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The design and synthesis of indazole and pyrazolopyridine based glucokinase activators for the treatment of Type 2 diabetes mellitus

Jeffrey A. Pfefferkorn [a,*], Meihua Tu [a], Kevin J. Filipski [a], Angel Guzman-Perez [b], Jianwei Bian [b], Gary E. Aspnes [b], Matthew F. Sammons [a], Wei Song [b], Jian-Cheng Li [b], Christopher S. Jones [b], Leena Patel [b], Tim Rasmusson [b], Dongxiang Zeng [b], Kapil Karki [b], Michael Hamilton [b], Richard Hank [b], Karen Atkinson [b], John Litchfield [b], Robert Aiello [b], Levenia Baker [b], Nicole Barucci [b], Patricia Bourassa [b], Francis Bourbounais [b], Theresa D'Aquila [b], David R. Derksen [b], Margit MacDougall [b], Alan Robertson [b]

[a] Pfizer Cardiovascular, Metabolic and Endocrine Disease Research Unit, Pfizer Worldwide Research and Development, 620 Memorial Drive, Cambridge, MA 02139, USA
[b] Pfizer Worldwide Research and Development, Eastern Point Road, Groton, CT 06442, USA

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ABSTRACT

Glucokinase activators represent a promising potential treatment for patients with Type 2 diabetes. Herein, we report the identification and optimization of a series of novel indazole and pyrazolopyridine based activators leading to the identification of 4-(6-(azetidine-1-carbonyl)-5-fluoropyridin-3-yloxy)-2-ethyl-*N*-(5-methylpyrazin-2-yl)-2*H*-indazole-6-carboxamide (**42**) as a potent activator with favorable preclinical pharmacokinetic properties and in vivo efficacy.

Type 2 diabetes mellitus (T2DM) is a rapidly growing public health problem affecting more than 300 million people worldwide.[1] Despite the availability of various anti-diabetic therapies, many patients fail to achieve and maintain treatment targets increasing their long term risk of microvascular and macrovascular complications. Hence, there remains a significant medical need for novel treatments.[2] Among the new therapies currently under investigation, small molecule activators of glucokinase (GK) enzyme represent a promising opportunity to help patients achieve improved glucose control.[3]

Glucokinase is responsible for the conversion of glucose to glucose-6-phosphate (G-6-P) and is an important regulator of glucose homeostasis.[4] In the liver, glucokinase regulates hepatic glucose uptake and output, whereas in the pancreas it functions as a glucostat establishing the threshold for β-cell glucose-stimulated insulin secretion. Glucokinase is also found in glucose sensing neurons of the ventromedial hypothalamus where it regulates the counter regulatory response (CRR) to hypoglycemia.[5] Therapeutically, it is envisioned that activation of glucokinase in the liver and pancreas would be an effective strategy for lowering blood glucose by up-regulating hepatic glucose utilization, down-regulating hepatic glucose output and enhancing glucose-stimulated insulin secretion.

In 2003, Grimsby and coworkers reported the first small molecule glucokinase activator which allosterically bound to the enzyme, increasing activity through modulation of both K_m (i.e. $S_{0.5}$) and V_{max}.[6] Subsequently, many structurally diverse small molecule activators of glucokinase have been reported.[7] These glucokinase activators have been shown to effectively lower blood glucose in a variety of diabetic animal models and multiple candidates have advanced into Phase 1 and 2 clinical studies where they have been found to effectively lower both fasting and postprandial glucose in T2DM patients.[8] However, despite the promising efficacy of this mechanism, there has been significant attrition in the clinical development of glucokinase activators driven by narrow therapeutic windows against hypoglycemia as well as concerns around durability and chemotype-specific safety issues.[8] These issues with early activators have fostered investigations into structurally diverse second generation activators designed to reduce hypoglycemia risk. We recently reported structure–activity studies of a 2-methyl benzofuran activator series (**1**, Fig. 1) culminating in the selection of **2** as a clinical development candidate.[9] Benzofuran **2** was specifically selected as a 'partial activator' of glucokinase designed to cause a less significant reduction in the glucokinase K_m relative to earlier candidates; this profile maintained increased glucose dependency of activation thereby reducing the risk of hypoglycemia. To expand upon this work, we sought to explore the use of various nitrogen-containing 5,6-heterocyclic scaffolds to identify novel activators with potentially increased lipophilic

* Corresponding author.
E-mail address: jeffrey.a.pfefferkorn@pfizer.com (J.A. Pfefferkorn).

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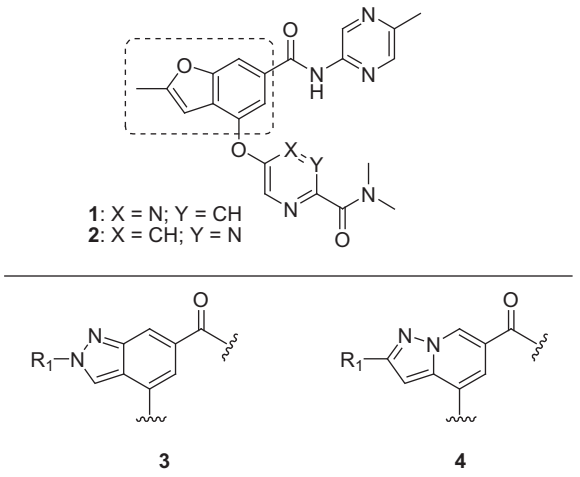
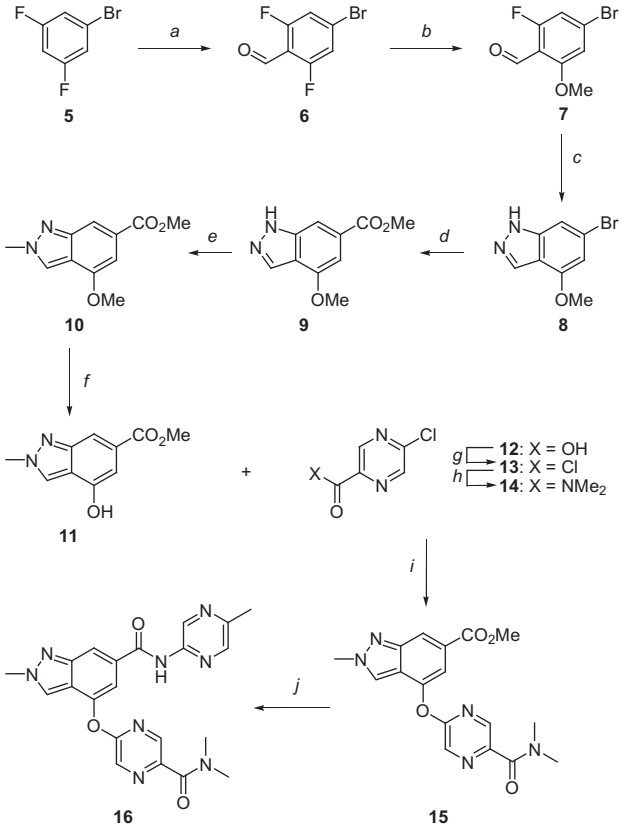


Figure 1. Structure benzofuran (**1**,**2**), indazole (**3**) and pyrazolopyridine (**4**) based glucokinase activators.

efficiency (LipE).[10] To help guide these efforts, we utilized the recently reported modeling tool NEAT (Novel and Electronically-equivalent Aromatic Template) to evaluate the electronic properties of a diverse array of substituted 5,6-heterocyclic ring systems.[11] This in silico analysis suggested that, among the nitrogen-containing heterocyclic systems examined, indazole (**3**) and pyrazolopyridine (**4**) were the most electronically comparable to the parent benzofuran (**2**). Herein, we report the synthesis and evaluation of activators based upon these two heterocyclic templates.

Schemes 1 and 2 illustrate the synthesis of prototype indazole and pyrazolopyridine activators **16** and **26**, respectively. As shown in Scheme 1 1-bromo-3,5-difluorobenzene (**5**) was selectively lithiated and then quenched with DMF to give benzaldehyde **6**.[12] Subsequent mono-displacement of an *ortho*-fluorine with sodium methoxide afforded **7**. Treatment of **7** with hydrazine resulted in a one pot condensation and cyclization to form indazole **8** in good yield. Palladium-catalyzed carbonylation provided ester **9** which was then selectively alkylated at the N-2 position using tri-methyloxonium tetrafluoroborate.[13] Hydroxyindazole **11** was formed by global demethylation with boron tribromide followed by re-esterification of the carboxylate with methyl alcohol and catalytic acid. Separately, chloropyrazine **14** was formed by amidation of the acid chloride formed from 5-chloropyrazine-2-carboxylic acid (**12**). In the penultimate step, biaryl ether bond formation was accomplished via base-mediated nucleophilic displacement of 2-chloropyrazine **14** with the indazole-phenol **11** to generate **15**. Finally, transamidation of **14** with 2-amino-5-methylpyrazine in the presence of Me_2AlCl afforded indazole **16**.

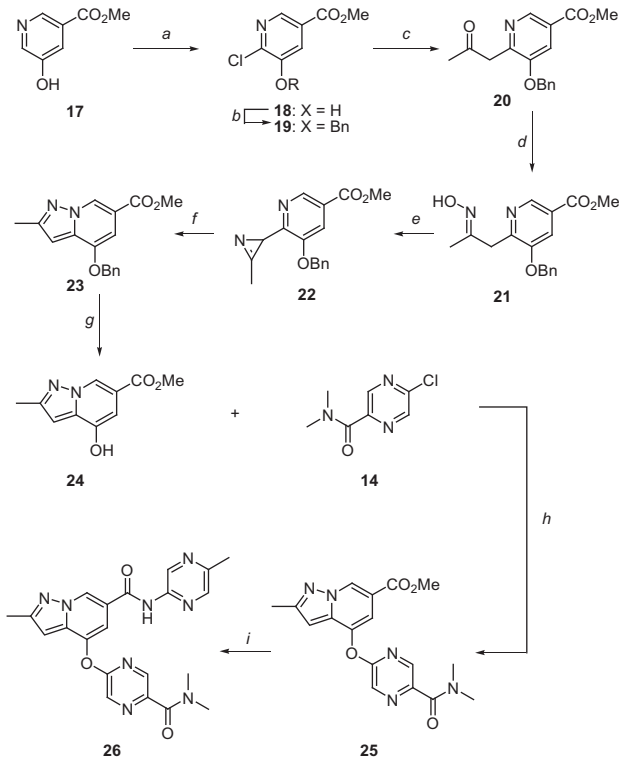
As shown in Scheme 2, pyrazolopyridine activator **26** was synthesized by initial chlorination of methyl-5-hydroxynicotinate (**17**) with bleach[14] to chloro-pyridine **18**. After benzyl protection of the phenol under standard conditions, a palladium-catalyzed coupling of **19** with the tributyltin enolate of isopropenyl acetate afforded ketone **20**.[15] Conversion of **20** to indazole **23** was accomplished by treatment with hydroxylamine hydrochloride to form intermediate oxime **21** which, upon treatment with trifluoroacetic anhydride and triethylamine, was converted to the azirine **22** followed by $FeCl_2$ catalyzed rearrangement.[16] Hydrogenolysis of the benzyl protecting group with catalytic palladium on carbon afforded **24** which underwent subsequent base-mediated coupling with **14** (from Scheme 1) to afford heteroaryl ether **25**. Aluminum-mediated transamidation of **25** with 2-amino-5-methylpyrazine then provided pyazolopyridine **26**. Through incorporation of alternative starting materials, the methods outlined in Schemes 1 and 2



Scheme 1. Synthesis of representative indazole **16**. Reagents and conditions: (a) diisopropylamine, *n*-BuLi, THF, DMF, −70 °C, 2 h, 63%; (b) NaOMe, MeOH, 0 °C – reflux, 3.5 h, 71%; (c) N_2H_4–H_2O, ethylene glycol, 95 °C, 24 h, 83%; (d) CO, $Pd(OAc)_2$, BINAP, Et_3N, MeOH, 50 psi, 80 °C, 24 h, 87%; (e) trimethyloxonium tetrafluoroborate, ethyl acetate, 23 °C, 16 h, 86%; (f) i) BBr_3, DCM, 0 °C, 48 h; ii) MeOH, cat. H_2SO_4, reflux, 2 h, 78%; (g) $(COCl)_2$, cat. DMF, DCM, 23 °C, 18 h, quant.; (h) Me_2N–HCl, Et_3N, DCM, 0 – 23 °C, 4 h, 85%; (i) Cs_2CO_3, CuI, DMF, 110 °C, 3 h, 63%; (j) 2-amino-5-methylpyrazine, Me_2AlCl (1.0 M in hexanes), DME, 90 °C, 16 h, 46%.

subsequently enabled the synthesis of all additional analogs investigated in these studies.

Biochemical evaluation of these prototype activators and subsequent analogs utilized recombinant human glucokinase, monitoring the rate of glucose 6-phosphate formation using G6PDH/NADP coupling. As previously described, this assay was performed in a matrix format wherein dose response determinations for an activator (at 22 different activator concentrations from 0 to 100 μM) were conducted at 16 different glucose concentrations (ranging from 0 to 100 mM).[9] Analyzing this data using a nonessential activator model enabled determination of an activator's maximum fold effect on reducing the glucokinase K_m for glucose defined as α and the maximum fold effect on altering the enzyme's V_{max} defined as β.[17] As previously described, α is the ratio of the enzyme's K_m at maximum activator concentration divided by the enzyme's K_m value in the absence of activator.[9] Values of α range from 0 to 1 with lower values of α representing more substantial reductions in the enzyme's glucose K_m. Activator potency or EC_{50} was formally defined as the concentration of activator affording a half-maximal reduction in K_m. The β value of an activator is defined as the ratio of the enzyme's velocity at maximum activator concentration divided by the enzyme's velocity in the absence of activator. Values of $\beta > 1$ represent activator induced increases in the enzyme's V_{max} whereas values of $\beta < 1$ represented decreases in the enzyme's V_{max}. Activators with $\beta = 1$ have no effect on V_{max}. Human microsomal (HLM) stability, passive permeability and kinetic solubility of the activators were also evaluated.



Scheme 2. Synthetic method for the synthesis of **26**. Reagents and conditions: (a) NaOCl, water, 0 °C, 1 h; (b) benzyl bromide, NaH, DMF, 23 °C–reflux, 40 min, 30%; (c) isopropenyl acetate, Bu_3SnOMe, $Pd(dba)_2$, S–Phos, toluene, 100 °C, 16 h, 36%; (d) NH_4OH-HCl, MeOH, aq. NaOH, 70 °C, 1 h; (e) trifluoroacetic anhydride, Et_3N, DME, 23 °C, 16 h; (f) $FeCl_2$, 75 °C, 2 h, 36% over 3 steps; (g) H_2, 10% Pd/C, EtOH, ethyl acetate, 30 psi, 23 °C, 16 h; (h) K_2CO_3, DMF, 60 °C, 16 h; (i) 2-amino-5-methylpyrazine, Me_2AlCl (1.0 M in hexanes), DME, reflux, 16 h, 43%.

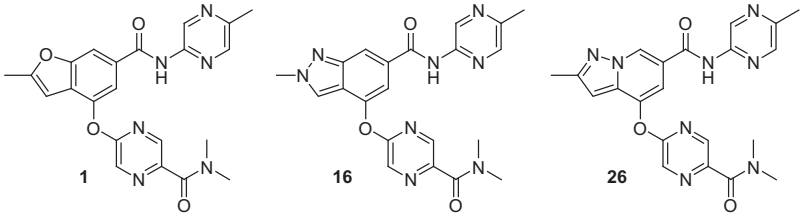
As shown in Table 1, indazole **16** and pyrazolopyridine **26**, were found to be 5- and 3-fold less potent, respectively, than benzofuran **1**. Encouragingly, despite its reduced potency, indazole **16** had a favorable activation profile ($\alpha = 0.11$, $\beta = 0.87$) and its reduced lipophilicity (Log $D = 0.83$) afforded an increase in lipophilic efficiency (LipE) relative to benzofuran **1**, suggesting that it may offer a favorable starting point for further optimization. While pyrazolopyridine **26** offered a slight potency improvement relative to indazole **16**, it had a non-optimal activation profile given its more significant suppression of K_m as indicated by $\alpha = 0.05$. Previous studies had suggested that glucokinase activators with $\alpha \geqslant 0.1$ may offer reduced hypoglycemia risk relative to those with lower α values.[9] Additionally, pyrazolopyridine **26** did not offer an improved LipE relative to the parent benzofuran (e.g. **1**). Based on these observations, our subsequent structure–activity efforts focused on the indazole template with the goal of increasing potency while retaining a favorable activation profile.

As summarized in Table 2, initial optimization efforts explored the structure–activity relationships of the A-Ring examining a variety of substituted aryl and heteroaryl rings. As a base case, indazole **27** bearing a 4-dimethyl amide substituted phenyl ring was found to have moderate potency ($EC_{50} = 0.71$ μM), but also a low β of 0.65 suggesting the potential of the molecule to inhibit glucokinase at high glucose concentrations. Subsequent modification of **27**, sought to improve potency, increase β and reduce metabolic instability by examining alternative substituents and heterocyclic ring systems. Initially, the amide of **27** was replaced by a series of sulfones and sulfonamides as illustrated by **28**–**33**. Relative to **27**, both the sulfones and sulfonamides offered increases in V_{max} (as reflected by $\beta > 1$), improved metabolic stability and comparable permeability; however, these sulfur containing activators also had reduced aqueous solubility with the exception of methyl sulfone **28**. Only cyclopropyl sulfone **30** and dimethyl sufonamide **31** offered potency improvements relative to **27**. Unable to overcome the limitations of these sulfone substituents, we next explored heterocyclic amides **34**–**36** (and prototype **16**) bearing pyridine, pyrazine and pryrimidine A-rings. Pyridines **34** and **35** offered moderate improvements in potency and metabolic turnover relative to **27**. Both pyrazine **16** and pyrimidine **36** also offered favorable properties but only moderate potency.

To explore additional opportunities for potency improvements, we next examined the effects of substitution at the N-2 position of the indazole as illustrated in Table 3.

For the purposes of synthetic feasibility, the A-ring was held constant as a 4-methylsulfone phenyl and the heterocyclic amide as 5-methyl-aminopyrazine. Increasing steric bulk at N-2 offered improvements in potency as illustrated by **38** ($R^1 = n$Pr, $EC_{50} = 0.31$ μM) >**37** (R^1 = Et, $EC_{50} = 0.77$ μM) >**28** (R^1 = Me, $EC_{50} = 1.93$ μM); however, these potency improvements were accompanied by a significant loss in aqueous solubility. Attempts to incorporate a hydroxyl ethyl group at R^1 (e.g. **39**) did not offer improvements in solubility or potency.

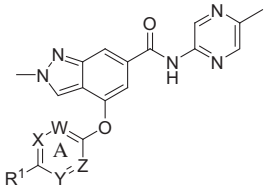
Table 1
Properties of prototype indazole (16) and pyrazolopyridine (26) glucokinase activators relative to benchmark benzofuran (1)

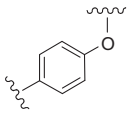
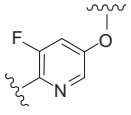
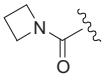
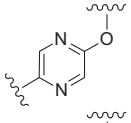
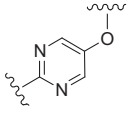


	Biochemical activation[a]			LogD[b]	LipE[c]	HLM Cl_{int}(ml/min/kg)	Permeability[d] (10^{-6}cm/s)	Solubility(μM)
	EC_{50}(μM)	α	β					
1	0.22	0.09	0.97	2.16	4.47	<8.0	22.3	176
16	0.99	0.11	0.87	0.83	5.18	<8.5	20.8	192
26	0.62	0.05	0.91	1.87	4.33	13.7	17.0	123

[a] Biochemical data reported as the geometric mean of >2 determinations.
[b] Experimental Log D determined by shake flask method.
[c] LipE = −log (EC_{50})−Log D.
[d] Passive permeability assessed in RRCK cell line.

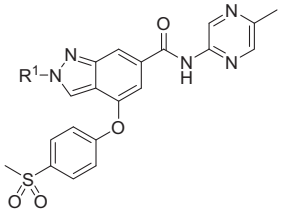
Table 2
Biochemical properties of glucokinase activators 16 and 27–36



A-Ring	Compound	R^1	Biochemical activation[a]			HLM Cl_{int}(ml/min/kg)	Permeability[b] (10^{-6}cm/s)	Kinetic solubility(μM)
			EC_{50}(μM)	α	β			
	27	$C(O)NMe_2$	0.71	0.16	0.65	12.3	14.6	351
	28	SO_2Me	1.93	0.20	1.05	<8.0	20.4	454
	29	SO_2Et	0.98	0.11	1.07	<8.0	10.6	69
	30	SO_2cPr	0.51	0.09	1.01	<8.0	17.8	73
	31	SO_2NMe_2	0.44	0.10	1.14	<8.0	13.6	134
	32	SO_2NHMe	0.88	0.07	1.18	<8.6	NT	27
	33	SO_2NH_2	2.32	0.50	1.14	NT	NT	NT
	34	$C(O)NMe_2$	0.40	0.11	0.80	<8.0	20.2	328
	35		0.34	0.14	0.71	<8.0	11.9	70
	16	$C(O)NMe_2$	0.99	0.11	0.86	<8.0	20.8	192
	36	$C(O)NMe_2$	0.91	0.13	0.82	<8.0	11.5	446

[a] Biochemical data reported as the geometric mean of >2 determinations.
[b] Passive permeability assessed in RRCK cell line; NT = not tested.

Table 3
Properties of glucokinase activators 28 and 37–40

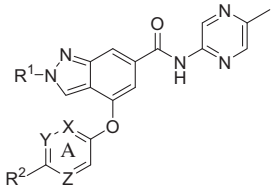


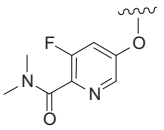
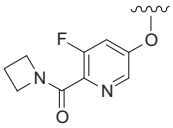
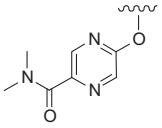
	R_1	Biochemical Activation[a]			HLM Cl_{int}(ml/min/kg)	Permeability[b] (10^{-6}cm/s)	Kinetic solubility(μM)
		EC_{50}(μM)	α	β			
28	Me	1.93	0.20	1.05	<8.0	20.4	454
37	Et	0.77	0.15	1.19	<8.0	13.4	2.1
38	*n*Pr	0.31	0.06	1.20	<8.0	14.2	2.3
39		1.54	0.10	1.07	<8.9	6.3	24.4
40	*c*Pr	2.03	0.13	1.16	<8.0	15.5	0.5

[a] Biochemical data reported as the geometric mean of >2 determinations.
[b] Passive permeability assessed in RRCK cell line.

In order to maintain the potency advantage offered by increasing steric bulk at N-2 but improve solubility, the N-2 ethyl core was then combined with several heterocyclic A-ring systems as summarized in Table 4. In particular, combination with 3-fluoro-*N*, *N*-dimethylpicolinamide (**41**) or the corresponding azetidine analog (**42**) offered an encouraging potency improvement. Comparing **41** and **42** to the original indazole prototype **16** revealed that the potency improvements of **41** and **42** came at the expense of increased

Table 4
Properties of glucokinase activators 16, 41 and 42



	R^1	A-Ring Heterocycle	Biochemical activation[a]			LogD[b]	LipE[c]	HLM Cl_{int} (ml/min/kg)	Permeability[d] (10^{-6}cm/s)	Kinetic solubility(μM)
			EC_{50}(μM)	α	β					
41	Et		0.23	0.06	0.80	1.80	4.83	10.4	13.8	367
42	Et		0.12	0.12	0.82	2.01	4.91	<8.0	16.3	84.8
16	Me		0.99	0.11	0.87	0.83	5.18	<8.0	20.8	192

[a] Biochemical data reported as the geometric mean of >2 determinations.
[b] Experimental LogD determined by shake flask method.
[c] LipE = −log (EC_{50})−Log*D*.
[d] Passive permeability assessed in RRCK cell line.

lipophilicity such that the LipE of these analogs (**41**: LipE = 4.83; **42**: LipE = 4.91) was slightly less than the indazole prototype (**16**: LipE = 5.18) yet still better than parent benzofuran (**1**: LipE = 4.47). Based on its overall balance of potency, activation profile, clearance (low), permeability (high) and solubility (moderate), activator **42** was selected for further pharmacological and pharmacokinetic characterization.

To support the further characterization of compound **42** in rat models, its potency for the recombinant rat glucokinase enzyme was first determined using the method described above for human glucokinase. Activator **42** was found to have an EC_{50} = 0.35 μM for rat glucokinase with an activation profile similar to that observed for the human glucokinase. Since within the pancreatic β-cell glucokinase establishes the threshold for glucose-stimulated insulin secretion, the effect of **42** on glucose-stimulated insulin secretion was next evaluated in a rat insulinoma (INS-1) cell line as shown in Figure 2. In this experiment, INS-1 cells were incubated in the presence of 5 mM glucose and then treated with increasing concentrations of **42**, demonstrating a dose dependent enhancement of glucose-stimulated insulin secretion (EC_{50} = 0.17 μM).

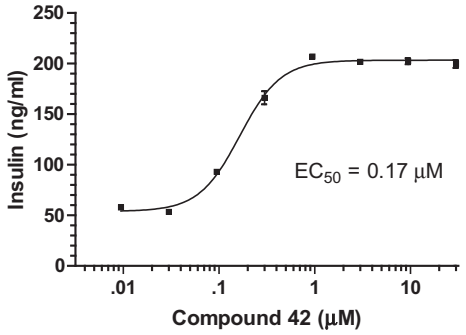


Figure 2. Effect of **42** on glucose-stimulated insulin secretion in rat INS-1 cells at 5 mM glucose.

The pharmacological selectivity and early safety of **42** was evaluated using a series of in vitro assessments. First, compound **42** was evaluated against a CEREP panel of 69 receptors, ion channels and enzymes; testing at 10 μM using a 30% threshold revealed no off target pharmacology. Activator **42** was negative for genetic toxicity in both Ames and in vitro micronucleus (IVMN) assessments. Finally, in a hERG patch clamp assay, **42** had an IC_{50} >300 μM.

The pharmacokinetic properties of **42** were next characterized in rat as summarized in Table 5. Compound **42** was found to have low clearance (10.5 ml/min/kg) and good oral bioavailability (69%). After the i.v. dose of **42**, less than 1% of the dose was excreted in urine suggesting negligible renal clearance. Activator **42** was also found to have moderate protein binding in rat (f_u = 0.18) and human (f_u = 0.20) plasma.

Table 5
Compound **42** pharmacokinetic properties[a]

Route	Dose (mg/kg)	C_{max}(ng/mL)	AUC (ng hr/mL)	$t_{1/2}$ (h)	CL (mL/min/kg)	V_{dss} (L/kg)	*F* (%)
i.v.	1	1820	1580	1.0	10.5	0.61	—
p.o.	5	1490	5440	2.6	—	—	69%

[a] Wistar-Han rats with *n* = 3 animals/group.

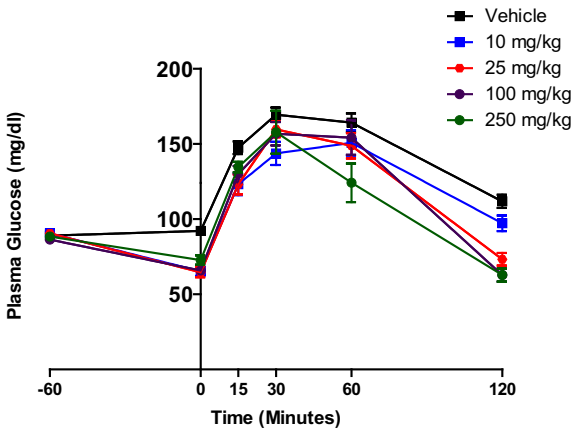


Figure 3. Oral glucose tolerance test (OGTT) for compound **42**. Dose dependent effect of **42** on plasma glucose following a single oral dose of 10, 25, 100 or 250 mg/kg during an oral glucose tolerance test. Glucose excursion data expressed as Means ± Standard Error ($n = 7$ animals/group).

To evaluate the in vivo efficacy and hypoglycemia safety, **42** was evaluated using an oral glucose tolerance test (OGTT) conducted in Sprague-Dawley rats as shown in Figure 3. Animals were fasted overnight and orally dosed at $t = -60$ min with **42** (10, 25, 100 and 250 mg/kg) as a suspension in 30% sulfobutylether/water. To evaluate efficacy, an oral glucose challenge (2 g/kg) was administered at $t = 0$ min and the effect of the activator at reducing the glucose AUC excursion was determined. As shown in Figure 3, 42 offered relatively dose-dependent glucose lowering with a 22% reduction in glucose AUC relative to vehicle control observed at the highest dose (250 mg/kg) evaluated. There were no occurrences of hypoglycemia (defined as blood glucose <60 mg/dL) in this study. For comparison, previously reported clinical candidate benzofuran **2** evaluated at doses of 10, 30 and 100 mg/kg in the same in vivo model offered glucose AUC reductions of 25, 38 and 43%, respectively.

In conclusion, herein we have reported the identification of a series of indazole-based glucokinase activators. Optimization efforts led to the identification of **42** as a potent activator with good preclinical pharmacokinetic properties. While **42** offered in vivo efficacy, the magnitude of this efficacy was inferior to that of benchmark clinical candidate **2**; hence, further clinical development of **42** was not pursued.

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