

b]oxazol-2-ylmethyl)piperazin-1-yl]acetate

¹H-NMR (CDCl₃) δppm:

1.25 (3H, t, J = 7.1 Hz), 1.60 (3H, s), 2.45 - 2.64
(6H, m), 2.55 (1H, d, J = 14.8 Hz), 2.72 - 2.81 (2H,
5 m), 2.87 (1H, d, J = 14.8 Hz), 3.14 (2H, s), 3.90 (1H,
d, J = 9.7 Hz), 4.16 (2H, q, J = 7.1 Hz), 4.31 (1H, d,
J = 9.7 Hz), 7.57 (1H, s).

Example 335

3-{3-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-
10 b]oxazol-2-ylmethyl)piperazin-1-yl]propyl}-3H-
benzoxazol-2-one

Melting point 123-126°C.

Example 336

1-(4-Chlorophenyl)-2-[4-(2-methyl-6-nitro-2,3-
15 dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-
yl]ethanone

¹H-NMR (CDCl₃) δppm:

1.60 (3H, s), 2.47 (4H, br), 2.53 (1H, d, J = 14.9 Hz),
2.57 - 2.65 (2H, m), 2.74 - 2.84 (2H, m), 2.87 (1H, d,
20 J = 14.9 Hz), 3.64 (1H, d, J = 16.7 Hz), 3.75 (1H, d, J
= 16.7 Hz), 3.90 (1H, d, J = 9.7 Hz), 4.30 (1H, d, J =
9.7 Hz), 7.42 (2H, d, J = 8.6 Hz), 7.54 (1H, s), 7.92
(2H, d, J = 8.6 Hz).

Example 337

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

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 (130 mg, 0.35 mmol), trifluoroacetic acid (3 ml) and methylene chloride (5 ml) was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methylene chloride (5 ml) and added triethylamine (107.5 mg, 1.06 mmol). To the solution, benzyl chloroformate (120 mg, 0.71 mmol) was added with cooling on ice-bath followed by stirring at room temperature for 1 hour. The reaction mixture was washed with water, a saturated sodium hydrogencarbonate solution 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 = 20/1) to afford a yellow oil. The oil was dissolved in ethyl acetate (5 ml). To the solution, a saturated hydrochloride solution in ethyl acetate was added, and the precipitates were filtered off to afford benzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-carboxylate hydrochloride (46.8 mg, yield 30%) as a white powder.

Melting point 130.5-132.1°C.

Using corresponding starting materials gave compounds of Examples 338 to 340 in the same manner as in Example 337.

Example 338

Phenyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

Melting point 81-85°C.

5

Example 339

Isopropyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

Melting point 158.3-159.8°C.

Example 340

10 n-Octyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

Melting point 138-139.4°C.

Example 341

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

15

To the solution 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) in methylene chloride (2 ml), trifluoroacetic acid (1 ml) was added followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in DMF (1 ml) and neutralized with triethylamine (1 ml).

20

25

To the solution, a mixture of 4-trifluoromethylbenzyl alcohol (297 mg, 1.69 mmol), 1,1'-carbonyldiimidazole (274 mg, 1.69 mmol) and DMF (1

ml) stirred at room temperature for 1 hour was added followed by stirring at room temperature for 3 hours. The reaction mixture was diluted with water and extracted with ethyl acetate twice. The organic phases
5 were combined, washed with water twice and then 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
10 = 20/1) to afford 4-trifluoromethylbenzyl 4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (322 mg, yield 63%) as a light yellow powder.

Melting point 120-122°C.

15 Using corresponding starting materials gave compounds of Examples 342 and 343 in the same manner as in Example 341.

Example 342

4-Trifluoromethylbenzyl 4-[2-(2-methyl-6-nitro-2,3-
20 dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]piperazine-1-carboxylate

Light yellow powder, yield 68%, melting point 139-140°C.

Example 343

4-Trifluoromethylbenzyl 4-[3-(2-methyl-6-nitro-2,3-
25 dihydroimidazo[2,1-b]oxazol-2-yl)propyl]piperazine-1-carboxylate

Light yellow powder, yield 57%, melting point 130-133°C.

Example 344

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

A mixture of 2-(4-tert-butoxycarbonyl-
5 piperazin-1-yl)methyl-2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole prepared in Example 306
(220 mg, 0.6 mmol), trifluoroacetic acid (1 ml) and
methylene chloride (2 ml) was stirred at room
temperature for 2 hours. The reaction mixture was
10 concentrated under reduced pressure. The residue was
dissolved in methylene (2 ml) chloride and neutralized
with triethylamine (1 ml, 7.17 mmol). The resulting
solution was concentrated under reduced pressure, and
the residue was dissolved in DMF (2 ml).

15 To the solution, a mixture of 3-(4-
trifluoromethylphenyl)-2-propyn-1-ol (110 ml, 0.55
mmol), 1,1'-carbonyldiimidazole (90 mg, 0.55 mmol) and
DMF (2 ml) stirred at room temperature for 2 hours was
added followed by stirring at room temperature
20 overnight. The reaction mixture was diluted with water
and extracted with ethyl acetate twice. The organic
phases were combined, washed with water twice and then
with a saturated saline solution, dried over sodium
sulfate and then filtered. The filtrate was
25 concentrated under reduced pressure. The residue was
purified by silica gel column chromatography (methylene
chloride/ethyl acetate = 5/1).

The resulting free form was dissolved in

ethanol (5 ml) and added a solution of maleic acid (96 mg, 0.83 mmol) in ethanol (5 ml). The precipitates were filtered off to afford 3-(4-trifluoromethylphenyl)-2-propynyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate maleate (227 mg, yield 68%) as a white powder.

Melting point 166°C (decomposition).

Example 345

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

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 (900 mg, 2.4 mmol) and trifluoroacetic acid (20 ml) was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methylene (20 ml) chloride and neutralized with triethylamine (6 ml, 43.05 mmol). The resulting mixture was concentrated under reduced pressure, and the residue was dissolved in DMF (5 ml).

To the solution, a mixture of 4-methylsulfanylbenzyl alcohol (470 mg, 3 mmol), 1,1'-carbonyldiimidazole (500 mg, 3.1 mmol) and DMF (10 ml) stirred at room temperature for 3 hours was added followed by stirring at room temperature overnight. To the reaction mixture, water was added, and the mixture

was extracted with ethyl acetate twice. The organic phases were combined, washed with water twice, and then with a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was

5 concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to afford 4-

methylsulfanylbenzyl 4-(2-methyl-6-nitro-2,3-

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

10 carboxylate (860 mg, yield 79%) as a white powder. Melting point 118-120°C.

Example 346

Preparation of 4-methanesulfinylbenzyl 4-(2-methyl-6-

nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-

15 piperazine-1-carboxylate

To a mixture of 4-methylsulfanylbenzyl 4-(2-

methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-

ylmethyl)piperazine-1-carboxylate prepared in Example

345 (300 mg, 0.67 mmol) and methylene chloride (10 ml),

20 m-chloroperbenzoic acid (210 mg, 0.85 mmol) was added followed by stirring for 2 hours with cooling on ice-bath. The reaction mixture was washed with a saturated sodium sulfite solution, a saturated sodium

hydrogencarbonate solution, and a saturated saline

25 solution in this order, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from isopropyl alcohol-ether to afford 4-

methanesulfinylbenzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (203 mg, yield 65%) as a white powder. Melting point 117-121°C.

5 Example 347

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

To a mixture of 4-(tert-butyldimethyl-
10 silanyloxy)benzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (400 mg, 0.75 mmol) and THF(10 ml), a 1M solution of tetrabutylammonium fluoride in THF (0.8 ml, 0.8 mmol) was added followed by stirring for 20 minutes
15 with cooling on ice-bath. To the reaction mixture, ethyl acetate was added, and the solution was washed with a saturated ammonium chloride solution, water and a saturated saline solution in this order, dried over magnesium sulfate and then filtered. The filtrate was
20 concentrated under reduced pressure. To the residue, diethyl ether was added, and the precipitates were filtered off to afford 4-hydroxybenzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (95 mg, yield 30%) as
25 a light yellow powder.

¹H-NMR (CDCl₃) δppm:

1.59 (3H, s), 2.30 - 2.70 (4H, m), 2.56 (1H, d, J = 15.0 Hz), 2.86 (1H, d, J = 15.0 Hz), 3.10 - 3.55 (4H,

m), 3.91 (1H, d, J = 10.0 Hz), 4.28 (1H, d, J = 10.0 Hz), 5.03 (2H, s), 5.30 (1H, brs), 6.84 (2H, d, J = 8.0 Hz), 7.24 (2H, d, J = 8.0 Hz), 7.53 (1H, s).

Example 348

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

A mixture of 4-(1,1-dimethoxyethyl)benzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (600 mg, 1.23 mmol),
10 1 N hydrochloric acid (10 ml, 10 mmol) and THF (15 ml) was stirred at room temperature for 2 hours, then neutralized with a saturated sodium hydrogencarbonate solution, and the resulting mixture was extracted with
15 ethyl acetate. The organic phase was washed with water and then with a saturated saline solution, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure. To the residue, diethyl ether was added, and the precipitates were
20 filtered off to afford 4-acetylbenzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (558 mg, yield 99%) as a white powder.

Melting point 101-102°C.

- 25 Example 349

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

Using 4-[dimethoxy(phenyl)methyl]benzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (800 mg, 1.45 mmol) gave 4-benzoylbenzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (630 mg, yield 86%) as a white powder in the same manner as in Example 348.

Melting point 105-107°C.

Example 350

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

A mixture of 4-(tert-butoxycarbonylamino)-benzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (340 mg, 0.66 mmol), trifluoroacetic acid (2 ml) and methylene chloride (10 ml) was stirred at room temperature for 2 hours, and then neutralized with a saturated sodium hydrogencarbonate solution. The organic phase was washed with water and a saturated saline solution in this order, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure. To the residue, diethyl ether was added, and the precipitates were filtered off to afford 4-aminobenzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (100 mg, yield 37%) as a light yellow powder.

¹H-NMR (CDCl₃) δppm:

1.61 (3H, s), 2.35 - 2.70 (4H, m), 2.56 (1H, d, J = 15.0 Hz), 2.85 (1H, d, J = 15.0 Hz), 3.05 - 3.55 (4H, m), 3.69 (2H, brs), 3.91 (1H, d, J = 10.0 Hz), 4.28 (1H, d, J = 10.0 Hz), 4.98 (2H, s), 6.55 (2H, d, J = 8.0 Hz), 7.14 (2H, d, J = 8.0 Hz), 7.53 (1H, s).

Example 351

Preparation of 4-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid phenylamide hydrochloride

10 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 (130 mg, 0.35 mmol) and trifluoroacetic acid (3 ml) was stirred at room temperature overnight. The reaction
15 mixture was concentrated under reduced pressure, and the residue was dissolved in methylene chloride (3 ml), then neutralized with triethylamine (2 ml, 14.35 mmol). To the solution, phenylisocyanate (63 mg, 0.53 mmol) was added followed by stirring at room temperature for
20 30 minutes, and then diluted with water. The solution was extracted with methylene chloride, and the organic phase was dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel
25 column chromatography (methylene chloride/methanol = 50/1) to afford an amorphous form.

The amorphous form was dissolved in ethyl acetate. To the solution, a saturated hydrochloric

acid solution in ethyl acetate was added, and the resulting precipitates were filtered off to afford 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid phenylamide hydrochloride (124 mg, yield 55%) as a light yellow powder.

¹H-NMR (DMSO-d₆) δppm:

1.55 (3H, s), 2.50 - 2.56 (4H, m), 2.75 (2H, s), 3.21 - 3.40 (4H, m), 4.05 (1H, d, J = 10.7 Hz), 4.24 (1H, d, J = 10.7 Hz), 6.92 - 6.99 (1H, m), 7.21 - 7.28 (2H, m), 7.44 - 7.48 (2H, m), 8.13 (1H, s), 8.59 (1H, s).

Example 352

Preparation of 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid isopropylamide

A mixture of tert-butyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 306 (140 mg, 0.38 mmol) and trifluoroacetic acid (3 ml) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in methylene chloride (3 ml), then neutralized with triethylamine (2 ml, 14.35 mmol). To the solution, isopropylisocyanate (75 μl, 0.76 mmol) was added followed by stirring at room temperature for 1 hour, then diluted with water. The solution was extracted with methylene chloride. The organic phase was 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 = 50/1) to afford 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid isopropylamide (90 mg, yield 67%) as a white powder. Melting point 175-176.3°C.

Using corresponding starting materials gave compounds of Examples 353 and 354 in the same manner as in Example 352.

Example 353

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (3-chlorophenyl)-amide

¹H-NMR (DMSO-d₆) δppm:

1.56 (3H, s), 2.50 - 2.56 (4H, m), 2.77 (2H, s), 3.21 - 3.40 (4H, m), 4.08 (1H, d, J = 10.7 Hz), 4.26 (1H, d, J = 10.7 Hz), 6.95 (1H, bd, J = 8.0 Hz), 7.23 (1H, t, J = 8.0 Hz), 7.36 (1H, bd, J = 8.0 Hz), 7.61 (1H, t, J = 2.0 Hz), 8.13 (1H, s), 8.61 (1H, s).

Example 354

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid cyclohexylamide
Melting point 216.5-218.5°C.

Example 355

Preparation of 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carbothioic acid (4-chlorophenyl)amide

2-Methyl-6-nitro-2-(piperazin-1-ylmethyl)-
2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride
prepared in Example 322 (196 mg, 0.73 mmol) was
suspended in methylene chloride (10 ml), then
5 neutralized with triethylamine (0.27 ml, 1.94 mmol).
To the solution, 4-chlorophenyl isothiocyanate (140 mg,
0.83 mmol) was added followed by stirring at room
temperature for 1 hour. The reaction mixture was
washed with water, a saturated sodium hydrogencarbonate
10 solution 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 = 30/1) to
15 afford 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
b]oxazol-2-ylmethyl)piperazine-1-carbothioic acid (4-
chlorophenyl)amide (128 mg, yield 40%) as a light brown
powder.

Melting point 204-206°C (decomposition).

20 Using corresponding starting materials gave
compounds of Examples 356 and 357 in the same manner as
in Example 355.

Example 356

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-
25 ylmethyl)piperazine-1-carbothioic acid phenylamide

Melting point 164-165°C (decomposition).

Example 357

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-

ylmethyl)piperazine-1-carbothioic acid (4-methoxyphenyl)amide

Melting point 189-191°C (decomposition).

Example 358

- 5 Preparation of 2-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]benzoxazole

2-(4-tert-Butoxycarbonylpiperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 306 (500 mg, 1.36 mmol) was dissolved in trifluoroacetic acid (10 ml) followed by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure, and added methylene chloride (1 ml) and triethylamine (1 ml). The solution was stirred at room temperature for 5 minutes, and then concentrated under reduced pressure. The residue was dissolved in methylene chloride. To the solution, 2-chlorobenzoxazole (0.19 ml, 1.63 mmol) and triethylamine (0.23 ml, 1.63 mmol) were 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 filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and crystallized from

methylene chloride-diisopropyl ether to afford 2-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]benzoxazole (325 mg, yield 62%) as a white powder.

5 MS 384 (M^+)

Melting point 228.0-229.5°C.

Using corresponding starting materials gave compounds of Examples 359 to 361 in the same manner as in Example 358.

10 Example 359

2-[4-(6-Nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]benzoxazole

White powder, yield 74%

MS 370 (M^+)

15 Melting point 206-209°C (decomposition).

Example 360

2-{4-[2-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]piperazin-1-yl}benzoxazole

White powder, yield 73%

20 MS 398 (M^+)

Melting point 187.6-189.6°C.

Example 361

2-{4-[3-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl]piperazin-1-yl}benzoxazole

25 White powder, yield 90%

MS 412 (M^+)

Melting point 172.0-174.4°C.

Example 362

Preparation of tert-butyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]piperazine-1-carboxylate

(R)-2-Chloro-1-[2-hydroxy-3-(4-methylbenzene-sulfonyloxy)propyl]-4-nitroimidazole prepared in Example 8 (16.86 g, 44.86 mmol) and tert-butyl piperazine-1-carboxylate (8.36 g, 44.89 mmol) were dissolved in acetonitrile (100 ml). To the solution, triethylamine (6.3 ml, 45.2 mmol) was added followed by stirring under reflux for 6 hours. The reaction mixture was allowed to return to room temperature, and concentrated under reduced pressure. To the residue, water (100 ml) was added and extracted with ethyl acetate (100 ml) twice. The organic phases were combined, washed with water (100 ml) and a saturated saline solution (100 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/methanol = 40/1) and then recrystallized from ethyl acetate/n-hexane to afford tert-butyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]piperazine-1-carboxylate (11.61 g, yield 66%) as a light yellow powder.

¹H-NMR (CDCl₃) δppm:

1.46 (9H, s), 2.21 - 2.50 (4H, m), 2.54 - 2.70 (2H, m), 3.39 - 3.48 (4H, m), 3.65 (1H, s), 3.89 - 4.10 (2H, m), 4.20 (1H, dd, J = 1.9 Hz, 13.5 Hz), 8.00 (1H, s).

Example 363

Preparation of tert-butyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]piperazine-1-carboxylate (alternative synthesis of the compound of
5 Example 362)

A mixture of (R)-2-chloro-1-(oxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 9 (1 g, 4.91 mmol), tert-butyl piperazine-1-carboxylate (1.01 g, 5.40 mmol) and DMF (3 ml) was stirred at 70°C for 6
10 hours. The reaction mixture was allowed to return to room temperature and added water (7 ml). The precipitates were filtered off, and purified by silica gel column chromatography (methylene chloride/methanol = 40/1) to afford tert-butyl (S)-4-[3-(2-chloro-4-
15 nitroimidazol-1-yl)-2-hydroxypropyl]piperazine-1-carboxylate (967 mg, 51%) as a light yellow powder.

Example 364

Preparation of tert-butyl (R)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]piperazine-1-
20 carboxylate

A mixture of 2-chloro-4-nitro-1H-imidazole (6.1 g, 41.35 mmol), (S)-(+)-glycidyl tosylate (12.27 g, 53.75 mmol) and sodium hydrogencarbonate (7.3 g, 86.89 mmol) in ethanol (30 ml) was stirred under reflux
25 for 9 hours. The reaction mixture was allowed to return to room temperature, then diluted with water, and the solution was extracted with methylene chloride twice. The extract was washed with a saturated saline

solution, dried over magnesium sulfate and then filtered. The filtrate was concentrated to afford a foam. The resulting foam was dissolved in DMF (60 ml). To the solution, tert-butyl piperazine-1-carboxylate
5 (8.47 g, 45.48 mmol), triethylamine (6.92 ml, 49.64 mmol) and sodium iodide (6.82 g, 45.5 mmol) were added followed by stirring at room temperature for 24 hours. The reaction mixture was poured into water, and extracted with ethyl acetate twice. The organic phases
10 were combined, washed with water three times, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate) to afford tert-butyl
15 (R)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]piperazin-1-carboxylate (6.43 g, yield 40%) as a light yellow oil.

¹H-NMR (CDCl₃) δppm:

1.48 (9H, s), 2.16 - 2.50 (4H, m), 2.55 - 2.69 (2H, m),
20 3.37 - 3.50 (4H, m), 3.65 (1H, s), 3.90 - 4.25 (3H, m), 8.00 (1H, s).

Example 365

Preparation of tert-butyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-
25 piperazine-1-carboxylate

A mixture of (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (7.00 g, 32.2 mmol) and tert-butyl piperazine-1-

carboxylate (6.29 g, 33.8 mmol) and DMF (70 ml) was stirred at 70°C for 8 hours. The reaction mixture was allowed to return to room temperature, then diluted with water, and then the solution was extracted with
5 ethyl acetate twice. The organic phases were combined, washed with water three times, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. To the residue, diethyl ether was added. The precipitates were
10 filtered off, and dried at room temperature under reduced pressure to afford tert-butyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-1-carboxylate (10.25 g, yield 79%) as a light yellow powder.
15 Optical purity >98.4% e.e.
 $[\alpha]_D^{27} = 25.488$ (concentration: 1.024, CHCl₃)
¹H-NMR (CDCl₃) δppm:
1.14 (3H, s), 1.46 (9H, s), 2.34 (1H, d, J = 13.9 Hz),
2.47 - 2.67 (5H, m), 3.26 (1H, s), 3.44 (4H, t, J = 4.4
20 Hz), 3.99 (2H, s), 8.04 (1H, s).

Example 366

Preparation of tert-butyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-piperazine-1-carboxylate (alternative synthesis of the
25 compound of Example 365)

To the solution of 2-Chloro-4-nitro-1H-imidazole (89.4 g, 606 mmol) and tert-butyl (S)-4-(2-methyloxiran-2-ylmethyl)piperazine-1-carboxylate (119

g, 466 mmol) in ethanol (475 ml), sodium hydrogen-carbonate (58.7 g, 699 mmol) was added followed by stirring under reflux for 6 hours. The reaction mixture was concentrated under reduced pressure, and
5 the residue was added water. The mixture was extracted with ethyl acetate, and the extract was dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was dispersed into ethyl acetate, and filtered off to
10 afford a solid. The filtrate was concentrated, and the residue was purified by silica gel column chromatography (n-hexane/acetone = 3/1) to afford a solid. The solids were combined and dried under reduced pressure to afford tert-butyl (S)-4-[3-(2-chloro-4-
15 nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-piperazine-1-carboxylate (84.7 g, yield 45%) as a white powder.

Example 367

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

A mixture of (S)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 18 (440 mg, 2.02 mmol), tert-butyl piperazine-1-carboxylate (414 mg, 2.22 mmol) and DMF (4 ml) was
25 stirred at 55-60°C for 9 hours. The reaction mixture was allowed to return to room temperature, then diluted with water (24 ml), and the solution was extracted with ethyl acetate (10 ml) twice. The organic phases were

combined, washed with water (20 ml) three times and a saturated saline solution (10 ml), dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue
5 treated with diethyl ether to afford tert-butyl (R)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazine-1-carboxylate (662 mg, yield 81%) as a light yellow powder.

¹H-NMR (CDCl₃) δppm:

10 1.15 (3H, s), 1.45 (9H, s), 2.34 (1H, d, J = 13.9 Hz),
2.48 - 2.67 (5H, m), 3.27 (1H, s), 3.44 (4H, t, J = 4.4 Hz), 3.99 (2H, s), 8.04 (1H, s).

Using 2-chloro-4-nitro-1H-imidazole and tert-butyl (R)-4-(2-methyloxiran-2-ylmethyl)piperazine-1-
15 carboxylate gave the compound of Example 368 in the same manner as in Example 366.

Example 368

Tert-butyl (R)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazine-1-carboxylate
20 (alternative synthesis of the compound of Example 367)
White powder, yield 20%.

Example 369

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

To a suspension of (S)-1-(2-methyloxiran-2-ylmethyl)-4-(4-trifluoromethoxyphenyl)piperazine (0.43 g, 1.37 mmol) and 2-chloro-4-nitro-1H-imidazole (0.22

g, 1.51 mmol) in acetonitrile (4 ml), sodium hydrogencarbonate (0.17 g, 2.06 mmol) was added followed by stirring under reflux for 9 hours. To the reaction mixture, water was added, and the mixture was
5 extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 3/1) to afford (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-
10 methyl-3-[4-(4-trifluoromethoxyphenyl)piperazin-1-yl]propan-2-ol (0.20 g, yield 31%) as a light yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.18 (3H, s), 2.41 (1H, d, $J = 13.8$ Hz), 2.56 (1H, d, $J = 13.8$ Hz), 2.67 - 2.80 (2H, m), 2.85 - 2.96 (2H, m),
15 3.13 - 3.25 (4H, m), 4.03 (2H, s), 6.83 - 6.93 (2H, m), 7.07 - 7.17 (2H, m), 8.07 (1H, s).

Example 370

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-
20 methyl-3-[4-(4-chlorophenyl)piperazin-1-yl]propan-2-ol

(R)-2-Chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (20 g, 91.9 mmol) and 1-(4-chlorophenyl)piperazine (20.8 g, 0.11 mol) were added to DMF (200 ml) followed by stirring at 70-
25 75°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, dried over

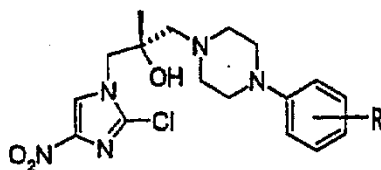
sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 20/1) to afford (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-chlorophenyl)piperazin-1-yl]propan-2-ol (33.0 g, yield 87%) as a yellow amorphous form.

¹H-NMR (CDCl₃) δppm:

1.53 (3H, s), 2.42 (1H, d, J = 13.9 Hz), 2.55 (1H, d, J = 13.9 Hz), 2.67 - 2.76 (2H, m), 2.81 - 2.90 (2H, m), 3.13 - 3.17 (4H, m), 3.43 (1H, s), 4.03 (2H, s), 6.78 - 6.85 (2H, m), 7.16 - 7.23 (2H, m), 8.06 (1H, s).

Using corresponding starting materials gave compounds of Examples 371 to 384 shown in the following table in the same manner as in Example 370.

Table 17



Example	R	Yield (%)	¹ H NMR (CDCl ₃) δ
371	4-CF ₃	82	1.18(3H, s), 2.41(1H, d, J=13.9Hz), 2.56(1H, d, J=13.9Hz), 2.68-2.79(2H, m), 2.82-2.91(2H, m), 3.26-3.31(5H, m), 4.03(2H, s), 6.91(2H, d, J=8.7Hz), 7.49(2H, d, J=8.7Hz), 8.06(1H, s).
372	4-H	92	1.17(3H, s), 2.40(1H, d, J=13.9Hz), 2.55(1H, d, J=13.9Hz), 2.69-2.78(2H, m), 2.83-2.91(2H, m), 3.18-3.22(4H, m), 3.42(1H, s), 4.01(2H, s), 6.85-6.93(3H, m), 7.24-7.31(2H, m), 8.06(1H, s).
373	4-F	43	1.16(3H, s), 2.41(1H, d, J=13.9Hz), 2.55(1H, d, J=13.9Hz), 2.69-2.77(2H, m), 2.82-2.91(2H, m), 3.10-3.14(4H, m), 3.41(1H, s), 4.01(2H, s), 6.83-7.00(4H, m), 8.06(1H, s).
374	4-OMe	99	1.15(3H, s), 2.42(1H, d, J=13.9Hz), 2.55(1H, d, J=13.9Hz), 2.69-2.78(2H, m), 2.82-2.91(2H, m), 3.07-3.11(4H, m), 3.77(3H, s), 4.02(2H, s), 6.81-6.91(4H, m), 8.07(1H, s).
375	4-COOEt	100	1.17(3H, s), 1.37(3H, t, J=7.1Hz), 2.42(1H, d, J=13.9Hz), 2.55(1H, d, J=13.9Hz), 2.68-2.76(2H, m), 2.81-2.89(2H, m), 3.31-3.35(4H, m), 3.40(1H, s), 4.04(2H, s), 4.33(2H, q, J=7.1Hz), 6.83-6.87(2H, m), 7.90-7.95(2H, m), 8.06(1H, s).
376	4-Me	86	1.15(3H, s), 2.27(3H, s), 2.41(1H, d, J=13.9Hz), 2.55(1H, d, J=13.9Hz), 2.68-2.77(2H, m), 2.82-2.90(2H, m), 3.12-3.16(4H, m), 3.47(1H, s), 4.01(2H, s), 6.81-6.85(2H, m), 7.06-7.09(2H, m), 8.06(1H, s).
377	4-CN	99	1.18(3H, s), 2.43(1H, d, J=13.9Hz), 2.56(1H, d, J=13.9Hz), 2.66-2.75(2H, m), 2.81-2.90(2H, m), 3.31-3.35(4H, m), 3.51(1H, s), 4.03(1H, d, J=14.3Hz), 4.09(1H, d, J=14.3Hz), 6.82-6.88(2H, m), 7.46-7.52(2H, m), 8.07(1H, s).
378	3,4-di-Cl	99	1.17(3H, s), 2.41(1H, d, J=13.9Hz), 2.55(1H, d, J=13.9Hz), 2.68-2.76(2H, m), 2.80-2.89(2H, m), 3.15-3.19(4H, m), 3.40(1H, s), 4.03(2H, s), 6.72(1H, dd, J=8.9, 2.9Hz), 6.94(1H, d, J=2.9Hz), 7.28(1H, d, J=8.9Hz), 8.05(1H, s).
379	3-CF ₃	99	1.17(3H, s), 2.42(1H, d, J=13.9Hz), 2.56(1H, d, J=13.9Hz), 2.69-2.78(2H, m), 2.83-2.93(2H, m), 3.22-3.27(4H, m), 3.36(1H, s), 4.03(2H, s), 7.03-7.11(3H, m), 7.32-7.39(1H, m), 8.06(1H, s).

Table 17 (Contn'd)

380	2-CF ₃	99	1.16(3H, s), 2.44(1H, d, J=14.0Hz), 2.57(1H, d, J=14.0Hz), 2.67-2.78(2H, m), 2.81-2.91(2H, m), 2.93-2.96(4H, m), 3.81(1H, s), 4.05(2H, s), 7.21-7.27(1H, m), 7.35-7.39(1H, m), 7.50-7.57(1H, m), 7.60-7.64(1H, m), 8.11(1H, s).
381	4-Cl-3-CF ₃	99	1.18(3H, s), 2.42(1H, d, J=13.9Hz), 2.56(1H, d, J=13.9Hz), 2.68-2.77(2H, m), 2.83-2.92(2H, m), 3.19-3.24(4H, m), 3.40(1H, s), 4.04(2H, s), 6.95(1H, dd, J=8.9, 2.9Hz), 7.16(1H, d, J=2.9Hz), 7.34(1H, d, J=8.9Hz), 8.06(1H, s).
382	4-COO'Bu	99	1.17(3H, s), 1.57(9H, s), 2.42(1H, d, J=13.9Hz), 2.55(1H, d, J=13.9Hz), 2.67-2.76(2H, m), 2.81-2.90(2H, m), 3.29-3.33(4H, m), 3.51(1H, s), 4.04(2H, s), 6.84(2H, d, J=9.0Hz), 7.87(2H, d, J=9.0Hz), 8.07(1H, s).
383	2-F	99	1.16(3H, s), 2.42(1H, d, J=13.9Hz), 2.57(1H, d, J=13.9Hz), 2.71-2.80(2H, m), 2.85-2.96(2H, m), 3.10-3.14(4H, m), 3.56(1H, s), 4.02(2H, s), 6.91-7.10(4H, m), 8.07(1H, s).
384	4-NMe ₂	82	1.14(3H, s), 2.40(1H, d, J=13.9Hz), 2.54(1H, d, J=13.9Hz), 2.70-2.77(2H, m), 2.81-2.91(8H, m), 3.05-3.09(4H, m), 3.66(1H, s), 4.01(2H, s), 6.72-6.76(2H, m), 6.86-6.91(2H, m), 8.07(1H, s).

Using corresponding starting materials gave compounds of Examples 385 and 386 in the same manner as in Example 370.

Example 385

- 5 (S)-1-(2-Chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-pyridyl)piperazin-1-yl]propan-2-ol

Yield 100%

¹H-NMR (CDCl₃) δppm:

1.18 (3H, s), 2.44 (1H, d, J = 13.9 Hz), 2.56 (1H, d, J = 13.9 Hz), 2.63 - 2.73 (2H, m), 2.77 - 2.91 (2H, m), 3.31 - 3.35 (4H, m), 3.54 (1H, s), 4.03 - 4.12 (2H, m), 6.63 - 6.66 (2H, m), 8.09 (1H, s), 8.23 - 8.27 (2H, m).

Example 386

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

pyridyl)piperazin-1-yl]propan-2-ol

Yield 81%

¹H-NMR (CDCl₃) δppm:

1.17 (3H, s), 2.44 (1H, d, J = 13.9 Hz), 2.57 (1H, d, J
5 = 13.9 Hz), 2.67 - 2.79 (2H, m), 2.84 - 2.93 (2H, m),
3.20 - 3.25 (4H, m), 3.85 (1H, bs), 4.06 (2H, s), 7.16
- 7.19 (2H, m), 8.07 - 8.11 (2H, m), 8.26 - 8.28 (1H,
m).

Using (R)-2-chloro-4-nitro-1-(oxiran-2-
10 ylmethyl)imidazole prepared in Example 9 gave compounds
of Examples 387 to 389 in the same manner as in Example
370.

Example 387

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-3-[4-(4-fluoro-
15 phenyl)piperazin-1-yl]propan-2-ol

Yield 86%

¹H-NMR (CDCl₃) δppm:

2.27 - 2.36 (1H, m), 2.49 - 2.63 (3H, m), 2.78 - 2.88
(2H, m), 2.97 - 3.18 (4H, m), 3.74 (1H, br), 3.96 -
20 4.08 (2H, m), 4.18 - 4.24 (1H, m), 6.84 - 7.01 (4H, m),
8.02 (1H, s).

Example 388

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-3-[4-(4-
trifluoromethylphenyl)piperazin-1-yl]propan-2-ol

25 Yield 49%

¹H-NMR (CDCl₃) δppm:

2.27 - 2.36 (1H, m), 2.49 - 2.63 (3H, m), 2.78 - 2.87
(2H, m), 3.28 - 3.31 (4H, m), 3.62 (1H, br), 3.95 -

4.11 (2H, m), 4.19 - 4.25 (1H, m), 6.92 (2H, d, $J = 8.6$ Hz), 7.49 (2H, d, $J = 8.6$ Hz), 8.02 (1H, s).

Example 389

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-3-[4-(4-cyanophenyl)piperazin-1-yl]propan-2-ol

Yield 100%

$^1\text{H-NMR}$ (CDCl_3) δppm :

2.28 - 2.37 (1H, m), 2.49 - 2.63 (3H, m), 2.76 - 2.85 (2H, m), 3.28 - 3.36 (4H, m), 3.58 (1H, br), 3.96 - 4.12 (2H, m), 4.19 - 4.25 (1H, m), 6.87 (2H, d, $J = 8.9$ Hz), 7.51 (2H, d, $J = 8.9$ Hz), 8.01 (1H, s).

Example 390

Preparation of 4-trifluoromethoxybenzyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-piperazine-1-carboxylate

A mixture of (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (15 g, 68.93 mmol) and 4-trifluoromethoxybenzyl piperazine-1-carboxylate (25.17 g, 82.72 mmol) in DMF (75 ml) was stirred at 65-70°C for 20 hours. The reaction mixture was allowed to return to room temperature and poured into water (475 ml), and extracted with ethyl acetate (150 ml). The aqueous layer was extracted with ethyl acetate (150 ml) again. The organic phases were combined, washed with water (400 ml) 3 times and a saturated saline solution (100 ml), dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was

purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/2) to afford 4-trifluoromethoxybenzyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-piperazine-1-carboxylate (29.98 g, yield 83%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.15 (3H, s), 2.36 (1H, d, J = 14.0 Hz), 2.42 - 2.75 (5H, m), 3.18 (1H, s), 3.42 - 3.58 (4H, m), 4.00 (2H, s), 5.12 (2H, s), 7.21 (2H, d, J = 8.6 Hz), 7.38 (2H, d, J = 8.6 Hz), 8.03 (1H, s).

Example 391

Preparation of 3-(4-trifluoromethylphenyl)-2-propenyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazine-1-carboxylate

A mixture of (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (4.24 g, 19.48 mmol) and 3-(4-trifluoromethylphenyl)-2-propenyl piperazine-1-carboxylate (6.73 g, 21.41 mmol) in DMF (21 ml) were stirred at 50-55°C for 24 hours. The reaction mixture was allowed to return to room temperature and poured into water (90 ml), and extracted with ethyl acetate (60 ml). The aqueous layer was extracted with ethyl acetate (60 ml) again. The organic phases were combined, washed with water (90 ml) 3 times and a saturated saline solution (60 ml), dried over sodium 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 = 1/1) to afford 3-(4-trifluoromethylphenyl)-2-propenyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazine-1-carboxylate (9.29 g, yield 90%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.16 (3H, s), 2.36 (1H, d, J = 14.0 Hz), 2.43 - 2.76 (5H, m), 3.17 (1H, s), 3.48 - 3.67 (4H, m), 4.00 (2H, s), 4.78 (2H, dd, J = 1.0 Hz, 6.1 Hz), 6.33 - 6.48 (1H, m), 6.66 (1H, d, J = 15.9 Hz), 7.48 (2H, d, J = 8.3 Hz), 7.58 (2H, d, J = 8.3 Hz), 8.04 (1H, s).

Using corresponding starting materials gave the compound of Example 392 in the same manner as in Example 391.

Example 392

3-(4-Trifluoromethoxyphenyl)-2-propenyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazine-1-carboxylate

¹H-NMR (CDCl₃) δppm:

1.15 (3H, s), 2.36 (1H, d, J = 13.9 Hz), 2.51 (1H, d, J = 13.9 Hz), 2.48 - 2.63 (2H, m), 2.63 - 2.78 (2H, m), 3.17 (1H, s), 3.39 - 3.63 (4H, m), 4.00 (2H, s), 4.75 (2H, dd, J = 1.1 Hz, 6.3 Hz), 6.28 (1H, dt, J = 6.3 Hz, 15.9 Hz), 6.62 (1H, d, J = 15.9 Hz), 7.15 - 7.18 (2H, m), 7.38 - 7.42 (2H, m), 8.03 (1H, s).

Example 393

Preparation of tert-butyl (S)-4-(2-methyl-6-nitro-2,3-

dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

Tert-butyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-piperazine-1-carboxylate prepared in Example 365 (10.25 g, 25.4 mmol) was dissolved in DMF (30 ml). To the solution, sodium hydride (1.12 g, 27.9 mmol) was added followed by stirring for 2 hours with cooling on ice-bath. To the reaction mixture, ethyl acetate (10 ml) and water (70 ml) were added. The precipitates were filtered off, and washed with water. The crude solids were recrystallized from ethyl acetate (70 ml) to afford tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (6.62 g, yield 71%) as a light yellow powder.

Optical purity >99.5% e.e.

$[\alpha]_D^{27} = -20.953^\circ$ (concentration: 0.492, CHCl_3)

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.44 (9H, s), 1.62 (3H, s), 2.45 - 2.66 (5H, m), 2.87 (1H, d, $J = 14.9$ Hz), 3.29 (4H, br), 3.92 (1H, d, $J = 9.7$ Hz), 4.30 (1H, d, $J = 9.7$ Hz), 7.53 (1H, s).

Example 394

Preparation of tert-butyl (S)-4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

Using tert-butyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]piperazine-1-

carboxylate prepared in Example 363 (11 g, 28.22 mmol) gave tert-butyl (S)-4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (7.5 g, yield 75%) as a light yellow powder in the same manner
5 as in Example 393.

Optical purity 96.6% e.e.

$[\alpha]_D^{22} = -11.91^\circ$ (concentration: 1.016, CHCl_3)

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.45 (9H, s), 2.49 - 2.59 (4H, m), 2.85 (2H, d, $J = 5.2$
10 Hz), 3.33 - 3.44 (4H, m), 4.19 (1H, dd, $J = 6.9$ Hz, 10.2 Hz), 4.35 (1H, dd, $J = 6.9$ Hz, 10.2 Hz), 5.36 - 5.49 (1H, m), 7.55 (1H, s).

Example 395

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

Tert-butyl (R)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]piperazine-1-carboxylate prepared in Example 364 (6.43 g, 16.49
20 mmol) was dissolved in 1,4-dioxane (35 ml). To the solution, sodium hydride (730 mg, 18.25 mmol) was added with cooling on ice-bath, and the resulting solution was stirred at room temperature overnight and then stirred under reflux for 24 hours. The reaction
25 mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, water was added slowly, the mixture was extracted with methylene chloride twice, dried over sodium sulfate and

then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate) to afford tert-butyl (R)-4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (1.23 g, yield 21%) as a white powder.

Optical purity >99% e.e.

$[\alpha]_D^{27} = 11.635^\circ$ (concentration: 1.004, CHCl_3)

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

10 1.45 (9H, s), 2.50 - 2.61 (4H, m), 2.85 (2H, d, $J = 5.3$ Hz), 3.31 - 3.50 (4H, m), 4.18 (1H, dd, $J = 6.9$ Hz, 10.2 Hz), 4.35 (1H, dd, $J = 8.4$ Hz, 10.2 Hz), 5.35 - 5.50 (1H, m), 7.55 (1H, s).

Example 396

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

Tert-butyl (R)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-piperazine-1-carboxylate prepared in Example 368 (376 mg, 0.93 mmol) was dissolved in 1,4-dioxane (10 ml). To the solution, sodium hydride (45 mg, 1.12 mmol) was added with cooling on ice-bath, and the resulting solution was stirred at room temperature for 30 minutes and then stirred under reflux for 24 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, water was added slowly, and the

solution was extracted with ethyl acetate twice. 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 (n-hexane/acetone = 3/1) to afford tert-butyl (R)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-carboxylate (239 mg, yield 70%) as a white powder. Optical purity 99.2% e.e.

10 $[\alpha]_D^{27} = 21.073^\circ$ (concentration: 0.522, CHCl_3)

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.45 (9H, s), 1.61 (3H, s), 2.45 - 2.64 (5H, m), 2.87 (1H, d, $J = 14.9$ Hz), 3.29 (4H, br), 3.92 (1H, d, $J = 9.7$ Hz), 4.33 (1H, d, $J = 9.7$ Hz), 7.52 (1H, s).

15 Example 397

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

To a solution of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethoxyphenyl)piperazin-1-yl]propan-2-ol prepared in Example 369 (5.85 g, 12.61 mmol) in THF (150 ml), sodium hydride (0.66 g, 18.92 mmol) was added with cooling on ice-bath followed by stirring under reflux for 6 hours.

25 The reaction mixture was concentrated under reduced pressure, and the residue was added water and ethyl acetate. The precipitates were filtered off, purified by silica gel column chromatography (n-hexane/ethyl

acetate = 1/1) and recrystallized from isopropanol to afford (S)-2-[4-(4-trifluoromethoxyphenyl)piperazin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (2.58 g, yield 48%) as a light yellow solid.

5 Optical purity 99.8% e.e.

$[\alpha]_D^{26} = 8.80^\circ$ (concentration: 1.000, CHCl_3)

Melting point 129-130°C.

Example 398

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

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-chlorophenyl)piperazin-1-yl]propan-2-ol prepared in Example 370 (33.0 g, 79.7 mmol) was dissolved in DMF (300 ml). To the solution, sodium hydride (3.7 g, 91.6 mmol) was added with cooling on ice-bath followed by stirring at room temperature overnight. To the reaction mixture, ice-water and ethyl acetate were added, and the solution was vigorously stirred. The precipitates were filtered off, washed with water and ethyl acetate, and dried under reduced pressure to afford 23.2 g of a crude light yellow powder. The crude powder was combined with another crude powder synthesized in the same manner (50 g), and the mixture was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 50/1) and crystallized from methylene chloride-ethyl acetate to afford (S)-2-[4-(4-

chlorophenyl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (45 g, yield 90%) as a white powder.

Optical purity 99.6% e.e.

5 $[\alpha]_D^{22} = -10.20^\circ$ (concentration: 0.5, CHCl_3)

Melting point 218-219.6°C.

Using corresponding starting materials gave compounds of Examples 399 to 403 in the same manner as in Example 398.

10 Example 399

(S)-2-[4-(4-Fluorophenyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Yield 42%, $[\alpha]_D^{28} = 2.10^\circ$ (concentration: 0.5, CHCl_3)

Melting point 178.5-179.5°C.

15 Example 400

(S)-2-[4-(3-Pyridyl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Yield 42%, melting point 145-147.7°C.

Example 401

20 (S)-2-[4-(4-Pyridyl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Yield 3%

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.65 (3H, s), 2.62 (1H, d, $J = 14.8$ Hz), 2.64 - 2.71
25 (2H, m), 2.79 - 2.89 (2H, m), 2.92 (1H, d, $J = 14.8$ Hz), 3.15 - 3.30 (4H, m), 3.95 (1H, d, $J = 9.7$ Hz), 4.33 (1H, d, $J = 9.7$ Hz), 6.60 (2H, d, $J = 6.2$ Hz), 7.53 (1H, s), 8.26 (2H, d, $J = 6.2$ Hz).

Example 402

(S)-2-[4-(4-Trifluoromethylphenyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Melting point 175.8-176.6°C.

5

Example 403

(S)-2-[4-(4-Cyanophenyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Melting point 211-211.5°C.

Example 404

10 Preparation of (S)-2-[4-(4-chlorophenyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
1-(4-Chlorophenyl)piperazine dihydrochloride (1.31 g, 4.86 mmol) was added to a sodium hydroxide solution, and the resulting mixture was extracted with
15 methylene chloride. The extract was dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure to afford 1-(4-chlorophenyl)piperazine.

Then, a mixture of 1-(4-chlorophenyl)-
20 piperazine obtained, (R)-2-chloro-1-(oxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 9 (763 mg, 3.75 mmol) and DMF (5 ml) was stirred at 70°C for 6 hours. To the solution, sodium hydride (219 mg, 5.48 mmol) was added with cooling on ice-bath followed by
25 stirring at room temperature for 2 hours. To the reaction mixture, ice-water was added, and precipitates were filtered off. The resulting solids were recrystallized from acetone/water to afford (S)-2-[4-

(4-chlorophenyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (250 mg, yield 18%) as a light yellow powder.

Melting point 183-183.5°C.

5 Example 405

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

4-Trifluoromethoxybenzyl (S)-4-[3-(2-chloro-
10 4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-piperazine-1-carboxylate prepared in Example 390 (4.3 g, 8.24 mmol) was dissolved in DMF (13 ml). To the solution, sodium hydride (430 mg, 10.7 mmol) was added followed by stirring at the same temperature for 2
15 hours with cooling on ice-bath. To the reaction mixture, ethyl acetate (4.3 ml) and water (30 ml) were added in this order, and the solution was stirred for 30 minutes. The precipitates were filtered off and washed with water. The solids obtained were
20 recrystallized from ethyl acetate/isopropyl ether and then recrystallized from isopropyl alcohol to afford 4-trifluoromethoxybenzyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (3.15 g, yield 79%) as a white powder.

25 Melting point 139.5-140.5°C

Optical purity >99.5% e.e.

$[\alpha]_D^{27} = 18.04^\circ$ (concentration: 1.020, CHCl_3)

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.60 (3H, s), 2.39 - 2.75 (5H, m), 2.87 (1H, d, J = 14.9 Hz), 3.14 - 3.56 (4H, m), 3.93 (1H, d, 9.7 Hz), 4.29 (1H, d, J = 9.7 Hz), 5.10 (2H, s), 7.19 (2H, d, J = 8.6 Hz), 7.36 (2H, d, J = 8.6 Hz), 7.54 (1H, s).

5 Example 406

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

3-(4-Trifluoromethylphenyl)-2-propenyl (S)-4-
10 [3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methyl-propyl]piperazine-1-carboxylate prepared in Example 391 (13.2 g, 24.81 mmol) was dissolved in DMF (40 ml). To the solution, sodium hydride (1.19 g, 29.78 mmol) was added followed by stirring for 1.5 hours with cooling
15 on ice-bath. To the reaction mixture, ethyl acetate (13 ml) and water (92 ml) were added in this order followed by stirring for 30 minutes. The precipitates were filtered off, washed with water and purified by silica gel column chromatography (ethyl acetate) to
20 afford 3-(4-trifluoromethylphenyl)-2-propenyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (10.17 g, yield 83%) as a light yellow powder.

Melting point 132-133°C

25 Optical purity 99.0% e.e.

$[\alpha]_D^{27} = -21.73^\circ$ (concentration: 0.866, CHCl₃)

¹H-NMR (CDCl₃) δppm:

1.62 (3H, s), 2.48 - 2.75 (5H, m), 2.88 (1H, d, J =

14.9 Hz), 3.15 - 3.57 (4H, m), 3.94 (1H, d, $J = 9.7$ Hz), 4.29 (1H, d, $J = 9.7$ Hz), 4.75 (2H, d, $J = 1.15$ Hz, 6.0 Hz), 6.29 - 6.42 (1H, m), 6.64 (1H, d, $J = 15.9$ Hz), 7.47 (2H, d, $J = 8.4$ Hz), 7.52 - 7.62 (3H, m).

- 5 Using corresponding starting materials gave the compound of Example 407 in the same manner as in Example 406.

Example 407

- 10 3-(4-Trifluoromethoxyphenyl)-2-propenyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

Melting point 91-93°C

$[\alpha]_D^{27} = -21.88^\circ$ (concentration: 0.786, CHCl_3)

$^1\text{H-NMR}$ (CDCl_3) δppm :

- 15 1.54 (3H, s), 2.38 - 2.71 (5H, m), 2.84 (1H, d, $J = 14.9$ Hz), 3.13 - 3.54 (4H, m), 3.92 (1H, d, $J = 9.7$ Hz), 4.29 (1H, d, $J = 9.7$ Hz), 4.73 (2H, dd, $J = 1.2$ Hz, 6.2 Hz), 6.15 - 6.33 (1H, m), 6.60 (1H, d, $J = 16.0$ Hz), 7.16 (2H, d, $J = 8.7$ Hz), 7.40 (2H, d, $J = 8.7$ Hz), 7.53 (1H, s).
- 20

Example 408

Preparation of (S)-2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride

- 25 Tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 393 (1.46 g, 3.98 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 ml). To the solution, a solution of a saturated
5 hydrogen chloride in ethyl acetate was added followed by stirring for 30 minutes with cooling on ice-bath. The precipitates were filtered off to afford (S)-2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride (994 mg, yield
10 73%) as a yellow powder.

¹H-NMR (DMSO-d₆) δppm:

1.63 (3H, s), 2.80 - 3.36 (6H, m), 4.11 (1H, d, J = 11.0 Hz), 4.25 - 4.98 (5H, m), 8.15 (1H, s), 9.31 (2H, br).

15 Example 409

Preparation of (S)-6-nitro-2-[4-(4-trifluoromethylbenzyl)piperazin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole

A mixture of tert-butyl (S)-4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 394 (100 mg, 0.27 mmol)
20 and trifluoroacetic acid (2 ml) was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was
25 dissolved in methylene chloride (5 ml) and neutralized with triethylamine (1 ml, 7.17 mmol), and then the solution was concentrated under reduced pressure. The residue was dissolved in methanol (5 ml), and the

solution was added 4-trifluoromethylbenzaldehyde (148 mg, 0.85 mmol), sodium cyanotrihydroborate (53 mg, 0.85 mmol), and acetic acid (49 μ l, 0.85 mmol) in this order followed by stirring at room temperature for 18 hours.

- 5 The reaction mixture was concentrated under reduced pressure. To the residue, a saturated sodium hydrogencarbonate solution was added, and the solution was extracted with methylene chloride twice. The organic phases were combined, washed with a saturated
- 10 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, and the residue was purified by silica gel column chromatography
- 15 (methylene chloride/ethyl acetate = 1/1) to afford (S)-6-nitro-2-[4-(4-trifluoromethylbenzyl)piperazin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole (53 mg, yield 46%) as a light yellow powder.
- Melting point 149-150°C.

20 Example 410

Preparation of (S)-2-[4-(biphenyl-4-ylmethyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

- A mixture of tert-butyl (S)-4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-
- 25 carboxylate prepared in Example 394 (7.2 g, 20.26 mmol), trifluoroacetic acid (24 ml) and methylene chloride (72 ml) was stirred at room temperature for 2 hours. The reaction mixture was concentrated under

reduced pressure, and the residue was dissolved in methylene chloride (100 ml), then neutralized with triethylamine (20 ml, 143.49 mmol). The solution was concentrated under reduced pressure, and the residue
5 was dissolved in methanol (72 ml). To the solution, 4-phenylbenzaldehyde (7.38 g, 40.52 mmol), sodium cyanotrihydroborate (3.82 g, 60.78 mmol), and acetic acid (3.48 ml, 60.78 mmol) were added in this order followed by stirring at room temperature for 24 hours.
10 The precipitates were filtered off, washed with methanol, and purified by silica gel column chromatography (methylene chloride/methanol = 10/1) to afford (S)-2-[4-(biphenyl-4-ylmethyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
15 (5.52 g, yield 65%) as a yellow powder.
Optical purity >99.0% e.e.
 $[\alpha]_D^{28} = -28.261^\circ$ (concentration: 0.046, DMSO)
Melting point 207-208°C.

Example 411

20 Preparation of (R)-2-[4-(biphenyl-4-ylmethyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
A mixture of tert-butyl (R)-4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 395 (101.5 mg, 0.29
25 mmol) and trifluoroacetic acid (2 ml) was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methylene chloride (5 ml) and neutralized

with triethylamine (2 ml, 14.35 mmol), and then the solution was concentrated under reduced pressure. The residue was dissolved in methanol (5 ml). To the solution, 4-phenylbenzaldehyde (156 mg, 0.86 mmol),
5 sodium cyanotrihydroborate (53 mg, 0.84 mmol) and acetic acid (0.05 ml, 0.87 mmol) were added in this order followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure. To the residue, a saturated sodium
10 hydrogencarbonate solution was added, and the solution was extracted with methylene chloride twice. The organic phases were combined, washed with a saturated sodium hydrogencarbonate solution and a saturated saline solution in this order, dried over magnesium
15 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 (R)-2-[4-(biphenyl-4-ylmethyl)piperazin-1-ylmethyl]-6-nitro-2,3-
20 dihydroimidazo[2,1-b]oxazole (56 mg, yield 46%) as a white powder.

$[\alpha]_D^{28} = 28.261^\circ$ (concentration: 0.046, DMSO).

Melting point 224-225°C

Using corresponding starting materials gave
25 the compound of Example 412 in the same manner as in Example 411.

Example 412

(R)-6-Nitro-2-[4-(4-trifluoromethylbenzyl)piperazin-1-

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

Yield 48%, melting point 141-143°C.

Example 413

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

A mixture of tert-butyl (S)-4-(2-methyl-6-
nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-
piperazine-1-carboxylate prepared in Example 393 (1.7
10 g, 4.6 mmol), trifluoroacetic acid (10 ml) and
methylene chloride (30 ml) was stirred at room
temperature for 3 hours. The reaction mixture was
concentrated under reduced pressure. The residue was
dissolved in methanol (30 ml). To the solution, 4'-
15 trifluoromethylbiphenyl-4-carboaldehyde (2.3 g, 9.19
mmol), sodium cyanotrihydroborate (580 mg, 9.23 mmol)
and acetic acid (0.55 ml, 9.62 mmol) were added in this
order followed by stirring at room temperature
overnight. The reaction mixture was concentrated under
20 reduced pressure. To the residue, a saturated sodium
hydrogencarbonate solution was added, and the solution
was extracted with methylene chloride twice. The
organic phases were combined, washed with a saturated
sodium hydrogencarbonate solution and a saturated
25 saline solution in this order, 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)-2-methyl-6-nitro-2-[4-(4'-trifluoromethylbiphenyl-4-ylmethyl)piperazin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole (1.47 g, yield 63%) as a white powder.

5 $[\alpha]_D^{28} = 1.831^\circ$ (concentration: 0.71, CHCl_3)

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.60 (3H, s), 2.20 - 2.45 (4H, m), 2.45 - 2.65 (4H, m),
2.50 (1H, d, $J = 15.0$ Hz), 2.86 (1H, d, $J = 15.0$ Hz),
3.48 (2H, s), 3.89 (1H, d, $J = 10.0$ Hz), 4.31 (1H, d, J
10 = 10.0 Hz), 7.37 (2H, d, $J = 8.0$ Hz), 7.50 - 7.56 (3H,
m), 7.68 (4H, s).

Using corresponding starting materials gave compounds of Examples 414 to 417 in the same manner as in Example 413.

15 Example 414

(S)-2-Methyl-6-nitro-2-[4-(4-trifluoromethylbenzyl)-piperazin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole
Melting point 110-112°C.

Example 415

20 (S)-2-[4-(Biphenyl-4-ylmethyl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Melting point 182-184°C.

Example 416

25 (S)-2-Methyl-6-nitro-2-[4-(4-trifluoromethoxybenzyl)-piperazin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole
Melting point 137-138°C.

Example 417

(S)-2-[4-[2-(4-Chlorophenyl)-4-methylthiazol-5-

ylmethyl]piperazin-1-ylmethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 174.3-175.5°C.

Example 418

- 5 Preparation of (R)-2-[4-(biphenyl-4-ylmethyl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

A mixture of tert-butyl (R)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-
10 piperazine-1-carboxylate prepared in Example 396 (100 mg, 0.27 mmol) and trifluoroacetic acid (2 ml) was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methylene chloride (5 ml) and
15 neutralized with triethylamine (1 ml, 7.17 mmol), and then the solution was concentrated under reduced pressure. The residue was dissolved in methanol (5 ml). To the solution, 4-phenylbenzaldehyde (149 mg, 0.82 mmol), sodium cyanotrihydroborate (51 mg, 0.82
20 mmol) and acetic acid (48 μ l, 0.82 mmol) were added in this order followed by stirring at room temperature for 15 hours. The reaction mixture was concentrated under reduced pressure, and the residue was added a saturated sodium hydrogencarbonate solution. The precipitates
25 were filtered off and purified by silica gel column chromatography (ethyl acetate) to afford (R)-2-(biphenyl-4-ylmethyl)piperazin-1-ylmethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (67 mg, yield

57%) as a light yellow powder.

Melting point 112-114°C.

Using corresponding starting materials gave the compound of Example 419 in the same manner as in
5 Example 418.

Example 419

(R)-2-Methyl-6-nitro-2-[4-(4-trifluoromethylbenzyl)-
piperazin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole
Melting point 93-95°C.

10 Example 420

Preparation of (S)-2-chloro-1-[4-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-
yl]ethanone

A mixture of tert-butyl (S)-4-(2-methyl-6-
15 nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-
piperazine-1-carboxylate prepared in Example 393 (1.5
g, 4.1 mmol) and trifluoroacetic acid (20 ml) was
stirred at room temperature for 3 hours. The reaction
mixture was concentrated under reduced pressure. The
20 residue was dissolved in methylene chloride (20 ml),
and the solution was added triethylamine (3 ml) and 4-
dimethylaminopyridine (100 mg, 0.82 mmol) in this
order. To the mixture, a solution of chloroacetyl
chloride (0.49 ml, 6.2 mmol) in methylene chloride (2
25 ml) was added slowly with cooling on ice-bath followed
by stirring at room temperature overnight. The
reaction mixture was washed with water twice, 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, and the residue was purified by silica gel column chromatography

- 5 (methylene chloride/methanol = 100/1) to afford (S)-2-chloro-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone (600 mg, yield 43%) as a light brown powder.

¹H-NMR (CDCl₃) δppm:

- 10 1.64 (3H, s), 2.50 - 2.70 (3H, m), 2.61 (1H, d, J = 15.0 Hz), 2.70 - 2.90 (1H, m), 2.89 (1H, d, J = 15.0 Hz), 3.15 - 3.55 (3H, m), 3.60 - 3.75 (1H, m), 3.97 (1H, d, J = 10.0 Hz), 4.03 (2H, s), 4.30 (1H, d, J = 10.0 Hz), 7.55 (1H, s).

15 Example 421

Preparation of (S)-2-(4-chlorophenoxy)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazin-1-yl]ethanone

- A mixture of (S)-2-chloro-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazin-1-yl]ethanone prepared in Example 420 (300 mg, 0.87 mmol), 4-chlorophenol (170 mg, 1.32 mmol), potassium carbonate (180 mg, 1.3 mmol) and DMF (5 ml) was stirred at 60°C for 3 hours. The reaction mixture
25 was allowed to return to room temperature, then diluted with water. The solution was extracted with ethyl acetate twice. The organic phases were combined, washed with a sodium hydroxide solution, water and a

saturated saline solution in this order, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from ethanol to afford (S)-2-(4-chlorophenoxy)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone (260 mg, yield 68%) as a light brown powder.

Melting point 179-180°C.

10 Example 422

Preparation of (S)-2-(4-chlorophenylsulfanyl)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone

Using a mixture of (S)-2-chloro-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone prepared in Example 420 (300 mg, 0.87 mmol) and 4-chlorothiophenol (190 mg, 1.32 mmol) gave (S)-2-(4-chlorophenylsulfanyl)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone (80 mg, yield 20%) as a white powder in the same manner as in Example 421. Melting point 142-145°C.

 Example 423

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

A mixture of tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-

piperazine-1-carboxylate prepared in Example 393 (300 mg, 0.82 mmol) and trifluoroacetic acid (6 ml) was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methylene chloride (15 ml), and the solution was added triethylamine (2 ml, 14.35 mmol). To the solution, 4-chlorobenzoyl chloride (150.7 mg, 0.86 mmol) was added with cooling on ice-bath followed by stirring at room temperature for 1 hour. The reaction mixture was washed with a saturated sodium 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 treated with diethyl ether-ethyl acetate to afford (S)-(4-chlorophenyl)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]methanone (282 mg, yield 85%) as a yellow powder. Melting point 173-174°C.

Using corresponding starting materials gave the compound of Example 424 in the same manner as in Example 423.

Example 424

(Biphenyl-4-yl)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]methanone

Melting point 116-118°C.

Example 425

Preparation of [4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]phenylmethanone

A mixture of 2-(4-tert-butoxycarbonyl-piperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydro-
5 imidazo[2,1-b]oxazole prepared in Example 306 (142 mg, 0.39 mmol), trifluoroacetic acid (1 ml) and methylene chloride (1 ml) was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in
10 methylene chloride (2 ml). To the mixture, triethylamine (2 ml, 14.35 mmol) was added. To the solution, benzoyl chloride (54 μ l, 0.46 mmol) was added with cooling on ice-bath followed by stirring at room temperature for 1 hour. The reaction mixture was
15 diluted with methylene chloride, washed with a saturated sodium 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
20 was treated with diethyl ether to afford [4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]phenylmethanone (72 mg, yield 50%) as a yellow powder.

Melting point 145-148.7°C.

25 Using corresponding starting materials gave compounds of Examples 426 to 433 in the same manner as in Example 425.

Example 426

(4-Chlorophenyl)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]methanone

Melting point 150.0-155.2°C.

5 Example 427

[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl](pyridin-4-yl)methanone

¹H-NMR (CDCl₃) δppm:

1.62 (3H, s), 2.25 - 2.75 (4H, m), 2.61 (1H, d, J =
10 14.9 Hz), 2.88 (1H, d, J = 14.9 Hz), 3.00 - 3.93 (4H, br), 3.95 (1H, d, J = 9.8 Hz), 4.30 (1H, d, J = 9.8 Hz), 7.26 - 7.55 (2H, m), 7.59 (1H, s), 8.67 - 8.72 (2H, m).

 Example 428

15 1-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-2-phenylethanone

Melting point 175.2-175.9°C.

 Example 429

20 1-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-3-phenylpropan-1-one

Melting point 166.8-169.1°C.

 Example 430

2-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-2-phenoxyethanone

25 Melting point 158-160.6°C.

 Example 431

2-(4-Chlorophenyl)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone

Melting point 184-187°C.

Example 432

(Biphenyl-4-yl)-[4-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-
5 yl]methanone

¹H-NMR (CDCl₃) δppm:

1.63 (3H, s), 2.45 - 2.80 (4H, m), 2.62 (1H, d, J =
14.9 Hz), 2.90 (1H, d, J = 14.9 Hz), 3.28 - 3.81 (4H,
br), 3.95 (1H, d, J = 9.8 Hz), 4.31 (1H, d, J = 9.8
10 Hz), 7.34 - 7.50 (5H, m), 7.55 (1H, s), 7.56 - 7.63
(4H, m).

Example 433

[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-
ylmethyl)piperazin-1-yl]-(4-trifluoromethylphenyl)-
15 methanone

Melting point 161-162°C.

Example 434

Preparation of (S)-[4-(2-methyl-6-nitro-2,3-dihydro-
imidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-(4-
20 trifluoromethylphenyl)methanone

(S)-2-Methyl-6-nitro-2-(piperazin-1-
ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydro-
chloride prepared in Example 408 (2.36 mg, 0.882 mmol)
was suspended in methylene chloride (10 ml). To the
25 suspension, triethylamine (1 ml, 7.17 mmol) was added.
To the solution, 4-(trifluoromethyl)benzoyl chloride
(193 mg, 0.926 mmol) was added with cooling on ice-bath
followed by stirring at room temperature for 1 hour.

The reaction mixture was washed with a saturated sodium hydrogencarbonate solution, water and a saturated saline solution in this order, dried over sodium sulfate and then filtered. The filtrate was

5 concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford (S)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-(4-
10 trifluoromethylphenyl)methanone (264 mg, yield 68%) as a white powder.

Melting point 183-184°C.

Using corresponding starting materials gave compounds of Example 435 to 438 in the same manner as
15 in Example 434. (Compounds in Examples 435 to 437 were prepared with 2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 322.)

Example 435

20 [4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-(4-methoxyphenyl)methanone
Melting point 135-137°C.

Example 436

[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-
25 ylmethyl)piperazin-1-yl]-(4-methylphenyl)methanone
Melting point 121-122°C.

Example 437

[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-

ylmethyl)piperazin-1-yl]-(3-trifluoromethylphenyl)-
methanone

Melting point 122-124°C.

Example 438

- 5 (S)-2-(4-Chlorophenyl)-1-[4-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-
yl]ethanone

Melting point 189-190°C.

Example 439

- 10 Preparation of (S)-2-(3,4-dichlorophenoxy)-1-[4-(2-
methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-
ylmethyl)piperazin-1-yl]ethanone

A mixture of 3,4-(dichlorophenoxy)acetic acid
(234 mg, 1.06 mmol) and thionyl chloride (5 ml) was
15 stirred under reflux for 30 minutes. The reaction
mixture was concentrated under reduced pressure to
afford corresponding acid chloride. It was dissolved
in methylene chloride (5 ml).

The solution was added to a mixture of (S)-2-
20 methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-
dihydroimidazo[2,1-b]oxazole dihydrochloride prepared
in Example 408 (236 mg, 0.88 mmol), methylene chloride
(10 ml), and triethylamine (1 ml, 7.17 mmol) with
cooling on ice-bath followed by stirring at room
25 temperature for 1 hour. The reaction mixture was
washed with a saturated sodium 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. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford (S)-2-(3,4-dichlorophenoxy)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazin-1-yl]ethanone (183 mg, yield 44%) as a white powder.

Melting point 164-166°C.

Using corresponding starting materials gave the compound of Example 440 in the same manner as in Example 439.

Example 440

(S)-1-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-4-(4-trifluoromethylphenyl)butan-1-one

Melting point 145-146°C.

Example 441

Preparation of (S)-3-(4-chlorophenyl)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazin-1-yl]propanone

A mixture of 4-chlorocinnamic acid (300 mg, 1.64 mmol), 1-hydroxybenzotriazole (HOBT) (240 mg, 1.77 mmol), WSCD (350 mg, 1.83 mmol) and methylene chloride (10 ml) stirred at room temperature for 30 minutes was added a mixture of (S)-2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 408 (434 mg, 1.64 mmol), methylene chloride (10 ml), and triethylamine (3.3 ml,

2.37 mmol) with cooling on ice-bath followed by stirring at room temperature for 3 hours. The reaction mixture was washed with a saturated sodium 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. The residue was purified by silica gel column chromatography (ethyl acetate) to afford (S)-3-(4-chlorophenyl)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]propenone (180 mg, yield 26%) as a white powder.

Melting point 220-222°C.

Using corresponding starting materials gave compounds of Examples 442 to 445 in the same manner as in Example 441.

Example 442

(S)-3-(Chlorophenyl)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]propan-1-one

Melting point 177-178°C.

Example 443

(S)-4-(4-Chlorophenyl)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]butan-1-one

Melting point 146-147°C.

Example 444

(S)-3-(3,4-Dichlorophenyl)-1-[4-(2-methyl-6-nitro-2,3-

dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]propanone

Melting point 213-215°C.

Example 445

- 5 (S)-5-(4-Chlorophenyl)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]pentan-1-one

Melting point 108-111°C.

Example 446

- 10 Preparation of 1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-2-(4-tolyl)ethanone

A mixture of 2-Methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole

- 15 dihydrochloride prepared in Example 322 (240 mg, 0.79 mmol), DMF (5 ml) and triethylamine (0.22 ml, 1.58 mmol) was added p-tolylacetic acid (140 mg, 0.93 mmol) and WSCD (180 mg, 0.93 mmol) in this order followed by stirring at room temperature for 1 hour. The reaction
- 20 mixture was diluted with ethyl acetate, washed with water twice, a saturated sodium hydrogencarbonate solution and a saturated saline solution in this order, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and
- 25 the residue was treated with diethylether to afford 1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-2-(4-tolyl)ethanone (172 mg, yield 64%) as a white powder.

Melting point 213-214°C.

Using corresponding starting materials gave the compound of Example 447 in the same manner as in Example 446.

5 Example 447

(4-Dimethylaminophenyl)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]methanone

Melting point 204-207°C.

10 Example 448

Preparation of (S)-2-{4-[3-(4-Chlorophenyl)propane-1-sulfonyl]piperazin-1-ylmethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

A mixture of tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazine-1-carboxylate prepared in Example 393 (300 mg, 0.82 mmol) and trifluoroacetic acid (10 ml) was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and 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 10 minutes, and then 3-(4-chlorophenyl)propane-1-sulfonyl chloride (300 mg, 1.19 mmol) was added followed by stirring at room temperature for 3 days. The reaction mixture 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 = 50/1) to afford (S)-2-{4-[3-(4-chlorophenyl)propane-1-sulfonyl]piperazin-1-ylmethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (330 mg, yield 84%) as a white powder.

Melting point 150-151°C.

Using 2-(4-tert-butoxycarbonylpiperazin-1-ylmethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 306 gave compounds of Examples 449 and 450 in the same manner as in Example 448.

Example 449

2-[4-(4-Chlorobenzenesulfonyl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Melting point 202-204°C.

Example 450

2-[4-(4-Chlorophenylmethanesulfonyl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Melting point 215-217°C.

Example 451

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

A mixture of (S)-2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 408 (236 mg, 0.88

mmol) and DMF (3 ml) was added potassium carbonate (500 mg, 3.62 mmol) and 2-(4-chlorophenyl)ethanesulfonyl chloride (240 mg, 1 mmol) in this order followed by stirring at room temperature overnight. To the
5 reaction mixture, water was added, and the solution was extracted with ethyl acetate. The organic phase was washed with water three times and saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure.
10 The residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford (S)-2-[4-[2-(4-chlorophenyl)ethanesulfonyl]piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (100
15 mg, yield 26%) as a white powder.
Melting point 192-193°C.

Using (S)-2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 408 gave compounds of
20 Examples 452 to 454 in the same manner as in Example 451. Also, using 2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 322 gave the compound of Example 455 in the same manner as in
25 Example 451.

Example 452

(S)-2-[4-(4-Chlorobenzenesulfonyl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-

b]oxazole

Melting point 216-218°C.

Example 453

(S)-2-[4-(4-Chlorophenylmethanesulfonyl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 204-206°C.

Example 454

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

Melting point 176-177°C.

Example 455

2-(4-[2-(4-Chlorophenyl)ethanesulfonyl]piperazin-1-ylmethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 182-184°C.

Example 456

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

A mixture of tert-butyl (S)-4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 394 (300 mg, 0.84 mmol) and methylene chloride (2 ml) was added trifluoroacetic acid (1 ml) followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved

in DMF (1 ml) and neutralized with triethylamine (1 ml).

To the solution, a mixture of 4-(trifluoromethyl)benzyl alcohol (297 mg, 1.69 mmol),
5 DMF (1 ml), and 1,1'-carbonyldiimidazole (274 mg, 1.69 mmol) stirred at room temperature for 1 hour was added followed by stirring at room temperature for 3 hours. To the reaction mixture, water was added, and the solution was extracted with ethyl acetate twice. The
10 organic phases were combined, washed with water twice 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
15 chloride/methanol = 20/1) to afford 4-(trifluoromethylbenzyl (S)-4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (273 mg, yield 71%) as a white powder.
[α]_D²⁸ = -14.851° (concentration: 0.404, CHCl₃)
20 Melting point 125-125.5°C.

Example 457

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

25 A mixture of tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 393 (1.87 g, 5.09 mmol) and methylene chloride (20 ml)

was added trifluoroacetic acid (20 ml) followed by stirring for 5 minutes, and then concentrated under reduced pressure. The residue was dissolved in DMF (20 ml). To the solution, a mixture of 1,1'-
5 carbonyldiimidazole (1.76 g, 10.9 mmol), 4-(trifluoromethyl)benzyl alcohol (1.92 g, 10.9 mmol) and DMF (20 ml) stirred at room temperature for 3 hours was added followed by stirring at room temperature overnight. The reaction mixture was extracted with
10 ethyl acetate. 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
15 column chromatography (n-hexane/acetone = 3/1), recrystallized from isopropyl alcohol. The resulting solids were filtered off and then dried under reduced pressure to afford 4-trifluoromethylbenzyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (1.48 g, yield 53%)
20 as a light yellow powder.

Melting point 140.4-141.6°C

Optical purity 99.9% e.e.

¹H-NMR (CDCl₃) δppm:

25 1.62 (3H, s), 2.52 - 2.69 (5H, m), 2.88 (1H, d, J = 14.9 Hz), 3.43 (4H, br), 3.93 (1H, d, J = 9.7 Hz), 4.28 (1H, d, J = 9.7 Hz), 5.16 (2H, s), 7.44 (2H, d, J = 8.1 Hz), 7.53 (1H, s), 7.61 (2H, d, J = 8.1 Hz).

Example 458

Preparation of 1,3,3-trimethyl-2-oxo-2,3-dihydro-1H-indol-5-ylmethyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

To a mixture of 3,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-5-ylmethyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (300 mg, 0.62 mmol) and DMF (3 ml), sodium hydride (27 mg, 0.68 mmol) was added followed by stirring for 30 minutes with cooling on ice-bath. To the reaction mixture, methyl iodide (97 mg, 0.68 mmol) was added followed by stirring at room temperature for 2 hours. To the reaction mixture, water was added, and the mixture was extracted with ethyl acetate twice. The organic phases were combined, washed with water twice 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 (ethyl acetate) to afford 1,3,3-trimethyl-2-oxo-2,3-dihydro-1H-indol-5-ylmethyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (140 mg, 45%) as a light yellow powder. Melting point 80-100°C (decomposition).

Using corresponding starting materials gave the compound of Example 459 in the same manner as in Example 458.

Example 459

1-Methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylmethyl
(S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
b]oxazol-2-ylmethyl)piperazine-1-carboxylate

5 Melting point 189-190°C.

Example 460

Preparation of 3,5-dichlorobenzyl (S)-4-(2-methyl-6-
nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-
piperazine-1-carboxylate

10 To a mixture of (S)-2-methyl-6-nitro-2-
(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole
dihydrochloride prepared in Example 408 (300 mg, 0.88
mmol) and DMF (3 ml), triethylamine (270 mg, 2.67 mmol)
was added for neutralization. To the solution, a
15 mixture of 3,5-dichlorobenzyl alcohol (180 mg, 1.02
mmol), DMF (3 ml) and 1,1'-carbonyldiimidazole (180 mg,
1.11 mmol) stirred at room temperature for 2 hours was
added followed by stirring at room temperature
overnight. To the reaction mixture, water was added,
20 and the mixture was extracted with ethyl acetate twice.
The organic phases were combined, washed with water
twice and a saturated saline solution, dried over
sodium sulfate and then filtered. The filtrate was
25 concentrated under reduced pressure, and the residue
was purified by silica gel column chromatography (ethyl
acetate) to afford 3,5-dichlorobenzyl (S)-4-(2-methyl-
6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-
ylmethyl)piperazine-1-carboxylate (220 mg, yield 53%)

as a white powder.

Melting point 129-130°C.

Example 461

Preparation of 3-(3-trifluoromethylphenyl)-2-propenyl

5 (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate maleate

Using tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 393 (1.09 g, 2.97 mmol)
10 gave 3-(3-trifluoromethylphenyl)-2-propenyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate maleate (945 mg, 63%) as a white powder in the same manner as in Example 344. Melting point 136-138°C.

15 Using corresponding starting materials gave compounds of Examples 462 to 465 in the same manner as in Example 461.

Example 462

[(E)-3-Methyl-3-(3-trifluoromethylphenyl)]-2-propenyl
20 (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate maleate
Melting point 142-143°C.

Example 463

3-(3-Chlorophenyl)-2-propenyl (S)-4-(2-methyl-6-nitro-
25 2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate maleate
Melting point 150-151°C.

Example 464

3-(2,4,6-Trifluorophenyl)-2-propenyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazine-1-carboxylate maleate

Melting point 158-159°C.

5 Example 465

[(Z)-3-Methyl-3-(3-trifluoromethylphenyl)]-2-propenyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate maleate
Melting point 124-125°C.

10 Example 466

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

Using tert-butyl (R)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 396 (106 mg, 0.29 mmol) gave 4-fluorobenzyl (R)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (79 mg, yield 66%) as a white powder in the same manner as in Example 457.

$[\alpha]_D^{28} = 19.70^\circ$ (concentration: 1.066, CHCl_3)

Melting point 167-169°C.

 Example 467

Preparation of (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid [3-(4-trifluoromethylphenyl)-2-propenyl]amide

A mixture of tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-

ylmethyl)piperazine-1-carboxylate prepared in Example 393 (926 mg, 2.52 mmol), trifluoroacetic acid (10 ml) and methylene chloride (3 ml) was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in DMF (3 ml) and neutralized with triethylamine (2 ml, 14.35 mmol). To the solution, a mixture of 3-(4-trifluoromethylphenyl)-2-propenylamine (761 mg, 3.78 mmol), 1,1'-carbonyldiimidazole (613 mg, 3.78 mmol) and DMF (3 ml) stirred at room temperature overnight was added followed by stirring at room temperature overnight. To the reaction mixture, water was added followed by extraction with ethyl acetate. The extract was washed with water three times and 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 = 20/1) to afford (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid [3-(4-trifluoromethylphenyl)-2-propenyl]amide (1.2 g, yield 96%) as a light yellow powder. Melting point 105-107°C.

Using 2-(4-tert-butoxycarbonylpiperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 306 gave compounds of Examples 468 to 470 in the same manner as in Example

467.

Example 468

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-trifluoro-
5 methylbenzyl) amide

Melting point 201-202.5°C.

Example 469

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-trifluoro-
10 methylphenyl) amide

Melting point 216-217°C.

Example 470

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-chloro-3-
15 trifluoromethylphenyl) amide

Melting point 222-224°C.

Example 471

Preparation of (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic
20 acid cyclohexylamide

(S)-2-Methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 408 (236 mg, 0.88 mmol) was dissolved in a mixture of methylene chloride (15
25 ml) and triethylamine (2 ml, 14.35 mmol). To the solution, cyclohexyl isocyanate (120 mg, 0.96 mmol) was added followed by stirring at room temperature for 1 hour. The reaction mixture was

washed with water 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

5 chromatography (methylene chloride/methanol = 20/1) to afford (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid cyclohexylamide (164 mg, 47%) as a light yellow powder. Melting point 98-101°C.

10 Using 2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 322 gave compounds of Examples 472 to 476 in the same manner as in Example 471.

15 Example 472
4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-methoxyphenyl)amide
Melting point 167-168°C.

20 Example 473
4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-chlorophenyl)-amide
Melting point 185-188°C (decomposition).

25 Example 474
4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (3-trifluoromethylphenyl)amide

Melting point 183-184°C.

Example 475

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (3,4-dichloro-phenyl)amide

Melting point 212-214°C (decomposition).

Example 476

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-methylphenyl)-amide

Melting point 202-203°C (decomposition).

Example 477

Preparation of (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-trifluoromethylphenyl)amide

(S)-2-Methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 408 (236 mg, 0.88 mmol) was dissolved in a mixture of methylene chloride (5 ml) and triethylamine (2 ml, 14.35 mmol). To the solution, a mixture of 4-aminobenzotrifluoride (142 mg, 0.882 mmol), 1,1'-carbonyldiimidazole (143 mg, 0.882 mmol) and DMF (6 ml) stirred at room temperature overnight was added followed by stirring at room temperature for 6 hours. To the reaction mixture, water was added, and the mixture was extracted with ethyl acetate. The organic phase was 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 = 30/1) to afford (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-trifluoromethylphenyl)amide (90 mg, yield 23%) as a white powder.

Melting point 150-152.5°C.

10 Using corresponding starting materials gave compounds of Examples 478 to 481 in the same manner as in Example 477.

Example 478

(S)-4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-methoxyphenyl)amide

Melting point 185.5-187.5°C.

Example 479

(S)-4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-trifluoromethylbenzyl)amide

Melting point 101-103.6°C.

Example 480

(S)-4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-chlorophenyl)amide

Melting point 156-159°C (decomposition).

Example 481

(S)-4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-methylphenyl)amide

Melting point 207-210°C (decomposition).

5 Example 482

Preparation of (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid N-methyl-N-(4-trifluoromethylphenyl)amide

10 A mixture of (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-trifluoromethylphenyl)amide prepared in Example 477 (200 mg, 0.44 mmol), DMF (4 ml), and sodium hydride (26 mg, 0.66 mmol) was stirred at room temperature for 1.5 hours. To the mixture, methyl
15 iodide (0.5 ml, 0.76 mmol) was added followed by stirring at room temperature overnight. To the reaction mixture, water was added, and the mixture was extracted with ethyl acetate. The organic phase was washed with water three times and a saturated saline
20 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 = 50/1) to afford (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid N-
25 methyl-N-(4-trifluoromethylphenyl)amide (35 mg, yield 17%) as a white powder.

Melting point 100.4-102.4°C.

Example 483

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

- 5 A mixture of tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazine-1-carboxylate prepared in Example 393 (1.17 g, 3.32 mmol), trifluoroacetic acid (5 ml) and methylene chloride (10 ml) was stirred at room
- 10 temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in methylene chloride (10 ml). To the resulting solution, triethylamine (5 ml, 35.87 mmol) was added followed by stirring at room temperature for
- 15 10 minutes. The solution was concentrated under reduced pressure, the residue was dissolved in DMF (15 ml). To the mixture, potassium carbonate (920 mg, 6.64 mmol) and a solution of 4-(4-trifluoromethylphenyl)-piperidine-1-carbonylchloride (1.07 g, 3.65 mmol) in
- 20 DMF (10 ml) was added slowly with cooling on ice-bath followed by stirring at room temperature overnight. To the reaction mixture, water was added followed by extraction with ethyl acetate. The extract was washed with water three times and a saturated saline solution,
- 25 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 = 30/1) to

afford (S)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-[4-(4-trifluoromethylphenyl)piperidin-1-yl]methanone (575 mg, yield 33%) as a white powder.

5 Melting point 179.1-181.9°C.

Example 484

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

10

A mixture of (S)-2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 408 (401 mg, 1.5 mmol), DMF (8 ml) and potassium carbonate (750 mg, 5.4 mmol) was stirred at room temperature for 10 minutes.

15 To the reaction mixture, a solution of 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine-1-carbonylchloride (400 mg, 1.56 mmol) in DMF (3 ml) was added slowly with cooling on ice-bath followed by

20 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 three times and a saturated saline solution, dried over sodium sulfate and then filtered.

25 The filtrate was concentrated under reduced pressure, and the residue was recrystallized from ethanol to afford (S)-[4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridin-1-yl]-[4-(2-methyl-6-nitro-2,3-

dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]methanone (380 mg, yield 53%) as a light yellow powder.

Melting point 161-162°C.

- 5 Using (S)-2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 408 gave compounds of Examples 485 and 486 in the same manner as in Example 484. Also, using 2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole
- 10 dihydrochloride prepared in Example 322 gave the compound of Example 487 in the same manner as in Example 484.

Example 485

- 15 (S)-[4-(4-Chlorophenyl)pyridin-1-yl]-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazin-1-yl]methanone

Melting point 156-159°C.

Example 486

- 20 (S)-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-[4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridin-1-yl]methanone

Melting point 168.4-171.7°C.

Example 487

- 25 [4-(4-Chlorophenyl)piperidin-1-yl]-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazin-1-yl]methanone

Melting point 186-187°C.

Example 488

Preparation of (S)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]benzoic acid

- 5 Tert-butyl (S)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]benzoate (300 mg, 0.68 mmol) in trifluoroacetic acid (10 ml) was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced
10 pressure, neutralized with triethylamine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1), crystallized from methanol-diisopropyl ether to afford (S)-4-[4-(2-methyl-6-nitro-
15 2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]benzoic acid (186 mg, yield 71%) as a white powder.
MS 387 (M⁺)
Melting point 248-252°C.

Example 489

- 20 Preparation of (S)-2-[4-(2,6-diphenylpyrimidin-4-yl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

- Tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-
25 carboxylate prepared in Example 393 (500 mg, 1.36 mmol) was dissolved in methylene chloride (2 ml). To the solution, trifluoroacetic acid (10 ml) was added followed by stirring at room temperature for 3 hours.

The reaction mixture was concentrated under reduced pressure, and added methylene chloride (4 ml) and triethylamine (4 ml). The reaction mixture was stirred at room temperature for 5 minutes and then concentrated under reduced pressure, and the residue was dissolved in DMF (5 ml). To the solution, 4-chloro-2,6-diphenylpyrimidine (400 mg, 1.50 mmol) and DBU (0.2 ml, 1.36 mmol) were added followed by stirring at 100°C for 5 hours. The reaction mixture was allowed to return to room temperature, poured into water, and then 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 filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and crystallized from methylene chloride-diisopropyl ether to afford (S)-2-[4-(2,6-diphenylpyrimidin-4-yl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (113 mg, yield 17%) as a white powder.

MS 498 (M+H)⁺

Melting point 202.5-205.4°C.

Using corresponding starting materials gave the compound of Example 490 in the same manner as in Example 489.

Example 490

(S)-2-[4-(4,6-Diphenylpyrimidin-2-yl)piperazin-1-

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

Yield 7%, melting point 201.2-205.4°C.

Example 491

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

2-Chloro-4-nitro-1H-imidazole (2.05 g, 13.9 mmol), tert-butyl 4-(2-methyloxiran-2-ylmethyl)-
10 piperazin-1-yl)carbamate (3.14 g, 11.6 mmol) and sodium hydrogencarbonate (1.46 g, 17.4 mmol) in 1-propanol (13 ml) were stirred under heating for 6 hours. The reaction mixture was extracted with ethyl acetate twice. The organic phases were combined, washed with a
15 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 = 2/1) to afford tert-butyl {4-[3-(2-
20 chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-1-yl}carbamate (1.55 g, yield 32%) as a white powder.

¹H-NMR (CDCl₃) δppm:

1.12 (3H, s), 1.46 (9H, s), 2.36 (1H, d, J = 13.9 Hz),
25 2.50 (1H, d, J = 13.9 Hz), 2.64 - 2.84 (8H, m), 3.32 (1H, s), 3.96 (2H, s), 5.46 (1H, br), 8.03 (1H, s).

Example 492

Preparation of tert-butyl {4-[3-(2-chloro-4-

nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-1-yl}carbamate (alternative synthesis of the compound of Example 491)

Using 2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 6 (4.36 g, 20.0 mmol) and tert-butyl piperazin-1-ylcarbamate (4.44 g, 22.0 mmol) gave tert-butyl {4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-1-yl}carbamate (6.08 g, yield 72%) as a white powder in the same manner as in Example 365.

Example 493

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

Using tert-butyl {4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-1-yl}carbamate prepared in Example 492 (6.87 g, 16.4 mmol) gave tert-butyl [4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]carbamate (2.71 g, yield 43%) as a white powder in the same manner as in Example 393.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.43 (9H, s), 1.60 (3H, s), 2.36 (1H, d, $J = 14.0$ Hz), 2.52 - 2.90 (9H, m), 3.90 (1H, d, $J = 9.7$ Hz), 4.27 (1H, d, $J = 9.7$ Hz), 5.35 (1H, br), 7.53 (1H, s).

Example 494

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

yl]carbamate

A mixture of tert-butyl [4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]carbamate prepared in Example 493 (150 mg, 0.39 mmol) and trifluoroacetic acid (4 ml) was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methylene chloride (4 ml) and neutralized with triethylamine (4 ml, 28.7 mmol). Subsequently, to the solution, benzyl chloroformate (100 mg, 0.59 mmol) was added with cooling on ice-bath followed by stirring at room temperature for 2 hours. To the reaction mixture, a saturated sodium hydrogencarbonate solution was added. The mixture was extracted with methylene chloride. The extract was washed with water 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 (n-hexane/acetone = 1/1) to afford benzyl [4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]carbamate (6.5 mg, yield 4%) as a light yellow powder.

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.60 (3H, s), 2.53 - 2.90 (10H, m), 3.89 (1H, d, $J = 9.6$ Hz), 4.27 (1H, d, $J = 9.6$ Hz), 5.11 (2H, s), 5.88 (1H, br), 7.25 - 7.34 (5H, m), 7.52 (1H, s).

Example 495

Preparation of N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-(4-trifluoromethoxybenzylidene)amine

A mixture of tert-butyl [4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]carbamate prepared in Example 493 (40 mg, 0.11 mmol), 4-trifluoromethoxybenzaldehyde (24 mg, 0.13 mmol), trifluoroacetic acid (0.08 ml) and methylene chloride (1 ml) was stirred at room temperature for 3 hours. The mixture was added a saturated sodium hydrogencarbonate solution for neutralization followed by extraction 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, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 3/1) to afford N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-(4-trifluoromethoxybenzylidene)amine (19 mg, yield 40%) as a white powder.

Melting point 189.2-190.9°C.

Example 496

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-{4-[(4-trifluoromethylbenzylidene)amino]-piperazin-1-yl}propan-2-ol

A mixture of (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12

(218 mg, 1 mmol), N-(piperazin-1-yl)-N-(4-trifluoromethylbenzylidene)amine (283 mg, 1.1 mmol) and DMF (2 ml) was stirred at 70-80°C for 7 hours. The reaction mixture was allowed to return to room temperature and then added water, and the resulting solution was extracted with ethyl acetate twice. The organic phases were combined, washed with water 3 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 (n-hexane/acetone = 1/1) to afford (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-{4-[(4-trifluoromethylbenzylidene)amino]piperazin-1-yl}propan-2-ol (402 mg, yield 85%) as a light yellow powder.

$[\alpha]_D^{27} = 19.01^\circ$ (concentration: 1.010, CHCl_3)

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.18 (3H, s), 2.42 (1H, d, $J = 13.9$ Hz), 2.57 (1H, d, $J = 13.9$ Hz), 2.71 - 2.95 (4H, m), 3.10 - 3.33 (5H, m), 4.02 (2H, s), 7.51 (1H, s), 7.58 (2H, d, $J = 8.4$ Hz), 7.68 (2H, d, $J = 8.4$ Hz), 8.05 (1H, s).

Example 497

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

Using (R)-2-chloro-1-(2-methyloxiran-2-yl)methyl-4-nitroimidazole prepared in Example 12 (29.8 g, 137 mmol) and tert-butyl piperazin-1-ylcarbamate

(28.9 g, 144 mmol) gave tert-butyl (S)-{4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-1-yl}carbamate (36.68 g, yield 64%) as a white powder in the same manner as in Example 496.

$[\alpha]_D^{27} = 17.793^\circ$ (concentration: 1.006, CHCl_3)

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.12 (3H, s), 1.45 (9H, s), 2.36 (1H, d, $J = 14.0$ Hz), 2.50 (1H, d, $J = 14.0$ Hz), 2.64 - 2.84 (8H, m), 3.32 (1H, s), 3.97 (2H, s), 5.47 (1H, br), 8.04 (1H, s).

Using corresponding starting materials gave compounds of Examples 498 to 500 in the same manner as in Example 497.

Example 498

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-2-methyl-3-{4-[(4-trifluoromethoxybenzylidene)amino]piperazin-1-yl}propan-2-ol

$[\alpha]_D^{27} = 12.326^\circ$ (concentration: 1.006, CHCl_3)

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.17 (3H, s), 2.41 (1H, d, $J = 13.9$ Hz), 2.56 (1H, d, $J = 13.9$ Hz), 2.71 - 2.95 (4H, m), 3.14 - 3.29 (5H, m), 4.01 (2H, s), 7.19 (2H, d, $J = 8.0$ Hz), 7.50 (1H, s), 7.62 (2H, d, $J = 8.0$ Hz), 8.05 (1H, s).

Example 499

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-2-methyl-3-{4-[(5-trifluoromethylbenzofuran)-2-ylmethylene]amino]piperazin-1-yl}propan-2-ol

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.18 (3H, s), 2.43 (1H, d, $J = 14.0$ Hz), 2.58 (1H, d, $J = 14.0$ Hz), 2.73 - 2.82 (2H, m), 2.86 - 2.95 (2H, m), 3.17 (1H, s), 3.31 (4H, s), 4.03 (2H, s), 6.82 (1H, s), 7.46 (1H, s), 7.52 (1H, d, $J = 8.7$ Hz), 7.59 (1H, d, $J = 8.7$ Hz), 7.83 (1H, s), 8.05 (1H, s).

Example 500

(S)-1-{4-[(5-Chlorobenzofuran)-2-ylmethylene]amino}-piperazin-1-yl}-3-(2-chloro-4-nitroimidazol-1-yl)-2-methylpropan-2-ol

10 $^1\text{H-NMR}$ (CDCl_3) δppm :

1.18 (3H, s), 2.42 (1H, d, $J = 14.0$ Hz), 2.57 (1H, d, $J = 14.0$ Hz), 2.71 - 3.00 (4H, m), 3.17 (1H, s), 3.23 - 3.38 (4H, m), 4.02 (2H, s), 6.71 (1H, s), 7.22 (1H, dd, $J = 2.1$ Hz, 8.7 Hz), 7.33 - 7.43 (2H, m), 7.50 (1H, d, $J = 2.1$ Hz), 8.05 (1H, s).

Example 501

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

20 Using (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (0.610 g, 2.82 mmol) and N-(piperazin-1-yl)-4-trifluoromethylaniline (0.760 g, 3.09 mmol) gave (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylphenylamino)piperazin-1-yl]propan-2-ol

25 (1.125 g, yield 86%) as a colorless solid in the same manner as in Example 496.

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.15 (3H, s), 2.39 (1H, d, $J = 14.0$ Hz), 2.54 (1H, d, $J = 14.0$ Hz), 2.60 - 2.95 (8H, m), 3.25 (1H, s), 3.99 (2H, s), 4.67 (1H, s), 6.90 (2H, d, $J = 8.6$ Hz), 7.43 (2H, d, $J = 8.6$ Hz), 8.04 (1H, s).

5 Example 502

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

 Using (S)-1-(2-chloro-4-nitroimidazol-1-yl)-
10 2-methyl-3-[4-(4-trifluoromethylphenylamino)piperazin-1-yl]propan-2-ol prepared in Example 501 (1.125 g, 2.43 mmol) gave (S)-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-4-trifluoromethylaniline (0.715 g, yield 69%) as a
15 white solid in the same manner as in Example 493.
Melting point 192.1-195.3°C.

 Example 503

Preparation of tert-butyl (S)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]carbamate
20

 Using tert-butyl (S)-{4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-1-yl}carbamate prepared in Example 497 (36.68 g) gave
tert-butyl (S)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]carbamate (19.51 g, yield 58%) as a white powder in
25 the same manner as in Example 493.
Optical purity >99.5% e.e.

$[\alpha]_D^{27} = 9.84^\circ$ (concentration: 1.016, CHCl_3)

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.43 (9H, s), 1.60 (3H, s), 2.35 (1H, d, $J = 14.0$ Hz),
2.52 - 2.92 (9H, m), 3.89 (1H, d, $J = 9.7$ Hz), 4.27
5 (1H, d, $J = 9.7$ Hz), 5.35 (1H, s), 7.53 (1H, s).

Example 504

Preparation of (S)-N-[4-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-(4-trifluoromethylbenzylidene)amine

10 To a mixture of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-{4-[(4-trifluoromethylbenzylidene)amino]piperazin-1-yl}propan-2-ol prepared in Example 496 (847 mg, 0.85 mmol) and DMF (4 ml), sodium hydride (69 mg, 1.73 mmol) was added followed by
15 stirring for 2.5 hours with cooling on ice-bath. To the reaction mixture, water was added, and the precipitates were filtered off. The resulting solid was washed with methanol and recrystallized from acetone/water to afford (S)-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-
20 N-(4-trifluoromethylbenzylidene)amine (248 mg, yield 69%) as a light yellow powder.

Melting point $201-202.3^\circ\text{C}$ (decomposition)

Optical purity $>99.5\%$ e.e.

25 $[\alpha]_D^{27} = -64.64^\circ$ (concentration: 1.018, CHCl_3)

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.64 (3H, s), 2.55 - 2.79 (3H, m), 2.80 - 3.20 (7H, m),
3.94 (1H, d, $J = 9.7$ Hz), 4.33 (1H, d, $J = 9.7$ Hz),

7.44 (1H, s), 7.48 - 7.67 (5H, m).

Using corresponding starting materials gave compounds of Examples 505 to 507 in the same manner as in Example 504.

5 Example 505

(S)-N-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-(4-trifluoromethylbenzylidene)amine

Melting point 188.4-191.2°C

10 Optical purity >99.0% e.e.

$[\alpha]_D^{27} = -58.30^\circ$ (concentration: 1.024, CHCl₃)

¹H-NMR (CDCl₃) δppm:

1.64 (3H, s), 2.55 - 2.77 (3H, m), 2.82 - 3.18 (7H, m),

3.94 (1H, d, J = 9.7 Hz), 4.33 (1H, d, J = 9.7 Hz),

15 7.16 (2H, d, J = 8.2 Hz), 7.43 (1H, s), 7.55 (1H, s),

7.58 (2H, d, J = 8.2 Hz).

Example 506

(S)-N-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-(5-trifluoro-

20 methylbenzofuran-2-ylmethylene)amine

Melting point 190.2-191.8°C

Optical purity 99.8% e.e.

$[\alpha]_D^{27} = -81.05^\circ$ (c = 0.992, CHCl₃)

¹H-NMR (CDCl₃) δppm:

25 1.64 (3H, s), 2.59 - 2.77 (3H, m), 2.86 - 3.00 (3H, m),

3.05 - 3.26 (4H, m), 3.96 (1H, d, J = 9.7 Hz), 4.33

(1H, d, J = 9.7 Hz), 6.79 (1H, s), 7.39 (1H, s), 7.41 -

7.57 (3H, m), 7.82 (1H, s).

Example 507

(S)-N-(5-Chlorobenzofuran-2-ylmethylene)-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]amine

5 Optical purity >99.0% e.e.

$[\alpha]_D^{27} = -84.48^\circ$ (concentration: 1.018, CHCl_3)

Melting point 213.8-215.7°C

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.63 (3H, s), 2.57 - 2.76 (3H, m), 2.81 - 2.95 (3H, m),
10 3.00 - 3.24 (4H, m), 3.94 (1H, d, $J = 9.7$ Hz), 4.32
(1H, d, $J = 9.7$ Hz), 6.67 (1H, s), 7.17 - 7.23 (1H, m),
7.30 - 7.43 (2H, m), 7.48 (1H, d, $J = 2, 1$ Hz), 7.53
(s, 1H).

Example 508

15 Preparation of (S)-N-(5-chlorobenzofuran-2-ylmethylene)-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]amine (alternative synthesis of the compound of Example 507)

20 To a mixture of tert-butyl (S)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]carbamate prepared in Example 503 (0.20 g, 0.523 mmol) and 5-chlorobenzofuran-2-carbaldehyde (0.113 g, 0.628 mmol) and methylene
25 chloride (4 ml), trifluoroacetic acid (0.4 ml) was added followed by stirring at room temperature for 2 hours. To the reaction mixture, a saturated sodium hydrogencarbonate solution was added followed by

extraction with methylene chloride. The organic phase was washed with a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure, and
5 the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 4/1) to afford (S)-N-(5-chlorobenzofuran-2-ylmethylene)-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]amine (0.137 g, yield 59%) as a
10 light yellow powder.

Example 509

Preparation of (S)-N-[1-(4-chlorophenyl)ethylidene]-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]amine

15 A mixture of tert-butyl (S)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazin-1-yl]carbamate prepared in Example 503 (200 mg, 0.52 mmol), trifluoroacetic acid (2 ml) and methylene chloride (4 ml) was stirred at room tempera-
20 ture for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in methylene chloride (4 ml) and then neutralized with triethylamine (4 ml, 28.7 mmol). To the neutralized solution, a solution of 4-
25 chloroacetophenone (97 mg, 0.63 mmol) in ethanol (4 ml) was added followed by stirring under reflux for 4 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 (n-hexane/acetone = 3/1) to afford (S)-N-[1-(4-chlorophenyl)ethylidene]-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]amine (39 mg, yield 18%) as a light yellow powder.

Melting point 164.6-166.5°C

Using corresponding starting materials gave compounds of Examples 510 to 513 in the same manner as in Example 509.

Example 510

(S)-N-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-[1-(4-trifluoromethylphenyl)ethylidene]amine

Melting point 167.9-169.4°C

Example 511

(S)-N-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-[1-(4-trifluoromethoxyphenyl)ethylidene]amine

Melting point 177.8-180.1°C

Example 512

(S)-N-Cyclohexylidene-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]amine

Melting point 178.6-179.3°C

Example 513

N-(2-Benzylideneheptylidene)-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-

yl]amine

Melting point 166.6-169.6°C.

Example 514

Preparation of (S)-N-[4-(2-methyl-6-nitro-2,3-dihydro-
5 imidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-(4-trifluoromethylbenzyl)amine

To a mixture of (S)-N-[4-(2-methyl-6-nitro-
2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-
yl]-N-(4-trifluoromethylbenzylidene)amine prepared in
10 Example 504 (100 mg, 0.23 mmol) and THF (4 ml), sodium
borohydride (13 mg, 0.34 mmol) was added with cooling
on ice-bath followed by stirring at room temperature
for 30 minutes. To the reaction mixture, methanol (1
ml) was added, and the solution was concentrated under
15 reduced pressure. The residue was purified by silica
gel column chromatography (n-hexane/ethyl acetate =
2/1) to afford (S)-N-[4-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-
N-(4-trifluoromethylbenzyl)amine (32 mg, yield 31%) as
20 a light yellow powder.

Melting point 131.3-135.5°C.

Example 515

Preparation of (S)-[4-(2-methyl-6-nitro-2,3-dihydro-
imidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]amine
25 dihydrochloride

A mixture of tert-butyl (S)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-
piperazin-1-yl]carbamate prepared in Example 503 (300

mg, 0.78 mmol), concentrated hydrochloric acid (2 ml) and methanol (4 ml) was stirred at 50°C for 30 minutes. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure.

- 5 The residue was recrystallized from methanol/ether to afford (S)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]amine dihydrochloride (265 mg, yield 91%) as a yellow powder. Melting point 176°C (decomposition).

10 Example 516

Preparation of 3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one

- To a suspension of 2-chloro-4-nitro-1H-imidazole (2.21 g, 14.98 mmol) and 3-(2-methyloxiran-2-ylmethyl)-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one (2.37 g, 7.49 mmol) in ethanol (25 ml), sodium hydrogencarbonate (1.32 g, 15.73 mmol) was added followed by stirring under reflux for 8 hours. To the reaction mixture, water was added, and the mixture was extracted with methylene chloride. The organic phase was dried over magnesium sulfate, and concentrated under reduced pressure to afford 3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one (3.27 g, yield 94%) as a light yellow amorphous form.
- 25

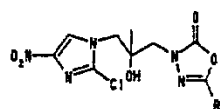
¹H-NMR (DMSO-d₆) δppm:

1.53 (3H, s), 3.67 (1H, d, J = 8.8 Hz), 3.81 (1H, d, J

= 8.8 Hz), 4.49 (2H, s), 7.42 - 7.66 (2H, m), 7.86 - 8.09 (2H, m), 8.54 (1H, s), 10.98 (1H, br).

Using corresponding starting materials gave compounds of Examples 517 to 523 shown in the following table in the same manner as in Example 516.

Table 18



Example	R		¹ H NMR δ	Yield (%)
517		CDCl ₃	1.59(3H, s), 3.78(1H, d, J=8.5Hz), 3.86(1H, d, J=8.5Hz), 4.29(1H, d, J=15.1Hz), 4.57(1H, d, J=15.1Hz), 7.61(2H, d, J=8.1Hz), 7.79(2H, d, J=8.1Hz), 8.06(1H, s), 9.17(1H, br).	70
518		CDCl ₃	1.61(3H, s), 3.79 (1H, d, J=8.5Hz), 3.85(1H, d, J=8.5Hz), 4.27(1H, d, J=15.0Hz), 4.56(1H, d, J=15.0Hz), 7.33-7.63 (7H, m), 7.78(2H, d, J=8.4Hz), 8.06(1H, s), 9.02(1H, br).	82
519		CDCl ₃	1.62(3H, s), 3.75(1H, d, J=8.5Hz), 3.83(1H, d, J=8.5Hz), 4.27(1H, d, J=15.0Hz), 4.54(1H, d, J=15.0Hz), 7.34(2H, dd, J=1.8Hz, 8.6Hz), 7.63(2H, dd, J=1.8Hz, 8.6Hz), 8.03(1H, s), 9.05(1H, br).	57
520		DMSO-d ₆	1.51(3H, s), 3.66(1H, d, J=8.8Hz), 3.79(1H, d, J=8.8Hz), 4.48(2H, s), 7.24-7.41(2H, m), 7.84-7.96(2H, m), 8.52(1H, s).	64
521		CDCl ₃	1.56(3H, s), 2.41-2.53(2H, m), 2.81-3.00(2H, m), 3.56(1H, d, J=8.5Hz), 3.63(1H, d, J=8.5Hz), 4.22(1H, d, J=15.0Hz), 4.42(1H, d, J=15.0Hz), 7.12(2H, d, J=8.4Hz), 7.26(2H, d, J=8.4Hz), 7.55(1H, br), 7.97(1H, s).	92
522		DMSO-d ₆	1.53(3H, s), 3.63(1H, d, J=8.8Hz), 3.77(1H, d, J=8.8Hz), 4.43(1H, d, J=15.0Hz), 4.51(1H, d, J=15.0Hz), 6.58(1H, d, J=15.9Hz), 7.43-7.55(3H, m), 7.64(2H, d, J=8.5Hz), 7.51(1H, s).	89
523		CDCl ₃	1.56(3H, s), 3.72(2H, s), 4.25(1H, d, J=15.1Hz), 4.44(1H, d, J=15.1Hz), 4.59(2H, s), 6.85(2H, dd, J=2.3Hz, 6.8Hz), 7.29(2H, dd, J=2.3Hz, 6.8Hz), 7.98(1H, s), 8.49 (1H, br).	98

Example 524

Preparation of 3-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)-5-(4-trifluoromethoxyphenyl)-

3H-[1,3,4]oxadiazol-2-one

To a solution of 3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one
5 prepared in Example 516 (3.27 g, 7.05 mmol) in 1,4-dioxane (70 ml), sodium hydride (0.37 g, 9.17 mmol) was added with cooling on ice-bath followed by stirring under reflux for 3 hours. The reaction mixture was concentrated under reduced pressure. To the solution,
10 water was added with cooling on ice-bath, and the mixture was extracted with ethyl acetate. The extract was dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene
15 chloride/ethyl acetate = 4/1) and recrystallized from acetonitrile-ethanol to afford 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one (1.43 g, yield 48%) as a white solid.
20 Melting point 190-191°C.

Using corresponding starting materials gave compounds of Examples 525 to 531 in the same manner as in Example 524.

Example 525

25 3-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-(4-trifluoromethylphenyl)-3H-[1,3,4]-oxadiazol-2-one
Melting point 230-231°C.

Example 526

3-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-(biphenyl-4-yl)-3H-[1,3,4]oxadiazol-2-one
Melting point 248-249°C.

5 Example 527

3-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-(4-chlorophenyl)-3H-[1,3,4]oxadiazol-2-one
Melting point 221-222°C.

Example 528

10 3-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-(4-fluorophenyl)-3H-[1,3,4]oxadiazol-2-one
Melting point 188-191°C.

Example 529

15 3-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-[2-(4-chlorophenyl)vinyl]-3H-[1,3,4]-oxadiazol-2-one
Melting point 249-252°C.

Example 530

20 3-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-[2-(4-chlorophenyl)ethyl]-3H-[1,3,4]-oxadiazol-2-one
Melting point 139-140°C.

Example 531

25 3-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-(4-chlorophenoxymethyl)-3H-[1,3,4]-oxadiazol-2-one
Melting point 64-66°C.

Example 532

Preparation of 3-(2-methyl-6-nitro-2,3-dihydroimidazo-
[2,1-b]oxazol-2-ylmethyl)-5-phenyl-3H-[1,3,4]oxadiazol-
2-one

A mixture of 2-chloro-4-nitro-1H-imidazole
5 (170 mg, 1.15 mmol), 3-(2-methyloxiran-2-ylmethyl)-5-
phenyl-3H-[1,3,4]oxadiazol-2-one (310 mg, 0.9 mmol),
sodium hydrogencarbonate (120 mg, 1.43 mmol) and
ethanol (2 ml) was stirred under reflux for 2.5 hours.
The reaction mixture was allowed to return to room
10 temperature, then diluted with water. The solution was
extracted with methylene chloride. The organic phase
was dried over magnesium sulfate and then filtered.
The filtrate was concentrated under reduced pressure,
the residue was dissolved in 1,4-dioxane (10 ml). To
15 the solution, sodium hydride (55 mg, 1.38 mmol) was
added followed by stirring at room temperature for 1
hour and then stirring under reflux for 1.5 hours. The
reaction mixture was allowed to return to room
temperature. To the solution, water was added, and the
20 mixture was extracted with methylene chloride. The
organic phase was dried over magnesium sulfate and then
filtered. The filtrate was concentrated under reduced
pressure, and the residue was recrystallized from
ethanol to afford 3-(2-methyl-6-nitro-2,3-dihydro-
25 imidazo[2,1-b]oxazol-2-ylmethyl)-5-phenyl-3H-[1,3,4]-
oxadiazol-2-one (127 mg, yield 32%) as a light brown
powder.

Melting point 225-227°C.

Example 533

Preparation of 5-(4-chlorobenzyl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-3H-[1,3,4]oxadiazol-2-one

5 A mixture of 2-methyloxiran-2-ylmethyl 4-methylbenzenesulfonate (3.98 g, 18.9 mmol), 5-(4-chlorobenzyl)-3H-[1,3,4]oxadiazol-2-one (5.5 g, 26.11 mmol), potassium carbonate (3.4 g, 24.6 mmol), sodium iodide (3.4 g, 22.68 mmol) and DMF (40 ml) was stirred
10 at room temperature for 21 hours. To the reaction mixture, water was added, and the mixture was extracted with ethyl acetate twice. The organic phases were combined, washed with water three times, dried over magnesium sulfate and then filtered. The filtrate was
15 concentrated under reduced pressure to afford a yellow oil (5.47 g).

 A mixture of 2.3 g of the yellow oil (11.02 mmol), 2,4-dinitro-1H-imidazole (2.26 g, 14.3 mmol), sodium acetate (1.81 g, 22.07 mmol) and ethanol (22 ml)
20 was stirred under reflux for 8 hours. The reaction mixture was allowed to return to room temperature. To the solution, water was added, and the mixture was extracted with ethyl acetate. The organic phase was washed with a saturated sodium hydrogencarbonate
25 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/ethyl acetate

= 3/1) to afford 5-(4-chlorobenzyl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-3H-[1,3,4]oxadiazol-2-one (240 mg, 9%) as a white solid. Melting point 151-153°C.

5 Example 534

Preparation of 5-(4-bromophenyl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-3H-[1,3,4]-oxadiazol-2-one

10 A mixture of 2-methyl-6-nitro-2,3-dihydro-
imidazo[2,1-b]oxazol-2-ylmethyl methanesulfonate
prepared in Example 41 (1.02 g, 3.67 mmol), 5-(4-bromophenyl)-3H-[1,3,4]oxadiazol-2-one (680 mg, 2.82 mmol), potassium carbonate (580 mg, 4.2 mmol), sodium iodide (890 mg, 5.94 mmol) and DMF (15 ml) was stirred
15 at 100°C for 3 hours. The reaction mixture was allowed to return to room temperature. To the solution, water was added, and the resulting solution was extracted with ethyl acetate twice. The organic phases were combined, washed with water three times, dried over
20 magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford 5-(4-bromophenyl)-3-(2-methyl-6-nitro-2,3-dihydro-
25 imidazo[2,1-b]oxazol-2-ylmethyl)-3H-[1,3,4]oxadiazol-2-one (17.4 mg, yield 2%) as a light yellow powder. Melting point 231-233°C.

Example 535

Preparation of 5-(4-bromophenyl)-3-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-3H-[1,3,4]-oxadiazol-2-one

Using 6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl methanesulfonate prepared in Example 40 (3.28 g, 12.46 mmol) and 5-(4-bromophenyl)-3H-[1,3,4]oxadiazol-2-one (1.5 g, 6.22 mmol) gave 5-(4-bromophenyl)-3-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-3H-[1,3,4]oxadiazol-2-one (312 mg, yield 12%) as a light brown powder in the same manner as in Example 534.

Melting point 264°C (decomposition).

Using corresponding starting materials gave the compound of Example 536 in the same manner as in Example 535.

Example 536

3-(6-Nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one
Melting point 204-207°C.

Example 537

Preparation of 3-[2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]-5-(pyridin-4-yl)-3H-[1,3,4]oxadiazol-2-one

A mixture of 5-(pyridin-4-yl)-3H-[1,3,4]-oxadiazol-2-one (150 mg, 0.92 mmol), sodium hydride (41 mg, 1.03 mmol) and DMF (1.5 ml) was stirred at room temperature for 1 hour. To the reaction mixture, 2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-

yl)ethyl methanesulfonate prepared in Example 42 (200 mg, 0.69 mmol) and sodium iodide (140 mg, 0.93 mmol) were added in this order followed by stirring at 50-60°C for 6 hours. The reaction mixture was allowed to
5 return to room temperature. To the solution, water was added, and the resulting solution was extracted with ethyl acetate twice. The organic phases were combined, washed with water three times, dried over magnesium sulfate and then filtered. The filtrate was
10 concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 25/1) to afford 3-[2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]-5-(pyridin-4-yl)-3H-[1,3,4]oxadiazol-2-one
15 (137 mg, yield 56%) as a white powder.
Melting point 147-149°C.

Using corresponding starting materials gave the compound of Example 538 in the same manner as in Example 537.

20 Example 538

3-[2-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]-5-(pyrazin-2-yl)-3H-[1,3,4]oxadiazol-2-one
Melting point 209-212°C.

 Example 539

25 Preparation of (R)-3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one

To a solution of 5-(4-trifluoromethoxy-

phenyl)-3H-[1,3,4]oxadiazol-2-one (0.68 g, 2.76 mmol) and (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (0.50 g, 2.30 mmol) in DMF (5 ml), potassium carbonate (0.38 g, 2.76 mmol) was added followed by stirring at room temperature for 16 hours, and then water was added. The solution was extracted with ethyl acetate, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 4/1) to afford (R)-3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one (1.06 g, quantitative yield) as a white amorphous form.

¹H-NMR (DMSO-d₆) δppm:
1.53 (3H, s), 3.67 (1H, d, J = 8.8 Hz), 3.81 (1H, d, J = 8.8 Hz), 4.49 (2H, s), 7.42 - 7.66 (2H, m), 7.86 - 8.09 (2H, m), 8.54 (1H, s), 10.98 (1H, br).

Example 540

Preparation of (R)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one

To a solution of (R)-3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one prepared in Example 539 (0.87 g, 1.88 mmol) in 1,4-dioxane (18 ml), sodium hydride (98 mg, 2.44 mmol) was added with cooling on ice-bath. The mixture was

stirred under reflux for 5 hours, concentrated under reduced pressure, then water was added with cooling on ice-bath. The solution was extracted with ethyl acetate, and the organic phase 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), and recrystallized from acetonitrile/isopropanol to afford (R)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one (0.32 g, yield 40%) as a white powder. Optical purity 98.2% e.e. $[\alpha]_D^{26} = -12.43^\circ$ (concentration: 0.668, CHCl_3)

15 Melting point 146-148°C.

Example 541

Preparation of 3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-3H-benzoxazol-2-one

To a suspension of 2-chloro-4-nitro-1H-imidazole (503 mg, 3.41 mmol), 3-(2-methyloxiran-2-ylmethyl)-3H-benzoxazol-2-one (700 mg, 3.41 mmol) in ethanol (7 ml), sodium acetate (336 mg, 4.1 mmol) was added followed by stirring under reflux for 8 hours. The reaction mixture was allowed to return to room temperature. To a mixture, water was added, and the resulting solution was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The filtrate was

20

25

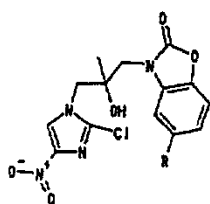
concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 30/1) to afford 3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-3H-benzoxazol-2-one (616 mg, yield 51%) as a light yellow powder.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.31 (3H, s), 3.04 (1H, s), 3.87 (1H, d, $J = 14.7$ Hz), 3.98 (1H, d, $J = 14.7$ Hz), 4.13 (1H, d, $J = 12.5$ Hz), 4.24 (1H, d, $J = 14.5$ Hz), 7.08 - 7.31 (4H, m), 8.04 (1H, s).

Using corresponding starting materials gave compounds of Examples 542 and 543 shown in the following table in the same manner as in Example 541.

Table 19



Example	R	$^1\text{H NMR } \delta$		Yield (%)
542	Cl	CDCl_3	1.32(3H, s), 3.14(1H, s), 3.87(1H, d, $J=14.7\text{Hz}$), 3.95(1H, d, $J=14.7\text{Hz}$), 4.11(1H, d, $J=14.4\text{Hz}$), 4.25(1H, d, $J=14.4\text{Hz}$), 7.10-7.23(3H, m), 8.03(1H, s).	35
543	F	CDCl_3	1.11(3H, s), 2.66(1H, s), 3.86(1H, d, $J=14.5\text{Hz}$), 3.94(1H, d, $J=14.5\text{Hz}$), 4.16(1H, d, $J=14.3\text{Hz}$), 4.24(1H, d, $J=14.3\text{Hz}$), 6.89-7.00(1H, m), 7.29 (1H, dd, $J=2.7\text{Hz}$, 8.8Hz), 7.37(1H, dd, $J=4.4\text{Hz}$, 8.8Hz), 8.01(1H, s).	33

15

Example 544

Preparation of 3-(2-methyl-6-nitro-2,3-dihydroimidazo-

[2,1-b]oxazol-2-ylmethyl)-3H-benzoxazol-2-one

A mixture of 3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-3H-benzoxazol-2-one prepared in Example 541 (615 mg, 1.74 mmol), sodium
5 hydride (76.6 mg, 1.91 mmol), 1,4-dioxane (15 ml) was stirred under reflux for 1 hour. The reaction mixture was allowed to return to room temperature. To the solution, water was added and the solution was
10 extracted with methylene chloride. The organic phase was 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 = 30/1) to afford 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
15 b]oxazol-2-ylmethyl)-3H-benzoxazol-2-one (209 mg, yield 38%) as a white powder.
Melting point 222.7-224.3°C.

Using corresponding starting materials gave compounds of Examples 545 and 546 in the same manner as
20 in Example 544.

Example 545

5-Chloro-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-3H-benzoxazol-2-one
Melting point 207.6-207.9°C.

25 Example 546

5-Fluoro-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-3H-benzoxazol-2-one
Melting point 246.2-246.8°C.

Example 547

Preparation of 5-bromo-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-3H-benzoxazol-2-one

A mixture of 2-chloro-4-nitro-1H-imidazole
5 (3.22 g, 21.8 mmol), 5-bromo-3-(2-methyloxiran-2-ylmethyl)-3H-benzoxazol-2-one (6.2 g, 21.8 mmol), sodium acetate (1.97 g, 24 mmol) and ethanol (50 ml) was stirred under reflux for 8 hours. The reaction mixture was allowed to return to room temperature and
10 concentrated under reduced pressure. To the residue, water was added, and the resulting solution was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure,
15 and the residue was dissolved in 1,4-dioxane (60 ml). To the solution, sodium hydride (528 mg, 13.21 mmol) was added followed by stirring at 70-80°C for 17 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure.
20 To the residue, water was added, extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography
25 (methylene chloride/methanol = 30/1) to afford 5-bromo-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-3H-benzoxazol-2-one (1.82 g, yield 37%) as a white powder.

Melting point 243-245.5°C.

Example 548

Preparation of 5-(2-chloro-4-nitroimidazol-1-ylmethyl)-3-(4-hydroxybiphenyl-3-yl)-5-methyloxazolidin-2-one

- 5 A mixture of 2-chloro-4-nitro-1H-imidazole (1.3 g, 8.78 mmol), 5-phenyl-3-(2-methyloxiran-2-ylmethyl)-3H-benzoxazol-2-one (2.47 g, 8.78 mmol), sodium acetate (792 mg, 9.66 mmol) and ethanol (30 ml) was stirred under reflux for 10 hours. The reaction
- 10 mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, water was added, and the resulting solution was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered.
- 15 The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 10/1) to afford 5-(2-chloro-4-nitroimidazol-1-ylmethyl)-3-(4-hydroxybiphenyl-3-yl)-5-methyloxazolidin-2-one (1.82 g,
- 20 yield 61%) as a white powder.

¹H-NMR (DMSO-d₆) δppm:

- 1.55 (3H, s), 3.85 (1H, d, J = 9.5 Hz), 3.98 (1H, d, J = 9.5 Hz), 4.46 (1H, d, J = 14.9 Hz), 4.56 (1H, d, J = 14.9 Hz), 6.99 (1H, d, J = 8.4 Hz), 7.27 (1H, t, J =
- 25 7.3 Hz), 7.36 - 7.57 (6H, m), 8.52 (1H, s), 10.06 (1H, s).

Example 549

Preparation of 3-(2-methyl-6-nitro-2,3-dihydroimidazo-

[2,1-b]oxazol-2-ylmethyl)-5-phenyl-3H-benzoxazol-2-one

A mixture of 5-(2-chloro-4-nitroimidazol-1-ylmethyl)-3-(4-hydroxybiphenyl-3-yl)-5-methyloxazolidin-2-one prepared in Example 548 (1.23 g, 2.88 mmol), sodium hydride (127 mg, 3.16 mmol) and DMF (10 ml) was stirred at 100°C for 4 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 water and 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 = 20/1) to afford 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-phenyl-3H-benzoxazol-2-one (172 mg, yield 15%) as a yellowish brown powder. Melting point 254-254.6°C.

Example 550

Preparation of 3-[2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]-3H-benzoxazol-2-one

A mixture of 2-benzoxazolinone (240 mg, 1.8 mmol), sodium hydride (67 mg, 1.95 mmol) and DMF (10 ml) was stirred at room temperature for 30 minutes. To the reaction mixture, 2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl methanesulfonate prepared in Example 42 (500 mg, 1.7 mmol) was added

followed by stirring at 50-60°C for 4 hours. The reaction mixture was allowed to return to room temperature and poured into ice-water. The precipitates were filtered off and recrystallized from ethanol to afford 3-[2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]-3H-benzoxazol-2-one (320 mg, yield 56%) as a light brown powder. Melting point 193-195°C.

Example 551

10 Preparation of 3-[5-(2-chloro-4-nitroimidazol-1-yl)-4-hydroxy-4-methylpentyl]-3H-benzoxazol-2-one

Using 3-[3-(2-methyloxiran-2-yl)propyl]-3H-benzoxazol-2-one (3.8 g, 16.3 mmol) gave 3-[5-(2-chloro-4-nitroimidazol-1-yl)-4-hydroxy-4-methylpentyl]-3H-benzoxazol-2-one (3.5 g, 68%) as a white powder in the same manner as in Example 541.

¹H-NMR (CDCl₃) δppm:

1.20 (3H, s), 1.49 - 1.70 (2H, m), 1.88 - 2.07 (2H, m), 2.68 (1H, s), 3.81 - 3.93 (2H, m), 4.00 (2H, s), 6.98
20 (1H, d, J = 7.3 Hz), 7.09 - 7.26 (3H, m), 8.00 (1H, s).

Example 552

Preparation of 3-[6-(2-chloro-4-nitroimidazol-1-yl)-5-hydroxy-5-methylhexyl]-3H-benzoxazol-2-one

Using 3-[4-(2-methyloxiran-2-yl)butyl]-3H-benzoxazol-2-one (1.2 g, 4.86 mmol) gave 3-[6-(2-chloro-4-nitroimidazol-1-yl)-5-hydroxy-5-methylhexyl]-3H-benzoxazol-2-one (1.2 g, 62%) as a white powder in the same manner as in Example 541.

¹H-NMR (CDCl₃) δppm:

1.16 (3H, s), 1.38 - 1.58 (4H, m), 1.67 - 1.86 (2H, m),
2.15 (1H, s), 3.87 (2H, t, J = 6.6 Hz), 3.98 (2H, s),
6.98 (1H, d, J = 7.8 Hz), 7.08 - 7.26 (3H, m), 8.01
5 (1H, s).

Example 553

Preparation of 3-[3-(2-methyl-6-nitro-2,3-dihydro-
imidazo[2,1-b]oxazol-2-yl)propyl]-3H-benzoxazol-2-one

Using 3-[5-(2-chloro-4-nitroimidazol-1-yl)-4-
10 hydroxy-4-methylpentyl]-3H-benzoxazol-2-one prepared in
Example 551 (3.5 g, 9.2 mmol) gave 3-[3-(2-methyl-6-
nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl]-3H-
benzoxazol-2-one (2.4 g, yield 76%) as a light yellow
powder in the same manner as in Example 544.

15 Melting point 180-181°C.

Example 554

Preparation of 3-[4-(2-methyl-6-nitro-2,3-dihydro-
imidazo[2,1-b]oxazol-2-yl)butyl]-3H-benzoxazol-2-one

Using 3-[6-(2-chloro-4-nitroimidazol-1-yl)-5-
20 hydroxy-5-methylhexyl]-3H-benzoxazol-2-one prepared in
Example 552 (1.2 g, 3 mmol) gave 3-[4-(2-methyl-6-
nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)butyl]-3H-
benzoxazol-2-one (780 mg, yield 72%) as a light yellow
powder in the same manner as in Example 544.

25 Melting point 155-158°C.

Example 555

Preparation of 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-
hydroxy-2-methylpropyl]-3-methyl-1,3-dihydro-

benzimidazol-2-one

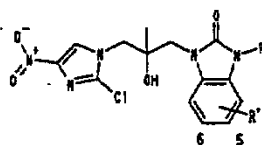
Using 1-methyl-3-(2-methyloxiran-2-ylmethyl)-
1,3-dihydrobenzimidazol-2-one (1.41 g, 6.46 mmol) gave
1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-
5 methylpropyl]-3-methyl-1,3-dihydrobenzimidazol-2-one
(1.23 g, yield 63%) as a white powder in the same
manner as in Example 541.

¹H-NMR (CDCl₃) δppm:

1.23 (3H, s), 3.47 (3H, s), 3.94 (1H, d, J = 12.4 Hz),
10 4.03 (1H, d, J = 12.4 Hz), 4.06 (1H, d, J = 11.9 Hz),
4.17 (1H, d, J = 11.9 Hz), 4.79 (1H, s), 7.00 - 7.21
(4H, m), 8.09 (1H, s).

Using corresponding starting materials gave
compounds of Examples 556 to 565 shown in the following
15 table in the same manner as in Example 555.

Table 20



Example	R	R'	¹ H NMR δ	Yield (%)
556		H	1.23(3H, s), 1.51(9H, s), 1.75-1.89(2H, m), 2.17(2H, s), 2.20-2.41(2H, m), 2.75-2.91(2H, m), 3.90(1H, d, J=14.2Hz), 4.16(1H, d, J=14.2Hz), 4.25-4.50(3H, m), 7.00-7.23(4H, m), 8.09(1H, s).	78
557	Me	6-Cl	1.24(3H, s), 3.45(3H, s), 3.94(2H, s), 4.06(1H, d, J=14.4Hz), 4.18(1H, d, J=14.4Hz), 6.96(1H, d, J=8.4Hz), 7.06(1H, d, J=1.9Hz), 7.16(1H, dd, J=1.9 Hz, 8.4 Hz), 8.08(1H, s)	69
558	Me	6-CF ₃	1.26(3H, s), 3.51(3H, s), 3.95(1H, d, J=8.5Hz), 4.03 (1H, d, J=8.5Hz), 4.14(1H, d, J=14.3Hz), 4.21(1H, d, J=14.3Hz), 7.13(1H, d, J=8.3Hz), 7.31(1H, s), 7.48 (1H, d, J=8.3Hz), 8.07(1H, s).	61
559	Me	5-Cl	1.23(3H, s), 3.47(3H, s), 3.91(1H, d, J=14.8Hz), 3.99 (1H, d, J=14.8Hz), 4.05(1H, d, J=14.0Hz), 4.17(1H, d, J=14.0Hz), 6.97(1H, d, J=8.4Hz), 7.06(1H, d, J=1.9Hz), 7.14(1H, dd, J=1.9Hz, 8.4Hz), 8.07(1H, s).	56
560	Me	6-F	1.24(3H, s), 3.46(3H, s), 3.90(1H, d, J=14.8Hz), 3.97 (1H, d, J=14.8Hz), 4.06(1H, d, J=14.3Hz), 4.17(1H, d, J=14.3Hz), 6.79-7.00(3H, m), 8.08(1H, s).	63
561	Et	6-Cl	1.21(3H, s), 1.36(3H, t, J=7.2Hz), 3.84-4.20(6H, m), 6.98(1H, d, J=8.4Hz), 7.06(1H, d, J=1.8Hz), 7.15 (1H, dd, J=1.8Hz, 8.4Hz), 8.08(1H, s).	77
562	isopropyl	6-Cl	1.24(3H, s), 1.55(6H, d, J=7.0Hz), 3.93(2H, s), 4.06 (1H, d, J=14.3Hz), 4.17(1H, d, J=14.3Hz), 4.55-4.75 (1H, m), 7.05(1H, s), 7.18(2H, s), 8.09(1H, s).	69
563	Me	6-NMe ₂	1.23(3H, s), 2.96(6H, s), 3.42(3H, s), 3.89(1H, d, J=14.8Hz), 3.99(1H, d, J=14.8 Hz), 4.05(1H, d, J= 14.3 Hz), 4.16(1H, d, J=14.3Hz), 6.39(1H, d, J= 2.2Hz), 6.60(1H, dd, J=2.2Hz, 8.6Hz), 6.92(1H, d, J=8.6Hz), 8.10(1H, s).	Crude
564	n-hexyl	6-Cl	0.87(3H, t, J=6.9Hz), 1.16-1.39(9H, m), 1.64 - 1.82 (2H, m), 3.80-3.93(4H, m), 4.05(1H, d, J=14.3Hz), 4.17(1H, d, J=14.3Hz), 6.97(1H, d, J=8.4Hz), 7.06 (1H, d, J=1.8Hz), 7.14(1H, dd, J=1.8Hz, 8.4Hz), 8.08 (1H, s).	55
565	Me	6-CO ₂ Et	1.25 (3H, s), 1.42 (3H, t, J=7.1Hz), 3.50 (3H, s), 3.93-4.11 (3H, m), 4.20 (1H, d, J=14.3Hz), 4.40 (2H, q, J=7.1Hz), 7.07 (1H, d, J=8.3Hz), 7.75 (1H, d, J= 1.5Hz), 7.94 (1H, dd, J=1.5Hz, 8.3Hz), 8.07 (1H, s).	48

Example 566

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

- 5 Using 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-3-methyl-1,3-dihydrobenzimidazol-2-one prepared in Example 555 (1.23 g, 3.37 mmol) gave 1-methyl-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydrobenzimidazol-2-one (563 mg, yield 51%) as a
10 white powder in the same manner as in Example 544. Melting point 203.2-204.4°C.

- Using corresponding starting materials gave compounds of Examples 567 to 576 in the same manner as
15 in Example 566.

Example 567

1-(1-Tert-butoxycarbonylpiperidin-4-yl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydrobenzimidazol-2-one

- 20 Melting point 218-219.1°C.

Example 568

5-Chloro-1-methyl-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydrobenzimidazol-2-one

- 25 Melting point 261.9-265.4°C (decomposition).

Example 569

1-Methyl-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-trifluoromethyl-1,3-

dihydrobenzimidazol-2-one

Melting point 232.4-234.7°C.

Example 570

6-Chloro-1-methyl-3-(2-methyl-6-nitro-2,3-dihydro-
5 imidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydro-
benzimidazol-2-one

Melting point 261.3-263.3°C.

Example 571

5-Fluoro-1-methyl-3-(2-methyl-6-nitro-2,3-dihydro-
10 imidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydro-
benzimidazol-2-one

Melting point 244.2-249.8°C (decomposition).

Example 572

5-Chloro-1-ethyl-3-(2-methyl-6-nitro-2,3-dihydro-
15 imidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydro-
benzimidazol-2-one

Melting point 240.9-245.6°C.

Example 573

5-Chloro-1-isopropyl-3-(2-methyl-6-nitro-2,3-dihydro-
20 imidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydro-
benzimidazol-2-one

Melting point 240.5-244.8°C.

Example 574

5-Dimethylamino-1-methyl-3-(2-methyl-6-nitro-2,3-
25 dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,3-
dihydrobenzimidazol-2-one

Melting point 264.6-268.3°C (decomposition).

Example 575

5-Chloro-1-(n-hexyl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydrobenzimidazol-2-one

5 Melting point 168.1-169.3°C.

Example 576

5-Ethoxycarbonyl-1-methyl-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydrobenzimidazol-2-one

10 Melting point 265.8-266.7°C.

Example 577

Preparation of 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-3-phenyl-1,3-dihydrobenzimidazol-2-one

15 Using 1-(2-methyloxiran-2-ylmethyl)-3-phenyl-1,3-dihydrobenzimidazol-2-one (758 mg, 2.7 mmol) gave 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-3-phenyl-1,3-dihydrobenzimidazol-2-one (70 mg, yield 13%) as a white powder in the same manner as
20 in Example 200.

Melting point 234.5-234.7°C.

Using corresponding starting materials gave the compound of Example 578 in the same manner as in Example 577.

25 Example 578

1-(4-Fluorophenyl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydrobenzimidazol-2-one

Melting point 254.1-254.7°C.

Example 579

Preparation of 1-(2-methyl-6-nitro-2,3-dihydroimidazo-
[2,1-b]oxazol-2-ylmethyl)-(3-piperidin-4-yl)-1,3-
5 dihydrobenzimidazol-2-one

A mixture of 1-(1-tert-butoxycarbonyl-
piperidin-4-yl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo-
[2,1-b]oxazol-2-ylmethyl)-1,3-dihydrobenzimidazol-2-one
prepared in Example 567 (371 mg, 0.74 mmol),
10 trifluoroacetic acid (1 ml) and methylene chloride (10
ml) was stirred at room temperature for 2 hours. The
reaction mixture was concentrated under reduced
pressure. To the residue, a saturated sodium
hydrogencarbonate solution, and the precipitates were
15 filtered off. The precipitates were washed with water
several times to afford 1-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-(3-piperidin-4-
yl)-1,3-dihydrobenzimidazol-2-one (255 mg, yield 86%)
as a light yellow powder.

20 Melting point 192.3-198.8°C (decomposition).

Example 580

Preparation of benzyl 4-[3-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-2-oxo-2,3-
dihydrobenzimidazol-1-yl]piperidine-1-carboxylate

25 To a mixture of 1-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-(3-piperidin-4-
yl)-1,3-dihydrobenzimidazol-2-one prepared in Example
579 (90 mg, 0.23 mmol) and methylene chloride (5 ml),

triethylamine (75 mg, 0.74 mmol) and benzyl chloroformate (126 mg, 0.74 mmol) were added in this order with cooling on ice-bath followed by stirring at room temperature for 3 hours. The reaction mixture was
5 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, and the residue was purified by silica gel column chromatography (n-hexane/acetone = 1/1) to afford benzyl 4-[3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-2-oxo-2,3-dihydrobenzimidazol-1-yl]piperidine-1-carboxylate (25 mg, yield 21%) as a white powder.
10
15 Melting point 181.7-184.6°C.

Example 581

Preparation of 1-benzyl-3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]imidazolidin-2-one

Using 1-benzyl-3-(2-methyloxiran-2-ylmethyl)-imidazolidin-2-one (680 mg, 2.76 mmol) gave 1-benzyl-3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]imidazolidin-2-one (580 mg, yield 59%) as a white powder in the same manner as in Example 541.

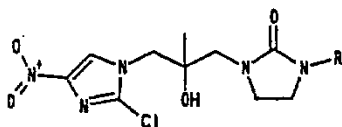
¹H-NMR (CDCl₃) δppm:

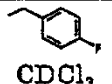
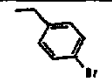
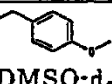
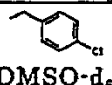
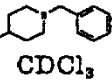
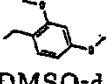
25 1.18 (3H, s), 3.17 - 3.54 (6H, m), 4.07 (2H, s), 4.37 (2H, s), 7.17 - 7.40 (5H, m), 8.13 (1H, s).

Using corresponding starting materials gave compounds of Examples 582 to 587 shown in the following

table in the same manner as in Example 581.

Table 21



Example	R (solvent)	¹ H NMR δ	Yield (%)
582	 CDCl ₃	1.19(3H, s), 3.16-3.52(6H, m), 4.06(2H, s), 4.33(2H, s), 6.93-7.09(2H, m), 7.18-7.30(2H, m), 8.13(1H, s).	43
583	 CDCl ₃	1.19(3H, s), 3.16-3.55(6H, m), 4.05(2H, s), 4.31(2H, s), 7.14 (2H, dd, J=2.0Hz, 8.6Hz), 7.46(2H, dd, J=2.0Hz, 8.6 Hz), 8.13 (1H, s).	64
584	 DMSO-d ₆	1.03(3H, s), 3.02-3.27(4H, m), 3.39-3.55(2H, m), 3.73(3H, s), 4.03(2H, s), 4.29(2H, s), 6.90(2H, d, J=8.6Hz), 7.17(2H, d, J=8.6Hz), 8.48(1H, s).	69
585	 DMSO-d ₆	1.04(3H, s), 3.05-3.25(4H, m), 3.36-3.48(2H, m), 4.03(2H, s), 4.22(2H, s), 7.28(2H, d, J=8.3Hz), 7.41(2H, d, J=8.3Hz), 8.48(1H, s).	60
586	 CDCl ₃	1.16(3H, s), 1.59-1.84(4H, m), 2.00-2.18(2H, m), 2.89-3.02 (2H, m), 3.09-3.50(8H, m), 3.61-3.80(1H, m), 4.00(1H, d, J =14.3Hz), 4.09(1H, d, J=14.3Hz), 7.18-7.36(5H, m), 8.12 (1H, s).	Crude
587	 DMSO-d ₆	1.03(3H, s), 3.05-3.23(4H, m), 3.30-3.50(2H, m), 3.75(3H, s), 3.77(3H, s), 4.02(2H, s), 4.20(2H, s), 6.47(1H, dd, J= 2.2Hz, 8.3Hz), 6.56(1H, d, J=2.2Hz), 7.06(1H, d, J=8.3Hz), 8.48 (1H, s).	58

Example 588

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

Using 1-benzyl-3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]imidazolidin-2-one prepared in Example 581 (580 mg, 1.47 mmol) gave 1-benzyl-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one (395 mg, yield

75%) as a white powder in the same manner as in Example 544.

Melting point 180.2-180.9°C.

Using corresponding starting materials gave
5 compounds of Examples 589 to 594 in the same manner as in Example 588.

Example 589

1-(4-Fluorobenzyl)-3-(2-methyl-6-nitro-2,3-dihydro-
imidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one

10 Melting point 182.5-183.3°C.

Example 590

1-(4-Bromobenzyl)-3-(2-methyl-6-nitro-2,3-dihydro-
imidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one

Melting point 205.7-208.1°C.

15 Example 591

1-(4-Methoxybenzyl)-3-(2-methyl-6-nitro-2,3-dihydro-
imidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one

Melting point 158.6-160.5°C.

Example 592

20 1-(4-Chlorobenzyl)-3-(2-methyl-6-nitro-2,3-dihydro-
imidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one

Melting point 208.7-209.8°C.

Example 593

1-(1-Benzylpiperidin-4-yl)-3-(2-methyl-6-nitro-2,3-
25 dihydroimidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-
one

¹H-NMR (CDCl₃) δppm:

1.41 - 1.72 (7H, m), 1.97 - 2.10 (2H, m), 2.88 - 2.95

(2H, m), 3.08 - 3.30 (4H, m), 3.43 - 3.70 (4H, m), 3.81 (1H, d, J = 15.0 Hz), 3.91 (1H, d, J = 10.3 Hz), 4.51 (1H, d, J = 10.3 Hz), 7.13 - 7.31 (5H, m), 7.47 (1H, s).

5 Example 594

1-(2,4-Dimethoxybenzyl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one

Melting point 175-175.4°C.

10 Example 595

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

Using 1-(2-methyloxiran-2-ylmethyl)-3-phenylimidazolidin-2-one (300 mg, 1.29 mmol) gave 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-3-phenylimidazolidin-2-one (59 mg, yield 26%) as a white powder in the same manner as in Example 200. Melting point 194.8-197.4°C.

 Example 596

20 Preparation of 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one

A mixture of 1-(2,4-dimethoxybenzyl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one prepared in Example 594 (100 mg, 0.24 mmol), trifluoroacetic acid (2 ml) and methylene chloride (2 ml) was stirred at room temperature for 1 hour. To the reaction mixture, a saturated sodium hydrogencarbonate solution was added

for neutralization. The resulting solution was extracted with methylene chloride. The organic phase was dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and
5 the residue was treated with diethyl ether to afford 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one (50 mg, yield 78%) as a white powder.

Melting point 224.8-229.1°C (decomposition).

10 Example 597

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

A mixture of 3-(2-methyloxiran-2-ylmethyl)-oxazolidin-2-one (2.87 g, 18.23 mmol), 2-chloro-4-
15 nitro-1H-imidazole (2.7 g, 18.23 mmol), sodium acetate (1.64 g, 20.05 mmol) and ethanol (30 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, methylene
20 chloride was added, and the resulting solution 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, and
25 the residue was dissolved in 1,4-dioxane (50 ml). To the solution, sodium hydride (610 mg, 15.25 mmol) was added followed by stirring 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 solution was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered.

- 5 The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to afford 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)oxazolidin-2-one (1.54 g, yield
10 40%) as a white powder.

¹H-NMR (DMSO-d₆) δppm:

1.59 (3H, s), 3.46 - 3.71 (4H, m), 4.11 - 4.30 (4H, m), 8.15 (1H, s).

Example 598

- 15 Preparation of 5-azidomethyl-3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-oxazolidin-2-one

A mixture of 2-chloro-4-nitro-1H-imidazole (350 mg, 2.37 mmol), 5-azidomethyl-3-(2-methyloxiran-2-ylmethyl)oxazolidin-2-one (500 mg, 2.37 mmol), sodium
20 acetate (214 mg, 2.61 mmol) and ethanol (5 ml) was stirred at 70°C for 8 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, water was
25 added, and the solution was extracted with methylene chloride. The organic phase was dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue

was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/2) to afford 5-azidomethyl-3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]oxazolidin-2-one (640 mg, yield 75%) as a
5 light yellow oil.

¹H-NMR (CDCl₃) δppm:

1.23 (3H, s), 3.17 - 3.35 (2H, m), 3.43 - 3.61 (2H, m),
3.67 - 3.84 (2H, m), 4.01 - 4.16 (2H, m), 4.68 - 4.81
(1H, m), 8.04 (1H, s).

10 Example 599

Preparation of 5-azidomethyl-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)oxazolidin-2-one

5-Azidomethyl-3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]oxazolidin-2-one

15 prepared in Example 598 (1 g, 2.78 mmol) was dissolved in 1,4-dioxane (10 ml). To the solution, sodium hydride (130 mg, 3.25 mmol) was added followed by stirring at 80°C for 4 hours. The reaction mixture was allowed to return to room temperature and added water.

20 The resulting solution was 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 filtered. The filtrate was concentrated under reduced
25 pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 20/1) to afford 5-azidomethyl-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)oxazolidin-

2-one (46 mg, yield 5%) as a light brown powder.

MS 323(M⁺)

Example 600

Preparation of 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-1,4-dihydrobenzo[d][1,3]oxazin-2-one

Using 1-(2-methyloxiran-2-ylmethyl)-1,4-dihydrobenzo[d][1,3]oxazin-2-one (5.13 g, 23.04 mmol) gave 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-1,4-dihydrobenzo[d][1,3]oxazin-2-one (1.54 g, yield 36%) as a light yellow oil in the same manner as in Example 541.

¹H-NMR (CDCl₃) δppm:

1.23 (3H, s), 3.96 (1H, br), 4.04 - 4.20 (4H, m), 5.28 (2H, s), 7.00 - 7.07 (1H, m), 7.11 - 7.24 (2H, m), 7.30 - 7.43 (1H, m), 8.07 (1H, s).

Example 601

Preparation of 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,4-dihydrobenzo[d][1,3]oxazin-2-one

Using 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-1,4-dihydrobenzo[d][1,3]oxazin-2-one prepared in Example 600 (1.54 g, 4.20 mmol) gave 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,4-dihydrobenzo[d][1,3]oxazin-2-one (0.58 g, yield 42%) as a light tan solid in the same manner as in Example 544.

Melting point 230-231°C.

Example 602

Preparation of 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-3,3-difluoro-1,3-dihydroindol-2-one

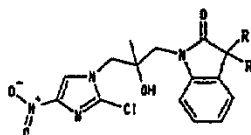
5 Using 3,3-difluoro-1-(2-methyloxiran-2-yl-methyl)-1,3-dihydroindol-2-one (1.14 g, 4.76 mmol) gave 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-3,3-difluoro-1,3-dihydroindol-2-one (968 mg, yield 53%) as a white powder in the same manner as
10 in Example 541.

^1H -NMR (DMSO- d_6) δ ppm:

1.09 (3H, s), 3.73 (1H, d, $J = 14.5$ Hz), 3.87 (1H, d, $J = 14.5$ Hz), 4.13 (1H, d, $J = 14.4$ Hz), 4.21 (1H, d, $J = 14.4$ Hz), 5.39 (1H, s), 7.20 - 7.26 (1H, m), 7.33 -
15 7.37 (1H, m), 7.57 - 7.64 (1H, m), 7.67 - 7.71. (1H, m).

Using corresponding starting materials gave compounds of Examples 603 and 604 shown in the following table in the same manner as in Example 602.

Table 22



Example	R	^1H NMR (CDCl $_3$) δ
603	Me	1.21(3H, s), 1.38(6H, s), 3.77(1H, d, $J=14.8\text{Hz}$), 3.87(1H, d, $J=14.8\text{Hz}$), 4.05 (1H, d, $J=14.3\text{Hz}$), 4.15(1H, d, $J=14.3\text{Hz}$), 6.91(1H, d, $J=7.7\text{Hz}$), 7.02-7.31 (3H, m), 8.07(1H, s).
604	H	1.24(3H, s), 3.64(2H, s), 3.79(1H, d, $J=14.8\text{Hz}$), 3.89(1H, d, $J=14.8\text{Hz}$), 4.09 (1H, d, $J=14.3\text{Hz}$), 4.19(1H, d, $J=14.3\text{Hz}$), 6.93(1H, d, $J=7.7\text{Hz}$), 7.12(1H, d, $J=7.5\text{Hz}$), 7.25-7.35(2H, m), 8.07(1H, s).

Example 605

Preparation of 3,3-difluoro-1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydroindol-2-one

- 5 Using 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-3,3-difluoro-1,3-dihydroindol-2-one prepared in Example 602 (903 mg, 2.34 mmol) gave 3,3-difluoro-1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydroindol-2-one (77 mg, yield 9%) as a white powder in the same manner as in Example 544. Melting point 202-206°C.

- Using corresponding starting materials gave the compound of Example 606 in the same manner as in
15 Example 605.

Example 606

3,3-Dimethyl-1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydroindol-2-one

¹H-NMR (DMSO-d₆) δppm:

- 20 1.25 (3H, s), 1.37 (3H, s), 1.78 (3H, s), 3.96 (1H, d, J = 15.1 Hz), 4.00 (1H, d, J = 10.7 Hz), 4.22 (1H, d, J = 15.1 Hz), 4.57 (1H, d, J = 10.7 Hz), 7.04 - 7.17 (3H, m), 7.24 - 7.31 (1H, m), 7.44 (1H, s).

Example 607

- 25 Preparation of 1-(2-chloro-4-nitroimidazol-1-yl)-4-(1-ethyl-1H-tetrazol-5-yl)-2-methylbutan-2-ol

 Using 1-ethyl-5-[2-(2-methyloxiran-2-yl)-ethyl]-1H-tetrazol (1.04 g, 5.59 mmol) gave 1-(2-

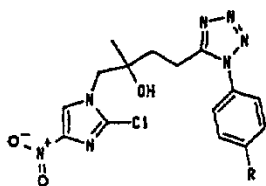
chloro-4-nitroimidazol-1-yl)-4-(1-ethyl-1H-tetrazol-5-yl)-2-methylbutan-2-ol (1.15 g, yield 69%) as a light yellow oil in the same manner as in Example 541.

¹H-NMR (CDCl₃) δppm:

- 5 1.29 (3H, s), 1.56 (3H, t, J = 7.3 Hz), 2.04 - 2.22 (2H, m), 2.91 - 3.11 (2H, m), 4.10 (2H, s), 4.24 (1H, br), 4.34 (2H, q, J = 7.3 Hz), 8.09 (1H, s).

Using corresponding starting materials gave compounds of Examples 608 and 609 shown in the following table in the same manner as in Example 607.

Table 23



Example	R	¹ HNMR (CDCl ₃) δ	Yield(%)
608	H	1.26(3H, s), 2.02-2.08(2H, m), 2.96-3.17(2H, m), 3.80(1H, s), 4.04(2H, s), 7.42-7.46(2H, m), 7.60-7.62(3H, m), 8.03(1H, s).	60
609	Cl	1.26(3H, s), 2.08-2.12(2H, m), 2.96-3.15(2H, m), 3.85(1H, s), 4.07(s, 2H), 7.40-7.44(2H, m), 7.56-7.61(2H, m), 8.04(1H, s).	66

Example 610

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

Using 1-(2-chloro-4-nitroimidazol-1-yl)-4-(1-ethyl-1H-tetrazol-5-yl)-2-methylbutan-2-ol prepared in Example 607 (1.15 g, 3.49 mmol) gave 2-[2-(1-ethyl-1H-tetrazol-5-yl)ethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (68 mg, yield 7%) as a

light yellow powder in the same manner as in Example 544.

Melting point 135-137°C.

Using corresponding starting materials gave
5 compounds of Examples 611 and 612 in the same manner as in Example 610.

Example 611

2-Methyl-6-nitro-2-[2-(1-phenyl-1H-tetrazol-5-yl)ethyl]-2,3-dihydroimidazo[2,1-b]oxazole

10 Melting point 158-159°C.

Example 612

2-(2-[1-(4-Chlorophenyl)-1H-tetrazol-5-yl]ethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 198-200°C.

15 Example 613

Preparation of 3-[2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]-5-(4-trifluoromethylbenzylidene)thiazolidine-2,4-dione

Using 2-(2-methyl-6-nitro-2,3-dihydroimidazo-
20 [2,1-b]oxazol-2-yl)ethyl methanesulfonate prepared in Example 42 (280 mg, 0.96 mmol) and 5-(4-trifluoromethylbenzylidene)thiazolidine-2,4-dione (320 mg, 1.17 mmol) gave 3-[2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]-5-(4-trifluoromethylbenzylidene)thiazolidine-2,4-dione (260
25 mg, yield 58%) as a light yellow powder in the same manner as in Example 537.
Melting point 257-258.5°C.

Example 614

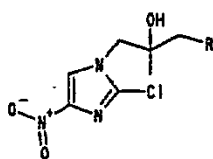
Preparation of 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]pyrrolidine-2,5-dione

5 Using 1-(2-methyloxiran-2-ylmethyl)-pyrrolidine-2,5-dione (1.96 g, 11 mmol) gave 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]pyrrolidine-2,5-dione (589 mg, yield 16%) as a white powder in the same manner as in Example 541.

10 $^1\text{H-NMR}$ (DMSO-d_6) δ ppm:
0.96 (3H, s), 2.68 (4H, s), 3.48 (2H, s), 4.02 (2H, s), 5.19 (1H, s), 8.34 (1H, s).

Using corresponding starting materials gave compounds of Examples 615 and 616 shown in the
15 following table in the same manner as in Example 614.

Table 24



Example	R	$^1\text{H NMR } \delta$ (CDCl_3)	Yield (%)
615		1.21(3H, s), 3.48(1H, s), 3.79(1H, d, $J=14.6\text{Hz}$), 3.90(1H, d, $J=14.6\text{Hz}$), 4.01(1H, d, $J=14.9\text{Hz}$), 4.16(1H, d, $J=14.9\text{Hz}$), 7.75-7.93(4H, m), 8.06(1H, s).	71
616		1.21(3H, s), 4.09(1H, d, $J=14.4\text{Hz}$), 4.18(1H, d, $J=14.4\text{Hz}$), 4.05(1H, d, $J=14.3\text{Hz}$), 4.15(1H, d, $J=14.3\text{Hz}$), 4.42(1H, d, $J=14.0\text{Hz}$), 4.49(1H, d, $J=14.0\text{Hz}$), 7.60-7.74(2H, m), 7.81-8.12 (2H, m).	55

Example 617

Preparation of 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)pyrrolidine-2,5-dione

Using 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]pyrrolidine-2,5-dione prepared in Example 614 (589 mg, 1.86 mmol) gave 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)pyrrolidine-2,5-dione (232 mg, yield 34%) as a white powder in the same manner as in Example 544.

10 Melting point 202.5-203.4°C.

Using corresponding starting materials gave compounds of Examples 618 and 619 in the same manner as in Example 617.

Example 618

15 2-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)isoindole-1,3-dione
Melting point 264.6-268.3°C.

Example 619

20 2-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,1-dioxo-1,2-dihydro[d]benzothiazol-3-one
Melting point 243-245°C (decomposition).

Example 620

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

25 Using 3-(2-methyloxiran-2-yl)pyridine (7.4 g, 54.75 mmol) gave 1-(2-chloro-4-nitroimidazol-1-yl)-2-(pyridin-3-yl)propan-2-ol (3.3 g, yield 24%) as a white powder in the same manner as in Example 541.

¹H-NMR (CDCl₃) δppm:

1.65 (3H, s), 4.19 (1H, d, J = 14.2 Hz), 4.27 (1H, d, J = 14.2 Hz), 5.82 (1H, s), 7.24 - 7.30 (1H, m), 7.68 - 7.72 (1H, m), 8.50 - 8.53 (1H, m), 8.68 (1H, d, J = 2.3 Hz).

Example 621

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

Using 1-(2-chloro-4-nitroimidazol-1-yl)-2-(pyridin-3-yl)propan-2-ol prepared in Example 620 (3.3 g, 11.7 mmol) gave 2-methyl-6-nitro-2-(pyridin-3-yl)-2,3-dihydroimidazo[2,1-b]oxazole (1.8 g, yield 63%) as a light brown powder in the same manner as in Example 544.

Melting point 212-214°C.

Example 622

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

To a mixture of 2-methyl-6-nitro-2-(pyridin-3-yl)-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 621 (800 mg, 3.3 mmol) and methylene chloride (25 ml), m-chloroperbenzoic acid (1 g, 4.06 mmol) was added with cooling on ice-bath followed by stirring at room temperature overnight. The reaction mixture was filtered, and the filtrate was washed with a 20% aqueous sodium sulfite solution, 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 2-methyl-6-nitro-2-(1-oxypyridin-3-yl)-2,3-dihydroimidazo[2,1-b]oxazole (330 mg, 39%) as a white powder.

5 ^1H -NMR (DMSO- d_6) δ ppm:

1.92 (3H, s), 4.51 (2H, s), 7.42 - 7.53 (2H, m), 8.14 (1H, s), 8.20 - 8.24 (1H, m), 8.42 (1H, s).

Example 623

Preparation of 1-(2-methyl-6-nitro-2,3-dihydroimidazo-
10 [2,1-b]oxazol-2-ylmethyl)piperidin-4-one

Using 1-(2-methyloxiran-2-ylmethyl)piperidin-4-one (2.2 g, 13 mmol) gave 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-one (50 mg, yield 1%) as a light yellow powder in the same
15 manner as in Example 597.

Melting point 124-126°C.

Example 624

Preparation of 4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-1-(4-trifluoromethylbenzyl)-
20 piperazin-2-one

Using 4-(2-methyloxiran-2-ylmethyl)-1-(4-trifluoromethylbenzyl)piperazin-2-one (1.6 g, 4.9 mmol) gave 4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-1-(4-trifluoromethylbenzyl)piperazin-2-
25 one (1 g, yield 43%) as a light yellow powder in the same manner as in Example 541.

^1H -NMR (CDCl $_3$) δ ppm:

1.18 (3H, s), 2.45 (1H, d, J = 13.9 Hz), 2.57 (1H, d, J

= 13.9 Hz), 2.72 - 2.98 (2H, m), 3.19 - 3.44 (3H, m), 3.55 (1H, d, $J = 16.5$ Hz), 4.00 (1H, d, $J = 14.3$ Hz), 4.10 (1H, d, $J = 14.3$ Hz), 4.64 (2H, s), 7.37 (2H, d, $J = 8.2$ Hz), 7.61 (2H, d, $J = 8.2$ Hz), 8.02 (1H, s).

5 Using corresponding starting materials gave the compound of Example 625 in the same manner as in Example 624.

Example 625

1-Tert-butyl-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-
10 hydroxy-2-methylpropyl]piperazin-2-one

$^1\text{H-NMR}$ (CDCl_3) δppm :

1.16 (3H, s), 1.44 (9H, s), 2.41 (1H, d, $J = 13.8$ Hz), 2.51 (1H, d, $J = 13.8$ Hz), 2.65 - 2.88 (3H, m), 2.93 - 3.09 (1H, m), 3.12 - 3.28 (2H, m), 3.99 (1H, d, $J =$
15 14.3 Hz), 4.08 (1H, d, $J = 14.3$ Hz), 8.05 (1H, s).

Example 626

Preparation of 4-(2-methyl-6-nitro-2,3-dihydroimidazo-
[2,1-b]oxazol-2-ylmethyl)-1-(4-trifluoromethylbenzyl)-
piperazin-2-one

20 Using 4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-1-(4-trifluoromethylbenzyl)-piperazin-2-one prepared in Example 624 (1 g, 2.1 mmol) gave 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1-(4-
25 trifluoromethylbenzyl)piperazin-2-one (206 mg, yield 22%) as a light yellow powder in the same manner as in Example 544.

Melting point 88-93°C.

Using corresponding starting materials gave the compound of Example 627 in the same manner as in Example 626.

Example 627

5 1-Tert-butyl-4-(2-methyl-6-nitro-2,3-dihydroimidazo-
[2,1-b]oxazol-2-ylmethyl)piperazin-2-one

Melting point 193-194°C.

Example 628

Preparation of 1-tert-butyl-4-[2-(2-methyl-6-nitro-2,3-
10 dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]piperazin-2-one

A mixture of 2-(2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazol-2-yl)ethyl methanesulfonate
prepared in Example 42 (290 mg, 1 mmol), 1-tert-
butylpiperazin-2-one hydrochloride (200 mg, 1.28 mmol),
15 triethylamine (242 mg, 2.39 mmol), potassium iodide
(250 mg, 1.5 mmol) and DMF (3 ml) was stirred at 70°C
for 4 hours. The reaction mixture was allowed to
return to room temperature. To the solution, water was
added, and the resulting solution was extracted with
20 ethyl acetate twice. The organic phases were combined,
washed with water twice and 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/methanol =
20/1) to afford 1-tert-butyl-4-[2-(2-methyl-6-nitro-
2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]piperazin-2-
one (27 mg, yield 8%) as a white powder.

Melting point 153-154°C.

Using corresponding starting materials gave the compound of Example 629 in the same manner as in Example 628.

5 Example 629

4-[2-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]-1-phenylpiperazin-2-one

Melting point 199-202°C (decomposition).

 Example 630

- 10 Preparation of 1-tert-butyl-4-[3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl]piperazin-2-one

 Using 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl methanesulfonate prepared in Example 39 (300 mg, 0.98 mmol) gave 1-tert-butyl-4-[3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl]piperazin-2-one (150 mg, yield 42%) as a white powder in the same manner as in Example 628. Melting point 147-149°C (decomposition).

 Example 631

- 20 Preparation of 1-(benzimidazol-1-yl)-3-(2-chloro-4-nitroimidazol-1-yl)-2-methylpropan-2-ol

 Using 1-(2-methyloxiran-2-ylmethyl)-1H-benzimidazole (350 mg, 1.86 mmol) gave 1-(benzimidazol-1-yl)-3-(2-chloro-4-nitroimidazol-1-yl)-2-methylpropan-2-ol (135 mg, yield 22%) as a white powder in the same manner as in Example 541.

¹H-NMR (DMSO-d₆) δppm:

0.99 (3H, s), 4.06 (1H, d, J = 14.2 Hz), 4.23 - 4.45

(3H, m), 5.44 (1H, s), 7.14 - 7.32 (2H, m), 7.57 - 7.77 (2H, m), 8.15 (1H, s), 8.36 (1H, s).

Using corresponding starting materials gave the compound of Example 632 in the same manner as in
5 Example 631.

Example 632

1-(Imidazol-1-yl)-3-(2-chloro-4-nitroimidazol-1-yl)-2-methylpropan-2-ol

¹H-NMR (CDCl₃) δppm:

10 1.19 (3H, s), 3.86 - 4.05 (3H, m), 4.13 (1H, d, J = 14.2 Hz), 6.87 (1H, s), 6.89 (1H, s), 7.47 (1H, s), 8.08 (1H, s).

Example 633

Preparation of 1-(2-methyl-6-nitro-2,3-dihydroimidazo-
15 [2,1-b]oxazol-2-ylmethyl)-1H-benzimidazole

Using 1-(benzimidazol-1-yl)-3-(2-chloro-4-nitroimidazol-1-yl)-2-methylpropan-2-ol prepared in Example 631 (135 mg, 0.4 mmol) gave 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1H-
20 benzimidazole (72 mg, yield 60%) as a white powder in the same manner as in Example 544.

Melting point 250.3-251.9°C (decomposition).

Using corresponding starting materials gave the compound of Example 634 in the same manner as in
25 Example 633.

Example 634

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

Melting point 245.5-247.8°C.

Example 635

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-3-(3,4-dihydro-2H-quinolin-1-yl)-2-methylpropan-2-ol

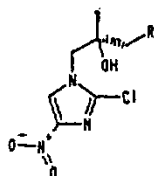
5 A mixture of (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (100 mg, 0.46 mmol), 1,2,3,4-tetrahydroquinoline (122 mg, 0.92 mmol) and DMF (1 ml) was stirred at 80°C for 8 hours. The reaction mixture was allowed to return to
10 room temperature. To the solution, water was added, and the resulting solution was extracted with ethyl acetate twice. The organic phases were combined, washed with water twice and a saturated saline solution, dried over magnesium sulfate and then
15 filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/1) to afford (S)-1-(2-chloro-4-nitroimidazol-1-yl)-3-(3,4-dihydro-2H-quinolin-1-yl)-2-methylpropan-2-ol (134 mg,
20 yield 83%) as an orange oil.

¹H-NMR (CDCl₃) δppm:

1.24 (3H, s), 1.94 - 2.04 (2H, m), 2.39 (1H, m), 2.79 - 2.85 (2H, m), 3.27 - 3.42 (4H, m), 6.66 - 6.72 (2H, m), 6.97 - 7.08 (2H, m), 8.04 (1H, s).

25 Using corresponding starting materials gave compounds of Examples 636 to 638 shown in the following table in the same manner as in Example 635.

Table 25



Example	R	¹ H NMR δ (CDCl ₃)	Yield (%)
636		1.18(3H, s), 2.51(1H, d, J=13.9Hz), 2.66(1H, d, J=13.9Hz), 2.82-2.98(4H, m), 3.76(1H, d, J=14.9Hz), 3.88(1H, d, J=14.9Hz), 4.08(2H, s), 7.00(1H, dd, J=2.3Hz, 7.7Hz), 7.06-7.20 (3H, m), 8.01(1H, s).	87
637		1.20(3H, s), 2.55(1H, d, J=13.8Hz), 2.71(1H, d, J=13.8Hz), 3.81(1H, d, J=14.8Hz), 3.91(1H, d, J=14.8Hz), 4.05(4H, s), 7.10-7.23(4H, m), 8.00(1H, s).	93
638		1.11(3H, s), 1.67-1.78(4H, m), 2.37(1H, d, J=14.0Hz), 2.51(1H, d, J=14.0Hz), 2.57-2.82(4H, m), 3.69(1H, s), 3.95(4H, s), 3.99(2H, s), 8.06(1H, s).	100

Example 639

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

Using (S)-1-(2-chloro-4-nitroimidazol-1-yl)-3-(3,4-dihydro-2H-quinolin-1-yl)-2-methylpropan-2-ol prepared in Example 635 (134 mg, 0.38 mmol) gave (S)-1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,2,3,4-tetrahydroquinoline (64 mg, 54%) as a white powder in the same manner as in Example 393. Melting point 168-172°C.

Using corresponding starting materials gave compounds of Examples 640 to 642 in the same manner as in Example 639.

Example 640

(S)-2-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-

b]oxazol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline

Melting point 153-155.3°C.

Example 641

(S)-2-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-
5 b]oxazol-2-ylmethyl)-2,3-dihydro-1H-isoindole

¹H-NMR (CDCl₃) δppm:

1.68 (3H, s), 3.01 (1H, d, J = 14.5 Hz), 3.24 (1H, d, J
= 14.5 Hz), 3.92 (1H, d, J = 9.6 Hz), 4.08 (4H, s),
4.50 (1H, d, J = 9.6 Hz), 7.13 - 7.21 (4H, m), 7.50
10 (1H, s).

Example 642

(S)-8-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-
b]oxazol-2-ylmethyl)-1,4-dioxo-8-azaspiro[4,5]decane

Melting point 166.5-168.2°C.

15 Example 643

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

A mixture of (R)-2-chloro-1-(2-methyloxiran-
20 2-ylmethyl)-4-nitroimidazole prepared in Example 12
(645 mg, 2.97 mmol), (S)-2-(4-trifluoromethoxyphenoxy-
methyl)pyrrolidine (930 mg, 3.56 mmol) and DMF (15 ml)
was stirred at 80°C for 8 hours. To the reaction
mixture, sodium hydride (154 mg, 3.86 mmol) was added
25 followed by stirring for 1 hour with cooling on ice-
bath. The reaction mixture was poured into ice-water,
and the mixture was extracted with ethyl acetate twice.
The organic phases were combined, washed with water

twice and 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

5 (methylene chloride) and recrystallized from methylene chloride-isopropyl ether to afford (2S)-methyl-6-nitro-2-[(2S)-(4-trifluoromethoxyphenoxy)methyl]pyrrolidin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole (505 mg, yield 41%) as a white powder.

10 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.42 - 1.52 (1H, m), 1.59 (3H, s), 1.61 - 1.79 (2H, m), 1.87 - 1.99 (1H, m), 2.50 - 2.61 (1H, m), 3.03 - 3.17 (2H, m), 3.06 (1H, d, $J = 14.7$ Hz), 3.20 (1H, d, $J = 14.7$ Hz), 3.72 - 3.79 (2H, m), 3.92 (1H, dd, $J = 9.2$ Hz, 3.7 Hz), 4.58 (1H, d, $J = 9.5$ Hz), 6.80 - 6.88 (2H, m), 7.15 - 7.19 (1H, m), 7.42 (1H, s).

Example 644

Preparation of tert-butyl 4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]homopiperazine-1-carboxylate

20 A mixture of 2-chloro-4-nitro-1H-imidazole (8.39 g, 56.88 mmol), tert-butyl 4-(2-methyloxiran-2-ylmethyl)homopiperazine-1-carboxylate (15.38 g, 56.88 mmol) and sodium acetate (5.13 g, 62.57 mmol) in 1-propanol (100 ml) was stirred under reflux for 10 hours. The reaction mixture was allowed to return to room temperature and then concentrated under reduced pressure. The residue was dissolved in methylene

chloride. The solution was washed with water, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column

5 chromatography (methylene chloride/ethyl acetate = 5/1) to afford tert-butyl 4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]homopiperazine-1-carboxylate (6.25 g, yield 27%) as a reddish yellow oil.

10 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.14 (3H, s), 1.48 (9H, s), 1.69 - 1.90 (2H, m), 2.40 - 2.55 (1H, m), 2.66 (1H, d, $J = 14.1$ Hz), 2.75 - 2.98 (5H, m), 3.30 - 3.59 (4H, m), 3.96 (2H, s), 8.06 (1H, s).

15 Example 645

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

Using tert-butyl 4-[3-(2-chloro-4-nitro-
20 imidazol-1-yl)-2-hydroxy-2-methylpropyl]homopiperazine-1-carboxylate prepared in Example 644 (6.25 g, 14.96 mmol) gave tert-butyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)homopiperazine-1-carboxylate (3.07 g, yield 54%) as a white powder in
25 the same manner as in Example 544.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.47 (9H, s), 1.59 (3H, s), 1.68 - 1.79 (2H, m), 2.63 - 2.90 (5H, m), 3.06 (1H, d, $J = 15.1$ Hz), 3.25 - 3.50

(4H, m), 3.91 (1H, d, $J = 9.7$ Hz), 4.33 (1H, d, $J = 9.7$ Hz), 7.54 (1H, s).

Example 646

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

A mixture of tert-butyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-homopiperazine-1-carboxylate prepared in Example 645 (250 mg, 0.655 mmol) and trifluoroacetic acid (10 ml) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in methylene chloride (10 ml). To the solution, triethylamine (0.27 ml, 1.96 mmol) and benzyl chloroformate (0.19 ml, 1.31 mmol) were added followed by stirring at room temperature for 3 hours. To the reaction mixture, water was added, and the mixture was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 1/1) to afford a light yellow oil. The resulting oil was dissolved in ethyl acetate. To the solution, a saturated hydrochloric acid/ethyl acetate solution was added, and the precipitates were filtered off to afford benzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-

ylmethyl)homopiperazine-1-carboxylate hydrochloride
(246 mg, yield 83%) as a white powder.

Melting point 115-117°C.

Example 647

- 5 Preparation of 2-[4-(biphenyl-4-ylmethyl)homopiperazin-
1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
b]oxazole

A mixture of tert-butyl 4-(2-methyl-6-nitro-
2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-
10 homopiperazin-1-carboxylate prepared in Example 645
(346 mg, 0.91 mmol) and trifluoroacetic acid (10 ml)
was stirred at room temperature overnight. The
reaction mixture was concentrated under reduced
pressure, and the residue was dissolved in methylene
15 chloride (10 ml). To the solution, triethylamine (0.27
ml, 1.96 mmol) was added. The solution was
concentrated under reduced pressure, and the residue
was dissolved in methanol (10 ml). To the solution, 4-
phenylbenzaldehyde (496 mg, 2.72 mmol), sodium
20 cyanotrihydroborate (171 mg, 2.72 mmol) and acetic acid
(0.17 ml, 2.72 mmol) were added in this order followed
by stirring at room temperature overnight. The
reaction mixture was poured into a saturated sodium
hydrogencarbonate solution, then extracted with
25 methylene chloride. The organic phase was dried over
magnesium sulfate and then filtered. The filtrate was
concentrated under reduced pressure, and the residue
was purified by silica gel column chromatography

(methylene chloride/ethyl acetate = 5/1) to afford 2-[4-(biphenyl-4-ylmethyl)homopiperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (251 mg, yield 62%) as a white powder.

5 Melting point 138-142.2°C.

Example 648

Preparation of 1'-tert-butoxycarbonyl-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazol-2,4'-piperidine]

2,4-Dinitro-1H-imidazole (1.0 g, 6.3 mmol),
10 tert-butyl 1-oxa-6-azaspiro[2,5]octane-6-carboxylate
(2.0 g, 9.5 mmol) and sodium acetate (612 mg, 7.5 mmol)
in ethanol (7 ml) were stirred under reflux for 10
hours. The reaction mixture was concentrated under
reduced pressure. To the residue, a saturated sodium
15 hydrogencarbonate solution and methylene chloride were
added followed by stirring vigorously, and then the
mixture was extracted with methylene chloride. The
organic phase was dried over sodium sulfate and then
filtered. The resulting filtrate was concentrated
20 under reduced pressure, and the residue was
crystallized from methylene chloride-diisopropyl ether
to afford 1'-tert-butoxycarbonyl-2,3-dihydro-6-
nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (586
mg, yield 29%) as a white powder.

25 Melting point 230-232°C.

Example 649

Preparation of tert-butyl 4-(2-chloro-4-nitroimidazol-1-ylmethyl)-4-hydroxypiperidine-1-carboxylate

2-Chloro-4-nitro-1H-imidazole (3.1 g, 21.0 mmol), tert-butyl 1-oxa-6-azaspiro[2,5]octane-6-carboxylate (4.4 g, 21.0 mmol) and sodium hydrogen-carbonate (1.94 g, 23.1 mmol) in ethanol (20 ml) were
5 stirred under reflux for 6 hours. The reaction mixture was concentrated under reduced pressure, and the residue was added water. The resulting solution was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered.
10 The resulting filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to afford tert-butyl 4-(2-chloro-4-nitroimidazol-1-ylmethyl)-4-hydroxypiperidine-1-carboxylate (5.4 g, yield 72%) as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.45 - 1.71 (5H, m), 1.46 (9H, s), 3.03 - 3.14 (2H, m), 3.90 - 4.03 (2H, m), 4.02 (2H, s), 7.91 (1H, s).

Example 650

20 Preparation of tert-butyl 4-{2-[4-(2-chloro-4-nitroimidazol-1-ylmethyl)-4-hydroxypiperidin-1-yl]-2-oxoethyl}piperazine-1-carboxylate

2-Chloro-4-nitro-1H-imidazole (1.29 g, 8.76 mmol), tert-butyl 4-{2-(1-oxa-6-azaspiro[2,5]octan-6-yl)-2-oxoethyl}piperazine-1-carboxylate (2.97 g, 8.76
25 mmol) and sodium hydrogencarbonate (809 mg, 9.64 mmol) in ethanol (10 ml) was stirred under reflux for 5 hours. The reaction mixture was concentrated under

reduced pressure, and a saturated sodium hydrogencarbonate solution was added. The solution was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered.

5 The resulting filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to afford tert-butyl 4-{2-[4-(2-chloro-4-nitroimidazol-1-ylmethyl)-4-hydroxypiperidin-1-yl]-2-oxoethyl}piperazine-1-carboxylate (2.58 g, yield 61%)
10 as a yellow oil.

¹H-NMR (CDCl₃) δppm:

1.45 (9H, s), 1.53 - 1.71 (4H, m), 2.44 (4H, br), 2.96 - 3.04 (1H, m), 3.10 - 3.27 (2H, m), 3.35 - 3.48 (4H,
15 m), 3.90 - 3.96 (2H, m), 4.05 (2H, s), 4.32 - 4.37 (2H, m), 8.04 (1H, s).

Using 6-(4-trifluoromethylphenyl)-1-oxa-6-azaspiro[2,5]octane gave the compound of Example 651 in the same manner as in Example 650.

20 Example 651

4-(2-Chloro-4-nitroimidazol-1-ylmethyl)-1-(4-trifluoromethylphenyl)piperidin-4-ol

Light pink powder, yield 54%

¹H-NMR (CDCl₃) δppm:

25 1.60 - 1.66 (2H, m), 1.82 - 1.93 (3H, m), 3.10 - 3.22 (2H, m), 3.62 - 3.67 (2H, m), 4.07 (2H, s), 6.95 (2H, d, J = 8.7 Hz), 7.50 (2H, d, J = 8.7 Hz), 7.99 (1H, s).

Example 652

Preparation of 1'-tert-butoxycarbonyl-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-(alternative synthesis method of the compound of Example 648)

- 5 Tert-butyl 4-(2-chloro-4-nitroimidazol-1-ylmethyl)-4-hydroxypiperidine-1-carboxylate prepared in Example 649 (26.7 g, 74.0 mmol) was dissolved in 1,4-dioxane (200 ml). To the solution, sodium hydride (3.6 g, 88.8 mmol) was added with cooling on ice-bath
- 10 followed by stirring under reflux for 8 hours. The reaction mixture was concentrated under reduced pressure. To the residue, ice-water and methylene chloride were added followed by stirring vigorously. The precipitates were filtered off, washed with water
- 15 and methanol, dried under reduced pressure to afford a solid (16.4 g). Then, the filtrate was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The organic phase was concentrated under reduced pressure. The residue
- 20 was crystallized with methanol to afford a solid (2.7 g). The solids were combined to afford 1'-tert-butoxycarbonyl-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (19.1 g, yield 79%) as a white powder.
- 25 Melting point 230-232°C.

Example 653

Preparation of tert-butyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazol-2,4'-piperidine]-1'-

yl)-2-oxoethyl]piperazine-1-carboxylate

Tert-butyl 4-{2-[4-(2-chloro-4-nitroimidazol-1-ylmethyl)-4-hydroxypiperidin-1-yl]-2-oxoethyl}-piperazine carboxylate prepared in Example 650 (2.58 g, 5.3 mmol) was dissolved in dioxane (30 ml). To the solution, sodium hydride (254 mg, 6.36 mmol) was added with cooling on ice-bath followed by stirring under reflux overnight. The reaction mixture was concentrated under reduced pressure. To the residue, ice-water and ethyl acetate were added followed by stirring vigorously. The precipitates were filtered off, washed with water and ethyl acetate, and then dried under reduced pressure to afford tert-butyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazol-2,4'-piperidine]-1'-yl)-2-oxoethyl]piperazine-1-carboxylate (996 mg, yield 42%) as a white powder. Melting point 211.0-213.0°C.

Using corresponding starting materials gave the compound of Example 654 in the same manner as in Example 653.

Example 654

2,3-Dihydro-6-nitro-1'-(4-trifluoromethylphenyl)spiro[imidazo[2,1-b]oxazole-2,4'-piperidine]

White powder, yield 79%

MS: 368 (M⁺)

Melting point 249.2-250.1°C.

Example 655

Preparation of 2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate

1'-Tert-butoxycarbonyl-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]

5 prepared in Example 652 (42 g, 0.13 mol) was suspended in methylene chloride (100 ml). To the suspension, trifluoroacetic acid (60 ml) was added slowly with cooling on ice-bath followed by stirring at room temperature overnight. The reaction mixture was
10 concentrated under reduced pressure, and the residue was crystallized with methanol. The solids were filtered off, washed with methanol and ethyl acetate, and then dried under reduced pressure to afford 2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-
15 piperidine] trifluoroacetate (43.6 g, yield 99%) as a light brown powder.

MS: 224 (M⁺)

Melting point 196-198°C (decomposition)

¹H-NMR (DMSO-d₆) δppm:

20 2.06 - 2.32 (4H, m), 3.12 - 3.35 (4H, m), 4.24 (2H, s), 8.21 (1H, s), 8.88 (2H, bs).

Example 656

Preparation of 1'-acetyl-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]

25 2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (85.5 mg, 0.25 mmol) was suspended in methylene chloride (5 ml). To the suspension,

triethylamine (74 μ l) and acetyl chloride (20 μ l) were added followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. To the residue, methanol and water
5 were added followed by stirring vigorously. The precipitates were filtered off, washed with water and isopropyl ether, and then dried under reduced pressure to afford 1'-acetyl-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (37.8
10 mg, yield 56%) as a white powder.

MS: 266 (M^+)

Melting point 232.0-234.0°C.

Example 657

Preparation of 1'-(4-trifluoromethylphenylacetyl)-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-
15 piperidine]

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (300 mg, 0.89 mmol) was suspended in
20 methylene chloride (5 ml). To the suspension, triethylamine (0.4 ml, 2.66 mmol) and (α,α,α -trifluoro-p-tolyl)acetyl chloride (2.7 ml, 1.33 mmol) were added followed by stirring at room temperature for 1 hour. The reaction mixture was poured into a saturated sodium
25 hydrogencarbonate solution, and the mixture was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced

pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford 1'-(4-trifluoromethyl-phenylacetyl)-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (143 mg, yield 39%) as a white powder.

MS: 410 (M^+)

Melting point 185.0-187.0°C.

10 Example 658

Preparation of 1'-(3,4-dichlorophenoxyacetyl)-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (300 mg, 0.89 mmol), (3,4-dichlorophenyl)-acetic acid (294 mg, 1.24 mmol) and WSCD (255 mg, 1.24 mmol) in DMF (5 ml) were stirred at room temperature for 1.5 hours. To the reaction mixture, water and diethyl ether was added followed by stirring vigorously. The precipitates were filtered off, washed with water and diethyl ether, and then dried under reduced pressure to afford 1'-(3,4-dichlorophenoxyacetyl)-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (96 mg, yield 25%) as a white powder. Melting point 218.0-220.0°C.

 Example 659

Preparation of 2,3-dihydro-1'-methyl-6-nitrospiro-

[imidazo[2,1-b]oxazole-2,4'-piperidine]

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (250 mg, 1.12 mmol) obtained by neutralization of 2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 was suspended in methanol (5 ml). To the suspension, a 37% formaldehyde solution (0.25 ml, 3.35 mmol), sodium cyanotrihydroborate (210 mg, 3.35 mmol) and acetic acid (0.19 ml, 3.35 mmol) were added followed by stirring at room temperature for 3 hours. The reaction mixture was poured into a saturated sodium hydrogencarbonate solution, 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 crystallized from methylene chloride-diisopropyl ether to afford 2,3-dihydro-1'-methyl-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (160 mg, yield 60%) as a white powder.

MS: 238 (M⁺)

Melting point 237.0-239.0°C (decomposition).

Example 660

Preparation of 1'-benzenesulfonyl-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (197 mg, 0.88 mmol) was suspended in

methylene chloride (5 ml). To the suspension, triethylamine (0.36 ml, 2.64 mmol) and benzenesulfonyl chloride (0.28 ml, 2.10 mmol) were added followed by stirring at room temperature for 30 minutes. To the
5 reaction mixture, diisopropyl ether and water were added followed by stirring vigorously. The precipitates were filtered off, washed with water and diisopropyl ether, and then dried under reduced pressure to afford 1'-benzenesulfonyl-2,3-dihydro-6-
10 nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (210 mg, yield 66%) as a white powder.

MS: 364 (M^+)

^1H -NMR ($\text{DMSO}-d_6$) δ ppm:

1.99 - 2.18 (4H, m), 2.49 - 2.63 (2H, m), 3.40 - 3.54
15 (2H, m), 4.10 (2H, s), 7.65 - 7.81 (5H, m), 8.21 (1H, s).

Using corresponding starting materials gave the compound of Example 661 in the same manner as in Example 660.

20 Example 661

1'-Methanesulfonyl-2,3-dihydro-6-nitrospiro[imidazo-
[2,1-b]oxazole-2,4'-piperidine]

^1H -NMR ($\text{DMSO}-d_6$) δ ppm:

1.98 - 2.22 (4H, m), 2.94 (3H, s), 3.04 - 3.13 (2H, m),
25 3.43 - 3.51 (2H, m), 4.16 (2H, s), 8.17 (1H, s).

 Example 662

Preparation of 1'-benzyloxycarbonyl-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (250 mg, 0.74 mmol) was suspended in methylene chloride (5 ml). To the suspension, triethylamine (0.40 ml, 2.96 mmol) and benzyl chloroformate (0.32 ml, 2.22 mmol) were added followed by stirring at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford 1'-benzyloxycarbonyl-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (224 mg, yield 84%) as a white powder. Melting point 175.0-177.0°C.

Example 663

Preparation of 1'-(4-trifluoromethylbenzyloxycarbonyl)-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (33 g, 97.6 mmol) was suspended in DMF (200 ml). To the suspension, triethylamine (20 ml, 0.15 mol) was added followed by stirring. To the solution, a mixture of 4-trifluoromethylbenzyl alcohol (25.8 g, 0.15 mol), 1,1'-carbonyldiimidazole (23.7 g, 0.15 mol) and DMF (100 ml) stirred at room temperature for 3 hours was added followed by stirring at 70°C for 2

hours. The reaction mixture was concentrated under reduced pressure. To the residue, water was added, and the precipitates were filtered off. The precipitates were purified by silica gel column chromatography

5 (methylene chloride/ethyl acetate = 10/1) and recrystallized from ethyl acetate-isopropyl ether to afford 1'-(4-trifluoromethylbenzyloxycarbonyl)-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (37.2 g, yield 90%) as a white powder.

10 Melting point 189-190°C.

Using corresponding starting materials gave compounds of Examples 664 and 665 in the same manner as in Example 663.

Example 664

15 1'-[(4-Trifluoromethoxy)benzyloxycarbonyl]-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]

¹H-NMR (CDCl₃) δppm:

1.80 - 1.93 (2H, m), 2.13 - 2.19 (2H, m), 3.32 - 3.42 (2H, m), 4.00 - 4.20 (2H, m), 4.03 (2H, s), 5.14 (2H, s), 7.20 - 7.23 (2H, m), 7.38 - 7.46 (2H, m), 7.54 (1H, s).

Example 665

1'-(4-Formylaminobenzyloxycarbonyl)-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]

25 ¹H-NMR (DMSO-d₆) δppm:

1.85 - 2.10 (4H, m), 3.15 - 3.40 (2H, m), 3.65 - 3.85 (2H, m), 4.16 (2H, s), 5.03 (2H, s), 7.33 (2H, d, J = 8.5 Hz), 7.58 (2H, d, J = 8.5 Hz), 8.15 (1H, s), 8.27

(1H, s).

Example 667

Preparation of 2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-carboxylic acid

5 phenylamide

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (100 mg, 0.30 mmol) was suspended in DMF (5 ml). To the suspension, triethylamine (43 μ l, 0.31 mmol) and phenylisocyanate (34 μ l, 0.31 mmol) were added followed by stirring at room temperature for 30 minutes. To the reaction mixture, water was added followed by stirring, and the precipitates were filtered off. The precipitates were purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and recrystallized from ethyl acetate, filtered off to afford 2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-carboxylic acid phenylamide (90 mg, yield 88%) as a white powder.

MS; 343(M⁺)

Melting point 229-232°C (decomposition).

Using pyridine 4-isocyanate or benzyl isocyanate gave compounds of Examples 668 and 669 in the same manner as in Example 667.

Example 668

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-carboxylic acid 4-pyridinamide

Melting point 217-219°C.

Example 669

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-carboxylic acid benzylamide

5 Melting point 244-247°C (decomposition).

Example 670

Preparation of tert-butyl 4-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-ylcarbonyl)piperazine-1-carboxylate

10 Triphosgene (227 mg, 0.77 mmol) was dissolved in toluene (10 ml). To the solution, tert-butyl piperazine-1-carboxylate (425 mg, 2.28 mmol) and diisopropylethylamine (0.4 ml, 2.28 mmol) were added followed by stirring for 1 hour with cooling on ice-
15 bath. To the solution, 2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (700 mg, 2.07 mmol) was added. The solution was stirred at room temperature for 1 hour and then stirred under reflux
20 for 1 hour. The reaction mixture was poured into 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
25 under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/acetone = 10/1) and then crystallized from methylene chloride-diisopropyl ether to afford tert-

butyl 4-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-ylcarbonyl)piperazine-1-carboxylate (342 mg, yield 38%) as a white powder. Melting point 260.0-265.0°C (decomposition).

5 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.47 (9H, s), 1.90 - 2.02 (2H, m), 2.10 - 2.16 (2H, m), 3.23 - 3.47 (10H, m), 3.60 - 3.66 (2H, m), 3.96 (2H, s), 7.54 (1H, s).

Using 4-trifluoromethylbenzyl piperazine-1-carboxylate or 1-(4-trifluoromethylbenzyl)piperazine gave compounds of Examples 671 and 672 in the same manner as in Example 670.

Example 671

4-Trifluoromethylbenzyl 4-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-ylcarbonyl)piperazine-1-carboxylate

Melting point 221-223°C.

Example 672

1-(2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-ylcarbonyl)-4-(4-trifluoromethylbenzyl)piperazine

Melting point 226-230°C (decomposition).

Example 673

Preparation of 2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-carboxylic acid 4-(dimethylamino)phenylamide

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in

Example 655 (200 mg, 0.59 mmol) was suspended in DMF (5 ml). To the suspension, triethylamine (0.1 ml, 0.72 mmol) was added followed by stirring. To the solution, a mixture of N,N-dimethyl-p-phenylenediamine (132 mg, 0.98 mmol), 1,1'-carbonyldiimidazole (82.7 mg, 1.02 mmol) and DMF (5 ml) stirred at room temperature for 3 hours was added followed by stirring at room temperature for 30 minutes. To the reaction mixture, water was added followed by stirring, and the precipitates were filtered off. The precipitates were purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and crystallized from ethyl acetate to afford 2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-carboxylic acid 4-(dimethylamino)phenylamide (181 mg, yield 79%) as a white powder.

MS 386(M⁺)

Melting point 244-247°C (decomposition).

Using 4-trifluoromethylbenzylamine or 4-trifluoromethoxybenzylamine gave compounds of Examples 674 and 675 in the same manner as in Example 673.

Example 674

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-carboxylic acid 4-trifluoromethylbenzylamide

Melting point 215-217°C.

Example 675

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-

piperidine]-1'-carboxylic acid 4-trifluoromethoxybenzylamide

Melting point 223-225°C.

Example 676

- 5 Preparation of 2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-carbothioic acid 4-chlorophenylamide

- 2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in
- 10 Example 655 (200 mg, 0.59 mmol) was suspended in DMF (5 ml). To the suspension, triethylamine (0.24 ml, 1.77 mmol) and 4-chlorophenyl isothiocyanate (200 mg, 1.18 mmol) were added followed by stirring at room temperature for 30 minutes. To the reaction mixture,
- 15 water was added followed by stirring, and the precipitates were filtered off, purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and crystallized from methylene chloride-diisopropyl ether to afford 2,3-dihydro-6-
- 20 nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-carbothioic acid 4-chlorophenylamide (222 mg, yield 87%) as a white powder.

¹H-NMR (DMSO-d₆) δppm:

- 2.02 - 2.19 (4H, m), 3.59 - 3.69 (2H, m), 4.19 (2H, s),
- 25 4.40 - 4.54 (2H, m), 7.30 - 7.37 (4H, m), 8.18 (1H, s), 9.48 (1H, s).

Example 677

Preparation of 4-[(2,3-dihydro-6-nitrospiro[imidazo-

[2,1-b]oxazole-2,4'-piperidin]))-1'-ylcarbonyl]amino-
benzoic acid

Tert-butyl 4-[(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]))-1'-
5 ylcarbonyl]aminobenzoate (150 mg, 0.68 mmol) was
dissolved in methylene chloride (1 ml). To the
solution, trifluoroacetic acid (5 ml) was added
followed by stirring at room temperature overnight.
The reaction mixture was concentrated under reduced
10 pressure. The residue was crystallized from methanol-
ethyl acetate to afford 4-[(2,3-dihydro-6-
nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]))-1'-
ylcarbonyl]aminobenzoic acid (59 mg, yield 45%) as a
white powder.

15 Melting point >300°C.

¹H-NMR (DMSO-d₆) δppm:

1.92 - 2.12 (4H, m), 3.32 - 3.39 (2H, m), 3.86 - 3.95
(2H, m), 4.17 (2H, s), 7.45 (2H, d, J = 8.8 Hz), 7.82
(2H, d, J = 8.8 Hz), 8.17 (1H, s), 8.97 (1H, s), 12.54
20 (1H, s).

Example 678

Preparation of 2-[(2,3-dihydro-6-nitrospiro[imidazo-
[2,1-b]oxazole-2,4'-piperidin]))-1'-yl]benzothiazole

2,3-Dihydro-6-nitrospiro[imidazo[2,1-
25 b]oxazole-2,4'-piperidine] trifluoroacetate prepared in
Example 655 (84 mg, 0.25 mmol) was suspended in DMF (3
ml). To the suspension, triethylamine (76 μl, 0.55
mmol) and 2-chlorobenzothiazole (40 μl, 0.30 mmol) were

added followed by stirring at 80°C for 1 hour. The reaction mixture was concentrated under reduced pressure. To the residue, water was added, and the precipitate was filtered off, crystallized from
5 methylene chloride-methanol to afford 2-[(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine])-1'-yl]benzothiazole (55 mg, yield 62%) as a white powder.

MS; 357 (M⁺)

10 ¹H-NMR (DMSO-d₆) δppm:

2.05 - 2.23 (4H, m), 3.52 - 3.63 (2H, m), 3.89 - 3.97 (2H, m), 4.18 (2H, s), 7.05 - 7.12 (1H, m), 7.26 - 7.32 (1H, m), 7.46 - 7.49 (1H, m), 7.76 - 7.80 (1H, m), 8.18 (1H, s).

15 Using 5-chloro-1-phenyl-1H-tetrazole gave the compound of Example 679 in the same manner as in Example 678.

Example 679

5-[(2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-
20 2,4'-piperidin])-1'-yl]-1-phenyl-1H-tetrazole

¹H-NMR (DMSO-d₆) δppm:

2.05 - 2.09. (4H, m), 3.24 - 3.40 (4H, m), 4.14 (2H, s), 7.59 - 7.72 (5H, m), 8.15 (1H, s).

Example 680

25 Preparation of tert-butyl 4-[(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-yl]acetyl]piperazine-1-carboxylate

2,3-Dihydro-6-nitrospiro[imidazo[2,1-

b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (700 mg, 2.07 mmol) was suspended in DMF (20 ml). To the suspension, tert-butyl 4-(chloroacetyl)piperazine-1-carboxylate (599 mg, 2.28 mmol), N,N-diisopropylethylamine (0.8 ml, 4.57 mmol) and sodium iodide (310 mg, 2.07 mmol) were added followed by stirring at 100°C for 3 hours. The reaction mixture was allowed to return to room temperature. To the solution, ethyl acetate and water were added followed by stirring vigorously. The precipitates were filtered off, washed with water and ethyl acetate, and then dried under reduced pressure to afford tert-butyl 4-[(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylacetyl]piperazine-1-carboxylate (688 mg, yield 74%) as a white powder.

Melting point >300°C.

¹H-NMR (DMSO-d₆) δppm:

1.41 (9H, s), 1.95 - 2.01 (4H, m), 2.43 - 2.64 (4H, m), 3.21 (2H, s), 3.26 - 3.42 (6H, m), 3.50 - 3.52 (2H, m), 4.12 (2H, s), 8.14 (1H, s).

Using 2-chloro-N-(4-trifluoromethylphenyl)-acetamide or 3-(3-chloropropyl)-3H-benzoxazol-2-one gave compounds of Examples 681 and 682 in the same manner as in Example 680.

Example 681

(2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylacetic acid (4-trifluoromethylphenyl)-amide

Melting point 273-275°C (decomposition).

Example 682

3-[3-(2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-yl]propyl-3H-benzoxazol-2-one

5 Melting point 190-192°C.

Example 683

Preparation of tert-butyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylethyl]piperazine-1-carboxylate

10 2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (200 mg, 0.59 mmol) was suspended in DMF (5 ml). To the suspension, tert-butyl 4-(2-chloroethyl)piperazine-1-carboxylate (150 mg, 0.60
15 mmol), triethylamine (0.25 ml, 1.79 mmol) and sodium iodide (108 mg, 0.72 mmol) were added followed by stirring at 50°C for 5 hours. The reaction mixture was allowed to return to room temperature. To the solution, ethyl acetate and water were added followed
20 by stirring vigorously. The precipitates were filtered off, washed with water and ethyl acetate, and then dried under reduced pressure to afford tert-butyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylethyl]piperazine-1-carboxylate (80 mg,
25 yield 31%) as a white powder.

Melting point 214-215°C.

Example 684

Preparation of 4-trifluoromethylbenzyl 4-[2-(2,3-

dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-yl)-2-oxoethyl]piperazine-1-carboxylate

- Tert-butyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazol-2,4'-piperidin]-1'-yl)-2-oxoethyl]piperazine-1-carboxylate prepared in Example 653 (300 mg, 0.67 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure. To the residue, methylene chloride (1 ml) and triethylamine (1 ml) were added. The reaction mixture was stirred at room temperature for 5 minutes and concentrated under reduced pressure, and the residue was dissolved in DMF (15 ml). To the solution, a mixture of 4-trifluoromethylbenzyl alcohol (293 mg, 1.67 mmol), 1,1'-carbonyldiimidazole (270 mg, 1.67 mmol) and 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, and 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 chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford 4-trifluoromethylbenzyl 4-[2-(2,3-

dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-yl)-2-oxoethyl]piperazine-1-carboxylate (324 mg, yield 88%) as a light pink powder.

MS 553(M+H)⁺

5 Melting point 139.0-141.0°C.

Using corresponding starting materials gave the compound of Example 685 in the same manner as in Example 684.

Example 685

10 4-Trifluoromethoxybenzyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-yl)-2-oxoethyl]piperazine-1-carboxylate
Melting point 137-139°C.

Using tert-butyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylethyl]piperazine-1-carboxylate prepared in Example 683 gave compounds of Examples 686 to 689 in the same manner as in Example 684.

Example 686

20 4-Chlorobenzyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylethyl]piperazine-1-carboxylate
Melting point 178-179°C.

Example 687

25 4-Trifluoromethylbenzyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylethyl]piperazine-1-carboxylate
Melting point 174-175°C.

Example 688

4-Trifluoromethoxybenzyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylethyl]piperazine-1-carboxylate

5 Melting point 176-177°C.

Example 689

Biphenyl-4-ylmethyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylethyl]piperazine-1-carboxylate

10 ¹H-NMR (CDCl₃) δppm:

1.90 - 2.05 (2H, m), 2.15 - 2.20 (2H, m), 2.40 - 2.80 (12H, m), 3.45 - 3.60 (4H, m), 3.99 (2H, s), 5.17 (2H, s), 7.31 - 7.62 (10H, m).

Using tert-butyl 4-[(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylacetyl]piperazine-1-carboxylate prepared in Example 680 gave the compound of Example 690 in the same manner as in Example 684.

Example 690

20 4-Trifluoromethylbenzyl 4-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylacetyl]piperazine-1-carboxylate

Melting point 137-139°C.

Example 691

25 Preparation of 1-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-yl)-2-[4-(4-trifluoromethylbenzyl)piperazin-1-yl]ethanone

Tert-butyl 4-[2-(2,3-dihydro-6-

nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-yl)-2-oxoethyl]piperazine-1-carboxylate prepared in Example 653 (300 mg, 0.67 mmol) was dissolved in methylene chloride (5 ml). To the solution,

5 trifluoroacetic acid (10 ml) was added followed by stirring at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure. To the solution, methylene chloride (1 ml) and triethylamine (1 ml) were added followed by stirring at

10 room temperature for 5 minutes. The solution was concentrated under reduced pressure and the residue was dissolved in methanol (10 ml). To the solution, 4-trifluoromethylbenzaldehyde (0.23 ml, 1.67 mmol), sodium cyanotrihydroborate (105 mg, 1.67 mmol) and

15 acetic acid (0.1 ml) were added with cooling on ice-bath followed by stirring at room temperature overnight. To the solution, a saturated aqueous sodium hydrogencarbonate solution and methylene chloride were added followed by stirring. The organic phase was

20 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 = 50/1) and crystallized from methylene chloride-

25 diisopropyl ether to afford 1-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-yl)-2-[4-(4-trifluoromethylbenzyl)piperazin-1-yl]ethanone (226 mg, yield 67%) as a white powder.

MS 508 (M)⁺

Melting point 145-147°C.

Using corresponding starting materials gave the compound of Example 692 in the same manner as in
5 Example 691.

Example 692

1-(2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-yl)-2-[(4-phenylbenzyl)piperazin-1-yl]ethanone

10 Melting point 187-188°C.

Using tert-butyl 4-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-ylacetyl)piperazine-1-carboxylate prepared in Example 680 gave compounds of Examples 693 and 694 in the same
15 manner as in Example 691.

Example 693

1-(2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-ylacetyl)-4-(4-trifluoromethylbenzyl)piperazine

20 Melting point 195-197°C (decomposition).

Example 694

1-(2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-ylacetyl)-4-(4-phenylbenzyl)piperazine
Melting point 226-227°C (decomposition).

25 Example 695

Preparation of 4-[(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-yl)-2-oxoethyl]-piperazine-1-carboxylic acid (4-trifluoromethyl-

phenyl) amide

Tert-butyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-yl)-2-oxoethyl]piperazine-1-carboxylate prepared in

5 Example 653 (300 mg, 0.67 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (10 ml) was added followed by stirring at room temperature for 4 hours. The reaction mixture was concentrated under reduced

10 pressure. To the solution, methylene chloride (1 ml) and triethylamine (1 ml) were added followed by stirring at room temperature for 5 minutes. The solution was concentrated under reduced pressure, and the residue was dissolved in DMF (10 ml). To the

15 solution, a mixture of 4-aminobenzotrifluoride (0.17 ml, 1.33 mmol) and 1,1'-carbonyldiimidazole (220 mg, 1.33 mmol) and DMF (5 ml) stirred at room temperature for 3 hours was added followed by stirring at room

temperature for 2 hours. The reaction mixture was

20 poured into water and extracted with 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, and the residue was purified by

25 silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford 4-[(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-

piperidin]-1'-yl)-2-oxoethyl]piperazine-1-carboxylic acid (4-trifluoromethylphenyl)amide (213 mg, yield 59%) as a white powder.

Melting point 153.0-155.0°C.

5 Example 696

Preparation of 2-{4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-yl)-2-oxoethyl]piperazin-1-yl}-N-(4-trifluoromethylphenyl)acetamide

10 Tert-butyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazol-2,4'-piperidin]-1'-yl)-2-oxoethyl]piperazine-1-carboxylate prepared in Example 653 (300 mg, 0.67 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid
15 (10 ml) was added followed by stirring at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure. To the residue, methylene chloride (1 ml) and triethylamine (1 ml) were added followed by stirring at room temperature for 5
20 minutes, and then the solution was concentrated under reduced pressure. The residue was dissolved in DMF (10 ml). To the solution, 2-bromo-N-(4-trifluoromethylphenyl)acetamide (207 mg, 0.73 mmol) and triethylamine (0.28 ml, 2.0 mmol) were added followed
25 by stirring at 100°C for 2 hours. 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, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and crystallized from methylene chloride-diisopropyl ether to afford 2-{4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-yl)-2-oxoethyl]piperazin-1-yl}-N-[4-trifluoromethylphenyl]acetamide (275 mg, yield 75%) as a white powder.

MS 552 (M+1)⁺

Melting point 133.0-135.0°C.

Example 697

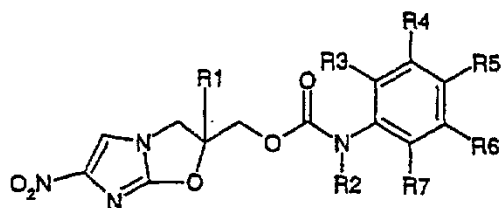
Preparation of 2-[4-(benzoxazol-2-yl)piperazin-1-yl]-1-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-yl)ethanone

Tert-butyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-yl)-2-oxoethyl]piperazine-1-carboxylate prepared in Example 653 (227 mg, 0.50 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure. To the residue, methylene chloride (1 ml) and triethylamine (1 ml) were added followed by stirring at room temperature for 5 minutes, and then the solution was concentrated under reduced pressure. The residue was dissolved in DMF (5 ml). To the solution,

triethylamine (0.21 ml, 1.52 mmol) and 2-chlorobenzoxazole (86 μ l, 0.76 mmol) were added followed by stirring at 80°C for 2 hours. To the reaction mixture, water was added, and the mixture was
5 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 crystallized from methylene chloride-ethyl acetate to afford 2-[4-(benzoxazol-2-yl)piperazin-1-yl]-1-(2,3-dihydro-6-
10 nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-yl)ethanone (99 mg, 42%) as a light yellow powder.
MS 467 (M^+)
Melting point 260.0-263.0°C (decomposition).

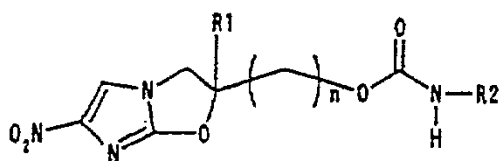
15 Compounds gave from appropriate starting materials in the same manner as in the above Examples 1 to 697 are shown in the following tables 26 to 77.

Table 26



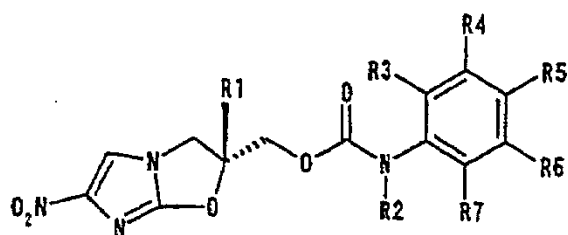
Example	R1	R2	R3	R4	R5	R6	R7	mp(°C)
698	-H	-H	-H	-H	-CH ₃	-H	-H	193-195
699	-H	-H	-H	-H	-CO ₂ C ₂ H ₅	-H	-H	195-197.5
700	-H	-H	-H	-H	-OCH ₃	-H	-H	189-190
701	-H	-H	-H	-H	-Cl	-Cl	-H	182-183
702	-H	-H	-H	-H	-H	-H	-H	185-186
703	-CH ₃	-H	-H	-H	-OCH ₃	-H	-H	177.5 - 179
704	-CH ₃	-H	-H	-H	-F	-H	-H	194-196
705	-CH ₃	-H	-H	-H	-CH ₃	-H	-H	145-147
706	-CH ₃	-H	-H	-H	-H	-Cl	-H	190.5-192
707	-CH ₃	-H	-H	-H	-H	-H	-Cl	163-164
708	-CH ₃	-H	-H	-H	-H	-H	-OCH ₃	177-180
709	-CH ₃	-H	-H	-H	-H	-CF ₃	-H	182-183.5
710	-CH ₃	-H	-H	-OCH ₃	-OCH ₃	-OCH ₃	-H	179-182
711	-CH ₃	-H	-H	-H	-H	-H	-F	142 - 144
712	-CH ₃	-H	-H	-H	-Br	-H	-H	197 - 199
713	-CH ₃	-H	-H	-H	-CONH ₂	-H	-H	234 - 235 dec
714	-CH ₃	-H	-H	-H	-CO ₂ C ₂ H ₅	-H	-H	151 - 152
715	-CH ₃	-H	-H	-H	-COCH ₃	-H	-H	196 - 199
716	-CH ₃	-H	-H	-H	-SO ₂ NH ₂	-H	-H	218 - 220 dec
717	-CH ₃	-H	-H	-H	-H	-CO ₂ C ₂ H ₅	-H	112 - 114
718	-CH ₃	-H	-H	-H	-H	-H	-CO ₂ C ₂ H ₅	132 - 134
719	-CH ₃	-CH ₃	-H	-H	-Br	-H	-H	132 - 133
720	-CH ₃	-H	-H	-H	-CF ₃	-H	-H	198.5 - 200
721	-CH ₃	-H	-H	-H	-OCF ₃	-H	-H	163.5 - 164.8
722	-CH ₃	-CH ₃	-H	-H	-CF ₃	-H	-H	129 - 130
723	-CH ₃	-CH ₃	-H	-H	-OCF ₃	-H	-H	138 - 140
724	-CH ₃	-H	-H	-H	Morpholino-	-H	-H	223-225
725	-CH ₃	-H	-H	-H	Morpholino-	-H	-H	134-135
726	-CH ₃	-H	-H	-H	C ₆ H ₅ NHCO-	-H	-H	197-198

Table 27



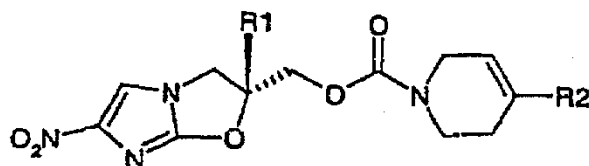
Example	n	R1	R2	mp(°C) or 1H NMR
727	1	-H	-CH ₂ Ph	143.5-145
728	1	-H	-cyclo-C ₆ H ₁₁	187-188.5
729	1	-CH ₃	-CH ₂ Ph	141-142
730	1	-CH ₃	-(CH ₂) ₂ Ph	124-127
731	1	-CH ₃	-cyclo-C ₆ H ₁₁	176-178
732	1	-CH ₃	-4-PYRIDYL	151-153 (dec)
733	1	-CH ₃	-CH(CH ₃) ₂	163-165
734	1	-CH ₃	-CH ₂ CO ₂ C ₂ H ₅	142-143
735	1	-CH ₃	-C ₆ H ₁₃	129-130
736	1	-CH ₃	-(CH ₂) ₂ CO ₂ C ₂ H ₅	94-96
737	1	-CH ₃	-CH ₂ CH ₂ Cl	DMSO-d ₆ , 1.59(3H, s), 3.22-3.33(2H, m), 3.57(2H, t, J=6.0Hz), 4.07(2H, dd, J=11.1Hz, 27.6Hz), 4.27(2H, dd, J=7.6Hz, 9.9Hz), 6.47-6.59(1H, m), 8.13(1H, s)
	1	-H	-C ₆ H ₁₁	DMSO-d ₆ , 0.85(3H, t, J=6.9Hz), 1.00-1.45(12H, m), 2.90-2.98(2H, m), 4.06(1H, dd, J=6.8Hz, 10.8Hz), 4.25-4.46(3H, m), 5.48-5.66(1H, m), 7.28(1H, t, J=5.6Hz), 8.13(1H, s)
738				
739	2	-H	C ₆ H ₁₇	86-88
740	2	-CH ₃	Ph-	131-133
741	2	-CH ₃	PhCH ₂ -	127-127.5
742	2	-CH ₃	PhCH ₂ CH ₂ -	124-125

Table 28



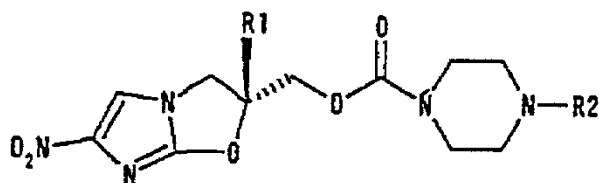
Example	R1	R2	R3	R4	R5	R6	R7	mp(°C)
743	-CH ₃	-CH ₃	-H	-H	-H	-Cl	-H	103 - 104
744	-CH ₃	-CH ₂ Ph	-H	-H	-Cl	-H	-H	168 - 169
745	-CH ₃	-C ₆ H ₁₃	-H	-H	-Cl	-H	-H	98 - 100
746	-CH ₃	-CH ₃	-H	-H	-Br	-H	-H	147 - 150
747	-CH ₃	-CH ₃	-H	-H	-CF ₃	-H	-H	140 - 141
748	-CH ₃	-CH ₃	-H	-H	-F	-H	-H	111 - 113
749	-CH ₃	-C ₄ H ₉	-H	-H	-Cl	-H	-H	114 - 116
750	-CH ₃	-C ₂ H ₅	-H	-H	-Cl	-H	-H	87 - 89
751	-CH ₃	-CH ₂ CH(CH ₃) ₂	-H	-H	-Cl	-H	-H	161 - 165
752	-CH ₃	4-ClPhCH ₂ -	-H	-H	-Cl	-H	-H	175 - 178

Table 29



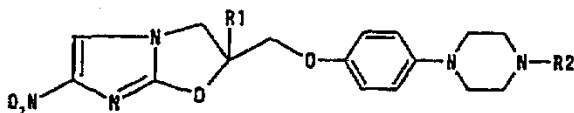
Example	R1	R2	mp(°C)
753	-CH ₃	4-CF ₃ OPh-	165 - 166
754	-CH ₃	4-CH ₃ OPh-	155 - 157
755	-CH ₃	4-ClPh-	157 - 158
756	-CH ₃	3-CF ₃ Ph-	100 - 101
757	-CH ₃	4-BrPh-	168 - 170
758	-CH ₃	4-FPh-	151 - 154

Table 30



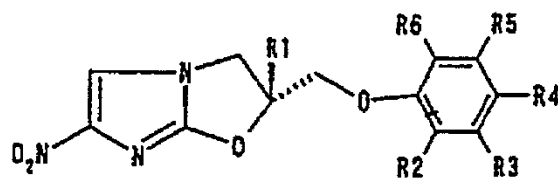
Example	R1	R2	mp(°C)
759	-CH ₃	4-CF ₃ Ph-	151 - 153
760	-CH ₃	4-ClPh-	143 - 144
761	-CH ₃	3-ClPh-	136 - 138
762	-CH ₃	3,4-Cl ₂ Ph-	142 - 143
763	-CH ₃	4-CH ₃ OPh-	163 - 164
764	-CH ₃	3-CF ₃ Ph-	105 - 107
765	-CH ₃	4-FPh-	139 - 140
766	-CH ₃	4-CF ₃ OPhCH ₂ OCO-	166 - 167
767	-CH ₃	4-CF ₃ PhCH=CHCH ₂ OCO-	186 - 188
768	-CH ₃	4-CF ₃ PhCH ₂ -	205 - 206
769	-CH ₃	4-CF ₃ OPhCH ₂ -	133 - 134

Table 31



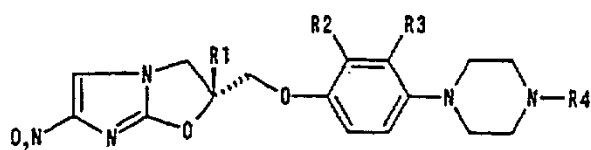
Example	R1	R2	mp(°C) or 1H NMR
770	-CH ₃	4-ClPh-	228.8 - 232.2
771	-CH ₃	4-CF ₃ OPh-	236.2 - 237.4
772	-CH ₃	4-CF ₃ OPhCH ₂ -	CDCl ₃ ; 1.76(3H, s), 3.03(4H, br), 3.62-3.67(4H, m), 4.01(1H, d, J=10.2Hz), 4.04(1H, d, J=10.2Hz), 4.18(1H, d, J=10.2Hz), 4.48(1H, d, J=10.2Hz), 5.15(2H, s), 6.76-6.80(2H, m), 6.85-6.89(2H, m), 7.19-7.23(2H, m), 7.38-7.42(2H, m), 7.54(1H, s)
773	-CH ₃	4-ClPhCH ₂ -	174.2 - 175
774	-CH ₃	4-CF ₃ OPhCH ₂ OCO-	155.5 - 156.5
775	-CH ₃	4-CF ₃ PhCH=CHCH ₂ OCO-	155 - 159.8

Table 32



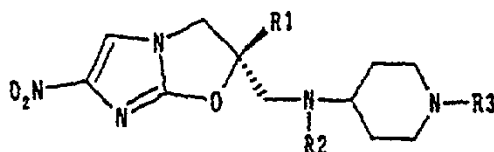
Example	R1	R2	R3	R4	R5	R6	mp(°C)
776	-CH ₃	-H	-H	-H	-H	-H	151 - 153.5
777	-CH ₃	-H	-H	-I	-H	-H	220 - 221
778	-CH ₃	-H	-H	-Cl	-H	-H	185 - 186.5
779	-CH ₃	-H	-H	Morpholino	-H	-H	238 - 240 dec
780	-CH ₃	-H	-H	Piperidino	-H	-H	217 - 218.5 dec

Table 33



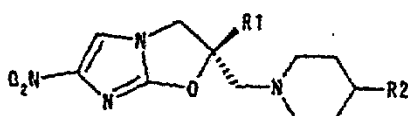
Example	R1	R2	R3	R4	mp(°C) or ¹ H NMR
781	-CH ₃	-H	-H	-CH ₃	230 - 231.5 dec
782	-CH ₃	-H	-Cl	-CH ₃	201 - 204.5 dec
783	-CH ₃	-H	-H	4-CF ₃ Ph	258 - 259 dec
784	-CH ₃	-H	-H	4-ClPhCH ₂ -	207 - 208.4
785	-CH ₃	-H	-H	4-ClPh	251 - 257 dec
786	-CH ₃	-H	-H	CH ₃ CO-	206 - 207.5
787	-CH ₃	-H	-Cl	C ₂ H ₅ OCO-	168.5 - 171
788	-CH ₃	-Cl	-H	t-BuOCO-	192 - 194.5
789	-CH ₃	-Cl	-H	C ₂ H ₅ OCO-	178.5 - 180.5
790	-CH ₃	-Cl	-Cl	t-BuOCO-	233 - 233.5 dec
791	-CH ₃	-Cl	-Cl	C ₂ H ₅ OCO-	224.2 - 225.7
792	-CH ₃	-H	-H	-CO ₂ CH ₂ CF ₃	213 - 216
793	-CH ₃	-H	-H	-CO ₂ C ₄ H ₉	197.5 - 199
794	-CH ₃	-H	-H	-CO ₂ (CH ₂) ₂ CH ₃	198 - 201
795	-CH ₃	-H	-H	-CO ₂ (CH ₂) ₂ OCH ₃	176 - 179
796	-CH ₃	-H	-Cl	4-CF ₃ OPhCH ₂ OCO-	153 - 155
797	-CH ₃	-Cl	-H	4-CF ₃ OPhCH ₂ OCO-	176 - 176.8
798	-CH ₃	-Cl	-Cl	4-CF ₃ OPhCH ₂ OCO-	196.5 - 197.5
799	-CH ₃	-H	-H	4-CF ₃ OPhCH ₂ OCO-	187 - 189
800	-CH ₃	-H	-H	4-CF ₃ PhCH ₂ OCO-	180.5 - 182.5
801	-CH ₃	-H	-H	4-CF ₃ PhCH=CHCH ₂ OCO-	185 - 187
802	-CH ₃	-H	-H	3,4-Cl ₂ PhCH ₂ OCO-	171 - 171.5
803	-CH ₃	-H	-H	4-CF ₃ OPhNHCO-	228 - 232 dec
804	-CH ₃	-H	-H	-CO ₂ (CH ₂) ₂ N(CH ₃) ₂	CDCl ₃ : 1.76(3H, s), 2.30(6H, s), 2.61(2H, t, J=5.8Hz), 2.99-3.04(4H, m), 3.60-3.64(4H, m), 4.03(1H, d, J=10.2Hz), 4.04(1H, d, J=10.1Hz), 4.18(1H, d, J=10.1Hz), 4.22(2H, t, J=5.8Hz), 4.49(1H, d, J=10.2Hz), 6.76-6.81(2H, m), 6.83-6.89(2H, m), 7.55(1H, s)

Table 34



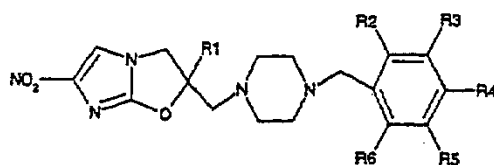
Example	R1	R2	R3	mp(°C)
805	-CH ₃	-CH ₃	4-CF ₃ OPh-	127.2 - 129.7
806	-CH ₃	-CH ₃	4-CF ₃ Ph-	131.5 - 133.6
807	-CH ₃	-CH ₃	4-NCPH-	149 - 152
808	-CH ₃	-CH ₃	4-CF ₃ OPhCH ₂ OCO-	84.2 - 86.8
809	-CH ₃	-CH ₃	4-ClPhCH ₂ OCO-	116.2 - 116.6

Table 35



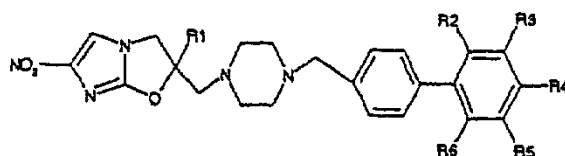
Example	R1	R2	mp(°C) or ¹ H NMR
810	-CH ₃	-OPh	153.2 - 154.8 CDCl ₃ : 1.16-1.42(2H,m), 1.61(3H,s), 1.87-2.01(2H,m), 2.31-2.60(3H,m), 2.78-3.02(4H,m), 3.24-3.30(1H,m), 3.82(1H,d,J=8.1Hz), 3.91(1H,d,J=9.7Hz), 4.29(1H,d,J=9.7Hz), 6.54(2H,d,J=8.6Hz), 6.98-7.36(2H,d,J=8.6Hz), 7.54(1H,s)
811	-CH ₃	4-CF ₃ PhNH-	130 - 131.8
812	-CH ₃	4-CF ₃ Ph-	117.5 - 118.5
813	-CH ₃	4-CF ₃ PhCH ₂ -	146.5-147.5
814	-CH ₃	4-ClPhCH ₂ -	177 - 179
815	-CH ₃	4-ClPhCO-	98 - 100
816	-CH ₃	4-CF ₃ PhCO-	119.4 - 120.7
817	-CH ₃	4-CF ₃ OPhO-	141 - 144
818	-CH ₃	4-ClPhO-	89 - 91.7
819	-CH ₃	3-CF ₃ PhO-	171 - 174.7
820	-CH ₃	4-NCPHO-	124 - 128
821	-CH ₃	4-FPhO-	113 - 115
822	-CH ₃	4-CF ₃ OPhCH ₂ O-	138 - 140
823	-CH ₃	4-ClPhCH ₂ O-	115 - 116.5
824	-CH ₃	4-PhPhCH ₂ O-	79 - 81
825	-CH ₃	PhCH ₂ CH ₂ O-	80.8 - 83.9
826	-CH ₃	4-PyridylCH ₂ O-	77 - 79
827	-CH ₃	3-PyridylCH ₂ O-	101 - 102
828	-CH ₃	4-CF ₃ OPhCH ₂ OCO-	153 - 155
829	-CH ₃	4-ClPhNHCO-	161 - 164
830	-CH ₃	4-ClPhCH ₂ NHCO-	159 - 161
831	-CH ₃	4-ClPhNH-	148.5 - 150
832	-CH ₃	4-NCPHNH-	180.2 - 181.1 dec
833	-CH ₃	4-ClPhN(CH ₃)-	188.5 - 191
834	-CH ₃	4-NCPHN(CH ₃)-	161 - 164
835	-CH ₃	4-CF ₃ PhN(CH ₃)-	178.5 - 180
836	-CH ₃	(4-ClPh) ₂ N-	

Table 36



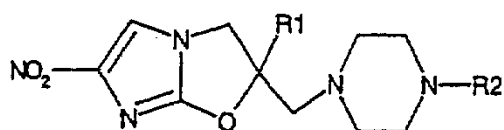
Example	R1	R2	R3	R4	R5	R6	mp(°C) or 1H NMR
837	-CH ₃	-H	-H	-CH(CH ₃) ₂	-H	-H	158.5 - 160
838	-CH ₃	-H	-Cl	-Cl	-H	-H	115 - 117.9
839	-CH ₃	-H	-H	-CF ₃	-H	-H	126 - 129.2
840	-H	-H	-H	-CF ₃	-H	-H	164 - 166
841	-CH ₃	-H	-H	-OPh	-H	-H	157 - 158.2
842	-CH ₃	-H	-OCH ₃	-OCH ₃	-OCH ₃	-H	147 - 151.9
843	-CH ₃	-H	-H	-CO ₂ CH ₃	-H	-H	151 - 152.5
844	-CH ₃	-H	-H	-3-PYRIDYL	-H	-H	140 - 143.8
845	-CH ₃	-H	-Ph	-H	-H	-H	94.6 - 96.5
846	-CH ₃	-H	-H	-cyclo-C ₆ H ₁₁	-H	-H	162 - 163.9
847	-CH ₃	-Ph	-H	-H	-H	-H	146.8 - 149
848	-CH ₃	-H	-H	-CH=CHPh	-H	-H	178.5 - 181.8
849	-CH ₃	-H	-CF ₃	-H	-CF ₃	-H	154 - 156.2
							CDCl ₃ , 1.59(3H, s), 2.34(4H, bs), 2.50-2.59(2H, m), 2.53(1H, d, J=14.8Hz), 2.67-2.76(2H, m), 2.85(1H, d, J=14.8Hz), 3.41(1H, d, J=12.9Hz), 3.47(1H, d, J=12.9Hz), 3.87(1H, d, J=9.6Hz), 4.30(1H, d, J=9.6Hz), 7.23-7.33(5H, m), 7.53(1H, s)
850	-CH ₃	-H	-H	-H	-H	-H	CDCl ₃ , 1.58(3H, s), 2.30(4H, br), 2.49-2.57(2H, m), 2.52(1H, d, J=14.9Hz), 2.65-2.73(2H, m), 2.84(1H, d, J=14.9Hz), 2.93(6H, s), 3.34(2H, d, J=3.50Hz), 3.86(1H, d, J=9.6Hz), 4.30(1H, d, J=9.6Hz), 6.67(2H, d, J=8.7Hz), 7.11(2H, d, J=8.7Hz), 7.52(1H, s)
851	-CH ₃	-H	-H	-N(CH ₃) ₄	-H	-H	CDCl ₃ , 1.59(3H, s), 2.31(4H, br), 2.50-2.58(2H, m), 2.53(1H, d, J=14.8Hz), 2.65-2.74(2H, m), 2.84(1H, d, J=14.8Hz), 3.35(1H, d, J=13.0Hz), 3.41(1H, d, J=13.0Hz), 3.79(3H, s), 3.88(1H, d, J=9.7Hz), 4.30(1H, d, J=9.7Hz), 6.83(2H, d, J=8.6Hz), 7.17(2H, d, J=8.6Hz), 7.52(1H, s)
852	-CH ₃	-H	-H	-OCH ₃	-H	-H	CDCl ₃ , 1.61(3H, s), 2.30-2.73(9H, m), 2.84(1H, d, J=14.8Hz), 3.49(2H, s), 3.87(1H, d, J=9.7Hz), 3.95(2H, s), 4.30(1H, d, J=9.7Hz), 7.09-7.33(9H, m), 7.52(1H, s)
853	-CH ₃	-H	-H	-CH ₂ Ph	-H	-H	

Table 37



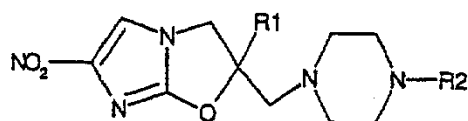
Example	R1	R2	R3	R4	R5	R6	mp(°C) or 1H NMR
854	-CH ₃	-H	-H	-Cl	-H	-H	176.8 - 181.3
855	-CH ₃	-H	-H	-Cl	-Cl	-H	111.8 - 114.8
856	-CH ₃	-H	-H	-OCH ₃	-H	-H	183.3 - 186.6
857	-CH ₃	-H	-H	-H	-H	-Cl	123.5 - 125.3
858	-CH ₃	-H	-H	-H	-H	-H	CDCl ₃ ; 1.59(3H, s), 2.37(4H, bs), 2.51-2.61(2H, m), 2.54(1H, d, J=14.8Hz), 2.69-2.76(2H, m), 2.86(1H, d, J=14.8Hz), 3.44(1H, d, J=13.1Hz), 3.51(1H, d, J=13.1Hz), 3.88(1H, d, J=9.6Hz), 4.31(1H, d, J=9.6Hz), 7.29-7.36(3H, m), 7.39-7.47(2H, m), 7.51-7.60(4Hm), 7.53(1H, s)
859	-CH ₃	-H	-H	-CF ₃	-H	-H	CDCl ₃ ; 1.60(3H, s), 2.37-2.75(9H, m), 2.87(1H, d, J=14.9Hz), 3.49(2H, s), 3.88(1H, d, J=9.6Hz), 4.30(1H, d, J=9.6Hz), 7.37(1H, d, J=8.0Hz), 7.53(1H, s), 7.54(1H, d, J=8.0Hz), 7.68(4H, s)
860	-CH ₃	-H	-H	-OCF ₃	-H	-H	CDCl ₃ ; 1.60(3H, s), 2.38(4H, br), 2.55(1H, d, J=14.9Hz), 2.60(2H, br), 2.71-2.76(2H, m), 2.87(1H, d, J=14.9Hz), 3.50(2H, s), 3.89(1H, d, J=9.7Hz), 4.30(1H, d, J=9.7Hz), 7.27(2H, d, J=6.6Hz), 7.36(2H, d, J=8.1), 7.47-7.52(2H, m), 7.53(1H, s), 7.55-7.61(2H, m)

Table 38



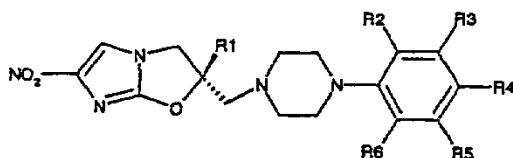
Example	R1	R2	mp(°C)
861	-CH ₃		134 - 138.8
862	-CH ₃		188.6 - 190.7
863	-CH ₃		127 - 131.5
864	-CH ₃		156 - 158.6
865	-CH ₃		102.8-104.9
866	-CH ₃		129 - 133
867	-CH ₃		164.0-168.5
868	-CH ₃		221.5 - 222.3
869	-CH ₃		158 - 159.4
870	-CH ₃		105 - 107
871	-CH ₃		142 - 145.4

Table 39



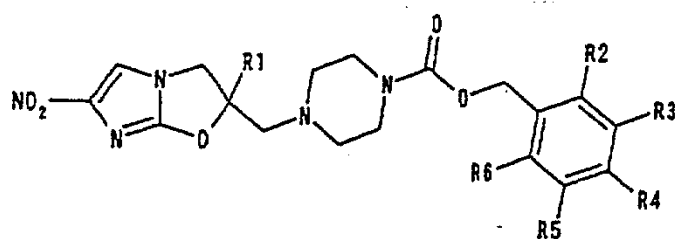
Example	R1	R2	mp(°C)
872	-CH ₃		196 - 199.4
873	-CH ₃		102 - 104
874	-CH ₃		215.5 - 217
875	-CH ₃		195 - 197.8

Table 40



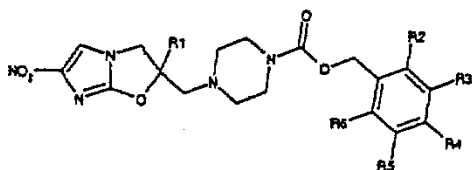
Example	R1	R2	R3	R4	R5	R6	mp(°C) or ¹ H NMR
876	-H	-H	-H	-CF ₃	-H	-H	175.8 - 176.6
877	-CH ₃	-H	-H	-H	-H	-H	180.6 - 184.2
878	-CH ₃	-H	-H	-F	-H	-H	175 - 179.5
879	-CH ₃	-H	-H	-OCH ₃	-H	-H	172 - 172.5
880	-CH ₃	-H	-H	-CO ₂ C ₂ H ₅	-H	-H	175 - 179.2
881	-CH ₃	-H	-H	-CH ₃	-H	-H	185 - 185.5
882	-CH ₃	-H	-H	-Cl	-Cl	-H	177 - 177.3
883	-CH ₃	-H	-H	-H	-CF ₃	-H	171.6 - 173.6
884	-CH ₃	-H	-H	-H	-H	-CF ₃	179.5 - 180.3
885	-CH ₃	-H	-H	-Cl	-CF ₃	-H	170.5 - 171.2
886	-CH ₃	-H	-H	-CO ₂ H	-H	-H	248 - 252
887	-CH ₃	-H	-H	-H	-H	-F	191 - 192.2
888	-CH ₃	-H	-H	-N(CH ₃) ₂	-H	-H	206 - 207
889	-H	-H	-H	-F	-H	-H	178.5 - 179.5
890	-H	-H	-H	-CN	-H	-H	211 - 211.5
891	-H	-H	-H	-Cl	-H	-H	183 - 183.5
892	-CH ₃	-H	-H	-CF ₃	-H	-H	CDCl ₃ : 1.64(3H, s), 2.59-2.75(2H, m), 2.62(1H, d, J=15Hz), 2.80-2.95(2H, m), 2.93(1H, d, J=15Hz), 3.00-3.25(4H, m), 3.94(1H, d, J=10Hz), 4.35(1H, d, J=10Hz), 6.86(2H, d, J=8Hz), 7.46(2H, d, J=8Hz), 7.53(1H, s)
893	-CH ₃	-H	-H	CO ₂ C(CH ₃) ₃	-H	-H	198.5 - 200.5

Table 41



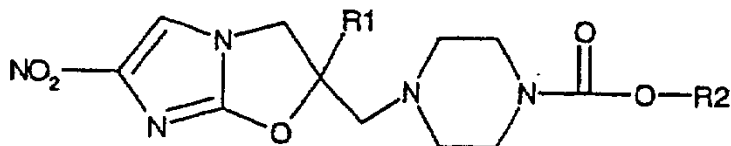
Example	R1	R2	R3	R4	R5	R6	mp(°C)
894	-CH ₃	-H	-H	-Cl	-H	-H	144.2 - 145.6
895	-CH ₃	-H	-H	-OCF ₃	-H	-H	153 - 156.9
896	-CH ₃	-H	-H	-Cl	-Cl	-H	114.5 - 116.6
897	-CH ₃	-H	-H	-H	-Cl	-H	132.4 - 136.3
898	-CH ₃	-H	-H	-H	-H	-Cl	143.5 - 145
899	-CH ₃	-H	-H	-Br	-H	-H	151 - 152
900	-CH ₃	-H	-H	-Ph	-H	-H	134 - 135.2
901	-CH ₃	-H	-H	-CO ₂ CH ₃	-H	-H	127 - 130.5
902	-CH ₃	-H	-H	-OCH ₃	-H	-H	128 - 130
903	-CH ₃	-H	-H	-OCH ₂ Ph	-H	-H	128 - 131
904	-CH ₃	-Cl	-H	-H	-H	-Cl	142 - 145.5
905	-CH ₃	-H	-Cl	-H	-Cl	-H	132 - 135.3
906	-CH ₃	-H	-H	-H	-CF ₃	-H	117 - 118
907	-CH ₃	-H	-H	-CH ₃	-H	-H	117 - 118
908	-CH ₃	-H	-H	-H	-OCH ₃	-H	106 - 108
909	-CH ₃	-H	-H	-H	-H	-CH ₃	143 - 145
910	-CH ₃	-H	-H	-H	-H	-OCH ₃	127 - 130
911	-CH ₃	-H	-H	-H	-H	-CF ₃	144 - 145
912	-CH ₃	-H	-H	-OC ₂ H ₅	-H	-H	126 - 127
913	-CH ₃	-H	-H	-NO ₂	-H	-H	156 - 158
914	-CH ₃	-H	-CF ₃	-H	-CF ₃	-H	159 - 160
915	-CH ₃	-H	-H	-CN	-H	-H	125 - 129
916	-CH ₃	-H	-H	-C(CH ₃) ₃	-H	-H	147 - 149
917	-CH ₃	-H	-H	-H	-CH ₃	-H	125 - 127
918	-CH ₃	-H	-H	-CH ₃	-CH ₃	-H	135 - 138
919	-CH ₃	-H	-H	-OCH ₃	-OCH ₃	-H	149 - 151
920	-CH ₃	-H	-H	-H	-H	-F	131 - 133
921	-CH ₃	-H	-H	-C ₂ H ₅	-H	-H	144 - 146
922	-CH ₃	-H	-H	-SO ₂ CH ₃	-H	-H	112 - 115
923	-CH ₃	-H	-H	-CON(CH ₃) ₂	-H	-H	108 - 111
924	-CH ₃	-H	-H	-CONHC ₂ H ₅	-H	-H	124 - 126
925	-CH ₃	-H	-H	-OCH(CH ₃) ₂	-H	-H	122 - 123
926	-CH ₃	-H	-H	-OSO ₂ CH ₃	-H	-H	100 - 104
927	-CH ₃	-H	-H	-I	-H	-H	132 - 134
928	-CH ₃	-H	-H	-NHCOCH ₃	-H	-H	105 - 109
929	-CH ₃	-H	-H	-CONH ₂	-H	-H	159 - 161
930	-CH ₃	-H	-H	-F	-Cl	-H	148 - 149

Table 42



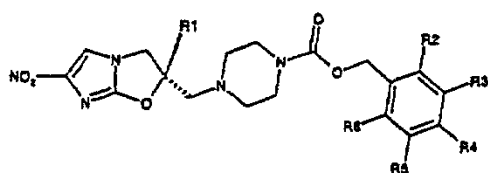
Example	R1	R2	R3	R4	R5	R6	mp(°C) or ¹ H NMR
931	-CH ₃	-H	-H	-F	-H	-H	CDCl ₃ , 1.62(3H, s), 2.38-2.70(4H, bm), 2.56(1H, d, J=14.9Hz), 2.87(1H, d, J=14.9Hz), 3.41(4H, bs), 3.92(1H, d, J=9.7Hz), 4.28(1H, d, J=9.7Hz), 5.06(2H, s), 6.99-7.07(2H, m), 7.28-7.34(2H, m), 7.53(1H, s)
932	-CH ₃	-H	-H	-CF ₃	-H	-H	CDCl ₃ , 1.62(3H, s), 2.45-2.75(4H, bm), 2.58(1H, d, J=14.9Hz), 2.86(1H, d, J=14.9Hz), 3.20-3.60(4H, br), 3.94(1H, d, J=9.8Hz), 4.29(1H, d, J=9.8Hz), 5.15(2H, s), 7.44(1H, d, J=8.0Hz), 7.54(1H, s), 7.61(1H, d, J=8.0Hz)
933	-CH ₃	-H	-H	-OH	-H	-H	CDCl ₃ , 1.59(3H, s), 2.30-2.70(4H, m), 2.56(1H, d, J=15Hz), 2.86(1H, d, J=15Hz), 3.10-3.55(4H, m), 3.91(1H, d, J=10Hz), 4.28(1H, d, J=10Hz), 5.03(2H, s), 5.30(1H, brs), 6.84(2H, d, J=8Hz), 7.24(2H, d, J=8Hz), 7.53(1H, s)
934	-CH ₃	-H	-H	-NH ₂	-H	-H	CDCl ₃ , 1.61(3H, s), 2.35-2.70(4H, m), 2.56(1H, d, J=15Hz), 2.85(1H, d, J=15Hz), 3.05-3.55(4H, m), 3.69(2H, brs), 3.91(1H, d, J=10Hz), 4.28(1H, d, J=10Hz), 4.98(2H, s), 6.55(2H, d, J=8Hz), 7.14(2H, d, J=8Hz), 7.53(1H, s)
935	-CH ₃	-H	-H	(CH ₃) ₃ C(CH ₃) ₂ Si-	-H	-H	114 - 115
936	-CH ₃	-H	-H	(CH ₃) ₃ COCONH-	-H	-H	124 - 127

Table 43



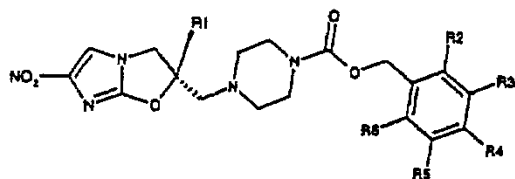
Example	R1	R2	mp(°C)
937	-CH ₃	-(CH ₂) ₂ Ph	143.5 - 144.6
938	-CH ₃	4-ClPh(CH ₂) ₂ -	118 - 119
939	-CH ₃	4-ClPhCH=CHCH ₂ -	121 - 123.3
940	-CH ₃	4-CF ₃ PhCH=CHCH ₂ -	121 - 122
941	-CH ₃	4-CF ₃ OPhCH=CHCH ₂ -	127 - 128

Table 44



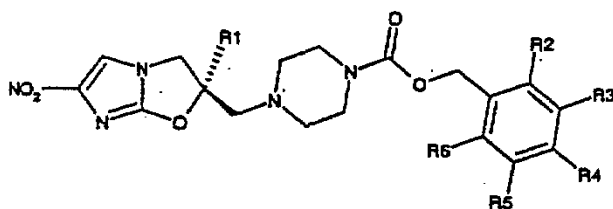
Example	R1	R2	R3	R4	R5	R6	mp(°C) or ¹ H NMR
942	-CH ₃	-H	-H	-H	-Cl	-H	83-85
943	-CH ₃	-H	-H	-F	-H	-H	174-175
944	-CH ₃	-H	-H	-H	-H	-CH ₃	187-188.5
945	-CH ₃	-H	-H	-H	-H	-H	163.5-165.5
946	-CH ₃	-H	-H	-Cl	-H	-H	172.5-174
947	-H	-H	-H	-OCF ₃	-H	-H	128-129
948	-CH ₃	-H	-H	-Cl	-Cl	-H	97-98
949	-CH ₃	-H	-H	-F	-F	-H	115-116
950	-CH ₃	-H	-H	-H	-F	-F	101-103
951	-CH ₃	-H	-F	-H	-F	-H	85-87
952	-CH ₃	-F	-F	-F	-F	-F	143-144
953	-CH ₃	-F	-H	-F	-H	-F	92-95
954	-CH ₃	-H	-F	-H	-H	-F	144-146
955	-CH ₃	-F	-H	-H	-H	-F	169-170
956	-CH ₃	-H	-H	-F	-H	-F	178-182
957	-CH ₃	-H	-H	-H	-F	-H	112-115
958	-CH ₃	-H	-H	-H	-CF ₃	-H	78-80
959	-CH ₃	-H	-H	-H	-H	-F	175-176
960	-CH ₃	-H	-H	-Br	-H	-H	166-167
961	-H	-H	-H	-F	-H	-H	121.5-122
962	-H	-H	-H	-Cl	-H	-H	112.9-116.7
963	-H	-H	-H	-Cl	-Cl	-H	105.5-106
964	-H	-H	-H	-H	-Cl	-H	97.5-98
965	-H	-H	-H	-H	-F	-H	93-94
966	-CH ₃	-H	-H	-OCHF ₂	-H	-H	134-135
967	-CH ₃	-H	-H	-F	-OCH ₃	-F	71-74
968	-CH ₃	-H	-H	-F	-OCHF ₂	-F	84-86
969	-CH ₃	-H	-H	-Cl	-OCHF ₂	-H	85-87
970	-CH ₃	-H	-H	-Cl	-H	-H	180-181
971	-CH ₃	-H	-H	-CF ₃	-H	-H	185-187
972	-CH ₃	-H	-H	-OCF ₃	-H	-H	172-173
973	-CH ₃	-H	-H	-OCH ₂ CF ₃	-H	-H	76-80
974	-CH ₃	-H	-H	-Cl	-OCH ₂ CF ₃	-H	139-140

Table 45



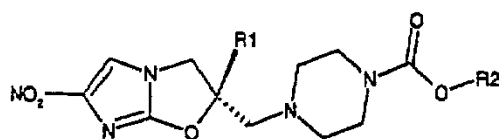
Example	R1	R2	R3	R4	R5	R6	mp(°C) or ¹ H NMR
975	-CH ₃	-H	-H	-OCH ₂ CF ₃	-Cl	-H	CDCl ₃ , 1.62(3H, s), 2.40-2.75(4H, m), 2.57(1H, d, J=15Hz), 2.87(1H, d, J=15Hz), 3.05-3.50(4H, m), 3.92(1H, d, J=10Hz), 4.28(1H, d, J=10Hz), 4.40(2H, q, J=8Hz), 5.02(2H, s), 6.40(2H, d, J=8Hz), 7.21(2H, dd, J=8,2Hz), 7.39(1H, d, J=2Hz), 7.53(1H, s)
976	-CH ₃	-H	-H	-OCHF ₂	-Cl	-H	CDCl ₃ , 1.62(3H, s), 2.40-2.70(4H, m), 2.59(1H, d, J=15Hz), 2.87(1H, d, J=15Hz), 3.10-3.55(4H, m), 3.96(1H, d, J=10Hz), 4.30(1H, d, J=10Hz), 5.13(2H, s), 6.53(1H, t, J=73Hz), 7.10-7.30(2H, m), 7.42(1H, s), 7.55(1H, s)
977	-CH ₃	-H	-H	-Br	-OCHF ₂	-F	CDCl ₃ , 1.62(3H, s), 2.40-2.65(4H, m), 2.59(1H, d, J=15Hz), 2.86(1H, d, J=15Hz), 3.00-3.50(4H, m), 3.96(1H, d, J=10Hz), 4.29(1H, d, J=10Hz), 5.14(2H, s), 6.59(1H, t, J=73Hz), 7.17(1H, m), 7.39(1H, m), 7.55(1H, s)

Table 46



Example	R1	R2	R3	R4	R5	R6	mp(°C)
978	-CH ₃	-H	-H	-CF ₃	-H	-H	139.8 141.7
979	-CH ₃	-H	-H	-H	-Cl	-H	108 - 111
980	-CH ₃	-H	-H	-H	-H	-CH ₃	185 - 186
981	-CH ₃	-H	-H	-Cl	-CF ₃	-H	115 - 115.5
982	-CH ₃	-H	-H	-CF ₃	-CH ₃	-H	91 - 91.5
983	-CH ₃	-H	-H	-SCF ₃	-H	-H	136.5 - 137
984	-CH ₃	-H	-H	-F	-Cl	-H	72.5 - 73
985	-CH ₃	-H	-H	-Cl	-H	-CH ₃	178.5 - 179

Table 47



Example	R1	R2	mp(°C)
986	-CH ₃	-CH ₂ -cyclo-C ₆ H ₁₁	101 - 103
987	-CH ₃	-cyclo-C ₆ H ₁₁	189.6 - 191.6
988	-CH ₃	-CH ₂ CF ₃	123.5 - 124
989	-CH ₃	-CH ₂ CH=C(CH ₃) ₂	138 - 138.5
990	-CH ₃	(E)-3,4-Cl ₂ PhCH=CHCH ₂ -	145 - 148
991	-CH ₃	(E)-4-ClPhCH=CHCH ₂ -	124 - 125
992	-CH ₃	(E)-4-CF ₃ OPhCH=CHCH ₂ -	60 - 61
993	-H	(E)-4-ClPhCH=CHCH ₂ -	113 - 114
994	-H	(E)-4-ClPhC(CH ₃)=CHCH ₂ -	109 - 110
995	-H	(Z)-4-ClPhC(CH ₃)=CHCH ₂ -	95 - 96
996	-CH ₃	(E)-4-CF ₃ PhCH=CHCH ₂ -	132 - 133
997	-CH ₃	(Z)-4-CF ₃ PhCH=CHCH ₂ -	138 - 140
998	-CH ₃	(E)-3-CF ₃ -4-ClPhCH=CHCH ₂ -	147 - 149
999	-CH ₃	(E)-4-FPhCH=CHCH ₂ -	155 - 156
1000	-CH ₃	(E)-4-CF ₃ PhCH=C(CH ₃)CH ₂ -	122 - 123
1001	-CH ₃	(4-CF ₃ Ph) ₂ C=CHCH ₂ -	145 - 146
1002	-CH ₃	4-ClPh(CH ₂) ₂ -	150 - 151
1003	-CH ₃	4-ClPh(CH ₂) ₃ -	96 - 97
1004	-CH ₃	4-ClPh(CH ₂) ₄ -	78 - 82
1005	-CH ₃	4-ClPhO(CH ₂) ₂ -	138 - 139
1006	-CH ₃	4-CF ₃ OPh(CH ₂) ₃ -	46 - 48
1007	-CH ₃	4-CF ₃ Ph(CH ₂) ₃ -	118 - 120
1008	-CH ₃	4-CF ₃ PhO(CH ₂) ₂ -	104 - 108
1009	-CH ₃	4-CF ₃ OPhN(CH ₃)(CH ₂) ₂ -	102 - 104
1010	-CH ₃	(E)-4-ClPhC(CH ₃)=CHCH ₂ -	CDCl ₃ , 1.62(3H, s), 2.02-2.10(3H, m), 2.57(1H, d, J=14.9Hz), 2.40-2.73(4H, m), 2.87(1H, d, J=14.9Hz), 3.06-3.62(4H, m), 3.93(1H, d, J=9.7Hz), 4.29(1H, d, J=9.7Hz), 4.76(2H, m), 5.87(1H, dt, J=1.3Hz, 6.7Hz), 7.23-7.37(4H, m), 7.54(1H, s)
1011	-CH ₃	(Z)-4-ClPhC(CH ₃)=CHCH ₂ -	CDCl ₃ , 1.62(3H, s), 2.02-2.10(3H, m), 2.58(1H, d, J=14.9Hz), 2.36-2.72(4H, m), 2.86(1H, d, J=14.9Hz), 3.04-3.56(4H, m), 3.94(1H, d, J=9.8Hz), 4.30(1H, d, J=9.8Hz), 4.46(2H, m), 5.66(1H, dt, J=1.4Hz, 7.0Hz), 7.04-7.12(2H, m), 7.23-7.35(2H, m), 7.53(1H, s)

Table 48

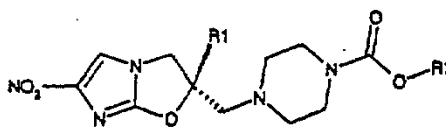
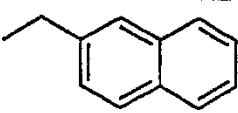
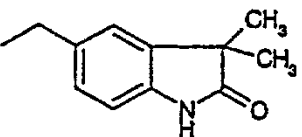
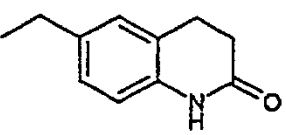
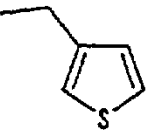
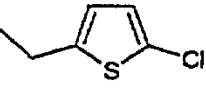
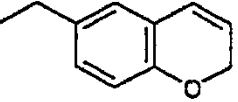
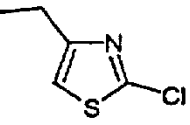
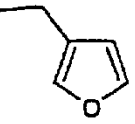
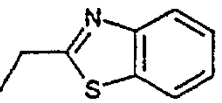
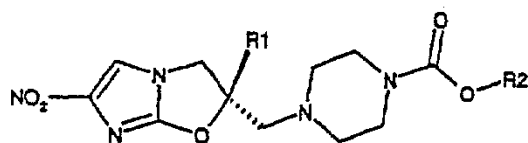
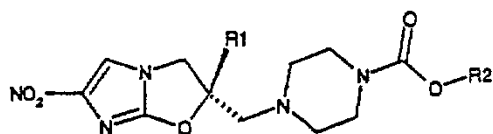
			
Example	R1	R2	mp(°C)
1012	-CH ₃		80 - 85
1013	-CH ₃		120 - 140
1014	-CH ₃		189 - 190
1015	-CH ₃		196.1 - 199.1
1016	-CH ₃		137.4 - 139.2
1017	-CH ₃		71 - 76.4
1018	-CH ₃		121.1 - 122.1
1019	-CH ₃		177.1 - 178.9
1020	-CH ₃		158.5 - 160.4

Table 49



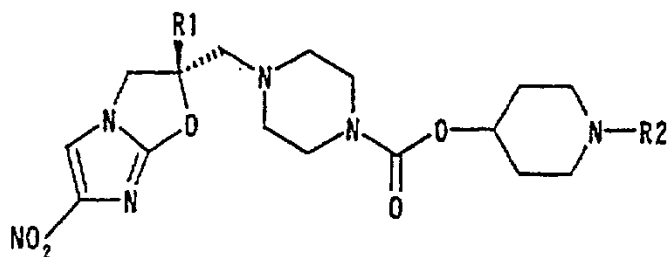
Example	R1	R2	mp(°C)
1021	-CH ₃		193.4 - 195.9
1022	-CH ₃		203.6 - 204.9
1023	-CH ₃		89.7 - 91.8
1024	-CH ₃		185.2 - 187.5
1025	-CH ₃		93.6 - 96.5
1026	-CH ₃		215.3 - 216.4
1027	-CH ₃		180.7 - 182.3
1028	-CH ₃		170.2 - 170.6
1029	-CH ₃		134.3 - 135.7
1030	-CH ₃		83.6 - 86.3
1031	-CH ₃		191.8 - 192.9

Table 50



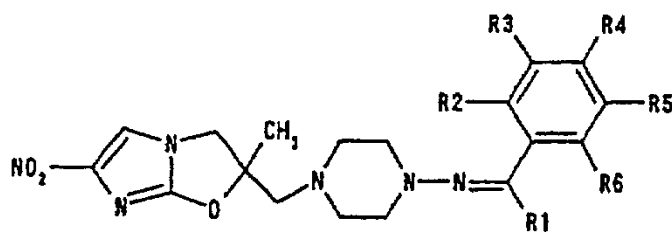
Example	R1	R2	mp(°C) or ¹ H NMR
1032	-CH ₃		174.3 - 179.2
1033	-CH ₃		108.9 - 113.1
1034	-CH ₃		193.5 - 194.7
1035	-H		152 - 153.5
1036	-H		190.3 - 191.2
1037	-H		177.5 - 180.9
1038	-CH ₃		127.5 - 128.1
1039	-CH ₃		140 - 141.5
1040	-CH ₃		114 - 117
1041	-CH ₃		CDCl ₃ , 1.40-1.62(5H, m), 1.80-1.93(2H, br), 2.46-2.64(13H, m), 2.87(1H, d, J=14.9Hz), 3.37(4H, br), 3.92(1H, d, J=9.7Hz), 4.20(2H, t, J=6.1), 7.53(1H, s)

Table 51



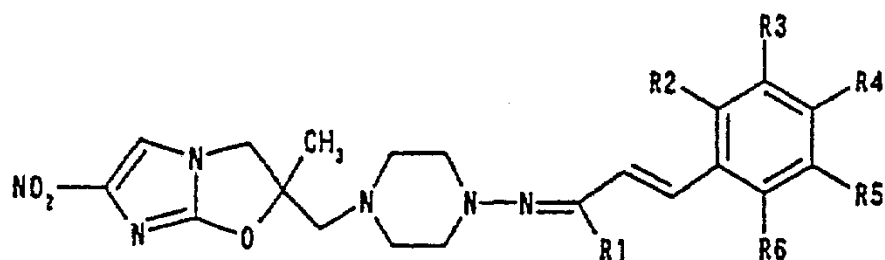
Example	R1	R2	mp(°C)
1042	-CH ₃	4-CF ₃ OPh-	160.5 - 161.4
1043	-CH ₃	4-CF ₃ Ph-	158.6 - 160.6
1044	-CH ₃	4-CH ₃ OPh-	138.5 - 139.5
1045	-CH ₃	Ph-	163 - 163.5
1046	-CH ₃	4-FPh-	159 - 160
1047	-CH ₃	PhCH ₂ -	141.5 - 142
1048	-CH ₃	4-ClPh-	177 - 178
1049	-CH ₃	4-NCPh-	158 - 159
1050	-CH ₃	4-ClPhCH ₂ -	144 - 145
1051	-CH ₃	4-CF ₃ PhCH ₂ -	95.5 - 97
1052	-CH ₃	4-CF ₃ OPhCH ₂ -	143 - 143.5
1053	-CH ₃	4-CF ₃ PhCO-	160.5 - 162.4
1054	-CH ₃	4-ClPhCO-	218 - 220.3
1055	-CH ₃	4-CF ₃ OPhCO-	169.8 - 172.7

Table 52



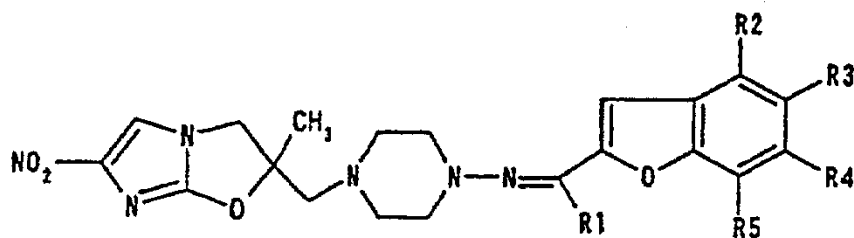
Example	R1	R2	R3	R4	R5	R6	Mp(°C)
1056	-H	-H	-H	-CF ₃	-H	-H	215.3 - 217.8
1057	-H	-H	-H	-Br	-H	-H	219.2 - 221.3
1058	-H	-F	-H	-Br	-H	-H	198.8 - 200.5
1059	-H	-H	-F	-Cl	-H	-H	199 - 199.5
1060	-H	-H	-H	-CN	-H	-H	180.2 - 184.1
1061	-H	-F	-F	-F	-H	-H	188.5 - 189.2
1062	-H	-H	-F	-F	-F	-H	191.7 - 192.6
1063	-H	-F	-H	-Cl	-H	-H	202.8 - 203.3

Table 53



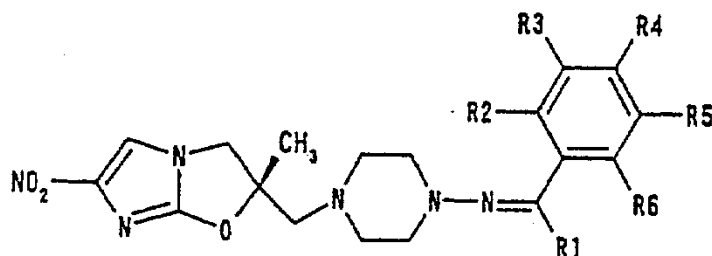
Example	R1	R2	R3	R4	R5	R6	mp(°C)
1064	-H	-H	-H	-Cl	-H	-H	214.2 - 214.8
1065	-H	-H	-Cl	-Cl	-H	-H	204.1 - 205.7
1066	-H	-H	-CF ₃	-H	-H	-H	127.8 - 131.8
1067	-H	-H	-H	-OCF ₃	-H	-H	204.2 - 205.3
1068	-H	-H	-H	-F	-H	-H	199.2 - 200.2

Table 54



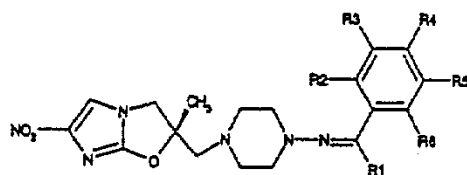
Example	R1	R2	R3	R4	R5	mp(°C)
1069	-H	-H	-Cl	-H	-H	164.6 - 165.9
1070	-H	-H	-CF ₃	-H	-H	194.9 - 196
1071	-H	-H	-OCF ₃	-H	-H	211.7 - 212.1
1072	-H	-H	-H	-CF ₃	-H	182.9 - 185.9

Table 55



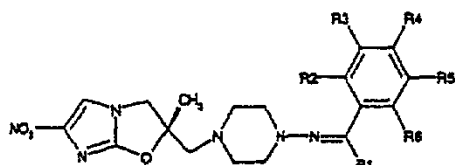
Example	R1	R2	R3	R4	R5	R6	mp(°C)
1073	-H	-H	-H	-F	-H	-H	202.5 - 203.1
1074	-H	-H	-H	-OCH ₃	-H	-H	205.4 - 206.4
1075	-H	-H	-H	-Cl	-H	-Cl	162.7 - 164
1076	-H	-H	-H	-Cl	-H	-H	233.7 - 236.2
1077	-H	-H	-H	-1-PYRRYL	-H	-H	249.1 - 249.7
1078	-H	-H	-H	-Ph	-H	-H	211.6 - 212
1079	-H	-H	-H	-OCH ₂ Ph	-H	-H	202.2 - 203.9
1080	-H	-H	-H	-Br	-H	-H	224.4 - 226.2
1081	-H	-H	-H	-OC ₈ H ₁₇	-H	-H	156.8 - 158.3
1082	-H	-H	-H	-CN	-H	-H	197.8 - 198.7
1083	-H	-H	-H	-OPh	-H	-H	198.1 - 200.1
1084	-H	-H	-F	-F	-F	-H	193.8 - 196
1085	-H	-CH ₃	-H	-CH ₃	-H	-CH ₃	177.9 - 178.3
1086	-H	-CH ₃	-H	-H	-H	-CH ₃	175.7 - 178.2
1087	-H	-H	-CF ₃	-H	-CF ₃	-H	200.2 - 202.3
1088	-H	-H	-H	-Cl	-F	-H	197.2 - 199.2
1089	-H	-H	-H	-Br	-H	-F	206.1 - 207.4
1090	-H	-H	-H	-F	-F	-F	174 - 174.7
1091	-H	-H	-H	-Cl	-H	-F	202.8 - 203.7
1092	-H	-H	-H	-C ₄ H ₉	-H	-H	162.2 - 165.1
1093	-H	-H	-H	-N(Ph) ₂	-H	-H	182.6 - 186.4
1094	-H	-H	-H	-H	-Cl	-Cl	223.5 - 224.5
1095	-H	-H	-H	-I	-H	-H	217 - 221.1
1096	-H	-H	-H	-1-(1,2,4-triazolyl)	-H	-H	200.6 - 202.3

Table 56



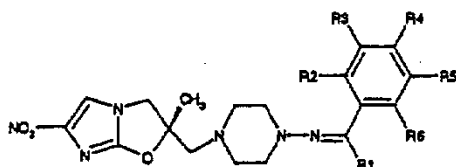
Example	R1	R2	R3	R4	R5	R6	MS
1097	-H	-H	-H	-H	-H	-H	370
1098	-H	-Cl	-H	-H	-H	-H	404
1099	-H	-H	-Cl	-H	-H	-H	404
1100	-H	-F	-H	-H	-H	-H	388
1101	-H	-H	-H	-CH(CH ₃) ₂	-H	-H	412
1102	-H	-H	-H	-NO ₂	-H	-H	415
1103	-H	-CF ₃	-H	-H	-H	-H	438
1104	-H	-H	-CF ₃	-H	-H	-H	438
1105	-H	-H	-H	-C(CH ₃) ₃	-H	-H	426
1106	-H	-H	-H	-OC ₂ H ₅	-H	-H	414
1107	-H	-Cl	-Cl	-H	-Cl	-H	472
1108	-H	-Cl	-Cl	-H	-H	-Cl	472
1109	-H	-H	-H	-H	-OPh	-H	462
1110	-H	-H	-F	-H	-H	-F	406
1111	-H	-F	-H	-F	-H	-H	406
1112	-H	-H	-H	-F	-F	-H	406
1113	-H	-H	-F	-H	-F	-H	406
1114	-H	-H	-H	-F	-F	-F	424
1115	-H	-H	-F	-H	-F	-F	424
1116	-H	-F	-H	-H	-F	-F	424
1117	-H	-H	-F	-F	-H	-F	424
1118	-H	-F	-H	-F	-H	-F	424
1119	-H	-OCF ₃	-H	-H	-H	-H	454
1120	-H	-H	-H	-C ₂ H ₅	-H	-H	398
1121	-H	-H	-H	-H	-Br	-H	448
1122	-H	-Br	-H	-H	-H	-H	448
1123	-H	-H	-H	-H	-F	-F	406
1124	-H	-Cl	-H	-H	-H	-Cl	438
1125	-H	-OC ₂ H ₅	-H	-H	-H	-H	414
1126	-H	-H	-H	-OC ₄ H ₉	-H	-H	442
1127	-H	-H	-H	-H	-H	-OCH ₂ Ph	476
1128	-H	-H	-H	-H	-NO ₂	-H	415
1129	-H	-H	-H	-H	-OCF ₃	-H	454
1130	-H	-H	-H	-Cl	-Cl	-H	438
1131	-H	-Cl	-H	-H	-Cl	-H	438
1132	-H	-H	-H	-H	-OCOCH ₃	-H	428
1133	-H	-NO ₂	-H	-H	-H	-H	415
1134	-H	-H	-H	-H	-F	-H	388
1135	-H	-H	-Cl	-H	-Cl	-H	438
1136	-H	-H	-H	-H	-CN	-H	395
1137	-H	-H	-OCH ₃	-H	-H	-H	400
1138	-H	-OCH ₃	-OCH ₃	-H	-H	-H	430
1139	-H	-OCH ₃	-H	-OCH ₃	-H	-H	430
1140	-H	-OCH ₃	-H	-H	-OCH ₃	-H	430

Table 57



Example	R1	R2	R3	R4	R5	R6	MS
1141	-H	-H	-H	-OCH ₃	-OCH ₃	-H	430
1142	-H	-H	-H	-OCH ₃	-OCH ₃	-OCH ₃	460
1143	-H	-H	-Cl	-H	-H	-NO ₂	449
1144	-H	-H	-H	-OCH ₃	-H	-NO ₂	445
1145	-H	-H	-OCH ₃	-H	-H	-NO ₂	445
1146	-H	-H	-H	-H	-Ph	-H	446
1147	-H	-NHSO ₂ CH ₃	-H	-H	-H	-H	463
1148	-H	-H	-H	-CH ₃	-H	-H	384
1149	-H	-H	-H	-CH ₃	-CH ₃	-H	398
1150	-H	-CH ₃	-H	-CH ₃	-H	-H	398
1151	-H	-H	-H	-H	-CH ₃	-H	384
1152	-H	-H	-CH ₃	-H	-H	-CH ₃	398
1153	-H	-H	-H	-H	-H	-CH ₃	384
1154	-H	-H	-H	-H	-CH ₃	-CH ₃	398
1155	-H	-H	-H	-OCOCH ₃	-H	-H	428
1156	-H	-H	-H	-OC ₂ H ₅	-H	-H	428
1157	-H	-H	-H	-NHCOCH ₃	-H	-H	427
1158	-H	-H	-CH ₃	-H	-CH ₃	-H	398
1159	-H	-H	-CH ₃	-CH ₃	-H	-CH ₃	412
1160	-H	-H	-H	-CO ₂ CH ₃	-H	-H	428
1161	-H	-H	-H	-CH=CHPh(trans)	-H	-H	472
1162	-H	-H	-H	-N(CH ₃) ₂	-H	-H	413
1163	-H	-H	-Br	-H	-H	-OCH ₃	478
1164	-H	-H	-H	-F	-H	-Cl	422
1165	-H	-H	-Br	-H	-H	-F	466
1166	-H	-H	-OCH ₃	-H	-H	-F	418
1167	-H	-H	-H	-CH ₂ CH(CH ₃) ₂	-H	-H	426
1168	-H	-Br	-H	-OCH ₃	-OCH ₃	-H	508
1169	-H	-F	-F	-F	-F	-F	460
1170	-H	-H	-H	-N(CH ₃) ₂	-H	-OCH ₃	443
1171	-H	-H	-OCH ₂ Ph	-H	-OCH ₂ Ph	-H	582
1172	-H	-H	-H	-OCH ₂ Ph	-OCH ₂ Ph	-H	582
1173	-H	-H	-H	-H	-OC ₂ H ₅	-H	414
1174	-H	-H	-H	-H	-OCH ₂ Ph	-H	476
1175	-H	-H	-H	-OCH ₂ Ph	-OCH ₃	-H	506
1176	-H	-H	-H	-SC ₂ H ₅	-H	-H	430
1177	-H	-H	-H	-OCHF ₂	-H	-H	436
1178	-H	-H	-H	-OCH(CH ₃) ₂	-H	-H	428
1179	-H	-H	-H	-OCH ₃	-Br	-H	478
1180	-H	-H	-H	-N(C ₂ H ₅) ₂	-H	-H	441
1181	-H	-H	-H	-OCH ₃	-F	-H	418
1182	-H	-H	-H	-OCH ₃	-CH ₃	-H	414
1183	-H	-OCH ₃	-H	-H	-F	-H	418
1184	-H	-Cl	-H	-H	-NO ₂	-H	449

Table 58



Example	R1	R2	R3	R4	R5	R6	MS
1185	-H	-H	-H	-OC ₂ H ₅	-OC ₂ H ₅	-H	458
1186	-H	-H	-H	-OCO CH ₃	-OCH ₃	-H	458
1187	-H	-NO ₂	-H	-OCH ₃	-OCH ₃	-H	475
1188	-H	-H	-H	-SCH ₃	-H	-H	416
1189	-H	-H	-H	-Cl	-NO ₂	-H	449
1190	-H	-H	-H	-SO ₂ CH ₃	-H	-H	448
1191	-H	-H	-H	-OCH ₃	-OCH ₂ Ph	-H	506
1192	-H	-H	-H	-Cl	-CF ₃	-H	472
1193	-H	-I	-H	-H	-H	-H	496
1194	-H	-H	-H	-H	-SCF ₃	-H	470
1195	-H	-OCH ₃	-H	-OCH ₃	-OCH ₃	-H	460
1196	-H	-H	-OCH ₃	-H	-OCH ₃	-H	430
1197	-H	-CO ₂ CH ₃	-H	-H	-H	-H	428
1198	-H	-OCH ₃	-H	-H	-H	-OCH ₃	430
1199	-H	-OCH ₃	-H	-OCH ₃	-H	-OCH ₃	460
1200	-H	-OCHF ₂	-H	-H	-H	-H	436
1201	-H	-H	-Br	-OCH ₃	-OCH ₃	-H	508
1202	-H	-H	-CH ₃	-OCH ₃	-H	-CH ₃	428
1203	-H	-H	-H	-OH	-H	-H	386
1204	-H	-H	-OCH ₃	-OH	-OCH ₃	-H	446
1205	-H	-H	-H	-OH	-H	-OH	402
1206	-H	-H	-H	-H	-H	-OCH ₃	400
1207	-H	-F	-H	-H	-H	-F	406
1208	-H	-H	-H	-3-PYRIDYL	-H	-H	447
1209	-H	-H	-H	-OCH ₂ Ph	-Cl	-H	510
1210	-H	-H	-H	-2-THIENYL	-H	-H	452
1211	-H	-H	-OCH ₃	-OCH ₃	-OCH ₃	-H	460
1212	-H	-H	-H	-cyclo-C ₆ H ₁₁	-H	-H	452
1213	-H	-H	-H	CH ₂ =CHCH ₂ O-	-H	-H	426
1214	-H	-H	-H	Pyrrolidinyl-	-H	-H	439
1215	-H	EtOCOCH ₂ O-	-H	-H	-H	-H	472
1216	-H	-H	-H	-OCH ₃	cyclo-C ₆ H ₉ O-	-H	484
1217	-H	-H	CF ₃ CF ₂ O-	-H	-H	-H	504
1218	-H	-H	-H	Imidazolyl-	-H	-H	436
1219	-H	-H	-H	Piperidino-	-H	-H	453
1220	-H	-H	-H	4-CF ₃ Ph-	-H	-H	514
1221	-H	-H	-H	4-CH ₃ OPh-	-H	-H	476
1222	-H	-H	-H	(CH ₃) ₂ N(CH ₂) ₃ O-	-H	-H	471
1223	-H	-H	-H	Morpholino-	-NO ₂	-H	500
1224	-H	-H	-H	Piperidino-	-NO ₂	-H	498
1225	-H	-H	-H	4-FPh-	-H	-H	464
1226	-H	-H	-H	4-CH ₃ (CH ₂) ₆ Ph-	-H	-H	572
1227	-H	-H	-H	3,4-F ₂ Ph-	-H	-H	482
1228	-H	-H	-H	4-CH ₃ (CH ₂) ₃ Ph-	-H	-H	502
1229	-H	-H	-H	3-Cl-4-FPh-	-H	-H	498