Synthesis and SAR of Adatanserin: Novel Adamantyl Aryl- and Heteroarylpiperazines with Dual Serotonin 5-HT_{1A} and 5-HT_2 Activity as Potential Anxiolytic and Antidepressant Agents

Magid A. Abou-Gharbia,* Wayne E. Childers, Jr., Horace Fletcher, Georgia McGaughey, Usha Patel, Michael B. Webb, John Yardley, Terrance Andree, Carl Boast, Robert J. Kucharik, Jr., Karen Marquis, Herman Morris, Rosemary Scerni, and John A. Moyer

Chemical Sciences and CNS Disorders, Wyeth-Ayerst Research, CN 8000, Princeton, New Jersey 08543-8000

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Several novel functionalized adamantyl aryl- and heteroarylpiperazine derivatives were prepared and examined in various receptor binding and behavioral tests to determine their serotonin receptor activities. Many compounds demonstrated modest to high affinity for 5-HT_{1A} receptors, with compounds **9**, **13**, **23**, **33**, **34**, and **43** being the most potent at this site. Compound **1**, 2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl adamantyl-1-carboxylate, demonstrated relatively high affinity for 5-HT_{1A} receptors (K_i = 8 nM) and acceptable selectivity versus D_2 receptors (K_i = 708 mM); however, it lacked in vivo activity in serotonergic behavioral models. In contrast, compounds **9** (WY-50,324, SEB-324, adatanserin), adamantyl-1-carboxylic acid 2-[4-(2-pyrimidinyl)-1-piperazinyl]ethylamide, and **13**, adamantyl-1-carboxylic acid 2-[4-(2-methoxyphenyl)-1-piperazinyl]ethylamide, demonstrated high affinity for 5-HT_{1A} binding sites (K_i = 1 nM for both) and moderate affinity for 5-HT_2 receptors (K_i = 73 and 75 nM, respectively). Both compounds also demonstrated partial 5-HT_{1A} agonist activity in vivo in rat serotonin syndrome and 5-HT_2 antagonist activity in quipazine- and DOI-induced head shake paradigms. The selective 5-HT_{1A} partial agonist and 5-HT_2 antagonist activity of **9** was accompanied by significant anxiolytic activity in an animal conflict model. On the basis of this profile, compound **9** entered development as a combined anxiolytic and antidepressant agent.

Introduction

Considerable advances have occurred during the past decade in the pharmacological treatment of anxiety and depression. The introduction of buspirone in the mid-1980s represented the first challenge in over 30 years to the anxiolytic monopoly held by the benzodiazepines and introduced the age of the azaspirones. The disclosure of several non-benzodiazepine azaspirone-derived arylpiperazine serotonergic agents, acting primarily on the 5-HT_{1A} receptor subtype, soon followed,[1] including gepirone, ipsapirone, tandospirone, and flesinoxan (Figure 1). Our interest in this area led to the discovery of zalospirone (Figure 1), a 5-HT_{1A} partial agonist which down-regulates 5-HT_2 receptors upon chronic administration,[2,3] and the 5-HT_{1A} full agonist WY-48723 (Figure 1).[3,4] Zalospirone entered clinical trials for the treatment of anxiety.[5]

Similarly, the treatment of depression was revolutionized by the marketing of the serotonin selective reuptake inhibitors (SSRIs) fluoxetine and fluvoxamine in the mid to late 1980s, and this was quickly followed by a series of SSRIs, including paroxetine and sertroline. Another therapeutic approach focused on the identification and development of a novel class of selective serotonin and norepinephrine reuptake inhibitors (SNRIs),[6] which resulted in the marketing of venlafaxine (Effexor) in 1994.[7]

Despite these advances, unmet medical needs still exist for the treatment of anxiety and depression.

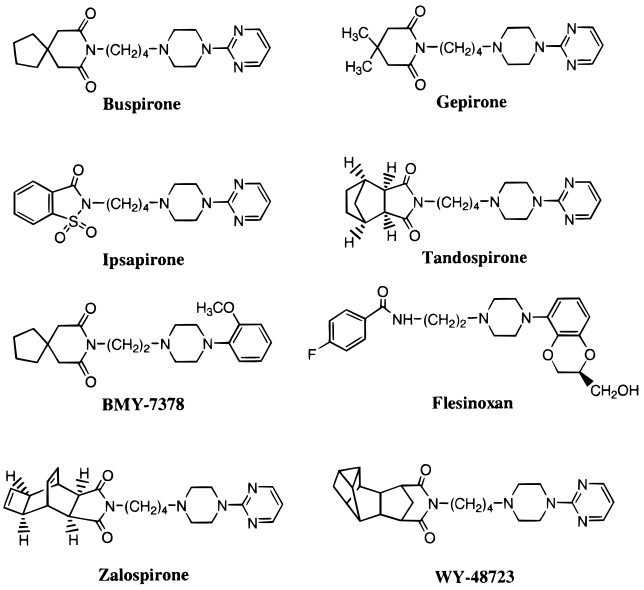

Figure 1. 5-HT_{1A} agonists and partial agonists possessing the azaspirone pharmacophore.

Among the deficiencies of current drugs are slow onset of action, lack of efficacy in refractory patients, and presence of unwanted gastrointestinal and sexual side effects. In addition, although anxiety and depression are considered to be separate neuropsychiatric diseases, there is considerable overlap among the clinical symptoms of these disorders and differential diagnosis is often difficult.[8] Anxiety frequently coexists with depression or may precede the development of depressive

* To whom correspondence should be addressed. Phone: (732) 274-4522. Fax: (732) 274-4500. E-mail: Abougam@war.wyeth.com.

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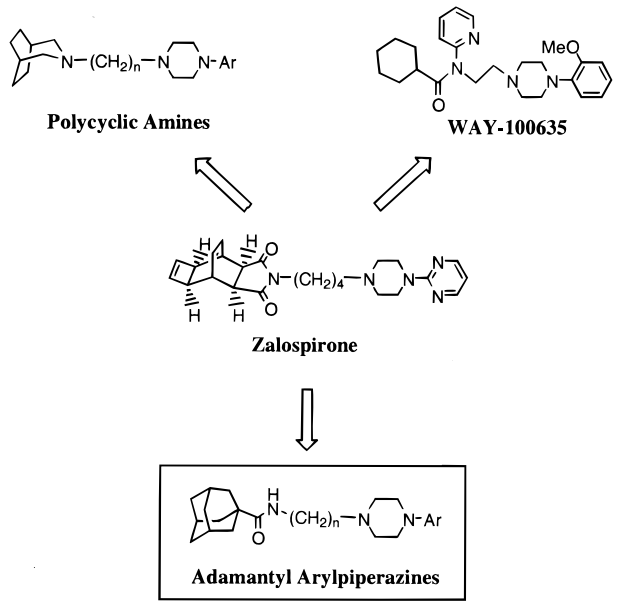


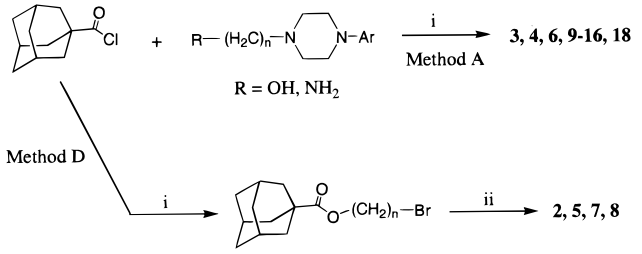
Figure 2. Evolution of 5-HT_{1A} partial agonists from zalospirone.

symptoms,[9] and anxiety and depression may be biochemically associated since there are many similarities in the neurological substrates thought to play a role in these diseases,[10−12] including a recent report describing a polymorphism in the serotonin transporter gene associated with both anxiety- and depression-related personality traits.[13] In addition, anxiolytic agents may have utility in treating depression,[14] and there is emerging clinical evidence that antidepressants may be effective in treating generalized anxiety disorder.[15]

Taking these similarities into account, it should be possible to identify and develop therapeutic agents with combined anxiolytic and antidepressant activity. Drug discovery efforts in this area have focused on agents with serotonergic activity, because of considerable research indicating their potential for anxiolytic[16] and antidepressant[3,17] activity. In particular, the focus of these efforts has been on combining 5-HT_{1A} and 5-HT_2 serotonin receptor activities which has led to the identification and characterization of WY-50,324 (SEB-324, adatanserin, **9**),[18] CGS 18102 A,[19] S14761,[20] FG 5893,[21] LEK 8804,[22] and BIM-17 (flibanserin).[23] While the previous agents are generally agonists or partial agonists at the 5-HT_{1A} receptor and antagonists at the 5-$HT_{2A/C}$ receptor, a recent publication discloses selective 5-HT_{1A} and 5-HT_{2A} antagonists with potential anxiolytic activity.[24]

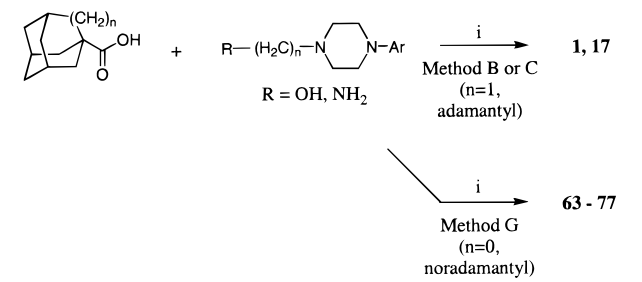
Our approach to this end included structural modification of the imide functionality in zalospirone to generate novel agents with multireceptor activity. It was postulated that these agents would possess either 5-HT uptake inhibition or 5-HT_2 antagonist activity in addition to their original 5-HT_{1A} activity, a profile which predicts combined clinical anxiolytic and antidepressant activity.[16a] This investigation led to the synthesis of several interesting series of compounds (Figure 2). Reduction of both imide carbonyl moieties resulted in polycyclic amines which possess 5-HT_{1A} activity as well as 5-HT uptake inhibitory property activity but lack in vivo activity in serotonergic behavioral models. These compounds will be the subject of another paper. Removal of one carbonyl group produced another series of adamantyl aryl- and heteroarylpiperazines. Previous work from our laboratories had demonstrated that the incorporation of a tertiary center next to an amide carbonyl could produce compounds with a favorable 5-HT_{1A}/D_2 profile.[25] This idea was further extended to the NAN-190 series by Glennon et al.,[26] although the greatest effect of this structural alteration was seen in the 5-HT_{1A}/adrenergic α_1 selectivity. Still, the concept of combining the tertiary center of the adamantyl group with an imide bioisostere lent itself as a potential means of producing high-affinity 5-HT_{1A} ligands which might possess selectivity versus D_2.[27] The resulting analogues demonstrated 5-HT_{1A} partial agonist and 5-HT_2 antagonist activities and also possessed in vivo activity in various serotonergic paradigms. This concept was subjected to extensive studies to fully explore the role of the amide functionality and its surrounding environment. These studies led to the discovery of novel 5-HT_{1A} antagonists such as WAY-100635,[28] which is currently widely used by many investigators as a standard silent 5-HT_{1A} antagonist. The design and synthesis of these selective 5-HT_{1A} antagonists will also be the subject of future publications. The present investigation describes the synthesis, receptor binding profile, and behavioral activity of our series of functionalized adamantyl aryl- and heteroarylpiperazines, as well as the structure−activity relationships (SARs) within this series which led to the discovery of adatanserin (**9**), a compound selected for development as an agent with mixed anxiolytic and antidepressant activities.

Scheme 1[a]



[a] Reagents and conditions: method A − (i) Et_3N (3 equiv); method D − (i) $HO(CH_2)_nBr$, Et_3N; (ii) appropriate arylpiperazine, Et_3N.

Scheme 2[a]

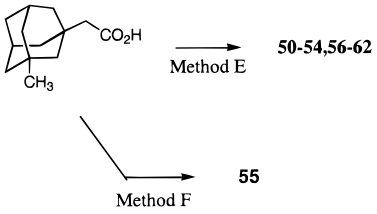


[a] Reagents and conditions: method B − (i) $(EtO)_2P(O)CN$, Et_3N; method C − (i) DCC, DMAP; method G − (i) carbonyldiimidazole.

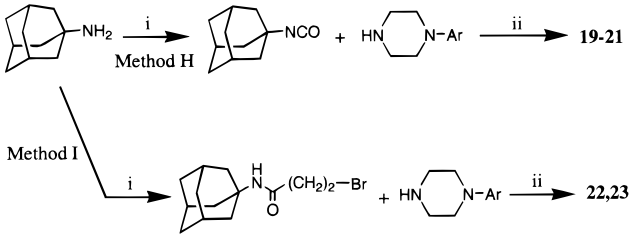
Chemistry

A variety of synthetic methods was used to prepare the arylpiperazinyl alkyl amides, esters, and ureas listed in Table 1, as illustrated in Schemes 1−8. The required intermediate amino- and hydroxyalkyl arylpiperazines were prepared using procedures previously

Scheme 3

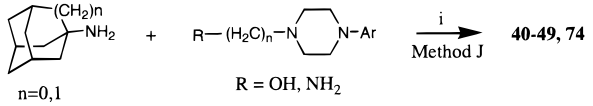


Scheme 4[a]



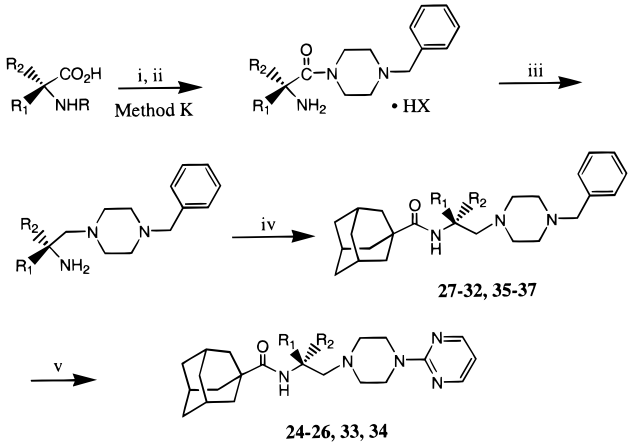
[a] Reagents and conditions: method H − (i) ref 29; (ii) Et_3N; method I − (i) 3-bromopropionyl chloride, Et_3N; (ii) $(i\text{-}Pr)_2NEt$.

Scheme 5[a]



[a] Reagents and conditions: method J − (i) trichloromethyl chloroformate, Et_3N.

Scheme 6[a]



[a] Reagents and conditions: method K − R = BOC for **25**−**27**, **29**, **30**, and **33**−**37**, R = Cbz for **24** and **28**; (i) $(EtO)_2P(O)CN$, *N*-methylmorpholine, HCl/EtOAc for R = BOC, 30% aq HBr for R = Cbz; (iii) BH_3/THF, Δ; (iv) adamantane-1-carboxylic acid, $(EtO)_2P(O)CN$, *N*-methylmorpholine; (v) H_2, Pd/C; (vi) 2-chloropyrimidine, K_2CO_3, Et_3N.

described in the literature. In general, hydroxyalkyl arylpiperazines were synthesized by treating commercially available arylpiperazines with 2-bromoethanol or 3-bromopropanol under basic catalysis. The desired aminoalkyl arylpiperazines were obtained by reacting arylpiperazines with bromoacetonitrile or bromopropionitrile followed by catalytic reduction of the nitrile grouping to the primary amine.

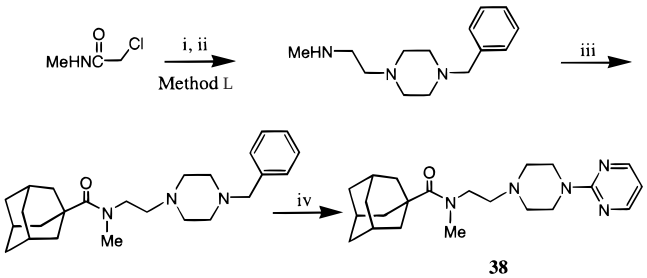
Three methods were used to synthesize the adamantyl esters and amides. Compounds **3**, **4**, **6**, **9**−**16**, and **18** were prepared by condensing 1-adamantanecarboxylic acid chloride with the appropriate amino- or hydroxyalkyl arylpiperazine in the presence of triethylamine (method A, Scheme 1). Coupling of 1-adamantanecarboxylic acid with [4-(2-pyrimidinyl)-1-piperazinyl]-ethanol in the presence of diethyl cyanophosphonate yielded **1** (method B, Scheme 2). A similar procedure employing dicyclohexylcarbodiimide/dimethylaminopyridine was applied to the synthesis of compound **17** (method C, Scheme 2). Esters **2**, **5**, **7**, and **8** were prepared in a two-step sequence (method D, Scheme 1) involving initial condensation of adamantanecarboxylic acid chloride with either 2-bromoethanol or 3-bromopropanol followed by treatment with the appropriate 4-arylpiperazine to give the desired product.

Using procedures which were identical to those employed in methods A and D (Scheme 3), the 3-methyl-1-adamantaneacetic acid analogues **50**−**54** and **56**−**62** were synthesized from 3-methyl-1-adamantaneacetic acid via its acid chloride (method E), and compound **55** was prepared using a two-step sequence (method F). The noradamantyl esters and amides **63**−**73** were prepared in good yield from noradamantane-1-carboxylic acid and the appropriate amino- or hydroxyalkyl arylpiperazine in dry chloroform using carbonyldiimidazole to effect the coupling (method G, Scheme 2).

Two synthetic sequences were used to prepare the reversed adamantyl amides. Compounds **19**−**21**, which lack an alkyl spacer chain between the amide and piperazine moieties, were synthesized by condensing adamantane-1-isocyanate[29] with the appropriate 4-arylpiperazine in the presence of triethylamine (method H, Scheme 4). A two-step method was employed to obtain the alkyl-containing analogues **22** and **23** (method I, Scheme 4). Condensation of 1-adamantanamine with 3-bromopropionyl chloride in the presence of triethylamine yielded the intermediate 3-bromopropylamide, which was subsequently treated with the appropriate 4-arylpiperazine in the presence of Hunig's base to give the desired product.

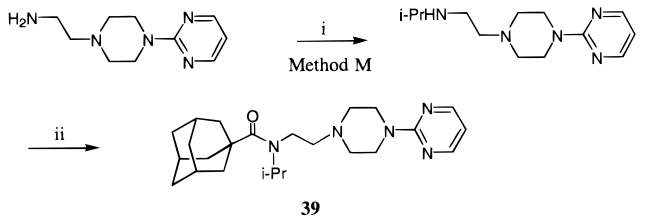
The required adamantyl and noradamantyl ureas **40**−**49** and **74** were obtained by condensing 1-adaman-

Scheme 7[a]



[a] Reagents and conditions: method L − (i) *N*-benzylpiperazine; (ii) $LiAlH_4$; (iii) adamantane-1-carboxylic acid chloride, Et_3N; (iv) H_2, Rh/Al_2O_3; (v) 2-chloropyrimidine, Na_2CO_3, Cs_2CO_3.

Scheme 8[a]



[a] Reagents and conditions: method M − (i) acetone, sodium cyanoborohydride; (ii) adamantane-1-carboxylic acid chloride, Et_3N.

tanamine or 1-noradamantanamine with the appropriate aminoalkyl arylpiperazine in the presence of trichloromethyl chlorofomate (method J, Scheme 5).

To examine the steric effects surrounding the amide moiety, analogues possessing branching on the α-carbon were prepared. Both enantiomers of compounds possessing a single substituent on the alkyl chain next to the amide nitrogen were stereospecifically synthesized (method K, Scheme 6) starting with enantiomerically pure alanine or phenylalanine which was protected as the *tert*-butoxycarbonyl derivative (BOC). Because of the lability of the pyrimidinyl group to borane, it was necessary to carry out the initial steps of the synthetic sequence on the *N*-benzylpiperazine derivatives and then insert the pyrimidinyl group in the last step of the synthesis. However, other arylpiperazines were stable to borane and could be introduced early in the synthetic sequence and carried through the reduction step.

Coupling of D-alanine-*N*-*tert*-butoxycarboxamide with *N*-benzylpiperazine in the presence of diethyl cyanophosphonate followed by deprotection with hydrochloric acid yielded the desired intermediate (*R*)-aminoamide as its hydrochloride salt. Reduction of the amide was accomplished using borane/THF followed by coupling with 1-adamantanecarboxylic acid to yield the benzylpiperazine derivative **29**. An identical sequence was applied to the synthesis of the (*S*)-enantiomer **30** from L-alanine-*tert*-butoxycarboxamide and to the preparation of compounds **35** and **36** beginning with D- and L-phenylalanine-*tert*-butoxycarboxamide, respectively. Each of these compounds, in turn, was subjected to catalytic hydrogenation to remove the benzyl group and was then treated with 2-chloropyrimidine under basic catalysis to yield the pyrimidyl analogues **25**, **26**, **33**, and **34**. The dimethyl derivatives **24** and **28** were also prepared using a similar sequence starting from 2-methylalanine protected as the benzylcarbamate (Cbz). Removal of the benzylcarbamate was accomplished using 30% aqueous hydrobromic acid. This general synthetic sequence was also applied to the synthesis of the benzyloxy analogue **37** starting with D-*O*-benzylserine-*N*-*tert*-butoxycarboxamide and *N*-benzylpiperazine (Scheme 6).

Compounds **27**, **31**, and **32**, which possessed aryl groups which were stable to borane, could be synthesized in a more direct application of the sequence. Coupling of the intact arylpiperazine to the appropriate BOC-protected alanine followed by removal of the protecting group, reduction of the tertiary amide, and coupling with 1-adamantanecarboxylic acid yielded the desired compounds in four steps.

Analogues which exemplified substitution on the amide nitrogen were also prepared. Compound **38**, an *N*-methyl amide, was synthesized in five steps (method L, Scheme 7). The corresponding *N*-isopropyl analogue **39** was synthesized in a much shorter sequence (method M, Scheme 8) using reductive amination conditions to introduce the isopropyl group.

Biochemistry and Pharmacology

The 5-HT_{1A} affinity values of compounds **1**−**74** were determined from their ability to displace [^{3}H]8-OH-DPAT from its recognition sites in rat hippocampus. The D_2 affinity was measured in rat limbic tissue using [^{3}H]-spiperone (30 nM ketanserin was present to exclude 5-HT_2 binding), and 5-HT_2 affinity was assessed in rat brain cortex tissue using [^{3}H]ketanserin. Results are reported either as K_i values or as percent displacement at the reported concentration. The 5-HT_{1A} functional activity was determined by examining the ability of the test compounds to induce the serotonin syndrome and/or antagonize agonist-induced serotonin syndrome in the rat, while 5-HT_2 antagonist activity was assessed using the rat quipazine- and DOI-induced head shake paradigms. Anxiolytic activity of lead compounds was assessed in a rat Geller−Seifter conflict model.

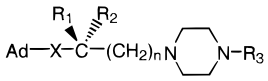
Results and Discussions

In Vitro Studies. The affinity of compounds **1**−**74** for central 5-HT_{1A} and D_2 receptors is shown in Tables 1−3. For derivatives with notable 5-HT_{1A} affinity and acceptable selectivity with respect to D_2 activity, we also evaluated the affinity for 5-HT_2. Several of the compounds in this series displayed affinity for the 5-HT_{1A} receptor which was equivalent or superior to that seen for buspirone (K_i = 10 nM). Most notable among these were compounds **9**, **10**, **11, 13**, and **34** with K_i values of 1 nM (Table 1) and the potent analogues **27**, **33**, **36**, **68**, and **69**, all of which displayed subnanomolar K_i values. Variations were made to five regions of the basic azaspirone pharmacophore, namely the imide, the lipophilic area associated with the imide, the steric zone surrounding the imide, the distance between the imide and basic nitrogen (i.e., the spacer chain), and the aryl group associated with the piperazine.

Arylpiperazine Variants. The results shown in Tables 1−3 lead to several conclusions regarding the SARs of these compounds. By holding the adamantyl amide moiety constant and varying the arylpiperazine group, it was possible to study the effect of the arylpiperazine moiety on 5-HT_{1A} affinity. The presence of either a 2-pyrimidinylpiperazine or a 2-methoxyphenylpiperazine group generally enhanced 5-HT_{1A} affinity, especially when combined with the amide functionality. The 2-methoxyphenylpiperazine moiety was better tolerated within the 5-HT_{1A} receptor than the 2-pyrimidinylpiperazine group, especially when the distance between the adamantyl amide and the piperazine was lengthened, as evidenced by the decrease in affinity seen in the 2-pyrimidinylpiperazine analogue **12** (K_i = 89 nM) compared to the K_i value of 1 nM for the analogous 2-methoxyphenylpiperazine derivative **13**. The 3-chlorophenylpiperazine group was also well-tolerated when the 2-carbon spacer was present (compound **11**) but tended to suffer some loss in affinity when combined with a 3-carbon spacer (e.g., analogue **14**). Relocating the chlorine to the 4-position of the aryl moiety also resulted in a decrease in 5-HT_{1A} affinity (as seen with compound **18**) as did the incorporation of the 2,3-dimethylphenyl group (derivatives **31** and **32**). Likewise, 5-HT_{1A} affinity was decreased when the arylpiperazine was extended to a benzylpiperazine (compound **17**) and lost altogether with the addition of another aryl group (analogue **8**). These results are in agreement with the literature.[30]

Imide Bioisosteres. While the role of the arylpiperazine in 5-HT_{1A} affinity has been the subject of numerous studies and theoretical pharmacophore mod-

Table 1. Adamantyl Aryl- and Heteroarylpiperazinyl Derivatives



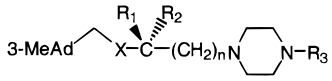
compd	X	R^1	R^2	*n*	R^3	mp, °C	formula[a]	method	affinities: K_i, nM (95% CI)[b] or % inhibn at 1 μM: 5-HT_{1A}[c]	D_2[d]
buspirone									10 (6−15)	119 (98−144)
ritanserin[e]									830	12
1	COO	H	H	1	2-pyrimidinyl	232−35	$C_{21}H_{30}N_4O_2$·2HCl[f]	B	8.5 (7−10.5)	708 (508−944)
2	COO	H	H	1	2-MeOPh	214−16	$C_{24}H_{34}N_2O_3$·2HCl	D	2.5 (1.98−3.14)	13.5 (11.5−15.5)
3	COO	H	H	2	2-pyrimidinyl	209−11	$C_{22}H_{32}N_4O_2$·2HCl[g]	A	72%	33%
4	COO	H	H	2	2-MeOPh	212−13	$C_{25}H_{36}N_2O_3$·2HCl	A	8.5 (7.5−10)	35 (29.5−42)
5	COO	H	H	2	3-ClPh	220−22	$C_{24}H_{33}N_2O_2Cl$·2HCl	D	80%	67%
6	COO	H	H	2	3-CF_3Ph	233−34	$C_{25}H_{33}N_2O_2$·HCl	A	75%	54%
7	COO	H	H	2	CH_2Ph	263−65	$C_{25}H_{36}N_2O_2$·2HCl[f]	D	63%	
8	COO	H	H	1	CH(4-FPh)$_2$	222−24	$C_{31}H_{38}N_4O_2F_2$·2HCl[f]	D	4%	
9	CONH	H	H	1	2-pyrimidinyl	235−38	$C_{21}H_{31}N_5O$·2HCl[f]	A	1 (0.5−1.5)	166 (118−212)
10	CONH	H	H	1	2-MeOPh	219−21	$C_{24}H_{35}N_3O_2$·2HCl	A	1 (0.55−1.5)	24 (20−29.5)
11	CONH	H	H	1	3-ClPh	213−14	$C_{23}H_{32}N_3OCl$·2HCl[h]	A	0.89 (0.72−1.08)	129 (79−213)
12	CONH	H	H	2	2-pyrimidinyl	140−48	$C_{22}H_{33}N_5O$·HCl[f]	A	89 (73−104)	6%
13	CONH	H	H	2	2-MeOPh	186−92	$C_{25}H_{37}N_3O_2$·HCl[g]	A	1 (0.7−1.4)	200 (175−227)
14	CONH	H	H	2	3-ClPh	209−10	$C_{24}H_{34}N_3OCl$·2HCl[i]	A	19 (16−24)	32%
15	COO	H	H	2	6-Cl-2-pyrazinyl	252−53	$C_{22}H_{31}N_4O_2$ Cl·2HCl[j,k]	A	5%[l]	
16	CO			0	2-pyrimidinyl	175−78	$C_{19}H_{26}N_4O$·HCl	A	9%	
17	CONH	H	H	1	CH_2Ph	259−60	$C_{24}H_{35}N_3O$·2HCl	C	46 (39−54)	8%
18	CONH	H	H	1	4-ClPh	108−09	$C_{24}H_{34}N_3OCl$	A	96 (76−122)	
19	NHCO			0	2-pyrimidinyl	174−75	$C_{19}H_{27}N_5O$	H	3%	
20	NHCO			0	2-MeOPh	179−80	$C_{22}H_{31}N_3O_2$	H	0%	
21	NHCO			0	3-ClPh	131−32	$C_{21}H_{28}N_3OCl$	H	0%	
22	NHCO	H	H	1	2-pyrimidinyl	273−75	$C_{21}H_{31}N_5O$·3HCl	I	131 (113−150)	14%
23	NHCO	H	H	1	2-MeOPh	232−34	$C_{24}H_{35}N_3O_2$·2HCl	I	9 (7−13)	93 (76−114)
24	CONH	CH_3	CH_3	1	2-pyrimidinyl	153−55	$C_{23}H_{35}N_5O$	K	127 (95−161)	
25	CONH	H	CH_3	1	2-pyrimidinyl	168−69	$C_{22}H_{33}N_5O$	K	1.1 (0.95−1.39)	153 (121−192)
26	CONH	CH_3	H	1	2-pyrimidinyl	162−64	$C_{22}H_{33}N_5O$	K	21%	1%
27	CONH	H	CH_3	1	2-MeOPh	194−98	$C_{25}H_{37}N_3O_2$·2HCl	L	0.22 (0.18−0.28)	21.5 (17.5−26)
28	CONH	CH_3	CH_3	1	CH_2Ph	256−58	$C_{26}H_{39}N_3O$·2HCl[g]	K	0%	
29	CONH	H	CH_3	1	CH_2Ph	240−42	$C_{25}H_{37}N_3O$·2HCl[j]	K	37 (31−44)	14%
30	CONH	CH_3	H	1	CH_2Ph	236−38	$C_{25}H_{37}N_3O^m$·2HCl[j,m]	K	0%[l]	
31	CONH	H	CH_3	1	2,3$(CH_3)_2$Ph	229−30	$C_{26}H_{39}N_3O$·2HCl[f,n]	L	0%[l]	
32	CONH	CH_3	H	1	2,3$(CH_3)_2$Ph	226−28	$C_{26}H_{36}N_2O_3$·2HCl	L	0%[l]	
33	CONH	H	CH_2Ph	1	2-pyrimidinyl	172−75	$C_{28}H_{37}N_5O$[g]	K	0.43 (0.36−0.5)	20 (16.5−24)
34	CONH	CH_2Ph	H	1	2-pyrimidinyl	172−75	$C_{28}H_{37}N_5O$	K	1 (0.95−1.25)	1693 (1261−2277)
35	CONH	H	CH_2Ph	1	CH_2Ph	261−63	$C_{31}H_{41}N_3O$·2HCl[o]	K	2.3 (1.91−2.66)	1402 (1040−1891)
36	CONH	CH_2Ph	H	1	CH_2Ph	263−66	$C_{31}H_{41}N_3O$·2HCl[o]	K	0.7 (0.63−0.85)	3394 (2128−5422)
37	CONH	H	CH_2OBz	1	CH_2Ph	140−42	$C_{32}H_{43}N_3O_2$·2HCl[o]	K	62 (52−62.5)	76 (41−140)
38	CONMe	H	H	1	2-pyrimidinyl	214−23	$C_{22}H_{33}N_5O$·2HCl[g]	M	60 (59−71)	
39	CONiPr	H	H	1	2-pyrimidinyl	194−210	$C_{24}H_{37}N_5O$·2HCl[j]	N	36%	
40	NHCONH	H	H	1	2-pyrimidinyl	170−71	$C_{21}H_{32}N_6O$[g,p]	J	77 (64−92)	72%
41	NHCONH	H	H	1	2-MeOPh	108−10	$C_{24}H_{36}N_4O_2$f	J	9 (7.5−11)	94%
42	NHCONH	H	H	1	3-ClPh	136−37	$C_{23}H_{33}N_4OCl$	J	61 (51−72)	56%
43	NHCONH	H	H	2	2-pyrimidinyl	172−73	$C_{25}H_{37}N_3O$·2HCl[j]	J	7 (4.5−10)	>10000
44	NHCONH	H	H	2	2-MeOPh	182−83	$C_{25}H_{37}N_3O$·2HCl[j,n]	J	1 (0.45−1.1)	176 (132−233)
45	NHCONH	H	H	2	3-ClPh	175−76	$C_{26}H_{39}N_3O$·2HCl[f,n]	J	45 (41−49)	38%
46	NHCONH	H	H	1	CH(4-ClPh)$_2$	212−13	$C_{26}H_{36}N_2O_3$·2HCl	J	9%[l]	
47	NHCOO	H	H	1	2-pyrimidinyl	245	$C_{28}H_{37}N_5O$[g,q]	J	34%[l]	
48	NHCOO	H	H	1	2-MeOPh	215−17	$C_{28}H_{37}N_5O$	J	40 (36−45)	95%
49	NHCOO	H	H	1	3-ClPh	198−200	$C_{31}H_{41}N_3O$·2HCl	J	76 (66−86)	36%

[a] All compounds had elemental analyses (C,H,N) within ±0.4% of the theoretical values. [b] 95% CI indicates values for 95% confidence interval. Data are the result of duplicate assays. [c] Rat hippocampal tissue. [d] Rat limbic tissue. [e] Data from ref 31d. [f] Hydrate. [g] Hemihydrate. [h] 3/4Hydrate. [i] N: calcd, 8.14; found, 7.69. [j] Sesquihydrate. [k] C: calcd, 58.17; found, 58.70. [l] @0.1 μM. [m] N: calcd, 8.12; found, 7.57. [n] Hemi-2-propanol. [o] Dihydrate. [p] C: calcd, 64.10; found, 64.52. [q] C: calcd, 49.17; found, 48.72.

els,[31] the contributions of the azaspirone group are less well-understood. Reports in the literature[32] demonstrate that an azaspirone group is not necessary for high 5-HT_{1A} affinity. However, studies by the group of Mokrosz[33] also support the notion that the electron density distribution within the amide group as well as the arrangement of those bonds can enhance the 5-HT_{1A} affinity of some azaspirone compounds, thus suggesting the possibility of multiple binding modes.

Early hints from the patent literature indicated that ring-opened bioisosteres could serve as feasible replacements for the imide moiety.[34] Therefore, the effect of altering the amide group in our series was probed in detail. The ester, amide, and urea moieties all proved to be adequate substitutions for the azaspirone group. However, the amide moiety was optimal for 5-HT_{1A} affinity within all three series of compounds (adamantyl, 3-methyladamantyl, and noradamantyl), giving analogues with greater affinity than those with the corresponding esters (compare, for example, amides **9**, **67**, and **68** with esters **1**, **63**, and **64**). Reversing the order of the carbonyl and nitrogen components of the amide to give reversed amides decreased 5-HT_{1A} affinity, as can be seen in analogues **19**−**23**, although it was again

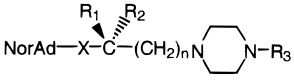
Table 2. 3-Methyladamantyl Aryl- and Heteroarylpiperazinyl Derivatives



compd	X	R^1	R^2	*n*	R^3	mp, °C	formula[a]	method	affinities: K_i, nM (95% CI)[b] or % inhibn at 1 μM: 5-HT_{1A}[c]	affinities: K_i, nM (95% CI)[b] or % inhibn at 1 μM: D_2[d]
50	COO	H	H	1	2-pyrimidinyl	202−07	$C_{23}H_{34}N_4O_2 \cdot 2HCl$[e]	E	72%	39%
51	COO	H	H	1	2-MeOPh	199−206	$C_{25}H_{38}N_2O_2Cl$[h]$\cdot HCl$[f]	E	86%	97%
52	COO	H	H	1	3-ClPh	176−78	$C_{25}H_{35}N_2O_2 \cdot 2HCl$[g]	E	34%	19%
53	COO	H	H	1	3-CF_3Ph	159−63	$C_{26}H_{35}N_2O_2F_3 \cdot HCl$	E	35%	29%
54	COO	H	H	2	2-MeOPh	203−06	$C_{28}H_{40}N_2O_3 \cdot 2HCl$	E	17 (14−20)	95%
55	COO	H	H	2	3-ClPh	182−84	$C_{26}H_{37}N_2O_2Cl \cdot 2HCl$	F	58%	
56	COO	H	H	2	3-CF_3Ph	177−80	$C_{27}H_{37}N_2O_2F_3 \cdot HCl$	E	56%	
57	CONH	H	H	1	2-pyrimidinyl	251−53	$C_{23}H_{35}N_5O \cdot 2HCl$[f]	E	30 (34−39.5)	27%
58	CONH	H	H	1	2-MeOPh	197−99	$C_{26}H_{39}N_3O_2 \cdot 2HCl$	E	11 (9.5−13)	70%
59	CONH	H	H	1	3-ClPh	182−85	$C_{25}H_{36}N_3OCl \cdot 2HCl$[h]	E	38 (32−40)	40%
60	CONH	H	H	2	2-pyrimidinyl	188−90	$C_{24}H_{37}N_5O \cdot 2HCl$[i]	E	68%	20%
61	CONH	H	H	2	2-MeOPh	210−18	$C_{27}H_{41}N_3O_2 \cdot 2HCl$	E	4.4 (3.3−6)	79%
62	CONH	H	H	2	3-ClPh	200−02	$C_{26}H_{38}N_3OCl \cdot 2HCl$	E	81%	41%

[a] All compounds had elemental analyses (C,H,N) within ±0.4% of the theoretical values. [b] 95% CI indicates values for 95% confidence interval. Data are the result of duplicate assays. [c] Rat hippocampal tissue. [d] Rat limbic tissue. [e] Hydrate. [f] Hemihydrate. [g] H: calcd, 7.96; found 7.49. [h] 2 1/2Hydrate. [i] Sesquihydrate.

Table 3. Noradamantyl Aryl- and Heteroarylpiperazinyl Derivatives[a]



compd	X	R^1	R^2	*n*	R^3	mp, °C	formula[a]	method	affinities: K_i, nM (95% CI)[b] or % inhibn at 1 μM: 5-HT_{1A}[c]	affinities: K_i, nM (95% CI)[b] or % inhibn at 1 μM: D_2[d]
63	COO	H	H	1	2-pyrimidinyl	219−20	$C_{20}H_{28}N_4O_2 \cdot 2HCl$	G	23 (20−26)	47%
64	COO	H	H	1	2-MeOPh	207−08	$C_{23}H_{33}N_2O_2 \cdot HCl$	G	4.8 (4.3−5.5)	100%
65	COO	H	H	2	2-pyrimidinyl	231−32	$C_{21}H_{30}N_4O_2 \cdot 2HCl$[e]	G	12%[f]	
66	COO	H	H	2	2-MeOPh	206−07	$C_{24}H_{34}N_2O_3 \cdot 2HCl$	G	26 (19−35)	100%
67	CONH	H	H	1	2-pyrimidinyl	210−12	$C_{20}H_{29}N_5O \cdot 2HCl$[g]	G	2.4 (2−2.85)	67%
68	CONH	H	H	1	2-MeOPh	192−93	$C_{23}H_{33}N_2O_2 \cdot 2HCl$	G	0.24 (0.2−0.28)	100%
69	CONH	H	H	1	3-ClPh	226−27	$C_{22}H_{30}N_3OCl \cdot 2HCl$	G	0.7 (0.59−0.83)	94%
70	CONH	H	H	1	3-CF_3Ph	222−23	$C_{23}H_{30}N_3OF_3 \cdot 2HCl$	G	83%	73%
71	CONH	H	H	2	2-pyrimidinyl	229−30	$C_{21}H_{31}N_5O \cdot 2HCl$	G	67 (49−90)	27%
72	CONH	H	H	2	2-MeOPh	201−02	$C_{24}H_{35}N_3O_2 \cdot 2HCl$	G	3.3 (2.7−3.95)	72%
73	CONH	H	H	2	3-ClPh	236−37	$C_{22}H_{30}N_3OCl \cdot 2HCl$	G	10 (6.5−14)	31%
74	NHCONH	H	H	2	2-pyrimidinyl	134−35	$C_{21}H_{32}N_6O \cdot 2HCl$[h]	J	69%[f]	6%

[a] All compounds had elemental analyses (C,H,N) within ±0.4% of the theoretical values. [b] 95% CI indicates values for 95% confidence interval. Data are the result of duplicate assays. [c] Rat hippocampal tissue. [d] Rat limbic tissue. [e] Dihydrate. [f] @0.1 μM. [g] Hydrate. [h] Mono-2-propanol.

Table 4. 5-HT_2 Affinity

compd	5-HT_2 affinity:[a] K_i, nM (95% CI)[b]	compd	5-HT_2 affinity:[a] K_i, nM (95% CI)[b]
buspirone[c]	2290	**34**	1360 (867−1856)
ritanserin[c]	7.8	**35**	722 (630−745)
1	2180 (1490−2870)	**36**	1890 (1272−2480)
2	712 (610−819)	**40**	71 (56−94.5)
4	180 (67−350)	**41**	38 (30−48)
9	73 (47−107)	**42**	89 (69−107)
10	274 (212−335)	**43**	1600 (950−2230)
11	16.4 (8.5−23.5)	**44**	348 (256−440)
12	21 (12−32)	**45**	277 (218−334)
13	75 (55−100)	**67**	262 (192−339)
22	47 (39−58)	**68**	8.2 (6.5−10)
23	77 (58.5−96)	**69**	2.3 (2.1−2.6)
25	961 (733−1220)	**71**	286 (217−355)
27	66 (48−85)	**72**	43.5 (34−42)
33	395 (269−521)	**73**	4.3 (3.6−5)

[a] Rat cortical tissue. [b] 95% CI indicates values for 95% confidence interval. Data are the result of duplicate assays. [c] Data taken from ref 63.

observed that the 2-methoxyphenylpiperazine was more well-tolerated than the 2-pyrimidinylpiperazine moiety. Likewise, substituting the amide with a third group to form a tertiary amide as in compounds **38** and **39** also curtailed 5-HT_{1A} affinity in this series. Homologating the amide to a urea resulted in compounds which were potent 5-HT_{1A} ligands. Again, the 2-methoxyphenylpiperazine group (e.g., **41** and **44**) was more well-tolerated than the 2-pyrimidinylpiperazine moiety (compounds **40** and **43**, respectively). Replacement of the urea with a carbamate caused a decrease in 5-HT_{1A} affinity.

Spacer Chain. The alkyl spacer chain also plays a role in the ability of the azaspirone analogues to bind to the 5-HT_{1A} receptor. Opinions differ as to whether the alkyl chain simply serves as a spacer between the arylpiperazine and the lipophilic amide[35] or actually interacts with the receptor in a lipophilic manner.[36] However, published SAR studies indicate that there is a preference by the 5-HT_{1A} receptor in most cases for amide analogues containing either a 2-carbon or 4-carbon spacer chain, especially when the molecule incorporates a bulky cycloalkyl amide.[32] The esters and amides of our series followed this general trend, with the 2-carbon spacer chain producing more potent 5-HT_{1A} ligands. This was especially true in the 2-pyrimidin-

Table 5. Effects of Compounds and Standards in 5-HT_{1A} and 5-HT_2 in Vivo Functional Assays

	ED_{50}, mg/kg ip (95% CI)[a]			
compd	induction of serotonin syndrome	antagonism of 8-OH-DPAT-induced serotonin syndrome	antagonism of quipazine-induced head shakes	antagonism of DOI-induced head shakes
buspirone	7.3 (3.4−15.8)	3.9 (1.6−9.4)		
ritanserin			0.4 (0.1−1.1)	0.3 (0.1−1.0)
9	12.9 (4.1−40.8)	2.2 (0.1−6.7)	0.6 (0.2−2.5)	1.8 (0.8−4.3)
13	9.0 (4.5−20.1)	5.8 (1.9−9.8)	4.5 (1.6−12.8)	4.4 (1.4−14.5)[b]

[a] 95% CI indicates values for 95% confidence interval. Data are the result of duplicate assays. [b] Compound administered po.

ylpiperazine analogues, which were the most sensitive to changes in the molecule. The exception to this trend was the urea analogues, which preferred the 3-carbon spacer chain as can be seen by comparing compounds **40** and **41** with the more potent analogues **43** and **44**. The reason for this preference is not clear, although one possible explanation may be the need for the added flexibility of the 3-carbon chain to accommodate the electronic distribution of the extended amide pharmacophore of the urea into its binding site on the 5-HT_{1A} receptor. This extended amide nature might make the urea analogue possessing a 3-carbon spacer look more like an amide with a 4-carbon spacer to the 5-HT_{1A} receptor.

Lipophilic Area. Glennon et al.[37] suggested that there should exist a region of lipophilic tolerance adjacent to the recognition site for the basic amine which stabilizes the binding interaction of the azaspirone-like molecules to the 5-HT_{1A} receptor. The literature contains numerous examples of potent 5-HT_{1A} ligands which are derived from combining arylpiperazines, which possess moderate 5-HT_{1A} affinity, with bulky lipophilic aryl or cycloalkyl groups, either with or without the inclusion of the azaspirone moiety. Therefore, we varied the lipophilic portion of our molecules to examine the effect on 5-HT_{1A} affinity and selectivity. Substitution of the adamantyl group (e.g., **9**, **10**, and **11**) with the 3-methyladamantylmethyl functionality (**30**, **31**, and **32**, respectively) resulted in compounds which displayed a decrease in 5-HT_{1A} affinity, regardless of the length of the spacer chain, thus suggesting a limit to the size of the lipophilic binding pocket located near the putative azaspirone binding site. The noradamantyl derivatives (Table 3) were found to be potent 5-HT_{1A} ligands, with affinities similar to or better than those seen with the adamantyl analogues. In fact, one of the most potent 5-HT_{1A} ligands in our series was compound **68** (K_i = 0.24 nM), which combines the noradamantyl group, the optimal 2-carbon spacer, and the well-tolerated 2-methoxyphenylpiperazine moiety. Unfortunately, the noradamantyl group was also quite attractive to the D_2 receptor, and most of the analogues incorporating this moiety lost selectivity.

Branched Alkyl Analogues. Variation of the steric environment surrounding the amide produced interesting results (Table 1). Addition of a methyl group to the carbon of the spacer chain that is adjacent to the amide nitrogen resulted in a pair of enantiomers which possessed dramatically differing affinity for the 5-HT_{1A} receptor. The (*R*)-isomer **25** retained much of the high affinity seen in **9**, while the affinity of the (*S*)-enantiomer **26** was greatly reduced. The α,α-dimethyl analogue **24** also suffered a considerable loss in 5-HT_{1A} affinity. This trend was maintained when the 2-pyrimidinyl group of the arylpiperazine was substituted with the less optimal benzyl moiety (compounds **29** and **30**). The result of this substitution was a pair of enantiomers with expectedly reduced 5-HT_{1A} affinity which still obeyed the stereochemical order of (*R*) > (*S*). Introduction of a benzyl group α to the amide resulted in two pairs of enantiomers with high affinity for the 5-HT_{1A} receptor. Again, the trend was observed, with the (*R*)-enantiomers **33** (K_i = 0.43 nM) and **35** (K_i = 0.7 nM) being more potent than their respective (*S*)-isomers **34** (K_i = 1 nM) and **36** (K_i = 2.3 nM). However, the difference in potencies between the enantiomers in the benzyl analogues was not as dramatic as that observed for the methyl compounds. The effect of branching in the 2-methoxyphenylpiperazine series was not examined in detail. However, incorporation of the (*R*)-methyl group next to the amide did result in compound **27** (K_i = 0.22 nM), which is one of the most potent 5-HT_{1A} ligands in the entire series. A similar steric effect was reported earlier by Cliffe et al.[38] in the binding profile of the enantiomers of the 5-HT_{1A} antagonist WAY-100135, although the (*S*)-enantiomer was the more potent 5-HT_{1A} ligand in that case.

The dramatic improvement in 5-HT_{1A} affinity obtained by introduction of the α-benzyl group suggests the presence of an additional binding interaction. This possibility is supported by two observations. First, the presence of the α-benzyl moiety compensates for much of the loss in affinity seen when the 2-pyrimidinyl group of the arylpiperazine is replaced by a benzyl functionality in compounds **35** and **36**. Second, substitution of an α-phenoxymethyl group (compound **37**) for the α-benzyl group (compound **35**) results in a loss of 5-HT_{1A} affinity, suggesting a limit to either the size or electronic requirements of this putative binding site. Further evidence can be seen in the structure of the potent 5-HT_{1A} antagonist WAY-100635.[28] The presence of the aryl group on the amide nitrogen imparts high 5-HT_{1A} affinity (IC_{50} = 1 nM) despite the tertiary amide character of the molecule. The poor affinity of compounds **38** and **39** (tertiary alkyl amides) suggests that the high affinity seen with WAY-100635 is the result of ligand/receptor interactions rather than conformational effects on the molecule itself.

5-HT_{1A}/D_2 Selectivity. Compounds which possessed acceptable 5-HT_{1A} affinity were also examined for their affinity at D_2 receptors. The majority of the compounds did not display suitable separation between the two affinities to warrant detailed investigation. In the adamantyl amides, the greatest impact on 5-HT_{1A}/D_2 selectivity was achieved by varying the arylpiperazine moiety, a result which is in agreement with SAR studies on flesinoxan.[39] In general, the 2-pyrimidinylpiperazine analogues displayed the greatest separation between these two activities. Amides analogues possessing the 3-chlorophenylpiperazine moiety also demonstrated some

selectivity for 5-HT_{1A} over D_2 (e.g., compounds **11** and **14**), while those incorporating or 3-trifluoromethylphenylpiperazine group suffered a loss in selectivity, apparently due to a decrease in 5-HT_{1A} affinity. Almost all derivatives possessing the 2-methoxyphenylpiperazine functionality displayed potent affinity for the D_2 receptor and poor selectivity. The lone exceptions to this trend were compounds **13** and **44**, which possessed a 200- and 176-fold separation between K_i values for the two affinities, respectively. It is not clear why compounds **13** and **44** disobey the trend, although it has been shown that spacer chain length can influence D_2 affinity,[40] and both compounds possess a 3-carbon spacer chain. The selectivity obtained with compounds **13** and **44** is reminiscent of that seen for BMY-7378 (Figure 1), another 2-methoxyphenylpiperazine derivative.[41]

In general, branching on the spacer chain improved 5-HT_{1A}/D_2 selectivity, usually by both increasing 5-HT_{1A} affinity and decreasing D_2 affinity. As with their 5-HT_{1A} affinity, compounds possessing the (*R*)-configuration (**25**, **33**, and **34**) displayed greater D_2 affinity than their (*S*)-isomers (**26**, **35**, and **36**, respectively). This steric effect was more pronounced in analogues where the arylpiperazine moiety was not optimal (e.g., the benzylpiperazine seen with analogues **33**−**36**). In these compounds, 5-HT_{1A} affinity was surprisingly high while D_2 affinity was reduced. The exception to this trend was the α-phenoxymethyl analogue **37**, where a loss in 5-HT_{1A} affinity was accompanied by an apparent increase in D_2 affinity (relative to other branched analogues).

The relatively inferior potency of the 3-methyladamantylmethyl analogues, when compared to the adamantyl amides, precluded an exhaustive examination of their 5-HT_{1A} and D_2 affinities. Indications of selectivity were observed in the urea analogues **42**−**44**, but these were not investigated in detail. In general, the noradamantyl 2-pyrimidinylpiperazine derivatives possessed somewhat poorer 5-HT_{1A}/D_2 selectivity than their adamantyl counterparts. The exception to this trend was the 3-chlorophenylpiperazine derivative **73**, which incorporates the longer 3-carbon spacer chain. This compound displayed reasonable 5-HT_{1A}/D_2 selectivity.

5-HT_2 Affinity. At the time of this work little was known of the diversity of 5-HT_2 receptor subtypes. Given the fact that ketanserin was the standard ligand, it can be assumed that the analogues in this paper interact with the 5-HT_{2A} receptor. However, no selectivity studies among the 5-HT_2 subtypes were performed. It had been shown that some simple arylpiperazines displayed 5-HT_2 affinity,[31f] although extended arylpiperazine analogues such as buspirone, gepirone, and ipsapirone possess relatively poor affinity for the 5-HT_2 site labeled by either the 5-HT_2 agonist DOB[42] or the 5-HT_2 antagonist spiperone.[31d] Nevertheless, more recent studies have revealed that some extended arylpiperazines can display 5-HT_2 affinity which rivals that seen in some of the more commonly acknowledged 5-HT_2 pharmacophores.[37,43]

Examination for 5-HT_2 affinity was limited to analogues which possessed both acceptable 5-HT_{1A} affinity and selectivity versus D_2 (Table 4). Thus, a thorough 5-HT_2 SAR analysis is not possible. However, some trends were evident. In the adamantyl series, amides displayed a higher affinity for 5-HT_2 receptors than the corresponding esters (e.g., compare compounds **9** and **13** to compounds **1** and **4**, respectively). 2-Pyrimidinylpiperazine analogues (compounds **9** and **12**) showed somewhat greater affinity than the corresponding 2-methoxyphenylpiperazine derivatives (compounds **10** and **13**), a trend which seemed to hold when the components of the amide group were reversed (compare compounds **22** and **23**). Within the adamantyl amides, the 3-carbon spacer chain (compound **9**) was somewhat preferred to the 2-carbon spacer (compound **12**), although the effect was not dramatic. In the adamantyl ureas, the 2-methoxyphenylpiperazine group imparts greater 5-HT_2 affinity than the pyrimidinylpiperazine moiety, a result which parallels the 5-HT_{1A} affinity results for these compounds. However, the shorter 2-carbon chain was preferred over the 3-carbon spacer (compare compounds **40**, **41**, and **42** to compounds **43**, **44**, and **45**, respectively) in the ureas. This finding is in contrast to the 5-HT_{1A} results, where the longer 3-carbon spacer chain is preferred.

In general, branching on the spacer chain resulted in a decrease in 5-HT_2 affinity. As was seen in the case of both 5-HT_{1A} and D_2 affinity, the (*R*)-enantiomers (**33** and **35**) were somewhat more potent than the corresponding (*S*)-isomers (**34** and **36**, respectively).

The 3-methyladamantylmethyl analogues were not examined for 5-HT_2 affinity because of their relatively poorer 5-HT_{1A} affinity and/or selectivity versus D_2. However, the noradamantyl amide analogues displayed an unexpected range of affinities for 5-HT_2. In contrast to the adamantyl analogues, the noradamantyl amides possessing the 2-methoxyphenylpiperazine group (compounds **68** and **72**) displayed superior affinity over those which contained a 2-pyrimidinylpiperazine moiety (compounds **67** and **71**). The 3-chlorophenylpiperazine group was also well-tolerated within the 5-HT_2 pharmacophore (e.g., **11**, **69**, and **73**). In fact, compounds **69** (K_i = 2.26 nM) and **73** (K_i = 4.28 nM) were found to be the most potent 5-HT_2 ligands among the analogues tested.

Molecular Modeling Results. Several groups have described topographic models of the interaction between the arylpiperazine moiety and the 5-HT_{1A} receptor.[44] Most of these models can, in general, be described as an aryl binding site and a recognition site for the basic amine group separated by a certain distance and a small torsion angle.[45] However, it is clear from our work and the vast body of SAR data in the literature that the interaction between the 5-HT_{1A} receptor and the azaspirone pharmacophore is a complex one which probably involves not only the arylpiperazine group but also the imide/amide moiety, the lipophilic group, and the spacer chain.[46] For example, additional binding stabilizations resulting from adding lipophilic groups to simple arylpiperazines can reduce the minimum distance between the aryl moiety and the basic nitrogen required for interaction with the 5-HT_{1A} receptor.[47a] Additionally, the molecular volume of the lipophilic group can have dramatic effects on 5-HT_{1A} affinity in certain series of ligands.[47b]

Originating with buspirone, 2-pyrimidinylpiperazine has often been considered as the quintessential arylpiperazine portion of the azaspirone pharmacophore, and indeed many of the 2-pyrimidinylpiperazine analogues

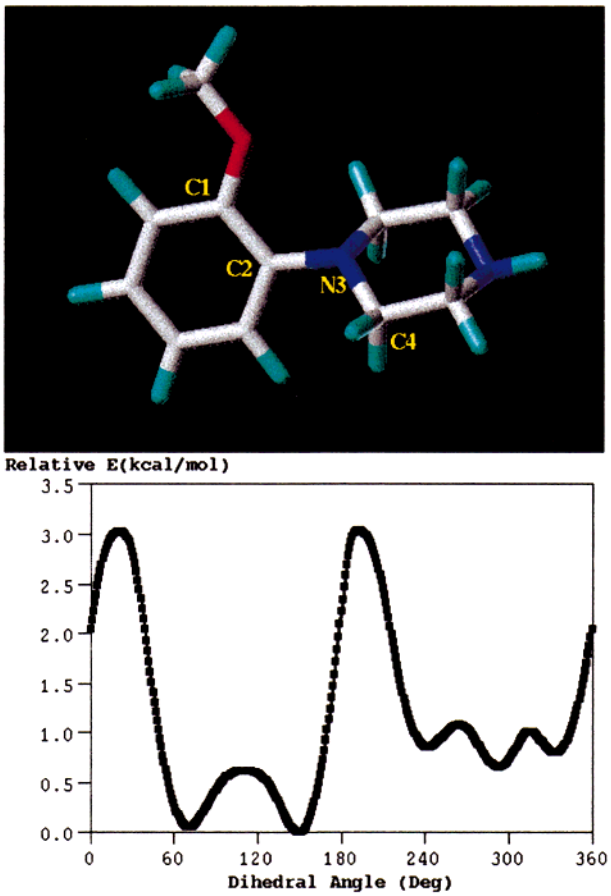


Figure 3. Minimum energy conformation of 2-methoxyphenylpiperazine and rotational energies of the 2-methoxyphenyl group.

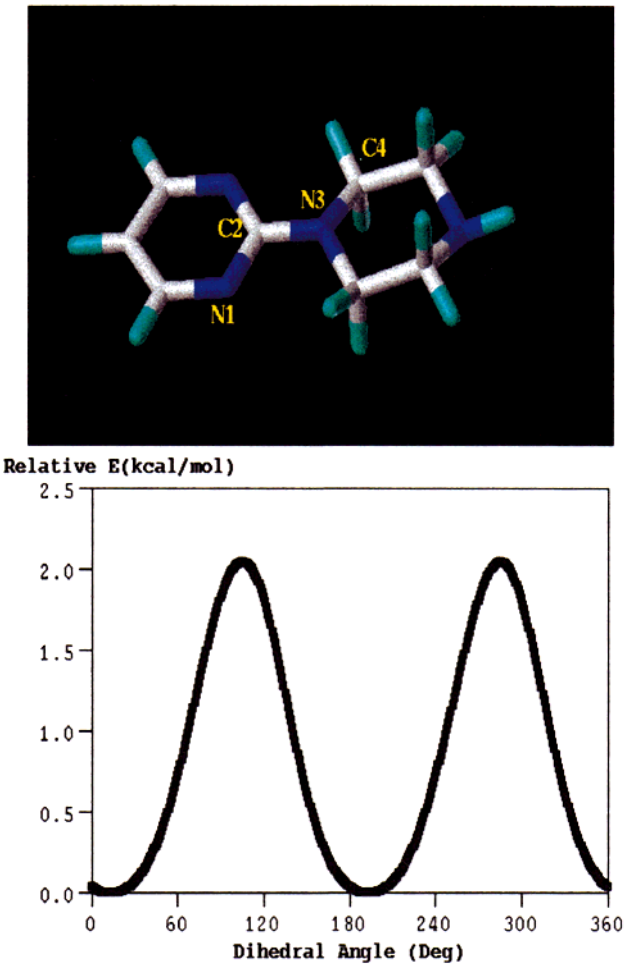


Figure 4. Minimum energy conformation of 2-pyrimidinylpiperazine and rotational energies of the 2-pyrimidinyl group.

within our series were found to be strong ligands for the 5-HT_{1A} receptor. However, 2-methoxyphenylpiperazine analogues are also high-affinity ligands for the 5-HT_{1A} receptor, often possessing greater affinity than their 2-pyrimidinylpiperazine counterparts.[48] Furthermore, 2-methoxyphenylpiperazine-derived azaspirones appear to be more tolerant of changes to the spacer chain and lipophilic portion of the molecule in our series than the 2-pyrimidinylpiperazine analogues, as has already been discussed above. One possible explanation for this difference could be the conformational differences exhibited by the two arylpiperazine pharmacophores.

MM3* calculations show that the preferred orientation of the aryl ring of the 2-methoxyphenyl group is skewed out of the plane relative to the piperazine due to the steric bulk of the 2-methoxy group (Figure 3).[49] The minimum energy conformation depicted in Figure 3 correlates to a dihedral angle τ_1 (τ_1 = C1−C2−N3−C4) of 145°. Furthermore, there are several low-energy conformations which the 2-methoxyphenylpiperazine can conceivably achieve, and the energy barrier between many of these is relatively small. In the 2-pyrimidinylpiperazine, however, the lone pair of the mixed sp^2/sp^3 nitrogen can delocalize into the aromatic system of the pyrimidine. As a result, the orientation of the pyrimidine prefers to be in the same plane as that of the piperazine, and the dihedral angle τ_2 (τ_2 = N1−C2−N3−C4) is now 165° (Figure 4). There are only two low-energy conformations, which are essentially isoenergetic, and the energy barriers between them are large. The skewed orientation of the 2-methoxyphenyl moiety, as well as the abundance of acceptable, interchangeable low-energy conformations, may result in an overall greater flexibility. As a result, this arylpiperazine can more easily adjust its overall interaction with the 5-HT_{1A} receptor in response to changes at the other end of the molecule as opposed to the 2-pyrimidinylpiperazine.

In Vivo Studies. Because of their interesting in vitro profile and favorable physicochemical properties, compounds **1**, **9**, and **13** were assessed for in vivo functional activity at the 5-HT_{1A} and 5-HT_2 receptors (Table 5).[18] The serotonin syndrome paradigm was used to assess 5-HT_{1A} functional activity. In these tests compound **1** was inactive, failing to produce 5-HT_{1A} agonist-like behavioral responses at doses up to 40 mg/kg ip (the highest dose examined). However, both **9** and **13** induced behavioral symptoms of the serotonin syndrome (ED_{50} = 12.9 and 9.0 mg/kg ip, respectively) and antagonized the serotonin syndrome produced by the selective 5-HT_{1A} agonist 8-OH-DPAT (**9**: ED_{50} = 2.2 mg/kg ip; **13**: ED_{50} = 5.8 mg/kg ip) at doses which were similar to that seen with the reference compound buspirone. This profile indicates that both compounds **9** and **13** can be considered as 5-HT_{1A} partial agonists. Compound **9** demonstrated 5-HT_2 antagonist activity by inhibiting both quipazine- and DOI-induced head shakes, with ED_{50} values of 0.6 and 1.8 mg/kg ip, respectively.

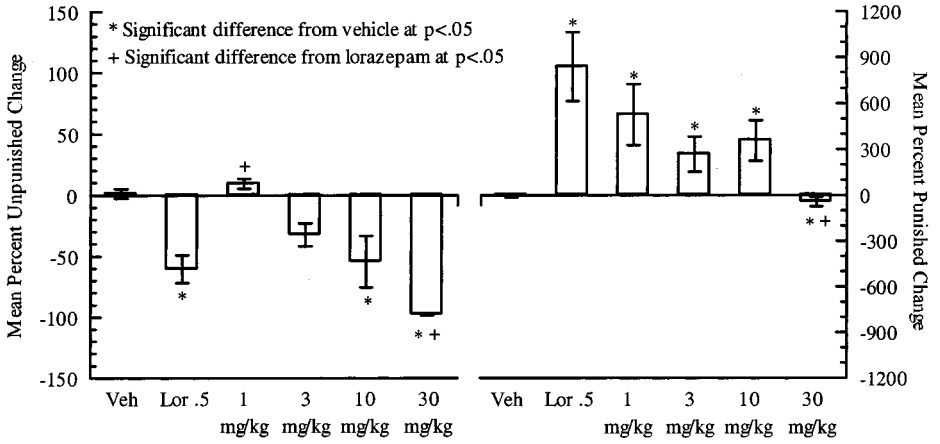


Figure 5. Buspirone: Geller−Seifter conflict paradigm, punished/unpunished behavior.

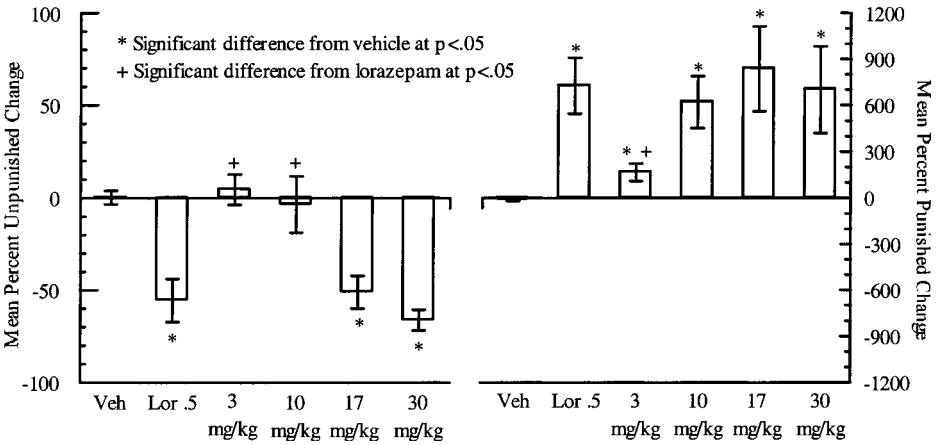


Figure 6. Compound **9**: Geller−Seifter conflict paradigm, punished/unpunished behavior.

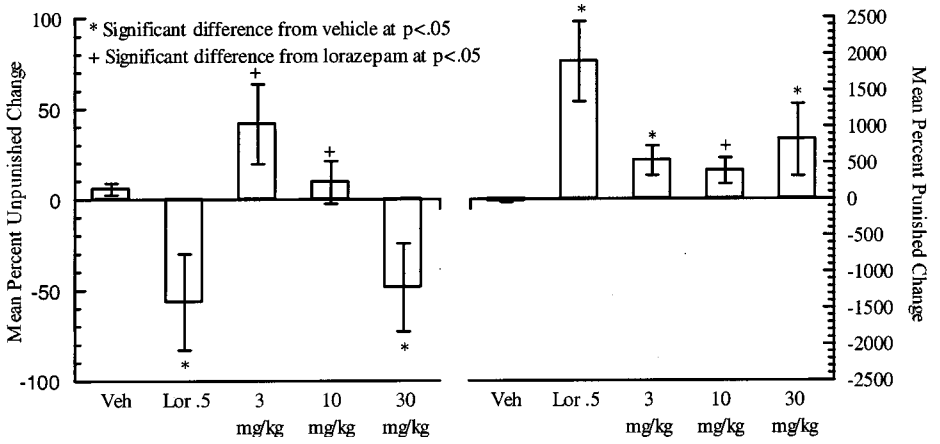


Figure 7. Compound **13**: Geller−Seifter conflict paradigm, punished/unpunished behavior.

The potency of **9** in these assays was similar to that seen with the potent 5-HT_2 antagonist ritanserin. As can be seen from Table 5, compound **13** was somewhat less potent in the 5-HT_2 antagonist tests, inhibiting quipazine- and DOI-induced head shakes with ED_{50} values of 4.5 mg/kg ip and 4.4 mg/kg po, respectively. The similarity in 5-HT_2 antagonist potency between compound **9** and ritanserin is unexpected, given the difference in potency as 5-HT_2 ligands between these two compounds. However, it has been shown that activation of the 5-HT_{1A} receptor can affect the expression of 5-HT_2 receptor-mediated behavior,[50,51] possibly through a presynaptic mechanism. This functional interplay between the two receptor subtypes might partially account for the unexpected in vivo potency of compound **9** as a 5-HT_2 antagonist.

To assess their anxiolytic potential, compounds **9** and **13** were compared to buspirone in the Geller−Seifter conflict model.[18] Results are presented in Figures 5−7. As expected, buspirone significantly increased punished responding (an indication of anxiolytic effect) at doses of 1, 3, and 10 mg/kg ip (Figure 5). However, a significant decrease in unpunished responding was also seen at doses of 10 and 30 mg/kg ip, indicating the presence of sedative effects. Compound **9** produced increases in punished responding at doses of 3, 10, 17, and 30 mg/kg ip, which were similar to those obtained with buspirone as well as with a 0.5 mg/kg ip dose of

lorazepam (Figure 6). No significant sedative effects (as measured by decreases in unpunished responding) were evident for **9** at doses up to 10 mg/kg ip. Compound **13** was less potent than **9** in this model (Figure 7), causing a significant increase in punished responding only at a dose of 30 mg/kg ip. Significant sedative effects were also displayed at this dose. Compound **9** also demonstrated efficacy in this model as well as an unexpectedly good separation between anxiolytic activity and sedative side effects following oral administration (no decreases in unpunished responding at doses up to 54 mg/kg po). Additionally, the efficacy of **9** has been confirmed in conflict studies in pigeons, a model extremely sensitive to anxiolytic effects of serotonergic agents.[52,53]

The antidepressant effects of compound **9** have been previously published, where it demonstrated potent preclinical antidepressant activity in a rat forced swimming model.[3] On the basis of its favorable anxiolytic and antidepressant profile, compound **9** was entered into clinical trials as adatanserin.

Conclusions

In summary, a series of adamantyl and noradamantyl arylpiperazines was synthesized which possess high affinity for both 5-HT_{1A} and 5-HT_2 receptors. Many of these analogues also possess selectivity for 5-HT_{1A}/5-HT_2 versus the D_2 receptor. Certain trends were seen in the SAR, including the ability of the 2-methoxyphenyl derivatives to tolerate changes to the lipophilic group and spacer chain more readily than the 2-pyrimidinylpiperazine analogues. One possible explanation for this enhanced flexibility might be the preference of the 2-methoxyphenyl group to exist in a conformation in which the plane of the aromatic ring is skewed relative to the plane of the piperazine ring, while the plane of the 2-pyrimidinyl ring is parallel to that of the piperazine due to delocalization of the sp^2/sp^3 nitrogen into the aromatic system.

Two compounds, **9** and **13**, which possessed acceptable affinities and selectivity, were assessed in in vivo functional models, where they exhibited potent 5-HT_{1A} partial agonist and 5-HT_2 antagonist properties. Compound **9** also displayed potent anxiolytic activity in a Geller−Seifter conflict model in both rats and pigeons and a superior separation between efficacy and sedative side effects compared to buspirone. Previously published studies have also demonstrated potent preclinical antidepressant activity for **9**. Thus, compound **9** has been shown to be a combined 5-HT_{1A} partial agonist/5-HT_2 antagonist which demonstrates potent preclinical mixed anxiolytic and antidepressant activities. Compound **9** was entered into clinical trials as adatanserin.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover capillary or an Electrothermal melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian XL-200 or Bruker AM-400 spectrometer using tetramethylsilane (TMS) as an internal standard. The chemical shifts are reported in parts per million (δ) downfield from TMS, and coupling constants are reported in hertz (Hz). Solvate, hydrate, and HCl protons are not included. Mass spectra were recorded on a Hewlett-Packard 5995A spectrometer or a Finnigan 8230 high-resolution instrument. The infared spectra were recorded on a Perkin-Elmer 784 spectrometer. C,H,N combustion analyses were determined on either a Perkin-Elmer 240 or 2400 analyzer, and all analyzed compounds are within ±0.4% of the theoretical value unless otherwise indicated. Flash chromatography was performed on 230−400 mesh silica. Preparatory HPLC was performed using a Waters Prep 500 instrument with silica Prep-Pak cartridges. Thin-layer chromatography was performed on silica gel 60 F-254 (0.25-mm thickness) plates. Visualization was accomplished with UV light and/or iodine vapor. Optical rotations were measured using a Perkin-Elmer 241-MC polarimeter.

Method A. General Procedure for Formation of Amides and Esters. Adamantane-1-carboxylic Acid *N*-[3-[4-(2-Pyrimidinyl)-1-piperazinyl]propyl]carboxamide Hydrochloride Dihydrate (12). To a solution of 4-(2-pyrimidinyl)-1-piperazinepropanamine (1.12 g, 5.06 mmol) and triethylamine (2.2 g, 21 mmol) in 40 mL of dry dichloromethane was added solid adamantane-1-carboxylic acid chloride (1.0 g, 5.03 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 days. The mixture was then washed with two 40-mL portions of water, dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator. The desired compound **12** was isolated by HPLC on silica gel using a gradient of methanol and ethyl acetate and converted to its hydrochloride salt with ethanolic HCl (1.59 g, 72%): mp 140−148 °C; ^{1}H NMR (DMSO-d_6) δ 8.45 (d, J = 5.1 Hz, 2H), 7.64 (t, J = 6.1 Hz, 1H), 6.77 (t, J = 5.1 Hz, 1H) 4.68 (m, 2H), 3.49 (m, 4H), 3.38 (m, 2H), 3.11 (m, 2H), 3.00 (m, 4H), 1.94 (s, 3H), 1.76 (s, 6H), 1.65 (m, 6H); IR (KBr) 1650 cm^{-1}. Anal. ($C_{22}H_{33}N_5O\cdot HCl\cdot 2H_2O$) C, H, N.

Using a similar procedure, **3**, **4**, **6**, **9**−**11**, **13**−**16**, and **18** were also prepared.

Method B. Adamantane-1-carboxylic Acid 2-[4-(2-Pyrimidinyl)-1-piperazinyl]ethyl Ester Dihydrochloride Dihydrate (1). Adamantane-1-carboxylic acid (5.0 g, 28 mmol), 4-(2-pyrimidinyl)-1-piperazineethanol (6.25 g, 30 mmol), and 4-(dimethylamino)pyridine (0.34 g, 2.8 mmol) were dissolved in 200 mL of dry dichloromethane. To the stirred solution was then added dicyclohexylcarbodiimide (6.19 g, 30 mmol) at room temperature. A white precipitate formed and the resulting mixture was stirred at room temperature overnight. The precipitate was then filtered and discarded and the supernatant was washed with three 50-mL portions of water, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator. Chromatography of the resulting gum on silica gel (ethyl acetate/methanol) followed by treatment with ethereal HCl gave 2.70 g (21%) of the desired compound **1** as the dihydrochloride salt: mp 232−235 °C; ^{1}H NMR (DMSO-d_6) δ 8.48 (d, J = 4.8 Hz, 2H), 6.83 (t, J = 4.8 Hz, 1H); 4.84 (bd, J = 14.4 Hz, 2H), 4.48 (m, 2H), 3.50 (m, 6H), 3.18 (m, 2H), 1.90 (m, 3H), 1.84 (m, 6H), 1.67 (m, 6H); IR (KBr) 1650 cm^{-1} (C=O); MS m/z 370 (M^+). Anal. ($C_{21}H_{30}N_4O_2\cdot 2HCl\cdot 2H_2O$) C, H, N.

Method C. Adamantane-1-carboxylic Acid *N*-[2-(4-Benzyl-1-piperazinyl)ethyl]carboxamide Dihydrochloride (17). A stirred solution of adamantane-1-carboxylic acid (11.85 g, 65.8 mmol) and 4-benzyl-1-piperazineethanamine (12.0 g, 52.8 mmol) in 200 mL of dry dichloromethane was treated at 4 °C with a solution of diethyl cyanophosphonate (11.8 mL, 65.8 mmol) in 50 mL of dry dichloromethane over a period of 30 min. Triethylamine (9.2 mL, 65.8 mmol) was then added and the mixture stirred at room temperature overnight. The resulting mixture was washed with 100 mL of 10% aqueous potassium carbonate followed by 100 mL of water. The resulting organic layer was dried over anhydrous sodium sulfate and concentrated on a rotary evaporator, and the desired compound **17** was isolated by crystallization from boiling hexane. The dihydrochloride salt (11.1 g, 51%) was prepared with HCl/ethyl acetate and recrystallized from methanol/2-propanol: mp 259−260 °C; ^{1}H NMR (DMSO-d_6) δ 7.80 (t, J = 8 Hz, 1H), 7.65 (m, 2H), 7.44 (m, 3H), 4.37 (bs, 2H), 3.70 (m, 2H), 3.6−3.3 (m, 8H), 3.10 (t, J = 14 Hz, 2H), 1.95 (m, 3H), 1.80 (m, 6H), 1.65 (q, J = 12 Hz, 6H); IR (KBr) 1665 cm^{-1} (C=O); MS m/z 381 (M^+). Anal. ($C_{24}H_{35}N_3O\cdot 2HCl$) C, H, N.

Method D. Two-Step Synthesis of Esters. Adamantane-1-carboxylic Acid 2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl Ester Dihydrochloride (2). Adamantane-1-carboxylic acid chloride (5.6 g, 28 mmol), 2-bromoethanol (5.0 g, 40 mmol), and triethylamine (4.0 g, 40 mmol) were dissolved in 200 mL of dry dichloromethane and allowed to stir overnight at room temperature. The resulting solution was concentrated on a rotary evaporator to remove excess triethylamine and then partitioned between 200 mL of dichloromethane and 100 mL of water. The organic layer was washed with two additional 100 mL portions of water, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator to give 10.7 g of a residue which contained the desired adamantane 1-(2-bromoethyl) ester. This residue was used in the next step without further purification.

The adamantane 1-(2-bromoethyl) ester described above (4.0 g, 13.9 mmol), 1-(2-methoxyphenyl)piperazine (2.7 g, 14 mmol), and triethylamine (1.5 g, 15 mmol) were dissolved in 100 mL of dry dimethylformamide and allowed to stir at room temperature overnight. The reaction mixture was concentrated on a rotary evaporator to remove the DMF, and the residue was partitioned between 150 mL of dichloromethane and 100 mL of water. The organic layer was washed with two additional 100-mL portions of water, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator. The desired compound **2** was isolated by chromatography on silica gel (ethyl acetate) and converted to its dihydrochloride salt with ethereal HCl (1.29 g, 21%): mp 214−216 °C; ^{1}H NMR (DMSO-d_6) δ 7.00 (m, 4H), 4.47 (t, J = 6 Hz, 2H), 3.78 (s, 3H), 3.52 (m, 6H), 3.25 (m, 4H), 1.95 (m, 3H), 1.84 (m, 6H), 1.67 (m, 6H); IR (KBr) 1635 cm^{-1} (C═O); MS m/z 398 (M^+). Anal. ($C_{24}H_{34}N_4O_2$·2HCl) C, H, N.

Using a similar procedure, **5**, **7**, and **8** were also prepared.

Method E. General Procedure for 3-Methyl-1-adamantane Esters and Amides. Synthesis of 3-Methyl-1-adamantaneacetic Acid Amides and Esters. 3-Methyl-1-adamantaneacetic Acid *N*-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]carboxamide Dihydrochloride (62). 3-Methyl-1-adamantaneacetic Acid Chloride. To a stirred solution of 3-methyladamantane-1-acetic acid (15 g, 72 mmol) in 250 mL of dry dichloromethane under a nitrogen atmosphere was added, at room temperature, oxalyl chloride (9.5 g, 75 mmol). When the evolution of gas had ceased, dimethylformamide (2 mL) was added dropwise in order to make the mixture homogeneous, and stirring was continued for 2 h. The mixture was then concentrated on a rotary evaporator. Fresh dichloromethane was added and the resulting mixture was concentrated again in order to remove all residual oxalyl chloride. In this way 16.64 g of crude intermediate 3-methyladamantane-1-acetic acid chloride was isolated.

3-Methyl-1-adamantaneacetic Acid *N*-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]carboxamide Dihydrochloride (62). A solution of the above-described 3-methyladamantane-1-acetic acid chloride (1.25 g, 5.5 mmol), 4-(3-chlorophenyl)-1-piperazinepropanamine (1.4 g, 5.5 mmol), and triethylamine (2.8 g, 27 mmol) in 50 mL of dry dichloromethane was stirred at room temperature overnight. The resulting mixture was washed with two 50-mL portions of water, dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator. The desired compound **62** was isolated by chromatography on silica gel (methanol/ethyl acetate) and converted to its dihydrochloride salt with ethanolic HCl (1.49 g, 52%): mp 200−202 °C; ^{1}H NMR (DMSO-d_6) δ 7.94 (t, J = 6 Hz, 1H), 7.26 (t, J = 8.5 Hz, 1H), 7.05 (m, 1H), 6.94 (m, 1H), 6.85 (m, 1H), 3.85 (d, J = 13.5 Hz, 2H), 3.49 (d, J = 12 Hz, 2H), 3.22 (t, J = 12 Hz, 2H), 3.15−3.00 (m, 6H), 1.95 (m, 2H), 1.92−1.80 (m, 4H), 1.55−1.02 (m, 12H), 0.98 (s, 3H); IR (KBr) 1660 cm^{-1}; MS m/z 443 (M^+). Anal. ($C_{26}H_{38}N_3OCl$·2HCl) C, H. N.

Using a similar procedure, **50**−**54** and **56**−**61** were also prepared.

Method F. 3-Methyl-1-adamantaneacetic Acid 3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl Ester Dihydrochloride (55). To a stirred solution of 3-methyladamantane-1-acetic acid (2.3 g, 11 mmol), 3-bromopropanol (1.53 g, 11 mmol), and 4-(dimethylamino)pyridine (0.15 g, 1.2 mmol) in 100 mL of dry dichloromethane at room temperature was added dicyclohexylcarbodiimide (2.3 g, 11 mmol). The resulting mixture was stirred at room temperature overnight. The white precipitate was then filtered and the supernatant was washed with three 50-mL portions of water, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator. The resulting residue, which was used without further purification, was then reacted with 1-(3-chlolophenyl)piperazine (2.57 g, 11 mmol) and triethylamine (3.08 g, 30.5 mmol) in 100 mL of dry dimethylformamide using a procedure identical to that described in general method D. Desired compound **55** was isolated by chromatography on silica gel (ethyl acetate) and converted to its dihydrochloride salt with ethereal HCl (0.57 g, 10%): mp 182−4 °C; ^{1}H NMR (DMSO-d_6) δ 7.22 (t, J = 9.1 Hz, 1H), 7.03 (t, J = 3.1 Hz, 1H), 6.95 (dd, J_a = 3.1 Hz, J_b = 9.1 Hz, 1H), 6.83 (dd, J_a = 9.1 Hz, J_b = 2.5 Hz, 1H), 4.72 (d, J = 15 Hz, 2H), 4.06 (t, J = 7.5 Hz, 2H), 3.58 (m, 4H), 3.12 (m, 6H), 2.10 (s, 2H), 2.05 (m, 2H), 1.95 (m, 2H), 1.60−1.20 (m, 10H), 0.79 (s, 3H); IR (KBr) 1645 cm^{-1}; MS m/z 444 (M^+). Anal. ($C_{26}H_{37}N_2O_2Cl$·2HCl) C, H, N.

Method G. General Procedure for Noradamantane Amides and Esters. Noradamantane-3-carboxylic Acid 2-[4-(2-Pyrimidinyl)-1-piperazinyl]ethyl Ester Dihydrochloride (63). A solution of noradamantane-3-carboxylic acid (1.0 g, 6 mmol) and carbonyldiimidazole (0.98 g, 6 mmol) in 25 mL of dry chloroform was stirred at room temperature under a nitrogen atmosphere for 2 h. Then a solution of 4-(2-pyrimidinyl)-1-piperazineethanol (1.25 g, 6 mmol) in 10 mL of dry chloroform was added and the reaction mixture was stirred at room temperature under nitrogen for 48 h. The resulting solution was diluted to 100 mL with chloroform and washed with three 50-mL portions of water. The organic layer was then dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. The desired compound **63** was isolated by chromatography on silica gel (methanol/ethyl acetate) and converted to its dihydrochloride salt with 2-propanolic HCl (1.0 g, 74%: mp 219−220 °C; ^{1}H NMR (DMSO-d_6) δ 8.44 (d, J = 4.8 Hz, 2H), 6.76 (t, J = 4.8 Hz, 1H), 4.67 (bd, J = 14 Hz, 2H), 4.47 (bt, J = 4.7 Hz, 2H), 3.48 (m, 6H), 3.10 (dd, J_a = 8.5 Hz, J_b = 10.8 Hz, 2H), 2.60 (m, 1H), 2.24 (m, 2H), 1.97 (bd, J = 10.8 Hz, 2H), 1.75 (m, 4H), 1.55 (m, 4H); IR (KBr) 1625 cm^{-1}; MS m/z 356 (M^+). Anal. ($C_{20}H_{28}N_4O_2$·2HCl) C, H, N.

Using a similar procedure, **64**−**73** were also prepared.

Method H. General Procedure for Reversed Amides Lacking an Alkyl Chain. 4-(2-Pyrimidinyl)piperazine-1-carboxylic Acid *N*-(1-Adamantyl)carboxamide (19). A solution of adamantane 1-isocyanate[29] (1.8 g, 10 mmol), 1-(2-pyrimidinyl)piperazine hydrochloride (2.37 g, 10 mmol), and triethylamine (2.02 g, 20 mmol) in 50 mL of dry dichloromethane was stirred at room temperature overnight. The mixture was then washed with three 50-mL portions of water, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator. The desired compound **19** (2.5 g, 74%) was isolated by crystallization of the residue from hexane (100 mL): mp 174−5 °C; ^{1}H NMR ($CDCl_3$) δ 8.30 (d, J = 4.7 Hz, 2H), 6.50 (t, J = 4.7 Hz, 1H), 4.2 (s, 1H), 3.8 (m, 4H), 3.4 (m, 4H), 2.1 (m, 3H), 1.9 (m, 6H), 1.6 (m, 6H); IR (KBr) 1650 cm^{-1} (C═O); MS m/z 321 (M^+). Anal. ($C_{19}H_{27}N_5O$) C, H, N.

Using a similar procedure, **20** and **21** were also prepared.

Method I. General Procedure for Reversed Amides Possessing an Alkyl Chain. 3-[4-(2-Pyrimidyl)-1-piperazinyl]propanoic Acid 1-Adamantylcarboxamide Dihydrochloride Hemihydrate (22). 3-Bromopropyl 1-Adamantylcarboxamide. To a stirred suspension of 1-adamantanamine hydrochloride (12.2 g, 65 mmol) and 3-bromopropionyl chloride (11.14 g, 65 mmol) in 330 mL of dichloromethane was added diisopropylethylamine (22.5 mL, 130 mmol) over a period of 0.5 h at room temperature. The mixture became homogeneous after all of the amine had been added. The reaction was stirred for an additional 3 h at room temperature and then washed with three 200-mL portions of water. The

organic layer was dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator to give 12.52 g (76%) of the desired 3-bromopropyl 1-adamantylcarboxamide, which was used without further purification: mp 95−102 °C; IR (KBr) 1669 cm^{-1} (C═O).

4-[(2-Pyrimidinyl)-*N*-(1-adamantyl)]-1-piperazinepropanamide Trihydrochloride (22). To 150 mL of anhydrous dimethylformamide were added 3-bromopropyl 1-adamantylcarboxamide (5.51 g, 19.2 mmol), 1-(2-pyrimidinyl)piperazine dihydrochloride (4.56 g, 19.2 mmol), and diisopropylethylamine (10.5 mL, 59 mmol) at room temperature. The mixture was then stirred at 55 °C for 48 h. The dimethylformamide was removed on a rotary evaporator and the residue was partitioned between dichloromethane (250 mL) and water (200 mL). The organic layer was washed with two 100-mL portions of water and then dried over magnesium sulfate. The solvent was removed on a rotary evaporator and the desired product **22** was isolated by chromatography on silica gel (EtOAc/MeOH) and converted to its trihydrochloride salt with ethanolic HCl: yield = 0.70 g (5% overall yield); mp 273−75 °C; ^{1}H NMR (DMSO-d_6) δ 8.45 (d, J = 4.8 Hz, 2H), 7.67 (s, 1H), 6.76 (t, J= 4.8 Hz, 1H), 4.65 (m, 2H), 3.44 (m, 4H), 3.25 (m, 2H), 3.01 (m, 2H), 2.64 (t, J = 7.2 Hz, 2H), 1.99 (m, 3H), 1.91 (m, 6H), 1.59 (m, 6H); IR (KBr) 1635 cm^{-1} (C═O); MS m/z 369 (M^+). Anal. ($C_{21}H_{31}N_5O\cdot 3HCl$) C, H, N.

Using a similar procedure, **23** was also prepared.

Method J. General Procedure for Adamantyl and Noradamantyl Ureas. *N*-1-Adamantyl-*N*′-2-[4-(2-pyrimidinyl)-1-piperazinyl]ethylurea Hemihydrate (40). To a stirred suspension of 1-aminoadamantane hydrochloride (2.5 g, 13 mmol) in dry dichloromethane (50 mL) was added triethylamine (5.3 g, 52 mmol) under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 30 min and then trichloromethyl chloroformate (0.81 mL, 6.5 mmol) was added slowly via syringe. The reaction mixture was refluxed for 3 h, then a solution of 4-(2-pyrimidinyl)-1-piperazineethanamine (2.70 g, 13 mmol) in 30 mL of dry dichloromethane was added, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted to 200 mL with dichloromethane and washed with three 100-mL portions of 5% aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. The desired compound **40** (3.55 g, 71%) was isolated by chromatography on silica gel (methanol/ethyl acetate): mp 170−171 °C; ^{1}H NMR ($CDCl_3$) δ 8.32 (d, J = 4.7 Hz, 2H), 6.54 (t, J = 4.7 Hz, 1H), 5.37 (bs, 1H), 4.55 (bs, 1H), 3.98 (t, J = 4.6 Hz, 4H) 3.39 (dd, J_a = 11 Hz, J_b = 5.3 Hz, 2H), 2.73 (m, 6H), 2.07 (m, 3H), 1.98 (m, 6H), 1.66 (m, 6H); IR (KBr) 1660, 1590 cm^{-1} (urea C═O); MS m/z 384 (M^+). Anal. ($C_{21}H_{32}N_6O\cdot 1/2H_2O$) C, H, N.

Using a similar procedure, **41**−**49** and **74** were also prepared.

Method K. Synthesis of Branched Adamantyl Amides. Total Synthesis of (*R*)-Adamantane-1-carboxylic Acid *N*-[1-Methyl-2-(4-benzyl-1-piperazinyl)ethyl]carboxamide Dihydrochloride Sesquihydrate Hemi-2-propanolate (29). (*R*)-Alanine-*N*-(4-benzyl-1-piperzinyl)carboxamide Dihydrochloride. D-Alanine-*N*-*tert*-butoxycarboxamide (BOC-D-alanine; 9.45 g, 50 mmol) and 1-benzylpiperazine (8.9 g, 50 mmol) were dissolved in 125 mL of dry dichloromethane and cooled in an ice bath. The stirred mixture was then treated with a solution of diethyl cyanophosphonate (8.34 g, 55 mmol) in 50 mL of dry dichloromethane over a period of 45 min. A solution of triethylamine (7.37 g, 52.5 mmol) in 50 mL of dry dichloromethane was then added over a period of 1 h. The resulting reaction mixture was stirred overnight, during which time it came up to room temperature. The solution was then washed with 100 mL of 10% aqueous potassium carbonate, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator to yield 19 g of the crude intermediate BOC-(*R*)-alanine-*N*-(4-benzyl-1-piperazinyl)carboxamide. This oil was dissolved in 50 mL of dichloromethane and treated with a 4.6 N solution of HCl in ethyl acetate (250 mL). After stirring at room temperature for 1 h (at which time CO_2 evolution ceased), 250 mL of dry diethyl ether was added. The desired dihydrochloride salt of (*R*)-alanine-*N*-(4-benzyl-1-piperazinyl)-carboxamide (13.25 g, 83%) precipitated and was isolated by filtration, washed with diethyl ether, and dried in vacuo: mp 199−200 °C; $[\alpha]^{25}_D$ = −3.7° (c = 1, MeOH); ^{1}H NMR (DMSO-d_6) δ 8.49 (s, 1H), 8.42 (s, 1H), 7.56 (d, J = 3 Hz, 2H), 7.40 (t, J = 3 Hz, 3H), 4.35 (m, 4H), 4.12 (m, 1H), 3.70 (t, J = 12 Hz, 1H), 3.25 (m, 4H), 3.00 (m, 1H), 1.36 (m, 3H); CIMS 249 (MH^+); IR (KBr) 1668 cm^{-1} (C═O).

(*R*)-[1-Methyl-2-(4-benzyl-1-piperazinyl)ethyl]amine. A solution of (*R*)-alanine-*N*-(4-benzyl-1-piperazinyl)carboxamide dihydrochloride (12.8 g, 40 mmol) in 350 mL of 0.5 M borane/tetrahydrofuran was refluxed with stirring for 4 h under a nitrogen atmosphere. The resulting mixture was cooled in an ice bath and quenched by slow addition of 100 mL of 2 N aqueous HCl. The resulting mixture was then refluxed with stirring overnight. The precipitate was removed by filtration. The filtrate was washed with five 50-mL portions of dichloromethane and then made strongly basic with 50% aqueous sodium hydroxide solution. The resulting alkaline mixture was then extracted with three 100-mL portions of dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and concentrated on a rotary evaporator to yield the desired (*R*)-[1-methyl-2-(4-benzyl-1-piperazinyl)ethyl-amine (9.6 g, 87%) as an oil which was used without further purification: $[\alpha]^{25}_D$ = −33.9° (c = 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.30 (d, J = 4.8 Hz, 5H), 3.50 (t, J = 6 Hz, 2H), 3.05 (m, 1H), 2.87−2.27 (m, 8H), 2.19−2.07 (m, 2H), 1.50 (s, 2H), 1.0 (d, J = 6 Hz 3H); IR (film) 3430 cm^{-1} (NH).

(*R*)-Adamantane-1-carboxylic Acid *N*-[1-Methyl-2-(4-benzyl-1-piperazinyl)ethyl]carboxamide Dihydrochloride Sesquihydrate Hemi-2-propanolate (29). To an ice-cooled solution of 1-adamantanecarboxylic acid (14.6 g, 81 mmol) and (*R*)-[1-methyl-2-(4-benzyl-1-piperazinyl)ethyl]amine (9.6 g, 41 mmol) in 150 mL of dry dichloromethane was added with stirring diethyl cyanophosphonate (14.6 g, 81 mmol) over a period of 30 min. Upon completed addition *N*-methylmorpholine (8.2 g, 81 mmol) was added and the resulting mixture was stirred overnight during which time it came up to room temperature. The reaction mixture was then washed with 100 mL of 10% aqueous potassium carbonate solution followed by 100 mL of water. The resulting organic layer was dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. The desired compound **29** was isolated by chromatography on silica gel using a gradient of ethyl acetate and hexane and then converted to its dihydrochloride salt (1.54 g, 32%) with HCl/ethyl acetate: mp = 240−242 °C; $[\alpha]^{25}_D$ = −12.6° (c = 1, MeOH); ^{1}H NMR (DMSO-d_6) δ 7.65 (t, J = 5 Hz, 2H), 7.44 (t, J = 5 Hz, 3H), 4.33 (s, 2H), 4.00−3.00 (m, 12H), 1.95 (s, 3H), 1.8 (s, 6H), 1.65 (t, J = 6 Hz, 6H), 1.13 (d, J = 7 Hz, 3H), 1.00 (d, J = 7 Hz, 3H); IR (KBr) 1630 cm^{-1} (C═O); MS m/z 395 (M^+). Anal. ($C_{25}H_{37}N_3O\cdot 2\ HCl\cdot 1\ 1/2H_2O\cdot 1/2C_3H_8O$) C, H, N.

(*S*)-Adamantane-1-carboxylic Acid *N*-[1-Methyl-2-(4-benzyl-1-piperazinyl)ethyl]-1-carboxamide Dihydrochloride Sesquihydrate Hemi-2-propanolate (30). Using a synthetic sequence identical to that described for the synthesis of compound **29** and starting with L-alanine-*N*-*tert*-butoxycarboxamide, compound **30** was prepared as its dihydrochloride salt in 12% yield: mp 236−38 °C; $[\alpha]^{25}_D$ = +13.8 (c = 1.02, MeOH); ^{1}H NMR identical to that described for compound **29**; IR (KBr) 1630 cm^{-1} (C═O); MS m/z 395 (M^+). Anal. ($C_{25}H_{37}N_3O\cdot 2HCl\cdot 1\ 1/2H_2O\cdot 1/2C_3H_8O$) C, H, N.

(*R*)-Adamantane-1-carboxylic Acid *N*-[1-Benzyl-2-(4-benzyl-1-piperazinyl)ethyl]carboxamide Dihydrochloride Dihydrate (35). Beginning with D-phenylalanine-*N*-*tert*-butoxycarboxamide, compound **35** was prepared using a synthetic sequence identical to that described for the synthesis of **29** from D-BOC-alanine. It was isolated as its dihydrochloride dihydrate salt in 9% overall yield: mp 261−263 °C; $[\alpha]^{25}_D$ = −12.5 (c = 1, MeOH); ^{1}H NMR (DMSO-d_6) δ 7.65 (t, J = 3.5 Hz, 1H), 7.43 (m, 4H), 7.30−7.10 (m, 5H), 4.46 (m, 2H). 4.00−3.15 (m, 12H), 2.93 (d, J = 2 Hz, 1H), 2.88 (t, J = 4.5 Hz, 1H), 1.97 (m, 3H), 1.80−1.50 (m, 12H); IR (KBr) 1640

cm^{-1} (C═O); CIMS *m/z* 472 (MH^+). Anal. ($C_{31}H_{41}N_3O\cdot 2HCl\cdot 2H_2O$) C, H, N.

(*S*)-Adamantane-1-carboxylic Acid *N*-[1-Benzyl-2-(4-benzyl-1-piperazinyl)ethyl]carboxamide Dihydrochloride Dihydrate (36). Beginning with L-phenylalanine-*N*-*tert*-butoxycarboxamide, **36** was prepared using a synthetic sequence identical to that described for the synthesis of **29** from D-BOC-alanine. It was isolated as its dihydrochloride dihydrate salt in 5% overall yield: mp 263−266 °C; $[\alpha]^{25}_D = +11.3$ (*c* = 1.03, MeOH); ^{1}H NMR identical to that described for compound **35**; IR (KBr) 1635 cm^{-1} (C═O); CIMS *m/z* 472 (MH^+). Anal. ($C_{31}H_{41}N_3O\cdot 2HCl\cdot 2H_2O$) C, H, N.

(*R*)-Adamantane-1-carboxylic Acid *N*-[1-Methyl-2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl]carboxamide (25). Compound **29** (6.9 g, 13.3 mmol) was hydrogenated over 10% Pd/C (1 g) in 200 mL of ethanol on a Parr shaker at a pressure of 36 psi overnight (until H_2 was no longer taken up). The catalyst was removed by filtration through Celite and the mixture concentrated on a rotary evaporator to yield the crude (*R*)-adamantane-1-carboxylic acid *N*-[1-methyl-2-(1-piperazinyl)ethyl]carboxamide (3.5 g) as an oil. This oil was dissolved in 50 mL of dry dimethylformamide. To the stirred solution was added 2-chloropyrimidine (1.05 g, 9.2 mmol), anhydrous potassium carbonate (12.4 g, 90 mmol), and triethylamine (1 mL), and the resulting mixture was heated at 70 °C overnight. The DMF was removed on a rotary evaporator and the residue was triturated with water. The resulting precipitate was washed with water, air-dried, and recrystallized from 50% aqueous methanol to yield the desired compound **25** (3.05 g, 42%): mp 168−9 °C; $[\alpha]^{25}_D = -26.4°$ (*c* = 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 8.30 (d, *J* = 4.5 Hz, 2H), 6.55 (t, *J* = 4.5 Hz, 1H), 6.05 (s, 1H), 4.00 (t, *J* = 4.5 Hz, 1H), 3.86 (t, *J* = 11 Hz, 4H), 2.60−2.30 (m, 6H), 2.05 (s, 3H), 1.93 (m, 6H), 1.75 (m, 6H), 1.27 (d, *J* = 3 Hz, 3H); IR (KBr) 1660 cm^{-1} (C═O); MS *m/z* 383 (M^+). Anal. ($C_{22}H_{33}N_5O$) C, H, N.

(*S*)-Adamantane-1-carboxylic Acid *N*-[1-Methyl-2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl]carboxamide (26). Compound **26** was prepared from compound **30** in 66% yield using a procedure identical to that described for the synthesis of compound **25**: mp 162−164 °C; $[\alpha]^{25}_D = +28.6$ (*c* = 1.04, MeOH); ^{1}H NMR identical to that described for compound **25**; IR (KBr) 1660 cm^{-1} (C═O); MS *m/z* 383 (M^+). Anal. ($C_{22}H_{33}N_5O$) C, H, N.

(*R*)-Adamantane-1-carboxylic Acid *N*-[1-Benzyl-2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl]carboxamide Hemihydrate (33). Using a procedure identical to that described for the synthesis of **29**, compound **33** was synthesized from **35** and 2-chloropyrimidine in 12% yield as a hemihydrate. It was purified by recrystallization from boiling hexane: mp 172−175 °C; $[\alpha]^{25}_D = -9.7$ (*c* = 1.07, MeOH); ^{1}H NMR (DMSO-d_6) δ 8.30 (d, *J* = 4.5 Hz, 2H), 7.20−7.00 (m, 4H), 6.93 (d, *J* = 8 Hz, 1H), 6.55 (t, *J* = 4.5 Hz, 1H), 4.15 (m, 1H), 3.60 (t, *J* = 4 Hz, 3H), 3.35 (m, 3H), 2.78 (, 1H), 2.65 (, 1H), 2.55 (m, 3H), 2.33 (d, *J* = 7 Hz, 2H), 1.87 (m, 3H), 1.65−1.50 (m, 12H); IR (KBr) 1635 cm^{-1} (C═O); CIMS *m/z* 460 (MH^+). Anal. ($C_{28}H_{37}N_5O\cdot 1/2H_2O$) C, H, N.

(*S*)-Adamantane-1-carboxylic Acid *N*-[1-Benzyl-2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl]carboxamide (34). Using a procedure identical to that described for the synthesis of **29**, compound **34** was synthesized from **36** and 2-chloropyrimidine in 78% yield. It was purified by recrystallization from boiling hexane: mp 172−175 °C; $[\alpha]^{25}_D = +7.2$ (*c* = 1.03, MeOH); ^{1}H NMR identical to that described for compound **33**; IR (KBr) 1635 cm^{-1} (C═O); CIMS *m/z* 460 (MH^+). Anal. ($C_{28}H_{37}N_5O$) C, H, N.

(*R*)-Adamantane-1-carboxylic Acid *N*-[1-Benzyloxymethyl-2-(4-benzyl-1-piperazinyl)ethyl]carboxamide Dihydrochloride Dihydrate (37). Using a synthetic sequence identical to that described for the preparation of compound **29**, compound **37** was prepared from d-*O*-benzylserine-*N*-*tert*-butoxycarboxamide and 1-benzylpiperazine in 5% overall yield. It was isolated as its dihydrochloride dihydrate salt: mp 140−42 °C; $[\alpha]^{25}_D = +19.0$ (*c* = 0.98, MeOH); ^{1}H NMR (DMSO-d_6) δ 7.45 (m, 5H), 7.30 (m, 5H), 4.55−4.30 (m, 4H), 4.20−3.05 (m, 14H), 1.95 (s, 3H), 1.85−1.78 (m, 6H), 1.75−1.60 (m, 6H); IR (KBr) 1630 cm^{-1} (C═O); CIMS *m/z* 502 (MH^+). Anal. ($C_{32}H_{43}N_3O_2\cdot 2HCl\cdot 2H_2O$) C, H, N.

Adamantane-1-carboxylic Acid *N*-[(1,1-Dimethyl-2-(4-benzyl-1-piperazinyl)ethyl]carboxamide Dihydrochloride Hemihydrate (28). Using a synthetic sequence similar to that described for the preparation of compound **29**, compound **28** was prepared from 2-methylalanine-*N*-benzylcarbamate (Cbz) and 1-benzylpiperazine in 12% overall yield, with the exception that removal of the Cbz group was accomplished using the following procedure. *N*-Cbz-2-methylalanine(4-benzyl-1-piperazinyl)carboxamide was stirred in a mixture of 30% aqueous HBr in acetic acid for 1 h at room temperature. Ether was added to the reaction mixture and the resulting dihydrobromide salt of the product was isolated by vacuum filtration. The desired 2-methylalanine(4-benzyl-1-piperazinyl)carboxamide was isolated by partitioning the hydrobromide salt between dichloromethane and aqueous NaOH. This intermediate was then converted to the desired compound **28**, which was isolated as its dihydrochloride hemihydrate salt: mp 256−58 °C; ^{1}H NMR (DMSO-d_6) δ 7.50 (m, 5H), 6.43 (s, 1H), 3.55 (s, 2H), 2.85 (s, 2H), 2.61 (m, 4H), 2.40 (m, 4H), 2.05 (s, 3H), 1.86 (s, 6H), 1.79−1.65 (m, 6H), 1.33 (s, 6H); IR (KBr) 1635 cm^{-1}; MS *m/z* 409 (M^+). Anal. ($C_{26}H_{39}N_3O\cdot 2HCl\cdot 1/2H_2O$) C, H, N.

Adamantane-1-carboxylic Acid *N*-[1,1-Dimethyl-2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl]carboxamide (24). Compound **24** was prepared from compound **28** in 39% yield using a procedure identical to that for the synthesis of compound **25**. The desired product was purified by recrystallization from methanol: mp 153−55 °C; ^{1}H NMR ($CDCl_3$) δ 8.30 (d, *J* = 5.4 Hz, 2H), 6.5 (t, *J* = 5.4 Hz, 1H), 6.2 (s, 1H), 2.90 (s, 2H), 2.70 (m, 4H), 2.45 (m, 4H), 2.05 (s, 3H), 2.85 (s, 6H), 2.70 (s, 6H), 1.45 (s, 6H); IR (KBr) 1640 cm^{-1}; MS *m/z* 397 (M^+). Anal. ($C_{23}H_{35}N_5O$) C, H, N.

(*R*)-Adamantane-1-carboxylic Acid *N*-[1-Methyl-2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]carboxamide Dihydrochloride (27). Compound **27** was prepared from D-alanine-*N*-*tert*-butoxycarboxamide and 1-(2-methoxyphenyl)piperazine using a synthetic sequence identical to that described for the synthesis of compound **29**. It was isolated in 30% overall yield as its dihydrochloride salt: mp 195−198 °C; $[\alpha]^{25}_D = -20.6$ (*c* = 1.04, MeOH); ^{1}H NMR (DMSO-d_6) δ 7.63 (d, *J* = 8 Hz, 1H), 7.04−6.90 (m, 3H), 6.35 (m, 1H), 4.34 (s, 1H), 3.75 (s, 3H), 3.50−3.00 (m, 10H), 1.95 (s, 3H), 1.85 (m, 6H), 1.66 (m, 6H), 1.12 (m, 3H); IR (KBr) 1645 cm^{-1} (C═O); MS *m/z* 411 (M^+). Anal. ($C_{25}H_{37}N_3O_2\cdot 2HCl$) C, H, N.

(*R*)-Adamantane-1-carboxylic Acid *N*-[1-Methyl-2-[4-(2,3-dimethylphenyl)-1-piperazinyl]ethyl]carboxamide Dihydrochloride Hydrate (31). Compound **31** was prepared from D-alanine-*N*-*tert*-butoxycarboxamide and 1-(2,3-dimethylphenyl)piperazine using a synthetic sequence identical to that described for the synthesis of compound **29**. It was isolated in 71% yield as its dihydrochloride monohydrate salt: mp 229−30 °C; $[\alpha]^{25}_D = -21.8$ (*c* = 1, MeOH); ^{1}H NMR (DMSO-d_6) δ 7.65 (d, *J* = 9 Hz, 1H), 7.08 (t, *J* = 8 Hz, 1H), 6.95 (t, *J* = 9 Hz, 1H), 6.51 (m, 1H), 4.30 (m, 1H), 3.55 (m, 2H), 3.40−3.00 (m, 8H), 2.22 (s, 3H), 2.19 (s, 3H), 1.95 (s, 3H), 1.85 (s, 6H), 1.72 (s, 6H), 1.15 (s, 3H); IR (KBr) 1635 cm^{-1} (C═O); MS *m/z* 409 (M^+). Anal. ($C_{26}H_{39}N_3O\cdot 2HCl\cdot H_2O$) C, H, N.

(*S*)-Adamantane-1-carboxylic Acid *N*-[1-Methyl-2-[4-(2,3-dimethylphenyl)-1-piperazinyl]ethyl]carboxamide Dihydrochloride Sesquihydrate (32). Compound **32** was prepared from L-alanine-*N*-*tert*-butoxycarboxamide and 1-(2,3-dimethylphenyl)piperazine using a synthetic sequence identical to that described for the synthesis of compound **29**. It was isolated in 34% yield as its dihydrochloride sesquihydrate salt: mp 226−28 °C; $[\alpha]^{25}_D = +20.6$ (*c* = 1, MeOH); ^{1}H NMR identical to that described for compund **31**; IR (KBr) 1635 cm^{-1} (C═O); MS *m/z* 409 (M^+). Anal. ($C_{26}H_{39}N_3O\cdot 2HCl\cdot 1\ 1/2H_2O$) C, H, N.

Method L. Synthesis of N-Substituted Adamantyl Amides. Total Synthesis of Adamantane-1-carboxylic Acid *N*-[2-[4-(2-Pyrimidinyl)-1-piperazinyl]ethyl]-*N*-

methylcarboxamide Dihydrochloride Hemihydrate (38). 2-(4-Benzyl-1-piperazinyl)-*N*-methylacetamide. To a solution of 1-benzylpiperazine (26.5 g, 150 mmol) in 800 mL of dry dimethylformamide at room temperature was added a solution of *N*-methylchloroacetamide[54] (16.1 g, 150 mmol) in 400 mL of dry tetrahydrofuran. The resulting solution was stirred at 70 °C for 48 h. The reaction mixture was then concentrated on a rotary evaporator and the residue was partitioned between 400 mL of dichloromethane and 200 mL of 1 M aqueous sodium hydroxide. The organic layer was washed with 200 mL of brine, dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator. The desired 2-(4-benzyl-1-piperazinyl)-*N*-methylacetamide (28.5 g, 68%) was isolated by HPLC on silica gel using a gradient of methanol and ethyl acetate: ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 7.15 (bs, 1H), 3.53 (s, 2H), 3.00 (s, 2H), 2.86 (s, 3H), 2.83 (s, 3H), 2.68−2.36 (m, 8H).

2-(4-Benzyl-1-piperazinyl)ethylmethylamine. To a warm solution of 2-(4-benzyl-1-piperazinyl)-*N*-methylacetamide (10.94 g, 44.2 mmol) in 450 mL of dry tetrahydrofuran under a nitrogen atmosphere was added portionwise, with stirring, lithium aluminum hydride (7.70 g, 20.3 mmol). The resulting mixture was then refluxed under nitrogen overnight. The excess LAH was quenched by slow addition of water (7.7 mL) followed by 15% aqueous sodium hydroxide (7.5 mL). Another portion of water was added (23 mL) and the resulting precipitate was removed by filtration. The precipitate was washed with 500 mL of tetrahydrofuran followed by 300 mL of dichloromethane. The washings were added to the original filtrate and the combined organic layers were dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. The desired 2-(4-benzyl-1-piperazinyl)ethylmethylamine (8.50 g, 82%) was isolated by HPLC on silica gel using a gradient of methanol, ethyl acetate, and ammonia: ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 3.52 (s, 2H), 2.67 (t, J = 6 Hz, 2H), 2.48 (m, 10H), 2.45 (s, 3H), 1.82 (bs, 1H).

Adamantane-1-carboxylic Acid *N*-[2-(4-Benzyl-1-piperazinyl)ethyl]-*N*-methylcarboxamide. A solution of adamantane-1-carboxylic acid chloride (7.23 g, 36.4 mmol) and (2-[4-benzyl-1-piperazinyl]ethyl)methylamine (8.49 g, 36.4 mmol) in 200 mL of dry dichloromethane was stirred for 1 h. Then triethylamine (4.9 g, 49 mmol) in 80 mL of dry dichloromethane was added and the resulting mixture was stirred at room temperature overnight. The reaction mixture was washed with 200 mL of brine. The aqueous layer was extracted with 100 mL of dichloromethane and the combined organic layers were dried over anhydrous sodium sulfate. Concentration on a rotary evaporator afforded the desired adamantane-1-carboxylic acid 2-(4-benzyl-1-piperazinyl)ethyl-*N*-methylcarboxamide (13.58 g, 94%), which was used in the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 5H), 3.55 (t, J = 6.5 Hz 2H), 3.16 (s, 3H), 2.64−2.38 (m, 12H), 2.08 (m, 9H), 1.76 (m, 6H).

Adamantane-1-carboxylic Acid *N*-[2-(1-Piperazinyl)-ethyl]-*N*-methylcarboxamide. A solution of adamantane-1-carboxylic acid *N*-[2-(4-benzyl-1-piperazinyl)ethyl]-*N*-methylcarboxamide (13.58 g, 34.3 mmol) in 450 mL of ethanol was subjected to hydrogenation on a Parr shaker at 50 psi over 5% Rh/Al_2O_3 (8.55 g) at room temperature for 72 h. The catalyst was removed by filtration through Celite 545 and the solvent was removed on a rotary evaporator. The desired adamantane-1-carboxylic acid 2-(1-piperazinyl)ethyl-*N*-methylcarboxamide (6.84 g, 65%) was isolated by chromatography on silica gel using dichloromethane/methanol. A significant amount of starting material (4.40 g) was also recovered: ^{1}H NMR ($CDCl_3$) δ 3.52 (t, J = 7 Hz, 2H), 3.16 (s, 3H), 2.93 (m, 4H), 2.52 (m, 7H), 2.04 (m, 9H), 1.74 (m, 6H).

Adamantane-1-carboxylic Acid *N*-[2-[4-(2-Pyrimidinyl)-1-piperazinyl]ethyl]-*N*-methylcarboxamide Hydrochloride Hemihydrate (38). To a stirred solution of adamantane-1-carboxylic acid *N*-[2-(1-piperazinyl)ethyl]-*N*-methylcarboxamide (6.84 g, 22.4 mmol) and 2-chloropyrimidine (3.65 g, 31.9 mmol) in 200 mL of dry dimethylformamide under a nitrogen atmosphere were added solid anhydrous sodium carbonate (2.20 g, 20.8 mmol) and cesium carbonate (1.07 g, 3.28 mmol). The heterogeneous mixture was stirred at 65 °C overnight. The DMF was then removed on a rotary evaporator and the residue partitioned between 250 mL of dichloromethane and 200 mL of water. The organic layer was dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. The desired adamantane-1-carboxylic acid *N*-[2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl]-*N*-methylcarboxamide (**38**) was isolated by HPLC on silica gel using a gradient of methanol and ethyl acetate. A 3.0-g portion of the free base was converted to the dihydrochloride hemihydrate salt with ethanolic HCl (1.45 g, 40%): mp 214−23 °C; ^{1}H NMR (DMSO-d_6) δ 8.44 (d, J = 5.6 Hz, 2H), 6.76 (t, J = 5.6 Hz, 1H), 3.73 (m, 2H), 3.66 (m, 2H), 3.55 (m, 2H), 3.41 (t, J = 12.5 Hz, 2H), 3.13 (s, 3H), 3.24−3.00 (m, 4H), 1.97 (m, 3H), 1.90 (m, 6H), 1.60−1.75 (m, 6H); IR (KBr) 1615 cm^{-1} (C=O); MS *m*/*z* 383 (M^+). Anal. ($C_{22}H_{33}N_5O\cdot 2HCl\cdot 1/2H_2O$) C, H, N.

Method M. Total Synthesis of Adamantane-1-carboxylic Acid *N*-[2-[4-(2-Pyrimidinyl)-1-piperazinyl]ethyl]-*N*-isopropylcarboxamide Dihydrochloride Sesquihydrate (39). *N*-Isopropyl-4-(2-pyrimidinyl)-1-piperazineethanamine. To a solution of 4-(2-pyrimidinyl)-1-piperazineethanamine (2.46 g, 11.9 mmol) in 45 mL of methanol at room temperature were added in rapid succession acetone (0.71 g, 12 mmol) and zinc chloride/sodium cyanoborohydride complex (24 mL of a 0.5 M solution, 12 mmol). After 1 h, additional $ZnCl_2\cdot NaBH_3CN$ (2 mL of a 0.5 M solution, 1 mmol) was added and stirring was continued overnight. 1 M aqueous sodium hydroxide (15 mL) was then added and the reaction mixture was concentrated on a rotary evaporator. The resulting residue was partitioned between 250 mL of dichloromethane and 200 mL of brine. The aqueous layer was reextracted with 100 mL of dichloromethane and the combined organic layers were dried over anhydrous sodium sulfate and then concentrated on a rotary evaporator. The desired *N*-isopropyl-4-(2-pyrimidinyl)-1-piperazineethanamine (1.28 g, 43%) was isolated by HPLC on silica gel using a gradient of methanol and ammonia: ^{1}H NMR ($CDCl_3$) δ 8.31 (d, J = 5.2 Hz, 2H), 6.47 (t, J = 5.2 Hz, 1H), 3.83 (m, 4H), 2.78 (m, 3H), 2.44−2.60 (m, 6H), 1.75 (s, 1H), 1.10 (d, J = 6.5 Hz, 6H).

Adamantane-1-carboxylic Acid *N*-[2-[4-(2-Pyrimidinyl)-1-piperazinyl]ethyl]-*N*-isopropylcarboxamide Dihydrochloride Sesquihydrate (39). To a solution of adamantane-1-carboxylic acid chloride (1.09 g, 5.5 mmol) and triethylamine (1.5 g, 1.4 mmol) in 30 mL of dry dichloromethane was added a solution of *N*-isopropyl-4-(2-pyrimidinyl)-1-piperazineethanamine (1.27 g, 5.5 mmol) in 15 mL of dry dichloromethane. The resulting reaction mixture was stirred at room temperature overnight. The mixture was then washed with 30 mL of water and the aqueous layer reextracted with 30 mL of dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. The desired adamantane-1-carboxylic acid *N*-[2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl]-*N*-isopropylamide was isolated by HPLC on silica gel using a gradient of methanol and ethyl acetate and converted to its dihydrochloride sesquihydrate salt with ethanolic HCl (1.87 g, 71%): mp 194−210 °C; ^{1}H NMR (DMSO-d_6) δ 8.45 (d, J = 5.4 Hz, 2H), 6.77 (t, J = 5.4 Hz, 1H), 4.64 (m, 2H), 4.54 (m, 1H), 3.64−3.51 (m, 4H), 3.43 (t, J = 11 Hz, 2H), 3.14−3.01 (m, 4H), 1.98 (m, 3H), 1.88 (m, 6H), 1.67 (m, 6H), 1.19 (d, J = 7.5 Hz, 6H); IR (KBr) 1625 cm^{-1} (C=O); MS *m*/*z* 411 (M^+). Anal. ($C_{24}H_{37}N_5O\cdot 2HCl\cdot 3/4H_2O$) C, H, N.

Molecular Modeling Calculations. All computations were performed on a Silicon Graphics Indigo2 workstation. Molecules were built de novo and minimized using the MM3* force field as implemented in Macromodel 6.0.[55] Calculations were performed on the unprotonated form of the piperazine. Dihedral angles τ_1 (Figure 3, τ_1 = C1−C2−N3−C4) and τ_2 (Figure 4, τ_2 = N1−C2−N3−C4) were defined and rotated in 1° increments from 0° to 360° using MM3*. The dihedral angles were then held constant, and the molecules were minimized. Relative energies in kcal/mol were plotted against

the dihedral angle. The conformations depicted in Figures 3 and 4 refer to the global minimum energy structures.

Pharmacology. Binding Assays. All radioligand binding assays were performed using membranes from male Sprague−Dawley rats weighing 150−250 g. Rats were killed by decapitation, and the respective brain regions were dissected and prepared as described below prior to storage at −70 °C. Aliquots were taken for protein determination by the Lowry method.[56] All radioligand receptor binding assays were terminated by addition of cold Tris buffer and rapid filtration through Whatman GF/B glass-fiber filters. The filters were then washed three times with buffer, dried, and placed in scintillation vials for counting.

5-HT$_{1A}$ Receptor. The receptor binding studies were performed using a modification of a previously described procedure.[57] Hippocampal tissue was homogenized on ice in 40 volumes of buffer (50 mM Tris HCl, pH = 7.7) and centrifuged at 20 000 rpm for 20 min. The membrane pellet was resuspended in 40 volumes of buffer at 37 °C and incubated for 10 min to remove endogenous serotonin. The homogenate was then centrifuged as above, and the pellet was resuspended in 100 volumes of a second buffer (50 mM Tris HCl, pH = 7.4, containing 0.1% ascorbate, 10 μM pargyline, and 4 mM $CaCl_2$) and sonicated. Fractions of the homogenate (0.4−0.6 mg of protein/sample) were incubated at 37 °C for 10 min with 100 μL (1.5−1.8 nM) of [^{3}H]8-OH-DPAT and various concentrations of the test drug in a final volume of 1 mL of buffer (50 nM Tris HCl, pH = 7.7, containing 0.1% ascorbate, 10 μM pargyline, and 4 mM $CaCl_2$). Specific binding was determined with 1 μM 5-HT.

5-HT$_2$ Receptor. The receptor binding studies were performed by NovaScreen using a modification of previously described procedures.[58,59] Fractions containing rat cortical membranes were incubated at 37 °C for 15 min in 50 mM Tris buffer (pH 7.6) with 1.0 nM [^{3}H]ketanserin and various concentrations of the test drug. Specific binding was determined using 100 μM methysergide.

D$_2$ Receptor. D_2 receptor affinity was determined using limbic tissue and a procedure identical to that described for the 5-HT$_2$ receptor assay. Specific binding was determined using 10 μM sulpride, and ketanserin (30 nM) was included in all assay tubes to exclude binding to 5-HT$_2$ recpetors. The method is a modification of a previously described procedure.[58]

Serotonin Syndrome. This method is a variation of a previously published procedure.[60] Male Sprague−Dawley CD (Charles River) rats weighing 150−250 g were housed in groups of 6 under a 12-h light/dark cycle and allowed to acclimate for 1 week prior to testing. Food and water were available ad libitum. Test compound or control vehicle was administered ip (N = 8/treatment), and serotonin agonist activity was determined by scoring for the presence of the serotonin syndrome during the first 15 min after compound administration. Scoring the serotonin syndrome consisted of rating each of the following behaviors: (1) forepaw treading, (2) head weaving, (3) tremor, (4) hindlimb abduction, (5) flattened body posture, and (6) Straub tail on a 4-point intensity scale (0, 1, 2, 3), with a score of 3 demonstrating greatest intensity. Therefore, if each individual behavior received a maximum score of 3, the total maximum score that may be obtained by a single subject was 18. Serotonin antagonist activity was subsequently determined in each animal by following with a challenge dose of 8-OH-DPAT (3 mg/kg ip) and then scoring the presence of the serotonin syndrome for an additional 15 min. ED_{50} values were determined using a nonlinear regression analysis with inverse prediction.

Head Shake Models. These methods are variations of previously published procedures.[61] Male Sprague−Dawley CD (Charles River) rats weighing 200−300 g were housed in groups of 6 under a 12-h light/dark cycle and allowed to acclimate for 1 week prior to testing. Food and water were available ad libitum. Forty rats were used for each experiment (N = 8/treatment). Test compounds or control vehicle was administered ip 30 min prior to a subsequent ip administration of either quipazine (2.5 mg/kg) or (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride (DOI) (1.0 mg/kg). The volume of all injections was 1 mL/kg. Head shakes were counted for 30 min after injection of the 5-HT$_2$ agonist. The head shake response was defined as a rhythmic shaking of the head in a radial motion. The total number of head shakes was recorded for each rat. ED_{50} values were determined using nonlinear regression analysis with inverse prediction.

Geller−Seifter Conflict Model. The experimental method used for the Geller−Seifter conflict studies has been published elsewhere.[2] The procedure is a variation on the original method described by Geller and Seifter.[62]

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Supporting Information Available: References for the hydroxy- and aminoalkyl arylpiperazines used in this manuscript. This material is available free of charge via the Internet at http://pubs.acs.org.

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