

SUPPORTING INFORMATION

1,2,3-Triazole-containing Uracil Derivatives with Excellent Pharmacokinetics as a Novel Class of Potent Human Deoxyuridine Triphosphatase Inhibitors

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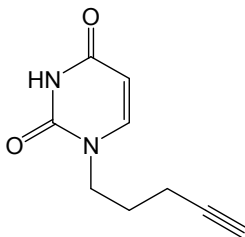
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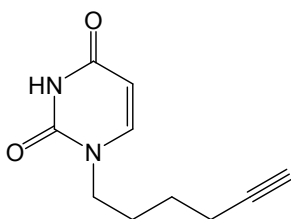
Experimental Section of chemistry

General Methods and Materials. All commercially available starting materials and solvents were reagent grade. Silica gel column chromatography was performed on Merck silica gel 60 (230-400 mesh). ^1H NMR spectra were measured at 270 MHz on a JEOL JNM-EX270 or 400 MHz on a JEOL JNM-LA400. ^{13}C NMR spectra were measured 100 MHz on a JEOL JNM-LA400. Chemical shifts were recorded in parts per million (ppm, δ) and were reported relative to the solvent peak or internal tetramethylsilane peak. High-resolution mass spectra (HRMS) were measured with JEOL JMS-700 (FAB) or Waters micromass Q-ToF-2 (TOF). Chemical purities of tested compounds were determined by combustion analysis or HPLC analysis and confirmed $\geq 95\%$ purity. Combustion analyses (C, H, N) were performed on a Thermo electron Corp. Flash EA 1112 series, and values were within $\pm 0.4\%$ of the theoretical values. Chemical purities of some tested compounds were determined by HPLC analysis with SHIMADZU Prominence HPLC system. Optical rotations were measured by HORIBA SEPA-200 polarimeter.



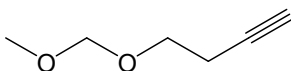
1-(Pent-4-ynyl)pyrimidine-2,4(1H,3H)-dione (**9a**)

To a suspension of 4-pentyn-1-ol **8b** (2.0 g, 23.8 mmol), triphenylphosphine (7.18 g, 28.5 mmol) and 3-*N*-benzoyluracil (6.16 g, 28.5 mmol) in THF (80 mL), was added a solution of diisopropyl azodicarboxylate (1.9 M, 15.0 mL, 28.5 mmol) in toluene at room temperature, the mixture was stirred at room temperature for 3 hr. The reaction mixture was evaporated *in vacuo* and the residue was purified by a silica gel column chromatography (1-2% MeOH in CHCl_3) to give a mixture of 3-benzoyl-1-(pent-4-ynyl)pyrimidine-2,4(1H,3H)-dione and triphenylphosphineoxide. The mixture was dissolved in a solution of methylamine (9.8 M, 10 mL) in MeOH and stirred at room temperature for 1 hr. The reaction mixture was evaporated *in vacuo* and the residue was suspended with CHCl_3 (3 mL). The slurry was filtered, and the resulting cake was washed with CHCl_3 (3 mL \times 3) to give **9a** (2.4 g, 57% as a colorless solid). ^1H NMR ($\text{DMSO}-d_6$) δ 1.76 (2H, quint, $J = 7.2$ Hz), 2.19 (2H, td, $J = 2.4, 6.8$ Hz), 2.82 (1H, t, $J = 2.4$ Hz), 3.71 (2H, t, $J = 7.2$ Hz), 5.54 (1H, d, $J = 8.0$ Hz), 7.60 (1H, d, $J = 8.0$ Hz), 11.21 (1H, brs); EI-HRMS m/z M: Calcd. for $\text{C}_9\text{H}_9\text{N}_2\text{O}_2$, 178.0742; Found, 178.0740



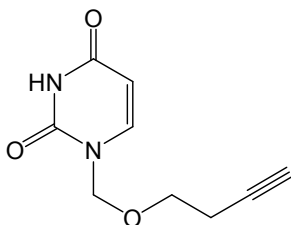
1-(Hex-5-ynyl)pyrimidine-2,4(1H,3H)-dione (**9b**)

To a suspension of 5-hexyn-1-ol **8c** (1.2 g, 12.2 mmol), triphenylphosphine (6.4 g, 24.4 mmol) and 3-*N*-benzoyluracil (3.96 g, 18.3 mmol) in THF (60 mL), was added a solution of diisopropyl azodicarboxylate (1.9 M, 12.8 mL, 24.4 mmol) in toluene at room temperature, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was evaporated *in vacuo* and the residue was purified by a silica gel column chromatography (1-2% MeOH in CHCl₃) to give a mixture of 3-benzoyl-1-(hex-5-ynyl)pyrimidine-2,4(1*H*,3*H*)-dione and triphenylphosphineoxide. The mixture was dissolved in a solution of methylamine (9.8 M, 10 mL) in MeOH and stirred at room temperature for 1 hr. The reaction mixture was evaporated *in vacuo* and the residue was purified by a silica gel column chromatography (2-4% MeOH in CHCl₃) to give **9b** (1.02 g, 43% as a colorless solid). ¹H NMR (DMSO-*d*₆) δ 1.41 (2H, quint, *J* = 7.6 Hz), 1.64 (2H, quint, *J* = 7.6 Hz), 2.16 (2H, td, *J* = 2.8, 7.2 Hz), 2.76 (1H, td, *J* = 0.8, 2.8 Hz), 3.65 (2H, t, *J* = 6.8 Hz), 5.53 (1H, dd, *J* = 0.4, 7.6 Hz), 7.63 (1H, dd, *J* = 7.6, 0.4 Hz), 11.20 (1H, brs); FAB-HRMS *m/z* [M-H]⁺: Calcd. for C₁₀H₁₁N₂O₂, 191.0821; Found, 191.0842



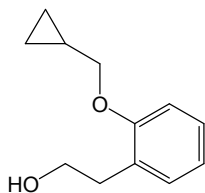
4-(Methoxymethoxy)but-1-yne (**10**)

To a mixture of but-3-yn-1-ol **8a** (3 g, 42.8 mmol) and *N*-ethyldiisopropylamine (22.4 mL, 128 mmol) in CH₂Cl₂ (40 mL), was added chloromethyl methyl ether (4.87 mL, 64.2 mmol) at room temperature, and the mixture was stirred at the same temperature for 5 hr. Saturated aq. NH₄Cl (30 mL) was added and the layers partitioned. The organic layer was washed with saturated aq. NH₄Cl (30 mL×3) and brine (20 mL), dried over Na₂SO₄, and filtered. The filtrate was evaporated *in vacuo* and the residue was co-evaporated with THF (5 mL) to give **11** (2.83 g, 58% as a colorless oil), and it was used for the next step without further purification. ¹H NMR (CDCl₃) δ 2.00 (1H, t, *J* = 2.43 Hz), 2.50 (2H, td, *J* = 2.43, 6.48 Hz), 3.39 (3H, s), 3.67 (2H, t, *J* = 6.48 Hz), 4.66 (2H, s)



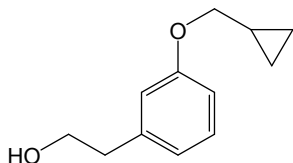
1-((But-3-ynyloxy)methyl)pyrimidine-2,4(1H,3H)-dione (11)

To a solution of **10** (1.0 g, 8.76 mmol) in dichloromethane (15 mL), was added a solution of borontrichloride (3.5 mL, 1.0 M, 3.5 mmol) in dichloromethane at 0 °C. The reaction mixture was stirred at room temperature for 1.5 hr. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in 1,2-dichloroethane (25 mL). Bis(trimethylsilyl)uracil¹ (2.7 g, 10.5 mmol) and iodine (56 mg, 0.22 mmol) were added to the solution, which was stirred at 90 °C for 2 hr. Water (50 mL) and saturated aq. sodium hydrogensulfite (10 mL) were carefully added to the mixture at the same temperature and the layers were partitioned. The organic layer was washed with water (30 mL) and brine (30 mL). The organic layer was dried over Na₂SO₄, and filtered. The filtrate was evaporated *in vacuo* and the residue was purified by silica gel column chromatography (1-4% MeOH in CHCl₃) to give **12** (320 mg, 19% as a colorless solid). ¹H NMR (DMSO-*d*₆) δ 2.36-2.42 (2H, m), 2.79 (1H, m), 3.56 (2H, t, *J* = 6.3 Hz), 5.08 (2H, s), 5.60 (1H, d, *J* = 7.9 Hz), 7.70 (1H, d, *J* = 7.9 Hz), 11.33 (1H, brs); FAB-HRMS *m/z* [M-H]⁻: Calcd. for C₉H₉N₂O₃, 193.0613; Found, 193.0628



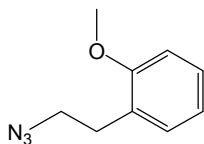
2-(2-(Cyclopropylmethoxy)phenyl)ethanol (13c)

A suspension of 2-hydroxyphenethyl alcohol **12a** (2.0 g, 14.5 mmol), (bromomethyl)cyclopropane (1.64 mL, 16.9 mmol) and potassium carbonate (4.45 g, 32.2 mmol) in DMF (20 mL) was stirred at 90 °C for 5 hr. The mixture was cooled to room temperature and diluted with AcOEt (10 mL), and was then washed with water (10 mL×2) and brine (10 mL). The organic layer was dried over Na₂SO₄, and filtered. The filtrate was evaporated *in vacuo* and the residue was purified by silica gel column chromatography (20-50% AcOEt in hexane) to give **13c** (2.03 g, 73% as a colorless oil). ¹H NMR (CDCl₃) δ 0.35 (2H, dd, *J* = 4.8, 10.0 Hz), 0.63 (2H, dd, *J* = 6.0, 13.2 Hz), 1.26-1.30 (1H, m), 1.97 (1H, brs), 2.95 (2H, t, *J* = 6.4 Hz), 3.83-3.89 (4H, m), 6.83 (1H, d, *J* = 8.0 Hz), 6.90 (1H, t, *J* = 6.8 Hz), 7.15-7.20 (2H, m); FAB-HRMS *m/z* [M+Na]⁺: Calcd. for C₁₂H₁₆O₂Na, 215.1048; Found, 215.1042



2-(3-(Cyclopropylmethoxy)phenyl)ethanol (13d)

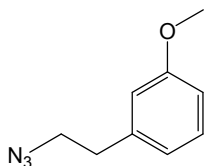
Compound **13d** (2.14 g, 77%, a colorless oil) was synthesized from **12b** (2.0 g, 14.5 mmol) according to the procedure described for the conversion of **12a** to **13c**. ^1H NMR (CDCl_3) δ 0.35 (2H, dd, $J = 4.8, 10.4$ Hz), 0.62-0.67 (2H, m), 1.22-1.32 (1H, m), 1.40 (1H, t, $J = 5.6$), 2.84 (2H, t, $J = 6.4$ Hz), 3.80 (2H, d, $J = 6.8$ Hz), 3.86 (2H, dd, $J = 6.4, 12.4$ Hz), 6.76-6.82 (3H, m), 7.20-7.24 (1H, m); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{12}\text{H}_{16}\text{O}_2\text{Na}$, 215.1048; Found, 215.1069



General procedure for the synthesis of **14a-14d**. Exemplified for

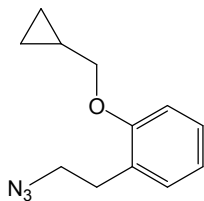
1-(2-Azidoethyl)-2-methoxybenzene (14a)

To a mixture of 2-methoxyphenethyl alcohol **13a** (500 mg, 3.3 mmol) and triethylamine (686 μL) in CH_2Cl_2 (5 mL) was added methanesulfonyl chloride (305 μL , 3.9 mmol) at 0 $^\circ\text{C}$, and the mixture was stirred at room temperature for 30 min. Saturated aq. NaHCO_3 (5 mL) was added and the layers were partitioned. The organic layer was washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was dissolved in DMF (8 mL). To the solution was added sodium azide (643 mg, 9.9 mmol) and the mixture was stirred at 50 $^\circ\text{C}$ for 12 hr. After the mixture was cooled to room temperature and diluted with AcOEt (10 mL), it was then washed with water (10 mL \times 2) and brine (10 mL). The organic layer was dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (5-10% AcOEt in hexane) to give **14a** (420 mg, 72% as a colorless oil). ^1H NMR (CDCl_3) δ 2.91 (2H, t, $J = 7.2$ Hz), 3.45 (2H, t, $J = 7.2$ Hz), 3.82 (3H, s), 6.84-6.91 (2H, m), 7.13-7.17 (1H, m), 7.20-7.24 (1H, m); EI-HRMS m/z M: Calcd. for $\text{C}_9\text{H}_{11}\text{N}_3\text{O}$, 177.0902; Found, 177.0886



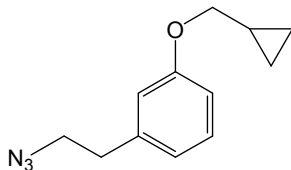
1-(2-Azidoethyl)-3-methoxybenzene (14b)

From 3-methoxyphenethyl alcohol **13b** (500 mg, 3.3 mmol), **14b** (443 mg, 76%) was obtained as a colorless oil. ^1H NMR (CDCl_3) δ 2.86 (2H, t, $J = 7.6$ Hz), 3.49 (2H, t, $J = 7.6$ Hz), 3.79 (3H, s), 6.74-6.80 (3H, m), 7.20-7.24 (1H, m); EI-HRMS m/z M: Calcd. for $\text{C}_9\text{H}_{11}\text{N}_3\text{O}$, 177.0902; Found, 177.0880



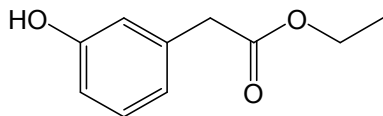
1-(2-Azidoethyl)-2-(cyclopropylmethoxy)benzene (14c)

From **13c** (634 mg, 3.3 mmol), **14c** (536 mg, 75%) was obtained as a colorless oil. ^1H NMR (CDCl_3) δ 0.33-0.40 (2H, m), 0.61-0.66 (2H, m), 1.23-1.33 (1H, m), 2.96 (2H, t, $J = 7.2$ Hz), 3.51 (2H, t, $J = 7.2$ Hz), 3.83 (2H, d, $J = 6.8$ Hz), 6.82 (1H, d, $J = 8.0$ Hz), 6.87-6.91 (1H, m), 7.15-7.22 (2H, m); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{ONa}$, 240.1113; Found, 240.1130



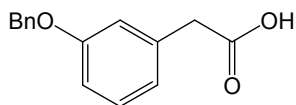
1-(2-Azidoethyl)-3-(cyclopropylmethoxy)benzene (14d)

From **13d** (634 mg, 3.3 mmol), **14d** (590 mg, 82%) was obtained as a colorless oil. ^1H NMR (CDCl_3) δ 0.35 (2H, dd, $J = 4.4, 10.4$ Hz), 0.62-0.67 (2H, m), 1.22-1.32 (1H, m), 2.86 (2H, t, $J = 7.2$ Hz), 3.50 (2H, t, $J = 7.2$ Hz), 3.80 (2H, d, $J = 6.8$ Hz), 6.77-6.81 (3H, m), 7.20-7.24 (1H, m); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{ONa}$, 240.1113; Found, 240.1108



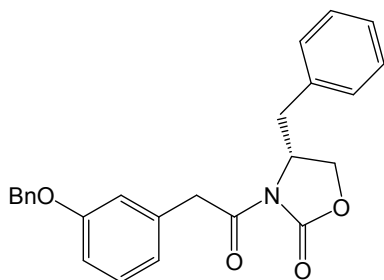
Ethyl 2-(3-hydroxyphenyl)acetate (16)

A solution of 3-hydroxyphenylacetic acid **15** (15 g, 98.6 mmol) and sulfonic acid (2.56 ml) in EtOH (200 mL) was heated to reflux for 4 hr. The mixture was cooled to room temperature and evaporated *in vacuo*. The residue was diluted with water (50 mL), neutralized with sodium hydrogencarbonate (4.5 g), and then extracted with AcOEt (200 mL). The organic layer was washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4 , and filtered. The filtrate was evaporated to give **16** (17.8 g, quant. as a colorless oil). ^1H NMR (CDCl_3) δ 1.24 (3H, t, $J = 7.3$ Hz), 3.54 (2H, s), 4.14 (2H, q, $J = 7.3$ Hz), 5.28 (1H, brs), 6.69-6.83 (3H, m), 7.16 (1H, t, $J = 8.1$ Hz); HR FAB-MS m/z $[\text{M}-\text{H}]^-$: Calcd. for $\text{C}_{10}\text{H}_{11}\text{O}_3$, 179.0708; Found, 179.0718



2-(3-(Benzyloxy)phenyl)acetic acid (**17**)

A suspension of **16** (17.8 g, 98.6 mmol), benzyl Bromide (14.1 mL, 118 mmol) and potassium carbonate (20.4 g, 148 mmol) in DMF (300 mL) was stirred at 90 °C for 5 hr. The mixture was cooled to room temperature, diluted with toluene (200 mL), and then washed with water (150 mL×3) and brine (150 mL). The organic layer was dried over Na₂SO₄, and filtered. The filtrate was evaporated *in vacuo*, and the residue was dissolved in EtOH (120 mL) and aq. 4.0 M NaOH (75 mL). The mixture was stirred at 60 °C for 4 hr. The mixture was cooled to room temperature and EtOH was removed by concentration. The residue was diluted water (100 mL), and was then washed with AcOEt (100 mL×2). The aqueous layer was acidified with aq. 4.0 M HCl (75 mL) and extracted with AcOEt (200 mL×2). The combined organic layer was washed with water (100 mL) and brine (100 mL), and dried over Na₂SO₄, and filtered. The filtrate was evaporated to give **17** (23.99 g, 90% as a colorless solid). ¹H NMR (DMSO-*d*₆) δ 3.52 (2H, s), 5.06 (2H, s), 6.83 (1H, d, *J* = 7.6 Hz), 6.87-6.91 (2H, m), 7.21 (1H, t, *J* = 8.0 Hz), 7.30-7.45 (5H, m); TOF-HRMS *m/z* [M+H]⁺: Calcd. for C₁₅H₁₅O₃, 243.1021; Found, 243.1029

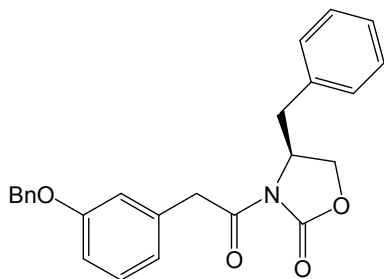


(*R*)-4-Benzyl-3-(2-(3-(benzyloxy)phenyl)acetyl)oxazolidin-2-one (**18a**)

A solution of **17** (5.0 g, 20.6 mmol) and DMF (100 μL) in thionyl chloride (50 mL) was stirred at 50 °C for 2 hr. The reaction mixture was evaporated *in vacuo*, and the residue was co-evaporated with toluene (50 mL×4) to give 2-(3-(benzyloxy)phenyl)acetyl chloride.

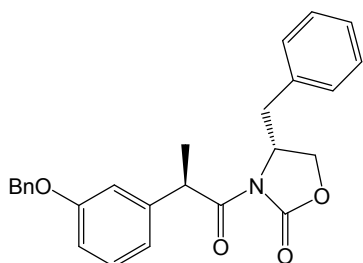
To a solution of (*R*)-4-benzyl-2-oxazolidine (3.66g, 20.6 mmol) in THF (60 mL) was added a solution of *n*-BuLi (7.92 mL, 2.64 M, 20.9 mmol) in THF at -78 °C and the reaction mixture was stirred at same temperature for 30 min. A solution of 2-(3-(benzyloxy)phenyl)acetyl chloride (20.6 mmol) in THF (10 mL) was added to the mixture via syringe, and the reaction mixture was stirred at 0 °C for 2hr. The reaction was quenched by the addition of saturated aq. NH₄Cl (30 mL) and the mixture was extracted with AcOEt (50 mL×2). The combined organic layer was washed with water (50 mL) and brine (50 mL), dried over Na₂SO₄, and filtered. The filtrate was evaporated *in vacuo*,

and the residue was purified by silica gel column chromatography (10-30% AcOEt in hexane) to give **18a** (6.78 g, 82% as a colorless syrup). ^1H NMR (DMSO- d_6) δ 2.86-2.99 (2H, m), 4.09 (1H, d, J = 16.4 Hz), 4.19 (1H, dd, J = 2.8, 8.8 Hz), 4.23 (1H, d, J = 16.0 Hz), 4.33 (1H, t, J = 8.8 Hz), 4.65-4.68 (1H, m), 5.08 (2H, s), 6.86 (1H, d, J = 7.2 Hz), 6.92-6.94 (2H, m), 7.12 (2H, d, J = 6.8 Hz), 7.21-7.46 (9H, m); TOF-HRMS m/z $[\text{M}+\text{H}]^+$: Calcd. for $\text{C}_{25}\text{H}_{24}\text{NO}_4$, 402.1705; Found, 402.1710



(S)-4-Benzyl-3-(2-(3-(benzyloxy)phenyl)acetyl)oxazolidin-2-one (18b)

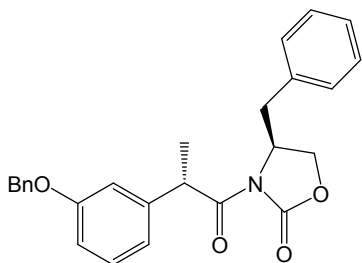
Compound **18b** (6.62 g, 80% as a colorless syrup) was synthesized from **17** (5.0 g, 20.6 mmol) and (S)-4-benzyl-2-oxazolidine (3.66g, 20.6 mmol) according to the procedure described for the conversion of **17** to **18a**. ^1H NMR (DMSO- d_6) δ 2.86-2.99 (2H, m), 4.09 (1H, d, J = 16.0 Hz), 4.19 (1H, dd, J = 2.8, 8.8 Hz), 4.23 (1H, d, J = 16.0 Hz), 4.33 (1H, t, J = 8.8 Hz), 4.65-4.68 (1H, m), 5.08 (2H, s), 6.86 (1H, d, J = 7.6 Hz), 6.92-6.94 (2H, m), 7.12 (2H, d, J = 6.8 Hz), 7.21-7.46 (9H, m); TOF-HRMS m/z $[\text{M}+\text{H}]^+$: Calcd. for $\text{C}_{25}\text{H}_{24}\text{NO}_4$, 402.1705; Found, 402.1697



(R)-4-Benzyl-3-((R)-2-(3-(benzyloxy)phenyl)propanoyl)oxazolidin-2-one (19a)

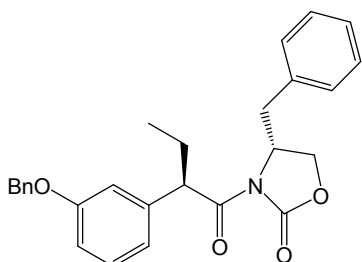
To a solution of **18a** (1.5 g, 3.74 mmol) in THF (10 mL) was added a solution of sodium bis(trimethylsilyl)amide (4.11 mL, 1.0 M, 4.11 mmol) in THF at -78 °C and the reaction was stirred at same temperature for 1 hr. Methyl iodide (1.05 mL, 16.8 mmol) was added to the mixture dropwise at -78 °C and the mixture was stirred at the same temperature for 4 hr. The reaction was quenched by the addition of saturated aq. NH_4Cl (10 mL) and the mixture was extracted with AcOEt (20 mL \times 2). The combined organic layer was washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (5-20% AcOEt in hexane) to give **19a** (1.23 g, 79% as a colorless

syrup). ^1H NMR ($\text{DMSO}-d_6$) δ 1.43 (3H, d, $J = 6.8$ Hz), 2.96-3.07 (2H, m), 4.19 (1H, dd, $J = 2.4, 8.8$ Hz), 4.26 (1H, t, $J = 8.8$ Hz), 4.63-4.68 (1H, m), 4.96 (1H, q, $J = 6.8$ Hz), 5.06 (2H, s), 6.85-6.91 (3H, m), 7.21-7.28 (4H, m), 7.31-7.35 (3H, m), 7.39 (2H, t, $J = 6.8$ Hz), 7.45 (2H, d, $J = 7.2$ Hz); TOF-HRMS m/z $[\text{M}+\text{H}]^+$: Calcd. for $\text{C}_{26}\text{H}_{26}\text{NO}_4$, 416.1862; Found, 416.1868



(S)-4-Benzyl-3-((S)-2-(3-(benzyloxy)phenyl)propanoyl)oxazolidin-2-one (19b)

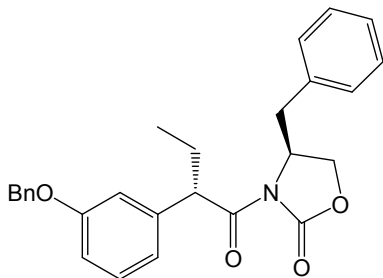
Compound **19b** (1.24 g, 80% as a colorless syrup) was synthesized from **18b** (1.5 g, 3.74 mmol) according to the procedure described for the conversion of **18a** to **19a**. ^1H NMR ($\text{DMSO}-d_6$) δ 1.42 (3H, d, $J = 6.8$ Hz), 2.95-3.05 (2H, m), 4.18 (1H, dd, $J = 2.8, 9.2$ Hz), 4.25 (1H, t, $J = 8.8$ Hz), 4.62-4.67 (1H, m), 4.94 (1H, q, $J = 7.2$ Hz), 5.05 (2H, s), 6.84-6.90 (3H, m), 7.20-7.27 (4H, m), 7.31-7.34 (3H, m), 7.38 (2H, t, $J = 7.2$ Hz), 7.44 (2H, d, $J = 7.6$ Hz); TOF-HRMS m/z $[\text{M}+\text{H}]^+$: Calcd. for $\text{C}_{26}\text{H}_{26}\text{NO}_4$, 416.1862; Found, 416.1861



(R)-4-Benzyl-3-((R)-2-(3-(benzyloxy)phenyl)butanoyl)oxazolidin-2-one (19c)

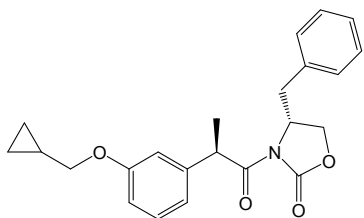
To a solution of **18a** (1.5 g, 3.74 mmol) in THF (10 mL) was added a solution of sodium bis(trimethylsilyl)amide (4.11 mL, 1.0 M, 4.11 mmol) in THF at -78 °C and the reaction was stirred at same temperature for 1 hr. Ethyl iodide (1.34 mL, 16.8 mmol) was added to the mixture dropwise at -78 °C and the reaction was stirred at -20 °C for 6 hr. The reaction was quenched by the addition of saturated aq. NH_4Cl (10 mL) and the mixture was extracted with AcOEt (20 mL \times 2). The combined organic layer was washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (5-20% AcOEt in hexane) to give **19c** (964 mg, 60% as a colorless syrup). ^1H NMR ($\text{DMSO}-d_6$) δ 0.84 (3H, t, $J = 7.2$ Hz), 1.70-1.77 (1H, m), 2.00-2.07 (1H, m), 2.96 (1H, dd, $J = 8.0, 13.6$ Hz), 3.06 (1H, dd, $J = 3.2, 13.6$ Hz), 4.16 (1H, dd, $J = 2.8, 8.8$ Hz), 4.23 (1H, t, $J = 8.00$ Hz),

4.62-4.66 (1H, m), 4.78 (1H, t, $J = 7.2$ Hz), 5.05 (2H, s), 6.86 (1H, d, $J = 7.2$ Hz), 6.89-6.91 (2H, m), 7.21-7.27 (4H, m), 7.30-7.33 (3H, m), 7.38 (2H, t, $J = 6.8$ Hz), 7.44 (2H, d, $J = 7.6$ Hz); TOF-HRMS m/z $[M+H]^+$: Calcd. for $C_{27}H_{28}NO_4$, 430.2018; Found, 430.2019



(S)-4-Benzyl-3-((S)-2-(3-(benzyloxy)phenyl)butanoyl)oxazolidin-2-one (19d)

Compound **19d** (851 mg, 53% as a colorless syrup) was synthesized from **18b** (1.5 g, 3.74 mmol) according to the procedure described for the conversion of **18a** to **19c**. 1H NMR (DMSO- d_6) δ 0.84 (3H, t, $J = 7.2$ Hz), 1.79-1.80 (1H, m), 2.00-2.09 (1H, m), 2.97 (1H, dd, $J = 7.6, 13.6$ Hz), 3.07 (1H, dd, $J = 3.6, 14.0$ Hz), 4.16 (1H, dd, $J = 2.8, 9.2$ Hz), 4.24 (1H, t, $J = 9.2$ Hz), 4.62-4.67 (1H, m), 4.79 (1H, t, $J = 7.6$ Hz), 5.06 (2H, s), 6.86 (1H, d, $J = 8.0$ Hz), 6.90-6.92 (2H, m), 7.21-7.27 (4H, m), 7.30-7.33 (3H, m), 7.38 (2H, t, $J = 6.8$ Hz), 7.44 (2H, d, $J = 7.6$ Hz); TOF-HRMS m/z $[M+H]^+$: Calcd. for $C_{27}H_{28}NO_4$, 430.2018; Found, 430.2016

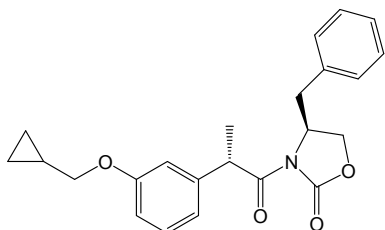


General procedure for the synthesis of 20a-d. Exemplified for

(R)-4-Benzyl-3-((R)-2-(3-(cyclopropylmethoxy)phenyl)propanoyl)oxazolidin-2-one (20a)

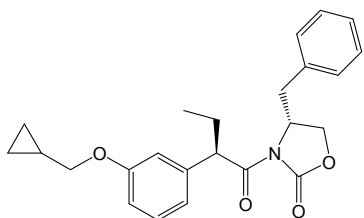
A suspension of **19a** (900 mg, 2.16 mmol) and $Pd(OH)_2 \cdot C$ (500 mg) in MeOH (10 mL) was stirred at room temperature for 1 hr under a hydrogen atmosphere. The mixture was filtered through a Celite pad, and the filtrate was evaporated *in vacuo*. The residue was dissolved in DMF (5 mL). bromomethylcyclopropane (1.22 mL, 12.6 mmol) and potassium carbonate (696 mg, 5.04 mmol) were added to the mixture which was then stirred at 90 °C for 2 hr. The mixture was cooled to room temperature and diluted with AcOEt (20 mL), and was then washed with water (20 mL \times 2) and brine (10 mL). The organic layer was dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (10-15% AcOEt in hexane) to give **20a** (493 mg, 60% as a colorless syrup). 1H NMR ($CDCl_3$) δ 0.33-0.36 (2H, m), 0.61-0.66 (2H, m), 1.22-1.30 (1H, m), 1.53 (3H, d, $J = 6.8$ Hz), 2.80 (1H, dd, $J = 9.6, 13.2$ Hz), 3.35 (1H, dd, $J =$

3.2, 13.2 Hz), 3.79 (2H, d, $J = 6.8$ Hz), 4.04-4.12 (2H, m), 4.56-4.62 (1H, m), 5.09 (1H, q, $J = 6.8$ Hz), 6.77-6.80 (1H, m), 6.92-6.95 (2H, m), 7.19-7.36 (6H, m); FAB-HRMS m/z $[M+H]^+$: Calcd. for $C_{23}H_{26}NO_4$, 380.1862; Found, 380.1860



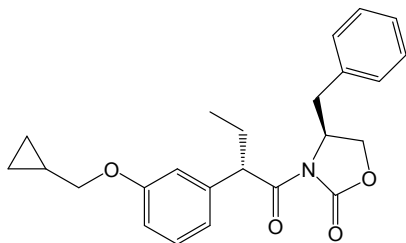
(*S*)-4-Benzyl-3-((*S*)-2-(3-(cyclopropylmethoxy)phenyl)propanoyl)oxazolidin-2-one (20b)

From **19b** (900 mg, 2.16 mmol), **20b** (434 mg, 53%) was obtained as a colorless syrup. 1H NMR ($CDCl_3$) δ 0.33-0.36 (2H, m), 0.61-0.66 (2H, m), 1.21-1.31 (1H, m), 1.53 (3H, d, $J = 6.8$ Hz), 2.79 (1H, dd, $J = 9.6, 13.2$ Hz), 3.35 (1H, dd, $J = 3.2, 13.2$ Hz), 3.79 (2H, d, $J = 7.2$ Hz), 4.04-4.12 (2H, m), 4.56-4.62 (1H, m), 5.09 (1H, q, $J = 6.8$ Hz), 6.77-6.80 (1H, m), 6.92-6.95 (2H, m), 7.19-7.36 (6H, m); FAB-HRMS m/z $[M+H]^+$: Calcd. for $C_{23}H_{26}NO_4$, 380.1862; Found, 380.1868



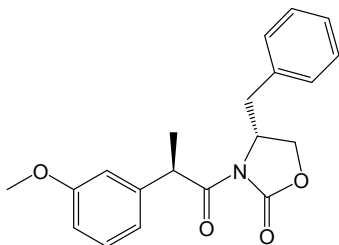
(*R*)-4-Benzyl-3-((*R*)-2-(3-(cyclopropylmethoxy)phenyl)butanoyl)oxazolidin-2-one (20c)

From **19c** (770 mg, 1.79 mmol), **20c** (150 mg, 21%) was obtained as a colorless syrup. 1H NMR ($DMSO-d_6$) δ 0.27-0.31 (2H, m), 0.51-0.56 (2H, m), 0.83 (3H, t, $J = 7.6$ Hz), 1.11-1.24 (1H, m), 1.69-1.78 (1H, m), 1.96-2.06 (1H, m), 2.95 (1H, dd, $J = 8.0, 13.6$ Hz), 3.04 (1H, dd, $J = 3.2, 13.6$ Hz), 3.75 (2H, d, $J = 6.8$ Hz), 4.14 (1H, dd, $J = 2.4, 8.8$ Hz), 4.23 (1H, t, $J = 8.8$ Hz), 4.61-4.67 (1H, m), 4.75 (1H, t, $J = 7.2$ Hz), 6.76-6.81 (3H, m), 7.16-7.32 (6H, m); FAB-HRMS m/z $[M+H]^+$: Calcd. for $C_{24}H_{28}NO_4$, 394.2018; Found, 394.2021



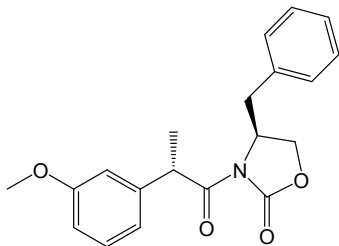
(S)-4-Benzyl-3-((S)-2-(3-(cyclopropylmethoxy)phenyl)butanoyl)oxazolidin-2-one (20d)

From **19d** (500 mg, 1.16 mmol), **20d** (240 mg, 53%) was obtained as a colorless syrup. ^1H NMR ($\text{DMSO}-d_6$) δ 0.27-0.32 (2H, m), 0.51-0.58 (2H, m), 0.84 (3H, t, $J = 7.0$ Hz), 1.11-1.25 (1H, m), 1.65-1.81 (1H, m), 1.97-2.08 (1H, m), 2.96 (1H, dd, $J = 7.6, 13.5$ Hz), 3.05 (1H, dd, $J = 3.5, 13.5$ Hz), 3.76 (2H, d, $J = 6.8$ Hz), 4.15 (1H, dd, $J = 3.0, 8.9$ Hz), 4.24 (1H, t, $J = 8.9$ Hz), 4.61-4.66 (1H, m), 4.76 (1H, t, $J = 7.3$ Hz), 6.76-6.83 (3H, m), 7.16-7.35 (6H, m); FAB-HRMS m/z $[\text{M}+\text{H}]^+$: Calcd. for $\text{C}_{24}\text{H}_{28}\text{NO}_4$, 394.2018; Found, 394.2032



(R)-4-Benzyl-3-((R)-2-(3-methoxyphenyl)propanoyl)oxazolidin-2-one (20e)

A suspension of **19a** (900 mg, 2.10 mmol) and $\text{Pd}(\text{OH})_2\text{-C}$ (500 mg) in MeOH (10 mL) was stirred at room temperature for 1 hr under a hydrogen atmosphere. The mixture was filtered through a Celite pad, and the filtrate was evaporated *in vacuo*. The residue was dissolved in DMF (5 mL). Iodomethane (828 μL , 13.3 mmol) and potassium carbonate (732 mg, 5.30 mmol) were added to the mixture which was then stirred at 70 $^\circ\text{C}$ for 2 hr. The mixture was cooled to room temperature and diluted with AcOEt (20 mL), and was then washed with water (20 mL \times 2) and brine (10 mL). The organic layer was dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (10-15% AcOEt in hexane) to give **20e** (441 mg, 62% as a colorless syrup). ^1H NMR (CDCl_3) δ 1.54 (3H, d, $J = 6.8$ Hz), 2.80 (1H, dd, $J = 9.6, 13.2$ Hz), 3.35 (1H, dd, $J = 3.2, 13.2$ Hz), 3.80 (3H, s), 4.04-4.14 (2H, m), 4.56-4.62 (1H, m), 5.11 (1H, q, $J = 7.2$ Hz), 6.78-6.81 (1H, m), 6.92-6.97 (2H, m), 7.21-7.36 (6H, m); TOF-HRMS m/z $[\text{M}+\text{H}]^+$: Calcd. for $\text{C}_{20}\text{H}_{22}\text{NO}_4$, 340.1549; Found, 340.1551

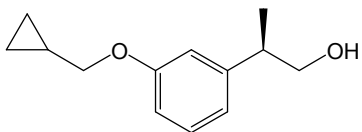


(S)-4-Benzyl-3-((S)-2-(3-methoxyphenyl)propanoyl)oxazolidin-2-one (20f)

Compound **20f** (421 mg, 59% as a colorless syrup) was synthesized from **19b** (900 mg, 2.10 mmol)

according to the procedure described for the conversion of **19a** to **19e**.

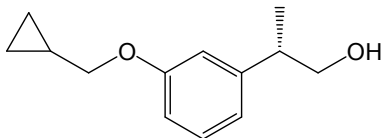
^1H NMR (CDCl_3) δ 1.54 (3H, d, $J = 7.2$ Hz), 2.80 (1H, dd, $J = 10.0, 13.6$ Hz), 3.35 (1H, dd, $J = 2.8, 13.2$ Hz), 3.80 (3H, s), 4.04-4.13 (2H, m), 4.56-4.62 (1H, m), 5.11 (1H, q, $J = 6.8$ Hz), 6.78-6.81 (1H, m), 6.93-6.97 (2H, m), 7.21-7.36 (6H, m); TOF-HRMS m/z $[\text{M}+\text{H}]^+$: Calcd. for $\text{C}_{20}\text{H}_{22}\text{NO}_4$, 340.1549; Found, 340.1558



General procedure for the synthesis of 21a-21f. Exemplified for

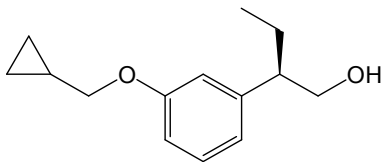
(*R*)-2-(3-(Cyclopropylmethoxy)phenyl)propan-1-ol (21a)

To a solution of **20a** (310 mg, 0.82 mmol) in THF (5 mL) was added a solution of lithium borohydride (1.0 mL, 2.0 M, 2.0 mmol) in THF at 0 °C, and the reaction mixture was stirred at the same temperature for 6 hr. The reaction mixture was quenched by the addition of brine (10 mL) at 0 °C and extracted with AcOEt (10 mL \times 2). The combined organic layer washed with saturated aq. NH_4Cl (10 mL) and brine (10 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (33-50% AcOEt in hexane) to give **21a** (110 mg, 65% as a colorless syrup). ^1H NMR (CDCl_3) δ 0.33-0.37 (2H, m), 0.63-0.67 (2H, m), 1.26 (3H, d, $J = 7.2$ Hz), 1.25-1.32 (2H, m), 2.88-2.97 (1H, m), 3.70 (2H, t, $J = 6.4$ Hz), 3.80 (2H, d, $J = 6.8$ Hz), 6.76-6.83 (3H, m), 7.23 (1H, t, $J = 8.4$ Hz); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{13}\text{H}_{18}\text{O}_2\text{Na}$, 229.1204; Found, 229.1233



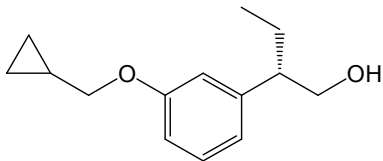
(*S*)-2-(3-(Cyclopropylmethoxy)phenyl)propan-1-ol (21b)

From **20b** (340 mg, 0.90 mmol), **21b** (120 mg, 65%) was obtained as a colorless syrup. ^1H NMR (CDCl_3) δ 0.32-0.38 (2H, m), 0.62-0.68 (2H, m), 1.26 (3H, d, $J = 7.2$ Hz), 1.22-1.35 (2H, m), 2.86-2.99 (1H, m), 3.70 (2H, t, $J = 5.4$ Hz), 3.80 (2H, d, $J = 7.0$ Hz), 6.75-6.84 (3H, m), 7.23 (1H, t, $J = 7.8$ Hz); HR FAB-MS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{13}\text{H}_{18}\text{O}_2\text{Na}$, 229.1204; Found, 229.1213



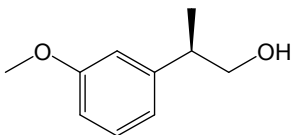
(R)-2-(3-(Cyclopropylmethoxy)phenyl)butan-1-ol (21c)

From **20c** (150 mg, 0.38 mmol), **21c** (50 mg, 60%) was obtained as a colorless syrup. ^1H NMR (CDCl_3) δ 0.33-0.38 (2H, m), 0.62-0.69 (2H, m), 0.84 (3H, t, $J = 7.3$ Hz), 1.21-1.33 (1H, m), 1.51-1.78 (2H, m), 2.61-2.71 (1H, m), 3.68-3.81 (2H, m), 3.80 (2H, d, $J = 7.0$ Hz), 6.76-6.81 (3H, m), 7.20-7.26 (1H, m); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_2\text{Na}$, 243.1361; Found, 243.1354



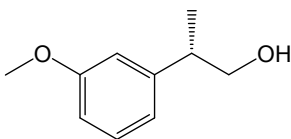
(S)-2-(3-(Cyclopropylmethoxy)phenyl)butan-1-ol (21d)

From **20d** (240 mg, 0.61 mmol), **21d** (100 mg, 74%) was obtained as a colorless syrup. ^1H NMR (CDCl_3) δ 0.33-0.37 (2H, m), 0.63-0.67 (2H, m), 0.84 (3H, t, $J = 7.2$ Hz), 1.23-1.29 (1H, m), 1.51-1.76 (2H, m), 2.64-2.70 (1H, m), 3.71-3.81 (2H, m), 3.80 (2H, d, $J = 7.2$ Hz), 6.76-6.80 (3H, m), 7.21-7.26 (1H, m); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_2\text{Na}$, 243.1361; Found, 243.1354



(R)-2-(3-Methoxyphenyl)propan-1-ol (21e)

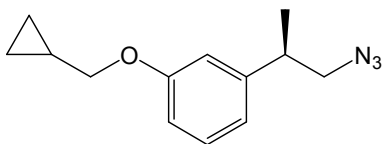
From **20e** (441 mg, 1.30 mmol), **21e** (138 mg, 64%) was obtained as a colorless syrup. ^1H NMR ($\text{DMSO}-d_6$) δ 1.17 (3H, d, $J = 6.8$ Hz), 2.71-2.80 (1H, m), 3.36-3.43 (1H, m), 3.47-3.54 (1H, m), 3.73 (3H, s), 4.60 (1H, t, $J = 5.2$ Hz), 6.73-6.79 (3H, m), 7.17-7.21 (1H, m); $[\alpha]_D^{25} = 16.26$ (c 1.07, CHCl_3); 92.1% e.e. [HPLC condition, Column: CHIRALPAK AD-3 (4.6 \times 250 mm), Column Temp.: 25 $^\circ\text{C}$, Mobile phase: hexane/ethanol (6:4), Flow rate: 0.8 mL/min., Detector: UV 230 nm, **21e** was eluted at 12.8 min]



(S)-2-(3-Methoxyphenyl)propan-1-ol (21f)

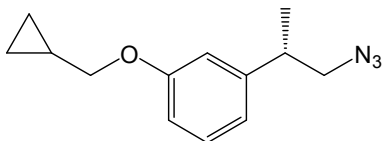
From **20f** (421 mg, 1.24 mmol), **21f** (128 mg, 62%) was obtained as a colorless syrup. ^1H NMR ($\text{DMSO}-d_6$) δ 1.17 (3H, d, $J = 6.8$ Hz), 2.71-2.80 (1H, m), 3.37-3.43 (1H, m), 3.47-3.55 (1H, m),

3.73 (3H, s), 4.61 (1H, t, $J = 5.6$ Hz), 6.73-6.80 (3H, m), 7.17-7.21 (1H, m); $[\alpha]_D^{25} = -16.14$ (c 1.09, CHCl_3), reference data² $[\alpha]_D^{25} = -16.6$ (c 1.09, CHCl_3 , >99%e.e.); 94.3%e.e. [HPLC condition, Column:CHIRALPAK AD-3 (4.6×250 mm), Column Temp.:25 °C, Mobile phase: hexane/ethanol (6:4), Flow rate: 0.8 mL/min., Detector: UV 230 nm, **21f** was eluted at 8.4 min]



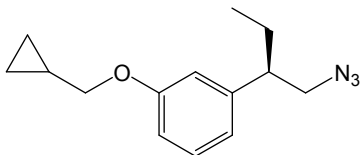
**General procedure for the synthesis of 22a-22d. Exemplified for
(R)-1-(1-Azidopropan-2-yl)-3-(cyclopropylmethoxy)benzene (22a)**

To a mixture of **21a** (120 mg, 0.58 mmol) and triethylamine (121 μL , 0.87 mmol) in CH_2Cl_2 (3 mL) was added methanesulfonyl chloride (54 μL , 0.70 mmol) at 0 °C, and the mixture was stirred at room temperature for 30 min. Saturated aq. NaHCO_3 (5 mL) was added and the layers were partitioned. The organic layer was washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was dissolved in DMF (5 mL). Sodium azide (113 mg, 1.74 mmol) was added to the mixture, and the mixture was stirred at 60 °C for 12 hr. The mixture was cooled to room temperature and diluted with AcOEt (10 mL), and was then washed with water (10 mL×2) and brine (10 mL). The organic layer was dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (5-10% AcOEt in hexane) to give **22a** (92 mg, 69% as a colorless syrup). ^1H NMR (CDCl_3) δ 0.33-0.40 (2H, m), 0.59-0.67 (2H, m), 1.22-1.32 (1H, m), 1.32 (3H, d, $J = 7.2$ Hz), 2.92-3.01 (1H, m), 3.35 (1H, dd, $J = 7.6, 12.4$ Hz), 3.46 (1H, dd, $J = 7.2, 12.0$ Hz), 3.80 (2H, d, $J = 6.8$ Hz), 6.76-6.81 (3H, m), 7.21-7.25 (1H, m); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{ONa}$, 254.1269; Found, 254.1284



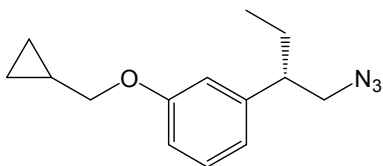
(S)-1-(1-Azidopropan-2-yl)-3-(cyclopropylmethoxy)benzene (22b)

From **21b** (120 mg, 0.58 mmol), **22b** (83 mg, 62%) was obtained as a colorless syrup. ^1H NMR (CDCl_3) δ 0.33-0.41 (2H, m), 0.61-0.67 (2H, m), 1.22-1.32 (1H, m), 1.32 (3H, d, $J = 7.2$ Hz), 2.92-3.01 (1H, m), 3.35 (1H, dd, $J = 7.2, 12.0$ Hz), 3.46 (1H, dd, $J = 7.2, 12.0$ Hz), 3.80 (2H, d, $J = 7.2$ Hz), 6.76-6.81 (3H, m), 7.21-7.26 (1H, m); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{ONa}$, 254.1269; Found, 254.1268



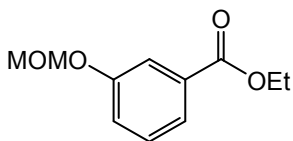
(R)-1-(1-Azidobutan-2-yl)-3-(cyclopropylmethoxy)benzene (22c)

From **21c** (50 mg, 0.23 mmol), **22c** (40 mg, 71%) was obtained as a colorless syrup. ^1H NMR (CDCl_3) δ 0.34-0.37 (2H, m), 0.61-0.67 (2H, m), 0.83 (3H, t, $J = 7.2$ Hz), 1.24-1.32 (1H, m), 1.56-1.65 (1H, m), 1.73-1.84 (1H, m), 2.64-2.72 (1H, m), 3.40-3.49 (2H, m), 3.80 (2H, d, $J = 6.8$ Hz), 6.75-6.79 (3H, m), 7.23 (1H, t, $J = 7.6$ Hz); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{14}\text{H}_{19}\text{N}_3\text{ONa}$, 268.1426; Found, 268.1422



(S)-1-(1-Azidobutan-2-yl)-3-(cyclopropylmethoxy)benzene (22d)

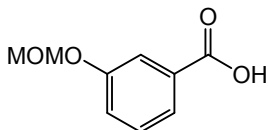
From **21d** (100 mg, 0.45 mmol), **22d** (85 mg, 77%) was obtained as a colorless syrup. ^1H NMR (CDCl_3) δ 0.34-0.37 (2H, m), 0.63-0.67 (2H, m), 0.83 (3H, t, $J = 7.6$ Hz), 1.24-1.29 (1H, m), 1.54-1.63 (1H, m), 1.75-1.82 (1H, m), 2.66-2.70 (1H, m), 3.42-3.49 (2H, m), 3.80 (2H, d, $J = 6.8$ Hz), 6.75-6.79 (3H, m), 7.23 (1H, t, $J = 7.2$ Hz); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{14}\text{H}_{19}\text{N}_3\text{ONa}$, 268.1426; Found, 268.1419



Ethyl 3-(methoxymethoxy)benzoate (24)

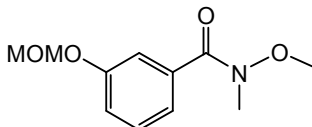
To a mixture of ethyl 3-hydroxybenzoate **23** (10 g, 60.18 mmol) and *N*-ethyldiisopropylamine (31.5 mL, 180 mmol) in CH_2Cl_2 (200 mL) was added chloromethyl methyl ether (6.8 mL, 90.3 mmol) at room temperature, and the mixture was stirred at the same temperature for 5 hr. Saturated aq. NH_4Cl (100 mL) was added to the reaction mixture and the layers were partitioned. The organic layer was washed with saturated aq. NH_4Cl (100 mL \times 3), aq. 1.0 M NaOH (50 mL \times 2) and brine (100 mL), dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was co-evaporated with toluene (50 mL \times 3) to give **24** (10.7 g, 85% as a colorless oil), and it was used for

the next step without further purification. ^1H NMR (CDCl_3) δ 1.39 (3H, t, $J = 7.6$ Hz), 3.49 (3H, s), 4.37 (2H, q, $J = 7.6$ Hz), 5.22 (2H, s), 7.21-7.24 (1H, m), 7.33-7.37 (1H, m), 7.68-7.71 (2H, m); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{11}\text{H}_{14}\text{O}_4\text{Na}$, 233.0790; Found, 233.0779.



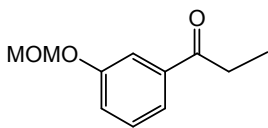
3-(Methoxymethoxy)benzoic acid (**25**)

To a solution of **24** (10.7 g, 51 mmol) in EtOH (60 mL), was added aq. 4.0 M NaOH (38 mL) and the reaction was stirred at 60 °C for 4 hr. The mixture was cooled to room temperature and EtOH was removed by concentration. The residue was diluted water (100 mL), and was acidified with aq. 4.0 M HCl (38 mL) and then extracted with AcOEt (200 mL \times 2). The combined organic layer was washed with water (100 mL) and brine (100 mL), and dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo* to give **25** (8.8 g, 95% as a colorless solid). ^1H NMR (CDCl_3) δ 3.50 (3H, s), 5.23 (2H, s), 7.26-7.29 (1H, m), 7.37-7.41 (1H, m), 7.75-7.76 (2H, m); FAB-HRMS m/z $[\text{M}-\text{H}]^-$: Calcd. for $\text{C}_9\text{H}_9\text{O}_4$, 181.0501; Found, 181.0521



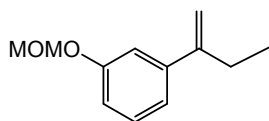
N-Methoxy-3-(methoxymethoxy)-N-methylbenzamide (**26**)

A mixture of **25** (8.8 g, 48.31 mmol), *N,O*-dimethylhydroxylamine hydrochloride (5.65 g, 57.97 mmol), EDC \cdot HCl (13.89 g, 72.5 mmol), triethylamine (8.36 mL, 60.4 mmol) and HOBt (7.83 g, 57.97 mmol) in DMF (150 mL) was stirred at room temperature for 6 hr. Water (150 mL) and AcOEt (150 mL) were added to the reaction mixture and the layers were partitioned. The aqueous layer was extracted with AcOEt (100 mL \times 2) and the combined organic layer was washed with brine (100 mL), dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (20-40% AcOEt in hexane) to give **26** (8.65 g, 79% as a colorless syrup). ^1H NMR (CDCl_3) δ 3.35 (3H, s), 3.48 (3H, s), 3.58 (3H, s), 5.19 (2H, s), 7.13 (1H, dt, $J = 2.4, 7.2$ Hz), 7.28-7.34 (3H, m); FAB-HRMS m/z $[\text{M}+\text{H}]^+$: Calcd. for $\text{C}_{11}\text{H}_{16}\text{NO}_4$, 226.1079; Found, 226.1078



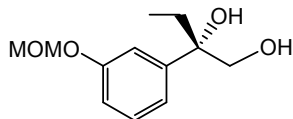
1-(3-(Methoxymethoxy)phenyl)propan-1-one (27)

A solution of ethylmagnesium bromide (3.0 M, 32 mL, 96 mmol) in Et₂O was added to a solution of **26** (8.65 g, 38.4 mmol) in THF (150 mL) dropwise over 10 min at 0 °C. After being stirred at the same temperature for 3 hr, the mixture was quenched by the addition of saturated aq. NH₄Cl (100 mL). The separated organic layer was washed with brine (10 mL), dried (Na₂SO₄), and concentrated to dryness *in vacuo*. The residue was purified by silica gel column chromatography (2-10% AcOEt in hexane) to give **27** (7.0 g, 94% as a colorless syrup). ¹H NMR (CDCl₃) δ 1.22 (3H, t, *J* = 7.2 Hz), 2.99 (2H, q, *J* = 7.2 Hz), 3.49 (3H, s), 5.22 (2H, s), 7.22-7.25 (1H, m), 7.37 (1H, t, *J* = 8.0 Hz), 7.59-7.63 (2H, m); FAB-HRMS *m/z* [M+H]⁺: Calcd. for C₁₁H₁₅O₃, 195.1021; Found, 195.1036



1-(But-1-en-2-yl)-3-(methoxymethoxy)benzene (28)

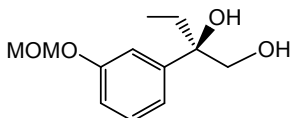
To a suspension of methyltriphenylphosphonium bromide (20.57 g, 57.6 mmol) in THF (150 mL), was added a solution of sodium bis(trimethylsilyl)amide (57.6 mL, 1.0 M, 57.6 mmol) in THF at 0 °C and the mixture was stirred at room temperature for 2 hr. A solution (10 mL) of **27** (7.0 g, 36 mmol) in THF was added dropwise at 0 °C and stirred at room temperature for 12 hr. The reaction was quenched by the addition of saturated aqueous NH₄Cl (100 mL) and extracted with AcOEt (100 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried over Na₂SO₄, and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (0-2% AcOEt in hexane) to give **28** (6.5 g, 94% as a colorless syrup). ¹H NMR (CDCl₃) δ 1.10 (3H, t, *J* = 7.2 Hz), 2.49 (2H, q, *J* = 7.2 Hz), 3.49 (3H, s), 5.06 (1H, d, *J* = 1.2 Hz), 5.19 (2H, s), 5.28 (1H, s), 6.89-6.97 (1H, m), 7.04-7.09 (2H, m), 7.22-7.26 (1H, m); EI-HRMS *m/z* [M]: Calcd. for C₁₂H₁₆O₂, 195.1150; Found, 195.1156



(S)-2-(3-(Methoxymethoxy)phenyl)butane-1,2-diol (29a)

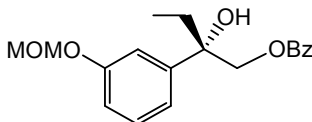
To a solution of **28** (6.0 g, 31.21 mmol) in *tert*-butanol (130 mL) and water (130 mL), was added AD-mix α (35 g) at 0 °C, and the mixture was stirred at 0 °C for 3 hr. The reaction was quenched by the addition of saturated aq. sodium hydrogensulfite (50 mL) at 0 °C and then extracted with AcOEt (200 mL). The separated organic layer was washed with water (100 mL) and brine (100 mL), dried over Na₂SO₄, and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (25-50% AcOEt in hexane) to give **29a** (6.9 g, 98% as a colorless

syrup). ^1H NMR (CDCl_3) δ 0.79 (3H, t, $J = 7.2$ Hz), 1.64 (1H, brs), 1.75-1.90 (2H, m), 2.59 (1H, d, $J = 2.8$ Hz), 3.49 (3H, s), 3.66-3.71 (1H, m), 3.84 (1H, dd, $J = 2.4, 11.2$ Hz), 5.19 (2H, s), 6.94-6.97 (1H, m), 7.01-7.04 (1H, m), 7.11 (1H, t, $J = 2.0$ Hz), 7.29 (1H, t, $J = 7.6$ Hz); FAB-HRMS m/z $[\text{M}-\text{H}]^-$: Calcd. for $\text{C}_{12}\text{H}_{17}\text{O}_4$, 225.1127; Found, 225.1151



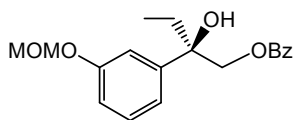
(R)-2-(3-(Methoxymethoxy)phenyl)butane-1,2-diol (29b)

To a solution of **28** (2.8 g, 14.56 mmol) in *tert*-butanol (70 mL) and water (70 mL) was added AD-mix β (16 g) at 0 °C, and the mixture was stirred at 0 °C for 3 hr. The reaction was quenched by the addition of saturated aq. sodium hydrogensulfite (20 mL) at 0 °C and then diluted with AcOEt (100 mL). The separated organic layer was washed with water (70 mL) and brine (50 mL), dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (25-50% AcOEt in hexane) to give **29b** (3.1 g, 94% as a colorless syrup). ^1H NMR (CDCl_3) δ 0.79 (3H, t, $J = 7.6$ Hz), 1.57-1.61 (1H, m), 1.77-1.88 (2H, m), 2.56 (1H, s), 3.49 (3H, s), 3.66-3.71 (1H, m), 3.84 (1H, dd, $J = 4.4, 11.2$ Hz), 5.19 (2H, s), 6.95-6.98 (1H, m), 7.01-7.04 (1H, m), 7.11 (1H, t, $J = 2.0$ Hz), 7.29 (1H, t, $J = 7.6$ Hz); TOF-HRMS m/z $[\text{M}+\text{NH}_4]^+$: Calcd. for $\text{C}_{12}\text{H}_{22}\text{NO}_4$, 244.1549; Found, 244.1550



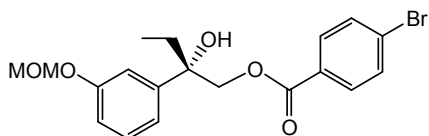
(S)-2-Hydroxy-2-(3-(methoxymethoxy)phenyl)butyl benzoate (30a)

To a mixture of **29a** (6.9 g, 30.5 mmol) and triethylamine (8.46 mL, 61 mmol) in dichloromethane (150 mL), was added benzoyl chloride (3.55 mL, 30.5 mmol) at 0 °C and the mixture was stirred at room temperature for 2 hr. The reaction was quenched by the addition of saturated aq. NaHCO_3 (100 mL). The separated organic layer was washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (10-25% AcOEt in hexane) to give **30a** (9.98 g, 99 % as a colorless solid). ^1H NMR (CDCl_3) δ 0.84 (3H, t, $J = 7.2$ Hz), 1.90-2.04 (2H, m), 2.51 (1H, s), 3.47 (3H, s), 4.49-4.56 (2H, m), 5.16-5.20 (2H, m), 6.95-6.98 (1H, m), 7.08-7.11 (1H, m), 7.19 (1H, t, $J = 2.4$ Hz), 7.25-7.31 (1H, m), 7.39-7.43 (2H, m), 7.53-7.57 (1H, m), 7.93-7.96 (2H, m); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{19}\text{H}_{22}\text{O}_5\text{Na}$, 353.1365; Found, 353.1370



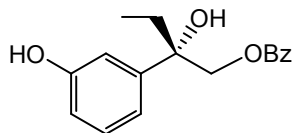
(R)-2-Hydroxy-2-(3-(methoxymethoxy)phenyl)butyl benzoate (30b)

Compound **30b** (4.35 g, 96%, a colorless solid) was synthesized from **29b** (3.1 g, 13.7 mmol) according to the procedure described for the conversion of **29a** to **30a**. ^1H NMR (CDCl_3) δ 0.84 (3H, t, $J = 7.2$ Hz), 1.94-2.00 (2H, m), 2.50 (1H, s), 3.47 (3H, s), 4.49-4.56 (2H, m), 5.16-5.20 (2H, m), 6.95-6.98 (1H, m), 7.09-7.11 (1H, m), 7.19 (1H, t, $J = 2.0$ Hz), 7.26-7.31 (1H, m), 7.40-7.43 (2H, m), 7.53-7.57 (1H, m), 7.94-7.96 (2H, m); TOF-HRMS m/z $[\text{M}+\text{NH}_4]^+$: Calcd. for $\text{C}_{19}\text{H}_{26}\text{NO}_5$, 348.1811; Found, 348.1808



(S)-2-Hydroxy-2-(3-(methoxymethoxy)phenyl)butyl 4-bromobenzoate (30c)

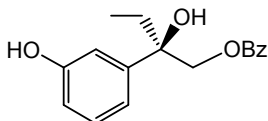
To a mixture of **29a** (200 mg, 0.88 mmol) and triethylamine (245 μL , 1.77 mmol) in dichloromethane (4 mL), was added 4-bromobenzoyl chloride (213 mg, 0.97 mmol) at 0 $^\circ\text{C}$ and the mixture was stirred at room temperature for 2 hr. The reaction mixture was quenched by the addition of saturated aq. NaHCO_3 (4 mL). The separated organic layer was washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (5-15% AcOEt in hexane) to give **30c** (310 mg, 86% as a colorless syrup). ^1H NMR (CDCl_3) δ 0.84 (3H, t, $J = 7.2$ Hz), 1.93-1.99 (2H, m), 2.41 (1H, s), 3.47 (3H, s), 4.48-4.55 (2H, m), 5.16-5.20 (2H, m), 6.96 (1H, dd, $J = 1.6, 7.6$ Hz), 7.08 (1H, brd, $J = 7.6$ Hz), 7.17 (1H, t, $J = 2.0$ Hz), 7.26-7.31 (1H, m), 7.52-7.57 (2H, m), 7.78-7.81 (2H, m); FAB-HR MS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{19}\text{H}_{21}\text{BrO}_5\text{Na}$, 431.0470; Found, 431.0471



(S)-2-Hydroxy-2-(3-hydroxyphenyl)butyl benzoate (31a)

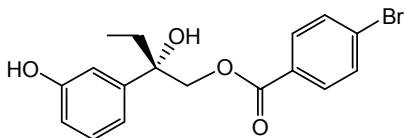
A solution of **30a** (21.6 g, 65.38 mmol) in 70% aq. AcOH (200 mL) and TFA (10 mL) was stirred at 50 $^\circ\text{C}$ for 3 hr. The reaction mixture was diluted with AcOEt (250 mL), and neutralized by the addition of aq. 4.0 M NaOH (250 mL). The separated organic layer was washed with water (150 mL) and brine (150 mL), dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was co-evaporated with *i*-PrOH (20 mL \times 3) to give a residue, which was crystallized

three times from *i*-PrOH-heptane to give **31a** (9.4 g, 50% as a colorless solid). ^1H NMR (CDCl_3) δ 0.83 (3H, t, $J = 8.0$ Hz), 1.88-2.02 (2H, m), 2.55 (1H, s), 4.50-4.56 (2H, m), 4.98 (1H, s), 6.75 (1H, dd, $J = 2.4, 8.0$ Hz), 6.99-7.03 (2H, m), 7.24 (1H, t, $J = 7.6$ Hz), 7.41 (2H, t, $J = 7.6$ Hz), 7.55 (1H, t, $J = 7.2$ Hz), 7.93-7.95 (2H, m); FAB-HRMS m/z $[\text{M}-\text{H}]^-$: Calcd. for $\text{C}_{17}\text{H}_{17}\text{O}_4$, 285.1127; Found, 285.1137; $[\alpha]_D^{25} = -2.03$ (c 1.08, CHCl_3); 96.1%e.e. [HPLC condition, Column: CHIRALPAK IA-3 (4.6 \times 250 mm), Column Temp.: 25 $^\circ\text{C}$, Mobile phase: hexane/ethanol (85:15), Flow rate: 0.8 mL/min., Detector: UV 230 nm, **31a** was eluted at 18.0 min]



(R)-2-Hydroxy-2-(3-hydroxyphenyl)butyl benzoate (31b)

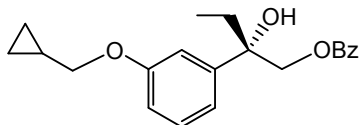
Compound **31b** (1.59 g, 42%, a colorless solid) was synthesized from **30b** (4.35 g, 13.2 mmol) according to the procedure described for the conversion of **30a** to **31a**. ^1H NMR (CDCl_3) δ 0.83 (3H, t, $J = 7.2$ Hz), 1.90-2.01 (2H, m), 2.52 (1H, s), 4.50-4.56 (2H, m), 4.81 (1H, s), 6.75 (1H, dd, $J = 2.4, 8.0$ Hz), 6.99-7.02 (2H, m), 7.24 (1H, t, $J = 7.6$ Hz), 7.42 (2H, t, $J = 7.6$ Hz), 7.55 (1H, t, $J = 7.2$ Hz), 7.93-7.95 (2H, m); TOF-HRMS m/z $[\text{M}+\text{H}]^+$: Calcd. for $\text{C}_{17}\text{H}_{19}\text{O}_4$, 287.1283; Found, 287.1279; $[\alpha]_D^{25} = 2.07$ (c 1.06, CHCl_3); 96.0%e.e. [HPLC condition, Column: CHIRALPAK IA-3 (4.6 \times 250 mm), Column Temp.: 25 $^\circ\text{C}$, Mobile phase: hexane/ethanol (85:15), Flow rate: 0.8 mL/min., Detector: UV 230 nm **31b** was eluted at 15.7 min]



(S)-2-Hydroxy-2-(3-hydroxyphenyl)butyl 4-bromobenzoate (31c)

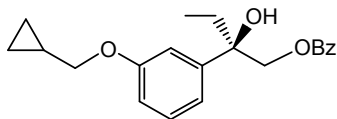
A solution of **30c** compound (310 mg, 0.76 mmol) in 70% aq. AcOH (2.5 mL) and TFA (250 μL) was stirred at 50 $^\circ\text{C}$ for 3 hr. The reaction mixture was diluted with AcOEt (5 mL), and neutralized by the addition of aq. 1.0 M NaOH (3 mL). The separated organic layer was washed with water (5 mL) and brine (5 mL) dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (10-25% AcOEt in hexane) to give a crude product, and it was then crystallized from AcOEt-hexane to give **31c** (130 mg, 47% as a colorless solid). ^1H NMR (CDCl_3) δ 0.83 (3H, t, $J = 7.6$ Hz), 1.89-1.99 (2H, m), 2.43 (1H, s), 4.49-4.55 (2H, m), 4.75 (1H, s), 6.73-6.76 (1H, m), 6.98-7.00 (2H, m), 7.22-7.26 (1H, m), 7.54-7.57 (2H, m), 7.77-7.80 (2H, m); HR FAB-MS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{17}\text{H}_{17}\text{BrO}_4\text{Na}$, 387.0208; Found,

387.0209



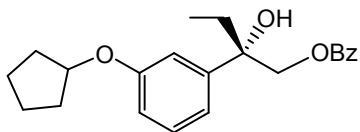
(S)-2-(3-(Cyclopropylmethoxy)phenyl)-2-hydroxybutyl benzoate (32a)

A suspension of **31a** (800 mg, 2.8 mmol), bromomethylcyclopropane (353 μ L, 3.63 mmol) and potassium carbonate (774 mg, 5.6 mmol) in DMF (7 mL) was stirred at 90 °C for 2 hr. The mixture was cooled to room temperature and diluted with AcOEt (20 mL), and was then washed with water (20 mL \times 2) and brine (10 mL). The organic layer was dried over Na₂SO₄, and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (10-25% AcOEt in hexane) to give **32a** (810 mg, 85% as a colorless syrup). ¹H NMR (CDCl₃) δ 0.33-0.39 (2H, m), 0.62-0.66 (2H, m), 0.83 (3H, t, *J* = 7.6 Hz), 1.22-1.32 (1H, m), 1.89-2.01 (2H, m), 2.48 (1H, s), 3.81 (2H, d, *J* = 6.8 Hz), 4.52 (2H, s), 6.81 (1H, dd, *J* = 2.8, 8.4 Hz), 7.02 (1H, d, *J* = 8.4 Hz), 7.08 (1H, t, *J* = 2.4 Hz), 7.27 (1H, t, *J* = 8.0 Hz), 7.39-7.46 (2H, m), 7.53-7.57 (1H, m), 7.93-7.96 (2H, m); FAB-HRMS *m/z* [M+Na]⁺: Calcd. for C₂₁H₂₄O₄Na, 363.1572; Found, 363.1572



(R)-2-(3-(Cyclopropylmethoxy)phenyl)-2-hydroxybutyl benzoate (32b)

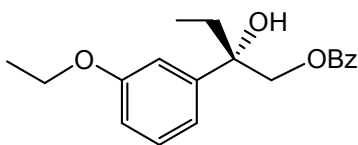
Compound **32b** (405 mg, 85%, a colorless syrup) was synthesized from **31b** (400 mg, 1.4 mmol) according to the procedure described for the conversion of **31a** to **32a**. ¹H NMR (CDCl₃) δ 0.33-0.37 (2H, m), 0.62-0.66 (2H, m), 0.83 (3H, t, *J* = 7.2 Hz), 1.25-1.29 (1H, m), 1.93-2.00 (2H, m), 2.47 (1H, s), 3.81 (2H, d, *J* = 6.8 Hz), 4.52 (2H, s), 6.81 (1H, dd, *J* = 2.4, 7.6 Hz), 7.02 (1H, d, *J* = 7.6 Hz), 7.08 (1H, t, *J* = 2.0 Hz), 7.27 (1H, t, *J* = 8.4 Hz), 7.39-7.43 (2H, m), 7.53-7.57 (1H, m), 7.93-7.96 (2H, m); TOF-HRMS *m/z* [M+NH₄]⁺: Calcd. for C₂₁H₂₈NO₄, 358.2018; Found, 358.2025



(S)-2-(3-(Cyclopentylloxy)phenyl)-2-hydroxybutyl benzoate (32c)

A suspension of **31a** (400 mg, 1.4 mmol), bromocyclopentane (225 μ L, 2.1 mmol) and potassium carbonate (387 mg, 2.8 mmol) in DMF (4 mL) was stirred at 90 °C for 5 hr. The mixture was cooled

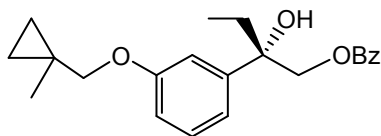
to room temperature and diluted with AcOEt (20 mL), and was then washed with water (20 mL×2) and brine (10 mL). The organic layer was dried over Na₂SO₄, and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (10-25% AcOEt in hexane) to give **32c** (387 mg, 78% as a colorless syrup). ¹H NMR (CDCl₃) δ 0.83 (3H, t, *J* = 7.6 Hz), 1.56-1.66 (2H, m), 1.74-2.17 (8H, m), 2.49 (1H, s), 4.52 (2H, dd, *J* = 11.6, 1.2 Hz), 4.75-4.80 (1H, m), 6.77-6.98 (1H, m), 7.00-7.14 (2H, m), 7.25 (1H, t, *J* = 8.0 Hz), 7.39-7.43 (2H, m), 7.52-7.57 (1H, m), 7.93-7.96 (2H, m); HR FAB-MS *m/z* [M+Na]⁺: Calcd. for C₂₂H₂₆O₄Na, 377.1729; Found, 377.1750



General procedure for the synthesis of 32d-32i. Exemplified for

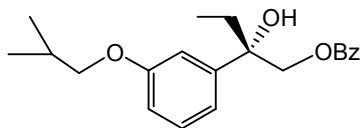
(S)-2-(3-Ethoxyphenyl)-2-hydroxybutyl benzoate (32d)

To a suspension of **31a** (300 mg, 1.05 mmol), triphenylphosphine (550 mg, 2.10 mmol) and EtOH (123 μL, 2.10 mmol) in THF (3 mL), was added a solution of diisopropyl azodicarboxylate (1.9 M, 1.11 mL, 2.10 mmol) in toluene at room temperature, and the mixture was stirred for 3 hr at room temperature. The reaction mixture was evaporated and the residue was purified by a silica gel column chromatography (10-20% AcOEt in hexane) to give **32d** (241 mg, 73% as a colorless syrup). ¹H NMR (CDCl₃) δ 0.83 (3H, t, *J* = 7.2 Hz), 1.41 (3H, t, *J* = 6.8 Hz), 1.89-2.03 (2H, m), 2.51 (1H, s), 4.04 (2H, q, *J* = 6.8 Hz), 4.53 (2H, dd, *J* = 11.6, 13.2 Hz), 6.79-6.82 (1H, m), 7.00-7.03 (1H, m), 7.07 (1H, t, *J* = 2.0 Hz), 7.27 (1H, t, *J* = 8.0 Hz), 7.39-7.43 (2H, m), 7.53-7.57 (1H, m), 7.93-7.96 (2H, m); FAB-HRMS *m/z* [M+Na]⁺: Calcd. for C₁₉H₂₂O₄Na, 337.1416; Found, 337.1396



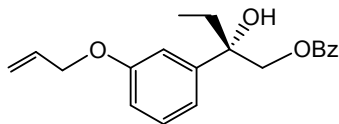
(S)-2-Hydroxy-2-(3-((1-methylcyclopropyl)methoxy)phenyl)butyl benzoate (32e)

From **31a** (300 mg, 1.05 mmol) and 1-methylcyclopropanemethanol (181 mg, 2.10 mmol), **32e** (320 mg, 86%) was obtained as a colorless syrup. ¹H NMR (CDCl₃) δ 0.41-0.44 (2H, m), 0.53-0.55 (2H, m), 0.84 (3H, t, *J* = 7.2 Hz), 1.23 (3H, s), 1.90-2.04 (2H, m), 2.49 (1H, s), 3.73 (2H, s), 4.52 (2H, s), 6.80 (1H, dd, *J* = 2.8, 8.4 Hz), 7.01 (1H, dd, *J* = 1.2, 8.0 Hz), 7.07 (1H, t, *J* = 2.0 Hz), 7.26 (1H, t, *J* = 8.4 Hz), 7.39-7.43 (2H, m), 7.52-7.57 (1H, m), 7.94-7.96 (2H, m); FAB-HRMS *m/z* [M+K]⁺: Calcd. for C₂₂H₂₆O₄K, 393.1468; Found, 393.1444



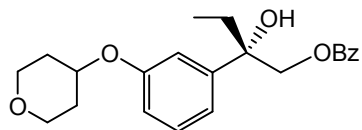
(S)-2-Hydroxy-2-(3-isobutoxyphenyl)butyl benzoate (32f)

From **31a** (300 mg, 1.05 mmol) and 2-methyl-1-propanol (156 μ L, 2.10 mmol), **32f** (310 mg, 86%) was obtained as a colorless syrup. ^1H NMR (CDCl_3) δ 0.84 (3H, t, $J = 7.6$ Hz), 1.02 (6H, d, $J = 6.8$ Hz), 1.90-2.00 (2H, m), 2.00-2.13 (1H, m), 2.50 (1H, s), 3.72 (2H, d, $J = 6.8$ Hz), 4.53 (2H, s), 6.80-6.82 (1H, m), 6.99-7.02 (1H, m), 7.07 (1H, t, $J = 2.0$ Hz), 7.27 (1H, t, $J = 8.4$ Hz), 7.40-7.43 (2H, m), 7.52-7.57 (1H, m), 7.94-7.97 (2H, m); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{21}\text{H}_{26}\text{O}_4\text{Na}$, 365.1729; Found, 365.1706



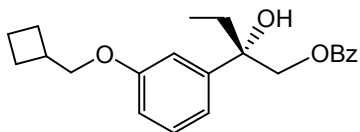
(S)-2-(3-(Allyloxy)phenyl)-2-hydroxybutyl benzoate (32g)

From **31a** (300 mg, 1.05 mmol) and allyl alcohol (143 μ L, 2.10 mmol), **32g** (274 mg, 80%) was obtained as a colorless syrup. ^1H NMR (CDCl_3) δ 0.83 (3H, t, $J = 7.2$ Hz), 1.89-2.03 (2H, m), 2.52 (1H, s), 4.53-4.56 (4H, m), 5.26-5.29 (1H, m), 5.38-5.44 (1H, m), 6.01-6.09 (1H, m), 6.83 (1H, dd, $J = 2.8, 8.4$ Hz), 7.02-7.04 (1H, m), 7.10 (1H, t, $J = 2.0$ Hz), 7.26-7.30 (1H, m), 7.39-7.43 (2H, m), 7.53-7.57 (1H, m), 7.93-7.95 (2H, m); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{20}\text{H}_{22}\text{O}_4\text{Na}$, 349.1416; Found, 349.1403



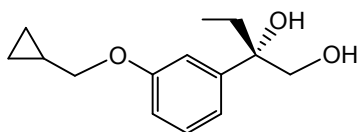
(S)-2-Hydroxy-2-(3-(tetrahydro-2H-pyran-4-yloxy)phenyl)butyl benzoate (32h)

From **31a** (300 mg, 1.05 mmol) and tetrahydro-4-pyranol (214 mg, 2.10 mmol), **32h** (331 mg, 85%) was obtained as a colorless solid. ^1H NMR (CDCl_3) δ 0.84 (3H, t, $J = 7.2$ Hz), 1.73-1.81 (2H, m), 1.92-2.03 (4H, m), 2.59 (1H, s), 3.52-3.58 (2H, m), 3.94-3.99 (2H, m), 4.46-4.52 (1H, m), 4.53 (2H, d, $J = 4.0$ Hz), 6.81-6.84 (1H, m), 7.02-7.04 (1H, m), 7.10 (1H, t, $J = 2.0$ Hz), 7.27 (1H, t, $J = 8.0$ Hz), 7.39-7.43 (2H, m), 7.53-7.57 (1H, m), 7.93-7.96 (2H, m); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{22}\text{H}_{26}\text{O}_5\text{Na}$, 393.1678; Found, 393.1670



(S)-2-(3-(Cyclobutylmethoxy)phenyl)-2-hydroxybutyl benzoate (32i)

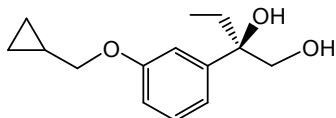
From **31a** (300 mg, 1.05 mmol) and cyclobutanemethanol (181mg, 2.10 mmol), **32i** (279 mg, 75%) was obtained as a colorless syrup. ^1H NMR (CDCl_3) δ 0.84 (3H, t, $J = 7.2$ Hz), 1.84-2.00 (6H, m), 2.12-2.16 (2H, m), 2.50 (1H, s), 2.71-2.82 (1H, m), 3.93 (2H, d, $J = 6.8$ Hz), 4.53 (2H, s), 6.80-6.83 (1H, m), 7.00-7.02 (1H, m), 7.08 (1H, t, $J = 2.0$ Hz), 7.27 (1H, t, $J = 8.0$ Hz), 7.39-7.43 (2H, m), 7.52-7.57 (1H, m), 7.94-7.97 (2H, m); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{22}\text{H}_{26}\text{O}_4\text{Na}$, 377.1729; Found, 377.1743



General procedure for the synthesis of 33a-33i. Exemplified for

(S)-2-(3-(Cyclopropylmethoxy)phenyl)butane-1,2-diol (33a)

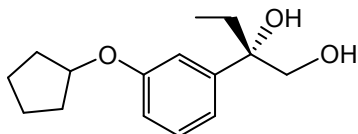
A solution of **32a** (810 mg, 2.38 mmol) in aq. 4.0 M NaOH (2.0 mL, 8 mmol) and MeOH (4.0 mL) was stirred at 50 °C for 2 hr. After MeOH was removed by concentration, AcOEt (10 mL) and water (10 mL) were added to the mixture and the layers were partitioned. The separated organic layer was washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (20-50% AcOEt in hexane) to give **33a** (540 mg, 96 % as a colorless syrup). ^1H NMR (CDCl_3) δ 0.34-0.38 (2H, m), 0.63-0.67 (2H, m), 0.78 (3H, t, $J = 7.6$ Hz), 1.24-1.31 (1H, m), 1.63 (1H, brs), 1.76-1.87 (2H, m), 2.57-2.58 (1H, m), 3.67 (1H, dd, $J = 8.4, 11.2$ Hz), 3.81-3.86 (3H, m), 6.78-6.81 (1H, m), 6.94-6.96 (1H, m), 7.01 (1H, t, $J = 2.4$ Hz), 7.27 (1H, t, $J = 7.6$ Hz); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{14}\text{H}_{19}\text{O}_3\text{Na}$, 259.1310; Found, 259.1300



(R)-2-(3-(Cyclopropylmethoxy)phenyl)butane-1,2-diol (33b)

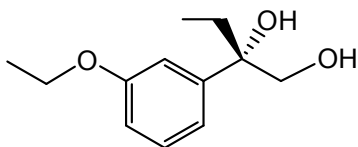
From **32b** (405 mg, 1.19 mmol), **33b** (273 mg, 97%) was obtained as a colorless syrup. ^1H NMR (CDCl_3) δ 0.34-0.38 (2H, m), 0.63-0.67 (2H, m), 0.78 (3H, t, $J = 7.2$ Hz), 1.23-1.33 (1H, m), 1.62 (1H, dd, $J = 4.8, 8.8$ Hz), 1.74-1.89 (2H, m), 2.57 (1H, s), 3.67 (1H, dd, $J = 8.8, 11.6$ Hz), 3.81-3.86 (3H, m), 6.78-6.81 (1H, m), 6.94-6.96 (1H, m), 7.01 (1H, t, $J = 2.0$ Hz), 7.27 (1H, t, $J = 8.0$ Hz);

FAB-HRMS m/z $[M-H]^-$: Calcd. for $C_{14}H_{19}O_3$, 235.1334; Found, 235.1335



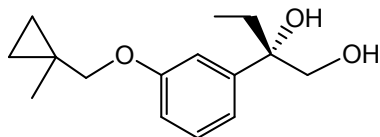
(S)-2-(3-(Cyclopentyloxy)phenyl)butane-1,2-diol (33c)

From **32c** (387 mg, 1.09 mmol), **33c** (240 mg, 88%) was obtained as a colorless syrup. 1H NMR ($CDCl_3$) δ 0.78 (3H, t, $J = 7.6$ Hz), 1.57-1.67 (3H, m), 1.74-1.97 (8H, m), 2.55 (1H, s), 3.67 (1H, dd, $J = 8.8, 11.2$ Hz), 3.84 (1H, dd, $J = 4.4, 10.8$ Hz), 4.76-4.80 (1H, m), 6.76-6.79 (1H, m), 6.91-6.93 (1H, m), 6.96 (1H, t, $J = 2.0$ Hz), 7.26 (1H, 7.6 Hz); FAB-HRMS m/z $[M+Na]^+$: Calcd. for $C_{15}H_{22}O_3Na$, 273.1467; Found, 273.1484



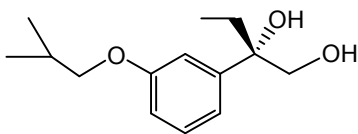
(S)-2-(3-Ethoxyphenyl)butane-1,2-diol (33d)

From **32d** (241 mg, 0.80 mmol), **33d** (161 mg, 95%) was obtained as a colorless syrup. 1H NMR ($CDCl_3$) δ 0.77 (3H, t, $J = 7.6$ Hz), 1.42 (3H, t, $J = 6.8$ Hz), 1.74-1.88 (3H, m), 2.64 (1H, s), 3.66 (1H, dd, $J = 8.8, 11.2$ Hz), 3.83 (1H, dd, $J = 4.0, 11.2$ Hz), 4.05 (2H, q, $J = 6.8$ Hz), 6.79 (1H, dd, $J = 2.8, 8.4$ Hz), 6.94 (1H, dd, $J = 0.8, 8.0$ Hz), 6.99 (1H, t, $J = 2.0$ Hz), 7.27 (1H, t, $J = 7.6$ Hz); FAB-HRMS m/z $[M+Na]^+$: Calcd. for $C_{12}H_{18}O_3Na$, 233.1154; Found, 233.1163



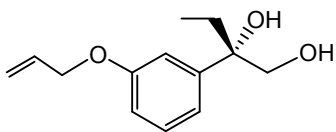
(S)-2-(3-((1-Methylcyclopropyl)methoxy)phenyl)butane-1,2-diol (33e)

From **32e** (320 mg, 0.84 mmol), **33e** (200 mg, 95%) was obtained as a colorless syrup. 1H NMR ($CDCl_3$) δ 0.42-0.45 (2H, m), 0.54-0.56 (2H, m), 0.78 (3H, t, $J = 7.6$), 1.24 (3H, s), 1.69 (1H, dd, $J = 4.4, 8.0$ Hz), 1.74-1.89 (2H, m), 2.60 (1H, s), 3.67 (1H, dd, $J = 8.4, 11.2$ Hz), 3.74 (2H, s), 3.84 (1H, dd, $J = 4.4, 11.2$ Hz), 6.77-6.80 (1H, m), 6.92-6.95 (1H, m), 7.00 (1H, t, $J = 2.0$ Hz), 7.26 (1H, t, $J = 8.0$ Hz); FAB-HRMS m/z $[M+Na]^+$: Calcd. for $C_{15}H_{22}O_3Na$, 273.1467; Found, 273.1455



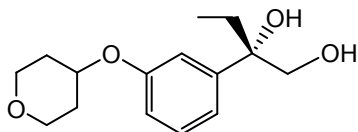
(S)-2-(3-Isobutoxyphenyl)butane-1,2-diol (33f)

From **32f** (310 mg, 0.90 mmol), **33f** (180 mg, 84%) was obtained as a colorless syrup. ^1H NMR (CDCl_3) δ 0.79 (3H, t, $J = 7.6$ Hz), 1.03 (6H, d, $J = 6.8$ Hz), 1.64 (1H, q, $J = 4.4$ Hz), 1.75-1.89 (2H, m), 2.03-2.13 (1H, m), 2.59 (1H, s), 3.68 (1H, dd, $J = 8.4, 10.8$ Hz), 3.73 (2H, d, $J = 6.4$ Hz), 3.85 (1H, dd, $J = 4.4, 10.8$ Hz), 6.78-6.81 (1H, m), 6.92-6.94 (1H, m), 7.00 (1H, t, $J = 2.0$ Hz), 7.27 (1H, t, $J = 8.0$ Hz); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{14}\text{H}_{22}\text{O}_3\text{Na}$, 261.1467; Found, 261.1461



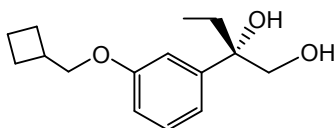
(S)-2-(3-(Allyloxy)phenyl)butane-1,2-diol (33g)

From **32g** (274 mg, 0.84 mmol), **33g** (151 mg, 81%) was obtained as a colorless syrup. ^1H NMR (CDCl_3) δ 0.77 (3H, t, $J = 7.6$ Hz), 1.74-1.89 (3H, m), 2.64 (1H, s), 3.67 (1H, dd, $J = 8.0, 11.2$ Hz), 3.83 (1H, dd, $J = 4.0, 11.2$ Hz), 4.54-4.56 (2H, m), 5.28-5.31 (1H, m), 5.40-5.45 (1H, m), 6.03-6.10 (1H, m), 6.80-6.83 (1H, m), 6.94-6.97 (1H, m), 7.03 (1H, t, $J = 2.0$ Hz), 7.25-7.29 (1H, m); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{13}\text{H}_{18}\text{O}_3\text{Na}$, 245.1154; Found, 245.1146



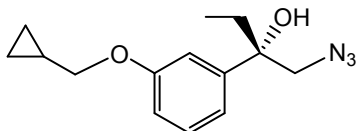
(S)-2-(3-(Tetrahydro-2H-pyran-4-yloxy)phenyl)butane-1,2-diol (33h)

From **32h** (331 mg, 0.89 mmol), **33h** (190 mg, 80%) was obtained as a colorless syrup. ^1H NMR (CDCl_3) δ 0.78 (3H, t, $J = 7.6$ Hz), 1.66 (1H, dd, $J = 4.4, 8.4$ Hz), 1.75-1.88 (4H, m), 1.99-2.06 (2H, m), 2.59 (1H, s), 3.56-3.61 (2H, m), 3.68 (1H, dd, $J = 8.4, 11.2$ Hz), 3.84 (1H, dd, $J = 4.4, 11.2$ Hz), 3.96-4.02 (2H, m), 4.48-4.54 (1H, m), 6.81 (1H, dd, $J = 2.0, 7.6$ Hz), 6.93-6.96 (1H, m), 7.04 (1H, t, $J = 1.6$ Hz), 7.27 (1H, t, $J = 8.0$ Hz); FAB-HRMS m/z $[\text{M}+\text{K}]^+$: Calcd. for $\text{C}_{15}\text{H}_{22}\text{O}_4\text{K}$, 305.1155; Found, 305.1174



(S)-2-(3-(Cyclobutylmethoxy)phenyl)butane-1,2-diol (33i)

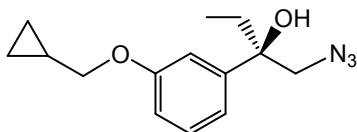
From **32i** (279 mg, 0.79 mmol), **33i** (183 mg, 93%) was obtained as a colorless syrup. ^1H NMR (CDCl_3) δ 0.78 (3H, t, $J = 7.6$ Hz), 1.72 (1H, dd, $J = 4.4$ Hz), 1.76-2.03 (6H, m), 2.11-2.18 (2H, m), 2.62 (1H, s), 2.71-2.82 (1H, m), 3.67 (1H, dd, $J = 8.0, 10.8$ Hz), 3.83 (1H, dd, $J = 3.6, 11.2$ Hz), 3.94 (2H, d, $J = 6.4$ Hz), 6.80 (1H, dd, $J = 2.4, 8.0$ Hz), 6.92-6.94 (1H, m), 7.00 (1H, t, $J = 2.0$ Hz), 7.26 (1H, t, $J = 8.0$ Hz); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{15}\text{H}_{22}\text{O}_3\text{Na}$, 273.1467; Found, 273.1448



General procedure for the synthesis of **34a-34i**. Exemplified for

(S)-1-Azido-2-(3-(cyclopropylmethoxy)phenyl)butan-2-ol (34a)

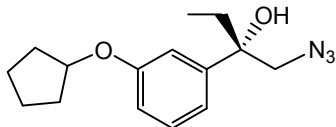
To a mixture of **33a** (500 mg, 2.12 mmol) and triethylamine (441 μL , 3.18 mmol) in CH_2Cl_2 (10 mL) was added methanesulfonyl chloride (197 μL , 2.54 mmol) at 0 $^\circ\text{C}$, and the mixture was stirred at room temperature for 30 min. Saturated aq. NaHCO_3 (10 mL) was added to the mixture and the layers were partitioned. The organic layer was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was dissolved in DMF (10 mL). Sodium azide (551 mg, 8.48 mmol) was added to the mixture, and the mixture was stirred at 90 $^\circ\text{C}$ for 12 hr. The mixture was cooled to room temperature and diluted with AcOEt (10 mL), and was then washed with water (10 mL \times 2) and brine (10 mL). The organic layer was dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (5-10% AcOEt in hexane) to give **34a** (410 mg, 74% as a colorless syrup). ^1H NMR (CDCl_3) δ 0.34-0.38 (2H, m), 0.63-0.67 (2H, m), 0.77 (3H, t, $J = 7.6$ Hz), 1.24-1.31 (1H, m), 1.81-1.92 (2H, m), 2.26 (1H, s), 3.50 (1H, d, $J = 12.0$ Hz), 3.64 (1H, d, $J = 12.0$ Hz), 3.82 (2H, d, $J = 7.2$ Hz), 6.81 (1H, dd, $J = 2.4, 8.4$ Hz), 6.92-6.93 (1H, m), 6.99 (1H, t, $J = 2.4$ Hz), 7.27 (1H, t, $J = 8.0$ Hz); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{14}\text{H}_{19}\text{N}_3\text{O}_2\text{Na}$, 284.1375; Found, 284.1379



(R)-1-Azido-2-(3-(cyclopropylmethoxy)phenyl)butan-2-ol (34b)

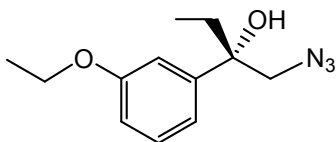
From **33b** (273 mg, 1.15 mmol), **34b** (241 mg, 80 %) was obtained as a colorless syrup. ^1H NMR (CDCl_3) δ 0.34-0.38 (2H, m), 0.63-0.68 (2H, m), 0.78 (3H, t, $J = 7.2$ Hz), 1.23-1.33 (1H, m), 1.79-1.94 (2H, m), 2.25 (1H, s), 3.50 (1H, d, $J = 12.4$ Hz), 3.64 (1H, d, $J = 12.4$ Hz), 3.82 (2H, d, $J =$

7.2 Hz), 6.80-6.83 (1H, m), 6.93 (1H, d, $J = 8.00$ Hz), 6.99 (1H, t, $J = 2.4$ Hz), 7.27 (1H, t, $J = 8.0$ Hz); FAB-HRMS m/z $[M+Na]^+$: Calcd. for $C_{14}H_{19}N_3O_2Na$, 284.1375; Found, 284.1370



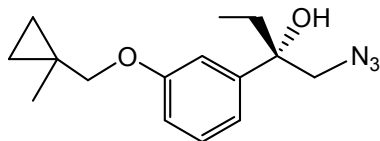
(S)-1-Azido-2-(3-(cyclopentyloxy)phenyl)butan-2-ol (34c)

From **33c** (220 mg, 0.88 mmol), **34c** (210 mg, 87%) was obtained as a colorless syrup. 1H NMR ($CDCl_3$) δ 0.78 (3H, t, $J = 7.6$ Hz), 1.60-1.64 (2H, m), 1.76-1.96 (8H, m), 2.25 (1H, s), 3.49 (1H, d, $J = 12.0$ Hz), 3.64 (1H, d, $J = 12.4$ Hz), 4.76-4.79 (1H, m), 6.78-6.80 (1H, m), 6.89-6.91 (1H, m), 6.94 (1H, t, $J = 2.0$ Hz), 7.26 (1H, t, $J = 8.0$ Hz); FAB-HRMS m/z $[M+Na]^+$: Calcd. for $C_{15}H_{21}N_3O_2Na$, 298.1531; Found, 298.1514



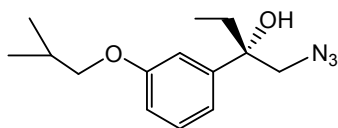
(S)-1-Azido-2-(3-ethoxyphenyl)butan-2-ol (34d)

From **33d** (161 mg, 0.76 mmol), **34d** (143 mg, 80 %) was obtained as a colorless syrup. 1H NMR ($CDCl_3$) δ 0.77 (3H, t, $J = 7.6$ Hz), 1.42 (3H, t, $J = 7.2$ Hz), 1.79-1.94 (2H, m), 2.29 (1H, s), 3.50 (1H, d, $J = 12.0$ Hz), 3.64 (1H, d, $J = 12.4$ Hz), 4.05 (2H, q, $J = 7.2$ Hz), 6.80-6.83 (1H, m), 6.91-6.94 (1H, m), 6.98 (1H, t, $J = 2.4$ Hz), 7.27 (1H, t, $J = 8.0$ Hz) HR FAB-MS m/z $[M+Na]^+$: Calcd. for $C_{12}H_{17}N_3O_2Na$, 258.1218; Found, 258.1209



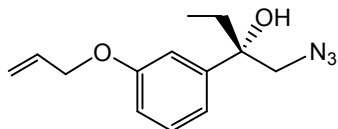
(S)-1-Azido-2-(3-((1-methylcyclopropyl)methoxy)phenyl)butan-2-ol (34e)

From **33e** (180 mg, 0.72 mmol), **34e** (137 mg, 69 %) was obtained as a colorless syrup. 1H NMR ($CDCl_3$) δ 0.42-0.45 (2H, m), 0.54-0.56 (2H, m), 0.78 (3H, t, $J = 7.2$ Hz), 1.24 (3H, s), 1.79-1.94 (2H, m), 2.28 (1H, s), 3.50 (1H, d, $J = 12.0$ Hz), 3.64 (1H, d, $J = 12.8$ Hz), 3.74 (2H, s), 6.79-6.81 (1H, m), 6.90-6.92 (1H, m), 6.99 (1H, t, $J = 2.4$ Hz), 7.26 (1H, t, $J = 8.0$ Hz); FAB-HRMS m/z $[M+Na]^+$: Calcd. for $C_{15}H_{21}N_3O_2Na$, 298.1531; Found, 298.1518



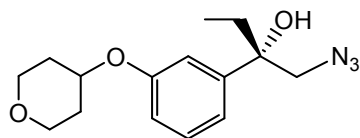
(S)-1-Azido-2-(3-isobutoxyphenyl)butan-2-ol (34f)

From **33f** (180 mg, 0.76 mmol), **34f** (149 mg, 75%) was obtained as a colorless syrup. ^1H NMR (CDCl_3) δ 0.78 (3H, t, $J = 7.6$ Hz), 1.03 (6H, d, $J = 6.4$ Hz), 1.79-1.94 (2H, m), 2.03-2.10 (1H, m), 2.13 (1H, s), 3.50 (1H, d, $J = 12.4$ Hz), 3.65 (1H, d, $J = 12.4$ Hz), 3.73 (2H, d, $J = 6.4$ Hz), 6.80-6.82 (1H, m), 6.89-6.92 (1H, m), 6.98 (1H, t, $J = 2.0$ Hz), 7.27 (1H, t, $J = 8.0$ Hz); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{14}\text{H}_{21}\text{N}_3\text{O}_2\text{Na}$, 286.1531; Found, 286.1537



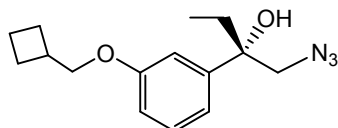
(S)-2-(3-(Allyloxy)phenyl)-1-azidobutan-2-ol (34g)

From **33g** (151 mg, 0.68 mmol), **34g** (118 mg, 70%) was obtained as a colorless syrup. ^1H NMR (CDCl_3) δ 0.77 (3H, t, $J = 7.6$ Hz), 1.79-1.94 (2H, m), 2.26 (1H, s), 3.50 (1H, d, $J = 12.4$ Hz), 3.64 (1H, d, $J = 12.4$ Hz), 4.55 (2H, dt, $J = 1.2, 5.2$ Hz), 5.28-5.31 (1H, m), 5.40-5.45 (1H, m), 6.02-6.12 (1H, m), 6.83 (1H, dd, $J = 2.4, 8.0$ Hz), 6.93-6.95 (1H, m), 7.01 (1H, t, $J = 2.0$ Hz), 7.26-7.30 (1H, m); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_2\text{Na}$, 270.1218; Found, 270.1207



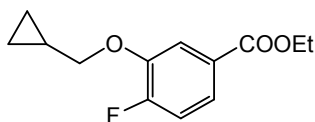
(S)-1-Azido-2-(3-(tetrahydro-2H-pyran-4-yloxy)phenyl)butan-2-ol (34h)

From **33h** (190 mg, 0.71 mmol), **34h** (131 mg, 63%) was obtained as a colorless syrup. ^1H NMR (CDCl_3) δ 0.78 (3H, t, $J = 7.6$ Hz), 1.75-1.94 (4H, m), 1.99-2.06 (2H, m), 2.29 (1H, s), 3.50 (1H, d, $J = 12.0$ Hz), 3.56-3.62 (2H, m), 3.64 (1H, d, $J = 12.0$ Hz), 3.96-4.02 (2H, m), 4.48-4.54 (1H, m), 6.83 (1H, dd, $J = 2.4, 8.0$ Hz), 6.92-6.94 (1H, m), 7.01 (1H, t, $J = 2.0$ Hz), 7.28 (1H, t, $J = 8.0$ Hz); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_4\text{Na}$, 314.1481; Found, 314.1477



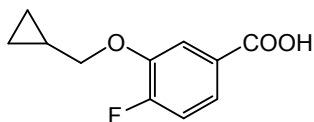
(S)-1-Azido-2-(3-(cyclobutylmethoxy)phenyl)butan-2-ol (34i)

From **33i** (183 mg, 0.73 mmol), **34i** (142 mg, 70%) was obtained as a colorless syrup. ^1H NMR (CDCl_3) δ 0.78 (3H, t, $J = 7.59$ Hz), 1.79-2.03 (6H, m), 2.11-2.18 (2H, m), 2.27 (1H, s), 2.73-2.83 (1H, m), 3.50 (1H, d, $J = 12.39$ Hz), 3.65 (1H, d, $J = 12.39$ Hz), 3.94 (2H, d, $J = 6.79$ Hz), 6.80-6.83 (1H, m), 6.90-6.93 (1H, m), 6.98 (1H, t, $J = 1.60$ Hz), 7.27 (1H, t, $J = 7.99$ Hz); FAB-HRMS m/z $[\text{M}+\text{Na}]^+$: Calcd. for $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_2\text{Na}$, 298.1531; Found, 298.1530



Ethyl 3-(cyclopropylmethoxy)-4-fluorobenzoate (**36**)

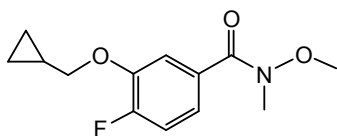
A solution of 4-fluoro-3-hydroxybenzoic acid **35** (15 g, 96 mmol) and sulfonic acid (3.2 mL) in EtOH (250 mL) was heated to reflux for 4 hr. The mixture was cooled to room temperature and evaporated *in vacuo*. The residue was diluted with water (50 mL) and neutralized with sodium hydrogencarbonate (5.0 g), and was then extracted with AcOEt (200 mL). The separated organic layer was washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo* to give ethyl 4-fluoro-3-hydroxybenzoate 17.6 g, quant. as a colorless solid. [^1H NMR (CDCl_3) δ 1.39 (3H, t, $J = 7.0$ Hz), 4.36 (2H, q, $J = 7.0$ Hz), 5.34 (1H, d, $J = 4.3$ Hz), 7.12 (1H, dd, $J = 8.6, 10.3$ Hz), 7.58-7.63 (1H, m), 7.71 (1H, dd, $J = 2.2, 8.6$ Hz).] A suspension of ethyl 4-fluoro-3-hydroxybenzoate (10 g, 54.3 mmol), (bromomethyl)cyclopropane (6.32 mL, 65.2 mmol) and potassium carbonate (15 g, 109 mmol) in DMF (100 mL) was stirred at 90 °C for 5 hr. The mixture was cooled to room temperature and diluted with toluene (200 mL), which was washed with water (100 mL \times 3), aq. 1.0 M NaOH (50 mL \times 2) and brine (100 mL). The organic layer was dried over Na_2SO_4 , and filtered. The filtrate was evaporated to give **36** (13.0 g, quant. as a colorless syrup), and it was used for the next step without further purification. ^1H NMR (CDCl_3) δ 0.36-0.40 (2H, m), 0.65-0.69 (2H, m), 1.27-1.36 (1H, m), 1.39 (3H, t, $J = 7.2$ Hz), 3.93 (2H, d, $J = 6.8$ Hz), 4.36 (2H, q, $J = 6.8$ Hz), 7.08-7.13 (1H, m), 7.61-7.64 (2H, m); HR FAB-MS m/z $[\text{M}+\text{H}]^+$: Calcd. for $\text{C}_{13}\text{H}_{16}\text{FO}_3$, 239.1083; Found, 239.1109



3-(Cyclopropylmethoxy)-4-fluorobenzoic acid (**37**)

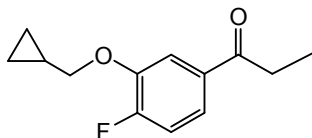
A solution of **36** (13 g, 54.3 mmol) in EtOH (80 mL) and aq. 4.0 M NaOH (40 mL) was stirred at 60 °C for 4 hr. The mixture was cooled to room temperature and EtOH was removed by concentration. The residue was diluted with water (100 mL), and was acidified with aq. 4.0 M HCl (38 mL) and then extracted with AcOEt (200 mL \times 2). The combined organic layer was washed with water (100

mL) and brine (100 mL), and dried over Na₂SO₄, and filtered. The filtrate was evaporated to give **37** (11.51 g, quant. as a colorless solid). ¹H NMR (CDCl₃) δ 0.36-0.40 (2H, m), 0.65-0.70 (2H, m), 1.27-1.35 (1H, m), 3.93 (2H, d, *J* = 7.2 Hz), 7.14 (1H, t, *J* = 10.4 Hz), 7.66-7.71 (2H, m); HR FAB-MS *m/z* [M-H]⁻: Calcd. for C₁₁H₁₀FO₃, 209.0614; Found, 209.0623



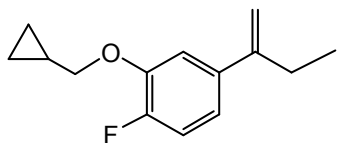
3-(Cyclopropylmethoxy)-4-fluoro-N-methoxy-N-methylbenzamide (**38**)

A mixture of **37** (11.51 g, 54.3 mmol), *N,O*-dimethylhydroxylamine hydrochloride (6.36 g, 65.2 mmol), EDC·HCl (15.75 g, 82.1 mmol), triethylamine (9.78 mL, 70.5 mmol) and HOBt (8.81 g, 65.2 mmol) in DMF (150 mL) was stirred at room temperature for 6 hr. Water (150 mL), AcOEt (150 mL) and Toluene (100 mL) were added to the reaction mixture and the layers were partitioned. The aqueous layer was extracted with AcOEt (100 mL) and the combined organic layer was washed with brine (100 mL), dried over Na₂SO₄, and filtered. The filtrate was evaporated *in vacuo*, and the residue purified by silica gel column chromatography (20-33% AcOEt in hexane) to give **38** (10.6 g, 77% as a colorless syrup). ¹H NMR (CDCl₃) δ 0.34-0.38 (2H, m), 0.63-0.68 (2H, m), 1.26-1.36 (1H, m), 3.35 (3H, s), 3.55 (3H, s), 3.90 (2H, d, *J* = 6.8 Hz), 7.09 (1H, dd, *J* = 8.0, 19.2 Hz), 7.26-7.32 (1H, m), 7.35 (1H, dd, *J* = 2.0, 8.4 Hz); FAB-HRMS *m/z* [M+H]⁺: Calcd. for C₁₃H₁₇FNO₃, 254.1192; Found, 254.1189



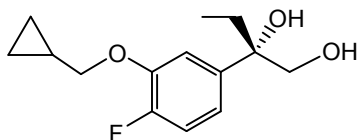
1-(3-(Cyclopropylmethoxy)-4-fluorophenyl)propan-1-one (**39**)

A solution of ethylmagnesium bromide (3.0 M, 35 mL, 105 mmol) in Et₂O was added to a solution of **38** (10.60 g, 41.9 mmol) in THF (150 mL) dropwise over 10 min at 0 °C under N₂ atmosphere, and stirred at the same temperature for 3 hr. The reaction was quenched by the addition of saturated aq. NH₄Cl (100 mL). The separated organic layer was washed with brine (100 mL), dried (Na₂SO₄), and concentrated to dryness *in vacuo*. The residue was purified by silica gel column chromatography (2-10% AcOEt in hexane) to give **39** (9.3 g, quant. as a colorless syrup). ¹H NMR (CDCl₃) δ 0.36-0.40 (2H, m), 0.64-0.69 (2H, m), 1.22 (3H, t, *J* = 7.2 Hz), 1.28-1.36 (1H, m), 2.96 (2H, q, *J* = 7.2 Hz), 3.94 (2H, d, *J* = 7.2 Hz), 7.13 (1H, dd, *J* = 8.4, 10.8 Hz), 7.51-7.54 (1H, m), 7.60 (1H, dd, *J* = 2.0, 8.4 Hz); HR FAB-MS *m/z* [M+H]⁺: Calcd. for C₁₃H₁₆FO₂, 223.1134; Found, 223.1127



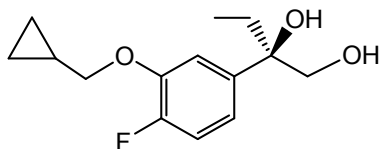
4-(But-1-en-2-yl)-2-(cyclopropylmethoxy)-1-fluorobenzene (**40**)

To a suspension of methyltriphenylphosphonium bromide (26.9 g, 75 mmol) in THF (200 mL), was added a solution of sodium bis(trimethylsilyl)amide (75 mL, 1.0 M, 75 mmol) in THF at 0 °C and the mixture was stirred at room temperature for 2 hr. A solution of **39** (9.3 g, 41.9 mmol) in THF (50 mL) was added to the mixture dropwise at 0 °C and the reaction was stirred at room temperature for 12 hr. The reaction was quenched by the addition of saturated aq. NH_4Cl (150 mL) and extracted with AcOEt (150 mL). The organic layer was washed with water (150 mL) and brine (150 mL), dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (0-2% AcOEt in hexane) to give **40** (8.75 g, 95% as a colorless syrup). ^1H NMR (CDCl_3) δ 0.35-0.38 (2H, m), 0.63-0.67 (2H, m), 1.07 (3H, t, $J = 7.2$ Hz), 1.24-1.34 (1H, m), 2.43-2.49 (2H, m), 3.89 (2H, d, $J = 6.8$ Hz), 5.03 (1H, d, $J = 1.2$ Hz), 5.19 (1H, s), 6.91-6.94 (1H, m), 6.98-7.04 (2H, m); FAB-HRMS m/z $[\text{M}+\text{H}]^+$: Calcd. for $\text{C}_{14}\text{H}_{18}\text{FO}$, 221.1342; Found, 221.1324



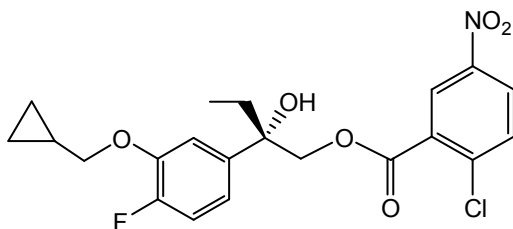
(S)-2-(3-(Cyclopropylmethoxy)-4-fluorophenyl)butane-1,2-diol (**41a**)

To a solution of **40** (7.0 g, 31.8 mmol) in *tert*-butanol (150 mL) and water (150 mL), was added AD-mix α (45 g) at 0 °C, and the mixture was stirred at 0 °C for 3 hr. The reaction was quenched by the addition of saturated aq. sodium hydrogensulfite (50 mL) at 0 °C and then extracted with AcOEt (200 mL). The separated organic layer was washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (25-50% AcOEt in hexane) to give **41a** (8.0 g, 99% as a colorless syrup). ^1H NMR (CDCl_3) δ 0.34-0.38 (2H, m), 0.63-0.67 (2H, m), 0.77 (3H, t, $J = 7.2$ Hz), 1.25-1.35 (1H, m), 1.72-1.88 (2H, m), 2.57 (1H, brs), 3.67 (1H, d, $J = 11.2$ Hz), 3.81 (1H, d, $J = 11.2$ Hz), 3.90 (2H, d, $J = 6.8$ Hz), 6.84-6.88 (1H, m), 7.03-7.11 (2H, m); FAB-HRMS m/z $[\text{M}-\text{H}]^-$: Calcd. for $\text{C}_{14}\text{H}_{18}\text{FO}_3$, 253.1240; Found, 253.1230



(R)-2-(3-(Cyclopropylmethoxy)-4-fluorophenyl)butane-1,2-diol (41b)

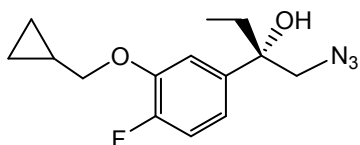
To a solution of **40** (500 mg, 2.27 mmol) in *tert*-butanol (8 mL) and water (8 mL) was added AD-mix β (3 g) at 0 °C, and the mixture was stirred at 0 °C for 3 hr. The reaction mixture was quenched by the addition of saturated aq. sodium hydrogensulfite (10 mL) at 0 °C and then extracted with AcOEt (50 mL). The separated organic layer was washed with water (50 mL) and brine (50 mL), dried over Na₂SO₄, and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (33-50% AcOEt in hexane) to give **41b** (577 mg, quant. as a colorless syrup). ¹H NMR (CDCl₃) δ 0.34-0.38 (2H, m), 0.63-0.67 (2H, m), 0.77 (3H, t, *J* = 7.6 Hz), 1.26-1.34 (1H, m), 1.56-1.59 (1H, m), 1.72-1.87 (2H, m), 2.54 (1H, s), 3.67 (1H, dd, *J* = 8.4, 11.2 Hz), 3.81 (1H, dd, *J* = 4.8, 11.2 Hz), 3.90 (2H, d, *J* = 6.8 Hz), 6.84-6.88 (1H, m), 7.03-7.11 (2H, m); TOF-HRMS *m/z* [M+NH₄]⁺: Calcd. for C₁₄H₂₃NO₃F, 272.1662; Found, 272.1661



(S)-2-(3-(Cyclopropylmethoxy)-4-fluorophenyl)-2-hydroxybutyl 2-chloro-5-nitrobenzoate (42)

To a mixture of **41a** (5.48 g, 21.55 mmol) and triethylamine (5.97 mL, 43.1 mmol) in dichloromethane (100 mL), was added 2-chloro-4-nitrobenzoyl chloride (5.22 g, 23.70 mmol) at 0 °C and the reaction was stirred at room temperature for 3 hr. The reaction mixture was quenched by the addition of saturated aq. NaHCO₃ (80 mL). The separated organic layer was washed with water (100 mL) and brine (100 mL), dried over Na₂SO₄, and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (15-25% AcOEt in hexane) to give crude **42** (7.74 g as a colorless solid). It was crystallized two times from AcOEt-hexane to give **42** (6.57 g, 70% as a colorless solid). ¹H NMR (DMSO-*d*₆) δ 0.29-0.32 (2H, m), 0.52-0.57 (2H, m), 0.70 (3H, t, *J* = 7.2 Hz), 1.14-1.25 (1H, m), 1.81-1.93 (2H, m), 3.86 (2H, d, *J* = 7.2 Hz), 4.44 (1H, d, *J* = 10.8 Hz), 4.52 (1H, d, *J* = 10.8 Hz), 5.39 (1H, s), 7.02-7.06 (1H, m), 7.14 (1H, dd, *J* = 8.4, 11.2 Hz), 7.24 (1H, dd, *J* = 2.0, 8.4 Hz), 7.86 (1H, d, *J* = 8.8 Hz), 8.36 (1H, dd, *J* = 2.8, 8.8 Hz), 8.42 (1H, d, *J* = 2.8 Hz); TOF-HRMS *m/z* [M+NH₄]⁺: Calcd. for C₂₁H₂₅N₂O₆FCl, 455.1385; Found, 455.1377; [α]_D²⁵ = -18.15 (c 1.08, CHCl₃); 99.8% e.e. [HPLC condition, Column: CHIRALPAK IA-3 (4.6×250

mm), Column Temp.:25 °C, Mobile phase: hexane/ethanol (70:30), Flow rate: 0.8 mL/min., Detector: UV 230 nm, **42** was eluted at 9.7 min]

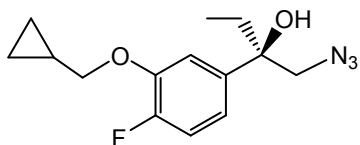


(S)-1-Azido-2-(3-(cyclopropylmethoxy)-4-fluorophenyl)butan-2-ol (43)

A solution of **42** (6.23 g, 14.23 mmol) in aq. 4.0 M NaOH solution (10.67 mL, 42.68 mmol) and MeOH (40 mL) was stirred at 50 °C for 2 hr. After MeOH was removed by concentration, AcOEt (100 mL) and water (100 mL) were added to the residue and the layers were partitioned. The separated organic layer was washed with water (50 mL) and brine (50 mL), dried over Na₂SO₄, and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (20-50% AcOEt in hexane) to give

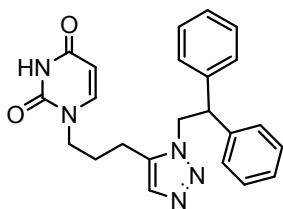
(S)-2-(3-(cyclopropylmethoxy)-4-fluorophenyl)butane-1,2-diol (3.55 g, 98 % as a colorless syrup).

It was then dissolved in dichloromethane (70 mL), and triethylamine (2.9 mL, 20.94 mmol), methanesulfonyl chloride (1.30 mL, 16.75 mmol) were added to the mixture at 0 °C which was then stirred at room temperature for 30 min. Saturated aq. NaHCO₃ (50 mL) was added to the mixture, and the layers were partitioned. The organic layer was washed with water (50 mL) and brine (50 mL), dried over Na₂SO₄, and filtered. The filtrate was evaporated *in vacuo*, and the residue was dissolved in DMF (70 mL). Sodium azide (551 mg, 8.48 mmol) was added to the mixture which was then stirred at 90 °C for 12 hr. The mixture was cooled to room temperature and diluted with AcOEt (150 mL), and washed with water (100 mL) and brine (100 mL). The organic layer was dried over Na₂SO₄, and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (5-10% AcOEt in hexane) to give **43** (2.53 mg, 65% as a colorless syrup).
¹H NMR (CDCl₃) δ 0.34-0.38 (2H, m), 0.63-0.67 (2H, m), 0.77 (3H, t, *J* = 7.6 Hz), 1.25-1.35 (1H, m), 1.77-1.93 (2H, m), 3.49 (1H, d, *J* = 12.4 Hz), 3.61 (1H, d, *J* = 12.4 Hz), 3.90 (2H, d, *J* = 6.8 Hz), 6.83-6.86 (1H, m), 7.00-7.09 (2H, m); HR FAB-MS *m/z* [M+Na]⁺: Calcd. for C₁₄H₁₈FN₃O₂Na, 302.1281; Found, 302.1295



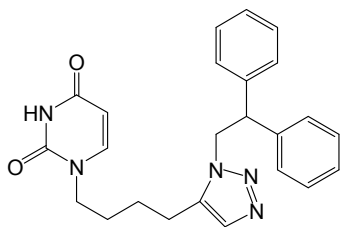
(R)-1-Azido-2-(3-(cyclopropylmethoxy)-4-fluorophenyl)butan-2-ol (44)

To a mixture of **41b** (150 mg, 0.59 mmol) and triethylamine (123 μ L, 0.89 mmol) in CH_2Cl_2 (2 mL), was added methanesulfonyl chloride (55 μ L, 0.71 mmol) at 0 $^\circ\text{C}$, and the mixture was stirred at room temperature for 30 min. Saturated aq. NaHCO_3 (5 mL) was added to the mixture and the layers were partitioned. The organic layer was washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was dissolved in DMF (3 mL). Sodium azide (153 mg, 2.36 mmol) was added to the mixture which was then stirred at 90 $^\circ\text{C}$ for 12 hr. The mixture was cooled to room temperature and diluted with AcOEt (10 mL), and washed with water (10 mL \times 2) and brine (10 mL). The organic layer was dried over Na_2SO_4 , and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (5-10% AcOEt in hexane) to give **44** (147 mg, 89% as a colorless syrup). ^1H NMR (CDCl_3) δ 0.34-0.38 (2H, m), 0.63-0.68 (2H, m), 0.77 (3H, t, J = 7.6 Hz), 1.25-1.34 (1H, m), 1.77-1.93 (2H, m), 2.23 (1H, s), 3.49 (1H, d, J = 12.4 Hz), 3.61 (1H, d, J = 12.4 Hz), 3.90 (2H, d, J = 7.2 Hz), 6.83-6.86 (1H, m), 7.03-7.09 (2H, m); FAB-HRMS m/z $[\text{M}+\text{K}]^+$: Calcd. for $\text{C}_{14}\text{H}_{18}\text{FN}_3\text{O}_2\text{K}$, 318.1020; Found, 318.1008



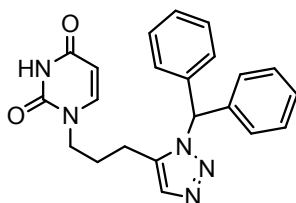
General procedure for the synthesis of 45a-b, 46a-b, 47a-g, 48a-d, 49a-h, 50a-d. Exemplified for 1-(3-(1-(2,2-Diphenylethyl)-1H-1,2,3-triazol-5-yl)propyl)pyrimidine-2,4(1H,3H)-dione (45a)

A mixture of **9a** (50 mg, 0.28 mmol), 2,2-diphenyl-azidoethane³ (63 mg, 0.28 mmol) and $\text{Cp}^*\text{RuCl}(\text{COD})$ (10 mg) in dioxane (2.0 mL) was stirred at 80 $^\circ\text{C}$ for 3 hr. The reaction mixture was evaporated *in vacuo* and the residue was purified by a silica gel column chromatography (1-5% MeOH in CHCl_3) to give **45a** (64 mg, 57% as a colorless solid). ^1H NMR (CDCl_3) δ 1.69-1.77 (2H, m), 2.00 (2H, t, J = 7.3 Hz), 3.56 (2H, t, J = 7.0 Hz), 4.71-4.80 (3H, m), 5.72 (1H, d, J = 7.8 Hz), 7.01 (1H, d, J = 7.8 Hz), 7.08-7.45 (11H, m), 9.52 (1H, brs); ^{13}C NMR ($\text{DMSO}-d_6$) δ 19.20, 26.23, 46.85, 50.93, 50.99, 100.98, 126.78, 127.89, 128.46, 130.90, 136.90, 141.33, 145.52, 150.95, 163.71; Anal. Calcd for $\text{C}_{23}\text{H}_{23}\text{N}_5\text{O}_2$: C, 68.81; H, 5.77; N, 17.44. Found: C, 68.46; H, 5.66; N, 17.44



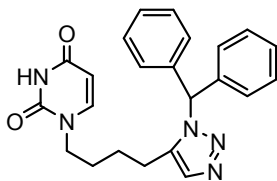
1-(4-(1-(2,2-Diphenylethyl)-1*H*-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1*H*,3*H*)-dione (45b)

From **9b** (50 mg, 0.26 mmol) and 2,2-diphenyl-azidoethane³ (58 mg, 0.26 mmol), **45b** (71 mg, 66%) was obtained as a colorless solid. ¹H NMR (DMSO-*d*₆) δ 1.30-1.39 (2H, m), 1.45-1.53 (2H, m), 2.40 (2H, t, *J* = 7.3 Hz), 3.61 (2H, t, *J* = 6.8 Hz), 4.65 (1H, t, *J* = 7.8 Hz), 4.91 (2H, d, *J* = 7.8 Hz), 5.54 (1H, d, *J* = 7.8 Hz), 7.15-7.34 (11H, m), 7.60 (1H, d, *J* = 7.8 Hz), 11.21 (1H, brs); ¹³C NMR (DMSO-*d*₆) δ 21.52, 24.39, 27.92, 47.01, 50.88, 51.01, 100.84, 126.75, 127.91, 128.43, 130.95, 137.48, 141.40, 145.61, 150.91, 163.71; Anal. Calcd for C₂₄H₂₅N₅O₂: C, 69.38; H, 6.06; N, 16.86. Found: C, 69.26; H, 6.06; N, 16.86



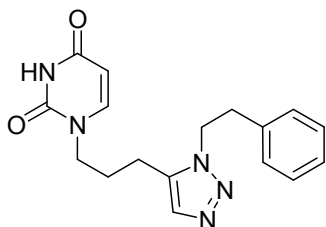
1-(3-(1-Benzhydryl-1*H*-1,2,3-triazol-5-yl)propyl)pyrimidine-2,4(1*H*,3*H*)-dione (46a)

From **9a** (50 mg, 0.28 mmol) and benzhydrylazide⁴ (59 mg, 0.28 mmol), **46a** (60 mg, 55%) was obtained as a colorless solid. ¹H NMR (DMSO-*d*₆) δ 1.82 (2H, t, *J* = 7.0 Hz), 2.68 (2H, t, *J* = 7.6 Hz), 3.65 (2H, t, *J* = 7.0 Hz), 5.50 (1H, d, *J* = 7.8 Hz), 7.04 (1H, s), 7.17 (4H, d, *J* = 8.1 Hz), 7.29-7.40 (6H, m), 7.50 (1H, d, *J* = 7.8 Hz), 7.67 (1H, s), 11.2 (1H, brs); ¹³C NMR (DMSO-*d*₆) δ 19.61, 26.79, 46.73, 63.84, 100.97, 127.94, 128.25, 128.53, 131.68, 137.10, 138.73, 145.40, 150.92, 163.66; Anal. Calcd for C₂₂H₂₁N₅O₂·0.2H₂O: C, 67.57; H, 5.52; N, 17.91. Found: C, 67.58; H, 5.45; N, 17.76



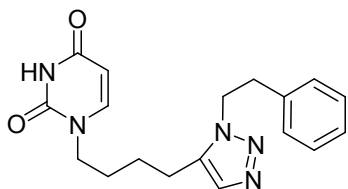
1-(4-(1-Benzhydryl-1*H*-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1*H*,3*H*)-dione (46b)

From **9b** (50 mg, 0.26 mmol) and benzhydrylazide⁴ (54 mg, 0.26 mmol), **46b** (59 mg, 57%) was obtained as a colorless solid. ¹H NMR (CDCl₃) δ 1.52-1.62 (4H, m), 2.66 (2H, t, *J* = 7.3 Hz), 3.61 (2H, t, *J* = 6.5 Hz), 5.66 (1H, d, *J* = 7.8 Hz), 6.75 (1H, s), 6.98 (1H, d, *J* = 7.8 Hz), 7.15-7.35 (10H, m), 7.53 (1H, s), 8.87 (1H, brs); ¹³C NMR (DMSO-*d*₆) δ 21.85, 24.82, 27.83, 46.91, 63.65, 100.86, 127.89, 128.22, 128.47, 131.79, 137.70, 138.95, 145.51, 150.89, 163.71; Anal. Calcd for C₂₃H₂₃N₅O₂·0.2H₂O: C, 68.20; H, 5.82; N, 17.29. Found: C, 68.28; H, 5.72; N, 17.19



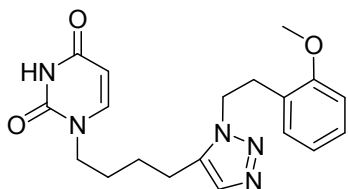
1-(3-(1-Phenethyl-1H-1,2,3-triazol-5-yl)propyl)pyrimidine-2,4(1H,3H)-dione (47a)

From **9a** (50 mg, 0.28 mmol) and phenethylazide⁵ (41 mg, 0.28 mmol), **47a** (74 mg, 81%) was obtained as a colorless solid. ¹H NMR (CDCl₃) δ 1.73-1.84 (2H, m), 2.16 (2H, t, *J* = 7.8 Hz), 3.25 (2H, t, *J* = 6.6 Hz), 3.60 (2H, t, *J* = 7.2 Hz), 4.43 (2H, t, *J* = 6.8 Hz), 5.71 (1H, d, *J* = 8.1 Hz), 6.95-7.01 (3H, m), 7.18-7.25 (3H, m), 7.42 (1H, s), 8.69 (1H, brs); ¹³C NMR (DMSO-*d*₆) δ 19.13, 26.58, 35.72, 46.83, 48.17, 100.97, 126.55, 128.36, 128.76, 131.11, 136.61, 137.72, 145.49, 150.93, 163.71; Anal. Calcd for C₁₇H₁₉N₅O₂·0.2H₂O: C, 62.07; H, 5.94; N, 21.29. Found: C, 62.00; H, 5.87; N, 21.57



1-(4-(1-Phenethyl-1H-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1H,3H)-dione (47b)

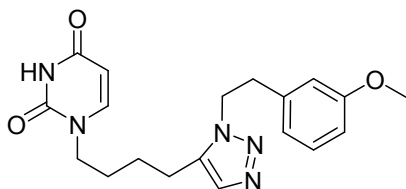
From **9b** (50 mg, 0.26 mmol) and phenethylazide⁵ (38 mg, 0.26 mmol), **47b** (69 mg, 78%) was obtained as a colorless solid. ¹H NMR (DMSO-*d*₆) δ 1.36-1.55 (4H, m), 2.42 (2H, t, *J* = 7.0 Hz), 3.10 (2H, t, *J* = 7.0 Hz), 3.63 (2H, t, *J* = 7.0 Hz), 4.47 (2H, t, *J* = 7.0 Hz), 5.54 (1H, d, *J* = 7.8 Hz), 7.09-7.12 (2H, m), 7.17-7.29 (3H, m), 7.44 (1H, s), 7.62 (1H, d, *J* = 7.8 Hz), 11.22 (1H, brs); ¹³C NMR (DMSO-*d*₆) δ 21.47, 24.32, 27.92, 35.79, 46.97, 48.08, 100.86, 126.57, 128.36, 128.81, 131.22, 137.16, 137.77, 145.62, 150.93, 163.71; Anal. Calcd for C₁₈H₂₁N₅O₂: C, 63.70; H, 6.24; N, 20.64. Found: C, 63.71; H, 6.13; N, 20.64



1-(4-(1-(2-Methoxyphenethyl)-1H-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1H,3H)-dione (47c)

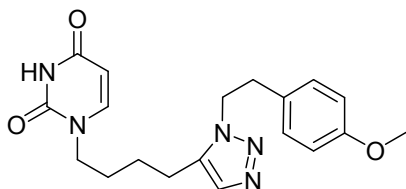
From **9b** (50 mg, 0.26 mmol) and **14a** (46 mg, 0.26 mmol), **47c** (77 mg, 80%) was obtained as a

colorless solid. ^1H NMR ($\text{DMSO-}d_6$) δ 1.40-1.57 (4H, m), 2.41-2.48 (2H, m), 3.02 (2H, t, $J = 7.2$ Hz), 3.63 (2H, t, $J = 6.9$ Hz), 3.78 (3H, s), 4.40 (2H, t, $J = 6.9$ Hz), 5.53 (1H, d, $J = 7.8$ Hz), 6.79 (1H, td, $J = 7.3, 0.8$ Hz), 6.92-6.97 (2H, m), 7.20 (1H, td, $J = 8.1, 1.9$ Hz), 7.42 (1H, s), 7.61 (1H, d, $J = 7.8$ Hz), 11.21 (1H, brs); ^{13}C NMR ($\text{DMSO-}d_6$) δ 21.48, 24.36, 28.00, 31.25, 46.52, 47.00, 55.31, 100.85, 110.62, 120.29, 125.25, 128.30, 130.39, 131.19, 136.96, 145.61, 150.93, 157.28, 163.71; Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{N}_5\text{O}_3 \cdot 0.5\text{H}_2\text{O}$: C, 60.30; H, 6.39; N, 18.51. Found: C, 60.20; H, 6.00; N, 18.26



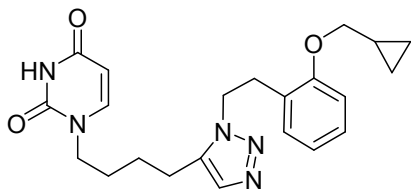
1-(4-(1-(3-Methoxyphenethyl)-1H-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1H,3H)-dione (47d)

From **9b** (50 mg, 0.26 mmol) and **14b** (46 mg, 0.26 mmol), **47d** (72 mg, 75%) was obtained as a colorless solid. ^1H NMR ($\text{DMSO-}d_6$) δ 1.37-1.55 (4H, m), 2.43 (2H, t, $J = 7.0$ Hz), 3.07 (2H, t, $J = 7.0$ Hz), 3.63 (2H, t, $J = 7.0$ Hz), 3.68 (3H, s), 4.46 (2H, t, $J = 7.0$ Hz), 5.54 (1H, d, $J = 7.8$ Hz), 6.64-6.70 (2H, m), 6.74-6.78 (1H, m), 7.16 (1H, t, $J = 7.8$ Hz), 7.44 (1H, s), 7.61 (1H, d, $J = 7.8$ Hz), 11.22 (1H, brs); ^{13}C NMR ($\text{DMSO-}d_6$) δ 21.47, 24.29, 27.91, 35.80, 46.98, 48.00, 54.89, 100.87, 112.11, 114.34, 121.00, 129.39, 131.19, 137.23, 139.30, 145.60, 150.92, 159.24, 163.72; Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{N}_5\text{O}_3$: C, 61.77; H, 6.28; N, 18.96. Found: C, 61.64; H, 6.18; N, 18.82



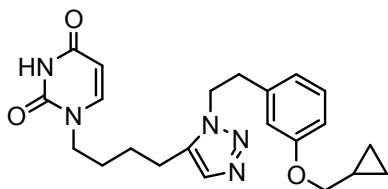
1-(4-(1-(4-Methoxyphenethyl)-1H-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1H,3H)-dione (47e)

From **9b** (50 mg, 0.26 mmol) and 1-(2-azidoethyl)-4-methoxybenzene⁶ (46 mg, 0.26 mmol), **47e** (74 mg, 77%) was obtained as a colorless solid. ^1H NMR ($\text{DMSO-}d_6$) δ 1.41-1.53 (4H, m), 2.44 (2H, t, $J = 7.0$ Hz), 3.03 (2H, t, $J = 7.0$ Hz), 3.63 (2H, t, $J = 7.0$ Hz), 3.70 (3H, s), 4.42 (2H, t, $J = 7.0$ Hz), 5.54 (1H, d, $J = 7.8$ Hz), 6.81 (2H, d, $J = 8.6$ Hz), 7.01 (2H, d, $J = 8.6$ Hz), 7.44 (1H, s), 7.61 (1H, d, $J = 7.8$ Hz), 11.22 (1H, brs); ^{13}C NMR ($\text{DMSO-}d_6$) δ 21.47, 24.31, 27.92, 34.93, 46.95, 48.34, 54.98, 100.87, 113.77, 129.56, 129.83, 131.21, 137.12, 145.58, 150.93, 158.01, 163.71; Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{N}_5\text{O}_3 \cdot 0.2\text{H}_2\text{O}$: C, 61.18; H, 6.32; N, 18.77. Found: C, 61.16; H, 6.22; N, 18.63



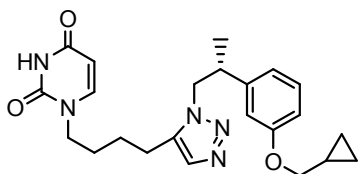
1-(4-(1-(2-(Cyclopropylmethoxy)phenethyl)-1H-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1H,3H)-dione (47f)

From **9b** (50 mg, 0.26 mmol) and **14c** (56 mg, 0.26 mmol), **47f** (84 mg, 79%) was obtained as a colorless solid. ^1H NMR ($\text{DMSO}-d_6$) δ 0.30-0.35 (2H, m), 0.52-0.59 (2H, m), 1.17-1.30 (1H, m), 1.39-1.58 (4H, m), 2.46-2.49 (2H, m), 3.02 (2H, t, $J = 7.2$ Hz), 3.61 (2H, t, $J = 6.6$ Hz), 3.82 (2H, d, $J = 6.8$ Hz), 4.43 (2H, t, $J = 7.3$ Hz), 5.51 (1H, d, $J = 7.8$ Hz), 6.76 (1H, t, $J = 7.3$ Hz), 6.89-6.95 (2H, m), 7.15 (1H, td, $J = 7.8, 1.9$ Hz), 7.42 (1H, s), 7.59 (1H, d, $J = 7.8$ Hz), 11.20 (1H, brs); ^{13}C NMR (CDCl_3) δ 3.27, 10.42, 22.18, 24.88, 28.48, 32.49, 47.26, 48.31, 72.74, 77.23, 102.41, 111.31, 120.67, 125.67, 128.45, 130.98, 131.63, 136.35, 144.02, 150.50, 157.04, 163.09; Anal. Calcd for $\text{C}_{22}\text{H}_{27}\text{N}_5\text{O}_3 \cdot 0.5\text{H}_2\text{O}$: C, 63.14; H, 6.74; N, 16.73. Found: C, 63.46; H, 6.71; N, 16.38



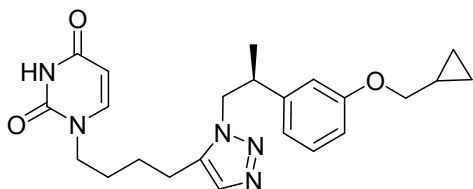
1-(4-(1-(3-(Cyclopropylmethoxy)phenethyl)-1H-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1H,3H)-dione (47g)

From **9b** (50 mg, 0.26 mmol) and **14d** (56 mg, 0.26 mmol), **47g** (94 mg, 88%) was obtained as a colorless solid. ^1H NMR (CDCl_3) δ 0.29-0.35 (2H, m), 0.60-0.67 (2H, m), 1.16-1.24 (1H, m), 1.38-1.49 (2H, m), 1.55-1.66 (2H, m), 2.28 (2H, t, $J = 7.6$ Hz), 3.18 (2H, t, $J = 7.0$ Hz), 3.65 (2H, t, $J = 7.0$ Hz), 3.71 (2H, d, $J = 7.0$ Hz), 4.41 (2H, t, $J = 7.0$ Hz), 5.70 (1H, dd, $J = 2.2, 7.8$ Hz), 6.52 (1H, t, $J = 1.9$ Hz), 6.61 (1H, d, $J = 7.6$ Hz), 6.76 (1H, dd, $J = 1.6, 7.3$ Hz), 7.09 (1H, d, $J = 7.8$ Hz), 7.17 (1H, t, $J = 7.8$ Hz), 7.37 (1H, s), 8.41 (1H, brs); ^{13}C NMR (CDCl_3) δ 3.22, 10.23, 22.27, 24.72, 28.50, 36.83, 48.07, 49.03, 72.79, 77.24, 102.48, 113.32, 115.00, 121.09, 129.80, 131.68, 136.66, 138.96, 144.04, 150.66, 159.27, 163.23; Anal. Calcd for $\text{C}_{22}\text{H}_{27}\text{N}_5\text{O}_3 \cdot 0.3\text{H}_2\text{O}$: C, 63.69; H, 6.71; N, 16.88. Found: C, 63.83; H, 6.63; N, 16.67



(*R*)-1-(4-(1-(2-(3-(Cyclopropylmethoxy)phenyl)propyl)-1*H*-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1*H*,3*H*)-dione (48a**)**

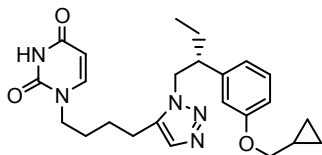
From **9b** (50 mg, 0.26 mmol) and **22a** (60 mg, 0.26 mmol), **48a** (78 mg, 69%) was obtained as a colorless gum. ¹H NMR (CDCl₃) δ 0.29-0.35 (2H, m), 0.60-0.72 (2H, m), 1.14-1.29 (1H, m), 1.35 (3H, d, *J* = 7.0 Hz), 1.39-1.66 (4H, m), 2.07-2.34 (2H, m), 3.36-3.48 (1H, m), 3.58-3.72 (4H, m), 4.15 (1H, dd, *J* = 7.8, 14 Hz), 4.42 (1H, dd, *J* = 6.8, 14.0 Hz), 5.71 (1H, dd, *J* = 1.9, 8.1 Hz), 6.58 (1H, brs), 6.66 (1H, d, *J* = 7.6 Hz), 6.75 (1H, dd, *J* = 2.4, 8.1 Hz), 7.10 (1H, d, *J* = 7.8 Hz), 7.17 (1H, t, *J* = 7.8 Hz), 7.33 (1H, s), 9.17 (1H, brs); ¹³C NMR (CDCl₃) δ 3.22, 10.24, 18.15, 22.27, 24.68, 28.52, 40.93, 48.08, 54.63, 72.79, 77.24, 102.47, 113.14, 113.65, 119.36, 129.73, 131.45, 136.79, 144.03, 144.12, 150.64, 159.23, 163.21; Anal. Calcd for C₂₃H₂₉N₅O₃·0.3H₂O: C, 64.41; H, 6.96; N, 16.33. Found: C, 64.38; H, 6.86; N, 16.12; [α]_D²⁵ = 46.92 (*c* 0.52, CHCl₃); 96.8%e.e. [HPLC condition, Column:CHIRALPAK IA-3 (4.6×250 mm), Column Temp.:30 °C, Mobile phase: hexane/ethanol (6:4), Flow rate: 0.8 mL/min., Detector: UV 230 nm, **48a** was eluted at 20.0 min]



(*S*)-1-(4-(1-(2-(3-(Cyclopropylmethoxy)phenyl)propyl)-1*H*-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1*H*,3*H*)-dione (48b**)**

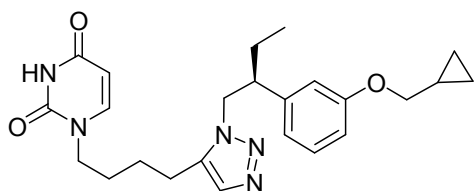
From **9b** (50 mg, 0.26 mmol) and **22b** (60 mg, 0.26 mmol), **48b** (76 mg, 69%) was obtained as a colorless gum. ¹H NMR (DMSO-*d*₆) δ 0.21-0.27 (2H, m), 0.47-0.54 (2H, m), 1.09-1.20 (1H, m), 1.18 (3H, d, *J* = 6.8 Hz), 1.30-1.50 (4H, m), 2.22-2.45 (2H, m), 3.22-3.32 (1H, m), 3.59 (2H, t, *J* = 6.8 Hz), 3.69 (2H, d, *J* = 7.0 Hz), 4.27-4.41 (2H, m), 5.50 (1H, d, *J* = 7.8 Hz), 6.64-6.70 (3H, m), 7.06-7.12 (1H, m), 7.36 (1H, s), 7.57 (1H, d, *J* = 7.8 Hz), 11.19 (1H, brs); ¹³C NMR (CDCl₃) δ 3.22, 10.24, 18.15, 22.27, 24.68, 28.52, 40.93, 48.08, 54.64, 72.79, 77.23, 102.47, 113.14, 113.65, 119.36, 129.73, 131.45, 136.79, 144.03, 144.12, 150.63, 159.23, 163.20; TOF-HRMS *m/z* [M+H]⁺: Calcd. for C₂₃H₃₀N₅O₃, 424.2349; Found, 424.2358; [α]_D²⁵ = -45.66 (*c* 0.53, CHCl₃); Purity: 97.42% (Column: Shim-pack XR-ODS 3 mmID×50 mm, 2.2 μm, Column temperature: 40 °C, Mobile phase: 10 mM Phosphate buffred solution pH 6.5 /Acetonitrile :0 min 90/10, 8 min 20/80, 10 min 20/80, Flow rate : 0.8 mL/min, **48b** was eluted at 5.4 min); 97.2%e.e. [HPLC condition,

Column:CHIRALPAK IA-3 (4.6×250 mm), Column Temp.:30 °C, Mobile phase: hexane/ethanol (6:4), Flow rate: 0.8 mL/min., Detector: UV 230 nm, **48b** was eluted at 23.3 min]



(R)-1-(4-(1-(2-(3-(Cyclopropylmethoxy)phenyl)butyl)-1H-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1H,3H)-dione (48c)

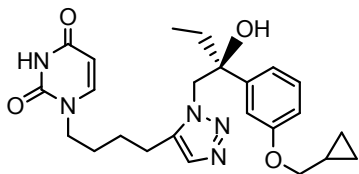
From **9b** (50 mg, 0.26 mmol) and **22c** (64 mg, 0.26 mmol), **48c** (69 mg, 61%) was obtained as a colorless gum. ¹H NMR (CDCl₃) δ 0.30-0.35 (2H, m), 0.60-0.67 (2H, m), 0.86 (3H, d, *J* = 7.3 Hz), 1.17-1.82 (7H, m), 2.03-2.31 (2H, m), 3.08-3.19 (1H, m), 3.63 (2H, t, *J* = 7.3 Hz), 3.70 (2H, d, *J* = 6.8 Hz), 4.11-4.52 (2H, m), 5.71 (1H, dd, *J* = 1.4, 7.8 Hz), 6.54 (1H, s), 6.63 (1H, d, *J* = 7.6 Hz), 6.75 (1H, dd, *J* = 2.7, 8.4 Hz), 7.08-7.19 (2H, m), 7.31 (1H, s), 8.80 (1H, brs); ¹³C NMR (CDCl₃) δ 3.22, 10.24, 11.91, 22.24, 24.67, 25.46, 28.51, 48.09, 48.74, 53.59, 72.78, 77.23, 102.44, 113.12, 114.23, 120.02, 129.69, 131.37, 136.82, 142.64, 144.03, 150.60, 159.24, 163.17; HR TOF-MS *m/z* [M+H]⁺: Calcd. for C₂₄H₃₂N₅O₃, 438.2505; Found, 438.2499; [α]_D²⁵ = 33.96 (*c* 0.53, CHCl₃); Purity: 100% (Column: Shim-pack XR-ODS 3 mmID×50 mm, 2.2 μm, Column temperature: 40 °C, Mobile phase: 10 mM Phosphate buffred solution pH 6.5 /Acetonitrile :0 min 90/10, 8 min 20/80, 10 min 20/80, Flow rate : 0.8 mL/min, **48c** was eluted at 5.4 min); 89.6%e.e. [HPLC condition, Column:CHIRALCEL OD-H (4.6×250 mm), Column Temp.:35 °C, Mobile phase: hexane/ethanol (7:3), Flow rate: 0.8 mL/min., Detector: UV 230 nm, **48c** was eluted at 27.6 min]



(S)-1-(4-(1-(2-(3-(Cyclopropylmethoxy)phenyl)butyl)-1H-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1H,3H)-dione (48d)

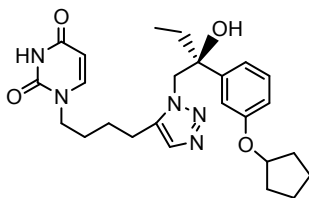
From **9b** (50 mg, 0.26 mmol) and **22d** (64 mg, 0.26 mmol), **48d** (83 mg, 73%) was obtained as a colorless gum. ¹H NMR (DMSO-*d*₆) δ 0.21-0.27 (2H, m), 0.47-0.53 (2H, m), 0.70 (3H, t, *J* = 7.3 Hz), 1.08-1.16 (1H, m), 1.23-1.52 (4H, m), 1.56-1.67 (2H, m), 2.19-2.41 (2H, m), 2.91-3.01 (1H, m), 3.58 (2H, t, *J* = 6.9 Hz), 3.69 (2H, d, *J* = 7.3 Hz), 4.25-4.46 (2H, m), 5.50 (1H, d, *J* = 7.8 Hz), 6.60-6.70 (3H, m), 7.08 (1H, t, *J* = 7.7 Hz), 7.33 (1H, s), 7.57 (1H, d, *J* = 7.8 Hz), 11.18 (1H, brs); ¹³C NMR (CDCl₃) δ 3.21, 10.24, 11.91, 22.24, 24.67, 25.46, 28.51, 48.09, 48.74, 53.58, 72.78, 77.23, 102.44,

113.12, 114.23, 120.02, 129.69, 131.37, 136.82, 142.64, 144.03, 150.59, 159.24, 163.15; TOF-HRMS m/z $[M+H]^+$: Calcd. for $C_{24}H_{32}N_5O_3$, 438.2505; Found, 438.2514; $[\alpha]_D^{25} = -33.20$ (c 0.53, $CHCl_3$); Purity: 97.56% (Column: Shim-pack XR-ODS 3 mmID \times 50 mm, 2.2 μ m, Column temperature: 40 $^{\circ}C$, Mobile phase: 10 mM Phosphate buffred solution pH 6.5 /Acetonitrile :0 min 90/10, 8 min 20/80, 10 min 20/80, Flow rate : 0.8 mL/min, **48d** was eluted at 5.8 min); 95.0%e.e. [HPLC condition, Column:CHIRALCEL OD-H (4.6 \times 250 mm), Column Temp.:35 $^{\circ}C$, Mobile phase: hexane/ethanol (7:3), Flow rate: 0.8 mL/min., Detector: UV 230 nm, **48d** was eluted at 22.4 min]



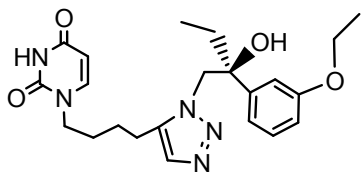
(S)-1-(4-(1-(2-(3-(Cyclopropylmethoxy)phenyl)-2-hydroxybutyl)-1H-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1H,3H)-dione (49a)

From **9b** (50 mg, 0.26 mmol) and **34a** (68 mg, 0.26 mmol), **49a** (79 mg, 67%) was obtained as a colorless foam. 1H NMR ($DMSO-d_6$) δ 0.28-0.30 (2H, m), 0.53-0.56 (2H, m), 0.67 (3H, t, $J = 7.3$ Hz), 1.10-1.25 (1H, m), 1.38-1.55 (4H, m), 1.63-2.02 (2H, m), 2.22-2.40 (2H, m), 3.62 (2H, t, $J = 6.8$ Hz), 3.73 (2H, d, $J = 6.9$ Hz), 4.41 (2H, s), 5.22 (1H, s), 5.54 (1H, d, $J = 7.9$ Hz), 6.77-6.85 (3H, m), 7.17 (1H, t, $J = 8.1$ Hz), 7.39 (1H, s), 7.61 (1H, d, $J = 7.9$ Hz), 11.3 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 3.22, 7.38, 10.24, 22.39, 24.62, 28.53, 31.98, 47.89, 57.59, 72.83, 76.88, 77.24, 102.62, 112.32, 113.17, 117.66, 129.38, 131.58, 137.85, 143.97, 144.25, 150.80, 159.14, 163.20; TOF-HRMS m/z $[M+H]^+$: Calcd. for $C_{24}H_{32}N_5O_4$, 454.2454; Found, 454.2458; $[\alpha]_D^{25} = 13.84$ (c 0.39, $CHCl_3$); Purity: 98.83% (Column: Shim-pack XR-ODS 3 mmID \times 50 mm, 2.2 μ m, Column temperature: 40 $^{\circ}C$, Mobile phase: 10 mM Phosphate buffred solution pH 6.5 /Acetonitrile :0 min 90/10, 8 min 20/80, 10 min 20/80, Flow rate : 0.8 mL/min, **49a** was eluted at 5.1 min); 96.1%e.e. [HPLC condition, Column:CHIRALPAK IA(4.6 \times 250 mm), Column Temp.:40 $^{\circ}C$, Mobile phase: hexane/ethanol (1:1), Flow rate: 0.8 mL/min., Detector: UV 240 nm, **49a** was eluted at 10.4 min]



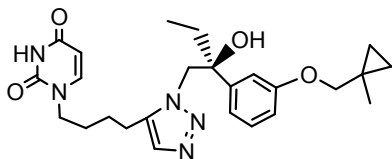
(S)-1-(4-(1-(2-(3-(Cyclopentyloxy)phenyl)-2-hydroxybutyl)-1H-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1H,3H)-dione (49b)

From **9b** (50 mg, 0.26 mmol) and **34c** (72 mg, 0.26 mmol), **49b** (77 mg, 63%) was obtained as a colorless foam. ^1H NMR ($\text{DMSO-}d_6$) δ 0.67 (3H, t, $J = 7.6$ Hz), 1.39-1.95 (14H, m), 2.20-2.35 (2H, m), 3.60 (2H, t, $J = 6.2$ Hz), 4.39 (2H, s), 4.71 (1H, brs), 5.22 (1H, s), 5.52 (1H, d, $J = 7.8$ Hz), 6.70-6.80 (3H, m), 7.14 (1H, t, $J = 8.1$ Hz), 7.37 (1H, s), 7.60 (1H, d, $J = 7.8$ Hz), 11.2 (1H, brs); ^{13}C NMR (CDCl_3) δ 7.39, 22.35, 24.02, 24.58, 28.50, 31.94, 32.77, 32.83, 47.93, 57.62, 79.24, 76.83, 77.24, 102.58, 113.33, 114.13, 117.25, 129.29, 131.54, 137.85, 144.00, 144.16, 150.84, 158.23, 163.34; TOF-HRMS m/z $[\text{M}+\text{H}]^+$: Calcd. for $\text{C}_{25}\text{H}_{34}\text{N}_5\text{O}_4$, 468.2611; Found, 468.2616; $[\alpha]^{25}_{\text{D}} = 16.84$ (c 0.38, CHCl_3); Purity: 100% (Column: Shim-pack XR-ODS 3 mmID \times 50 mm, 2.2 μm , Column temperature: 40 $^\circ\text{C}$, Mobile phase: 10 mM Phosphate buffred solution pH 6.5 /Acetonitrile :0 min 90/10, 8 min 20/80, 10 min 20/80, Flow rate : 0.8 mL/min, **49b** was eluted at 5.6 min)



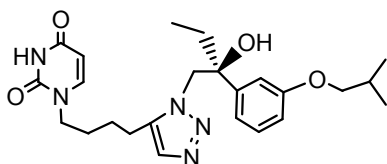
(S)-1-(4-(1-(2-(3-Ethoxyphenyl)-2-hydroxybutyl)-1H-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1H,3H)-dione (49c)

From **9b** (50 mg, 0.26 mmol) and **34d** (61 mg, 0.26 mmol), **49c** (66 mg, 59%) was obtained as a colorless gum. ^1H NMR (CDCl_3) δ 0.82 (3H, t, $J = 7.3$ Hz), 1.39 (3H, t, $J = 7.0$ Hz), 1.44-1.72 (4H, m), 1.74-1.87 (1H, m), 1.97-2.11 (1H, m), 2.31-2.51 (2H, m), 3.71 (2H, t, $J = 6.8$ Hz), 3.93-4.03 (2H, m), 4.08 (1H, brs), 4.42 (2H, dd, $J = 14, 37$ Hz), 5.71 (1H, dd, $J = 2.2, 7.8$ Hz), 6.73-6.77 (1H, m), 6.87-6.89 (2H, m), 7.10 (1H, d, $J = 7.8$ Hz), 7.21 (1H, t, $J = 8.1$ Hz), 7.35 (1H, s), 8.69 (1H, brs); ^{13}C NMR (CDCl_3) δ 7.35, 14.78, 22.32, 24.56, 28.49, 31.94, 47.84, 57.57, 63.44, 76.83, 102.59, 112.20, 112.97, 117.55, 129.34, 131.52, 137.85, 143.96, 144.22, 150.84, 159.02, 163.31; TOF-HRMS m/z $[\text{M}+\text{H}]^+$: Calcd. for $\text{C}_{22}\text{H}_{30}\text{N}_5\text{O}_4$, 428.2298; Found, 428.2303; $[\alpha]^{25}_{\text{D}} = 15.11$ (c 0.45, CHCl_3); Purity: 100% (Column: Shim-pack XR-ODS 3 mmID \times 50 mm, 2.2 μm , Column temperature: 40 $^\circ\text{C}$, Mobile phase: 10 mM Phosphate buffred solution pH 6.5 /Acetonitrile :0 min 90/10, 8 min 20/80, 10 min 20/80, Flow rate : 0.8 mL/min, **49c** was eluted at 4.6 min)



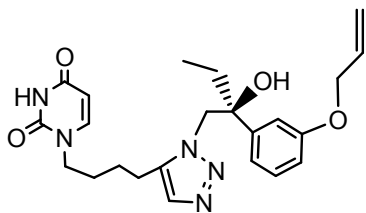
(S)-1-(4-(1-(2-(3-((1-methylcyclopropyl)methoxy)phenyl)-2-hydroxybutyl)-1H-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1H,3H)-dione (49d)

From **9b** (50 mg, 0.26 mmol) and **34e** (72 mg, 0.26 mmol), **49d** (84 mg, 69%) was obtained as a colorless foam. ^1H NMR (CDCl_3) δ 0.40-0.45 (2H, m), 0.49-0.54 (2H, m), 0.82 (3H, t, $J = 7.3$ Hz), 1.21 (3H, s), 1.48-1.72 (4H, m), 1.76-1.87 (1H, m), 1.97-2.10 (1H, m), 2.31-2.48 (2H, m), 3.64-3.73 (4H, m), 4.03 (1H, brs), 4.42 (2H, dd, $J = 14, 37$ Hz), 5.71 (1H, dd, $J = 2.4, 8.1$ Hz), 6.73-6.89 (3H, m), 7.83 (1H, d, $J = 7.8$ Hz), 7.20 (1H, t, $J = 4.6$ Hz), 7.35 (1H, s), 8.56 (1H, brs); ^{13}C NMR (CDCl_3) δ 7.39, 11.22, 15.65, 21.02, 22.39, 24.59, 28.50, 31.97, 47.93, 57.59, 75.99, 76.89, 102.60, 112.33, 113.25, 117.54, 129.32, 131.54, 137.85, 143.97, 144.21, 150.80, 159.53, 163.23; Anal. Calcd for $\text{C}_{25}\text{H}_{33}\text{N}_5\text{O}_4$: C, 64.22; H, 7.11; N, 14.98. Found: C, 64.14; H, 7.22; N, 14.76; $[\alpha]_D^{25} = 15.00$ (c 0.56, CHCl_3)



(*S*)-1-(4-(1-(2-Hydroxy-2-(3-isobutoxyphenyl)butyl)-1*H*-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1*H*,3*H*)-dione (49e**)**

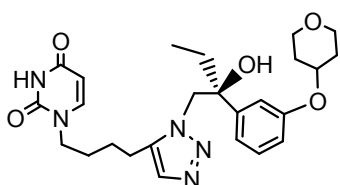
From **9b** (50 mg, 0.26 mmol) and **34f** (68 mg, 0.26 mmol), **49e** (85 mg, 72%) was obtained as a colorless foam. ^1H NMR (CDCl_3) δ 0.81 (3H, t, $J = 7.3$ Hz), 1.01 (6H, d, $J = 6.5$ Hz), 1.48-2.11 (7H, m), 2.33-2.47 (2H, m), 3.61-3.73 (4H, m), 4.02 (1H, s), 4.42 (2H, dd, $J = 14, 37$ Hz), 5.70 (1H, d, $J = 7.8$ Hz), 6.73-6.88 (3H, m), 7.09 (1H, d, $J = 8.1$ Hz), 7.20 (1H, t, $J = 8.1$ Hz), 7.35 (1H, s), 8.44 (1H, brs); ^{13}C NMR (CDCl_3) δ 7.40, 19.28, 22.37, 24.58, 28.29, 28.50, 31.97, 47.92, 57.60, 74.41, 76.89, 102.60, 112.23, 113.11, 117.43, 129.32, 131.54, 137.86, 143.98, 144.21, 150.84, 159.43, 163.32; Anal. Calcd for $\text{C}_{24}\text{H}_{33}\text{N}_5\text{O}_4$: C, 63.28; H, 7.30; N, 15.37. Found: C, 63.17; H, 7.45; N, 15.16; $[\alpha]_D^{25} = 14.61$ (c 0.52, CHCl_3)



(*S*)-1-(4-(1-(2-(3-Allyloxy)phenyl)-2-hydroxybutyl)-1*H*-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1*H*,3*H*)-dione (49f**)**

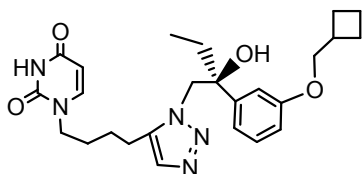
From **9b** (50 mg, 0.26 mmol) and **34g** (64 mg, 0.26 mmol), **49f** (72 mg, 63%) was obtained as a colorless foam. ^1H NMR (CDCl_3) δ 0.82 (3H, t, $J = 7.6$ Hz), 1.47-1.69 (4H, m), 1.77-1.85 (1H, m), 2.00-2.08 (1H, m), 2.36-2.44 (2H, m), 3.70 (2H, t, $J = 7.3$ Hz), 4.06 (1H, s), 4.33-4.52 (4H, m), 5.25-5.31 (1H, m), 5.36-5.43 (1H, m), 5.71 (1H, dd, $J = 2.4, 8.1$ Hz), 5.96-6.08 (1H, m), 6.76-6.80

(1H, m), 6.88-6.92 (2H, m), 7.09 (1H, d, $J = 7.8$ Hz), 7.21 (1H, t, $J = 8.1$ Hz), 7.35 (1H, s), 8.30 (1H, brs); ^{13}C NMR (CDCl_3) δ 7.37, 22.35, 24.60, 28.52, 32.00, 47.88, 57.57, 68.80, 76.86, 102.61, 112.47, 113.27, 117.82, 117.89, 129.40, 131.56, 133.09, 137.85, 143.98, 144.31, 150.79, 158.69, 163.21; TOF-HRMS m/z $[\text{M}+\text{H}]^+$: Calcd. for $\text{C}_{23}\text{H}_{30}\text{N}_5\text{O}_4$, 440.2298; Found, 440.2303; $[\alpha]_D^{25} = 15.42$ (c 0.35, CHCl_3); Purity: 96.7% (Column: Shim-pack XR-ODS 3 mmID \times 50 mm, 2.2 μm , Column temperature: 40 $^\circ\text{C}$, Mobile phase: 10 mM Phosphate buffered solution pH 6.5 /Acetonitrile :0 min 90/10, 8 min 20/80, 10 min 20/80, Flow rate : 0.8 mL/min, **49f** was eluted at 4.8 min)



(S)-1-(4-(1-(2-Hydroxy-2-(3-(tetrahydro-2H-pyran-4-yloxy)phenyl)butyl)-1H-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1H,3H)-dione (49g)

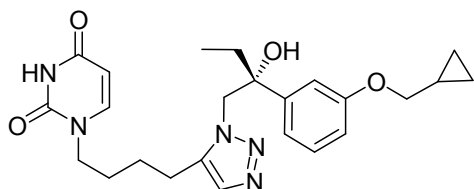
From **9b** (50 mg, 0.26 mmol) and **34h** (76 mg, 0.26 mmol), **49g** (97 mg, 77%) was obtained as a colorless solid. ^1H NMR (CDCl_3) δ 0.82 (3H, t, $J = 7.0$ Hz), 1.44-1.87 (7H, m), 1.92-2.10 (3H, m), 2.33-2.53 (2H, m), 3.52-3.60 (2H, m), 3.72 (2H, t, $J = 6.8$ Hz), 3.93-4.00 (2H, m), 4.12 (1H, brs), 4.33-4.52 (3H, m), 5.71 (1H, dd, $J = 1.9, 7.8$ Hz), 6.77 (1H, dd, $J = 2.4, 8.1$ Hz), 6.87-6.93 (2H, m), 7.10 (1H, d, $J = 8.1$ Hz), 7.21 (1H, t, $J = 7.8$ Hz), 7.35 (1H, s), 8.71 (1H, brs); ^{13}C NMR (CDCl_3) δ 7.39, 22.38, 24.62, 28.52, 31.76, 31.84, 32.02, 47.88, 57.54, 65.12, 71.69, 76.87, 77.24, 102.65, 113.91, 114.77, 117.92, 129.45, 131.55, 137.82, 143.94, 144.44, 150.83, 157.30, 163.23; Anal. Calcd for $\text{C}_{25}\text{H}_{33}\text{N}_5\text{O}_5$: C, 62.10; H, 6.88; N, 14.48. Found: C, 61.98; H, 7.01; N, 14.36; $[\alpha]_D^{25} = 14.50$ (c 0.51, CHCl_3)



(S)-1-(4-(1-(2-(3-(Cyclobutylmethoxy)phenyl)-2-hydroxybutyl)-1H-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1H,3H)-dione (49h)

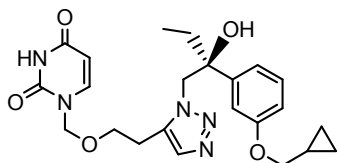
From **9b** (50 mg, 0.26 mmol) and **34i** (72 mg, 0.26 mmol), **49h** (83 mg, 68%) was obtained as a colorless foam. ^1H NMR (CDCl_3) δ 0.82 (3H, t, $J = 7.3$ Hz), 1.05-2.21 (13H, m), 2.34-2.45 (2H, m), 2.71-2.79 (1H, m), 3.70 (2H, t, $J = 7.3$ Hz), 3.87 (2H, dd, $J = 1.6, 6.8$ Hz), 4.42 (2H, dd, $J = 14, 38$ Hz), 5.71 (1H, dd, $J = 2.2, 7.6$ Hz), 6.74-6.89 (3H, m), 7.09 (1H, d, $J = 8.1$ Hz), 7.21 (1H, t, $J = 8.4$ Hz)

Hz), 7.36 (1H, brs), 8.32 (1H, brs); ^{13}C NMR (CDCl_3) δ 7.40, 18.60, 22.38, 24.59, 24.90, 28.51, 31.97, 34.60, 47.92, 57.60, 72.13, 76.89, 77.24, 102.59, 112.27, 113.15, 117.50, 129.34, 131.55, 137.86, 143.98, 144.20, 150.80, 159.42, 163.25; TOF-HRMS m/z $[\text{M}+\text{H}]^+$: Calcd. for $\text{C}_{25}\text{H}_{34}\text{N}_5\text{O}_4$, 468.2611; Found, 468.2607; $[\alpha]_D^{25} = 15.42$ (c 0.35, CHCl_3); Purity: 100% (Column: Shim-pack XR-ODS 3 mmID \times 50 mm, 2.2 μm , Column temperature: 40 $^\circ\text{C}$, Mobile phase: 10 mM Phosphate buffred solution pH 6.5 /Acetonitrile :0 min 90/10, 8 min 20/80, 10 min 20/80, Flow rate : 0.8 mL/min, **49h** was eluted at 5.8 min)



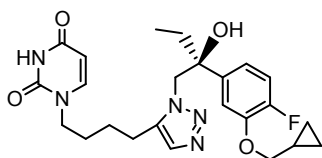
(*R*)-1-(4-(1-(2-(3-(Cyclopropylmethoxy)phenyl)-2-hydroxybutyl)-1*H*-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1*H*,3*H*)-dione (50a**)**

From **9b** (50 mg, 0.26 mmol) and **34b** (68 mg, 0.26 mmol), **50a** (77 mg, 65%) was obtained as a colorless foam. ^1H NMR (CDCl_3) δ 0.32-0.37 (2H, m), 0.60-0.67 (2H, m), 0.81 (3H, t, $J = 7.3$ Hz), 1.19-1.30 (1H, m), 1.47-1.71 (4H, m), 1.73-1.84 (1H, m), 1.99-2.10 (1H, m), 2.38-2.48 (2H, m), 3.73 (2H, q, $J = 7.3$ Hz), 3.75 (2H, d, 7.0 Hz), 4.04 (1H, s), 4.35 (1H, d, $J = 14.0$ Hz), 4.49 (1H, d, $J = 14.0$ Hz), 5.71 (1H, dd, $J = 2.2, 7.8$ Hz), 6.74-6.78 (1H, m), 6.87-6.91 (2H, m), 7.10 (1H, d, $J = 7.8$ Hz), 7.18-7.24 (1H, m), 7.36 (1H, s), 8.27 (1H, brs); ^{13}C NMR (CDCl_3) δ 3.22, 7.39, 10.25, 22.39, 24.61, 28.52, 31.98, 47.90, 57.60, 72.82, 76.88, 77.24, 102.62, 112.32, 113.18, 117.66, 129.37, 131.56, 137.89, 144.00, 144.26, 150.88, 159.14, 163.36; TOF-HRMS m/z $[\text{M}+\text{H}]^+$: Calcd. for $\text{C}_{24}\text{H}_{32}\text{N}_5\text{O}_4$, 454.2454; Found, 454.2446; $[\alpha]_D^{25} = -13.68$ (c 0.38, CHCl_3); Purity: 100% (Column: Shim-pack XR-ODS 3 mmID \times 50 mm, 2.2 μm , Column temperature: 40 $^\circ\text{C}$, Mobile phase: 10 mM Phosphate buffred solution pH 6.5 /Acetonitrile :0 min 90/10, 8 min 20/80, 10 min 20/80, Flow rate : 0.8 mL/min, **50a** was eluted at 5.1 min); 95.2%e.e. [HPLC condition, Column:CHIRALPAK IA(4.6 \times 250 mm), Column Temp.:40 $^\circ\text{C}$, Mobile phase: hexane/ethanol (1:1), Flow rate: 0.8 mL/min., Detector: UV 240 nm, **50a** was eluted at 14.8 min]



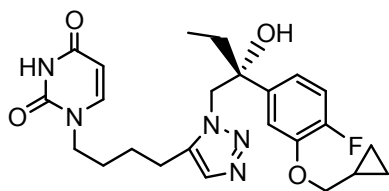
(*S*)-1-(2-(1-(2-(3-(Cyclopropylmethoxy)phenyl)-2-hydroxybutyl)-1*H*-1,2,3-triazol-5-yl)ethoxy)methylpyrimidine-2,4(1*H*,3*H*)-dione (50b**)**

From **11** (50 mg, 0.26 mmol) and **34a** (73 mg, 0.26 mmol), **50b** (71 mg, 60%) was obtained as a colorless foam. ^1H NMR ($\text{DMSO-}d_6$) δ 0.30-0.34 (2H, m), 0.54-0.57 (2H, m), 0.66 (3H, t, $J = 7.3$ Hz), 1.10-1.25 (1H, m), 1.68-1.73 (1H, m), 1.94-1.99 (1H, m), 2.70 (2H, d, $J = 6.1$ Hz), 3.61 (2H, t, $J = 6.4$ Hz), 3.76 (2H, d, $J = 6.9$ Hz), 4.45 (2H, dd, $J = 14, 22$ Hz), 5.06 (2H, s), 5.23 (1H, s), 5.61 (1H, d, $J = 7.9$ Hz), 6.76-6.89 (3H, m), 7.18 (1H, t, $J = 8.1$ Hz), 7.42 (1H, s), 7.67 (1H, d, $J = 7.9$ Hz), 11.3 (1H, brs); ^{13}C NMR (CDCl_3) δ 3.20, 7.36, 10.24, 23.52, 31.94, 57.78, 67.43, 72.80, 103.56, 112.32, 113.11, 117.58, 129.41, 132.20, 135.31, 142.87, 144.15, 150.92, 159.15, 162.72; Anal. Calcd for $\text{C}_{23}\text{H}_{29}\text{N}_5\text{O}_5$: C, 60.65; H, 6.42; N, 15.37. Found: C, 60.42; H, 6.46; N, 15.12; $[\alpha]^{25}_{\text{D}} = 20.00$ (c 0.50, CHCl_3)



(S)-1-(4-(1-(2-(3-(Cyclopropylmethoxy)-4-fluorophenyl)-2-hydroxybutyl)-1H-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1H,3H)-dione (50c)

From **9b** (50 mg, 0.26 mmol) and **43** (73 mg, 0.26 mmol), **50c** (60 mg, 49%) was obtained as a colorless foam. ^1H NMR ($\text{DMSO-}d_6$) δ 0.29-0.31 (2H, m), 0.54-0.57 (2H, m), 0.67 (3H, t, $J = 7.3$ Hz), 1.11-1.21 (1H, m), 1.46-1.50 (4H, m), 1.71-1.81 (1H, m), 1.93-2.03 (1H, m), 2.37-2.38 (2H, m), 3.63 (2H, t, $J = 6.5$ Hz), 3.78 (2H, d, $J = 7.0$ Hz), 4.42 (2H, s), 5.29 (1H, s), 5.22 (1H, d, $J = 7.8$ Hz), 6.91-7.12 (3H, m), 7.39 (1H, s), 7.61 (1H, d, $J = 7.6$ Hz), 11.21 (1H, brs); ^{13}C NMR (CDCl_3) δ 3.29, 7.35, 10.21, 22.35, 24.61, 28.50, 32.09, 47.88, 57.56, 74.52, 77.23, 102.66, 113.51, 115.76, 115.95, 117.72, 131.60, 137.77, 138.93, 143.98, 146.78, 150.57, 150.79, 163.14; Anal. Calcd for $\text{C}_{24}\text{H}_{30}\text{FN}_5\text{O}_4 \cdot 0.2\text{H}_2\text{O}$: C, 60.67; H, 6.45; N, 14.74. Found: C, 60.68; H, 6.47; N, 14.78; $[\alpha]^{25}_{\text{D}} = 7.55$ (c 0.45, CHCl_3); >99.9%e.e. [HPLC condition, Column: CHIRALPAK AD-H (4.6×250 mm), Column Temp.: 25 °C, Mobile phase: hexane/2-propanol/isopropylamine (7:3:0.1), Flow rate: 0.7 mL/min., Detector: UV 240 nm, **50c** was eluted at 13.0 min]

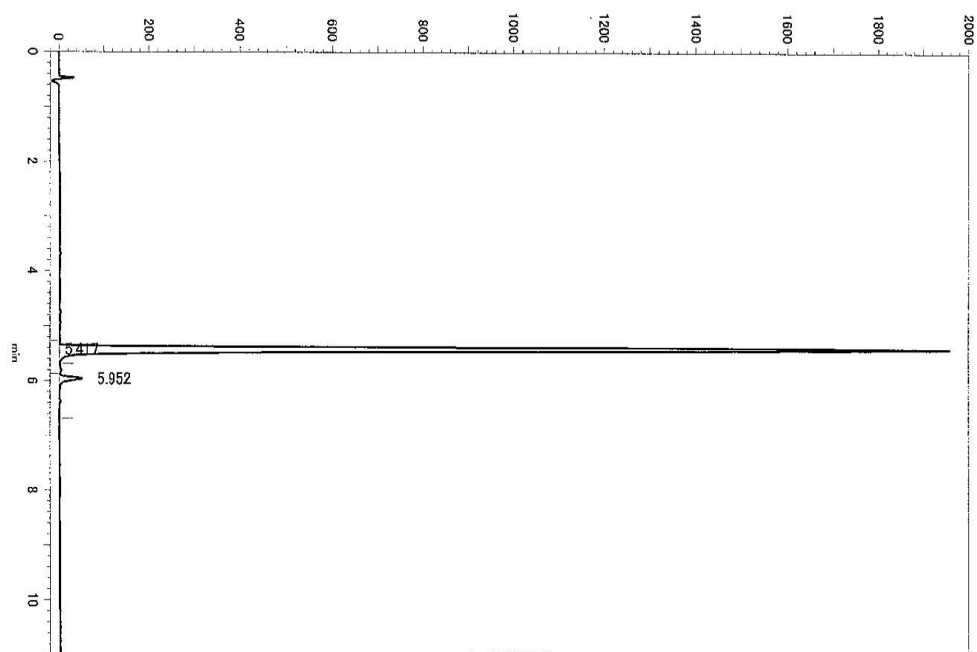


(R)-1-(4-(1-(2-(3-(Cyclopropylmethoxy)-4-fluorophenyl)-2-hydroxybutyl)-1H-1,2,3-triazol-5-yl)butyl)pyrimidine-2,4(1H,3H)-dione (50d)

From **9b** (50 mg, 0.26 mmol) and **44** (73 mg, 0.26 mmol), **50d** (83 mg, 68%) was obtained as a

colorless foam. ^1H NMR ($\text{DMSO}-d_6$) δ 0.28-0.32 (2H, m), 0.54-0.58 (2H, m), 0.68 (3H, t, $J = 7.2$ Hz), 1.11-1.21 (1H, m), 1.42-1.55 (4H, m), 1.73-1.79 (1H, m), 1.97-2.02 (1H, m), 2.33-2.43 (2H, m), 3.63 (2H, t, $J = 6.8$ Hz), 3.79 (2H, d, $J = 7.2$ Hz), 4.39-4.46 (2H, m), 5.29 (1H, s), 5.52 (1H, d, $J = 7.6$ Hz), 6.83-7.11 (3H, m), 7.39 (1H, s), 7.61 (1H, d, $J = 7.6$ Hz), 11.21 (1H, brs); ^{13}C NMR (CDCl_3) δ 3.29, 7.36, 10.23, 22.35, 24.61, 28.51, 32.09, 47.87, 57.57, 74.52, 77.23, 102.68, 113.54, 115.76, 115.95, 117.75, 131.60, 137.82, 138.97, 144.02, 146.78, 150.58, 150.93, 163.35; TOF-HRMS m/z $[\text{M}+\text{H}]^+$: Calcd. for $\text{C}_{24}\text{H}_{31}\text{FN}_5\text{O}_4$, 472.2360; Found, 472.2367; $[\alpha]_{\text{D}}^{25} = -5.45$ (c 0.42, CHCl_3); Purity: 100% (Column: Shim-pack XR-ODS 3 mmID \times 50 mm, 2.2 μm , Column temperature: 40 $^\circ\text{C}$, Mobile phase: 10 mM Phosphate buffred solution pH 6.5 /Acetonitrile :0 min 90/10, 8 min 20/80, 10 min 20/80, Flow rate : 0.8 mL/min, **50d** was eluted at 5.2 min); 94.7%e.e. [HPLC condition, Column:CHIRALPAK AD-H (4.6 \times 250 mm), Column Temp.:25 $^\circ\text{C}$, Mobile phase: hexane/2-propanol/isopropylamine (7:3:0.1), Flow rate: 0.7 mL/min., Detector: UV 240 nm, **50d** was eluted at 15.7 min]

HPLC analysis chart of 48b

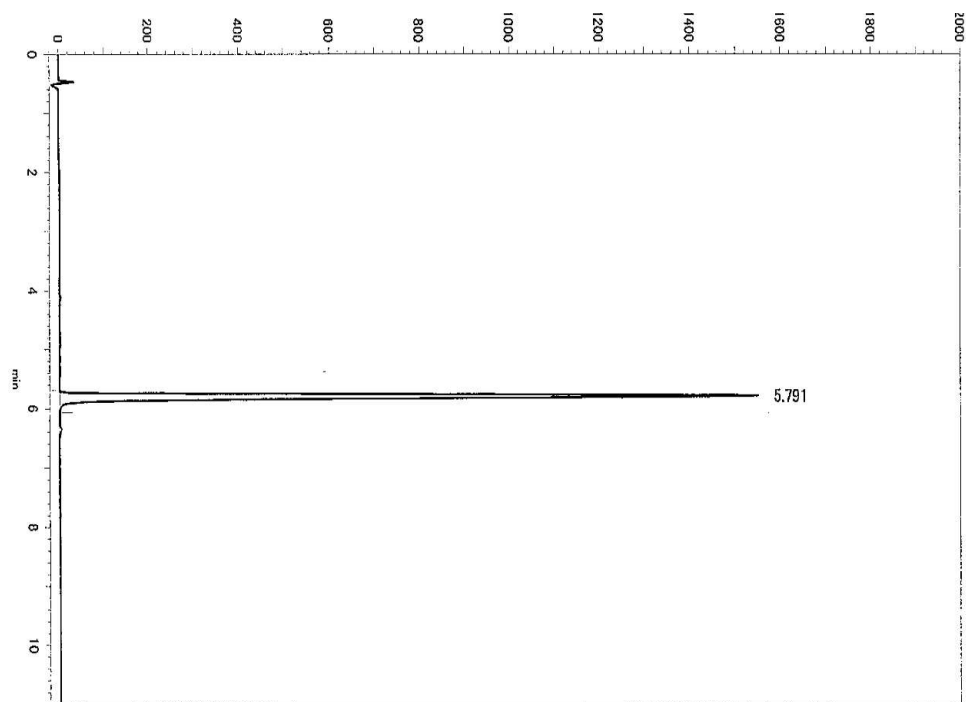


peak number	retention time	area	area%
1	5.417	9310305	97.42
2	5.952	246570	2.58

Total		9556876	100.00
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Column: Shim-pack XR-ODS 3 mmID X 50mm, 2.2um
Column Temp. : 40
Mobile phase : 10mM PB(pH6.5) /Acetonitrile 0 min : [90:10] 8min : [20:80] 10min : [20:80]
Flow rate : 0.8 mL/min

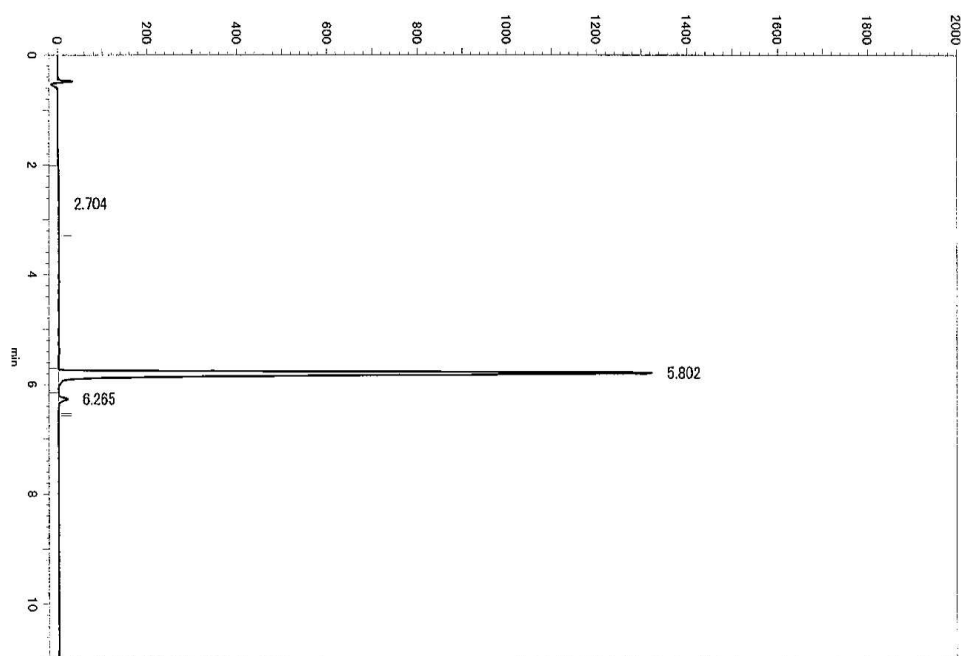
HPLC analysis chart of 48c



peak number	retention time	area	area%
1	5.791	7147217	100.00
Total		7147217	100.00

Column: Shim-pack XR-ODS 3 mmID X 50mm, 2.2um
Column Temp. : 40
Mobile phase : 10mM PB(pH6.5) /Acetonitrile 0 min : [90:10] 8min : [20:80] 10min : [20:80]
Flow rate : 0.8 mL/min

HPLC analysis chart of 48d

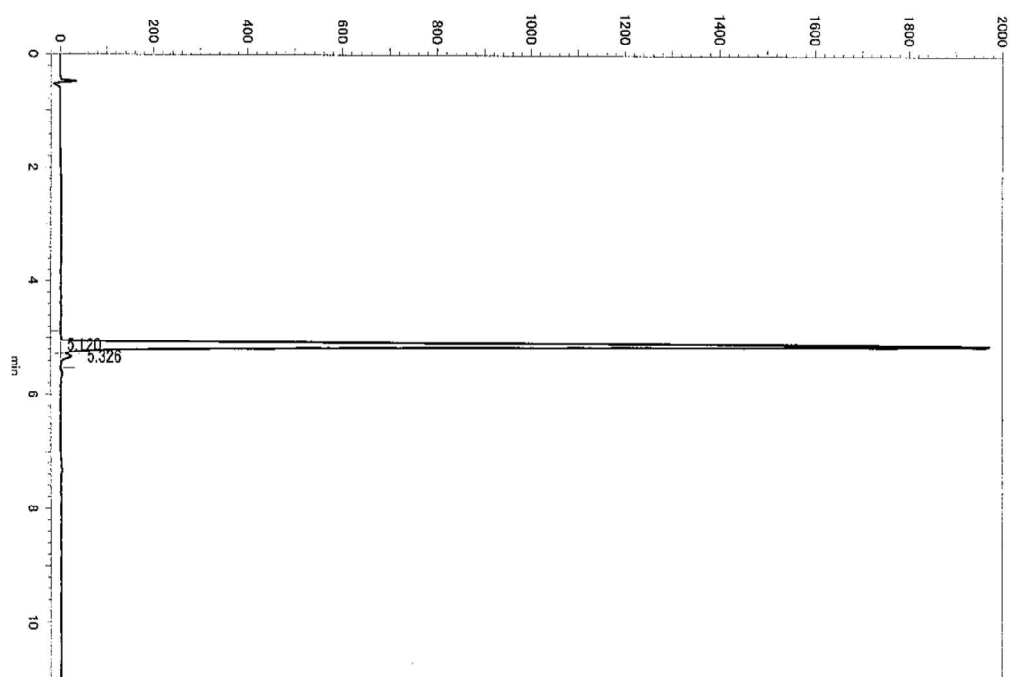


peak number	retention time	area	area%
1	2.704	55402	0.90
2	5.802	5986458	97.56
3	6.265	94431	1.54

Total		6136291	100.00
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Column: Shim-pack XR-ODS 3 mmID X 50mm, 2.2um
Column Temp. : 40
Mobile phase : 10mM PB(pH6.5) /Acetonitrile 0 min : [90:10] 8min : [20:80] 10min : [20:80]
Flow rate : 0.8 mL/min

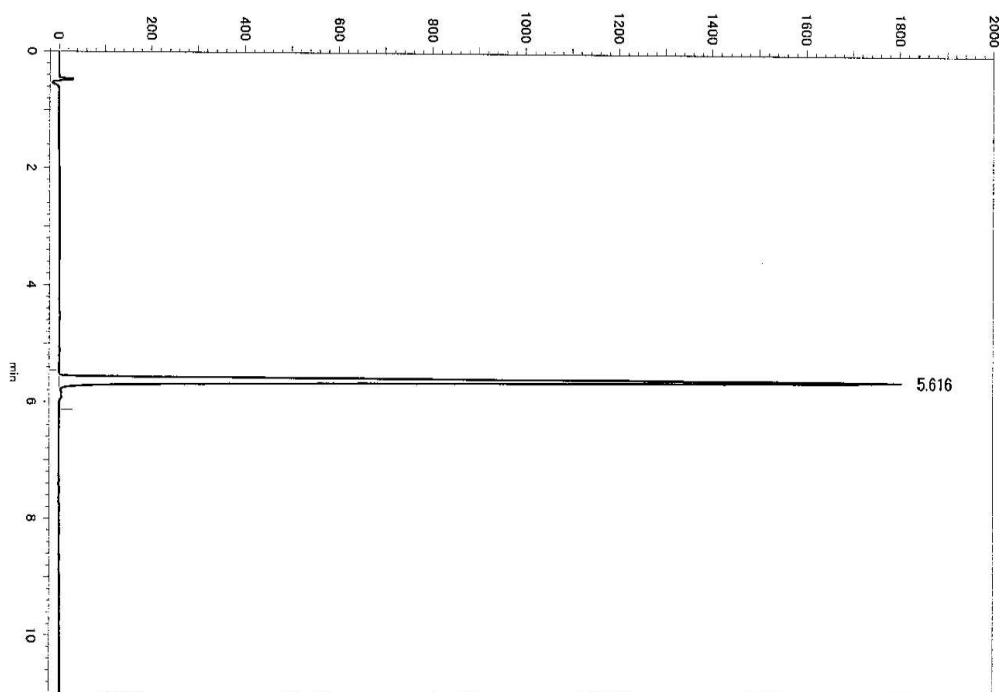
HPLC analysis chart of 49a



peak number	retention time	area	area%
1	5.120	9203217	98.83
2	5.326	108493	1.17
Total		9311710	100.00

Column: Shim-pack XR-ODS 3 mmID X 50mm, 2.2um
Column Temp. : 40
Mobile phase : 10mM PB(pH6.5) /Acetonitrile 0 min : [90:10] 8min : [20:80] 10min : [20:80]
Flow rate : 0.8 mL/min

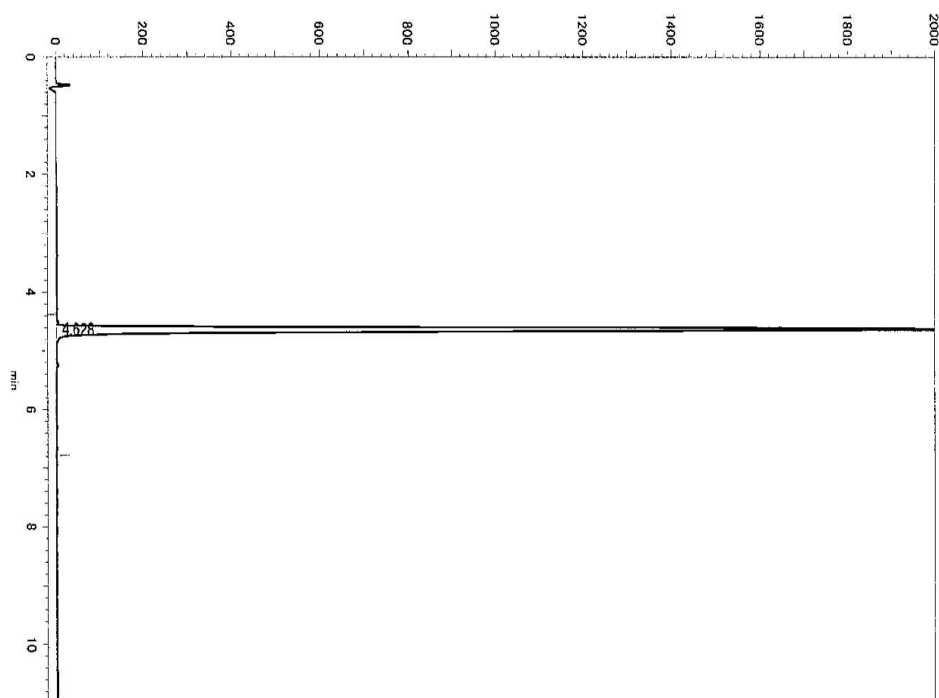
HPLC analysis chart of 49b



peak number	retention time	area	area%
1	5.616	8102789	100.00
Total		8102789	100.00

Column: Shim-pack XR-ODS 3 mmID X 50mm, 2.2um
Column Temp. : 40
Mobile phase : 10mM PB(pH6.5) /Acetonitrile 0 min : [90:10] 8min : [20:80] 10min : [20:80]
Flow rate : 0.8 mL/min

HPLC analysis chart of 49c

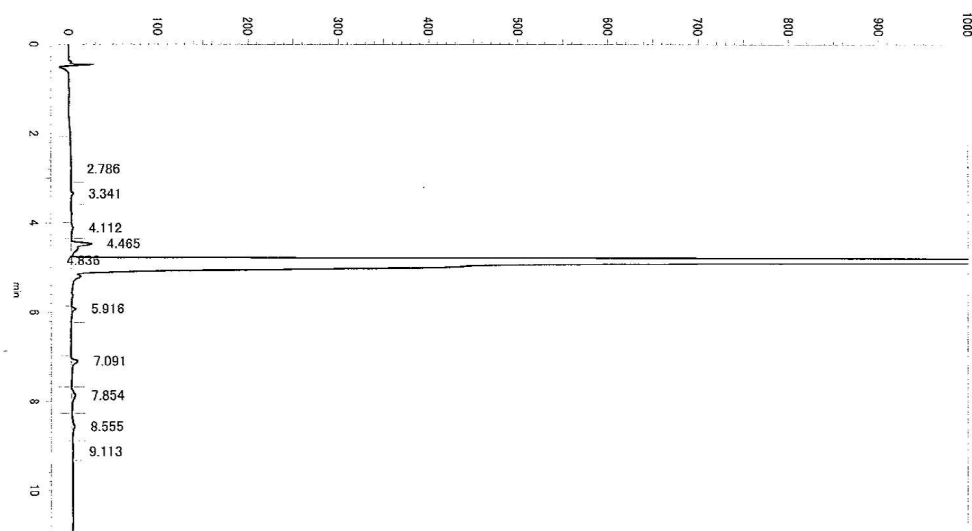


peak number	retention time	area	area%
1	4.628	9379129	100.00

Total		9379129	100.00
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Column: Shim-pack XR-ODS 3 mmID X 50mm, 2.2um
Column Temp. : 40
Mobile phase : 10mM PB(pH6.5) /Acetonitrile 0 min : [90:10] 8min : [20:80] 10min : [20:80]
Flow rate : 0.8 mL/min

HPLC analysis chart of 49f

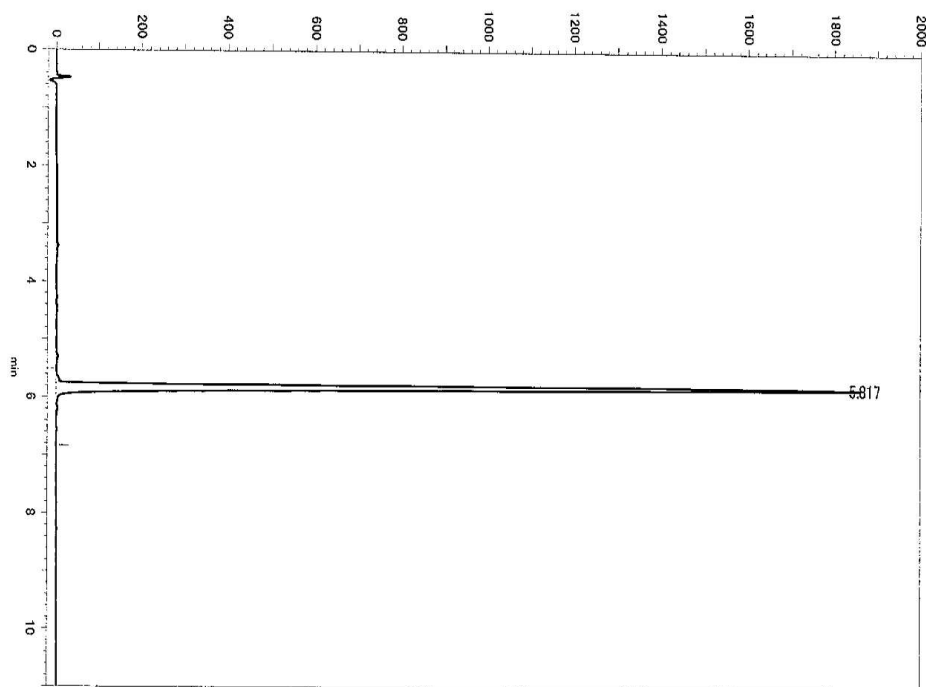


peak number	retention time	area	area%
1	2.786	32961	0.21
2	3.341	20315	0.13
3	4.112	28988	0.19
4	4.465	172316	1.10
5	4.836	15119716	96.71
6	5.916	27735	0.18
7	7.091	73813	0.47
8	7.854	65871	0.42
9	8.555	60481	0.39
10	9.113	31894	0.20

Total		15634091	100.00
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Column: Mightysil RP18 4.6 X 150mm, 5um
 Column Temp.: 40
 Mobile phase: 0.1% TFA /Acetonitrile 0 min : [45:55] 12min : [45:55] 40min : [30:70]
 Flow rate: 1.1 mL/min
 Sample: 1 mg/mL, 5 uL injection

HPLC analysis chart of 49h

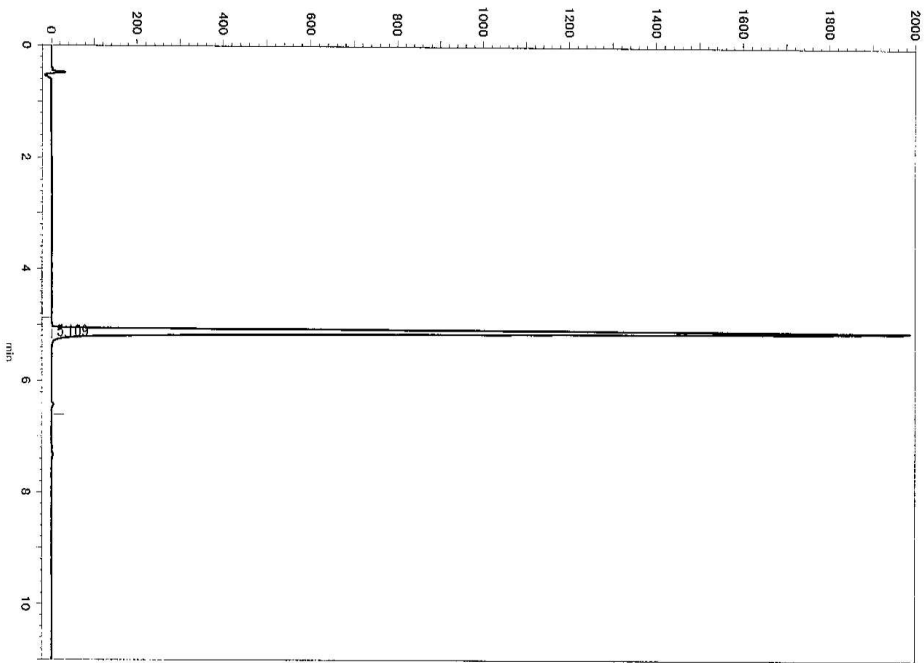


peak number	retention time	area	area%
1	5.817	8921688	100.00

Total		8921688	100.00
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Column: Shim-pack XR-ODS 3 mmID X 50mm, 2.2um
 Column Temp. : 40
 Mobile phase : 10mM PB(pH6.5) /Acetonitrile 0 min : [90:10] 8min : [20:80] 10min : [20:80]
 Flow rate : 0.8 mL/min

HPLC analysis chart of 50a

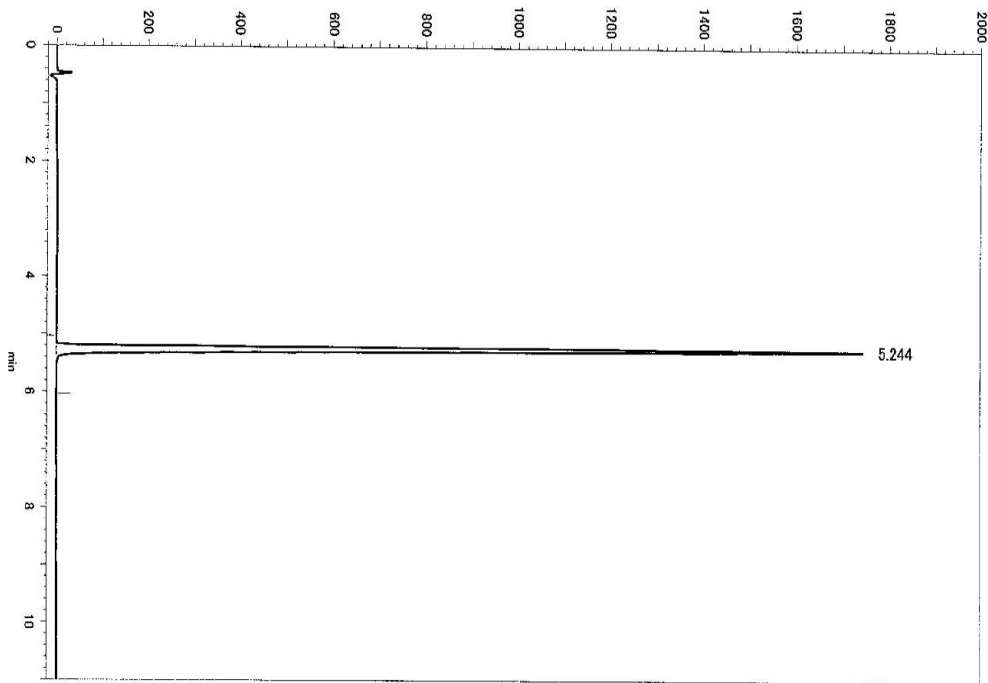


peak number	retention time	area	area%
1	5.109	9283005	100.00

total		9283005	100.00
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Column: Shim-pack XR-ODS 3 mmID X 50mm, 2.2um
Column Temp. : 40
Mobile phase : 10mM PB(pH6.5) /Acetonitrile 0 min : [90:10] 8min : [20:80] 10min : [20:80]
Flow rate : 0.8 mL/min

HPLC analysis chart of 50d



peak number	retention time	area	area%
1	5.244	7951859	100.00

Total		7951859	100.00
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Column: Shim-pack XR-ODS 3 mmID X 50mm, 2.2um
Column Temp. : 40
Mobile phase : 10mM PB(pH6.5) /Acetonitrile 0 min : [90:10] 8min : [20:80] 10min : [20:80]
Flow rate : 0.8 mL/min

Binding model of amide-containing uracil compound **6b**

We build binding model of the *cis* conformation of **6b** in the active site of human dUTPase on the basis of the X-ray diffraction data (PDB: 3ARA) of **7**, on the premise that stacking interaction between uracil ring and phenyl ring are essential for dUTPase inhibition activity. First, possible conformations of free **6b** were generated exhaustively with OMEGA (version 2.3.2).⁷ Next, best aligned conformation of **6b** to the binding conformation of **7**, which was extracted from the X-ray structure, was selected with vROCS (version 3.1.2). For the alignment, two pharmacophores, which are uracil ring and one of the terminal phenyl rings which is stacked with the uracil ring, were used as constraints. Finally, best aligned conformation of **6b** was superposed to the active site of X-ray structure of **7** and the energy minimization was performed in the active site to afford the binding model of **6b**.

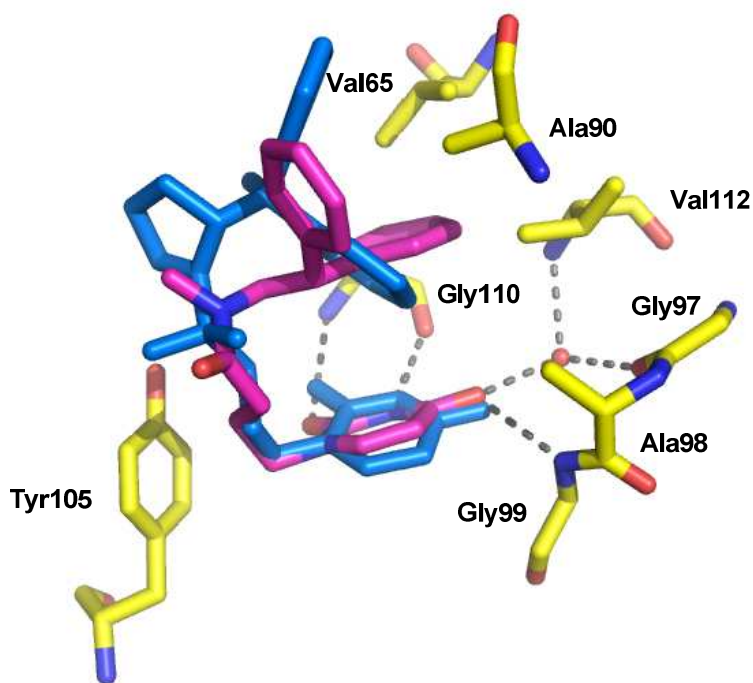


Figure S1. Binding model of *cis* isomer of **6b** (pink stick) and X-ray structure of **7** (blue stick) in the catalytic site of human dUTPase (PDB code: 3ARA). Supposed polar interaction (gray dash) and water (small spheres) are shown.

HPLC analysis chart at 0.5 hr after oral administration of 48c and 49a at 50 mg/kg in Balb/cA mice

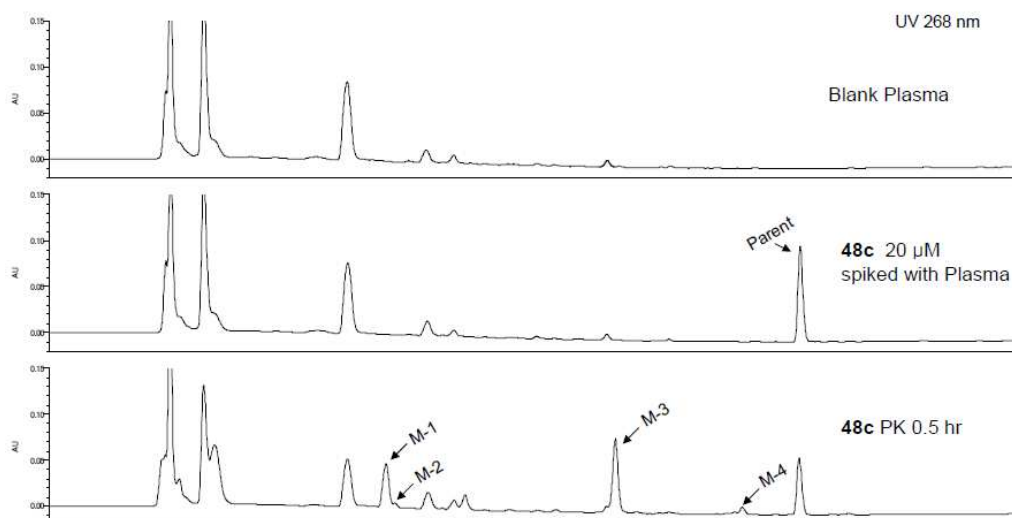


Figure S2. HPLC analysis chart at 0.5 hr after oral administration of **48c** at 50 mg/kg in Balb/cA mice

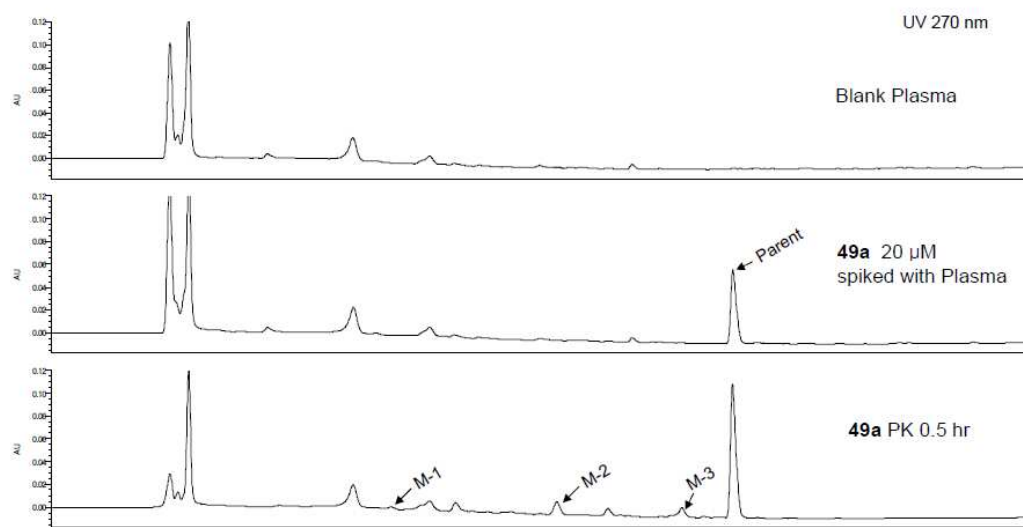


Figure S3. HPLC analysis chart at 0.5 hr after oral administration of **49a** at 50 mg/kg in Balb/cA mice

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