

Small Molecule Disruptors of the Glucokinase- Glucokinase Regulatory Protein Interaction: 1. Discovery of a Novel Tool Compound for In Vivo Proof-of-Concept

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Supporting Information

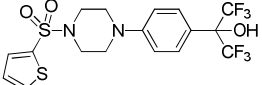
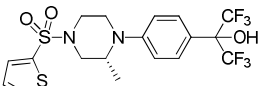
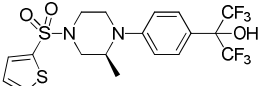
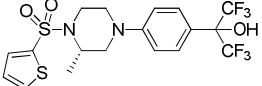
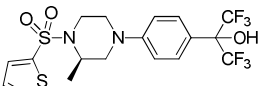
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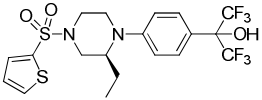
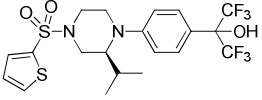
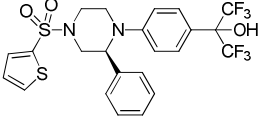
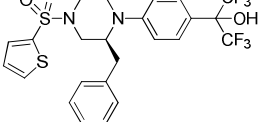
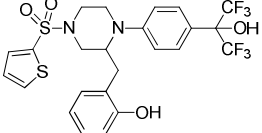
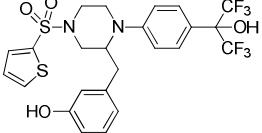
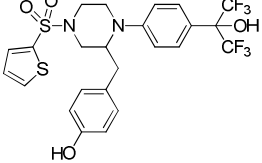
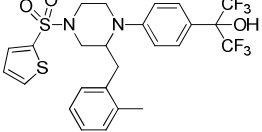
Standard Deviations for Tables 1, 2 and 4.....	S-2 to S-5
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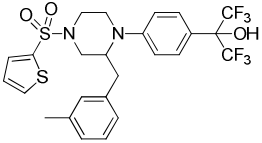
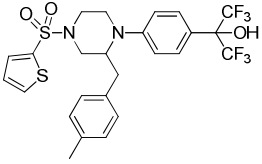
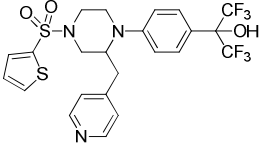
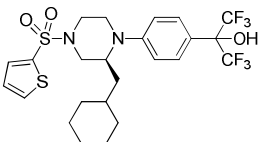
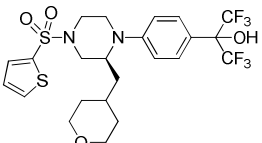
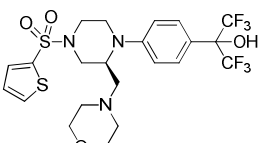
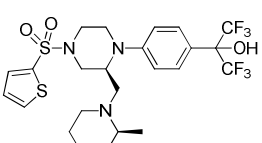
Table 1. Activity and rat in vivo PK properties of HTS hit 1.

Cmpd	rGK Translocation EC ₅₀ ^a (μM)	RLM CL _{int} ^b (μL/min/mg)	CL ^c (L/h/kg)	V _{ss} ^c (L/kg)	C _{max} ^d (μM)	F ^d (%)	f _u ^e (%)
1	3.64 ± 2.8	150	2.64	6.81	0.35	28	0.62

^a Data reported as the mean±SD where n≥3^b In vitro microsomal stability measurements were conducted in the presence of NADPH at 37 °C for 30 min at a final compound concentration of 1 μM^c 2 mg/kg intravenous dose (100 % DMSO)^d 10 mg/kg oral dose (0.1% Tween 80, 0.5 % CMC, 99.4 % water)^e Fraction unbound, determined via rapid equilibrium dialysis**Table 2.** Piperazine substituent SAR.

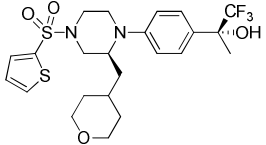
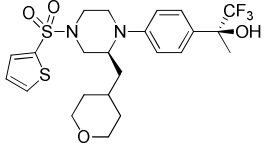
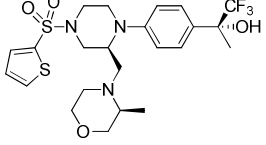
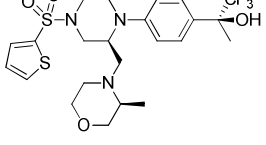
Cmpd	Structure	AlphaScreen [®] IC ₅₀ ^a (μM)
1		1.42 ± 1.63
2		9.15 ± 4.27
3		0.30 ± 0.138
4		3.17 ± 1.44
5		4.18 ± 2.17

6		1.44 ± 0.77
7		5.34 ± 1.35
8		2.06 ± 0.57
9		0.701 ± 0.36
10		0.215 ± 0.15
11		1.93 ± 0.66
12		0.85 ± 0.25
13		1.23 ± 0.36

14		1.01 ± 0.33
15		4.31 ± 1.67
16		1.56 ± 0.44
17		1.50 ± 0.69
18		0.058 ± 0.025
19		0.036 ± 0.016
20		0.0097 ± 0.006

^a Data reported as the mean $\pm$ SD where $n \geq 3$

Table 4. Effect of the Me/CF₃ moiety.

Cmpd	Structure	AlphaScreen[®] IC₅₀^a (μM)	rGK Translocation EC₅₀^a (μM)
23		0.095 ± 0.02	0.89 ± 0.93
24		0.10 ± 0.01	4.76 ± 1.24
25		0.021 ± 0.02	0.082 ± 0.07
26		0.012 ± 0.01	0.22 ± 0.13

^a Data reported as the mean±SD where n≥3