# Design, Synthesis, and Antidiabetic Activity of 4-Phenoxynicotinamide and 4-Phenoxypyrimidine-5-carboxamide Derivatives as Potent and Orally Efficacious TGR5 Agonists

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Ⓢ *Supporting Information*

**ABSTRACT:** 4-Phenoxynicotinamide and 4-phenoxypyrimidine-5-carboxamide derivatives as potent and orally efficacious TGR5 agonists are reported. Several 4-phenoxynicotinamide derivatives were found to activate human and mouse TGR5 (hTGR5 and mTGR5) with $EC_{50}$ values in the low nanomolar range. Compound **23g**, with an $EC_{50}$ value of 0.72 nM on hTGR5 and an $EC_{50}$ value of 6.2 nM on mTGR5, was selected for further in vivo efficacy studies. This compound exhibited a significant dose-dependent glucagon-like peptide-1 (GLP-1) secretion effect. A single oral dose of **23g** (50 mg/kg) significantly reduced blood glucose levels in *db/db* mice and caused a 49% reduction in the area under the blood glucose curve $(AUC)_{0-120 \text{ min}}$ following an oral glucose tolerance test (OGTT) in imprinting control region (ICR) mice. However, **23g** stimulated gallbladder filling, which might result in side effects to the gallbladder.
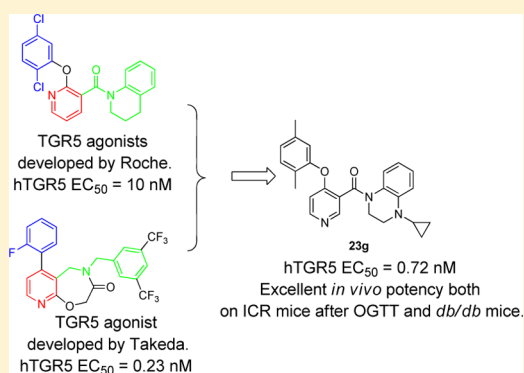
## ■ INTRODUCTION

Type 2 diabetes mellitus (T2DM), commonly referred to as non-insulin-dependent diabetes mellitus (NIDDM), is a metabolic syndrome characterized by high blood glucose levels.[1−3] Although a wide range of antidiabetic medications are available for this metabolic syndrome problem, many patients are unable to achieve satisfactory glycemic control with these treatments.[4−6] Therefore, the development of some novel drugs with new modes of action to supplement the existing therapies for the treatment of patients with uncontrolled T2DM is necessary.

TGR5, a G protein-coupled receptor (GPCR) for bile acids (BAs), was first identified independently by two groups in 2002 and 2003.[7,8] Before its identification, the orphan farnesoid X receptor (FXR) was the only known receptor activated by BAs. The expression levels of TGR5 vary among different tissues, with the highest expression in the gallbladder, moderate expression in the placenta, spleen, and intestine, and low expression in brown adipose tissue, liver, and skeletal muscle.[9] The activation of TGR5 can stimulate glucagon-like peptide-1 (GLP-1) secretion from intestinal enteroendocrine cells by increasing the intracellular cAMP concentration; in addition, it can boost energy expenditure in brown adipose tissue and muscle by increasing the basal metabolic rate.[10−12] GLP-1 belongs to the family of incretins and plays multiple physiological roles in the modulation of glucose homeostasis, such as glucose-dependent stimulation of insulin, suppression of glucagon release, slowing of gastric emptying, and appetite

suppression.[13] Exogenous GLP-1 mimetics (e.g., exendin-4 or liraglutide) and dipeptidyl peptidase-IV (DPP-IV) inhibitors, which prolong the half-life of endogenous GLP-1, are currently clinically used as GLP-1-based therapies for diabetes.[14] An approach that stimulates endogenous GLP-1 secretion is a new strategy for the treatment of T2DM, and a TGR5 agonist that can enhance the secretion of GLP-1 may be a promising alternative for the treatment of metabolic diseases.

There are currently two categories of TGR5 agonists. One series is structurally based on BAs, including naturally occurring TGR5 agonists, such as cholic acid (CA) and lithocholic acid (LCA),[7] and semisynthetic derivatives, such as 6α-ethyl-23(*S*)-methylcholic acid (**1**; see Figure 1),[15] which is a selective TGR5 agonist as an antidiabetic drug candidate prepared by Intercept Corp. Another series includes some synthetic small molecular TGR5 agonists,[16−18] which are usually more potent than BA derivatives, such as [2-(2,5-dichlorophenoxy)pyridin-3-yl]-(3,4-dihydro-2*H*-quinolin-1-yl)methanone (**2**),[19] a pyridine derivative published in a patent by Roche Corp. in the middle of 2010, and 4-(3,5-bis(trifluoromethyl)benzyl)-6-(2-fluorophenyl)-4,5-dihydropyrido[3,2-*f*][1,4]oxazepin-3(2*H*)-one (**3**),[20] another pyridine derivative developed by Takeda Corp.

In our effort to discover more potent TGR5 agonists, we noticed that compound **2** showed some structural similarities to compound **3** (Figure 2). If we treat the pyridine ring of
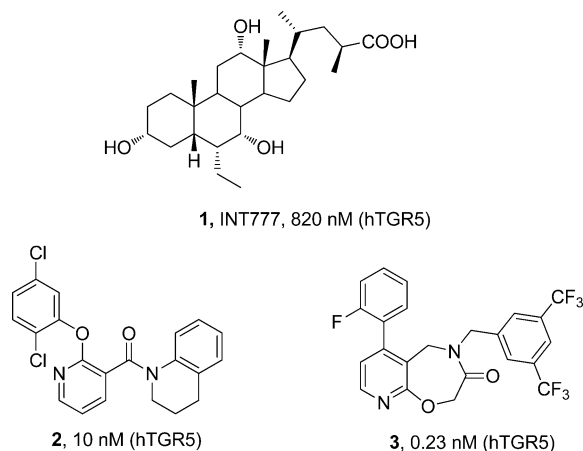
**Figure 1.** Structures of some known TGR5 agonists and their $EC_{50}$ values on hTGR5.

compounds **2** and **3** as the core moiety, we can observe that the upper phenyl ring is linked to the core pyridine ring directly or via an oxygen atom; in addition, the other phenyl ring is linked to the pyridine ring through a two—three atom amide chain adjacent to the upper phenyl ring substituent. The different positions of the nitrogen atom on the core pyridine ring of these two compounds likely indicate that the location of the nitrogen atom on the pyridine ring of compound **2** does not play an important role in the potency. Thus, on the basis of the structure of **2**, analogues **4**, which incorporated various heterocyclic scaffolds with one or two nitrogen atoms in different positions of the core six-membered aromatic rings, were designed, synthesized, and assayed as TGR5 agonists to investigate the role that the central aromatic ring may play (Table 1). The biological activity data showed that, of all these compounds we prepared, compounds **8**, **12a**, and **12b**, having core six-membered rings that all had a nitrogen atom at the position adjacent to the amide chain, were not active as TGR5 agonists. In contrast, 4-phenoxypyrimidine-5-carboxamide derivative **18a** and 4-phenoxynicotinamide derivative **22a** exhibited TGR5 agonist activity on hTGR5 with $EC_{50}$ values of 155 and 49 nM, respectively.[21] The core six-membered rings of **18a** and **22a** both contained a nitrogen atom para to the phenoxy group substituent, similar to compound **3**, which had

an upper phenyl ring substituted at the C-4 position of the pyridine ring, indicating that the TGR5 receptor preferred a nitrogen atom on the core ring in the para position to the upper phenyl ring substituent. Consequently, the 4-phenoxynicotinamide series and 4-phenoxypyrimidine-5-carboxamide series were chosen for further optimization to evaluate substituent effects on activity.

## ■ CHEMISTRY

A similar synthetic strategy was applied to prepare the target compounds with various scaffolds (Schemes 1−4). The phenoxy moiety was usually introduced to the central ring using a standard CuI-catalyzed Ullmann cross-coupling reaction or a simple nucleophilic reaction under alkaline conditions. Condensation of the carboxylic acid with the corresponding aniline analogues produced the amide side chains. As shown in Scheme 1, after esterification of the commercially available 3-aminopyrazine-2-carboxylic acid, methyl 3-amino-2-pyrazine-carboxylate (**5**) was formed, which was then converted into a bromide derivative (**6**) through diazotization in the presence of bromine in 33% yield.[22] Subsequent hydrolysis of the ester (**6**) using sodium hydroxide yielded the corresponding acid, which was condensed with tetrahydroquinoline via acyl chloride formation to yield **7**. Next, compound **7** was converted into the desired 3-phenoxypyrazine-2-carboxamide derivative (**8**) by coupling with 2,5-dichorophenol through a CuI-catalyzed Ullmann cross-coupling reaction in moderate yield. The preparation of the 3-phenoxypyridine-2-carboxamide derivative and the 3-phenoxypyrimidine-4-carboxamide derivative is shown in Scheme 2. First, 2-furancarboxylic acid was transformed into compound **9** in 57% yield by reaction with liquid bromine in refluxing water for 2 h.[23] Subsequent condensation with formamidine under alkaline conditions provided 5-bromo-4-pyrimidinecarboxylic acid (**10**).[24] Next, compound **10** was reacted with 2,5-dichorophenol through the Ullmann cross-coupling reaction to give intermediate **11b**, which was condensed with tetrahydroquinoline by the acyl chloride formation to afford the desired TGR5 agonist (**12b**) in 50% overall yield for the two steps. Likewise, 3-bromo-2-picolinic acid was converted into **12a** under similar reaction conditions, although a lower yield was obtained.

The synthesis routes of 4-phenoxypyrimidine-5-carboxamide and 4-phenoxynicotinamide derivatives varied slightly from the
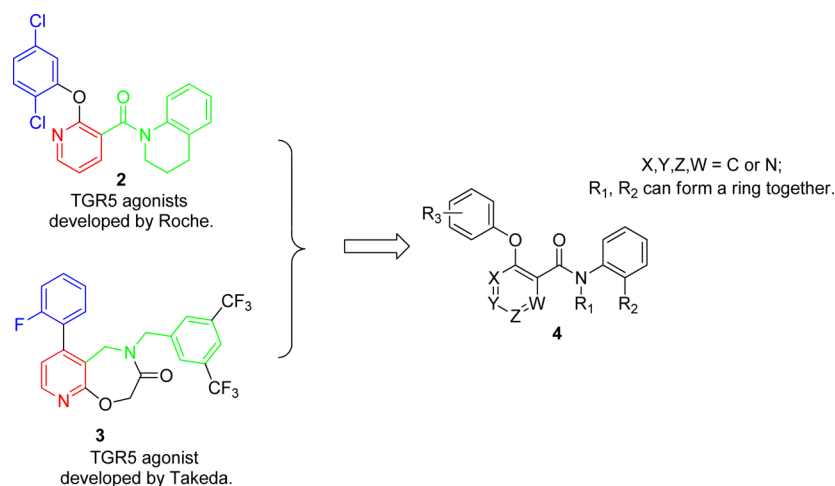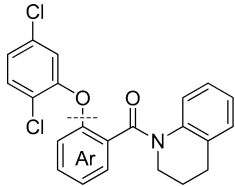


**Figure 2.** Design strategy of TGR5 agonists.

**Table 1. In Vitro Activity of Compounds with Various Central Aromatic Rings[a]**



| Compd | Ar | hTGR5 EC$_{50}$ (nM) | Compd | Ar | hTGR5 EC$_{50}$ (nM) |
|---|---|---|---|---|---|
| 8 | | 5422 ± 864 | 18a | | 155 ± 29 |
| 12a | | >10000 | 22a | | 49 ± 8.3 |
| 12b | | 3871 ± 639 | | | |

[a]EC$_{50}$ values given are expressed as the mean ± SEM of three independent experiments.

**Scheme 1. Synthesis of 3-Phenoxypyrazine-2-carboxamide Derivatives[a]**
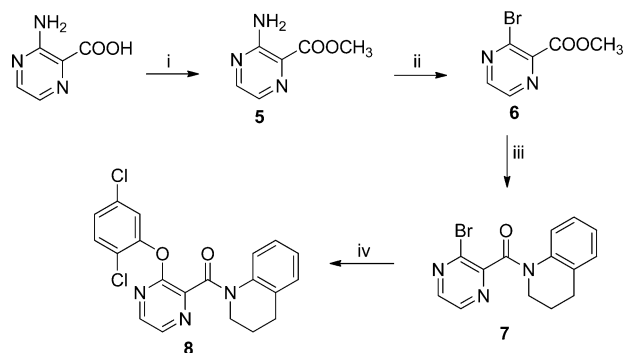


[a]Reagents and conditions: (i) H$_2$SO$_4$, MeOH, rt, 72%; (ii) NaNO$_2$, HBr, Br$_2$, H$_2$O, 0 °C, 33%; (iii) (step a) NaOH, MeOH, H$_2$O, rt; (step b) (COCl)$_2$, Et$_3$N, tetrahydroquinoline, rt, 72% for steps a and b; (iv) 2,5-dichlorophenol, CuI, Cu, K$_2$CO$_3$, DMF, reflux, 81%.

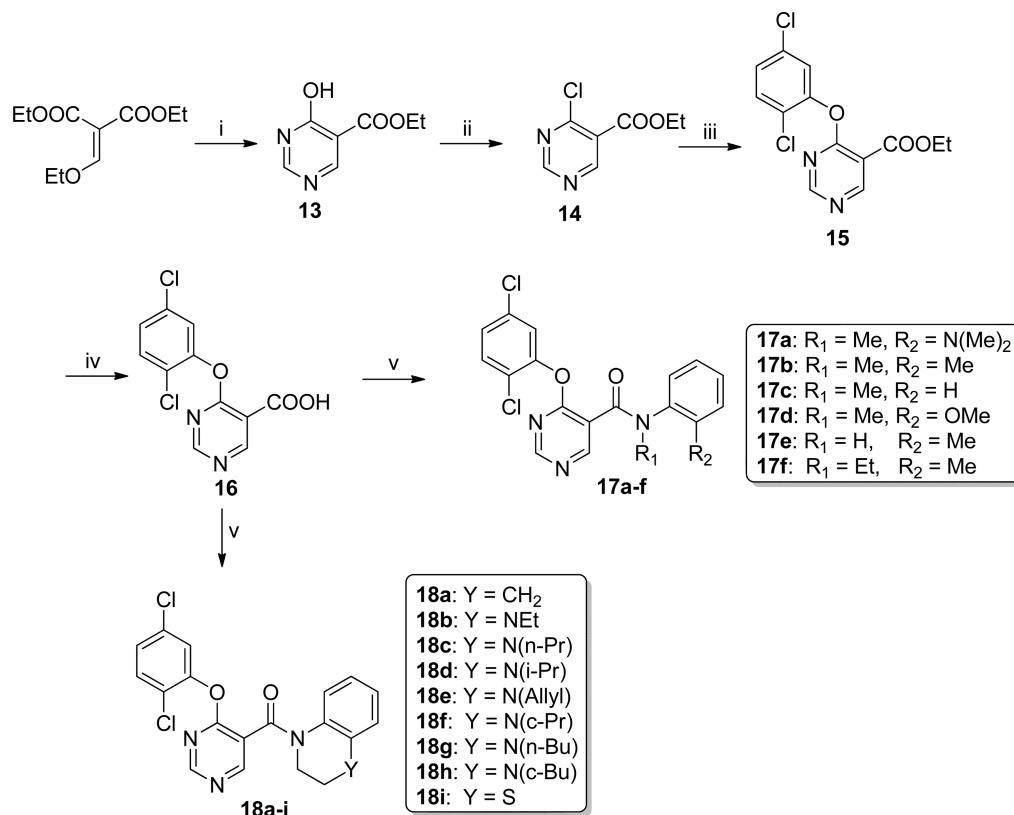**Scheme 2. Synthesis of 3-Phenoxypyridine-2-carboxamide and 3-Phenoxypyrimidine-4-carboxamide Derivatives[a]**
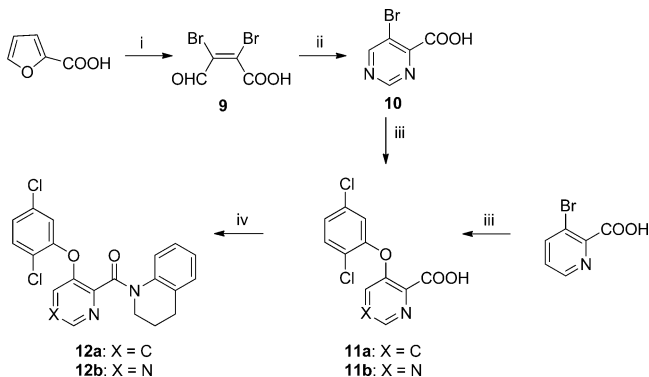


[a]Reagents and conditions: (i) Br$_2$, H$_2$O, reflux, 57%; (ii) formamidine, Na, EtOH, rt, 52%; (iii) 2,5-dichlorophenol, CuI, K$_3$PO$_4$, picolinic acid, DMF, reflux; (iv) (COCl)$_2$, Et$_3$N, tetrahydroquinoline, rt, 30−50% for steps iii and iv.

route described above. As shown in Scheme 3, condensation of diethyl 2-(ethoxymethylene)malonate and formamidine in the presence of sodium ethoxide in ethanol provided the pyrimidine intermediate (13) in 80% yield.[25] Compound 13 was chlorinated with phosphorus oxychloride in the presence of N,N-diisopropylethylamine using toluene as the solvent, and ethyl-4-chloropyrimidine-5-carboxylate (14),[26] an unstable compound at room temperature, was produced. Immediate reaction of compound 14 with 2,5-dichorophenol in DMF containing sodium hydride at room temperature afforded compound 15 in 55% yield,[27] and subsequent hydrolysis of the ester (15) using sodium hydroxide provided the corresponding carboxylic acid (16) in 95% yield. Next, acid 16 was condensed with a variety of substituted anilines, which were commercially available or prepared according to previously published procedures,[19,28] via the acyl chloride formation to produce the final 4-phenoxypyrimidine-5-carboxamide derivatives (17a−f, 18a−i) in yields ranging from 45 to 60%. Scheme 4 shows the synthetic strategy for the 4-phenoxynicotinamide derivatives. First, 4-chloronicotinic acid was converted into the acid chloride, and then it was esterified with ethanol to provide ethyl 4-chloronicotinate (19). The reaction of compound 19 with a series of phenols in DMF containing potassium carbonate at 100 °C for several hours produced the corresponding ethyl 4-phenoxynicotinate analogues in good yields. After ester hydrolysis with sodium hydroxide at room temperature, the desired acids (21a−k) were produced. The obtained acids were converted into acid chlorides by treatment with oxalyl chloride, and then they were reacted with various substituted anilines to provide the final compounds (22a−h, 23a−j) in yields ranging from 50 to 75%. Analogues 23k and 23l were prepared from 23j through a Pd(dppf)Cl$_2$·CH$_2$Cl$_2$-catalyzed Negishi cross-coupling reaction with organozinc reagents in yields ranging from 75 to 80%.[29]

## ■ RESULTS AND DISCUSSION

Rapid exploration of the substitution patterns at the two phenyl rings of these compounds was carried out via parallel chemistry. Starting from 18a and 22a, our initial effort was aimed at identifying suitable cyclic anilines as depicted in Table 2 to

**Scheme 3. Synthesis of 4-Phenoxypyrimidine-5-carboxamide Derivatives**[a]



17a: $R_1$ = Me, $R_2$ = N(Me)$_2$
17b: $R_1$ = Me, $R_2$ = Me
17c: $R_1$ = Me, $R_2$ = H
17d: $R_1$ = Me, $R_2$ = OMe
17e: $R_1$ = H, $R_2$ = Me
17f: $R_1$ = Et, $R_2$ = Me

18a: Y = CH$_2$
18b: Y = NEt
18c: Y = N(n-Pr)
18d: Y = N(i-Pr)
18e: Y = N(Allyl)
18f: Y = N(c-Pr)
18g: Y = N(n-Bu)
18h: Y = N(c-Bu)
18i: Y = S

[a]Reagents and conditions: (i) formamidine, Na, EtOH, rt, 80%; (ii) POCl$_3$, DIPEA, toluene, 80 °C; (iii) 2,5-dichlorophenol, NaH, DMF, rt, 55% for steps ii and iii; (iv) NaOH, MeOH, H$_2$O, rt, 95%; (v) (COCl)$_2$, Et$_3$N, aniline series, rt, 45−60%.

replace the piperidine ring and exploring the structure−activity relationship (SAR) around the aniline moiety. Compounds with a morpholine ring (**22b**) or a thiomorpholine ring (**18i**) had slightly less TGR5 agonist activity than the lead compounds **22a** and **18a**. Pleasingly, the N-substituted piperazine series exhibited a dramatic improvement in potency compared with the piperidine derivatives. Introduction of a cyclopropyl group to position 4 of the piperazine ring provided the potent compounds **18f** and **22g**, with EC$_{50}$ values of 2.9 and 1.5 nM on hTGR5, respectively. For the piperazine series, a larger substituent such as the *n*-propyl group (**18c**, **22d**) was not desirable compared to a smaller group such as the cyclopropyl group (**18f**). Compounds with larger substituents such as isopropyl (**18d**, **22e**) and *n*-butyl (**18g**) were poor agonists. For example, the isopropyl derivative **18d** displayed an EC$_{50}$ value of only 710 nM on hTGR5, suggesting that large groups were harmful to the interaction of the compound with the receptor.

Next, the 2-substituted *N*-methylaniline series, which comprised some ring-opening derivatives, were prepared to evaluate the importance of the cyclic structure of the aniline moiety to the TGR5 agonist activity (Table 3). Acyclic *N,N,N′*-trimethyl-1,2-diaminobenzene analogue **17a**, the direct piperazine ring-opened compound, lost its potency completely, suggesting that the *N,N*-dimethyl substituent formed by piperazine ring-opening may drastically change the spatial configuration of the molecule. Next, we substituted the *N,N*-dimethyl group of **17a** with some other smaller groups, and moderate activity was observed with analogues carrying an array of substituents such as a methyl group (**17b**), methoxy group

(**17d**), and chloro group (**17g**). For this 2-substituted *N*-methylaniline series, the *N*-methyl group was necessary for the activity, and either a hydrogen atom (**17e**) or an ethyl group (**17f**) introduced here to replace the methyl group led to inactive analogues (**17e** vs **17b**, **17f** vs **17b**). The decreased activity of ring-opening derivatives compared to the ring analogues demonstrated that the restricted conformation provided by the piperidine/piperazine rings was critical for the activity.

Table 2 shows that the 4-phenoxynicotinamide series was more potent as TGR5 agonists than the 4-phenoxypyrimidine-5-carboxamide series when the upper phenyl ring and the aniline moiety had the same substitutents (**18b** vs **22c**, **18c** vs **22d**, **18d** vs **22e**, **18e** vs **22f**, and **18h** vs **22h**). Thus, the 4-phenoxynicotinamide series was selected for further optimization, and the favored 4-cyclopropylpiperidine group for the amide moiety was kept intact. Then we turned our attention toward modification of the upper phenoxy moiety (Table 4). Compound **23a** with an unsubstituted upper phenyl ring was designed and prepared first, and it showed moderate agonist activity on hTGR5 (EC$_{50}$ = 47 nM). The introduction of several substituents to the upper phenyl ring indicated that a variety of groups were well tolerated at this position. The 3-chlorine derivative (**23c**) was slightly more potent compared with the unsubstituted derivative (**23a**). The further improved potency of the 2,5-dichloro derivative (**22g**) indicated that the chloro substituent may induce a positive influence on the activity. Therefore, a third chloro group was introduced, and the 2,4,5-trichloro-substituted compound (**23h**) was prepared to further investigate the SAR. As we anticipated, this trichloro
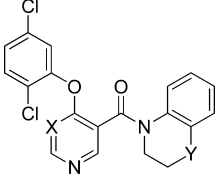
**Scheme 4. Synthesis of 4-Phenoxynicotinamide Derivatives$^a$**
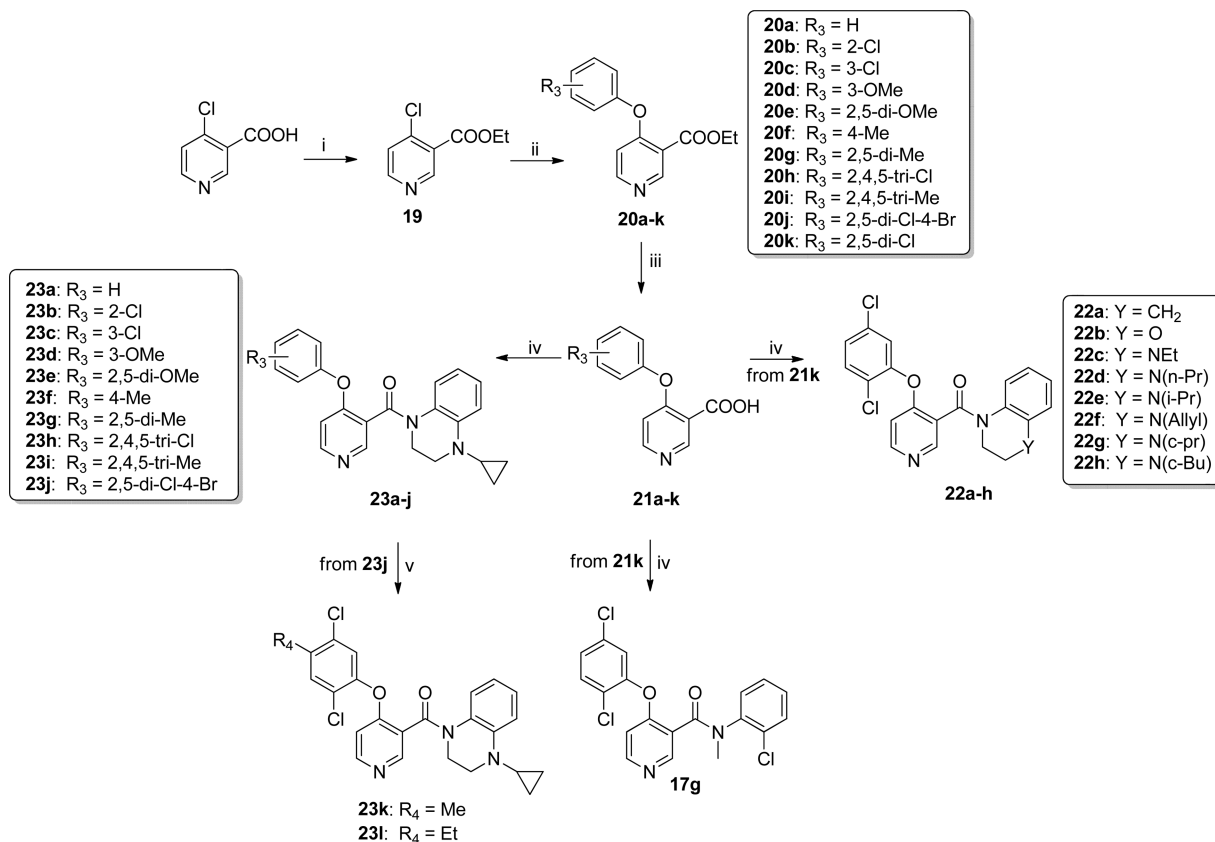


$^a$Reagents and conditions: (i) $SOCl_2$, EtOH, rt, 81%; (ii) 2,5-dichlorophenol, $K_2CO_3$, DMF, 100 °C, 65−80%; (iii) NaOH, MeOH, $H_2O$, rt; (iv) $(COCl)_2$, $Et_3N$, aniline series, rt, 50−75% for steps iii and iv; (v) $Zn(R_4)_2$, $Pd(dppf)Cl_2·CH_2Cl_2$, 1,4-dioxane, reflux, 75−80%.

analogue exhibited excellent agonist activity on both hTGR5 ($EC_{50}$ = 0.46 nM) and mTGR5 ($EC_{50}$ = 2.0 nM).

Previous studies have shown that because TGR5 activation on the gallbladder causes smooth muscle relaxation and promotes gallbladder filling, compound **1** would obviously increase the gallbladder volume. After intraperitoneal (ip) injection of compound **1** (60 mg/kg) into normal mice, the gallbladder volume increased approximately 1-fold, and obvious side effects of the gallbladder were observed.[30] Likewise, other TGR5 agonists can induce similar gallbladder symptoms, indicating a severe problem in developing TGR5 agonists as drugs for the treatment of T2DM.[30] Therefore, the search for novel TGR5 agonists without gallbladder toxicity is a challenge. However, owing to the high expression level of TGR5 in the gallbladder and the relatively low expression level in the intestine, once the agonist that activated TGR5 in the intestine is exposed to the systemic plasma, TGR5 in the gallbladder would also be activated inevitably, gallbladder filling would be stimulated, and the side effect would appear. This hypothesis suggests that only by low-systemic or nonsystemic TGR5 agonist administration that exclusively activates TGR5 in the intestine rather than TGR5 in the gallbladder can gallbladder toxicity be avoided. Considering that TGR5 is distributed in the intestine and that GLP-1 is also secreted from intestinal L-cells, a local intracolonic mechanism for TGR5-stimulated GLP-1 release may be possible for a TGR5 agonist to lower blood glucose levels.[13,18] Consequently, preparing some easily metabolized TGR5 agonists would be a good strategy to activate TGR5 in the intestine and lower the blood glucose
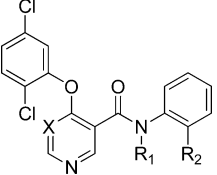
level, as well as avoid gallbladder toxicity. This type of locally acting agonist can be metabolized by a first-pass effect from the liver after stimulating TGR5 in the intestine; hence, the low plasma exposure of the compound would no longer activate TGR5 in the gallbladder and the gallbladder side effect would be avoided. Furthermore, considering that the safety requirement for antidiabetic drugs is very high because most T2DM patients need life-long continuous treatment to maintain normal or near-normal glycemic control, a TGR5 agonist with low plasma exposure would also be beneficial to prevent some other potential side effects in the long-term course of medication.

In the development of sulfonylureas as antidiabetic agents, to improve the metabolic stability, the methyl group of tolbutamide was substituted with a chloro group, and chlorpropamide, with a lower metabolic clearance rate and a longer half-life, was obtained.[31] Encouraged by the fact that the chloro group was less prone to metabolization compared to the methyl group, although the chloro substituent was beneficial for the activity, the labile methyl group was introduced to replace the chloro group to decrease the metabolic stability of the molecule. Consequently, the 2,5-dimethyl analogue (**23g**) was designed to accelerate the metabolism and maintain its TGR5 agonist activity. Pleasingly, **23g** displayed excellent potency both on hTGR5 ($EC_{50}$ = 0.72 nM) and mTGR5 ($EC_{50}$ = 6.2 nM). In addition, considering that the chloro group as an electron-withdrawing group likely reduced oxidation of the phenyl ring[32,33] and glucuronidation of phenolic hydroxyl groups,[34] some electron-donating groups were introduced. The

**Table 2. In Vitro Activity of 18a−i and 22a−h[a]**



| Compd | X | Y | hTGR5 EC$_{50}$ (nM) | mTGR5 EC$_{50}$ (nM) |
|---|---|---|---|---|
| 18a | N | CH$_2$ | 156 ± 29 | – |
| 18b | N | N— | 20 ± 1.0 | – |
| 18c | N | N— | 30 ± 3.0 | – |
| 18d | N | N— | 710 ± 100 | – |
| 18e | N | N— | 30 ± 1.0 | – |
| 18f | N | N— | 2.9 ± 0.43 | 30 ± 4.2 |
| 18g | N | N— | 590 ± 123 | – |
| 18h | N | N— | 23 ± 5.3 | – |
| 18i | N | S | 164 ± 13 | – |
| 22a | C | CH$_2$ | 49 ± 8.3 | – |
| 22b | C | O | 127 ± 14 | – |
| 22c | C | N— | 3.1 ± 0.24 | 24 ± 0.6 |
| 22d | C | N— | 7.1 ± 0.72 | 76 ± 4.3 |
| 22e | C | N— | 69 ± 9.4 | – |
| 22f | C | N— | 6.2 ± 0.62 | 66 ± 10.9 |
| 22g | C | N— | 1.5 ± 0.21 | 18 ± 1.1 |
| 22h | C | N— | 2.8 ± 0.15 | 31 ± 1.2 |

[a]EC$_{50}$ values given are expressed as the mean ± SEM of three independent experiments. −, not tested.
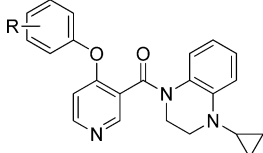
**Table 3. In Vitro Activity of Compounds 17a−g[a]**



| compd | X | R$_1$ | R$_2$ | hTGR5 EC$_{50}$ (nM) |
|---|---|---|---|---|
| 17a | N | Me | N(Me)$_2$ | 3711 ± 543 |
| 17b | N | Me | Me | 535 ± 46 |
| 17c | N | Me | H | 3151 ± 410 |
| 17d | N | Me | OMe | 160 ± 23 |
| 17e | N | H | Me | >10000 |
| 17f | N | Et | Me | 4886 ± 1448 |
| 17g | C | Me | Cl | 451 ± 19 |

[a]EC$_{50}$ values given are expressed as the mean ± SEM of three independent experiments.

3-methoxy derivative (**23d**) and the 2,5-dimethoxy derivative (**23e**) both exhibited an EC$_{50}$ value of 12 nM on hTGR5, which is a 4-fold improvement in affinity compared with the unsubstituted compound (**23a**) but a slightly lower potency compared to the 2,5-dichloro derivative (**22g**). Considering that the methyl derivative possesses better potency than the chloro analogue, the excellent activity of the 2,4,5-trichloro-substituted compound (**23h**) encouraged us to produce some additional 2,4,5-trisubstituted analogues. The 2,5-dichloro-4-methyl (**23k**), 2,5-dichloro-4-ethyl (**23l**), and 2,4,5-trimethyl (**23i**) derivatives all exhibited high activity on hTGR5 with EC$_{50}$ values <1 nM, suggesting that 2,4,5-trisubstituted analogues are a series of potent TGR5 agonists.

hTGR5 shares only 83% amino acid identity with that in mouse,[6] and the potency of the reported compounds on mTGR5 was usually less than that on hTGR5.[17] The in vitro activity on mTGR5 was also vital to the study. A previous paper has indicated that the weak potency on mTGR5 may affect the in vivo activity measurement.[17] Therefore, our compounds with

**Table 4. In Vitro Activity of 22g, 23a−i,k,l[a]**



| compd | R | hTGR5 EC$_{50}$ (nM) | mTGR5 EC$_{50}$ (nM) | FXR (% effect at 10 μM) |
|---|---|---|---|---|
| 22g | 2, 5-di-Cl | 1.5 ± 0.21 | 18 ± 1.1 | − |
| 23a | H | 47 ± 7.3 | − | − |
| 23b | 2-Cl | 27 ± 3.7 | 30 ± 5.7 | − |
| 23c | 3-Cl | 7.9 ± 0.09 | 31 ± 2.0 | − |
| 23d | 3-OMe | 12 ± 1.8 | 26 ± 3.0 | −1.1 |
| 23e | 2,5-di-OMe | 12 ± 1.5 | − | − |
| 23f | 4-Me | 12 ± 1.2 | 15 ± 1.9 | − |
| 23g | 2,5-di-Me | 0.72 ± 0.08 | 6.2 ± 1.51 | −3.0 |
| 23h | 2,4,5-tri-Cl | 0.46 ± 0.03 | 2.0 ± 0.30 | 5.0 |
| 23i | 2,4,5-tri-Me | 0.60 ± 0.10 | 2.1 ± 0.89 | 1.4 |
| 23k | 2,5-di-Cl-4-Me | 0.31 ± 0.04 | 0.98 ± 0.19 | 3.8 |
| 23l | 2,5-di-Cl-4-Et | 0.72 ± 0.07 | 2.3 ± 0.60 | 0.4 |

[a]EC$_{50}$ values given are expressed as the mean ± SEM of three independent experiments. −, not tested.

high activity on hTGR5 were selected for the mTGR5 activity study. As shown in Tables 2 and 4, most compounds tested displayed high agonist activities on mTGR5. In particular, the EC$_{50}$ values of the 2,4,5-trisubstituted series compounds 23h, 23i, 23k, and 23l were only 2.0, 2.1, 0.98, and 2.3 nM on mTGR5, respectively, making them the most potent mTGR5 agonists ever reported.

Because many bile acid derived TGR5 agonists can also activate the nuclear BA receptor FXR,[15] the selectivity versus FXR of our compounds with potent TGR5 activity was also measured. As shown in Table 4, all of the tested TGR5 agonists exhibited no obvious activity against FXR.

Among all of the compounds we prepared, the dimethyl analogue (23g), with an EC$_{50}$ of 0.72 nM on hTGR5 and an EC$_{50}$ of 6.2 nM on mTGR5, attracted most of our attention, not only for its excellent in vitro activity and good selectivity versus FXR but also for the dimethyl group introduced here. Compound 23g was selected to carry out a further pharmacokinetic evaluation. The in vivo pharmacokinetic study in rats revealed that 23g exhibited rather low plasma exposure, with a $C_{max}$ value of 56 ng/mL and a $t_{1/2}$ value of 1.5 h at an oral dose of 5 mg/kg (Table 5). We supposed that the intestinal exposure of 23g after oral dosing may be sufficient to activate TGR5 in the intestine and thus increase GLP-1 secretion and lower the blood glucose level, and the low systemic exposure of 23g may prevent side effects to the gallbladder.

To test the hypothesis that low systemic exposure of the TGR5 agonist can stimulate GLP-1 secretion,[18] compound 23g was used in an in vivo GLP-1 secretion study in imprinting

control region (ICR) mice. A single oral administration of 23g at doses of 25, 50, and 100 mg/kg increased the plasma active GLP-1 levels by 31, 96, and 282% of vehicle control, respectively (Figure 3). Just as we anticipated, significant
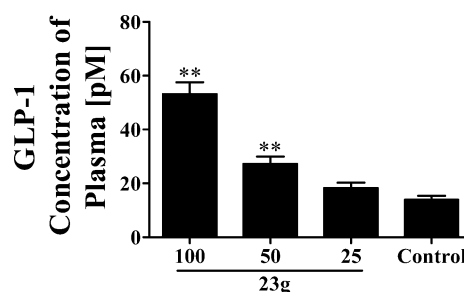


**Figure 3.** GLP-1 secretion study of 23g in ICR mice. The numbers 100, 50, and 25 correspond to doses of 100, 50, and 25 mg/kg of 23g. Compound 23g or 0.25% CMC (vehicle control) was orally administered to ICR mice ($n$ = 10 animals/group) 1 h prior to the oral glucose load (4 g/kg). The blood samples were collected 5 min after the glucose load and placed in Eppendorf tubes containing the DPP-IV inhibitor valine pyrrolidide with final concentrations of 1% blood samples and 25 mg/mL EDTA to measure serum active GLP-1[7-36 amide] levels. (∗∗) $P$ < 0.01 versus control. Error bar indicates SEM.

GLP-1 secretion elevation was observed with 23g administration. Compound 23g was further tested on several other GPCRs that can also stimulate GLP-1 secretion, such as GPR40, GPR119, and GPR120.[35] It was found to exhibit no significant affinity to these targets.

Compound 23g caused elevated plasma levels of GLP-1, and a high concentration of GLP-1 could possibly lower blood glucose levels. Accordingly, the favorable GLP-1 secretion result encouraged us to further evaluate the in vivo glucose-lowering activity with an oral glucose tolerance test (OGTT) in ICR mice. The areas under the curve (AUC)$_{0-120\ min}$ for glucose levels versus time were calculated after a single oral administration of 23g (50 mg/kg), and it was found to cause a 49% reduction in blood glucose AUC$_{0-120\ min}$ compared with the vehicle control group (Figure 4).

Next, to assess the in vivo efficacy further, the hypoglycemic effect of 23g was tested in the *db/db* mouse model, a genetic T2DM rodent model characterized by obesity, severe insulin resistance, and marked hyperglycemia. After a single oral dose of 23g (50 mg/kg), a significant blood glucose reduction at 4, 6, 10, and 24 h was achieved in *db/db* mice compared with the vehicle control group (Figure 5).

Unfortunately, a single oral administration of 23g (50 mg/kg) to ICR mice caused an increase of the gallbladder volume by 231% (Figure 6). This unfavorable result prompted us to analyze the drug levels of 23g. As shown in Table 6, after an oral administration of 23g (50 mg/kg), the $C_{max}$ values of 23g in the plasma, bile, and gallbladder tissue were 1455 ng/mL (3.6 μM), 1496 ng/mL (3.7 μM), and 523 ng/g, respectively. The $C_{max}$ values of 23g in the plasma and bile of the gallbladder were 581- and 597-fold greater than the mTGR5 EC$_{50}$,

**Table 5. Pharmacokinetic Properties of 23g after Oral Administration to Rats[a]**

| compd | $T_{max}$ (h) | $C_{max}$ (ng/mL) | AUC$_{0-t}$ (ng·h/mL) | AUC$_{0-\infty}$ (ng·h/mL) | MRT (h) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| 23g | 0.9 ± 0.3 | 56 ± 18 | 147 ± 31 | 155 ± 33 | 2.4 ± 0.3 | 1.5 ± 0.4 |

[a]$n$ = 4 animals/group; male SD rats; po, 5 mg/kg; formulated in 0.9% sodium chloride.
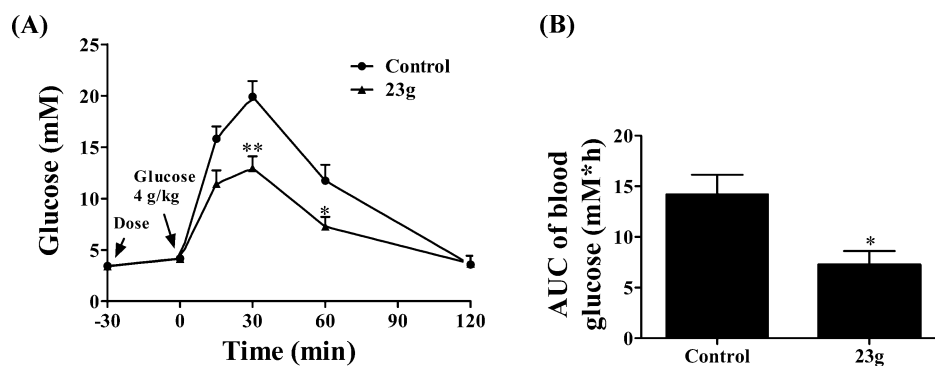
**(A)**



**(B)**



**Figure 4.** Effect of **23g** on OGTT in ICR mice: (A) blood glucose; (B) blood glucose $AUC_{0-120\ min}$. Compound **23g** (50 mg/kg) or 0.25% CMC (vehicle control) was administered orally to ICR mice at 0.5 h prior to oral glucose load (4.0 g/kg). Blood glucose levels were measured before and after glucose load. $n = 7-8$ animals/group. ($*$) $P < 0.05$; ($**$) $P < 0.01$ versus control. Error bar indicates SEM.
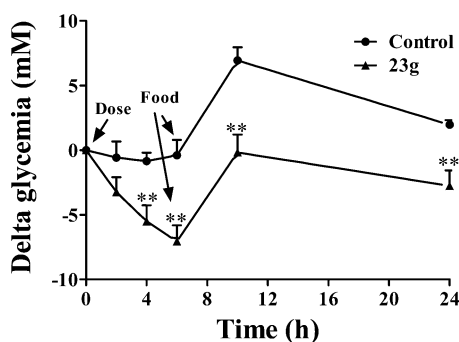


**Figure 5.** Effects of **23g** on blood glucose levels in *db/db* mice ($n = 8$ animals/group). Compound **23g** (50 mg/kg) or 0.25% CMC (vehicle control) was orally administered to 2 h fasted mice, and blood glucose was measured at 0, 2, 4, 6, 10, and 24 h after dosing. The animals were refed at 6 h after dosing. Delta blood glucose reflects changes in blood glucose levels from time 0 h within each experimental group. ($**$) $P < 0.01$ versus control. Error bar indicates SEM.
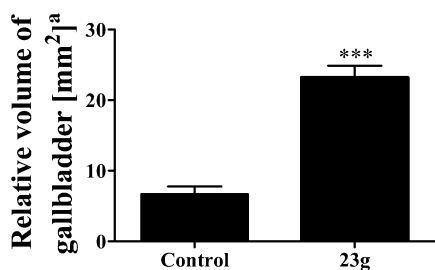


**Figure 6.** Relative volume of the gallbladder after compound **23g** (50 mg/kg) or 0.25% CMC (vehicle) was orally administered to ICR mice ($n = 7-8$ animals/group). After the OGTT experiment, the fasting mice were refed for 2 h. Then, the gallbladders were removed, and the volume was measured using a vernier caliper. The relative volume of the gallbladder was measured by the length of the gallbladder multiplied by the width of the gallbladder. ($***$) $P < 0.001$ versus control. Error bar indicates SEM.

respectively. The concentration of **23g** exposed to the gallbladder was sufficient to activate TGR5 in the gallbladder.

## CONCLUSIONS

A variety of 4-phenoxynicotinamide and 4-phenoxypyrimidine-5-carboxamide derivatives as a series of potent and selective TGR5 agonists were designed and synthesized. The $EC_{50}$ values of some 4-phenoxynicotinamide derivatives on both hTGR5 and mTGR5 were <1 nM. Compound **23g**, with an

**Table 6. Drug Levels of Compound 23g in Plasma, Bile, and Gallbladder Tissue after Oral Administration to ICR Mice**[a]

| time (h) | sampling location | | |
| --- | --- | --- | --- |
| | plasma (ng/mL) | bile (ng/mL) | gallbladder tissue (ng/g) |
| 0.5 | 1243 (3.1 $\mu$M) | 677 (1.7 $\mu$M) | 294 |
| 1 | 936 (2.3 $\mu$M) | 839 (2.1 $\mu$M) | 393 |
| 2.5 | 783 (2.0 $\mu$M) | 804 (2.0 $\mu$M) | 306 |
| 4.5 | 205 (0.51 $\mu$M) | 792 (2.0 $\mu$M) | 217 |
| $AUC_{0-4.5\ h}$ (ng·h·mL$^{-1}$) | 3132 | 3376 | 1292 |

[a]Compound **23g** was orally administered at 50 mg/kg to ICR mice. Four animals were used at each time point.

$EC_{50}$ value of 0.72 nM on hTGR5 and an $EC_{50}$ value of 6.2 nM on mTGR5, was selected as a potential candidate to execute further in vivo studies. An in vivo glucose-lowering study indicated that a single oral dose of **23g** (50 mg/kg) could significantly reduce blood glucose levels in *db/db* mice and cause a 49% reduction of blood glucose $AUC_{0-120\ min}$ following an OGTT in ICR mice. However, after oral administration of **23g** (50 mg/kg) to ICR mice, **23g** was obviously observed in the gallbladder, and the volume of the gallbladder increased about 231%. Consequently, a much lower systemic exposure or even a nonsystemic exposure may be necessary for the development of a nontoxic TGR5 agonist. Because few in vivo activity and gallbladder data have been published regarding this target, **23g**, with its oral efficacy and gallbladder side effect data demonstrated here, provides a good foundation for further studies on TGR5 agonists. Further studies on oral nonabsorbed TGR5 agonists without systemic exposure are now underway, and the research results will be delivered in the near future.

## EXPERIMENTAL SECTION

**In Vitro TGR5 Assay.** hTGR5/CRE/HEK293 or mTGR5/CRE/HEK293 stable cell line was obtained by transfection of HEK293 cells with human or mouse TGR5 expression plasmid (hTGR5-pcDNA3.1 or mTGR5-pcDNA3.1) and CRE-driven luciferase reporter plasmid (pGL4.29, Promega, Madison, WI, USA) and employed to assess the activity of test compounds by reporter gene assay. Briefly, cells were seeded into 96-well plates and incubated overnight in DMEM supplemented with 10% FBS in 5% $CO_2$ at 37 °C. Then, cells were incubated with fresh medium containing different concentrations of test compounds or 20 $\mu$M compound **1** as a positive control for 5.5 h. Luciferase activity in cell lysate was determined using the Steady-Glo Luciferase Assay System (Promega) according to the manufacturer's instructions.

**FXR Assay.** FXR activation was tested using a LanthaScreen TR-FRET Farnesoid X Receptor Coactivator Assay Kit. All of the procedures followed the manufacturer's instructions. Efficacy (effect % at 10 $\mu$M) was calculated as effect % of 10 $\mu$M GW4064.

**Animals.** Male ICR mice were purchased from the Shanghai SLAC Laboratory Animal Co. Ltd. (Shanghai, China). B6.Cg-m +/+ $Lepr^{db}$/J ($db/db$) mice (from Jackson Laboratory, Bar Harbor, ME, USA) were bred at the Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences. The animals were maintained under a 12 h light−dark cycle with free access to water and food. Animal experiments were approved by the Animal Care and Use Committee, Shanghai Institute of Materia Medica, Chinese Academy of Sciences.

**GLP-1 Secretion in ICR Mice.** To examine the in vivo effect of compound **23g** on GLP-1 secretion, 25, 50, or 100 mg/kg compound **23g** was administered orally to overnight-fasted ICR mice ($n$ = 10 animals/group). One hour later, all of the mice were challenged with 4 g/kg glucose, and blood samples were collected at 5 min after the glucose load and placed in Eppendorf tubes containing the DPP-IV inhibitor valine pyrrolidide (Linco Research, DPP-IV-010) with a final concentration of 1% blood samples and 25 mg/mL EDTA to measure serum active GLP-1[7-36 amide] levels.

**Oral Glucose Tolerance Test (OGTT) and Gallbladder Volume Measurement in ICR Mice.** To examine the acute effect of compounds on blood glucose after an oral glucose challenge, 50 mg/kg of test compounds or vehicle (0.25% CMC) was administered orally to overnight-fasted ICR mice ($n$ = 7−8 mice/group) 30 min prior to the oral glucose load (4 g/kg). Blood glucose levels were measured via blood drops obtained by clipping the tail of the mice using an Accu-Chek Advantage II Glucose Monitor (Roche, Indianapolis, IN, USA) before compound dosing and 0, 15, 30, 60, and 120 min after the glucose load. The area under the concentration−time curve from 0 to 120 min ($AUC_{0−120\ min,\ Glu}$) of blood glucose after the glucose load was calculated by the trapezoidal rule (using the 0 time glucose level for each animal as that animal's baseline). After the OGTT experiment, the fasting mice were refed for 2 h. Then, gallbladders were removed, and the volume was measured using vernier caliper.

**Acute Efficacy in *db/db* Mice.** Seven-week-old *db/db* mice were divided into two groups ($n$ = 8 mice/group) based on nonfasting and 6 h fasting blood glucose and body weight. Compound **23g** (50 mg/kg) or 0.25% CMC (vehicle) was orally administered to 2 h fasted mice, and blood glucose was measured at 2, 4, 6, 10, and 24 h after dosing. The animals were refed at 6 h after dosing. Delta blood glucose values were calculated by the changes in blood glucose values from time 0 h within each experimental group.

**Drug Levels Test in Plasma, Bile, and Gallbladder Tissue after Oral Administration to ICR Mice.** Plasma, bile, and gallbladder were taken from experiments performed in accordance with the guidelines for the use of experimental animals in the Shanghai Laboratory Animal Administration (Shanghai, China). Compound **23g** (50 mg/kg) was administered orally to male ICR mice. Four animals were used per time point, and the time points collected were 0.5, 1.0, 2.5, and 4.5 h after oral administration. Blood samples were collected through cardiac puncture into heparinized tubes, and plasma was harvested by centrifugation. Bile and gallbladder tissue were collected from each mouse after blood withdrawal. To 10 mg of gallbladder was added 100 $\mu$L of methanol, and the mixture was homogenized. A 15 $\mu$L aliquot of bile samples was diluted with 100 $\mu$L of methanol and then mixed. Plasma, bile, and tissue homogenate were stored at −20 °C. These samples were protein precipitated with acetonitrile using clopidogrel as the internal standard, and the supernatant was injected onto a LC-MS/MS system for the quantification of **23g**. Chromatographic separation was performed on a Luna $C_{18}$ column (50 mm × 2.0 mm i.d., 5 $\mu$m, Phenomenex, Torrance, CA, USA) using 5 mM ammonium acetate and acetonitrile (1:1, v/v) containing 0.02% formic acid as the mobile phase, which was delivered at a flow rate of 0.8 mL min$^{-1}$. The MS detection was carried out in multiple reaction monitoring mode using a positive electrospray ionization interface. The calibration curve of **23g** was established from 3.0 to 3000 ng/mL for plasma and bile and from 3.0 to 3000 ng/g for gallbladder tissue.

To confirm accuracy, quality control samples were analyzed in duplicate at three different concentrations. The bioanalytical run met the acceptance criteria, which require that at least three-fourths of the calibration standards were within 15% of theoretical and that greater than two-thirds of all quality control samples were within 15% of theoretical.

**Statistical Analysis.** All data were expressed as the mean ± SEM. The statistical analysis between two groups was performed using an unpaired Student's $t$ test. $P$ < 0.05 was considered to be statistically significant.

**Synthetic Materials and Methods.** All reagents were purchased from commercial suppliers and used without further purification. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker AC300 or a Bruker AC400 NMR spectrometer using tetramethylsilane as an internal reference. ESI-MS spectra were obtained on a Krats MS 80 mass spectrometer. The purity of tested compounds was determined by HPLC (Agilent LC1260, Agilent ChemStation, Agilent Eclipse XDB-C18, 5 $\mu$M, 4.6 × 150 mm, UV 254 nM, 30 °C, flow rate = 1.0 mL min$^{-1}$). All of the assayed compounds possess >95% purity. Column chromatography was performed on silica gel (200−300 mesh).

*Ethyl 4-Hydroxypyrimidine-5-carboxylate (13).* Sodium metal (1.6 g, 70 mmol) was added to 50 mL of absolute ethanol. After the reaction was complete, the solution was cooled in an ice bath. Formamidine acetate (7.3 g, 70 mmol) was added to the mixed solution, and diethyl 2-(ethoxymethylene)malonate (15.1 g, 70 mmol) was added dropwise to the mixture. The reaction was stirred under 0 °C for 3 h. Then a solution of sodium ethoxide obtained from sodium (1.6 g, 70 mmol) in 50 mL of anhydrous ethanol was added slowly into the above solution, and the mixed solution was stirred at room temperature overnight. After the reaction was complete, most of the ethanol was evaporated and the residue was dissolved in hot water (100 mL). The solution was cooled to room temperature and washed with ether (100 mL). The pH of aqueous layer was adjusted to 3 with concentrated hydrochloric acid, and a light yellow solid was formed. The resulting suspension was filtered, and **13** as a light yellow solid was obtained (9.4 g, 80%). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.82 (s, 1H), 8.56 (s, 1H), 4.42 (q, $J$ = 5.4 Hz, 2H), 1.42 (t, $J$ = 5.4 Hz, 3H). LC-MS (ESI+): 169 (M + H)$^+$.

*Ethyl 4-(2,5-Dichlorophenoxy)pyrimidine-5-carboxylate (15).* To a solution of **13** (3 g, 17.6 mmol) in 35 mL of toluene was added slowly in portions phosphorus oxychloride (1.8 mL, 19.6 mmol), and then *N,N*-diisopropylethylamine (3.4 mL, 19.6 mmol) was added dropwise. The mixed reaction was heated at 80 °C for 1 h. After the reaction was complete, the solution was cooled to room temperature and poured into ice water (50 mL) to quench the reaction and extracted with ethyl acetate (50 mL × 3). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified with flash column chromatography to yield **14**, an unstable colorless liquid (2.4 g, 72%). The product was taken on to the next reaction immediately. To the solution of 2,5-dichlorophenol (2.1 g, 12.84 mmol) in anhydrous DMF (20 mL) was added slowly sodium hydride (650 mg, 16.06 mmol) under an ice bath. After the suspension was stirred for 0.5 h at this temperature, **14** (2.0 g, 10.7 mmol) was added into the solution. The reaction was moved to room temperature and stirred for 2 h. After the reaction was complete, the solution was poured into ice water (100 mL) and extracted with ethyl acetate (50 mL × 3). The organic layers were combined, washed with brine (100 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified with flash column chromatography (petroleum/ethyl acetate = 4:1) to yield **15** (2.2 g, 55%). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.18 (s, 1H), 8.79 (d, $J$ = 5.1 Hz, 1H), 7.43 (d, $J$ = 8.5 Hz, 1H), 7.30−7.22 (m, 3H), 4.55−4.36 (q, $J$ = 7.1 Hz, 2H), 1.43 (t, $J$ = 7.1 Hz, 3H). LC-MS (ESI+): 313 (M + H)$^+$.

*4-(2,5-Dichlorophenoxy)pyrimidine-5-carboxylate (16).* To a solution of **15** (1.0 g, 3.19 mmol) in H$_2$O (20 mL) and ethanol (20 mL) was added sodium hydroxide (192 mg, 4.79 mmol). The solution was stirred at ambient temperature for 0.5 h. After ethanol was

evaporated under vacuum, the pH of the residue aqueous layer was adjust to 4. The formed precipitate was filtered, washed with cold water, and dried under vacuum, providing **16** (0.87 g, 95%). $^1$H NMR (300 MHz, DMSO-$d_6$): δ 9.14 (s, 1H), 8.88 (s, 1H), 7.66−7.69 (m, 2H), 7.45 (dd, J = 8.4, 2.4 Hz, 1H). LC-MS (ESI−): 283 (M − H) $^-$.

**General Procedure for 17a–f, 18a–i. 16** (0.30 mmol) was dissolved in 2 mL of thionyl chloride, and the solution was refluxed for 1 h. After evaporation of the solvent, the residue was dissolved in toluene and evaporated to dryness three times. The residue was dissolved in dichloromethane, and corresponding aniline (0.27 mmol) and Et$_3$N (0.90 mmol) were added to the mixed solution slowly. After stirring at room temperature for 2 h, the reaction was washed with H$_2$O and brine and then dried over anhydrous sodium sulfate, and the solvent was removed under vacuum. After purification with flash column chromatography (petroleum/ethyl acetate = 4:1 to 1:1), the final compounds were obtained.

*4-(2,5-Dichlorophenoxy)-N-(2-dimethylamionphenyl)-N-methyl-5-pyrimidinecarboxamide (17a).* The title compound was obtained as an off-white solid from **16** and N,N,N′-trimethyl-1,2-diaminobenzene according to the general procedure in 68% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.66 (s, 1H), 8.50 (s, 1H), 7.36 (d, J = 8.7 Hz, 1H), 7.19 (m, 3H), 6.97 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 6.68 (s, 1H), 3.53 (s, 3H), 2.63 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 164.93, 162.76, 157.97, 157.84, 148.61, 148.34, 134.77, 132.72, 130.99, 130.89, 128.86, 128.76, 127.06, 125.84, 124.13, 122.08, 119.38, 119.09, 42.71, 36.72. HRMS (ESI+) m/z calcd for C$_{19}$H$_{15}$Cl$_2$N$_3$O$_2$Na (M + Na)$^+$ 439.0705, found 439.0677.

*4-(2,5-Dichlorophenoxy)-N-(2-methylphenyl)-N-methyl-5-pyrimidinecarboxamide (17b).* The title compound was obtained as an off-white solid from **16** and N,2-dimethylaniline according to the general procedure in 56% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.55 (s, 1H), 8.52 (s, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.22 (m, 1H), 7.21 (m, 2H), 7.11 (m, 2H), 6.83 (d, J = 2.4 Hz, 1H), 3.42 (s, 3H), 2.31 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 164.27, 163.08, 158.06, 156.73, 148.08, 141.19, 135.20, 133.00, 131.68, 131.08, 36.85, 17.79. HRMS (ESI+) m/z calcd for C$_{19}$H$_{15}$Cl$_2$N$_3$O$_2$Na (M + Na)$^+$ 410.0439, found 410.0448.

*4-(2,5-Dichlorophenoxy)-N-phenyl-N-methyl-5-pyrimidinecarboxamide (17c).* The title compound was obtained as an off-white solid from **16** and N-methylaniline according to the general procedure in 61% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.58 (s, 1H), 8.55 (s, 1H), 7.37 (d, J = 8.7 Hz, 1H), 7.28 (m, 2H), 7.18 (m, 3H), 6.71 (d, J = 1.8 Hz, 1H), 3.55 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.91, 162.86, 158.26, 157.65, 148.11, 142.87, 132.99, 131.00, 129.47, 127.72, 127.36, 126.86, 125.81, 124.03, 118.97, 37.62. HRMS (ESI+) m/z calcd for C$_{18}$H$_{13}$Cl$_2$N$_3$O$_2$Na (M + Na)$^+$ 396.0283, found 396.0297.

*4-(2,5-Dichlorophenoxy)-N-(2-methoxyphenyl)-N-methyl-5-pyrimidinecarboxamide (17d).* The title compound was obtained as an off-white solid from **16** and 2-methoxy-N-methylaniline according to the general procedure in 55% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.58 (s, 1H), 8.51 (s, 1H), 7.38 (d, J = 8.7 Hz, 1H), 7.18−7.26 (m, 3H), 6.80−6.90 (m, 3H), 3.79 (s, 3H), 3.40 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 164.73, 163.03, 158.07, 156.77, 154.32, 148.34, 132.92, 131.05, 129.95, 129.20, 127.25, 125.90, 124.09, 120.84, 119.17, 111.76, 55.39, 36.46. HRMS (ESI+) m/z calcd for C$_{19}$H$_{15}$Cl$_2$N$_3$O$_3$Na (M + Na)$^+$ 426.0388, found 426.0392.

*4-(2,5-Dichlorophenoxy)-N-(2-methylphenyl)-5-pyrimidinecarboxamide (17e).* The title compound was obtained as an off-white solid from **16** and N-methylaniline according to the general procedure in 49% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 9.55 (s, 1H), 9.16 (s, 1H), 8.84 (s, 1H), 8.19 (d, J = 8.1 Hz, 1H), 7.50 (dd, J = 8.1, 0.9 Hz, 1H), 7.37 (m, 1H), 7.33 (m, 1H), 7.22 (m, 1H), 7.13 (m, 1H), 2.29 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 164.24, 162.57, 160.00, 159.16, 147.39, 135.51, 133.68, 131.37, 130.54, 128.38, 128.25, 126.99, 125.46, 124.63, 122.43, 114.37, 17.90. HRMS (ESI+) m/z calcd for C$_{18}$H$_{13}$Cl$_2$N$_3$O$_2$Na (M + Na)$^+$ 396.0283, found 396.0291.

*4-(2,5-Dichlorophenoxy)-N-(2-methylphenyl)-N-ethyl-5-pyrimidinecarboxamide (17f).* The title compound was obtained as a light yellow solid from **16** and N-ethyl-2-methylaniline according to the general procedure in 59% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.51

(s, 2H), 7.39 (d, J = 8.1 Hz, 1H), 7.22 (m, 3H), 7.11 (m, 2H), 6.90 (d, J = 2.4 Hz, 1H), 4.38 (m, 1H), 3.45 (m, 1H), 2.30 (s, 3H), 1.25 (t, J = 7.5 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.83, 162.98, 158.03, 156.69, 148.17, 139.30, 135.56, 132.97, 131.63, 131.07, 129.90, 128.62, 127.33, 126.68, 125.85, 124.02, 119.27, 43.78, 17.90, 12.42. HRMS (ESI+) m/z calcd for C$_{20}$H$_{17}$Cl$_2$N$_3$O$_2$Na (M + Na)$^+$ 424.0596, found 424.0595.

*[4-(2,5-Dichlorophenoxy)pyrimidin-5-yl]-(3,4-dihydro-2H-quinolin-1-yl)methanone (18a).* The title compound was obtained as a light yellow solid from **16** and tetrahydroquinoline according to the general procedure in 52% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.91 (s, 1H), 8.70 (s, 1H), 7.35 (d, J = 6.6 Hz, 1H), 7.16 (m, 3H), 6.97 (s, 1H), 6.65 (m, 1H), 6.08 (m, 1H), 3.93 (m, 2H), 2.75 (m, 2H), 2.01 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.33, 162.48, 159.07, 158.62, 147.77, 138.42, 134.03, 132.85, 130.82, 128.68, 127.27, 126.06, 125.81, 125.59, 123.70, 123.51, 119.17, 43.55, 26.72, 23.76. HRMS (ESI+) m/z calcd for C$_{20}$H$_{15}$Cl$_2$N$_3$O$_2$Na (M + Na)$^+$ 422.0439, found 422.0433.

*[4-(2,5-Dichlorophenoxy)pyrimidin-5-yl]-(4-ethyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (18b).* The title compound was obtained from **16** and 1-ethyl-1,2,3,4-tetrahydroquinoxaline according to the general procedure in 56% yield. $^1$H NMR (300 MHz, CD$_3$OD): δ 7.13 (m, 1H), 7.05 (d, J = 5.7 Hz, 1H), 7.01 (d, J = 6.3 Hz, 1H), 6.85 (m, 1H), 3.50 (q, J = 5.4 Hz, 2H), 1.24 (t, J = 5.4 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 147.75, 138.75, 132.61, 130.88, 130.59, 128.79, 127.30, 126.93, 125.30, 124.19, 123.63, 123.50, 119.02, 114.66, 111.40, 48.09, 44.61, 39.82, 10.32. HRMS (ESI+) m/z calcd for C$_{21}$H$_{18}$Cl$_2$N$_4$O$_2$Na (M + Na)$^+$ 451.0705, found 451.0724.

*[4-(2,5-Dichlorophenoxy)pyrimidin-5-yl]-(4-propyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (18c).* The title compound was obtained as a brown solid from **16** and 1-propyl-1,2,3,4-tetrahydroquinoxaline according to the general procedure in 56% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.94 (s, 1H), 8.70 (s, 1H), 7.30 (d, J = 6.6 Hz, 1H), 7.12 (dd, J = 6.6, 1.5 Hz, 1H), 7.06 (td, J = 6.0 Hz, 1.2 Hz, 1H), 6.60 (d, J = 6.0 Hz, 1H), 6.45 (d, J = 6.0 Hz, 1H), 6.34 (t, J = 6.0 Hz, 1H), 5.96 (d, J = 1.5 Hz, 1H), 3.50 (s, 2H), 3.25 (m, 4H), 1.26 (m, 2H), 0.74 (t, J = 5.7 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 162.40, 162.20, 159.13, 158.91, 147.77, 139.01, 132.63, 130.53, 127.25, 126.93, 125.40, 124.00, 123.70, 123.46, 118.96, 114.58, 111.47, 52.31, 49.22, 39.68, 19.09, 11.26. HRMS (ESI+) m/z calcd for C$_{22}$H$_{20}$Cl$_2$N$_4$O$_2$Na (M + Na)$^+$ 465.0861, found 465.0848.

*[4-(2,5-Dichlorophenoxy)pyrimidin-5-yl]-(4-isopropyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (18d).* The title compound was obtained as a yellow solid from **16** and 1-isopropyl-1,2,3,4-tetrahydroquinoxaline according to the general procedure in 56% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.92 (s, 1H), 8.70 (s, 1H), 7.30 (d, J = 6.6 Hz, 1H), 7.12 (d, J = 6.6 Hz, 1H), 7.08 (d, J = 8.7 Hz, 1H), 6.81 (d, J = 8.7 Hz, 1H), 6.50 (d, J = 7.8 Hz, 1H), 6.43 (t, J = 7.8 Hz, 1H), 6.01 (s, 1H), 3.90 (m, 1H), 3.46 (m, 4H), 0.98 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 162.51, 162.08, 158.97, 158.82, 147.74, 139.38, 132.58, 130.53, 127.35, 126.94, 125.31, 124.64, 123.64, 118.92, 114.46, 111.64, 47.03, 40.89, 40.06, 18.46. HRMS (ESI+) m/z calcd for C$_{22}$H$_{21}$Cl$_2$N$_4$O$_2$ (M + H)$^+$ 443.1042, found 443.1016.

*[4-(2,5-Dichlorophenoxy)pyrimidin-5-yl]-(4-allyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (18e).* The title compound was obtained as a brown solid from **16** and 1-allyl-1,2,3,4-tetrahydro-quinoxaline according to the general procedure in 60% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.94 (s, 1H), 8.70 (s, 1H), 7.32 (d, J = 6.6 Hz, 1H), 7.12 (dd, J = 6.6, 1.8 Hz, 1H), 7.04 (td, J = 5.7 Hz, 1.2 Hz, 1H), 6.56 (d, J = 5.7 Hz, 1H), 6.46 (dd, J = 5.7, 1.2 Hz, 1H), 6.36 (t, J = 5.7 Hz, 1H), 5.98 (d, J = 1.8 Hz, 1H), 5.51 (m, 1H), 5.03 (dd, J = 12.6, 1.2, 1H), 4.93 (dd, J = 7.8, 1.2 Hz, 1H), 3.73 (m, 2H), 3.53 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 162.36, 162.23, 159.08, 158.86, 147.67, 138.99, 132.62, 131.59, 130.49, 127.21, 126.88, 125.24, 124.19, 123.61, 123.29, 118.90, 116.45, 115.09, 111.90, 52.76, 48.69, 39.92. HRMS (ESI+) m/z calcd for C$_{22}$H$_{18}$Cl$_2$N$_4$O$_2$Na (M + Na)$^+$ 441.0885, found 441.0885.

*[4-(2,5-Dichlorophenoxy)pyrimidin-5-yl]-(4-cyclopropyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (18f).* The title compound was obtained as a yellow solid from **16** and 1-cyclopropyl-1,2,3,4-tetrahydroquinoxaline according to the general procedure in 58% yield. $^1$H NMR (300 M Hz, CDCl$_3$): δ 8.92 (s, 1H), 8.69 (s, 1H), 7.32

(d, *J* = 9.0 Hz, 1H), 7.10 (m, 3H), 6.44 (m, 2H), 5.95 (s, 1H), 3.52 (m, 3H), 2.32 (m, 1H), 1.62 (m, 1H), 0.71 (m, 3H), 0.29 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 162.44, 162.19, 159.06, 158.83, 147.60, 140.35, 132.43, 130.60, 126.89, 125.14, 124.91, 123.43, 122.90, 118.85, 115.70, 113.30, 48.61, 40.34, 30.85. HRMS (ESI+) *m/z* calcd for C$_{22}$H$_{18}$Cl$_2$N$_4$O$_2$Na (M + Na)$^+$ 463.0705, found 463.0691.

*[4-(2,5-Dichlorophenoxy)pyrimidin-5-yl]-(4-butyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (18g).* The title compound was obtained as a light yellow solid from **16** and 1-butyl-1,2,3,4-tetrahydroquinoxaline according to the general procedure in 58% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.94 (s, 1H), 8.70 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.12 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.06 (td, *J* = 7.5 Hz, 1.2 Hz, 1H), 6.60 (d, *J* = 8.4 Hz, 1H), 6.44 (d, *J* = 7.5 Hz, 1H), 6.33 (t, *J* = 7.5 Hz, 1H), 5.94 (d, *J* = 2.1 Hz, 1H), 3.50 (m, 5H), 1.63 (m, 1H) 1.18 (m, 4H), 0.73 (t, *J* = 6.6 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 162.30, 162.15, 159.15, 158.87, 147.74, 138.86, 132.61, 130.56, 127.18, 126.92, 125.40, 124.00, 123.75, 123.37, 118.88, 114.53, 111.43, 50.33, 49.17, 39.58, 27.75, 20.02, 13.70. HRMS (ESI+) *m/z* calcd for C$_{23}$H$_{22}$Cl$_2$N$_4$O$_2$Na (M + Na)$^+$ 479.1018, found 479.1011.

*[4-(2,5-Dichlorophenoxy)pyrimidin-5-yl]-(4-cyclobutyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (18h).* The title compound was obtained as a brown solid from **16** and 1-cyclobutyl-1,2,3,4-tetrahydroquinoxaline according to the general procedure in 50% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.91 (s, 1H), 8.69 (s, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.10 (t, *J* = 9.0 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.60 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 7.5 Hz, 1H), 6.38 (t, *J* = 7.5 Hz, 1H), 5.94 (s, 1H), 3.90 (m, 1H), 3.50 (m, 3H), 2.08 (m, 3H), 1.63 (m, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 162.56, 162.30, 159.04, 158.92, 147.74, 132.70, 130.62, 127.12, 127.04, 125.54, 125.37, 123.64, 123.32, 118.85, 116.06, 113.09, 53.42, 44.32, 40.93, 27.71, 14.75. HRMS (ESI+) *m/z* calcd for C$_{23}$H$_{20}$Cl$_2$N$_4$O$_2$Na (M + Na)$^+$ 477.0861, found 477.0852.

*[4-(2,5-Dichlorophenoxy)pyrimidin-5-yl]-(2,3-dihydrobenzo[1,4]-thiazin-4-yl)methanone (18i).* The title compound was obtained as a light yellow solid from **16** and 3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine according to the general procedure in 57% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.81 (s, 1H), 8.67 (s, 1H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.08–7.20 (m, 3H), 6.83 (t, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.24 (s, 1H), 4.21 (m, 1H), 3.33 (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.05 (s), 162.72 (s), 158.86 (s), 158.51 (s), 147.76 (s), 136.64 (s), 132.78 (s), 130.85 (s), 129.89 (s), 127.36 (s), 127.26 (s), 126.77 (s), 125.61 (s), 125.54 (s), 124.11 (s), 123.49 (s), 118.55 (s), 41.46 (s), 28.61 (s). HRMS (ESI+) *m/z* calcd for C$_{19}$H$_{14}$Cl$_2$N$_3$O$_2$S (M + H)$^+$ 418.0184, found 418.0199.

*Ethyl 4-Chloronicotinate (19).* 4-Chloronicotinic acid (1.0 g, 6.35 mmol) was dissolved in 10 mL of thionyl chloride, and the solution was refluxed for 1.5 h. Then the solvent was removed under reduced pressure. The residue was dissolved in 5 mL of toluene and concentrated to dryness. Then 20 mL of ethanol was added to the residue, and the solution mixture was stirred at room temperature overnight. The solution was diluted with 30 mL of H$_2$O and extracted with dichloromethane (20 mL × 3). The combined organic phase was washed with a saturated solution of sodium bicarbonate (50 mL) and brine (50 mL) and then dried over anhydrous sodium sulfate. The product was purified by flash column chromatography to yield **19** as a colorless oil (0.95 g, 81%). LC-MS (ESI+): 186 (M + H)$^+$. $^1$H NMR (300 MHz, CD$_3$OD): δ 9.20 (s, 1H), 8.82 (d, *J* = 6.1 Hz, 1H), 8.08 (d, *J* = 6.1 Hz, 1H), 4.58–4.37 (m, 2H), 1.50–1.36 (m, 3H).

**General Procedure for 20a–k.** To a solution of **19** (1 mmol) in 3 mL of anhydrous DMF were added corresponding phenol (1.2 mmol) and potassium carbonate (3 mmol). After the solution was heated at 90 °C for 3 h, the reaction was cooled to room temperature and poured into 10 mL of H$_2$O. The mixture was extracted with ethyl acetate three times, and the combined organic phase was washed with brine. After drying over anhydrous sodium sulfate, the product was purified with flash column chromatography (petroleum/ethyl acetate = 4:1) to yield the desired compound.

*Ethyl 4-Phenoxynicotinate (20a).* The title compound was obtained from **19** and phenol according to the general procedure in 72% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 9.01 (d, *J* = 6.6 Hz, 1H), 8.48 (d, *J* = 5.9 Hz, 1H), 7.42 (q, *J* = 7.9 Hz, 2H), 7.25–7.18 (m, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.68 (d, *J* = 5.9 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1, 3H).

*Ethyl 4-(2-Chlorophenoxy)nicotinate (20b).* The title compound was obtained from **19** and 2-chlorophenol according to the general procedure in 75% yield. $^1$H NMR (300 gMHz, CDCl$_3$): δ 9.05 (s, 1H), 8.49 (d, *J* = 5.8 Hz, 1H), 7.51 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.33 (ddd, *J* = 7.3, 6.7, 1.5 Hz, 1H), 7.23 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.20–7.11 (m, 1H), 6.53 (d, *J* = 5.8 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).

*Ethyl 4-(3-Chlorophenoxy)nicotinate (20c).* The title compound was obtained from **19** and 3-chlorophenol according to the general procedure in 72% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 9.05 (s, 1H), 8.54 (d, *J* = 5.8 Hz, 1H), 7.36 (t, *J* = 8.1 Hz, 1H), 7.28–7.20 (m, 1H), 7.11 (dd, *J* = 4.8, 2.8 Hz, 1H), 7.03–6.95 (m, 1H), 6.74 (d, *J* = 5.8 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.35 (q, *J* = 7.4 Hz, 3H).

*Ethyl 4-(3-Methoxyphenoxy)nicotinate (20d).* The title compound was obtained from **19** and 3-methoxyphenol according to the general procedure in 68% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 9.01 (s, 1H), 8.48 (d, *J* = 5.8 Hz, 1H), 7.30 (m, 2H), 6.84–6.75 (m, 1H), 6.74–6.63 (m, 3H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H).

*Ethyl 4-(2,5-Dimethoxyphenoxy)nicotinate (20e).* The title compound was obtained from **19** and 2,5-dimethoxyphenol according to the general procedure in 78% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 9.01 (s, 1H), 8.43 (d, *J* = 5.8 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 1H), 6.78 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.72 (d, *J* = 2.9 Hz, 1H), 6.55 (d, *J* = 5.9 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 3.71 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H).

*Ethyl 4-(4-Methylphenoxy)nicotinate (20f).* The title compound was obtained from **19** and 4-methylphenol according to the general procedure in 72% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.99 (s, 1H), 8.45 (d, *J* = 5.9 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.21 (s, 1H), 7.00 (s, 1H), 6.97 (s, 1H), 6.64 (d, *J* = 5.9 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.38 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H).

*Ethyl 4-(2,5-Dimethylphenoxy)nicotinate (20g).* The title compound was obtained from **19** and 2,5-dimethylphenol according to the general procedure in 80% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.99 (s, 1H), 8.43 (d, *J* = 5.8 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 6.99 (d, *J* = 7.7 Hz, 1H), 6.84 (s, 1H), 6.50 (d, *J* = 5.9 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.32 (s, 3H), 2.12 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H).

*Ethyl 4-(2,4,5-Trichlorophenoxy)nicotinate (20h).* The title compound was obtained from **19** and 2,4,5-trichlorophenol according to the general procedure in 72% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 9.10 (s, 1H), 8.57 (d, *J* = 5.8 Hz, 1H), 7.62 (d, *J* = 4.7 Hz, 1H), 7.23 (s, 1H), 6.63 (d, *J* = 5.8 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.43–1.31 (t, *J* = 7.1 Hz, 3H).

*Ethyl 4-(2,4,5-Trimethylphenoxy)nicotinate (20i).* The title compound was obtained from **19** and 2,4,5-trimethylphenol according to the general procedure in 69% yield. $^1$H NMR (400 MHz, CDCl$_3$): δ 9.00 (s, 1H), 8.40 (d, *J* = 5.9 Hz, 1H), 7.04 (s, 1H), 6.80 (s, 1H), 6.51 (d, *J* = 5.9 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.23 (s, 3H), 2.21 (s, 3H), 2.08 (s, 3H), 1.44–1.33 (m, 3H).

*Ethyl 4-(2,5-Dichloro-4-bromophenoxy)nicotinate (20j).* The title compound was obtained from **19** and 2,5-dichloro-4-bromophenol according to the general procedure in 65% yield. $^1$H NMR (400 MHz, CDCl$_3$): δ 9.09 (s, 1H), 8.57 (d, *J* = 5.7 Hz, 1H), 7.26 (s, 1H), 7.22 (d, *J* = 4.3 Hz, 1H), 6.62 (d, *J* = 5.8 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H).

*Ethyl 4-(2,5-Dichlorophenoxy)nicotinate (20k).* The title compound was obtained from **19** and 2,5-dichlorophenol according to the general procedure in 72% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 9.09 (s, 1H), 8.55 (d, *J* = 6.0 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 6.60 (d, *J* = 6.0 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H).

**General Procedure for the Synthesis of 17g, 22a–h, 23a–j.** To a solution of **20a–k** (0.30 mmol) in 1,4-dioxane and H$_2$O (1:1) was added sodium hydroxide (0.60 mmol). The reaction was stirred at ambient temperature for 3 h. After the solvent was evaporated, the residue was dissolved in H$_2$O and the pH was adjusted to 3 with

concentrated hydrochloric acid. The formed precipitated was filtered, washed with cold water, and dried under vacuum, providing **21a−k**. The obtained compound was dissolved in 2 mL of oxalyl chloride, and the solution was refluxed for 2 h. The solvent was evaporated, and the remaining oxalyl chloride was removed by azeotropic distillation with toluene. After the residue was dissolved in anhydrous dichloromethane, corresponding anilines (0.27 mmol) and Et$_3$N (0.90 mmol) were added to this solution. The reaction was stirred at room temperature for 2 h. After the reaction was complete, the solution was washed with brine, dried over anhydrous sodium sulfate, and purified by flash column chromatography (petroleum/ethyl acetate = 4:1 to 1:1) to provide the desired product.

*4-(2,5-Dichlorophenoxy)-N-(2-chlorophenyl)-N-methyl-3-nicotin-carboxamide (17g).* The title compound was obtained as an off-white solid from **20k** and 2-chloro-*N*-methylaniline according to the general procedure in 72% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.54 (s, 1H), 8.26 (d, *J* = 6.0 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 7.35 (m, 2H), 7.14−7.25 (m, 3H), 6.92 (d, *J* = 2.1 Hz, 1H), 6.30 (d, *J* = 6.0 Hz, 1H), 3.44 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 165.59, 159.15, 151.72, 149.68, 149.31, 140.32, 133.56, 132.48, 131.59, 130.62, 130.19, 129.59, 127.63, 127.13, 125.41, 123.17, 123.00, 109.49, 36.28. HRMS (ESI+) *m/z* calcd for C$_{19}$H$_{14}$Cl$_3$N$_2$O$_2$ (M + H)$^+$ 407.0121, found 407.0141.

*[4-(2,5-Dichlorophenoxy)pyridin-3-yl]-(3,4-dihydro-2H-quinolin-1-yl)methanone (22a).* The title compound was obtained as an off-white solid from **20k** and tetrahydroquinoline according to the general procedure in 50% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.81 (s, 1H), 8.42 (d, *J* = 4.8 Hz, 1H), 7.35 (d, *J* = 9.0 Hz, 1H), 7.11 (m, 3H), 6.91 (m, 1H), 6.66 (m, 1H), 6.25 (m, 1H), 5.89 (m, 1H), 2.67 (m, 2H), 2.05 (m, 2H), 1.77 (m, 2H). HRMS (ESI+) *m/z* calcd for C$_{21}$H$_{16}$Cl$_2$N$_2$O$_2$Na (M + Na)$^+$ 421.0487, found 421.0483.

*[4-(2,5-Dichlorophenoxy)pyridin-3-yl]-(2,3-dihydro-2H-benzo-[1,4]oxazin-4-yl)methanone (22b).* The title compound was obtained as an off-white solid from **20k** and benzomorpholine according to the general procedure in 56% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.85 (s, 1H), 8.48 (d, *J* = 6.0 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 6.6 Hz, 1H), 7.06 (t, *J* = 6.6 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.55 (m, 2H), 6.30 (d, *J* = 3.6 Hz, 1H), 5.85 (s, 1H), 4.94 (m, 1H), 4.37 (m, 2H), 3.40 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.81, 158.70, 152.74, 151.62, 148.88, 147.22, 133.44, 131.35, 127.12, 126.66, 125.95, 125.20, 123.21, 122.37, 122.16, 119.56, 117.43, 109.23, 66.76, 40.29, 29.66. HRMS (ESI+) *m/z* calcd for C$_{20}$H$_{15}$Cl$_2$N$_2$O$_3$ (M + H)$^+$ 401.0460, found 401.0475.

*[4-(2,5-Dichlorophenoxy)pyridin-3-yl]-(4-ethyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (22c).* The title compound was obtained as a brown solid from **20k** and 1-ethyl-1,2,3,4-tetrahydroquinoxaline according to the general procedure in 65% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.86 (s, 1H), 8.44 (d, *J* = 4.5 Hz, 1H), 7.32 (d, *J* = 6.3 Hz, 1H), 7.09 (dd, *J* = 6.3, 1.8 Hz, 1H), 7.01 (td, *J* = 6.3, 0.9 Hz, 1H), 6.48 (d, *J* = 6.3 Hz, 1H), 6.47 (dd, *J* = 5.7, 0.9 Hz, 1H), 6.38 (d, *J* = 4.5 Hz, 1H), 6.30 (t, *J* = 5.7 Hz, 1H), 5.77 (d, *J* = 1.8 Hz, 1H), 4.95 (m, 1H), 3.59 (m, 1H), 3.29 (m, 3H), 2.99 (m, 1H), 0.81 (t, *J* = 5.7 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.59, 158.41, 152.05, 151.67, 149.20, 138.69, 133.02, 130.97, 126.96, 126.38, 124.67, 124.28, 123.93, 123.38, 121.68, 114.32, 111.08, 109.49, 48.09, 44.48, 39.72, 10.33. HRMS (ESI+) *m/z* calcd for C$_{22}$H$_{20}$Cl$_2$N$_3$O$_2$ (M + H)$^+$ 428.0933, found 428.0940.

*[4-(2,5-Dichlorophenoxy)pyridin-3-yl]-(4-propyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (22d).* The title compound was obtained as an off-white solid from **20k** and 1-propyl-1,2,3,4-tetrahydroquinoxaline according to the general procedure in 62% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.87 (s, 1H), 8.44 (d, *J* = 6.0 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.11 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.00 (t, *J* = 8.4 Hz, 1H), 6.46 (m, 2H), 6.34 (d, *J* = 6.0 Hz, 1H), 6.29 (t, *J* = 7.8 Hz, 1H), 5.74 (d, *J* = 2.1 Hz, 1H), 4.94 (m, 1H), 3.62 (m, 1H), 3.41 (m, 1H), 3.22 (m, 2H), 2.84 (m, 1H), 1.26 (m, 2H), 0.74 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.51, 158.58, 151.94, 151.53, 149.16, 139.02, 133.11, 130.95, 126.96, 126.50, 124.86, 124.12, 123.92, 123.37, 121.98, 114.28, 111.19, 109.47, 52.25, 49.31, 39.64, 19.07, 11.28. HRMS (ESI+) *m/z* calcd for C$_{23}$H$_{22}$Cl$_2$N$_3$O$_2$ (M + H)$^+$ 442.1089, found 442.1091.

*[4-(2,5-Dichlorophenoxy)pyridin-3-yl]-(4-isopropyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (22e).* The title compound was obtained as a light yellow solid from **20k** and 1-isopropyl-1,2,3,4-tetrahydroquinoxaline according to the general procedure in 59% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.84 (s, 1H), 8.42 (d, *J* = 5.7 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.09 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 6.49 (d, *J* = 7.8 Hz, 1H), 6.30 (m, 2H), 5.76 (d, *J* = 1.5 Hz, 1H), 4.95 (m, 1H), 3.78 (m, 1H), 3.40 (m, 2H), 3.17 (m, 1H), 1.11 (m, 3H), 0.87 (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.45, 158.73, 152.02, 151.52, 149.24, 139.35, 133.07, 130.96, 127.10, 126.56, 124.88, 124.78, 124.15, 123.32, 122.03, 114.15, 111.32, 109.34, 46.88, 41.02, 39.94, 18.44. HRMS (ESI+) *m/z* calcd for C$_{23}$H$_{21}$Cl$_2$N$_3$O$_2$Na (M + Na)$^+$ 464.0909, found 464.0915.

*[4-(2,5-Dichlorophenoxy)pyridin-3-yl]-(4-allyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (22f).* The title compound was obtained as a light yellow solid from **20k** and 1-allyl-1,2,3,4-tetrahydroquinoxaline according to the general procedure in 68% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.87 (s, 1H), 8.44 (d, *J* = 6.3 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.09 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.49 (d, *J* = 7.5 Hz, 1H), 6.42 (d, *J* = 8.4 Hz, 1H), 6.33 (m, 2H), 5.75 (d, *J* = 2.4 Hz, 1H), 5.48 (m, 1H), 5.01 (d, *J* = 17.4 Hz, 1H), 4.94 (d, *J* = 10.5 Hz, 1H), 3.16−3.82 (m, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.75, 158.29, 152.27, 151.85, 149.25, 139.05, 133.10, 131.76, 130.92, 126.95, 126.31, 124.61, 124.47, 123.84, 123.31, 121.66, 116.33, 114.84, 111.66, 109.55, 52.66, 48.72, 39.96. HRMS (ESI+) *m/z* calcd for C$_{23}$H$_{20}$Cl$_2$N$_3$O$_2$ (M + H)$^+$ 440.0933, found 440.0929.

*[4-(2,5-Dichlorophenoxy)pyridin-3-yl]-(4-cyclopropyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (22g).* The title compound was obtained as an off-white solid from **20k** and 1-cyclopropyl-1,2,3,4-tetrahydroquinoxaline according to the general procedure in 72% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.85 (s, 1H), 8.43 (d, *J* = 5.7 Hz, 1H), 7.33 (d, *J* = 8.7 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.49 (d, *J* = 7.8 Hz, 1H), 6.38 (t, *J* = 7.8 Hz, 1H), 6.32 (d, *J* = 5.7 Hz, 1H), 5.66 (s, 1H), 4.91 (m, 1H), 3.48 (m, 2H), 3.16 (m, 1H), 2.24 (m, 1H), 0.66 (m, 3H), −0.30 (m, 1H). ESI-MS: 440 [M + H$^+$].

*[4-(2,5-Dichlorophenoxy)pyridin-3-yl]-(4-cyclobutyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (22h).* The title compound was obtained as an off-white solid from **20k** and 1-cyclobutyl-1,2,3,4-tetrahydroquinoxaline according to the general procedure in 68% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.85 (s, 1H), 8.44 (d, *J* = 4.5 Hz, 1H), 7.34 (d, *J* = 6.6 Hz, 1H), 7.11 (dd, *J* = 6.6, 1.5 Hz, 1H), 7.01 (td, *J* = 6.6, 0.9 Hz, 1H), 6.49 (t, *J* = 5.7 Hz, 2H), 6.35 (m, 2H), 5.73 (d, *J* = 0.9 Hz, 1H), 4.91 (m, 1H), 3.79 (m, 1H), 3.48 (s, 3H), 3.33 (m, 1H), 2.11 (m, 2H), 1.94 (m, 1H), 1.60 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.59, 158.58, 152.12, 151.64, 149.23, 139.51, 133.06, 130.94, 126.83, 126.43, 125.30, 124.79, 123.73, 123.28, 121.81, 115.02, 112.21, 109.40, 53.10, 44.21, 40.65, 27.75, 14.82. HRMS (ESI+) *m/z* calcd for C$_{24}$H$_{22}$Cl$_2$N$_3$O$_2$ (M + H)$^+$ 454.1089, found 454.1092.

*(4-Phenoxypyridin-3-yl)-(4-cyclopropyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (23a).* The title compound was obtained as an off-white solid from **20a** according to the general procedure in overall 55% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.78 (s, 1H), 8.32 (d, *J* = 5.4 Hz, 1H), 7.26−7.22 (m, 2H), 7.18−7.15 (m, 1H), 7.01−6.96 (m, 2H), 6.51−6.49 (m, 1H), 6.39−6.36 (m, 1H), 6.31−6.26 (m, 3H), 4.94 (m, 1H), 3.44 (m, 2H), 3.12 (m, 1H), 2.2 (m, 1H), 0.55 (m, 3H), −0.32 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 164.48, 160.18, 152.69, 151.96, 151.22, 140.39, 129.65, 126.16, 125.47, 123.38, 123.09, 120.37, 115.45, 113.12, 109.21, 48.69, 40.30, 30.78, 7.61. HRMS (ESI+) *m/z* calcd for C$_{23}$H$_{21}$N$_3$O$_2$Na (M + Na)$^+$ 394.1531, found 394.1521.

*[4-(2-Chlorophenoxy)pyridin-3-yl]-(4-cyclopropyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (23b).* The title compound was obtained as an brown solid from **20b** according to the general procedure in overall 50% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.79 (s, 1H), 8.35 (d, *J* = 4.5 Hz, 1H), 7.40 (d, *J* = 5.7 Hz, 1H), 7.09 (m, 2H), 6.96 (m, 2H), 6.53 (d, *J* = 5.7 Hz, 1H), 6.36 (t, *J* = 5.7 Hz, 1H), 6.25 (d, *J* = 4.5 Hz, 1H), 5.88 (d, *J* = 5.7 Hz, 1H), 4.85 (br, 1H), 3.49 (m, 2H), 3.24 (m, 1H), 2.25 (m, 1H), 0.64 (m, 3H), −0.27 (br, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.92, 159.25, 151.92, 151.39,

148.55, 140.24, 130.64, 127.90, 126.54, 126.42, 126.22, 125.36, 123.38, 123.02, 121.90, 115.44, 113.09, 108.97, 48.79, 40.25, 30.82, 7.64. HRMS (ESI+) $m/z$ calcd for $C_{23}H_{20}ClN_3O_2Na$ (M + Na)$^+$ 428.1142, found 428.1122.

*[4-(3-Chlorophenoxy)pyridin-3-yl]-(4-cyclopropyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (23c).* The title compound was obtained as a yellow solid from **20c** according to the general procedure in overall 55% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.82 (s, 1H), 8.38 (d, $J$ = 5.7 Hz, 1H), 7.16 (m, 2H), 7.00 (m, 2H), 6.47 (d, $J$ = 6.6 Hz, 1H), 6.39 (d, $J$ = 7.5 Hz, 1H), 6.32 (m, 2H), 6.12 (m, 1H), 4.91 (br, 1H), 3.44 (br, 2H), 3.12 (br, 1H), 2.22 (m, 1H), 0.63 (m, 3H), −0.28 (br, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.98, 159.67, 153.35, 151.83, 151.18, 140.41, 135.11, 130.60, 126.49, 125.77, 125.17, 123.43, 123.37, 120.72, 118.49, 115.52, 113.16, 109.53, 48.74, 40.26, 30.83, 7.65. HRMS (ESI+) $m/z$ calcd for $C_{23}H_{21}ClN_3O_2$ (M + H)$^+$ 406.1322, found 406.1323.

*[4-(3-Methoxyphenoxy)pyridin-3-yl]-(4-cyclopropyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (23d).* The title compound was obtained as a yellow solid from **20d** according to the general procedure in overall 47% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.78 (s, 1H), 8.33 (d, $J$ = 5.7 Hz, 1H), 7.14 (t, $J$ = 8.1 Hz, 1H), 7.00 (d, $J$ = 3.9 Hz, 2H), 6.71 (d, $J$ = 8.1 Hz, 1H), 6.49 (d, $J$ = 7.2 Hz, 1H), 6.37 (m, 1H), 6.30 (d, $J$ = 5.7 Hz, 1H), 5.97 (d, $J$ = 7.8 Hz, 1H), 5.83 (s, 1H), 4.92 (br, 1H), 3.71 (s, 3H), 3.46 (br, 2H), 3.17 (br, 1H), 2.25 (m, 1H), 0.63 (br, 3H), −0.14 (br, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 164.44, 160.79, 160.13, 153.59, 151.94, 151.17, 140.43, 130.26, 126.18, 125.47, 123.36, 122.98, 115.42, 113.05, 112.51, 111.80, 109.20, 105.90, 55.48, 48.68, 40.33, 30.85, 7.66. HRMS (ESI+) $m/z$ calcd for $C_{24}H_{23}N_3O_3Na$ (M + Na)$^+$ 424.1637, found 424.1633.

*[4-(2,5-Dimethoxyphenoxy)pyridin-3-yl]-(4-cyclopropyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (23e).* The title compound was obtained as a brown solid from **20e** according to the general procedure in overall 58% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.64 (s, 1H), 8.30 (d, $J$ = 5.4 Hz, 1H), 7.04 (m, 2H), 6.86 (d, $J$ = 8.7 Hz, 1H), 6.69 (d, $J$ = 8.1 Hz, 1H), 6.56 (d, $J$ = 7.2 Hz, 1H), 6.36 (m, 1H), 6.21 (d, $J$ = 4.5 Hz, 1H), 5.67 (s, 1H), 4.69 (br, 1H), 3.67 (s, 3H), 3.63 (s, 3H), 2.35 (m, 1H), 0.71 (m, 3H), 0.14 (br, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 164.35, 160.25, 153.87, 151.71, 150.72, 145.40, 141.29, 140.38, 126.06, 125.73, 123.30, 122.36, 115.69, 113.84, 112.93, 112.00, 108.69, 108.09, 56.33, 55.90, 48.75, 40.43, 31.05, 7.83. HRMS (ESI+) $m/z$ calcd for $C_{25}H_{26}N_3O_4$ (M + H)$^+$ 432.1923, found 432.1919.

*[4-(4-Methylphenoxy)pyridin-3-yl]-(4-cyclopropyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (23f).* The title compound was obtained as an off-white solid from **20f** according to the general procedure in overall 51% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.76 (s, 1H), 8.30 (d, $J$ = 5.4 Hz, 1H), 7.04−6.99 (m, 4H), 6.47 (m, 1H), 6.37−6.33 (m, 1H), 6.24 (d, $J$ = 5.7 Hz, 1H), 6.20−6.17 (m, 2H), 4.90 (m, 1H), 3.44 (m, 2H), 3.19 (m, 1H), 2.31 (s, 3H), 2.23 (m, 1H), 0.58 (m, 3H), −0.23 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 164.57, 160.53, 151.89, 151.07, 150.35, 140.40, 135.23, 130.26, 126.12, 125.49, 123.33, 122.94, 120.23, 115.44, 113.09, 109.04. HRMS (ESI+) $m/z$ calcd for $C_{24}H_{24}N_3O_2$ (M + H)$^+$ 386.1869, found 386.1883.

*[4-(2,5-Dimethylphenoxy)pyridin-3-yl]-(4-cyclopropyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (23g).* The title compound was obtained as a brown solid from **20g** according to the general procedure in overall 55% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.76 (s, 1H), 8.31 (d, $J$ = 5.4 Hz, 1H), 7.05−6.95 (m, 3H), 6.86 (d, $J$ = 7.8 Hz, 1H), 6.53 (d, $J$ = 7.8 Hz, 1H), 6.38 (m, 1H), 6.21 (d, $J$ = 5.4 Hz, 1H), 5.47 (s, 1H), 4.89 (m, 1H), 3.45 (m, 2H), 3.20 (m, 1H), 2.24 (m, 1H), 2.15 (s, 3H), 1.93 (s, 3H), 0.59−0.46 (m, 3H), −0.26 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 164.43, 160.22, 151.81, 150.96, 150.79, 140.43, 137.21, 130.91, 126.61, 126.30, 126.14, 125.51, 123.44, 122.99, 120.82, 115.51, 113.16, 109.19, 48.81, 40.29, 30.81, 20.59, 15.22, 7.57. HRMS (ESI+) $m/z$ calcd for $C_{25}H_{26}N_3O_2$ (M + H)$^+$ 400.2025, found 400.2025. Anal. calcd for $C_{25}H_{25}N_3O_2$: C, 75.16; H, 6.31; N, 10.52. Found: C, 74.98; H, 6.31; N, 10.29.

*[4-(2,4,5-Trichlorophenoxy)pyridin-3-yl]-(4-cyclopropyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (23h).* The title compound was obtained as an off-white solid from **20h** according to the general procedure in overall 58% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.85

(s, 1H), 8.44 (d, $J$ = 5.5 Hz, 1H), 7.51 (s, 1H), 7.03 (t, $J$ = 7.7 Hz, 1H), 6.95 (d, $J$ = 8.0 Hz, 1H), 6.47 (d, $J$ = 7.6 Hz, 1H), 6.37 (t, $J$ = 7.4 Hz, 1H), 6.30 (d, $J$ = 5.7 Hz, 1H), 5.76 (s, 1H), 4.88 (s, 1H), 3.48 (s, 2H), 3.18 (s, 1H), 2.87 (s, 1H), 2.25 (s, 1H), 0.69 (m, 3H), −0.22 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.41, 158.37, 152.25, 151.87, 147.73, 140.26, 131.61, 131.13, 129.70, 126.67, 125.35, 125.04, 123.50, 123.33, 122.80, 115.49, 113.12, 109.30, 48.82, 40.15, 30.97, 7.76. HRMS (ESI+) $m/z$ calcd for $C_{23}H_{18}Cl_3N_3O_2Na$ (M + Na)$^+$ 496.0362, found 496.0386.

*[4-(2,4,5-Trimethylphenoxy)pyridin-3-yl]-(4-cyclopropyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (23i).* The title compound was obtained as an off-white solid from **20i** according to the general procedure in overall 56% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.73 (s, 1H), 8.30 (d, $J$ = 5.4 Hz, 1H), 7.00 (m, 2H), 6.91 (s, 1H), 6.52 (d, $J$ = 7.8 Hz, 1H), 6.37 (s, 1H), 6.20 (d, $J$ = 5.4 Hz, 1H), 5.49 (s, 1H), 4.88 (s, 1H), 3.46 (s, 2H), 3.23 (s, 1H), 2.53 (s, 1H), 2.27 (s, 1H), 2.17 (s, 3H), 2.06 (s, 3H), 1.88 (m, 3H), 0.61 (s, 3H), −0.18 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 164.53, 160.51, 151.76, 150.81, 148.68, 140.43, 135.54, 133.86, 132.14, 126.74, 126.12, 125.54, 123.42, 122.89, 121.38, 115.56, 113.16, 109.05, 48.77, 40.32, 30.89, 19.00, 15.07, 7.69. HRMS (ESI+) $m/z$ calcd for $C_{26}H_{27}N_3O_2Na$ (M + Na)$^+$ 414.2182, found 414.2197.

*[4-(2,5-Dichloro-4-bromophenoxy)pyridin-3-yl]-(4-cyclopropyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (23j).* The title compound was obtained from **20j** according to the general procedure in overall 60% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.85 (d, $J$ = 4.2 Hz, 1H), 8.44 (d, $J$ = 4.2 Hz, 1H), 7.67 (s, 1H), 7.02 (t, $J$ = 5.7 Hz, 1H), 6.94 (d, $J$ = 5.7 Hz, 1H), 6.47 (d, $J$ = 5.7 Hz, 1H), 6.38 (t, $J$ = 5.7 Hz, 1H), 6.30 (d, $J$ = 4.2 Hz, 1H), 5.76 (s, 1H), 4.89 (m, 1H), 3.49 (m, 2H), 3.16 (m, 1H), 2.25 (m, 1H), 0.69 (m, 3H), −0.23 (br, 1H).

**General Procedure for the Synthesis of 23k,l.** A solution of **23j** (0.25 mmol) in 5 mL of 1,4-dioxane, Pd(dppf)Cl$_2$·CH$_2$Cl$_2$ (0.0125 mmol), and organozinc (0.5 mmol, 1.2 M solution in toluene) were added under a nitrogen atmosphere. After the mixture was refluxed for 2 h, the solution was cooled to room temperature. Dichloromethane and H$_2$O were added to the solution. The organic layer was washed with brine and anhydrous sodium sulfate and purified by flash column chromatography (petroleum/ethyl acetate = 3:1) to provide the desired product.

*[4-(2,5-Dichloro-4-methylphenoxy)pyridin-3-yl]-(4-cyclopropyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (23k).* The title compound was obtained as a brown solid from **23j** according to the general procedure in 75% yield. $^1$H NMR (300 MHz, DMSO): δ 8.75 (s, 1H), 8.42 (s, 1H), 7.64 (s, 1H), 6.99 (d, $J$ = 8.0 Hz, 1H), 6.90 (m, 1H), 6.50 (m, 2H), 6.35 (m, 1H), 5.62 (m, 1H), 4.69 (s, 1H), 3.40 (s, 1H), 2.29 (s, 3H), 0.64 (m, 4H), −0.37 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.48, 159.29, 151.59, 151.05, 146.70, 140.31, 134.95, 133.05, 131.79, 126.64, 125.13, 124.36, 123.29, 122.22, 115.53, 113.16, 109.21, 48.81, 40.26, 30.93, 19.43, 7.71. HRMS (ESI+) $m/z$ calcd for $C_{24}H_{21}Cl_2N_3O_2Na$ (M + Na)$^+$ 476.0909, found 476.0916.

*[4-(2,5-Dichloro-4-ethylphenoxy)pyridin-3-yl]-(4-cyclopropyl-3,4-dihydro-2H-quinoxalin-1-yl)methanone (23l).* The title compound was obtained as a yellow solid from **23j** according to the general procedure in overall 80% yield. $^1$H NMR (300 MHz, DMSO): δ 8.76 (s, 1H), 8.43 (s, 1H), 7.59 (s, 1H), 6.99 (t, $J$ = 7.8 Hz, 1H), 6.87 (m, 1H), 6.53 (m, 2H), 6.35 (s, 1H), 5.57 (s, 1H), 4.71 (s, 1H), 3.40 (m, 2H), 2.66 (d, $J$ = 7.5 Hz, 2H), 2.22 (s, 1H), 1.23 (s, 1H), 1.15 (t, $J$ = 7.5 Hz, 3H), 0.61 (s, 2H), 0.52−0.33 (m, 1H), −0.43 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.73, 158.89, 152.11, 151.57, 146.78, 140.28, 132.35, 130.46, 126.59, 125.14, 124.53, 123.42, 123.06, 122.23, 115.43, 113.09, 109.22, 48.82, 40.18, 30.87, 26.12, 13.82, 7.64. HRMS (ESI+) $m/z$ calcd for $C_{25}H_{23}Cl_2N_3O_2Na$ (M + Na)$^+$ 490.1065, found 490.1041.

## ■ ASSOCIATED CONTENT

**Ⓢ Supporting Information**

Synthesis of **5−10**, **11a,b**, **12a,b**; analytical data; $^1$H NMR spectra, $^{13}$C NMR spectra, HRMS, and HPLC for all the final

compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ABBREVIATIONS USED

T2DM, type 2 diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; $EC_{50}$, effective concentration for 50% inhibition; BA, bile acids; CA, cholic acid; LCA, lithocholic acid; ICR, imprinting control region; DPP-IV, dipeptidyl peptidase IV; OGTT, oral glucose tolerance test; AUC, area under curve; GLP-1, glucagons-like peptide; FXR, farnesoid X receptor; cAMP, 3′,5′-cyclic adenosine monophosphate; SAR, structure−activity relationship; DMF, N,N-dimethylformamide; THF, tetrahydrofuran; $t_{1/2}$, half-time; ip, intraperitoneal; EDTA, ethylenediaminetetraacetic acid

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