SAR, Pharmacokinetics, Safety, and Efficacy of Glucokinase Activating 2-(4-Sulfonylphenyl)-*N*-thiazol-2-ylacetamides: Discovery of PSN-GK1

Lisa S. Bertram,[†] Daniel Black,[‡] Paul H. Briner,[†] Rosemary Chatfield,[†] Andrew Cooke,[‡] Matthew C. T. Fyfe,*[,†] P. John Murray,[†] Frédéric Naud,[§] Masao Nawano,[||] Martin J. Procter,[†] Günaj Rakipovski,[⊥] Chrystelle M. Rasamison,[†] Christine Reynet,[†] Karen L. Schofield,[†] Vilas K. Shah,[†] Felix Spindler,[§] Amanda Taylor,[†] Roy Turton,[‡] Geoffrey M. Williams,[†] Philippe Wong-Kai-In,[†] and Kosuke Yasuda[||]

(OSI) Prosidion, Windrush Court, Watlington Road, Oxford OX4 6LT, United Kingdom, (OSI) Pharmaceuticals, Inc., 2860 Wilderness Place, Boulder, Colorado 80301, Solvias AG, Klybeckstrasse 191, Postfach CH-4002 Basel, Switzerland, Mitsubishi Tanabe Pharma Corporation, 2-2-50 Kawagishi, Toda-shi, Saitama 335-8505, Japan, and Rheoscience A/S, Glerupvej 2, 2610 Rødovre, Denmark

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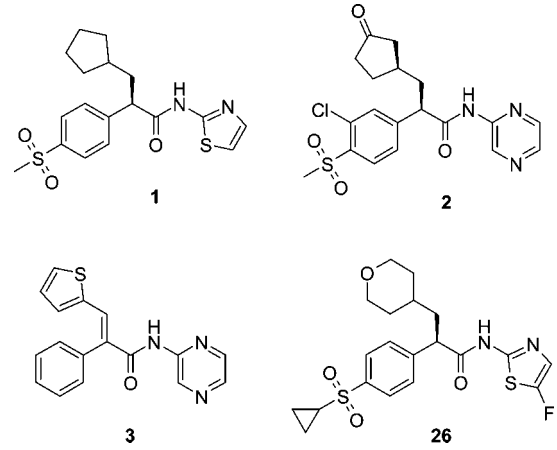
Allosteric activators of the glucose-sensing enzyme glucokinase (GK) are currently attracting much interest as potential antidiabetic therapies because they can achieve powerful blood glucose lowering through actions in multiple organs. Here, the optimization of a weakly active high-throughput screening hit to (2*R*)-2-(4-cyclopropanesulfonylphenyl)-*N*-(5-fluorothiazol-2-yl)-3-(tetrahydropyran-4-yl)propionamide (PSN-GK1), a potent GK activator with an improved pharmacokinetic and safety profile, is described. Following oral administration, this compound elicited robust glucose lowering in rats.

Introduction

Type 2 diabetes (T2D),[a] a disease characterized by elevated blood glucose concentrations, i.e., hyperglycemia, is becoming ever more prevalent as a result of the recent dramatic rise in obesity levels.[1] Currently, no single marketed drug is capable of achieving enduring blood glucose control in the majority of T2D patients.[2] Therefore, many physicians now advocate the use of combination therapies at an earlier stage in the treatment of the disease.[3] The glucose-phosphorylating enzyme glucokinase (GK) represents an attractive target for T2D therapies[4] because it plays a critical role in whole-body glucose control through its actions in multiple organs.[5–8] In particular, in the β-cells of the pancreas, GK acts as the glucose sensor that determines the threshold for insulin secretion, while in the liver, this enzyme is rate-determining for glucose metabolism. Compounds that activate[9–17] GK by binding to an allosteric pocket[18,19] some 20 Å remote from the glucose binding site have been discovered recently. These GK activators have been shown[9,12,20,21] to engender potent antihyperglycemic actions in rodents, both by increasing pancreatic insulin secretion and by augmenting hepatic glucose metabolism. In effect, these dual pancreatic and hepatic actions represent a "double whammy" on the hyperglycemia associated with T2D, and it may be that GK activators could provide enhanced glycemic control by combining, in a single molecule, the glucose-lowering effects of insulin secretagogues, e.g., sulfonylureas, with hepatic antidiabetic actions reminiscent of the biguanide metformin. As a result of promising preclinical data, several GK activators, e.g., RO-28-1675 (**1**)[9,22] and piragliatin (**2**),[23] have entered human clinical trials as prospective T2D therapies. Here, we describe the discovery of the weakly activating high-throughput screening (HTS) hit **3** and its subsequent optimization to **26** (PSN-GK1), a novel, potent GK activator with excellent oral bioavailability and in vivo efficacy in rodents.[21]



Results and Discussion

The (*E*)-α,β-unsaturated amide[24] **3** was obtained following a HTS campaign where GK activity was assayed by coupling the production of glucose 6-phosphate (G6P) by human liver GK—expressed as its glutathione *S*-transferase fusion protein—to the generation of NADPH by G6P dehydrogenase (G6PDH).[11] Rapid analoguing of **3** was straightforward because (*E*)-2-aryl-3-thiophen-2-ylacrylic acids[25] are easily prepared by the Perkin condensation reaction.[26] The amide **4**, wherein the aminopyrazine group of **3** is replaced by 2-aminothiazole, displayed enhanced activity (Table 1). Activity could be further improved

* To whom correspondence should be addressed. Phone: +44 (0)1865 782 622. Fax: +44 (0)1865 871 279. E-mail: mfyfe@prosidion.com.
[†] (OSI) Prosidion.
[‡] (OSI) Pharmaceuticals, Inc.
[§] Solvias AG.
[||] Mitsubishi Tanabe Pharma Corporation.
[⊥] Rheoscience A/S.

[a] Abbreviations: APCI, atmospheric pressure chemical ionization; AUC, area under the curve; CDI, 1,1′-carbonyldiimidazole; DMF, dimethylformamide; EDCI, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; ee, enantiomeric excess; ES, electrospray; G6P, glucose 6-phosphate; G6PDH, glucose 6-phosphate dehydrogenase; GK, glucokinase; HOBt, 1-hydroxybenzotriazole; HTS, high-throughput screening; LDA, lithium diisopropylamide; LHMDS, lithium bis(trimethylsilyl)amide; *m*CPBA, 3-chloroperbenzoic acid; MMPP, magnesium monoperoxyphthalate; NADPH, nicotinamide adenine dinucleotide phosphate (reduced form); nbd, norbornadiene; NBS, *N*-bromosuccinimide; PK, pharmacokinetic; po, per os (by mouth); T2D, type 2 diabetes; THF, tetrahydrofuran; 4-THP, 4-tetrahydropyranyl; TLC, thin-layer chromatography.

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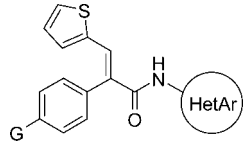
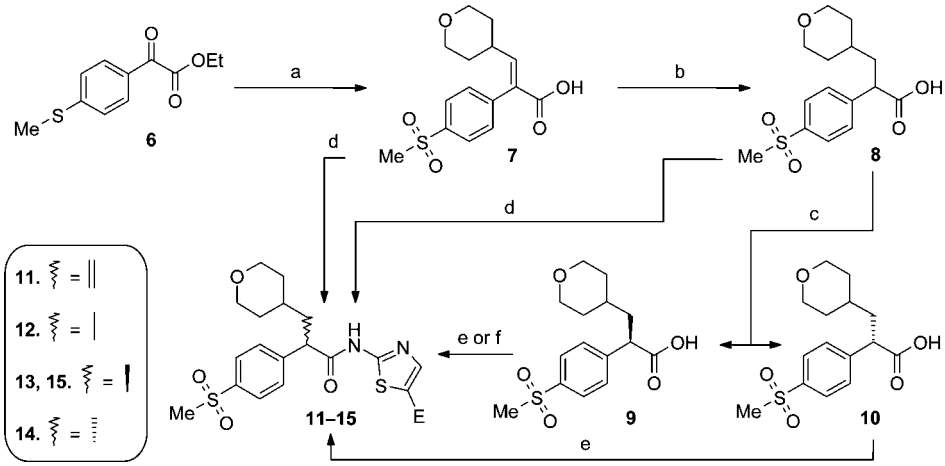
Table 1. Activation of Glucokinase by (*E*)-2-Aryl-3-thiophen-2-ylacrylamides[a]



Cmpd	G	HetAr	EC_{50} (μM)	Max Act[b]	2× Act (μM)[c]
3	H		26.01 ± 2.37	2.3 ± 0.0	68.44 ± 0.93
4	H		10.77 ± 1.07	3.7 ± 0.1	6.93 ± 0.92
5	$MeSO_2$		0.56 ± 0.07	5.4 ± 0.3	0.17 ± 0.03

[a] Data reported as means ± SEM. [b] Maximum fold activation of GK over control levels. [c] Concentration required to double GK activity.

Scheme 1[a]



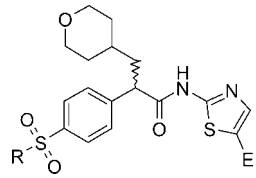
[a] Reagents and conditions: (a) (i) 4-THP-CH_2PPh_3I, $C_6H_{13}Li$, THF, 0 °C, (ii) *m*CPBA, CH_2Cl_2, 0−25 °C, (iii) NaOH, H_2O, MeOH, 64−66 °C. (b) H_2, 10% Pd/C, EtOAc, 20 °C. (c) (i) *t*-BuCOCl, NEt_3, THF, 0 °C, (ii) (*R*)-(+)-4-benzyl-2-oxazolidinone, *n*-BuLi, THF, −78 to 20 °C, (iii) LiOH, H_2O_2, H_2O, THF, 0 °C. (d) 2-Aminothiazole, EDCI, HOBt, DMF, 20 °C. (e) For **13** and **14**: (i) $(COCl)_2$, DMF, CH_2Cl_2, −20 °C, (ii) 2-aminothiazole, collidine, −15 °C. (f) For **15**: (i) NBS, PPh_3, CH_2Cl_2, 0−20 °C, (ii) 2-amino-5-fluorothiazole hydrochloride, pyridine.

by situating a 4-methanesulfonyl substituent[27] on the phenyl ring, as evidenced by the reduced concentration of **5** required to double GK activity. Unfortunately, potent GK activator **5** had very poor aqueous solubility at pH 6.5 (0.5 μg/mL), a feature that was accompanied by relatively low stability in mouse liver microsomes ($t_{1/2}$ = 27 min). As a consequence, this compound exhibited poor exposure when administered orally at 30 mg/kg to female C57Bl/6J mice in 10% aqueous Gelucire 44/14 ($C_{0.5\ h}$ = 35 ng/mL). Moreover, an additional peak, which could possibly correspond to the (*Z*)-isomer of **5**, was detected in the plasma samples with targeted MS/MS detection.

To enhance solubility and increase metabolic stability,[28] we decided to replace the 2-thienyl ring of **5** with another, more polar, heterocyclic group. The 4-tetrahydropyranyl (4-THP) group[29] was selected in this regard because it (1) reduces calculated Log *P* values by ca. 1.7 compared to 2-thienyl, (2) does not add a further chiral center, unlike other heterocyclic ring systems such as 2-tetrahydrofuranyl, and (3) does not have a heteroatom conjugated with the electron-deficient unsaturated amide−arylsulfone π-system, which might facilitate (*E*)−(*Z*)-isomerization. The syntheses of 4-THP-containing amides are delineated in Schemes 1 and 2. The (*E*)-α,β-unsaturated carboxylic acid **7** was obtained (Scheme 1) following saponification/isomerization of a mixture of the corresponding (*E*)- and (*Z*)-ethyl esters.[30] This acid was condensed with 2-aminothiazole to afford the enamide **11**. Although **11** activated GK less potently than **5**, it displayed markedly improved aqueous solubility and microsomal stability, traits that led to enhanced plasma exposure in a mouse PK screen (Table 2). However, it was found that this compound's exposure did not increase following oral administration to rats at doses greater than 10 mg/kg, probably as a result of solubility-limited absorption.[31]

The hydrogenated analogue **12** was found to have improved solubility compared to **11**, albeit with a further reduction in potency. The acid precursor of **12**, i.e., **8**, was resolved—via diastereoisomeric acyloxazolidinones[32]—and the resulting homochiral acids coupled with 2-aminothiazole to provide the enantiomeric amides **13** and **14**. The (*R*)-enantiomer **13**, whose absolute configuration was confirmed by X-ray crystallography,[26] was found to be the eutomer (Table 2). This compound regained some of the potency lost on saturating the double bond of **11**, unlike its antipode **14**, which was inactive. Pleasingly, in addition to enhanced potency, **13** also exhibited improved

Table 2. Data for GK-Activating, 4-THP-Containing 2-(4-Sulfonylphenyl)-*N*-thiazol-2-ylacetamides[a]

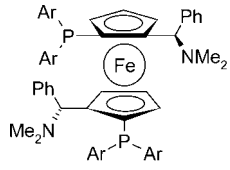


Cmpd	R		E	EC_{50} (μM)	Max Act[b]	2× Act (μM)[c]	MLM $t_{1/2}$ (min)[d]	Sol (μg/mL)[e]	$C_{0.5h}$ (ng/mL)[f] / Dose (mg/kg)
11	Me	‖	H	2.30 ± 0.10	5.6 ± 0.3	0.63 ± 0.09	>200	13	3681 ± 369 / 10
12	Me	|	H	8.93 ± 0.30	5.3 ± 0.0	2.74 ± 0.09	>200	97	–
13	Me	▮	H	3.47 ± 0.12	5.2 ± 0.2	1.00 ± 0.00	>200	410	5152 ± 422 / 10
14	Me	⋮	H	>10	–	–	–	–	–
24	*c*-Pr	▮	H	0.57 ± 0.03	4.7 ± 0.1	0.19 ± 0.01	144	147	1855 ± 580 / 10
25	*c*-Pr	▮	Me	0.58 ± 0.08	3.5 ± 0.1	0.34 ± 0.02	53	40	1643 ± 113 / 10
26	*c*-Pr	▮	F	0.13 ± 0.01	4.4 ± 0.2	0.05 ± 0.00	90	58	5012 ± 439 / 10
15	Me	▮	F	1.43 ± 0.06	4.8 ± 0.1	0.46 ± 0.03	125	298	8275 ± 520 / 10
27	*c*-Bu	▮	F	0.14 ± 0.02	3.2 ± 0.4	0.12 ± 0.02	27	60	1181 ± 240 / 5
28	*c*-Pe	▮	F	0.07 ± 0.00	3.4 ± 0.1	0.05 ± 0.00	16	24	168 ± 33 / 10

[a] In vitro activation and concentration data reported as means ± SEM. [b] Maximum fold activation of GK over control levels. [c] Concentration required to double GK activity. [d] Half-life in mouse liver microsomes. [e] Solubility in pH 6.5 buffer. [f] Compound concentration achieved 0.5 h after administration to female C57Bl/6 mice in 10% aqueous Gelucire 44/14.

solubility, a feature that allowed it to display linear pharmacokinetics in rats following oral administration at doses up to 300 mg/kg.

An asymmetric route to the (*R*)-carboxylic acids **18** and **19** was developed (Scheme 2),[33] which relied on the enantioselective hydrogenation of the corresponding (*E*)-α,β-unsaturated carboxylic acids **16** and **17** in the presence of a rhodium catalyst and the Mandyphos ligand **29**.

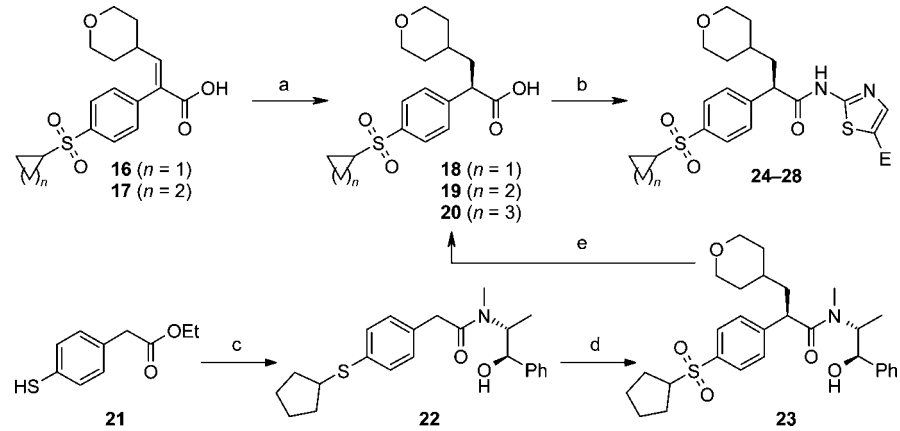


29 Ar = 4-MeO-3,5-$Me_2C_6H_2$

Condensation of the enantiopure cyclopropanesulfonyl-containing carboxylic acid **18** with 2-aminothiazole furnished amide **24**. This compound was a substantially more potent GK activator than its methanesulfonyl-bearing counterpart **13** despite only showing slight reductions in its aqueous solubility and microsomal stability (Table 2). Unfortunately, **13** and **24** were both found to be extremely toxic in acute toxicology studies in rats, causing death in many instances at doses of 100 mg/kg po or greater. 2-Aminothiazole derivatives like **13** and **24** are now recognized[34] as structural alerts for bioactivation-related toxicities. These toxicities are a consequence of the oxidative ring-opening of the thiazole moiety,[35] a process that yields toxic thioureas[36] in vivo (Figure 1). Indeed, analysis of plasma samples obtained following administration of a 250 mg/kg po dose of **24** to male Sprague−Dawley rats revealed a peak having the mass of the corresponding thiourea (m/z = 397 $[M + H]^+$). To block the oxidative metabolism that leads to the ring-opening process, methyl and fluorine substituents were situated on the 5-position of the thiazole ring. Of the resulting amides, the 5-fluorothiazole **26** was clearly better than its 5-methylthiazole counterpart **25** because it displayed improved exposure in mouse pharmacokinetic screening and enhanced potency. Gratifyingly, this compound displayed no evidence of overt toxicity when administered at 250 mg/kg po to male Sprague−Dawley rats in 10% aqueous Gelucire 44/14, a dose that gave significant exposure (C_{max} = 49.2 ± 3.6 μg/mL; $AUC_{0-24\ h}$ = 897.8 ± 69.1 μg·h/mL). Moreover, in contrast to the situation found for **24**, masses for the putative thiourea metabolites could not be detected in the plasma samples by scanning time-of-flight mass spectrometry.

2-Amino-5-fluorothiazole amides were investigated in more detail following the discovery that the fluorine atom enhances both the potencies and the safety profiles of the GK activators. The methanesulfonyl-containing amide **15**, prepared (Scheme 1) by condensing resolved acid **9** with 2-amino-5-fluorothiazole,[37] was significantly less potent than the corresponding cyclopropanesulfonyl-bearing compound **26**. Amides containing cyclobutanesulfonyl (**27**) and cyclopentanesulfonyl (**28**) moieties were prepared from their respective acid precursors **19** and **20**, which were themselves obtained through the Mandyphos-induced asymmetric reduction (vide supra) and the asymmetric

Scheme 2[a]



[a] Reagents and conditions: (a) H_2 (50 bar), $[Rh(nbd)_2](BF_4)$, **29**, MeOH, PhMe, 30 °C. (b) (i) $(COCl)_2$, DMF, CH_2Cl_2, −20 °C, (ii) appropriate 2-aminothiazole, collidine, −15 °C. (c) (i) *c*-C_5H_9Br, NaOH, EtOH, H_2O, 20 °C, (ii) CDI, THF, 20 °C, (iii) (1*R*,2*R*)-(−)-pseudoephedrine, 20 °C. (d) (i) LDA, THF, −60 °C, (ii) 4-THP-CH_2I, −60 to 20 °C, (iii) MMPP, EtOH, H_2O, 80 °C. (e) HCl, H_2O, dioxane, 100 °C.

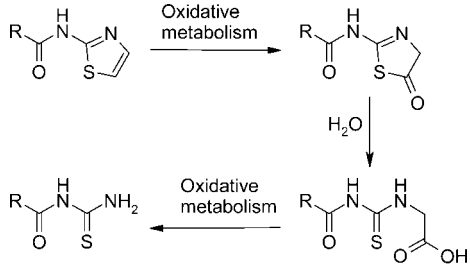


Figure 1. Oxidative metabolism of 2-amidothiazoles gives rise to thioureas, compounds which often display severe toxicities.

alkylation[38] of pseudoephedrine amide **22** (Scheme 2). Although **27** and **28** were both potent GK activators, they were much less stable in mouse liver microsome preparations than their cyclopropanesulfonyl-containing counterpart **26**, a feature that led to reduced exposures in vivo (Table 2).

GK activator **26** exhibited an excellent pharmacokinetic profile, with high oral bioavailability, in the rat (Table 3). This compound's glucose-lowering properties were evaluated in mildly fasted, male Sprague−Dawley rats, where marked reductions in blood glucose levels were seen (Figure 2). These blood glucose reductions were accompanied by a trend toward increased pancreatic insulin release, as evidenced by the insulin AUCs for the 6 h following compound administration (**26**: 431 ± 51 pM·h; vehicle: 314 ± 36 pM·h, $p = 0.08$). Separately, the antihyperglycemic actions of **26** have been shown to be a result of both pancreatic and hepatic effects.[21] In addition, this GK activator engenders potent antihyperglycemic effects in diabetic rodents without causing hypoglycemia, an undesirable characteristic common to many other antidiabetic therapies.

Conclusions

Optimization of the weak HTS hit **3** afforded **26**, a potent GK activator displaying excellent oral bioavailability and in vivo efficacy in rodents.[21] Key to the discovery of **26** were the findings that (1) replacement of the 2-thienyl ring of **3** with a 4-THP group enhanced solubility and increased metabolic stability, resulting in improved oral exposure in rodents, (2) the more flexible saturated amides had superior solubilities, which led to dose-dependent pharmacokinetics, (3) a 4-cyclopropanesulfonyl substituent on the phenyl ring provided the optimum potency-pharmacokinetic profile, and (4) no potentially toxic thiourea metabolites could be detected in plasma following administration of the 2-amino-5-fluorothiazoles to rats. It is hoped that the powerful antihyperglycemic effects of **26** in rodents,[21] effects that are a consequence of multiorgan actions, will pave the way for GK activators that exhibit efficacies greater than those of currently available antidiabetic therapies. Thus, the results of clinical trials with GK activators are eagerly awaited.

Experimental Section

Triphenyl(tetrahydropyran-4-ylmethyl)phosphonium Iodide (31). A mixture of 4-iodomethyltetrahydropyran (350 g, 1.55 mol) and PPh_3 (406 g, 1.55 mol) in MeCN (1.6 L) was heated under reflux for 27 h. On cooling, the mixture was filtered, then the filter cake was washed with Et_2O and air-dried to provide the title compound as a white solid (504 g). The filtrate and washings were returned to reflux, before being concentrated to ca. 750 mL. Reflux was maintained for 16 h, then the reaction mixture was cooled and diluted with Et_2O (1.2 L). The mixture was stirred for 30 min, then the precipitate formed was collected, washed with Et_2O (2 × 300 mL), and air-dried to yield a further crop (100 g). The overall yield of the title compound was 604 g (80%). ^1H NMR ($CDCl_3$): δ 1.51−1.73 (m, 4H), 2.00−2.17 (m, 1H), 3.16−3.28 (m, 2H), 3.76−3.90 (m, 4H), 7.68−7.77 (m, 6H), 7.78−7.86 (m, 3H), 7.88−7.97 (m, 6H). *m/z* (ES^+) = 361 $[M]^+$.

Ethyl (4-Cyclopropylsulfonylphenyl)oxoacetate (32). $AlCl_3$ (104.6 g, 0.79 mol) was suspended in CH_2Cl_2 (1.15 L), then the mixture was cooled in an ice-salt bath to 0 °C with stirring. $ClCOCO_2Et$ (84.8 g, 0.62 mol) was then added over 10 min, the temperature being maintained at 0−2 °C. The mixture was then stirred for 30 min at 0 °C, then cyclopropyl phenyl sulfide (85.0 g, 0.57 mol) was added over 45 min, the temperature being kept at 0−8 °C. The resulting mixture was allowed to warm to room temperature and then stirred for a further 2 h. Ice−water (275 mL) was added, employing ice bath cooling to keep the temperature at 20 °C. The organic layer was separated and washed with H_2O (2 × 250 mL), saturated aqueous $NaHCO_3$ (2 × 250 mL), and H_2O (250 mL), before being dried ($MgSO_4$), filtered, and concentrated to provide ethyl (4-cyclopropylsulfanylphenyl)oxoacetate (134.0 g, 94%). ^1H NMR ($CDCl_3$): δ 0.67−0.78 (m, 2H), 1.11−1.22 (m, 2H), 1.41 (t, $J = 7$ Hz, 3H), 2.15−2.25 (m, 1H), 4.43 (q, $J = 7$ Hz, 2H), 7.43 (d, $J = 9$ Hz, 2H), 7.90 (d, $J = 9$ Hz, 2H). A stirred solution of this thioether (49.4 g, 0.2 mol) in CH_2Cl_2 (180 mL) was treated with a solution of *m*CPBA (75%, 92.0 g, 0.40 mol) in CH_2Cl_2 (650 mL) over 45 min, the temperature being maintained at 15−25 °C. TLC (CH_2Cl_2−EtOAc, 1:10) indicated that starting material still remained, so more *m*CPBA (75%, 7.8 g, 34 mmol) was added, then the reaction continued for 3.5 h. Thereupon, the reaction was treated with 2 M Na_2CO_3 (500 mL), then the aqueous

Table 3. Pharmacokinetic Data for **26** in Male Sprague−Dawley Rats Following Intravenous and Oral Administration

route	*Cl* (min/mL/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (μg·h/mL)	C_{max} (μg/mL)	t_{max} (h)	F_{po} (%)
intravenous[a]	10.0	2.1	3.2	1.66			
oral[b]			3.4	10.74	1.13	1.0	129

[a] Administered at 1 mg/5 mL/kg in 40% DMSO−60% saline. [b] Administered at 5 mg/10 mL/kg in 10% aqueous Gelucire 44/14.

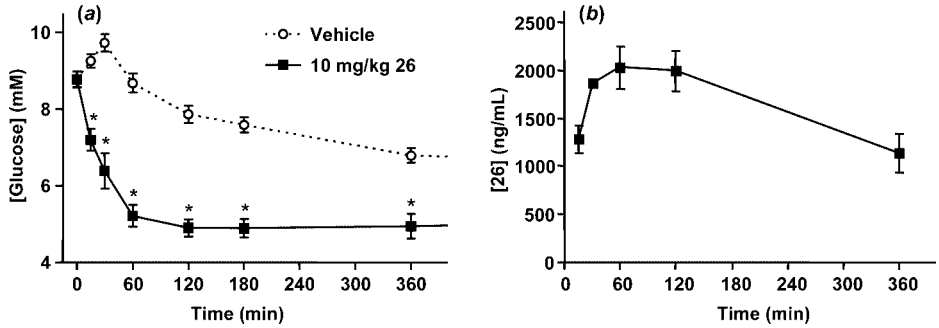


Figure 2. (a) At 10 mg/kg po, GK activator **26** lowers blood glucose concentrations significantly in mildly fasted male Sprague−Dawley rats, as compared to vehicle control (10% aqueous Gelucire 44/14); $*p < 0.05$. (b) Accompanying pharmacokinetic profile.

layer was separated and its pH raised to 9−10 before re-extraction with CH_2Cl_2. The combined organic extracts were washed with water (2 × 400 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to yield the title compound (54.1 g, 96%). ^{1}H NMR ($CDCl_3$): δ 0.99−1.06 (m, 2H), 1.25−1.32 (m, 2H), 1.36 (t, J = 7 Hz, 3H), 2.42−2.50 (m, 1H), 4.41 (q, J = 7 Hz, 2H), 7.97 (d, J = 8 Hz, 2H), 8.14 (d, J = 8 Hz, 2H).

(*E*)-2-(4-Cyclopropanesulfonylphenyl)-3-(tetrahydropyran-4-yl)acrylic Acid (16). A solution of LHMDS (1.05 M in THF, 4.39 kg, 5.18 mol) was added over 30 min to a suspension of triphenyl(tetrahydropyran-4-ylmethyl)phosphonium iodide (**31**, 2.49 kg, 5.10 mol) in anhydrous THF (5 L) at −5 to 0 °C. The resulting mixture was then warmed to 15 °C, stirred for 2 h, and recooled to 0−5 °C. A solution of ethyl (4-cyclopropylsulfonylphenyl)oxoacetate (**32**, 1.25 kg, 4.43 mol) in anhydrous THF (2.5 L) was then added over 1 h, the temperature being maintained at 0−5 °C. The reaction was stirred for 16 h at 20−25 °C before being quenched with brine (3.8 L).The phases were separated with the aid of additional brine (1.3 L), then the aqueous phase was re-extracted with *t*-BuOMe (2 × 2.5 L). The combined organic extracts were washed with brine (2 × 3.8 L) before being concentrated under reduced pressure. The residue was dissolved in MeOH (15 L), then aqueous NaOH (2 M, 4.34 L) was added and the reaction heated at 65−67 °C for 4 h. The mixture was cooled, and the solvents removed under vacuum at 35−40 °C until water started to distill. The residue was diluted with water (15 L), then the solid Ph_3PO was filtered off and washed with water (2.5 L). The filtrate was separated, then the aqueous phase was washed with *t*-BuOMe (5 and 3.5 L) before being acidified with 5 M HCl (1.9 L) in the presence of *t*-BuOMe (10 L). The organic phase was separated, then the aqueous phase was re-extracted with *t*-BuOMe (5 L). The combined organic extracts were washed with saturated brine (2 × 1 L) before being concentrated under reduced pressure. MeOH (2 L) was added and then removed under vacuum in a process that was then repeated. The residue was brought to a total weight of 4.0 kg by addition of MeOH, then the mixture was stirred at ambient temperature to crystallize the product. Filtration of the solid and washing with chilled MeOH (500 mL) gave, after vacuum-drying at 40 °C, the title compound (654 g, 41%). ^{1}H NMR ($CDCl_3$): δ 1.04−1.12 (m, 2H), 1.36−1.43 (m, 2H), 1.47−1.53 (m, 2H), 1.56−1.69 (m, 2H), 2.25−2.38 (m, 1H), 2.47−2.55 (m, 1H), 3.24−3.34 (m, 2H), 3.89−3.97 (m, 2H), 7.05 (d, J = 11 Hz, 1H), 7.37 (d, J = 8 Hz, 2H), 7.93 (d, J = 8 Hz, 2H). m/z (ES^+) = 673.5 $[2M + H]^+$.

(2*R*)-2-(4-Cyclopropanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid (18). A solution of $[Rh(nbd)_2](BF_4)$ (30.5 mg, 0.08 mmol) and All-MOD-Mandyphos (**29**, 90.4 mg, 0.08 mmol) in MeOH (10 mL) was stirred at ambient temperature for 1 h. This catalyst solution was then added to a solution of (*E*)-2-(4-cyclopropanesulfonylphenyl)-3-(tetrahydropyran-4-yl)acrylic acid (**16**, 110 g, 0.327 mol) in MeOH/PhMe (5:1, 1.4 L). The mixture was transferred to a 2.5 L autoclave, which was pressurized to 50 bar of H_2, and heated to 30 °C. After 18 h, the pressure was released, then the solution was treated with active charcoal (3 g). The mixture was stirred for 1 h, before being filtered to remove the charcoal. Further filtrations over Hyflo and a Zeta-Bond filter gave a solution that was concentrated under partial pressure to furnish a solid that was dried under high vacuum. This solid (105 g) was recrystallized from *i*-BuOAc-*n*C_7H_{16} to yield the title compound (77.2 g, 70%, 99% ee). ^{1}H NMR ($CDCl_3$): δ 1.05 (m, 2H), 1.20−1.50 (m, 5H), 1.60 (m, 2H), 1.75 (m, 1H), 2.10 (m, 1H), 2.45 (m, 1H), 3.35 (m, 2H), 3.80 (t, J = 8 Hz, 1H), 3.95 (br d, 2H), 7.50 (d, J = 7 Hz, 2H), 7.85 (d, J = 7 Hz, 2H). m/z (ES^+) = 694.5 $[2M + NH_4]^+$. $[\alpha]_D^{23}$ −48.8 (c = 1.02, $CHCl_3$). Anal. calcd for $C_{17}H_{22}O_5S$: C, 60.34; H, 6.55; S, 9.47. Found: C, 60.36; H, 6.44; S, 9.44.

(2*R*)-2-(4-Cyclopropanesulfonylphenyl)-*N*-(5-fluorothiazol-2-yl)-3-(tetrahydropyran-4-yl)propionamide (26). A mixture of anhydrous CH_2Cl_2 (1.35 L) and DMF (35.9 mL, 0.465 mol) was cooled to −20 °C, then $(COCl)_2$ (39.4 mL, 0.465 mol) was added slowly. After stirring for 45 min, (2*R*)-2-(4-cyclopropanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid (**18**, 105.0 g, 0.310 mol) was added. After a further 1 h at −20 °C, collidine (185 mL, 1.395 mol) was added slowly. Stirring was continued for 15 min, then 2-amino-5-fluorothiazole hydrochloride[37] (52.7 g, 0.341 mol) was added at −15 °C. The resulting suspension was kept at −15 °C for 2 h, after which the ice bath was removed and the reaction slowly warmed to ambient temperature over 2 h. The mixture was evaporated to dryness to afford a semisolid, which was treated portionwise with 4 M HCl (1.5 mL). The remainder was extracted with EtOAc (3 L) and the organic fraction washed with H_2O (1 L) and saturated aqueous $NaHCO_3$ (1 L). The solvent was removed under partial vacuum to give the title compound (135.0 g, 99%). ^{1}H NMR ($CDCl_3$): δ 1.00−1.06 (m, 2H), 1.25−1.50 (m, 5H), 1.55−1.65 (m, 2H), 1.75−1.85 (m, 1H), 2.15−2.25 (m, 1H), 2.42−2.51 (m, 1H), 3.25−3.33 (m, 2H), 3.76−3.85 (m, 1H), 3.88−3.96 (m, 2H), 7.02 (d, J = 2 Hz, 1H), 7.46 (d, J = 7 Hz, 2H), 7.84 (d, J = 7 Hz, 2H), 10.49 (s, 1H). m/z (ES^+) = 439 $[M + H]^+$. $[\alpha]_D^{31}$ −60.9 (c = 0.97, $CHCl_3$). Anal. calcd for $C_{20}H_{23}FN_2O_4S_2$: C, 54.78; H, 5.29; N, 6.39; S, 14.62. Found: C, 54.21; H, 5.41; N, 5.99; S, 14.60.

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Supporting Information Available: Further experimental details and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Moller, D. E. New drug targets for type 2 diabetes and the metabolic syndrome. *Nature* **2001**, *414*, 821–827.
(2) Gershell, L. Type 2 diabetes market. *Nature Rev. Drug Discovery* **2005**, *4*, 367–368.
(3) Bell, D. S. H. A comparison of agents used to manage type 2 diabetes mellitus: Need for reappraisal of traditional approaches. *Treat. Endocrinol.* **2004**, *3*, 67–76.
(4) Sarabu, R.; Tilley, J. Recent advances in therapeutic approaches to type 2 diabetes. *Annu. Rep. Med. Chem.* **2005**, *40*, 167–181.
(5) Sarabu, R.; Grimsby, J. Targeting glucokinase activation for the treatment of type 2 diabetes: A status review. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 631–637.
(6) Kietzmann, T.; Ganjam, G. K. Glucokinase: old enzyme, new target. *Expert Opin. Ther. Pat.* **2005**, *15*, 705–713.
(7) Guertin, K. R.; Grimsby, J. Small molecule glucokinase activators as glucose lowering agents: a new paradigm for diabetes therapy. *Curr. Med. Chem.* **2006**, *13*, 1839–1843.
(8) Johnson, T. O.; Humphries, P. S. Glucokinase activators for the treatment of type 2 diabetes. *Annu. Rep. Med. Chem.* **2006**, *41*, 141–154.
(9) Grimsby, J.; Sarabu, R.; Corbett, W. L.; Haynes, N.-E.; Bizzarro, F. T.; Coffey, J. W.; Guertin, K. R.; Hilliard, D. W.; Kester, R. F.; Mahaney, P. E.; Marcus, L.; Qi, L.; Spence, 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) Bebernitz, G. R. Substituted (thiazol-2-yl)-amide or sulfonamide as glucokinase activators useful in the treatment of type 2 diabetes. International Patent WO 2004/050645, 2004.
(11) Castelhano, A. L.; Dong, H.; Fyfe, M. C. T.; Gardner, L. S.; Kamikozawa, Y.; Kurabayashi, S.; Nawano, M.; Ohashi, R.; Procter, M. J.; Qiu, L.; Rasamison, C. M.; Schofield, K. L.; Shah, V. K.; Ueta, K.; Williams, G. M.; Witter, D.; Yasuda, K. Glucokinase-activating ureas. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1501–1504.
(12) Efanov, A. M.; Barrett, D. G.; Brenner, M. B.; Briggs, S. L.; Delaunois, A.; Durbin, J. D.; Giese, U.; Guo, H.; Radloff, M.; Gil, G. S.; Sewing, S.; Wang, Y.; Weichert, A.; Zaliani, A.; Gromada, J. A novel glucokinase activator modulates pancreatic islet and hepatocyte function. *Endocrinology* **2005**, *146*, 3696–3701.
(13) Murray, A.; Lau, J.; Jeppesen, L.; Vedsø, P.; Ankersen, M.; Lundbeck, J. M.; Kristiansen, M.; Valcarce-Lopéz, M. C.; Polisetti, D. R.; Subramanian, G.; Andrews, R. C.; Christen, D. P.; Cooper, J. T.; Santhosh, K. C. Heteroaryl-ureas and their use as glucokinase activators. International Patent WO 2005/066145, 2005.
(14) McKerrecher, D.; Allen, J. V.; Caulkett, P. W. R.; Donald, C. S.; Fenwick, M. L.; Grange, E.; Johnson, K. M.; Johnstone, C.; Jones, C. D.; Pike, K. G.; Rayner, J. W.; Walker, R. P. Design of a potent, soluble glucokinase activator with excellent in vivo efficacy. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2705–2709.
(15) Bian, H.; Dudash, J.; Patel, M.; Rybczynski, P.; Zhang, Y. Dihydroisoindolones as allosteric modulators of glucokinase. International Patent WO 2007/053662, 2007.
(16) Aicher, T. D.; Boyd, S. A.; Chicarelli, M. J.; Condroski, K. R.; Hinklin, R. J.; Singh, A.; Turner, T. M.; Rustam, F. G. Glucokinase activators. International Patent WO 2007/089512, 2007.
(17) Cheruvallath, Z.; Feng, J.; Guntupalli, P.; Gwaltney, S. L.; Kaldor, S. W.; Miura, J.; Sabat, M.; Tang, M.; Wolgast, B. Glucokinase activators. International Patent WO 2007/104034, 2007.
(18) Kamata, K.; Mitsuya, M.; Nishimura, T.; Eiki, J.-I.; Nagata, Y. Structural basis for allosteric regulation of the monomeric allosteric enzyme human glucokinase. *Structure* **2004**, *12*, 429–438.
(19) Dunten, P.; Swain, A.; Kammlott, U.; Crowther, R.; Lukacs, C. M.; Levin, W.; Reik, L.; Grimsby, J.; Corbett, W. L.; Magnuson, M. A.; Matschinsky, F. M.; Grippo, J. F. Crystal structure of human liver glucokinase bound to a small molecule allosteric activator. In *Glucokinase and Glycemic Disease: From Basics to Novel Therapeutics*; Matschinsky, F. M., Magnuson, M. A., Eds.; Karger: Basel, Switzerland, 2004; pp 145−154.
(20) Coope, G. J.; Atkinson, A. M.; Allott, C.; McKerrecher, D.; Johnstone, C.; Pike, K. G.; Holme, P. C.; Vertigan, H.; Gill, D.; Coghlan, M. P.; Leighton, B. Predictive blood glucose lowering efficacy by glucokinase activators in high fat fed female Zucker rats. *Br. J. Pharmacol.* **2006**, *149*, 328–335.
(21) Fyfe, M. C. T.; White, J.; Taylor, A.; Chatfield, R.; Wargent, E.; Printz, R. L.; Sulpice, T.; McCormack, J. G.; Procter, M. J.; Reynet, C.; Widdowson, P. S.; Wong-kai-in, P. Glucokinase activator PSN-GK1 displays enhanced antihyperglycemic and insulinotropic actions. *Diabetologia* **2007**, *50*, 1277–1287.
(22) Grimsby, J. Antidiabetic Effects of Glucokinase Activators: From Benchside to Bedside. Keystone Symposium. Diabetes Mellitus, Insulin Action and Resistance, Keystone, CO, 22−27 January 2008; Abstract 151.
(23) Daniewski, A. R.; Liu, W.; Radinov, R. N. Process for the preparation of a glucokinase activator. International Patent WO 2007/115968, 2007.
(24) Corbett, W. L.; Sarabu, R.; Sidduri, A. Trans olefinic glucokinase activators. International Patent WO 2001/044216, 2001.
(25) Karminski-Zamola, G.; Bajic, M. Synthesis of (5-styryl-2-thienyl)phenylacrylic Acids. *Heterocycles* **1985**, *23*, 1497–1501.
(26) See Supporting Information.
(27) Bizzarro, F. T.; Corbett, W. L.; Focella, A.; Grippo, J. F.; Haynes, N.-E.; Holland, G. W.; Kester, R. F.; Mahaney, P. E.; Sarabu, R. Glucokinase activators. International Patent WO 2000/058293, 2000.
(28) Van de Waterbeemd, H.; Smith, D. A.; Beaumont, K.; Walker, D. K. Property-based design: Optimization of drug absorption and pharmacokinetics. *J. Med. Chem.* **2001**, *44*, 1313–1333.
(29) Corbett, W. L.; Grimsby, J. S.; Haynes, N. E.; Kester, R. F.; Mahaney, P. E.; Racha, J. K.; Sarabu, R.; Wang, K. Substituted phenylacetamides and their use as glucokinase activators. International Patent WO 2003/095438, 2003.
(30) Heuser, S.; Barrett, D. G.; Berg, M.; Bonnier, B.; Kahl, A.; Luz De La Puente, M.; Oram, N.; Riedl, R.; Roettig, U.; Sanz Gil, G.; Seger, E.; Steggles, D. J.; Wanner, J.; Weichert, A. G. Synthesis of novel cyclopropylic sulfones and sulfonamides acting as glucokinase activators. *Tetrahedron Lett.* **2006**, *47*, 2675–2678.
(31) Willmann, S.; Schmitt, W.; Keldenich, J.; Lippert, J.; Dressman, J. B. A physiological model for the estimation of the fraction dose absorbed in humans. *J. Med. Chem.* **2004**, *47*, 4022–4031.
(32) Haigh, D.; Birrell, H. C.; Cantello, B. C. C.; Hindley, R. M.; Ramaswamy, A.; Rami, H. K.; Stevens, N. C. Non-thiazolidinedione antihyperglycemic agents. Part 4: Synthesis of (±)-, (*R*)-(+)-, and (*S*)-(−)-enantiomers of 2-oxy-3-arylpropanoic acids. *Tetrahedron: Asymmetry* **1999**, *10*, 1335–1351.
(33) Briner, P. H.; Fyfe, M. C. T.; Madeley, J. P.; Murray, P. J.; Procter, M. J.; Spindler, F. Enantioselective process. International Patent WO 2006/016178, 2006.
(34) Guengerich, F. P.; MacDonald, J. S. Applying mechanisms of chemical toxicity to predict drug safety. *Chem. Res. Toxicol.* **2007**, *20*, 344–369.
(35) Hobbs, D. C.; Twomey, T. M. Metabolism of sudoxicam by the rat, dog, and monkey. *Drug Metab. Dispos.* **1977**, *5*, 75–81.
(36) Onderwater, R. C. A.; Commandeur, J. N. M.; Menge, W. M. P. B.; Vermeulen, N. P. E. Activation of microsomal glutathione *S*-transferase and inhibition of cytochrome P450 1A1 activity as a model system for detecting protein alkylation by thiourea-containing compounds in rat liver microsomes. *Chem. Res. Toxicol.* **1999**, *12*, 396–402.
(37) Briner, P. H.; Fyfe, M. C. T.; Martin, P.; Murray, P. J.; Naud, F.; Procter, M. J. Practical synthesis of 2-amino-5-fluorothiazole hydrochloride. *Org. Process Res. Dev.* **2006**, *10*, 346–348.
(38) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. Pseudoephedrine as a practical chiral auxiliary for the synthesis of highly enantiomerically enriched carboxylic acids, alcohols, aldehydes, and ketones. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.

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