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RESEARCH PAPER

Optimisation of novel 4, 8-disubstituted dihydropyrimido[5,4-*b*][1,4]oxazine derivatives as potent GPR 119 agonists

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ABSTRACT

GPR119 is a promising target for discovery of anti-type 2 diabetes mellitus agents. We described the optimisation of a novel series of pyrimido[5,4-*b*][1,4]oxazine derivatives as GPR119 agonists. Most designed compounds exhibited good agonistic activities. Among them, compound **10** and **15** demonstrated the potent EC_{50} values (13 and 12 nM, respectively) and strong inherent activities. Moreover, significant hypoglycaemic effect of compound **15** was observed by reducing the blood glucose AUC_{0-2h} at the dose of 30 mg/kg, which is stronger than Vildagliptin (23.4% reduction vs. 17.9% reduction).

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Optimisation; pyrimidodihydrooxazine; GPR 119 agonists; type 2 diabetes mellitus

1. Introduction

Type 2 diabetes mellitus (T2DM) is a complex chronic disease characterised by metabolic disorder and hyperglycaemia due to insulin resistance, hepatic glucose overproduction and/or insufficient insulin secretion[1–3]. Although there are a number of pharmacotherapy options for T2DM, most of current anti-diabetes drug have shown known adverse effects and loss of their overall efficacy in a long-term glycaemic control[4–6]. Thus, there is still a critical need of novel therapeutic targets or approaches for treatment T2DM by good glycaemic control.

G protein-coupled receptor 119 (GPR119) is a member of class A (rhodopsin-type) GPCR family, with highly expressed in pancreatic β-cells and the K and L cells of the gastrointestinal tract[7–9]. Activation of GPR119 increases the intracellular cyclic AMP (cAMP) level, which in turn directly stimulate the glucose-dependent insulin secretion and regulate glucagon-like peptide 1 (GLP-1), leading to improve the glucose tolerance in T2DM patients[10–14]. In addition, GPR119 agonists showed β-cells function preservation, which is also an important role in current T2DM therapy[15–17]. As a result, GPR119 agonists are used for discovery of anti-T2DM agents by lowering the blood glucose level and improving β-cells function. Indeed, numerous synthetic, small molecule GPR119 agonists were revealed by academia and industry to date, and some of which have advanced into clinical trials such as **MBX-2982**, **BMS-903452**, **LEZ763**, **ZYG-19**[18–30]. Despite tremendous endeavours, none of GPR119 agonists were approved to market by FDA up to now.

In our efforts to discover GPR119 agonists, we previously have evaluated some series of pyrimidine derivatives, and some compounds displayed quite good agonistic potency[31,32]. Among them, pyrimidopyrimidine compounds **1** and **2** exhibited single digit EC_{50} values (2.2 nM and 8.1 nM respectively); however, these two agonists did not show the significant glucose-lowering effect in oral glucose tolerance test (oGTT) in mice compared with positive control. Therefore, we sequentially attempted to optimise the core fragment with the aim to enhance the biological activity both *in vitro* and *in vivo*. With this purpose, we introduced pyrimido[5,4-*b*][1,4]oxazine as the core using the strategy of scaffold hopping. We also identified whether introduction of several conformation restricted azabicyclic amines were beneficial to agonistic potency or not (Figure 1). In this paper, we described our optimisation to synthesise and evaluate a series of novel pyrimido[5,4-*b*][1,4]oxazine derivatives as GPR119 agonists, also including an *in vivo* efficacy study.

2. Results and discussion

2.1. Chemistry

The intermediates amine or bicyclic amines **3**–**6** could be purchased or synthesised according to the reported procedures[33–36]. Coupling reaction of 4,6-dichloro-5-methoxypyrimidine with 4-amino-3-fluorobenzonitrile in DMF under basic condition afforded compound **7**, followed by demethylation using BBr_3 solution in dichloromethane under reflux condition gave hydroxyl compound **8**. Cyclisation of **8** with 1-bromo-2-chloroethane and K_2CO_3 in DMF generated key intermediate **9**. Buchwald–Hartwig reaction of **9** and amines **3**–**6** with $Pd_2(dba)_3$, X-Phos and Cs_2CO_3 under reflux conditions and N_2 atmosphere overnight resulted in target compounds **10**–**13** (Scheme 1).

Removing Boc group of derivative **10** in 3 M HCl ethanol solution obtained amine compound **14** in good yield, which was treated with various chloro-fragments in base conditions to receive desired final compounds **15**–**20** (Scheme 2).

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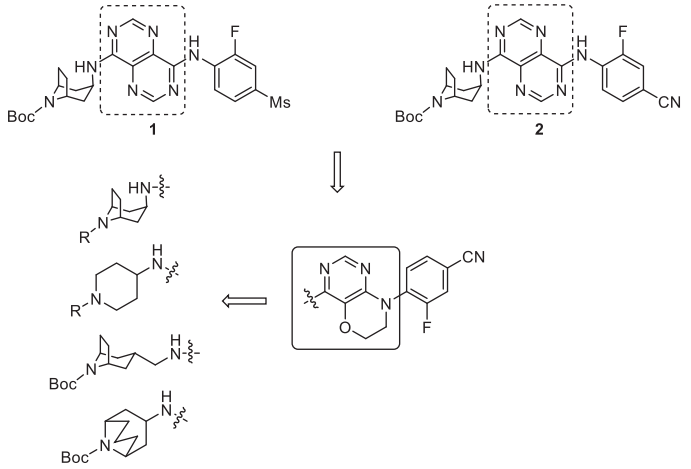


Figure 1. The design of target compounds.

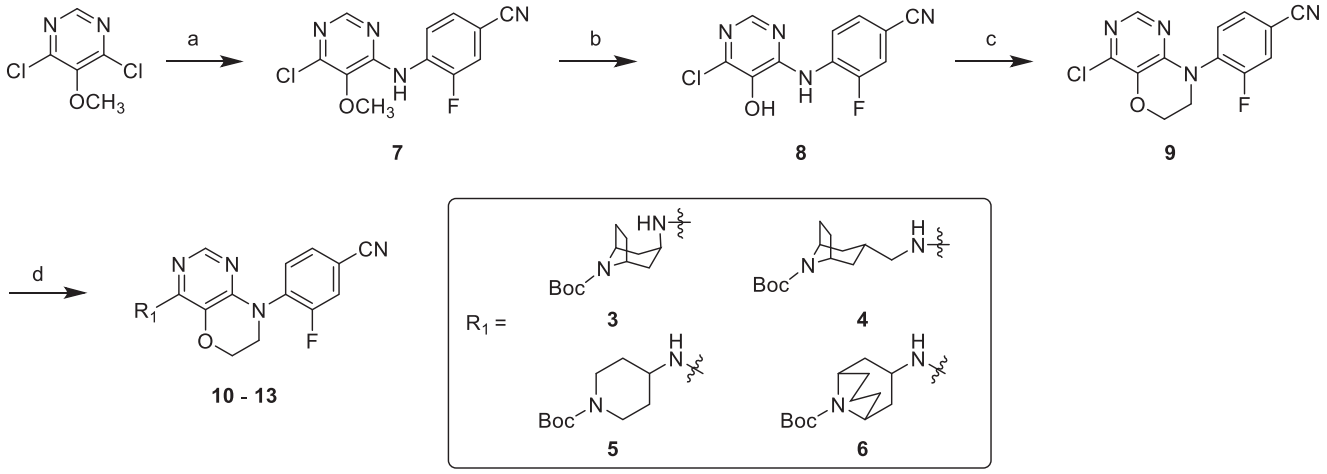
The general synthetic procedures of the pyrimidooxazine derivatives **22**–**25** were synthesised as shown in Scheme 3, following similar methods with compounds **15**–**20**.

2.2. Biological activity

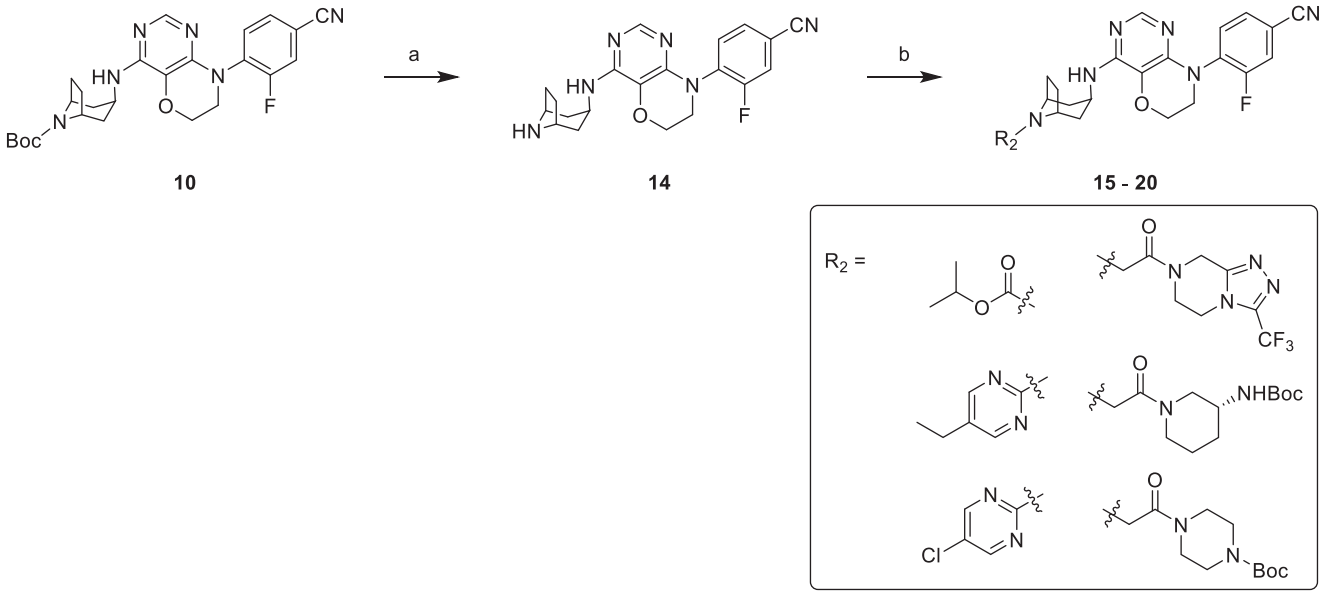
2.2.1. GPR119 activation

GPR119 agonistic activity of target compounds **10**–**13**, **15**–**20**, and **22**–**25** were measured using a reporter assay with the human GPR119 receptor stably expressed in CHO K1 cells. A GPR119 agonist **GSK-1292263** was chose for the reference. The results expressed the activity as EC_{50} values and the inherent activity (IA) as percentages (%max) of response which were compared to the reference **GSK-1292263** (defined the maximal effect activation).

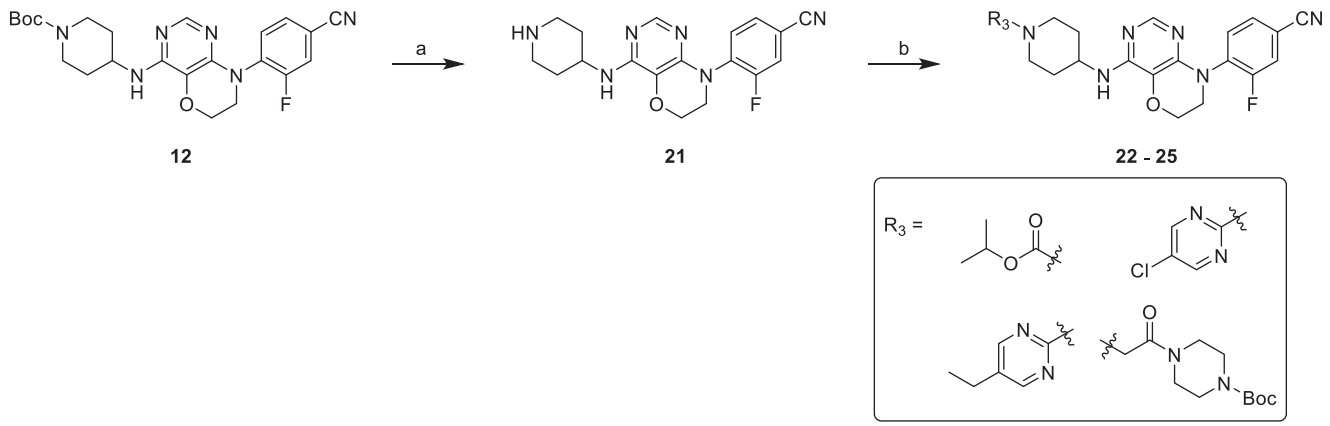
At first, we evaluated pyrimidooxazine derivatives **10**–**13** for the GPR119 agonistic activity and intrinsic activity (Table 1). As a



Scheme 1. Synthesis of compounds **10**–**13**. Reagents and conditions: (a) 4-amino-3-fluorobenzonitrile, K_2CO_3, DMF, 65 °C, overnight. (b) 1 M BBr_3 in DCM, anhydrous DCM, r. t. – reflux, 2 h. (c) 1-bromo-2-chloroethane, K_2CO_3, DMF, 40 °C, overnight. (d) amines **3**–**6**, $Pd_2(dba)_3$, X-Phos, Cs_2CO_3, 1,4-Dioxane, reflux, under N_2 overnight.

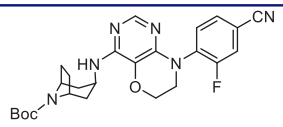
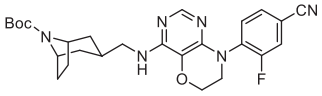
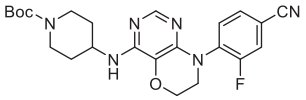
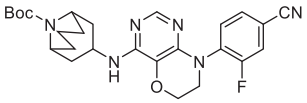


Scheme 2. Synthesis of compounds **15**–**20**. Reagents and conditions: (a) 3 M HCl in EtOH, r. t., overnight. (b) chloro-fragments, Et_3N, DCM, r. t., overnight or Cs_2CO_3, DMF, r. t., overnight.



Scheme 3. Synthesis of compounds **22–25**. Reagents and conditions: (a) 3 M HCl in EtOH, r. t., overnight. (b) chloro-fragments, Et_3N, DCM, r. t., overnight or Cs_2CO_3, DMF, r. t., overnight.

Table 1. GPR119 agonistic activities of compounds **10–13**.

		GPR119 activation		
Compound	Structure	EC_{50} (nM)	%max[a]	Clog*P*[b]
10		13	83.9	4.0
11		1800	45.9	4.6
12		200	63.5	3.5
13		>10000	22.7	4.5
GSK-1292263		6.6	100	

[a]%max: cAMP stimulation % compared to maximal effect of **GSK1292263**.
[b]Clog*P* was calculated using ACD software from Discovery Studio 4.5.

result, good activities were observed with compounds **10** and **12** (EC_{50} = 13 and 200 nM respectively), which contained tropine amine and piperidine amine scaffolds with moderate lipophilicity (Clog*P* = 4.0 and 3.5 respectively).

Next, we focussed on the modification of Boc group in head part with various moieties. The biological results were shown in Table 2, all compounds exhibited moderate to potent agonistic activities (EC_{50} values range from 250 nM to 12 nM). The substitution of 2-pyrimidyl on the nitrogen of tropine ring yielded compounds **16** and **17**, which showed the moderate EC_{50} values (130 nM and 250 nM, respectively). However, the compounds **23** and **24**, bearing same substituents on the nitrogen of piperidine ring, demonstrated significant agonistic activities (EC_{50} = 44 nM and 40 nM) and lower lipophilicity. But the reverse results were observed for carbamate substituted derivatives (**15** vs. **22**), and compound **15** exhibited 10 times EC_{50} values than compound **22**. Furthermore, compound **15** revealed the strongest inherent activity (%max 146.5%) and best agonistic activity (EC_{50} = 12 nM) with suitable Clog*P* value (3.8). Consequently, compounds **15** and **10** were selected and examined the oral glucose tolerance test (oGTT) *in vivo* as promising GPR119 agonists.

2.2.2. oGTT in mice

Based on the good agonistic activity, we conducted oGTT of compounds **10** and **15** with a single dose (15 and 30 mg/kg) in C57BL/6N mice with DPP-4 inhibitor vildagliptin as a positive control. The results were outlined in Figure 2, compounds **10** and **15** both showed blood glucose reduction effect in dose-dependent manner. Vildagliptin reduced the area under curve from 0 to 120 min ($AUC_{0-120\,min}$) by 17.9% (Vehicle: 24.69 ± 3.08, Vildagliptin: 20.26 ± 2.14) at the dose of 30 mg/kg. Meanwhile compounds **10** and **15** reduced $AUC_{0-120\,min}$ by 10.7% (22.07 ± 4.28) and 14.5% (21.10 ± 3.92) at the dosage of 15 mg/kg, respectively. However, **10** and **15** showed significant improved efficacy by the reduction of value to 18.8% (20.05 ± 2.27) and 23.4% (18.91 ± 2.58) at the dosage of 30 mg/kg, respectively.

3. Conclusion

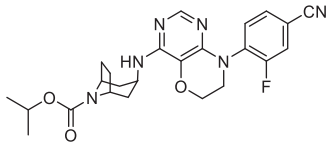
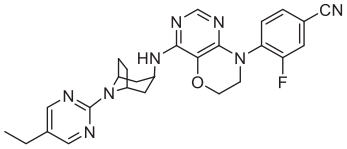
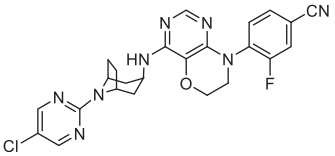
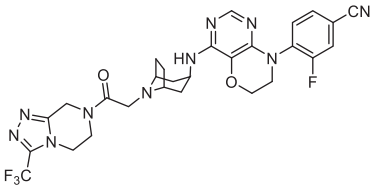
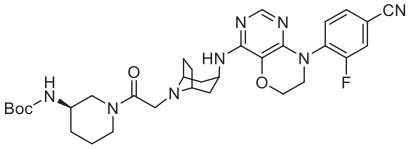
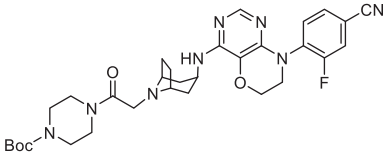
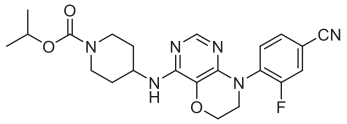
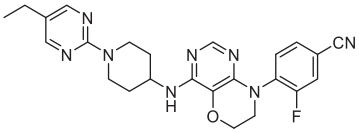
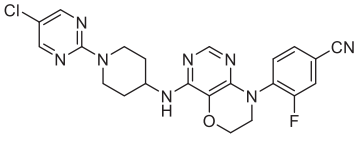
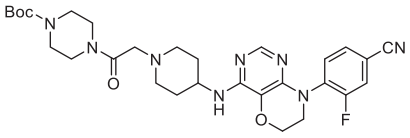
In summary, we have designed, synthesised and biologically evaluated a series of novel pyrimido[5,4-*b*][1,4]oxazine derivatives as potent GPR119 agonists. *In vitro*, half derivatives exhibited strong EC_{50} values (<100 nM). Among the aliphatic amine moieties of this scaffold, the compound **10** with tropine amine ring displayed much more potent agonistic activity than piperidine amine and other rigid bicyclic amines. In the further optimisation of *N*-substitution, only isopropyl carbamate of tropine ring **15** improved the EC_{50} values and showed the greatest inherent activity. Accordingly, compounds **10** and **15** were conducted the oGTT in C57BL/6N mice. Both two agonists demonstrated blood glucose reduction effect in a dose-dependent manner. Furthermore, the optimised compound **15** was exerted improved 23.4% reduction in blood glucose AUC_{0-2h} at the dose of 30 mg/kg comparing with Vildagliptin (17.9% reduction). Follow-up studies and their results will be reported in due course.

4. Experimental

4.1. Chemistry

All starting materials were obtained from commercial suppliers and used without further purification. ^{1}H-NMR and 13C-NMR spectra were recorded on a Bruker AVANCE III HD 600 (600 Hz) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield relative to tetramethylsilane as an internal standard. Peak splitting patterns are abbreviated as s (singlet), br s (broad singlet), d (doublet), t (triplet), dd (doublet of doublet), and m (multiplet). MS spectra were recorded on a Thermo Fisher (LCQ

Table 2. GPR119 agonistic activities of compounds **15–20** and **22–25**.

Compound	Structure	GPR119 activation		ClogP[b]
		EC_{50} (nM)	%max[a]	
15		12	146.3	3.8
16		130	60.5	4.6
17		250	71.2	4.3
18		110	100	3.0
19		68	75.6	3.7
20		82	79.6	3.3
22		120	66.1	3.3
23		44	70.7	4.0
24		40	62.7	3.8
25		90	100	2.7
GSK-1292263		6.6	100	

[a]%max: cAMP stimulation % compared to maximal effect of **GSK1292263**.
[b]Clog*P* was calculated using ACD software from Discovery Studio 4.5.

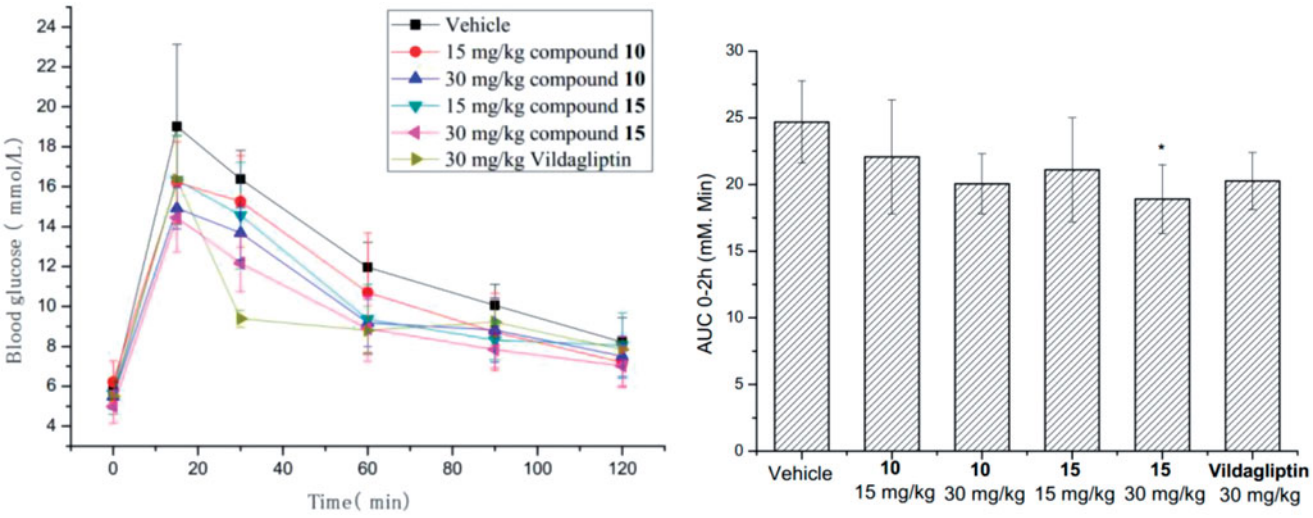


Figure 2. Single dose of compounds **10** and **15** on oGTT in C57BL/6N mice. The results are presented as the mean ± SE. $^{*}p < 0.05$ compared to vehicle group ($n = 8$).

Fleet). HR-MS spectra were recorded on an AB SCIEX (Triple TOF 5600+). TLC was performed on silica F254 purchased from Branch of Qingdao Haiyang Chemical Co. (Qingdao, China) and detected by UV light at 254, 365 nm or by charring with sulphuric acid. Column chromatography was performed on silica gel column (200–300 mesh, Branch of Qingdao Haiyang Chemical Co.). Analytical HPLC was performed on a Waters Acquity® Arc™ with 2998 PDA detector and all final compounds possessed purities of >90% after purification.

4.1.1. 4-((6-Chloro-5-methoxypyrimidin-4-yl)amino)-3-fluorobenzonitrile (7)

To a solution of 4,6-dichloro-5-methoxypyrimidine (1 g, 5.7 mmol) in DMF (20 ml), 4-amino-3-fluorobenzonitrile (0.6 g, 4.4 mmol) and K_2CO_3 (2.4 g, 17 mmol) were added. The reaction was stirrd at 65 °C for overnight. Then the mixture was poured into ice water. The mix solution was extracted with ethyl acetate for two times, washed with brine for two times. The organic layer was dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (petroleum ether: EtOAc = 3: 1) to afford the desired product as a claybank solid (0.68 g, 55%). ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.94 (t, $J = 8.8$ Hz, 1H), 8.35 (s, 1H), 7.73 (s, 1H), 7.59 (d, $J = 8.8$ Hz, 1H), 7.52 (d, $J = 10.2$ Hz, 1H), 3.10 (s, 3H). MS-ESI: $[M + H]^+$: 279.3.

4.1.2. 4-((6-Chloro-5-hydroxypyrimidin-4-yl)amino)-3-fluorobenzonitrile (8)

To a solution of compound **7** (0.5 g, 1.9 mmol) in anhydrous dichloromethane (15 ml), 1 M BBr_3 in dichloromethane solution (5.7 ml, 5.7 mmol) was added at room temperature (r. t.) The reaction was reflux for 2 h. Then the reaction was quenched by water. The mixture was extracted with dichloromethane for two times, washed by brine for two times. The organic layer was dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (petroleum ether: EtOAc = 1: 1) to give the desired product as a yellow solid (0.3 g, 72%). ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.92 (t, $J = 8.4$ Hz, 1H), 8.32 (s, 1H), 7.68 (s, 1H), 7.53 (d, $J = 8.6$ Hz, 1H), 7.46 (d, $J = 10.8$ Hz, 1H). MS-ESI: $[M + H]^+$: 265.1.

4.1.3. 4-(4-Chloro-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-8-yl)-3-fluorobenzonitrile (9)

To a solution of compound **8** (0.4 g, 1.4 mmol) in DMF (10 ml), 1-bromo-2-chloroethane (0.62 g, 4.3 mmol) and K_2CO_3 (0.6 g, 4.3 mmol) were added. The reaction was stirred at 40 °C for overnight. Then the mixture was poured into ice water. The mix solution was extracted with ethyl acetate for two times, washed with brine for two times. The organic layer was dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (petroleum ether: EtOAc = 2: 1) to afford the desired product as a claybank solid (0.68 g, 55%). ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.04 (s, 1H), 8.35 (s, 1H), 7.73–7.44 (m, 3H), 4.51 (t, $J = 4.4$ Hz, 2H), 3.95 (t, $J = 4.3$ Hz, 2H). MS-ESI: $[M + H]^+$: 291.5.

4.1.4. General procedure of compounds 10–13

To the solution of compound **9** (0.22 mmol) and substituted amines (0.22 mmol) in 1,4-dioxane (2 ml), $Pd_2(dba)_3$ (0.05 mmol), X-Phos (0.05 mmol), and Cs_2CO_3 (0.55 mmol) were added. The reaction was heated to reflux under nitrogen gas for overnight. Then the mixture was diluted with ethyl acetate, washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography to give the product.

4.1.5. tert-Butyl (endo)-3-((8-(4-cyano-2-fluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-4-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (10)

Yellowish solid, 52% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.93 (s, 1H), 7.54–7.50 (m, 1H), 7.47 (m, 2H), 5.38 (d, $J = 7.0$ Hz, 1H), 4.46–4.37 (m, 2H), 4.33 (m, 2H), 4.22 (s, 1H), 3.89 (s, 2H), 2.39 (s, 1H), 2.30–2.20 (m, 1H), 2.12 (t, $J = 7.4$ Hz, 2H), 2.07–1.92 (m, 2H), 1.84 (d, $J = 27.1$ Hz, 2H), 1.49 (s, 9H). 13C-NMR (150 MHz, $CDCl_3$) δ (ppm): 156.4 (d, $J = 250.5$ Hz), 153.4, 151.3, 149.8, 143.9, 135.4 (d, $J = 10.5$ Hz), 128.5 (d, $J = 3.5$ Hz), 128.4 (d, $J = 2.6$ Hz), 121.8, 120.6 (d, $J = 23.7$ Hz), 117.6 (d, $J = 2.6$ Hz), 109.4 (d, $J = 9.2$ Hz), 79.5, 64.5, 53.1, 52.2, 48.2 (d, $J = 3.9$ Hz), 43.1, 35.8, 35.3, 28.5 (x3), 28.3, 27.9. HRMS-TOF (*m/z*) calcd for $C_{25}H_{29}FN_6O_3$ $[M + H]^+$: 481.2358, found 481.2436.

4.1.6. tert-Butyl (exo)-3-(((8-(4-cyano-2-fluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-4-yl)amino)methyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (11)

Yellowish solid, 45% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.92 (s, 1H), 7.55–7.51 (m, 1H), 7.50–7.44 (m, 2H), 5.00 (t, $J = 6.1$ Hz, 1H), 4.39–4.35 (m, 2H), 4.30 (s, 1H), 4.20 (s, 1H), 3.95–3.81 (m, 2H), 3.37 (d, $J = 23.7$ Hz, 2H), 2.29–2.14 (m, 1H), 1.97 (s, 2H), 1.72–1.63 (m, 4H), 1.65 (s, 2H), 1.49 (s, 9H). HRMS-TOF (*m/z*) calcd for $C_{26}H_{31}FN_6O_3$ $[M+H]^+$: 495.2514, found 495.2592.

4.1.7. tert-Butyl 4-((8-(4-cyano-2-fluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-4-yl)amino)piperidine-1-carboxylate (12)

Yellowish solid, 76% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.93 (s, 1H), 7.56–7.51 (m, 1H), 7.48 (m, 2H), 4.83 (d, $J = 8.1$ Hz, 1H), 4.38 (t, $J = 4.3$ Hz, 2H), 4.17–4.11 (m, 3H), 3.89–3.87 (t, $J = 3.7$, 2H), 2.98 (m, 2H), 2.07–2.05 (m, 2H), 1.49 (s, 9H), 1.43–1.40 (m, 2H). 13C-NMR (150 MHz, $CDCl_3$) δ (ppm): 156.4 (d, $J = 250.7$ Hz), 154.8, 151.2, 149.7, 144.2, 135.4 (d, $J = 10.5$ Hz), 128.5 (d, $J = 3.6$ Hz), 128.4 (d, $J = 2.6$ Hz), 121.7, 120.6 (d, $J = 23.7$ Hz), 117.6 (d, $J = 2.7$ Hz), 109.5 (d, $J = 9.0$ Hz), 79.7, 64.3, 48.2 (d, $J = 3.8$ Hz), 47.6, 43.0, 32.5 (x2), 28.5 (x3). HRMS-TOF (*m/z*) calcd for $C_{23}H_{27}FN_6O_3$ $[M+H]^+$: 455.2201, found 455.2275.

4.1.8. tert-Butyl 3-((8-(4-cyano-2-fluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-4-yl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate (13)

Yellowish solid, 52% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.91 (s, 1H), 7.52 (t, $J = 7.8$ Hz, 1H), 7.50–7.43 (m, 2H), 4.71 (d, $J = 8.3$ Hz, 1H), 4.60 (t, $J = 9.0$ Hz, 1H), 4.46 (d, $J = 12.3$ Hz, 1H), 4.36 (dt, $J = 6.2$, 4.8 Hz, 2H), 4.03 (m, 1H), 3.93–3.81 (m, 2H), 2.52 (m, 2H), 2.09–1.94 (m, 2H), 1.85 (m, 1H), 1.77–1.74 (m, 1H), 1.72–1.69 (m, 1H), 1.66-.1.61 (m, 1H), 1.58–1.57 (m, 1H), 1.50 (s, 9H), 1.43–1.41 (m, 2H). HRMS-TOF (*m/z*) calcd for $C_{26}H_{31}FN_6O_3$ $[M+H]^+$: 495.2514, found 495.2600.

4.1.9. 4-(4-(((endo)-8-Azabicyclo[3.2.1]octan-3-yl)amino)-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-8-yl)-3-fluorobenzonitrile (14)

To a solution of compound **10** (1 mmol) in 3 M HCl/EtOH (40 ml) was stirred at r. t. for overnight. Then the mixture was filtered to obtain the product **14**, which was used for next step without purification. MS-ESI: $[M+H]^+$: 381.3.

4.1.10. Isopropyl (endo)-3-((8-(4-cyano-2-fluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-4-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (15)

To a solution of compound **14** (0.1 g, 0.26 mmol) in dichloromethane (3 ml), isopropyl carbonochloridate (30 μL, 0.34 mmol) and Et_3N (73 μL, 1 mmol) were added. The reaction was stirred at r.t. for overnight. Then mixture was diluted with dichloromethane, washed with brine for two times. The organic layer was dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (petroleum ether: EtOAc = 1: 1) to afford the desired product as a light yellow solid (70 mg, 58%). ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.93 (s, 1H), 7.54–7.51 (m, 1H), 7.48 (m, 2H), 5.38 (d, $J = 6.9$ Hz, 1H), 4.98 (dt, $J = 12.5$, 6.2 Hz, 1H), 4.40–4.37 (m, 3H), 4.34 (m, 2H), 3.89 (m, 2H), 2.37 (m, 1H), 2.24 (m, 1H), 2.13 (m, 2H), 2.02 (m, 2H), 1.87 (m, 2H), 1.28 (s, 3H), 1.27 (s, 3H). 13C-NMR (150 MHz, $CDCl_3$) δ (ppm): 156.4 (d, $J = 250.5$ Hz), 153.6, 151.3, 149.8, 143.9, 135.4 (d, $J = 10.5$ Hz), 128.5 (d, $J = 3.6$ Hz), 128.4 (d, $J = 2.5$ Hz), 121.8, 120.6 (d, $J = 23.7$ Hz), 117.6 (d, $J = 2.4$ Hz), 109.4 (d, $J = 9.2$ Hz), 68.1, 64.5, 53.1, 52.6, 48.2 (d, $J = 4.4$ Hz), 43.1, 35.9, 35.4, 28.3, 27.9, 22.3 (x2). HRMS-TOF (*m/z*) calcd for $C_{24}H_{27}FN_6O_3$ $[M+H]^+$: 467.2201, found 467.2282.

4.1.11. General procedure of compounds 16–20

To a solution of compound **14** (0.26 mmol) in DMF (3 ml), chlorofragments (0.34 mmol) and K_2CO_3 (1 mmol) were added. The reaction was stirred at r. t. for overnight. Then the mixture was poured into ice water. The mix solution was extracted with ethyl acetate for two times, washed with brine for 2 times. The organic layer was dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography to afford the desired product.

4.1.12. 4-(4-(((endo)-8-(5-Ethylpyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)amino)-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-8-yl)-3-fluorobenzonitrile (16)

Yellowish solid, 47% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.22 (s, 2H), 7.92 (s, 1H), 7.55–7.51 (m, 1H), 7.47 (m, 2H), 5.52 (d, $J = 7.2$ Hz, 1H), 4.78 (s, 2H), 4.43–4.37 (m, 2H), 4.30 (q, $J = 6.6$ Hz, 1H), 3.92–3.85 (m, 2H), 2.50 (q, $J = 7.6$ Hz, 2H), 2.38 (m, 2H), 2.25–2.18 (m, 2H), 2.13 (m, 2H), 1.89 (d, $J = 14.2$ Hz, 2H), 1.23 (t, $J = 7.6$ Hz, 3H). 13C-NMR (150 MHz, $CDCl_3$) δ (ppm): 159.1, 157.5 (x2), 156.4 (d, $J = 250.7$ Hz), 151.4, 149.9, 143.8, 135.5 (d, $J = 10.4$ Hz), 128.5 (d, $J = 3.5$ Hz), 128.4 (d, $J = 2.6$ Hz), 124.6, 121.8, 120.6 (d, $J = 23.7$ Hz), 117.6 (d, $J = 2.7$ Hz), 109.4 (d, $J = 9.2$ Hz), 64.5, 52.6 (x2), 48.3 (d, $J = 3.9$ Hz), 43.5, 34.7 (x2), 28.1 (x2), 22.8, 15.6. HRMS-TOF (*m/z*) calcd for $C_{26}H_{27}FN_8O$ $[M+H]^+$: 487.2365, found 487.2462.

4.1.13. 4-(4-(((endo)-8-(5-Chloropyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)amino)-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-8-yl)-3-fluorobenzonitrile (17)

Yellowish solid, 51% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.27 (s, 2H), 7.92 (s, 1H), 7.53 (t, $J = 7.8$ Hz, 1H), 7.51–7.44 (m, 2H), 5.48 (d, $J = 7.1$ Hz, 1H), 4.87–4.67 (m, 2H), 4.49–4.38 (m, 2H), 4.28 (q, $J = 6.6$ Hz, 1H), 3.95–3.83 (m, 2H), 2.34 (m, 2H), 2.26–2.19 (m, 2H), 2.14 (m, 2H), 1.96–1.88 (m, 2H). 13C-NMR (150 MHz, $CDCl_3$) δ (ppm): 158.0, 156.4 (d, $J = 250.6$ Hz), 156.3 (x2), 151.3, 149.9, 143.9, 135.4 (d, $J = 10.5$ Hz), 128.5 (d, $J = 3.6$ Hz), 128.4 (d, $J = 2.5$ Hz), 121.8, 120.6 (d, $J = 23.7$ Hz), 118.1, 117.6 (d, $J = 2.6$ Hz), 109.4 (d, $J = 9.2$ Hz), 64.5, 52.8 (x2), 48.2 (d, $J = 3.9$ Hz), 43.4, 34.6 (x2), 28.1 (x2). HRMS-TOF (*m/z*) calcd for $C_{24}H_{22}ClFN_8O$ $[M+H]^+$: 493.1662, found 493.1751.

4.1.14. 3-Fluoro-4-(4-(((endo)-8-(2-oxo-2-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)ethyl)-8-azabicyclo[3.2.1]octan-3-yl)amino)-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-8-yl)benzonitrile (18)

Yellowish solid, 44% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.91 (s, 1H), 7.53–7.50 (m, 1H), 7.49–7.43 (m, 2H), 5.30 (m, 2H), 5.05 (s, 1H), 4.38 (m, 2H), 4.33–4.16 (m, 4H), 4.11 (t, $J = 5.6$ Hz, 1H), 3.87 (t, $J = 4.3$ Hz, 2H), 3.36 (d, $J = 3.8$ Hz, 2H), 3.26 (m, 2H), 2.29–2.08 (m, 4H), 1.97 (m, 2H), 1.82 (m, 2H). HRMS-TOF (*m/z*) calcd for $C_{28}H_{28}FN_{10}O_2$ $[M+H]^+$: 613.2406, found 613.2508.

4.1.15. tert-Butyl ((R)-1-(2-((endo)-3-((8-(4-cyano-2-fluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-4-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)acetyl)piperidin-3-yl)carbamate (19)

Yellowish solid, 50% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.92 (s, 1H), 7.52 (m, 1H), 7.47 (m, 2H), 5.47–5.32 (m, 2H), 4.44–4.35 (m, 2H), 4.30 (m, 1H), 3.88 (m, 2H), 3.74–3.67 (m, 3H), 3.61–3.15 (m, 6H), 2.49–2.30 (m, 2H), 2.23 (m, 2H), 1.97 (m, 2H), 1.93–1.74 (m, 6H), 1.48 (s, 9H). HRMS-TOF (*m/z*) calcd for $C_{32}H_{41}FN_8O_4$ $[M+H]^+$: 621.3308, found 621.3405.

4.1.16. tert-Butyl 4-(2-((endo)-3-((8-(4-cyano-2-fluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-4-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)acetyl)piperazine-1-carboxylate (20)

Yellowish solid, 68% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.92 (s, 1H), 7.55–7.50 (m, 1H), 7.47 (m, 2H), 5.34 (d, $J=7.1$ Hz, 1H), 4.44–4.35 (m, 2H), 4.26 (q, $J=6.7$ Hz, 1H), 3.91–3.84 (m, 2H), 3.72–3.67 (m, 2H), 3.60 (s, 2H), 3.53–3.47 (m, 2H), 3.43 (m, 2H), 3.32 (m, 2H), 3.28 (m, 2H), 2.29 (m, 2H), 2.21–2.13 (m, 2H), 1.96 (m, 2H), 1.83 (d, $J=14.3$ Hz, 2H), 1.50 (s, 9H). 13C-NMR (150 MHz, $CDCl_3$) δ (ppm): 168.8, 156.4 (d, $J=250.6$ Hz), 154.6, 151.3, 149.8, 143.8, 135.5 (d, $J=10.5$ Hz), 128.5 (d, $J=3.5$ Hz), 128.4 (d, $J=2.5$ Hz), 121.8, 120.6 (d, $J=23.7$ Hz), 117.6 (d, $J=2.5$ Hz), 109.4 (d, $J=9.1$ Hz), 80.3, 70.6, 64.4, 58.8, 56.0 (x2), 48.2 (d, $J=3.8$ Hz), 45.8, 43.5 (x2), 42.4, 41.7, 36.9 (x2), 28.4 (x3), 26.2. HRMS-TOF (*m/z*) calcd for $C_{31}H_{39}FN_8O_4$ $[M+H]^+$: 607.3151, found 607.3239.

4.1.17. 3-Fluoro-4-(4-(piperidin-4-ylamino)-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-8-yl)benzonitrile (21)

Follow the similar procedure of **14**. Yellow solid, 72% yield. MS-ESI: $[M+H]^+$: 355.7.

4.1.18. Isopropyl 4-((8-(4-cyano-2-fluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-4-yl)amino)piperidine-1-carboxylate (22)

Follow the similar procedure of **15**. Yellowish solid, 70% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.93 (s, 1H), 7.56–7.51 (m, 1H), 7.48 (m, 2H), 4.95 (dt, $J=12.5$, 6.2 Hz, 1H), 4.83 (d, $J=8.1$ Hz, 1H), 4.43–4.33 (m, 2H), 4.27–4.08 (m, 3H), 3.93–3.85 (m, 2H), 3.00 (t, $J=12.0$ Hz, 2H), 2.13–2.04 (m, 2H), 1.50–1.37 (m, 2H), 1.28 (s, 3H), 1.27 (s, 3H). 13C-NMR (150 MHz, $CDCl_3$) δ (ppm): 156.4 (d, $J=250.6$ Hz), 155.2, 151.2, 149.8, 144.2, 135.4 (d, $J=10.4$ Hz), 128.5 (d, $J=3.8$ Hz), 128.4 (d, $J=2.6$ Hz), 121.7, 120.6 (d, $J=23.7$ Hz), 117.6 (d, $J=2.7$ Hz), 109.5 (d, $J=9.2$ Hz), 68.7, 64.3, 48.2 (d, $J=3.9$ Hz), 47.6, 42.8 (x2), 32.5 (x2), 22.3 (x2). HRMS-TOF (*m/z*) calcd for $C_{22}H_{25}FN_6O_3$ $[M+H]^+$: 441.2045, found 441.2144.

4.1.19. 4-(4-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)amino)-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-8-yl)-3-fluorobenzonitrile (23)

Follow the similar procedure of **16**–**20**. Yellowish solid, 54% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.20 (s, 2H), 7.95 (s, 1H), 7.56–7.51 (m, 1H), 7.48 (m, 2H), 4.87 (d, $J=8.2$ Hz, 1H), 4.68 (m, 2H), 4.42–4.32 (m, 2H), 4.32–4.17 (m, 1H), 3.92–3.84 (m, 2H), 3.24–3.10 (m, 2H), 2.49 (q, $J=7.6$ Hz, 2H), 2.21–2.12 (m, 2H), 1.50 (m, 2H), 1.21 (t, $J=7.6$ Hz, 3H). 13C-NMR (150 MHz, $CDCl_3$) δ (ppm): 160.8, 157.2 (x2), 156.4 (d, $J=250.9$ Hz), 151.4, 149.8, 144.1, 135.4 (d, $J=10.5$ Hz), 128.5 (d, $J=3.7$ Hz), 128.4 (d, $J=2.6$ Hz), 124.5, 121.7, 120.6 (d, $J=23.8$ Hz), 117.7 (d, $J=2.6$ Hz), 109.4 (d, $J=9.0$ Hz), 64.3, 48.2 (d, $J=3.9$ Hz), 48.0, 43.1 (x2), 32.5 (x2), 22.7, 15.7. HRMS-TOF (*m/z*) calcd for $C_{24}H_{25}FN_8O$ $[M+H]^+$: 461.2208, found 461.2318.

4.1.20. 4-(4-((1-(5-Chloropyrimidin-2-yl)piperidin-4-yl)amino)-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-8-yl)-3-fluorobenzonitrile (24)

Follow the similar procedure of **16**–**20**. Yellowish solid, 58% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.25 (s, 2H), 7.95 (s, 1H), 7.58–7.51 (m, 1H), 7.48 (m, 2H), 4.86 (d, $J=8.1$ Hz, 1H), 4.74–4.61 (m, 2H), 4.47–4.33 (m, 2H), 4.28 (m, 1H), 3.96–3.79 (m, 2H), 3.27–3.11 (m, 2H), 2.21–2.12 (m, 2H), 1.48 (m, 2H). 13C-NMR (150 MHz, $CDCl_3$) δ (ppm): 159.8, 156.4 (d, $J=250.9$ Hz), 155.9 (x2), 151.3, 149.8, 144.2, 135.4 (d, $J=10.4$ Hz), 128.5 (d, $J=3.6$ Hz), 128.4 (d, $J=2.5$ Hz), 121.7, 120.6 (d, $J=23.7$ Hz), 118.0, 117.6, 109.4 (d, $J=9.2$ Hz), 64.3, 48.2 (d, $J=3.8$ Hz), 47.8, 43.2 (x2), 32.8 (x2). HRMS-TOF (*m/z*) calcd for $C_{22}H_{20}ClFN_8O$ $[M+H]^+$: 467.1505, found 467.1613.

4.1.21. tert-Butyl 4-(2-(4-((8-(4-cyano-2-fluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-4-yl)amino)piperidin-1-yl)acetyl)piperazine-1-carboxylate (25)

Follow the similar procedure of **16**–**20**. Yellowish solid, 63% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.91 (s, 1H), 7.54–7.49 (m, 1H), 7.46 (m, 2H), 4.84 (d, $J=8.1$ Hz, 1H), 4.50–4.30 (m, 2H), 4.01 (m, 1H), 3.94–3.81 (m, 2H), 3.59 (s, 4H), 3.51–3.45 (m, 2H), 3.42 (s, 2H), 3.22 (s, 2H), 2.89 (m, 2H), 2.32 (m, 2H), 2.08 (m, 2H), 1.65–1.53 (m, 2H), 1.49 (s, 9H). 13C-NMR (150 MHz, $CDCl_3$) δ (ppm): 168.4, 156.4 (d, $J=250.6$ Hz), 154.7, 151.4, 149.8, 144.0, 135.5 (d, $J=10.5$ Hz), 128.5 (d, $J=3.6$ Hz), 128.4 (d, $J=2.5$ Hz), 121.7, 120.6 (d, $J=23.7$ Hz), 117.6 (d, $J=2.6$ Hz), 109.4 (d, $J=9.1$ Hz), 80.3, 64.3, 61.4, 52.8, 50.8, 48.2 (d, $J=3.8$ Hz), 47.0, 45.5, 43.6 (x2), 41.7, 32.6 (x2), 28.4 (x3). HRMS-TOF (*m/z*) calcd for $C_{29}H_{37}FN_8O_4$ $[M+H]^+$: 581.2995, found 581.3136.

4.2. hGPR119 agonistic activity

CHO K1 cells stably transfected with human GPR119 were grown at 37 °C, 95%O_2 and 5% CO_2 in 75 cm flasks containing DMEM/F12 (1:1) media with added 10% FBS (Gibco®), Geneticin (Gibco®) and grown until 90% confluent. Cells were then washed (PBS), lifted with cell dissociation solution (Invtrogen®), counted and used for cAMP accumulation assays and/or passaging (1:10). Following the manufacturer's instructions for the LANCE® Ultra cAMP assay (Perkin Elmer), cell transfected with *h*GPR119 were centrifuged (1000 rpm, 5 min), re-suspended in cAMP assay buffer (HBSS, 0.1% BSA, 0.5 mM IBMX and 5 mM HEPES) and seeded at 5000 cells/well in optiplate-384 (Perkin Elmer). Cells were treated with compounds or reference **GSK1292263** over a range of concentrations (10 μM-0.6 μM) and incubated for 1 h. Cell lysis buffers (4X Eu-cAMP tracer solution and 4X ULight™-anti-cAMP solution) were added to each well, and the plates were incubated at r. t. for 1 h before being read on Envision (Perkin Elmer). The assay was performed for three replicates for each concentration.

4.3. oGTT in C57BL/6N mice

For the acute single dose study, vehicle (0.5% carboxymethylcellulose sodium, 10 ml/kg), compound **10**, compound **15** (15 and 30 mg/kg) and vildagliptin (30 mg/kg) were administered to C57BL/6N mice after 16-h starvation, then the oral glucose tolerance test (3 g/kg) was conducted after 4 h of the single dose, the

blood glucose level at 0, 15, 30, 60, 90, and 120 min were recorded for area under curve calculation (AUC_{0-2h}). $AUC_{0-2h}(mmol/L) = (BG_0+BG_{15})\times0.25/2 + (BG_{15}+BG_{30})\times0.25/2 + (BG_{30}+BG_{60})\times0.5/2 + (BG_{60}+BG_{90})\times0.5/2 + (BG_{90}+BG_{120})\times0.5/2$.

Disclosure statement

No potential conflict of interest was reported by the authors.

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