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Design, synthesis, and pharmacological evaluation of 2-(4-sulfonylphenyl)-2-[(*E*)-pyrrolidin-1-ylimino]-*N*-thiazoleacetamides as glucokinase activators

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ABSTRACT

This paper presents the synthesis and glucokinase activity of novel hydrazone derivatives. The 2-(4-cyclopropylsulfonylphenyl)-2-[(*E*)-pyrrolidin-1-ylimino]-acetamide derivatives **5a**-**5h** presented the in vitro glucokinase activities and in vivo blood glucose-lowering effects in mice. Particularly, **5h** showed an oral hypoglycemic effect in rats at 1 mg/kg. These hydrazone derivatives are a potential new class of glucokinase activators for the treatment of type 2 diabetes.

Type 2 diabetes mellitus is a progressive and multifactorial disease, and it is difficult to maintain appropriate glycemic controls even with several glucose-lowering agents.[1] Thus, there is a need for new agents with a complementary mechanism of action. Glucokinase (GK) is one of the four enzymes in the hexokinase family in mammalian, which catalyzes the conversion of glucose to glucose-6-phosphate (G6P) at the initial step of glucose metabolism.[2] Its major expression organs are the liver hepatocyte and the pancreatic beta-cell. In the high blood glucose level, GK contributes to glucose consumption in the liver and increasing G6P in the pancreas beta-cell enhances glucose stimulating insulin secretion. Thus, GK activators are considered to be a promising drug target for type 2 diabetes with both hepatic and pancreatic effects.[3]

Representative GK activators and our designed compounds are depicted in Figure 1. In early study, Hoffman La Roche group pioneered the field of allosteric GK activators by developing phenylacetamide derivatives **1** and **2**,[4] followed by compound **3** (PSN-GK1) from OSI-Prosidion.[5] Compound **1** was reported as an orally active GK activator but withdrawn from the development in human because of its potential cardiovascular risk represented with a human ether-a-go-go related gene (hERG) channel inhibition.[6] Based on that knowledge, we designed a novel hydrazone derivative **4a**, in which the central carbon-carbon double bond in **2** was replaced with carbon-nitrogen double bond, to avoid

hERG channel inhibition by reducing lipophilicity.[7] Here we describe the synthesis, in vitro GK activity, and in vivo hypoglycemic effects of novel hydrazone derivatives **4a** and **5a-5h**.

The synthetic route is outlined in Scheme 1. The 2-oxo-2phenylacetates **6** and **9** were set as the key intermediates and prepared by known procedures.[8] For the synthesis of **4a**, the ester **6**[8a] was hydrolyzed with aqueous hydrochloric acid to obtain the acid **7**, which was converted to the hydrazone **8** through condensation reaction with 1-aminopyrrolidine hydrochloride. Then, **8** and 2-aminothiazole were coupled by employing 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and catalytic amounts of 4-dimethylaminopyridine (DMAP) to give **4a**. The geometric stereochemistry in **4a** was determined as the *E*-isomer by ^{1}H NMR nuclear overhauser effect (NOE) analysis.[9] For the synthesis of **5a-5h** having a cyclopropylsulfonyl group in the molecule, a common intermediate **11** was prepared as follows. The known ester **9**[8b] was treated with 1-aminopyrrolidine hydrochloride and triethylamine to give the hydrazone ester as an *E/Z* mixture, which could be separated by SiO_2 column chromatography. The polar isomer **10** was hydrolyzed with aqueous sodium hydroxide to give carboxylic acid **11**. The geometric stereochemistry of **11** was determined as the *E*-isomer using ^{1}H NMR NOE analysis.[9] The acid **11** was then converted to the corresponding amides **5a-5f** and **12** by

condensation with various heteroarylamines. During the conversion process, the isomerization of *E*/*Z* stereochemistry at the hydrazone moiety was not observed. Further, reductive amination of 5-formylthiazol-2-ylamide **12** with the corresponding 1-substituted piperazine derivatives gave **5g** and **5h**.[10]

The effects of these hydrazone derivatives on human GK activity and blood glucose reduction were evaluated in fasted C57BL/6J mice. The structure−activity relationships are shown in Table 1. First, we confirmed that the hydrazone derivative had sufficient efficacy as GK activator because methylsulfonylphenyl derivative **4a** showed GK activation at the micromolar level. To improve in vitro potency, we adopted cyclopropylsulfonylphenyl substituent, which was searched by Bertram et al., in the development of compound **3**.[5] As a result, the cyclopropylsulfonyl-substituted hydrazone derivative **5a** had a 10-fold higher in vitro potency than **4a**. Furthermore, **5a** exhibited an oral glucose-lowering effect in mice at 10 mg/kg. By introducing 5-chloro substituent onto thiazole ring, **5b** showed 10-fold more potent GK activation than **5a**. However, **5b** indicated low water solubility in pH 6.5 buffer. Further, **5a** and **5b** also displayed hERG inhibitory activity which could be associated with cardiotoxicity caused by QT interval prolongation.[10] Thus, we focused on increasing solubility and avoiding hERG channel inhibition while maintaining sufficient GK activation. As a result, other heteroarylamide

derivatives **5c-5f** were investigated. Pyridin-2-ylamide derivative **5c** showed lower in vitro GK activation and in vivo efficacy than thiazol-2-ylamide derivative **5a**. 1,3,5-Thiadiazole-2-ylamide derivative **5d** had moderate in vitro GK activation. On the other hand, 5-methyl substituted thiazole-2-ylamide **5e** and 1,3,4-thiadiazole-2-ylamide **5f** showed good in vitro GK activation and in vivo efficacy. Unlike the 5-chloro-thiazole-2-ylamide derivative **5b**, the 5-methylthiazole-2-ylamide derivative **5e** was found incapable of performing hERG channel inhibitory activity. To increase the water solubility, amino substituents were introduced onto the methyl group in **5e**. 4-Methylpiperazin-1-ylmethyl derivative **5g** exhibited good water solubility and in vitro GK activation but showed hERG inhibitory activity. We supposed that the terminal basic amine in **5g** interacted with hERG channel. In contrast, **5h** having a 4-acetylpiperazin-1-ylmethyl substituent showed moderate GK activity without hERG channel inhibition. Therefore, we conclude that **5h** is a well-balanced compound with in vivo GK efficacy in mice and good water solubility.

Based on the results described above, **5h** was advanced to evaluate single oral administration in overnight-fasted Sprague-Dawley rats. As a result, this compound reduced blood glucose levels at 1, 3, 10 and 30 mg/kg in a dose-dependent manner compared to the vehicle control group. Furthermore, the 10 and 30 mg/kg groups showed

sustained hypoglycemic effects with statistically significant differences from the vehicle group even 7 hours after administration (Figure 2).

In summary, we can conclude that among the synthetic hydrazone derivatives, cyclopropylsulfonylphenyl substituted hydrazone **5a-5h** showed in vitro GK activation and hypoglycemic effects in mice. Particularly, **5h** was compatible with good water solubility and hERG inhibition avoidance. The **5h** presented a dose-dependent oral hypoglycemic effect in rats. These hydrazone derivatives have potential as a new chemical class of glucokinase activators for type 2 diabetes treatment.

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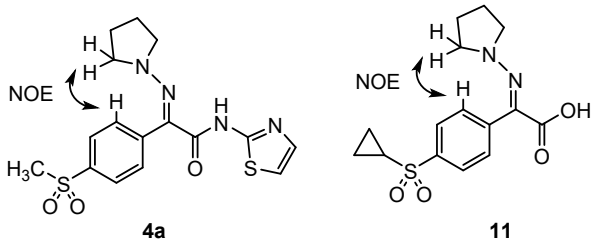
9. In the ^{1}H-NMR studies of **4a** and **11**, NOEs were observed as shown below.



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Supplementary Material

Detailed synthetic procedure for **4a** and **5a-5h**; description of in vitro GK assay. This material is available free of charge via the internet.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

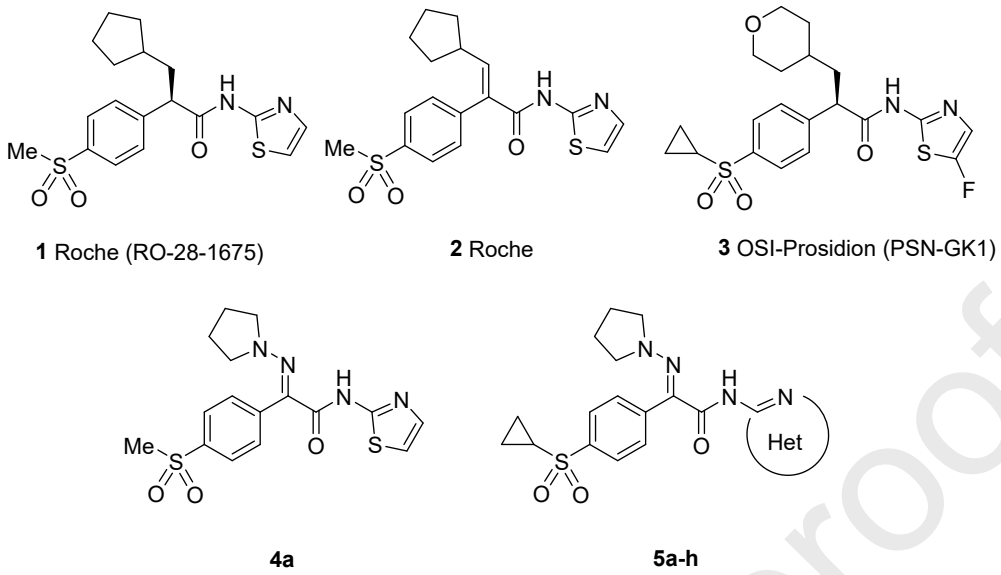
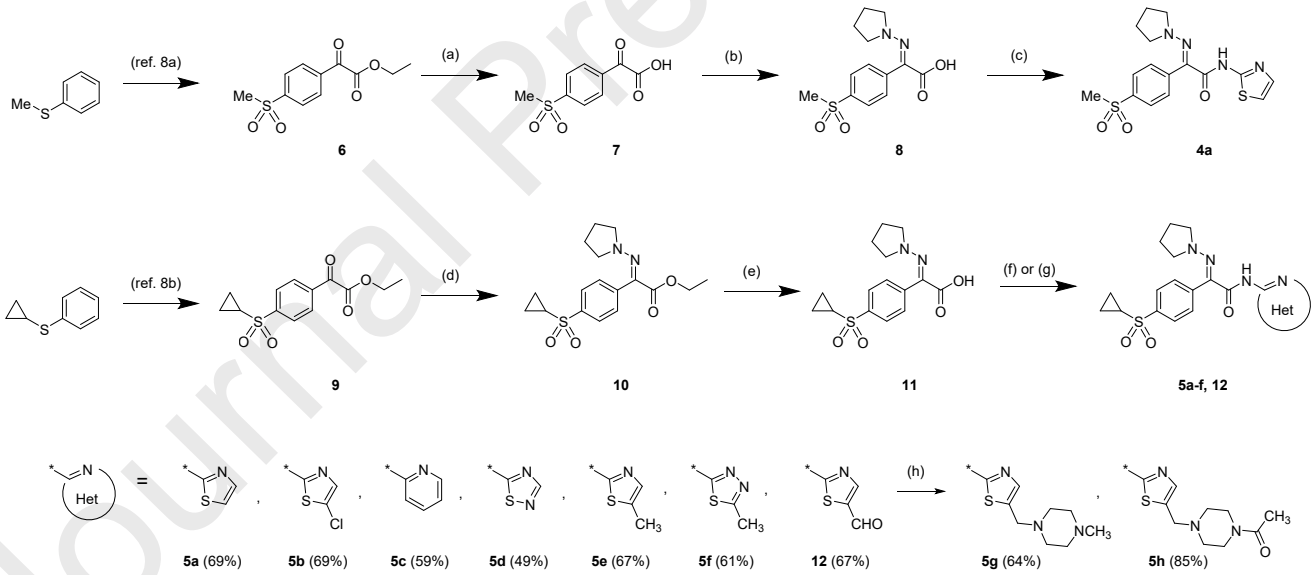


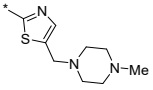
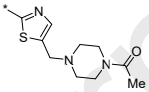
Figure 1. Structures of glucokinase activators and our design for novel hydrazone derivatives.



Scheme 1. Reagents and reaction conditions: (a) 16% aq. HCl, 100 °C, 24 h (68%); (b) 1-amino-pyrrolidine hydrochloride (4.0 equiv.), AcONa (8.0 equiv.), MeOH, RT, 5 h (crude); (c) 2-aminothiazole (4.0 equiv.), EDC (2.0 equiv.), DMAP (catalytic amounts), CH_2Cl_2, RT, 5 h (2 steps, 13%); (d) 1-amino-pyrrolidine hydrochloride (3.0 equiv.), Et_3N (3.0 equiv.), THF, reflux, 3 d, then SiO_2 column chromatography (40%, polar isomer); (e) 2M aq. NaOH, EtOH, RT, 4 h (81%); (f) heteroarylamine (1.5-3.0 equiv.), EDC·HCl (1.5 equiv.), DMAP (1.5 equiv.), CH_2Cl_2, RT, 24 h; (g) heteroarylamine hydrochloride (3.0 equiv.), EDC (1.5 equiv.), DMAP (1.5 equiv.), CH_2Cl_2, RT, 24 h; (h) 1-substituted piperazine (2.4 equiv.), sodium tri-acetoxy borohydride (3.0 equiv.), CH_2Cl_2, RT, 20

h.

Table 1. SAR exploration of hydrazone derivatives.

Compd	Heteroaryl	GK activation EC_{50} (μM) [a)]	Maximum blood glucose reduction [b)]	Solubility in buffer (μg/mL) [d)]	hERG inhibition IC_{50} (μM)
4a		5.60	N.A. [c)]	5.4	N.D. [e)]
5a		0.42	-36%	2.4	17.5
5b		0.041	-37%	0.1	16.7
5c		2.40	-19%	0.9	N.D. [e)]
5d		0.16	-45%	7.7	5.3
5e		0.22	-32%	1.2	>100
5f		1.17	-41%	6.5	>100
5g		0.70	-41%	345.0	16.9
5h		1.92	-42%	78.0	>100

a) EC_{50} was measured at 5 mM glucose.

b) C57BL/6J fasted mice, 10 mg/kg, p.o. vs vehicle control.

c) N.A. = Not active.

d) Solubility in pH 6.5 phosphate buffer was determined.

e) N.D. = Not determined.

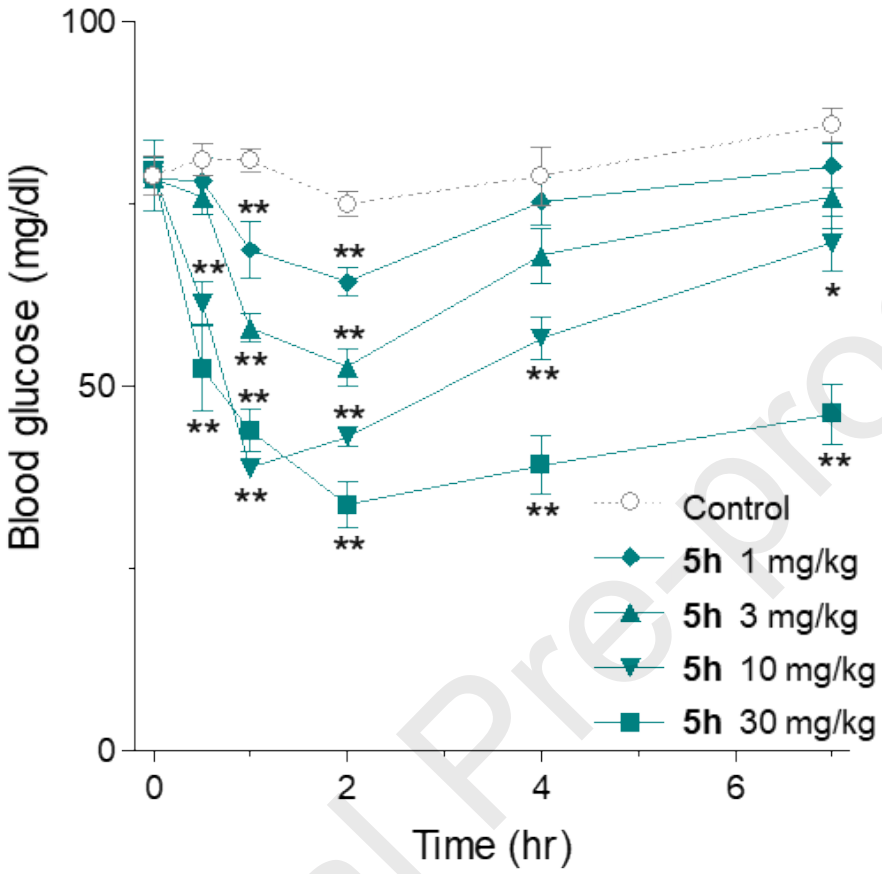
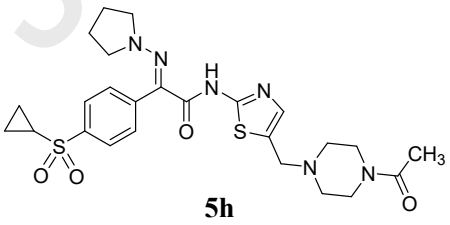


Figure 2. Effect of **5h** on blood glucose level in overnight fasted Sprague-Dawley (SD) rats. **5h** or vehicle (10% Gelucire) was orally administered to overnight fasted SD rats at 0 hour. Values are mean ± S.E.M. (n=5). ***P*<0.01, **P*<0.05 vs. control (Dunnett's method)



5h

GK EC_{50} 1.92 μM
No hERG inhibition