Supporting Information

Design, synthesis and structure-activity relationship studies of novel fused heterocycles-linked triazoles with good activity and water solubility

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Contents

I. Experimental details

General Chemical Methods. Compounds not described below were purchased from commercial vendors. Provided samples were of greater than 95% purity, as determined by the suppliers, via NMR.

Melting points (uncorrected) were determined on an X-4 melting point apparatus. Optical rotations were determined with a Perkin-Elmer 241 polarimeter at 22 °C and at 589 nm using a sodium lamp and a 1 ml cell. Data are reported as follows: $[\alpha]^{22}_{D}$ (concentration g/100ml, solvent). ^{1}HNMR spectral data were recorded on a Bruker 300 NMR or a Bruker 400 NMR or a Bruker 500 NMR spectrometer using TMS as an internal standard, chemical shifts are given in parts per million (d) values and coupling constants (*J*) in Hertz. EI-MS spectra were obtained on a Finnigan MAT 95 mass spectrometer and ESI-MS spectra were obtained on a Krats MS 80 mass spectrometer. Elemental analysis was obtained *via* a vario EL spectrometer. HPLC analysis was conducted for all assayed compounds on an Agilent 1100 series LC system (PLATISILTM ODS 5μm 250 × 4.6 mm) with two solvent systems (acetonitrile/water or methanol/buffer (0.1% CF3COOH in water)). All the assayed compounds possess ≥ 95% purity. Silica gel thin-layer chromatography was performed on precoated plates GF254 (Qindao Haiyang Chemical, China). Column chromatography was performed on silica gel H (200-300 mesh) , and the solvent proportions were expressed on a volume:volume basis. Chemicals and solvents used were commercially available without any pretreatment. Focused microwave irradiations were carried out with a CEM DiscoverTM focused microwave reactor (300W, 2455 MHz, monomode system).

N-benzyl-N-(2-hydroxyethyl)prop-2-yn-1-amine (14a). A solution of N-Benzylethanol-amine (37.8 g, 0.25 mol) in dry CH_3CN (500 ml) was mixed with potassium carbonate (51.8 g, 0.37 mol) and 3-Chloropropyne (22.4g, 0.30 mol). The resulting mixture was heated under reflux for 6 hours. Then the reaction mixture was cooled to room temperature and then filtered, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum: ethyl acetate 8:1~6:1) to give **14a** (34.5 g, 72.9%) as pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.36-7.28 (m, 5H), 3.64 (t, *J* =5.49 Hz, 2H), 3.62 (s, 2H), 3.27 (d, 2H), 2.76 (t, *J* =5.49 Hz, 2H), 2.23 (t, 1H). MS (ESI) m/z: 190.1 $(M + 1)^{+}$.

4-(benzyl(2-hydroxyethyl)amino)but-2-ynyl acetate (14b). Compound **14b** (2.50g, 59.4%) was prepared from **13** (2.43 g, 16.10 mmol) and 4-chlorobut-2-ynyl acetate (2.36 g, 16.10 mmol) in the same manner as described for **14a**. yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.34-7.31 (m, 5H), 4.76 (t, *J* =1.83 Hz, 2H), 3.67 (s, 2H), 3.62 (t, *J* =5.32 Hz, 2H), 3.35 (t, *J* =1.83Hz, 2H), 2.78 (t, *J* =5.32 Hz, 2H), 2.12 (s, 3H). MS (ESI) m/z: 262.1 $(M + 1)^{+}$.

5-benzyl-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine (15a). Thionyl chloride (14.2 g, 0.12 mol) was added dropwise to a stirred mixture of N-benzyl-N-(2-hydroxyethyl)prop-2-yn-1-amine **14a** (12.6g, 0.07 mmol) and pyridine (7.86 g, 0.10 mol), and dichloromethane (200 ml) at 0°C. The mixture was stirred for 2 h at room temperature, then extracted with dichloromethane (200 ml) and water (200 ml). The combined organic layers were washed with brine (100 ml),

dried over anhydrous Na_2SO_4, and filtrated, and the solvent was evaporated under reduced pressure to afford dark brown oil, which was used for the following reaction without further purification.

A solution of dark brown oil in dry DMF (100 ml) was mixed with NaN_3(4.55 g, 0.07mol). The resulting mixture was heated at 80 °C for 8 hours. Then the reaction mixture was cooled to room temperature and then extracted with ethyl acetate (200 ml×3) and water (200 ml×2), the combined organic layers were washed with water (200 ml×2) and brine (200 ml×2), dried over anhydrous Na_2SO_4, and filtrated, and the solvent was evaporated under reduced pressure. Chromatography on silica gel with petroleum/ethyl acetate (10:1~5:1) gave 2.11 g (8.6g, 56.8%) of **15a** as a pale yellow solid. Mp: 86-88 °C. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.45 (s, 1H), 7.38-7.34 (m, 5H), 4.42 (t, J =5.49 Hz, 2H), 3.76 (s, 2H), 3.73 (s, 2H), 2.98 (t, J =5.49 Hz, 2H). MS (ESI) m/z: 215.1 $(M + 1)^+$.

(5-benzyl-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazin-3-yl)methyl acetate (15b). Compound **15b** (1.86g, 67.4%) was prepared from **14b** (2.51 g, 9.60 mmol) in the same manner as described for **15a**. yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.41-7.26 (m, 5H), 5.17 (s, 2H), 4.41 (t, J =5.50 Hz, 2H), 3.77 (s, 2H), 3.75 (s, 2H), 2.88 (t, J =5.50 Hz, 2H), 2.06 (s, 3H). MS (ESI) m/z: 287.2 $(M + 1)^+$.

4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine (16a). Compound **15a** (6.42 g, 30.0 mmol) was dissolved in methanol (50 ml) followed by the addition of 10% $Pd(OH)_2$ (0.60 g, 4.00 mmol) at ambient temperature. The mixture was stirred under hydrogen (1 atm) at 50°C overnight and then filtered, concentrated under reduced pressure to give **16a** (2.79 g, 75.0%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.41 (s, 1H), 4.31 (t, J =5.42 Hz, 2H), 4.08 (s, 2H), 3.32 (t, J =5.49 Hz, 2H). MS (ESI) m/z: 125.0 $(M + 1)^+$.

4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazin-3-yl)methyl acetate (16b). Compound **16b** (3.08g, 80.3%) was prepared from **15b** (5.6 g, 19.6mmol) in the same manner as described for **16a**. colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 5.18 (s, 2H), 4.36 (t, J =5.50 Hz, 2H), 3.75 (s, 2H), 3.26 (t, J =5.50 Hz, 2H), 2.08 (s, 3H). MS (ESI) m/z: 197.2 $(M + 1)^+$.

5-Boc-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine (17a). A mixture of compound **16a** (1.24 g, 0.01 mol), triethylamine (1.21 g, 0.012 mol), di-*tert*-butyl dicarbonate (2.40 g, 0.011 mol) and dichloromethane (30 ml) was stirred at room temperature for 4 h, then extracted with dichloromethane (50 ml) and water (30 ml). The combined organic layers were washed with brine (30 ml), dried over anhydrous Na_2SO_4, and filtrated, and the solvent was evaporated under reduced pressure. The resulting product was purified by silica gel column chromatography (petroleum: ethyl acetate 8:1~6:1) to give **17a** (1.90 g, 85.0%) as a white solid. Mp: 116-118 °C. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.43 (s, 1H), 4.65 (s, 2H), 4.43 (t, J =5.41Hz, 2H), 3.86 (t, J =5.41Hz, 2H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.88, 130.01, 129.15, 81.41, 45.57 (3C, overlap), 28.18. MS (ESI) m/z: 225.1 $(M + 1)^+$.

(5-Boc-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazin-3-yl)methyl acetate (17b). 17b (3.97g, 75.0%) was prepared from **16b** (3.5 g, 17.8 mmol) and Di-*tert*-butyl dicarbonate (4.28 g, 19.6 mmol) in the same manner as described for **17a**. colorless oil. ^{1}H NMR (300 MHz,

$CDCl_3$)：δ 5.18 (s, 2H), 4.76 (s, 2H), 4.39 (t, J =5.50 Hz, 2H), 3.87 (s, 2H), 2.08 (s, 3H) , 1.51 (s, 9H). MS (ESI) m/z: 297.2 $(M + 1)^+$.

3-bromo-5-Boc-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine (17c). 17a (1.34 g, 6.00 mmol) was dissolved in CH_3CN (20 ml). N-bromosuccinimide (1.28 g, 7.20 mmol) was added dropwise at 0 °C. The reaction mixture was allowed to warm to 60 °C and stirred for 12 hours. After concentration in vacuo, the residue was purified by silica gel column chromatography (petroleum: ethyl acetate 6:1~4:1) to give **17c** (0.64 g, 35.0%) as a yellow solid. Mp: 96-98 °C. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 4.61 (s, 2H), 4.41 (t, J =5.28 Hz, 2H), 3.85 (t, J =5.28 Hz, 2H), 1.51 (s, 9H). MS (ESI) m/z: 303.0 $(M + 1)^+$.

3-chloro-5-Boc-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine (17d). 17a (1.34 g, 6.00 mmol) was dissolved in CH_3CN (20 ml). N-bromosuccinimide (1.28g, 7.20 mmol) was added dropwise at 0 °C. The reaction mixture was allowed to warm to 60 °C and stirred for 12 hours. After concentration in vacuo, the residue was purified by silica gel column chromatography (petroleum: ethyl acetate 8:1~4:1)) to give **17d** (0.48 g, 32.0%) as a yellow solid. Mp: 88-86 °C. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 4.65 (s, 2H), 4.42 (t, J =5.49 Hz, 2H), 3.83 (t, J =5.49 Hz, 2H), 1.50 (s, 9H). MS (ESI) m/z: 259.1 $(M + 1)^+$.

3-hydroxymethyl-5-Boc-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine (17e). A solution of **17b** (4.3 g, 14.5 mmol) in MeOH (40 ml) and H_2O (10 ml) was treated with Lithium hydroxide monohydrate (1.83 g, 43.5 mmol). The resulting mixture was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure, and extracted with ethyl acetate (100 ml×2) and H_2O (30 ml). The combined extract was washed with brine (30 ml), dried over anhydrous Na_2SO_4, and filtrated, the solvent was evaporated under reduced pressure to give compound **17e** (2.10g, 57.0%) as a white solid. Mp: 108-109 °C. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 4.99 (t, J =5.50 Hz, 2H), 4.70(s, 2H), 4.65 (s, 2H), 3.99 (t, J =5.50 Hz, 2H), 1.50 (s, 9H). MS (ESI) m/z: 255.1 $(M + 1)^+$.

3-bromo-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine (11c). To a solution of compound **17c** (3.03 g, 10.0mmol) in dioxane (15 ml) was added 20 ml 4N HCl/dioxane. The resulting mixture was stirred at room temperature for 6h. The solvent was evaporated under reduced pressure. The residue was diluted with water (30 ml), basified with Na_2CO_3, and extracted with CH_2Cl_2 (50 ml×2). The combined extract was washed with water (50 ml×2) and brine (50 ml×2), dried over anhydrous Na_2SO_4, then filtrated, and the solvent was evaporated under reduced pressure to give compound **11c** as a white solid (1.73 g, 85.0%). Mp: 108-110 °C. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 4.41 (t, J = 5.46 Hz, 2H), 4.21 (s, 2H), 3.26 (t, J = 5.46 Hz, 2H). MS (ESI) m/z: 203.0 $(M + 1)^+$.

3-chloro-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine (11d). 11d (1.30g, 82.0%) was prepared from **17d** (2.59 g, 10.0 mmol) in the same manner as described for **11c**. colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 4.36 (t, J= 5.50Hz, 2H), 4.18 (s, 2H), 3.28 (t, J = 5.50 Hz, 2H). MS (ESI) m/z: 159.0 $(M + 1)^+$.

3-hydroxymethyl-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine (11e). 11e (1.18 g, 76.5%) was prepared from **17e** (2.54 g, 10.0 mmol) in the same manner as described for **11c**.

White solid. Mp: 145-146 °C. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 4.68 (s, 2H), 4.38 (t, J =5.45 Hz, 2H), 4.16 (s, 2H), 3.31 (t, J =5.45 Hz, 2H). MS (ESI) m/z: 155.1 $(M + 1)^+$.

3-chloromethyl-5-Boc-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine (17f). A solution of **17e** (1.20 g, 4.72 mmol) in dichloromethane (30 ml) was cooled to 0 °C. pyridine (1.12 g, 15.0 mmol) was added, followed by thionyl chloride (1.41g, 11.58mmol) in dichloromethane (10 ml) dropwise. The reaction mixture was stirred for 6 h at room temperature, then extracted with dichloromethane (50 ml) and water (25 ml). The combined organic layers were washed with brine (20 ml), dried over anhydrous Na_2SO_4, and filtrated, and the solvent was evaporated under reduced pressure to afford dark brown oil, which was purified by silica gel column chromatography (petroleum: ethyl acetate 6:1~4:1) to afford **17f** (0.64g, 49.8%) as white solid. Mp: 101-103 °C. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 4.76 (s, 2H), 4.72 (s, 2H), 4.41 (t, J =5.27 Hz, 2H), 3.92 (t, J =5.28 Hz, 2H), 1.49 (s, 9H). MS (ESI) m/z: 273.8 $(M + 1)^+$.

3-methyl-5-Boc-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine (17g). A solution of Compound **17f** (0.41 g, 1.50 mmol) in methanol (20 ml) was added 10% palladium on carbon (0.32 g) at room temperature. The mixture was stirred under hydrogen at 1 atm overnight and then filtered, concentrated under reduced pressure to give **17g** (0.25 g, 70.0%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 4.75(s, 2H), 4.45 (t, J =5.28 Hz, 2H), 4.07 (t, J =5.28 Hz, 2H), 2.47(s, 3H), 1.51 (s, 9H). MS (ESI) m/z: 239.1 $(M + 1)^+$.

3-methyl-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine (11f). 11f (0.14g, 95.2%) was prepared from **17g** (0.25 g, 4.20 mmol) in the same manner as described for **11c**. white solid. Mp: 90-91 °C. ^{1}H NMR (300 MHz, DMSO-d_6)：δ 4.15 (t, J =5.36 Hz, 2H), 3.80 (s, 2H), 3.06 (t, J =5.36 Hz, 2H), 2.12(s, 3H). MS (ESI) m/z: 139.1 $(M + 1)^+$.

3-(2,2,2-trifluoroethyl)-5-Boc-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine-3-carboxylate (17h). Under nitrogen flow, iodine (3.75 g, 14.80 mmol) and K_2CO_3 (2.04g, 14.8 mmol) was added to a stirred solution of compound **17e** (1.50 g, 5.90 mmol) in CF_3CH_2OH (20 ml). After addition, the reaction was heated at 50 °C for 4 h. Then the reaction mixture was cooled to room temperature, washed with saturated sodium sulfite solution, dried over anhydrous Na_2SO_4, and filtered, the filtrate was evaporated at reduced pressure. The residue was purified by silica gel column chromatography (petroleum: ethyl acetate 4:1) to give **17h** (0.62 g, 30.1%) as white solid. Mp: 151-152 °C. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 4.93 (s, 2H), 4.76 (s, 2H), 4.45 (t, J =5.56 Hz, 2H), 3.96 (t, J =5.56Hz, 2H), 1.50 (s, 9H). MS (ESI) m/z: 351.1 $(M + 1)^+$.

3-(N,N-dimethyl)-5-Boc-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine-3-carboxamide (17i). 17h (0.35 g, 1.00 mmol) was dissolved in dry CH_3CN (10 ml) followed by addition of K_2CO_3 (1.65 g, 12.0 mmol) and dimethylamine hydrochloride (0.49 g, 6.00 mmol) under nitrogen. The mixture was stirred at 60 °C for 8 hours. After concentration in vacuo, water (20 ml) was added, and the aqueous solution was extracted with ethyl acetate (20 ml×2). The combined organic layers were washed with brine and dried over Na_2SO_4, and filtered, the filtrate was evaporated at reduced pressure. The residue was purified by silica gel column chromatography (petroleum: ethyl acetate 2:1) to give **17i** (0.13 g, 44.0%) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 4.95 (s, 2H), 4.45 (t, J =5.27 Hz, 2H), 3.91 (t, J =5.27 Hz, 2H), 3.65 (s, 3H), 3.11 (s, 3H), 1.51 (s, 9H). MS (ESI) m/z: 296.1 $(M + 1)^+$.

3-(N,N-dimethyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine-3-carboxamide (11g). 11g (0.10g, 92.0%) was prepared from **17d** (0.16 g, 0.56 mmol) in the same manner as described for **11c**. Yellow viscous oil. ^{1}H NMR (300 MHz, DMSO-d_6)：δ 4.68 (s, 2H), 4.18 (t, J =5.38 Hz, 2H), 3.76 (t, J=5.38 Hz, 2H), 3.41 (s, 3H), 2.96 (s, 3H). MS (ESI) m/z: 196.1 $(M + 1)^+$.

(*2R, 3R*)-3-(3-bromo-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (12c). Under nitrogen flow, the mixture of epoxide **10** (62.75 mg, 0.25 mmol), CH_3CN (10 ml), $LiClO_4$ (40.0 mg, 0.38 mmol) and 3-bromo-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine **11c** (76.1 mg, 0.38 mmol) was stirred under refluxed for 24h. The solvent was evaporated under reduced pressure. The residue was diluted with H_2O (20 ml) and extracted with ethyl acetate (20 ml ×2). The combined organic layers were washed with H_2O (20 ml ×2) and brine (20 ml ×2), dried over anhydrous Na_2SO_4, and filtrated, then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH 100:1~50:1) to give **12c** (53.1 mg, 46.8%) as a white solid: mp 149-150 °C. $[\alpha]^{22}_D$ –74.4°(*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.77 (s, 1H), 7.46-7.37 (m, 1H), 6.80-6.70 (m, 2H), 5.08 (s, 1H), 4.96-4.88 (m, 2H), 4.54-4.38 (m, 2H), 4.08-4.02 (m, 1H), 3.86-3.81 (m, 2H), 3.32 (q, J =6.9 Hz, 1H), 2.91-2.83 (m, 1H), 0.98 (d, J =6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.02, 143.98, 131.32, 130.61, 124.32, 124.22 (2C, overlap), 115.98, 111.82, 104.03, 79.87, 62.93, 55.98 (2C, overlap), 55.93, 47.21, 6.91. MS (EI) m/z: 453 (M^+). HRMS (EI): Anal. Calcd for $C_{17}H_{18}BrF_2N_7O$: 453.0765, Found: 453.0786.

(*2R, 3R*)-3-(3-chloro-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (12d). 12d (56.0 mg, 41.4%) was prepared from epoxide **10** (82.3 mg, 0.33 mmol) and **11d** (104.0 mg, 0.66 mmol) in the same manner as described for **12c**. white solid: mp 132-134 °C. $[\alpha]^{22}_D$ –68.6°(*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.83 (s, 1H), 7.78 (s, 1H), 7.46-7.38 (m, 1H), 6.80-6.69 (m, 2H), 5.08(s, 1H), 4.95-4.82 (m, 2H), 4.51-4.37 (m, 2H), 4.11-4.07(m, 1H), 3.90-3.85(m, 2H), 3.36 (q, J =6.7 Hz, 1H), 2.90-2.87 (m, 1H), 0.99 (d, J=6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.03, 143.01, 131.23, 130.56, 124.36, 124.26 (2C, overlap), 115.86, 111.78, 104.08, 79.86, 62.95, 55.96 (2C, overlap), 55.91, 47.25, 6.93. MS (EI) m/z: 409 (M^+). HRMS (EI): Anal. Calcd for $C_{17}H_{18}ClF_2N_7O$: 409.1218, Found: 409.1216.

(*2R, 3R*)-3-(3-methyl-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (12f). 12f (88.4 mg, 38.0%) was prepared from epoxide **10** (150.0 mg, 0.60 mmol) and **11f** (165.3 mg, 1.20 mmol) in the same manner as described for **12c**. white solid: mp 99-101 °C. $[\alpha]^{22}_D$ –56.8°(*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$)：δ 7.82 (s, 1H), 7.77 (s, 1H), 7.49 -7.38 (m, 1H), 6.78-6.70 (m, 2H), 5.04 (s, 1H), 4.92-4.83 (m, 2H), 4.48 -4.35 (m, 2H), 4.05-4.03 (m, 1H), 3.82-3.71 (m, 2H), 3.31 (q, J =6.9 Hz, 1H), 2.86-2.81 (m, 1H), 2.27 (s, 3H), 0.97 (d, J= 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.78, 144.01, 137.55, 130.53, 128.92, 124.43, 124.32 (2C, overlap), 111.71, 104.14, 79.75, 63.11, 56.00 (2C, overlap), 55.95, 46.53, 9.88, 6.92. ESI-MS 390.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{18}H_{21}F_2N_7ONa$: 412.1284, Found: 412.1273.

(*2R,3R*)-3-(3-(dimethylamino)carbonyl-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-

yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (12g). 12g (52.1 mg, 36.6%) was prepared from epoxide **10** (80.0 mg, 0.32 mmol) and **11g** (124.3 mg, 0.64 mmol) in the same manner as described for **12c**. white solid: mp 175-177 °C. $[\alpha]^{22}_{D}$ –47.2°(*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$)：δ 7.81(s, 1H), 7.77 (s, 1H), 7.45-7.40 (m, 1H), 6.77-6.73 (m, 2H), 5.06 (s, 1H), 4.95-4.86 (m, 2H), 4.46-4.37 (m, 2H), 4.05-4.01(m, 1H), 3.86-3.76(m, 2H), 3.63 (s, 3H), 3.51 (s, 3H), 3.35 (q, *J* =6.9 Hz, 1H), 2.89-2.81 (m, 1H), 0.99 (d, *J* =6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.01, 151.96, 143.96, 138.09, 137.79, 130.49, 124.43, 124.30 (2C, overlap) , 111.69, 104.19, 79.2, 62.47, 56.04 (2C, overlap), 55.99, 46.84, 38.76, 36.14, 6.78. MS (EI) m/z: 446 (M^+). HRMS (EI): Anal. Calcd for $C_{20}H_{24}F_2N_8O_2$: 446.1978, Found: 446.1991.

(*2R*,*3R*)-3-(6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (12a). Compound **12c** (136.0 mg, 0.30 mmol) was dissolved in methanol (10 ml) followed by the addition of 10% palladium on carbon (200 mg) at ambient temperature. The mixture was stirred under hydrogen (1 atm) at room temperature overnight and then filtered, and the solvent was evaporated under reduced pressure. The resulting product was purified by silica gel column chromatography (CH_2Cl_2: MeOH 100:1~50:1) to give **12a** (61.8 mg, 55.0%) as white solid. white solid: mp 127-129 °C. $[\alpha]^{22}_{D}$ –80.8°(*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.82 (s, 1H), 7.76 (s, 1H), 7.49 (s, 1H), 7.46-7.38 (m, 1H), 6.80-6.68 (m, 2H), 5.06 (s, 1H), 4.94-4.83 (m, 2H), 4.55-4.39 (m, 2H), 4.22-4.18(m, 1H), 3.95-3.90(m, 1H), 3.81-3.75(m, 1H), 3.31 (q, *J* =6.9 Hz, 1H), 2.93-2.88 (m, 1H), 0.97 (d, *J* =6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.95, 143.98, 132.24, 130.56, 129.18, 124.43, 124.32 (2C, overlap), 111.76, 104.16, 79.80, 63.06, 55.98 (2C, overlap), 55.93, 46.45, 6.83. MS (EI) m/z: 375(M^+). HRMS (EI): Anal. Calcd for $C_{17}H_{19}F_2N_7O$: 375.1621, Found: 375.1618.

(*2R*,*3R*)-3-(3-phenyl-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (12h). A mixture of **12c** (68.11 mg, 0.15 mmol), Cesium carbonate (97.75 mg, 0.30 mmol), phenylboronic acid (23.77 mg, 0.19 mmol) and tetrakis(triphenylphosphine)palladium (0) (23.11 mg, 0.02 mmol) in dioxane (10 ml) and H_2O (5ml) was degassed and flushed with argon. The mixture was hearted at 80 °C for 12 h. The solvent was evaporated under reduced pressure. The residue was diluted with H_2O (30 ml) and extracted with ethyl acetate (40 ml ×2). The combined organic layers were washed with H_2O (20 ml ×2) and brine (20 ml ×2), dried over anhydrous Na_2SO_4, and filtrated, then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH 200:1~50:1) to give **12h** (38.15mg, 56.4%) as a white solid: mp 139-141 °C. $[\alpha]^{22}_{D}$ –47.2°(*c* 0.125, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.76 (s, 1H), 7.69 (d, *J* =7.5 Hz, 2H), 7.47 (t, *J* =7.4 Hz, 3H), 7.42-7.38 (m, 1H), 6.81-6.67 (m, 2H), 5.14 (s, 1H), 4.98-4.83 (m, 2H), 4.59-4.52 (m, 1H), 4.50-4.43 (m, 1H), 4.36-4.31 (m, 1H), 4.17-4.04 (m, 1H), 3.86-3.82 (m, 1H), 3.38 (q, *J* = 6.6 Hz, 1H), 2.95-2.92 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 151.46, 143.50, 141.10, 130.69, 130.18, 128.42, 128.31, 127.24, 125.65, 123.96, 123.82 (2C, overlap), 111.29, 103.66, 79.43, 62.57, 55.51 (2C, overlap), 55.46, 46.35, 6.49. MS (ESI) m/z: 452.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{23}H_{24}F_2N_7O$: 452.2005, Found: 452.2027.

(*2R*,*3R*)-3-(3-(pyridin-3-yl)-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (12i). 12i (67.91 mg, 62.0%) was prepared from **12c** (110.00 mg, 0.24 mmol) and 3-Pyridineboronic acid pinacol ester (59.61 mg,

0.29 mmol) in the same manner as described for **12h** white solid: mp 103-106 °C. $[\alpha]^{22}_{D}$ –48.8° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, *J* =1.7 Hz, 1H), 8.58 (dd, *J* =4.8, 1.5 Hz, 1H), 8.14 (dt, *J* =7.9, 1.9 Hz, 1H), 7.81 (s, 1H), 7.75 (s, 1H), 7.49-7.36 (m, 2H), 6.82-6.69 (m, 2H), 5.13 (s, 1H), 4.96-4.82 (m, 2H), 4.56-5.52 (m, 3H), 4.12 (d, *J* = 15.9 Hz, 1H), 3.88-3.84 (m, 1H), 3.40 (q, *J* = 6.7 Hz, 1H), 2.98-2.95 (m, 1H), 1.03 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 151.94, 148.72, 146.87, 143.91, 138.65, 133.44, 130.54, 129.46, 127.39, 124.29, 124.13 (2C, overlap), 123.90, 111.72, 104.15, 79.85, 62.99, 55.94 (2C, overlap), 55.88, 46.89, 6.94. MS (ESI) m/z: 453.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{22}H_{23}F_2N_8O$: 453.1967, Found: 453.1978.

(*2R*,*3R*)-3-(3-(pyridin-4-yl)-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (12j). **12j** (63.53mg, 58.0%) was prepared from **12c** (110.00 mg, 0.24 mmol) and 4-Pyridineboronic acid (35.73 mg, 0.29 mmol) in the same manner as described for **12h** white amorphous solid. $[\alpha]^{22}_{D}$ –35.2° (*c* 0.125, $CHCl_3$). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (d, *J* =5.8 Hz, 2H), 8.26 (s, 1H), 7.71 (d, *J* =5.9 Hz, 2H), 7.64 (s, 1H), 7.38-7.29 (m, 1H), 7.21-7.13 (m, 1H), 6.98-6.90 (m, 1H), 5.74 (s, 1H), 4.86 (q, *J* = 14.8 Hz, 2H), 4.58-4.55 (m, 2H), 4.41-4.36 (m, 2H), 3.58-3.55 (m, 2H), 2.96-2.91 (m, 1H), 0.90 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 150.95, 150.73, 145.15, 138.74, 138.35, 132.47, 130.66, 125.96, 125.83 (2C, overlap), 120.34, 111.26, 104.32, 79.36, 62.22, 56.16 (2C, overlap), 56.12, 47.00.8.07. MS (ESI) m/z: 453.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{22}H_{23}F_2N_8O$: 453.1958, Found: 453.1952.

(*2R*,*3R*)-3-(3-(pyrimidin-5-yl)-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (12k). **12k** (69.71 mg, 63.5%) was prepared from **12c** (110.00 mg, 0.24 mmol) and pyrimidine-5-boronic acid pinacol ester (59.91 mg, 0.29 mmol) in the same manner as described for **12h** white solid: mp 78-80 °C. $[\alpha]^{22}_{D}$ –36.8° (*c* 0.125, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (s, 1H), 9.10 (s, 2H), 7.82 (s, 1H), 7.76 (s, 1H), 7.47-7.38 (m,, 1H), 6.85-6.66 (m, 2H), 5.12 (s, 1H), 4.90 (m, 2H), 4.66-4.59 (m, 1H), 4.58-4.47 (m, 2H), 4.14 (d, *J* = 15.1 Hz, 1H), 3.95-3.81 (m, 1H), 3.42 (q, *J* = 6.6 Hz, 1H), 3.05-2.95 (m, 1H), 1.03 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.99, 153.29, 151.55, 143.45, 135.27, 130.09, 129.93, 125.24, 123.70, 123.62 (2C, overlap), 111.40, 103.76, 79.50, 62.59, 55.48 (2C, overlap), 55.43, 46.53, 6.51. MS (ESI) m/z: 454.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{21}H_{21}F_2N_9ONa$: 476.1735, Found: 476.1733.

(*2R*,*3R*)-3-(3-(2-cyano-pyridin-5-yl)-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (12l). **12l** (70.54 mg, 61.6%) was prepared from **12c** (110.00 mg, 0.24 mmol) and 2-Cyanopyridine-5-boronic acid pinacol ester (66.90 mg, 0.29 mmol) in the same manner as described for **12h** white solid: mp 88-92 °C. $[\alpha]^{22}_{D}$ –31.2° (*c* 0.125, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (d, *J* =1.6 Hz, 1H), 8.30 (dd, *J* =8.1, 2.1 Hz, 1H), 7.83-7.80 (m, 2H), 7.77 (s, 1H), 7.47-7.40 (m, 1H), 6.82-6.72 (m, 2H), 5.13 (s, 1H), 4.91 (m, 2H), 4.67-4.52 (m, 3H), 4.17 (d, *J* = 15.2 Hz, 1H), 3.91-3.83 (m, 1H), 3.44 (q, *J* = 6.5 Hz, 1H), 3.09-2.98 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.60, 147.42, 143.46, 136.67, 133.11, 130.51, 130.09, 128.25, 123.67, 123.59 (2C, overlap), 116.80, 111.43, 103.75, 79.48, 62.59, 55.46 (2C, overlap), 55.41, 46.58, 6.54. MS (ESI) m/z: 478.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{23}H_{22}F_2N_9O$: 478.1835, Found: 478.1836.

2-(trifluoromethyl)imidazo[1,2-*a*]pyrazine (22a). To a solution of aminopyrazine **20** (4.15 g, 43.60 mmol) in ethanol (120 ml) was added 1-bromo-3,3,3-trifluoroacetone **21a** (10.00 g, 52.36 mmol) at room temperature . The mixture was stirred at reflux for 12 h, and the solvent was evaporated under reduced pressure, the residue was partitioned between ethyl acetate (100 ml) and saturated aqueous sodium bicarbonate solution (50 ml). The organic phase was wash with saturated brine solution, dried over Na_2SO_4, and filtrated, then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum: ethyl acetate 2:1~1:1) to give **22a** (1.80 g, 21.8%) as a white solid: mp 148-150 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21(s, 1H), 8.13-8.11 (m, 1H), 8.11-8.01(m, 2H). MS (ESI) m/z: 188.1 (M + 1)$^+$.

2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine (18a). A solution of Compound **22a** (1.00 g, 5.35 mmol) in methanol (30 ml) was added 10% palladium on carbon (0.20 g) at room temperature. The mixture was stirred under hydrogen at 1 atm overnight and then filtered, concentrated under reduced pressure, residue solid were collected and washed with 30ml petroleum/ethyl acetate (5:1) to give **18a** (0.69 g, 67.5%) as yellow solid: mp 60-62 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (s, 1H), 4.11(s, 2H), 4.11-3.97(t, J =5.52 Hz, 2H), 3.28-3.24(t, J =5.52 Hz, 2H). MS (ESI) m/z: 192.1 (M + 1)$^+$.

Ethyl imidazo[1,2-*a*]pyrazine-2-carboxylate (22b). A solution of aminopyrazine **20** (5.00 g, 52.58 mmol) in dry 1,2-dimethoxyethane (60 ml) was mixed with ethyl 3-bromo-2-ketopropionate **21b** (12.30 g, 63.10 mmol). The resulting mixture was stirred at 60 °C for 12h. Then the reaction mixture was filtered and solid was wash with ethyl acetate (100 ml×2). The solid was dissolve in ethanol (40 ml) and stirred at reflux for 3h. Then the reaction mixture was cooled to room temperature, and the solvent was evaporated under reduced pressure. The residue was partitioned between ethyl acetate (100 ml) and saturated aqueous sodium bicarbonate (50 ml), the aqueous layer was extracted with ethyl acetate (50 ml×2). The organic phase was wash with saturated brine solution, dried over Na_2SO_4, and filtrated, then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum: ethyl acetate 5:1~1:1) to give **22b** (3.58 g, 35.6%) as a white solid: mp 173-176°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.26-7.98(m, 3H), 4.48 (q, J =7.1 Hz, 2H), 1.45 (t, J =7.1 Hz, 3H). MS (ESI) m/z: 192.2 (M + 1)$^+$.

Ethyl 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-2-carboxylate (18b). 18b (65.0 mg, 56.6%) was prepared from **22b** (112.49 mg, 0.59 mmol) in the same manner as described for **18a**. Yellow solid: mp 62-65 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 1H), 4.42(s, 2H), 4.19(q, J =7.1 Hz, 2H), 4.02(t, J =5.2 Hz, 2H), 3.05(t, J =5.0 Hz, 2H), 1.24 (t, J =7.1 Hz, 3H). MS (ESI) m/z: 196.1 (M + 1). MS (ESI) m/z: 196.1 (M + 1)$^+$.

2-(*Tert*-Butyl)imidazo[1,2-*a*]pyrazine (22c). 22c (0.94 g, 25.6%) was prepared from aminopyrazine **20** (2.00 g, 21.03 mmol) and 1-bromo-3,3-dimethylbutan-2-one **21c** (4.51g, 25.23mmol) in the same manner as described for **22a**. White solid: mp 73-76 °C. ^{1}H NMR (300 MHz, $CDCl_3$)**:** δ 9.18 (s, 1H), 8.21-7.92 (m, 3H), 1.52-1.33(m, 9H). MS (ESI) m/z: 176.2 (M + 1)$^+$.

2-(*Tert*-Butyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine (18c). 18c (0.98 g, 76.6%) was prepared from **22c** (1.24 g, 0.59 mmol) in the same manner as described for **18a**. Yellow solid:

mp 66-68 °C. ^{1}H NMR (300 MHz, CD_3OD)：δ 7.19 (s, 1H), 4.22 (s, 2H), 4.11 (t, J =5.5 Hz, 2H), 3.37-3.32 (m, 2H), 1.33 (s, 9H). MS (ESI) m/z: 180.3 $(M + 1)^+$.

3-chloropyrazin-2-amine (24). 2,3-dichloropyrazine **23** (20.00 g, 0.13 mol) was dissolved in NH_4OH aq.(100 ml) and the reaction mixture was stirred at 85° C in a closed pressure vessel for 2 days. The mixture was cooled to 25° C, water (100 ml) was added, and the mixture was filtered. The solid was washed with water (100 ml×2) and dichloromethane (100 ml×2), then dried under vacuum to afford **24** (7.35g, 43.6%) as a white solid. : mp 100-103 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.94 (d, J =2.55 Hz, 1H), 7.56(d, J =2.55 Hz, 1H), 6.80 (s, 2H). MS (EI) m/z: 129(M^+).

8-chloro-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyrazine (25d). A solution of 3-chloropyrazin-2-amine **24** (1.95 g, 15.10 mmol) in DMF (40 ml) was treated with 2-bromo-1-(4-methoxyphenyl) ethanone **21d** (4.13 g, 18.03 mmol) at 40 °C for 18 h. The mixture was partitioned between ethyl acetate (200 ml) and H_2O (100 ml), the aqueous layer was extracted with ethyl acetate (50 ml×2). The combined organic phase was wash with saturated brine solution, dried over Na_2SO_4, and filtrated, then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum: ethyl acetate 10:1~4:1) to give **25d** (1.40 g, 35.8%) as a white solid: mp 165-168°C. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 8.05-8.01(m, 1H), 7.98-7.78 (m, 3H), 7.64-7.63(m, 1H), 7.01-6.96 (m, 2H), 3.86 (s, 3H). MS (ESI) m/z: 260.2 $(M + 1)^+$.

2-(4-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, hydrochloride (18d). 8-chloro-2-(4-methoxyphenyl)imidazo[1,2-a]pyrazine **25d** (0.85 g, 3.28 mmol) was hydrogenated under atmospheric hydrogen with 10% palladium on carbon (0.18 g) as a catalyst in methanol (30 ml) at ambient temperature for 12 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure, residue solid were collected and washed with 20ml petroleum/acetone (6:1) to give **18d** (0.61 g, 70.5%) as yellow solid: mp 212-216 °C. ^{1}H NMR (300 MHz, CD_3OD)：δ 7.61 (d, J =8.85 Hz, 2H), 7.55(s, 1H), 6.99 (d, J =8.82 Hz, 2H), 4.37(s, 2H), 4.26 (t, J =5.7 Hz, 2H), 3.82 (s, 3H), 3.55 (t, J =5.8 Hz, 2H). MS (ESI) m/z: 230.1 (M + 1).

8-chloro-2-(4-fluorophenyl)imidazo[1,2-*a*]pyrazine (25e). 25e (1.16 g, 40.6%) was prepared from **24** (1.50g, 11.5mmol) and 2-bromo-1-(4-fluorophenyl) ethanone **21e** (3.01 g, 13.90 mmol) in the same manner as described for **25d**. White solid: mp 188-190 °C. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 8.05-8.03 (m, 1H), 7.98-7.80 (m, 3H), 7.70-7.63(m, 1H), 7.18-7.13 (m, 2H). MS (ESI) m/z: 248.0 $(M + 1)^+$.

2-(4-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, hydrochloride (18e). 18e (0.64 g, 83.6%) was prepared from **25e** (0.75 g, 3.04 mmol) in the same manner as described for **18d**. Yellow solid: mp 221-223 °C. ^{1}H NMR (300 MHz, CD_3OD)：δ 7.71 (d, J =8.94 Hz, 2H), 7.59 (s, 1H), 7.15 (d, J =8.94 Hz, 2H), 4.45 (s, 2H), 4.33 (t, J =6.0Hz, 2H), 3.68 (t, J =6.0Hz, 2H). MS (ESI) m/z: 218.1 $(M + 1)^+$.

8-chloro-2-(4-(trifluoromethyl)phenyl)imidazo[1,2-*a*]pyrazine (25f). 25f (1.16g, 51.8%) was prepared from **24** (1.95 g, 15.06 mmol) and 2-bromo-1-(4-(trifluoromethyl)phenyl) ethanone **21f** (5.23 g, 19.60 mmol) in the same manner as described for **25d**. White solid: mp 186-188 °C.

^{1}H NMR (300 MHz, $CDCl_3$)：δ 8.12-7.98 (m, 4H), 7.76-7.68(m, 3H). MS (ESI) m/z: 298.0 $(M + 1)^+$.

2-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, hydrochloride (18f). 18f (0.98 g, 76.3%) was prepared from **25f** (1.26 g, 4.23 mmol) in the same manner as described for **18d**. Yellow solid: mp 226-228 °C. ^{1}H NMR (300 MHz, CD_3OD)：δ 7.91(d, J =8.52 Hz, 2H), 7.75(s, 1H), 7.67(d, J =8.52 Hz, 2H), 4.51(s, 2H), 4.39 (t, J =5.7Hz, 2H), 3.76 (t, J =5.7Hz, 2H). MS (ESI) m/z: 268.1 $(M + 1)^+$.

8-chloro-2-(2,4-difluorophenyl)imidazo[1,2-*a*]pyrazine (25g). 25g (0.60 g, 31.9%) was prepared from **24** (0.92 g, 7.72 mmol) and 2-bromo-1-(2,4-difluorophenyl)ethanone **21g** (2.00 g, 8.51 mmol) in the same manner as described for **25d**. White solid: mp 155-158 °C. H NMR (400 MHz, $CDCl_3$)：δ 8.06 (d, J =4.3 Hz, 1H), 8.01 (s, 1H), 7.83-7.66 (m, 2H), 7.46-7.44 (m, 1H), 7.06-6.86(m, 1H). MS (ESI) m/z: 266.0 $(M + 1)^+$.

2-(2,4-difluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, hydrochloride (18g). 18g (0.17 g, 32.8%) was prepared from **25g** (0.50 g, 1.89 mmol) in the same manner as described for **18d**. Yellow viscous oil. ^{1}H NMR (400 MHz, CD_3OD)：δ7.63 (s, 1H), 7.53-7.51 (m, 1H), 7.43-7.41 (m, 1H),7.03 (dd, J= 8.1, 5.6 Hz, 1H), 4.46 (s, 2H), 4.37-4.33 (m, 2H), 3.68 (t, J= 5.8 Hz, 2H). MS (ESI) m/z: 236.2 $(M + 1)^+$.

8-chloro-2-(4-methylphenyl)imidazo[1,2-*a*]pyrazine (25h). 25h (1.35g, 36.8%) was prepared from **24** (1.95 g, 15.06 mmol) and 2-bromo-1-(4-methylphenyl) ethanone **21h** (3.85 g, 18.07 mmol) in the same manner as described for **25d**. White solid: mp 169-171 °C. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 8.05-8.00 (m,1H), 7.99 (s, 1H), 7.90 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 4.5Hz, 1H), 7.27 (d, J = 7.8 Hz, 2H), 2.40 (s, 3H). MS (ESI) m/z: 245.0 $(M + 1)^+$.

2-(4-methylphenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, hydrochloride (18h). 18h (0.42 g, 67.8%) was prepared from **25h** (0.60 g, 2.46 mmol) in the same manner as described for **18d**. White solid: mp 220-223 °C. ^{1}H NMR (300 MHz, CD_3OD)：δ 7.59 (d, J =4.8 Hz, 2H), 7.56 (s, 1H), 7.24 (d, J =7.9 Hz, 2H), 4.38 (s, 2H), 4.27 (t, J =5.7 Hz, 2H), 3.57 (t, J =5.7 Hz, 2H), 2.35 (s, 3H). MS (ESI) m/z: 214.0 $(M + 1)^+$.

8-chloro-2-(3-methoxyphenyl)imidazo[1,2-*a*]pyrazine (25i). 25i (1.84 g, 47.2%) was prepared from **24** (1.95 g, 15.06 mmol) and 2-bromo-1-(3-methoxyphenyl) ethanone **21i** (4.50 g, 19.58mmol) in the same manner as described for **25d**. White solid: mp 156-158 °C. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 8.03 (d, J =4.5 Hz, 1H), 8.00 (s, 1H), 7.67 (d, J =4.5 Hz, 1H), 7.56 (dd, J =9.2, 4.9 Hz, 2H), 7.37 (t, J =7.9 Hz, 1H), 6.94 (dd, J =8.2, 2.6 Hz, 1H), 3.90 (s, 3H). MS (ESI) m/z: 260.1 $(M + 1)^+$.

2-(3-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, hydrochloride (18i). 18i (0.53 g, 61.0%) was prepared from **25i** (0.85 g, 3.28 mmol) in the same manner as described for **18d**. White solid: mp 216-218 °C. ^{1}H NMR (300 MHz, CD_3OD)：δ 7.65 (s, 1H), 7.29 (dd, J =9.8, 5.0 Hz, 3H), 6.92-6.85 (m, 1H), 4.42 (s, 2H), 4.34-4.26 (m, 2H), 3.83 (s, 3H), 3.65-3.59 (m, 2H). MS (ESI) m/z: 230.2 $(M + 1)^+$.

8-chloro-2-(3-fluorophenyl)imidazo[1,2-*a*]pyrazine (25j). 25j (0.46 g, 44.7%) was prepared from **24** (0.55 g, 4.19 mmol) and 2-bromo-1-(3-fluorophenyl) ethanone **21j** (1.01 g, 4.67mmol) in the same manner as described for **25d**. White solid: mp 212-215 °C. ^{1}H NMR (400 MHz, $CDCl_3$)：δ 8.05 (d, J =4.5 Hz, 1H), 8.03 (s, 1H), 7.80-7.66 (m, 3H), 7.46-7.44 (m, 1H), 7.16-7.08 (m, 1H). MS (ESI) m/z: 248.0 $(M + 1)^+$.

2-(3-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, hydrochloride (18j). 18j (0.30 g, 65.8%) was prepared from **25j** (0.45 g, 1.82 mmol) in the same manner as described for **18d**. White solid: mp 218-221 °C. ^{1}H NMR (400 MHz, CD_3OD)：δ 7.66 (s, 1H), 7.55-7.51 (m, 1H), 7.46-7.41 (m, 2H),7.01 (dd, J= 8.1, 5.6 Hz, 1H), 4.48 (s, 2H), 4.38-4.33 (m, 2H), 3.72 (t, J= 5.8 Hz, 2H). MS (ESI) m/z: 218.2 $(M + 1)^+$.

8-chloro-2-(3-(trifluoromethyl)phenyl)imidazo[1,2-*a*]pyrazine (25k). 25k (1.30 g, 29.2%) was prepared from **24** (1.95 g, 15.06 mmol) and 2-bromo-1-(3-(trifluoromethyl)phenyl) ethanone **21k** (5.20 g, 19.50 mmol) in the same manner as described for **25d**. White solid: mp 172-176 °C. ^{1}H NMR (400 MHz, CDCl3) δ 8.25-8.21 (m, 2H), 8.10 (s, 1H), 8.07 (d, J =4.5 Hz, 1H), 7.72 (d, J =4.5Hz, 1H), 7.61 (dd, J =17.1, 9.4 Hz, 2H). MS (ESI) m/z: 298.0 $(M + 1)^+$.

2-(3-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, hydrochloride (18k). 18k (0.58 g, 66.5%) was prepared from **25k** (0.85 g, 2.86mmol) in the same manner as described for **18d**. White solid: mp 220-223 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.00 (s, 1H), 7.92 (d, J =7.3 Hz, 1H), 7.54-7.47 (m, 3H), 4.06 (t, J =5.6Hz, 2H), 4.03 (s, 2H), 3.24-3.21 (m, 2H). MS (ESI) m/z: 268.1 $(M + 1)^+$.

8-chloro-2-phenylimidazo[1,2-*a*]pyrazine (25l). 25l (1.26 g, 36.6%) was prepared from **24** (1.95 g, 15.06 mmol) and 2-bromo-1-phenylethanone **21l** (3.58 g, 17.99 mmol) in the same manner as described for **25d**. White solid: mp 206-208 °C. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 8.06-7.95(m, 4H), 7.71-7.64(m, 1H), 7.51-7.44(m, 3H).MS (ESI) m/z: 230.0 $(M + 1)^+$.

2-phenyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, hydrochloride (18l). 18l (0.58 g, 60.0%) was prepared from **25l** (0.94 g, 4.11 mmol) in the same manner as described for **18d**. White solid: mp 211-212 °C. ^{1}H NMR (300 MHz, CD_3OD)：δ 7.67(d, J =5.36Hz, 2H), 7.38(s, 1H), 7.35-7.31(m, 2H), 7.23-7.19(m, 1H), 4.08-4.05(m, 4H), 3.27-3.25(m, 2H). MS (ESI) m/z: 200.1 $(M + 1)^+$.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-3-(2-(trifluoromethyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(8*H*)-yl)butan-2-ol (19a). To a solution of epoxide **10** (125.50 mg, 0.50 mmol) in 15 ml of dry acetonitrile was added **18a** (191.00 mg, 1.00 mmol) and $LiClO_4$ (106.39 mg, 1.00 mmol) under nitrogen. The reaction was stirred at 80 °C for 24 h. The solvent was evaporated under reduced pressure. The residue was diluted with H_2O (20 ml) and extracted with ethyl acetate (30 ml ×2). The combined organic layers were washed with H_2O (20 ml ×2) and brine (20 mL ×2), dried over anhydrous Na_2SO_4, and filtrated, then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH 150:1~50:1) to give **19a** (93.0 mg, 42.1%) as a white solid: mp 141-143 °C. $[\alpha]^{22}_D$ –97.6°(*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.77 (s, 1H), 7.48-7.36 (m, 1H), 7.20 (s, 1H), 6.81-6.66 (m, 2H), 5.01 (s, 1H), 4.96-4.79 (m, 2H), 4.18-

4.00 (m, 3H), 3.95-3.87 (m, 1H), 3.75-3.79 (m, 1H), 3.27 (q, *J* = 6.8 Hz, 1H), 2.92 -2.71 (m, 1H), 0.96 (d, *J* =6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.81, 144.60, 143.86, 130.47, 124.32, 124.25 (2C, overlap), 122.75, 120.62, 117.60, 111.82, 104.03, 79.70, 62.93, 55.90 (2C, overlap), 55.84, 45.06, 6.44. MS (ESI) m/z: 442.9 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{19}H_{19}F_5N_6ONa$: 465.1438, Found: 465.1446.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-3-(2-(ethoxycarbonyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(8*H*)-yl)butan-2-ol (19b). 19b (0.58 g, 43.6%) was prepared from epoxide **10** (0.75 g, 2.98 mmol) and **18b** (1.17 g, 5.98 mmol) in the same manner as described for **19a**. White solid: mp 106-107 °C. $[\alpha]^{22}_D$ –98.4°(*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.75 (s, 1H), 7.55 (s, 1H), 7.39-7.25 (m, 1H), 6.76-6.69 (m, 2H), 5.00 (s, 1H), 4.98-4.86 (m, 2H), 4.37-4.33 (q, *J*= 5.4 Hz, 2H), 4.03-4.10 (m, 3H), 3.91-3.85 (m, 1H), 3.76-3.73 (m, 1H), 3.32 -3.16 (q, *J* =6.9 Hz, 1H), 2.89 -2.78 (m, 1H), 1.37(t, *J* =5.4 Hz, 3H), 0.98 (d, *J* =6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.92, 151.78, 144.34, 143.88, 132.72, 130.45, 124.36, 124.26 (2C, overlap), 123.86, 111.58, 104.03, 79.69, 62.94, 60.44, 55.89 (2C, overlap), 55.84, 45.14, 14.33, 6.52. MS (ESI) m/z: 447.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{21}H_{25}F_2N_6O3$: 447.1956, Found: 447.1962.

(2R,3R)-3-(2-*tert*-butyl-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (19c). 19c (82.18 mg, 36.8%) was prepared from epoxide **10** (130.52 mg, 0.52 mmol) and **18c** (187.36 mg, 1.05 mmol) in the same manner as described for **19a**. Pale yellow solid: mp 129-131 °C. $[\alpha]^{22}_D$ –60.0° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.75 (s, 1H), 7.39-7.26 (m, 1H), 6.79-6.67 (m, 2H), 6.62 (s, 1H), 5.02 (s, 1H), 4.97-4.80 (m, 2H), 4.28-4.21 (m, 2H), 4.12-3.94 (m, 3H), 3.29 (q, *J* =6.8 Hz, 1H), 2.89-2.74 (m, 1H), 1.35 (s, 9H), 0.94 (d, *J* =6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.51, 146.60, 144.08, 142.31, 130.30, 124.12, 124.10 (2C, overlap), 112.76, 111.46, 104.00, 79.64, 62.58, 55.92 (2C, overlap), 55.88, 45.30, 31.17, 29.52, 6.77. MS (ESI) m/z: 431.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{22}H_{29}F_2N_6O$: 431.2361, Found: 431.2358.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(4-methoxyphenyl)-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (19d). 19d (92.65 mg, 38.8%) was prepared from epoxide **10** (130.52 mg, 0.52 mmol) and **18d** (237.64 mg, 1.05 mmol) in the same manner as described for **19a**. Pale yellow solid: mp 151-152 °C. $[\alpha]^{22}_D$ –96.0°(*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.83 (s, 1H), 7.76 (s, 1H), 7.66 (d, *J* =8.8 Hz, 2H), 7.45-7.36 (m, 1H), 7.04 (s, 1H), 6.91 (d, *J* =8.8 Hz, 2H), 6.82-6.63 (m, 2H), 5.00 (s, 1H), 4.91-4.87 (m, 2H), 4.12-4.06 (m, 3H), 3.87-3.98 (m, 1H), 3.82 (s, 3H), 3.75-3.71 (m, 1H), 3.26 (q, *J* =6.8 Hz, 1H), 2.94-2.69 (m, 1H), 0.98 (d, *J* =6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.45, 151.75, 143.90, 143.29, 140.88, 130.51, 127.00, 125.83, 124.55, 124.55 (2C, overlap), 79.58, 63.09, 55.93 (2C, overlap), 55.88, 55.15, 44.60, 6.50. MS (ESI) m/z: 481.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{25}H_{27}F_2N_6O_2$: 481.2164, Found: 481.2158.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(4-fluorophenyl)-5,6-dihydroimidazo[1,2-*a*]pyraz-in-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (19e). 19e (76.74 mg, 41.2%) was prepared from epoxide **10** (100.00 mg, 0.40 mmol) and **18e** (172.50 mg, 0.80 mmol) in the same manner as described for **19a**. Pale yellow solid: mp 185-187 °C. $[\alpha]^{22}_D$ –87.2°(*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.83 (s, 1H), 7.76 (s, 1H), 7.69(m, 2H), 7.49-7.36 (m, 1H), 7.12 -6.98 (m,

3H), 6.73-6.60(m, 2H), 4.99 (s, 1H), 4.95-4.89 (m, 2H), 4.24-4.01 (m, 3H), 3.95-3.87 (m, 1H), 3.75-3.68 (m, 1H), 3.26 (q, *J* =6.8 Hz, 1H), 2.91 -2.74 (m, 1H), 0.98 (d, *J* =6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.81, 143.89, 143.61, 140.08, 130.52, 130.14, 126.16, 124.46, 124.36 (2C, overlap), 115.38, 112.98, 111.56, 104.05, 79.63, 63.06, 55.93 (2C, overlap), 55.88, 44.73, 6.50. MS (ESI) m/z: 469.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{24}H_{24}F_3N_6O$: 469.1964, Found: 469.1973.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(4-(trifluoromethyl)phenyl)-5,6-dihydroimidazo[1,2-*a*]pyraz-in-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (19f). 19f (73.19 mg, 35.5%) was prepared from epoxide **10** (100.00 mg, 0.40 mmol) and **18f** (212.35mg, 0.80mmol) in the same manner as described for **19a**. Pale yellow solid: mp 200-202 °C. $[\alpha]^{22}_D$ (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.83 (d, *J* =8.0 Hz, 2H), 7.77 (s, 1H), 7.62 (d, *J* =8.0 Hz, 2H), 7.48-7.36(m, 1H), 7.23 (s, 1H), 6.86-6.66 (m, 2H), 5.01 (s, 1H), 4.95-4.90 (m, 2H), 4.19-3.81 (m, 4H), 3.76-3.67 (m, 1H), 3.27 (q, *J* =6.9 Hz, 1H), 2.83-2.79 (m, 1H), 0.98 (d, *J* =6.9 Hz, 3H). Anal. Calcd for $C_{25}H_{23}F_5N_6O$: C, 57.91; H, 4.47; N, 16.21. Found: C, 57.89; H, 4.51; N, 16.13. MS (ESI) m/z: 519.3 $(M+1)^+$.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(2,4-difluorophenyl)-5,6-dihydroimidazo[1,2-*a*]pyr-azin-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (19g). 19g (68.18 mg, 35.2%) was prepared from epoxide **10** (100.00 mg, 0.40 mmol) and **18g** (186.85 mg, 0.80 mmol) in the same manner as described for **19a**. Pale yellow foam. $[\alpha]^{22}_D$ (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10-8.05 (m, 1H), 7.83 (s, 1H), 7.76 (s, 1H), 7.47-7.38 (m, 1H), 7.27 (s, 1H), 6.96-6.67 (m, 4H), 5.00 (s, 1H), 4.95-4.87 (m, 2H), 4.04-3.85 (m, 4H), 3.75-3.67 (m, 1H), 3.32 -3.18 (q, *J* =6.9 Hz, 1H), 2.91-2.78 (m, 1H), 0.98 (d, *J* =6.9 Hz, 3H). Anal. Calcd for $C_{24}H_{22}F_4N_6O$: C, 59.26; H, 4.56; N, 17.28. Found: C, 59.31; H, 4.46; N, 17.16. MS (ESI) m/z: 487.1 $(M+1)^+$.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(4-methylphenyl)-5,6-dihydroimidazo[1,2-*a*]pyraz-in-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (19h). 19h (65.21 mg, 35.2%) was prepared from epoxide **10** (100.00 mg, 0.40 mmol) and **18h** (170.16 mg, 0.80 mmol) in the same manner as described for **19a**. Pale yellow solid: mp 81-82 °C. $[\alpha]^{22}_D$ –51.2°(*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.76 (s, 1H), 7.63 (d, *J* =8.0 Hz, 2H), 7.47-7.37 (m, 1H), 7.17 (d, *J* =8.0 Hz, 2H), 7.09 (s, 1H), 6.81-6.66 (m, 2H), 4.99 (s, 1H), 4.95-4.88 (m, 2H), 4.19-3.91 (m, 4H), 3.76-3.63 (m, 1H), 3.26 (q, *J* =6.9 Hz, 1H), 2.86-2.79 (m, 1H), 2.35 (s, 3H), 0.98 (d, *J* =6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.90. 144.02, 143.49, 141.08, 136.43, 131.19, 130.64, 129.30, 124.89, 124.62 , 124.52 (2C, overlap), 112.98, 111.67, 104.15, 79.73, 63.19, 56.07 (2C, overlap), 56.02, 44.81, 21.23, 6.62. MS (ESI) m/z: 465.3 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{25}H_{27}F_2N_6O$: 465.2214, Found: 465.2205.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(3-methoxyphenyl)-5,6-dihydroimidazo[1,2-*a*]pyraz-in-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (19i). 19i (98.38 mg, 41.2%) was prepared from epoxide **10** (125.00 mg, 0.50 mmol) and **18i** (227.59 mg, 1.00 mmol) in the same manner as described for **19a**. Pale yellow solid: mp 82-84 °C. $[\alpha]^{22}_D$ –93.6°(*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.69 (s, 1H), 7.56-7.50 (m, 3H), 7.43-7.38 (m, 1H), 7.10 (s, 1H), 6.98-6.89(m, 1H), 6.80 -6.68 (m, 2H), 5.01 (s, 1H), 4.93-4.90(m, 2H), 4.10-4.03 (m, 3H), 3.98-3.93 (m, 1H), 3.81 (s, 3H), 3.76-3.71(m, 1H), 3.27 (q, *J*= 6.8 Hz, 1H), 2.94 -2.69 (m, 1H), 0.98 (d, *J*= 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.86, 151.70, 143.93, 143.49, 140.11,

134.62, 130.54, 129.54, 124.47, 124.34 (2C, overlap), 117.21, 113.76, 113.02, 111.54, 109.76, 104.02, 79.60, 63.00, 55.92 (2C, overlap), 55.87, 55.21, 44.83, 6.55. MS (ESI) m/z: 481.1 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{25}H_{27}F_2N_6O_2$: 481.2126, Found: 481.2128.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(3-fluorophenyl)-5,6-dihydroimidazo[1,2-*a*]pyraz-in-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (19j). 19j (98.01 mg, 42.1%) was prepared from epoxide **10** (100.00 mg, 0.40 mmol) and **18j** (172.51 mg, 0.80 mmol) in the same manner as described for **19a**. Pale yellow solid: mp 80-81 °C. $[\alpha]^{22}_D$ –56.0° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.81 (s, 1H), 7.56-7.49(m, 3H), 7.45-7.36 (m, 1H), 7.21-6.98 (m, 2H), 6.78-6.71 (m, 2H), 4.97 (s, 1H), 4.95-4.90 (m, 2H), 4.23-4.01 (m, 3H), 3.97-3.91(m, 1H), 3.76-3.71 (m, 1H), 3.26 (q, *J* =6.8 Hz, 1H), 2.96 -2.77 (m, 1H), 0.98 (d, *J* =6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) MS (ESI) m/z: 469.1 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{24}H_{24}F_3N_6O$: 469.1921, Found: 469.1918.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(3-(trifluoromethyl)phenyl)-5,6-dihydroimidazo[1,2-*a*]pyraz-in-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (19k). 19k (98.00 mg, 37.8%) was prepared from epoxide **10** (125.00 mg, 0.50 mmol) and **18k** (265.43 mg, 1.00 mmol) in the same manner as described for **19a**. Pale yellow solid: mp 107-109 °C. $[\alpha]^{22}_D$ –79.2° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.83-7.79 (m, 2H), 7.76 (s, 1H), 7.48-7.34(m, 1H), 7.21 (s, 1H), 6.86-6.65 (m,3H), 5.00 (s, 1H), 4.95-4.90 (m, 2H), 4.16-3.85 (m, 4H), 3.73-3.65 (m, 1H), 3.26 (q, *J* =6.9 Hz, 1H), 2.86-2.79 (m, 1H), 0.96 (d, *J* =6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) : δ 151.79, 144.01, 143.89, 139.65, 134.86, 130.82, 130.51, 128.90, 127.67, 125.25, 124.49, 124.36 (2C, overlap), 123.09, 121.32, 114.13, 111.56, 104.03, 79.64, 63.08, 55.93 (2C, overlap), 55.88, 44.81, 6.49. MS (ESI) m/z: 519.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{25}H_{24}F_5N_6O$: 519.1916, Found: 519.1923

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(3-phenyl)-5,6-dihydroimidazo[1,2-*a*]pyraz-in-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (19l). 19l (94.45 mg, 42.1%) was prepared from epoxide **10** (125.00 mg, 0.50 mmol) and **18l** (199.50 mg, 1.00 mmol) in the same manner as described for **19a**. Pale yellow solid: mp 107-108 °C. $[\alpha]^{22}_D$ –85.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.83 (s, 1H), 7.76 (s, 1H), 7.78-7.72 (m, 2H), 7.45-7.41 (m, 1H), 7.38-7.35 (m, 2H), 7.21-7.12 (m, 1H), 7.14 (s, 1H), 6.80-6.67 (m, 2H), 5.00 (s, 1H), 4.93-4.86 (m, 2H), 4.15-4.10 (m, 3H), 3.98-3.90 (m, 1H), 3.78-3.71 (m, 1H), 3.32 -3.16 (q, *J* =6.9 Hz, 1H), 2.89-2.78 (m, 1H), 0.98 (d, *J* =6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) : δ 151.78, 143.90, 143.55, 140.98, 134.04, 130.58, 128.47, 126.60, 124.62, 124.51, 124.40 (2C, overlap) 113.32, 111.5, 104.05, 79.66, 63.08, 55.95 (2C, overlap), 55.89, 44.70, 6.50. MS (ESI) m/z: 451.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{24}H_{25}F_2N_6O$: 451.2016, Found: 451.2023.

2,2,2-trifluoro-N-(pyrazin-2-yl)acetamide (30). 2-aminopyrazine **20** (22.75 g, 0.24 mol) was dissolved in dry CH_2Cl_2 (350 ml) followed by addition of triethylamine (26.71g, 0.26mol) and trifluoroacetic anhydride (26.71 g, 0.26 mol) at 0 °C. The mixture was stirred at room temperature for 2 hours. Then the reaction mixture was filtered and solid was wash with CH_2Cl_2 (50 ml×2), then dried under vacuum to afford **30** (16.80 g, 36.8%) as a white solid. : mp 150-152 °C. ^{1}H NMR (300 MHz, CD_3OD)：δ 9.35(d, *J* =1.4Hz, 1H), 8.51-8.43(m, 2H). MS (EI) m/z: 191 (M^+).

(*E*)-2,2,2-trifluoro-N'-hydroxy-N-(pyrazin-2-yl)acetimidamide (31). To a suspension of 2,2,2-trifluoro-N-(pyrazin-2-yl) acetamide **30** (33.50 g, 0.18mol) in CH_2Cl_2 (600ml) was added phosphorous pentachloride (54.70 g, 0.26 mol) portionwise. The mixture was refluxed for 4h. The solvent was evaporated under reduced pressure. The residue was suspended in THF(350 ml).50% aqueous hydroxylamine (50 ml) was added to the above mixture. After stirring at room temperature for 2h, the solvent was evaporated under reduced pressure. The residue was diluted with H_2O (50 ml) and extracted with ethyl acetate (200 ml ×2) and aqeous sodium bicarbonate (100ml). The organic phase was wash with saturated brine solution, dried over Na_2SO_4, and filtrated, then the solvent was evaporated under reduced pressure to afford **31** (16.33 g, 45.6%) as a yellow solid. : mp 187-189 °C. ^{1}H NMR (300 MHz, CD_3OD)：δ 8.18(s, 1H), 8.08-8.03(m, 2H). ESI-MS 207.1$(M+1)^+$.

2-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-*a*]pyrazine (26a). A mixture of 2,2,2-trifluoro-N'-hydroxy-N-(pyrazin-2-yl)acetimidamide **31** (1.50 g, 7.28 mmol) and poly-phosphoric acid (15 ml) was heated to 100 °C for 2h. The solution was added to ice and neutralized by addition of ammonium hydroxide. The aqueous solution was extracted with CH_2Cl_2 (30 ml ×3) , the combined organic phase was wash with saturated brine solution, dried over Na_2SO_4, and filtrated, the solution was concentrated in vacuo to give a yellow crude solid, which was uesd for the following reaction without further purification.

The crude solid was dissolved in methanol (15 ml), to the solution was added 10% palladium on carbon (0.16 g) at room temperature. The mixture was stirred under hydrogen at 1 atm overnight and then filtered, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH 50:1~20:1) to give **26a** (0.71 g, 50.8%) as a colorless viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27-4.14 (m, 4H), 3.36 (t, J = 5.5 Hz, 2H). MS (ESI) m/z: 193.1 $(M+1)^+$.

(*E*)-N'-hydroxy-N-(pyrazin-2-yl)formimidamide (32). A solution of **20** (18.98 g, 0.20 mol) in toluene (150 ml) was treated with N,N-dimethylformamide dimethyl acetal (26.21 g, 0.22 mol). The resulting mixture was heated under reflux for 3 hours. The solvent was evaporated under reduced pressure to give a crude brown oil, which was uesd for the following reaction without further purification.

The crude solid was dissolved in methanol (500 ml), to the solution was added hydroxylamine hydrochloride (15.20 g, 0.22 mol), sodium acetate (18.10 g, 0.22 mol). The mixture was stirred at 0 °C overnight, then concentrated under reduced pressure. Residue solid were collected and washed with 200 ml CH_2Cl_2/MeOH (9:1) to give **32** (15.93 g, 57.6%) as gray solid: mp 201-203 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.52-8.35 (m, 1H), 8.14 (dd, J = 2.7, 1.5 Hz, 1H), 8.05 (d, J = 2.7 Hz, 1H), 7.76 (s, 1H). MS (ESI) m/z: 139.1 $(M + 1)^+$.

[1,2,4]triazolo[1,5-*a*]pyrazine (33). A mixture of (*E*)-N'-hydroxy-N-(pyrazin-2-yl)formimidamide **32** (10.00 g, 72.43 mmol) and poly-phosphoric acid (30 ml) was heated to 100 °C for 2h. The solution was added to ice and neutralized by addition of ammonium hydroxide. The aqueous solution was extracted with CH_2Cl_2 (100 ml ×2) , the combined organic phase was wash with saturated brine solution, dried over Na_2SO_4, and filtrated, the solution was concentrated in vacuo to give a yellow crude solid, which was purified by recrystallization from ethanol to afford **33** (5.48 g, 63.0%) as white solid: mp 123-126 °C. ^{1}H NMR (300 MHz,

$CDCl_3$)：δ 9.34 (d, J =1.5 Hz, 1H), 8.58 (dd, J =4.5, 1.5 Hz, 1H), 8.50 (s, 1H), 8.22 (d, J =4.5 Hz, 1H). MS (ESI) m/z: 121.1 $(M + 1)^+$.

5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-*a*]pyrazine (26b). A solution of Compound **33** (3.00 g, 24.98 mmol) in methanol (20 ml) was added 10% palladium on carbon (0.30 g) at room temperature. The mixture was stirred under hydrogen at 1 atm overnight and then filtered, concentrated under reduced pressure to give **26b** (2.65 g, 85.5%) as colorless viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.83 (s, 1H), 4.17-4.09 (m, 4H), 3.30 (t, J =5.6 Hz, 2H). MS (ESI) m/z: 125.0 $(M + 1)^+$.

[1,2,4]triazolo[1,5-*a*]pyrazin-2-amine (35). isothiocyanate **34** (25.00 g, 0.19 mol) was added dropwise to a stirred mixture of 2-aminopyrazine **20** (16.5 g, 0.17 mol) and 1,4-dioxane (300 ml) at 0°C. The mixture was stirred for 12 h at room temperature, and the solvent was evaporated under vacuum. The residual solid was dissolved in methanol (400 ml). To this solution was added triethanolamine (52.62 g, 0.52 mol) and hydroxylamine hydrochloride (50.00 g, 0.72 mol). The reaction mixture was stirred at room temperature for 2h then was heated to reflux for 4h. Then the reaction mixture was cooled to room temperature, and the solvent was evaporated under reduced pressure. Residue solid were collected and washed with 300 ml CH_2Cl_2/MeOH (8:1) to give crude solid. The solid was taken into ethyl acetate (600 ml) and H_2O (300 ml), and the aqueous solution was extracted with ethyl acetate (200 ml×2). The combined organic layers were washed with brine and dried over Na_2SO_4, and filtered, the filtrate was evaporated at reduced pressure to afford **35** as white solid : mp 198-201°C. ^{1}H NMR (300 MHz, DMSO-d_6)：δ 8.81 (d, J =1.5 Hz, 1H), 8.67 (dd, J =4.3, 1.5 Hz, 1H), 7.96 (d, J =4.3Hz, 1H), 6.44 (br, 2H). MS (ESI) m/z: 136.1 $(M + 1)^+$.

2-bromo-[1,2,4]triazolo[1,5-*a*]pyrazine (36) A solution of **35** (9.50 g, 70.33 mmol) in acetic acid (60 ml) was cooled to 0 °C. 40% hydrobromic acid (40 ml) was added, followed by $NaNO_2$(5.82 g, 84.36 mmol) in H_2O (50 ml) dropwise. The reaction mixture was stirred for 2 h at 0 °C. To this mixture was added CuBr (2.52 g, 17.56 mmol) , then the mixture was stirred under the refluxing condition for 8 h. The reaction mixture was cooled to room temperature, and the solvent was evaporated under reduced pressure. The residue was triturated with H_2O (50 ml) and extracted with ethyl acetate (200 ml×2). The combined organic layers were washed with brine (100 ml), dried over anhydrous Na_2SO_4, and filtrated, and the solvent was evaporated under reduced pressure to afford yellow crude solid, which was purified by silica gel column chromatography (petroleum: ethyl acetate 10:1~8:1) to afford **36** (8.51g, 61.1%) as white solid : mp 130-133°C. ^{1}H NMR (300 MHz, DMSO-d_6)：^{1}H NMR (300 MHz, $CDCl_3$)：δ 9.24 (s, 1H), 8.51 (d, J =4.5Hz, 1H), 8.24 (d, J =4.5 Hz, 1H). MS (ESI) m/z: 199.1 $(M + 1)^+$.

2-bromo-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-*a*]pyrazine (28) A solution of 2-bromo-[1,2,4]triazolo[1,5-*a*]pyrazine **36** (7.50 g, 37.88 mmol) in dry EtOH (300 ml) was mixed with $LiBH_4$ (3.30 g, 151.51 mmol). The resulting mixture was heated at 50 °C for 6h. After concentration in vacuo, the residue was treated with 1 M hydrochloric acid (50 ml) and extracted with ethyl acetate (100 ml×2). The aqueous layer was basified with sodium carbonate solution, and extracted with CH_2Cl_2 (200 ml×2). The combined organic layers were washed with brine (50 ml), dried over anhydrous Na_2SO_4, and filtrated, and the solvent was evaporated under reduced pressure to afford yellow solid **28** (5.82g, 76.0%). mp 143-144°C. ^{1}H NMR (300 MHz,

$CDCl_3$)：δ 4.15-4.10 (m, 4H), 3.32 (t, J =5.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.43, 140.90, 49.06, 44.80, 44.09. MS (ESI) m/z: 203.0 $(M + 1)^+$.

***tert*-butyl 2-bromo-5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazine-7(8*H*)-carboxylate (37).** A mixture of compound **28** (2.50 g, 12.4 mmol), triethylamine (1.51 g, 14.90 mmol), Di-*tert*-butyl dicarbonate (2.96 g, 13.6 mmol) and dichloromethane (50 ml) was stirred at room temperature for 2 h, then extracted with dichloromethane (60 ml) and water (30 ml). The combined organic layers were washed with brine (30 ml), dried over anhydrous Na_2SO_4, and filtrated, and the solvent was evaporated under reduced pressure. The resulting product was purified by silica gel column chromatography (petroleum: ethyl acetate 10:1~8:1) to give **37** (3.20 g, 85.6%) as a white solid. Mp: 66-68 °C. ^1H NMR (400 MHz, $CDCl_3$)：δ 4.71 (s, 2H), 4.17 (t, J =5.4 Hz, 2H), 3.92 (t, J =5.4 Hz, 2H), 1.49 (s, 9H). MS (ESI) m/z: 303.1$(M + 1)^+$.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27a). To a solution of epoxide **10** (125.50 mg, 0.50 mmol) in 20 ml of dry acetonitrile was added **26a** (192.00 mg, 1.00 mmol) and $LiClO_4$ (106.39 mg, 1.00 mmol) under nitrogen. The reaction was stirred at 80 °C for 24 h. The solvent was evaporated under reduced pressure. The residue was diluted with H_2O (30 ml) and extracted with ethyl acetate (40 ml ×2). The combined organic layers were washed with H_2O (20 ml ×2) and brine (30 mL ×2), dried over anhydrous Na_2SO_4, and filtrated, then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH 150:1~50:1) to give **27a** (81.29mg, 36.7%) as a white solid: mp 178-180 °C. $[\alpha]^{22}_D$ − 63.2°(*c* 0.125, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.77 (s, 1H), 7.45-7.38 (m, 1H), 6.85-6.57 (m,2H), 5.09 (s, 1H), 4.98-4.78 (m, 2H), 4.37-4.20 (m, 3H), 4.05-4.00 (m, 1H), 3.90-3.85 (m, 1H), 3.42-3.25 (q, J =6.9 Hz, 1H), 3.02-2.86 (m, 1H), 0.98 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.56, 152.90, 152.04, 143.92, 130.51, 124.22, 124.15 (2C, overlap), 118.18, 111.71, 104.15, 79.84, 62.86, 55.90 (2C, overlap), 55.86, 47.67, 6.75. MS (ESI) m/z: 376.1 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{18}H_{19}F_5N_7O$: 444.1466, Found: 444.1487.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-3-(2-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)butan-2-ol (27b). **27b** (80.00 mg, 42.6%) was prepared from epoxide **10** (125.50 mg, 0.50 mmol) and **26b** (124.0 mg, 1.00 mmol) in the same manner as described for **27a**. white solid: mp 88-89 °C. $[\alpha]^{22}_D$ –68.0°(*c* 0.125, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$)：δ 7.88 (s, 1H), 7.82 (s, 1H), 7.77 (s, 1H), 7.45-7.39 (m, 1H), 6.81-6.76(m, 2H), 5.04 (s, 1H), 4.94-4.85 (m, 2H), 4.37-4.20 (m, 3H), 3.99-3.87(m, 1H), 3.85-3.81(m, 1H), 3.36 -3.24 (q, J =6.8 Hz, 1H), 2.97 -2.83 (m, 1H), 0.98 (d, J =6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.36, 152.41, 152.33, 145.36, 131.97, 125.87, 125.74 (2C, overlap), 113.18, 105.50, 81.25, 64.34, 57.41 (2C, overlap), 57.35, 48.42, 8.05. MS (ESI) m/z: 376.1 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{17}H_{20}F_2N_7O$: 376.1576, Found: 376.1595.

(2*R*,3*R*)-3-(2-bromo-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (29). To a solution of epoxide **10** (125.50 mg, 0.50 mmol) in 5 ml of acetonitrile was added **28** (303.00 mg, 1.50 mmol) and $LiClO_4$ (212.80 mg, 2.00 mmol). The reaction mixture was irradiated for 4h in a microwave oven (Discover, CEM), programmed to obtain reflux with a maximum power output of 80 W. After cooling, the mixture was evaporated under reduced pressure. The residue was diluted with H_2O (30 ml) and extracted

with ethyl acetate (30 ml ×2). The combined organic layers were washed with H_2O (20 ml ×2) and brine (20 ml ×2), dried over anhydrous Na_2SO_4, and filtrated, then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH 200:1~100:1) to give **29** (110.07mg, 48.6%) as white solid : mp 195-197 °C. $[\alpha]^{22}_D$ –76.8° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$)：δ 7.82 (s, 1H), 7.76 (s, 1H), 7.45-7.32 (m, 1H), 6.76-7.71 (m, 2H), 5.06 (s, 1H), 4.98-4.78 (m, 2H), 4.26-4.16 (m, 3H), 3.96-3.87 (m, 1H), 3.86-3.80 (m, 1H), 3.30 (q, *J* =6.9 Hz, 1H), 2.98 -2.85 (m, 1H), 0.96 (d, *J* =6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.90, 153.89, 145.80, 141.52, 132.46, 126.17, 126.07 (2C, overlap), 113.66, 106.02, 81.74, 64.75, 57.79 (2C, overlap), 57.7, 49.10, 8.65. MS (EI) m/z: 453 (M^+). HRMS (EI): Anal. Calcd for $C_{17}H_{18}BrF_2N_7O$: 453.0712, Found: 453.0720.

(2*R*,3*R*)-3-(2-phenyl-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27c). A mixture of **29** (100.00 mg, 0.22 mmol), Cesium carbonate (143.85 mg, 0.44 mmol), phenylboronic acid (31.00 mg, 0.26 mmol) and tetrakis(triphenylphosphine)palladium (0) (25.51 mg, 0.02 mmol) in dioxane (15 ml) and H_2O (5 ml) was degassed and flushed with argon. The mixture was hearted at 80 °C for 8 h. The solvent was evaporated under reduced pressure. The residue was diluted with H_2O (30 ml) and extracted with ethyl acetate (40 ml ×2). The combined organic layers were washed with H_2O (20 ml ×2) and brine (20 ml ×2), dried over anhydrous Na_2SO_4, and filtrated, then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH 200:1~50:1) to give **27c** (61.22mg, 61.6%) as a white solid: mp 190-192 °C. $[\alpha]^{22}_D$ –76.8°(*c* 0.125, $CHCl_3$). ^{1}H NMR (300MHz, $CDCl_3$)：δ 8.09-8.05 (m, 2H), 7.82 (s, 1H), 7.76 (s, 1H), 7.52-7.33 (m, 4H), 6.80-6.69 (m, 2H), 5.05 (s, 1H), 4.97-4.85 (m, 2H), 4.32-4.21 (m, 3H), 4.11-4.01 (m, 1H), 3.87-3.82 (m, 1H), 3.33 (q, *J* =7.0 Hz, 1H), 2.98-2.95 (m, 1H), 0.99 (d, *J* =6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.63, 151.90, 151.75, 143.88, 130.91, 130.49, 129.14, 128.55, 126.13, 124.44, 124.28 (2C, overlap), 111.67, 104.07, 79.77, 62.94, 55.93 (2C, overlap), 55.86, 47.00, 6.67. MS (EI) m/z: 451 (M^+). HRMS (EI): Anal. Calcd for $C_{23}H_{23}F_2N_7O$: 453.1918, Found: 451.1929.

(2*R*,3*R*)-3-(2-(4-cyanophenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27d). 27d (64.90 mg, 61.6%) was prepared from **29** (100.00 mg, 0.22 mmol) and 4-cyanophenylboronic acid pinacol ester (60.69 mg, 0.26 mmol) in the same manner as described for **27c**. white solid: mp 239-242 °C. $[\alpha]^{22}_D$ –86.4° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 8.18 (d, *J* =8.3 Hz, 2H), 7.82 (s, 1H), 7.77 (s, 1H), 7.72 (d, *J* = 8.3Hz, 2H), 7.45-7.40 (m, 1H), 6.82-6.66 (m, 2H), 5.06 (s, 1H), 4.98-4.79 (m, 2H), 4.35-4.26 (m, 3H), 4.02-4.01(m, 1H), 3.88-3.79 (m, 1H), 3.35 (q, *J* =6.8 Hz, 3H), 2.99-2.95 (m, 1H), 1.00 (d, *J* =6.8 Hz, 3H). 1 (m, 1H), 3.87-3.82 (m, 1H), 3.33 (q, *J* =7.0 Hz, 1H), 2.98-2.95 (m, 1H), 0.99 (d, *J* =6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.98, 152.45, 152.00, 143.93, 135.28, 132.45, 130.65, 126.60, 124.38, 124.21 (2C, overlap), 118.78, 112.43, 111.76, 104.15, 79.86, 62.99, 55.94 (2C, overlap), 55.88, 47.28, 6.76. MS (EI) m/z: 476 (M^+). HRMS (EI): Anal. Calcd for $C_{24}H_{22}F_2N_8O$: 476.1875, Found: 476.1882.

(2*R*,3*R*)-3-(2-(3-methylphenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27e). 27e (52.88 mg, 51.5%) was prepared from **29** (100.0 mg, 0.22 mmol) and 3-methylphenylboronic acid (35.92 mg, 0.26 mmol) in the same manner as described for **27c**. white solid: mp 106-109 °C. $[\alpha]^{22}_D$ –91.2° (*c* 0.125,

$CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$)：δ 7.90 (s, 1H), 7.87 (m, 1H), 7.83 (m, 1H), 7.76 (s, 1H), 7.46-7.38 (m, 1H), 7.36-7.18 (m, 2H), 6.81-6.68 (m, 2H), 5.05 (s, 1H), 4.99-4.83 (m, 2H), 4.32-4.23 (m, 3H), 4.02 (m, 1H), 3.83 (m, 1H), 3.37-3.29 (q, J = 6.9 Hz, 1H), 3.02-2.89 (m, 1H), 2.41 (s, 3H), 0.99 (d, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.71, 151.86, 151.69, 143.89, 138.24, 130.73, 130.51, 129.95, 128.49, 126.7, 124.44, 124.34 (2C, overlap), 123.26, 111.59, 104.08, 79.74, 62.95, 55.93 (2C, overlap), 55.88, 46.99, 21.30, 6.69. MS (EI) m/z: 465 (M^+). HRMS (EI): Anal. Calcd for $C_{24}H_{25}F_2N_7O$: 465.2115, Found: 465.2106.

(2*R*,3*R*)-3-(2-(4-bromophenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27f). **27f** (51.15 mg, 36.5%) was prepared from **29** (120.00 mg, 0.26 mmol) and 4-bromophenylboronic acid (63.56 mg, 0.32 mmol) in the same manner as described for **27c**. white solid: mp 165-170℃. $[\alpha]^{22}_D$ –76.2° (*c* 0.125, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$)：δ 7.94 (d, J =8.7 Hz, 2H), 7.82 (s, 1H), 7.77 (s, 1H), 7.56 (d, J =8.7 Hz, 2H), 7.45-7.39 (m, 1H), 6.78-6.71 (m, 2H), 4.96-4.85 (m, 2H), 4.30-4.23 (m, 3H), 4.05-3.96 (m, 1H), 3.85-3.80 (m, 1H), 3.33 (q, J =6.8 Hz, 1H), 3.03-2.87 (m, 1H), 0.99 (d, J =6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.74, 152.02, 151.99, 144.00, 131.83, 130.58, 129.87, 127.79, 124.41, 124.33 (2C, overlap), 123.48, 111.86, 104.18, 79.81, 63.00, 56.00 (2C, overlap), 55.95, 47.18, 6.76. MS (EI) m/z: 529 (M^+). HRMS (EI): Anal. Calcd for $C_{23}H_{22}F_2N_7OBr$: 529.1016, Found: 529.1022.

(2*R*,3*R*)-3-(2-(4-fluorophenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27g). 27g (78.30 mg, 64.2%) was prepared from **29** (120.00 mg, 0.26 mmol) and 4-fluorophenylboronic acid (44.51 mg, 0.32 mmol) in the same manner as described for **27c**. white solid: mp 121-123℃. $[\alpha]^{22}_D$ –80.8° (*c* 0.125, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$)：δ 8.05 (d, J =8.7 Hz, 2H), 7.82 (s, 1H), 7.76 (s, 1H), 7.45-7.43 (m, 1H), 7.11 (d, J =8.7 Hz, 2H), 6.81-6.67 (m, 2H), 5.05 (s, 1H), 5.00-4.71 (m, 2H), 4.33-4.22 (m, 3H), 4.06-3.98 (m, 1H), 3.87-3.82 (m, 1H), 3.39-3.28 (q, J =6.8Hz, 1H), 3.02-2.85 (m, 1H), 0.99 (d, J =6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.87, 151.94, 151.88, 143.93, 130.61, 128.04, 127.21, 127.19, 124.40, 124.33 (2C, overlap), 115.49, 111.73, 104.12, 79.79, 62.98, 55.96 (2C, overlap), 55.91, 47.04, 6.73. MS (EI) m/z: 469 (M^+). HRMS (EI): Anal. Calcd for $C_{23}H_{22}F_3N_7O$: 469.1836, Found: 469.1843.

(2*R*,3*R*)-3-(2-(4-chlorophenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27h). 27h (59.97 mg, 56.0%) was prepared from **29** (100.00 mg, 0.22 mmol) and 4-chlorophenylboronic acid (41.18 mg, 0.26 mmol) in the same manner as described for **27c**. white solid: mp 120-123℃. $[\alpha]^{22}_D$ –71.2° (*c* 0.125, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$)：δ 8.01 (d, J =8.6 Hz, 2H), 7.82 (s, 1H), 7.77 (s, 1H), 7.42 (d, J= 8.6 Hz, 2H), 7.45-7.40 (m, 1H), 6.81-6.68 (m, 2H), 5.05 (s, 1H), 4.97-4.84 (m, 2H), 4.33-4.24 (m, 3H), 4.01-3.95 (m, 1H), 3.85-3.80 (m,1H), 3.34 (q, J =6.8 Hz, 1H), 2.98-2.95(m, 1H), 0.99 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.58, 152.01, 151.94, 143.96, 135.22, 130.62, 129.29, 128.91, 127.54, 124.42, 124.27 (2C, overlap), 111.80, 104.18, 79.84, 62.99, 55.99 (2C, overlap), 55.94, 47.19, 6.77. MS (EI) m/z: 485 (M^+). HRMS (EI): Anal. Calcd for $C_{23}H_{22}F_2N_7OCl$: 485.1536, Found: 485.1527.

(2*R*,3*R*)-3-(2-(3-chlorophenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27i). 27i (45.83 mg, 53.5%) was

prepared from **29** (80.00 mg, 0.18 mmol) and 3-chlorophenylboronic acid (27.55 mg, 0.22 mmol) in the same manner as described for **27c**. white solid: mp 120-122℃. $[\alpha]^{22}_{D}$ –68.8° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 8.11-8.08 (m, 1H), 7.98-7.95 (m, 1H), 7.83 (s, 1H), 7.77 (s, 1H), 7.73-7.62 (m, 1H),7.50-7.44 (m, 1H), 7.41-7.34 (m, 1H), 6.76 (m, 2H), 5.06 (s, 1H), 4.98-4.85 (m, 2H), 4.35-4.21 (m, 3H), 4.01-3.99 (m, 1H), 3.84-3.81 (m, 1H), 3.34 (q, *J* = 6.9 Hz, 1H), 3.06- 2.91 (m, 1H), 1.00 (d, *J* = 6.87 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.49, 152.00, 151.96, 143.96, 134.67, 132.74, 130.63, 129.90, 129.19, 126.34, 124.41, 124.37 (2C, overlap), 124.24, 111.68, 104.15, 79.82, 62.99, 55.98 (2C, overlap), 55.93, 47.19, 6.74. MS (EI) m/z: 485 (M^+). HRMS (EI): Anal. Calcd for $C_{23}H_{22}F_2N_7OCl$: 485.1535, Found: 485.1516.

(2*R*,3*R*)-3-(2-(3-bromophenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27j). 27j (92.83 mg, 53.0%) was prepared from **29** (150.00 mg, 0.33 mmol) and 3-bromophenylboronic acid (79.18 mg, 0.40 mmol) in the same manner as described for **27c**. white solid: mp 113-115℃. $[\alpha]^{22}_{D}$ –73.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 8.13-8.06 (m, 1H), 7.98-7.91 (m, 1H), 7.85 (s, 1H), 7.78 (s, 1H), 7.71-7.60 (m, 1H), 7.53-7.44 (m, 1H), 7.40-7.31 (m, 1H), 6.75 (m, 2H), 5.01 (s, 1H), 4.95-4.85 (m, 2H), 4.33-4.26 (m, 3H), 4.00-3.98 (m, 1H), 3.85-3.81 (m, 1H), 3.36 (q, *J* = 6.9 Hz, 1H), 3.06- 2.93 (m, 1H), 1.00 (d, *J* = 6.87 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.29, 151.96, 151.92, 143.88, 132.91, 132.04, 130.55, 130.11, 129.14, 124.61, 124.36, 124.23 (2C, overlap), 122.72, 111.69, 104.08, 79.77, 63.01, 55.89 (2C, overlap), 55.77, 47.08, 6.78. MS (EI) m/z: 529 (M^+). HRMS (EI): Anal. Calcd for $C_{23}H_{22}F_2N_7OBr$: 529.1036, Found: 529.1022.

(2*R*,3*R*)-3-(2-(3-(trifluoromethyl)phenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27k). 27k (56.50 mg, 58.0%) was prepared from **29** (85.00 mg, 0.19 mmol) and 3-(trifluoromethyl) phenylboronic acid (42.76 mg, 0.22 mmol) in the same manner as described for **27c**. white solid: mp 117-118℃. $[\alpha]^{22}_{D}$ –66.5° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 8.36-8.34 (m, 1H), 8.26-8.19 (m, 1H), 7.83 (s, 1H), 7.77 (s, 1H), 7.65-7.61 (m, 1H), 7.56-7.53 (m, 1H), 7.49-7.37 (m, 1H), 6.81-6.66 (m, 2H), 5.07 (s, 1H), 5.02-4.85 (m, 2H), 4.38-4.25 (m, 3H), 4.03 (m, 1H), 3.86-3.81 (m, 1H), 3.35 (q, *J* = 6.9 Hz, 1H), 2.98-2.86 (m, 1H), 1.00 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.46, 152.18, 152.03, 143.99, 131.80, 131.26, 131.00, 130.63, 129.14, 125.78, 125.14, 124.41, 124.34 (2C, overlap), 123.13, 111.74, 104.19, 79.85, 63.03, 56.01 (2C, overlap), 55.96, 47.23, 6.77. MS (EI) m/z: 519 (M^+). HRMS (EI): Anal. Calcd for $C_{24}H_{22}F_5N_7O$: 519.1816, Found: 519.1798.

(2*R*,3*R*)-3-(2-(4-(trifluoromethyl)phenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-o (27l). 27l (63.26 mg, 55.2%) was prepared from **29** (100.00 mg, 0.19 mmol) and 4-(trifluoromethyl) phenylboronic acid (50.34 mg, 0.26 mmol) in the same manner as described for **27c**. white solid: mp 127-130℃. $[\alpha]^{22}_{D}$ –63.2° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 8.19 (d, *J* =8.4 Hz, 2H), 7.82 (s, 1H), 7.77 (s, 1H), 7.69 (d, *J* =8.4 Hz, 2H), 7.45-7.40(m, 1H), 6.81 -6.65 (m, 2H), 5.06 (s, 1H), 4.99-4.82 (m, 2H), 4.33-4.26 (m, 3H), 4.02 (m, 1H), 3.87-3.81 (m, 1H), 3.40-3.30 (q, J =6.8 Hz, 1H), 3.03-2.92 (m, 1H), 1.00 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.41, 152.17, 151.99, 143.93, 134.37, 130.60, 126.38, 125.58, 125.19, 124.41, 124.28 (2C, overlap), 123.03,

111.65, 104.14, 79.81, 62.99, 55.95 (2C, overlap), 55.90, 47.20, 6.72. MS (EI) m/z: 519 (M^+). HRMS (EI): Anal. Calcd for $C_{24}H_{22}F_5N_7O$: 519.1825, Found: 519.1812.

(2*R*,3*R*)-3-(2-(2,4-difluorophenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-o (27m). 27m (56.6 mg, 62.0%) was prepared from **29** (85.00 mg, 0.19 mmol) and 2, 4-difluorophenylboronic acid (35.58 mg, 0.23 mmol) in the same manner as described for **27c**. white solid: mp 127-129℃. $[\alpha]^{22}_D$ –101.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (m, 1H), 7.82 (s, 1H), 7.76 (s, 1H), 7.43-7.39 (m, 1H), 6.99 -6.88 (m, 2H), 6.75-6.70(m, 2H), 5.05 (s, 1H), 4.95-4.90(m, 2H), 4.31-4.35(m, 3H), 4.05-4.01 (m, 1H), 3.85-3.79 (m, 1H), 3.39-3.26 (q, J =6.8 Hz, 1H), 2.98-2.96 (m, 1H), 0.99 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.41, 151.99, 151.60, 143.96, 130.97, 130.62, 124.45, 124.42 (2C, overlap), 124.35, 124.32 (2C, overlap), 115.55, 111.71, 104.83, 104.16, 79.87, 63.00, 55.99 (2C, overlap), 55.94, 47.26, 6.75. MS (EI) m/z: 487 (M^+). HRMS (EI): Anal. Calcd for $C_{23}H_{21}F_4N_7O$: 487.1756, Found: 487.1765.

(2*R*,3*R*)-3-(2-(3-isopropylphenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27n). 27n (40.03 mg, 56.6%) was prepared from **29** (65.00 mg, 0.14 mmol) and 3-isopropylphenylboronic acid (28.26 mg, 0.17 mmol) in the same manner as described for **27c**. white solid: mp 142-144℃. $[\alpha]^{22}_D$ –57.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 7.94 (s, 1H), 7.88 (d, *J* =7.7 Hz, 1H), 7.83 (s, 1H), 7.76 (s, 1H), 7.45-7.41(m, 1H), 7.36 (d, *J* = 7.7 Hz, 1H), 7.27 (s, 1H), 6.80-6.69 (m, 2H), 5.05 (s, 1H), 4.98-4.81 (m, 2H), 4.38-4.21 (m, 3H), 4.12-3.99 (m, 1H), 3.92-3.87 (m, 1H), 3.33 (q, *J* = 6.8 Hz, 1H), 3.01-2.94 (m, 2H), 1.29 (d, *J* = 6.9 Hz, 6H), 0.99 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.90, 151.96, 151.75, 149.35, 143.96, 130.79, 130.63, 128.65, 127.46, 124.49, 127.46 (2C, overlap), 124.37, 123.82, 111.76, 104.18, 79.86, 63.02, 56.01 (2C, overlap), 55.96, 47.10, 34.22, 23.99, 6.75. MS (EI) m/z: 493 (M^+). HRMS (EI): Anal. Calcd for $C_{26}H_{29}F_2N_7O$: 493.2426, Found: 493.2435.

(2*R*,3*R*)-3-(2-(4-methylphenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27o). 27o (63.23 mg, 61.6%) was prepared from **29** (100.00 mg, 0.22 mmol) and 4-methylphenylboronic acid (36.03 mg, 0.26 mmol) in the same manner as described for **27c**. white solid: mp 106-108 °C. $[\alpha]^{22}_D$ –64.5 ° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 7.95 (d, *J* =8.1 Hz, 2H), 7.82 (s, 1H), 7.76 (s, 1H), 7.41-7.38 (m, 1H), 7.24 (d, *J* =8.1 Hz, 2H), 6.82-6.67 (m, 2H), 5.05-5.01 (m, 1H), 4.96-4.84 (m, 2H), 4.32 -4.16 (m, 3H), 4.05-3.96 (m, 1H), 3.83-3.80 (m, 1H), 3.36-3.25 (q, *J* = 6.8 Hz, 1H), 3.00-2.87 (m, 1H), 2.38 (s, 3H), 0.99 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.75, 151.98, 151.68, 143.96, 139.21, 130.59, 129.35, 128.15, 126.13, 124.51, 124.38 (2C, overlap), 111.68, 104.17, 79.86, 63.01, 56.00 (2C, overlap), 55.95, 47.05, 21.42, 6.74. MS (EI) m/z: 465 (M^+). HRMS (EI): Anal. Calcd for $C_{24}H_{25}F_2N_7O$: 465.2075, Found: 465.2080.

(2*R*,3*R*)-3-(2-(4-methoxyphenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27p). 27p (44.30 mg, 55.6%) was prepared from **29** (75.00 mg, 0.17 mmol) and 4-methoxyphenylboronic acid (30.20 mg, 0.20 mmol) in the same manner as described for **27c**. white solid: mp 102-104 °C. $[\alpha]^{22}_D$ –72.0 ° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 7.99 (d, *J* =8.9 Hz, 2H), 7.82 (s, 1H), 7.76 (s, 1H), 7.49-7.37 (m, 1H), 6.95 (d, *J* =8.9 Hz, 2H), 6.80-6.63 (m, 2H), 5.04 (s, 1H), 4.95-4.84 (m,

2H), 4.32-4.16 (m, 3H), 3.99-3.96 (m, 1H), 3.88-3.85 (m, 1H), 3.80 (s, 3H), 3.32 (q, *J* =6.9 Hz, 1H), 2.98-2.95 (m, 1H), 0.99 (d, *J* =6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.13, 160.01, 151.52, 151.18, 143.50, 130.20, 127.16, 124.07, 123.94, 123.29 (2C, overlap), 113.52, 111.20, 103.70, 79.39, 62.57, 55.53 (2C, overlap), 55.48, 54.84, 46.53, 6.28. MS (EI) m/z: 481 (M^+). HRMS (EI): Anal. Calcd for $C_{24}H_{25}F_2N_7O_2$: 481.2035, Found: 481.2016.

(2*R*,3*R*)-3-(2-(3-fluorophenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27q). 27q (66.30 mg, 51.2%) was prepared from **29** (125.00 mg, 0.28 mmol) and 3-fluorophenylboronic acid (46.35 mg, 0.33 mmol) in the same manner as described for **27c**. white solid: mp 85-87℃. $[\alpha]^{22}_D$ –86.4° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$)：δ 7.88-7.84 (m, 1H), 7.83 (s, 1H), 7.79-7.75 (m, 2H), 7.47-7.35 (m, 2H), 7.13-7.05 (m, 1H), 6.80-6.69 (m, 2H), 5.06 (s, 1H), 4.98-4.85 (m, 2H), 4.32-4.26 (m, 3H), 4.02 (m, 1H), 3.84 (m, 1H), 3.39-3.29 (q, *J* = 6.8 Hz, 1H), 3.00-2.92 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.65, 151.95, 143.90, 133.11, 131.96, 130.61, 130.17, 128.46, 124.38, 124.27 (2C, overlap), 121.76, 115.99, 113.14, 111.79, 104.10, 79.82, 62.96, 55.93 (2C, overlap), 55.88, 47.10, 6.69. MS (EI) m/z: 469 (M^+). HRMS (EI): Anal. Calcd for $C_{23}H_{22}F_3N_7O$: 469.1815, Found: 469.1826.

(2*R*,3*R*)-3-(2-(3-cyanophenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27r). 27r (58.25 mg, 65.2%) was prepared from **29** (85.00 mg, 0.19 mmol) and 3-cyanophenylboronic acid (33.11 mg, 0.23 mmol) in the same manner as described for **27c**. white solid: mp 153-155℃. $[\alpha]^{22}_D$ –71.2° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 8.39 (s, 1H), 8.30 (d, *J* =7.9 Hz, 1H), 7.82 (s, 1H), 7.77 (s, 1H), 7.67 (d, *J* =7.8 Hz, 1H), 7.54 (t, *J* =7.8 Hz, 1H), 7.45-7.41 (m, 1H), 6.92-6.36 (m, 2H), 5.07 (s, 1H), 5.01-4.80 (m, 2H), 4.37-4.19 (m, 3H), 4.06-3.96 (m, 1H), 3.91-3.85 (m, 1H), 3.35 (q, *J* = 6.8 Hz, 1H), 3.08 -2.86 (m, 1H), 1.00 (d, *J* =6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.15, 153.75, 153.43, 145.29, 133.82, 133.79, 132.07, 131.65, 131.24, 130.91, 125.82, 125.70 (2C, overlap), 120.00, 114.31, 113.22, 105.61, 81.26, 64.42, 57.41 (2C, overlap), 57.39, 48.68, 8.21. MS (EI) m/z: 476 (M^+). HRMS (EI): Anal. Calcd for $C_{24}H_{22}F_2N_8O$: 476.1831, Found: 476.1836.

(2*R*,3*R*)-3-(2-(3-methoxyphenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27s). 27s (62.01 mg, 55.6%) was prepared from **29** (105.00 mg, 0.23 mmol) and 3-methoxyphenylboronic acid (42.29 mg, 0.28 mmol) in the same manner as described for **27c**. white solid: mp 110-112 °C. $[\alpha]^{22}_D$ –104.8 ° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.83 (s, 1H), 7.77 (s, 1H), 7.68 (d, *J* =7.7 Hz, 1H), 7.62 (s, 1H), 7.44-7.40 (m, 1H), 7.35-7.31 (m, 1H), 6.96-6.90 (m, 1H), 6.81 -6.68 (m, 2H), 5.05 (s, 1H), 5.01-4.79 (m, 2H), 4.33-4.25 (m, 3H), 4.05-4.01 (m, 1H), 3.89 (s, 3H), 3.85-3.76 (m, 1H), 3.34 (q, *J* = 6.8 Hz, 1H), 3.02 -2.90 (m, 1H), 1.00 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.44, 159.87, 152.00, 151.78, 144.03, 132.26, 130.68, 129.71, 124.56, 124.35 (2C, overlap), 118.72, 115.98, 111.97, 110.65, 104.17, 79.85, 63.15, 56.00 (2C, overlap), 55.94, 55.41, 47.20, 6.64. MS (EI) m/z: 481 (M^+). HRMS (EI): Anal. Calcd for $C_{24}H_{25}F_2N_7O_2$: 481.1998, Found: 481.2006.

(2*R*,3*R*)-3-(2-(4-isopropylphenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27t). 27t (35.10 mg, 58.6%) was

prepared from **29** (55.00 mg, 0.12 mmol) and 4-isopropylphenylboronic acid (23.90 mg, 0.15 mmol) in the same manner as described for **27c**. white solid: mp 123-124℃. $[\alpha]^{22}_{D}$ –83.2° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 7.99 (d, *J* =8.1 Hz, 2H), 7.83 (s, 1H), 7.76 (s, 1H), 7.48-7.39 (m, 1H), 7.30 (d, *J* =8.1 Hz, 2H), 6.80-6.67 (m, 2H), 5.05 (s, 1H), 4.98-4.85 (m, 2H), 4.33-4.23 (m, 3H), 4.08-4.01(m, 1H), 3.86-3.78 (m, 1H), 3.33 (q, *J* = 6.8 Hz, 1H), 2.99-2.89 (m, 2H), 1.27 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.67, 152.00, 151.62, 150.16, 143.97, 130.66, 128.41, 126.72, 126.24, 124.51, 124.41 (2C, overlap), 111.68, 104.16, 79.87, 63.00, 56.02 (2C, overlap), 55.97, 47.06, 34.03, 23.90, 6.74. MS (EI) m/z: 493 (M^+). HRMS (EI): Anal. Calcd for $C_{26}H_{29}F_2N_7O$: 493.2215, Found: 493.2226.

(2*R*,3*R*)-3-(2-(thiophen-2-yl)phenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27u). **27u** (36.55 mg, 51.0%) was prepared from **29** (71.00 mg, 0.16 mmol) and 2-thienylboronic acid (24.06 mg, 0.19 mmol) in the same manner as described for **27c**. white solid: mp 96-98℃. $[\alpha]^{22}_{D}$ –66.8° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.77 (s, 1H), 7.66 (dd, *J* =3.6, 1.1 Hz, 1H), 7.45-7.42 (m, 1H), 7.34 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.80-6.68 (m, 2H), 5.05 (s, 1H), 4.98-4.81 (m, 2H), 4.31-4.25 (m, 3H), 4.00 (d, *J* =15.7 Hz, 1H), 3.86-3.82 (m, 1H), 3.33 (q, *J* = 6.9 Hz, 1H), 2.95 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.76, 151.95, 151.75, 143.90, 133.81, 130.63, 127.71, 126.26, 125.84, 124.41, 124.28 (2C, overlap), 111.79, 104.09, 79.76, 62.93, 55.91 (2C, overlap), 55.86, 47.05, 6.69. MS (EI) m/z: 457 (M^+). HRMS (ESI): Anal. Calcd for $C_{21}H_{21}F_2N_7OS$: 457.1465, Found: 457.1477.

(2*R*,3*R*)-3-(2-(furan-2-yl)phenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27v). 27v (36.35 mg, 51.5%) was prepared from **29** (71.00 mg, 0.16 mmol) and 2-furanylboronic acid (22.80 mg, 0.20 mmol) in the same manner as described for **27c**. white solid: mp 165-168℃. $[\alpha]^{22}_{D}$ –48.0° (*c* 0.125, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.78 (s, 1H), 7.53 (s, 1H), 7.47-7.39 (m, 1H), 6.96 (d, *J* = 3.3 Hz, 1H), 6.81-6.68 (m, 2H), 6.52 (dd, *J* = 3.1, 1.7 Hz, 1H), 5.07 (s, 1H), 4.90 (q, *J* =15.0 Hz, 2H), 4.27 (dd, *J* = 21.1, 15.6 Hz, 3H), 4.00 (d, *J* = 15.6 Hz, 1H), 3.89-3.80 (m, 1H), 3.34 (q, *J* =6.7 Hz, 1H), 3.05-2.86 (m, 1H), 1.00 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.84, 151.96, 151.74, 146.41, 143.89, 143.12, 130.57, 124.41, 124.28 (2C, overlap), 111.71, 111.41, 108.92, 104.10, 79.79, 62.91, 55.93 (2C, overlap), 55.87, 47.10, 6.71. MS (EI) m/z: 441(M^+). HRMS (ESI): Anal. Calcd for $C_{21}H_{21}F_2N_7O_2$: 441.1726, Found: 441.1736.

(2*R*,3*R*)-3-(2-(thiophen-3-yl)phenyl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27w). **27w** (36.55 mg, 51.0%) was prepared from **29** (71.00 mg, 0.16 mmol) and 3-thienylboronic acid (26.07 mg, 0.20 mmol) in the same manner as described for **27c**. white solid: mp 98-100℃. $[\alpha]^{22}_{D}$ –83.2° (*c* 0.125, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 2.8, 1H), 7.83 (s, 1H), 7.76 (s, 1H), 7.63 (d, *J* =5.8 Hz, 1H), 7.46-7.40 (m, 1H), 7.40-7.35 (m, 1H), 6.80-6.70 (m, 2H), 5.07 (s, 1H), 4.91 (q, *J* =14.9 Hz, 2H), 4.33-4.20 (m, 3H), 3.99 (d, *J* =15.5 Hz, 1H), 3.85-3.74 (m, 1H), 3.34 (q, *J* =6.7 Hz, 1H), 3.03-2.87 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.57, 151.81, 151.54, 143.90, 132.98, 130.60, 126.12, 126.03, 124.41, 124.34 (2C, overlap), 123.46, 111.62, 104.10, 79.68, 62.96, 55.92 (2C, overlap), 55.87, 46.95, 6.70. MS (ESI) m/z: 457 (M^+). HRMS (ESI): Anal. Calcd for $C_{21}H_{21}F_2N_7OS$: 457.1528, Found: 457.1536.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(pyridin-4-yl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27x). 27x (46.42 mg, 46.5%) was prepared from **29** (100.00 mg, 0.22 mmol) and 4-pyridinylboronic acid (35.28 mg, 0.29 mmol) in the same manner as described for **27c**. white solid: mp 150-154℃. $[\alpha]^{22}_{D}$ –72.0° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$)：δ 8.69 (d, *J* =6.1 Hz, 2H), 7.93 (d, *J* =6.1 Hz, 2H), 7.82 (s, 1H), 7.77 (s, 1H), 7.45-7.41(m, 1H), 6.78-6.75 (m, 2H), 5.07 (s, 1H), 4.95-4.90 (m, 2H), 4.33-4.28 (m, 3H), 4.05-4.01 (m, 1H), 3.86-3.80(m, 1H), 3.35 (q, *J* =6.8 Hz, 1H), 3.02 -2.95 (m, 1H), 1.00 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.40, 152.42, 151.99, 150.14, 143.94, 138.52, 130.53, 124.39, 124.26 (2C, overlap), 120.41, 111.86, 104.23, 79.82, 62.99, 55.98 (2C, overlap), 55.91, 47.34, 6.79. MS (ESI) m/z: 452 (M^+). HRMS (ESI): Anal. Calcd for $C_{22}H_{22}F_2N_8O$: 452.1868, Found: 452.1873.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(pyridin-3-yl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27y). 27y (55.20 mg, 55.5%) was prepared from **29** (100.00 mg, 0.22 mmol) and 3-pyridinylboronic acid pinacol ester (58.85 mg, 0.29 mmol) in the same manner as described for **27c**. white solid: mp 120-122℃. $[\alpha]^{22}_{D}$ –119.2° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 9.31 (d, *J* =1.3 Hz, 1H), 8.63 (dd, *J* =4.9, 1.3 Hz, 1H), 8.32 (dt, *J* =7.9, 1.9 Hz, 1H), 7.82 (s, 1H), 7.77 (s, 1H), 7.45-7.40 (m, 1H), 7.37 (dd, *J* =7.9, 4.9 Hz, 1H), 6.81-6.68 (m, 2H), 5.05 (s, 1H), 4.98-4.86 (m, 2H), 4.32-4.28 (m, 3H), 4.05-3.98 (m, 1H), 3.89-3.85 (m, 1H), 3.35 (q, *J* =6.9 Hz, 1H), 2.99-2.96 (m, 1H), 1.00 (d, *J* =6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.22, 152.19, 151.94, 149.83, 147.51, 143.91, 133.60, 130.59, 127.11, 124.40, 124.29 (2C, overlap), 123.53, 111.73, 104.13, 79.82, 62.97, 55.95 (2C, overlap), 55.90, 47.18, 6.74. MS (ESI) m/z: 452 (M^+). HRMS (ESI): Anal. Calcd for $C_{22}H_{22}F_2N_8O$: 452.1878, Found: 452.1885.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(pyrimidin-5-yl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]-pyrazin-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27z). 27z (56.60 mg, 56.2%) was prepared from **29** (100.00 mg, 0.22 mmol) and 5-pyrimidinylboronic acid pinacol ester (59.13 mg, 0.29 mmol) in the same manner as described for **27c**. white solid: mp 115-117℃. $[\alpha]^{22}_{D}$ –106.4° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 9.40 (d, *J* =2.1 Hz, 1H), 8.46 (dd, *J* =8.1, 2.1 Hz, 1H), 7.78-7.74 (m, 3H), 7.53-7.31 (m, 1H), 6.84-6.64 (m, 2H), 5.07(s, 1H), 4.97-4.84 (m, 2H), 4.34-4.25 (m, 3H), 4.05-4.01(m, 1H), 3.91-3.85 (m, 1H), 3.36 (q, *J* = 6.8 Hz, 1H), 3.07-2.85 (m, 1H), 1.00 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.69, 156.74, 154.39, 152.57, 151.99, 143.91, 130.57, 125.30, 124.34, 124.24 (2C, overlap), 111.87, 104.15, 79.87, 62.97, 55.95 (2C, overlap), 55.90, 47.33, 6.77. MS (ESI) m/z: 453 (M^+). HRMS (ESI): Anal. Calcd for $C_{22}H_{22}F_2N_8O$: 453.1808, Found: 453.1816.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(2-cyanopyridin-5-yl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27aa). A mixture of **29** (530.00 mg, 1.17 mmol), Cesium carbonate (762.42 mg, 2.34 mmol), 2-cyanopyridine-5-boronic acid pinacol ester (350.00 mg, 1.52 mmol) and tetrakis(triphenylphosphine)palladium (0) (135.12 mg, 0.12 mmol) in dioxane (60 ml) and H_2O (20 ml) was degassed and flushed with argon. The mixture was hearted at 80 °C for 8 h. The solvent was evaporated under reduced pressure. The residue was diluted with H_2O (120 ml) and extracted with ethyl acetate (200 ml ×2). The combined organic layers were washed with H_2O (50 ml ×2) and brine (50 ml ×2), dried over anhydrous

Na_2SO_4, and filtrated, then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH 200:1~50:1) to give **27aa** (268.53 mg, 48.1%) as a white solid: mp 177-179℃. $[\alpha]^{22}_D$ –55.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 9.40 (d, J =2.1 Hz, 1H), 8.46 (dd, J =8.1, 2.1 Hz, 1H), 7.78-7.74 (m, 3H), 7.53-7.31 (m, 1H), 6.84-6.64 (m, 2H), 5.07 (s, 1H), 4.97-4.84 (m, 2H), 4.34-4.25 (m, 3H), 4.06-4.01 (m, 1H), 3.91-3.85 (m, 1H), 3.36 (q, J =6.8 Hz, 1H), 3.07-2.85 (m, 1H), 1.00 (d, J =6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.70, 152.76, 151.96, 148.85, 143.93, 133.85, 133.40, 130.52, 130.06, 128.35, 124.33, 124.20 (2C, overlap), 111.24, 111.84, 104.15, 79.82, 62.98, 55.94 (2C, overlap), 55.89, 47.42, 6.80. MS (ESI) m/z: 500.18 $(M+Na)^+$. HRMS (ESI): Anal. Calcd for $C_{23}H_{21}F_2N_9ONa$: 500.1735, Found: 500.1724.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(2-fluoropyridin-5-yl)-5,6-dihydro-[1,2,4]triazolo-[1,5-*a*]pyrazin-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27ab). 27ab (50.45 mg, 48.6%) was prepared from **29** (100.00 mg, 0.22 mmol) and 2-fluoropyridine-5-boronic acid (40.50 mg, 0.29 mmol) in the same manner as described for **27c**. white solid: mp 184-186℃. $[\alpha]^{22}_D$ –81.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 8.92 (d, *J* =2.4 Hz, 1H), 8.46-8.41 (m, 1H), 7.82 (s, 1H), 7.77 (s, 1H), 7.46-7.43 (m, 1H), 7.00 (dd, *J* =8.5, 2.9 Hz, 1H), 6.81-6.67 (m, 2H), 5.06 (s, 1H), 4.97-4.85 (m, 2H), 4.39-4.20 (m, 3H), 4.06-3.99 (m, 1H), 3.86-3.81 (m, 1H), 3.35 (q, *J* =6.8 Hz, 1H), 3.01-2.95 (m, 1H), 1.00 (d, *J* =6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.37, 152.35, 151.87, 145.78, 143.95, 138.99, 138.91, 130.60, 125.34, 124.40, 124.27 (2C, overlap), 111.66, 109.68, 104.16, 79.74, 62.99, 55.98 (2C, overlap), 55.92, 47.09, 6.78. MS (ESI) m/z: 470 (M^+). HRMS (ESI): Anal. Calcd for $C_{22}H_{21}F_3N_8O$: 470.1803, Found: 470.1779.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(3-fluoropyridin-5-yl)-5,6-dihydro-[1,2,4]triazolo-[1,5-*a*]pyrazin-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27ac). 27ac (66.22 mg, 63.8%) was prepared from **29** (100.00 mg, 0.22 mmol) and 3-fluoropyridine-5-boronic acid pinacol ester (63.68 mg, 0.29 mmol) in the same manner as described for **27c**. white solid: mp 101-102℃. $[\alpha]^{22}_D$ –146.4° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (d, 1H), 8.48 (d, *J* =2.7 Hz, 1H), 8.05 (d, *J* =9.3 Hz, 1H), 7.82 (s, 1H), 7.77 (s, 1H), 7.43 (dd, *J* =15.5, 8.9 Hz, 1H), 6.80-6.71 (m, 2H), 5.06 (s, 1H), 4.98- 4.85 (m, 2H), 4.33-4.26 (m, *J* = 5.2 Hz, 3H), 4.02 (d, *J* = 15.7 Hz, 1H), 3.89-3.80 (m, 1H), 3.39-3.28 (m, 1H), 3.02-2.93 (m, 1H), 1.00 (d, *J* =6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.25, 154.60, 153.92, 152.46, 145.84, 138.24, 132.48, 129.37, 126.20, 126.12 (2C, overlap), 118.24, 113.60, 111.92, 106.06, 81.72, 64.86, 57.84 (2C, overlap), 57.79, 49.27, 8.69. MS (ESI) m/z: 470 (M^+). HRMS (ESI): Anal. Calcd for $C_{22}H_{21}F_3N_8O$: 470.1833, Found: 470.1836.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(3-cyanopyridin-5-yl)-5,6-dihydro-[1,2,4]triazolo-[1,5-*a*]pyrazin-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27ad). 27ad (22.38 mg, 42.5%) was prepared from **29** (50.00 mg, 0.11 mmol) and 3-cyanopyridine-5-boronic acid pinacol ester (32.88 mg, 0.14 mmol) in the same manner as described for **27c**. white solid: mp 110-113℃. $[\alpha]^{22}_D$ –108.2° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (d, *J* =2.0 Hz, 1H), 8.88 (d, *J* =2.0 Hz, 1H), 8.62-8.60 (m, *J* = 2.1 Hz, 1H), 7.83 (s, 1H), 7.78 (s, 1H), 7.48-7.38 (m, 1H), 6.80-6.70 (m, 2H), 5.07 (s, 1H), 4.97-4.87 (m, 2H), 4.35-4.27 (m, 3H), 4.03 (d, *J* =15.7 Hz, 1H), 3.93-3.82 (m, 1H), 3.36 (q, *J* = 7.1 Hz, 1H), 3.04-2.95 (m, 1H), 1.00 (d, *J* = 6.9 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$): δ 160.11, 154.26, 153.83, 145.80, 145.30, 140.23, 140.05, 132.45, 130.52, 130.49, 126.26, 126.13 (2C, overlap), 121.98, 113.55, 106.02, 81.69, 64.84, 57.83 (2C,

overlap), 57.78, 49.14, 8.64. MS (EI) m/z: 477 $(M)^+$. HRMS (EI): Anal. Calcd for $C_{23}H_{21}F_2N_9O$: 477.1785, Found: 477.1812.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(2-methoxypyridin-5-yl)-5,6-dihydro-[1,2,4]triazolo-[1,5-*a*]pyrazin-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27ae). 27ae (42.60 mg, 67.0%) was prepared from **29** (60.00 mg, 0.13 mmol) and 2-methoxy-5-pyridinylboronic acid (26.33 mg, 0.17 mmol) in the same manner as described for **27c**. white solid: mp 88-90℃. $[\alpha]^{22}_D$ –64.8° (*c* 0.125, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (d, *J* = 2.0 Hz, 1H), 8.21 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.83 (d, *J* = 10.4 Hz, 1H), 7.80-7.75 (m, 1H), 7.43 (m, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 6.79-6.71 (m, 2H), 5.07 (s, 1H), 4.97-4.86 (m, 2H), 4.34-4.19 (m, 3H), 4.05-4.01 (m, 1H), 3.99 (s, 3H), 3.87-3.79 (m, 1H), 3.34 (q, *J* = 6.7 Hz, 1H), 3.01-2.88 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.66, 159.60, 151.98, 151.90, 145.20, 143.94, 136.61, 130.64, 124.44, 124.31 (2C, overlap), 120.66, 111.78, 110.77, 104.18, 79.81, 62.98, 55.99 (2C, overlap), 55.94, 53.72, 47.07, 6.73. MS (EI) m/z: 482 $(M)^+$. HRMS (EI): Anal. Calcd for $C_{23}H_{24}F_2N_8O_2$: 482.2115, Found: 482.2112.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(2-methylpyrimidin-5-yl)-5,6-dihydro-[1,2,4]triazolo-[1,5-*a*]pyrazin-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27af). 27af (32.10 mg, 52.9%) was prepared from **29** (60.00 mg, 0.13 mmol) and 2-methylpyrimidine-5-boronic acid pinacol ester (35.00 mg, 0.16 mmol) in the same manner as described for **27c**. white solid: mp 98-100℃. $[\alpha]^{22}_D$ –32.0° (*c* 0.125, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (s, 2H), 7.85 (s, 1H), 7.79 (s, 1H), 7.44 (m, 1H), 6.84-6.70 (m, 2H), 5.08 (s, 1H), 4.93 (q, *J* = 14.9 Hz, 2H), 4.32 (m, 3H), 4.04 (d, *J* = 15.7 Hz, 1H), 3.93-3.81 (m, 1H), 3.37 (q, *J* = 6.7 Hz, 1H), 3.06-2.93 (m, 1H), 2.83 (s, 3H), 1.01 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.41, 157.23, 154.58, 152.44, 152.04, 143.94, 130.57, 124.37, 124.27 (2C, overlap), 122.20, 111.78, 104.19, 79.89, 62.99, 55.98 (2C, overlap), 55.93, 47.31, 26.04, 6.78. MS (EI) m/z: 467 $(M)^+$. HRMS (EI): Anal. Calcd for $C_{22}H_{23}F_2N_9O$: 467.2035, Found: 467.2028.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(2-methoxypyrimidin-5-yl)-5,6-dihydro-[1,2,4]triazolo-[1,5-*a*]pyrazin-7(8*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (27ag). 27af (49.30 mg, 42.5%) was prepared from **29** (110.00 mg, 0.24 mmol) and 2-methoxypyrimidine-5-boronic acid pinacol ester (68.80 mg, 0.29 mmol) in the same manner as described for **27c**. white solid: mp 92-93℃. $[\alpha]^{22}_D$ –65.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (s, 2H), 7.84 (s, 1H), 7.77 (s, 1H), 7.47-7.39 (m, 1H), 6.80 - 6.70 (m, 2H), 5.08 (s, 1H), 4.92 (q, *J* = 14.6 Hz, 2H), 4.34-4.26 (m, 3H), 4.11-3.99 (m, 4H), 3.93-3.77 (m, 1H), 3.36 (q, *J* = 6.4 Hz, 1H), 3.05- 2.85 (m, 1H), 1.00 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.79, 157.19, 157.14, 152.22, 151.99, 143.94, 130.60, 124.41, 124.28 (2C, overlap), 119.45, 111.84 104.16, 79.82, 62.99, 55.96 (2C, overlap), 55.91, 55.18, 47.19, 6.77. MS (EI) m/z: 483 $(M)^+$. HRMS (EI): Anal. Calcd for $C_{22}H_{23}F_2N_9O_2$: 483.1961, Found: 483.1952.

2-amino-5-*tert*-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine (41). Pyrrolidine (75.00 g, 1.05 mol) and p-toluenesulfonic acid monohydrate (0.95 g, 5.00 mmol) was added to a solution of N-*tert*-butoxycarbonyl-4-piperidone **40** (200.00 g, 1.00 mol) in cyclohexane (1000 ml). The reaction mixture was refluxed for 2 h with Dean-Stark trap. After cooling, the mixture was filtered and the filtrate was evaporated under reduced pressure to afford crude residue, which was used for the following reaction without further purification.

The residue was dissolved in methanol (300 ml) followed by the addition of elemental sulfur (32.00 g, 0.13 mol) in one portion, then the solution of cyanamide (42.04 g, 1.00 mol) in MeOH (40 ml) was added dropwise to the stirred mixture at 0 °C. The reaction mixture was stirred for 6 h at room temperature then reaction mixture was filtered and solid was washed with ethyl acetate (200 ml×2), then dried under vacuum to afford **41** (163.00 g, 64.0%) as a pale yellow solid. : mp 92-95 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.81 (s, 2H), 4.31 (s, 2H), 3.58 (t, J =5.7 Hz, 2H), 2.45 (t, J =5.5 Hz, 1H), 1.43 (s, 9H). MS (EI) *m/z* 255 (M^+).

2-Bromo-5-*tert*-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine (42). *t*-BuONO (5.20 g, 44.39 mol) was added to a stirred suspension of $CuBr_2$ (7.95 g, 35.60 mmol) in dry DMF (300 ml) followed by addition of **41** (7.56 g, 29.65 mmol) in portions. The reaction mixture was stirred at 50 °C for 4 h. After cooling, the mixture was evaporated under reduced pressure to afford crude residue, which was diluted with H_2O (100 ml) and extracted with ethyl acetate (200 ml×2). The combined organic layers were washed with H_2O (100 ml×2) and brine (100 ml×2), dried over anhydrous Na_2SO_4, and filtrated, then the solvent was evaporated under reduced pressure to give crude oil, which was purified by silica gel column chromatography (petroleum: ethyl acetate 20:1~10:1) to afford **42** (3.65 g, 38.8%) as a white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (s, 2H), 3.72 (J =5.6 Hz, 2H), 2.84 (s, 2H), 1.47 (s, 9H). MS (EI) *m/z* 318 (M^+).

2-bromo-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine (43). To a solution of compound **42** (3.65 g, 11.48 mmol) in dioxane (20 ml) was added 15 ml 4N HCl/dioxane. The resulting mixture was stirred at room temperature for 8h. The solvent was evaporated under reduced pressure. The residue was diluted with water (30 ml), basified with Na_2CO_3, and extracted with CH_2Cl_2 (60 ml×2). The combined extract was washed with water (30 ml×2) and brine (30 ml×2), dried over anhydrous Na_2SO_4, then filtrated, and the solvent was evaporated under reduced pressure to give compound **43** as a pale yellow solid (2.19g, 87.5%). Mp: 110-113 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.82 (t, J =1.9 Hz, 2H), 2.97 (t, J =5.8 Hz, 2H), 2.66-2.57 (m, 2H). MS (EI) *m/z* 218 (M^+).

(2*R*,3*R*)-3-(2-bromo-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (44). To a solution of epoxide **10** (0.63 g, 2.51 mmol) in 20 ml of acetonitrile was added **43** (1.10 g, 5.02 mmol) and $LiClO_4$ (0.80 g, 7.53 mmol). The reaction mixture was irradiated for 10h in a microwave oven (Discover, CEM), programmed to obtain reflux with a maximum power output of 80 W. After cooling, the mixture was evaporated under reduced pressure. The residue was diluted with H_2O (50 ml) and extracted with ethyl acetate (100 ml ×2). The combined organic layers were washed with H_2O (30 ml ×2) and brine (30 ml ×2), dried over anhydrous Na_2SO_4, and filtrated, then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH 200:1~100:1) to give **44** (0.61 g, 51.6%) as a yellow amorphous solid. $[\alpha]^{22}_D$ –69.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.75 (s, 1H), 7.51-7.38 (m, 1H), 6.82-6.68 (m, 2H), 5.04-4.80 (m, 2H), 4.04 (d, J =14.9 Hz, 1H), 3.71 (d, J =14.7 Hz, 1H), 3.42-3.15 (m, 2H), 2.92-2.69 (m, 3H), 0.98 (d, J =6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.30, 148.61, 147.58, 143.67, 130.27, 128.62, 124.29, 124.18 (2C, overlap), 111.12, 103.68, 78.76, 63.18, 55.44 (2C, overlap), 55.40, 27.37, 6.91. MS (EI) m/z: 469 (M^+). HRMS (EI): Anal. Calcd for $C_{18}H_{18}BrF_2N_5OS$: 469.0451, Found: 469.0456.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-phenyl-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45a). A mixture of **44** (100.00 mg, 0.21mmol), Cesium carbonate (138.94 mg, 0.43 mmol), phenylboronic acid (33.81 mg, 0.28 mmol) and tetrakis(triphenylphosphine)palladium (0) (50.00 mg, 0.04 mmol) in dioxane (10 ml) and H_2O (4 ml) was degassed and flushed with argon. The mixture was heated at 80 °C for 10 h. The solvent was evaporated under reduced pressure. The residue was diluted with H_2O (20 ml) and extracted with ethyl acetate (30 ml ×2). The combined organic layers were washed with H_2O (20 ml ×2) and brine (20 ml ×2), dried over anhydrous Na_2SO_4, and filtrated, then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH 200:1~100:1) to give **45a** (62.85 mg, 52.6%) as a pale yellow solid: mp 72-73 °C. $[\alpha]^{22}_D$ –47.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.92 (s, 1H), 7.91-7.86 (m, 2H), 7.78 (s, 1H), 7.57-7.36 (m, 4H), 6.84-6.68 (m, 2H), 5.12 (s, 1H), 4.98-4.82 (m, 2H), 4.11 (d, *J* =14.8 Hz, 1H), 3.81 (d, *J*= 14.8 Hz, 1H), 3.35-3.28 (m, 1H), 3.24 (q, *J* =6.8 Hz, 1H), 2.98-2.93 (m, 2H), 2.82- 2.69 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.47, 151.58, 150.15, 144.12, 133.67, 130.71, 129.68, 128.83, 127.13, 126.22, 124.72, 124.58 (2C, overlap), 111.51, 104.07, 78.87, 63.60, 55.84 (2C, overlap), 55.78, 27.93, 7.37. MS (ESI) m/z: 468.1 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{24}H_{24}F_2N_5OS$: 468.1670, Found: 468.1664.

(2*R*,3*R*)-3-(2-(4-chlorophenyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45b). 45b (50.15 mg, 56.0%) was prepared from **44** (120.00 mg, 0.26 mmol) and 4-chlorophenylboronic acid (47.90 mg, 0.30 mmol) in the same manner as described for **45a**. pale yellow solid: mp 74-75℃. $[\alpha]^{22}_D$ –48.0° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.91 (s, 1H), 7.82 (d, *J* =8.5 Hz, 2H), 7.78 (s, 1H), 7.49-7.41(m, 1H), 7.39 (d, *J* =8.5 Hz, 2H), 6.76 (m, 2H), 5.11 (s, 1H), 4.98- 4.80 (m, 2H), 4.12 (d, *J* =14.9 Hz, 1H), 3.81 (d, *J* =14.9 Hz, 1H), 3.37-3.28 (m, 1H), 3.25 (q, *J* =6.8 Hz, 1H), 2.94 (m, 2H), 2.81-2.76 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.07, 151.57, 150.38, 144.10, 135.54, 132.16, 130.63, 129.04, 127.56, 127.38, 124.65, 124.56 (2C, overlap), 111.53, 104.08, 78.95, 63.59, 55.84 (2C, overlap), 55.78, 27.90, 7.36. MS (EI) m/z: 501 (M^+). HRMS (EI): Anal. Calcd for $C_{24}H_{22}ClF_2N_5OS$: 501.1216, Found: 501.1224.

(2*R*,3*R*)-3-(2-(4-(trifluoromethyl)phenyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluo-rophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45c). 45c (49.18 mg, 43.1%) was prepared from **44** (100.00 mg, 0.21 mmol) and 4-(trifluoromethyl) phenylboronic acid (48.62 mg, 0.26 mmol) in the same manner as described for **45a**. pale yellow solid: mp 81-82℃. $[\alpha]^{22}_D$ –45.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.93 (s, 1H), 7.85 (d, *J* =8.5 Hz, 2H), 7.76 (s, 1H), 7.45-7.41(m, 1H), 7.36 (d, *J* =8.5 Hz, 2H), 6.78-6.71 (m, 2H), 5.10 (s, 1H), 4.96-4.80 (m, 2H), 4.11 (d, *J* =14.9 Hz, 1H), 3.83 (d, *J* =14.9 Hz, 1H), 3.36-3.28 (m, 1H), 3.26 (q, *J* = 6.8 Hz, 1H), 2.98-2.95 (m, 2H), 2.83-2.76 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.44, 151.59, 150.85, 144.08, 136.77, 131.30, 131.04, 130.62, 128.57, 126.34, 125.82, 124.68, 124.58 (2C, overlap), 111.53, 104.08, 79.03, 63.59, 55.83 (2C, overlap), 55.79, 27.91, 7.32. MS (EI) m/z: 535 (M^+). HRMS (EI): Anal. Calcd for $C_{25}H_{22}F_5N_5OS$: 535.1536, Found: 535.1543.

(2*R*,3*R*)-3-(2-(4-methoxyphenyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45d). 45d (48.97 mg, 61.6%) was prepared from **44** (75.00 mg, 0.16 mmol) and 4-methoxyphenylboronic acid (29.18 mg, 0.19 mmol) in the same manner as described for **45a**. pale yellow solid: mp 93-95 °C. $[\alpha]^{22}_{D}$ –33.6 ° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.92 (s, 1H), 7.82 (d, *J* =8.4 Hz, 2H), 7.78 (s, 1H), 7.50-7.45 (m, 1H), 6.93 (d, *J* =8.5 Hz, 2H), 6.76-6.68 (m, 2H), 4.97-4.84 (m, 2H), 4.07 (d, *J* =14.8Hz, 1H), 3.85 (s, 3H), 3.78 (d, *J* = 14.8 Hz, 1H), 3.35-3.28 (m, 1H), 3.27 (q, *J* = 6.8 Hz, 1H), 2.92-2.71 (m, 2H), 2.81-2.73 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.07, 151.57, 150.38, 144.10, 135.54, 132.16, 130.57, 129.04, 127.56, 127.38, 124.65, 124.56 (2C, overlap), 111.52, 104.08, 78.95, 63.59, 55.84 (2C, overlap), 55.78, 29.62, 27.90, 7.36. MS (EI) m/z: 497 (M^+). HRMS (EI): Anal. Calcd for $C_{25}H_{25}F_2N_5O_2S$: 497.1766, Found: 497.1755.

(2*R*,3*R*)-3-(2-(4-methylphenyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45e). 45e (54.58 mg, 53.2%) was prepared from **44** (100.00 mg, 0.21 mmol) and 4-methylphenylboronic acid (34.79 mg, 0.26 mmol) in the same manner as described for **45a**. pale yellow solid: mp 86-87 °C. $[\alpha]^{22}_{D}$ –44.0 ° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.92 (s, 1H), 7.78 (d, *J* =8.0 Hz, 2H), 7.76 (s, 1H), 7.50-7.45 (m, 1H), 7.22 (d, *J* =8.0 Hz, 2H), 6.81-6.76 (m, 2H), 4.98-4.82 (m, 2H), 4.09(d, *J* =14.8 Hz, 1H), 3.79 (d, *J* =14.8 Hz, 1H), 3.35-3.28 (m, 1H), 3.27 (q, *J* =6.8 Hz, 1H), 2.96-2.92 (m, 2H), 2.85-2.71 (m, 1H), 2.38 (s, 3H), 1.03 (d, *J* = 6.8Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.83, 151.60, 149.97, 144.23, 140.01, 131.07, 130.72, 129.60, 126.65, 126.22, 124.77, 124.64 (2C, overlap), 111.51, 104.15, 78.88, 63.70, 55.93 (2C, overlap), 55.86, 27.98, 21.40, 7.48. MS (EI) m/z: 481 (M^+). HRMS (EI): Anal. Calcd for $C_{25}H_{25}F_2N_5OS$: 481.1726, Found: 481.1735.

(2*R*,3*R*)-3-(2-(4-fluorophenyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45f). 45f (72.75 mg, 58.6%) was prepared from **44** (120.00 mg, 0.26 mmol) and 4-fluorophenylboronic acid (43.00 mg, 0.31 mmol) in the same manner as described for **45a**. pale yellow solid: mp 94-95℃. $[\alpha]^{22}_{D}$ –42.8° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.91 (s, 1H), 7.87 (d, *J* =8.6, 2H), 7.78 (s, 1H), 7.55-7.43 (m, 1H), 7.10 (d, *J* =8.6 Hz, 2H), 6.83-6.65 (m, 2H), 4.98-4.83 (m, 2H), 4.11 (d, *J* =14.8 Hz, 1H), 3.80 (d, *J* =14.8 Hz, 1H), 3.36-3.28 (m, 1H), 3.26 (q, *J* =6.8 Hz, 1H), 2.96-2.92 (m, 2H), 2.91-2.77 (m, 1H), 1.03 (d, *J* =6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.29, 151.62, 150.19, 144.13, 130.59, 130.02, 128.05, 127.16, 124.70, 124.56 (2C, overlap), 115.99, 115.82, 111.61, 104.09, 78.91, 63.61, 55.84 (2C, overlap), 55.78, 27.91, 7.37. MS (EI) m/z: 485 (M^+). HRMS (EI): Anal. Calcd for $C_{24}H_{22}F_3N_5OS$: 485.1556, Found: 485.1551.

(2*R*,3*R*)-3-(2-(4-bromophenyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45g). 45g (35.13 mg, 46.5%) was prepared from **44** (65.00 mg, 0.14 mmol) and 4-bromophenylboronic acid (33.2 6mg, 0.17 mmol) in the same manner as described for **45a**. pale yellow solid: mp 82-83℃. $[\alpha]^{22}_{D}$ –44.8° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.90 (s, 1H), 7.78 (s, 1H), 7.76 (d, *J* =8.9 Hz, 2H), 7.55 (d, *J* =8.9Hz, 2H), 7.49-7.46 (m, 1H), 6.86-6.75 (m, 2H), 4.97-4.84 (m, 2H), 4.11 (d, *J* = 15.1 Hz, 1H), 3.81 (d, *J* = 15.1 Hz, 1H), 3.37-3.25 (m, 1H), 3.26 (q, *J* = 6.8 Hz, 1H), 2.98-2.91 (m, 2H), 2.81-2.76 (m, 1H), 1.02 (d, *J* =6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.14, 151.62,

150.47, 144.15, 132.63, 132.03, 130.68, 127.98, 127.65, 124.74, 124.63 (2C, overlap), 123.87, 111.56, 104.12, 79.01, 63.64, 58.89 (2C, overlap), 55.83, 27.95, 7.41. MS (ESI) m/z: 546.1 $(M+1)^+$. HRMS (EI): Anal. Calcd for $C_{24}H_{23}BrF_2N_5OS$: 546.0775, Found: 546.0768.

(2*R*,3*R*)-3-(2-(4-isopropylphenyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45h). 45h (51.72 mg, 63.5%) was prepared from **44** (75.00 mg, 0.16 mmol) and 4-isopropylphenylboronic acid (31.50 mg, 0.19 mmol) in the same manner as described for **45a**. pale yellow solid: mp 76-77℃. $[\alpha]^{22}_D$ –36.8° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.92 (s, 1H), 7.82 (s, 1H), 7.78 (d, *J* =7.6 Hz, 2H), 7.51-7.49 (m, 1H), 7.27 (d, *J* =7.6 Hz, 2H), 6.78-6.76 (m, 2H), 5.13 (s, 1H), 4.97-4.84 (m, 2H), 4.09 (d, *J* = 14.9 Hz, 1H), 3.79 (d, *J* = 14.9 Hz, 1H), 3.37-3.25 (m, 1H), 3.26 (q, *J* = 6.8 Hz, 1H), 2.98-2.91 (m, 3H), 2.83-2.76 (m, 1H), 1.26 (d, *J* =6.9 Hz, 6H), 1.03 (d, *J* =6.8Hz, 3H). Anal. Calcd for $C_{27}H_{29}F_2N_5OS$: C, 63.63; H, 5.74; N, 13.74. Found: C, 63.68; H, 5.78; N, 13.68. MS (EI) m/z: 509 (M^+).

(2*R*,3*R*)-3-(2-(3-chlorophenyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45i). 45i (39.00 mg, 36.5%) was prepared from **44** (100.00 mg, 0.21 mmol) and 3-chlorophenylboronic acid (39.92 mg, 0.26 mmol) in the same manner as described for **45a**. pale yellow solid: mp 73-76℃. $[\alpha]^{22}_D$ –33.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$)：δ 7.93-7.89 (m, 2H), 7.76 (s, 1H), 7.74-7.72 (m, 1H),7.54-7.44 (m, 1H), 7.39-7.31 (m, 2H), 6.84-6.68 (m, 2H), 4.96-4.85 (m, 2H), 4.13 (d, *J* = 15.7 Hz, 1H), 3.82 (d, *J* = 14.6Hz, 1H), 3.36-3.25 (m, 1H), 3.27 (q, *J* = 6.8 Hz, 1H), 2.96-2.93(m, 2H), 2.86-2.77 (m, 1H), 1.02 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.07, 151.65, 150.54, 144.15, 135.34, 134.96, 130.68, 130.13, 129.62, 127.98, 126.13, 124.71, 124.61 (2C, overlap), 124.38, 111.50, 104.14, 79.02, 63.65, 55.90 (2C, overlap), 55.85, 27.95, 7.40. MS (ESI) m/z: 502.1 $(M+1)^+$. HRMS (EI): Anal. Calcd for $C_{24}H_{23}ClF_2N_5OS$: 502.1280, Found: 502.1270.

(2*R*,3*R*)-3-(2-(3-fluorophenyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45j). 45j (31.63 mg, 55.6%) was prepared from **44** (55.00 mg, 0.12 mmol) and 3-fluorophenylboronic acid (19.70 mg, 0.14 mmol) in the same manner as described for **45a**. pale yellow solid: mp 85-87℃. $[\alpha]^{22}_D$ –61.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.91 (s, 1H), 7.91-7.87 (dd, J = 8.6, 5.3 Hz, 2H), 7.78 (s, 1H), 7.55-7.43 (m, 1H), 7.12-7.08 (m, 2H), 6.83- 6.65 (m, 2H), 4.98-4.83 (m, 2H), 4.11 (d, J =14.8 Hz, 1H), 3.80 (d, J=14.8 Hz, 1H), 3.36-3.25 (m, 1H), 3.27 (q, *J* =6.8 Hz, 1H), 2.96-2.93 (m, 2H), 2.83-2.77 (m, 1H), 1.03 (d, J =6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.03, 151.65, 150.49, 144.15, 135.80, 135.73, 130.70, 130.43, 127.91, 124.73, 124.62 (2C, overlap), 121.96, 116.60, 112.95, 111.48, 104.11, 78.95, 63.64, 55.89 (2C, overlap), 55.83, 27.95, 7.39. MS (EI) m/z: 486.1 $(M+1)^+$. HRMS (EI): Anal. Calcd for $C_{24}H_{23}F_3N_5OS$: 486.1535, Found: 486.1526.

(2*R*,3*R*)-3-(2-(3-methylphenyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45k). 45k (31.66 mg, 55.1%) was prepared from **44** (56.00 mg, 0.12 mmol) and 3-methylphenylboronic acid (19.50 mg, 0.14 mmol) in the same manner as described for **45a**. pale yellow solid: mp 80-83 °C. $[\alpha]^{22}_D$ –28.0 ° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$)：δ 7.92 (s, 1H), 7.78 (s, 1H), 7.75-7.71 (m, 1H), 7.66 (d, *J* =8.3 Hz, 1H), 7.53-7.44 (m, 1H), 7.32-7.30 (m, 1H), 7.21 (d, *J* =8.3 Hz, 1H), 6.82-6.70 (m, 2H),

5.13 (s, 1H), 4.98-4.82 (m, 2H), 4.10 (d, *J* = 15.2 Hz, 1H), 3.81 (d, *J* = 15.2 Hz, 1H), 3.32-3.28 (m, 1H), 3.23 (q, *J* = 6.8 Hz, 1H), 2.97-2.93 (m, 2H), 2.83-2.77 (m, 1H), 1.01 (d, J =6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.83, 151.60, 149.97, 144.23, 140.01, 131.07, 130.72, 129.60, 126.65, 126.22, 124.77, 124.64 (2C, overlap), 111.51, 104.15, 78.88, 63.70, 55.93 (2C, overlap), 55.86, 27.98, 21.40, 7.48. MS (EI) m/z: 481 (M^+). HRMS (EI): Anal. Calcd for $C_{25}H_{25}F_2N_5OS$: 481.1726, Found: 481.1735. ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.76, 151.50, 150.04, 144.17, 138.66, 133.56, 130.66, 130.57, 128.77, 127.01, 126.71, 124.71, 124.61 (2C, overlap), 123.52, 111.43, 104.09, 78.92, 63.63, 55.89 (2C, overlap), 55.83, 27.94, 21.29, 7.43. MS (EI) m/z: 481 (M^+). HRMS (EI): Anal. Calcd for $C_{25}H_{25}F_2N_5OS$: 481.1735, Found: 481.1726.

(2*R*,3*R*)-3-(2-(3-bromophenyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45l). 45l (36.10 mg, 36.5%) was prepared from **44** (85.00 mg, 0.18 mmol) and 3-bromophenylboronic acid (43.50 mg, 0.22 mmol) in the same manner as described for **45a**. pale yellow amorphous solid. $[\alpha]^{22}_D$ –30.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-8.03 (m, 1H), 7.90 (s, 1H), 7.80-7.74 (m, 2H), 7.52-7.43 (m, 2H), 7.30-7.22 (m, 1H), 6.81-6.70 (m, 2H), 4.98-4.82 (m, 2H), 4.11 (d, *J* =14.1 Hz, 1H), 3.81 (d, *J* =14.9 Hz, 1H), 3.39-3.18 (m, 2H), 3.04-2.87 (m, 2H), 2.80-2.66 (m, 1H), 1.01 (d, *J* =6.8 Hz, 3H). Anal. Calcd for $C_{24}H_{22}BrF_2N_5OS$: C, 52.75; H, 4.06; N, 12.82. Found: C, 52.71; H, 4.11; N, 12.78. MS (EI) m/z: 545 (M^+).

(2*R*,3*R*)-3-(2-(3-methoxyphenyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45m). 45m (36.84 mg, 63.2%) was prepared from **44** (55.00 mg, 0.12 mmol) and 3-methoxyphenylboronic acid (21.40 mg, 0.14 mmol) in the same manner as described for **45a**. pale yellow solid: mp 61-63 °C. $[\alpha]^{22}_D$ –50.4 ° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.76 (s, 1H), 7.55-7.41 (m, 3H), 7.36-7.28 (m, 1H), 6.96-6.91 (m, 1H), 6.82-6.69 (m, 2H), 5.02-4.82 (m, 2H), 4.18-3.99 (m, 1H), 3.83 (s, 3H), 3.79 (d, *J* = 14.9 Hz, 1H), 3.38-3.17 (m, 2H), 3.00-2.87 (m, 2H), 2.78-2.68 (m, 1H), 1.02 (d, *J* = 6.9, 1.3 Hz, 3H). Anal. Calcd for $C_{25}H_{25}F_2N_5O_2S$: C, 60.35; H, 5.06; N, 14.08. Found: C, 60.31; H, 4.98; N, 14.13. MS (ESI) m/z: 520.2 $(M+Na)^+$.

(2*R*,3*R*)-3-(2-(4-cyanophenyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45n). 45n (61.29 mg, 53.1%) was prepared from **44** (110.00 mg, 0.23 mmol) and 4-cyanophenylboronic acid pinacol ester (59.11 mg, 0.26 mmol) in the same manner as described for **45a**. pale yellow solid: mp 97-98 °C. $[\alpha]^{22}_D$ –85.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)： δ 7.99 (d, *J* =8.5 Hz, 2H), 7.90 (s, 1H), 7.78 (s, 1H), 7.70 (d, *J* =8.5 Hz,2H), 7.52-7.40 (m, 1H), 6.76-6.75 (m, 2H), 4.97-4.83 (m, 2H), 4.17 (d, *J* =15.3 Hz, 1H), 3.85 (d, *J* =15.3 Hz, 1H), 3.37-3.25 (m, 1H), 3.26 (q, *J* =6.8 Hz, 1H), 2.98-2.95 (m, 2H), 2.86-2.78 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.69, 151.66, 151.27, 144.08, 137.50, 132.65, 130.60, 129.40, 126.49, 124.69, 124.56 (2C, overlap), 118.44, 112.69, 111.44, 104.07, 79.14, 63.56, 55.85 (2C, overlap), 55.79, 27.93, 7.35. MS (ESI) m/z: 493.1 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{25}H_{23}F_2N_6OS$: 493.1621, Found: 493.1622.

(2*R*,3*R*)-3-(2-(3-cyanophenyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45o). 45o (37.16 mg, 46.6%) was prepared from **44** (76.00 mg, 0.16 mmol) and 3-cyanophenylboronic acid (26.20 mg, 0.18 mmol) in the same manner as described for **45a**. pale yellow solid: mp 67-68 °C. $[\alpha]^{22}_D$ –68.0° (*c* 0.125,

$CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 8.22-8.18 (m, 1H), 8.12-8.07 (m, 1H), 7.90 (s, 1H), 7.78 (s, 1H), 7.52-7.42(m, 3H), 6.85-6.70 (m, 2H), 5.09 (s, 1H), 4.99-4.84 (m, 2H), 4.17 (d, *J* =15.2 Hz, 1H), 3.85 (d, *J* =15.2Hz, 1H), 3.40-3.34 (m, 1H), 3.27 (q, *J* =6.8 Hz, 1H), 3.03-2.91 (m, 2H), 2.89-2.74 (m, 1H), 1.03 (d, *J* =6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.45, 151.68, 151.03, 144.18, 134.89, 132.84, 132.67, 130.68, 130.22, 129.82, 129.55, 124.79, 124.66 (2C, overlap), 118.22, 113.26, 111.50, 104.15, 79.20, 63.64, 55.96 (2C, overlap), 55.90, 27.98, 7.45. MS (ESI) m/z: 493.1 $(M+1)^+$. HRMS (EI): Anal. Calcd for $C_{25}H_{23}F_2N_6OS$: 493.1616, Found: 493.1623.

(2*R*,3*R*)-3-(2-(thiophen-2-yl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45p). 45p (47.16 mg, 55.0%) was prepared from **44** (85.00 mg, 0.18 mmol) and 2-thienylboronic acid (30.71 mg, 0.24 mmol) in the same manner as described for **45a**. pale yellow solid: mp 83-85℃. $[\alpha]^{22}_D$ –56.8° (*c* 0.125, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.78 (s, 1H), 7.54-7.48 (m, 1H), 7.46-7.43 (m, 1H), 7.38-7.34 (m, 1H), 7.09-7.03 (m, 1H), 6.82-6.70 (m, 2H), 5.13 (s, 1H), 4.97-4.83 (m, 2H), 4.09 (d, *J* =14.8 Hz, 1H), 3.79 (d, *J* =14.9 Hz, 1H), 3.34-3.17 (m, 2H), 2.95-2.88 (m, 2H), 2.82-2.70 (m, 1H), 1.02 (d, *J* = 6.9, 1.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.68, 151.22, 149.34, 143.73, 136.98, 130.20, 127.34, 126.75, 126.06, 125.63, 124.29, 124.22 (2C, overlap), 111.10, 103.66, 78.58, 63.20, 55.44 (2C, overlap), 55.39, 27.49, 7.00. MS (EI) m/z: 473 (M^+). HRMS (EI): Anal. Calcd for $C_{22}H_{21}F_2N_5OS_2$: 473.1265, Found: 473.1253.

(2*R*,3*R*)-3-(2-(furan-2-yl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45q). 45q (36.35 mg, 51.5%) was prepared from **44** (85.00 mg, 0.18 mmol) and 2-furanylboronic acid (26.85 mg, 0.24 mmol) in the same manner as described for **45a**. pale yellow solid: mp 68-70℃. $[\alpha]^{22}_D$ –35.2° (*c* 0.125, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.75 (s, 1H), 7.58-7.52 (m, 1H), 7.50-7.43 (m, 1H), 6.97-6.89 (m, 1H), 6.81-6.71 (m, 2H), 6.55-6.47 (m, 1H), 5.14 (s, 1H), 4.98-4.81 (m, 2H), 4.23-4.05 (m, 1H), 3.80 (d, *J* =14.9 Hz, 1H), 3.38-3.26 (m, 1H), 3.24 (q, *J* = 6.8 Hz, 1H), 2.99-2.84 (m, 2H), 2.79-2.67 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$): δ 154.95, 151.17, 149.55, 148.42, 143.71, 142.85, 130.25, 126.0, 124.33, 124.19 (2C, overlap), 111.68, 111.19, 107.95, 103.66, 78.59, 63.17, 55.46 (2C, overlap), 55.40, 27.46, 6.99. MS (EI) m/z: 457(M^+). HRMS (EI): Anal. Calcd for $C_{22}H_{21}F_2N_5O_2S$: 457.1426, Found: 457.1436.

(2*R*,3*R*)-3-(2-(thiophen-3-yl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45r). 45r (51.95 mg, 51.5%) was prepared from **44** (100.00 mg, 0.21 mmol) and 3-thienylboronic acid (35.83 mg, 0.28 mmol) in the same manner as described for **45a**. pale yellow solid: mp 69-71℃. $[\alpha]^{22}_D$ –51.2° (*c* 0.125, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.80-7.75 (m, 2H), 7.70-7.63 (m, 1H), 7.52-7.49 (m, 1H), 7.39-7.34 (m, 1H), 6.81-6.70 (m, 2H), 5.12 (s, 1H), 5.01-4.80 (m, 2H), 4.10 (d, *J* =14.8 Hz, 1H), 3.78 (d, *J* = 14.8 Hz, 1H), 3.40-3.25 (m, 1H), 3.22 (q, *J* =6.7 Hz, 1H), 2.98-2.85 (m, 2H), 2.83-2.68 (m, 1H), 1.02 (d, *J* =6.9, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.07, 151.20, 149.28, 143.73, 135.35, 130.32, 126.17, 125.89, 125.63, 124.29, 124.22 (2C, overlap), 122.7, 111.05, 103.69, 78.48, 63.21, 55.45 (2C, overlap), 55.39, 27.49, 7.00. MS (EI) m/z: 473 (M^+). HRMS (EI): Anal. Calcd for $C_{22}H_{21}F_2N_5OS_2$: 473.1226, Found: 473.1233.

(2*R*,3*R*)-3-(2-(pyridin-4-yl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45s). 45s (111.85 mg, 41.5%) was prepared from **44** (270.00 mg, 0.58 mmol) and 4-pyridinylboronic acid (92.68 mg, 0.75 mmol) in the same manner as described for **45a**. pale yellow solid: mp 133-134℃. $[\alpha]^{22}_{D}$ –69.2° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* =6.1 Hz, 2H), 7.89 (s, 1H), 7.80-7.76 (m, 3H), 7.53-7.43 (m, 1H), 6.82-6.69 (m, 2H), 5.08 (s, 1H), 4.96-4.86 (m, 2H), 4.19 (d, *J* =15.9 Hz, 1H), 3.87 (d, *J* =15.4 Hz, 1H), 3.38-3.36 (m, 1H), 3.27 (q, *J* =6.9 Hz, 1H), 3.02-2.98 (m, 2H), 2.85-2.81 (m, 1H), 1.02 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.87, 151.30, 150.94, 150.13, 143.70, 140.04, 130.25, 129.16, 124.31, 124.20 (2C, overlap), 119.61, 111.18, 103.71, 78.76, 63.21, 55.48 (2C, overlap), 55.43, 27.57, 6.96. MS (ESI) m/z: 469.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{23}H_{23}F_2N_6OS$: 469.1622, Found: 469.1618.

(2*R*,3*R*)-3-(2-(pyridin-3-yl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45t). 45t (111.85 mg, 41.5%) was prepared from **44** (270.00 mg, 0.58 mmol) and 3-pyridinylboronic acid pinacol ester (152.00 mg, 0.75 mmol) in the same manner as described for **45a**. pale yellow amorphous solid. $[\alpha]^{22}_{D}$ –60.0° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)**:** δ 9.11 (d, *J* =1.6 Hz, 1H), 8.63 (dd, *J* =4.8, 1.6 Hz, 1H), 8.21-8.16 (m, 1H), 7.91 (s, 1H), 7.78 (s, 1H), 7.53-7.43 (m, 1H), 7.37 (m, 1H), 6.84-6.66 (m,, 2H), 5.10 (s, 1H), 4.99-4.83 (m, 2H), 4.16 (d, *J* =15.1 Hz, 1H), 3.85 (d, *J* =15.1 Hz, 1H), 3.44-3.32 (m, 1H), 3.26 (q, *J* =6.8 Hz, 1H), 3.02-2.94 (m, 2H), 2.84-2.75 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 163.97, 162.02, 160.64, 151.95, 143.90, 133.15, 130.58, 130.16, 124.38, 124.28 (2C, overlap), 121.77, 116.00, 113.14, 111.71, 104.11, 78.80, 62.96, 55.93 (2C, overlap), 55.88, 29.64, 6.69. MS (ESI) m/z: 469.1 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{23}H_{23}F_2N_6OS$: 469.1635, Found: 469.1626.

(2*R*,3*R*)-3-(2-(3-fluoropyridin-5-yl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluoroph-enyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45u). 45u (66.22 mg, 63.8%) was prepared from **44** (150.00 mg, 0.32 mmol) and 3-fluoropyridine-5-boronic acid pinacol ester (92.35 mg, 0.42 mmol) in the same manner as described for **45a**. pale yellow solid: mp 75-76℃. $[\alpha]^{22}_{D}$ –58.0° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (t, *J* =1.6 Hz, 1H), 8.49 (d, *J* =2.6 Hz, 1H), 7.96 (t, *J* = 2.2 Hz, 1H), 7.93 (s, 1H), 7.78 (s, 1H), 7.53-7.43 (m, 1H), 6.84-6.66 (m, 2H), 4.99-4.93 (m, 2H), 4.23 (d, *J* =15.1 Hz, 1H), 3.93 (d, *J* =15.0 Hz, 1H), 3.44-3.31 (m, 2H), 3.06-2.97 (m, 2H), 2.91-2.79 (m, 1H), 1.04 (d, *J* =6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.56, 160.03, 158.51, 151.71, 151.16, 144.11, 143.17, 138.82, 130.65, 128.51, 124.76, 124.65 (2C, overlap), 119.81, 111.67, 104.10, 79.22, 63.62, 55.90 (2C, overlap), 55.85, 27.93, 7.37. MS (ESI) m/z: 487.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{23}H_{22}F_3N_6OS$: 487.1528, Found: 487.1525.

(2*R*,3*R*)-3-(2-(3-cyanopyridin-5-yl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluoroph-enyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45v). 45v (29.81 mg, 46.5%) was prepared from **44** (60.00 mg, 0.13 mmol) and 3-cyanopyridine-5-boronic acid pinacol ester (36.21 mg, 0.16 mmol) in the same manner as described for **45a**. pale yellow solid: mp 101-102℃. $[\alpha]^{22}_{D}$ –52.0° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (d, *J* =2.2 Hz, 1H), 8.86 (d, *J* =2.1 Hz, 1H), 8.60-8.36 (m, 1H), 7.89 (s, 1H), 7.78 (s, 1H), 7.56-7.38 (m, 1H), 6.85-6.68 (m, 2H), 5.01-4.83 (m, 2H), 4.23 (d, *J* =15.2 Hz, 1H), 3.90 (d, *J* =15.3 Hz, 0H), 3.47-3.35 (m, 1H), 3.31 (q, *J* = 7.9 Hz, 1H), 3.07-2.89 (m, 1H), 2.88-2.71 (m, 2H), 1.03 (d, *J* =6.8 Hz,

3H).^{13}C NMR (126 MHz, $CDCl_3$): δ 167.06, 160.65, 151.66, 151.10, 149.79, 149.10, 144.31, 132.29, 130.65, 129.68, 129.21, 129.02, 124.71, 124.57 (2C, overlap), 111.59, 104.10, 79.19, 63.62, 55.91 (2C, overlap), 55.87, 27.90, 7.42. MS (ESI) m/z: 494.1 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{24}H_{22}F_2N_7OS$: 494.1575, Found: 494.1585.

(2*R*,3*R*)-3-(2-(2-cyanopyridin-5-yl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluoroph-enyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45w). 45w (65.14 mg, 41.3%) was prepared from **44** (150.00 mg, 0.32 mmol) and 2-cyanopyridine-5-boronic acid pinacol ester (95.63 mg, 0.42 mmol) in the same manner as described for **45a**. pale yellow solid: mp 135-136℃. $[\alpha]^{22}_D$ –53.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (d, *J* = 2.1 Hz, 1H), 8.31 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.89 (s, 1H), 7.78 (s, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.53-7.42 (m, 1H), 6.83-6.69 (m, 2H), 5.06 (s, 1H), 4.97-4.86 (m, 2H), 4.22 (d, *J* = 15.3 Hz, 1H), 3.89 (d, *J* = 15.5 Hz, 1H), 3.45-3.37 (m, 1H), 3.29 (q, *J* = 6.5 Hz, 1H), 3.03-2.95 (m, 2H), 2.88-2.75 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.23, 151.93, 151.67, 148.31, 144.06, 133.53, 133.41, 132.34, 130.48, 128.48, 124.66, 124.55 (2C, overlap), 116.99, 111.46, 104.07, 79.23, 63.54, 55.85 (2C, overlap), 55.80, 27.90, 7.34. MS (ESI) m/z: 494.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{24}H_{22}F_2N_7OS$: 494.1536, Found: 494.1528.

(2*R*,3*R*)-3-(2-(pyrimidin-5-yl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45x). A mixture of **44** (200.00 mg, 0.43 mmol), cesium carbonate (277.10 mg, 0.85 mmol), 5-pyrimidinylboronic acid pinacol ester (105.50 mg, 0.51 mmol) and tetrakis(triphenylphosphine)palladium (0) (98.28 mg, 0.09 mmol) in dioxane (20 ml) and H_2O (10 ml) was degassed and flushed with argon. The mixture was heated at 80 °C for 10 h. The solvent was evaporated under reduced pressure. The residue was diluted with H_2O (30 ml) and extracted with ethyl acetate (50 ml ×2). The combined organic layers were washed with H_2O (30 ml ×2) and brine (30 ml ×2), dried over anhydrous Na_2SO_4, and filtrated, then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH 200:1~100:1) to give **45x** (87.62 mg, 43.8%) as a pale yellow solid: mp 96-98℃. $[\alpha]^{22}_D$ –57.2° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.29-9.13 (m, 3H), 7.89 (s, 1H), 7.78 (s, 1H), 7.57-7.38 (m, 1H), 6.86-6.68 (m, 2H), 4.99-4.87 (m, 2H), 4.21 (d, *J* = 14.9 Hz, 1H), 3.88 (d, *J* = 15.0 Hz, 1H), 3.47-3.21 (m, 2H), 3.09-2.92 (m, 2H), 2.89-2.72 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.87, 158.15, 153.99, 151.77, 151.56, 144.14, 130.67, 129.37, 128.00, 124.72, 124.59 (2C, overlap), 111.73, 104.16, 79.22, 63.65, 55.93 (2C, overlap), 55.87, 27.95, 7.41. MS (ESI) m/z: 470.1 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{22}H_{22}F_2N_7OS$: 470.1575, Found: 470.1577.

(2*R*,3*R*)-3-(2-(2-fluoropyridin-5-yl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45y). 45y (43.56 mg, 42.0%) was prepared from **44** (100.00 mg, 0.21 mmol) and 2-fluoropyridine-5-boronic acid (39.06 mg, 0.28 mmol) in the same manner as described for **45a**. pale yellow solid: mp 85-86℃. $[\alpha]^{22}_D$ –39.2° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 2.5 Hz, 1H), 8.30 (d, *J* = 2.2 Hz, 1H), 7.90 (s, 1H), 7.78 (s, 1H), 7.47 (m, 1H), 7.01 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.83-6.69 (m, 2H), 5.09 (s, 1H), 4.98-4.83 (m, 2H), 4.15 (d, *J* = 14.0 Hz, 1H), 3.84 (d, *J* = 15.0 Hz, 1H), 3.43-3.31 (m, 1H), 3.26 (q, *J* = 6.9 Hz, 1H), 3.00-2.89 (m, 2H), 2.84-2.70 (m, 1H), 1.02 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.50, 162.57, 160.08, 151.29, 150.39, 145.10, 143.69, 138.40, 130.22, 127.76, 124.26, 124.16 (2C, overlap), 111.10, 109.30, 103.71, 78.68, 63.20, 55.46 (2C, overlap),

55.40, 27.50, 6.96. MS (ESI) m/z: 487.1 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{23}H_{22}F_3N_6OS$: 487.1535, Found: 487.1531.

(2*R*,3*R*)-3-(2-(2-methoxypyridin-5-yl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-di-fluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45z). 45z (50.00 mg, 47.8%) was prepared from **44** (100.00 mg, 0.21 mmol) and 2-methoxy-5-pyridinylboronic acid (42.82 mg, 0.28 mmol) in the same manner as described for **45a**. pale yellow solid: mp 68-70℃. $[\alpha]^{22}_D$ – 38.4° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 2.3 Hz, 1H), 8.07 (dd, J = 8.7, 2.5 Hz, 1H), 7.92 (s, 1H), 7.77 (s, 1H), 7.54-7.42 (m, 1H), 6.83-6.68 (m, 3H), 5.11 (s, 1H), 4.97-4.83 (m, 2H), 4.18-4.04 (m, 1H), 3.97 (s, 3H), 3.78 (d, J = 14.8 Hz, 1H), 3.33-3.26 (m, 1H), 3.22 (q, J = 6.8 Hz, 1H), 2.97-2.85 (m, 2H), 2.82-2.60 (m, 1H), 1.01 (d, J = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.95, 162.50, 151.16, 150.17, 145.09, 144.16, 136.46, 130.70, 126.76, 124.75, 124.58 (2C, overlap), 123.76, 111.63, 111.18, 104.18, 78.96, 63.69, 55.95 (2C, overlap), 55.88, 53.84, 27.93, 7.46. MS (ESI) m/z: 499.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{24}H_{25}F_2N_6O_2S$: 499.1625, Found: 499.1622.

(2*R*,3*R*)-3-(2-(2-methylpyrimidin-5-yl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-di-fluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45aa). 45aa (23.85 mg, 46.3%) was prepared from **44** (50.00 mg, 0.11 mmol) and 2-methylpyrimidine-5-boronic acid pinacol (28.60 mg, 0.13 mmol) in the same manner as described for **45a**. pale yellow solid: mp 76-78℃. $[\alpha]^{22}_D$ –56.0° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 2H), 7.89 (s, 1H), 7.77 (s, 1H), 7.53-7.40 (m, 1H), 6.84-6.68 (m, 2H), 5.08 (s, 1H), 4.97-4.84 (m, 2H), 4.17 (d, J = 15.1 Hz, 1H), 3.85 (d, J = 15.1 Hz, 1H), 3.45-3.31 (m, 1H), 3.26 (q, J = 13.7, 6.8 Hz, 1H), 3.01-2.90 (m, 2H), 2.87-2.67 (m, 4H), 1.01 (d, J = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.82, 158.76, 154.07, 151.79, 151.23, 143.14, 130.72, 128.71, 125.05, 124.74, 124.61 (2C, overlap), 111.64, 104.18, 79.20, 63.66, 55.94 (2C, overlap), 55.87, 27.98, 26.02, 7.41. MS (ESI) m/z: 484.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{23}H_{24}F_2N_7OS$: 484.1712, Found: 484.1708.

(2*R*,3*R*)-3-(2-(2-methoxypyrimidin-5-yl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-di-fluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (45ab). 45ab (33.76 mg, 42.3%) was prepared from **44** (75.00 mg, 0.16 mmol) and 2-methoxypyrimidine-5-boronic acid pinacol (45.30 mg, 0.19 mmol) in the same manner as described for **45a**. pale yellow solid: mp 76-78℃. $[\alpha]^{22}_D$ –45.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (s, 2H), 7.95 (s, 1H), 7.78 (s, 1H), 7.48 (dd, J = 15.7, 8.9 Hz, 1H), 6.84-6.67 (m, 2H), 5.11 (s, 1H), 5.02-4.86 (m, 2H), 4.15 (d, J = 8.2 Hz, 1H), 4.02 (s, 3H), 3.84 (d, J = 15.0 Hz, 1H), 3.43-3.31 (m, 1H), 3.26 (d, J = 6.8 Hz, 1H), 3.01-2.91 (m, 2H), 2.88-2.73 (m, 1H), 1.03 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.89, 158.82, 156.88, 151.74, 150.82, 144.16, 130.76, 127.77, 124.74, 124.45 (2C, overlap), 122.45, 111.72, 104.19, 79.17, 63.65, 55.92 (2C, overlap), 55.86, 55.42, 27.95, 7.43. MS (ESI) m/z: 500.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{23}H_{24}F_2N_7O_2S$: 500.1626, Found: 500.1618.

(2*R*,3*R*)-3-(2-(pyrimidin-5-yl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluoro-phenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol, disulfate salt (58). A solution of **45x** (400.00 mg, 0.85 mmol) in ethyl acetate (10 ml) was treated with a solution of sulfuric acid (179.00 mg, 1.79 mmol) in ethyl acetate (2.0 ml) at room temperature , resulting in the slow appearance of fine white precipitate. After complete precipitation, the title product **58** (435.0mg, 72.8%) was

obtained upon filtration. white solid: mp 151-155℃. $[\alpha]^{22}_{D}$ –6.8° (*c* 0.125, DMF). ^{1}H NMR (400 MHz, D_2O) δ 9.26 (s, 2H), 9.23 (s, 1H), 8.91 (s, 1H), 8.21 (s, 1H), 7.73-7.53 (m, 1H), 7.14 (m, 2H), 5.18 (q, *J* = 14.9 Hz, 2H), 4.83-4.75 (m, 2H), 4.31-4.23 (m, 1H), 3.78-2.98 (m, 4H), 1.55 (d, *J* = 7.1 Hz, 2H). ^{13}C NMR (126 MHz, D_2O) δ 162.57, 161.42, 157.50, 154.26, 148.22, 143.61, 129.35, 129.33 (2C, overlap), 127.11, 123.67, 119.43, 112.59, 105.41, 75.82, 68.36, 56.16 (2C, overlap), 56.12, 23.40, 8.78. Anal. ($C_{22}H_{21}F_2N_7OS\cdot 2H_2SO_4\cdot 2H_2O$) C, 37.66; H, 4.17; N, 13.97; S, 13.71. Found: C, 37.72; H, 4.25; N, 14.06; S, 13.66.

N-Boc-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (47). A solution of 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine hydrochloride **46** (22.83 g, 0.13 mol) in dichloromethane (300 ml) was treated with triethylamine (26.29 g, 0.26 mol), Di-*tert*-butyl dicarbonate (31.19 g, 0.14 mol). the mixture was stirred at room temperature for 6 h, then extracted with dichloromethane (200 ml) and water (100 ml). The combined organic layers were washed with brine (100 ml), dried over anhydrous Na_2SO_4, and filtrated, and the solvent was evaporated under reduced pressure. The residue solid were collected and washed with 50ml petroleum/ethyl acetate (10:1) to give **47** (28.69 g, 92.3%) as a white solid. Mp: 60-63 °C. ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.12 (d, *J* = 5.1 Hz, 1H), 6.78 (d, *J* = 5.1 Hz, 1H), 4.50 (s, 2H), 3.72 (t, *J* =5.4 Hz, 2H), 2.84 (t, *J* =5.4 Hz, 2H), 1.48 (s, 9H). MS (ESI) m/z: 240.1 $(M+1)^+$.

2-bromo-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrobromide (48). Compound **47** (19.15 g, 80.0 mmol) was dissolved in chloroform (200 ml). Bromine (14.10 g, 88.0 mmol) was slowly added dropwise at 0 °C. The reaction mixture was allowed to warm to 30 °C and stirred for 12 hours. The slowly precipitated solid was filtered and washed with ethyl acetate (30 ml×2). White solid were collected and dried under reduced pressure to afford 2-bromo-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrobromide (12.30 g, 51.6%). Mp: 186-188°C. ^{1}H NMR (400 MHz, CD_3OD) δ 6.95 (s, 1H), 4.24 (s, 2H), 3.54 (t, *J* = 6.2 Hz, 2H), 3.07 (t, *J* = 6.2 Hz, 2H). MS (ESI) m/z: 218.0 $(M+1)^+$.

(2*R*,3*R*)-3-(2-bromo-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (49). To a solution of epoxide **10** (1.00 g, 4.00 mmol) in 20 ml of CH_3CN was added **48** (3.56 g, 12.00 mmol) and $LiClO_4$ (1.28 g, 12.00 mmol). The reaction was stirred at 80 °C for 24 h. After cooling, the solvent was evaporated under reduced pressure. The residue was diluted with H_2O (30 ml) and extracted with ethyl acetate (30 ml ×2). The combined organic layers were washed with H_2O (15 ml) and brine (15 ml), dried over anhydrous Na_2SO_4, and filtrated, then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH 200:1~100:1) to give **49** (1.61 g, 86.0%) as a white solid: mp 60-61 °C. $[\alpha]^{22}_{D}$ –52.0°(*c* 0.125, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.76 (s, 1H), 7.51-7.43 (m, 1H), 6.81-6.70 (m, 2H), 6.67 (s, 1H), 5.15 (s, 1H), 4.86 (q, *J* = 14.7 Hz, 2H), 3.79 (d, *J* = 14.3 Hz, 1H), 3.53 (d, *J* = 14.3 Hz, 1H), 3.29-3.18 (m, 1H), 3.11 (q, *J* = 6.8 Hz, 1H), 2.85-2.54 (m, 3H), 0.99 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.52, 144.13, 135.17, 134.87, 130.61, 127.82, 124.69, 124.59 (2C, overlap), 111.44, 109.31, 104.05, 78.67, 63.52, 55.79 (2C, overlap), 55.73, 26.05, 7.09. MS (EI) m/z: 468 (M^+). HRMS (EI): Anal. Calcd for $C_{19}H_{19}BrF_2N_4OS$: 468.0428, Found: 468.0436.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-phenyl-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (50a). A mixture of **49** (100.00 mg, 0.21mmol), Cesium

carbonate (139.23 mg, 0.43 mmol), phenylboronic acid (33.91 mg, 0.28 mmol) and tetrakis(triphenylphosphine)palladium (0) (24.69 mg, 0.02 mmol) in dioxane (12 ml) and H_2O (4 ml) was degassed and flushed with argon. The mixture was heated at 80 °C for 10 h. The solvent was evaporated under reduced pressure. The residue was diluted with H_2O (25 ml) and extracted with ethyl acetate (30 ml ×2). The combined organic layers were washed with H_2O (15 ml ×2) and brine (15 ml ×2), dried over anhydrous Na_2SO_4, and filtrated, then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH 200:1~100:1) to give **50a** (51.00 mg, 52.0%) as a white solid: mp 128-129 °C. $[\alpha]^{22}_D$ –48.8° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.95 (s, 1H), 7.78 (s, 1H), 7.56-7.50 (m, 3H), 7.41-7.31 (m, 2H), 7.28-7.21 (m, 1H), 6.93 (s, 1H), 6.78-6.71 (m, 2H), 5.25 (s, 1H), 4.91-4.83 (m, 2H), 3.86 (d, *J* = 14.4 Hz, 1H), 3.60 (d, *J* = 14.6 Hz, 1H), 3.21-3.12 (m, 2H), 2.93-2.82 (m, 2H), 2.68-2.57 (m, 1H), 1.05 (d, *J* = 5.0 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$): δ 151.51, 144.28, 141.65, 135.32, 134.48, 133.41, 130.76, 128.80, 127.19, 125.49, 124.82, 124.69 (2C, overlap), 121.11, 111.59, 104.10, 78.45, 63.69, 55.86 (2C, overlap), 55.80, 26.25, 7.27. MS (ESI) m/z: 467.1 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{25}H_{25}F_2N_4OS$: 467.1717, Found: 467.1714.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(4-fluorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (50b). 50b (65.15 mg, 49.8%) was prepared from **49** (125.00 mg, 0.27 mmol) and 4-fluorophenylboronic acid (48.62 mg, 0.35 mmol) in the same manner as described for **50a**. white solid: mp 108-109℃. $[\alpha]^{22}_D$ –57.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$)：δ 7.95 (s, 1H), 7.78 (s, 1H), 7.56-7.43 (m, 3H), 7.10-6.99 (m, 2H), 6.85 (s, 1H), 6.83-6.71 (m, 2H), 5.25 (s, 1H), 4.91-4.86 (m, 2H), 3.85 (d, *J* = 16.2 Hz, 1H), 3.59 (d, *J* =14.7 Hz, 1H), 3.26-3.18 (m, 1H), 3.17-3.12 (m, 1H), 2.88-2.86 (m, 3H), 1.04 (d, *J* = 5.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.51, 144.26, 140.53, 135.39, 133.39, 130.78, 127.14, 127.07, 124.78, 124.67 (2C, overlap), 121.11, 115.81, 115.64, 111.48, 104.10, 78.53, 63.66, 55.85 (2C, overlap), 55.79, 26.21, 7.23. MS (ESI) m/z: 485.1 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{25}H_{24}F_3N_4OS$: 485.1623, Found: 485.1619.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(4-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (50c). 50c (49.76 mg, 43.6%) was prepared from **49** (100.00 mg, 0.21 mmol) and 4-(trifluoromethyl) phenylboronic acid (53.21 mg, 0.28 mmol) in the same manner as described for **50a**. pale yellow solid: mp 73-74℃. $[\alpha]^{22}_D$ –46.2° (*c* 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)：δ 7.94 (s, 1H), 7.78 (s, 1H), 7.65-7.57 (m, 4H), 7.55-7.45 (m, 1H), 7.02 (s, 1H), 6.84-6.70 (m, 2H), 5.20 (s, 1H), 5.01-4.86 (m, 2H), 3.89 (d, *J* = 14.6 Hz, 1H), 3.62 (d, *J* =14.5 Hz, 1H), 3.29- 3.12 (m, 2H), 2.91-2.85 (m, 2H), 2.70-2.61 (m, 1H), 1.04 (d, *J* = 5.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.57, 144.23, 139.75, 137.84, 135.77, 135.11, 130.71, 128.95, 128.69, 125.82, 125.39, 124.77, 124.66 (2C, overlap), 122.51, 111.59, 104.11, 78.66, 63.65, 55.87 (2C, overlap), 55.81, 26.43, 7.19. MS (ESI) m/z: 535.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{26}H_{24}F_5N_4OS$: 535.1591, Found: 535.1590.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(4-chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (50d). 50d (46.58 mg, 43.6%) was prepared from **49** (100.00 mg, 0.21 mmol) and 4-chlorophenylboronic acid (43.34 mg, 0.28 mmol) in the same manner as described for **50a**. white solid: mp 98-99℃. $[\alpha]^{22}_D$ –37.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR

(300 MHz, $CDCl_3$)：δ 7.94 (s, 1H), 7.78 (s, 1H), 7.51-7.43(m, 3H), 7.31 (d, J = 8.6 Hz, 2H), 6.90 (s, 1H), 6.83-6.68 (m, 2H), 4.96-4.86 (m, 2H), 3.86 (d, J = 14.3 Hz, 1H), 3.60 (d, J = 14.4 Hz, 1H), 3.31-3.12 (m, 2H), 2.89-2.61 (m, 3H), 1.04 (d, J = 5.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.50, 144.25, 140.27, 135.51, 133.90, 133.00, 132.83, 130.72, 128.93, 126.61, 124.76, 124.68 (2C, overlap), 121.48, 111.44, 104.11, 78.55, 63.66, 55.86 (2C, overlap), 55.81, 26.26, 7.23. MS (EI) m/z: 500 (M^+). HRMS (EI): Anal. Calcd for $C_{25}H_{23}F_2N_4OSCl$: 500.1236, Found: 500.1239.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(4-methylphenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (50e). 50e (63.20 mg, 61.6%) was prepared from **49** (100.00 mg, 0.21 mmol) and 4-methylphenylboronic acid (37.78 mg, 0.28 mmol) in the same manner as described for **50a**. white solid: mp 108-109℃. $[\alpha]^{22}_D$ –50.4° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$)：δ 7.96 (s, 1H), 7.78 (s, 1H), 7.54-7.50 (m 1H), 7.42 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 6.88 (s, 1H), 6.83-6.71 (m, 2H), 4.99-4.86 (m, 2H), 3.84 (d, J = 14.3 Hz, 1H), 3.59 (d, J = 14.3 Hz, 1H), 3.24-3.08 (m, 2H), 2.88-2.83 (m, 2H), 2.65-2.58 (m,1H), 2.35 (s, 3H), 1.05 (d, J = 4.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.49, 144.29, 141.84, 137.06, 135.19, 132.80, 131.70, 130.73, 129.45, 125.42, 124.80, 124.69 (2C, overlap), 120.58, 111.42 104.12, 78.43, 63.70, 55.87 (2C, overlap), 55.81, 26.23, 21.12, 7.28. MS (EI) m/z: 480 (M^+). HRMS (EI): Anal. Calcd for $C_{26}H_{26}F_2N_4OS$: 480.1786, Found: 480.1790.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(4-cyanophenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (50f). 50f (46.92 mg, 52.6%) was prepared from **49** (85.00 mg, 0.18 mmol) and 4-cyanophenylboronic acid pinacol ester (52.65 mg, 0.24 mmol) in the same manner as described for **50a**. white solid: mp 78-79℃. $[\alpha]^{22}_D$ –45.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$)：δ 7.92 (s, 1H), 7.78 (s, 1H), 7.67-7.58 (m, 4H), 7.51-7.46 (m, 1H), 7.06 (s, 1H), 6.81-6.76 (m, 2H), 4.91-4.87 (m, 2H), 3.90 (d, J = 15.0 Hz, 1H), 3.63 (d, J = 13.9 Hz, 1H), 3.23-3.17 (m, 2H), 2.91-2.61 (m, 3H), 1.03 (d, J = 5.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.58, 144.20, 139.16, 138.74, 136.19, 136.08, 132.64, 130.66, 125.48, 124.78, 124.67 (2C, overlap), 123.22, 118.89, 111.45, 110.05, 104.13, 78.70, 63.62, 55.86 (2C, overlap), 55.80, 26.39, 7.18. MS (EI) m/z: 491 (M^+). HRMS (EI): Anal. Calcd for $C_{26}H_{23}F_2N_5OS$: 491.1616, Found: 491.1609.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(3-methylphenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (50g). 50g (68.45 mg, 55.6%) was prepared from **49** (120.00 mg, 0.26 mmol) and 3-methylphenylboronic acid (41.86 mg, 0.31 mmol) in the same manner as described for **50a**. white solid: mp 68-70℃. $[\alpha]^{22}_D$ –31.2° (*c* 0.125, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.80 (s, 1H), 7.58-7.49 (m, 1H), 7.36 (d, J = 8.6 Hz, 2H), 7.30-7.22 (m, 1H), 7.09 (d, J = 7.5 Hz, 1H), 6.93 (s, 1H), 6.84-6.73 (m, 2H), 5.30 (s, 1H), 4.90 (q, J = 14.6 Hz, 2H), 3.86 (d, J = 14.2 Hz, 1H), 3.61 (d, J = 14.2 Hz, 1H), 3.29-3.08 (m, 2H), 2.97-2.75 (m, 2H), 2.67-2.56 (m, 1H), 2.39 (s, 3H), 1.06 (d, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.50, 144.30, 141.83, 138.43, 135.24, 134.40, 133.21, 130.75, 128.70, 128.02, 126.24, 124.80, 124.69 (2C, overlap), 122.66, 121.01, 111.49 104.13, 78.46, 63.71, 55.87 (2C, overlap), 55.82, 26.25, 21.43, 7.29. MS (EI) m/z: 480 (M^+). HRMS (EI): Anal. Calcd for $C_{26}H_{26}F_2N_4OS$: 480.1806, Found: 480.1812.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(3-fluorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (50h). 50h (52.96 mg, 51.2%) was prepared from **49** (100.00 mg, 0.21 mmol) and 3-fluorophenylboronic acid (35.90 mg, 0.26 mmol) in the same manner as described for **50a**. white solid: mp 71-72℃. $[\alpha]^{22}_{D}$ –32.0° (*c* 0.125, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.79 (s, 1H), 7.56-7.48 (m, 1H), 7.34-7.30 (m, 2H), 7.26-7.21 (m, 1H), 6.99-6.92 (m, 2H), 6.84-6.73 (m, 2H), 5.24 (s, 1H), 4.90 (q, *J* = 14.7 Hz, 2H), 3.87 (d, *J* = 14.2 Hz, 1H), 3.62 (d, *J* = 14.3 Hz, 1H), 3.29-3.22 (m, 1H), 3.16 (q, *J* = 6.8 Hz, 1H), 2.96-2.87 (m, 1H), 2.86-2.78 (m, 1H), 2.69-2.57 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.54, 144.25, 140.19, 136.65, 136.59, 135.49, 134.23, 130.71, 130.30, 124.81, 124.71 (2C, overlap), 121.86, 121.12, 113.97, 112.12, 111.58, 104.13, 78.60, 63.67, 55.88 (2C, overlap), 55.82, 26.27, 7.23. MS (ESI) m/z: 485.1 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{25}H_{24}F_3N_4OS$: 485.1612, Found: 485.1615.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(3-cyanophenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (50i). 50i (53.73 mg, 51.2%) was prepared from **49** (100.00 mg, 0.21 mmol) and 3-cyanophenylboronic acid pinacol ester (58.75 mg, 0.26 mmol) in the same manner as described for **50a**. white solid: mp 68-68℃. $[\alpha]^{22}_{D}$ –18.4° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$)：δ 7.92 (s, 1H), 7.78 (s, 1H), 7.75-7.62 (m, 4H), 7.47-7.40 (m, 1H), 7.06 (s, 1H), 6.83-6.71 (m, 2H), 4.93-4.85 (m, 2H), 3.91 (d, *J* = 14.0 Hz, 1H), 3.64 (d, *J* = 13.9 Hz, 1H), 3.26-3.15 (m, 2H), 2.90-2.66 (m, 3H), 1.01 (d, *J* = 5.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.56, 144.22, 138.75, 135.52, 135.27, 132.85, 130.70, 130.24, 129.67, 129.74, 128.65, 124.77, 124.69 (2C, overlap), 122.53, 118.60, 113.03, 111.53, 104.13, 78.68, 63.64, 55.90 (2C, overlap), 55.84, 26.33, 7.21. MS (EI) m/z: 491 (M^+). HRMS (EI): Anal. Calcd for $C_{26}H_{23}F_2N_5OS$: 491.1623, Found: 491.1618.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(3-chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (50j). 50j (46.50 mg, 43.5%) was prepared from **49** (100.00 mg, 0.21 mmol) and 3-chlorophenylboronic acid (40.00 mg, 0.26 mmol) in the same manner as described for **50a**. white solid: mp 78-80℃. $[\alpha]^{22}_{D}$ –33.6° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.78 (s, 1H), 7.54-7.46 (m, 2H), 7.42-7.37 (m, 1H), 7.30-7.23 (m, 1H), 7.23-7.18 (m, 1H), 6.93 (s, 1H), 6.83-6.72 (m, 2H), 5.23 (s, 1H), 4.85 (q, *J* = 14.7 Hz, 2H), 3.83 (d, *J* = 14.6 Hz, 1H), 3.57 (d, *J* = 14.0 Hz, 1H), 3.28-3.18 (m, 1H), 3.13 (q, *J* = 6.9 Hz, 1H), 2.96-2.74 (m, 2H), 2.68-2.54 (m, 1H), 1.02 (d, 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.53, 144.25, 139.90, 136.24, 135.54, 134.68, 134.35, 130.73, 130.03, 127.04, 125.35, 124.78, 124.68 (2C, overlap), 123.56, 121.91, 111.58, 104.13, 78.60, 63.67, 55.88 (2C, overlap), 55.82, 26.28, 7.23. MS (EI) m/z: 500 (M^+). HRMS (EI): Anal. Calcd for $C_{25}H_{23}F_2N_4OSCl$: 500.1226, Found: 500.1221.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(3-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (50k). 50k (58.51 mg, 46.6%) was prepared from **49** (110.00 mg, 0.21 mmol) and 3-(trifluoromethyl) phenylboronic acid (49.13 mg, 0.26 mmol) in the same manner as described for **50a**. pale yellow solid: mp 70-71℃. $[\alpha]^{22}_{D}$ –32.0° (*c* 0.125, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.79 (d, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 7.4 Hz, 1H), 7.57-7.45 (m, 3H), 7.02 (s, 1H), 6.85-6.69 (m, 2H), 5.28 (s, 1H), 4.91 (q, *J* = 14.6 Hz, 2H), 3.90 (d, *J* = 14.2 Hz, 1H), 3.63 (d, *J* = 14.3 Hz, 1H), 3.32-3.23 (m, 1H), 3.17 (q, *J* = 6.7 Hz, 1H), 2.99-2.88 (m, *J* = 19.7, 11.7 Hz, 1H), 2.88-2.82 (m, 1H), 2.71-2.59 (m, 1H),

1.06 (d, J = 6.0 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$): δ 151.54, 144.23, 139.80, 135.69, 135.28, 134.66, 130.70, 129.31, 128.55, 125.06, 124.78, 124.71 (2C, overlap), 123.60, 122.89, 122.19, 122.01, 111.50, 104.10, 78.65, 63.66, 55.89 (2C, overlap), 55.83, 26.29, 7.21. MS (ESI) m/z: 535.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{26}H_{24}F_5N_4OS$: 535.1563, Found: 535.1558.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(pyrimidin-5-yl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (50l). 50l (66.00 mg, 52.2%) was prepared from **49** (125.00 mg, 0.27 mmol) and 5-pyrimidinylboronic acid pinacol ester (71.52 mg, 0.35 mmol) in the same manner as described for **50a**. pale yellow solid: mp 96-98℃. $[\alpha]^{22}_D$ –38.4° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10-9.03 (m, 1H), 8.84 (d, J = 10.6 Hz, 2H), 7.90 (d, J = 7.9 Hz, 1H), 7.75 (d, J = 10.2 Hz, 1H), 7.48 (m, 1H), 7.03 (s, 1H), 6.85-6.69 (m, 2H), 5.15 (s, 1H), 4.88 (q, J = 14.7 Hz, 2H), 3.91 (d, J = 14.2 Hz, 1H), 3.64 (d, J = 14.4 Hz, 1H), 3.35-3.25 (m, 1H), 3.16 (q, J = 6.9 Hz, 1H), 2.98-2.82 (m, 2H), 2.74-2.60 (m, 1H), 1.02 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.89, 152.95, 151.62, 144.18, 136.39, 136.21, 133.31, 130.66, 128.78, 124.79, 124.66 (2C, overlap), 123.37, 111.53, 104.13, 78.80, 63.60, 55.88 (2C, overlap), 55.83, 26.38, 7.16. MS (ESI) m/z: 469.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{23}H_{23}F_2N_6OS$: 469.1526, Found: 469.1521.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(2-cyanopyridin-5-yl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (50m). 50m (57.04 mg, 45.2%) was prepared from **49** (120.00 mg, 0.26 mmol) and 2-cyanopyridine-5-boronic acid pinacol ester (70.15 mg, 0.31 mmol) in the same manner as described for **50a**. white solid: mp 180-181℃. $[\alpha]^{22}_D$ –44.0° (*c* 0.125, $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$)：δ 8.86 (d, J = 2.2 Hz, 1H), 7.90 (s, 1H), 7.87 (dd, J = 8.2, 2.3 Hz, 1H), 7.78 (s, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.53-7.43 (m, 1H), 7.13 (s, 1H), 6.69-6.73 (m, 2H), 4.96-4.82 (m, 2H), 3.94 (d, J = 14.6 Hz, 1H), 3.65 (d, J = 14.7 Hz, 1H), 3.23-3.20 (m, 2H), 2.91-2.65 (m, 3H), 1.02 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.63, 147.39, 144.16, 137.73, 136.58, 135.33, 133.61, 132.19, 131.02, 130.66, 128.50, 124.77, 124.64 (2C, overlap), 124.40, 117.35, 111.61, 104.12, 78.90, 63.58, 55.88 (2C, overlap), 55.82, 26.48, 7.14. MS (ESI) m/z: 493.1 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{25}H_{23}F_2N_6OS$: 493.1622, Found: 493.1627.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(pyridin-4-yl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (50n). 50n (65.15 mg, 51.6%) was prepared from **49** (125.00 mg, 0.27 mmol) and 4-pyridinylboronic acid (42.68 mg, 0.35 mmol) in the same manner as described for **50a**. pale yellow solid: mp 90-92℃. $[\alpha]^{22}_D$ –42.4° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 5.3 Hz, 2H), 7.91 (s, 1H), 7.76 (s, 1H), 7.56-7.43 (m, 1H), 7.39 (d, J = 6.1 Hz, 2H), 7.12 (s, 1H), 6.83-6.63 (m, 2H), 4.88 (q, J = 14.7 Hz, 2H), 3.89 (d, J = 13.9 Hz, 1H), 3.62 (d, J = 14.4 Hz, 1H), 3.34-3.22 (m, 1H), 3.16 (q, J = 6.7 Hz, 1H), 2.96-2.77 (m, 2H), 2.72-2.54 (m, 1H), 1.01 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.59, 149.79, 144.20, 141.86, 138.02, 136.68, 136.09, 130.69, 124.76, 124.69 (2C, overlap), 123.72, 119.41, 111.53, 104.12, 78.79, 63.62, 55.88 (2C, overlap), 55.82, 26.45, 7.19. MS (ESI) m/z: 468.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{24}H_{24}F_2N_5OS$: 468.1636, Found: 468.1629.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(pyridin-3-yl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (50o). 50o (55.85 mg, 44.3%) was prepared from **49** (125.00 mg, 0.27 mmol) and 3-pyridinylboronic acid pinacol ester (71.20 mg, 0.35 mmol) in the

same manner as described for **50a**. pale yellow solid: mp 85-86℃. $[\alpha]^{22}_{D}$ –30.4° (*c* 0.125, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.46 (d, *J* = 4.2 Hz, 1H), 7.93 (s, 1H), 7.78 (d, *J* = 12.1 Hz, 2H), 7.55-7.43 (m, 1H), 7.31-7.23 (m, 1H), 6.98 (s, 1H), 6.83-6.68 (m, 2H), 4.88 (q, *J* = 14.7 Hz, 2H), 3.88 (d, *J* = 14.1 Hz, 1H), 3.62 (d, *J* = 14.4 Hz, 1H), 3.30-3.21 (m, 1H), 3.16 (q, *J* = 6.7 Hz, 1H), 2.96-2.78 (m, 2H), 2.72-2.55 (m, 1H), 1.02 (d, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.56, 147.89, 146.35, 144.24, 137.48, 135.71, 134.95, 132.65, 130.70, 130.59, 124.75, 124.64 (2C, overlap), 123.65, 122.35, 111.52, 104.13, 78.63, 63.66, 55.88 (2C, overlap), 55.82, 26.28, 7.24. MS (ESI) m/z: 468.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{24}H_{24}F_2N_5OS$: 468.1626, Found: 468.1618.

2-(thiophen-3-yl) ethanamine hydrochloride (52). Borane methyl sulfide complex (30.60 ml, 61.21 mmol) was add slowly to a solution of thiophen-3-yl-acetonitrile (3.77 g, 30.61 mmol) in tetrahedrofuran (60ml) at 0 °C. The resulting mixture was heated under reflux for 12 hours. Then the reaction mixture was cooled to room temperature. Slowly quench the reaction with methanol (20 ml) until no foaming is observed. To this mixture slowly add hydrogen chloride (10 ml) then stir the mixture at reflux for 30 min before concentrating *in vacuo*. Add methanol (20 ml×2) to the mixture and concentrat under reduced pressure, residue solid were collected and washed with MTBE (30ml×2) to give **52** (3.93 g, 78.5%) as white solid: mp 200-204 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (dd, *J* = 5.0, 2.9 Hz, 1H), 7.24-7.21 (m, *J* = 2.9, 1.3 Hz, 1H), 7.04 (dd, *J* = 5.0, 1.3 Hz, 1H), 3.18 (t, *J* = 7.3 Hz, 2H), 2.99 (t, *J* = 7.6 Hz, 2H). MS (ESI) m/z: 128.1 $(M + 1)^+$.

N-*tert*-butoxycarbonyl- 2-(3-thienyl) ethylamine (53). A mixture of compound **52** (0.65 g, 3.98 mmol), K_2CO_3 (1.10 g, 7.98 mmol), Di-*tert*-butyl dicarbonate (0.96 g, 4.38 mmol) and THF/H_2O(30ml/10ml) was stirred at room temperature for 6 h. The solvent was evaporated under reduced pressure then extracted with ethyl acetate (30 ml×2) and water (20 ml). The combined organic layers were washed with brine (20 ml), dried over anhydrous Na_2SO_4, and filtrated, and the solvent was evaporated under reduced pressure. The resulting product was purified by silica gel column chromatography (petroleum: ethyl acetate 30:1~10:1) to give **53** (0.52 g, 57.3 %) as a white solid. Mp: 45-48 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.00 (d, *J* = 1.7 Hz, 1H), 6.95 (d, *J* = 4.9 Hz, 1H), 4.57 (s, 1H), 3.37 (t, *J* = 6.9 Hz, 2H), 2.82 (t, *J* = 6.9 Hz, 2H), 1.43 (s, 9H). MS (ESI) m/z: 228.1 $(M + 1)^+$.

6-*tert*-butoxycarbonyl-4,5,6,7-tetrahydrothieno[2, 3-*c*]pyridine (54). A solution of compound **53** (0.41 g, 1.81 mmol), powdered paraformaldehyde (0.11 g, 3.61 mmol) and p-toluenesulfonic acid monohydrate (17.17 mg, 0.10 mmol) in 50 ml of toluene was refluxed under dehydrating conditions for 2 hours. The reaction mixture was cooled to room temperature, the solvent was evaporated under reduced pressure, then extracted with ethyl acetate (30 ml×2) and water (20 ml). The combined organic layers were washed with aqueous sodium hydrogen carbonate (30 ml) and brine (20 ml). The organic layer was dried over anhydrous Na_2SO_4, and filtrated, and the solvent was evaporated under reduced pressure. The resulting product was purified by silica gel column chromatography (petroleum: ethyl acetate 30:1~20:1) to give **54** (0.33 g, 76.0%) as a white solid. Mp: 52-55 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 5.0 Hz, 1H), 6.79 (d, *J* = 5.0 Hz, 1H), 4.63 (s, 2H), 3.68 (s, 2H), 2.71 (s, 2H), 1.48 (s, 9H). MS (ESI) m/z: 240.1 $(M + 1)^+$.

2-bromo-4,5,6,7-tetrahydrothieno[2,3-*c*] pyridine hydrobromide (55). Under nitrogen flow, bromine (0.22 g, 1.38 mmol) was added to a stirred solution of compound **54** (0.30 g, 1.25 mmol) in $CHCl_3$ (5 ml) at 0 °C. After addition, the reaction was stirred at room temperature for 12 h. The resultant precipitate was collected by filtration, washed with diethyl ether then dried under vacuum to afford title compound as an off-white solid (0.24 g, 65.0%). Mp: 226-228 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 9.12 (s, 1H), 7.08 (s, 1H), 4.27 (s, 2H), 3.36 (t, J = 6.2 Hz, 2H), 2.82 (t, J = 6.0 Hz, 2H). MS (ESI) m/z: 218.0 $(M + 1)^+$.

(2*R*, 3*R*)-3-(2-bromo-4, 5-dihydrothieno[2, 3-*c*]pyridin-6(7*H*)-yl)-2-(2, 4-difluorophenyl)-1-(1*H*-1, 2, 4-triazol-1-yl)butan-2-ol (56). To a solution of epoxide **10** (62.80 mg, 0.25 mmol) in 10 ml of CH_3CN was added **55** (148.56 mg, 0.50 mmol) and $LiClO_4$ (53.20 mg, 0.50 mmol). The reaction was stirred at 80 °C for 24 h. After cooling, the solvent was evaporated under reduced pressure. After cooling, the solvent was evaporated under reduced pressure. The residue was diluted with H_2O (10 ml) and extracted with ethyl acetate (20 ml ×2). The combined organic layers were washed with H_2O (10 ml) and brine (10 ml), dried over anhydrous Na_2SO_4, and filtrated, then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH 200:1~100:1) to give **56** (65.58 mg, 56.0%) as a pale yellow solid: mp 86-88 °C. $[\alpha]^{22}_D$ –56.0°(*c* 0.125, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.78 (s, 1H), 7.53-7.45 (m, 1H), 6.80 (m, 2H), 6.75 (s, 1H), 4.89 (q, J = 14.7 Hz, 2H), 3.92 (d, J = 14.0 Hz, 1H), 3.63 (d, J = 14.6 Hz, 1H), 3.15 (m, 2H), 2.70-2.57 (m, 3H), 1.01 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.60, 144.24, 135.11, 134.58, 130.74, 129.66, 124.78, 124.64 (2C, overlap), 111.58, 109.36, 104.17, 78.80, 63.82, 55.91 (2C, overlap), 55.88, 26.40, 7.35. MS (ESI) m/z: 469.4 $(M+1)^+$. HRMS (EI): Anal. Calcd for $C_{19}H_{20}BrF_2N_4OS$: 469.0509, Found: 469.0502.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(pyridin-4-yl)-4,5-dihydrothieno[2,3-*c*]pyridin-6(7*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (57a). A mixture of **56** (120.00 mg, 0.26mmol), Cesium carbonate (169.43 mg, 0.52 mmol), 4-pyridinylboronic acid (40.26 mg, 0.33 mmol) and tetrakis(triphenylphosphine)palladium (0) (29.63 mg, 0.02 mmol) in dioxane (10 ml) and H_2O (4 ml) was degassed and flushed with argon. The mixture was heated at 80 °C for 10 h. The solvent was evaporated under reduced pressure. The residue was diluted with H_2O (20 ml) and extracted with ethyl acetate (30 ml ×2). The combined organic layers were washed with H_2O (15 ml ×2) and brine (15 ml ×2), dried over anhydrous Na_2SO_4, and filtrated, then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH 200:1~100:1) to give **57a** (63.70 mg, 53.2%) as a pale yellow solid: mp 116-118 °C. $[\alpha]^{22}_D$ –24.0° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 6.2 Hz, 2H), 7.92 (s, 1H), 7.78 (s, 1H), 7.52-7.44 (m, 1H), 7.39 (d, J = 6.6 Hz, 2H), 7.20 (s, 1H), 6.82-6.70 (m, 2H), 4.90 (q, J = 14.9 Hz, 2H), 4.05 (d, J = 14.9 Hz, 1H), 3.76 (d, J = 15.0 Hz, 1H), 3.29-3.13 (m, 2H), 2.96-2.68 (m, 3H), 1.02 (d, J = 5.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.60, 148.10, 146.54, 144.26, 137.30, 132.68, 130.76, 130.56, 124.77, 124.66 (2C, overlap), 124.19, 123.67, 111.51, 104.16, 78.73, 63.85, 55.94 (2C, overlap), 55.88, 26.59, 7.38. MS (ESI) m/z: 468.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{24}H_{24}F_2N_5OS$: 468.1635, Found: 468.1626.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(pyridin-3-yl)-4,5-dihydrothieno[2,3-*c*]pyridin-6(7*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (57b). 57b (49.81 mg, 41.6%) was prepared from **56**

(120.00 mg, 0.26 mmol) and 3-pyridinylboronic acid pinacol ester (62.78 mg, 0.31 mmol) in the same manner as described for **57a**. pale yellow solid: mp 76-78℃. $[\alpha]^{22}_{D}$ –12.8° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, *J* = 2.3 Hz, 1H), 8.47 (dd, *J* = 4.8 Hz, 1.6 Hz, 1H), 7.93 (s, 1H), 7.81-7.79 (m, 1H), 7.78 (s, 1H), 7.53-7.45 (m, 1H), 7.30-7.27 (m, 1H), 7.06 (s, 1H), 6.83-6.68 (m, 2H), 4.89 (q, *J* = 14.8 Hz, 2H), 4.03 (d, *J* = 14.9 Hz, 1H), 3.75 (d, *J* = 14.9 Hz, 1H), 3.25-3.11 (m, 2H), 2.78-2.62 (m, 3H), 1.03 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.56, 147.89, 146.35, 144.24, 137.48, 135.71, 134.95, 132.65, 130.70, 130.59, 124.75, 124.64 (2C, overlap), 123.65, 122.35, 111.52, 104.13, 78.63, 63.66, 55.88 (2C, overlap), 55.82, 26.28, 7.24. MS (ESI) m/z: 468.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{24}H_{24}F_2N_5OS$: 468.1618, Found: 468.1612.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(pyrimidin-5-yl)-4,5-dihydrothieno[2,3-*c*]pyridin-6(7*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (57c). 57c (53.60 mg, 53.6%) was prepared from **56** (100.00 mg, 0.21 mmol) and 5-pyrimidinylboronic acid pinacol ester (52.82 mg, 0.26 mmol) in the same manner as described for **57a**. pale yellow solid: mp 85-86℃. $[\alpha]^{22}_{D}$ –35.2° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.88 (s, 2H), 7.92 (s, 1H), 7.78 (s, 1H), 7.58-7.43 (m, 1H), 7.11 (s, 1H), 6.84-6.70 (m, 2H), 4.90 (q, *J* = 15.0 Hz, 2H), 4.08 (d, *J* = 15.2 Hz, 1H), 3.78 (d, *J* = 15.2 Hz, 1H), 3.20 (m, 2H), 2.79-2.56 (m, 3H), 1.03 (d, *J* = 5.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.94, 153.01, 151.66, 144.21, 136.26, 135.82, 133.08, 130.74, 128.81, 125.26, 124.79, 124.61 (2C, overlap), 111.59, 104.18, 78.90, 63.81, 55.94 (2C, overlap), 55.88, 26.58, 7.33. MS (ESI) m/z: 469.2 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{23}H_{23}F_2N_6OS$: 469.1532, Found: 469.1536.

(2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-(2-cyanopyridin-5-yl)-4,5-dihydrothieno[2,3-*c*]pyridin-6(7*H*)-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (57d). 57d (48.10 mg, 41.6%) was prepared from **56** (110.00 mg, 0.24 mmol) and 2-cyanopyridine-5-boronic acid pinacol ester (69.97 mg, 0.31 mmol) in the same manner as described for **57a**. white solid: mp 81-82℃. $[\alpha]^{22}_{D}$ –64.0° (*c* 0.125, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, *J* = 2.3 Hz, 1H), 7.91 (s, 1H), 7.89 (d, *J* = 2.3 Hz, 1H), 7.78 (s, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.51-7.42 (m, 1H), 7.20 (s, 1H), 6.82-6.71 (m, 2H), 5.11 (s, 1H), 4.90 (q, *J* = 14.7 Hz, 2H), 4.09 (d, *J* = 16.2 Hz, 1H), 3.79 (d, *J* = 15.4 Hz, 1H), 3.30-3.15 (m, 2H), 2.81-2.62 (m, 3H), 1.02 (d, *J* = 5.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.63, 147.39, 144.16, 137.73, 136.58, 135.33, 133.61, 132.19, 131.02, 130.66, 128.50, 124.77, 124.64 (2C, overlap), 124.40, 117.35, 111.61, 104.12, 78.90, 63.58, 55.88 (2C, overlap), 55.82, 26.48, 7.14. MS (ESI) m/z: 493.3 $(M+1)^+$. HRMS (ESI): Anal. Calcd for $C_{25}H_{23}F_2N_6OS$: 493.1622, Found: 493.1631.