ACS Medicinal Chemistry Letters

Letter

pubs.acs.org/acsmedchemlett

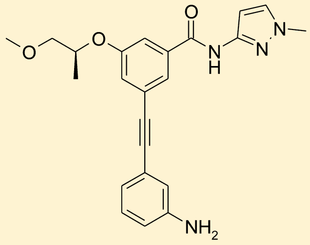
Design and Synthesis of Acetylenyl Benzamide Derivatives as Novel Glucokinase Activators for the Treatment of T2DM

Kaapjoo Park,* Byoung Moon Lee, Kwan Hoon Hyun, Taedong Han, Dong Hoon Lee, and Hyun Ho Choi

Yuhan Research Institute, 25, Tapsil-ro 35beon-gil, Giheung-gu, Yongin-si, Gyeonggi-do, Republic of Korea

Supporting Information

ABSTRACT: Novel acetylenyl-containing benzamide derivatives were synthesized and screened using an *in vitro* assay measuring increases in glucokinase activity stimulated by 10 mM glucose concentration and glucose uptake in rat hepatocytes. Lead optimization of an acetylenyl benzamide series led to the discovery of several active compounds via *in vitro* enzyme assays (EC_{50} < 40 nM) and *in vivo* OGTT assays (AUC reduction > 40% at 50 mg/kg). Of the active compounds tested, 3-(3-amino-phenylethynyl)-5-(2-methoxy-1-methyl-ethoxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-benzamide (**19**) was identified as a potent glucokinase activator exhibiting an EC_{50} of 27 nM and eliciting a 2.16-fold increase in glucose uptake. Compound **19** caused a glucose AUC reduction of 47.4% (30 mg/kg) in an OGTT study in C57BL/6J mice compared to 22.6% for sitagliptin (30 mg/kg). Single treatment of the compound **19** in C57BL/6J mice elicited basal glucose lowering activity without any significant evidence for hypoglycemia risk. Compound **19** was therefore selected as a candidate for further preclinical development for the treatment of type 2 diabetes.



19

GK EC_{50} = 27 nM, AUC reduction in OGTT = 47.4% (30 mg/kg)

KEYWORDS: *Type 2 diabetes mellitus, T2DM, glucokinase, glucokinase activator, GKA, acetylenyl benzamide derivatives*

Type 2 diabetes mellitus (T2DM) has established itself as a rapidly growing public epidemic now affecting over 300 million people worldwide. The first-line oral therapy for T2DM is metformin and there exist several second-line oral therapies together with which it is administrated in combination, including dipeptidyl peptidase-4 (DPP-4) and sodium-glucose cotransporter 2 (SGLT2) inhibitors. However, currently available antidiabetic agents have limited long-term efficacy and/or significant side effects. To address these clinical unmet needs for T2DM patients, great efforts have been made to develop new therapeutics, focusing on safety and efficacious glycemic control.

Glucokinase (GK, also called hexokinase IV or hexokinase D) is a hexokinase isozyme of 465 amino acids (molecular weight = 50 kDa). GK facilitates phosphorylation of glucose to glucose-6-phosphate and is expressed in cells of the liver, pancreas, gut, and brain of humans and many other vertebrates. GK activity[1−3] varies substantially with the concentration of glucose present, unlike other hexokinases. Glucokinase activator (GKA) is associated with a dual mechanism for lowering blood glucose concentrations by enhancing glucose uptake in the liver and increasing insulin secretion from pancreatic beta cells. Therefore, GK has become an attractive target for antidiabetic therapy over the last two decades. Several GKA candidates have advanced to clinical studies[4] and have been shown to lower both fasting and postprandial glucose levels in healthy subjects and T2DM patients. Hypoglycemia and liver or testicular toxicity[5] have been revealed as the primary adverse effects of concern for GKAs. To address the hypoglycemia issue, several clinical strategies have been utilized including dose titration, more frequent dosing times, and the design of partial or liver-selective glucose activators.[6,7] Although significant progress in GKA development has not been achieved to date,[8] several small molecule GKAs are currently in clinical studies (phase I and II).

A number of allosteric small molecule GKAs have been investigated by numerous research groups over the past decade[4] (representative small molecule GKAs are shown in Figure 1). Since the first report of small molecule allosteric GKAs in 2003,[9] a phenylacetamide series (**1**[10] and **2**[11]) a number of benzamides (**3**,[12] **4**,[13] and **5**[4]) and an imidazolylacetamide (**6**)[6] have also been identified as potent GKAs. GKAs putatively bind to allosteric sites of the protein to achieve antihyperglycemic effects, according to structural information derived from GK-GKA complexes published in 2009.[14,15] More recently, Park et al. identified novel phenylethyl benzamide GKAs, **7a** (YH-GKA)[16] and pyridyl benzamide **7b**,[17] which exhibit good biological and pharmacological activities with favorable pharmacokinetics. Herein, we report the lead optimization of an acetylenyl containing benzamide series for the development of novel glucokinase activators for the treatment of type 2 diabetes mellitus.

The benzamide scaffold was chosen as a starting point for the synthesis due to the existence of unambiguous structural information from the known cocrystal complexes.[14] Through initial diversification and structure−activity relationship (SAR)

Received: November 17, 2014
Accepted: January 14, 2015
Published: January 14, 2015

DOI: 10.1021/ml5004712
ACS Med. Chem. Lett. 2015, 6, 296−301

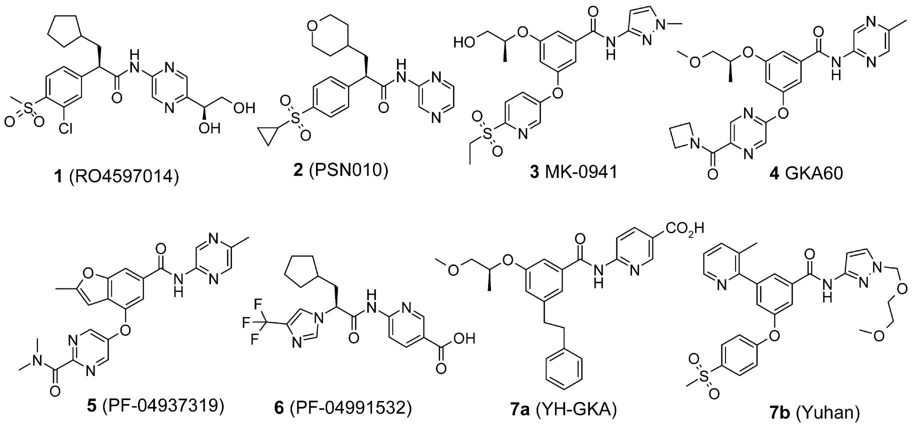


Figure 1. Representative structures of GKAs.

analysis of the acetylenyl containing benzamide scaffold, the 1-methyl-1*H*-pyrazol moiety was selected in the A-region for a strong hydrogen bond interaction with ARG63, and the (*R*)-(−)-2-methoxy-1-methyl-ethoxy moiety was fixed in the B-region for a hydrophobic interaction with TYR214, TYR215, and GLY97 (Figure 2).

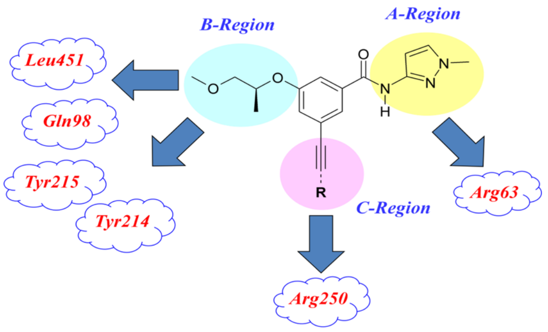


Figure 2. Synthetic strategy for benzamide GKAs.

The pocket in the C-region of the enzyme is relatively large and the end portion of the C-moiety has the potential for a hydrogen bond interaction with Arg250, which may increase binding affinity. Therefore, the C-region was analyzed systematically by introducing a variety of acetylenyl containing alkyl, aryl, or heteroaryl groups, which led to the identification of several active moieties in the C-region as targets for GKA compounds, as summarized in Tables 1 and 2. The synthesis of acetylenyl containing benzamide derivatives is described in Schemes 1−3.

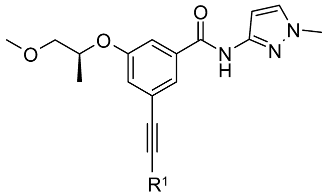
Various propargyl or acetylenyl groups containing benzamides were synthesized as shown in Scheme 1. The synthesis began with a Mitsunobu reaction of 3-bromo-5-hydroxy benzoic acid with (*R*)-(−)-1-methoxy-2-propanol, known for an optimized moiety in the A-region. Then, ester **8** was hydrolyzed to give acid **9**, and subsequent amide coupling of acid **9** with 1-methyl-1*H*-pyrazol-3-amine provided the key intermediate benzamide **10**. The acetylenyl group was introduced to a meta-position on the benzamide ring using Pd-mediated coupling reactions. The coupling reaction between compound **10** and tetrahydro-2-(2-propynyloxy)-2*H*-pyran followed by removal of the pyran protection group gave **11**. The resulting propargyl alcohol **11** was treated with PBr_3 to afford propargyl bromide **12**. Various propargyl alkoxy analogues **13** were synthesized by simple alkylation reactions of **12**. Compound **10** was also coupled with substituted aryl acetylene compounds or Boc-propargylamine to give **14** and **15**, respectively. Removal of the Boc protection group followed by alkylation reactions of the resulting amine with a variety of alkyl chloride provided analogues **16**.

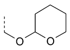
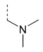
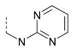
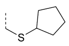
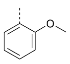
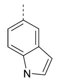
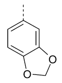
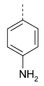
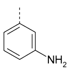
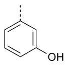
More substituted aryl acetylenyl benzamide derivatives **18** were prepared from the key intermediate **10** in two steps as shown in Scheme 2. A Sonogashira coupling reaction of **10** with trimethylsilylacetylene followed by Pd-catalyzed coupling reactions of acetylene **17** with a variety of aryl iodides yielded aryl acetylenyl benzamides **18**.

meta-Acetylenyl N-substituted anilines **20** and 1,3-alkoxy acetylenly benzene **22** were prepared by Pd-catalyzed coupling reactions with 3-ethynylaniline or 3-ethynylphenol followed by S_N2 alkylation reaction of the resulting aniline **19** or phenol **21** with appropriate alkyl chlorides in the presence of a base (Scheme 3).

Biological activity data for the selected acetylenyl benzamide derivatives have been summarized in Tables 1 and 2. Among the compounds in Table 1, **13b** showed excellent potency with an EC_{50} of 6 nM. Several compounds including **16c**, **18a**, **18d**, **19**, and **21**, which contain similar-sized moieties to the moiety of **13b** in the R^1 position, exhibited favorable enzyme activity ($EC_{50} < 40$ nM) presumably due to the van der Waals interaction in the C-pocket of glucokinase. In addition, the compounds **18b** and **18c** containing a bicyclic moiety such as indole and benzo[1,3]-dioxole in the R^1 position showed favorable activity with EC_{50} values of 12 and 30 nM, respectively. However, a small R^1 group showed a tendency to decrease enzyme potency as seen in compounds **13a** and **16a**. On the basis of the potency and physicochemical properties of the compounds, more derivatives of aniline **19** and phenol **21** were synthesized for further establishment of the structure−activity relationship. For the aniline series shown in Table 2, N^1,N^1-dimethylethane-1,2-diamine (**20c**), 2-pyrrolidin-1-yl-ethylamine (**20d**) and 2-piperidin-1-yl-ethylamine (**20e**) in the R^2 position led to an improvement in the potency of the enzyme (EC_{50} = 6 nM) by 4.5-fold compared to a simple amine (NH_2) moiety in the same position (**19**, EC_{50} = 27 nM), while compound **20f** containing a 2-morpholin-1-yl-ethylamine moiety (EC_{50} = 20 nM) and compound **20a** with an N^1,N^1-dimethyl moiety (EC_{50} = 37 nM) in the R^2 position maintained similar potency to **19**. In addition, heterocyclic ethylamine such as 2-(2-methyl-imidazol-1-yl)-ethylamine (**20h**) as an R^2 group improved enzyme potency by 3-fold (EC_{50} for **20h** = 9 nM). In contrast, N^1,N^1-diethyl amine (**20b**) in the R^2 position slightly decreased the potency by 6-fold (EC_{50} = 163 nM). Furthermore, a similar SAR

Table 1. *In Vitro* Glucokinase Activity of the Acetylenyl Benzamide Derivatives **13a–b**, **16a–c**, **18a–d**, **19**, and **21**

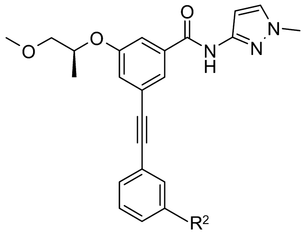


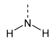
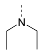
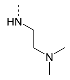
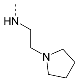
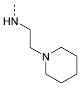
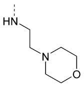
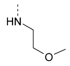
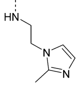
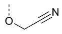
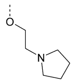
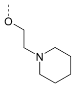
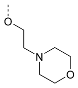
Compounds	R^1	EC_{50} at10 mM glucose, (μM)[a]	Glucose uptake at 5.6 mM glucose, (fold)	$S_{0.5}$, (mM)[b]
13a		1.87	1.71	4.04
13b		0.006	2.50	0.55
16a		7.7	1.31	5.51
16b		0.301	2.37	3.88
16c		0.025	3.38	0.72
18a		0.021	2.64	0.73
18b		0.012	1.99	0.46
18c		0.030	2.64	2.13
18d		0.034	2.05	0.73
19		0.027	2.16	0.84
21		0.039	1.57	1.37

[a] Data represented as the mean values of data obtained from triplicate runs. [b] Recombinant human pancreatic glucokinase was used, and the activity was measured at 1 μM concentration.

trend has been observed in a 3-phenol series (**21**) compared to a 3-anline series (**19**). 2-Pyrrolidin-1-yl-ethyloxy (**22c**) and 2-piperidin-1-yl-ethyloxy (**22d**) as an R^2 moiety improved the potency of enzyme activity by 6-fold (EC_{50} = 6–7 nM) compared to an OH moiety in the R^2 position (**21**, EC_{50} = 39 nM), while a 2-morpholin-1-yl-ethyloxy moiety in the R^2 position (**22e**) slightly increased the potency by 2.4-fold (EC_{50} = 16 nM). The compounds **22a–b** containing relatively small groups in the R^2 position maintained similar potency to compound **21**. Other derivatives of 4-aminophenylethynyl series (**18d**) were synthesized for further investigation, but no significant increases in enzyme potency were observed (data not shown).

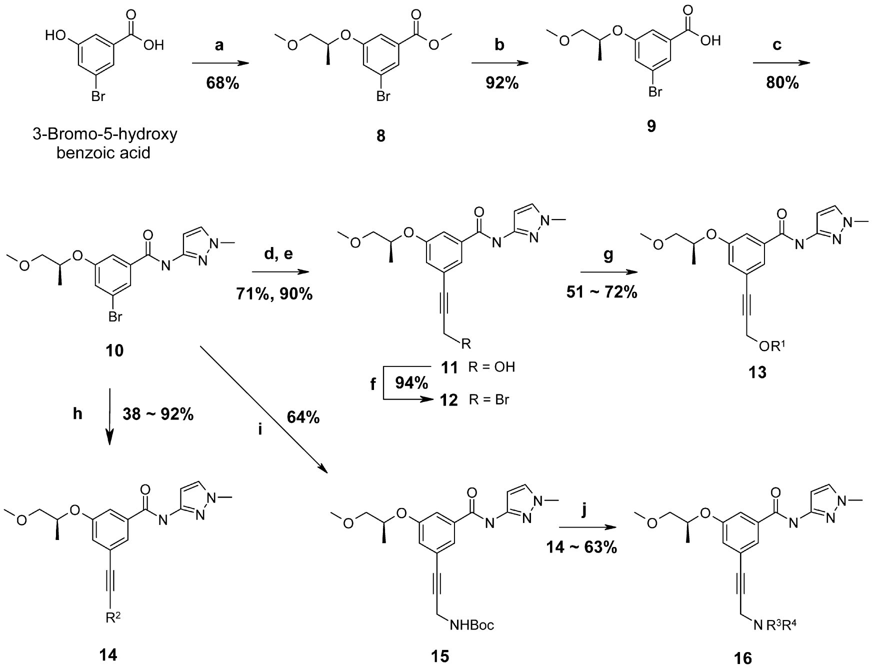
Table 2. *In Vitro* Glucokinase Activity of m-Substituted Ethynylphenyl Benzamide Derivatives **20a–h** and **22a–e**



Compounds	R	EC_{50} at10 mM glucose, (μM)[a]	Glucose uptake at 5.6 mM glucose, (fold)	$S_{0.5}$, (mM)[b]
19		0.027	2.16	0.84
20a		0.037	2.43	0.76
20b		0.163	1.91	2.01
20c		0.006	2.03	0.17
20d		0.006	2.83	0.51
20e		0.006	2.79	0.61
20f		0.02	2.62	0.55
20g		0.039	2.18	1.23
20h		0.009	2.36	0.90
22a		0.053	2.03	1.84
22b		0.046	1.75	0.95
22c		0.006	2.43	0.73
22d		0.007	2.36	2.25
22e		0.016	1.89	0.35

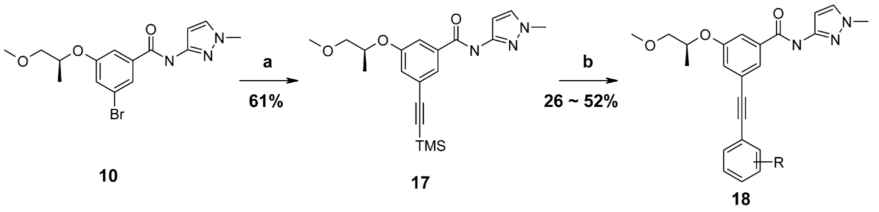
[a] Data represented as the mean values of data obtained from triplicate runs. [b] Recombinant human pancreatic glucokinase was used, and the activity was measured at 1 μM concentration.

Scheme 1[a]



[a]Reagents and conditions: (a) (i) MeOH, c.H_2SO_4, reflux; (ii) (*R*)-(−)-1-methoxy-2-propanol, DIAD, PPh_3, THF, 0 °C → RT; (b) NaOH, THF/MeOH/H_2O; (c) 1-methyl-1*H*-pyrazol-3-amine, EDAC, HOBT, DIEA, CH_2Cl_2; (d) TBAF, $PdCl_2(PPh_3)_2$, tetrahydro-2-(2-propynyloxy)-2*H*-pyran, 85 °C; (e) *p*-toluenesulfonic acid, MeOH; (f) PBr_3, THF; (g) R^1OH, Cs_2CO_3, DMF; (h) $PdCl_2(PPh_3)_2$, substituted aryl acetylene (R^2CCH), TBAF, 85 °C; (i) $PdCl_2(PPh_3)_2$, Boc-propargylamine, TBAF, 85 °C; (j) (i) TFA, CH_2Cl_2, 0 °C → RT; (ii) R^3Cl, K_2CO_3, KI, DMF, 80 °C.

Scheme 2[a]

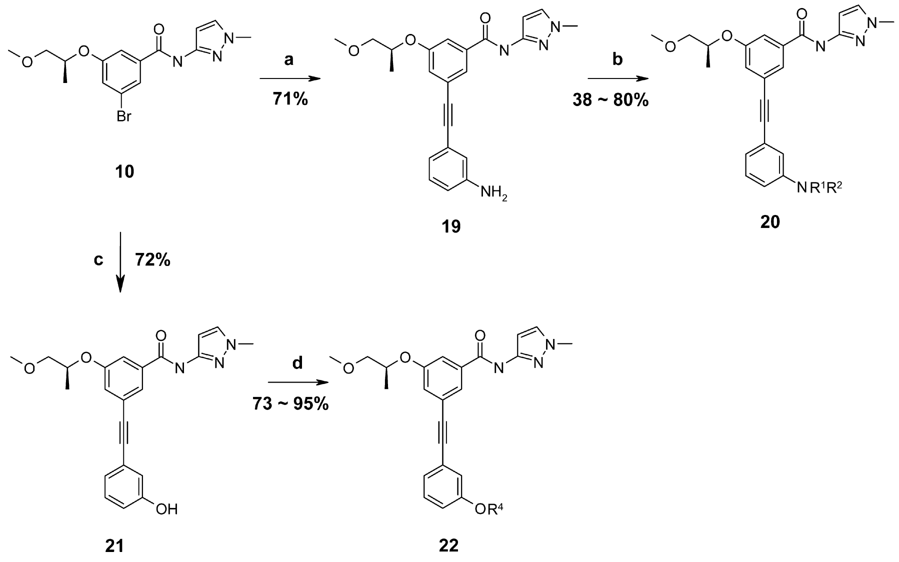


[a]Reagents and conditions: (a) (i) trimethylsilylacetylene, $PdCl_2(dppf)$, TEA, CuI; (b) substituted aryl iodide (RPhI), $PdCl_2(PPh_3)_2$, TBAF, 85 °C.

The improvement in potency appears to result from the size, ionic, hydrophobic, and hydrogen bonding effects of the moiety in the C-region of the GK pocket and/or the electrostatic interaction with the pocket. According to a binding mode analysis of **19** with the binding site of glucokinase generated by Surflex-Dock[18] (Figure 3), the 1-methyl-1*H*-pyrazol moiety elicits a strong hydrogen bond with ARG63 and the (*R*)-(−)-2-methoxy-1-methyl-ethoxy moiety is oriented toward the hydrophobic pocket surrounded by TYR214, TYR215, and GLY97. 3-Amino-phenylethynyl group orients to the C-region in the GK pocket, which is relatively larger than the A- or B-region, and the amine group can be extended to the solvent-exposed region for hydrogen bonding with ARG250.

Most of the submicromolar active compounds in the GK enzyme assay elicited favorable glucose uptake activity with >1.7-fold increase under glucose stimulated conditions (glucose of 0 mM → 5.6 mM). Compounds that exhibited EC_{50} values of <300 nM in the GK activity assay, >2.0-fold increase in the glucose uptake assay, and good physicochemical properties were chosen for *in vivo* oral glucose tolerance test (OGTT) experiments (Table 3). Unsurprisingly, many compounds measured by *in vivo* OGTT showed significant area under the curve (AUC) reduction (>40%) at 30 or 50 mg/kg including several compounds that exhibited >50% AUC reduction (**18d**, **19**, **20c−e**, and **22c**). Of the active compounds in the *in vivo* OGTT, compound **19** was chosen for dose-dependent *in vivo* OGTT and the fasted glucose tolerance test. Compound **19** exhibited human pancreatic glucokinase activity of EC_{50} = 27 nM at 10 mM glucose with a maximum reaction rate (V_{max}) of 126% and a half maximal saturation concentration ($S_{0.5}$)[3] of 0.84 mM. Compound **19** also enhanced glucose uptake in rat primary hepatocytes by 2.16-fold, did not affect hexokinase I or II, and increased insulin secretion by 2.13-fold from rat pancreatic islets under glucose stimulated conditions (glucose of 0 mM → 5.6 mM). In addition, compound **19** exhibited favorable pharmacokinetics[19] and improved oral glucose tolerance in C57BL/6J mice in a dose-dependent manner (Figure 4). *In vivo* OGTT values for **19** at 30 mg/kg in C57Bl/6J mice revealed a blood glucose AUC reduction of 47.4%, which was significantly greater than that of 22.6% for sitagliptin at 30 mg/kg. The fasted glucose tolerance test of **19** due to fasting without glucose challenge indicated that the mean value of glucose level after 60 min was maintained above 55 mg/dL, the minimum glucose level at which symptoms of hypoglycaemia do not occur, and showed

Scheme 3[a]



[a]Reagents and conditions: (a) $PdCl_2(PPh_3)_2$, 3-ethynylaniline, TBAF, 85 °C; (b) method (A) R^2Cl, DIEA, NMP, 160 °C; method (B) R^2Cl, TEA, CH_2Cl_2, rt.; (c) $PdCl_2(PPh_3)_2$, 3-ethynylphenol, TBAF, 85 °C; (d) method (A) R^4Cl, DIEA, NMP, 160 °C; method (B) R^4Cl, TEA, CH_2Cl_2, rt.

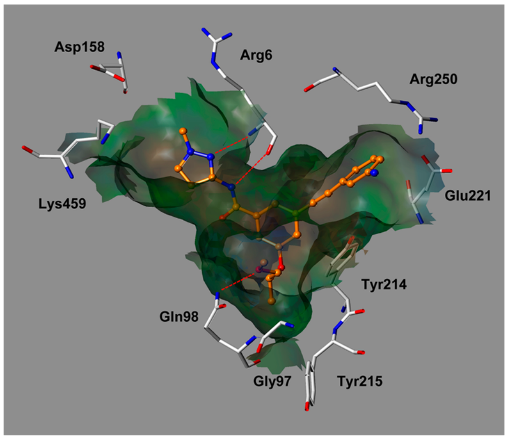


Figure 3. Docked conformer of **19** (at the active site of glucokinase as generated by Surflex-Dock), based on the X-ray structure of the known cocrystallized ligand. Specific binding of **19** to glucokinase shows potential hydrogen bonds in red dotted lines.

Table 3. ***In Vivo* OGTT Results for the Selected Acetylenyl Benzamide Derivatives**

Compounds	OGTT at 50 mg/kg, (AUC reduction, %)
13b	44.7
18a	49.1[a]
18d	53.5
19	52.1, 47.4[a]
20a	43.7
20c	56.0[a]
20d	51.4
20e	54.0
20f	47.9
20g	41.0[a]
22c	51.6
22d	46.0

[a]Measured OGTT at 30 mpk (AUC reduction, %).

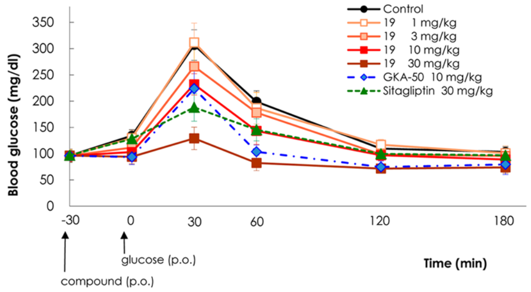


Figure 4. Plasma blood glucose lowering effect of **19** in C57BL/6J mice OGTT; po, per os (oral administration).

very similar results as for GKA50,[20] a potent GKA compound from AstraZeneca (Figure 5).

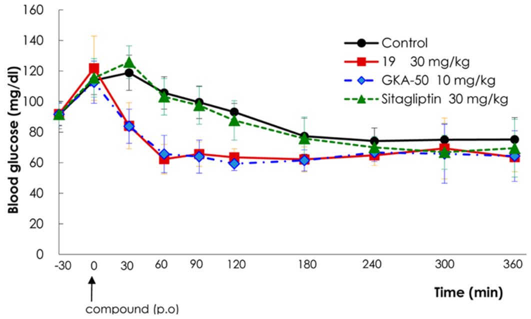


Figure 5. Fasted glucose tolerance test of **19** in C57BL/6J mice.

In summary, lead optimization and SAR analysis of an acetylenyl containing benzamide series led to the discovery of several novel glucokinase activators. Compound **19**, 3-(3-Amino-phenylethynyl)-5-(2-methoxy-1-methyl-ethoxy)-N-(1-methyl-1*H*-pyrazol-3-yl)-benzamide, was found to be an active GKA with an EC_{50} of 27 nM and elicited an excellent AUC reduction of 47.4% (30 mg/kg) in an *in vivo* OGTT study with favorable pharmacokinetics. These study results strongly support the notion that GKA **19** is a promising candidate for further preclinical investigation as a potential therapeutic agent for type 2 diabetes mellitus.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Description of synthesis of **19**, procedure of bioassays, and pharmacokinetics protocol. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +82 31 899 4274. Fax: +82 31 275 6145. E-mail: kaapjoo@yuhan.co.kr.

Funding

This study was supported by a grant from the Chungcheong Leading Industry Office for Medicine and Bio Projects, Ministry of Knowledge Economy, Republic of Korea (C-2-1, 500108, and 7007618).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors would like to thank Mr. Wonee Chong for his contribution to the pharmacokinetic study of **19** and Dr. Su Youn Nam for her helpful discussion at Yuhan Research Institute. We also thank Lee Farrand for proofreading the manuscript

■ ABBREVIATIONS

GK, glucokinase; GKA, glucokinase activator; DPP-4, dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter 2; SAR, structure−activity relationship; T2DM, type 2 diabetes mellitus; OGTT, oral glucose tolerance test

■ REFERENCES

(1) Matschinsky, F. M. A lesson in metabolic regulation inspired by the glucokinase glucose sensor paradigm. *Diabetes* **1996**, *45*, 223−241.

(2) Antoine, M.; Boutin, J. A.; Ferry, G. Binding kinetics of glucose and allosteric activators to human glucokinase reveal multiple conformational states. *Biochemistry* **2009**, *48*, 5466−5482.

(3) Heredia, V. V.; Thomson, J.; Nettleton, D.; Sun, S. Glucose-induced conformational changes in glucokinase mediate allosteric regulation: transient kinetic analysis. *Biochemistry* **2006**, *45*, 7553−7562.

(4) Filipski, K. J.; Pfefferkorn, J. A. A patent review of glucokinase activators and disruptors of the glucokinase−glucokinase regulatory protein interaction: 2011 − 2014. *Expert Opin. Ther. Pat.* **2014**, *24*, 875−891.

(5) Waring, M. J.; Brogan, I. J.; Coghlan, M.; Johnstone, C.; Jones, H. B.; Leighton, B.; Mckerrecher, D.; Pike, K. G.; Robb, G. R. Overcoming retinoic acid receptor-α based testicular toxicity in the optimization of glucokinase activators. *MedChemComm* **2011**, *2*, 771−774.

(6) Pfefferkorn, J. A.; Guzman-Perez, A.; Litchfield, J.; Aiello, R.; Treadway, J. L.; Pattersen, J.; Minich, M. L.; Filipski, K. J.; Jones, C. S.; Tu, M.; Aspnes, G.; Risley, H.; Bian, J.; Stevens, B. D.; Bourassa, P.; D'Aquila, T.; Baker, L.; Barucci, N.; Robertson, A. S.; Bourbonais, F.; Derksen, D. R.; MacDougall, M.; Cabrera, O.; Chen, J.; Lapworth, A. L.; Landro, J. A.; Zavadoski, W. J.; Atkinson, K.; Haddish-Berhane, N.; Tan, B.; Yao, L.; Kosa, R. E.; Varma, M. V.; Feng, B.; Duignan, D. B.; El-Kattan, A.; Murdande, S.; Liu, S.; Ammirati, M.; Knafels, J.; DaSilva-Jardine, P.; Sweet, L.; Liras, S.; Rolph, T. P. Discovery of (*S*)-6-(3-cyclopentyl-2-(4-(trifluoromethyl)-1*H*-imidazol-1-yl)propanamido)-nicotinic acid as a hepatoselective glucokinase activator clinical candidate for treating type 2 diabetes mellitus. *J. Med. Chem.* **2012**, *55*, 1318−1333.

(7) Massa, M. L.; Gagliardino, J. J.; Francini, F. Liver glucokinase: An overview on the regulatorymechanisms of its activity. *Life* **2011**, *63*, 1−6.

(8) Matschinsky, F. M. GKAs for diabetes therapy: why no clinically useful drug after two decades of trying? *Trends Pharmacol. Sci.* **2013**, *34*, 90−99.

(9) Grimsby, J.; Sarabu, R.; Corbett, W. L.; Hayne, 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.; Soence, C. L.; Tengi, J.; Magnuson, M. A.; Chu, C. A.; Dvorozniak, M. T.; Matschinsky, F. M.; Grippo, J. F. Allosteric activators of glucokinase: potential role in diabetes therapy. *Science* **2003**, *301*, 370−373.

(10) Qian, Y.; Corbett, W. L.; Berthel, S. J.; Choi, D.-S.; Dvorozniak, M. T.; Geng, W.; Gillespie, P.; Guertin, K. R.; Haynes, N.-E.; Kester, R. F.; Mennona, F. A.; Moore, D.; Racha, J.; Radinov, R.; Sarabu, R.; Scott, N. R.; Grimsby, J.; Mallalieu, N. L. Identification of RO4597014, a glucokinase activator studied in the clinic for the treatment of type 2 diabetes. *ACS Med. Chem. Lett.* **2013**, *4*, 414−418.

(11) Yamagami, T.; Moriyama, N.; Kyuhara, M.; Moroda, A.; Uemura, T.; Matsumae, H.; Moritani, Y.; Inoue, I. Scalable synthesis of a nonracemic alpha-arylpropionic acid via ketenedesymmetrization for a glucokinase activator. *Org. Process Res. Dev.* **2014**, *18*, 437−445.

(12) Meininger, G. E.; Scott, R.; Alba, R.; Shentu, Y.; Luo, E.; Amin, H.; Davies, M. J.; Kaufman, K. D.; Goldstein, B. J. Effects of MK-0941, a novel glucokinase activator, on glycemic control in insulin-treated patients with type 2 diabetes. *Diabetes Care* **2011**, *34*, 2560−2566.

(13) Pike, K. G.; Allen, J. V.; Caulkett, P. W.; Clarke, D. S.; Donald, C. S.; Fenwick, M. L.; Johnson, K. M.; Johnstone, C.; McKerrecher, D.; Rayner, J. W.; Walker, R. P.; Wilson, I. Design of a potent, soluble glucokinase activator with increased pharmacokinetic half-life. *Bioorg. Med. Chem. Lett.* **2011**, *11*, 3467−3470.

(14) Mitsuya, M.; Kamata, K.; Bamba, M.; Watanabe, H.; Sasaki, Y.; Sasaki, K.; Ohyama, S.; Hosaka, H.; Nagata, Y.; Eiki, J.; Nishimura, T. Discovery of novel 3,6-disubstituted 2-pyridinecarboxamide derivatives as GK activators. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2718−2721.

(15) Iino, T.; Hashimoto, N.; Sasaki, K.; Ohyama, S.; Yoshimoto, R.; Hosaka, H.; Hasegawa, T.; Chiba, M.; Nagata, Y.; Eiki, J.; Nishimura, T. Structure−activity relationships of 3,5-disubstituted benzamides as glucokinase activators with potent in vivo efficacy. *Bioorg. Med. Chem.* **2009**, *17*, 3800−3809.

(16) Park, K.; Lee, B.-M.; Kim, Y.- H.; Han, T.; Yi, W.; Lee, D.-H.; Choi, H.-H.; Chong, W.; Lee, C.-H. Discovery of a novel phenylethyl benzamide glucokinase activator for the treatment of type 2 diabetes mellitus. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 537−542.

(17) Park, K.; Lee, B. M.; Hyun, K. H.; Lee, D. H.; Choi, H. H.; Kim, H.; Chong, W.; Kim, K. B.; Nam, S. Y. Discovery of 3-(4-methanesulfonylphenoxy)-N-[1-(2-methoxyethoxymethyl)-1H-pyrazol-3-yl]-5-(3-methylpyridin-2-yl)-benzamide as a novel glucokinase activator (GKA) for the treatment of type 2 diabetes mellitus. *Bioorg. Med. Chem.* **2014**, *22*, 2280−2293.

(18) Jain, A. N. Surflex: fully automatic flexible molecular docking using a molecular similarity-based search engine. *J. Med. Chem.* **2003**, *46*, 499−511.

(19) Pharmacokinetic study of **19** in mice established clearance of 2.59 L/h/kg, distribution volume (V_{dss}) of 1.44 L/kg, elimination half-life ($T_{1/2}$) of 1.1 h, and bioavailability (F) of 49%. Physicochemical properties of **19**: solubility (pH 7.4) = 22.2 μM, $P_{\mathrm{app,PAMPA}}$ (10^{-6} cm/s) = 3.43, ClogP = 2.64.

(20) Johnson, D.; Shepherd, R. M.; Gill, D.; Gorman, T.; Smith, D. M.; Dunne, M. J. Glucose-dependent modulation of insulin secretion and intracellular calcium ions by GKA50, a glucokinase activator. *Diabetes* **2007**, *56*, 1694−1702.