Bioorganic & Medicinal Chemistry Letters 24 (2014) 1133–1137

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Discovery and optimization of 5-(2-((1-(phenylsulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)oxy)pyridin-4-yl)-1,2,4-oxadiazoles as novel gpr119 agonists

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ARTICLE INFO

Article history:
Received 12 November 2013
Revised 29 December 2013
Accepted 31 December 2013
Available online 8 January 2014

Keywords:
GPR119
Agonists
Oxadiazole
Constrain
Free fraction

ABSTRACT

We describe the discovery and optimization of 5-(2-((1-(phenylsulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)oxy)pyridin-4-yl)-1,2,4-oxadiazoles as novel agonists of GPR119. Previously described aniline **2** had suboptimal efficacy in signaling assays using cynomolgus monkey (cyno) GPR119 making evaluation of the target in preclinical models difficult. Replacement of the aniline ring with a tetrahydroquinoline ring constrained the rotation of the aniline C–N bond and gave compounds with increased efficacy on human and cyno receptors. Additional optimization led to the discovery of **10**, which possesses higher free fraction in plasma and improved pharmacokinetic properties in rat and cyno compared to **2**.

GPR119 is a class A GPCR that is predominantly expressed in beta-cells of pancreas and gastrointestinal tract.[1] Endogenously-occurring phospholipids and lipid amides, such as oleoylethanolamide, have been identified as GPR119 ligands.[2,3] Activation of the receptor results in increased intracellular cAMP levels.[2–4]

Activation of GPR119 causes receptor-dependent, glucose-stimulated insulin secretion in isolated pancreatic beta-cells and improves glucose tolerance in vivo without causing hypoglycemia.[4] The improvement in glucose tolerance was specific where it was observed in wild-type but not in GPR119 knockout mice.[4] In addition, GPR119 agonists increase gastric inhibitory peptide and glucagon-like protein-1 (GLP-1) secretion in a receptor-dependent manner.[5] Co-administration of GPR119 agonists and inhibitors of dipeptidyl peptidase IV, which function to prevent degradation of GLP-1, resulted in a greater improvement in glucose tolerance than with either agent alone.[6] Chronic administration of GPR119 agonist APD668 to Zucker diabetic fatty rats for 8 weeks resulted in significant reduction of blood glucose and glycated hemoglobin levels without causing hypoglycemia.[7] In addition, APD668 improved glucose tolerance in acute studies in cynomolgus monkeys (cyno).[7]

Several GPR119 agonists have been studied in clinical trials,[8] and many patents describing GPR119 agonists have been disclosed.[9] However, whether GPR119 agonists will ultimately prove to be a safe and effective treatment for metabolic diseases such as type 2 diabetes remains to be shown.[10]

In this Letter we describe the optimization of a new chemical series of GPR119 agonists, focusing on improvements in potency, efficacy, and pharmacokinetic (PK) profile.

We previously reported the optimization of a high-throughput screening (HTS) hit compound **1** to compound **2** (Fig. 1), which showed an improved potency and PK profile.[11] However, compound **2** had lower efficacy (58%) in the cyno cAMP assay than compound **3**, a very close analog of APD668.[7] As a result, we determined that this compound was not ideal for in vivo efficacy studies in cyno and made improving the efficacy a major focus of our SAR campaign.

We first explored a few structural modifications on compound **1** that were considered likely to be promising as observed from examples, which included N-alkylation of the sulfonamide, replacement of the methyl or chlorine with a cyclopropyl at the 6-pyridinyl position, or maintaining substituents such as CN at the 3-pyridinyl position. None of these modifications were proven to be consistent (data not shown). However, we did observe a trend of increasing efficacy when we constrained the sulfonamide nitro-

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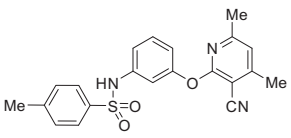
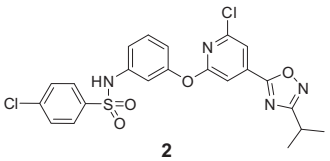
http://dx.doi.org/10.1016/j.bmcl.2013.12.127



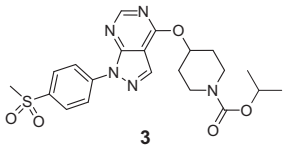
1

human EC50(μM)/Emax(%): 0.31/105
cyno EC50(μM)/Emax(%): 3.09/71



2

human EC50(μM)/Emax(%): 0.02/85
cyno EC50(μM)/Emax(%): 0.08/58

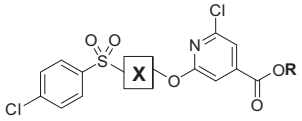


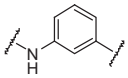
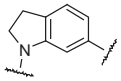
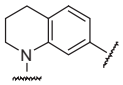
3

human EC50(μM)/Emax(%): 0.04/100
cyno EC50(μM)/Emax(%): 0.17/100

Figure 1. HTS hit **1**, previously optimized compound **2**, and reference compound **3** (% efficacy relative to **3**, values are means of two or more experiments).

Table 1
Constraining the sulfonamide nitrogen increases efficacy of pyridyl esters



Compds	X	Human GPR119 cAMP EC_{50} (μM)/efficacy[a,b] (%)	Cyno GPR119 cAMP EC_{50} (μM)/ efficacy[a,b] (%)
4 (R = Et)		0.02/92	0.14/50
5 (R = Me)		0.03/102	0.27/76
6 (R = Me)		0.10/108	0.30/94
7 (R = Et)		0.10/117	0.20/103

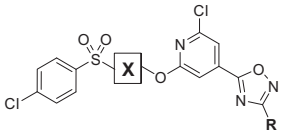
[a] Values are means of two or more experiments, see Ref. 11 for assay protocol (accession numbers of the GPR119 sequences transfected in HEK cells: human = NM_178471.2, cyno = XM_005594569.1).
[b] Efficacy relative to compound **3**.

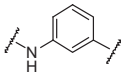
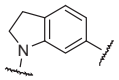
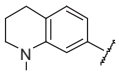
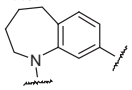
gen to the middle phenyl ring with an ester at the 4-pyridyl position (Table 1). Compared to the unconstrained ester **4**, compound **5** showed increased efficacy on both the human and cyno receptors. Compounds **6** and **7** improved the efficacy even further.

We then combined structural features that both enhanced efficacy (observed by constraining the sulfonamide nitrogen as shown in Table 1) and improved PK profiles (observed with heterocyclic replacement of the esters, as exemplified with compound **2**[11]). Replacement of the aniline ring of **2** with an indoline, a terahydroquinoline, or a tetrahydrobenzoazepine provided compounds **8**–**11** (Table 2), each of which showed an increase in efficacy on the cyno GPR119 receptor. The indoline and tetrahydroquinoline-containing compounds (**8**–**10**) offer a good balance of efficacy and potency (**8**–**10**). In addition, fractions unbound (fu, or free fraction) in plasma increased 7–33 fold across species for **8** and **10** compared to **2**. Compound **10** showed comparable potency and efficacy to compound **3** in both human and cyno cAMP assays.

The SAR around the substituted phenyl ring on the sulfonamide was very sensitive to modifications (Table 3). Substitution at the *ortho*- and *meta*-positions were generally not tolerated (**13**–**18**),

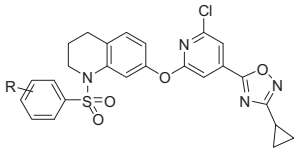
Table 2
Constraining the sulfonamide nitrogen increases efficacy of heterocycles



Compds	X	Human GPR119 cAMP EC_{50} (μM)/ efficacy[a,b] (%)	Cyno GPR119 cAMP EC_{50} (μM)/ efficacy[a,b] (%)	%Fu in plasma r/c/h[c]
2 (R = ^{i}Pr)		0.02/85	0.08/58	0.5/1.2/ 0.8
8 (R = ^{c}Pr)		0.06/109	0.21/99	3.5/10/ 26
9 (R = ^{i}Pr)		0.05/108	0.16/96	NA
10 (R = ^{c}Pr)		0.05/107	0.14/106	5.3/15/ 11
11 (R = ^{c}Pr)		4.3/102[d]	9.0/106[d]	NA

[a] Values are means of two or more experiments, see Ref. 11 for assay protocol.
[b] Efficacy relative to compound **3**.
[c] Fraction unbound (fu) values are means of three experiments using ultracentrifugation method; r for rat, c for cyno, h for human.
[d] From one experiment.

Table 3
Sulfonamide SAR

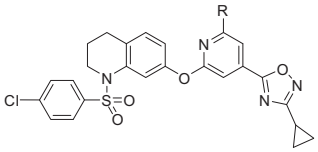


Compds	R	Human GPR119 cAMP EC_{50} (μM)/ efficacy[a,b] (%)	Cyno GPR119 cAMP EC_{50} (μM)/ efficacy[a,b] (%)
12	H	0.29/87[c]	>30/0[c]
13	2-CN	0.27/44[c]	>30/0[c]
14	3-CN	0.55/52	>30/0
15	3-F	0.32/90	0.35/5[c]
16	3-Cl	0.54/69	>30/0
17	3-OMe	0.59/65	>30/0
18	3-SO_2Me	0.18/99	0.63/65
19	4-CN	0.03/98	0.11/122
20	4-F	0.09/102	0.33/65
10	4-Cl	0.05/107	0.14/106
21	4-OMe	0.09/94	0.28/43
22	4-SO_2Me	0.77/55	>30/0
23	4-Me	0.08/103	0.24/63
24	2,4-Di F	0.86/43[c]	>30/0[c]
25	3,4-Di F	0.09/100	0.33/74
26	3,4-Di Cl	0.07/96	0.43/54

[a] Values are means of two or more experiments, see Ref. 11 for assay protocol.
[b] Efficacy relative to compound **3**.
[c] From one experiment.

and the *para*-position was quite sensitive in terms of cyno efficacy to size of substituent: Cl (**10**) ~ CN (**19**) > F (**20**) >> H (**12**). Although OMe (**21**) and Me (**23**) had good activities on the human receptor, both showed low efficacy on the cyno receptor (43% and 63%, respectively). Di-substitutions (**24**–**26**) and 4-SO_2Me (**22**) were not preferred.

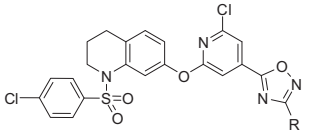
Table 4
SAR of 6-pyridyl substituents



Compds	R	Human GPR119 cAMP EC_{50} (μM)/efficacy[a,b] (%)	Cyno GPR119 cAMP EC_{50} (μM)/efficacy[a,b] (%)
10	Cl	0.05/107	0.14/106
27	F	0.10/106	0.31/106
28	Me	0.12/98	0.23/87
29	OH	>30/0[c]	>30/0[c]
30	OMe	0.27/122[c]	1.1/65[c]
31	^{c}Pr	0.13/93[c]	2.6/24[c]

[a] Values are means of two or more experiments, see Ref. 11 for assay protocol.
[b] Efficacy relative to compound **3**.
[c] From one experiment.

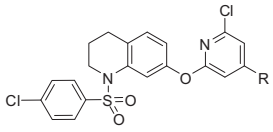
Table 5
SAR of 1,2,4-oxadiazole substituents

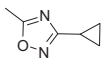
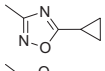
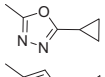
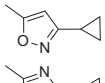
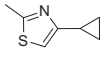


Compds	R	Human GPR119 cAMP EC_{50} (μM)/efficacy[a,b] (%)	Cyno GPR119 cAMP EC_{50} (μM)/efficacy[a,b] (%)
32	Me	0.18/118	0.67/128
33	CF_3	0.11/101	0.66/97
34	Et	0.08/106	0.20/101
35	CH_2CF_3	0.19/98[c]	0.44/70[c]
36	$CH_2{}^{c}Pr$	0.06/109	0.27/79
9	^{i}Pr	0.05/108	0.16/96
10	^{c}Pr	0.05/107	0.14/106
37	^{t}Bu	0.05/108	0.49/87

[a] Values are means of two or more experiments, see Ref. 11 for assay protocol.
[b] Efficacy relative to compound **3**.
[c] From one experiment.

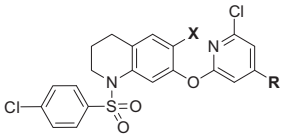
Table 6
SAR of 5-membered heterocycles

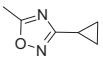
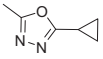


Compds	R	Human GPR119 cAMP EC_{50} (μM)/efficacy[a,b] (%)	Cyno GPR119 cAMP EC_{50} (μM)/efficacy[a,b] (%)
10		0.05/107	0.14/106
38		0.14/93	0.81/27
39		0.08/117	0.16/119
40		0.10/100	0.43/95
41		1.5/89[c]	17/25[c]

[a] Values are means of two or more experiments, see Ref. 11 for assay protocol.
[b] Efficacy relative to compound **3**.
[c] From one experiment.

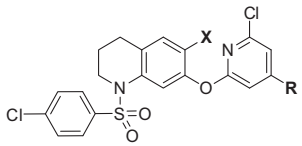
Table 7
SAR of substituents on the tetrahydroquinoline



Compds	X	R	Human GPR119 cAMP EC_{50} (μM)/efficacy[a,b] (%)	Cyno GPR119 cAMP EC_{50} (μM)/efficacy[a,b] (%)	Rat CL[c] (L/h/kg)	%Fu in Plasma[d] r/c/h
10	H		0.05/107	0.14/106	1.0	NA
42	F		0.04/109	0.09/117	0.91	5.5/10/28
43	Cl		0.08/102	0.33/102	0.41	4.3/12/14
39	H		0.08/117	0.16/119	3.8	2.5/8.5/13
44	F		0.07/116	0.09/133	2.9	NA
45	Cl		0.08/112	0.10/123	1.1	3.0/15/12

[a] Values are means of two or more experiments, see Ref. 11 for assay protocol.
[b] Efficacy relative to compound **3**.
[c] Dosed intravenously at 0.5 mg/kg.
[d] Fraction unbound (fu) values are means of three experiments using ultracentrifugation method; r for rat, c for cyno, h for human.

Table 8
SAR of the middle fused ring



Compds	Z	Human GPR119 cAMP EC_{50} (μM)/efficacy[a,b] (%)	Cyno GPR119 cAMP EC_{50} (μM)/efficacy[a,b] (%)
10	C	0.05/107	0.14/106
46	O	0.06/119	0.12/135
47	S	0.10/111[c]	1.26/73[c]
48	SO_2	0.31/93[c]	1.19/34[c]

[a] Values are means of two or more experiments, see Ref. 11 for assay protocol.
[b] Efficacy relative to compound **3**.
[c] From one experiment.

The replacement of the chlorine at the 6 position of the pyridine with other substituents were also studied (Table 4). Overall, substitution of the chlorine at the 6 position with a different group resulted in a loss either potency or efficacy. The fluoro-pyridine **27** showed only a 2-fold decrease in potency, while maintaining the same efficacy (106%). The methyl substituted pyridine compound (**28**) showed a small decrease in both potency and efficacy. Introduction of an OH produces an inactive compound (**29**). Potency and efficacy values of the methoxy (**30**) and cyclopropyl (**31**) substituted pyridyl compounds were far superior on the human receptor compared to the corresponding values obtained with the cyno receptor.

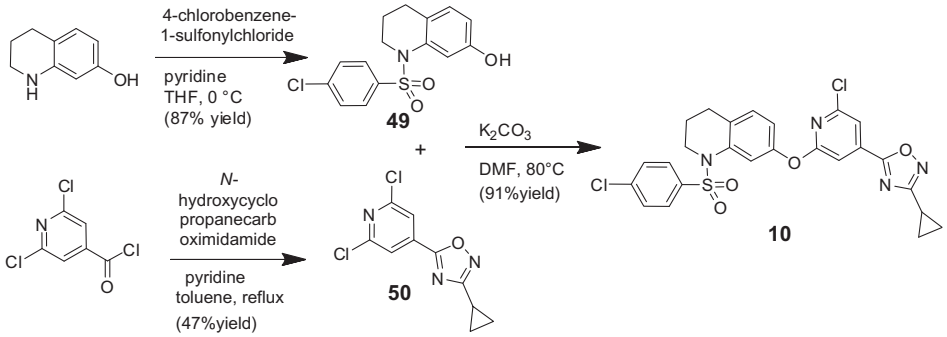
We next explored substituents at the 3-position of the 1,2,4-oxadiazole moiety (Table 5). Introduction of a CF_3 group (**33** vs **32**; **35** vs **34**) and increased substituent size (larger than 3 carbons: **36** and **37**) are detrimental to efficacy on the cyno receptor, although neither has a significant impact on efficacy on the human receptor.

Other 5-membered heterocycles were explored on the 4-pyridyl position (Table 6). While 1,3,4-oxadiazole **39** and isoxazole **40** are

Table 9
Pharmacokinetic properties[a]

Compds	CL (L/h/kg)	AUC (μM∗h)	$t_{1/2}$ (h)	V_{dss} (L/kg)	Species	%fu[b]
2	1.86	0.54	5.1	5.1	rat	0.5
42	0.91	0.99	6.8	4.1	rat	5.5
43	0.41	2.09	7.9	1.6	rat	4.3
45	1.1	0.79	5.9	6.4	rat	3.8
46	0.74	1.26	7.8	3.4	rat	2.9
10	1.00	0.92	5.8	2.8	rat	5.3
10	0.35	2.86	17	2.8	cyno	15

[a] Dosed intravenously at 0.5 mg/kg.
[b] Fraction unbound (fu) values are means of three experiments using ultracentrifugation method.



Scheme 1. Synthesis of **10**.

well tolerated, the 1,2,4-oxadiazole **38** and thiazole **41** show dramatically reduced activity on the cyno receptor.

Adding a fluoro- or chloro-substituent ortho to the oxygen on the tetrahydroquinoline ring in two oxadiazole series maintains potency, while decreasing the in vivo clearance in rat (**10** vs **42** or **43**; and **39** vs **44** or **45**) (Table 7). Since the unbound fractions are similar between **42** and **43** as well as between **39** and **45**, the decrease in clearance is not related to plasma protein binding.

The 4-position of the middle ring linker was also explored (Table 8). This position can tolerate carbon (**10**) and oxygen (**46**), but potency and efficacy on the cyno receptor is negatively impacted by sulfur (**47**) or sulfone (**48**).

Compared to compound **2**, many compounds showed improved rat PK properties and fraction unbound in plasma (Table 9). Compound **10** was tested in cyno and showed good cyno PK profiles. In addition to its significantly reduced human plasma protein binding, **10** does not bind to the human ether-à-go-go-related gene (hERG) potassium ion channel or inhibit the bile salt export pump (BSEP) transporter.

Compound **10** can be prepared in three steps with good overall yield (Scheme 1).[12]

In summary, we discovered 5-(2-((1-(phenylsulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)oxy)pyridin-4-yl)-1,2,4-oxadiazoles as a novel class of GPR119 agonists, and presented the SAR in detail. Compounds were optimized to have good potency and efficacy on both the human and cyno receptors. Additional characterization of these compounds in vitro and in vivo will be necessary to determine if they can further developed for the treatment of type 2 diabetes or other disorders. This is particularly important given reports of limited efficacy of other GPR119 agonists in clinical trials.[13]

References and notes

1. Fredriksson, R.; Hoglund, P. J.; Gloriam, D. E. I.; Lagerstrom, M. C.; Schioth, H. B. *FEBS Lett.* **2003**, *554*, 381.
2. Soga, T.; Ohishi, T.; Matsui, T.; Saito, T.; Matsumoto, M.; Takasaki, J.; Matsumoto, S.; Kamohara, M.; Hiyama, H.; Yoshida, S.; Momose, K.; Ueda, Y.; Matsushime, H.; Kobori, M.; Furuichi, K. *Biochem. Biophys. Res. Commun.* **2005**, *326*, 744.
3. Overton, H. A.; Babbs, A. J.; Doel, S. M.; Fyfe, M. C. T.; Gardner, L. S.; Griffin, G.; Jackson, H. C.; Procter, M. J.; Rasamison, C. M.; Tang-Christensen, M.; Widdowson, P. S.; Williams, G. M.; Reynet, C. *Cell Metab.* **2006**, *3*, 167.
4. Chu, Z.-L.; Jones, R. M.; He, H.; Carroll, C.; Gutierrez, V.; Lucman, A.; Moloney, M.; Gao, H.; Mondala, H.; Bagnol, D.; Unett, D.; Liang, Y.; Demarest, K.; Semple, G.; Behan, D. P.; Leonard, J. *Endocrinology* **2007**, *148*, 2601.
5. Chu, Z.-L.; Carroll, C.; Alfonso, J.; Gutierrez, V.; He, H.; Lucman, A.; Pedraza, M.; Mondala, H.; Gao, H.; Bagnol, D.; Chen, R.; Jones, R. M.; Behan, D. P.; Leonard, J. *Endocrinology* **2008**, *149*, 2038.
6. Ansarullah; Lu, Y.; Holstein, M.; DeRuyter, B.; Rabinovitch, A.; Guo, Z. *PLoS ONE* **2013**, *8*, e53345.
7. Semple, G.; Ren, A.; Fioravanti, B.; Pereira, G.; Calderon, I.; Choi, K.; Xiong, Y.; Shin, Y.-J.; Gharbaoui, T.; Sage, C. R.; Morgan, M.; Xing, C.; Chu, Z.-L.; Leonard, J. N.; Grottick, A. J.; Al-Shamma, H.; Liang, Y.; Demarest, K. T.; Jones, R. M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3134 (APD668 is compound **3k** in Ref. 7. We used compound **3c** in Ref. 7 as the reference compound in our assays).
8. Zhu, X.; Huang, W.; Qian, H. 'GPR119 Agonists: A Novel Strategy for Type 2 Diabetes Treatment', chapter 4 of 'Diabetes Mellitus—Insights and Perspectives', 2013, Prof. Oluwafemi Oguntibeju (Ed.), ISBN: 978-953-51-0939-6, InTech, DOI: 10.5772/48444.
9. Jones, R. M.; Leonard, J. N.; Buzard, D. J.; Lehmann, J. *Expert Opin. Ther. Patents* **2009**, *19*, 1339.
10. Cornall, L. M.; Mathai, M. L.; Hryciw, D. H.; McAinch, A. J. *Expert. Opin. Invest. Drugs* **2013**, *22*, 487.
11. Zhang, J.; Li, A.-R.; Yu, M.; Wang, Y.; Zhu, J.; Kayser, F.; Medina, J. C.; Siegler, K.; Conn, M.; Shan, B.; Grillo, M. P.; Eksterowicz, J.; Coward, P.; Liu, J. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3609.
12. *1-(4-Chlorophenylsulfonyl)-1,2,3,4-tetrahydroquinolin-7-ol (**49**):* To a solution of 1,2,3,4-tetrahydroquinolin-7-ol (4.68 g, 31.4 mmol, Astatech) and pyridine (3.04 mL, 37.6 mmol) in THF (30 mL) at 0 °C was added a solution of 4-chlorobenzene-1-sulfonyl chloride (6.95 g, 32.9 mmol) in THF (15 mL) dropwise. The reaction was stirred at 0 °C for 4 h. The reaction mixture was concentrated with silica gel and purified by flash chromatography (10–40% EtOAc in hexanes) to give **49** (8.8 g, 87%) as a pale-yellow solid. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.54–7.58 (2H, m), 7.37–7.41 (2H, m), 7.36 (1H, d, J = 2.5 Hz), 6.89 (1H, d, J = 8.4 Hz), 6.64 (1H, dd, J = 8.4, 2.5 Hz), 3.76–3.82 (2H, m), 2.40 (2H, t, J = 6.7 Hz), 1.57–1.65 (2H, m). MS ESI (pos.) M/E: 324 (M+H).
*3-Cyclopropyl-5-(2,6-dichloropyridin-4-yl)-1,2,4-oxadiazole (**50**):* To a solution of 2,6-dichloroisonicotinoyl chloride (21.02 g, 100 mmol, Maybridge) in toluene (300 mL), was added *N*-hydroxycyclopropanecarboximidamide (11.0 g, 110 mmol, Maybridge) and pyridine (24.23 mL, 300 mmol). The mixture was

refluxed (145 °C) with a Dean–Stark trap for 6 h, concentrated and purified by flash chromatography (0–20% EtOAc in hexanes) to give **50** (11.9 g, 47%) as a white solid. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.91 (2H, s), 2.12–2.32 (1H, m), 1.05–1.24 (4H, m). MS ESI (pos.) *M*/*E*: 256 (M+H).

*5-(2-Chloro-6-(1-(4-chlorophenylsulfonyl)-1,2,3,4-tetrahydroquinolin-7-yloxy)pyridin-4-yl)-3-cyclopropyl-1,2,4-oxadiazole (**10**):* A mixture of **49** (162 mg, 0.5 mmol), **50** (128 mg, 0.5 mmol) and potassium carbonate (104 mg, 0.75 mmol) in DMF (1.5 mL) was stirred at 80 °C for 1 h. The reaction mixture was loaded directly onto a silica gel cartridge and purified by flash chromatography (0–20% EtOAc in hexanes) to give **10** (248 mg, 91% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.78 (1H, d, *J* = 1.0 Hz), 7.59–7.72 (4 H, m), 7.55 (1H, d, *J* = 1.2 Hz), 7.48 (1H, d, *J* = 2.5 Hz), 7.19 (1H, d, *J* = 8.2 Hz), 7.00 (1H, dd, *J* = 8.2, 2.3 Hz), 3.83 (2H, dd, *J* = 7.8, 3.9 Hz), 2.25 (2H, m), 1.62 (2H, m), 1.11–1.19 (2H, m), 1.02–1.00 (2H, m). MS ESI (pos.) *M*/*E*: 543 (M+H).

13. Katz, L. B.; Gambale, J. J.; Rothenberg, P. L.; Vanapalli, S. R.; Vaccaro, N.; Xi, L.; Sarich, T. C.; Stein, P. P. *Diabetes Obes. Metab.* **2012**, *14*, 709.