Bioorganic & Medicinal Chemistry 17 (2009) 2733–2743

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

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

Discovery of potent and orally active 3-alkoxy-5-phenoxy-*N*-thiazolyl benzamides as novel allosteric glucokinase activators

Tomoharu Iino *, Daisuke Tsukahara, Kenji Kamata, Kaori Sasaki, Sumika Ohyama, Hideka Hosaka, Takuro Hasegawa, Masato Chiba, Yasufumi Nagata, Jun-ichi Eiki, Teruyuki Nishimura

Banyu Tsukuba Research Institute, Banyu Pharmaceutical Co. Ltd, Okubo 3, Tsukuba 300-2611, Ibaraki, Japan

ARTICLE INFO

Article history:
Received 15 January 2009
Revised 16 February 2009
Accepted 19 February 2009
Available online 25 February 2009

Keywords:
Glucokinase
Glucokinase activators
3-Alkoxy-5-phenoxy-*N*-thiazolyl benzamides
Glucose-lowering effect

ABSTRACT

Identification and synthesis of novel 3-alkoxy-5-phenoxy-*N*-thiazolyl benzamides as glucokinase activators are described. Removal of an aniline structure of the prototype lead (**2a**) and incorporation of an alkoxy or phenoxy substituent led to the identification of 3-Isopropoxy-5-[4-(methylsulfonyl)phenoxy]-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide (**27e**) as a novel, potent, and orally bioavailable GK activator. Rat oral glucose tolerance test indicated that **27e** exhibited a glucose-lowering effect after 10 mg/kg oral administration.

1. Introduction

There are three key aspects of Type 2 diabetes pathogenesis which are the focus of current and future therapies: insulin resistance, defective insulin secretion, and increased hepatic glucose production. The major classes of oral antidiabetic drugs used to treat this disorder include thiazolidinediones, biguanides, alpha-glucosidase inhibitors, sulfonylureas, and meglitinides. Each of the preceding drugs has documented limitations, and despite these treatment options, it is difficult to effectively treat Type 2 diabetes in the long term.[1] Currently, no single marketed drug is capable of achieving enduring blood glucose control in the majority of Type 2 diabetic patients.[2,3] Therefore, there is an unmet medical need for the development of new, safe, and effective antidiabetic therapies with multiple modes of action.

Glucokinase (GK), a member of the hexokinase family, is expressed in the liver and in pancreatic β-cells.[4] This enzyme catalyzes the key initial step for glucose metabolism, that is, phosphorylation of glucose to glucose 6-phosphate. In the liver, GK promotes glycogen synthesis, whilst it enhances insulin secretion from pancreatic β-cells.[5,6] Therefore, GK activators (GKAs) can be expected to function as a hypoglycemic drug, by both increasing glucose uptake in the liver and the potentiation of insulin secretion from pancreatic beta-cells.

Compounds that activate GK, by binding to an allosteric pocket some 20 Å remote from the glucose binding site, have recently been discovered.[7–9] These GKAs have been shown to engender potent antihyperglycemic actions in rodents, both by increasing pancreatic insulin secretion and by augmenting hepatic glucose metabolism.[10]

Thus far, several structure classes of GKAs including RO281675[11], piragliatin (Roche)[12], LY-2121260 (Lilly)[13], GKA50 (AstraZeneca),[14] and PSN-GK1 (OSI)[15] have been disclosed. Among them, RO281675[11] and piragliatin[12] are reported to enter human clinical trials as prospective Type 2 diabetes therapies.

We have been involved with a GKA program to identify and develop novel, potent and orally bioavailable GKAs for the treatment of Type 2 diabetes. In previous publications, we described the SARs of 2-aminobenzamide GKAs, the binding mode of the representative 2-aminobenzamide GKAs (**1** and **2a**) with GK, and their in vitro and/or in vivo profiles (Fig. 1).[7,10,16] Using crystal structure analysis, we revealed that the interaction between the aniline part of **1** or **2a** and Tyr215 of GK played an important role in enhancing GK activation, in addition to the interaction between the aminothiazole moiety of **2a** and Arg63 of the hinge region of GK (Fig. 2).

Meanwhile, 2-aminobenzamides (represented by **2a**) have an aniline structure. It is known that aniline compounds sometimes exert the potential risk for mutagenecity.[17,18] Therefore, from the point of view of drug discovery, it was important to remove this aniline part from the core structure. However, since *N*-methylamine derivative (**2b**) reduced GK activity, alternative approaches for increasing GK potency are strongly required.

* Corresponding author. Tel.: +81 29 877 2035; fax +81 29 877 2029.
E-mail address: tomoharu_iino@merck.com (T. Iino).

0968-0896/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2009.02.038

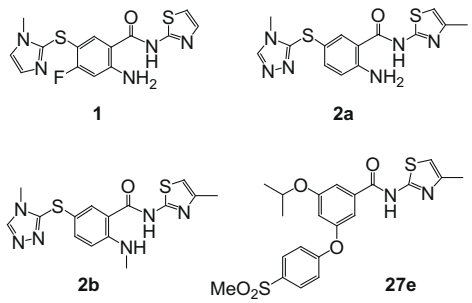


Figure 1. Discovery of 3-alkoxy-5-phenoxy-*N*-thiazolyl benzamides as novel GK activators.

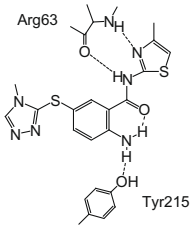


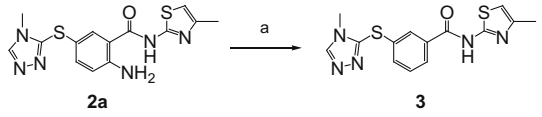
Figure 2. Binding mode between 2-aminobenzamide GK activator **2a** and GK.

Here, we describe the optimization of our lead GKA **2a** and discovery of 3-alkoxy-5-phenoxy-*N*-thiazolyl-benzamide represented by **27e**,[19] and in addition, we describe the in vivo profile of **27e**, such as the oral bioavailability and glucose lowering effect in rodents.

2. Chemistry

Preparation of compounds is summarized in Schemes 1–5. Diazonium reaction and Cu_2O work-up gave the des-amino derivative **3** (Scheme 1).

Scheme 2 shows synethesis of 3-phenoxybenzamides **7a–l**. The aniline compounds **6a–h, 6k**, and **6l** were prepared from nitro compound **4**.[16] Des-amination reaction afforded **7a–g, 7k**, and **7l**. The 2-methanesulfonyl derivative **7h** was obtained by *m*CPBA oxidation after des-amination reaction.



Scheme 1. Synthesis of des-amino derivative **3**. Reagents and conditions: (a) $NaNO_2$, cH_2SO_4, AcOH followed by Cu_2O, EtOH.

Preparation of the 3- and 4-methanesulfonyl derivatives **7i** and **7j** was started from commercially available methyl 3-hydroxybenzoate **8**. Coupling reactions using boronic acids in the presence of $Cu(OAc)_2$ afforded compounds **9i** and **9j**. Oxidation using *m*CPBA gave the 3- and 4-methanesulfonyl derivatives. Saponification of the methyl esters, followed by a condensation reaction with 2-amino-4-methylthiazole, led to the desired amides **7i** and **7j**.

Synthesis of methanesulfonyl substituted phenoxy derivatives **16a-c** is shown in Scheme 3. A substitution reaction of **10** with PhOH under 60 °C condition, afforded the nitro compound **11**. Reduction of **11** in the presence of Fe followed by substitution reaction with 2-MeS-C_6H_4OH at 80 °C followed by an oxidation reaction with *m*CPBA produced **13**. 2-Methanesufonyl derivative **16a** was obtained after des-amination.

3- or 4-methanesulfonyl substituted derivatives **16b** and **16c** were prepared from the phenoxy compound **14**. Cross-coupling with corresponding boronic acids followed by the same manner as described in Scheme 2 gave **16b** and **16c**.

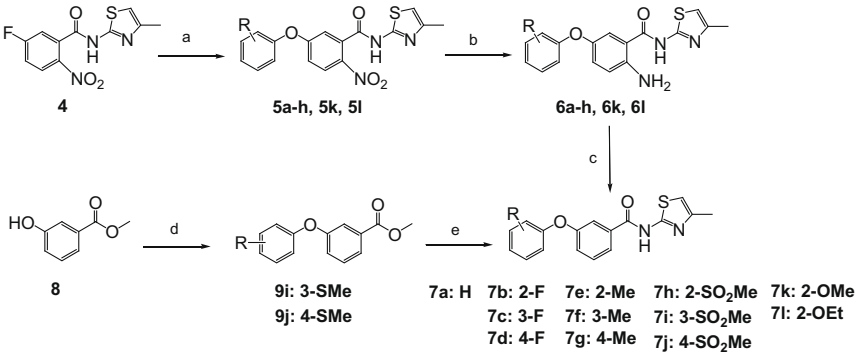
Scheme 4 depicts the preparation of 2-substituted derivatives **20a** and **20b**. Alkylation of 2-hydroxy-5-iodobenzoate **17** followed by coupling with 2-methylthiophenol, in the presence of $Cu(OTf)_2PhH$ complex, produced thioether **19**. Oxidation using *m*CPBA, hydrolysis and an amidation reaction afforded amide **20a**. A substitution reaction of methyl 2-bromo-5-hydroxybenzoate **21** with 2-methanesulfonylfluorobenzene, followed by a coupling reaction with phenol in the presence of CuO, produced the methyl ester **23**. Hydrolysis and an amidation reaction gave the amide **20b**.

Alkoxy derivatives **27a–e** were prepared from the methyl 3,5-dihydroxybenzoate **24**. Treatment of **24** with alkyl halide gave the mono alkoxy intermediates **25a–c**. Substitution reactions of them with 2-methanesulfonylfluorobenzene afforded sulfone compounds **26a–c**. The amide derivatives **27a–c** were obtained in the same manner.

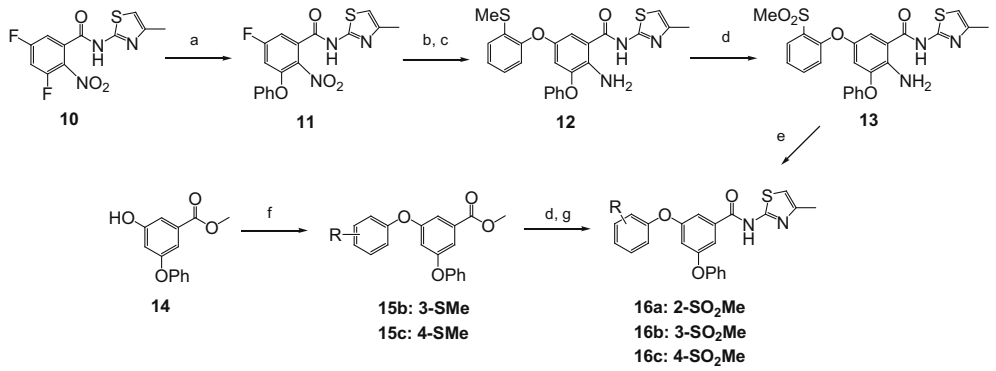
Isopropoxy derivatives **29d** and **29e**, possessing a methanesulfonyl group at the 3- or 4-position on the terminal benzene ring, were prepared by cross-coupling of **24** with corresponding boronic acids and alkylation. Oxidation, hydrolysis and an amidation reaction afforded the amide derivatives **27d** and **27e** (Scheme 5).

3. Biological results and discussion

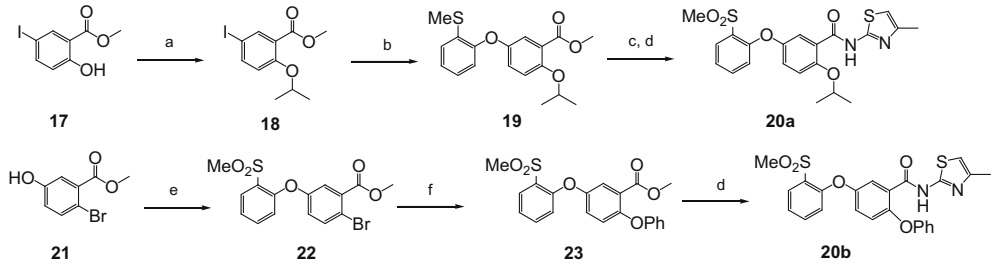
An in vitro GK assay was conducted at two different glucose concentrations, 2.5 mM and 10 mM, which were simulated to be



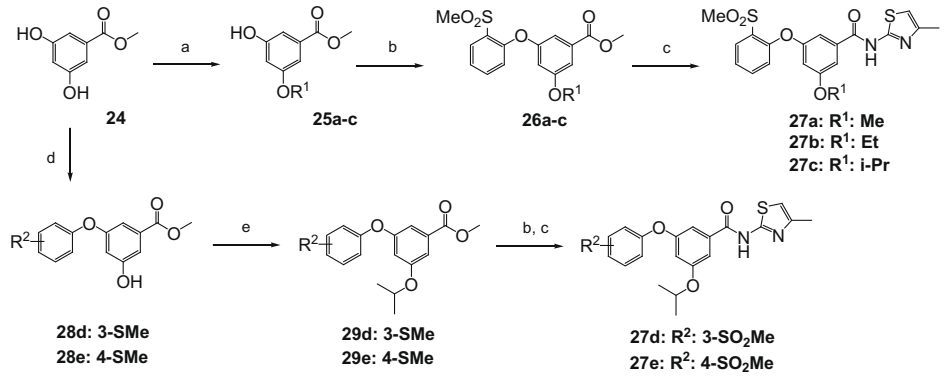
Scheme 2. Synthesis of 3-phenoxybenzamide **7a–l**. Reagents and conditions: (a) R-C_6H_4OH, Et_3N or K_2CO_3, DMF, 80–100 °C; (b) Fe powder, sat-NH_4Cl, *i*-PrOH, reflux; (c) (i) $NaNO_2$, cH_2SO_4, AcOH followed by Cu_2O, EtOH; (ii) *m*CPBA, THF, 0 °C (**7h**); (d) 3-MeS-$C_6H_4B(OH)_2$ (**9i**) or 4-MeS-$C_6H_4B(OH)_2$ (**9j**), $Cu(OAc)_2$, Et_3N, CH_2Cl_2; (e) (i) *m*CPBA, THF, 0 °C; (ii) NaOHaq, MeOH; (iii) 2-amino-4-methylthiazole, WSC, HOBT, $CHCl_3$.



Scheme 3. Synthesis of methanesulfonyl substituted phenoxy derivatives **16a–c**. Reagents and conditions: (a) Phenol, K_2CO_3, DMF, 60 °C; (b) 2-MeS-C_6H_4OH, K_2CO_3, DMF, 80 °C; (c) Fe powder, sat-NH_4Cl, *i*-PrOH, reflux; (d) *m*CPBA, THF, 0 °C; (e) $NaNO_2$, cH_2SO_4, AcOH followed by Cu_2O, EtOH; (f) 3-MeS-$C_6H_4B(OH)_2$ (**15b**) or 4-MeS-$C_6H_4B(OH)_2$ (**15c**), $Cu(OAc)_2$, Et_3N, CH_2Cl_2; (g) (i) NaOHaq, MeOH; (ii) 2-amino-4-methylthiazole, WSC, HOBT, $CHCl_3$.



Scheme 4. Synthesis of 2-substituted benzamides **20a** and **20b**. Reagents and conditions: (a) 2-bromopropane, K_2CO_3, DMF, 60 °C; (b) 2-MeS-C_6H_4OH, $Cu(OTf)_2PhH$, Cs_2CO_3, toluene, EtOAc, 110 °C; (c) *m*CPBA, THF, 0 °C; (d) (i) NaOHaq, MeOH; (ii) 2-amino-4-methylthiazole, WSC, HOBT, $CHCl_3$; (e) 2-$MeSO_2$-F-benzene, Cs_2CO_3, DMF, 80 °C; (f) Phenol, K_2CO_3, CuO, pyridine, 130 °C.

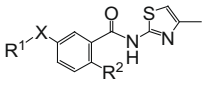


Scheme 5. Synthesis of 3-alkoxy derivatives **27a–e**. Reagents and conditions: (a) MeI (**25a**) or EtI (**25b**) or 2-Bromopropane (**25c**), K_2CO_3, DMF, 60 °C; (b) 2-$MeSO_2$-F-benzene, Cs_2CO_3, DMF, 80 °C; (c) (i) NaOHaq, MeOH; (ii) 2-amino-4-methylthiazole, WSC, HOBT, $CHCl_3$; (d) 3-MeS-$C_6H_4B(OH)_2$ (**28d**) or 4-MeS-$C_6H_4B(OH)_2$ (**28e**), $Cu(OAc)_2$, Et_3N, CH_2Cl_2; (e) 2-bromopropane, K_2CO_3, DMF, 60 °C.

low and high (postprandial) blood glucose conditions, respectively. GK activity was evaluated as EC_{50} values and maximal effective responses (E_{max}). For comparison of derivatives in each assay, the EC_{50} and E_{max} values of **2a** were used as the internal standard (E_{max} value of **2a** is 1.0). We suppose that not only the EC_{50} values, but also the E_{max} values of GKAs, have an impact on the efficacy of in vivo experiments.

Prior to the selection of the lead compound from the benzamide class, we prepared **3** and **7a** (which have no aniline structure). The deletion of the amine part from the core benzene ring resulted in an approximately 10-fold reduction in the potency, as compared with that of the aniline compounds **2a** and **6a**. This reduction would be explicable by the lack of interaction between **2a** (**6a**) and Tyr215 of GK.[16] In developing the lead compound with no aniline structure, we paid attention to 3-phenoxy-benzamide **7a**, because various substituents could be incorporated on the phenoxy portion at the 3-position of the core benzamide. First, we checked the effect of the regio-chemical structure of a fluoro atom, a methyl group or a methanesulfonyl group on GK potency (Table 1). As was expected[16], the GK activity of the 2-substituted derivatives (**7b, 7e**, and **7h**) was tolerable, in terms of both EC_{50} and E_{max} values, whilst the 3- and 4-substituted derivatives (**7c, 7d, 7f, 7g, 7i**, and **7j**) showed a significant drop in activity, especially in E_{max} values. GK activity of the other 2-substituted derivatives (**7k** and **7l**) was also tolerable. Among the 2-substituted derivatives (**7b**, **7e**, **7h**, **7k**, and **7l**), the E_{max} value of 3-(2-methanesulfonyl)phenoxy-benzamide **7h** was as high as that of the aniline compound **2a**, and thus **7h** was selected as the lead compound for further modifications.

Table 1
SAR of 3-phenoxy-benzamide derivatives



Compd	R^1			2.5 mM Glc		10 mM Glc	
		X	R^2	EC_{50}[a] (μM)	E_{max}[b]	EC_{50}[a] (μM)	E_{max}[b]
2a		S	NH_2	0.42	1.0	0.14	1.0
3		S	H	7.3	0.76	1.5	0.61
6a	Ph	O	NH_2	0.70	0.91	0.13	0.95
7a	Ph	O	H	19	0.63	0.8	0.66
7b	2-F-C_6H_4	O	H	2.4	0.76	0.45	0.73
7c	3-F-C_6H_4	O	H	6.3	0.55	2.2	0.74
7d	4-F-C_6H_4	O	H	21	0.53	4.2	0.59
7e	2-Me-C_6H_4	O	H	3.2	0.63	0.82	0.63
7f	3-Me-C_6H_4	O	H	8.2	0.45	2.3	0.69
7g	4-Me-C_6H_4	O	H	5.9	0.28	6.4	0.56
7h	2-$MeSO_2$-C_6H_4	O	H	5.5	1.0	1.1	1.1
7i	3-$MeSO_2$-C_6H_4	O	H	18	0.48	1.1	0.48
7j	4-$MeSO_2$-C_6H_4	O	H	29	0.60	3.4	0.66
7k	2-MeO-C_6H_4	O	H	2.2	0.84	0.49	0.85
7l	2-EtO-C_6H_4	O	H	5.4	0.53	1.9	0.69

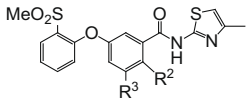
[a] Values are the means of two or more independent assays. Compound **2a** is the internal standard (EC_{50}: 0.42 ± 0.09 and 0.14 ± 0.04).
[b] The maximal activating response elicited the compounds as a ratio of the maximal response evoked by **2a** at each concentration independently.

To enhance the GK activity of **7h**, we hypothesized that installation of a substituent into the 2- or 3-position of the core benzamide may result in an alternative noncovalent interaction with the GK enzyme. Based on this hypothesis, an alkoxy or phenoxy group was incorporated into the 2- or 3-position of the core structure in **7h** (Table 2). Unfortunately, the incorporation of an alkoxy (**20a**) or a phenoxy (**20b**) substituent at the 2-position led to a complete loss of GK activity, which was probably due to the hydrogen bonding interaction of the N–H of aminothiazole and the oxygen atom of the alkoxy or phenoxy part. In contrast, the 3-isopropoxy (**27c**) and 3-phenoxy (**16a**) derivatives significantly improved GK potency as compared to the lead compound **7h**. The 3-ethoxy compound (**27b**) had activity comparable to the isoprpoxy analog (**27c**), but the 3-methoxy (**27a**) substituent did not affect the GK potency of **7h** probably due to a lack of bulkiness.

This result suggested that the introduction of the bulky substitution onto the 3-position of the benzene ring was quite effective in increasing GK activity. Then, a 3,5-bis substituted benzamide, such as compounds **27c** and **16a**, was found to be a promising template, showing good GK potency without an aniline moiety in the structure.

Finally, further optimization on the substituent (R^1) of the benzamides **27c** and **16a** was performed (Table 3). The EC_{50} values of the 4-(methanesulfonyl)phenoxy derivatives (**16c** and **27e**) were superior to those of 2- (**27c** and **16a**) or 3-(methanesulfonyl)phenoxy derivatives (**16b** and **27d**), although the E_{max} value of **16c** was relatively low. It is noteworthy that this trend that the incorporation of 4-(methanesulfonyl)phenoxy group in 3,5-disubstituted benzamides (**16c** and **27e**) is effective in increasing GK potency, is opposite to that seen in the 3-monosubstituted benzamides (**7h–j**). We speculate that the binding mode of the 3,5-disubstituted benzamides in GK is slightly different from that of the 3-monosubstituted benzamides and, as a result, the 4-(methanesulfonyl)phenoxy group of **16c** or **27e** occupies the additional interaction space of GK. To confirm this hypothesis, we are attempting to co-crystallize these derivatives with GK.

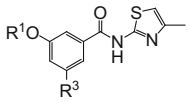
Table 2
GK activity of 2- or 3-substituted 5-phenoxy-benzamides



Compd	R^3	R^2	2.5 mM Glc		10 mM Glc	
			EC_{50}[a] (μM)	E_{max}[b]	EC_{50}[a] (μM)	E_{max}[b]
7h	H	H	5.5	1.0	1.1	1.1
20a	H	O-*i*Pr	>30	0.05	>30	0.20
20b	H	OPh	>30	0.06	>30	0.14
27a	OMe	H	11	0.75	1.9	0.99
27b	OEt	H	2.4	1.0	2.1	1.2
27c	O-*i*Pr	H	2.1	0.98	0.44	0.91
16a	OPh	H	1.1	0.81	0.61	0.98

[a] Values are the means of two or more independent assays. Compound **2a** is the internal standard (EC_{50}: 0.42 ± 0.09 and 0.14 ± 0.04).
[b] The maximal activating response elicited the compounds as a ratio of the maximal response evoked by **2a** at each concentration independently.

Table 3
Effects of the position of the methanesulfonyl group on the benzene ring



Compd	R^1	R^3	2.5 mM Glc		10 mM Glc	
			EC_{50}[a] (μM)	E_{max}[b]	EC_{50}[a] (μM)	E_{max}[b]
16a	2-$MeSO_2$-C_6H_4	PhO	1.1	0.81	0.61	0.98
16b	3-$MeSO_2$-C_6H_4	PhO	1.1	0.60	0.94	0.68
16c	4-$MeSO_2$-C_6H_4	PhO	0.42	0.73	0.35	0.83
27c	2-$MeSO_2$-C_6H_4	*i*PrO	2.1	0.97	0.44	0.91
27d	3-$MeSO_2$-C_6H_4	*i*PrO	1.1	0.73	0.09	0.79
27e	4-$MeSO_2$-C_6H_4	*i*PrO	0.33	0.99	0.13	1.0

[a] Values are the means of two or more independent assays. Compound **2a** is the internal standard (EC_{50}: 0.42 ± 0.09 and 0.14 ± 0.04).
[b] The maximal activating response elicited the compounds as a ratio of the maximal response evoked by **2a** at each concentration independently.

4. Pharmacological results and discussion

To assess the lead potential of this structure class, in vivo efficacy studies on the identified potent GKAs, the phenoxy-(**16c**) and isopropoxy (**27e**) derivatives, were conducted. In the normal fed mice, **27e** significantly reduced the plasma glucose AUC level after 30 mg/kg oral dosing, while **16c** did not show a significant glucose-lowering effect at 30 mg/kg (Fig. 3).

Next, we conducted the PK study and oral glucose tolerance test (OGTT) in rats, using **27e**. The data indicated that **27e** had a moderate PK profile in SD rats (Table 4). In the OGTT, **27e** exhibited glucose-lowering effects in a dose-dependent manner using concentrations of 3 to 30 mg/kg (Figs. 4–1 and 4–2). In particular, the decrease in glucose AUC seen with **27e** administration was almost equivalent to that of the original compound with an aniline moiety (**2a**).

5. Conclusion

In conclusion, modifications performed on the class of 2-aminobenzamide derivatives with the aim to identify a potent and orally active GK activator without an aniline structure, led to the discovery of compound **27e**. This compound was potent and orally bioavailable, and exhibited significant glucose-lowering efficacy in the OGTT study in rats, at 10 and 30 mg/kg oral administration. This was achieved by the deletion of the amine part of the benzam-

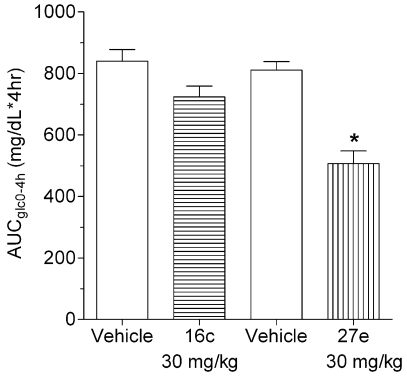


Figure 3. Glucose AUC of **16c** and **27e** in normal fed mouse.

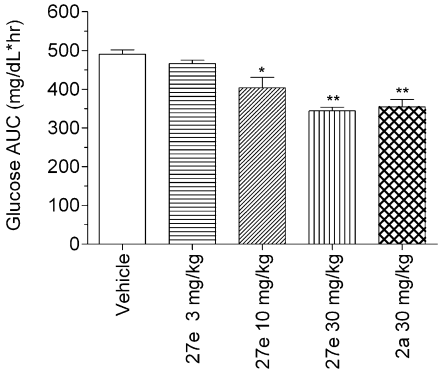
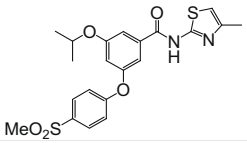


Figure 4-2. Glucose AUC of **27e** and **2a** in rat OGTT.

Table 4
Pharmacokinetic parameters of compound **27e** in SD rat



	$AUC_{0-\infty}$ (μM h)	CL_{tot} (mL/min/kg)	$T_{1/2}$ (h)	V_{dss} (L/kg)	C_{max} (μM)	T_{max} (h)	F (%)
IV (1 mg/kg, 60% PEG)	9.7	4.1	1.1	0.4			
PO (3 mg/kg, 0.5% MC)	12				2.9	1.0	40

F: oral bioavailability.
PEG: polyethylene glycol 400.
MC: methylcellulose.

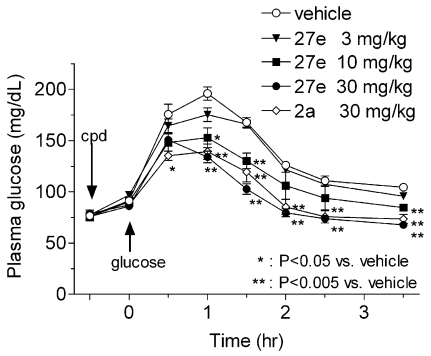


Figure 4-1. Blood glucose levels of **27e** and **2a** in rat OGTT.

ide core structure, followed by the incorporation of an isopropoxy moiety at the 3-position. Further SAR study of this class is underway to identify a development candidate.

6. Experimental

6.1. Chemistry

In general, reagents and solvents were used as purchased and without further purification. The ^{1}H NMR spectra were obtained at 300 MHz on a Gemini-300, 400 MHz on a MERCURY-400 (Varian) or 400 MHz on a JMN-AL400 (JEOL) spectrometer, with chemical shift (δ, ppm) expressed relative to TMS as an internal standard. Mass spectra were recorded with electronspray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on a Waters micromass ZQ, micromass Quattro II or micromass Q-Tof-2 instrument. Flash chromatography was carried out with prepacked silica gel columns (KP-Sil silica) from Biotage or (Purif-Pack) from Moritex. Preparative thin-layer chromatography (TLC) was performed on a TLC Silica Gel 60 F (Merck KGaA). Preparative HPLC purification was carried out on a YMC-Pack Pro C18 (YMC, 50 mm × 30 mm id), eluting with a gradient of CH_3CN/0.1% aq CF_3CO_2H) 10:90–50:50 over 8 min at a flow rate of 40 mL/min. High resolution mass spectra were recorded with electron-spray ionization on a micromass Q-Tof-2 instrument. HPLC analysis was performed on a SPELCO Ascentis Express (4.6 × 150 mm id), eluting with a gradient of (a) 5:95–90:10 CH_3CN: 0.1% aqueous H_3PO_4, linear gradient over 7 min followed by 90:10 isocratic over 1 min and (b) 5:95–80:20 CH_3CN: 10 mM potassium phosphate buffer, linear gradient over 7 min followed by 80:20 isocratic over 1 min (detection at 210 nm). All solvent and reagent were obtained from commercial sources and used without purification.

6.2. N-(4-Methyl-1,3-thiazol-2-yl)-3-[(4-methyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]benzamide (3)

To a solution of $NaNO_2$ (13.0 mg, 0.19 mmol) in concd. H_2SO_4 (0.085 mL) was added **2a** (24.7 mg, 0.071 mmol) in AcOH (0.3 mL), and the mixture was stirred at room temperature for 20 min. To the reaction mixture was added Cu_2O (12 mg, 0.084 mmol) in EtOH (0.3 mL), and the mixture was stirred at 100 °C for 30 min. After cooling, the reaction was quenched with saturated $NaHCO_3$ solution and the resulting mixture was extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel (10% MeOH/$CHCl_3$) to give **3** (5.6 mg, 24%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (3H, d, J = 1.0 Hz), 3.64 (3H, s), 6.56 (1H, d, J = 1.0 Hz), 7.44 (1H, t, J = 7.7 Hz), 7.78 (1H, ddd, J = 1.0, 1.8, 7.7 Hz), 7.85 (1H, ddd, J = 1.0, 1.8, 7.7 Hz), 7.96 (1H, t, J = 1.8 Hz), 8.29 (1H, s); MS (ESI) m/z = 332 $[M+H]^+$; HRMS (ESI) calcd for $C_{14}H_{14}N_5OS_2$ 332.0640; found 332.0645 $[M+H]^+$.

6.3. 5-(2-Fluorophenoxy)-*N*-(4-methyl-1,3-thiazol-2-yl)-2-nitrobenzamide (5b)

To a solution of **4** (204 mg, 0.73 mmol) in DMF (2.0 mL) were added Et_3N (1.21 mL, 8.71 mmol) and 2-fluorophenol (0.39 mL, 4.35 mmol), and the mixture was stirred at 100 °C overnight. After cooling, the reaction was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (33% EtOAc/hexane) to give **5b** (244 mg, 90%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98 (3H, br s), 6.56 (1H, s), 6.98 (1H, s), 7.07–7.24 (5H, m), 8.11 (1H, d, J = 9.0 Hz); MS (ESI) m/z = 374 $[M+H]^+$.

6.4. 2-Amino-5-(2-fluorophenoxy)-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide (6b)

To a solution of **5b** (240 mg, 0.64 mmol) in *i*PrOH (4.0 mL) were added saturated NH_4Cl solution (3.0 mL) and Fe (2.0 g), and the mixture was stirred at 100 °C for 20 min. After cooling, the mixture was filtered through a pad of Celite and the filtrate was evaporated under reduced pressure. The residue was diluted with water and EtOAc, and the organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (25% EtOAc/hexane) to give **6b** (196 mg, 89%) as colorless foam. ^{1}H NMR (300 MHz, CD_3OD) δ 2.27 (3H, s), 6.61 (1H, s), 6.83 (1H, d, J = 9.0 Hz), 6.94–7.19 (5H, m), 7.42 (1H, d, J = 2.8 Hz); MS (ESI) m/z = 344 $[M+H]^+$.

6.5. 3-(2-Fluorophenoxy)-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide (7b)

Compound **7b** was prepared from **6b** in a similar manner as described for compound **3** as colorless foam. Yield: 25%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09 (3H, d, J = 1.0 Hz), 6.54 (1H, d, J = 1.0 Hz), 7.05–7.24 (5H, m), 7.39 (1H, s), 7.45 (1H, t, J = 7.8 Hz), 7.58 (1H, d, J = 7.8 Hz); MS (ESI) m/z = 329 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{14}N_2O_2FS$ 329.0760; found 329.0769 $[M+H]^+$.

6.6. N-(4-Methyl-1,3-thiazol-2-yl)-3-phenoxybenzamide (7a)

Compound **7a** was prepared from **4** in a similar manner as described for compound **6b** and **3** as colorless foam. Yield: 16%; **6a**; ^{1}H NMR (300 MHz, $CDCl_3$) δ *2.21–2.24* (3H, m), 5.53 (1H, s), 6.51 (1H, s), 6.75 (1H, d, J = 8.8 Hz), 6.86–6.89 (5H, m), 7.03–7.14 (3H, m), 7.25–7.30 (2H, m); MS (ESI) m/z = 326 $[M+H]^+$; **7a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (3H, d, J = 1.0 Hz), 6.54 (1H, d, J = 1.0 Hz), 6.98 (2H, d, J = 7.8 Hz), 7.12–7.25 (3H, m), 7.26–7.45 (3H, m), 7.57–7.58 (1H, m); MS (ESI) m/z = 311 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{15}N_2O_2S$ 311.0854; found 311.0864 $[M+H]^+$.

6.7. 3-(3-Fluorophenoxy)-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide (7c)

Compound **7c** was prepared from **4** in a similar manner as described for compound **6b** and **3** as colorless foam. Yield: 6%; **6c**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (3H, s), 6.52 (1H, d, J = 1.0 Hz), 6.59–6.79 (4H, m), 7.08 (1H, dd, J = 2.7, 8.8 Hz), 7.16–7.26 (2H, m); MS (ESI) m/z = 344 $[M+H]^+$; **7c**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (3H, s), 6.56 (1H, s), 6.72–6.86 (3H, m), 7.25–7.32 (2H, m), 7.49 (1H, t, J = 8.0 Hz), 7.56 (1H, s), 7.65 (1H, d, J = 8.0 Hz); MS (ESI) m/z = 329 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{14}N_2O_2FS$ 329.0760; found 329.0766 $[M+H]^+$.

6.8. 3-(4-Fluorophenoxy)-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide (7d)

Compound **7d** was prepared from **4** in a similar manner as described for compound **6b** and **3** as colorless foam. Yield: 6%; **6d**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (3H, s), 5.53 (2H, s), 6.51 (1H, s), 6.75 (1H, d, J = 9.2 Hz), 6.78–6.83 (2H, m), 6.93–6.97 (2H, m), 7.03–7.06 (2H, m); MS (ESI) m/z = 344 $[M+H]^+$; **7d**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (3H, s), 6.55 (1H, s), 6.94–7.07 (4H, m), 7.19–7.22 (1H, m), 7.40–7.44 (2H, m), 7.57 (1H, d, J = 8.0 Hz); MS (ESI) m/z = 329 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{14}N_2O_2FS$ 329.0760; found 329.0767 $[M+H]^+$.

6.9. 3-(2-Methylphenoxy)-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide (7e)

Compound **7e** was prepared from **4** in a similar manner as described for compound **6b** and **3** as colorless foam. Yield: 51%; **6e**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (6H, s), 6.52 (1H, s), 6.71–6.76 (2H, m), 6.99–7.10 (4H, m), 7.21 (1H, d, J = 6.7 Hz); MS (ESI) m/z = 340 $[M+H]^+$; **7e**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05 (3H, s), 2.18 (3H, s), 6.53 (1H, s), 6.85 (1H, dd, J = 1.0, 7.9 Hz), 7.05–7.25 (4H, m), 7.33 (1H, t, J = 1.0 Hz), 7.41 (1H, t, J = 7.9 Hz), 7.54 (1H, d, J = 7.9 Hz); MS (ESI) m/z = 325 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{17}N_2O_2S$ 325.1011; found 325.1021 $[M+H]^+$.

6.10. 3-(3-Methylphenoxy)-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide (7f)

Compound **7f** was prepared from **4** in a similar manner as described for compound **6b** and **3** as colorless foam. Yield: 16%; **6f**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (6H, s), 6.53 (1H, s), 6.71–6.77 (3H, m), 6.86–6.89 (1H, m), 7.08 (1H, dd, J = 2.7, 8.9 Hz), 7.16–7.21 (2H, m); MS (ESI) m/z = 340 $[M+H]^+$; **7f**; ^{1}H NMR (300 MHz, $CDCl_3$) δ *2.20–2.24* (3H, m), 2.34 (3H, s), 6.55 (1H, s), 6.79–6.85 (2H. m), 6.97 (1H, dd, J = 0.8, 7.6 Hz), 7.21–7.26 (2H, m), 7.44 (1H, t, J = 7.6 Hz), 7.48–7.50 (1H, m), 7.58 (1H, d, J = 7.6 Hz); MS (ESI) m/z = 325 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{17}N_2O_2S$ 325.1011; found 325.1017 $[M+H]^+$.

6.11. 3-(4-Methylphenoxy)-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide (7g)

Compound **7g** was prepared from **4** in a similar manner as described for compound **6b** and **3** as colorless foam. Yield: 8%; **6g**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (3H, s), 2.24 (3H, s), 5.48 (2H, s), 6.50 (1H, s), 6.72–6.75 (3H, m), 7.02–7.09 (4H, m); MS (ESI) m/z = 340 $[M+H]^+$; **7g**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (3H, br s), 2.29 (3H, s), 6.55 (1H, s), 6.85–6.89 (2H. m), 7.13–7.16 (2H, m), 7.23–7.26 (1H, m), 7.38 (1H, s), 7.41–7.46 (1H, m), 7.56–7.58 (1H, m); MS (ESI) m/z = 325 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{17}N_2O_2S$ 325.1011; found 325.1021 $[M+H]^+$.

6.12. 3-(2-Methoxyphenoxy)-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide (7k)

Compound **7k** was prepared from **4** in a similar manner as described for compound **6b** and **3** as colorless foam. Yield: 4%; **6k**; ^{1}H NMR (300 MHz, $CDCl_3$) δ *2.25–2.27* (3H, m), 3.86 (3H, s), 6.51 (1H, s), 6.73 (1H, d, J = 9.2 Hz), 6.80–6.90 (2H, m), 7.04–7.10 (4H, m); MS (ESI) m/z = 356 $[M+H]^+$; **7k**; ^{1}H NMR (300 MHz, $CDCl_3$) δ *2.02–2.10* (3H, m), 3.79 (3H, s), 6.53 (1H, s), 6.92–7.01 (3H, m), 7.12–7.22 (2H, m), 7.33–7.44 (2H, m), 7.53 (1H, d, J = 7.6 Hz); MS (ESI) m/z = 341 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{17}N_2O_3S$ 341.0960; found 341.0965 $[M+H]^+$.

6.13. 3-(2-Ethoxyphenoxy)-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide (7l)

Compound **7l** was prepared from **4** in a similar manner as described for compound **6b** and **3** as colorless foam. Yield: 47%; **6l**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (3H, t, J = 7.0 Hz), 2.05–2.27 (3H, m), 4.07 (2H, q, J = 7.0 Hz), 5.44 (1H, s), 6.50 (1H, s), 6.73 (1H, d, J = 9.4 Hz), 6.81–6.86 (2H, m), 6.93–7.08 (4H, m); MS (ESI) m/z = 370 $[M+H]^+$; **7l**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (3H, t, J = 7.1 Hz), 2.17–2.27 (3H, m), 4.01 (2H, q, J = 7.1 Hz), 6.54 (1H, d, J = 1.0 Hz), 6.94–7.05 (3H, m), 7.12–7.20 (2H, m), 7.38–7.43 (2H, m), 7.53 (1H, d, J = 7.7 Hz); MS (ESI) m/z = 355 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{19}N_2O_3S$ 355.1116; found 355.1127 $[M+H]^+$.

6.14. 3-[2-(Methylsulfonyl)phenoxy]-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide (7h)

To a solution of **4** (427 mg, 1.52 mmol) in DMF (5.0 mL) were added K_2CO_3 (2.50 g, 18.2 mmol) and 2-(methylthio)phenol (0.80 mL, 9.10 mmol), and the mixture was stirred at 100 °C overnight. After cooling, the mixture was partitioned between water and EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (50% EtOAc/hexane) to give **5h** (607 mg, 99%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (3H, br s), 2.41 (3H, s), 6.56 (1H, s), 6.91–6.98 (2H, m), 7.07–7.32 (4H, m), 8.10–8.13 (1H, m); MS (ESI) m/z = 402 $[M+H]^+$.

To a solution of **5h** (310 mg, 0.77 mmol) in *i*PrOH (5 mL) were added saturated NH_4Cl solution (6.0 mL) and Fe (3.0 g), and the mixture was stirred at 100 °C for 20 min. After cooling, the mixture was filtered through a pad of Celite and the filtrate was evaporated under reduced pressure. The residue was diluted with water and EtOAc, and the organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (30% EtOAc/hexane) to give **6h** (137 mg, 48%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (3H, d, J = 1.0 Hz), 2.46 (3H, s), 6.51 (1H, d, J = 1.0 Hz), 6.74 (1H, d, J = 9.3 Hz), 7.05–7.11 (4H, m), 7.23–7.26 (1H, m); MS (ESI) m/z = 372 $[M+H]^+$.

To a suspension of $NaNO_2$ (28.0 mg, 0.40 mmol) in concentrated H_2SO_4 (0.2 mL) was added a solution of **6h** (58.0 mg, 0.15 mmol) in AcOH (3.0 mL), and the mixture was stirred at room temperature for 20 min. To the mixture was added Cu_2O (28.0 mg) in EtOH (1.0 mL), and the mixture was further stirred at 50 °C for 30 min. After cooling, the mixture was partitioned between saturated $NaHCO_3$ solution and $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by preparative TLC on silica gel (60% EtOAc/hexane) to give 3-[2-(methylsulfanyl)phenoxy]-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide (18.0 mg) as a colorless oil.

To a solution of the above obtained compound (16.0 mg, 0.042 mmol) in $CHCl_3$ (2.0 mL) was added *m*CPBA (36.0 mg, 0.19 mmol) at 0 °C, and the mixture was stirred for 50 min. The reaction was quenched with saturated $Na_2S_2O_3$ solution and the resulting mixture was extracted with EtOAc. The organic phase was washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated. The residue was purified by preparative TLC on silica gel (50% EtOAc/hexane) to provide **7h** (19.2 mg, 47%) as colorless foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (3H, d, J = 1.0 Hz), 3.23 (3H, s), 6.56 (1H, d, J = 1.0 Hz), 6.94 (1H, dd, J = 0.9, 8.2 Hz), 7.28–7.33 (2H, m), 7.47–7.59 (2H, m), 7.63 (1H, d, J = 1.2 Hz), 7.70 (1H, dd, J = 1.2, 7.6 Hz), 8.08 (1H, dd, J = 1.4, 7.8 Hz); MS (ESI) m/z = 389 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{17}N_2O_4S_2$ 389.0630; found 389.0628 $[M+H]^+$.

6.15. Methyl 3-[3-(methylsulfanyl)phenoxy]benzoate (9i)

To a solution of **8** (1.0 g, 6.57 mmol) and [3-(methylthio)phenyl]boronic acid (1.22 g, 7.23 mmol) in $CHCl_3$ (50 mL) were added $Cu(OAc)_2$ (1.31 g, 7.23 mmol) and Et_3N (4.58 mL, 32.9 mmol), and the mixture was stirred at room temperature overnight. The mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (20% EtOAc/hexane) to give **9i** (198 mg, 11%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (3H, s), 3.90 (3H, s), 6.74–6.76 (1H, m), 6.90 (1H, t, J = 2.0 Hz), 7.01–7.02 (1H, m), 7.21–7.22 (1H, m), 7.26–7.27 (1H, m), 7.41 (1H, d, J = 8.0 Hz), 7.66 (1H, dd, J = 1.5, 2.0 Hz), 7.78–7.80 (1H, m); MS (ESI) m/z = 275 $[M+H]^+$.

6.16. 3-[3-(Methylsulfonyl)phenoxy]-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide (7i)

To a solution of **9i** (195 mg, 0.71 mmol) in $CHCl_3$ (10 mL) was added *m*CPBA (613 mg, 3.55 mmol) at 0 °C, and the mixture was stirred for 2 h. The reaction was quenched with saturated $Na_2S_2O_3$ solution and the resulting mixture was extracted with EtOAc. The organic phase was washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated to provide methanesulfonyl derivative as colorless foam.

To a solution of the above obtained sulfone compound in a mixture of $CHCl_3$ (1.0 mL) and MeOH (3.0 mL) was added 5 N NaOH solution (0.85 mL, 4.26 mmol), and the mixture was stirred at room temperature overnight. The mixture was neutralized with 5 N HCl solution and extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. To a solution of the above–obtained carboxylic acid in $CHCl_3$ (3.0 mL) were added 2-amino-4-methylthiazole (162 mg, 1.42 mmol), HOBt-hydrate (109 mg, 0.71 mmol) and EDCI (273 mg, 1.42 mmol), and the mixture was stirred at room temperature overnight. The mixture was evaporated and the residue was purified by silica gel column chromatography (80% EtOAc/hexane) to give **7i** (172 mg, 62%) as colorless foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (1H, d, J = 1.0 Hz), 3.08 (3H, s), 6.58 (1H, d, J = 1.0 Hz), 7.28–7.29 (2H, m), 7.50–7.60 (4H, m), 7.66–7.68 (1H, m), 7.71–7.73 (1H, m), 10.31 (1H, br s); MS (ESI) m/z = 389 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{17}N_2O_4S_2$ 389.0630; found 389.0628 $[M+H]^+$.

6.17. Methyl 3-[4-(methylsulfanyl)phenoxy]benzoate (9j)

Compound **9j** was prepared from **8** in a similar manner as described for compound **9i** as colorless foam. Yield: 9%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (3H, s), 3.90 (3H, s), 6.95–6.97 (1H, m), 7.20 (1H, dd, J = 1.3, 8.2 Hz), 7.26–7.30 (2H, m), 7.40 (1H, t, J = 8.2 Hz), 7.63 (1H, dd, J = 1.3, 2.4 Hz), 7.77 (1H, dd, J = 1.3, 8.2 Hz); MS (ESI) m/z = 275 $[M+H]^+$.

6.18. 3-[4-(Methylsulfonyl)phenoxy]-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide (7j)

Compound **7j** was prepared from **9j** in a similar manner as described for compound **7i** as colorless foam. Yield: 36%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (3H, d, J = 1.0 Hz), 3.09 (3H, s), 6.59 (1H, d, J = 1.0 Hz), 7.14 (2H, dd, J = 2.0, 7.3 Hz), 7.33 (2H, dd, J = 2.0, 7.3 Hz), 7.57 (1H, t, J = 8.0 Hz), 7.64 (1H, t, J = 2.2 Hz), 7.72 (1H, d, J = 8.0 Hz), 7.94 (1H, dd, J = 2.0, 7.3 Hz); MS (ESI) m/z = 389 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{17}N_2O_4S_2$ 389.0630; found 389.0631 $[M+H]^+$.

6.19. 3,5-Difluoro-*N*-(4-methyl-1,3-thiazol-2-yl)-2-nitrobenzamide (10)

To 3,5-difluorobenzoic acid (1.00 g, 6.33 mmol) was added fuming HNO_3 (3.0 mL), and the mixture was stirred at room temperature for 3 days. The mixture was poured into ice-cold water (150 mL) and extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. To a solution of the residual compound in $CHCl_3$ (15 mL) were added 2-amino-4-methylthiazole (720 mg, 6.30 mmol), Et_3N (2.20 mL, 15.8 mmol) and 2-chloro-1,3-dimethylimidazolinium chloride (1.33 g, 7.88 mmol), and the mixture was stirred at room temperature overnight. The mixture was partitioned between water and $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (50% EtOAc/hexane) to give **10** (485 mg, 26%) as yellow foam. ^{1}H NMR (300 MHz, $CDCl_3$)

δ 2.28 (3H, d, J = 1.1 Hz), 6.50 (1H, d, J = 1.1 Hz), 7.13 (1H, ddd, J = 2.5, 7.6, 9.4 Hz), 7.42 (1H, ddd, J = 1.8, 2.5, 8.0 Hz); MS (ESI) m/z = 300 $[M+H]^+$.

6.20. 5-Fluoro-*N*-(4-methyl-1,3-thiazol-2-yl)-2-nitro-3-phenoxybenzamide (11)

To a solution of **10** (130 mg, 0.43 mmol) in DMF (4.0 mL) were added phenol (289 mg, 3.03 mmol) and Et_3N (0.85 mL, 6.07 mmol), and the mixture was stirred at 120 °C for 11 h. After cooling, the mixture was concentrated in vacuo. The residue was purified by preparative TLC on silica gel (40% EtOAc/hexane) to give **11** (110 mg, 68%) as yellow foam. ^1H NMR (300 MHz, $CDCl_3$) δ 2.18 (3H, d, J = 1.0 Hz), 6.55 (1H, d, J = 1.0 Hz), 6.71 (1H, dd, J = 2.6, 9.0 Hz), 7.04 (1H, dd, J = 2.6, 7.8 Hz), 7.09 (2H, d, J = 7.6 Hz), 7.26 (1H, t, J = 7.6 Hz), 7.43 (2H, d, J = 7.6 Hz); MS (ESI) m/z = 374 $[M+H]^+$.

6.21. 2-Amino-*N*-(4-methyl-1,3-thiazol-2-yl)-5-[2-(methylthio)phenoxy]-3-phenoxybenzamide (12)

To a solution of **11** (85.0 mg, 0.23 mmol) in DMF (4.0 mL) were added K_2CO_3 (315 mg, 2.28 mmol) and 2-(methylthio)phenol (0.10 mL, 1.14 mmol), and the mixture was stirred at 100 °C overnight. After cooling, the mixture was diluted with water and EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (50% EtOAc/hexane) to give the 5-[2-(methylthio)phenoxy]-2-nitro-3-phenoxybenzamide derivative (78.0 mg) as colorless foam.

Compound **12** was prepared from the above obtained compound in a similar manner as described for compound **7h** as colorless foam. Yield: 53%; ^1H NMR (300 MHz, $CDCl_3$) δ 2.27 (3H, s), 2.43 (3H, s), 6.53 (1H, s), 6.72–6.75 (1H, m), 6.77 (1H, d, J = 2.5 Hz), 6.90 (1H, d, J = 2.5 Hz), 7.03–7.07 (4H, m), 7.11–7.23 (2H, m), 7.33–7.38 (2H, m); MS (ESI) m/z = 464 $[M+H]^+$.

6.22. 2-Amino-5-[2-(methylsulfonyl)phenoxy]-*N*-(4-methyl-1,3-thiazol-2-yl)-3-phenoxybenzamide (13)

Compound **13** was prepared from **12** in a similar manner as described for compound **7h** as colorless foam. Yield: 20%; ^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (3H, s), 3.28 (3H, s), 6.54 (1H, s), 6.81 (1H, d, J = 2.4 Hz), 6.86 (1H, d, J = 7.8 Hz), 7.05 (2H, d, J = 8.2 Hz), 7.16–7.22 (2H, m), 7.19 (1H, d, J = 2.4 Hz), 7.37 (2H, t, J = 8.2 Hz), 7.50 (1H, dt, J = 1.4, 7.8 Hz), 8.04 (1H, dd, J = 1.4, 7.9 Hz); MS (ESI) m/z = 496 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{22}N_3O_5S_2$ 496.1001; found 496.0991 $[M+H]^+$.

6.23. 3-[2-(Methylsulfonyl)phenoxy]-*N*-(4-methyl-1,3-thiazol-2-yl)-5-phenoxybenzamide (16a)

Compound **16a** was prepared from **13** in a similar manner as described for the synthesis of **3** as colorless foam. Yield: 56%; ^1H NMR (300 MHz, $CDCl_3$) δ 2.17 (3H, s), 3.27 (3H, s), 6.55 (1H, s), 6.99 (1H, t, J = 2.1 Hz), 6.99 (1H, d, J = 7.8 Hz), 7.02 (2H, d, J = 8.1 Hz), 7.17 (1H, t, J = 7.8 Hz), 7.31 (1H, d, J = 2.1 Hz), 7.30–7.39 (1H, m), 7.34 (1H, d, J = 2.1 Hz), 7.36 (1H, t, J = 8.1 Hz), 7.59 (1H, t, J = 7.8 Hz), 8.08 (1H, d, J = 7.8 Hz); MS (ESI) m/z = 481 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{21}N_2O_5S_2$ 481.0892; found 481.0885 $[M+H]^+$.

6.24. Methyl 3-[3-(methylthio)phenoxy]-5-phenoxy-benzoate (15b)

To a suspension of methyl 3-hydroxy-5-phenoxybenzoate **14** (190 mg, 0.79 mmol), MS4A (1.0 g) and [3-(methylthio)phenyl]boronic acid (160 mg, 0.94 mmol) in $CHCl_3$ (10 mL) were added $Cu(OAc)_2$ (140 mg, 0.79 mmol) and Et_3N (0.55 mL, 3.93 mmol), and the mixture was stirred at room temperature overnight. The mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (20% EtOAc/hexane) to give **15b** (81.0 mg, 28%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 2.46 (3H, s), 3.86 (3H, s), 6.76–6.79 (1H, m), 6.86–6.92 (2H, m), 6.96–7.05 (3H, m), 7.14–7.28 (2H, m), 7.34–7.39 (4H, m).

6.25. 3-[3-(Methylsulfonyl)phenoxy]-*N*-(4-methyl-1,3-thiazol-2-yl)-5-phenoxybenzamide (16b)

Compound **16b** was prepared from **15b** in a similar manner as described for compound **7h** as colorless foam. Yield: 77%; ^1H NMR (400 MHz, $CDCl_3$) δ 2.29 (3H, s), 3.08 (3H, s), 6.56 (1H, s), 6.92 (1H, d, J = 2.2 Hz), 7.07 (2H, d, J = 7.6 Hz), 7.20–7.22 (3H, m), 7.30–7.42 (3H, m), 7.56–7.62 (2H, m), 7.74 (1H, d, J = 7.6 Hz); MS (ESI) m/z = 481 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{21}N_2O_5S_2$ 481.0892; found 481.0897 $[M+H]^+$.

6.26. Methyl 3-[4-(methylthio)phenoxy]-5-phenoxy-benzoate (15c)

Compound **15c** was prepared from **14** in a similar manner as described for compound **15b**. Yield: 33%; ^1H NMR (300 MHz, $CDCl_3$) δ 2.05 (3H, s), 2.45 (3H, s), 6.53 (1H, s), 6.89–7.36 (12H, m); MS (ESI) m/z = 449 $[M+H]^+$.

6.27. 3-[4-(Methylsulfonyl)phenoxy]-*N*-(4-methyl-1,3-thiazol-2-yl)-5-phenoxybenzamide (16c)

Compound **16c** was prepared from **15c** in a similar manner as described for compound **7h** as colorless foam. Yield: 54%; ^1H NMR (300 MHz, $CDCl_3$) δ 2.29 (3H, s), 3.08 (3H, s), 6.56 (1H, s), 6.92 (1H, d, J = 2.2 Hz), 7.07 (2H, d, J = 7.6 Hz), 7.20–7.22 (3H, m), 7.30–7.42 (3H, m), 7.56–7.62 (2H, m), 7.74 (1H, d, J = 7.6 Hz); MS (ESI) m/z = 481 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{21}N_2O_5S_2$ 481.0892; found 481.0900 $[M+H]^+$.

6.28. Methyl 5-iodo-2-(propan-2-yloxy)benzoate (18)

To a solution of methyl **17** (2.0 g, 7.19 mmol) in DMF (15 mL) were added K_2CO_3 (1.49 g, 10.8 mmol) and 2-bromopropane (0.88 mL, 9.35 mmol), and the mixture was stirred at 60 °C overnight. After cooling, the mixture was partitioned between water and EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (20% EtOAc/hexane) to give **18** (2.30 g, 93%) as a colorless solid. ^1H NMR (400 MHz, $CDCl_3$) δ *1.32–1.40* (6H, m), 3.87 (3H, s), 4.52–4.59 (1H, m), 6.75 (1H, d, J = 8.8 Hz), 7.68 (1H, dd, J = 2.6, 8.8 Hz), 8.02 (1H, d, J = 2.6 Hz).

6.29. Methyl 5-[2-(methylsulfanyl)phenoxy]-2-(propan-2-yloxy)benzoate (19)

To a solution of **18** (540 mg, 1.69 mmol) in toluene (30 mL) were added 2-(methylsulfanyl)phenol (473 mg, 3.37 mmol), copper(I) trifluoromethanesulfonate benzene complex (1.69 g, 3.37 mmol) and Cs_2CO_3 (1.65 g, 5.06 mmol) and EtOAc (3 drops), and the mixture was stirred at 120 °C overnight. After cooling, the reaction mixture was quenched with water and filtered through a pad of Celite. The filtrate was evaporated and the residue was partitioned between water and EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (10% EtOAc/hexane) to give **19**

(34.0 mg, 6%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (6H, d, J = 6.3 Hz), 2.46 (3H, s), 3.85 (3H, s), 4.46–4.52 (1H, m), 6.79–6.87 (1H, m), 6.96 (1H, d, J = 9.3 Hz), 7.07–7.13 (3H, m), 7.25–7.28 (1H, m), 7.41 (1H, d, J = 2.9 Hz; MS (ESI) m/z = 333 $[M+H]^+$.

6.30. 5-[2-(Methylsulfonyl)phenoxy]-*N*-(4-methyl-1,3-thiazol-2-yl)-2-(propan-2-yloxy)benzamide (20a)

Compound **20a** was prepared from **19** in a similar manner as described for the synthesis of **7i** as colorless foam. Yield: 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (6H, d, J = 6.3 Hz), 2.38 (3H, d, J = 1.0 Hz), 3.31 (3H, s), 4.79–4.85 (1H, m), 6.56 (1H, s), 6.92 (1H, dd, J = 1.0, 8.3 Hz), 7.09 (1H, d, J = 9.3 Hz), 7.23–7.27 (1H, m), 7.31 (1H, dd, J = 3.2, 9.3 Hz), 7.51–7.55 (1H, m), 8.05–8.07 (2H, m), 11.34 (1H, s); MS (ESI) m/z = 447 $[M+H]^+$; HRMS (ESI) calcd for $C_{21}H_{23}N_2O_5S_2$ 447.1048; found 447.1049 $[M+H]^+$.

6.31. Methyl 2-bromo-5-[2-(methylsulfonyl)phenoxy]benzoate (22)

To a solution of **21** (1.08 g, 4.67 mmol) in DMF (15 mL) were added Cs_2CO_3 (3.05 g, 9.35 mmol) and 2-fluorophenymethylsulfone (1.22 g, 7.01 mmol), and the mixture was stirred at 80 °C for 6 h. After cooling, the mixture was partitioned between water and EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (50% EtOAc/hexane) to give **22** (1.06 g, 59%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.29 (3H, s), 3.92 (3H, s), 6.96 (1H, dd, J = 1.4, 8.5 Hz), 7.08 (1H, dd, J = 2.9, 8.5 Hz), 7.30–7.33 (1H, m), 7.55 (1H, d, J = 2.9 Hz), 7.59 (1H, dd, J = 1.4, 8.5 Hz), 7.67 (1H, d, J = 8.5 Hz), 8.09 (1H, dd, J = 1.4, 8.5 Hz).

6.32. Methyl 5-[2-(methylsulfonyl)phenoxy]-2-phenoxybenzoate (23)

To a solution of **22** (400 mg, 1.04 mmol) in pyridine (2.5 mL) were added phenol (195 mg, 2.08 mmol), K_2CO_3 (287 mg, 2.08 mmol) and CuO (165 mg, 2.08 mmol), and the mixture was stirred at 130 °C overnight. After cooling, the mixture was diluted with saturated NH_4Cl solution and filtered through a pad of Celite. The filtrate was evaporated and the residue was diluted with water and EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (50% EtOAc/hexane) to give **23** (172 mg, 42%) as yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (3H, s), 3.80 (3H, s), 6.96–6.98 (3H, m), 7.03 (1H, d, J = 9.3 Hz), 7.09–7.12 (1H, m), 7.21–7.30 (2H, m), 7.33–7.36 (2H, m), 7.54–7.59 (1H, m), 7.68 (1H, d, J = 2.9 Hz), 8.08–8.09 (1H, m); MS (ESI) m/z = 399 $[M+H]^+$.

6.33. 5-[2-(Methylsulfonyl)phenoxy]-*N*-(4-methyl-1,3-thiazol-2-yl)-2-phenoxybenzamide (20b)

Compound **20b** was prepared from **23** in a similar manner as described for the synthesis of **7i** as colorless foam. Yield: 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (3H, d, J = 1.0 Hz), 3.31 (3H, s), 6.57 (1H, d, J = 1.0 Hz), 6.86 (1H, d, J = 8.8 Hz), 6.97–6.99 (1H, m), 7.19–7.21 (3H, m), 7.27–7.32 (2H, m), 7.45–7.48 (2H, m), 7.54–7.58 (1H, m), 8.07–8.09 (2H, m), 10.91 (1H, s);.MS (ESI) m/z = 481 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{21}N_2O_5S_2$ 481.0892; found 482.0882 $[M+H]^+$.

6.34. Methyl 3-hydroxy-5-methoxybenzoate (25a)

To a solution of methyl 3,5-dihydroxybenzoate **24** (300 mg, 1.78 mmol) in DMF (1.0 mL) were added K_2CO_3 (490 mg, 3.57 mmol) and iodomethane (0.22 mL, 3.57 mmol), and the mixture was stirred at 60 °C overnight. After cooling, the mixture was partitioned between water and EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (30% EtOAc/hexane) to give **25a** (42.9 mg, 13%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (3H, s), 3.90 (3H, s), 5.17 (1H, s), 6.61 (1H, t, J = 2.2 Hz), 7.12 (1H, dd, J = 1.5, 2.2 Hz), 7.16–7.17 (1H, m).

6.35. Methyl 3-ethoxy-5-hydroxybenzoate (25b)

Compound **25b** was prepared from **24** in a similar manner as described for compound **25a**. Yield: 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (3H, t, J = 6.9 Hz), 3.88 (3H, s), 4.05 (2H, q, J = 6.9 Hz), 5.10 (1H, s), 6.60 (1H, t, J = 2.2 Hz), 7.10 (1H, dd, J = 1.5, 2.2 Hz), 7.15 (1H, dd, J = 1.5, 2.2 Hz).

6.36. Methyl 3-hydroxy-5-isopropoxybenzoate (25c)

Compound **25c** was prepared from **24** as described for compound **25a**. Yield: 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ *1.32–1.33* (6H, m), 3.88 (3H, s), 4.52–4.61 (1H, m), 5.50 (1H, s), 6.60 (1H, t, J = 2.2 Hz), 7.12 (1H, dd, J = 1.5, 2.2 Hz), 7.15 (1H, dd, J = 1.5, 2.2 Hz).

6.37. Methyl 3-methoxy-5-[2-(methylsulfonyl)phenoxy]-benzoate (26a)

To a solution of **25a** (40.0 mg, 0.22 mmol) in DMF (1.5 mL) were added Cs_2CO_3 (215 mg, 0.66 mmol) and 2-fluorophenymethylsulfone (76.0 mg, 0.44 mmol), and the mixture was stirred at 130 °C for 2 h. After cooling, the mixture was partitioned between water and EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (50% EtOAc/hexane) to give **26a** (54.2 mg, 73%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.30 (3H, s), 3.86 (3H, s), 3.90 (3H, s), 6.87 (1H, d, J = 2.2 Hz), 6.96 (1H, d, J = 8.0 Hz), 7.24–7.30 (1H, m), 7.35 (1H, d, J = 1.5 Hz), 7.43 (1H, dd, J = 1.5, 2.2 Hz), 7.54–7.58 (1H, m), 8.08 (1H, dd, J = 1.5, 8.0 Hz); MS (ESI) m/z = 337 $[M+H]^+$.

6.38. Methyl 3-ethoxy-5-[2-(methylsulfonyl)phenoxy]-benzoate (26b)

Compound **26b** was prepared from **25b** in a similar manner as described for compound **26a**. Yield: 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ *1.41–1.44* (3H, m), 3.29 (3H, s), 3.90 (3H, s), 4.04–4.11 (2H, m), 6.85 (1H, d, J = 2.2 Hz), 6.96 (1H, d, J = 8.0 Hz), 7.27–7.29 (1H, m), 7.34 (1H, d, J = 1.5 Hz), 7.42 (1H, d, J = 1.5 Hz), 7.53–7.58 (1H, m), 8.08 (1H, dd, J = 1.5, 8.0 Hz); MS (ESI) m/z = 351 $[M+H]^+$.

6.39. Methyl 3-isopropoxy-5-[2-(methylsulfonyl)phenoxy]-benzoate (26c)

Compound **26c** was prepared from **25c** in a similar manner as described for compound **26a**. Yield: 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ *1.33–1.35* (6H, m), 3.30 (3H, s), 3.88 (3H, s), 4.56–4.62 (1H, m), 6.83 (1H, d, J = 2.2 Hz), 6.97 (1H, dd, J = 1.5, 8.0 Hz), 7.24–7.29 (1H, m), 7.32 (1H, d, J = 1.5, 2.2 Hz), 7.41 (1H, dd, J = 1.5, 2.2 Hz), 7.53–7.58 (1H, m), 8.07 (1H, dd, J = 1.5, 8.0 Hz); MS (ESI) m/z = 365 $[M+H]^+$.

6.40. 3-Methoxy-5-[2-(methylsulfonyl)phenoxy]-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide (27a)

To a solution of **26a** (50.0 mg, 0.15 mmol) in a mixture of $CHCl_3$ (1.0 mL) and MeOH (1.0 mL) was added 5 N NaOH solution

(0.15 mL, 0.74 mmol), and the mixture was stirred at room temperature overnight. The mixture was neutralized with 5 N HCl solution and extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. To a solution of the above obtained carboxylic acid in $CHCl_3$ (3.0 mL) were added 2-amino-4-methylthiazole (33.3 mg, 0.29 mmol), HOBt-hydrate (67.0 mg, 0.44 mmol) and EDCI (55.9 mg, 0.29 mmol), and the mixture was stirred at room temperature overnight. The mixture was evaporated and the residue was purified by silica gel column chromatography (70% EtOAc/hexane) to give **27a** (42.4 mg, 70%) as colorless foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ *2.23–2.30* (3H, m), 3.29 (3H, s), 3.84 (3H, s), 6.57 (1H, d, J = 1.0 Hz), 6.88 (1H, d, J = 2.2 Hz), 6.99–7.01 (1H, m), 7.16 (1H, t, J = 1.7 Hz), 7.28–7.29 (1H, m), 7.30–7.33 (1H, m), 7.56–7.60 (1H, m), 8.08 (1H, dd, J = 1.7, 8.0 Hz), 10.01 (1H, br s); MS (ESI) m/z = 419 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{19}N_2O_5S_2$ 419.0735; found 419.0728 $[M+H]^+$.

6.41. 3-Ethoxy-5-[2-(methylsulfonyl)phenoxy]-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide (27b)

Compound **27b** was prepared from **26b** in a similar manner as described for compound **27a** as colorless foam. Yield: 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (3H, t, J = 7.1 Hz), 2.29 (3H, s), 3.27 (3H, s), 4.06 (1H, q, J = 7.1 Hz), 6.57 (1H, s), 6.86 (1H, d, J = 2.2 Hz), 6.99–7.01 (1H, m), 7.16 (1H, t, J = 1.7 Hz), 7.26–7.27 (1H, m), 7.30–7.34 (1H, m), 7.56–7.60 (1H, m), 8.09 (1H, dd, J = 1.7, 7.0 Hz), 10.00 (1H, br s); MS (ESI) m/z = 433 $[M+H]^+$; HRMS (ESI) calcd for $C_{20}H_{21}N_2O_5S_2$ 433.0892; found 483.0888 $[M+H]^+$.

6.42. 3-Isopropoxy-5-[2-(methylsulfonyl)phenoxy]-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide (27c)

Compound **27c** was prepared from **26c** in a similar manner as described for compound **27a** as colorless foam. Yield: 52%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (6H, s), 2.29 (3H, s), 3.29 (3H, s), 4.55–4.61 (1H, m), 6.57 (1H, s), 6.85 (1H, d, J = 2.2 Hz), 7.00 (1H, d, J = 8.0 Hz), 7.12–7.13 (1H, m), 7.25 (1H, s), 7.31 (1H, d, J = 8.0 Hz), 7.56–7.60 (1H, m), 8.09 (1H, dd, J = 1.7, 7.0 Hz), 10.00 (1H, br s); MS (ESI) m/z = 447 $[M+H]^+$; HRMS (ESI) calcd for $C_{21}H_{23}N_2O_5S_2$ 447.1048; found 447.1042 $[M+H]^+$.

6.43. Methyl 3-hydroxy-5-[4-(methylthio)phenoxy]-benzoate (28e)

Compound **28e** was prepared from **24** as described for compound **15b**. Yield: 22%; ^{1}H NMR (300 MHz, CD_3OD) δ 2.46 (3H, s), 3.82 (3H, s), 6.58 (1H, t, J = 1.0 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.01 (1H, t, J = 1.0 Hz), 7.14 (1H, t, J = 1.0 Hz), 7.30 (2H, d, J = 8.8 Hz).

6.44. Methyl 3-isopropoxy-5-[4-(methylthio)phenoxy]-benzoate (29e)

Compound **29e** was prepared from **28e** as described for the synthesis of **25a**. Yield: 89%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (6H, s), 2.48 (3H, s), 3.88 (3H, s), 4.52–4.61 (1H, m), 6.70 (1H, d, J = 1.0 Hz), 6.96 (2H, d, J = 8.8 Hz), 7.18 (1H, t, J = 1.0 Hz), 7.26–7.31 (3H, m).

6.45. Methyl 3-isopropoxy-5-[3-(methylthio)phenoxy]-benzoate (29d)

Compound **29d** was prepared from **24** as described for the synthesis of **15b** and **25a**. Yield: 11%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (6H, d, J = 6.3 Hz), 2.46 (3H, s), 3.88 (3H, s), 4.55–4.61 (1H, m), 6.72 (1H, d, J = 2.1 Hz), 4.75–4.78 (1H, m), 6.91 (1H, t, J = 2.1 Hz), 7.00–7.02 (1H, m), 7.21–7.23 (1H, m), 7.26–7.27 (1H, m), 7.29–7.31 (1H, m); MS (ESI) m/z = 333 $[M+H]^+$.

6.46. 3-Isopropoxy-5-[3-(methylsulfonyl)phenoxy]-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide (27d)

Compound **27d** was prepared from **29d** in a similar manner as described for compound **7h** as colorless foam. Yield: 20%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (6H, d, J = 6.3 Hz), 2.30 (3H, s), 3.08 (3H, s), 4.55–4.61 (1H, m), 6.58 (1H, s), 6.77 (1H, t, J = 2.0 Hz), 7.08 (1H, t, J = 2.0 Hz), 7.23 (1H, t, J = 2.0 Hz), 7.30 (1H, dd, J = 2.0, 7.9 Hz), 7.56–7.59 (2H, m), 7.72 (1H, d, J = 7.9 Hz); MS (ESI) m/z = 447 $[M+H]^+$; HRMS (ESI) calcd for $C_{21}H_{23}N_2O_5S_2$ 447.1048; found 447.1047 $[M+H]^+$.

6.47. 3-Isopropoxy-5-[4-(methylsulfonyl)phenoxy]-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide (27e)

Compound **27e** was prepared from **29e** in a similar manner as described for compound **7h** as colorless foam. Yield: 56%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (6H, d, J = 6.0 Hz), 2.22 (3H, d, J = 0.7 Hz), 3.08 (3H, s), 4.53–4.57 (1H, m), 6.57 (1H, d, J = 0.7 Hz), 6.80 (1H, t, J = 2.0 Hz), 7.11 (1H, d, J = 2.0 Hz), 7.12 (2H, d, J = 8.8 Hz), 7.27 (1H, d, J = 2.0 Hz), 7.92 (2H, d, J = 8.8 Hz); MS (ESI) m/z = 447 $[M+H]^+$; HRMS (ESI) calcd for $C_{21}H_{23}N_2O_5S_2$ 447.1048; found 447.1053 $[M+H]^+$; HPLC (a) 99.6%; (b) 99.7%.

7. Biology

7.1. In vitro GK assay

The recombinant human liver GK used in this assay was expressed in *Escherichia coli* as a FLAG fusion protein. GK activity was measured by the glucose-6-phosphate dehydrogenase coupled continuous spectrophotometric assay. GK was incubated with DMSO solution in assay buffer containing 25 mM Hepes, pH 7.2, 1 mM dithiothreitol, 0.5 mM thionicotinamide adenine dinucleotide, 2 mM $MgCl_2$, 1 mM ATP, 2 U/mL glucose-6-phosphate dehydrogenase and 2.5 or 10 mM glucose at 30 °C. Reaction velocities were obtained from the rate of increase in absorbance at 405 nm after 5 min of reaction. The OD values were measured at each concentration of the evaluated compound, using the OD value of the DMSO control as 100%. The EC_{50} (μM) values were calculated from the OD value at each concentration, and used as indices of GK activator potency of the compound.

7.2. In vivo assay in mice

Ten-to-eleven-week old male ICR mice[†] (n = 4–5) were freely fed prior to performing the test. The mice were orally administrated compounds **16c**, **27e** or vehicle alone (0.5% methylcellulose solution). Blood glucose concentrations were measured just prior to and following oral dosing (0.5, 1, 1.5, 2, 3 and 4 h). AUC values were calculated from the data (from 0 h to 4 h).

7.3. Oral glucose tolerance test (OGTT)

Nine-week old male Wistar rats (n = 5) were fasted overnight before performing the test. The rats were orally administrated compounds **27e**, **2a** or vehicle alone (0.5% methylcellulose solution), followed 30 min later by an oral glucose challenge (2 g/kg). Plasma glucose concentrations were measured just prior to and fol-

[†] ICR mice: mice used for general purposes and established at The Institute for Cancer Research.

lowing the glucose challenge (30, 60, 90, and 120 min). AUC values were calculated from the data (from −30 min to 120 min).

Acknowledgments

The authors are grateful to Hirokazu Ohsawa and Miyoko Miyashita for the analytical and spectral studies and Hiroshi Takehana for the PK study in rats. We would also like to thank Dr. J. Sakaki and Dr. N. Ohtake for critical reading of the manuscript.

References and notes

1. Nathan, D. M. *N. Engl. J. Med.* **2002**, *347*, 1342.
2. Gershell, L. *Nat. Rev. Drug. Disc.* **2005**, *4*, 367.
3. Bell, D. S. H. *Treat. Endocrinol.* **2004**, *3*, 67.
4. Grimsby, J.; Sarabu, R.; Corbett, W. L.; Haynes, N. E.; Bizzarro, F. T.; Coffey, J. W.; Guertin, K. R.; Hilliard, D. W.; Kester, R. F.; Mahaney, P. E.; Marcus, L.; Qi, L. D.; Spence, C. L.; Tengi, J.; Magnuson, M. A.; Chu, C. A.; Dvorozniak, M. T.; Matschinsky, F. M.; Grippo, J. F. *Science* **2003**, *301*, 370.
5. Sarabu, R.; Grimsby, J. *Curr. Opin. Drug. Disc. Dev.* **2005**, *8*, 631.
6. Matschinsky, F. M.; Glaser, B.; Magnuson, M. A. *Diabetes* **1998**, *47*, 307.
7. Kamata, K.; Mitsuya, M.; Nishimura, T.; Eiki, J. I.; Nagata, Y. *Structure* **2004**, *12*, 429.
8. Guertin, K. R.; Grimsby, J. *Curr. Med. Chem.* **2006**, *13*, 1839.
9. Coghlan, M.; Leighton, B. *Exp. Opin. Invest. Drugs* **2008**, *17*, 145.
10. Futamura, M.; Hosaka, H.; Kadotani, A.; Shimazaki, H.; Shimazaki, H.; Sasaki, K.; Ohyama, S.; Nishimura, T.; Eiki, J.; Nagata, Y. *J. Biol. Chem.* **2006**, *281*, 37668.
11. Sarabu, R.; Berthel, S. J.; Kester, R. F.; Tilley, J. W. *Exp. Opin. Ther. Patents* **2008**, *18*, 759.
12. Daniewski, A.R.; Liu, W.; Radinov, R.N. WO Patent 2007/115968 .
13. Efanov, A. M.; Barrett, D. G.; Brenner, B. M.; Briggs, S. L.; Delaunois, A.; Durbin, J. D.; Giese, U.; Guo, H.; Radloff, M.; Sanz, G. G.; Sewing, S.; Wang, Y.; Weichert, A.; Zaliani, A.; Gromada, J. *Endocrinology* **2005**, *136*, 2696.
14. McKerrecher, D.; Allen, J. V.; Caulkett, P. W. R.; Donald, C. S.; Fenwick, M. L.; Grange, E.; Johnson, K. M.; Johnstone, C.; Jones, C. D.; Pike, K. G.; Rayner, J. W.; Walker, R. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2705.
15. Bertram, L. S.; Black, D.; Briner, P. H.; Chatfield, R.; Cooke, A.; Fyfe, M. C. T.; Murray, P. J.; Naud, F.; Nawano, M.; Procter, M. J.; Rakipovski, G.; Rasamison, C. M.; Reynet, C.; Schofield, K. L.; Shah, V. K.; Spindler, F.; Taylor, A.; Turton, R.; Williams, G. M.; Wong-Kai-In, P.; Yasuda, K. *J. Med. Chem.* **2008**, *51*, 4340.
16. Nishimura, T.; Iino, T.; Mitsuya, M.; Bamba, M.; Watanabe, H.; Tsukahara, D.; Kamata, K.; Sasaki, K.; Ohyama, S.; Hosaka, H.; Futamura, M.; Nagata, Y.; Eiki, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1357.
17. Kugler-Steigmeimer, M. E.; Friederich, U.; Graf, U.; Lutz, W. K.; Maier, P.; Schlatter, C. *Mutat. Res.* **1989**, *211*, 279.
18. Munoz, E. R.; Barnett, B. M. *Mutat. Res.* **1998**, *413*, 15.
19. Iino, T.; Hashimoto, N.; Takahashi, K.; Nakashima, H.; Eiki, J.; Nishimura, T. WO Patent 2004/076420.