1-Ethyl-6-fluoro-1,4-dihydro-7-(1-imidazolyl)-8-(methylthio)-4-oxo-3-quinolinecarboxylic Acid (22). A solution of **20** (80 mg) in 1 N NaOH (0.4 mL) and a 15% $NaSCH_3$ aqueous solution (0.25 mL) were stirred at room temperature for 5 h. The reaction mixture was neutralized with CH_3COOH to yield a pale yellow solid, which was collected by filtration, washed with water, and dried. The solid was purified by preparative TLC ($CHCl_3$–MeOH, 10:1) and recrystallized to yield **22** as colorless needles. ^1H NMR (DMSO-d_6): δ 1.28 (3 H, t, J = 7.5 Hz, NCH_2CH_3), 2.09 (3 H, s, SCH_3), 5.11 (2 H, q, J = 7.5 Hz, NCH_2CH_3), 7.19 (1 H, br s, imidazole H), 7.52 (1 H, br s, imidazole H), 7.97 (1 H, br s, imidazole H), 8.28 (1 H, d, J = 10 Hz, C_5-H), 9.04 (1 H, s, C_2-H), 14.27 (1 H, br s, COOH). MS: m/e 347 (M^+).

1-Ethyl-8-fluoro-1,4-dihydro-7-(1-imidazolyl)-6-(dimethylamino)-4-oxo-3-quinolinecarboxylic Acid (23). A mixture of **20** (80 mg), dimethylamine hydrochloride (62 mg), and 1 N NaOH (1.2 mL) was heated at 150 °C for 6 h in a sealed tube. The reaction mixture was cooled, water was added, and the mixture was neutralized with acetic acid. The precipitated red solid was collected by filtration, purified by preparative TLC ($CHCl_3$–MeOH, 10:1), and recrystallized to yield **23** as pale yellow needles. ^1H NMR (DMSO-d_6): δ 1.46 (3 H, dt, J = 1.0 and 7.0 Hz, NCH_2CH_3), 4.40–4.80 (2 H, m, NCH_2CH_3), 7.20 (1 H, br s, imidazole H), 7.48 (1 H, br s, imidazole H), 7.68 (1 H, d, J = 2 Hz, C_5-H), 7.96 (1 H, br s, imidazole H), 8.90 (1 H, s, C_2-H), 14.75 (1 H, br s, COOH). MS: m/e 344 (M^+).

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Registry No. **4**, 68077-26-9; **5**, 109687-07-2; **6**, 109687-08-3; **7**, 109687-10-7; „ 109719-25-7; **9**, 109687-11-8; **10**, 109687-09-4; **11**, 109687-12-9; **12**, 75001-63-7; **13**, 91524-15-1; **14**, 109687-14-1; **15**, 109687-13-0; **16**, 109687-15-2; **17**, 75338-42-0; **18**, 109687-16-3; **19**, 109687-17-4; **20**, 93242-59-2; **21**, 109687-29-8; **22**, 109687-30-1; **23**, 109687-31-2; **24**, 109687-18-5; **25**, 93242-60-5; **26**, 109687-19-6; **27**, 109687-20-9; **28**, 109687-21-0; **29**, 109687-22-1; **30**, 109687-23-2; **31**, 109687-24-3; **32**, 109687-25-4; **33**, 109687-26-5; **34**, 109687-27-6; **35**, 109687-28-7; 2-methyl-1*H*-imidazole, 693-98-1; 4-methyl-1*H*-imidazole, 822-36-6; 4-nitro-1*H*-imidazole, 3034-38-6; 4-bromo-1*H*-imidazole, 2302-25-2; 4-imidazolyl-carboxylic acid methyl ester, 17325-26-7; *N,N*-dimethyl-4-carbamyl-1*H*-imidazole, 56486-26-1; 4-carboxaldehyde-1*H*-imidazole, 3034-50-2; 1*H*-imidazol-4-yl-methanol, 822-55-9; 1*H*-imidazol-4-yl-*N,N*-dimethylmethanamine, 104926-40-1; 1*H*-imidazole-4-carboxaldehyde oxime, 57090-90-1; benzimidazol-1-yl, 51-17-2; 4,5,6,7-tetrahydrobenzimidazol-1-yl, 3752-24-7; 2,5-dimethoxy-tetrahydrofuran, 696-59-3; imidazole, 288-32-4; pyrazole, 288-13-1; dimethylformamide azine, 16114-05-9.

N-Substituted 1,2,3,4,4a,5,6,10b-Octahydrobenzo[*f*]quinolines and 3-Phenylpiperidines: Effects on Central Dopamine and σ Receptors

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N-Substituted analogues of *trans*-7- and *trans*-9-hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (*trans*-7- and *trans*-9-OH-OHBQ) were tested for dopamine (DA) D2 receptor affinity by using in vitro [^3H]spiperone and in vivo 5,6-di-*n*-Pr-ADTN binding assays. Potencies at central pre- (auto-) and postsynaptic DA receptors were determined by a biochemical and a behavioral method, respectively. Corresponding data were included for analogous, resolved 3-(3-hydroxyphenyl)piperidines and a few other substituted, racemic 3-phenylpiperidines. Beside the central dopaminergic effects of these compounds, previously reported σ receptor affinity data [[^3H]-(+)-3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine; [^3H]-(+)-3-PPP] were also taken into account for a comparison of the structure–activity/affinity relationships of these compounds at these two receptor types. Larger N-substituents in both phenylpiperidines and OHBQs increase both pre- and postsynaptic dopaminergic activity. An *n*-propyl group gives high dopaminergic efficacy at both receptor sites (pre- and postsynaptic) in all series. However, even higher dopaminergic potency is observed for *trans*-7-OH-OHBQs and (*S*)-3-(3-hydroxyphenyl)piperidines with N-substituents larger than *n*-propyl. In contrast, *trans*-4-*n*-Bu-9-OH-OHBQ is inactive, and (*R*)-3-(3-hydroxyphenyl)-*N*-*n*-butylpiperidine is less active at central DA receptors than its corresponding *n*-propyl analogue. This implies interesting differences in N-substituent sensitivity for the different classes of compounds with respect to the direction of their respective N-substituents at the drug–receptor interaction. The stereochemical and steric demands for σ receptor affinity are much less stringent. The general trend is that, up to a certain size, the more lipophilic the N-substituent, the higher the affinity for σ receptor sites.

Recently presented developments[1-3] of current dopamine (DA) receptor concepts[4-6] emphasize two different main directions, referred to as upward and downward in Figure 1, of the N-substituents of dopaminergic agonists. This new concept was developed on the basis of a study of resolved *trans*-7- and *trans*-9-hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines (*trans*-7- and *trans*-9-OH-OHBQ).[1,2] The intimate relationship between central pre- (auto-) and postsynaptic DA receptors has recently been demonstrated by Carlsson, using (*S*)-3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine ((*S*)-3-PPP, (*S*)-**4**) as the investigation tool.[7] *trans*-(4a*S*,10b*S*)-7-OH-OHBQ ((4a*S*,10b*S*)-HW165; (4a*S*,10b*S*)-**11**) has been demon-

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‡Department of Pharmacology, University of Göteborg.
§The Johns Hopkins School of Medicine.

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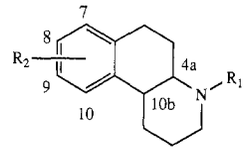
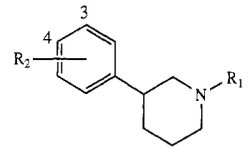
Table I. Physical Data for *cis*- or *trans*-OH-OHBQ[a]



compd	cis/trans	R_1	R_2	prepn method	yield,[b] %	mp, °C (recryst solvent)
11	trans	H	7-OH	*c*	38	320–330 dec (MeOH/ether)
(*R*,*R*)**11**[d]	trans	H	7-OH	*c*	76	320–330 dec (EtOH)
(*S*,*S*)-**11**[d]	trans	H	7-OH	*c*	91	320-330 dec (EtOH)
12	trans	Me	7-OH	A	52	230–234 (CH_3CN/ether)
13	trans	Et	7-OH	C	55	300-302 (MeOH/ether)
16	trans	Pheth	7-OH	B	38	287-288 (MeOH/ether)
18	trans	H	9-OH		75	265-266 (EtOH/ether)
19	trans	Me	9-OH	A	25	240-250 dec (MeOH/ether)
20	trans	Et	9-OH	A	36	302-307 (MeOH/ether)
22	trans	*n*-Bu	9-OMe	C	75	184-188 (EtOH/ether)
25	trans	Bn	9-OH	*e*	87	290-295 (MeOH/ether)
26	trans	Pheth	9-OMe	B	44	248-252[f]
27	trans	Pheth	9-OH	B	29	289–293 (MeOH/ether)
28	cis	H	7-OH	*e*	64	325-330 (MeOH/ether)
31	cis	H	9-OH	*c*	78	233-234 (MeOH/ether)
33	cis	*n*-Bu	9-OH	C	10	224-226 (MeOH)

[a] The compounds presented here are racemates unless indicated. [b] Yield given for the last step. [c] The synthesis has been described previously (cf. ref 1, 2, and 12). [d] *R*,*R* and *S*,*S* means 4a*R*,10b*R* and 4a*S*,10b*S*, respectively. [e] The synthesis of the methoxy precursor of this product has been described in ref 12. [f] (EtOH/ether/petroleum ether).

Table II. Pharmacological Data for 3-Phenylpiperidines



			binding			DOPA acc:[a]	motor activity[a]	
			in vitro: IC_{50}, nM		in vivo:[b] %	ED_{50}, nmol/kg	dose,	
compd	R_1	R_2	σ	D_2	of contr, D2	limbic	μmol/kg	acc counts, 30 min
(*R*)-**1**	H	3-OH	4570	435		17000	265	47 ± 7*
(*R*)-**2**	Me	3-OH	373	4120		2200	133	88 ± 22*
(*R*)-**3**	Et	3-OH	111	3490		2400	133	141 ± 28*
(*R*)-**4**	*n*-Pr	3-OH	32	1710	84 ± 10*	1000	13	78 ± 14*
(*R*)-**5**	*i*-Pr	3-OH	247	12150		6700	53	49 ± 29*
(*R*)-**6**	*n*-Bu	3-OH	9	2670	74 ± 1*	9200	14	180 ± 23*
(*R*)-**7**	Pheth	3-OH	8	1240		9200	14	26 ± 8*
(*S*)-**1**	H	3-OH	15600	1750		I[c]	200	I[d]
(*S*)-**2**	Me	3-OH	1910	1950		6800	100	36 ± 8*
(*S*)-**3**	Et	3-OH	1030	1320		6400	100	I
(*S*)-**4**	*n*-Pr	3-OH	165	420	33 ± 3*	800	213	12 ± 2 ns
(*S*)-**5**	*i*-Pr	3-OH	208	355		370	3.3	38 ± 8*
(*S*)-**6**	*n*-Bu	3-OH	31	275	43 ± 13*	860	53	63 ± 4*
(*S*)-**7**	Pheth	3-OH	16	44		170	7	71 ± 12*
8	*n*-Pr	3-CF_3	17	786		I		
9	*n*-Pr	3-F	49	8055		I		
10	*n*-Pr	4-OH	276	13000		I		

[a] Data taken from ref 9 and 13. [b] Doses of the test compounds, used in the in vivo binding experiments, were as follows: compounds(*R*)-**4**, (*R*)-**6**, (*S*)-**4**, and (*S*)-**6**, 53.3 μmol/kg. [c] I means inactive concerning DOPA accumulation at doses <50 μmol/kg. [d] I in this column means that control values (4 ± 2) were registered at the dose given.

strated to be a centrally acting DA receptor agonist with presynaptic selectivity,[8] while its *n*-Pr analogue is nonselective; i.e., it potently stimulates both pre- and postsynaptic DA receptors. Consequently, we decided to study the dependence of the size of the *N*-alkyl group with respect to dopaminergic affinity and potency for both the upward (*trans*-7-OH-OHBQs) and the downward (*trans*-9-OH-OHBQs) direction. Similar biological data are available for N-alkylated (*R*)- and (*S*)-3-(3-hydroxyphenyl)piperidines,[9] and we have included these two series of compounds in the present paper. In vitro and in vivo binding affinities for DA D2 receptors were determined for most of the test compounds with [^{3}H]spiperone and nonradiolabeled 5,6-di-*n*-Pr-ADTN,[10] respectively.

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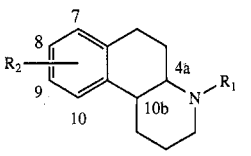
Table III. Pharmacological Data for *trans*-OHBQs and *cis*-OHBQs



compd	R_1	R_2	binding: in vitro: IC_{50}, nM: σ	binding: in vitro: IC_{50}, nM: D2	binding: in vivo:[b] % of contr, D2	dopa acc:[a] ED_{50}, nmol/kg limbic	motor activity[a]: dose, μmol/kg	motor activity[a]: acc counts, 30 min
				trans-OHBQs				
rac-11[c]	H	7-OH			58 ± 3	1000	106	10 ± 5 ns
(*R,R*)-11[d]	H	7-OH	2370	1550		50000		
(*S,S*)-11[d]	H	7-OH	3610	92		620		
rac-12	Me	7-OH	610	114	33 ± 5	630	100	40 ± 16*
rac-13	Et	7-OH	236	102	54 ± 8	170	3.1	19 ± 8*
rac-14	*n*-Pr	7-OH			63 ± 11		3.1	163 ± 28*
(*R,R*)-14[d]	*n*-Pr	7-OH	48	160		320	3.1	59 ± 11*
(*S,S*)-14[d]	*n*-Pr	7-OH	438	34		14	3.1	78 ± 11*
rac-15	*n*-Bu	7-OH	23	38	57 ± 4	80	3.1	196 ± 27*
rac-16	Pheth	7-OH	65	6	67 ± 9	43	25	143 ± 58*
rac-17	*n*-Pr	8-OH	10	730		540		
rac-18	H	9-OH	1940	895	90 ± 7	25000	106	10 ± 4 ns
rac-19	Me	9-OH	221	265	57 ± 7	400	106	60 ± 9*
rac-20	Et	9-OH	70	110	57 ± 9	17	1.06	47 ± 10*
rac-21	*n*-Pr	9-OH	19	101	68 ± 10	8	1.06	188 ± 23*
(*R,R*)-21[d]	*n*-Pr	9-OH	21	25		4	1.06	155 ± 32*
(*S,S*)-21[d]	*n*-Pr	9-OH	520			250	10.6	28 ± 2*
rac-22	*n*-Bu	9-OMe	5	3840		I[e]	50	135 ± 66*
rac-23	*n*-Bu	9-OH	10	2990		I	50	75 ± 16*[f]
rac-24	Bn	9-OMe	5	5520		I	50	21 ± 10*
rac-25	Bn	9-OH	11	3440		I	50	78 ± 51*
rac-26	Pheth	9-OMe	14	435				
rac-27	Pheth	9-OH	27	990		I	25	72 ± 17*
				cis-OHBQs				
rac-28	H	7-OH	14900	7500		I		
(*R,S*)-29[d]	*n*-Pr	7-OH	416	2100		I		
(*S,R*)-29[d]	*n*-Pr	7-OH	197	>100000		I		
rac-30	*n*-Pr	8-OH	40	13000		I		
rac-31	H	9-OH	11600	30400		I		
rac-32	*n*-Pr	9-OH	66	6700		I		
rac-33	*n*-Bu	9-OH	35	10400		I		*g*
rac-34	*n*-Pr	10-OH	1930	61800		I		

[a] Data on previously published compounds were taken from ref 2 and 3. [b] Doses of the test compounds, used in the in vivo binding experiments, were as follows: compounds *rac*-11, *rac*-12, *rac*-13, *rac*-14, and *rac*-15, 30 μmol/kg; *rac*-16, *rac*-18, *rac*-19, *rac*-20, and *rac*-21, 34.5 μmol/kg. [c] rac means racemic mixture. [d] *R,R*, *S,S*, *R,S*, and *S,R* means 4a*R*,10*R*, 4a*S*,10b*S*, 4a*R*,10b*S*, and 4a*S*,10b*R*, respectively. [e] I means inactive. No effects on DOPA accumulation were seen at doses <50 μmol/kg. [f] This effect was not blocked by haloperidol (0.5 mg/kg ip 30 min before administration of the test compound), but gave accumulated counts (54 ± 10) not significantly different from the result obtained without haloperidol pretreatment. [g] The test animals died within 2 and 5 min when given the doses 50 and 10 μmol/kg, respectively. These animals were not subject to biochemical analysis.

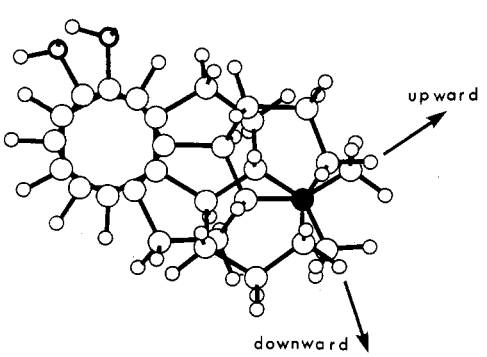


Figure 1. Structural fit of *trans*-(4a*S*,10b*S*)-7- and *trans*-4a*R*,10b*R*)-9-OH-4-Me-OHBQ. The aromatic carbon atoms were fitted in a least-squares fit, keeping the nitrogens fixed to the same point and the aromatic rings parallel in the *xy* plane. Nitrogens have been tinted black. This figure was plotted from the CHEMX graphics system with a Calcomp plotter.

σ receptor affinity data for all of these compounds are available[11] and are included here for a comparison between the structure–activity/affinity relationships for these compounds at these two receptor sites.

Physical data for the new compounds synthesized and pharmacological data for all compounds are presented in Tables I–III.

Chemistry

The new OHBQs were synthesized from *trans*-7- or *trans*-9-OMe-OHBQ[12] via N-alkylation with the appropriate aldehyde and $NaBH_3CN$ (method A), acylation with the appropriate acyl chloride and reduction with $LiAlH_4$ (method B), or reflux in benzene in the presence of an organic acid/$NaBH_4$ complex (method C). The phenols were achieved through ether cleavage with 48% aqueous HBr under N_2.

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3-[3-(Trifluoromethyl)phenyl]-*N*-*n*-propylpiperidine was synthesized by coupling the Grignard reagent of 3-(trifluoromethyl)bromobenzene and 3-bromopyridine according to a method previously used for the preparation of analogous 3-phenylpiperidines.[13]

Pharmacology

Biochemistry. The in vivo biochemical test utilizes the well-established phenomenon of receptor-mediated feedback inhibition of the presynaptic DA neuron.[14] The synthesis rate of DA and norepinephrine (NE) are inhibited by agonists (and activated by antagonists) at dopaminergic and α-adrenergic receptors, respectively. Similarly, the synthesis rate of 5-HT is inhibited by 5-HT receptor agonists.[15,16] The DOPA accumulation, following decarboxylase inhibition by means of 3-hydroxybenzylhydrazine (NSD 1015), was used as a measure of the DA synthesis rate in the DA-rich areas (i.e., limbic system, corpus striatum) and the NE synthesis rate in NE-rich hemispheres (primarily cortex). 5-HTP accumulation was taken as an indicator of the 5-HT synthesis rate in each of the three brain areas.

Locomotor Activity. Postsynaptic dopaminergic effects of the test compounds were assessed by the increase in locomotor activity (with reserpine pretreatment). Motor activity recordings were carried out as previously described with the use of motility meters.[17]

Binding Studies. Methods for the determination of in vivo 5,6-di-*n*-Pr-ADTN (D2) binding and in vitro [^{3}H]spiperone (D2) and [^{3}H]-(+)-3-PPP (σ) binding are described in the Experimental Section.

Results and Discussion

D2 Receptor Affinity versus Intrinsic Efficacy. In vivo and in vitro DA receptor affinity data are not fully consistent with each other (Tables II and III). Differences in pharmacokinetic properties and in regional distribution might explain some of the discrepancies seen between these two methods. The (*R*)-3-(3-hydroxyphenyl)piperidines have, with one exception ((*R*)-**1**), consistently lower DA receptor affinities than their *S*-enantiomeric counterparts. It is well-established that (*R*)-3-PPP ((*R*)-**4**) is a postsynaptically active DA receptor agonist, while (*S*)-3-PPP ((*S*)-**4**) behaves as a partial agonist and consequently blocks the low-responding normosensitive postsynaptic DA receptors.[18] This emphasizes that the ability of an agonist to stimulate the receptor (intrinsic efficacy) is a more important factor for the agonist effects than the receptor affinity in itself.[19] This is further seen for both *trans*-7- and *trans*-9-OH-OHBQs. Racemic *trans*-7-OH-OHBQs carrying the N-substituents H (**11**), Me (**12**), and Et (**13**) have essentially similar DA receptor affinities in vivo and in vitro (Table III). However, their pre- (ED_{50} value) and postsynaptic (motor activity) dopaminergic potencies vary to a great extent (Table III). A similar trend is seen for the *trans*-9-OH-OHBQs (Table III).

To summarize the DA receptor affinity data, the major trend is that the affinity increases with the size of the N-substituent. This trend is broken for the *trans*-9-OH-OHBQs with N-substituents larger than *n*-propyl. The low DA receptor affinity of these analogues is consistent with the dramatic loss of presynaptic (ED_{50} value) dopaminergic effects of these N-substituted analogues (Table III). However, some of these analogues, i.e., those with *N*-*n*-Bu (**23**), *N*-Bn (**25**), or *N*-2-phenylethyl (*N*-Pheth; **27**) have very high σ affinity (see below). Interestingly, the 5-HT receptor agonist **34**[11] has low affinity for D2 and no affinity for σ receptor sites.

Compound 8: A Potential DA Autoreceptor Antagonist. The phenylpiperidines **8–10** are all inactive as agonists at both pre- and postsynaptic DA receptors.[13] Compound **8** has the highest D2 affinity (IC_{50} = 786 nM) of these analogues, which might indicate weak antagonistic effects. Indeed, in one single experiment (four nonpretreated rats; 100 μmol/kg, sc), compound **8** increased DOPA accumulation to 168 ± 9, 229 ± 13, and 127 ± 7% of saline controls in the limbic system, corpus striatum, and hemispheres, respectively. These preliminary data indicate that compound **8** might be a DA antagonist in the central nervous system and are in concert with the idea that the structural elements of **8** contribute to D2 affinity, but the lack of a hydrogen bond donor (e.g., OH) on the aromatic ring prevents it from having intrinsic efficacy at these receptors.[1] Very interestingly, compound **8** did not decrease locomotor activity in nonpretreated rats (100 μmol/kg, sc). On the contrary, a locomotor stimulation was observed (161 ± 11% of controls). The profile of increased DA synthesis rate and locomotor stimulation in nonpretreated rats coupled with no locomotor stimulation and no decrease in DA synthesis rate in reserpinized rats is compatible with a dopaminergic antagonist with preference for DA autoreceptors.[20,21] Compound **8** has been reported previously to potentiate stereotypies provoked by dextroamphetamine and to have anorectic effects in both mice and dogs.[22] Consequently, all pharmacological effects reported for **8** support the idea that this compound is a DA receptor antagonist with preferential action at DA autoreceptors. However, interpretation of the pharmacological data for **8** should be made with caution, since σ receptor affinity is pronounced for this compound.

σ Receptor Site Affinity. The obvious structure–affinity relationship emanating from the σ receptor binding data on these compounds is that high σ receptor affinity is achieved with compounds having the phenylpiperidine moiety (free or embedded in a ring system) with the piperidine nitrogen carrying an N-substituent of reasonable size like *n*-Bu, Bn, or Pheth.[11] Both *cis*- and *trans*-OHBQs show σ receptor affinity; however, *cis*-9-OH-OHBQs with large N-substituents produce convulsions. The reason for this is not clear, but these effects are probably not directly related to interaction with σ receptors since the corresponding trans analogues have similar σ receptor affinities but show no toxicity even at the highest dose tested (50 μmol/kg, sc).

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There are stereoselectivity trends for σ receptor affinity for the *R* enantiomers of the 3-(3-hydroxyphenyl)-piperidines and the 4a*R*,10b*R* enantiomers of the *trans*-OHBQs. However, these stereoselectivities decrease with increased potency, which is very unusual (cf. ref 23). The stereoselectivity in the OHBQ series seems not to be dependent on the position of the hydroxy group, i.e., positions 7 and 9, and this is quite contrary to the relationship between stereochemistry and OH position regarding the dopaminergic effects of these isomers (Table III). The more potent enantiomers for DA effects are *trans*-(4a*S*,10b*S*)-7-OH- and *trans*-(4a*R*,10b*R*)-9-OH-OHBQs.[1-3] These results suggest several excellent strategies for selecting high-affinity σ receptor ligands with little to no effects on DA systems. Such candidate compounds would be (*R*)-**6**, (*R*)-**9**, and **22–25**. These σ receptor ligands might be useful tools for studying agonist/antagonist relationships at this receptor site.

As seen from Table III, the σ-selective compounds **23**, **25**, and **27** all cause increased locomotor activity in reserpinized animals, a locomotor activity that is obviously unrelated to dopaminergic activation. In an attempt to further substantiate this, we monitored the increased locomotor activity produced upon administration of the methoxy derivatives **22** and **24**. Dopaminergic effects are less pronounced for methoxy, as compared to hydroxy substitution. If the locomotor activity monitored for the hydroxy compounds **23**, **25**, and **27** is directly linked to a σ agonist effect, this offers an opportunity to investigate if σ agonist effects are dependent on hydrogen bond donor functions like OH, or if a hydrogen bond acceptor function like OMe works as well. Table III shows that the methoxy analogue **22**, but not **24**, induces higher locomotor activity than its corresponding hydroxy analogue. This makes compound **22** an extremely interesting and selective tool for studying σ receptors and their possible functions.

It is more difficult to find compounds with high D2 and at the same time low σ receptor affinity (Tables II and III) in these series of compounds. The best such candidates are (*R*)-**1** and (4a*S*,10b*S*)-HW165 ((4a*S*,10b*S*)-**11**). (*S*)-3-PPP ((*S*)-**4**) has, in terms of its dopaminergic effects, clinical implications against psychotic conditions.[18] Whether the σ receptor site affinity of this compound (IC_{50} = 155 nM) reflects σ receptor agonism or antagonism is not yet clear. However, some caution is warranted for potential σ receptor effects when interpreting possible future clinical data. In this view, (4a*S*,10b*S*)-HW165 ((4a*S*,10b-*S*)-**11**) might be a better candidate as a potential, atypical antipsychotic agent, since its affinity for σ receptor sites is low.

Conclusions

In summary, the data presented in this paper show that *N*-alkyl substituent size and direction, relative to aromatic hydroxy function, in the *trans*-OHBQs has a great impact upon intrinsic efficacy of these dopaminergic compounds. The increase in pre-/postsynaptic dopaminergic potency observed is obviously more dependent upon elevations in intrinsic efficacy than in receptor affinity enhancement. However, receptor affinity is also dependent on the size of the N-substituent. The most dramatic effect is seen with N-substituents larger than *n*-Pr in the *trans*-9-OH/OMe-OHBQs, causing lower affinity. This loss of dopaminergic properties is parallel in biochemical effects as well. On the other hand, σ receptor affinity is extremely high for these analogues, making them the most interesting and selective σ ligands in this study. These compounds might prove useful for the elucidation of σ receptor function in the future.

This study also shows that caution is warranted when studying these and maybe also other classes of dopaminergic compounds with large N-substituents. Such compounds could have σ receptor effects that might disturb the pharmacological profile of the compounds studied. [^{3}H]-3-PPP binding assays, which selectively monitor σ receptor affinity, should be helpful in sorting out these problems.

Experimental Section

Chemistry. Melting points (uncorrected) were determined with a melting point microscope (Reichert Thermovar). ^{1}H NMR spectra were recorded with a Bruker 260-MHz or a Varian EM-360 instrument (Me_4Si). GC was performed with a Hewlett Packard 5830A instrument with a flame-ionization detector. A fused silica column (11 m, 0.22 mm i.d.) coated with crosslinked SE-54 (film thickness 0.3 μm, He gas, flow 40 cm/s) was used throughout. GC/MS spectra were recorded on a HP5970A Mass Selective Detector working at 70 eV and interfaced with a HP5700 gas chromatograph (fused silica as described above). High-resolution MS spectra were recorded on a ZAB-HF mass spectrometer (VG-Analytical) working in the EI mode (60 eV) with direct inlet. All spectra were in accordance with assigned structures. The elemental analyses (C, H, N) for the new substances were within 0.4% of the theoretical values. To establish homogeneity TLC was performed on fluorescent silica gel plates developed in at least two different systems. For all compounds only one spot (visualized by UV light and I_2 vapor) was obtained.

***trans*-7-Hydroxy-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (12). Method A.** *trans*-7-Methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline hydrochloride[12] (500 mg, 2.0 mmol) was dissolved in methanol (25 mL) and paraformaldehyde (10 mmol in methanol), $NaBH_3CN$ (410 mg, 6.6 mmol), and molecular sieves (3.5 g, 3 Å) were added, and the mixture was stirred with a magnetic stirrer at room temperature. Glacial acetic acid was added dropwise until wet litmus paper showed pH 5. After 6 h, concentrated HCl (10 mL) was added (caution, HCN evolves) and, after 30 min of continuous stirring, water (20 mL) was added and the acidic water phase was washed with ether. The water was basified (10% Na_2CO_3) and extracted with ether. The ether layer was dried (Na_2SO_4) and filtered and the ether was evaporated, yielding an oil (400 mg, 88%) which was used without further purification in the ether cleavage step (2 h at 125 °C in 48% aqueous HBr under N_2), yielding 200 mg (52%) of white crystals as the hydrochloride salt melting at 230–234 °C.

***trans*-7-Hydroxy-4-(2-phenylethyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (16). Method B.** *trans*-7-Methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline hydrochloride[12] (350 mg, 1.4 mmol) was added to CH_2Cl_2 (20 mL) containing Et_3N (1.0 mL). Phenylacetyl chloride (500 mg, 3.6 mmol) was dissolved in CH_2Cl_2 (10 mL) and added dropwise with stirring at room temperature. After the acid chloride had been added, the mixture was allowed to stir for another 30 min and then 10% aqueous Na_2CO_3 was added. The organic layer was separated and the aqueous phase was extracted with another portion of CH_2Cl_2 (30 mL). The organic phases were combined, dried (Na_2SO_4), and filtered, and the solvent was evapoarted, yielding a raw oil (520 mg, 111%), which was dissolved in ether (20 mL) and reduced by dropwise addition of this solution to a suspension of $LiAlH_4$ (600 mg, 18 mmol) in ether (20 mL). Workup in the usual way (0.6 mL of H_2O, 0.6 mL of 15% aqueous NaOH, and 1.8 mL of H_2O) gave an oil (400 mg, 89%), which was chromatographed on SiO_2, with methanol as eluant. The fractions containing pure product were collected, and the solvent was evaporated, yielding 280 mg (0.86 mmol, 62%) of an oil which was converted to the phenol as described under method A, yielding 130 mg (39%) of white crystals melting at 287–288 °C.

***trans*-7-Hydroxy-4-ethyl-1,2,3,4,4a,5,6,10b-Octahydrobenzo[*f*]quinoline (13). Method C.** *trans*-7-Methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline hydrochloride[12] (500 mg, 2.0 mmol) was alkylated in refluxing dry benzene (20 mL)

(23) Van de Waterbeemd, H.; El Tayar, N.; Testa, B.; Wikström, H.; Largent, B., accepted for publication in *J. Med. Chem.*

for 6 h with a $NaBH_4$ (370 mg, 10 mmol)/acetic acid (1.5 mL, 34 mmol) complex. NaOH (2 N, 10 mL) was added and the mixture was stirred for 1 h. The product was extracted with ether and the organic layer was dried (Na_2SO_4), filtered, and evaporated to yield an oil (410 mg, 85%). Part of this oil (300 mg, 1.2 mmol) was converted to the phenol as described under method A to yield 210 mg (55%) of white crystals melting at 300–302 °C.

3-[3-(Trifluoromethyl)phenyl]-*N*-*n*-propylpiperidine (8). 3-(Trifluoromethyl)bromobenzene (5.0 g, 22 mmol) was coupled with 3-bromopyridine (1.9 mL, 19 mmol) following the procedure used for synthesizing many analogous 3-phenylpiperidines.[13] Workup and distillation in vacuo gave 0.56 g (2.51 mmol) of an oil, which was dissolved in EtOH (50 mL) and concentrated HCl (5 mL) and reduced in a Parr apparatus using PtO_2 (50 mg) as the catalyst. Workup gave 0.35 g (1.5 mmol, 87% purity according to GC) of an oil, which was N-alkylated with *n*-bromopropane in CH_3CN (25 mL) in the presence of finely ground K_2CO_3 with stirring at room temperature. Ten percent aqueous Na_2CO_3 (50 mL) and ether (50 mL) were added. The organic layer was separated, dried (Na_2SO_4), and filtered, and the solvent was evaporated, yielding 0.35 g of the desired product as the base, which was converted to the hydrochloride with ethereal HCl. Recrystallization (acetone/ether) gave **8**·HCl (0.30 g, 74%) melting at 187–190 °C. High-resolution MS was performed and showed M^+ at *m/e* 271 (3.6%) ($C_{15}H_{20}NF_3$·HCl, calcd 271.155, found 271.155 ± 10) and the base peak at *m/e* 242. No impurities were detected by GC or TLC.

Pharmacology. Animals used in the biochemical and in vivo binding experiments were male rats of a Sprague–Dawley strain (ALAB, Sollentuna, Sweden), weighing 200–300 g. They were housed, five per cage, under conditions of constant temperature (about 25 °C) and humidity (about 60%) with food and water available. The animal room was maintained on a 14/10 light/dark cycle (light 5 a.m.–7 p.m.). The rats were allowed 1 week before being used for the experiments. All substances to be tested were dissolved in saline solution immediately before use, occasionally with the addition of a few drops of glacial acetic acid and/or moderate heating in order to obtain complete dissolution. Reserpine was dissolved in a few drops of glacial acetic acid and diluted with 5.5% glucose. Injection volumes were 5 or 10 mL/kg, and all solutions had neutral pH (except for solutions of reserpine).

Biochemistry. The biochemical experiments and the determinations of DOPA and 5-HTP by means of HPLC with electrochemical detection were performed as previously described.[2] Separate dose–response curves based on four to six dose levels for each substance (sc administration) and each brain area were constructed. From these curves the dose of the drug yielding a half-maximal decrease (ED_{50} value) of the DOPA level was estimated (Tables II and III).

In Vivo 5,6-Di-*n*-Pr-ADTN Binding (D2). The ligand (0.25 μmol/kg sc) was administered 60 min before the test compound (30 μmol/kg sc), which in turn was administered 40 min before the animals were sacrificed. The data given stem from the striatal tissues with cerebellum as a blank. The details of the experimental procedure have been described previously.[24] Results are presented as percent of controls in Tables II and III.

[^{3}H]Spiperone (D2) and [^{3}H]-(+)-3-PPP (σ) Binding. In membrane-homogenate binding studies, fresh rat brain tissues (male Sprague–Dawley rats, 150–250 g) were homogenized in 25 volumes of ice-cold 50 mM Tris·HCl buffer (pH 7.7 at 25 °C) and centrifuged at 45000*g* for 10 min at 4 °C. Pellets were then suspended in fresh buffer and recentrifuged. This procedure was repeated once more before membranes were finally suspended in an appropriate volume of 50 mM Tris·HCl buffer (pH 8.0 at 25 °C for σ receptor assays and pH 7.7 at 25 °C for dopamine D2 receptor assays; incubation buffer) for use in binding assays. This tissue preparation typically resulted in a tissue homogenate containing approximately 6% protein by original wet weight with the Pierce BCA protein assay reagent (Pierce Chemical Co., Rockford, IL).

For σ receptor assays, 1–3 nM [^{3}H]-(+)-3-PPP was incubated in the presence of various concentrations of unlabeled drug with the equivalent of 7.5 mg of whole brain tissue (original wet weight; approximately 450 μg of protein) for 90 min at room temperature in a final assay volume of 0.25 mL. Dopamine D2 receptor assays were performed by the incubation of 0.2–0.4 nM [^{3}H]spiperone in the presence of salts (100 mM NaCl and 3 mM $MgCl_2$) and various concentrations of unlabeled drug with the equivalent of 2 mg of striatal tissue (original wet weight; approximately 120 μg of protein) in a final assay volume of 1 mL for 15 min at 37 °C. All experiments were performed in the linear tissue and radioligand concentration ranges for binding and with an incubation time appropriate for the attainment of equilibrium. Nonspecific binding for each radioligand was estimated by inclusion of 1 μM haloperidol in the incubation and was less than 25% of the total binding in every case.

Incubations were terminated by the addition of 2.5 mL ice-cold 5 mM Tris·HCl buffer (pH 7.7 at 25 °C; wash buffer) and membranes were collected by filtration under vacuum onto glass fiber filters (Schleicher and Schuell No. 32; pretreated with 0.5% polyethylenimine). Filters were washed with two consecutive 5-mL aliquots of wash buffer. The total time taken for the filtration/washing procedure was less than 10 s. Radioactivity remaining on the filters was measured by liquid scintillation spectrometry at 60% efficiency. Drug competition binding data were analyzed with the iterative curve-fitting computer program EBDA.[25] Additional experimental details are given in ref 11.

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Registry No. **12**, 110192-32-0; **12**·HCl, 110268-04-7; **13**, 110267-92-0; **13**·HCl, 110311-32-5; **14**, 83118-49-4; **15**, 83118-50-7; **18**, 110267-93-1; **18**·HCl, 110311-31-4; **19**, 90131-01-4; **19**·HCl, 110192-25-1; **20**, 110192-33-1; **20**·HCl, 110268-05-8; **21**, 110192-34-2; **21**·HCl, 110268-06-9; **22**, 110192-35-3; **22**·HCl, 110268-07-0; **23**, 110192-36-4; **23**·HCl, 110268-08-1; **24**, 110267-94-2; **24**·HCl, 110311-33-6; **25**, 110267-95-3; **25**·HCl, 110311-34-7; **26**, 110267-96-4; **26**·HCl, 110311-35-8; **27**, 110267-97-5; **27**·HCl, 110311-36-9; **28**, 85977-24-8; **30**, 85977-25-9; **31**, 110192-37-5; **32**, 22333-08-0; **33**, 5356-09-2; (*E*)-**34**, 110192-27-3; (*Z*)-**34**, 110192-38-6; **35**, 110192-39-7; **36**, 110267-98-6; **37**, 110192-40-0; **38**, 110192-41-1; **39**, 110192-42-2; **40**, 110267-99-7; **41**, 110192-43-3; **42**, 110192-44-4; **43**, 110192-45-5; **44**, 110192-46-6; **45**, 110192-47-7; **46**, 110205-01-1; **47**, 110192-48-8; **48**, 110192-49-9; **49**, 110269-06-2; **50**, 110192-50-2; **51** (3-CF_3), 110192-51-3; **51** (2-CF_3), 110192-26-2; **52**, 110192-52-4; **53**, 110192-53-5; **54**, 110192-54-6; **55**, 110192-55-7; **56**, 110192-56-8; **57**, 110192-57-9; **58**, 110192-58-0; **59**, 110192-59-1; **60**, 110192-60-4; **61**, 110192-61-5; (*E*)-**62**, 110192-28-4; (*Z*)-**62**, 110192-62-6; (*E*)-**63**, 110192-29-5; (*Z*)-**63**, 110192-63-7; (*E*)-**64**, 110192-30-8; (*Z*)-**64**, 110192-64-8; (*E*)-**65**, 110192-31-9; (*Z*)-**65**, 110192-65-9; **66**, 110192-66-0; **67**, 110268-00-3; **68**, 110192-67-1; **69**, 110268-01-4; **70**, 110192-68-2; **71**, 110268-02-5; **72**, 110192-69-3; **73**, 110268-03-6; PNMT, 9037-68-7; cyclohexadiene, 592-57-4; 3,5-dinitrobenzoyl chloride, 24376-18-9.

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