Structurally constrained hybrid derivatives containing octahydrobenzo[*g* or *f*]quinoline moieties for dopamine D2 and D3 receptors: Binding characterization at D2/D3 receptors and elucidation of a pharmacophore model

Dennis A. Brown[a], Prashant S. Kharkar[a], Ingrid Parrington[b], Maarten E.A. Reith[b], Aloke K. Dutta[a*]

Elemental analysis of final targets:

Compound	Calculated			Found		
	C	H	N	C	H	N
2	67.94	8.95	4.61	67.66	9.25	4.88
1	64.46	7.51	4.18	64.86	7.78	4.40
9 0.5 H_2O	58.88	7.31	8.24	59.03	7.45	8.12
24a	64.65	7.60	9.05	64.36	7.61	8.79
24b	55.73	6.28	7.79	55.36	6.36	7.47
35a H_2O	62.23	7.73	8.71	62.00	7.60	8.60
35b	56.30	6.24	7.88	56.17	6.28	7.30
35c	61.30	7.62	7.94	61.64	7.73	7.80
(±)-(**8**) 0.5 H_2O	64.65	7.60	9.05	64.31	7.70	8.90
(-)-(**8**)	64.65	7.60	9.05	64.32	7.69	8.91
(+)-(**8**)	64.65	7.60	9.05	64.23	7.69	8.82
43a	59.30	7.28	8.29	59.34	7.51	7.99
43b	56.30	6.24	7.88	56.60	6.59	8.35

Resolution of *trans*- 7-Methoxy-1, 2,3,4,4a, 5,6,10b-octahydro-benzo[f]quinoline (36).

  This amine was resolved following the procedure described by Wikstrom *et al*. Thionyl chloride (8 ml), (*R*)-(-)-α-methoxyphenyl acetic (842 mg, 5 mmol), and dichloromethane (30 ml) were refluxed for 30 min. The mixture was cooled and the volatiles were removed, and the crude acid chloride was dissolved in 20 ml of dichloromethane. The mixture was then added to a well-stirred solution of amine **(±)-36** (1 g, 5 mmol), in dichloromethane (30ml), and 5% NaOH (60 ml). After 30 min of stirring, the phases were separated, washed once with water, dried, filtered, and concentrated to yield a mixture of diasteriomers.

(+)-(4aR, 10aR)-*trans*- 7-Methoxy-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinoline (36). The crude mixture of diasteriomers (1.7 g) obtained above was dissolved in a minimal amount of ether and the solution was allowed to stand at rt overnight. The resulting precipitate was collected washed with ether, and dried. The recovered

precipitate **39b** (300 mg) was analyzed by a normal phase analytical HPLC column (Nova-Pak Silica, 60 Å, 4 µm) (mobile phase Hex:EtOAc:isopropanol 95.5:3.75:0.75, flow rate of 1 ml/min, t_R = 4.2 min) and found to be 98.8 % pure.

Amide **39b** (550 mg, 1.5 mmol) was dissolved in dry THF (40 ml) and sodium *t*-butoxide (1.87g, 20.5 mmol), and water (185 µl, 10.5 mmol) was added with stirring at rt overnight. The mixture was then partitioned between ether and water. The organic layer was separated, dried, filtered, and concentrated. The crude residue (400 mg) was then dissolved in 30 ml of MeOH and 5 ml of 6 M HCl was added. The mixture was refluxed for 3 hrs and cooled. The residue was evaporated to dryness, and the product was converted to its HCl salt. This was then recrystallized from EtOAc/EtOH to give 166 mg (44%) of the hydrochloride salt of **(+)-36**. $[\alpha]_D$ = +97.8^o (*c* = 0.7 in MeOH) ^{1}HNMR (CDCl$_3$) (free base) δ 7.13-7.17 (t, 1H, *J* = 8 Hz), 6.90-6.92 (d, 1H, *J* = 8 Hz), 6.69-6.71 (d, 1H, *J* = 8 Hz), 3.81 (s, 3H), 3.12-3.16 (m, 1H), 2.91-2.97 (m, 1H), 2.59-2.76 (m, 2H), 2.40-2.53 (m, 3H), 1.83-1.94 (m, 3H), 1.63-1.76 (m, 2H), 1.22-1.32 (m, 1H).

(-)-(4aS, 10bS)-*trans*- 7-Methoxy-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinoline (36). The mother liquor obtained from above was concentrated and dissolved in 30 ml of CH$_2$Cl$_2$. 2 ml of this solution was injected onto a semiprep HPLC using hex: EtOAc: isopropanol (95.5:3.75:0.75) as mobile phase and a flow rate of 15 ml/min. The desired isomer eluted with a retention time of 12.5 min. Eight injections provided 370 mg of diasteriomer **39a** with an optical purity of 94%.

Amide **39a** (370 mg, 1.01 mmol) was cleaved following the procedure above to give 150 mg (58%) of the hydrochloride salt of **(-)-36**. $[\alpha]_D$ = -97.2^o (*c* = 0.73 in MeOH). ^{1}HNMR (CDCl$_3$) (free base) δ 7.12-7.16 (t, 1H, *J* = 8 Hz), 6.90-6.93 (d, 1H, *J* = 8 Hz), 6.70-6.72 (d, 1H, *J* = 8 Hz), 3.80 (s, 3H), 3.14-3.18 (m, 1H), 2.90-2.99 (m, 1H), 2.61-2.75 (m, 2H), 2.42-2.51 (m, 3H), 1.86-1.93 (m, 3H), 1.61-1.76 (m, 2H), 1.19-1.33 (m, 1H).

Synthesis of compound 9:
Scheme 1.
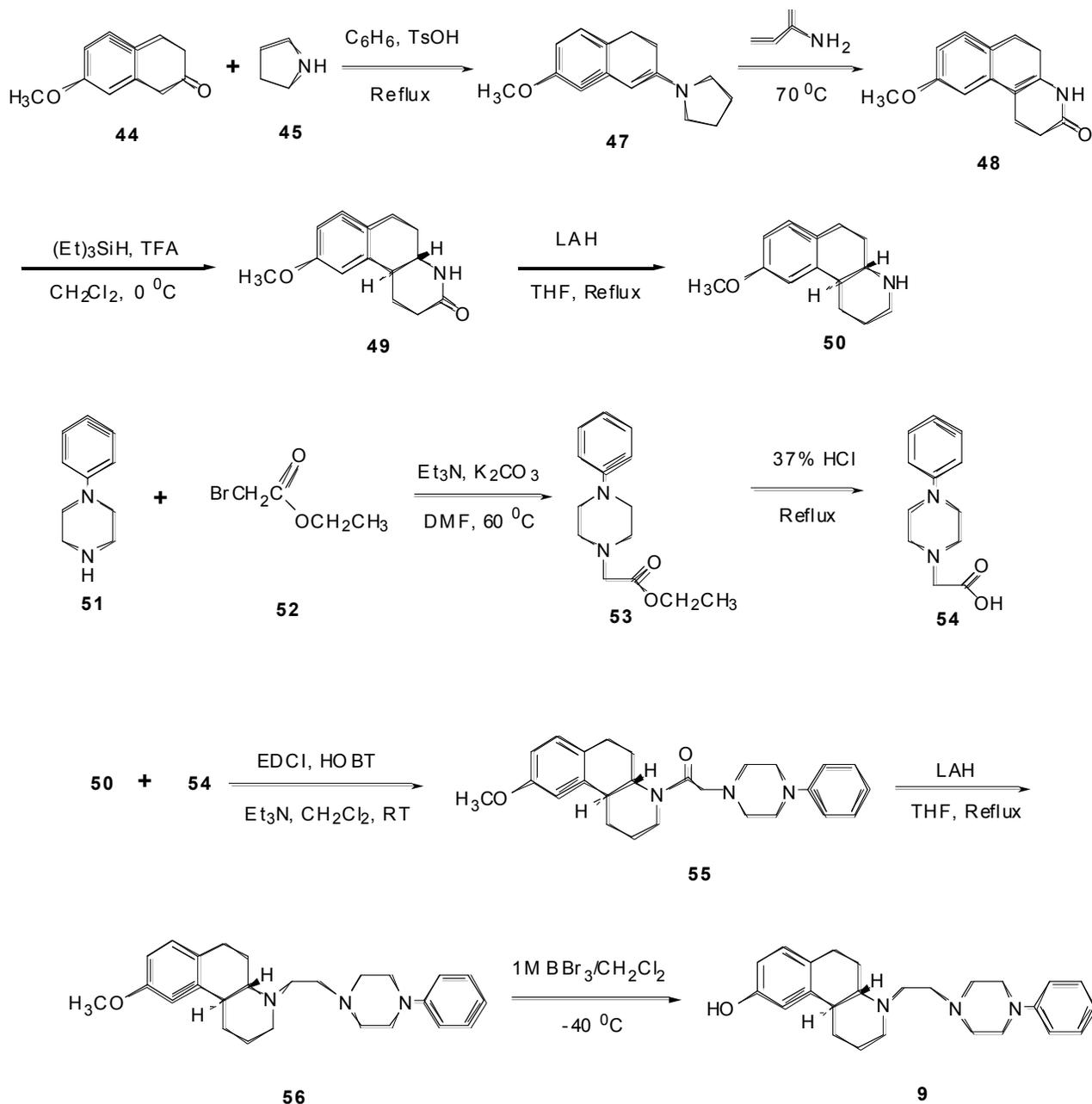
Synthesis of 9-methoxy-1,4,5,6-tetrahydrobenzo[f]quinoline-3-(2H)-one (48). To a refluxing solution of 7-methoxy-2-tetralone **44** (0.20 g, 1.13 mmol) and TsOH (0.01 g, 0.06 mmol) in benzene (40 mL) in a Dean-Stark apparatus was added a solution of pyrrolidine **45** (0.15 mL) in benzene (5 mL). After heating the reaction mixture for 2 h volatiles were distilled in a N_2 stream under reduced pressure followed by the addition of acrylamide (0.30 g, 4.22 mmol). The solution was stirred at 70 ^{0}C for 2h and H_2O (5 mL) was added and stirred for 0.5 h more. The mixture was brought to room temperature and ethyl acetate (30 mL) and water (25 mL) were added. The organic phase was separated, washed with brine and dried over $MgSO_4$. The crude product was purified by flash chromatography over a silica gel column using hexane:EtOAc (1:1) to

furnish the title compound (0.03 g, 12%). ^{1}H-NMR (400 MHz, CDCl$_3$), 2.33 (t, J=8.4 Hz, 2H), 2.63-2.73 (m, 4H), 2.84 (t, J=7.6 Hz, 2H), 3.80 (s, 3H), 6.62 (dd, J=2.4 Hz, J=8.0 Hz, 1H), 6.68 ((d, J=2.4 Hz, 1H), 6.95 (bs, 1H), 7.03 (d, J=8.4 Hz, 1H), ^{13}C (400 MHz, CDCl$_3$) 21.0, 26.5, 27.0, 30.5, 55.5, 108.5, 109.0, 109.8, 125.0, 128.0, 132.4, 135.8, 158.5, 171.2..

Synthesis of *trans*-9-methoxy-1,4,4a,5,6,10b-hexahydrobenzo[f[quinoline-3-(2H)-one (49). To a solution of **48** (0.08 g, 0.35 mmol) and Et$_3$SiH (0.45 mL, 2.8 mmol) in dry CH$_2$Cl$_2$ (10 mL) at 0 ^{0}C was added a 99% solution of TFA (0.81 mL). The reaction was stirred at room temperature overnight. The mixture was neutralized with a saturated solution of Na$_2$CO$_3$ and extrated with CH$_2$Cl$_2$ (3 x 10 mL). All organic portions were pooled and dried over MgSO$_4$. The crude product was purified by flash chromatography over a silica gel column using hexane:EtOAc (1:1) to furnish the title compound (0.06 g, 75%). ^{1}H-NMR (400 MHz, CDCl$_3$) 1.64-1.90 (m, 2H), 2.03-2.14 (m, 1H), 2.52-2.76 (m, 4H), 2.91 (dd, J=4.0 Hz, J=8.8 Hz, 2H), 3.36 (dt, J=3.2 Hz, J=11.2 Hz, 1H), 3.79 (s, 3H), 6.75 (dd, J=2.0 Hz, J=8.0 Hz, 1H), 6.83 (d, J=2.0 Hz, 1H), 6.99 (bs, 1H), 7.04 (d, J=8.4 Hz). ^{13}C (400 MHz, CDCl$_3$) 25.3, 27.6, 30.3, 31.6, 41.1, 55.4, 55.5, 111.4, 112.4, 127.9, 130.2, 137.5, 158.3, 172.7.

Synthesis of *trans*-9-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[f[quinoline (50). A solution of **49** (0.03 g, 0.14 mmol) in dry THF (5 mL) was added dropwise into a suspension of lithium aluminum hydride (0.03 g, 0.87 mmol) in dry THF (10 mL) under N$_2$ at 0 ^{0}C. The reaction mixture was refluxed for 5 h and was brought to room temperature followed by cooling in an ice water bath. A 10% NaOH solution (10 mL) was added dropwise into the cold solution. The mixture was filtered, dried over Na$_2$SO$_4$ and evaporated to produce **50** (0.03 g, 98%). ^{1}H-NMR (400 MHz, CDCl$_3$) 1.20-1.36 (m, 1H), 1.60-1.90 (m, 5H), 2.34-2.54 (m, 3H), 2.66-2.77 (m, 1H), 2.78-2.96 (m, 2H), 3.10-3.18 (m, 1H), 3.77 (s, 3H), 6.70 (dd, J=2.8 Hz, J=8.8 Hz, 1H), 6.81 (d, J=2.0 Hz, 1H), 6.99 (d, J=8.0 Hz, 1H). ^{13}C (400 MHz, CDCl$_3$) 27.2, 28.3, 28.5, 29.6, 31.1, 43.8, 47.1, 55.5, 59.5, 111.2, 111.5, 111.6, 128.6, 129.8, 140.5, 158.1.

Synthesis of ethyl 2-(4-phenyl-piperarazin-1-yl) acetate (53). To a suspension of K$_2$CO$_3$ (7.2 g, 52.17 mmol) and Et$_3$N (1.83 mL, 13.15 mmol) in DMF (20 mL) was added 1-phenylpiperazine **51** (1.0 mL, 6.58 mmol) and the mixture was stirred for 20 min followed by the addition of ethyl bromoacetate (1.46 mL, 13.16 mmol) dropwise. The suspension was stirred at 60 ^{0}C under N$_2$ for 4h. Water (25 mL) was added and the mixture was extracted with diethyl ether (2 x 25 mL). All organic portions were pooled, washed with brine (2 x 20 mL) dried over MgSO$_4$ and evaporated under vacuum to give the crude product, which was purified by flash chromatography over a silica gel column using hexane:EtOAc (1:1) to furnish **53** (1.16 g, 71%). ^{1}H-NMR (400 MHz, CDCl$_3$) 1.29 (t, J=7.6 Hz, 3H), 2.75 (t, J=4.8 Hz, 4H), 3.26 (t, J=4.8 Hz, 4H), 3.28 (s, 2H), 4.21 (q, J=7.2 Hz, 2H), 6.86 (t, J=6.4 Hz, 1H), 6.94 (d, J=8.0 Hz, 2H), 7.23-7.30 (m, 2H).

Synthesis of *trans*-9-methoxy-1,2,3,4,4a,5,6,10b-octahydro-N-[2'-(4-phenyl-piperazin-1-yl)-ethyl-1'-one]-benzo[f[quinoline (55). A solution of **53** (0.20 g, 0.80 mmol) in 37 % HCl (2 mL) was heated at 75 ^{0}C for 6h. Solvent was evaporated under

vacuum to produce compound **54** (0.17 g, 99%), which was used without further purification. To a solution of **54** (0.18g, 0.82 mmol) in CH_2Cl_2 (20 mL) and Et_3N (5 mL) was added 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (0.23 g, 1.20 mmol) followed by 1-hydroxybenzotriazole (0.19g, 1.40 mmol). The solution was stirred at room temperature for 2h, and into it was added a solution of **50** (0.09g, 0.40 mmol) in CH_2Cl_2. The solution was stirred at room temperature for 20 h. The organic solution was washed with saturated Na_2CO_3, brine and dried over $MgSO_4$. The crude product was purified by flash chromatography using hexane:EtOAc (1:4) to give **55** (0.11 g, 33%). ^{1}H-NMR (400 MHz, CDCl$_3$) 1.33-1.46 (m, 1H), 1.72-1.86 (m, 1H), 1.90-2.02 (m, 1H), 2.12-2.27 (m, 1H), 2.32-2.40 (m, 1H), 2.41-2.50 (m, 1H), 2.62-2.76 (m, 4H), 2.84-2.98 (m, 3H), 3.16-3.30 (m, 6H), 3.44 (dt, J=3.20 Hz, J=11.20 Hz, 1H), 3.48-3.59 (m, 1H), 3.60-3.70 (m, 1H), 3.77 (s, 3H), 6.70 (dd, J=2.8 Hz, J=8.4 Hz, 1H), 6.75 (d, J=2.0 Hz, 1H), 6.85 (t, 7.2 Hz, 1H), 6.92 (d, J=8.0 Hz, 2H), 7.01 (d, J=8.4 Hz, 1H), 7.26 (t, J=8.0 Hz, 2H). ^{13}C (400 MHz, CDCl$_3$) 25.0, 25.8, 26.5, 27.9, 29.0, 39.4, 49.3, 53.6, 55.5, 61.3, 62.4, 68.2, 111.3, 111.6, 116.3, 119.9, 128.7, 129.3, 129.8, 140.5, 151.5, 158.1, 169.2.

Synthesis of *trans*-9-methoxy-1,2,3,4,4a,5,6,10b-octahydro-N-[2'-(4-phenyl-piperazin-1-yl)-ethyl]-benzo[f[quinoline (56). A solution of **55** (0.11 g, 0.26 mmol) in dry THF (10 mL) was added dropwise into a suspension of lithium aluminum hydride (0.10 g, 2.63 mmol) in dry THF (10 mL) under N_2 at 0 ^{0}C. The reaction mixture was refluxed for 3 h and was brought to room temperature followed by cooling in an ice water bath. A 10% NaOH solution (10 mL) was added dropwise into the cold solution. The mixture was filtered, dried over Na_2SO_4 and evaporated under vacuum to produce **56** (0.01 g, 91%). 1.20-1.36 (m, 1H), 1.54-1.70 (m, 1H), 1.74-1.88 (m, 2H), 2.14-2.50 (m, 4H), 2.52-2.78 (m, 8H), 2.78-2.92 (m, 2H), 2.96-3.12 (m, 2H), 3.16-3.28 (t, J=4.8 Hz, 4H), 3.78 (s, 3H), 6.70 (dd, J=2.8 Hz, J=8.4 Hz, 1H), 6.80-6.90 (m, 2H), 6.90-6.96 (d, J=8.0 Hz, 2H), 7.00 (d, J=8.4 Hz, 1H), 7.22-7.30 (m, 2H). ^{13}C (400 MHz, CDCl$_3$) 25.6, 27.7, 28.5, 29.7, 42.5, 49.3, 50.4, 54.0, 54.2, 55.5, 55.7, 64.2, 111.5, 111.6, 116.3, 119.9, 128.6, 129.3, 129.4, 140.9, 151.5, 158.1.

Synthesis of *trans*-9-ol-1,2,3,4,4a,5,6,10b-octahydro-N-[2'-(4-phenyl-piperazin-1-yl)-ethyl]-benzo[f[quinoline (9). Borontribromide (0.5 mL, 1M solution in CH_2Cl_2) was added to a solution of **56** (0.10g, 0.25 mmol) in anhydrous CH_2Cl_2 (10 mL) at -40 ^{0}C under N_2. The reaction mixture was stirred at -40 ^{0}C for 2 h and then at room temperature overnight. The reaction was quenched by the addition of saturated NaHCO$_3$ solution and the mixture was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, evaporated under vacuum, and the crude product was purified by flash chromatography EtOAc:MeOH:Et$_3$N (95:4:1) to afford compound **47** (0.04 g, 37%). ^{1}H-NMR (400 MHz, CDCl$_3$) 1.14-1.30 (m, 1H), 1.54-1.69 (m, 1H), 1.70-1.86 (m, 2H), 2.16-2.29 (m, 2H), 2.29-2.44 (m, 2H), 2.50-2.86 (m, 10H), 2.98-3.14 (m, 2H), 3.14-3.28 (m, 4H), 6.54-6.62 (dd, J=2.0 Hz, J=8.0 Hz, 1H), 6.70 (d, J=1,2 Hz, 1H), 6.82-6.96 (m, 4H), 7.20-7.30 (t, J=8.0 Hz, 2H). ^{13}C (400 MHz, CDCl$_3$) 25.1, 27.4, 28.5, 29.6, 41.9, 49.2, 49.9, 53.9, 54.0, 55.3, 64.3, 113.0, 113.7, 116.4, 120.1, 127.6, 129.4, 129.5, 140.7, 151.4, 154.7. Free base was converted into its HCl salt. Anal. ($C_{25}H_{33}N_3$·3HCl·0.5 H_2O).

1H NMR study with N-benzyl derivatives

Scheme 2^a

(±)-21

a →

(±)-57

(±)-32

a →

(±)-58
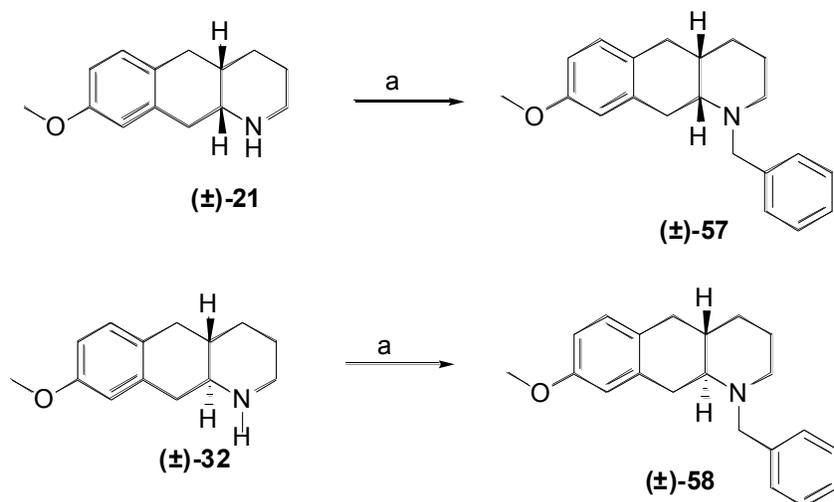
^aReagents and conditions: (a) benzyl bromide, K_2CO_3, CH_3CN, reflux

Synthesis of (±)-*cis*-1-Benzyl-8-methoxy-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-(57). Amine **(±)-(21)** (50 mg, 0.230 mmol), benzyl bromide (42 mg, 0.230 mmol), K_2CO_3 (64 mg, 0.461 mmol), and acetonitrile (20 ml) were refluxed for 1 hr, at which time the reaction mixture was cooled, filtered, and concentrated. The crude residue was then portioned between water and ethyl acetate. The organic layer was separated, dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (90% EtOAc/ 10% MeOH) to yield 61 mg (84 %) of the titled product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33-1.45 (m, 2H), 1.60-1.66 (m, 2H), 2.17-2.20 (m, 1H), 2.50-2.51 (m, 1H), 2.54-2.58 (m, 1H), 2.61-6.62 (m, 1H), 2.65-2.66 (m, 1H), 2.68-2.72 (q, 2H, J = 3 Hz, J = 12 Hz), 2.86-2.91 (m, 1H), 3.07-3.15 (m, 2H), 3.64-3.74 (q, 2H N-benzyl, J = 13.6 Hz, J = 40 Hz), 3.76 (s, 3H), 6.59 (m, 1H), 6.65-6.68 (m, 1H), 6.94-6.96 (d, 1H, J = 8 Hz), 7.19-7.33 (m, 5H).

Synthesis of (±)-*trans*-1-Benzyl-8-methoxy-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-(58). Amine **(±)-(32)** (50 mg, 0.230 mmol), benzyl bromide (42 mg, 0.230 mmol), K_2CO_3 (64 mg, 0.461 mmol), and acetonitrile (20 ml) were refluxed for 1 hr, at which time the reaction mixture was cooled, filtered, and concentrated. The crude residue was then portioned between water and ethyl acetate. The organic layer was separated, dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (90% EtOAc/ 10% MeOH) to yield 61 mg (84 %) of the titled product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09-1.11 (m, 1H), 1.60-1.62 (m, 2H), 1.71-1.78 (m, 1H), 1.82-1.86 (m, 1H), 2.01-2.02 (m, 1H), 2.23-2.24 (m, 1H), 2.40-2.47 (m 1H),

2.70-2.89 (m, 3H), 3.25-4.21 (q, 2H N-benzyl, *J* = 13 Hz, *J* = 372 Hz), 3.77 (s, 3H), 6.66-6.71-m, 2H), 6.95-6.97 (d, 1H, *J* = 8Hz), 7.21-7.38 (m, 5H).

Figure 1. X-Ray Crystal Structure of Amine **21** (HBr)
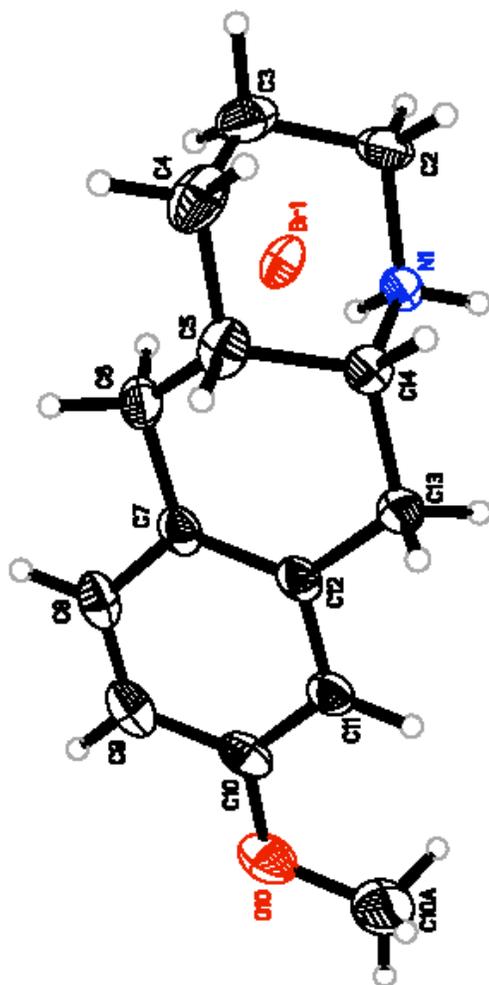
Earlier Dopamine (DA) receptor models and their significance in relation to hybrid analogues described in the present investigation

Previously reported DA-receptor models (Ref. 15-17) describe the importance of the orientation of N-substituent and the chirality at the ring carbon next to amine N. The two possible, upward or downward, orientations of N-substituent leads to proposition of "small" (tolerates alkyl groups n-propyl or smaller) and "large" (tolerates groups bigger than n-propyl) alkyl-binding sites. The downward orientation leads to placing the N-substituent in the small alkyl-binding pocket whereas upward orientation leads to occupation of large site. Also the stereochemistry of ring C next to N should be either 'S' or 'R" for trans-7-OH and trans-9-OH octahydrobenz[f]quinoline, respectively, as shown in Figure 2.

Figure 2. Influence of stereochemistry and orientation of N-substituent on DA receptor activity

4aR,10bR
Distomer

4aS,10bS
Eutomer

4aR,10bR
Eutomer

4aS,10bS
Distomer

4aS,10bS

N-n-Bu derivative - More potent
than the N-n-Pr analogue

Upwards

4aR,10bR

N-n-Bu derivative - Inactive

Downward

Wilstrom's DA-receptor
Model (Ref. 16)
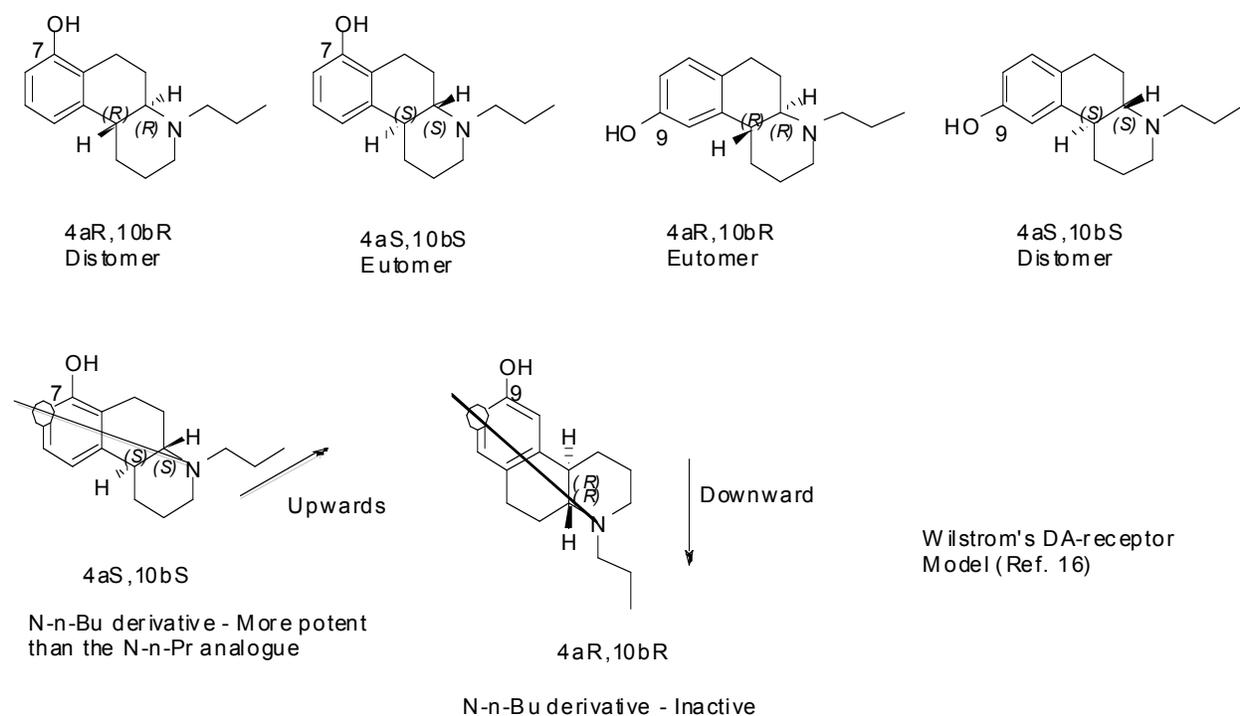
As seen from Figure 2, the hybrid analogs can be considered as bearing N-substituent bigger than n-Pr. Depending on the orientation of the N-substituent, either upward or downward, and the stereochemistry at the ring C next to N, one enatiomer exhibits higher activity than the other. Compound 8 obeys this DA-receptor model; the (4aS,10bS) enantiomer (Scheme 3) is more active than the (4aR,10bR) isomer (Table 1)