(±)-28·HCl, 140465-62-9; (±)-29, 140465-92-5; (±)-29·HCl, 140465-63-0; (±)-30, 140465-93-6; (±)-30·HCl, 140465-64-1; (±)-31, 140465-94-7; (±)-31·HCl, 140465-65-2; (±)-32, 140465-95-8; (±)-32·HCl, 140465-66-3; (±)-33, 140465-96-9; (±)-33·HCl, 140465-67-4; (±)-34, 140465-97-0; (±)-34·HCl, 140465-68-5; (±)-35, 140465-98-1; (±)-35·HCl, 140465-69-6; (±)-36, 140465-99-2; (±)-36·HCl, 140465-70-9; (±)-37, 140466-00-8; (±)-37·HCl, 140465-71-0; (±)-38, 140466-01-9; (±)-38·HCl, 140465-72-1; (±)-39, 140466-02-0; (±)-39·HCl, 140465-73-2; (±)-40, 140466-03-1; (±)-40·HCl, 140465-74-3; 41, 139702-13-9; 41·HCl, 140465-75-4; 42, 139702-11-7; 42·HCl, 140465-76-5; 43, 139702-16-2; 43·HCl, 140465-77-6; 44, 139714-10-6; 44·HCl, 140465-78-7; 45, 139702-12-8; 45·HCl, 140605-04-5; (±)-46, 140466-04-2; 47, 54125-88-1; 48, 767-60-2; 49, 91843-52-6; $CH_3(CH_2)_2NH_2$·HCl, 556-53-6; $CH_3(CH_2)_3NH_2$·HCl, 3858-78-4; $Ph(CH_2)_2NH_2$·HCl, 156-28-5; CH_2=$CHCH_2Br$, 106-95-6; CH_2=$CH(CH_2)_2Br$, 5162-44-7; $(CH_3)_2C$=$CHCH_2Br$, 870-63-3; $PhCH_2Br$, 100-39-0; $Ph(CH_2)_2Br$, 103-63-9; $Ph(CH_2)_3Br$, 637-59-2; 4-$MeOC_6H_4CH_2Br$, 2746-25-0; 4-t-$BuC_6H_4CH_2Br$, 18880-00-7; 4-$NO_2C_6H_4CH_2Br$, 100-11-8; 4-$ClC_6H_4CH_2Br$, 622-95-7; 4-$NO_2C_6H_4(CH_2)_2Br$, 5339-26-4; cyclohexanamine hydrochloride, 4998-76-9; 1-adamantanamine hydrochloride, 665-66-7; 2-adamantanamine hydrochloride, 10523-68-9; 1-indanone, 83-33-0; cyclopropylmethyl bromide, 7051-34-5; 2-naphthylmethyl bromide, 939-26-4; 2-picolyl bromide, 55401-97-3; 2-thiophenecarbonyl chloride, 5271-67-0; 2-furancarbonyl chloride, 527-69-5; 1-benzosuberone, 826-73-3.

Supplementary Material Available: Tables of X-ray crystallographic data (5 pages). Ordering information is given on any current masthead page.

Spiropiperidines as High-Affinity, Selective σ Ligands

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A variety of achiral conformationally restricted spirocyclic piperidines have been prepared in an attempt to investigate the functional role of the central σ recognition site. All the compounds possessed a lipophilic N-substituent incorporating either a tetralin, indan, or benzocycloheptane skeleton. Their in vitro affinity at the σ site was assessed in radioligand displacement experiments with guinea pig cerebellum homogenates using the σ-specific radioligand [^{3}H]-*N*,*N*′-di-*o*-tolylguanidine ([^{3}H]-DTG, [^{3}H]-**6**). A study of the structure–activity relationships identified the *N*-butyl and *N*-dimethylallyl substituents as the optimum groups for high affinity and selectivity at the σ site (e.g., 3,4-dihydro-1′-(3-methylbut-2-enyl)spiro[1*H*-indene-1,4′-piperidine] (**48**), pIC_{50} = 8.9 vs [^{3}H]-**6** and greater than 10 000-fold selective over the dopamine D_2 receptor). Such compounds are amongst the highest affinity σ ligands reported to date, with excellent selectivity over the dopamine D_2 receptor, and may serve as a useful tool for exploring the physiological role of the σ site.

Introduction

The functional significance of the central σ recognition site has been a focus of considerable research in recent years.[1,2] This followed a suggestion by Martin et al. which implicated the σ site in psychosis[3] and the discovery that potent neuroleptic agents, such as haloperidol (**1**)[4] and perphenazine (**2**),[2,5] as well as the atypical antipsychotic agents remoxipride (**3**)[6] and BMY14802 (**4**)[6,7] (Chart I) exhibited high affinity for this site. Since most neuroleptic agents are dopamine D_2 antagonists and have undesirable side effects associated with them, the σ site may provide a novel therapeutic target for a new class of antipsychotics. Our aim was to develop potent, selective σ ligands as tools for investigating the possible role of the σ site in psychosis.

It has been suggested by Wikström and Largent that a 3- or 4-phenylpiperidine group and a lipophilic nitrogen substituent are important features in most classes of high affinity σ ligands.[2,8] For example, (+)-3-(3-hydroxyphenyl)-*N*-(1-propyl)piperidine (**5**) ((+)-3PPP), has a σ affinity of 40 nM vs [^{3}H]-DTG ([^{3}H]-**6**).[9] As an extension of the σ ligand pharmacophore proposed by Wikström and Largent, in the current paper we report the synthesis of a series of achiral spiropiperidines **10** (Figure 1) and their in vitro affinities at the σ site. The structure–activity relationships are described, and for the highest affinity σ ligands their affinity at the dopamine D_2 receptor was

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† Department of Chemistry.
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(1) (a) Chavkin, C. The Sigma Enigma: Biochemical and Functional Correlates Emerge for the Haloperidol-Sensitive Sigma Binding Site. *Trends Pharmacol. Sci.* **1990**, *11*, 213–215. (b) Connick, J.; Fox, P.; Nicholson, D. Psychotomimetic Effects and Sigma Ligands. *Trends Pharmacol. Sci.* **1990**, *11*, 274–275.

(2) Largent, B. L.; Wikström, H.; Gundlach, A. L.; Snyder, S. H. Structural Determinants of σ Receptor Affinity. *Mol. Pharmacol.* **1987**, *32*, 772–784.

(3) Martin, W. R.; Eades, C. G.; Thompson, J. A.; Harper, R. E.; Gilbert, P. E. The Effects of Morphine- and Nalorphine-Like Drugs in the Nondependent and Morphine-Dependent Chronic Spinal Dog. *J. Pharmacol. Exp. Ther.* **1976**, *197*, 517–532.

(4) (a) Su, T. P. Evidence for Sigma Opioid Receptor: Binding of [^{3}H]SKF-10,047 to Etorphine-Inaccessible Sites in Guinea-Pig Brain. *J. Pharmacol. Exp. Ther.* **1982**, *223*, 284–290. (b) Tam, S. W. Naloxone-Inaccessible σ Receptor in Rat Central Nervous System. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 6703–6707.

(5) Tam, S. W.; Cook, L. σ-Opiates and Certain Antipsychotic Drugs Mutually Inhibit (+)-[^{3}H]SKF 10,047 and [^{3}H]-Haloperidol Binding in Guinea Pig Brain Membranes. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 5618–5621.

(6) (a) Largent, B. L.; Wikström, H.; Snowman, A. M.; Snyder, S. H. Novel Antipsychotic Drugs Share High Affinity for σ Receptors. *Eur. J. Pharmacol.* **1988**, *155*, 345–347. (b) Wadworth, A. N.; Heel, R. C. Remoxipride: A Review of its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Potential in Schizophrenia. *Drugs* **1990**, *40*, 863–879.

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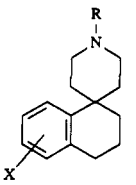
Table I. Spirotetralins



no.	R	X	binding data: pIC_{50} ± SEM[a] σ[c]	D_2[d]	mp, °C	microanalysis[b]	method of synthesis
24	$(CH_3)_2C{=}CHCH_2$	H	8.98 ± 0.08	5.26	274–7	$C_{19}H_{27}N{\cdot}HCl{\cdot}0.6H_2O$[e]	C
25	$CH_3(CH_2)_3$	H	8.92 ± 0.06	4.96 ± 0.04	245–8	$C_{18}H_{27}N{\cdot}HCl$	B
26	cyclohexylmethyl	H	8.64 ± 0.11	5.71	287–90	$C_{21}H_{31}N{\cdot}HCl$	B
27	$CH_3(CH_2)_5$	H	8.54 ± 0.13	5.69	266–9	$C_{20}H_{31}N{\cdot}HCl$	B
28	$Ph(CH_2)_2$	H	8.30 ± 0.06		272–4	$C_{22}H_{27}N{\cdot}HCl$	B
29	$CH_2{=}CH(CH_2)_2$	H	8.18 ± 0.13		276–9	$C_{18}H_{25}N{\cdot}HCl$	B
30	cyclopropylmethyl	H	7.99 ± 0.07		283–5	$C_{18}H_{25}N{\cdot}HCl{\cdot}0.6H_2O$	C
31	$CH_2{=}CHCH_2$	H	7.74 ± 0.10		239–42	$C_{17}H_{23}N{\cdot}HCl{\cdot}0.8H_2O$[f]	C
32	$4\text{-}CH_3C_6H_4CH_2$	H	8.85 ± 0.08	6.76 ± 0.15	255–8	$C_{22}H_{27}N{\cdot}HCl{\cdot}0.3H_2O$	B
33	$4\text{-}CH_3OC_6H_4CH_2$	H	8.78	6.92 ± 0.14	259–62	$C_{22}H_{27}NO{\cdot}HCl{\cdot}0.2H_2O$	B
34	$PhCH_2$	H	8.42 ± 0.04	6.02 ± 0.13	284–6[g]	$C_{21}H_{25}N{\cdot}HCl$	A
35	$4\text{-}ClC_6H_4CH_2$	H	8.17 ± 0.08		261–4	$C_{21}H_{24}ClN{\cdot}HCl$	B
36	$4\text{-}NO_2C_6H_4CH_2$	H	7.85 ± 0.07		237–40	$C_{21}H_{24}N_2O_2{\cdot}HCl$	B
37	2-tetrahydrofurylmethyl	H	8.26 ± 0.14		249–52	$C_{19}H_{27}NO{\cdot}HCl{\cdot}0.2H_2O$	B
38	2-thienylmethyl	H	8.20 ± 0.12		257–60	$C_{19}H_{23}NS{\cdot}HCl$	D
39	2-furylmethyl	H	8.02 ± 0.12		264–6	$C_{19}H_{23}NO{\cdot}HCl$	D
40	2-picolyl	H	7.95		214–7	$C_{20}H_{24}N_2{\cdot}2HCl{\cdot}1.3H_2O$[h]	B
41	$PhCH_2$	6-Me	8.26 ± 0.08		161–4	$C_{22}H_{27}N{\cdot}HCl{\cdot}0.2H_2O$	A
42	$PhCH_2$	6-Cl	8.17 ± 0.11		264–7	$C_{21}H_{24}Cl{\cdot}HCl$	A
43	$PhCH_2$	7-OH	7.16 ± 0.08		164–6	$C_{21}H_{25}NO{\cdot}HCl{\cdot}H_2O$	A
44	$PhCH_2$	7-OMe	7.13 ± 0.19		229–32	$C_{22}H_{27}NO{\cdot}HCl{\cdot}0.4H_2O$	A

[a] Binding results are expressed as $-\log_{10}(IC_{50})$ and are the mean of two to three independent determinations. Values without error limits were obtained from the mean of two independent experiments. [b] Elemental analyses for all compounds are within ±0.4% of the theoretical values for the indicated formula. [c] σ binding was measured by displacement of [^{3}H]-*N*,*N*′-di-*o*-tolylguanidine ([^{3}H]-**6**) from guinea pig cerebellum homogenates. Haloperidol had a pIC_{50} of 8.38 ± 0.05 in this assay. [d] D_2 binding was measured by displacement of [^{3}H]-(−)-sulpiride from rat striatal homogenates. [e] H: calcd 9.29, found 8.78. [f] H: calcd 8.83, found 8.14. [g] Lit.[25a] mp 285–287 °C. [h] H: calcd 7.41, found 6.97.

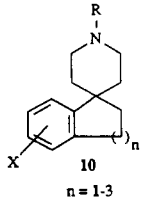


Figure 1. Proposed spirocyclic σ ligands.

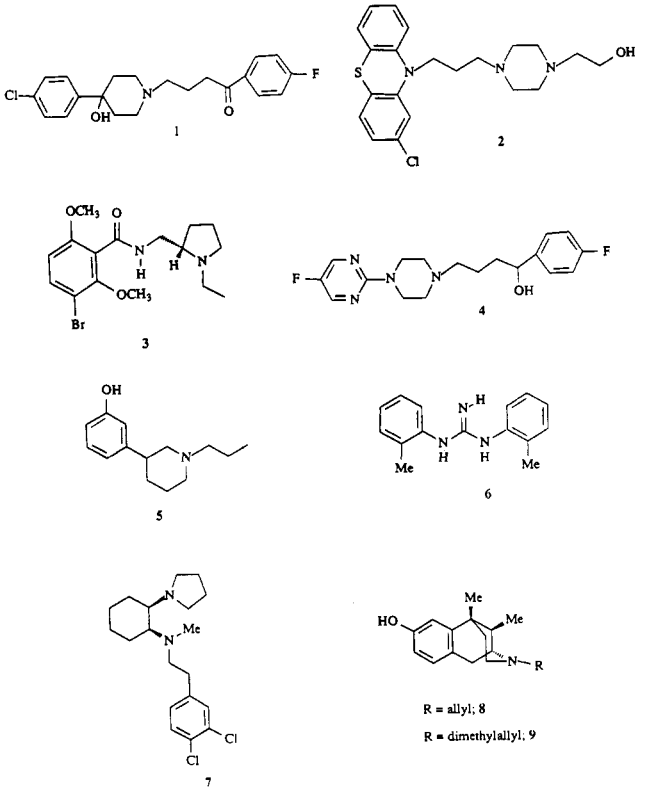
evaluated.

Chemistry

A general synthetic route to the tetralin and benzocycloheptane derivatives **10** (n = 2 and 3, respectively) is presented in Scheme I.

Using a procedure described by Ainsworth et al.,[10] *N*-

Chart I

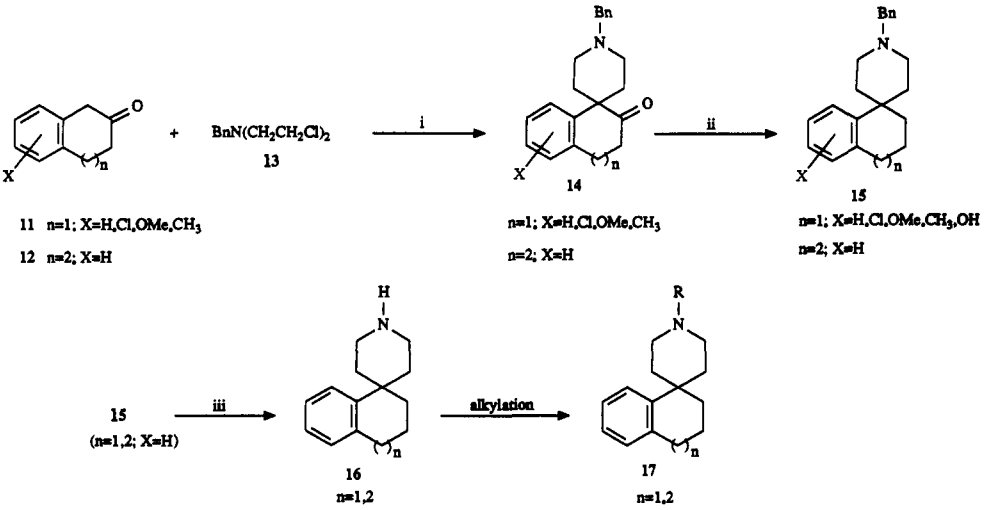


(7) (a) Taylor, D. P.; Dekleva, J. Potential Antipsychotic BMY 14802 Selectively Binds to Sigma Sites. *Drug Dev. Res.* **1987**, *11*, 65–70. (b) Taylor, D. P.; Elson, M. S.; Lobeck, W. G.; Riblet, L. A.; Temple, D. L.; Yevich, J. P. BMY 14802: A Potential Antipsychotic Agent That Does Not Bind to D-2 Dopamine Sites. *Soc. Neurosci. Abstr.* **1985**, *11*, 114.

(8) (a) Wikström, H.; Andersson, B.; Elebring, T.; Svensson, K.; Carlsson, A.; Largent, B. L. N-Substituted 1,2,3,4,4a,5,6,10b-Octahydrobenzo[*f*]quinolines and 3-Phenylpiperidines: Effects on Central Dopamine and σ Receptors. *J. Med. Chem.* **1987**, *30*, 2169–2174. (b) Van de Waterbeemd, H.; El Tayar, N.; Testa, B.; Wikström, H.; Largent, B. L. Quantitative Structure–Activity Relationships and Eudismic Analyses of the Presynaptic Dopaminergic Activity and Dopamine D2 and σ Receptor Affinities of 3-(3-Hydroxyphenyl)piperidines and Octahydrobenzo[*f*]quinolines. *J. Med. Chem.* **1987**, *30*, 2175–2181.

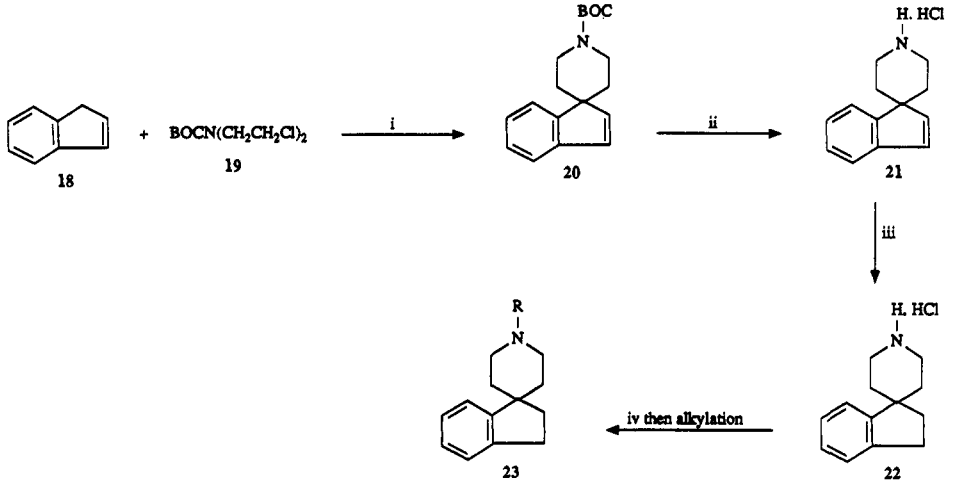
(9) Weber, E.; Sonders, M.; Quarum, M.; McLean, S.; Pou, S.; Keana, J. F. W. 1,3-Di(2-[5-^{3}H]tolyl)guanidine: A Selective Ligand That Labels σ-Type Receptors for Psychotomimetic Opiates and Antipsychotic Drugs. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 8784–8788.

Scheme I. Synthesis of the Tetralin and Benzocycloheptane Derivatives[a]



[a] Reagents: (i) KO-*t*-Bu, *t*-BuOH, DMSO; (ii) $NH_2NH_2{\cdot}H_2O$, KOH, diethylene glycol, reflux; (iii) H_2, $Pd(OH)_2$ on C, EtOH, HCO_2H then KOH(aq).

Scheme II. Synthesis of the Spirocyclic Indans[a]



[a] Reagents: (i) lithium bis(trimethylsilyl)amide, THF; (ii) HCl, EtOAc; (iii) H_2, Pd on C, EtOH; (iv) Na_2CO_3(aq).

benzylbis(2-chloroethyl)amine (**13**)[11] was reacted with an aryl-substituted 2-tetralone (**11**)[12] or 2-benzosuberone (**12**)[13] in the presence of potassium *tert*-butoxide to afford the spiropiperidines **14**. This alkylation proceeded in approximately 20% yield for the 2-tetralones and only 8% for 2-benzosuberone. The piperidine moiety was introduced exclusively at C-1, with no C-3 substituted products being isolated.

Attempts to remove the ketone function by sodium cyanoborohydride reduction of the corresponding tosylhydrazone[14] proved unsuccessful. However, transformation to the saturated analogues **15** was accomplished effectively using the Huang-Minlon[15] modification of the Wolff-Kishner reduction.[16] When this procedure was carried out on the 7-methoxytetralin derivative **14** (n = 1, X = 7-MeO), efficient reduction of the carbonyl group proceeded with concomitant conversion of the 7-methoxy substituent to 7-hydroxy. The extent of this exchange was dependent on the time allowed for the conversion, and, if desired, by careful monitoring of the reaction, complete replacement of the methoxy group could be achieved.

(10) Ainsworth, C.; Hackler, R. E.; Boaz, H. E. Nuclear Magnetic Resonance Studies on Spiro[tetralin-1,4′-piperidine] Compounds. *J. Org. Chem.* **1966**, *31*, 3345–3349.

(11) (a) Szarvasi, E.; Festal, D.; Grand, M.; Depin, J.-C.; Chabert, J. Spiro-[piperidine-4′:6 thiazolo[3,2,-*a*]pyrimidines] Thymoanaleptiques et Anti-Agregants Plaquettaires. *Eur. J. Med. Chem.-Chim. Ther.* **1976**, *11*, 115–124. (b) Handley, J.; Dow, A. Process for Preparing *N,N*-Bis(2-hydroxyethyl)benzylamine and *N,N*-Bis(2-chloroethyl)benzylamine. US Patent 4,748,246, 1985.

(12) (a) Shner, V.; Przhiyaglovskaya, N. M. Compounds of the β-Tetralone Series. *Russ. Chem. Rev. (Engl. Transl.)* **1966**, *35*, 523–531. (b) Rosowsky, A.; Battaglia, J.; Chen, K. K. N.; Modest, E. J. Synthesis of New Chlorine-Substituted Derivatives of 2-Tetralone. *J. Org. Chem.* **1968**, *33*, 4288–4290. (c) Sims, J. J.; Cadogan, M.; Selman, L. H. Improvement of a β-Tetralone Synthesis: 5-, 6-, 7- and 8-Methyl-β-Tetralones. *Tetrahedron Lett.* **1971**, 951–954.

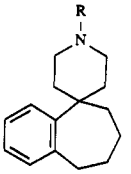
(13) Thies, R. W.; Chiraello, R. H. Ring-Size Effects in the Reaction of Benzocycloalkadiene Epoxides With Lithium Diisopropylamide. *J. Org. Chem.* **1979**, *44*, 1342–1344.

(14) Caglioti, L. The Reduction of Tosylhydrazones and of Acyl-Tosylhydrazones. *Tetrahedron* **1966**, *22*, 487–493.

(15) (a) Huang-Minlon. A Simple Modification of the Wolff-Kishner Reduction. *J. Am. Chem. Soc.* **1946**, *68*, 2487–2488. (b) Huang-Minlon. Reduction of Steroid Ketones and Other Carbonyl Compounds by Modified Wolff-Kishner Method. *J. Am. Chem. Soc.* **1949**, *71*, 3301–3303.

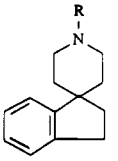
(16) (a) Todd, D. *Organic Reactions*; John Wiley: New York, 1948; Vol. IV, pp 378–422. (b) Szmant, H. H. The Mechanism of the Wolff-Kishner Reduction, Elimination and Isomerisation Reactions. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 120–128.

Table II. Benzocycloheptanes



no.	R	binding data: $pIC_{50} \pm SEM$ σ	binding data: $pIC_{50} \pm SEM$ D_2	mp, °C	microanalysis	method of synthesis
46	$PhCH_2$	8.17 ± 0.32	5.43 ± 0.17	273–5	$C_{22}H_{27}N\cdot HCl$	A
47	$CH_3(CH_2)_3$	8.32 ± 0.11	5.60	291–4	$C_{19}H_{29}N\cdot HCl\cdot 0.3H_2O$	B

Table III. Spiroindans



no.	R	binding data: $pIC_{50} \pm SEM$ σ	binding data: $pIC_{50} \pm SEM$ D_2	mp, °C	microanalysis	method of synthesis
48	$(CH_3)_2C{=}CHCH_2$	8.93 ± 0.22	4.77 ± 0.06	264–6	$C_{18}H_{25}N\cdot HCl\cdot 1.8H_2O$[a]	C
49	cyclohexylmethyl	8.87 ± 0.05	5.18 ± 0.12	304–6	$C_{20}H_{29}N\cdot HCl$	B
50	$CH_3(CH_2)_5$	8.82 ± 0.06	5.26 ± 0.05	284–7	$C_{19}H_{29}N\cdot HCl\cdot 0.1H_2O$	B
51	$CH_3(CH_2)_3$	8.69 ± 0.09	5.40[b]	231–4	$C_{17}H_{25}N\cdot HCl\cdot 0.1H_2O$	B
52	$PhCH_2$	9.14 ± 0.15	6.05	275–7	$C_{20}H_{23}N\cdot HCl\cdot 0.1H_2O$	B
53	$Ph(CH_2)_2$	8.56 ± 0.06		287–90	$C_{21}H_{25}N\cdot HCl$	B
54	$4\text{-}CH_3OC_6H_4CH_2$	8.46 ± 0.13	6.21 ± 0.07	259–61	$C_{21}H_{25}NO\cdot HCl$	B
55	$4\text{-}CH_3C_6H_4CH_2$	8.23 ± 0.12		284–6	$C_{21}H_{25}N\cdot HCl$	B
56	2-tetrahydrofurylmethyl	8.50 ± 0.06		216–9	$C_{18}H_{25}NO\cdot HCl\cdot 0.1H_2O$	B
57	2-picolyl	7.79 ± 0.19		209–12	$C_{19}H_{23}N_2\cdot HCl$	B

[a] H: calcd 8.65, found 9.20. [b] Value obtained from a single determination.

For the unsubstituted aryl spiropiperidines 15 (X = H), the *N*-benzyl group was removed using palladium-catalyzed hydrogenation in the presence of formic acid. After liberating the free base 16 subsequent alkylation was accomplished using the methods indicated in Tables I and II, and described in the Experimental Section, to give a variety of spirocyclic tetralin and benzocycloheptane derivatives 17.

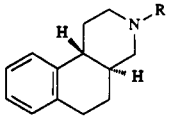
The spiroindans 23 listed in Table III were prepared according to Scheme II. Indene (18) was alkylated at C-1 using lithium bis(trimethylsilyl)amide and *N*-(*tert*-butyloxycarbonyl)bis(2-chloroethyl)amine (19) to afford the protected spirocyclic indene 20 in 58% yield. The BOC group was quantitatively removed under acidic conditions and the resulting amine hydrochloride 21 reduced by catalytic hydrogenation to give the indan derivative 22. After liberation of the free base, alkylation, using the procedures shown in Table III, produced a range of N-substituted spiroindans.

Biological Evaluation Procedures

Affinity at the σ binding site was evaluated by an in vitro radioligand binding assay using homogenized guinea pig cerebellum and [^{3}H]-DTG ([^{3}H]-6).[9] The highest affinity σ ligands in each series were subsequently examined for affinity at the dopamine D_2 receptor by an in vitro radioligand binding assay using rat striatal homogenates and [^{3}H]-(−)-sulpiride. The results are presented as $-\log_{10}$ (IC_{50}) values in Tables I–III and the procedures described in detail in the Experimental Section.

Results and Discussion

The radioligand binding results for the tetralin analogues are shown in Table I. There are several examples (24–28, 32–34) which exhibit comparable σ binding to some of the highest affinity σ ligands currently known, including haloperidol (pIC_{50}, 8.4) and 1*S*,2*R*-(−)-*cis*-*N*-methyl-*N*-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine [(−)-7] (pIC_{50}, 8.9).[17]



45

Figure 2. *trans*-Octahydrobenz[*f*]isoquinoline derivatives.

An examination of simple N-alkyl-substituted derivatives 24–31 identified the *N*-dimethylallyl (24) (pIC_{50}, 9.0) and *N*-butyl (25) (pIC_{50}, 8.9) substituents as optimum for σ binding. Further increases in the size of the lipophilic nitrogen substituent to hexyl (27) or phenethyl (28) failed to produce an increase in affinity, whereas a small decrease in chain length to the cyclopropylmethyl (30) and allyl (31) spiropiperidines resulted in a significant decrease in σ binding affinity. The 17-fold increase in σ affinity when replacing allyl with dimethylallyl is analogous to the result observed in the benzomorphan series in which (+)-pentazocine (9) displays a 15-fold preference for the σ site compared to (+)-SKF 10,047 (8).[9]

Benzyl-substituted derivatives 32–36 also had good affinity for the σ site, with the *p*-methyl (32) and *p*-methoxy (33) analogues displaying a marginal increase in σ affinity

(17) Costa, B. R.; Rice, K. C.; Bowen, W. D.; Thurkauf, A.; Rothman, R. B.; Band, L.; Jacobson, A. E.; Radesca, L.; Contreras, P. C.; Gray, N. M.; Daly, I.; Iyengar, S.; Finn, D. T.; Vazirani, S.; Walker, J. M. Synthesis and Evaluation of N-Substituted *cis*-*N*-Methyl-2(1-pyrrolidinyl)cyclohexylamines as High Affinity σ Receptor Probes. *J. Med. Chem.* **1990**, *33*, 3100–3110.

compared to the unsubstituted compound **34**. However, as was described by Russell et al.,[18] the *p*-nitro (**36**) substituent proved detrimental to binding. In fact, the structure–activity relationships described throughout this paper are remarkably similar to those reported by Russell et al. for the *trans*-octahydrobenz[*f*]isoquinoline derivatives **45** (Figure 2) and confirms the observation by Largent et al.[2,8] that, up to a certain size, σ binding affinity increases with increasing lipophilicity of the nitrogen substituent. A few N-heteroalkyl-substituted derivatives (**37–40**) were also examined and found to possess comparably good σ affinity.

The effect of introducing an aryl substituent into the tetralin moiety was also investigated. The results demonstrate that such groups offer no advantage over the unsubstituted analogue **34**. While the 6-methyl (**41**) and 6-chloro (**42**) compounds had equivalent σ affinity to **34**, the 7-hydroxy (**43**) and 7-methoxy (**44**) derivatives lost more than 10-fold affinity for the σ site.

Those ligands which had a pIC_{50} greater than 8.3 at the σ site were then submitted for the dopamine D_2 binding assay. In each case excellent selectivity for the σ site was observed. The dimethylallyl (**24**) and butyl (**25**) derivatives exhibited an outstanding preference for σ over the D_2 receptor (greater than 5000- and 9000-fold, respectively). The least selective spiropiperidine was the *p*-methoxybenzyl analogue **33** which displayed some 70-fold preference for the σ site.

The radioligand binding results for spiropiperidines **46** and **47**, possessing a benzocycloheptane nucleus, are shown in Table II. While these compounds retained good affinity for the σ recognition site, neither displayed improved binding compared to its tetralin counterpart (cf. **34** and **25**). The benzocycloheptanes exhibited high selectivity for the σ site over the D_2 receptor (**47**, 520-fold; **46**, 550-fold).

A variety of spirocyclic indans **48–57** were synthesized which incorporated the optimal nitrogen substituents established in the tetralin series. These compounds have very high affinity for the σ site, comparable to that of their tetralin analogues. The benzyl derivative **52** was identified as the highest affinity spirocyclic σ ligand, with a pIC_{50} of 9.1. Generally, compared to the analogous tetralins and benzocycloheptanes, the indans had improved selectivity for the σ site over the D_2 receptor. In most cases examined, selectivity for the σ site was greater than 1,000-fold.

In conclusion, a series of achiral spirocyclic piperidines have been identified as high-affinity σ ligands. The effective σ binding displayed by many of these derivatives has demonstrated that this site is tolerant of large variations in the identity of the nitrogen substituent. This observation is comparable to that reported by Scherz et al. for the *N*,*N*′-di-*o*-tolylguanidine analogues,[19] when describing the structural insensitivity of the σ site. The spiropiperidines also exhibited excellent selectivity for the σ site over the dopamine D_2 receptor. In particular, the *N*-dimethylallyl-substituted derivative **48** had greater than 10000-fold preference for the σ binding site and may serve as a useful tool for exploring the physiological role of this site.

Experimental Section

General Methods. Melting points were determined on a Reichert Thermovar melting point apparatus and are uncorrected. Proton NMR spectra were obtained using either a Bruker AM360 or a Bruker AC250 spectrometer. Chemical shifts are reported in parts per million relative to Me_4Si as an internal standard. Mass spectra (MS) were recorded on a VB70-250 instrument operating either in the electron impact (EI) or chemical ionization (CI) mode as indicated. Elemental analyses for carbon, hydrogen, and nitrogen were performed by CHN Analysis Ltd. (Leicester) or Butterworth Laboratories Ltd. (Teddington) and are within ±0.4% of the theoretical values for the given formulas. Analytical thin-layer chromatography was conducted on precoated silica gel 60 F_{254} plates (Merck). Flash chromatography was conducted on silica gel 60, 220–440 mesh (Fluka). HPLC analyses were performed on a Waters WISP 710B instrument, using a μ Bondapak C18 column (Waters), eluting on a 30-min gradient from 5 to 95% acetonitrile/water (containing 0.1% trifluoroacetic acid) and detecting on a Waters Lambda-Max 481LC spectrophotometer at 254 nm. Solutions were evaporated under reduced pressure on a Büchi rotary evaporator. Solvents were either reagent or HPLC grade. Starting materials were commercially available and used as received, unless otherwise indicated. Petroleum ether refers to that fraction having a boiling point range of 60–80 °C. All reactions were carried out under an atmosphere of nitrogen, unless stated otherwise.

Method A. 1′-Benzyl-3,4-dihydrospiro[naphthalene-1(2*H*),4′-piperidine] (34).[20] A solution of 1′-benzyl-3,4-dihydro-2-oxospiro[naphthalene-1(2*H*),4′-piperidine] (**14**, n = 1, X = H)[21] (0.73 g, 2.4 mmol), KOH (0.48 g, 8.6 mmol), and hydrazine hydrate (0.4 mL, 8.6 mmol) in diethylene glycol (6 mL) was heated at reflux for 2 h. After this time the reflux condenser was replaced with an air condenser and the mixture heated at 200 °C for a further 2 h. Finally, the solution was heated at reflux for 3 h and then allowed to cool to ambient temperature. EtOAc (100 mL) was added and the mixture partitioned with water (70 mL). The organic layer was separated and the aqueous phase extracted with EtOAc (2 × 50 mL). The organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel, using petroleum ether–Et_2O (1:1) as the eluent, to afford **34** (0.42 g, 60%) as a white solid. The hydrochloride salt was prepared using ethereal hydrogen chloride and recrystallized from EtOAc–EtOH: mp 284–286 °C (lit.[20a] mp 285–287 °C); ^1H NMR (D_2O) δ 1.76 (6 H, m), 2.24 (2 H, td, J = 10 and 4 Hz), 2.80 (2 H, t, J = 5 Hz), 3.28 (2 H, td, J = 10 and 3 Hz), 3.42 (2 H, m), 4.40 (2 H, s, CH_2Ph), 7.20–7.60 (9 H, m, ArH); MS (CI, NH_3) m/z 292 (M + 1 of free base). Anal. ($C_{21}H_{25}N$·HCl) C, H, N.

1′-Benzyl-3,4-dihydro-6-methylspiro[naphthalene-1(2*H*),4′-piperidine] (41). Prepared in the same way as that described for **34**, using 1′-benzyl-3,4-dihydro-6-methyl-2-oxospiro[naphthalene-1(2*H*),4′-piperidine] (**14**, n = 1, X = 6-Me)[21] (84 mg, 0.26 mmol), hydrazine hydrate (46 μL, 0.95 mmol), KOH (53 mg, 0.95 mmol), and diethylene glycol (3 mL). The residue was purified by flash chromatography on silica gel, using petroleum ether–Et_2O (1:1) as the eluent, to afford the title compound **41** (28 mg, 35%) as a pale yellow oil. Hydrochloride salt: mp 161–164 °C (sublimed); ^1H NMR (MeOH-d_4) δ 1.73–1.91 (6 H, m), 2.25 (5 H, m), 2.72 (2 H, t, J = 6 Hz), 3.31 (4 H, m), 4.35 (2 H, s, NCH_2Ph), 6.98 (1 H, s, ArH), 7.06 (1 H, d, J = 8 Hz, ArH), 7.29 (1 H, d, J = 8 Hz, ArH), 7.54 (5 H, s, ArH); MS (EI) m/z 305 (M^+ of free base). Anal. ($C_{22}H_{27}N$·HCl·0.2H_2O) C, H, N.

1′-Benzyl-6-chloro-3,4-dihydrospiro[naphthalene-1(2*H*),4′-piperidine] (42). Prepared in the same way as that

(18) Russell, M. G. N.; Baker, R.; Billington, D. C.; Knight, A. K.; Middlemiss, D. N.; Noble, A. J. Benz[*f*]isoquinoline Analogues as High Affinity σ Ligands. *J. Med. Chem.*, previous paper in this issue.

(19) Scherz, M. W.; Fialeix, M.; Fischer, J. B.; Reddy, N. L.; Server, A. C.; Sonders, M. S.; Tester, B. C.; Weber, E.; Wong, S. T.; Keana, J. F. W. Synthesis and Structure–Activity Relationships of *N*,*N*′-Di-*o*-Tolylguanidine Analogues, High-Affinity Ligands for the Haloperidol-Sensitive σ Receptor. *J. Med. Chem.* **1990**, *33*, 2421–2429.

(20) An alternative procedure for the preparation of 1′-benzyl-3,4-dihydrospiro[naphthalene-1(2*H*),4′-piperidine] is described by: (a) Janssen, C. Procedé de Préparation de *N*-(3,3-Diphenyl-3-alcanoyl)-propylspiro-(tétraline 1,4′-piperidines). Fr. Patent 1,335,831, 1964. (b) Hashigaki, K.; Hiramatsu, K.; Yamato, M.; Tasaka, K. Synthesis and Structure–Activity Relationship of Spiro[isochromanpiperidine]Analogs for Inhibition of Histamine Release IV. *Chem. Pharm. Bull.* **1984**, *32*, 3561–3568.

(21) Prepared using *N*-benzylbis(2-chloroethyl)amine[11] (**13**) and the appropriately substituted aryl tetralone, using the procedure described in ref 10.

described for **34**, using 1'-benzyl-6-chloro-3,4-dihydro-2-oxospiro[naphthalene-1(2*H*),4'-piperidine] (**14**, n = 1, X = 6-Cl)[21] (1.1 g, 3.3 mmol), hydrazine hydrate (0.6 g, 15.3 mmol), KOH (0.86 g, 15.3 mmol), and diethylene glycol (50 mL). The residue was purified by flash chromatography on silica gel, using petroleum ether–Et_2O (1:1) as the eluent, to afford **42** (410 mg, 38%) as a white solid. Hydrochloride salt: mp 264–267 °C (sublimed); ^1H NMR (DMSO-d_6) δ 1.67 (4 H, m), 1.85 (2 H, m), 2.43 (2 H, m), 2.70 (2 H, t, J = 6 Hz), 3.18 (4 H, m), 4.33 (2 H, d, J = 5 Hz, NCH_2Ph), 7.13 (1 H, s, ArH), 7.23 (1 H, d, J = 9 Hz, ArH), 7.47 (4 H, m, ArH), 7.63 (2 H, m, ArH); MS (EI) m/z 325 (M^+ of free base). Anal. ($C_{21}H_{24}ClN$·HCl) C, H, N.

1'-Benzyl-3,4-dihydro-7-methoxyspiro[naphthalene-1(2*H*),4'-piperidine] (44) and 1'-Benzyl-3,4-dihydro-7-hydroxyspiro[naphthalene-1(2*H*),4'-piperidine] (43). A solution of 1'-benzyl-3,4-dihydro-7-methoxy-2-oxospiro[naphthalene-1(2*H*),4'-piperidine] (**14**, n = 1, X = 7-OMe)[21] (400 mg, 1.2 mmol), KOH (0.3 g, 5.3 mmol), and hydrazine hydrate (0.2 mL, 4.3 mmol) in diethylene glycol (4 mL) was heated at reflux for 1.5 h. After this time the reflux condenser was replaced with an air condenser and the mixture heated at 210 °C for a further 2 h. Finally, the solution was heated at reflux for 3 h and then allowed to cool to ambient temperature. EtOAc (30 mL) was added and the mixture partitioned with water (30 mL). The organic layer was separated and the aqueous phase extracted with EtOAc (2 × 30 mL). The organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$), and evaporated. The residue was purified on silica gel, using petroleum ether–EtOAc (1:1) as the eluent, to afford **44** (185 mg, 49%) (R_f 0.4) as a colorless oil and **43** (124 mg, 35%) (R_f 0.3) as a white solid. Hydrochloride salt of **43**: mp 164–166 °C; ^1H NMR (D_2O) δ 1.69–1.89 (6 H, m), 2.18 (2 H, t, J = 11 Hz), 2.68 (2 H, t, J = 6 Hz), 3.29 (2 H, t, J = 13 Hz), 3.42 (2 H, m), 4.37 (2 H, s, NCH_2Ph), 6.72 (1 H, dd, J = 8 and 2 Hz, ArH), 6.88 (1 H, s, ArH), 7.05 (1 H, d, J = 8 Hz, ArH), 7.55 (5 H, m, ArH); MS (EI) m/z 307 (M^+ of free base). Anal. ($C_{21}H_{25}NO$·HCl·H_2O) C, H, N.

Hydrochloride salt of **44**: mp 229–232 °C; ^1H NMR (MeOH-d_4) δ 1.75–1.87 (4 H, m), 1.95 (2 H, m), 2.34 (2 H, td, J = 12 and 3 Hz), 2.71 (2 H, t, J = 7 Hz), 3.32 (4 H, m), 3.75 (3 H, s, OCH_3), 4.37 (2 H, s, NCH_2Ph), 6.70 (1 H, dd, J = 9 and 1 Hz, ArH), 6.92 (1 H, s, ArH), 6.97 (1 H, d, J = 9 Hz, ArH), 7.54 (5 H, m, ArH); MS (EI) m/z 321 (M^+ of free base). Anal. ($C_{22}H_{27}NO$·HCl·0.4H_2O) C, H, N.

Method B. 3,4-Dihydrospiro[naphthalene-1(2*H*),4'-piperidine] (16, n = 1).[20a] A solution of 1'-benzyl-3,4-dihydrospiro[naphthalene-1(2*H*),4'-piperidine] (**34**) (0.85 g, 2.9 mmol) and formic acid (2 mL) in EtOH (20 mL) was hydrogenated at 50 psi, in the presence of palladium hydroxide on carbon (Pearlman's catalyst) (0.22 g, 25% (w/w)), for 18 h. The catalyst was filtered off and the solvent evaporated. The residue was partitioned between EtOAc (50 mL) and aqueous KOH (50 mL of a 5% (w/v) solution) and the organic phase separated. The aqueous layer was extracted once more with EtOAc (20 mL), and the combined organic layers were dried ($MgSO_4$). The solvent was removed to afford the title amine (0.37 g, 64%) as a white solid. Hydrochloride salt: mp 278–280 °C; ^1H NMR (D_2O) δ 1.76–1.98 (6 H, m), 2.22 (2 H, td, J = 10 and 4 Hz), 2.82 (2 H, t, J = 5 Hz), 3.35 (4 H, m), 7.20–7.54 (4 H, m, ArH); MS (CI, NH_3) m/z 202 (M + 1 of free base). Anal. ($C_{14}H_{19}N$·HCl·0.2H_2O) C, H, N.

1'-Cyclohexylmethyl-3,4-dihydrospiro[naphthalene-1(2*H*),4'-piperidine] (26). To a stirred solution of 3,4-dihydrospiro[naphthalene-1(2*H*),4'-piperidine] (176 mg, 0.87 mmol) in DMF (10 mL) was added K_2CO_3 (145 mg, 1.1 mmol) and cyclohexylmethyl bromide (146 μL, 1.1 mmol). The mixture was heated at 100 °C for 1 h and then allowed to cool to room temperature. The solvent was evaporated and the residue taken up in Et_2O (20 mL) and then washed with water (2 × 20 mL). The organic layer was separated, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel, using petroleum ether–Et_2O (1:1) as the eluent, to give the desired amine **26** (158 mg, 61%) as a colorless oil. Hydrochloride salt: mp 287–290 °C; ^1H NMR (D_2O) δ 1.07 (2 H, m), 1.28–1.98 (15 H, m), 2.33 (2 H, td, J = 11 and 2 Hz), 2.80 (2 H, t, J = 6 Hz), 3.03 (2 H, d, J = 7 Hz), 3.25 (2 H, m), 3.51 (2 H, m), 7.22–7.30 (3 H, m, ArH), 7.48 (1 H, d, J = 8 Hz, ArH); MS (CI, NH_3) m/z 298 (M + 1 of free base). Anal. ($C_{21}H_{31}N$·HCl) C, H, N.

Method C. 3,4-Dihydro-1'-(3-methylbut-2-enyl)spiro[naphthalene-1(2*H*),4'-piperidine] (24). To a stirred solution of 3,4-dihydrospiro[naphthalene-1(2*H*),4'-piperidine] (0.14 g, 0.69 mmol) in CH_2Cl_2 (10 mL) was added 4-bromo-2-methyl-2-butene (0.1 g, 0.69 mmol). After 3 h the solution was partitioned between CH_2Cl_2 (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The organic layer was separated, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel, eluting with CH_2Cl_2–MeOH (93:7) to produce the title compound **24** (75 mg, 40%) as a white solid. Hydrochloride salt: mp 274–277 °C; ^1H NMR (D_2O) δ 1.75–1.96 (12 H, m), 2.25 (2 H, td, J = 15 and 4 Hz), 2.80 (2 H, t, J = 6 Hz), 3.23 (2 H, t, J = 13 Hz), 3.47 (2 H, m), 3.77 (2 H, d, J = 8 Hz), 5.35 (1 H, t, J = 8 Hz, CH), 7.21–7.32 (3 H, m, ArH), 7.46 (1 H, d, J = 8 Hz, ArH); MS (EI) m/z 269 (M^+ of free base); high-resolution MS (EI) m/z 269.2125 (269.2144 calcd for $C_{19}H_{27}N$). Anal. ($C_{19}H_{27}N$·HCl·0.6H_2O) C, H, N.

Method D. 1'-(2-Furylmethyl)-3,4-dihydrospiro[naphthalene-1(2*H*),4'-piperidine] (39). A solution of 3,4-dihydrospiro[naphthalene-1(2*H*),4'-piperidine] (0.2 g, 1 mmol), triethylamine (0.35 mL, 2.5 mmol), and 2-furoyl chloride (0.2 mL, 2 mmol) in CH_2Cl_2 (9 mL) was stirred at room temperature for 1.5 h. The solvent was evaporated and the residue partitioned between Et_2O (20 mL) and water (20 mL). The organic layer was separated and the aqueous phase extracted with Et_2O (20 mL). The combined ethereal layers were dried ($MgSO_4$) and evaporated.

The residue was dissolved in THF (15 mL), and to the stirred solution was added, dropwise, a solution of lithium aluminum hydride in THF (3 mL of a 1 M solution, 3 mmol). After 2 h, EtOAc (2 mL) was added, followed by saturated aqueous ammonium chloride (6 mL). The mixture was filtered and the filtrate dried ($MgSO_4$) and evaporated. The crude residue was purified by flash chromatography on silica gel, eluting with petroleum ether–Et_2O (1:1), to afford **39** (103 mg, 37%) as a colorless oil. Hydrochloride salt: mp 264–266 °C; ^1H NMR (D_2O) δ 1.76 (2 H, m), 1.92 (4 H, m), 2.26 (2 H, m), 2.79 (2 H, t, J = 6 Hz), 3.40 (4 H, m), 4.43 (2 H, s), 6.57 (1 H, dd, J = 3 and 2 Hz, H$^{4''}$), 6.75 (1 H, d, J = 3 Hz, H$^{3''}$), 7.21–7.31 (3 H, m, ArH), 7.44 (1 H, d, J = 8 Hz, ArH), 7.68 (1 H, d, J = 2 Hz, H$^{5''}$); MS (EI) m/z 281 (M^+ of free base). Anal. ($C_{19}H_{23}NO$·HCl) C, H, N.

1'-Benzyl-6,7,8,9-tetrahydrospiro[5*H*-benzocycloheptene-5,4'-piperidine] (46). 1'-Benzyl-6,7,8,9-tetrahydro-6-oxospiro[5*H*-benzocycloheptene-5,4'-piperidine] (**14**, n = 2, X = H) was reacted with hydrazine hydrate and KOH, using the same procedure as that described for **34**, to afford the title amine **46** as a pale yellow oil (57%). Hydrochloride salt: mp 273–275 °C; ^1H NMR (MeOH-d_4) δ 1.67 (2 H, m), 1.88 (4 H, m), 2.24 (4 H, m), 2.98 (2 H, m), 4.32 (2 H, s, CH_2Ph), 7.15 (3 H, m, ArH), 7.29 (1 H, d, J = 8 Hz, ArH), 7.50 (5 H, m, ArH); MS (EI) m/z 305 (M^+ of free base). Anal. ($C_{22}H_{27}N$·HCl) C, H, N.

***N*-(*tert*-Butyloxycarbonyl)bis(2-chloroethyl)amine (19).** Triethylamine (74 mL, 0.58 mol) was added dropwise to a stirred solution of di-*tert*-butyl dicarbonate (125 g, 0.57 mol) and bis(2-chloroethyl)amine hydrochloride (85 g, 0.48 mol) in CH_2Cl_2 (600 mL). After 1 h more triethylamine (6 mL, 0.04 mol) was added and the mixture stirred overnight. The solvent was evaporated and the resulting oil taken up in Et_2O (500 mL) and washed with water (500 mL). The organic phase was separated and the aqueous layer extracted once more with Et_2O (500 mL). The ethereal layers were combined, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel, using petroleum ether–Et_2O (1:1) as the eluent to give **19** (102 g, 88%) as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 1.48 (9 H, s, $(CH_3)_3$), 3.64 (8 H, m, $(CH_2CH_2)_2$); MS (CI, NH_3) m/z 242/244 (M + 1).

1'-(*tert*-Butyloxycarbonyl)spiro[1*H*-indene-1,4'-piperidine] (20). To a stirred solution of indene (**18**) (5.1 mL, 0.04 mol) in THF (15 mL), at 0 °C, was added lithium bis(trimethylsilyl)amide (82 mL of a 1 M solution in THF, 0.08 mol) over 15 min. The mixture was stirred for a further 30 min and then added dropwise to a stirred solution of *N*-(*tert*-butyloxycarbonyl)bis(2-chloroethyl)amine (**19**) (9.9 g, 0.04 mol) in THF at 0 °C. After 2 h the mixture was allowed to warm to ambient temperature, then the solvent was removed. The resulting oil was purified by flash chromatography on silica gel, using petroleum ether–Et_2O (5:1) as the eluent, to give **20** (7.1 g, 58%) as a pale

yellow solid: mp 129–131 °C; ^{1}H NMR ($CDCl_3$) δ 1.28 (2 H, d, J = 12 Hz), 1.50 (9 H, s, $(CH_3)_3$), 2.00 (2 H, td, J = 12 and 4 Hz), 3.13 (2 H, td, J = 12 and 2 Hz), 4.20 (2 H, m), 6.79 (1 H, d, J = 6 Hz, CH), 6.84 (1 H, d, J = 6 Hz, CH), 7.30 (4 H, m, ArH); MS (EI) m/z 285 (M^+). Anal. ($C_{18}H_{23}NO_2$) C, H, N.

Spiro[1*H*-indene-1,4′-piperidine] Hydrochloride (21). Hydrogen chloride was bubbled through a stirred solution of **20** (3.0 g, 0.01 mol) in EtOAc (150 mL) at 0 °C for 30 min. The mixture was evaporated to dryness and then azeotroped with EtOAc (3 × 100 mL). The solid residue was stirred with Et_2O (200 mL) and filtered to afford the desired amine hydrochloride **21** (2.3 g, 99%) as a pale yellow solid: mp 291–294 °C; ^{1}H NMR (D_2O) δ 1.54 (2 H, d, J = 14 Hz), 2.31 (2 H, td, J = 14 and 4 Hz), 3.57 (2 H, td, J = 13 and 2 Hz), 3.66 (2 H, m), 6.95 (1 H, d, J = 6 Hz, CH), 6.99 (1 H, d, J = 6 Hz, CH), 7.31–7.52 (4 H, m, ArH); MS (EI) m/z 185 (M^+ of free base). Anal. ($C_{13}H_{15}N$·HCl·0.2H_2O) C, H, N.

3,4-Dihydrospiro[1*H*-indene-1,4′-piperidine] Hydrochloride (22).[20a] A solution of spiro[1*H*-indene-1,4′-piperidine] hydrochloride (**21**) (1.9 g, 8.6 mmol) in EtOH (50 mL) was hydrogenated at 50 psi for 1 h, in the presence of 10% palladium on carbon (0.3 g, 16% (w/w)). The catalyst was filtered off and the EtOH evaporated. The remaining solid was recrystallized from EtOAc–EtOH (4:1) to produce **22** (0.81 g, 43%) as a white crystalline solid: mp 288–290 °C (lit.[20a] mp 288–290 °C); ^{1}H NMR (D_2O) δ 1.79 (2 H, d, J = 14 Hz), 2.06 (2 H, td, J = 14 and 4 Hz), 2.14 (2 H, t, J = 7 Hz), 2.98 (2 H, t, J = 7 Hz), 3.25 (2 H, td, J = 14 and 2 Hz), 3.48 (2 H, m), 7.33 (4 H, m, ArH); MS (EI) m/z 187 (M^+ of free base). Anal. ($C_{13}H_{17}N$·HCl) C, H, N.

3,4-Dihydro-1′-(2-phenylethyl)spiro[1*H*-indene-1,4′-piperidine] (53). 3,4-Dihydrospiro[1*H*-indene-1,4′-piperidine] hydrochloride (**22**) was partitioned between EtOAc and aqueous Na_2CO_3 to liberate the free base. This was then reacted with 2-phenylethyl bromide, using the same procedure as that described for **26**, to give **53** as a pale yellow oil (68%). Hydrochloride salt: mp 287–290 °C; ^{1}H NMR (DMSO-d_6) δ 1.67 (2 H, d, J = 14 Hz), 2.07 (2 H, t, J = 7 Hz), 2.26 (2 H, m), 2.90 (2 H, t, J = 7 Hz), 3.12 (4 H, m), 3.31 (2 H, m), 3.57 (2 H, d, J = 11 Hz), 7.24 (9 H, m, ArH), 10.82 (1 H, brs, NH^+); MS (CI, NH_3) m/z 292 (M + 1 of free base). Anal. ($C_{21}H_{25}N$·HCl) C, H, N.

Radioligand Binding Assays. Radioligand binding assays were performed using crude P_2 pellets from guinea pig cerebellum (σ) or rat striatum (dopamine D_2).

For full experimental details see the preceding paper by Russell et al.[18] and references cited therein.

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Registry No. **6**, 106916-81-8; **11** (X = H), 530-93-8; **11** (X = 6-Cl), 17556-18-2; **11** (X = 7-OMe), 4133-34-0; **11** (X = 6-CH_3), 31706-57-7; **12**, 34663-15-5; **13**, 55-51-6; **14** (n = 1, X = H), 134697-63-5; **14** (n = 1, X = 6-CH_3), 134697-66-8; **14** (n = 1, X = 7-OMe), 134697-67-9; **14** (n = 1, X = 6-Cl), 134697-65-7; **14** (n = 2, X = H), 137730-68-8; **16** (n = 1), 134697-64-6; **16** (n = 2), 137730-69-9; **19**, 118753-70-1; **20**, 137419-24-0; **21**, 137730-67-7; **22**, 96651-85-3; **23** (R = H), 428-38-6; **24**, 134697-99-7; **24**·HCl, 134698-00-3; **25**, 134697-69-1; **25**·HCl, 134697-70-4; **26**, 134697-83-9; **26**·HCl, 134697-84-0; **27**, 134697-91-9; **27**·HCl, 134697-92-0; **28**, 134697-81-7; **28**·HCl, 134697-82-8; **29**, 134697-93-1; **29**·HCl, 134697-94-2; **30**, 134697-97-5; **30**·HCl, 134697-98-6; **31**, 134697-95-3; **31**·HCl, 134697-96-4; **32**, 134697-75-9; **32**·HCl, 134697-76-0; **33**, 134697-73-7; **33**·HCl, 134697-74-8; **34**, 95417-67-7; **34**·HCl, 95417-61-1; **35**, 134697-87-3; **35**·HCl, 134697-88-4; **36**, 134697-85-1; **36**·HCl, 134697-86-2; **37**, 134697-89-5; **37**·HCl, 134697-90-8; **38**, 134698-03-6; **38**·HCl, 134698-04-7; **39**, 134698-01-4; **39**·HCl, 134698-02-5; **40**, 134697-71-5; **40**·2HCl, 140468-29-7; **41**, 134698-07-0; **41**·HCl, 134698-12-7; **42**, 134698-05-8; **42**·HCl, 134698-06-9; **43**, 134698-13-8; **43**·HCl, 134698-08-1; **44**, 134697-79-3; **44**·HCl, 134697-80-6; **46**, 137730-62-2; **46**·HCl, 140468-30-0; **47**, 137730-63-3; **47**·HCl, 137730-82-6; **48**, 137730-58-6; **48**·HCl, 137730-78-0; **49**, 137730-54-2; **49**·HCl, 137730-72-4; **50**, 137730-65-5; **50**·HCl, 137730-74-6; **51**, 137730-64-4; **51**·HCl, 137730-70-2; **52**, 137730-52-0; **52**·HCl, 102981-00-0; **53**, 137730-66-6; **53**·HCl, 137730-77-9; **54**, 137730-55-3; **54**·HCl, 137730-73-5; **55**, 137730-53-1; **55**·HCl, 137730-71-3; **56**, 137730-57-5; **56**·HCl, 137730-76-8; **57**, 137730-56-4; **57**·HCl, 137730-75-7; $NH(CH_2CH_2Cl)_2$·HCl, 821-48-7; indene, 95-13-6.