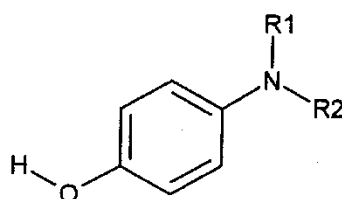
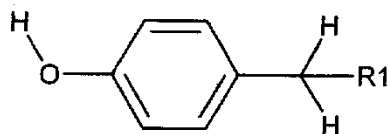


Table 11



Reference Example	R1	R2	NMR or Ms
429	-C ₆ H ₅	4-CF ₃ OPhCH ₂ -	¹ H NMR (CDCl ₃) δ 4.72 (1H, brs), 4.89 (2H, brs), 6.75-6.83 (5H, m), 7.05-7.18 (6H, m), 7.34-7.37 (2H, m).
430	-C ₆ H ₅	4-CF ₃ PhCH ₂ -	¹ H NMR (CDCl ₃) δ 4.67 (1H, brs), 4.95 (2H, brs), 6.74-6.83 (5H, m), 7.06-7.18 (4H, m), 7.44-7.47 (2H, m), 7.54-7.57 (2H, m).
431	-C ₆ H ₅	4-ClPhCH ₂ -	¹ H NMR (CDCl ₃) δ 4.64 (1H, brs), 4.86 (2H, brs), 6.74-6.82 (5H, m), 7.04-7.08 (2H, m), 7.12-7.17 (2H, m), 7.26 (4H, brs).
432	-COCH ₃	4-CF ₃ OPhCH ₂ -	¹ H NMR (CDCl ₃) δ 1.89 (3H, s), 4.83 (2H, s), 6.54 (1H, brs), 6.82 (4H, m), 7.09-7.12 (2H, m), 7.20-7.26 (2H, m).
433	-CH ₃	4-CF ₃ PhCO-	¹ H NMR (CDCl ₃) δ 3.46 (3H, s), 6.28 (1H, brs), 6.68-6.71 (2H, m), 6.85-6.92 (2H, m), 7.33-7.44 (4H, m).
434	-CH ₃	4-ClPhCO-	¹ H NMR (CDCl ₃) δ 3.44 (3H, s), 5.12 (1H, brs), 6.67-6.72 (2H, m), 6.88-6.91 (2H, m), 7.13-7.16 (2H, m), 7.21-7.24 (2H, m).
435	-H	4-CF ₃ OPhCO-	¹ H NMR (CDCl ₃) δ 6.71-6.76 (2H, m), 7.48-7.52 (4H, m), 8.02-8.05 (2H, m), 9.25 (1H, s), 10.10 (1H, brs).
436	-CH ₃	4-CF ₃ OPhCO-	¹ H NMR (CDCl ₃) δ 3.45 (3H, s), 6.13 (1H, brs), 6.69-6.72 (2H, m), 6.87-6.89 (2H, m), 6.99-7.02 (2H, m), 7.31-7.34 (2H, m).
437	-CH ₃	4-CF ₃ OPhO(CH ₂) ₃ -	¹ H NMR (CDCl ₃) δ 1.97-2.06 (2H, m), 2.85 (3H, s), 3.42 (2H, t, J=6.9Hz), 3.99 (2H, t, J=6.0Hz), 4.28 (1H, brs), 6.65-6.75 (4H, m), 6.86-6.89 (2H, m), 7.11-7.14 (2H, m).
438	-H		219 (M ⁺ - 1)

Table 12



Refer- ence Example	R1	NMR or Ms
439		Ms: 367 (M+)
440		^1H NMR (CDCl_3) δ 2.96 (3H, s), 4.43 (2H, brs), 4.68 (1H, s), 6.63-6.66 (2H, m), 6.76-6.80 (2H, m), 7.05-7.08 (2H, m), 7.12-7.15 (2H, m).
441		^1H NMR (CDCl_3) δ 1.90 (3H, brs), 4.83 (2H, s), 5.88 (1H, brs), 6.74-6.76 (2H, m), 7.02-7.06 (2H, m), 7.10-7.13 (2H, m), 7.60-7.63 (2H, m).
442		^1H NMR (CDCl_3) δ 3.06 (3H, s), 4.52 (2H, s), 4.70 (1H, s), 6.71-6.81 (4H, m), 7.05-7.07 (2H, m), 7.41-7.44 (2H, m).
443		^1H NMR (CDCl_3) δ 2.99 (3H, s), 4.44 (2H, s), 4.68 (1H, s), 6.66-6.70 (2H, m), 6.77-6.81 (2H, m), 7.04-7.10 (4H, m).
444		^1H NMR (CDCl_3) δ 3.95 (1H, brs), 4.21 (2H, s), 4.69 (1H, brs), 6.53-6.56 (2H, m), 6.79-6.82 (2H, m), 7.09-7.12 (2H, m), 7.20-7.23 (2H, m).
445		^1H NMR (CDCl_3) δ 4.28 (3H, brs), 4.71 (1H, brs), 6.60-6.63 (2H, m), 6.79-6.83 (2H, m), 7.21-7.23 (2H, m), 7.38-7.40 (2H, m).
446		^1H NMR (CDCl_3) δ 2.16 (3H, s), 3.45 (2H, s), 3.48 (2H, s), 4.82 (1H, brs), 6.76-6.79 (2H, m), 7.14-7.22 (4H, m), 7.35-7.38 (2H, m).
447		^1H NMR (CDCl_3) δ 4.03 (1H, brs), 4.22 (2H, s), 4.72 (1H, brs), 6.56-6.69 (2H, m), 6.80-6.83 (2H, m), 7.01-7.04 (2H, m), 7.21-7.24 (2H, m).

Example 1

Preparation of 2-chloro-1-(3-chloro-2-hydroxypropyl)-4-nitroimidazole

Sodium hydrogencarbonate (1.25 g, 14.91 mmol)

5 was added to a solution of 2-chloro-4-nitro-1H-imidazole (2 g, 13.56 mmol) and epichlorohydrin (1.38 g, 14.91 mmol) in acetonitrile (60 ml), and the resulting mixture was stirred under reflux for 4 hours. The reaction mixture was allowed to return to room
10 temperature, and concentrated under reduced pressure. To the residue, water (20 ml) was added, the resulting mixture was extracted with methylene chloride (15 ml) twice, and the extracts were dried over sodium sulfate, and then filtrated. The filtrate was concentrated
15 under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1) to afford 2-chloro-1-(3-chloro-2-hydroxypropyl)-4-nitroimidazole (2.04 g, yield 63%) as a light yellow oil.

20 $^1\text{H-NMR}$ (CDCl_3) δppm :
3.51 - 3.70 (2H, m), 4.02 - 4.35 (4H, m), 7.92 (1H, s).

Example 2

Preparation of 2-chloro-4-nitro-1-(oxiran-2-ylmethyl)-imidazole

25 2-Chloro-1-(3-chloro-2-hydroxypropyl)-4-nitroimidazole prepared in Example 1 (2.04 g, 8.5 mmol) was dissolved in methylene chloride (20 ml), and 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) (2.04 ml, 13.67

mmol) was added to the solution. The resulting mixture was stirred at room temperature overnight. The reaction mixture was washed with 3N hydrochloric acid (20 ml) and a saturated saline solution (20 ml) in this order, dried over sodium 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 = 20/1) to afford 2-chloro-4-nitro-1-(oxiran-2-ylmethyl)imidazole (190 mg, yield 11%) as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:
2.55 - 2.69 (1H, m), 2.97 (1H, t, $J = 4.2$ Hz), 3.26 - 3.43 (1H, m), 3.94 (1H, dd, $J = 6.4$ Hz, 15.0 Hz), 4.52 (1H, dd, $J = 2.6$ Hz, 15.0 Hz), 7.88 (1H, s).

Example 3

Preparation of 2-chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole

2-Chloro-4-nitro-1H-imidazole (6.78 g, 46 mmol) and 2-methyloxiran-2-ylmethyl 4-nitrobenzoate (12 g, 51 mmol) were dissolved in ethyl acetate (24 ml), and triethylamine (1.3 ml, 9.2 mmol) was added to the solution. The resulting mixture was stirred under reflux for 14 hours. The reaction mixture was concentrated under reduced pressure, and methylene chloride (40 ml) was added to the residue. The resulting precipitates were filtered off, and dissolved in methanol (120 ml). To the solution, potassium

carbonate (318 mg, 2.3 mmol) was added, and the resulting mixture was stirred at room temperature for 1 hour. To the resulting mixture, 6 N hydrochloric acid (0.8 ml) and magnesium sulfate (8 g) were added in this
5 order with cooling on ice-bath, and the resulting mixture was stirred for 30 minutes. Insoluble matters were removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. To the residue, ethyl acetate (6 ml) and toluene (60 ml)
10 were added. The resulting precipitates were filtered off and dried at 50°C to afford 2-chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole (7.88 g, yield 72%) as a white powder.

¹H-NMR (DMSO-d₆) δppm:

15 1.02 (3H, s), 3.25 (2H, d, J = 5.3 Hz), 4.04 (2H, s), 4.98 (1H, s), 5.10 (1H, t, J = 5.4 Hz), 8.29 (1H, s).

Example 4

Preparation of 2-chloro-1-(2-hydroxy-3-methanesulfonyloxy-2-methylpropyl)-4-nitroimidazole

20 Methanesulfonyl chloride (2.01 ml, 25.72 mmol) was added to a solution of 2-chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole prepared in Example 3 (5.05 g, 21.43 mmol) in pyridine (10 ml) with cooling on ice-bath and the resulting mixture was
25 stirred at room temperature for 1.5 hours. 6N hydrochloric acid was added to the mixture, and the resulting mixture was extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, and

then concentrated under reduced pressure to afford 2-chloro-1-(2-hydroxy-3-methanesulfonyloxy-2-methylpropyl)-4-nitroimidazole (6.72 g, quantitative) as a yellow oil.

5 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.31 (3H, s), 2.10 (1H, s), 3.11 (3H, s), 4.08 - 4.23 (4H, m), 8.02 (1H, s).

Example 5

Preparation of 2-chloro-1-[2-hydroxy-2-methyl-3-(4-methylbenzenesulfonyloxy)propyl]-4-nitroimidazole
10 2-Chloro-4-nitro-1H-imidazole (1 g, 6.78 mmol), 2-methyloxiran-2-ylmethyl paratoluenesulfonate (2.46 g, 10.15 mmol), benzyl(triethyl) ammonium chloride (1.50 mg, 0.66 mmol) and acetonitrile (10 ml)
15 were stirred under reflux for 8 hours. The reaction mixture was allowed to return to room temperature, diluted with ethyl acetate. The organic phase was washed with a saturated aqueous sodium bicarbonate solution twice, dried over magnesium sulfate and then
20 filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 6/1) to afford 2-chloro-1-[2-hydroxy-2-methyl-3-(4-methylbenzenesulfonyloxy)propyl]-4-nitroimidazole (1.86
25 g, yield 70%) as a light yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.25 (3H, s), 2.46 (3H, s), 2.80 (1H, s), 3.91 (1H, d, $J = 10.4$ Hz), 3.95 (1H, d, $J = 10.4$ Hz), 4.04 - 4.16

(2H, m), 7.38 (2H, d, $J = 8.0$ Hz), 7.76 (2H, d, $J = 8.0$ Hz), 7.93 (1H, s).

Example 6

Preparation of 2-chloro-1-(2-methyloxiran-2-ylmethyl)-
5 4-nitroimidazole

2-Chloro-1-(2-hydroxy-3-methanesulfonyloxy-2-methylpropyl)-4-nitroimidazole prepared in Example 4 (6.72 g, 21.43 mmol) was treated in the same manner as in Example 2 to afford 2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole (5.6 g, yield 94%) as a
10 white powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.39 (3H, s), 2.62 (2H, d, $J = 4.0$ Hz), 2.78 (1H, d, $J = 4.0$ Hz), 4.00 (1H, d, $J = 14.9$ Hz), 4.38 (1H, d, $J =$
15 14.9 Hz), 7.87 (1H, s).

Example 7

Preparation of 2-chloro-1-(2-methyloxiran-2-ylmethyl)-
4-nitro-1H-imidazole

Using 2-chloro-1-[2-hydroxy-2-methyl-3-(4-methylbenzenesulfonyloxy)propyl]-4-nitroimidazole
20 prepared in Example 5 (1.11 g, 2.84 mmol) gave 2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitro-1H-imidazole (523 mg, yield 85%) as a light yellow powder in the same manner as in Example 2.

25 The properties of the obtained compound were same as those of the compound obtained in Example 6.

Example 8

Preparation of (R)-2-chloro-1-[2-hydroxy-3-(4-

methylbenzenesulfonyloxy)propyl]-4-nitroimidazole

- 2-Chloro-4-nitro-1H-imidazole (10 g, 67.79 mmol) and (R)-(-)-glycidyl tosylate (17.02 g, 74.58 mmol) were dissolved in acetonitrile (50 ml), sodium hydrogencarbonate (6.26 g, 74.15 mmol) was added to the solution, and the resulting mixture was stirred under reflux for 3.5 hours. The reaction mixture was allowed to return to room temperature. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/2) to afford (R)-2-chloro-1-[2-hydroxy-3-(4-methylbenzenesulfonyloxy)propyl]-4-nitroimidazole (16.9 g, yield 66%) as a light yellow oil.
- ¹H-NMR (CDCl₃) δppm:
2.47 (3H, s), 3.65 (1H, d, J = 5.8 Hz), 3.93 - 4.33 (5H, m), 7.38 (2H, d, J = 8.3 Hz), 7.70 (2H, d, J = 8.3 Hz), 7.86 (1H, s).

Example 9

- Preparation of (R)-2-chloro-4-nitro-1-(oxiran-2-yl-methyl)imidazole

2-Chloro-4-nitro-1H-imidazole (1 g, 6.78 mmol) and (R)-(-)-glycidyl tosylate (1.7 g, 7.45 mmol) were dissolved in tetrahydrofuran (THF) (10 ml), sodium hydrogencarbonate (600 mg, 7.14 mmol) was added to the solution, and the resulting mixture was stirred under reflux for 11 hours. The reaction mixture was concentrated under reduced pressure, water was added to

- the solution, and the resulting mixture was extracted with ethyl acetate. The organic phase was washed with water and a saturated saline solution in this order, dried over sodium sulfate, and filtered. The filtrate
- 5 was concentrated, and the residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1) to afford (R)-2-chloro-4-nitro-1-(oxiran-2-ylmethyl)imidazole (1.45 g, yield 57%) as a light yellow oil.
- 10 Optical purity 79.2% e.e.
 $[\alpha]_D^{27} = 42.55^\circ$ (concentration: 1.262, CHCl_3)
 $^1\text{H-NMR}$ (CDCl_3) δ ppm:
 2.61 (1H, t, $J = 2.5$ Hz, 4.3 Hz), 2.97 (1H, t, $J = 4.3$ Hz), 3.25 - 3.34 (1H, m), 3.95 (1H, dd, $J = 6.4$ Hz,
 15 15.0 Hz), 4.51 (1H, dd, $J = 2.6$ Hz, 15.0 Hz), 7.88 (1H, s).

Example 10

Preparation of (R)-2-chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole

- 20 2-Chloro-4-nitro-1H-imidazole (600 g, 4.07 mol) and (R)-2-methyloxiran-2-ylmethyl 4-nitrobenzoate (1060 g, 4.47 mol) were dissolved in ethyl acetate (2124 ml), triethylamine (113.64 ml, 0.82 mol) was added to the solution, and the resulting mixture was
- 25 stirred under reflux for 16 hours. The reaction mixture was concentrated under reduced pressure, and ethyl acetate (530 ml) and toluene (5300 ml) were added to the residue. The resulting precipitates were

filtered off and dissolved in methanol (10.6 l). Potassium carbonate (55.4 g, 0.4 mol) was added to the solution, the resulting mixture was stirred at room temperature for 1 hour, concentrated hydrochloric acid (66 ml) and magnesium sulfate (671 g) were added in this order with cooling on ice-bath, and the resulting mixture was stirred for 30 minutes. Insoluble matters were removed by filtration, and the filtrate was concentrated under reduced pressure. To the residue, ethyl acetate (530 ml) and toluene (5300 ml) were added. The resulting precipitates were filtered off and dried at 50°C to afford (R)-2-chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole (879.1 g, yield 92%) as a light brown powder.

Optical purity 99.0% e.e.

$[\alpha]_D^{27} = 17.38^\circ$ (concentration: 1.03, DMSO)

$^1\text{H-NMR}$ (DMSO- d_6) δ ppm:

1.01 (3H, s), 3.25 (2H, d, $J = 5.3$ Hz), 4.05 (2H, s), 5.01 (1H, s), 5.11 (1H, t, $J = 5.4$ Hz), 8.32 (1H, s).

Example 11

Preparation of (R)-2-chloro-1-(2-hydroxy-3-methanesulfonyloxy-2-methylpropyl)-4-nitroimidazole

(R)-2-Chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole prepared in Example 10 (879 g, 3.73 mol) was dissolved in pyridine (1778 ml) and cooled to 5°C. To this solution, methanesulfonyl chloride (432.7 ml, 5.59 mol) was added dropwise below 15°C, and the resulting mixture was stirred at the same

temperature for 1 hour. To the mixture, 6N
hydrochloric acid (5500 ml) was added below 30°C, and
the resulting mixture was stirred for 40 minutes with
cooling on ice-bath. The precipitates were filtered
5 off and washed with water and toluene in this order to
afford primary crystals. In addition, the filtrate was
extracted with ethyl acetate (5 liters) twice. The
organic phase was washed with water, dried over
magnesium sulfate, and filtered to afford a solid. The
10 filtrate was concentrated under reduced pressure. To
the residue, toluene was added and the precipitates
were filtered off to afford a solid. The solids were
combined and dried at 60°C to afford (R)-2-chloro-1-(2-
hydroxy-3-methanesulfonyloxy-2-methylpropyl)-4-
15 nitroimidazole (942.6 g, yield 81%) as a white powder.

¹H-NMR (DMSO-d₆) δppm:

1.12 (3H, s), 3.23 (3H, s), 4.09 (2H, s), 4.13 (2H, s),
5.60 (1H, br), 8.34 (1H, s).

Example 12

20 Preparation of (R)-2-chloro-1-(2-methyloxiran-2-yl-
methyl)-4-nitroimidazole

(R)-2-Chloro-1-(2-hydroxy-3-methane-
sulfonyloxy-2-methylpropyl)-4-nitroimidazole prepared
in Example 11 (942.6 g, 3 mol) was suspended in ethyl
25 acetate (9426 ml). DBU (494 ml, 3.3 mol) was added to
the suspension, and the resulting mixture was stirred
at room temperature for 1 hour. The reaction mixture
was washed with water (5 liters). The water layer was

extracted with ethyl acetate (5 liters) twice. The organic phases were combined together, and the mixture was washed with a saturated saline solution (5 liters), dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/2) to afford (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole (600.7 g, yield 92%) as a white powder.

Optical purity 98.8% e.e.
 $[\alpha]_D^{26} = 31.11^\circ$ (concentration: 2.02, CHCl_3)
 $^1\text{H-NMR}$ (CDCl_3) δ ppm:
 1.38 (3H, s), 2.62 (1H, d, $J = 4.0$ Hz), 2.78 (1H, d, $J = 4.0$ Hz), 4.00 (1H, d, $J = 14.9$ Hz), 4.38 (1H, d, $J = 14.9$ Hz), 7.87 (1H, s).

Example 13

Preparation of (R)-2-chloro-1-[2-hydroxy-2-methyl-3-(4-methylbenzenesulfonyloxy)propyl]-4-nitroimidazole

2-Chloro-4-nitro-1H-imidazole (18.4 g, 125 mmol) and (R)-2-methyloxiran-2-ylmethyl 4-methylbenzene sulfonate (36.2 g, 149 mmol) were suspended in acetonitrile (150 ml). Benzyl(triethyl) ammonium chloride (5.7 g, 25 mmol) was added to the suspension, and the resulting mixture was stirred under reflux for 8 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 20/1) to afford (R)-2-chloro-1-[2-hydroxy-2-

methyl-3-(4-methylbenzenesulfonyloxy)propyl]-4-nitroimidazole (20.1 g, 43%) as a white amorphous form.

¹H-NMR (CDCl₃) δppm:

1.24 (3H, s), 2.47 (3H, s), 2.81 (1H, s), 3.90 (1H, d,
5 J = 10.4 Hz), 3.95 (1H, d, J = 10.4 Hz), 4.04 - 4.14
(2H, m), 7.39 (2H, d, J = 8.0 Hz), 7.76 (2H, d, J = 8.0
Hz), 7.91 (1H, s).

Example 14

Preparation of (R)-2-chloro-1-(2-methyloxiran-2-yl-
10 methyl)-4-nitroimidazole (another method for synthesis
of the compound of Example 12)

2-Chloro-4-nitro-1H-imidazole (1.51 g, 10.17
mmol) and (R)-2-methyloxiran-2-ylmethyl 4-methylbenzene
sulfonate (3.70 g, 15.25 mmol) were suspended in
15 acetonitrile (150 ml). Benzyl(triethyl) ammonium
chloride (0.23, 1.02 mmol) was added to this
suspension, and the resulting mixture was stirred under
reflux for 10 hours. After the reaction mixture was
allowed to return to room temperature, ethyl acetate
20 was added to the solution. The resulting mixture was
washed with an aqueous sodium hydrogencarbonate, dried
over magnesium sulfate and then filtered. The filtrate
was concentrated under reduced pressure and dissolved
in ethyl acetate (40 ml). DBU (1.57 ml, 10.17 mmol)
25 was added to the solution with cooling on ice-bath, and
the resulting mixture was stirred at room temperature
for 1.5 hours. The reaction mixture was washed with
water, dried over magnesium sulfate, and then concen-

trated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 7/3) to afford (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole (1.50 g, 5 yield 68%) as a light yellow oil.

Example 15

Preparation of (S)-2-chloro-4-nitro-1-[2-hydroxy-3-(4-nitrobenzoyloxy)-2-methylpropyl]imidazole

2-Chloro-4-nitro-1H-imidazole (3 g, 20.34 10 mmol) and (S)-2-methyloxiran-2-ylmethyl 4-nitrobenzoate (5.31 g, 22.37 mmol) were dissolved in ethyl acetate (10 ml). Triethylamine (0.57 ml, 4.07 mmol) was added to the solution, and the resulting mixture was stirred at 60-65°C for 10 hours. The reaction mixture was 15 concentrated under reduced pressure. Ethyl acetate (3 ml) and toluene (30 ml) were added to the residue, and the resulting precipitates were filtered off to afford (S)-2-chloro-4-nitro-1-[2-hydroxy-3-(4-nitrobenzoyloxy)-2-methylpropyl]imidazole (6.82 g, 20 yield 87%) as a yellow powder.

¹H-NMR (DMSO-d₆) δppm:

1.23 (3H, s), 4.11 - 4.33 (4H, m), 5.61 (1H, s), 8, 25 (2H, d, J = 8.9 Hz), 8.31 - 8.45 (3H, m).

25 Example 16

Preparation of (S)-2-chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole

(S)-2-Chloro-4-nitro-1-[2-hydroxy-3-(4-

nitrobenzoyloxy)-2-methylpropyl]imidazole prepared in Example 15 (6.8 g, 17.67 mmol) was dissolved in methanol (68 ml). Potassium carbonate (122 mg, 0.88 mmol) was added to the solution, and the resulting mixture was stirred at room temperature overnight. The mixture was cooled on ice-bath, 6N hydrochloric acid (0.3 ml) and magnesium sulfate (3 g) were added to the mixture in this order, and the mixture was stirred for 30 minutes. Insoluble matters were removed by filtration, and the filtrate was concentrated under reduced pressure. Ethyl acetate (3.4 ml) and toluene (34 ml) were added to the residue, and the resulting precipitates were filtered off to afford (S)-2-chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole (4.09 g, yield 97%) as a yellow powder.

¹H-NMR (DMSO-d₆) δppm:

1.02 (3H, s), 3.25 (2H, d, J = 5.3 Hz), 4.05 (2H, s), 4.98 (1H, s), 5.11 (1H, t, J = 5.2 Hz), 8.30 (1H, s).

Example 17

Preparation of (S)-2-chloro-1-(2-hydroxy-2-methyl-3-methanesulfonyloxypropyl)-4-nitroimidazole

(S)-2-Chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole prepared in Example 16 (4.05 g, 16.9 mmol) was dissolved in pyridine (8 ml), and this solution was cooled to 4°C. Methanesulfonyl chloride (1.6 ml, 20.28 mmol) was added dropwise to the solution below 15°C followed by stirring at the same temperature for 1 hour. 6N hydrochloric acid (33 ml)

was added to the mixture below 30°C. The reaction mixture was extracted with methylene chloride (20 ml) three times. The organic phases were combined, washed with water (20 ml) and a saturated saline solution (20 ml), dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. Toluene (10 ml) was added to the residue, and the resulting precipitates were filtered off to afford (S)-2-chloro-1-(2-hydroxy-2-methyl-3-methanesulfonyloxypropyl)-4-nitroimidazole (3.04g, yield 57%) as a white powder.

¹H-NMR (DMSO-d₆) δppm:

1.12 (3H, s), 3.24 (3H, s), 4.09 (2H, s), 4.13 (2H, s), 5.62 (1H, br), 8.34 (1H, s).

Example 18

Preparation of (S)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole

(S)-2-Chloro-1-(2-hydroxy-2-methyl-3-methanesulfonyloxypropyl)-4-nitroimidazole prepared in Example 17 (3.02 g, 9.51 mmol) was dissolved in methylene chloride (30 ml). DBU (1.7 ml, 11.41 mmol) was added to the solution, and the resulting mixture was stirred at room temperature for 1.5 hours. The reaction mixture was washed with 3N hydrochloric acid (30 ml) and saturated saline solution (20 ml) in this order, dried over magnesium sulfate and then filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography (methylene

chloride/ethyl acetate = 20/1) to afford (S)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole (1.89 g, yield 91%) as a light yellow solid.

Optical purity 93.2% e.e.

5 $[\alpha]_D^{27} = -29.15^\circ$ (concentration: 1.18, CHCl_3)

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.39 (3H, s), 2.63 (1H, d, $J = 4.0$ Hz), 2.79 (1H, d, $J = 4.0$ Hz), 4.00 (1H, d, $J = 14.9$ Hz), 4.38 (1H, d, $J = 14.9$ Hz), 7.88 (1H, s).

10 Example 19

Preparation of 2-tert-butoxymethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

2,4-Dinitro-1H-imidazole (10 g, 63.3 mmol), 2-tert-butoxymethyloxirane (27 ml, 189 mmol) and sodium acetate (5.19 g, 189 mmol) were suspended in ethanol (100 ml) followed by stirring under reflux for 17 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. Water was added to the residue, and the resulting mixture was extracted with methylene chloride. The organic phase was dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford 2-tert-butoxymethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (3.2 g, yield 21%) as a white powder.

25 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.18 (9H, s), 3.63 - 3.80 (2H, m), 4.22 - 4.36 (2H, m),
5.27 - 5.42 (1H, m), 7.53 (1H, s).

Using 2-methyl-2-(2-methoxymethoxyethyl)
oxirane, 2-ethyl-2-methoxymethoxymethyloxirane or 2-
5 isopropyl-2-methoxymethoxymethyloxirane gave compounds
of Examples 20 to 22 in the same manner as in Example
19.

Example 20

2-(2-Methoxymethoxyethyl)-2-methyl-6-nitro-2,3-
10 dihydroimidazo[2,1-b]oxazole

White powder, yield 48%, MS = 257

Example 21

2-Ethyl-2-methoxymethoxymethyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole

15 Light yellow powder, yield 49%

$^1\text{H-NMR}$ (DMSO- d_6) δppm :

0.91 (3H, t, $J = 7.5$ Hz), 1.91 (2H, q, $J = 7.5$ Hz),
3.24 (3H, s), 3.72 (1H, d, $J = 11.2$ Hz), 3.78 (1H, d, J
= 11.2 Hz), 4.15 (1H, d, $J = 11.2$ Hz), 4.23 (1H, d, $J =$
20 11.2 Hz), 4.59 (2H, s), 8.10 (1H, s).

Example 22

2-Isopropyl-2-methoxymethoxymethyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole

Light yellow powder, yield 90%

25 $^1\text{H-NMR}$ (DMSO- d_6) δppm :

0.94 (6H, d, $J = 6.9$ Hz), 2.16 - 2.32 (1H, m), 3.24
(3H, s), 3.76 (1H, d, $J = 13.0$ Hz), 3.82 (1H, d, $J =$
13.0 Hz), 4.18 (1H, d, $J = 13.0$ Hz), 4.25 (1H, d, $J =$

13.0 Hz), 4.59 (2H, s), 8.09 (1H, s).

Example 23

Preparation of 2-chloro-1-(2-hydroxy-4-methoxymethoxy-butyl)-4-nitroimidazole

5 Sodium acetate (3.51 g, 42.82 mmol) and 2-(2-methoxymethoxyethyl) oxirane (10.3 g, 77.86 mmol) were added to 2-chloro-4-nitro-1H-imidazole (5.74 g, 38.93 mmol) in ethanol (60 ml), and the resulting mixture was stirred under reflux for 13.5 hours. The reaction
10 mixture was concentrated under reduced pressure. Water was added to the residue, and the resulting mixture was extracted with methylene chloride. The extract was dried over magnesium sulfate and then concentrated under reduced pressure, and the residue was purified by
15 silica gel column chromatography (methylene chloride/methanol = 100/1) and then crystallized from methylene chloride-diisopropyl ether to afford 2-chloro-1-(2-hydroxy-4-methoxymethoxybutyl)-4-nitroimidazole (8.51 g, yield 78%) as a light yellow
20 powder.

¹H-NMR (CDCl₃) δppm:

1.67 (2H, m), 3.38 (3H, s), 3.46 (1H, d, J = 2.4 Hz),
3.78 - 3.83 (2H, m), 4.00 (1H, dd, J = 7.6 Hz, 14.3 Hz), 4.11 - 4.21 (2H, m), 4.63 (2H, s), 7.96 (1H, s).

25 Using 2-methyl-2-methoxymethoxymethyloxirane gave a compound of Example 24 in the same manner as in Example 23.

Example 24

2-Chloro-1-(2-hydroxy-3-methoxymethoxypropyl)-4-nitroimidazole

Colorless liquid, yield 63%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

5 1.20 (3H, s), 3.08 (1H, s), 3.42 (3H, s), 3.53 (2H, dd, $J = 10.4 \text{ Hz}, 13.8 \text{ Hz}$), 4.67 (2H, s), 8.01 (1H, s).

Example 25

Preparation of 2-(2-methoxymethoxyethyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

10 Sodium hydride (1.33 g, 33.23 mmol) was added to a solution of 2-chloro-1-(2-hydroxy-4-methoxymethoxybutyl)-4-nitroimidazole prepared in Example 23 (8.45 g, 30.21 mmol) in 1,4-dioxane (100 ml) with cooling on ice-bath followed by stirring under
15 reflux for 40 hours. The reaction mixture was concentrated under reduced pressure, and cooled on ice-bath. Water was added to the residue, and the resulting mixture was extracted with methylene chloride. The organic phase was dried over magnesium
20 sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and crystallized from methylene chloride-diisopropyl ether to afford 2-(2-methoxymethoxyethyl)-6-nitro-2,3-
25 dihydroimidazo[2,1-b]oxazole (3.4 g, yield 47%) as a light yellow powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

2.11 - 2.35 (2H, m), 3.36 (3H, s), 3.75 (2H, dd, $J =$

4.8 Hz, 6.8 Hz), 4.08 (1H, dd, $J = 7.6$ Hz, 10.3 Hz),
4.40 (1H, dd, $J = 7.6$ Hz, 10.3 Hz), 4.61 (2H, s), 5.43
- 5.54 (1H, m), 7.53 (1H, s).

Using 2-chloro-1-(2-hydroxy-3-methoxymethoxy-
5 propyl)-4-nitroimidazole prepared in Example 24 gave a
compound of Example 26 in the same manner as in Example
25.

Example 26

2-Methoxymethoxymethyl-2-methyl-6-nitro-2,3-
10 dihydroimidazo[2,1-b]oxazole

Light yellow powder, yield 38%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.66 (3H, s), 3.34 (3H, s), 3.63 (1H, d, $J = 11.0$ Hz),
3.84 (1H, d, $J = 11.0$ Hz), 3.93 (1H, d, $J = 9.9$ Hz),
15 4.37 (1H, d, $J = 9.9$ Hz), 4.62 (2H, s), 7.52 (1H, s).

Example 27

Preparation of (R)-2-chloro-1-(2-hydroxy-3-methoxy-
methoxy-2-methylpropyl)-4-nitroimidazole

(R)-2-Chloro-1-(2,3-dihydroxy-2-methyl-
20 propyl)-4-nitroimidazole prepared in Example 10 (7.4 g,
31 mmol) was dissolved in methylene chloride (120 ml).
N, N-diisopropylethylamine (13.1 ml, 74 mmol) and
chloromethylmethyl ether (7.1 ml, 74 mmol) were added
to the solution followed by stirring at room
25 temperature for 46 hours. The reaction mixture was
washed with water, dried over magnesium sulfate and
then concentrated under reduced pressure. The residue
was purified by silica gel column chromatography

(methylene chloride/ethyl acetate = 9/1) to afford (R)-2-chloro-1-(2-hydroxy-3-methoxymethoxy-2-methylpropyl)-4-nitroimidazole (6.0 g, yield 69%) as a light yellow oil.

5 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.20 (3H, s), 3.08 (1H, s), 3.42 (3H, s), 3.50 (1H, d, $J = 10.4$ Hz), 3.55 (1H, d, $J = 10.4$ Hz), 4.05 (1H, d, $J = 14.4$ Hz), 4.15 (1H, d, $J = 14.4$ Hz), 4.67 (2H, s), 8.01 (1H, s).

10 Example 28

Preparation of (R)-2-methoxymethoxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Sodium hydride (1.0 g, 25 mmol) was added to a solution of (R)-2-chloro-1-(2-hydroxy-3-methoxymethoxy-2-methylpropyl)-4-nitroimidazole prepared in Example 27 (6.0 g, 21 mmol) in DMF (30 ml) with cooling on ice-bath followed by stirring at room temperature for 1.5 hours. Ice-water was added to the reaction mixture, and the precipitates were filtered off and washed with water to afford (R)-2-methoxymethoxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (3.1 g, yield 59%) as a yellow solid.

25 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.66 (3H, s), 3.34 (3H, s), 3.63 (1H, d, $J = 11.0$ Hz), 3.84 (1H, d, $J = 11.0$ Hz), 3.93 (1H, d, $J = 10.0$ Hz), 4.42 (1H, d, $J = 10.0$ Hz), 4.63 (2H, s), 7.52 (1H, s).

Example 29

Preparation of 2-chloro-1-(5-acetoxy-2-hydroxy-2-methylpentyl)-4-nitroimidazole

2-Chloro-4-nitro-1H-imidazole (6.8 g, 43
5 mmol), 2-(3-acetoxypropyl)-2-methyloxirane (5.8 g, 39.3
mmol) and sodium acetate (3.9 g, 47.6 mmol) were
suspended in ethanol (60 ml) followed by stirring under
reflux overnight. The reaction mixture was allowed to
return to room temperature and concentrated under
10 reduced pressure. Water was added to the residue, and
the resulting mixture was extracted with methylene
chloride twice. The organic phases were combined,
washed with a saturated aqueous sodium bicarbonate
solution and a saturated saline solution in this order,
15 dried over sodium sulfate and then filtered. The
filtrate was concentrated under reduced pressure to
afford 2-chloro-1-(5-acetoxy-2-hydroxy-2-methylpentyl)-
4-nitroimidazole (9.5 g, yield 79%) as a light brown
oil.

20 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.21 (3H, s), 1.50 - 1.81 (4H, m), 2.05 (3H, s), 3.91 -
4.12 (4H, m), 8.02 (1H, s).

Example 30

Preparation of 2-(3-acetoxypropyl)-2-methyl-6-nitro-
25 2,3-dihydroimidazo[2,1-b]oxazole

Using 2-chloro-1-(5-acetoxy-2-hydroxy-2-methylpentyl)-4-nitroimidazole (9.5 g, 31.1 mmol)
prepared in Example 29 gave 2-(3-acetoxypropyl)-2-

methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (5.2 g, yield 62%) as a light orange-colored powder in the same manner as in Example 25.

¹H-NMR (CDCl₃) δppm:

5 1.67 (3H, s), 1.67 - 2.00 (4H, m), 2.05 (3H, s), 3.91 - 4.14 (4H, m), 7.52 (1H, s).

Example 31

Preparation of 2-(2-hydroxyethyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

10 Trifluoroacetic acid (2 ml) was added to a solution of 2-(2-methoxymethoxyethyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 25 (0.2 g, 0.822 mmol) in methylene chloride (10 ml) followed by stirring at room temperature overnight.

15 The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1), and crystallized from methanol-diisopropyl ether to afford 2-(2-hydroxyethyl)-6-nitro-2,3-

20 dihydroimidazo[2,1-b]oxazole (0.11 g, yield 65%) as a light yellow powder.

¹H-NMR (DMSO-d₆) δppm:

1.92 - 2.14 (2H, m), 3.52 - 3.63 (2H, m), 4.05 (1H, dd, J = 7.6 Hz, 10.6 Hz), 4.43 (1H, dd, J = 7.6 Hz, 10.6

25 Hz), 4.72 (1H, t, J = 2.7 Hz), 5.38 - 5.53 (1H, m), 8.12 (1H, s).

Example 32

Preparation of 2-hydroxymethyl-6-nitro-2,3-

dihydroimidazo[2,1-b]oxazole

Using 2-tert-butoxymethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 19 (5.82 g, 24.1 mmol) gave 2-hydroxymethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (4.25 g, yield 95%) as a white powder in the same manner as in Example 31.

¹H-NMR (DMSO-d₆) δppm:

3.55 - 3.67 (1H, m), 3.72 - 3.88 (1H, m), 4.12 (1H, dd, J = 6.5 Hz, 10.5 Hz), 4.36 (1H, t, J = 10.4 Hz), 5.25 - 5.50 (2H, m), 8.11 (1H, s).

Example 33

Preparation of 2-hydroxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Using 2-methoxymethoxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 26 (4.14 g, 38 mmol) gave 2-hydroxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (2.17 g, yield 64%) as a light yellow powder in the same manner as in Example 31.

Melting point 166-168°C

¹H-NMR (DMSO-d₆) δppm:

1.51 (3H, s), 3.53 (1H, d, J = 12.1 Hz), 3.64 (1H, d, J = 12.1 Hz), 4.03 (1H, d, J = 10.6 Hz), 4.24 (1H, d, J = 10.6 Hz), 5.40 (1H, br), 8.10 (1H, s).

Example 34

Preparation of 2-(2-hydroxyethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Using 2-(2-methoxymethoxyethyl)-2-methyl-6-

nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 20 (13.4 g, 52.1 mmol) gave 2-(2-hydroxyethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (2.32 g, yield 21%) as a light yellow powder in the same
5 manner as in Example 31.

¹H-NMR (DMSO-d₆) δppm:

1.58 (3H, s), 1.93 - 2.17 (2H, m), 3.59 (2H, t, J = 6.4 Hz), 4.04 (1H, d J = 10.9 Hz), 4.33 (d, 1H, J = 10.9 Hz), 8.11 (1H, s).

10 Example 35

Preparation of 2-ethyl-2-hydroxymethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

2-Ethyl-2-methoxymethoxymethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 21
15 (21.5 g, 83.7 mmol) was suspended in methanol (430 ml). Concentrated hydrochloric acid (2.15 ml) was added to this suspension followed by stirring under reflux for 5 hours. The reaction mixture was concentrated under reduced pressure, and the precipitates were filtered
20 off to afford 2-ethyl-2-hydroxymethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (7.14 g, yield 40%) as a light yellow powder.

¹H-NMR (DMSO-d₆) δppm:

0.89 (3H, t, J = 7.4 Hz), 1.95 (2H, q, J = 7.4 Hz),
25 3.53 - 3.69 (2H, m), 4.08 (1H, d, J = 10.8 Hz), 4.21 (1H, d, J = 10.8 Hz), 5.39 (t, 1H, J = 5.6 Hz), 8.09 (1H, s).

Using corresponding starting materials gave a

compound of Example 36 in the same manner as in Example 35.

Example 36

2-Hydroxymethyl-2-isopropyl-6-nitro-2,3-dihydro-
5 imidazo[2,1-b]oxazole

Light yellow powder, yield 50%

¹H-NMR (DMSO-d₆) δppm:

0.91 (6H, d, J = 6.9 Hz), 2.12 - 2.23 (1H, m), 3.60 -
3.77 (2H, m), 4.16 (2H, s), 5.35 (1H, t, J = 5.6 Hz),
10 8.08 (1H, s).

Example 37

Preparation of (R)-2-hydroxymethyl-2-methyl-6-nitro-
2,3-dihydroimidazo[2,1-b]oxazole

Trifluoroacetic acid (15 ml) was added to a
15 solution of (R)-2-methoxymethoxymethyl-2-methyl-6-
nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in
Example 28 (3.1 g, 13 mmol) in methylene chloride (30
ml) followed by stirring at room temperature for 25
hours. The reaction mixture was concentrated under
20 reduced pressure. Methanol was added to the solution,
and the resulting mixture was concentrated under
reduced pressure. To the residue, 2-propanol was
added, and the precipitates were filtered off and
washed with 2-propanol to afford (R)-2-hydroxymethyl-2-
25 methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (1.2 g,
yield 46%) as a light yellow powder.

Melting point 162-163°C

Optical purity 97% e.e.

$[\alpha]_D^{26} = -19.01^\circ$ (concentration: 0.526, DMSO)

Example 38

Preparation of 2-methyl-2-(3-hydroxypropyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

5 A mixture of 2-(3-acetoxypentyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 30 (3.2 g, 11.88 mmol), potassium carbonate (320 mg, 2.32 mmol) and methanol (35 ml) was stirred at room temperature for 2 hours. The reaction mixture was
10 concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 25/1) to afford 2-methyl-2-(3-hydroxypropyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (2.1 g, 78%) as a light
15 yellow powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.67 - 1.72 (5H, m), 1.91 - 2.07 (2H, m), 3.51 - 3.65 (2H, m), 4.01 (1H, d, $J = 10.5$ Hz), 4.15 (1H, d, $J = 10.5$ Hz), 7.66 (1H, s).

20 Example 39

Preparation of 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl methanesulfonate

 Methanesulfonyl chloride (1.4 ml, 18.09 mmol) in methylene chloride (10 ml) was added dropwise to a
25 mixture of 2-methyl-2-(3-hydroxypropyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 38 (2.1 g, 9.24 mmol), triethylamine (2.8 g, 20.09 mmol), 4-dimethylaminopyridine (50 mg, 0.41 mmol) and

methylene chloride (80 ml) with cooling on ice-bath followed by stirring at room temperature overnight.

The reaction mixture was concentrated. 10%

hydrochloric acid was added to the residue, and the

5 resulting mixture was stirred for 30 minutes with cooling on ice-bath. The precipitates were filtered off and washed with water to afford 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl methanesulfonate (2.6 g, yield 92%) as a white powder.

10 ¹H-NMR (DMSO-d₆) δppm:

1.58 (3H, s), 1.65 - 2.02 (4H, m), 3.17 (3H, s), 4.05 - 4.26 (4H, m), 8.12 (1H, s).

Using corresponding starting materials gave compounds of Examples 40 to 42 in the same manner as in
15 Example 39.

Example 40

6-Nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl methanesulfonate

Light yellow powder, yield 82%

20 ¹H-NMR (DMSO-d₆) δppm:

3.25 (3H, s), 4.11 (1H, dd, J = 6.6 Hz, 11.0 Hz), 4.47 (1H, t, J = 9.1 Hz), 4.55 - 4.70 (2H, m), 5.60 - 5.75 (1H, m), 8.14 (1H, s).

Example 41

25 2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl methanesulfonate

Light yellow powder, yield 87%

¹H-NMR (DMSO-d₆) δppm:

1.64 (3H, s), 3.24 (3H, s), 4.17 (1H, d, $J = 11.2$ Hz),
4.27 (1H, d, $J = 11.2$ Hz), 4.52 (2H, br), 8.14 (1H, s).

Example 42

2-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-
5 yl)ethyl methanesulfonate

Light yellow powder, yield 87%

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm:

1.61 (3H, s), 2.38 (2H, t, $J = 6.5$ Hz), 3.19 (3H, s),
4.11 (1H, d, $J = 11.0$ Hz), 4.25 (1H, d, $J = 11.0$ Hz),
10 4.36 (2H, t, $J = 6.5$ Hz), 8.14 (1H, s).

Example 43

Preparation of tert-butyl 5-(2-chloro-4-nitroimidazol-
1-yl)-4-hydroxy-4-methylpentanoate

Sodium acetate (0.59 g, 7.18 mmol) was added
15 to a suspension of tert-butyl 3-(2-methyloxiran-2-
yl)propionate (1.00 g, 5.39 mmol) and 2-chloro-4-nitro-
1H-imidazole (0.53 g, 3.59 mmol) in ethanol (5 ml)
followed by stirring under reflux for 6 hours.

Insoluble matters were removed by filtration, and the
20 filtrate was concentrated under reduced pressure. The
residue was purified by silica gel column
chromatography (methylene chloride/methanol = 100/1) to
afford tert-butyl 5-(2-chloro-4-nitroimidazol-1-yl)-4-
hydroxy-4-methylpentanoate (0.94 g, yield 78%) as a
25 light yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.17 (3H, s), 1.45 (9H, s), 1.78 - 1.87 (2H, m), 2.43 -
2.54 (2H, m), 3.59 (1H, br), 3.99 (2H, s), 8.06 (1H,

s).

Example 44

Preparation of tert-butyl 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propionate

- 5 Sodium hydride (0.12 g, 3.07 mmol) was added to a solution of tert-butyl 5-(2-chloro-4-nitroimidazol-1-yl)-4-hydroxy-4-methylpentanoate prepared in Example 43 (0.93 g, 2.79 mmol) in 1,4-dioxane (10 ml) with cooling on ice-bath followed by
- 10 stirring under reflux for 7.5 hours. The reaction mixture was concentrated under reduced pressure. Water was added to the solution, and the resulting mixture was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then
- 15 concentrated under reduced pressure. The residue was treated with diethyl ether to afford tert-butyl 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propionate (0.35 g, 42%) as a white solid.

¹H-NMR (CDCl₃) δppm:

- 20 1.45 (9H, s), 1.65 (3H, s), 2.12 - 2.25 (2H, m), 2.37 - 2.46 (2H, m), 3.98 (1H, d, J = 10.3 Hz), 4.10 (1H, d, J = 10.3 Hz), 7.52 (1H, s).

Example 45

- Preparation of 3-(2-methyl-6-nitro-2,3-dihydroimidazo-
25 [2,1-b]oxazol-2-yl)propionic acid

Trifluoroacetic acid (2 ml) was added to a solution of tert-butyl 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl) propionate prepared

in Example 44 (0.72 g, 2.42 mmol) in methylene chloride (14 ml) followed by stirring at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure. The residue was crystallized from ethanol-methylene chloride to afford 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propionic acid (0.30 g, 51%) as a light yellow solid.

¹H-NMR (DMSO-d₆) δppm:

1.32 (3H, s), 1.91 - 2.09 (1H, m), 2.12 - 2.26 (1H, m),
10 2.41 - 2.74 (2H, m), 3.89 (2H, s), 7.96 (1H, s), 12.19 (1H, br).

Example 46

Preparation of 2-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethoxy)benzoxazole

15 Sodium hydride (77 mg, 1.9 mmol) was added to a solution of 2-hydroxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 33 (0.32 g, 1.6 mmol) in DMF (3 ml) with cooling on ice-bath followed by stirring at 0°C for 30 minutes. To the
20 reaction mixture, 2-chlorobenzoxazole (0.30 g, 1.9 mmol) in DMF (3 ml) was added with cooling on ice-bath followed by stirring at room temperature for 44 hours. Ice-water was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate.
25 The organic phase was washed with water, dried over magnesium sulfate and then concentrated. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and

recrystallized from acetonitrile-isopropanol to afford 2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)benzoxazole (0.20 g, 39%) as a light yellow solid.

5 Melting point 200-203°C

Example 47

Preparation of (R)-2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)benzoxazole

Sodium hydride (0.1 g, 2.4 mmol) was added to
10 a solution of (R)-2-hydroxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 37 (0.40 g, 2.0 mmol) in DMF (4 ml) followed by stirring for 30 minutes with cooling on ice-bath. To the reaction mixture, 2-chlorobenzoxazole (0.38 g, 2.4
15 mmol) in DMF (4 ml) was added with cooling on ice-bath followed by stirring at room temperature for 48 hours. Ice-water was added to the reaction mixture. The precipitates were filtered off, washed with water, and then recrystallized from acetonitrile-isopropanol to
20 afford (R)-2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)benzoxazole (0.15 g, yield 24%) as a light yellow solid.

Melting point 232-233°C

Optical purity > 99.5% e.e.

25 $[\alpha]_D^{26} = +11.20^\circ$ (concentration: 0.518, DMSO)

Example 48

Preparation of 2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethylthio)benzoxazole

Sodium hydride (50 mg, 1.25 mmol) was added to a mixture of 2-mercaptobenzoxazole (200 mg, 1.3 mmol) and DMF (3 ml) followed by stirring at room temperature for 1 hour. To the reaction mixture, 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl methanesulfonate prepared in Example 41 (330 mg, 1.2 mmol) was added, and the resulting mixture was stirred at 60-70°C for 5 hours. The reaction mixture was allowed to return to room temperature. Water was added to the solution, and the resulting mixture was extracted with ethyl acetate twice. The organic phases were combined, washed with 5% sodium hydroxyde solution and water three times, 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 = 1/1) to afford 2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethylthio)benzoxazole (37 mg, yield 9%) as a white powder.

Melting point 163-166°C

Example 49

Preparation of 2-[2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethylthio]benzoxazole

Using 2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl methanesulfonate prepared in Example 42 (300 mg, 1 mmol) gave 2-[2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethylthio]benzoxazole (296 mg, yield 83%) as a white

powder in the same manner as in Example 48.

Melting point 174-175°C

Example 50

Preparation of 1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-(1-phenyl-1H-tetrazol-5-ylthio)propane-2-ol

A mixture of 2-chloro-4-nitro-1H-imidazole (1.2 g, 8.13 mmol), 5-(2-methyloxiran-2-ylmethylthio)-1-phenyl-1H-tetrazole (1.9 g, 7.65 mmol), sodium acetate (700 mg, 8.53 mmol) and ethanol (20 ml) was stirred under reflux overnight. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, water was added, and the resulting mixture was extracted with ethyl acetate twice. The organic phases were combined, washed with a saturated aqueous sodium bicarbonate solution twice, then washed with water and a saturated saline solution in this order, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford 1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-(1-phenyl-1H-tetrazol-5-ylthio)propane-2-ol to afford (2.1 g, yield 69%) as a light yellow powder.

¹H-NMR (CDCl₃) δppm:

1.38 (3H, s), 3.54 (1H, d, J = 14.8 Hz), 3.62 (1H, d, J = 14.8 Hz), 4.19 (2H, s), 4.58 (1H, s), 7.50 - 7.67 (5H, m), 8.08 (1H, s).

Example 51

Preparation of 2-methyl-6-nitro-2-(1-phenyl-1H-tetrazol-5-ylthiomethyl)-2,3-dihydroimidazo[2,1-b]oxazole

- 5 Sodium hydride (220 mg, 5.5 mmol) was added to a mixture of 1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-(1-phenyl-1H-tetrazol-5-ylthio)propane-2-ol prepared in Example 50 (2.1 g, 5.3 mmol) and 1,4-dioxane (40 ml), and the resulting mixture was stirred
- 10 under reflux for 24 hours. The reaction mixture was allowed to return to room temperature, and concentrated under reduced pressure. Water was added to the residue, and the resulting mixture was extracted with ethyl acetate twice. The organic phases were combined,
- 15 washed with water and a saturated saline solution in this order, 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 = 1/1) to
- 20 afford 2-methyl-6-nitro-2-(1-phenyl-1H-tetrazol-5-ylthiomethyl)-2,3-dihydroimidazo[2,1-b]oxazole (500 mg, yield 26%) as a light brown powder.

Melting point 140-147°C

Example 52

- 25 Preparation of tert-butyl(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxycarbonylamino) acetate

Glycine tert-butyl ester monohydrochloride (0.52 g, 2.27 mmol) in methylene chloride (5 ml) and

N,N-diisopropylethylamine (1.05 ml, 4.53 mmol) were added to a triphosgene (0.30 g, 0.76 mmol) in methylene chloride (10 ml) with cooling on ice-bath followed by stirring at room temperature for 2 hours. Insoluble matters were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was added to a solution of 2-hydroxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 33 (0.30 g, 1.51 mmol) in DMF (3 ml) with cooling on ice-bath. Then cuprous chloride (75 mg, 0.76 mmol) was added to the resulting mixture followed by stirring at room temperature for 22 hours. Water was added to the reaction mixture, the resulting mixture was extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 3/2) to afford tert-butyl(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxycarbonylamino)acetate (40 mg, yield 7%) as a white solid.

Melting point 104-106°C

Example 53

Preparation of 6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl (4-morpholinophenyl)carbamate

1,1'-Carbonyldiimidazole (0.44 g, 2.69 mmol) was added to a solution of 4-morpholinoaniline (0.40 g, 2.24 mmol) in THF (4 ml) followed by stirring for 2

hours with cooling on ice-bath. The reaction mixture was filtered and washed with diethyl ether. The filtrate was added to a solution of 2-hydroxymethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (0.30 g, 1.62 mmol) in DMF (3 ml) with cooling on ice-bath. Then, cuprous chloride (75 mg, 0.76 mmol) was added to the resulting mixture followed by stirring at room temperature for 2 hours. Water was added to the reaction mixture, the resulting mixture was extracted with ethyl acetate, and the extract was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/acetone = 9/1), and washed with methylene chloride-ethyl acetate to afford 6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl (4-morpholinophenyl)carbamate (34 mg, yield 5%) as a white solid.

¹H-NMR (DMSO-d₆) δppm:

2.93 - 3.09 (4H, m), 3.64 - 3.80 (4H, m), 4.13 (1H, dd, J = 6.8 Hz, 10.9 Hz), 4.34 - 4.55 (3H, m), 5.55 - 5.73 (1H, m), 6.77 - 6.95 (2H, m), 7.18 - 7.41 (2H, m), 8.15 (1H, s), 9.52 (1H, br).

Example 54

Preparation of 2-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl 4-chlorophenylcarbamate

4-Chlorophenylisocyanate (169 ml, 1.1 mmol) and cuprous chloride (50 mg, 0.5 mmol) was added to a

solution of 2-hydroxyethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 31 (0.2 g, 1.0 mmol) in DMF (5 ml) with cooling on ice-bath followed by stirring at room temperature for 4 hours. The mixture was cooled on ice-bath and added 10% hydrochloric acid. The resulting mixture was extracted with ethyl acetate, and the extract was 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 = 100/1) and crystallized from methylene chloride-isopropyl ether to afford 2-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl 4-chlorophenylcarbamate (0.16 g, yield 45%) as a white solid.

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm:

2.16 - 2.38 (2H, m), 4.08 (1H, dd, $J = 7.4$ Hz, 10.6 Hz), 4.16 - 4.36 (2H, m), 4.47 (1H, dd, $J = 7.4$ Hz, 10, 6 Hz), 5.44 - 5.55 (1H, m), 7.30 - 7.36 (2H, m), 7.46 - 7.52 (2H, m), 8.14 (1H, s), 9.83 (1H, br).

Using phenylisocyanate and 2-hydroxyethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole, 2-ethyl-2-hydroxymethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole or 2-hydroxymethyl-2-isopropyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole gave compounds of Examples 55 to 57 in the same manner as in Example 54. In addition, using 2-hydroxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole and 3-

fluorophenylisocyanate or 4-tert-butoxycarbonylphenylisocyanate gave compounds of Examples 58 and 59 in the same manner as in Example 54.

Example 55

5 2-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl phenylcarbamate

Yellow solid, yield 17%

¹H-NMR (DMSO-d₆) δppm:

1.63 (3H, s), 2.30 (2H, t, J = 6.9 Hz), 4.13 (1H, d, J
10 = 10.9 Hz), 4.21 - 4.32 (3H, m), 6.96 - 7.02 (1H, m),
7.24 - 7.27 (2H, m), 7.43 - 7.46 (2H, m), 8.12 (1H, s),
9.60 (1H, br).

Example 56

15 2-Ethyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl phenylcarbamate

White solid, yield 60%

¹H-NMR (DMSO-d₆) δppm:

0.93 (3H, t, J = 7.4 Hz), 1.89 - 2.11 (2H, m), 4.19 -
4.29 (2H, m), 4.39 - 4.50 (2H, m), 6.99 (1H, t, J = 7.2
20 Hz), 7.23 - 7.29 (2H, m), 7.34 - 7.55 (2H, m), 8.14
(1H, s), 9.70 (1H, br).

Example 57

25 2-Isopropyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl phenylcarbamate
White solid, yield 73%

¹H-NMR (DMSO-d₆) δppm:

0.97 (6H, dd, J = 2.7 Hz, 6.9 Hz), 2.25 - 2.39 (1H, m),
4.20 (1H, d, J = 11.4 Hz), 4.30 (1H, d, J = 11.4 Hz),

4.48 (2H, s), 6.99 (1H, t, $J = 7.1$ Hz), 7.23 - 7.29 (2H, m), 7.32 - 7.52 (2H, m), 8.13 (1H, s), 9.67 (1H, br).

Example 58

- 5 2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 3-fluorophenylcarbamate

White solid, yield 71%

Melting point 168-169°C

Example 59

- 10 Tert-butyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxycarbonylamino) benzoate

White solid, yield 32%

Melting point 177-178°C

Example 60

- 15 Preparation of 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxycarbonylamino)benzoic acid

Trifluoroacetic acid (1 ml) was added to a suspension of tert-butyl 4-(2-methyl-6-nitro-2,2-dihydroimidazo[2,1-b]oxazol-2-

- 20 ylmethoxycarbonylamino)benzoate prepared in Example 59 (185 ml, 0.44 mmol) in methylene chloride (10 ml) with cooling on ice-bath followed by stirring at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate. The solution was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was washed with ethyl acetate to afford 4-(2-methyl-6-

nitro-2,3-dihydromidazo[2,1-b]oxazol-2-ylmethoxycarbonylamino)benzoic acid (50 mg, yield 31%) as a white solid.

Melting point 248°C (decomposition)

5 Example 61

Preparation of 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-chlorophenylcarbamate

2-Methyloxiran-2-ylmethyl 4-chlorophenylcarbamate (1.1 g, 4.4 mmol) and 2,4-dinitro-1H-imidazole (0.35 g, 2.2 mmol) were suspended in ethanol (1 ml), and the resulting mixture was stirred at room temperature for 24 hours. Then, sodium acetate (0.36 g, 4.4 mmol) and ethanol (2 ml) were added to the mixture followed by stirring under reflux
15 for 6 hours. The reaction mixture was concentrated under reduced pressure. The residue was added water, and the resulting mixture was extracted with ethyl acetate. The extract was dried over magnesium sulfate and then concentrated under reduced pressure. The
20 residue was crystallized from methylene chloride-diethyl ether to afford 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-chlorophenylcarbamate (0.17 g, yield 22%) as a light yellow solid.

Melting point 179-181°C

25 Example 62

Preparation of 3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-(4-chlorophenyl)-N-methylcarbamate

2-Methyloxiran-2-ylmethyl N-(4-chlorophenyl)-N-methylcarbamate (1.7 g, 6.6 mmol) and 2-chloro-4-nitro-1H-imidazole (0.98 g, 6.6 mmol) were suspended in ethanol (10 ml) added sodium acetate (0.85 g, 10 mmol) followed by stirring under reflux for 4 hours. The reaction mixture was concentrated under reduced pressure. A saturated aqueous sodium hydrogencarbonate was added to the residue, and the resulting mixture was extracted with methylene chloride. The extract was dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford 3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-(4-chlorophenyl)-N-methylcarbamate (2.7 g, quantitative) as a light yellow oil.

¹H-NMR (CDCl₃) δppm:

1.15 (3H, br), 3.28 (3H, s), 3.78 - 4.28 (4H, m), 7.11 - 7.24 (2H, m), 7.30 - 7.41 (2H, m), 7.90 (1H, br).

Example 63

Preparation of 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-(4-chlorophenyl)-N-methylcarbamate

Sodium hydride (0.32 g, 7.9 mmol) was added to a solution of 3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-(4-chlorophenyl)-N-methylcarbamate prepared in Example 62 (2.7 g, 6.6 mmol) in 1,4-dioxane (30 ml) with cooling on ice-bath

followed by stirring under reflux for 12 hours. The reaction mixture was concentrated under reduced pressure. The residue was cooled on ice-bath and added water, and the resulting solution was extracted with 5 methylene chloride. The extract was dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate) and crystallized from methylene chloride-ethanol to afford 2-methyl-6-10 nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-(4-chlorophenyl)-N-methylcarbamate (0.88 g, yield 36%) as a white solid.

Melting point 146-148°C

Example 64

15 Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-chlorophenylcarbamate

A THF solution (15 ml) of 4-chlorophenylisocyanate (1.3 g, 85 mmol) and triethylamine (0.1 ml) were added to a suspension of 20 (R)-2-chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole prepared in Example 10 (1.5 g, 6.5 mmol) in THF (30 ml) followed by stirring at room temperature for 19 hours. Insoluble matters were removed by filtration, and the filtrate was concentrated under 25 reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-

chlorophenylcarbamate (2.1 g, yield 83%) as a white solid.

$^1\text{H-NMR}$ (DMSO-d_6) δppm :

1.15 (3H, s), 3.99 (2H, s), 4.07 (2H, s), 7.29 - 7.39
5 (2H, m), 7.45 - 7.58 (2H, m), 8.33 (1H, s), 9.86 (1H, br).

Using various kinds of corresponding phenylisocyanates gave compounds of Examples 65 to 69 in the same manner as in Example 64. In addition,
10 using benzylisocyanate or methylisocyanate gave compounds of Examples 70 and 71 in the same manner as in Example 64.

Example 65

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-
15 methylpropyl 3-chlorophenylcarbamate

Yield 41%

$^1\text{H-NMR}$ (DMSO-d_6) δppm :

1.15 (3H, s), 4.00 (2H, s), 4.13 (2H, s), 5.41 (1H, s),
7.04 - 7.09 (1H, m), 7.29 - 7.41 (2H, m), 7.55 - 7.66
20 (1H, m), 8.33 (1H, s), 9.93 (1H, br).

Example 66

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-
methylpropyl 4-bromophenylcarbamate

Yield 62%

25 $^1\text{H-NMR}$ (DMSO-d_6) δppm :

1.15 (3H, s), 3.99 (2H, s), 4.13 (2H, s), 5.40 (1H, s),
7.34 - 7.53 (4H, m), 8.33 (1H, s), 9.86 (1H, br).

Example 67

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-trifluoromethylphenylcarbamate

Yield 83%

$^1\text{H-NMR}$ (DMSO-d_6) δppm :

5 1.16 (3H, s), 4.02 (2H, s), 4.14 (2H, s), 5.42 (1H, s),
7.58 - 7.74 (4H, m), 8.34 (1H, s), 10.14 (1H, br).

Example 68

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-trifluoromethoxyphenylcarbamate

10 Yield 58%

$^1\text{H-NMR}$ (DMSO-d_6) δppm :

1.15 (3H, s), 3.99 (2H, s), 4.13 (2H, s), 5.41 (1H, s),
7.31 (2H, d, $J = 8.5$ Hz), 7.58 (2H, d, $J = 8.5$ Hz),
8.33 (1H, s), 9.92 (1H, br).

15 Example 69

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-fluorophenylcarbamate

Yield 95%

$^1\text{H-NMR}$ (DMSO-d_6) δppm :

20 1.15 (3H, s), 3.98 (2H, s), 4.12 (2H, s), 5.39 (1H, s),
7.10 - 7.17 (2H, m), 7.45 - 7.51 (2H, m), 8.33 (1H, s),
9.73 (1H, br).

Example 70

25 (R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl benzylcarbamate

Yield 72%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.20 (3H, s), 3.61 (1H, br), 3.97 - 4.04 (3H, m), 4.23

(1H, d, $J = 12.0$ Hz), 4.70 - 4.89 (1H, m), 7.13 - 7.39 (5H, m), 8.01 (1H, s).

Example 71

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl methylcarbamate

Yield 73%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.21 (3H, s), 2.80 (3H, d, $J = 4.8$ Hz), 3.57 (1H, br), 3.98 - 4.16 (3H, m), 4.24 (1H, d, $J = 12.3$ Hz), 4.72 - 4.91 (1H, m), 8.03 (1H, s).

Example 72

Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-methyl-N-(4-trifluoromethoxybenzyl)carbamate

(R)-2-Chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole prepared in Example 10 (2.16 g, 9.18 mmol), N,N-diisopropylethylamine (2.67 ml, 15.30 mmol) and 4-dimethylaminopyridine (0.19 g, 1.53 mmol) were added to a suspension of N-methyl-N-(4-trifluoromethoxybenzyl)carbamoylechloride (2.05 g, 7.65 mmol) in toluene (40 ml) followed by stirring at 100°C for 3.5 hours. The reaction mixture was diluted with ethyl acetate, and the solution washed with 10% hydrochloric acid, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-

methylpropyl N-methyl-N-(4-trifluoromethoxybenzyl)carbamate (2.74 g, yield 77%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

5 1.25 (3H, s), 2.83 (3H, s), 3.87 - 4.17 (4H, m), 4.44 (2H, s), 7.18 - 7.25 (4H, m), 8.05 (1H, s).

Example 73

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-methyl-N-(4-trifluoromethoxybenzyl)carbamate

Sodium hydride (0.28 g, 7.04 mmol) was added to a solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-methyl-N-(4-trifluoromethoxybenzyl)carbamate prepared in Example 72 (2.74 g, 5.87 mmol) in DMF (20 ml) followed by stirring for 1 hour with cooling on ice-bath. To the reaction mixture, ice-water was added, and the precipitates were filtered off, washed with water and then recrystallized from isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-methyl-N-(4-trifluoromethoxybenzyl)carbamate (1.40 g, yield 55%) as a white solid.

Melting point 123-124°C

Example 74

25 Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-(4-chlorophenyl)-N-cyclohexylcarbamate

(R)-2-Chloro-1-(2,3-dihydroxy-2-methyl-

propyl)-4-nitroimidazole prepared in Example 10 (0.95 g, 4.03 mmol), N, N-diisopropylethylamine (1.45 ml, 8.06 mmol) and 4-dimethylaminopyridine (0.10 g, 0.81 mmol) were added to a suspension of N-(4-chlorophenyl)-N-cyclohexylcarbamoylchloride (1.56 g, 6.05 mmol) in toluene (10 ml) followed by stirring at 100°C for 3 hours. The reaction mixture was diluted with ethyl acetate, and the solution was washed with 10% hydrochloric acid, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl-N-(4-chlorophenyl)-N-cyclohexylcarbamate (0.75 g, yield 40%) as a white amorphous form.

¹H-NMR (CDCl₃) δppm:

0.78 - 1.22 (6H, m), 1.24 - 1.48 (2H, m), 1.54 - 1.67 (1H, m), 1.70 - 1.93 (4H, m), 2.87 - 3.13 (1H, m), 3.72 - 3.98 (3H, m), 4.00 - 4.24 (2H, m), 7.00 - 7.06 (2H, m), 7.35 - 7.41 (2H, m), 7.80 (1H, br).

Example 75

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-(4-chlorophenyl)-N-cyclohexylcarbamate

Sodium hydride (76 mg, 1.91 mmol) was added to a solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-(4-chlorophenyl)-N-cyclohexylcarbamate prepared in Example 74 (0.75 g,

1.59 mmol) in DMF (7 ml) followed by stirring for 0.5 hours with cooling on ice-bath. To the reaction mixture, ice-water was added, and the resulting mixture was extracted with ethyl acetate. The extract was
5 washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was recrystallized from isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-(4-chlorophenyl)-N-cyclohexylcarbamate (0.53
10 g, yield 77%) as a white solid.
Melting point 175-177°C

Example 76

Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-methyl-N-(4-trifluoro-
15 methoxyphenyl)carbamate

N-Methyl-N-(4-trifluoromethoxyphenyl)-carbamoyl chloride (1.33 g, 5.23 mmol), N,N-diisopropylethylamine (1.2 ml, 6.97 mmol) and 4-dimethylaminopyridine (85 mg, 0.70 mmol) were added to
20 a suspension of (R)-2-chloro-1-(2,3-dihydroxy-2-methyl)propyl-4-nitroimidazole prepared in Example 10 (0.82 g, 3.48 mmol) in toluene (10 ml) followed by stirring at 100°C for 5 hours. The reaction mixture was diluted with ethyl acetate, and the solution was washed
25 with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 2/1) to afford (R)-3-(2-chloro-

4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-methyl-N-(4-trifluoromethoxyphenyl)carbamate (1.04 g, yield 65%) as a light yellow amorphous form.

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm:

- 5 1.02 (3H, s), 3.26 (3H, s), 3.80 - 4.00 (4H, m), 5.39 (1H, s), 7.37 - 7.40 (2H, m), 7.47 - 7.52 (2H, m), 8.25 (1H, s).

Example 77

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-methyl-N-(4-trifluoromethoxyphenyl)carbamate

Sodium hydride (0.48 g, 11.9 mmol) was added to a solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl N-methyl-N-(4-trifluoromethoxyphenyl)carbamate prepared in Example 76 (4.50 g, 9.94 mmol) in DMF (13.5 ml) with cooling on ice-bath followed by stirring at room temperature for 1 hour. Water and ethyl acetate were added to the reaction mixture, and the precipitates were filtered off. The precipitates were recrystallized from isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-methyl-N-(4-trifluoromethoxyphenyl)carbamate (2.95 g, yield 71%) as a light yellow solid.

25 Melting point 144-145°C

Optical purity 99.8% e.e.

$[\alpha]_D^{24} = 7.68^\circ$ (concentration: 0.938, CHCl_3)

Using corresponding starting materials gave

compounds of Examples 78 and 79 in the same manner as in Example 77.

Example 78

(R)-2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl methylcarbamate

Yield 26%, melting point 175-178°C

Example 79

(R)-2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl diethylcarbamate

Yield 27%, melting point 196-197°C

Example 80

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-(4-chlorophenyl)-N-methylcarbamate

Iodomethane (0.71 ml, 11.4 mmol) and potassium hydroxide (0.64 g, 11.4 mmol) were added to a solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-chlorophenylcarbamate prepared in Example 64 (1.5 g, 3.8 mmol) in DMSO (40 ml) followed by stirring at room temperature for 4 hours. The mixture was cooled on ice-bath and added 10% hydrochloric acid. The resulting mixture was extracted with ethyl acetate, and the extract was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/1) and recrystallized from isopropanol to afford (R)-2-methyl-6-nitro-2,3-

dihydroimidazo[2,1-b]oxazol-2-ylmethyl N-(4-chlorophenyl)-N-methylcarbamate (0.67 g, 60%) as a white solid.

Melting point 131-133°C

5 Optical purity 99.8% e.e.

$[\alpha]_D^{26} = 22.86^\circ$ (concentration: 1.028, CHCl_3)

Example 81

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl bis(4-chlorophenyl)carbamate

Pyridine (0.37 ml, 4.5 mmol) and triphosgene (0.16 g, 0.5 mmol) were added to a suspension of (R)-2-hydroxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 37 (0.30 g, 1.5 mmol) in 15 methylene chloride (15 ml) with cooling on ice-bath followed by stirring at room temperature for 2.5 hours. To the reaction mixture, bis(4-chlorophenyl)amine (0.39 g, 1.6 mmol) was added, and the resulting mixture was stirred at room temperature for 20 hours. The reaction 20 mixture was cooled on ice-bath and added 10% hydrochloric acid. The resulting mixture was extracted with methylene chloride, and the extract was dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silicagel column 25 chromatography (methylene chloride/ethyl acetate = 19/1) and recrystallized from isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl bis(4-chlorophenyl)carbamate (82 mg, yield

12%) as a white solid.

Melting point 200-201°C

Example 82

Preparation of 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
5 b]oxazol-2-ylmethyl piperidine-1-carboxylate

Pyridine (0.37 ml, 4.5 mmol) and triphosgene (0.18 g, 0.6 mmol) were added to a suspension of 2-hydroxymethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 33 (0.3 g, 1.5 mmol) in
10 methylene chloride (15 ml) with cooling on ice-bath followed by stirring at room temperature for 2 hours. The reaction mixture was cooled on ice-bath and added piperidine (0.16 ml, 1.7 mmol). The resulting mixture was stirred at room temperature for 3 hours. The
15 reaction mixture was cooled on ice-bath and added 10% hydrochloric acid, and the insoluble matters were removed by filtration. The filtrate was extracted with methylene chloride, and the organic phase was dried over magnesium sulfate and then concentrated under
20 reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 3/2) and recrystallized from methylene chloride-diisopropyl ether to afford 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl piperidine-1-
25 carboxylate (65 mg, yield 14%) as a white solid.

Melting point 152-154°C

Example 83

Preparation of 3-(2-chloro-4-nitroimidazol-1-yl)-2-

hydroxy-2-methylpropyl 4-(4-trifluoromethoxyphenyl)-
piperazine-1-carboxylate

4-(4-Trifluoromethoxyphenyl)piperazine-1-
carbonylchloride (0.26 g, 0.85 mmol), N, N-
5 diisopropylethylamine (0.30 ml, 1.7 mmol) and 4-
dimethylaminopyridine (21 mg, 0.17 mmol) were added to
a suspension of 2-chloro-1-(2,3-dihydroxy-2-
methylpropyl)-4-nitroimidazol prepared in Example 3
(0.30 g, 1.3 mmol) in toluene (5 ml) followed by
10 stirring at 100°C for 2.5 hours. The mixture was
diluted 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/ethyl
15 acetate = 9/1) to afford 3-(2-chloro-4-nitroimidazol-1-
yl)-2-hydroxy-2-methylpropyl 4-(4-
trifluoromethoxyphenyl)piperazine-1-carboxylate (0.24
g, yield 55%) as a light yellow oil.

¹H-NMR (CDCl₃) δppm:

20 1.26 (3H, s), 3.02 - 3.17 (4H, m), 3.39 - 3.72 (4H, m),
3.91 (1H, s), 3.99 - 4.18 (3H, m), 4.34 (1H, d, J =
12.3 Hz), 6.85 - 6.98 (2H, m), 7.09 - 7.22 (2H, m),
8.05 (1H, s).

Example 84

25 Preparation of 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
b]oxazol-2-ylmethyl 4-(4-trifluoromethoxyphenyl)-
piperazine-1-carboxylate

Sodium hydride (23 mg, 0.56 mmol) was added

to a solution of 3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethoxyphenyl)-piperazine-1-carboxylate prepared in Example 83 (0.24 g, 0.47 mmol) in DMF (2 ml) followed by stirring at 0°C
5 for 1 hour. Ice-water was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by
10 silica gel column chromatography (ethyl acetate) and then washed with diisopropyl ether to afford 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethoxyphenyl)piperazine-1-carboxylate (0.13 g, yield 58%) as a white solid.
15 Melting point 138-140°C

Example 85

Preparation of 3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate
20 2-Chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole prepared in Example 3 (0.13 g, 0.57 mmol), N,N-diisopropylethylamine (0.13 ml, 0.76 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) were added to a suspension of 4-(4-trifluoromethylphenyl)-
25 1,2,3,6-tetrahydropyridine-1-carbonylchloride (0.10 g, 0.38 mmol) in toluene (3 ml) followed by stirring at 100°C for 2.5 hours. The reaction mixture was diluted 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/ethyl acetate = 9/1) to afford 3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (0.11 g, yield 59%) as a colorless oil.

^1H -NMR (CDCl_3) δ ppm:

1.26 (3H, s), 2.43 - 2.50 (2H, m), 3.50 - 3.78 (2H, m),
10 3.93 - 4.24 (5H, m), 7.46 (1H, d, $J = 8.3$ Hz), 7.60
(1H, d, $J = 8.3$ Hz), 8.05 (1H, s).

Example 86

Preparation of 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate

Sodium hydride (11 mg, 0.28 mmol) was added to a solution of 3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate prepared in
20 Example 85 (0.11 g, 0.23 mmol) in DMF (1 ml) followed by stirring for 1 hour with cooling on ice-bath. Ice-water was added to the reaction mixture, the resulting mixture was extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and
25 then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 4/1) and then washed with diisopropyl ether to afford 2-methyl-6-

nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (0.04 g, yield 39%) as a white solid.

Melting point 113-115°C

5 Example 87

Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-tert-butoxycarbonylpiperazine-1-carboxylate

(R)-2-Chloro-1-(2,3-dihydroxy-2-methyl-
10 propyl)-4-nitroimidazole prepared in Example 10 (4.43 g, 18.79 mmol), N,N-diisopropylethylamine (4.68 ml, 26.84 mmol) and 4-dimethylaminopyridine (0.33 g, 2.68 mmol) were added to a suspension of tert-butyl 4-chlorocarbonylpiperazine-1-carboxylate (3.34 g, 13.42
15 mmol) in toluene (70 ml), and the resulting mixture was stirred at 100°C for 4.5 hours. The reaction mixture was diluted with ethyl acetate, washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by
20 silica gel column chromatography (n-hexane/methylene chloride/ethyl acetate = 45/45/10) to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-tert-butoxycarbonylpiperazine-1-carboxylate (4.12 g, yield 69%) as a colorless oil.

25 ¹H-NMR (CDCl₃) δppm:

1.23 (3H, s), 1.47 (9H, s), 3.33 - 3.50 (8H, m), 3.91 (1H, s), 3.99 - 4.16 (3H, m), 4.30 (1H, d, J = 12.1 Hz), 8.04 (1H, s).

Using 4-(4-trifluoromethoxybenzyloxy-carbonyl)piperazine-1-carbonylchloride or 4-[3-(4-trifluoromethylphenyl)-2-propenyloxycarbonyl]-piperazine-1-carbonylchloride gave compounds of

5 Examples 88 and 89 in the same manner as in Example 87.

Example 88

(R)-2-Chloro-1-{3-[4-(4-trifluoromethoxybenzyloxy-carbonyl)piperazin-1-ylcarbonyloxy]-2-hydroxy-2-methylpropyl}-4-nitroimidazole

10 Yield 81%

¹H-NMR (CDCl₃) δppm:

1.24 (3H, s), 3.28 - 3.61 (8H, m), 3.89 (1H, s), 4.00 - 4.20 (3H, m), 4.31 (1H, d, J = 12.5 Hz), 5.14 (2H, s), 7.22 (2H, d, J = 8.7 Hz), 7.39 (2H, d, J = 8.7 Hz),

15 8.04 (1H, s).

Example 89

(R)-2-Chloro-1-{3-[4-[3-(4-trifluoromethylphenyl)-2-propenylcarbonyl]piperazin-1-ylcarbonyloxy]-2-hydroxy-2-methylpropyl}-4-nitroimidazole

20 Yield 95%

¹H-NMR (CDCl₃) δppm:

1.24 (3H, s), 3.33 - 3.61 (8H, m), 3.90 (1H, s), 3.99 - 4.17 (3H, m), 4.31 (1H, d, J = 12.1 Hz), 4.79 (2H, d, J = 6.1 Hz), 6.39 (1H, dt, J = 6.1 Hz, 15.9 Hz), 6.67

25 (1H, d, J = 15.9 Hz), 7.39 (2H, d, J = 8.3 Hz), 7.49 (2H, d, J = 8.3 Hz), 8.04 (1H, s).

Example 90

Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-

hydroxy-2-methylpropyl 4-(4-chlorobenzyl)piperazine-1-carboxylate

(R)-2-Chloro-1-(2,3-dihydroxy-2-methyl)propyl-4-nitroimidazole prepared in Example 10
 5 (2.28 g, 9.66 mmol), N,N-diisopropylethylamine (2.81 ml, 16.10 mmol) and 4-dimethylaminopyridine (0.20 g, 1.61 mmol) were added to a suspension of 4-(4-chlorobenzyl)piperazine-1-carbonylchloride (2.20 g, 8.05 mmol) in toluene (30 ml) followed by stirring 100°C
 10 for 3 hours. The reaction mixture was diluted 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/ethyl acetate = 9/1)
 15 to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-chlorobenzyl)piperazine-1-carboxylate (1.82 g, yield 48%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.23 (3H, s), 2.17 - 2.50 (4H, m), 2.55 (1H, s), 3.26 -
 20 3.52 (6H, m), 3.98 - 4.20 (3H, m), 4.30 (1H, d, J = 12.4 Hz), 7.23 - 7.32 (4H, m), 8.05 (1H, s).

Using corresponding starting materials gave compounds of Examples 91 and 92 in the same manner as in Example 90.

25 Example 91

(R)-2-Chloro-1-{3-[4-(4-trifluoromethylbenzyl)-piperazin-1-ylcarbonyloxy]-2-hydroxy-2-methylpropyl}-4-nitroimidazole

Yield 31%

¹H-NMR (CDCl₃) δppm:

1.23 (3H, s), 2.24 - 2.54 (4H, m), 3.24 - 3.50 (4H, m),
3.56 (2H, s), 3.97 - 4.20 (3H, m), 4.32 (1H, d, J =
5 12.4 Hz), 7.45 (2H, d, J = 8.0 Hz), 7.58 (2H, d, J =
8.0 Hz), 8.05 (1H, s).

Example 92

(R)-2-Chloro-1-{3-[4-(4-trifluoromethoxybenzyl)-
piperazin-1-ylcarbonyloxy]-2-hydroxy-2-methylpropyl}-4-
10 nitroimidazole

Yield 47%

¹H-NMR (CDCl₃) δppm:

1.23 (3H, s), 2.22 - 2.54 (4H, m), 3.30 - 3.54 (4H, m),
3.50 (2H, s), 3.97 - 4.16 (3H, m), 4.32 (1H, d, J =
15 12.5 Hz), 7.15 - 7.18 (2H, m), 7.32 - 7.36 (2H, m),
8.05 (1H, s).

Example 93

Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-
hydroxy-2-methylpropyl 4-(4-trifluoromethoxy-
20 phenyl)piperazine-1-carboxylate

4-(4-Trifluoromethoxyphenyl)piperazine-1-
carbonylchloride (1.25 g, 4.2 mmol), N, N-
diisopropylethylamine (0.96 ml, 5.6 mmol) and 4-
dimethylaminopyridine (67 mg, 0.56 mmol) were added to
25 a suspension of (R)-2-chloro-1-(2,3-dihydroxy-2-
methylpropyl)-4-nitroimidazole prepared in Example 10
(0.65 g, 2.8 mmol) in toluene (13 ml) followed by
stirring at 100°C for 8.5 hours. The reaction mixture

was diluted 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/ethyl acetate = 19/1) to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethoxyphenyl)piperazine-1-carboxylate (1.29 g, yield 92%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

10 1.26 (3H, s), 3.02 - 3.17 (4H, m), 3.39 - 3.72 (4H, m), 3.91 (1H, s), 3.99 - 4.18 (3H, m), 4.34 (1H, d, J = 12.3 Hz), 6.85 - 6.98 (2H, m), 7.09 - 7.22 (2H, m), 8.05 (1H, s).

Using corresponding starting materials gave compounds of Examples 94 to 102 in the same manner as in Example 93.

Example 94

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenyl)piperazine-1-carboxylate

Yield 48%

¹H-NMR (CDCl₃) δppm:

1.26 (3H, s), 3.13 - 3.35 (4H, m), 3.48 - 3.72 (4H, m), 3.94 (1H, s), 4.00 - 4.18 (3H, m), 4.33 (1H, d, J = 12.3 Hz), 6.93 (2H, d, J = 8.6 Hz), 7.50 (2H, d, J = 8.6 Hz), 8.05 (1H, s).

Example 95

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-

methylpropyl 4-(4-methoxyphenyl)piperazine-1-carboxylate

Yield 54%

¹H-NMR (CDCl₃) δppm:

- 5 1.24 (3H, s), 2.93 - 3.09 (4H, m), 3.52 - 3.63 (4H, m),
3.77 (3H, s), 3.96 (1H, s), 4.00 - 4.19 (3H, m), 4.32
(1H, d, J = 12.3 Hz), 6.82 - 6.92 (4H, m), 8.05 (1H,
s).

Example 96

- 10 (R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-chlorophenyl)piperazine-1-carboxylate
Yield 81%

¹H-NMR (CDCl₃) δppm:

- 1.25 (3H, s), 3.00 - 3.13 (4H, m), 3.52 - 3.65 (4H, m),
15 3.93 (1H, s), 4.00 - 4.17 (3H, m), 4.33 (1H, d, J =
12.5 Hz), 6.82 - 6.86 (2H, m), 7.20 - 7.25 (2H, m),
8.05 (1H, s).

Example 97

- (R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(3-chlorophenyl)piperazine-1-carboxylate
20 Yield 87%

¹H-NMR (CDCl₃) δppm:

- 1.25 (3H, s), 3.04 - 3.22 (4H, m), 3.43 - 3.70 (4H, m),
3.89 (1H, s), 4.00 - 4.17 (3H, m), 4.33 (1H, d, J =
25 12.3 Hz), 6.78 (1H, ddd, J = 1.6 Hz, 2.4 Hz, 8.4 Hz),
6.85 - 6.88 (2H, m), 7.19 (1H, t, J = 8.4 Hz), 8.05
(1H, s).

Example 98

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(3,4-dichlorophenyl)piperazine-1-carboxylate

Yield 47%

5 $^1\text{H-NMR}$ (DMSO-d_6) δppm :

1.12 (3H, s), 3.15 - 3.26 (4H, m), 3.39 - 3.61 (4H, m),
3.88 (1H, d, $J = 11.0$ Hz), 3.93 (1H, d, $J = 11.0$ Hz),
4.07 (1H, d, $J = 14.7$ Hz), 4.15 (1H, d, $J = 14.7$ Hz),
6.96 (1H, dd, $J = 2.9$ Hz, 9.1 Hz), 7.16 (1H, d, $J = 2.9$
10 Hz), 7.42 (1H, d, $J = 9.1$ Hz), 8.34 (1H, s).

Example 99

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-fluorophenyl)piperazine-1-carboxylate

Yield 100%

15 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.25 (3H, s), 2.96 - 3.09 (4H, m), 3.50 - 3.67 (4H, m),
3.98 (1H, s), 4.05 - 4.16 (3H, m), 4.33 (1H, d, $J =$
12.3 Hz), 6.85 - 7.02 (4H, m), 8.05 (1H, s).

Example 100

20 (R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(3-trifluoromethylphenyl)piperazine-1-carboxylate

Yield 83%

$^1\text{H-NMR}$ (CDCl_3) δppm :

25 1.25 (3H, s), 3.11 - 3.26 (4H, m), 3.48 - 3.70 (4H,
m), 3.91 (1H, s), 4.00 - 4.24 (3H, m), 4.33 (1H, d, $J =$
12.3 Hz), 7.02 - 7.20 (3H, m), 7.38 (1H, t, $J = 8.0$
Hz), 8.05 (1H, s).

Example 101

(R)-2-Chloro-1-(3-diethylaminocarbonyloxy-2-hydroxy-2-methylpropyl)-4-nitroimidazole

Yield 37%

5 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.11 (6H, t, $J = 7.1$ Hz), 1.20 (3H, s), 3, 16 (4H, q, $J = 7.1$ Hz), 3.76 (1H, br), 4.06 - 4.11 (3H, m), 4.26 (1H, d, $J = 11.1$ Hz), 8.05 (1H, s).

Example 102

10 2-Chloro-1-(3-morpholinocarbonyloxy-2-hydroxy-2-methylpropyl)-4-nitroimidazole

Yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.23 (3H, s), 3.35 - 3.52 (4H, m), 3.61 - 3.72 (4H, m),
15 3.99 - 4.16 (3H, m), 4.31 (1H, d, $J = 12.3$ Hz), 8.05 (1H, s).

Example 103

Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-

20 trifluoromethylbenzylideneamino)piperazine-1-carboxylate

(R)-2-Chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole prepared in Example 10 (2.75 g, 11.66 mmol), N,N-diisopropylethylamine (2.71 ml, 15.54 mmol) and 4-dimethylaminopyridine (0.19 g, 1.55 mmol) were added to a suspension of 4-(4-trifluoromethylbenzylideneamino)piperazine-1-carbonylchloride (2.48 g, 7.77 mmol) in toluene (40 ml)

followed by stirring at 100°C for 2.5 hours. The reaction mixture was diluted with ethyl acetate, washed with 10% hydrochloric acid, dried over magnesium sulfate and then concentrated under reduced pressure.

- 5 The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylbenzylideneamino)piperazine-1-carboxylate (4.03 g, quantitative) as a yellow oil.
- ¹H-NMR (CDCl₃) δppm:
- 1.25 (3H, s), 3.04 - 3.33 (4H, m), 3.48 - 3.76 (4H, m), 3.83 (1H, s), 4.00 - 4.17 (3H, m), 4.33 (1H, d, J = 12.3 Hz), 7.55 (1H, s), 7.59 (2H, d, J = 8.4 Hz), 7.69
- 15 (2H, d, J = 8.4 Hz), 8.04 (1H, s).

Example 104

Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenoxy)-piperidine-1-carboxylate

- 20 (R)-2-Chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole prepared in Example 10 (1.16 g, 4.68 mmol) and triethylamine (1.63 ml, 11.70 mmol) were added to a suspension of 4-(4-trifluoromethylphenoxy)piperidine-1-carbonylchloride (0.72 g, 2.34
- 25 mmol) in toluene (40 ml) followed by stirring at 100°C for 2.5 hours. The reaction mixture was diluted 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/ethyl acetate = 9/1) to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenoxy)-piperidine-1-carboxylate (184 mg, yield 16%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

1.24 (3H, s), 1.72 - 1.98 (4H, m), 3.33 - 3.67 (4H, m), 3.91 - 4.20 (3H, m), 4.24 - 4.39 (1H, m), 4.52 - 4.65 (1H, m), 6.96 (2H, d, J = 8.7 Hz), 7.55 (2H, d, J = 8, 7 Hz), 8.05 (1H, s).

Example 105

Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenyl-amino)piperidine-1-carboxylate

(R)-2-Chloro-1-(2,3-dihydroxy-2-methylpropyl)-4-nitroimidazole prepared in Example 10 (1.54 g, 7.01 mmol), N,N-diisopropylethylamine (1.63 ml, 9.34 mmol) and 4-dimethylaminopyridine (0.11 g, 0.93 mmol) were added to a suspension of 4-(4-trifluoromethylphenylamino)piperidine-1-carbonylchloride (1.43 g, 4.67 mmol) in toluene (30 ml) followed by stirring at 100°C for 2.5 hours. The reaction mixture was diluted 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/ethyl acetate = 9/1) to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-

hydroxy-2-methylpropyl 4-(4-trifluoromethylphenyl-amino)piperidine-1-carboxylate (1.44 g, yield 61%) as a light yellow oil.

¹H-NMR (CDCl₃) δppm:

- 5 1.25 (3H, s), 1.30 - 1.48 (2H, m), 1.98 - 2.13 (2H, m), 2.83 - 3.13 (2H, m), 3.37 - 3.61 (1H, m), 3.83 - 3.96 (2H, m), 3.96 - 4.22 (4H, m), 4.34 (1H, d, J = 11.8 Hz), 7.40 (2H, d, J = 8.5 Hz), 7.60 (2H, d, J = 8.5 Hz), 8.07 (1H, s).

10 Example 106

Preparation of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate

- (R)-2-Chloro-1-(2,3-dihydroxy-2-methyl)-
15 propyl-4-nitroimidazole prepared in Example 10 (0.74 g, 3.11 mmol) and triethylamine (1.74 ml, 12.42 mmol) were added to a suspension of 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carbonylchloride (0.60 g, 2.07 mmol) in toluene (36 ml) followed by stirring at
20 100°C for 16 hours. The mixture was diluted 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/ethyl acetate = 9/1)
25 to afford (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (0.32 g, yield 31%) as a light yellow oil.

¹H-NMR (CDCl₃) δppm:

1.26 (3H, s), 2.43 - 2.50 (2H, m), 3.50 - 3.78 (2H, m),
3.93 - 4.24 (5H, m), 7.46 (2H, d, J = 8.3 Hz), 7.60
(2H, d, J = 8.3 Hz), 8.05 (1H, s).

- 5 Using corresponding starting materials gave
compounds of Examples 107 to 112 in the same manner as
in Example 106.

Example 107

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-
10 methylpropyl 4-(4-chlorophenyl)-1,2,3,6-
tetrahydropyridine-1-carboxylate

Yield 94%

¹H-NMR (CDCl₃) δppm:

1.25 (3H, s), 2.41 - 2.59 (2H, m), 3.50 - 3.78 (2H, m),
15 3.93 - 4.22 (6H, m), 4.35 (1H, d, J = 12.3 Hz), 5.87 -
6.13 (1H, m), 7.26 - 7.37 (4H, m), 8.05 (1H, s).

Example 108

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-
methylpropyl 4-(4-trifluoromethoxyphenyl)-1,2,3,6-
20 tetrahydropyridine-1-carboxylate

Yield 92%

¹H-NMR (CDCl₃) δppm:

1.26 (3H, s), 2.46 - 2.59 (2H, m), 3.13 - 3.37 (1H, m),
3.50 - 3.74 (2H, m), 4.00 - 4.14 (6H, m), 4.36 (1H, d,
25 J = 12.4 Hz), 7.19 (2H, d, J = 8.0 Hz), 7.37 (2H, d, J
= 8.0 Hz), 8.05 (1H, s).

Example 109

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-

methylpropyl 4-(4-methoxyphenyl)-1,2,3,6-tetrahydro-
pyridine-1-carboxylate

Yield 63%

¹H-NMR (CDCl₃) δppm:

- 5 1.23 (3H, s), 2.43 - 2.61 (2H, m), 3.52 - 3.74 (2H, m),
3.82 (3H, s), 4.01 - 4.16 (5H, m), 4.34 (1H, d, J =
12.6 Hz), 5.83 - 6.00 (1H, m), 6.88 (2H, d, J = 8.8
Hz), 7.30 (2H, d, J = 8.8 Hz), 8.05 (1H, s).

Example 110

- 10 (R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-
methylpropyl 4-(3-trifluoromethylphenyl)-1,2,3,6-
tetrahydropyridine-1-carboxylate

Yield 54%

¹H-NMR (CDCl₃) δppm:

- 15 1.25 (3H, s), 2.46 - 2.70 (2H, m), 3.50 - 3.78 (2H, m),
4.00 - 4.32 (6H, m), 4.35 (1H, d, J = 12.6 Hz), 5.98 -
6.22 (1H, m), 7.39 - 7.67 (4H, m), 8.06 (1H, s).

Example 111

- 20 (R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-
methylpropyl 4-(4-bromophenyl)-1,2,3,6-
tetrahydropyridine-1-carboxylate

Yield 80%

¹H-NMR (CDCl₃) δppm:

- 25 1.25 (3H, s), 2.41 - 2.63 (2H, m), 3.50 - 3.76 (2H, m),
3.96 - 4.20 (6H, m), 4.35 (1H, d, J = 12.3 Hz), 5.87 -
6.13 (1H, m), 7.15 - 7.26 (2H, m), 7.43 - 7.48 (2H, m),
8.05 (1H, s).

Example 112

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate

Yield 57%

5 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.25 (3H, s), 2.41 - 2.63 (2H, m), 3.50 - 3.76 (2H, m), 3.89 - 4.22 (6H, m), 4.35 (1H, d, $J = 12.6$ Hz), 5.83 - 6.04 (1H, m), 6.99 - 7.06 (2H, m), 7.29 - 7.35 (2H, m), 8.05 (1H, s).

10 Using 5-chloro-2,3-dihydroindole-1-carbonylchloride, 5-chloro-1,3-dihydroisoindol-2-carbonylchloride, 6-chloro-3,4-dihydro-1H-isoquinoline-2-carbonylchloride or 6-chloro-3,4-dihydro-2H-quinoline-1-carbonylchloride gave compounds of Examples
15 113 to 116 in the same manner as in Example 106.

Example 113

(R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 5-chloroindolinyl-1-carboxylate

Light yellow amorphous form, yield 50%

20 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.27 (3H, s), 3.14 (2H, t, $J = 8.5$ Hz), 3.42 (1H, br), 3.91 - 4.28 (5H, m), 4.37 (1H, d, $J = 11.8$ Hz), 7.04 - 7.24 (2H, m), 7.73 (1H, d, $J = 8.3$ Hz), 8.04 (1H, s).

Example 114

25 (R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 5-chloroisoindolinyl-2-carboxylate

Brown solid, yield 19%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.27 (3H, s), 3.93 (1H, d, $J = 7.8$ Hz), 4.04 - 4.24 (7H, m), 4.32 (1H, d, $J = 11.8$ Hz), 7.16 - 7.29 (3H, m), 8.07 (1H, s).

Example 115

- 5 (R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 6-chloro-3,4-dihydro-1H-isoquinoline-2-carboxylate

Light yellow oil, yield 63%

$^1\text{H-NMR}$ (CDCl_3) δppm :

- 10 1.24 (3H, s), 2.83 (2H, t, $J = 5.8$ Hz), 3.46 - 3.76 (2H, m), 3.90 (1H, d, $J = 5.3$ Hz), 4.01 - 4.15 (3H, m), 4.34 (1H, d, $J = 12.3$ Hz), 4.43 - 4.65 (2H, m), 6.93 - 7.09 (1H, m), 7.09 - 7.22 (2H, m), 8.04 (1H, s).

Example 116

- 15 (R)-3-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 6-chloro-3,4-dihydro-2H-quinoline-1-carboxylate

Light yellow oil, yield 70%

$^1\text{H-NMR}$ (CDCl_3) δppm :

- 20 1.26 (3H, s), 1.87 - 2.00 (2H, m), 2.76 (2H, t, $J = 6.5$ Hz), 3.27 (1H, br), 3.57 - 3.83 (2H, m), 3.98 - 4.17 (3H, m), 4.33 (1H, d, $J = 12.0$ Hz), 7.12 - 7.16 (2H, m), 7.41 - 7.61 (1H, br), 7.98 (1H, s).

Example 117

- 25 Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-tert-butoxycarbonylpiperazine-1-carboxylate

To the solution of (R)-3-(2-chloro-4-

nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-tert-butoxycarbonylpiperazine-1-carboxylate prepared in Example 87 (4.12 g, 9.20 mmol) in DMF (30 ml), sodium hydride (0.44 g, 11.04 mmol) was added followed by
5 stirring for 1 hour with cooling on ice-bath. Ice-water was added to the reaction mixture, and the precipitates were filtered off, purified by silica gel column chromatography (ethyl acetate) and then washed with isopropanol to afford (R)-2-methyl-6-nitro-2,3-
10 dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-tert-butoxycarbonylpiperazine-1-carboxylate (2.24 g, yield 59%) as a white solid.
Melting point 211-212°C.

Example 118

15 Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethoxyphenyl)piperazine-1-carboxylate

To the solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-
20 trifluoromethoxyphenyl)piperazine-1-carboxylate prepared in Example 93 (1.29 g, 2.5 mmol) in DMF (13 ml), sodium hydride (0.12 g, 3 mmol) was added followed by stirring for 1 hour with cooling on ice-bath. To the reaction mixture, ice water was added, and the
25 precipitates were filtered off, washed with water and recrystallized from isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethoxyphenyl)piperazine-1-carboxylate

(0.70 g, yield 59%) as a white solid.

Optical purity 99.6% e.e.

$[\alpha]_D^{25} = 0.99^\circ$ (concentration: 0.704, CHCl_3)

Melting point 168-169°C.

5 Example 119

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-chlorobenzyl)piperazine-1-carboxylate

To the solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-chlorobenzyl)piperazine-1-carboxylate prepared in Example 90 (1.82 g, 3.85 mmol) in DMF (10 ml), sodium hydride (0.31 g, 7.70 mmol) was added followed by stirring for 1 hour with cooling on ice-bath. To the reaction mixture, ice-water was added, and the precipitates were filtered off and washed with isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-chlorobenzyl)piperazine-1-carboxylate (0.46 g, yield 28%) as a light yellow solid.

Melting point 161-163°C.

Example 120

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethylbenzylideneamino)piperazine-1-carboxylate

To the solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-

trifluoromethylbenzylideneamino)piperazine-1-carboxylate prepared in Example 103 (4.03 g, 7.77 mmol) in DMF (20 ml), sodium hydride (0.37 g, 9.32 mmol) was added followed by stirring for 1 hour with cooling on
5 ice-bath. To the reaction mixture, ice water was added, and the precipitates were filtered off, washed with water and recrystallized from acetonitrile-isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-
10 trifluoromethylbenzylideneamino)piperazine-1-carboxylate (2.60 g, yield 69%) as a white solid. Melting point 176-178°C.

Example 121

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-
15 trifluoromethylphenylamino)piperidine-1-carboxylate

To the solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenylamino)piperidine-1-carboxylate
20 prepared in Example 105 (1.44 g, 2.85 mmol) in DMF (10 ml), sodium hydride (0.14 g, 3.42 mmol) was added followed by stirring for 1 hour with cooling on ice-bath. To the reaction mixture, ice-water was added, and the solution was extracted with ethyl acetate. The
25 organic phase was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate) and

recrystallized from acetonitrile-isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethylphenylamino)piperidine-1-carboxylate (0.42 g, yield 31%) as a white solid.

5 Melting point 137-140°C.

Example 122

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethylphenoxy)piperidine-1-carboxylate

10 To the solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenoxy)piperidine-1-carboxylate prepared in Example 104 (0.18 g, 0.36 mmol) in DMF (2 ml), sodium hydride (19 mg, 0.47 mmol) was added
15 followed by stirring for 1.5 hours with cooling on ice-bath. To the reaction mixture, ice-water was added, and the solution was extracted with ethyl acetate. The organic phase was washed with water, dried over
20 magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) and recrystallized from isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethylphenoxy)piperidine-1-
25 carboxylate (0.08 g, yield 47%) as a white solid. Melting point 165-166°C.

Example 123

Preparation of (R)-2-methyl-6-nitro-2,3-

dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate

To the solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate prepared in Example 106 (0.32 g, 0.65 mmol) in DMF (3 ml), sodium hydride (31 mg, 0.78 mmol) was added followed by stirring for 1.5 hours with cooling on ice-bath. To the reaction mixture, ice-water was added, and the solution was extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) and recrystallized from isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (0.14 g, yield 49%) as a white solid. Optical purity 98.4% e.e.
 $[\alpha]_D^{26} = 2.50^\circ$ (c0.560, CHCl₃).
Melting point 169-171°C.

Example 124

25 Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 5-chloro-2,3-dihydroindole-1-carboxylate

To the solution of (R)-3-(2-chloro-4-

nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 5-chloro-
2,3-dihydroindole-1-carboxylate prepared in Example 113
(0.60 g, 1.44 mmol) in DMF (6 ml), sodium hydride (70
mg, 1.73 mmol) was added followed by stirring 1 hour
5 with cooling on ice-bath. To the reaction mixture,
ice-water was added, and the precipitates were filtered
off, washed with water and recrystallized from
acetonitrile-isopropanol to afford (R)-2-methyl-6-
nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 5-
10 chloro-2,3-dihydroindole-1-carboxylate (0.30 g, yield
55%) as a white solid.
Melting point 189-191°C.

Example 125

Preparation of (R)-2-methyl-6-nitro-2,3-
15 dihydroimidazo[2,1-b]oxazol-2-ylmethyl 5-chloro-1,3-
dihydroisoindol-2-carboxylate

To the solution of (R)-3-(2-chloro-4-
nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 5-chloro-
1,3-dihydro-isoindol-2-carboxylate prepared in Example
20 114 (0.13 g, 0.31 mmol) in DMF (2 ml), sodium hydride
(15 mg, 0.37 mmol) was added followed by stirring for 1
hour with cooling on ice-bath. To the reaction
mixture, ice-water was added, and the solution was
extracted with ethyl acetate. The organic phase was
25 washed with water, dried over magnesium sulfate and
then concentrated under reduced pressure. The residue
was purified by silica gel column chromatography (ethyl
acetate) to afford (R)-2-methyl-6-nitro-2,3-

dihydroimidazo[2,1-b]oxazol-2-ylmethyl 5-chloro-1,3-dihydroisoindole 2-carboxylate (7 mg, yield 6%) as a light yellow solid.

Melting point 182°C (decomposition).

5 Example 126

Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 6-chloro-3,4-dihydro-1H-isoquinoline-2-carboxylate

To the solution of (R)-3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 6-chloro-3,4-dihydro-1H-isoquinoline-2-carboxylate prepared in Example 115 (0.26 g, 0.61 mmol) in DMF (2 ml), sodium hydride (30 mg, 0.73 mmol) was added followed by stirring for 1 hour with cooling on ice-bath. To the reaction mixture, ice-water was added, and the solution was extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate, concentrated under reduced pressure and recrystallized from isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 6-chloro-3,4-dihydro-1H-isoquinoline-2-carboxylate (0.12 g, 49%) as a light yellow solid.

Melting point 180-182°C.

 Example 127

25 Preparation of (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 6-chloro-3,4-dihydro-2H-quinoline-1-carboxylate

To the solution of (R)-3-(2-chloro-4-

nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl 6-chloro-3,4-dihydro-2H-quinoline-1-carboxylate prepared in Example 116 (1.84 g, 4.29 mmol) in DMF (10 ml), sodium hydride (0.21 g, 5.15 mmol) was added followed by

5 stirring for 1 hour with cooling on ice-bath. To the reaction mixture, ice-water was added, the solution was extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue

10 was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) and recrystallized from acetonitrile-isopropanol to afford (R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl 6-chloro-3,4-dihydro-2H-quinoline-1-

15 carboxylate (0.68 g, yield 40%) as a white solid. Melting point 172-174°C.

Example 128

Preparation of 2-methyl-6-nitro-2-(4-trifluoromethoxyphenoxy-methyl)-2,3-dihydroimidazo[2,1-b]oxazole

20 4-Trifluoromethoxyphenol (198 mg, 1.11 mmol) was dissolved in DMF (5 ml). To the solution, sodium hydride (48 mg, 1.21 mmol) was added at room temperature, and the solution was stirred for 20 minutes at 80°C. To the resulting solution, 2-chloro-1-(2-

25 methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 6 (220 mg, 1.01 mmol) was added with cooling on ice-bath, and the solution was stirred for 15 minutes at 80°C. The reaction mixture was poured into ice-

water, and the mixture was extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and then crystallized from methylene chloride-diisopropyl ether to afford 2-methyl-6-nitro-2-(4-trifluoromethoxyphenoxymethyl)-2,3-dihydroimidazo[2,1-b]oxazole (170 mg, yield 47%) as a white powder.

Melting point 126.8-127.9°C

MS 358 (M-1)⁺

Example 129

15 Preparation of 2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole

4-[4-(4-Trifluoromethoxyphenoxy)piperidin]-1-ylphenol (244 mg, 0.69 mmol) was dissolved in DMF (10 ml). To the solution, sodium hydride (33 mg, 0.83 mmol) was added at room temperature, and the solution was stirred for 20 minutes at 80°C. To the solution, 2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 6 (150 mg, 0.69 mmol) was added with cooling on ice-bath, and the solution was stirred at 80°C for 20 minutes. To the reaction mixture, ice-water was added, and the solution was stirred vigorously. The precipitates were filtered off, washed

with water and dissolved in methylene chloride. The solution was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced
5 pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and then crystallized from methylene chloride/ethyl acetate to afford 2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-
10 yl]phenoxyethyl}-2,3-dihydroimidazo[2,1-b]oxazole (103 mg, yield 28%) as a white powder.
Melting point 165.4-166.3°C.

Example 130

Preparation of 2-methyl-6-nitro-2-{4-[4-(4-trifluoro-
15 methylphenyl)piperazin-1-yl]phenoxyethyl}-2,3-dihydroimidazo[2,1-b]oxazole

4-[4-(4-Trifluoromethylphenyl)piperazin-1-yl]phenol (296 mg, 0.92 mmol) was dissolved in DMF (10 ml). To the solution, sodium hydride (44 mg, 1.1 mmol)
20 was added at room temperature, and the solution was stirred for 20 minutes at 80°C. To the solution, 2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 6 (200 mg, 0.92 mmol) was added with cooling on ice-bath, and the solution was stirred
25 for further 20 minutes at 80°C. To the reaction mixture, ice-water was added, and the solution was stirred vigorously. The precipitates were filtered off, washed with water and dissolved in methylene

chloride. The solution was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by
5 silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and then crystallized from methylene chloride/ethyl acetate to afford 2-methyl-6-nitro-2-{4-[4-(4-trifluoromethylphenyl)piperazin-1-yl]phenoxyethyl}-
10 2,3-dihydroimidazo[2,1-b]oxazole (178 mg, yield 38%) as a white powder.

Melting point 230.7-233.1°C.

Example 131

Preparation of tert-butyl 4-[4-(2-methyl-6-nitro-2,3-
15 dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperazine-1-carboxylate

Tert-butyl 4-(4-hydroxyphenyl)piperazine-1-carboxylate (2.01 g, 7.23 mmol) was dissolved in DMF (20 ml). To the solution, sodium hydride (320 mg, 8
20 mmol) was added at room temperature, and the solution was stirred for 20 minutes at 70°C. To the solution, 2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 6 (1.5 g, 7.23 mmol) was added with cooling on ice-bath, and the solution was stirred for
25 further 20 minutes at 80°C. To the reaction mixture, ice-water was added, and the solution was stirred vigorously. The precipitates were filtered off, washed with water and dissolved in methylene chloride. The

solution was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel
5 column chromatography (methylene chloride/ethyl acetate = 20/1) and then crystallized from methylene chloride/ethyl acetate to afford tert-butyl 4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]piperazine-1-carboxylate (1.5 g, yield
10 45%) as a white powder.

¹H-NMR (CDCl₃) δppm:

1.48 (9H, s), 1.77 (3H, s), 2.99 - 3.03 (4H, m), 3.55 -
3.59 (4H, m), 4.02 (1H, d, J = 10.2 Hz), 4.04 (1H, d, J
= 10.1 Hz), 4.18 (1H, d, J = 10.1 Hz), 4.49 (1H, d, J =
15 10.2 Hz), 6.76 - 6.81 (2H, m), 6.84 - 6.89 (2H, m),
7.55 (1H, s).

Melting point 212.0-214.5°C

MS 459(M⁺).

Example 132

20 Preparation of tert-butyl 4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperidine-1-carboxylate

Tert-butyl 4-(4-hydroxyphenyl)piperidine-1-carboxylate (364 mg, 1.31 mmol) was dissolved in DMF
25 (10 ml). To the solution, sodium hydride (58 mg, 1.44 mmol) was added at room temperature, and the solution was stirred for 20 minutes at 80°C. To the solution, 2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole

prepared in Example 6 (300 mg, 1.38 mmol) was added with cooling on ice-bath followed by stirring for further 20 minutes at 80°C. To the reaction mixture, ice-water was added, and the solution was stirred vigorously. The precipitates were filtered off, washed with water and dissolved in methylene chloride. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and then crystallized from methylene chloride-diisopropyl ether to afford tert-butyl 4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]piperidine-1-carboxylate (248 mg, yield 41%) as a white powder. Melting point 207.8-209.1°C.

Example 133

Preparation of 3,4-dichlorobenzyl 4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]piperazine-1-carboxylate

Tert-butyl 4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]piperazine-1-carboxylate prepared in Example 131 (118 mg, 0.26 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (5 ml) was added, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated

under reduced pressure and added methylene chloride (2 ml) and triethylamine (2 ml). The solution was stirred at room temperature for 5 minutes and then concentrated under reduced pressure. The residue was dissolved in 5 DMF (15 ml) and the solution was added a solution of 3,4-dichlorobenzyl alcohol (136 mg, 0.77 mmol) and 1,1'-carbonyldiimidazole (125 mg, 0.77 mmol) in DMF (5 ml) stirred at room temperature for 3 hours followed by stirring at room temperature overnight. The reaction 10 mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by 15 silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford 3,4-dichlorobenzyl 4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)-phenyl]piperazine-1-carboxylate (101 mg, yield 70%) as 20 a light yellow powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.77 (3H, s), 3.01 - 3.06 (4H, m), 3.62 - 3.67 (4H, m),
4.02 (1H, d, $J = 10.2$ Hz), 4.04 (1H, d, $J = 10.2$ Hz),
25 4.18 (1H, d, $J = 10.2$ Hz), 4.49 (1H, d, $J = 10.2$ Hz),
5.09 (2H, s), 6.76 - 6.81 (2H, m), 6.84 - 6.89 (2H, m),
7.18 - 7.22 (1H, m), 7.41 - 7.47 (2H, m), 7.55 (1H, s).

Example 134

Preparation of 2-methyl-6-nitro-2-(4-[4-(4-trifluoro-methylbenzyl)piperazin-1-yl]phenoxy)methyl}-2,3-dihydroimidazo[2,1-b]oxazole

Tert-butyl 4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperazine-1-carboxylate prepared in Example 131 (88 mg, 0.19 mmol) was dissolved in trifluoroacetic acid (5 ml), and the solution was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure and added methylene chloride (2 ml) and triethylamine (2 ml). The solution was stirred at room temperature for 5 minutes and then concentrated under reduced pressure. The residue was dissolved in dichloroethane and added 4-trifluoromethylbenzaldehyde (40 μ l, 0.29 mmol) and sodium triacetoxyborohydride (82 mg, 0.38 mmol) with cooling on ice-bath followed by stirring at room temperature overnight. To the solution, a saturated sodium hydrogencarbonate solution and methylene chloride were added. The mixture was extracted with methylene chloride, and the organic phase was dried over magnesium sulfate and filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-ethyl acetate to afford 2-methyl-6-nitro-2-(4-[4-(4-trifluoromethylbenzyl)piperazin-1-yl]phenoxy)methyl}-2,3-dihydroimidazo[2,1-b]oxazole (53 mg, yield 53%) as

a white powder.

Melting point 171.8-173.1°C.

Using tert-butyl 4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-
5 piperidine-1-carboxylate prepared in Example 132 gave the compound of Example 135 in the same manner as in Example 134.

Example 135

2-Methyl-6-nitro-2-(4-[1-(4-trifluoromethoxybenzyl)-
10 piperidin-4-yl]phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole

Yield 45%, melting point 160.6-161.1°C.

Example 136

Preparation of (R)-2-methyl-6-nitro-2-(4-trifluoro-
15 methoxyphenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole

4-Trifluoromethoxyphenol (1.1 g, 6.17 mmol) was dissolved in DMF (20 ml). To the solution, sodium hydride (260 mg, 6.45 mmol) was added at room temperature, and the solution was stirred for 15
20 minutes at 80°C. To the solution, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (1.22 g, 5.61 mmol) was added with cooling on ice-bath, and the solution was stirred for further 2 hours at 80°C. The reaction mixture was poured into
25 ice-water, and the solution was stirred vigorously. The precipitates were filtered off, washed with water and dissolved in methylene chloride. The solution was washed with a saturated saline solution, dried over

magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and then crystallized from methylene chloride-diisopropyl ether to afford (R)-2-methyl-6-nitro-2-(4-trifluoromethoxyphenoxymethyl)-2,3-dihydroimidazo[2,1-b]oxazole (1.03 g, yield 51%) as a white powder.

10 Optical purity >99% e.e.

$[\alpha]_D^{28} = 7.67^\circ$ (concentration: 1.030, CHCl_3)

MS 359 (M^+)

Melting point 176.5-178.0°C.

Using corresponding starting materials gave compounds of Examples 137 to 139 in the same manner as in Example 136.

Example 137

(R)-2-Methyl-6-nitro-2-[4-(thiomorpholin-4-yl)phenoxy-methyl]-2,3-dihydroimidazo[2,1-b]oxazole

20 Yield 38%, melting point 227.5-229.0°C, MS 376 (M^+).

Example 138

(R)-2-Methyl-6-nitro-2-[4-(imidazol-1-yl)phenoxy-methyl]-2,3-dihydroimidazo[2,1-b]oxazole

Yield 44%, melting point 172-175°C.

25 Example 139

(R)-2-Methyl-6-nitro-2-[4-(1,2,4-triazol-1-yl)phenoxy-methyl]-2,3-dihydroimidazo[2,1-b]oxazole

Yield 53%, melting point 236.0-238.7°C.

Using ethyl 1-(4-hydroxyphenyl)piperidine-4-carboxylate gave the compound of Example 140 in the same manner as in Example 136.

Example 140

- 5 Ethyl (R)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]piperidine-4-carboxylate

Yield 30%, melting point 208.2-211.5°C.

Example 141

- 10 Preparation of (R)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxy-methyl}-2,3-dihydroimidazo[2,1-b]oxazole

4-[4-(4-Trifluoromethoxyphenoxy)piperidin-1-yl]phenol (17.4 g, 49.0 mmol) was dissolved in DMF (150
15 ml). To the solution, sodium hydride (2.15 g, 53.8 mmol) was added at room temperature, and the solution was stirred for 20 minutes at 80°C. To the solution, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (14.9 g, 68.6
20 mmol) was added with cooling on ice-bath, and the solution was stirred for further 20 minutes at 80°C. To the reaction mixture, ice-water was added, and the mixture was stirred vigorously. The precipitates were filtered off, washed with water and dissolved in
25 methylene chloride. The solution was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was

purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and then crystallized from methylene chloride/ethyl acetate to afford (R)-2-methyl-6-nitro-2-{4-[4-(4-

5 trifluoromethoxyphenoxy)piperidin-1-yl]phoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole (14.3 g, yield 55%) as a light yellow powder.

MS 535(M+1)⁺

Optical purity 99.9% e.e.

10 $[\alpha]_D^{28} = -9.94^\circ$ (concentration: 1.006, CHCl₃)

Melting point 194.5-196°C

¹H-NMR (CDCl₃) δ ppm:

1.77 (3H, s), 1.87 - 2.00 (2H, m), 2.05 - 2.16 (2H, m),
2.95 - 3.05 (2H, m), 3.32 - 3.41 (2H, m), 4.02 (1H, d,
15 J = 10.2 Hz), 4.04 (1H, d, J = 10.2 Hz), 4.18 (1H, d, J
= 10.2 Hz), 4.36 - 4.45 (1H, m), 4.49 (1H, d, J = 10.2
Hz), 6.74 - 6.81 (2H, m), 6.87 - 6.94 (4H, m), 7.11 -
7.16 (2H, m), 7.55 (1H, s).

Example 142

20 Preparation of (R)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenyl)piperazin-1-yl]phoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole

4-[4-(4-Trifluoromethoxyphenyl)piperazin-1-yl]phenol (1.7 g, 5.02 mmol) was dissolved in DMF (20
25 ml). To the solution, sodium hydride (221 mg, 5.53 mmol) was added at room temperature, and the solution was stirred for 20 minutes at 80°C. To the solution, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-

nitroimidazole prepared in Example 12 (1.2 g, 5.53 mmol) was added with cooling on ice-bath, and the solution was stirred for further 20 minutes at 80°C. To the reaction mixture, ice-water was added, and the solution was stirred vigorously. The precipitates were filtered off, washed with water and dissolved in methylene chloride. The solution was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and then recrystallized from ethyl acetate to afford (R)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenyl)piperazin-1-yl]phenoxyethyl}-2,3-dihydroimidazo[2,1-b]oxazole (1.02 g, yield 39%) as a light yellow powder.

MS 519(M⁺)

Optical purity >99% e.e.

$[\alpha]_D^{28} = -18.02^\circ$ (concentration: 1.160, CHCl₃)

Melting point 262.5-265°C.

Example 143

Preparation of tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperidine-1-carboxylate

Tert-butyl 4-(4-hydroxyphenyl)piperidine-1-carboxylate (1.07 g, 3.86 mmol) was dissolved in DMF (10 ml). To the solution, sodium hydride (185 mg, 4.63 mmol) was added at room temperature, and the solution

was stirred for 20 minutes at 80°C. To the solution, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (923 mg, 4.24 mmol) was added with cooling on ice-bath, and the solution was stirred for further 20 minutes at 80°C. To the reaction mixture, ice-water was added, and the solution was stirred vigorously. The precipitates were filtered off, washed with water and dissolved in methylene chloride. The solution was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and then crystallized from ethyl acetate-diisopropyl ether to afford tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]piperidine-1-carboxylate (857 mg, yield 48%) as a white powder.

MS 458 (M⁺)

Optical purity >99% e.e.

$[\alpha]_D^{28} = -1.07^\circ$ (concentration: 1.028, CHCl₃)

Melting point 227.5-228.3°C (decomposition).

Using corresponding starting materials gave the compound of Example 144 in the same manner as in Example 143.

Example 144

Tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-

1,2,3,6-tetrahydropyridine-1-carboxylate

Melting point 183.0-189.0°C (decomposition).

Example 145

Preparation of tert-butyl (R)-4-[4-(2-methyl-6-nitro-
5 2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)benzoyl]-
piperazine-1-carboxylate

Tert-butyl 4-(4-hydroxybenzoyl)piperazine-1-
carboxylate (6.6 g, 21.5 mmol) was dissolved in DMF
(50 ml). To the solution, sodium hydride (991 mg,
10 24.8 mmol) was added at room temperature, and the
solution was stirred for 20 minutes at 80°C. To the
solution, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-
nitroimidazole prepared in Example 12 (5.16 mg,
23.7 mmol) was added with cooling on ice-bath, and the
15 solution was stirred for further 20 minutes at 80°C. To
the reaction mixture, ice-water was added, and the
solution was stirred vigorously. The precipitates were
filtered off, washed with water, dissolved in methylene
chloride. The organic phase was washed with a
20 saturated saline solution, dried over magnesium sulfate
and then filtered. The resulting filtrate was
concentrated under reduced pressure. The residue was
purified by silica gel column chromatography (methylene
chloride/methanol = 100/1) and then crystallized from
25 methylene chloride-diisopropyl ether to afford tert-
butyl (R)-4-[4-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-
ylmethoxy)benzoyl]piperazine-1-carboxylate (7.35 g,

yield 70%) as a white powder.

MS 488 (M+1)⁺

Melting point 222.5-224.0°C.

Example 146

- 5 Preparation of tert-butyl (R)-4-[2-chloro-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)-phenyl]piperazine-1-carboxylate

Tert-butyl 4-(2-chloro-4-hydroxyphenyl)-piperazine-1-carboxylate (2.7 g, 8.63 mmol) was
10 dissolved in DMF (20 ml). To the solution, sodium hydride (397 mg, 9.92 mmol) was added at room temperature, and the solution was stirred for 20 minutes at 80°C. To the solution, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12
15 (2.1 g, 9.50 mmol) was added with cooling on ice-bath, and the solution was stirred for further 20 minutes at 80°C. To the reaction mixture, ice-water was added, and the solution was stirred vigorously. The precipitates were filtered off, washed with water and dissolved in
20 methylene chloride. The solution was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene
25 chloride/methanol = 200/1) and then crystallized from methylene chloride-ethyl acetate to afford tert-butyl (R)-4-[2-chloro-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-

ylmethoxy)phenyl]piperazine-1-carboxylate (2.34 g, yield 55%) as a white powder.

MS 493(M⁺)

Melting point 207.0-209.5°C.

5 Example 147

Preparation of tert-butyl (R)-4-[3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperazine-1-carboxylate

Tert-butyl 4-(3-hydroxyphenyl)piperazine-1-carboxylate (3.23 g, 11.6 mmol) was dissolved in DMF (40 ml). To the solution, sodium hydride (557 mg, 13.9 mmol) was added at room temperature, and the solution was stirred for 20 minutes at 80°C. To the solution, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (2.78 g, 12.8 mmol) was added with cooling on ice-bath, and the solution was stirred for further 20 minutes at 80°C. To the reaction mixture, ice-water was added, and the solution was stirred vigorously. The precipitates were filtered off, washed with water and dissolved in methylene chloride. The solution was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and then crystallized from methylene chloride-ethyl acetate to afford tert-butyl (R)-4-[3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-

b]oxazol-2-ylmethoxy)phenyl]piperazine-1-carboxylate
(1.4 g, yield 26%) as a white powder.

MS 459(M⁺)

Melting point 179.5-182.0°C.

5 Example 148

Preparation of tert-butyl (R)-4-[4-(2-methyl-6-nitro-
2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-
piperazine-1-carboxylate

Tert-butyl 4-(4-hydroxyphenyl)piperazine-1-
10 carboxylate (13.5 g, 48.8 mmol) was dissolved in DMF
(100 ml). To the solution, sodium hydride (2.15 g,
53.7 mmol) was added at room temperature, and the
solution was stirred for 20 minutes at 70°C. To the
solution, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-
15 nitroimidazole prepared in Example 12 (10.6 g, 48.8
mmol) was added with cooling on ice-bath, and the
solution was stirred for further 20 minutes at 80°C. To
the reaction mixture, ice-water was added, and the
solution was stirred vigorously. The precipitates were
20 filtered off, washed with water and dissolved in
methylene chloride. The solution was washed with a
saturated saline solution, dried over magnesium sulfate
and then filtered. The resulting filtrate was
concentrated under reduced pressure. The residue was
25 purified by silica gel column chromatography (methylene
chloride/methanol = 100/1) and then crystallized from
methylene chloride-ethyl acetate to afford tert-butyl
(R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-

b]oxazol-2-ylmethoxy)phenyl]piperazine-1-carboxylate
(9.9 g, yield 44%) as a white powder.

Optical purity >99.5% e.e.

$[\alpha]_D^{28} = -10.85^\circ$ (concentration: 1.014, CHCl_3)

5 MS 459 (M^+)

Melting point 230-232°C

^1H -NMR (CDCl_3) δ ppm:

1.48 (9H, s), 1.76 (3H, s), 2.99 - 3.03 (4H, m), 3.54 -
3.59 (4H, m), 4.02 (1H, d, $J = 10.2$ Hz), 4.04 (1H, d, J
10 = 10.1 Hz), 4.18 (1H, d, $J = 10.1$ Hz), 4.49 (1H, d, $J =$
10.2 Hz), 6.76 - 6.81 (2H, m), 6.85 - 6.89 (2H, m),
7.58 (1H, s).

Example 149

Preparation of (R)-[4-(2-methyl-6-nitro-2,3-
15 dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-
piperazine dihydrochloride

Tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-
piperazine-1-carboxylate prepared in Example 148 (300
20 mg, 0.65 mmol) was dissolved in trifluoroacetic acid
(5 ml) followed by stirring at room temperature for 3
hours. The reaction mixture was concentrated under
reduced pressure, and the residue was dissolved in
methanol. To the solution, a saturated hydrogen
25 chloride (5 ml) in ethyl acetate was added, and the
precipitates were filtered off and dried under reduced
pressure to afford (R)-[4-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)-

phenyl]piperazine dihydrochloride (279 mg, yield 99%)
as a light yellow powder.

MS 359 (M^+)

Melting point 212-220°C (decomposition)

5 $^1\text{H-NMR}$ (DMSO-d_6) δ ppm:

1.67 (3H, s), 3.22 - 3.31 (8H, m), 4.18 (1H, d, $J =$
10.9 Hz), 4.23 (2H, s), 4.37 (1H, d, $J = 10.9$ Hz), 6.85
(2H, d, $J = 9.1$ Hz), 7.00 (2H, d, $J = 9.1$ Hz), 8.16
(1H, s), 9.37 (3H, br).

10 Example 150

Preparation of (R)-2-methyl-6-nitro-2-{4-[4-(4-
trifluoromethylbenzyl)piperazin-1-yl]phenoxymethyl}-
2,3-dihydroimidazo[2,1-b]oxazole

A mixture of tert-butyl (R)-4-[4-(2-methyl-6-
15 nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)-
phenyl]piperazine-1-carboxylate prepared in Example 148
(800 mg, 1.74 mmol) and trifluoroacetic acid (3 ml) was
stirred at room temperature for 7 hours. The reaction
mixture was concentrated under reduced pressure, and
20 the residue was dissolved in methylene chloride
(10 ml). To the solution, triethylamine (3 ml, 21.52
mmol) was added followed by stirring at room
temperature for 5 minutes. The mixture was
concentrated under reduced pressure, and the residue
25 was dissolved in methanol (10 ml). To the solution, 4-
trifluoromethylbenzaldehyde (910 mg, 5.23 mmol), sodium
cyanotrihydroborate (328 mg, 5.23 mmol) and acetic acid
(0.33 ml, 5.23 mmol) were added followed by stirring at

room temperature overnight. To the reaction mixture, a saturated sodium hydrogencarbonate solution and methylene chloride were added, and the solution was stirred and then extracted with methylene chloride.

- 5 The organic phase was dried over magnesium sulfate and filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) to afford (R)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethylbenzyl)piperazin-1-yl]phenoxyethyl}-2,3-dihydroimidazo[2,1-b]oxazole (667 mg, yield 74%) as a light yellow powder. Melting point 205.5-207°C.

Example 151

- 15 Preparation of ethyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperazine-1-carboxylate

- Tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperazine-1-carboxylate prepared in Example 148 (300 mg, 0.65 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure and then added methylene chloride (5 ml), triethylamine (2 ml) and ethyl chloroformate (0.11 ml, 1.31 mmol) followed by stirring at room temperature for 1 hour. The reaction mixture was

poured into water and extracted with methylene chloride. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was
5 concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford ethyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-
10 2-ylmethoxy)phenyl]piperazine-1-carboxylate (182 mg, yield 65%) as a white powder.

$[\alpha]_D^{28} = -9.86^\circ$ (concentration: 1.014, CHCl_3).

MS 431 (M^+)

Melting point 210.5-212.0°C.

15 Example 152

Preparation of 4-chlorobenzyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)-phenyl]piperazine-1-carboxylate

 Tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-
20 dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperazine-1-carboxylate prepared in Example 148 (300 mg, 0.65 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 3
25 hours. The reaction mixture was concentrated under reduced pressure and then added methylene chloride (2 ml) and triethylamine (2 ml). After stirring at room temperature for 5 minutes, the solution was

concentrated under reduced pressure, and the residue was dissolved in DMF (15 ml). To the solution, a mixture of 4-chlorobenzyl alcohol (186 mg, 1.31 mmol), 1,1'-carbonyldiimidazole (212 mg, 1.31 mmol) in DMF (5 ml) stirred at room temperature for 3 hours was added followed by stirring at room temperature overnight. The reaction mixture was poured into water, extracted from ethyl acetate, and the organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford 4-chlorobenzyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]piperazine-1-carboxylate (313 mg, yield 91%) as a light yellow powder.

$[\alpha]_D^{28} = -10.84^\circ$ (concentration: 1.006, CHCl_3)

MS 527 (M^+)

Melting point 184.5-187.5°C.

Using corresponding starting materials gave the compound of Example 153 in the same manner as in Example 152.

Example 153

5-Chlorobenzofuran-2-ylmethyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)-phenyl]piperazine-1-carboxylate

Yield 79%, melting point 195-197°C.

Using tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperidine-1-carboxylate prepared in Example 143, tert-
5 butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo-
[2,1-b]oxazol-2-ylmethoxy)phenyl]-1,2,3,6-tetrahydro-
pyridine-1-carboxylate prepared in Example 144, tert-
butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo-
[2,1-b]oxazol-2-ylmethoxy)benzoyl]piperazine-1-
10 carboxylate prepared in Example 145, or tert-butyl (R)-
4-[3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-
2-ylmethoxy)phenyl]piperazine-1-carboxylate prepared in
Example 147 gave compounds of Examples 154 to 158 in
the same manner as in Example 152.

15 Example 154

4-Trifluoromethoxybenzyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperidine-1-carboxylate

Yield 54%, melting point 202.5-204°C.

20 Example 155

4-Trifluoromethoxybenzyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-1,2,3,6-tetrahydropyridine-1-carboxylate

Yield 67%, melting point 174.3-174.8°C.

25 Example 156

4-Trifluoromethoxybenzyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)benzoyl]-piperazine-1-carboxylate

Yield 86%, melting point 168.5-172°C.

Example 157

Ethyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo-
[2,1-b]oxazol-2-ylmethoxy)benzoyl]piperazine-1-

5 carboxylate

Yield 85%, melting point 132-135°C.

Example 158

4-Trifluoromethoxybenzyl (R)-4-[3-(2-methyl-6-nitro-
2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-

10 piperazine-1-carboxylate

Yield 50%, melting point 136.5-138°C.

Example 159

Preparation of (R)-2-methyl-6-nitro-2-{4-[4-(4-
trifluoromethoxybenzyl)piperazin-1-yl]phenoxymethyl}-

15 2,3-dihydroimidazo[2,1-b]oxazole

Tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-
piperazine-1-carboxylate prepared in Example 148 (4.22
g, 9.60 mmol) was dissolved in methylene chloride (10

20 ml). To the solution, trifluoroacetic acid (30 ml) was
added followed by stirring at room temperature for 5
hours. The reaction mixture was concentrated under
reduced pressure and added methylene chloride (10 ml)
and triethylamine (10 ml). The solution was stirred at
25 room temperature for 5 minutes and then concentrated
under reduced pressure. The residue was dissolved in
dichloroethane. To the solution, 4-
trifluoromethoxybenzaldehyde (1.64 ml, 11.5 mmol) and

sodium triacetoxyborohydride (3.05 g, 14.4 mmol) were added with cooling on ice-bath followed by stirring at room temperature overnight. To the reaction mixture, a saturated sodium hydrogencarbonate solution and

5 methylene chloride were added, and the solution was stirred and extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by

10 silica gel column chromatography (methylene chloride/methanol = 200/1) and then crystallized from methylene chloride-ethyl acetate to afford (R)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxybenzyl)piperazin-1-yl]phenoxyethyl}-

15 2,3-dihydroimidazo[2,1-b]oxazole (3.23 g, yield 63%) as a light yellow powder.

Optical purity >99.5% e.e.

$[\alpha]_D^{28} = -8.25^\circ$ (concentration: 1.018, CHCl_3)

MS 533 (M^+)

20 Melting point 213.5-217°C.

The compound of Example 159 was prepared also with the following Example 160.

Example 160

Preparation of (R)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxybenzyl)piperazin-1-yl]phenoxyethyl}-

25 2,3-dihydroimidazo[2,1-b]oxazole

4-[4-(4-Trifluoromethoxybenzyl)piperazin-1-yl]phenol (3.36 g, 9.54 mmol) was dissolved in of DMF

(20 ml). To the solution, sodium hydride (420 mg, 10.5 mmol) was added at room temperature, and the solution was stirred for 15 minutes at 80°C. To the reaction mixture, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (2.18 g, 10.0 mmol) was added with cooling on ice-bath followed by stirring for further 15 minutes at 80°C. To the reaction mixture, ice-water was added, and the solution was stirred vigorously. The precipitates were filtered off, washed with water and dissolved in methylene chloride. The solution was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and then crystallized from methylene chloride-ethyl acetate to afford (R)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxybenzyl)piperazin-1-yl]phenoxyethyl}-2,3-dihydroimidazo[2,1-b]oxazole (2.0 g, yield 40%) as a light yellow powder.

Using tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperidine-1-carboxylate prepared in Example 143, gave tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-1,2,3,6-tetrahydropyridine-1-carboxylate prepared in Example 144, or tert-butyl (R)-4-[4-(2-methyl-6-nitro-

2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)benzoyl]-piperazine-1-carboxylate prepared in Example 145 gave compounds of Examples 161-163 in the same manner as in Example 159.

5 Example 161

(R)-2-Methyl-6-nitro-2-{4-[1-(4-trifluoromethoxybenzyl)piperidin-4-yl]phenoxy-methyl}-2,3-dihydroimidazo[2,1-b]oxazole
Yield 45%, melting point 186-188°C.

10 Example 162

(R)-2-Methyl-6-nitro-2-{4-[1-(4-trifluoromethoxybenzyl)-1,2,3,6-tetrahydropyridin-4-yl]phenoxy-methyl}-2,3-dihydroimidazo[2,1-b]oxazole
Yield 61%, melting point 168-174°C.

15 Example 163

(R)-4-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)benzoyl]-1-(4-trifluoromethoxybenzyl)piperazine
Yield 83%, melting point 155-156°C.

20 Example 164

Preparation of (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperazin-1-carboxylic acid 4-trifluoromethoxybenzylamide

25 Tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperazine-1-carboxylate prepared in Example 148 (120 mg, 0.26 mmol) was dissolved in methylene chloride (5

ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure, then added methylene chloride (2 ml) and triethylamine (2 ml). The solution was stirred at room temperature for 5 minutes and then concentrated under reduced pressure. The residue was dissolved in DMF (10 ml). To the solution, a mixture of 4-trifluoromethoxybenzylamine (125 mg, 0.65 mmol) and 1,1'-carbonyldiimidazole (110 mg, 0.68 mmol) in DMF (5 ml) stirred at room temperature for 3 hours was added followed by stirring at room temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]piperazine-1-carboxylic acid 4-trifluoromethoxybenzylamide (48 mg, yield 32%) as a white powder.

MS 558 (M-18)⁺

Melting point 166.5-168.5°C.

Example 165

Preparation of (R)-2-methyl-6-nitro-2-(4-[4-(4-trifluoromethoxybenzoyl)piperazin-1-yl]phenoxy)methyl}-2,3-dihydroimidazo[2,1-b]oxazole

Tert-butyl (R)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)phenyl]-piperazine-1-carboxylate prepared in Example 148 (300 mg, 0.65 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure and added methylene chloride (10 ml), triethylamine (2 ml) and 4-trifluoromethoxybenzoyl chloride (0.15 ml, 0.98 mmol). The reaction mixture was stirred at room temperature for 1 hour, then poured into water, and extracted with methylene chloride. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and crystallized from methylene chloride-diisopropyl ether to afford (R)-2-methyl-6-nitro-2-(4-[4-(4-trifluoromethoxybenzoyl)piperazin-1-yl]phenoxy)methyl}-2,3-dihydroimidazo[2,1-b]oxazole (263 mg, yield 74%) as a white powder.

MS 547 (M^+)

Melting point 201.5-203.2°C.

Example 166

Preparation of (R)-2-methyl-6-nitro-2-[4-(1-oxothiomorpholin-4-yl)phenoxyethyl]-2,3-dihydroimidazo[2,1-b]oxazole

- 5 (R)-2-Methyl-6-nitro-2-[4-(thiomorpholin-4-yl)phenoxyethyl]-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 137 (85 mg, 0.23 mmol) was dissolved in methylene chloride (5 ml). To the solution, m-chloroperbenzoic acid (59 mg, 0.24 mmol)
- 10 was added followed by stirring at room temperature for 20 minutes. The reaction mixture was diluted with methylene chloride. The solution was washed with a sodium thiosulfate solution, a saturated sodium hydrogencarbonate solution and a saturated saline
- 15 solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was crystallized from methylene chloride-isopropyl ether to afford (R)-2-methyl-6-nitro-2-[4-(1-oxothiomorpholin-4-
- 20 yl)phenoxyethyl]-2,3-dihydroimidazo[2,1-b]oxazole (59 mg, yield 67%) as a white powder.

MS 392 (M^+)

Melting point 198-200°C.

Example 167

- 25 Preparation of N-methyl-N-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-2-(4-trifluoromethoxyphenoxy)ethylamine

A mixture of 2-chloro-1-(2-methyloxiran-2-

ylmethyl)-4-nitroimidazole prepared in Example 6 (84 mg, 0.39 mmol), N-methyl-2-(4-trifluoromethoxyphenoxy)ethylamine (100 mg, 0.43 mmol) and DMF (1 ml) was stirred at 65-70°C for 8 hours. The reaction mixture was allowed to return to room temperature, poured into water and extracted with ethyl acetate. The organic phase was washed with a saturated saline solution 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/ethyl acetate = 20/1) to afford a yellow oil.

The yellow oil was dissolved in DMF (1 ml). To the solution, sodium hydride (11 mg, 0.28 mmol) was added followed by stirring at room temperature for 1 hour. To the reaction mixture, ice-water was added, and the solution was extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and crystallized from methylene chloride-diisopropyl ether to afford N-methyl-N-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-2-(4-trifluoromethoxyphenoxy)ethylamine (34 mg, yield 21%) as a white powder.

Melting point 86.4-89.2°C.

Example 168

Preparation of tert-butyl N-methyl-N-{2-[N-methyl-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)amino]ethyl}carbamate

5 A mixture of 2-chloro-4-nitro-1H-imidazole (5.97 g, 27.43 mmol), tert-butyl N-methyl-{2-[N-methyl-(2-methyloxiran-2-ylmethyl)amino]ethyl}carbamate (10.53 g, 40.76 mmol), triethylamine (0.76 ml, 5.49 mmol) and 1-propanol (60 ml) was stirred under reflux for 5
10 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, water was added, and the solution was extracted with methylene chloride. The organic phase was washed with a saturated saline
15 solution 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/methanol = 20/1) to afford a yellow oil.

20 The yellow oil was dissolved in 1,4-dioxane (200 ml). To the solution, sodium hydride (500 mg, 12.5 mmol) was added followed by stirring under reflux overnight. The reaction mixture was allowed to return to room temperature and concentrated under reduced
25 pressure. To the residue, ice-water was added, and the solution was extracted with methylene chloride. The organic phase was washed with a saturated saline solution, dried over sodium sulfate and then filtered.

The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to afford tert-butyl N-methyl-N-(2-[N-methyl-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)amino]ethyl)carbamate (1.94 g, yield 13%) as a white powder.

¹H-NMR (CDCl₃) δppm:

1.45 (9H, s), 1.58 (3H, s), 2.38 (3H, s), 2.57 - 2.69 (3H, m), 2.79 (3H, s), 2.89 (1H, d, J = 14.9 Hz), 3.15 - 3.25 (2H, bm), 3.85 (1H, d, J = 14.9 Hz), 4.33 (1H, br), 7.52 (1H, s).

Example 169

Preparation of (S)-N-methyl-N-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-2-[4-[4-(trifluoromethyl)phenyl]piperazin-1-yl]ethylamine

(R)-2-Chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (523 mg, 2.41 mmol) and N-methyl-2-[4-(4-trifluoromethylphenyl)-piperazin-1-yl]ethylamine (900 mg, 3.13 mmol) were added to DMF (15 ml) followed by stirring at 70-80°C for 5 hours. The reaction mixture was allowed to return to room temperature, poured into water and extracted with ethyl acetate. The organic phase was washed with a saturated saline solution 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/ethyl acetate = 20/1) to afford a yellow oil.

The yellow oil was dissolved in DMF (15 ml). To the solution, sodium hydride (115 mg, 2.89 mmol) was added followed by stirring at room temperature for 1
5 hour. To the reaction mixture, ice-water was added, and the solution was extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated
10 under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and crystallized from methylene chloride-diisopropyl ether to afford (S)-N-methyl-N-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
15 b]oxazol-2-ylmethyl)-2-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)ethylamine (173 mg, yield 15%) as a white powder.

MS 468 (M⁺)

Melting point 148.0-150.5°C.

20 Using corresponding starting materials gave compounds of Examples 170 to 177 in the same manner as in Example 169.

Example 170

(S)-N-Methyl-N-(2-methyl-6-nitro-2,3-dihydroimidazo-
25 [2,1-b]oxazol-2-ylmethyl)-2-(4-trifluoromethyl-phenoxy)ethylamine

White powder, yield 12%

MS 399 (M-H)⁺

Melting point 123.0-126.0°C.

Example 171

(S)-N-Methyl-N-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-2-(4-
5 trifluoromethoxyphenoxy)ethylamine

White powder, yield 45%

MS 416(M⁺)

Melting point 112.5-115.0°C.

Example 172

10 (S)-N,N'-Dimethyl-N-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-N'-(4-
trifluoromethylphenyl)-1,2-ethylenediamine

White powder, yield 24%

MS 413(M⁺)

15 Melting point 135.5-137.5°C.

Example 173

Tert-butyl (S)-4-[2-(N-methyl-2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethylamino)ethyl]-
piperazine-1-carboxylate

20 White powder, yield 30%

MS 425(M+H)⁺

Melting point 149.5-151.8°C.

Example 174

(S)-N-Benzyl-N-[2-(4-trifluoromethoxyphenoxy)ethyl]-2-
25 methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-
ylmethylamine

White powder, yield 25%

Melting point 96.5-97°C.

Example 175

(S)-N-Methyl-N-[3-(4-trifluoromethoxyphenoxy)propyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethanamine

5 White powder, yield 50%

Melting point 92-95°C.

Example 176

(S)-N-Methyl-N-[2-(4-chlorophenoxy)ethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethanamine

10 White powder, yield 27%

Melting point 130.5-132°C.

Example 177

(S)-N-Methyl-N-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-2-[4-(4-trifluoromethylphenoxy)piperidin-1-yl]ethanamine

15 Light brown powder, yield 26%

¹H-NMR (CDCl₃) δppm:

1.58 (3H, s), 1.70 - 1.85 (2H, m), 1.98 (2H, br), 2.37 (3H, s), 2.25 - 2.50 (4H, m), 2.50 - 2.80 (5H, m), 2.90 (1H, d, J = 14.9 Hz), 3.85 (1H, d, J = 9.5 Hz), 4.37 (1H, m), 4.52 (1H, d, J = 14.9 Hz), 7.42 (2H, d, J = 8.7 Hz), 7.52 (1H, s), 7.53 (2H, d, J = 8.7 Hz).

Example 178

Preparation of N-(2-ethoxycarbonylphenyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethanamine

25 A mixture of 2-chloro-4-nitro-1H-imidazole (891 mg, 6.04 mmol), 1-(2-methyloxiran-2-ylmethyl)-1H-benzo[d][1,3]oxazin-2,4-dione (1.41 g, 6.04 mmol),

sodium acetate (545 mg, 6.64 mmol) and ethanol (10 ml) was stirred under reflux for 10 hours. The reaction mixture was allowed to return to room temperature, and concentrated under reduced pressure. To the residue, 5 water was added, and the solution was extracted with methylene chloride. The organic phase was washed with a saturated saline solution and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the residue 10 was dissolved in 1,4-dioxane (20 ml). To the solution, sodium hydride (219 mg, 5.48 mmol) was added followed by stirring under reflux for 5 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, 15 ice-water was added, and the precipitates were filtered off, which were purified by silica gel column chromatography (methylene chloride/ethyl acetate = 20/1) to afford N-(2-ethoxycarbonylphenyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethylamine 20 (1.15 g, yield 55%) as a white powder. Melting point 162.5-163.2°C.

Example 179

Preparation of (S)-1-[2-hydroxy-3-(N-methyl-benzyl-amino)-2-methylpropyl]-2-chloro-4-nitroimidazole

25 A mixture of (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (500 mg, 2.3 mmol), N-methylbenzylamine (334 mg, 2.76 mmol) and DMF (2.5 ml) was stirred at 60°C for 9 hours.

The reaction mixture was allowed to return to room temperature and added water followed by extraction with ethyl acetate twice. The organic phases were combined, washed with water three times, 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/ethyl acetate = 1/1) to afford (S)-1-[2-hydroxy-3-(N-methyl-N-benzylamino)-2-methylpropyl]-2-chloro-4-nitroimidazole (712 mg, yield 91%) as a yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.13 (3H, s), 2.37 - 2.57 (5H, m), 3.51 (1H, d, J = 12.9 Hz), 3.72 (1H, d, J = 12.9 Hz), 3.85 (2H, s), 7.16 - 7.39 (5H, m), 7.87 (1H, s).

Using corresponding starting materials gave compounds of Examples 180 to 187 in the same manner as in Example 179.

Example 180

(S)-1-{2-Hydroxy-3-[N-methyl-(3-chlorobenzyl)]amino-2-methyl}propyl-2-chloro-4-nitroimidazole

Yield 98%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.15 (3H, s), 2.35 - 2.57 (5H, m), 3.53 (1H, d, J = 13.3 Hz), 3.67 (1H, d, J = 13.3 Hz), 3.92 (2H, s), 7.10 - 7.31 (4H, m), 7.95 (1H, s).

Example 181

(S)-1-{2-Hydroxy-3-(N-methyl-4-chlorobenzylamino)-2-

methylpropyl]-2-chloro-4-nitroimidazole

Yield 86%

¹H-NMR (CDCl₃) δppm:

1.13 (3H, s), 2.33 - 2.59 (5H, m), 3.53 (1H, d, J =
5 13.2 Hz), 3.68 (1H, d, J = 13.2 Hz), 3.92 (2H, s), 7.19
(2H, d, J = 8.4 Hz), 7.31 (2H, d, J = 8.4 Hz), 7.96
(1H, s).

Example 182

(S)-1-[2-Hydroxy-3-(N-methyl-4-trifluoromethoxybenzyl-
10 amino)-2-methylpropyl]-2-chloro-4-nitroimidazole

Yield 98%

¹H-NMR (CDCl₃) δppm:

1.13 (3H, s), 2.37 (3H, s), 2.47 (1H, d, J = 13.9 Hz),
2.58 (1H, d, J = 13.9 Hz), 3.58 (1H, d, J = 13.3 Hz),
15 3.72 (1H, d, J = 13.3 Hz), 3.94 (2H, s), 7.19 (2H, d, J
= 8.6 Hz), 7.31 (2H, d, J = 8.6 Hz), 7.99 (1H, s).

Example 183

(S)-1-[2-Hydroxy-3-(N-methyl-4-trifluoromethylbenzyl-
amino)-2-methylpropyl]-2-chloro-4-nitroimidazole

20 Yield 100%

¹H-NMR (CDCl₃) δppm:

1.15 (3H, s), 2.38 (3H, s), 2.50 (1H, d, J = 13.9 Hz),
2.60 (1H, d, J = 13.9 Hz), 3.65 (1H, d, J = 13.6 Hz),
3.79 (1H, d, J = 13.6 Hz), 3.97 (2H, s), 7.41 (2H, d, J
25 = 8.2 Hz), 7.61 (2H, d, J = 8.2 Hz), 8.00 (1H, s).

Example 184

(S)-1-[2-Hydroxy-3-(N-methyl-4-methoxybenzylamino)-2-

methylpropyl]-2-chloro-4-nitroimidazole

Yield 85%

¹H-NMR (CDCl₃) δppm:

1.12 (3H, s), 2.36 - 2.50 (5H, m), 3.45 (1H, d, J =
5 12.8 Hz), 3.64 (1H, d, J = 12.8 Hz), 3.80 (3H, s), 3.84
(2H, s), 6.84 (2H, dd, J = 1.9 Hz, 8.6 Hz), 7.13 (2H,
dd, J = 1.9 Hz, 8.6 Hz), 7.89 (1H, s).

Example 185

(S)-1-[2-Hydroxy-3-(N-methyl-4-dimethylaminobenzyl-
10 amino)-2-methylpropyl]-2-chloro-4-nitroimidazole

Yield 94%

¹H-NMR (CDCl₃) δppm:

1.11 (3H, s), 2.34 - 2.47 (5H, m), 2.93 (s, 6H), 3.39
(1H, d, J = 12.8 Hz), 3.60 (1H, d, J = 12.8 Hz), 3.81
15 (2H, s), 6.65 (2H, d, J = 8.7 Hz), 7.03 (2H, d, J = 8.7
Hz), 7.87 (1H, s).

Example 186

(S)-1-[2-Hydroxy-3-(N-methyl-phenylamino)-2-
methylpropyl]-2-chloro-4-nitroimidazole

20 Yield 92%

¹H-NMR (CDCl₃) δppm:

1.24 (3H, s), 3.06 (3H, s), 3.40 (2H, s), 4.05 (1H, d,
J = 14.2 Hz), 4.13 (1H, d, J = 14.2 Hz), 6.74 - 6.89
(3H, m), 7.17 - 7.34 (2H, m), 8.04 (1H, s).

25

Example 187

(S)-1-[2-Hydroxy-3-(N-methyl-4-chlorophenylamino)-2-
methylpropyl]-2-chloro-4-nitroimidazole

Yield 92%

¹H-NMR (CDCl₃) δppm:

1.24 (3H, s), 3.04 (3H, s), 3.38 (2H, s), 4.08 (2H, s),
6.74 (2H, dd, J = 2.1 Hz, 7.2 Hz), 7.19 (2H, dd, J =
2.1 Hz, 7.2 Hz), 8.02 (1H, s).

5 Example 188

Preparation of (S)-2-(N-benzyl-N-methyl)aminomethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

To a mixture of (S)-1-[2-hydroxy-3-(N-methyl-benzylamino)-2-methylpropyl]-2-chloro-4-nitroimidazole
10 prepared in Example 179 (710 mg, 2.1 mmol) and DMF (2.1 ml), sodium hydride (101 mg, 2.51 mmol) was added followed by stirring for 2 hours with cooling on ice-bath. To the reaction mixture, ethylacetate (0.7 ml) and water (5 ml) were added in this order. The
15 precipitates were filtered off and dissolved in isopropyl alcohol (10 ml) with stirring under reflux. To the solution, activated carbon(28 mg) was added followed by stirring under reflux for 20 minutes. After filtration, isopropyl ether (3 ml) was added to
20 the solution, and the mixture was allowed to stand. The precipitates were collected to afford (S)-2-(N-benzyl-N-methyl)aminomethyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (248 mg, yield 39%) as a yellow powder.

25 Melting point 132.5-133°C.

Using corresponding starting materials gave compounds of Examples 189 to 196 in the same manner as in Example 188.

Example 189

(S)-2-[N-(4-Chlorobenzyl)-N-methylamino]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Yield 44%, melting point 129-129.5°C.

5 Example 190

(S)-2-[N-(3-Chlorobenzyl)-N-methylamino]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Yield 65%, melting point 177.5-178.5°C.

Example 191

10 (S)-2-[N-(4-Trifluoromethoxybenzyl)-N-methylamino]-methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Yield 53%, melting point 145-146°C.

Example 192

15 (S)-2-[N-(4-Trifluoromethylbenzyl)-N-methylamino]-methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Yield 49%, melting point 130-132°C.

Example 193

20 (S)-2-[N-(4-Methoxybenzyl)-N-methylamino]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Yield 59%, melting point 144-147°C.

Example 194

(S)-2-[N-(4-Dimethylaminobenzyl)-N-methylamino]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
25 Yield 47%, melting point 168-169°C.

Example 195

(S)-2-(N-Phenyl-N-methylamino)methyl-2-methyl-6-nitro-

2,3-dihydroimidazo[2,1-b]oxazole

Yield 55%, melting point 147-148°C.

Example 196

(S)-2-[N-(4-Chlorophenyl)-N-methylamino]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Yield 34%, melting point 174-175°C.

Example 197

Preparation of 4-trifluoromethylbenzyl (S)-4-[2-(N-methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethylamino)ethyl]piperazine-1-carboxylate

Tert-butyl (S)-4-[2-(N-methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethylamino)-ethyl]piperazine-1-carboxylate prepared in Example 173 (300 mg, 0.71 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure and added methylene chloride (2 ml) and triethylamine (2 ml). After stirring for 5 minutes at room temperature, the solution was concentrated under reduced pressure. The residue was dissolved in DMF (15 ml). To the solution, a mixture of 4-trifluoromethylbenzyl alcohol (373 mg, 2.12 mmol) and 1,1'-carbonyldiimidazole (344 mg, 2.12 mmol) in DMF (5 ml) stirred at room temperature for 3 hours was added followed by stirring at room temperature for 1 hour. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was

washed with a saturated saline solution and dried over magnesium sulfate. After filtration, the resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column

- 5 chromatography (methylene chloride/methanol = 50/1) and crystallized from methylene chloride-isopropyl ether to afford 4-trifluoromethylbenzyl (S)-4-[2-(N-methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethylamino)ethyl]piperazine-1-carboxylate (196 mg, 10 yield 53%) as a white powder.

MS 509(M-H₂O)⁺

Melting point 77.2-76.9°C.

Example 198

- Preparation of (S)-N-methyl-N-(2-methyl-6-nitro-2,3-
15 dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-2-[4-(4-trifluoromethylbenzyl)piperazin-1-yl]ethylamine

- Tert-butyl (S)-4-[2-(N-methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethylamino)-ethyl]piperazine-1-carboxylate prepared in Example 173
20 (400 mg, 0.94 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure and added methylene chloride (2 ml)
25 and triethylamine (2 ml). After stirring for 5 minutes at room temperature, the solution was concentrated under reduced pressure. The residue was dissolved in methanol (10 ml). To the solution, 4-(trifluoro-

methyl)benzaldehyde (0.4 ml, 2.83 mmol), sodium cyanotrihydroborate (178 mg, 2.83 mmol) and acetic acid (0.2 ml) were added followed by stirring at room temperature for 30 minutes. To the solution, a saturated sodium hydrogencarbonate solution and methylene chloride were added followed by stirring, and the mixture was extracted with methylene chloride. The organic phase was dried over magnesium sulfate. After filtration, the resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford (S)-N-methyl-N-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-2-[4-(4-trifluoromethylbenzyl)piperazin-1-yl]ethylamine (307 mg, yield 68%) as a white powder.

MS 482 (M⁺)

Melting point 102.0-104.5°C.

20 Example 199

Preparation of ethyl (6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate

2,4-Dinitro-1H-imidazole (0.678 g, 3.92 mmol) and phenyl oxiran-2-ylmethylcarbamate (1.04 g, 5.87 mmol) were dissolved in ethanol (20 ml). To the solution, sodium acetate (0.386 g, 4.70 mmol) was added followed by stirring under reflux overnight. To the reaction mixture, a saturated sodium hydrogencarbonate

solution and methylene chloride were added, and the solution was extracted with methylene chloride. The organic phase was dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) and treated with diisopropyl ether to afford ethyl (6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate (0.116 g, yield 11.6%) as a light brown solid.

¹H-NMR (DMSO-d₆) δppm:

1.15 (3H, t, J = 7.1 Hz), 3.41 - 3.51 (2H, m), 3.93 - 4.11 (3H, m), 4.38 (1H, dd, J = 8.6 Hz, 10.7 Hz), 5.31 - 5.47 (1H, m), 7.52 (1H, br), 8.13 (1H, s).

Example 200

Preparation of benzyl (2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate

2,4-Dinitro-1H-imidazole (3 g, 19 mmol) and benzyl (2-methyloxiran-2-ylmethyl)carbamate (4.31 g, 19 mmol) were dissolved in ethanol (20 ml). To the solution, sodium acetate (1.56 g, 19.0 mmol) was added followed by stirring at 70°C overnight. To the reaction mixture, a saturated sodium hydrogencarbonate solution and methylene chloride were added, and the solution was extracted with methylene chloride. The organic phase was dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column

chromatography (n-hexane/ethyl acetate = 1/1, methylene chloride/methanol = 50/1) and recrystallized from ethyl acetate-methylene chloride to afford benzyl (2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate (0.298 g, yield 4.7%) as a colorless solid.

Melting point 171.3-172.2°C

¹H-NMR (DMSO-d₆) δppm:

1.55 (3H, s), 3.46 (2H, d, J = 6.3 Hz), 4.06 (1H, d, J = 11.0 Hz), 4.25 (1H, d, J = 11.0 Hz), 5.03 (2H, s), 7.19 - 7.41 (5H, m), 7.76 (1H, t, J = 6.3 Hz), 8.13 (1H, s).

Example 201

Preparation of 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethylamine trifluoroacetate

A mixture of benzyl (2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate prepared in Example 200 (190 mg, 0.57 mmol), trifluoroacetic acid (4 ml) and methylene chloride (5 ml) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure. To the residue was treated with diethyl ether to afford 2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethylamine trifluoroacetate (120 mg, yield 67%) as a light yellow powder.

¹H-NMR (DMSO-d₆) δppm:

1.35 (3H, s), 3.23 (1H, d, J = 9.6 Hz), 3.49 (1H, d, J = 9.6 Hz), 3.82 - 3.98 (2H, m), 7.98 (1H, s), 12.22

(1H, s).

Using corresponding starting materials gave compounds of Examples 202 to 204 in the same manner as in Example 200.

5 Example 202

Benzyl N-methyl-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)carbamate

Yield 14%, melting point 150.3-151.6°C.

 Example 203

10 Benzyl (6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate

Yield 11%

¹H-NMR (DMSO-d₆) δppm:

3.45 - 3.59 (2H, m), 4.07 (1H, dd, J = 6.6 Hz, 10.8
15 Hz), 4.39 (1H, dd, J = 8.6 Hz, 10.8 Hz), 5.04 (2H, s),
5.32 - 5.50 (1H, m), 7.23 - 7.41 (5H, m), 7.71 (1H,
br), 8.13 (1H, s).

 Example 204

20 Tert-butyl (6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate

Yield 27%

¹H-NMR (CDCl₃) δppm:

1.43 (9H, s), 3.65 (2H, dd, J = 4.3 Hz, 6.2 Hz), 4.20
(1H, dd, 7.0 Hz, 10.5 Hz), 4.36 (1H, dd, J = 8.6 Hz,
25 10.5 Hz), 5.20 (1H, t, J = 6.2 Hz), 5.35 - 5.48 (1H,
m), 7.56 (1H, s).

 Example 205

Preparation of 4-chlorobenzyl (2-methyl-6-nitro-2,3-

dihydroimidazo[2,1-b]oxazol-2-ylmethyl) carbamate

2,4-Dinitro-1H-imidazole (0.518 g, 3.28 mmol)
and 4-chlorobenzyl (2-methyloxiran-2-ylmethyl) carbamate
(2.097 g, 8.20 mmol) and sodium acetate (0.538 g, 6.56
5 mmol) in ethanol (6 ml) was stirred under reflux for 1
hour. To the solution, water was added and the
precipitates were filtered off. The resulting solid
was treated with diethyl ether to afford 4-chlorobenzyl
(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-
10 ylmethyl) carbamate (0.197 g, yield 16%) as a colorless
solid.

Melting point 221.0-221.8°C.

Using benzyl N-methyl-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethyl) carbamate
15 prepared in Example 202 gave the compound of Example
206 in the same manner as in Example 201.

Example 206

N-Methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
b]oxazol-2-ylmethylaniline trifluoroacetate
20 Melting point 176.2-178.8°C.

Using corresponding starting materials gave
compounds of Examples 207 to 211 in the same manner as
in Example 205.

Example 207

25 4-Fluorobenzyl (2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethyl) carbamate
Yield 25%, melting point 200.4-202.1°C.

Example 208

Ethyl (2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate

Yield 26%, melting point 182.5-183.4°C.

Example 209

5 4-Trifluoromethoxybenzyl (2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate

Yield 17%, melting point 182.3-184.4°C.

Example 210

4-Chlorobenzyl (6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate

Yield 17%, melting point 182.6-182.9°C.

Example 211

4-Fluorobenzyl (6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate

15 Yield 17%, melting point 164.6-165.1°C.

Example 212

Preparation of 4-fluorobenzyl [3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-N-methylcarbamate

20 2-Chloro-4-nitro-1H-imidazole (0.953 g, 6.46 mmol) and 4-fluorobenzyl N-methyl-(2-methyloxiran-2-ylmethyl)carbamate (1.964 g, 7.75 mmol) were dissolved in ethanol (20 ml). To the solution, sodium acetate (0.583 g, 7.11 mmol) was added followed by stirring

25 under reflux overnight. The reaction mixture was concentrated under reduced pressure. To the residue, ethyl acetate and water were added, and the solution was extracted with ethyl acetate. The organic phase

was dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/1) to afford
5 4-fluorobenzyl [3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-N-methylcarbamate (1.683 g, yield 65%) as a colorless oil.

¹H-NMR (CDCl₃) δppm:

1.17 (3H, s), 3.06 (3H, s), 3.25 (1H, d, J = 14.7 Hz),
10 3.51 (1H, d, J = 14.7 Hz), 4.00 (2H, s), 5.12 (2H, s), 6.95 - 7.09 (2H, m), 7.27 - 7.41 (2H, m), 8.07 (1H, s).

Using 4-fluorobenzyl N-methyl-(oxiran-2-yl-methyl)carbamate gave the compound of Example 213 in the same manner as in Example 212.

15 Example 213

4-Fluorobenzyl [3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]-N-methylcarbamate

Yield 51%

¹H-NMR (CDCl₃) δppm:

20 3.04 (3H, s), 3.27 - 3.55 (2H, m), 3.73 - 4.23 (4H, m), 5.11 (2H, s), 7.00 - 7.14 (2H, m), 7.27 - 7.41 (2H, m), 7.96 (1H, s).

Example 214

Preparation of 4-fluorobenzyl N-methyl-(2-methyl-6-
25 nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate

4-Fluorobenzyl [3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-N-methylcarbamate

prepared in Example 212 (1.683 g, 4.20 mmol) was dissolved in 1,4-dioxane (30 ml). To the solution, sodium hydride (0.185 g, 4.62 mmol) was added followed by stirring at room temperature for 1 hour and then
5 stirred under reflux for 7 hours. The reaction mixture was concentrated under reduced pressure. To the residue, water was added, and the precipitates were filtered off and purified by silica gel column chromatography (n-hexane/acetone = 2/1). The resulting
10 solid was treated with a mixture of n-hexane and ethyl acetate to afford 4-fluorobenzyl N-methyl-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)carbamate (0.381 g, yield 25%) as a colorless solid.

15 Melting point 168.9-169.9°C.

Using 4-fluorobenzyl [3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]-N-methylcarbamate prepared in Example 213 gave the compound of Example 215 in the same manner as in Example 214.

20 Example 215

4-Fluorobenzyl N-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethylcarbamate

Yield 16%, melting point 124.5-128.1°C.

Using corresponding starting materials gave
25 compounds of Examples 216 to 220 in the same manner as in Example 179.

Example 216

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-3-[[1-(4-

chlorophenyl)piperidin-4-yl]-N-methylamino}-2-hydroxy-2-methylpropane

Yellow oil, yield 98%

¹H-NMR (CDCl₃) δppm:

- 5 1.13 (3H, s), 1.57 - 1.82 (4H, m), 2.38 - 2.71 (4H, m), 2.40 (3H, m), 3.65 - 3.71 (2H, m), 3.82 (1H, s), 3.89 - 4.01 (2H, m), 6.81 - 6.86 (2H, m), 7.16 - 7.22 (2H, m), 8.06 (1H, s).

Example 217

- 10 (S)-1-(2-Chloro-4-nitroimidazol-1-yl)-3-([1-(4-trifluoromethoxyphenyl)piperidin-4-yl]-N-methylamino)-2-hydroxy-2-methylpropane

Yellow oil, yield 91%

¹H-NMR (CDCl₃) δppm:

- 15 1.13 (3H, s), 1.59 - 1.83 (4H, m), 2.41 (3H, s), 2.43 - 2.73 (5H, m), 3.66 - 3.73 (2H, m), 3.84 (1H, s), 3.93 (1H, d, J = 14.2 Hz), 4.00 (1H, d, J = 14.2 Hz), 6.86 - 6.91 (2H, m), 7.07 - 7.12 (2H, m), 8.06 (1H, s).

Example 218

- 20 (S)-1-(2-Chloro-4-nitroimidazol-1-yl)-3-([1-(4-trifluoromethylphenyl)piperidin-4-yl]-N-methylamino)-2-hydroxy-2-methylpropane

Yellow oil, yield 96%

¹H-NMR (CDCl₃) δppm:

- 25 1.13 (3H, s), 1.54 - 1.70 (2H, m), 1.77 - 1.84 (2H, m), 2.40 (3H, s), 2.42 - 2.60 (3H, m), 2.72 - 2.82 (2H, m), 3.79 (1H, s), 3.84 - 3.89 (2H, m), 3.92 (1H, d, J = 14.2 Hz), 3.99 (1H, d, J = 14.2 Hz), 6.91 (2H, d, J =

8.7 Hz), 7.46 (2H, d, $J = 8.7$ Hz), 8.06 (1H, s).

Example 219

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-3-([1-(4-cyanophenyl)piperidin-4-yl]-N-methylamino)-2-hydroxy-2-methylpropane

Yellow oil, yield 89%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.13 (3H, s), 1.51 - 1.65 (2H, m), 1.77 - 1.84 (2H, m),
2.39 (3H, s), 2.42 - 2.62 (3H, m), 2.76 - 2.88 (2H, m),
10 3.75 (1H, s), 3.88 - 4.03 (4H, m), 6.81 - 6.88 (2H, m),
7.45 - 7.53 (2H, m), 8.05 (1H, s).

Example 220

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-3-([1-(tert-butoxycarbonyl)piperidin-4-yl]-N-methylamino)-2-hydroxy-2-methylpropane

Yellow oil

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.11 (3H, s), 1.46 (9H, s), 1.50 - 1.80 (4H, m), 2.37
(3H, s), 2.40 - 2.75 (5H, m), 3.90 (1H, d, $J = 14.2$
20 Hz), 3.99 (1H, d, $J = 14.2$ Hz), 4.22 (2H, br), 8.05
(1H, s).

Using compounds prepared in Examples 216 to 220 gave compounds of Examples 221 to 225 in the same manner as in Example 188.

25 Example 221

(S)-2-([1-(4-Chlorophenyl)piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

White powder, yield 47%

MS 406(M+1)⁺

Melting point 179.2-182.1°C.

Example 222

- 5 (S)-2-([1-(4-Trifluoromethoxyphenyl)piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Melting point 127.2-129.7°C.

Example 223

- 10 (S)-2-([1-(4-Trifluoromethylphenyl)piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Melting point 131.5-133.6°C.

Example 224

- 15 (S)-2-([1-(4-Cyanophenyl)piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Melting point 149-152°C.

Example 225

- 20 (S)-2-([1-(Tert-butoxycarbonyl)piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Light yellow powder, yield 37%
Melting point 138.5-140.3°C.

- 25 Example 226

Preparation of (S)-2-([1-(4-trifluoromethylbenzyloxy-carbonyl)piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

(S)-2-([1-(Tert-butoxycarbonyl)piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 225 (400 mg, 1.01 mmol) was dissolved in methylene chloride (1 ml). To the solution, trifluoroacetic acid (1 ml) was added followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure and added methylene (1 ml) chloride and triethylamine (2 ml). The solution was stirred at room temperature for 5 minutes and then concentrated under reduced pressure, and the residue was dissolved in DMF (8 ml). To the solution, a mixture of 4-(trifluoromethyl)benzyl alcohol (267 mg, 1.51 mmol) and 1,1'-carbonyldiimidazole (246 mg, 1.51 mmol) in DMF (2 ml) stirred at room temperature for 4 hours was added followed by stirring at room temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford (S)-2-([1-(4-trifluoromethyl-benzyloxycarbonyl)piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (341 mg, yield 68%) as a light yellow powder.

Melting point 110.6-113.1°C.

Using corresponding starting materials gave compounds of Examples 227 and 228 in the same manner as in Example 226.

5 Example 227

(S)-2-([1-(4-Trifluoromethoxybenzyloxycarbonyl)-piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 84.2-86.8°C.

10 Example 228

(S)-2-([1-(4-Chlorobenzyloxycarbonyl)piperidin-4-yl]-N-methylaminomethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 116.2-116.6°C.

15 Example 229

Preparation of 2-methyl-6-nitro-2-[4-(4-trifluoromethylbenzyloxy)piperidin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole

20 2-Chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 6 (122 mg, 0.56 mmol) and 4-[4-(trifluoromethyl)benzyloxy]piperidine (188 mg, 4.86 mol) were dissolved in DMF (10 ml) followed by stirring at 70-75°C for 5 hours. The reaction mixture was allowed to return to room
25 temperature, poured into water, extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, 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 a yellow oil.

The yellow oil was dissolved in DMF (10 ml).

- 5 To the solution, sodium hydride (134 mg, 3.36 mmol) was added with cooling on ice-bath, and the solution was stirred at room temperature for 1 hour. The reaction mixture was poured into water, extracted with ethyl acetate. The organic phase was washed with a saturated
10 saline solution, 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 = 10/1) and crystallized from ethyl acetate-diisopropyl
15 ether to afford 2-methyl-6-nitro-2-[4-(4-trifluoromethylbenzyloxy)piperidin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole (41 mg, yield 17%) as a white powder.

MS 440 (M-1)⁺

- 20 ¹H-NMR (CDCl₃) δppm:

1.45 - 1.70 (2H, m), 1.60 (3H, s), 1.75 - 1.88 (2H, m),
2.26 - 2.40 (1H, m), 2.45 - 2.55 (2H, m), 2.72 - 2.95
(3H, m), 3.38 (1H, m), 3.89 (1H, d, J = 9.6 Hz), 4.31
(1H, d, J = 9.6 Hz), 4.54 (2H, s), 7.43 (2H, d, J = 8.2
25 Hz), 7.53 (1H, s), 7.79 (2H, d, J = 8.2 Hz).

Example 230

Preparation of 1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylphenoxy)piperidin-1-

yl]propan-2-ol

To a solution of 2-chloro-1-[2-hydroxy-2-methyl-3-(4-methylbenzenesulfonyloxy)propyl]-4-nitroimidazole prepared in Example 5 (0.30 g, 0.77 mmol) and 4-(4-trifluoromethylphenoxy)piperidine (0.21 g, 0.85 mmol) in DMF (6 ml), sodium iodide (0.13 g, 0.77 mmol) and triethylamine (0.12 ml, 0.77 mmol) were added followed by stirring at 80°C for 7 hours. To the reaction mixture, water was added, and the resulting solution was extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford 1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylphenoxy)piperidin-1-yl]propan-2-ol (0.23 g, yield 63%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.14 (3H, s), 1.76 - 2.04 (4H, m), 2.36 (1H, d, J = 14.0 Hz), 2.43 - 2.72 (3H, m), 2.76 - 3.00 (2H, m), 3.46 - 3.52 (1H, br), 3.98 (2H, s), 4.37 - 4.50 (1H, m), 6.91 - 7.00 (2H, m), 7.48 - 7.61 (2H, m), 8.05 (1H, s).

Using corresponding starting materials gave the compound of Example 231 in the same manner as in Example 230.

Example 231

1-(2-Chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-

trifluoromethoxyphenoxy)piperidin-1-yl]propan-2-ol

Yield 61%

¹H-NMR (CDCl₃) δppm:

1.14 (3H, s), 1.74 - 2.04 (4H, m), 2.35 (1H, d, J =
5 13.9 Hz), 2.40 (1H, d, J = 13.9 Hz), 2.43 - 2.70 (2H,
m), 2.74 - 3.00 (2H, m), 3.98 (2H, s), 4.25 - 4.41 (1H,
m), 6.86 - 6.92 (2H, m), 7.11 - 7.15 (2H, m), 8.05 (1H,
s).

Example 232

- 10 Preparation of 1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethoxyphenylamino)piperidin-1-yl]propan-2-ol

A solution of 2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 6 (0.3
15 g, 1.38 mmol) and N-(piperidin-4-yl)-4-trifluoromethoxyaniline (0.43 g, 1.66 mmol) in DMF (8 ml) was stirred at 80°C for 2 hours. To the reaction mixture, water was added, and the solution was extracted with ethyl acetate, dried over magnesium sulfate and then
20 concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/1) to afford 1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethoxyphenylamino)piperidin-1-yl]propan-2-ol
25 (0.37 g, yield 56%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.13 (3H, s), 1.39 - 1.63 (2H, m), 1.96 - 2.09 (2H, m),
2.47 (1H, d, J = 13.9 Hz), 2.43 - 2.63 (3H, m), 2.67 -

2.83 (1H, m), 2.87 - 3.02 (1H, m), 3.15 - 3.39 (1H, m),
3.41 - 3.72 (2H, m), 3.97 (2H, s), 6.46 - 6.59 (2H, m),
6.96 - 7.09 (2H, m), 8.05 (1H, s).

Example 233

5 Preparation of 2-methyl-6-nitro-2-[4-(4-trifluoro-
methoxy)phenyl]piperidin-1-ylmethyl]-2,3-
dihydroimidazo[2,1-b]oxazole

To a solution of 1-(2-chloro-4-nitroimidazol-
1-yl)-2-methyl-3-[4-(4-trifluoromethylphenoxy)-
10 piperidin-1-yl]propan-2-ol prepared in Example 230 (225
mg, 0.49 mmol) in DMF (2.5 ml), sodium hydride (23 mg,
0.59 mmol) was added followed by stirring for 1 hour
with cooling on ice-bath. To the reaction mixture,
ice-water and ethyl acetate were added. The
15 precipitates were filtered off, washed with water,
recrystallized from methylene chloride-diisopropyl
ether and then washed with n-hexane to afford 2-methyl-
6-nitro-2-[4-(4-trifluoromethylphenoxy)piperidin-1-
ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole (80 mg,
20 yield 39%) as a light yellow solid.
Melting point 113-114°C.

Using corresponding starting materials gave
the compound of Example 234 in the same manner as in
Example 233.

25 Example 234

2-Methyl-6-nitro-2-[4-(4-trifluoromethoxyphenoxy)-
piperidin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole
Melting point 117-119°C.

Example 235

Preparation of 2-[4-(4-trifluoromethoxyphenyl)-aminopiperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

- 5 Using 1-(2-chloro-4-nitro-imidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethoxyphenylamino)piperidin-1-yl]propan-2-ol prepared in Example 233 (369 mg, 0.77 mmol) gave 2-[4-(4-trifluoromethoxy-phenylamino)piperidin-1-yl]methyl-2-methyl-6-nitro-2,3-
10 dihydroimidazo[2,1-b]oxazole (25 mg, yield 7%) as a yellow powder in the same manner as in Example 232.

MS 441(M⁺)

¹H-NMR (CDCl₃) δppm:

- 1.11 - 1.40 (2H, m), 1.61 (3H, s), 1.85 - 2.01 (2H, m),
15 2.37 (1H, dt, J = 2.7 Hz, 11.4 Hz), 2.46 - 2.59 (2H, m), 2.76 - 2.84 (1H, m), 2.87 (1H, d, J = 14.9 Hz),
2.95 - 3.03 (1H, m), 3.10 - 3.25 (1H, m), 3.50 (1H, d, J = 7.8 Hz), 3.90 (1H, d, J = 9.7 Hz), 4.29 (1H, d, J = 9.7 Hz), 6.46 - 6.52 (2H, m), 6.98 - 7.01 (2H, m), 7.50
20 (1H, s).

Example 236

- Preparation of tert-butyl N-methyl-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate

2-Chloro-4-nitro-1H-imidazole (1.08 g, 7.31 mmol), tert-butyl N-methyl-[1-(2-methyloxiran-2-ylmethyl)piperidin-4-yl]carbamate (2.08 g, 7.31 mmol) and

sodium acetate (660 mg, 8.04 mmol) in 1-propanol (15 ml) were stirred under reflux overnight. The reaction mixture was concentrated under reduced pressure. The residue was added water, and the mixture was extracted with methylene chloride. The organic phase was dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1), crystallized from methylene chloride-isopropyl ether to afford tert-butyl N-methyl-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate (348 mg, yield 12%) as a white powder. MS 396(M+1)⁺

15 Melting point 198.8-201.1°C.

Example 237

Preparation of benzyl N-methyl-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate

20 Tert-butyl N-methyl-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate prepared in Example 236 (207 mg, 0.52 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure. To the residue, methylene chloride (5 ml), triethylamine (1 ml) and benzyl chlorocarbonate (0.15

ml, 1.05 mmol) were added followed by stirring at room temperature for 30 minutes. The reaction mixture was poured into water, extracted with methylene chloride. The organic phase was dried over sodium sulfate and
5 then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from ethyl acetate-isopropyl ether to afford benzyl N-methyl-[1-
10 (2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate (184 mg, yield 82%) as a white powder.

MS 430 (M+H)⁺

Melting point 138.7-139.2°C.

15 Using 4-chlorobenzyl chlorocarbonate gave the compound of Example 238 in the same manner as in Example 237. Also, using 4-chlorophenylacetyl chloride gave the compound of Example 239 in the same manner as in Example 237.

20

Example 238

4-Chlorobenzyl N-methyl-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate

25 Melting point 147.2-149.2°C.

Example 239

2-{4-[N-(4-Chlorophenylacetyl)-N-methyl]aminopiperidin-1-yl}methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-

b]oxazole

Melting point 206.8-208°C.

Example 240

Preparation of 2-methyl-2-{4-[N-methyl-N-(4-trifluoro-
5 methoxyphenyl)]aminopiperidin-1-yl}methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole

To a solution of 2-[4-(4-trifluoromethoxy-
phenyl)aminopiperidin-1-yl]methyl-2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole prepared in Example 235
10 (60 mg, 0.14 mmol) in methanol (2 ml), a 37%
formaldehyde solution (51 μ l, 0.70 mmol) and sodium
cyanotrihydroborate (26 mg, 0.42 mmol) were added
followed by stirring at room temperature for further 30
minutes. To the reaction mixture, acetic acid (23 μ l,
15 0.42 mmol) was added followed by stirring at room
temperature for 1 hour with cooling on ice-bath. To
the reaction mixture, a sodium hydrogencarbonate
solution was added, and the mixture was extracted with
methylene chloride. The organic phase was dried over
20 magnesium sulfate and then concentrated under reduced
pressure. The residue was purified by silica gel
column chromatography (methylene chloride/ethyl acetate
= 1/1) and crystallized from diisopropyl ether to
afford 2-methyl-2-{4-[N-methyl-N-(4-
25 trifluoromethoxyphenyl)]aminopiperidin-1-yl}methyl-6-
nitro-2,3-dihydroimidazo[2,1-b]oxazole (40 mg, yield
65%) as a light yellow solid.
Melting point 135-136°C.

Example 241

Preparation of 2-[4-(4-chlorobenzyl)oxypiperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

- 5 A mixture of 2-chloro-4-nitro-1H-imidazole (1.5 g, 10.17 mmol), 4-(4-chlorobenzyloxy)-1-(2-methyloxiran-2-ylmethyl)piperidine (2.5 g, 8.45 mmol), sodium hydrogencarbonate (0.86 g, 10.24 mmol) and ethanol (15 ml) was stirred under reflux for 15 hours.
- 10 The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, water was added, and the solution was extracted with methylene chloride. The organic phase was dried over sodium sulfate and then concentrated
- 15 under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) to afford 2-[4-(4-chlorobenzyl)oxypiperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (662 mg, yield 16%) as
- 20 a white powder.

Melting point 129-130°C.

Example 242

- Preparation of 2-{4-[N-(4-chlorophenyl)-N-methyl]amino-piperidin-1-yl}methyl-2-methyl-6-nitro-2,3-
- 25 dihydroimidazo[2,1-b]oxazole

A mixture of 2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 6 (350 mg, 1.61 mmol), 4-[N-(4-chlorophenyl)-N-methylamino]-

piperidine (373 mg, 1.66 mmol) and DMF (15 ml) was stirred at 70°C for 5 hours. To the reaction mixture, sodium hydride (77 mg, 1.93 mmol) was added followed by stirring for 1 hour with cooling on ice-bath. The
5 reaction mixture was poured into ice-water and extracted with ethyl acetate twice. The organic phases were combined, washed with water three times, washed with a saturated saline solution, dried over sodium sulfate and then concentrated under reduced pressure.
10 The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 1/1) to afford 2-{4-[N-(4-chlorophenyl)-N-methyl]aminopiperidin-1-yl}methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (307 mg, yield 47%) as a
15 light yellow powder.
Melting point 186-187.8°C.

Using 4-(4-trifluoromethoxybenzyl)piperidine, 4-(4-trifluoromethylbenzyl)piperidine, 4-(4-chlorobenzyl)piperidine and 4-(chlorobenzoyl)piperidine gave
20 compounds of Examples 243 to 246 in the same manner as in Example 242.

Example 243

2-Methyl-6-nitro-2-[4-(4-trifluoromethoxybenzyl)-piperidin-1-yl]methyl-2,3-dihydroimidazo[2,1-b]oxazole
25 Melting point 143.5-145°C.

Example 244

2-Methyl-6-nitro-2-[4-(4-trifluoromethylbenzyl)-piperidin-1-yl]methyl-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 125-126°C.

Example 245

2-[4-(4-Chlorobenzyl)piperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

5 Melting point 109-110.5°C

Example 246

2-[4-(4-Chlorobenzoyl)piperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 165-167°C.

10 Example 247

Preparation of 2-methyl-6-nitro-2-[4-(4-trifluoromethylbenzoyl)piperidin-1-yl]methyl-2,3-dihydroimidazo[2,1-b]oxazole

A mixture of 2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 6 (80 mg, 0.37 mmol), 4-(4-trifluoromethylbenzoyl)piperidine (95 mg, 0.37 mmol), sodium acetate (150 mg, 1.83 mmol) and DMF (2 ml) was stirred at 80°C overnight. The reaction mixture was poured into water, and extracted with ethyl acetate twice. The organic phases were combined, washed with water three times, washed with a saturated saline solution, dried over sodium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1) to afford 2-methyl-6-nitro-2-[4-(4-trifluoromethylbenzoyl)piperidin-1-yl]methyl-2,3-dihydroimidazo[2,1-b]oxazole (46 mg, yield 29%) as a

white powder.

Melting point 172-174°C.

Using corresponding starting materials gave the compound of Example 248 in the same manner as in
5 Example 247.

Example 248

2-Methyl-6-nitro-2-[4-(4-trifluoromethoxybenzoyl)-
piperidin-1-yl]-2,3-dihydroimidazo[2,1-b]oxazole
Melting point 165-167°C.

10 Example 249

Preparation of (S)-2-[4-(3,4-dichlorobenzyloxy)-
piperidin-1-ylmethyl]-2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole

(R)-2-Chloro-1-(2-methyloxiran-2-ylmethyl)-4-
15 nitroimidazole prepared in Example 12 (396 mg, 1.82
mmol) and 4-(3,4-dichlorobenzyloxy)piperidine (614 mg,
2.36 mol) in DMF (15 ml) were stirred at 70-75°C for 4
hours. The reaction mixture was allowed to return to
room temperature, poured into water, extracted with
20 ethyl acetate. The organic phase was washed with a
saturated saline water, 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
25 = 50/1) to afford a yellow oil.

The yellow oil was dissolved in DMF (15 ml).
To the solution, sodium hydride (87 mg, 2.18 mmol) was
added with cooling on ice-bath followed by stirring at

room temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with a saturated saline solution, dried over magnesium sulfate and then
5 filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and crystallized from methylene chloride-diisopropyl ether to afford (S)-2-[4-(3,4-
10 dichlorobenzyloxy)piperidin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (431 mg, yield 44%) as a white powder.

MS 441 (M⁺)

Melting point 132.0-136.0°C.

15 Example 250

Preparation of (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-(4-trifluoromethoxyphenyl)methanone

 Using (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (1.0
20 g, 4.6 mmol) and 4-(4-trifluoromethoxybenzoyl)piperidine (1.3 g, 4.8 mmol) gave (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-(4-
25 trifluoromethoxyphenyl)methanone (771 mg, yield 37%) as a light yellow powder.

Melting point 113.0-115.0°C.

 Example 251

Preparation of ethyl (S)-1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-carboxylate

2-Chloro-4-nitro-1H-imidazole (3.7 g, 25.1 mmol), ethyl (S)-1-(2-methyloxiran-2-ylmethyl)-piperidine-4-carboxylate (4.8 g, 21.1 mmol) and sodium hydrogencarbonate (2.2 g, 25.1 mmol) in ethanol (25 ml) were stirred under reflux overnight. The reaction mixture was concentrated under reduced pressure. To the residue, water was added, and the solution was extracted with methylene chloride. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 3/1) and crystallized from diethyl ether to afford ethyl (S)-1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidine-4-carboxylate (1.4 g, yield 20%) as a white powder.

Melting point 101.0-103.0°C.

Example 252

Preparation of (S)-2-methyl-6-nitro-2-[4-(4-trifluoromethoxyphenyl)-1,2,3,6-tetrahydropyridin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole

4-(4-Trifluoromethoxyphenyl)-1,2,3,6-tetrahydropyridine (0.985 g, 4.05 mmol) and (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole

prepared in Example 12 (0.839 g, 3.86 mmol) were added to DMF (15 ml), and the solution was stirred at 60°C for 8 hours. The reaction mixture was added water and extracted with ethyl acetate. The organic phases was washed with water and a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 4/1) to afford as oil. The oil was dissolved in DMF (20 ml), and sodium hydride (94 mg, 2.35 mmol) was added with cooling on ice-bath followed by stirring at room temperature overnight. To the reaction mixture, water was added, and the solution was extracted with ethyl acetate. The organic phase was washed with water and a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/1) to afford (S)-2-methyl-6-nitro-2-[4-(4-trifluoromethoxyphenyl)-1,2,3,6-tetrahydropyridin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole (0.192 g, yield 23%) as a light yellow solid.

¹H-NMR (CDCl₃) δppm:

1.68 (3H, s), 2.46 - 3.39 (8H, m), 3.95 (1H, d, J = 10.2 Hz), 4.49 (1H, br), 5.98 (1H, s), 7.16 (2H, d, J = 8.3 Hz), 7.35 (2H, d, J = 8.3 Hz), 7.53 (1H, s).

Example 253

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylphenoxy)piperidin-1-yl]propan-2-ol

(R)-2-Chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (500 mg, 2.30 mmol) and 4-(4-trifluoromethylphenoxy)piperidine (730 mg, 3.0 mmol) in DMF (10 ml) were stirred at 70-75°C for 5 hours. The reaction mixture was allowed to return to room temperature, poured into water, and extracted with ethyl acetate. The extract was washed with a saturated saline solution, 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 = 50/1) to afford (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylphenoxy)piperidin-1-yl]propan-2-ol (1.06 g, yield 99%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.14 (3H, s), 1.80 - 2.04 (4H, m), 2.38 (1H, d, J = 14.0 Hz), 2.48 - 2.68 (2H, m), 2.52 (1H, d, J = 14.0 Hz), 2.77 - 2.95 (2H, m), 3.73 (1H, s), 4.01 (2H, s), 4.39 - 4.46 (1H, m), 6.93 - 6.97 (2H, m), 7.49 - 7.55 (2H, m), 8.08 (1H, s).

Example 254

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylbenzyloxy)piperidin-1-yl]propan-2-ol

(R)-2-Chloro-1-(2-methyloxiran-2-ylmethyl)-4-

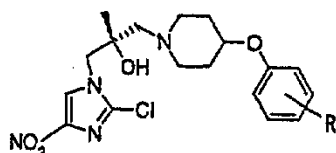
nitroimidazole prepared in Example 12 (700 mg, 3.22 mmol) and 4-(4-trifluoromethylbenzyloxy)piperidine (1.09 g, 4.86 mol) in DMF (10 ml) were stirred at 70-75°C for 4 hours. The reaction mixture was allowed to return to room temperature, poured into water and extracted with ethyl acetate. The extract was washed with a saturated saline solution, 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 = 50/1) to afford (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylbenzyloxy)piperidin-1-yl]propan-2-ol (1.36 g, yield 87%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.12 (3H, s), 1.61 - 1.78 (2H, m), 1.88 - 1.96 (2H, m), 2.32 (1H, d, J = 13.9 Hz), 2.35 - 2.56 (2H, m), 2.47 (1H, d, J = 13.9 Hz), 2.72 - 2.81 (1H, m), 2.86 - 2.95 (1H, m), 3.44 - 3.51 (1H, m), 3.63 (1H, bs), 3.97 (2H, s), 4.59 (2H, s), 7.43 - 7.47 (2H, m), 7.58 - 7.62 (2H, m), 8.05 (1H, s).

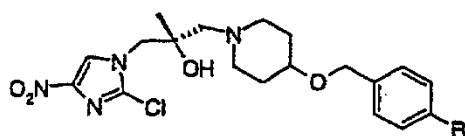
Using corresponding starting materials gave compounds of Examples 255 to 260 shown in the following table in the same manner as in Example 254.

Table 13



Example	R	¹ H NMR (CDCl ₃) δ	Yield (%)
255	4-OCF ₃	1.13(3H, s), 1.77-1.89(2H, m), 1.91-2.01(2H, m), 2.37(1H, d, J=13.9Hz), 2.45-2.67(2H, m), 2.51(1H, d, J=13.9Hz), 2.75-2.95(2H, m), 3.71(1H, s), 4.00(2H, s), 4.17-4.34(1H, m), 6.85-6.91(2H, m), 7.11-7.15(2H, m), 8.07(1H, s).	99
256	4-Cl	1.13(3H, s), 1.73-1.88(2H, m), 1.91-2.02(2H, m), 2.36(1H, d, J=13.9Hz), 2.44-2.63(2H, m), 2.50(1H, d, J=13.9Hz), 2.76-2.95(2H, m), 3.64(1H, s), 3.99(2H, s), 4.26-4.35(1H, m), 6.79-6.86(2H, m), 7.18-7.26(2H, m), 8.06(1H, s).	99
257	4-CN	1.14(3H, s), 1.81-1.92(2H, m), 1.95-2.03(2H, m), 2.36(1H, d, J=13.9Hz), 2.47-2.68(2H, m), 2.51(1H, d, J=13.9Hz), 2.77-2.94(2H, m), 3.53(1H, s), 4.00(2H, s), 4.40-4.47(1H, m), 6.90-6.96(2H, m), 7.53-7.60(2H, m), 8.06(1H, s).	99
258	3-CF ₃	1.14(3H, s), 1.81-1.91(2H, m), 1.94-2.02(2H, m), 2.37(1H, d, J=13.9Hz), 2.47-2.68(2H, m), 2.51(1H, d, J=13.9Hz), 2.77-2.97(2H, m), 3.61(1H, s), 3.99(2H, s), 4.38-4.44(1H, m), 7.04-7.12(2H, m), 7.18-7.22(1H, m), 7.35-7.42(1H, m), 8.07(1H, s).	99

Table 14



Example	R	¹ H NMR (CDCl ₃) δ
259	OCF ₃	1.12(3H, s), 1.66-1.76(2H, m), 1.86-1.95(2H, m), 2.32(1H, d, J=13.9Hz), 2.36-2.55(2H, m), 2.46(1H, d, J=13.9Hz), 2.72-2.82(1H, m), 2.85-2.96(1H, m), 3.42-3.49(1H, m), 3.69(1H, s), 4.00(2H, s), 4.52(2H, s), 7.17-7.21(2H, m), 7.35-7.39(2H, m), 8.06(1H, s).
260	Cl	1.10(3H, s), 1.65-1.74(2H, m), 1.85-1.92(2H, m), 2.31(1H, d, J=13.9Hz), 2.38-2.54(2H, m), 2.46(1H, d, J=13.9Hz), 2.71-2.79(1H, m), 2.84-2.95(1H, m), 3.38-3.48(1H, m), 3.72(1H, s), 3.96(2H, s), 4.48(2H, s), 7.23-7.32(2H, m), 8.05(1H, s).

Example 261

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(3-phenyl-2-propenyloxy)piperidin-1-yl]-propan-2-ol

- 5 Using (R)-2-chloro-1-(2-methyloxiran-2-yl-methyl)-4-nitroimidazole prepared in Example 12 (0.198 g, 0.910 mmol) and 4-(3-phenyl-2-propenyloxy)piperidine (0.198 g, 0.910 mmol) gave (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(3-phenyl-2-propenyloxy)piperidin-1-yl]propan-2-ol (0.192 g, yield 49%) as a brown oil in the same manner as in Example 254.

¹H-NMR (CDCl₃) δppm:

- 1.12 (3H, s), 1.55 - 1.98 (4H, m), 2.28 - 2.94 (6H, m),
15 3.41 - 3.49 (1H, m), 3.62 (1H, br), 3.95 (2H, s), 4.16 (1H, d, J = 6.0 Hz), 4.17 (1H, d, J = 6.0 Hz), 6.28 (1H, ddd, J = 6.0 Hz, 6.0 Hz, 15.9 Hz), 6.60 (1H, d, J = 15.9 Hz), 7.21 - 7.42 (5H, m), 8.05 (1H, s).

Example 262

- 20 Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-3-{4-[3-(4-chlorophenyl)-2-propenyloxy]piperidin-1-yl}-2-methylpropan-2-ol

- Using (R)-2-chloro-1-(2-methyloxiran-2-yl-methyl)-4-nitroimidazole prepared in Example 12 (0.217
25 g, 1.00 mmol) and 4-[3-(4-chloro-phenyl)-2-propenyloxy]piperidine (0.250 g, 0.995 mmol) gave (S)-1-(2-chloro-4-nitroimidazol-1-yl)-3-{4-[3-(4-chlorophenyl)-2-propenyloxy]piperidin-1-yl}-2-

methylpropan-2-ol (0.263 g, yield 56%) as a brown liquid in the same manner as in Example 254.

¹H-NMR (CDCl₃) δppm:

1.12 (3H, s), 1.55 - 2.01 (4H, m), 2.28 - 2.99 (6H, m),
5 3.40 - 3.51 (1H, m), 3.60 (1H, br), 3.96 (2H, s), 4.13
- 4.16 (2H, m), 6.20 - 6.31 (1H, m), 6.56 (1H, d, J =
15.7 Hz), 7.19 - 7.34 (4H, m), 8.05 (1H, s).

Example 263

Preparation of (S)-2-{4-[3-(4-chlorophenyl)propoxy]-
10 piperidin-1-ylmethyl}-2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole

(R)-2-Chloro-1-(2-methyloxiran-2-ylmethyl)-4-
nitroimidazole prepared in Example 12 (0.103 g, 0.473
mmol) and 4-[3-(4-chlorophenyl)propoxy]piperidine
15 (0.109 g, 0.430 mmol) were dissolved in DMF (10 ml),
and the solution was stirred at 60°C for 4 hours. The
reaction mixture was added water and extracted with
ethyl acetate. The organic phase was combined, washed
with water and a saturated saline solution, dried over
20 sodium sulfate and then filtered. The resulting
filtrate was concentrated under reduced pressure. The
residue was purified by silica gel column
chromatography (n-hexane/ethyl acetate = 2/3) to afford
an oil. The oil was dissolved in DMF (2 ml). To the
25 solution, sodium hydride (15 mg, 0.375 mmol) was added
with cooling on ice-bath followed by stirring at room
temperature for 3 hours. To the reaction mixture,
water was added, and the precipitates were filtered

off, purified by silica gel column chromatography (methylene chloride/ethyl acetate = 6/1) and then recrystallized from ethyl acetate/n-hexane = 1/3 (6 ml) to afford (S)-2-{4-[3-(4-chlorophenyl)propoxy]-piperidin-1-ylmethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (36 mg, yield 19%) as a white powder.

Melting point 88.8-91.9°C.

Example 264

10 Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-3-{4-[2-(4-chlorophenyl)ethoxy]piperidin-1-yl}-2-methylpropan-2-ol

Using (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (0.076 g, 0.350 mmol) and 4-[2-(4-chlorophenyl)ethoxy]piperidine (0.080 g, 0.334 mmol) gave (S)-1-(2-chloro-4-nitroimidazol-1-yl)-3-{4-[2-(4-chlorophenyl)ethoxy]piperidin-1-yl}-2-methylpropan-2-ol (0.109 g, yield 71%) as a light yellow oil in the same manner as in

20 Example 254.

¹H-NMR (CDCl₃) δppm:

1.10 (3H, s), 1.51 - 1.72 (2H, m), 1.78 - 1.92 (2H, m), 2.24 - 2.50 (4H, m), 2.55 - 2.88 (4H, m), 3.29 - 3.39 (1H, m), 3.58 - 3.66 (3H, m), 3.94 (2H, s), 7.15 (2H, d, J = 8.5 Hz), 7.24 (2H, d, J = 8.5 Hz), 8.04 (1H, s).

25

Example 265

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-{4-[2-(4-trifluoromethylphenyl)ethoxy]}-

piperidin-1-yl}propan-2-ol

Triphenyl-(4-trifluoromethylbenzyl)-
phosphonium bromide (3.00 g, 5.98 mmol) was dissolved
in DMSO (50 ml). To the solution, sodium hydride
5 (0.239 g, 5.98 mmol) was added with cooling on ice-bath
followed by stirring at room temperature for 1 hour.
To the solution, a solution of benzyl 4-
formyloxypiperidine-1-carboxylate (1.497 g, 5.69 mmol)
in DMSO (10 ml) was added dropwise followed by stirring
10 at 60°C for 7 hours. The reaction mixture was added
water and extracted with ethyl acetate twice. The
organic phases were combined, washed with water and a
saturated saline solution, dried over sodium sulfate
and then filtered. The filtrate was concentrated under
15 reduced pressure. The residue was purified by silica
gel column chromatography (n-hexane/ethyl acetate =
4/1) and then purified by silica gel column
chromatography (methylene chloride/ethyl acetate = 9/1)
to afford benzyl 4-[2-(4-trifluoromethylphenyl)-
20 vinyloxy]piperidin-1-carboxylate as a colorless oil.

The resulting benzyl 4-[2-(4-trifluoromethyl-
phenyl)vinyloxy]piperidin-1-carboxylate was dissolved
in ethanol (10 ml) and reduced by catalytic
hydrogenation over 10%Pd/C (90 mg) at room temperature
25 under atmospheric pressure. The reaction mixture was
filtered through Celite. The filtrate was concentrated
under reduced pressure to afford 4-[2-(trifluoromethyl-
phenyl)ethoxy]piperidine as a brown liquid.

Using the resulting 4-[2-(trifluoromethyl-phenyl)ethoxy]piperidine and (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (0.184 g, 0.844 mmol) gave (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-[2-(4-trifluoromethylphenyl)ethoxy]piperidin-1-yl]propan-2-ol (0.088 g, yield 3%) as a brown oil in the same manner as in Example 254.

¹H-NMR (CDCl₃) δppm:

10 1.10 (3H, s), 1.49 - 1.92 (4H, m), 2.24 - 2.81 (6H, m), 2.92 (2H, t, J = 6.8 Hz), 3.30 - 3.35 (1H, m), 3.65 (2H, t, J = 6.8 Hz), 3.94 (2H, s), 7.34 (2H, d, J = 8.2 Hz), 7.54 (2H, d, J = 8.2 Hz), 8.04 (1H, s).

Example 266

15 Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethoxyphenylamino)piperidin-1-yl]propan-2-ol

Using (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 and N-(piperidin-4-yl)-4-trifluoromethoxyaniline gave (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethoxyphenylamino)piperidin-1-yl]propan-2-ol (1.36 g, yield 88%) as a yellow oil in the same manner as in Example 254.

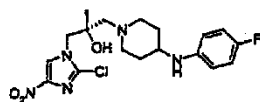
25 ¹H-NMR (CDCl₃) δppm:

1.13 (3H, s), 1.41 - 1.57 (2H, m), 2.03 - 2.08 (2H, m), 2.34 (1H, d, J = 13.9 Hz), 2.49 - 2.59 (3H, m), 2.65 - 2.77 (2H, m), 3.08 - 2.16 (2H, m), 3.24 - 3.41 (1H, m),

3.97 (2H, s), 6.47 - 6.55 (2H, m), 6.98 - 7.04 (2H, m), 8.05 (1H, s).

Using corresponding starting materials gave compounds of Examples 267 to 269 shown in the following table in the same manner as in Example 266.

Table 15



Example	R	Yield (%)	¹ H NMR (CDCl ₃) δ
267	Cl	99	1.13(3H, s), 1.40-1.53(2H, m), 2.00-2.06(2H, m), 2.35(1H, d, J=13.9Hz), 2.45-2.59(3H, m), 2.71-3.01(2H, m), 3.18(1H, br), 3.48-3.58(2H, m), 3.97(2H, s), 6.47-6.54(2H, m), 7.07-7.14(2H, m), 8.05(1H, s).
268	CF ₃	99	1.14(3H, s), 1.42-1.59(2H, m), 2.03-2.08(2H, m), 2.35(1H, d, J=13.9Hz), 2.49-2.60(2H, m), 2.50(1H, d, J=13.9Hz), 2.74-2.98(2H, m), 3.31-3.39(1H, m), 3.51(1H, s), 3.87(1H, d, J=9.3Hz), 3.97(2H, s), 6.58(2H, d, J=8.7Hz), 7.39(2H, d, J=8.7Hz), 8.05(1H, s).
269	CN	99	1.13(3H, s), 1.40-1.53(2H, m), 2.00-2.06(2H, m), 2.35(1H, d, J=13.9Hz), 2.45-2.59(2H, m), 2.49(1H, d, J=13.9Hz), 2.71-3.01(2H, m), 3.18(1H, br), 3.48-3.58(2H, m), 3.97(2H, s), 6.51-6.57(2H, m), 7.38-7.44(2H, m), 8.05(1H, s).

Example 270

Preparation of (S)-1-(4-piperidinopiperidin-1-yl)-3-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-propan-2-ol

(R)-2-Chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (0.500 g, 2.29 mmol) and 4-piperidinopiperidine (0.425 g, 2.53 mmol) were dissolved in DMF (5 ml), and the solution was stirred at 70°C for 5 hours. The reaction mixture was added water and extracted with ethyl acetate twice. The organic phases were combined, washed with water and

a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 3/2) using basic silica gel to afford (S)-1-(4-piperidinopiperidin-1-yl)-3-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-propan-2-ol (0.656 g, yield 74%) as a brown oil.

¹H-NMR (CDCl₃) δppm:

10 1.11 (3H, s), 1.38 - 1.89 (10H, m), 2.18 - 2.55 (9H, m), 2.70 - 2.81 (1H, m), 2.89 - 3.01 (1H, m), 3.67 (1H, br), 3.94 (1H, s), 8.05 (1H, s).

Example 271

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-([4-(4-trifluoromethoxyphenyl)sulfanyl]-piperidin-1-yl)propan-2-ol

Using (R)-2-chloro-1-(2-methyloxiran-2-yl-methyl)-4-nitroimidazole prepared in Example 12 and 4-[4-(trifluoromethoxy)phenylsulfanyl]piperidine gave (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-([4-(4-trifluoromethoxyphenyl)sulfanyl]piperidin-1-yl)propan-2-ol (3.4 g, yield 99%) as a yellow oil in the same manner as in Example 270.

¹H-NMR (CDCl₃) δppm:

25 1.11 (3H, s), 1.58 - 1.73 (2H, m), 1.91 - 1.99 (2H, m), 2.32 (1H, d, J = 13.9 Hz), 2.41 - 2.50 (2H, m), 2.46 (1H, d, J = 13.9 Hz), 2.75 - 3.09 (4H, m), 3.97 (2H, s), 7.11 - 7.17 (2H, m), 7.36 - 7.53 (2H, m), 8.04 (1H,

s).

Example 272

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethoxybenzyl)piperidin-1-yl]propan-2-ol

Using 4-(4-trifluoromethoxybenzyl)piperidine and (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 gave (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethoxybenzyl)piperidin-1-yl]propan-2-ol (crude) as a yellow oil in the same manner as in Example 270.

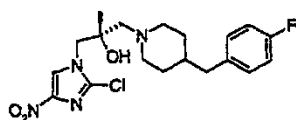
¹H-NMR (CDCl₃) δppm:

1.10 (3H, m), 1.22 - 1.71 (5H, m), 2.26 - 2.55 (6H, m), 2.66 - 2.96 (3H, m), 3.94 (2H, s), 7.09 - 7.18 (4H, m), 8.06 (1H, s).

Using corresponding starting materials gave compounds of Examples 273 and 274 shown in the following table in the same manner as in Example 272.

20

Table 16



25

Example	R	Yield (%)	¹ H NMR (CDCl ₃) δ
273	4-CF ₃	56	1.10(3H, s), 1.14-1.38(2H, m), 1.47-1.64(3H, m), 2.29(1H, d, J=13.9Hz), 2.30-2.40(2H, m), 2.43(1H, d, J=13.9Hz), 2.60(2H, d, J=6.5Hz), 2.69(1H, d, J=11.7Hz), 2.90(1H, d, J=11.7Hz), 3.74(1H, br), 3.94(2H, s), 7.22-7.26(2H, m), 7.52-7.54(2H, m), 8.05(1H, s).
274	4-Cl	65	1.10(3H, s), 1.14-1.63(5H, m), 2.26-2.52(7H, m), 2.68(1H, d, J=11.5Hz), 2.90(1H, d, J=11.5Hz), 3.94(2H, s), 7.00-7.08(2H, m), 7.20-7.29(2H, m), 8.05(1H, s).

Example 275

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)propan-2-ol

5 4-Phenyl-1,2,3,6-tetrahydropyridine hydrochloride (0.495 g, 2.53 mmol) was added to a sodium hydroxide solution, and the solution was extracted with methylene chloride. The organic phase was dried over sodium sulfate and then filtered. The
10 filtrate was concentrated under reduced pressure. To the residue, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (0.5 g, 2.29 mmol) and DMF (5 ml) were added followed by stirring at 70°C for 5 hours. The reaction mixture was
15 poured into water and extracted with ethyl acetate twice. The organic phases were combined, washed with water and a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure, and
20 the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 2/1) to afford (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)propan-2-ol (0.492 g, yield 57%) as a yellow oil.

25 ¹H-NMR (CDCl₃) δppm:

1.17 (3H, s), 2.47 (1H, d, J = 13.9 Hz), 2.58 - 2.64 (3H, m), 2.78 - 3.00 (2H, m), 3.27 - 3.40 (2H, m), 3.62 (1H, br), 4.01 (2H, s), 6.02 - 6.05 (1H, m), 7.23 -

7.41 (5H, m), 8.07 (1H, s).

Example 276

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-(4-phenylpiperidin-1-yl)propan-2-ol

- 5 4-Phenylpiperidine hydrochloride (0.522 g, 2.64 mmol) was added to a sodium hydroxide solution, and extracted with methylene chloride. The organic phase was dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure.
- 10 To the residue, (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (0.5 g, 2.29 mmol) and DMF (5 ml) were added followed by stirring at 70°C for 5 hours. The reaction mixture was poured into water and extracted with ethyl acetate
- 15 twice. The organic phases were combined, washed with water and a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column
- 20 chromatography (n-hexane/ethyl acetate = 2/1) to afford (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-(4-phenylpiperidin-1-yl)propan-2-ol (0.703 g, yield 81%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

- 25 1.14 (3H, s), 1.76 - 1.89 (4H, m), 2.36 (1H, d, J = 13.9 Hz), 2.48 - 2.61 (4H, m), 2.75 - 2.89 (1H, m), 2.98 - 3.09 (1H, m), 3.75 (1H, br), 3.98 (2H, s), 7.18 - 7.35 (5H, m), 8.08 (1H, s).

Example 277

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylphenyl)piperidin-1-yl]propan-2-ol

5 (R)-2-Chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (0.329 g, 1.51 mmol) and 4-(4-trifluoromethylphenyl)piperidine (0.40 g, 1.66 mmol) were dissolved in DMF (5 ml) followed by stirring at 70°C for 3 hours. The reaction mixture was
10 poured into water and extracted with ethyl acetate twice. The organic phases were combined, washed with water and a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The
15 residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 2/1) to afford (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylphenyl)piperidin-1-yl]propan-2-ol (0.361 g, yield 54%) as a brown oil.

20 ¹H-NMR (CDCl₃) δppm:

1.13 (3H, s) 1.71 - 1.93 (4H, m), 2.36 (1H, d, J = 14.0 Hz), 2.48 - 2.65 (4H, m), 2.77 - 2.90 (1H, m), 3.01 - 3.14 (1H, m), 3.64 (1H, br), 3.99 (2H, s), 7.32 (2H, d, J = 8.1 Hz), 7.57 (2H, d, J = 8.1 Hz), 8.07 (1H, s).

25 Example 278

Preparation of tert-butyl (S)-{1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperidin-4-yl}carbamate

Using (R)-2-chloro-1-(2-methyloxiran-2-yl-methyl)-4-nitroimidazole prepared in Example 12 and tert-butyl piperidin-4-ylcarbamate gave tert-butyl (S)-{1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperidin-4-yl}carbamate (yield 92%) a yellow oil in the same manner as in Example 277.

¹H-NMR (CDCl₃) δppm:

1.11 (3H, s), 1.32 - 1.51 (2H, m), 1.44 (9H, m), 1.90 - 1.96 (2H, m), 2.32 (1H, d, J = 13.9 Hz), 2.39 - 2.55 (2H, m), 2.46 (1H, d, J = 13.9 Hz), 2.67 - 2.96 (3H, m), 3.44 (1H, br), 3.59 (1H, s), 3.96 (2H, s), 8.05 (1H, s).

Example 279

Preparation of tert-butyl (S)-{1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methyl-propyl]piperidin-4-yl}-N-[2-(4-trifluoromethylphenyl)-ethyl]carbamate

Using (R)-2-chloro-1-(2-methyloxiran-2-yl-methyl)-4-nitroimidazole prepared in Example 12 (0.332 g, 0.891 mmol) and tert-butyl piperidin-4-yl-N-[2-(4-trifluoromethylphenyl)ethyl]carbamate (0.194 g, 0.891 mmol) gave tert-butyl (S)-{1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methyl-propyl]piperidin-4-yl}-N-[2-(4-trifluoromethylphenyl)-ethyl]carbamate (0.370 g, yield 70%) as a light yellow oil in the same manner as in Example 277.

¹H-NMR (CDCl₃) δppm:

1.12 (3H, s), 1.49 (9H, s), 1.55 - 1.80 (4H, m), 2.17 -

2.57 (4H, m), 2.70 - 2.98 (4H, m), 3.21 - 3.30 (2H, m),
3.50 (1H, s), 3.95 (2H, s), 7.31 (2H, d, $J = 8.2$ Hz),
7.57 (2H, d, $J = 8.2$ Hz), 8.05 (1H, s).

Example 280

- 5 Preparation of (S)-2-methyl-6-nitro-2-[4-(4-trifluoro-
methylphenoxy)piperidin-1-ylmethyl]-2,3-dihydroimidazo-
[2,1-b]oxazole

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-2-
methyl-3-[4-(4-trifluoromethylphenoxy)piperidin-1-
10 yl]propan-2-ol prepared in Example 253 (1.06 g, 2.3
mmol) was dissolved in DMF (15 ml). To the solution,
sodium hydride (110 mg, 2.76 mmol) was added with
cooling on ice-bath followed by stirring at room
temperature overnight. The reaction mixture was poured
15 into water and extracted with ethyl acetate. The
organic phase was washed with a saturated saline
solution, 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/ethyl acetate
= 5/1) and crystallized from methylene chloride-
diisopropyl ether to afford (S)-2-methyl-6-nitro-2-[4-
(4-trifluoromethylphenoxy)piperidin-1-ylmethyl]-2,3-
dihydroimidazo[2,1-b]oxazole (431 mg, yield 44%) as a
25 white powder.

MS 427(M+1)⁺

Optical purity 97.8% e.e.

$[\alpha]_D^{27} = -2.07^\circ$ (concentration: 1.064, CHCl₃)

¹H-NMR (CDCl₃) δppm:

1.61 (3H, s), 1.67 - 1.92 (4H, m), 2.41 - 2.51 (1H, m),
2.57 (1H, d, J = 14.9 Hz), 2.58 - 2.67 (1H, m), 2.88
(1H, d, J = 14.9 Hz), 2.74 - 2.98 (2H, m), 3.91 (1H, d,
5 J = 9.7 Hz), 4.31 (1H, d, J = 9.7 Hz), 4.28 - 4.36 (1H,
m), 6.91 (2H, d, J = 8.7 Hz), 7.51 (2H, d, J = 8.7 Hz),
7.54 (1H, s).

Example 281

10 Preparation of (S)-2-methyl-6-nitro-2-[4-(4-trifluoro-
methylbenzyloxy)piperidin-1-ylmethyl]-2,3-
dihydroimidazo[2,1-b]oxazole

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-2-
methyl-3-[4-(4-trifluoromethylbenzyloxy)piperidin-1-
15 yl]propan-2-ol prepared in Example 254 (1.36 g, 2.8
mmol) was dissolved in DMF (15 ml). To the solution,
sodium hydride (134 mg, 3.36 mmol) was added with
cooling on ice-bath followed by stirring at room
temperature overnight. The reaction mixture was poured
20 into water and extracted with ethyl acetate. The
organic phase was washed with a saturated saline
solution, 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 (methylene chloride/ethyl acetate
= 10/1) and crystallized from methylene chloride-
diisopropyl ether to afford (S)-2-methyl-6-nitro-2-[4-
(4-trifluoromethylbenzyloxy)piperidin-1-ylmethyl]-2,3-

dihydroimidazo[2,1-b]oxazole (431 mg, yield 44%) as a white powder.

MS 440(M-1)⁺

Melting point 91-92°C

5 Optical purity 99.6% e.e.

$[\alpha]_D^{27} = -8.63^\circ$ (concentration: 1.066, CHCl₃)

¹H-NMR (CDCl₃) δppm:

1.44 - 1.66 (2H, m), 1.60 (3H, s), 1.71 - 1.85 (2H, m),
2.28 - 2.38 (1H, m), 2.44 - 2.56 (1H, m), 2.52 (1H, d,
10 J = 14.9 Hz), 2.72 - 2.81 (1H, m), 2.84 (1H, d, J =
14.9 Hz), 2.87 - 2.94 (1H, m), 3.33 - 3.41 (1H, m),
3.88 (1H, d, J = 9.6 Hz), 4.31 (1H, d, J = 9.6 Hz),
4.54 (2H, s), 7.41 - 7.44 (2H, m), 7.52 (1H, s), 7.56 -
7.60 (2H, m).

15 Example 282

Preparation of (S)-2-[4-(4-trifluoromethoxyphenyl)aminopiperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Using (S)-1-(2-chloro-4-nitroimidazol-1-yl)-
20 2-methyl-3-[4-(4-trifluoromethoxyphenylamino)piperidin-1-yl]propan-2-ol prepared in Example 266 gave (S)-2-[4-(4-trifluoromethoxyphenyl)aminopiperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (yield
73%) as a white powder in the same manner as in Example
25 281.

Melting point 107.5-109.0°C

MS 441(M⁺)

Optical purity 99.8% e.e.

$[\alpha]_D^{27} = 19.19^\circ$ (concentration: 1.006, CHCl_3).

Example 283

Preparation of tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate

Using tert-butyl (S)-{1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperidin-4-yl}carbamate prepared in Example 278 gave tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate (yield 49%) as a white powder in the same manner as in Example 281.

MS 381 (M^+)

Melting point 158.5-160.7°C.

Example 284

Preparation of tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-N-[2-(4-trifluoromethylphenyl)ethyl]carbamate

Using tert-butyl (S)-{1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methyl-propyl]piperidin-4-yl}-N-[2-(4-trifluoromethylphenyl)ethyl]carbamate prepared in Example 279 (0.37 g, 0.627 mmol) gave tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-N-[2-(4-trifluoromethylphenyl)ethyl]carbamate (0.211 g, yield 63%) as a light yellow powder in the same manner as in Example 281.

Melting point 206.8-208.6°C.

Example 285

Preparation of (S)-2-methyl-6-nitro-2-{4-[4-(trifluoromethoxyphenyl)sulfanyl]piperidin-1-ylmethyl}-2,3-dihydroimidazo[2,1-b]oxazole

- 5 Using (S)-1-(2-chloro-4-nitro-imidazol-1-yl)-2-methyl-3-{[4-(4-trifluoromethoxyphenyl)sulfanyl]piperidin-1-yl}propan-2-ol prepared in Example 271 gave (S)-2-methyl-6-nitro-2-{4-[4-(trifluoromethoxyphenyl)sulfanyl]piperidin-1-ylmethyl}-
10 2,3-dihydroimidazo[2,1-b]oxazole (yield 62%) as a white powder in the same manner as in Example 281.

MS 458 (M⁺)

Melting point 133.0-137.4°C.

Example 286

- 15 Preparation of (S)-2-methyl-6-nitro-2-[4-(4-trifluoromethoxybenzyl)piperidin-1-yl]methyl-2,3-dihydroimidazo[2,1-b]oxazole

- Using (S)-1-(2-chloro-4-nitro-imidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethoxybenzyl)piperidin-1-yl]propan-2-ol prepared in Example 272 gave (S)-2-methyl-6-nitro-2-[4-(4-trifluoromethoxybenzyl)piperidin-1-yl]methyl-2,3-dihydroimidazo[2,1-b]oxazole (yield 55%) as a white powder in the same manner as in Example 281.

- 25 Melting point 111.0-112.5°C

MS: 440 (M⁺)

Optical purity 99.0% e.e.

$[\alpha]_D^{27} = 5.38^\circ$ (concentration: 1.004, CHCl₃).

Example 287

Preparation of (S)-2-methyl-6-nitro-2-(4-phenyl-1,2,3,6-tetrahydropyridin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole

- 5 (S)-1-(2-Chloro-4-nitro-imidazol-1-yl)-2-methyl-3-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)propan-2-ol prepared in Example 275 (0.492 g, 1.31 mmol) was dissolved in DMF (8 ml). To the solution, sodium hydride (63 mg, 1.57 mmol) was added with
- 10 cooling on ice-bath followed by stirring at room temperature for 3 hours. To the reaction mixture, water was added. After extraction with ethyl acetate, the organic phase was washed with water and a saturated saline solution, dried over sodium sulfate and then
- 15 filtered. The resulting filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/acetone = 4/1) and recrystallized from methylene chloride-ethyl acetate to afford (S)-2-methyl-6-nitro-2-(4-phenyl-
- 20 1,2,3,6-tetrahydropyridin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole (0.059 g, yield 13%) as a light yellow solid.
- Melting point 200.1-201°C.

Example 288

- 25 Preparation of (S)-2-methyl-6-nitro-2-(4-phenylpiperidin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole
- (S)-1-(2-Chloro-4-nitro-imidazol-1-yl)-2-methyl-3-(4-phenylpiperidin-1-yl)propan-2-ol prepared

in Example 276 (0.703 g, 1.86 mmol) was dissolved in DMF (5 ml). To the solution, sodium hydride (89 mg, 2.23 mmol) was added with cooling on ice-bath followed by stirring at room temperature for 3 hours. To the
5 reaction mixture, water was added. The precipitates were filtered off, purified by silica gel column chromatography (n-hexane/acetone = 3/1) and recrystallized from ethyl acetate to afford (S)-2-methyl-6-nitro-2-(4-phenylpiperidin-1-ylmethyl)-2,3-
10 dihydroimidazo[2,1-b]oxazole (0.230 g, yield 36%) as a white powder.

Melting point 158.8-163.9°C.

Using corresponding starting materials gave compounds of Examples 289 to 294 in the same manner as
15 in Example 288.

Example 289

(S)-1'-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-[1,4']bipiperidinyl

Melting point 163.4-164.9°C.

20 Example 290

(S)-2-Methyl-6-nitro-2-[4-(4-trifluoromethylphenyl)-piperidin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 138.7-139.9°C.

Example 291

25 (S)-2-Methyl-6-nitro-2-[4-(3-phenyl-2-propenyloxy)-piperidin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 91.3-92.7°C.

Example 292

(S)-2-{4-[3-(4-Chlorophenyl)-2-propenyloxy]piperidin-1-ylmethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 140.6-142.8°C.

5 Example 293

(S)-2-Methyl-6-nitro-2-{4-[2-(4-trifluoromethylphenyl)ethoxy]piperidin-1-ylmethyl}-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 84.6-86.8°C.

10

 Example 294

(S)-2-{4-[2-(4-Chlorophenyl)ethoxy]piperidin-1-ylmethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

15 Melting point 92.5-94°C.

 Example 295

Preparation of (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-N-methyl-4-trifluoromethoxyaniline

20 (S)-2-[4-(4-Trifluoromethoxyphenyl)amino-piperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 282 (400 mg, 0.90 mmol) was dissolved in methanol (10 ml). To the solution, a 37% formaldehyde solution (0.13 ml, 4.52 mmol), sodium cyanotrihydroborate (170 mg, 2.71 mmol) and acetic acid (0.17 ml, 2.71 mmol) were added followed by stirring at room temperature for 30 minutes. The reaction mixture was poured into a

saturated sodium hydrogencarbonate solution and extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced
 5 pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and recrystallized from methylene chloride-diisopropyl ether to afford (S)-N-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-N-methyl-4-trifluoromethoxyaniline (309 mg, yield
 10 78%) as a light yellow crystals.

Optical purity 99.9% e.e.

$[\alpha]_D^{17} = 7.77$ (concentration: 1.042, CHCl_3)

MS 455 (M^+)

15 Melting point 133.2-134.4°C.

Example 296

Preparation of (S)-N-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-N-(4-trifluoromethoxyphenyl)acetamide

20 (S)-2-[4-(4-Trifluoromethoxyphenyl)amino-piperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 282 (153 mg, 0.35 mmol) was dissolved in methylene chloride (5 ml). To the solution, triethylamine (30 μl) and
 25 acetyl chloride (30 μl) were added followed by stirring at room temperature for 1.5 hours. The reaction mixture was poured into water and extracted with methylene chloride. The organic phase was dried over

magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and crystallized from methylene chloride-diisopropyl ether to afford (S)-N-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-N-(4-trifluoromethoxyphenyl)acetamide (82 mg, yield 49%) as a white powder.

10 MS 484(M+1)⁺

Melting point 137.0-138.7°C.

Example 297

Preparation of (S)-2-{4-N-[(4-trifluoromethylphenyl)-acetyl]aminopiperidin-1-yl}methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

15

Tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate prepared in Example 283 (0.1 g, 0.262 mmol) was dissolved in ethanol (4 ml). To the

20 solution, 6 N hydrochloric acid (3 ml) was added followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure. To the residue, methylene (4 ml) chloride and triethylamine (4 ml) were added. The resulting

25 mixture was stirred at room temperature for 5 minutes and then concentrated. To the residue, toluene (10 ml) was added. The solution was concentrated to remove water azeotropically. To the residue, 4-

trifluoromethylphenylacetic acid (0.064 g, 0.315 mmol), methylene chloride (4 ml), triethylamine (0.06 ml, 0.393 mmol) and 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride (WSCD) (0.065 g, 0.341 mmol) were added followed by stirring at room temperature overnight. To the reaction mixture, water was added, and the mixture was extracted with methylene chloride twice. The organic phases were combined, washed with water and a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/acetone = 3/2) and recrystallized from ethyl acetate (3 ml) to afford (S)-2-{4-N-[(4-trifluoromethylphenyl)acetyl]aminopiperidin-1-yl}methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (32 mg, yield 26%) as a white powder. Melting point 152.7-154.3°C.

Example 298

Preparation of 4-trifluoromethylbenzyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate

Tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate prepared in Example 283 (0.300 g, 0.787 mmol) was dissolved in methylene chloride (4 ml). To the solution, trifluoroacetic acid (2 ml) was added followed by stirring at room temperature for 2 hours.

The reaction mixture was concentrated under reduced pressure, and added methylene chloride (4 ml) and triethylamine (4 ml). The mixture was stirred at room temperature for 5 minutes and concentrated under
5 reduced pressure. The residue was dissolved in DMF (6 ml). To the solution, a mixture of 4-(trifluoromethyl)benzyl alcohol (0.166 g, 0.944 mmol) in DMF (4 ml) and 1,1'-carbonyldiimidazole (0.153 g, 0.944 mmol) stirred at room temperature for 4 hours was
10 added followed by stirring at room temperature overnight and then at 65°C for 8 hours. To the reaction mixture, water was added, and the solution was extracted with ethyl acetate twice. The organic phases were combined, washed with water and a saturated saline
15 solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/acetone = 2/1) and recrystallized from ethyl acetate to afford 4-
20 trifluoromethylbenzyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate (0.107 g, yield 28%) as a light yellow powder.

Melting point 141.2-144°C.

25 Using corresponding starting materials gave compounds of Examples 299 and 300 in the same manner as in Example 298.

Example 299

1-(4-Trifluoromethylphenyl)piperidin-4-yl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate

Melting point 134.4-136.9°C.

5 Example 300

4-Trifluoromethoxybenzyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate

Melting point 156.2-158.5°C.

10 Example 301

Preparation of (S)-N-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-4-trifluoromethylbenzylamine

 Tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-
15 dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate prepared in Example 283 (0.300 g, 0.787 mmol) was dissolved in methylene chloride (4 ml). To the solution, trifluoroacetic acid (2 ml) was added followed by stirring at room temperature for 1 hour.
20 The reaction mixture was concentrated under reduced pressure and added methylene chloride (4 ml) and triethylamine (4 ml). The mixture was stirred at room temperature for 20 minutes and then concentrated under reduced pressure. The residue was dissolved in
25 methanol (5 ml). To the solution, 4-trifluoromethylbenzaldehyde (0.164 g, 0.945 mmol), sodium cyanotrihydroborate (0.099 g, 1.57 mmol) and acetic acid (0.09 ml, 1.57 mmol) were added followed by

stirring at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure. To the residue, water was added, and the solution was extracted with methylene chloride. The organic phases
5 were combined, washed with a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol =
10 20/1) and recrystallized from isopropyl alcohol to afford (S)-N-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-4-trifluoromethylbenzylamine (0.078 g, yield 22%) as a light yellow powder.
15 Melting point 148.6-152.9°C.

Example 302

Preparation of (S)-1-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-3-(4-trifluoromethylphenyl)urea

20 Tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate prepared in Example 283 (0.300 g, 0.787 mmol) was dissolved in methylene chloride (4 ml). To the solution, trifluoroacetic acid (2 ml) was added
25 followed by stirring at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure and added methylene chloride (4 ml) and triethylamine (4 ml). The mixture was stirred at room

temperature for 5 minutes and concentrated under reduced pressure. The residue was called "residue 1".

On the other hand, 4-(trifluoromethyl)aniline (0.139 g, 0.865 mmol) and pyridine (0.07 ml, 0.865 mmol) was dissolved in THF (4 ml). To the solution, Phenyl chloroformate (0.108 ml, 0.865 mmol) was added with cooling on ice-bath followed by stirring at room temperature for 1 hour. The reaction mixture was added water and extracted with ethyl acetate. The organic phase was washed with water, 10% hydrochloric acid and a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure.

The resulting residue was dissolved in dimethylsulfoxide (6 ml). To the solution, the "residue 1" was added followed by stirring at room temperature overnight. To the reaction mixture, water was added, and the solution was extracted with ethyl acetate twice. The organic phases were combined, washed with water, a saturated sodium hydrogencarbonate solution and a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (n-hexane/acetone = 2/1) and recrystallized from isopropyl alcohol-n-hexane (1:1) (6 ml) to afford (S)-1-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-3-(4-

trifluoromethylphenyl)urea (0.064 g, yield 17%) as a light yellow powder.

Melting point 136.8-139.9°C.

Example 303

- 5 Preparation of (S)-2-[4-N-(4-trifluoromethylbenzoyl)-aminopiperidin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]carbamate prepared in Example 283 (360 mg, 0.92 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure and added methylene chloride (10 ml) and triethylamine (2 ml). To the solution, 4-trifluoromethylbenzoyl chloride (0.3 ml, 1.85 mmol) was added followed by stirring at room temperature for 1 hour. The reaction mixture was poured into water and extracted with methylene chloride. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) and crystallized from ethyl acetate-diisopropyl ether to afford (S)-2-[4-N-(4-trifluoro-

10

15

20

25

methylbenzoyl)aminopiperidin-1-yl]methyl-2-methyl-6-

nitro-2,3-dihydroimidazo[2,1-b]oxazole (232 mg, yield 55%) as a white powder.

MS 454 (M+H)⁺

Melting point 170.5-171.7°C.

5 Example 304

Preparation of (S)-N-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-2-(4-trifluoromethylphenyl)ethylamine

10 Tert-butyl (S)-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]-N-[2-(4-trifluoromethylphenyl)ethyl]carbamate prepared in Example 284 (0.196 g, 0.354 mmol) was dissolved in methylene chloride (2 ml). To the solution, trifluoroacetic acid (1 ml) was added followed by

15 stirring at room temperature for 4 hours. To the reaction mixture, a saturated sodium hydrogencarbonate solution was added, and the solution was extracted with methylene chloride twice. The organic phases were combined, dried over sodium sulfate and then filtered.

20 The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and treated with isopropyl ether to afford (S)-N-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-

25 2-ylmethyl)piperidin-4-yl]-2-(4-trifluoromethylphenyl)ethylamine (0.020 g, yield 12%) as a light yellow powder.

Melting point 80.7-84.2°C.

Example 305

Preparation of (S)-2-methyl-6-nitro-2-{4-[4-(trifluoromethoxy)benzenesulfinyl]piperidin-1-ylmethyl}-2,3-dihydroimidazo[2,1-b]oxazole

- 5 (S)-2-Methyl-6-nitro-2-{4-[4-(trifluoromethoxyphenyl)sulfanyl]piperidin-1-ylmethyl}-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 285 (300 mg, 0.65 mmol) was dissolved in methylene chloride (5 ml). To the solution, m-chloroperbenzoic acid (169
10 mg, 0.69 mmol) was added followed by stirring at room temperature for 30 minutes. The reaction mixture was diluted with methylene chloride. The solution was washed with a sodium thiosulfate solution, a saturated sodium hydrogencarbonate solution and a saturated
15 saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) and crystallized from ethyl
20 acetate-isopropyl ether to afford (S)-2-methyl-6-nitro-2-{4-[4-(trifluoromethoxy)benzenesulfinyl]piperidin-1-ylmethyl}-2,3-dihydroimidazo[2,1-b]oxazole (219 mg, yield 71%) as a white powder.

MS 475(M+H)⁺

- 25 Melting point 107-109°C.

Example 306

Preparation of 2-(4-tert-butoxycarbonylpiperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-

b]oxazole

2-Chloro-4-nitro-1H-imidazole (3.19 g, 21.6 mmol) and tert-butyl 4-(2-methyloxiran-2-ylmethyl)-piperazine-1-carboxylate (5.53 g, 21.6 mmol) and sodium acetate (1.95 g, 23.8 mmol) were dissolved in 1-propanol (50 ml) followed by stirring under reflux for 48 hours. The reaction mixture was diluted with methylene chloride. The solution was washed with water and a saturated saline solution, dried over sodium 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) and treated with methylene chloride-diisopropyl ether to afford 2-(4-tert-butoxy-carbonylpiperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (1.85 g, yield 23%) as a white powder.

¹H-NMR (CDCl₃) δppm:

1.43 (9H, s), 1.62 (3H, s), 2.45 - 2.68 (5H, m), 2.87 (1H, d, J = 14.9 Hz), 3.30 (4H, br), 3.93 (1H, d, J = 9.7 Hz), 4.30 (1H, d, J = 9.7 Hz), 7.54 (1H, s).

Using corresponding starting materials gave the compound of Example 307 in the same manner as in Example 306.

25 Example 307

2-[4-(4-Cyanophenyl)piperazin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Yield 18%

¹H-NMR (CDCl₃) δppm:

1.67 (3H, s), 2.60 - 2.80 (3H, m), 2.80 - 3.00 (3H, m),
3.22 (4H, br), 3.97 (1H, d, J = 9.8 Hz), 4.35 - 4.50
(1H, m), 6.78 - 6.85 (2H, m), 7.46 - 7.51 (2H, m), 7.55
5 (1H, s).

Example 308

Preparation of 2-[4-(4-trifluoromethylphenyl)piperazin-
1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
b]oxazole

10 To a solution of 2-chloro-4-nitro-1H-
imidazole (1.59 g, 10.8 mmol) and 1-(2-methyloxiran-2-
ylmethyl)-4-(4-trifluoromethylphenyl)piperazine (3.23
g, 10.8 mmol) in 1-propanol (20 ml), sodium
hydrogencarbonate (1.95 g, 23.8 mmol) was added
15 followed by stirring under reflux overnight. The
reaction mixture was concentrated under reduced
pressure. The residue was added water, and the
solution was extracted with methylene chloride. The
organic phase was dried over sodium sulfate and then
20 filtered. The filtrate was concentrated under reduced
pressure. The residue was purified by silica gel
column chromatography (methylene chloride/methanol =
100/1) and crystallized from methylene chloride-
isopropyl ether to afford 2-[4-(4-trifluoro-
25 methylphenyl)piperazin-1-yl]methyl-2-methyl-6-nitro-
2,3-dihydroimidazo[2,1-b]oxazole (1.34 g, yield 29%) as
a light yellow powder.

MS 411 (M⁺)

Melting point 159-160°C.

Also, the above purification by silica gel column chromatography gives an intermediate, 2-chloro-1-{3-[4-(4-trifluoromethylphenyl)piperazin-1-yl]-2-hydroxy-2-methyl}propyl-4-nitroimidazole (697 mg, yield 15%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.17 (3H, s), 2.32 - 2.91 (6H, s), 3.26 - 3.31 (4H, m), 4.03 (2H, s), 6.71 (1H, s), 6.89 - 6.93 (2H, m), 7.45 - 7.51 (2H, m), 8.06 (1H, s).

Using corresponding starting materials gave compounds of Examples 309 to 311 in the same manner as in Example 308.

Example 309

2-[4-(Biphenyl-4-yl)piperazin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Yield 32%, melting point 223-227.8°C.

Example 310

2-[4-(4-Chlorophenyl)piperazin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Yield 14%, melting point 196.6-197.3°C.

Example 311

2-[4-(4-Trifluoromethoxyphenyl)piperazin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Yield 18%

¹H-NMR (CDCl₃) δppm:

1.61 (3H, s), 2.61 (1H, d, J = 14.8 Hz), 2.65 - 2.73 (2H, m), 2.82 - 2.95 (2H, m), 2.93 (1H, d, J = 14.8

Hz), 2.99 - 3.09 (4H, m), 3.94 (1H, d, $J = 9.7$ Hz), 4.34 (1H, d, $J = 9.7$ Hz), 6.78 - 6.86 (2H, m), 7.06 - 7.11 (2H, m), 7.53 (1H, s).

Example 312

- 5 Preparation of 1-[3-(4-tert-butoxycarbonylpiperazin-1-yl)-2-hydroxy-2-methyl]propyl-2-chloro-4-nitroimidazole
- 2-Chloro-4-nitro-1H-imidazole (863 mg, 5.85 mmol) and tert-butyl 4-(2-methyloxiran-2-ylmethyl)-piperazine-1-carboxylate (1.5 g, 5.85 mmol) was
- 10 dissolved in 1-propanol (10 ml) followed by stirring under reflux for 6 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene
- 15 chloride/methanol = 100/1) to afford 1-[3-(4-tert-butoxycarbonylpiperazin-1-yl)-2-hydroxy-2-methyl]propyl-2-chloro-4-nitroimidazole (705 mg, yield 29.8%) as a white powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

- 20 1.15 (3H, s), 1.45 (9H, s), 2.35 (1H, d, $J = 13.9$ Hz), 2.45 - 2.65 (5H, m), 3.25 (1H, s), 3.42 (4H, t, $J = 4.3$ Hz), 4.00 (2H, s), 8.05 (1H, s).

- Using 2-chloro-4-nitro-1H-imidazole and tert-butyl 4-(oxiran-2-ylmethyl)piperazine-1-carboxylate,
- 25 tert-butyl 4-[2-(2-methyloxiran-2-yl)ethyl]piperazine-1-carboxylate or benzyl 4-(2-methyloxiran-2-ylmethyl)-piperazine-1-carboxylate gave compounds of Examples 313 to 315 in the same manner as in Example 312.

Example 313

Tert-butyl 4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]piperazine-1-carboxylate

Light yellow powder, yield 43%

5 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.46 (9H, s), 2.16 - 2.50 (4H, m), 2.55 - 2.70 (2H, m),
3.40 - 3.51 (4H, m), 3.64 (1H, s), 3.91 - 4.09 (2H, m),
4.17 (1H, dd, $J = 2.0$ Hz, 13.5 Hz), 8.00 (1H, s).

Example 314

10 Tert-butyl 4-[4-(2-chloro-4-nitroimidazol-1-yl)-3-hydroxy-3-methylbutyl]piperazine-1-carboxylate

White powder, yield 17%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.23 (3H, s), 1.40 - 1.74 (11H, m), 2.23 - 2.58 (5H,
15 m), 2.81 - 2.95 (1H, m), 3.26 - 3.51 (4H, m), 3.91 (1H,
d, $J = 14.0$ Hz), 3.99 (1H, d, $J = 14.0$ Hz), 6.94 (1H,
s), 8.07 (1H, s).

Example 315

20 Benzyl 4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazine-1-carboxylate

Light yellow oil, yield 81%

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.14 (3H, s), 2.35 - 2.76 (6H, m), 3.43 - 3.61 (4H, m),
4.01 (2H, s), 5.13 (2H, s), 7.28 - 7.43 (5H, m), 8.04
25 (1H, s).

Example 316

Preparation of isobutyl 4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazine-1-carboxylate

A mixture of 1-[3-(4-tert-butoxycarbonyl-piperazin-1-yl)-2-hydroxy-2-methyl]propyl-2-chloro-4-nitroimidazole prepared in Example 312 (150 mg, 0.37 mmol) and trifluoroacetic acid (5 ml) was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methylene chloride (5 ml). To the solution, triethylamine (0.23 ml, 1.63 mmol) and isobutyl chloroformate (112 mg, 0.82 mmol) were added in this order followed by stirring at room temperature for 30 minutes. The reaction mixture was washed with water, a saturated sodium hydrogencarbonate solution and a saturated saline solution in this order, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure to afford isobutyl 4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazine-1-carboxylate, which was used in the next step without purification.

¹H-NMR (CDCl₃) δppm:

0.93 (6H, d, J = 6.7 Hz), 1.14 (3H, s), 1.82 - 2.00 (1H, m), 2.39 (1H, d, J = 13.9 Hz), 2.47 - 2.73 (5H, m), 3.11 (1H, d, J = 7.3 Hz), 3.17 (1H, d, J = 7.3 Hz), 3.41 - 3.55 (4H, m), 3.87 (2H, s), 4.04 (1H, s), 8.10 (1H, s).

Example 317

Preparation of benzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

To a mixture of benzyl 4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-piperazine-1-carboxylate prepared in Example 315 (55.22 g, 126.11 mmol) and 1,4-dioxane (550 ml), sodium hydride (6.05 g, 151.25 mmol) was added followed by stirring under reflux for 14 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, water was added, and the solution was extracted with methylene chloride twice. The organic phases were washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate) to afford benzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (26.54 g, yield 52%) as a white powder. Melting point 130.5-132.1°C

¹H-NMR (CDCl₃) δppm:

1.61 (3H, s), 2.38 - 2.69 (5H, m), 2.86 (1H, d, J = 14.8 Hz), 3.10 - 3.50 (4H, m), 3.92 (1H, d, J = 9.9 Hz), 4.33 (1H, d, J = 9.9 Hz), 5.11 (2H, s), 7.23 - 7.38 (5H, m), 7.53 (1H, s).

Using corresponding starting materials gave compounds of Examples 318 to 320 in the same manner as in Example 317.

Example 318

Isobutyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-

b]oxazol-2-ylmethyl)piperazine-1-carboxylate

Light yellow powder, yield 39%, melting point 176.5-177.3°C.

Example 319

- 5 Tert-butyl 4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

White powder, yield 45%.

Melting point 185-188°C (decomposition)

¹H-NMR (CDCl₃) δppm:

- 10 1.45 (9H, s), 2.48 - 2.58 (4H, m), 2.85 (2H, d, J = 5.1 Hz), 3.31 - 3.45 (4H, m), 4.20 (1H, dd, J = 6.9 Hz, 10.3 Hz), 4.34 (1H, dd, J = 8.4 Hz, 10.3 Hz), 5.35 - 5.48 (1H, m), 7.55 (1H, s).

Example 320

- 15 Tert-butyl 4-[2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]piperazine-1-carboxylate

Light yellow powder, yield 70%, melting point 190-191°C (decomposition).

Example 321

- 20 Preparation of tert-butyl 4-[3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl]piperazine-1-carboxylate

A mixture of 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl methane-
25 sulfonate (2 g, 6.6 mmol), tert-butyl piperazine-1-carboxylate (1.4 g, 7.5 mmol), triethylamine (1.3 g, 12.85 mmol), potassium iodide (1.8 g, 10.8 mmol) and DMF (15 ml) was stirred at 60°C overnight. The reaction

mixture was allowed to return to room temperature and then added water, and the resulting solution was extracted with ethyl acetate three times. The organic phases were combined, washed with water twice and then
5 with a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate 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-(2-
10 methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl]piperazine-1-carboxylate (1.9 g, yield 73%) as a white powder.

Melting point 166-167°C.

Example 322

15 Preparation of 2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride

2-(4-Tert-butoxycarbonylpiperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
20 b]oxazole prepared in Example 306 (1.19 g, 3.24 mmol) was dissolved in trifluoroacetic acid (30 ml) followed by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methanol (30
25 ml) and added a solution of hydrogen chloride in ethyl acetate slowly followed by stirring for 30 minutes with cooling on ice-bath. The precipitates were filtered off to afford 2-methyl-6-nitro-2-(piperazin-1-

ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole

dihydrochloride (1.06 g, yield 96%) as a yellow powder.

$^1\text{H-NMR}$ (DMSO-d_6) δ ppm:

1.68 (3H, s), 3.00 - 3.59 (6H, m), 4.14 (1H, d, $J =$
5 11.1 Hz), 4.36 (1H, d, $J = 11.1$ Hz), 4.50 - 6.12 (4H,
br), 8.17 (1H, s), 9.62 (2H, br).

Example 323

Preparation of 2-[4-(biphenyl-4-ylmethyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

10 A mixture of tert-butyl 4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 319 (400 mg, 1.13 mmol) and trifluoroacetic acid (10 ml) was stirred at room temperature for 4 hours. The reaction mixture was
15 concentrated. The residue was dissolved in methylene chloride (10 ml) and neutralized with triethylamine (2 ml, 14.35 mmol). The resulting solution was concentrated under reduced pressure, and the residue was dissolved in methanol (10 ml). To the solution, 4-
20 phenylbenzaldehyde (515 mg, 2.83 mmol), sodium cyanotrihydroborate (214 mg, 3.41 mmol) and acetic acid (0.21 mg, 3.67 mmol) were added in this order followed by stirring at room temperature overnight. The reaction mixture was concentrated. To the residue,
25 water was added, and the solution was extracted with methylene chloride twice. The organic phases were combined, washed with a saturated sodium hydrogen-carbonate solution and a saturated saline solution in

this order, 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 = 5 20/1) to afford 2-[4-(biphenyl-4-ylmethyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (188 mg, yield 40%) as a white powder. Melting point 183-185°C (decomposition).

Using corresponding starting materials gave 10 compounds of Examples 324 to 329 in the same manner as in Example 323.

Example 324

2-{2-[4-(4-Trifluoromethylbenzyl)piperazin-1-yl]ethyl}-
2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
15 White powder, yield 36%, melting point 148-149°C.

Example 325

2-Methyl-6-nitro-2-{3-[4-(4-trifluoromethylbenzyl)-
piperazin-1-yl]propyl}-2,3-dihydroimidazo[2,1-b]oxazole
White powder, yield 57%.
20 Melting point 154-156°C.

Example 326

2-{2-[4-(Biphenyl-4-ylmethyl)piperazin-1-yl]ethyl}-2-
methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
White powder, yield 53%.
25 Melting point 181-182°C.

Example 327

2-{3-[4-(Biphenyl-4-ylmethyl)piperazin-1-yl]propyl}-2-
methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

White powder, yield 65%.

Melting point 176-178°C.

Example 328

4-(N,N-Dimethylamino)-4'-[4-(2-methyl-6-nitro-2,3-
5 dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-
ylmethyl]biphenyl

White powder, yield 68%

¹H-NMR (CDCl₃) δppm:

1.58 (3H, s), 2.36 (4H, br), 2.50 - 2.60 (2H, m), 2.54
10 (1H, d, J = 14.8 Hz), 2.67 - 2.76 (2H, m), 2.84 (1H, d,
J = 14.8 Hz), 2.99 (6H, s), 3.41 (1H, d, J = 12.9 Hz),
3.48 (1H, d, J = 12.9 Hz), 3.87 (1H, d, J = 9.7 Hz),
4.30 (1H, d, J = 9.7 Hz), 6.76 - 6.82 (2H, m), 7.25 -
7.29 (2H, m), 7.46 - 7.51 (4H, m), 7.53 (1H, s).

15 Example 329

2-Methyl-6-nitro-2-[4-(2-phenyl-1H-imidazol-4-
ylmethyl)piperazin-1-ylmethyl]-2,3-dihydroimidazo[2,1-
b]oxazole

White powder, yield 93%

20 ¹H-NMR (DMSO-d₆) δppm:

1.52 (3H, s), 2.10 - 2.64 (6H, m), 2.67 (1H, d, J =
15.4 Hz), 2.74 (1H, d, J = 15.4 Hz), 3, 10 - 3.70 (4H,
br), 4.04 (1H, d, J = 10.7 Hz), 4.21 (1H, d, J = 10.7
Hz), 6.97 (1H, br), 7.27 - 7.34 (1H, m), 7.38 - 7.45
25 (2H, m), 7.88 - 7.93 (2H, m), 8.12 (1H, s).

Example 330

Preparation of 2-(3,4-dichlorophenyl)-1-[4-(2-methyl-6-
nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-

piperazin-1-yl]ethanone

A mixture of 3,4-(dichlorophenyl)acetic acid (418 mg, 2.04 mmol) and thionyl chloride (3 ml) was stirred under reflux for 6 hours. The reaction mixture
5 was concentrated under reduced pressure to afford a corresponding acid chloride.

On the other hand, a mixture of 2-(4-tert-butoxycarbonylpiperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example
10 306 (300 mg, 0.816 mmol) and trifluoroacetic acid (6 ml) was stirred at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methylene chloride (10 ml) and added triethylamine (2 ml, 14.35
15 mmol). To the solution, a solution of the acid chloride obtained above in methylene chloride (5 ml) was added with cooling on ice-bath followed by stirring at room temperature for 30 minutes. The reaction mixture was washed with a saturated sodium
20 hydrogencarbonate solution, water and a saturated saline solution in this order, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography
25 (methylene chloride/methanol = 100/1) to afford 2-(3,4-dichlorophenyl)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone (255 mg, yield 69%) as a white powder.

Melting point 189-191°C.

Using corresponding starting materials gave compounds of Examples 331 and 332 in the same manner as in Example 330.

5 Example 331

1-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-2-(4-trifluoromethylphenyl)ethanone

Melting point 168-171.4°C.

10 Example 332

2-(3,4-Dichlorophenoxy)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone

Melting point 209-211°C.

15 Example 333

Preparation of 2-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-(4-trifluoromethylphenyl)acetamide

20 A mixture of 2-(4-tert-butoxycarbonyl-piperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 306 (500 mg, 1.36 mmol) and trifluoroacetic acid (15 ml) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced
25 pressure. The residue was dissolved in methylene chloride (10 ml) and added triethylamine (2 ml, 14.35 mmol). The solution was concentrated under reduced pressure, and the residue was dissolved in DMF (10 ml).

To the solution, 2-bromo-N-(4-trifluoromethylphenyl)acetamide (423 mg, 1.5 mmol), potassium carbonate (207 mg, 1.5 mmol), and sodium iodide (204 mg, 1.36 mmol) were added followed by stirring at room temperature for 5 hours. To the reaction mixture, water was added, and the solution was extracted with ethyl acetate twice. The organic phases were combined, washed with water three times and a saturated saline solution, dried over sodium 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 2-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-(4-trifluoromethylphenyl)acetamide (389 mg, yield 61%) as a white powder.

¹H-NMR (CDCl₃) δppm:

1.62 (3H, s), 2.53 - 2.84 (9H, m), 2.88 (1H, d, J = 14.8 Hz), 3.06 (1H, d, J = 16.7 Hz), 3.14 (1H, d, J = 16.7 Hz), 3.93 (1H, d, J = 9.7 Hz), 4.30 (1H, d, J = 9.7 Hz), 7.55 (1H, s), 7.55 - 7.59 (2H, m), 7.65 - 7.71 (2H, m), 9.20 (1H, s).

Using corresponding starting materials gave compounds of Examples 334 to 336 in the same manner as in Example 333.

Example 334

Ethyl [4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-