Articles

Rigid Analogues of Dopamine: Synthesis and Interaction of 6-*exo*- and 6-*endo*-(3′,4′-Dihydroxyphenyl)-2-azabicyclo[2.2.2]octanes with Dopamine Uptake Sites and Receptors

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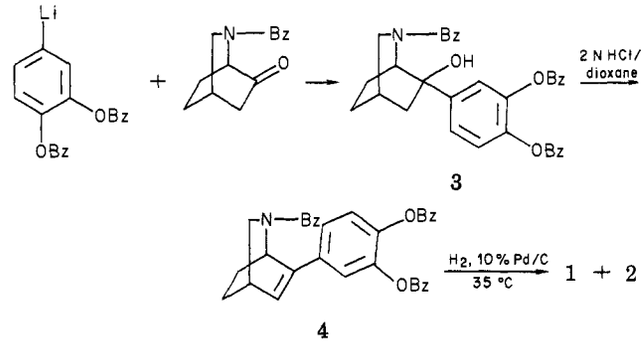
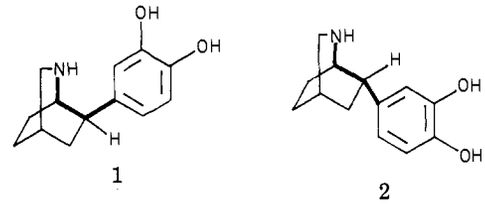
Two isomeric 6-*endo*- and 6-*exo*-(3′,4′-dihydroxyphenyl) derivatives (**1** and **2**) of 2-azabicyclo[2.2.2]octane were synthesized as semirigid analogues of dopamine (DA) to help evaluate the preferred conformation of dopamine at the uptake site of the presynaptic nerve terminal and at the DA receptor. Against the uptake of 0.1 μM [^{3}H]DA by a synaptosomal preparation of corpus striatum from the reserpine-pretreated rat, **2** was found to have a weak inhibitory effect that was three times greater than that of **1** (IC_{50} = 32 vs. 110 μM). Interactions with DA receptors were assessed with competition for binding of [^{3}H]apomorphine (APO) and on the effect on DA-sensitive adenylate cyclase. Compounds **1** and **2** were both virtually inactive against the binding of 0.5 nM [^{3}H]APO at a screening concentration of 100 μM. The experimental compounds also exhibited only slight adenylate cyclase stimulation in rat striatal homogenates, with **1** appearing to be somewhat more active (at 50 or 400 μM). The weak activities of **1** and **2** and their relatively small differences in activity in these test systems suggest that the DA analogues interact only weakly with the DA transport and receptor sites, possibly as a result of the steric interference caused by the bulky bicyclic ring.

Efforts to elucidate the conformation of dopamine (DA) prevailing at DA receptors have included the use of rigid ring structures, such as aporphines, or semirigid aminodihydroxytetralins (ADTNs) and tetrahydroisoquinolines which incorporate DA in the trans (extended) or cis (folded) conformation, respectively. The potent dopaminergic activities exhibited by (−)-10,11-dihydroxyaporphine derivatives and (+)-6,7-ADTN in various in vivo[1,2] and in vitro[3–5] biological systems vs. the weak or absent activities of 1,2-dihydroxyaporphine[6] and 6,7-dihydroxytetrahydroisoquinoline[3] have suggested that a trans relationship of the two key structural features of DA (catechol and amino functions) rather than a cis relationship is preferred at the DA receptor site.

On the other hand, among the few studies investigating the conformational selectivity of the DA uptake mechanism at the presynaptic nerve terminal, contradictory findings implicating an anti or gauche relationship between the catechol and the amino groups of DA have been recorded. By examining various *trans*-decalin rigid analogues of (−)-norepinephrine (NE) in the system of synaptosome-rich homogenates of the rat corpus striatum, Tuomisto and co-workers[7] concluded that the preferred conformation of the interaction of DA with this uptake site is gauche. Through the study of two semirigid analogues of DA, (+)-6,7-ADTN and 6,7-dihydroxytetrahydroisoquinoline, however, Horn[8] suggested that the preferred conformation for DA at the uptake site is anti. More recently, in a series of phenylcyclobutylamines,[9] the trans isomers were found to be slightly more potent inhibitors of uptake than the corresponding cis isomers. Previous investigations[10,11] in one of our laboratories of the substituted 2-azabicyclo[2.2.2]octane ring system to study conformational factors involved in the interaction of acetylcholine, procaine, and mescaline with their corresponding biological receptors prompted us to extend this approach to the preparation of rigid analogues (**1** and **2**)

Scheme I





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(6) J. L. Neumeyer, M. McCarthy, S. P. Battista, F. J. Rosenberg, and D. G. Teiger, *J. Med. Chem.*, **16**, 1228 (1973).
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Scheme II

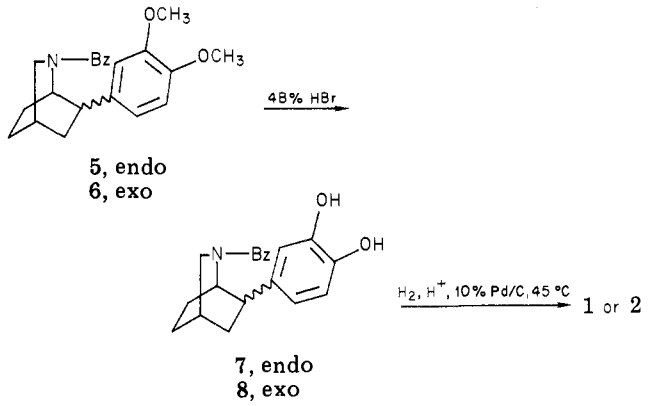

Table I. IC_{50} Values of 6-*endo*- (1) and 6-*exo*-(3',4'-Dihydroxyphenyl)-2-azabicyclo[2.2.2]octane (2) for the Inhibition of the Uptake of [^{3}H]DA (0.1 μM) by Corpus Striatum Synaptosomes of Reserpine-Pretreated Rat

compd	IC_{50}, μM	95% CL, M
1·HCl	110	3.2×10^{-6}-3.5×10^{-3}
2·HCl	32	1.1×10^{-6}-8.9×10^{-4}
(±)-tranylcypromine hydrochloride	0.9[a]	6.8×10^{-8}-1.2×10^{-5}

[a] Reported half-maximally effective concentration (IC_{50}) = 1.7 μM vs. 0.1 μM [^{3}H]DA.[15]

of DA. Analogue 1 (endo isomer)[12] represents a DA conformation in which the catechol and amino groups are restricted in a gauche relationship, while in analogue 2 (exo isomer) the two groups are in an antiperiplanar relationship. The present report describes the synthesis of 1 and 2, as well as the pharmacological evaluation of the inhibition of DA at presynaptic uptake sites and high-affinity ligand binding sites and interactions with DA-sensitive adenylate cyclase.

Chemistry. The methods leading to the preparation of a mixture of 1 and 2 are outlined in Scheme I. The precursor 3,4-bis(benzyloxy)phenyl bromide was prepared as reported by Pines et al.[13] The bromide then underwent lithium exchange and was treated with *N*-benzyl-2-azabicyclo[2.2.2]octan-6-one[14] to give, exclusively, the *endo*-alcohol 3, whose infrared spectrum showed associated hydroxyl absorption at 3420 cm^{-1} upon high dilution (0.001 M) in carbon tetrachloride. Dehydration of 3 with 2 N HCl in dioxane yielded 4. As anticipated, hydrogenation of 4 removed the protecting benzyl groups and reduced the double bond to generate the two target compounds. However, the highly polar nature and close R_f values of the resulting mixture of 1 and 2 did not permit separation by column chromatography. Thus, the approach outlined in Scheme II was utilized. The dimethoxyphenyl derivatives 5 and 6 were obtained as described previously,[11b] and their stereochemistry is well established. They were refluxed individually with 48% HBr to give the O-demethylated products 7 and 8, respectively. The *N*-benzyl protecting group of each isomer was removed by hydrogenolysis to give the target compounds 1 and 2.

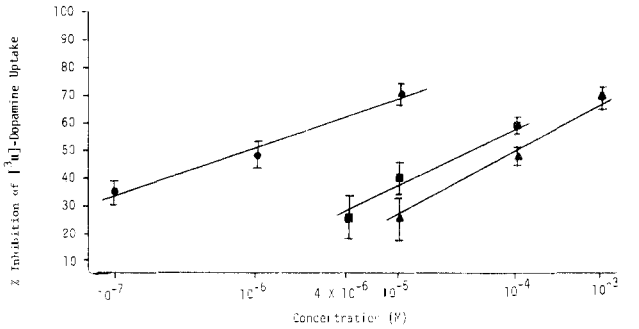

Figure 1. Dose–response curves for the inhibition of [^{3}H]dopamine uptake into rat corpus striatal synaptosomes by various concentrations of dopamine analogues: (▲) 1; (■) 2; (●) (±)-tranylcypromine; N = 3–5 determinations per dose.

Table II. Effects of 6-*endo*- (1) and 6-*exo*-(3',4'-Dihydroxyphenyl)-2-azabicyclo[2.2.2]octane (2) on DA-Sensitive Adenylate Cyclase Activity in Rat Striatal Homogenates

condition (μM)	% of basal act.[a] ± SEM
basal (control) act.	100 ± 17.9
dopamine (50)	210 ± 5.0[b]
1·HCl (400)	117 ± 4.0
2·HCl (400)	93 ± 7.6

[a] Basal activity = 4.20 ± 0.20 pmol of cAMP formed per assay (N = 4-5). [b] $p < 0.05$ by Student's t test.

Table III. Effects of 6-*endo*- (1) and 6-*exo*-(3',4'-Dihydroxyphenyl)-2-azabicyclo[2.2.2]octane (2) on the Stimulatory Activity of Exogenous DA toward DA-Sensitive Adenylate Cyclase in Rat Striatal Homogenates

condition (μM)	% of basal act.[a] ± SEM
basal (control) act.	100 ± 12.7
dopamine (DA) alone (50)	167 ± 5.1
DA (50) + 1·HCl (50)	183 ± 12.7
DA (50) + 2·HCl (50)	169 ± 14.0

[a] Basal activity = 4.20 ± 0.20 pmol of cAMP formed per assay (N = 4-5). Note that the effect of DA alone (50 μM) varied from 167 to 210% stimulation between separate experiments.

Pharmacology. Inhibition of in vitro uptake of [^{3}H]DA by 1, 2, and the amphetamine-like agent (±)-tranylcypromine, which is known to block DA uptake,[15] was evaluated by the method of Horn and Synder.[15] The results are summarized in Figure 1 and as IC_{50} values in Table I, with 95% confidence limits determined by the method of Litchfield and Wilcoxon.[16] All test drugs inhibited the accumulation of 0.1 μM [^{3}H]DA in a concentration-dependent manner. Although 1 and 2 were less active than tranylcypromine, the exo isomer 2 was three fold more active than the endo isomer 1 (Table I).

(9) H. I. Komiskey, F. L. Hsu, F. J. Bossart, J. W. Fowble, D. D. Miller, and P. N. Patil, *Eur. J. Pharmacol.*, **52**, 37 (1978).
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(12) Previous publications from our laboratory utilized exo and endo nomenclature based on conventional usage. Nomenclature in this paper reflects systematic stereochemical designations which are necessarily opposite from designations used in our previous publications.
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Competition for binding of [^{3}H]apomorphine (APO, 0.5 nM, at one-tenth the apparent K_d) was evaluated with a subsynaptosomal membrane preparation of caudate nucleus tissue from calf brain.[17,18] Weak inhibitory (less than 10%) activity with both **1** and **2** was found at a screening concentration of 100 μM, indicating EC_{50} values above 500 μM (and probably above 1000 μM) or virtual inactivity.

Interaction of **1** and **2** with DA-sensitive adenylate cyclase was evaluated with rat striatal homogenates[19,20] at 400 μM with DA (50 μM) as a positive control (Table II). DA produced strong (twofold) stimulation of cAMP formation, while **1** produced weak stimulation and **2** was inactive. Potential interactions of the two compounds with exogenous DA were also examined with the same cyclase assay (Table III). At 50 μM the endo isomer **1** slightly but insignificantly increased (16%) the stimulatory activity of exogenous DA (50 μM). No effect was observed with the exo isomer **2** at the same concentration, and neither compound inhibited the effects of DA.

Discussion

The introduction of the catechol moiety at the 6 position of the 2-azabicyclo[2.2.2]octane ring structure resulted in two isomeric semirigid analogues of DA, **1** and **2** representing the DA molecule fixed in gauche and anti conformations, corresponding to endo or exo orientations of the catechol function, respectively. Compounds **1** and **2** had only weak effects on DA uptake and stimulation of adenylate cyclase (Tables I–III; Figure 1). Interestingly, although **2** had somewhat more inhibitory activity than **1** against DA uptake, **1** was slightly more active at the receptors represented by DA-sensitive production of cAMP. Obviously, the relatively high IC_{50} values and the small differences in activity between **1** and **2**, as well as the virtual inactivity of the compounds vs. [^{3}H]APO binding, do not provide sufficient evidence to permit a conclusion regarding the preferred DA conformation at DA uptake and receptor sites.

There have been consistent suggestions from previous investigations of a preferred anti conformation of DA at its receptor sites, when different series of DA analogues were evaluated by pharmacological methods ranging from in vivo behavioral studies to in vitro ligand binding assays and the stimulation of DA-sensitive adenylate cyclase. Thus, the mere threefold superiority in potency of **2** over **1** against DA uptake and their even weaker interactions with adenylate cyclase (**1** slightly greater than **2**) may reflect a drastic change brought about by incorporating the trans form of the DA molecule into the bicyclic ring structure. This unfavorable change is probably due to steric hindrance created by the ethylene bridge (C_7 and C_8) that makes the bicyclic ring semirigid. This reasoning is supported by structural (Dreiding) models of the exo isomer (**2**, analogous to the anti conformation of DA) and of the potent DA analogue (–)-apomorphine (APO). Analogue **2** can be viewed as a biplanar structure (Figure 2). Plane A, which contains the DA moiety, superimposes exactly with the pharmacophore of (–)-APO. Plane B, which consists of C_1, C_4, C_7, and C_8, projects downward perpendicularly from plane A. Because of this downward-projecting plane B, a close fit of **2** to DA active sites

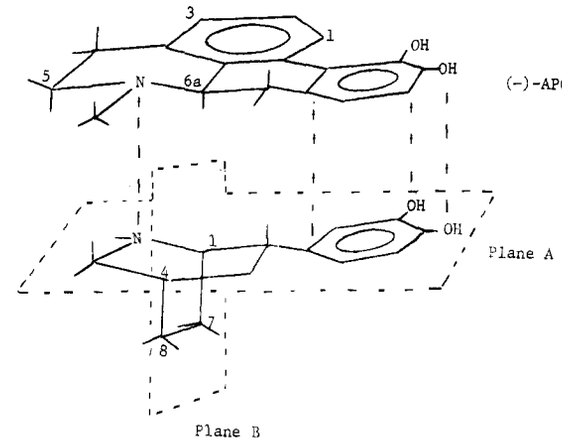

Figure 2. Superimposition of 6-*exo*-(3',4'-dihydroxyphenyl)-2-azabicyclo[2.2.2]octane (**2**) and the pharmacophore of (–)-apomorphine.

may be prevented. Neumeyer et al.[21] recently proposed DA receptor boundaries to explain the activity and inactivity of a series of aporphines and related DA agonists. The inactivity in pharmacological tests of DA-receptor stimulation of (+)-APO, which has an upward C_{6a} axial proton (Figure 2), and the weak activity of **2** in the present test systems for DA uptake and receptors suggest that for certain modes of dopaminergic receptor binding there is very limited space where an ethylene carbon neighboring the amino group can position itself. The same could hold true for the DA uptake mechanism. Further support is provided by the weak interaction of α-Me-DA with binding of [^{3}H]APO[17,18] or with DA-sensitive adenylate cyclase.[22] The result of the poor fit of **2** to the receptors is thus reflected in its weak competition in the [^{3}H]APO binding assay at the screening concentration of 100 μM. Similarly, the bulkiness of the azabicyclic ring may explain the weak activity of **1** in addition to the possible factor of an unfavorable gauche relationship between the catechol and the amino functions.

In summary, the utilization of the 2-azabicyclo[2.2.2]-octane ring system to prepare rigid analogues of DA for conformational evaluation has been found to generate unfavorable bulkiness in the amino portion of the DA molecule. The expectation that one of the analogues (especially the exo isomer, **2**) might compare more favorably than the other in the assay systems used was not found at low concentrations, but the results obtained suggest that the bulk of the azabicyclic ring system precludes strong binding at DA receptors or uptake sites.

Experimental Section

All melting points were taken on a Thomas-Hoover Unimelt or a Mel-Temp apparatus and are corrected. Infrared spectra were obtained on a Perkin-Elmer Model 257 or a Beckman IR 33 spectrometer. All NMR spectra were obtained on a JEOLCO Model C-60HL spectrometer, and all values are reported in parts per million (δ) from Me_4Si or DSS. Mass spectral data were obtained on a Dupont Model 21-492 spectrometer. NMR and mass spectral data were consistent with the assigned structures. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. (±)-Tranylcypromine was obtained from Aldrich Chemical Co., Inc., Milwaukee, WI. [^{3}H]Dopamine (ring-6, 5.0 Ci/mmol) was purchased from Amersham Corp., Arlington Heights, IL; (–)-[8,9-^{3}H]Apomorphine hydrochloride (40 Ci/mmol)

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was obtained from New England Nuclear Corp., Boston, MA. Reserpine phosphate was from Ciba Pharmaceutical Co., Summit, NJ.

2-Benzyl-6-*endo*-hydroxy-6-*exo*-[3′,4′-bis(benzyloxy)-phenyl]-2-azabicyclo[2.2.2]octane (3). To a solution of *n*-butyllithium prepared[11b] from *n*-butyl bromide (77.0 g, 0.55 mol) and lithium metal (4.2 g, 0.60 g-atom) in anhydrous ether cooled at −70 °C was added a solution of 3,4-bis(benzyloxy)phenyl bromide (55.2 g, 0.149 mol) in 450 mL of anhydrous ether over a 1-h period. A white suspension was obtained. The resulting mixture was allowed to warm to −45 °C and diluted with an additional 100 mL of anhydrous ether. A solution of *N*-benzyl-2-azabicyclo[2.2.2]octan-6-one[14] (11.0 g, 0.051 mol) in 100 mL of anhydrous ether was added over a 30-min period at −40 °C. The mixture was allowed to warm to room temperature after the addition was complete, stirred overnight, and then treated at 0 °C with water until a clear solution resulted. The ether layer was separated, and the aqueous layer was extracted with ether. The organic phases were combined and extracted with 10% HCl (5 × 60 mL). The acidic aqueous layer and an oily material that separated from the ether phase and was insoluble in the aqueous phase were washed with ether (2 × 100 mL), neutralized with ammonium hydroxide, and extracted with ether (4 × 200 mL). The combined extracts were dried over magnesium sulfate and evaporated in vacuo to give a residue. The residue was triturated with a minimum amount of anhydrous ether and filtered to give a white solid: yield 10.7 g (42%); mp 107–109 °C. An analytical sample was obtained by passing the solid through a silica gel column packed and eluted with ether–petroleum ether (1:2) to give white crystals: mp 108–110 °C; IR (CCl_4) 3420 (OH, associated) cm^{-1}. Anal. ($C_{34}H_{35}NO_3$) C, H, N.

2-Benzyl-6-[3′,4′-bis(benzyloxy)phenyl]-2-azabicyclo-[2.2.2]oct-5-ene (4). A solution of **3** (10.0 g, 0.0198 mol) in 100 mL of 2 N HCl in 1,4-dioxane was stirred at room temperature for 24 h and evaporated in vacuo to give a residue, which was then treated with water (150 mL), neutralized with ammonium hydroxide, and extracted with ether (3 × 150 mL). The combined extracts were dried over magnesium sulfate and evaporated to give a viscous oil. Chromatography of the oil on a silica gel column packed and eluted with ether–petroleum ether (1:3) gave pure **4**: yield 7.68 g (80%). Anal. ($C_{34}H_{33}NO_2$) C, H, N.

6-*endo*-(3′,4′-Dihydroxyphenyl)-2-azabicyclo[2.2.2]octane (1). A solution of **5**[11b] (1.01 g, 0.003 mol) in 12 mL of 48% hydrobromic acid was refluxed under nitrogen for 1.5 h. The reaction mixture was cooled, neutralized with ammonium hydroxide, and extracted with chloroform–methanol (5:1) in three 20-mL portions. The combined extracts were dried over magnesium sulfate and evaporated in vacuo to give a residue, which was chromatographed on a silica gel column packed and eluted with 5% methanol/chloroform to give a blue solid, **7**. A solution of the solid in 0.5 mL of concentrated hydrochloric acid and 30 mL of ethanol was flushed with nitrogen, 10% palladium on charcoal (0.045 g) was added, and the mixture was hydrogenated at 3.15 kg/cm² at 45 °C for 2 days. The catalyst was removed by filtration, and the filtrate was evaporated in vacuo to give a residue, which was chromatographed on a silica gel column packed and eluted with 5% methanol/chloroform to give 105 mg of unreacted intermediate and the desired product **1** as the hydrochloride salt (150 mg, 13% based on the starting **5**). Recrystallization of the HCl salt of **1** from methanol–chloroform gave white crystals, mp 265–267 °C. Anal. ($C_{13}H_{18}ClNO_2$) C, H, N.

6-*exo*-(3′,4′-Dihydroxyphenyl)-2-azabicyclo[2.2.2]octane (2). In a manner similar to that described for the preparation of **1**, a solution of **6** (1.84 g, 0.0054 mol) in 35 mL of 48% hydrobromic acid was refluxed and worked up to give a dark residue, which was chromatographed to give a solid (**8**, 0.57 g), mp 132–136 °C. A mixture of the solid and 10% palladium on charcoal (0.09 g) in 50 mL of ethanol containing 0.5 mL of concentrated HCl was similarly hydrogenated, worked up, and purified to give a highly viscous hydrochloride salt of **2** (0.202 g, 15% yield based on starting **6**). The picrate was prepared in the normal manner, mp 219–220 °C. Anal. ($C_{19}H_{20}N_4O_9$) C, H, N.

Inhibition of [³H]Dopamine Uptake. The method was essentially that described by Horn and Snyder.[15] [³H]Dopamine was incubated at 0.1 μM with rat striatal homogenates. The ability of compounds **1**, **2**, and the positive control, (±)-tranylcypromine hydrochloride, to inhibit [³H]dopamine uptake was tested at varying concentrations as shown in Figure 1. The ranges of concentration were chosen to include the half-maximally effective concentration (IC_{50}).

[³H]APO Binding Assay. (−)-[³H]Apomorphine hydrochloride was incubated at 0.5 nM with a subsynaptosomal membrane fraction (P_4) prepared from caudate nucleus tissue of calf brain. Experimental compounds were screened at 100 μM (N = 4). Tissue was recovered by filtration. The methods are described in detail elsewhere.[17,18]

Interactions with DA-Sensitive Adenylate Cyclase. Rat corpus striatum homogenates were evaluated with DA (50 μM) as a positive control. Concentrations of **1** and **2** were tested for ability to stimulate formation of cAMP as measured by a binding assay which has been described elsewhere.[19,20,22] Concentrations of 50, 100, 200, and 400 μM of test compounds were screened. There were only weak effects of **1** at 400 μM alone (Table II) and at 50 μM when combined with 50 μM DA (Table III).

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Aminotetralins as Narcotic Antagonists. 2. Synthesis and Opiate-Related Activity of 1-Phenyl-3-aminotetralins[1]

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The synthesis and analgetic agonist and antagonist activities of several 3-[*N*-(cyclopropylmethyl)-*N*-methylamino]-1-phenyltetralins are reported. The design of these agents was based partially on the possibility of two aryl receptor binding sites on the opiate receptor. The agents lack the phenolic hydroxyl and quaternary carbon functionalities generally associated with opiate activity; yet both the *cis*- and *trans*-1-phenyl-3-aminotetralins displayed significant agonist and antagonist activity. In preliminary studies, the trans isomer neither suppressed nor precipitated withdrawal signs in addicted monkeys.

The ultimate objective of the research described in this report is to discover, from among aminotetralin congeners, a mixed opiate agonist–antagonist and/or a pure narcotic antagonist. A mixed agonist–antagonist remains a prom-

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