Synthesis and Pharmacological Evaluation of 1-Phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes as Ligands for a Novel Receptor with σ-like Neuromodulatory Activity

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Certain novel 1-phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes (1-phenyl-3-aminotetralins, PATs) produced stimulation (ca. 30% above basal levels) of tyrosine hydroxylase (TH) activity at 0.1 μM concentrations in rodent brain tissue. This effect on TH was blocked by the putative σ-receptor antagonist BMY-14802, suggesting involvement of a novel neuromodulatory σ-like receptor. Within the new phenylaminotetralin series, a correlation was found between the ability to stimulate TH and the potency to compete for binding sites labeled by (±)-[^{3}H]1-phenyl-3-(*N,N*-dimethylamino)-6-chloro-7-hydroxy-1,2,3,4-tetrahydronaphthalene {[^{3}H](±)-4}. *trans*-Catechol analogs had low affinity for [^{3}H]4 sites, and although they inhibited TH activity, this effect was not blocked by known σ or dopamine antagonists. Analogs with dihydroxy substituents (catechols), as well as nitrogen substituents larger than methyl, had little affinity for [^{3}H]4 binding sites and did not significantly affect TH activity. The pharmacology of the [^{3}H]4 binding site is unique from that of any known σ or dopamine receptor, thus the effects appear to be mediated by a previously uncharacterized binding site/receptor. The site has stereoselectivity for the (1*R*,3*S*)-(−)-isomer of 1-phenyl-3-(*N,N*-dimethylamino)-1,2,3,4-tetrahydronaphthalene; this isomer is also more active at stimulating TH. Thus, certain 1-phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes appear to be selective probes of a novel receptor type that mediates σ-like neuromodulatory activity and may have pharmacotherapeutic utility in conditions in which modulation of dopamine function is important.

Introduction

Sigma (σ) receptors were first described as a subtype of the opioid receptor class; however, it was subsequently recognized that these sites displayed nonopioid pharmacology. Although the psychopharmacological effects of these receptors have been of great interest, no endogenous agonist for σ receptors has been identified yet in the mammalian central nervous system (CNS). Since the receptor(s) have not been purified or cloned, their function is controversial and poorly understood. Certain σ ligands inhibit the ability of cholinergic agonists to stimulate phosphoinositide turnover, and guanine nucleotides reportedly can regulate σ-ligand binding.[1] Such data suggest that at least some σ-receptors are in the G-protein superfamily. In fact, multiple forms of σ receptors have been suggested,[2-4] and a classification scheme proposed in which σ_1 sites bind (+)-*N*-allylnormetazocine [(+)-NANM, (1)] and (+)-pentazocine (2, Figure 1) with moderate to high affinity, whereas 1 and 2 bind with lower affinity to σ_2 sites.[3]

Despite the relative scarcity of data about the σ-binding site/receptor, it appears that the function of these receptors often may be linked to catecholamine systems. For example, high concentrations of σ-binding sites have been identified by autoradiography on cell bodies of dopamine (DA) neurons in the zona compacta of substantia nigra in mammalian midbrain.[5,6] The σ ligand 3-(hydroxyphenyl)-*N*-propylpiperidine [(+)-3-PPP] enhances electrically-stimulated release of norepinephrine from mouse vas deferens,[7] and doubles spontaneous efflux of [^{3}H]dopamine (DA) from striatal slices (the latter function not fully blocked by D_2 dopamine antagonists).[8] (+)-3-PPP also has been found to inhibit firing of nigral dopaminergic neurons in a dose-dependent manner;[9,10] this effect is blocked by the proposed σ antagonist BMY-14802, a piperazinebutanol.[10] These findings suggest that σ re-

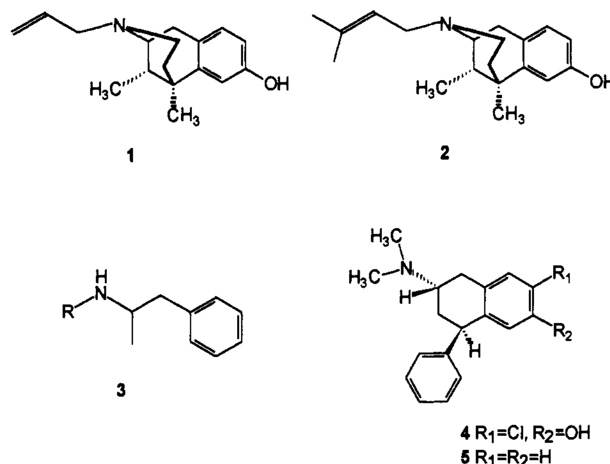

Figure 1. Structures of (+)-NANM (1), (+)-pentazocine (2), N-substituted 1-phenyl-2-aminopropane (3), and the 1-phenyl-3-aminotetralins 4 and 5.

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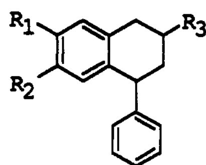
Table I. 1-Phenyl-3-substituted-1,2,3,4-tetrahydronaphthalenes



compd no.	config	R1	R2	R3	salt form	mp (°C)	% yield	solvent	formula	anal.
15	*cis*	OCH_3	OCH_3	OH		gum	36	$CH_2Cl_2ET_2O$ (7:3)[a]	$C_{18}H_{20}O_3$	
16	*cis*	H	H	OH		112–115	49	CH_2Cl_2/ET_2O (9:1)[a]	$C_{16}H_{16}O$	
17	*cis*	Cl	OCH_3	OH		55–58	40	CH_2Cl_2/ET_2O (7:3)[a]	$C_{17}H_{17}ClO_2$	
18	*trans*	H	H	$O_2CC_6H_5$		94–97	57	CCl_4[a]	$C_{18}H_{20}O_2$	
19	*trans*	OCH_3	OCH_3	O_2CH		gum	56	toluene[a]	$C_{18}H_{20}O_4$	
20	*trans*	Cl	OCH_3	$O_2CC_6H_5$		170–173	50	CCl_4/toluene[a]	$C_{24}H_{21}ClO_3$	
21	*trans*	Cl	OCH_3	OH		gum	100	not purified	$C_{17}H_{17}ClO_2$	
22	*trans*	H	H	OH		gum	56[c]	not purified	$C_{16}H_{16}O$	
23	*trans*	OCH_3	OCH_3	OH		42–43	47[c]	CH_2Cl_2/ET_2O (8:2)[a]	$C_{18}H_{20}O_3$	
24	*trans*	OCH_3	OCH_3	N_3		gum	100	not purified	$C_{18}H_{19}N_3O_2$	
25	*cis*	OCH_3	OCH_3	N_3		gum	101	not purified	$C_{18}H_{19}N_3O_2$	
26	*trans*	Cl	OCH_3	N_3		gum	99	not purified	$C_{17}H_{16}ClN_3O$	
27	*cis*	Cl	OCH_3	N_3		gum	100	not purified	$C_{17}H_{16}ClN_3O$	
28	*cis*	H	H	N_3		gum	100	not purified	$C_{16}H_{15}N_3$	
29	*trans*	H	H	N_3		gum	100	not purified	$C_{16}H_{15}N_3$	
30	*trans*	OCH_3	OCH_3	NH_2	base	gum	76	not purified	$C_{18}H_{21}NO_2$	
31	*cis*	OCH_3	OCH_3	NH_2	base	272–275	72	CH_2Cl_2/ET_2O[a]	$C_{18}H_{21}NO_2$	
32	*trans*	Cl	OCH_3	NH_2	base	gum	60	CH_2Cl_2/ET_2O (9:1)[a]	$C_{17}H_{18}ClNO$	
33	*cis*	Cl	OCH_3	NH_2	base	gum	52	CH_2Cl_2/MeOH (9:1)[a]	$C_{17}H_{18}ClNO$	
34	*cis*	H	H	NH_2	base	gum	16	CH_2Cl_2/MeOH (95:5)[a]	$C_{16}H_{17}N$	
35	*trans*	H	H	NH_2	HCl	270–272	62	EtOAc/EtOH[b]	$C_{16}H_{18}ClN$	C,H
36	*trans*	OCH_3	OCH_3	$N(CH_3)_2$	base	gum	98	not purified	$C_{20}H_{25}NO_2$	
37	*cis*	OCH_3	OCH_3	$N(CH_3)_2$	base	gum	100	not purified	$C_{20}H_{25}NO_2$	
38	*trans*	Cl	OCH_3	$N(CH_3)_2$	base	gum	110	not purified	$C_{18}H_{22}ClNO$	
39	*cis*	Cl	OCH_3	$N(CH_3)_2$	base	gum	48	CH_2Cl_2/MeOH (95:5)[a]	$C_{18}H_{22}ClNO$	
40	*cis*	H	H	$N(CH_3)_2$	HCl	105–107	47	EtOH/Et_2O[b]	$C_{18}H_{22}Cl$	C,H
5	*trans*	H	H	$N(CH_3)_2$	HCl	186–188	46	EtOH/ET_2O[b]	$C_{18}H_{22}ClN$	C,H
41	*trans*	OH	OH	$N(CH_3)_2$	HBr	245–246	64	EtOH[b]	$C_{18}H_{22}BrNO_2$	C,H
42	*cis*	OH	OH	$N(CH_3)_2$	HBr	246–248	9	*i*-PrOH[b]	$C_{18}H_{22}BrNO_2$	C,H
4	*trans*	Cl	OH	$N(CH_3)_2$	HCl	192–194	20	EtOH[b]	$C_{18}H_{21}Cl_2NO$	C,H
43	*cis*	Cl	OH	$N(CH_3)_2$	HCl	263–266	25	EtOH/Et_2O[b]	$C_{18}H_{21}Cl_2NO$	C,H
44	*trans*	OH	OH	NH_2	HBr	238–240	55	EtOAC/MeOH[b]	$C_{16}H_{18}BrNO_2$	C,H
45	*cis*	OH	OH	NH_2	HBr	286–288	49	*i*-PrOH:Et_2O[b]	$C_{16}H_{18}BrNO_2$	C,H
46	*trans*	Cl	OH	$NH(CH_3)$	base	208–210	38	$CHCl_3$/THF/NH_4OH (70:30:1)[a]	$C_{17}H_{18}ClNO$	C,H
47	*trans*	H	H	$NH(CH_3)$	base	gum	56	$CHCl_3$/THF/NH_4OH (70:30:1)[a]	$C_{17}H_{19}N$	
48	*trans*	H	H	$N(CH_3)C_3H_5$	HCl	169–172	60	EtOAC/Et_2O[b]	$C_{20}H_{24}ClN$	C,H
49	*trans*	H	H	$NH(C_3H_5)$	HCl	194–196	13	CH_2Cl_2/THF (9:1)[a]	$C_{19}H_{22}ClN$	C,H
50	*trans*	H	H	$N(C_3H_5)_2$	HCl	150–152	4	CH_2Cl_2/THF (9:1)[c]	$C_{22}H_{26}ClN$	C,H
51	*trans*	H	H	$N(C_2H_5)_2$	HCl	197–199	12	EtOAC/Et_2O[b]	$C_{20}H_{26}ClN$	C,H

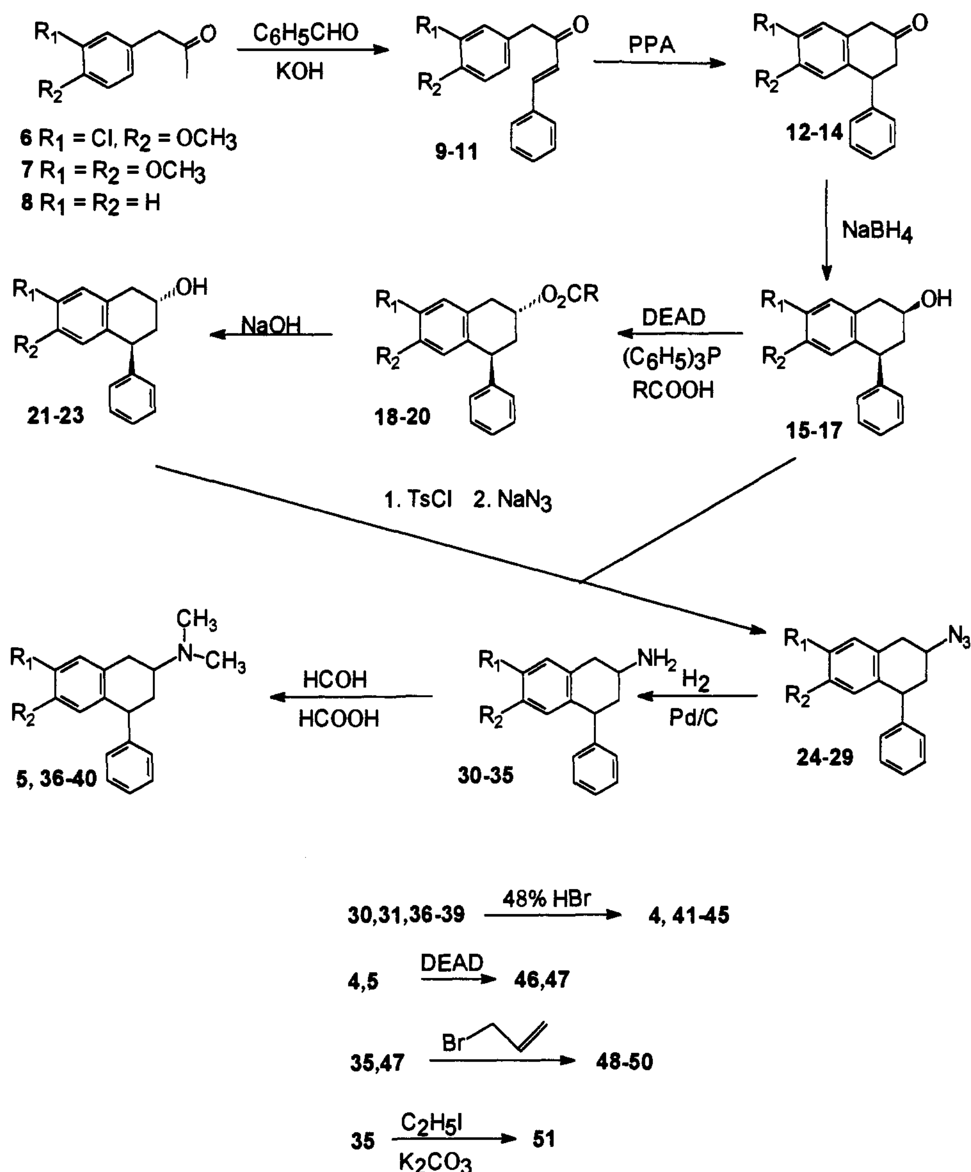
[a] Eluent used for column chromatography. [b] Solvent used for recrystallization. [c] Yield of *trans*-alcohol is based upon amount of *cis*-alcohol used in the epimerization.

ceptors may have functional effects on catecholamine neurotransmission. Consistent with this hypothesis, BMY-14802 can inhibit conditioned avoidance behavior in rats, suggesting it has antipsychotic activity.[11] Several σ ligands, including the substituted propylpiperazinecarbazole, rimcazole, have shown activity in animal models for antipsychotic efficacy,[11] and also have been promising in clinical trials with psychotic patients, showing a low incidence of extrapyramidal side effects.[12,13]

Glennon has proposed that the pharmacophore for the σ receptor is an N-substituted 1-phenyl-2-aminopropane moiety (**3**, Figure 1) or 3-aminotetralin moiety.[14] It is important to note that this hypothesis was derived solely on considerations of ligand binding without regard to functional effect.[14] The benzomorphans **1** and **2** discussed above contain this 3-aminotetralin substructure. Recently, we reported that **1** and **2** (Figure 1), at a concentration of 0.1 μM, stimulated synthesis of DA *in vitro* in rat corpus striatum tissue by approximately 25%.[15] Conversely, no stimulation of DA synthesis was caused by phencyclidine (PCP) or PCP analogs that also bind to σ sites, or μ- and κ-opiate agonists, even at concentrations as high as 10 μM. The stimulation of DA synthesis by **1** and **2** was antagonized by BMY-14802, but not naloxone, suggesting that this effect may be mediated by a type of σ receptor. We have proposed that σ-receptor-mediated effects on tyrosine hydroxylase (TH) activity (DA synthesis) may be a useful functional endpoint for studying this population of binding sites/receptors.[16a,b]

We also have reported a similar stimulatory effect on DA synthesis by racemic *trans*-1-phenyl-3-(*N*,*N*-dimethylamino)-6-chloro-7-hydroxy-1,2,3,4-tetrahydronaphthalene and racemic *trans*-1-phenyl-3-(*N*,*N*-dimethylamino)-1,2,3,4-tetrahydronaphthalene (**4** and **5**, respectively).[16a,b] Compound **4** was stimulatory at 0.1 μM, but inhibitory at 1.0 and 10 μM. This inhibition was not blocked by BMY-14802 but was abolished by pretreatment of test animals with reserpine to deplete endogenous catecholamines and by spiperone to block DA D_2-type autoreceptors. This suggested that the inhibition of TH at higher concentrations may be due to a DA-releasing effect resulting in direct D_2 autoreceptor-mediated inhibition of DA synthesis. The ring-unsubstituted analog **5** stimulated TH in a concentration-dependent manner without reserpine pretreat-

Scheme I



ment. Thus, it appears that one can separate the stimulatory effect on TH common to both 4 and 5 from the DA releasing effect produced by 4.[16a,b] As further evidence that these effects involve a novel mechanism, we have synthesized [^{3}H]4[17] and demonstrated that it labels a high affinity (~31 pM) saturable binding site with selectivity that appears to be a previously uncharacterized receptor.[16a,b] The present work reports the synthesis and pharmacological activity of additional 1-phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes (PATs) (Table I), including their effects on *in vitro* DA synthesis as measured by TH activity as well as selectivity for [^{3}H]4 binding sites versus known σ and DA receptors. Compounds such as the 1-phenyl-3-aminotetralins that act as neuromodulatory agonists at σ-like receptors may show promise as therapeutic agents for movement disorders such as Parkinson's disease and levodopa-responsive dystonia[18] by stimulating DA synthesis.

Chemical Synthesis

Initial attempts to prepare 1-phenyl-3-aminotetralins involved synthesis of the corresponding 3-tetralones 12–14 (Scheme I) with the intention of converting the tetralone to the amine by reductive amination. The procedure of Fine and Stern[19] for synthesis of the tetralones by cyclizing the corresponding 1,4-diphenyl-1-buten-3-ones 9–11 using $AlCl_3$ in CS_2 was unproductive; however, the 1,4-diphenyl-1-buten-3-ones were prepared in suitable yield by the procedure of Southwick and Sapper.[20] After attempting ring closure unsuccessfully with several acid catalysts, polyphosphoric acid (PPA) in xylenes was found to afford a rapid (minutes), quantitative conversion to those tetralones activated by electron donating groups or unsubstituted on the aromatic ring, whereas the chloro-substituted analog required approximately 3 h for complete reaction (Scheme I). The pure tetralone was then subjected to several reductive amination procedures without success. NMR and mass spectral analysis indicated that the tetralones dimerized immediately in the presence of weak bases such as the amines employed. Attempts to prepare the 1-phenyl-3-aminotetralins via the Schmidt reaction,[21] starting with the corresponding 1-phenyl-1,2,3,4-tetrahydro-3-naphthoic acid, also were unsuccessful and resulted in isolation of an unusually stable isocyanate intermediate that could not be converted to the amine.

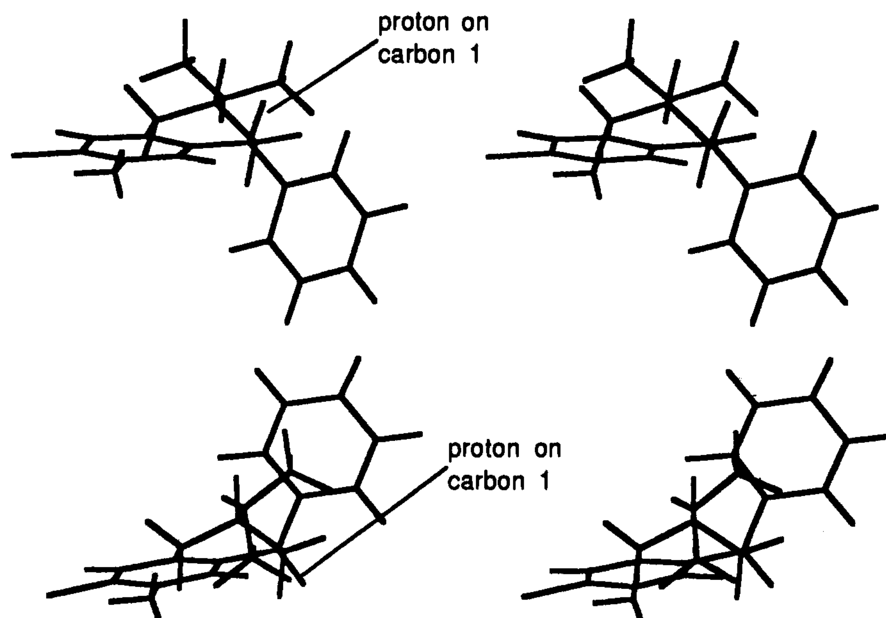


Figure 2. Stereoview (crossed) of *cis* 4 (upper) and *trans* 4 (lower) in their minimum-energy conformations as determined from molecular mechanics calculations. The proton on chiral carbon number one is indicated. This proton is evenly disposed between the two adjacent protons for the *trans* isomer resulting in a triplet at 4.3 ppm in the ^{1}H NMR spectrum. The corresponding proton for the *cis* isomer is approximately *gauche* to one and *anti* to the other of the two adjacent protons and appears as a doublet of doublets at 4.1 ppm.

The crude tetralones were reduced with $NaBH_4$ to the tetralols **15–17** (Scheme I). Configurational analysis by ^{1}H NMR indicated that the resulting mixture of alcohols was composed of approximately 85% *cis* and 15% *trans* diastereomers. This composition was confirmed by gas chromatography. The predominantly *cis*-tetralols were converted to the *trans* primary amines by the procedure of Laus et al.[22] for the synthesis of 1-phenyl-2-aminotetralins. Tosylation of the tetralols proceeded smoothly, followed by reaction of the *cis*-tosylates with sodium azide in aqueous DMF to afford the *trans*-azides **24**, **26**, and **29** in nearly quantitative yield. The *trans*-azides were then reduced catalytically with hydrogen over 10% Pd/C in 2-propanol to afford an acceptable yield of the *trans*-1-phenyl-3-aminotetralins **30**, **32**, and **35**. The primary amines were then methylated to afford compounds **5**, **36**, and **38** by the Eschweiler–Clark method[23] or allylated to afford **48–50** by reaction with 0.5 equiv of allyl bromide. O-Demethylation of the methoxy-substituted intermediates **30**, **31**, and **36–39** using 48% HBr afforded the corresponding phenolic analogs **4** and **41–45**. In all cases where the predominantly *cis*-tetralol was employed, the *trans*-amine product was obtained in an approximate ratio of 85% *trans* to 15% *cis*. Attempts to separate the *trans* from the *cis* isomers by fractional recrystallization of the free bases were unsuccessful. Conversion of the diastereomeric mixtures to the hydrochloride or hydrobromide salts with subsequent recrystallization afforded the pure racemic *trans* products.

To prepare the racemic *cis*-1-phenyl-3-aminotetralins, **31**, **33**, **34**, **37**, **39**, **40**, **42**, **43**, and **45**, the corresponding *cis*-tetralols **15–17** were epimerized via the ester intermediates **18–20** to the *trans*-alcohols **21–23** by the procedure of Bose et al.[24] using triphenylphosphine, diethyl azodicarboxylate, and formic or benzoic acid. The monomethyl aminotetralins **46** and **47** were prepared by N-demethylation of the pure racemic *trans*-(dimethylamino)-tetralins **4** and **5** using diethyl azodicarboxylate by the procedure of Booher and Pohland.[25]

Initial configurational assignments for the 1-phenyl-3-aminotetralins (*cis* vs *trans*) above were based on ^{1}H NMR spectral correlations with molecular mechanics-generated minimum-energy conformations as shown in Figure 2 and agree with the assignments made by Fries[26] for a similar series of aminotetralins. For the minimum energy conformations of the *cis* and *trans* isomers of **4** with the amino substituent in the equatorial orientation, the proton on the C-1 chiral carbon is evenly disposed between the two adjacent protons at the C-2 position for the *trans* isomer, whereas for the *cis* isomer, the analogous proton is approximately *anti* to one and *gauche* to the other of the adjacent protons. The *trans* configuration was assigned to the diastereomer for which the NMR spectrum showed a distinct triplet at 4.35 ppm for the proton at the C-1 position, whereas the *cis* configuration was assigned to the diastereomer for which the analogous proton signal appeared as a doublet of doublets at 4.1 ppm. X-ray crystallographic analysis of *trans*-(−)-**35** (resolution of the racemate described below) was employed to confirm this preliminary assignment of *cis* vs *trans* as well as to elucidate the absolute configuration.

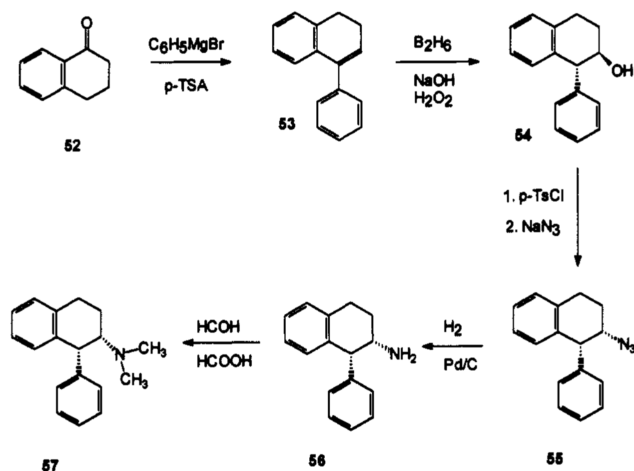
In order to resolve the enantiomers of **35**, the free base of (±)-*trans*-**35** was converted to the (1*R*)-(−)-camphor-10-sulfonic acid diastereomeric salts and repeatedly recrystallized from acetonitrile/methanol at room temperature to afford the pure levorotatory isomer, but with poor efficiency. In addition to optical rotation measurements, progress of the resolution was monitored by derivatization to the (*R*)-(−)-α-methoxy-α-[(trifluoromethyl)phenyl]acetamide[27] diastereomers with subsequent ^{1}H NMR or gas chromatographic (GC) analysis of the mixture. The proton on the chiral C-1 position that appears as a triplet at 4.35 ppm for the racemic primary amine, appeared as two completely resolved triplets of equal integration at 4.25 and 4.10 ppm for the diastereomers formed by derivatization of the racemic mixture. X-ray crystallographic analysis revealed the absolute stereochemistry of the levorotatory isomer of *trans*-**35**, that corresponds to the

Table II. Effects on Tyrosine Hydroxylase Activity and Binding Affinities of 1-Phenyl-3-amino-1,2,3,4-tetrahydronaphthalene Analogs for [^{3}H]-4-labeled binding sites and σ and Dopamine D_1 and D_2 Receptors

compd no.	IC_{50} (nM) vs [^{3}H]4	IC_{50} (nM) vs [^{3}H]DTG	IC_{50} (nM) D_1	IC_{50} (nM) D_2	TH activity % of control ± SEM: 0.1 μM
4	0.29 ± 0.05	3,400 ± 320	1 890 ± 196	4 130 ± 106	128 ± 3.4[a]
(±)-**5**	0.51 ± 0.05	5,312 ± 374	ca. 3 100	1 500 ± 39	138 ± 9.3[a]
(1*R*,3*S*)-(−)-**5**	0.20 ± 0.04	1883 ± 239	nd	nd	132 ± 7.0[a]
(1*S*,3*R*)-(+)-**5**	9.00 ± 1.70	1788 ± 226	nd	nd	99 ± 3.1
35	3305 ± 241	>10 000	>10 000	>10 000	86 ± 12
40	3.47 ± 0.56	960 ± 56	nd	nd	101 ± 6.4
41	34.3 ± 7.4	>10 000	>10 000	>5 000	75 ± 4.6[b]
42	12.2 ± 1.1	>10 000	>1 000	>5 000	100 ± 2.1
43	1.40 ± 0.24	1483 ± 408	nd	nd	94 ± 6.9
44	>10 000	>10 000	>30 000	>30 000	71 ± 6.4[b]
45	>10 000	>10 000	>30 000	>10 000	95 ± 5.2
46	21.1 ± 2.1	>10 000	849 ± 57	ca. 10 000	99 ± 2.1
48	8.9 ± 0.85	1549 ± 398	nd	nd	72 ± 9.1
49	117 ± 30	1733 ± 285	ca. 10 000	6 000	102 ± 7.0
50	26.5 ± 4.4	538 ± 66	ca. 10 000	4 000	104 ± 5.1
51	4.49 ± 0.35	207 ± 29	nd	nd	95 ± 4.9
57	2755 ± 361	3342 ± 340	nd	nd	111 ± 9.9

[a] Effect blocked by BMY-14802. [b] Effect not blocked by BMY-14802. Affinities were determined by competition assays of test compounds. σ assays used homogenates of guinea pig brains (minus cerebellum) in 10 mM Tris-HCl buffer (pH 7.4) without added cations, at 25 °C, and the dopamine receptor assays used rat striatal homogenates in Tris-HCl buffer (pH 7.4) containing 150 mM NaCl, at 30 °C. σ assays used [^{3}H]ditolylguanidine (DTG) as ligand (2.0 nM) and haloperidol (10 μM) to define binding at nonspecific sites. D_1 assays (30 min) used [^{3}H]SCH23390 (0.3 nM) as ligand and *cis*-flupenthixol (0.3 μM) to define binding at nonspecific sites. D_2 assays (90 min) used [^{3}H]YM09151-2 (0.065 nM) and (+)-butaclamol (0.2 μM) to define binding at nonspecific sites. Test agents were included at 4–8 concentrations (10 pM to 10 μM) in dupliate, with 3 replications, and resulting data were curve-fit with the ALLFIT program. The abbreviation nd stands for not done.

Scheme II



pharmacologically more active levorotatory isomer of *trans*-**5**, to be 1*R*,3*S*. The dextrorotatory isomer was obtained using (1*S*)-(+)-camphor-10-sulfonic acid as the resolving agent and has the 1*S*,3*R* configuration. Both enantiomers of **35** were subsequently converted to corresponding enantiomers of **5**.

The *cis*-1-phenyl-2-(*N*,*N*-dimethylamino)-1,2,3,4-tetrahydronaphthalene (**57**) (Scheme II) was prepared by N,N-dimethylation of the corresponding primary amine **56** as described above for the 1-phenyl-3-aminotetralins. The synthesis of **56** has been reported previously.[22]

Results and Discussion

Subsequent to our recent findings that the 6,7-benzomorphans **1** and **2** stimulate DA synthesis by stimulation of TH activity in rat striatal tissue at 0.1 μM,[15] we speculated that other aminotetrahydronaphthalene derivatives, such as the 1-phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes reported herein, also might possess such neuromodulatory activity on DA neurons. We previously reported that (±)-*trans*-1-phenyl-3-(*N*,*N*-dimethylamino)-6-chloro-7-hydroxy-1,2,3,4-tetrahydronaphthalene (**4**) stimulated TH by approximately 25–30% ($p < 0.05$, Student's t test) at 0.1 μM in rat striatal minces.[16a,b] This effect was blocked by the purported σ antagonist BMY-14802, suggesting mediation through a receptor with σ-like neuromodulatory activity.[16a,b] Although BMY-14802 is also a 5-HT_{1A} agonist, we have shown that 5-HT agonists do not stimulate TH in our assay.[28]

Except for **4** and **5**, no other phenylaminotetralin analogs shown in Table II produced significant stimulation of TH at 0.1 μM. It is noteworthy that the *trans* catechol analogs **41** and **44** *inhibited* TH by 25% and 29%, respectively, at 0.1 μM, and this effect was not blocked by BMY-14802. This inhibitory effect of **41** and **44** may be a result of direct competition of these analogs for the enzyme's biopterin cofactor as has been observed for other catechols.[29] Interestingly, neither of the *cis* catechol analogs **42** and **45** demonstrated this inhibitory effect, suggesting that stereochemical configuration may be important for the catechol-like inhibition of TH. As noted previously, only the racemic *trans* diastereomers **4** and **5** stimulated TH; the *cis* analogs **40** and **43** were inactive at 0.1 μM. Analogs of **5** with *N*-alkyl substituents other than dimethyl, such as **48–51**, also lacked stimulatory activity up to 10 μM (not shown). The *N*-methyl-*N*-allyl analog **48** produced moderate TH inhibition at 0.1 μM. Since **48** is not a catechol analog, its inhibitory effect may be due to a nonspecific DA releasing effect as observed for (+)-amphetamine.[30] Of the two enantiomers of **5**, (1*R*,3*S*)-(−)-**5** and (1*S*,3*R*)-(+)-**5**, TH stimulatory activity appears to be associated mainly with the former, which stimulated TH enzyme activity by 32% above control at 0.1 μM (Table II). The 1-phenyl-2-(*N*,*N*-dimethylamino) analog **57** was inactive with regard to TH.

Table II also shows results of radioreceptor assays for the 1-phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes in competition for sites labeled by [^{3}H](±)-**4**, or [^{3}H]DTG (σ), [^{3}H]SCH23390 (D_1), and [^{3}H]YM09151-2 or [^{3}H]-spiperone (D_2). Previously, we found the pharmacologic profile of brain sites labeled by [^{3}H]**4** to be inconsistent with known dopaminergic, serotonergic, adrenergic,

NMDA, or opioid receptors or monoamine oxidase or P-450 oxidase sites.[16a,b] In addition, preliminary results revealed that neither 4 nor 5 have affinity for excitatory amino acid, benzodiazepine, GABA, adenosine, or PCP receptors or ion channel binding sites.[31] Interestingly, the 6,7-benzomorphan σ ligands 1 and 2 showed little affinity for the [^{3}H]4 binding site and actually possess the opposite stereochemical configuration to that of our most potent[16] phenylaminotetralin analog, (1*R*,3*S*)-(−)-**5**. As noted earlier, however, 1 and 2 do stimulate TH activity. These results indicate that our initial hypothesis—that the (+)-benzomorphans and phenylaminotetralins act at the same site—is clearly not the case. Rather, these phenylaminotetralins either produce stimulatory effects on TH at different "σ-like" receptors or act at a novel receptor with neuromodulatory activity. With regard to the latter possibility, it is clear that none of the analogs in Table I had appreciable affinity for D_1 or D_2 DA receptors; IC_{50} values ranged from 849 nM for **46** to >30 000 nM for **44** and **45** (Table II). The 1-phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes also have little affinity for σ sites labeled by [^{3}H]DTG in guinea pig brain; IC_{50} values ranged from 207 nM for **51** to >10 000 nM for **41**, **42**, and **44**–**46** (Table II).

Not unexpectedly, (±)-**4** showed very high affinity (IC_{50} = 0.29 nM, Table II) for the proposed neuromodulatory site labeled by [^{3}H]4. The enantiomers of analog **5** bound stereoselectively to the [^{3}H]4 site; the (−) isomer of **5** (IC_{50} = 0.2 nM, Table II) was about 45 times more potent than (+)-**5** (IC_{50} = 9.0 nM, Table II); as would be predicted, (±)-**5** was about half as potent (IC_{50} = 0.5 nM, Table II) as the more active isomer. It is noteworthy that analogs with high affinity for the [^{3}H]4 labeled site also stimulated TH activity at 0.1 μM suggesting a functional parallel between binding at the [^{3}H]4 site and modulation of DA synthesis in rodent striatum. Also, for the racemic mixture and purified enantiomers of **5**, the rank order for affinity at the proposed neuromodulatory [^{3}H]4-labeled binding site agreed with that for potency in stimulating TH [(−) > (±) > (+)] (Table II). Analogs with moderate affinity, and those with virtually no affinity, for the [^{3}H]4 site produced no *stimulation* of TH at 0.1 μM (Table II). Likewise, the low affinity of the catechol analog **44** may preclude its inhibition of TH *via* the proposed [^{3}H]4 neuromodulatory binding site and suggests direct effects on the enzyme. In agreement with its lack of effect upon TH, the 1-phenyl-2-(*N*,*N*-dimethylamino) analog **57** showed no affinity (IC_{50} = 2755 nM) for the [^{3}H]4 σ-like binding site.

In summary, certain novel 1-phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes produced significant stimulation of TH activity at 0.1 μM in rodent brain tissue and this effect was blocked by the putative σ-receptor antagonist BMY-14802, suggesting that this effect may be mediated through a novel receptor with σ-like neuromodulatory activity. Within the new phenylaminotetralin series, a relationship was found between TH stimulation and affinity for a novel site labeled by [^{3}H](±)-4. This binding site is clearly distinct from known σ sites and DA receptors. For the *trans* analogs, catechol substitutions on the aromatic ring, N-alkylation with groups larger than methyl, and positioning of the amino substituent in the 2 position (**57**) as opposed to the 3 position of the tetrahydronaphthalene ring system, resulted in loss of ability to stimulate TH and attenuation of affinity for the receptor labeled by [^{3}H](±)-4. Also, the *cis* isomers of the corresponding active *trans* analogs **4** and **5** were inactive in the TH assay and possessed less affinity for the receptor labeled by [^{3}H]-(±)-4. 1-Phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes may show utility in the treatment of disease states characterized by reduced levels of DA in the CNS such as Parkinson's disease, or in levodopa-responsive forms of dystonia,[18] and may also serve as probes of a novel hypothesized receptor with σ-like neuromodulatory activity.

Experimental Procedures

All chemicals were used as received from the manufacturers. 4-Methoxyphenyl acetone and 3,4-dimethoxyphenyl acetone (**7**) were obtained from Aldrich Chemical Co. 3-Chloro-4-methoxyphenyl acetone (**6**) was prepared by the procedure of Toussaint.[32] The synthesis for unsubstituted phenyl acetone **8** from 1-phenyl-2-propanol was accomplished by oxidation with pyridinium chlorochromate.[33] Melting points were determined on a Mel-temp apparatus and are uncorrected. Proton NMR spectra were obtained on a Bruker AC300 300-MHz spectrometer using $CDCl_3$ as solvent (TMS) unless otherwise noted. Gas chromatographic analysis was performed using a Shimadzu GC-8A chromatograph with 2.0-m column packed with 3% OV-17 on chromasorb. Thin-layer chromatography was performed using silica gel 60-coated glass plates (Fisher Scientific) and column chromatography was performed using silica gel 60 (70–230 mesh). Elemental compositions of test compounds were determined by MHW Laboratories (Phoenix, AZ) and agreed with theoretical values ±0.4%. The absolute stereochemistry of (−)-**35** was determined by an X-ray crystallographic analysis performed at Duke University, Durham, NC. Sprague–Dawley albino rats (250–300 g) were obtained from Charles River Labs, Wilmington, MA.

1,4-Diphenyl-1-buten-3-one (9). The procedure of Southwick et al.[20] was used to prepare **9** in 58% yield as a colorless solid from **8** and benzaldehyde: mp 66–69 °C; ^{1}H NMR δ 7.7–7.25 (m, 10H, ArH), 6.82 (s, 1H, styryl), 6.78 (s, 1H, styryl), 3.97 (s, 2H, CH_2).

4-(3-Chloro-4-methoxyphenyl)-1-phenyl-1-buten-3-one (10). Compound **10** was prepared in 33% yield as a yellow solid using **6** and benzaldehyde by the same procedure as **9**: mp 87–89 °C; ^{1}H NMR δ 7.7–6.9 (m, 8H, ArH), 6.82 (s, 1H, styryl), 6.78 (s, 1H, styryl), 3.89 (s, 3H, OCH_3), 6.87 (s, 2H, CH_2).

4-(3,4-Dimethoxyphenyl)-1-phenyl-1-buten-3-one (11). 3,4-Dimethoxyphenyl lactone (**7**) and benzaldehyde were reacted as above for **9** to afford **11** in 70% yield as a colorless solid: mp 151–154 °C; ^{1}H NMR δ 7.7–6.9 (m, 8H, ArH), 3.98 (s, 8H, OCH_3 + CH_2).

1-Phenyl-3-oxo-1,2,3,4-tetrahydronaphthalene (12). A solution of 19.0 g (0.086 mol) of **9** in 200 mL of xylenes was added to a mechanically stirred suspension of 81.7 g of polyphosphoric acid (PPA) in 1000 mL of xylenes. After approximately 20 min at reflux, gas chromatographic analysis indicated absence of starting material (t_R = 1.9 min, 215 °C) and appearance of a product peak (t_R = 1.7 min, 215 °C). The cooled xylene layer was decanted and evaporated *in vacuo* to afford 24.6 g (128%) of the crude product ketone as a gum which was used in the next synthetic step without purification: ^{1}H NMR δ 7.5–6.95 (m, 9H, ArH), 4.5 (t, 1H, PhCHPh), 3.65 (dd, 2H, $PhCH_2$), 2.8 (m, 2H, CH_2CO).

1-Phenyl-3-oxo-6-chloro-7-methoxy-1,2,3,4-tetrahydronaphthalene (13). A solution of 12.6 g (0.044 mol) of **10** in xylenes was reacted with PPA as above for **12** for a total of 3 h to afford 7.9 g (64%) of product ketone as a gum after column chromatography on silica gel (toluene, CH_2Cl_2): ^{1}H NMR δ 7.4–7.1 (m, 6H, ArH_5), 6.55 (s, 1H, ArH_8), 4.45 (t, 1H, PhCHPh), 3.45 (s, 3H, OCH_3), 3.55 (dd, 2H, $PhCH_2$), 2.85 (m, 2H, CH_2CO).

1-Phenyl-3-oxo-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene (14). A solution of 32.2 g (0.114 mol) of **11** in xylenes was reacted with PPA as above for **12** for a total of 20 min to afford 42.2 g (130%) of crude product ketone as a gum which was used in the next synthetic step without purification: ^{1}H NMR δ 7.5–7.05 (m, 5H, ArH), 6.65 (s, 1H, ArH_5), 6.5 (s, 1H, ArH_8), 4.4 (t,

1H, PhCH$_2$Ph), 3.85 (s, 3H, OCH$_3$), 3.7 (s, 3H, OCH$_3$), 3.5 (dd, 2H, PhCH$_2$), 2.9 (m, 2H, CH$_2$CO).

(±)-*cis*-1-Phenyl-3-hydroxy-1,2,3,4-tetrahydronaphthalenes (15–17). General Procedure. Solid NaBH$_4$ (9.5 g, 0.25 mol) was added cautiously in portions to a magnetically stirred solution of 0.072 mol of the appropriate ketone (12–14) in 525 mL of methanol with cooling in an ice bath. The reaction was then stirred at reflux overnight, cautiously diluted with 100 mL of water, and the volatiles were removed *in vacuo*. The residue was dissolved in CH$_2$Cl$_2$ and extracted with water, dried (Na$_2$SO$_4$), and evaporated *in vacuo* to afford the crude alcohol which was purified by either recrystallization or column chromatography to afford an approximately 85:15 mixture of *cis*:*trans* products (see Table I). A representative ^{1}H NMR for 15 is given: δ 7.35–7.1 (m, 5H, ArH), 6.62 (s, 1H, ArH$_5$), 6.2 (s, 1H, ArH$_8$), 4.1 (dd, 1H, PhCHPh), 3.88 (s, 3H, OCH$_3$), 3.75 (m, 1H, CHOH), 3.58 (s, 3H, OCH$_3$), 3.2–2.7 (m, 2H, PhCH$_2$), 2.4 (m, 1H, CHCO), 1.85 (q, 1H, CHCO).

(±)-*trans*-1-Phenyl-3-hydroxy-1,2,3,4-tetrahydronaphthalenes (21–23). General Procedure. The procedure of Bose et al.[24] was employed to epimerize alcohols 15–17. Diethyl azodicarboxylate (DEAD) (0.054 mol) was added to a solution of 0.027 mol of 15–17, 0.054 mol of triphenylphosphine, and, in the case of 15, 0.054 mol of 98% formic acid or, in the case of 16 and 17, 0.054 mol of benzoic acid in 350 mL of tetrahydrofuran. After stirring at 55 °C for 4 h, the volatiles were evaporated *in vacuo* and the residue chromatographed on a column of silica gel using toluene to afford the *trans*-formate 19 or benzoates 18 and 20. Hydrolysis to the *trans*-alcohol using 2 equiv of NaOH in methanol at room temperature was complete in 5 min in the case of 19. Hydrolysis of the benzoate esters 18 and 20 required refluxing the reaction for 1 h. The methanol was evaporated *in vacuo*, and the residue was column chromatographed on silica gel to afford an approximately 85:15 mixture of *trans*:*cis* products. A representative ^{1}H NMR for 23 is given: δ 7.35–7.1 (m, 5H, ArH), 6.62 (s, 1H, ArH$_5$), 6.35 (s, 1H, ArH$_8$), 4.3 (t, 1H, PhCHPh), 4.22 (m, 1H, CHOH), 3.88 (s, 3H, OCH$_3$), 3.65 (s, 3H, OCH$_3$), 3.2–2.7 (m, 2H, PhCH$_2$), 2.25–2.0 (m, 2H, CH$_2$CO).

(±)-*trans*-1-Phenyl-3-azido-1,2,3,4-tetrahydronaphthalenes (24, 26, and 29). General Procedure.[22] A solution of 4.2 g (0.022 mol) of *p*-toluenesulfonyl chloride in 30 mL of dry pyridine was added to a solution of 0.011 mol of 15, 16, or 17 in 30 mL of dry pyridine. The reaction was allowed to stand for 5 days at 5 °C and was then poured into ice–water with stirring. If the resulting precipitates solidified (those from 15 and 17), they were filtered, washed with ice–water and dried *in vacuo* to afford the product tosylate. In the case of 16, the product precipitated as a gum and was extracted into ether. This ether solution was extracted with 200 mL of 1.0 N HCl, dried (Na$_2$SO$_4$), and evaporated *in vacuo* to afford the crude tosylate. A solution of 1.5 g (0.023 mol) of sodium azide in 6 mL of water was added in small portions to a stirred solution of 0.01 mol of the tosylate in 30 mL of DMF. The reaction was stirred for 4 h at 45–50 °C, at which time all of the tosylate was consumed. The reaction was poured into ice–water and extracted with CH$_2$Cl$_2$. The organic extracts were evaporated *in vacuo* to afford the *trans*-azides as gums.

(±)-*cis*-1-Phenyl-3-azido-1,2,3,4-tetrahydronaphthalenes (25, 27, and 28). Compounds 21–23 were converted to the corresponding *cis*-azides as above for the *trans*-azides.

(±)-*trans* and (±)-*cis*-1-Phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes (30–35). General Procedure.[22] The corresponding azides 24–29 (0.01 mol) were dissolved in 200 mL of 2-propanol containing 10 mL of CH$_2$Cl$_2$ and were shaken on a Parr hydrogenation apparatus over 0.1 g of 10% Pd on carbon at 45 psig overnight. The catalyst was filtered off and the filtrate evaporated *in vacuo* to afford the crude amine as a gum. The crude product was column chromatographed on silica gel to afford the racemic predominantly *cis* or *trans* products as a gum (see Table I). Compounds 34 and 35 were obtained as an approximately 85:15 mixture of diastereomers which were purified to the single diastereomer by conversion to the hydrochloride salt followed by recrystallization. A representative ^{1}H NMR for 30 (*trans* free base) is given: δ 7.35–7.15 (m, 5H, ArH), 6.62 (s, 1H, ArH$_5$), 6.4 (s, 1H, ArH$_8$), 4.27 (t, 1H, PhCHPh), 3.9 (s, 3H, OCH$_3$), 3.68 (s, 3H, OCH$_3$), 3.23 (m, 1H, CHNH$_2$), 3.05 (m, 1H, PhCH), 2.55 (dd, 1H, PhCH), 2.0 (t, 2H, CH$_2$CN). A representative ^{1}H NMR for 31 (*cis* free base) is given: δ 7.35–7.15 (m, 5H, ArH), 6.6 (s, 1H, ArH$_5$), 6.22 (s, 1H, ArH$_8$), 4.05 (dd, 1H, PhCHPh), 3.88 (s, 3H, OCH$_3$), 3.6 (s, 3H, OCH$_3$), 3.2 (m, 1H, CHNH$_2$), 3.1–2.6 (m, 2H, PhCH$_2$), 2.25 (m, 1H, CHCN), 1.62 (q, 1H, CHCN).

(±)-*trans* and (±)-*cis*-1-Phenyl-3-(*N,N*-dimethylamino)-1,2,3,4-tetrahydronaphthalenes (36–40 and 5). General Procedure. The procedure of Eschweiler and Clark[23] was used. A suspension of 0.003 mol of the appropriate primary amine 30–35 in 12 mL of 95% formic acid and 8 mL of 38% formaldehyde was stirred at reflux for 4 h during which time a solution formed. The volatiles were evaporated *in vacuo* and the residue was dissolved in CH$_2$Cl$_2$ and partitioned with saturated aqueous NaHCO$_3$. The organic phase was dried (Na$_2$SO$_4$) and evaporated *in vacuo* to afford the crude products which were either used in the next synthetic step without purification or were column chromatographed on silica gel. Final products 40 and 5 were converted to the hydrochloride salts and recrystallized to afford the pure *cis* and *trans* diastereomers. A representative ^{1}H NMR for 36 is given: δ 7.35–7.15 (m, 5H, ArH), 6.65 (s, 1H, ArH$_5$), 6.4 (s, 1H, ArH$_8$), 4.3 (t, 1H, PhCHPh), 3.9 (s, 3H, OCH$_3$), 3.7 (s, 3H, OCH$_3$), 2.6 (m, 1H, CHN), 3.0–2.7 (m, 2H, PhCH$_2$), 2.25 (s, 6H, N(CH$_3$)$_2$), 2.1 (t, 2H, CH$_2$CN). A representative ^{1}H NMR for 37 (*cis* free base) is given: δ 7.4–7.2 (m, 5H, ArH), 6.63 (s, 1H, ArH$_5$), 6.22 (s, 1H, ArH$_8$), 4.05 (dd, 1H, PhCHPh), 3.88 (s, 3H, OCH$_3$), 3.58 (s, 3H, OCH$_3$), 2.8 (m, 1H, CHN), 3.0–2.85 (m, 2H, PhCH$_2$), 2.38 (s, 6H, N(CH$_3$)$_2$), 2.3 (m, 1H, CHCN), 1.62 (q, 1H, CHCN).

O-Demethylation of Methoxy-Substituted 1-Phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes (41–45 and 4). General Procedure. A suspension of 0.003 mol of the corresponding methoxy intermediate (30, 31, and 36–39) in 35 mL of 48% HBr was stirred at reflux for 4 h during which time a solution formed. The volatiles were evaporated *in vacuo* and the residue was either recrystallized as the hydrobromide salt (41, 42, 44, and 45) to afford the pure racemic diastereomer or partitioned between CH$_2$Cl$_2$ and saturated aqueous NaHCO$_3$ to afford the free base. The organic phase was dried (Na$_2$SO$_4$) and evaporated *in vacuo* to afford the crude free base (4 and 43) which was converted to the hydrochloride salt and recrystallized to afford the pure racemic diastereomer. A representative ^{1}H NMR for 41 (HBr salt in CD$_3$OD) is given: δ 7.35–7.15 (m, 5H, ArH), 6.7 (s, 1H, ArH$_5$), 6.4 (s, 1H, ArH$_8$), 4.38 (t, 1H, PhCHPh), 3.45 (m, 1H, CHN), 3.2–2.85 (m, 2H, PhCH$_2$), 2.75 (s, 6H, N(CH$_3$)$_2$), 2.3 (t, 2H, CH$_2$CN).

(±)-*trans*-1-Phenyl-3-(methylamino)-1,2,3,4-tetrahydronaphthalenes (46 and 47). General Procedure. The procedure of Booher and Pohland[25] was employed to N-demethylate 4 and 5. The corresponding dimethylamine (0.24 mmol) was dissolved in 5 mL of toluene and 0.041 mL (0.26 mmol) of diethyl azodicarboxylate was added dropwise with stirring and stirred at 50 °C overnight. The volatiles were evaporated *in vacuo*, and the residue was dissolved in 2.5 mL of ethanol and added to a solution of 2.5 mL of saturated aqueous NH$_4$Cl. This solution was then stirred at reflux for 3 h. The volatiles were evaporated *in vacuo* and the residue dissolved in 10 mL of water. The aqueous solution was extracted with 10 mL of CHCl$_3$, adjusted to pH 8–9 with NH$_4$OH and re-extracted with CHCl$_3$. The organic extracts were dried (Na$_2$SO$_4$) and evaporated *in vacuo* to afford the crude product which was column chromatographed on silica gel to afford the pure diastereomer. A representative ^{1}H NMR for 47 (free base in CDCl$_3$ + DMSO-d_6) is given: δ 7.3–7.0 (m, 8H, ArH), 6.48 (s, 1H, ArH$_8$), 4.12 (t, 1H, PhCHPh), 3.05–2.82 (m, 2H, PhCH$_2$), 2.25 (s, 3H, NCH$_3$), 2.0–1.85 (m, 2H, CH$_2$CN).

(±)-*trans*-1-Phenyl-3-(allyl-substituted-amino)-1,2,3,4-tetrahydronaphthalenes (48–50). General Procedure. A solution of 1.34 mmol of the corresponding amine (35 and 47) as the free base was dissolved in 4 mL of CHCl$_3$ and to this solution was added 81 mg (0.067) mmol of allyl bromide. The reaction was stirred overnight at room temperature, and the volatiles were evaporated *in vacuo*. The residue was column chromatographed on silica gel to obtain the allylated products which were converted to the hydrochloride salts and recrystallized to afford the pure diastereomers. A representative ^{1}H NMR for 48 is given: δ 7.35–6.9 (m, 9H, ArH), 5.75 (m, 1H, vinyl), 4.95 (m, 2H, vinyl), 4.4 (t,

1H, PhCHPh), 3.2–2.8 (m, 5H, $PhCH_2$ + CH_2vinyl + CHN), 2.25 (s, 3H, NCH_3), 2.12 (t, 2H, CH_2CHN).

(±)-*trans*-1-Phenyl-3-(*N,N*-diethylamino)-1,2,3,4-tetrahydronaphthalene (51). Potassium carbonate (169 mg, 1.22 mmol) was suspended with stirring in a solution of 219 mg (0.981 mmol) of **35** in 11 mL of DMF. Iodoethane (153 mg, 0.981 mmol) in 2 mL of DMF was added dropwise to the stirred suspension, and the reaction mixture was heated to 50–55 °C for 5 h. The cooled reaction mixture was then poured into water, the aqueous suspension was extracted with ether, and the ether extracts were dried (Na_2SO_4) and evaporated *in vacuo* to afford 245 mg of crude, brown gum. Chromatography on 8 g of silica gel (CH_2Cl_2–THF 9:1) afforded 65 mg of pure product as an approximately 85:15 mixture of *trans* to *cis* isomers. Conversion to the hydrochloride salt as above and recrystallization from ethyl acetate–ether afforded 36 mg (12%) of pure *trans*-hydrochloride (see Table I).

(±)-*cis*-1-Phenyl-2-(*N,N*-dimethylamino)-1,2,3,4-tetrahydronaphthalene (57). Compound **56**[22] (450 mg, 2.0 mmol) was *N,N*-dimethylated with formic acid (9.0 mL) and formaldehyde (6.0 mL) as described above to afford 220 mg (38%) of colorless crystals as the HCl salt: mp 236–238 °C; ^{1}H NMR ($CDCl_3$) δ 7.35–6.90 (m, 9H, ArH_9), 4.25 (d, 1H, PhCHPh; *J* = 5.1 Hz), 3.4 (m, 1H, $CHNH_2$), 3.0 (m, 2H, $PhCH_2$), 2.4 (s, 6H, $N(CH_3)_2$), 1.75 (m, 2H, $PhCH_2CH_2$).

Resolution of (±)-*trans*-1-Phenyl-3-amino-1,2,3,4-tetrahydronaphthalene (35). Compound **35** (4.0 g, 0.018 mol, containing approximately 15% *cis* isomer) and 4.2 g (0.018 mol) of (1*R*)-(−)-camphor-10-sulfonic acid were dissolved in 150 mL of acetonitrile/methanol 2:1 under reflux. After standing overnight at room temperature, the precipitate was filtered, washed with acetonitrile, and dried *in vacuo* to afford 4.9 g of colorless crystals. A small sample was converted to 5.0 mg of free base by partitioning between CH_2Cl_2 and saturated aqueous $NaHCO_3$. Treatment of the free base with a 10% excess of (*R*)-(−)-α-methoxy-α-[(trifluoromethyl)phenyl]acetyl chloride[27] in 0.25 mL of CH_2Cl_2 containing 50 μL of dry pyridine for 1 h at room temperature afforded a quantitative conversion to the diastereomeric amides which were analyzed by ^{1}H NMR ($CDCl_3$) and/or gas chromatography (programmed from 200–300 °C at 2 °C/min) without purification. This analysis indicated an approximate 55:45 ratio of diastereomers with the predominant isomer showing a triplet at 4.1 ppm corresponding to the proton on the one position chiral carbon and a gas chromatography retention time of 29 min. The other *trans*- and *cis*-amide diastereomers had retention times of 30 and 32 min, respectively. Three subsequent recrystallizations as above afforded 290 mg of pure *trans* levorotatory diastereomer as colorless prisms corresponding to the predominant isomer above: mp 218–220 °C; $[\alpha]^{25}_D$ −70.5° (absolute EtOH). The salt was converted to free base by stirring in a mixture of 10 mL of CH_2Cl_2 and 5 mL of saturated aqueous $NaHCO_3$ to afford 133 mg of (−)-**35** as a light yellow solid: mp 57–59 °C; $[\alpha]^{25}_D$ −91.4° (absolute EtOH). Single-crystal X-ray crystallographic analysis of the above (1*R*)-(−)-camphor-10-sulfonic acid salt indicated the absolute configuration to be 1*R*,3*S*.

To obtain the dextrorotatory isomer of **35**, a solution of 8.7 g (0.038 mol) of (1*S*)-(+)-camphor-10-sulfonic acid in 150 mL of acetonitrile was added to a solution of 8.4 g (0.038 mol) of (±)-**35** (containing approximately 15% *cis* isomer) in 150 mL of acetonitrile. The resulting suspension was evaporated *in vacuo* and dissolved under reflux in 160 mL of acetonitrile/methanol 2:1 and allowed to stand overnight at room temperature. The crystalline precipitate was filtered and washed with acetonitrile and dried to afford 4.3 g of colorless solid. Derivatization as above to the diastereomeric amides and subsequent analysis indicated an approximately 2:1 ratio of *trans* isomers plus a small amount of *cis* isomer(s) with the predominant isomer corresponding to that desired showing a triplet at 4.25 ppm by ^{1}H NMR and possessing a gas chromatography retention time of 30 min. Two subsequent recrystallizations as above afforded 1.1 g of dextrorotatory *trans* diastereomer corresponding to the predominant isomer above (t_R 30 min) as a colorless solid but containing approximately 10% of the *cis* isomer(s): mp 215–217 °C, $[\alpha]^{25}_D$ + 57.6° (absolute EtOH). It was decided to use this slightly contaminated isomer in the subsequent N-methylation step and to subsequently remove the *cis* isomer from the final product by recrystallization of the hydrochloride salt as performed above for the racemic mixtures. The above diastereomeric salt was converted to free base by stirring in a mixture of 30 mL of CH_2Cl_2 and 10 mL of saturated aqueous $NaHCO_3$ to afford 553 mg of *trans*-(1*S*,3*R*)-(+)-**35** as an oil which solidified upon standing: mp 57–59 °C, $[\alpha]^{25}_D$ +75.1°.

***trans*-(1*R*,3*S*)-(−)-1-Phenyl-3-(*N,N*-dimethylamino)-1,2,3,4-tetrahydronaphthalene ((−)-5).** Compound (−)-**35** (133 mg, 0.596 mmol) was *N,N*-dimethylated as above for (±)-**35** to afford 133 mg (89%) of (−)-**5** as a light yellow gum which solidified upon standing: mp 62–63 °C; $[\alpha]^{25}_D$ −52.9° (absolute EtOH). The free base was converted to the hydrochloride salt by treatment of an ethereal solution with ethereal HCl: mp 208–210 °C.

***trans*-(1*S*,3*R*)-(+)-1-Phenyl-3-(*N,N*-dimethylamino)-1,2,3,4-tetrahydronaphthalene ((+)-5).** Compound (+)-**35** (553 mg, 2.5 mmol) was *N,N*-dimethylated as above for (±)-**35** to afford 605 mg of (+)-**5** as a light yellow gum. The free base was converted to the hydrochloride salt by treatment of an ethanolic solution with ethereal HCl and the salt was recrystallized from ethanol/ether to afford 462 mg (64%) of colorless solid: mp 205–208 °C. A small amount of the pure *trans* enantiomer hydrochloride salt (free of cis isomer(s)) was converted to free base to afford a yellow solid: mp 60–61 °C; $[\alpha]^{25}_D$ +52.2° (absolute EtOH).

Single-Crystal X-ray Diffraction Determination of Absolute Stereochemistry of (1*R*,3*S*)-(−)-1-Phenyl-3-amino-1,2,3,4-tetrahydronaphthalene (1*R*)-(−)-Camphor-10-sulfonic Acid Salt ((1*R*,3*S*)-(−)-35). Crystal Data: $[C_{16}H_{18}N^+][C_{10}H_{15}O_4S^-]$; *M* = 455.62; orthorhombic; *a* = 11.723(2), *b* = 29.533(3), c = 6.914(1) Å; *V* = 2394(1) Å^3; *Z* = 4; D_{calcd} = 1.264 g cm^{-3}, m(Cu Kα radiation, 1 = 1.5418 Å) = 14.2 cm^{-1}; crystal dimensions 0.14 × 0.30 × 0.50 mm; space group $P2_12_12_1(D_2^4)$; no. 19 uniquely established by the systematic absences—*h*00 when $h \neq 2n$, 0*k*0 when $k \neq 2n$, 00*l* when $l \neq 2n$. Preliminary unit-cell dimensions and space group information were obtained from oscillation and Weissenberg photographs. Refined unit-cell parameters were derived by least-squares treatment of the diffractometer setting angles for 25 reflections (36° < *q* < 40°) widely separated in reciprocal space. One octant of intensity data was recorded on an Enraf-Nonius CAD-4 diffractometer [Cu Kα radiation, 1 = 1.5418 Å, graphite monochromator; ω − 2θ scans, scanwidth (0.70 + 0.14 tan θ)°]. The intensities of four reference reflections, remeasured every 2 h during data collection, showed no significant variation (<1% overall). The data were corrected for the usual Lorentz and polarization effects and an empirical absorption correction (T_{max}:T_{min} = 1.00:0.79), based on the *f* dependency of the intensities of several reflections with c ca. 90°, was also applied. From a total of 2824 nonequivalent measurements, those 2532 reflections with $I > 3.0\sigma(I)$ were retained for the analysis.

The crystal structure was solved by direct methods (MULTAN11/82). Approximate positions for the non-hydrogen atoms were derived from an *E* map. Coordinates for the camphorsulfonate ion were chosen to afford with the known 1*R* configuration and this defined the absolute stereochemistry of the cation. Positional and thermal parameters of the non-hydrogen atoms (at first isotropic and then anisotropic) were adjusted by means of several full-matrix least-squares iterations following which a difference Fourier synthesis was evaluated and found to contain significant positive regions at sites corresponding to calculated hydrogen atom positions. In the subsequent rounds of least-squares parameter refinement, hydrogen atoms were incorporated at their calculated positions and in the later cycles an extinction correction was included as a variable. The refinement converged (max shift:esd = 0.01) at $R = \sum||F_o| - |F_c||/\sum|F_o| = 0.036$, $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2} = 0.049$, GOF = $[\sum wD^2/(N_{observations} - N_{parameters})]^{1/2}$ = 1.63. A final difference Fourier synthesis contained no unusual features (D_r = 0.18(max), −0.26(min) e/Å^3). A view of the solid-state conformation is presented in Figure 3.

Crystallographic calculations were performed on PDP11/44 and MicroVAX computers by use of the Enraf-Nonius Structure Determination Package (SDP). In the least-squares iterations, $\sum wD^2[w = 1/s^2(|F_o|), D = (|F_o| - |F_c|)]$ was minimized. For all structure-factor calculations, neutral atom scattering factors and their anomalous dispersion corrections were taken from *International Tables for X-Ray Crystallography*; Vol. IV (The Kynoch Press: Birmingham, England, 1974).

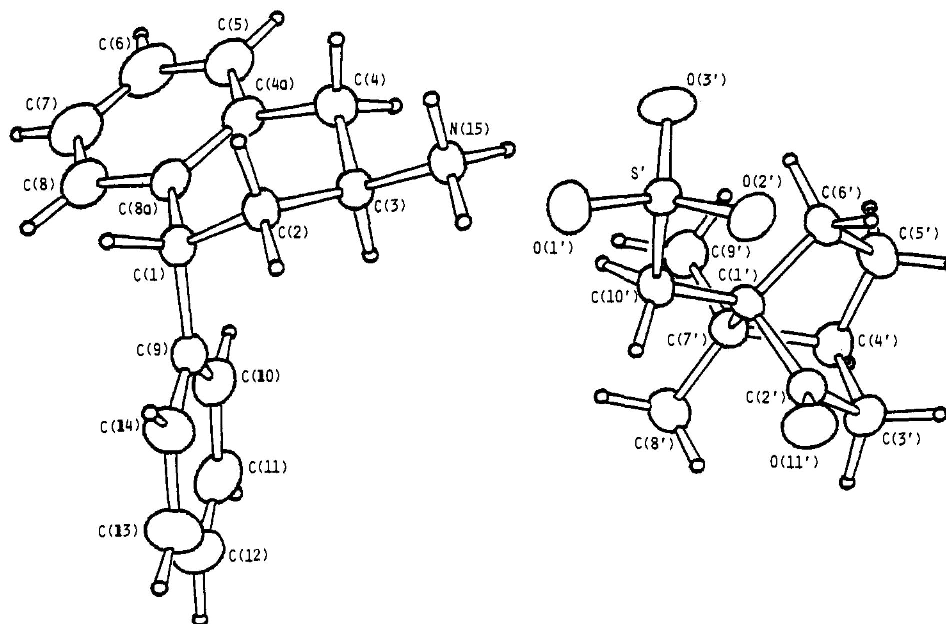


Figure 3. X-ray crystal structure (ORTEP diagram, 40% probability elipsoids) for (1*R*,3*S*)-(−)-**35** 1-(*R*)-(−)-camphor-10-sulfonic acid salt showing atom numbering scheme and solid-state conformations of the ions in crystals. Small circles represent hydrogen atoms.

Molecular Mechanics Calculation of Minimum-Energy Conformation of 4. The minimum-energy conformations for *cis* and *trans* **4** which were correlated with NMR spectra for initial assignment of *cis* versus *trans* configuration were calculated by first entering the structures into Sybyl 5.4 using the Sketch function. Initial low-energy conformation/geometry optimization was performed using the Maximin2 molecular mechanics routine with an energy tolerance of 0.001 kcal/mol. Various heterocyclic ring conformations were examined by utilizing the Random Search routine. The lowest energy conformation for the heterocyclic ring was that of a half-chair with the amino substituent in the equatorial position. These low-energy conformations were then submitted to the Systemmatic Conformational Search routine by driving the C1–C9 and C3-N bonds through 360° in 10° increments. The lowest energy conformation found for each diastereomer was subsequently reminimized using Maximin2 to afford the global minimum energy conformation.

Tyrosine Hydroxylase Assay. DA synthesis was assessed as TH activity in rat striatal minces by measuring formation of $^{14}CO_2$ evolved during the decarboxylation of L-dihydroxyphenylalanine (DOPA) to form DA, starting from [1-^{14}C]-L-tyrosine, as described previously.[30]

Radioreceptor Assays. Competition radioreceptor assays were used to determine the affinity (IC_{50}'s) of the phenylaminotetralins and other reference ligands for σ and D_1 and D_2 dopamine receptors. σ assays were performed using homogenates of whole guinea pig brain (minus cerebellum) in 10 mM Tris-HCl buffer (pH 6.4) without added cations, at 25 °C and with 2-h incubations. The radioligand was 2.0 nM [^{3}H]ditolylguanidine (DTG),[34] with haloperidol (10 μM) used to define nonspecific binding. The K_D of DTG under these conditions was determined to be 2.8 nM. The dopamine receptor assays used rat striatal homogenates in a Tris-HCl buffer (pH 7.4) containing 150 mM NaCl, at 30 °C. D_1 assays used a 30-min incubation with used [^{3}H]SCH23390[35] (0.3 nM) as the radioligand, and *cis*-(*Z*)-flupenthixol (0.3 μM) defining nonspecific binding. D_2 assays used a 90-min incubation with [^{3}H]YM-09151-2[36,37] (0.065 nM) with (+)-butaclamol (0.25 μM) defining nonspecific binding. Under these conditions, the K_D of [^{3}H]SCH23390 was 0.34 nM and that of [^{3}H]-YM-09151-2 was 0.045 nM. Test agents were evaluated by running, in duplicate, six or more concentrations that bracketed the IC_{50}. Three replications were performed, and the resulting data were analyzed using the ALLFIT program.

The binding of the novel radioligand [^{3}H](±)-**4** to brain membranes was characterized using assay conditions similar to those developed for the σ ligand [^{3}H]DTG.[34] Briefly, frozen guinea pig brain (minus cerebellum; obtained from Keystone Biologicals, Cleveland, OK) was thawed and homogenized (10 mL/g tissue) in ice-cold 10 mM Tris-HCl buffer containing 0.32 M sucrose, pH 7.0; the homogenate was centrifuged at 1000*g* for 15 min at 4 °C and the supernatant recentrifuged at 31 000*g* for 15 min at 4 °C. The P_2 pellet was suspended in 10 mM Tris buffer (pH 7.4, 25 °C) at 3 mL/g tissue and incubated at room temperature for 15 min before recentrifuging at 31 000*g* for 15 min at 4 °C. The resulting pellet was stored at −70 °C in 10 mM Tris (pH 7.4) at 20 mg protein/mL. To determine binding parameters, a ligand saturation curve was constructed with 1.0 mg of brain protein (50 μL) in glass tubes (triplicate) containing six concentrations (0.02–2.0 nM) of free ligand (*F*) in 50 mM Tris-HCl buffer, pH 7.4 (2.0 mL total vol), with excess BMY-14802 (5.0 μM) used to define specific binding. Tubes were incubated for 60 min at 30° and then filtered in a Brandel cell harvester through glass fiber sheets, subsequently cut and counted for tritium by liquid scintillation spectrometry. Results first were plotted in Scatchard-Rosenthal linearized form as ratio of bound/free ligand (B/F) vs specific binding (B), to provide estimates of apparent affinity K_D (slope) and binding site density B_{max} (*x* intercept); these values were verified with the LIGAND curve-fitting program[38] adapted to the MacIntosh microcomputer.[39] Under these conditions, the K_D of [^{3}H]**4** was 0.031 nM. For competitive binding assays, tubes were incubated (60 min, 30 °C) with 50 pM (ca. K_D) [^{3}H]**4**, with 5 μM BMY-14802 used to define nonspecific binding. From 4–8 concentrations (10 pM to 10 μM) of test compounds were used; and the resulting competition data were computer curve-fitted using ALLFIT for the MacIntosh to determine IC_{50} ± SEM.[40]

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