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General Methods for the Preparation of 4-Amido-2*H*-benzo[*b*]pyran-3-ols 5.

Method A

trans 6-Acetyl-4*S*-amino-3,4-dihydro-2,2-dimethyl-2H-benzo[*b*]pyran-3*R*-ol **4b** (0.61g; 2.6mmol) and dry triethylamine (2ml) in CH_2Cl_2 (70ml) were cooled to 0°C and treated with benzoyl chloride (0.4ml; 3.4mmol) according to the published procedure.[4a] Recrystallization from ethyl acetate/*n*-pentane gave compound **5m** (0.61g; 70%)

m.p. 188-91°C; $[\alpha_D]^{20}$ + 20.5° (c.0.89% in MeOH); NMR ($CDCl_3$) δ 1.34 [s, 3H, CMe_2], 1.54 [s, 3H, CMe_2), 2.50 [s, 3H, COMe], 3.78 [d, *J* = 7 Hz, 1H, H-3], 4.62 [br, 1H, OH], 5.27 [t, *J* = 8 Hz, 1H, H-4], 6.68 [d, *J* = 8 Hz, 1H, NHCO], 6.90 [d, *J* = 8 Hz, 1H, H-8], 7.36 - 7.62 [m, 3H, aromatic], 7.73 - 7.90 [m, 3H, aromatic], 7.97 (d, *J* = 1 Hz, 1H, H-5)

Method B

8-Acetyl-3,4-epoxy-3,4-dihydro-2,2-dimethyl-2*H*-benzo[*b*]pyran (0.60g; 2.8mmol) and 4-fluorobenzamide **2e** (0.77g; 5.5mmol) in *t*-butanol (18ml) was stirred at 25° and treated with potassium *t*-butoxide (0.62g; 5.5mmol) under argon. After 3h, the mixture was heated to 45°C for 5h and then allowed to cool. The mixture was poured into saturated NH_4Cl solution and extracted with EtAc (×2). The organic extracts were washed with water, brine and dried over anhydrous Na_2SO_4. Filtration and evaporation gave the crude product as a beige solid (1.15g). Chromatography on Kieselgel 60 using an ethyl acetate-*n*-pentane gradient elution, followed by recrystallization from ethyl acetate gave compound **5e** as off white crystals (0.26g; 26%).

m.p. 263-4°C; NMR [$(CD_3)_2SO$] δ 1.27 [s, 3H, $C(Me)_2$], 1.51 [s, 3H, $C(Me)_2$], 2.56 [s, 3H, COMe], 3.82 [dd, *J* = 10,5 Hz, 1H, H-3], 5.11 [t, *J* = 8 Hz, 1H, H-4], 5.73 [d, *J* = 5 Hz, 1H, OH], 6.96 [t, *J* = 7

Hz, 1H, H-6], 7.31 [m, 3H, H-7 + aromatic, overlapping], 7.46 [dd, $J = 7$, 1 Hz, 1H, H-5], 8.02 [m, 2H, aromatic], 8.84 [d, 8, 1H, CONH].

Anticonvulsant Properties in the Mouse MEST Test[7]

In this model, groups of 10-20 naive mice (male CD1-Charles River, 25-30g) were lightly restrained. The threshold current (*ca.*12mA, applied *via* corneal electrodes) for the induction of tonic hindlimb extension seizures in 50% (CC_{50}) of the animals was determined using a Hugo Sachs Elektronic stimulator which delivered a constant current (0.1s duration, 50Hz, sinewave form, fully adjustable between 1-300mA). Mice were assessed for production of a tonic hindlimb extension seizure following a single corneal electroshock using an "up and down" method of shock titration.[7] The effects of drug treatment were expressed as a percentage change from vehicle control values and statistical comparisons between groups were made according to the method of Litchfield and Wilcoxon.[12] The compounds were administered orally as a fine suspension in 1% methylcellulose one hour before electroshock application.

Radioligand Binding Studies

[^{3}H] SB 204269 selectively labels a novel class of CNS receptor sites. Displacement of this specific binding *in vitro* by novel compounds in well-washed, frozen rat whole forebrain membranes was as described by Herdon *et al.*[6] Ki values were determined by using the Cheng-Prusoff equation and all determinations were performed in triplicate.

Analytical Data for 4-Amido-2*H*-benzo[*b*]pyran-3-ols in Table 1

Cpd No.	Found			Theoretical			Formula	$[\alpha_D]^{20}$ (c.1% in MeOH)
	C	H	N	C	H	N		
5a	- Nd	-	-	-	-	-	$C_{20}H_{20}FNO_4$[a]	(±)
5b	65.32	5.55	3.90	65.57	5.74	3.83	$C_{20}H_{20}FNO_4$ $0.5H_2O$	+25.7°
5c	65.53	5.79	3.91	65.57	5.74	3.83	$C_{20}H_{20}FNO_4$ $0.5H_2O$	-25.9°
5d	- Nd	-	-	-	-	-	$C_{20}H_{20}FNO_4$[b]	(±)
5e	66.99	5.67	3.99	67.22	5.64	3.92	$C_{20}H_{20}FNO_4$	(±)
5f	67.05	5.07	8.35	67.05	5.03	8.23	$C_{19}H_{17}FN_2O_3$	+39.2°
5g	60.05	4.78	7.89	60.00	4.76	7.77	$C_{18}H_{17}FN_2O_5$	(±)
5h	62.23	4.97	3.23	63.28	4.87	3.07	$C_{24}H_{22}FNO_5S$	(±)
5i	55.64	4.04	3.29	55.43	3.95	3.23	$C_{20}H_{17}F_6NO_4$	+71.2°
5j	64.47	5.12	4.22	64.86	5.14	4.20	$C_{18}H_{17}F_2NO_3$	(±)
5k	69.83	6.50	4.07	69.29	6.12	4.25	$C_{19}H_{20}FNO_3$[c]	(±)
5l	67.82	6.00	3.53	67.91	5.97	3.77	$C_{21}H_{22}FNO_4$	(±)
5m	71.53	5.38	3.66	71.59	5.29	3.34	$C_{25}H_{22}FNO_4$	(±)
5n	63.95	5.66	4.03	64.34	5.40	3.75	$C_{20}H_{20}FNO_5$	(±)
5o	63.62	5.32	7.84	63.68	5.34	7.82	$C_{19}H_{19}FN_2O_4$	(±)
5p	70.39	6.29	4.12	70.78	6.19	4.13	$C_{20}H_{21}NO_4$	+20.5°
5q	64.01	5.43	3.93	64.26	5.39	3.75	$C_{20}H_{20}ClNO_4$	(±)
5r	64.08	5.24	4.08	64.26	5.39	3.75	$C_{20}H_{20}ClNO_4$	+6.8°
5s	64.13	5.44	3.87	64.26	5.39	3.75	$C_{20}H_{20}ClNO_4$	+21.9°
5t	51.71	4.40	3.05	51.63	4.33	3.01	$C_{20}H_{20}INO_4$	+15.5°
5u	69.32	7.65	4.17	69.54	7.88	4.05	$C_{20}H_{27}NO_4$	(±)

a CIMS m/z 358.1346 (MH^+)
b EIMS m/z 357.1379 (M^+)
c EIMS m/z 329(M^+; 2%), 311 (10), 296 (60), 123 (100)
Nd: Not determined.

250MHz ^{1}H NMR Data for 4-Amido-2*H*-benzo[*b*]pyran-3-ols 5

5a NMR[$(CD_3)_2SO$]δ 1.22 [s, 3H, C$(Me)_2$], 1.41 [s, 3H, C$(Me)_2$], 2.29 [s, 3H, COMe], 3.68 [m, 1H, H-3], 5.16 [m, 1H, H-4], 5.45 [d, *J* = 5 Hz, 1H, OH], 6.88 [d, *J* = 8 Hz, 1H, H-8], 7.27 [m, 3H, aromatic], 7.89 [m, 2H, aromatic], 8.68 [d, *J* = 8 Hz, 1H, NHCO]

5b NMR[$(CD_3)_2SO$]δ 1.24 [s, 3H, C$(Me)_2$], 1.44 [s, 3H, C$(Me)_2$], 2.44 [s, 3H, COMe], 3.78 [m, 1H, H-3], 5.08 [m, 1H, H-4], 5.72 [d, *J* = 5 Hz, 1H, OH], 6.90 [d, *J* = 8 Hz, 1H, H-8], 7.35 [m, 2H, aromatic], 7.70 [s, 1H, aromatic H-5], 7.80 [m, 1H, aromatic], 8.03 [m, 2H, aromatic], 8.82 [d, *J* = 8 Hz, 1H, NHCO]

5c NMR [$(CD_3)_2SO$]δ 1.30 [s, 3H, C$(Me)_2$], 1.52 [s, 3H, C$(Me)_2$], 2.50 [s, 3H, COMe], 3.85 [m, 1H, H-3], 5.26 [m, 1H, H-4], 5.80 [d, *J* = 5 Hz, 1H, OH], 6.90 [d, *J* = 8 Hz, 1H, H-8], 7.43 [m, 2H, aromatic], 7.77 [s, 1H, aromatic H-5], 7.85 [m, 1H, aromatic], 8.10 [m, 2H, aromatic], 8.90 [d, *J* = 8 Hz, 1H, NHCO]

5d NMR($CDCl_3$) δ 1.31 [s, 3H, C$(Me)_2$], 1.52 [s, 3H, C$(Me)_2$], 2.54 [s, 3H, COMe], 3.79 [dd, *J* = 10, 5 Hz, 1H, H-3], 4.31 [d, *J* = 5 Hz, 1H, OH], 5.29 [t, *J* = 8 Hz, 1H, H-4], 6.55 [d, *J* = 9 Hz, 1H, CONH], 7.17 [t, *J* = 7 Hz, 2H, aromatic], 7.38 [m, 2H, aromatic], 7.50 [d, *J* = 7 Hz, 1H, aromatic], 7.86 [m, 2H, aromatic]

5e NMR [$(CD_3)_2SO$] δ 1.27 [s, 3H, C$(Me)_2$], 1.51 [s, 3H, C$(Me)_2$], 2.56 [s, 3H, COMe], 3.82 [dd, *J* = 10, 5 Hz, 1H, H-3], 5.11 [t, *J* = 8 Hz, 1H, H-4], 5.73 [d, *J* = 5 Hz, 1H, OH], 6.96 [t, *J* = 7 Hz, 1H, H-6], 7.31 [m, 3H, aromatic], 7.46 [dd, *J* = 6, 1 Hz, 1H, H-5]. 8.02 [m, 2H, aromatic], 8.84 [d, *J* = 8 Hz, 1H, NHCO]

5f NMR ($CDCl_3$) δ 1.34 [s, 3H, C$(Me)_2$], 1.55 [s, 3H, C$(Me)_2$], 3.77 [dd, *J* = 10, 5 Hz, 1H, H-3], 4.13 [d, *J* = 5 Hz, 1H, OH], 5.28 [t, *J* = 8 Hz, 1H, H-4], 6.33 [d, *J* = 8 Hz, 1H, NHCO], 6.94 [d, *J* = 8 Hz, 1H, aromatic H- 8], 7.18 [t, *J* = 7 Hz, 2H, aromatic], 7.51 [dd, *J* = 8, 1 Hz, 1H, H-7], 7.62 [d, *J* = 1 Hz, 1H, H-5], 7.86 [m, 2H, aromatic]

5g NMR[$(CD_3)_2SO$] δ 1.34 [s, 3H, C$(Me)_2$], 1.56 [s, 3H, C$(Me)_2$] 3.91 [dd, *J* = 10, 5Hz, 1H, H-3], 5.18 [t, *J* = 8Hz, 1H, H-4], 5.96 [d, *J* = 5 Hz, 1H, OH], 7.10 [d, *J* = 8Hz, 1H, H-8], 7.44 [m, 2H, aromatic], 8.04 [m, 1H, aromatic], 8.14 [m, 3H, aromatic], 9.02 [d, *J* = 8Hz, CONH]

5h NMR[$(CD_3)_2SO$] δ 1.29 [s, 3H, C$(Me)_2$], 1.50 [s, 3H, C$(Me)_2$], 3.82 [dd, *J* = 9, 6Hz, 1H, H-3], 5.12 [t, *J* = 8Hz, 1H, H-4], 5.90 [d, *J* = 6Hz, 1H, OH], 7.08 [d, *J* = 8Hz, 1H, H-8], 7.48 [m, 2H, aromatic], 7.60-7.95 [m, 7H, aromatic], 8.08 [dd, *J* = 8, 5Hz, 2H, aromatic], 8.92 [d, *J* = 8Hz, 1H, CONH]

5i NMR[$(CD_3)_2SO$] δ 1.22 [s, 3H, C$(Me)_2$], 1.45 [s, 3H, C$(Me)_2$], 3.79 [dd, *J* = 10, 5Hz, 1H, H-3], 5.07 [t, *J* = 8Hz, 1H, H-4], 5.78 [d, *J* = 5Hz, 1H, OH], 7.01 [d, *J* = 8Hz, 1H, H-8], 7.35 [m, 3H, aromatic], 7.45 [m, 1H, aromatic], 7.99 [m, 2H, aromatic], 8.86 [d, *J* = 8Hz, 1H, CONH]

5j NMR($CDCl_3$) δ 1.30 [s, 3H, C$(Me)_2$], 1.49 [s, 3H, C$(Me)_2$], 3.75 [d, *J* = 10, 5 Hz, 1H, H-3], 4.33 [br, s, 1H, OH], 5.21 [t, *J* = 8 Hz, 1H, H-4], 6.40 [d, *J* = 9 Hz, 1H, NHCO], 6.83 [dd, *J* = 8, 1 Hz, 1H, H-8], 6.96 [m, 2H, aromatic], 7.17 [m, 2H, aromatic], 7.85 [m, 2H, aromatic]

5k NMR($CDCl_3$) δ 1.28 [s, 3H, C(Me)$_2$], 1.50 [s, 3H, C(Me)$_2$], 2.30 [s, 3H, Me], 3.74 [d, J = 8 Hz, 1H, H-3], 4.45 [br, s, 1H, OH], 5.18 [t, J = 8 Hz, 1H, H-4], 6.44 [d, J = 9 Hz, 1H, NHCO], 6.78 [d, J = 8 Hz, 1H, H-8], 7.05 [d, J = 7 Hz, 2H, aromatic], 7.17 [m, 2H, aromatic], 7.86 [m, 2H, aromatic]

5l NMR($CDCl_3$) δ 1.15 [s, 3H, C(Me)$_2$, 1.32 (s, 3H, C(Me)$_2$], 1.53 [s, 3H, COMe], 2.88 [q, J = 8 Hz, 2H, CH_2Me], 3.25 - 4.00 [br, 1H, OH], 3.82 [d, J = 8 Hz, 1H, H-3], 5.30 [t, J = 8 Hz, 1H, H-4], 6.86 [d, J = 8 Hz, 1H, H-8], 7.13 [m, 2H, NHCO and aromatic], 7.79 [dd, J = 8, 1 Hz, 1H, aromatic], 7.91 [narrrow m, 1H, aromatic], 8.03 [m, 2H, aromatic], 8.18 [d, J = 1 Hz, 1H, H-5].

5m NMR[$(CD_3)_2SO$] δ 1.25 [s, 3H, C(Me)$_2$], 1.45 [s, 3H, C(Me)$_2$], 3.81 [dd, J = 10, 5Hz, 1H, H-3], 5.08 [t, J = 9Hz, 1H, H-4], 5.75 [d, J = 5Hz, 1H, OH], 6.94 [d, J = 9Hz, 1H, H-8], 7.29-7.50 [m, 4H, aromatic], 7.50-7.70 [m, 5H, aromatic], 7.96 [m, 2H, H-5 + aromatic], 8.86 [d, J = 9Hz, 1H, CONH]

5n NMR[$CD_3)_3SO$] δ 1.21 [s, 3H, C(Me)$_2$], 1.42 [s, 3H, C(Me)$_2$], 3.72 [s, 3H, COMe], 3.76 [m, 1H, H-3], 5.06 [m, 1H, H-4], 5.69 [d, J = 5 Hz, 1H, OH], 6.87 [d, J = 8 Hz, 1H, H-8], 7.32 [m, 2H, aromatic], 7.71 [m, 2H, aromatic], 8.00 [m, 2H, H-5 + aromatic], 8.79 [d, J = 8 Hz, 1H, NHCO].

5o NMR[$(CD_3)_2SO$] δ 1.23 [s, 3H, C(Me)$_2$], 1.46 [s, 3H, C(Me)$_2$], 3.73 [m, 1H, H-3], 5.12 [m, 1H, H-4], 5.66 [d, J = 5 Hz, 1H, OH], 6.82 [d, J = 8 Hz, 1H, H-8], 7.15 [br, 1H, CONH], 7.36 [m, 2H, aromatic], 7.71 [m, 2H, aromatic], 7.84 [br, 1H, CONH], 8.06 [m, 2H, aromatic], 8.78 [d, J = 8 Hz, 1H, NHCO].

5p NMR($CDCl_3$) δ 1.34 [s, 3H, CMe$_2$], 1.54 [s, 3H, CMe$_2$), 2.50 [s, 3H, COMe], 3.78 [d, J = 8 Hz, 1H, H-3], 4.62 [br, 1H, OH], 5.27 [t, J = 8 Hz, 1H, H-4], 6.68 [d, J = 9Hz, 1H, NHCO], 6.90 [d, J = 8 Hz, 1H, H-8], 7.36-7.62 [m, 3H, aromatic], 7.73-7.90 [m, 3H, aromatic], 7.97 [d, J = 1 Hz, 1H, H-5]

5q NMR[$(CD_3)_2SO$] δ 1.22 [s, 3H, C(Me)$_2$], 1.45 [s, 3H, C(Me)$_2$], 2.43 [s, 3H, COMe], 3.77 [m, 1H, H-3], 5.08 [m, 1H, H-4], 5.73 [d, J = 5 Hz, 1H, OH], 6.98 [d, J = 8 Hz, 1H, H-8], 7.59 [m, 2H, aromatic], 7.68 [s, 1H, H-5], 7.89 [m, 1H, aromatic], 7.96 [m, 2H, aromatic], 8.88 [d, J = 8 Hz, 1H, CONH]

5r NMR[$(CD_3)_2SO$] δ 1.31 [s, 3H, C(Me)$_2$], 1.53 [s, 3H, C(Me)$_2$], 2.57 [s, 3H, COMe], 3.76 [s, 1H, H-3], 5.14 [s, 1H, H-4], 5.88 [d, J = 5 Hz, 1H, OH], 6.96 [d, J = 8 Hz, 1H, H-8], 7.30 [m, 2H, aromatic] 7.72 [m, 2H, aromatic], 7.88 [m, 1H, H-7], 8.09 [s, 1H, H-5], 8.95 [d, J = 8 Hz, 1H, CONH]

5s NMR[$(CD_3)_2SO$] δ 1.22 [s, 3H, C(Me)$_2$], 1.47 [s, 3H, C(Me)$_2$], 2.45 [s, 3H, COMe], 3.78 [m, 1H, H-3], 5.08 [m, 1H, H-4], 5.73 [d, J = 5 Hz, 1H, OH], 6.89 [d, J = 8 Hz, 1H, H-8], 7.56 [m, 1H, aromatic], 7.65 [m, 1H, aromatic], 7.68 [m, 1H, aromatic], 7.80 [m, 1H, aromatic], 7.92 [m, 1H, aromatic], 7.99 [m, 1H, H-5], 8.81 [d, J = 8 Hz, 1H, CONH]

5t NMR (CD_3) δ 1.30 [s, 3H, C(Me)$_2$], 1.52 [s, 3H, C(Me)$_2$], 2.41 [s, 3H, COMe], 3.79 [d, J = 8 Hz, 1H, H-3], 5.28 [t, J = 8 Hz, 1H, H-4], 6.85 [d, J = 8 Hz, 1H, aromatic], 7.01 [d, J = 8 Hz, 1H, NHCO], 7.15 [t, J = 8 Hz, 1H, aromatic], 7.72 [m, 1H, aromatic], 7.84 [m, 2H, aromatic], 7.94 [narrow m, 1H, aromatic], 8.24 [narrow m, 1H, aromatic].

5u NMR($CDCl_3$) δ 1.28 [s, 3H, C(Me)$_2$], 1.51 [s, 3H, C(Me)$_2$], 1.60 - 2.10 [m, 10H, cyclohexyl], 2.30 [m, 1H, COCH cyclohexyl], 2.53 [s, 3H, COMe], 3.65 [d, J = 8 Hz, 1H, H-3], 4.55 [s, 1H, OH], 5.06 [t, J = 8 Hz, 1H, H-4], 5.90 [d, J = 9Hz, 1H, CONH], 6.89 [d, J = 8 Hz, 1H, H-8], 7.80 [dd, J = 8,1 Hz, 1H, H-7], 7.88 [br, 1H, H-6]