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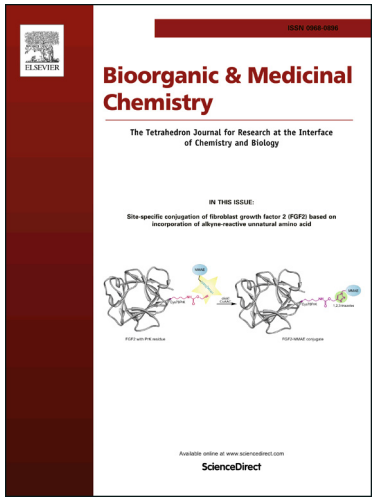

Novel 3*H*-[1,2,3]triazolo[4,5-*c*]pyridine derivatives as GPR119 agonists: Synthesis and structure-activity/solubility relationships

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Novel 3*H*-[1,2,3]triazolo[4,5-*c*]pyridine derivatives as GPR119 agonists: Synthesis and structure-activity/solubility relationships

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1. Introduction

Diabetes is a complex metabolic disorder afflicting more than 400 million people worldwide, and the prevalence is expected to rise to 642 million by 2040.[1] Type 2 diabetes mellitus (T2DM) is the most common form of diabetes characterized by hyperglycemia resulting from impaired insulin secretion and insulin resistance. Long-term hyperglycemia results in an increased risk of microvascular and macrovascular complications which can lead to blindness, renal failure, diabetic foot disorders, heart attacks and strokes. Although multiple oral antidiabetic agents, such as sulfonylureas, meglitinides, biguanides, thiazolidinediones, α-glucosidase inhibitors and dipeptidyl-peptidase-4 (DPP-4) inhibitors, have been used for the treatment of T2DM, many patients fail to achieve the desired level of glycemic control.[2,3] Recently, a sodium-dependent glucose co-transporter 2 (SGLT2) inhibitor has been used clinically; this inhibitor exerts a glucose-lowering effect without causing hypoglycemia or weight gain. However, a significant need for the development of new antidiabetic agents with greater safety and efficacy continues to exist.

GPR119 is a G-protein coupled receptor (GPCR) that is predominantly expressed in the pancreatic β-cells and gastrointestinal L-cells. Oleoyl-lysophosphatidylcholine and oleoylethanolamide (OEA) have been identified as endogenous agonists for the GPR119 receptor.[4,5] The activation of the GPR119 receptor increases the cellular cAMP levels, leading to glucose-dependent insulin secretion from pancreatic β-cells.[6] In addition, the activation of the GPR119 receptor in the gut results in the release of incretins, such as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), from enteroendocrine cells.[7] GLP-1 and GIP stimulate insulin secretion from

β-cells in a glucose-dependent manner and protect β-cells against apoptosis.[8,9] This glucose-dependent dual mechanism of action suggests that GPR119 agonists can improve glycemic control without inducing hypoglycemia.

To date, multiple small-molecule GPR119 agonists have been investigated by several research groups,[10,11] which has led to the development of some clinical compounds such as APD668,[12] GSK1292263,[13] and MBX-2982[14] (Figure 1).

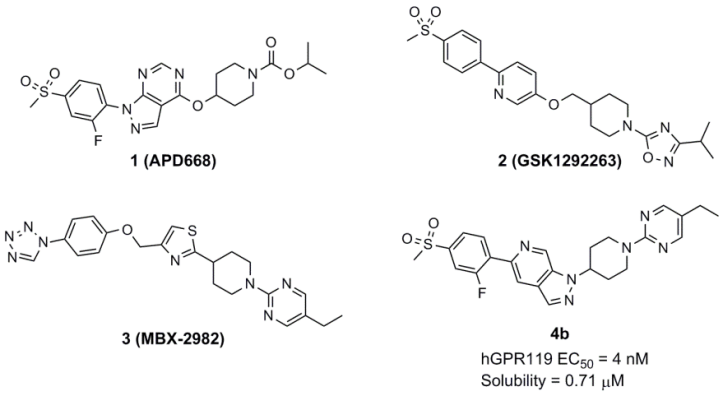


Figure 1. Representative GPR119 receptor agonists.

We previously reported a series of 1*H*-pyrazolo[3,4-*c*]pyridine derivatives as a new class of GPR119 agonists,[15] and compound **4b** (TP0456330) was found to be a highly potent GPR119 agonist with an EC_{50} of 4 nM (Figure 1). However, compound **4b** had a poor aqueous solubility (0.71 μM), leading to a low bioavailability in rats. Generally, a poor aqueous solubility does not only cause low bioavailability, but also produces erratic assay results in *in vitro* studies (such as hERG binding assays). In addition, researchers at AstraZeneca reported that the development of compounds with a poor aqueous solubility (< 10 μM) carries a high risk of not advancing because of potential toxicity that might not be recognized during preclinical studies.[16] Therefore, we defined an aqueous solubility of more than 10 μM as a goal for further optimization to generate a preclinical candidate.

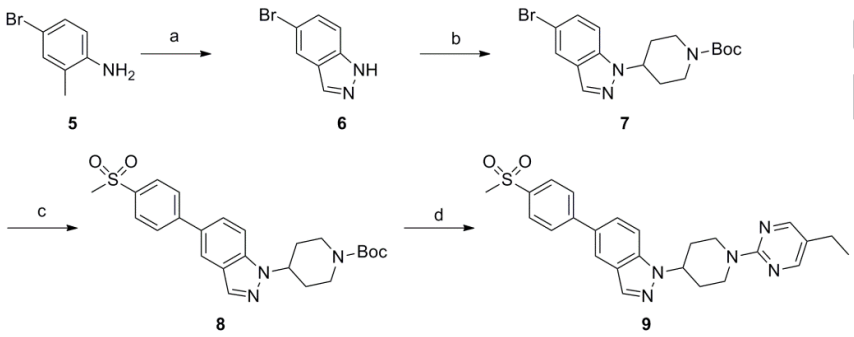
Herein, we describe the synthesis and optimization of 1*H*-pyrazolo[3,4-*c*]pyridine and 3*H*-[1,2,3]triazolo[4,5-*c*]pyridine derivatives with improved aqueous solubilities obtained by reducing lipophilicity and lowering the melting point.[17]

2. Chemistry

The 1*H*-pyrazolo[3,4-*c*]pyridine derivatives **4a-g** shown in Tables 1 and 3 were synthesized as described in our previous paper.[15]

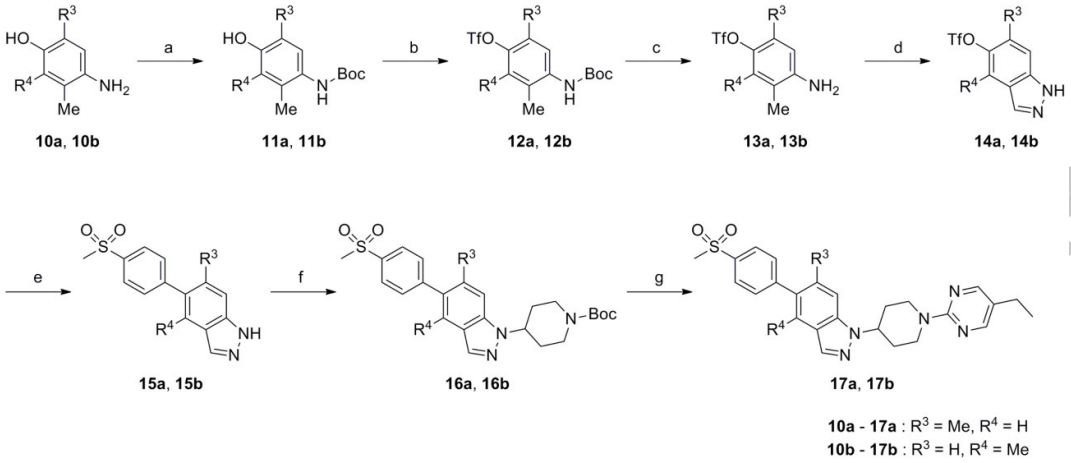
The synthesis of the indazole derivatives **9**, **17a** and **17b** in Table 1 is shown in Schemes 1 and 2. For the synthesis of compound **9**, a commercially available starting material,

4-bromo-2-methylaniline (**5**), was cyclized with $NaNO_2$ under acidic conditions to form 5-bromo-1*H*-indazole (**6**); a coupling reaction of **6** with *tert*-butyl 4-[(methanesulfonyl)oxy]piperidine-1-carboxylate followed by separation of the mixture of regioisomers using silica-gel column chromatography then provided **7**. Subsequent Suzuki coupling of **7** with arylboronic acid under microwave irradiation yielded **8**. Finally, the removal of the *tert*-butoxycarbonyl group (Boc) under acidic conditions followed by treatment with *N*,*N*-diisopropylethylamine (DIPEA) and 2-chloro-5-ethylpyrimidine under heating conditions yielded the desired product **9**.



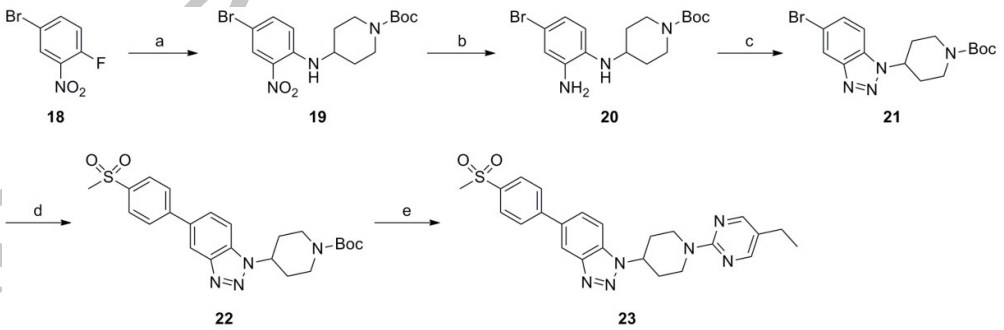
Scheme 1. (a) $NaNO_2$, AcOH, H_2O, rt; (b) NaH, *tert*-butyl 4-[(methanesulfonyl)oxy]piperidine-1-carboxylate, DMF, 90 ˚C; (c) [4-(methanesulfonyl)phenyl]boronic acid, $PdCl_2(dppf)\cdot CH_2Cl_2$, Na_2CO_3, H_2O, DMF, microwave, 110 ˚C; (d) (1) HCl, MeOH, 1,4-dioxane, rt; (2) 2-chloro-5-ethylpyrimidine, DIPEA, DMF, 100 ˚C.

Methyl substituted indazole derivatives **17a** and **17b** were synthesized from commercially available aminophenol derivatives **10a** and **10b**. The amino group was protected by a Boc group using di-*tert*-butyl dicarbonate (Boc_2O) and the phenol moiety was then trifluoromethanesulfonylated using triflic anhydride (Tf_2O) to yield **12a** and **12b**, respectively. After the removal of the Boc group of **12a** and **12b** under acidic conditions, the resulting aniline was cyclized with $NaNO_2$ to yield indazole derivatives **14a** and **14b**; Suzuki coupling with [4-(methanesulfonyl)phenyl]boronic acid under a condition similar to that of **7** in Scheme 1 was then performed, producing **15a** and **15b**. Furthermore, the nitrogen atom of indazole structure was alkylated with *tert*-butyl 4-[(methanesulfonyl)oxy]piperidine-1-carboxylate to provide **16a** and **16b**, respectively. Finally, the removal of the Boc group followed by treatment with 2-chioro-5-ethylpyrimidine yielded the methyl substituted indazole derivatives **17a** and **17b**.



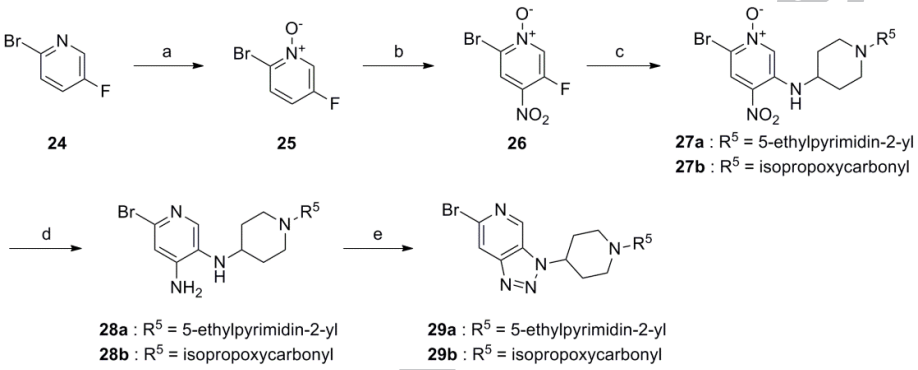
Scheme 2. (a) Et_3N, Boc_2O, MeOH, rt; (b)Tf_2O, pyridine, $CHCl_3$, rt; (c) HCl, EtOAc, rt; (d) $NaNO_2$, AcOH, H_2O, rt; (e) [4-(methanesulfonyl)phenyl]boronic acid, $PdCl_2(dppf)\cdot CH_2Cl_2$, Na_2CO_3, H_2O, DMF, microwave, 130 ˚C; (f) Cs_2CO_3, *tert*-butyl 4-[(methanesulfonyl)oxy]piperidine-1-carboxylate, DMSO, 90 ˚C; (g) (1) HCl, MeOH, 1,4-dioxane, rt; (2) 2-chloro-5-ethylpyrimidine, Cs_2CO_3, DMSO, 120 ˚C.

Scheme 3 shows the synthesis of the benzotriazole derivative **23** (Table 1). An S_NAr reaction between the commercially available 4-bromo-1-fluoro-2-nitrobenzene (**18**) and *tert*-butyl 4-aminopiperidine-1-carboxylate in the presence of Cs_2CO_3 yielded **19**. Reduction of the nitro group of **19** with iron powder and ammonium chloride, followed by the cyclization of the resulting aniline **20** with $NaNO_2$, yielded benzotriazole derivative **21**. Finally, Suzuki coupling, the removal of the Boc group and an *N*-arylation reaction were performed to yield the desired product **23**.



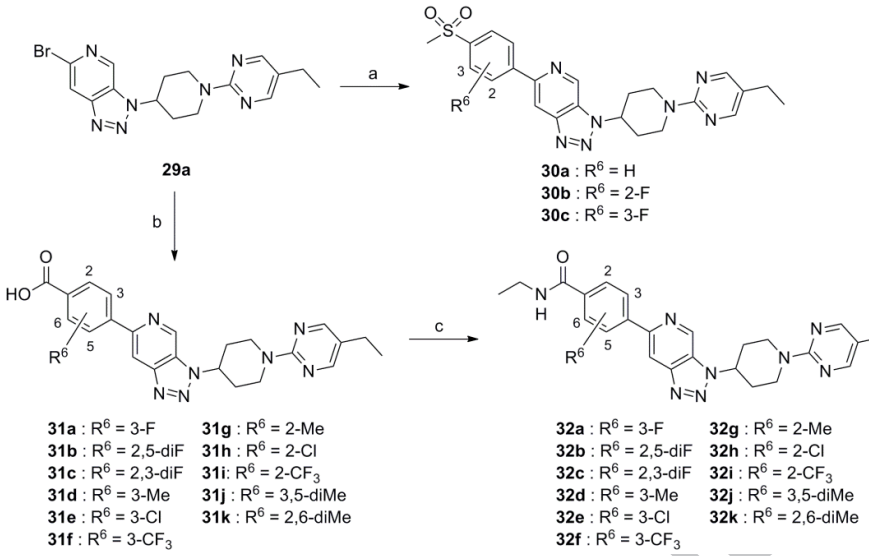
Scheme 3. (a) Cs_2CO_3, *tert*-butyl 4-aminopiperidine-1-carboxylate, DMSO, 100 ˚C; (b) Fe, NH_4Cl, EtOH, H_2O, 78 ˚C; (c) $NaNO_2$, AcOH, H_2O, rt; (d) [4-(methanesulfonyl)phenyl]boronic acid, $PdCl_2(dppf)\cdot CH_2Cl_2$, Na_2CO_3, H_2O, DMF, microwave, 100 ˚C; (e) (1) HCl, MeOH, 1,4-dioxane, rt; (2) 2-chloro-5-ethylpyrimidine, DIPEA, IPA, 80 ˚C.

The synthesis of the 3*H*-[1,2,3]triazolo[4,5-*c*]pyridine derivatives was performed using commercially available 2-bromo-5-fluoropyridine (**24**), as shown in Schemes 4-6. After the *N*-oxidation of **24** with urea hydrogen peroxide and trifluoroacetic anhydride (TFAA),[18] nitration of the resulting **25** with fuming nitric acid and concentrated sulfuric acid gave **26**. Furthermore, compounds **27a** and **27b** were obtained by the S_NAr reaction of **26** with the corresponding amine, and the resulting nitro groups were reduced by Fe to yield **28a** and **28b** respectively. The cyclization reaction of **28a** and **28b** was accomplished in the presence of $NaNO_2$ and trifluoroacetic acid (TFA) to yield the 3*H*-[1,2,3]triazolo[4,5-*c*]pyridine intermediates **29a** and **29b**, respectively, although the reaction did not proceed using AcOH instead of TFA, probably because of the lack of nucleophilicity of the amines.

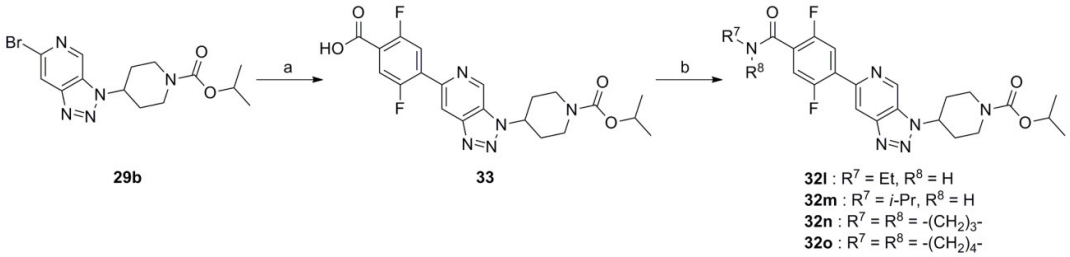


Scheme 4. (a) H_2O_2-urea, TFAA, $CHCl_3$, rt; (b) fuming HNO_3, H_2SO_4, 100 ˚C; (c) for **27a**, Cs_2CO_3, 1-(5-ethylpyrimidin-2-yl)piperidin-4-amine, DMSO, rt; for **27b**, Cs_2CO_3, isopropyl 4-aminopiperidine-1-carboxylate, DMSO, rt; (d) Fe, AcOH, 100 ˚C; (e) $NaNO_2$, TFA, H_2O, rt.

Compounds **30a-c** and **32a-o** were synthesized as shown in Schemes 5 and 6. Suzuki coupling of **29a** with arylboronic acids produced **30a-c**. Amide compounds **32a-k** were synthesized via the corresponding carboxylic acid intermediates **31a-k** prepared by Suzuki coupling between **29a** and COOH-substituted arylboronic acid derivatives, followed by condensation with ethylamine under a standard condition (Scheme 5). The preparation of compounds **32l-o** was also performed by Suzuki coupling of **29b** with a boronic acid pinacol ester followed by condensation with amines under conditions similar to those described above (Scheme 6).



Scheme 5. (a) $ArB(OH)_2$, $PdCl_2(dppf)\cdot CH_2Cl_2$, Na_2CO_3, H_2O, DMF, 100˚C; (b) for **31a**, 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid, $PdCl_2(dppf)\cdot CH_2Cl_2$, Na_2CO_3, H_2O, DMF, 110 ˚C; for **31b-k**, $ArB(OH)_2$ or ArBpin, $Pd(PPh_3)_4$, Cs_2CO_3, H_2O, EtOH, microwave, 150-160˚C; (c) $EtNH_2$, EDCI·HCl, HOBt·H_2O, Et_3N, DMF, rt.



Scheme 6. (a) 2,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid, $Pd(PPh_3)_4$, Na_2CO_3, H_2O, EtOH, microwave, 160˚C; (b) R^7R^8NH, EDCI·HCl, HOBt·H_2O, Et_3N, DMF, rt.

3. Results and Discussion

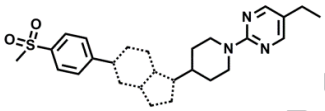
The synthesized compounds were evaluated for their GPR119 agonist potency using a cAMP assay in a human GPR119 cell line and their thermodynamic solubility was assessed in pH6.8 phosphate buffer.

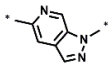
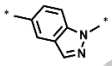
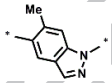
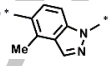
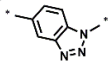
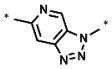
Initially we designed and synthesized compounds bearing various 5-6 fused ring spacers to investigate the effect of the lipophilicity and methyl substitution of the whole molecules on both the solubility and potency (Table 1). Compound **9** with an indazole spacer exhibited a potency comparable to that of 1*H*-pyrazolo[3,4-*c*]pyridine **4a**, while its thermodynamic solubility was at the

lower limit of quantitation and its *C*log*P* value was higher than that of **4a**. In order to evaluate the effect of substitution in the spacer, 6- or 4-methyl-substituted indazole derivatives **17a** and **17b** were prepared. **17a** and **17b** showed decreased potency by a factor of 5 and 245, respectively, compared with **9**. These results indicated that substitution at these positions of the spacer was unfavorable for agonist activity. Benzotriazole derivative **23** was found to have not only a tolerable potency (EC_{50} = 31 nM) but also a lipophilicity lower than that of **9**. Unfortunately, the solubility of **23** was undetectable. Therefore, 3*H*-[1,2,3]triazolo[4,5-*c*]pyridine was designed and synthesized with the aim of achieving a further reduction in the lipophilicity of the spacer,. The resulting derivative **30a** showed a comparable potency (EC_{50} = 21 nM) and solubility (0.28 μM), along with the lowest *C*log*P* value (1.73); therefore, we selected the 3*H*-[1,2,3]triazolo[4,5-*c*]pyridine spacer for used in a further optimization study, described below.

Table 1

Structure-activity/solubility relationships of spacers



Cpd.	Spacer	hGPR119 EC_{50} (nM)	*C*log*P*[a]	Solubility (μM)[b]
4a		13	2.03	0.26
9		14	2.86	<0.11
17a		70	3.06	NT[c]
17b		3423	3.06	NT[c]
23		31	2.28	<0.13
30a		21	1.73	0.28

[a] The *C*log*P* value was calculated using software from Daylight Chemical Information Systems, Inc.

[b] Thermodynamic solubility in pH6.8 phosphate buffer.

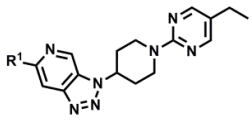
[c] Not tested.

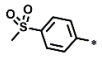
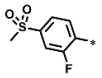
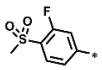
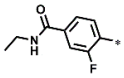
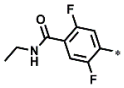
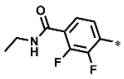
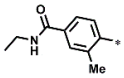
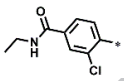
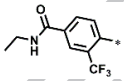
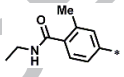
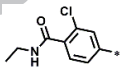
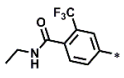
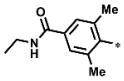
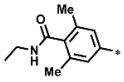
Next, we conducted an optimization study of **30a** focusing on the substituent (R^1) at the 6-position of the 3*H*-[1,2,3]triazolo[4,5-*c*]pyridine spacer (Table 2). **30a** was a crystalline compound possessing a significantly high melting point (269-270 ˚C). We considered that this high melting point was one of the causes of its poor solubility and hypothesized that it resulted from the strong molecular interaction associated with its molecular planarity. Ishikawa and Hashimoto reported that a decrease in the crystal packing energy (melting point) by the disruption of molecular planarity led to an improvement in solubility.[17] Additionally, researchers at AstraZeneca reported the improvement in aqueous solubility of a series of GPR119 agonists through disruption of crystal packing.[19,20] Therefore, in this study, we attempted to improve solubility by lowering the melting point without loss of potency.

Installation of a fluorine atom into the 2- or 3-position of the 4-(methanesulfonyl)phenyl group of **30a** yielded compounds **30b** and **30c** respectively, which ameliorated the potency by 3-fold and 2-fold compared with **30a**[21], but these compounds did not improve the aqueous solubility along with the high melting point. In our previous study, a fluorine substituted ethylcarbamoylphenyl group as an R^1 moiety was shown to enhance potency.[15] Therefore, the installment of a 2-fluoro (**32a**), 2,5-difluoro (**32b**), or 2,3-difluoro (**32c**) substituted ethylcarbamoylphenyl group into R^1 was successively examined. Among these three options, compound **32b** showed excellent potency (EC_{50} = 2 nM), while its aqueous solubility was not improved and was almost equal to that of **30a**. In this case, the installation of a fluorine atom into an aryl ring was insufficient to lower the melting point. Subsequently, the incorporation of a larger substituent than a fluorine atom at the 2-position of the aryl ring was examined. While neither a 2-methyl (**32d**) nor a 2-chloro (**32e**) substitution improved solubility, a 2-trifluoromethyl (**32f**) substitution produced a significant lowering of the melting point (104-106 ˚C) and an improved solubility to a limited degree (1.20 μM). We next investigated substitution at the 3-position of the aryl ring. Although 3-methyl (**32g**), 3-chloro (**32h**) and 3-CF_3 (**32i**) substitution produced little or no improvement in solubility, the melting points of **32g** and **32i** were slightly lower than that of **32b**. Encouraged by the reduction in the melting points of compounds **32d**-**g** and **32i**, we finally investigated di-substitution of the 4-ethylcarbamoylphenyl group. Di-substitution of the methyl groups at the 2,6-position (**32j**) and the 3,5-position (**32k**) of the aryl ring resulted in significant reductions in the melting points, compared with the mono-methyl substitutions (**32d** and **32g**). These results were speculated to be due to the disruption of molecular planarity. Although **32k** showed an improvement in solubility (5.01 μM), the solubility was still insufficient for advancement to *in vivo* studies. We concluded that achieving the target solubility (10 μM) through the modification of this chemical class with a 4-ethylpyrimidine side chain was quite difficult.

Table 2

Structure-activity/solubility relationships of R^1 group



Cpd.	R^1	hGPR119 EC_{50} (nM)	*C*log*P*[a]	Melting point (°C)	Solubility (μM)[b]
30a		21	1.73	269-270	0.28
30b		7	1.95	269-270	<0.12
30c		9	1.95	229-230	<0.15
32a		15	2.92	239	NT[c]
32b		2	2.70	235-236	0.24
32c		10	2.63	224-225	NT[c]
32d		19	2.86	179-180	<0.09
32e		13	3.24	197-198	0.24
32f		60	3.81	104-106	1.20
32g		18	2.82	206-207	1.79
32h		18	2.66	242-245	<0.16
32i		39	2.60	219-221	0.51
32j		83	3.06	109-113	1.86
32k		27	2.98	110-112	5.01

[a] The *C*log*P* value was calculated using software from Daylight Chemical

Information Systems, Inc.

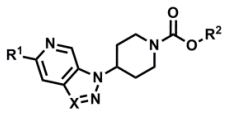
[b] Thermodynamic solubility in pH6.8 phosphate buffer.

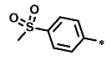
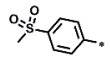
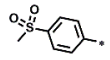
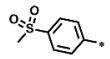
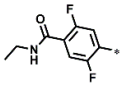
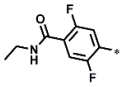
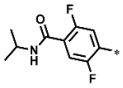
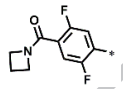
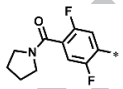
[c] Not tested.

Next, we focused on compounds possessing an alkyl carbamate moiety instead of 4-ethylpyrimidine as the right-hand *N*-capping group (R^2) as shown in Table 3, since reducing the number of aromatic rings in a compound is generally believed to have a positive impact on aqueous solubility.[22] In fact, 1*H*-pyrazolo[3,4-*c*]pyridine derivative **4c** containing isopropyl carbamate resulted in a slight increase in solubility, along with a reduction in the melting point (189-190 ˚C) compared with **4a** (243-244 ˚C). The replacement of isopropylcarbamate with *tert*-butylcarbamate (**4d**) or isobutylcarbamate (**4e**) improved the potency, compared with **4c**. While compound **4e** had a solubility that was comparable to that of **4c**, it was unstable in a human liver microsomal assay, probably because of the lability of the lipophilic isobutylcarbamate moiety. To prevent metabolism, fluorine atoms were introduced into the alkyl group of carbamate. Fluorinated *tert*-butylcarbamate (**4f**) was stable in human liver microsomes but had a low solubility (0.28 μM). Finally, we selected the isopropyl group as an R^2 moiety because of its solubility potential and low melting point. The loss of potency was restored by the installment of a di-fluorine substituted ethylcarbamoylphenyl group into R^1. The resulting compound **4g** exhibited a 4-fold improvement in potency (10 nM), as expected, and a 2-fold improvement in solubility (2.84 μM) compared with **4c**. Switching the spacer to 3*H*-[1,2,3]triazolo[4,5-*c*]pyridine (**32l**) improved the solubility (5.50 μM) because of the lower lipophilicity. Encouraged by this result, the ethylcarbamoyl moiety was optimized by replacement with isopropylcarbamoyl (**32m**), azetidine-1-carbonyl (**32n**), and pyrrolidine-1-carbonyl (**32o**) to evaluate the effects on agonist potency and aqueous solubility. As a result, the isopropylcarbamoyl derivative **32m** was equipotent to the ethylcarbamoyl derivative **32l**, while the azetidine-1-carbonyl derivative **32n** was less potent than **32l** and **32m**. Regarding the solubility, **32m** and **32n** were lower than **32l**. In contrast, pyrrolidine-1-carbonyl (**32o**) exhibited a significant improvement in solubility (15.9 μM) meeting the criteria of > 10 μM and good potency (EC_{50} = 65 nM). Since the melting point of **32o** was the lowest (147-148 ˚C) among these amide compounds, the relatively bulky pyrrolidine moiety was thought to disrupt the coplanarity between the amide group and the phenyl ring. Furthermore, compound **32o** was stable in human liver microsomes.

Table 3

Structure-activity/solubility relationships of R^1 and R^2 group



Cpd.	R^1	X	R^2	hGPR119 EC_{50} (nM)	*C*log*P*[a]	Melting point (°C)	Solubility (μM)[b]	hMS (%)[c]
4c		CH	*i*-Pr	42	2.21	189-190	1.51	24.1
4d		CH	*t*-Bu	20	2.60	NT[d]	NT[d]	NT[d]
4e		CH	*i*-Bu	11	2.82	212-213	1.18	79.8
4f		CH	$C(CH_3)_2CHF_2$	23	2.65	204-205	0.28	3.9
4g		CH	*i*-Pr	10	3.18	150-151	2.84	12.4
32l		N	*i*-Pr	37	2.87	183	5.50	11.0
32m		N	*i*-Pr	33	3.18	197-198	0.84	NT[d]
32n		N	*i*-Pr	61	2.40	195-196	2.7	5.4
32o		N	*i*-Pr	65	2.95	147-148	15.9	9.3

[a] The *C*log*P* value was calculated using software from Daylight Chemical Information Systems, Inc.

[b] Thermodynamic solubility in pH6.8 phosphate buffer.

[c] % Metabolized after 15-min incubation with human liver microsomes (1 mg protein/mL).

[d] Not tested.

Given the promising solubility and good potency and metabolic stability, we conducted a pharmacokinetic study of compound **32o** (TP0459107) in SD rats. The resulting PK parameters of **32o** and **4b** are shown in Table 4. Unfortunately, the bioavailability of compound **32o** was comparable to that of **4b**. On the other hand, the systemic clearance of compound **32o** was higher than that of **4b**. Both compounds exhibited high membrane permeability in the PAMPA. These data indicated that the increased solubility of compound **32o**, compared with **4b**, contributed to an

improvement in oral absorption but it was compromised by higher clearance than **4b**. To identify compounds for *in vivo* efficacy studies, further optimization would be required.

Table 4

Pharmacokinetic parameters in SD rats and permeability of **4b** and **32o**

Compound	IV (3 mg/kg)[a]			PO (10 mg/kg)[b]		
	CL (mL/h/kg)	Vdss (mL/kg)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng · h/mL)	%F	PAMPA ($\times 10^{-6}$ cm/s at pH6.2)
4b[15]	759	537	0.617	1930	12.6	112
32o	1630	557	0.241	1030	16.7	97

[a] Dosing vehicle: 20% 2-hydroxypropyl-β-cyclodextrin (**4b**, **32o**)

[b] Dosing vehicle: 0.5% methylcellulose (MC) (**4b**), 0.5% MC containing 0.1% Tween80 (**32o**)

4. Conclusion

In summary, in addition to the 1*H*-pyrazolo[3,4-*c*]pyridine derivatives that we previously reported, a new series of 3*H*-[1,2,3]triazolo[4,5-*c*]pyridine derivatives was designed, synthesized and evaluated for their GPR119 agonist potency and thermodynamic solubility in pH6.8 phosphate buffer. To improve the aqueous solubility of the new series, we performed an optimization study based on a strategy of lowering the melting point while simultaneously reducing molecular lipophilicity. While a substitution into the left-hand aryl ring did not meet the solubility criteria, a reduction in the number of aromatic rings in the compound and the optimization of the left-hand amide group resulted in a sufficient improvement in solubility with a reduction in the melting point. The resulting compound **32o** had promising aqueous solubility (15.9 μM) and potency (EC_{50} = 65 nM). However, its bioavailability in rats was insufficient for advancement to *in vivo* efficacy studies.

5. Experimental section

5.1. Human GPR119 agonist activity

GPR119 agonists were evaluated in Flp-In-T-Rex-HEK293 cells overexpressing human GPR119. The cells were treated with tetracycline for 24 h and plated on to 96-well plates at 5000 cells/well in assay buffer (D-MEM, 1 mM 3-isobutyl-1-methylxanthine, 0.01% bovine serum albumin), then incubated with the test compound for 30 min at 37 ˚C. Changes in the cellular cAMP levels were measured using a cAMP HiRange assay kit (Cisbio), according to the manufacturer's protocol. Responses were determined by subtracting the basal cAMP levels from agonist-stimulated cAMP levels. The EC_{50} values were determined as the concentration of the test compound required to achieve 50% of the maximal response. Data were calculated from the dose-response curves using

XLfit software (IDBS).

5.2. Thermodynamic Solubility

An excess amount of each compound was added to pH6.8 phosphate buffer and shaken on a shaker (model SR-2DS; TAITEC) at 25 °C for 24 hours. The suspensions were centrifuged at 3000 and 11000 rpm for 10min and the resulting supernatant was diluted with 50% aqueous acetonitrile solution. The concentrations were measured using HPLC. The HPLC analysis was performed using a Shimadzu HPLC system composed of a LC-20AD, SPD-20A and SIL-20AC. The conditions for HPLC were as follows: mobile phase, 0.1% phosphoric acid aqueous solution/acetonitrile; flow rate, 0.8 mL/min; column, reversed- phase (Shimpack XR-ODS , 2.2 µm, 3.0 x 75 mm; SHIMADZU) at 40 °C; and detection wavelength, 210 nm.

5.3. Pharmacokinetic evaluation

Pharmacokinetic profile of test article was investigated in fasted male Sprague-Dawley (SD) rats. After a single intravenous or oral administration of test article, blood was taken from the tail vein at each sampling time point and centrifuged to prepare plasma. The quantitative analysis of the target analyte in plasma samples was performed using liquid chromatography-tandem mass spectrometry. Pharmacokinetic parameters were calculated by a non-compartmental analysis with Phoenix WinNonlin (pharmacokinetic analysis software).

5.4. Chemistry

All the solvents and reagents were obtained from commercial suppliers and were used without further purification or were prepared according to published procedures. The melting points were determined using a Yanaco micro-melting point apparatus MP-500D. The ^{1}H NMR and ^{13}C NMR spectra were recorded using a JOEL JNM-ECA600, Varian Inova300 or Gemini2000, and all the chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded using a Shimadzu LCMS 2010 EV spectrometer. High resolution mass spectral data were acquired using a Shimadzu LCMS-IT-TOF equipped with an ESI/APCI dual ion source.

*5.4.1. 1-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-5-[4-(methanesulfonyl)phenyl]-1H-pyrazolo[3,4-c]pyridine (**4a**)*

The title compound was synthesized as described in our previous paper.[15] Purification of the crude compound **4a** by silica gel column chromatography (EtOAc/hexanes) and the combined fractions containing **4a** were concentrated *in vacuo* afforded a crystalline solid, which was not recrystallized.

Mp 243-244 ˚C (EtOAc/hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 1.22 (t, J = 7.5 Hz, 3H),

2.14-2.25 (m, 2H), 2.26-2.45 (m, 2H), 2.50 (q, *J* = 7.5 Hz, 2H), 3.10 (s, 3H), 3.13-3.25 (m, 2H), 4.81-4.93 (m, 1H), 4.93-5.03 (m, 2H), 8.02-8.08 (m, 2H), 8.11-8.14 (m, 2H), 8.20-8.27 (m, 4H), 9.14 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 15.6, 22.8, 31.6, 43.5, 44.7, 58.2, 112.5, 124.9, 127.6, 127.9, 129.1, 133.1, 133.6, 135.4, 139.6, 145.2, 145.6, 157.3, 160.7; HRMS ESI/APCI Dual *m/z* calcd for $C_{24}H_{26}N_6O_2S$ 463.1911 $[M+H]^+$, found 463.1904.

*5.4.2. 1-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-5-[2-fluoro-4-(methanesulfonyl)phenyl]-1H-pyrazolo[3,4-c]pyridine (**4b**)*

The title compound was synthesized as described in our previous paper.[15] Purification of the crude compound **4b** by silica gel column chromatography ($CHCl_3$/hexanes) and the combined fractions containing **4b** were concentrated *in vacuo* afforded a crystalline solid, which was not recrystallized. Mp 229-230 ˚C ($CHCl_3$/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 1.22 (t, *J* = 7.6 Hz, 3 H), 2.17-2.23 (m, 2 H), 2.31-2.39 (m, 2 H) 2.50 (q, *J* = 7.6 Hz, 2 H), 3.11 (s, 3 H), 3.15-3.22 (m, 2 H), 4.85-4.91 (m, 1 H), 4.95-5.01 (m, 2 H), 7.78 (d, *J* = 8.5 Hz, 1 H), 7.85 (d, *J* = 8.5 Hz, 1 H), 8.13 (s, 1 H), 8.22 (s, 2 H), 8.24 (s, 1 H), 8.32-8.36 (m, 1 H) 9.15 (s, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 15.7, 22.8, 31.6, 43.5, 44.6, 58.2, 115.9 (d, *J* = 27.0 Hz), 116.7 (d, *J* = 9.0 Hz), 123.4, 125.0, 128.7, 132.6, 133.2 (d, *J* = 12.5 Hz), 133.3, 133.7, 135.1, 140.8, 141.0 (d, *J* = 9.2 Hz), 157.3, 159.8 (d, *J* = 243.3 Hz), 160.7; HRMS ESI/APCI Dual *m/z* calcd for $C_{24}H_{25}FN_6O_2S$ 481.1816 $[M+H]^+$, found 481.1808.

*5.4.3. Propan-2-yl 4-{5-[4-(methanesulfonyl)phenyl]-1H-pyrazolo[3,4-c]pyridin-1-yl}piperidine-1-carboxylate (**4c**)*

The title compound was synthesized as described in our previous paper.[15] Purification of the crude compound **4c** by silica gel column chromatography gave a crystalline solid, which was dissolved in $CHCl_3$. To the solution were added hexanes, and the resulting solution was stirred at room temperature. The precipitate was collected by filtration to afford **4c**.

Mp 189-190 ˚C ($CHCl_3$/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.29 (d, *J* = 6.4 Hz, 6 H), 2.06-2.19 (m, 2 H), 2.21-2.39 (m, 2 H), 2.98-3.15 (m, 5 H), 4.31-4.48 (m, 2 H), 4.68-4.84 (m, 1 H), 4.90-5.04 (m, 1 H), 8.01-8.09 (m, 2 H), 8.11-8.15 (m, 2 H), 8.21-8.27 (m, 2 H), 9.09-9.13 (m, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 22.3, 31.7, 43.0, 44.7, 57.3, 69.0, 112.5, 127.6, 128.0, 129.2, 133.3, 133.4, 135.3, 139.7, 145.1, 145.7, 155.1; HRMS ESI/APCI Dual *m/z* calcd for $C_{22}H_{26}N_4O_4S$ 443.1748 $[M+H]^+$, found 443.1735.

*5.4.4. tert-Butyl 4-{5-[4-(methanesulfonyl)phenyl]-1H-pyrazolo[3,4-c]pyridin-1-yl}piperidine-1-carboxylate (**4d**)*

The title compound was synthesized as described in our previous paper.[15]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.51 (s, 9 H), 2.06-2.17 (m, 2 H), 2.19-2.37 (m, 2 H), 2.95-3.09 (m, 2 H), 3.11 (s, 3 H), 4.25-4.42 (m, 2 H), 4.66-4.83 (m, 1 H), 8.01-8.08 (m, 2 H), 8.11-8.15 (m, 2 H), 8.21-8.27 (m, 2 H), 9.11 (s, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 28.5, 31.8, 42.7 (br), 44.7, 57.5, 80.1, 112.5, 127.6, 128.0, 129.1, 133.2, 133.5, 135.3, 139.6, 145.1, 145.7, 154.6; HRMS ESI/APCI Dual *m/z* calcd for $C_{23}H_{28}N_4O_4S$ 457.1904 $[M+H]^+$, found 457.1903.

*5.4.5. 2-Methylpropyl 4-{5-[4-(methanesulfonyl)phenyl]-1H-pyrazolo[3,4-c]pyridin-1-yl}piperidine -1-carboxylate (**4e**)*

The title compound was synthesized as described in our previous paper.[15] Purification of the crude compound **4e** by silica gel column chromatography afforded a crystalline solid, which was dissolved in $CHCl_3$. To the solution were added hexanes, and the resulting solution was stirred at room temperature. The precipitate was collected by filtration to afford **4e** as a colorless crystalline solid.

Mp 212-213 ˚C ($CHCl_3$/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.97 (d, J = 6.7 Hz, 6 H), 1.88-2.06 (m, 1 H), 2.08-2.20 (m, 2 H), 2.22-2.41 (m, 2 H), 2.99-3.21 (m, 5 H), 3.92 (d, J = 6.5 Hz, 2 H), 4.26-4.52 (m, 2 H), 4.68-4.84 (m, 1 H), 8.02-8.08 (m, 2 H), 8.12-8.15 (m, 2 H), 8.21-8.27 (m, 2 H), 9.11 (t, J = 1.0 Hz, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 19.2, 28.1, 31.7, 43.1, 44.7, 57.2, 71.9, 112.5, 127.6, 128.0, 129.2, 133.3, 133.4, 135.4, 139.7, 145.1, 145.7, 155.5; HRMS ESI/APCI Dual *m/z* calcd for $C_{23}H_{28}N_4O_4S$ 457.1904 $[M+H]^+$, found 457.1893.

*5.4.6. 1,1-Difluoro-2-methylpropan-2-yl 4-{5-[4-(methanesulfonyl)phenyl]-1H-pyrazolo[3,4-c]pyrid in-1-yl}piperidine-1-carboxylate (**4f**)*

The title compound was synthesized as described in our previous paper.[15] Purification of the crude compound **4f** by silica gel column chromatography ($CHCl_3$/MeOH) and the fractions containing **4f** were concentrated *in vacuo* afforded a colorless crystalline solid, which was not recrystallized.

Mp 204-205 ˚C ($CHCl_3$/MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.51-1.60 (m, 6 H), 2.07-2.19 (m, 2 H), 2.22-2.39 (m, 2 H), 2.98-3.20 (m, 2 H), 3.10 (s, 3 H), 4.17-4.46 (m, 2 H), 4.69-4.82 (m, 1 H), 5.98-6.39 (m, 1 H), 8.02-8.09 (m, 2 H), 8.12-8.16 (m, 2 H), 8.21-8.27 (m, 2 H), 9.11 (s, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 20.1, 31.6, 43.2 (br), 44.7, 57.0, 79.6 (d, J = 23.7 Hz), 112.5, 115.2 (t, J = 247.9 Hz), 127.6, 127.9, 129.1, 133.3, 135.3, 139.6, 145.0, 145.7, 153.4; HRMS ESI/APCI Dual *m/z* calcd for $C_{23}H_{26}F_2N_4O_4S$ 493.1716 $[M+H]^+$, found 493.1707.

*5.4.7. Propan-2-yl 4-{5-[4-(ethylcarbamoyl)-2,5-difluorophenyl]-1H-pyrazolo[3,4-c]pyridin-1-yl}pi peridine-1-carboxylate (**4g**)*

The title compound was synthesized as described in our previous paper.[15] Purification of the crude compound **4g** by silica gel column chromatography to afford the crystalline solid, which was dissolved in 2-propanol under heating and to the mixture were added hexanes. The resulting solution

was stirred and allowed to cool to room temperature. The precipitate was collected by filtration to afford **4g** as a colorless crystalline solid.

Mp 150-151 ˚C (2-propanol/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 1.24-1.30 (m, 9 H), 2.05-2.18 (m, 2 H), 2.22-2.33 (m, 2 H), 3.05 (br s, 2 H), 3.50-3.57 (m, 2 H), 4.29-4.48 (m, 2 H), 4.70-4.79 (m, 1 H), 4.96 (dt, *J* = 12.4, 6.2 Hz, 1 H), 6.75-6.85 (m, 1 H), 7.89-8.02 (m, 2 H), 8.12 (s, 1 H), 8.28 (s, 1 H), 9.08 (s, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 14.8, 22.3, 31.7, 35.1, 43.0, 57.3, 69.0, 116.5 (d, *J* = 12.1 Hz), 118.0 (d, *J* = 30.0 Hz), 119.4 (d, *J* = 28.2 Hz), 121.4 (dd, *J* = 8.5, 14.5 Hz), 128.8, 132.1 (dd, *J* = 9.2, 14.8 Hz), 133.3, 133.5, 135.1, 140.7, 155.1, 156.3 (d, *J* = 246.4 Hz), 156.6 (d, *J* = 243.8 Hz), 161.9; HRMS ESI/APCI Dual *m/z* calcd for $C_{24}H_{27}F_2N_5O_3$ 472.2155 $[M+H]^+$, found 472.2158.

*5.4.8. 5-Bromo-1H-indazole (**6**)*

To a solution of 4-bromo-2-methylaniline (10.5g, 56.3 mmol) in acetic acid (300 mL) were added $NaNO_2$ (3.89 g, 56.3 mmol) and water (10 mL). After stirring at room temperature for 5 h, the reaction mixture was concentrated *in vacuo*. The residue was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0-50% EtOAc in hexanes) and solidified with hexanes to afford **6** as a brown solid (6.81 g, 61% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 7.35-7.43 (m, 1H), 7.45-7.52 (m, 1H), 7.92 (d, *J* = 2.2 Hz, 1H), 8.03 (d, *J* = 0.9 Hz, 1H); MS ESI/APCI Dual *m/z* 195 $[M-H]^-$.

*5.4.9. tert-Butyl 4-(5-bromo-1H-indazol-1-yl)piperidine-1-carboxylate (**7**)*

To a solution of **6** (6.81 g, 34.6 mmol) in *N*,*N*-dimethylformamide (DMF) (200 mL) was added NaH (60% in oil, 2.12 g, 53.0 mmol). After the mixture being stirred at room temperature for 10 min, *tert*-butyl 4-[(methanesulfonyl)oxy]piperidine-1-carboxylate (14.8 g, 53.0 mmol) was added to the mixture. After stirring at 90 ˚C for 2 h, the reaction was quenched with water at 0 ˚C and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20-50% EtOAc in hexanes) to afford **7** as a pale yellow solid (6.97 g, 53% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 1.48 (s, 9H), 1.95-2.03 (m, 2H), 2.15-2.25 (m, 2H), 2.88-3.02 (m, 2H), 4.21-4.38 (m, 2H), 4.48-4.55 (m, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.44 (dd, *J* = 8.8, 1.7 Hz, 1H), 7.87 (d, *J* = 1.7 Hz, 1H), 7.93 (s, 1H).

*5.4.10. tert-Butyl 4-{5-[4-(methanesulfonyl)phenyl]-1H-indazol-1-yl}piperidine-1-carboxylate (**8**)*

To a solution of **7** (200 mg, 0.526 mmol) in DMF (3.00 mL) were added

[4-(methanesulfonyl)phenyl]boronic acid (128 mg, 0.640 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (43 mg, 0.0526 mmol) and 2 M Na_2CO_3 aqueous solution (0.800 mL, 1.60 mmol). The mixture was stirred at 110 ˚C under microwave irradiation for 30 min. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (10-80% EtOAc in hexanes) and solidified with hexanes and Et_2O to afford **8** as a colorless solid (136 mg, 57% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 1.50 (s, 9H), 1.97-2.13 (m, 2H), 2.15-2.38 (m, 2H), 2.89-3.08 (m, 2H), 3.11 (s, 3H), 4.23-4.43 (m, 2H), 4.51-4.70 (m, 1H), 7.50-7.60 (m, 1H), 7.61-7.68 (m, 1H), 7.76-7.86 (m, 2H), 7.95-8.02 (m, 2H), 8.03-8.07 (m, 1H), 8.09 (s, 1H); MS ESI/APCI Dual *m/z* 478 $[M+Na]^+$.

*5.4.11. 1-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-5-[4-(methanesulfonyl)phenyl]-1H-indazole (**9**)*

To a solution of **8** (239 mg, 0.525 mmol) in MeOH (30 mL) was added 4 N HCl in 1,4-dioxane (10 mL) and the mixture was stirred at room temperature for 1 h. The reaction was quenched with 8 M NaOH aqueous solution and extracted with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by NH silica gel column chromatography (10-100% EtOAc in hexanes, then 10% MeOH in $CHCl_3$) to afford 5-[4-(methanesulfonyl)phenyl]-1-(piperidin-4-yl)-1*H*-indazole as a colorless gum (174 mg, 93% yield).

To a solution of 5-[4-(methanesulfonyl)phenyl]-1-(piperidin-4-yl)-1*H*-indazole (70 mg, 0.197 mmol) in DMF (2 mL) were added 2-chloro-5-ethylpyrimidine (43 mg, 0.302 mmol) and *N*,*N*-diisopropylethylamine (78 mg, 0.604 mmol). The mixture was stirred at 100 ˚C overnight. 2-Chloro-5-ethylpyrimidine (43 mg, 0.302 mmol) and *N*,*N*-diisopropylethylamine (78 mg, 0.604 mmol) were added to the mixture and stirred at 100 ˚C for 6 h. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (10-50% EtOAc in $CHCl_3$), followed by NH silica gel column chromatography (50-100% $CHCl_3$ in hexanes) and solidified with hexanes and Et_2O to afford **9** as a colorless solid (63 mg, 69% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 1.21 (t, J = 7.6 Hz, 3H), 2.10-2.16 (m, 2H), 2.28-2.36 (m, 2H), 2.49 (q, J = 7.6 Hz, 2H), 3.10 (s, 3H), 3.11-3.17 (m, 2H), 4.71-4.78 (m, 1H), 4.95-4.99 (m, 2H), 7.58-7.61 (m, 1H), 7.63-7.65 (m, 1H), 7.80-7.83 (m, 2H), 7.97 (s, 1H), 8.00-8.03 (m, 2H), 8.07 (s, 1H), 8.20 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 15.7, 22.8, 31.4, 43.6, 44.7, 57.1, 109.8, 120.3, 124.8, 124.9, 125.9, 128.0, 128.1, 132.1, 133.7, 138.7, 147.1, 157.3, 160.7; HRMS ESI/APCI Dual *m/z* calcd for $C_{25}H_{27}N_5O_2S$ 462.1958 $[M+H]^+$, found 462.1947.

*5.4.12. tert-Butyl (4-hydroxy-2,5-dimethylphenyl)carbamate (**11a**)*

To a solution of 4-amino-2,5-dimethylphenol (5.00 g, 36.4 mmol) in MeOH (73 mL) were added triethylamine (10.2 mL, 72.8 mmol) and di-*tert*-butyl dicarbonate (8.75 g, 40.1 mmol). After stirring at room temperature for 13 h, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (5-30% EtOAc in hexanes) to afford **11a** as a purple solid (6.96 g, 80% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.51 (s, 9H), 2.14 (s, 3H), 2.15 (s, 3H), 5.25 (br s, 1H), 6.02 (br s, 1H), 6.48 (s, 1H), 7.23 (s, 1H); MS ESI/APCI Dual *m/z* 236 $[M-H]^-$.

*5.4.13. 4-[(tert-Butoxycarbonyl)amino]-2,5-dimethylphenyl trifluoromethanesulfonate (**12a**)*

To a solution of **11a** (6.95 g, 29.3 mmol) and pyridine (3.55 mL, 44.0 mmol) in $CHCl_3$ (100 mL) was added trifluoromethanesulfonic anhydride (5.77 mL, 34.3 mmol) while maintaining the temperature at below 18 ˚C. After stirring at room temperature for 5 min, the reaction was quenched with ice-cooled water. The organic layer was washed with 2 N HCl aqueous solution and brine, dried over anhydrous Na_2SO_4 and filtered. The solvent was removed *in vacuo* to afford **12a** as a brown solid (10.9 g, quantitative yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.52 (s, 9H), 2.23 (s, 3H), 2.33 (s, 3H), 6.27 (br s, 1H), 7.01 (s,1H), 7.87 (s, 1H); MS ESI/APCI Dual *m/z* 368 $[M-H]^-$.

*5.4.14. 4-Amino-2,5-dimethylphenyl trifluoromethanesulfonate (**13a**)*

To a suspension of **12a** (10.8 g, 29.2 mmol) in EtOAc (20 mL) was added 4 N HCl in EtOAc (45 mL) and the mixture was stirred at room temperature for 15 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The solvent was removed *in vacuo* to afford **13a** as a brown oil (8.05 g, quantitative yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.13 (s, 3H), 2.26 (s, 3H), 3.65 (br s, 2H), 6.53 (s, 1H), 6.90 (s, 1H); MS ESI/APCI Dual *m/z* 270 $[M+H]^+$.

*5.4.15. 6-Methyl-1H-indazol-5-yl trifluoromethanesulfonate (**14a**)*

To a solution of **13a** (8.05g, 29.9 mmol) in acetic acid (40 mL) were added $NaNO_2$ (2.02 g, 29.2 mmol) in water (6.4 mL) at 4-9 ˚C and the mixture was stirred at room temperature for 20 h. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (5-35% EtOAc in hexanes) to afford **14a** as a brown solid (4.02 g, 48% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.51 (s, 3H), 7.42 (s, 1H), 7.67 (s, 1H), 8.09 (s, 1H); MS ESI/APCI Dual *m/z* : 281 $[M+H]^+$, 279 $[M-H]^-$, 315 $[M+Cl]^-$.

*5.4.16. 5-[4-(Methanesulfonyl)phenyl]-6-methyl-1H-indazole (**15a**)*

To a solution of **14a** (1.50 g, 5.35 mmol) in DMF (30 mL) were added [4-(methanesulfonyl)phenyl]boronic acid (3.21 g, 16.0 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (437 mg, 0.535 mmol) and 2 M Na_2CO_3 aqueous solution (10.7 mL, 21.4 mmol). The mixture was stirred at 130 ˚C under microwave irradiation for 30 min. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (5-50% EtOAc in hexanes) to afford **15a** as a pale yellow solid (1.16 g, 76% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.36 (s, 3H), 3.14 (s, 3H), 7.43 (d, J = 0.8 Hz, 1H), 7.53-7.61 (m, 3H), 7.98-8.04 (m, 2H), 8.05-8.11 (m, 1H); MS ESI/APCI Dual *m/z* : 287 $[M+H]^+$, 309 $[M+Na]^+$, 285 $[M-H]^-$.

5.4.17. tert-Butyl
*4-{5-[4-(methanesulfonyl)phenyl]-6-methyl-1H-indazol-1-yl}piperidine-1-carboxylate (**16a**)*

To a solution of **15a** (300 mg, 1.05 mmol) in dimethyl sulfoxide (DMSO) (4.0 mL) were added *tert*-butyl 4-[(methanesulfonyl)oxy]piperidine-1-carboxylate (579 mg, 2.07 mmol) and Cs_2CO_3 (1.02 g, 3.13 mmol). The mixture was stirred at 90 ˚C for 1.5 h. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by NH silica gel column chromatography (10-50% EtOAc in hexanes) to afford **16a** as a pale yellow solid (204 mg, 41% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.50 (s, 9H), 1.99-2.11 (m, 2H), 2.16-2.34 (m, 2H), 2.38 (s, 3H), 2.91-3.07 (m, 2H), 3.14 (s, 3H), 4.25-4.43 (m, 2H), 4.51-4.64 (m, 1H), 7.36 (s, 1H), 7.52-7.59 (m, 3H), 7.97-8.04 (m, 3H); MS ESI/APCI Dual *m/z* : 470 $[M+H]^+$, 492 $[M+Na]^+$, 504 $[M+Cl]^-$.

*5.4.18. 1-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-5-[4-(methanesulfonyl)phenyl]-6-methyl-1H-indazole (**17a**)*

To a suspension of **16a** (200 mg, 0.426 mmol) in MeOH (0.85 mL) was added 4 N HCl in 1,4-dioxane (2.1 mL) and the mixture was stirred at room temperature for 13 h. The reaction was concentrated *in vacuo* to afford 5-[4-(methanesulfonyl)phenyl]-6-methyl-1-(piperidin-4-yl)-1*H*-indazole hydrochloride as a pale yellow solid (176 mg, quantitative yield).

To a suspension of 5-[4-(methanesulfonyl)phenyl]-6-methyl-1-(piperidin-4-yl)-1*H*-indazole

hydrochloride (82 mg, 0.202 mmol) in DMSO (2.0 mL) were added 2-chloro-5-ethylpyrimidine (43 mg, 0.302 mmol) and Cs_2CO_3 (329 mg, 1.01 mmol). The mixture was stirred at 120 ˚C for 4 h. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (5-50% EtOAc in hexanes) and recrystallized with MeOH to afford **17a** as a colorless solid (29 mg, 30% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.22 (t, J = 7.6 Hz, 3H), 2.07-2.19 (m, 2H), 2.24-2.36 (m, 2H), 2.38 (s, 3H), 2.49 (q, J = 7.6 Hz, 2H), 3.08-3.22 (m, 5H), 4.63-4.78 (m, 1H), 4.90-5.02 (m, 2H), 7.40 (s, 1H), 7.51-7.59 (m, 3H), 7.94-8.04 (m, 3H), 8.21 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 15.7, 16.6, 22.8, 31.4, 43.6, 44.7, 57.0, 106.9, 124.7, 125.4, 127.3, 128.4, 128.7, 130.9, 131.6, 132.5, 138.2, 138.7, 147.6, 157.2, 160.7; HRMS ESI/APCI Dual *m/z* calcd for $C_{26}H_{29}N_5O_2S$ 476.2115 $[M+H]^+$, found 476.2111.

*5.4.19. tert-Butyl (4-hydroxy-2,3-dimethylphenyl)carbamate (**11b**)*

The title compound was synthesized according to the procedure described for compound **11a** from 4-amino-2,3-dimethylphenol (84%yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.51 (s, 9H), 2.13 (s, 3H), 2.15 (s, 3H), 5.23 (br s, 1H), 6.05 (br s, 1H), 6.52 (d, J = 8.5 Hz, 1H), 7.07 (d, J = 8.5 Hz, 1H); MS ESI/APCI Dual *m/z* 236 $[M-H]^-$.

*5.4.20. 4-[(tert-Butoxycarbonyl)amino]-2,3-dimethylphenyl trifluoromethanesulfonate (**12b**)*

The title compound was synthesized according to the procedure described for compound **12a** from **11b** (99%yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.52 (s, 9H), 2.20 (s, 3H), 2.30 (s, 3H), 6.28 (br s, 1H), 7.09 (d, J = 9.0 Hz, 1H), 7.68 (d, J = 9.0 Hz, 1H); MS ESI/APCI Dual *m/z* 368 $[M-H]^-$.

*5.4.21. 4-Amino-2,3-dimethylphenyl trifluoromethanesulfonate (**13b**)*

The title compound was synthesized according to the procedure described for compound **13a** from **12b** (quantitative yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.10 (s, 3H), 2.26 (s, 3H), 3.68 (br s, 2H), 6.54 (d, J = 8.7 Hz, 1H), 6.92 (d, J = 8.7 Hz, 1H); MS ESI/APCI Dual *m/z* 270 $[M+H]^+$.

*5.4.22. 4-Methyl-1H-indazol-5-yl trifluoromethanesulfonate (**14b**)*

The title compound was synthesized according to the procedure described for compound **14a** from **13b** (64%yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.65 (s, 3H), 7.24-7.31 (m, 1H), 7.35-7.42 (m, 1H), 8.17 (s, 1H;MS ESI/APCI Dual *m/z* : 281 $[M+H]^+$, 279 $[M-H]^-$, 315 $[M+Cl]^-$.

*5.4.23. 5-[4-(Methanesulfonyl)phenyl]-4-methyl-1H-indazole (**15b**)*

The title compound was synthesized according to the procedure described for compound **15a** from **14b** (72%yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.56 (s, 3H), 3.14 (s, 3H), 7.24-7.33 (m, 1H), 7.39-7.46 (m, 1H), 7.54-7.62 (m, 2H), 7.98-8.05 (m, 2H), 8.19 (s, 1H); MS ESI/APCI Dual *m/z* : 287 $[M+H]^+$, 309 $[M+Na]^+$, 285 $[M-H]^-$.

*5.4.24. tert-Butyl 4-{5-[4-(methanesulfonyl)phenyl]-4-methyl-1H-indazol-1-yl}piperidine-1-carboxylate (**16b**)*

The title compound was synthesized according to the procedure described for compound **16a** from **15b** (68%yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.50 (s, 9H), 1.99-2.10 (m, 2H), 2.18-2.35 (m, 2H), 2.53 (s, 3H), 2.90-3.07 (m, 2H), 3.13 (s, 3H), 4.25-4.42 (m, 2H), 4.52-4.65 (m, 1H), 7.24-7.30 (m, 1H), 7.34-7.40 (m, 1H), 7.53-7.60 (m, 2H), 7.98-8.04 (m, 2H), 8.09 (s, 1H); MS ESI/APCI Dual *m/z* : 470 $[M+H]^+$, 492 $[M+Na]^+$, 504 $[M+Cl]^-$.

*5.4.25. 1-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-5-[4-(methanesulfonyl)phenyl]-4-methyl-1H-indazole (**17b**)*

The title compound was synthesized according to the procedure described for compound **17a** from **16b** (38%yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.22 (t, J = 7.6 Hz, 3H), 2.07-2.18 (m, 2H), 2.24-2.41 (m, 2H), 2.44-2.56 (m, 5H), 3.07-3.21 (m, 5H), 4.65-4.79 (m, 1H), 4.91-5.02 (m, 2H), 7.23-7.30 (m, 1H), 7.37-7.44 (m, 1H), 7.53-7.60 (m, 2H), 7.98-8.04 (m, 2H), 8.08 (s, 1H), 8.21 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 15.7, 21.8, 22.8, 31.4, 43.7, 44.7, 56.9, 110.0, 121.9, 122.8, 124.8, 127.3, 130.6, 133.1, 133.9, 134.0, 138.8, 138.9, 148.1, 157.3, 160.8; HRMS ESI/APCI Dual *m/z* calcd for $C_{26}H_{29}N_5O_2S$ 476.2115 $[M+H]^+$, found 476.2100.

*5.4.26. tert-Butyl 4-(4-bromo-2-nitroanilino)piperidine-1-carboxylate (**19**)*

To a solution of 4-bromo-1-fluoro-2-nitrobenzene (25.0 g, 114 mmol) in DMSO (114 mL) were added *tert*-butyl 4-aminopiperidine-1-carboxylate (20.7 g, 103 mmol) and Cs_2CO_3 (37.1 g, 114 mmol). The mixture was stirred at 100 ˚C for 1 h. The reaction was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was recrystallized with hexanes and EtOAc to afford orange solid. The filtrate was evaporated to dryness and recrystallized with hexanes and EtOAc to afford orange solid. The resulting solids were combined to afford **19** as an orange solid (40.5 g, 98% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 1.48 (s, 9H), 1.43-1.69 (m, 2H), 1.96-2.13 (m, 2H), 2.94-3.15 (m, 2H), 3.54-3.76 (m, 1H), 3.93-4.12 (m, 2H), 6.79 (d, *J* = 9.2 Hz, 1H), 7.49 (dd, *J* = 9.2, 2.4 Hz, 1H), 8.00-8.13 (m, 1H), 8.32 (d, *J* = 2.4 Hz, 1H); MS ESI/APCI Dual *m/z* 422 $[M+Na]^+$, 398 $[M-H]^-$.

*5.4.27. tert-Butyl 4-(2-amino-4-bromoanilino)piperidine-1-carboxylate (**20**)*

To a suspension of **19** (40.5 g, 101 mmol) in EtOH (337 mL) were added Fe powder (28.2g, 505 mmol) and NH_4Cl (540 mg, 10.1 mmol) in water (101 mL). After stirring at 78 ˚C for 5 h, the reaction was filtered and concentrated *in vacuo*. The residue was diluted with brine and extracted with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford **20** as a brown gum (37.4 g, quantitative yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 1.24-1.51 (m, 2H), 1.47 (s, 9H), 1.91-2.09 (m, 2H), 2.84-3.03 (m, 2H), 3.24-3.45 (m, 1H), 3.94-4.12 (m, 2H), 6.52 (d, *J* = 8.4 Hz, 1H), 6.81-6.92 (m, 2H); MS ESI/APCI Dual *m/z* : 392 $[M+Na]^+$, 404 $[M+Cl]^-$.

*5.4.28. tert-Butyl 4-(5-bromo-1H-benzotriazol-1-yl)piperidine-1-carboxylate (**21**)*

To a solution of **20** (37.4g, 101 mmol) in acetic acid (337 mL) was added $NaNO_2$ (10.5 g, 152 mmol) in water (33.7 mL) under ice cooling and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water and stirred at room temperature for 1 h. The resulting precipitate was filtered and washed with water and hexanes. The solid was dissolved in $CHCl_3$ and washed with brine. The organic layer was separated and concentrated *in vacuo*. The residue was purified by NH silica gel column chromatography ($CHCl_3$) and recrystallized with hexanes and EtOAc to afford **21** as a brown solid (29.3 g, 76% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 1.50 (s, 9H), 2.08-2.46 (m, 4H), 2.92-3.14 (m, 2H), 4.24-4.44 (m, 2H), 4.71-4.90 (m, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.58 (dd, *J* = 8.8, 1.8 Hz, 1H), 8.24 (d, *J* = 1.8 Hz, 1H); MS ESI/APCI Dual *m/z* 381 $[M+H]^+$, 403 $[M+Na]^+$, 415 $[M+Cl]^-$.

*5.4.29. tert-Butyl 4-{5-[4-(methanesulfonyl)phenyl]-1H-benzotriazol-1-yl}piperidine-1-carboxylate (**22**)*

The title compound was synthesized according to the procedure described for compound **8** from **21** (25%yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 1.52 (s, 9H), 2.15-2.27 (m, 2H), 2.29-2.47 (m, 2H), 2.98-3.15 (m, 2H), 3.12 (s, 3H), 4.29-4.43 (m, 2H), 4.82-4.96 (m, 1H), 7.68 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.75 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.81-7.87 (m, 2H), 8.04-8.09 (m, 2H), 8.29-8.31 (m, 1H); MS ESI/APCI Dual *m/z* 457 $[M+H]^+$, 479 $[M+Na]^+$, 491 $[M+Cl]^-$.

5.4.30. 1-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-5-[4-(methanesulfonyl)phenyl]-1H-benzotriazole

*(**23**)*

To a solution of **22** (694 mg, 1.52 mmol) in MeOH (5.07 mL) was added 4 N HCl in 1,4-dioxane (15.2 mL). After stirring at room temperature for 3 h, the reaction was concentrated *in vacuo*. The resulting solid was washed with EtOAc to afford 5-[4-(methanesulfonyl)phenyl]-1-(piperidin-4-yl)-1*H*-benzotriazole hydrochloride as a pale pink powder (612 mg, quantitative yield).

To a suspension of 5-[4-(methanesulfonyl)phenyl]-1-(piperidin-4-yl)-1*H*-benzotriazole hydrochloride (200 mg, 0.509 mmol) in 2-propanol (IPA) (5.09 mL) were added 2-chloro-5-ethylpyrimidine (145 mg, 1.02 mmol) and *N*,*N*-diisopropylethylamine (526 mg, 4.07 mmol). The mixture was stirred at 80 ˚C for 90 h. The reaction was quenched with water and extracted with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (67% EtOAc in hexanes) and recrystallized with hexanes and EtOAc to afford **23** as a colorless solid (74 mg, 31% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 1.23 (t, J = 7.7 Hz, 3H), 2.20-2.60 (m, 6H), 3.12 (s, 3H), 3.12-3.30 (m, 2H), 4.90-5.12 (m, 3H), 7.65-7.79 (m, 2H), 7.80-7.89 (m, 2H), 8.01-8.11 (m, 2H), 8.24 (s, 2H), 8.29 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 15.6, 22.7, 31.4, 43.3, 44.7, 58.0, 110.4, 118.9, 125.1, 127.0, 128.2, 128.4, 132.3, 135.6, 139.5, 146.1, 146.9, 157.3, 160.5; HRMS ESI/APCI Dual *m/z* calcd for $C_{24}H_{26}N_6O_2S$ 463.1911 $[M+H]^+$, found 463.1904.

*5.4.31. 2-Bromo-5-fluoropyridine 1-oxide (**25**)*

To a solution of 2-bromo-5-fluoropyridine (2.00 g, 11.4 mmol) in $CHCl_3$ (22.7 mL) were added urea hydrogen peroxide (2.14 g, 22.7 mmol) and trifluoroacetic anhydride (4.77 g, 22.7 mmol). After stirring at room temperature for 15 h, the reaction was quenched with saturated Na_2SO_3 aqueous solution under ice cooing and stirred at room temperature for 15 min. Saturated aqueous $NaHCO_3$ solution was added to the mixture and extracted with $CHCl_3$. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford **25** as a colorless solid (2.18 g, quantitative yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 6.98 (ddd, J = 9.2, 6.6, 2.6 Hz, 1H), 7.63 (dd, J = 9.2, 6.6 Hz, 1H), 8.34 (dd, J = 4.0, 2.6 Hz, 1H); MS ESI/APCI Dual *m/z* 192 $[M+H]^+$, 190 $[M-H]^-$.

*5.4.32. 2-Bromo-5-fluoro-4-nitropyridine 1-oxide (**26**)*

To a solution of **25** (3.79 g, 19.7 mmol) in H_2SO_4 (65.8 mL) was added fuming nitric acid (32.9 mL) under ice cooling and the mixture was stirred at 100 ˚C for 4 h. The reaction mixture was added dropwise to ice cooled water and extracted with $CHCl_3$. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford **26** as a pale yellow solid (3.72 g,

80%yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 8.43 (d, J = 5.8 Hz, 1H), 8.45 (d, J = 8.6 Hz, 1H); MS ESI/APCI Dual m/z 237 $[M+H]^+$, 235 $[M-H]^-$.

*5.4.33. 6-Bromo-N-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-4-nitropyridin-3-amine 1-oxide (**27a**)*

To a solution of **26** (700 mg, 2.95 mmol) in dimethyl sulfoxide (DMSO) (9.83 mL) were added 1-(5-ethylpyrimidin-2-yl)piperidin-4-amine (609 mg, 2.95 mmol) and Cs_2CO_3 (1.15 g, 3.53 mmol). The mixture was stirred at room temperature for 1 h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford **27a** as a yellow solid (1.08 g, 86% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 1.20 (t, J = 7.6 Hz, 3H), 1.50-1.73 (m, 2H), 2.07-2.24 (m, 2H), 2.49 (q, J = 7.6 Hz, 2H), 3.11-3.32 (m, 2H), 3.51-3.73 (m, 1H), 4.54-4.71 (m, 2H), 7.71-7.82 (m, 1H), 8.20 (s, 3H), 8.42 (s, 1H); MS ESI/APCI Dual m/z 423 $[M+H]^+$, 445 $[M+Na]^+$, 421 $[M-H]^-$.

*5.4.34. 6-Bromo-N^3-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]pyridine-3,4-diamine (**28a**)*

To a solution of **27a** (1.08 g, 2.55 mmol) in AcOH (8.51 mL) was added Fe powder (712 mg, 12.8 mmol) and the mixture was stirred at 100 ˚C for 2 h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (50% EtOAc in $CHCl_3$) to afford **28a** as a pale yellow solid (696 mg, 72% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 1.19 (t, J = 7.6 Hz, 3H), 1.32-1.54 (m, 2H), 1.99-2.16 (m, 2H), 2.47 (q, J = 7.6 Hz, 2H), 3.00-3.17 (m, 2H), 3.29-3.48 (m, 1H), 4.05-4.18 (m, 2H), 4.55-4.69 (m, 2H), 6.74 (s, 1H), 7.69 (s, 1H), 8.18 (s, 2H); MS ESI/APCI Dual m/z 377 $[M+H]^+$.

*5.4.35. 6-Bromo-3-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridine (**29a**)*

To a solution of **28a** (50 mg, 0.133 mmol) in trifluoroacetic acid (TFA) (1.33 mL) was added $NaNO_2$ (13.7 mg, 0.199 mmol) in water (0.133 mL). After stirring at room temperature for 1 h, the reaction mixture was concentrated *in vacuo*. The residue was diluted with saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by NH silica gel column chromatography ($CHCl_3$) and recrystallized with hexanes and EtOAc to afford **29a** as a pale yellow solid (34 mg, 66% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 1.23 (t, J = 7.6 Hz, 3H), 2.23-2.45 (m, 4H), 2.51 (q, J = 7.6 Hz, 2H), 3.11-3.30 (m, 2H), 4.92-5.19 (m, 3H), 8.17 (d, J = 1.3 Hz, 1H), 8.23 (s, 2H), 8.93 (d, J = 1.3 Hz, 1H); MS ESI/APCI Dual m/z 388 $[M+H]^+$, 410 $[M+Na]^+$.

*5.4.36. Propan-2-yl 4-[(6-bromo-4-nitro-1-oxidepyridin-3-yl)amino]piperidine-1-carboxylate (**27b**)*

The title compound was synthesized according to the procedure described for compound **27a** from **26** and isopropyl 4-aminopiperidine-1-carboxylate (quantitative yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.06-1.34 (m, 6H), 1.43-1.65 (m, 2H), 1.98-2.24 (m, 2H), 2.96-3.16 (m, 2H), 3.42-3.66 (m, 1H), 3.94-4.28 (m, 2H), 4.70-5.15 (m, 1H), 7.74 (d, J = 7.6 Hz, 1H), 8.17 (s, 1H), 8.42 (s, 1H); MS ESI/APCI Dual *m/z* 421 $[M+Na]^+$, 433 $[M+Cl]^-$.

*5.4.37. Propan-2-yl 4-[(4-amino-6-bromopyridin-3-yl)amino]piperidine-1-carboxylate (**28b**)*

The title compound was synthesized according to the procedure described for compound **28a** from **27b** (quantitative yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.06-1.53 (m, 8H), 1.89-2.01 (m, 2H), 2.93 (br t, J = 11.4 Hz, 2H), 3.31 (br s, 1H), 3.98-4.23 (m, 3H), 4.91 (dt, J = 12.2, 5.9 Hz, 2H), 6.74 (s, 1H), 7.65 (s, 1H); MS ESI/APCI Dual *m/z* 357 $[M+H]^+$, 391 $[M+Cl]^-$.

*5.4.38. Propan-2-yl 4-(6-bromo-3H-[1,2,3]triazolo[4,5-c]pyridin-3-yl)piperidine-1-carboxylate (**29b**)*

The title compound was synthesized according to the procedure described for compound **29a** from **29b** (35% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.29 (d, J = 6.2 Hz, 6H), 2.17-2.46 (m, 4H), 3.10 (br s, 2H), 4.29-4.55 (m, 2H), 4.89-5.07 (m, 2H), 8.18 (d, J = 1.1 Hz, 1H), 8.93 (d, J = 1.1 Hz, 1H); MS ESI/APCI Dual *m/z* : 390 $[M+Na]^+$, 402 $[M+Cl]^-$.

*5.4.39. 3-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-6-[4-(methanesulfonyl)phenyl]-3H-[1,2,3]triazolo[4,5-c]pyridine (**30a**)*

To a solution of **29a** (35 mg, 0.0901 mmol) in DMF (0.901 mL) were added [4-(methanesulfonyl)phenyl]boronic acid (27 mg, 0.135 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (7.36 mg, 0.00901 mmol) and 2 M Na_2CO_3 aqueous solution (0.135 mL). After stirring at 100 ˚C for 2 h, the reaction was quenched with water and extracted with EtOAc. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and reduced under pressure. The residue was purified by silica gel column chromatography (67-80% EtOAc in $CHCl_3$) to afford **30a** as a colorless crystalline solid (20 mg, 48% yield), which was not recrystallized.

Mp 269-270 ˚C (EtOAc/$CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 1.24 (t, J = 7.6 Hz, 3H), 2.34-2.41 (m, 2H), 2.41-2.50 (m, 2H), 2.53 (q, J = 7.6 Hz, 2H), 3.11 (s, 3H), 3.21-3.34 (m, 2H), 5.03 (d, J = 13.6 Hz, 2H), 5.13-5.21 (m, 1H), 8.08 (d, J = 8.7 Hz, 2H), 8.23-8.31 (m, 4H), 8.43 (s, 1H), 9.26 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 15.6, 22.8, 31.7, 43.3, 44.7, 59.1, 111.1, 125.3, 128.0, 128.1, 129.5, 134.7, 140.4, 144.2, 149.1, 151.0, 157.4, 160.6; HRMS ESI/APCI Dual *m/z*

calcd for $C_{23}H_{25}N_7O_2S$ 464.1863 $[M+H]^+$, found 464.1848.

*5.4.40. 3-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-6-[2-fluoro-4-(methanesulfonyl)phenyl]-3H-[1,2,3]triazolo[4,5-c]pyridine (**30b**)*

The title compound was synthesized according to the procedure described for compound **30a** from **29a** and [2-fluoro-4-(methanesulfonyl)phenyl]boronic acid (56% yield).

Mp 269-270 ˚C (EtOAc/$CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 1.22 (t, J = 7.6 Hz, 3H), 2.32-2.38 (m, 2H), 2.39-2.48 (m, 2H), 2.51 (q, J = 7.6 Hz, 2H), 3.11 (s, 3H), 3.19-3.26 (m, 2H), 4.98-5.04 (m, 2H), 5.12-5.19 (m, 1H), 7.80 (dd, J = 10.1, 1.7 Hz, 1H), 7.86 (dd, J = 8.2, 1.7 Hz, 1H), 8.23 (s, 2H), 8.33 (dd, J = 8.2, 7.6 Hz, 1H), 8.54 (s, 1H), 9.26 (d, J = 1.2 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 15.6, 22.8, 31.7, 43.3, 44.5, 59.1, 115.4 (d, J = 12.0 Hz), 116.1 (d, J = 27.0 Hz), 123.4, 125.4, 129.4, 132.3 (d, J = 9.0 Hz), 132.8, 134.7, 141.8 (d, J = 9.0 Hz), 144.3, 150.6, 157.4, 159.9 (d, J = 204.3 Hz), 160.9; HRMS ESI/APCI Dual *m/z* calcd for $C_{23}H_{24}FN_7O_2S$ 482.1769 $[M+H]^+$, found 482.1762.

*5.4.41. 3-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-6-[3-fluoro-4-(methanesulfonyl)phenyl]-3H-[1,2,3]triazolo[4,5-c]pyridine (**30c**)*

The title compound was synthesized according to the procedure described for compound **30a** from **29a** and [3-fluoro-4-(methanesulfonyl)phenyl]boronic acid (51% yield).

Mp 229-230 ˚C (EtOAc/$CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 1.22 (t, J = 7.6 Hz, 3H), 2.32-2.38 (m, 2H), 2.39-2.47 (m, 2H), 2.51 (q, J = 7.6 Hz, 2H), 3.19-3.25 (m, 2H), 3.27 (s, 3H), 4.98-5.04 (m, 2H), 5.11-5.19 (m, 1H), 7.99-8.10 (m, 3H), 8.23 (s, 2H), 8.42 (d, J = 1.2 Hz, 1H), 9.24 (d, J = 1.2 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 15.6, 22.8, 31.7, 43.3, 44.0, 59.2, 111.3, 115.7 (d, J = 24.1 Hz), 122.7, 125.4, 128.0 (d, J = 15.0 Hz), 129.8, 130.3, 134.8, 147.1 (d, J = 9.0 Hz), 147.7, 157.4, 159.8 (d, J = 213.0 Hz), 160.8; HRMS ESI/APCI Dual *m/z* calcd for $C_{23}H_{24}FN_7O_2S$ 482.1769 $[M+H]^+$, found 482.1764.

*5.4.42. 4-{3-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl}-3-fluorobenzoic acid (**31a**)*

To a solution of **29a** (500 mg, 1.29 mmol) in DMF (12.9 mL) were added 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (514 mg, 1.94 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (52.3 mg, 0.0645 mmol) and 2 M Na_2CO_3 aqueous solution (1.93 mL). After stirring at 110 ˚C for 3 h, the reaction was quenched with water, filtered, and concentrated *in vacuo*. The resulting residue was dissolved in 10% NaOH aqueous solution. The aqueous layer was washed with EtOAc, neutralized with 1 M HCl aqueous solution and extracted with 10% MeOH in $CHCl_3$. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*.

The resulting solid was washed with EtOAc-hexanes to afford **31a** as a pale purple solid (376 mg, 65% yield).

^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.16 (t, J = 7.6 Hz, 3H), 2.13-2.23 (m, 2H), 2.30-2.37 (m, 2H), 2.47 (q, J = 7.6 Hz, 2H), 3.19-3.26 (m, 2H), 4.80-4.87 (m, 2H), 5.42-5.51 (m, 1H), 7.80-7.84 (m, 1H), 7.90-7.94 (m, 1H), 8.13-8.18 (m, 1H), 8.31 (s, 2H), 8.48 (s, 1H), 9.66 (d, J = 1.2 Hz, 1H); MS ESI/APCI Dual *m/z* 448 $[M+H]^+$.

*5.4.43. 4-{3-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl}-2,5-difluorobenzoic acid (**31b**)*

To a solution of **29a** (500 mg, 1.29 mmol) in EtOH (12.9 mL) were added 2,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (549 mg, 1.93 mmol), $Pd(PPh_3)_4$ (74.5 mg, 0.0645 mmol) and 2 M Cs_2CO_3 aqueous solution (1.29 mL). After the mixture being stirred at 150˚C under microwave irradiation for 30 min, 2 M Cs_2CO_3 aqueous solution was added to the mixture. The aqueous layer was washed with EtOAc, neutralized with 1 M HCl aqueous solution and extracted with 10% MeOH in $CHCl_3$. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting solid was washed with EtOAc-hexanes to afford **31b** as a colorless solid (290 mg, 48% yield).

^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.16 (t, J = 7.6 Hz, 3H), 2.13-2.22 (m, 2H), 2.30-2.36 (m, 2H), 2.47 (q, J = 7.6 Hz, 4H), 3.19-3.26 (m, 2H), 4.80-4.86 (m, 2H), 5.44-5.52 (m, 1H), 7.78-7.83 (m, 1H), 7.92-7.97 (m, 1H), 8.32 (s, 2H), 8.54 (s, 1H), 9.66-9.68 (m, 1H).

*5.4.44. 4-{3-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl}-2,3-difluorobenzoic acid (**31c**)*

The title compound was synthesized according to the procedure described for compound **31b** from **29a** and 4-borono-2,3-difluorobenzoic acid (46% yield).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.16 (t, J = 7.6, 3H), 2.03-2.38 (m, 4H), 2.39-2.47 (m, 2H), 3.13-3.28 (m, 2H), 4.75-4.92 (m, 2H), 5.37-5.55 (m, 1H), 7.39-7.44 (m, 1H), 7.58-7.67 (m, 1H), 8.31 (s, 2H), 8.39 (s, 1H), 9.62 (d, J = 1.4 Hz, 1H); MS ESI *m/z* 465 $[M+H]^+$.

*5.4.45. 4-{3-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl}-3-methylbenzoic acid (**31d**)*

The title compound was synthesized according to the procedure described for compound **31b** from **29a** and 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (81% yield).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.16 (t, J = 7.6 Hz, 3H), 2.08-2.34 (m, 4H), 2.37 (s, 3H), 2.41-2.47 (m, 2H), 3.17-3.28 (m, 2H), 4.78-4.90 (m, 2H), 5.37-5.52 (m, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.77-7.90 (m, 2H), 8.17 (s, 1H), 8.32 (s, 2H), 9.58 (s, 1H); MS ESI/APCI Dual *m/z* 442

$[M-H]^-$.

*5.4.46. 3-Chloro-4-{3-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl}benzoic acid (**31e**)*

To a solution of **29a** (500 mg, 1.29 mmol) in EtOH (13 mL) were added 4-borono-3-chlorobenzoic acid (387 mg, 1.93 mmol), $Pd(PPh_3)_4$ (74 mg, 0.064 mmol) and 2 M Cs_2CO_3 aqueous solution (1.3 mL). After the mixture being stirred at 80 ˚C for 5 h, 2 M KOH aqueous solution and EtOAc were added to the mixture. The aqueous layer was separated, washed with EtOAc, and neutralized with saturated NH_4Cl aqueous solution. The resulting precipitate was filtered and dried to afford **31e** as a pale yellow solid (466 mg, 78% yield).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.16 (t, J = 7.6 Hz, 3H), 2.07-2.27 (m, 2H), 2.28-2.39 (m, 2H), 2.41-2.48 (m, 2H), 3.13-3.29 (m, 2H), 4.77-4.93 (m, 2H), 5.37-5.54 (m, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.98 (s, 1H), 8.25-8.36 (m, 3H), 9.60 (s, 1H); MS ESI/APCI Dual m/z 464 $[M+H]^+$, 462 $[M-H]^-$.

*5.4.47. 4-{3-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl}-3-(trifluoromethyl)benzoic acid (**31f**)*

The title compound was synthesized according to the procedure described for compound **31b** from **29a** and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoic acid (33% yield).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.22-1.34 (m, 3H), 2.31-2.59 (m, 6H), 3.19-3.33 (m, 2H), 4.96-5.09 (m, 2H), 5.12-5.27 (m, 1H), 7.59-7.70 (m, 1H), 7.83-7.91 (m, 1H), 8.25-8.32 (m, 1H), 8.35-8.40 (m, 2H), 8.56 (s, 1H), 9.28 (d, J = 1.2 Hz, 1H); MS ESI/APCI Dual m/z 498 $[M+H]^+$.

*5.4.48. 4-{3-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl}-2-methylbenzoic acid (**31g**)*

The title compound was synthesized according to the procedure described for compound **31b** from **29a** and 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (58% yield).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.09-1.25 (m, 3H), 2.08-2.38 (m, 4H), 2.41-2.47 (m, 2H), 2.63 (s, 3H), 3.13-3.30 (m, 2H), 4.78-4.89 (m, 2H), 5.44 (br s, 1H), 7.93 (d, J = 8.2 Hz, 1H), 8.04-8.19 (m, 2H), 8.32 (s, 2H), 8.71 (s, 1H), 9.59 (s, 1H); MS ESI/APCI Dual m/z : 444 $[M+H]^+$, 442 $[M-H]^-$.

*5.4.49. 2-Chloro-4-{3-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl}benzoic acid (**31h**)*

The title compound was synthesized according to the procedure described for compound **31e** from

29a and 4-borono-2-chlorobenzoic acid (72% yield).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.16 (t, J = 7.6 Hz, 3H), 2.07-2.23 (m, 2H), 2.25-2.38 (m, 2H), 2.39-2.47 (m, 2H), 3.16-3.28 (m, 2H), 4.78-4.89 (m, 2H), 5.34-5.50 (m, 1H), 7.49 (d, J = 7.9 Hz, 1H), 8.04 (d, J = 7.9 Hz, 1H), 8.13 (s, 1H), 8.32 (s, 2H), 8.65 (s, 1H), 9.56 (s, 1H); MS ESI/APCI Dual *m/z* 464 $[M+H]^+$, 462 $[M-H]^-$.

*5.4.50. 4-{3-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl}-2-(trifluoromethyl)benzoic acid (**31i**)*

The title compound was synthesized according to the procedure described for compound **31b** from **29a** and 4-borono-2-(trifluoromethyl)benzoic acid (81% yield).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.11-1.21 (m, 3H), 2.07-2.38 (m, 4H), 2.41-2.46 (m, 2H), 3.17-3.23 (m, 4H), 4.77-4.89 (m, 2H), 5.39-5.54 (m, 1H), 7.96 (d, J = 8.1 Hz, 1H), 8.32 (s, 2H), 8.58 (d, J = 8.1 Hz, 1H), 8.65 (s, 1H), 8.91 (s, 1H), 9.64 (s, 1H); MS ESI/APCI Dual *m/z* 496 $[M-H]^-$.

*5.4.51. 4-{3-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl}-3,5-dimethylbenzoic acid (**31j**)*

The title compound was synthesized according to the procedure described for compound **31b** from **29a** and 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (30% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.17-1.27 (m, 3H), 2.09 (s, 6H), 2.22-2.59 (m, 6H), 3.14-3.33 (m, 2H), 4.93-5.29 (m, 3H), 7.82-7.95 (m, 3H), 8.17-8.32 (m, 2H), 9.25-9.33 (m, 1H); MS ESI *m/z* 458 $[M+H]^+$, 456 $[M-H]^-$.

*5.4.52. 4-{3-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl}-2,6-dimethylbenzoic acid (**31k**)*

The title compound was synthesized according to the procedure described for compound **31b** from **29a** and 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (62% yield).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.16 (t, J = 7.6 Hz, 3H), 2.07-2.54 (m, 12H), 3.11-3.30 (m, 2H), 4.75-4.90 (m, 2H), 5.36-5.52 (m, 1H), 7.90 (s, 2H), 8.32 (s, 2H), 8.61 (s, 1H), 9.55 (s, 1H); MS ESI *m/z* 456 $[M-H]^-$.

*5.4.53. N-Ethyl-4-{3-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl}-3-fluorobenzamide (**32a**)*

To a solution of **31a** (50.0 mg, 0.112 mmol) in DMF (1.12 mL) were added 70% ethylamine aqueous solution (10.8 mg, 0.168 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl) (32.2 mg, 0.168 mmol), 1,2,3-benzotriazol-1-ol monohydrate (HOBt·H_2O) (25.7 mg, 0.168 mmol) and triethylamine (34.0 mg, 0.335 mmol). After stirring at room temperature overnight,

the reaction was quenched with water and extracted with $CHCl_3$. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by NH silica gel column chromatography ($CHCl_3$). The resulting solid was dissolved in EtOAc under heating and hexanes were added to the mixture. The solution was stirred and allowed to cool to room temperature. The precipitated solid was collected by filtration to afford **32a** as a colorless solid (87% yield).

Mp 239 ˚C (EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 1.23 (t, J = 7.6 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H), 2.32-2.38 (m, 2H), 2.40-2.49 (m, 2H), 2.52 (q, J = 7.6 Hz, 2H), 3.19-3.28 (m, 2H), 3.49-3.58 (m, 2H), 4.98-5.05 (m, 2H), 5.12-5.20 (m, 1H), 6.08-6.15 (m, 1H), 7.62-7.68 (m, 2H), 8.12-8.18 (m, 1H), 8.24 (s, 2H), 8.51 (s, 1H), 9.25 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 14.9, 15.6, 22.8, 31.7, 35.2, 43.3, 59.0, 114.8 (d, J = 12.0 Hz), 115.5 (d, J = 26.6 Hz), 122.6, 125.3, 129.1, 129.7 (d, J = 12.4 Hz), 131.6, 134.4, 136.7 (d, J = 6.0 Hz), 145.4, 150.7, 157.4, 160.3 (d, J = 250.2 Hz), 160.6, 165.8; HRMS ESI/APCI Dual *m/z* calcd for $C_{25}H_{27}FN_8O$ 475.2365 $[M+H]^+$, found 475.2362.

*5.4.54. N-Ethyl-4-{3-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl }-2,5-difluorobenzamide (**32b**)*

The title compound was synthesized according to the procedure described for compound **32a** from **31b** (57% yield).

Mp 235-236 ˚C (EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 1.23 (t, J = 7.6 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H), 2.32-2.39 (m, 2H), 2.40-2.48 (m, 2H), 2.52 (q, J = 7.2 Hz, 2H), 3.19-3.27 (m, 2H), 3.51-3.59 (m, 2H), 4.99-5.05 (m, 2H), 5.11-5.20 (m, 1H), 6.75-6.84 (m, 1H), 7.92-8.02 (m, 2H), 8.24 (s, 2H), 8.60 (s, 1H), 9.22-9.25 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 14.8, 15.6, 22.8, 31.7, 35.2, 43.3, 59.1, 115.2 (d, J = 12.0 Hz), 118.2 (d, J = 33.0 Hz), 119.6 (d, J = 27.0 Hz), 122.3 (dd, J = 6.1, 15.1 Hz), 125.3, 129.3, 131.1 (dd, J = 7.3, 14.1 Hz), 134.4, 144.1, 150.7, 156.5 (d, J = 243.2 Hz), 157.4, 160.6, 161.7; HRMS ESI/APCI Dual *m/z* calcd for $C_{25}H_{26}F_2N_8O$ 493.2270 $[M+H]^+$, found 493.2263.

*5.4.55. N-Ethyl-4-{3-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl }-2,3-difluorobenzamide (**32c**)*

To a solution of **31c** (80.0 mg, 0.172 mmol) in DMF (2 mL) were added 70% ethylamine aqueous solution (16.6 mg, 0.258 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl) (49.4 mg, 0.258 mmol), 1,2,3-benzotriazol-1-ol monohydrate (HOBt·H_2O) (39.5 mg, 0.258 mmol) and triethylamine (26.1 mg, 0.258 mmol). After stirring at room temperature overnight, the reaction was quenched with water and extracted with $CHCl_3$. The organic layer was washed with water, separated and concentrated *in vacuo*. The residue was dissolved in 2-propanol under heating,

and to the mixture were added hexanes. The resulting solution was stirred and allowed to cool to room temperature. The precipitate was collected by filtration to afford **32c** as a colorless crystalline solid (51.4 mg, 61% yield).

Mp 224-225 ˚C (2-propanol/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.16-1.35 (m, 6H), 2.29-2.59 (m, 6H), 3.16-3.31 (m, 2H), 3.51-3.65 (m, 2H), 4.95-5.09 (m, 2H), 5.11-5.25 (m, 1H), 6.60-6.74 (m, 1H), 7.93-7.98 (m, 2H), 8.25 (s, 2H), 8.51 (t, *J* = 1.2 Hz, 1H), 9.24-9.27 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 14.8, 15.6, 22.8, 31.7, 35.2, 43.3, 59.1, 114.9 (d, *J* = 12.0 Hz), 122.7 (d, *J* = 10.1 Hz), 125.3, 125.6, 125.8, 129.3, 131.4 (d, *J* = 8.8 Hz), 134.6, 144.5, 148.6 (dd, *J* = 17.1, 252.1 Hz), 149.5 (dd, *J* = 15.5, 250.2 Hz), 150.6, 160.5, 162.0; HRMS ESI/APCI Dual *m/z* calcd for $C_{25}H_{26}F_2N_8O$ 493.2270 $[M+H]^+$, found 493.2253.

*5.4.56. N-Ethyl-4-{3-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl}-3-methylbenzamide (**32d**)*

The title compound was synthesized according to the procedure described for compound **32a** from **31d** (75% yield).

Mp 179-180 ˚C (EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 1.23 (t, *J* = 7.6 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 2.32-2.40 (m, 2H), 2.41-2.48 (m, 5H), 2.52 (q, *J* = 7.6 Hz, 2H), 3.20-3.28 (m, 2H), 3.50-3.58 (m, 2H), 4.99-5.05 (m, 2H), 5.12-5.20 (m, 1H), 6.11-6.18 (m, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.65-7.68 (m, 1H), 7.75 (s, 1H), 8.04 (d, *J* = 1.2 Hz, 1H), 8.24 (s, 2H), 9.23 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 15.0, 15.6, 20.6, 22.8, 31.7, 35.0, 43.3, 59.0, 113.8, 124.4, 125.3, 128.7, 129.6, 130.4, 133.9, 134.6, 136.7, 142.8, 150.4, 152.4, 157.3, 160.6, 167.2; HRMS ESI/APCI Dual *m/z* calcd for $C_{26}H_{30}N_8O$ 471.2615 $[M+H]^+$, found 471.2611.

*5.4.57. 3-Chloro-N-ethyl-4-{3-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl}benzamide (**32e**)*

The title compound was synthesized according to the procedure described for compound **32c** from **31e** (57% yield).

Mp 197-198 ˚C (2-propanol/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.16-1.35 (m, 6H), 2.30-2.58 (m, 6H), 3.16-3.31 (m, 2H), 3.48-3.61 (m, 2H), 4.93-5.07 (m, 2H), 5.09-5.24 (m, 1H), 6.16 (br s, 1H), 7.67-7.81 (m, 2H), 7.94 (s, 1H), 8.24 (s, 2H), 8.32 (d, *J* = 1.2 Hz, 1H), 9.25 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 14.9, 15.6, 22.8, 31.7, 35.2, 43.3, 59.1, 115.0, 125.3, 125.4, 129.0, 132.2, 132.9, 134.3, 136.1, 141.2, 149.1, 150.1, 157.4, 160.6, 165.8; HRMS ESI/APCI Dual *m/z* calcd for $C_{25}H_{27}ClN_8O$ 491.2069 $[M+H]^+$, found 491.2066.

*5.4.58. N-Ethyl-4-{3-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl}-3-(trifluoromethyl)benzamide (**32f**)*

The title compound was synthesized according to the procedure described for compound **32c** from **31f** (19% yield).

Mp 104-106 ˚C (2-propanol/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.18-1.37 (m, 6H), 2.31-2.62 (m, 6H), 3.17-3.31 (m, 2H), 3.51-3.65 (m, 2H), 4.96-5.08 (m, 2H), 5.10-5.25 (m, 1H), 6.19 (br s, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.99-8.13 (m, 2H), 8.21 (s, 1H), 8.24 (s, 2H), 9.22 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 14.9, 15.6, 22.8, 31.7, 35.3, 43.3, 59.1, 114.0, 123.7 (q, J = 274.0 Hz), 125.3, 125.4, 129.0, 129.1, 130.1, 132.6, 134.0, 135.1, 142.2, 150.0, 150.0, 157.3, 160.6, 165.7; HRMS ESI/APCI Dual *m/z* calcd for $C_{26}H_{27}F_3N_8O$ 525.2333 $[M+H]^+$, found 525.2316.

*5.4.59. N-Ethyl-4-{3-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl}-2-methylbenzamide (**32g**)*

The title compound was synthesized according to the procedure described for compound **32c** from **31g** (88% yield).

Mp 206-207 ˚C (2-propanol/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.18-1.34 (m, 6H), 2.27-2.58 (m, 9H), 3.15-3.30 (m, 2H), 3.47-3.58 (m, 2H), 4.94-5.06 (m, 2H), 5.07-5.23 (m, 1H), 5.79-5.89 (m, 1H), 7.43-7.53 (m, 1H), 7.83-7.89 (m, 1H), 7.91-7.96 (m, 1H), 8.24 (s, 2H), 8.30-8.34 (m, 1H), 9.18-9.24 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 15.0, 15.6, 20.1, 22.8, 31.6, 34.8, 43.3, 59.0, 110.1, 124.4, 125.3, 127.4, 129.1, 129.6, 134.3, 136.8, 136.9, 140.2, 150.5, 151.1, 157.3, 160.6, 169.7; HRMS ESI/APCI Dual *m/z* calcd for $C_{26}H_{30}N_8O$ 471.2615 $[M+H]^+$, found 471.2609.

*5.4.60. 2-Chloro-N-ethyl-4-{3-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl}benzamide (**32h**)*

The title compound was synthesized according to the procedure described for compound **32c** from **31h** (58% yield).

Mp 242-245 ˚C (2-propanol/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.17-1.34 (m, 6H), 2.28-2.58 (m, 6H), 3.17-3.31 (m, 2H), 3.50-3.62 (m, 2H), 4.96-5.07 (m, 2H), 5.09-5.23 (m, 1H), 6.29 (br s, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.99 (dd, J = 8.2, 1.2 Hz, 1H), 8.17 (d, J = 1.2 Hz, 1H), 8.24 (s, 2H), 8.36 (d, J = 1.2 Hz, 1H), 9.22 (d, J = 1.2 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 14.8, 15.6, 22.8, 31.7, 35.2, 43.3, 59.1, 110.5, 125.3, 128.7, 129.4, 130.8, 131.4, 134.5, 135.0, 141.9, 148.7, 151.0, 157.4, 160.6, 166.0; HRMS ESI/APCI Dual *m/z* calcd for $C_{25}H_{27}ClN_8O$ 491.2069 $[M+H]^+$, found 491.2054.

*5.4.61. N-Ethyl-4-{3-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl}-2-(trifluoromethyl)benzamide (**32i**)*

The title compound was synthesized according to the procedure described for compound **32c** from **31i** (64% yield).

Mp 219-221 ˚C (2-propanol/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.18-1.33 (m, 6H), 2.30-2.58 (m, 6H), 3.17-3.31 (m, 2H), 3.48-3.59 (m, 2H), 4.96-5.07 (m, 2H), 5.08-5.24 (m, 1H), 5.76-5.86 (m, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 8.20-8.29 (m, 3H), 8.40 (d, *J* = 1.2 Hz, 1H), 8.46 (s, 1H), 9.24 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 14.6, 15.6, 22.8, 31.7, 35.2, 43.3, 59.1, 110.4, 123.7 (q, *J* = 273.3 Hz), 125.0, 125.0, 125.3, 127.9 (q, *J* = 31.9 Hz), 129.4, 130.0, 134.6, 136.0, 140.4, 148.7, 151.0, 157.4, 160.6, 167.5; HRMS ESI/APCI Dual *m/z* calcd for $C_{26}H_{27}F_3N_8O$ 525.2333 $[M+H]^+$, found 525.2329.

*5.4.62. N-Ethyl-4-{3-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl }-3,5-dimethylbenzamide (**32j**)*

The title compound was synthesized according to the procedure described for compound **32c** from **31j** (69% yield).

Mp 109-113 ˚C (2-propanol/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.15-1.35 (m, 6H), 2.08 (s, 6H), 2.32-2.58 (m, 6H), 3.17-3.32 (m, 2H), 3.47-3.59 (m, 2H), 4.97-5.09 (m, 2H), 5.10-5.25 (m, 1H), 6.07-6.16 (m, 1H), 7.54 (s, 2H), 7.86 (d, *J* = 1.2 Hz, 1H), 8.24 (s, 2H), 9.26 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 15.0, 15.6, 20.5, 22.8, 31.7, 35.0, 43.3, 59.0, 114.0, 125.3, 126.2, 128.6, 134.4, 134.6, 136.9, 142.8, 150.4, 151.8, 157.3, 160.6, 167.4; HRMS ESI/APCI Dual *m/z* calcd for $C_{27}H_{32}N_8O$ 485.2772 $[M+H]^+$, found 485.2756.

*5.4.63. N-Ethyl-4-{3-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]-3H-[1,2,3]triazolo[4,5-c]pyridin-6-yl }-2,6-dimethylbenzamide (**32k**)*

The title compound was synthesized according to the procedure described for compound **32c** from **31k** (34% yield).

Mp 110-112 ˚C (2-propanol/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 1.22 (t, *J* = 7.6 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 2.30-2.36 (m, 2H), 2.37-2.47 (m, 8H), 2.51 (q, *J* = 7.2 Hz, 2H), 3.18-3.28 (m, 2H), 3.52-3.59 (m, 2H), 4.95-5.02 (m, 2H), 5.08-5.18 (m, 1H), 5.66 (t, *J* = 5.8 Hz, 1H), 7.69 (s, 2H), 8.23 (s, 2H), 8.29 (d, *J* = 1.2 Hz, 1H), 9.18 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 15.0, 15.6, 19.4, 22.7, 31.6, 34.5, 43.3, 58.9, 110.0, 125.3, 126.2, 129.0, 134.1, 135.0, 138.2, 139.1, 150.8, 151.1, 157.3, 160.5, 170.0; HRMS ESI/APCI Dual *m/z* calcd for $C_{27}H_{32}N_8O$ 485.2772 $[M+H]^+$, found 485.2761.

*5.4.64. 2,5-Difluoro-4-[3-(1-{[(propan-2-yl)oxy]carbonyl}piperidin-4-yl)-3H-[1,2,3]triazolo[4,5-c]p yridin-6-yl]benzoic acid (**33**)*

To a solution of **29b** (825 mg, 2.24 mmol) in EtOH (20 mL) were added 2,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (679 mg, 3.36 mmol), $Pd(PPh_3)_4$ (129 mg, 0.112 mmol) and 2 M Na_2CO_3 aqueous solution (2 mL). After stirring at 160 ˚C

under microwave irradiation for 30 min, the reaction was diluted with EtOAc and the resulting precipitate was filtered. The solid was dissolved in 1 M KOH aqueous solution and the aqueous layer was washed with EtOAc. The aqueous layer was separated and acidified with concentrated HCl, and the precipitate was filtered to afford **33** as a gray solid (222 mg, 22% yield).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.23 (d, J = 6.2 Hz, 6H), 2.04-2.21 (m, 2H), 2.22-2.33 (m, 2H), 3.04-3.20 (m, 2H), 4.12-4.26 (m, 2H), 4.83 (dt, J = 12.4, 6.3 Hz, 1H), 5.30-5.44 (m, 1H), 7.80 (dd, J = 11.0, 6.1 Hz, 1H), 7.94 (dd, J = 11.0, 6.1 Hz, 1H), 8.54 (s, 1H), 9.65 (s, 1H), 13.67 (br s, 1H); MS ESI m/z 444 $[M-H]^-$.

*5.4.65. Propan-2-yl 4-{6-[4-(ethylcarbamoyl)-2,5-difluorophenyl]-3H-[1,2,3]triazolo[4,5-c]pyridin-3-yl}piperidine-1-carboxylate (**32l**)*

The title compound was synthesized according to the procedure described for compound **32c** from **33** (66% yield).

Mp 183 ˚C (2-propanol/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.24-1.37 (m, 9H), 2.23-2.49 (m, 4H), 3.05-3.20 (m, 2H), 3.48-3.63 (m, 2H), 4.35-4.50 (m, 2H), 4.93-5.12 (m, 2H), 6.83 (br s, 1H), 7.89-8.06 (m, 2H), 8.61 (s, 1H), 9.23 (d, J = 1.1 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 14.8, 22.3, 31.8, 35.2, 42.8, 58.3, 69.3, 115.2 (d, J = 12.1 Hz), 118.3 (d, J = 30.0 Hz), 119.6 (d, J = 27.0 Hz), 122.4 (dd, J = 6.0, 15.1 Hz), 129.3, 131.0 (dd, J = 9.0, 12.5 Hz), 134.2, 144.2, 150.7, 155.0, 156.5 (d, J = 245.5 Hz), 161.7; HRMS ESI/APCI Dual m/z calcd for $C_{23}H_{26}F_2N_6O_3$ 473.2107 $[M+H]^+$, found 473.2093.

*5.4.66. Propan-2-yl 4-(6-{2,5-difluoro-4-[(propan-2-yl)carbamoyl]phenyl}-3H-[1,2,3]triazolo[4,5-c]pyridin-3-yl)piperidine-1-carboxylate (**32m**)*

The title compound was synthesized according to the procedure described for compound **32c** from **33** and propan-2-amine (40% yield).

Mp 197-198 ˚C (2-propanol/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.30 (d, J = 6.1 Hz, 12H), 2.23-2.48 (m, 4H), 3.05-3.22 (m, 2H), 4.25-4.53 (m, 3H), 4.93-5.12 (m, 2H), 6.57-6.71 (m, 1H), 7.89-8.05 (m, 2H), 8.61 (s, 1H), 9.24 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 22.3, 22.8, 31.8, 42.3, 42.8, 58.3, 69.3, 115.2 (d, J = 15.1 Hz), 118.2 (d, J = 30.0 Hz), 119.6 (d, J = 28.2 Hz), 122.6 (dd, J = 6.0, 15.0 Hz), 129.3, 131.0 (dd, J = 9.1, 15.5 Hz), 134.2, 144.2, 150.7, 155.0, 156.4 (d, J = 249.0 Hz), 156.5 (d, J = 246.3 Hz), 160.9; HRMS ESI/APCI Dual m/z calcd for $C_{24}H_{28}F_2N_6O_3$ 487.2264 $[M+H]^+$, found 487.2251.

5.4.67. Propan-2-yl

*4-{6-[4-(azetidine-1-carbonyl)-2,5-difluorophenyl]-3H-[1,2,3]triazolo[4,5-c]pyridin-3-yl}piperidine -1-carboxylate (**32n**)*

The title compound was synthesized according to the procedure described for compound **32c** from **33** and azetidine (73% yield).

Mp 195-196 ˚C (2-propanol/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.30 (d, J = 6.2 Hz, 6H), 2.22-2.50 (m, 6H), 3.05-3.20 (m, 2H), 4.13-4.30 (m, 4H), 4.35-4.51 (m, 2H), 4.93-5.12 (m, 2H), 7.41 (dd, J = 10.5, 5.4 Hz, 1H), 7.92 (dd, J = 10.5, 5.4 Hz, 1H), 8.50-8.60 (m, 1H), 9.23 (d, J = 1.2 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 15.8, 22.3, 31.8, 42.8, 48.8, 51.1, 51.2, 58.3, 69.3, 115.0 (d, J = 12.0 Hz), 117.8 (d, J = 24.0 Hz), 118.3 (d, J = 30.0 Hz), 123.4 (dd, J = 7.0, 20.0 Hz), 129.3, 130.2 (dd, J = 9.0, 15.1 Hz), 134.3, 144.4, 150.6, 155.0, 155.1 (d, J = 247.2 Hz), 156.3 (d, J = 248.2 Hz), 164.7; HRMS ESI/APCI Dual *m/z* calcd for $C_{24}H_{26}F_2N_6O_3$ 485.2107 $[M+H]^+$, found 485.2093.

5.4.68. Propan-2-yl

*4-{6-[2,5-difluoro-4-(pyrrolidine-1-carbonyl)phenyl]-3H-[1,2,3]triazolo[4,5-c]pyridin-3-yl}piperidine-1-carboxylate (**32o**)*

The title compound was synthesized according to the procedure described for compound **32c** from **33** and pyrrolidine (75% yield).

Mp 147-148 ˚C (2-propanol/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.30 (d, J = 6.2 Hz, 6H), 1.85-2.09 (m, 4H), 2.22-2.48 (m, 4H), 3.05-3.22 (m, 2H), 3.41 (t, J = 6.2 Hz, 2H), 3.68 (t, J = 6.8 Hz, 2H), 4.32-4.53 (m, 2H), 4.92-5.12 (m, 2H), 7.22-7.36 (m, 1H), 7.92 (dd, J = 10.1, 6.1 Hz, 1H), 8.55 (s, 1H), 9.23 (d, J = 1.2 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 22.3, 24.5, 26.0, 31.8, 42.8, 46.1, 47.9, 58.2, 69.3, 114.8 (d, J = 15.0 Hz), 116.8 (d, J = 27.0 Hz), 118.2 (d, J = 24.0 Hz), 126.8 (dd, J = 8.5, 16.0 Hz), 129.2, 129.3 (dd, J = 9.2, 15.1 Hz), 134.2, 144.5, 150.7, 154.5 (d, J = 246.1 Hz), 155.0, 156.3 (d, J = 249.3 Hz), 163.4; HRMS ESI/APCI Dual *m/z* calcd for $C_{25}H_{28}F_2N_6O_3$ 499.2264 $[M+H]^+$, found 499.2258.

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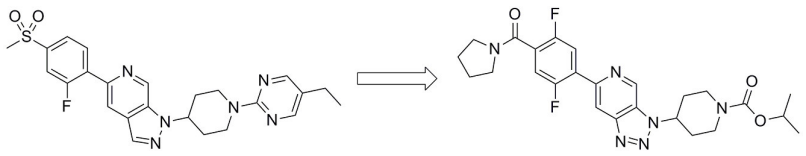
Graphical abstract



4b
hGPR119 EC_{50} = 4 nM
Melting point = 229-230 °C
Solubility = 0.71 μM

32o
hGPR119 EC_{50} = 65 nM
Melting point = 147-148 °C
Solubility = 15.9 μM