Supporting Information

Discovery and Biological Evaluation of 5-Aryl-2-Furfuramides, Potent and Selective Blockers of the $Na_v1.8$ Sodium Channel with Efficacy in Models of Neuropathic and Inflammatory Pain

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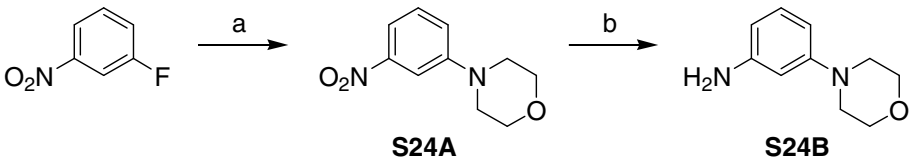
*1. Preparation of Precursors to Compounds **24**, **28**, and **30**.*

Scheme A[a]



S24A **S24B**

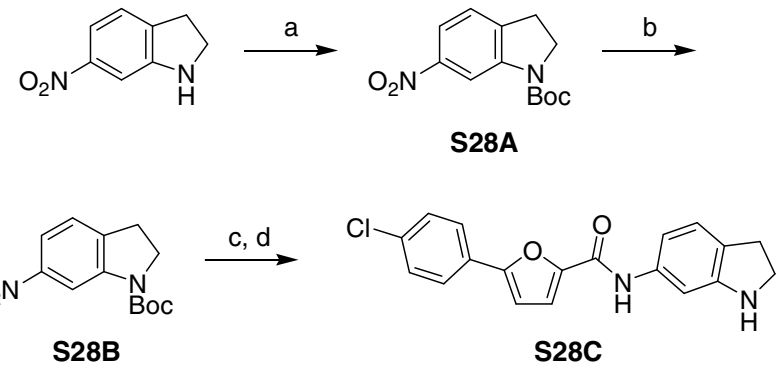
[a]Reagents: (a) morpholine, DMSO, 110 °C, 52%; (b) H_2, 5% Pd/C, EtOAc, 23 °C, 94%.

4-(3-Nitrophenyl)morpholine (S24A). To a solution of 1-fluoro-3-nitrobenzene (2.00 g, 14.2 mmol) in DMSO (10 mL) was added morpholine (6.18 g, 71.0 mmol). The reaction mixture was stirred at 110 °C for 6 h, then poured into cold water (10 mL). A dark, oily precipitate was formed which was collected by filtration and further purified by filtration through a small plug of silica gel (elution with 50% EtOAc/hexanes) to provide 1.52 g (7.31 mmol, 52%) of the desired compound as a yellow-orange powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.66 (t, *J*=2.4 Hz, 1H), 7.64-7.59 (m, 1H), 7.49 (t, *J*=8.1 Hz, 1H), 7.41 (dd, *J*=8.1, 2.3 Hz, 1H), 3.77-3.74 (m, 2H), 3.25-3.22 (m, 2H); MS (DCI/NH_3) *m/z* 209 $(M+H)^+$.

3-Morpholin-4-yl-phenylamine (S24B). 4-(3-Nitrophenyl)morpholine (1.50 g, 7.21 mmol) was dissolved in EtOAc (25 mL) and treated with 5% Pd/C (100 mg). The reaction vessel was equipped with a balloon of hydrogen (2 purge/fill cycles in vacuo) and stirred at ambient temperature for 6 h. The mixture was then filtered through a plug of silica gel (5 g) mixed with Celite® (5 g) and the filtrate was concentrated to provide 1.21 g (6.76 mmol, 94%) of the desired product as a white crystalline solid. ^{1}H NMR

(300 MHz, DMSO-d_6) δ 6.85 (t, *J*=8.5 Hz, 1H), 6.15-6.09 (m, 2H), 6.05 (ddd, *J*=7.8, 2.1, 1.0 Hz, 1H), 4.85 (br s, 2H), 3.71-3.68 (m, 2H), 3.00-2.97 (m, 2H); MS (DCI/NH_3) *m/z* 179 $(M+H)^+$.

Scheme B[a]



[a]Reagents: (a) Boc_2O, Et_3N, CH_2Cl_2, 23 °C; (b) H_2, 5% Pd/C, EtOAc, 23 °C, 35% for 2 steps; (c) **21**, $(COCl)_2$, cat. DMF, CH_2Cl_2, 23 °C; then **S28B**, Et_3N, CH_2Cl_2, 23 °C; (d) CF_3CO_2H, CH_2Cl_2, 23 °C, 55% for 2 steps.

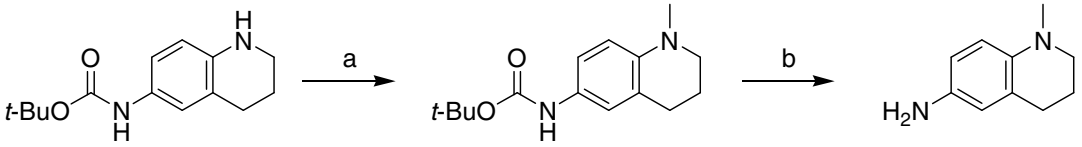
6-Nitro-2,3-dihydroindole-1-carboxylic acid, *tert*-butyl ester (S28A). 6-Nitroindoline (2.40 g, 15.0 mmol) in dichloromethane (50 mL) was reacted with di-*tert*-butyl-dicarbonate (4.91 g, 22.5 mmol) and triethylamine (22.5 mmol) at ambient temperature for 24 h. The reaction mixture was concentrated and purified by flash chromatography on silica gel (elution with 20% EtOAc/hexanes) to yield 3.80 g of the desired product which was used immediately for the subsequent preparation of **S28B**. MS (DCI/NH_3) *m/z* 265 $(M+H)^+$.

6-Amino-2,3-dihydroindole-1-carboxylic acid, *tert*-butyl ester (S28B). 6-Nitro-2,3-dihydroindole-1-carboxylic acid *tert*-butyl ester (**S28A**) (3.80 g, 14.3 mmol) from the previous step was dissolved in EtOAc (50 mL) and treated with 5% Pd/C (150 mg). The reaction vessel was equipped with a balloon of hydrogen (2 purge/fill cycles in vacuo) and stirred at ambient temperature for 6 h. The mixture was then filtered through a plug

of silica gel (5 g) mixed with Celite (5 g) and the filtrate was concentrated. The residue obtained was purified by flash chromatography on silica gel (elution with 20 % EtOAc/hexanes) to provide 1.20 g (5.12 mmol, 35% for two steps) of the desired product as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.05 (br s, 1H), 6.79 (d, *J*=8.1 Hz, 1H), 6.13 (dd, *J*=7.8, 2.0 Hz, 1H), 4.91 (s, 2H), 3.82 (t, *J*=8.1 Hz, 2H), 2.85 (t, *J*=8.5 Hz, 2H), 1.49 (s, 9H); MS (DCI/NH_3) *m/z* 235 $(M+H)^+$.

5-(4-Chlorophenyl)-*N*-(2,3-dihydro-1H-indol-6-yl)furan-2-carboxamide (S28C). Prepared from **21** and **S28B** (1.20 g as obtained above) using Method A followed by treatment with trifluoroacetic acid (3 mL) in dichloromethane (15 mL) at ambient temperature to provide 962 mg (2.84 mmol, 55% overall yield) of the desired product as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.12 (d, *J*=1.7 Hz, 1H), 8.01 (d, *J*=8.5 Hz, 2H), 7.57 (d, *J*=8.8 Hz, 2H), 7.44 (br s, 1H), 7.39 (d, *J*=3.7 Hz, 1H), 7.21 (d, *J*=3.7 Hz, 1H), 7.16 (d, *J*=8.1 Hz, 1H), 3.93 (t, *J*=8.6 Hz, 2H), 3.03 (t, *J*=8.5 Hz, 2H); MS (DCI/NH_3) *m/z* 339 $(M+H)^+$.

Scheme C[a]



S30A **S30A**

[a]Reagents: (a) aq. HCHO, $NaCNBH_3$, MeOH, 23 °C; (b) CF_3CO_2H, CH_2Cl_2, 23 °C, 80% for 2 steps.

1-Methyl-(1,2,3,4-tetrahydroquinolin-6-yl)-carbamic acid, *tert*-butyl ester (S30A). A solution of (1,2,3,4-tetrahydro-quinolin-6-yl)-carbamic acid *tert*-butyl ester (500 mg, 2.00 mmol; Tyger Chemicals) in methanol (10 mL) was reacted with a 37% solution of formaldehyde in water (1 mL) and $NaCNBH_3$ (120 mg, 10.0 mmol) at ambient

temperature. The reaction mixture was then adjusted to pH 5 with acetic acid. After 4 h of stirring at ambient temperature, the reaction mixture was concentrated and partitioned between EtOAc (25 mL) and water (10 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was filtered through a short plug (~5 g) of silica gel (elution with 15% EtOAc/CH_2Cl_2) to provide 422 mg of the desired compound which was used without purification. MS (DCI/NH_3) *m/z* 262 $(M+H)^+$.

1-Methyl-1,2,3,4-tetrahydroquinolin-6-ylamine (S30B). A solution of 1-methyl-1,2,3,4-tetrahydroquinolin-6-yl)-carbamic acid *tert*-butyl ester (420 mg, 1.60 mmol) in dichlormethane (10 mL) was reacted with trifluoroacetic acid (2 mL) at ambient temperature. The mixture was stirred at ambient temperature for 2 h then concentrated. The residue was diluted with CH_2Cl_2 (10 mL) and washed with aqueous sodium bicarbonate (8 mL) and brine (8 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was filtered through a short plug (~5 g) of silica gel (elution with 15% EtOAc/CH_2Cl_2) to provide 259 mg (1.60 mmol, 80%) of the desired product as a pale yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.38 (d, *J*=8.5 Hz, 1H), 6.30 (dd, *J*=8.4, 2.7 Hz, 1H), 6.24-6.22 (m, 1H), 4.26-4.21 (br s, 2H), 2.98-2.94 (m, 2H), 2.66 (s, 3H), 2.57 (t, *J*=6.6 Hz, 2H), 1.88-1.79 (m, 2H); MS (DCI/NH_3) *m/z* 163 $(M+H)^+$.

2. Table of Microanalyses.

Cmpd	Formula	C (calcd)	C (found)	H (calcd)	H (found)	N (calcd)	N (found)
3	$C_{12}H_{10}BrNO_2$	51.45	51.57	3.60	3.50	5.00	4.91
6	$C_{18}H_{14}ClNO_2 \cdot H_2O$	69.35	69.33	4.53	4.37	4.49	4.43
7	$C_{19}H_{14}N_2O_2$	75.48	75.24	4.67	4.43	9.27	9.13
8	$C_{19}H_{14}F_3NO_3$	63.13	62.96	3.91	3.62	3.88	3.89
9	$C_{19}H_{14}N_2O_2$	64.21	63.97	4.82	4.88	3.94	4.00
10	$C_{19}H_{14}N_2O_2 \cdot 0.25\ H_2O$	74.37	73.99	4.76	4.40	9.13	8.92
11	$C_{19}H_{14}F_3NO_2$	66.09	65.93	4.09	3.69	4.06	3.97
13	$C_{18}H_{14}ClNO_2 \cdot 0.5\ H_2O$	67.40	67.35	4.71	4.34	4.37	4.37
16	$C_{18}H_{14}ClNO_2$	69.35	69.08	4.53	4.15	4.49	4.46
18	$C_{18}H_{14}ClN_2O.HCl \cdot 0.75\ H_2O$	60.10	60.06	4.62	4.49	7.79	7.63
20	$C_{19}H_{14}ClN_3O$	67.96	68.12	4.20	4.06	12.51	12.34
22	$C_{19}H_{16}ClNO_2$	70.05	69.82	4.95	4.64	4.30	4.31
23	$C_{19}H_{15}Cl_2NO_2$	63.35	63.47	4.20	3.89	3.89	3.84
24	$C_{21}H_{19}ClN_2O_3.HCl$	60.15	60.11	4.81	4.42	6.68	6.55
25	$C_{20}H_{15}ClN_2O_3.HCl \cdot 0.75\ H_2O$	57.64	57.55	4.23	4.01	6.72	6.42
26	$C_{19}H_{13}ClN_2O_2$	67.76	67.45	3.89	3.85	8.32	8.11
26	$C_{19}H_{16}ClNO_4$	63.78	63.64	4.51	4.40	3.91	3.77
27	$C_{20}H_{17}ClN_2O_2.HCl$	61.71	61.31	4.66	4.29	7.60	7.22
28	$C_{20}H_{17}ClN_2O_3$	65.13	64.78	4.65	4.51	7.60	7.46
29	$C_{21}H_{19}ClN_2O_2.HCl$	62.54	62.63	5.00	5.07	6.75	6.75
30	$C_{20}H_{13}ClN_2O_2.HCl \cdot 1.1\ H_2O$	59.30	58.90	4.03	3.99	6.74	6.77
32	$C_{19}H_{13}ClN_2O_2$	67.76	67.37	3.89	3.58	8.32	7.96
33	$C_{17}H_{13}ClN_2O_2.HCl$	58.47	58.07	4.04	3.86	8.02	7.81
34	$C_{17}H_{13}ClN_2O_2.HCl$	58.47	58.27	4.04	3.81	8.02	7.84

35	$C_{19}H_{16}ClNO_2$	70.05	70.22	4.95	5.09	4.30	4.17
36	$C_{18}H_{21}ClN_2O_2$	64.96	64.79	6.36	6.44	8.42	8.51
37	$C_{15}H_{14}ClNO_3$	61.76	61.71	4.80	4.88	4.80	4.65