Centrally Acting Serotonergic Agents. Synthesis and Structure-Activity Relationships of C-1- or C-3-Substituted Derivatives of 8-Hydroxy-2-(di-*n*-propylamino)tetralin

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The synthesis and structure-activity relationships (SAR) of C-1- or C-3-substituted derivatives of 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) are described. These analogs were synthesized via alkylation of the tetralone derivatives followed by reductive amination. All of the analogs were inactive at the dopamine D_2 receptor. Among the 8-OMe or 8-OH C-1,N-disubstituted analogs synthesized, the cis analogs were more potent in the 5-HT_{1A} binding assay than the corresponding trans analogs. However, in the case of 1-(cyclopropylmethyl)-*N*-*n*-propyl analogs, the trans isomer has a slightly higher 5-HT_{1A} affinity than its cis counterpart. The order of binding potency for C-1 substitution was found to be allyl > hydroxymethyl > *n*-propyl > cyclopropylmethyl ≫ carbomethoxy. Interestingly, the 5-OMe analogs were found to be inactive in both the 5-HT_{1A} and dopamine D_2 binding assays. In the C-3 allyl-substituted analogs, 5-HT_{1A} agonist activity was found to be considerably lower. In these examples, the trans analogs showed weak 5-HT_{1A} binding activity whereas the cis analogs were inactive. Analogs with C-1,N,N-trisubstitution also showed a marked decrease in 5-HT_{1A} binding affinity. Overall, the SAR study showed that cis C-1 substitution maintains the 5-HT_{1A} agonist activity of 8-OH-DPAT whereas trans C-1 substitution displays somewhat diminished activity. On the other hand, the trans C-3 substitution shows modest agonist activity whereas cis C-3 substitution removes the activity completely.

Introduction

Since its discovery in 1948, the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) has been linked to various central nervous system (CNS) related activities. In 1981, the aminotetralin derivative 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) was found by Arvidsson et al.[1] to be a potent centrally active 5-HT receptor agonist. Later, Middlemiss and Fozard[2] showed that 8-OH-DPAT selectively binds to the 5-HT_{1A} receptor subtype and is devoid of 5-HT_2 receptor activity. In the past decade, considerable effort has been devoted to the structure-activity relationships (SAR) of 8-OH-DPAT related analogs.[3] Furthermore, the 5-HT_{1A} receptor agonists were implicated in playing an important role in the control of anxiety and depression without hallucinogenic activity[4] and in the regulation of sympathetic nerve activity which may regulate blood pressure.[5]

By examining the superimposed structures of 5-HT and 8-OH-DPAT, some interesting observations were made about their structural similarities. As illustrated in Figure 1, when mutual bonds are set in bold face, two exclusive regions designated as A and B became apparent. Earlier work on the SAR of 5-HT derivatives suggests that the pyrrole ring portion of region B may be important for 5-HT_2 receptor binding.[6] The presence of this pyrrole ring may be influential in 5-HT's lack of selectivity at the 5-HT_{1A} receptor. Analogs with selectivity for the 5-HT_{1A} receptor have been synthesized with substitution in region A at the C-1 position. Arvidsson et al. reported that the

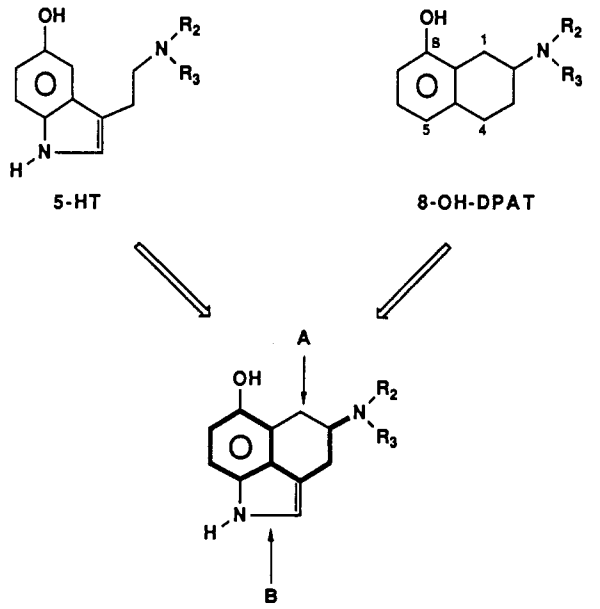

Figure 1. Superposition of 5-hydroxytryptamine (5-HT) and 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT). Mutual bonds are set in bold face, while exclusive regions are designated as A and B.

C-1-methylated 8-OH-DPAT analogs exhibit potent 5-HT_{1A} receptor agonist activity.[7] In addition, Mellin et al. reported that 8-OH-DPAT analogs with methyl substitution at the C-3 position show diminished 5-HT_{1A} activity.[8]

There have been a number of publications which present more complicated and sophisticated molecular modeling based calculations for predicting the activity of aminotetralin analogs.[9] Based on these calculations and our analysis shown in Figure 1, a longer side chain such as

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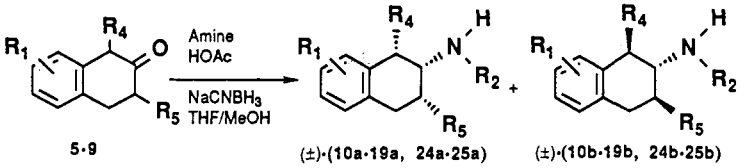
Table I. Ratio of Cis/Trans Products from Reductive Amination of 1- or 3-Substituted 2-Tetralones with Various Amines



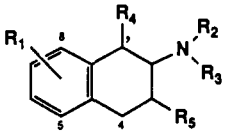
5-9 (±)-(10a-19a, 24a-25a) (±)-(10b-19b, 24b-25b)

tetralone						
R_1	R_4	R_5	R_2NH_2, R_2	products	ratio cis/trans	yield (%)
H	allyl	H	*n*-propyl	**10a/10b**	6.0	69
H	allyl	H	allyl	**11a/11b**	10.0	74
8-OMe	allyl	H	*n*-propyl	**12a/12b**	5.4	60
8-OMe	allyl	H	allyl	**13a/13b**	5.0	83
8-OMe	cpm[a]	H	*n*-propyl	**14a/14b**	5.0	78
8-OMe	cpm[a]	H	allyl	**15a/15b**	4.2	89
8-OMe	cpm[a]	H	cpm[a]	**16a/16b**	3.6	40
8-OMe	allyl	H	cpm[a]	**17a/17b**	3.4	30
5-OMe	allyl	H	*n*-Propyl	**18a/18b**	7.5	88
8-OMe	CO_2Me	H	allyl	**19a/19b**	3.4	84
8-OMe	H	allyl	*n*-propyl	**24a/24b**	6.0	79
8-OMe	H	allyl	allyl	**25a/25b**	6.0	86

[a] Cyclopropylmethyl group.

n-propyl instead of a methyl group at C-1 of 8-OH-DPAT structure, may have a more profound effect in restricting the rotation and conformation in this region. Therefore, activity at the 5-HT_{1A} receptor may be greatly affected. The bonds attached at the C-3 and C-4 positions are shared atoms with 5-HT, and therefore, substituents placed in this region may decrease affinity for the 5-HT_{1A} receptor.

Our efforts were concentrated on incorporating various substituents at the C-1 position of generic structure 1 to determine the flexibility of substitution. Analogs with



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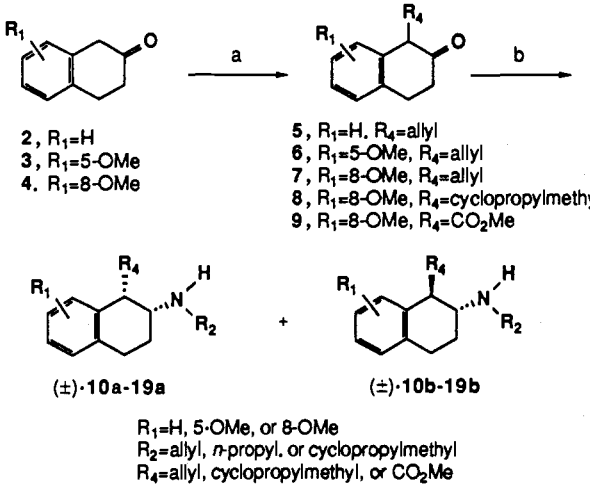
allyl substitution at the C-3 position were synthesized in order to demonstrate that activity at the 5-HT_{1A} receptor would be reduced. Herein we describe the synthetic methodology used in the preparation of various analogs. For our initial SAR work, analogs were evaluated as racemates for 5-HT_{1A} and dopamine D_2 binding activities in vitro. In addition, a select number of compounds have been investigated in more detail by means of biochemical and behavioral tests.

Chemistry

The regiospecific alkylation of the 2-tetralone derivatives[10] **2**, **3**, and **4** was accomplished by selectively generating an anion at the C-1 position using a base at low temperature followed by treatment with various substituted halides as shown in Scheme I. The anion at the C-1 position is exclusively formed upon treatment with a base such as LDA, since C-1 is flanked by both a neighboring aryl and a carbonyl group. LDA was used exclusively as the base since other bases such as potassium *tert*-butoxide, sodium methoxide, and lithium hexamethyldisilazide yielded more side products. Two factors affected the ratio of monoalkyl product to bisalkyl product. First, the 8-substituted tetralones were found less likely to yield the bisalkyl product due to the presence of a bulky group at the peri position. For example, tetralone (**2**) yielded 33% of monoallyl product **5** and 37% of the diallyl product, whereas 8-methoxy-2-tetralone (**4**) gave 86% of the monoallyl product **7** (see the Experimental Section). Secondly, the rate of reaction was affected by the nature of the alkylating agents used. For example, alkylation of 8-methoxy-2-tetralone (**4**) with allyl bromide was completed within a few hours at room temperature. However, when (bromomethyl)cyclopropane or dimethyl carbonate were used to alkylate tetralone **4**, refluxing conditions and excess reagent were necessary to yield the monoalkyl products **8** and **9**, respectively.

Scheme I[a]

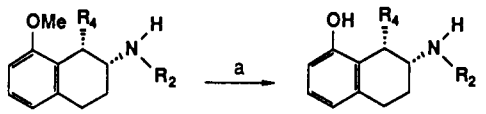


[a] Reagents and conditions: (a) LDA, allyl bromide, cyclopropylmethyl bromide, or dimethyl carbonate, in THF; (b) allylamine, *n*-propylamine, or (aminomethyl)cyclopropane, HOAc, $NaCNBH_3$, THF/MeOH.

After establishing appropriate alkylation conditions, subsequent reductive amination of these ketones to form the mono-N-substituted products **10**–**19** was accomplished using the well-established Borch procedure[11] with yields in the 60–90% range (see Table I). In most cases, excess amine (4–5 equiv) was needed to obtain the optimum yield. As shown in Table I, the cis/trans ratios range from 3 to 10, since reduction of the iminium ion by sodium cyanoborohydride approaches from the less sterically hindered side resulting in predominant formation of the cis product. The chromatographic separation of both isomers

could not be achieved in most cases. Fortunately, we found that the hydrochloric acid salts of the cis and trans isomers have very different solubilities. Therefore we were able to isolate both isomers cleanly by fractional recrystallization. The cis compounds were recrystallized from ethyl acetate/methanol whereas the trans compounds could be recrystallized from the mother liquor using ethyl acetate/hexane. Identification of both the cis and trans products was performed by ^{1}H NMR decoupling experiments and X-ray crystallography of one representative compound 12a (see Figure 2). The molecular formula and melting point for the analogs synthesized are listed in Table II. Two phenolic analogs in this class of compounds, **20** and **21**, were synthesized via demethylation of the corresponding methoxy analogs, **12a** and **13a**. As shown in Scheme II, the demethylation was accomplished by refluxing the methoxy analogs with lithium diphenylphosphine in THF.[12]

Scheme II[a]

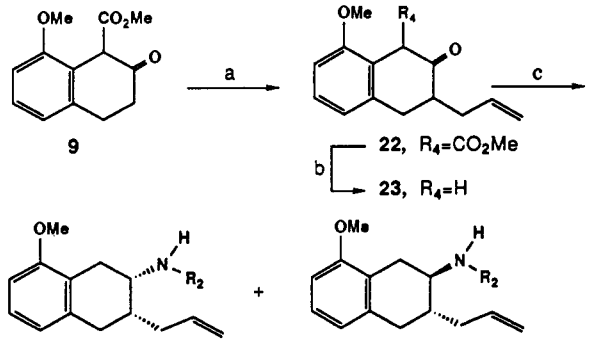


(±)-**12a**, R_2=*n*-propyl, R_4=allyl (±)-**20**, R_2=*n*-propyl, R_4=allyl
(±)-**13a**, R_2=R_4=allyl (±)-**21**, R_2=R_4=allyl

[a] Reagents and conditions: (a) Ph_2PH, *n*-BuLi, THF, Δ.

Synthesis of the 3-substituted analogs required a more complicated synthetic approach. Since selective alkylation of the C-3 position on the tetralone moiety cannot be accomplished directly, we had to resort to an indirect approach. This approach was originally demonstrated by Aristoff et al.[13] in their benzindene chemistry. As shown in Scheme III, keto ester **9**, with a carbomethoxy substitution at the C-1 position, was subjected to allylation using LDA and allyl bromide. The resulting 3-allyl-1-carbomethoxy ketone **22** was heated with LiCl/DMSO/H_2O to yield the 3-allyl ketone **23**. The reductive amination with *n*-propylamine or allylamine afforded the desired analogs **24a**/**24b** and **25a**/**25b**, respectively.

Scheme III[a]



(±)-**24a**, R_2=*n*-propyl (±)-**24b**, R_2=*n*-propyl
(±)-**25a**, R_2=allyl (±)-**25b**, R_2=allyl

[a] Reagents and conditions: (a) LDA, allyl bromide, THF; (b) LiCl, DMSO, H_2O, Δ; (c) allylamine or *n*-propylamine, HOAc, $NaCNBH_3$, THF/MeOH.

Two approaches were used to obtain the 1,N,N-trisubstituted analogs **26**, **29**, and **30**. The first approach (ketone **4** to analog **26**), as shown in Scheme IV, was shorter but less efficient. The one-pot reaction was carried out by converting **4** to an enamine using di-*n*-propylamine

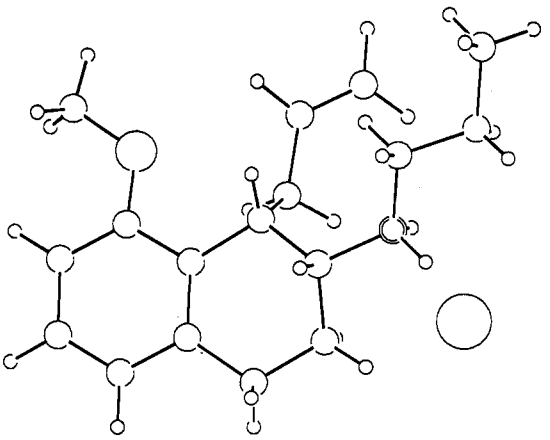
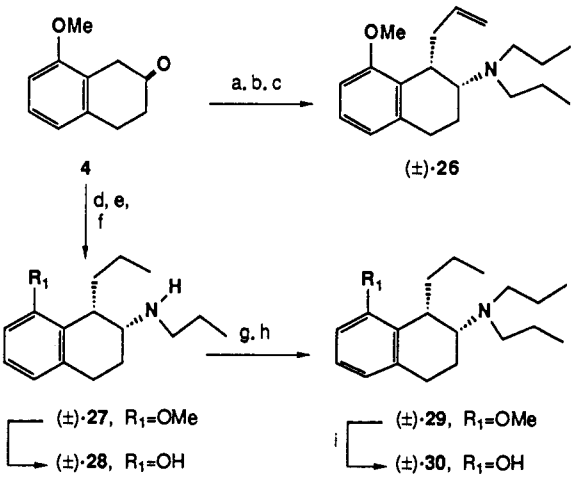


Figure 2. The X-ray crystallographic structure of **12a**, confirmed as *cis*-(±)-1,2,3,4-tetrahydro-8-methoxy-1-(2-propenyl)-*N*-*n*-propyl-2-naphthalenamine hydrochloride.

followed by allylation with allyl bromide. Treatment of the resulting product with $NaCNBH_3$ in HOAc/THF/2-PrOH afforded the desired product **26**. Unfortunately, the reaction required repeated chromatographic purification, and the overall yield was only 24%. In the second approach, the monopropyl analog **27** was synthesized first. As shown in Scheme IV, this was accomplished by allylation of tetralone **4** followed by reductive amination with *n*-propylamine and catalytic hydrogenation of the allyl group. Treatment of **27** with propionyl chloride/pyridine in methylene chloride followed by reduction of the resulting propionamide with LAH in THF afforded the trisubstituted analog **29**. Demethylation of **27** and **29** with 48% HBr led to the hydroxy analogs **28** and **30**, respectively.

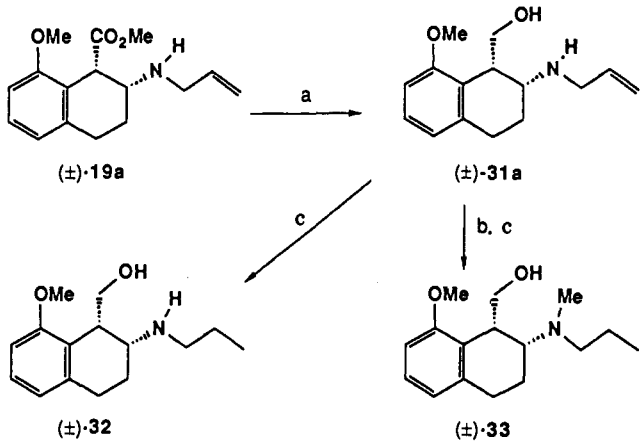
Scheme IV[a]



[a] Reagents and conditions: (a) di-*n*-propylamine, *p*-TsOH, tol, Δ; (b) allylamine, THF, Δ; (c) $NaCNBH_3$, HOAC, THF/2-PrOH; (d) LDA, allyl bromide, THF; (e) *n*-propylamine, HOAc, $NaCNBH_3$, THF/MeOH; (f) H_2, Pd/C, MeOH; (g) propionyl chloride, py, CH_2Cl_2; (h) LAH/THF, Δ; (i) 48% HBr, Δ.

The syntheses of the 1-hydroxymethyl analogs **31a**, **32**, and **33** are illustrated in Scheme V. The synthesis of the 1-hydroxymethyl analog **31a** was achieved by LAH reduction of the corresponding ester **19a**. Similarly, the trans analog **19b** was converted into the trans 1-hydroxymethyl analog **31b** (see the Experimental Section). The cis *n*-propyl analog **32** was obtained by hydrogenation of the corresponding allyl analog **31a**. Reductive amination of **31a** with formaldehyde followed by hydrogenation of the allyl group yielded the *N*-methyl-*N*-propyl analog **33**.

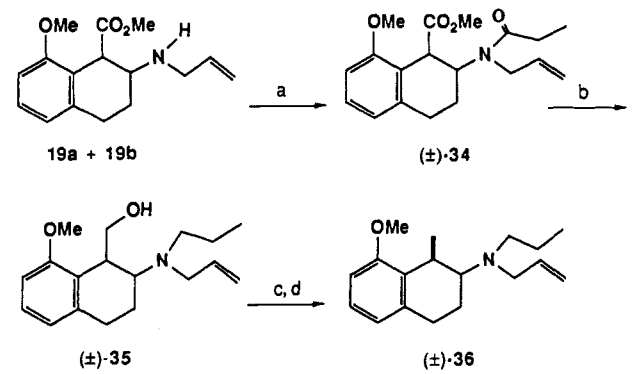
Scheme V[a]



[a] Reagents and conditions: (a) LAH/THF, Δ; (b) HCHO, $NaCNBH_3$, THF/MeCN; (c) H_2, Pd/C, 95% EtOH.

The synthesis of the 1-methylene analog **36** was achieved via a four-step sequence. As shown in Scheme VI, a mixture of **19a** and **19b** was treated with propionic anhydride and pyridine in methylene chloride to give the propionamide **34** which was then reduced with LAH/THF to yield alcohol **35**. Tosylation of this alcohol followed by elimination with potassium *tert*-butoxide afforded the desired 1-methylene analog **36**.

Scheme VI[a]



[a] Reagents and conditions: (a) $(EtCO)_2O$, py, CH_2Cl_2; (b) LAH/THF, Δ; (c) *p*-TsCl, py, CH_2Cl_2; (d) *t*-BuOK, THF, Δ.

Pharmacological Results and Discussion

The compounds were evaluated for their in vitro binding affinity at 5-HT_{1A} receptors in homogenate of bovine hippocampus using [^{3}H]-8-OH-DPAT as a ligand. They were also tested for dopamine D_2 binding affinity using [^{3}H]raclopride in rat striatum. All of the new compounds were found to display <50% inhibition of [^{3}H]raclopride displacement at 1 μmol/L concentration. The analogs active in the 5-HT_{1A} binding screen have been evaluated for their ability to produce hypothermia in mice. The results from these assays are listed in Table III. The compounds were also tested for central 5-HT receptor activity by use of in vivo biochemical and behavioral methods. Interactions with brain dopamine and serotonin receptors in vivo were evaluated by the effects on the synthesis rates of dopamine and serotonin (represented by DOPA and 5-HTP accumulation, Table IV) in rats. The face to face assay and the isolation-induced aggression asay were two behavioral paradigms performed in mice to measure a compound's anxiolytic potential (Table V). The cardiovascular effects were also studied for selected compounds by measuring the change in blood pressure and sympathetic nerve activity in the anesthetized cat (Table VI).

Compounds **12a/12b** to **17a/17b** represent 8-methoxy compounds with allyl, *n*-propyl, or cyclopropylmethyl substitution on the nitrogen and with either an allyl or cyclopropylmethyl substitution at C-1. Analogs with a cis relationship are generally more potent than the corresponding trans analogs as 5-HT_{1A} agonists in in vitro tests (see Table III). Compounds **14a** and **14b** were an exception, where *trans*-**14b** showed a more potent binding affinity for the 5-HT_{1A} receptor than *cis*-**14a**. In agreement with this result, *trans*-**14b** was also more efficacious in decreasing brain 5-HTP accumulation at the single dose tested (at 10 μmol/kg, see Table IV). However, **14b** was inactive in the in vivo behavioral models (Table V). The analogs studied also depressed the body temperature of mice via sc route more than 6 °F where the maximum decrease for 8-OH-DPAT was 7.2 °F (see Table III). Analogs **12b**, **13b**, and **17b** elicited a >10 °F drop in body temperature. In the isolation induced aggression assay, *cis*-**13a** was active at 3.4, 10, and 34 μmol/kg (ip), whereas *trans*-**12b** was more efficacious than **13a** at equal doses (see Table V). However, both were roughly equipotent to 8-OH-DPAT. Effects on brain biochemistry are exemplified by compounds **12a** and **12b**. As shown on Table IV, *cis*-**12a** was a selective 5-HT_{1A} agonist displaying a decrease in 5-HTP accumulation. On the other hand, *trans*-**12b** showed a tendency toward a decrease in 5-HTP accumulation, but statistical significance was not reached. Three of the cis/trans pairs (**12a/12b**, **13a/13b**, and **17a/17b**) were studied for cardiovascular effects by measuring the change in blood pressure and sympathetic nerve activity in the anesthetized cat, as illustrated in Table VI. The cis analogs (**12a/13a**) were shown to be more potent in inhibiting sympathetic nerve activity than the trans analogs (**12b/13b**). However, cis/trans pair (**17a/17b**) was found equally efficacious in reducing blood pressure and sympathetic nerve activity.

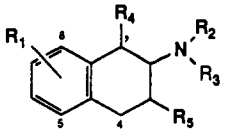
Substitution at the C-1 position with a carbomethoxy group decreased the 5-HT_{1A} agonist activity. As shown in Table III, *cis*-**19a** showed a weak 5-HT_{1A} binding activity whereas *trans*-**19b** showed no activity in the receptor binding assays.

Substitution at the C-1 position with a hydroxymethyl group led to compounds **31a**, **32**, and **33** which displayed potent 5-HT_{1A} binding activity in in vitro tests. Following the previously discussed trends, *cis*-**31a** was found to be the active isomer whereas the corresponding *trans*-**31b** was inactive. Furthermore, as shown in Table VI, *cis*-**31a** was an effective sympatholytic agent which displayed an ED_{50} of 0.09 μmol/kg iv for inhibition of SND in the cat and potently reduced the mouse rectal temperature (ED_{50} 1.4 μmol/kg sc, see Table III). Interestingly, as illustrated in Table V, the *N*-methyl-*N*-*n*-propyl analog **33** also showed potent activity in the in vivo face to face behavioral model (0.3 μmol/kg po).

Those analogs without substitution on the aromatic ring (**10a** and **11a**) displayed weak binding affinity for the 5-HT_{1A} receptor (see Table III). Naiman et al. has previously presented the *N*-propylaminotetralin with no substitution on the aromatic ring as having a weak affinity for the 5-HT_{1A} receptor.[3b]

It is interesting to note that the 5-methoxy analogs **18a** and **18b** were inactive in the in vitro binding assays and displayed no significant interactions with brain dopamine or serotonin receptors in in vivo tests at 10 μmol/kg (see

Table II. Physical Properties of Racemic C-1- or C-3-Substituted 2-Aminotetralins



compd	substituents					relation of C-1,2 or C-2,3	mp (°C)	formula[a]
	R_1	R_2	R_3	R_4	R_6			
10a	H	*n*-propyl	H	allyl	H	cis	150–151	$C_{16}H_{23}N$·HCl
10b	H	*n*-propyl	H	allyl	H	trans	186–187	$C_{16}H_{23}N$·HCl
11a	H	allyl	H	allyl	H	cis	138–139	$C_{16}H_{21}N$·HCl
11b	H	allyl	H	allyl	H	trans	151–153	$C_{16}H_{21}N$·HCl
12a	8-OMe	*n*-propyl	H	allyl	H	cis	199–201	$C_{17}H_{25}NO$·HCl
12b	8-OMe	*n*-propyl	H	allyl	H	trans	178–180	$C_{17}H_{25}NO$·HCl
13a	8-OMe	allyl	H	allyl	H	cis	187–188	$C_{17}H_{23}NO$·HCl
13b	8-OMe	allyl	H	allyl	H	trans	143–144	$C_{17}H_{23}NO$·HCl
14a	8-OMe	*n*-propyl	H	cpm[b]	H	cis	229–230	$C_{18}H_{27}NO$·HCl
14b	8-OMe	*n*-propyl	H	cpm[b]	H	trans	136–140	$C_{18}H_{27}NO$·HCl
15a	8-OMe	allyl	H	cpm[b]	H	cis	214–215	$C_{18}H_{25}NO$·HCl
15b	8-OMe	allyl	H	cpm[b]	H	trans	146–148	$C_{18}H_{25}NO$·HCl
16a	8-OMe	cpm[b]	H	cpm[b]	H	cis	218–219	$C_{19}H_{27}NO$·HCl
16b	8-OMe	cpm[b]	H	cpm[b]	H	trans	149–150	$C_{19}H_{27}NO$·HCl
17a	8-OMe	cpm[b]	H	allyl	H	cis	186–187	$C_{18}H_{25}NO$·HCl
17b	8-OMe	cpm[b]	H	allyl	H	trans	185–186	$C_{18}H_{25}NO$·HCl
18a	5-OMe	*n*-propyl	H	allyl	H	cis	183–184	$C_{17}H_{25}NO$·HCl
18b	5-OMe	*n*-propyl	H	allyl	H	trans	197–198	$C_{17}H_{25}NO$·HCl
19a	8-OMe	allyl	H	CO_2Me	H	cis	223–225	$C_{16}H_{21}NO_3$·HCl
19b	8-OMe	allyl	H	CO_2Me	H	trans	170–173	$C_{16}H_{21}NO_3$·HCl
20	8-OH	*n*-propyl	H	allyl	H	cis	162–164	$C_{16}H_{23}NO$·HCl
21	8-OH	allyl	H	allyl	H	cis	190–191	$C_{16}H_{21}NO$·HCl
24a	8-OMe	*n*-propyl	H	H	allyl	cis	216–219	$C_{17}H_{25}NO$·HCl
24b	8-OMe	*n*-propyl	H	H	allyl	trans	153–155	$C_{17}H_{25}NO$·HCl
25a	8-OMe	allyl	H	H	allyl	cis	165–167	$C_{17}H_{23}NO$·HCl
25b	8-OMe	allyl	H	H	allyl	trans	123–125	$C_{17}H_{23}NO$·HCl
26	8-OMe	*n*-propyl	*n*-propyl	allyl	H	cis	159–160	$C_{20}H_{31}NO$·HCl
27	8-OMe	*n*-propyl	H	*n*-propyl	H	cis	249–250	$C_{17}H_{27}NO$·HCl
28	8-OH	*n*-propyl	H	*n*-propyl	H	cis	244–245	$C_{16}H_{25}NO$·HCl
29	8-OMe	*n*-propyl	*n*-propyl	*n*-propyl	H	cis	152–154	$C_{20}H_{33}NO$·HCl
30	8-OH	*n*-propyl	*n*-propyl	*n*-propyl	H	cis	237–239	$C_{19}H_{31}NO$·HCl
31a	8-OMe	allyl	H	CH_2OH	H	cis	203–204	$C_{15}H_{21}NO_2$·HCl
31b	8-OMe	allyl	H	CH_2OH	H	trans	161–162	$C_{15}H_{21}NO_2$·HCl
32	8-OMe	*n*-propyl	H	CH_2OH	H	cis	233–234	$C_{15}H_{23}NO_2$·HCl
33	8-OMe	*n*-propyl	Me	CH_2OH	H	cis	190–192	$C_{16}H_{25}NO_2$·HCl
36	8-OMe	allyl	*n*-propyl	methylene[c]	H		131–132	$C_{18}H_{25}NO$·HCl

[a] The elemental analyses are within ±0.4% of theoretical values. [b] Cyclopropylmethyl group. [c] Methylene group at C-1 position.

Table IV). However, when tested at higher dose (100 μmol/kg), analog **18a** produced a decrease in DOPA and 5-HTP accumulation with only the 5-HTP response was statistically significant. This result suggests that **18a** is a weak, mixed serotonin and dopamine agonists.

Taken together, the order of potency in the 5-HT_{1A} binding assay for C-1 substitution (R_4) was allyl > hydroxymethyl > *n*-propyl > cyclopropylmethyl ≫ carbomethoxy. Differences in effects were also noted as the substitution was varied on the nitrogen. When R_4 = allyl, the order of 5-HT_{1A} binding affinities was allyl, *n*-propyl > cyclopropylmethyl. However, when the cyclopropylmethyl group was present at C-1, the order of 5-HT_{1A} binding affinities becomes cyclopropylmethyl > allyl > *n*-propyl.

There was a marked decrease in 5-HT_{1A} binding affinities (3 fold) in analogs with C-1,N,N-trisubstitution as shown by analogs **26**, **29**, and **30**. For example, analog **29** had potent in in vitro 5-HT_{1A} receptor binding activity but no effect on 5-HTP or DOPA accumulation. Moreover, it displayed how efficacy and potency in in vivo tests as a 5-HT_{1A} agonist, with virtually no effect in both hypothermia and cardiovascular assays. Interestingly, conversion of the methoxy analog **29** to a hydroxy analog **30** did not increase 5-HT_{1A} binding affinity. It has been previously demonstrated that the binding affinity is usually increased 2–3 times by demethylation to the hydroxyl analogs. In analogs with C-1,N-disubstitution, this was found to be the case. The hydroxyl analogs **20**, **21**, and **28** were 2–3 times more potent in the in vitro 5-HT_{1A} binding assay than their methoxy equivalents, **12a**, **13a**, and **27**, respectively. Although **20** showed a potent effect on cardiovascular endpoints (reduction of SND ED_{50} 0.09 μmol/kg), it showed no selectivity in brain biochemistry with a decrease in 5-HTP and an increase in DOPA accumulation. These analogs did not display activity in the face to face behavior assay; however, **28** was active in the isolation-induced aggression assay both ip and orally at 3.5 and 10.6 μmol/kg and 35.2 μmol/kg orally (see Table V).

Introduction of a substituent at the C-3 position resulted in low 5-HT_{1A} binding affinities for the trans analogs **24b** and **25b** whereas the corresponding cis analogs **24a** and **25a** were found inactive (see Table III). Similar findings have been reported with the C-3 methyl-substituted compounds.[8]

The C-1 methylene analog **36** also showed potent 5-HT_{1A} binding activity in in vitro as well as potent activity in the face to face behavioral model (see Tables III and V). The double bond in the C-1 position adds rigidity to this molecule. However, **36** was not selective in the in vivo biochemical assay at 3.2 μmol/kg sc where it showed effects as both a dopamine agonist and 5-HT agonist by decreasing DOPA and 5HTP accumulation (see Table IV).

Table III. Affinities at Central 5-HT_{1A} Sites in Vitro and Effects on Hypothermia in the Mouse

compd	5-HT_{1A} binding affinity[a] K_i,[b] nM (SEM)	mouse hypothermia assay		
		ED_{50} (μmol/kg)[c]	max. temp decrease (°F)	route
8-OH-DPAT	1.6 (±0.3)	1.0 (0.5–1.8)	7.2	sc
		9.7 (5.2–18)	7.5	oral
10a	174 (±89)	NT[f]		
10b	>1000	NT[f]		
11a	152 (±58)	NT[f]		
11b	>1000	NT[f]		
12a	1.8 (±0.1)	3.4 (1.1–9.5)	7.6	sc
		78 (43–141)	6.0	oral
12b	19 (±3)	14 (7.8–25)	10.2	sc
		59[e]	5.8	oral
13a	1.5 (±0.2)	7.9 (4.4–14)	9.8	sc
		44 (26–76)	6.6	oral
13b	10 (±1.7)	5.9 (0.3–13)	11.5	sc
		79 (44–142)	6.6	oral
14a	15 (±1.7)	31 (17–58)	7.4	sc
14b	9.3 (±1.3)	13 (7.4–24)	9.9	sc
		99 (50–197)	2.0	oral
15a	9.4 (±2.3)	32 (14–70)	7.1	sc
15b	15 (±3)	24 (14–41)	6.2	sc
		>97[d]		oral
16a	8.5 (±0.9)	23 (13–39)	6.8	sc
		>93[d]		oral
16b	642 (±1006)	NT[f]		
17a	2.9 (±0.3)	18[e]	8.8	sc
		134 (74–241)	1.5	oral
17b	4.1 (±0.3)	10 (1.6–6.1)	11.5	sc
		>97[d]		oral
18a	>1000	NT[f]		
18b	>1000	NT[f]		
19a	81 (±10)	NT[f]		
19b	>1000	NT[f]		
20	0.5 (±0.03)	1.1 (0.6–2.2)	9.5	sc
		61 (28–137)	6.9	oral
21	1.0 (±0.2)	1.1 (0.6–2.2)	11.2	sc
		>107[d]	2.4	oral
24a	>1000	NT[f]		
24b	106 (±32)	NT[f]		
25a	>1000	NT[f]		
25b	322 (±17)	NT[f]		
26	6.3 (±0.7)	>89[d]		sc
27	11 (±0.8)	14 (8–25)	6.5	sc
		>100.7[d]		oral
28	2.9 (±0.4)	6.1 (2.7–14)	10.4	sc
		46 (27–78)	7.5	oral
29	7.6 (±1.4)	51[e]	2.8	sc
30	11 (±2.1)	9.5 (4.8–19)	6.9	sc
		>92.0[d]		oral
31a	2.0 (±0.3)	1.4 (0.1–0.3)	9.4	sc
		>106[d]	1.6	oral
31b	>1000	NT[f]		
32	5.4 (±3.2)	3.5 (1.0–9.8)	8.0	sc
		81 (34–192)	2.6	oral
33	5.0 (±1.5)	5.7[e]	9.1	sc
		32 (17–60)	5.0	oral
36	3.8 (±0.6)	>97[d]	3.6	sc

[a] [^{3}H]-8-OH-DPAT labeled 5-HT_{1A} sites in bovine hippocampus. [b] K_i values followed by ± SEM. [c] ED_{50}'s are followed by 95% confidence intervals. [d] As approximate ED_{50}'s, higher doses were not tested to determine 95% confidence intervals. [e] Dose–response curve was too steep to calculate 95% confidence intervals. [f] Not tested.

In summary, this SAR study has shown that C-1 substitution (as indicated by region A in Figure 1) preserves the 5-HT_{1A} agonist activity. The stereochemical environment in this region also has a profound effect in a compound's ability to bind to the 5-HT_{1A} receptor. The cis C-1,N-disubstituted analogs were found to be more potent than the corresponding trans analogs in both in vitro and in vivo assays. However, in the case of 1-(cyclopropylmethyl)-*N*-*n*-propyl analogs, the trans isomer has slightly higher in vitro 5-HT_{1A} affinity than its cis counterpart. The order of binding potency for C-1 substitution was allyl > hydroxymethyl > *n*-propyl > methylcyclopropyl ≫ carbomethoxy. With regard to substitution on the aromatic ring, the hydroxy analogs at C-8 were found to be more potent than the corresponding methoxy analogs in the 5-HT_{1A} binding assay but were not selective in in vivo assays. Analogs without aromatic substitution, on the other hand, showed a weak activity in in vitro assays. Those analogs with C-1,N,N-trisubstitution also showed a marked decrease in 5-HT_{1A} binding affinity. In this case, the hydroxy analog **30** was not more potent than its methoxy analog **29**. The methoxy analogs at C-5 were found to be inactive in either the 5-HT_{1A} or D_2 binding assays. As for C-3,N-disubstituted analogs, the activity as 5-HT_{1A} agonists was found to be considerably lower. In this case, the trans analogs showed a weak binding activity whereas the cis analogs were inactive.

Table IV. Effects of Selected Compounds on the Synthesis Rates of Dopamine and Serotonin (DOPA and 5-HTP Accumulation) in the Rat Ventral Limbic Brain Region

compd	dose (μmol/kg)	DOPA[a]	5HTP[a]
8-OH-DPAT	3.0	3.2	−48*
	0.3	16	−37*
12a	3.4	2.2	−50*
12b	68	8.1	−16
	3.4	−4.3	−6.9
13a	3.4	−21*	−60*
14a	9.7	5.0	−25.8*
14b	9.7	18.7	−43.7*
18a	10	35	17
	100	−24	−36*
18b	10	−15	2.7
20	3.5	14	−53*
21	3.6	38*	−48*
29	2.9	−14	−3.9
36	3.2	−36*	−52*

[a] As a percent change from NSD 1015 and saline treated controls. *$p < 0.05$.

Experimental Section

Synthesis. Analytical TLC was performed on Analtech 10- × 20-cm (250 μm) silica gel GF prescored glass plates which were developed in the solvent systems described. The plates were checked under ultraviolet light and developed by dipping in ammonium molybdate/cerium sulfate/10% sulfuric acid solution and heating on a hot plate. ^{1}H NMR spectra were obtained at 300 MHz on a Bruker Model AM-300 spectrometer in $CDCl_3$ solution unless noted otherwise. Chemical shifts (δ) are reported in parts per million relative to internal tetramethylsilane. Flash column chromatography and medium-pressure liquid chromatography were performed with 400 g to 1 kg silica gel 60 (230–400 mesh) purchased from EM Science. All commercial chemicals were used as received from Aldrich unless noted otherwise. HPLC-grade methylene chloride, methanol, tetrahydrofuran, ethyl acetate, and hexane were used. All reactions were performed under a nitrogen atmosphere. Melting points were determined in open capillary tubes on a Mettler FP-62 melting point apparatus and are uncorrected. The amine-based products were converted into the HCl salts by dissolving the free base in a methanolic HCl solution.[14] The solvent was removed and azeotroped with toluene in vacuo followed by recrystallization from an appropriate solvent. Other physical data, such as IR (Infrared spectra), MS (Mass spectra), and elemental analyses were performed by the Physical and Analytical Chemistry Unit of the Upjohn Laboratories. The elemental analyses reported are within 0.4% of the calculated values.

(±)-1,2,3,4-Tetrahydro-2-oxo-1-(2-propenyl)naphthalene (5). A solution of 2-tetralone (**2**, 7.3 g, 50 mmol) in THF (75 mL) was treated with LDA (36.7 mL, 55 mmol, 1.5 M in cyclohexane) at −30 °C over a 30-min period. Allyl bromide (5.6 mL, 65 mmol) was added and the mixture was stirred at room temperature for 24 h. The reaction was quenched with 10% sodium bisulfate to pH 2–3, and THF was removed in vacuo. The concentrate was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was then purified by chromatography, eluting with hexane followed by 5% ethyl

Table V. Effects of Selected Compounds in the Face to Face and Isolation-Induced Aggression Behavioral Assays in the Mouse

	behavior					
	face to face			isolation-induced aggression		
compound	dose (μmol/kg)	route	time (s)	dose (μmol/kg)	route	time (s)
8-OH-DPAT[a]	0	sc	1.1	0	ip	6
	3.0	sc	1.6	0.3	ip	11
	30	sc	5.0	0.9	ip	20
	30	sc	4.4*			
				0	ip	177
				3.0	ip	310*
				9.1	ip	437*
				30	ip	351*
12b	0	ip	0.4	0	ip	3
	1.0	ip	0.9	1.0	ip	3
	3.4	ip	0.4	3.4	ip	305*
	10	ip	0.9	10	ip	600*
	34	ip	2.1*	34	ip	600*
13a	0	sc	1.1	0	ip	14
	0.3	sc	0.9	0.3	ip	4
	3.4	sc	1.4	1.0	ip	2
	34	sc	4.3*	3.4	ip	45*
				10	ip	130*
				34	ip	290*
14b	0	po	2.0	0	po	5
	0.3	po	1.5	3.2	po	7
	3.2	po	1.6	9.7	po	8
	32	po	1.5	32	po	105
19a	0	po	0.7	0	po	56
	0.3	po	1.0	32	po	120
	3.2	po	1.1			
	32	po	0.8			
20	0	sc	2.8			
	0.4	sc	2.9			
	3.5	sc	3.9			
	36	sc	3.8			
21	0	sc	0.8			
	0.4	sc	0.8			
	3.6	sc	0.5			
	36	sc	2.6*			
28[a]	0	po	1.1	0	ip	8
	3.5	po	1.1	3.5	ip	97*
	11	po	1.3	11	ip	125*
	35	po	1.1			
				0	po	11
				3.5	po	28
				11	po	146
				35	po	54*
33[a]	0	po	1.1	0	ip	6
	0.03	po	1.7	10	ip	329*
	0.3	po	2.0*			
	3.3	po	1.7*	0	po	43
	33	po	2.1*	10	po	125
				33	po	269*
36	0	po	0.7	0	po	56
	0.3	po	1.9*	9.7	po	61
	3.2	po	1.9*	32.5	po	416*
	32.5	po	2.5*			

[a] Compound was tested on two occasions, using different doses or different routes of administration. *$p < 0.05$.

acetate/hexane to yield pure **5** as a colorless oil (3.1 g, 33%): ^{1}H NMR δ 7.27–7.16 (m, 4 H), 5.81–4.95 (m, 3 H), 3.54–2.45 (m, 7 H); IR (film) ν_{max} 1717, 1640, and 1582 cm^{-1}; MS, M$^+$ 186, other ions at *m/z* 168, 145, 128, 117. In addition, 4.2 g (37%) of less polar fraction was identified by ^{1}H NMR as the bisallyl product.

(±)-1,2,3,4-Tetrahydro-5-methoxy-2-oxo-1-(2-propenyl)-naphthalene (6). 5-Methoxy-2-tetralone (3) was reacted under the same conditions as in the preparation of **5** to afford the title compound **6** in 16% yield as an oil: ^{1}H NMR δ 7.21 (t, *J* = 7.8 Hz, 1 H), 6.78 (d, *J* = 7.8 Hz, 2 H), (m, 3 H), 5.75–4.97 (m, 3 H), 3.85 (s, 3 H), 3.52–2.49 (m, 7 H); IR (film) ν_{max} 1717, 1641, and 1586 cm^{-1}; MS, M$^+$ 216, other ions at *m/z* 175, 159, 147. The bisallyl product was obtained in 33% yield.

(±)-1,2,3,4-Tetrahydro-8-methoxy-2-oxo-1-(2-propenyl)-naphthalene (7). 8-Methoxy-2-tetralone (4) was reacted under the same conditions as in the preparation of **5** to afford the title compound **7** in 86% yield as an oil: ^{1}H NMR δ 7.18 (t, *J* = 7.8 Hz, 1 H), 6.80 (d, *J* = 7.8 Hz, 1 H), 6.78 (d, *J* = 7.8 Hz, 1 H), 5.73–4.87 (m, 3 H), 3.82 (s, 3 H), 3.88–3.82 (m, 1 H), 3.32–2.43 (m, 6 H); IR (film) ν_{max} 1712, 1640, 1586 cm^{-1}; MS calcd for $C_{14}H_{16}O_2$ 216.1150, found 216.1151; M$^+$ 216, other ions at *m/z* 175, 147, 115, 91.

(±)-1,2,3,4-Tetrahydro-8-methoxy-1-(methylcyclopropyl)-2-oxonaphthalene (8). 8-Methoxy-2-tetralone (4) was reacted with 1.2 equiv of LDA and 1.8 equiv of methylcyclopropyl bromide in THF at 70 °C for 72 h to afford the title compound **8** in 98% yield as an oil: ^{1}H NMR δ 7.17 (t, *J* = 7.8 Hz, 1 H), 6.81 (d, *J* = 7.8 Hz, 1 H), 6.76 (d, *J* = 7.8 Hz, 1 H), 3.91 (t, *J* = 7 Hz 1 H), 3.81 (s, 3 H), 3.33–1.62 (m, 6 H), 0.64–0.09 (m, 5 H); IR (film) ν_{max} 1711 cm^{-1}; MS calcd for $C_{15}H_{18}O_2$ 230.1307, found 230.1290; M$^+$ 230, other ions at *m/z* 176, 147, 115, 91.

(±)-1,2,3,4-Tetrahydro-8-methoxy-2-oxo-1-naphthalenecarboxylic Acid Methyl Ester (9). 8-Methoxy-2-tetralone (4) was reacted with 1.3 equiv of LDA and 10 equiv of dimethyl carbonate in THF at 70 °C for 24 h to afford the title compound **9** in 90% yield as an oil: ^{1}H NMR δ 7.25 (t, *J* = 7.8 Hz, 1 H), 6.85 (d, *J* = 7.8 Hz, 1 H), 6.78 (d, *J* = 7.8 Hz, 1 H), 4.72 (s, 1 H), 3.80 (s, 3 H), 3.72 (s, 3 H), 3.32–2.17 (m, 4 H); IR (film) ν_{max} 1750, 1718, and 1588 cm^{-1}; MS, M$^+$ 234, other ions at *m/z* 202, 191, 174, 147, 131, 115, 103, 91. Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.49; H, 5.93.

***cis*-(±)-1,2,3,4-Tetrahydro-8-methoxy-1-(2-propenyl)-*N*-*n*-propyl-2-naphthalenamine Hydrochloride (12a) and *trans*-(±)-1,2,3,4-Tetrahydro-8-methoxy-1-(2-propenyl)-*N*-*n*-propyl-2-naphthalenamine Hydrochloride (12b).** A solution of ketone **7** (22 g, 0.1 mol) and *n*-propylamine (32.8 mL, 0.4 mol) in 400 mL of MeOH/THF (1:1) was treated with HOAc (80 mL) dropwise at 0–5 °C to adjust the pH to 4–5. The reaction mixture was stirred for 30 min followed by addition of sodium cyanoborohydride (12.6 g, 0.2 mol). The reaction mixture was stirred at room temperature for 48 h and quenched with 20% sodium hydroxide to pH > 13. The solution was extracted with ethyl acetate (2 × 1 L), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting oil was purified by liquid chromatography on 1 kg of silica gel eluting with 4 L of methylene chloride and 3 L of methylene chloride–methanol (19:1) collecting 40-mL fractions. Fractions 58–70 gave 3.3 g (15%) of alcohol (reduction product of **7**), and fractions 72–112 afforded 15.5 g (60%) of a mixture of the cis and trans isomers. The mixture was treated with hydrochloric acid/methanol and concentrated in vacuo. The resulting solid was recrystallized by dissolving in ethyl acetate/methanol and concentrating on a steam bath until the crystals started to appear. The mixture was allowed to stand in the freezer (at −20 °C), and the crystals were collected (14 g). This white solid was assigned as pure cis isomer **12a** by decoupling experiments with 500-MHz ^{1}H NMR which showed the proton coupling between the C-1 and C-2 to be *J* = 4.31 Hz, thereby indicating both substituents to be diequatorial. The physical data for **12a** showed the following: ^{1}H NMR δ 7.14 (t, *J* = 7.8 Hz, 1 H), 6.71 (d, *J* = 7.8 Hz, 1 H), 6.68 (d, *J* = 7.8 Hz, 1 H), 5.98–4.92 (m, 3 H), 3.83 (s, 3 H), 3.72–1.68 (m, 12 H), 1.02 (t, *J* = 7.4 Hz, 3 H); IR (mull) ν_{max} 1638, 1586, and 1567 cm^{-1}; MS, M$^+$ 259, other ions at *m/z* 244, 230, 217, 202, 188, 174, 159, 144, 115. Anal. ($C_{17}H_{25}NO$·HCl) C, H, N. The mother liquor was free-based by treatment with saturated sodium bicarbonate to pH > 8 and extracted with methylene chloride. The resulting oil was purified by liquid chromatography on 600 g of silica gel, eluting with methylene chloride–methanol (20:1) and collecting 40-mL fractions. Fractions homogeneous by TLC were combined and concentrated. The resulting oil was converted into the HCl salt and recrystallized from ethyl acetate/hexane to yield a white solid (2.6 g). This white solid was assigned as the trans isomer **12b** by default: ^{1}H NMR δ 7.13 (t, *J* = 7.8 Hz, 1 H), 6.71 (d, *J* = 7.8 Hz, 1 H), 6.69 (d, *J* = 7.8 Hz, 1 H), 5.32–4.86 (m, 3 H), 3.81 (s, 3 H), 3.62–1.82 (m, 13 H), 0.93 (t, *J* = 7.4 Hz, 3 H); IR (mull) ν_{max} 1640, 1606, and 1583 cm^{-1}; MS, M$^+$ 259, other ions at *m/z* 244, 230, 217, 174, 159, 144, 115. Anal. ($C_{17}H_{25}NO$·HCl) C, H,

Table VI. Effect of Selected Compounds on Arterial Blood Pressure (BP) and Sympathetic Nerve Activity (SND) in the Anesthetized Cat

compd	SND[a] ED_{50} (μmol/kg)	max. decrease SND (% control)	% BP (at SND ED_{50})	max. decrease BP[b] (% control)
8-OH-DPAT	0.03	2.0 (±0.5)	66 (±6.0)	57 (±3)
12a	0.27	10 (±3.2)	85 (±6.8)	57 (±4.5)
12b	1.35	16 (±3.0)	71 (±11)	66 (±11)
13a	0.54	18 (±6.1)	70 (±7)	58 (±0.5)
13b	1.19	10 (±0)	59 (±0.5)	45 (±8)
17a	0.27	10 (±7)	65 (±0.54)	58 (±4.5)
17b	0.81	21 (±11)	65 (±10)	46 (±12)
20	0.09	10 (±2.5)	77 (±3.2)	55 (±1.7)
29	>2.94	137 (±23)		87 (±4.5)
31a	0.09	5.0 (±5.0)	82 (±2.2)	48 (±1.0)
36	0.91	20 (±7.2)	59 (±3)	51 (±2)

[a] Dose at which the SND has been reduced to 50% of the pretreatment value. [b] Maximum decrease observed following 1 mg/kg dose via iv route.

N. Note: Analogs **10a–19a** and **10b–19b** were synthesized using the same reaction conditions as for **12a** and **12b** above from the corresponding ketones **5**, **6**, **7**, or **8**. The analyses and high-resolution mass spectral data are listed in the supplementary material. The ratio of cis and trans products and yields of these reactions are listed in Table I. The molecular formulas and melting points are listed in Table II.

***cis*-(±)-5,6,7,8-Tetrahydro-8-(2-propenyl)-7-(*n*-propylamino)-1-naphthalenol Hydrochloride (20).** A solution of diphenylphosphine (2.8 mL, 16.0 mmol) in 16 mL of THF in a three-neck, round-bottomed flask, equipped with a condenser and a septum, was treated with *n*-butyllithium (10 mL, 16.0 mmol, 1.6 M in hexane) at 0 °C. The mixture was stirred at room temperature for 10 min, and the free base of **13a** (1.0 g, 4.0 mmol) in 12 mL of THF was added. The red solution was refluxed for 48 h (bath temperature 70 °C). The reaction was quenched with water and extracted with ethyl acetate (2 × 500 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give a yellow oil. This oil was purified by liquid chromatography on 400 g of silica gel, eluting with 2 L of 10% and 3 L of 20% acetone/hexane, and collecting 40-mL fractions. Fractions 88–115 gave a light yellow oil (0.85 g, 87%). This oil was converted into the HCl salt by treating with hydrochloric acid/methanol and recrystallized from ethyl acetate/methanol to give pure **20** as a white solid: ^{1}H NMR (CD_3OD) δ 6.97 (t, J = 7.8 Hz, 1 H), 6.60 (dd, J = 7.8 and 3 Hz, 2 H), 6.00–4.90 (m, 3 H), 3.73–1.73 (m, 12 H), 1.05 (t, J = 7.4 Hz, 3 H); IR (mull) ν_{max} 3400, 1610, and 1587 cm^{-1}; MS, M$^+$ 245, other ions at m/z 230, 216, 203, 188, 145, 131, 115. Anal. ($C_{16}H_{23}NO\cdot HCl$) C, H, N.

***cis*-(±)-5,6,7,8-Tetrahydro-8-(2-propenyl)-7-(*n*-propylamino)-1-naphthalenol Hydrochloride (21).** Compound **13a** was reacted under the same conditions as in the preparation of **20** to afford the title compound **21** in 34% yield: ^{1}H NMR (CD_3OD) δ 7.00 (t, J = 7.8 Hz, 1 H), 6.60 (d, J = 7.8 Hz, 2 H), 6.03–5.50 (m, 6 H), 3.83–1.60 (m, 10 H); IR (mull) ν_{max} 3405, 1610, and 1588 cm^{-1}; MS, M$^+$ 243, other ions at m/z 228, 202, 188, 160, 145, 131, 115. Anal. ($C_{16}H_{21}NO\cdot HCl$) C, H, N.

(±)-1,2,3,4-Tetrahydro-8-methoxy-2-oxo-3-(2-propenyl)-1-naphthalenecarboxylic Acid Methyl Ester (22). To a solution of keto ester **9** (10.2 g, 43.5 mmol) in 108 mL of THF in a three-neck, round-bottomed flask, equipped with a dropping funnel, was added LDA (63.8 mL, 95.7 mmol, 1.5 M in cyclohexane) slowly at −30 to −40 °C under a nitrogen atmosphere. The solution was allowed to warm to 0 °C, and allyl bromide (6.0 mL, 69.6 mmol) was added. After the mixture was stirred for 1 h at room temperature, TLC analysis showed no starting material remaining. The reaction was quenched with 3 N hydrochloric acid to pH 2–3 and extracted with ethyl acetate (2 × 1 L). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting oil was purified by liquid chromatography on 800 g of silica gel, eluting with hexane/acetone (3:1) and collecting 40-mL fractions. Fractions 36–63 yielded pure **22** as a yellow oil (10.3 g, 87%): ^{1}H NMR δ 7.24 (t, J = 7.8 Hz, 1 H), 6.83 (d, J = 7.8 Hz, 1 H), 6.77 (d, J = 7.8 Hz, 1 H), 5.89–5.02 (m, 3 H), 4.75, 4.59 (2 s, 1 H), 3.80 (s, 3 H), 3.81 (s, 3 H). 3.32–1.64 (m, 5 H); IR (film) ν_{max} 1751, 1717, and 1589 cm^{-1}; MS, M$^+$ 274, other ions at m/z 242, 233, 214, 201, 187, 173, 159, 145. Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.73; H, 6.65.

(±)-1,2,3,4-Tetrahydro-8-methoxy-3-(2-propenyl)-2-oxonaphthalene (23). A solution of allyl keto ester **22** (10.3 g, 37.6 mmol) in DMSO (26.3 mL) and water (1.1 mL) was treated with lithium chloride (1.9 g, 45.1 mmol). The reaction mixture was heated at 125 °C (bath temperature) for 5 h. The mixture was cooled to room temperature and extracted with ethyl acetate (1 L). The organic layer was washed with 10% aqueous calcium sulfate (an efficient way of removing DMSO from the organic layer), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by liquid chromatography on 800 g of silica gel, eluting with hexane/ethyl acetate (3:1) and collecting 40-mL fractions. Fractions 26–53 yielded pure **23** as a yellow oil (7.65 g, 94%): ^{1}H NMR δ 7.16 (t, J = 7.8 Hz, 1 H), 6.80 (d, J = 7.8 Hz, 1 H), 6.74 (d, J = 7.8 Hz, 1 H), 5.95–4.95 (m, 3 H), 3.82 (s, 3 H), 3.70–2.08 (m, 7 H); IR (film) ν_{max} 1756, 1710, and 1589 cm^{-1}; MS, M$^+$ 216, other ions at m/z 185, 174, 159, 146, 134, 115, 104. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.21; H, 7.65.

***cis*-(±)-1,2,3,4-Tetrahydro-8-methoxy-3-(2-propenyl)-*N*-*n*-propyl-2-naphthalenamine Hydrochloride (24a) and *trans*-(±)-1,2,3,4-Tetrahydro-8-methoxy-3-(2-propenyl)-*N*-*n*-propyl-2-naphthalenamine Hydrochloride (24b).** Compound **23** was reacted under the same conditions as in the preparation of **12a**/**12b** using *n*-propylamine. Two products were obtained in 79% yield (ratio 6:1 cis/trans). The major product was assigned as cis compound **24a** (by analogy to **12a** and **12b**): ^{1}H NMR δ 7.16 (t, J = 7.8 Hz, 1 H), 6.80 (d, J = 7.8 Hz, 1 H), 6.74 (d, J = 7.8 Hz, 1 H), 5.92–4.95 (m, 3 H), 3.78 (s, 3 H), 3.54–1.55 (m, 12 H), 1.02 (t, J = 7.4 Hz, 3 H); IR (mull) ν_{max} 1604 and 1587 cm^{-1}. Anal. ($C_{17}H_{25}NO\cdot HCl$) C, H, N. The minor product was assigned as the trans compound **24b**: ^{1}H NMR δ 7.16 (t, J = 7.8 Hz, 1 H), 6.80 (d, J = 7.8 Hz, 1 H), 6.74 (d, J = 7.8 Hz, 1 H), 5.88–5.06 (m, 3 H), 3.78 (s, 3 H), 3.38–1.60 (m, 12 H), 0.99 (t, J = 7.4 Hz, 3 H); IR (mull) ν_{max} 1605 and 1593 cm^{-1}. Anal. ($C_{17}H_{25}NO\cdot HCl$) C, H, N.

***cis*-(±)-1,2,3,4-Tetrahydro-8-methoxy-*N*,3-di-2-propenyl-2-naphthalenamine Hydrochloride (25a) and *trans*-(±)-1,2,3,4-Tetrahydro-8-methoxy-*N*,3-di-2-propenyl-2-naphthalenamine Hydrochloride (25b).** Compound **23** was reacted under the same conditions as in the preparation of **12a**/**12b** using allylamine. Two products were obtained in 86% yield (ratio 6:1 cis/trans). The major product was assigned as the cis compound **25a** (by analogy to **12a** and **12b**): ^{1}H NMR δ 7.16 (t, J = 7.8 Hz, 1 H), 6.80 (d, J = 7.8 Hz, 1 H), 6.74 (d, J = 7.8 Hz, 1 H), 6.30–4.95 (m, 6 H), 3.78 (s, 3 H), 3.96–1.88 (m, 10 H); IR (mull) ν_{max} 1604 and 1587 cm^{-1}. Anal. ($C_{17}H_{23}NO\cdot HCl$) C, H, N. The minor product was assigned as the trans compound **25b**: ^{1}H NMR δ 7.16 (t, J = 7.8 Hz, 1 H), 6.80 (d, J = 7.8 Hz, 1 H), 6.74 (d, J = 7.8 Hz, 1 H), 6.22–5.02 (m, 6 H), 3.79 (s, 3 H), 3.82–1.60 (m, 10 H); IR (mull) ν_{max} 1602 and 1592 cm^{-1}. Anal. ($C_{17}H_{23}NO\cdot HCl$) C, H, N.

***cis*-(±)-1,2,3,4-Tetrahydro-8-methoxy-1-(2-propenyl)-*N*,*N*-di-*n*-propyl-2-naphthalenamine Hydrochloride (26).** A round-bottomed flask, equipped with a Dean–Stark moisture trap, was charged with ketone **4** (7.05 g, 40.0 mmol), dipropylamine (11 mL, 80.0 mmol), *p*-toluenesulfonic acid monohydrate (76 mg),

and toluene (100 mL). The mixture was refluxed for 24 h, and another portion of 11 mL of dipropylamine was added and refluxed for an additional 24 h. An aliquot was taken, concentrated in vacuo, and examined by ^{1}H NMR for the enamine hydrogen peak at δ 5.54. The reaction appeared to be 85% complete. The mixture was then concentrated in vacuo. The concentrate was dissolved in THF (100 mL), allyl bromide (13.8 mL, 160 mmol) was added, and the mixture was refluxed for 48 h. The solvent was removed in vacuo, and ^{1}H NMR showed no enamine remaining. This crude product was dissolved in 2-propanol/THF (1:1, 160 mL), and acetic acid (5 mL) was added. The mixture was treated with sodium cyanoborohydride (5.03 g, 80 mmol) and stirred at room temperature for 48 h. The reaction was quenched with 50 mL of water, stirred for 30 min, basified with saturated sodium bicarbonate, and extracted with methylene chloride (2 × 600 mL). The combined organic layers were washed with water, brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. This crude product was purified by liquid chromatography on 560 g of silica gel, eluting with 10% ethyl acetate/hexane (0.5% triethylamine) and collecting 40-mL fractions. Fractions 22–53 were combined and concentrated in vacuo. The resulting brown oil was repurified by the same column, but eluting this time with 2 L of methylene chloride and 4 L of methylene chloride–methanol (20:1) and collecting 40-mL fractions. Fractions 64–155 yielded product as a yellow oil (2.96 g, 24.5%). This oil was treated with hydrochloric acid/methanol and concentrated in vacuo. Recrystallization from ethyl acetate/methanol afforded pure **26** as a white solid (2.18 g): ^{1}H NMR (CD_3OD) δ 7.16 (t, J = 7.8 Hz, 1 H), 6.78 (d, J = 7.8 Hz, 1 H), 6.75 (d, J = 7.8 Hz, 1 H), 5.78–4.89 (m, 3 H), 3.80 (s, 3 H), 3.58–1.74 (m, 16 H), 1.05 (t, J = 7.4 Hz, 6 H). Decoupling experiments (500-MHz ^{1}H NMR) showed that the coupling constant of C-1 and C-2 protons is 4.31 Hz, indicating the substituents are diequatorial (cis). IR (mull) ν_{max} 1640 and 1586; MS, M$^+$ 301, other ions at m/z 286, 272, 259, 230, 201, 173, 159, 147, 127. Anal. ($C_{20}H_{31}NO$·HCl) C, H, N.

***cis*-(±)-1,2,3,4-Tetrahydro-8-methoxy-*N*,1-di-*n*-propyl-2-naphthalenamine Hydrochloride (27).** A mixture of **12a** (2.95 g, 10 mmol), 10% palladium on carbon (0.3 g, Engelhard), and methanol (100 mL) was reacted in a Parr shaker apparatus under a hydrogen atmosphere at 40 psi for 2 h. The mixture was filtered through a Celite pad and concentrated in vacuo. The resulting solid was recrystallized from ethyl acetate/methanol to yield pure **27** as a white solid (2.74 g, 92%): ^{1}H NMR δ 7.13 (t, J = 7.8 Hz, 1 H), 6.72 (d, J = 7.8 Hz, 1 H), 6.69 (d, J = 7.8 Hz, 1 H), 3.68–3.55 (m, 1 H), 3.38–1.20 (m, 14 H), 1.04 (t, J = 7.4 Hz, 3 H), 0.99 (t, J = 7.4 Hz, 3 H); IR (mull) ν_{max} 1601 and 1584 cm^{-1}; MS, M$^+$ 261, other ions at m/z 232, 219, 203, 190, 173, 160, 147, 135, 125. Anal. ($C_{17}H_{27}NO$·HCl) C, H, N.

***cis*-(±)-5,6,7,8-Tetrahydro-8-propyl-7-(*n*-propylamino)-1-naphthalenol Hydrochloride (28).** A solution of **27** (0.57 g, 2.0 mmol) in 10 mL of 48% hydrobromic acid was refluxed for 8 h (bath temperature, 120 °C). The mixture was cooled to room temperature, treated with 20% sodium hydroxide to pH 7–8, and extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The oil was converted into the HCl salt with excess anhydrous hydrochloric acid/methanol and recrystallized from ethyl acetate to yield pure **28** as a white solid (0.36 g, 64%): ^{1}H NMR (CD_3OD) δ 6.96 (t, J = 7.8 Hz, 1 H), 3.63–1.36 (m, 14 H), 1.05 (t, J = 7.4 Hz, 3 H), 0.98 (t, J = 7.4 Hz, 6 H); IR (mull) ν_{max} 3226, 1609, and 1586 cm^{-1}; MS, M$^+$ 247, other ions at m/z 232, 218, 204, 189, 176, 156, 146, 133, 120, 105. Anal. ($C_{16}H_{25}NO$·HCl) C, H, N.

***cis*-(±)-1,2,3,4-Tetrahydro-8-methoxy-*N*,*N*,1-tri-*n*-propyl-2-naphthalenamine Hydrochloride (29).** A solution of **27** (1.79 g, 6.0 mmol), propionyl chloride (4.2 mL, 48 mmol), pyridine (9.6 mL), and methylene chloride (24 mL) was stirred at room temperature for 24 h. The reaction was quenched with 4 mL of methanol and stirred for 1 h. The mixture was then treated with water followed by 20% sodium hydroxide to pH 7–8 and extracted with ethyl acetate. The organic layer was washed with water, 10% sodium bisulfate, saturated sodium bicarbonate, and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The brown oil was purified by liquid chromatography on 560 g of silica gel, eluting with hexane/acetone (9:1) and collecting 40-mL fractions. Fractions 38–70 gave 1.8 g of a yellow oil. This oil was dissolved in 96 mL of THF and treated with lithium aluminum hydride (0.91 g, 24 mmol, Alfa). The mixture was refluxed for 5 h, cooled to room temperature, diluted with 200 mL of THF, and transferred into an Erlenmeyer flask equipped with a magnetic stirring bar, and saturated sodium sulfate was added dropwise to destroy the excess lithium aluminum hydride. After the gray suspension became white, the mixture was diluted with ethyl acetate (800 mL), dried ($MgSO_4$), filtered, and concentrated to afford a light yellow oil. This oil was purified by liquid chromatography on 800 g of silica gel, eluting with hexane–acetone (9:1) and collecting 40-mL fractions. Fractions 41–48 yielded the free base of **29** (1.27 g, 70%) as a near colorless oil. About 0.5 g of this material was converted into hydrochloric acid salt and recrystallized from ethyl acetate/hexane to give pure **29** as a white solid: ^{1}H NMR δ 7.15 (t, J = 7.8 Hz, 1 H), 6.73 (t, J = 7.8 Hz, 2 H), 3.81 (s, 3 H), 3.78–1.24 (m, 18 H), 1.07, 0.99, 0.91 (3 t, J = 7.4 Hz, 9 H); IR (mull) ν_{max} 1599 and 1588 cm^{-1}; MS, M$^+$ 303, other ions at m/z 274, 260, 246, 232, 203, 176, 161, 147, 126, 115. Anal. ($C_{20}H_{33}NO$·HCl) C, H, N.

***cis*-(±)-5,6,7,8-Tetrahydro-7-(di-*n*-propylamino)-8-*n*-propyl-1-naphthalenol Hydrochloride (30).** A solution of **29** (0.76 g, 2.5 mmol) in 4 mL of 48% hydrobromic acid was refluxed for 24 h (bath temperature, 120 °C). The mixture was cooled to room temperature, treated with 20% sodium hydroxide to pH 7–8, and extracted with ethyl acetate (2 × 500 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting oil was converted into the HCl salt and recrystallized from ethyl acetate/methanol to yield pure **30** as a white solid (0.52 g, 64%): ^{1}H NMR (CD_3OD) δ 6.98 (t, J = 7.8 Hz, 1 H), 6.62 (d, J = 7.8 Hz, 2 H), 3.82–1.22 (m, 18 H), 1.03 (2 t, J = 7.4 Hz, 6 H), 0.93 (t, J = 7.4 Hz, 3 H); IR (mull) ν_{max} 3400, 1607 and 1591 cm^{-1}; MS, M$^+$ 289, other ions at m/z 274, 260, 246, 218, 189, 147, 135, 115. Anal. ($C_{19}H_{31}NO$·HCl) C, H, N.

***cis*-(±)-1,2,3,4-Tetrahydro-8-methoxy-2-(2-propenylamino)-1-naphthalenemethanol Hydrochloride (31a).** A solution of the free base of amino ester **19a** (4.13 g, 15 mmol) in 30 mL of THF cooled to 0–5 °C was treated with lithium aluminum hydride (1.14 g, 30 mmol). The mixture was stirred at room temperature for 24 h. The mixture was then quenched by slow addition of saturated sodium sulfate until the gray suspension became white. To this mixture were added 20 mL of methanol and 500 mL of THF, and the resulting mixture was dried over anhydrous magnesium sulfate by stirring for 1 h. The mixture was filtered through a Celite pad and concentrated in vacuo. The crude product was purified by liquid chromatography on 400 g of silica gel, eluting with 1 L of 25% acetone/hexane and 2 L of 50% acetone/hexane and collecting 40-mL fractions. Fractions 42–95 afforded the desired alcohol (3.22 g, 87%). Treatment with HCl/MeOH and recrystallization from ethyl acetate/methanol yielded **31a** as a white solid (2.24 g): ^{1}H NMR (CD_3OD) δ 7.10 (t, J = 7.8 Hz, 1 H), 6.78 (d, J = 7.8 Hz, 1 H), 6.71 (d, J = 7.8 Hz, 1 H), 6.30–5.38 (m, 3 H); 3.84 (s, 3 H), 4.12–2.10 (m, 10 H); IR (mull) ν_{max} 3320, 1645, 1600, and 1585 cm^{-1}; MS, M$^+$ 247, other ions at m/z 229, 214, 202, 188, 174, 160, 146, 135, 115. Anal. ($C_{15}H_{21}NO_2$·HCl) C, H, N.

***trans*-(±)-1,2,3,4-Tetrahydro-8-methoxy-2-(2-propenylamino)-1-naphthalenemethanol Hydrochloride (31b).** Compound **19b** was reacted under the same conditions as in the preparation of **31a** to afford the title compound **31b** as a white solid (90%): ^{1}H NMR δ 7.12 (t, J = 7.8 Hz, 1 H), 6.71 (d, J = 7.8 Hz, 1 H), 6.68 (d, J = 7.8 Hz, 1 H), 6.24–5.42 (m, 3 H), 3.75 (s, 3 H), 4.38–1.90 (m, 10 H); IR (mull) ν_{max} 3370, 1649, 1603, and 1594 cm^{-1}; MS, M$^+$ 247, other ions at m/z 229, 214, 202, 188, 174, 160, 146, 135, 115. Anal. ($C_{15}H_{21}NO_2$·HCl) C, H, N.

***cis*-(±)-1,2,3,4-Tetrahydro-8-methoxy-2-(*n*-propylamino)-1-naphthalenemethanol Hydrochloride (32).** A mixture of amino alcohol **31a** (0.99 g, 4.0 mmol) and 10% palladium on carbon (0.5 g) in 80 mL of 95% ethanol was reacted in a Parr shaker apparatus under 50 psi of hydrogen atmosphere. After 18 h, the mixture was filtered through a Celite pad and concentrated in vacuo. The resulting oil was treated with HCl/MeOH and recrystallized from ethyl acetate/methanol to yield pure **32** as a white solid (0.75 g, 66%): ^{1}H NMR δ 7.15 (t, J = 7.8 Hz, 1 H), 6.68 (dd, J = 7.8, 3 Hz, 2 H), 3.83 (s, 3 H), 4.14–1.90 (m, 12 H), 1.05 (t, J = 7.4 Hz, 3 H); IR (mull) ν_{max} 3308, 1602, 1585, and 1561 cm^{-1}; MS, M$^+$ 249, other ions at m/z 231, 220, 202, 190, 173, 160, 147, 135, 105. Anal. ($C_{15}H_{23}NO_2$·HCl) C, H, N.

cis-(±)-1,2,3,4-Tetrahydro-8-methoxy-2-(N-methyl-N-n-propylamino)-1-naphthalenemethanol Hydrochloride (33). The mixture of amino alcohol **31a** (3.1 g, 12.5 mmol) and 37% formaldehyde solution (9.4 mL, 125 mmol, Mallinckrodt) in 62.5 mL of THF/CH_3CN (3:1) was cooled to 0–5 °C. To this mixture was added acetic acid (9.4 mL), the resulting mixture was stirred for 30 min, and sodium cyanoborohydride (1.57 g, 25 mmol) was added. The mixture was stirred at room temperature for 24 h, and the reaction was quenched with 20% sodium hydroxide and extracted with methylene chloride (2 × 500 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The oil was purified by LC on 400 g of silica gel, eluting with hexane–acetone (2:1) and collecting 40-mL fractions. Fractions homogeneous by TLC were combined and concentrated in vacuo to yield the N-methylated product (2.7 g, 83%). This oil (2.61 g, 10 mmol) was dissolved in 100 mL of ethyl acetate/ethanol (9:1), and 0.26 g of 10% palladium on carbon was added. The mixture was shaken in a Parr shaker apparatus under 30 psi of hydrogen atmosphere. After 2 h, the mixture was filtered through a Celite pad and concentrated in vacuo. The resulting oil was purified by LC on 400 g of silica gel, eluting with hexane–acetone (2:1) to yield a light yellow oil (1.84 g, 71%). The oil was treated with HCl/MeOH and recrystallized. The salt was extremely hygroscopic and failed to form crystals. The oil was dried in a vacuum oven at 90 °C to yield **33** as a pale yellow solid: ^{1}H NMR δ 7.17 (t, J = 7.8 Hz, 1 H), 6.70 (t, J = 7.8 Hz, 2 H), 4.18–4.08 (m, 2 H), 3.86, 3.85 (2 s, 3 H), 3.82–3.62 (m, 2 H), 3.18, 2.95 (2 sets of d, J = 7.4 Hz, 3 H), 3.40–1.68 (m, 8 H), 1.07 (2 sets of t, J = 7.4 Hz, 3 H); IR (mull) ν_{max} 3289, 1601, and 1587 cm^{-1}; MS, M$^+$ 263, other ions at m/z 246, 234, 218, 202, 173, 160, 147, 129, 115.

(±)-1,2,3,4-Tetrahydro-8-methoxy-1-methylene-N-2-propenyl-N-n-propylnaphthalenamine Hydrochloride (36). A solution of a free-based mixture of **19a** and **19b** (1.38 g, 5.0 mmol) in 5 mL of pyridine and 10 mL of methylene chloride was treated with propionic anhydride (2.5 mL, 20 mmol). The mixture was stirred for 3 h, and TLC analysis showed no starting material remaining. The mixture was quenched with 1 mL of lactic acid to destroy excess reagent and extracted with methylene chloride. The organic layer was washed with 10% sodium bisulfate, brine, 10% sodium hydroxide, and brine, dried ($MgSO_4$), filtered, and concentrated to give light yellow oil. The oil was purified by liquid chromatography on 400 g of silica gel, eluting with acetone/hexane (2:1) and collecting 40-mL fractions. Fractions 10–20 afforded amide **34** (1.4 g, 84%). ^{1}H NMR showed this material is consistent with the desired product. This material (1.33 g, 4 mmol) was then dissolved in 40 mL of THF and treated with lithium aluminum hydride (0.91 g, 24 mmol). The mixture was refluxed for 3 h. The reaction was quenched with saturated sodium sulfate, diluted with THF (500 mL), dried ($MgSO_4$), filtered, and concentrated to give an oil. This oil was purified by liquid chromatography on 560 g of silica gel, eluting with hexane/acetone (2:1) and collecting 40-mL fractions. Fractions 24–28 afforded a light yellow oil **35** which failed to crystallize upon conversion into HCl salt. This oil was dissolved in a solution containing 2 mL of pyridine and 4 mL of methylene chloride and treated with p-toluenesulfonyl chloride (0.76 g, 4 mmol), and the mixture was stirred for 24 h. The reaction was quenched with 2 mL of saturated sodium bicarbonate, followed by 2 mL of methanol. After the mixture was stirred for 1 h, the solution was extracted with methylene chloride (2 × 300 mL). The organic layer was washed with water, saturated sodium bicarbonate, and brine, dried ($MgSO_4$), filtered, and concentrated to give a brown oil. This oil was purified by liquid chromatography on 400 g of silica gel, eluting with hexane/acetone (4:1) and collecting 40-mL fractions. Fractions 15–22 afforded 0.53 g of a light yellow oil which was consistent with the structure of the tosylate by ^{1}H NMR. This oil was then dissolved in 4 mL of THF, treated with potassium *tert*-butoxide (2 mL, 2 mmol, 1 M in THF), and refluxed for 2 h. The mixture was quenched with brine and extracted with methylene chloride (2 × 300 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The concentrate was purified by liquid chromatography on 400 g of silica gel, eluting with hexane/acetone (9:1) and collecting 40-mL fractions. Fractions 13–18 afforded a light yellow oil (0.11 g, 18% overall yield from **19a,b**) which was treated with HCl/methanol. Recrystallization from ethyl acetate/hexane gave pure **36** as an off-white solid: ^{1}H NMR δ 7.08 (t, J = 7.8 Hz, 1 H), 6.74 (d, J = 7.8 Hz, 1 H), 6.71 (d, J = 7.8 Hz, 1 H), 5.92 (s, 1 H), 5.53 (s, 1 H), 5.90–5.00 (m, 3 H), 3.84 (s, 3 H), 3.50–1.32 (m, 11 H), 0.76 (t, J = 7.4 Hz, 3 H); IR (mull) ν_{max} 1630, 1600, and 1580 cm^{-1}; MS, M$^+$ 271, other ions at m/z 256, 242, 200, 174, 158, 145, 128, 115. Anal. ($C_{18}H_{25}NO$·HCl) C, H, N.

X-ray Structure Determination of 12a. $C_{17}H_{25}NO$·HCl, formula weight = 295.8; monoclinic; space group $P2_1/c$; Z = 4; a = 10.188 (2), b = 8.025 (2), c = 21.692 (6) Å, b = 113.83 (2)°, V = 1622.4 (4) Å^3; calculated density = 1.21 g cm^{-3}, absorption coefficient μ = 1.94 mm^{-1}. Intensity data were collected on a clear needle 0.06 × 0.08 × 0.35 mm mounted on a glass fiber on a Siemens $P2_1$ diffractometer.

Graphite monochromatized Cu Kα radiation was used, (λ(Cu Kα) = 1.5418 Å), with $2\Theta_{max}$ = 138°. Intensity data were measured at low temperature [T = 153 (2) °K] using $\theta/2\theta$ scans with scan widths ≥ 3.2° and a scan rate of 4 deg/min. The total time spent counting background, half at each end of the scan, was equal to the time spent scanning. Of the 2986 unique reflections measured, 2147 had intensities > 3σ. Ten reflections periodically monitored showed no trend toward deterioration; $\sigma^2(I)$ was approximated by $\sigma^2(I)$ from counting statistics + $(0.018I)^2$, where the coefficient of I was calculated from the variations in intensities of the monitored reflections. Cell parameters were determined by least squares fit of Kα_1 2θ values (λKα_1 = 1.5402) for 25 high 2θ reflections.[15] An Lp correction appropriate for a monochromator with 50% perfect character was applied, and the data were corrected for absorption.[16]

The structure was solved by direct methods, using DIREC.[17] Least squares refinement included coordinates for all atoms and anisotropic thermal parameters for non-hydrogen atoms. The function minimized in the refinement was $\sum\omega(F_o^2 - F_c^{*2})^2$, where weights ω were $1/\sigma^2(F_o^2)$ and F_c^{*2} was as defined by Larson.[18] In the final refinement cycle all shifts were ≤0.2σ. The final agreement index R was 0.053 for all 2986 reflections, and 0.037 for the 2147 reflections having $F_o^2 \geq 3\sigma$. The standard deviation of fit was 1.5. Atomic form factors were from Doyle and Turner,[19] and, for hydrogen, from Stewart, Davidson, and Simpson.[20] The CRYM system of computer programs was used.[17]

The nitrogen is protonated, and both amine hydrogens are involved in hydrogen bonds to a chlorine. The nitrogen–chlorine distance for the strongest bond is 3.085 (1) Å; the other hydrogen bond is to a chlorine related by $-x$, $y - 1/2$, $1/2 - z$, with N–Cl distance 3.214 (2) Å.

The atomic coordinates and thermal parameters are deposited at the Cambridge Crystallographic Data Centre. In addition, the following tables—bond lengths and angles, torsion angles, and close intermolecular contacts—are available as supplementary material.

Serotonin Binding Assay. Receptor binding studies for the 5-HT_{1A} receptor was carried out using [^{3}H]-8-OH-DPAT (sp act. 85 Ci/mmol, NEN) using homogenates of bovine hippocampus prepared with a Polytron and diluted 1:400.[21] Samples were incubated for 1 h at room temperature and then filtered over SS #24 filters (pretreated with 0.05% PEI) and rinsed 3 times with 0.5 mL of 50 mM TRIS pH 7.4 buffer. Nonspecific binding was determined using serotonin (1 μM). IC_{50} and K_i values were calculated by probit analysis, using at least four concentrations of the drug, in triplicate.

Hypothermia Assay. Charles River CF-1 mice (18–22 g, 4 per dose) were individually housed in clear plastic cages with sawdust bedding and perforated metal tops for 20 min prior to testing. After control rectal temperatures were measured, test compounds were given sc in 0.1-mL volume; 20 min later, rectal temperatures were again measured. A decrease of 2 or more °F was considered to be a positive hypothermic response. Drug doses started at 30 mg/kg and were decreased by half-log value until 0 out of 4 mice showed a positive hypothermic response. ED_{50}'s and 95% confidence intervals were determined by Spearman–Karber's method.[22] Oral dosing was similar to sc dosing, except a rounded oral 18-gauge hypodermic needle was used and the volume given was 0.2 mL. Regardless of the route of administration, the mean maximum temperature drop 20 min following any dose was noted as an index of drug efficacy and indirect estimate of intrinsic activity.

Amine Synthesis and Metabolism. Brain levels of DOPA and 5-HTP in the rat were determined as described previously.[23]

Briefly, male Sprague–Dawley rats were injected sc with test drug or vehicle at time zero. Fifteen minutes later the rats received an aromatic decarboxylase inhibitor (NSD 1015 at 100 mg/kg ip). The rats were sacrificed 30 min later, and the tissues in the ventral limbic brain area were removed and frozen for later analysis. Tissues were weighed and extracted in 0.1 N perchloric acid containing an internal standard of dihydroxybenzylamine (2 μg/mL). The extract was then analyzed by HPLC using a Bioanalytical Systems ODS column. DOPA and 5-HTP were detected electrochemically and quantified by peak integration using Waters Maxima software. Biochemical differences were compared between a control ($N = 6$) and a test group ($N = 6$) by unpaired t test.

Face to Face Test for Anxiolytics (a Social Interaction Test in Mice). When two mice are placed together from separate cages into a small chamber, they investigate each other as well as the environment. The prior administration of anxiolytic drugs increases the amount of social interaction, including the amount of face to face interaction. This test is a simplified version of Sandra File's social interaction test in rats.[24] Male CF-1 mice (Charles River, 19–29 g, 8 pairs per dose) were injected subcutaneously, intraperitoneally, or orally. Compounds were dissolved or suspended in 0.25% methylcellulose or 0.1% citric acid. During the 30 min absorption time, mice were housed 2/cage with a familiar partner (i.e., a mouse from the same home cage). Pairs of mice from different home cages were then placed together into a small plastic cage (7 in. × 5 1/2 in.) with a cardboard lid and with fresh wood litter on the floor. Duration of face to face interaction was measured visually for 3 min. Groups were compared by Wilcoxon's rank sum (two-tailed). A significant increase ($p < 0.05$) above the daily control value was interpreted as an anxiolytic effect.

Isolation-Induced Aggression Test for Anxiolytic Activity in Mice. Aggressiveness in adult male mice increases following a period of social isolation. Anxiolytic compounds and sedatives suppress the aggressiveness (i.e., increase the latency to fighting). Male CF-1 mice (20–22 g) were obtained from Charles River or Harlan and separated into two groups. Isolated "resident" mice were housed singly for at least 1 month. Group-housed "intruder" mice were housed 4–6/cage. Food and water were available ad libitum. Mice weighted 28–30 g at the time of the first tests. Compounds were dissolved or suspended in 0.25% methylcellulose vehicle or 0.1% citric acid. Drugs were tested blindly, with 6 mice/treatment group ($n = 12$ for vehicle). Each isolated "resident" mouse was injected ip or orally with drug 30 min before introduction of an untreated, group-housed "intruder" mouse into the resident's home cage. The number of seconds until fighting began was recorded, and the intruder was removed as soon as fighting began. The isolated resident mice were allowed a minimum of 3 days recovery before reuse. Groups were compared statistically by Wilcoxon's rank sum. Mice which failed to fight within 10 min were arbitrarily assigned 600 s.

Sympathetic Nerve Activity. Adult cats (2.5–4.0 kg) were anesthetized by intramuscular injection of ketamine (11 mg/kg), followed by intravenous chloralose (80 mg/kg). This dose of anesthetic was sufficient to maintain an appropriate level of anesthesia for the duration of the experiments. Each animal was placed in a stereotaxic apparatus, and a femoral artery and vein were cannulated for recording blood pressure and for peripheral drug administration, respectively. Heart rate was recorded continuously with a Grass 7P4 tachograph triggered by the electrocardiogram. A glass tracheal cannula was inserted, and, following surgery, the animals were artificially ventilated and paralyzed with gallamine (4 mg/kg iv). Rectal temperature was maintained between 37 and 38 °C using a heating pad.

Sympathetic nerve discharge (SND) was recorded from the central end of the sectioned left inferior cardiac nerve. The nerve was located distal to its exit from the stellate ganglion and was isolated outside the pleural cavity after removal of the vertebral portion of the first rib. Nerve activity was recorded under mineral oil using a bipolar platinum electrode with capacity coupled preamplification at low and high frequency half-amplitude responses of 1 and 500 Hz, respectively. Sympathetic activity was quantitated using cumulative integration. Cumulative intravenous doses of a compound were tested at 20-min intervals.

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Supplementary Material Available: A table of C, H, N analyses and high-resolution mass spectrum results as well as tables of atomic coordinates, isotropic thermal parameters, bond lengths and angles, torsion angles, anisotropic thermal parameters, hydrogen bonds, and close intermolecular contacts (7 pages). Ordering information is given on any current masthead page.

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