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Design and synthesis of orally bioavailable serum and glucocorticoid-regulated kinase 1 (SGK1) inhibitors

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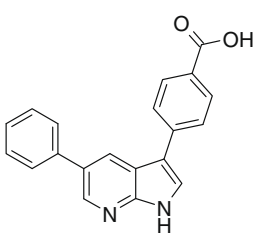
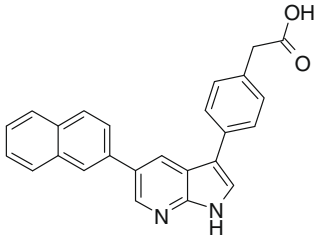
ABSTRACT

The lead serum and glucocorticoid-related kinase 1 (SGK1) inhibitors 4-(5-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzoic acid (**1**) and {4-[5-(2-naphthalenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]phenyl}acetic acid (**2**) suffer from low DNAUC values in rat, due in part to formation and excretion of glucuronic acid conjugates. These PK/glucuronidation issues were addressed either by incorporating a substituent on the 3-phenyl ring *ortho* to the key carboxylate functionality of **1** or by substituting on the group in between the carboxylate and phenyl ring of **2**. Three of these analogs have been identified as having good SGK1 inhibition potency and have DNAUC values suitable for in vivo testing.

Epithelial sodium channels (ENaCs) are responsible for reabsorption of sodium from the distal nephron of the kidney which contributes to the regulation of sodium homeostasis, extracellular fluid volume, and blood pressure. Aldosterone is known to activate ENaCs through intermediary activation of serum and glucocorticoid-induced kinase 1 (SGK1), resulting in increased extracellular fluid volume and blood pressure. SGK1 potentiates ENaC activity, and consequently sodium retention and increased blood pressure, by inhibiting Nedd4-2, a ligase that catalyzes the internalization and degradation of ENaCs.[1] Consequently, inhibition of SGK1 is expected to decrease ENaC activity, which in turn would lead to an increase in sodium excretion and a reduction in extracellular fluid volume and blood pressure. In support of this hypothesis, SGK1 knockout mice are known to be aldosterone resistant and have less ability to retain sodium and maintain blood pressure when given a reduced-sodium diet.[2]



1
SGK1 IC_{50} = 40 nM
M-1 SCC IC_{50} = 1.3 μM



2
SGK1 IC_{50} = 63 nM
M-1 SCC IC_{50} = 0.88 μM

As part of a program to study the role of SGK1, an effort to identify small-molecule SGK1 inhibitors was initiated. Azaindoles **1** and **2** were identified as nanomolar inhibitors of SGK1[3] with micromolar or lower activity in a whole-cell M-1 short circuit current (SCC) assay,[4] a measure of epithelial Na^+ ion transport. The use of **1** or **2** as in vivo tool compounds, however, was limited by poor oral

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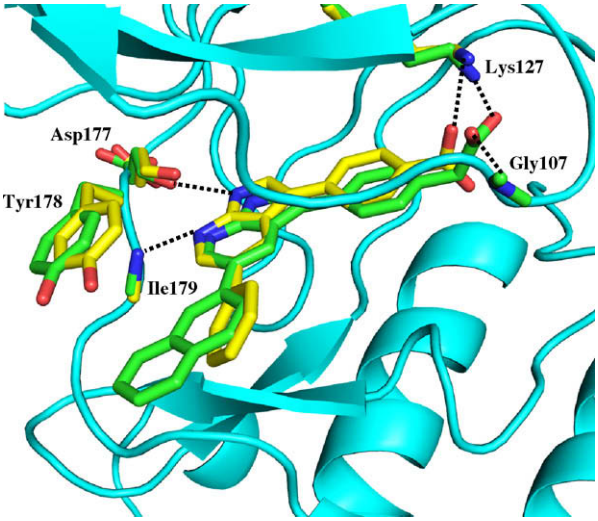
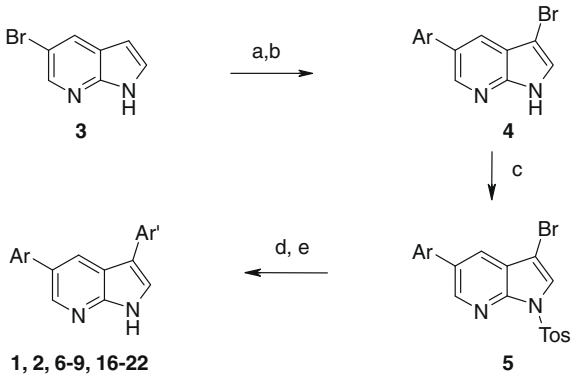


Figure 1. Key interactions for the binding of **1** and **2** to SGK1. Enzyme backbone is cyan, compound **1** is yellow, compound **2** is in green, and selected backbone residues are shown in the color corresponding to the respective ligands.

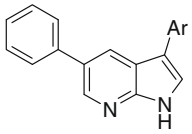
exposure in rats, likely due at least in part to the carboxylic acid moiety found on both. This functionality can contribute to poor oral PK by either limiting absorption through its polar, hydrogen-bonding properties, by favoring elimination through mechanisms such as glucuronic acid conjugation[5] or a combination of both. In fact, rat PK data was suggestive of glucuronidation and included the presence of secondary input peaks in the rat oral exposure curves for **1** and **2**[6] and mass spectral identification of glucuronidated parent compound after incubation of **1** in rat hepatocytes.

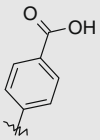
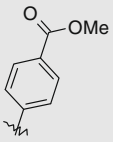
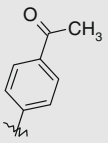
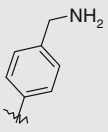
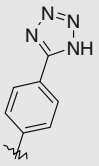
The SGK-bound crystal structures determined for **1** and **2** show the azaindole nitrogens of both compounds forming donor-acceptor interactions in the hinge region of the enzyme, while their respective carboxylates are engaged in an interaction with the catalytic lysine (Lys127, Fig. 1).[7] In addition, the second carboxylate oxygen of compound **2** appears to interact with the backbone nitrogen of Gly107. However, with the significance of the carboxylates of **1** and **2** to binding interactions perhaps being offset by their contributions to poor in vivo exposure, a strategy involving replacement of this functionality with other groups having the potential to form similar interactions without adversely influencing PK properties was adopted.



Scheme 1. Reagents and conditions: (a) $ArB(OH)_2$, $PdCl_2(dppf)$, K_2CO_3, 2.5:1 dioxane/water, 80 °C; (b) Br_2, $CHCl_3$ or NBS, $CHCl_3$; (c) TsCl, Bu_4NHSO_4, 6 N NaOH/CH_2Cl_2, rt, 1 h or (i) LDA, THF, −78 °C, (ii) TsCl, −78 °C→rt; (d) $Ar'B(OH)_2$, $PdCl_2(dppf)$, K_2CO_3, 2.5:1 dioxane/water, 80 °C, 12 h, or $Ar'B(OH)_2$, $PdCl_2(dppf)$, K_2CO_3, 2.5:1 dioxane/water, μv, 150 °C, 5 min; (e) 2.5 N NaOH, dioxane, reflux, 1 h, Bu_4NF, THF, 60 °C, 30 min, or NaOH, MeOH, 80 °C, 12 h.

Table 1
SGK1 inhibition by 3-aryl-5-phenyl-7-azaindoles **1** and **5–9**

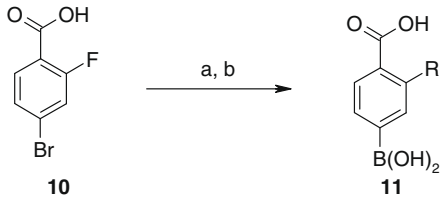


Entry	Ar	SGK1 IC_{50} (nM)
1		40
6		3160
7		5000
8		400
9		160

Analogs of the 7-azaindole **1** were prepared as shown in Scheme 1.[8,9] Suzuki reaction of 5-bromoazaindole **3** with an arylboronic acid was followed by selective bromination at the 3-position of the azaindole to afford intermediate **4**. The bromide **4** was converted to 1-tosyl-7-azaindole **5**, and Suzuki reaction and subsequent removal of the tosyl group afforded the target 3,5-diaryl-7-azaindoles **1** and **6–9**.

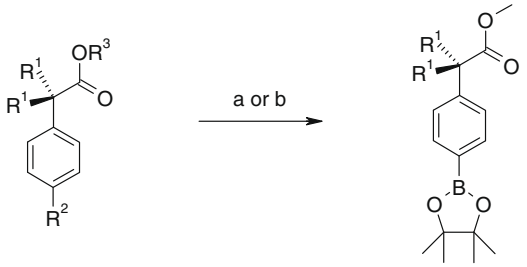
Relative to **1**, the non-carboxylate-containing analogs prepared demonstrated significantly reduced potency and further highlighted the importance of the carboxylate group (Table 1). The methyl ester **6** was nearly 80-fold less potent than the parent acid **1**, and the ketone **7** and primary amine **8** also suffered from significantly reduced potency. Tetrazole **9**, at 160 nM, was closest in potency to **1**, suggesting that the acidic natures of both the tetrazole of **9** and the carboxylic acid of **1** contributed to their enhanced inhibition potencies over non-acidic analogs **6–8**. In fact, the relative acidities of tetrazole and benzoic acid (pK_a = 4.9 vs pK_a = 4.2) are directly proportional to the SGK inhibition potencies of **9** and **1**, which supports a proposed salt bridge interaction between the acidic group and Lys127. In an attempt to maintain these proposed electrostatic interactions, strategies that would allow for improvement of in vivo exposure along with retention of the carboxylate group were considered.

One proposed means of increasing oral exposure while keeping the carboxylate group was to introduce steric bulk around the carboxylate groups of **1** and **2**.[10] The rationale behind this was two-



Scheme 2. (a) RMgBr, THF, 0 °C; (b) $(i\text{-PrO})_3B$, *n*-BuLi, THF, −78 °C, then HCl, 0 °C.

fold: first, obstruction of the carboxylate might suppress any conjugate formation; and second, addition of lipophilic substituents would decrease the overall polarity of the molecule and improve solubility and permeability. The structure of **1** bound to SGK suggested that introduction of phenyl ring substituents in the position

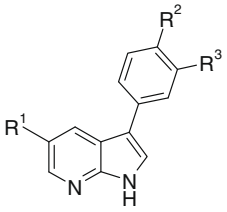


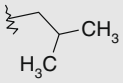
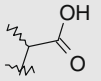
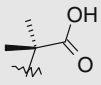
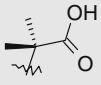
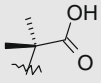
12 R^1, R^3 = H,
R^2 = $B(OC(CH_3)_2C(CH_3)_2O)$,
14 R^1, R^3 = CH_3, R^2 = Br

13 R^1 = H
15 R^1 = CH_3

Scheme 3. (a) HCl, MeOH, rt; (b) bis(pinacolato)diboron, $Pd(dppf)Cl_2$, KOAc, dioxane, 95 °C.

Table 2
SGK1 in vitro inhibition, and rat pharmacokinetic parameters for azaindoles **1**, **2**, and **16–22**



Entry	R^1	R^2	R^3	SGK1 IC_{50} (nM)	M-1 SCC IC_{50} (μM)	Rat PK parameters[a]				
						CLp (mL/min/kg)	Vd_{ss} (L/kg)	iv $t_{½}$[b] (min)	Oral $AUC_{0\text{-}t}$ (ng h/mL)	Oral $DNAUC_{0\text{-}t}$ (ng h/mL/mg/kg)
1	Ph	$-CO_2H$	H	40	1.30	64.4[c,f]	8.8[c,f]	564[c,f]	392 (74)[c,f]	154 (28)[c,f]
16	Ph	$-CO_2H$		20	0.71	9.4 (1.2)[d]	0.43 (0.15)[d]	97 (9)[d]	1499 (188)[d]	600 (80)[d]
17	Ph	$-CO_2H$		5	0.58	21.9 (4.2)[d]	0.62 (0.20)[d]	70 (29)[d]	373 (105)[d]	176 (48)[d]
18	Ph	$-CO_2H$		13	0.58	25.7 (4.7)[d]	0.77 (0.29)[d]	95 (54)[d]	313 (113)[d]	134 (43)[d]
2	β-Naphthyl	$-CH_2CO_2H$	H	63	0.88	21.3[c,f]	1.3[c,f]	253[c,f]	467 (304)[c,f]	225 (143)[c,f]
19	β-Naphthyl		H	125	NT	NT				
20	β-Naphthyl		H	63	0.87	4.32 (0.57)[e]	0.67 (0.21)[e]	264 (81)[e]	4173 (1075)[e]	2100 (550)[e]
21	Ph		H	50	1.46	NT				
22	3-CN–Ph		H	40	2.0	6.56[e,f]	2.5[e,f]	488[e,f]	1913 (316)[e,f]	905 (143)[e,f]

[a] Values are means of three experiments, standard deviation is given in parentheses.
[b] Terminal half life unless indicated.
[c] Discrete study.
[d] Part of a cassette study conducted on a mixture of five compounds.
[e] Part of a cassette study conducted on a mixture of four compounds.
[f] Average of two values. NT = not tested.

ortho to the carboxylate might be accommodated; while that of **2** indicated that the α-carbon would also tolerate substitution without disrupting binding. Boronic acid intermediates needed for the synthesis of *ortho*-substituted analogs of **1** were accessed as shown in Scheme 2.[11] The starting 4-bromo-2-fluorobenzoic acid **10** was treated with Grignard reagents to afford the 2-alkyl-4-bromobenzoic acid intermediates,[12] which were converted to boronic acids **11** using a protocol involving metal-halogen exchange, trapping with triisopropyl borate and hydrolysis with aqueous HCl. For the latter approach, two boronates, **13** and **15** were prepared as shown in Scheme 3. Phenylacetic acid boronate **12** was esterified to its methyl ester **13**,[13] while the bromide **14** was converted to its boronate ester **15**.[14] The boronic acids **11**, **13**, and **15** were then utilized in the syntheses of target azaindoles **16**–**22** as detailed in Scheme 1.[15]

The *ortho*-substituted analogs of **1** behaved very favorably in the SGK1 in vitro assays, having improved inhibition potencies relative to **1** (Table 2, compounds **16–18**). In general, increasing the size of the substituent trended toward a corresponding increase in isolated SGK1 inhibition and whole-cell potency. Phenylacetic acid derivatives **19–22** also demonstrated good in vitro potencies. These analogs appeared to be relatively insensitive to methyl substitution at the α-position of the phenylacetic acid, with potency against the isolated enzyme for compounds **2**, **19**, and **20** all within twofold of each other. In addition, the whole-cell potency remained unchanged across the set. Compound **21** was essentially equipotent to its direct analog **1**, and substitution of the phenyl ring in the 5-position with a *meta*-cyano group (**22**) also did not significantly change either isolated enzyme or whole-cell potency.

As hypothesized, steric obstruction of the carboxylate group also resulted in significantly different rat pharmacokinetic properties (Table 2). The *ortho*-substituted azaindoles **16**–**18** showed significantly lower plasma clearances, reduced volumes of distribution, and shorter iv half-lives. The parameters for compound **16** were sufficiently improved such that the DNAUC following oral dosing was nearly fourfold improved over that for **1**. Although the rat oral plasma concentration versus time plot for **16** indicated a secondary input peak, it was significantly smaller than that for **1**. Interestingly, the DNAUC values for **17** and **18** were very similar to that of **1** and significant secondary input peaks were observed for both after oral dosing (data not shown). The most marked improvement in rat oral exposure was observed for analogs with substitution inserted in between the carboxylate and the phenyl ring. Plasma clearance values for compounds **20** and **22** were at least threefold lower and the DNAUC values were as much as 10-fold higher than those of **2** and no secondary input peaks were observed in either of their oral exposure curves.

In summary, inhibitors of SGK1 were designed to address the poor rat PK properties of lead azaindoles **1** and **2**. Improvement of oral exposure while maintaining SGK1 inhibition potency proved to be the key challenge, as the carboxylate moiety was believed to be good for the latter but detrimental for the former. Rat PK could be improved by addition of alkyl substituents *ortho* to the carboxylate of **1** or by introducing geminal dimethyl groups α to the carboxylate of **2**. Ultimately, several of the azaindoles described were determined to meet the criteria set forth for in vivo testing in pharmacological models.[16]

References and notes

1. Pearce, D.; Kleyman, T. R. *J. Clin. Invest.* **2007**, *117*, 592.
2. Wulff, P.; Vallon, V.; Huang, D. Y.; Volkl, H.; Yu, F.; Richter, K.; Jansen, M.; Schlunz, M.; Klingel, K.; Loffing, J.; Kauselmann, G.; Bosl, M. R.; Lang, F.; Kuhl, D. *J. Clin. Invest.* **2002**, *110*, 1263.
3. The SGK1 assay used fluorescence polarization to monitor the binding of test compounds to the enzyme. The FP ligand, 3′,6′-diamino-*N*-[2-({3-[5-amino-6-(1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-2-pyrazinyl]phenyl}amino)-2-oxoethyl]-3-oxo-3H-spiro[2-benzofuran-1,9′-xanthene]-5-carboxamide, diluted to a final concentration of 0.5 nM, and SGK1, diluted to a final concentration of 1 nM in buffer containing 50 nM HEPES (pH 7.5), 1 mM CHAPS, 10 nM $MgCl_2$, and 1 mM DTT, were incubated for 15 min at RT. Azaindole inhibitors were dissolved in DMSO and diluted into buffer for concentration-response curve determination. The fluorescence signal was measured using an Acquest (Molecular Devices; Sunnyvale, CA) at excitation and emission wavelengths of 485 nm and 530 nm, respectively. SGK1 inhibition IC_{50} was calculated from these data using GraphPad Prism 3 Software (GraphPad Software, San Diego, CA).
4. Nakhoul, N. L.; Hering-Smith, K. S.; Gambala, C. T.; Hamm, L. L. *Am. J. Physiol.* **1998**, *275*, F998.
5. Dutton, G. J. *Glucuronidation of Drugs and Other Compounds*; CRC Press: Boca Raton, 1980. p 268.
6. Roberts, M. S.; Magnusson, B. M.; Burczynski, F. J.; Weiss, M. *Clin. Pharmacokinet.* **2002**, *41*, 751.
7. Crystallographic data has been deposited in the PDB with deposition codes 3HDM for compound **1** and 3HDN for compound **2**.
8. All target compounds met purity requirements of ⩾95% as determined by LCMS and/or ^{1}H NMR.
9. *Example azaindole preparation (1)*: Step 1: $PdCl_2$(dppf) (1.04 g, 1.27 mmol, 0.05 equiv) was added in one portion to a suspension of 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (5.00 g, 25.4 mmol, 1 equiv), phenylboronic acid (3.70 g, 30.5 mmol, 1.2 equiv), and K_2CO_3 (10.5 g, 76.1 mmol, 3 equiv) in 2.5:1 dioxane/water (253 mL). The reaction mixture heated in an oil bath set to 80 °C. After 22.5 h, the reaction mixture was cooled to room temperature, acidified with 6 N HCl, and partitioned between EtOAc and water. The mixture was filtered through a pad of pressed Celite, and the filtrate layers were separated. The aqueous layer was extracted with EtOAc and the combined organics were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified using DOWEX 50WX2-400 ion exchange resin to provide 5-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine as a light brown solid (4.86 g, 99%). Step 2: Br_2 (1.27 mL, 3.95 g, 24.7 mmol, 1 equiv) was added over a period of 35 min to a solution of 5-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (4.8 g, 24.7 mmol, 1 equiv) in $CHCl_3$ (247 mL). The reaction mixture was stirred at room temperature for 15 min and then concentrated in vacuo. The pale orange foam, 3-bromo-5-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine, was carried to the next reaction without further purification. Step 3: $(Bu_4N)HSO_4$ (100 mg, catalytic) was added to a mixture of 3-bromo-5-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (24.7 mmol, 1 equiv) and *p*-toluenesulfonyl chloride (5.65 g, 29.6 mmol, 1.2 equiv) in a bilayer of CH_2Cl_2 (308 mL) and 6 N NaOH (50 mL). After 1 h the reaction mixture was diluted with water, filtered through a plug of Celite, and the filtrate layers separated. The aqueous layer was extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4 and were concentrated. Purification of the residue by silica gel chromatography (CH_2Cl_2 grading to 10% EtOAc/CH_2Cl_2) afforded 3-bromo-1-[(4-methylphenyl)sulfonyl]-5-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (7.19 g, 68% over two steps) as a tan solid. Step 4: $PdCl_2$(dppf) complex with CH_2Cl_2 (246 mg, 0.30 mmol, 0,05 equiv) was added to a suspension of 3-bromo-1-[(4-methylphenyl)sulfonyl]-5-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (2.57 g, 6.01 mmol, 1 equiv), 4-carboxyphenylboronic acid (1.2 g, 7.21 mmol, 1.2 equiv) and K_2CO_3 (2.49 g, 18.0 mmol, 3 equiv) in 2.5:1 dioxane/water (60 mL). The reaction mixture was refluxed for 3 h and then cooled to rt and acidified with concentrated HCl. The mixture was filtered through a pad of Celite, and the filtrate was partitioned between EtOAc and water. The layers were separated, and the aqueous layer was further extracted with EtOAc. The combined organics were dried over Na_2SO_4 and were concentrated. The 4-[5-phenyl-1-(toluene-4-sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-benzoic acid was used directly in the next step without further purification. Step 5: Crude 4-[5-phenyl-1-(toluene-4-sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-benzoic acid was taken up in a mixture of MeOH (50 mL) and 2.5 N NaOH (20 mL). The reaction mixture was heated at 50 °C for 30 min and then acidified with concentrated HCl and partitioned between EtOAc and water. The precipitate that formed was collected by filtration and set aside. The aqueous layer was further extracted with EtOAc, and the combined organics were dried over anhydrous Na_2SO_4 and concentrated. The original precipitate was combined with the residue from the organics, and the combination was stirred with 10% MeOH in CH_2Cl_2 for 30 min. The insolubles were again collected by filtration and combined with the first crop. This process was repeated once more to provide 4-(5-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-benzoic acid 1 (1.13 g, 60%). ^{1}H NMR (400 MHz, CD_3OD) d 8.54 (s, 2H), 8.14 (d, 2H, *J* = 8 Hz), 7.87 (m, 3H), 7.73 (d, 2H, *J* = 8.8 Hz), 7.51 (t, 2H, *J* = 7.6 Hz), 7.40 (t, 1H, *J* = 7.2 Hz). LCMS (ES) *m*/*z* 315 $[M+H]^+$.
10. Although the introduction of steric bulk near the site of glucuronidation would appear to be a common strategy for reducing conjugate formation, extensive literature searching turned up only a single report of such an observation: Franklin, T. J.; Jacobs, V. N.; Jones, G.; Ple, P. *Drug Metab. Dispos.* **1997**, *25*, 367.
11. *Example preparation of 4-(dihydroxyboranyl)-2-ethylbenzoic acid:* Step 1: EtMgBr (1 M in THF, 32.0 mL, 32.0 mmol) was added to a solution of 4-bromo-2-fluorobenzoic acid (2 g, 9.13 mmol) in THF (15 mL) at 0 °C. After 4 h 25 mL of 2 N HCl was added slowly at 0 °C. EtOAc (30 mL) was added, and the layers were separated. Aq NaOH (30 mL, 2.5 N) was added to the organic layer and the mixture stirred for 30 min. The layers were separated, and the aqueous layer was washed with EtOAc (10 mL) and then acidified to pH 2 with 6 N HCl. The aqueous layer was extracted three times with EtOAc (30 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated to give 4-bromo-2-ethylbenzoic acid as a white solid (0.575 g, 28%). Step 2: B(*O*-*i*-Pr)$_3$ (3.52 mL, 15.3 mmol) was added to the acid (0.250 g, 1.09 mmol) in THF (18 mL). The mixture was cooled to −78 °C and *n*-butyllithium (2.5 M in hexanes, 6.1 mL, 15.3 mmol) was added over 10 min. The reaction temperature

was held at −78 °C for 3 h and then warmed to 0 °C and quenched with 10 mL of 2 N HCl. The aqueous layer was extracted twice with EtOAc and the combined organics were stirred with 2.5 N NaOH (10 mL) for 10 min. The layers were separated, and the aqueous layer was acidified to pH 3 with 6 N HCl, extracted twice with EtOAc, dried over Na_2SO_4 and concentrated. The crude material was stirred in CH_2Cl_2 and filtered to obtain the title compound as a white solid (0.120 g, 57%). ^{1}H NMR (400 MHz, CD_3OD) d 7.82 (m, 1H), 7.50 (m, 2H), 3.00 (q, J = 7.2 Hz, 2H), 1.24 (t, J = 7.6 Hz, 3H). LCMS (ES) m/z 194.2 $[M+H]^+$.

12. Bennetau, B.; Mortier, J.; Moyroud, J.; Guesnet, J. L. *J. Chem. Soc., Perkin Trans.1* **1995**, 1265.
13. Concentrated HCl (two drops) was added to a solution of [4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetic acid (1 g, 3.8 mmol) in MeOH (19 mL) and the mixture was stirred at rt for 12 h. The solvent was removed and the residue was extracted with CH_2Cl_2. The organic layer was washed with satd aq $NaHCO_3$ and concentrated to give the product as a colorless oil (1 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.31 (d, 2H, J = 8 Hz), 7.08 (d, 2H, J = 8 Hz), 3.70 (3H, s), 3.67 (s , 2H), 1.36 (s, 12H).
14. Pd(dppf)Cl_2 (0.29 g, 0.36 mmol) and KOAc (3.44 g, 35 mmol) were added to a solution of methyl 2-(4-bromophenyl)-2-methylpropanoate (3 g, 11.67 mmol) and bis(pinacolato)diboron (4.45 g, 17.5 mmol) in dioxane (42 mL). The reaction mixture was stirred at 95 °C for 8 h. After cooling to room temperature, EtOAc and brine were added and the mixture was filtered through Celite. The layers were separated and the organic layer was concentrated and purified by flash column chromatography. The crude product was then recrystallized with hot hexane to give the pure product (2.08 g, 59%) as colorless crystals. MS (ES) m/e 305.4 $[M+H]^+$.
15. Frazee, J. S.; Hammond, M.; Kano, K.; Manns, S.; Nakamura, H.; Thompson, S. K.; Washburn, D. G. WO 06/063167, 2006.
16. The use of compound **18**, a.k.a. GSK650394, as an in vitro tool to elucidate the role of SGK-1 in different systems has been reported elsewhere: (a) Sherk, A. B.; Frigo, D. E.; Schnackenberg, C. G.; Bray, J. D.; Laping, N. J.; Trizna, W.; Hammond, M.; Patterson, J. R.; Thompson, S. K.; Kazmin, D.; Norris, J. D.; McDonnell, D. P. *Cancer Res.* **2008**, *68*, 7475; (b) Saad, S.; Agapiou, D. J.; Chen, X. M.; Stevens, V.; Pollock, C. A. *Nephrol. Dial. Transplant.* **2009**, *24*, 1130.