Supporting information to:

Synthesis and Biological Evaluation of a 6-Aminofuro[3,2-c]pyridin-3(2H)-one Series of GPR 119 Agonists

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Preparation of 6-Amino-3-hydroxy-pyridine-2-carboxylic acid methyl ester (2b)

A solution of S1 (6.00 g, 43.1 mmol) and H₂SO₄ (6.90 mL, 129 mmol) in MeOH (120 mL) was refluxed for 19 h. The mixture was concentrated, diluted with water, and brought to pH 6 with 1 N NaOH, and then extracted with CHCl₃. The organic layer was dried over Na₂SO₄ and evaporated under reduced pressure to give S2 (5.08 g, yield 77%). ¹H NMR (CDCl₃) δ: 10.64 (s, 1H), 8.34-8.25 (m, 1H), 7.51-7.35 (m, 2H), 4.07 (s, 3H).

To a solution of S2 (4.04 g, 26.4 mmol) in DMF (20 mL) was added NaH (60 percent in oil, 1.06 g, 26.4 mmol) at 0 °C. After stirring at the same temperature for 1 h, benzyl bromide (3.47 mL, 29.0 mmol) was added dropwise to the reaction mixture. After completion of the addition, the reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was diluted with water and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography (EtOAc : hexane = 1 : 1) to give S3 (4.32 g, yield 67%). ¹H NMR (CDCl₃) δ: 8.35-8.24 (m, 1H), 7.53-7.30 (m, 7H), 5.22 (s, 2H), 3.99 (s, 3H).

A solution of S3 (4.32 g, 17.8 mmol) and 3-chloroperoxybenzoic acid (4.44 g, 69% peracid) in CH₂Cl₂ (80 mL) was stirred at room temperature for 72 h. The mixture was diluted with 1 N NaOH solution and extracted with CHCl₃. The organic layer was dried over Na₂SO₄ and evaporated under reduced pressure to give S4 (3.96 g, yield 86%). ¹H NMR (CDCl₃) δ: 7.90-7.88 (m, 1H), 7.46-7.32 (m, 5H), 7.22-7.12 (m, 1H), 6.87 (d, J = 8.7 Hz, 1H), 5.18 (s, 2H), 4.00 (s, 3H). ESI-MS (m/e): 260 [M-H]+.
A solution of S4 (3.96 g, 15.3 mmol), trimethylsilylazide (4.00 mL, 30.5 mmol) and \( N,N \)-dimethylcarbamoyl chloride (1.42 mL, 15.3 mmol) in \( \text{CH}_3\text{CN} \) (40 mL) was refluxed for 16 h. Again, trimethylsilylazide (2.00 mL, 15.3 mmol) and \( N,N \)-dimethylcarbamoyl chloride (0.709 mL, 7.65 mmol) were added to the mixture, and the resulting mixture was refluxed for an additional 10 h. This manipulation was repeated once. After being cooled to room temperature, the reaction mixture was carefully added to an ice-cooled satd. NaHCO\textsubscript{3}. Formed crystals were collected by filtration, washed with water, and then dried. The crude product was dissolved in MeOH (40 mL), and ammonium formate (4.47 g, 70.9 mmol) and 10\% palladium activated carbon (605 mg) were added therein. The suspension was stirred at room temperature for 72 h. The catalyst was filtered off, the filtrate was evaporated to leave crude 2b, which was washed with diisopropyl ether to give the title compound 2b (1.81 g, yield 76\%).

\( ^1\text{H NMR (CDCl}_3 \) \( \delta \): 10.22 (s, 2H), 7.23 (d, \( J = 8.9 \) Hz, 1H), 6.77-6.74 (m, 1H), 4.35 (s, 2H), 4.02 (s, 3H). ESI-MS (m/e): 169 [M-H]+.

Preparation of methyl 2-amino-5-hydroxyisonicotinate (2d)

To a suspension of NaH (60 percent in oil, 1.38 g, 34.4 mmol) in DMF (20 mL) was added dropwise a solution of S6 (5.0 g, 28.7 mmol) in DMF (8 mL) over 30 min at room temperature. After stirring for 1 h, methoxymethyl chloride (2.4 mL, 31.6 mmol) was added dropwise to the solution over 20 min and the reaction mixture was stirred overnight. The mixture was diluted with EtOAc and water, the aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated. The residue was purified by silica gel column chromatography (EtOAc : hexane = 1 : 7) to give S7 (5.43 g, yield 87\%).

\( ^1\text{H NMR (CDCl}_3 \) \( \delta \): 8.17 (d, \( J = 2.9 \) Hz, 1H), 7.38 (d, \( J = 8.8 \) Hz, 1H), 7.26 (dd, \( J = 8.8, 2.9 \) Hz, 1H), 5.17 (s, 2H), 3.48 (s, 3H). ESI-MS (m/e): 219 [M+H]+.

To a solution of S7 (218 mg, 1.0 mmol) in THF (3 mL) was added dropwise 2 M lithium diisopropylamide in heptane/THF/ethylbenzene (550 \( \mu \)L) at -78 °C, and the mixture
was stirred for 2 h at the same temperature. Carbon dioxide was bubbled into the solution for 5 min and the reaction mixture was allowed to warm to room temperature. The mixture was partitioned between 0.1 N NaOH (10 mL) and Et₂O. The aqueous phase was acidified to pH 3 with 2 N HCl and extracted with EtOAc. The EtOAc layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was solved in DMF (4 mL), K₂CO₃ (280 mg, 2.0 mmol) was added therein. After stirring for 30 min, methyl iodide (200 μL, 3.2 mmol) was added and the resulting mixture was stirred for further 3 h. The mixture was diluted with EtOAc and water, and the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography (EtOAc : hexane = 1 : 3) to give S₈ (250 mg, yield 76%) as colorless oil.

¹H NMR (CDCl₃): δ: 8.38 (1H, s), 7.74 (1H, s), 5.27 (2H, s), 3.93 (3H, s), 3.53 (3H, s).

ESI-MS (m/e): 277 [M+H]+.

To a degassed solution of S₈ (4.2 g, 15.2 mmol) and benzophenone imine (5.12 mL, 30.5 mmol) in toluene (120 mL) were added cesium carbonate (24.8 g, 76.2 mmol), 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl (949 mg, 1.52 mmol) and palladium acetate (171 mg, 0.762 mmol). The reaction mixture was heated to 110 °C overnight. The mixture was allowed to cool to room temperature, filtrated, the residue was washed with EtOAc and the filtrate was concentrated. The residue was solved in THF (100 mL) and 1 N HCl (50 mL), and the mixture was stirred for 30 min. The mixture was partitioned between EtOAc and satd. NaHCO₃, and the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography (EtOAc : hexane = 1 : 1) to give S₉ (2.38 g, yield 74%) as a white solid.

¹H NMR (CDCl₃): δ: 8.05 (1H, d, J = 0.6 Hz), 6.81 (1H, d, J = 0.6 Hz), 5.10 (2H, s), 4.34 (2H, brs), 3.90 (3H, s), 3.53 (3H, s). ESI-MS (m/e): 213 [M+H]+.

To a solution of S₉ (4.3 g, 20 mmol) in CH₂Cl₂ was added dropwise 4 N HCl dioxane solution (50 mL, 200 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The mixture was concentrated, azeotroped with
toluene and dried under reduced pressure to give the title compound 1d (3.3 g, yield 99%).

$^1$H NMR (DMSO-$d_6$) $\delta$: 10.16 (1H, brs), 7.63 (1H, s), 7.14 (1H, s), 7.12 (2H, brs), 3.87 (3H, s). ESI-MS (m/e): 169 [M+H]$^+$. 

Preparation of pyrimidine derivatives S12-15

To a 4 M hydrogen chloride/dioxane solution (10 mL) was added S10 (3.0 g, 12.4 mmol) at 0 °C, and the mixture was stirred for 3.5 h at 30 °C. The solvent was removed in vacuo and the residue was partitioned between CH$_2$Cl$_2$ and satd. NaHCO$_3$, and the organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo to afford S11 (1.77 g, yield 99%) as a white solid.

$^1$H NMR (CDCl$_3$) $\delta$: 3.64 (t, $J = 6.7$ Hz, 2H), 3.05 (dt, $J = 11.6$, 2.8 Hz, 2H), 2.57 (dt, $J = 11.6$, 2.5 Hz, 2H), 1.68 (d, $J = 13.2$ Hz, 2H), 1.55-1.61 (m, 2H), 1.21-1.43 (m, 3H), 1.09 (ddd, $J = 24.1$, 12.1, 4.0 Hz, 2H). ESI-MS (m/e): 144 [M+H]$^+$. 

A mixture of S11 (3.18 mmol), the corresponding 2-chloropyrimidine (6.36 mmol) and N,N-diisopropylethylamine (2.77 mL, 15.9 mmol) in 2-propanol (15 mL) was heated under reflux for 23 h. The mixture was concentrated and the residue was partitioned between EtOAc and satd. NaHCO$_3$, and the organic layer was dried over anhydrous Na$_2$SO$_4$ and then concentrated. The residue was purified by silica gel column chromatography to give the desired product.

S12: $^1$H NMR (CDCl$_3$) $\delta$: 8.16 (s, 2H), 4.68 (dt, $J = 13.2$, 2.2 Hz, 2H), 3.65 (dd, $J = 11.7$, 6.6 Hz, 2H), 2.84 (dt, $J = 11.7$, 2.7 Hz, 2H), 2.45 (q, $J = 7.6$ Hz, 2H), 1.77 (d, $J = 11.7$ Hz, 2H), 1.48-1.66 (m, 3H), 1.12-1.36 (m, 7H). ESI-MS (m/e): 250 [M+H]$^+$. 

S13: $^1$H NMR (CDCl$_3$) $\delta$: 8.46 (s, 2H), 4.54-4.67 (m, 2H), 3.80 (s, 3H), 3.65 (d, $J = 11.7$ Hz, 2H), 2.84 (dt, $J = 11.7$, 2.8 Hz, 2H), 1.50-1.86 (m, 5H), 1.12-1.44 (m, 4H). ESI-MS (m/e):
252 [M+H]+.

**S14**: 1H NMR (CDCl₃) δ: 8.17 (s, 2H), 4.67-4.59 (m, 2H), 3.66 (dd, J = 11.9, 6.5 Hz, 2H), 2.85 (td, J = 12.9, 2.6 Hz, 2H), 1.77 (d, J = 12.9 Hz, 2H), 1.62 (dt, J = 11.4, 6.6 Hz, 2H), 1.57-1.46 (m, 1H), 1.37-1.29 (m, 2H), 1.26-1.10 (m, 2H). ESI-MS (m/e): 240 [M+H]+.

**S15**: 1H NMR (CDCl₃) δ: 8.46 (d, J = 0.7 Hz, 2H), 4.89-4.80 (m, 2H), 3.65 (d, J = 12.5 Hz, 2H), 2.90 (dt, J = 13.1, 2.6 Hz, 2H), 1.50-1.85 (m, 5H), 1.12-1.44 (m, 4H). ESI-MS (m/e): 290 [M+H]+.

Preparation of *trans*-3-(8-(5-ethylpyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)propan-1-ol (S21)

![Chemical Reaction Diagram]

To a solution of S16 (27.8 g, 200 mmol) in 1,2-dichloroethane (150 mL) was added dropwise 1-chloroethyl chloroformate (24.0 mL, 220 mmol) at room temperature. The reaction mixture was refluxed for 13 h, and then concentrated under reduced pressure. The crude product was dissolved with MeOH (150 mL), the resulting solution was refluxed for 8 h and then diluted with Acetone (150 mL). The foamed precipitate was filtered to give S17 as a white solid (24.0 g, yield 74%).

1H NMR (DMSO-d₆) δ: 10.04 (br s, 2H), 4.32-4.13 (m, 2H), 3.35 (s, 1H), 3.04 (dd, J = 17.3, 4.6 Hz), 2.42 (d, J = 1.5 Hz), 2.37 (d, J = 1.5 Hz), 2.16-2.04 (m, 2H), 1.84-1.72 (m, 2H). ESI-MS (m/e): 126 [M+H]+.
A suspension of S17 (3.23 g, 20 mmol), benzyl bromide (2.61 mL, 22 mmol) and Na₂CO₃ (5.30 g, 50 mmol) in CH₃CN (30 mL) was stirred under reflux for 8 h. The reaction mixture was poured into water (20 mL) and extracted with Et₂O. The organic layer was slowly acidified to pH 1-2 with 1 N HCl. The separated aqueous layer was basified with 5 N NaOH solution until pH 13-14 and then extracted with Et₂O. This organic layer was dried over anhydrous Na₂SO₄ and concentrated to give S18 as a brown oil (3.98 g, yield 92 %).

1H NMR (CDCl₃) δ: 7.50-7.25 (m, 5H), 3.80 (s, 2H), 3.54 (s, 2H), 2.80-2.66(m, 2H), 2.30-2.02 (m, 4H), 1.70-1.60(m, 2H). ESI-MS (m/e): 216 [M+H]+.

To a suspension of (3-benzyloxypropyl)triphenylphosphonium bromide (1.07 g, 5.0 mmol) in THF (10 mL) was added NaH (60 percent in oil, 0.40 g, 10 mmol) at 0 °C, and the mixture was stirred for 10 min at room temperature. A solution of S18 in THF (10 mL) was added dropwise to the mixture over a period of 5 min. The resulting mixture was refluxed for 13 h. The mixture was quenched with satd. NH₄Cl at 0 °C and poured into water (20 mL) and then extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography (EtOAc : hexane = 1 : 5 to 1 : 2) to give S19 as a colorless oil (1.54 g, yield 89 %).

1H NMR (CDCl₃) δ: 7.41-7.22 (m, 10H), 5.30-5.20 (m, 1H), 4.52 (s, 2H), 3.61 (s, 2H), 3.48-3.43 (m, 2H), 3.23-3.19 (m, 2H), 2.57-2.54 (m, 1H), 2.37-2.24 (m, 2H), 2.23 (s, 2H), 1.91-1.85 (m, 2H), 1.64-1.38 (m, 3H). ESI-MS (m/e): 347 [M+H]+.

To a solution of S19 (1.74 g, 5 mmol) in EtOH (18 mL) was added 20% palladium activated carbon (0.35 g). Medium pressure Hydrogenation (4.5 atm) was conducted at 60 °C for 70 h and then at room temperature for 7 h in the presence of conc. HCl (0.83 mL, 10 mmol). The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give S20 as a white solid (0.87 g, yield 85%).

1H NMR (CDCl₃) δ: 9.62-9.18 (m, 2H), 4.02 (br s, 2H), 3.68 (s, 2H), 2.57-2.46 (m, 2H), 2.32-2.25 (m, 2H), 1.96-1.91 (m, 3H), 1.59-1.51 (m, 6H). ESI-MS (m/e): 170 [M+H]+.

A suspension of S20 (514 mg, 2.5 mmol), 2-chloro-5-ethylpyrimidine (330 μL, 2.75 mmol) and Cs₂CO₃ (1.71 g, 5.25 mmol) in DMF (5 mL) was stirred at 80 °C for 45 h. The
reaction mixture was diluted with EtOAc (20 mL), washed with satd. NH₄Cl, water and brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography (EtOAc : hexane = 1 : 5 to 1 : 2) to give S21 as a white solid (424 mg, yield 62 %).

¹H NMR (CDCl₃) δ: 8.16 (s 2H), 4.66-4.62 (m, 2H), 3.61-3.54 (m, 2H), 2.48-2.42 (m, 2H), 2.30-2.22 (m, 2H), 2.06-2.00 (m, 2H), 1.81-1.75 (m, 2H), 1.61-1.48 (m, 5H), 1.32-1.25 (m, 2H), 1.23-1.18 (m, 3H). ESI-MS (m/e): 276 [M+H]⁺.

Preparation of trans-3-((8-(5-ethylpyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)oxy) propan-1-ol (S25).

A solution of S22 (2.54 g, 20 mmol), 2-chloro-5-ethylpyrimidine (2.64 mL, 22 mmol), Cs₂CO₃ (7.82 g, 24 mmol) in N-methylpyrrolidone (15 mL) was stirred at 80 °C for 21 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (20 mL) and washed with satd. NH₄Cl and brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography (EtOAc : hexane = 1 : 1 to 1 : 0) to give S23 as a pale yellow solid (4.30 g, yield 92 %).

¹H NMR (CDCl₃) δ: 8.17 (s 2H), 4.65-4.62 (m, 2H), 4.13-4.07 (m, 1H), 2.49-2.42 (m, 2H), 2.32-2.27 (m, 2H), 2.20-2.16 (m, 2H), 2.08-2.01 (m, 2H), 1.76-1.72 (m, 2H), 147-1.45 (m, 1H), 1.23-1.18 (m, 3H). ESI-MS (m/e): 234 [M+H]⁺.

To a solution of S23 and tert-butyl acrylate (174 μL, 1.2 mmol) in THF (3 mL) was added NaH (60 percent in oil, 42 mg, 1.05 mmol) at 0 °C. The mixture was stirred for
14 h at room temperature and then quenched by addition of satd. NH₄Cl at 0 °C. The resulting mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography (EtOAc : hexane=1 : 3 to 1 : 2) to give S₂₄ as a colorless oil (256.8 mg, yield 71%).

\[ \text{H NMR (CDCl}_3\nu \delta: 8.17 (s, 2H), 4.59 (s, 2H), 3.64-3.61 (m, 2H), 3.54-3.52 (m, 1H), 2.48-2.42 (m, 4H), 2.20-2.17 (m, 2H), 2.05-1.85 (m, 4H), 1.71 (s, 1H), 1.47 (s, 9H), 1.46-1.44 (m, 1H), 1.21-1.17 (m, 3H). } \]

ESI-MS (m/e): 361 [M+H]^+.

To a solution of S₂₄ (241.8 mg, 0.67 mmol) in dry THF (3 mL) was slowly added LiAlH₄ (50.8 mg, 1.34 mmol) at 0 °C. The mixture was stirred for 3 h at room temperature and then quenched by addition of satd. NH₄Cl at 0 °C. The resulting mixture was extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated to give S₂₅ as a white solid (184 mg, yield 94%).

\[ \text{H NMR (CDCl}_3\nu \delta: 8.18 (s, 2H), 4.62 (s, 2H), 3.81 (t, J = 5.7 Hz, 2H), 3.59 (t, J = 5.7 Hz, 2H), 3.56-3.52 (m, 1H), 2.65 (br s, 1H), 2.46 (q, J = 7.6 Hz, 2H), 2.07-2.09 (m, 2H), 1.90-1.83 (m, 3H), 1.19 (t, J = 7.6 Hz, 3H). } \]

ESI-MS (m/e): 291 [M+H]^+.

Preparation of 3-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)propan-1-ol (S₂₇)

A solution of S₁₁ (10.0 g, 70 mmol) in CH₂Cl₂ (170 mL) was mixed with a suspension of NaHCO₃ (17.7 g, 210 mmol) in water (40 mL). To this stirred mixture was added dropwise a solution of cyanogen bromide (8.9 g, 84 mmol) in CH₂Cl₂ (30 mL) at 0 °C, and the resulting mixture was stirred at same temperature for 30 min and then at room temperature overnight. The mixture was poured into satd. NaHCO₃ and extracted with CHCl₃. The organic layer was dried over anhydrous Na₂SO₄ and concentrated to give crude product S₂₆ (10.8 g, yield 91%) as a colorless oil, which was used in the next step without further purification.

\[ \text{H NMR (CDCl}_3\nu \delta: 3.65 (dd, J = 11.4, 6.6 Hz, 2H), 3.42 (d, J = 13.2 Hz, 2H), 2.99 (t, J = } \]
11.4 Hz, 2H), 1.71-1.75 (m, 2H), 1.55-1.60 (m, 2H), 1.24-1.37 (m, 5H). ESI-MS (m/e): 169 [M+H]+.

Zinc chloride (1.0 M in Et₂O, 77 mL, 77 mmol) was added to a stirred solution of S26 obtained above (10.8 g, 64 mmol) and N-hydroxyisobutyramidine (7.85 g, 77 mmol) in EtOAc (130 mL)/THF (130 mL) over 30 min. After a 1 day of stirring, the precipitates were filtered and washed with Et₂O (30 mL). This precipitate was dissolved in a mixture of EtOH (250 mL) and conc. HCl (37 mL), and the solution was stirred at 70 °C for 17 h. The solvent was removed in vacuo, the residue was dissolved with satd. NaHCO₃ and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography (EtOAc) to give S27 (13.6 g, yield 77%) as a colorless oil.

1H NMR (CDCl₃) δ: 4.10-4.14 (m, 2H), 3.66 (q, J = 6.0 Hz, 2H), 3.02 (dt, J = 12.8, 2.8 Hz, 2H), 2.87 (sep, J = 7.0 Hz, 1H), 1.78 (d, J = 13.5 Hz, 2H), 1.45-1.64 (m, 3H), 1.38-1.20 (m, 10H).

ESI-MS (m/e): 254 [M+H]+.

Preparation of 3-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)butan-1-ol (S23)

Ethyl 2-(diethoxyphosphoryl)acetate (4.23 mL, 21.1 mmol) was added to a suspension of NaH (60 percent in oil, 845 mg, 21.1 mmol) in THF (40 mL) at 0 °C and the resulting mixture was stirred at the same temperature for 15 min. A solution of tert-butyl 4-acetylpiperidine-1-carboxylate S28 (4.0 g, 17.6 mmol) in THF (10 mL) was added to the mixture at 0 °C and heated to 30 °C. After stirring for 12 h, the reaction mixture was quenched by chilled water, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried
over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (EtOAc : hexane = 1 : 4) to give a (E) and (Z)-mixture of S₂⁹ (4.92 g) as a colorless oil, which was used in the next reaction without further purification.

To a mixture of S₂⁹ (4.90 g, 16.5 mmol) in MeOH (20 mL) was added 10% palladium activated carbon (500 mg), and the mixture was stirred at 30 °C for 15 h under hydrogen atmosphere. After filtering through celite pad, the solvent was distilled off under reduced pressure to give S₃₀ (4.93 g, yield 93%) as a colorless oil.

1H NMR (CDCl₃) δ: 4.11-4.16 (m, 4H), 2.60-2.66 (m, 2H), 2.34-2.39 (m, 1H), 2.07-2.13 (m, 1H), 1.88-1.95 (m, 1H), 1.57-1.61 (m, 2H), 1.45 (s, 9H), 1.31-1.35 (m, 1H), 1.26 (t, J = 8.0 Hz, 3H), 1.14-1.22 (m, 2H), 0.92 (d, J = 4.0 Hz, 3H). ESI-MS (m/e): 300 [M+H]⁺.

To a solution of S₃₀ (4.93 g, 16.5 mmol) in THF (40 mL) was added portionwise LiAlH₄ (625 mg, 16.5 mmol) at 0 °C under argon atmosphere, the mixture was stirred at the same temperature for 1 h and allowed to warm to room temperature. After stirring for 3 h, the reaction mixture was quenched with crashed ice, diluted with EtOAc, washed with brine and dried over anhydrous Na₂SO₄. The solvent was distilled off under reduced pressure to provide S₃₁ (4.2 g, yield 99%) as a colorless oil.

1H NMR (CDCl₃) δ: 4.13 (m, 2H), 3.61-3.76 (m, 2H), 2.63 (m, 2H), 1.17-1.71 (m, 21H), 0.87 (d, J = 4.0 Hz, 3H). ESI-MS (m/e): 258 [M+H]⁺.

To a 4M HCl dioxane solution (10 mL) was added S₃₁ (3.2 g, 12.4 mmol) at 0 °C, and the mixture was stirred for 3.5 h at 30 °C. The solvent was evaporated and dissolved in CH₂Cl₂, this solution was washed with satd. NaHCO₃, dried over anhydrous Na₂SO₄ and concentrated in vacuo to afford S₃₂ (1.94 g, yield 99%) as a white solid.

1H NMR (CDCl₃) δ: 3.60-3.74 (m, 2H), 3.10-3.13 (m, 2H), 2.54-2.62 (m, 2H), 2.15 (s, 2H), 1.18-1.73 (m, 8H), 0.88 (d, J = 4.0 Hz, 3H). ESI-MS (m/e): 158 [M+H]⁺.
was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography (EtOAc: hexane = 2:1) to give S₃₃ (830 mg, yield 99%) as a colorless oil.

\[^1\text{H} \text{NMR} \ (\text{CDCl}_3) \ \delta \ : \ 8.16 \ (s, 2H), 4.73-4.78 \ (m, 2H), 3.62-3.77 \ (m, 2H), 2.74-2.82 \ (m, 2H), 2.45 \ (q, \ J = 16 \ Hz, 8 \ Hz, 2H), 1.24-1.53 \ (m, 8H), 1.18 \ (t, \ J = 8.0 \ Hz, 3H), 0.88 \ (d, \ J = 8.0 \ Hz, 3H). \ \text{ESI-MS (m/e): 264 [M+H]}^+.

Preparation of 3-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)butan-1-ol (S₃₅)

To a solution of S₃₂ (500 mg, 3.18 mmol) in CH₂Cl₂ (10 mL) were added successively a suspension of NaHCO₃ (801 mg, 9.54 mmol) in water (3.0 mL) and a solution of cyanogen bromide (505 mg, 4.77 mmol) in CH₂Cl₂ (3.0 mL) 0 °C, and the resulting mixture was stirred at the same temperature for 30 min and then to room temperature overnight. The mixture was poured into satd. NaHCO₃ and extracted with CHCl₃. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude product of S₃₄ (600 mg) as a colorless oil, which was used in the next step without further purification.

\[^1\text{H} \text{NMR} \ (\text{CDCl}_3) \ \delta \ : \ 7.27 \ (s, 2H), 3.61-3.76 \ (m, 2H), 3.43-3.47 \ (m, 2H), 2.94-3.02 \ (m, 2H), 1.26-1.70 \ (m, 8H), 0.89 \ (d, \ J = 8.0 \ Hz, 3H). \ \text{ESI-MS (m/e): 183 [M+H]}^+.

Zinc chloride (1.0 M in Et₂O, 3.95 mL, 3.95 mmol) was added over 5 min to a stirred solution of S₃₄ obtained above (600 mg) and N-hydroxyisobutyramidine (404 mg, 3.95 mmol) in EtOAc (8.0 mL)/THF (7.0 mL). After a 1 day of stirring, the precipitate was filtered and washed with Et₂O (2.0 mL). This precipitate was dissolved in a mixture of EtOH (15 mL) and conc. HCl (2.0 mL), and the solution was stirred at 70 °C for 17 h. The solvent was evaporated and the residue was dissolved with satd. NaHCO₃ and EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and
concentrated. The residue was purified by silica gel column chromatography (EtOAc) to give S35 (550 mg, yield 65%) as a colorless oil.

$^1$H NMR (CDCl$_3$) $\delta$: 4.16-4.19 (m, 2H), 3.63-3.77 (m, 2H), 2.95-3.03 (m, 2H), 2.85-2.92 (m, 14H), 1.31-1.73 (m, 8H), 1.29 (d, $J = 4.0$ Hz, 6H), 0.89 (d, $J = 8.0$ Hz, 3H). ESI-MS (m/e): 268 [M+H]$^+$. 