the positional and thermal parameters and bond angles and distances are available as supplementary material. Figure 2 is a computer-generated drawing of 12 from the final X-ray coordinates.

Acknowledgment. We thank J. Springer and K. Hoogsteen (MSD Rahway) for the X-ray crystal structure of 12, R. Herbert and R. Williams for NMR, mass spectrum, and pK_a data, R. Barnaby for log P data, and S. Burton for typing this manuscript.

Registry No. 1, 63-75-2; 1·HBr, 300-08-3; 4·HCl, 128164-84-1; 5, 114724-55-9; 6·HCl, 129594-87-2; 7·HCl, 131041-73-1; 8, 114724-86-6; 9·HCl, 129594-88-3; 10, 131041-74-2; 11·HCl, 131041-75-3; 12·CF_3CO_2H, 131041-77-5; 13·Oxalate, 131041-79-7; 14·oxalate, 131041-81-1; 15, 131041-82-2; 15·HCl, 131041-83-3; 16·oxalate, 124218-45-7; 17·oxalate, 131041-85-5; 18, 124218-27-5; 18·HCl, 124218-41-3; 19, 131041-86-6; 19·HCl, 131041-87-7; 20·oxalate, 131041-89-9; 21, 57933-84-3; 22, 125097-83-8; 23, 131041-90-2; 24, 131041-91-3; 25, 131041-92-4; 26, 131041-93-5; 27, 98-92-0; 29, 128164-72-7; 31, 5470-70-2; 32, 63065-25-8; 33, 26563-33-7; 33·oxalate, 131041-94-6; 34, 131041-95-7; 36, 40871-16-7; 37, 124218-55-9; 38, 124218-56-0; 39, 124232-59-3; 40, 131041-96-8; 41, 131041-97-9; 42, 53370-50-6; 43, 131041-98-0; 44, 17521-49-2; 45, 131041-99-1; 46, 131042-00-7; 47, 131042-01-8; *N,N*-dimethylhydroxyguanidine hydrochloride, 32098-89-8; acetamide oxime, 22059-22-9; hydroxyguanidine hemisulfate, 6345-29-5; dimethylformamide dimethylacetal, 4637-24-5; hydroxylamine *O*-sulfonic acid, 2950-43-8; propionamide oxime, 29335-36-2; di-*tert*-butyl carbonate, 34619-03-9; hydroxylamine hydrochloride, 5470-11-1; 3-hydroxypropionitrile, 109-78-4; palladium hydroxide, 63310-18-9; bromomethane, 74-83-9; vinyl chloroformate, 5130-24-5; glycolic acid nitrile, 107-16-4; [^{3}H]-*N*-methylscopolamine, 83945-36-2; methyl 1-[(*tert*-butoxy)carbonyl]-4-hydroxy-5-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate, 124218-57-1; methyl 1-[(*tert*-butoxy)carbonyl]-5-methyl-4-(methylsulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate, 124218-58-2; [^{3}H]oxotremorine-M, 131042-02-9.

Supplementary Material Available: Tables of the atomic positional and thermal parameters, bond distances, and bond angles for 12, microanalyses for all novel compounds, and molecular modeling details (11 pages). Ordering information is given on any current masthead page.

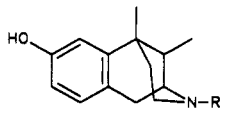
Identification and Exploitation of the σ-Opiate Pharmacophore

Richard A. Glennon,*,† J. Doyle Smith,† Abd M. Ismaiel,† Mahmoud El-Ashmawy,† George Battaglia,‡ and James B. Fischer§

Department of Medicinal Chemistry, School of Pharmacy, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298-0540, Department of Pharmacology, Loyola University of Chicago, Maywood, Illinois 60153, and Cambridge NeuroScience Research, Cambridge, Massachusetts 02139. *Received August 9, 1990*

Certain benzomorphan "σ-opiates" such as *N*-allylnormetazocine (NANM) bind at σ receptors with modest affinity and with little selectivity (i.e., they also bind at phencyclidine or PCP sites). In order to identify the primary pharmacophore of the benzomorphans, we prepared several amine-substituted derivatives of 1-phenyl-2-aminopropane. Several simple alkyl-substituted analogues were shown to bind at σ sites with affinities comparable to that of NANM itself; among these was the *N*-benzyl derivative **9** (K_i = 117 nM). Lengthening the spacer between the terminal amine and the phenyl group from one to five methylene units resulted in a significant increase in affinity (e.g. **15**, K_i = 6.3 nM). In addition, unlike the benzomorphans, these phenalkylamines do not bind at PCP sites. The results of the present study reveal that (a) the 1-phenyl-2-aminopropane nucleus of the benzomorphans is sufficient for binding at σ sites provided that the terminal amine is not a primary amine and that (b) introduction of (phenylalkyl)amine substituents affords compounds that represent a new class of high-affinity σ-selective agents.

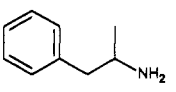
Certain benzomorphan opiates, in particular cyclazocine (**1**), pentazocine (**2**), and *N*-allylnormetazocine (SKF-10047; NANM) (**3**), are capable of producing psychotomimetic effects in animals and in humans.[1-3] An examination of the optical isomers of these benzomorphan derivatives reveals that their classical opiate agonist or antagonist actioins are primarily attributable to their (-)-isomers (e.g. ref 4), and binding profiles suggest that (-)-NANM, for example, may be acting at μ and κ opiate receptors.[5,6] (+)-NANM, on the other hand, displays a low affinity for these receptors.[5-7] Furthermore, most of the behavioral effects of (+)-NANM, unlike those of (-)-NANM, can not be antagonized by classical opiate antagonists such as naloxone.[8-12] Martin et al.[3] postulated the existence of "σ-opiate" receptors to account for the actions of these agents (i.e. "σ-opiates").



1 R = $-CH_2-C_3H_5$

2 R = $-CH_2CH=C(CH_3)_2$

3 R = $-CH_2CH=CH_2$



4

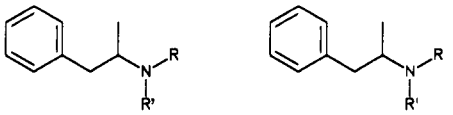
Because the σ-opiates can produce behavioral effects similar to those of phencyclidine (PCP),[11-17] and because they bind at PCP sites,[18,19] it was initially thought that the

† Virginia Commonwealth University.
‡ Loyola University of Chicago.
§ Cambridge NeuroScience Research.

(1) Haertzen, C. A. *Psychophamacologia (Berlin)* **1970**, *18*, 466.
(2) Keats, A. S.; Telford, J. In *Molecular Modification in Drug Design*; Gould, R. F., Ed.; Advances in Chemisitry Series 45; American Chemical Society: Washington, DC, 1964; p 170.
(3) Martin, W. R.; Eades, C. G.; Thompson, J. A.; Huppler, R. E.; Gilbert, P. E. *J. Pharmacol. Exp. Ther.* **1976**, *187*, 517.
(4) Aceto, M.; May, E. *Eur. J. Pharmacol.* **1983**, *91*, 267.
(5) Martin, B. R.; Katzen, J. S.; Woods, J. A.; Tripathi, H. L.; Harris, L. S.; May, E. *J. Pharmacol. Exp. Ther.* **1984**, *231*, 539.
(6) Tam, S. W. *Eur. J. Pharmacol.* **1985**, *109*, 33.
(7) Tam, S. W.; Cook, L. *Proc. Nat. Acad. Sci. U.S.A.* **1984**, *81*, 5618.
(8) Cowan, A. *Life Sci.* **1981**, *28*, 1559.
(9) Iwamoto, E. T. *J. Pharmacol. Exp. Ther.* **1981**, *217*, 451.
(10) Vaupel, D. B. *Eur. J. Pharmacol.* **1983**, *92*, 269.
(11) Brady, K. L.; Balster, R. L.; May, E. L. *Science* **1982**, *215*, 178.
(12) Katz, J. L.; Spealman, R. D.; Clark, R. D. *J. Pharmacol. Exp. Ther.* **1985**, *232*, 452.
(13) White, J. M.; Holtzman, S. G. *Psychopharmacology* **1983**, *80*, 1.
(14) Shannon, H. E. *J. Pharmacol. Exp. Ther.* **1983**, *225*, 144.
(15) Browne, R. *Science* **1982**, *217*, 1157.
(16) Khazan, N.; Young, G. A.; El-Fakahany, E. E.; Hong, O.; Calligaro, D. *Neuropharmacology* **1984**, *23*, 983.
(17) Shannon, H. E. *Eur. J. Pharmacol.* **1982**, *84*, 225.
(18) Zukin, R. S.; Zukin, S. R. *Mol. Pharmacol.* **1981**, *20*, 246.
(19) Quirion, R.; Hammer, R. P.; Herkenham, M.; Pert, C. B. *Proc. Nat. Acad. Sci. U.S.A.* **1981**, *78*, 5881.

0022-2623/91/1834-1094$02.50/0 © 1991 American Chemical Society

Table I. Physicochemical Properties of (Phenylalkyl)amines



compd	R	R′	isomer	$[\alpha]^{23}$ [a]	preparation[b]			mp, °C	formula[c]
6	$-CH_2CH_3$	H	*R*(−)	−	C	15%	C	151–153[d]	
7	$-CH_2CH_2CH_3$	H	*R*(−)	−	C	43%	MK	182–184[e]	
8	$-CH_2C_3H_5$	H	*R*(−)	−9.7 (M, 10)	B[f]	30%	PT	162–163	$C_{13}H_{19}N$·Mal
9	$-CH_2Ph$[g]	H	*R*(−)	−22.7 (M, 1)	C	51%	MK	173–175	$C_{16}H_{19}N$·HCl
10	$-CH(CH_3)Ph$[h]	H	*S*,*S*(−)	−22.6 (M, 10)	A	5%	MT	229–230	$C_{17}H_{21}N$·CHl
11	$-CH_2CH_2Ph$	H	*R*(−)	−13.6 (M, 1)	A	49%	MK	184–186	$C_{17}H_{21}N$·HCl
		H	*S*(+)	+13.3 (M, 1)	A	22%	MK	184–186	$C_{17}H_{21}N$·HCl
12	$-CH_2CH_2Ph$	Me	*S*(+)	+16.1 (M, 1)	A	56%	MK	184–186	$C_{18}H_{23}N$·HCl
13	$-(CH_2)_3Ph$	H	*R*(−)	−10.0 (M, 1)	A	80%	MK	215–217	$C_{18}H_{23}N$·HCl
		H	*S*(+)	+9.7 (M, 2)	B[i]	61%	PO	214–215	$C_{18}H_{23}N$·HCl
14	$-(CH_2)_4Ph$[j]	H	±	−	A	30%	EO	158–159	$C_{19}H_{25}N$·HCl
		H	*S*(+)	+6.0 (M, 2)	B[k]	71%	P	172–173	$C_{19}H_{25}N$·Mal
15	$-(CH_2)_5Ph$	H	*S*(+)	+14.3 (E, 1)	B[l]	58%	P	159–160	$C_{20}H_{27}N$·HCl
16	$-(CH_2)_5Ph$	Me	*S*(+)	+11.5 (M, 1)	D	74%	EO	89–90	$C_{21}H_{29}N$·HCl[m]
17	$-CH_2C{\equiv}CPh$	H	*R*(−)	−7[n] (E, 1)	E	14%	AE	223–224	$C_{18}H_{19}N$·HCl[o]
18	$-CH_2CH_2OPh$	H	*R*(−)	−15.2 (M, 1)	E	8%	MK	178–179	$C_{17}H_{21}NO$·HCl
19	$-CH_2CH_2C(=O)Ph$	H	*R*(−)	−16.2 (M, 1)	F	11%	T	146–147	$C_{18}H_{21}NO$·HCl

[a] Optical rotations were obtained in methanol (M), or 95% ethanol (E), at the specified concentration (g/100 mL). [b] Preparation: First column represents method employed (see Experimental Section); this is followed by percent yield and recrystallization solvent (A = MeCN, C = acetone, M = MeOH, E = 95% ethanol, K = MEK, O = Et_2O, P = 2-PrOH, T = EtOAc). [c] Compounds analyzed within 0.4% of theoretical; Mal = maleate salt. [d] HCl salt, lit[38] 155–156 °C. [e] HCl salt, lit[39] mp 176.5–178.5 °C. [f] Intermediate amide: mp 75–77 °C (94%, crude). [g] Benzoate salt, mp 103 °C; lit[40] 101–103 °C. [h] The *R*,*R*(+) isomer (α = +21.0) has been previously reported.[41] [i] Intermediate amide: mp 91–92 °C (78%, from petroleum ether). [j] Tosylate salt, mp 132–133 °C; lit[40] mp 130–132 °C. [k] Intermediate amide: mp 80–81 °C (79%, from petroleum ether). [l] Intermediate amide: mp 53–54 °C (74%, from petroleum ether). [m] Crystallized with 0.25 mol of H_2O. [n] Value is approximate due to limited sample. [o] Crystallized with 0.1 mol of H_2O.

psychotomimetic effects of σ-opiates might be mediated through PCP receptors or "PCP/σ sites". Subsequent studies employing [^{3}H]NANM as a radioligand to label σ sites demonstrated that the regional distribution of these sites is not identical with the regional distribution of PCP sites.[20,21] Furthermore, sites labeled by (+)-[^{3}H]NANM are different from those labeled by (−)-[^{3}H]NANM.[22] The neuroleptic agent haloperidol can also distinguish between PCP and σ sites; whereas haloperidol possesses a high affinity for [^{3}H]NANM-labeled σ sites, it binds with significantly lower affinity at PCP sites.[7,20,21] [^{3}H]Haloperidol, in the presence of agents to preclude binding at dopamine receptors, is commonly used now to label these sites,[7,23] and the regional distribution of [^{3}H]haloperidol-labeled σ sites is dissimilar to that of PCP sites.[24-26] In addition, these sites appear to be different from dopamine sites.[24,27-29] Thus, there are convincing arguments to support the concept that dopamine receptors, PCP sites, and σ sites represent distinct entities.

Benzomorphan analogues used for the study of σ pharmacology possess relatively low affinity for σ receptors and/or lack selectivity for these sites (e.g. NANM). Whereas careful selection of conditions might not interfere with the use of tritiated analogues of such agents in radioligand binding studies, these agents may be inappropriate for use in in vivo studies. As a consequence, identification of a function for σ receptors has been hindered, in part, because most agents that bind at these sites also produce effects that can be attributed to their actions at other sites. For example, the neuroleptic agent haloperidol binds with high affinity both at dopamine and at σ receptors; because of speculation that σ receptors may be involved in various types of mental disorders,[7] drugs acting at σ receptors might constitute a new mechanistic class of neuroleptics that lacks many of the undesirable side effects associated with classical neuroleptic therapy. However, like haloperidol, agents with demonstrated effectiveness (e.g. fluphenazine, trifluperazine, clopenthixol, and pimozide)[7,24,27,30,31] bind at dopamine receptors as well as at σ sites. There exists a need for the development of σ-selective agents that lack affinity for PCP sites and for dopamine receptors. Because benzomorphans derivatives typically display low affinity for dopamine receptors, the purpose of the present investigation was to identify an active pharmacophore of the benzomorphan σ-opiates with the expectation that derivatives thereof might display greater selectivity than the benzomorphans for σ sites relative to PCP sites.

Chemistry

All of the compounds were prepared by one of the six standard methods (see Table I): reductive alkylation of 1-phenyl-2-aminopropane (or one of its optical isomers) using catalytic (method A) or sodium cyanoborohydride

(20) Su, T. *J. Pharmacol. Exp. Ther.* **1982**, *223*, 284.
(21) Tam, S. W. *Proc. Nat. Acad. Sci. U.S.A.* **1983**, *80*, 6703.
(22) Compton, D. R.; Bagley, R. B.; Katzen, J. S.; Martin, B. R. *Life Sci.* **1987**, *40*, 2195.
(23) Tam, S. W.; Cook, L. *Fed. Proc.* **1984**, *43*, 1093.
(24) Largent, B. L.; Gundlach, A. L.; Snyder, S. H. *Proc. Nat. Acad. Sci. U.S.A.* **1984**, *81*, 4983.
(25) Steinfels, G. F.; Tam, S. W.; Cook, L. *Psychopharmacology* **1987**, *91*, 5.
(26) Contreras, P. C.; Quirion, R.; Gehlert, D. R.; Contreras, M. L.; Donohue, T. L. *Neurosci. Lett.* **1987**, *75*, 133.
(27) Largent, B. L.; Wikstrom, H.; Gundlach, A. L.; Snyder, S. H. *Mol. Pharmacol.* **1987**, *32*, 772.
(28) Wikstrom, H.; Andersson, B.; Elebing, T.; Svensson, K.; Carlsson, A.; Largent, B. *J. Med. Chem.* **1987**, *30*, 2169.
(29) van deWaterbeemd, H. V.; Tayar, N.; Testa, B.; Wikstrom, H.; Largent, B. *J. Med. Chem.* **1987**, *30*, 2175.
(30) Weber, E.; Sonders, M.; Quarum, M.; McLean, S.; Pou, S. *Proc. Nat. Acad. Sci. U.S.A.* **1986**, *83*, 8784.
(31) Largent, B.; Gundlach, A. L.; Snyder, S. H. *Eur. J. Pharmacol.* **1986**, *124*, 183.

Table II. Affinities of (Phenylalkyl)amine Derivatives at σ Binding Sites

compd	R	R'	isomer	K_i, nM[a] guinea pig [^{3}H]DTG	K_i, nM[a] rat [^{3}H]Halo	K_i, nM[a] guinea pig [^{3}H]Halo
3	(NANM)		(+)	429 (±106)		
4	H	H	±	-	>50000	
	H	H	R(-)	46400 (±24)		
5	Me	H	R(-)	8320 (±1240)		
6	Et	H	R(-)	660 (±25)		
7	nPr	H	R(-)	1640 (±170)		
8	$-CH_2C_3H_5$	H	R(-)	660 (±140)	664 (±85)	
9	$-CH_2Ph$	H	R(-)	117 (±17)	103 (±3)	
10	$-CH(CH_3)Ph$	H	S,S(-)	275 (±2)		
11	$-CH_2CH_2Ph$	H	R(-)	60 (±9)	46 (±9)	61 (±3)
		H	S(+)	31 (±2)	4.8 (±1.4)	
12	$-CH_2CH_2Ph$	Me	S(+)	6.6 (±0.2)	16 (±2)	4.8 (±1.2)
13	$-(CH_2)_3Ph$	H	R(-)	28 (±4)	14 (±5)	17 (±4)
		H	S(+)	22 (±2)		
14	$-(CH_2)_4Ph$	H	±	9.3 (±0.5)	3.9 (±1.2)	
		H	S(+)	6.6 (±4.1)		
15	$-(CH_2)_5Ph$	H	S(+)	6.3 (±3.4)		
16	$-(CH_2)_5Ph$	Me	S(+)	2.6 (±1.3)		
17	$-CH_2C{\equiv}CPh$	H	R(-)	97 (±44)		
18	$-CH_2CH_2OPh$	H	R(-)	45 (±6)	32 (±9)	
19	$-CH_2CH_2C(=O)Ph$	H	R(-)	56 (±8)	73 (±14)	

[a] Either guinea pig or rat cerebellar homogenates were employed, with either tritiated DTG or haloperidol used as radioligand. See Experimental Section for details. K_i values are followed by SEM in parentheses. [^{3}H]DTG data represent 2–5 determinations; other data reflect a minimum of three. Hill slopes for the new compounds in the [^{3}H]DTG assay ranged from 0.8 to 1.01, with the exception of compound *17* (Hill slope = 0.77).

(method C) reduction, acylation of an amine followed by reduction of the resulting amide with $LiAlH_4$ (method B), direct alkylation of the amine (methods D and E), and use of the amine in a Mannich reaction (method F).

Results and Discussion

Although the binding of various opiates to σ sites has been investigated, apparently no attempt has been made to determine what portion of the benzomorphan nucleus is important for σ affinity and/or selectivity. In this regard, we initially inspected the structures of the three most popular σ-opiates (i.e., cyclazocine, pentazocine, and NANM, **1–3**, respectively); because they differ in structure only with respect to their amine substituents, it was assumed that they could all interact with the receptor in a similar manner and that any difference in affinity would most likely be a reflection of the different terminal amine groups. Next, the structure of the benzomorphan nucleus was reduced to a simpler form: 1-phenyl-2-aminopropane (**4**). Compound **4** had been examined earlier and was found to lack affinity for σ sites; this was confirmed in the present investigation (racemic **4**; K_i > 50000 nM, Table II). However, because there is no evidence that benzomorphan derivatives bearing a primary amine bind at σ sites, we prepared and evaluated the cyclopropylmethyl (i.e., the cyclazocine) derivative of **4** (i.e. **8**). Because compound **8** was found to bind at σ sites with significantly greater affinity (K_i = 660 nM) than **4**, we undertook a more systematic investigation of alkyl-substituted derivatives of **4**.

As shown in Table II, simple *N*-alkyl derivatives of **4** (e.g. **5–8**) bind with higher affinity than **4** itself. The benzyl derivative **9** binds with even higher affinity (K_i = 117 nM) and is the first 1-phenyl-2-aminopropane derivative to bind with higher affinity than NANM (K_i = 429 nM). The branched α-methyl benzyl derivative **10** binds with somewhat lower affinity than **9**, whereas the phenethyl (i.e., phenazocine) derivative **11** (K_i = 60 nM) binds with twice the affinity of **9**. Increasing the length of the alkyl spacer between the amine and the phenyl group from two to five carbon atoms (i.e., **13** to **15**) results in a progressive increase in affinity. The 5-phenylpentyl derivative **15** (K_i = 6.3 nM) and its *N*-methyl analogue **16** (K_i = 2.6 nM) bind with a significantly greater affinity than the unsubstituted derivative **4** and even with a greater affinity than NANM (Table II).

Stereochemistry seems to play only a minor role; for example, there is less than a 10-fold difference in the affinity of the optical isomers of **11** and **13** (Table II). This finding is consistent with the observation that there is little (typically about a 3-fold) difference in the affinity of the isomers of benzomorphans **1–3**.[5]

Finally, we compared the affinity for the phenylpropyl derivative *R*-(−)-**13** with that of three analogues where a benzylic methylene group is replaced with either an sp hybridized carbon, an oxygen atom, or a carbonyl group (i.e., **16–18**); in each case, affinity (K_i = 96, 45, and 56 nM, respecively; Table II) was somewhat lower than that of *R*-(−)-**13**.

Because several radioligands and different animal species have been used in the past to study σ binding sites, several compounds were selected for a more thorough investigation. Table II shows the results for some of these compounds with both guinea pig and rat brain homogenates with either [^{3}H]DTG or [^{3}H]haloperidol used as radioligand. Due to the small differences observed, the use of multiple assay systems was discontinued.

All of the phenylalkyl-substituted derivatives of **4** (i.e., **9–15**) bind at σ sites with a higher affinity than NANM (K_i = 429 nM). Because σ-opiates typically bind at PCP sites, all of the compounds were examined for their ability to bind at these sites. The *N*-methyl derivative **12** binds at PCP sites with low affinity (K_i = 5000 nM) whereas its desmethyl analogue *R*-(−)-**11** binds with even lower affinity (K_i = 9000 nM). The remainder of the agents in Table II did not bind at PCP sites (i.e., K_i > 10000 nM). At this concentration, percent inhibition of binding ranged from less than 1% (compound **15**) to no more than 40%. Compounds **12** and *R*-(−)-**11** were examined in greater detail and were found to inhibit 93% and 100% of binding, respectively, at a concentration of 100000 nM. Unlike haloperidol, σ-opiates do not bind at D2 dopamine receptors; nevertheless, compound *R*-(−)-**13** was selected for

evaluation at dopamine receptors and at glutamate receptor types in addition to the PCP complex. The affinity (K_i values) of *R*-(−)-**13** for these sites/receptors is as follows: D1 dopamine, >10 000 nM; D2 dopamine, 4650 ± 430 nM; kainate, >10 000 nM; Quis/AMPA, >10 000 nM.

The results of the present study indicate that the 1-phenyl-2-aminopropane nucleus of the σ-opiates is sufficient for binding at σ sites provided that the terminal amine is not a primary amine, and that the phenylethylamine moiety most likely constitutes the primary pharmacophore of the benzomorphan σ-opiates. Furthermore, with the appropriate terminal amine substituents, the affinity of the 1-phenyl-2-aminopropane analogues is significantly greater than that of NANM. Most importantly, these agents, unlike the σ-opiates, do not bind at PCP sites. Thus, these compounds constitute a novel class of high-affinity σ-selective agents.

Experimental Section

Synthesis. Proton magnetic resonance spectra were obtained with a JEOL FX90Q spectrometer with tetramethylsilane as an internal standard. Spectral data are consistent with the assigned structures. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Optical rotations were determined by using a Perkin-Elmer Model 141 polarimeter with either MeOH or 95% EtOH as solvent. In one instance, limited sample size precluded the determination of a reliable optical rotation. Elemental analysis was performed by Atlantic Microlab and are within 0.4% of theory. Each of the experimentals below illustrate one of the methods described in Table I; see Table I for details.

(*R*)-(−)-*N*-(1-Methyl-2-phenylethyl)-2-phenyl-1-aminopropane Hydrochloride (*R*-(−)-13) (Method A). A mixture of hydrocinnamaldehyde (1.11 g, 8.2 mmol) and (*R*)-(−)-1-phenyl-2-aminopropane (0.94 g, 7 mmol) in MeOH (20 mL) was hydrogenated over 5% Pt/C at 45 psig at room temperature until the theoretical amount of H_2 was absorbed. The catalyst was removed by filtration and the methanolic solution was treated with 10% HCl until the mixture was strongly acidic. The solvent was removed under reduced pressure, and the crude solid product was recrystallized from MeOH/MEK to give 1.6 g (80%) of colorless crystals: mp 215–217 °C.

(*S*)-(+)-*N*-(1-Methyl-2-phenylethyl)-2-phenyl-1-aminopropane Hydrochloride (*S*-(+)-13) (Method B). Hydrocinnamoyl chloride (0.25 g, 1.5 mmol) was added dropwise to a stirred mixture of (*S*)-(+)-1-phenyl-2-aminopropane (0.2 g, 1.5 mmol), NEt_3 (0.15 g, 1.5 mmol), and CH_2Cl_2 (10 mL) at 0 °C. After the addition was complete, the reaction mixiture was allowed to stir at room temperature for 2 h, and the solvent was evaporated under reduced pressure. The residue was triturated with H_2O (10 mL), and the solid material was collected by filtration, washed with H_2O, and allowed to air dry. Recrystallization of the crude amide from petroleum ether gave 0.3 g (78%) of product as colorless needles: mp 91–92 °C. This product was used without further characterization. A solution of the amide (0.3 g, 1.1 mmol) in dry THF (10 mL) was added in a dropwise manner, and under a nitrogen atmosphere, to a stirred suspension of $LiAlH_4$ (0.2 g, 5.5 mmol) in THF (20 mL) at 0 °C. The mixture was heated at reflux for 7 h, the reaction flask was cooled on an ice bath and excess $LiAlH_4$ was decomposed by the dropwise addition of wet THF until the evolution of gas ceased. The reaction mixture was filtered, the solid material was washed with Et_2O (ca. 15 mL), and the combined filtrates were dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residual oil in anhydrous Et_2O was treated with an saturated ethereal solution of HCl to afford a crude salt. The salt was recrystallized from a 2-PrOH/Et_2O mixture to give 0.2 g (61%) of (*S*)-(+)-**13** as white crystals: mp 214–215 °C.

(*R*)-(−)-*N*-Benzyl-1-phenyl-2-aminopropane Hydrochloride (9) (Method C). Sodium cyanoborohydride (0.26 g, 4 mmol) was added over a 1-h period to a stirred mixture of (*R*)-(−)-1-phenyl-2-aminopropane sulfate (0.63 g, 3.4 mmol), benzaldehyde (0.55 g, 5.2 mmol), MeOH (3 mL), and glacial HOAc (0.5 g) at room temperature. During the addition, pH was maintained between 5.5 and 6 by the addition of HOAc. The mixture was allowed to stir at room temperature for 20 h, and the solvent was removed under reduced pressure; the residue was treated with excess 10% NaOH, and the product was extracted into Et_2O (20 mL). The ethereal solution was extracted with 10% HCl solution (3 mL), the aqueous portion was decanted, and the H_2O was removed under reduced pressure to give a solid product. Recrystallization from MeOH/MEK afforded 0.5 g (51%) of **9** as colorless crystals: mp 173–175 °C.

(*S*)-(+)-*N*-Methyl-*N*-(1-methyl-2-phenylethyl)-5-phenyl-1-aminopentane Hydrochloride (16) (Method D). A stirred solution of **15** (free base; 0.08 g, 0.28 mmol) and 37% formaldehyde (1 mL) in 90% formic acid (2 mL) was heated at reflux for 5 h. The reaction mixture was evaporated to dryness in vacuo, the residue was dissolved in a mixture of 1 N NaOH (10 mL) and Et_2O (10 mL), and the organic portion was separated, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The yellow oily product in anhydrous Et_2O was treated with an ethereal solution of HCl, and the crude hydrochloride salt was recrystallized from an absolute EtOH/anhydrous Et_2O mixture to give 70 mg (74%) of **16**: mp 89–90 °C.

(*R*)-(−)-*N*-(2-Phenoxyethyl)-1-phenyl-2-aminopropane Hydrochloride (18) (Method E). A mixture of 1-chloro-2-phenoxyethane (0.34 g, 2.1 mmol) and 1-phenyl-2-aminopropane (0.29 g, 2.1 mmol) was heated in a 5-mL sealed reaction tube at 95 °C for 20 h. The reaction mixture was allowed to cool to room temperature and was washed repeatedly with Et_2O to afford a solid product. Recrystallization from MeOH/MEK gave 50 mg (8%) of **18** as colorless crystals: mp 178–179 °C.

(*R*)-(−)-3-[*N*-(1-Methyl-2-phenylethyl)amino]propiophenone Hydrochloride (19) (Method F). A stirred mixture of (*R*)-(−)-1-phenyl-2-aminopropane hydrochloride (0.26 g, 1.5 mmol), acetophenone (0.64 g, 5.3 mmol), paraformaldehyde (87 mg), MeOH (1.2 mL), and concentrated HCl (1 drop) was heated at 65 °C for 24 h. The solvent was removed under reduced pressure, the crude semisolid residue was dissolved in H_2O (5 mL), and the aqueous solution was extracted with hexanes (2 × 10 mL). The aqueous portion was basified by the addition of 10% NaOH (0.5 mL) and extracted with hexanes (10 mL). The combined hexanes portion was extracted with 10% HCl (2 × 5 mL), and the aqueous portioin was evaporated to dryness under vacuum. Recrystallization of the crude product from EtOAc afforded 50 mg (11%) of **19** as colorless crystals: mp 146–147 °C.

Radioligand Binding. Guinea Pig/[^{3}H]DTG. σ-Receptor binding assays, using [^{3}H]DTG (ditolylguanidine) as radioligand and guinea pig brain membranes as source of receptor, were performed, as previously described by Weber and co-workers.[32] Briefly, guinea pig brain membranes (P2 microsomal fraction) were prepared from frozen guinea pig brains (Taconic) to a final protein concentration of 3 mg/mL and stored at −70 °C. For the assay, the membranes were thawed and diluted 1:3 with 50 mM Tris-HCl (pH 7.4), and 0.4 mL was combined with 50 μL of [^{3}H]DTG (1–2 nM final concentration) and 50 μL of unlabeled competing drug or buffer. The mixtures were incubated for 90 min at room temperature and incubation was terminated by rapid filtration under vacuum through Whatman GF/B or Schleicher & Schuell #32 glass fiber filters with use of a Brandel 48-well cell harvester. The filters were washed three times with 5 mL of cold Tris-HCl buffer and each filter was suspended in 5 mL of Cytoscint (ICN Biomedicals); radioactivity was measured by liquid scintillation spectrometry at a counting efficiency of 50%. Nonspecific binding was measured in the presence of 10 μM haloperidol and DTG.

Rat/[^{3}H]Haloperidol. Assays were performed with use of homogenates of cerebellum from male Sprague-Dawley rats. Tissues were weighed, homogenized in at least 25 volumes of ice-cold 50 mM Tris-HCl (pH 7.7 at room temperature) buffer, and centrifuged at 39000*g* for 15 min. This procedure was carried out twice more with intermediate resuspensioin of the pellet in fresh buffer. The final pellet was resuspended to 30 mg original wet weight per milliliter in ice-cold Tris-HCl (pH 7.7) buffer.

(32) Weber, E.; Sonders, M.; Quarum, M.; McLean, S.; Pou, S.; Keana, J. F. W. *Proc. Nat. Acad. Sci. U.S.A.* **1986**, *83*, 8784.

Guinea Pig/[^{3}H]Haloperidol. The same protocol used for rat was used in the guinea pig cerebellum assays.

Competition studies for [^{3}H]haloperidol-labeled σ receptors were conducted by incubating at least nine concentrations of competing drug with 1 nM [^{3}H]haloperidol (in the presence of 25 nM spiperone to preclude binding to D2 dopamine receptors) and 3 mg (original wet weight) of cerebellar homogenate in 2.5 mL of 50 mM Tris-HCl (pH 7.7) buffer. Nonspecific binding was determined in the presence of 10 μM DTG. Incubations were carried out for 90 min followed by rapid filtration under vacuum onto glass fiber filters (Whatman GF/C). Filters were washed with 15 mL of 50 mM Tris-HCl (pH 7.7) buffer and radioactivity was counted by liquid scintillation spectrometry.

Data represent the mean and SEM of at least three competition curves (unless otherwise stated). IC_{50} values were determined by analyzing displacement curves by using nonlinear least-squares regression analysis (e.g. see ref 33). IC_{50} values were converted to K_i values by using the Cheng–Prusoff equation.

Other Assays. High-affinity [^{3}H]kainate binding to kainate-type glutamate receptors[34] and [^{3}H]AMPA binding to quisqualate/AMPA glutamate receptors[35] were measured by using rat brain membranes as previously described.[35] Dopamine D1 ([^{3}H]SCH-23390) and D2 ([^{3}H]domperidone) receptor assays[36,37] were performed by using washed membranes prepared from frozen rat striata resuspended in a buffer containing 50 mM Tris-HCl, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$ (pH 7.4 at 37 °C). Phencyclidine (PCP) receptor binding assays were also performed as previously described[42,43] by using rat brain membranes with [^{3}H]MK-801 (97 Ci/mmol, synthesized as described[43]) as the radioligand.

Acknowledgment. This work was supported in part by funding from Cambridge NeuroScience Research and from the Virginia Center for Innovative Technology. We also wish to thank Kathleen J. Burke Howie for assistance with many of the receptor binding assays.

(33) Fischer, J. B.; Sconbrunn, A. *J. Biol. Chem.* **1988**, *263*, 2808.
(34) Murphy, D. E.; Snowhill, E. W.; Williams, M. *Neurochem. Res.* **1987**, *12*, 775.
(35) Bilard, W.; Ruperto, V.; Crosby, G.; Ioria, L. C.; Barnett, A. *Life Sci.* **1984**, *35*, 1885.
(36) Baudry, M.; Martres, M. P.; Schwartz, J. C. *Naunyn-Shmiedeberg's Arch. Pharmacol.* **1979**, *308*, 231.
(37) Honore, T.; Drejer, J.; Nielsen, M. *Neurosci. Lett.* **1986**, *65*, 47.
(38) Sterling Drug Inc. Brit. Patent 814,339, June 3, 1959; *Chem. Abstr.* **1959**, *53*, 19972g.
(39) Coutts, R. T.; Dawson, G. W.; Beckett, A. H. *J. Pharm. Pharmacol.* **1976**, *28*, 815.
(40) Schaeffer, J. C.; Cho, A. K.; Nagami, G. T.; Takimoto, G. S. *J. Pharm. Sci.* **1975**, *64*, 1462.
(41) Nichols, D. E.; Barfknecht, C. F.; Rusterholz, D. B.; Benington, F.; Morin, R. D. *J. Med. Chem.* **1973**, *16*, 480.
(42) Keana, J. F. W.; McBurney, R. N.; Scherz, M. W.; Fischer, J. B.; Hamilton, P. N.; Smith, S. M.; Server, A. C.; Finkbeiner, S.; Stevens, C. F.; Jahr, C.; Weber, E. *Proc. Nat. Acad. Sci. U.S.A.* **1989**, *86*, 5631.
(43) Keana, J. F. W.; Scherz, M. W.; Quarum, M.; Sonders, M. S.; Weber, E. *Life Sci.* **1988**, *43*, 965.