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1-Phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes and Related Derivatives as Ligands for the Neuromodulatory σ_3 Receptor: Further Structure−Activity Relationships

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A series of 1-phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes (1-phenyl-3-aminotetralins, PATs) previously was found to stimulate tyrosine hydroxylase activity and dopamine synthesis in rat brain through interaction with a novel σ_3 receptor. Specifically, the *trans*-1*R*,3*S*-(−) isomer of H_2-PAT showed highest affinity for σ_3 receptors and also produced maximal stimulation of tyrosine hydroxylase activity and dopamine synthesis, as compared to the *trans*-1*S*,3*R*-(+) isomer. Affinity for σ_3 receptors and functional potency at stimulating dopamine synthesis were attenuated either by altering the position or dimethyl substitution pattern of the amino group or by hydroxylating the tetralin aromatic ring. A preliminary binding model can accommodate many PAT analogs and several non-PATs with a wide range of affinities for the σ_3 receptor. Here, we report the synthesis and evaluation of additional analogs in order to expand previous structure−activity relationship studies. Further molecular modifications include synthesis of 1-phenyl-1-methyl-3-amino, 1-phenyl-2-amino, 1-phenyl-3-(trimethylammoniumyl), and 1-phenyl-3-(phenylalkyl) analogs, as well as ring-expanded tetrahydrobenzocycloheptenes. In general, the above modifications decreased σ_3 receptor affinity and, in some cases, caused a reversal of the σ_3 binding selectivity of *trans*- versus *cis*-PATs found previously. Most analogs were selective for σ_3 receptors and showed little or no affinity for either σ_1/σ_2 or dopamine D_1, D_2, and D_3 receptors. *N*-Phenylalkyl substituents, such as *N*-phenylethyl, however, endowed the 1-phenyl-3-aminotetralins with enhanced σ_1/σ_2 and dopamine receptor affinity while decreasing σ_3 affinity, thus abolishing σ_3 selectivity.

Introduction

The σ site was initially considered to be an opioid receptor but later shown to display non-opioid pharmacology. For example, (−)-benzomorphans possess higher affinity for opioid receptors, whereas (+)-benzomorphans, such as (+)-*N*-allylnormetazocine (NANM) and (+)-pentazocine, are selective for σ sites. Efforts to characterize σ sites have been impeded due to lack of identification of an endogenous ligand or a clearly linked neural function, and the receptor has not been isolated or cloned. Multiple subtypes of σ receptors have been suggested,[1−4] and it is proposed that σ sites which bind (+)-benzomorphans with high affinity be categorized as σ_1 while those that bind these ligands with lower affinity be categorized as σ_2.[2] There now is substantial evidence to suggest that σ receptors may play a neuromodulatory role specifically with regard to catecholamine systems.[5−10] There is also a suggestion that at least some σ sites may belong to the family of G-protein-coupled receptors.[11]

We have reported that certain 1-phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes (1-phenyl-3-aminotetralins, PATs) bind stereoselectively and with high affinity ($K_d \approx 130$ pM) to a novel σ_3 receptor in rodent striatum. The PATs have negligable affinity for other known σ or more than two dozen other central nervous system (CNS) recognition sites in mammalian brain.[12] We found that this novel σ_3 receptor is linked to modulation of tyrosine hydroxylase (TH) activity and dopamine (DA) synthesis in rat and guinea pig forebrain. At 0.1 μM, certain PATs stimulate TH activity and DA synthesis in rat striatum to ca. 50% above basal levels,[12] and this effect is blocked by the piperazinebutanol BMY-14802, a σ receptor antagonist. Preliminary structure−activity relationships (SARs)[13,14] in our initial PAT series revealed that there is little steric tolerance for alkyl substituents on the 3-amino nitrogen and that the dimethyl substituent affords highest affinity for σ_3 receptors and the most potent functional effect on TH activity. Of the aromatic substitutions examined thus far, both the 6-chloro-7-hydroxy-PAT (Cl,OH-PAT, **1**; Figure 1) and unsubstituted PAT (H_2-PAT, **2**) analogs demonstrated similar binding affinity for the σ_3 receptor and stimulation of TH activity. Conversely, catechol analogs were found to have little affinity for σ_3 receptors and failed to stimulate rodent brain TH activity.[13] Due to the more complicated pharmacological profile displayed by **1**,[12] we chose to emphasize the congeners of the aryl-unsubstituted analog **2**. The 1*R*,3*S*-(−) isomer of **2** was found to have highest affinity for σ_3 receptors and potent agonist effects on TH activity.[13]

To assess further structure−affinity and selectivity requirements at σ_3 receptors, we now report additional structural modifications of **2**. Specifically, we report on analogs **3** and **4** which have a methyl group in addition

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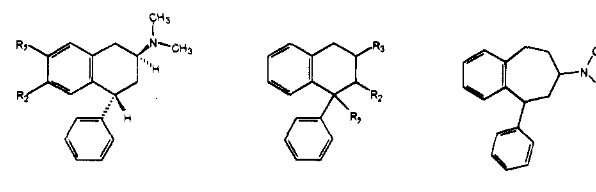


1 (*trans*)-(1*R*,3*S*) R_1=Cl, R_2=OH
2 (*trans*)-(1*R*,3*S*) R_1=R_2=H

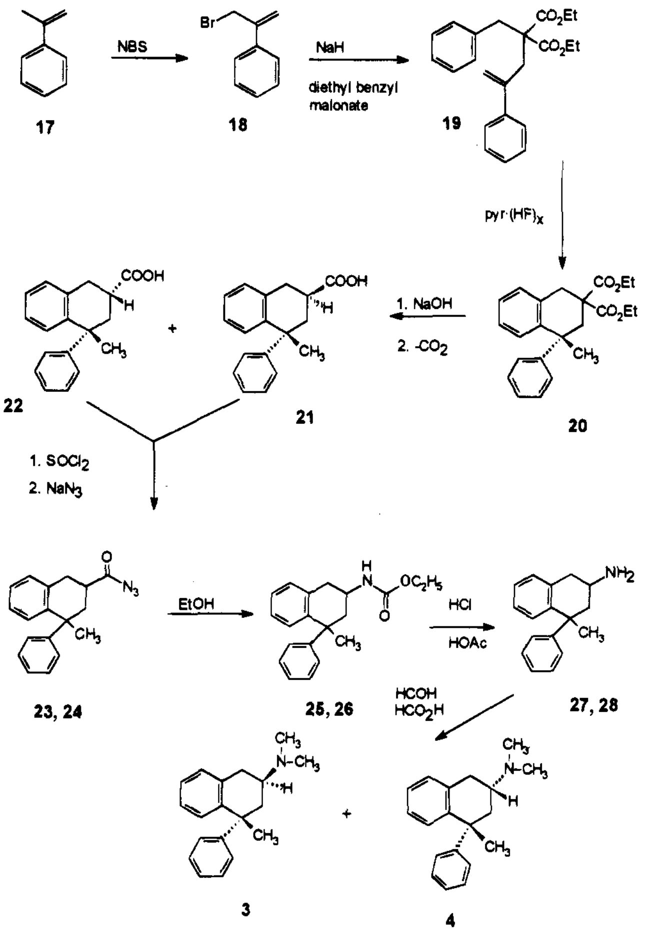
3 (*trans*) R_1=CH_3, R_2=H, R_3=*N*$(CH_3)_2$
4 (*cis*) R_1=CH_3, R_2=H, R_3=*N*$(CH_3)_2$
7 (*trans*) R_1=H, R_2=*N*$(CH_3)_2$, R_3=H
8 (*cis*) R_1=H, R_2=*N*$(CH_3)_2$, R_3=H
9 (*trans*) R_1=R_2=H, R_3=*N*HCH_3
10 (*trans*) R_1=R_2=H, R_3=*N*$(CH_3)_3$
12 (*trans*) R_1=R_2=H, R_3=*N*$H(CH_2)_3Ph$
13 (*trans*) R_1=R_2=H, R_3=*N*$H(CH_2)_4Ph$
14 (*trans*) R1=R_2=H, R_3=*N*-CH_3-*N*-$(CH_2)_2Ph$
15 (*trans*) R_1=R_2=H, R_3=*N*-CH_3-*N*-$(CH_2)_3Ph$
16 (*trans*) R_1=R_2=H, R_3=*N*-CH_3-*N*-$(CH_2)_4Ph$
17 (*cis*) R_1=R_2=H, R_3=*N*$(CH_3)_2$

5 (*trans*)
6 (*cis*)

Figure 1. Structures of (phenylamino)tetralins and related analogs. Cl,OH-PAT (1), H_2-PAT (**2**), *trans*-(**3**) and *cis*-(**4**) 1-phenyl-1-methyl-3-(dimethylamino)-1,2,3,4-tetrahydronaphthalenes, *trans*-(**5**) and *cis*-(**6**) 5-phenyl-7-(dimethylamino)-5,6,7,8-tetrahydro-9*H*-benzocycloheptenes, *trans*-(**7**) and *cis*-(**8**) 1-phenyl-2-(dimethylamino)-1,2,3,4-tetrahydronaphthalenes, *trans*-1-phenyl-3-(methylamino)-1,2,3,4-tetrahydronaphthalene (**9**), *trans*-1-phenyl-3-(trimethylammoniumyl)-1,2,3,4-tetrahydronaphthalene iodide (**10**), *trans*-1-phenyl-3-[(3-phenylpropyl)amino]-1,2,3,4-tetrahydronaphthalene (**12**) *trans*-1-phenyl-3-[(4-phenylbutyl)amino]-1,2,3,4-tetrahydronaphthalene (**13**), *trans*-1-phenyl-3-[(2-phenylethyl)-*N*-methylamino]-1,2,3,4-tetrahydronaphthalene (14), *trans*-1-phenyl-3-[(3-phenylpropyl)-*N*-methylamino]-1,2,3,4-tetrahydronaphthalene (15), *trans*-1-phenyl-3-[(4-phenylbutyl)-*N*-methylamino]-1,2,3,4-tetrahydronaphthalene (16), and (*cis*)-1-phenyl-3-(dimethylamino)-1,2,3,4-tetrahydronaphthalene (*cis*-H_2-PAT) (17).

to the phenyl ring at the 1-position of the tetrahyronapthalene ring. This modification not only affords information regarding the steric tolerance at the 1-position of the PAT but also provides a PAT with a methyl substituent in the position analogous to that on (+)-benzomorphans that also show σ receptor-mediated stimulation of brain TH activity.[15] The (±)-*trans*- and (±)-*cis*-5-phenyl-7-(dimethylamino)-5,6,7,8-tetrahydro-9*H*-benzocycloheptenes (**5** and **6**) were prepared in order to assess how σ_3 activity is affected by a more extended (phenylalkyl)amino conformation versus the less extended conformation of (±)-*trans*- and (±)-*cis*-1-phenyl-2-(dimethylamino)tetralin (**7** and **8**)[13] compared to **2**. The *N*-normethyl analog, **9**, of **2** was prepared to investigate whether *N*-dealkylation results in loss of affinity as it does in the 6-Cl-7-OH series.[13] It has been reported,[16] recently, that quaternization of high-affinity σ_1 ligands dramatically decreases affinity at the σ_1 site. In order to assess whether the amino group of PATs interacts with the σ_3 binding site ionically or as a hydrogen bond donor, the trimethylammonium quaternary analog **10** also was prepared and tested for σ_3 affinity. Molecular modeling studies[17] indicate that the *N*-3-phenylpropyl group of GBR-12909 (a DA transport blocker that also possesses very high affinity for the σ_3 receptor) is accommodated well by the nitrogen domain of the σ_3 receptor. Glennon[16,18] also has reported that 3-phenylpropyl and other extended phenylalkyl nitrogen substituents provide certain 1-phenyl-2-aminopropane and aminotetralin derivatives with high affinity for σ_1 receptors. Therefore, the *N*-2-phenylethyl, *N*-3-phenylpropyl, and *N*-4-phenylbutyl PAT analogs **12**–**16** were prepared to examine whether a possible auxiliary binding pocket on the σ_3 receptor may accommodate large nitrogen substituents on the PATs.

Scheme 1

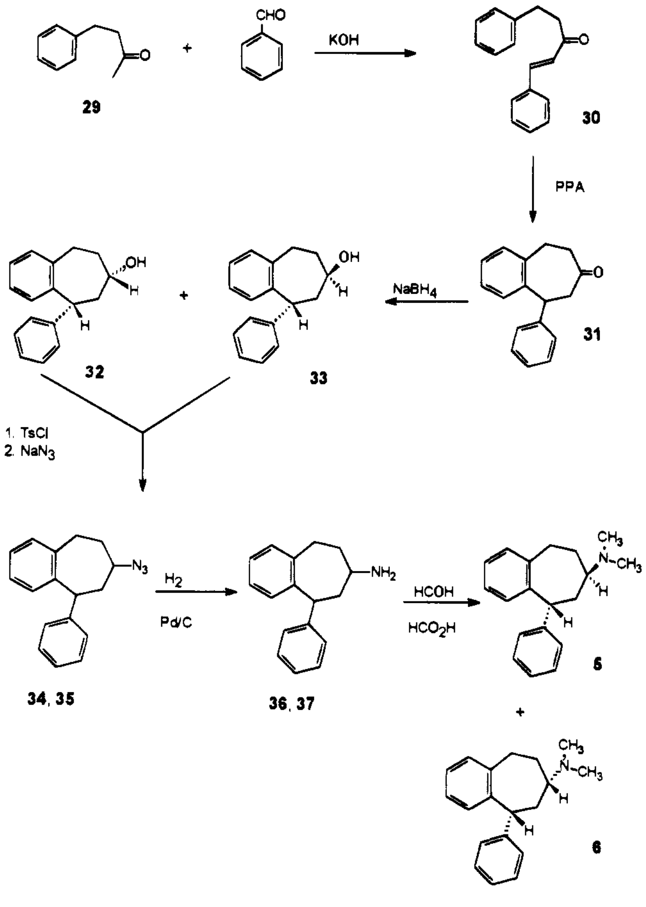


Chemical Synthesis

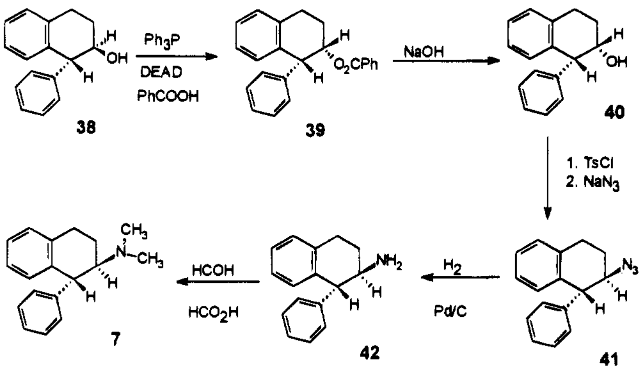
The preparation of 1-phenyl-3-aminotetralins was described in a previous report.[13] The 1-phenyl-1-methyl-3-aminotetralins (Scheme 1) were prepared by a modification of the procedure of Kandeel and Martin.[19] Diethyl benzylmalonate was alkylated with 3-bromo-2-phenyl-1-propene (**18**) to afford **19** which was cyclized with anhydrous pyridinium poly(hydrogen fluoride) to afford **20** in excellent yield. This reagent was more efficient than the reported anhydrous hydrogen fluoride. Saponification of the diester **20** with subsequent decarboxylation afforded the *trans* and *cis* monoacids **21** and **22** which were separated by fractional recrystallization from glacial acetic acid. A modification of the reported Curtius rearrangement[19] was employed to convert the acyl azides **23** and **24** to the corresponding urethanes **25** and **26** by refluxing in ethanol. Hydrolysis of the *cis* and *trans* urethanes to the primary amines **27** and **28** followed by Eschweiler–Clark dimethylation[20] afforded the *trans* and *cis* products **3** and **4**.

Preparation of the *trans*- and *cis*-5-phenyl-7-(dimethylamino)-5,6,7,8-tetrahydro-9*H*-benzocycloheptenes (**5** and **6**; Scheme 2) was carried out by procedures similar to those previously reported for the 1-phenyl-3-(dimethylamino)tetralins.[13] Compared to the 1-phenyl-3-(dimethylamino)tetralins, the tetrahydrobenzocycloheptenes required considerably longer reaction times to effect ring closure to the tetrahydrobenzocycloheptanone **31** and were obtained in a lower yield. Also,

Scheme 2



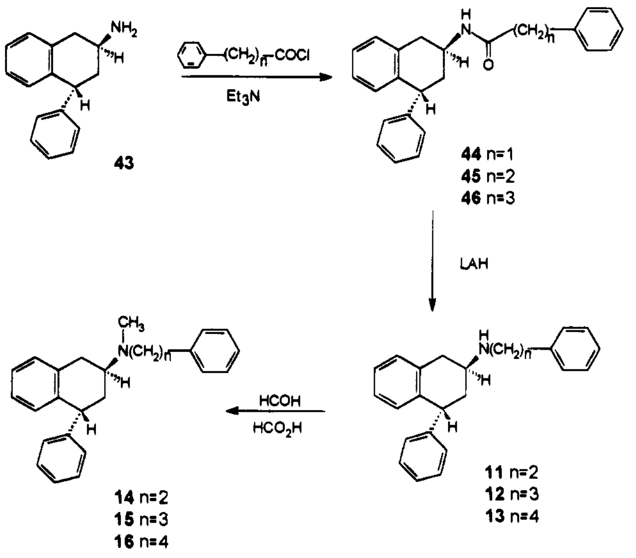
Scheme 3



upon reduction of the ketone intermediate **31** with $NaBH_4$, nearly equal proportions of *cis* and *trans* diastereomers **32** and **33** were obtained, in contrast to the ca. 85:15 *cis* to *trans* mixture obtained by reduction of the 1-phenyl-3-tetralones.[13] Separation of the isomers by chromatography alleviated the need to epimerize the *cis* alcohol intermediate **32** in order to obtain the final *cis* amine product. In addition, the *cis* isomer was considerably less reactive than the *trans* with regard to reaction times for such procedures as tosylation, derivatization for gas chromatographic analysis, and subsequent reaction of the tosylates with sodium azide.

Previously, we reported the preparation of the *cis*-1-phenyl-2-(dimethylamino)tetralin (**8**; Figure 1).[13] Preparation of the *trans* isomer **7** (Scheme 3) was accomplished by epimerization of the *trans* alcohol intermediate **38**[21] with diethyl azodicarboxylate and triphenylphosphine[22] to afford the *cis* ester intermediate **39** which was saponified to the *cis* alcohol **40** as previously described.[13,22] The remainder of the synthesis (intermediates **41** and **42**) was carried out as for the *cis* isomer and afforded the *trans* product **7**.

Scheme 4



The *N*-normethyl analog, **9**, of **2** was prepared by treatment of **2** with diethyl azodicarboxylate in toluene followed by treatment with ammonium chloride as described previously for the *N*-demethylation of **1**.[13] The *N*-phenylethyl, *N*-phenylpropyl, and *N*-phenylbutyl analogs **11–13**, respectively, were prepared by acylation of the *trans* primary amine **43** followed by LAH reduction to the secondary amines. *N*-Methyl-*N*-phenylalkyl analogs **14–16** were prepared by Eschweiler–Clark methylation of **11–13** (Scheme 4). As previously reported,[13] stereochemical assignments (*cis* versus *trans*) were made by correlating ^{1}H-NMR spectra with calculated low-energy conformations or by comparison with results previously reported.[19]

Results and Discussion

The affinities of analogs **1–17** for the σ_3, σ_1/σ_2, and DA D_1, D_2, and D_3 receptors are shown in Table 1 and discussed below.

Affinity for the σ_3 Receptor. None of the new PAT analogs **3–17** demonstrated binding affinity and selectivity for the σ_3 site comparable to that of the lead PATs **1** and **2**. Highest affinity in this new series is associated with the *cis*-1-methyl-1-phenyl analog **4** ($K_{0.5}$ = 2.5) which has 30-fold greater affinity than the corresponding *cis*-1-phenyl-1-normethyl analog **17**[13] ($K_{0.5}$ = 74 nM). The corresponding *trans*-1-phenyl-1-methyl isomer **3** ($K_{0.5}$ = 18.2 nM) had more than 16-fold *lower* affinity than the corresponding *trans*-1-phenyl-1-normethyl analog **2** ($K_{0.5}$ = 1.1 nM). These results indicate that the presence of a 1-methyl group (analogous to that found in the (+)-benzomorphans) enhances σ_3 affinity for the *cis* analogs (compare **4** to **17**). In the *trans* isomers, however, the presence of a 1-methyl substituent decreases σ_3 affinity (compare **2** to **3**). In addition, for the 1-methyl analog **4**, higher affinity is observed for the *cis* isomer, whereas in the 1-normethyl analog **2**, higher affinity is associated with the *trans* isomer.[13]

Extending the phenethylamine conformation of the *cis*- and *trans*-1-phenyl-3-aminotetralins[13] by expanding

Table 1. Binding Affinities of Phenylaminotetralin Derivatives for the [^{3}H]-(−)-**2**-Labeled σ_3, [^{3}H]DTG-Labeled σ_1/σ_2, [^{3}H]SCH-23390-Labeled D_1, and [^{3}H]Emonapride-Labeled D_2 and D_3 Dopamine Receptors[a]

	$K_{0.5}$ (nM)				
compd	σ_3	σ_1/σ_2	D_1	D_2	D_3
1	0.3 ± 0.1	2000 ± 200	420 ± 66	260 ± 120	ca. 300
2	1.1 ± 0.2	3100 ± 22	ca. 2500	ca. 5000	ca. 1000
(−)-**2**	0.5 ± 0.1	1100 ± 140	>5000	>5000	>1000
(+)-**2**	13.5 ± 2.3	1040 ± 130	>5000	>5000	ca. 1000
3	18.2 ± 1.4	690 ± 54	>5000	>5000	>1000
4	2.5 ± 0.5	1100 ± 58	>2500	>5000	ca. 1000
5	21.8 ±. 2.5	670 ± 70	>5000	ca. 5000	ca. 1000
6	120 ± 15	970 ± 160	>5000	>5000	>1000
7	980 ± 48	>5000	>5000	>5000	>1000
8	1300 ± 120	2000 ± 200	>5000	>5000	>1000
9	120 ± 34	970 ± 320	>5000	>5000	>1000
10	35.0 ± 4.0	ca. 6000	>5000	>2500	>1000
12	2530 ± 410	900 ± 300	>5000	ca. 5000	nd
13	1050 ± 570	720 ± 140	1530 ± 110	1600 ± 55	nd
14	150 ± 32	140 ± 26	54 ± 10	370 ± 53	nd
15	300 ± 25	300 ± 60	380 ± 60	540 ± 110	nd
16	280 ± 39	210 ± 29	440 ± 38	240 ± 17	nd
17	74 ± 9.2	560 ± 33	nd	nd	nd

[a] See experimental procedures for binding assay conditions. Compound **11** was not included since this PAT was used only as a synthetic intermediate.

the partially saturated carbocyclic ring of the tetralin system affords the *trans*- and *cis*-tetrahydrobenzocycloheptenes **5** ($K_{0.5} = 21.8$) and **6** ($K_{0.5} = 120$). These data indicate that extending the phenethylamine conformation of the *trans* configuration (as in **5**) results in a 20-fold decrease in σ_3 affinity compared to the less extended *trans* configuration (as in **2**, $K_{0.5} = 1.1$). Extending the phenethylamine conformation in the *cis* isomer (as in **6**) results in only a modest 1.6-fold decrease in σ_3 affinity (compared to **17**, $K_{0.5} = 74$ nM). The stereoselectivity (*trans* > *cis*), however, is similar for the tetrahydrobenzocycloheptenes **5** and **6** and the tetrahydronaphthalenes **2** and **17**.

Contracting the phenethylamine conformation of the *cis*- and *trans*-1-phenyl-3-aminotetralins by placing the amino group in the two position of the tetrahydronaphthalene ring affords the 1-phenyl-2-aminotetralins **7** ($K_{0.5} = 980$ nM) and **8** ($K_{0.5} = 1300$ nM). These results indicate that placing the amino group in the less extended 1-phenyl-2-amino conformation significantly decreases σ_3 affinity for both the *cis* and *trans* isomers as compared to the corresponding 1-phenyl-3-aminotetralins **2** and **17**.

Molecular modeling studies in our laboratory led to the proposition that the PATs interact with the σ_3 receptor in a four-sitepoint binding model which included the protonated nitrogen as a ligand-associated hydrogen bond donor sitepoint.[17] Results indicate that the cationic quaternary amine analog **10**, which is incapable of hydrogen bond donation, possesses moderate but significantly less affinity for the σ_3 receptor as compared to the tertiary amine analog **2**.[13] This result suggests that ligand affinity may be maximized by simultaneous ionic and hydrogen bond donation. Glennon[16] also reported that quaternization of aminopropanes dramatically decreases their affinity for σ_1 receptors. In further consideration of nitrogen substitution, the *trans* secondary amine analog **9** demonstrated ca. 100 less affinity compared to the *trans* tertiary amine analog **2**.

Glennon[16,18] has found that affinity of aminopropane σ_1 ligands benefits from *N*-phenylalkyl substitution. Although molecular modeling studies[17] indicate that large *N*-substituents such as those on GBR-12909 and ketanserin are well accommodated by the σ_3 receptor, the *N*-methyl-*N*-phenylethyl, *N*-methyl-*N*-phenylpropyl, and *N*-methyl-*N*-phenylbutyl analogs **14**−**16** do not appear to be well tolerated by the σ_3 receptor ($K_{0.5} =$ 150, 300, and 280 nM, respectively), suggesting that further refinement of the reported σ_3 binding model[17] is required. The corresponding *N*-normethyl analogs **12** and **13** possessed even lower affinity ($K_{0.5} = 2530 \pm 410$ and 1050 ± 570 nM) for the σ_3 receptor.

Affinity for σ_1 and σ_2 Receptors. As shown in Table 1, most of the present PATs (**1**−**13**) showed little affinity for σ_1/σ_2 receptors ($K_{0.5} > 300$). Interestingly, however, the large *N*-phenylalkyl substituents (as in analogs **14**−**16**) that decreased affinity for the σ_3 receptor enhanced affinity ($K_{0.5} \leq 560$) at σ_1/σ_2 receptors as compared to the dimethyl analog **2**.[13] These results are in accordance with the σ_1 binding pharmacophore suggested by Glennon.[18]

Affinity for Dopamine D_1, D_2, and D_3 Receptors. As shown in Table 1, most PAT analogs showed no significant affinity (i.e., $K_{0.5} > 300$ nM) for DA D_1, D_2, or D_3 receptors. The *N*-methyl-*N*-phenethyl analog **14**, however, showed moderate affinity ($IC_{50} = 54 \pm 10$ nM) for D_1 receptors.

The results discussed above further support our hypothesis that the neuromodulatory functional effects produced by the 1-phenyl-3-aminotetralins[13] involve a novel σ receptor (σ_3) that is distinct from σ_1/σ_2 sites and DA receptors in mammalian forebrain. *N*-Phenylalkyl substituents, such as *N*-phenylethyl, endowed the 1-phenyl-3-aminotetralins with enhanced σ_1/σ_2 and dopamine receptor affinity while decreasing σ_3 affinity, thus abolishing σ_3 selectivity.

Experimental Section

All chemicals were used as received from the manufacturers. 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%. Sprague−Dawley albino rats (250−300 g) were obtained from Charles River Labs, Wilmington, MA.

3-Bromo-2-phenyl-1-propene (**18**). The procedure of Kandeel and Martin[19] was used to prepare 18 by bromination of α-methylstyrene (**17**) with *N*-bromosuccinimide in the presence of benzoyl peroxide. Of the 37.5 g of a clear, yellow oil obtained, gas chromatographic analysis revealed an ca. 4:1 ratio of product to 1-bromo-2-phenyl-1-propene, and therefore 17.2 g (42%) of product was afforded and used without further purification.

2,5-Diphenyl-4,4-bis(ethoxycarbonyl)-1-pentene (**19**). The procedure of Kandeel and Martin[19] was used to prepare **19** from 24.3 g (0.097 mol) of diethyl benzylmalonate and 17.2 g (0.088 mol) of **18**. Column chromatography of the crude oil on silica gel using hexanes and then toluene as eluant afforded 27.2 g (84%) of product as a yellow oil: ^{1}H-NMR δ 7.25 (m, 10H, ArH_{10}), 5.25 (m, 2H, $=CH_2$), 3.85 (m, 4H, CH_3CH_2), 3.20 (s, 2H, $PhCH_2$), 3.1 (s, 2H, CH_2), 1.10 (t, 6H, CH_3CH_2).

(±)-**1-Phenyl-1-methyl-3,3-bis(ethoxycarbonyl)-1,2,3,4-tetrahydronaphthalene** (**20**).[19] Compound **19** (27.2 g, 0.074 mol) was placed in a 500 mL poly(propylene) bottle, and 75 g of pyridinium poly(hydrogen fluoride) was added. The mixture was then stirred overnight at room temperature. The excess hydrogen fluoride was neutralized by addition of water followed by 200 mL of 20% aqueous NaOH, and the organic material was extracted into ether. The combined ether extracts were dried (Na_2SO_4) and evaporated *in vacuo* to afford 27.3 g (100%) of a light orange oil. Gas chromatographic and ^{1}H-NMR analysis indicated essentially pure product which was used in the next step without further purification: ^{1}H-NMR δ 7.20 (m, 9H, ArH_9), 4.18 (q, 4H, CH_2CH_3), 3.75 (m, 2H, $PhCH_2$), 3.35 (m, 2H, CH_2), 1.68 (s, 3H, CH_3), 1.20 (t, 3H, CH_2CH_3), 1.00 (m, 3H, CH_2CH_3).

***trans*- and *cis*-(±)-1-Phenyl-1-methyl-3-carboxy-1,2,3,4-tetrahydronaphthalene (21 and 22).** The procedure of Kandeel and Martin[19] was used to convert 27.2 g (0.075 mol) of **20** to 18.5 g (93%) of a mixture of **21** and **22** as colorless solids. Separation of the *cis* and *trans* diastereomers was accomplished by careful recrystallization from glacial acetic acid to afford 4.5 g of the racemic *cis* (mp 178–184 °C) and 3.4 g of the *trans* (mp 167–174 °C) diastereomers: ^{1}H-NMR (*cis* isomer) δ 6.91–7.30 (m, 9H, ArH_9), 3.12 (m, 2H, $PhCH_2$), 2.58 (m, 1H, CHCOOH), 2.02–2.40 (m, 2H, CH_2), 1.78 (s, 3H, CH_3); ^{1}H-NMR (*trans* isomer) δ 6.80–7.40 (m, 9H, ArH_9), 3.05 (m, 2H, $PhCH_2$), 2.21 (m, 2H, CH_2), 1.70 (s, 3H, CH_3).

(±)-*cis*-1-Phenyl-1-methyl-3-amino-1,2,3,4-tetrahydronaphthalene (27). A mixture of 4.5 g (0.017 mol) of *cis*-**22** and 30 mL of thionyl chloride was stirred at reflux for 4 h. The excess thionyl chloride was removed *in vacuo* to afford 5.0 g of the crude acid chloride which was dissolved in 40 mL of dry acetone. This solution was cooled in an ice bath and treated with a solution of 1.2 g (0.019 mol) of sodium azide in 4 mL of water. After stirring for 45 min, 80 mL of cold water was added and the azide was extracted into CH_2Cl_2. The organic extracts were washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated *in vacuo* to afford 4.6 g of a light yellow solid. The crude acyl azide **23** was dissolved in 40 mL of ethanol and refluxed overnight. The solvent was removed *in vacuo* to afford 5.1 g of the urethane as a yellow gum. Column chromatography of this gum on silica gel (CH_2Cl_2) afforded 1.9 g (37%) of pure urethane **25**. This urethane was dissolved in a 2:1 mixture of concentrated HCl and glacial acetic acid, and the solution was stirred at reflux for 16 h. The volatiles were removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to afford 1.6 g (100%) of the amine **27** as a brown gum: ^{1}H-NMR δ 6.90–7.32 (m, 9H, ArH_9), 3.00 (m, 2H, $PhCH_2$), 2.63 (m, 1H, $CHNH_2$), 2.15 (m, 2H, CH_2), 1.80 (s, 3H, CH_3).

(±)-*trans*-1-Phenyl-1-methyl-3-amino-1,2,3,4-tetrahydronaphthalene (28). The *trans* acyl azide **24** was obtained as above for **23** from 3.4 g (0.013 mol) of the corresponding *trans* acid **21**. The acyl azide (3.5 g) was converted to 3.8 g of the urethane **26** which was hydrolyzed to afford 1.3 g (100%) of the amine **28** as a brown gum: ^{1}H-NMR δ 6.90–7.42 (m, 9H, ArH_9), 3.15 (m, 2H, $PhCH_2$), 2.63 (m, 1H, $CHNH_2$), 2.15 (m, 2H, CH_2), 1.70 (s, 3H, CH_3).

(±)-*trans*-1-Phenyl-1-methyl-3-(dimethylamino)-1,2,3,4-tetrahydronaphthalene (3). The *trans* primary amine **28** (0.94 g, 3.8 mmol), 18 mL of 96% formic acid, and 12 mL of 37% aqueous formaldehyde were combined and stirred at reflux for 5 h. The volatiles were removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4) and evaporated *in vacuo* to afford 1.1 g of greenish colored gum. This gum was converted to the hydrochloride salt by dissolution in ether and treatment of this solution with ethereal HCl. The hydrochloride salt was recrystallized from ethanol/ether to afford 305 mg (51%) of product as a colorless solid: mp 247–249 °C; ^{1}H-NMR δ 6.70–7.35 (m, 9H, ArH_9), 2.95 (m, 2H, $PhCH_2$), 2.38 (s, 6H, $N(CH_3)_2$), 2.35 (m, 1H, CHN), 1.98 (m, 2H, CH_2), 1.70 (s, 3H, CH_3). Anal. Calcd for $C_{19}H_{21}ClN$: C, 75.61; H, 8.02; N, 4.63. Found: C, 76.06; H, 8.13; N, 4.65.

(±)-*cis*-1-Phenyl-1-methyl-3-(dimethylamino)-1,2,3,4-tetrahydronaphthalene (4). The *cis* primary amine **27** was converted to the tertiary amine 4 as above to afford 1.1 g of a green gum. This gum was converted to the hydrochloride salt by dissolution in ether and treatment of this solution with ethereal HCl. The hydrochloride salt was recrystallized from ethanol/ether to afford 750 mg (60%) of product as a colorless solid: mp 250–251 °C; ^{1}H-NMR δ 6.90–7.35 (m, 9H, ArH_9), 2.85 (m, 2H, $PhCH_2$), 2.43 (m, 1H, $CHNH_2$), 2.23 (m, 2H, CH_2), 1.75 (m, 3H, CH_3). Anal. Calcd for $C_{19}H_{21}ClN$: C, 75.61; H, 8.02; N, 4.63. Found C, 75.57; H, 8.16; N, 4.51.

1,5-Diphenylpent-1-en-3-one (30). A solution of 25.0 g (0.169 mol) of benzylacetone (**29**) and 37.2 g (0.351 mol) of benzaldehyde was added in one portion to a mechanically stirred solution of 4.8 g (0.085 mol) of KOH in 1400 mL of water. The reaction mixture was stirred at 55 °C overnight. The cooled mixture was acidified to pH = 4 with concentrated HCl and extracted with CH_2Cl_2. The volatiles were removed on a rotary evaporator with the aid of a vacuum pump, and the residual oil was crystallized from methanol to afford 18.9 g (%) of yellow crystals: mp 44–45 °C; ^{1}H-NMR δ 7.30–7.60 (m, 10H, ArH_{10}), 6.73 (d, 2H, styrylH), 3.05 (s, 4H, $PhCH_2CH_2$).

(±)-5-Phenyl-7-oxo-5,6,7,8-tetrahydro-9*H*-benzocycloheptene (31). A solution of 18.9 g (mol) of **30** in 200 mL of xylenes was added to a mechanically stirred suspension of 80 g of polyphosphoric acid (PPA) in 800 mL of xylenes. After 5 h at reflux, gas chromatographic analysis indicated absence of starting material and appearance of a product peak. The cooled xylene layer was decanted and evaporated *in vacuo* to afford 26.5 g (>100%) of the crude product ketone as a gum. Column chromatography on silica gel with toluene afforded 3.5 g (19%) of product as a gum: ^{1}H-NMR δ 7.00–7.50 (m, 9H, ArH_9), 4.45 (dd, 1H, PhCHPh), 2.60–3.35 (m, 4H, $PhCH_2CH_2$), 2.20 (m, 2H, $CHCH_2CO$).

(±)-*cis*- and *trans*-5-Phenyl-7-hydroxy-5,6,7,8-tetrahydro-9*H*-benzocycloheptene (32 and 33). Solid $NaBH_4$ (1.7 g, 0.045 mol) was added cautiously in portions to a magnetically stirred solution of 3.5 g (0.015 mol) of **31** in 100 mL of methanol with cooling in an ice bath. The reaction mixture was then stirred at reflux overnight and cautiously diluted with 50 mL of water, and the volatiles were removed *in vacuo*. The residue was dissolved in CH_2Cl_2, extracted with water, dried (Na_2SO_4), and evaporated *in vacuo* to afford 3.2 g of an ca. 60:40 mixture of the crude *cis* and *trans* alcohols which were resolved by column chromatography on silica gel (CH_2Cl_2/toluene, 1:1) to afford 0.7 g of the predominantly *trans* isomer and 0.9 g of the predominantly *cis* isomer as gums. The total yield of alcohols was 46%. The separated isomers were carried on through the subsequent synthetic steps individually: ^{1}H-NMR (*trans* isomer **33**) δ 6.81–7.45 (m, 9H, ArH_9), 4.65 (d, 1H, PhCHPh), 3.15 (m, 1H, CHOH), 2.53 (m, 2H, $PhCH_2$), 1.85 (m, 2H, $PhCH_2CH_2$); ^{1}H-NMR (*cis* isomer) **32** δ 6.50–7.45 (m, 9H, ArH_9), 4.05 (m, 1H, PhCHPh), 2.88 (m, 2H, $PhCH_2$), 2.95 (m, 2H, $PhCH_2CH_2$), 2.50 (m, 1H, CHOH), 1.89 (q, 2H, $CHCH_2CHOH$).

(±)-*trans*-5-Phenyl-7-azido-5,6,7,8-tetrahydro-9*H*-benzocycloheptene (34). A solution of 2.0 g (10.7 mmol) of *p*-toluenesulfonyl chloride in 25 mL of dry pyridine was added to a solution of 900 mg (3.78 mmol) of *cis* **32** in 25 mL of dry pyridine. The reaction mixture was allowed to stand for 5 days at 5 °C and then poured into ice water with stirring. The product precipitated as a gum and was extracted into ether. This ether solution was extracted with 100 mL of 1.0 N HCl, dried (Na_2SO_4), and evaporated *in vacuo* to afford 1.4 g (95%) of the crude tosylate as a gum. A solution of 0.6 g (9.3 mmol) of sodium azide in 2 mL of water was added in small portions to a stirred solution of 1.4 g (3.7 mmol) of the tosylate in 20 mL of DMF. The reaction mixture was stirred for 30 h at 45–50 °C, at which time all of the tosylate was consumed. The reaction mixture was poured into ice water and extracted with ether. The organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to afford 900 mg (91%) of the *trans* azide **34** as a gum which was used in the next step without further purification: ^{1}H-NMR δ 6.70–7.40 (m, 9H, ArH_9), 4.55 (d, 1H, PhCHPh), 3.78 (m, 1H, CHN_3), 1.80–3.15 (m, 6H, $(CH_2)_3$).

(±)-*cis*-5-Phenyl-7-azido-5,6,7,8-tetrahydro-9*H*-benzocycloheptene (35). *trans*-**33** was converted to the *cis* azide **31** as above for the *trans* azide to afford 600 g (78%) of product as a yellow gum. Reaction time (7 h) for conversion of the tosylate to the azide was much shorter than for the *trans* azide: ^{1}H-NMR δ 6.52–7.50 (m, 9H, ArH_9), 4.14 (d, 1H, PhCHPh), 3.70 (m, 1H, CHN_3), 2.95 (m, 2H, $PhCH_2$), 2.45 (m, 2H, $PhCH_2CH_2$), 2.00 (q, 2H, $PhCHPhCH_2$).

(±)-*cis* and *trans*-5-Phenyl-7-amino-5,6,7,8-tetrahydro-9*H*-benzocycloheptene (36 and 37). The corresponding azides **34** and **35** (2.3 mmol of the *cis*, 3.4 mmol of the *trans*) were dissolved in 30 mL of 2-propanol containing 2 mL of CH_2Cl_2 and shaken on a Parr hydrogenation apparatus over 0.1 g of 10% Pd on carbon at 45 ps overnight. The catalyst was filtered off and the filtrate evaporated *in vacuo* to afford the crude amines as gums. The crude products were column chromatographed on silica gel (CH_2Cl_2/MeOH, 9:1) to afford the racemic *cis* product (92%) as a colorless solid (mp 95–97 °C) and the *trans* product (87%) as a gum: ^{1}H-NMR (*trans* isomer **33**) δ 6.90–7.35 (m, 9H, ArH_9), 4.40 (d, 1H, PhCHPh), 3.21 (m, 2H, $PhCH_2$), 1.40–2.95 (m, 5H, CH_2CHCH_2); ^{1}H-NMR (*cis* isomer **32**) δ 6.30–7.45 (m, 9H, ArH_9), 4.10 (d, 1H, PhCHPh), 3.45 (m, 2H, $PhCH_2$), 2.85 (m, 2H, $PhCH_2CH_2$), 2.45 (m, 1H, $CHNH_2$), 1.85 (q, 2H, CH_2CHNH_2).

(±)-*trans* and *cis*-5-Phenyl-7-(dimethylamino)-5,6,7,8-tetrahydro-9*H*-benzocycloheptene (5 and 6). The appropriate primary amines (**32** and **33**) were dimethylated as above for **3** to afford crude **5** and **6**. The *trans* isomer **5** resisted crystallization after conversion to the hydrochloride salt and was therefore column chromatographed as the free base on silica gel with EtOAc/hexanes/EtOH/NH_4OH (60:25:14:1) to afford 168 mg (21%) of pure *trans* product **5** as a gum. The crude *cis* isomer **6** was converted to the hydrochloride salt and recrystallized from EtOAc to afford 247 mg (39%) of product **6** as a colorless solid: 265–267 °C; ^{1}H-NMR (*cis* isomer, HCl salt) δ 6.50–7.45 (m, 9H, ArH_9), 4.12 (d, 1H, PhCHPh), 2.90 (m, 3H, $PhCH_2$, CHN), 2.45 (s, 6H, $N(CH_3)_2$), 1.85 (m, 2H, CH_2CH_2), 1.45 (m, 2H, $CHCH_2$); ^{1}H-NMR (*trans* isomer, free base) δ 7.00–7.35 (m, 9H, ArH_9), 4.53 (d, 1H, PhCHPh), 1.50–2.90 (m, 7H, $CH_2CH_2CHCH_2$), 2.35 (s, 6H, $N(CH_3)_2$). Anal. Calcd for $C_{19}H_{24}ClN$ (*cis* as monohydrate): C, 71.37; H, 8.14. Found: C, 71.31; H, 8.23. Anal. Calcd for $C_{19}H_{24}ClN$ (*trans* as monohydrate): C, 71.37; H, 8.14. Found: C, 71.76; H, 8.00.

(±)-*cis*-1-Phenyl-2-hydroxy-1,2,3,4-tetrahydronaphthalene (40). The synthesis of the *trans* alcohol **38** has been previously described.[13,21] As in our previous report, the *trans*-1-phenyl-3-hydroxy-1,2,3,4-tetrahydronaphthalenes were epimerized to the *cis* form by the procedure of Bose.[22] The *trans* alcohol **38** (2.5 g, 0.011 mol), 8.8 g (0.034 mol) of triphenylphosphine, and 4.1 g (0.034 mol) of benzoic acid were dissolved in 60 mL of dry THF. A solution of 5.9 g (0.034 mol) of diethyl azodicarboxylate in 20 mL of dry THF was added over a 10 min period. The reaction mixture was then stirred at 40 °C for 5 h. The volatiles were removed *in vacuo*, and the residue was dissolved in CCl_4. After storage at 10 °C for 2 h, the precipitated triphenylphosphine oxide was filtered off and the filtrate evaporated *in vacuo* to afford the crude *cis* benzoate ester. Column chromatography on silica gel (CCl_4) afforded 1.9 g (52%) of the pure *cis* ester as a gum. A total of 2.1 g (6.4 mmol) of the ester was dissolved in 50 mL of methanol, and a solution of 1.1 g (19.2 mmol) of KOH in 20 mL of methanol was added. The reaction mixture was stirred at reflux for 4 h, at which time the methanol was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and water. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to afford 1.0 g (70%) of the *cis* alcohol as a light orange gum: ^{1}H-NMR δ 6.90–7.40 (m, 9H, ArH_9), 4.38 (d, 1H, PhCHPh), 4.20 (m, 1H, CHOH), 3.15 (m, 1H, PhCH), 2.90 (m, 1H, PhCH), 1.95 (m, 2H, $PhCH_2CH_2$).

(±)-*trans*-1-Phenyl-2-azido-1,2,3,4-tetrahydronaphthalene (41). *p*-Toluenesulfonyl chloride (2.2 g, 11.3 mmol) was added to a cooled solution of **40** in 50 mL of dry pyridine. After standing at 5 °C for 5 days, the reaction mixture was poured into 800 mL of ice water. The gummy precipitate was extracted into ether, and the ether extracts were washed with 1.0 N HCl, dried (Na_2SO_4), and evaporated *in vacuo* to afford 1.3 g (87%) of the tosylate as a light orange gum which was converted to the azide without further purification. A solution of 0.6 g (8.5 mmol) of NaN_3 in 2 mL of water was added to a solution of 1.3 g (3.4 mmol) of the tosylate, and the reaction mixture was stirred at 50 °C for 24 h. The reaction mixture was poured into 400 mL of water and extracted with ether. The ether extracts were dried (Na_2SO_4) and evaporated *in vacuo* to afford 0.9 g (100%) of the *trans* azide as a light yellow gum which was converted to the primary amine below without further purification.

(±)-*trans*-1-Phenyl-2-amino-1,2,3,4-tetrahydronaphthalene (42). A solution of 0.4 g (1.6 mmol) of the *trans* azide **41** in 130 mL of 2-propanol was shaken for 48 h over 100 mg of 10% Pd on charcoal on a Parr shaker apparatus under 55 ps of hydrogen at room temperature. The catalyst was filtered off and the filtrate evaporated *in vacuo* to afford a tan gum. Column chromatography on silica gel (CH_2Cl_2 and then CH_2Cl_2/MeOH, 95:5) afforded 50 mg (15%) of the amine as a gum: ^{1}H-NMR δ 6.70–7.40 (m, 9H, ArH_9), 3.80 (d, 1H, PhCHPh), 3.00 (m, 2H, $PhCH_2$), 2.13 (m, 1H, $CHNH_2$), 1.75 (m, 2H, CH_2).

(±)-*trans*-1-Phenyl-2-(dimethylamino)-1,2,3,4-tetrahydronaphthalene (7). The primary amine **38** (50 mg, 0.22 mmol) was dimethylated as above for **3** to afford the crude tertiary amine as a light green gum. The hydrochloride salt was formed by treatment of an ethanolic solution of the crude amine with ethereal HCl. The salt was recrystallized from ethyl acetate/ether to afford 38 mg (65%) of the pure product as a light yellow solid: mp 168–170 °C; ^{1}H-NMR δ 6.70–7.40 (m, 9H, ArH_9), 3.80 (d, 1H, PhCHPh), 3.00 (m, 2H, $PhCH_2$), 2.58 (s, 6H, $N(CH_3)_2$), 2.13 (m, 1H, $CHNH_2$), 1.75 (m, 2H, CH_2). Anal. Calcd for $C_{18}H_{22}ClN$: C, 75.11; H, 7.71. Found: C, 75.12; H, 7.79.

(±)-*trans*-1-Phenyl-3-(*N*-methylamino)-1,2,3,4-tetrahydronaphthalene (9). Diethyl azodicarboxylate (77 mg, 0.44 mmol) in 3 mL of toluene was added to 90 mg (0.36 mmol) of **2** in 4 mL of toluene, and the reaction mixture was stirred at 50 °C overnight. The volatiles were removed *in vacuo*, and the residue was stirred at reflux in 2 mL of EtOH/saturated NH_4Cl (1:1) for 4 h. The volatiles were removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was dried (Na_2SO_4) and evaporated *in vacuo* to afford 80 mg of crude gum which was column chromatographed on silica gel with CH_2Cl_2 and CH_2Cl_2/MeOH (95:5) to afford the product as free base. This gum was converted to the hydrochloride salt by treatment with ethereal HCl, and the salt was recrystallized from EtOH/Et_2O to afford 17 mg (17%) of colorless crystals: mp 215–218 °C; ^{1}H-NMR δ 6.90–7.52 (m, H, ArH9), 4.3 (t, 1H, PhCHPh), 2.6 (m, 1H, CHN), 3.0–2.7 (m, 2H, $PhCH_2$), 2.25 (s, 6H, $N(CH_3)_2$). Anal. Calcd for $C_{17}H_{20}ClN$: C, 74.6; H, 7.37; N, 5.12. Found: C, 73.83; H, 7.63; N, 4.93.

(±)-*trans*-1-Phenyl-3-(trimethylammoniumyl)-1,2,3,4-tetrahydronaphthalene Iodide (10). Methyl iodide (130 mg, 0.92 mmol) was added to a solution of **2** (46 mg, 0.184 mmol) in 20 mL of anhydrous ether, and the reaction mixture was allowed to stand at room temperature overnight. The methiodide salt precipitated and was filtered and dried to afford the crude product. Recrystallization from EtOAc/Et_2O afforded 29 mg (40%) of pure product as a colorless solid: mp 245–247 °C; ^{1}H-NMR δ 6.90–7.30 (m, 9H, ArH_9), 4.61 (t, 3H, PhCHPh), 3.38 (m, 1H, CHN), 2.62 (s, 9H, $N(CH_3)_3$). Anal. Calcd for $C_{19}H_{24}IN$: C, 58.02; H, 6.15; N, 3.56. Found: C, 58.12; H, 6.23; N, 3.41.

(±)-*trans*-1-Phenyl-3-(phenylacetamido)-1,2,3,4-tetrahydronaphthalene (44). Phenylacetyl chloride (500 mg, 3.25 mmol) in 5 mL of CH_2Cl_2 was added dropwise under N_2 to a stirred solution of 600 mg (2.69 mmol) of the primary amine **43** and 2 mL of triethylamine in 10 mL of CH_2Cl_2 (Scheme 4). The reaction mixture was stirred for 24 h at room temperature. The volatiles were removed *in vacuo*, and the residue was dissolved in Et_2O and extracted with water, saturated $NaHCO_3$, and then dilute HCl. The organic phase was dried (Na_2SO_4) and evaporated *in vacuo* to afford 300 mg of a gum. Column chromatography of this gum on silica gel (CH_2Cl_2, CH_2Cl_2/Et_2O, 9:1) afforded 270 mg (29%) of product as a light yellow gum: ^{1}H-NMR δ 6.9–7.4 (m, 14H, ArH_{14}), 5.40 (d, 1H, NH), 4.4 (m, 1H, CHN), 4.05 (t, 1H, PhCHPh), 3.55 (s, 2H, CH_2CO), 3.3 (dd, 1H, $PhCH_2$), 2.6 (dd, 1H, $PhCH_2$), 2.1 (m, 2H, $PhCHPhCH_2$).

(±)-*trans*-1-Phenyl-3-(3-phenylpropionamido)-1,2,3,4-tetrahydronaphthalene (45). Hydrocinnamoyl chloride (441 mg, 2.69 mmol) in 5 mL of CH_2Cl_2 was added dropwise under N_2 to a stirred solution of 500 mg (2.24 mmol) of the primary amine **43** and 2 mL of triethylamine in 10 mL of CH_2Cl_2 (Scheme 4). The reaction mixture was stirred for 24 h at room temperature. The volatiles were removed *in vacuo*, and the residue was dissolved in Et_2O and extracted with water, saturated $NaHCO_3$, and then dilute HCl. The organic phase was dried (Na_2SO_4) and evaporated *in vacuo* to afford a gum. Column chromatography of this gum on silica gel (CH_2Cl_2, CH_2Cl_2/Et_2O, 9:1) afforded 520 mg (67%) of product as a light yellow gum: ^{1}H-NMR δ 6.9–7.4 (m, 14H, ArH_{14}), 5.38 (d, 1H, NH), 4.4 (m, 1H, CHN), 4.05 (t, 1H, PhCHPh), 3.3 (dd, 1H, $PhCH_2$), 2.95 (t, 2H, $PhCH_2CH_2$), 2.6 (dd, 1H, $PhCH_2$), 2.45 (t, 2H, $PhCH_2CH_2$), 2.1 (m, 2H, $PhCHPhCH_2$).

(±)-*trans*-1-Phenyl-3-(4-phenylbutyramido)-1,2,3,4-tetrahydronaphthalene (46). Compound **43** was converted to the amide **46** as above by treatment with 614 mg (3.36 mmol) of 4-phenylbutyryl chloride to afford 700 mg (85%) of product as a light yellow gum: ^{1}H-NMR δ 6.9–7.4 (m, 14H, ArH_{14}), 5.38 (d, 1H, NH), 4.4 (m, 1H, CHN), 4.15 (t, 1H, PhCHPh), 3.35 (dd, 1H, $PhCH_2$), 2.7 (dd, 1H, $PhCH_2$), 2.65 (t, 2H, $PhCH_2CH_2$), 2.15 (t, 2H, $PhCH_2CH_2$), 2.1 (m, 2H, $PhCHPhCH_2$), 2.0 (m, 2H, $PhCH_2CH_2CH_2$).

(±)-*trans*-1-Phenyl-3-[(2-phenylethyl)amino]-1,2,3,4-tetrahydronaphthalene (11). Compound **44** (270 mg, 0.79 mmol) in 20 mL of Et_2O was added dropwise to a stirred slurry of 90 mg (2.4 mmol) of lithium aluminum hydride (LAH) in 20 mL of Et_2O under N_2. The reaction mixture was then stirred at reflux for 6 h and cooled in ice, and the excess LAH was decomposed by cautious dropwise addition of ice water. The mixture was suction filtered and the filter cake washed thoroughly with Et_2O. The organic phase was dried (Na_2SO_4) and evaporated *in vacuo* to afford 202 mg (77%) of product as a light yellow solid which was ca. 95% pure by thin layer chromatography: mp 58–56 °C; ^{1}H-NMR (free base) δ 6.8–7.35 (m, 14H, ArH_{14}), 4.25 (t, 1H, PhCHPh), 2.60–3.05 (m, 6H, $PhCH_2$, $PhCH_2CH_2N$), 2.05 (t, 2H, NCH_2), 1.75 (m, 4H, $PhCH_2CH_2CH_2$, $PhCHCH_2$).

(±)-*trans*-1-Phenyl-3-[(3-phenylpropyl)amino]-1,2,3,4-tetrahydronaphthalene (12). Compound **45** (500 mg, 1.4 mmol) in 20 mL of Et_2O was added dropwise to a stirred slurry of 160 mg (4.2 mmol) of LAH in 20 mL of Et_2O under N_2. The reaction mixture was then stirred at reflux for 6 h and cooled in ice, and the excess LAH was decomposed by cautious dropwise addition of ice water. The mixture was suction filtered and the filter cake washed thoroughly with Et_2O. The organic phase was dried (Na_2SO_4) and evaporated *in vacuo* to afford 277 mg (56%) of product as a light yellow gum which was ca. 95% pure by thin layer chromatography. This gum (122 mg) was dissolved in 20 mL of MeOH and treated with 0.5 mL of concentrated HCl. The solution was evaporated *in vacuo*, and the solid residue was recrystallized from EtOAc–EtOH to afford 62 mg (13%) of colorless solid: mp 175–177 °C; ^{1}H-NMR (free base) δ 6.9–7.35 (m, 14H, ArH_{14}), 4.3 (t, 1H, PhCHPh), 3.05 (m, 2H, $PhCH_2$), 2.6 (m, 3H, CHN, $PhCH_2$), 2.05 (t, 2H, NCH_2), 1.75 (m, 4H, $PhCH_2CH_2CH_2$, $PhCHCH_2Ph$). Anal. Calcd for $C_{25}H_{28}ClN$: C, 79.49; H, 7.41; N, 3.71. Found: C, 79.02; H, 7.64; N, 3.79.

(±)-*trans*-1-Phenyl-3-[(4-phenylbutyl)amino]-1,2,3,4-tetrahydronaphthalene (13). Amide **46** (700 mg, 1.9 mmol) was reduced as above to afford 600 mg of **13** as a gum. Conversion to the hydrochloride salt followed by recrystallization from EtOAc–EtOH afforded 312 mg (42%) of pale yellow crystals: mp 52–55 °C; ^{1}H-NMR (free base) δ 6.9–7.35 (m, 14H, ArH_{14}), 4.3 (t, 1H, PhCHPh), 3.05 (m, 2H, $PhCH_2$), 2.6 (m, 3H, CHN, $PhCH_2$), 2.05 (t, 2H, NCH_2), 1.5 (m, 6H, $PhCH_2CH_2CH_2$, $PhCHCH_2Ph$). Anal. Calcd for $C_{26}H_{29}N\cdot{}^1/_2H_2O$: C, 86.44; H, 8.21; N, 3.87. Found: C, 86.78; H, 8.14; N, 3.87.

(±)-*trans*-1-Phenyl-3-[(2-phenylethyl)-*N*-methylamino]-1,2,3,4-tetrahydronaphthalene (14). Compound **11** (202 mg, 0.59 mmol) was methylated as above for **3** to afford the tertiary amine **15** as a gum. This gum was converted to the hydrochloride salt which resisted recrystallization. Therefore, the salt was converted back to free base and column chromatographed on silica gel (CH_2Cl_2/MeOH, 95:5) to afford 80 mg (38%) of gum: ^{1}H-NMR (free base) δ 6.9–7.35 (m, 14H, ArH_{14}), 4.3 (t, 1H, PhCHPh), 3.05 (m, 2H, $PhCH_2$), 2.6 (m, 2H, $PhCH_2$), 2.4 (s, 3H, CH_3), 2.05 (t, 2H, NCH_2). Anal. Calcd for $C_{25}H_{27}N$: C, 87.98; H, 7.91; N, 4.10. Found: C, 86.66; H, 7.95; N, 3.89.

(±)-*trans*-1-Phenyl-3-[(3-phenylpropyl)-*N*-methylamino]-1,2,3,4-tetrahydronaphthalene (15). Compound **12** (155 mg, 0.454 mmol) was methylated as above for **3** to afford the tertiary amine **15** as a gum. This gum was converted to the hydrochloride salt which resisted recrystallization. Therefore, the salt was converted back to free base and column chromatographed on silica gel (CH_2Cl_2/MeOH, 95:5) to afford 83 mg (45%) of gum: ^{1}H-NMR (free base) δ 6.9–7.35 (m, 14H, ArH_{14}), 4.3 (t, 1H, PhCHPh), 3.05 (m, 2H, $PhCH_2$), 2.6 (m, 2H, $PhCH_2$), 2.4 (s, 3H, CH_3), 2.05 (t, 2H, NCH_2), 1.75 (m, 4H, $PhCH_2CH_2CH_2$, $PhCHCH_2Ph$). Anal. Calcd for $C_{26}H_{29}N\cdot{}^1/_2H_2O$: C, 86.44; H, 8.21; N, 3.87. Found: C, 86.66; H, 8.49; N, 3.88.

(±)-*trans*-1-Phenyl-3-[(4-phenylbutyl)-*N*-methylamino]-1,2,3,4-tetrahydronaphthalene (16). Compound **13** (259 mg, 0.73 mmol) was methylated as above for **3** to afford 323 mg of the tertiary amine **14** as a gum. This gum was converted to the hydrochloride salt which resisted recrystallization. Therefore, the salt was converted back to free base and column chromatographed on silica gel (CH_2Cl_2/MeOH, 95:5) to afford the pure gum which was then converted back to 101 mg (38%) of the hydrochloride salt as pale yellow crystals: mp 50–53 °C; ^{1}H-NMR (free base) δ 6.9–7.35 (m, 14H, ArH_{14}), 4.3 (t, 1H, PhCHPh), 3.05 (m, 2H, $PhCH_2$), 2.6 (m, 2H, $PhCH_2$), 2.42 (s, 3H, CH_3), 2.05 (t, 2H, NCH_2), 1.5 (m, 6H, $PhCH_2CH_2CH_2$, $PhCHCH_2Ph$). Anal. Calcd for $C_{27}H_{31}N\cdot{}^1/_3H_2O$): C, 85.72; H, 8.24; N, 3.84. Found: C, 85.46; H, 8.63; N, 3.65.

Radioreceptor Assays. Specific high-affinity radioreceptor assays using rodent brain tissue homogenates were used to determine affinity of test compounds for σ (σ_1/σ_2, σ_3) and dopamine (D_1, D_2, D_3) receptors. Test ligands were evaluated at six to eight concentrations (spanning 0.01–10 000 nM, in triplicate glass tubes) in competition with receptor-specific radioligands, and results were analyzed by nonlinear regression using sigmoidal curve-fitting algorithms in the microcomputer program ALLFIT[23,25] or Prism[26] to obtain IC_{50} values. IC50 values then were converted to corresponding $K_{0.5}$ values using the equation $K_{0.5} = IC_{50}/(1 + L/K_D)$, where L is the concentration of radioligand having affinity K_D.[27] Each assay was repeated twice to determine $K_{0.5} \pm$ SEM.

For σ radioreceptor assays, frozen guinea pig brain (minus cerebellum; Rockford Biologicals, Gilbertsville, PA) was thawed and homogenized (10 mL/g of tissue) in ice-cold 10 mM Tris buffer (pH 7.4) containing 0.32 M sucrose. The homogenate was centrifuged at 1000*g* for 15 min at 4 °C and the supernatant recentrifuged at 31000*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 of tissue and incubated at room temperature for 15 min before recentrifuging at 31000*g* for 15 min at 4 °C. The resulting P_3 pellet was stored at −70 °C in 10 mM Tris (pH 7.4) at ca. 5.0 mg of protein/mL.

Initially, a saturation isotherm was constructed to determine kinetic parameters for the σ_3 radioligand [^{3}H]-(−)-H_2-PAT ([^{3}H]-[−]-**2**; specific activity = 85 Ci/mmol).[28] Eight concentrations (spanning 0.01–5.0 nM, in triplicate) of [^{3}H]-(−)-H_2-PAT were incubated for 60 min at 30 °C with 0.5 mg of protein homogenate from guinea pig brain and 10.0 μM ketanserin (to define nonspecific binding) in 10 mM Tris buffer (pH 7.4; total assay vol 1.0 mL). Assay mixtures then were filtered in a Cambridge Technology cell harvester through glass fiber sheets (GF/B) which were subsequently washed with ice-cold 10 mM Tris (pH 7.4) and counted for tritium by liquid scintillation spectrometry at 50% efficiency. Results were analyzed as a rectangular hyperbola using nonlinear regression with Prism to determine [^{3}H]-(−)-H_2-PAT apparent affinity (K_D = 0.13 nM) and density of binding sites (B_{max} = 30 fmol/mg of protein).

For σ receptor competitive binding assays, test ligands were incubated in 10 mM Tris buffer (pH 7.4) with 0.10 nM [^{3}H]-

(−)-H$_2$-PAT, 0.25 mg of protein homogenate prepared from guinea pig brain, and 10.0 μM ketanserin (for σ_3 assays; total vol 1.0 mL) or 2.0 nM [^{3}H]ditolylguanidine (specific activity = 39 Ci/mmol; DuPont New England Nuclear), 0.5 mg of protein, and 1.0 μM haloperidol (for σ_1/σ_2 assays; total vol 0.5 mL).[24] Mixtures were incubated for 60 min at 30 °C and then filtered and counted, as above.

For dopamine D$_1$ and D$_2$ receptor competitive binding assays,[29−31] test ligands were incubated with 30 μg of protein homgenate prepared from rat corpus striatum in 10 mM Tris buffer (containing 150 mM NaCl, pH 7.4) at 30 °C with 0.3 nM [^{3}H]SCH-23390 and 300 nM *cis*-(*Z*)-flupenthixol for 30 min (D$_1$) or 0.065 nM [^{3}H]emanoapride (YM-09151) and 250 nM (+)-butaclamol for 90 min (D$_2$). Dopamine D$_3$ receptor binding assays[32,33] used 40 μg of protein homogenate prepared from mouse fibroblast cells transfected to express human D$_3$ receptors (RBI, Natick, MA), 0.08 nM [^{3}H]emonapride, and 10.0 nM eticlopride incubated at 30 °C for 60 min in the same buffer and were then filtered and counted as above.

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References

(1) Walker, J. M.; Bowen, W. D.; Walker, F. O.; Matsumoto, R. R.; de Costa, B.; and Rice, K. C. Sigma Receptors: Biology and Function. *Pharmacol. Rev.* **1990**, *42*, 355−402.

(2) Quirion, R.; Bowen, W. D.; Itzhak, Y.; Junien, J. L.; Musacchio, J. M.; Rothman, R. B.; Su, T. P.; Tam, S. W.; Taylor, D. P. A Proposal for the Classification of Sigma Binding Sites. *Trends Pharmacol. Sci.* **1992**, *13*, 85−86.

(3) Itzhak, Y.; Stein, I. Sigma Binding Sites in the Brain: An Emerging Concept for Multiple Sites and Their Relevance for Psychiatric Disorders. *Life Sci.* **1990**, *47*, 1073−1081.

(4) Vilner, B. J.; Bowen, W. D. Sigma Receptor-active Neuroleptics are Cytotoxic to C6 Glioma Cells in Culture. *Eur. J. Pharmacol.* **1993**, *244*, 199−201.

(5) Largent, B. L.; Gundlach, A. L.; Snyder, S. H. Psychomimetic Opiate Receptors Labeled and Visualized with (+)-[^{3}H]-3-(3-hydroxyphenyl)-*N*-(1-propyl)piperidine. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 4983−4987.

(6) Gundlach, A. L.; Largent, B.; Snyder, S. H. Autoradiographic Localization of Sigma Receptor Binding Sites in Guinea Pig and Rat Central Nervous System with (+)-[^{3}H]-3-(3-hydroxyphenyl)-*N*-(1-propyl)-piperidine. *J. Neurosci.* **1986**, *6*, 1757−1770.

(7) Campbell, B. G.; Bobker, D. H.; Leslie, F. M.; Mefford, I. N.; Weber, E. Both the Sigma Receptor-specific Ligand (+)-3-PPP and the PCP Receptor-specific Ligand TCP Act in the Mouse Vas Deferens via Augmentation of Electrically Evoked Norepinephrine Release. *Eur. J. Pharmacol.* **1987**, *138*, 447−449.

(8) Arbilla, J. S.; Langer, S. Z. Differential Effects of the Stereoisomers of 3-PPP on Dopaminergic and Cholinergic Neurotransmission in Superfused Slices of the Corpus Striatum. *Naunyn-Schmiedebergs Arch. Pharmacol.* **1984**, *327*, 6−13.

(9) Wachtel, S. R.; White, F. J. Electrophysiological Effects of BMY-14802, A New Potential Antipsychotic Drug, on Midbrain Dopamine Neurons in the Rat: Acute and Chronic Studies. *J. Pharmacol. Exp. Ther.* **1988**, *244*, 410−416.

(10) Steinfels, G. F.; Tam, W. S. Selective Sigma Receptor Agonist and Antagonist Affect Dopamine Neuronal Activity. *Eur. J. Pharmacol.* **1989**, *163*, 167−170.

(11) Itzhak, Y.; Stein, I. Regulation of Sigma Receptors and Responsiveness to Guanine Nucleotides Following Repeated Exposure of Rats to Haloperidol: Further Evidence for Multiple Sigma binding Sites. *Brain Res.* **1991**, *566*, 166−172.

(12) Booth, R. G.; Wyrick, S. D.; Baldessarini, R. J.; Kula, N. S.; Myers, A. M.; Mailman, R. B. A New Sigma-like Receptor Recognized by Novel Phenylaminotetralins: Ligand Binding and Functional Studies. *Mol. Pharmacol.* **1993**, *44*, 1232−1239.

(13) Wyrick, S. D.; Booth, R. G.; Myers, A. M.; Kula, N. S.; Baldessarini, R. J.; McPhail, A. T.; Mailman, R. B. Synthesis and Pharmacological Evaluation of 1-Phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes as Ligands for a Novel Receptor with Sigma-like Neuromodulatory Activity. *J. Med. Chem.* **1993**, *36*, 2542−2551.

(14) Booth, R. G.; Wyrick, S. D. A Novel Brain Receptor Recognized by Phenylamino- tetralins May Represent a Sigma (σ_3) Receptor Subtype. *Med. Chem. Res.* **1994**, *4*, 225−237.

(15) Booth, R. G.; Baldessarini, R. J. (+)-6,7-Benzomorphan Sigma Ligands Stimulate Dopamine Synthesis in Rat Corpus Striatum. *Brain Res.* **1991**, *557*, 349−352.

(16) Glennon, R. A.; Ablordeppey, S. Y.; Ishmaiel, A. M.; El-Ashmawy, M.; Fischer, J.; BurkeHowie, K. Structural Features Important for σ_1 Receptor Binding. *J. Med. Chem.* **1994**, *37*, 1214−1219.

(17) Myers, A. M.; Wyrick, S. D.; Charifson, P. S.; Booth, R. G.; Owens, C. E.; Kula, N. S.; Baldessarini, R. J.; McPhail, A. T. Conformational Analyses, Pharmacophore Identification, and Comparative Molecular Field Analyses of Ligands for the Neuromodulatory σ_3 Receptor. *J. Med. Chem.* **1994**, *37*, 4109−4117.

(18) Glennon, R. A.; Smith, J. D.; Ishmaiel, A. M.; Yousif, M.; El-Ashmawy, M.; Herndon, J. L.; Fischer, J.; Server, A. C. Binding of Substituted and Conformationally Restricted Derivatives of *N*-(3-phenyl-*N*-propyl)-1-phenyl-3-aminopropane at σ Receptors. *J. Med. Chem.* **1991**, *34*, 1855−1859.

(19) Kandeel, E. M.; Martin, A. R. Substituted Tetralines. 5. Analgesic Properties of Some Diastereomeric Dimethyl-4-phenyl-1,2,3,4-tetrahydro-2-naphthylamines. *J. Med. Chem.* **1973**, *16*, 947−948.

(20) Eschweiler, W. Ersatz von an Stickstoff Gebundenen Wasserstoffatomen durch die Methylgruppe mit Hilfe von Formaldehyd. *Chem. Ber.* **1905**, *38*, 880−882.

(21) Laus, G.; Tourwe, D.; Van Binst, G. Benzo- and Indoloquinolizidine Derivatives XIX. Synthesis and Pharmacological Activity of Quinolizidine Derivatives. Analogs of Butaclamol. *Heterocycles* **1984**, *22*, 311−331.

(22) Bose, A. K.; Lal, B.; Hoffman, W. A.; Manhas, M. S. Steroids IX. Facile Inversion of Unhindered Sterol Configuration. *Tetrahedron Lett.* **1973**, *18*, 1619−1622.

(23) Teicher, M. H. *ALLFIT: Conversion of Dose-response Analysis Program of A. DeLean, P. J. Munson and D. Rodbard to the MacIntosh Computer*; McLean Hospital: Belmont, MA, 1991; unpublished software.

(24) Weber, E.; Sonders, M.; Quarum, M.; McLean, S.; Pou, S.; Keana, J. F. W.; 1,3-di-(-2-[5-^{3}H]tolyl)-guanidine: A Selective Ligand that Labels Sigma-type Receptors for Psychotomimetic Opiates and Antipsychotic Drugs. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 8784−8788.

(25) Munson, P. J.; Rodbard, D. LIGAND: A Versatile Computerized Approach for Characterization of Ligand-Binding Systems. *Anal. Biochem.* **1980**, *107*, 220−239.

(26) Graphpad Prism, version 1.01, 1994; San Diego, CA.

(27) Cheng, Y.-C.; Prusoff, W. H., Relationship between the inhibition constant (Ki) and the concentration of inhibitor which causes 50 percent inhibition (IC50) of an enzymatic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.

(28) Wyrick, S. D.; Myers, A. M.; Booth, R. G.; Kula, N. S.; Baldessarini, R. J.; Owens, C. E.; Mailman, R. B. Synthesis of [N-C^{3}H$_3$]-*trans*-(1*R*,3*S*)-(−)-1-Phenyl-3-diethylamino-1,2,3,4-tetrahydronaphthalene (H2-PAT). *J. Labelled Compd. Radiopharm.* **1994**, *34*, 131−134.

(29) Faedda, G.; Kula, N. S.; Baldessarini, R. J. Pharmacology of Binding of ^{3}H-SCH-23390 to D1 Dopaminergic Receptor Sites in Rat Striatal Tissue. *Biochem. Pharmacol.* **1989**, *38*, 473−480.

(30) Jarvie, K. R.; Niznik, G. B.; Seeman, P. Dopamine D$_2$ Receptors in Canine Brain: Ionic Effects on [3H]-neuroleptic binding. *Eur. J. Pharmacol.* **1987**, *144*, 163−171.

(31) Kula, N. S.; George, T.; Baldessarini, R. J. Rate of Recovery of D1 and D2 Dopaminergic Receptors in Young vs. Adult Rat Striatal Tissue Following Alkylation with Ethoxycarbonylethoxy-dihydroquinoline (EEDQ). *Dev. Brain Res.* **1992**, *66*, 286−289.

(32) Baldessarini, R. J.; Kula, N. S.; McGrath, C.; Kebabian, J. W.; Neumeyer, J. L. Isomeric selectivity of D$_3$ dopamine receptors. *Eur. J. Pharmacol.* **1993**, *239*, 269−270.

(33) Kula, N. S.; Baldessarini, R. J.; Kebabian, J. W.; Neumeyer, J. L. S-(+)-aporphines are not selective for human D$_3$ dopamine receptors. *Cell. Mol. Neurobiol.*, in press.

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