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C5-Alkyl-2-methylurea-Substituted Pyridines as a New Class of Glucokinase Activators

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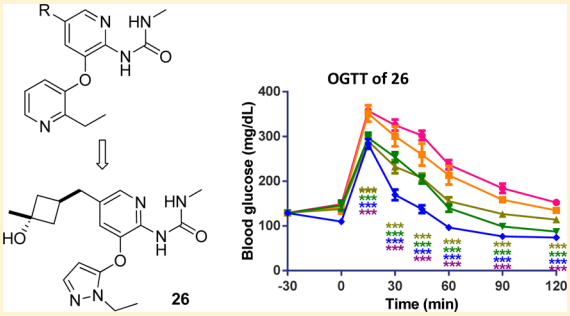
Supporting Information

ABSTRACT: Glucokinase (GK) activators represent a class of type 2 diabetes therapeutics actively pursued due to the central role that GK plays in regulating glucose homeostasis. Herein we report a novel C5-alkyl-2-methylurea-substituted pyridine series of GK activators derived from our previously reported thiazolylamino pyridine series. Our efforts in optimizing potency, enzyme kinetic properties, and metabolic stability led to the identification of compound **26** (**AM-9514**). This analogue showed a favorable combination of *in vitro* potency, enzyme kinetic properties, acceptable pharmacokinetic profiles in preclinical species, and robust efficacy in a rodent PD model.



KEYWORDS: *Type 2 diabetes, glucokinase activator, GKA, methyl urea-substituted pyridines*

Type 2 diabetes is a chronic metabolic disease affecting over 300 million people worldwide.[1] It is characterized by elevated fasting plasma and hepatic glucose production and insulin resistance. It is a major risk factor for both microvascular and macrovascular diseases.[2−4] Despite the availability of multiple antihyperglycemic agents, many patients still remain unable to safely achieve and maintain tight glycemic control, underscoring the need for more effective therapies.

Glucokinase (GK) is a member of the hexokinase family of intracellular enzymes. It is responsible for the conversion of glucose to glucose-6-phosphate, the first step in glucose utilization.[5] GK is present in both pancreatic β-cells and liver hepatic cells. In the pancreas, it serves as a glucose sensor to control glucose-stimulated insulin secretion, while hepatic GK plays an important role in regulating net glucose utilization and production.[6]

It has been demonstrated that glucokinase activators (GKAs) can influence the enzyme's kinetic profile by modulating both K_m for glucose (also known as $S_{0.5}$) and V_{max} (maximal velocity of the glucose phosphorylation reaction catalyzed by GK).[7] As a result, GKAs control blood glucose concentrations by enhancing the ability of pancreatic β-cells to sense glucose and increase insulin secretion in a glucose-dependent manner. In addition, GKAs act in the liver to improve glucose disposal by increasing glycogen storage and decreasing hepatic glucose output. The possible synergistic effect of this dual mechanism may provide an advantage in the treatment of type 2 diabetes.[8] To date, a number of GK activators have advanced into clinical trials for the treatment of type 2 diabetes.[9−11]

We have previously disclosed a series of thiadiazolylamino pyridine GKAs represented by compound **A**.[12,13] To identify GKAs that are structurally distinct from that, we pursued a novel methyl urea-substituted pyridine series, where the critical bidentate hydrogen bond to Arg63 was maintained by the methyl urea moiety.[14] Compound **A** had thioether substitutions at C5 of the middle pyridine ring. In pursuing more structure diversity, we would like to replace the thioether in compound **A** with a carbon-based linker in compound **B** as shown in Figure 1.

Hypoglycemia is a key dose limiting adverse effect of glucokinase activators.[15−17] In an attempt to mitigate this risk, we targeted GKAs that would not lower the $S_{0.5}$ below a certain limit nor raise V_{max} above a certain limit, preferably with $S_{0.5}$ > 0.6 mM and V_{max} between 0.8 and 1.3 of unactivated GK. A similar strategy has been proposed by others.[10,11,18] Our threshold values were chosen in part based on data with Piragliatin ($S_{0.5}$ of 0.28 mM and V_{max} of 1.7) and MK-0941 ($S_{0.5}$ of 0.25 mM

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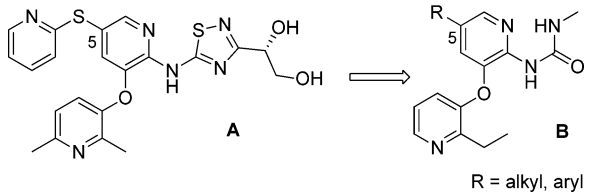


Figure 1. From thioether-substituted thiazolylamino pyridines (**A**) to methyl urea-substituted pyridines (**B**).

and V_{max} of 1.3),[19] developed by Roche and Merck, respectively. Both compounds were associated with increased risk of hypoglycemia in clinical trials.[16,20] In addition, compounds with V_{max} lower than 0.8 could result in the phosphorylation rate of the enzyme-activator complex to be lower than the native enzyme at glucose concentrations obtainable in the fed state.[21] Therefore, we targeted GKAs with V_{max} between 0.8 and 1.3.

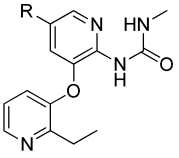
A number of C5-alkyl substituted analogues with 3-*O*-ethylpyridine substitution are summarized in Table 1. The simple isobutyl substituted analogue **1** was potent (EC_{50} = 0.12 μM) but metabolically unstable, indicated by the relatively high turnover rate in both rat and human liver microsomes. The microsomal stability of this series was improved by the incorporation of a variety of polar functional groups such as alcohols and ethers into the structure (compounds **2** and **4**−**7**). For the ethers, potency improved when elongating the linker from two carbon to three and four (**2**, **3**, and **4**). However, the V_{max} values for these compounds were lower than the target range. For the alcohols, although they were less potent than their ether analogues (**2** vs **5**; **4** vs **6**), one of the primary alcohols, **6**, had acceptable potency, kinetic parameters, and microsomal stability. However, compound **6** had poor stability in primary human hepatocytes (88% was metabolized).[22] To reduce the hepatic clearance, the tertiary alcohol **7** was made. Although this improved the stability in primary human hepatocytes (28% metabolized),[22] it also reduced the V_{max} to an unacceptable level (0.73).

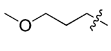
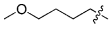
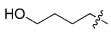
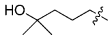
We then explored cyclic moieties with one carbon linker such as cyclohexyl methyl or THP methyl substitution. The V_{max} values for these compounds (**8** and **9**) were also low.

Because of the suboptimal V_{max} associated with 3-*O*-ethylpyridine substitution, we changed the substitution to 3-*O*-ethylpyrazole. Table 2 shows that the analogues with 3-*O*-ethylpyrazole had improved V_{max} values compared to the 3-*O*-ethylpyridines, although the potency was reduced somewhat (**10** vs **4**; **11** vs **7**; **12** vs **9**). These compounds generally had good microsomal stability.

Compound **12** had acceptable potency, kinetic parameters, and good stability in microsomes and primary human hepatocytes (15% metabolized).[22] Furthermore, it has a low molecular weight (359) and very good solubility (718 μg/mL at pH 7.4, PBS buffer). Table 3 shows the pharmacokinetic properties of **12** in mice and rats. Although it had modest clearance in both rat and mouse, it had excellent bioavailability in mouse (81%). In addition, we studied the interspecies differences in the kinetic properties of compound **12**−GK complex. Compound **12** had a

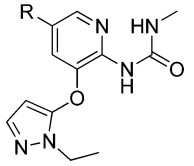
Table 1. Exploration of C5 Substitution of GKAs with 3-*O*-Ethylpyridine

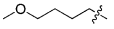
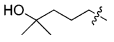
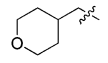


Compd	R	GKA EC_{50}[a,b] (μM)	T.O.[a,c] r/h (%)	$S_{0.5}$[a] (mM)	V_{max}[a,d] ratio
1		0.12	95/56	0.66	0.82
2		0.59	76/21	0.88	0.70
3		0.44	-/-	0.87	0.78
4		0.11	41/23	0.82	0.74
5		1.59	10/10	-	-
6		0.35	33/20	0.85	0.86
7		0.11	17/31	0.82	0.73
8		0.014	95/99	0.76	0.73
9		0.29	-/-	0.85	0.75

[a]Mean standard deviations for the EC_{50}, $S_{0.5}$, and V_{max} are ±30%, 17%, and 4%, respectively (n = 2). Also, human recombinant GK was used in all the assays. [b]For the EC_{50} assay, the glucose concentration was fixed at 5 mM. [c]Percent turnover: percentage of parent compound being metabolized after incubating in 0.25 mg/mL of rat or human liver microsomes for 30 min at 37 °C with an initial parent concentration of 1 μM. [d]Maximal velocity of the glucose phosphorylation reaction catalyzed by activated GK/unactivated GK.

Table 2. Exploration of C5 Substitution of GKAs with 3-*O*-Pyrazole



Compd	R	GKA EC_{50}[a,b] (μM)	T.O.[a,c] r/h (%)	$S_{0.5}$[a] (mM)	V_{max}[a,d] ratio
10		0.46	31/10	0.86	0.83
11		0.37	10/10	0.84	0.75
12		0.35	25/10	0.84	0.80

[a]Mean standard deviations for the EC_{50}, $S_{0.5}$, and V_{max} are ±30%, 17%, and 4%, respectively (n = 2). Also, human recombinant GK was used in all the assays. [b]For the EC_{50} assay, the glucose concentration was fixed at 5 mM. [c]Percent turnover: percentage of parent compound being metabolized after incubating in 0.25 mg/mL of rat or human liver microsomes for 30 min at 37 °C with an initial parent concentration of 1 μM. [d]Maximal velocity of the glucose phosphorylation reaction catalyzed by activated GK/unactivated GK.

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Table 3. Pharmacokinetics Properties of 12

		IV[a]			PO[a]	
compd	species	CL (L/h/kg)	Vss (L/kg)	$T_{1/2}$ (h)	F (%)	AUC (μM·h)
12	rat	1.5	0.8	0.41	19	3.51
12	mouse	1.7	1.5	0.72	81	13.3

[a]Rat and mouse: IV dose 1 mg/kg, n = 3; PO dose 10 mg/kg, n = 3.

V_{max} of 1.12 and a $S_{0.5}$ of 0.82 in mouse. Although the difference in the V_{max} between human and mouse was significant, it was within our target range. Compound **12** (**AM-0822**) was chosen to proceed into *in vivo* studies to verify its efficacy.

Compound **12** (**AM-0822**) was tested in a dose−response oral glucose tolerance test (OGTT) using C57Bl/6 mice[23] (Figure 2)

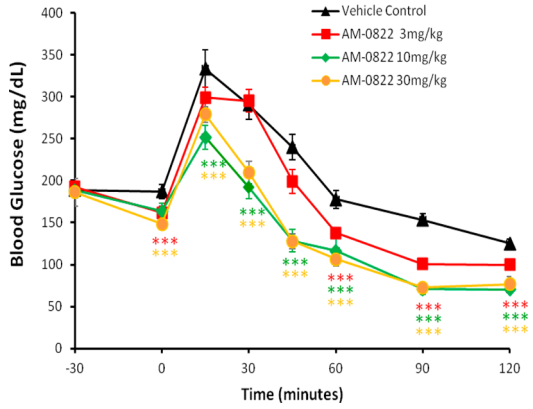


Figure 2. OGTT data for **12** (**AM-0822**) in C57Bl/6 mice. Statistical significance compared to vehicle treatment is denoted by *(p < 0.05), **(p < 0.01), ***(p < 0.001), and ****(p < 0.0001), as determined by two-way ANOVA, and is color-coded to the treatment in the figure legends.

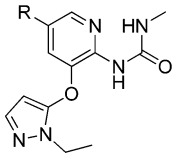
and showed efficacy at 3 mg/kg, the lowest dose administered. The area-under-the-curve (AUC) for the blood glucose was decreased by 15% at 3 mg/kg and 32% at 10 mg/kg. The 10 mg/kg dose was equally efficacious as the 30 mg/kg dose. The plasma glucose level stabilized at 77 mg/dL between 1.5 and 2 h for the 30 mg/kg dose, well above the hypoglycemic range (<50 mg/dL), thus confirming our target range for the kinetic parameters on GK induced by our GKA.

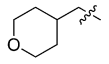
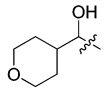
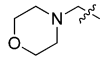
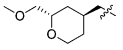
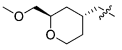
However, compound **12** had significant brain penetration in rat. The unbound concentrations in the brain were 29% of unbound concentrations in plasma in rat. Because of the fact that GK is also expressed in brain, there will be risk of interfering with counter regulation once GKA penetrates the brain and lowers the brain blood glucose level. Therefore, this was considered to be an undesirable attribute in a potential GKA therapeutic. We then continued to seek GKAs with less brain penetration (less than 10% is desired) in addition to a similar or better overall profile than **12**.

Our subsequent efforts were centered on modifications of **12**, and Table 4 shows some of the analogues explored. Hydroxyl group substitution at the benzylic position (**13**), morpholino replacement of THP (**14**), and *alpha* substitution to the oxygen of THP (**15**) all led to compounds with decreased potency. The only compound with similar potency (**16**) displayed a V_{max} less than 0.8.

Table 5 shows modifications on the pyrazole ring. These analogues (**17** and **18**) are also less potent than **12**.

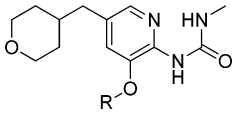
Table 4. Modifications of the THP Group at C5

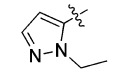
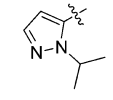
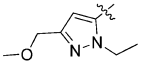


Compd	R	GKA EC_{50}[a,b] (μM)	$S_{0.5}$[a] (mM)	V_{max}[a,c] ratio
12		**0.35**	**0.84**	**0.80**
13		**16.8**	**1.2**	**0.82**
14		**7.98**	**0.86**	**0.78**
15		**0.49**	**0.94**	**0.76**
16		**0.35**	**0.88**	**0.78**

[a]Mean standard deviations for the EC_{50}, $S_{0.5}$, and V_{max} are ±30%, 17%, and 4%, respectively (n = 2). Also, human recombinant GK was used in all the assays. [b]For the EC_{50} assay, the glucose concentration was fixed at 5 mM. [c]Maximal velocity of the glucose phosphorylation reaction catalyzed by activated GK/unactivated GK.

Table 5. Modifications on the 3-*O*-Pyrazole



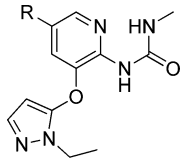
Compd	R	GKA EC_{50}[a,b] (μM)	$S_{0.5}$[a] (mM)	V_{max}[a,c] ratio
12		**0.35**	**0.84**	**0.80**
17		**2.76**	**0.95**	**0.60**
18		**0.82**	**0.85**	**0.71**

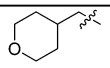
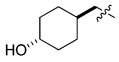
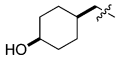
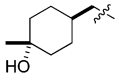
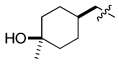
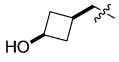
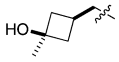
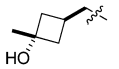
[a]Mean standard deviations for the EC_{50}, $S_{0.5}$, and V_{max} are ±30%, 17%, and 4%, respectively (n = 2). Also, human recombinant GK was used in all the assays. [b]For the EC_{50} assay, the glucose concentration was fixed at 5 mM. [c]Maximal velocity of the glucose phosphorylation reaction catalyzed by activated GK/unactivated GK.

We then investigated cyclic alcohols at C5 (Table 6). Secondary or tertiary hydroxyl would prevent secondary metabolism as shown in **7**. Cyclic compounds would also reduce the degrees of freedom in the molecule, which might improve

dx.doi.org/10.1021/ml500341w | ACS Med. Chem. Lett. XXXX, XXX, XXX−XXX

Table 6. Cyclic Alcohols at C5



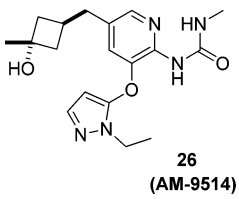
Compd	R	GKA EC_{50} [a,b] (μM)	$S_{0.5}$ [a] (mM)	V_{max} [a,c] ratio
12		0.35	0.84	0.80
19		0.068	0.71	0.79
20		0.12	0.76	0.66
21		0.11	0.69	0.71
22		0.097	0.56	0.82
23		0.53	0.72	0.88
24		0.50	0.63	0.96
25		0.71	0.82	0.80
26		0.29	0.68	0.91

[a]Mean standard deviations for the EC_{50}, $S_{0.5}$, and V_{max} are ±30%, 17%, and 4%, respectively (n = 2). Also, human recombinant GK was used in all the assays. [b]For the EC_{50} assay, the glucose concentration was fixed at 5 mM. [c]Maximal velocity of the glucose phosphorylation reaction catalyzed by activated GK/unactivated GK.

pharmacokinetic properties.[24] Another advantage of alcohols is that they generally have increased polarity and polar surface area than ethers, which might lower the brain penetration level.[25] The cyclohexanols (**19**–**22**) were more potent than **12**, but most of them had lower V_{max} with the exception of compound **22**; however, for **22**, the $S_{0.5}$ was out of the desired range.

The V_{max} parameters in the cyclobutanols were more encouraging. Both cis and trans isomers (**23** and **24**) had higher V_{max} values than **12**, with one of the isomers, **24**, having a V_{max} of 0.96. To improve their potency to a more desirable range, a methyl group was added to form the tertiary cyclobutyl alcohols. One of the isomers, **26**, had a V_{max} of 0.91 and an EC_{50} of 0.29 μM, both improved over **12**. The $S_{0.5}$ decreased to 0.68 mM but was still within our target range.

Compound **26** (**AM-9514**) had excellent solubility, permeability, *in vitro* clearances and free fractions in plasma protein binding (Figure 3). It had desirable pharmacokinetics in mouse and dog with a clearance of 0.91 L/h/kg in mouse and 0.64 L/h/kg in dog (Table 7). It also had excellent oral



26
(AM-9514)

MW - 359.42
EC_{50} - 0.29 μM
4% HSA EC_{50} - 0.28 μM
Solubility (pH 7.4) -480 μM
LLC PK Permeability (10^{-6} cm/s) - High (32.4)
Predicted Microsome CL(T.O.) - 10 (h), 12(r)
% PPB (h, r, mu) - 56 /50/ 56

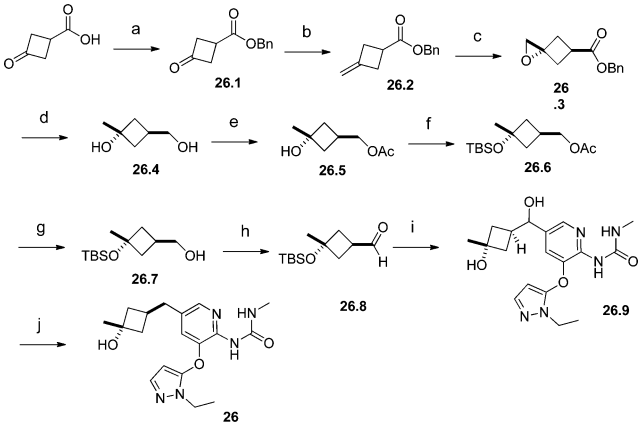
Figure 3. *In vitro* parameters of **26**: 4% HSA EC_{50} (the EC_{50} measured in the presence of 4% human serum albumin (HSA)).

Table 7. Pharmacokinetic Properties of 26

		IV			PO	
compd	species	CL (L/h/kg)	Vss (L/kg)	$T_{1/2}$ (h)	F (%)	AUC (μM·h)
26	rat[a]	1.6	0.8	2.0	9	0.39
26	mouse[b]	0.91	1.2	1.2	44	6.84
26	dog[a]	0.64	2.2	5.5	72	6.4

[a]Rat and dog: IV dose 0.5 mg/kg, n = 3; PO dose 2.0 mg/kg, n = 3. [b]Mouse: IV dose 1.0 mg/kg, n = 3; PO dose 5.0 mg/kg, n = 3.

Scheme 1. Synthesis of 26[a]



[a]Reagents and conditions: (a) BnBr, K_2CO_3, CH_3CN, 93%; (b) Tebbe reagent, THF, 58%; (c) H_2O_2, CCl_3CN, DCM, separate the trans/cis isomers, 48%; (d) $LiAlH_4$, THF, 90%; (e) Ac_2O, pyridine, DCM, 94%; (f) TBSOTf, DIEPA, DCM, 87%; (g) K_2CO_3, MeOH, 94%; (h) iodobenzene diacetate, TEMPO, DCM, 85%; (i) 1-(5-bromo-3-((1-ethyl-1*H*-pyrazol-5-yl)oxy)pyridin-2-yl)-3-methylurea, MeLi, BuLi, aldehyde, THF; then $MeSO_3H$, MeOH, 57% overall yield; (j) $MeSO_3H$, 10% Pd/C, H_2, MeOH, 59%.

bioavailability in dog. It was scaled up for further *in vivo* studies. The synthesis is shown in Scheme 1.

The synthesis of **26** started from 3-oxocyclobutanecarboxylic acid. It was protected with a benzyl group and then converted to benzyl 3-methylenecyclobutanecarboxylate **26.2** through the Tebbe olefination. Epoxidation of the double bond in **26.2** and isolation of the less polar isomer led to **26.3**, which was reduced to diol **26.4** with lithium aluminum hydride. The primary hydroxyl group in **26.4** was selectively protected with an acetate group (**26.5**), and the tertiary hydroxyl group was protected with a TBS group (**26.6**). Deprotection of the acetate group in **26.6** freed the primary hydroxyl group for further functional group transformations. Compound **26.7** was oxidized to aldehyde **26.8** under mild conditions. Lithiation of 1-(5-bromo-3-((1-ethyl-1*H*-pyrazol-5-yl)oxy)pyridin-2-yl)-3-methylurea[26] and addition of the organolithium generated to aldehyde **26.8** followed by subsequent deprotection of the TBS protection group resulted in diol **26.9**.

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The benzylic hydroxyl group in **26.9** was removed through hydrogenation under strong acidic conditions to provide compound **26**. The cis relationship of the methyl group and the benzylic methyl group relative to the cyclobutane ring in **26** was confirmed by 2D-NMR experiments.

Before further *in vivo* study, we measured the kinetic properties of **26** on mouse GK (V_{max} = 1.14 and $S_{0.5}$ = 0.69) and found them within our target range and also closer to human parameters compared to compound **12**. The antidiabetic efficacy of **26** was tested in an OGTT at doses of 0.3, 1, 3, and 10 mg/kg in fasted ob/ob mice (Figure 4). It showed dose-proportional lowering of blood glucose, with a 43% AUC decrease at 10 mg/kg.

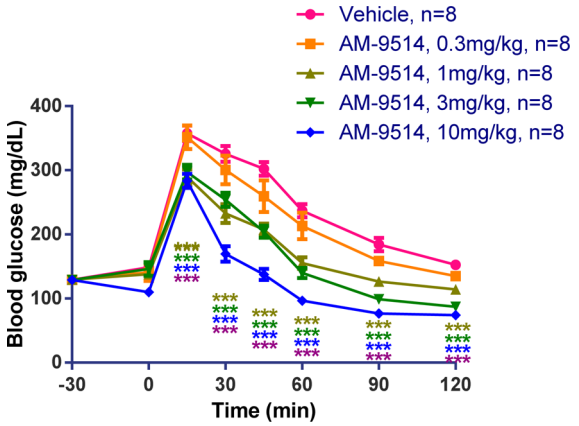

Figure 4. OGTT data of **26** (**AM-9514**) in ob/ob mice. Compound **26** lowered blood glucose in a dose-dependent manner. Statistical significance compared to vehicle treatment is denoted by *($p < 0.05$), **($p < 0.01$), ***($p < 0.001$), and ****($p < 0.0001$), as determined by two-way ANOVA, and is color-coded to the treatment in the figure legends.

Compound **26** was further tested in a normoglycemic glucose lowering test to evaluate its hypoglycemic risk. Fed male C57Bl/6 mice were orally dosed with vehicle or **26** without glucose challenge and then food was removed for 4 h. Blood glucose levels were measured at various time points (Figure 5). The elevation in glucose seen with the vehicle is presumably the result of handling stress on animals. Blood glucose levels were maintained above 85 mg/dL at all time points for both 10 and 30 mg/kg doses, well above its efficacious dose of 1 mg/kg. Therefore, **26** showed no hypoglycemia at the doses tested. Similar results of normoglycemic glucose lowering test were also obtained in rat of compound **26**. In addition, compound **26** showed low brain penetration in rat. The unbound concentrations in the brain were 4% of unbound plasma concentrations in rat.

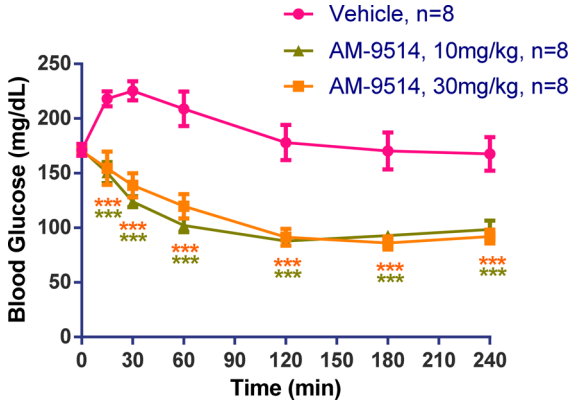

Figure 5. Normoglycemic glucose lowering test of **26** (**AM-9514**) in C57Bl/6 mice. Compound **26** showed no hypoglycemia during the test. Statistical significance compared to vehicle treatment is denoted by *($p < 0.05$), **($p < 0.01$), ***($p < 0.001$), and ****($p < 0.0001$), as determined by two-way ANOVA, and is color-coded to the treatment in the figure legends.

In conclusion, a new class of C5-alkyl-2-methylurea-substituted pyridines as glucokinase activators was developed based on our previous thiazolylamino pyridine GKAs. We optimized the potency and kinetic parameters of this class and identified compound **26** (**AM-9514**) with good potency, desirable GK kinetic parameters, and favorable *in vitro* and *in vivo* profiles including pharmacokinetic properties.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Assay, *in vivo* procedures, experimental procedures, and data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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