0.31 (system F). Anal. ($C_{31}H_{37}N_5O_8$) C, H, N.

HCl·H-Gln-D-Trp(CHO)-Phe-OBzl (4c). A solution of **4a** (0.5 g) in 4 N hydrochloric acid (10 mL) in dioxane was stirred under ice-cooling for 0.5 h and then at room temperature for 2 h. The reaction mixture was concentrated, and the residue was triturated with Et_2O. The resulting precipitates were filtered and dried to give **4c** (0.40 g, 99.0%) as an amorphous solid: $[\alpha]^{25}_D$ = +14.40° (c = 0.92, DMF); IR (Nujol) 3200 (br), 1735 (sh), 1710 (sh), 1690, 1675 (sh), 1660, 1605, 1545 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.5–2.2 (4 H, m), 2.6–3.3 (4 H, m), 3.6–4.0 (1 H, m), 4.4–5.0 (2 H, m), 5.14 (2 H, s), 6.90 (1 H, br s), 7.27 (5 H, s), 7.38 (5 H, s), 7.0–7.8 (5 H, m), 8.33 (4 H, br s), 8.7–9.2 (2 H, m), 9.3 (1 H, br s); R_f = 0.13 (system F). Anal. ($C_{33}H_{36}ClN_5O_6 \cdot 0.25HCl \cdot 1.3H_2O$) C, H, N, Cl.

Benz[*f*]isoquinoline Analogues as High-Affinity σ Ligands

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This paper describes the synthesis of some conformationally restricted 4-phenylpiperidine analogues and their affinities for the guinea pig cerebellum σ recognition site ([^{3}H]-DTG) and the rat striatum dopamine D_2 receptor ([^{3}H]-(−)-sulpiride) in order to develop potent selective σ ligands as tools in the investigation of this site in psychosis. It was found that both hexa- and octahydrobenz[*f*]isoquinolines with lipophilic N-substituents had high affinities for the σ site. Notably, *trans*-3-cyclohexyl-1,2,3,4,4a,5,6,10b-octahydrobenz[*f*]isoquinoline (**26**) had an affinity of 0.25 nM making it the highest affinity σ ligand reported to date. Moreover, it is at least 10 000-fold selective over the D_2 receptor and could prove to be a valuable tool in the study of σ sites. Other analogues such as 1*H*-indeno[2,1-*c*]pyridines and 1*H*-benzo[3,4]cyclohepta[1,2-*c*]pyridines also displayed high σ site affinity.

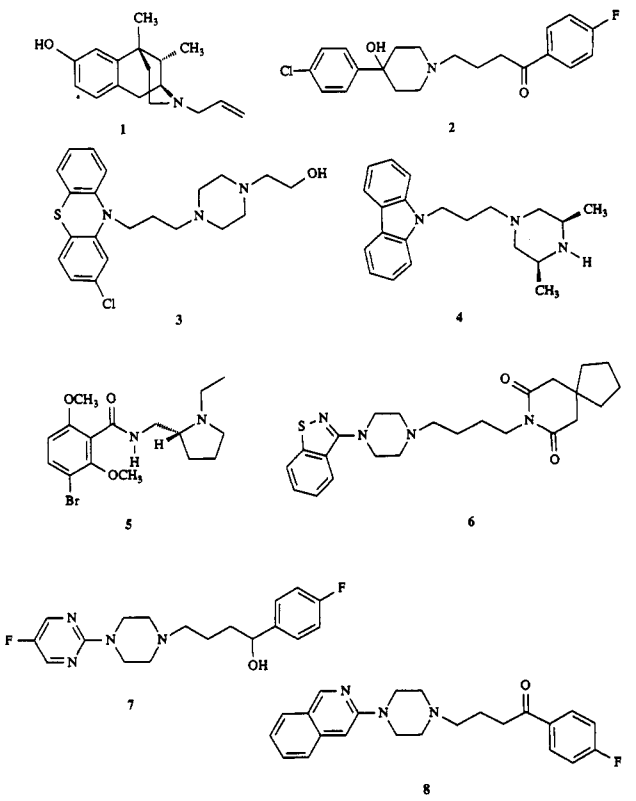
Introduction

The existence of σ receptors was first postulated by Martin et al.[1] as a result of a study of the actions of *N*-allylnormetazocine (SKF-10047, 1) (Chart I), which had been shown to elicit psychotomimetic effects in humans.[2] It was found that 1 caused autonomic stimulation and "canine delirium" in the chronic spinal dog leading to the suggestion that these effects involved a unique subtype of opiate receptor, which was termed σ. However, unlike conventional opiate receptors, behavioral effects appeared to be confined to the dextrorotatory (+) isomer and were not antagonized by opiate antagonists such as naloxone or naltrexone.[3-9] The origin of these effects is, however, unclear since 1 also interacts strongly with the NMDA ion-channel complex.[10,11]

Nevertheless, there is evidence that implicates the involvement of σ sites in psychosis. Firstly, some traditional and clinically useful neuroleptics such as haloperidol (**2**) and perphenazine (**3**), which act as dopamine D_2 receptor antagonists, also have a high affinity for the σ site.[12,13] Secondly, several new atypical antipsychotic agents, such as rimcazole (BW 234U, **4**),[14-18] remoxipride (**5**),[19-24] tiaspirone (BMY 13859, **6**),[25] BMY 14802 (**7**),[26] and cinuperone (HR 375, **8**),[27] may not act primarily at D_2 receptors but have a reasonable affinity for the σ site,[28-31] and furthermore appear to be devoid of the extrapyramidal side effects associated with D_2 antagonists. Thirdly, post mortem brain tissue studies have shown that schizophrenics contained a significantly lower number of σ sites than normal patients,[32] which seems to be due to haloperidol treatment,[33] and may be relevant to its antipsychotic action.

Although σ sites have been implicated in regulation of neurotransmitter release,[34] smooth muscle contraction,[34-36] intestinal alkaline secretion,[37-39] control of motor behavior,[40-42] and modulation of phosphoinositide turnover[43] (though the latter is probably due to muscarinic receptor blockade[44,45]), the poor receptor selectivity of the known σ ligands makes convincing functional correlations difficult to obtain.[46] Our aim, therefore, was to develop potent, selective σ ligands as tools in the investigation of the role of this recognition site in psychosis.

Chart I



† Department of Chemistry.
‡ Department of Biochemistry.

(1) Martin, W. R.; Eades, C. G.; Thompson, J. A.; Huppler, 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.
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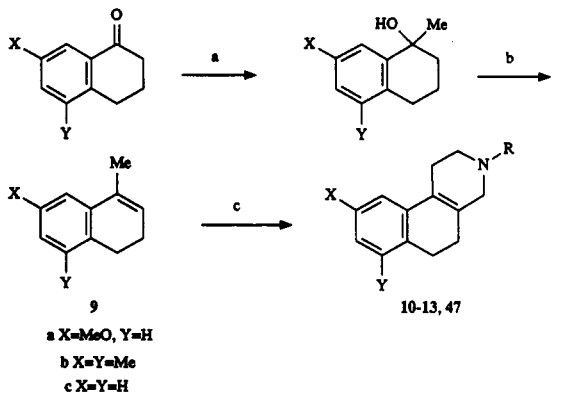
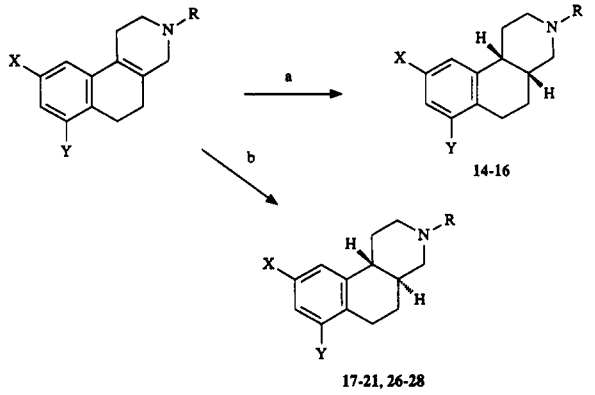
Scheme I[a]



[a] Reagents: (a) MeMgBr, Et_2O; (b) *p*-toluenesulfonic acid, toluene, reflux; (c) CH_2O, RNH_3Cl, AcOH, H_2O.

Scheme II[a]



[a] Reagents: (a) H_2, PtO_2, HCl, EtOH; (b) Li, NH_3(l), $PhNH_2$, THF, -78 °C (method A).

The structural requirements for high-affinity binding to the σ site have been discussed by Wikström and Largent et al.[47-49] who found that a 3- or 4-phenylpiperidine ring system and a lipophilic N-substituent are key features in

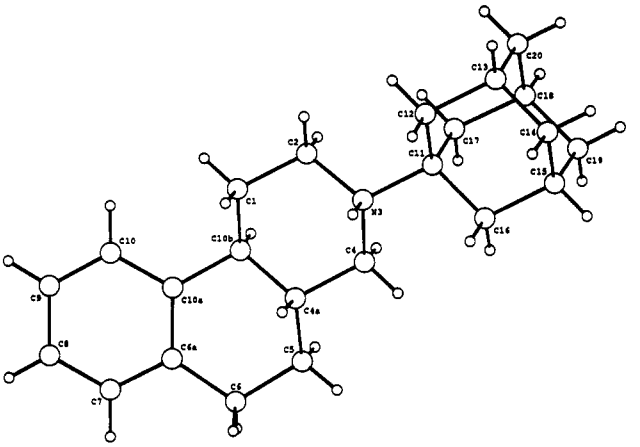
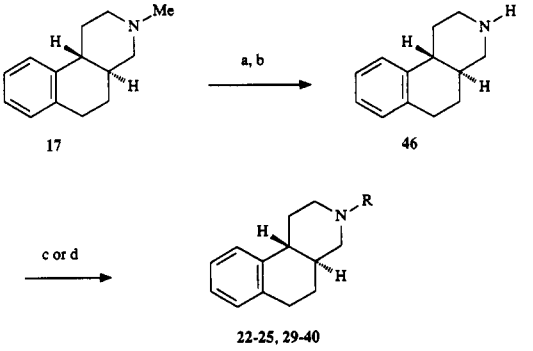


Figure 1. Computer-generated drawing of **27** showing its stereochemistry.

Scheme III[a]



[a] Reagents: (a) CNBr, $CHCl_3$; (b) 2 N HCl; (c) RX, K_2CO_3, DMF, 100 °C (method B); (d) (i) R'COCl, Et_3N, CH_2Cl_2; (ii) $LiAlH_4$, THF (method C) (R' = thienyl or furyl).

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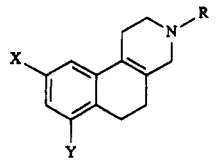
Table I. Hexahydrobenz[*f*]isoquinolines

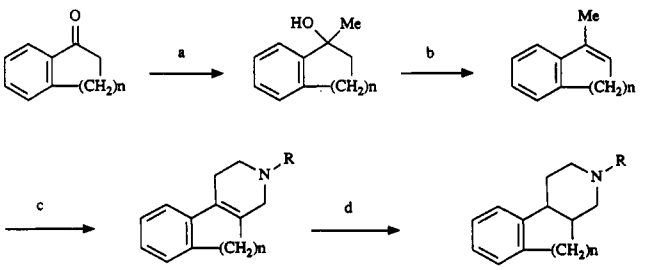


no.	R	X	Y	mp, °C	microanalysis[a]	pIC_{50}[b] σ[c]	pIC_{50}[b] D_2[d]
10	Me	MeO	H	236–238[e]	$C_{15}H_{19}NO\cdot HCl\cdot 1.3H_2O$[f]	5.46 ● 0.06	
11[g]	$CH_3(CH_2)_2$	H	H	213–215	$C_{16}H_{21}N\cdot HCl\cdot 0.1H_2O$	7.67 ± 0.14	
12	$CH_3(CH_2)_3$	H	H	162–163 dec	$C_{17}H_{23}N\cdot HCl\cdot 0.5H_2O$	8.12 ± 0.05	7.20 ± 0.07
13	$PhCH_2CH_2$	H	H	194–196	$C_{21}H_{23}N\cdot HCl\cdot 0.1H_2O$	7.78 ± 0.13	

[a] Elemental analysis for carbon, hydrogen, and nitrogen are within ±0.4% of the theoretical values for the formula indicated. [b] pIC_{50} values are mean ± SEM and are the result of at least three experiments unless otherwise indicated. Values without error limits were obtained from single determinations. [c] Displacement of [^{3}H]-DTG. The pIC_{50} of haloperidol in this assay was 8.38 ± 0.05. [d] Displacement of [^{3}H]-(−)-sulpiride. [e] Lit.[51] mp 229–232 °C. [f] H: calcd 7.88, found 7.35. [g] Contains 13% of the 2,3,4,4a,5,6-hexahydrobenz[*f*]isoquinoline.

most classes of high affinity σ ligands. This paper describes the synthesis of some conformationally restricted

Scheme IV[a]



[a] Reagents: (a) MeMgBr, Et_2O; (b) *p*-toluenesulfonic acid, toluene, reflux; (c) CH_2O, RNH_3Cl, AcOH, H_2O; (d) Li, $NH_3(l)$, $PhNH_2$, THF, −78 °C.

4-phenylpiperidine analogues and their affinities for the σ site. We have also measured the binding of the more

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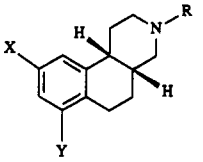
Table II. *cis*-Octahydrobenz[*f*]isoquinolines



no.	R	X	Y	mp, °C	microanalysis[a]	pIC_{50}[b] σ[c]	pIC_{50}[b] D_2[d]
14	Me	H	H	192–194	$C_{14}H_{19}N\cdot HCl\cdot 1.0H_2O$	6.47 ± 0.16	
15	Me	MeO	H	223–226	$C_{15}H_{21}NO\cdot HCl$	5.93 ● 0.02	
16	$CH_3(CH_2)_3$	H	H	185–191	$C_{17}H_{25}N\cdot HCl\cdot 0.9H_2O$[e]	8.20 ± 0.40	6.84 ± 0.09

[a–d] See corresponding footnotes in Table I. [e] H: calcd 9.46, found 9.88.

interesting compounds to the dopamine D_2 receptor and discuss structure–activity relationships in this series of compounds.

Chemistry

Hexahydrobenz[*f*]isoquinolines **10–13** were synthesized using the methods of Ménard et al.[50] and Zimmerman[51] by treatment of the appropriate 1-tetralone with methylmagnesium bromide followed by dehydration with *p*-toluenesulfonic acid in refluxing toluene to afford the corresponding 1-methyl-3,4-dihydronaphthalene **9** (Scheme I). Aminomethylation of **9** with the appropriate amine hydrochloride salt and formaldehyde in aqueous acetic acid gave the hexahydrobenz[*f*]isoquinoline.

Octahydrobenz[*f*]isoquinolines were prepared by reduction of the corresponding hexahydrobenz[*f*]isoquinolines either by catalytic hydrogenation with platinum oxide to give the 4a,10b-cis isomers **14–16** or by lithium in liquid ammonia and THF in the presence of aniline to give the 4a,10b-trans isomers **17–21** and **26–28** (Scheme II). The trans stereochemistry was confirmed both by NMR and by the application of X-ray crystallography (Figure 1).

Unfortunately, Kumar et al.[52] had found that *N*-benzyl substituents could not be introduced directly by the method of Scheme I, which led instead to 3-benzyl-4a-(hydroxymethyl)-2,3,4,4a,5,6-hexahydrobenz[*f*]isoquinoline. Furthermore, the use of ammonium chloride afforded only very low yields of the N-unsubstituted hexahydrobenz[*f*]isoquinoline.

This problem was circumvented by deprotection of the *trans*-3-methyloctahydrobenz[*f*]isoquinoline (**17**) with cyanogen bromide followed by acidic hydrolysis to give the unsubstituted *trans*-octahydrobenz[*f*]isoquinoline (**46**) (Scheme III). This was subsequently alkylated with the appropriate alkyl halide in the presence of potassium carbonate in DMF (**22–25, 29–38**). Alternatively, alkylation could be carried out in a two-step process by acylation with the appropriate acid chloride, followed by reduction with lithium aluminum hydride (**39, 40**). This enabled a wide range of N-substituents to be introduced.

The 1*H*-indeno[2,1-*c*]pyridines **41** and **42** and 1*H*-benzo[3,4]cyclohepta[1,2-*c*]pyridines **43–45** were synthesized in an analogous fashion (Scheme IV). However, the ring-junction stereochemistry after reduction with lithium in liquid ammonia, THF, and aniline could not be determined for either series by the techniques used for the benz[*f*]isoquinolines detailed above, and attempted catalytic hydrogenation led to a complex mixture in the case of the indenopyridine **41** and no reaction at all in the case of the benzocycloheptapyridine **43**.

Results and Discussion

The affinity of compounds at the σ recognition site and the dopamine D_2 receptor were measured using in vitro radioligand binding assays involving displacement of [^{3}H]ditolylguanidine ([^{3}H]-DTG) in guinea pig cerebellum or [^{3}H]-(−)-sulpiride in rat striatum, respectively. The results are presented in Tables I–IV.

The hexahydrobenz[*f*]isoquinolines (Table I) were found to have a reasonable affinity for the σ site when larger lipophilic N-substituents were present, though the large phenethyl group (**13**) gave the same affinity as the propyl substituent (**11**) and slightly lower than the butyl analogue (**12**). However, **12** was not very selective over D_2 receptors.

A dopamine receptor interaction model based on superimposition of calculated structures of known ligands of the phenylpiperidine series has shown that the nitrogen atoms are located 0.2 Å above the aromatic ring plane.[53]

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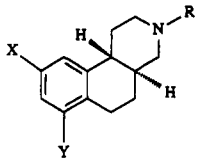
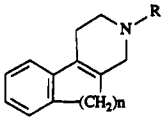
Table III. *trans*-Octahydrobenz[*f*]isoquinolines



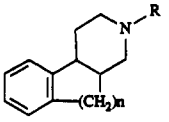
no.	R	X	Y	method	yield, %	mp, °C	microanalysis[a]	pIC$_{50}$[b] σ^c	pIC$_{50}$[b] D_2^d
17	Me	H	H	A	62	277–285 dec	$C_{14}H_{19}N$·HCl	6.35 ± 0.13	
18	Me	MeO	H	A	18[e]	284–285 dec	$C_{15}H_{21}NO$·HCl·0.1H_2O	6.47 ± 0.32	
19	$CH_3(CH_2)_2$	H	H	A	30[e]	257–259 dec	$C_{16}H_{23}N$·HCl	8.59 ± 0.29	
20	$CH_3(CH_2)_3$	H	H	A	15[e]	217–221 dec	$C_{17}H_{25}N$·HCl	8.51 ± 0.26	6.41 ± 0.13
21	$CH_3(CH_2)_3$	Me	Me	A	15[e]	260–263 dec	$C_{19}H_{29}N$·HCl·0.7H_2O[f]	8.69 ± 0.16	
22	CH_2=$CHCH_2$	H	H	B	35	224–228	$C_{16}H_{21}N$·HCl	8.34 ± 0.02	
23	CH_2=$CH(CH_2)_2$	H	H	B	62	174–182	$C_{17}H_{23}N$·HCl	8.73 ± 0.39	
24	$(CH_3)_2C$=$CHCH_2$	H	H	B	16	222–225	$C_{18}H_{25}N$·HCl[g]	8.93 ± 0.06	
25	cyclopropylmethyl	H	H	B	62	255–257	$C_{17}H_{23}N$·HCl·1.0H_2O	8.61 ± 0.19	
26	cyclohexyl	H	H	A	18[e]	279–280 dec	$C_{19}H_{27}N$·HCl	9.60 ± 0.21	5.57 ± 0.16
27	1-adamantyl	H	H	A	12[e]	252–255	$C_{23}H_{31}N$·HCl	8.64 ± 0.08	<5.00
28	2-adamantyl	H	H	A	24[e]	247–252	$C_{23}H_{31}N$·HCl·0.5H_2O	8.66 ± 0.19	
29	$PhCH_2$	H	H	B	54	242–244	$C_{20}H_{23}N$·HCl	8.74 ± 0.43	
30	4-$MeOC_6H_4CH_2$	H	H	B	53	267–271 dec	$C_{21}H_{25}NO$·HCl	8.70 ± 0.30	7.45 ± 0.55
31	4-*t*-$BuC_6H_4CH_2$	H	H	B	27	229–230 dec	$C_{24}H_{31}N$·HCl·0.4H_2O	7.01 ± 0.23	6.54[h]
32	4-$NO_2C_6H_4CH_2$	H	H	B	20	198–201	$C_{22}H_{27}N$·HCl	8.06 ± 0.15	
33	4-$ClC_6H_4CH_2$	H	H	B	33	257–259	$C_{20}H_{22}ClN$·HCl	8.33 ± 0.09	
34	$PhCH_2CH_2$	H	H	B	25	277–283 dec	$C_{21}H_{25}N$·HCl	9.49 ± 0.19	6.79 ± 0.42
35	4-$NO_2C_6H_4(CH_2)_2$	H	H	B	37	232–233 dec	$C_{21}H_{24}N_2O_2$·HCl·0.3H_2O	8.46 ± 0.56	6.23 ± 0.17
36	$PhCH_2CH_2CH_2$	H	H	B	26	196–201	$C_{22}H_{27}N$·HCl·0.2H_2O	8.37 ± 0.07	
37	2-naphthylmethyl	H	H	B	15	175–177	$C_{24}H_{25}N$·HCl	7.09 ± 0.26	
38	2-picolyl	H	H	B	14	230–237 dec	$C_{19}H_{22}N_2$·1.7HCl	7.78 ± 0.25	
39	2-thienylmethyl	H	H	C	17	214–215	$C_{18}H_{21}NS$·HCl	8.15 ± 0.24	
40	2-furylmethyl	H	H	C	38	214–223 dec	$C_{18}H_{21}NO$·HCl	8.18 ± 0.29	

[a–d] See corresponding footnotes in Table I. [e] These values are over the two steps from the corresponding 3,4-dihydronaphthalenes. [f] H: calcd 9.88, found 9.41. [g] This compound failed to yield a satisfactory microanalysis: HRMS M^+ (m/z) calcd for $C_{18}H_{25}N$ 255.1987, M^+ found 255.1975. [h] This value is the mean of two determinations.

Table IV. Indeno[2,1-*c*]pyridines and Benzo[3,4]cyclohepta[1,2-*c*]pyridines



I



II

no.	structure	*n*	R	mp, °C	microanalysis[a]	pIC$_{50}$[b] σ^c	pIC$_{50}$[b] D_2^d
41	I	1	$CH_3(CH_2)_3$	196–200 dec	$C_{16}H_{21}N$·HCl	8.73 ± 0.11	7.22 ± 0.25
42	II	1	$CH_3(CH_2)_3$	159–163	$C_{16}H_{23}N$·HCl·0.1H_2O	7.96 ± 0.17	
43	I	3	$CH_3(CH_2)_3$	130–150 dec	$C_{18}H_{25}N$·HCl	8.40 ± 0.38	7.21 ± 0.09
44	II	3	$CH_3(CH_2)_3$	185–190 dec	$C_{18}H_{27}N$·HCl	8.67 ± 0.18	6.78 ± 0.09
45	II	3	cyclohexyl	272–275	$C_{20}H_{29}N$·HCl[e]	8.85 ± 0.03	

[a–d] See corresponding footnotes in Table I. [e] H: calcd 9.45, found 9.90.

It has also been suggested that the N-aromatic ring plane distance is not critical for σ receptor interaction and varies substantially from 0.08–2.9 Å.[49]

Modeling of the hexahydrobenz[*f*]isoquinolines using a molecular mechanics force field[54] showed that the calculated N-aromatic ring plane distance of the energy-minimized structure was 0.43 Å. We hypothesized that increasing this distance would decrease dopamine receptor affinity but maintain σ site affinity. It was envisaged that this could be achieved by reducing the ring junction double bond in either a cis or a trans fashion. The calculated N-aromatic ring plane distances for the energy-minimized structures of the resulting octahydrobenz[*f*]isoquinolines were found to be 1.44 Å for the trans compound and 1.12 and 2.71 Å for the two different cis conformers. Both the cis conformers should be considered since they differ in energy by only 1.2 kcal, with the smaller distance (i.e., 1.12 Å) relating to the more stable conformer. All the above calculations were performed on the unsubstituted unprotonated amines, it being not known whether the biologically relevant nitrogen type in these compounds is amine or ammonium.

The *cis*-octahydrobenz[*f*]isoquinolines (Table II) were found to have similar affinities for the σ site as the corresponding hexahydrobenz[*f*]isoquinolines (cf. **16** and **12**) with marginally improved selectivity over the D_2 receptor found in the case of the butyl derivative **16**.

The *trans*-octahydrobenz[*f*]isoquinolines (Table III), on the other hand, displayed generally higher σ affinities than either of the previous series (cf., **20**, **16**, and **12**). For simple

(54) With use of the OPTIMOL program within the Merck molecular modeling facility (Dr. T. Halgren, Rahway, unpublished results).

straight-chain alkyl substituents, affinity increased markedly from methyl (17) to propyl (19) and butyl (20). The allyl derivative 22 had a slightly lower affinity than the more lipophilic butenyl (23) and dimethylallyl (24) analogues. Increasing the steric bulk further with cycloalkyl groups produced a dramatic result. The cyclopropyl analogue 25 was similar to the *n*-propyl (19) but the more lipophilic cyclohexyl compound 26 had an IC_{50} of 0.25 nM, making it the highest affinity σ ligand reported to date. The bulkier 1- and 2-adamantyl analogues 27 and 28 still possessed good affinities though lower than the cyclohexyl derivative 26.

Benzyl-substituted derivatives were also found to have good affinities for the σ site, though compounds with para substituents, whether electron donating or withdrawing, showed no improvement on the affinity of the unsubstituted analogue 29 with the bulky *tert*-butyl derivative 31 showing a marked drop in affinity which may suggest a limit to the size of the lipophilic pocket of the σ site.

The phenethyl analogue 34 had a very high affinity, similar to that of the cyclohexyl compound 26, but a *p*-nitro substituent 35 was detrimental to binding affinity. The phenpropyl derivative 36 was some 10-fold less active than the phenethyl analogue 34 lending support to the proposition that the site has a limit for its hydrophobic cleft. This is augmented by the fact that naphthylmethyl (37) has a fairly low affinity. Compounds substituted with heteroaromatic groups (38–40) were found to have lower affinities than the more lipophilic benzyl-substituted derivative 29. Introduction of methoxy (18) or methyl (21) substituents on to the aromatic ring of the benz[*f*]isoquinoline moiety made little difference to the binding.

All the compounds in Table III are racemates. However, the butyl analogue 20 was resolved on a chiral HPLC column, and it was found that the binding affinities of the enantiomers were very similar [(−)-20, $pIC_{50} = 8.20 \pm 0.36$; (+)-20, $pIC_{50} = 8.35$ ($n = 2$ only)].

In addition to having high σ affinities, the trans derivatives generally were more selective over the D_2 receptor than the cis isomers and the unsaturated analogues. Thus, the *p*-methoxybenzyl derivative 30 was between 10- and 100-fold selective for σ over D_2, the butyl (20) and phenethyl (34) analogues were between 100- and 1000-fold selective, and the 1-adamantyl compound 27 was over 1,000-fold selective. Gratifyingly, the cyclohexyl derivative 26, as well as having the highest σ affinity, was the most selective showing greater than 10 000-fold selectivity over D_2.

It was also found that the indenopyridines and benzocycloheptapyridines (Table IV), which have five- and seven-membered central rings, retained good affinity for the σ site, though introduction of the cyclohexyl group into the octahydrobenzocycloheptapyridine series failed to produce the same level of affinity seen in the octahydrobenz[*f*]isoquinolines (cf. 45 and 26). The selectivity of these compounds over the D_2 receptor showed a similar pattern to that of the octahydrobenz[*f*]isoquinolines with the unsaturated derivatives 41 and 43 exhibiting less selectivity than the reduced analogue 44, which had comparable selectivity to the corresponding *trans*-butyloctahydrobenz[*f*]isoquinoline 20.

The results presented above are consistent with the structural requirements of the σ site discussed by Wikström and Largent et al.[47-49] that σ affinity increases with increasing lipophilicity of the N-substituent, but we have found that there appears to be a limit to the size of this lipophilic cleft. The results would also appear to be consistent with data recently reported by Scherz et al.[55] for *N,N'*-di-*o*-tolylguanidine analogues, in which saturated carbocyclic substituents also led to a significant increase in affinity (e.g., *N-exo*-2-norbornyl-*N'*-(2-iodophenyl)-guanidine, IC_{50} = 3 nM vs [^{3}H]-DTG).

In conclusion, we have identified a novel series of compounds which have high affinity for the σ site. In particular the *trans*-cyclohexyloctahydrobenz[*f*]isoquinoline compound 26 is the highest affinity σ ligand reported to date and is greater than 10 000-fold selective over the D_2 receptor making it a valuable physiological tool in the study of the σ recognition site.

Experimental Section

General Methods. Melting points were determined on either a Reichert Thermovar hot stage or a Büchi capillary melting point apparatus and are uncorrected. Proton NMR spectra were obtained by using either a Bruker AM360 or a Bruker AC250 spectrometer. Mass spectra were recorded on a VB70-250 instrument operating either in the electron impact (EI), chemical ionization (CI), or fast atom bombardment (FAB) mode as indicated. HPLC analysis was performed on a Waters WISP 710B instrument, using a Bondapak C18 column (Waters), eluting with a gradient of 5–95% acetonitrile/water (containing 0.1% trifluoroacetic acid) over 30 min, and detecting on a Waters Lambda-Max 481 LC spectrophotometer at 254 nm. Elemental analyses for carbon, hydrogen, and nitrogen were performed by CHN Analysis Ltd. (Leicester). Analytical thin-layer chromatography (TLC) was conducted either on precoated silica gel 60 F_{254} plates (Merck) or on precoated aluminum oxide 60 F_{254} neutral (type E) aluminum sheets (Merck). Visualization of the plates was accomplished by using UV light and/or iodine and/or chlorine followed by tolidine spray. Chromatography was conducted either on silica gel 60, 220–440 mesh (Fluka), under low pressure, a Lobar Chroprep SI 60 (40–63-cm) column (Merck) under medium pressure, or aluminum oxide 90, activity II–III (Merck) under gravity. Solutions were evaporated on a Büchi rotary evaporator under reduced pressure. All starting materials were obtained from commercial sources and used as received unless otherwise indicated. Petroleum ether refers to that fraction having a boiling point range of 60–80 °C.

The method of synthesis for each of the *trans*-octahydrobenz[*f*]isoquinolines is indicated in Table III, and a detailed experimental protocol for only one example of each method is provided below.

3,4-Dihydro-7-methoxy-1-methylnaphthalene (9a) was prepared by literature procedures[51] from 7-methoxy-1-tetralone. **3,4-Dihydro-1,5,7-trimethylnaphthalene (9b)**[56] and **3,4-dihydro-1-methylnaphthalene (9c)**[57] were also prepared by the same procedures from 1-tetralone and 5,7-dimethyl-1-tetralone in 74% and 82% yield, respectively. **1,2,3,4,5,6-Hexahydro-9-methoxy-3-methylbenz[*f*]isoquinoline (10)** and **1,2,3,4,5,6-hexahydro-3-methylbenz[*f*]isoquinoline (47)** were prepared by literature procedures[50,51,58] from **9a** and **9c**, respectively. The same procedure was also used in the preparation of the novel hexahydrobenz[*f*]isoquinolines 11–13 and is exemplified below.

3-Butyl-1,2,3,4,5,6-hexahydrobenz[*f*]isoquinoline (12). A solution of **9c** (5.2 g, 36 mmol) and 37% formaldehyde (7 g, 86 mmol) in acetic acid (60 mL) was heated at 70 °C for 1 h with stirring. While the temperature was maintained below 70 °C, *n*-butylamine hydrochloride[59] (11 g, 100 mmol) was added and

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the mixture was stirred at 70 °C for 5 h under nitrogen. The solution was cooled to room temperature, diluted with ice-cold water (50 mL), and washed with ether (2 × 100 mL). The aqueous layer was made basic with 50% sodium hydroxide solution and extracted with ether (2 × 100 mL). The combined ether extracts were dried (K_2CO_3) and evaporated to leave a brown oil. Chromatography on flash silica preeluted with 1% NH_3(aq)/dichloromethane, eluting with 0–10% methanol/dichloromethane, gave a brown oil (2.0 g, 20%). The hydrochloride salt was prepared using ethereal hydrogen chloride: mp 162–163 °C dec (IPA/Et_2O); ^{1}H NMR (D_2O) δ 0.95 (3 H, t), 1.45 (2 H, m), 1.80 (2 H, m), 2.25 (2 H, t), 2.90 (4 H, m), 3.30 (3 H, m), 3.90 (3 H, m), 7.30 (4 H, m); MS (CI^+, NH_3) m/z 242 $(M + H)^+$, 198 $(M - CH_2CH_2CH_3)^+$.

11: 7%; hydrochloride salt; mp 213–215 °C; ^{1}H NMR (D_2O) δ 1.00 (3 H, t, J = 7.4 Hz), 1.82 (2 H, m), 2.22 (2 H, m), 2.71–2.96 (4 H, m), 3.18–3.38 (3 H, m), 3.71–3.97 (3 H, m), 7.26–7.30 (4 H, m); MS (CI^+, NH_3) m/z 228 $(M + H)^+$, 198 $(M - CH_2CH_3)^+$.

13: hydrochloride salt; mp 194–196 °C; ^{1}H NMR (D_2O) δ 2.22 (2 H, m), 2.84 (4 H, m), 3.18 (2 H, t, J = 8.0 Hz), 3.42 (1 H, m), 3.55 (2 H, t, J = 8.0 Hz), 3.79–3.96 (3 H, m), 7.27–7.46 (9 H, m); MS (CI^+, NH_3) m/z 290 $(M + H)^+$, 198 $(M - CH_2C_6H_5)^+$.

***cis*-3-Methyl-1,2,3,4,4a,5,6,10b-octahydrobenz[*f*]isoquinoline (14).** A mixture of **47·HCl** (0.50 g, 2.5 mmol) and 0.075 g of PtO_2 in ethanol (50 mL) was hydrogenated at 50 psi for 4 h. The mixture was filtered and evaporated to leave a white solid (0.45 g, 90%): mp 192–194 °C; ^{1}H NMR (D_2O) δ 1.78–2.42 (4 H, m), 2.70–3.24 (7 H, m), 3.30–3.42 (1 H, m), 3.51 (1 H, m), 3.68–3.81 (1 H, m), 3.89 (1 H, m), 7.22–7.33 (4 H, m); MS (FAB$^+$) m/z 202 $(M + H)^+$.

***cis*-9-Methoxy-3-methyl-1,2,3,4,4a,5,6,10b-octahydrobenz-[*f*]isoquinoline (15)** was prepared from **9a** with use of the procedures described for **10** and **14** in 18% yield. Hydrochloride salt: mp 223–226 °C (EtOH/EtOAc); ^{1}H NMR (D_2O) δ 1.82–1.96 (3 H, m), 2.12 (1 H, m), 2.32 (1 H, m), 2.75–2.88 (6 H, m), 3.02–3.16 (2 H, m), 3.35 (1 H, dd, J = 12.9 and 4.0 Hz), 3.50 (1 H, m), 3.81 (3 H, s), 6.85 (2 H, m), 7.15 (1 H, d, J = 8.1 Hz); MS (CI^+, NH_3) m/z 232 $(M + H)^+$.

***cis*-3-Butyl-1,2,3,4,4a,5,6,10b-octahydrobenz[*f*]isoquinoline (16)** was prepared from **12·HCl** with use of the procedure described for **14**. Hydrochloride salt: mp 185–191 °C; ^{1}H NMR (D_2O) δ 0.95 (3 H, t), 1.35 (2 H, m), 1.6–2.2 (6 H, m), 2.25–3.85 (11 H, m), 7.2 (4 H, m); MS (CI^+, NH_3) m/z 244 $(M + H)^+$, 200 $(M - CH_2CH_2CH_3)^+$.

***trans*-3-Methyl-1,2,3,4,4a,5,6,10b-octahydrobenz[*f*]isoquinoline (17) (Method A).** A solution of **47·HCl** (0.64 g, 2.71 mmol) in anhydrous THF (25 mL) and aniline (0.25 mL) was added dropwise to a solution of lithium wire (0.126 g) in liquid ammonia (100 mL) cooled by a dry ice/acetone bath. The solution was stirred for 1 h under nitrogen before the cooling bath was removed and the solution stirred for a further 2 h. The reaction was then quenched carefully with water (6 mL), and the solvents were allowed to evaporate overnight. The residue was partitioned between ether and water, and the aqueous layer was reextracted with more ether. The combined ether extracts were dried (K_2CO_3) and evaporated to leave a brown oil. Chromatography on flash silica eluting with 5–10% methanol/dichloromethane and then on alumina eluting with 25% ethyl acetate/petroleum ether gave a colorless oil (0.340 g, 62%). The hydrochloride salt was prepared using ethereal hydrogen chloride: mp 277–285 °C dec; ^{1}H NMR (D_2O) δ 1.52–1.92 (4 H, m), 2.63–2.75 (2 H, m), 2.86–2.98 (3 H, m), 2.92 (3 H, s), 3.19 (1 H, td, J = 13 and 3 Hz), 3.56 (1 H, m), 3.70 (1 H, m), 7.22–7.28 (3 H, m), 7.33–7.36 (1 H, m); MS (CI^+, NH_3) m/z 202 $(M + H)^+$.

***trans*-1,2,3,4,4a,5,6,10b-Octahydrobenz[*f*]isoquinoline (46).** A solution of **17** (0.218 g, 1.08 mmol) in chloroform (3 mL) was added over 25 min to a solution of cyanogen bromide (0.140 g, 1.32 mmol) in chloroform (1 mL) while being stirred under nitrogen. After completion of the addition, the reaction was heated to reflux for 75 min and then allowed to cool. The solvent was evaporated, 2 M hydrogen chloride solution (5 mL) was added, and the reaction was heated at reflux for 6 h while being stirred magnetically. After being allowed to cool, the reaction mixture was made alkaline with 2 M sodium hydroxide solution and extracted with ether (3 × 30 mL). The combined ether extracts were dried (K_2CO_3) and evaporated to leave a white solid (0.186 g, 92%) which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 1.35–1.56 (3 H, m), 1.74–1.82 (1 H, m), 2.35–2.50 (3 H, m), 2.78–2.92 (3 H, m), 3.11 (1 H, m), 3.27 (1 H, m), 7.06–7.17 (3 H, m), 7.24 (1 H, d).

***trans*-3-Allyl-1,2,3,4,4a,5,6,10b-octahydrobenz[*f*]isoquinoline (22) (Method B).** To a solution of crude **46** (0.152 g, 0.810 mmol) in anhydrous DMF (10 mL) was added anhydrous potassium carbonate (0.123 g, 0.890 mmol) and allyl bromide (0.074 mL, 0.855 mmol), and the reaction was heated at 100 °C for 80 min while being stirred magnetically under nitrogen. The solvent was then evaporated and the residue partitioned between ethyl acetate and water. The ethyl acetate layer was dried (K_2CO_3) and evaporated to leave an oil. This was chromatographed on flash silica, eluting with 3–7% methanol/dichloromethane, and then on alumina, eluting with 2–5% ethyl acetate/petroleum ether, to give a colorless oil (0.064 g, 35%). The hydrochloride salt was prepared using ethereal hydrogen chloride: mp 224–228 °C (EtOAc/EtOH); ^{1}H NMR (D_2O) δ 1.57 (1 H, m), 1.69 (1 H, m), 1.80–1.92 (2 H, m), 2.66–2.77 (2 H, m), 2.88–2.95 (3 H, m), 3.18 (1 H, t, J = 11.4 Hz), 3.60 (1 H, m), 3.77 (1 H, m), 3.81 (2 H, d, J = 7.2 Hz), 5.60–5.65 (2 H, m), 5.98 (1 H, m), 7.22–7.29 (3 H, m), 7.35–7.37 (1 H, m); MS (CI^+, NH_3) m/z 228 $(M + H)^+$.

***trans*-1,2,3,4,4a,5,6,10b-Octahydro-3-(2-thienylmethyl)-benz[*f*]isoquinoline (39) (Method C).** To a solution of crude **46** (0.179 g, 0.954 mmol) in anhydrous dichloromethane (8 mL) was added triethylamine (0.332 mL, 2.38 mmol) and then 2-thiophenecarbonyl chloride (0.204 mL, 1.91 mmol), and the reaction was stirred for 2.5 h under nitrogen. The solvent was evaporated, and the residue was partitioned between ether and water. The ether layer was dried ($MgSO_4$) and evaporated to leave an oil. This was dissolved in anhydrous THF (15 mL), and a 1.0 M solution of lithium aluminum hydride in THF (2.9 mL) was added dropwise under nitrogen. The reaction was stirred for 2 h and then heated to reflux for 1 h before being quenched with ethyl acetate (2 mL). The inorganic salts were precipitated with saturated ammonium chloride solution (1 mL), and the mixture was filtered, washing the solid with ethyl acetate. The filtrate was evaporated to leave a pale yellow oil. Chromatography on flash silica, eluting with 30% ethyl acetate/petroleum ether, gave a white solid (0.046 g, 17%). The hydrochloride salt was made using ethereal hydrogen chloride: mp 214–215 °C; ^{1}H NMR (D_2O/CD_3CN) δ 1.54 (1 H, m), 1.68 (1 H, m), 1.79–1.87 (2 H, m), 2.61–2.73 (2 H, m), 2.89–2.95 (3 H, m), 3.20 (1 H, t), 3.54 (1 H, m), 3.72 (1 H, m), 4.61 (2 H, s), 7.18–7.25 (4 H, m), 7.30–7.33 (1 H, m), 7.36 (1 H, d, J = 2.9 Hz), 7.65 (1 H, dd, J = 5.2 and 1.1 Hz); MS (CI^+, NH_3) m/z 284 $(M + H)^+$.

(+)- and (−)-*trans*-3-Butyl-1,2,3,4,4a,5,6,10b-octahydrobenz[*f*]isoquinoline [(+)-20 and (−)-20]. A solution of racemic **20·HCl** (37.8 mg, 0.135 mmol) was injected in 450-μg batches onto a chiral 5-μm AGP column (10- × 10-mm i.d.), eluted at 3.5 mL/min with 15% 2-propanol in 10 mM K_2HPO_4 made to pH 6.2 with H_3PO_4, and detected at 220 nm. The pooled fractions of each isomer were separately evaporated in vacuo, redissolved in water, basified to pH 12 with 50% NaOH solution, extracted with ether, dried (K_2CO_3), and evaporated in vacuo. The hydrochloride salt was prepared using ethereal hydrogen chloride to give 8.8 mg of **(+)-20** $[[\alpha]^D = +67°$ (c = 0.2, MeOH); HPLC enantiomeric purity = 99.7%] and 7.2 mg of **(−)-20**: $[\alpha]^D = -78°$ (c = 0.05, MeOH); HPLC enantiomeric purity = 98.7%.

3-Methyl-1*H*-indene (48)[60] and **6,7-dihydro-9-methyl-5*H*-benzocycloheptene (49)**[60,61] were both prepared by the same procedure[51] as **9a** from 1-indanone and 1-benzosuberone in 59% and 74% yields, respectively.

2-Butyl-2,3,4,9-tetrahydro-1*H*-indeno[2,1-*c*]pyridine (41) was prepared from **48** with use of the procedure described for **12**

(59) Prepared by treating *n*-butylamine with ethereal hydrogen chloride.

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in 5% yield. Hydrochloride salt: mp 196–200 °C dec (EtOH/EtOAc); ^{1}H NMR (D_2O/DCl) δ 0.96 (3 H, t, J = 7.3 Hz), 1.43 (2 H, m), 1.81 (2 H, m), 2.92 (2 H, m), 3.31–3.46 (5 H, m), 3.79 (1 H, m), 4.08 (1 H, m), 4.36 (1 H, m), 7.30–7.33 (1 H, m), 7.40 (2 H, m), 7.55–7.57 (1 H, m); MS (CI$^+$, NH_3) m/z 228 (M + H)$^+$, 184 (M – $CH_2CH_2CH_3$)$^+$.

2-Butyl-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine (42) was prepared from **48** with use of the procedures described for **12** and **17** in 5% yield. Hydrochloride salt: mp 159–163 °C (EtOH/EtOAc); ^{1}H NMR (D_2O) at 358 K δ 0.91 (3 H, t, J = 7.3 Hz), 1.37 (2 H, m), 1.67 (2 H, m), 2.36 (2 H, m), 2.65 (2 H, m), 2.85–3.05 (4 H, m), 3.13 (1 H, dd, J = 15.9 and 6.2 Hz), 3.33–3.46 (3 H, m), 7.28–7.38 (4 H, m); MS (CI$^+$, NH_3) m/z 230 (M + H)$^+$, 186 (M – $CH_2CH_2CH_3$)$^+$.

3-Butyl-2,3,4,5,6,7-hexahydro-1*H*-benzo[3,4]cyclohepta-[1,2-*c*]pyridine (43) was prepared from **49** with use of the procedure described for **12** in 16% yield. Hydrochloride salt: mp 135–150 °C dec (EtOAc/Pet ether); ^{1}H NMR (D_2O) δ 0.96 (3 H, m), 1.43 (2 H, m), 1.81 (4 H, m), 2.16 (2 H, m), 2.59 (2 H, t), 2.79 (2 H, m), 3.25–3.35 (3 H, m), 3.71–3.75 (1 H, m), 3.86 (1 H, m), 4.03–4.18 (1 H, m), 7.28–7.36 (4 H, m); MS (CI$^+$, NH_3) m/z 256 (M + H)$^+$, 212 (M – $CH_2CH_2CH_3$)$^+$.

3-Butyl-2,3,4,4a,5,6,7,11b-octahydro-1*H*-benzo[3,4]cyclohepta[1,2-*c*]pyridine (44) was prepared from **49** with use of the procedures described for **12** and **17**, in 21% yield. Hydrochloride salt: mp 185–190 °C dec (EtOAc/EtOH); ^{1}H NMR (D_2O) δ 0.95 (3 H, t, J = 7.4 Hz), 1.36–1.47 (4 H, m), 1.71–1.80 (4 H, m), 1.97–1.99 (1 H, m), 2.26–2.32 (2 H, m), 2.81–3.19 (7 H, m), 3.49 (1 H, m), 3.77 (1 H, m), 7.24–7.33 (4 H, m); MS (CI$^+$, NH_3) m/z 258 (M + H)$^+$, 214 (M – $CH_2CH_2CH_3$)$^+$.

3-Cyclohexyl-2,3,4,4a,5,6,7,11b-octahydro-1*H*-benzo[3,4]-cyclohepta[1,2-*c*]pyridine (45) was prepared from **49** with use of the procedures described for **12** and **17** in 12% yield. Hydrochloride salt: mp 272–275 °C (EtOH/EtOAc); ^{1}H NMR (D_2O) δ 1.13–1.24 (1 H, m), 1.31–1.57 (6 H, m), 1.68–1.79 (3 H, m), 1.91–1.95 (3 H, m), 2.10–2.12 (2 H, m), 2.24–2.36 (2 H, m), 2.80–2.86 (1 H, m), 2.92–3.05 (3 H, m), 3.14–3.26 (2 H, m), 3.40 (1 H, m), 3.68 (1 H, m), 7.24–7.33 (4 H, m); MS (CI$^+$, NH_3) m/z 284 (M + H)$^+$.

X-ray Crystallography. X-ray Crystal Structure Analysis of 27. Crystals of **27** ($C_{23}H_{32}ClN$) formed in space group $Pna2_1$ with a = 25.417 (1) Å, b = 10.189 (1) Å, c = 7.320 (6) Å, for Z = 4 and a calculated density of 1.254 g/cm^3. An automatic four-circle diffractometer equipped with Cu Kα radiation (λ = 1.5418 Å) was used to measure 1948 potential diffraction peaks of which 1438 were observed ($I > 3\sigma I$). Application of a multisolution tangent formula approach to phase solution gave an initial model for the structure[62] which was subsequently refined with least squares and Fourier methods. Anisotropic temperature parameters were refined for the non-hydrogen atoms. The function $\sum\omega(|F_o| - |F_c|)^2$ with $\omega = 4F_o^2/\sigma^2(F_o^2)$ was minimized with full matrix least squares to give an unweighted residual of 0.056. Figure 1 is a computer-generated drawing of **27** showing its stereochemistry.

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

Radioligand binding to the σ recognition site was performed as described by Weber et al.[63] The cerebellum from male Dunkin-Hartley guinea pigs (350–400 g) was homogenized in 10 volumes of ice-cold 0.32 M sucrose using 8 strokes of a glass Teflon homogenizer. The homogenate was centrifuged at 900g for 10 min at 4 °C and the supernatant centrifuged at 22000g for 20 min. The pellet from this high speed centrifugation was suspended in 10 volumes of assay buffer (50 mM Tris-HCl, pH 7.4) and centrifuged at 22000g for 20 min. Pellets were resuspended in 10 volumes of assay buffer and stored at –70 °C until needed.

On the day of the experiment, the frozen homogenate was thawed, homogenized, and diluted 7.7-fold in assay buffer. Radioligand binding assays were carried out in 1-mL final volume containing 750 μL of membrane preparation, 100 μL of drug solution or buffer or 100 μL of 100 μM haloperidol to determine nonspecific binding, 100 μL of 50 nM [^{3}H]-1,3,di(2-[5-^{3}H]tolyl)-guanidine ([^{3}H]DTG), and 50 μL of assay buffer. The binding assay was performed at 25 °C for 90 min and terminated by rapid filtration through GF/B filters, presoaked in 0.1% polyethylenimine, using a Brandel M24 cell harvester followed by washing with 3 × 5 mL of ice-cold buffer. The retaining radioactivity in the filters was determined by liquid scintillation spectrophotometry using Ready Gel (Beckmann) or Hydrofluor (National Diagnostics) scintillation fluid and a Beckmann LS 3801 spectrophotometer. Inhibition curves with drugs were described by 5 or 10 concentrations each performed in duplicate. Curves were analyzed using a computer-assisted iteritive curve-fitting function and the data expressed as pIC_{50} ($-\log_{10}$ of the concentration of drug to inhibit specific binding by 50%) and are the mean of three independent experiments.

Radioligand binding to the D_2 receptor was performed as described by Woodruff and Freedman.[64] The striata from male Sprague-Dawley rats (250–300 g) were homogenized in 10 volumes of ice-cold 0.32 M sucrose/5 mM HEPES buffer (pH 6.5) using 10 strokes of a glass Teflon homogenizer. The homogenate was centrifuged at 800g for 15 min at 4 °C and the supernatant retained. The pellet was rehomogenized in 10 volumes of sucrose/HEPES buffer and centrifuged at 800g for 15 min. The combined supernatants were then centrifuged at 17000g for 20 min and the resultant pellet resuspended in 10 vol of HEPES buffer (5 mM, pH 8.0) and centrifuged at 50000g for 15 min. The pellet from this centrifugation was suspended in 10 volumes of a HEPES/Krebs buffer containing 20 mM HEPES, pH 7.4, 118 mM NaCl, 4.7 mM KCl, 1.2 mM $MgSO_4$, 5 mM $NaHCO_3$, 1.2 mM KH_2PO_4, 2.5 mM $CaCl_2$, and 11 mM glucose and incubated at 37 °C for 10 min to reduce endogenous levels of dopamine. This homogenate was frozen at –20 °C until the day of the assay.

On the day of the experiment, the frozen homogenate was thawed and diluted 3-fold in the HEPES/Krebs assay buffer containing 10 μM pargyline. Radioligand binding assays were performed using 100 μL of membrane preparation, 50 μL of drug solution or buffer or 50 μL of 10 μM haloperidol to define nonspecific binding, 50 μL of 100 nM [^{3}H]-(–)-sulpiride, and assay buffer to a final volume of 500 μL. The incubation was performed for 10 min at 25 °C and terminated by rapid cooling for 2 min on ice followed by filtration through a Brandel cell harvester, liquid scintillation spectrophotometry, and analysis as described above.

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Registry No. **9a**, 30021-91-1; **9b**, 53156-11-9; **9c**, 4373-13-1; **10**, 91404-68-1; **10**·HCl, 91404-71-6; **11**, 134795-01-0; **11**·HCl, 140465-46-9; **12**, 134794-73-3; **12**·HCl, 134794-74-4; **13**, 140465-79-8; **13**·HCl, 140465-47-0; **14**, 140465-80-1; **14**·HCl, 140465-48-1; **15**, 140465-81-2; **15**·HCl, 140465-49-2; **16**, 134794-51-7; **16**·HCl, 140465-50-5; (±)-**17**, 140465-82-3; (±)-**17**·HCl, 140465-51-6; (±)-**18**, 140465-83-4; (±)-**18**·HCl, 140465-52-7; (±)-**19**, 140605-05-6; (±)-**19**·HCl, 140465-53-8; (±)-**20**, 140465-84-5; (±)-**20**·HCl, 140465-54-9; (+)-**20**, 140466-05-3; (+)-**20**·HCl, 140465-44-7; (–)-**20**, 140604-89-3; (–)-**20**·HCl, 140465-45-8; (±)-**21**, 140465-85-6; (±)-**21**·HCl, 140465-55-0; (±)-**22**, 140465-86-7; (±)-**22**·HCl, 140465-56-1; (±)-**23**, 140465-87-8; (±)-**23**·HCl, 140465-57-2; (±)-**24**, 140465-88-9; (±)-**24**·HCl, 140465-58-3; (±)-**25**, 140465-89-0; (±)-**25**·HCl, 140465-59-4; (±)-**26**, 140605-06-7; (±)-**26**·HCl, 140465-60-7; (±)-**27**, 140465-90-3; (±)-**27**·HCl, 140465-61-8; (±)-**28**, 140465-91-4;

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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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