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

Authors
M. Sakairi, M. Kogami, M. Torii, Y. Kuno, Y. Ohsawa, M. Makino, D. Kataoka, R. Okamoto, T. Miyazawa, M. Inoue, N. Takahashi, S. Harada, N. Watanabe

Affiliation
Drug Discovery Laboratories, Sanwa Kagaku Kenkyusho Co., Ltd.; Hokusei-cho, Inabe, Mie, Japan

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- 6-aminofuro[3,2-*c*]pyridin-3(2*H*)-one
- gastric emptying
- glucagon-like peptide-1

Abstract

G protein-coupled receptor 119 (GPCR 119 (GPR119)) agonists have received considerable attention as a promising therapeutic option for treatment of type 2 diabetes mellitus. GPR119 is one of the GPCRs expressed in pancreatic islet β-cells and its activation enhances stimulation of insulin secretion in a glucose-dependent manner. We have recently described a series of 6-amino-1*H*-indan-1-ones as potent, selective, and orally bioavailable GPR119 agonists with an amino group that plays important roles not only in their drug-like properties, such as high aqueous solubility, but also in their potent agonistic activity. However, many of these compounds displayed strong to moderate inhibition of human ether-à-go-go related gene channel. Attenuation of the basicity of the amino group by replacing the adjacent benzene ring with electron-deficient heteroaromatic rings provided several heterocyclic cores among which 6-aminofuro[3,2–*c*]pyridin-3(2*H*)-one was selected as a promising scaffold. Further optimization around the side chain moiety led to the discovery of **17i**, which showed not only strong human GPR119 agonistic activity (EC_{50} = 14 nM), but also beneficial effects on gastric emptying and plasma total glucagon-like peptide-1 levels in mice.

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Correspondence
N. Watanabe
Drug Discovery Laboratories
Sanwa Kagaku Kenkyusho Co., Ltd.
363 Shiosaki
Hokusei-cho
Inabe
Mie 511-0406
Japan
Tel.: +81/594/72 6221
Fax: +81/594/82 0072
no_watanabe@skk-net.com

Introduction

Obesity is strongly associated with insulin resistance and can therefore be problematic for management of type 2 diabetes mellitus [1,2]. However, oral medications such as sulfonylureas and thiazolidinediones are known to be difficult to achieve weight loss. Glucose-dependent insulin secretagogues, such as glucagon-like peptide-1 (GLP-1) analogs and dipeptidyl peptidase IV (DPP-4) inhibitors, have recently emerged as new agents for the treatment of type 2 diabetes mellitus [3]. In addition to improving glycemic control and minimizing hypoglycemia, GLP-1 analogs have been demonstrated to produce weight loss, while DPP-4 inhibitors have been shown to induce no body weight gain.

In line with GLP-1 related drugs, G protein-coupled receptor 119 (GPCR 119 (GPR119)) agonists have received considerable attention as a promising therapeutic option for the treatment of type 2 diabetes mellitus [4,5]. GPR119 is expressed in pancreatic islet β-cells, and its activation enhances stimulation of insulin secretion in a glucose-dependent manner. In mice, expression of GPR119 has been detected in intestinal L- and K-cell lines, and a GPR119 agonist, AR231453, has been shown to enhance secretion of GLP-1 and glucose-dependent insulinotropic polypeptide in glucose-challenged mice [6]. Therefore, several agonists such as APD668 [7], MBX-2982 and GSK-1292263A have been under development (**Fig. 1**) [5–9].

In previous communications [10,11], we reported a series of 6-amino-1*H*-indan-1-ones (**1a-c**) as potent, selective, orally bioavailable GPR119 agonists with an amino group that plays important roles not only in their drug-like properties, such as high aqueous solubility, but also in their potent agonistic activity. However, many of these compounds displayed strong to moderate inhibition of human ether-à-go-go related gene (hERG) channel. Further optimization efforts have been made to overcome this problem. Herein, we report a 6-aminofuro[3,2-*c*]pyridine series of GPR119 agonists with enhanced activity and reduced hERG channel inhibition.

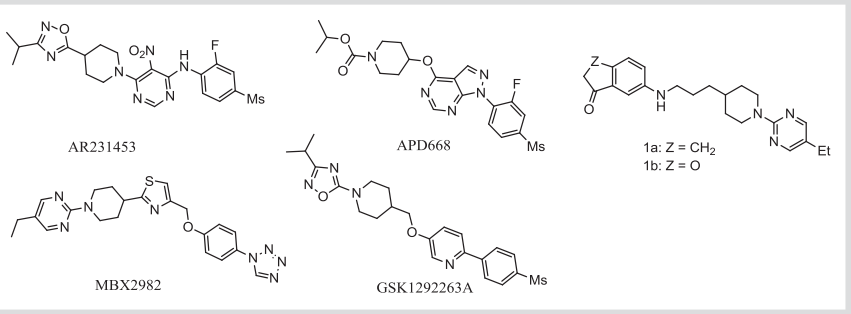


Fig. 1 GPR119 agonists.

Materials and methods

Chemistry

All commercially available reagents and solvents were used without further purification. Reactions were carried out using oven-dried flasks or glassware, mixtures were stirred with magnetic stirring bars and concentrated using a standard rotary evaporator, unless otherwise noted. Procedures for preparation of intermediates **2b, d** and corresponding alcohols in **Fig. 5** were carried out as described previously. ^{1}H NMR spectra were recorded by a JEOL JNM-ECP400 spectrometer operating at 400 MHz at 25 °C with tetramethylsilane as internal standard. Data are reported as follows: chemical shift in ppm (δ), integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), and coupling constant (Hz). LC/MS spectra were determined on a Waters ZMD2000 equipped with a Waters 2690 injector and a PDA detector operating at 210–400 nm and interfaced with a Micromass ZMD mass spectrometer. High-resolution mass spectra (HRMS) were recorded on a Thermo. LTQ Orbitrap.

Representative procedure for compound 4

Methyl 6-amino-3-(3-methoxy-3-oxopropyl)picolinate (3a)

Method A: To a degassed solution of **2a** (5.57 g, 24.1 mmol), methyl acrylate (6.5 mL, 72.3 mmol), triethylamine (10.1 mL, 72.3 mmol) in DMF (30 mL) was added dichlorobis(tri-*o*-tolyl-phosphine) palladium (II) (0.95 g, 1.2 mmol). The resulting solution was stirred with heating at 80 °C for 17 h under argon atmosphere. The reaction mixture was then evaporated, and the residue was diluted with Et_2O/hexane=1/1. The resultant precipitate was filtered and washed with hexane to give an unsaturated ester as a yellow solid (4.42 g): ^{1}H NMR ($CDCl_3$) δ: 8.20 (d, 1H), 7.76 (d, 1H), 6.66 (d, 1H), 6.23 (d, 1H), 4.87 (br s, 2H), 3.99 (s, 3H), 3.80 (s, 3H): ESI-MS (m/e): 236 $[M+H]^+$, which was used in the next reaction without further purification.

To a solution of the unsaturated ester obtained above (4.42 g, 18.7 mmol) in EtOH (40 mL) was added 10% Pd/C (0.44 g). The mixture was stirred under hydrogen atmosphere at 50 °C for 8 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give the title compound as a yellow solid (4.16 g, yield 72%, 2 steps).

^{1}H NMR (DMSO-d_6) δ: 7.36 (d, J=8.5 Hz, 1H), 6.54 (d, J=8.4 Hz, 1H), 6.10 (br s, 1H), 3.78 (s, 3H), 3.57 (s, 3H), 2.69–2.65 (m, 2H), 2.35–2.30 (m, 2H). ESI-MS (m/e): 238 $[M+H]^+$.

Methyl 2-amino-5-(3-methoxy-3-oxopropyl)isonicotinate (3c)

^{1}H NMR ($CDCl_3$) δ: 8.04 (s, 1H), 6.95 (s, 1H), 4.49 (brs, 2H), 3.90 (s, 3H), 3.66 (s, 3H), 3.10 (t, J=7.6 Hz, 2H), 2.60 (t, J=7.6 Hz, 2H). ESI-MS (m/e): 239 $[M+H]^+$.

6-Amino-3-methoxycarbonylmethoxy-pyridine-2-carboxylic acid methyl ester (3b)

Method B: A suspension of **2b** (1.81 g, 10.8 mmol), methyl bromoacetate (1.04 mL, 11.3 mmol) and cesium carbonate (7.57 g, 23.2 mmol) in acetonitrile (75 mL) was stirred at room temperature for 15 h. Methyl bromoacetate (500 µL, 5.43 mmol) was further added, and the mixture was stirred at room temperature for an additional 7 h. The mixture was then diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and evaporated, and the residue was purified by silica gel column chromatography (MeOH: $CHCl_3$=1: 10) to give **3b** (2.12 g, yield 82%).

^{1}H NMR ($CDCl_3$) δ: 7.35–7.30 (m, 1H), 6.66–6.61 (m, 1H), 4.63 (s, 2H), 4.50 (s, 2H), 3.95 (s, 3H), 3.79 (s, 3H). ESI-MS (m/e): 241 $[M+H]^+$.

Methyl 2-amino-5-(2-methoxy-2-oxoethoxy) isonicotinate (3d)

^{1}H NMR ($CDCl_3$) δ: 8.14 (d, J=0.8 Hz, 1H), 6.69 (d, J=0.8 Hz, 1H), 4.62 (s, 2H), 4.35 (brs, 2H), 3.92 (s, 3H), 3.83 (s, 3H). ESI-MS (m/e): 241 $[M+H]^+$.

2-Amino-5H-cyclopenta-[*b*]pyridin-7(6*H*)-one (4a)

To a solution of **3a** (2.0 g, 8.39 mmol) in dry DMF (40 mL) under argon was stirred potassium *tert*-butoxide (2.22 g, 16.8 mmol) at 0 °C. The mixture was warmed to room temperature and stirred at the same temperature for 1.5 h. Next, the mixture was cooled to 0 °C and neutralized with 2N HCl (10 mL). Sodium chloride (984 mg, 16.8 mmol) was then added to the mixture, and the resulting suspension was stirred at 140 °C for 30 min. The reaction mixture was evaporated, and the residue was diluted with 90% methanolic $CHCl_3$. Insoluble materials were filtered off, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (MeOH: $CHCl_3$=1: 50) to give **4a** as a brown solid (0.697 g, yield 56%).

^{1}H NMR ($CDCl_3$) δ: 7.60 (d, J=8.4 Hz, 1H), 6.71 (d, J=8.4 Hz, 1H), 6.44 (d, J=5.3 Hz, 1H), 4.75 (br s, 2H), 3.03–2.94 (m, 2H), 2.75–2.65 (m, 2H). ESI-MS (m/e): 149 $[M+H]^+$.

5-Amino-furo[3,2–*b*]pyridin-3-one (4b)

^{1}H NMR ($CDCl_3$) δ: 7.52–7.48 (m, 1H), 6.75 (d, J=9.1 Hz, 1H), 6.19 (s, 2H). ESI-MS (m/e): 151 $[M+H]^+$.

3-Amino-6,7-dihydro-5H-cyclopenta[*c*]pyridin-5-one (4c)

^{1}H NMR ($CDCl_3$) δ: 8.35 (s, 1H), 6.75 (s, 1H), 4.67 (brs, 2H), 3.12–3.02 (m, 2H), 2.76–2.66 (m, 2H). ESI-MS (m/e): 149 $[M+H]^+$.

5-Aminofuro[2,3-*c*]pyridin-3(2*H*)-one (4d)

^{1}H NMR ($CDCl_3$) δ: 8.24 (d, J=1.1 Hz, 1H), 6.68 (d, J=1.1 Hz, 1H), 4.63 (s, 2H), 4.39 (brs, 2H). ESI-MS (m/e): 151 $[M+H]^+$.

Ethyl 4-(2-ethoxy-2-oxoethoxy)-2-((4-methoxybenzyl) amino)pyrimidine-5-carboxylate (6)

Sodium hydride (40% in oil, 1.76 g, 44 mmol) was added to a solution of ethyl glycolate (2.1 mL, 22 mmol) in THF (50 mL) at 0 °C, and the mixture was stirred for 30 min. Next, **5** (4.6 g, 20 mmol) was added, and the mixture was stirred at room temperature and quenched with crashed ice. The resulting mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (EtOAc: hexane = 1: 3) to give an ester as a white solid (2.4 g, yield 40%): ^{1}H NMR ($CDCl_3$) δ: 8.86 (s, 1H), 4.99 (s, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.51 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H): ESI-MS (m/e): 301 $[M+H]^+$, which was used in the next step without further purification.

To a solution of the ester prepared above (4.1 g, 13.7 mmol) in CH_2Cl_2 (110 mL) was added *m*-chloroperoxybenzoic acid (6.82 g, 27.3 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2 h. Water (100 mL) and 5 N NaOH solution (8 mL, 40 mmol) were then added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was dissolved in *N*-methylpyrrolidone (45 mL), and *p*-methoxybenzylamine (2.14 mL, 16.4 mmol) and triethylamine (4.57 mL, 32.8 mmol) were added to the solution. The resulting mixture was stirred overnight, poured into H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (EtOAc: hexane = 1: 3) to give **6** (3.35 g, yield 63%) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 8.82 (brs, 0.75H), 8.70 (brs, 0.75H), 7.21 (d, *J* = 7.7 Hz, 2H), 6.87 (d, *J* = 7.7 Hz, 2H), 5.88 (brs, 0.75H), 5.45 (brs, 0.25H), 4.89 (s, 2H), 4.61 (brs, 0.5H), 4.49 (brs, 1.5H), 4.32 (q, *J* = 7.1 Hz, 2H), 4.15 (brs, 2H), 3.80 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.21 (brs, 3H). ESI-MS (m/e): 390 $[M+H]^+$.

Ethyl 2-amino-5-oxo-5,6-dihydrofuro[2,3-*d*]pyrimidine-6-carboxylate (7)

A solution of **6** (2.73 g, 7 mmol) in trifluoroacetic acid (40 mL) was refluxed for 2 days, evaporated, and then azeotroped with toluene. Chloroform and satd. $NaHCO_3$ were added to the residue and the phases were separated. The aqueous layer was extracted with $CHCl_3$, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was triturated in Et_2O, filtered, rinsed with cold Et_2O and dried under reduced pressure to give an ester (1.72 g, yield 91%) as a yellow powder: ^{1}H NMR ($CDCl_3$) δ: 1.26 (t, *J* = 7.0 Hz, 3H), 1.36 (t, *J* = 7.0 Hz, 3H), 4.23 (q, *J* = 7.0 Hz, 2H), 4.34 (q, *J* = 7.0 Hz, 2H), 4.93 (s, 2H), 5.23 (brs, 2H), 8.75 (s, 1H): ESI-MS (m/e): 270 $[M+H]^+$, which was used in the next step without further purification.

To a solution of the ester obtained above (470 mg, 1.74 mmol) in DMF (15 mL) was added potassium *tert*-butoxide (490 mg, 4.4 mmol) at −15 °C, and the mixture was allowed to warm to room temperature. After stirring for 30 min, the solution was cooled to 0 °C, neutralized with 6 N HCl and evaporated. The residue was purified by silica gel column chromatography (MeOH: $CHCl_3$ = 1: 50) to give **7** (80 mg, yield 21%) as a brown solid.

^{1}H NMR (DMSO-d_6) δ: 8.65 (1H, s), 8.32 (1H, brs), 8.23 (1H, brs), 5.57 (1H, s), 4.21 (q, *J* = 7.1 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H). ESI-MS (m/e): 224 $[M+H]^+$.

2-Aminofuro[2,3-*d*]pyrimidin-5(6*H*)-one (8)

To a suspension of **7** (61 mg, 0.27 mmol) in MeOH (2 mL) was added conc. HCl (455 µL, 5.4 mmol), and the mixture was refluxed for 1 h. The mixture was then cooled to 0 °C and neutralized with satd. $NaHCO_3$. The precipitate was filtrated and washed with H_2O, and the filtrate was extracted with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by PLC (MeOH: $CHCl_3$ = 1: 9) to give **8** (20 mg, yield 49%) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 8.58 (s, 1H), 8.04 (brs, 1H), 7.96 (brs, 1H), 4.72 (s, 2H). ESI-MS (m/e): 152 $[M+H]^+$.

Methyl 4-(benzyloxy)-6-chloronicotinate (10)

To a solution of benzyl alcohol (269 mL, 2.6 mol) in THF (2 L) was added NaH (104 g in oil, 2.6 mol) at 0 °C. After stirring at room temperature for 30 min, a solution of **9** (192 g, 1 mol) in THF (100 mL) was added dropwise to the mixture at 0 °C. The resulting mixture was stirred at room temperature overnight and then diluted with water (1 L). The solvent was evaporated in vacuum, and the residue was washed with Et_2O. The aqueous layer was acidified with 6 N HCl to pH 1 and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was dissolved in DMF (1 L), and K_2CO_3 (138 g, 1 mol) was added portionwise to the solution. After stirring at room temperature for 30 min, iodomethane (258 g, 1.82 mol) was added dropwise to the mixture, and the resulting mixture was stirred at room temperature for an additional 2 h, and then partitioned between H_2O (1 L) and EtOAc (1 L). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum to give **10** (230 g, 90%) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 8.74 (s, 1H), 7.33–7.49 (m, 5H), 5.24 (s, 2H), 3.92 (s, 3H). ESI-MS (m/e): 278 $[M+H]^+$.

Methyl 4-hydroxy-6-((4-methoxybenzyl)amino) nicotinate (11)

To a solution of **10** (52 g, 187 mmol) in *N*-methylpyrrolidone (500 mL) were added *p*-methoxybenzyl amine (51 g, 374 mmol) and triethylamine (75 g, 748 mmol), and the mixture was stirred at 80 °C overnight. The reaction mixture was then diluted with H_2O (300 mL) and extracted with EtOAc (300 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (EtOAc: hexane = 1:1) to give an ester as a white solid (28 g, yield 40%): ^{1}H NMR ($CDCl_3$) δ: 8.63 (s, 1H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.81 (s, 1H), 5.19 (s, 2H), 5.11 (s, 2H), 4.41 (d, *J* = 5.6 Hz, 2H), 3.85 (s, 3H), 3.81 (s, 3H): ESI-MS (m/e): 379 $[M+H]^+$, which was used in the next step without further purification.

A mixture of the ester obtained above (28 g, 75 mmol) and 10% Pd/C (2.8 g) in MeOH (1 L) was stirred under hydrogen atmosphere for 2 h at room temperature, and $CHCl_3$ (2.0 L) was added. The catalyst was filtered off and rinsed with 90% methanolic $CHCl_3$, and the filtrate was concentrated to give **11** (20 g, yield 92%), which was pure enough for the next reaction.

^{1}H NMR (DMSO-d_6) δ: 8.40 (s, 1H), 8.10 (brs, 1H), 7.26 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.04 (s, 1H), 4.43 (d, *J* = 4.8 Hz, 2H), 3.81 (s, 3H), 3.73 (s, 3H). ESI-MS (m/e): 289 $[M+H]^+$.

Methyl 4-(2-methoxy-2-oxoethoxy)-6-((4-methoxybenzyl)amino)nicotinate (12)

A suspension of **11** (22 g, 75 mmol) and K_2CO_3 (16 g, 113 mmol) in DMF (50 mL) was stirred at 30 °C for 30 min, and methyl bro-

moacetate (17.17 g, 113 mmol) was added. The resulting mixture was stirred at 30 °C overnight, diluted with water (100 mL), and then extracted with EtOAc (150 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, evaporated, and the residue was washed with MeOH (100 mL) to give **12** as a white solid (15 g, yield 56 %).
^{1}H NMR ($CDCl_3$) δ: 8.65 (s, 1H), 7.25 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.60 (s, 1H), 5.23 (brs, 1H), 4.65 (s, 2H), 4.43 (d, *J* = 5.6 Hz, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H). ESI-MS (m/e): 361 $[M+H]^+$.

6-Aminofuro[3,2-*c*]pyridin-3(2*H*)-one (13)

To a solution of **12** (18 g, 50 mmol) in THF (150 mL) was added LDA (2M, 50 ml, 200 mmol) at −40 °C, and the mixture was stirred at the same temperature for 2 h. The mixture was then quenched with satd. NH_4Cl (100 mL) and extracted with EtOAc. The organic layer was concentrated and the residue was recrystallized from MeOH to give the β-keto ester as a white solid (11.5 g, yield 70 %): ^{1}H NMR ($CDCl_3$) δ: 8.49 (s, 1H), 7.26 (d, *J* = 8.7 Hz, 8H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.01 (d, *J* = 0.5 Hz, 1H), 5.75 (brs, 1H), 5.14 (s, 1H), 4.47 (brs, 2H), 3.86 (s, 3H), 3.81 (s, 3H). ESI-MS (m/e): 329 $[M+H]^+$, which was used in the next reaction without further purification.
To a solution of the β-keto ester obtained above (11.5 g, 35 mmol) in MeOH (100 mL) was added conc. HCl (100 mL), and the reaction mixture was refluxed for 2 h. The resulting mixture was concentrated to give the corresponding decarboxylated product as a yellow solid (9.5 g, yield 99 %): ^{1}H NMR ($CDCl_3$) δ: 8.46 (s, 1H), 7.26 (d, *J* = 8.7 Hz, 7H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.93 (s, 1H), 4.62 (s, 2H), 4.45 (d, *J* = 5.6 Hz, 2H), 3.81 (s, 3H): ESI-MS (m/e): 271 $[M+H]^+$.
A solution of the decarboxylated product prepared above (28.5 g, 105 mmol) in TFA (15 mL) was heated at 60 °C for 4 h. The mixture was evaporated, and the residue was partitioned between EtOAc (500 mL) and 6 N HCl. The pH of the aqueous layer was adjusted to pH 9 with $NaHCO_3$ in an ice-bath, and the precipitates were collected to give 4.6 g of **13** as a yellow solid. The filtrate was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give an additional 8.2 g of **13** (combined yield 80 %).
^{1}H NMR (DMSO-d_6) δ: 8.31 (s, 1H), 7.13 (br, 2H), 5.98 (s, 1H), 4.69 (s, 2H). ESI-MS (m/e): 151 $[M+H]^+$.

Preparation of compounds 15a–c, 16a–b and 17a–j

General procedure for preparation of aldehydes

To a solution of the corresponding alcohol (1 mmol) in CH_2Cl_2 (10 mL) was added Dess-Martin periodinane (1.1 mmol) at 0 °C, and the mixture was stirred for 3 h at room temperature. To the mixture was the added H_2O and 5 N NaOH solution (6 mmol), and the whole was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated and the crude product was subjected to the next reaction without further purification.

Method A: General procedure with reductive amination To a solution of amine (0.1 mmol) and aldehyde (0.1 mmol) in CH_2Cl_2 (2 mL) was added $NaBH(OAc)_3$ (0.2 mmol), and the reaction mixture was stirred overnight at room temperature. The mixture was poured into satd. $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by PLC.

Method B: General procedure with reductive amination To a solution of amine (0.1 mmol) and aldehyde (0.1 mmol) in AcOH (500 µL) was added $NaBH(OAc)_3$ (0.2 mmol), and the reaction mixture was stirred for 1 h at room temperature. The mixture was then neutralized with satd. $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by PLC.

2-((3-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)propyl) amino)-5*H*-cyclopenta[*b*]pyridin-7(6*H*)-one (15a)

^{1}H NMR ($CDCl_3$) δ: 8.15 (s, 2H), 7.56 (d, *J* = 8.6 Hz, 1H), 6.61 (d, *J* = 8.6 Hz, 1H), 4.83 (s, 1H), 4.72–4.63 (m, 2H), 3.38–3.32 (m, 2H), 3.08–2.90 (m, 2H), 2.86–2.76 (m, 2H), 2.73–2.55 (m, 2H), 2.50–2.45 (m, 2H), 1.78–1.71 (m, 2H), 1.68–1.62 (m, 2H), 1.61–1.45 (m, 1H), 1.40–1.30 (m, 2H), 1.24–1.10 (m, 4H). HRMS ESI calcd for $C_{22}H_{29}N_5O$ 380.2445, found 380.2448.

5-((3-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)propyl) amino)furo[3,2-*b*]pyridin-3(2*H*)-one (15b)

^{1}H NMR ($CDCl_3$) δ: 8.16 (s, 2H), 7.33 (d, *J* = 9.2 Hz, 1H), 6.69 (d, *J* = 9.2 Hz, 1H), 4.70 (s, 1H), 4.67–4.65 (m, 3H), 4.58 (s, 1H), 3.37 (dd, *J* = 12.5, 7.0 Hz, 2H), 2.83 (td, *J* = 13.1, 2.6 Hz, 2H), 2.45 (q, *J* = 7.6 Hz, 2H), 1.79–1.73 (m, 2H), 1.68–1.64 (m, 2H), 1.59–1.51 (m, 1H), 1.40–1.24 (m, 4H), 1.18 (t, *J* = 7.6 Hz, 3H). HRMS ESI calcd for $C_{21}H_{27}N_5O_2$ 382.2237, found 382.2239.

5-((3-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)propyl) amino)furo[2,3-*c*]pyridin-3(2*H*)-one (15c)

^{1}H NMR ($CDCl_3$) δ: 8.35 (s, 1H), 8.16 (s, 1H), 6.60 (s, 1H), 4.70–4.48 (m, 3H), 3.30–3.20 (m, 2H), 3.09–3.02 (m, 2H), 2.95–2.80 (m, 2H), 2.73–2.67 (m, 2H), 2.45 (q, *J* = 7.6 Hz, 2H), 1.80–1.60 (m, 4H), 1.61–1.47 (m, 2H), 1.42–1.32 (m, 2H), 1.23–1.13 (m, 5H). HRMS ESI calcd for $C_{22}H_{29}N_5O$ 380.2444, found 380.2448.

2-((3-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)propyl) amino)furo[2,3-*d*]pyrimidin-5(6*H*)-one (16a)

^{1}H NMR ($CDCl_3$) δ: 8.67 (s, 0.4H), 8.56 (s, 0.6H), 8.16 (s, 2H), 6.05 (brs, 0.6H), 5.83 (brs, 0.4H), 4.67–4.71 (m, 2H), 4.66 (s, 1.3H), 4.63 (s, 0.7H), 3.49–3.58 (m, 2H), 2.80–2.86 (m, 2H), 2.45 (q, *J* = 7.6Hz, 2H), 1.66–1.78 (m, 4H), 1.54–1.56 (m, 1H), 1.32–1.38 (m, 2H), 1.18 (t, *J* = 7.6 Hz, 3H), 1.12–1.23 (m, 2H). HRMS ESI calcd for $C_{20}H_{26}N_6O_2$ 383.2189, found 383.2197.

Tert-butyl 4-(3-((5-oxo-5,6-dihydrofuro[2,3-*d*]pyrimidin-2-yl) amino)propyl)piperidine-1-carboxylate (16b)

^{1}H NMR ($CDCl_3$) δ: 8.67 (s, 0.4H), 8.56 (s, 0.6H), 6.21 (brs, 0.6H), 5.94 (brs, 0.4H), 4.66 (s, 1.3H), 4.63 (s, 0.7H), 4.10 (brs, 2H), 3.48–3.57 (m, 2H), 2.67 (t, *J* = 11.7 Hz, 2H), 1.63–1.71 (m, 5H), 1.45 (s, 9H), 1.33–1.39 (m, 2H), 1.12–1.23 (m, 2H). HRMS ESI calcd for $C_{19}H_{28}N_4O_4$ 377.2183, found 377.2193.

6-((3-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)propyl) amino)furo[3,2-*c*]pyridin-3(2*H*)-one (17a)

^{1}H NMR ($CDCl_3$) δ: 8.46 (s, 1H), 8.16 (s, 2H), 5.88 (s, 1H), 5.32 (brs, 1H), 4.70 (d, *J* = 12.5 Hz, 2H), 4.61 (s, 2H), 3.28 (dd, *J* = 12.5, 6.3, 2H), 2.84 (td, *J* = 13.1, 2.6 Hz, 2H), 2.45 (q, *J* = 7.6 Hz, 2H), 1.83–1.63 (m, 5H), 1.43–1.32 (m, 2H), 1.26–1.11 (m, 5H). HRMS ESI calcd for $C_{21}H_{27}N_5O_2$ 382.2237, found 382.2244.

Tert-butyl
4-(3-((3-oxo-2,3-dihydrofuro[3,2-*c*]pyridin-6-yl)amino)propyl)piperidine-1-carboxylate (17b)
^{1}H NMR ($CDCl_3$) δ: 8.46 (s, 1H), 5.87 (s, 1H), 5.34 (brs, 1H), 4.61 (s, 2H), 4.09 (brs, 2H), 3.27 (d, *J* = 6.6, 2H), 2.67 (t, *J* = 12.6 Hz, 2H), 1.71–1.64 (m, 5H), 1.45 (s, 9H), 1.38–1.32 (m, 2H), 1.25–1.10 (m, 2H). HRMS ESI calcd for $C_{20}H_{29}N_3O_4$ 376.2230, found 376.2240.

6-((3-(1-(5-Methoxypyrimidin-2-yl)piperidin-4-yl)propyl)amino)furo[3,2-*c*]pyridin-3(2H)-one (17c)
^{1}H NMR ($CDCl_3$) δ: 8.46 (s, 1H), 8.08 (s, 2H), 5.88 (s, 1H), 5.45 (brs, 1H), 4.67–4.54 (m, 4H), 3.79 (s, 3H), 3.28 (d, *J* = 6.2, 2H), 2.82 (td, *J* = 13.1, 2.6 Hz, 2H), 1.86–1.61 (m, 4H), 1.59–1.53 (m, 1H), 1.44–1.32 (m, 2H), 1.27–1.12 (m, 2H). HRMS ESI calcd for $C_{20}H_{25}N_5O_3$ 384.2029, found 384.2041.

6-((3-(1-(5-Fluoropyrimidin-2-yl)piperidin-4-yl)propyl)amino)furo[3,2–*c*]pyridin-3(2H)-one (17d)
^{1}H NMR ($CDCl_3$) δ: 8.46 (s, 1H), 8.17 (s, 2H), 5.88 (s, 1H), 5.31 (brs, 1H), 4.59–4.69 (m, 4H), 3.22–3.34 (m, 2H), 2.79–2.90 (m, 2H), 1.11–1.82 (m, 9H). HRMS ESI calcd for $C_{19}H_{22}FN_5O_2$ 372.1830, found 372.1835.

6-((3-(1-(5-(Trifluoromethyl)pyrimidin-2-yl)piperidin-4-yl)propyl)amino)furo[3,2–*c*]pyridin-3(2*H*)-one (17e)
^{1}H NMR ($CDCl_3$) δ: 8.50–8.41 (m, 3H), 5.88 (d, *J* = 0.5 Hz, 1H), 5.46 (brs, 1H), 4.87–4.78 (m, 2H), 4.61 (s, 2H), 3.29 (dd, *J* = 12.5, 6.4 Hz, 2H), 2.91 (td, *J* = 13.1, 2.6 Hz, 2H), 1.85–1.76 (m, 2H), 1.75–1.67 (m, 2H), 1.65–1.57 (m, 1H), 1.43–1.33 (m, 2H), 1.23–1.11 (m, 2H). HRMS ESI calcd for $C_{20}H_{22}F_3N_5O_2$ 422.1798, found 422.1803.

6-((3-((1*R*,3*S*,5*S*)-8-(5-Ethylpyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)propyl)amino)furo[3,2-*c*]pyridin-3(2H)-one (17f)
^{1}H NMR ($CDCl_3$) δ: 8.45 (s, 1H), 8.16 (s, 2H), 5.85 (s, 1H), 5.41 (s, 1H), 4.68–4.63 (m, 2H), 4.62–4.59 (m, 2H), 3.25–3.19 (m, 2H), 2.49–2.42 (m, 2H), 2.32–2.29 (m, 2H), 2.08–2.04 (m, 2H), 1.78–1.75 (m, 2H), 1.68–1.64 (m, 2H), 1.64–1.60 (m, 2H), 1.58–1.55 (m, 1H), 1.32–1.28 (m, 2H), 1.31–1.19 (m, 3H). HRMS ESI calcd for $C_{23}H_{29}N_5O_2$ 408.2394, found 408.2393.

6-((3-(((1*R*,5*S*)-8-(5-Ethylpyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)oxy)propyl)amino)furo[3,2-*c*]pyridin-3(2*H*)-one (17g)
^{1}H NMR ($CDCl_3$) δ: 8.46 (s, 1H), 8.18 (s, 2H), 6.06 (s, 1H), 5.91 (s, 1H), 4.64–4.61 (m, 4H), 3.56–3.52 (m, 3H), 3.45–3.39 (m, 2H), 2.46 (q, *J* = 7.6 Hz, 2H), 2.24–2.13 (m, 2H), 2.12–1.98 (m, 4H), 1.98–1.84 (m, 4H), 1.19 (t, *J* = 7.6 Hz, 3H). HRMS ESI calcd for $C_{23}H_{29}N_5O_3$ 424.2343, found 424.2341.

6-((3-(1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)propyl)amino)furo[3,2-*c*]pyridin-3(2*H*)-one (17h)
^{1}H NMR ($CDCl_3$) δ: 8.47 (s, 1H), 5.88 (s, 1H), 5.31 (s, 1H), 4.62 (s, 2H), 4.13 (d, *J* = 12.9 Hz, 2H), 3.29 (dd, *J* = 12.3, 6.2 Hz, 2H), 3.02 (td, *J* = 13.0, 2.8 Hz, 2H), 2.88 (sep, *J* = 7.0 Hz, 1H), 1.78 (d, *J* = 11.9 Hz, 2H), 1.74–1.64 (m, 2H), 1.55–1.44 (m, 1H), 1.43–1.34 (m, 2H), 1.34–1.19 (m, 8H).
HRMS ESI calcd for $C_{20}H_{27}N_5O_3$ 386.2186, found 386.2195.

6-((3-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)butyl)amino)furo[3,2–*c*]pyridin-3(2*H*)-one (17i)
^{1}H NMR ($CDCl_3$) δ: 8.46 (s, 1H), 8.16 (s, 2H), 5.88 (s, 1H), 5.35 (brs, 1H), 4.75–4.79 (m, 2H), 4.61 (s, 2H), 3.20–3.41 (m, 2H), 2.75–2.83 (m, 2H), 2.45 (q, *J* = 8.0 Hz, 2H), 1.74–1.81 (m, 1H), 1.66–1.70 (m, 2H), 1.45–1.52 (m, 3H), 1.23–1.36 (m, 2H), 1.18 (t, *J* = 8.0 Hz, 3H), 0.94 (d, *J* = 8.0 Hz, 3H). HRMS ESI calcd for $C_{22}H_{29}N_5O_2$ 396.2393, found 396.2387.

6-((3-(1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)butyl)amino)furo[3,2-*c*]pyridin-3(2*H*)-one (17j)
^{1}H NMR ($CDCl_3$) δ: 8.46 (s, 1H), 5.88 (s, 1H), 5.29 (brs, 1H), 4.62 (s, 2H), 4.15–4.23 (m, 2H), 3.21–3.43 (m, 2H), 2.96–3.03 (m, 2H), 2.83–2.93 (m, 1H), 1.68–1.80 (m, 3H), 1.32–1.58 (m, 5H), 1.28 (d, *J* = 8.0 Hz, 6H), 0.95 (d, *J* = 8.0 Hz, 3H). HRMS ESI calcd for $C_{21}H_{29}N_5O_3$ 400.2342, found 400.2339.

Biology

In vitro assays

hERG binding assay

hERG channel inhibition was assessed using Predictor™ hERG Fluorescence Polarization Assay Kit (Invitrogen, Carlsbad, CA). The positive control, E-4031, and test compounds were dissolved in DMSO. The assay was performed according to the manufacture's protocol.

Cell-based cAMP functional assay

Cellular cAMP was measured using HTRF cAMP HiRange reagent (CISBIO, Cedex, France). CHO-K1 cells expressing human GPR119 receptors were obtained from Applied Cell Sciences and were grown in flasks containing F-12 medium supplemented with 10% FBS, 1% non essential amino acids, 20 mM HEPES, 50 units/ml penicillin, 50 µL/mL streptomycin, and 400 µg/mL geneticin. CHO-K1 cells expressing mouse GPR119 receptors were prepared in house and were grown in flasks containing F-12 medium supplemented with 10% FBS, 1% non essential amino acids, 20 mM HEPES, 50 units/mL penicillin, 50 µL/mL streptomycin, and 400 µg/ml geneticin. For the hGPR119 or mGPR119 functional assay, cells expressing hGPR119 or mGPR119 were harvested, re-suspended in incubation buffer (F-12 medium, 20 mM HEPES, 1 mM IBMX), and dispensed into 384-well plates at a density of 1.5×10^4 cells/well in the presence or absence of test compounds. The cells were then incubated at 37 °C for 30 min, after which cAMP-d2–conjugated antibody and anti-cAMP-cryptase–conjugated antibody were added to the plate. After incubation for 60 min at room temperature, cellular cAMP was measured using a HTRF® (TR-FRET) Microplate Reader ARTEMIS (Furuno Electric Co., Ltd., Tokyo, Japan). Data were analyzed based on the ratio of fluorescence intensity of each well at 620 and 665 nm. Sigmoidal dose-response equation was used to determine EC_{50} and Emax values, which represent relative efficacy defined as the ratio of test compound response to AR231453 maximum response.

In vivo assays

All in vivo protocols were approved by Sanwa Kagaku Kenkyusho Animal Care Committee.
Male C57BL/6J mice (Charles River Laboratories, Yokohama, Japan) were housed under a 12-h light-dark cycle and allowed free access to water and a standard laboratory diet.

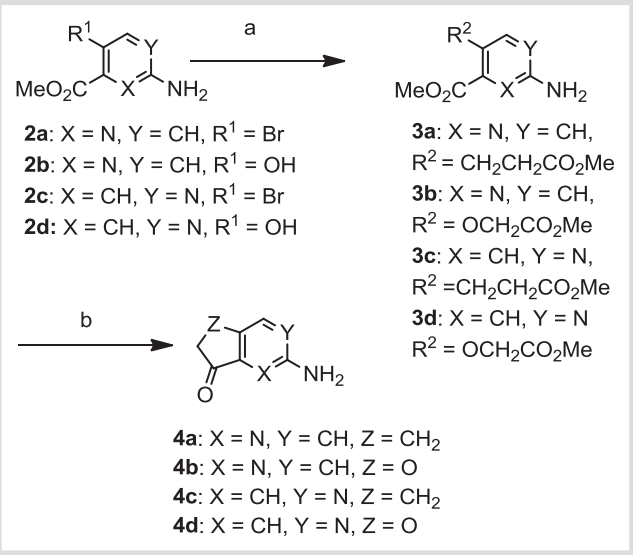


Fig. 2 Synthesis of compounds **4**. Reagents and conditions: from **2a** and **2c** to **4a** and **4c** respectively. **a** (i) Methyl acrylate, $PdCl_2(Po\text{-}Tol_3)_2$, Et_3N, DMF (ii) H_2, Pd/C, EtOH **b** (i) *tert*-BuOK, DMF (ii) NaCl. Reagents and conditions: from **2b** and **2d** to **4b** and **4d** respectively. **a** $BrCH_2CO_2Me$, Cs_2CO_3, DMF **b** (i) *tert*-BuOK, DMF (ii) NaOH.

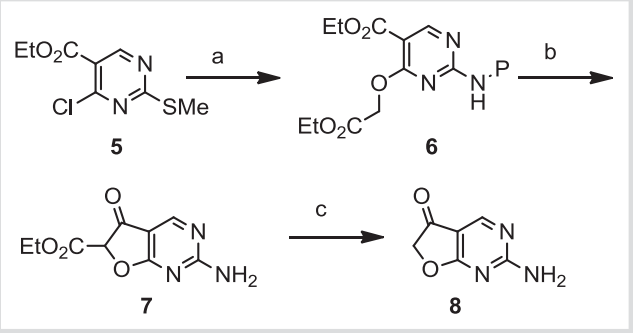


Fig. 3 Synthesis of compound **8**. Reagents and conditions: **a** (i) $HOCH_2CO_2Et$, NaH, THF (ii) *m*-CPBA, DCM (iii) *p*-$MPMNH_2$, Et_3N, NMP **b** (i) TFA(ii) *tert*-BuOK, DMF **c** conc. HCl, MeOH.

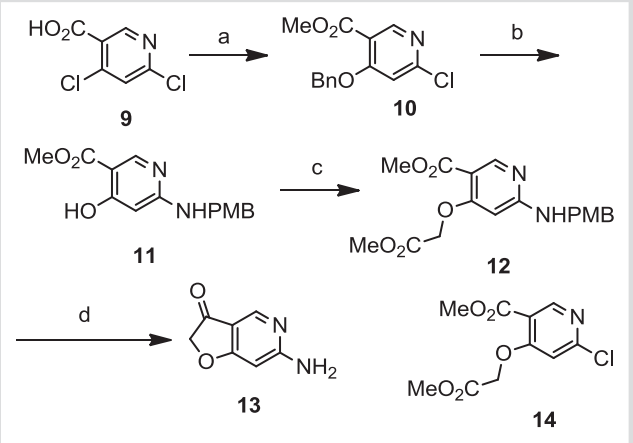


Fig. 4 Synthesis of compound **13**. Reagents and conditions: **a** (i) BnOH, NaH, THF (ii) MeI, K_2CO_3, DMF **b** (i) *p*-$MPMNH_2$, Et_3N, NMP (ii) H_2, Pd/C, MeOH **c** $BrCH_2CO_2Me$, K_2CO_3, DMF **d** (i) LDA, THF (ii) conc. HCl, MeOH (iii) TFA.

Gastric emptying

Liquid-phase gastric emptying was assessed using the acetaminophen absorption test according to a literature method [19]. Male C57BL/6J mice, 11 week of age, were fasted overnight, and orally given 10 mg/kg of **17i** or vehicle (5% DMSO, 0.1% Tween 80 and 0.5% methylcellulose) 30 min before oral administration of an aqueous solution of 20% glucose and 1% acetaminophen (Sigma-Aldrich, St. Louis, MO) at a dose of 2 g/kg glucose–100 mg/kg acetaminophen. Blood samples (40 µL) were collected 10 and 20 min after acetaminophen administration and plasma acetaminophen levels were measured using an acetaminophen assay kit (Cambridge Life Sciences, Cambridge, U.K.).

GLP-1 secretion

Male C57BL/6J mice, 10 week of age, were fasted 5 h, and orally administered 30 mg/kg of **17i** or vehicle (5% DMSO, 0.1% Tween 80 and 0.5% methylcellulose). Plasma total GLP-1 (both intact GLP-1 (7-36) amide and its primary metabolite) levels 30 min after administration were measured by ELISA using anti-GLP-1 monoclonal antibodies.

Statistical significance

The data are expressed as the mean ± SEM (standard error of mean). Statistical significance was determined using one-way ANOVA and Dunnett multiple comparison test.

Results and Discussion

Chemistry

Following a known approach to hERG optimization [12], our strategy was based on attenuating the basicity of the amino group by replacing the adjacent benzene ring with electron-deficient heteroaromatic rings. From a literature precedent [13], the bicyclic core systems containing these heteroaromatic rings could be constructed by intramolecular Dieckmann condensation. Synthesis of the target compounds **15**–**17** could be accomplished by decarboxylation followed by hydrophobic chain elongation achieved by reductive amination. This synthetic route allowed for 2-round optimization with an array of heterocyclic cores and side chains.

Thus, Heck reaction of **2a** and **2c** with methyl acrylate proceeded smoothly without protecting the 2-amino group. After hydrogenation, Dieckmann condensation of **3a** and **3c** followed by decarboxylation gave the desired compounds **4a** and **4c** in good yields. Synthesis of the oxa-analogues **4b** and **4d** followed the same reaction sequence, except that selective *O*-aklylation of **2b** and **2d** with α-haloacetate esters was carried out at the first step of introduction of the requisite acetate function (**Fig. 2**). By analogy, the 2-aminofuro[2,3-*d*]pyrimidin-5(6*H*)-one **8** and its pyridine analogue **13** were prepared from the commercially available pyrimidine **5** and pyridine **9**, respectively (**Fig. 3, 4**). An attempt to replace the chlorine atom of **14** with a *p*-methoxybenzyl amine was not successful, which made our synthetic scheme of **13** lengthy.

With the fused heterocyclic cores **4**, **8** and **13** in hand, the stage was set for chain elongation. In our previous survey of reductive amination conditions for analogous amines [10], $NaBH(OAc)_3$ was found to be a suitable reagent. Likewise, reaction of **4**, **8** and **13** with the corresponding aldehydes gave all target compounds in moderate to good yields with the exception of **15d**, due to instability of **4d** under the reaction conditions described in **Fig. 5**.

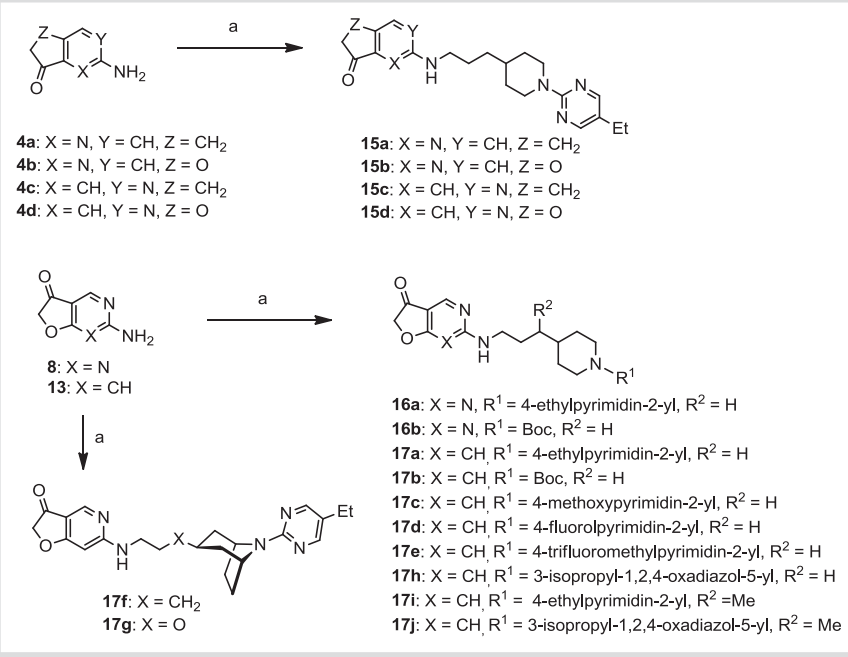
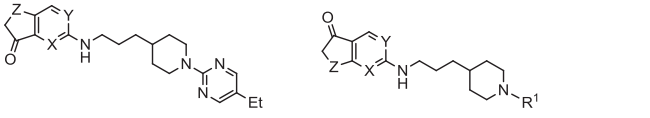


Fig. 5 Synthesis of compounds **15–17**. Reagents and conditions: **a** (i) Corresponding alcohol, Dess-martin periodinane, DCM (ii) $NaBH(OAc)_3$, AcOH (Method A) or DCM (Method B).

Table 1 Test compounds agonistic activity for human and mouse GPR119 receptors, and their hERG channel inhibition.**Table 1** Test compounds agonistic activity for human and mouse GPR119 receptors, and their hERG channel inhibition.



1a: X = Y = CH, Z = CH_2
1b: X = Y = CH, Z = O
15a: X = N, Y = CH, Z = CH_2
15b: X = N, Y = CH, Z = O
15c: X = CH, Y = N, Z = CH_2

1c: X = Y = CH, Z = CH_2, R^1 = Boc
16a: X = Y = N, Z = O, R^1 = 4-ethylpyrimidin-2-yl
16b: X = Y = N, Z = O, R^1 = Boc
17a: X = CH, Y = N, Z = O, R^1 = 4-ethylpyrimidin-2-yl
17b: X = CH, Y = N, Z = O, R^1 = Boc

Compound	Compounds agonistic activity[b] for GPR119 Human (nM) EC_{50}	Emax	Mouse (nM) EC_{50}	Emax	hERG inhibition (%)[c]
1a[a]	51	113	167	110	14
1b[a]	58	110	160	109	21
15a	78	115	54	110	NT[d]
15b	1098	110	1319	97	NT[d]
15c	114	117	147	113	NT[d]
1c[a]	52	94	66	108	0
16a	46	112	75	105	0
16b	(26%)	110	513	120	3
17a	31	111	45	103	0
17b	(57%)	108	255	113	9

[a] Reported in ref [10]. [b] Values in parentheses indicate agonistic activity at 100 µM. Emax is %maximum, compared to the maximum response of AR231453. [c] Values indicate %inhibition at 3 µM in competitive hERG binding assay using ^3H defetilide. [d] Not tested

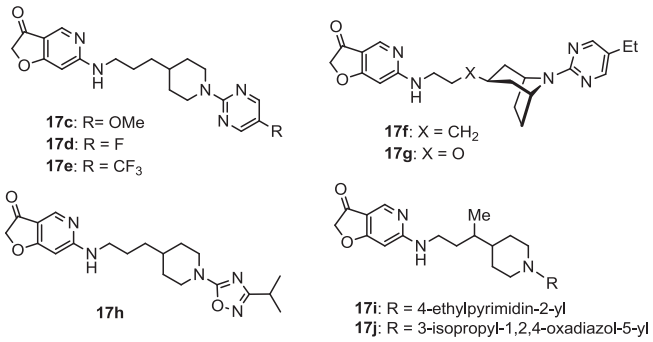
Biology

Results of test compounds biological evaluation are summarized in **Table 1**. In the aza-analogues of the parent compounds **1a** and **1b**, compounds **15a**–**c** showed reduced agonistic activity for human GPR119, while **15a** and **15c** maintained agonistic activity for mouse GPR119. In the 6-aminobenzofuran-3(2*H*)-one series, the parent compound **1c** exhibited good agonistic activity for both human and mouse GPR119 (EC_{50}: 52 and 66 nMs in human and mouse respectively) with no significant hERG channel inhibition. The heterocyclic analogues **16a** and **17a** showed somewhat improved agonistic activity for both type of receptors with undetected levels of hERG channel inhibition, although the pyridine analogue **17a** seemed to have more potent agonistic activity than the pyrimidine analogue **16a**. This trend was also observed with the *N-tert*-butoxycarbonyl analogues **16b** and **17b**. Based on these findings, **17a** was chosen as starting point for further optimization, which shifted to exploring the side chain.

Pioneering works have revealed productive substituents, such as fluoro and methyl groups, around the side chains and indicated their favorable topological location [6–8, 14–19]. Taking this information into account, we prepared compounds **17c**–**j** with the hope of improved agonistic activity for GPR119 receptors (**Table 2**). Gratifyingly, acceptable levels of hERG channel inhibition were observed with all compounds, suggesting that 6-aminofuro[3,2–*c*]pyridin-3(2*H*)-one may be a promising scaffold for design of GPR119 agonists. Replacement of the ethyl group in **17a** by a methoxy, fluoro, or trifluoromethyl group (e.g. **17c**–**e**) had no positive effects on the agonistic activity. Unlike earlier observation that replacement of the piperidine moiety with a constrained 7-azabicyclo[3.3.1]nonane ring enhances GPR119 agonistic activity in the pyridin-3-yloxypyrimidine series, significant loss in activity was observed with compounds **17f** and **17g**. Introduction of 3-isopropyl-1,2,4-oxadiazole, a known surrogate for the pyrimidine moiety, also gave a slight loss in activity, while **17h** was equipotent with **17c**–**e**. As our exploration around the side chain terminus resulted in no improvement, we moved to introduction of a methyl group adjacent to the terminal piperidine moiety. Compounds **17i** and **17j** were thus prepared and tested. Fortunately, **17i** showed 2-fold improved activity with a human EC_{50} value of 14 nM. Also, this subtle effect of the methyl group was observed with **17j** with a human EC_{50} value of 18 nM.

With **17i** in hand, we briefly examined the effect of this compound on gastric emptying, using acetaminophen absorption method [10, 11, 20]. Fasted mice were treated with 10 mg/kg of **17i,** and 30 min later with 100 mg/kg of acetaminophen as a 2 g/kg glucose-containing aqueous solution. Plasma acetaminophen

Table 2 Optimized compounds agonistic activity for human and mouse GPR119 receptors, and their hERG channel inhibition.



Compound	Compounds agonistic activity[a] for GPR119 Human (nM) EC_{50}	Emax	mouse (nM) EC_{50}	Emax	hERG inhibition (%)[b]
17c	64	106	126	104	0
17d	51	111	70	98	0
17e	51	94	30	72	NT[c]
17f	(58%)	100	NT[c]	NT[c]	3
17g	890	91	>10000	14	NT[c]
17h	51	108	79	108	0
17i	14	112	68	104	1
17j	18	110	61	106	0

[a]Values in parentheses indicate agonistic activity at 100 µM. Emax is %maximum, compared to the maximum response of AR231453. [b] Values indicate %inhibition at 3 µM in competitive hERG binding assay using ^{3}H defetilide. [c] Not tested

Table 3 Effects of **17i** on gastric emptying and plasma levels of total GLP-1[a]

	Plasma acetaminophen conc. (mM) 10 min	20 min	$AUC_{0-20\,min}$ (mM·min)	total GLP-1 (pM)[b] 30 min
Control	0.355 ± 0.019	0.364 ± 0.013	5.38 ± 0.23	4.40 ± 0.72
17i	0.263 ± 0.022**	0.284 ± 0.018***	4.05 ± 0.30**	9.76 ± 0.65***

[a]Statistical significance was tested using one-way ANOVA and Dunnett multiple comparison test. **, p<0.01 vs. vehicle control.***, p<0.001 vs. vehicle control. Data are expressed as the mean ± SEM. [b] Determined by ELISA 30 min after administration

concentrations were determined at 10 and 20 min after acetaminophen oral administration. Compound **17i** produced a significant decrease in acetaminophen plasma levels at both time points, indicating a delay in gastric emptying (**Table 3**). These encouraging results on gastric emptying led us to further examine plasma levels of total GLP-1. Thus, fasted mice were orally treated with 30 mg/kg of **17i** as an aqueous suspension and plasma total GLP-1 levels were assayed by ELISA. **17i** produced a significant increase in plasma total GLP-1 levels 30 min after treatment, while no significant change was observed in the vehicle control compared to pretreatment baseline (data not shown). These findings suggest that **17i** has acceptable potential as GPR119 agonist.

Conclusion

In summary, based on a strategy for attenuating the basicity of the nitrogen atom of the parent compound **1a** by replacing the adjacent benzene ring with electron-deficient heteroaromatic rings, several heterocyclic cores were prepared and 6-aminofuro[3,2-*c*]pyridin-3(2*H*)-one was found as a promising scaffold for GPR119 agonists. Further optimization around the side chain moiety led to discovery of **17i**, which showed not only potent human GPR119 agonistic activity with EC_{50} value of 14 nM, but also a delay gastric emptying and increase in total plasma GLP-1 levels in mice.

Conflict of Interest

The authors report no conflict of interest.

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