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Discovery and structure–activity relationships of a novel class of quinazoline glucokinase activators

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ABSTRACT

We describe design, syntheses and structure–activity relationships of a novel class of 4,6-disubstituted quinazoline glucokinase activators. Prototype quinazoline leads (**4** and **5**) were designed based on the X-ray analyses of the previous 2-aminobenzamide lead classes. Modifications of the quinazoline leads led to the identification of a potent GK activator (**21d**).

Type 2 diabetes (T2D), a disease characterized by hyperglycemia (elevated blood glucose concentrations), is becoming more prevalent as a result of the recent dramatic rise in obesity levels. Current antidiabetic drugs to treat this disease include metformin, insulin, thiazolinediones, alpha-glucosidase inhibitors, sulfonylureas and DPPIV inhibitors. Despite these multiple treatment options, it is difficult to effectively treat T2D by single treatment option in the long term.[1–3] Therefore, there is an unmet medical need for the development of new, safe and effective antidiabetic therapies with novel and multiple mode of action.

Glucokinase (GK), a glucose-phosphorylating enzyme, represents an attractive target for T2D therapies,[4,5] because it plays a critical role in whole-body glucose control through its actions in multiple organs. In particular, in the β-cells of the pancreas, GK acts as the glucose sensor that determines the threshold for insulin secretion, while in the liver, this enzyme is rate-determining for glucose metabolism.[6–10] As a result of promising preclinical data, many pharmaceutical companies have actively pursued the program aiming at the development of GK activators (GKAs).[10–18] Of these, several companies including Roche, Astra-Zeneca and OSI/Prosidion have entered their compounds into clinical study.[12,14]

We previously reported a 2-aminobenzamide class of allosteric GKAs exemplified by compound **1** (Fig. 1).[15] Compound **1** showed potent GK activation and glucose lowering effect in a rat OGTT model. Moreover, the crystal structure of **1** with GK protein revealed a unique binding mode at an allosteric site distinct from the glucose binding and catalytic sites. This structure elucidation

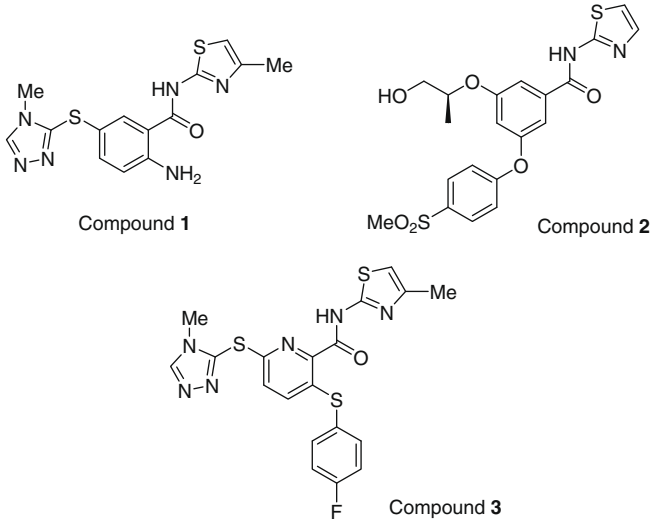

Figure 1. Structures of GK activators **1**–**3**.

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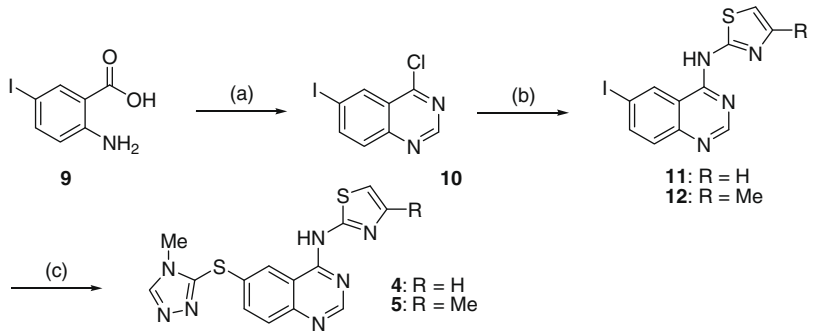
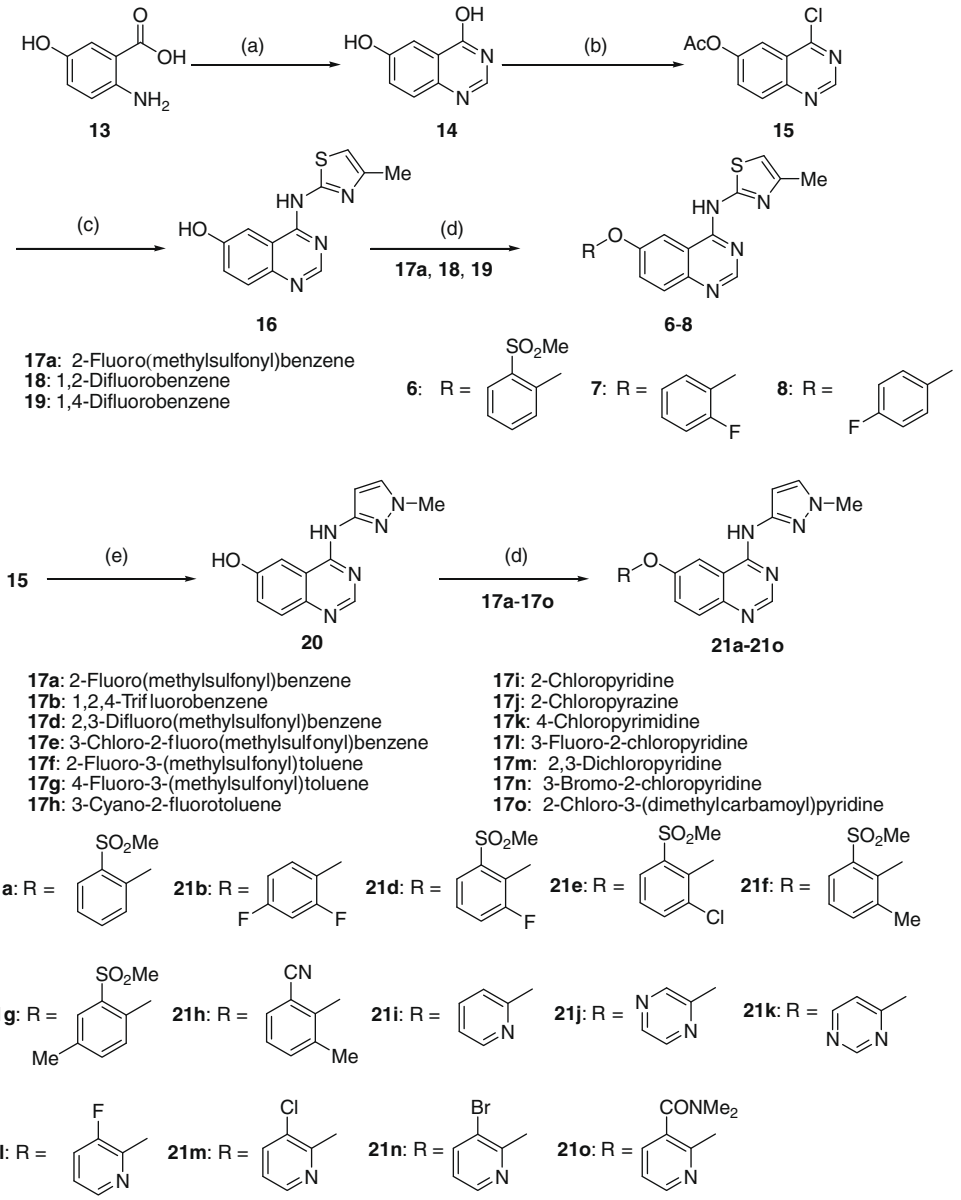
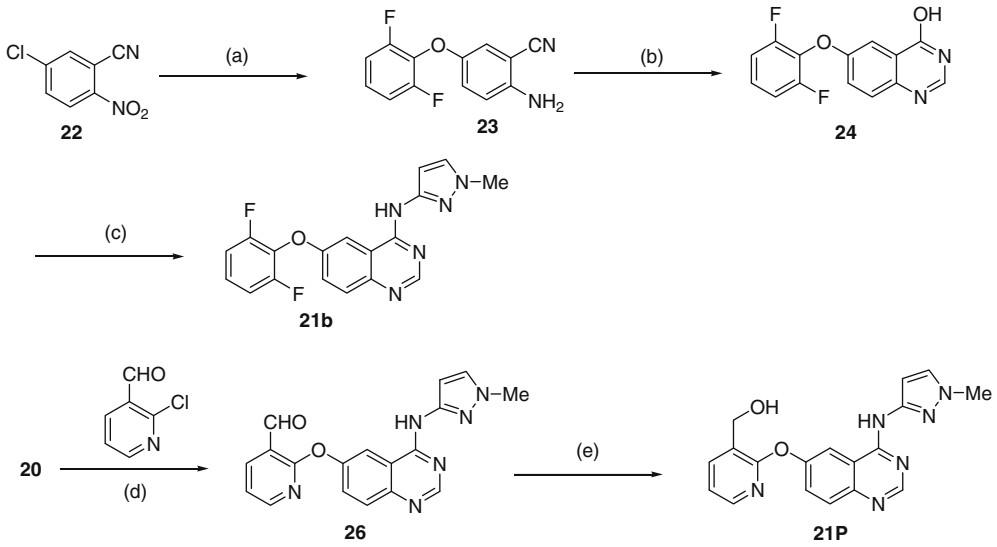


Scheme 1. Reagents and conditions: (a) (1) $HCONH_2$, 160 °C, 93%; (2) $POCl_3$, reflux, CH_3CN, 81%; (b) thiazol-2-ylamine or 4-methylthazol-2-ylamine, phenol, 120 °C, 28%; (c) 4-methyl-1,2,4-triazol-3-ylthiol, CuI, Cs_2CO_3, DMA, 140 °C, 40%.

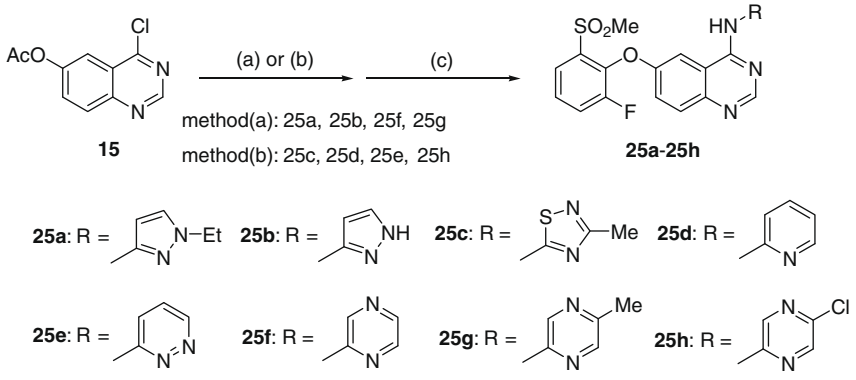


Scheme 2. Reagents and conditions: (a) $HCONH_2$, 160 °C, 77%; (b) (1) Ac_2O, Py, rt; (2) $SOCl_2$, cat. DMF, reflux, 89%; (c) (1) 4-methylthiazol-2-ylamine, phenol, 120 °C; (2) aq NH3, MeOH, 28%; (d) *t*-BuOK, DMA,130 °C, 20–50%; (e) (1) 3-amino-1-methylpyrazole, phenol, 80 °C; (2) aq NH_3, MeOH, 50%.

has provided helpful information to further perform SAR study. However, there is a potential toxicity concern associated with an aniline moiety contained in the structure of **1**.[19,20] Therefore, a new structure class without the aniline group was strongly desired to further develop GKAs. We have developed heteroaromatic amides GKAs represented by compounds (**2** and **3**) and reported



Scheme 3. Reagents and conditions: (a) (1) 2,6-difluorophenol, Cs_2CO_3, DMF, 80 °C; (2) H_2, 10% Pd–C, THFMeOH, rt, 3 h; (b) HCO_2H, 110 °C, 14 h; (c) (1) $SOCl_2$, cat. DMF, 80 °C; (2) *N*-methylpyrazole, phenol, 120 °C; 30 min; (d) *t*-BuOK, DMA, 130 °C, 45%; (e) $NaBH_4$, MeOH, 55%.



Scheme 4. Reagents and conditions: (a) (1) RNH_2, phenol, 120 °C; (2) aq NH_3, MeOH, 50%; (b) RNH_2, $Pd_2(dba)_3$ (0.1 equiv), BNAP (0.1 equiv), Cs_2CO_3 (2 equiv), toluene, 3 h, 120 °C; (2) aq NH_3, MeOH, 50%; (c) 2,3-difluoromethanesulfonylbenzene, *t*-BuOK, DMA,130 °C, 25–50%.

previously.[16,18] Here we described the design and synthesis of a novel class of 4,6-disubstituted quinazoline GK activators which eliminate the aniline group of the lead compound (**1**), and thus overcome any potential toxicity issue.

General synthetic methods of quinazoline derivatives (**4–8**, **21a–o**, **25a–h**) are summarized in Schemes 1–4. A key quinazoline intermediate (**10**) was prepared from commercially available 2-amino-5-iodobenzoic acid **9** by the following two step sequences (Scheme 1); (1) quinazoline ring closure by treatment with $HCONH_2$ at 160 °C, (2) chlorination by $POCl_3$ in CH_3CN at reflux. This intermediate (**10**) was regio-selectively coupled with 2-aminothiazole or 2-amino-4-methylthiazole to afford 6-iodo-4-(thiazol-2-ylamino)quinazoline (**11**) or 6-iodo-4-(4-methylthiazol-2-ylamino)quinazoline (**12**). Subsequently, these quinazoline compounds were coupled with 4-methyl-4*H*-1,2,4-triazole-3-thiol at the 6-position to produce the derivatives (**4** and **5**), respectively. Similarly, 6-hydroxy-4-(4-methylthiazol-2-ylamino)quinazoline intermediate **16** was prepared from 2-amino-5-hydroxybenzoic acid **13** (Scheme 2). More specifically, 4,6-dihydroxyquinazoline **14** was treated with acetic anhydride in pyridine to protect the hydroxyl group at the 6-position as an acetate. Subsequently, the hydroxyl moiety at the 4-position was chlorinated by thionyl chloride to afford 6-acetoxy-4-chloroquinazoline **15** in an excellent yield. Coupling of **15** with 2-amino-4-methylthiazole led to **16** in a moderate yield. Finally, nucleophilic aromatic substitution reaction of **16** with 2-fluoro(methanesulfonyl)benzene **17a**, 1,2-difluorobenzene **18** and 1,4-difluorobenzene **19** afforded quinazoline derivatives (**6–8**), respectively.

The 4-(1-methylpyrazol-3-ylamino)quinazoline derivatives (**21a–o**) were prepared from 6-hydroxy-4-(1-methylpyrazol-3-ylamino)quinazoline **20** in a similar manner described for the synthesis of **6** in 20–50% yields. Due to extremely low yield in the nucleophilic aromatic substitution (S_NAr) reaction of **16**, an alternative synthetic method was developed (Scheme 3). More specifically, S_NAr reaction of 2,6-difluorophenol with commercially available 4-chloro-2-cyanonitrobenzene provided **23** in a 50% yield. Catalytic hydrogenation of the nitro group followed by quinazoline ring closure reaction (HCO_2H, 110 °C) led to **24** in a 40% yield. Compound **24** was converted into **21c** by the following methods; (1) $SOCl_2$ in the presence of catalytic amount of DMF, (2) 3-amino-1-methylpyrazole in phenol at 80 °C. Hydroxymethyl derivative (**21p**) was prepared from formyl intermediates by reduction reaction.

Preparation of 4-heteroarylamino-6-(2-methanesulfonyl-6-fluorophenoxy)quinazoline derivatives (**25a–h**) was accomplished by similar methods as described for **21a** or a slightly modified pro-

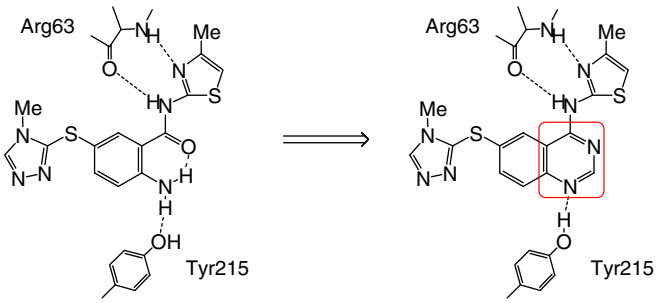
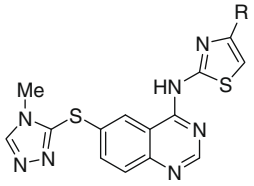


Figure 2. Design of novel quinazoline lead.

Table 1
Profiles of compounds (**4** and **5**)



Compd	R	2.5 mM Glc		10 mM Glc	
		EC_{50}[a] (μM)	E_{max}[b]	EC_{50}[a] (μM)	E_{max}[b]
4	H	2.1	0.69	0.21	0.47
5	Me	2.1	0.67	0.92	0.70
1	—	0.42	1.0	0.14	1.0

Compound **1** is the internal standard (EC_{50}: 0.42 ± 0.09 and 0.14 ± 0.04).
n.t.: not tested.
[a] Values are the means of two or more independent assays.
[b] The maximal activating response elicited the compounds as a ratio of the maximal response evoked by **1** at each concentration independently.

tocol utilizing the coupling reaction of **15** with heteroaromatic amines in the presence of $Pd_2(dba)_3$ and BINAP.

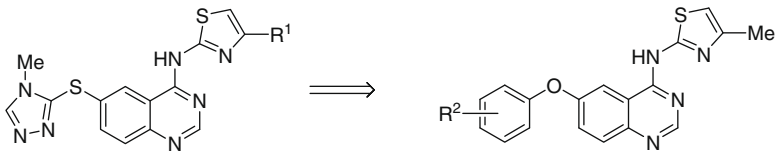
Compounds prepared herein were evaluated in an in vitro GK assay, which was conducted at two different glucose concentrations (2.5 mM and 10 mM).[10] These glucose concentrations simulate low and high blood glucose conditions, respectively. GK activity of compounds was described as EC_{50} values and maximal effective responses (E_{max}). For comparison of compounds in each assay, the EC_{50} and E_{max} values of compound **1** were used as an internal standard (E_{max} value of **1** = 1.0). We suppose that not only the EC_{50} values, but also the E_{max} values of GK activators are important for the efficacy of in vivo experiments.

As previously reported, the aniline NH_2 group of compound **1** played a critical role in GK activation based on the crystal structure analysis of GK and **1** complex and the SAR study around the 2-aminobenzamide class.[15,21] More specifically, the co-crystal structure analysis revealed that the aniline NH of **1** interacted with Tyr215-OH of GK via hydrogen bonding, and that another aniline NH formed an intra-molecular hydrogen bond with the amide carbonyl group in **1** to fix the conformation and preferably bound to Arg63 backbone. Based on these data, we further designed 4-(thiazolamino)-6-(*N*-methyl-1,2,4-triazol-5-ylthio)quinazoline (**4**) and its 4-methylthiazol-2-ylamino analogue (**5**), in which we assumed the nitrogen atom of the thiazole ring and thiazolamine NH was favorably arranged to interact with Arg63 of GK and the nitrogen atom at the 1-position of the quinazoline core interacted with Tyr215-OH of GK. We speculate that the hydrogen bonding pattern associated with Tyr215 changes on going from the 2-carboxamidoaniline to the quinazoline (Fig. 2). In the first situation, Tyr215 acts as an H-bond acceptor, while, in the second situation, it acts as a H-bond donor.

These compounds (**4** and **5**) exhibited moderate GKA potency (**4**: EC_{50} = 2.1 μM, **5**: EC_{50} = 2.1 μM), indicating that the quinazoline structure deserved attention as a novel class of GK activator leads (Table 1). To optimize this novel lead class, we initially focused on modifications at the 4- and 6-position of the quinazoline core.

In the previous SAR study of the 2-aminobenzamide class, it was revealed that replacement of the triazol-2-ylthio group of compound **1** with a substituted phenoxy moiety was feasible.[15,17] We applied this approach to the modifications of the current quinazoline leads (Fig. 3). Initially, the triazol-2-ylthio moiety in **5** was replaced with 2-(methylsulfonyl)phenoxy-(**6**), 2-fluorophenoxy-(**7**), or 4-fluorophenoxy-(**8**) group as representative surrogates. Interestingly, compounds **6** and **7** exhibited significant improvement in GK activation (**6**: EC_{50} = 0.23 μM, **7**: EC_{50} = 0.15 μM) as compared with **5**, while **8** had a comparable GK activation potency (**8**: EC_{50} = 1.0 μM), suggesting that replacement of the 4-methyl-1,2,4-triazol-3-ylthio group with substituted phenoxy moieties was tolerable (Table 2). These results prompted us to further optimize the quinazoline leads. However, lipophilic compounds, particularly neutral compounds, may worsen the aqueous solubility, which influence their ADME aspects, posing challenges for drug development.[22] Therefore, during the modifications of the quinazoline leads, we elected to pay attention to the physicochemical properties of compounds, particularly the lipophilicity (*c*log *P* or measured log $D_{pH\ 7.4}$) and aqueous solubility which was measured in high-speed solubility screening assay using DMSO solution of compounds.[23,24]

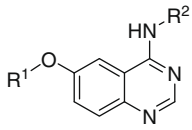
Our initial attempt was to focus on optimizing a substituent of the phenoxy group at the 6-position of the quinazoline core whilst holding a 1-methylpyrazol-3-ylamino group[15] at the 4-position constant, because this heteroaromatic amino group retained in GKA potency and more importantly this would give rise to a more hydrophilic nature as compared with the 4-methylthiazol-2-ylamino moiety. As a basis for initial attempts, we incorporated a methylsulfonyl group into the 2-position (**21a**), or fluorine atoms at the 2- and 4-positions (**21b**) or 2- and 6-positions (**21c**) of the phenoxy group. The compound (**21a**) exhibited moderate GKA

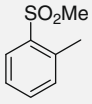
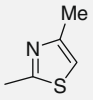
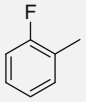
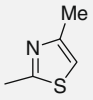
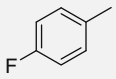
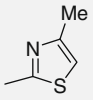
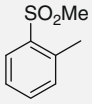
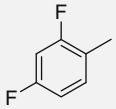
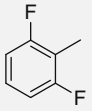
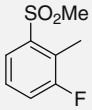
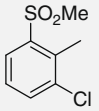
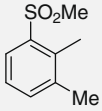
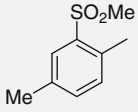
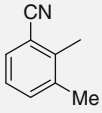


4: R^1 = H
5: R^1 = Me
6: R^2 = 2-(SO_2Me)
7: R^2 = 2-F
8: R^2 = 4-F

Figure 3. Design of novel quinazoline leads **4**–**8**.

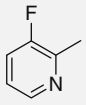
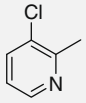
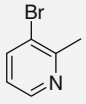
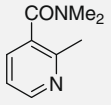
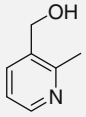
Table 2
Profiles of compounds (**6**–**8**, **21a**–**q**)



Compd	R^1	R^2	2.5 mM Glc		10 mM Glc		Log D[c] (pH7.4)	Aqueous solubility[d] (μM)
			EC_{50}[a] (μM)	E_{max}[b]	EC_{50}[a] (μM)	E_{max}[b]		
6			0.23	0.80	0.08	0.73	4.3[e]	n.t.
7			0.15	0.61	0.05	0.56	5.8[e]	n.t.
8			1.03	0.48	0.10	0.46	5.8[e]	n.t.
21a			0.53	0.76	0.08	0.76	1.9 (3.0[e])	2.5
21b			0.30	0.93	0.06	0.40	3.6	41
21c			0.09	0.96	0.03	0.84	3.7	7.2
21d			0.14	0.88	0.04	0.88	1.9	>170
21e			0.32	0.92	0.08	0.90	2.3	2.8
21f			0.45	1.1	0.11	1.1	2.1	>170
21g			5.1	0.78	0.57	0.68	n.t.	n.t.
21h			0.07	0.91	0.01	0.85	3.4	7.0
21i			2.0	0.74	0.2	0.57	2.1	>170

(*continued on next page*)

Table 2 (*continued*)

Compd	R^1	R^2	2.5 mM Glc		10 mM Glc		Log D^c (pH7.4)	Aqueous solubility[d] (μM)
			EC_{50}[a] (μM)	E_{max}[b]	EC_{50}[a] (μM)	E_{max}[b]		
21j			6.1	0.71	0.80	0.53	1.9	140
21k			14	0.77	2.7	0.81	1.7	>170
21l			0.34	0.84	0.04	0.63	2.4	15
21m			0.21	0.86	0.04	0.80	2.9	35
21n			0.11	0.86	0.02	0.80	3.4	16
21o			11	0.36	4.0	0.54	1.4	>170
21p			1.5	0.81	0.15	0.74	1.7	>170

Compound **1** is the internal standard (EC_{50}: 0.42 ± 0.09 and 0.14 ± 0.04).
n.t.: not tested.
[a] Values are the means of two or more independent assays.
[b] The maximal activating response elicited the compounds as a ratio of the maximal response evoked by **1** at each concentration independently.
[c] Log *D* value is actually measured using reported method.[24]
[d] Aqueous solubility is measured in high-speed solubility screening assay using DMSO solutions (values are the means of two independent assays).[23]
[e] *c*log P.

potency as well as suitable lipophilicity ($\log D_{pH\ 7.4} = 1.9$), whilst the aqueous solubility was poor (2.5 μM). The compound (**21c**) had excellent GK activity, although it showed relatively high lipophilicity ($\log D_{pH\ 7.4} = 3.7$) and low aqueous solubility (7.2 μM).

Based on the GKA potency and physicochemical properties of **21a** and **21c**, a 6-[2-fluoro-6-(methylsulfonyl)phenoxy]quinazoline lead (**21d**) was designed and prepared. This compound retained good GKA potency ($EC_{50} = 0.14$ μM) and suitable lipophilicity ($\log D_{pH7.4} = 1.9$). Furthermore, it was worthy to note that **21d** exhibited an excellent aqueous solubility (>170 μM). Replacement of the fluorine atom in **21d** with a methyl group retained the good aqueous solubility, while replacement of a chlorine atom led to a dramatic decrease in the aqueous solubility.

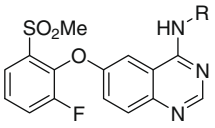
Next, a heteroaryloxy group such as a pyridin-2-yloxy-(**21i**), pyrazin-2-yloxy-(**21j**) or pyrimidin-4-yloxy-(**21k**) was incorporated in place of the phenoxy to improve the aq solubility. While these compounds showed excellent aqueous solubility, they had reduced GKA potencies. Since **21i** had the best GKA potency among these, a halogen atom was incorporated into the 3-position of pyridine-2-yloxy moiety. The resulting compounds (**21l** and **21m**) resulted in improvement in the GKA potency, while the aq solubility was deteriorated.

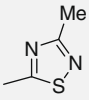
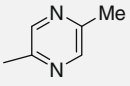
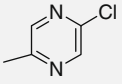
Optimization studies on the 6-substitunet of the quinazoline core described above indicated that 2-fluoro-6-(methylsulfonyl)phenoxy was a well-balanced functional group in terms of the GKA potency and physicochemical properties. With these data in hand, we elected to focus further on the SAR study on the 4-substituent of the quinazoline core. Table 3 highlights the GKA potency associated with the lipophilicity and aq solubility of the 4-substituted quinazoline leads. The results demonstrated that **21d** was one of the well-balanced compounds in this class.

As a representative quinazoline GK activator, further characterization of **21d** was conducted. The rat PK study revealed that **21d** was orally absorbed and exhibited good oral bioavailability (Table 4). The acute in vivo efficacy of **21d** was evaluated in high fat diet (HFD) mice.[17] Administration of a 10 mg/kg oral dose of **21d** compared with vehicle alone (0.5% methylcellulose solution) delivered a statistically significant reduction in plasma glucose levels (Fig. 4). The glucose lowering effects of **21d** was comparable or superior to that of **2**.

In conclusion, we designed and synthesized a novel class of quinazoline GK activators based on the X-ray analysis data of the 2-aminobenzamide and related GK activators to eliminate the aniline structure. Subsequent structure–activity relationship studies of this class were performed with the aim of identifying a potent and orally active GK activator having a suitable balance of potency and physicochemical properties, leading to the discovery of 6-[2-fluoro-6-(methylsulfonyl)phenoxy]-4-(1-methylpyrazol-3-

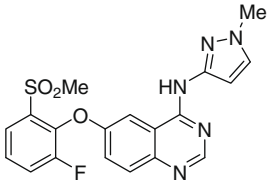
Table 3
Profiles of compounds (**25a–25h**)



Compd	R	2.5 mM Glc		10 mM Glc		Log D^c (pH7.4)	Aqueous solubility[d] (μM)
		EC_{50}[a] (μM)	E_{max}[b]	EC_{50}[a] (μM)	E_{max}[b]		
21d		0.14	0.88	0.04	0.88	1.9	>170
25a		0.19	0.85	0.03	0.75	2.4	>170
25b		0.12	0.76	0.04	0.62	1.8	>170
25c		0.11	1.0	0.04	1.1	3.1	68
25d		0.18	0.60	33	0.34	3.6	41
25e		8.7	0.56	0.24	0.25	2.0	>170
25f		0.57	0.87	0.07	0.86	2.2	165
25g		0.31	0.75	0.04	0.54	2.5	163
25h		6.1	0.85	0.95	0.87	n.t.	n.t.

Compound **1** is the internal standard (EC_{50}: 0.42 ± 0.09 and 0.14 ± 0.04).
n.t.: not tested.
[a] Values are the means of two or more independent assays.
[b] The maximal activating response elicited the compounds as a ratio of the maximal response evoked by **1** at each concentration independently.
[c] Log *D* value is actually measured using reported method.[24]
[d] Aqueous solubility is measured in high-speed solubility screening assay using DMSO solutions (values are the means of two independent assays).[23]

Table 4
Profiles of the representative quinazoline lead (**21d**) in SD rats



Compd	$AUC_{0-\infty}$ (μM h)	CLp (mL/min/kg)	$T_{1/2}$ (h)	V_{dss} (L/kg)	C_{max} (μM)	T_{max} (h)	*F* (%)
IV (1 mg/kg, 100% PEG)	6.3	6.8	1.3	0.5	—	—	—
PO (3 mg/kg, 0.5% MC)	13.3	—	—	—	5.8	0.9	71

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

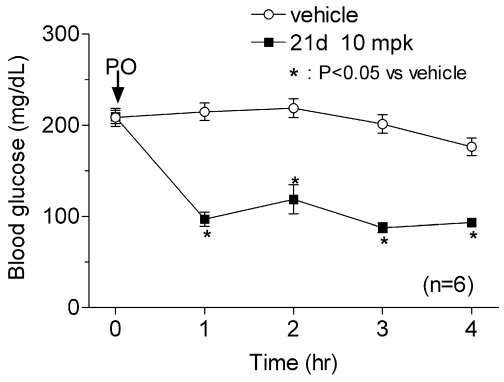


Figure 4. Blood glucose levels of **21d** in HFD mice.

ylamino)quinazoline (**21d**). These results were achieved by incorporating substituted aromatic and heteroaromatic rings into the 4- and 6-position of the quinazoline core part. Comparison studies between **21d** and the other types of GK activators such as compounds (**2** and **3**) in vitro and in vivo are underway.

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