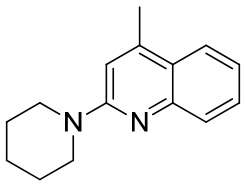
SUPPLERMENTARY MATERIAL:

SAR chemistry

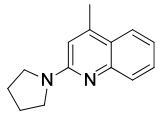
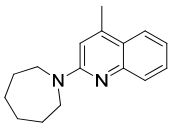
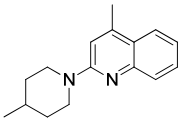
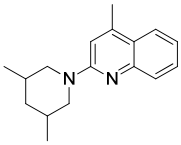
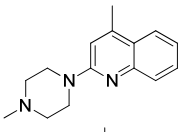
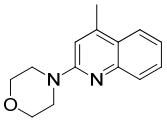
Methods. All NMR spectra were recorded on a 400 MHz AMX Bruker NMR spectrometer. ^{1}H chemical shifts are reported in δ values in ppm downfield with the deuterated solvent as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, coupling constant (Hz). Low resolution mass spectra were obtained on an Agilent 1200 series 6130 mass spectrometer with electrospray ionization. High resolution mass spectra were recorded on a Waters Q-TOF API-US plus Acquity system with electrospray ionization. Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Analytical HPLC was performed on an Agilent 1200 series with UV detection at 214 nm and 254 nm along with ELSD detection. LC/MS: Method 1 = (J-Sphere80-C18, 3.0 x 50 mm, 4.1 min gradient, 5%[0.05%TFA/CH_3CN]:95%[0.05%TFA/H_2O] to 100%[0.05%TFA/CH_3CN]; Method 2 = (Phenomenex-C18, 2.1 X 30 mm, 2 min gradient, 7%[0.1%TFA/CH_3CN]:93%[0.1%TFA/H_2O] to 100%[0.1%TFA/CH_3CN]; Method 3 = (Phenomenex-C18, 2.1 X 30 mm, 1 min gradient, 7%[0.1%TFA/CH_3CN]:93%[0.1%TFA/H_2O] to 95%[0.1%TFA/CH_3CN]. Preparative purification was performed on a custom HP1100 purification system with collection triggered by mass detection. Solvents for extraction, washing and chromatography were HPLC grade. All reagents were purchased from Aldrich Chemical Co. and were used without purification.

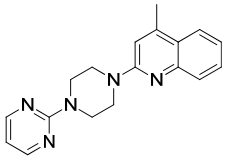
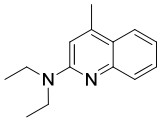
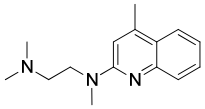
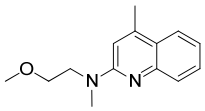
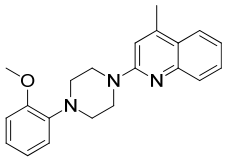
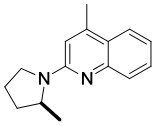
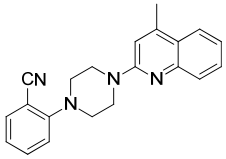
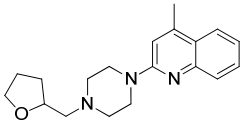
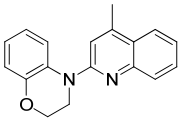
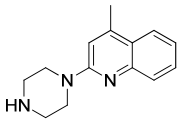
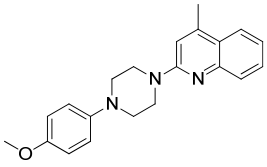
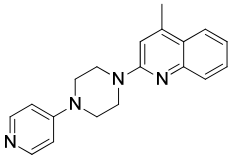


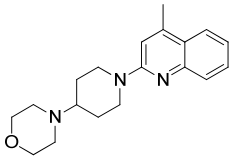
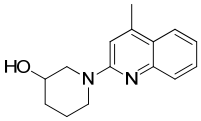
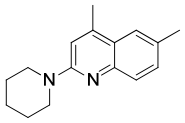
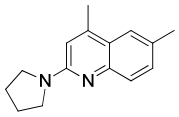
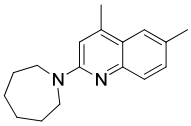
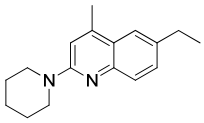
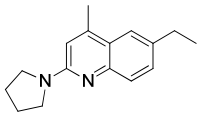
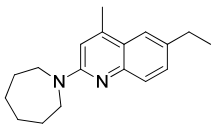
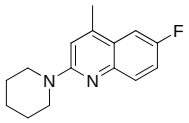
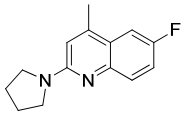
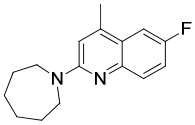
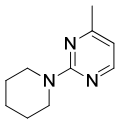
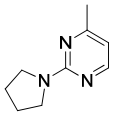
4-methyl-2-(piperidin-1-yl)quinoline (ML204, 1).

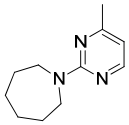
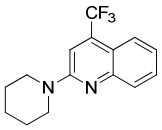
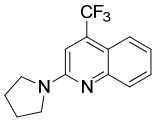
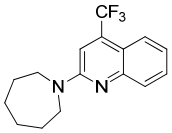
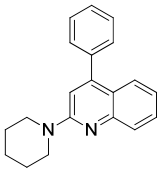
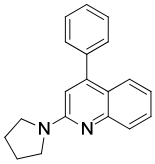
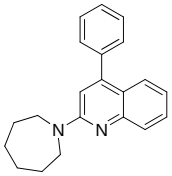
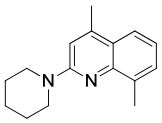
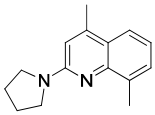
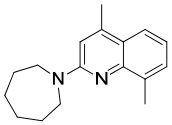
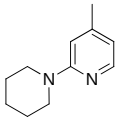
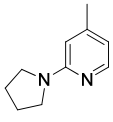
The chloro-quinoline (100 mg, 0.56 mmol) and piperidine (0.22 ml, 2.25 mmol) were stirred in a microwave reaction vial. The vial was sealed and then irradiated under microwave at 200ºC with stirring for 15 minutes. LC/MS indicate the reaction is done. The reaction was diluted with MeOH and then concentrated under vacuum. The residue was dissolved in 3% aqueous HCl (10 ml) and washed with dichloromethane (2x5 ml). The aqueous layer was treated with 2N NaOH until the pH was 8, resulting in a white slurry. The slurry was extracted with dichloromethane (3x20 ml). The combined organic layers were dried over Na_2SO_4 and concentrated to give 70 mg (55%) of the product as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.75 (d, J = 8.1 Hz, 1H), 7.52-7.45 (m, 2H), 7.21-7.17 (m, 1H), 7.10 (s, 1H), 3.67 (bs, 4H), 2.54 (s, 3H), 1.62-1.55 (m, 6H). LC/MS: R_T = 0.65 min., m/z = 227.2 $[M + H]^+$.

All compounds were synthesized using the above procedure.

Cmpd		Name	Purity
2		4-methyl-2-(pyrrolidin-1-yl)quinoline	LCMS: M+H= 255.2; >98% @ 220 and 254 nm.
3		2-(azepan-1-yl)-4-methylquinoline	LCMS: M+H= 241.3; >98% @ 220 and 254 nm, and ELSD.
4		4-methyl-2-(4-methylpiperidin-1-yl)quinoline	LCMS: M+H= 241.2; >98% @ 220 and 254 nm.
5		2-(3,5-dimethylpiperidin-1-yl)-4-methylquinoline	LCMS: M+H= 255.2; >98% @ 220 and 254 nm.
6		4-methyl-2-(4-methylpiperazin-1-yl)quinoline	LCMS: M+H= 242.2; >98% @ 220 and 254 nm.
7		4-(4-methylquinolin-2-yl)morpholine	LCMS: M+H= 229.2; >98% @ 220 and 254 nm.

8		4-methyl-2-(4-(pyrimidin-2-yl)piperazin-1-yl)quinoline	LCMS: M+H= 306.2; >98% @ 220 and 254 nm, and ELSD.
9		N,N-diethyl-4-methylquinolin-2-amine	LCMS: M+H= 215.2; >98% @ 220 and 254 nm.
10		N1,N1,N2-trimethyl-N2-(4-methylquinolin-2-yl)ethane-1,2-diamine	LCMS: M+H= 244.2; >98% @ 220 and 254 nm.
11		N-(2-methoxyethyl)-N,4-dimethylquinolin-2-amine	LCMS: M+H= 231.2; >98% @ 220 and 254 nm.
12		2-(4-(2-methoxyphenyl)piperazin-1-yl)-4-methylquinoline	LCMS: M+H= 334.2; >98% @ 220 and 254 nm.
13		(S)-4-methyl-2-(2-methylpyrrolidin-1-yl)quinoline	LCMS: M+H= 227.2; >98% @ 220 and 254 nm.
14		2-(4-(4-methylquinolin-2-yl)piperazin-1-yl)benzonitrile	LCMS: M+H= 329.2; >98% @ 220 and 254 nm.
15		4-methyl-2-(4-((tetrahydrofuran-2-yl)methyl)piperazin-1-yl)quinoline	LCMS: M+H= 312.2; >98% @ 220 and 254 nm.
16		4-(4-methylquinolin-2-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazine	LCMS: M+H= 277.2; >98% @ 214 nm and ELSD.
17		4-methyl-2-(piperazin-1-yl)quinoline	LCMS: M+H= 228.2; >98% @ 220 and 254 nm.
18		2-(4-(4-methoxyphenyl)piperazin-1-yl)-4-methylquinoline	LCMS: M+H= 334.2; >98% @ 220 and 254 nm.
19		4-methyl-2-(4-(pyridin-4-yl)piperazin-1-yl)quinoline	LCMS: M+H= 334.2; >98% @ 214 and 254 nm.

20		4-(1-(4-methylquinolin-2-yl)piperidin-4-yl)morpholine	LCMS: M+H= 312.2; >98% @ 220 and 254 nm.
21		1-(4-methylquinolin-2-yl)piperidin-3-ol	LCMS: M+H= 243.2; >98% @ 220 and 254 nm.
22		4,6-dimethyl-2-(piperidin-1-yl)quinoline	LCMS: M+H= 241.2; >98% @ 215 and 254 nm.
23		4,6-dimethyl-2-(pyrrolidin-1-yl)quinoline	LCMS: M+H= 227.2; >98% @ 215 and 254 nm.
24		2-(azepan-1-yl)-4,6-dimethylquinoline	LCMS: M+H= 255.3; >98% @ 220 and 254 nm, and ELSD.
25		6-ethyl-4-methyl-2-(piperidin-1-yl)quinoline	LCMS: M+H= 255.2; >98% @ 215 and 254 nm.
26		6-ethyl-4-methyl-2-(pyrrolidin-1-yl)quinoline	LCMS: M+H= 241.2; >98% @ 215 and 254 nm.
27		2-(azepan-1-yl)-6-ethyl-4-methylquinoline	LCMS: M+H= 269.4; >98% @ 220 and 254 nm, and ELSD.
28		6-fluoro-4-methyl-2-(piperidin-1-yl)quinoline	LCMS: M+H= 245.2; >98% @ 215 and 254 nm.
29		6-fluoro-4-methyl-2-(pyrrolidin-1-yl)quinoline	LCMS: M+H= 231.2; >98% @ 215 and 254 nm.
30		2-(azepan-1-yl)-6-fluoro-4-methylquinoline	LCMS: M+H= 259.2; >98% @ 220 and 254 nm, and ELSD.
31		4-methyl-2-(piperidin-1-yl)pyrimidine	LCMS: M+H= 178.2; >98% @ 215 and 254 nm.
32		4-methyl-2-(pyrrolidin-1-yl)pyrimidine	LCMS: M+H= 164.2; >98% @ 215 and 254 nm.

33		1-(4-methylpyrimidin-2-yl)azepane	LCMS: M+H= 192.2; >98% @ 220 and 254 nm, and ELSD.
34		2-(piperidin-1-yl)-4-(trifluoromethyl)quinoline	LCMS: M+H= 281.2; >98% @ 220 and 254 nm.
35		2-(pyrrolidin-1-yl)-4-(trifluoromethyl)quinoline	LCMS: M+H= 267.2; >98% @ 215 and 254 nm.
36		2-(azepan-1-yl)-4-(trifluoromethyl)quinoline	LCMS: M+H= 295.3; >98% @ 220 and 254 nm.
37		4-phenyl-2-(piperidin-1-yl)quinoline	LCMS: M+H= 289.2; >98% @ 215 and 254 nm.
38		4-phenyl-2-(pyrrolidin-1-yl)quinoline	LCMS: M+H= 275.2; >98% @ 215 and 254 nm.
39		2-(azepan-1-yl)-4-phenylquinoline	LCMS: M+H= 303.3; >98% @ 220 and 254 nm and ELSD.
40		4,8-dimethyl-2-(piperidin-1-yl)quinoline	LCMS: M+H= 241.2; >98% @ 215 and 254 nm.
41		4,8-dimethyl-2-(pyrrolidin-1-yl)quinoline	LCMS: M+H= 227.2; >98% @ 215 and 254 nm.
42		2-(azepan-1-yl)-4,8-dimethylquinoline	LCMS: M+H= 255.2; >98% @ 220 and 254 nm and ELSD.
43		4-methyl-2-(piperidin-1-yl)pyridine	LCMS: M+H= 177.2; >98% @ 215 and 254 nm.
44		4-methyl-2-(pyrrolidin-1-yl)pyridine	LCMS: M+H= 163.2; >98% @ 215 and 254 nm.

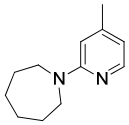
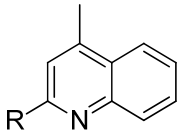
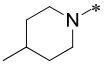
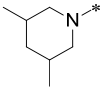
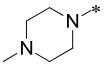
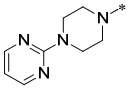
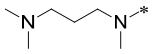
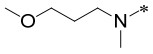
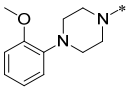
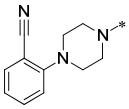
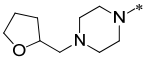
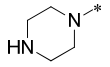
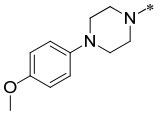
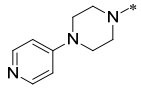
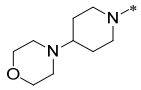
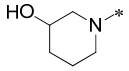
45		1-(4-methylpyridin-2-yl)azepane	LCMS: M+H= 191.2; >98% @ 220 and 254 nm and ELSD.

Table S1. SAR Evaluation of the left-hand portion.

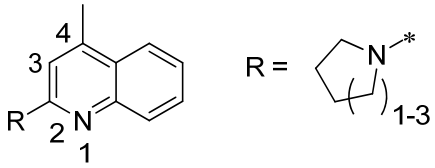


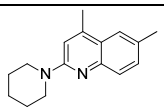
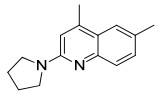
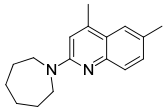
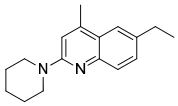
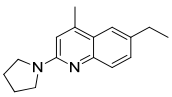
Cmpd	R	TRPC4 mOR, μM[a] (% inhib. @ 20 μM)	QPatch[a] (μM)	TRPC6, μM[b] (% inhib. @ 20 μM)	Selectivity
1		0.96 ± 0.26	2.6[b]	18.4	19
2		2.75 ± 0.79	8.02 ± 2.16	14.93	5.4
3		1.50[b]	1.96 ± 0.22	9.74	6.5
4		5.31 ± 3.85	2.6 ± 0.95	>20	>4
5		12.63[b]	11.9 ± 1.97	>20	~1
6		(-93.7**)	nd	23.8	N/A
7		>20 (39.4)	>20[b]	23.22	1
8		>20 (23.2)	nd	nd	N/A
9		5.24[b]	7.54 ± 0.63	>20	~4
10		(-121.3**)	nd	>20	N/A
11		20.82[b]	nd	>20	N/A
12		6.40[b]	9.89 ± 0.13	>20	~3.1
13		2.49 ± 0.4	5.46 ± 1.12	14.23	5.7
14		10.97[b]	8.90 ± 0.53	(-3.3%**)	N/A
15		(-0.09**)	nd	>20	N/A

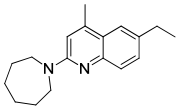
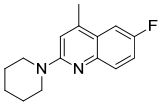
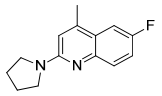
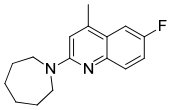
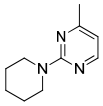
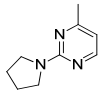
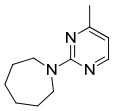
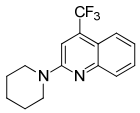
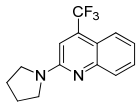
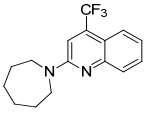
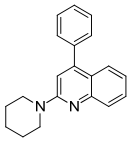
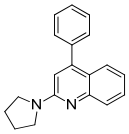
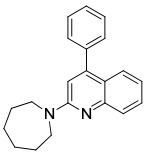
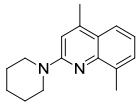
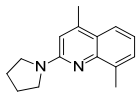
16		11.97[b]	24.51 ± 6.7	>20	~2
17		(-155.7**)	nd	20.45	N/A
18		(-65.2**)	nd	>20	N/A
19		19.92[b]	8.8 ± 3.95	13.18	0.7
20		>20[b] (37.8)	nd	18.82	N/A
21		7.32[b]	9.4 ± 0.68	>20	~2

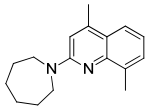
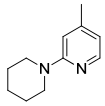
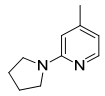
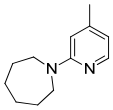
[a] The IC_{50} is the average of at least three independent titrations (Mean ± SD shown in table). [b] The IC_{50} is either the result of a group fit, or a single dose titration. [c] Compounds with <50% inhibition at 20 µM were not further profiled for IC_{50} data indicated by nd

Table S2. SAR Evaluation of the right-hand (quinoline) portion.



Cmpd	R	TRPC4 mOR, µM[a] (% inhib. @ 20 µM)	QPatch[a] (µM)	TRPC6, µM[b] (% inhib. @ 20 µM)	Selectivity
22		5.82[b]	3.93[b]	8.58	3
23		1.5 ± 0.47	3.91± 0.57	2.03	0.52
24		1.30[b]	0.9 ± 0.12	12.83	14.2
25		(45.8)	3.73 ± 0.5	14.99	4.0
26		0.58 ± 0.09	2.06 ± 0.2	4.24	7.3

27		7.37[b]	3.3 ± 0.37	(42.7%)	N/A
28		10.50[b]	6.38 ± 0.26	20.21	2
29		1.05 ± 0.28	3.94 ± 0.16	7.15	7
30		3.99[b]	1.63 ± 0.4	(10.3%)	N/A
31		(22.4)	nd	(-15.9%**)	N/A
32		(-11.5**)	nd	(-6.8%**)	N/A
33		(-8.7**)	nd	(-51.8%**)	N/A
34		(17.2)	nd	(-17.3%**)	N/A
35		(-40.0**)	nd	>20	N/A
36		(9.7)	nd	(-14.9%**)	N/A
37		(36.7)	nd	(-9.4%)	N/A
38		(21.0)	nd	(37.5%)	N/A
39		(15.0)	nd	(6.8%)	N/A
40		(30.7)	nd	(30.4%)	N/A
41		10.66[b]	9.96 ± 2.01	9.80	1

42		(30.6)	nd	(38.4%)	N/A
43		(23.9)	nd	(-2.2%**)	N/A
44		(16.8)	nd	(7.2%)	N/A
45		(55.0)	nd	(-16.7%**)	N/A

[a] The IC_{50} is the average of at least three independent titrations (Mean ± SD shown in table). [b] The IC_{50} is either the result of a group fit, or a single dose titration. [c] S/C = synthesized material or catalog material. [d] Compounds with <50% inhibition at 20 µM were not further profiled for IC_{50} data indicated by nd.