Supporting Information

Further structure-activity relationship studies on 4-((((3*S*,6*S*)-6-benzhydryltetrahydro-2*H*-pyran-3-yl)amino)methyl)phenol: Identification of compounds with triple uptake inhibitory activity as potential antidepressant agents

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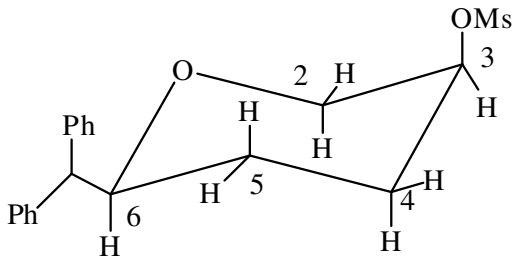
(3S,6S)-6-benzhydryltetrahydro-2H-pyran-3-yl methanesulfonate (6b)



Spectral data for **6b**: Mp: 101-103°C. $[\alpha]^{25}_{D}$= (-) 80.6°, *c* = 0.5 in MeOH. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.37-1.41 (m, 1H, H-5ax), 1.66-1.86 (m, 2H, H-4ax, H-5eq), 2.15-2.21 (m, 1H, H-4eq), 3.02 (s, 3H, CH_3), 3.65 (dd, *J* = 1.2, 13.2 Hz, 1H, H-2ax), 3.98

(d, J = 9.2 Hz, 1H, Ph_2CH), 4.07 (dt, J = 1.6, 10.8 Hz, 1H, H-6ax), 4.14-4.20 (m, 1H, H-2eq), 4.77 (s, 1H, H-3eq), 7.10-7.34 (m, 10H, aromatic).

Singlet at 4.77 ppm for H-3 indicates that there is no coupling with other protons, its possible only if it is in equatorial position. If it is in axial, there should have been large J value because of axial-axial couplings. Moreover, doublet of double at 3.65 for H-2ax with J values 1.2, 13.2 Hz is possible only when H-3 proton is in an equatorial position resulting in a small coupling 1.2 Hz corresponding to interaction of H2 axial-H3 equatorial coupling and a large coupling of 13.2 Hz corresponds geminal coupling with H-2 equatorial proton.

Table 1: Binding affinity of **10f** for CNS receptors.[a]

Target Receptor	Radioligand	% Inhibition of Binding at 10 μM **10f**	Ki for D-161 (nM)
D1	[3H]SCH 23390	21.2	
D2	[3H]N-methylspiperone	19.4	
D3	[3H]N-methylspiperone	45	
D4	[3H]N-methylspiperone	-0.3	
D5	[3H]SCH 23390	15.7	
5HT1a	[3H]8-OH-DPAT	34.3	
5HT1b	[3H]GR-125743	-0.2	
5HT1e	[3H]5-HT	-1.9	
5HT1d	[3H]GR-125743	36.4	
5HT2a	[3H]ketanserin	26.5	

5HT2b	[3H]LSD	55.4	6687 ± 593
5HT2c	[3H]Mesulergine	56.5	6527 ± 933
5HT3	[3H] LY 278,584	44.6	
5HT5a	[3H]LSD	65.2	3430 ± 284
5HT6	[3H]LSD	16	
5HT7	[3H]LSD	46.1	
GABA A	[3H]Muscimol	4.8	
5-HT1e	[3H]5-HT		
Alpha1A	[3H]Prazosin	71.3	1909 ± 80
Alpha1B	[3H]Prazosin	63.6	1652 ± 250
Alpha1D	[3H]Prazosin	43.7	
Alpha2A	[3H]Clonidine	-8.6	
Alpha 2B	[3H]Clonidine	56.3	7186 ± 1473
Alpha 2C	[3H]Clonidine	45.7	
Beta1	[125I]Iodopindolol	8.1	
Beta2	[125I]Iodopindolol	14.9	
Beat3	[125I]Iodopindolol	44	
BZP Rat Brain Site	3H-Flunitrazepam	29	
Ca2+ Channel	[3H]Nitrendipine	25.7	
d-opioid	[3H]DADLE	53	1054 ± 132
k-opioid	[3H]Bremazocine	80.1	155 ± 26
H1	[3H]Pyrilamine	9.7	

H2	[3H]Tiotodine	84.4	154 ± 44
H3	[3H]Alpha methyl Histamine	7.6	
H4	[3H]Histamine	-17.1	
m-Opioid	[3H]Diprenorphine	91	47 ± 5
Mı	[3H]QNB	3.1	
M2	[3H]QNB	11	
M3	[3H]QNB	12	
M4	[3H]QNB	-7.8	
M5	[3H]QNB	10.3	
NMDA PCP Site	MK801	3.6	

a. The default concentration of drugs for primary binding experiments was 10 μM, and % inhibition (mean of 4 determinations) is shown.

Elemental Analysis of target compounds

Compound	Molecular formula	Elemental Analysis					
		Calculated			Found		
		C	H	N	C	H	N
9a, D-386	$C_{26}H_{29}NO_2$ HCl	73.65	7.13	3.30	73.31	7.32	3.35
9b, D-387	$C_{26}H_{29}NO_2$ HCl	73.65	7.13	3.30	73.25	7.18	3.36
9c, D-388	$C_{26}H_{28}NO_2F$ HCl	70.66	6.61	3.17	70.87	6.87	3.02

9d, D-389	$C_{26}H_{28}NO_2F$ HCl $0.4H_2O$	69.52	6.69	3.12	69.57	6.76	3.11
9e, D-409	$C_{27}H_{31}NO_3$ HCl $0.2H_2O$	70.87	7.14	3.06	70.32	6.98	3.06
9f, D-404	$C_{27}H_{31}NO_3$ HCl	71.43	7.10	3.09	71.38	7.16	3.10
10a, D-410	$C_{24}H_{26}N_2O$ 2HCl	66.82	6.54	6.49	66.62	6.60	6.40
10b, D-394	$C_{24}H_{26}N_2O$ 2HCl	66.82	6.54	6.49	66.72	6.67	6.50
10c, D-396	$C_{24}H_{26}N_2O$ 1.8HCl	67.97	6.61	6.61	68.13	6.81	6.44
10d, D-392	$C_{29}H_{29}NO$ HCl $0.4H_2O$	77.19	6.88	3.10	77.03	6.90	3.08
10e, D-393	$C_{25}H_{27}NO_2$ HCl $0.3H_2O$	72.29	6.94	3.37	72.30	7.12	3.28
10f, D-391	$C_{25}H_{27}NO_2$ HCl $0.5H_2O$	71.67	6.98	3.34	71.51	7.17	3.35
10g, D-395	$C_{23}H_{25}NOS$ HCl $0.1H_2O$	68.76	6.57	3.49	68.58	6.75	3.49
10h, D-421	$C_{23}H_{25}NO_2$ HCl $0.3H_2O$	70.96	6.89	3.60	70.91	6.87	3.63
10i, D-423	$C_{23}H_{26}N_2O$ HCl $0.3H_2O$	71.14	7.16	7.21	71.19	7.38	7.03
10j, D-411	$C_{26}H_{29}NO_2$ HCl $0.3H_2O$	72.73	7.18	3.26	72.71	7.19	3.37