Binding of Substituted and Conformationally Restricted Derivatives of *N*-(3-Phenyl-*n*-propyl)-1-phenyl-2-aminopropane at σ-Receptors

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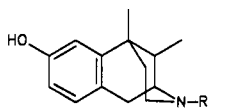
Certain benzomorphans, such as *N*-allylnormetazocine, are classical "σ-opiates" that bind both at σ and phencyclidine (PCP) binding sites with modest affinity. Recently, we identified N-substituted 2-phenylaminoethane as being the primary σ-pharmacophore of the benzomorphans and demonstrated that 1-phenyl-2-aminopropane (**2**) derivatives, depending upon their terminal amine substituents, constitute a novel class of high-affinity σ-selective agents. With this pharmacophore, it is shown in the present investigation that the aromatic hydroxyl group (a prime feature of all the σ-opiates) contributes little to the binding of **2** at σ-sites. It is also demonstrated that an N-substituted aminotetralin moiety (such as **17**, a conformationally restricted analogue of **2**) may also be considered a σ-opiate pharmacophore. Unlike the σ-opiates, derivatives of **2** and **17** display no affinity for PCP sites and must consequently lack those structural features important for the binding of benzomorphans at PCP sites. Because 3-phenylpiperidines and related σ-ligands also possess a phenylalkylamine imbedded within their structures, we propose that the 2-phenylaminoethane moiety is a common σ-pharmacophore for derivatives of **2**, the 3-phenylpiperidines, and the σ-opiates.

In addition to producing some effects similar to those of the classical opiates, certain benzomorphan derivatives such as *N*-allylnormetazocine (NANM; SKF 10,047; **1**, R



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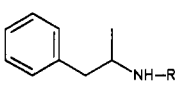

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= $CH_2CH{=}CH_2$) and pentazocine (**1**, R = $CH_2CH{=}C(CH_3)_2$) are capable of producing psychotomimetic effects in humans.[1] Whereas the opiate-like actions of NANM and related agents are primarily attributable to their interaction at μ- and κ-opiate receptors, these agents also interact with other populations of binding sites. These agents, termed "σ-opiates",[2] bind with modest affinity at σ-sites and at phencyclidine (i.e., PCP) sites. Central σ-sites can be labeled by (+)-[^{3}H]NANM.[1] Although relatively little is known about the structural requirements for the interaction of benzomorphan analogues at σ-sites (e.g. see refs 1, 3), the benzomorphan structure is not a requirement for binding. For example, haloperidol ($K_i \approx$ 5 nM) binds at σ-sites with a 20–200-fold higher affinity than that of most benzomorphans and [^{3}H]haloperidol, under the appropriate assay conditions, is also commonly used for labeling σ-sites in radioligand binding studies.[1]

Recently, we reported that amine-substituted 2-phenylaminoethanes constitute the primary pharmacophore of the σ-opiate benzomorphans.[4] Furthermore, we demonstrated that 1-phenyl-2-aminopropanes (**2**) bind at σ-sites and that introduction of various amine substituents results in agents with a higher affinity than most benzomorphans for these sites.[5] For example, **3** (**2**, R = $CH_2CH_2CH_2Ph$; PPAP) not only binds at σ-sites with high affinity (K_i = 22 nM) but, unlike NANM, it displays essentially no affinity for PCP sites, and it does not bind at D1 and D2 dopamine receptors as does haloperidol.[5] Because the phenylalkylamines **2** are more selective, and are structurally simpler, than the benzomorphans, e.g. they possess only a single asymmetric center (the stereochemistry at which is seemingly unimportant for σ-binding), they offer convenient templates with which to investigate structure–affinity relationships.

The distance between the terminal amine and the aromatic ring, and the distance between the amine and the phenolic (i.e., 2′) hydroxyl group, have been raised as possible issues of importance for the binding of benzomorphan-related agents at σ-sites.[6,7] Interestingly, the necessity of this hydroxyl group for binding has not been adequately demonstrated. Indeed, systematic structure–activity studies have been hampered by the lack of available benzomorphan derivatives, and those derivatives that are generally available typically possess a 2′-hydroxyl group. If this feature is important for binding, the 4-hydroxyl analogue of **2** should bind at σ-sites with higher affinity than the parent compound. Furthermore, if **2** constitutes a pharmacophore of the benzomorphans, conformationally restricted analogues of **2** should also bind at σ-sites; it might be noted that the benzomorphans **1** contain an aminotetralin moiety. Thus, the purpose of the present investigation was 2-fold: (a) to determine the influence of ring substituents, and in particular a 4-hydroxyl group, on the binding of **3** at σ-sites and (b) to determine whether conformationally restricted analogues of **3** retain affinity for these sites.

Chemistry

Synthesis of the target compounds was fairly trivial and involved one of several different methods (Table I). The appropriate unsubstituted or substituted 1-phenyl-2-aminopropane was alkylated with 3-phenylpropion-

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(3) For example, see: Largent, B. L.; Gundlach, A. L.; Snyder, S. H. *Proc. Nat. Acad. Sci. U.S.A.* **1984**, *81*, 4983–4987. Martin, B. R.; Katzen, J. S.; Woods, J. A.; Tripathi, H. L.; Harris, L. S.; May, E. L. *J. Pharmacol. Exp. Ther.* **1984**, *231*, 539–544.
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(7) Largent, B. L.; Wikstrom, H.; Gundlach, A. L.; Snyder, S. H. *Mol. Pharmacol.* **1987**, *32*, 772–784.

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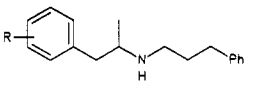
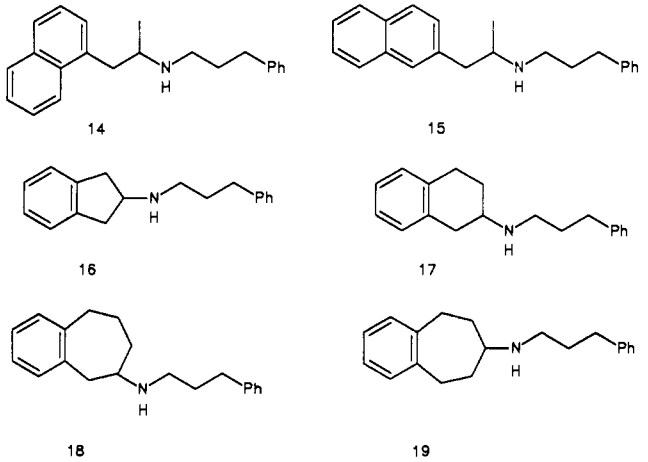
Table I. Physicochemical and σ-Binding Properties of Derivatives of **2**



	R	method[a]	% yield	RS[b]	mp, °C	formula[c]	K_i, nM (±SEM)[d]
R-(−)-**3**[e]	H						21.8 (2.1)
4	4-OH	A	88	EO	159–160	$C_{18}H_{23}NO{\cdot}HBr$	10.4 (0.0)
5	4-OMe	B	67	A	192–194	$C_{19}H_{25}NO{\cdot}HCl$	9.5 (0.5)
6	4-*n*-Pr	B	38	EO	183–184	$C_{21}H_{29}N{\cdot}HCl$	6.2 (0.5)
7	4-OEt	B	36	B	183–184	$C_{20}H_{27}NO{\cdot}HCl$	6.8 (3.8)
8	4-OBenzyl	C	43	E	181–183	$C_{25}H_{29}NO{\cdot}HCl$	27.1 (1.9)
9	3-Br	C[f]	35	IO	184–185	$C_{18}H_{22}BrN{\cdot}HCl$	6.0 (0.4)
10	4-Br	C[g]	19	EO	176–178	$C_{18}H_{22}BrN{\cdot}HCl$	8.8 (0.6)
11	3,4-Cl_2	C[h]	8	C	159–161	$C_{18}H_{21}Cl_2N{\cdot}HCl$	12.0 (0.6)
12[i]	4-I	D	28	EO	154–155	$C_{18}H_{22}IN{\cdot}HCl$	8.3 (0.7)
13	3-CF_3	E	37	C	167–169	$C_{19}H_{22}F_3N{\cdot}HCl$	3.9 (0.2)
14		B	50	EO	212–213	$C_{22}H_{25}N{\cdot}HCl$	17.6 (2.7)
15		B	50	EO	188–189	$C_{22}H_{25}N{\cdot}HCl$	6.3 (1.8)
16		B	62	EO	246–247	$C_{18}H_{21}N{\cdot}HCl$	27.4 (5.2)
17[e]							20.0 (0.7)
18[j]		F	70	I	225	$C_{20}H_{25}N{\cdot}HCl$	83.2 (26.1)
19[k]		F	81	I	250–251	$C_{20}H_{25}N{\cdot}HCl$	7.9 (0.8)
23	(+)-3-PPP						78.5 (13.4)
25	DTG						28.8 (3.8)

[a] Method of preparation; see Experimental Section. [b] Recrystallization solvent; A = EtOAc, B = 2-butanone, C = acetone, E = absolute EtOH, I = 2-PrOH, O = anhydrous Et_2O. [c] All new compounds analyzed correctly (±0.4%) for C, H, N. [d] K_i values represent duplicate determinations except for **3** (n = 4) and **11** (n = 5). K_i values for (+)-3-PPP (**23**) (n = 3) and ditolyl guanidine (DTG; **25**) (n = 6) are included for purposes of comparison. [e] Synthesis of **3** and **17** previously reported (refs 5 and 23). We previously reported a K_i value for *R*-(−)-**3** of 28 nM; the K_i value was redetermined for the present study. [f] Intermediate amide: mp 96–97 °C (64% from CCl_4/hexanes). [g] Intermediate amide: mp 112–113 °C (63% from CCl_4/hexanes). [h] Intermediate amide: mp 129–133 °C (crude product). [i] *R*-(−)-isomer. [j] Intermediate amide: mp 146 °C (55% from aqueous EtOH). [k] Intermediate amide: mp 211–213 °C (74% from aqueous EtOH).

aldehyde under reductive (H_2/Pd) conditions to afford compounds **5–7** and **14–16**; compound **4** was prepared by



14 **15**

16 **17**

18 **19**

O-demethylation of **5** with concentrated HBr. A similar reductive alkylation reaction was used to prepare **13**. Compounds **8–11**, **18**, and **19** were prepared by acylation of the appropriate amine with 3-phenylpropionyl chloride followed by reduction of the resulting amide with either $LiAlH_4$, or, in those instances where halogen was present, AlH_3. Synthesis of iodo derivative **12** involved nitration of amine-protected ($COCF_3$) (*R*)-(−)-1-phenyl-2-aminopropane, catalytic reduction of the nitro group to an amine and subsequent conversion of the amine to a triazene (via the diazonium salt), reaction of the triazene with KI, and deprotection of the amine with mild base.

Results and Discussion

The 4-unsubstituted compound (*R*)-(−)-**3** [(*R*(−)PPAP] binds at σ-sites with an affinity (K_i value) of 21.8 nM (Table I); its *S*-(+)-enantiomer binds with a similar (K_i = 22 nM)[5] affinity. 4-Hydroxylation of **3** enhances affinity by about 2-fold (**4**; K_i = 10.4 nM); thus, the 4-hydroxyl group does not appear to play a major role in the binding of these compounds at σ-sites. O-Methylation of this hydroxyl group (**5**; K_i = 9.5 nM) has no effect on affinity. The presence of a 2′-hydroxyl group is important for the analgesic activity of the benzomorphans; replacement of this hydroxyl group by halogen decreases this activity.[8] However, the effect of aromatic halogen-substitution on σ-binding is unknown. This prompted us to prepare the halogen analogues **9–13**; interestingly, all bind with an affinity comparable to that of the hydroxy analogue **4** (i.e., K_i = 3.9–12 nM; Table I). Although **4**, **5**, and **9–13** bind with an affinity that is somewhat greater than that of the unsubstituted parent compound, the changes in affinity are small and never exceed 6-fold. It may be argued that these substituents contribute to binding, but the evidence is less than convincing. The possibility also exists that there is a region of bulk tolerance that can accommodate these substituents. To test this hypothesis, we prepared several 4-substituted derivatives and two benz-fused analogues. 4-*n*-Propyl derivative **6** (K_i = 6.2 nM) and 4-ethoxy derivative **7** (K_i = 6.8) bind with affinities comparable to those of the 4-hydroxy and 4-bromo analogues **4** and **10**, suggesting that they are tolerated and that the slight enhancement seen relative to the affinity of **3** is probably not related to hydrophobic or electronic effects. Even the bulkier 4-benzyloxy derivative **8** binds with an affinity (K_i = 27.1 nM) comparable to that of the unsubstituted derivative **3**. Both ring-fused analogues (**14** and **15**; K_i = 17.6 and 6.3 nM, respectively) also bind with high affinity (Table I). Taken together, these findings suggest the existence of a region of bulk tolerance in the vicinity of the binding site associated with the aromatic portion of the PPAP series. However, due to the small, but possibly real, increases in affinity noted with some of the compounds, the possibility of rotameric binding cannot be ruled out at this time.

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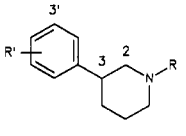
Aminotetralin **17**, a conformationally restricted analogue of **3**, binds at σ-sites with an affinity (K_i = 20 nM) identical with that of **3** itself. Because the aminotetralin moiety is also present in the structure of benzomorphans **1**, an amine-substituted aminotetralin may also be considered a benzomorphan pharmacophore. Contracting the aminotetralin to an aminoindan has little effect on affinity (**16**; K_i = 27.4 nM). 2-Aminobenzocycloheptane analogue **18** (K_i = 83 nM) binds at σ-sites with one-fourth the affinity of **3** whereas the 3-aminobenzocycloheptane **19** (K_i = 7.9 nM) binds with nearly 3 times the affinity of **3**.

After the present investigation had been nearly completed, a computer graphics study by Manallack and Beart[6] appeared in which they proposed a σ-receptor model with an optimal aromatic ring to terminal amine distance of 5.06 Å. For a variety of different agents that bind at σ-sites, Largent and co-workers[7] reported shortly thereafter that the ring to amine distance is not a critical factor for binding. Agents with distances of 4.3–6.4 Å apparently bind at these sites;[7] however, the highest affinity agent in that study (i.e. haloperidol; IC_{50} = 3 nM) has a ring to amine distance of 5.7 Å. Distances for compounds **16** (4.77 Å), **17** (5.12 Å), **18** (5.02 Å), and **19** (5.67 Å) fall within the broad range found by Largent et al.[7] Both groups of investigators commented on the importance of a hydroxyl group;[6,7] however, the present investigation would seem to suggest that with the PPAP type compounds, the hydroxyl group does not play a very significant role in binding.

Because benzomorphans **1** bind at PCP sites with significant affinity, compounds **4–19** were examined for their binding at these sites as an initial measure of selectivity; none of these compounds displayed significant affinity (i.e., K_i > 10000 nM). Compounds **5**, **11**, **12**, and **19** were further evaluated at several other binding sites at which σ and/or PCP-related ligands have occasionally been found to bind. As shown in Table II, all four agents display significant selectivity. Compound **19**, in particular, binds with at least a 1000-fold selectivity for σ versus most other binding sites.

A Common Pharmacophore. Since the time of our initial report on PPAP analogues,[9] Largent and co-workers have reported that 3-phenylpiperidines constitute a primary pharmacophore at σ-sites.[7] Obviously, because the 3-phenylpiperidine moiety, which is found in the σ-/dopamine ligands *N*-*n*-propyl-3-(3′-hydroxyphenyl)piperidine (3-PPP; **23**, R = *n*-propyl, R′ = 3′-hydroxy) and in the corresponding tricyclic analogues **24**, is not contained within the structure of the benzomorphans, it cannot be considered a primary pharmacophore of the latter agents. Nevertheless, there are certain structural similarities between the 3-phenylpiperidines **23** and **24** and the PPAP



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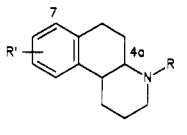

24

(i.e., **2**) analogues. Increasing the length of the alkyl chain on the amine results in a progressive increase in affinity in all three cases.[5,7,10] 3-Phenylpiperidines **23** do not bear a substituent α to the amine group (i.e., at the piperidine 2-position) and we have demonstrated that removal of the α-methyl group of **3** has no effect on affinity (i.e., α-desmethyl **3**, K_i = 18.7 nM; unpublished data). When this α-methyl group is present (as in **2**), there is no difference, or only a very small difference, in the affinity of the two optical isomers.[5] This is consistent with what is found with tricyclic analogues **24**; although the tricyclic analogues possess two asymmetric centers, it appears that the stereochemistry at the 4a-position (i.e., that position corresponding to the α-position of the PPAP analogues) plays a very small role in binding. In two instances where data are available, the two isomers bind either with identical affinity or with less than a 4-fold difference in affinity.[13] In addition, if the structures of **24** and **17** are compared, both are found to possess a common 2-aminotetralin moiety. Manallack and co-workers[6,11] have proposed a binding model wherein the presence of an aromatic hydroxyl group, or at least an electronegative substituent, may be important for binding. In this respect, the present data do not fit the proposed model. However, for the substituted compounds examined by Mannalack and Beart,[6,11] the corresponding unsubstituted compounds were not examined. Although there is no information available on analogues of **23** that lack aromatic substituents, it appears that replacement of the 3′-hydroxyl group with a fluoro or trifluoromethyl group, or replacement of the 3′-hydroxyl group with a 4′-hydroxyl group, has little (i.e., less than a 10-fold) effect on affinity, comparable results were observed in the tricyclic **24** series.[7,10] Results of the present study would suggest that electronegative substituents do not contribute significantly to receptor affinity and may simply occupy a region of bulk tolerance. Taken together, it would seem that an amine-substituted phenylethylamine moiety constitutes a common primary pharmacophore of the benzomorphans, 3-phenylpiperidines **23**, and their tricyclic counterparts **24**. In this manner, all four classes of compounds can be related to one another. Furthermore, although many 3-phenylpiperidines bind at dopamine receptors,[10] the PPAP analogues typically display very little affinity for either D1 or D2 dopamine receptors.[5] Thus, features present on the 3-phenylpiperidines, but lacking in derivatives of **3**, may contribute to their affinity for dopamine receptors.

Summary. It appears that **2** (actually its 2-phenylaminoethane skeleton) is the primary pharmacophore of the benzomorphan σ-opiates and that 4-hydroxylation has little influence on σ-affinity. (It should be emphasized, however, that the role of this hydroxyl group on intrinsic activity remains to be determined.) Substitution on the terminal amine is a major determinant for σ-affinity.[5] Where this amine substituent is held constant as *N*-3-phenylpropyl, substitution on the parent aromatic ring by 4-hydroxy, 4-methoxy, 4-ethoxy, 4-*n*-propyl, 4-benzyloxy, 3- or 4-bromo, 4-iodo, 3,4-dichloro, or 3-(trifluoromethyl) has relatively little (less than 10-fold) effect on affinity. Further, benz-fusion of the aromatic ring also has little effect on affinity; these results suggest that the σ-binding site is able to accommodate the added bulk of this fused ring and that fusion (as in **15**) may even slightly enhance σ-binding. An amine-substituted aminotetralin, due to its presence in the benzomorphan nucleus, may also be considered a pharmacophore of the benzomorphans. In addition, because **2** and aminotetralin **17** lack appreciable

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Table II. Binding Profile for Selected Derivatives of 2

binding site	IC_{50} values, nM (±SEM)			
	5	11	12	19
D1 dopamine	>10000	>10000	>10000	>10000
D2 dopamine	9320 (4500)	1790 (20)	3800 (970)	5800 (800)
muscarinic	>10000	7400 (730)	>10000	9500 (1800)
β-adrenergic	4940 (980)	1240 (120)	5570 (650)	>10000
kainate	>10000	>10000	>10000	>10000
quisqualate	>10000	>10000	>10000	>10000
PCP	>10000	>10000	>10000	>10000

[a] IC_{50} values from duplicate or triplicate determinations.

affinity for PCP sites, they must lack those structural features that contribute to the binding of benzomorphans to PCP sites. Finally, because the amine-substituted 2-phenylaminoethane moiety is found in 3-phenylpiperidines (i.e., 3-PPP analogues), it may serve as a common pharmacophore.

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, determined with a Thomas-Hoover melting point apparatus, are uncorrected. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter. Elemental analysis was performed by Atlantic Microlab, and determined values are within 0.4% of the theoretical values. Experimentals below illustrate the methods (methods A–F) described in Table I.

***N*-[3-(4-Hydroxyphenyl)prop-2-yl]-1-phenyl-3-aminopropane Hydrobromide (4). Method A.** A suspension of 5 (free base, 0.2 g, 0.63 mmol) in 48% HBr (5 mL) was heated at reflux for 6 h. The hot solution was filtered and allowed to cool to room temperature; the solid precipitate was collected by filtration, washed with anhydrous Et_2O (3 × 5 mL), and recrystallized from absolute EtOH/anhydrous Et_2O to afford 0.2 g (88%) of 4 as white crystals: mp 159–160 °C. Anal. ($C_{18}H_{23}NO$·HBr) C, H, N.

***N*-(3-Phenylpropyl)-2-aminoindan Hydrochloride (16). Method B.** A mixture of 2-aminoindan (0.3 g, 2.26 mmol), 3-phenylpropionaldehyde (0.3 g, 2.26 mmol), and a catalytic amount of 10% Pd/C in 95% EtOH (10 mL) was hydrogenated at 45 psig for 2 h. The catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. An Et_2O solution of the residue was treated with hydrogen chloride gas and the resultant precipitate was collected by filtration, washed well with Et_2O, and recrystallized from an absolute EtOH/anhydrous Et_2O mixture to yield 0.4 g (62%) of 16 as white crystals: mp 246–247 °C. Anal. ($C_{18}H_{21}N$·HCl) C, H, N.

***N*-(3-Phenylpropyl)-1-(4-bromophenyl)-2-aminopropane Hydrochloride (10). Method C.** A solution of 3-phenylpropionyl chloride (0.18 g, 1.5 mmol) in dry THF (10 mL) was added in a dropwise manner to a stirred solution of 1-(4-bromophenyl)-2-aminopropane[12] (0.3 g, 1.4 mmol) and NEt_3 (0.18 g, 1.8 mmol) in THF (15 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature overnight; the solid material was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. An Et_2O solution of the oily residue was washed successively with 5% HCl (10 mL), 5% Na_2CO_3 solution (100 mL), and water (30 mL). The Et_2O portion was dried ($MgSO_4$) and the solvent was removed under reduced pressure to afford 0.3 g (63%) of the amide intermediate as a white solid after recrystallization from CCl_4/hexanes: mp 112–113 °C.

AlH_3 was prepared by the careful addition of $AlCl_3$ (0.07 g, 0.5 mmol) to a suspension of $LiAlH_4$ (0.06 g, 1.68 mmol) in anhydrous Et_2O (50 mL) at 0 °C under an N_2 atmosphere. A solution of the above amide (0.1 g, 0.3 mmol) in Et_2O (10 mL) was added in a dropwise manner to the stirred suspension of AlH_3. The reaction mixture was allowed to stir for 30 min at 0 °C. Excess AlH_3 was decomposed by the successive addition of crushed ice (1 g) and 15% NaOH solution (2 mL) at 0 °C. The mixture was filtered and the organic portion of the filtrate was washed with water (3 × 15 mL) and dried ($MgSO_4$). The Et_2O solution was treated with hydrogen chloride gas to afford the crude salt; recrystallization from absolute EtOH/anhydrous Et_2O gave 0.02 g (19%) of 10 as white crystals: mp 176–178 °C. Anal. ($C_{18}H_{22}BrN$·HCl) C, H, N.

***(R)*-(−)-*N*-(3-Phenylpropyl)-1-(4-iodophenyl)-2-aminopropane Hydrochloride (12). Method D.** A solution of (*R*)-(−)-1-(4-iodophenyl)-2-aminopropane hydrochloride (22) (0.1 g, 0.33 mmol) in MeOH (2 mL) was adjusted to pH 5 by the addition of several drops of glacial HOAc. 3-Phenylpropionaldehyde (45 mg, 0.33 mmol) and $NaBH_3CN$ (21 mg, 0.33 mmol) were added, and the reaction mixture was allowed to stir at room temperature for 24 h. The solvent was removed under reduced pressure and the solid residue was suspended in a small amount of water; the pH was adjusted to 2 by the addition of 10% HCl and the mixture was extracted with Et_2O (3 × 10 mL) to remove unreacted aldehyde. The aqueous portion was basified by the addition of 20% NaOH and the mixture was again extracted with Et_2O (3 × 10 mL). The combined Et_2O solution was dried ($MgSO_4$) and saturated with hydrogen chloride gas to afford 40 mg (28%) of 12 after recrystallization from absolute EtOH/anhydrous Et_2O: mp 154–155 °C; $[\alpha]^{25} \approx -52°$ (*c* 0.3%, MeOH) (Note: a small sample size precluded an accurate determination of optical rotation.) Anal. ($C_{18}H_{22}IN$·HCl) C, H, N.

***N*-(3-Phenylpropyl)-1-[3-(trifluoromethyl)phenyl]-2-aminopropane Hydrochloride (13). Method E.** A mixture of 1-[3-(trifluoromethyl)phenyl]-2-propanone (102 mg, 0.5 mmol), 3-phenyl-1-propylamine (86 mg, 0.64 mmol), glacial HOAc (8 mg, 0.13 mmol), and MeOH (2 mL) was allowed to stir at room temperature for 0.5 h. To this mixture was added over a 4-h period sodium borohydride (19 mg, 0.5 mmol) and the mixture was allowed to stir at room temperature for 20 h. The solvents were removed under reduced pressure with gentle warming to give a small amount of an oil which was cooled and treated with 10% HCl. The crude product was collected by filtration and recrystallized from acetone to give 66 mg (37%) of 13 as colorless crystals: mp 167–169 °C. Anal. ($C_{19}H_{22}F_3N$·HCl) C, H, N.

7-[(3-Phenylpropyl)amino]-6,7,8,9-tetrahydro-5*H*-benzocycloheptane Hydrochloride (19). Method F. A mixture of 7-amino-6,7,8,9-tetrahydro-5*H*-benzocycloheptane hydrochloride[13] (0.23 g, 1.2 mmol) and triethylamine (0.5 mL, 3.6 mmol) in dry THF (25 mL) was stirred for about 15 min; a solution of 3-phenylpropionyl chloride (0.2 g, 1.2 mmol) in dry THF (5 mL) was added dropwise with stirring and the reaction mixture was allowed to stir at room temperature overnight. The solid material was collected by filtration and was washed with THF (2 × 10 mL). The combined filtrate and washings were evaporated under reduced pressure to obtain a solid residue that was washed with 5% HCl (20 mL) and with water (20 mL); the solid material was dried and recrystallized from aqueous EtOH to give 0.25 g (74%) of the intermediate amide as a white solid: mp 211–213 °C. A solution of the amide (230 mg, 0.8 mmol) in dry THF (30 mL) was added dropwise at 0 °C to a stirred suspension of $LiAlH_4$ (120 mg, 4 mmol) in dry THF (20 mL). After complete addition, the reaction mixture was heated at reflux with stirring overnight; the reaction mixture was cooled to 0 °C and excess $LiAlH_4$ was decomposed by addition of a few drops of water followed by several drops of 30% NaOH. The reaction mixture was filtered and the solid material was washed with THF (ca. 20 mL). The combined filtrates and washings were evaporated under reduced pressure, and an Et_2O (30 mL) solution of the oily residue was washed with water (2 × 10 mL), dried ($MgSO_4$), and saturated with hydrogen chloride gas to give a white solid hydrochloride salt. Recrystallization from 2-propanol gave 200 mg (81%) of 19 as white crystals: mp 250–251 °C. Anal. ($C_{20}H_{25}N$·HCl) C, H, N.

(*R*)-(−)-*N*-(Trifluoroacetyl)-1-(4-nitrophenyl)-2-aminopropane (20). (*R*)-(−)-1-phenyl-2-aminopropane (1 g) was added in small portions, with stirring, over a 1-h period to fuming HNO_3 (5 mL) at −20 °C; after the addition was complete, stirring was allowed to continue for an additional 2 h. The reaction mixture was then shaken with approximately four times its volume of crushed ice. The acid solution was washed with benzene to remove any nonbasic organic products and the solution was made strongly basic by the addition of 6 M NaOH solution. The cloudy solution was extracted with benzene (3 × 15 mL), the organic portion was dried (anhydrous K_2CO_3), and the solvent was evaporated under reduced pressure. Trifluoroacetic anhydride (0.3 g, 1.4 mmol) was added in a dropwise manner to a stirred solution of this crude amine (0.23 g, 1.3 mmol) in dry benzene (10 mL). After the addition was complete, the reaction mixture was allowed to heat at reflux for 3 h, and the solid product that formed upon cooling was collected by filtration. The white solid product was washed with 1 N HCl (5 mL) and recrystallized from $CHCl_3$ to give 0.2 g of **20**: mp 171–172 °C; $[\alpha]^{20} = -35.2°$ (*c* 10, THF) [for the *S*-(+)-isomer: lit.[14] mp 172–173 °C; lit.[14] $[\alpha] = +35.5°$].

(*R*)-(+)-*N*-(Trifluoroacetyl)-1-(4-aminophenyl)-2-aminopropane (21). A solution of **20** (0.4 g, 1.45 mmol) in absolute EtOH (20 mL) was hydrogenated with a catalytic amount of 10% Pd/C at 40 psig for 2 h. The catalyst was removed by filtration and the solvent was removed under reduced pressure. The residue was recrystallized from hexanes to afford 0.23 g (65%) of **21**: mp 84–85 °C; $[\alpha]^{20} = +14.5°$ (*c* 1.0, $CHCl_3$) [for the *S*-(−)-isomer: lit.[14] mp 76–77 °C; lit.[14] $[\alpha] = -13.9°$].

(*R*)-(−)-1-(4-Iodophenyl)-2-aminopropane Hydrochloride (22). Concentrated HCl (0.4 mL) was slowly added to a suspension of **21** (0.17 g, 0.7 mmol) in water (8 mL) and the mixture was allowed to stir until a homogeneous slurry was obtained (ca. 30 min). The slurry was cooled to 0–5 °C on an ice bath and a solution of $NaNO_2$ (0.07 g) in water (1 mL) was added in a dropwise manner. After 30 min, a solution of piperidine (1.7 g) in water (20 mL) was added and stirring was allowed to continue for another 30 min. The crude product was collected by filtration and recrystallized from aqueous EtOH to give 0.2 g (84%) of the triazene; mp 145–146 °C. A solution of CF_3COOH (0.1 g, 1 mmol) in dry MeCN (10 mL) was added in a dropwise manner to a stirred solution of the triazene (0.17 g, 0.5 mmol) and NaI (0.072 g, 0.5 mmol) in MeCN at 0 °C. The yellow reaction mixture was allowed to stir at room temperature for 20 h; water (200 mL) was added and the solution was extracted with Et_2O (3 × 20 mL). The combined ethereal extracts were evaporated to dryness under reduced pressure to afford 110 mg of the *N*-trifluoroacetyl-protected free base of **22**: mp 144–146 °C, after recrystallization from aqueous EtOH. Deprotection was accomplished by allowing the trifluoroacetyl derivative to stir with 10% NaOH (10 mL) at room temperature for 3 h. The aqueous mixture was extracted with Et_2O (3 × 5 mL), and the Et_2O solution was dried ($MgSO_4$) and treated with hydrogen chloride gas. Recrystallization from an absolute EtOH/anhydrous Et_2O mixture afforded 0.06 g (70%) of the title compound: mp 260–262 °C; $[\alpha]^{25} = -5.7°$ (*c* 7, MeOH). Compound **22** has been previously synthesized,[15,16] but no optical rotation was reported.

Modeling. Interactive molecular modeling was performed with the Sybyl (version 5.3) software package on a VAX 6420 and an Evans and Sutherland PS 390 display terminal. Starting coordinates were generated with Concord and minimized with Maximin2. The atomic charges were calculated by the Gasteiger–Hückel method. Ring conformations were searched with the Search program using a step size of 3°. The number of conformations generated varied depending upon ring size (i.e. range of 28 for 16 to 275 for 19). Lowest energy conformations were subsequently optimized as described above.

Radioligand Binding Studies. Guinea Pig/[^{3}H]DTG. σ receptor binding assays, using [^{3}H]DTG (ditolyl guanidine; **25**) as radioligand and guinea pig brain membranes as source of receptor, were performed as previously described by Weber and co-workers.[17] 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 using 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.

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 18). IC_{50} values were converted to K_i values with the Cheng-Prusoff equation.

Other Assays. High-affinity [^{3}H]kainate binding to kainate-type glutamate receptors[19] and [^{3}H]AMPA binding to quisqualate/AMPA glutamate receptors[20] were measured with rat brain membranes as previously described.[20] Dopamine D1 ([^{3}H]SCH-23390) and D2 ([^{3}H]domperidone) receptor assays[21,22] were performed with 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). PCP binding assays[24,25] were performed with rat brain membranes using [^{3}H]MK-801 (97 Ci/mmol, synthesized as described[25]) as radioligand. Binding to muscarinic and β-adrenergic receptors was measured as previously described with [^{3}H]QNB[26] and [^{3}H]dihydroalprenolol,[27] respectively, in rat brain membrane preparations.

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