), 6.56 (2H, d, $J = 8.6$ Hz), 7.39 (2H, d,
 $J = 8.6$ Hz).

Reference Example 133

tert-butyl 4-(4-cyanophenylamino)piperidine-1-
25 carboxylate

a yellow powder, yield 92%

^1H -NMR (CDCl_3) δ ppm:

1.26 - 1.54 (2H, m), 1.47 (9H, s), 1.99 - 2.05 (2H, m),

2.87 - 2.99 (2H, m), 3.41 - 3.53 (1H, br), 4.02 - 4.14 (3H, m), 6.52 - 6.58 (2H, m), 7.39 - 7.45 (2H, m).

Reference Example 134

Preparation of 4-(4-chlorophenylamino)piperidine

5 Tert-butyl 4-(4-chlorophenylamino)piperidine-1-carboxylate (2.67 g, 8.59 mmol) prepared in Reference Example 131 was dissolved in methylene chloride (20 ml), to which trifluoroacetic acid (15 ml) was added dropwise, and the mixture was stirred at room
10 temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was then dissolved in methylene chloride. This solution was neutralized with sodium hydroxide aqueous solution, and the mixture was extracted with methylene
15 chloride. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to afford 4-(4-chlorophenylamino)piperidine as a pale yellow powder.

20 ¹H-NMR (CDCl₃) δppm:

1.22 - 1.38 (2H, m), 2.02 - 2.07 (2H, m), 2.65 - 2.76 (2H, m), 3.08 - 3.16 (2H, m), 3.25 - 3.38 (1H, m), 3.50 - 3.54 (1H, m), 6.48 - 6.55 (2H, m), 7.06 - 7.26 (2H, m).

25 Using corresponding starting materials, compounds of Reference Examples 135 to 136 were prepared in the same manner as described in Reference Example 134.

Reference Example 135

4-(4-trifluoromethylphenylamino)piperidine

a yellow powder, yield 97%

¹H-NMR (CDCl₃) δppm:

- 5 1.26 - 1.42 (2H, m), 2.04 - 2.09 (2H, m), 2.67 - 2.78
(2H, m), 3.09 - 3.17 (2H, m), 3.34 - 3.46 (1H, m), 3.86
- 3.90 (1H, m), 6.59 (2H, d, J = 8.6 Hz), 7.38 (2H, d,
J = 8.6 Hz).

Reference Example 136

10 4-(4-cyanophenylamino)piperidine

a yellow powder, yield 98%

¹H-NMR (CDCl₃) δppm:

- 1.27 - 1.45 (2H, m), 2.02 - 2.07 (2H, m), 2.67 - 2.78
(2H, m), 3.09 - 3.17 (2H, m), 3.34 - 3.46 (1H, m), 4.09
15 - 4.13 (1H, m), 6.51 - 6.57 (2H, m), 7.38 - 7.44 (2H,
m).

Reference Example 137

Preparation of tert-butyl 4-(toluene-4-sulfonyloxy)-
piperidine-1-carboxylate

- 20 Tert-butyl 4-hydroxypiperidine-1-carboxylate
(2.22 g, 10.0 mmol) was dissolved in acetonitrile (40
ml), to which triethylamine (2.74 ml, 19.7 mmol) and
N,N,N',N'-tetramethyl-1,6-diaminohexane (0.57 ml, 2.64
mmol) were added, and the mixture was cooled in an
25 ice-bath. p-Toluenesulfonyl chloride (2.75 g, 14.4
mmol) was added to this mixture, which was allowed to
return to room temperature and stirred overnight.
Water was poured into the reaction mixture, and the

mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica
5 gel column chromatography (methylene chloride/methanol = 100/1) to afford tert-butyl 4-(toluene-4-sulfonyloxy)piperidine-1-carboxylate (4.16 g, yield 89%) as a pale yellow powder.

^1H -NMR (CDCl_3) δ ppm:

10 1.44 (9H, s), 1.64 - 1.82 (4H, m), 2.44 (3H, s), 3.19 - 3.30 (2H, m), 3.54 - 3.64 (2H, m), 4.63 - 4.72 (1H, m), 7.31 - 7.37 (2H, m), 7.78 - 7.82 (2H, m).

Reference Example 138

Preparation of tert-butyl 4-(4-trifluoro-
15 methoxyphenylsulfanyl)piperidine-1-carboxylate

4-(Trifluoromethoxy)thiophenol (2.0 g, 10.3 mmol) was dissolved in THF (30 ml), and this solution was cooled in an ice-bath. To which sodium hydride (453 mg, 11.3 mmol) was added, and the mixture was
20 stirred for 30 minutes. To which tert-butyl 4-(toluene-4-sulfonyloxy)piperidine-1-carboxylate (3.66 g, 10.3 mmol) prepared in Reference Example 137 was added, and the resulting mixture was stirred at room temperature for 30 minutes, and then heated under
25 reflux for 1 hour. Water was added to the reaction mixture, and the mixture was extracted with methylene chloride. The extract was dried over magnesium sulfate, and then filtered, and the filtrate was

concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl chloride = 20/1) to afford tert-butyl 4-(4-trifluoromethoxyphenylsulfanyl)piperidine-1-

5 carboxylate (3.12 g, yield 80%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.45 (9H, s), 1.46 - 1.60 (2H, m), 1.87 - 1.95 (2H, m), 2.86 - 2.98 (2H, m), 3.14 - 3.23 (1H, m), 3.94 - 4.00 (2H, m), 7.13 - 7.17 (2H, m), 7.40 - 7.47 (2H, m).

10 Reference Example 139

Preparation of 4-(4-trifluoromethoxyphenylsulfanyl)-piperidine

Using tert-butyl 4-(4-trifluoromethoxyphenylsulfanyl)piperidine-1-carboxylate prepared in

15 Reference Example 138, 4-(4-trifluoromethoxyphenylsulfanyl)piperidine (yield 92%) as a colorless oil was prepared in the same manner as described in Reference Example 134.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

20 1.43 - 1.59 (2H, m), 1.91 - 1.98 (2H, m), 2.59 - 2.70 (2H, m), 3.06 - 3.20 (3H, m), 7.12 - 7.16 (2H, m), 7.40 - 7.46 (2H, m).

Reference Example 140

Preparation of tert-butyl 4-(4-trifluoromethoxybenzyl)-piperidine-1-carboxylate

25 Triphenyl-(4-trifluoromethoxybenzyl)-phosphonium bromide (2.0 g, 3.87 mmol) was dissolved in DMSO (20 ml), to which sodium hydride (168 mg, 4.2

mmol) was added, and the mixture was stirred for 30 minutes. Tert-butyl 4-oxopiperidine-1-carboxylate (700 mg, 3.51 mmol) was added to the mixture, and the resulting mixture was stirred at 60°C for 2 hours. The
5 reaction mixture was poured into water, and extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to afford
10 a colorless crystalline powder.

A mixture of this intermediate and a catalytic amount of 10% Pd/C in methanol (30 ml) was stirred at room temperature under an atmospheric
15 pressure of hydrogen for 3 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to afford tert-butyl 4-(4-trifluoromethoxybenzyl)piperidine-1-carboxylate (1.28 g, yield 60%) as a colorless oil.

20 ¹H-NMR (CDCl₃) δppm:
1.06 - 1.21 (2H, m), 1.45 (9H, s), 1.57 - 1.70 (3H, m),
2.52 - 2.69 (4H, m), 4.08 (2H, br), 7.09 - 7.17 (4H, m).

Reference Example 141

25 Preparation of 4-(4-trifluoromethoxybenzyl)piperidine

Using tert-butyl 4-(4-trifluoromethoxybenzyl)piperidine-1-carboxylate prepared in Reference Example 140, 4-(4-trifluoromethoxybenzyl)piperidine was

prepared in the same manner as described in Reference Example 134.

Colorless solid, yield 99%

^1H -NMR (CDCl_3) δ ppm:

5 1.06 - 1.22 (2H, m), 1.50 (1H, s), 1.53 - 1.68 (3H, m),
2.48 - 2.60 (4H, m), 3.02 - 3.08 (2H, m), 7.09 - 7.17
(4H, m).

Reference Example 142

Preparation of 1-benzyl-4-(4-trifluoromethoxy-
10 benzylidene)piperidine

Triphenyl-(4-trifluoromethoxybenzyl)
phosphonium bromide (21.6 g, 41.75 mmol) was dissolved
in DMSO (110 ml), to which sodium hydride (1.82 g,
45.52 mmol) was added, and the mixture was stirred for
15 30 minutes. 1-Benzyl-4-piperidone (7.18 g, 37.96 mmol)
was added to the mixture, and the resulting mixture was
stirred at 60°C for 2 hours. The reaction mixture was
poured into ice water, and extracted with ethyl
acetate. The extract was washed with brine, dried over
20 magnesium sulfate, and then filtered. The filtrate was
concentrated under reduced pressure. The residue was
purified by silica gel column chromatography (methylene
chloride/ethyl acetate = 10/1) to afford 1-benzyl-4-(4-
trifluoromethoxybenzylidene)piperidine (9.75 g, yield
25 74%) as a yellow oil.

^1H -NMR (CDCl_3) δ ppm:

2.36 - 2.55 (8H, m), 3.53 (2H, s), 6.23 (1H, s), 7.11 -
7.34 (9H, m).

Using a corresponding starting material, a compound of Reference Example 143 was prepared in the same manner as described in Reference Example 142.

Reference Example 143

- 5 1-benzyl-4-(4-trifluoromethylbenzylidene)piperidine
a yellow oil, yield 52%

$^1\text{H-NMR}$ (CDCl_3) δppm :

2.38 - 2.57 (8H, m), 3.53 (2H, s), 6.28 (1H, m), 7.24 -
7.56 (9H, m).

10 Reference Example 144

Preparation of 4-(4-trifluoromethoxybenzyl)piperidine
(an alternative method for synthesis of the compound in
Reference Example 141)

- A mixture of 1-benzyl-4-(4-
15 trifluoromethylbenzylidene)piperidine (9.7 g, 27.92
mmol) prepared in Reference Example 142, 6 N
hydrochloric acid (9.3 ml), and 10% palladium/carbon
(970 mg) in ethanol (100 ml) was stirred at 50°C under
an atmospheric pressure of hydrogen for 5 hours. The
20 reaction mixture was filtered through Celite, and the
filtrate was concentrated under reduced pressure.
Water and 10% sodium hydroxide aqueous solution were
added to the residue, and the mixture was extracted
with methylene chloride. The extract was washed with
25 brine, dried over magnesium sulfate, and then filtered.
The filtrate was concentrated under reduced pressure to
afford 4-(4-trifluoromethoxybenzyl)piperidine (6.77 g,
yield 94%) as a colorless crystalline powder.

¹H-NMR (CDCl₃) δppm:

1.06 - 1.22 (2H, m), 1.50 (1H, s), 1.53 - 1.68 (3H, m),
2.48 - 2.60 (4H, m), 3.02 - 3.08 (2H, m), 7.09 - 7.17
(4H, m).

- 5 Using corresponding starting materials,
compounds of Reference Examples 145 and 146 were
prepared in the same manner as described in Reference
Example 144.

Reference Example 145

- 10 4-(4-trifluoromethylbenzyl)piperidine

a colorless crystalline powder, yield 94%

¹H-NMR (CDCl₃) δppm:

1.06 - 1.29 (2H, m), 1.50 - 1.69 (4H, m), 2.48 - 2.60
(4H, m), 3.02 - 3.09 (2H, m), 7.23 - 7.29 (2H, m), 7.51

- 15 - 7.54 (2H, m).

Reference Example 146

4-(4-chlorobenzyl)piperidine

a colorless crystalline powder, yield 94%

¹H-NMR (CDCl₃) δppm:

- 20 1.07 - 1.21 (2H, m), 1.53 - 1.82 (4H, m), 2.47 - 2.59
(4H, m), 3.02 - 3.08 (2H, m), 7.04 - 7.08 (2H, m), 7.22
- 7.27 (2H, m).

Reference Example 147

- Preparation of 1-benzylpiperidine-4-carboxylic acid N-
25 methyl-N-methoxyamide

1-benzylpiperidine-4-carboxylic acid

hydrochloride (21 g, 82.3 mmol) was suspended in
chloroform, to which DMF (1 ml) and thionyl chloride

(30 ml) were added at room temperature, and the mixture was heated under reflux for 2 hours. The mixture was concentrated under reduced pressure to prepare an acid chloride compound.

5 In another vessel, N,O-dimethylhydroxylamine hydrochloride (12 g, 0.12 mol) was dissolved in acetone (200 ml)-water (20 ml), to which potassium carbonate (34.12 g, 246.9 mmol) was added, and the mixture was stirred while cooling in an ice-bath. A solution of
10 the previously prepared acid chloride compound in acetone (120 ml) was added dropwise to this mixture, which was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, to which water was added, and the mixture was
15 extracted with methylene chloride. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to afford 1-benzylpiperidine-4-carboxylic acid N-methyl-N-methoxyamide (16.8 g, yield
20 78%) as a brown oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.65 - 1.92 (4H, m), 1.97 - 2.07 (2H, m), 2.62 - 2.68 (1H, m), 2.91 - 2.96 (2H, m), 3.17 (3H, s), 3.51 (2H, s), 3.69 (3H, s), 7.20 - 7.32 (5H, m).

25 Reference Example 148

Preparation of 1-benzyl-4-(4-trifluoromethoxybenzoyl)-piperidine

1-Bromo-4-trifluoromethoxybenzene (5.3 g,

22.0 mmol) was dissolved in dry THF (70 ml) under a nitrogen atmosphere, and this solution was cooled to -60°C. n-Butyllithium (1.6 M) hexane solution (15 ml, 24.0 mmol) was added dropwise to the solution, and the mixture was allowed to reach a temperature of -30°C and stirred for 1 hour. This mixture was cooled to -60°C again, to which a solution of 1-benzylpiperidine-4-carboxylic acid N-methyl-N-methoxyamide (4.1 g, 15.6 mmol) prepared in Reference Example 147 in THF (10 ml) was added dropwise, and the mixture was stirred for 1 hour and then at 0°C for 3 hours. The reaction mixture was poured into saturated ammonium chloride aqueous solution, and extracted with diethyl ether. The extract was washed with water and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 4/1) to afford 1-benzyl-4-(4-trifluoromethoxybenzoyl)piperidine (4.8 g, yield 85%) as a pale yellow oil.

¹H-NMR (CDCl₃) δppm:

1.80 - 1.89 (4H, m), 2.04 - 2.18 (2H, m), 2.94 - 3.01 (2H, m), 3.15 - 3.24 (1H, m), 3.55 (2H, s), 7.19 - 7.34 (7H, m), 7.95 - 8.01 (2H, m).

Using a corresponding starting material, a compound of Reference Example 149 was prepared in the same manner as described in Reference Example 148.

Reference Example 149

1-benzyl-4-(4-trifluoromethylbenzoyl)piperidine

a pale yellow oil, yield 66%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.78 - 1.89 (4H, m), 2.09 - 2.19 (2H, m), 2.94 - 3.02
5 (2H, m), 3.16 - 3.29 (1H, m), 3.55 (2H, m), 7.26 - 7.34
(5H, m), 7.70 - 7.74 (2H, m), 8.00 - 8.04 (2H, m).

Reference Example 150

Preparation of 4-(4-trifluoromethoxybenzoyl)piperidine

1-Benzyl-4-(4-trifluoromethoxybenzoyl)-

10 piperidine (4.8 g, 13.22 mmol) prepared in Reference
Example 148 was dissolved in methylene chloride (60
ml), and this solution was cooled in an ice-bath. 2-
Chloroethyl chloroformate (2.9 ml, 26.4 mmol) was added
dropwise to the solution, and the mixture was stirred
15 at the same temperature for 30 minutes. The reaction
mixture was concentrated under reduced pressure,
methanol (100 ml) was added to the residue, and the
resulting mixture was heated under reflux for 15
minutes. Water was added to the reaction mixture,
20 which was stirred for 30 minutes, and neutralized with
sodium hydroxide aqueous solution. The mixture was
extracted with methylene chloride. The extract was
washed with brine, dried over magnesium sulfate, and
then filtered. The filtrate was concentrated under
25 reduced pressure, and the residue was purified by
silica gel column chromatography (n-hexane/ethyl acetate
= 1/1) to afford 4-(4-trifluoromethoxybenzoyl)-
piperidine (1.3 g, yield 36%) as a pale orange-colored

crystalline powder.

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.57 - 1.88 (5H, m), 2.71 - 2.81 (2H, m), 3.15 - 3.23
(2H, m), 3.29 - 3.42 (1H, m), 7.27 - 7.28 (2H, m), 7.95
5 - 8.05 (2H, m).

Using corresponding starting materials,
compounds of Reference Examples 151 and 152 were
prepared in the same manner as described in Reference
Example 150.

10 Reference Example 151

4-(4-trifluoromethylbenzoyl)piperidine

a colorless crystalline powder, yield 68%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.61 - 1.76 (3H, m), 1.82 - 1.89 (2H, m), 2.72 - 2.83
15 (2H, m), 3.16 - 3.24 (2H, m), 3.32 - 3.44 (1H, m), 7.72
- 7.76 (2H, m), 8.01 - 8.05 (2H, m).

Reference Example 152

4-(4-chlorobenzoyl)piperidine

a colorless crystalline powder, yield 100%

20 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.60 - 1.84 (5H, m), 2.72 - 2.83 (2H, m), 3.16 - 3.24
(2H, m), 3.30 - 3.40 (1H, m), 7.41 - 7.47 (2H, m), 7.85
- 7.91 (2H, m).

Reference Example 153

25 Preparation of N-(2-[4-(4-trifluoromethylphenyl)-
piperazin-1-yl]ethyl)phthalimide

A mixture of 1-(4-trifluoromethylphenyl)-
piperazine (5.2 g, 22.59 mmol), N-(2-bromoethyl)-

phthalimide (5.22 g, 20.53 mmol) and potassium carbonate (3.36 g, 24.28 mmol) in DMF (30 ml) was stirred at 100°C for 2 hours. The reaction mixture was allowed to return to room temperature, to which water
5 was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene
10 chloride/ethyl acetate = 50/1), and the resulting solid was washed with methanol, and then dried *in vacuo* to afford N-{2-[4-(4-trifluoromethylphenyl)piperazin-1-yl]ethyl} phthalimide (4.85 g, yield 53%) as a white powder.

15 ¹H-NMR (CDCl₃) δppm:

2.64 - 2.72 (6H, m), 3.18 - 3.23 (4H, m), 3.86 (2H, t, J = 6.4 Hz), 6.89 (2H, d, J = 8.7 Hz), 7.45 (2H, d, J = 8.7 Hz), 7.70 - 7.75 (2H, m), 7.81 - 7.86 (2H, m).

Reference Example 154

20 Preparation of 2-[4-(4-trifluoromethylphenyl)piperazin-1-yl]ethylamine

N-{2-[4-(4-trifluoromethylphenyl)piperazin-1-yl]ethyl}phthalimide (4 g, 9.92 mmol) prepared in Reference Example 153 was suspended in ethanol (30 ml),
25 to which hydrazine monohydrate (0.53 ml, 10.91 mmol) was added, and the mixture was heated under reflux for 5 hours. The reaction mixture was allowed to return to room temperature, and the resulting precipitates were

collected by filtration. This was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 100/1) to afford 2-[4-(4-trifluoromethylphenyl)piperazin-1-yl]ethylamine (2.87 g, yield 5 100%) as a colorless crystalline powder.

^1H -NMR (CDCl_3) δ ppm:

1.33 (2H, bs), 2.49 (2H, t, $J = 6.1$ Hz), 2.59 - 2.63 (4H, m), 2.84 (2H, t, $J = 6.1$ Hz), 3.26 - 3.31 (4H, m), 6.92 (2H, d, $J = 8.7$ Hz), 7.48 (2H, d, $J = 8.7$ Hz).

10 Reference Example 155

Preparation of N-{2-[4-(4-trifluoromethylphenyl)-piperazin-1-yl]ethyl}formamide

A mixture of 2-[4-(4-trifluoromethylphenyl)piperazin-1-yl]ethylamine (906 mg, 3.32 mmol) prepared 15 in Reference Example 154 and ethyl formate (10 ml) was heated under reflux for 5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to 20 afford N-{2-[4-(4-trifluoromethylphenyl)piperazin-1-yl]ethyl} formamide (942 mg, yield 94%) as a white powder.

^1H -NMR (CDCl_3) δ ppm:

2.53 - 2.65 (6H, m), 3.26 - 3.31 (4H, m), 3.42 - 3.49 25 (2H, m), 6.05 (1H, bs), 6.92 (2H, d, $J = 8.7$ Hz), 7.49 (2H, d, $J = 8.7$ Hz), 8.21 (1H, s).

Reference Example 156

Preparation of N-methyl-{2-[4-(4-trifluoromethyl-

phenyl)piperazin-1-yl]ethyl} amine

Lithium aluminum hydride (237 mg, 6.25 mmol) was suspended in THF (20 ml), which was stirred while cooling in an ice-bath. To which a solution of N-{2-
5 [4-(4-trifluoromethylphenyl)piperazin-1-yl]ethyl}-formamide (942 mg, 3.13 mmol) prepared in Reference Example 155 in THF (10 ml) was added dropwise, and the mixture was stirred at room temperature for 2 hours and then heated under reflux for 2 hours. The reaction
10 mixture was allowed to return to room temperature, to which water and a 15% sodium hydroxide aqueous solution were added carefully. To the mixture, sodium sulfate was added, and the resulting mixture was vigorously stirred and filtered through Celite. The filtrate was
15 concentrated under reduced pressure to afford N-methyl-{2-[4-(4-trifluoromethylphenyl)piperazin-1-yl]ethyl}-amine (900 mg, yield 100%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

2.47 (3H, s), 2.52 - 2.74 (8H, m), 3.26 - 3.30 (4H, m),
20 3.71 - 3.77 (1H, m), 6.91 (2H, d, J = 8.7 Hz), 7.47
(2H, d, J = 8.7 Hz).

Reference Example 157

Preparation of tert-butyl 4-(2-methylaminoethyl)-piperazine-1-carboxylate

25 Tert-butyl 4-(2-chloroethyl)piperazine-1-carboxylate (3.13 g, 12.58 mmol) was dissolved in methanol (20 ml), to which 40% methylamine methanol solution (30 ml) was added, and the mixture was heated

under reflux for 5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in methylene chloride. The mixture was washed with saturated sodium hydrogencarbonate aqueous solution. The organic layer was dried over magnesium sulfate, and then filtered, and the filtrate was concentrated under reduced pressure to afford tert-butyl 4-(2-methylaminoethyl)piperazine-1-carboxylate (3.0 g, yield 98%) as a pale yellow oil.

10 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.46 (9H, m), 1.66 (1H, s), 2.36 - 2.41 (4H, m), 2.45 (3H, s), 2.46 - 2.53 (2H, m), 2.65 - 2.70 (2H, m), 3.40 - 3.44 (4H, m).

Reference Example 158

15 Preparation of N-[2-(4-trifluoromethylphenoxy)ethyl]-phthalimide

A mixture of N-(2-hydroxyethyl)phthalimide (3.59 g, 18.75 mmol), 4-hydroxybenzotrifluoride (3.04 g, 18.75 mmol), diethyl azodicarboxylate (4.37 ml, 28.13 mmol) and triphenylphosphine (7.38 g, 28.13 mmol) in THF (50 ml) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 5/1) to afford N-[2-(4-trifluoromethylphenoxy)ethyl]phthalimide (4.05 g, yield 69%) as a colorless crystalline powder.

25 $^1\text{H-NMR}$ (CDCl_3) δppm :

4.11 - 4.16 (2H, m), 4.25 - 4.30 (2H, m), 6.92 - 6.96 (2H, m), 7.48 - 7.52 (2H, m), 7.72 - 7.77 (2H, m), 7.83 - 7.89 (2H, m).

Reference Example 159

5 Preparation of 2-(4-trifluoromethylphenoxy)ethylamine

Using N-[2-(4-trifluoromethylphenoxy)ethyl]-phthalimide prepared in Reference Example 158, 2-(4-trifluoromethylphenoxy) ethylamine was prepared in the same manner as described in Reference Example 154.

10 a colorless oil, yield 95%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.36 (2H, s), 3.11 (2H, t, $J = 5.1$ Hz), 4.03 (2H, t, $J = 5.1$ Hz), 6.97 (2H, d, $J = 8.6$ Hz), 7.54 (2H, d, $J = 8.6$ Hz).

15 Reference Example 160

Preparation of N-[2-(4-trifluoromethylphenoxy)ethyl]-formamide

A mixture of 2-(4-trifluoromethylphenoxy) ethylamine (1.38 g, 6.72 mmol) prepared in Reference
20 Example 159 and ethyl formate (10 ml) was heated under reflux for 5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to afford N-[2-
25 (4-trifluoromethylphenoxy)ethyl]formamide (1.51 g, yield 97%) as a white powder.

$^1\text{H-NMR}$ (CDCl_3) δppm :

3.72 - 3.78 (2H, m), 4.09 - 4.13 (2H, m), 6.02 (1H,

bs), 6.96 (2H, d, $J = 8.6$ Hz), 7.56 (2H, d, $J = 8.6$ Hz), 8.24 (1H, s).

Reference Example 161

Preparation of N-methyl-N-[2-(4-
5 trifluoromethylphenoxy)ethyl]amine

N-[2-(4-trifluoromethylphenoxy)ethyl]-
formamide (2.02 g, 8.66 mmol) prepared in Reference
Example 160 was dissolved in THF (20 ml). Borane-THF
complex (1 M) THF solution (21.7 ml, 21.7 mmol) was
10 added dropwise to this solution while cooling in an
ice-bath, and the mixture was stirred overnight. The
reaction mixture was cooled, to which water and 6N
hydrochloric acid were added, and the mixture was
stirred for 20 minutes. The reaction mixture was
15 neutralized with a sodium hydroxide aqueous solution,
and the mixture extracted with methylene chloride. The
extract was dried over magnesium sulfate, and then
filtered. The filtrate was concentrated under reduced
pressure. The residue was purified by silica gel
20 column chromatography (methylene chloride/ methanol =
200/1) to afford N-methyl-N-[2-(4-
trifluoromethylphenoxy)ethyl]amine (1.05 g, yield 55%)
as a white powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

25 2.68 (3H, d, $J = 5.8$ Hz), 3.05 - 3.28 (2H, m), 4.06
(1H, br), 4.10 - 4.18 (1H, m), 4.45 - 4.54 (1H, m),
6.98 (2H, d, $J = 8.5$ Hz), 7.58 (2H, d, $J = 8.5$ Hz).

Reference Example 162

Preparation of N-methyl-N-[2-(4-trifluoromethoxyphenoxy)ethyl]amine

1-(2-Bromoethoxy)-4-(trifluoromethoxy)benzene (2.2 g, 7.72 mmol) was dissolved in methanol (20 ml), to which 40% methylamine methanol solution (20 ml) was added, and the mixture was heated under reflux for 5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in methylene chloride, and the mixture was washed with saturated sodium hydrogencarbonate aqueous solution. The organic layer was dried over magnesium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to afford N-methyl-N-[2-(4-trifluoromethoxyphenoxy)ethyl]amine (1.44 g, yield 79%) as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.54 (1H, s), 2.51 (3H, s), 2.97 (2H, t, $J = 5.1$ Hz), 4.06 (2H, t, $J = 5.1$ Hz), 6.85 - 6.92 (2H, m), 7.10 - 7.17 (2H, m).

Reference Example 163

Preparation of N-methyl-N-[2-(4-trifluoromethylphenoxy)ethyl]amine

Using 1-(2-bromoethoxy)-4-(trifluoromethyl)benzene, N-methyl-N-[2-(4-trifluoromethylphenoxy)ethyl]amine was prepared in the same manner as described in Reference Example 162.

a white powder, yield 82%

$^1\text{H-NMR}$ (CDCl_3) δppm :

2.68 (3H, d, $J = 5.8$ Hz), 3.02 - 3.28 (2H, m), 3.92 - 4.18 (2H, m), 4.41 - 4.54 (1H, m), 6.98 (2H, d, $J = 8.5$ Hz), 7.58 (2H, d, $J = 8.5$ Hz)

Reference Example 164

5 Preparation of N,N'-dimethyl-N-[4-(trifluoromethyl)-phenyl]-1,2-ethylenediamine

A mixture of 4-bromobenzotrifluoride (3.0 g, 13.3 mmol), N,N'-dimethylethylenediamine (9.4 g, 0.11 mol), palladium acetate (60 mg, 0.27 mmol), BINAP (250
10 mg, 0.40 mmol) and sodium tert-butoxide (1.80 g, 18.7 mmol) in toluene (20 ml) was refluxed under a nitrogen atmosphere for 3 hours. Ethyl acetate and water were added to the reaction mixture, and the mixture was stirred for a while. The insoluble substances were
15 removed by filtration through Celite, and the filtrate was then extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by
20 silica gel column chromatography (methylene chloride/methanol = 10/1) to afford N,N'-dimethyl-N-[4-(trifluoromethyl)phenyl]-1,2-ethylenediamine (650 mg, yield 21%) as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

25 1.53 (1H, s), 2.47 (3H, s), 2.82 (2H, t, $J = 6.7$ Hz), 3.02 (3H, s), 3.52 (2H, t, $J = 6.7$ Hz), 6.74 (2H, d, $J = 8.8$ Hz), 7.43 (2H, d, $J = 8.8$ Hz).

Reference Example 165

Preparation of tert-butyl N-[1-(4-chlorophenyl)-
piperidin-4-yl]-N-methylcarbamate

A mixture of p-bromochlorobenzene (3.13 g, 16.3 mmol), tert-butyl (piperidin-4-yl)-N-methylcarbamate (3.5 g, 10.8 mmol), palladium acetate (73 mg, 0.33 mmol), (S)-(-)-BINAP (305 mg, 0.49 mmol) and sodium tert-butoxide (2.2 g, 22.9 mmol) in toluene (30 ml) was refluxed under a nitrogen atmosphere for 3 hours. Ethyl acetate and water were added to the reaction mixture, the mixture was stirred for a while. The insoluble substances were removed by filtration through Celite, and the filtrate was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) to afford tert-butyl N-[1-(4-chlorophenyl)piperidin-4-yl]-N-methylcarbamate (4.7 g, yield 89%) as a yellow powder.

¹H-NMR (CDCl₃) δppm:

1.47 (9H, s), 1.70 - 1.90 (4H, m), 2.73 - 2.82 (2H, m), 2.74 (3H, s), 3.64 - 3.71 (2H, m), 4.08 (1H, br), 6.81 - 6.87 (2H, m), 7.15 - 7.22 (2H, m).

Using corresponding starting materials, compounds of Reference Examples 166 to 168 were prepared in the same manner as described in Reference Example 165.

Reference Example 166

tert-butyl N-[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]-N-methylcarbamate

yield 88%

5 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.48 (9H, s), 1.72 - 1.91 (4H, m), 2.76 (3H, s), 2.79 - 2.85 (2H, m), 3.67 - 3.73 (2H, m), 4.10 (1H, br), 6.86 - 6.93 (2H, m), 7.07 - 7.11 (2H, m).

Reference Example 167

10 tert-butyl N-[1-(4-trifluoromethylphenyl)piperidin-4-yl]-N-methylcarbamate

yield 91%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.47 (9H, s), 1.72 - 1.87 (4H, m), 2.74 (3H, s), 2.82 - 15 2.94 (2H, m), 3.83 - 3.89 (2H, m), 4.12 (1H, br), 6.92 (2H, d, $J = 8.7$ Hz), 7.46 (2H, d, $J = 8.7$ Hz).

Reference Example 168

tert-butyl N-[1-(4-cyanophenyl)piperidin-4-yl]-N-methylcarbamate

20 yield 73%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.47 (9H, s), 1.69 - 1.77 (4H, m), 2.73 (3H, s), 2.87 - 3.00 (2H, m), 3.89 - 3.97 (2H, m), 4.16 (1H, br), 6.84 - 6.89 (2H, m), 7.45 - 7.51 (2H, m).

25 Reference Example 169

Preparation of N-[1-(4-chlorophenyl)piperidin-4-yl]-N-methylamine

Tert-butyl N-[1-(4-chlorophenyl)piperidin-4-

- yl]-N-methylcarbamate (4.71 g, 14.5 mmol) prepared in Reference Example 165 was dissolved in methylene chloride (30 ml), to which trifluoroacetic acid (20 ml) was added dropwise, and the mixture was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was then dissolved in methylene chloride. The solution was neutralized with sodium hydroxide aqueous solution, and the mixture was extracted with methylene chloride.
- 10 The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to afford N-[1-(4-chlorophenyl)piperidin-4-yl]-N-methylamine (3.1 g, yield 95%) as a pale brown oil.
- 15 $^1\text{H-NMR}$ (CDCl_3) δppm :
0.99 (1H, s), 1.38 - 1.54 (2H, m), 1.95 - 2.00 (2H, m), 2.44 - 2.54 (1H, m), 2.46 (3H, s), 2.71 - 2.82 (2H, m), 3.55 - 3.63 (2H, m), 6.81 - 6.87 (2H, m), 7.14 - 7.21 (2H, m).
- 20 Using corresponding starting materials, compounds of Reference Examples 170 to 172 were prepared in the same manner as described in Reference Example 169.

Reference Example 170

- 25 N-[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]-N-methylamine
a pale brown powder, yield 100%
 $^1\text{H-NMR}$ (CDCl_3) δppm :

0.96 (1H, s), 1.39 - 1.55 (2H, m), 1.96 - 2.02 (2H, m),
 2.44 - 2.57 (1H, m), 2.47 (3H, s), 2.73 - 2.84 (2H, m),
 3.58 - 3.66 (2H, m), 6.86 - 6.92 (2H, m), 7.05 - 7.10
 (2H, m).

5 Reference Example 171

N-[1-(4-trifluoromethylphenyl)piperidin-4-yl]-N-
 methylamine

a pale brown powder, yield 100%

¹H-NMR (CDCl₃) δppm:

10 0.96 (1H, s), 1.36 - 1.52 (2H, m), 1.96 - 2.02 (2H, m),
 2.47 (3H, s), 2.50 - 2.62 (1H, m), 2.82 - 2.94 (2H, m),
 3.72 - 3.80 (2H, m), 6.92 (2H, d, J = 8.8 Hz), 7.45
 (2H, d, J = 8.8 Hz).

Reference Example 172

15 N-[1-(4-cyanophenyl)piperidin-4-yl]-N-methylamine

a pale brown powder, yield 99%

¹H-NMR (CDCl₃) δppm:

1.05 (1H, s), 1.34 - 1.49 (2H, m), 1.95 - 2.02 (2H, m),
 2.47 (3H, s), 2.55 - 2.67 (1H, m), 2.90 - 3.01 (2H, m),
 20 3.76 - 3.84 (2H, m), 6.82 - 6.90 (2H, m), 7.43 - 7.50
 (2H, m).

Reference Example 173

Preparation of benzyl N-(2-methyl-2-propenyl)carbamate

2-Methallylamine hydrochloride (21.52 g, 0.2
 25 mol) was dissolved in water (200 ml), to which benzyl
 chloroformate (37.53 g, 0.22 mol) was added, and the
 mixture was cooled in an ice-bath. Sodium carbonate
 (46.63 g, 0.44 mol) was gradually added to this

mixture, which was stirred at room temperature for 3 hours. After the reaction mixture was extracted with methylene chloride twice, the extracts were combined, dried over sodium sulfate, and then filtered, and the
5 filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 7/1) to afford benzyl N-(2-methyl-2-propenyl)carbamate (41.58 g, quantitative) as a colorless oil.

10 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.74 (3H, s), 3.75 (2H, d, $J = 6.2$ Hz), 4.69 - 4.94 (2H, m), 5.13 (2H, s), 7.26 - 7.39 (5H, m).

Reference Example 174

Production of 4-chlorobenzyl N-(2-methyl-2-propenyl)-
15 carbamate

4-chlorobenzyl alcohol (3.00 g, 21.0 mmol) and triphosgene (3.12 g, 10.5 mmol) were dissolved in toluene (15 ml), to which N-ethyldiisopropylamine (3.6 ml, 21.0 mmol) was added while cooling in an ice-bath,
20 and the mixture was stirred for 1 hour. The reaction mixture was poured into water, and extracted with methylene chloride twice. The extracts were combined and dried over magnesium sulfate, and then filtered. The filtrate was concentrated under a reduced pressure.
25 A solution of 2-methallylamine hydrochloride (2.49 g, 23.1 mmol) in water (40 ml) were added to the residue, to which sodium carbonate (5.15 g, 48.6 mmol) was added under while cooling in an ice-bath, and the mixture was

stirred for 15 minutes. The reaction mixture was extracted with methylene chloride twice, and the extracts were combined, dried over magnesium sulfate, and then filtered, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 10/1) to afford 4-chlorobenzyl N-(2-methyl-2-propenyl)carbamate (4.06 g, yield 80%) as a colorless liquid.

10 ^1H -NMR (CDCl_3) δ ppm:

1.74 (3H, s), 3.74 (2H, d, $J = 5.8$ Hz), 4.73 - 4.91 (2H, m), 5.08 (2H, s), 7.26 - 7.41 (4H, m).

Reference Example 175

Preparation of 4-fluorobenzyl N-(2-methyl-2-propenyl)-
15 carbamate

4-Fluorobenzyl alcohol (3.00 g, 23.8 mmol) was dissolved in THF (60 ml), to which 1,1'-carbonyldiimidazole (4.05 g, 25.0 mmol) was added while cooling in an ice-bath, and the mixture was stirred for 20 30 minutes. 2-Methallylamine hydrochloride (2.81 g, 26.2 mmol) and triethylamine (3.98 g, 28.5 mmol) were added to the mixture, which was stirred for 2 hours. After the reaction mixture was concentrated under reduced pressure, water were added to the residue, and 25 the mixture was extracted with methylene chloride twice. The extracts were combined, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was

purified by silica gel column chromatography (n-hexane/ethyl acetate = 10/1) to afford 4-fluorobenzyl N-(2-methyl-2-propenyl)carbamate (4.69 g, yield 88%) as a colorless oil.

5 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.73 (3H, s), 3.74 (2H, d, $J = 5.8$ Hz), 4.55 - 4.95 (3H, m), 5.08 (2H, s), 6.95 - 7.14 (2H, m), 7.27 - 7.41 (2H, m).

Reference Example 176

10 Preparation of 3-methoxymethoxy-2-methyl-1-propene

Chloromethyl methyl ether (105 ml, 1386 mmol) and N-ethyldiisopropylamine (265 ml, 1525 mmol) were added to a solution of 2-methyl-2-propen-1-ol (50 g, 693 mmol) in THF (500 ml) while cooling in an ice-bath, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was filtered and washed with diethyl ether, and the filtrate was concentrated under a reduced pressure. The residue was dissolved in diethyl ether, washed with water, a saturated sodium hydrogencarbonate solution and then water, dried over magnesium sulfate. After filtration, the filtrate was concentrated under a reduced pressure to afford 3-methoxymethoxy-2-methylpropene (9.7 g, yield 12%) as colorless liquid.

25 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.76 (3H, s), 3.39 (3H, s), 3.97 (2H, s), 4.65 (2H, s), 4.85 - 4.94 (1H, m), 4.98 - 5.06 (1H, m).

Reference Example 177

Preparation of 2-methoxymethoxymethyl-2-methyloxirane

m-Chloroperbenzoic acid (22.7 g, 92 mmol) was gradually added to a solution of 3-methoxymethoxy-2-methyl-1-propene (9.7 g, 84 mmol) prepared in Reference
5 Example 176 in methylene chloride (200 ml) while cooling in an ice-bath and the mixture was stirred at room temperature for 6 hours. Sodium hydrogencarbonate (14.1 g, 168 mmol), water and methylene chloride were added to the reaction mixture, which was stirred for a
10 while. The organic layer was separated, washed with sodium hydrogencarbonate aqueous solution, sodium thiosulfate aqueous solution and then sodium hydrogencarbonate aqueous solution, and dried over magnesium sulfate. After filtration, the filtrate was
15 concentrated under reduced pressure to afford 2-methoxymethoxymethyl-2-methyloxirane (6.8 g, yield 62%) as a green-colored oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.40 (3H, s), 2.65 (1H, d, $J = 4.9$ Hz), 2.78 (1H, d, $J = 4.9$ Hz), 3.38 (3H, s), 3.53 (1H, d, $J = 11.1$ Hz),
20 3.62 (1H, d, $J = 11.1$ Hz), 4.65 (2H, s).

Reference Example 178

Preparation of tert-butyl 4-(4-chlorobenzyl)piperazine-1-carboxylate

25 Potassium carbonate (1.45 g, 10.47 mmol) and 4-chlorobenzyl chloride (1.82 g, 8.86 mmol) were added to a solution of tert-butyl piperazine-1-carboxylate (1.5 g, 8.05 mmol) in DMF (10 ml), and the mixture was

stirred at 50°C for 1 hour. The reaction mixture was diluted with ethyl acetate, and the mixture was washed with water, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford tert-butyl 4-(4-chlorobenzyl)piperazine-1-carboxylate (2.50 g, quantitative) as a colorless oil.

10 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.45 (9H, s), 2.36 (4H, t, $J = 5.0$ Hz), 3.42 (4H, t, $J = 5.0$ Hz), 3.46 (2H, s), 7.23 - 7.31 (4H, m).

Reference Example 179

Preparation of 1-(4-chlorobenzyl)piperazine

15 Trifluoroacetic acid (8 ml) was added to a solution of tert-butyl 4-(4-chlorobenzyl)piperazine-1-carboxylate (2.50 g, 8.05 mmol) prepared in Reference Example 178 in methylene chloride (16 ml), and the mixture was stirred at room temperature for 5 hours.

20 The reaction mixture was concentrated under reduced pressure. Sodium hydroxide aqueous solution was added to the residue, and the mixture was extracted with methylene chloride. The extract was dried over sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to afford 1-(4-chlorobenzyl)piperazine (1.70 g, quantitative) as a colorless oil.

25 $^1\text{H-NMR}$ (DMSO-d_6) δ ppm:

2.55 - 2.74 (4H, m), 3.57 - 3.76 (6H, m), 7.35 - 7.45 (4H, m), 8.55 - 8.88 (1H, br).

Reference Example 180

Preparation of 1-(4-trifluoromethylbenzyl)piperazine

- 5 Using tert-butyl 4-(4-trifluoromethylbenzyl)-piperazine-1-carboxylate, 1-(4-trifluoromethylbenzyl)-piperazine was prepared in the same manner as described in Reference Example 179.

yield 100%

- 10 ¹H-NMR (CDCl₃) δppm:

2.72 (4H, t, J = 4.9 Hz), 3.16 - 3.26 (4H, m), 3.62 (2H, s), 7.44 (2H, d, J = 8.1 Hz), 7.59 (2H, d, J = 8.1 Hz).

Reference Example 181

- 15 Preparation of 1-(4-trifluoromethoxybenzyl)piperazine

 Using tert-butyl 4-(4-trifluoromethoxybenzyl)piperazine-1-carboxylate, 1-(4-trifluoromethoxybenzyl)piperazine was prepared in the same manner as described in Reference Example 179.

- 20 yield 100%

¹H-NMR (CDCl₃) δppm:

2.70 (4H, t, J = 4.9 Hz), 3.19 (4H, t, J = 4.9 Hz), 3.56 (2H, s), 7.17 (2H, d, J = 7.9 Hz), 7.33 (2H, d, J = 7.9 Hz).

- 25 Reference Example 182

Preparation of 4-[4-(4-

trifluoromethoxybenzyl)piperazin-1-yl]phenol

4-(4-hydroxyphenyl)piperazine (3 g, 16.8

mmol) and 4-trifluoromethoxy benzaldehyde (3.36 g, 17.7 mmol) were dissolved in methanol (60 ml) and methylene chloride (15 ml). Sodium cyanoborohydride (1.59 g, 25.3 mmol) and acetic acid (1.6 ml) were added to this solution while cooling in an ice-bath, and the mixture was stirred for 2 hours. Saturated sodium hydrogen-carbonate aqueous solution and methylene chloride were added to the reaction mixture, which was extracted with methylene chloride. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to afford 4-[4-(4-trifluoromethoxybenzyl)piperazin-1-yl]phenol (3.36 g, yield 57%) as a colorless crystalline powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

2.59 - 2.64 (4H, m), 3.05 - 3.10 (4H, m), 3.56 (2H, s), 4.90 - 5.40 (1H, br), 6.69 - 6.75 (2H, m), 6.79 - 6.85 (2H, m), 7.16 (2H, d, $J = 8.4$ Hz), 7.37 (2H, d, $J = 8.4$ Hz).

Reference Example 183

Preparation of 1-[4-(tetrahydropyran-2-yloxy)phenyl]-4-(4-trifluoromethoxyphenyl)piperazine

A mixture of 1-(4-trifluoromethoxyphenyl)-piperazine (4.4 g, 17.8 mmol), 2-(4-bromophenoxy)-tetrahydropyran (4.6 g, 17.8 mmol), palladium acetate (159 mg, 0.71 mmol), BINAP (666 mg, 1.07 mmol) and

sodium tert-butoxide (2.2 g, 23.1 mmol) in toluene (40 ml) was refluxed under a nitrogen atmosphere for 5 hours. Ethyl acetate and water were added to the reaction mixture, which was stirred for a while. The insoluble substances were removed by filtration through Celite, and the filtrate was then extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 20/1) to afford 1-[4-(tetrahydropyran-2-yloxy)phenyl]-4-(4-trifluoromethoxyphenyl)piperazine (2.7 g, yield 35%) as a white powder.

¹H-NMR (CDCl₃) δppm:

1.54 - 2.05 (6H, m), 3.21 - 3.34 (8H, m), 3.55 - 3.64 (1H, m), 3.89 - 3.99 (1H, m), 5.31 - 5.34 (1H, m), 6.90 - 7.03 (6H, m), 7.11 - 7.16 (2H, m).

This title compound was also prepared by the method described in Reference Example 185.

Reference Example 184

Preparation of 1-[4-(tetrahydropyran-2-yloxy)phenyl]-piperazine

A mixture of 2-(4-bromophenoxy)-tetrahydropyran (7.8 g, 30.3 mmol), piperazine (15.7 g, 180 mmol), palladium acetate (136 mg, 0.61 mmol), BINAP (567 mg, 0.91 mmol) and sodium tert-butoxide (3.8 g, 39.4 mmol) in toluene (50 ml) was refluxed under a

nitrogen atmosphere for 2 hours. Ethyl acetate and water were added to the reaction mixture, which was stirred for a while. The insoluble substances were removed by filtration through Celite, and the filtrate
5 was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/ethyl
10 acetate = 20/1) to afford 1-[4-(tetrahydropyran-2-yloxy)phenyl]piperazine (6.8 g, yield 85%) as a pale gray powder.

¹H-NMR (CDCl₃) δppm:

1.57 - 2.04 (6H, m), 3.00 - 3.06 (8H, m), 3.53 - 3.66
15 (1H, m), 3.89 - 3.99 (1H, m), 5.29 - 5.32 (1H, m), 6.84 - 6.90 (2H, m), 6.95 - 7.02 (2H, m).

Reference Example 185

Preparation of 1-[4-(tetrahydropyran-2-yloxy)phenyl]-4-(4-trifluoromethoxyphenyl)piperazine (an alternative
20 method for synthesis of the compound in Reference Example 183)

A mixture of 1-[4-(tetrahydropyran-2-yloxy)phenyl]piperazine (2.1 g, 8.05 mmol) prepared in Reference Example 184, 4-trifluoromethoxy-1-
25 bromobenzene (1.9 g, 8.05 mmol), palladium acetate (72 mg, 0.32 mmol), BINAP (300 mg, 0.48 mmol) and sodium tert-butoxide (1.0 g, 10.5 mmol) in toluene (30 ml) was refluxed under a nitrogen atmosphere for 5 hours.

Ethyl acetate and water were added to the reaction mixture, which was stirred for a while. The insoluble substances were removed by filtration through Celite, and the filtrate was extracted with ethyl acetate. The
5 extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 20/1) to afford 1-[4-
10 (tetrahydropyran-2-yloxy)phenyl]-4-(4-trifluoromethoxyphenyl)piperazine (3.1 g, yield 90%) as a white powder.

Reference Example 186

Preparation of 4-[4-(4-
15 trifluoromethoxyphenyl)piperazin-1-yl]phenol

A mixture of 1-[4-(tetrahydropyran-2-yloxy)phenyl]-4-(4-trifluoromethoxyphenyl)piperazine (2.65 g, 6.27 mmol) prepared in Reference Example 185 and pyridinium p-toluene sulfonate (473 mg, 1.88 mmol)
20 in ethanol (50 ml) was stirred at 70°C for 5 hours. The reaction mixture was concentrated under reduced pressure, and methylene chloride and a saturated sodium hydrogencarbonate aqueous solution were added to the residue, which was stirred for a while. The mixture
25 was extracted with methylene chloride, and the extract was dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column

chromatography (methylene chloride/ethyl acetate = 10/1) to afford 4-[4-(4-trifluoromethoxyphenyl)-piperazin-1-yl]phenol (1.95 g, yield 92%) as a white powder.

5 ^1H -NMR (CDCl_3) δ ppm:

3.19 - 3.24 (4H, m), 3.29 - 3.34 (4H, m), 4.50 (1H, s),
6.76 - 6.80 (2H, m), 6.87 - 6.97 (4H, m), 7.11 - 7.15
(2H, m).

Using corresponding starting materials,
10 compounds of Reference Examples 187 and 188 were prepared in the same manner as described in Reference Example 186.

Reference Example 187

4-[4-(4-trifluoromethylphenyl)piperazin-1-yl]phenol

15 a white powder, yield 82%

^1H -NMR (CDCl_3) δ ppm:

3.18 - 3.23 (4H, m), 3.41 - 3.45 (4H, m), 4.47 (1H, s),
6.76 - 6.82 (2H, m), 6.87 - 7.00 (4H, m), 7.48 - 7.52
(2H, m).

20 Reference Example 188

4-[4-(4-chlorophenyl)piperazin-1-yl]phenol

a white powder, yield 23%

^1H -NMR (CDCl_3) δ ppm:

3.18 - 3.23 (4H, m), 3.28 - 3.32 (4H, m), 4.45 (1H, s),
25 6.77 - 6.81 (2H, m), 6.87 - 6.92 (4H, m), 7.21 - 7.24
(2H, m).

Reference Example 189

Preparation of tert-butyl 4-(4-

trifluoromethoxyphenoxy)piperidine-1-carboxylate

Tert-butyl 4-hydroxypiperidine-1-carboxylate (56.5 g, 0.28 mol), 4-trifluoromethoxyphenol (50 g, 0.28 mol) and triphenylphosphine (108 g, 0.42 mol) were dissolved in THF (500 ml). Diethyl azodicarboxylate (65 ml, 0.42 mol) was added dropwise to this solution under reflux, and the mixture was refluxed for 5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 5/1) to afford tert-butyl 4-(4-trifluoromethoxyphenoxy)-piperidine-1-carboxylate (92 g, yield 91%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.47 (9H, s), 1.69 - 1.80 (2H, m), 1.85 - 1.96 (2H, m), 3.28 - 3.39 (2H, m), 3.64 - 3.75 (2H, m), 4.40 - 4.46 (1H, m), 6.85 - 6.92 (2H, m), 7.11 - 7.15 (2H, m).

Reference Example 190

Preparation of 4-(4-trifluoromethoxyphenoxy)piperidine

Tert-butyl 4-(4-trifluoromethoxyphenoxy)-piperidine-1-carboxylate (92 g, 254.59 mmol) prepared in Reference Example 189 was dissolved in methylene chloride (100 ml). Trifluoroacetic acid (200 ml) was added dropwise to this solution at room temperature, and the mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure, and the residue was then dissolved in methylene chloride, which was neutralized with a sodium hydroxide aqueous

solution. The mixture was extracted with methylene chloride. The extract was washed with brine, dried over sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the
5 residue was then purified by silica gel column chromatography (methylene chloride/methanol = 5/1) to afford 4-(4-trifluoromethoxyphenoxy)piperidine (55 g, yield 83%) as a white powder.

¹H-NMR (CDCl₃) δppm:

10 1.65 - 1.78 (2H, m), 2.00 - 2.07 (2H, m), 2.73 - 2.83 (2H, m), 3.12 - 3.21 (2H, m), 4.32 - 4.38 (2H, m), 6.85 - 6.92 (2H, m), 7.10 - 7.15 (2H, m).

Reference Example 191

Preparation of 1-[4-(tetrahydropyran-2-yloxy)phenyl]-4-
15 (4-trifluoromethoxyphenoxy)piperidine

A mixture of 4-(4-trifluoromethoxyphenoxy)piperidine (30.3 g, 0.116 mol) prepared in Reference Example 190, 2-(4-bromophenoxy)tetrahydropyran (30 g, 0.116 mol), palladium acetate (1.0 g, 4.64 mmol), BINAP
20 (4.3 g, 6.96 mmol) and cesium carbonate (49 g, 0.151 mol) in toluene (300 ml) was refluxed under a nitrogen atmosphere for 30 hours. Ethyl acetate and water were added to the reaction mixture, which was stirred for a while. The insoluble substances were removed by
25 filtration through Celite, and the filtrate was then extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced

pressure, and the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 20/1) to afford 1-[4-(tetrahydropyran-2-yloxy)phenyl]-4-(4-trifluoromethoxyphenoxy)piperidine (32.6 g, yield 64%)

5 as a yellow powder.

¹H-NMR (CDCl₃) δppm:

1.55 - 1.75 (3H, m), 1.81 - 2.20 (7H, m), 2.95 - 3.04
(2H, m), 3.38 - 3.42 (2H, m), 3.55 - 3.66 (1H, m), 3.87
- 3.99 (1H, m), 4.36 - 4.45 (1H, m), 5.29 - 5.32 (1H,
10 m), 6.89 - 7.01 (6H, m), 7.11 - 7.16 (2H, m).

Reference Example 192

Preparation of 4-[4-(4-trifluoromethoxyphenoxy)-
piperidin-1-yl]phenol

A mixture of 1-[4-(tetrahydropyran-2-
15 yloxy)phenyl]-4-(4-trifluoromethoxyphenoxy)piperidine
(30.1 g, 68.8 mmol) prepared in Reference Example 191
and pyridinium p-toluene sulfonate (5.2 g, 20.6 mmol)
in ethanol (450 ml) was stirred at 70°C for 24 hours.
The reaction mixture was concentrated under reduced
20 pressure, and methylene chloride and a saturated sodium
hydrogencarbonate aqueous solution were added to the
residue, which was stirred for a while. The mixture
was extracted with methylene chloride, and the extract
was dried over magnesium sulfate, and then filtered.
25 The filtrate was concentrated under reduced pressure,
and the residue was purified by silica gel column
chromatography (methylene chloride/ethyl acetate =
10/1) to afford 4-[4-(4-trifluoromethoxyphenoxy)-

piperidin-1-yl]phenol (22.9 g, yield 94%) as a pale brown powder.

¹H-NMR (CDCl₃) δppm:

1.88 - 2.02 (2H, m), 2.06 - 2.16 (2H, m), 2.92 - 3.02
5 (2H, m), 3.30 - 3.39 (2H, m), 4.36 - 4.44 (1H, m), 4.74
(1H, s), 6.71 - 6.78 (2H, m), 6.85 - 6.94 (4H, m), 7.10
- 7.16 (2H, m).

Reference Example 193

Preparation of tert-butyl 4-[2-chloro-4-(tetrahydro-
10 pyran-2-yloxy)phenyl]piperazine-1-carboxylate

A mixture of tert-butyl piperazine-1-carboxylate (3.94 g, 21.6 mmol), 2-(4-bromo-3-chlorophenoxy)tetrahydropyran (5.61 g, 19.2 mol),
palladium acetate (86.4 mg, 0.39 mmol), BINAP (172 mg,
15 0.58 mmol) and sodium tert-butoxide (2.4 g, 25.0 mmol)
in toluene (40 ml) was refluxed under a nitrogen
atmosphere for 2 hours. Ethyl acetate and water were
added to the reaction mixture, which was stirred for a
while. The insoluble substances were removed by
20 filtration through Celite, and the filtrate was
extracted with ethyl acetate. The extract was washed
with brine, dried over magnesium sulfate, and then
filtered. The filtrate was concentrated under reduced
pressure, and the residue was purified by silica gel
25 column chromatography (n-hexane/ethyl acetate = 20/1)
to afford tert-butyl 4-[2-chloro-4-(tetrahydropyran-2-yloxy)phenyl]piperazine-1-carboxylate (4.72 g, yield 62%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.48 (9H, s), 1.51 - 2.04 (6H, m), 2.88 - 2.93 (4H, m),
3.56 - 3.63. (5H, m), 3.83 - 3.94 (1H, m), 5.31 - 5.34
(1H, m), 6.88 - 6.96 (2H, m), 7.10 - 7.13 (1H, m).

5 Reference Example 194

Preparation of tert-butyl 4-(2-chloro-4-hydroxyphenyl)-
piperazine-1-carboxylate

A mixture of tert-butyl 4-[2-chloro-4-
(tetrahydropyran-2-yloxy)phenyl]piperazine-1-
10 carboxylate (4.73 g, 11.9 mmol) prepared in Reference
Example 193 and a catalytic amount of pyridinium p-
toluene sulfonate in ethanol (50 ml) was stirred at 70°C
for 1 hour. The reaction mixture was concentrated
under reduced pressure, and methylene chloride and
15 saturated sodium hydrogencarbonate aqueous solution
were added to the residue, which was stirred for a
while. The resulting precipitates were collected by
filtration, and dried in vacuo to afford tert-butyl 4-
(2-chloro-4-hydroxyphenyl)piperazine-1-carboxylate
20 (2.68 g, yield 72%) as a white powder.

¹H-NMR (CDCl₃) δppm:

1.49 (9H, s), 2.87 - 2.91 (4H, m), 3.55 - 3.60 (4H, m),
5.19 (1H, br), 6.68 - 6.74 (1H, m), 6.88 - 6.93 (2H,
m).

25 Reference Example 195

Preparation of tert-butyl 4-(4-acetoxybenzoyl)-
piperazine-1-carboxylate

p-Acetoxybenzoic acid (11 g, 61.1 mmol) was

dissolved in methylene chloride (100 ml), to which DMF (3 drops) and thionyl chloride (5.54 ml, 76.3 mmol) were added, and the mixture was heated under reflux for 2 hours. The mixture was cooled in an ice-bath, to which a solution of tert-butyl piperazine-1-carboxylate (10.3 g, 55.5 mmol) and pyridine (12 ml, 0.15 mol) in methylene chloride (100 ml) was added dropwise, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with methylene chloride, and the mixture was washed with water, 10% hydrochloric acid, saturated sodium hydrogencarbonate aqueous solution and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ ethyl acetate = 20/1) to afford tert-butyl 4-(4-acetoxybenzoyl)piperazine-1-carboxylate (18.5 g, yield 87%) as a colorless crystalline powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.47 (9H, s), 2.31 (3H, s), 3.46 (8H, br), 7.12 - 7.18 (2H, m), 7.41 - 7.46 (2H, m).

Reference Example 196

Preparation of tert-butyl 4-(4-hydroxybenzoyl)-piperazine-1-carboxylate

A mixture of tert-butyl 4-(4-acetoxybenzoyl)piperazine-1-carboxylate (18.5 g, 53.1 mmol) prepared in Reference Example 195 and potassium carbonate (370 mg, 2.65 mmol) in methanol (200 ml) was

stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, 5% hydrochloric acid and methylene chloride were added to the residue, and the mixture was vigorously stirred.

- 5 The resulting precipitates were collected by filtration, and washed with water and methylene chloride, and then dried *in vacuo* to afford tert-butyl 4-(4-hydroxybenzoyl)piperazine-1-carboxylate (14.9 g, yield 92%) as a white powder.

- 10 ^1H -NMR (CDCl_3) δ ppm:

1.48 (9H, s), 3.46 (4H, br), 3.60 (4H, br), 6.75 - 6.79 (2H, m), 7.22 - 7.28 (2H, m).

Reference Example 197

Preparation of 1-benzyl-4-[4-(tetrahydropyran-2-

- 15 yloxy)phenyl]piperidin-4-ol

A solution of 2-(4-bromophenoxy)-tetrahydropyran (7.2 g, 28 mmol) in THF (70 ml) was cooled to -60°C , to which n-butyl lithium (1.53 M) hexane solution (20 ml, 30.8 mmol) was added dropwise, and the mixture was stirred for 30 minutes. Then, a solution of 1-benzyl-4-piperidone (5.3 g, 28 mmol) in THF (20 ml) was added dropwise to this mixture, which was stirred for 3 hours while being allowed to reach a temperature of 0°C . Saturated ammonium chloride aqueous solution was added to the reaction mixture, which was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced

pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 20/1) to afford 1-benzyl-4-[4-(tetrahydropyran-2-yloxy)phenyl]piperidin-4-ol (5.27 g, yield 51%) as an orange-colored oil.

^1H -NMR (CDCl_3) δ ppm:

1.52 - 2.21 (11H, m), 2.41 - 2.52 (2H, m), 2.74 - 2.78 (2H, m), 3.57 (2H, s), 3.56 - 3.63 (1H, m), 3.83 - 3.96 (1H, m), 5.39 - 5.42 (1H, m), 6.98 - 7.04 (2H, m), 7.20 - 7.44 (7H, m).

Reference Example 198

Preparation of tert-butyl 4-(4-hydroxyphenyl)piperidine-1-carboxylate

A solution of 1-benzyl-4-[4-(tetrahydropyran-2-yloxy)phenyl]piperidin-4-ol (1.67 g, 4.55 mmol) prepared in Reference Example 197 in acetonitrile (45 ml) was cooled to -10°C , to which triethylsilane (2.9 ml, 18.2 mmol) and boron trifluoride diethyl ether complex (1.1 ml, 9.1 mmol) were added, and the mixture was stirred at room temperature for 2 days. Water was added to the reaction mixture, and the mixture was extracted with methylene chloride. The extract was dried over magnesium sulfate, and then filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethanol (50 ml), to which a catalytic amount of 20% palladium hydroxide/carbon was added. The mixture was stirred at room temperature under an atmospheric pressure of hydrogen overnight.

The reaction mixture was filtered through Celite, di-tert-butyl dicarbonate (1.1 ml, 4.78 mmol) was added to the filtrate, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford tert-butyl 4-(4-hydroxyphenyl)piperidine-1-carboxylate (1.07 g, yield 85%) as a colorless crystalline powder.

10 ^1H -NMR (CDCl_3) δ ppm:

1.41 - 1.63 (2H, m), 1.49 (9H, s), 1.73 - 1.80 (2H, m), 2.50 - 2.62 (1H, m), 2.73 - 2.83 (2H, m), 4.19 - 4.24 (2H, m), 5.87 (1H, bs), 6.76 - 6.81 (2H, m), 7.02 - 7.08 (2H, m).

15 Reference Example 199

Preparation of tert-butyl 4-[3-(tetrahydropyran-2-yloxy)phenyl]piperazine-1-carboxylate

A mixture of tert-butyl piperazine-1-carboxylate (2.94 g, 15.8 mmol), 2-(3-bromophenoxy)tetrahydropyran (3.69 g, 14.4 mmol), palladium acetate (64 mg, 0.29 mmol), BINAP (285 mg, 0.43 mmol) and sodium tert-butoxide (1.8 g, 18.7 mmol) in toluene (40 ml) was refluxed under a nitrogen atmosphere for 2 hours. Ethyl acetate and water were added to the reaction mixture, which was stirred for a while. The insoluble substances were removed by filtration through Celite, and the filtrate was then extracted with ethyl acetate. The extract was washed

with brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 20/1) to afford tert-butyl 4-[3-(tetrahydropyran-2-yloxy)phenyl]piperazine-1-carboxylate (5.3 g, yield 99%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.48 (9H, s), 1.52 - 2.04 (6H, m), 3.10 - 3.15 (4H, m), 3.53 - 3.64 (5H, m), 3.87 - 3.94 (1H, m), 5.38 - 5.41 (1H, m), 6.53 - 6.63 (3H, m), 7.12 - 7.19 (1H, m).

Reference Example 200

Preparation of tert-butyl 4-(3-hydroxyphenyl)piperazine-1-carboxylate

A mixture of tert-butyl 4-[3-(tetrahydropyran-2-yloxy)phenyl]piperazine-1-carboxylate (5.20 g, 14.4 mmol) prepared in Reference Example 199 and a catalytic amount of pyridinium p-toluene sulfonate in ethanol (100 ml) was stirred at 70°C for 1.5 hours. The reaction mixture was concentrated under reduced pressure, and methylene chloride and a saturated sodium hydrogencarbonate aqueous solution were added to the residue, which was stirred for a while. The resulting precipitates were collected by filtration, and then dried *in vacuo* to afford tert-butyl 4-(3-hydroxyphenyl)piperazine-1-carboxylate (3.73 g, yield 93%) as a pale brown powder.

¹H-NMR (CDCl₃) δppm:

1.49 (9H, s), 3.09 - 3.14 (4H, m), 3.54 - 3.59 (4H, m),
5.38 (1H, br), 6.33 - 6.41 (2H, m), 6.47 - 6.52 (1H,
m), 7.08 - 7.15 (1H, m).

5 Reference Example 201

Preparation of 3-methyl-2-methylene butylaldehyde

3-methyl-2-methylene butylaldehyde was
prepared according to the method described in Journal
of American Chemical Society, 1957, p. 3267 (J. Am.
10 Chem. Soc., 3267, 1957), that is, a mixture of
isovaleraldehyde (100 ml, 932 mmol), 37% formalin (83.8
ml, 1120 mmol) and dimethylamine hydrochloride (91.2 g,
1120 mmol) was stirred at 70°C for 30 hours. The
mixture was steam distilled to separate the fraction,
15 and thus obtained aqueous layer was extracted with
diethyl ether. The extracts were combined, dried over
sodium sulfate, and filtered. The filtrate was
concentrated under reduced pressure. The residue was
distilled to afford 3-methyl-2-methylene butylaldehyde
20 (65.5 g, yield 72%) as a colorless oil.

boiling point : 105 - 115°C

¹H-NMR (CDCl₃) δppm:

1.08 (6H, d, J = 6.9 Hz), 2.75 - 2.89 (1H, m), 5.95
(1H, s), 6.24 (1H, s), 9.53 (1H, s).

25 Reference Example 202

Preparation of 3-methyl-2-methylene-butan-1-ol

A solution of 3-methyl-2-methylene
butylaldehyde (65 g, 668 mmol) prepared in Reference

Example 201 in THF (30 ml) was added dropwise to a suspension of lithium aluminum hydride (14.15 g, 373 mmol) in THF (1000 ml) while cooling in an ice-bath, and the mixture was allowed to return to room temperature, and stirred for 2 hours. While cooling, water, 15% sodium hydroxide aqueous solution, and then water were added to the reaction mixture, which was filtered. The filtrate was dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford 3-methyl-2-methylenebutan-1-ol (61.5 g, yield 93%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.07 (6H, d, $J = 6.9$ Hz), 1.42 (1H, t, $J = 6.1$ Hz),
2.25 - 2.43 (1H, m), 4.13 (2H, d, $J = 6.1$ Hz), 4.84 -
4.93 (1H, m), 4.98 - 5.05 (1H, m).

Reference Example 203

Preparation of 2-methoxymethoxymethyl-3-methyl-1-butene

Chloromethyl methyl ether (98 ml, 1292 mmol) and N-ethyldiisopropylamine (234 ml, 1344 mmol) were added to a solution of 3-methyl-2-methylenebutane-1-ol (61.5 g, 615 mmol) prepared in Reference Example 202 in THF (500 ml) while cooling in an ice-bath, and the mixture was stirred at room temperature for 22 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in diethyl ether, and the mixture was washed with water and brine, dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced

pressure to afford 2-methoxymethoxymethyl-3-methyl-1-butene (89 g, quantitative) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.07 (6H, d, $J = 6.9$ Hz), 2.25 - 2.41 (1H, m), 3.39
5 (3H, s), 4.05 (2H, s), 4.65 (2H, s), 4.87 - 4.95 (1H, m), 5.00 - 5.05 (1H, m).

Reference Example 204

Preparation of 2-methylenebutylaldehyde

A mixture of butylaldehyde (100 ml, 1110
10 mmol), 37% formalin (99.8 ml, 1330 mmol) and dimethylamine hydrochloride (108.6 g, 1330 mmol) was stirred at 70°C for 23 hours. The mixture was steam distilled to separate the fraction, and thus obtained aqueous layer was extracted with diethyl ether. The extracts were
15 combined, dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was distilled to afford 2-methylenebutylaldehyde (66.9 g, yield 72%) as a colorless oil.

20 boiling point : 70 - 93°C

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.08 (3H, t, $J = 7.5$ Hz), 2.27 (2H, q, $J = 7.5$ Hz),
5.98 (1H, s), 6.25 (1H, s), 9.56 (1H, s).

Reference Example 205

25 Preparation of 2-methylene-1-butanol

2-Methylenebutylaldehyde (66.9 g, 796 mmol) prepared in Reference Example 204 was added dropwise to a suspension of lithium aluminum hydride (15.1 g, 398

mmol) in THF (1000 ml) while cooling in an ice-bath, and the mixture was stirred for 1 hour. Water, 15% sodium hydroxide aqueous solution and then water were added to the reaction mixture, which was filtered, and 5 the filtrate was dried over sodium sulfate. After filtration, and the filtrate was concentrated under reduced pressure to afford 2-methylene-1-butanol (65.1 g, yield 95%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δppm :

10 1.07 (3H, t, $J = 7.5$ Hz), 1.44 (1H, t, $J = 6.0$ Hz),
2.13 (2H, q, $J = 7.5$ Hz), 4.09 (2H, d, $J = 6.0$ Hz),
4.82 - 4.93 (1H, m), 4.98 - 5.07 (1H, m).

Reference Example 206

Preparation of 2-methoxymethoxymethyl-1-butene

15 Chloromethyl methyl ether (103.4 ml, 1363 mmol) and N-ethyldiisopropylamine (247.2 ml, 1419 mmol) were added to a solution of 2-methylene-1-butanol (65.1 g, 757 mmol) prepared in Reference Example 205 in THF (750 ml) while cooling in an ice-bath, and the mixture 20 was stirred at room temperature for 3 days. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in diethyl ether, and the mixture was washed with water and brine, dried over sodium sulfate, and 25 filtered. The filtrate was concentrated under reduced pressure to afford 2-methoxymethoxymethyl-1-butene (98 g, quantitative) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.07 (3H, t, $J = 7.5$ Hz), 2.09 (2H, q, $J = 7.5$ Hz),
3.38 (3H, s), 4.01 (2H, s), 4.64 (2H, s), 4.86 - 4.95
(1H, m), 5.00 - 5.05 (1H, m).

Reference Example 207

5 Preparation of tert-butyl 4-[2-oxo-2-(4-oxopiperidin-1-yl)ethyl]piperazine-1-carboxylate

1-(2-Chloroacetyl)piperidin-4-one (5.17 g,
29.4 mmol) was dissolved in acetonitrile (50 ml). To
this solution, tert-butyl piperazine-1-carboxylate
10 (5.48 g, 29.4 mmol) and N-ethyldiisopropylamine (6.2
ml, 35.3 mmol) were added, and the mixture was heated
under reflux for 2 hours. The reaction mixture was
allowed to return to room temperature, to which water
was added, and the mixture was extracted with ethyl
15 acetate. The extract was washed with brine, dried over
magnesium sulfate, and then filtered. The filtrate was
concentrated under reduced pressure, and the residue
was purified by silica gel column chromatography
(methylene chloride/methanol = 100/1) to afford tert-
20 butyl 4-[2-oxo-2-(4-oxopiperidin-1-yl)ethyl]piperazine-
1-carboxylate (6.49 g, yield 68%) as a pale yellow
crystalline powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.46 (9H, s), 2.44 - 2.54 (8H, m), 3.28 (2H, s), 3.42 -
25 3.47 (4H, m), 3.85 - 3.90 (4H, m).

Reference Example 208

Preparation of 4-methyl-4-pentenyl acetate

Potassium tert-butoxide (9.4 g, 84 mmol) was

added to a mixture of methyltriphenylphosphonium bromide (30 g, 84 mmol) in THF (300 ml), and the mixture was stirred at room temperature for 40 minutes. To the mixture a solution of 4-oxopentyl acetate (9.9 g, 68.8 mmol) in THF (30 ml) was gradually added dropwise while cooling in an ice-bath, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into ice water, and extracted with diethyl ether twice. The extracts were combined, washed with brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 4/1) to afford 4-methyl-4-pentenyl acetate (5.9 g, yield 60.4%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.70 - 1.86 (5H, m), 2.00 - 2.14 (5H, m), 4.07 (2H, t, $J = 6.7$ Hz), 4.69 (1H, s), 4.74 (1H, s).

Reference Example 209

Preparation of benzyl 4-(2-methyl-2-oxiranylmethyl)-piperazine-1-carboxylate

Trimethylsulfoxonium iodide (1.96 g, 8.91 mmol) was added to a suspension of sodium hydride (0.37 g, 9.32 mmol) in DMSO (20 ml) while cooling in an ice-bath, and the mixture was stirred at room temperature for 30 minutes. To the mixture a solution of benzyl 4-(2-oxopropyl)piperazine-1-carboxylate (2.24 g, 8.10

mmol) in DMSO (10 ml) was added, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into ice water, and extracted with diethyl ether. The extract was washed with water, 5 dried over magnesium sulfate, and then concentrated under reduced pressure to afford benzyl 4-(2-methyl-2-oxiranylmethyl)piperazine-1-carboxylate (1.51 g, yield 64%) as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

10 1.37 (3H, s), 2.27 - 2.63 (8H, m), 3.44 - 3.63 (4H, m), 5.13 (2H, s), 7.29 - 7.44 (5H, m).

Reference Example 210

Preparation of tert-butyl 4-(2-methyl-2-oxiranylmethyl)homopiperazine-1-carboxylate

15 Trimethylsulfoxonium iodide (22.95 g, 104 mmol) was gradually added to a suspension of sodium hydride (4.3 g, 109 mmol) in DMSO (200 ml), and the mixture was stirred at room temperature for 2 hours. To which a solution tert-butyl 4-(2-oxopropyl)homopiperazine-1-carboxylate (24.3 g, 94.8 20 mmol) prepared in Reference Example 10 in DMSO (25 ml) was gradually added dropwise, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into ice water, and extracted with 25 diethyl ether. The extract was washed with water, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column

chromatography (methylene chloride/methanol = 100/1) to afford tert-butyl 4-(2-methyl-2-oxiranyl-methyl)homopiperazine-1-carboxylate (15.38 g, yield 60%) as a pale yellow oil.

5 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.38 (3H, s), 1.43 (9H, s), 1.69 - 1.90 (2H, m), 2.40 - 2.75 (8H, m), 3.36 - 3.55 (4H, m).

Reference Example 211

Preparation of tert-butyl 4-[2-(2-methyl-2-oxiranyl)-
10 ethyl]piperazine-1-carboxylate

Trimethylsulfoxonium iodide (7.8 g, 35 mmol) was gradually added to a suspension of sodium hydride (1.2 g, 35 mmol) in DMSO (120 ml), under a nitrogen atmosphere, and the mixture was stirred at room
15 temperature for 2 hours. To which a solution of tert-butyl 4-(3-oxobutyl)piperazine-1-carboxylate (6.1 g, 23.8 mmol) in DMSO (10 ml) was gradually added dropwise, and the mixture was stirred at room
temperature for 1.5 hours, and then at 50 to 60°C for
20 1.5 hours. The reaction solution was allowed to return to room temperature, poured into iced water, and extracted with ethyl acetate three times. The extracts were combined, washed with water three times and then washed with a saturated saline solution, and dried over
25 sodium sulfate. After filtration, the filtrate was concentrated under a reduced pressure to afford tert-butyl 4-[2-(2-methyl-2-oxiranyl)ethyl]piperazine-1-carboxylate (5.6 g, 87%) as a light yellow oil.

¹H-NMR (CDCl₃) δppm:

1.33 (3H, s), 1.46 (9H, s), 1.66 - 1.85 (2H, m), 2.28 - 2.50 (6H, m), 2.55 - 2.66 (2H, m), 3.34 - 3.47 (4H, m).

Reference Example 212

5 Preparation of 1-(2-methyl-2-oxiranylmethyl)-4-(4-trifluoromethylphenyl)piperazine

Trimethylsulfoxonium iodide (2.5 g, 11.6 mmol) was gradually added to a suspension of sodium hydride (484 mg, 12.1 mmol) in dimethylsulfoxide (30 ml), and the mixture was stirred at room temperature for 1 hour. To which a solution of 1-{4-(4-trifluoromethylphenyl)piperazin-1-yl}propan-2-one (3.4 g, 11.9 mmol) in dimethylsulfoxide (20 ml) was added, and the mixture was stirred at room temperature for 15 hour. The reaction mixture was poured into iced water, and extracted with diethyl ether. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate, and then filtered. The resultant filtrate was concentrated under a reduced pressure, and 20 the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to afford 1-(2-methyl-2-oxiranylmethyl)-4-(4-trifluoromethylphenyl)piperazine (3.2 g, yield 98%) as a light yellow powder.

25 ¹H-NMR (CDCl₃) δppm:

1.40 (3H, s), 2.33 (1H, d, J = 13.0 Hz), 2.53 - 2.73 (7H, m), 3.26 - 3.30 (4H, m), 6.91 (2H, d, J = 8.7 Hz), 7.47 (2H, d, J = 8.7 Hz).

Compounds of Reference Examples 213 to 217 were prepared in the same manner as described in Reference Example 212.

Reference Example 213

5 1-(2-methyl-2-oxiranylmethyl)-4-(4-biphenylyl)piperazine

a pale yellow powder, yield 99%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.41 (3H, s), 2.37 (1H, d, $J = 12.9$ Hz), 2.58 - 2.76
10 (7H, m), 3.23 - 3.28 (4H, m), 6.97 - 7.01 (2H, m), 7.24
- 7.30 (1H, m), 7.37 - 7.43 (2H, m), 7.49 - 7.58 (4H,
m).

Reference Example 214

1-(2-methyl-2-oxiranylmethyl)-4-(4-chlorophenyl)-

15 piperazine

a pale yellow powder, yield 99%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.39 (3H, s), 2.34 (1H, d, $J = 12.9$ Hz), 2.54 - 2.73
(7H, m), 3.14 - 3.18 (4H, m), 6.81 - 6.87 (2H, m), 7.16
20 - 7.22 (2H, m).

Reference Example 215

1-(2-methyl-2-oxiranylmethyl)-4-(4-trifluoromethoxy-phenyl)piperazine

a pale yellow powder, yield 99%

25 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.40 (3H, s), 2.34 (1H, d, $J = 12.9$ Hz), 2.54 - 2.73
(7H, m), 3.16 - 3.20 (4H, m), 6.85 - 6.92 (2H, m), 7.08
- 7.13 (2H, m).

Reference Example 216

1-(2-methyl-2-oxiranylmethyl)-4-(pyridine-2-yl)-
piperazine

a pale yellow powder, yield 99%

5 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.41 (3H, s), 2.35 (1H, d, $J = 12.9$ Hz), 2.50 - 2.69
(7H, m), 3.48 - 3.60 (4H, m), 6.59 - 6.66 (2H, m), 7.43
- 7.50 (1H, m), 8.17 - 8.20 (1H, m).

Reference Example 217

10 1-(2-methyl-2-oxiranylmethyl)-4-(pyrimidin-2-yl)-
piperazine

a pale yellow powder, yield 99%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.41 (3H, s), 2.36 (1H, d, $J = 12.9$ Hz), 2.45 - 2.64
15 (7H, m), 3.81 - 3.85 (4H, m), 6.47 (1H, t, $J = 4.8$ Hz),
8.30 (2H, d, $J = 4.8$ Hz).

Reference Example 218

Preparation of tert-butyl N-methyl-[1-(2-methyl-2-
oxiranylmethyl)piperidin-4-yl]carbamate

20 Trimethylsulfoxonium iodide (1.96 g, 8.89
mmol) was gradually added to a suspension of sodium
hydride (372 mg, 9.32 mmol) in dimethylsulfoxide (20
ml), and the mixture was stirred at room temperature
for 1.5 hours. To which a solution of tert-butyl N-
25 methyl-[1-(2-oxopropyl)piperidin-4-yl]carbamate (2.3 g,
8.5 mmol) in dimethylsulfoxide (20 ml) was added, and
the mixture was stirred at room temperature for 2
hours. The reaction mixture was poured into iced

water, and extracted with diethyl ether. The extract was washed with a saturated saline solution, dried over magnesium sulfate, and then filtered. The resultant filtrate was concentrated under a reduced pressure, and
5 the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to afford tert-butyl N-methyl-[1-(2-methyl-2-oxiranylmethyl)piperidin-4-yl]carbamate (2.1 g, yield 86%) as a light yellow oily material.

10 ¹H-NMR (CDCl₃) δppm:

1.36 (3H, s), 1.46 (9H, s), 1.55 - 1.79 (5H, m), 1.97 - 2.13 (2H, m), 2.30 (1H, d, J = 12.9 Hz), 2.49 (1H, d, J = 12.9 Hz), 2.59 (2H, s), 2.74 (3H, s), 2.88 - 3.06 (2H, m).

15 Reference Example 219

Preparation of 3-(2-methyl-2-oxiranyl)-pyridine

Using 3-acetylpyridine (8 g, 66.1 mmol), a light brown oil of 3-(2-methyl-2-oxiranyl)pyridine (7 g, yield 78.4%) was produced in the same manner as in

20 Reference Example 218.

¹H-NMR (CDCl₃) δppm:

1.74 (3H, s), 2.82 (1H, d, J = 5.2 Hz), 3.02 (1H, d, J = 5.2 Hz), 7.21 - 7.33 (1H, m), 7.58 - 7.70 (1H, m), 8.54 (1H, dd, 1.6 Hz, 4.8 Hz), 8.65 (1H, d, J = 2.3
25 Hz).

Reference Example 220

Preparation of tert-butyl 1-oxa-6-azaspiro[2,5]octane-6-carboxylate

Trimethylsulfoxonium iodide (70 g, 0.32 mol) was gradually added to a suspension of sodium hydride (13.3 g, 0.33 mol) in dimethylsulfoxide (600 ml), and the mixture was stirred at room temperature for 1 hour.

5 To which tert-butyl 4-oxo-piperidine-1-carboxylate (58 g, 0.291 mol) was gradually added, and the mixture was stirred at 55°C for 1 hour. The reaction mixture was poured into iced water, and extracted with diethyl ether. The organic phase was washed with a saturated

10 saline solution, dried over magnesium sulfate, and then filtered. The resultant filtrate was concentrated under a reduced pressure, and the residue was crystallized from n-hexane to afford tert-butyl 1-oxa-6-azaspiro[2,5]octane-6-carboxylate (61.7 g, yield 96%)

15 as a white powder.

¹H-NMR (CDCl₃) δppm:

1.40 - 1.53 (2H, m), 1.47 (9H, s), 1.72 - 1.85 (2H, m), 2.69 (2H, s), 3.37 - 3.48 (2H, m), 3.67 - 3.77 (2H, m).

Reference Example 221

20 Preparation of tert-butyl 4-[2-(1-oxa-6-azaspiro[2,5]-octan-6-yl)-2-oxoethyl]piperazine-1-carboxylate

Trimethylsulfoxonium iodide (2.02 g, 9.20 mmol) was gradually added to a suspension of sodium hydride (385 mg, 9.64 mmol) in dimethylsulfoxide (50

25 ml), and the resultant mixture was stirred at room temperature for 1 hour. To which tert-butyl 4-[2-oxo-2-(4-oxopiperidin-1-yl)ethyl]piperazine-1-carboxylate (2.85 g, 8.76 mmol) in DMSO (10 ml) was added, and the

mixture was stirred at room temperature for 2 hours, and stirred at 55°C for 1 hour. The reaction mixture was poured into iced water, and extracted with diethyl ether. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate, and filtered. The resultant filtrate was concentrated under a reduced pressure to afford tert-butyl 4-[2-(1-oxa-6-azaspiro[2,5]octan-6-yl)-2-oxoethyl]piperazine-1-carboxylate (2.97 g, yield 99%) as a white solid.

10 ^1H -NMR (CDCl_3) δ ppm:

1.45 - 1.54 (1H, m), 1.48 (9H, s), 1.78 - 1.93 (1H, m), 2.44 - 2.49 (4H, m), 2.62 (2H, s), 2.73 (2H, s), 3.42 - 3.47 (2H, m), 3.52 - 3.68 (1H, m), 3.77 - 3.88 (1H, m).

Reference Example 222

15 Preparation of 6-(4-trifluoromethylphenyl)-1-oxa-6-azaspiro[2,5]octane

Trimethylsulfoxonium iodide (2.00 g, 9.02 mmol) was gradually added to a suspension of sodium hydride (361 mg, 9.02 mmol) in dimethylsulfoxide (30 ml), and the mixture was stirred at room temperature for 1 hour. To which a solution of 1-(4-trifluoromethylphenyl)piperidin-4-one (2.00 g, 8.2 mmol) in DMSO (10 ml) was added, and the mixture was stirred overnight. The reaction mixture was poured into ice water, and extracted with diethyl ether. The extract was washed with brine, dried over sodium sulfate, and then filtered. The residue was purified by silica gel column chromatography (n-hexane/ethyl

acetate = 5/1) to afford 6-(4-trifluoromethylphenyl)-1-oxa-6-azaspiro[2,5]octane (1.51 g, yield 72%) as a pale yellow crystalline powder.

¹H-NMR (CDCl₃) δppm:

- 5 1.54 - 1.65 (2H, m), 1.91 - 2.04 (2H, m), 2.54 - 2.59 (2H, m), 2.73 (2H, s), 3.38 - 3.48 (1H, m), 3.52 - 3.62 (1H, m), 6.95 (2H, d, J = 8.7 Hz), 7.48 (2H, d, J = 8.7 Hz).

Reference Example 223

- 10 Preparation of 3-(2-methyl-2-oxyranyl)propyl acetate
m-Chloroperbenzoic acid (12.3 g, 71.30 mmol)
was gradually added to a solution of 4-methyl-4-pentenyl acetate (5.9 g, 41.5 mmol) prepared in
Reference Example 208 in methylene chloride (60 ml)
15 while cooling in an ice-bath, and the mixture was stirred at room temperature for 2 hours. Saturated sodium sulfite aqueous solution and saturated sodium carbonate aqueous solution were added to the mixture while cooling in an ice-bath, which was stirred for 30
20 minutes, and the organic layer was separated. The aqueous layer was extracted with methylene chloride. The extracts were combined, washed with saturated sodium bicarbonate aqueous solution and brine, and dried over sodium sulfate. After filtration, the
25 filtrate was concentrated under reduced pressure to afford 3-(2-methyl-2-oxyranyl)propyl acetate (6.9 g, quantitative) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

1.33 (3H, s), 1.56 - 1.79 (4H, m), 2.05 (3H, s), 2.56 - 2.70 (2H, m), 4.08 (2H, t, $J = 6.5$ Hz).

Reference Example 224

Preparation of 1-ethyl-5-[2-(2-methyl-2-oxiranyl)ethyl]-1H-tetrazole

m-Chloroperbenzoic acid (1.97 g, 7.99 mmol) was gradually added to a solution of 1-ethyl-5-(3-methyl-3-butenyl)-1H-tetrazole (0.95 g, 5.71 mmol) in methylene chloride (20 ml) while cooling in an ice-bath, and the mixture was stirred at room temperature for 21 hours. To the reaction mixture, sodium thiosulfate aqueous solution and sodium hydrogencarbonate aqueous solution were added, and the resulting mixture was filtered. The organic layer was separated, washed with sodium hydrogencarbonate aqueous solution, dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford 1-ethyl-5-[2-(2-methyl-2-oxiranyl)ethyl]-1H-tetrazole (1.2 g, quantitative) as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.40 (3H, s), 1.55 (3H, t, $J = 7.3$ Hz), 2.00 - 2.16 (1H, m), 2.20 - 2.37 (1H, m), 2.66 (2H, s), 2.78 - 2.98 (2H, m), 4.32 (2H, q, $J = 7.3$ Hz).

Using corresponding starting materials, compounds of Reference Examples 225 and 226 were prepared in the same manner as described in Reference Example 224.

Reference Example 225

1-phenyl-5-[2-(2-methyl-2-oxiranyl)ethyl]-1H-tetrazole
yield 100%

¹H-NMR (CDCl₃) δppm:

- 5 1.32 (3H, s), 2.01 - 2.28 (2H, m), 2.59 (2H, s), 2.92 -
2.99 (2H, m), 7.43 - 7.47 (2H, m), 7.58 - 7.63 (3H, m).

Reference Example 226

1-(4-chlorophenyl)-5-[2-(2-methyl-2-oxiranyl)ethyl]-1H-
tetrazole

- 10 yield 100%

¹H-NMR (CDCl₃) δppm:

- 1.33 (3H, s), 2.00 - 2.12 (1H, m), 2.19 - 2.31 (1H, m),
2.60 (2H, s), 2.90 - 2.97 (2H, m), 7.39 - 7.45 (2H, m),
7.56 - 7.62 (2H, m).

- 15 Reference Example 227

Preparation of 1-(2-methyl-2-oxiranylmethyl)-1, 4-
dihydrobenzo[d][1,3]oxazin-2-one

- m-Chloroperbenzoic acid (13.76 g, 55.81 mmol)
was added to a solution of 1-(2-methyl-2-propenyl)-1,4-
20 dihydrobenzo[d][1,3]oxazin-2-one (7.09 g, 34.88 mmol)
in methylene chloride (150 ml), and the mixture was
stirred at room temperature for 24 hours. To the
mixture, sodium thiosulfate aqueous solution and sodium
hydrogencarbonate aqueous solution were added, and the
25 resulting mixture was filtered. The organic layer was
separated, washed with sodium hydrogencarbonate aqueous
solution, dried over magnesium sulfate. After
filtration, the filtrate was concentrated under reduced

pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 4/1) to afford 1-(2-methyl-2-oxiranylmethyl)-1,4-dihydrobenzo[d][1,3]oxazin-2-one (5.13 g, 67%) as a
5 pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.39 (3H, s), 2.70 (1H, d, $J = 4.4$ Hz), 2.78 (1H, d, $J = 4.4$ Hz), 3.79 (1H, d, $J = 15.5$ Hz), 4.51 (1H, d, $J = 15.5$ Hz), 5.23 (2H, s), 7.04 - 7.13 (2H, m), 7.21 -
10 7.27 (1H, m), 7.29 - 7.38 (1H, m).

Reference Example 228

Preparation of 3-(2-methyl-2-oxiranylmethyl)-3H-benzoxazol-2-one

m-Chloroperbenzoic acid (1.66 g, 9.65 mmol)
15 was added to a mixture of 3-(2-methyl-2-propenyl)-3H-benzoxazol-2-one (1.66 g, 8.77 mmol) in methylene chloride (30 ml) while cooling in an ice-bath, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered, and the filtrate was
20 washed with a 20% sodium sulfite aqueous solution, saturated sodium bicarbonate aqueous solution and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was treated with methylene
25 chloride/n-hexane, and the resulting precipitates were collected by filtration to afford 3-(2-methyl-2-oxiranylmethyl)-3H-benzoxazol-2-one (1.78 g, yield 99%) as a white powder.

¹H-NMR (CDCl₃) δppm:

1.38 (3H, s), 2.73 (1H, d, J = 4.3 Hz), 2.81 (1H, d, J = 4.3 Hz), 3.68 (1H, d, J = 15.0 Hz), 4.26 (1H, d, J = 15.0 Hz), 7.09 - 7.29 (4H, m).

- 5 Using corresponding starting materials, compounds of Reference Examples 229 to 232 were prepared in the same manner as described in Reference Example 228.

Reference Example 229

- 10 5-chloro-3-(2-methyl-2-oxiranylmethyl)-3H-benzoxazol-2-one

yield 93%

¹H-NMR (CDCl₃) δppm:

- 1.38 (3H, s), 2.75 (1H, d, J = 4.2 Hz), 2.79 (1H, d, J = 4.2 Hz), 3.60 (1H, d, J = 15.1 Hz), 4.28 (1H, d, J = 15.1 Hz), 7.05 - 7.16 (2H, m), 7.20 - 7.27 (1H, m).

Reference Example 230

5-fluoro-3-(2-methyl-2-oxiranylmethyl)-3H-benzoxazol-2-one

- 20 yield 97%

¹H-NMR (CDCl₃) δppm:

- 1.38 (3H, s), 2.75 (1H, d, J = 4.3 Hz), 2.80 (1H, d, J = 4.3 Hz), 3.60 (1H, d, J = 15.1 Hz), 4.29 (1H, d, J = 15.1 Hz), 6.75 - 6.85 (1H, m), 7.01 (1H, dd, J = 2.6 Hz, 7.9 Hz), 7.13 (1H, dd, J = 4.2 Hz, 8.8 Hz).

Reference Example 231

5-phenyl-3-(2-methyl-2-oxiranylmethyl)-3H-benzoxazol-2-one

yield 92%

¹H-NMR (CDCl₃) δppm:

1.40 (3H, s), 2.74 (1H, d, J = 4.3 Hz), 2.82 (1H, d, J = 4.3 Hz), 3.70 (1H, d, J = 15.0 Hz), 4.32 (1H, d, J = 15.0 Hz), 7.25 (1H, d, J = 8.4 Hz), 7.29 - 7.49 (5H, m), 7.57 (2H, dd, J = 1.6 Hz, 8.5 Hz).

Reference Example 232

5-bromo-3-(2-methyl-2-oxiranylmethyl)-3H-benzoxazol-2-one

10 yield 80%

¹H-NMR (CDCl₃) δppm:

1.38 (3H, s), 2.75 (1H, d, J = 4.2 Hz), 2.79 (1H, d, J = 4.2 Hz), 3.61 (1H, d, J = 15.1 Hz), 4.27 (1H, d, J = 15.1 Hz), 7.08 (1H, d, J = 8.5 Hz), 7.18 - 7.31 (1H, m), 7.38 (1H, d, J = 1.9 Hz).

Reference Example 233

Preparation of 1-(2-methyl-2-oxiranylmethyl)-3-phenyl-1,3-dihydrobenzimidazol-2-one

Using 1-(2-methyl-2-propenyl)-3-phenyl-1,3-dihydrobenzimidazol-2-one (720 mg, 2.72 mmol), 1-(2-methyl-2-oxiranylmethyl)-3-phenyl-1,3-dihydrobenzimidazol-2-one (758 mg, yield 99%) as a pale yellow oil was prepared in the same manner as described in Reference Example 228.

25 ¹H-NMR (CDCl₃) δppm:

1.40 (3H, s), 2.73 (1H, d, J = 4.5 Hz), 2.86 (1H, d, J = 4.5 Hz), 3.82 (1H, d, J = 15.0 Hz), 4.38 (1H, d, J = 15.0 Hz), 7.02 - 7.30 (4H, m), 7.34 - 7.45 (1H, m),

7.50 - 7.57 (4H, m).

Using corresponding starting materials, compounds of Reference Examples 234 to 245 were prepared in the same manner as described in Reference
5 Example 233.

Reference Example 234

1-(4-fluorophenyl)-3-(2-methyl-2-oxiranylmethyl)-1, 3-dihydrobenzimidazol-2-one

yield 96%

10 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.40 (3H, s), 2.73 (1H, d, $J = 4.5$ Hz), 2.85 (1H, d, $J = 4.5$ Hz), 3.81 (1H, d, $J = 15.0$ Hz), 4.38 (1H, d, $J = 15.0$ Hz), 7.00 - 7.30 (6H, m), 7.43 - 7.57 (2H, m).

Reference Example 235

15 1-(1-tert-butoxycarbonylpiperidin-4-yl)-3-(2-methyl-2-oxiranylmethyl)-1,3-dihydrobenzimidazol-2-one

yield 40%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.34 (3H, s), 1.54 (9H, s), 1.71 - 1.87 (2H, m), 2.20 -
20 2.42 (2H, m), 2.70 (1H, d, $J = 4.5$ Hz), 2.71 - 2.89 (3H, m), 3.75 (1H, d, $J = 15.0$ Hz), 4.20 - 4.53 (4H, m), 7.00 - 7.13 (3H, m), 7.15 - 7.25 (1H, m).

Reference Example 236

1-methyl-3-(2-methyl-2-oxiranylmethyl)-1,3-

25 dihydrobenzimidazol-2-one

yield 68%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.34 (3H, s), 2.69 (1H, d, $J = 4.5$ Hz), 2.78 (1H, d, J

= 4.5 Hz), 3.44 (3H, s), 3.76 (1H, d, $J = 15.0$ Hz),
4.31 (1H, d, $J = 15.0$ Hz), 6.91 - 7.00 (1H, m), 7.05 -
5.25 (3H, m).

Reference Example 237

5 5-chloro-1-methyl-3-(2-methyl-2-oxiranylmethyl)-1,3-
dihydrobenzimidazol-2-one

yield 89%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.34 (3H, s), 2.70 (1H, d, $J = 4.4$ Hz), 2.76 (1H, d, J
10 = 4.4 Hz), 3.42 (3H, s), 3.69 (1H, d, $J = 15.1$ Hz),
4.28 (1H, d, $J = 15.1$ Hz), 6.88 (1H, d, $J = 8.3$ Hz),
7.09 (1H, dd, $J = 1.9$ Hz, 8.3 Hz), 7.22 (1H, d, $J = 1.9$
Hz).

Reference Example 238

15 1-methyl-3-(2-methyl-2-oxiranylmethyl)-5-trifluoro-
methyl-1,3-dihydrobenzimidazol-2-one

yield 99%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.36 (3H, s), 2.71 (1H, d, $J = 4.4$ Hz), 2.77 (1H, d, J
20 = 4.4 Hz), 3.47 (3H, s), 3.74 (1H, d, $J = 15.1$ Hz),
4.38 (1H, d, $J = 15.1$ Hz), 7.04 (1H, d, $J = 8.2$ Hz),
7.39 (1H, dd, $J = 1.9$ Hz, 8.2 Hz), 7.45 (1H, d, $J = 1.9$
Hz).

Reference Example 239

25 6-chloro-1-methyl-3-(2-methyl-2-oxiranylmethyl)-1,3-
dihydrobenzimidazole-2-one

yield 99%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.32 (3H, s), 2.69 (1H, d, $J = 4.6$ Hz), 2.75 (1H, d, $J = 4.6$ Hz), 3.41 (3H, s), 3.68 (1H, d, $J = 15.1$ Hz), 4.33 (1H, d, $J = 15.1$ Hz), 6.97 (1H, d, $J = 1.9$ Hz), 7.07 (1H, dd, $J = 1.9$ Hz, 8.4 Hz), 7.13 (1H, d, $J = 8.4$ Hz).

Reference Example 240

5-fluoro-1-methyl-3-(2-methyl-2-oxiranylmethyl)-1,3-dihydrobenzimidazol-2-one

yield 66%

10 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.34 (3H, s), 2.70 (1H, d, $J = 4.4$ Hz), 2.77 (1H, d, $J = 4.4$ Hz), 3.42 (3H, s), 3.77 (1H, d, $J = 15.0$ Hz), 4.33 (1H, d, $J = 15.0$ Hz), 6.74 - 6.91 (2H, m), 7.00 (1H, dd, $J = 2.2$ Hz, 8.6 Hz).

15 Reference Example 241

5-chloro-1-ethyl-3-(2-methyl-2-oxiranylmethyl)-1,3-dihydrobenzimidazol-2-one

yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

20 1.25 - 1.39 (6H, m), 2.70 (1H, d, $J = 4.4$ Hz), 2.76 (1H, d, $J = 4.4$ Hz), 3.69 (1H, d, $J = 15.1$ Hz), 3.93 (2H, q, $J = 7.3$ Hz), 4.30 (1H, d, $J = 15.1$ Hz), 6.90 (1H, d, $J = 8.3$ Hz), 7.07 (1H, dd, $J = 2.0$ Hz, 8.3 Hz), 7.23 (1H, d, $J = 2.0$ Hz).

25 Reference Example 242

5-chloro-1-isopropyl-3-(2-methyl-2-oxiranylmethyl)-1,3-dihydrobenzimidazole-2-one

yield 100%

¹H-NMR (CDCl₃) δppm:

1.34 (3H, s), 1.53 (6H, dd, J = 2.1 Hz, 6.7 Hz), 2.70
(1H, d, J = 4.5 Hz), 2.75 (1H, d, J = 4.5 Hz), 3.68
(1H, d, J = 15.1 Hz), 4.28 (1H, d, J = 15.1 Hz), 4.65 -
5 4.79 (1H, m), 7.04 (2H, s), 7.22 (1H, s).

Reference Example 243

5-dimethylamino-1-methyl-3-(2-methyl-2-oxiranylmethyl)-
1,3-dihydrobenzimidazol-2-one

yield 100%

10 ¹H-NMR (DMSO-d₆) δppm:

1.33 (3H, s), 2.69 (1H, d, J = 4.5 Hz), 2.79 (1H, d, J
= 4.5 Hz), 2.92 (6H, s), 3.39 (3H, s), 3.67 (1H, d, J =
15.0 Hz), 4.32 (1H, d, J = 15.0 Hz), 6.55 (1H, dd, J =
2.4 Hz, 8.6 Hz), 6.71 (1H, d, J = 2.4 Hz), 6.85 (1H, d,
15 J = 8.6 Hz).

Reference Example 244

5-chloro-1-(n-hexyl)-3-(2-methyl-2-oxiranylmethyl)-1,
3-dihydrobenzimidazol-2-one

yield 100%

20 ¹H-NMR (CDCl₃) δppm:

0.87 (3H, t, J = 6.9 Hz), 1.18 - 1.43 (9H, m), 1.64 -
1.80 (2H, m), 2.70 (1H, d, J = 4.4 Hz), 2.75 (1H, d, J
= 4.4 Hz), 3.69 (1H, d, J = 15.0 Hz), 3.86 (2H, t, J =
7.4 Hz), 4.30 (1H, d, J = 15.0 Hz), 6.88 (1H, d, J =
25 8.4 Hz), 7.06 (1H, dd, J = 1.9 Hz, 8.4 Hz), 7.22 (1H,
d, J = 1.9 Hz).

Reference Example 245

5-ethoxycarbonyl-1-methyl-3-(2-methyl-2-

oxiranylmethyl)-1,3-dihydrobenzimidazol-2-one

yield 100%

¹H-NMR (CDCl₃) δppm:

1.32 - 1.43 (6H, m), 2.69 (1H, d, J = 4.5 Hz), 2.78
5 (1H, d, J = 4.5 Hz), 3.47 (3H, s), 3.87 (1H, d, J =
15.0 Hz), 4.28 (1H, d, J = 15.0 Hz), 4.39 (2H, q, J =
7.2 Hz), 7.00 (1H, d, J = 8.2 Hz), 7.85 (1H, d, J = 1.5
Hz), 7.90 (1H, dd, J = 1.5 Hz, 8.2 Hz).

Reference Example 246

10 Preparation of 1-benzyl-3-(2-methyl-2-oxiranylmethyl)-
imidazolidin-2-one

Using 1-benzyl-3-(2-methyl-2-propenyl)-
imidazolidin-2-one (1.63 g, 7.05 mmol), 1-benzyl-3-(2-
methyl-2-oxiranylmethyl)imidazolidin-2-one (680 mg,
15 yield 39%) as a pale yellow oil was prepared in the
same manner as described in Reference Example 228.

¹H-NMR (CDCl₃) δppm:

1.35 (3H, s), 2.62 (1H, d, J = 4.7 Hz), 2.69 (1H, d, J
= 4.7 Hz), 3.05 - 3.25 (3H, m), 3.27 - 3.49 (2H, m),
20 3.61 (1H, d, J = 14.6 Hz), 4.39 (2H, s), 7.20 - 7.34
(5H, m).

Using corresponding starting materials,
compounds of Reference Examples 247 to 250 were
prepared in the same manner as described in Reference
25 Example 246.

Reference Example 247

1-(2-methyl-2-oxiranylmethyl)-3-phenylimidazolidin-2-
one

yield 58%

¹H-NMR (CDCl₃) δppm:

1.37 (3H, s), 2.65 (1H, d, J = 4.6 Hz), 2.72 (1H, d, J = 4.6 Hz), 3.18 (1H, d, J = 14.7 Hz), 3.48 - 3.61 (2H, m), 3.64 (1H, d, J = 14.7 Hz), 3.77 - 3.91 (2H, m), 7.03 (1H, t, J = 7.3 Hz), 7.25 - 7.36 (2H, m), 7.56 (2H, d, J = 7.9 Hz).

Reference Example 248

1-(4-fluorobenzyl)-3-(2-methyl-2-oxiranylmethyl)-
imidazolidin-2-one

yield 34%

¹H-NMR (CDCl₃) δppm:

1.35 (3H, s), 2.62 (1H, d, J = 4.7 Hz), 2.68 (1H, d, J = 4.7 Hz), 3.12 (1H, d, J = 14.6 Hz), 3.16 - 3.20 (2H, m), 3.27 - 3.45 (2H, m), 3.61 (1H, d, J = 14.6 Hz), 4.35 (2H, s), 6.89 - 7.07 (2H, m), 7.14 - 7.27 (2H, m).

Reference Example 249

1-(4-bromobenzyl)-3-(2-methyl-2-oxiranylmethyl)-
imidazolidin-2-one

yield 51%

¹H-NMR (CDCl₃) δppm:

1.34 (3H, s), 2.62 (1H, d, J = 4.7 Hz), 2.67 (1H, d, J = 4.7 Hz), 3.12 (1H, d, J = 14.7 Hz), 3.16 - 3.25 (2H, m), 3.27 - 3.50 (2H, m), 3.61 (1H, d, J = 14.7 Hz), 4.33 (2H, s), 7.15 (2H, d, J = 8.4 Hz), 7.45 (2H, d, J = 8.4 Hz).

Reference Example 250

1-(4-methoxybenzyl)-3-(2-methyl-2-oxiranylmethyl)-

imidazolidin-2-one

yield 43%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.34 (3H, s), 2.61 (1H, d, $J = 4.7$ Hz), 2.67 (1H, d, $J = 4.7$ Hz), 3.07 - 3.23 (3H, m), 3.27 - 3.50 (2H, m), 3.58 (1H, d, $J = 14.6$ Hz), 3.80 (3H, s), 4.32 (2H, s), 6.86 (2H, d, $J = 8.4$ Hz), 7.19 (2H, d, $J = 8.4$ Hz).

Reference Example 251

1-(4-chlorobenzyl)-3-(2-methyl-2-oxiranylmethyl)-
10 imidazolidin-2-one

Sodium hydride (99 mg, 2.49 mmol) was added to a solution of 2-methyl-2-oxiranylmethyl toluene-4-sulfonate (500 mg, 2.37 mmol) in DMF (5 ml) while cooling in an ice-bath, and the mixture was stirred at
15 room temperature for 1 hour. To which a solution of 1-(4-chlorobenzyl)imidazolidin-2-one (633 mg, 2.61 mmol) in DMF (5 ml) was added while cooling in an ice-bath, and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture,
20 and the mixture was extracted with diethyl ether twice. The extracts were combined, washed with water twice and then with brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel
25 column chromatography (n-hexane/acetone = 3/1) to afford 1-(4-chlorobenzyl)-3-(2-methyl-2-oxiranylmethyl)imidazolidin-2-one (399 mg, 60%) as a pale yellow oil.

¹H-NMR (CDCl₃) δppm:

1.35 (3H, s), 2.62 (1H, d, J = 4.7 Hz), 2.68 (1H, d, J = 4.7 Hz), 3.05 - 3.25 (3H, m), 3.27 - 3.49 (2H, m), 3.61 (1H, d, J = 14.7 Hz), 4.35 (2H, s), 7.21 (2H, dd, J = 2.0 Hz, 6.7 Hz), 7.30 (2H, dd, J = 2.0 Hz, 6.7 Hz).

Using corresponding starting materials, compounds of Reference Examples 252 and 253 were prepared in the same manner as described in Reference Example 251.

10 Reference Example 252

1-(1-benzylpiperidin-4-yl)-3-(2-methyl-2-oxiranylmethyl)imidazolin-2-one

yield 54%

¹H-NMR (CDCl₃) δppm:

15 1.35 (3H, s), 1.59 - 1.80 (4H, m), 2.00 - 2.16 (2H, m), 2.60 (1H, d, J = 4.7 Hz), 2.66 (1H, d, J = 4.7 Hz), 2.84 - 3.00 (2H, m), 3.07 (1H, d, J = 14.7 Hz), 3.22 - 3.43 (4H, m), 3.50 (2H, s), 3.54 (1H, d, J = 14.7 Hz), 3.68 - 3.86 (1H, m), 7.16 - 7.34 (5H, m).

20 Reference Example 253

1-(2,4-dimethoxybenzyl)-3-(2-methyl-2-oxiranylmethyl)imidazolin-2-one

yield 40%

¹H-NMR (CDCl₃) δppm:

25 1.34 (3H, s), 2.60 (1H, d, J = 4.7 Hz), 2.67 (1H, d, J = 4.7 Hz), 3.10 (1H, d, J = 14.6 Hz), 3.14 - 3.34 (4H, m), 3.56 (1H, d, J = 14.6 Hz), 3.80 (6H, s), 4.35 (2H, s), 6.32 - 6.43 (2H, m), 7.18 (1H, d, J = 8.9 Hz).

Reference Example 254

Preparation of 1-(2-methyl-2-oxiranylmethyl)pyrrolidine-2,5-dione

Using 1-(2-methyl-2-propenyl)pyrrolidine-2,5-dione, 1-(2-methyl-2-oxiranylmethyl)pyrrolidine-2,5-dione was prepared in the same manner as described in Reference Example 228.

yield 86%

$^1\text{H-NMR}$ (DMSO- d_6) δppm :

10 1.34 (3H, s), 2.58 (1H, d, $J = 4.6$ Hz), 2.67 - 2.79 (5H, m), 3.56 (1H, d, $J = 13.9$ Hz), 3.84 (1H, d, $J = 13.9$ Hz).

Reference Example 255

Preparation of 2-(2-methyl-2-oxiranylmethyl)phthalimide

15 Using 2-(2-methyl-2-propenyl)phthalimide, 2-(2-methyl-2-oxiranylmethyl)phthalimide was prepared in the same manner as described in Reference Example 228.
yield 98%

$^1\text{H-NMR}$ (DMSO- d_6) δppm :

20 1.38 (3H, s), 2.62 (1H, d, $J = 4.6$ Hz), 2.82 (1H, d, $J = 4.6$ Hz), 3.71 (1H, d, $J = 14.3$ Hz), 4.01 (1H, d, $J = 14.3$ Hz), 7.73 (2H, dd, $J = 2.9$ Hz, 8.6 Hz), 7.87 (2H, dd, $J = 2.9$ Hz, 8.6 Hz).

Reference Example 256

25 Preparation of 1-(2-methyl-2-oxiranylmethyl)-1H-benzimidazole

Using 1-(2-methyl-2-propenyl)-1H-benzimidazole, 1-(2-methyl-2-oxiranylmethyl)-1H-

benzimidazole was prepared in the same manner as described in Reference Example 228.

yield 11%

¹H-NMR (CDCl₃) δppm:

5 1.32 (3H, s), 2.60 (1H, d, J = 4.4 Hz), 2.71 (1H, d, J = 4.4 Hz), 4.17 (1H, d, J = 15.1 Hz), 4.44 (1H, d, J = 15.1 Hz), 7.23 - 7.41 (2H, m), 7.48 (1H, dd, J = 2.2 Hz, 7.8 Hz), 7.80 (1H, dd, J = 2.2 Hz, 7.8 Hz), 7.93 (1H, s).

10 Reference Example 257

Preparation of 1-(2-methyl-2-oxiranylmethyl)-1H-imidazole

Using 1-(2-methyl-2-propenyl)-1H-imidazole, 1-(2-methyl-2-oxiranylmethyl)-1H-imidazole was prepared
15 in the same manner as described in Reference Example 228.

yield 53%

¹H-NMR (CDCl₃) δppm:

1.26 (3H, s), 2.57 (1H, d, J = 4.4 Hz), 2.69 (1H, d, J = 4.4 Hz), 3.94 (1H, d, J = 14.7 Hz), 4.16 (1H, d, J = 14.7 Hz), 6.97 (1H, s), 7.08 (1H, s), 7.49 (1H, s).

Reference Example 258

Preparation of 3-[3-(2-methyl-2-oxiranyl)propyl]-3H-benzoxazol-2-one

25 Using 3-(4-methyl-4-pentenyl)-3H-benzoxazol-2-one (3.4 g, 15.65 mmol), 3-[3-(2-methyl-2-oxiranyl)propyl]-3H-benzoxazol-2-one (3.8 g, quantitative) as a colorless crystalline powder was

prepared in the same manner as described in Reference Example 228.

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.33 (3H, s), 1.56 - 1.77 (2H, m), 1.80 - 1.95 (2H, m),
5 2.59 (1H, d, $J = 4.8$ Hz), 2.63 (1H, d, $J = 4.8$ Hz),
3.85 (2H, t, $J = 7.4$ Hz), 6.99 (1H, d, $J = 7.9$ Hz),
7.05 - 7.23 (3H, m).

Reference Example 259

Preparation of 3-[4-(2-methyl-2-oxiranyl)butyl]-3H-
10 benzoxazol-2-one

Using 3-(5-methyl-5-hexenyl)-3H-benzoxazol-2-one (1.1 g, 4.8 mmol), 3-[4-(2-methyl-2-oxiranyl)butyl]-3H-benzoxazol-2-one (1.2 g, quantitative) as a colorless oil was prepared in the
15 same manner as described in Reference Example 228.

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.30 (3H, s), 1.42 - 1.67 (4H, m), 1.74 - 1.88 (2H, m),
2.57 (1H, d, $J = 4.9$ Hz), 2.60 (1H, d, $J = 4.9$ Hz),
3.84 (2H, t, $J = 7.2$ Hz), 6.98 (1H, d, $J = 8.1$ Hz),
20 7.02 - 7.30 (3H, m).

Reference Example 260

Preparation of 3-(2-methyl-2-oxiranylmethyl)oxazolidin-2-one

25 Using 3-(2-methyl-2-propenyl)oxazolidin-2-one (4.28 g, 30.35 mmol), 3-(2-methyl-2-oxiranylmethyl)-oxazolidin-2-one (2.87 g, yield 62%) as a colorless oil was prepared by the method in Reference Example 228.

¹H-NMR (CDCl₃) δppm:

1.36 (3H, s), 2.66 (1H, d, J = 4.5 Hz), 2.70 (1H, d, J = 4.5 Hz), 3.15 (1H, d, J = 14.7 Hz), 3.57 - 3.75 (3H, m), 4.25 - 4.39 (2H, m).

5 Reference Example 261

Preparation of 3,3-difluoro-1-(2-methyl-2-oxiranylmethyl)-1,3-dihydroindol-2-one

Using 3,3-difluoro-1-(2-methyl-2-propenyl)-1,3-dihydroindol-2-one (1.08 g, 4.83 mmol), 3,3-difluoro-1-(2-methyl-2-oxiranylmethyl)-1,3-dihydroindol-2-one (1.14 g, yield 99%) as a pale yellow powder was prepared in the same manner as described in Reference Example 228.

¹H-NMR (CDCl₃) δppm:

15 1.35 (3H, s), 2.71 (1H, d, J = 4.3 Hz), 2.77 (1H, d, J = 4.3 Hz), 3.46 (1H, d, J = 15.0 Hz), 4.26 (1H, d, J = 15.0 Hz), 7.12 - 7.24 (2H, m), 7.45 - 7.61 (2H, m).

Using corresponding starting materials, compounds of Reference Examples 262 and 263 were prepared in the same manner as described in Reference Example 261.

Reference Example 262

3,3-dimethyl-1-(2-methyl-2-oxiranylmethyl)-1,3-dihydroindol-2-one

25 ¹H-NMR (CDCl₃) δppm:

1.31 (3H, s), 1.39 (6H, s), 2.67 (1H, d, J = 4.5 Hz), 2.74 (1H, d, J = 4.5 Hz), 3.53 (1H, d, J = 14.0 Hz), 4.22 (1H, d, J = 14.0 Hz), 7.00 - 7.10 (2H, m), 7.16 -

7.31 (2H, m).

Reference Example 263

1-(2-methyl-2-oxiranylmethyl)-1,3-dihydroindol-2-one

¹H-NMR (CDCl₃) δppm:

5 1.34 (3H, s), 2.67 (1H, d, J = 4.5 Hz), 2.76 (1H, d, J = 4.5 Hz), 3.49 - 3.61 (3H, m), 4.22 (1H, d, J = 14.9 Hz), 7.00 - 7.10 (2H, m), 7.18 - 7.35 (2H, m).

Reference Example 264

Preparation of benzyl (2-methyl-2-oxiranylmethyl)-
10 carbamate

Benzyl N-(2-methyl-2-propenyl)carbamate (3.90 g, 19.0 mmol) prepared in Reference Example 173 was dissolved in methylene chloride (80 ml), to which m-chloroperbenzoic acid (5.15 g, 20.9 mmol) was added,
15 and the mixture was stirred at room temperature overnight. Sodium thiosulfate aqueous solution and saturated sodium hydrogencarbonate aqueous solution were added to the reaction mixture, which was stirred for a while. The organic layer was separated, washed
20 with saturated sodium hydrogencarbonate aqueous solution, dried over sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to afford benzyl(2-methyl-2-oxiranylmethyl)carbamate (4.31 g, quantitative) as a colorless oil.

25 ¹H-NMR (CDCl₃) δppm:

1.35 (3H, s), 2.61 (1H, d, J = 4.5 Hz), 2.72 (1H, d, J = 4.5 Hz), 3.28 - 3.53 (2H, m), 4.90 (1H, br), 5.11 (2H, s), 7.26 - 7.44 (5H, m).

Using corresponding starting materials, compounds of Reference Examples 265 to 276 were prepared in the same manner as described in Reference Example 264.

5 Reference Example 265

benzyl N-methyl-N-(2-methyl-2-oxiranylmethyl)carbamate
yield 42%

¹H-NMR (CDCl₃) δppm:

1.26 (1.5H, s), 1.31 (1.5H, s), 2.57 (1H, s), 2.61 (1H,
10 s), 2.99 (3H, s), 3.24 (1H, d, J = 15.1 Hz), 3.62
(0.5H, d, J = 15.1 Hz), 3.72 (0.5H, d, J = 15.1 Hz),
5.14 (2H, s), 7.27 - 7.41 (5H, m).

Reference Example 266

4-chlorobenzyl(2-methyl-2-oxiranylmethyl)carbamate
15 yield 98%

¹H-NMR (CDCl₃) δppm:

1.35 (3H, s), 2.62 (1H, d, J = 4.4 Hz), 2.71 (1H, d, J
= 4.4 Hz), 3.27 - 3.50 (2H, m), 4.88 (1H, br), 5.06
(2H, s), 7.23 - 7.41 (4H, m).

20

Reference Example 267

4-fluorobenzyl(2-methyl-2-oxiranylmethyl)carbamate
yield 100%

¹H-NMR (CDCl₃) δppm:

25 1.34 (3H, s), 2.61 (1H, d, J = 4.5 Hz), 2.71 (1H, d, J
= 4.5 Hz), 3.32 - 3.50 (2H, m), 4.86 (1H, br), 5.06
(2H, s), 6.95 - 7.09 (2H, m), 7.27 - 7.41 (2H, m).

Reference Example 268

ethyl(2-methyl-2-oxiranylmethyl)carbamate

yield 82%

¹H-NMR (CDCl₃) δppm:

1.24 (3H, t, J = 7.1 Hz), 1.35 (3H, s), 2.62 (1H, d, J
5 = 4.5 Hz), 2.74 (1H, d, J = 4.5 Hz), 3.27 - 3.50 (2H,
m), 4.12 (2H, q, J = 7.1 Hz), 4.78 (1H, br).

Reference Example 269

4-trifluoromethoxybenzyl(2-methyl-2-oxiranylmethyl)-
carbamate

10 yield 99%

¹H-NMR (CDCl₃) δppm:

1.35 (3H, s), 2.62 (1H, d, J = 4.4 Hz), 2.71 (1H, d, J
= 4.4 Hz), 3.42 (2H, d, J = 5.6 Hz), 4.90 (1H, br),
5.10 (2H, s), 7.20 (2H, d, J = 8.3 Hz), 7.38 (2H, d, J
15 = 8.3 Hz).

Reference Example 270

4-fluorobenzyl N-methyl-N-(2-methyl-2-oxiranylmethyl)-
carbamate

yield 73%

20 ¹H-NMR (CDCl₃) δppm:

1.25 (1.5H, s), 1.30 (1.5H, s), 2.56 (1H, s), 2.61 (1H,
s), 2.97 (3H, s), 3.22 (1H, d, J = 14.8 Hz), 3.61
(0.5H, d, J = 14.8 Hz), 3.72 (0.5H, d, J = 14.8 Hz),
5.10 (2H, s), 6.95 - 7.09 (2H, m), 7.27 - 7.41 (2H, m).

25 Reference Example 271

4-chlorobenzyl oxiranylmethylcarbamate

yield 97%

¹H-NMR (CDCl₃) δppm:

2.59 (1H, dd, $J = 2.6$ Hz, 4.6 Hz), 2.79 (1H, t, $J = 4.3$ Hz), 3.11 (1H, br), 3.20 - 3.32 (1H, m), 3.50 - 3.73 (1H, m), 4.93 (1H, br), 5.07 (2H, s), 7.23 - 7.41 (4H, m).

5 Reference Example 272

4-fluorobenzyl oxiranylmethylcarbamate

yield 89%

$^1\text{H-NMR}$ (CDCl_3) δppm :

2.59 (1H, dd, $J = 2.6$ Hz, 4.6 Hz), 2.79 (1H, t, $J = 4.3$ Hz), 3.11 (1H, br), 3.21 - 3.32 (1H, m), 3.45 - 3.73 (1H, m), 4.92 (1H, br), 5.07 (2H, s), 6.95 - 7.09 (2H, m), 7.27 - 7.41 (2H, m).

Reference Example 273

4-fluorobenzyl N-methyl-N-oxiranylmethylcarbamate

15 yield 34%

$^1\text{H-NMR}$ (CDCl_3) δppm :

2.51 (1H, br), 2.76 (1H, br), 3.01 (3H, s), 3.02 - 3.27 (2H, m), 3.55 - 3.91 (1H, m), 5.10 (2H, s), 6.95 - 7.09 (2H, m), 7.27 - 7.41 (2H, m).

20

Reference Example 274

tert-butyl oxiranylmethylcarbamate

yield 83%

$^1\text{H-NMR}$ (CDCl_3) δppm :

25 1.45 (9H, s), 2.59 (1H, dd, $J = 2.6$ Hz, 4.6 Hz), 2.78 (1H, t, $J = 4.4$ Hz), 3.09 (1H, br), 3.16 - 3.28 (1H, m), 3.38 - 3.66 (1H, br), 4.53 - 4.91 (1H, br).

Reference Example 275

benzyl oxiranylmethylcarbamate

yield 72%

^1H -NMR (DMSO- d_6) δ ppm:

2.67 (1H, t, J = 4.5 Hz), 2.91 - 3.32 (4H, m), 4.91 -
5 5.09 (3H, m), 7.23 - 7.55 (5H, m).

Reference Example 276

phenyl oxiranylmethylcarbamate

Yield 90%

^1H -NMR (DMSO- d_6) δ ppm:

10 2.57 (1H, dd, J = 2.5 Hz, 5.0 Hz), 2.73 (1H, t, J = 4.5
Hz), 3.00 - 3.45 (3H, m), 7.10 (2H, d, J = 7.6 Hz),
7.20 (1H, t, J = 7.6 Hz), 7.38 (2H, t, J = 7.6 Hz),
7.94 (1H, br).

Reference Example 277

15 Preparation of (2-methyl-2-oxiranylmethyl)(4-chloro-
phenyl)carbamate

m-Chloroperbenzoic acid (1.6 g, 6.6 mmol) was
added to a solution of 2-methyl-2-propenyl(4-
chlorophenyl)carbamate (1.0 g, 4.4 mmol) in methylene
20 chloride (20 ml) while cooling in an ice-bath, and the
mixture was stirred at room temperature for 4 hours.
To which sodium thiosulfate aqueous solution was added
and the mixture was filtered, and sodium
hydrogencarbonate aqueous solution was added to the
25 filtrate. The organic layer was separated, dried over
magnesium sulfate, and concentrated under reduced
pressure to afford (2-methyl-2-oxiranylmethyl)(4-
chlorophenyl)carbamate (1.1 g, quantitative) as a pale

yellow crystalline powder.

¹H-NMR (CDCl₃) δppm:

1.42 (3H, s), 2.71 (1H, d, J = 4.6 Hz), 2.82 (1H, d, J = 4.6 Hz), 4.01 (1H, d, J = 11.9 Hz), 4.37 (1H, d, J = 11.9 Hz), 6.79 (1H, br), 7.23 - 7.37 (4H, m).

Reference Example 278

Preparation of (2-methyl-2-oxiranylmethyl) N-(4-chlorophenyl)-N-methylcarbamate

m-Chloroperbenzoic acid (2.5 g, 10.1 mmol) was added to a solution of 2-methyl-2-propenyl N-(4-chlorophenyl)-N-methylcarbamate (1.78 g, 6.7 mmol) in methylene chloride (20 ml) while cooling in an ice-bath, and the mixture was stirred at room temperature for 6.5 hours. To which sodium thiosulfate aqueous solution was added and the mixture was filtered, and sodium hydrogencarbonate aqueous solution was added to the filtrate. The organic layer was separated, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to afford (2-methyl-2-oxiranylmethyl) N-(4-chlorophenyl)-N-methylcarbamate (1.7 g, quantitative) as a pale yellow oil.

¹H-NMR (CDCl₃) δppm:

1.32 (3H, s), 2.62 (1H, d, J = 4.6 Hz), 2.69 (1H, d, J = 4.6 Hz), 3.30 (3H, s), 3.99 (1H, d, J = 11.8 Hz), 4.30 (1H, d, J = 11.8 Hz), 7.15 - 7.25 (2H, m), 7.31 - 7.38 (2H, m).

Reference Example 279

Preparation of tert-butyl 4-oxiranylmethylpiperazine-1-carboxylate

A mixture of tert-butyl piperazine-1-carboxylate (6.2 g, 33.29 mmol), epibromohydrin (5.4 g, 39.42 mmol) and potassium carbonate (5.5 g, 39.79 mmol) in acetonitrile (70 ml) was heated under reflux for 3 hours. The reaction mixture was concentrated under reduced pressure, and water was added to the residue. The mixture was extracted with methylene chloride. The extract was washed with brine, dried over sodium sulfate, and then filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate) to afford tert-butyl 4-oxiranylmethylpiperazine-1-carboxylate (6.2 g, yield 77%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.46 (9H, s), 2.21 - 2.60 (6H, m), 2.70 - 2.81 (2H, m), 3.05 - 3.12 (1H, m), 3.35 - 3.56 (4H, m).

Reference Example 280

Preparation of tert-butyl[4-(2-methyl-2-oxiranylmethyl)piperazin-1-yl]carbamate

A mixture of (2-methyl-2-oxiranylmethyl)toluene-4-sulfonate (9.75 g, 40.3 mmol), tert-butyl piperazin-1-yl-carbamate (6.75 g, 33.5 mmol) prepared in Reference Example 36, triethylamine (7 ml, 50.3 mmol) and potassium iodide (6.68 g, 33.5 mmol) in DMF

(70 ml) was stirred at room temperature overnight. The reaction mixture was poured into water, and extracted with ethyl acetate. The extract was washed with water and brine, dried over sodium sulfate, and filtered.

- 5 The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/acetone = 4/1) to afford tert-butyl[4-(2-methyl-2-oxiranylmethyl)piperazin-1-yl]carbamate (4.66 g, yield 51%) as a colorless
- 10 crystalline powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.35 (3H, s), 1.46 (9H, s), 2.31 (1H, d, $J = 12.9$ Hz), 2.49 - 2.84 (11H, m), 5.37 (1H, br).

Reference Example 281

- 15 Preparation of 3-(2-methyl-2-oxiranylmethyl)-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one

A mixture of 5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one (3.18 g, 12.92 mmol) prepared in Reference Example 49, (2-methyl-2-oxiranylmethyl)

20 toluene-4-sulfonate (4.80 g, 19.38 mmol), potassium carbonate (2.14 g, 15.50 mmol) and sodium iodide (2.90 g, 19.38 mmol) in DMF (30 ml) was stirred at room temperature for 24 hours, and then at 60°C for 4 hours. The reaction mixture was poured into water, and

25 extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromato-

graphy (hexane/ethyl acetate = 9/1) to afford 3-(2-methyl-2-oxiranylmethyl)-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one (2.37 g, yield 58%) as a colorless crystalline powder.

5 ^1H -NMR (DMSO- d_6) δ ppm:

1.43 (3H, s), 2.72 (1H, d, J = 4.4 Hz), 2.86 (1H, d, J = 4.4 Hz), 3.93 (2H, dd, J = 14.8 Hz, 22.2 Hz), 7.28 - 7.41 (2H, m), 7.83 - 7.98 (2H, m).

Using 5-substituted-3H-[1,3,4]oxadiazol-2-one
10 and (2-methyl-2-oxiranylmethyl) toluene-4-sulfonate, compounds of Reference Examples 282 to 289 were prepared in the same manner as described in Reference Example 281.

Reference Example 282

15 3-(2-methyl-2-oxiranylmethyl)-5-phenyl-3H-[1,3,4]-oxadiazol-2-one
yield 41%

^1H -NMR (CDCl_3) δ ppm:

1.44 (3H, s), 2.72 (1H, d, J = 4.5 Hz), 2.88 (1H, d, J = 4.5 Hz), 3.87 (1H, d, J = 14.7 Hz), 3.99 (1H, d, J = 14.7 Hz), 7.40 - 7.57 (3H, m), 7.79 - 7.87 (2H, m).

Reference Example 283

3-(2-methyl-2-oxiranylmethyl)-5-(4-trifluoromethylphenyl)-3H-[1,3,4]oxadiazol-2-one

25 Yield 34%

^1H -NMR (CDCl_3) δ ppm:

1.45 (3H, s), 2.73 (1H, d, J = 4.5 Hz), 2.87 (1H, d, J = 4.5 Hz), 3.92 (1H, d, J = 14.8 Hz), 4.00 (1H, d, J =

14.8 Hz), 7.75 (2H, d, $J = 8.3$ Hz), 8.01 (2H, d, $J = 8.3$ Hz).

Reference Example 284

3-(2-methyl-2-oxiranylmethyl)-5-(4-biphenylyl)-3H-
5 [1,3,4]oxadiazol-2-one
yield 38%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.45 (3H, s), 2.73 (1H, d, $J = 4.5$ Hz), 2.89 (1H, d, $J = 4.5$ Hz), 3.89 (1H, d, $J = 14.8$ Hz), 4.00 (1H, d, $J =$
10 14.8 Hz), 7.33 - 7.50 (3H, m), 7.57 - 7.75 (4H, m),
7.93 (2H, d, $J = 8.6$ Hz).

Reference Example 285

3-(2-methyl-2-oxiranylmethyl)-5-(4-chlorophenyl)-3H-
[1,3,4]oxadiazol-2-one
15 yield 52%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.44 (3H, s), 2.72 (1H, d, $J = 4.4$ Hz), 2.86 (1H, d, $J = 4.4$ Hz), 3.89 (1H, d, $J = 14.8$ Hz), 3.97 (1H, d, $J =$
14.8 Hz), 7.46 (2H, d, $J = 8.7$ Hz), 7.80 (2H, d, $J =$
20 8.7 Hz).

Reference Example 286

3-(2-methyl-2-oxiranylmethyl)-5-(4-fluorophenyl)-3H-
[1,3,4]oxadiazol-2-one
yield 72%

25 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.43 (3H, s), 2.72 (1H, d, $J = 4.5$ Hz), 2.87 (1H, d, $J = 4.5$ Hz), 3.88 (1H, d, $J = 14.7$ Hz), 3.96 (1H, d, $J =$
14.7 Hz), 7.11 - 7.21 (2H, m), 7.74 - 7.89 (2H, m).

Reference Example 287

3-(2-methyl-2-oxiranylmethyl)-5-[2-(4-chlorophenyl)-ethyl]-3H-[1,3,4]oxadiazol-2-one
yield 78%

5 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.32 (3H, s), 2.64 (1H, d, $J = 4.5$ Hz), 2.72 (1H, d, $J = 4.5$ Hz), 2.79 - 2.90 (2H, m), 2.93 - 3.04 (2H, m), 3.74 (1H, d, $J = 14.8$ Hz), 3.79 (1H, d, $J = 14.8$ Hz), 7.12 (2H, d, $J = 8.6$ Hz), 7.27 (2H, d, $J = 8.6$ Hz).

10 Reference Example 288

3-(2-methyl-2-oxiranylmethyl)-5-[2-(4-chlorophenyl)vinyl]-3H-[1,3,4]oxadiazol-2-one
yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

15 1.41 (3H, s), 2.71 (1H, d, $J = 4.4$ Hz), 2.83 (1H, d, $J = 4.4$ Hz), 3.88 (2H, s), 6.60 (1H, d, $J = 16.4$ Hz), 7.28 - 7.47 (5H, m).

Reference Example 289

3-(2-methyl-2-oxiranylmethyl)-5-(4-chlorophenoxy-methyl)-3H-[1,3,4]oxadiazol-2-one
20 yield 59%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.37 (3H, s), 2.68 (1H, d, $J = 4.4$ Hz), 2.78 (1H, d, $J = 4.4$ Hz), 3.86 (2H, s), 4.90 (2H, s), 6.91 (2H, dd, $J = 2.3$ Hz, 6.9 Hz), 7.29 (2H, dd, $J = 2.3$ Hz, 6.9 Hz).
25

Reference Example 290

Preparation of 2-(2-methyl-2-oxiranylmethyl)-1,1-dioxo-1,2-dihydrobenzo[d]isothiazol-3-one

Using saccharin and (2-methyl-2-oxiranylmethyl) toluene-4-sulfonate, 2-(2-methyl-2-oxiranylmethyl)-1,1-dioxo-1,2-dihydrobenzo[d]isothiazol-3-one was prepared in the same manner as described in Reference Example 281. a colorless crystalline powder, yield 43%

¹H-NMR (CDCl₃) δppm:

1.49 (3H, s), 2.74 (1H, d, J = 4.5 Hz), 2.96 (1H, d, J = 4.5 Hz), 3.73 (1H, d, J = 15.5 Hz), 4.04 (1H, d, J = 15.5 Hz), 7.81 - 8.00 (3H, m), 8.09 (1H, dd, J = 2.4 Hz, 6.6 Hz).

Reference Example 291

Preparation of 1-(2-methyl-2-oxiranylmethyl)piperidin-4-one

Using 4-piperidone hydrochloride monohydrate-hydrate, 1-(2-methyl-2-oxiranylmethyl)piperidin-4-one was prepared in the same manner as described in Reference Example 281.

a colorless oil, yield 50%

¹H-NMR (CDCl₃) δppm:

1.43 (3H, s), 2.35 - 2.51 (5H, m), 2.58 - 2.93 (7H, m).

Reference Example 292

Preparation of 4-(2-methyl-2-oxiranylmethyl)-1-(4-trifluoromethylbenzyl)piperazin-2-one

Using 1-(4-trifluoromethylbenzyl)piperazin-2-one, 4-(2-methyl-2-oxiranylmethyl)-1-(4-trifluoromethylbenzyl)piperazin-2-one was prepared in the same manner as described in Reference Example 281.

a colorless crystalline powder, yield 63%

^1H -NMR (CDCl_3) δ ppm:

1.37 (3H, s), 2.34 (1H, d, $J = 12.9$ Hz), 2.53 - 2.67
(4H, m), 2.77 - 2.91 (1H, m), 3.14 - 3.37 (4H, m), 4.62
5 (1H, d, $J = 15.1$ Hz), 4.69 (1H, d, $J = 15.1$ Hz), 7.38
(2H, d, $J = 8.2$ Hz), 7.60 (2H, d, $J = 8.2$ Hz).

Reference Example 293

Preparation of 4-(2-methyl-2-oxiranylmethyl)-1-(tert-butyl)piperazin-2-one

10 Using 1-(tert-butyl)piperazin-2-one, 4-(2-methyl-2-oxiranylmethyl)-1-(tert-butyl)piperazin-2-one was prepared in the same manner as described in Reference Example 281.

a colorless crystalline powder, yield 39%

15 ^1H -NMR (CDCl_3) δ ppm:

1.38 (3H, s), 1.45 (9H, s), 2.31 (1H, d, $J = 12.9$ Hz),
2.42 - 2.55 (4H, m), 2.74 - 2.88 (1H, m), 3.02 (1H, d,
 $J = 16.1$ Hz), 3.20 (1H, d, $J = 16.1$ Hz), 3.28 - 3.37
(2H, m).

20 Reference Example 294

Preparation of (S)-1-(2-methyl-2-oxiranylmethyl)-4-(4-trifluoromethoxyphenyl)piperazine

A solution of (2-methyl-2-oxiranylmethyl)(R)-toluene-4-sulfonate (0.80 g, 3.30 mmol), 1-(4-
25 trifluoromethoxyphenyl)piperazine (0.91 g, 3.36 mmol), and triethylamine (0.55 ml, 3.96 mmol) in DMF (8 ml) was stirred at room temperature for 22 hours. The reaction mixture was poured into water, and extracted

with ethyl acetate, washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol =
5 100/1) to afford (S)-1-(2-methyl-2-oxiranylmethyl)-4-(4-trifluoromethoxyphenyl)piperazine (0.46 g, yield 44%) as a pale yellow oil.

¹H-NMR (CDCl₃) δppm:

1.40 (3H, s), 2.34 (1H, d, J = 12.9 Hz), 2.52 - 2.77
10 (7H, m), 3.10 - 3.27 (4H, m), 6.81 - 6.94 (2H, m), 7.06 - 7.17 (2H, m).

Reference Example 295

Preparation of ethyl(S)-1-(2-methyl-2-oxiranylmethyl)-piperidine-4-carboxylate

15 A solution of (2-methyl-2-oxiranylmethyl)(R)-toluene-4-sulfonate (13.5 g, 55.8 mmol), ethyl piperidine 4-carboxylate (8.9 g, 50.9 mmol), and triethylamine (6.5 g, 64.4 mmol) in DMF (70 ml) was stirred at room temperature for 2 days. The reaction
20 mixture was poured into water, and extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column
25 chromatography (n-hexane/ethyl acetate = 3/1) to afford ethyl(S)-1-(2-methyl-2-oxiranylmethyl)piperidine-4-carboxylate (5.4 g, yield 47%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

1.25 (3H, t, $J = 7.1$ Hz), 1.36 (3H, s), 1.67 - 1.93 (4H, m), 1.97 - 2.08 (2H, m), 2.19 - 2.37 (2H, m), 2.48 (1H, d, $J = 11.5$ Hz), 2.58 (2H, s), 2.78 - 2.97 (2H, m), 4.13 (2H, q, $J = 7.1$ Hz).

- 5 Using corresponding starting materials, compounds of Reference Examples 296 to 299 were prepared in the same manner as described in Reference Example 295.

Reference Example 296

- 10 4-trifluoromethylbenzyl(S)-1-(2-methyl-2-oxiranylmethyl)piperidine-4-carboxylate
a colorless oil, yield 18%
 $^1\text{H-NMR}$ (CDCl_3) δ ppm:
1.35 (3H, s), 1.69 - 2.10 (6H, m), 2.25 - 2.37 (1H, m),
15 2.28 (1H, d, $J = 12.9$ Hz), 2.48 (1H, d, $J = 12.9$ Hz),
2.58 (2H, s), 2.81 - 3.00 (2H, m), 5.11 (2H, s), 7.20 (2H, d, $J = 8.0$ Hz), 7.38 (2H, d, $J = 8.0$ Hz).

Reference Example 297

- 20 4-chlorobenzyl(S)-1-(2-methyl-2-oxiranylmethyl)piperidine-4-carboxylate
a colorless oil, yield 26%
 $^1\text{H-NMR}$ (CDCl_3) δ ppm:
1.36 (3H, s), 1.75 - 2.16 (7H, m), 2.27 (1H, d, $J =$
25 12.9 Hz), 2.50 (1H, d, $J = 12.9$ Hz), 2.58 (2H, s), 2.87 - 3.09 (2H, m), 5.13 (2H, s), 7.17 - 7.21 (2H, m), 7.27 - 7.31 (2H, m).

Reference Example 298

N-(4-chlorobenzyl) (S)-1-(2-methyl-2-oxiranylmethyl)
piperidine-4-carboxamide

a colorless oil, yield 26%

¹H-NMR (CDCl₃) δppm:

- 5 1.36 (3H, s), 1.75 - 2.16 (7H, m), 2.27 (1H, d, J =
12.9 Hz), 2.50 (1H, d, J = 12.9 Hz), 2.58 (2H, s), 2.87
- 3.09 (2H, m), 4.41 (2H, d, J = 5.8 Hz), 5.78 (1H,
br), 7.17 - 7.21 (2H, m), 7.27 - 7.31 (2H, m).

Reference Example 299

- 10 N-(4-chlorophenyl) (S)-1-(2-methyl-2-oxiranyl-
methyl)piperidine-4-carboxamide

a colorless oil, yield 33%

¹H-NMR (CDCl₃) δppm:

- 1.37 (3H, s), 1.82 - 2.08 (6H, m), 2.13 - 2.27 (1H, m),
15 2.30 (1H, d, J = 13.0 Hz), 2.53 (1H, d, J = 13.0 Hz),
2.60 (2H, s), 2.93 - 3.12 (2H, m), 7.16 (1H, bs), 7.26
- 7.31 (2H, m), 7.45 - 7.49 (2H, m).

Reference Example 300

- 20 Preparation of 5-(2-methyl-2-oxiranylmethylsulfanyl)-1-
phenyl-1H-tetrazole

A mixture of 1-phenyl-5-mercapto-1H-tetrazole
(3.5 g, 19.64 mmol), (2-methyl-2-oxiranylmethyl)
toluene-4-sulfonate (5 g, 20.64 mmol), potassium
25 carbonate (3 g, 21.71 mmol), and sodium iodide (4.5 g,
30.02 mmol) in DMF (30 ml) was stirred at 60°C for 6
hours. The reaction mixture was poured into water,
and extracted with ethyl acetate twice. The extracts

were combined, washed with 5% sodium hydroxide aqueous solution and then with water three times, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue
5 was purified by silica gel column chromatography (n-hexane/ethyl acetate = 2/1) to afford 5-(2-methyl-2-oxiranylmethylsulfanyl)-1-phenyl-1H-tetrazole (1.9 g, yield 39%) as a colorless oil.

^1H -NMR (CDCl_3) δ ppm:

10 1.46 (3H, s), 2.73 (1H, d, $J = 4.5$ Hz), 2.91 (1H, d, $J = 4.5$ Hz), 3.61 (1H, d, $J = 13.9$ Hz), 3.77 (1H, d, $J = 13.9$ Hz), 7.50 - 7.65 (5H, m).

Reference Example 301

Preparation of tert-butyl 3-(2-methyl-2-oxiranyl)-
15 propionate

Trimethylsulfoxonium iodide (19.54 g, 88.78 mmol) was added to a suspension of sodium hydride (3.71 g, 92.82 mmol) in DMSO (50 ml) while cooling in an ice-bath, and the mixture was stirred for 2.5 hours. To
20 which a solution of tert-butyl 4-oxopentanoate (13.90 g, 80.71 mmol) in DMSO (20 ml) was added, and the mixture was stirred at room temperature for 15 hours. The mixture was poured into ice water, extracted with diethyl ether. The extract was washed with water,
25 dried over magnesium sulfate, and concentrated under reduced pressure to afford tert-butyl 3-(2-methyl-2-oxiranyl)propionate (10.1 g, yield 67%) as a pale yellow oil.

¹H-NMR (CDCl₃) δppm:

1.32 (3H, s), 1.44 (9H, s), 1.85 - 1.94 (2H, m), 2.27 - 2.33 (2H, m), 2.58 (1H, d, J = 4.7 Hz), 2.63 (1H, d, J = 4.7 Hz).

5 Reference Example 302

Preparation of 2-isopropyl-2-methoxymethoxymethyloxirane

m-Chloroperbenzoic acid (213 g, 861 mmol) was gradually added to a solution of 2-
10 methoxymethoxymethyl-3-methyl-1-butene (89 g, 615 mmol) in methylene chloride (800 ml) while cooling in an ice-bath, and the mixture was stirred at room temperature for 18 hours. The reaction mixture was washed with 10% potassium sulfide aqueous solution and sodium
15 hydrogencarbonate aqueous solution, dried over sodium sulfate, and then concentrated under reduced pressure to afford 2-isopropyl-2-methoxymethoxymethyloxirane (98 g, quantitative) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

20 0.95 (3H, d, J = 7.0 Hz), 1.02 (3H, d, J = 7.0 Hz), 1.84 - 2.05 (1H, m), 2.66 (1H, d, J = 4.9 Hz), 2.75 (1H, d, J = 4.9 Hz), 3.37 (3H, s), 3.63 (1H, d, J = 11.3 Hz), 3.70 (1H, d, J = 11.3 Hz), 4.62 (2H, s).

Reference Example 303

25 Preparation of 2-ethyl-2-methoxymethoxymethyloxirane

m-Chloroperbenzoic acid (143.7 g, 833 mmol) was gradually added to a solution of 2-methoxymethoxymethyl-1-butene (98 g, 757 mmol) prepared

in Reference Example 206 in methylene chloride (8800 ml) while cooling in an ice-bath, and the mixture was stirred at room temperature overnight. The reaction mixture was washed with water, 10% sodium sulfide

5 aqueous solution and sodium hydrogencarbonate aqueous solution, dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford 2-ethyl-2-methoxymethoxymethyloxirane (111 g, quantitative) as a colorless oil.

10 $^1\text{H-NMR}$ (CDCl_3) δppm :

0.96 (3H, t, $J = 7.5$ Hz), 1.60 - 1.73 (1H, m), 1.77 - 1.93 (1H, m), 2.66 (1H, d, $J = 4.8$ Hz), 2.74 (1H, d, $J = 4.8$ Hz), 3.37 (3H, s), 3.56 (1H, d, $J = 11.2$ Hz), 3.65 (1H, d, $J = 11.2$ Hz), 4.64 (2H, s).

15 Reference Example 304

Preparation of 2-(2-methoxymethoxyethyl)oxirane

m-Chloroperbenzoic acid (20.6 g, 95.6 mmol) was gradually added to a solution of 4-methoxymethoxy-1-butene (10.46 g, 90.1 mmol) in methylene chloride

20 (250 ml) while cooling in an ice-bath, the mixture was stirred at room temperature for 6 hours. The reaction mixture was filtered, and the filtrate was washed with a 10% sodium sulfide aqueous solution and sodium hydrogencarbonate aqueous solution, dried over
25 magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford 2-(2-methoxymethoxyethyl) oxirane (10.3 g, 86%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

1.69 - 1.96 (2H, m), 2.53 (1H, dd, J = 2.7 Hz, 4.9 Hz),
2.79 (1H, t, J = 4.9 Hz), 3.02 - 3.08 (1H, m), 3.38
(3H, s), 3.68 (2H, t, J = 5.9 Hz), 4.64 (2H, s).

5 Reference Example 305

Preparation of 4-(4-trifluoromethylphenoxy)piperidine-
1-carbonylchloride

A mixture of 4-(4-trifluoromethylphenoxy)
piperidine (0.6 g, 2.45 mmol), triphosgene (0.25 g,
10 0.86 mmol), and pyridine (0.4 ml, 4.90 mmol) in toluene
(6 ml) was heated under reflux for 2.5 hours. To which
ethyl acetate was added, and the mixture was washed
with 10% hydrochloric acid, dried over magnesium
sulfate. After filtration, the filtrate was
15 concentrated under reduced pressure to afford 4-(4-
trifluoromethylphenoxy)piperidine-1-carbonylchloride
(0.72 g, yield 96%) as a pale yellow oil.

¹H-NMR (CDCl₃) δppm:

1.79 - 2.10 (4H, m), 3.50 - 3.96 (4H, m), 4.58 - 4.75
20 (1H, m), 6.97 (2H, d, J = 8.8 Hz), 7.56 (2H, d, J = 8.8
Hz).

Reference Example 306

Preparation of 4-(4-trifluoromethylphenylamino)-
piperidine-1-carbonylchloride

25 A mixture of (4-trifluoromethylphenylamino)-
piperidine (1.14 g, 4.67 mmol), triphosgene (0.55 g,
1.87 mmol), and triethylamine (0.98 ml, 7.01 mmol) in
methylene chloride (10 ml) was stirred at room

temperature for 1.5 hours. The reaction mixture was washed with water, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford 4-(4-

5 trifluoromethylphenylamino)piperidine-1-carbonylchloride (1.43 g, quantitative) as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.33 - 1.65 (2H, m), 2.09 - 2.24 (2H, m), 3.02 - 3.22 (1H, m), 3.22 - 3.41 (1H, m), 3.48 - 3.70 (1H, m), 4.20
10 - 4.35 (2H, m), 6.66 (2H, d, $J = 8.5$ Hz), 7.43 (2H, d, $J = 8.5$ Hz).

As shown in Reference Example 305 or 306, amines, cyclic amines, and benzene-condensed heterocyclic compounds were allowed to react in the
15 presence of triphosgene and triethylamine or pyridine to afford compounds of Reference Examples 307 to 324.

Reference Example 307

5-chloro-2,3-dihydroindole-1-carbonylchloride

20 a pale yellow crystalline powder, yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

3.19 (2H, t, $J = 8.3$ Hz), 4.28 (2H, t, $J = 8.3$ Hz),
7.18 - 7.22 (2H, m), 7.80 (1H, d, $J = 9.5$ Hz).

Reference Example 308

25 6-chloro-3,4-dihydro-1H-isoquinoline-2-carbonylchloride

a pale yellow oil, yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

2.83 - 3.00 (2H, m), 3.83 (1H, t, $J = 6.0$ Hz), 3.90

(1H, t, $J = 6.0$ Hz), 4.71 (1H, s), 4.80 (1H, s), 7.06 (1H, d, $J = 8.0$ Hz), 7.13 - 7.28 (2H, m).

Reference Example 309

6-chloro-3,4-dihydro-2H-quinoline-1-carbonylchloride

5 a yellow oil, yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.99 - 2.09 (2H, m), 2.79 (2H, t, $J = 6.5$ Hz), 3.94 (2H, t, $J = 6.3$ Hz), 7.14 - 7.20 (2H, m), 7.62 (1H, d, $J = 8.5$ Hz).

10 Reference Example 310

5-chloro-1,3-dihydroisoindole-2-carbonylchloride

a yellow oil, yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

3.19 (2H, t, $J = 8.3$ Hz), 4.28 (2H, t, $J = 8.3$ Hz),
15 7.18 - 7.22 (2H, m), 7.80 (1H, d, $J = 9.5$ Hz).

Reference Example 311

tert-butyl 4-chlorocarbonylpiperazine-1-carboxylate

a pale yellow crystalline powder, yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

20 1.47 (9H, s), 3.16 - 3.29 (2H, m), 3.37 - 3.55 (4H, m),
3.55 - 3.78 (2H, m).

Reference Example 312

4-(4-trifluoromethoxybenzyloxycarbonyl)piperazine-1-carbonylchloride

25 Yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

3.43 - 3.80 (8H, m), 5.15 (2H, s), 7.15 - 7.25 (2H, m),
7.33 - 7.45 (2H, m).

Reference Example 313

4-[3-(4-trifluoromethylphenyl)-2-propenyloxycarbonyl]-
piperazine-1-carbonylchloride

Yield 100%

5 $^1\text{H-NMR}$ (CDCl_3) δppm :

3.54 - 3.65 (4H, m), 3.65 - 3.72 (2H, m), 3.72 - 3.83
(2H, m), 4.80 (2H, dd, $J = 1.1$ Hz, 6.1 Hz), 6.39 (1H,
dt, $J = 6.1$ Hz, 15.9 Hz), 6.68 (1H, d, $J = 15.9$ Hz),
7.49 (2H, d, $J = 8.4$ Hz), 7.59 (2H, d, $J = 8.4$ Hz).

10 Reference Example 314

4-(4-chlorobenzyl)piperazine-1-carbonylchloride

a brown oil, yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

2.65 - 2.96 (4H, m), 3.67 - 4.08 (6H, m), 7.36 - 7.39

15 (4H, m).

Reference Example 315

4-(4-trifluoromethylbenzyl)piperazine-1-carbonyl-
chloride

a brown oil, yield 100%

20 $^1\text{H-NMR}$ (CDCl_3) δppm :

2.97 - 3.12 (4H, m), 3.91 - 4.06 (2H, m), 4.06 - 4.21
(2H, m), 4.15 (2H, s), 7.58 - 7.73 (4H, m).

Reference Example 316

4-(4-trifluoromethoxybenzyl)piperazine-1-carbonyl-
25 chloride

a brown oil, yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

2.58 - 2.85 (4H, m), 3.58 - 3.90 (6H, m), 7.17 - 7.25

(2H, m), 7.35 - 7.46 (2H, m).

Reference Example 317

4-(4-trifluoromethoxyphenyl)-1,2,3,6-tetrahydro-
pyridine-1-carbonylchloride

5 a pale brown oil, yield 57%

¹H-NMR (CDCl₃) δppm:

2.54 - 2.67 (2H, m), 3.85 (1H, t, J = 5.7 Hz), 3.94

(1H, t, J = 5.7 Hz), 4.28 (1H, d, J = 2.7 Hz), 4.36

(1H, d, J = 2.7 Hz), 5.94 - 6.06 (1H, m), 7.16 - 7.21

10 (2H, m), 7.36 - 7.41 (2H, m).

Reference Example 318

4-(4-methoxyphenyl)-1,2,3,6-tetrahydropyridine-1-
carbonylchloride

a pale brown oil, yield 60%

15 ¹H-NMR (CDCl₃) δppm:

2.54 - 2.67 (2H, m), 3.51 (1H, t, J = 5.6 Hz), 3.81

(3H, s), 3.92 - 4.02 (1H, m), 4.23 - 4.31 (1H, m), 4.31

- 4.37 (1H, m), 5.87 - 5.96 (1H, m), 6.85 - 6.90 (2H,

m), 7.29 - 7.35 (2H, m).

20 Reference Example 319

4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-
1-carbonylchloride

a pale brown oil, yield 100%

¹H-NMR (CDCl₃) δppm:

25 2.58 - 2.71 (2H, m), 3.87 (1H, t, J = 5.7 Hz), 3.96

(1H, t, J = 5.7 Hz), 4.31 (1H, d, J = 2.8 Hz), 4.39

(1H, d, J = 2.8 Hz), 6.04 - 6.15 (1H, m), 7.45 - 7.63

(4H, m).

Reference Example 320

4-(4-bromophenyl)-1,2,3,6-tetrahydropyridine-1-carbonylchloride

a pale brown oil, yield 100%

5 $^1\text{H-NMR}$ (CDCl_3) δppm :

2.52 - 2.67 (2H, m), 3.84 (1H, t, $J = 5.7$ Hz), 3.93 (1H, t, $J = 5.7$ Hz), 4.27 (1H, d, $J = 2.6$ Hz), 4.35 (1H, d, $J = 2.6$ Hz), 5.94 - 6.06 (1H, m), 7.21 - 7.24 (2H, m), 7.43 - 7.49 (2H, m).

10 Reference Example 321

4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine-1-carbonylchloride

a pale brown oil, yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

15 2.54 - 2.67 (2H, m), 3.84 (1H, t, $J = 5.7$ Hz), 3.93 (1H, t, $J = 5.7$ Hz), 4.27 (1H, d, $J = 2.6$ Hz), 4.35 (1H, d, $J = 2.6$ Hz), 5.90 - 6.00 (1H, m), 7.00 - 7.07 (2H, m), 7.24 - 7.35 (2H, m).

Reference Example 322

20 N-(4-chlorophenyl)-N-cyclohexylcarbamyldichloride

a pale yellow crystalline powder, yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

0.79 - 1.06 (1H, m), 1.14 (2H, t, $J = 3.5$ Hz, 12.5 Hz), 1.23 - 1.44 (2H, m), 1.50 - 1.65 (1H, m), 1.67 - 1.81 (2H, m), 1.87 - 2.00 (2H, m), 4.78 (1H, m), 7.06 - 7.10 (2H, m), 7.36 - 7.41 (2H, m).

Reference Example 323

N-methyl-N-(4-trifluoromethoxybenzyl)carbamyldichloride

a yellow oil, yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

3.09 (3H, s), 4.58 (2H, s), 7.16 - 7.33 (4H, m).

Reference Example 324

5 4-[(4-trifluoromethylbenzylidene)amino]piperazine-1-carbonylchloride

a brown oil, yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

3.17 - 3.39 (4H, m), 3.74 - 4.02 (4H, m), 7.56 (1H, s),

10 7.60 (2H, d, $J = 8.3$ Hz), 7.69 (2H, d, $J = 8.3$ Hz).

Reference Example 325

Preparation of 4-(4-trifluoromethoxyphenyl)piperazine-1-carbonylchloride

A mixture of 1-(4-trifluoromethoxyphenyl)

15 piperazine (1.0 g, 4.1 mmol), triphosgene (0.42 g, 1.4 mmol), and pyridine (0.66 ml, 8.2 mmol) in toluene (20 ml) was stirred at 100°C for 4.5 hours. To which ethyl acetate was added, and the mixture was washed with water, dried over magnesium sulfate. After filtration,
20 the filtrate was concentrated under reduced pressure to afford 4-(4-trifluoromethoxyphenyl)piperazine-1-carbonylchloride (1.3 g, quantitative) as a brown oil.

$^1\text{H-NMR}$ (CDCl_3) δppm :

3.08 - 3.30 (4H, m), 3.67 - 4.00 (4H, m), 6.79 - 6.98

25 (2H, m), 7.08 - 7.17 (2H, m).

Using corresponding starting materials, compounds of Reference Examples 326 to 332 were quantitatively prepared in the same manner as described

in Reference Example 325.

Reference Example 326

4-(4-trifluoromethylphenyl)piperazine-1-carbonylchloride

5 $^1\text{H-NMR}$ (CDCl_3) δppm :

3.26 - 3.39 (4H, m), 3.76 - 3.87 (2H, m), 3.87 - 3.98 (2H, m), 6.87 - 6.98 (2H, m), 7.48 - 7.59 (2H, m).

Reference Example 327

4-(4-methoxyphenyl)piperazine-1-carbonylchloride

10 $^1\text{H-NMR}$ (CDCl_3) δppm :

3.04 - 3.15 (4H, m), 3.52 - 3.75 (2H, m), 3.75 - 3.92 (2H, m), 3.78 (3H, s), 6.81 - 6.98 (4H, m).

Reference Example 328

4-(4-chlorophenyl)piperazine-1-carbonylchloride

15 $^1\text{H-NMR}$ (CDCl_3) δppm :

3.10 - 3.25 (4H, m), 3.37 - 3.52 (2H, m), 3.73 - 3.90 (2H, m), 6.83 - 6.88 (2H, m), 7.20 - 7.25 (2H, m).

Reference Example 329

4-(3-chlorophenyl)piperazine-1-carbonylchloride

20 $^1\text{H-NMR}$ (CDCl_3) δppm :

3.15 - 3.29 (4H, m), 3.73 - 3.94 (4H, m), 6.77 - 6.81 (1H, m), 6.88 - 6.91 (2H, m), 7.20 (1H, t, $J = 8.3$ Hz).

Reference Example 330

4-(3,4-dichlorophenyl)piperazine-1-carbonylchloride

25 $^1\text{H-NMR}$ (CDCl_3) δppm :

3.08 - 3.27 (4H, m), 3.37 - 3.48 (2H, m), 3.60 - 3.73 (1H, m), 3.73 - 3.90 (1H, m), 6.75 (1H, dd, $J = 2.9$ Hz, 9.0 Hz), 6.96 - 6.98 (1H, m), 7.30 (1H, dd, $J = 5.1$ Hz,

9.0 Hz).

Reference Example 331

4-(4-fluorophenyl)piperazine-1-carbonylchloride

¹H-NMR (CDCl₃) δppm:

- 5 3.04 - 3.19 (4H, m), 3.40 - 3.50 (2H, m), 3.62 - 3.75 (1H, m), 3.75 - 3.92 (1H, m), 6.86 - 7.03 (4H, m).

Reference Example 332

4-(3-trifluoromethylphenyl)piperazine-1-carbonylchloride

10 ¹H-NMR (CDCl₃) δppm:

- 3.21 - 3.35 (4H, m), 3.42 - 3.54 (2H, m), 3.77 - 3.96 (2H, m), 7.02 - 7.19 (3H, m), 7.31 - 7.46 (1H, m).

Reference Example 333

Preparation of tert-butyl 4-[1-(4-trifluoromethoxy-
15 phenyl)piperidin-4-yl]piperazine-1-carboxylate

- A mixture of tert-butyl 4-piperidin-4-ylpiperazine-1-carboxylate (1.5 g, 5.67 mmol), 4-(trifluoromethoxy)bromobenzene (3.36 g, 13.92 mmol), palladium acetate (25 mg, 0.11 mmol), BINAP (87 mg, 0.14 mmol), and sodium tert-butoxide (1.07 g, 11.14 mmol) in toluene (20 ml) was stirred at 80°C under a nitrogen atmosphere for 8 hours. The reaction mixture was allowed to return to room temperature, to which ethyl acetate (10 ml) and brine (20 ml) were added, and
25 the mixture was filtered. The organic layer was separated, and dried over sodium sulfate. After filtration, the filtrate was concentrated, and the residue was purified by silica gel column

chromatography (methylene chloride/methanol = 20/1) to afford tert-butyl 4-[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]piperazine-1-carboxylate (1.01 g, 42%) as a yellow powder.

5 $^1\text{H-NMR}(\text{CDCl}_3)$ δppm

1.49(9H, s), 1.52-1.75(2H, m), 1.83-1.99(2H, m), 2.31-2.52(5H, m), 2.64-2.81(2H, m), 3.36-3.49(4H, m), 3.62-3.75(2H, m), 6.86(2H, d, $J = 8.5$ Hz), 7.09(2H, d, $J = 8.5$ Hz).

10 Reference Example 334

Preparation of 1-[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]piperazine

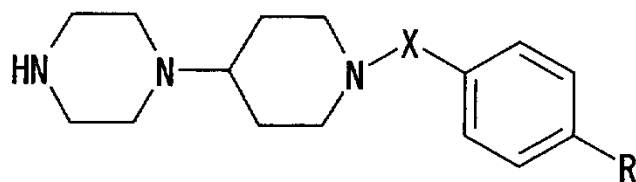
Tert-butyl 4-[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]piperazine-1-carboxylate (1 g, 2.33 mmol) was dissolved in methylene chloride (10 ml), to which trifluoroacetic acid (10 ml) was added while cooling in an ice-bath, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was washed with a 25% sodium hydroxide aqueous solution (40 ml) and brine (10 ml), and dried over sodium sulfate. After filtration, the filtrate was concentrated to afford 1-[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]piperazine (770 mg, quantitative) as a yellow amorphous form.

25 $^1\text{H-NMR}(\text{CDCl}_3)$ δppm

1.52-1.75(2H, m), 1.83-1.99(2H, m), 2.25-2.38(1H, m), 2.48-2.76(6H, m), 2.79-2.99(4H, m), 3.56-3.75(2H, m), 6.89(2H, d, $J = 8.5$ Hz), 7.09(2H, d, $J = 8.5$ Hz).

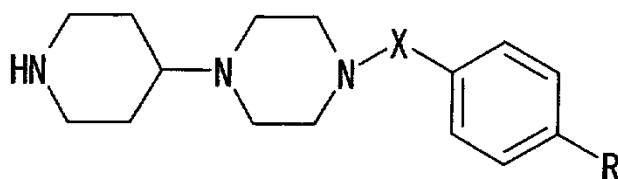
Following compounds were prepared in the same manner as described in Reference Example 334.

Table 1



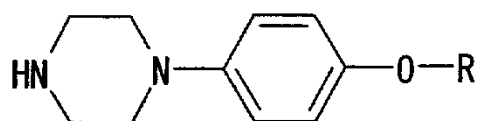
Reference Example	X	R	¹ H-NMR (CDCl ₃) δ ppm
335	none	OCF ₃	1.52-1.75 (2H, m), 1.83-1.99 (2H, m), 2.25-2.35 (1H, m), 2.48-2.76 (6H, m), 2.79-2.99 (4H, m), 3.56-3.75 (2H, m), 6.89 (2H, d, J=8.5Hz), 7.09 (2H, d, J=8.5Hz)
336	C=O	Cl	1.31-1.55 (2H, m), 1.69-1.98 (2H, m), 2.36-2.60 (5H, m), 2.69-3.00 (6H, m), 3.69-3.86 (1H, m), 4.55-4.79 (1H, m), 7.24-7.43 (4H, m)
337	C=O	OCF ₃	1.31-1.60 (2H, m), 1.71-2.00 (2H, m), 2.38-2.60 (5H, m), 2.67-3.07 (6H, m), 3.62-3.86 (1H, m), 4.57-4.83 (1H, m), 7.25 (2H, d, J=2.3Hz, 8.7Hz), 7.45 (2H, d, J=2.3Hz, 8.7Hz).
338	CH ₂	Cl	1.45-1.60 (2H, m), 1.67-1.83 (2H, m), 1.86-2.00 (2H, m), 2.12-2.24 (1H, m), 2.45-2.57 (4H, m), 2.79-2.93 (6H, m), 3.44 (2H, s), 7.14-7.31 (4H, m)
339	CH ₂	OCF ₃	1.48-1.81 (4H, m), 1.85-2.00 (2H, m), 2.12-2.29 (1H, m), 2.43-2.57 (4H, m), 2.76-2.98 (6H, m), 3.46 (2H, s), 7.15 (2H, d, J=8.5Hz), 7.33 (2H, d, J=8.5Hz)

Table 2



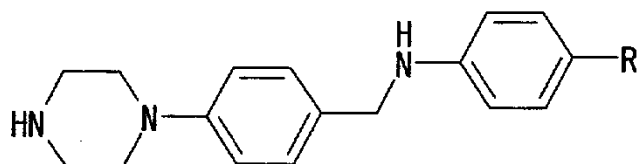
Reference Example	X	R	¹ H-NMR (CDCl ₃) δ ppm
340	C=O	Cl	1.29-1.48 (2H, m), 1.67-1.86 (2H, m), 2.31-2.69 (7H, m), 3.07-3.21 (2H, m), 3.31-3.50 (2H, m), 3.60-3.83 (2H, m), 7.26-7.45 (4H, m)
341	C=O	OCF ₃	1.31-1.50 (2H, m), 1.64-1.83 (2H, m), 2.29-2.69 (7H, m), 3.07-3.21 (2H, m), 3.31-3.50 (2H, m), 3.64-3.83 (2H, m), 7.25 (2H, d, J=8.7Hz), 7.45 (2H, d, J=8.7Hz)
342	CH ₂	OCF ₃	1.25-1.48 (2H, m), 1.69-1.86 (2H, m), 2.19-2.62 (11H, m), 3.00-3.17 (2H, m), 3.50 (2H, s), 7.15 (2H, d, J=8.6Hz), 7.34 (2H, d, J=8.6Hz)
343	CH ₂	Cl	1.24-1.43 (2H, m), 1.74-1.86 (2H, m), 2.21-2.60 (11H, m), 3.02-3.17 (2H, m), 3.46 (2H, s), 7.19-7.33 (4H, m)
344	none	OCF ₃	1.31-1.51 (2H, m), 1.76-1.93 (2H, m), 2.29-2.45 (1H, m), 2.52-2.79 (6H, m), 3.10-3.26 (6H, m), 6.88 (2H, d, J=8.6Hz), 7.10 (2H, d, J=8.6Hz).
345	none	Cl	1.33-1.52 (2H, m), 1.81-1.98 (2H, m), 2.26-2.43 (1H, m), 2.52-2.74 (6H, m), 3.05-3.21 (6H, m), 6.84 (2H, d, J=6.9Hz), 7.19 (2H, d, J=6.9Hz)

Table 3



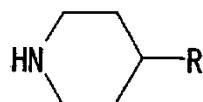
Reference Example	R	¹ H-NMR (CDCl ₃) δ ppm
346	4-ClPh-	2.98-3.12 (8H, m), 6.80-6.94 (6H, m), 7.24 (2H, d, J=2.3Hz, 6.8Hz)
347	4-CF ₃ PhCH ₂ -	3.04 (8H, s), 5.08 (2H, s), 6.90 (4H, s), 7.54 (2H, d, J=8.2Hz), 7.63 (2H, d, J=8.2Hz)
348	4-ClPhCH ₂ -	3.03 (8H, s), 4.98 (2H, s), 6.89 (4H, s), 7.35 (4H, s).
349	4-CF ₃ OPhCH ₂ -	3.04 (8H, s), 5.01 (2H, s), 6.90 (4H, s), 7.22 (2H, d, J=8.5Hz), 7.45 (2H, d, J=8.5Hz)
350	4-CF ₃ OPh-	2.96-3.14 (8H, m), 6.82-6.98 (6H, m), 7.06-7.16 (2H, m)
351	4-CF ₃ Ph-	2.96-3.14 (8H, m), 6.84-7.00 (6H, m), 7.53 (2H, d, J=8.6Hz)

Table 4



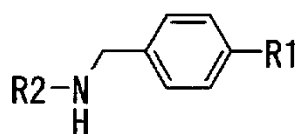
Reference Example	R	¹ H-NMR (CDCl ₃) δ ppm
352	Cl-	2.96-3.16 (8H, m), 3.97 (1H, br), 4.20 (1H, d, J=5.4Hz), 6.55 (1H, d, J=8.8Hz), 6.60 (1H, d, J=8.8Hz), 6.90 (1H, d, J=8.8Hz), 7.00-7.14 (4H, m), 7.18-7.25 (1H, m)
353	CF ₃ O-	2.94-3.20 (8H, m), 4.00 (1H, br), 4.21 (1H, d, J=5.3Hz), 6.57 (1H, d, J=6.8Hz), 6.64 (1H, d, J=8.8Hz), 6.80-7.12 (5H, m), 7.16-7.25 (1H, m)

Table 5



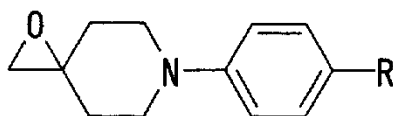
Reference Example	R	¹ H-NMR (CDCl ₃) δ ppm
354		1.51-1.73 (2H, m), 1.76-1.92 (2H, m), 2.51-2.82 (3H, m), 3.10-3.27 (2H, m), 6.92-7.08 (4H, m), 7.12-7.27 (2H, m), 7.56 (2H, d, J=8.6Hz)
355		1.33-1.60 (4H, m), 1.69-2.02 (4H, m), 2.29-2.64 (5H, m), 2.76-2.88 (2H, m), 3.05-3.17 (2H, m), 4.14-4.31 (1H, m), 6.85 (2H, d, J=8.7Hz), 7.12 (2H, d, J=8.7Hz)
356		1.52-1.98 (4H, m), 2.26-2.43 (1H, m), 2.55-2.74 (2H, m), 3.10-3.26 (2H, m), 7.18 (2H, d, J=8.4Hz), 7.55 (2H, d, J=8.4Hz)
357		1.60-1.81 (4H, m), 2.57-2.74 (3H, m), 3.05-3.21 (6H, m), 3.60-3.83 (4H, m), 6.90 (2H, d, J=8.4Hz), 7.13 (2H, d, J=8.4Hz)
358		1.56-1.73 (2H, m), 1.83-1.89 (3H, m), 2.57-2.82 (3H, m), 3.18-3.24 (2H, m), 6.95-7.05 (4H, m), 7.20-7.25 (2H, m), 7.53-7.57 (2H, m)
359		1.57-1.86 (4H, m), 2.52-2.81 (4H, m), 3.19-3.25 (2H, m), 5.03 (2H, s), 6.89-6.94 (2H, m), 7.11-7.25 (4H, m), 7.44-7.48 (2H, m)
360		1.51-1.68 (3H, m), 1.78-1.84 (2H, m), 2.50-2.64 (1H, m), 2.67-2.79 (2H, m), 3.15-3.21 (2H, m), 5.11 (1H, s), 6.87-6.94 (2H, m), 7.12-7.18 (2H, m), 7.52-7.57 (2H, m), 7.62-7.66 (2H, m)
361		1.60-2.12 (5H, m), 2.52-2.66 (1H, m), 2.71-2.83 (2H, m), 3.22-3.28 (2H, m), 5.01 (2H, s), 6.88-6.93 (2H, m), 7.11-7.18 (2H, m), 7.30-7.41 (4H, m)
362		1.86-2.18 (3H, m), 2.35-2.52 (1H, m), 2.61-2.69 (1H, m), 2.93-3.01 (5H, m), 3.24-3.59 (3H, m), 4.49 (2H, s), 6.67-6.70 (2H, m), 7.07-7.17 (4H, m), 7.23-7.27 (2H, m)

Table 6



Reference Example	R1	R2	¹ H-NMR (CDCl ₃) δ ppm
363		CH ₃	1.50 (9H, s), 2.44 (3H, s), 3.00-3.14 (4H, m), 3.49-3.57 (4H, m), 3.72 (2H, s), 6.89 (2H, d, J=7.2 Hz), 7.26 (2H, d, J=7.2 Hz).
364		C ₂ H ₅	1.15 (3H, t, J=7.1 Hz), 1.48 (9H, s), 2.18 (1H, brs), 2.69 (2H, q, J=7.1 Hz), 3.09-3.12 (4H, m), 3.55-3.59 (4H, m), 3.73 (2H, s), 6.86-6.92 (2H, m), 7.23-7.26 (2H, m).
365		CH ₃	1.09-1.16 (3H, m), 1.78-1.88 (2H, m), 2.49 (3H, s), 2.73-2.80 (2H, m), 3.17-3.31 (3H, m), 3.62-3.79 (5H, m), 3.92 (2H, s), 6.67-6.70 (2H, m), 6.91-6.93 (2H, m), 7.13-7.19 (2H, m), 7.39-7.42 (2H, m).

Table 7



Reference Example	R	¹ H-NMR (CDCl ₃) δ ppm
366	-Cl	1.51-1.67 (2H, m), 1.90-2.04 (2H, m), 2.72 (2H, s), 3.18-3.43 (4H, m), 6.89 (2H, d, J=8.4Hz), 7.21 (2H, d, J=8.4Hz)
367	-OCF ₃	1.53-1.67 (2H, m), 1.86-2.04 (2H, m), 2.73 (2H, s), 3.22-3.45 (4H, m), 6.93 (2H, d, J=8.4Hz), 7.11 (2H, d, J=8.4Hz).
368		1.53-1.63 (2H, m), 1.90-2.06 (2H, m), 2.73 (2H, s), 3.24 (3H, s), 3.27-3.45 (4H, m), 6.72 (2H, d, J=8.4Hz), 6.90-7.10 (6H, m).
369		1.54-1.69 (2H, m), 1.92-2.06 (2H, m), 2.73 (2H, s), 3.20-3.43 (4H, m), 6.84-6.96 (6H, m), 7.14 (2H, d, J=8.4Hz)
370		1.58-1.69 (2H, m), 1.88-2.15 (6H, m), 2.71 (2H, s), 2.90-3.04 (2H, m), 3.17-3.44 (6H, m), 4.31-4.46 (1H, m), 6.85-6.94 (6H, m), 7.14 (2H, d, J=8.4Hz)
371		1.55-1.71 (2H, m), 1.92-2.04 (2H, m), 2.72 (2H, s), 3.12-3.35 (12H, m), 6.86-7.00 (6H, m), 7.14 (2H, d, J=8.5Hz).

Following compounds were prepared in the same manner as described in Reference Example 186.

Reference Example 372

1-(4-Hydroxyphenyl)-4-phenylpiperidin-4-ol

5 MS: 269 (M⁺)

Reference Example 373

4-(4-chlorophenyl)-1-(4-hydroxyphenyl)piperidin-4-ol

MS: 349 ($M^+ - 1$)

Reference Example 374

5 1-(4-hydroxyphenyl)-4-(4-trifluoromethoxy-
phenyl)piperidin-4-ol

MS: 353 (M^+)

Reference Example 375

(4-hydroxyphenyl)-[4-(4-trifluoromethoxyphenoxy)-
10 piperidin-1-yl]methanone

MS: 381 (M^+)

Reference Example 376

tert-butyl 1-(4-hydroxyphenyl)piperidine-4-carboxylate

$^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm 1.46 (9H, s), 1.76-2.05 (4H, m), 2.23-
15 2.34 (1H, m), 2.62-2.73 (2H, m), 3.39-3.48 (2H, m), 4.39-
4.49 (1H, m), 4.78 (1H, s), 6.72-6.78 (2H, m), 6.82-
6.89 (2H, m).

Reference Example 377

4-(4-phenylpiperidin-1-yl)phenol

20 MS: 253 (M^+)

Reference Example 378

4-(4,4-diethoxypiperidin-1-yl)phenol

MS: 265 (M^+)

Reference Example 379

25 2-dimethylaminomethyl-4-[4-(4-trifluoromethoxy-
phenoxy)piperidin-1-yl]phenol

MS: 410 (M^+)

Reference Example 380

4-(4-[1,3]dioxolan-2-ylpiperidin-1-yl)phenol

¹H NMR(CDCl₃) δppm 1.51-1.70(2H, m), 1.80-1.92(2H, m),
2.53-2.66(2H, m), 3.48-3.57(2H, m), 3.84-3.92(2H, m),
5 3.92-4.02(2H, m), 4.63(1H, brs), 4.69(1H, d, J = 4.9
Hz), 6.70-6.78(2H, m), 6.83-6.91(2H, m).

Reference Example 381

4-[4-(4-trifluoromethoxyphenyl)piperazin-1-yl]phenol

MS: 337(M⁺)

10 Reference Example 382

tert-butyl 4-(4-hydroxyphenoxy)piperidine-1-carboxylate

MS: 293(M⁺)

Reference Example 383

4-[1-(4-trifluoromethylphenyl)piperidin-4-yloxy]phenol

15 MS: 337(M⁺)

Reference Example 384

4-(1,4-dioxa-8-azaspiro[4,5]decan-8-yl)phenol

¹H NMR(CDCl₃) δppm 1.87(4H, t, J = 5.7 Hz), 3.18(4H, t,
J = 5.7 Hz), 3.99(4H, s), 6.74(2H, d, J = 8.9 Hz),
20 6.88(2H, d, J = 8.9 Hz).

Reference Example 385

4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)phenol

MS: 251(M⁺)

Reference Example 386

25 tert-butyl 4-(4-hydroxyphenyl)piperazine-1-carboxylate

¹H NMR(CDCl₃) δppm 1.49(9H, s), 2.95-3.00(4H, m), 3.55-
3.60(4H, m), 5.77(1H, s), 6.74-6.86(4H, m).

Reference Example 387

4-[4-(4-trifluoromethoxyphenyl)piperazin-1-yl]phenol

¹H NMR(CDCl₃) δppm 3.19-3.24(4H, m), 3.29-3.34(4H, m),
4.51(1H, s), 6.76-6.82(2H, m), 6.87-6.97(4H, m), 7.11-
5 7.16(2H, m).

Reference Example 388

4-{4-[(4-trifluoromethoxybenzylidene)amino]piperazin-1-yl}phenol

MS: 349(M⁺-1)

10 Reference Example 389

4-[4-(4-chlorobenzyl)piperazin-1-yl]phenol

¹H NMR(CDCl₃) δppm 2.60(4H, t, J = 4.8 Hz), 3.08(4H, t,
J = 4.8 Hz), 3.53(2H, s), 6.71-6.78(2H, m), 6.81-
6.89(2H, m), 7.27-7.42(4H, m).

15 Reference Example 390

3-(4-hydroxyphenyl)oxazolidin-2-one

¹H NMR(CDCl₃) δppm 3.94-4.01(2H, m), 4.35-4.42(2H, m),
6.73-6.80(2H, m), 7.29-7.36(2H, m), 9.34(1H, s).

Reference Example 391

20 4-(4-pyridyl)phenol

¹H NMR(CDCl₃) δppm 6.87-6.93(2H, m), 7.60-7.70(4H, m),
8.54-8.57(2H, m), 9.85(1H, s).

Reference Example 392

4-hydroxy-N-(4-trifluoromethoxyphenyl)benzamide

25 ¹H NMR(CDCl₃) δppm 6.84-6.87(2H, m), 7.31-7.34(2H, m),
7.83-7.87(4H, m), 10.11(1H, brs), 10.15(1H, brs).

Reference Example 393

(4-hydroxyphenyl)-(4-trifluoromethoxyphenyl)methanone

^1H NMR(CDCl_3) δ ppm 6.08(1H, s), 6.92-6.96(2H, m), 7.30-7.33(2H, m), 7.76-7.83(4H, m).

Reference Example 394

(4-hydroxyphenyl)-(4-trifluoromethylphenyl)methanone

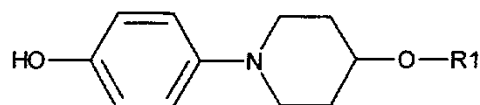
5 MS: 266(M^+)

Reference Example 395

4-(4-trifluoromethoxyphenoxy)phenol

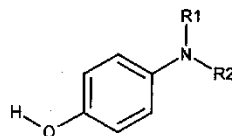
^1H NMR(CDCl_3) δ ppm 4.67(1H, brs), 6.81-6.85(2H, m), 6.90-6.96(4H, m), 7.13-7.16(2H, m).

Table 8



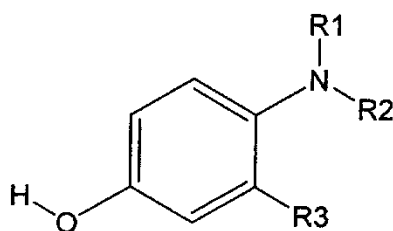
Refer- ence Example	R1	NMR or Ms
396	4-ClPh-	^1H NMR (CDCl_3) δ 1.87-2.01 (2H, m), 2.04-2.16 (2H, m), 2.91-3.02 (2H, m), 3.29-3.39 (2H, m), 4.34-4.44 (1H, m), 4.85 (1H, s), 6.71-6.78 (2H, m), 6.82-6.92 (4H, m), 7.20-7.26 (2H, m).
397	4-CF ₃ Ph-	^1H NMR (CDCl_3) δ 1.90-2.05 (2H, m), 2.08-2.20 (2H, m), 2.94-3.05 (2H, m), 3.30-3.40 (2H, m), 4.46-4.56 (1H, m), 4.64 (1H, s), 6.72-6.80 (2H, m), 6.86-6.93 (2H, m), 6.96-7.00 (2H, m), 7.52-7.56 (2H, m).
398	4-FPh-	^1H NMR (CDCl_3) δ 1.86-2.00 (2H, m), 2.04-2.16 (2H, m), 2.90-3.00 (2H, m), 3.30-3.40 (2H, m), 4.29-4.39 (1H, m), 4.72 (1H, s), 6.71-6.78 (2H, m), 6.83-7.01 (6H, m).
399	4-CH ₃ OPh-	^1H NMR (CDCl_3) δ 1.86-2.00 (2H, m), 2.05-2.13 (2H, m), 2.88-2.99 (2H, m), 3.31-3.41 (2H, m), 3.77 (3H, s), 4.25-4.35 (1H, m), 4.72 (1H, s), 6.72-6.77 (2H, m), 6.80-6.92 (6H, m).
400	4-CH ₃ Ph-	^1H NMR (CDCl_3) δ 1.87-2.01 (2H, m), 2.04-2.16 (2H, m), 2.29 (3H, s), 2.90-3.00 (2H, m), 3.30-3.40 (2H, m), 4.33-4.43 (1H, m), 4.85 (1H, s), 6.71-6.78 (2H, m), 6.80-6.92 (4H, m), 7.06-7.10 (2H, m).
401	-C ₆ H ₅	^1H NMR (CDCl_3) δ 1.89-2.03 (2H, m), 2.04-2.18 (2H, m), 2.92-3.02 (2H, m), 3.31-3.41 (2H, m), 4.39-4.49 (1H, m), 4.92 (1H, s), 6.70-6.78 (2H, m), 6.84-6.98 (5H, m), 7.24-7.33 (2H, m).
402	4-CNPh-	^1H NMR (CDCl_3) δ 1.90-2.04 (2H, m), 2.09-2.18 (2H, m), 2.94-3.04 (2H, m), 3.29-3.39 (2H, m), 4.49-4.55 (1H, m), 6.75-6.80 (2H, m), 6.86-6.90 (2H, m), 6.93-7.00 (2H, m), 7.55-7.62 (2H, m).
403	-CH ₂ -cyclo-C ₆ H ₁₁	Ms: 289 (M ⁺)
404		^1H NMR (CDCl_3) δ 1.54-2.07 (11H, m), 2.74-2.87 (2H, m), 3.31-3.43 (2H, m), 3.47-3.57 (1H, m), 3.72-3.83 (1H, m), 3.88-3.98 (1H, m), 4.74-4.78 (1H, m), 6.69-6.76 (2H, m), 6.83-6.88 (2H, m).

Table 9



Refer- ence Example	R1	R2	NMR
405	-CH ₃	4-CF ₃ OPh-	¹ H NMR (CDCl ₃) δ 3.23(3H, s), 4.88(1H, s), 6.66-6.73(2H, m), 6.80-6.87(2H, m), 6.99-7.08(4H, m).
406	-CH ₃	4-ClPh-	¹ H NMR (CDCl ₃) δ 3.22(3H, s), 4.69(1H, brs), 6.66-6.68(2H, m), 6.81-6.84(2H, m), 7.01-7.04(2H, m), 7.10-7.13(2H, m).
407	-CH ₃	4-CF ₃ Ph-	¹ H NMR (CDCl ₃) δ 3.28(3H, s), 4.80(1H, brs), 6.68-6.71(2H, m), 6.85-6.88(2H, m), 7.06-7.09(2H, m), 7.37-7.40(2H, m).
408	-C ₂ H ₅	4-CF ₃ OPh-	¹ H NMR (CDCl ₃) δ 1.19(3H, t, J=7.1Hz), 3.66(2H, q, J=7.1Hz), 4.75(1H, brs), 6.62-6.66(2H, m), 6.83-6.87(2H, m), 6.98-7.05(4H, m).
409	4-CF ₃ OPhCH ₂ -	4-CF ₃ OPhCH ₂ -	¹ H NMR (CDCl ₃) δ 4.34(1H, bs), 4.49(4H, brs), 6.61-6.72(4H, m), 7.14-7.16(4H, m), 7.24-7.26(4H, m).
410	-C ₂ H ₅	4-CF ₃ Ph-	¹ H NMR (CDCl ₃) δ 1.21(3H, t, J=7.1Hz), 3.70(2H, q, J=7.1Hz), 4.87(1H, brs), 6.62-6.65(2H, m), 6.85-6.91(2H, m), 7.03-7.09(2H, m), 7.34-7.37(2H, m).
411	-C ₂ H ₅	4-ClPh-	¹ H NMR (CDCl ₃) δ 1.17(3H, t, J=7.1Hz), 3.65(2H, q, J=7.1Hz), 4.73(1H, brs), 6.59-6.63(2H, m), 6.82-6.85(2H, m), 6.98-7.03(2H, m), 7.06-7.10(2H, m).
412	-CH ₃	4-CF ₃ OPhCH ₂ -	¹ H NMR (CDCl ₃) δ 2.90(3H, s), 4.33(1H, brs), 4.40(2H, brs), 6.66-6.70(2H, m), 6.72-6.76(2H, m), 7.13-7.16(2H, m), 7.25-7.27(2H, m).
413	-CH ₃	4-ClPhCH ₂ -	¹ H NMR (CDCl ₃) δ 2.88(3H, s), 4.34(1H, brs), 4.36(2H, brs), 6.65-6.69(2H, m), 6.71-6.76(2H, m), 7.15-7.18(2H, m), 7.25-7.28(2H, m).
414	-CH ₃	4-CF ₃ PhCH ₂ -	¹ H NMR (CDCl ₃) δ 2.92(3H, s), 4.35(1H, brs), 4.46(2H, brs), 6.65-6.68(2H, m), 6.73-6.76(2H, m), 7.34-7.37(2H, m), 7.55-7.58(2H, m).
415	-C ₂ H ₅	4-CF ₃ OPhCH ₂ -	¹ H NMR (CDCl ₃) δ 1.14(3H, t, J=7.1Hz), 4.12(2H, q, J=7.1Hz), 4.28(1H, brs), 4.39(2H, brs), 6.50-6.80(4H, m), 7.13-7.15(2H, m), 7.26-7.28(2H, m).
416	-C ₂ H ₅	4-CF ₃ PhCH ₂ -	¹ H NMR (CDCl ₃) δ 1.16(3H, t, J=7.0Hz), 3.38(2H, brs), 4.29(1H, brs), 4.45(2H, brs), 6.61-6.70(4H, m), 7.35-7.38(2H, m), 7.54-7.56(2H, m).
417	-C ₂ H ₅	4-ClPhCH ₂ -	¹ H NMR (CDCl ₃) δ 1.14(3H, t, J=7.0Hz), 3.35(2H, brs), 4.28(1H, brs), 4.36(2H, brs), 6.62-6.70(4H, m), 7.17-7.19(2H, m), 7.25-7.28(2H, m).
418	-COCH ₃	-C ₆ H ₅	¹ H NMR (CDCl ₃) δ 2.06(3H, s), 6.27(1H, brs), 6.69-6.80(2H, m), 7.08-7.33(7H, m).
419	-COCH ₃	4-ClPh-	¹ H NMR (CDCl ₃) δ 2.06(3H, s), 6.50(1H, brs), 6.63-6.85(2H, m), 7.05-7.08(2H, m), 7.18-7.38(4H, m).

Table 10



Refer- ence Example	R1	R2	R3	NMR
420	$-\text{CH}_3$	$4-\text{CF}_3\text{OPh}-$	$-\text{F}$	^1H NMR (CDCl_3) δ 3.22 (3H, s), 5.02 (1H, brs), 6.57-6.71 (4H, m), 7.01-7.14 (3H, m).
421	$-\text{CH}_3$	$4-\text{ClPh}-$	$-\text{F}$	^1H NMR (CDCl_3) δ 3.20 (3H, s), 5.02 (1H, brs), 6.54-6.70 (4H, m), 7.07-7.13 (3H, m).
422	$-\text{CO}_2\text{CH}_3$	$-\text{C}_6\text{H}_5$	$-\text{H}$	^1H NMR (CDCl_3) δ 3.75 (3H, s), 5.86 (1H, brs), 6.69-6.72 (2H, m), 7.05-7.08 (2H, m), 7.18-7.31 (5H, m).
423	$-\text{CO}_2\text{CH}_3$	$4-\text{ClPh}-$	$-\text{H}$	^1H NMR (CDCl_3) δ 3.75 (3H, s), 5.52 (1H, brs), 6.73-6.76 (2H, m), 7.04-7.07 (2H, m), 7.16-7.18 (2H, m), 7.26-7.29 (2H, m).
424	$-\text{COCH}_3$	$4-\text{CF}_3\text{Ph}-$	$-\text{H}$	^1H NMR (CDCl_3) δ 2.08 (3H, s), 6.04 (1H, brs), 6.83-6.86 (2H, m), 7.09-7.12 (2H, m), 7.37-7.40 (2H, m), 7.56-7.59 (2H, m).
425	$-\text{COCH}_3$	$4-\text{CF}_3\text{OPh}-$	$-\text{H}$	^1H NMR (CDCl_3) δ 2.07 (3H, s), 6.60-6.92 (3H, m), 6.98-7.30 (6H, m).
426	$-\text{CH}_3$	$-\text{C}_6\text{H}_5$	$-\text{H}$	^1H NMR (CDCl_3) δ 3.24 (3H, s), 4.63 (1H, brs), 6.76-6.84 (5H, m), 7.01-7.05 (2H, m), 7.17-7.22 (2H, m).
427	$-\text{COCH}_3$	$4-\text{ClPh}-$	$-\text{F}$	^1H NMR (CDCl_3) δ 2.07 (3H, brs), 6.46-6.61 (2H, m), 6.96-7.36 (6H, m).
428	$-\text{COCH}_3$	$4-\text{CF}_3\text{OPh}-$	$-\text{F}$	^1H NMR (CDCl_3) δ 2.07 (3H, brs), 6.48-6.62 (2H, m), 6.90-7.42 (6H, m).