Dopamine D_3 Receptor Antagonists. 1. Synthesis and Structure−Activity Relationships of 5,6-Dimethoxy-*N*-alkyl- and *N*-Alkylaryl-Substituted 2-Aminoindans

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5,6-Dimethoxy-2-(*N*-dipropyl)-aminoindan (**3**, PNU-99194A) was found to be a selective dopamine D_3 receptor antagonist with potential antipsychotic properties in animal models. To investigate the effects of nitrogen substitution on structure−activity relationships, a series of 5,6-dimethoxy-*N*-alkyl- and *N*-alkylaryl-substituted 2-aminoindans were synthesized and evaluated in vitro for binding affinity and metabolic stability. The results indicate that substitution at the amine nitrogen of the 2-aminoindans is fairly limited to the di-*N*-propyl group in order to achieve selective D_3 antagonists. Thus, combinations of various alkyl groups were generally inactive at the D_3 receptor. Although substitution with an *N*-alkylaryl or *N*-alkylheteroaryl group yields compounds with potent D_3 binding affinity, the D_2 affinity is also enhanced, resulting in a less than 4-fold preference for the D_3 receptor site, and no improvements in metabolic stability were noted. A large-scale synthesis of the D_3 antagonist **3** has been developed that has proven to be reproducible with few purification steps. The improvements include the use of 3,4-dimethoxybenzaldehyde as a low-cost starting material to provide the desired 5,6-dimethoxy-1-indanone **5c** in good overall yield (65%) and the formation of a soluble silyl oxime **17** that was reduced efficiently with $BH_3 \cdot Me_2S$. The resulting amino alcohol was alkylated and then deoxygenated using a Lewis acid and Et_3SiH to give the desired product **3** in good overall yield of (∼65%) from the indanone **5c**.

Introduction

The neurotransmitter dopamine (DA) plays a central role in CNS-related disorders such as schizophrenia and Parkinson's disease. According to the traditional "dopamine hypothesis", schizophrenia and psychotic symptoms are related to an overactivity of dopamine pathways in the mesolimbic system, while in Parkinson's disease there is a hypoactivity in the nigro-striatal dopamine neurons.[1] This hypothesis is based primarily on pharmacological findings. All antipsychotics currently in use block dopamine receptors in the brain, and amphetamine and other dopaminomimetics can exacerbate psychotic symptoms in patients. On the other hand, nigro-striatal neurons are degenerated in Parkinson patients, and their symptoms can be treated with L-DOPA and other dopamine agonists. Furthermore, most antipsychotic compounds produce Parkinson-like side effects as a result of blockade of dopamine receptors in the striatum.[2]

Dopamine research has during the past decade focused on the discovery of various receptor subpopulations.[3] At present, the family of G-protein coupled dopamine receptors has been divided into five subtypes. The D1 family consists of the D_1 and D_5 receptors, while the D2 family includes the D_2−D_4 subtypes. Of these receptor subtypes, the D_2 receptor is the one that is best understood, both clinically and preclinically. Blockade of this receptor (e.g., by means of remoxipride) results in antipsychotic effects but also in extrapyramidal side effects. The precise functional roles of the other receptor subtypes are still under investigation.

Sokoloff and co-workers found that the D_3 receptor mRNA has a high abundance in limbic brain areas associated with cognitive and emotional functions.[4] This is in contrast to the D_2 receptor subtype, which shows a high density in both limbic and striatal areas of the brain. It has been suggested that antagonists with selectivity for the D_3 receptors may offer some advantages as antipsychotics due to increased efficacy, especially against the deficit aspects of schizophrenia (including negative symptoms and cognitive impairments) and fewer side effects.[5]

To identify new lead structures as dopamine D_3 receptor ligands, a variety of dopaminergic compounds were screened in an in vitro binding assay. It was found (Table 1) that the 5-hydroxy indan analogue **1** displayed a slight preference for the D_3 site (K_i ratio $D_2/D_3 = 3$) whereas the corresponding 4-hydroxy analogue **2** displayed a preference for the D_2 site (K_i ratio $D_2/D_3 = 0.08$). **2** was reported as a mixed 5-HT_{1A} and D_2 agonist whereas **1** was inactive.[6] On the basis of this, we hypothesized that disubstitution on the aromatic ring in the C5 and C6 positions may increase the preference for the D_3 receptor by creating a symmetrical compound.

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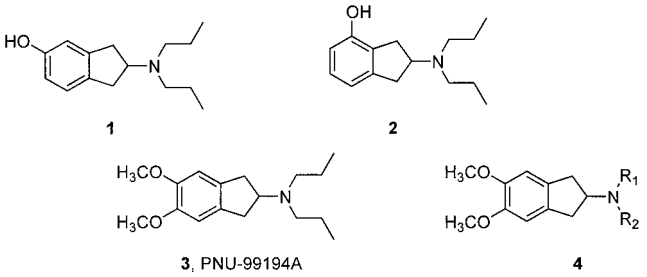
Table 1.

compd	binding affinity K_i, nM (SD or 95% CI)[a]			
	D_2	D_3	ratio D_2/D_3	other
1	53 (±13)	14 (±1.2)	3.7	5-HT_{1A} > 3000
2	5.2 (±1.2)	42 (±4.6)	0.12	5-HT_{1A} 19.5
3	992 (810−1214)	31 (26−37)[b]	32	
7a	4.2 (3.3−5.4)	45 (37−54)	0.09	5-HT_{1A} 5.1 (2.9−8.9)
7b	263 (200−346)	84 (60−117)	3.1	

[a] Binding studies were performed using membranes prepared from CHO cells stably transfected with cloned rat D_2 and D_3 receptors using [^{3}H]-PNU-86170 and [^{3}H]spiperone, respectively. [b] Using [^{3}H]-7-OH-DPAT as a radiolabeled ligand. Binding affinity represented by K_i (nM) followed by statistical significance as standard deviation (SD) or 95% confidence interval (CI).

To test this, **3** was synthesized using modifications of the published route.[7] It was found that this compound did indeed possess a 30-fold preference for the D_3 receptor site in vitro.



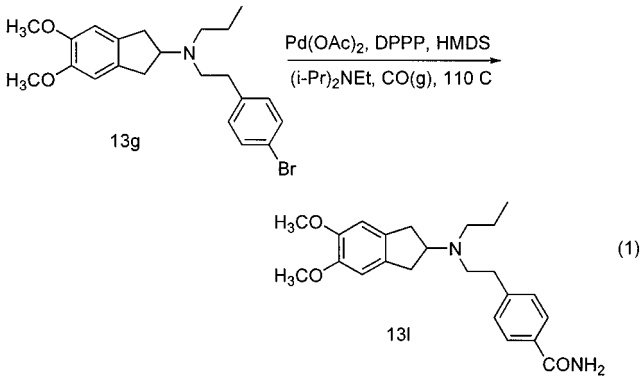
As the first report in this series, we will describe the synthesis and preliminary biological evaluation of the 2-aminoindan analogues represented by the generic structure **4**. The aim of this project was to investigate the effects of variable nitrogen substitution on D_3 affinity and selectivity in this series.

Chemistry

The 2-aminoindan analogues were synthesized using modifications of published procedures.[7] As shown in Scheme 1, the 1-indanones **5a**−**c** were converted to the oximino derivatives **6a**−**c** by reacting with *n*-butylnitrite in MeOH/HCl. The oximino derivatives precipitated from the reaction mixture and were isolated as a solid. Yields varied between 71% and 95% with only a small amount of the product soluble in the methanol. The conversion of the oximino derivatives **6a**−**c** to the N-dialkylated analogues **7a**−**e** could be achieved using a one-pot protocol. Hydrogenolysis of **6a**−**c** (Pd/C, HOAc, H_2SO_4, 6 h at 50 psi of hydrogen atmosphere) yielded the primary amine **8** after filtration and concentration. The crude product, which contained residual sulfuric acid, was neutralized with triethylamine followed by reductive amination at pH 4−5 (aldehyde, HOAc, and sodium triacetoxyborohydride in dichloroethane). The overall yields for this two-step, one-pot sequence were generally in the 40−85% range.

As an alternative to the one-pot synthesis, the primary amine could be isolated after the hydrogenolysis by base extraction with chloroform. We found that the choice of this solvent was crucial to isolate the primary amine. This stepwise process carried along fewer side products, thus the purification of the final product after reductive amination was found to be easier.

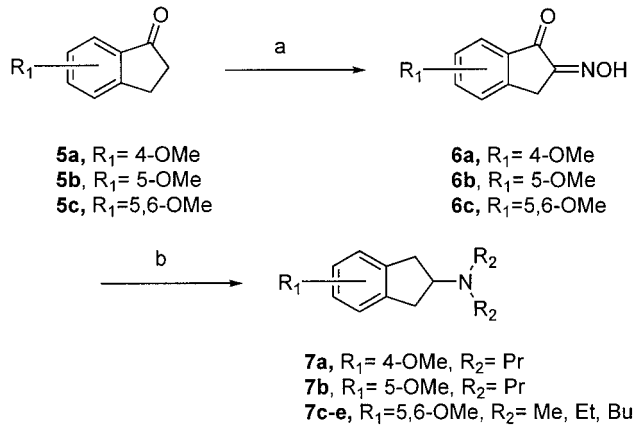
As shown in Scheme 2, the dimethoxy primary amine **8** was easily converted into a variety of N-substituted derivatives. Diethylcyanophosphonate (DEPC) coupling of **8** with propionic acid followed by lithium aluminum hydride (LAH, THF) reduction yielded the monopropyl analogue **9**. This compound was alkylated under standard conditions or subjected to reductive amination with aldehydes to yield additional analogues (**10a**−**c**). Similar treatment of **8** gave analogues **11a**−**g**. The azacylic analogues **12a**−**c** were synthesized via alkylation of the primary amine **8** with the appropriate dihalide. The *N*-propyl-*N*-alkylaryl analogues **13a**−**k,m**−**o** were synthesized by DEPC coupling of the acid with the secondary amine **9** followed by subsequent reduction with borane (BH_3·THF) or lithium aluminum hydride (LAH, THF). An additional analogue bearing a 4-carboxamide phenyl moiety (**13l**) was synthesized in good yield via a palladium-catalyzed carbonylation of the arylbromide **13g** (eq 1) using $Pd(OAc)_2$, 1,3-bis(diphenyl)phosphine (DPPP), and hexamethyldisiliazane for the amine source at 110 °C. It was important to maintain a temperature of 110 °C for the reaction to proceed as lower temperatures resulted in isolation of the starting material even after prolonged reaction times (3−4 days).



(1)

The synthesis of **3** was reexamined to overcome some of the limitations anticipated in large-scale preparation, as larger amounts were needed for more extensive testing, and it also served as a versatile starting material to further investigate the structure−activity relationship (SAR) around the D_3 receptor. The commercially available 5,6-dimethoxy-1-indanone **5c** proved to be an expensive starting material. In contrast, 3,4-dimethoxybenzaldehyde **14** is an inexpensive starting material available in bulk quantities. As shown in Scheme 3, the condensation of **14** with malonic acid in pyridine with catalytic piperidine yielded the cinnamic acid **15** in 75−80% yield. This reaction could be scaled up to >500 g in lab-scale equipment without reducing the yield. The cinnamic acid **15** was reduced via catalytic hydrogenation using Pd/C in EtOH in quan-

Scheme 1[a]



[a] Reagents and conditions: (a) *n*-butylnitrite, MeOH, HCl, △; (b) i: Pd/C, H_2SO_4, HOAc. ii: RCHO, TABH (sodium triacetoxyborohydride), $(ClCH_2)_2$, HOAc, TEA.

titative yield. Because of the limited solubility of the cinnamic acid **15** in EtOH, the reaction conditions were modified to include 1 N NaOH, which greatly increased the capacity of the hydrogenation. Up to 100 g of this material could be reduced in 1 L of solvent in a 2-L Parr apparatus. Alternatively, it was found that the reduction could be achieved using formamide and Pd/C in EtOH at room temperature; however, this procedure required a tedious aqueous workup. The reduction could also be done using Pd/C and formic acid/MeOH; however, this procedure allows for the formation of large quantities of H_2 gas that could be problematic on larger scale. The acid **16**, which could be isolated as a sodium salt, was then converted to the desired 1-indanone **5c** using a two-step Friedel−Crafts cyclization that involved initial acid chloride formation via oxalyl chloride followed by cyclization with $AlCl_3$. The resulting product can be purified by simply stirring in EtOAc with activated charcoal followed by filtration to give >80% yield. This reaction and purification were reproducible even on a 50-g scale.

The indanone was easily converted to the oximino derivative as previously discussed. The catalytic reduction of the oximino derivative **6c** proved to be difficult on larger scale due to limited solubility in the acidic medium as well as incomplete reduction. The latter was confirmed via TLC observations and side product isolation after the subsequent reductive amination reaction. The reaction size was also restricted due to equipment and solubility limitations. A manuscript was published during this effort that outlined a synthesis of a silylated oxime and subsequent asymmetric reduction with a chiral ligand to give a chiral amino alcohol in good yield.[8] Thus, the oximino derivative **6c** was converted to the *tert*-butyldimethylsilyl (TBDMS) oximino derivative **17** using TBDMSCl and imidazole in DMF (88%). This intermediate proved to have greatly enhanced solubility as compared to its precursor, thus making it more amenable to a variety of reactions.

The silyl oxime **17** was converted in a three-step procedure without isolation of the intermediates to the desired **3**. Slow addition of $BH_3 \cdot Me_2S$ (2 equiv) to a heated solution of the silyl oxime **17** in THF afforded the hydroxylamine **18** after only 2 h. This reduction could also be affected using LAH in refluxing THF to give **18** but the yields were slightly lower. The crude **18** was then converted to the dipropyl intermediate **19** under reductive amination conditions using propionaldehyde and sodium triacetoxyborohydride in good yield. A small amount of enamine **20** was also observed. The crude material was deoxygenated/reduced with triethylsilane and $BF_3 \cdot OEt_2$ or TFA[9] to give the final product **3** (PNU-99194) in 70−85% yield from the oxime **6c**. The yields for the final deoxygenation step were greatly improved by substituting refluxing 1,2-dichloroethane for CH_2Cl_2. Deoxygenation was also attempted via catalytic hydrogenation using 10% Pd/C concentrated HCl, under H_2 atmosphere, but afforded only starting material and unidentified side products. The process described in Scheme 3 is an improvement as compared to the initial procedure (Scheme 1), which gave variable yields from the oxime **6c**. This process also has the advantages of being amenable to multigram synthesis with reproducible yields of ∼65% from indanone **5c** and few purifications via chromatography.

Pharmacological Results and Discussion

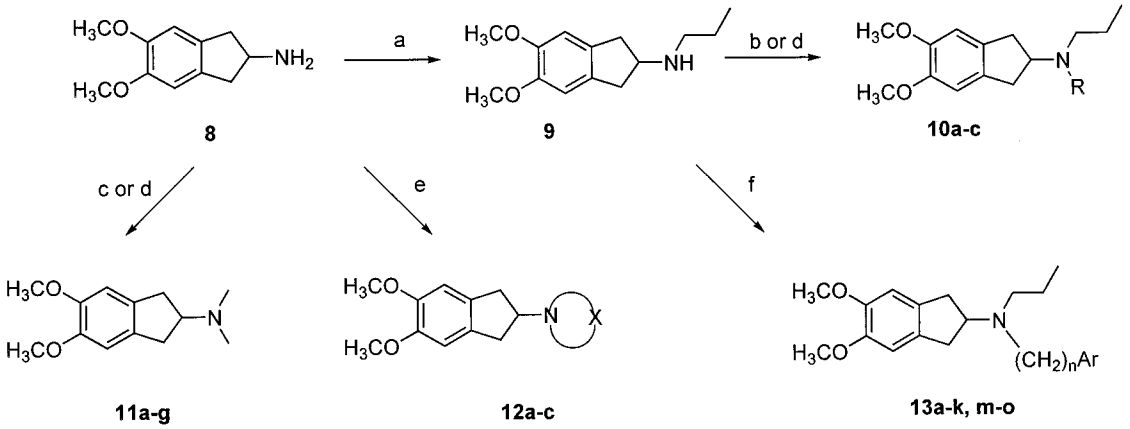
The preference for the dopamine D_3 receptor relative to the D_2 was determined by the comparison of binding affinities for the two receptor subtypes in vitro as shown in Tables1−3. The binding assays were performed using ^{3}H-PNU-86170-labeled D_2 and ^{3}H-7-OH-DPAT-labeled D_3 receptors expressed in stably-transfected CHO cells. In addition, the compounds did not show affinity for other monoaminergic, opioid, and adrenergic receptors when tested at a 1 μmol/L concentration in a profile binding assay except where noted.

Compounds **2** and **7a**, with substitution in the C4 position, showed a slight preference for the D_2 site over the D_3 site. In addition, both analogues showed potent 5-HT_{1A} binding affinity. Interestingly, both methoxy and hydroxy analogues had similar K_i values for the D_2 site. In other structural series such as the 2-aminotetralins or 3-phenylpiperidines, there is an increase in affinity with the hydroxy substitution.[10] As compared to substitution at the C4 position, substitution at the C5 position reduces the D_2 binding affinity. The 5-methoxy (**7b**) and 5-OH (**1**) analogues show a modest 3-fold selectivity for the D_3 receptor site.

The most interesting substitution pattern found was the 5,6-disubstitution as demonstrated by the di-*n*-propyl analogue **3**. This compound displayed a 30-fold preference for the D_3 receptor site as compared to the D_2 and did not have any appreciable affinity at the other receptors tested. Modifications of the N-alkyl substitution greatly affected the binding affinity at the D_3 receptor. For example, replacement of the dipropyl group by dimethyl (**7c**) or diethyl (**7d**)[7] resulted in complete loss of binding activity. Also, by increasing the alkyl chain length to di-*n*-butyl (**7e**), the binding affinity was reduced 4-fold to 180 nM. In addition, the secondary amine (**8**) and the monopropyl (**9**) analogues were completely inactive at all receptors tested.

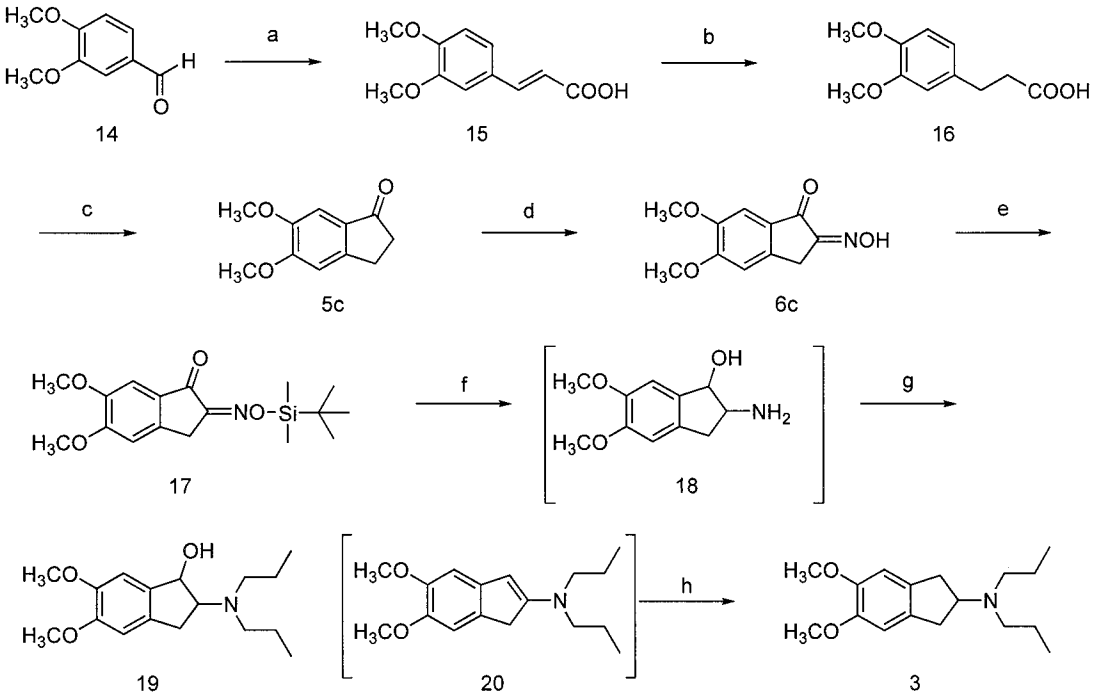
Combinations of an *n*-propyl and another alkyl group were also less effective. The propyl butyl analogue **10b** was 2 times less potent at the D_3 receptor, and the D_2 affinity also was enhanced relative to **3**. Even compounds substituted with propyl and ethyl (**10a**), methylcyclopropyl (**10c**), 1-methylpropyl (**11a**), or 3-fluoro-

Scheme 2[a]



[a] Reagents and conditions: (a) i: EtCOOH, TEA, CH_2Cl_2, DEPC; ii: LAH/THF. (b) RCHO, $NaCNBH_3$, CH_2Cl_2, HOAc. (c) RCHO or RC(O), $(CH_2Cl)_2$, HOAc, TABH. (d) RBr, DMK/K_2CO_3, or NaH/THF. (e) $Br(CH_2)_nBr$, DMF/CH_3CN, Na_2CO_3. (f) i: $Ar(CH_2)_nCOOH$, DEPC, TEA; ii: LAH/THF or BH_3THF.

Scheme 3[a]



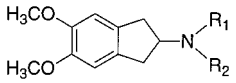
[a] Reagents and conditions: (a) malonic acid, pyridine, Δ, cat. piperidine. (b) NaOH/EtOH, H_2, Pd/C. (c) i: $(ClCO)_2$, DMF/CH_2Cl_2; ii: $AlCl_3$, CH_2Cl_2. (d) butylnitrite, MeOH/HCl, Δ. (e) TBDMSiCl, imidazole, DMF, Δ. (f) BH_3Me_2S, THF, Δ. (g) EtCHO, $Na(OAc)_3BH$, THF; (h) Et_3SiH, $(CH_2Cl)_2$, BF_3OEt_2 (or TFA), Δ.

propyl (**11g**) groups were essentially inactive in the binding assays. The dimethylcyclopropyl (**11c**) and diallyl (**11d**) substitution also proved to be ineffective. Attempts to place the propyl groups in a restricted azacyclic confirmation, such as in the pyrrolo (**12a**), azepino (**12b**), and morpholino (**12c**) analogues, failed to yield compounds with activity at the D_3 receptor.

As shown in Table 3, the *N*-propyl-*N*-alkylaryl-substituted analogues **13a**−**o** did show some binding affinity to the D_3 receptor and some modest D_3/D_2 selectivity. The 3-thiophene **13d** showed a substantially greater binding affinity at the D_3 receptor than the methylene analogue **13b**. The unsubstituted phenyl compound **13e** was equipotent at the D_2 and D_3 receptor sites and showed modest affinity for the 5-HT_{1A} receptor. In general, substitution on the phenyl ring decreased the affinity for the D_3 receptor. The substitution by halogens (**13f** or **13g**), electron-donating (**13h** or **13i**) or electron-withdrawing groups (**13j** or **13l**) did not increase the D_3 affinity or selectivity over the D_2 receptor. Although substitution with an *N*-alkylaryl or *N*-alkylheteroaryl group affords compounds with potent D_3 affinity, the D_2 affinity is also enhanced resulting in a less than 4-fold preference for the D_3 receptor site. The exception to this is **13j**, which shows a 9-fold selectivity for the D_3 receptor. The results in this paper illustrate the strict structural requirements for the amine substituents of the 2-aminoindans and the challenge to identify substitution patterns that maintain selective D_3 activity and preference.

The metabolic stability of selected test compounds was evaluated after incubation in the presence of freshly isolated rat hepatocytes in vitro (Table 4). This in vitro screening model was used to assess likely first pass

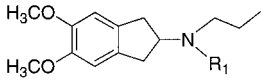
Table 2. Binding Affinities at the Dopamine D2 and D3 Receptors for *N*-Alkyl 2-Aminoindan Derivatives



			affinity (% inhibition or K_i in nM)	
compd	R_1	R_2	D_2 binding[a]	D_3 binding[b]
7c	methyl	methyl	19%[d]	26%[d]
7d	ethyl	ethyl	9%[d]	20%[d]
3	propyl	propyl	992 (810−1214)[e]	31 (26−37)[e]
7e	butyl	butyl	22%[d]	180 (±34)[c,e]
8	H	H	2%[d]	0%[d]
9	propyl	H	19%[d]	17%[d]
10a	propyl	H	20%[d]	25%[d]
10b	propyl	ethyl	374 (187−751)[e]	65 (49−87)[c,e]
10c	propyl	mcp[f]	1796 (1406−2294)[e]	492 (296−819)[e]
11a	H	1-methylpropyl	4%[d]	0%[d]
11b	H	1-ethylpropyl	0%[d]	0%[d]
11c	mcp[f]	mcp	15%[d]	0%[d]
11d	allyl	allyl	19%[d]	12%[d]
11e	3-fluoropropyl	3-fluoropropyl	−19%[d]	3%[d]
11f	propyl	1-methylpropyl	2%[d]	16%[d]
11g	propyl	3-fluoropropyl	1840 (1302−2599)[e]	342 (276−425)[e]
12a	$-CH_2(CH_2)_2CH_2-$		13%[d]	4%[d]
12b	$-CH_2(CH_2)_4CH_2-$		2%[d]	3%[d]
12c	$-CH_2CH_2OCH_2CH_2-$		10%[d]	−2%[d]

[a] ^{3}H-PNU-86170-labeled D_2 sites in cloned CHO cells. [b] ^{3}H-7-OH-DPAT-labeled D_3 sites in cloned CHO cells. Binding affinity represented by K_i (nM) followed by statistical significance as standard deviation (SD) or 95% confidence interval (CI). [c] ^{3}H-spiperone-labeled D_3 sites in cloned CHO cells. [d] Expressed as mean % inhibition ($n = 2$) of radioligand binding at 1000 nM compound concentration. K_i values were not determined for these low potency compounds. [e] K_i expressed in nM (95% CI). [f] mcp, methylcyclpropyl.

Table 3. Binding Affinities at the Dopamine D_2 and D_3 Receptors for the *N*-Propyl-*N*-alkylaryl 2-Aminoindan Derivatives



		affinity K_i, nM (95% CI)		
compd	R_1	D_2 binding[a]	D_3 binding[b]	ratio D_2/D_3 K_i
13a	$-CH_2$-2-thiophene	20%[c]	35%[c]	
13b	$-CH_2$-3-thiophene	1244 (951−1627)	374 (303−463)	3.3
13c	$-(CH_2)_2$-2-thiophene	86%[c]	78 (58−105)	>12
13d[d]	$-(CH_2)_2$-3-thiophene	61 (47−79)	14 (12−15)	4.3
13e[d]	$-(CH_2)_2$-phenyl	27 (23−32)	32 (26−39)	0.84
13f	$-(CH_2)_2$-(3-F-phenyl)	125 (96−162)	30 (21−43)	4.0
13g	$-(CH_2)_2$-(4-Br-phenyl)	97 (74−127)	22 (17−29)	4.4
13h	$-(CH_2)_2$-(4-OMe-phenyl)	163 (128−208)	39 (32−48)	4.1
13i	$-(CH_2)_2$-(3,4-OMe-phenyl)	66 (44−99)	29 (20−42)	2.3
13j	$-(CH_2)_2$-(4-CF_3-phenyl)	310 (254−379)	34 (27−43)	9.1
13k	$-(CH_2)_2$-3-aniline	162 (134−196)	45 (35−57)	3.6
13l	$-(CH_2)_2$-(4-$CONH_2$-phenyl)	123 (98−154)	42 (31−57)	2.9
13m	$-(CH_2)_2$−4-(2-NH_2-thiazole)	265 (216−324)	136 (113−164)	2.0
13n	$-(CH_2)_2$-(3-pyridine)	286 (229−358)	134 (93−193)	2.1
13o	$-(CH_2)_3$-phenyl	155 (126−191)	23 (18−31)	6.7

[a] ^{3}H-PNU-86170-labeled D_2 sites in cloned CHO cells. [b] ^{3}H-7-OH-DPAT-labeled D_3 sites in cloned CHO cells. Binding affinity represented by K_i (nM) followed by statistical significance as standard deviation (SD) or 95% confidence interval (CI). [c] Expressed as the mean % inhibition ($n = 2$) of radioligand binding at 1000 nM compound concentration. [d] Activity also observed in ^{3}H-8-OH-DPAT-labeled 5-HT_{1A} sites in cloned CHO cells. **13d**, K_i = 388 nM (310−486); **13e**, K_i = 324 nM (204−513).

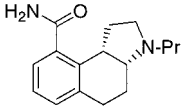
hepatic metabolism in vivo. The extent of metabolism of a compound under this test was determined using HPLC analysis with UV detection. Intrinsic clearance values for each compound were compared to that obtained for a reference compound PNU-93385 [*cis*-(3a*R*)-(−)-2,3,3a,4,5,9b-hexahydro-3-propyl-1*H*-benz[*e*]-indole-9-carboxamide] incubated at the same time to generate a value for relative metabolic stability. PNU-93385 has been shown to display acceptable PK in the rat (oral bioavailability 46%).[11] For a compound series where hepatic first-pass metabolism is the major determinant of oral bioavailability, this in vitro assay helps to develop a structure−metabolism relationship (SMR) and provides a rapid means to evaluate the effect of different substitution patterns on metabolism. As shown in Table 4, these N-substituted analogues all displayed equal or lower relative metabolic stability in comparison to **3**. The dimethyl analogue **7c** and the *N*-propylphenyl analogue **13o** showed improved metabolic stability in vitro. Since these compounds do not show an improved binding profile, they were not examined further. The absolute oral bioavailability of **3** was determined to be <10% in the rat, as predicted by the low value for relative metabolic stability determined in vitro.

The use of **3** in pharmacological assays has led to a hypothesis of the functional role of the dopamine D_3 receptor in the brain[12] and has been a valuable tool to

Table 4. Determination of In Vitro Metabolic Stability in Rat Hepatocytes

PNU no.	relative metabolic stability[a]	PNU no.	relative metabolic stability[a]
PNU-93385	1	**11g**	0.09
7c	0.59	**12b**	0.32
3	0.38	**12c**	0.41
7e	0.13	**13a**	0.35
10a	0.40	**13b**	0.15
10b	0.42	**13c**	0.26
10c	0.23	**13d**	0.14
11c	0.22	**13e**	0.12
11d	0.13	**13h**	0.53
11e	0.08	**13o**	0.67

[a] In vitro metabolic stabilities are expressed relative to the stability of a standard PNU-93385 (see Experimental Section for details).



PNU-93385

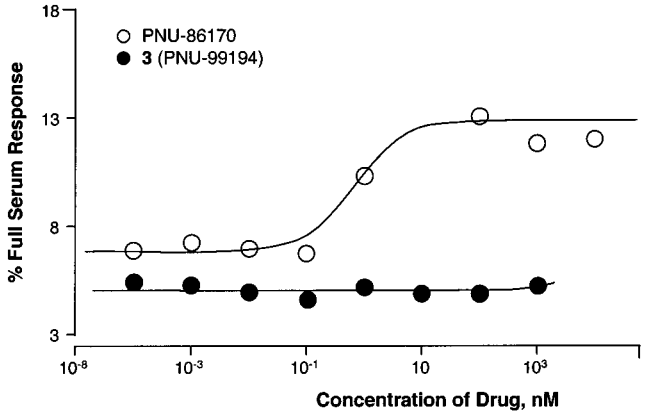


Figure 1. Effect of the DA agonist PNU-86170 and the D_3 antagonst PNU-99194A on mitogenic activity in D_3 cells.

study various aspects of dopamine D_3 receptor-mediated behavioral effects.[13] **3** was tested for agonist activity at the D_3 receptor using D_3 receptor-stimulated mitogenesis and D_3 receptor-stimulated extracellular acidification.[14] While PNU-86170, a dopamine D_2 selective agonist,[15] stimulated D_3 receptor-mediated mitogenesis in transfected CHO cells, **3** at concentrations up to 1 μM had no effect (Figure 1). Likewise, dopamine (10 nM) induced a rapid increase in the extracellular acidification rate in D_3 receptor-transfected CHO cells, but 10 μM **3** had no effect by itself and blocked the changes stimulated by 10 nM dopamine. These data indicate that **3** is a functional D_3 receptor antagonist with no apparent intrinsic activity (Figure 2).

In contrast to typical antipsychotics, **3** did not affect the locomotor activity in actively exploring rats. In habituated rats, however, this compound increased locomotor activity to approximately 600% of control over a wide dose range.[12] A similar locomotor stimulation including rearing, sniffing, licking, and eating was also reported by Clifford and Waddington.[16] In addition, other D_3 receptor antagonists such as nafadotride,[17] S-(+)-14297,[18] and a newly discovered series of dimeric benzimidazoles[19] appear to share these behavioral stimulatory properties. The locomotor stimulation induced by **3** is likely to be mediated via a dopaminergic

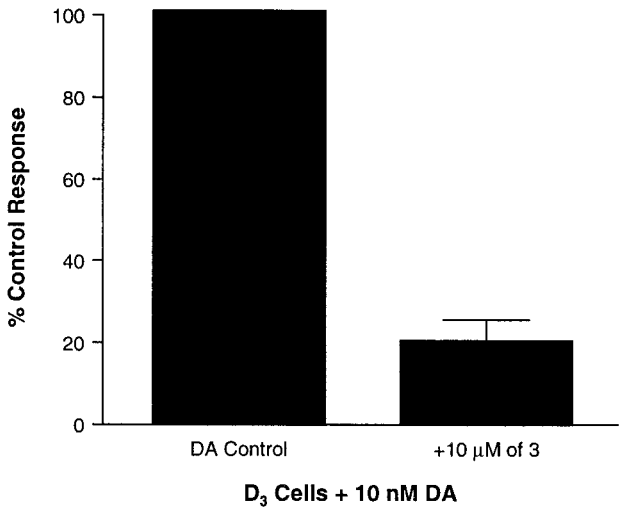


Figure 2. PNU-99194 blocks D_3-mediated acidification.

mechanism since it could be blocked by reserpine or a low dose of haloperidol.[13,17]

The release and metabolism of dopamine, as measured by means of microdialysis in the rat striatum or nucleus accumbens, was only significantly elevated at high doses of **3**, indicating that the D_3 receptor does not possess dopamine autoreceptor functions. Data from D_3 knock-out mice also support this contention.[20] On the basis of these initial behavioral and neurochemical findings, we postulated that the functional D_3 receptor is postsynaptically located where it exerts an inhibitory control on locomotor function.[13] Thus, **3** likely increases locomotion in rodents by antagonism of inhibitory postsynaptic D_3 receptors.

Compound **3** was shown to establish conditioned place preference in the rat.[21] This is of particular interest since a number of studies have indicated a role for dopamine D_3 receptors in the reinforcing effects of pschostimulants.[22] However, it has been reported that while **3** established and maintained discriminative stimulus control in the rat,[23] it failed to substitute for cocaine or D-amphetamine.[24] Recent results have shown that the two antimuscarinic compounds trihexiphenidyl and scopolamine substitute for **3** in a drug discrimination paradigm in rats.[24] This effect is likely not directly mediated via muscarinic receptors since available in vitro binding data show low affinity for the oxotremorine binding site (K_i > 1000 nM). In addition, **3** shows weak affinity for cloned human M1 receptors (K_i = 2090 nM).[25] Thus, given the unique behavioral profile of D_3 receptor antagonists, i.e., a weak behavioral activation, there is a potential use of these agents as adjunctive treatments for psychostimulant use.

The important question that arises is whether a dopamine D_3 selective antagonist is optimal for the treatment of psychosis. **3** was shown to potentiate the locomotor stimulant effects of D-amphetamine, although very high doses tended to antagonize D-amphetamine.[13,26] In line with this, a high dose of **3** has been shown to antagonize the effects of D-amphetamine on 2-deoxyglucose utilization in the rat brain.[27] (+)-MK-801, an NMDA receptor antagonist, produced a profound locomotor stimulation in rats. As shown in Table 5, this effect was dose dependently reversed by **3** with a complete antagonism by the highest dose tested (200

Table 5. Antagonism of (+)-MK-801-Induced Hyperactivity in Rats by **3**

treatment		% of vehicle control	
	3 (μmol/kg, ip)	(±SEM)	no. of animals
Veh[a]+ veh	0	100 ± 14	9
Veh + MK[b]	0	544 ± 34[c]	26
MK[b]	10	583 ± 72[c]	8
MK[b]	30	447 ± 37[c,d]	16
MK[b]	100	391 ± 31[a,d]	8
MK[b]	200	143 ± 54[e]	8

[a] Veh = vehicle (0.9% NaCl in 0.25% methylcellulose). [b] Dose of (+)-MK-801 = 0.2 mg/kg, sc. [c] $p < 0.001$ vs vehicle. [d] $p < 0.05$ vs (+)-MK-801. [e] $p < 0.001$ vs (+)-MK-801.

μmol/kg, ip). However, activity was not reduced below that of vehicle-treated controls. MK-801 is a PCP like compound that has been reported to be psychotic in man. Thus, it is possible that this assay may reflect antipsychotic properties of **3**. This is of particular interest on the basis of the hypoglutamtergic hypothesis for schizophrenia.[28]

Interestingly, in an assay studying the expression of the immediate early gene Fos, **3** and clozapine were both found to increase this measurement in the infralimbic cortex.[29] This is of particular interest since classical antipsychotics increase c-fos primarily in the caudate while atypical agents are known to be more active in the prefrontal cortex. Taken together, these data indicate possible atypical antipsychotic properties of **3** for treating both positive and negative symptoms of schizophrenia.

In conclusion, a series of 5,6-dimethoxy-*N*-alkyl- and *N*-alkylaryl-substituted 2-aminoindans were synthesized and evaluated in vitro for D_3 and D_2 binding affinity and metabolic stability. The results indicate that the substitution at the amine nitrogen of the 2-aminoindans is essentially limited to the di-*N*-propyl group. In addition, the synthesis of the D_3 antagonist **3** has been improved by using 3,4-dimethoxybenzaldehyde as a low-cost starting material to provide the desired 5,6-dimethoxy-1-indanone **5c** in good overall yield (65%) with very little purification necessary. This route is applicable to large scale synthesis. Another key improvement was the formation of a soluble silyl oxime **17** that was reduced efficiently with $BH_3 \cdot Me_2S$. The resulting amino alcohol was alkylated then deoxygenated using a Lewis acid and Et_3SiH to give the desired product **3** in good overall yield (65%) from the indanone **5c**. This procedure has proven to be reproducible with few purification steps and allows for the multigram preparation of **3**. Compound **3** shows approximately a 30-fold preference for the dopamine D_3 vs D_2 receptor subtypes in vitro. Our pharmacological findings indicate possible antipsychotic efficacy with weak behavioral activating properties. Compounds with this profile may prove beneficial in the treatment of psychiatric disorders such as schizophrenia and depression. A mild stimulant could also prove useful in neuro-geriatric disorders and in the rehabilitation of substance abusers. However, due to the low in vitro metabolic stability and oral bioavailability **3** is clearly not a viable drug candidate.

Experimental Section

Synthesis. Analytical TLC was performed on Analtech 10 × 20 cm (250 μm) silica gel GF prescored glass plates that were developed in the solvent systems described. The plates were checked under UV light and developed by dipping in an ammonium molybdate/cerium sulfate/10% sulfuric acid solution and heating on a hot plate. Electrospray (ES) mass spectra were obtained on a Micromass Platform II. GC/MS spectra were recorded on a Hewlett-Packard GCD. The GCD is equipped with a Hewlett-Packard 5880A instrument with an EI detector. A HP-5 column (30 m, 0.25 mm i.d.) coated with cross-linked 5% PhMe silicone (flow = 1.0 mL/min, He gas) was used throughout. The general program run on the GCD was with initial temperature 65 °C, initial time = 2 min, and rate = 3 °C/min to 300 °C final temperature, hold at 300 °C for 3 min (total time = 12.8 min) unless otherwise noted. ^{1}H NMR spectra were obtained at 300 MHz on a Brucker model AM-300 spectrometer. NMR data were obtained in $CDCl_3$ solution unless noted otherwise, and chemical shifts (δ) are reported in parts per million relative to internal tetramethylsilane. Flash column chromatography and medium-pressure liquid chromatography were performed with silica gel 60 (230−400 mesh) purchased from EM Science. Certain chromatographies were performed on the Biotage Flash 40**3** system using either 40- or 90-g cartridges packed with KP-SIL (32−63 μm) silica gel. All commercial chemicals were used as received from Aldrich unless noted otherwise. All reactions were performed under nitrogen atmosphere. Melting points were determined in open capillary tubes on a Mettler FP-62 melting point apparatus and are uncorrected. Final products were converted into the HCl salts. The general procedure for conversion to an HCl salt was the addition of excess methanolic HCl solution[30] to a solution of the compound in methanol. The solvent was removed in vacuo and azeotroped with toluene and then recrystallized from an appropriate solvent. Other physical data, such as IR (infrared spectra), MS (mass spectra), and analyses (elemental analyses) were performed by the Structural, Analytical and Medicinal Chemistry Unit at Pharmacia.

4-Methoxy-2-oximino-1-indanone (6a). To a solution of 4-methoxy-1-indanone (2.00 g, 12.4 mmol) in methanol (30 mL) at 40 °C was added *n*-butylnitrite (1.60 mL, 13.5 mmol) followed by concentrated HCl (1.2 mL). The solution was stirred for 30 min during which time a precipitate was formed. The precipitate was collected and dried to yield a white solid (1.67 g, 71%): mp 237−238 °C dec. ^{1}H NMR ($CDCl_3$ δ): 7.21−7.19 (m, 2H), 6.94−6.91 (m, 1H), 3.72 (s, 3H), 3.48 (s, 3H). IR (mull): 3328, 1708, 1627, 1603, 1496 cm^{-1}. MS (EI): *m*/*z* 191 (M^+), 174 (bp), 131, 116, 103. HRMS (EI) calcd for $C_{10}H_9NO_2$: 191.0582. Found: 191.0589. Anal. ($C_{10}H_9NO_3$) C, H, N.

5-Methoxy-2-oximino-1-indanone (6b). This compound was prepared from 5-methoxy-1-indanone (500 mg, 3.08 mmol) using the same procedure described in the preparation of **6a** to yield an off-white solid (460 mg, 85%): mp 226−227 °C. ^{1}H NMR ($CDCl_3$ + CD_3OD δ): 7.85−7.88 (m, 1H), 6.94 (m, 2H), 3.92 (s, 3H), 3.7 (m, 2H). IR (mull): γ_{max} 3252, 1722, 1596, 1493 cm^{-1}. MS (EI): *m*/*z* 191 (M^+), 174 (bp), 146, 131, 116, 103, 91. HRMS (EI) calcd for $C_{10}H_9NO_3$: 191.0589. Found: 191.0582. Anal. ($C_{10}H_9NO_3$) C, H, N.

5,6-Dimethoxy-2-oximino-1-indanone (6c). This compound was prepared from 5,6-dimethoxy-1-indanone (5 g, 26 mmol), using the same procedure described in the preparation of **6a** to yield a white solid (5.47 g, 95%): mp 227−228 °C. ^{1}H NMR ($CDCl_3$ δ): 7.31 (s, 1H), 6.93 (s, 1H), 4.00 (s, 3H), 3.93 (s, 3H), 3.74 (s, 2H), 2.27 (bs, 1H). IR (mull): γ_{max} 3197, 1699, 1313 cm^{-1}. MS (EI): *m*/*z* 221 (M^+), 204 (bp), 176, 132. HRMS (EI) calcd for $C_{11}H_{11}NO_4$: 221.0688. Found: 221.0690. Anal. ($C_{11}H_{11}NO_4$) C, H, N.

4-Methoxy-2-(dipropylamino)indan (7a). To a solution of **6a** (1.0 g, 5.2 mmol) in acetic acid (60 mL) and sulfuric acid (5 mL) was added 10% Pd/C (500 mg). This mixture was hydrogenated at 50 psi for 7 h, then filtered over Celite (using methanol), concentrated to remove the acetic acid, basified to pH 13, and extracted with chloroform. The combined organic layers were concentrated to yield the primary amine as an oily solid (360 mg, 42%).^{1}H NMR (CD_3OD δ): 7.09 (t, J = 7.8 Hz, 1H), 6.79−6.69 (m, 2H), 4.85 (bs, 2H), 3.77 (s, 3H), 3.73 (m, 1H), 3.14−3.06 (m, 2H), 2.71−2.57 (m, 2H). ^{13}C NMR (δ):

157.6, 144.48, 130.0, 129.1, 120.48, 109.2, 55.7, 53.5, 43.2, 39.5. To a solution of the crude primary amine (360 mg, 2.2 mmol) in 1,2-dichloroethane (30 mL) was added triethylamine to adjust to pH 4−5 followed by propionaldehyde (0.63 mL, 8.8 mmol) and sodium triacetoxyborohydride (1.39 g, 6.6 mmol). After 24 h, the reaction was concentrated to dryness, 1 N HCl was added, followed by basification using 1 N NaOH. The solution was extracted with ethyl acetate (4 × 50 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to yield an oil (480 mg). The crude oil was chromatographed on 100 g of silica gel, eluting with CH_2Cl_2/MeOH (9:1). Homogeneous fractions were combined and concentrated to yield an oil (340 mg, 62%). The oil was converted into the HCl salt and recrystallized using MeOH/EtOAc/ether: 189−190 °C. ^{1}H NMR ($CDCl_3$ δ): 7.18 (t, J = 7.8 Hz, 1H), 6.81−6.79 (d, J = 7.5 Hz, 1H), 6.72−6.69 (d, J = 8.2 Hz, 1H), 4.00 (m, 1H), 3.81 (s, 3H), 3.65 (m, 1H), 3.42−2.90 (m, 7H), 2.0−1.75 (m, 4H), 1.04−0.97 (m, 6H). IR (mull): 2434, 1608, 1594, 1489, 1481, 1443, 1271 cm^{-1}. MS (EI): m/z 247 (M^+), 218 (bp), 147, 115. HRMS (EI) calcd for $C_{16}H_{25}NO$: 247.1936. Found: 247.1943. Anal. ($C_{16}H_{25}NO$·HCl) C, H, N.

5-Methoxy-2-(dipropylamino)indan (7b). This compound was prepared from **6b** (4 g, 30 mmol), using the same procedure described in the preparation of **7a** to yield an oil (1.85 mg, 35%). A 250-mg portion of the oil was converted into the HCl salt and recrystallized using MeOH/EtOAc to yield a white solid (144 mg): mp 165−167 °C. ^{1}H NMR ($CDCl_3$ δ): 7.08−7.05 (d, J = 8.3 Hz, 1 H), 6.73−6.67 (m, 2 H), 3.77 (s, 3 H), 3.77−3.69 (m, 1 H), 3.02−2.80 (m, 4 H), 2.60−2.52 (m, 4 H), 1.58−1.50 (m, 4 H), 0.92−0.87 (t, J = 7.3 Hz, 6H). ^{13}C NMR ($CDCl_3$ δ): 158.7, 142.9, 133.5, 124.9, 112.3, 109.9, 63.6, 55.4, 53.2, 36.7, 35.5, 19.6, 11.9. IR (mull): γ_{max} 2954, 2853, 1614, 1500, 1500, 1464, 1446 cm^{-1}. MS (EI): m/z 247 (M^+), 218, 202, 176, 160, 147, 131, 115. HRMS (EI) calcd for $C_{16}H_{25}NO$: 247.1936. Found: 247.1931. Anal. ($C_{16}H_{25}NO$·HCl) C, H, N.

5,6-Dimethoxy-2-(dimethylamino)indan (7c). This compound was prepared from **6c** (1.0 g, 4.5 mmol) and formaldehyde (2.5 mL, 90 mmol), using the same procedure described in the preparation of **7a** to yield a solid (430 mg, 43%). The solid was converted into the HCl salt and recrystallized using MeOH/EtOAc to yield a white solid (383 mg): mp 276−277 °C. ^{1}H NMR ($CDCl_3$ δ): 6.76 (s, 2H), 4.04 (m, 1H), 3.85 (s, 6H), 3.37−3.31 (m, 4H), 2.79 (s, 6H). IR (mull): γ_{max} 2564, 2516, 1611,1509 cm^{-1}. MS (EI): m/z 221 (M^+), 206 (bp), 176, 165, 146. Calcd for $C_{13}H_{19}NO_2$: 221.1416. Found: 221.1423. Anal. ($C_{13}H_{19}NO_2$·HCl) C, H, N.

5,6-Dimethoxy-2-(diethylamino)indan (7d). This compound was prepared from **6c** (1.0 g, 4.5 mmol) and acetaldehyde (2.0 mL, 36 mmol) using the same procedure described in the preparation of **7a** to yield a solid (430 mg, 43%). The solid was converted to the HCl salt and recrystallized using MeOH/EtOAc to yield a white solid (383 mg): mp 177−178 °C. ^{1}H NMR ($CDCl_3$ δ): 6.71 (s, 2 H), 4.04−4.02 (m, 1 H), 3.85 (s, 6 H), 3.62−3.54 (m, 2 H), 3.25−3.05 (m, 6H), 1.47 (t, J = 7.3 Hz, 6H). IR (mull): γ_{max} 2433,1500 cm^{-1}. MS (EI): m/z 249 (M^+), 234 (bp), 177, 146, 133. HRMS (EI) calcd for $C_{15}H_{23}NO_2$: 249.1729. Found: 249.1720. Anal. ($C_{15}H_{23}NO_2$·HCl) C, H, N.

5,6-Dimethoxy-2-(dipropylamino)indan (3). This compound was prepared from **6c** (4.0 g, 30 mmol) using the same procedure described in the preparation of **7a** to yield an oil (2.04 g, 41%). This oil (200 mg) was converted into the HCl salt and recrystallized using MeOH/EtOAc to yield a white solid (140 mg): mp 210−214 °C (lit. 210−214 °C). ^{1}H NMR ($CDCl_3$, free base δ): 6.72 (s, 2 H), 3.83 (s, 6 H), 3.72−3.62 (m, 1 H), 2.98−2.93 (m, 4 H), 2.58−2.52 (m, 4 H), 1.60−1.50 (m, 4 H), 0.93−0.88 (t, J = 7.3 Hz, 6 H). ^{13}C NMR ($CDCl_3$, free base δ): 148.0, 133.0, 107.8, 63.5, 55.9, 53.2, 36.3, 19.5, 11.9. IR (mull): γ_{max} 2479, 1605, 1508 cm^{-1}. MS (EI): m/z 277 (M^+), 262, 248 (bp), 232, 216, 193, 177, 161, 146. HRMS (EI) calcd for $C_{17}H_{27}NO_2$: 277.2042. Found: 277.2032. Anal. ($C_{17}H_{27}NO_2$·HCl) C, H, N.

5,6-Dimethoxy-2-(dibutylamino)indan (7e). This compound was prepared from **6c** (1.0 g, 4.5 mmol) and butyraldehyde (2.0 mL, 22.5 mmol) using the same procedure described in the preparation of **7a** to yield an oil (1.01 g, 74%). The oil was converted into the HCl salt and recrystallized using MeOH/EtOAc to yield a white solid (611 mg): mp 142−143 °C. ^{1}H NMR ($CDCl_3$ δ): 6.71 (s, 2 H), 4.00 (m, 1H), 3.84 (s, 6 H), 3.56 (m, 2 H), 3.17−2.96 (m, 6 H), 2.00−1.41 (m, 8H), 0.98 (t, J = 7.3 Hz, 6 H). IR (mull): γ_{max} 3125, 2398, 1508, 1483 cm^{-1}. MS (EI): m/z 305 (M^+), 262 (bp), 177, 161, 146. HRMS (EI) calcd. for $C_{19}H_{31}NO_2$: 305.2355. Found: 305.2354. Anal. ($C_{19}H_{31}NO_2$·HCl·0.3H_2O) C, H, N.

5,6-Dimethoxy-2-aminoindan (8). To a solution of **6c** (22.1 g, 100 mmol) in acetic acid (1 L) and sulfuric acid (80 mL) was added 10% Pd/C (10 g). This mixture was hydrogenated at 50 psi for 7 h, then filtered over Celite (using MeOH), concentrated to remove the acetic acid, basified to pH 13, and extracted with chloroform. The combined organic layers were concentrated to yield the primary amine as an oily solid. This crude brown oil was converted into the HCl salt and concentrated to dryness. The resulting solid was refluxed in methanol (100 mL), diluted with EtOAc (100 mL), and allowed to stand in the freezer overnight. The solid was filtered and dried in a vacuum oven overnight (70 °C) to yield an off-white solid (12.0 g, 52%): mp > 300 °C dec. ^{1}H NMR (CD_3OD δ): 6.90 (s, 2 H), 4.08 (m, 1 H), 3.80 (s, 6 H), 2.42−2.92 (m, 4 H). IR (mull): 3163, 3140, 3120, 3035, 2743, 1613, 1525, 1505, 1315, 1267, 1243, 1226, 1214, 1142, 1081 cm^{-1}. % water (KF): 1.07. MS (EI): m/z 193 (M^+), 193, 178, 176, 165, 161, 151, 105, 91, 77. HRMS (FAB) calcd for $C_{11}H_{15}NO_2$+H: 194.1181. Found: 194.1179. Anal. ($C_{11}H_{15}NO_2$·HCl·1.07% H_2O) C, H, N: calcd, 7.07; found, 6.63.

5,6-Dimethoxy-2-(propylamino)indan (9). To a suspension of **8** (6.0 g, 26 mmol), propionic acid (2.5 mL, 34 mmol), and triethylamine (9.12 mL, 65.5 mmol) in methylene chloride (100 mL) was added diethylcyanophosphonate (5.15 mL, 34.0 mmol). The solution stirred for 3 h at room temperature and concentrated to yield a solid. The crude material was chromatographed on 1 kg of silica gel, eluting with CH_2Cl_2/MeOH (19:1) to give the amide (6.67 g, 100% yield: note the presence of some TEA by NMR). GC/MS: t_r 9.6 min; (EI) m/z 249 (M+), 176 (99), 161. ^{1}H NMR ($CDCl_3$ δ): 6.76 (s, 2 H), 6.65 (m, 1 H), 4.75 (m, 1 H), 3.85 (s, 6 H), 3.28 (dd, J = 7.1, 15.8 Hz, 2 H), 2.72 (dd, J = 4.3, 15.8 Hz, 2 H), 2.17 (q, J = 7.6 Hz, 2 H), 1.14 (t, J = 7.6 Hz, 3 H). To a suspension of LAH (0.23 g, 6.0 mmol) in THF (10 mL) was added the crude amide formed above (0.75 g, 3.0 mmol) in THF (10 mL) dropwise. The solution was stirred at room temperature for 3 h and then heated to reflux for 2 h. The reaction was cooled and water, and 1 N NaOH was added slowly to quench the reaction. Ethyl acetate was added and stirred. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to yield an oil. The crude material was chromatographed on 500 g of silica gel, eluting with CH_2Cl_2/MeOH (9:1) to yield the desired product **9** as an oil (0.6 g, 85%). ^{1}H NMR ($CDCl_3$ δ): 6.72 (s, 2 H), 3.83 (s, 6 H), 3.59 (m, 1 H), 3.17−3.09 (dd, J = 7.2, 15.2 Hz, 2 H), 2.92 (s, 1 H), 2.82−2.74 (dd, J = 7.2, 15.2 Hz, 2 H), 2.66 (t, J = 7.3 Hz, 2 H), 1.65−1.52 (m, 2 H), 0.94 (t, J = 7.3 Hz, 3 H). GC/MS: t_r 8.64 min; (EI) m/z 235 (M^+), 220, 206, 166 (99), 151, 131, 115. A portion of this oil (200 mg) was converted to the HCl salt and recrystallized with MeOH/EtOAc to yield a white solid (140 mg): mp 255−256 °C. ^{1}H NMR ($CDCl_3$ δ): 6.71 (s, 2 H), 4.0 (m, 1 H), 3.83 (s, 6 H), 3.8−3.6 (m, 4 H), 2.8 (m, 2H), 2.0 (m, 2 H), 1.61 (s, 1 H), 1.01 (t, J = 7.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$ δ): 148.9, 130.6, 107.6, 58.3, 58.2, 56.1, 47.8, 47.7, 36.0, 19.8, 11.5. IR (mull): γ_{max} 2432, 2346, 1595, 1510 cm^{-1}. MS (EI): m/z 235 (M^+), 220, 206, 177, 166, 151, 133. HRMS (EI) calcd for $C_{12}H_{21}NO_2$: 235.1572. Found: 235.1574. Anal. ($C_{14}H_{21}NO_2$·HCl·1% H_2O) C, H, N.

5,6-Dimethoxy-2-[(ethyl)propylamino]indan (10a). A cooled solution of the amine **9** (0.24 g, 1.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C was treated with acetaldehyde (0.34 mL, 6.0 mmol) and adjusted the pH to 4−5 with a few drops of glacial acetic acid. Sodium cyanoborohydride (0.38 g, 6.0 mmol) was added, and the slurry was stirred at 0 °C for 1.5 h. The reaction

was slowly quenched with H_2O and concentrated HCl and then concentrated. The aqueous slurry was basified with 5 N NaOH to pH > 12 and stirred for 10 min. The solution was extracted with EtOAc (2 × 150 mL), and the organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a yellow oil. Flash chromatography on 30 g of silica gel, eluting with 10:1 CH_2Cl_2/MeOH saturated with NH_3 afforded 0.06 g of the desired product and 0.18 g of impure product. This latter mixture was further purified by MPLC on 200 g of silica gel, eluting with 1:1 hexane/EtOAc (1 L), 4:1 EtOAc/hexane (1 L), 100% EtOAc (1 L), and 10:1 CH_2Cl_2/MeOH (1 L) to give an additional 0.03 g of product for a combined yield of 0.09 g (35%). ^{1}H NMR ($CDCl_3$ δ): 6.70 (s, 2 H), 3.82 (s, 6 H), 3.66 (sext, J = 8.3 Hz, 1 H), 2.97 (dd, J = 7.7, 15.0 Hz, 2 H), 2.85 (dd, J = 8.6, 15.0 Hz, 2 H), 2.66 (q, J = 7.1 Hz, 2 H), 2.48 (m, 2 H), 1.50 (m, 2 H), 1.05 (t, J = 7.1 Hz, 3 H), 0.88 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (δ): 148.0, 140.0, 133.3, 126.3, 107.9, 63.3, 56.0, 52.5, 44.9, 36.7, 20.1, 12.0, 11.7. The oil was converted into an HCl salt and recrystallized from THF/Et_2O to give a tan solid: mp 173−174 °C. IR (mull): 2596, 2573, 2544, 2500, 2454, 1509, 1332, 1319, 1309, 1256, 1239, 1222, 1189, 1099, 991 cm^{-1}. MS (EI): *m*/*z* 263 (M^+), 263, 248, 235, 234, 178, 177, 176, 146, 117, 58. HRMS (EI) calcd for $C_{16}H_{25}NO_2$: 263.1885. Found: 263.1890. Anal. C, H, N.

5,6-Dimethoxy-2-[(butyl)propylamino]indan (10b). This compound was prepared from **9** (0.24 g, 1.0 mmol) and butryaldehyde (0.53 mL, 6.0 mmol) using the same procedure described in the preparation of **10a** to yield the desired product as an oil (0.17 g, 59% yield). ^{1}H NMR ($CDCl_3$ δ): 6.72 (s, 2 H), 3.84 (s, 6 H), 3.68 (quint, J = 8.1 Hz, 1 H), 2.97 (dd, J = 7.7, 14.9 Hz, 2 H), 2.89 (dd, J = 8.6, 15.1 Hz, 2 H), 2.50 (m, 4 H), 1.49 (m, 4 H), 1.31 (sext, J = 7.8 Hz, 2 H), 0.90 (m, 6 H). ^{13}C NMR (δ): 148.0, 133.5, 107.9, 63.6, 56.1, 53.4, 51.2, 36.5, 29.2, 20.8, 20.3, 14.1, 12.0. The oil was converted into an HCl salt and recrystallized twice from THF/Et_2O to give a white solid as a hydrate: mp 142−144 °C. IR (mull): 3509, 2614, 2556, 2535, 1509, 1428, 1331, 1319, 1305, 1259, 1236, 1220, 1195, 1099, 990 cm^{-1}. MS (EI): *m*/*z* 291 (M^+), 291, 276, 263, 262, 249, 248, 178, 177, 176, 146. HRMS (EI) calcd for $C_{18}H_{29}NO_2$: 291.2198. Found: 291.2201. Anal. ($C_{18}H_{29}NO_2$·HCl·4.75% H_2O) C, H, N.

5,6-Dimethoxy-2-[(methylcyclopropyl)propylamino]-indan (10c, U-143468A). To a solution of the amine **9** (0.50 g, 2.1 mmol) and (bromomethyl)cyclopropane (1.02 mL, 10.5 mmol) in DMF (20 mL) was added anhydrous K_2CO_3 (1.45 g, 10.5 mmol). The slurry was stirred at room temperature and quenched with H_2O (250 mL) after 4 days. The solution was extracted with EtOAc (2 × 100 mL), and the organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give an oil. The oil was purified by MPLC on 200 g of silica gel, eluting with 20:1 CH_2Cl_2/MeOH saturated with NH_3 to give **10c** (0.36 g, 59%). ^{1}H NMR ($CDCl_3$ δ): 6.71 (s, 2 H), 3.94−3.83 (m, 7 H), 3.05−2.87 (m, 4 H), 2.66 (m, 2 H), 2.53 (d, J = 6.5 Hz, 2 H), 1.59 (m, 2 H), 0.92 (m, 4 H), 0.55 (m, 2 H), 0.17 (q, J = 5.1 Hz, 2 H). ^{13}C NMR (δ): 148.2, 133.0, 107.9, 63.2, 56.2, 56.1, 52.7, 36.2, 19.6, 12.0, 8.5, 4.1. This oil was converted into the HCl salt and crystallized from CH_2Cl_2/EtOAc, followed by recrystallized from hot EtOAc to give a white solid: mp 202−203 °C. IR (mull): 2536, 2491, 1508, 1444, 1333, 1319, 1260, 1234, 1220, 1190, 1095, 1031, 989, 853, 838 cm^{-1}. MS (EI): *m*/*z* 289 (M^+), 289, 261, 260, 231, 206, 177, 176, 146, 124, 55. HRMS (EI) calcd for $C_{18}H_{27}NO_2$: 289.2042. Found: 289.2043. Anal. ($C_{18}H_{27}NO_2$·HCl·0.19% H_2O·0.39% CH_2Cl_2) C, H, N.

5,6-Dimethoxy-2-(1-methylpropylamino)indan (11a). To a solution of the amine **8** (0.20 g, 1.0 mmol) in 1,2-dichloroethane (20 mL) was added 2-butanone (0.37 mL, 4.1 mmol), and the pH was adjusted to 4−5 with glacial acetic acid. Sodium triacetoxyborohydride (0.65 g, 3.0 mmol) was added portionwise over 10 min, and the solution was stirred for 20 h. The reaction was concentrated, and the residue was diluted in H_2O and CH_2Cl_2 (5 mL). Concentrated HCl was added to break up any borane salts and stirred for 15 min. The slurry was then basified with 5 N NaOH until pH >12 and stirred for 1 h. The cloudy solution was extracted with EtOAc (2 × 100 mL), and the organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give an oil. Flash chromatography on 70 g of silica gel, eluting with 10:1 CH_2Cl_2/MeOH saturated with NH_3 afforded **11a** (0.19 g, 73%). ^{1}H NMR (free base, $CDCl_3$ δ): 6.74 (s, 2 H), 3.84 (s, 6 H), 3.78 (m, 1 H), 3.17−3.08 (m, 2 H), 2.74−2.62 (m, 3 H), 1.56−1.03 (m, 2 H), 1.09 (d, J = 6.3 Hz, 3 H), 0.91 (t, J = 7.4 Hz, 3 H). The oil was converted into an HCl salt and recrystallized with MeOH/EtOAc to give a white solid: mp 256−258 °C. IR (mull): 2763, 2747, 2720, 2691, 2623, 2590, 2499, 2478, 1511, 1314, 1256, 1241, 1222, 1196, 1097 cm^{-1}. MS (EI): *m*/*z* 249 (M^+), 249, 221, 220, 177, 166, 165, 151, 146, 110, 57. HRMS (EI) calcd for $C_{15}H_{23}NO_2$: 249.1729. Found: 249.1738. Anal. ($C_{15}H_{24}ClNO_2$) C, H, N.

5,6-Dimethoxy-2-(3-pentylamino)indan (11b). This compound was prepared from **8** (0.24 g, 1.0 mmol) and 3-pentanone (0.44 mL, 4.1 mmol) using the same procedure described in the preparation of **11a** to yield the desired product as an oil (0.23 g, 85% yield). ^{1}H NMR ($CDCl_3$ δ): 6.74 (s, 2 H), 3.87 (s, 6 H), 3.73 (m, 1 H), 3.16−3.08 (dd, J = 7.1, 14.8 Hz, 2 H), 2.70−2.63 (dd, J = 7.1, 15.0 Hz, 2 H), 2.52 (m, 1 H), 1.53−1.39 (m, 4 H), 0.90 (t, J = 7.4 Hz, 6 H). ^{13}C NMR (δ): 148.0, 133.3, 108.0, 58.2, 57.5, 56.0, 40.5, 26.1, 10.0. The oil was converted into an HCl salt and recrystallized with MeOH/EtOAc to give a white solid: mp 140 °C (softens), 220 °C dec. IR (mull): 2761, 2714, 2655, 2621, 2594, 2522, 2479, 1511, 1315, 1253, 1242, 1220, 1191, 1097, 994 cm^{-1}. MS (EI): *m*/*z* 263 (M^+), 263, 235, 234, 177, 166, 165, 146, 117, 71, 58. HRMS (EI) calcd for $C_{16}H_{25}NO_2$: 263.1885. Found: 263.1878. Anal. ($C_{16}H_{26}ClNO_2$) C, H, N.

5,6-Dimethoxy-2-(dimethylcyclopropylamino)indan (11c). This compound was prepared from amine **8** (0.38 g, 1.6 mmol) and cyclopropane carboxaldehyde (0.97 mL, 13.0 mmol) using the same procedure described in the preparation of **11a** to yield the desired product as an oil (0.45 g,94%). ^{1}H NMR ($CDCl_3$ δ): 6.71 (s, 2 H), 4.13 (quint, J = 7.7 Hz, 1 H), 3.84 (s, 6 H), 3.11−2.95 (m, 4 H), 2.66 (d, J = 6.5 Hz, 4 H), 1.02 (m, 2 H), 0.58 (m, 4 H), 0.21 (q, J = 5.5 Hz, 4 H). ^{13}C NMR (δ): 148.3, 132.8, 107.7, 62.6, 56.1, 55.7, 35.8, 8.2, 4.4. The oil was converted into an HCl salt and crystallized with hot EtOAc/CH_2Cl_2. The resulting solid was recrystallized from hot EtOAc/hexane to give an off-white solid: mp 192−195 °C. IR (mull): 2560, 2536, 2503, 2488, 1507, 1442, 1319, 1261, 1233, 1190, 1093, 1040, 1021, 855, 838 cm^{-1}. MS (EI): *m*/*z* 301 (M^+), 302, 301, 286, 260, 177, 176, 165, 136, 82, 55. HRMS (EI) calcd for $C_{19}H_{27}NO_2$: 301.2042. Found: 301.2038. Anal. ($C_{19}H_{28}ClNO_2$·1.19% H_2O·0.37% CH_2Cl_2·1.2% EtOAc) C, H, N.

5,6-Dimethoxy-2-(di-2-propenylamino)indan (11d). To a solution of amine **8** (0.20 g, 1.03 mmol), DMF (20 mL), and Et_3N (0.77 mL, 5.15 mmol) was added allyl bromide (0.22 mL, 2.58 mmol). The clear solution was stirred for 2 h, and TLC and GC/MS showed both mono- and dialkylated products. After 1 h, additional allyl bromide (0.11 mL, 1.29 mmol) was added. The reaction was quenched after 1 h with H_2O and extracted with Et_2O (2 × 100 mL) followed by EtOAc (1 × 100 mL). The organic layers were combined and washed with brine, dried ($MgSO_4$), and concentrated to give an orange solution. The crude oil was purified by flash chromatography on 30 g of silica gel, eluting with hexane/EtOAc (1:1, 1 L) and CH_2Cl_2/MeOH (10:1) to give 0.10 g of the desired product as well as the monoalkylated product. This monoalkylated product was subjected to the akylation conditions as described above and afforded an additional 0.04 g of desired product **11d**, which was combined with previous for a total yield of 0.15 g (52%). ^{1}H NMR ($CDCl_3$ δ): 6.72 (m, 2 H), 5.98−5.85 (m, 2 H), 5.23 (m, 1 H), 5.17 (m, 3 H), 3.84 (s, 6 H), 3.71 (m, 1 H), 3.20 (d, J = 6.5 Hz, 4 H), 3.00 (dd, J = 7.7, 15.0 Hz, 2 H), 2.88 (dd, J = 8.0, 15.1 Hz, 2 H). ^{13}C NMR (δ): 147.9, 135.3, 133.2, 117.5, 107.7, 62.5, 55.9, 53.7, 36.4, 32.8. The oil was converted into the HCl salt and recrystallized from hot EtOAc to give a white solid: 166−167 °C. IR (mull): 2405, 2376, 2332, 2251, 1507, 1437, 1329, 1311, 1259, 1222, 1188, 1102, 1083, 947, 850 cm^{-1}. MS (EI): *m*/*z* 273 (M^+), 273, 258, 232, 177, 176, 165, 108, 41,

39, 35. HRMS (EI) calcd for $C_{17}H_{23}NO_2$: 273.1729. Found: 273.1721. Anal. ($C_{17}H_{23}NO_2$·HCl·7.48% H_2O) C, H, N.

5,6-Dimethoxy-2-(di-3-fluoropropylamino)indan (11e). To a slurry of washed NaH (0.16 g, 4.1 mmol) in DMF (10 mL) was added a slurry of amine **8** (0.20 g, 1.0 mmol) in DMF (10 mL) and warmed to 110 °C. After 15 min, 1-bromo-3-fluoropropane (0.44 g, 3.1 mmol) was added. TLC after 20 h indicated the remaining starting material as well as a monoalkylated product, so an additional amount of 1-bromo-3-fluoropropane (0.44 g, 3.09 mmol) was added and stirred for 5 h. The reaction was quenched with H_2O and extracted with EtOAc (2 × 150 mL). The organic layers were washed with brine, dried (Na_2SO_4), and concentrated. TLC indicated the presence of mono- and dialkylated products but no starting material. The products were subjected once again to the above reaction conditions using NaH (0.21 g, 5.2 mmol), 1-bromo-3-fluoropropane (1.45 g, 10.3 mmol), and DMF (30 mL). After 5 h, the reaction was quenched and worked up as before to give an oil. MPLC on 200 g of silica gel, eluting with 1:1 hexane/EtOAc, afforded 0.10 g of slightly impure product as an oil (31% yield). ^{1}H NMR ($CDCl_3$ δ): 6.72 (s, 2 H), 4.60 (t, J = 5.8 Hz, 2 H), 4.44 (t, J = 5.7 Hz, 2 H), 3.84 (s, 6 H), 3.74 (quint, J = 8.0 Hz, 1 H), 2.96 (dd, J = 7.8, 15.1 Hz, 2 H), 2.85 (dd, J = 8.1, 15.2 Hz, 2 H), 2.66 (t, J = 7.0 Hz, 4 H), 1.94−1.77 (2 quints, J = 7.2, 6.5 Hz, 4 H, slightly overlapped). ^{13}C NMR (δ): 148.5, 133.6, 108.3, 83.4, 81.8, 63.2, 52.4, 47.2, 47.1, 36.3, 29.0, 28.8. The oil was converted into the HCl salt and crystallized from hot EtOAc/hexane to give an off-white solid as a hydrate: mp 185−186 °C. IR (mull): 3422, 2592, 2508, 2440, 1510, 1331, 1312, 1256, 1238, 1219, 1191, 1094, 1034, 989, 904 cm^{-1}. MS (EI): m/z 313 (M^+), 314, 313, 298, 267, 266, 178, 177, 176, 146, 133. HRMS (EI) calcd for $C_{17}H_{25}F_2NO_2$: 313.1853. Found: 313.1849. Anal. ($C_{17}H_{25}F_2NO_2$·HCl·4.97% H_2O) C, H, N.

5,6-Dimethoxy-2-[(1-methylpropyl)propylamino]indan (11f). To a solution of **11a** (0.08 g, 0.31 mmol) in 1,2-dichloroethane (10 mL) was added propionaldehyde (0.04 mL, 0.62 mmol), and the pH was adjusted to 4−5 with glacial acetic acid. Sodium triacetoxyborohydride (0.13 g, 0.62 mmol) was added, and the reaction was stirred at room temperature overnight. The reaction was concentrated, diluted in H_2O, and acidified with concentrated HCl to break up any borane salts. The slurry was then basified with 5 N NaOH until pH >12 and stirred for 1 h. The cloudy solution was extracted with EtOAc (2 × 100 mL), and the organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give a semisolid. Flash chromatography on 30 g of silica gel, eluting with 1:1 hexane/EtOAc, afforded the product as an oil (0.06 g, 70%). ^{1}H NMR ($CDCl_3$ δ): 6.72 (d, J = 2.7 Hz, 2 H), 3.84 (s, 6 H), 3.74 (m, 1 H), 2.93−2.66 (m, 5 H), 2.49−2.40 (m, 2 H), 1.59−1.39 (m, 3 H), 1.35−1.20 (m, 1 H), 1.00 (d, J = 6.6 Hz, 3 H), 0.94−0.83 (m, 6 H). ^{13}C NMR (δ): 147.8, 133.9, 133.7, 107.9, 107.8, 60.6, 56.3, 56.0, 48.6, 38.5, 37.0, 27.6, 23.6, 15.9, 11.9. MS (EI): m/z 291 (M^+), 291, 276, 263, 262, 178, 177, 176, 146, 131, 85. HRMS (EI) calcd for $C_{18}H_{29}NO_2$: 291.2198. Found: 291.2201.

5,6-Dimethoxy-2-[(3-fluoropropyl)propylamino]indan (11g). To a slurry of washed NaH (0.10 g, 2.6 mmol) (washed with hexane, 20 mL) in THF (10 mL) was added a slurry of the amine **8** (0.20 g, 1.0 mmol) in THF (10 mL). The slurry was refluxed at 75 °C for 20 min and then 1-bromo-3-fluoropropane (0.36 g, 2.6 mmol) was added and heated for 1.5 h. The reaction was quenched slowly with H_2O and concentrated. The solution was diluted with more H_2O and extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give an orange oil (0.17 g). Flash chromatography on 30 g of silica gel, eluting with 10:1 CH_2Cl_2/MeOH saturated with NH_3, afforded 0.04 g of the monoalkylated product as well as 0.09 g of recovered starting material. This starting material was reacted as described above using washed NaH (0.10 g, 2.6 mmol), DMF (10 mL), and 1-bromo-3-fluoropropane (0.36, 2.6 mmol) and warmed to 110 °C for 17 h. The reaction was then quenched with H_2O and extracted with EtOAc (3 × 150 mL). The organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a brown solution. MPLC on 200 g of silica gel, eluting with 10:1 CH_2Cl_2/MeOH saturated with NH_3, afforded an additional 0.05 g of the monoalkylated product for a combined yield of 0.09 g (35%). Also recovered was 46% of the starting material. ^{1}H NMR ($CDCl_3$ δ): 6.74 (s, 2 H), 4.63 (t, J = 5.8 Hz, 1 H), 4.47 (t, J = 5.8 Hz, 1 H), 3.85 (s, 6 H), 3.65 (quint, J = 6.4 Hz, 1 H), 3.14 (dd, J = 7.1, 15.4 Hz, 2 H), 2.83 (t, J = 7.1 Hz, 2 H), 2.73 (dd, J = 6.1, 15.3 Hz, 2 H), 2.00−1.85 (m, 3 H). To a solution of the monoalkylated material (0.09 g, 0.36 mmol) in MeOH (15 mL) was added propionaldehyde (0.10 mL, 1.4 mmol), and the pH was adjusted to 4−5 with a few drops of glacial acetic acid. Sodium cyanoborohydride (0.07 g, 1.1 mmol) was added, and the reaction was stirred at room temperature. After 3 h, TLC indicated that starting material was still present, and additional amounts of propionaldehyde (0.10 mL, 1.42 mmol) and sodium cyanoborohydride (0.07 g, 1.08 mmol) were added. The reaction was slowly quenched with H_2O and concentrated HCl after 2.5 h and concentrated. The slurry was basified with 5 N NaOH to pH >12 and stirred for 30 min. The solution was extracted with EtOAc (2 × 100 mL), and the organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give 0.13 g of a yellow oil. Flash chromatography on 30 g of silica gel, eluting with 1:1 hexane/EtOAc, afforded a slightly impure product as an oil (0.09 g, 89% yield). ^{1}H NMR ($CDCl_3$ δ): 6.72 (s, 2 H), 4.61 (t, J = 5.8 Hz, 1 H), 4.45 (t, J = 5.8 Hz, 1 H), 3.85 (s, 6 H), 3.70 (quint, J = 8.1 Hz, 1 H), 2.98 (dd, J = 7.7, 15.0 Hz, 2 H), 2.85 (dd, J = 8.3, 15.1 Hz, 2 H), 2.66 (t, J = 7.1 Hz, 2 H), 2.48 (m, 2 H), 1.93−1.80 (m, 2 H), 1.51 (sext, J = 7.6 Hz, 2 H), 0.89 (t, J = 7.3 Hz, 3 H). ^{13} C NMR (δ): 148.4, 133.7, 108.3, 83.7, 82.1, 63.6, 56.4, 53.8, 47.3, 47.2, 36.6, 31.4, 29.0, 28.8, 20.8, 12.3. The oil was converted into the HCl salt and recrystallized from EtOAc/hexane to yield a white solid: mp 199−201 °C. IR (mull): 2549, 2460, 1606, 1508, 1443, 1319, 1260, 1236, 1215, 1188, 1096, 1031, 989, 854, 837 cm^{-1}. MS (EI): m/z 295 (M^+), 295, 280, 267, 266, 248, 178, 177, 176, 146, 133. HRMS (EI) calcd for $C_{17}H_{26}FNO_2$: 295.1947. Found: 295.1955. Anal. ($C_{17}H_{26}FNO_2$·HCl·4.09% H_2O) C, H, N.

5,6-Dimethoxy-2-(pyrrolidino)indan (12a). To a solution of the amine **8** (480 mg, 2.50 mmol) in DMF/acetonitrile (1:6, 49 mL) was added 1,4-dibromobutane (0.33 mL, 2.7 mmol) and Na_2CO_3 (620 mg, 13.5 mmol). This mixture was heated at 100 °C overnight. The solution was diluted with ethyl acetate and filtered to yield an oily solid (680 mg). This material was chromatographed on 400 g of silica gel, eluting with CH_2Cl_2/MeOH (9:1) to yield a yellow oil (118 mg, 20%). The HCl salt was formed and recrystallized from MeOH/EtOAc as a pale yellow solid (70 mg): mp 267−269 °C. ^{1}H NMR ($CDCl_3$ δ): 6.60 (s, 2 H); 4.0 (m, 1 H); 3.55 (s, 6 H), 3.6−2.0 (m, 12 H). IR (mull): γ_{max} 3563, 3457, 2678, 2601, 1663, 1623, 1507, 1444 cm^{-1}. MS (EI): m/z 247 (M^+), 232 (bp), 176. HRMS (EI) calcd for $C_{15}H_{21}NO_2$: 247.1572. Found: 247.1570. Anal. ($C_{15}H_{21}NO_2$·HCl) C, H, N.

5,6-Dimethoxy-2-(azepino)indan (12b). A solution of amine **8** (0.69 g, 3.0 mmol), 1-bromo-6-chloro-hexane (0.72 g, 3.6 mmol), and ground Na_2CO_3 (1.58 g, 15.0 mmol) in CH_3CN (150 mL) was stirred at 60 °C for 6 h and at 80 °C for 3 days. The reaction was cooled to room temperature, and the CH_3CN was removed in vacuo. The residue was quenched with H_2O (100 mL) and extracted with EtOAc (800 mL). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give a brown solid. The solid was purified by MPLC on 400 g of silica gel, eluting with 100% acetone to give the product as a light brown solid (0.70 g, 84% yield). The solid was converted to an HCl salt using methanolic HCl and recrystallized from MeOH/EtOAc to give a white solid: mp 221−222 °C. ^{1}H NMR ($CDCl_3$ δ): 6.72 (s, 2 H), 4.05 (quint, J = 8.1 Hz, 1 H), 3.85 (s, 6 H), 3.62−1.58 (m, 16 H). IR (mull): 3626, 2636, 2581, 2545, 2514, 1511, 1338, 1256, 1246, 1222, 1196, 1098, 1088, 993, 849 cm^{-1}. MS (EI): m/z 275 (M^+), 276, 275, 261, 260, 178, 177, 176, 161, 110, 55. HRMS (EI) calcd for $C_{17}H_{25}NO_2$: 275.1885. Found: 275.1892. Anal. ($C_{17}H_{25}NO_2$·HCl·1.27% H_2O) C, H, N.

5,6-Dimethoxy-2-(morpholino)indan (12c). This compound was prepared from amine **8** (1.15 g, 5.0 mmol) and 2-bromoethyl ether (0.63 mL, 5.0 mmol) using the same procedure described in the preparation of **12b** to yield the product as a light yellow solid (1.07 g, 81% yield). The solid was dissolved in hot Et_2O, filtered through folded filter paper and concentrated. Recrystallized from Et_2O/hexane gave a light yellow, needle-shaped solid: mp 113−114 °C. ^{1}H NMR ($CDCl_3$ δ): 6.72 (s, 2 H), 3.84 (s, 6 H), 3.78 (t, J = 4.7 Hz, 4 H), 3.22 (quint, J = 8.0 Hz, 1 H), 3.03 (dd, J = 7.2, 14.6 Hz, 2 H), 2.88 (dd, J = 8.3, 14.8 Hz, 2 H), 2.57 (m, 4 H). ^{13}C NMR (δ): 148.2, 132.8, 107.8, 67.6, 66.8, 56.0, 51.9, 36.6. IR (mull): 2798, 1508, 1333, 1307, 1270, 1263, 1244, 1233, 1221, 1187, 1149, 1119, 1100, 888, 857, cm^{-1}. MS (EI): m/z 263 (M^+), 264, 263, 248, 177, 176, 161, 133, 105, 91, 55. Anal. ($C_{15}H_{21}NO_3$) C, H, N.

***N*-(2,3-Dihydro-5,6-dimethoxy-1*H*-inden-2-yl)-*N*-propyl-2-thiophenemethanamine (13a).** A solution of **9** (0.50 g, 2.1 mmol), 2-thiophenecarboxylic acid (0.35 g, 2.8 mmol), and Et_3N (0.74 mL, 5.3 mmol) in CH_2Cl_2 (25 mL) was treated dropwise with diethyl cyanophosphonate (DEPC) (0.42 mL, 2.8 mmol). The dark solution was stirred at room temperature for 24 h (gradually turned from orange to black). The reaction was quenched with H_2O and extracted with CH_2Cl_2 (2 × 100 mL). The organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give a brown oil. The crude oil was purified on silica gel (200 g), eluting with 20:1 CH_2Cl_2/MeOH saturated with NH_3 to give a light yellow oil (0.58 g, 79%). ^{1}H NMR ($CDCl_3$ δ): 7.40 (dd, J = 1.1, 4.9 Hz, 1 H), 7.31 (dd, J = 1.1, 3.7 Hz, 1 H), 7.02 (m, 1 H), 6.73 (s, 2 H), 5.12 (quintet, J = 8.0 Hz, 1 H), 3.84 (s, 6 H), 3.35 (m, 2 H), 3.11 (d, J = 8.0 Hz, 4 H), 1.69 (m, 2 H), 0.85 (t, J = 7.4 Hz, 3 H). ^{13}C NMR ($CDCl_3$ δ): 164.8, 148.5, 138.5, 132.2, 128.2, 128.0, 126.7, 107.7, 59.3, 56.1, 37.3, 22.6, 11.5. To a slurry of LAH (0.12 g, 3.2 mmol) in THF (50 mL) was added dropwise a solution of the amide (0.55 g, 1.6 mmol) in THF (50 mL). The reaction was stirred at room temperature for 1.5 h followed by a slow quench with 5 N NaOH. The mixture was transferred to an Erlenmeyer flask, diluted with THF (300 mL), Na_2SO_4 was added, the mixture was filtered and concentrated to give a yellow oil. The crude material was purified on silica gel (200 g), eluting with hexane/EtOAc (3:2) to give a yellow oil (0.44 g, 83%). ^{1}H NMR ($CDCl_3$ δ): 7.20 (dd, J = 1.2, 5.0 Hz, 1 H), 6.95−6.90 (m, 2 H), 6.72 (s, 2 H), 3.88 (s, 2 H), 3.84 (s, 6 H), 3.77 (quintet, J = 7.9 Hz, 1 H), 3.01 (dd, J = 7.8, 15.1 Hz, 2 H), 2.90 (dd, J = 7.9, 15.3 Hz, 2 H), 2.50 (m, 2 H), 1.56 (sextet, J = 7.5 Hz, 2 H), 0.90 (t, J = 7.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$ δ): 148.0, 144.1, 133.5, 126.4, 124.9, 124.4, 107.9, 62.4, 56.1, 52.8, 49.7, 36.4, 20.6, 11.9. The oil was converted into an HCl salt and crystallized from hot EtOAc/MeOH to give a white solid that was dried in a vacuum oven: mp 210−212 °C. IR (mull): 3055, 2361, 2321, 1504, 1442, 1315, 1302, 1287, 1256, 1225, 1186, 1104, 1033, 858, 754, cm^{-1}. % water (KF) = 0.13; melt solvate = 0.17% MeOH, 0.05% EtOAc. MS (EI): m/z 331 (M^+), 331, 303, 302, 234, 204, 203, 177, 176, 165, 97. Anal. ($C_{19}H_{25}NO_2S$·HCl·0.13% H_2O) C, H, N.

***N*-(2,3-Dihydro-5,6-dimethoxy-1*H*-inden-2-yl)-*N*-propyl-3-thiophenemethanamine (13b).** The amide was prepared from **9** (0.51 g, 2.2 mmol) and 3-thiophenecarboxylic acid (0.37 g, 2.9 mmol) using the same procedure as **13a** to give an orange oil. The crude product was purified on silica gel (200 g), eluting with 4:1 hexane/EtOAc (2 L), 3:2 hexane/EtOAc (2 L) to give the desired product as a clear oil (0.71 g, 93%). ^{1}H NMR ($CDCl_3$ δ): 7.49 (dd, J = 1.2, 2.9 Hz, 1 H), 7.31 (m, 1 H), 7.20 (dd, J = 1.3, 5.1 Hz, 1 H), 6.72 (s, 2 H), 4.92 (m, 1 H), 3.85 (s, 6 H), 3.30 (m, 2 H), 3.06 (m, 4 H), 1.66 (m, 2 H), 0.84 (m, 3 H). To a solution of amide (0.70 g, 2.0 mmol) in THF (30 mL) was slowly added dropwise BH_3·THF (1M, 10.0 mL, 10.0 mmol). The yellow solution was stirred at room temperature for 2 h and then warmed to reflux. After 2 h, the reaction was cooled to room temperature and slowly quenched with 1 N HCl and then concentrated. The residue was basified with saturated Na_2CO_3 and then extracted with EtOAc (2 × 100 mL). The organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give a clear oil. Purification was done on silica gel (200 g), eluting with 4:1 hexane/EtOAc afforded two products; one was the desired product, and the other was a borane complex of the desired product. The two products were combined, dissolved in 50 mL of 3:1 acetone/3 N HCl, and stirred for 15 min. The solution was concentrated, and the residue was basified and worked up as before. A single desired product was afforded by TLC as a yellowish oil (0.59 g, 89%). The oil was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give a white solid that was dried in a vacuum oven: mp 221−222 °C. ^{1}H NMR ($CDCl_3$ δ): 7.26 (m, 1 H), 7.13 (m, 1 H), 7.08 (dd, J = 1.1, 4.9 Hz, 1 H), 6.72 (s, 2 H), 3.84 (s, 6 H), 3.79−3.68 (m, 3 H), 3.02−2.85 (m, 4 H), 2.47 (m, 2 H), 1.52 (sextet, J = 7.5 Hz, 2 H), 0.86 (t, J = 7.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$ δ): 148.0, 133.5, 128.4, 125.3, 122.1, 107.9, 62.7, 56.1, 52.9, 50.3, 36.2, 20.3, 11.9. IR (mull): 3040, 2437, 2401, 2374, 1504, 1441, 1314, 1301, 259, 1223, 1185, 1104, 1083, 826, 816, cm^{-1}. MS (EI): m/z 331 (M^+), 331, 303, 302, 204, 203, 177, 176, 165, 98, 97. Anal. ($C_{19}H_{26}ClNO_2S$) C, H, N.

***N*-(2,3-Dihydro-5,6-dimethoxy-1*H*-inden-2-yl)-*N*-propyl-2-thiopheneethanamine (13c).** The amide was prepared from **9** (0.50 g, 2.1 mmol) and 2-thiopheneacetic acid (0.39 g, 2.8 mmol) using the same procedure as **13a** to give a brown oil (1.04 g). The crude product was purified on silica gel (200 g), eluting with hexane/EtOAc (1:1) to give the desired product as a light yellow oil (0.8 g, 100%). ^{1}H NMR indicated two conformations in a 1:1 ratio. ^{1}H NMR ($CDCl_3$ δ): 7.20 (dd, J = 1.0, 5.2 Hz, 1 H), 6.94 (m, 2 H), 6.72 (m, 2 H), 5.11 (m, 0.5 H), 4.80 (m, 0.5 H), 3.98 (s, 1 H), 3.89 (s, 1 H), 3.84 (s, 6 H), 3.22−2.91 (m, 6 H), 1.67−1.59 (m, 2 H), 0.84 (m, 3 H).^{13}C NMR ($CDCl_3$ δ): 170.0, 169.6, 148.6, 148.3, 137.1, 132.8, 131.8, 126.8, 126.7, 125.9, 124.8, 124.7, 107.7, 58.9, 56.4, 56.1, 47.9, 44.9, 37.1, 36.7, 36.1, 35.6, 24.4, 22.0, 11.6, 11.4. To a slurry of LAH (0.08 g, 2.2 mmol) in THF (10 mL) was added dropwise a solution of the amide (0.40 g, 1.1 mmol) in THF (10 mL). The slurry stirred at room temperature for 3.5 h, then slowly quenched with 5 N NaOH, transferred to an Erlenmeyer flask, and diluted with more THF (300 mL). Na_2SO_4 was added to dry, then the slurry was filtered and concentrated to give an orange oil (0.50 g). The crude material was purified on silica gel (200 g), eluting with hexane/EtOAc (3:2) to give a yellow oil (0.24 g, 63%). ^{1}H NMR ($CDCl_3$ δ): 7.13 (dd, J = 1.1, 5.2 Hz, 1 H), 6.93 (m, 1 H), 6.81 (m, 1 H), 6.73 (s, 2 H), 3.85 (s, 6 H), 3.75 (quintet, J = 8.0 Hz, 1 H), 2.98 (m, 4 H), 2.85 (m, 4 H), 2.55 (m, 2 H), 1.56 (m, 2 H), 0.91 (t, J = 7.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$ δ): 148.1, 143.1, 133.4, 126.7, 124.5, 123.3, 107.9, 63.5, 56.1, 53.6, 53.3, 36.6, 28.1, 20.8, 12.1. The oil was converted to the HCl salt and crystallized from hot EtOAc/hexane. The resulting tan solid was recrystallized from hot EtOAc to give an off-white solid: mp 84−86 °C. IR (mull): 2589, 2523, 2489, 2386, 1508, 1330, 1314, 1257, 1238, 1222, 1189, 1102, 1090, 990, 852, cm^{-1}. % water (KF) = 2.0; melt solvate = 0.02% EtOAc. MS (FAB): m/z 346 (MH^+), 348, 347, 346, 248, 177, 176, 139, 111, 105, 91. HRMS (FAB) calcd for $C_{20}H_{27}NO_2S$+H: 346.1841. Found: 346.1842. Anal. ($C_{20}H_{27}NO_2S$·HCl·2.0% H_2O) C, H, N.

***N*-(2,3-Dihydro-5,6-dimethoxy-1*H*-inden-2-yl)-*N*-propyl-3-thiopheneethanamine (13d).** The amide was prepared from **9** (0.50 g, 2.1 mmol) and 3-thiopheneacetic acid (0.60 g, 4.2 mmol) using the same procedure as **13a** to give an orange oil. The crude product was purified on silica gel (200 g), eluting with 4:1 hexane/EtOAc to give the desired product as a light yellow oil (0.75 g, 99%). NMR indicated two different conformations in a 1:1.25 ratio. ^{1}H NMR ($CDCl_3$ δ): 7.28 (m, 1 H), 7.05 (m, 2 H), 6.70 (m, 2 H), 5.09 (quintet, J = 8.0 Hz, 0.44 H), 4.75 (quintet, J = 8.2 Hz, 0.56 H), 3.84 (s, 6 H), 3.81 (s, 1 H), 3.71 (s, 1 H), 3.20−2.77 (m, 6 H), 1.64 (m, 2 H), 0.84 (t, J = 7.4 Hz, 3 H). To a solution of the amide (0.75 g, 2.1 mmol) in THF (25 mL) was slowly added dropwise BH_3·THF (1M, 10.5 mL, 10.5 mmol). The yellow solution was warmed to reflux for 2 h and then cooled to room temperature. The reaction was slowly quenched with H_2O and then concentrated. The residue was diluted with 40 mL of 3:1 acetone/3N HCl, stirred for 15 min, and concentrated. The resulting residue was basified with

saturated Na_2CO_3 and then extracted with EtOAc (3 × 100 mL). The organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give a clear oil. Purification was done on silica gel (200 g), eluting with hexane/EtOAc (3:2) to give the desired product (0.58 g, 79%). ^{1}H NMR ($CDCl_3$ δ): 7.25 (m, 1 H), 6.96 (m, 2 H), 6.72 (s, 2 H), 3.84 (s, 6 H), 3.76 (quintet, J = 8.1 Hz, 1 H), 3.04−2.84 (m, 8 H), 2.57 (m, 2 H), 1.57 (m, 2 H), 0.91 (t, J = 7.4 Hz, 3 H). ^{13}C NMR ($CDCl_3$ δ): 148.1, 133.1, 128.3, 125.3, 120.6, 107.9, 63.6, 56.1, 53.4, 52.2, 36.5, 28.0, 20.4, 12.0. The oil was converted to an HCl salt and recrystallized from hot EtOAc/Et_2O to give a white solid that was dried in a vacuum oven: mp 160−161 °C. IR (mull): 2567, 2527, 2468, 1508, 1317, 1307, 1255, 1240, 1219, 1187, 1105, 1083, 993, 849, 811, cm^{-1}. MS (EI): m/z 345 (M^+), 249, 248, 178, 177, 176, 146, 131, 124, 111, 72. Anal. ($C_{20}H_{28}ClNO_2S$) C, H, N.

2,3-Dihydro-5,6-dimethoxy-*N*-(2-phenylethyl)-*N*-propyl-1*H*-inden-2-amine (13e). The amide was prepared from **9** (0.36 g, 1.5 mmol) and phenylacetic acid (0.41 g, 3.0 mmol) using the same procedure as **13a** to give an orange oil. The crude product was purified on silica gel (200 g), eluting with 1:1 hexane/EtOAc to give the desired product (0.56 g, 99%). NMR indicated two different conformations in a 1:1.25 ratio. ^{1}H NMR ($CDCl_3$ δ): 7.27 (m, 5 H), 6.71 (m, 2 H), 5.09 (m, 0.44 H), 4.76 (m, 0.56 H), 3.83 (m, 8 H), 3.73 (bs, 1 H), 3.20−2.82 (m, 7 H), 1.62 (m, 2 H), 0.83 (t, J = 7.5 Hz, 3 H). To a solution of the amide (0.56 g, 1.6 mmol) in THF (25 mL) was slowly added dropwise BH_3·THF (1M, 8.0 mL, 8.0 mmol). The resulting solution was warmed to reflux for 2 h and then cooled to room temperature. The reaction was slowly quenched with H_2O and then concentrated. The residue was diluted with 20 mL of 3:1 acetone/3 N HCl, stirred for 15 min, and concentrated. The resulting residue was basified with saturated Na_2CO_3 and then extracted with EtOAc (3 × 100 mL). The organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give a clear oil. Purification was done on silica gel (200 g), eluting with hexane/EtOAc (1:1) to give the desired product as a light yellow oil (0.48 g, 89%). ^{1}H NMR ($CDCl_3$ δ): 7.28 (m, 2 H), 7.20 (m, 3 H), 6.73 (s, 2 H), 3.85 (s, 6 H), 3.77 (m, 1 H), 3.05−2.82 (m, 8 H), 2.60 (m, 2 H), 1.59 (m, 2 H), 0.92 (t, J = 7.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$ δ): 148.2, 133.0, 128.7, 128.5, 126.1, 107.9, 63.6, 56.1, 53.3, 36.5, 33.3, 20.2, 11.9. The oil was converted to an HCl salt using methanolic HCl and recrystallized from hot EtOAc/Et_2O to give a white solid that was dried in a vacuum oven: mp 155−156 °C. IR (mull): 2405, 2390, 2376, 2342, 1510, 1433, 1334, 1315, 1255, 1222, 1192, 1102, 1091, 732, 697 cm^{-1}. MS (EI): m/z 339 (M^+), 249, 248, 178, 177, 176, 146, 124, 105, 91, 72. HRMS (FAB) calcd for $C_{22}H_{29}NO_2$+H_1: 340.2276. Found: 340.2273. Anal. ($C_{22}H_{30}ClNO_2$) C, H, N.

***N*-[2-(3-fluorophenyl)ethyl]-2,3-dihydro-5,6-dimethoxy-*N*-propyl-1*H*-inden-2-amine (13f).** The amide was prepared from **9** (0.30 g, 1.1 mmol) and 3-fluorophenylacetic acid (0.22 g, 1.4 mmol) using the same procedure as **13a** to give a yellow semisolid. The crude product was purified on silica gel (200 g), eluting with 4:1 hexane/EtOAc (1.5 L), 3:1 (1.5 L), 2:1 (2 L), and 1:1 (1 L) to give the desired product as a clear oil (0.40 g, 98%). NMR indicated two different conformations in a 1:1 ratio. ^{1}H NMR ($CDCl_3$ δ): 7.31−7.24 (m, 1 H), 7.01−6.92 (m, 3 H), 6.72 (s, 1 H), 6.68 (s, 1 H), 5.09 (m, 0.5 H), 4.72 (m, 0.5 H), 3.84 (s, 6 H), 3.81 (s, 1 H), 3.71 (s, 1 H), 3.20−2.84 (m, 6 H), 1.61 (m, 2 H), 0.84 (t, J = 7.4 Hz, 3 H). MS (ES^+) for $C_{22}H_{26}FNO_3$: m/z 372 ($M + H^+$). To a solution of the amide (0.40 g, 1.1 mmol) in THF (40 mL) was slowly added dropwise BH_3·THF (1M, 5.5 mL, 5.5 mmol). The solution was warmed to reflux for 5 h and then cooled to room temperature. The reaction was slowly quenched with MeOH and then concentrated. The residue was diluted with 40 mL of 3:1 acetone/3 N HCl, stirred for 15 min, and concentrated. The resulting residue was basified with saturated Na_2CO_3 and then extracted with EtOAc (2 × 100 mL). The organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give a semisolid. The crude material was purified on a Biotage Flash 40S system, eluting with 4:1 hexane/acetone to give the desired product as a clear oil (0.22 g, 56%). ^{1}H NMR ($CDCl_3$ δ): 7.27−7.20 (m, 1 H), 6.97−6.86 (m, 3 H), 6.72 (s, 2 H), 3.84 (s, 6 H), 3.74 (quintet, J = 8.0 Hz, 1 H), 3.00 (dd, J = 7.7, 15.0 Hz, 2 H), 2.89−2.79 (m, 6 H), 2.57 (m, 2 H), 1.54 (sextet, J = 7.7 Hz, 2 H), 0.91 (t, J = 7.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$ δ): 164.5, 161.2, 148.1, 143.2, 143.1, 133.2, 129.8, 129.7, 124.4, 124.3, 115.7, 115.4, 113.0, 112.7, 107.9, 63.5, 56.1, 53.4, 53.0, 36.5, 33.4, 20.5, 11.9. The oil was converted to a malonate salt using malonic acid (1.1 equiv) and MeOH. The product was slurried in hot Et_2O, cooled, and filtered to give a white solid that was dried in the vacuum oven at room temperature: mp 102−103 °C. IR (mull): 1731, 1610, 1591, 1508, 1491, 1336, 1306, 1255, 1221, 1192, 1147, 1104, 1093, 989, 750 cm^{-1}. MS (FAB): m/z 358 ($M + H^+$), 360, 359, 358, 357, 356, 248, 177, 176, 146, 123. HRMS (FAB) calcd for $C_{22}H_{28}FNO_2$+H_1: 358.2182. Found: 358.2185; Anal. ($C_{22}H_{28}FNO_2$·$C_3H_4O_4$·0.84% H_2O) C, H, N.

***N*-[2-(4-Bromophenyl)ethyl]-2,3-dihydro-5,6-dimethoxy-*N*-propyl-1*H*-inden-2-amine (13g).** The amide was prepared from **9** (0.50 g, 1.8 mmol) and 4-bromophenylacetic acid (0.52 g, 2.4 mmol) using the same procedure as **13a** to give an orange oil. The crude product was purified on a Biotage Flash 40M system, eluting with 4:1 hexane/EtOAc to give the desired product as a clear oil (0.80 g, 99%). NMR indicated two different conformations in a 1:1.33 ratio. ^{1}H NMR ($CDCl_3$ δ): 7.46 (d, J = 8.4 Hz, 2 H), 7.16 (d, J = 8.3 Hz, 2 H), 6.70 (s, 2 H), 5.1 (m, 0.43 H), 4.8 (m, 0.57 H), 3.84−3.68 (m, 8 H), 3.20−2.87 (m, 6 H), 1.60 (m, 2 H), 0.84 (t, J = 7.4 Hz, 3 H). MS (ES^+) for $C_{22}H_{26}BrNO_3$: m/z 432 ($M + H^+$). To a solution of amide (0.80 g, 1.8 mmol) in THF (50 mL) was slowly added dropwise BH_3·THF (1M, 9.0 mL, 9.0 mmol). The resulting solution was warmed to reflux for 3.5 h and then cooled to room temperature. The reaction was slowly quenched with MeOH and then concentrated. The residue was diluted with 40 mL of 3:1 acetone/3 N HCl, stirred for 15 min, and concentrated. The resulting residue was basified with saturated Na_2CO_3 and then extracted with EtOAc (2 × 100 mL). The organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give an oil. Purification was done on a Biotage Flash 40M system, eluting with hexane/acetone (4:1) to give the desired product (0.61 g, 81%). ^{1}H NMR ($CDCl_3$ δ): 7.41 (m, 2 H), 7.07 (m, 2 H), 6.72 (s, 2 H), 3.84 (s, 6 H), 3.72 (quintet, J = 8.1 Hz, 1 H), 3.03−2.77 (m, 8 H), 2.58 (m, 2 H), 1.54 (sextet, J = 7.7 Hz, 2 H), 0.91 (t, J = 7.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$ δ): 148.1, 139.4, 133.1, 131.4, 130.5, 119.8, 107.8, 63.4, 56.0, 53.3, 53.1, 36.5, 32.9, 20.4, 12.0. A small portion of the oil was converted to an HCl salt using methanolic HCl and recrystallized from hot EtOAc/hexane to give an off-white solid that was dried in a vacuum oven: mp 110 °C. IR (mull): 2509, 2410, 1507, 1489, 1315, 1271, 1256, 1238, 1222, 1189, 1100, 1072, 1012, 990, 851 cm^{-1}. MS (ES+) for $C_{22}H_{28}BrNO_2$·HCl: m/z 418 ($M + H^+$). Anal. ($C_{22}H_{28}BrNO_2$·HCl·1.1% EtOAc) C, H, N.

2,3-Dihydro-5,6-dimethoxy-*N*-[2-(4-methoxyphenyl)-ethyl]-*N*-propyl-1*H*-inden-2-amine (13h). The amide was prepared from **9** (0.22 g, 0.90 mmol) and 4-methoxyphenylacetic acid (0.30 g, 1.8 mmol) using the same procedure as **13a** to give an oil. The crude product was purified on silica gel (200 g), eluting with 1:1 hexane/EtOAc to give the desired product as an oil (0.33 g, 97%). NMR indicated two different conformations in a 1:1.3 ratio. ^{1}H NMR ($CDCl_3$ δ): 7.18 (m, 2 H), 6.87 (d, J = 8.6 Hz, 2 H), 6.71 (m, 2 H), 5.09 (m, 0.43 H), 4.77 (m, 0.57 H), 3.83 (s, 6 H), 3.79 (m, 4 H), 3.66 (s, 1 H), 3.19−2.82 (m, 6 H), 1.61 (m, 2 H), 0.83 (t, J = 7.4 Hz, 3 H). To a solution of the amide (0.33 g, 0.86 mmol) in THF (25 mL) was slowly added dropwise BH_3·THF (1M, 4.3 mL, 4.3 mmol). The yellow solution was warmed to reflux for 2 h and then cooled to room temperature. The reaction was slowly quenched with H_2O and then concentrated. The residue was diluted with 40 mL of 3:1 acetone/3 N HCl, stirred for 15 min, and concentrated. The resulting residue was basified with saturated Na_2CO_3 and then extracted with EtOAc (3 × 100 mL). The organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give a semisolid. Purification was done on silica gel (200 g), eluting with hexane/EtOAc (3:2) to give the desired product as a clear

oil (0.24 g, 75%). ^{1}H NMR ($CDCl_3$ δ): 7.12 (m, 2 H), 6.84 (m, 2 H), 6.72 (s, 2 H), 3.84 (s, 6 H), 3.79 (m, 4 H), 3.04−2.59 (m, 10 H), 1.57 (m, 2 H), 0.92 (t, J = 7.3 Hz, 3 H). The oil was converted to an HCl salt and recrystallized from hot EtOAc/Et_2O to give a white solid that was dried in a vacuum oven: mp 137−138 °C. IR (mull): 2473, 2419, 1612, 1514, 1506, 1315, 1304, 1254, 1237, 1219, 1178, 1108, 1101, 1089, 1034 cm^{-1}. MS (FAB): m/z 370 (MH^+), 446, 372, 371, 370, 369, 368, 248, 177, 176, 135. HRMS (FAB) calcd for $C_{23}H_{31}NO_3$+H: 370.2382. Found: 370.2387. Anal. ($C_{23}H_{32}ClNO_3$) C, H, N.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2,3-dihydro-5,6-dimethoxy-*N*-propyl-1*H*-inden-2-amine (13i).** The amide was prepared from **9** (0.50 g, 1.84 mmol) and (3,4-dimethoxy)-phenylacetic acid (0.47 g, 2.40 mmol) using the same procedure as **13a** to give an orange oil. The crude product was purified on a Biotage Flash 40M system, eluting with 1:1 hexane/EtOAc to give the desired product as a light yellow oil (0.86 g, 100%). NMR indicated two different conformations in a 1:1.2 ratio. ^{1}H NMR ($CDCl_3$ δ): 6.85−6.67 (m, 5 H), 5.09 (quintet, J = 8.0 Hz, 0.45 H), 4.77 (quintet, J = 8.2 Hz, 0.55 H), 3.88−3.83 (m, 12 H), 3.76 (s, 1 H), 3.65 (s, 1 H), 3.19−2.74 (m, 6 H), 1.70−1.61 (m, 3 H), 0.84 (t, J = 7.4 Hz, 3 H). To a solution of the amide (0.80 g, 1.9 mmol) in THF (50 mL) was slowly added dropwise BH_3·THF (1M, 9.7 mL, 9.7 mmol). The solution was warmed to reflux for 1.5 h and then cooled to room temperature. The reaction was slowly quenched with H_2O and then concentrated. The residue was diluted with 20 mL of 3:1 acetone/3 N HCl, stirred for 15 min, and concentrated. The resulting residue was diluted with H_2O and extracted with EtOAc (3 × 75 mL) followed by $CHCl_3$ (3 × 50 mL). The organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give a clear, foamy oil (0.80 g). Purification was done on silica gel (200 g), eluting with 4:1 hexane/acetone (2 L), 1:1 (1 L), and 1:1 $CHCl_3$/acetone (1 L) to give the desired product as a light yellow oil (0.63 g, 83%). ^{1}H NMR ($CDCl_3$ δ): 6.80−6.70 (m, 5 H), 3.87−3.75 (m, 13 H), 3.04−2.77 (m, 8 H), 2.60−2.58 (m, 2 H), 1.59 (sextet, J = 7.5 Hz, 2 H), 0.92 (t, J = 7.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$ δ): 148.9, 148.1, 147.4, 133.1, 120.5, 112.1, 111.3, 107.8, 63.5, 56.1, 55.9, 53.5, 53.4, 36.4, 33.2, 20.5, 12.0. IR (mull) 2805, 1511, 1439, 1334, 1306, 1260, 1249, 1233, 1217, 1158, 1137, 1100, 1027, 855, 795 cm^{-1}. MS (FAB): m/z 400 (MH^+), 401, 400, 398, 397, 249, 248, 177, 176, 165, 151. Anal. ($C_{24}H_{33}NO_4$·0.51% $CHCl_3$) C, H, N.

2,3-Dihydro-5,6-dimethoxy-*N*-propyl-*N*-[2-[4-(trifluoromethyl)phenyl]ethyl]-1*H*-inden-2-amine (13j). The amide was prepared from **9** (0.50 g, 1.8 mmol) and (2-trifluoro-*p*-tolyl)-acetic acid (0.49 g, 2.4 mmol) using the same procedure as **13a** to give a yellow oil. The crude product was purified on a Biotage Flash 40M, eluting with 4:1 hexane/EtOAc to give the desired product as a light yellow oil (0.78 g, 99+%). NMR indicated two different conformations in a 1:1.1 ratio. ^{1}H NMR ($CDCl_3$ δ): 7.59 (d, J = 8.1 Hz, 2 H), 7.39 (d, J = 8.0 Hz, 2 H), 6.70 (s, 2 H), 5.15 (m, 0.47 H), 4.65 (m, 0.53 H), 4.08−3.78 (m, 8 H), 3.22−3.16 (m, 6 H), 1.60 (m, 2 H), 0.85 (t, J = 7.2 Hz, 3 H). MS (ES^+) for $C_{23}H_{26}NF_3O_3$ m/z 422 (M + H^+). To a solution of the amide (0.78 g, 1.8 mmol) in THF (50 mL) was slowly added dropwise BH_3·THF (1M, 9.0 mL, 9.0 mmol). The solution was warmed to reflux for 3.5 h and then cooled to room temperature. The reaction was slowly quenched with MeOH and then concentrated. The residue was diluted with 40 mL of 3:1 acetone/3 N HCl, stirred for 15 min, and concentrated. The resulting residue was basified with saturated Na_2CO_3 and then extracted with EtOAc (3 × 100 mL). The organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give an oil. Purification was done on a Biotage Flash 40M system, eluting with 4:1 hexane/acetone to give the desired product (0.63 g, 86%). ^{1}H NMR ($CDCl_3$ δ): 7.54 (d, J = 8.0 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 6.72 (s, 2 H), 3.84 (s, 6 H), 3.76 (quintet, J = 8.1 Hz, 1 H), 3.03−2.83 (m, 8 H), 2.58 (m, 2 H), 1.56 (sextet, J = 7.7 Hz, 2 H), 0.91 (t, J = 7.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$ δ): 149.2, 140.3, 130.5, 130.1, 130.0, 129.6, 129.1, 126.0, 125.9, 125.8, 125.7, 122.1, 107.5, 63.7, 56.1, 52.4, 51.8, 34.7, 34.6, 30.3, 16.9, 11.4. The oil was converted to the HCl salt and recrystallized from hot EtOAc/hexane to give a white solid that was dried in a vacuum oven at room temperature: mp 116−118 °C. IR (mull): 2207, 1508, 1326, 1257, 1238, 1220, 1190, 1163, 1121, 1101, 1082, 1069, 1017, 987, 846 cm^{-1}. MS (ES+) for $C_{23}H_{28}F_3NO_2$·HCl m/z 408 (M + H^+). % water (KF) = 0.51. Anal. ($C_{23}H_{28}F_3NO_2$·HCl·0.51% H_2O) C, H, N.

***N*-[2-(3-Aminophenyl)ethyl]-2,3-dihydro-5,6-dimethoxy-*N*-propyl-1*H*-inden-2-amine (13k).** The amide was prepared from **9** (0.30 g, 1.1 mmol) and 3-aminophenylacetic acid (0.22 g, 1.4 mmol) using the same procedure as **13a** to give a yellow oil. The crude product was purified on silica gel (200 g), eluting with hexane/EtOAc (1:1−1:2) to give the desired product as a semisolid (0.37 g, 90%). NMR indicated two different conformations in a 1:1 ratio. ^{1}H NMR ($CDCl_3$ δ): 7.09 (m, 1 H), 6.71−6.59 (m, 4 H), 5.06 (quintet, J = 8.0 Hz, 0.5 H), 4.76 (quintet, J = 8.0 Hz, 0.5 H), 3.83 (s, 6 H), 3.72 (s, 1 H), 3.62 (s, 1 H), 3.18−2.81 (m, 8 H), 1.63 (m, 2 H), 0.83 (t, J = 7.4 Hz, 3 H). MS (ES^+) for $C_{22}H_{28}N_2O_3$ m/z 369 (M + H). To a solution of amide (0.37 g, 1.0 mmol) in THF (40 mL) was slowly added dropwise BH_3·THF (1 M, 5.0 mL, 5.0 mmol). The solution was warmed to reflux for 5 h and then cooled to room temperature. The reaction was slowly quenched with MeOH and then concentrated. The residue was diluted with 40 mL of 3:1 acetone/3 N HCl, stirred for 30 min, and concentrated. The resulting residue was basified with saturated Na_2CO_3 and then extracted with EtOAc (3 × 100 mL). The organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give an oil. The crude material was purified on silica gel (200 g), eluting with 2:1 hexane/acetone to give the desired product as an oil (0.22 g, 63%). ^{1}H NMR ($CDCl_3$ δ): 7.06 (t, J = 8.5 Hz, 1 H), 6.73 (s, 2 H), 6.59 (d, J = 7.5 Hz, 1 H), 6.53−6.50 (m, 2 H), 3.84 (s, 6 H), 3.80−3.62 (m, 3 H), 3.05−2.68 (m, 8 H), 2.58 (m, 2 H), 1.59 (sextet, J = 7.7 Hz, 2 H), 0.92 (t, J = 7.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$ δ): 148.1, 146.5, 141.7, 133.2, 129.3, 119.0, 115.5, 112.9, 107.9, 63.7, 56.1, 53.4, 53.3, 36.7, 33.3, 20.4, 12.0. IR (liq.): 2954, 2936, 1610, 1509, 1494, 1465, 1453, 1328, 1305, 1247, 1225, 1216, 1097, 845, 695 cm^{-1}. MS (FAB): m/z 355 (MH^+), 356, 355, 353, 249, 248, 177, 176, 146, 120, 72. HRMS (FAB) calcd for $C_{22}H_{30}N_2O_2$+H: 355.2385. Found: 355.2385.

4-[2-[(2,3-Dihydro-5,6-dimethoxy-1*H*-inden-2-yl)propylamino]ethyl]benzamide (13l). To a solution of Pd(OAc) (0.02 g, 0.08 mmol) and 1,3-bis(diphenyl)phosphine (DPPP) (0.04 g, 0.11 mmol) in DMF (4 mL) was added *N*-[2-(4-bromophenyl)-ethyl]-2,3-dihydro-5,6-dimethoxy-*N*-propyl-1*H*-inden-2-amine (**13g**) (0.17 g, 0.41 mmol) in DMF (6 mL) followed by Hunig's base (diisopropylethylamine, 0.16 mL, 0.90 mmol) and hexamethyldisilazane (0.61 mL, 2.9 mmol) while bubbling nitrogen through the resulting solution. The nitrogen was replaced with carbon monoxide (CO), and the reaction was warmed to 110 °C. After 24 h, the reaction was cooled to room temperature and quenched with 5 N NaOH and H_2O. The solution was extracted with EtOAc (3 × 50 mL), and the organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give a black oil. The crude product was purified on silica gel (200 g), eluting with CH_2Cl_2/MeOH saturated with NH_3 (15:1) to give the desired product as a yellow oil (0.11 g, 69%). ^{1}H NMR ($CDCl_3$ δ): 7.74 (d, J = 8.3 Hz, 2 H), 7.24 (d, J = 8.3 Hz, 2 H), 6.70 (s, 2 H), 6.18 (bs, 2 H), 3.82 (s, 6 H), 3.73 (quintet, J = 8.0 Hz, 1 H), 3.01−2.93 (dd, J = 7.7, 15.0 Hz, 2 H), 2.85−2.77 (m, 6 H), 2.56 (m, 2 H), 1.52 (sextet, J = 7.6 Hz, 2 H), 0.90 (t, J = 7.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$ δ): 169.5, 148.1, 145.2, 133.2, 131.1, 129.0, 127.5, 107.9, 63.4, 56.1, 53.4, 53.0, 36.6, 33.6, 20.6, 12.0. IR (mull): 3355, 3195, 1664, 1612, 1568, 1505, 1443, 1415, 1308, 1248, 1225, 1188, 1099, 851, 758 cm^{-1}. MS (FAB): m/z 383 (MH^+), 384, 383, 382, 381, 380, 249, 248, 177, 176, 146. HRMS (FAB) calcd for $C_{23}H_{30}N_2O_3$+H_1: 383.2334. Found: 383.2331.

2-Amino-*N*-(2,3-dihydro-5,6-dimethoxy-1*H*-inden-2-yl)-*N*-propyl-4-thiazoleethanamine (13m). The amide was prepared from **9** (1.0 g, 3.7 mmol) and 2-amino-4-thiazoleacetic acid (0.76 g, 4.8 mmol) using the same procedure as **13a** to give an oil (1.73 g). The crude product was purified on silica gel (200 g), eluting with CH_2Cl_2/MeOH saturated with NH_3

(9:1) to obtain the desired product as a foamy tan solid that was dried in the vacuum oven at room temperature: mp 55−60 °C. NMR indicated two different conformations in a 1:1 ratio. ^{1}H NMR ($CDCl_3$ δ): 6.72 (s, 2 H), 6.32 (s, 0.5 H), 6.28 (s, 0.5 H), 5.09 (quintet, J = 8.0 Hz, 0.5 H), 4.83 (quintet, J = 8.0 Hz, 0.5 H), 3.84 (m, 6 H), 3.73 (s, 1 H), 3.64 (s, 1 H), 3.25−2.93 (m, 6 H), 1.61 (m, 2 H), 0.85 (quartet, J = 7.1 Hz, 3 H). IR (mull): 3405, 3311, 3188, 1630, 1526, 1505, 1425, 1331, 1312, 1251, 1228, 1221, 1187, 1175, 1100 cm^{-1}. HRMS (EI) calcd for $C_{19}H_{25}N_3O_3S$: 375.1617. Found: 375.1610. Anal. Calcd for $C_{19}H_{25}N_3O_3S$: C, 60.78; H, 6.71; N, 11.19; S, 8.54. Found: C, 59.60; H, 6.57; N, 10.96; Cl, 0.79; S, 8.23. MS (ES+) for $C_{19}H_{25}N_3O_3S$ m/z 376 (M + H$^+$). To a cooled, pale green solution of $NaBH_4$ (0.11 g, 3.0 mmol) and $TiCl_4$ (0.16 mL, 1.5 mmol) in 1,2-dimethoxyethane (10 mL) was added dropwise a solution of the amide (0.38 g, 1.0 mmol) in 1,2-dimethoxyethane (10 mL). The reaction turned dark brown, and a precipitate formed upon addition. After 15 min at 0 °C, the reaction was warmed to room temperature, and stirring was continued for 24 h. The slurry was slowly quenched with 30% NH_4OH until pH >11. The solution was diluted with H_2O and extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give a clear oil (0.28 g). The crude product was purified on silica gel (200 g), eluting with 1:1 hexane/EtOAc (3 L) and 10:1 CH_2Cl_2/MeOH saturated with NH_3 to afford the desired product as an orange oil (0.16 g, 44%), which turned to a tan foamy solid under high vacuum for 48 h: mp 125−126 °C (softens at 119 °C). ^{1}H NMR ($CDCl_3$ δ): 6.70 (s, 2 H), 6.12 (s, 1 H), 5.27 (bs, 2 H), 3.81 (m, 7 H), 3.05−2.87 (m, 6 H), 2.75 (m, 2 H), 2.59 (m, 2 H), 1.58 (sextet, J = 7.8 Hz, 2 H), 0.88 (t, J = 7.4 Hz, 3 H). ^{13}C NMR ($CDCl_3$ δ): 167.7, 150.7, 148.1, 133.0, 107.9, 102.9, 63.6, 56.1, 53.4, 50.6, 36.4, 29.1, 20.1, 11.9. IR (mull): 3399, 3149, 3112, 1639, 1535, 1504, 1439, 1341, 1329, 1307, 1246, 1226, 1217, 1098, 840 cm^{-1}. MS (FAB): m/z 362 (MH$^+$), 438, 364, 363, 362, 361, 360, 249, 248, 177, 176. HRMS (FAB) calcd for $C_{19}H_{27}N_3O_2S+H_1$: 362.1902. Found: 362.1899.

***N*-(2,3-Dihydro-5,6-dimethoxy-1*H*-inden-2-yl)-*N*-propyl-3-pyridineethanamine (13n).** The amide was prepared from **9** (0.50 g, 1.8 mmol) and 3-pyridylacetic acid hydrochloride (0.40 g, 2.3 mmol) using the same procedure as **13a** to give a light yellow oil. The crude product was slurried in silica gel with 1:1 hexane/EtOAc and then filtered through a plug of additional silica gel, eluting with hexane/EtOAc (1:1) followed by CH_2Cl_2/MeOH (10:1) to obtain the desired product (0.76 g, 100%). NMR indicated two different conformations in a 1:1 ratio. ^{1}H NMR ($CDCl_3$ δ): 8.55 (m, 2 H), 7.89 (d, J = 7.9 Hz, 0.5 H), 7.82 (d, J = 8.0 Hz, 0.5 H), 7.42 (m, 1 H), 6.71 (s, 2 H), 5.07 (quintet, J = 8.0 Hz, 0.5 H), 4.76 (quintet, J = 8.0 Hz, 0.5 H), 3.84 (m, 7 H), 3.76 (s, 1 H), 3.26−2.95 (m, 6 H), 1.62 (m, 2 H), 0.89 (t, J = 7.3 Hz, 1.5 H), 0.83 (t, J = 7.4 Hz, 1.5 H). MS (ES+) for $C_{21}H_{26}N_2O_3$ m/z 355 (M + H$^+$). To a solution of the amide (0.76 g, 2.1 mmol) in THF (30 mL) was slowly added dropwise BH_3·THF (1M, 6.3 mL, 6.3 mmol). The solution was warmed to reflux for 2 h and then cooled to room temperature. The reaction was slowly quenched with MeOH and then concentrated. The residue was diluted with 40 mL of 3:1 acetone/3 N HCl, stirred for 15 min, and concentrated. The resulting residue was basified with saturated Na_2CO_3 and then extracted with EtOAc (3 × 100 mL). The organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification was done using a Biotage Flash 40M system, eluting with 20:1 CH_2Cl_2/MeOH to give the desired product as an orange oil (0.50 g, 70%). ^{1}H NMR ($CDCl_3$ δ): 8.45 (m, 2 H), 7.52 (m, 1 H), 7.22 (m, 1 H), 6.71 (s, 2 H), 3.83 (m, 7 H), 3.02−2.80 (m, 8 H), 2.59 (m, 2 H), 1.56 (sextet, J = 7.7 Hz, 2 H), 0.89 (t, J = 7.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$ δ): 150.1, 148.1, 147.6, 136.3, 135.7, 132.9, 123.3, 107.7, 63.3, 56.0, 53.2, 52.8, 36.3, 30.7, 20.3, 11.9. The oil was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give a white solid that was dried in a vacuum oven: mp 186−188 °C. IR (mull): 3541, 3362, 3120, 3031, 2719, 2672, 2596, 2550, 2456, 1508, 1337, 1317, 1258, 1221, 1101 cm^{-1}. MS (FAB): m/z 341 (MH$^+$), 343, 342, 341, 340, 339, 248, 177, 176, 165, 106. HRMS (FAB) calcd for $C_{21}H_{28}N_2O_2+H_1$: 341.2229. Found: 341.2226. % water (KF): 6.50. Anal. ($C_{21}H_{28}N_2O_2$·6.5% H_2O) C, H, N.

2,3-Dihydro-5,6-dimethoxy-*N*-(3-phenylpropyl)-*N*-propyl-1*H*-inden-2-amine (13o). The amide was prepared from **9** (0.50 g, 2.1 mmol) and hydrocinnamic acid (0.63 g, 4.2 mmol) using the same procedure as **13a** to give an orange oil. The crude product was purified on silica gel (400 g), eluting with hexane/EtOAc (1:1) to give the desired product as an orange oil (0.67 g, 87%). NMR indicated two different conformations in a 1:1 ratio. ^{1}H NMR ($CDCl_3$ δ): 7.35−7.15 (m, 5 H), 6.72 (m, 2 H), 5.16 (m, 0.5 H), 4.67 (m, 0.5 H), 3.84 (s, 6 H), 3.25−2.90 (m, 8 H), 2.75−2.60 (m, 2 H), 1.70−1.45 (m, 2 H), 0.86−0.77 (m, 3 H). To a solution of the amide (0.65 g, 1.7 mmol) in THF (50 mL) was slowly added dropwise BH_3·THF (1M, 8.8 mL, 8.8 mmol). The resulting solution was warmed to reflux for 3 h and then cooled to room temperature. The reaction was slowly quenched with H_2O and then concentrated. The residue was diluted with 40 mL of 3:1 acetone/3 N HCl, stirred for 15 min, and concentrated. The resulting residue was again treated with the 3:1 solution and concentrated. The crude material was then basified with saturated Na_2CO_3 and then extracted with EtOAc (3 × 75 mL). The organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give a clear oil. Purification was done on silica gel (200 g), eluting with hexane/EtOAc (1:1) to give the desired product as a yellow oil (0.51 g, 85%). ^{1}H NMR ($CDCl_3$ δ): 7.30−7.26 (m, 2 H), 7.20−7.17 (m, 3 H), 6.71 (s, 2 H), 3.84 (s, 6 H), 3.70 (quintet, J = 8.1 Hz, 1 H), 2.99−2.82 (m, 4 H), 2.65−2.48 (m, 6 H), 1.86 (m, 2 H), 1.52 (m, 2 H), 0.89 (t, J = 7.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$ δ): 148.1, 142.2, 133.3, 128.3, 125.8, 107.8, 63.5, 56.1, 53.3, 50.9, 36.3, 33.8, 28.7, 20.2, 12.0. The oil was converted to the HCl salt and recrystallized from MeOH/Et_2O to give a white solid that was dried in a vacuum oven: mp 150−151 °C. IR (mull): 2564, 2529, 2502, 2463, 2360, 1508, 1443, 1312, 1254, 1236, 1223, 1091, 834, 765, 707 cm^{-1}. % water (KF): 1.20. Anal. ($C_{23}H_{31}NO_2$·HCl·1.20% H_2O) C, H, N.

3,4-Dimethoxy Cinnamic Acid (15). A mixture of 3,4-dimethoxybenzaldehyde **14** (10 g, 60 mmol) and malonic acid (9.4 g, 90 mmol) in pyridine (30 mL) and piperidine (1 mL) was heated at 120 °C for 6 h. The reaction was cooled to room temperature and concentrated HCl was added to pH <3. The white solid was collected and dried in a vacuum oven overnight (10.08 g, 81%): mp 182−183 °C. ^{1}H NMR (DMSO-d_6 δ): 12.1 (s, 1 H), 7.52−7.47 (d, J = 15.9 Hz, 1 H), 7.29−7.28 (d, J = 1.8 Hz, 1 H), 7.19−7.16 (dd, J = 8.3, 1.8 Hz, 1 H), 6.96−6.93 (d, J = 8.3 Hz, 1 H), 6.44−6.38 (d, J = 15.6 Hz, 1 H), 3.78 (s, 3 H), 3.76 (s, 3 H). IR (mull): 1684, 1626, 1597, 1585, 1516, 1427, 1341, 1319, 1314, 1300, 1265, 1233, 1211, 1144, 1027 cm^{-1}. MS (EI): m/z 208 (M$^+$), 209, 208, 193, 147, 133, 119, 103, 91, 77, 51. Anal. ($C_{11}H_{12}O_4$) C, H, N.

3,4-Dimethoxybenzenepropanoic Acid (16). To a solution of **15** (1.0 g, 4.8 mmol) in absolute ethanol (100 mL) was added Pd/C, and it was hydrogenated at 30 psi H_2 for 30 min. The reaction was filtered over solka floc, and the filtrate was concentrated to yield a white solid that was dried in the vacuum oven (1.01 g, 100%): mp 96−97 °C. ^{1}H NMR (DMSO-d_6 δ): 12.0 (s, 1 H), 6.83−6.80 (m, 2 H), 6.70−6.68 (m, 1 H), 3.70 (s, 3 H), 3.68 (s, 3 H), 3.29 (m, 2 H), 2.75−2.70 (m, 2 H). IR (mull): 3024, 1701, 1592, 1518, 1432, 1344, 1308, 1254, 1238, 1215, 1149, 1029, 842, 810, 770 cm^{-1}. MS (EI): m/z 210 (M$^+$), 210, 152, 151, 149, 107, 91, 78, 77, 65, 55. Anal. ($C_{11}H_{14}O_4$) C, H, N. Note: Alternatively the reaction could be done in a mixture of ethanol/1 N NaOH (4:3) to obtain the sodium salt. This allowed for 100 g of cinnamic acid to be dissolved in 700 mL of solvent to yield the sodium salt. ^{1}H NMR (CD_3OD δ): 6.85−6.74 (m, 3 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 2.86−2.81 (m, 2 H), 2.47−2.42 (m, 2 H).

5,6-Dimethoxy-1-indanone (5c). To a suspension of **16** (50 g, 215 mmol, as the sodium salt) in methylene chloride (850 mL) and DMF (1 mL) was added oxalyl chloride (75.2 mL, 862 mmol) dropwise over 1 h. The reaction was stirred overnight and then concentrated. ^{1}H NMR ($CDCl_3$ δ): 6.81−6.79 (d, J = 8.0 Hz, 1 H), 36.74−6.69 (m, 2 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.18 (t, J = 7.4 Hz, 2 H), 2.95 (t, J = 7.4 Hz, 2 H). The crude

acid chloride was suspended in methylene chloride (1.5 L) at 0 °C, and $AlCl_3$ (57.5 g, 431 mmol) was added portionwise. The reaction was stirred at room temperature for 3 h and cooled to 0 °C, and water was slowly added to quench the excess $AlCl_3$. The layers were separated, and the aqueous layer was extracted with methylene chloride (4 × 500 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The solid was dissolved in ethyl acetate (1.5 L), treated with activated carbon, and stirred overnight. The material was filtered, and the filtrate was concentrated to yield a solid (40.2 g, 97%): mp 119−120 °C. ^{1}H NMR ($CDCl_3$ δ): 7.16 (s, 1 H), 6.87 (s, 1 H), 3.94 (s, 3 H), 3.88 (s, 3 H), 3.03 (t, J = 5.4 Hz, 2 H), 2.67−2.63 (m, 2 H). The regioisomer 6,7-dimethoxy-1-indanone was not observed from these reactions.

5,6-Dimethoxy-1*H*-indene-1,2(3*H*)-dione-2-[*O*-[(1,1-dimethylethyl)dimethylsilyl]oxime] (17). A three-neck 3-L round-bottom flask equipped with a condensor, thermometer, and mechanical stirrer was charged with oxime **6c** (100.0 g, 0.45 mol) and imidazole (92.3 g, 1.36 mol) in DMF (1 L). The resulting slurry was treated dropwise with a solution of *tert*-butyl dimethylsilyl chloride (102.2 g, 0.68 mol) in DMF (300 mL), and the slurry gradually turned to a clear orange solution. This solution was heated to 95 °C for 1.5 h at which time TLC indicated that no starting material was present. The reaction was cooled to room temperature and stirred overnight. A nice precipitate (long, needlelike crystals) formed. The slurry was transferred to a 4-L Erlenmeyer flask, and H_2O (1.5 L) was added while stirring vigorously. A yellow precipitate formed, and the slurry was warmed slightly. The slurry was cooled in the refrigerator, and after 2 h, the solid was collected via filtration, washed with additional H_2O, and air-dried for 2 h. The yellow solid was further dried in a vacuum oven at 70 °C overnight to give 132.9 g (88%) of the desired product. The purity could be increased by recrystallization from hot acetone/EtOAc to give a yellow solid: mp 178−179 °C. ^{1}H NMR ($CDCl_3$ δ): 7.29 (s, 1 H), 6.88 (s, 1 H), 3.97 (s, 3 H), 3.91 (s, 3 H), 3.73 (s, 2 H), 0.96 (s, 9 H), 0.26 (s, 6 H). IR (mull): 1693 (s), 1605, 1581, 1504, 1317 (s), 1312 (s), 1261, 1255, 1232, 1120 (s), 1017, 968, 908, 837, 791, cm^{-1}. MS (EI) *m*/*z* (rel intensity): 335 (M, 0), 280 (4), 279 (13), 278 (67), 234 (8), 205 (13), 204 (99), 176 (11), 132 (5), 131 (5), 75 (14). HRMS (EI) calcd for $C_{17}H_{25}NO_4Si$: 335.1553. Found: 335.1561; Anal. ($C_{17}H_{25}NO_4Si$) C, H, N.

2-(*N*-Dipropyl)-5,6-dimethoxy-1-indanol (19) and 2-(*N*-Dipropyl)-5,6-dimethoxyindene (20). To a heated solution (63 °C) of the silyl oxime **7** (32.0 g, 95.4 mmol) in THF (500 mL) was added dropwise BH_3·Me_2S (10−10.2 M; 19.1 mL, 190.8 mmol). During the addition, an exotherm occurred during the first equivalent, and vigorous bubbling was noted followed by the temperature returning to the preset 63 °C. After the addition was completed, the reaction was stirred for 30 min, and MS indicated that no starting material remained. The reaction was cooled to room temperature and slowly quenched with MeOH until bubbling ceased. The reaction was then concentrated, and the resulting residue was azeotroped with MeOH/toluene numerous times to give a white foam. MS indicated that the desired primary amino alcohol was present. The foam was dissolved in THF (300 mL), and propionaldehyde (20.7 mL, 286.2 mmol) was added. Rapid bubbling occurred immediately following this addition. After 20 min, a slurry of sodium triacetoxyborohydride (60.7 g, 286.2 mmol) in THF (500 mL) was added through an addition funnel over 30 min. The resulting slurry was stirred for 2 h at room temperature, and MS indicated that the desired product formed but also that some monopropyl was present. After an additional 4 h, MS showed no change in product ratios, so an additional 0.5 equiv of propionaldehyde (47.7 mmol, 3.4 mL) and sodium triacetoxyborohydride (10.1 g, 47.7 mmol) was added. After 17 h, the reaction was quenched slowly with H_2O and 5 N NaOH and then concentrated. The residue was diluted with H_2O, and the pH was adjusted to 5−6 with 5 N NaOH. This slurry was extracted with EtOAc (2 × 500 mL), the organic layers were set aside, and the aqueous was further adjusted to pH >12. The aqueous was extracted with EtOAc (3 × 500 mL), and the organic layers were washed with H_2O, brine, dried ($MgSO_4$), and concentrated to give the desired product as a light greenish oil (26.32 g, 94%). A small amount the enamine product **20** was also present. MS (ES+) for $C_{17}H_{27}N_1O_3$ *m*/*z* 294 $(M + H)^+$ and MS (ES+) for $C_{17}H_{25}N_1O_2$ *m*/*z* 276 $(M + H)^+$.

2-(*N*-Dipropyl)-5,6-dimethoxyaminoindan (3). To a solution of the crude amino alcohol **19** (23.5 g, 80.0 mmol) and Et_3SiH (25.6 mL, 160.0 mmol) in 1,2-dichloroethane (DCE, 500 mL) was added dropwise a solution of BF_3·OEt_2 (19.7 mL, 160.0 mmol) in DCE (100 mL) at room temperature. The resulting orange slurry was refluxed at 83 °C for 1.5 h, cooled to room temperature, and quenched with H_2O and 5 N NaOH to pH >11. The solution was extracted with CH_2Cl_2 (2 × 500 mL), and the organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give a dark oil. This crude product was slurried onto silica gel and filtered through a plug of silica gel with 20% acetone/hexane to give the desired product as a dark orange oil (20.19 g, 91%).

In Vitro Binding. Competition radioligand binding experiments employed 11 drug concentrations run in duplicate. Radioligands used were [^{3}H]-U-86170[15] (D_2 dopamine filtration and scintillation proximity assays, 62 Ci/mmol, 2 nM), [^{3}H]-spiperone (D_3 dopamine filtration assays, 123 Ci/mmol, 0.3 nM), and [^{3}H]-7-OH-DPAT (D_3 dopamine scintillation proximity assays, 154 Ci/mmol). Nonspecific binding (75−95% of total) was defined with cold haloperidol added in excess (3 μM). Total binding was determined with buffer. Buffers (pH 7.4) used were 20 mM HEPES and 10 mM $MgSO_4$ (D_2) and 20 mM HEPES, 10 mM $MgSO_4$, 150 mM NaCl, and 1 mM EDTA (D_3). Cloned rat receptors permanently expressed in CHO cells were the source of all binding sites.[31] Membranes were prepared by mechanical disruption of cell pellets in ice cold 50 mM Tris, 5 mM EDTA, and 5 mM EGTA, pH 7.4, followed by low- (1000*g*), medium- (20000*g*), and high- (80000*g*) speed centrifugation steps. For filtration assays, binding mixtures were made in deep 96-well titer plates by the addition of 50 μL of drug dilution, 50 μL of radioligand, and 800 μL of membranes (20−60 μg of protein) in binding buffer. After room temperature incubation for 1 h, reactions were stopped by vacuum filtration using a Brandel harvester. Counting was with a LKB/Wallac 1205 β-plate scintillation counter using Meltilex as scintillant. For scintillation proximity assays, binding mixtures were made in flexible, 96-well, Wallac Micro-Beta plates by the addition of 11 μL of drug dilution, 11 μL of radioligand, and 178 μL of membrane/SPA bead suspension (100 mg of WGA-coated SPA beads incubated with 5−15 μg of protein/plate in 10 mL of binding buffer for 30 min at room temperature followed by low-speed centrifugation and resuspension in 2 mL binding buffer). After being sealed and incubated at room temperature for 1 h, the plates were counted in a Wallac Micro-Beta scintillation counter. IC_{50} values from both assay methods were estimated by fitting the data to a one-site competition model:

$$Y = T/(1 + 10^{\log(X)-\log(IC_{50})})$$

where Y is the specific CPM bound at concentration X and T is the specific CPM bound in the absence of competitor. Inhibition constants (K_i) were calculated using the Cheng−Prushoff equation.[32] Single point assays (1000 nM compound concentration in duplicate) were sometimes run to predetermine approximate binding affinities. Usually, when these single point assays revealed <50% inhibition of radioligand binding, no further dose response experiments were carried out, and results were expressed as percent inhibition at 1000 nM.

Determination of In Vitro Metabolic Stability. Rat hepatocytes were prepared by a modification of the collagenase perfusion method.[33] The in vitro intrinsic clearance (CL_{int}) was assessed following incubation of each compound at three concentrations in rat hepatocyte suspensions (5 million cells mL^{-1}). The initial rate of metabolism at each substrate concentration was calculated from each concentration/time curve, and values of the apparent V_{max} and K_m of metabolism

of each compound were obtained from application of the initial rate data to the direct linear plot procedure.[34] V_{max}/K_m = intrinsic clearance (CL_{int}). A standard compound (PNU-93385: *cis*-(3a*R*)-(−)-2,3,3a,4,5,9b-hexahydro-3-propyl-1*H*-benz[*e*]indole-9-carboxamide) was incubated on each occasion, and the metabolic stability of each test compound was compared to that of the standard (CL_{int} standard/CL_{int} test compound = relative metabolic stability). Using this procedure results obtained on different days could be compared.

In Vitro Intrinsic Activity Mitogenesis. CHO cells expressing D_2 or D_3 receptors or control cells negative for dopamine receptors were seeded into 96-well plates at a density of 5000 cells/well and grown at 37 °C in αMEM with 10% fetal calf serum for 48 h. The cells were rinsed twice with serum-free αMEM, and 80 μL of fresh αMEM or αMEM containing 30 nM quinpirole was added along with 20 μL of varying concentrations of test compound diluted in serum free media. Nine concentrations of compound were tested. Some wells on each plate received serum-free media alone, and some received media containing 10% fetal bovine serum. After culture for 16−18 h, 1 μCi/well [^{3}H]thymidine was added, and the cells were incubated for 2 h at 37 °C. The cells were trypsinized and harvested onto filter mats with a Tomtec cell harvester, and the filters were counted in a Betaplate counter. At each concentration tested, the incorporation of [^{3}H]thymidine (cpm) in the presence of test compound was compared to that obtained with serum (full stimulation). For studies of antagonism, the incorporation of [^{3}H]thymidine (cpm) in the presence of test compound and the agonist quinpirole was compared to that obtained with 30 nM quinpirole alone. Dose−response curves were analyzed by a nonlinear, least-squares fit equation: $A = B[C/(D + C)] + G$ where A is the measured response; B is the maximal effect minus baseline; C is the EC_{50}; D is the concentration of the compound; and G is the maximal effect. Parameters B, C, and G were determined by Simplex optimization.

Extracellular Acidification Rate. Extracellular acidification rates were measured using a Cytosensor microphysiometer (Molecular Devices Corp.). CHO cells were seeded into 12-mm capsule cups (Molecular Devices Corp.) at 4×10^5 cells/cup in αMEM supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 10 units/mL penicillin, and 10 μg/mL streptomycin. The cells were incubated at 37 °C in 5% CO_2 for 24 h. The capsule cups were loaded into the sensor chambers of the microphysiometer, and the chambers were perfused with running buffer (bicarbonate-free αMEM supplemented with 4 mM L-glutamine, 10 units/mL penicillin, 10 μg/mL streptomycin, and 26 mM NaCl) at a flow rate of 100 μL/min. Test compounds were diluted into running buffer and perfused through a second fluid path. During each 60-s pump cycle, the pump was on for 38 s and off for the remaining 22 s. The pH of the running buffer in the sensor chamber was recorded from 43 to 58 s, and the pump was started at 60 s to start the next cycle. The rate of acidification of the running buffer during the recording time was calculated by the Cytosoft program. Changes in the rates of acidification were calculated by subtracting the baseline value (the average of four rate measurements immediately before drug addition) from the highest rate measurement obtained after drug addition. The instrument detects 61 mV/pH unit.

Antagonism of MK-801-Induced Locomotor Activity in Rats. Male Sprague−Dawley rats from Harlan, 170−190 g, were kept on a light/dark cycle of 12/12 h with lights on from 6 am till 6 pm; rats were grouped housed in hanging wire cages, received food and water ad lib, and were given at least 2 days after arrival to acclimate. Testing was done between 9:00 and 18:00. All injections were given at 2 mL/kg. (+)-MK801 hydrogen maleate (RBI, Natick, MA) was given subcutaneously (sc) at 0.2 mg/kg in 0.25% methylcellulose. **3** was given in 0.25% methylcellulose in 0.9% NaCl. On test day, rats were injected with (+)-MK801 and immediately placed back into their home cage. One hour after (+)-MK801 injection, rats were given an intraperitoneal (ip) injection of **3** or vehicle and immediately placed in single into 16 in. × 16 in. plexiglass open field cages with absorbent cage papers lining the floors, which were changed between rats. Activity was monitored by Omnitech Digiscan Monitors (Accuscan, Columbus, OH) with data collected at 10-min intervals for 30 min after test drug injection. Data are presented as the accumulated total activity counts for the 30-min period expressed as mean ± SEM. Statistics were performed by means of ANOVA and least significant difference test (LSD) with p values <0.05 regarded as statistically significant.

Supporting Information Available: Analytical and CHN analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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