Synthesis and Structure−Activity Relationships of Naphthamides as Dopamine D_3 Receptor Ligands

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A series of naphthamides were synthesized, and the affinities of these compounds were determined for dopamine D_2 and D_3 receptors using radioligand binding techniques. The naphthamide compounds that were prepared include *N*-(1-alkylpiperidin-4-yl)-4-bromo-1-methoxy-2-naphthamides (**1**−**6**), (*S*)-*N*-(1-alkylpyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamides (**7**−**12**), (*R*)-*N*-(1-alkylpyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamides (**13**−**18**), (*S*)-*N*-(1-alkyl-2-pyrrolidinylmethyl)-4-bromo-1-methoxy-2-naphthamides (**19**−**25**), (*R*)-*N*-(1-alkyl-2-pyrrolidinylmethyl)-4-bromo-1-methoxy-2-naphthamides (**26**−**31**), and *N*-(9-alkyl-9-azabicyclo-[3.3.1]nonan-3β-yl)-4-bromo-1-methoxy-2-naphthamides (**32**, **33**). The results of in vitro radioligand binding studies indicated that the majority of the naphthamide analogues bound with high affinity at both the D_2 and D_3 dopamine receptor subtypes and most of the compounds demonstrated some selectivity for the dopamine D_3 dopamine receptor subtype. These results demonstrated that both the structure of the central amine moiety (piperidine, pyrrolidine, and 9-azabicyclo[3.3.1]nonane) ring and the *N*-(alkyl) substitution on the amine significantly effects the binding affinity at D_2 and D_3 dopamine receptors. The bulkiness of the *N*-(1-alkyl) substituent was found to (a) have no effect on pharmacologic selectivity, (b) increase the affinity at D_3 receptors, or (c) decrease the affinity at D_2 receptors. The most potent analogue in this series was (*S*)-*N*-(1-cycloheptylpyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamide (**10**), which had equilibrium dissociation (K_i) values of 1.8 and 0.2 nM for D_2 and D_3 receptors, respectively. The most selective analogue was (*R*)-*N*-(1-cycloheptyl-2-pyrrolidinylmethyl)-4-bromo-1-methoxy-2-naphthamide (**30**), which had K_i values of 62.8 and 2.4 nM for D_2 and D_3 receptors, respectively. Radioligand binding results for σ receptors indicated that the structure of the amine moiety and the *N*-(1-alkyl) substitutions also significantly influence the affinity and selectivity of these compounds at the σ_1 and σ_2 sigma receptor subtypes. The two naphthamides containing a 9-azabicyclo[3.3.1]nonan-3β-yl central ring were found to be selective for σ_2 receptors.

Introduction

Multiple neurological and neuropsychiatric disorders, including Parkinson's disease, Tourette's syndrome, tardive dyskinesia, schizophrenia, schizoaffective disorders, and addiction to psychostimulants, appear to reflect disturbances of the dopaminergic system.[1−3] Molecular genetic studies have identified five subtypes of dopamine receptors: D_1, D_2, D_3, D_4, and D_5.[4,5] The dopamine receptor subtypes are generally grouped into two families of dopamine receptors, D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4) receptors based on similar pharmacologic properties and primary structure homology.[4−7] However, a complete understanding of the pharmacological and physiological roles of the dopamine receptor subtypes has been hindered by a lack of compounds with selectivity for each individual dopamine receptor subtype.

Recent studies have indicated that the dopamine D_3 receptor subtype may be an important biological target for pharmacotherapeutic agents used in the treatment of schizophrenia[2,8] and/or substance abuse.[3,9] Essentially all clinically effective neuroleptics are antagonists at dopamine D_2 and D_3 receptors.[10] Therefore, it has been hypothesized that the blockade of dopamine D_2 receptors in the caudate putamen region of the brain may be responsible for extrapyramidal side effects,[11] while the blockade of dopamine D_2/D_3 receptors in the limbic regions of the brain may be associated with antipsychotic effects.[10,12] The localization of the D_3 receptors in the limbic regions of the brain suggests that this receptor subtype may be an appropriate pharmacologic target for the development of antipsychotic agents with lower risk of extrapyramidal side effects.[8,13]

Recent studies have also suggested that dopamine D_3 receptors play an important role in mediating the reinforcing effects of the psychostimulant cocaine.[14,15] Selective dopamine D_3 receptor antagonists have been found to block the reinforcing effects of cocaine in animal studies. Therefore, D_3 receptor selective compounds may prove to be useful for the treatment of individuals who abuse cocaine.[15,16]

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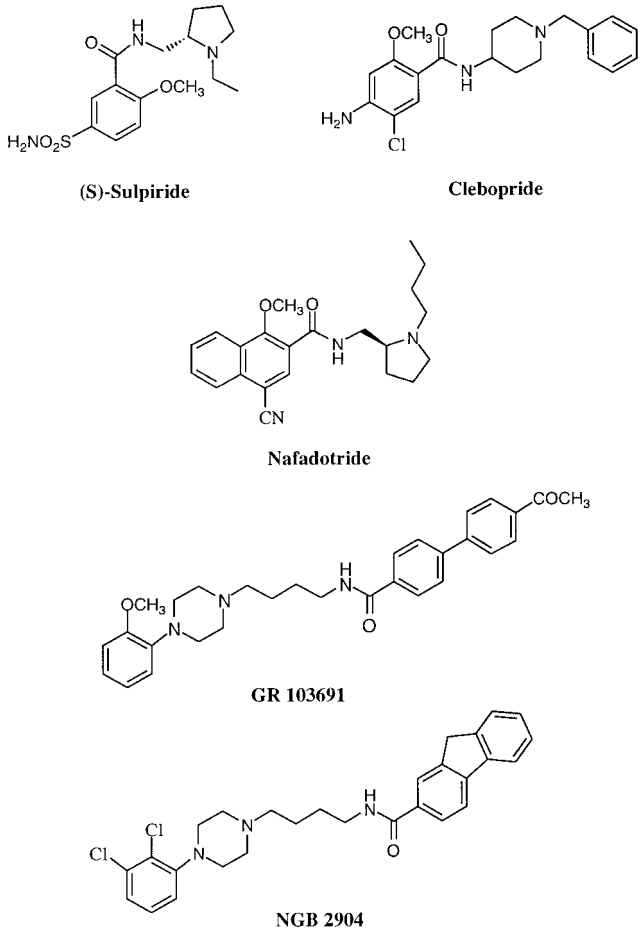
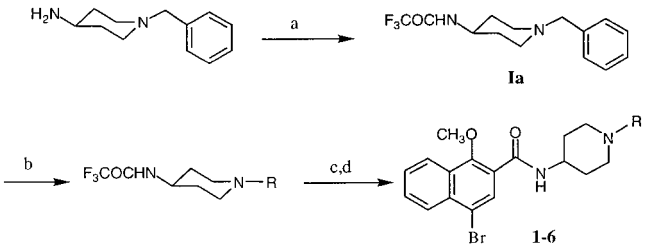
Chart 1



The benzamides are a class of drugs that have nanomolar to subnanomolar affinity for D_2-like dopamine receptors. Representative compounds include sulpiride,[17] clebopride,[18] GR103691,[19] and NGB2094 (Chart 1).[20] We previously reported a panel of benzamide analogues that bound with high affinity at dopamine D_2 and D_3 receptors.[21−23] In those studies our research efforts focused on the replacement of the substituents on the benzamide aromatic ring and on the modifications of the *N*-phenylalkyl group on the basic nitrogen. The results of those studies led to analogues that were more selective for dopamine D_2 receptors than for D_3 receptors.

The goal of the current study was to explore the structure−activity relationships of the N substituent of a series of naphthamides as candidate D_3 receptor selective ligands. Naphthamides have been identified as potent dopamine D_2 and D_3 receptor ligands.[23,24] We previously reported that replacement of the phenyl ring of the benzamide D_2/D_3 receptor ligands with a naphthyl ring to form naphthamides resulted in an increased affinity for D_3 receptors.[23] In addition, a series of (*S*)-*N*-(1-alkyl-3-pyrrolidinyl)-5-chloro-4-[(cyclopropylcarbonyl)amino]-2-methoxybenzamide analogues were reported to have high affinity and selectivity for D_3 receptors.[25] In vitro binding studies with those compounds indicated that an increase in the bulkiness and the lipophilicity of the *N*-alkyl group on the basic nitrogen consistently enhanced the selectivity of the compounds at D_3 receptors. In this report we describe the synthesis and binding properties of a new series of

Scheme 1[a]



[a] Reagents: (a) $(CF_3CO)_2O/CH_2Cl_2$, room temperature; (b) ketone/H_2/PdOH/C, Pd/C; (c) NH_4OH/CH_3OH; (d) 4-bromo-1-methoxy-2-napthoyl chloride/CH_2Cl_2/Et_3N.

N-(1-alkylpyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamides, and related analogues, for dopamine D_2 and D_3 receptors. The affinity of the new naphthamide analogues was also determined for σ_1 and σ_2 receptors because previous studies indicated that benzamide analogues may bind with high affinity at σ receptors.[24,43,44] In addition, binding at σ receptor subtypes, particularly the σ_1 receptor, may be a component of clinical efficacy of a number of antipsychotics.[29,30] The results of this study led to the identification of a number of compounds having a high affinity for dopamine D_2 versus D_3 receptors and varying affinity for σ_1 and σ_2 receptors.

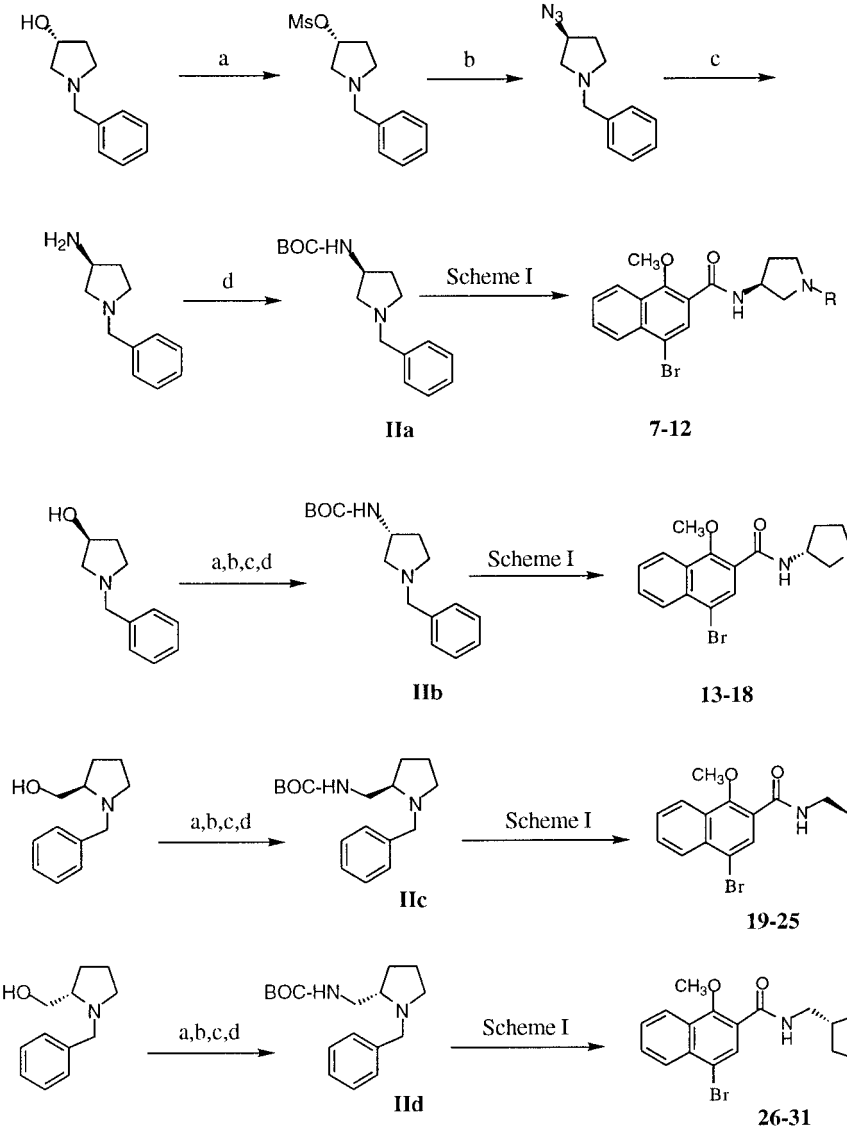
Chemistry

The synthesis of *N*-(1-alkylpiperidin-4-yl)-4-bromo-1-methoxy-2-naphthamide is outlined in Scheme 1. 4-Amino-1-benzylpiperidine was treated with trifluoroacetic anhydride, followed by debenzylation and reductive alkylation using a combination of Pd hydroxide/C and Pd/C as the cocatalyst. After removal of the trifluoroacetyl group, the 4-amino-1-alkylpiperidine was condensed with 4-bromo-1-methoxy-2-naphthoyl chloride to afford compounds **1**−**6**.

The synthetic strategy for the preparation of (*S*)-1-benzyl-3-(*tert*-butoxycarbonylamino)pyrrolidine (**IIa**), (*R*)-1-benzyl-3-(*tert*-butoxycarbonylamino)pyrrolidine (**IIb**), (*S*)-*N*-(1-benzyl-2-pyrrolidinylmethyl)-*tert*-butoxycarbamide (**IIc**), and (*R*)-*N*-(1-benzyl-2-pyrrolidinylmethyl)-*tert*-butoxycarbamide (**IId**) is shown in Scheme 2**.** The hydroxyl group was mesylated with mesyl chloride, followed by reaction with sodium azide, reduction with lithium aluminum hydride, and condensation with di-*tert*-butyl dicarbonate to give the corresponding intermediate (**IIa**−**IId**). The intermediates (**IIa**−**IId**) then underwent the same procedures shown for **Ia** of Scheme 1 to afford compounds **7**−**12**, **13**−**18**, **19**−**25**, and **26**−**31**.

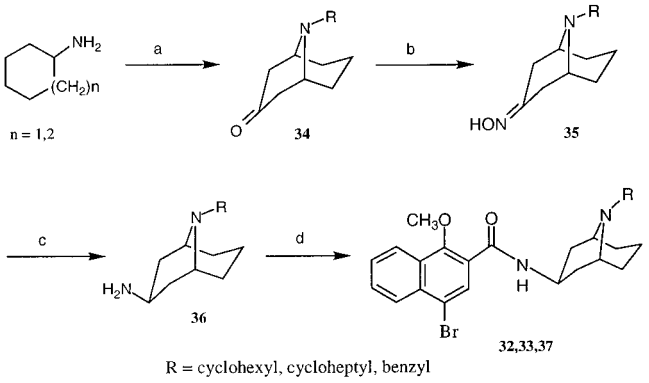
Compounds **32** and **33** were prepared from the corresponding 3β-amino-9-cyclohexyl-9-azabicyclo[3.3.1]-nonane and 3β-amino-9-cycloheptyl-9-azabicyclo[3.3.1]-nonane, respectively, by condensing with 4-bromo-1-methoxy-2-naphthoyl chloride. 3β-Amino-9-cyclohexyl-9-azabicyclo[3.3.1]nonane and 3β-amino-9-cycloheptyl-9-azabicyclo[3.3.1]nonane were obtained by a Mannich reaction to form the corresponding 9-cycloalkyl-9-azabicyclo[3.3.1]non-3-one, **34**.[18] This process was followed by conversion into the corresponding oxime, **35**. Reduction with sodium in amyl alcohol gave the desired exo amine, **36**, in quantitative yield (Scheme 3).

Scheme 2[a]



[a] Reagents: (a) methanesulfonyl chloride/Et_3N/THF, 0°C; (b) NaN_3/DMF, reflux; (c) $LiAlH_4$/THF, reflux; (d) $(BOC)_2O/CH_2Cl_2$.

Scheme 3[a]



[a] Reagents: (a) as in ref 18; (b) $NH_2OH{\cdot}HCl$/EtOH, reflux; (c) Na/amyl alcohol, reflux; (d) 4-bromo-1-methoxy-napthyl chloride.

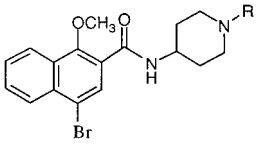
Pharmacological Assays

In vitro dopamine receptor radioligand binding studies were performed using membranes prepared from *Spodoptera frugiperda* (Sf9) cells that express high levels of either D_2 (long) or D_3 dopamine receptors. The radioligand used was [^{125}I]IABN, and the assay conditions were analogous to those previously described.[21] In vitro σ_1 receptor binding affinity was measured using guinea pig brain membranes (Rockland Biological, Gilbertsville, PA) and the σ_1-selective radioligand [^{3}H]-(+)-pentazocine (DuPont-NEN, Bilerica, MA) according to the methods previously described.[27] In vitro σ_2 receptor affinity was determined using rat liver membranes with [^{3}H]DTG (DuPont-NEN, Bilerica, MA) as the radioligand. The equilibrium dissociate constants, K_i values, were calculated from the corresponding IC_{50} values using the method of Cheng and Prusoff.[26]

Results and Discussion

A common feature of drugs used clinically as antipsychotics is that they are antagonists at both the D_2 and D_3 dopamine receptor subtypes. The goal of the studies presented in this communication was to explore variations in the structure of naphthamides in an effort to identify novel compounds that bind with selectivity at the D_3 receptor compared to the D_2 dopamine receptor subtype. It has been hypothesized that the antipsychotic effects of the neuroleptics may be due to the antagonism of both dopamine D_2 and D_3 receptors in the limbic

Table 1. Dopamine D_2 and D_3 Receptor Binding Profiles of *N*-(1-Alkylpiperidin-4-yl)-4-bromo-1-methoxy-2-naphthamides



	R	K_i [a] (nM) D_2[b]	K_i [a] (nM) D_3[c]	D_2/D_3[d]	K_i [a] (nM) σ_1[e]	K_i [a] (nM) σ_2[f]
1	benzyl	5.5 ± 2.8	1.1 ± 0.4	5	5.6 ± 0.5	35 ± 3
2	cyclopentyl	210 ± 37.1	899 ± 22	0.2	1.2 ± 0.2	6.8 ± 0.6
3	cyclohexyl	94 ± 22	430 ± 54	0.2	1.1 ± 0.1	2.1 ± 0.3
4	cycloheptyl	23 ± 6	58 ± 17	0.4	1.1 ± 0.2	2.6 ± 0.3
5	bicyclo[3.3.1]nonan-9-yl	771 ± 175	1431 ± 350	0.5	1.9 ± 0.1	2.4 ± 0.7
6	2-adamantyl	96 ± 46	92 ± 31	1.0	121 ± 13	55 ± 7

[a] Mean ± SEM, K_i values were determined from at least three experiments. [b] K_i values for D_2 receptors were measured on rat $D_{2(long)}$ expressed in Sf9 cells using [^{125}I]IABN as the radioligand. [c] K_i values for D_3 receptors were measured on rat D_3 expressed in Sf9 cells using [^{125}I]IABN as the radioligand. [d] K_i for D_2 receptor/K_i for D_3 receptor. [e] K_i values for σ_1 receptors were measured on guinea pig brain membranes using [^{3}H](+)-pentazocine as the radioligand. [f] K_i values for σ_2 receptors were measured on rat liver membranes using [^{3}H]-DTG as the radioligand in the presence of (+)-pentazocine.

region of the brain, while the extrapyramidal side effects result after chronic blockade of the D_2 receptors in the nigrostriatal region. The long-term goal would be to develop a new generation of antipsychotic drugs that retain clinical efficacy without extrapyramidal side effects. However, it has been difficult to develop compounds that bind with substantially higher affinity at D_3 receptors than at the D_2 dopamine receptor subtype because the amino acid sequences of the transmembrane spanning regions that construct the neurotransmitter binding sites of these two G protein associated receptor subtypes are 75−80% homologous.

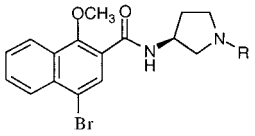
Recent studies have suggested that the σ_1 receptors may also play a role in the regulation of psychosis because a number of antipsychotic drugs bind with affinity at σ_1 receptors rather than at dopamine receptors.[29] This observation has led to the hypothesis that the pharmacologic blockade of σ_1 receptors may be important for antipsychotic activity, without contributing to the extrapyramidal side effects of antipsychotic drugs.[30] In addition, antagonism of σ_1 receptors may correlate with the ability to block the development of sensitization to cocaine and other psychostimulants.[31,32] Recent clinical studies using the σ receptor selective ligand panamesine in patients with schizophrenia reported an improvement in psychometric variables with no observed extrapyramidal side effects.[33] Therefore, σ_1 receptor antagonists may play a role in preventing schizophrenics from deteriorating or relapsing.[32] Since the blockade of D_2 receptors, D_3 receptors, and σ_1 receptors has been indicated to be associated with the antipsychotic effects of many neuroleptics, a compound that possesses (a) high affinity for D_3 dopamine receptors and σ_1 receptors with (b) moderate to low affinity for D_2 dopamine receptors and σ_2 receptors may potentially be useful for the treatment of schizophrenia. The results of radioligand binding studies designed to determine the affinity of naphthamides at D_2 and D_3 dopamine receptors and σ_1 and σ_2 receptors are shown in Tables 1−6.

Except for compound **1**, the piperidine series of naphthamides exhibited relatively low affinity (K_i values greater than 20 nM) for both D_2 and D_3 receptors. Compound **1**, which has a benzyl group substitution on the basic nitrogen of the central piperidine ring rather than the cycloalkyl groups of the other compounds in this series (Table 1), has high affinity (K_i = 1−5 nM) for both D_2 and D_3 dopamine receptors with a 5-fold selectivity for D_3 receptors. This result is in agreement with our previously published results of the *N*-(9-benzyl-9-azabicyclo[3.3.1]nonan-3β-yl) benzamide analogues.[23] The affinity for D_2 and D_3 receptors (compounds **2**−**6**) decreased when the benzyl group of compound **1** was replaced by cycloalkyl groups. This result is consistent with the D_2-like dopamine receptor binding site model proposed by Rognan and co-workers.[28] In the Rognan model the D_2 receptor has three aromatic binding regions within the neurotransmitter binding site, termed AR1, AR2, and AR3, and a subsite that is complementary to a basic nitrogen atom of the central ring. The naphthamide aromatic moiety of compounds **1**−**6** is hypothesized to interact with the AR1 region, while the benzyl group of compound **1** would likely bind to either the AR2 or AR3 region. On the basis of this model, the cycloalkyl moieties of compounds **2**−**6** would not be accommodated well within either the AR2 or AR3 region.

The results of σ receptor binding studies indicated that compounds **2**−**5** had higher affinity (K_i ranged from 1 to 7 nM) for both σ_1 and σ_2 receptors than for D_2 or D_3 receptors. Compounds **1** and **6** had moderate to low affinity (K_i values of 6−120 nM) for σ receptors. Therefore, in this series of compounds the benzyl group played a crucial role in D_2-like dopamine receptor binding affinity and selectivity with respect to σ receptors. Of this series of six compounds, compound **1** had the most pharmacologically desirable properties because (a) it bound D_3 receptors with nanomolar affinity, (b) it was 5-fold-selective for the D_3 receptor compared to the selectivity for D_2 and σ_1 receptors, and (c) it was 32-fold-selective for D_3 dopamine compared to the selectivity for the σ_2 receptor.

Ohmori and co-workers reported a series of (*S*)-*N*-(1-benzylpyrrolidin-3-yl)-5-chloro-4-[(cyclopropylcarbonyl)-amino]-2-methoxybenzamide compounds that bound with high affinity and selectivity at D_3 dopamine receptors.[25] Therefore, either a (*S*)- or a (*R*)-1-alkylpyrrolidin-3-yl moiety was incorporated into our naphthamide analogues to determine the effect of these groups on the affinity and selectivity of the naphthamide

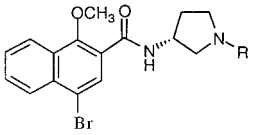
Table 2. Dopamine D_2 and D_3 Receptor Binding Profiles of (*S*)-*N*-(1-Alkylpyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamides



		K_i [a] (nM)			K_i [a] (nM)	
	R	D_2[b]	D_3[c]	D_2/D_3[d]	σ_1[e]	σ_2[f]
7	benzyl	9.7 ± 2.3	1.0 ± 0.5	9.7	3.2 ± 0.4	42 ± 0.4
8	cyclopentyl	19 ± 11	2.5 ± 1.0	7.7	3.6 ± 0.2	27 ± 3
9	cyclohexyl	5.9 ± 1.8	0.8 ± 0.3	7.4	5.8 ± 0.2	25 ± 2
10	cycloheptyl	1.8 ± 0.4	0.2 ± 0.1	9.0	4.8 ± 0.6	17 ± 0.4
11	bicyclo[3.3.1]nonan-9-yl	132 ± 22	12 ± 5	11	400 ± 2	137 ± 2
12	2-adamantyl	5.8 ± 3.6	0.4 ± 0.1	14.5	28 ± 3	70 ± 10

[a–f] See Table 1.

Table 3. Dopamine D_2 and D_3 Receptor Binding Profiles of (*R*)-*N*-(1-Alkylpyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamides



		K_i [a] (nM)			K_i [a] (nM)	
	R	D_2[b]	D_3[c]	$D_{2/D3}$[d]	σ_1[e]	σ_2[f]
13	benzyl	12.0 ± 4.7	1.6 ± 0.4	7.5	5.9 ± 0.5	20.8 ± 2.6
14	cyclopentyl	283 ± 21	75 ± 32	3.8	0.7 ± 0.03	15.3 ± 0.6
15	cyclohexyl	74 ± 13	5.7 ± 2.8	13	1.2 ± 0.1	9.8 ± 1.4
16	cycloheptyl	19 ± 7	2.9 ± 1.8	6.7	1.7 ± 0.2	10.0 ± 2.8
17	bicyclo[3.3.1]nonan-9-yl	75 ± 22	13.2 ± 4.3	5.7	6.2 ± 0.2	279 ± 8
18	2-adamantyl	62 ± 19	13.0 ± 6.6	4.8	6.2 ± 0.1	21.4 ± 1.1

[a–f] See Table 1.

compounds at the D_2 and D_3 dopamine receptor subtypes. The binding data for the (*S*) series is shown in Table 2, and data for the (*R*) series are shown in Table 3. The results in both Tables 2 and 3 indicated that the (*S*)- and the (*R*)-*N*-(1-alkylpyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamide analogues demonstrated a 4- to 15-fold selectivity for D_3 compared to the selectivity for D_2 dopamine receptors. The benzyl (compounds **7** and **13**) and the bicyclo[3.3.1]nonan-9-yl (compounds **11** and **17**) substituted analogues had similar affinity and selectivity for dopamine D_2 and D_3 receptors. When compared to the corresponding (*R*)-series analogues (Table 3), the remaining (*S*)-*N*-(1-alkylpyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamide analogues (Table 2) were found (a) to bind with higher affinity at both D_2 and D_3 receptors and (b) to have higher selectivity for D_3 receptors than the (*R*)-series analogues. This observation is consistent with the results reported by Ohmori and co-workers.[25]

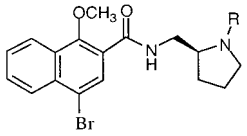
The (*S*)-series compounds **8**−**10** and the (*R*)-series compounds **14**−**16** both demonstrated an increased affinity for both D_2 and D_3 receptors as a function of increased ring size in the order $K_{i(cyclopentyl)} > K_{i(cyclohexyl)} > K_{i(cycloheptyl)}$. Although the bicyclo[3.3.1]nonan-9-yl derivatives (**11** and **17**) had a significantly lowered affinity for both D_2 and D_3 receptors, they maintained a D_3 receptor selectivity comparable to corresponding cycloheptyl analogues (**10** and **16**, respectively). Compounds with the 2-adamantyl moiety had (a) high affinity at D_2 and D_3 receptors with good D_3 selectivity in the (*S*) series (**12**) and (b) moderate affinity at D_2 and D_3 receptors with a good D_3 selectivity in the (*R*) series (**18**).

While the size of the alkylpyrrolidin-3-yl moiety for the (*R*)- and the (*S*)-series compounds clearly influenced affinity at D_2 and D_3 dopamine receptor, it seems to have less effect on the affinity at σ receptors. The affinity at σ receptors was found to be higher for the (*R*) series than for the (*S*) series for the majority of compounds in these series (Tables 2 and 3). Of the (*R*)- and the (*S*)-alkylpyrrolidin-3-yl derivatives, compound **12** had the most pharmacologically desirable properties because it bound D_3 receptors with nanomolar affinity ($K_i = 0.4$ nM) and was 15-fold selective at D_3 compared to the selectivity at D_2 receptors. In addition, compound **12** was found to be 70- to 175-fold selective at D_3 receptors compared to the selectivity of the σ receptor subtypes.

The in vitro σ receptor binding results indicated that the (*S*)- and (*R*)-*N*-(1-alkylpyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamide analogues bound with high affinity for σ_1 receptors (except for **11**) and moderate to low affinity for σ_2 receptors. As a result, many of these compounds (Tables 2 and 3) were found to be selective for both D_3 and σ_1 receptors. For example, compound **17** had a K_i value of 13 nM at D_3 receptors and a 6-fold selectivity for D_3 versus D_2 receptors. Compound **17** had a K_i value of 6 nM at σ_1 receptors with a 45-fold selectivity for σ_1 versus σ_2 receptors.

Tables 4 and 5 contain the in vitro binding results for (*S*)- and (*R*)-*N*-(1-alkyl-2-pyrrolidinylmethyl)-4-bromo-

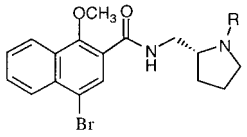
Table 4. Dopamine D_2 and D_3 Receptor Binding Profiles of (*S*)-*N*-(1-Alkyl-2-pyrrolidinylmethyl)-4-bromo-1-methoxy-2-naphthamides



	R	K_i [a] (nM) D_2[b]	K_i [a] (nM) D_3[c]	D_2/D_3[d]	K_i [a] (nM) σ_1[e]	K_i [a] (nM) σ_2[f]
19	benzyl	151 ± 52	14.6 ± 3.6	10.3	56 ± 6	222 ± 3
20	cyclobutyl	11.8 ± 1.5	1.9 ± 0.8	6.2	4.0 ± 0.7	152 ± 13
21	cyclopentyl	59 ± 8	52 ± 11	1.1	2.5 ± 0.1	51 ± 2
22	cyclohexyl	442 ± 36	334 ± 89	1.3	57 ± 4.5	147 ± 10
23	cycloheptyl	80 ± 11	50 ± 11	1.6	12.7 ± 0.4	44 ± 0.1
24	bicyclo[3.3.1]nonan-9-yl	26 ± 5.1	7.5 ± 1.6	3.4	16.7 ± 1.6	267 ± 9
25	2-adamantyl	300 ± 28	68 ± 10	4.4	23.4 ± 0.1	141 ± 13

[a–f] See Table 1.

Table 5. Dopamine D_2 and D_3 Receptor Binding Profiles of (*R*)-*N*-(1-Alkyl-2-pyrrolidinylmethyl)-4-bromo-1-methoxy-2-naphthamides



	R	K_i [a] (nM) D_2[b]	K_i [a] (nM) D_3[c]	D_2/D_3[d]	K_i [a] (nM) σ_1[e]	K_i [a] (nM) σ_2[f]
26	benzyl	11.4 ± 8.6	1.4 ± 0.7	8	230 ± 5	207 ± 23
27	cyclobutyl	277 ± 67	90 ± 16	3	48.± 2	95 ± 2
28	cyclopentyl	157 ± 86.	30 ± 9	5	31 ± 7	35 ± 5
29	cyclohexyl	58 ± 24	3.2 ± 1.1	18.4	20.7 ± 1.7	25 ± 1
30	cycloheptyl	63 ± 26	2.4 ± 1.1	26	59 ± 3.3	57 ± 9
31	2-adamantyl	22.9 ± 3.8	2.6 ± 0.3	8.8	375 ± 11	317 ± 12

[a–f] See Table 1.

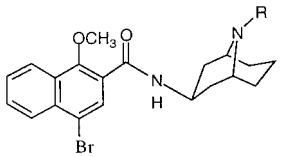
1-methoxy-2-naphthamides. The compounds in this series are structurally similar to nafadotride (Chart 1), which was reported to be 10-fold-selective for D_3 receptors compared to the selectivity for the D_2 dopamine receptor subtype.[34] Except for the cyclobutyl (**20** versus **27**) and cyclopentyl (**21** versus **28**) substituted analogues, the (*R*) isomers (Table 5) were found to bind with higher affinity at D_3 receptors than the corresponding (*S*)-isomers (Table 4). The size of the alkyl moiety for the (*R*)- and the (*S*)-pyrrolidinylmethyl series of compounds influenced the affinity of the compounds at D_2 and D_3 dopamine receptors, but the size influenced the affinity in opposite directions. For the (*S*)-pyrrolidinylmethyl derivatives, increasing the size of the cycloalkyl group from a cyclobutyl to a cyclohexyl group resulted in a decrease in affinity at both D_2 and D_3 dopamine receptors and a loss of D_3 receptor selectivity (Table 4). In contrast, a similar increase in the size of the cycloalkyl group in the (*R*) series of compounds resulted in an increase in affinity at D_2-like dopamine receptors, with increasing selectivity at the D_3 receptor compared to that at the D_2 dopamine receptor subtype. Consequently, the cyclohexyl- and the cycloheptyl-substituted (*R*) isomers, compounds **29** and **30**, exhibited an 18-fold and 26-fold selectivity for D_3 receptors, respectively.

The σ receptor binding results revealed that the (*S*) isomers (Table 4) had a generally higher affinity at σ_1 than at σ_2 receptors, whereas the (*R*) isomers (Table 5) showed almost identical affinity at both σ_1 and σ_2 receptors. The cyclobutyl-substituted (*S*) isomer, compound **20**, had high affinity for both D_3 and σ_1 receptors, a moderate affinity for D_2, and a low affinity for σ_2 receptors. This analogue displayed a 6-fold selectivity for D_3 versus D_2 receptors and a 38-fold selectivity for σ_1 versus σ_2 receptors.

The final two naphthamides prepared for this study, compounds **32** and **33**, have a 9-azabicyclo[3.3.1]nonan-3β-yl moiety (Table 6) as the central ring. The affinities of compounds **32** and **33** at D_2 and D_3 receptors were significantly decreased in comparison to the corresponding 9-benzyl-substituted analogue, **37** (K_i = 0.20 and 0.04 nM for D_2 and D_3 receptors, respectively).[23] However, compounds **32** and **33** showed a moderate selectivity for D_3 receptors, whereas the corresponding 1-alkylpiperidin-4-yl analogues, **3** and **4**, had a moderate selectivity for the D_2 receptor (Table 1). The relatively low dopamine receptor affinity of compounds **2**−**6**, **32**, and **33** indicates that the *N*-cycloalkyl is not favorable for either D_2 or D_3 receptor binding for the piperidin-4-yl and 9-azabicyclononan-3β-yl analogues, whereas the *N*-benzyl moiety is beneficial for both D_2 and D_3 receptor binding. The high affinity of **32** and **33** for σ_2 receptors versus σ_1, D_2, and D_3 receptors indicates that these analogues may be useful lead compounds for developing σ_2-selective ligands.

In conclusion, a series of naphthamides have been synthesized and assessed for their binding affinity at D_2 and D_3 dopamine and the σ_1 and σ_2 receptor subtypes. This research extends previous efforts to explore the fundamental structure−activity relationships of benzamide-related analogues as potential selective antagonists for the D_3 dopamine receptor sub-

Table 6. Dopamine D_2 and D_3 Receptor Binding Profiles of *N*-(9-Alkyl-9-azabicyclo[3.3.1]nonan-3β-yl)-4-bromo-1-methoxy-2-naphthamides



		K_i [a] (nM)			K_i [a] (nM)	
	R	D_2[b]	D_3[c]	D_2/D_3[d]	σ_1[e]	σ_2[f]
32	cyclohexyl	150 ± 42	48 ± 17	3	69 ± 4	4.8 ± 0.6
33	cycloheptyl	152 ± 14	41 ± 16	3.7	96 ± 3	7.9 ± 1.2
37[g]	benzyl	0.20 ± 0.08	0.04 ± 0.01	5.0	74 ± 3	250 ± 5
haloperidol		7.6 ± 2.0	47 ± 19	0.16	1.5 ± 0.2	17 ± 0.6
IABN[h]		0.05 ± 0.01[i]	0.04 ± 0.004[i]	1.2	>1000	419 ± 32

[a–f] See Table 1. [g] Reference 23. [h] *N*-(9-benzyl-9-azabicyclo[3.3.1]nonan-3β-yl)-2,3-dimethoxy-5-iodobenzamide. [i] K_d values from Scatchard studies.

type.[21–23] In this report the steric effects of the N-substituent naphthamides on the binding affinity for D_2 and D_3 dopamine receptors have been investigated. Naphthamides having the *N*-(1-cycloalkylpiperidin-4-yl) moiety were found to bind with low affinity at both D_2 and D_3 receptors, while most of the compounds having either the (*S*)- or (*R*)-*N*-(1-cycloalkylpyrrolidin-3-yl), or the (*S*)- or (*R*)-*N*-(1-cycloalkyl-2-pyrrolidinylmethyl) moiety had moderate to high affinity for D_3 receptors and moderate to low affinity at D_2 receptors. The σ receptor binding results indicated that the majority of the naphthamide analogues had moderate to high affinity for the σ_1 and σ_2 receptor subtypes. The piperidine derivatives (**2**–**5**) were potent σ_1 and σ_2 nonselective ligands, with lower affinity at D_2-like receptors. The pyrrolidine-containing derivatives (**7**–**10** and **12**–**18**) were potent σ_1 receptor selective ligands with varying affinity at D_2-like dopamine receptors. The pyrrolidinylmethyl derivatives (**19**–**31**) were either slightly σ_1 selective or nonselective at σ_1 and σ_2 receptors with varying affinity at D_2-like dopamine receptors. The 9-cycloalkyl-9-azabicyclo[3.3.1]nonane derivatives (**32**, **33**) were found to be σ_2 receptor selective ligands. A number of the analogues described above showed high affinity and moderate selectivity for D_3 versus D_2 receptors, as well as high affinity and high selectivity for σ_1 versus σ_2 receptors. Preliminary studies using the ^{35}S-GTPγS binding assay in rat striatal tissue indicate that a number of the compounds described above function as antagonists of the D_2-like receptors (unpublished data). Therefore, the pharmacologic properties of the compounds prepared for this report suggest that naphthamide-type drugs are potential pharmacotherapeutic agents for the treatment of neuropsychiatric disorders or for the rehabilitation of patients who abuse psychostimulants.

Experimental Section

Chemistry. Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Where molecular formulas were indicated, analyses were found to be within 0.4% of the theoretical values unless otherwise noted. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AVANCE300 spectrometer. All ^{1}HNMR spectra were obtained in either $CDCl_3$ or DMSO-d_6, and results were recorded as parts per million (ppm) downfield to tetramethylsilane (TMS). The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, dt = double triplet, dq = double quartet, br = broad. All starting materials and solvents were purchased from Aldrich, Fisher, or Lancaster and were used without further purification.

4-Bromo-1-methoxy-2-naphthoyl Chloride. Bromine was added (31.96 g, 0.2 mol) to a solution of 1-hydroxy-2-naphthoic acid (37.64 g, 0.2 mol) in acetic acid (500 mL). The mixture was stirred at room temperature overnight. The solid was filtered and dried to give 4-bromo-1-hydroxy-2-naphthoic acid (53.2 g, 99%), which was used for the next reaction without further purification. ^{1}H NMR (acetone-d_6): δ 6.37–6.40 (d, 1H), 6.10–6.13 (d, 1H), 6.06 (s, 1H), 5.78–5.84 (dt, 1H), 5.63–5.69 (dt, 1H).

A mixture of 4-bromo-1-hydroxy-2-naphthoic acid (51.0 g, 0.19 mol), dimethyl sulfate (48.17 g, 0.38 mol), potassium carbonate (52.78 g, 0.38 mol), and acetone (500 mL) was refluxed overnight. The solid was filtered, and the solution was condensed to give a solid residue, which was recrystallized from ethyl acetate/hexane to afford methyl 4-bromo-1-methoxy-2-naphthoate (54.0 g, 96%); mp 84–85 °C. ^{1}H NMR ($CDCl_3$): δ 8.29–8.32 (d, 1H), 8.20–8.23 (d, 1H), 8.19 (s, 1H), 7.68–7.74 (dt, 1H), 7.60–7.66 (dt, 1H), 4.06 (s, 3H), 3.99 (s, 3H).

NaOH (40%, 20 mL) was added slowly to a solution of methyl 4-bromo-1-methoxy-2-naphthoate (54 g, 0.18 mol) in methanol (500 mL) and refluxed for 3 h. The methanol was removed, and the residue was added to an ice-cold 6 N HCl solution to give pH ≤ 2. The solid was filtered, dried, and recrystallized from ethyl acetate to give 4-bromo-1-methoxy-2-naphthoic acid (46.3 g, 90%); mp 180–181 °C. ^{1}H NMR ($CDCl_3$): δ 8.39 (s, 1H), 8.23–8.30 (q, 2H), 7.74–7.80 (dt, 1H), 7.65–7.71 (dt, 1H), 4.15 (s, 3H).

Thionyl chloride (33.91 g, 0.28 mol) was added to a solution of 4-bromo-1-methoxy-2-naphthoic acid (40.0 g, 0.14 mol) in benzene (200 mL). After the mixture was refluxed overnight, the solvent was removed and the residue was recrystallized from ethyl acetate/hexane to give 4-bromo-1-methoxy-2-naphthoyl chloride (39.05 g, 92%); mp 99–100 °C. ^{1}H NMR ($CDCl_3$): δ 8.34 (s, 1H), 8.30–8.33 (d, 1H), 8.23–8.26 (d, 1H), 7.76–7.82 (dt. 1H), 7.65–7.71 (dt, 1H), 4.06 (s, 3H).

1-Benzyl-4-trifluoroacetamidopiperidine (Ia). Trifluoroacetic anhydride (12.6 g, 60 mmol) and 5 mL of triethylamine was added to a solution of 4-amino-1-benzylpiperidine (9.5 g, 50 mmol) in dry dichloromethane (200 mL) under ice. After the mixture was stirred at room temperature for 12 h, the solvent was removed under vacuo and the residue was dissolved in ethyl acetate, washed with aqueous $NaHCO_3$ and water, and dried over Na_2SO_4. The solvent was removed, and the product was recrystallized from ethyl acetate to give **Ia** (13.5 g, 94%); mp 110–111 °C. ^{1}H NMR (free amine in $CDCl_3$): δ 7.29–7.38 (m, 5H), 6.55–6.62 (d, 1H), 3.87–3.96 (m, 1H), 3.69 (s, 2H), 3.02–3.06 (d, 2H), 2.27–2.36 (dt, 2H), 1.98–2.01 (m, 2H), 1.67–1.81 (dq, 2H).

General Methods for Preparation of *N*-(1-Alkylpiperidin-4-yl)-4-bromo-1-methoxy-2-naphthamide (2−6). Compounds **2**−**6** were prepared by a reductive alkylation of **Ia** with a cycloketone under catalytical hydrogenation and followed by cleavage of the trifluoroacetyl moiety and condensation with 4-bromo-1-methoxy-2-naphthoyl chloride.

***N*-(1-Cyclopentylpiperidin-4-yl)-4-bromo-1-methoxynaphthamide (2).** A mixture of **Ia** (0.57 g, 2 mmol), cyclopentanone (0.5 g, 5.9 mmol), and 20% palladium hydroxide on carbon (25 mg) and 10% palladium on activated carbon (25 mg) in methanol (100 mL) was hydrogenated under 50 psi for 12 h at room temperature. The catalyst was removed by filtration. The filtrate was concentrated, and ammonium hydroxide (30%, 20 mL) and methanol (50 mL) was then added. This mixture was refluxed for 4 h and then gradually cooled to room temperature. The mixture was concentrated in vacuo, and the residue was dissolved in 2 N HCl (25 mL) and extracted with ethyl acetate (3 × 30 mL). The aqueous phase was separated and adjusted to pH ≥ 10 with 6 N NaOH. The product was extracted with dichloromethane (3 × 20 mL) and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration. 4-Bromo-1-methoxy-2-naphthoyl chloride (0.6 g, 2 mmol) and triethylamine (0.5 mL) was added to the filtrate, and the mixture was stirred overnight. The solution was concentrated. The residue was extracted with dichloromethane (3 × 30 mL) and dried over Na_2SO_4. The product was purified by a silica gel column with $CHCl_3$/ethanol (9.5:0.5) as the elutant and recrystallized from ethyl acetate/hexane to give *N*-(1-cyclopentylpiperidin-4-yl)-4-bromo-1-methoxy-2-naphthamide, **2** (0.48 g, 56%); mp 171−173 °C. ^{1}H NMR ($CDCl_3$): δ 8.41 (s, 1H), 8.23−8.26 (dd, 1H), 8.15−8.18 (dd, 1H), 7.84−7.87 (d, 1H, CO−NH), 7.66−7.72 (dt, 1H), 7.60−7.66 (dt, 1H), 4.05−4.12 (m, 1H), 3.97 (s, 3H, OCH_3), 2.99−3.03 (d, 2H), 2.44−2.59 (m, 1H), 2.09−2.48 (m, 2H), 1.86−1.95 (m, 2H), 1.48−1.63 (m, 10H). Analysis results for ($C_{22}H_{27}N_2O_2Br$) C, H, N are in Supporting Information.

***N*-(1-Cyclohexylpiperidin-4-yl)-4-bromo-1-methoxy-2-naphthamide (3).** Yield of 45% from **Ia** (three steps); mp 167−168 °C. ^{1}H NMR ($CDCl_3$): δ 8.41 (s, 1H), 8.23−8.26 (dd, 1H), 8.15−8.18 (dd, 1H), 7.83−7.86 (d, 1H, CO−NH), 7.66−7.72 (dt, 1H), 7.60−7.66 (dt, 1H), 4.07−4.14 (m, 1H), 3.97 (s, 3H, OCH_3), 2.95−3.00 (d, 2H), 2.41−2.54 (m, 1H), 2.09−2.18 (m, 2H), 1.80−1.96 (m, 4H), 1.57−1.64 (m, 6H), 1.18−1.29 (m, 4H). Analysis results for ($C_{23}H_{29}N_2O_2Br$) C, H, N are in Supporting Information.

***N*-(1-Cycloheptylpiperidin-4-yl)-4-bromo-1-methoxy-2-naphthamide (4).** Yield of 27% from **Ia** (three steps); mp 152−153 °C. ^{1}H NMR ($CDCl_3$): δ 8.41 (s, 1H), 8.23−8.26 (dd, 1H), 8.15−8.18 (dd, 1H), 7.83−7.86 (d, 1H, CO−NH), 7.66−7.72 (dt, 1H), 7.60−7.66 (dt, 1H), 4.03−4.12 (m, 1H), 3.97 (s, 3H, OCH_3), 2.82−2.86 (d, 2H), 2.55−2.65 (m, 1H), 2.43−2.51 (m, 2H), 1.82−1.88 (m, 2H), 1.44−1.67 (m, 12H). Analysis results for ($C_{24}H_{31}N_2O_2Br$) C, H, N are in Supporting Information.

***N*-(1-(Bicyclo[3.3.1]nonan-9-yl)piperidin-4-yl)-4-bromo-1-methoxy-2-naphthamide (5).** Yield of 31% from **Ia** (three steps); mp 169−171 °C. ^{1}H NMR ($CDCl_3$): δ 8.41 (s, 1H), 8.23−8.26 (dd, 1H), 8.16−8.19 (dd, 1H), 7.85−7.88 (d, 1H, CO−NH), 7.66−7.72 (dt, 1H), 7.60−7.66 (dt, 1H), 4.04−4.15 (m, 1H), 3.97 (s, 3H, OCH_3), 2.91−2.95 (d, 2H), 2.78−2.87 (m, 1H), 2.37−2.44 (m, 2H), 1.62−1.73 (m, 6H), 1.22−1.27 (m, 2H), 1.09−1.11 (d, 8H). Analysis results for ($C_{26}H_{33}N_2O_2Br$) C, H, N are in Supporting Information.

***N*-(1-(Adamantan-2-yl)piperidin-4-yl)-4-bromo-1-methoxy-2-naphthamide (6).** Yield of 21% from **Ia** (three steps); mp 189−190 °C. ^{1}H NMR ($CDCl_3$): δ 8.41 (s, 1H), 8.23−8.26 (dd, 1H), 8.16−8.19 (dd, 1H), 7.83−7.85 (d, 1H, CO−NH), 7.66−7.72 (dt, 1H), 7.60−7.66 (dt, 1H), 4.03−4.13 (m, 1H), 3.99 (s, 3H, OCH_3), 2.94−3.02 (d, 2H), 2.065−2.09 (m, 9H), 1.79−1.89 (m, 4H), 1.59−1.71 (m, 6H), 1.36−1.44 (d, 2H). Analysis results for ($C_{27}H_{33}N_2O_2Br$) C, H, N are in Supporting Information.

(*S*)-1-Benzyl-3-(*tert*-butoxycarbonylamino)pyrrolidine (IIa). Methanesulfonyl chloride (3.88 g, 33.87 mmol) was added to a solution of (*R*)-1-benzyl-3-pyrrolidinol (5.0 g, 28.2 mmol) and triethylamine (5.71 g, 56.4 mmol) in dry THF (50 mL) at −10 °C. The mixture was stirred at −10 to 0 °C for 4 h and then stirred at room temperature overnight. The solvent was removed, and the residue was purified by a silica gel column with $CHCl_3$/ethyl acetate (9:1) as the elutant to give (*R*)-1-benzyl-3-pyrrolidinol methanesulfate as an oil (6.96 g, 96.7%). ^{1}H NMR ($CDCl_3$): δ 7.23−7.35 (m, 5H), 5.15−5.22 (m, 1H), 3.59−3.71 (q, 2H), 2.99 (s, 3H), 2.76−2.86 (m, 3H), 2.46−2.54 (m, 1H), 2.27−2.35 (m, 1H), 2.07−2.11 (m, 1H).

The above oil (6.96 g, 27.3 mmol) was dissolved in dry DMF (50 mL). Sodium azide (6.5 g, 100 mmol) was added, and the mixture was heated at 80 °C overnight. The mixture was poured into ice-cold water (150 mL), extracted with dichloromethane (3 × 30 mL), and dried over Na_2SO_4. The solvent was removed, and the residue was dissolved in dry THF (100 mL). Lithium aluminum hydride (1.04 g, 27.4 mmol) was slowly added, and the mixture was refluxed for 6 h and then cooled to room temperature. Water (2 mL) and 2 N NaOH (2 mL) was added to the mixture dropwise. The solid was removed by filtration, and the solution was concentrated in vacuo. The residue was purified by a silica gel column with $CHCl_3$/ethanol (8:2) as the elutant to give (*R*)-3-amino-1-benzylpyrrolidine (3.79 g, 79%). ^{1}H NMR ($CDCl_3$): δ 7.24−7.32 (m, 5H), 3.55−3.65 (q, 2H), 3.48−3.52 (m, 1H), 2.68−2.73 (m, 2H), 2.45−2.48 (m, 1H), 2.31−2.35 (m, 1H), 2.16−2.22 (m, 1H), 1.45−1.52 (m, 1H).

A solution of containing (*R*)-3-amino-1-benzylpyrrolidine (3.50 g, 20 mmol) and di-*tert*-butyl dicarbonate (4.34 g, 20 mmol) in dichloromethane (30 mL) was stirred at room temperature overnight. The mixture was washed with 1 N NaOH (30 mL) and then with water and dried over Na_2SO_4. The solvent was removed, and the residue was purified by a silica gel column with $CHCl_3$/ethanol (9:1) as the elutant to give **IIa** (4.27 g, 77%); mp 69−70 °C. ^{1}H NMR ($CDCl_3$): δ 7.21−7.34 (m, 5H), 4.16 (m, 1H), 3.58 (s, 2H), 2.77−2.82 (m, 1H), 2.43−2.63 (m, 2H), 2.19−2.31 (m, 2H), 1.70−1.75 (m, 1H), 1.56−1.62 (m, 1H), 1.43 (s, 9H). Analysis results for ($C_{16}H_{24}N_2O_2$) C, H, N are in Supporting Information.

(*R*)-1-Benzyl-3-(*tert*-butoxycarbonylamino)pyrrolidine (**IIb**), (*S*)-*N*-(1-benzyl-2-pyrrolidinylmethyl)-*tert*-butoxycarbamide (**IIc**), and (*R*)-*N*-(1-benzyl-2-pyrrolidinylmethyl)-*tert*-butoxycarbamide (**IId**) were prepared with methods similar to those described above and were used directly in subsequent reactions.

General Methods for the Preparation of Naphthamides 1, 7, 13, 19, 26, 32, and 33. These compounds were obtained directly by condensing the amines and the 4-bromo-1-methoxy-2-naphthoyl chloride at room temperature.

***N*-(1-Benzylpiperidin-4-yl)-4-bromo-1-methoxy-2-naphthamide (1).** Yield of 93% from 1-benzyl-4-aminopiperidine; mp 145−146 °C. ^{1}H NMR ($CDCl_3$): δ 8.40 (s, 1H), 8.23−8.26 (dd, 1H), 8.15−8.18 (dd, 1H), 7.82−7.85 (d, 1H, CO−NH), 7.66−7.72 (dt, 1H), 7.60−7.66 (dt, 1H), 7.26−7.34 (m, 5H), 4.05−4.17 (m, 1H), 3.95 (s, 3H, OCH_3), 3.56 (s, 2H), 2.84−2.88 (d, 2H), 2.21−2.28 (dt, 2H), 2.04−2.09 (m, 2H), 1.60−1.72 (m, 2H). Analysis results for ($C_{24}H_{25}N_2O_2Br$) C, H, N are in Supporting Information.

(*S*)-*N*−(1-Benzylpyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamide (7). Yield of 65% from (*S*)-1-benzyl-3-aminopyrrolidine; mp 162−164 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.39 (s, 1H), 8.22−8.25 (dd, 2H), 8.17−8.20 (dd, 2H), 7.66−7.72 (dt, 1H), 7.60−7.66 (dt, 1H), 7.22−7.39 (m, 5H), 4.68−4.76 (m, 1H), 3.92 (s, 3H, OCH_3), 3.60−3.73 (q, 2H), 2.64−2.76 (m, 2H), 2.33−2.44 (m, 2H), 1.72−1.84 (m, 2H). Analysis results for ($C_{25}H_{25}N_2O_6Br$) C, H, N are in Supporting Information.

(*R*)-*N*-(1-Benzylpyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamide (13). Yield of 49% from (*R*)-1-benzyl-3-aminopyrrolidine; mp 150−152 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.40 (s, 1H), 8.22−8.25 (dd, 2H), 8.17−8.20 (dd, 2H), 7.66−7.72 (dt, 1H), 7.60−7.66 (dt, 1H), 7.23−7.39 (m, 5H), 4.69−4.76 (m, 1H), 3.92 (s, 3H, OCH_3), 3.60−3.71 (q, 2H), 2.64−2.76 (m, 2H), 2.33−2.46 (m, 2H), 1.71−1.84 (m, 2H).

Analysis results for ($C_{25}H_{25}N_2O_6Br$) C, H, N are in Supporting Information.

(*S*)-*N*-(1-Benzyl-2-pyrrolidinylmethyl)-4-bromo-1-methoxy-2-naphthamide (19). Yield of 57% from (*S*)-1-benzyl-2-pyrrolidinylmethylamine; mp 112−114 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.45 (s, 1H), 8.34−8.40 (b, 1H, CO−NH), 8.19−8.27 (m, 2H), 7.64−7.70 (m, 2H), 7.21−7.39 (m, 5H), 3.97 (s, 3H, OCH_3), 3.45−3.55 (m, 2H), 2.75−2.85 (m, 2H), 2.20−2.30 (m, 1H), 1.65−1.80 (m, 6H). Analysis results for ($C_{26}H_{27}N_2O_6Br$) C, H, N are in Supporting Information.

(*R*)-*N*-(1-Benzyl-2-pyrrolidinylmethyl)-4-bromo-1-methoxy-2-naphthamide (26). Yield of 76% from (*R*)-1-benzyl-2-pyrrolidinylmethylamine; mp 98−100 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.45 (s, 1H), 8.36−8.46 (b, 1H, CO−NH), 8.25−8.28 (m, 2H), 7.65−7.75 (m, 2H), 7.21−7.45 (m, 5H), 3.94 (s, 3H, OCH_3), 3.50−3.55 (m, 2H), 2.70−2.80 (m, 2H), 2.20−2.30 (m, 1H), 1.78−1.82 (m, 6H). Analysis results for ($C_{26}H_{27}N_2O_6Br\cdot 1H_2O$) C, H, N are in Supporting Information.

***N*-(9-Cyclohexyl-9-azabicyclo[3.3.1]nonan-3β-yl)-4-bromo-1-methoxy-2-naphthamide (32).** 3β-Amino-9-cyclohexyl-9-azabicyclo[3.3.1]nonane was prepared in three steps. First, a Mannich reaction of cyclohexylamine, glutaric dialdehyde, and 1,3-acetonedicarboxylic acid was performed to give 9-cyclohexyl-9-azabicyclo[3.3.1]non-3-one, using the methods previously described.[18] The product was then converted into an oxime by reaction with hydroxylamine hydrochloride in refluxing ethanol (50% yield). Finally, the oxime was reduced using sodium in amyl alcohol to give 3β-amino-9-cyclohexyl-9-azabicyclo[3.3.1]nonane in quantitative yield.

N-(9-Cyclohexyl-9-azabicyclo[3.3.1]nonan-3β-yl)-4-bromo-1-methoxy-2-naphthamide was obtained in 74% yield from 3β-amino-9-cyclohexyl-9-azabicyclo[3.3.1]nonane; mp 164−166 °C. ^{1}H NMR ($CDCl_3$): δ 8.40 (s, 1H), 8.25−8.28 (d, 1H), 8.18−8.21 (d, 1H), 7.62−7.74 (m, 3H), 4.98−5.06 (m, 1H), 4.01 (s, 3H, OCH_3), 3.36 (b, 2H), 3.09 (b, 1H), 1.28−2.20 (m, 20H). Analysis results for ($C_{26}H_{33}N_2O_2Br$) C, H, N are in Supporting Information.

***N*-(9-Cycloheptyl-9-azabicyclo[3.3.1]nonan-3β-yl)-4-bromo-1-methoxy-2-naphthamide (33).** 3β-Amino-9-cycloheptyl-9-azabicyclo[3.3.1]nonane was prepared with methods similar to those described above.

N-(9-Cycloheptyl-9-azabicyclo[3.3.1]nonan-3β-yl)-4-bromo-1-methoxy-2-naphthamide was obtained with a 64% yield from 3β-amino-9-cycloheptyl-9-azabicyclo[3.3.1]nonane; mp 169−170 °C. ^{1}H NMR ($CDCl_3$): δ 8.38 (s, 1H), 8.22−8.25 (d, 1H), 8.15−8.18 (d, 1H), 7.59−7.71 (m, 3H), 4.94−5.04 (m, 1H), 3.98 (s, 3H, OCH_3), 3.35 (s, 2H), 3.09 (m, 1H), 1.45−2.15 (m, 22H). Analysis results for ($C_{27}H_{35}N_2O_2Br$) C, H, N are in Supporting Information.

General Methods for Preparation of Naphthamides 8−12, 14−18, 20−25, and 27−31. (*S*)-1-Benzyl-3-(*tert*-butoxycarbonylamino)pyrrolidine (**IIa**), (*R*)-1-benzyl-3-(*tert*-butoxycarbonylamino)pyrrolidine (**IIb**), (*S*)-*N*-(1-benzyl-2-pyrrolidinylmethyl)-*tert*-butoxycarbamide (**IIc**), or (*R*)-*N*-(1-benzyl-2-pyrrolidinylmethyl)-*tert*-butoxycarbamide (**IId**) was dissolved in methanol (100 mL). Two equivalents of cycloketone, 5% palladium hydroxide on carbon, and 5% palladium on activated carbon was then added to the solution. After the mixture was hydrogenated at 50 psi for 12 h, the catalyst was removed by filtration and the solution was concentrated in vacuo. The residue was dissolved in dichloromethane (30 mL), and trifluoroacetic acid (5 mL) was added. The reaction mixture was stirred at room temperature for 1 h, poured into ice-cold water, and adjusted to give pH > 10 with 2 N NaOH. The filtrate was extracted with dichloromethane (3 × 30 mL) and dried over Na_2SO_4. After the Na_2SO_4 was removed by filtration, 4-bromo-1-methoxy-2-naphthoyl chloride and triethylamine (1 mL) were added to the filtrate and the reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo, and the residue was dissolved in dichloromethane, washed with 1 N NaOH and water and dried over Na_2SO_4. The solvent was removed, and the residue was purified by silica gel column with $CHCl_3$/ethanol (9.5:0.5) as the elutant to give a free amine product, which was converted into an oxalate salt, using oxalic acid (2 equiv) in ethyl acetate.

(*S*)-*N*-(1-Cyclopentylpyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamide (8). Yield of 37% from **IIa** (three steps); mp 70−73 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.40 (s, 1H), 8.22−8.25 (dd, 1H), 8.16−8.19 (dd, 2H), 7.66−7.72 (dt, 1H), 7.59−7.65 (dt, 1H), 4.71−4.74 (m, 1H), 3.99 (s, 3H, OCH_3), 2.94−2.97 (m, 1H), 2.77−2.83 (m, 2H), 2.33−2.54 (m, 4H), 1.69−1.85 (m, 8H). Analysis results for ($C_{23}H_{27}N_2O_6Br\cdot 1H_2O$) C, H, N are in Supporting Information.

(*S*)-*N*-(1-Cyclohexylpyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamide (9). Yield of 29% from **IIa** (three steps); mp 66−68 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.40 (s, 1H), 8.23−8.26 (dd, 2H), 8.16−8.19 (dd, 1H), 7.66−7.72 (dt, 1H), 7.60−7.65 (dt, 1H), 4.71−4.74 (m, 1H), 3.99 (s, 3H, OCH_3), 3.00−3.10 (m, 1H), 2.85−2.93 (m, 2H), 2.32−2.52 (m, 2H), 1.65−1.75 (m, 2H), 1.22−1.28 (m, 10H). Analysis results for ($C_{24}H_{29}N_2O_6Br\cdot 2H_2O$) C, H, N are in Supporting Information.

(*S*)-*N*-(1-Cycloheptylpyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamide (10). Yield of 63% from **IIa** (three steps); mp 83−85 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.39 (s, 1H), 8.22−8.25 (dd, 2H), 8.16−8.19 (dd, 1H), 7.66−7.71 (dt, 1H), 7.60−7.65 (dt, 1H), 4.71−4.76 (m, 1H), 3.99 (s, 3H, OCH_3), 3.04−3.12 (m, 1H), 2.85−2.93 (m, 2H), 2.48−2.56 (m, 2H), 2.30−2.40 (m, 2H), 1.82−1.92 (m, 4H), 1.35−1.70 (m, 8H). Analysis results for ($C_{25}H_{31}N_2O_6Br\cdot 1H_2O$) C, H, N are in Supporting Information.

(*S*)-*N*-(1-(Bicyclo[3.3.1]nonan-9-yl)pyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamide (11). Yield of 63% from **IIa** (three steps); mp 73−75 °C (oxalate); ^{1}H NMR (free amine in $CDCl_3$): δ 8.39 (s, 1H), 8.22−8.25 (dd, 2H), 8.15−8.19 (dd, 1H), 7.66−7.71 (dt, 1H), 7.59−7.65 (dt, 1H), 4.73−4.79 (m, 1H), 3.99 (s, 3H, OCH_3), 3.00−3.10 (m, 1H), 2.85−2.90 (m, 2H), 2.35−2.53 (m, 4H), 1.80−1.90 (m, 4H), 1.13−1.18 (m, 10H). Analysis results for ($C_{27}H_{33}N_2O_6Br\cdot 1/2H_2O$) C, H, N are in Supporting Information.

(*S*)-*N*-(1-(2-Adamantyl)pyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamide (12). Yield of 35% from **IIa** (three steps); mp 77−80 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.44 (s, 1H), 8.29−8.31 (d, 1H, CO−NH), 8.23−8.26 (dd, 1H), 8.17−8.20 (dd, 1H), 7.66−7.71 (dt, 1H), 7.60−7.65 (dt, 1H), 4.68−4.75 (m, 1H), 3.99 (s, 3H, OCH_3), 3.00−3.08 (m, 1H), 2.50−2.60 (m, 2H), 2.15−2.24 (m, 4H), 1.90−2.10 (m, 8H), 1.55−1.65 (m, 4H), 1.45−1.53 (m, 2H). Analysis results for ($C_{28}H_{33}N_2O_6Br\cdot 1.5H_2O$) C, H, N are in Supporting Information.

(*R*)-*N*-(1-Cyclopentylpyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamide (14). Yield of 24% from **IIb** (three steps); mp 88−91 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.40 (s, 1H), 8.22−8.25 (dd, 1H), 8.16−8.19 (dd, 2H), 7.66−7.72 (dt, 1H), 7.60−7.65 (dt, 1H), 4.71−4.76 (m, 1H), 3.99 (s, 3H, OCH_3), 2.96−2.99 (m, 1H), 2.78−2.96 (m, 2H), 2.33−2.55 (m, 4H), 1.70−1.82 (m, 8H). Analysis results for ($C_{23}H_{27}N_2O_6Br\cdot 1H_2O$) C, H, N are in Supporting Information.

(*R*)-*N*-(1-Cyclohexylpyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamide (15). Yield of 50% from **IIb** (three steps); mp 75−78 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.40 (s, 1H), 8.22−8.25 (dd, 2H), 8.16−8.19 (dd, 1H), 7.66−7.72 (dt, 1H), 7.60−7.65 (dt, 1H), 4.64−4.74 (m, 1H), 3.98 (s, 3H, OCH_3), 2.97−3.04 (m, 1H), 2.81−2.83 (m, 2H), 2.37−2.43 (m, 2H), 1.65−1.73 (m, 2H), 1.24−1.31 (m, 10H). Analysis results for ($C_{24}H_{29}N_2O_6Br\cdot 1/2H_2O$) C, H, N are in Supporting Information.

(*R*)-*N*-(1-Cycloheptylpyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamide (16). Yield of 39% from **IIb** (three steps); mp 73−75 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.41 (s, 1H), 8.22−8.25 (dd, 2H), 8.17−8.20 (dd, 1H), 7.66−7.71 (dt, 1H), 7.60−7.66 (dt, 1H), 4.66−4.72 (m, 1H), 3.99 (s, 3H, OCH_3), 2.95−3.03 (m, 1H), 2.79−2.81 (m, 2H), 2.29−2.48 (m, 4H), 1.24−1.84 (m, 12H). Analysis results for ($C_{25}H_{31}N_2O_6Br\cdot 1H_2O$) C, H, N are in Supporting Information.

(*R*)-*N*-(1-(Bicyclo[3.3.1]nonan-9-yl)pyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamide (17). Yield of 30% from **IIb** (three steps); mp 78−80 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.44 (s, 1H), 8.30−8.33 (d, 1H, CO−NH), 8.22−8.26 (dd, 1H), 8.17−8.20 (dd, 1H), 7.66−7.72 (dt, 1H), 7.60−

7.65 (dt, 1H), 4.67−4.74 (m, 1H), 3.99 (s, 3H, OCH_3), 3.00−3.03 (m, 1H), 2.82−2.86 (m, 1H), 2.49−2.55 (m, 1H), 2.20−2.40 (m, 4H), 1.44−2.04 (m, 16H). Analysis results for ($C_{27}H_{33}N_2O_6Br\cdot1.5H_2O$) C, H, N are in Supporting Information.

(*R*)-*N*-(1-(2-Adamantyl)pyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamide (18). Yield of 42% from **IIb** (three steps); mp 86−88 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.44 (s, 1H), 8.29−8.31 (d, 1H, CO−NH), 8.23−8.26 (dd, 1H), 8.17−8.20 (dd, 1H), 7.66−7.72 (dt, 1H), 7.60−7.65 (dt, 1H), 4.67−4.75 (m, 1H), 3.99 (s, 3H, OCH_3), 2.98−3.05 (m, 1H), 2.82−2.86 (m, 1H), 2.50−2.56 (m, 1H), 2.20−2.38 (m, 6H), 1.70−1.90 (m, 10H), 1.45−1.53 (m, 2H). Analysis results for ($C_{28}H_{33}N_2O_6Br\cdot1.5H_2O$) C, H, N are in Supporting Information.

(*S*)-*N*-(1-Cyclobutyl-2-pyrrolidinylmethyl)-4-bromo-1-methoxy-2-naphthamide (20). Yield of 25% from **IIc** (three steps); mp 64−66 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.45 (s, 1H), 8.32−8.40 (b, 1H, CO−NH), 8.23−8.26 (dd, 1H), 8.19−8.22 (dd, 1H), 7.66−7.72 (dt, 1H), 7.60−7.66 (dt, 1H), 4.35 (m, 1H), 4.04 (s, 3H), 4.02 (s, 3H, OCH_3), 1.6−2.8 (m, 16H). Analysis results for ($C_{23}H_{27}N_2O_6Br\cdot2H_2O$) C, H, N are in Supporting Information.

(*S*)-*N*-(1-Cyclopentyl-2-pyrrolidinylmethyl)-4-bromo-1-methoxy-2-naphthamide (21). Yield of 36% from **IIc** (three steps); mp 66−68 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.45 (s, 1H), 8.30−8.42 (b, 1H, CO−NH), 8.22−8.25 (d, 1H), 8.17−8.20 (d, 1H), 7.66−7.71 (dt, 1H), 7.60−7.65 (dt, 1H), 4.00 (s, 3H, OCH_3), 3.70−3.85 (m, 1H), 2.95−3.10 (m, 1H), 2.50−2.65 (m, 2H), 1.60−1.80 (m, 14H). Analysis results for ($C_{24}H_{29}N_2O_6Br\cdot1.5H_2O$) C, H, N are in Supporting Information.

(*S*)-*N*-(1-Cyclohexyl-2-pyrrolidinylmethyl)-4-bromo-1-methoxy-2-naphthamide (22). Yield of 30% from **IIc** (three steps); mp 67−70 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.51−8.53 (b, 1H, CO−NH), 8.46 (s, 1H), 8.18−8.25 (m, 2H), 7.59−7.70 (m, 2H), 4.26−4.34 (m, 1H), 4.01 (s, 3H, OCH_3), 1.10−2.70 (m, 19H). Analysis results for ($C_{25}H_{31}N_2O_6Br\cdot1.5H_2O$) C, H, N are in Supporting Information.

(*S*)-*N*-(1-Cycloheptyl-2-pyrrolidinylmethyl)-4-bromo-1-methoxy-2-naphthamide (23). Yield of 51% from **IIc** (three steps); mp 70−73 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.44 (s, 1H), 8.37−8.55 (b, 1H, CO−NH), 8.22−8.25 (d, 1H), 8.18−8.21 (d, 1H), 7.66−7.71 (dt, 1H), 7.60−7.65 (dt, 1H), 4.33−4.40 (b, 1H), 4.00 (s, 3H, OCH_3), 1.20−2.70 (m, 21H). Analysis results for ($C_{26}H_{33}N_2O_6Br\cdot1.5H_2O$) C, H, N are in Supporting Information.

(*S*)-*N*-(1-(Bicyclo[3.3.1]non-9-yl)-2-pyrrolidinylmethyl)-4-bromo-1-methoxy-2-naphthamide (24). Yield of 21% from **IIc** (three steps); mp 69−71 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.47 (s, 1H), 8.42−8.44 (b, 1H, CO−NH), 8.23−8.26 (d, 1H), 8.18−8.21 (d, 1H), 7.66−7.71 (dt, 1H), 7.60−7.65 (dt, 1H), 4.00 (s, 3H, OCH_3), 3.68−3.90 (m, 1H), 3.00−3.10 (m, 1H), 1.90−2.10 (m, 2H), 1.40−1.80 (m, 18H), 1.20−1.30 (m, 2H). Analysis results for ($C_{28}H_{35}N_2O_6Br\cdot2H_2O$) C, H, N are in Supporting Information.

(*S*)-*N*-(1-(2-Adamantyl)-2-pyrrolidinylmethyl)-4-bromo-1-methoxy-2-naphthamide (25). Yield of 37% from **IIc** (three steps); mp 119−121 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.45 (s, 1H), 8.26−8.32 (b, 1H, CO−NH), 8.23−8.26 (d, 1H), 8.18−8.21 (d, 1H), 7.66−7.71 (dt, 1H), 7.60−7.65 (dt, 1H), 4.00 (s, 3H, OCH_3), 3.77−3.90 (m, 1H), 3.15−3.35 (m, 1H), 1.20−2.20 (m, 22H). Analysis results for ($C_{29}H_{35}N_2O_6Br\cdot2H_2O$) C, H, N are in Supporting Information.

(*R*)-*N*-(1-Cyclobutyl-2-pyrrolidinylmethyl)-4-bromo-1-methoxy-2-naphthamide (27). Yield of 48% from **IId** (three steps); mp 95−97 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.46 (s, 1H), 8.36−8.42 (b, 1H, CO−NH), 8.19−8.26 (m, 2H), 7.62−7.69 (m, 2H), 4.35 (m, 1H), 4.05 (s, 3H), 4.02 (s, 3H, OCH_3), 1.5−3.0 (m, 12). Analysis results for ($C_{23}H_{27}N_2O_6Br\cdot1H_2O$) C, H, N are in Supporting Information.

(*R*)-*N*-(1-Cyclopentyl-2-pyrrolidinylmethyl)-4-bromo-1-methoxy-2-naphthamide (28). Yield of 53% from **IId** (three steps); mp 81−83 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.45 (s, 1H), 8.30−8.40 (b, 1H, CO−NH), 8.17−8.24 (m, 2H), 7.61−7.67 (m, 2H), 4.35 (m, 1H), 4.01 (s, 3H, OCH_3), 1.50−2.50 (m, 17H). Analysis results for ($C_{24}H_{29}N_2O_6Br\cdot2H_2O$) C, H, N are in Supporting Information.

(*R*)-*N*-(1-Cyclohexyl-2-pyrrolidinylmethyl)-4-bromo-1-methoxy-2-naphthamide (29). Yield of 42% from **IId** (three steps); mp 74−76 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): 8.50−8.53 (b, 1H, CO−NH), 8.46 (s, 1H), 8.19−8.25 (m, 2H), 7.62−7.70 (m, 2H), 4.34 (m, 1H), 4.02 (s, 3H, OCH_3), 1.15−2.50 (m, 19H). Analysis results for ($C_{25}H_{31}N_2O_6Br\cdot2H_2O$) C, H, N are in Supporting Information.

(*R*)-*N*-(1-Cycloheptyl-2-pyrrolidinylmethyl)-4-bromo-1-methoxy-2-naphthamide (30). Yield of 63% from **IId** (three steps); mp 83−85 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.53 (b, 1H, CO−NH), 8.46 (s, 1H), 8.19−8.26 (m, 2H), 7.61−7.70 (m, 2H), 4.35 (b, 1H), 4.02 (s, 3H, OCH_3), 1.20−2.30 (m, 21H). Analysis results for ($C_{26}H_{33}N_2O_6Br\cdot2H_2O$) C, H, N are in Supporting Information.

(*R*)-*N*-(1-(2-Adamantyl)-2-pyrrolidinylmethyl)-4-bromo-1-methoxy-2-naphthamide (31). Yield of 51% from **IId** (three steps); mp 126−128 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$): δ 8.44 (s, 1H), 8.29 (b, 1H, CO−NH), 8.19−8.24 (m, 2H), 7.60−7.71 (m, 2H), 4.03 (s, 3H, OCH_3), 3.76−3.88 (m, 1H), 3.17−3.32 (m, 1H), 1.15−2.30 (m, 22H). Analysis results for ($C_{29}H_{35}N_2O_6Br\cdot2H_2O$) C, H, N are in Supporting Information.

In Vitro Dopamine Receptor Binding Studies. Radiolabeled [^{125}I]IABN was prepared using the peracetic acid protocol previously described.[35,36] The tributyltin precursor (50 μg) was combined with 5−10 mCi of [^{125}I]NaI in 300 μL of 500 μM ammonium acetate, pH 4.0. Peracetic acid (50 μL of 0.32% solution in water) was allowed to react for 2 min at room temperature. Sodium metabisulfite (100 μL of 200 μg/mL solution) was added to stop the reaction. After addition of excess saturated sodium bicarbonate, the sample was extracted with ethyl acetate to separate the free [^{125}I]NaI from the radiolabeled product. The organic phase was removed by drying under N_2, and the residue was dissolved in absolute ethanol. The precursor and the labeled product were separated on PRI reverse HPLC column using isocratic conditions with an acetonitrile/ammonium phosphate (4 mM, pH 7.0) solvent system (82:18).[35−36, 37]

Rat dopamine D_2-long and D_3 receptors were expressed in Sf9 cells infected using the appropriate recombinant baculovirus.[36,38] Membrane homogenates were suspended in 50 mM Tris-HCl/150 mM NaCl/1.0 mM EDTA buffer, pH 7.5, and incubated with the radioligand at 37 °C for 60 min in the presence or absence of competing ligands. For competition experiments the radioligand concentration was approximately equal to the K_d value of [^{125}I]IABN and the concentration of the competitive inhibitors ranged over 5 orders of magnitude with two concentrations of inhibitor per decade. Nonspecific binding was defined by the addition of 3 μM (+)-butaclamol. Binding was terminated by the addition of cold wash buffer (10 mM Tris-HCl/150 mM NaCl, pH 7.5 at 4 °C) and rapid filtration over a glass-fiber filter (Schleicher and Schuell No.30). Filters were washed with 10 mL of cold buffer, and the bound radioactivity was measured using a Cobra II Packard γ counter. The protein concentration was determined using a BCA reagent (Pierce) with bovine serum albumin as the protein standard.

Data from dopamine receptor competition experiments were modeled using nonlinear regression analysis to determine the concentration of inhibitor that inhibits 50% of the specific binding of the radioligand (IC_{50} value). IC_{50} values were converted to equilibrium dissociation constants (K_i values) using the Cheng and Prusoff correction.[26] The K_d value used for [^{125}I]IABN at D_2 and D_3 dopamine receptors expressed in Sf9 cells was 0.05 and 0.04 nM, respectively.[36] Nonlinear curve-fitting procedures utilized Jandel Scientific Tablecurve software. All competitive radioligand binding studies were performed with $n \geq 3$, and the K_i values are reported as the mean with ±SEM (standard error of the mean).

In Vitro σ Receptor Binding Studies. Crude synaptosomal (P_2) membrane homogenates were prepared from frozen guinea pig brains without cerebellum.[40,41] Brains were allowed

to thaw slowly on ice before homogenization. Crude P_2 membranes were also prepared from the livers of male Sprague−Dawley rats (300−350 g). The livers were minced before homogenization at 4 °C, using a Potter-Elvehjem tissue grinder. The crude homogenate was centrifuged for 10 min at 1000 *g* and the supernant was kept on ice. The pellet was resuspended in 2 mL/g tissue weight of ice-cold 10 mM Tris-HCl/0.32 M sucrose, pH 7.4. After centrifuging at 1000 *g* for 10 min, the supernatants were combined and centrifuged at 31 000 *g* for 15 min. The pellet was resuspended in 3 mL/g 10 mM Tris-HCl, pH 7.4, and the suspension was allowed to incubate at 25 °C for 15 min. Following centrifugation at 31 000 *g* for 15 min, the aliquots were stored at −80 °C until used. The protein concentration of the suspension was determined using the method of Bradford protocol.[42]

For σ_1 receptor binding studies guinea pig brain membrane homogenates (100 μg of protein) were incubated with 3 nM [^{3}H](+)-pentazocine (31.6 Ci/mmol) in 50 mM Tris-HCl (pH 8.0) at 25 °C for either 120 or 240 min. Test compounds were dissolved in ethanol and then diluted in buffer for a total incubation volume of 0.5 mL. Test compounds were added in concentrations ranging from 0.005 to 1000 nM. Assays were terminated by the addition of ice-cold 10 mM Tris-HCl (pH 8.0) followed by rapid filtration through Whatman GF/B glass-fiber filters (presoaked in 0.5% polyethylenimine) using a Brandel cell harvester (Gaithersburg, MD). Filters were washed twice with 5 mL of ice cold buffer. Nonspecific binding was determined in the presence of 10 μM (+)-pentazocine. Liquid scintillation counting was carried out in EcoLite(+) (ICN Radiochemicals; Costa Mesa, CA) using a Beckman LS 6000IC spectrometer with a counting efficiency of 50%.

For σ_1 receptor binding studies rat liver membrane homogenates (35 μg of protein) were incubated with 3 nM [^{3}H]DTG (38.3 Ci/mmol) in the presence of 100 nM (+)-pentazocine to block σ_1 receptor binding sites. Incubations were carried out in 50 mM Tris-HCl (pH 8.0) for 120 min at 25 °C in a total incubation volume of 0.5 mL. Test compounds were added in concentrations ranging from 0.005 to 1000 nM. Assays were terminated by the addition of ice-cold 10 mM Tris-HCl (pH 8.0) followed by rapid filtration through Whatman GF/B glass-fiber filters (presoaked in 0.5% polyethylenimine) using a Brandel cell harvester (Gaithersburg, MD). Filters were washed twice with 5 mL of ice-cold buffer. Nonspecific binding was determined in the presence of 5 μM DTG. Liquid scintillation counting was carried out in EcoLite(+) (ICN Radiochemicals, Costa Mesa, CA) using a Beckman LS 6000IC spectrometer with a counting efficiency of 50%.

The IC_{50} values at σ sites were determined for $n \geq 3$ from nonlinear regression analysis of binding data. K_i values were calculated using the method of Cheng and Prusoff [26] and reported as mean values with ±SEM. The K_d value used for [^{3}H]DTG in rat liver was 17.9 nM and was 4.8 nM for [^{3}H]-(+)-pentazocine in guinea pig brain.[27,40]

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Supporting Information Available: Table listing results from elemental analyses of compounds **1**−**33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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