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Discovery and biological evaluation of novel G protein-coupled receptor 119 agonists for type 2 diabetes

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Abstract

G protein-coupled receptor 119 (GPR119) is a member of the GPCR family promising to be the target for type 2 diabetes mellitus (T2DM) treatment. In this work, 30 novel compounds were designed, synthesized, and evaluated by *in vitro* cAMP activation assay, where compounds **II–14** and **II–18** showed the best potency with EC_{50} values of 69 and 99 nM, respectively. In the oral glucose tolerance test, compound **II–18** showed even more efficacious activity in lowering blood excursions than MBX-2982 at a fixed dose of 30 mg/kg. Here, we report that compound **II–18** with its excellent agonistic activity and its orally effective activity in decreasing blood glucose deviations may serve as a potent GPR119 agonist for the treatment of T2DM.

KEYWORDS
agonistic activity, biological evaluation, GPR119, synthesis, type 2 diabetes

1 | INTRODUCTION

G protein-coupled receptor 119 (GPR119) is a member of the class A (rhodopsin-type) GPCR family, which is highly expressed on only a limited number of tissues, such as pancreatic β-cells and enteroendocrine cells of the gastrointestinal tract in humans.[1–3] The activation of GPR119 has the stimulatory effects of glucose-dependent insulin secretion in pancreatic β-cells as well as intestinal secretion of incretin hormones including glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1). Taken together, these effects represented a potential mechanism for modulation of glucose homeostasis and an attractive approach to the treatment of type 2 diabetes mellitus (T2DM).[4–8]

Several phospholipids and lipid amides such as lysophosphatidylcholine (LPC), oleoylethanolamide (OEA), and oleoyldopamine (OLDA) have been identified as endogenous GPR119 agonists.[9,10] However, these endogenous agonists showed low activity and poor selectivity at GPR119 receptor in cellular assays, which led to the development of many synthetic GPR119 agonists over the past several years.[11–13] For example, AR231453 from Arena Pharmaceuticals and PSN632408 from Prosidion Ltd. were two of the earlier potent and orally efficacious GPR119 agonists with significant, published preclinical data. However, owing to the loss of efficacy as well as indicate tachyphylaxis, the positive results obtained in preclinical studies did not appear in the phase II clinical trials, which brought uncertainty to the clinical prospects of GPR119 agonists for the treatment of T2DM.[14,15] With the expectation of discovering new drugs, a few more novel GPR119 agonists with diverse chemical structures have been reported to be under clinical trials (Figure 1).[16,17] Many of the disclosed chemical structures share a common structural motif including an aryl or heteroaryl group linked via a space group to a piperidine moiety capped with a carbamate or heterocycle group. From previous researches we knew that the conformational restriction of the piperidine scaffold played an important role for bioactivity, as well as the methylsulfonylphenyl fragment.[17,18] With the hope of identifying a template with superior druggability, thus improving the overall pharmacokinetic properties over existing series, we reported a series of 2-(4-(methylsulfonyl)phenyl)pyridine derivatives as GPR119 agonists in our former studies. For further exploration, we kept the

Ying Zhou and Youzhi Wang contributed equally to this work.

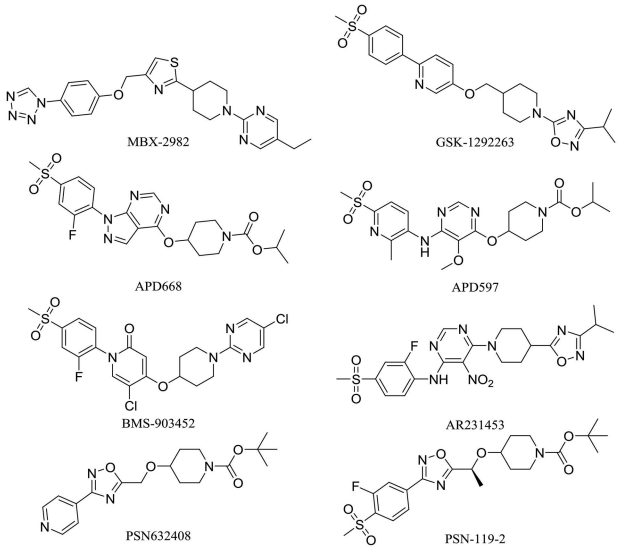


FIGURE 1 Structures of selected GPR119 agonists under clinical development

active pharmacophores of the common structural motif, and changed the linker as well as the "tail group" with various moieties to produce new benzene, pyridine, and pyrazine analogs (Figure 2). Herein, we reported the synthesis, biological evaluation, and structure–activity relationship of novel GPR119 agonists for the treatment of T2DM.

2 | RESULTS AND DISCUSSION

The synthesis of these series of compounds started from reacting 4-bromophenol (**I-A**) with *N*-Boc-protected piperidine alcohol to provide intermediate **I-B** over a Mitsunobu reaction (PPh_3, DEAD, THF). Following with a Suzuki coupling reaction, intermediate **I-B** was coupled with 4-(methylsulfonyl)phenylboronic acid to afford

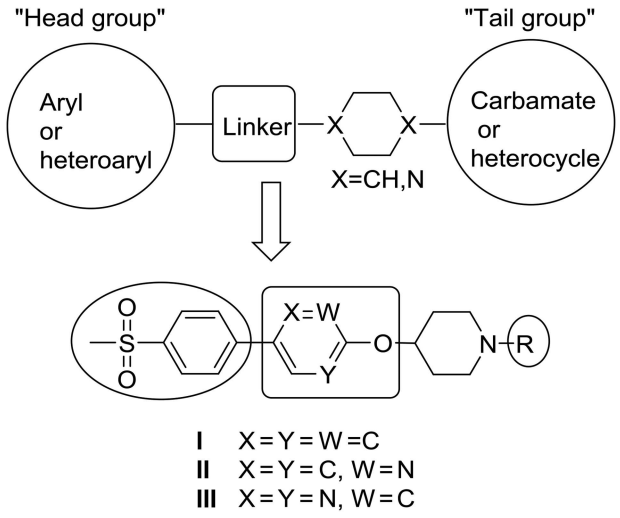
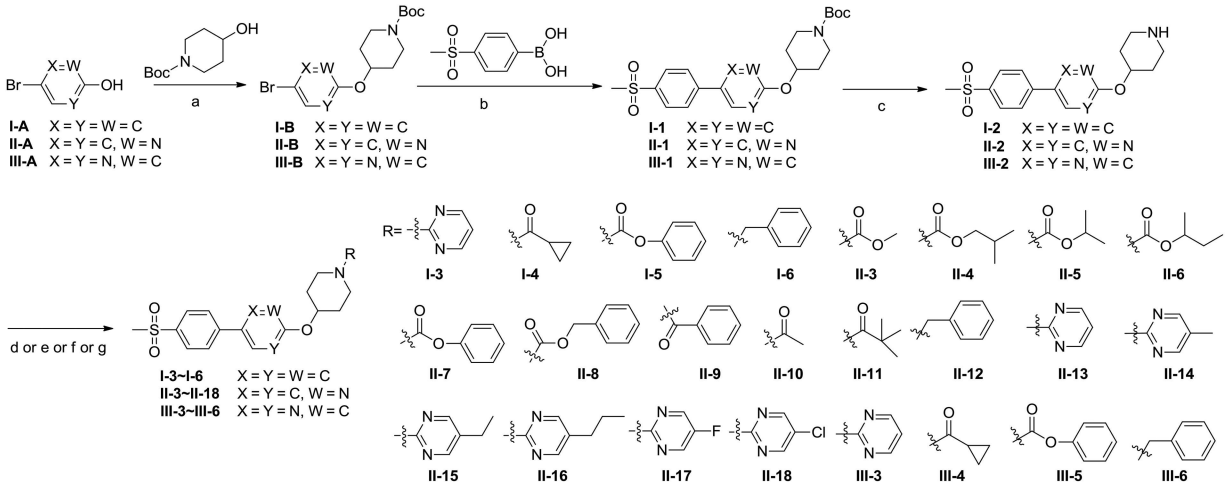


FIGURE 2 Common structural motif shared by most GPR119 agonist and structure of novel GPR119 agonists in this study

compound **I–1**. In the presence of trifluoroacetic acid (TFA), compound **I–2** was achieved through the deprotection of Boc group. Following the similar procedure, compounds **II–2** and **III–2** were prepared with different starting material of 5-bromopyridin-2-alcohol (**II-A**) and 5-bromopyrazin-2-alcohol (**III-A**), respectively. Preparation of the final compounds **I-3–I-6**, **II-3–II-18**, **III-3–III-6** was accomplished by derivatization of the N-position of the piperidine ring with a set of halogenated reagents (Scheme 1).

In order to evaluate the ability of our synthesized compounds in activating GPR119, we carried out cAMP activation assays by measuring stimulate increases in cAMP levels in CHO cells stably expressing human GPR119. Along with the results from cAMP tests, we also calculated ligand efficiency (LE) and ligand efficiency dependent lipophilicity (LELP) of the synthesized compounds as well, which are shown in Table 1. In our former studies, we found that high lipophilicity might cause missing of target or toxic effects, so our goal was aimed at maintaining or improving agonistic potency while reducing lipophilicity, which was presented by lower LELP scores. First, we explored the effects of different linkers among the three series on the agonistic activity. With the same substituent in the N-position of the piperidine ring, compounds **III-1**, **III-3**, and **III-5** showed more activity with lower scores of LELP compared to compounds **II-1**, **II-13**, and **II-7**, respectively, which indicated a better agonistic potency and druggability with pyrazine linker than benzene and pyridine linker. In the pyridine series, we studied the substitutional effect in the N-positon. The carbamate substitutional compounds were effective, while by removing it (compound **II-12**) or replacing it with amide groups (compounds **II-10**, **II-11**), the agonistic activities were lost, suggesting that the piperidine carbamate or heterocycle region seemed to make pharmacologically very important interaction with the receptor, which was also demonstrated by our former study with 2-(4-(methylsulfonyl)phenyl)pyridine derivatives. Gratifyingly, compounds substituted by pyrimidine ring showed better agonistic activity than that by carbamate, and the introduction of a substitute in the 5-position of pyrimidine brought an improvement to the activity as well as LELP score compared with none substitute. From the comparison of pyridine series with our former study results, we found that in both series, the introduction of pyrimidine ring increased activity while piperidine carbamate or heterocycle region reduced or even eliminated activity, which showed that the position-changing of N atom in the pyridine ring had not as much contribution on agonistic activity changes as the substituent of R. Here we found compounds **II-14** and **II-18** performed the best potency with EC_{50} value less than 100 nM and ClogP lower than MBX-2982, leading to satisfying LELP score that indicates impressive drugability.

In order to assess the relevance of the cAMP results *in vivo*, we selected compounds **II-14** and **II-18** for profiling in a mouse (ICR) oral glucose tolerance test (OGTT) at a fixed dose of 30 mg/kg. The results are shown in Figure 3, where significant glucose-lowering effect was observed. Compound **II-18** with the best performance in cAMP assays showed the most efficacious activity in lowering blood glucose, even better than the positive control MBX-2982. Compound **II-14** also had



SCHEME 1 Synthesis of compounds **I-1–I-6**, **II-1–II-18**, **III-1–III-6**. Reagents and conditions: (a) PPh_3, diethyl azodicarboxylate (DEAD), anhydrous THF, N_2, 0–25°C, 12 h; (b) K_2CO_3, $Pd(PPh_3)_4$, 1,4-dioxane/H_2O, N_2, 80°C, 6–8 h; (c) trifluoroacetic acid, DCM, reflux, 1 h; (d) R_2-Cl, Cs_2CO_3, acetone, 40–70°C, 12 h, (for **I–3**, **II-13–II-16**, **III-3**); (e) R_2-Cl, NaOH, THF/H_2O (v/v = 2:1), 0–25°C, 1.5 h, (for **I-4–I-5**, **II-3–II-11**, **III-4–IIII-5**); (f) R_2-Br, triethylamine, DCM, 25°C, 8 h, (for **I-6**, **II-12**, **III-6**); (g) R_2-Cl, NaH, DMF, 100°C, 12 h, (for **II-17–II-18**)

glucose-lowering effect observed, comparing to the blank group, at the same level with MBX-2982.

3 | CONCLUSION

In conclusion, we have developed three novel series of (4-(methylsulfonyl)phenyl)aryl derivatives as small molecular GPR119 agonists for the treatment of T2DM. Thirty novel compounds were successfully synthesized and characterized by ESI-MS, ^{1}H NMR and ^{13}C NMR, and also evaluated for their biological activity for GPR119 agonism. The results from *in vitro* and *in vivo* tests led to the identification of compound **II-18**, 5-chloro-2-(4-((5-(4-(methylsulfonyl)phenyl)pyridin-2-yl)oxy)piperidin-1-yl)pyrimidine, showing excellent agonistic activity in *in vitro* cAMP assay with EC_{50} value of 99 nM and oral effectiveness in lowering blood glucose level and improving glucose tolerance.

TABLE 1 *In vitro* GPR119 agonistic activities and lipophilic properties of synthesized compounds

Compd	EC_{50}[a] (nM)	ClogP[b]	LE[c] (kcal/mol)	LELP[d]	Compd	EC_{50}[a] (nM)	ClogP[b]	LE[c] (kcal/mol)	LELP[d]
I-1	320	3.94	0.30	12.94	**II-12**	NA[e]	3.67	–	–
I-3	280	2.34	0.31	7.55	**II-13**	620	1.77	0.29	6.1
I-4	130	1.64	0.33	4.97	**II-14**	69	2.27	0.32	7.09
II-1	510	2.92	0.28	12.04	**II-15**	100	2.8	0.31	9.03
II-3	NA[e]	2.13	–	–	**II-16**	100	3.32	0.3	11.07
II-4	930	3.59	0.27	13.3	**II-17**	290	1.94	0.3	6.47
II-5	960	2.97	0.28	10.61	**II-18**	99	2.51	0.32	7.84
II-6	350	3.49	0.29	12.03	**III-1**	200	2.76	0.3	9.2
II-7	630	3.12	0.27	11.56	**III-2**	NA[e]	0.83	–	–
II-8	270	4.55	0.27	16.85	**III-3**	430	1.16	0.3	3.87
II-9	2500	2.3	0.25	9.2	**III-4**	NA[e]	0.46	–	–
II-10	NA[e]	0.48	–	–	**III-5**	290	2.51	0.28	8.96
II-11	NA[e]	1.72	–	–	**III-6**	1400	3.06	0.27	11.33
MBX-2982	3.9	3.13	0.36	8.69					

[a]Concentration for 50% cAMP stimulation of GSK 1292263 at 1 μM.
[b]ClogP was calculated by ChemBioDraw.
[c]LE = $1.36pEC_{50}/N_{heavy\ atoms}$.
[d]LELP = ClogP/LE.
[e]NA = not active.

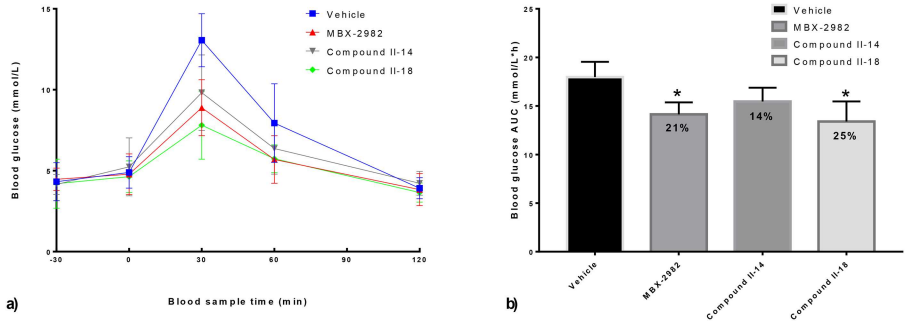


FIGURE 3 Effects of selected compounds and MBX-2982 (30 mg/kg) on glucose excursion in an OGTT in male ICR mice. (a) Blood glucose levels at various times relative to glucose injection; (b) percentage reduction in blood glucose AUC. *$p < 0.05$, significantly different from vehicle-treated mice

Additional study of pharmacokinetic properties of these compounds will be necessary to determine if they can represent a new type of GPR119 agonists for the orally effective treatment of T2DM or other disorders. We are currently producing further modification of these new agonist scaffolds that will be examined soon. The follow-up studies will be reported as results become available.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

All chemicals were reagent grade and used as purchased. All reactions were performed using distilled dry solvent. Column chromatography (CC) was carried out using silica gel 60 100–200 mesh. Thin layer chromatography (TLC) was performed on silica gel 60 F254 plates (250 mm; Qingdao Ocean Chemical Company, China). ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker AVIII 400 MHz/100 MHz spectrometer. The chemical shifts were given in parts per million (ppm) using the 7.26 signal of $CDCl_3$ (^{1}H NMR) and the 77.0 signal of $CDCl_3$ (^{13}C NMR) as internal standards. MS data were obtained by Waters Micromass Platform LCZ mass spectrometer utilizing electrospray ionization (ESI). Elemental analyses were obtained using elementar vario MICRO cube.

The InChI codes of the investigated compounds together with some biological activity data are provided as Supporting Information.

4.1.2 | Synthesis of *tert*-butyl 4-(4-bromophenoxy)-piperidine-1-carboxylate (intermediate I-B)

A solution of diazenedicarboxylic acid (DEAD) (30.3 g, 174 mmol) diluted by tetrahydrofuran (THF) (40 mL) was added dropwise into a solution containing 4-bromophenol (20.0 g, 116 mmol), *tert*-butyl 4-hydroxypiperidine-1-carboxylate (23.3 g, 116 mmol), triphenylphosphine (PPh_3) (45.6 g, 174 mmol) and THF (40 mL) under the protection of nitrogen at 0°C and then the reaction was stirred overnight at room temperature. TLC monitoring showed complete consumption of starting material. After completion of the reaction, the solvent was removed by two thirds under diminished pressure along with a solid precipitation. The mixture was filtered and washed with THF (30 mL, two times). The filtrate was concentrated under diminished pressure and the residue was purified by column chromatography (petroleum ether/EtOAc = 15:1) to give white solid intermediate IB (27.8 g, 67.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 (d, J = 9.2 Hz 2H, −ArH), 6.78 (dd, J = 8.8 Hz, 2H, −ArH), 4.38–4.44 (m, 1H, −CH), 3.64–3.71 (m, 2H, $-CH_2$), 3.30–3.36 (m, 2H, $-CH_2$), 1.86–1.92 (m, 2H, $-CH_2$), 1.68–1.76 (m, 2H, $-CH_2$), 1.47 (s, 9H, $OC(CH_3)_3$).

Intermediates **II-B**, **III-B** were prepared in a manner similar to that described for intermediate **I-B**.

tert-Butyl 4-((5-bromopyridin-2-yl)oxy)piperidine-1-carboxylate (intermediate II-B)

Yield 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (dd, J_1 = 2.8 Hz, J_2 = 0.8 Hz, 1H, −ArH), 7.63 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H, −ArH), 6.63 (dd, J_1 = 8.4 Hz, J_2 =0.4 Hz, 1H, −ArH), 5.12–5.18 (m, 1H, −CH), 3.73–3.76 (m, 2H, $-CH_2$), 3.24–3.31 (m, 2H, $-CH_2$), 1.93–1.98 (m, 2H, $-CH_2$), 1.65–1.74 (m, 2H, $-CH_2$), 1.47 (s, 9H, $OC(CH_3)_3$).

tert-Butyl 4-((5-bromopyrazin-2-yl)oxy)piperidine-1-carboxylate (intermediate III-B)

Yield 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (d, J = 1.6 Hz, 1H, −ArH), 7.99 (d, J = 1.2 Hz, 1H, −ArH), 5.10–5.17 (m, 1H, −CH), 3.74–3.78 (m, 2H, $-CH_2$), 3.25–3.32 (m, 2H, $-CH_2$), 1.94–1.99 (m, 2H, $-CH_2$), 1.68–1.77 (m, 2H, $-CH_2$), 1.47 (s, 9H, $-C(CH_3)_3$).

4.1.3 | Synthesis of *tert*-butyl 4-((4′-(methylsulfonyl)-[1,1′-biphenyl]-4-yl)oxy)piperidine-1-carboxylate (compound I–1)

A mixture of (4-(methylsulfonyl)phenyl)boronic acid (6.7 g, 33.7 mmol), compound **I-B** (10 g, 28.1 mmol), $Pd(PPh_3)_4$ (3.3 g, 2.81 mmol), K_2CO_3 (9.7 g, 70.3 mmol), 1,4-dioxane (80 mL) and water (35 mL) was reacted by stirring at 80°C for 8 h. TLC monitoring showed complete consumption of starting material. After completion of the reaction, 1,4-dioxane was removed under diminished pressure, the residue was

extracted twice with a mixture of ethyl acetate (400 mL) and water (150 mL). The organic phases were collected and washed, respectively, with saturated sodium carbonate solution (150 mL, two times) and saturated sodium chloride solution (100 mL, two times). The organic phase was dried over anhydrous sodium sulfate, filtered, evaporated, and purified by column chromatography (petroleum ether/EtOAc = 20:1) to give white powder compound **I-1** (6.1 g, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, J = 8.4 Hz, 2H, −ArH), 7.72 (d, J = 8.4 Hz, 2H, −ArH), 7.55 (d, J = 8.8 Hz, 2H, −ArH), 7.01 (d, J = 8.8 Hz, 2H, −ArH), 4.52–4.58 (m, 1H, −CH), 3.69 –3.75 (m, 2H, $-CH_2$), 3.34–3.41 (m, 2H, $-CH_2$), 3.09 (s, 3H, $-SO_2CH_3$), 1.93–1.98 (m, 2H, $-CH_2$), 1.75–1.83 (m, 2H, $-CH_2$), 1.48 (s, 9H, $-OC(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.9, 154.8, 146.2, 138.5, 131.7, 128.6, 127.9, 127.4, 116.5, 79.7, 72.3, 44.7, 30.5, 28.5; MS (ESI): m/z calcd. for $C_{23}H_{30}NO_5S$, $[M+H]^+$ 432.7, found 433.7 $[M+H]^+$. Anal. calcd. C, 64.01; H, 6.77; N, 3.25; S, 7.43, found: C, 64.15; H, 6.75; N, 3.26; S, 7.42.

Compounds **II-1**, **III-1** were prepared in a manner similar to that described for compound **I-1**.

tert-Butyl 4-((5-(4-(methylsulfonyl)phenyl)pyridin-2-yl)oxy)-piperidine-1-carboxylate (compound II-1)

Yield 50%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, J = 2.4 Hz, 1H, −ArH), 8.01 (d, J = 8 Hz, 2H, −ArH), 7.82 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, −ArH), 7.71 (d, J = 8.4 Hz, 2H, −ArH), 6.83 (d, J = 8.4 Hz, 1H, −ArH), 5.27–5.31 (m, 1H, −CH), 3.77–3.82 (m, 2H, $-CH_2$), 3.28–3.35 (m, 2H, $-CH_2$), 3.09 (s, 3H, $-SO_2CH_3$), 1.98–2.04 (m, 2H, $-CH_2$), 1.72–1.80 (m, 2H, $-CH_2$), 1.48 (s, 9H, $OC(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4, 154.9, 145.5, 143.5, 139.2, 137.6, 128.2, 128.0, 127.3, 112.0, 79.6, 70.8, 44.6, 30.8, 28.5; MS (ESI): m/z calcd. for $C_{22}H_{29}N_2O_5S$, $[M+H]^+$ 433.1, found 433.5 $[M+H]^+$. Anal. calcd. C, 61.09; H, 6.52; N, 6.48; S, 7.41, found: C, 60.96; H, 6.53; N, 6.47; S, 7.38.

tert-Butyl 4-((5-(4-(methylsulfonyl)phenyl)pyrazin-2-yl)oxy)-piperidine-1-carboxylate (compound III-1)

Yield 47%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.56 (d, J = 1.2 Hz, 1H, −ArH), 8.30 (d, J = 1.6 Hz, 1H, −ArH), 8.14–8.15 (m, 1H, −ArH), 8.12–8.12 (m, 1H, −ArH), 8.05–8.06 (m, 1H, −ArH), 8.02–8.03 (m, 1H, −ArH), 5.24–5.30 (m, 1H, −CH), 3.81 (br, 2H, $-CH_2$), 3.29–3.36 (m, 2H, $-CH_2$), 3.1 (s, 3H, $-SO_2CH_3$), 2.03 (br, 2H, $-CH_2$), 1.75–1.83 (m, 2H, $-CH_2$), 1.49 (s, 9H, $-C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.2, 154.8, 142.9, 141.7, 140.2, 138.1, 135.8, 128.0, 126.8, 79.7, 71.8, 44.6, 30.5, 28.5; MS (ESI): m/z calcd. for $C_{21}H_{28}N_3O_5S$, $[M+H]^+$ 434.1, found 434.7 $[M+H]^+$. Anal. calcd. C, 58.18; H, 6.28; N, 9.69; S, 7.40, found: C, 58.09; H, 6.30; N, 9.72; S, 7.43.

4.1.4 | Synthesis of 4-((4′-(methylsulfonyl)-[1,1′-biphenyl]-4-yl)oxy)piperidine (compound I-2)

Trifluoroacetic acid (5 mL) was added to a solution of compound **I-1** (4 g, 9.28 mmol) and dichloromethane (20 mL). The reaction mixture was stirred and refluxed for 30 min. TLC monitoring showed complete consumption of starting material. After completion of the reaction, cooled to room temperature and removed the solvent under diminished pressure. The residue was dissolved in water (30 mL), basified with aqua ammonia (3 mL) to pH 9–10, filtered, and washed with water (30 mL) twice to afford white solid compound **I-2** (2.85 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96–7.98 (m, 2H, −ArH), 7.89–7.92 (m, 2H, −ArH), 7.71–7.74 (m, 2H, −ArH), 7.13–7.17 (m, 2H, −ArH), 4.73–4.78 (m, 1H, −CH), 3.54 (br, 2H, $-CH_2$), 3.25 (s, 3H, $-SO_2CH_3$), 3.12 (br, 2H, $-CH_2$), 2.09–2.16 (m, 2H, $-CH_2$), 1.80–1.89 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.6, 145.1, 139.4, 131.6, 129.0, 128.1, 127.4, 116.8, 69.5, 44.1, 41.1, 27.7; MS (ESI): m/z calcd. for $C_{18}H_{22}NO_3S$, $[M+H]^+$ 332.1, found 332.3 $[M+H]^+$. Anal. calcd. C, 65.23; H, 6.39; N, 4.23; S, 9.67, found: C, 65.17; H, 6.38; N, 4.25; S, 9.70.

Compounds **II-2**, **III-2** were prepared in a manner similar to that described for compound **I-2**.

5-(4-(Methylsulfonyl)phenyl)-2-(piperidin-4-yloxy)pyridine (compound II-2)

Yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.40 (dd, J_1 = 2.8 Hz, J_2 = 0.8 Hz, 1H, −ArH), 8.02 (d, J = 8.4 Hz, 2H, −ArH), 7.81 (dd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, 1H, −ArH), 7.71 (d, J = 8.4 Hz, 2H, −ArH), 6.83 (dd, J_1 = 8.8 Hz, J_2 = 0.8 Hz, 1H, −ArH), 5.18–5.24 (m, 1H, −CH), 3.14–3.20 (m, 2H, $-CH_2$), 3.10 (s, 3H, $-SO_2CH_3$), 2.79–2.86 (m, 2H, $-CH_2$), 2.08–2.12 (m, 2H, $-CH_2$), 1.80 (br, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.8, 145.8, 142.4, 140.0, 138.8, 128.4, 128.2, 127.6, 112.0, 68.0, 44.0, 41.3, 27.9; MS (ESI): m/z calcd. for $C_{17}H_{21}N_2O_3S$, $[M+H]^+$ 333.1, found 333.6 $[M+H]^+$. Anal. calcd. C, 61.42; H, 6.06; N, 8.43; S, 9.65, found: C, 61.56; H, 6.08; N, 8.41; S, 9.62.

2-(4-(Methylsulfonyl)phenyl)-5-(piperidin-4-yloxy)pyrazine (compound III-2)

Yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.94 (d, J = 1.6 Hz, 1H, −ArH), 8.86 (s, 1H, −NH), 8.47 (d, J = 1.6 Hz, 1H, −ArH), 8.31–8.32 (m, 1H, −ArH), 8.29–8.30 (m, 1H, −ArH), 8.05–8.06 (m, 1H, −ArH), 8.03–8.04 (m, 1H, −ArH), 5.31–5.36 (m, 1H, −CH), 3.32–3.38 (m, 2H, $-CH_2$), 3.28 (s, 3H, $-SO_2CH_3$), 3.15–3.21 (m, 2H, $-CH_2$), 2.16–2.23 (m, 2H, $-CH_2$), 1.92–2.00 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.9, 143.1, 141.1, 141.1, 139.1, 135.8, 128.1, 127.0, 68.9, 44.0, 41.1, 27.7; MS (ESI): m/z calcd. for $C_{16}H_{20}N_3O_3S$, $[M+H]^+$ 334.1, found 334.4 $[M+H]^+$. Anal. calcd. C, 57.64; H, 5.74; N, 12.60; S, 9.62, found: C, 57.78; H, 5.76; N, 12.59; S, 9.63.

4.1.5 | Synthesis of 2-(4-((4′-(methylsulfonyl)-[1,1′-biphenyl]-4-yl)oxy)piperidin-1-yl)pyrimidine (compound I-3)

A mixture of compound **I-2** (0.1 g, 0.3 mmol), 2-chloropyrimidine (41 mg, 0.36 mmol), caesium carbonate (0.2 g, 0.6 mmol), and acetone (15 mL) was stirred at 50°C overnight. TLC monitoring showed complete consumption of starting material. After completion of the reaction, cooled to room temperature and removed acetone under diminished pressure. The residue was purified by column chromatography (petroleum ether/EtOAc = 10:1) to give white solid compound **I-**

3 (51 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (d, J = 4.8 Hz, 2H, −ArH), 7.97–8.00 (m, 2H, −ArH), 7.72–7.54 (m, 2H, −ArH), 7.55–7.59 (m, 2H, −ArH), 7.04–7.07 (m, 2H, −ArH), 6.49 (t, J = 4.8 Hz, 1H, −ArH), 4.62–4.68 (m, 1H, −CH), 4.16–4.22 (m, 2H, $-CH_2$), 3.71–3.78 (m, 2H, $-CH_2$), 3.09 (s, 3H, $-SO_2CH_3$), 2.03–2.10 (m, 2H, $-CH_2$), 1.83–1.91 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.6, 158.1, 157.8, 146.2, 138.5, 131.7, 128.7, 127.9, 127.4, 116.6, 109.7, 72.9, 44.7, 40.8, 30.5; MS (ESI): m/z calcd. for $C_{22}H_{24}N_3O_3S$, $[M+H]^+$ 410.1, found 410.4 $[M+H]^+$. Anal. calcd. C, 64.53; H, 5.66; N, 10.26; S, 7.83, found: C, 64.72; H, 5.64; N, 10.27; S, 7.84.

Compounds **II-13–16**, **III-3** were prepared in a manner similar to that described for compound **I-3**.

2-(4-((5-(4-(Methylsulfonyl)phenyl)pyridin-2-yl)oxy)piperidin-1-yl)pyrimidine (compound II-13)

Yield 50%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.41 (d, J = 2.4 Hz, 1H, −ArH), 8.32 (d, J = 4.8 Hz, 2H, −ArH), 8.02 (d, J = 8.4 Hz, 2H, −ArH), 7.83 (dd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, 1H, −ArH), 7.72 (dd, J_1 = 6.4 Hz, J_2 = 2 Hz, 2H, −ArH), 6.84–6.87 (d, J = 8.8 Hz, 1H, −ArH), 6.47–6.49 (t, J = 4.8 Hz, 1H, −ArH), 5.38–5.42 (m, 1H, −CH), 4.27–4.33 (m, 2H, $-CH_2$), 3.63–3.69 (m, 2H, $-CH_2$), 3.09 (s, 3H, $-SO_2CH_3$), 2.09–2.15 (m, 2H, $-CH_2$), 1.80–1.88 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5, 161.7, 157.8, 145.5, 143.5, 139.2, 137.6, 128.2, 128.0, 127.3, 112.0, 109.6, 71.3, 44.6, 41.2, 30.7; MS (ESI): m/z calcd. for $C_{21}H_{22}N_4O_3S$, $[M+H]^+$ 410.1, found 411.8 $[M+H]^+$. Anal. calcd. C, 61.44; H, 5.40; N, 13.65; S, 7.81, found: C, 61.41; H, 5.42; N, 13.59; S, 7.83.

5-Methyl-2-(4-((5-(4-(methylsulfonyl)phenyl)pyridin-2-yl)oxy)-piperidin-1-yl)pyrimidine (compound II-14)

Yield (42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.44 (d, J = 2.8 Hz, 1H, −ArH), 8.15 (t, J = 7.6 Hz, 4H, −ArH), 8.02 (d, J = 8.4 Hz, 2H, −ArH), 7.74 (d, J = 8.8 Hz, 1H, −ArH), 7.34(dd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, 1H, −ArH), 4.65–4.69 (m, 1H, −CH), 4.16–4.22 (m, 2H, $-CH_2$), 3.64–3.73 (m, 2H, $-CH_2$), 3.09 (s, 3H, $-SO_2CH_3$), 2.14 (s, 3H, $-ArCH_3$), 2.05–2.11 (m, 2H, $-CH_2$), 1.83–1.90 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.6, 157.8, 153.7, 147.7, 144.2, 139.7, 139.5, 127.8, 127.1, 123.2, 121.6, 118.3, 73.9, 44.6, 41.0, 30.3, 14.6; MS (ESI): m/z calcd. for $C_{22}H_{25}N_4O_3S$, $[M+H]^+$ 425.1, found 425.5 $[M+H]^+$. Anal. calcd. C, 62.24; H, 5.70; N, 13.20; S, 7.55, found: C, 62.07; H, 5.66; N, 13.21; S, 7.54.

5-Ethyl-2-(4-((5-(4-(methylsulfonyl)phenyl)pyridin-2-yl)oxy)-piperidin-1-yl)pyrimidine (compound II-15)

Yield 45%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.41 (d, J = 2.4 Hz, 1H, −ArH), 8.19 (s, 2H, −ArH), 8.01 (d, J = 8.4 Hz, 2H, −ArH), 7.82 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, −ArH), 7.72 (d, J = 8.4 Hz, 2H, −ArH), 6.84 (d, J = 8.8 Hz, 1H, −ArH), 5.36–5.40 (m, 1H, −CH), 4.26–4.32 (m, 2H, $-CH_2$), 3.58–3.64 (m, 2H, $-CH_2$), 3.09 (s, 3H, $-SO_2CH_3$), 2.48 (q, J = 7.6 Hz, 2H, $-C\underline{H}_2CH_3$), 2.09–2.11 (m, 2H, $-CH_2$), 1.81–1.88 (m, 2H, $-CH_2$), 1.20 (t, J = 7.6 Hz, 3H, $-CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5, 160.8, 157.2, 145.5, 143.5, 139.2, 137.6, 128.2, 127.9, 127.3, 127.3, 124.3, 112.0, 71.5, 44.6, 41.5, 30.7, 22.7, 15.6; MS (ESI): m/z calcd. for $C_{23}H_{27}N_4O_3S$, $[M+H]^+$ 439.1, found 439.5 $[M+H]^+$. Anal. calcd. C, 62.99; H, 5.98; N, 12.78; S, 7.31, found: C, 63.14; H, 5.96; N, 12.82; S, 7.33.

2-(4-((5-(4-(Methylsulfonyl)phenyl)pyridin-2-yl)oxy)piperidin-1-yl)-5-propylpyrimidine (compound II-16)

Yield 32%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.41 (d, J = 2.4 Hz, 1H, −ArH), 8.17 (s, 2H, −ArH), 8.01 (d, J = 8.4 Hz, 2H, −ArH), 7.82 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, −ArH), 7.72 (d, J = 8.4 Hz, 2H, −ArH), 6.84 (d, J = 8.8 Hz, 1H, −ArH), 5.36–5.40 (m, 1H, −CH), 4.25–4.31 (m, 2H, $-CH_2$), 3.58–3.64 (m, 2H, $-CH_2$), 3.10 (s, 3H, $-SO_2CH_3$), 2.41 (t, J = 7.6 Hz, 2H, $-C\underline{H}_2CH_2CH_3$), 2.10–2.16 (m, 2H, $-CH_2$), 1.82–1.87 (m, 2H, $-CH_2$), 1.57 (q, J = 7.6 Hz, 2H, $-CH_2C\underline{H}_2CH_3$), 0.94 (t, J = 7.2 Hz, 3H, $-CH_2CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.5, 157.6, 153.7, 147.7, 144.2, 139.7, 139.4, 127.8, 127.1, 123.2, 123.1, 121.6, 73.8, 44.6, 41.0, 31.5, 30.3, 24.4, 13.5; MS (ESI): m/z calcd. for $C_{24}H_{29}N_4O_3S$, $[M+H]^+$ 453.1, found 453.9 $[M+H]^+$. Anal. calcd. C, 63.69; H, 6.24; N, 12.38; S, 7.09, found: C, 63.74; H, 6.26; N, 12.42; S, 7.11.

2-(4-((5-(4-(Methylsulfonyl)phenyl)pyrazin-2-yl)oxy)piperidin-1-yl)pyrimidine (compound III-3)

Yield 45%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (d, J = 1.2 Hz, 1H, −ArH), 8.34 (s, 1H, −ArH), 8.32 (s, 1H, −ArH), 8.31 (d, J = 1.6 Hz, 1H, −ArH), 8.14–8.15 (m, 1H, −ArH), 8.12–8.13 (m, 1H, −ArH), 8.05–8.06 (m, 1H, −ArH), 8.03–8.04 (m, 1H, −ArH), 6.50 (t, J = 4.4 Hz, 1H, −ArH), 5.35–5.41 (m, 1H, −CH), 4.29–4.35 (m, 2H, $-CH_2$), 3.63–3.70 (m, 2H, $-CH_2$), 3.10 (s, 3H, $-SO_2CH_3$), 2.10–2.17 (m, 2H, $-CH_2$), 1.82–1.91 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.6, 159.3, 157.8, 142.8, 141.8, 140.2, 138.2, 135.9, 128.0, 126.8, 109.8, 72.4, 58.5, 44.6, 41.1, 30.5, 18.4; MS (ESI): m/z calcd. for $C_{20}H_{22}N_5O_3S$, $[M+H]^+$ 412.1, found 412.3 $[M+H]^+$. Anal. calcd. C, 58.38; H, 5.14; N, 17.02; S, 7.79, found: C, 58.25; H, 5.16; N, 17.06; S, 7.82.

4.1.6 | Synthesis of cyclopropyl(4-((4′(methylsulfonyl)-[1,1′-biphenyl]-4-yl)oxy)piperidin-1-yl)methanone (compound I-4)

Cyclopropanecarbonyl chloride (30.0 mg, 0.29 mmol) was added dropwise slowly into a solution of compound **I-2** (80 mg, 0.24 mmol), NaOH (19 mg, 0.48 mmol), THF (8 mL), and water (4 mL) at 0°C. The mixture was then reacted at room temperature for 1.5 h. TLC monitoring showed complete consumption of starting material. THF was removed under diminished pressure, and then the residue was extracted twice with a mixture of ethyl acetate (50 mL) and water (25 mL). The organic phases were collected, washed twice with saturated sodium chloride solution (100 mL), dried over anhydrous sodium sulfate, evaporated under diminished pressure to give white solid compound **I–4** (41 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99–8.00 (m, 1H, −ArH), 7.97–7.98 (m, 1H, −ArH), 7.74–7.75 (m, 1H, −ArH), 7.72–7.73 (m, 1H, −ArH), 7.57–7.58 (m, 1H, −ArH), 7.55–7.56 (m, 1H, −ArH), 7.04–7.05 (m, 1H, −ArH), 7.02–7.03 (m, 1H, −ArH), 4.62–4.67 (m, 1H, −CH), 3.82–3.93 (m, 2H, $-CH_2$), 3.65–3.71 (m, 2H, $-CH_2$), 3.09

(s, 3H, $-SO_2CH_3$), 1.85–2.02 (m, 4H, $-CH_2$), 1.76–1.82 (m, 1H, −CH), 0.98–1.02 (m, 2H, $-CH_2$), 0.76–0.80 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.9, 157.8, 146.1, 138.6, 131.9, 128.7, 127.9, 127.4, 116.5, 72.0, 44.7, 11.0, 7.3; MS (ESI): *m/z* calcd. for $C_{22}H_{26}NO_4S$, $[M+H]^+$ 400.1, found 400.4 $[M+H]^+$. Anal. calcd. C, 66.14; H, 6.31; N, 3.51; S, 8.03, found: C, 66.01; H, 6.33; N, 3.53; S, 8.05.

Compounds **I-5**, **II-3–11**, **III-4–5** were prepared in a manner similar to that described for compound **I-4**.

Phenyl 4-((4′-(methylsulfonyl)-[1,1′-biphenyl]-4-yl)oxy)-piperidine-1-carboxylate (compound I-5)

Yield 44%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99–8.00 (m, 1H, −ArH), 7.97–7.98 (m, 1H, −ArH), 7.74–7.75 (m, 1H, −ArH), 7.72–7.73 (m, 1H, −ArH), 7.58–7.59 (m, 1H, −ArH), 7.56–7.57 (m, 1H, −ArH), 7.35–7.40 (m, 2H, −ArH), 7.19–7.23 (m, 1H, −ArH), 7.11–7.14 (m, 2H, −ArH), 7.03–7.07 (m, 2H, −ArH), 4.63–4.68 (m, 1H, −CH), 3.63–3.90 (m, 4H, $-CH_2$), 3.09 (s, 3H, $-SO_2CH_3$), 2.05 (br, 2H, $-CH_2$), 1.95 (br, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.8, 153.8, 151.4, 146.1, 146.1, 138.6, 132.0, 129.3, 129.3, 128.7, 127.9, 127.4, 125.3, 121.7, 116.6, 71.7, 44.7; MS (ESI): *m/z* calcd. for $C_{25}H_{26}NO_5S$, $[M+H]^+$ 452.1, found 452.9 $[M+H]^+$. Anal. calcd. C, 66.50; H, 5.58; N, 3.10; S, 7.10, found: C, 66.72; H, 5.55; N, 3.11; S, 7.11.

Methyl 4-((5-(4-(methylsulfonyl)phenyl)pyridin-2-yl)oxy)-piperidine-1-carboxylate (compound II-3)

Yield 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, J = 2.4 Hz, 1H, −ArH), 8.01 (d, J = 8 Hz, 2H, −ArH), 7.82 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, −ArH), 7.71 (d, J = 8.4 Hz, 2H, −ArH), 6.84 (d, J = 8.4 Hz, 1H, −ArH), 5.28–5.33 (m, 1H, −CH), 3.82 (br, 2H, $-CH_2$), 3.72 (s, 3H, $-COOCH_3$), 3.36–3.43 (m, 2H, $-CH_2$), 3.09 (s, 3H, $-SO_2CH_3$), 2.02–2.04 (m, 2H, $-CH_2$), 1.78–1.80 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3, 156.0, 145.4, 143.4, 139.2, 137.6, 128.2, 128.1, 127.3, 112.0, 70.4, 52.6, 44.6, 41.2, 30.7; MS (ESI): *m/z* calcd. for $C_{19}H_{23}N_2O_5S$, $[M+H]^+$ 391.1, found 391.6 $[M+H]^+$. Anal. calcd. C, 58.45; H, 5.68; N, 7.17; S, 8.21, found: C, 58.57; H, 5.70; N, 7.14; S, 8.23.

Isobutyl 4-((5-(4-(methylsulfonyl)phenyl)pyridin-2-yl)oxy)-piperidine-1-carboxylate (compound II-4)

Yield 54%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, J = 2.4 Hz, 1H, −ArH), 8.01 (d, J = 8 Hz, 2H, −ArH), 7.82 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, −ArH), 7.71 (d, J = 8.4 Hz, 2H, −ArH), 6.84 (d, J = 8.4 Hz, 1H, −ArH), 5.28–5.33 (m, 1H, −CH), 3.88 (d, J = 6.0 Hz, 2H, $-C\underline{H}_2CH(CH_3)_2$), 3.82–3.85 (m, 2H, $-CH_2$), 3.36–3.43 (m, 2H, $-CH_2$), 3.09 (s, 3H, $-SO_2CH_3$), 2.01–2.04 (m, 2H, $-CH_2$), 1.92–1.99 (m, 1H, $-CH_2C\underline{H}(CH_3)_2$), 1.75–1.83 (m, 2H, $-CH_2$), 0.95 (d, J = 6.4 Hz, 6H, $-CH_2CH(C\underline{H}_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3, 155.7, 145.5, 143.5, 139.2, 137.6, 128.2, 128.1, 127.3, 112.0, 71.6, 70.5, 44.6, 41.2, 30.7, 29.7, 28.1, 19.1; MS (ESI): *m/z* calcd. for $C_{22}H_{29}N_2O_5S$, $[M+H]^+$ 433.1, found 433.5 $[M+H]^+$. Anal. calcd. C, 61.09; H, 6.52; N, 6.48; S, 7.41, found: C, 60.89; H, 6.55; N, 6.47; S, 7.39.

Isopropyl 4-((5-(4-(methylsulfonyl)phenyl)pyridin-2-yl)oxy)-piperidine-1-carboxylate (compound II-5)

Yield 54%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (dd, J_1 = 0.8 Hz, J_2 = 2.4 Hz, 1H, −ArH), 8.01 (d, J = 8.4 Hz, 2H, −ArH), 7.82 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, −ArH), 7.71 (d, J = 8.4 Hz, 2H, −ArH), 6.84 (d, J_1 = 0.8 Hz, J_2 = 8.8 Hz, 1H, −ArH), 5.27–5.33 (m, 1H, −CH), 4.91–4.97 (m, 1H, $-C\underline{H}(CH_3)_2$), 3.81 (br, 2H, $-CH_2$), 3.33–3.39 (m, 2H, $-CH_2$), 3.09 (s, 3H, $-SO_2CH_3$), 2.01–2.04 (m, 2H, $-CH_2$), 1.76–1.79 (m, 2H, $-CH_2$), 1.26 (d, J = 6.4 Hz, 6H, $-CH(C\underline{H}_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3, 155.3, 145.5, 143.5, 139.2, 137.6, 128.2, 128.0, 127.3, 112.0, 70.6, 68.6, 44.6, 41.1, 30.7, 22.3; MS (ESI): *m/z* calcd. for $C_{21}H_{27}N_2O_5S$, $[M+H]^+$ 419.1, found 419.7 $[M+H]^+$. Anal. calcd. C, 60.27; H, 6.26; N, 6.69; S, 7.66, found: C, 60.42; H, 6.25; N, 6.70; S, 7.67.

sec-Butyl 4-((5-(4-(methylsulfonyl)phenyl)pyridin-2-yl)oxy)-piperidine-1-carboxylate (compound II-6)

Yield 67%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (dd, J_1 = 2.4 Hz, J_2 = 0.8 Hz, 1H, −ArH), 8.01 (d, J = 8 Hz, 2H, −ArH), 7.82 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, −ArH), 7.71 (d, J = 8.4 Hz, 2H, −ArH), 6.84 (d, J_1 = 8.8 Hz, J_2 = 0.8 Hz, 1H, −ArH), 5.28–5.33 (m, 1H, −CH), 4.73–4.81 (m, 1H, $-C\underline{H}(CH_3)CH_2CH_3$), 3.81–3.86 (m, 2H, $-CH_2$), 3.33–3.40 (m, 2H, $-CH_2$), 3.09 (s, 3H, $-SO_2CH_3$), 2.02 (br, 2H, $-CH_2$), 1.77–1.81 (m, 2H, $-CH_2$), 1.50–1.68 (m, 2H, $-CH(CH_3)C\underline{H}_2CH_3$), 1.23 (d, J = 6.0 Hz, 3H, $-CH(C\underline{H}_3)CH_2CH_3$), 0.92 (t, J = 7.6 Hz, 3H, $-CH(CH_3)CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3, 155.4, 145.4, 143.5, 139.2, 137.6, 128.2, 128.0, 127.3, 112.0, 73.2, 70.6, 44.6, 41.1, 30.7, 29.1, 19.9, 9.7; MS (ESI): *m/z* calcd. for $C_{22}H_{29}N_2O_5S$, $[M+H]^+$ 433.1, found 433.8 $[M+H]^+$. Anal. calcd. C, 61.09; H, 6.52; N, 6.48; S, 7.41, found: C, 61.02; H, 6.54; N, 6.49; S, 7.43.

Phenyl 4-((5-(4-(methylsulfonyl)phenyl)pyridin-2-yl)oxy)-piperidine-1-carboxylate (compound II-7)

Yield 49%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.40 (dd, J_1 = 2.8 Hz, J_2 = 0.8 Hz, 1H, −ArH), 8.02 (d, J = 8 Hz, 2H, −ArH), 7.84 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, −ArH), 7.72 (d, J = 8.4 Hz, 2H, −ArH), 7.34–7.40 (m, 2H, −ArH), 7.19–7.22 (m, 1H, −ArH), 7.11–7.14 (m, 2H, −ArH), 6.87 (dd, J_1 = 8.8 Hz, J_2 = 0.8 Hz, 1H, −ArH), 5.35–5.41 (m, 1H, −CH), 3.95 (d, J = 34 Hz, 2H, $-CH_2$), 3.58 (d, J = 39.2 Hz, 2H, $-CH_2$), 3.09 (s, 3H, $-SO_2CH_3$), 2.11 (br, 2H, $-CH_2$), 1.90–1.93 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.2, 153.8, 151.4, 145.5, 143.4, 139.3, 137.7, 129.3, 128.2, 127.4, 125.3, 121.7, 112.0, 100.0, 70.1, 44.6; MS (ESI): *m/z* calcd. for $C_{24}H_{25}N_2O_5S$, $[M+H]^+$ 453.1, found 453.1 $[M+H]^+$. Anal. calcd. C, 63.70; H, 5.35; N, 6.19; S, 7.09, found: C, 63.79; H, 5.37; N, 6.17; S, 7.10.

Benzyl 4-((5-(4-(methylsulfonyl)phenyl)pyridin-2-yl)oxy)-piperidine-1-carboxylate (compound II-8)

Yield 43%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.41 (d, J = 2.8 Hz, 1H, −ArH), 8.13 (d, J = 8.4 Hz, 2H, −ArH), 8.00 (dd, J = 8.4 Hz, 2H, −ArH), 7.73 (d, J = 8.8 Hz, 2H, −ArH), 7.30–7.38 (m, 6H, −ArH), 5.15 (s, 2H, $-OCH_2Ph$), 4.59–4.64 (m, 1H, −CH), 3.74–3.81 (m, 2H, $-CH_2$), 3.48–3.54 (m, 2H, $-CH_2$), 3.09 (s, 3H, $-SO_2CH_3$), 1.99 (br, 2H, $-CH_2$), 1.85 (br, 2H, $-CH_2$);

^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.3, 153.4, 147.9, 144.1, 139.8, 139.4, 136.7, 128.5, 128.1, 127.9, 127.9, 127.8, 127.1, 127.1, 123.2, 123.0, 121.6, 72.7, 67.3, 44.6, 40.6, 30.3, 30.2; MS (ESI): *m/z* calcd. for $C_{25}H_{27}N_2O_5S$, $[M+H]^+$ 467.1, found 467.2 $[M+H]^+$. Anal. calcd. C, 64.36; H, 5.62; N, 6.00; S, 6.87, found: C, 64.44; H, 5.64; N, 5.97; S, 6.85.

(4-((5-(4-(Methylsulfonyl)phenyl)pyridin-2-yl)oxy)piperidin-1-yl)-(phenyl)methanone (compound II-9)

Yield 52%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, J = 2.8 Hz, 1H, −ArH), 8.02–8.03 (m, 1H, −ArH), 8.00–8.01 (m, 1H, −ArH), 7.84 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, −ArH), 7.72–7.73 (m, 1H, −ArH), 7.70–7.71 (m, 1H, −ArH), 7.40–7.46 (m, 5H, −ArH), 6.85 (d, J = 8.6 Hz, 1H, −ArH), 5.37–5.43 (m, 1H, −CH), 3.40–4.12 (m, 4H, $-CH_2$), 3.10 (s, 3H, $-SO_2CH_3$), 1.80–2.15 (m, 4H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.5, 163.2, 145.4, 143.4, 139.3, 137.7, 136.1, 129.7, 128.5, 128.2, 128.2, 127.4, 126.9, 112.0, 70.2, 44.6; MS (ESI): *m/z* calcd. for $C_{24}H_{25}N_2O_4S$, $[M+H]^+$ 437.1, found 437.9 $[M+H]^+$. Anal. calcd. C, 66.03; H, 5.54; N, 6.42; S, 7.35, found: C, 66.23; H, 5.51; N, 6.39; S, 7.37.

1-(4-((5-(4-(Methylsulfonyl)phenyl)pyridin-2-yl)oxy)piperidin-1-yl)ethan-1-one (compound II-10)

Yield 37%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.43 (d, J = 2.8 Hz, 1H, −ArH), 8.15–8.16 (m, 1H, −ArH), 8.13–8.14 (m, 1H, −ArH), 8.02–8.03 (m, 1H, −ArH), 8.00–8.01 (m, 1H, −ArH), 7.75 (d, J = 8.8 Hz, 1H, −ArH), 7.33 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H, −ArH), 4.65–4.70 (m, 1H, −CH), 3.43–3.83 (m, 4H, $-CH_2$), 3.09 (s, 3H, $-SO_2CH_3$), 2.14 (s, 3H, $-COCH_3$), 1.81–2.06 (m, 4H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.0, 153.4, 148.0, 144.0, 139.8, 139.3, 127.9, 127.1, 123.2, 121.6, 72.5, 44.6, 42.9, 38.0, 31.0, 30.0, 21.4; MS (ESI): *m/z* calcd. for $C_{19}H_{23}N_2O_4S$, $[M+H]^+$ 375.1, found 375.5 $[M+H]^+$. Anal. calcd. C, 60.94; H, 5.92; N, 7.48; S, 8.56, found: C, 61.09; H, 5.93; N, 7.50; S, 8.58.

2,2-Dimethyl-1-(4-((5-(4-(methylsulfonyl)phenyl)pyridin-2-yl)-oxy)piperidin-1-yl)propan-1-one (compound II-11)

Yield 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, J = 1.6 Hz, 1H, −ArH), 8.03–8.04 (m, 1H, −ArH), 8.00–8.01 (m, 1H, −ArH), 7.83 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, −ArH), 7.72–7.73 (m, 1H, −ArH), 7.70–7.71 (m, 1H, −ArH), 6.85 (d, J = 8.6 Hz, 1H, −ArH), 5.33–5.39 (m, 1H, −CH), 3.97–4.03 (m, 2H, $-CH_2$), 3.49–3.55 (m, 2H, $-CH_2$), 3.10 (s, 3H, $-SO_2CH_3$), 2.03–2.10 (m, 2H, $-CH_2$), 1.76–1.85 (m, 2H, $-CH_2$), 1.31 (s, 9H, $-C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.3, 163.3, 145.4, 143.4, 139.2, 137.7, 128.2, 128.1, 127.3, 112.0, 70.6, 44.6, 42.4, 38.8, 31.2, 28.4; MS (ESI): *m/z* calcd. for $C_{22}H_{29}N_2O_4S$, $[M+H]^+$ 417.1, found 417.3 $[M+H]^+$. Anal. calcd. C, 63.44; H, 6.78; N, 6.73; S, 7.70, found: C, 63.53; H, 6.79; N, 6.74; S, 7.72.

Cyclopropyl(4-((5-(4-(methylsulfonyl)phenyl)pyrazin-2-yl)oxy)-piperidin-1-yl)methanone (compound III-4)

Yield 50%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 (d, J = 1.6 Hz, 1H, −ArH), 8.32 (d, J = 1.6 Hz, 1H, −ArH), 8.14–8.15 (m, 1H, −ArH), 8.12–8.13 (m, 1H, −ArH), 8.05–8.06 (m, 1H, −ArH), 8.03–8.04 (m, 1H, −ArH), 5.33–5.39 (m, 1H, −CH), 3.98–4.04 (m, 2H, $-CH_2$), 3.53–3.64 (m, 2H, $-CH_2$), 3.10 (s, 3H, $-SO_2CH_3$), 2.11 (br, 2H, $-CH_2$), 1.89 (br, 1H, −CH), 1.77–1.83 (m, 2H, $-CH_2$), 0.99–1.03 (m, 2H, $-CH_2$), 0.77–0.81 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.0, 159.1, 143.0, 141.7, 140.3, 138.0, 135.8, 128.1, 126.8, 100.0, 71.6, 44.6, 11.0, 7.4; MS (ESI): *m/z* calcd. for $C_{20}H_{24}N_3O_4S$, $[M+H]^+$ 402.1, found 402.3 $[M+H]^+$. Anal. calcd. C, 59.83; H, 5.77; N, 10.47; S, 7.99, found: C, 59.96; H, 5.79; N, 10.45; S, 7.98.

Phenyl 4-((5-(4-(methylsulfonyl)phenyl)pyrazin-2-yl)oxy)-piperidine-1-carboxylate (compound III-5)

Yield 52%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (d, J = 1.2 Hz, 1H, −ArH), 8.34 (d, J = 1.2 Hz, 1H, −ArH), 8.15–8.16 (m, 1H, −ArH), 8.13–8.14 (m, 1H, −ArH), 8.06–8.07 (m, 1H, −ArH), 8.04–8.04 (m, 1H, −ArH), 7.35–7.40 (m, 2H, −ArH), 7.19–7.24 (m, 1H, −ArH), 7.14–7.15 (m, 1H, −ArH), 7.11–7.12 (m, 1H, −ArH), 5.34–5.39 (m, 1H, −CH), 3.92–4.00 (m, 2H, $-CH_2$), 3.55–3.64 (m, 2H, $-CH_2$), 3.10 (s, 3H, $-SO_2CH_3$), 2.12–2.16 (m, 2H, $-CH_2$), 1.92–1.95 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1, 153.7, 151.4, 143.1, 141.7, 140.3, 138.1, 135.8, 129.3, 128.1, 126.8, 125.3, 121.7, 71.2, 44.6; MS (ESI): *m/z* calcd. for $C_{23}H_{24}N_3O_5S$, $[M+H]^+$ 454.1, found 453.8 $[M+H]^+$. Anal. calcd. C, 60.91; H, 5.11; N, 9.27; S, 7.07, found: C, 61.04; H, 5.13; N, 9.32; S, 7.06.

4.1.7 | Synthesis of 1-benzyl-4-((4′-(methylsulfonyl)-[1,1′-biphenyl]-4-yl)oxy)piperidine (compound I-6)

A mixture of compound **I-2** (0.1 g, 0.3 mmol), benzyl bromide (45.36 mg, 0.36 mmol), trimethylamine (45.45 mg, 0.45 mmol), and dichloromethane (20 mL) was stirred at room temperature overnight. TLC monitoring showed complete consumption of starting material. After completion of the reaction, the mixture was extracted with dichloromethane (30 mL) and water (20 mL), washed twice with saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, evaporated under diminished pressure to give white solid compound **I-6** (71 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96–7.98 (m, 2H, −ArH), 7.71–7.73 (m, 2H, −ArH), 7.52–7.56 (m, 2H, −ArH), 7.31–7.35 (m, 4H, −ArH), 7.27–7.29 (m, 1H, −ArH), 6.99–7.02 (m, 2H, −ArH), 4.38–4.42 (m, 1H, −CH), 3.56 (s, 2H, $-CH_2$), 3.08 (s, 3H, $-SO_2CH_3$), 2.77 (br, 2H, $-CH_2$), 2.34 (br, 2H, $-CH_2$), 2.04 (br, 2H, $-CH_2$), 1.82–1.90 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.2, 146.3, 138.4, 131.4, 129.1, 128.6, 128.3, 127.9, 127.3, 127.1, 116.5, 63.0, 50.5, 44.7, 30.8; MS (ESI): *m/z* calcd. for $C_{25}H_{28}NO_3S$, $[M+H]^+$ 422.1, found 421.9 $[M+H]^+$. Anal. calcd. C, 71.23; H, 6.46; N, 3.32; S, 7.61, found: C, 71.28; H, 6.48; N, 3.33; S, 7.64.

Compounds **II-12**, **III-6** were prepared in a manner similar to that described for compound **I-6**.

2-((1-Benzylpiperidin-4-yl)oxy)-5-(4-(methylsulfonyl)phenyl)-pyridine (compound II-12)

Yield 34%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (dd, J_1 = 2.8 Hz, J_2 = 0.8 Hz, 1H, −ArH), 8.00 (d, J = 8.4 Hz, 2H, −ArH), 7.80 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H, −ArH), 7.72 (d, J = 8.8 Hz, 2H, −ArH), 7.27–7.36 (m, 6H, −ArH), 5.11–5.17 (m, 1H, −CH), 3.56 (s, 2H, $-NCH_2Ph$),

3.09 (s, 3H, $-SO_2CH_3$), 2.77–2.80 (m, 2H, $-CH_2$), 2.33–2.38 (m, 2H, $-CH_2$), 2.06 (br, 2H, $-CH_2$), 1.81–1.89 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.5, 143.6, 137.4, 129.2, 128.2, 128.1, 127.7, 127.3, 127.1, 112.0, 63.1, 50.9, 44.6, 31.0; MS (ESI): *m/z* calcd. for $C_{24}H_{27}N_2O_3S$, $[M+H]^+$ 423.1, found 423.0 $[M+H]^+$. Anal. calcd. C, 68.22; H, 6.20; N, 6.63; S, 7.59, found: C, 68.16; H, 6.17; N, 6.65; S, 7.62.

2-((1-Benzylpiperidin-4-yl)oxy)-5-(4-(methylsulfonyl)phenyl)-pyrazine (compound III-6)

Yield 39%. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.55 (d, J = 1.2 Hz, 1H, −ArH), 8.28 (d, J = 1.6 Hz, 1H, −ArH), 8.13–8.14 (m, 1H, −ArH), 8.10–8.11 (m, 1H, −ArH), 8.04–8.05 (m, 1H, −ArH), 8.02–8.02 (m, 1H, −ArH), 7.31–7.36 (m, 4H, −ArH), 7.27–7.29 (m, 1H, −ArH), 5.10–5.16 (m, 1H, −CH), 3.56 (s, 2H, $-NCH_2Ph$), 3.09 (s, 3H, $-SO_2CH_3$), 2.77–2.81 (m, 2H, $-CH_2$), 2.36 (t, J = 20.8 Hz, 2H, $-CH_2$), 2.06 (br, 2H, $-CH_2$), 1.84–1.92 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.5, 142.6, 141.9, 140.1, 138.1, 135.9, 129.1, 128.3, 128.0, 127.1, 126.7, 72.4, 63.0, 50.7, 44.6, 30.8; MS (ESI): *m/z* calcd. for $C_{23}H_{26}N_3O_3S$, $[M+H]^+$ 424.1, found 424.5 $[M+H]^+$. Anal. calcd. C, 65.23; H, 5.95; N, 9.92; S, 7.57, found: C, 65.10; H, 5.97; N, 9.94; S, 7.59.

4.1.8 | Synthesis of 5-fluoro-2-(4-((5-(4-(methylsulfonyl)phenyl)pyridin-2-yl)oxy)piperidin-1-yl)-pyrimidine (compound II-17)

A mixture of compound **I-2** (0.2 g, 0.6 mmol), sodium hydride (27.6 mg, 1.2 mmol) and dimethyl formamide (20 mL) was stirred at 100°C for 1 h. Then 2-chloro-5-fluoropyrimidine (95.04 mg, 0.72 mmol) was added into the mixture and stirred at 100°C overnight. TLC monitoring showed complete consumption of starting material. After completion of the reaction, the mixture was extracted with ethyl acetate (30 mL) and water (20 mL), washed twice with saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, evaporated under diminished pressure to give white solid compound **II-17** (120 mg, 47%). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.41 (d, J = 2.4 Hz, 1H, −ArH), 8.21 (s, 2H, −ArH), 8.01 (d, J = 8.4 Hz, 2H, −ArH), 7.82 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, −ArH), 7.72 (d, J = 8.4 Hz, 2H, −ArH), 6.85 (d, J = 8.8 Hz, 1H, −ArH), 5.36–5.40 (m, 1H, −CH), 4.20–4.26 (m, 2H, $-CH_2$), 3.59–3.66 (m, 2H, $-CH_2$), 3.09 (s, 3H, $-SO_2CH_3$), 2.08–2.13 (m, 2H, $-CH_2$), 1.81–1.86 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5, 158.9, 152.7, 150.2, 145.5, 145.3, 145.1, 143.5, 139.2, 137.6, 128.2, 128.0, 127.3, 112.0, 71.1, 44.6, 41.9, 30.6; MS (ESI): *m/z* calcd. for $C_{21}H_{22}FN_4O_3S$, $[M+H]^+$ 429.1, found 429.6 $[M+H]^+$. Anal. calcd. C, 58.87; H, 4.94; N, 13.08; S, 7.48, found: C, 58.99; H, 4.96; N, 13.05; S, 7.47.

Compound **II-18** was prepared in a manner similar to that described for compound **II-17**.

5-Chloro-2-(4-((5-(4-(methylsulfonyl)phenyl)pyridin-2-yl)oxy)-piperidin-1-yl)pyrimidine (compound II-18)

Yield 39%. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.41 (d, J = 2.4 Hz, 1H, −ArH), 8.23 (s, 2H, −ArH), 8.01 (d, J = 8.4 Hz, 2H, −ArH), 7.83 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, −ArH), 7.72 (d, J = 8.4 Hz, 2H, −ArH), 6.85 (d, J = 8.8 Hz, 1H, −ArH), 5.38–5.42 (m, 1H, −CH), 4.20–4.26 (m, 2H, $-CH_2$), 3.63–3.70 (m, 2H, $-CH_2$), 3.09 (s, 3H, $-SO_2CH_3$), 2.08–2.13 (m, 2H, $-CH_2$), 1.81–1.86 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4, 159.8, 155.9, 155.9, 145.5, 143.5, 139.2, 137.6, 128.2, 128.0, 127.3, 117.9, 112.0, 70.9, 44.6, 41.5, 30.6; MS (ESI): *m/z* calcd. for $C_{21}H_{22}ClN_4O_3S$, $[M+H]^+$ 425.1, found 425.5 $[M+H]^+$. Anal. calcd. C, 56.69; H, 4.76; N, 12.59; S, 7.21, found: C, 56.60; H, 4.73; N, 12.62; S, 7.24.

4.2 | Biological evaluation

4.2.1 | *In vitro* GPR119 agonist activity

Intracellular cAMP in CHO human GPR119 stable cell line was measured using the LANCE Ultra cAMP Detection Kit (PerkinElmer). The assay was performed according to the manufacturer's protocol. Compounds were tested on CHO human GPR119 stable cell line. Cells were diluted in assay buffer (5 mM HEPES pH 7.4, Hank's Balanced Salt Solution, 0.1% BSA, 0.5 mM IBMX) and used at 2×10^3 cells/well in 384-well plates. Cells were incubated with compound for 60 min before addition of 5 µL 4X Eu-cAMP tracer solution and 5 µL 4X ULight™-anti-cAMP solution. Signal = 665 nm Raw Data/615 nm Raw Data × 10000. %Activation = (1 − (Max signal − Compound signal)/(Max signal − Min signal)) × 100. Min signal was obtained from the DMSO negative control with only DMSO. Max signal was obtained from the action of reference-positive control GSK1292263 at 1 µM. EC_{50} was calculated using GraphPad Prism V5.0 software: Sigmoidal dose-response (variable slope).[19]

4.2.2 | Oral glucose tolerance test (OGTT)

The animal study was performed according to the international rules considering animal experiments and the internationally accepted ethical principles for laboratory animal use and care. Synthesized compounds and positive control were formulated in 0.5% methylcellulose. Male ICR mice (18–22 g, obtained from Shanghai SLAC Laboratory Animal Co. Ltd.) were fasted overnight and randomly stratified (n = 6/group) to vehicle and test compound groups. Body weights were recorded on the morning of the study (post-fasting) for dose volume calculation. Blood samples were collected via the tail vein from all mice prior to dosing with either vehicle (0.5% methylcellulose) or test compound via oral gavage (30 mg/kg). Thirty minutes later mice were bled and immediately dosed with oral glucose (2 g/kg). The mice were re-bled at 30, 60, and 120 min post-glucose load. Glucose levels were measured on a SANNUO hand-held monitor. AUC was calculated using GraphPad Prism 7 software.[20,21]

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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SUPPORTING INFORMATION

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