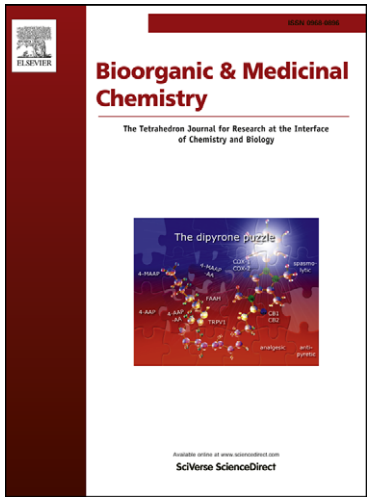

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Synthesis and biological evaluation of novel 2,4-disubstituted quinazoline analogues as GPR119 agonists

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ABSTRACT
GPR119 agonist has emerged as a promising target for the treatment of type 2 diabetes. A series of novel 2,4-disubstituted quinazoline analogues was prepared and evaluated their agonistic activity against human GPR119. The analogues bearing azabicyclic amine substituents (**12a, 12c** and **12g**) exhibited better EC_{50} values than that of OEA though they appeared to be partial agonists.

Keywords: GPR119 agonist, type 2 diabetes, quinazoline analogues, azabicyclic amines

1. Introduction

Type 2 diabetes, formerly known as non-insulin-dependent diabetes mellitus, is a complex metabolic disorder that affects millions of people worldwide. It is characterized by high blood glucose that caused by insulin resistance or insufficient insulin secretion, accounting for approximately 90% of all cases of diabetes.[1] Currently, metformin is generally recommended as a first line treatment for type 2 diabetes beside others such as sulfonyl ureas, thiazolidinediones, α-glucosidase inhibitors,[1] and the two most recently approved classes: glucagon-like-pepetide 1 (GLP-1) receptor agonists,[1-3] and dipeptidyl peptidase-4 (DPP-4) inhibitors.[2,3] Although the number of patients with type 2 diabetes that successfully achieve target glucose levels is steadily improving, a substantial number of subjects continue to fall short of acceptable treatment goals, leaving them at high risk of development of diabetes-associated complications. Furthermore, most of these medications remain side effects such as hypoglycemia, weight gain, bone fractures.[1,2] Therefore, new drugs that exhibit improved efficacy and safety relative to current available medications are clearly needed.

GPR119 is a G-protein-coupled receptor predominantly express on pancreatic beta cells and intestinal enteroendocrine cells. GPR119 can be activated by oleoylethanolamine (OEA), lysophosphatidylcholine, *N*-oleoyldopamin, ovalnil…and OEA most probably represents the endogenous ligand.[4-7] GPR119 agonist stimulates glucose-dependent insulin secretion in vitro and lowers an elevated blood glucose level in vivo.[5,6] Furthermore, they have been demonstrated to stimulate the release of the incretin (GLP-1 and GIP).[5-7] Therefore, GPR119 agonist has emerged as a promising target for the treatment of type 2 diabetes and obesity by improving glucose homoeostasis while concurrently slowing gastric emptying, reducing food intake and promoting weight loss.[4-6] To date, several candidates were entered clinical trials for treatment of type 2 diabetes. However, very limited information is yet available from these trials in the form of scientific publications.[6,7]

Diverse fused aromatic heterocycle scaffolds were found in the precedent literatures and patents of GPR119 agonists (Fig. 1).[6-14] As a congener of bicyclic heterocycle scaffolds, we were interested in quinazoline scaffold since quinazoline derivatives were found to possess diverse promising biological activities including anticancer, antihypertension, anticonvulsant, antidiabetic, antimalarial etc.[15-17] Some of them are used in clinical treatment such as terazosin, alfuzosin, doxazosin,[15] gefitinib, erlotinib.[16] Also piperidine moieties were attached to the aromatic heterocycle scaffolds in most compounds under development.[6-13] It was suggested from precedent literatures that piperidine carbamate region makes H-bond acceptor interactions that plays very important role for GPR119 agonistic activity. We also found that modifications in this region may affect to bioactivity. Therefore, we designed analogs bearing conformationally restricted azabicyclic rings instead of piperidines to evaluate effect on GPR119 activation. Thus we designed novel quinazoline derivatives bearing piperidine and azabicyclic analogues and herein we report the synthesis, biological evaluation and structural-activity relationship of novel 2,4-disubstituted quinazoline analogues as GPR119 agonists for the treatment of type 2 diabetes.

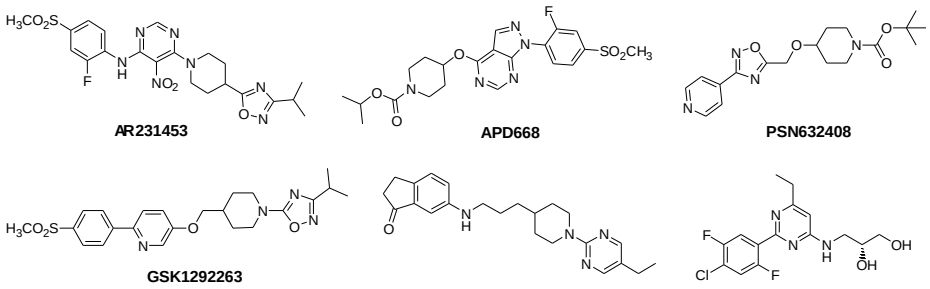
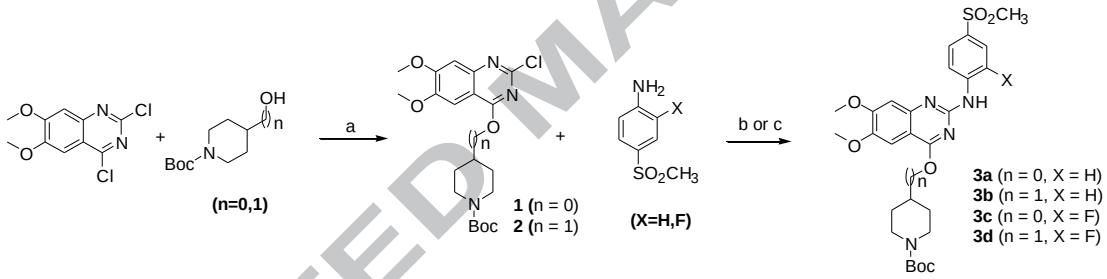


Fig. 1. Structures of selected synthetic GPR119 agonists

2. Results and discussion

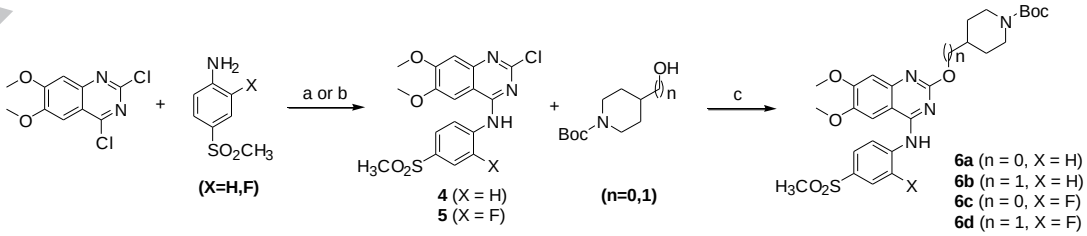
2.1. Chemistry

The synthesis of 2-arylamino-4-alkyloxy-6,7-dimethoxyquinazoline **3a-d** are outlined in Scheme 1. *N*-Boc-4-hydroxypiperidine, *N*-Boc-4-hydroxymethylpiperidine and 4-methylsulfonylaniline are commercial available products**.** 2-Fluoro-4-methylsulfonylaniline was prepared according to previously reported procedure.[18] Incorporating *N*-Boc piperidine alcohols into 2,4-dichloro-6,7-dimethoxyquinazoline in the presence of NaH yielded 4-alkoxy-2-chloro-6,7-dimethoxyquinazoline (**1** and **2**).[11] Coupling reactions of these intermediates (**1** and **2**) with 4-methylsulfonylaniline and 2-fluoro-4-methylsulfonylaniline under acid catalyst[19] followed by treatment with Boc_2O in the presence of TEA gave target products **3a-d.**[20]



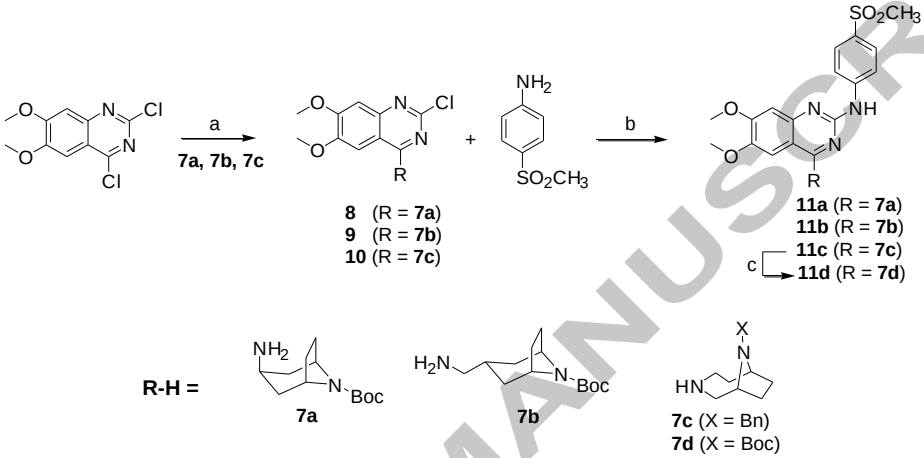
Scheme 1. Synthesis of 2-arylamino-4-alkyloxy-6,7-dimethoxyquinazolines (**3a-d**). Reagents and conditions: (a) NaH, THF, rt, overnight (b) (i) HCl, *n*-BuOH, reflux, overnight (ii) Boc_2O, TEA, CH_2Cl_2, rt, 2h (for **3a**, **3b**) (c) (i) HCl, AcOH, reflux, overnight (ii) Boc_2O, TEA, CH_2Cl_2, rt, 2h (for **3c**, **3d**).

Quinazoline analogues **6a-d** were synthesized according to Scheme 2. 2,4-Dichloro-6,7-dimethoxyquinazoline was reacted with 4-methylsulfonylaniline under acid catalyst to afford a key intermediate **4**.[21] By contrast**,** another key intermediate **5** was achieved with 2,4-dichloro-6,7-dimethoxyquinazoline and 2-fluoro-4-methylsulfonylanilne in the presence of NaH. Finally, these intermediates were converted into desire products **6a-d** by treatment with *N*-Boc piperidine alcohols using NaOH as a base.



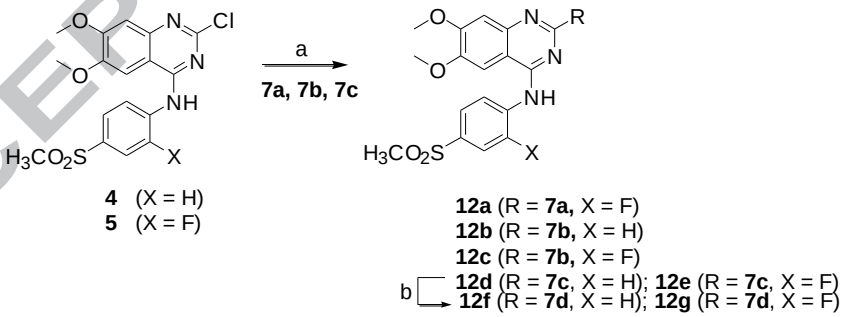
Scheme 2. Synthesis of 2-alkyloxy-4-arylamino-6,7-dimethoxyquinazolines (**6a-d**). Reagents and conditions: (a) HCl, EtOH, 60 ^{o}C, overnight *(for **6a, 6b**)* (b) NaH, THF, reflux, overnight (for **6c, 6d**) (c) NaOH, 140 ^{o}C, overnight.

Azabicyclic amines (**7a-c**) were generated following the previously reported procedures and ^{1}H NMR data were consistent with that reported in the literature.[22] 4-Alkylamino-2-chloro-6,7-dimethoxyquinazolines (**8-10**)**,** obtained from 2,4-dichloro-6,7-dimethoxyquinazoline and azabicyclic amines (**7a-c**)[23] were reacted with 4-methylsulfonylaniline to afford product **11a-c**[19] while the reactions between 4-Alkylamino-2-chloro-6,7-dimethoxyquinazolines (**8-10**) and 2-fluoro-4-methylsulfonylanilne did not yield target products. Hydrogenolysis of compound **11c** followed by reaction with Boc_2O yielded compound **11d** (Scheme 3).



Scheme 3. Synthesis of 4-alkylamino-2-(4-methylsulfonylphenylamino)-6,7-dimethoxyquinazolines (**11a-d**). Reagents and conditions: (a) Hunig's base, *i*-PrOH, rt, overnight (b) (i) HCl, *n*-BuOH, reflux, overnight (ii) Boc_2O, TEA, CH_2Cl_2, rt, 2h (for **11a, 11b**) (c) (i) H_2, Pd/C, MeOH, rt, 5h (ii) Boc_2O, TEA, CH_2Cl_2, rt, 2h.

2-Alkylamino-4-arylamino-6,7-dimethoxyquinazolines **12a-e** were synthesized from intermediates (**4** and **5)** and azabicyclic amines (**7a-c**) in the presence of Hunig's base as a catalyst.[21] Hydrogenolysis of compounds (**12d** and **12e)** followed by treatment with Boc_2O yielded compounds (**12f** and **12g**) (Scheme 4).



Scheme 4. Synthesis of 2-alkylamino-4-arylamino-6,7-dimethoxyquinazolines (**12a-g**). Reagents and conditions: (a) Hunig's base, *n*-BuOH, reflux, 1 day (b) (i) H_2, Pd/C, MeOH, rt, 5h (ii) Boc_2O, TEA, CH_2Cl_2, rt, 2h.

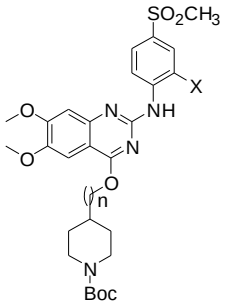
2.2. Biological activity

Compounds **3a-d**, **6a-d**, **11a-d** and **12a-g** were evaluated their abilities to active the human GPR119 receptor in a cell-based cAMP assay and expressed in EC_{50} and %max values. The EC_{50} values represent

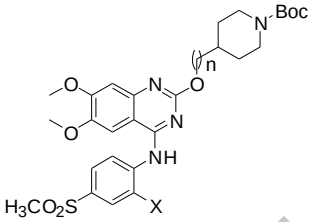
the concentration of the tested compounds for 50% cAMP of OEA, while the %max values present the relative response (%) of the tested compounds compared to the maximal effect of OEA.

As shown in Table 1, the quinazoline analogues (**3a**, **6a),** possessing *N*-Boc-4-piperidinol and 4-methylsulfonylphenylamino groups either at C-2 or C-4 positions, were identified as weak GPR119 agonists (EC_{50}> 10 μM and %max=20.6, 17.9, respectively) and their agonistic activities were much less potent than OEA. Replacement of *N*-Boc-4-piperidinol with *N*-Boc-4-piperidinemethanol also gave similar results. The compounds **3b** and **6b** exhibited weak to negligible GPR119 activation activities. The derivatives with (2-fluoro-4-methylsulfonyl)phenylamino group (**3c, 3d, 6c, 6d**) showed similar GPR119 activation activities. These results indicated that the position of (2-fluoro-4-methylsulfonyl)phenylamino and heterocyclic alcohol groups did not significantly affect to GPR119 activation activity.

Table 1
In vitro GPR119 agonistic activities of **3a-d** and **6a-d**



3a-d



6a-d

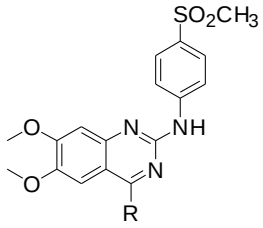
Compound	X	n	hGPR119 activity	
			EC_{50}[a] (μM)	%max[b]
3a	H	0	>10	20.6
6a	H	0	>10	17.9
3b	H	1	>10	17.4
6b	H	1	NE[c]	NE[c]
3c	F	0	>10	19.7
6c	F	0	>10	19.6
3d	F	1	>10	21.3
6d	F	1	>10	33.2
OEA			2.2	100

[a] concentration for 50% cAMP stimulation of OEA
[b] cAMP stimulation % compared to maximal effect of OEA
[c] Not effective at 10 μM

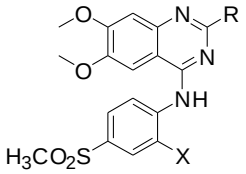
To explore the steric influence on bioactivity, analogues bearing azabicyclic amines such as **7a-d** instead of 4-piperidinol and piperidine-4-methanol were prepared and evaluated their hGPR119 agonistic activities as shown in table 2. The quinazoline analogues (**11a-d**, **12b, 12d and 12f),** possessing azabicyclic amines and 4-methylsulfonylphenylamino groups either at C-2 or C-4 positions, did not improve agonistic activity compared to those of analogues with heterocyclic alcohols. However, the analogues (**12a, 12c** and **12g**) bearing both (2-fluoro-4-methylsulfonyl)phenylamino and azabicyclic amine groups showed strong agonistic activities and exhibited better EC_{50} values than that of OEA but they were proved as partial agonists as shown by their relatively low %max values. These results suggest that the combination of fluorine atom on benzene ring and azabicyclic amines proved to have significantly synergistic effect. These analogues (**12a, 12c** and **12g**) possessed equi-potential for agonistic activities as shown by similar values of EC_{50} and %max. From these findings, we speculated that while the sterically bulky of azabicyclic carbamate would likely be favorable for agonistic activity, the length of this region (one or two carbon elongation) as well as the configuration (endo, exo) were not essential for the in vitro hGPR119 agonistic

activity. Also it was observed that the analogue with *N*-Boc exhibited better agonistic activity than that of the analogue with *N*-Bn (**12g** *vs.* **12e**) suggesting that hydrogen-bond acceptor interactions in this region was important for showing potent agonistic activity.

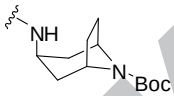
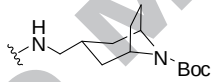
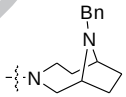
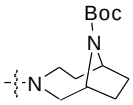
Table 2
In vitro GPR119 agonistic activities of **11a-d** and **12a-g**



11a-d



12a-g

Compound	X	R	hGPR119 activity	
			EC_{50}[a] (μM)	%max[b]
11a	-		>10	17.0
12a	F		1.0	46.2
11b	-		>10	15.1
12b	H		>10	19.9
12c	F		1.0	53.7
11c	-		>10	32.8
12d	H		>10	23.4
12e	F		>10	44.3
11d	-		>10	37.5
12f	H		>10	32.7
12g	F		1.0	56.9
OEA			2.2	100

[a] concentration for 50% cAMP stimulation of OEA
[b] cAMP stimulation % compared to maximal effect of OEA

3. Conclusion

In summary, we have synthesized and characterized a series of novel 2,4-disubstituted quinazolines with heterocyclic alcohols and azabicyclic amine groups as GPR119 agonists for the treatment of type 2 diabetes. We found that the analogues bearing (2-fluoro-4-methylsulfonyl)phenylamino and azabicyclic amine groups with *N*-Boc (**12a**, **12c** and **12g**) exhibited better EC_{50} values than that of OEA even though they appeared to be partial agonists. Our present results suggest that the steric bulkyness of introduced groups seems to influence on bioactivity (**3c**, **3d**, **6c**, **6d** *vs.* **12a**, **12c**, **12g**) while the configuration (endo *vs.* exo) affects not much on bioactivity (**12a** *vs.* **12c**). The electronic effects of the substituted groups at 2-position of benzene ring (**11a** *vs.* **12a**; **12b** *vs.* **12c**; **12f** *vs.* **12g**) as well as *N*-Boc group of azabicyclic amines (**12e**

vs. **12g**) may play a very important role for better bioactivity. Further SAR research to discover more potent GPR119 agonists with diverse heterocyclic scaffolds is under progress.

4. Experimental section

All starting materials were obtained from commercial suppliers and used without further purification. ^{1}H NMR spectra were recorded on a Bruker DPX 300 (300 MHz) 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), brs (broad singlet), d (doublet), t (triplet), dd (doublet of doublet) and m (multiplet). MALDI-TOF mass spectra were recorded on a Voyager-DE STR. Melting points were recorded on a Fisher-Johns microscopic scale melting point apparatus. TLC was performed on silica F_{254} and detected by UV light at 254 nm or by charring with either ninhydrin or iodine. Column chromatography was performed on Kieselgel 60 (230~400 mesh, Merck).

4.1. General procedure to generate 4-alkoxy-2-chloro-6,7-dimethoxyquinazoline (1-2)

To a stirred solution of sodium hydride (4.0 mmol) in dry THF (3 ml) was added solution of alcohols (2.4 mmol) in dry THF (6 ml) and the resulting reaction mixture was stirred for 1 hour under N_2 gas. The reaction mixture was cooled to 0 ^{o}C and a solution of 2,4-dichloro-6,7-dimethoxyquinazoline (2.0 mmol) in dry THF (6 ml) was added and stirred for overnight. The reaction was quenched with water and extracted with dichloromethane. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (hexane-acetone 20:1).

4.1.1. *tert*-Butyl 4-(2-chloro-6,7-dimethoxyquinazolin-4-yloxy)piperidine-1-carboxylate (1)

Following the general procedure, the title compound was prepared from 2,4-dichloro-6,7-dimethoxyquinazoline and *N*-Boc-4-hydroxypiperidine in 64% yield; white solid; mp 190-191 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$): δ 7.28 (s, 1H), 7.20 (s, 1H), 5.61-5.53 (m, 1H), 4.02 (s, 6H), 3.88-3.84 (m, 2H), 3.40-3.32 (m, 2H), 2.16-2.07 (m, 2H), 1.93-1.82 (m, 2H), 1.47 (s, 9H).

4.1.2. *tert*-Butyl 4-((2-chloro-6,7-dimethoxyquinazolin-4-yloxy)methyl)piperidine-1-carboxylate (2)

Following the general procedure, the title compound was prepared from 2,4-dichloro-6,7-dimethoxyquinazoline and *N*-Boc-4-hydroxmethylypiperidine in 73% yield; white solid; mp 176 ^{o}C ; ^{1}H NMR (300MHz, $CDCl_3$): δ 7.27 (s, 1H), 7.21 (s, 1H), 4.45 (d, J = 6.6 Hz, 2H), 4.21 (brs, 2H), 4.02 (s, 6H), 2.79 (t, J = 2.2 Hz, 2H), 2.14-2.10 (m, 1H), 1.86 (d, J = 2.5 Hz, 2H), 1.47 (s, 9H), 1.42-1.29 (m, 2H).

4.2. General procedure to generate 2-arylamino-4-alkyloxy-6,7-dimethoxyquinazoline (3a-d)

To the solution of 4-alkyloxy-2-dichloro-6,7-dimethoxyquinazoline (**1** or **2**, 1.0 mmol) in *n*-BuOH *(for **3a** and **3b**)* or AcOH *(for **3c** and **3d**)* were added arylamine (1.5 mmol) and 1N HCl aqueous solution (2.0 mmol) and the reaction mixture was stirred at 130 ^{o}C for overnight. The reaction mixture was cooled to room temperature then neutralized with 1N NaOH aqueous solution and concentrated under reduced pressure. To the solution of crude product in CH_2Cl_2 were added TEA (2.0 mmol) and Boc_2O (1.5 mmol) and the reaction mixture was stirred for 2 hours. After extraction with CH_2Cl_2, the combined organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated under reduced pressure. Purification of the crude product by silica gel chromatography ($CHCl_3$-MeOH 200:1) yielded product.

4.2.1. *tert*-Butyl 4-(6,7-dimethoxy-2-(4-(methylsulfonyl)phenylamino)quinazolin-4-yloxy)piperidine-1-carboxylate (3a)

Following the general procedure, the title compound was prepared from compound **1** and 4-methylsulfonylaniline in 65% yield; white solid; mp 159-161 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$): δ 7.99-7.96 (m, 2H), 7.91-7.88 (m, 2H), 7.37 (s, 1H), 7.26 (s, 1H), 7.08 (s, 1H), 5.50-5.45 (m, 1H), 4.03 (s, 3H), 4.00 (s, 3H), 3.90-3.85 (m, 2H), 3.42-3.33 (m, 2H), 3.06 (s, 3H), 2.15-2.08 (m, 2H), 1.96-1.86 (m, 2H), 1.5 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.70, 156.30, 155.18, 154.85, 149.97, 148.01, 145.65, 132.54, 129.12, 118.27, 107.20, 106.01, 102.30, 80.23, 72.49, 56.65, 56.55, 45.30, 31.06, 28.85; MS (MALDI-TOF, 2,5-dihydroxybenzoic acid as matrix): m/z (100%): 558.2002 M^+.

4.2.2. *tert*-Butyl 4-((6,7-dimethoxy-2-(4-(methylsulfonyl)phenylamino)quinazolin-4-yloxy)methyl)piperidine-1-carboxylate (3b)

Following the general procedure, the title compound was prepared from compound **2** and 4-methylsulfonylaniline in 60% yield; white solid; mp 140-142 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$): δ 8.00-7.97 (m, 2H), 7.91-7.88 (m, 2H), 7.39 (s, 1H), 7.26 (s, 1H), 7.09 (s, 1H), 4.40 (d, J = 6.5 Hz, 2H), 4.22 (brs, 2H), 4.04 (s, 3H), 4.00 (s, 3H), 3.06 (s, 3H), 2.83-2.76 (m, 2H), 2.14-2.09 (m, 1H), 1.89-1.82 (m, 2H), 1.48 (s, 9H), 1.43-1.26 (m, 2H); MS (MALDI-TOF, 2,5-dihydroxybenzoic acid as matrix): m/z (100%): 572.2022 M^{+}.

4.2.3. *tert*-Butyl 4-(2-(2-fluoro-4-(methylsulfonyl)phenylamino)-6,7-dimethoxyquinazolin-4-yloxy)piperidine-1-carboxylate (3c)

Following the general procedure, the title compound was prepared from compound **1** and 2-fluoro-4-methylsulfonylaniline in 15% yield; yellow solid; mp 204 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$): δ 9.14 (t, J = 8.2Hz, 1H), 7.79 (dd, J = 1.3 Hz, 8.7 Hz, 1H), 7.69 (dd, J = 2.0 Hz, 10.6 Hz, 1 H), 7.42 (d, J = 3.0 Hz, 1H), 7.27 (s, 1H), 7.11 (s, 1H), 5.53-5.48 (m, 1H), 4.06 (s, 3H), 4.00 (s, 3H), 3.86 (brs, 2H), 3.43-3.34 (m, 2H), 3.08 (s, 3H), 2.15-2.10 (m, 2H), 1.96-1.86 (m, 2H), 1.50 (s, 9H); MS (MALDI-TOF, 2,5-dihydroxybenzoic acid as matrix): m/z (100%): 599.2000 $[M+Na]^{+}$.

4.2.4. *tert*-Butyl 4-((2-(2-fluoro-4-(methylsulfonyl)phenylamino)-6,7-dimethoxyquinazolin-4-yloxy)methyl)piperidine-1-carboxylate (3d)

Following the general procedure, the title compound was prepared from compound **2** and 2-fluoro-4-methylsulfonylaniline in 14% yield; yellow solid; mp 120-123 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$): δ 9.14 (t, J = 8.2 Hz, 1H), 7.79 (dd, J = 1.2 Hz, 8.7 Hz, 1H), 7.68 (dd, J = 2.0 Hz, 10.6 Hz, 1H), 7.40 (d, J = 3.9 Hz, 1H), 7.27 (s, 1H), 7.11 (s, 1H), 4.42 (d, J = 6.6 Hz, 2H), 4.22-4.19 (m, 2H), 4.05 (s, 3H), 4.04 (s, 3H), 3.07 (s, 3H), 2.80 (t, J = 11.5 Hz, 2H), 2.14-2.12 (m, 1H), 1.87 (d, J = 12.6 Hz, 2H), 1.48 (s, 9H), 1.46-1.31 (m, 2H); MS (MALDI-TOF, 2,5-dihydroxybenzoic acid as matrix): m/z (100%): 613.2001 $[M+Na]^{+}$.

4.3. 2-Chloro-4-(4-methylsulfonylphenylamino)-6,7-dimethoxyquinazoline (4)

To the solution of 2,4-dichloro-6,7-dimethoxyquinazoline (0.52 g, 2.0 mmol) in EtOH (20 ml) were added 4-methylsulfonylaniline (0.34 g, 2.0 mmol) and 1N HCl aqueous solution (2 ml) and the reaction mixture was stirred at 60 ^{o}C for overnight. The reaction mixture was neutralized with 1N NaOH aqueous solution and the precipitate was filtered and washed with CH_2Cl_2 to obtain product as a white solid in 75% yield; mp 240 ^{o}C; ^{1}H NMR (300MHz, DMSO): δ 10.17 (s, 1H), 8.3-8.1 (m, 2H), 8.05-8.02 (m, 2H), 7.94 (s, 1H), 7.27 (s, 1H), 4.03 (s, 3H), 4.00 (s, 3H), 3.30 (s, 3H).

4.4. 2-Chloro-4-(2-fluoro-4-methylsulfonylphenylamino)-6,7-dimethoxyquinazoline (5)

To a stirred solution of sodium hydride (0.05 g, 2.1 mmol) in dry THF (2 ml) was added a solution of 2-fluoro-4-methylsulfonylaniline (0.2 g, 1.1 mmol) in dry THF (5 ml). The reaction mixture was stirred for 1 hour under N_2 gas. The solution of 2,4-dichloro-6,7-dimethoxyquinazoline (0.3 g, 1.2 mmol) in dry THF (2 ml) was added to the reaction mixture at 0 ^{o}C and refluxed for overnight. The reaction was cooled to room temperature, quenched with water and extracted with EtOAc. The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude residue by silica gel chromatography ($CHCl_3$-MeOH 200:1) yielded product as a yellow solid in 75% yield; mp 270 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$+MeOD): δ 8.71 (t, J = 7.5 Hz, 1H), 7.83 (d, J = 5.7 Hz, 1H), 7.75 (dd, J = 1.3 Hz, 10.1 Hz, 1H), 7.25-7.32 (m, 2H), 4.09 (s, 3H), 4.04 (s, 3H), 3.12 (s, 3H).

4.5. General procedure to generate 2-alkyloxy-4-arylamino-6,7-dimethoxyquinazoline (6a-d)

NaOH (5 mmol) and alcohol (3.0 mmol) were added to a flask containing 2-chloro-4-arylamino-6,7-dimethoxyquinazoline (**4** or **5**, 1.0 mmol) and the resulting mixture was heated at 140 ^{o}C for overnight then cooled to room temperature. The residue was purified by silica gel chromatography ($CHCl_3$-MeOH 200:1) to obtain product.

4.5.1. *tert*-Butyl 4-(6,7-dimethoxy-4-(4-(methylsulfonyl)phenylamino)quinazolin-2-yloxy)piperidine-1-carboxylate (6a)

Following the general procedure, the title compound was prepared from compound **4** and *N*-Boc-4-hydroxypiperidine in 22% yield; white solid; mp 182 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.88-

7.80 (m, 4H), 7.22 (s, 1H), 7.09 (s, 1H), 5.25-5.20 (m, 1H), 4.02 (s, 6H), 3.88-3.83 (m, 2H), 3.31-3.23 (m, 2H), 3.07 (s, 3H), 2.05-2.04 (m, 2H), 1.85-1.77 (m, 2H), 1.48 (s, 9H); MS (MALDI-TOF, 2,5-dihydroxybenzoic acid as matrix): m/z (100%): 581.2015 $[M+Na]^+$.

4.5.2. *tert*-Butyl 4-((6,7-dimethoxy-4-(4-(methylsulfonyl)phenylamino)quinazolin-2-yloxy)methyl)piperidine-1-carboxylate (6b)

Following the general procedure, the title compound was prepared from compound **4** and *N*-Boc-4-hydroxymethylpiperidine in 26% yield; white solid; mp 156 ^oC; ^1H NMR (300MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.88-7.86 (m, 2H), 7.80-7.78 (m, 2H), 7.30 (s, 1H), 7.10 (s, 1H), 4.25 (d, J = 6.6 Hz, 2H), 4.13 (brs, 2H), 4.01 (s, 3H), 4.00 (s, 3H), 3.05 (s, 3H), 2.82-2.72 (m, 2H), 2.02-1.97 (m, 1H), 1.87-1.82 (m, 2H), 1.46 (s, 9H), 1.34-1.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.50, 156.23, 155.23, 154.85, 149.82, 148.00, 145.67, 132.49, 129.11, 118.30, 106.97, 106.04, 102.25, 79.91, 71.35, 56.64, 56.57, 45.30, 36.13, 29.31, 28.86; MS (MALDI-TOF, 2,5-dihydroxybenzoic acid as matrix): m/z (100%): 595.2114 $[M+Na]^+$.

4.5.3. *tert*-Butyl 4-(4-(2-fluoro-4-(methylsulfonyl)phenylamino)-6,7-dimethoxyquinazolin-2-yloxy)piperidine-1-carboxylate (6c)

Following the general procedure, the title compound was prepared from compound **5** and *N*-Boc-4-hydroxypiperidine in 29% yield; yellow solid; mp 114 ^oC; ^1H NMR (300MHz, $CDCl_3$): δ 8.90 (t, J = 7.8 Hz, 1H), 7.82 (dd, J = 1.1 Hz, 8.6 Hz, 1H), 7.75 (dd, J = 2.0 Hz, 10.3 Hz, 1H), 7.62 (d, J = 4.3 Hz, 1H), 7.24 (s, 1H), 6.99 (s, 1H), 5.31-5.23 (m, 1H), 4.05 (s, 3H), 4.04 (s, 3H), 3.92-3.81 (m, 2H), 3.34-3.26 (m, 2H), 3.10 (s, 3H), 2.08 (brs, 2H), 1.88-1.84 (m, 2H), 1.49 (s, 9H); MS (MALDI-TOF, 2,5-dihydroxybenzoic acid as matrix): m/z (100%): 599.2029 $[M+Na]^+$.

4.5.4. *tert*-Butyl 4-((4-(2-fluoro-4-(methylsulfonyl)phenylamino)-6,7-dimethoxyquinazolin-2-yloxy)methyl)piperidine-1-carboxylate (6d)

Following the general procedure, the title compound was prepared from compound **5** and *N*-Boc-4-hydroxymethylpiperidine in 14% yield; yellow solid; mp 162 ^oC**;** ^1H NMR (300MHz, $CDCl_3$): δ 8.98 (t, J = 8.4 Hz, 1H), 7.84-7.81 (m, 1H), 7.76 (dd, J = 2.0 Hz, 10.4 Hz, 1H), 7.57 (d, J = 4.6 Hz, 1H), 7.14 (s, 1H), 6.96 (s, 1H), 4.30 (d, J = 6.5 Hz, 2H), 4.19 (brs, 2H), 4.04 (s, 3H), 4.03 (s, 3H), 3.09 (s, 3H), 2.78 (t, J = 12.1 Hz, 2H), 2.08-2.05 (m, 1H), 1.92-1.87 (m, 2H), 1.47 (s, 9H), 1.36-1.30 (m, 2H); MS (MALDI-TOF, 2,5-dihydroxybenzoic acid as matrix): m/z (100%): 613.1971 $[M+Na]^+$.

4.6. General procedure to generate 4-alkylamino-2-chloro-6,7-dimethoxyquinazoline (8-10)

Azabicyclic amine (**7a-c**, 1.2 mmol) and Hunig's base (2.0 mmol) were added to a solution of 2,4-dichloro-6,7-dimethoxyquinazoline (1.0 mmol) in *i*-PrOH (4 ml) and the resulting mixture was stirred at room temperature for overnight and then concentrated in vacuo. The residue was purified by column chromatography ($CHCl_3$-MeOH 200:1) to obtain product.

4.6.1. *tert*-Butyl *endo*-3-(2-chloro-6,7-dimethoxyquinazolin-4-ylamino)-8-azabicyclo[3.2.1]octane-8-carboxylate (8)

Following the general procedure, the title compound was prepared from 2,4-dichloro-6,7-dimethoxyquinazoline and compound **7a** in 80% yield; white solid; mp 125 ^oC**;** ^1H NMR (300 MHz, $CDCl_3$): δ 7.12 (s, 1H), 6.75 (s, 1H), 5.92 (d, J = 6.4 Hz, 1H), 4.54 (m, 1H), 4.30 (brs, 2H), 3.98 (s, 6H), 2.50-1.80 (m, 8H), 1.50 (s, 9H).

4.6.2. *tert*-Butyl *exo*-3-((2-chloro-6,7-dimethoxyquinazolin-4-ylamino)methyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (9)

Following the general procedure, the title compound was prepared from 2,4-dichloro-6,7-dimethoxyquinazoline and compound **7b** in 82% yield; yellow solid; mp 242 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20-7.05 (m, 3H), 4.20 (brs, 2H), 3.90 (s, 6H), 3.10 (brs, 1H), 2.42 (m, 1H), 2.00-1.20 (m, 18H).

4.6.3. (±)-4-(9-benzyl-3,9-diazabicyclo[4.2.1]nonan-3-yl)-2-chloro-6,7-dimethoxyquinazoline (10)

Following the general procedure, the title compound was prepared from 2,4-dichloro-6,7-dimethoxyquinazoline and compound **7c** in 81% yield; yellow solid; mp 134 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.25 (m, 6H), 7.16 (s, 1H), 4.42 (brs, 1H), 4.00-3.90 (m, 8H), 3.80 (s, 2H), 3.60-3.30 (m, 3H), 2.40-1.50 (m, 6H).

4.7. General procedure to generate 4-alkylamino-2-(4-methylsulfonylphenylamino)-6,7-dimethoxyquinazoline (11a-c)

To the solution of 4-alkylamino-2-chloro-6,7-dimethoxyquinazoline (**8-10**, 1.0 mmol) in *n*-BuOH were added 4-methylsulfonylaniline (1.5 mmol) and 1N HCl aqueous solution (2 mmol) and the reaction mixture was stirred at 130 ^{o}C for overnight. The reaction mixture was cooled to room temperature, neutralized with 1N NaOH aqueous solution and concentrated under reduced pressure. To the solution of crude product in CH_2Cl_2 were added TEA (2.0 mmol) and Boc_2O (1.5 mmol) and the reaction mixture was stirred for 2 hours. After extraction with CH_2Cl_2, the combined organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated under reduced pressure. Purification of the crude product by silica gel chromatography ($CHCl_3$-MeOH 200:1) yielded product.

4.7.1. *tert*-Butyl *endo*-3-(6,7-dimethoxy-2-(4-(methylsulfonyl)phenylamino)quinazolin-4-ylamino)-8-azabicyclo[3.2.1]octane-8-carboxylate (11a)

Following the general procedure, the title compound was prepared from compound **8** and 4-methylsulfonylaniline in 77% yield; yellow solid; mp 168-170 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (m, 4H), 7.70 (s, 1H), 7.00 (s, 1H), 6.80 (s, 1H), 5.90 (s, 1H), 4.50-4.20 (m, 3H), 4.00 (s, 6H), 3.06 (s, 3H), 2.50-1.90 (m, 8H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.77, 155.52, 155.39, 153.75, 147.58, 145.98, 132.02, 128.97, 118.20, 106.68, 105.18, 100.73, 80.03, 56.73, 55.57, 45.27, 44.33, 28.94; MS (MALDI-TOF, 2,5-dihydroxybenzoic acid as matrix): m/z (100%): 606.2369 $[M+Na]^+$.

4.7.2. *tert*-Butyl *exo*-3-((6,7-dimethoxy-4-(4-(methylsulfonyl)phenylamino)quinazolin-2-ylamino)methyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (11b)

Following the general procedure, the title compound was prepared from compound **9** and 4-methylsulfonylaniline in 65% yield; yellow solid; mp 156-158 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00-7.80 (m, 4H), 7.65 (s, 1H), 7.10 (s, 1H), 6.90 (s, 1H), 6.66 (brs, 1H), 4.25 (brs, 2H), 3.90 (m, 7H), 3.20 (m, 4H), 2.50 (m, 1H), 2.10-1.40 (m, 17H); MS (MALDI-TOF, 2,5-dihydroxybenzoic acid as matrix): m/z (100%): 597.2533 M^+.

4.7.3. (±)-4-(9-Benzyl-3,9-diazabicyclo[4.2.1]nonan-3-yl)-6,7-dimethoxy-*N*-(4-(methyl sulfonyl)phenyl) quinazolin-2-amine (11c)

Following the general procedure, the title compound was prepared from compound **10** and 4-methylsulfonylaniline in 54% yield; yellow solid; mp 171 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (m, 4H), 7.45-7.20 (m, 7H), 7.05 (s, 1H), 4.30 (s, 1H), 4.05-3.75 (m, 10H), 3.60-3.30 (m, 3H), 3.05 (s, 3H), 2.40-1.50 (m, 6H).

4.7.4. *tert*-Butyl (±)-3-(6,7-dimethoxy-2-(4-(methylsulfonyl)phenylamino)quinazolin-4-yl)-3,9-diazabicyclo[4.2.1]nonane-9-carboxylate (11d)

Reaction mixture of compound **11c** (0.15 mmol) and 10% Pd/C (0.1 mmol) in dry MeOH (3 ml) was hydrogenated for 5 hours at atmospheric pressure. The reaction mixture was filtered through celite and concentrated under reduced pressure. To the solution of crude product in CH_2Cl_2 were added TEA (0.3 mmol) and Boc_2O (0.2 mmol) and the reaction mixture was stirred for 2 hours. After extraction with CH_2Cl_2, the combined organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated under reduced pressure. Purification of the crude product by silica gel chromatography ($CHCl_3$-MeOH 200:1) yielded product as a yellow solid in 54% yield; mp 162 ^{o}C; ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.90 (m, 4H), 7.31 (s, 1H), 7.24 (d, J = 7.4 Hz, 1H), 7.06 (d, J = 7.4 Hz, 1H), 4.50-4.25 (m, 3H), 4.10-3.30 (m, 8H), 3.06 (s, 3H), 2.70-1.40 (m, 16H); MS (MALDI-TOF, α-cyano-4-hydroxycinnamic acid as matrix): m/z (100%): 584.2455 $[M+H]^+$.

4.8. General procedure to generate 2-alkylamino-4-arylamino-6,7-dimethoxyquinazoline (12a-e)

Azabicyclic amine (**7a-c**, 1.2 mmol) and Hunig's base (4.0 mmol) were added to a solution of compound **(4** or **5**, 1.0 mmol) in *n*-BuOH (2 ml) and the resulting mixture was stirred at reflux for 1 day. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and the residue was purified by column chromatography ($CHCl_3$-MeOH 200:1) to obtain product.

4.8.1. *tert*-Butyl *endo*-3-(4-(2-fluoro-4-(methylsulfonyl)phenylamino)-6,7-dimethoxyquinazolin-2-ylamino)-8-azabicyclo[3.2.1]octane-8-carboxylate (12a)

Following the general procedure, the title compound was prepared from azabicyclic amine **7a** and compound **5** in 14% yield; yellow solid; mp 178-181 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$): δ 8.87 (s, 1H), 7.82-7.74 (m, 2H), 7.56 (brs, 1H), 6.94-6.91 (m, 2H), 4.27-4.25 (m, 4H), 4.01 (s, 3H), 4.00 (s, 3H), 3.11 (s, 3H), 2.36-2.31 (m, 3H), 1.90 (d, J = 4.5, 2H), 1.65 (brs, 3H), 1.50 (s, 9H); MS (MALDI-TOF, 2,5-dihydroxybenzoic acid as matrix): m/z (100%): 602.2225 $[M+H]^+$.

4.8.2. *tert*-Butyl *exo*-3-((6,7-dimethoxy-4-(4-(methylsulfonyl)phenylamino)quinazolin-2-ylamino)methyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (12b)

Following the general procedure, the title compound was prepared from azabicyclic amine **7b** and compound **4** in 27% yield; yellow solid; mp 181 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$ + MeOD): δ 7.95 (m, 4H), 6.98 (s, 1H), 6.90 (s, 1H), 4.25 (brs, 2H), 4.00 (s, 6H), 3.35 (m, 2H), 3.09 (s, 3H), 2.20 (m, 1H), 2.00-1.40 (m, 17H); MS (MALDI-TOF, 2,5-dihydroxybenzoic acid as matrix): m/z (100%): 598.2514 $[M+H]^+$.

4.8.3. *tert*-Butyl *exo*-3-((4-(2-fluoro-4-(methylsulfonyl)phenylamino)-6,7-dimethoxyquinazolin-2-ylamino)methyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (12c)

Following the general procedure, the title compound was prepared from azabicyclic amine **7b** and compound **5** in 43% yield; white solid; mp 220 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$): δ 8.93 (t, J = 8.2 HZ, 1H), 7.78-7.73 (m, 2H), 7.51 (s, 1H), 6.95 (s, 1H), 6.89 (s, 1H), 5.02 (brs, 1H), 4.29-4.22 (m, 2H), 4.01 (s, 6H), 3.37 (t, J = 6.1 Hz, 2H) , 3.10 (s, 3H), 2.26-2.18 (m, 1H), 1.96-1.95 (m, 2H), 1.71-1.45 (m, 6H), 1.47 (s, 9H); MS (MALDI-TOF, 2,5-dihydroxybenzoic acid as matrix): m/z (100%): 616.2614 $[M+H]^+$.

4.8.4. (±)-2-(9-Benzyl-3,9-diazabicyclo[4.2.1]nonan-3-yl)-6,7-dimethoxy-*N*-(4-(methylsulfonyl)phenyl) quinazolin-4-amine (12d)

Following the general procedure, the title compound was prepared from azabicyclic amine **7c** and compound **4** in 57% yield; yellow solid; mp 208 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$): δ 7.92-7.87 (m, 2H), 7.84-7.79 (m, 2H), 7.55 (s, 1H), 7.42-7.40 (m, 2H), 7.34-7.21 (m, 3H), 7.02 (s, 1H), 6.93 (s, 1H), 4.52 (brs, 1H), 4.26 (brs, 1H), 3.97 (s, 6H), 3.77 (s, 2H), 3.74-3.62 (m, 1H), 3.39-3.31 (m, 3H), 3.07 (s, 3H), 2.02-1.75 (m, 4H), 1.34-1.28 (m, 2H).

4.8.5. (±)-2-(9-Benzyl-3,9-diazabicyclo[4.2.1]nonan-3-yl)-*N*-(2-fluoro-4-(methylsulfonyl)phenyl)-6,7-dimethoxyquinazolin-4-amine (12e)

Following the general procedure, the title compound was prepared from azabicyclic amine **7c** and compound **5** in 50% yield; yellow solid; mp 218 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$): δ 8.93 (s, 1H), 7.75-7.72 (d, 2H), 7.44-7.40 (m, 3H), 7.34-7.24 (m, 3H), 6.93 (s, 1H), 6.85 (s, 1H), 4.51 (brs, 1H), 4.23 (brs, 1 H), 4.00 (s, 3H), 3.99 (s, 3H), 3.78-3.68 (m, 3H), 3.41-3.35 (m, 3H), 3.08 (s, 3H), 2.22-2.10 (m, 1H), 2.05-1.95 (m, 2H), 1.80-1.75 (m, 2H), 1.37-1.26 (m, 1H); MS (MALDI-TOF, 2,5-dihydroxybenzoic acid as matrix): m/z (100%): 592.2611 $[M+H]^+$.

4.8.6. *tert*-Butyl (±)-3-(6,7-dimethoxy-4-(4-(methylsulfonyl)phenylamino)quinazolin-2-yl)-3,9-diazabicyclo[4.2.1]nonane-9-carboxylate (12f)

The title compound was prepared from compound **12d** according to the procedure for compound **11d.** Yield: 40%; yellow solid; mp 173 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (m, 4H), 7.55 (s, 1H), 7.00 (s, 2H), 4.50-4.20 (m, 3H), 4.00 (s, 6H), 3.10 (m, 5H), 2.30-1.30 (m, 16H); MS (MALDI-TOF, α-cyano-4-hydroxycinnamic acid as matrix): m/z (100%): 584.2572 $[M+H]^+$.

4.8.7. *tert*-Butyl (±)-3-(4-(2-fluoro-4-(methylsulfonyl)phenylamino)-6,7-dimethoxyquinazolin-2-yl)-3,9-diazabicyclo[4.2.1]nonane-9-carboxylate (12g)

The title compound was prepared from compound **12e** according to the procedure for compound **11d.** Yield: 50%; yellow solid; mp 170-172 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$): δ 8.92 (s, 1H), 7.80-7.73 (m, 2H), 7.47 (s, 1H), 6.93 (s, 1H), 6.86 (s, 1H), 4.46-4.23 (m, 3H), 4.00 (s, 6H), 3.37-3.33 (m, 1H), 3.10 (m, 4H), 2.17-2.15 (m, 2H), 1.97-1.84 (m, 3H), 1.49 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.94, 155.58, 155.38, 153.69, 153.51, 152.52, 150.89, 146.33, 133.34, 124.21, 121.00, 114.29, 106.24, 103.15, 99.54, 79.29, 58.23, 56.37, 56.17, 54.05, 53.78, 45.58, 44.74, 31.79, 29.69, 28.53; MS (MALDI-TOF, 2,5-dihydroxybenzoic acid as matrix): m/z (100%): 602.2386 $[M+H]^+$.

4.9. Human GPR119 cAMP reporter assay

HEK293 cells ($4x10^3$ cells/well) were seeded on 96 half-well plates and incubated for 24h. The cells were transected with GPR119 expression plasmid (OriGene Technologies, Inc., USA) using Lipofectamine and Plus reagent (Life Technologies Corporation., USA). After 24h, transfected cells were incubated with compounds dissolved in assay buffer (KRBH buffer containing 0.1% BSA and 500 μM 3-isobutyl-1-methylxanthine) for 60 min at 37 ^{o}C. Subsequently, cells were harvested with lysis buffer (50 mM phosphate buffer containing 1 M KF and 1.25% Triton X-100, pH 7.0) for 10 min at room temperature and the assay was performed using the cAMP homogeneous time-resolved fluorescence kit (CIS bio international, France).

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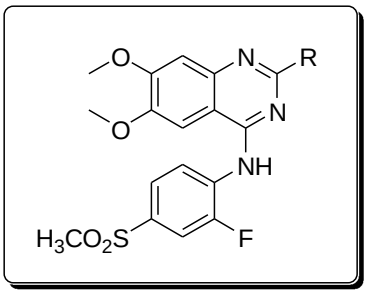
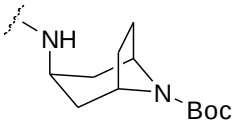
*Graphical Abstract (for review)



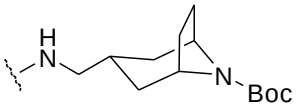
human GPR119 agonists

EC_{50} = 1 μM

R



12a



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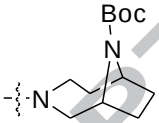

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