Piperidinyltetralin σ Ligands

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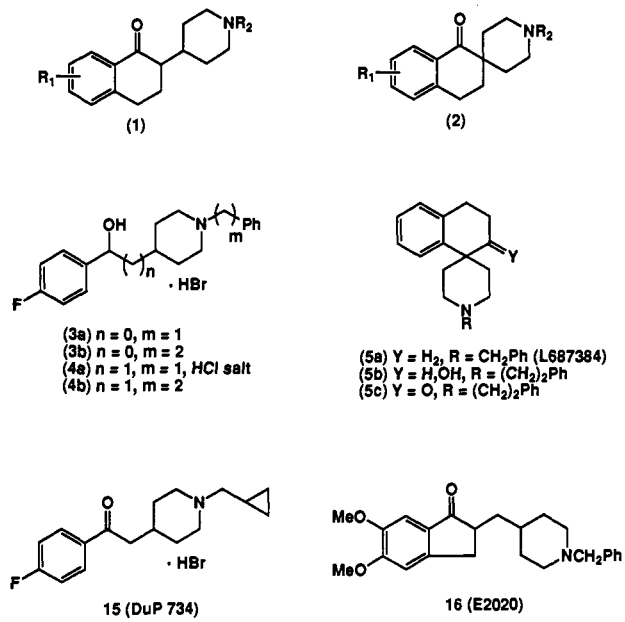
σ receptor ligands have been proposed to be potential antipsychotic drugs based on their activity profile in animal behavioral models and their indirect modulation of dopaminergic function. Compound **15** (DuP 734) is a combined antagonist of σ-1 and serotonin $5HT_2$ receptors, which has been entered into phase I clinical trials as a potential antipsychotic drug. Tetralins **1** and **2** were prepared to determine whether restriction of the conformation of **15** and its analogs may lead to differences in binding selectivity or *in vivo* profile. The syntheses and the structure-activity relationships of these compounds are reported herein. A reduced derivative, **14**, had high affinity for σ-1 and serotonin $5HT_2$ receptors as well as excellent oral activity in some animal antipsychotic models. Furthermore, compound **14** failed to cause catalepsy in the rat up to 90 mg/kg (po).

σ receptor ligands have been proposed to be potential antipsychotic drugs based on their activity profile in animal behavioral models and their indirect modulation of dopaminergic function.[1-5] Compound **15** (DuP 734) is a combined antagonist of σ-1 and serotonin $5HT_2$ receptors, which has been entered into phase I clinical trials as a potential antipsychotic drug.[6-8]

Restriction of the conformation of **15** may lead to improvements in binding selectivity or *in vivo* activity. Tetralins **1**, wherein the chain connecting the 4-position of the piperidine ring in **15** is partially constrained by attachment to the phenyl ring distal to the basic nitrogen (Scheme 1), were prepared to test this possibility. While related structures (e.g. **16** (E2020), Scheme 1) have been disclosed to be acetylcholinesterase inhibitors[9-11] useful for the treatment of cognition deficits, no data has been published, to our knowledge, on whether these compounds are σ ligands. Spirotetralins **2** were also prepared and tested since they were more structurally rigid than their counterparts **1**. Compounds **2** have been generically disclosed to be antiarrhythmic drugs, but no data on their σ binding affinity has been published.[12,13] The distance between the basic nitrogen and the tetralin nucleus is shorter for compounds **2** than for their homologs **1**. However, for compound **15** and analogs, reduction of the distance between the distal phenyl group and piperidine nitrogen by one bond length did not appear to adversely affect σ binding affinity or selectivity. For example, compounds **3a** and **4a** (Scheme 1) had comparable affinities and selectivities for the σ receptor (σK_i = 8 and 6 nM, dopamine D_2 K_i = >10 000 and >10 000 nM, serotonin $5HT_2$ K_i = 427 and 323 nM, respectively). Isomeric tetralin structures **5** have been reported to be potent σ ligands, but the prototype compound, **5a** (L687384), is surprisingly less potent *in vivo* than compounds **2** (vide infra).[14,15]

Scheme 1



Chemistry

Scheme 2 depicts a facile synthesis of tetralins **1**. The anion of ethyl 4-pyridinylacetate was generated with sodium bis(trimethylsilyl)amide and alkylated with substituted phenethyl bromides to produce compounds **6**. Formation of the pyridinium salts with various halides, followed by hydrogenation, afforded intermediates **7**. Saponification and electrophilic cyclization (polyphosphoric acid (PPA) or P_2O_5-CH_3SO_3H[16] (7% by weight)) produced the desired targets (Table 1). Alternatively, intermediates **6** were hydrolyzed to the corresponding acids, which were cyclized immediately to the tetralones **8** by treatment with PPA. Saponification of compounds **6** is sometimes accompanied by decarboxylation to afford the corresponding 4-(phenylpropyl)pyridines. Pyridines **8** were then converted to the corresponding pyridinium salts by reaction with various halides; hydrogenation produced compounds **1**.

Tetralins **2** were prepared from ethyl piperidine-4-carboxylate in six steps (Scheme 3). The starting piperidine was protected first as its *tert*-butyl carbamate and then alkylated after treatment with lithium diisopropylamide (LDA) and various phenethyl halides at 0 °C. The resulting intermediates (**10**) were then deprotected via reaction with trifluoroacetic acid (TFA) and alkylated in the presence of triethylamine and various halides. Saponification, followed by treatment with P_2O_5-CH_3SO_3H (7% by weight), afforded tetralones **2** (Table 2).

Pharmacology

The structure-activity relationships (SAR) for σ-1 binding affinity and selectivity of the tetralins paralleled

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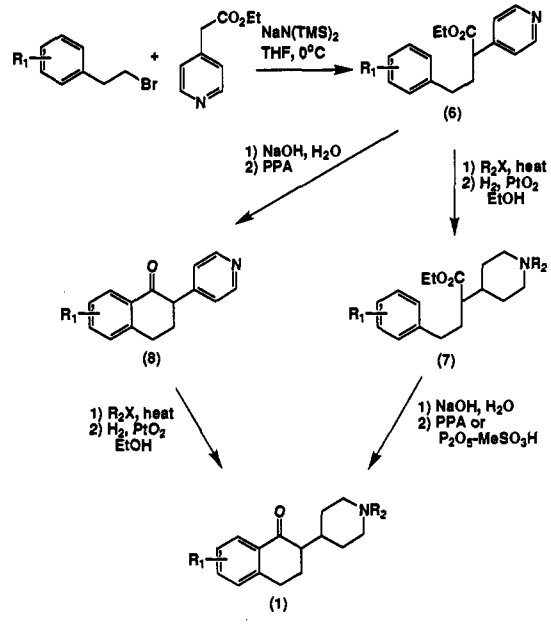
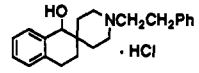
Scheme 2



those of their counterparts in the acyclic series containing compound **15** (Tables 3 and 4). Substitution at the piperidine nitrogen terminus could be varied widely with minimal changes in σ-1 binding affinity. However, selectivity for σ-1 sites (i.e., those sites labeled by [^{3}H]-SKF10047) over serotonin $5HT_2$ receptors appears to be governed by the chemical nature of the hydrophobic group tethered to the piperidine nitrogen as well as the distance between this moiety and the basic nitrogen. The *N*-phenethyltetralones in this study had equally good affinity for σ-1 and $5HT_2$ receptors; in some cases, their *N*-benzyl counterparts showed more selectivity for σ-1 sites over $5HT_2$ receptors (compare **1a** to **1b** or **1i** to **1j**). Butyrophenone **2j** had excellent affinity for dopamine D_2 sites, which was consistent with the literature precedent.[17] Similar trends were noted for compound **15** and its analogs.[6] Most of the *N*-aralkyltetralones had good selectivity for σ-1 sites over dopamine D_2 receptors, but there were some unusual exceptions (entries **1c**, **1g**, and **1i**). Halogen and methoxy substituents on the aromatic portion of the tetralin nucleus appeared to be comparable to hydrogen in their effects on σ-1 binding affinity and selectivity. Derivatives with electron-withdrawing substituents (as defined by their Hansch resonance factors[18]) on the tetralin nucleus were not readily prepared by the synthetic routes described above. Most of the tetralones in Tables 3 and 4 had σ-1 binding affinity and selectivity, which was superior to that for **17** (rimcazole) and **18** (BMY14802), two standard σ ligands, and comparable to that for **15**. None of the tetralins in this study had affinity for the phencyclidine (PCP) receptor as determined in displacement studies, using [^{3}H]MK801.[7]

There are striking differences between the acyclic series containing compound **15** and the tetralins in SAR for *in vivo* activity (Tables 3 and 4). The above compounds were evaluated in the mouse antimescaline test,[19] in which the ability of a compound to block the behavioral effects of a hallucinogen was measured. The *N*-phenethyltetralins **1** and **2** generally had the best activity in this model; in contrast, the *N*-(cyclopropylmethyl)piperidines had the best *in vivo* activity in the acyclic series.[6] None of the tetralins in Tables 3 and 4 had the potency and the spectrum of *in vivo* activity possessed by **15**. In the mouse antiaggression model,[20,21] the tetralins **1** and **2** were inactive ($ED_{50} \geq 30$ mg/kg, po) in blocking aggressive behavior caused by prolonged isolation, while **15** was potent (ED_{50} = 1.9 mg/kg, po).[8] Those compounds, which had good affinity for $5HT_2$ receptors, were less active than **15** in the rat 5-hydroxytryptophan (5HTP)-induced head twitch test,[22,23] a measure of $5HT_2$ antagonism *in vivo* (e.g., ED_{50} = 10, 5.3, and 7 mg/kg (po) for compounds **1b**, **1k**, and **1m**, respectively, vs ED_{50} = 1.8 mg/kg (po)[8] for **15**; $ED_{50} \geq 30$ mg/kg (po) for all other compounds **1** and **2** with $5HT_2$ $K_i \leq 20$ nM).

The carbonyl group in acyclic series containing compound **15** may be reduced to the alcohol without substantial changes in activity,[6] but there was an exception in the tetralin series, where a significant improvement of potency occurred. Tetralone **2i** was reduced with sodium borohydride to provide alcohol **14**, a combined ligand for σ-1



(14)

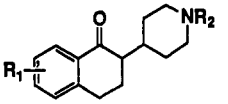
and serotonin $5HT_2$ receptors. Compound **14** had outstanding oral activity in the antimescaline and 5HTP head twitch tests (Table 5) relative to **2i**, **15**, **17**, and **18**. In the antiaggression test, **14** was less potent than **15**, but it was superior to the other two standards. Alcohol **14** was inactive in blocking the climbing behavior induced by apomorphine in mice[24,25] (ED_{50} > 30 mg/kg (po)), which was consistent with its low affinity for dopamine D_2 receptors. Furthermore, compound **14** did not induce catalepsy in the rat up to 90 mg/kg (po). These data suggest **14**, a combined σ-1 and $5HT_2$ ligand, may be a potential antipsychotic drug which may not induce extrapyramidal side effects.

Compound **14** was superior to isomeric tetralins **5a** (L687384), **5b**, and **5c** *in vivo* (Table 5). The latter compounds were inactive in the antimescaline model, and **5a** was also inactive in the antiaggression protocol (ED_{50}'s > 30 mg/kg, po). The inactivity of **5a** in the antimescaline and antiaggression tests may not be attributed to its low affinity for $5HT_2$ receptors, since it has been shown previously that σ-selective compounds are potent in these two models.[6] These data show the σ binding requirements for the tetralin isomers to be flexible, but the location of the spiro ring junction seems to be important to good *in vivo* activity in our animal models.

Conclusion

Tetralin **14** has good affinity for σ-1 and serotonin $5HT_2$ receptors as well as excellent oral activity in some animal antipsychotic models relative to **15**, unlike tetralins **1** and **2** and isomeric tetralins **5a**, **5b**, and **5c**. The differences in the activities of **14** and **2i** are not easily explained. The calculated log *P* values for **14** and **2i** are similar (4.06 and 4.11, respectively).[26] The rigidity of the spirotetralin system offered no consistent advantage *in vivo* for compounds **2** relative to their counterparts **1** (compare **1a** and **2a**, **1b** and **2i**, **1c** and **2b**) nor does it seem to dramatically alter σ binding affinity or selectivity. Compound **14** has a binding profile comparable to that for its acyclic counterpart **3b** (Table 5). Compound **3b** (Scheme 1) also has excellent activity in the anti-mescaline and 5HTP head twitch tests. Therefore, restriction of conformation in the tetralins **1** and **2** does not appear to uniformly improve

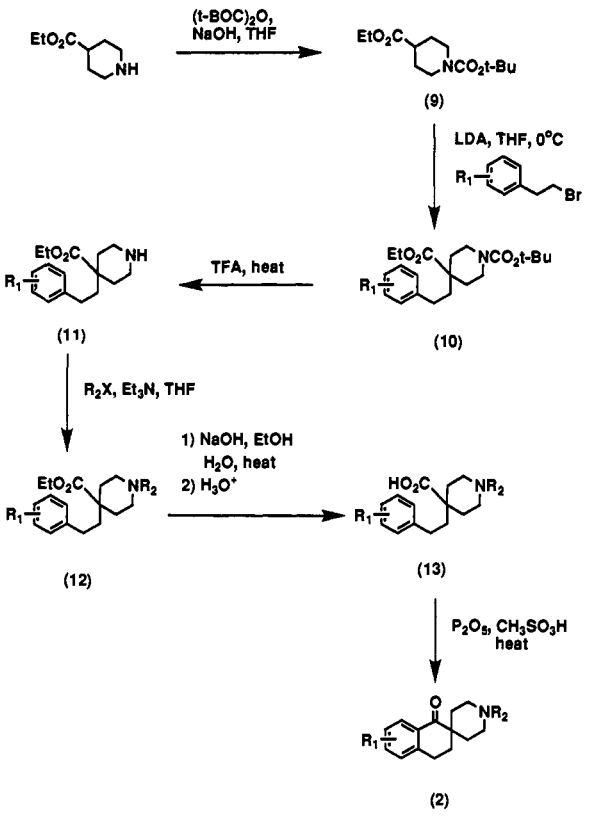
Table 1. Physical Data for Tetralins (1)



example	R_1	R_2	salt	mp (°C)	analysis[a]
1a	H	CH_2Ph	HCl	240–243	$C_{22}H_{25}NO\cdot HCl$
1b	H	$(CH_2)_2Ph$	HBr	>250	$C_{23}H_{27}NO\cdot HBr$
1c	H	4-$FC_6H_4CH_2$	HCl	>250	$C_{22}H_{24}FNO\cdot HCl$
1d	H	CH_2-c-C_3H_7	HBr	159–160	$C_{19}H_{25}NO\cdot HBr$[b]
1e	H	$CH(CH_3)$-c-C_3H_7	HBr	134–136	$C_{20}H_{27}NO\cdot HBr$[c]
1f	H	4-t-$BuC_6H_4CH_2$		240	$C_{26}H_{33}NO\cdot HCl\cdot 0.25H_2O$
1g	H	4-$MeC_6H_4CH_2$	H_2O	78	$C_{23}H_{27}NO\cdot 0.25H_2O$
1h	H	4-$CF_3C_6H_4CH_2$	HCl	270	$C_{23}H_{24}F_3NO\cdot HCl\cdot 0.2H_2O$
1i	6-F	CH_2Ph		243 dec	$C_{22}H_{25}FNO\cdot HCl$
1j	6-F	$(CH_2)_2Ph$		112–113	$C_{23}H_{26}FNO\cdot 0.25H_2O$
1k	5-F	$(CH_2)_2Ph$	HCl	>250	$C_{23}H_{26}FNO\cdot HCl\cdot 0.1H_2O$
1l	6-Cl	$(CH_2)_2Ph$	HCl	>250	$C_{23}H_{27}ClNO\cdot HCl$
1m	6-OMe	$(CH_2)_2Ph$		oil	*d, f*
1n	6-OMe	CH_2Ph		oil	*e, f*

[a] Combustion analyses gave results within 0.4% of theoretical values, unless otherwise noted. [b] Hygroscopic, requires storage under argon. [c] Calcd: H, 7.63; found: H, 7.10. [d] CI-HRMS: calcd 364.1789, found 364.1800. [e] CI-HRMS: calcd 349.4678, found 349.4670. [f] **1m** and **1n** were prepared via intermediates **7**, whereas all the other entries were prepared via intermediates **8**.

Scheme 3

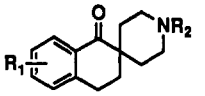


activity relative to the acyclic series containing compound **15**. Compound **14** is negative in the modified Ames test and it has been advanced into drug metabolism studies.

Experimental Section

Chemistry. Analytical data were recorded for the compounds described below using the following general procedures. Infrared spectra were recorded on a Perkin-Elmer Model 1600 FT-IR spectrometer; absorbances are recorded in cm^{-1}, and intensities are denoted s (strong), m (moderate), and w (weak). Proton NMR spectra were recorded on a Varian FT-NMR spectrometer (300 MHz); chemical shifts were recorded in ppm (δ) from an internal tetramethylsilane standard in deuteriochloroform or deuteriodimethyl sulfoxide and coupling constants (J) are reported in hertz. Chemi-ionization mass spectra (CI-MS) or chemi-ionization high-resolution mass spectra (CI-HRMS) were recorded on a Finnegan MAT 8230 or a Hewlett-Packard 5988A spectrometer. Melting points were recorded on a Buchi Model 510 melting point apparatus and are uncorrected. Boiling points are uncorrected. Combustion analyses were performed by Quantitative Technologies, Whitehouse, NJ.

Table 2. Physical Data for Tetralins 2



example	R_1	R_2	salt	mp (°C)	analysis[a]
2a	H	$PhCH_2$	HCl	>250	$C_{21}H_{23}NO\cdot HCl$
2b	H	4-$FC_6H_4CH_2$	HCl	>250	$C_{21}H_{22}FNO\cdot HCl$
2c	H	4-t-$BuC_6H_4CH_2$	HCl	241–243	$C_{25}H_{31}NO\cdot HCl\cdot 0.2H_2O$
2d	H	4-$MeOC_6H_4CH_2$	HCl	242–243	$C_{22}H_{25}NO_2\cdot HCl$
2e	H	4-$CF_3C_6H_4CH_2$	mal	197–198	$C_{22}H_{22}F_3NO\cdot C_4H_4O_4$
2f	H	4-$NO_2C_6H_4CH_2$	HCl	>250	$C_{21}H_{22}N_2O_3\cdot HCl$
2g	H	c-$C_6H_{11}CH_2$	HCl	>250	$C_{21}H_{29}NO\cdot HCl$
2h	H	2-$C_{10}H_7CH_2$	mal	204	$C_{25}H_{25}NO\cdot C_4H_4O_4$
2i	H	$Ph(CH_2)_2$	HCl	>250	$C_{22}H_{25}NO\cdot HCl$
2j	H	4-$FC_6H_4CO(CH_2)_3$	HCl	224–225	$C_{24}H_{26}FNO_2\cdot HCl$
2k	H	CH_3	HCl	237 dec	$C_{15}H_{19}NO\cdot HCl\cdot 0.5H_2O$
21	6,8-F_2	$Ph(CH_2)_2$	fum	176 dec	$C_{21}H_{21}F_2NO\cdot C_4H_4O_4$
2m	6-Cl	$Ph(CH_2)_2$		96–97	$C_{22}H_{24}ClNO$

[a] Combustion analyses gave results within 0.4% of theoretical values.

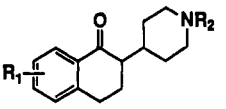
Reagents were purchased from commercial sources and, where necessary, purified prior to use according to the literature procedures.[27] For hydrogenations, the reaction solvent was purged by bubbling anhydrous nitrogen through it before addition of the substrate(s) or the catalyst. Nitrogen was used in all reactions requiring an inert atmosphere. Chromatography was performed on silica gel (230–400 mesh ASTM, EM Science) using the solvent systems indicated below. For mixed solvent systems, the volume ratios are given. Parts and percentages are by weight unless otherwise specified.

The standard workup after all extractions consisted of drying the combined organic layers over magnesium sulfate, filtration, and removal of solvent *in vacuo*. Diethyl ether was used for extractions as well as triturations and is referred to as "ether" below. Drying of solids *in vacuo* was accomplished using an Abderhalen apparatus with refluxing hexanes as the circulating solvent.

Common abbreviations include: NaHMDS (sodium bis(trimethylsilyl)amide), THF (tetrahydrofuran), EtOAc (ethyl acetate), DMF (*N,N*-dimethylformamide), PPA (polyphosphoric acid), EtOAc (ethyl acetate), TFA (trifluoroacetic acid), MeOH (methanol), and EtOH (ethanol).

4-(3-Phenyl-1-carbethoxypropyl)pyridine (6a). A solution of ethyl 4-pyridinylacetate[28] (16.5 g, 100 mmol) in anhydrous

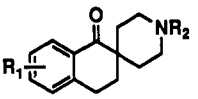
Table 3. Biological Data for Tetralins 1[a]



example	R_1	R_2	salt	K_i (nM) σ	K_i (nM) D_2	K_i (nM) $5HT_2$	antimescaline ED_{50} (mg/kg, po)
1a	H	CH_2Ph	HCl	4	1000	294	4.5
1b	H	$(CH_2)_2Ph$	HBr	10	600	7.3	6.4
1c	H	4-$FC_6H_4CH_2$	HCl	11	61	326	10
1d	H	CH_2-c-C_3H_7	HBr	26	1079	260	>10
1e	H	$CH(CH_3)$-c-C_3H_7	HBr	26	776	365	>30
1f	H	4-t-$BuC_6H_4CH_2$		26	410	176	>10
1g	H	4-$MeC_6H_4CH_2$	H_2O	8	37	52	>10
1h	H	4-$CF_3C_6H_4CH_2$	HCl	19	577	233	>10
1i	6-F	CH_2Ph		9	62	101	>10
1j	6-F	$(CH_2)_2Ph$		4	344	7	1.9
1k	5-F	$(CH_2)_2Ph$	HCl	5	202	9	6.8
1l	6-Cl	$(CH_2)_2Ph$	HCl	9	125	7	5.4
1m	6-OMe	$(CH_2)_2Ph$		13	219	7	6.5
1n	6-OMe	CH_2Ph		7	540	282	NT[b]
15	(DuP734)			10	1630	15	0.35
17	(rimcazole)			820	>10000	2482	22
18	(BMY14802)			174	2431	410	6

[a] The radioligands and the tissues used for the binding studies were σ, [^{3}H]SKF10047 (guinea pig whole brain); dopamine D_2, [^{3}H]spiperone (guinea pig striatum); serotonin $5HT_2$, [^{3}H]ketanserin (guinea pig frontal cortex). All values are single measurements, except for the standards rimcazole, BMY14802, and DuP 734, which are averages of three measurements. All ED_{50}'s are expressed as free base weights. [b] NT = not tested.

Table 4. Biological Data for Tetralins 2[a]



example	R_1	R_2	salt	K_i (nM) σ	K_i (nM) D_2	K_i (nM) $5HT_2$	antimescaline ED_{50} (mg/kg, po)
2a	H	$PhCH_2$	HCl	1	3506	264	>10
2b	H	4-$FC_6H_4CH_2$	HCl	4	1137	4448	>10
2c	H	4-t-$BuC_6H_4CH_2$	HCl	15	389	5358	>10
2d	H	4-$MeOC_6H_4CH_2$	HCl	3	1417	91	>10
2e	H	4-$CF_3C_6H_4CH_2$	mal	24	2192	6336	>10
2f	H	4-$NO_2C_6H_4CH_2$	HCl	1.9	1969	502	>10
2g	H	c-$C_6H_{11}CH_2$	HCl	2	1168	>10000	>10
2h	H	2-$C_{10}H_7CH_2$	mal	11	>10000	1969	>10
2i	H	$Ph(CH_2)_2$	HCl	56	2189	16	10
2j	H	4-$FC_6H_4CO(CH_2)_3$	HCl	46	25	10	0.65
2k	H	CH_3	HCl	1042	>10000	6275	>10
21	6,8-F_2	$Ph(CH_2)_2$	fum	2	515	276	>10
2m	6-Cl	$Ph(CH_2)_2$		35	>10000	119	10
15	(DuP734)			10	1630	15	0.35
17	(rimcazole)			820	>10000	2482	22
18	(BMY14802)			174	2431	410	6

[a] The radioligands and the tissues used for the binding studies were σ, [^{3}H]SKF10047 (guinea pig whole brain); dopamine D_2, [^{3}H]spiperone (guinea pig striatum); serotonin $5HT_2$, [^{3}H]ketanserin (guinea pig frontal cortex). All values are single measurements, except for the standards rimcazole, BMY14802, and DuP 734, which are averages of three measurements. All ED_{50}'s are expressed as free base weights.

Table 5. Compound 14 and Standards: Comparative Data[a]

	14	2i	15	17	18	5a	5b	5c
				Binding Affinity Data				
σ K_i (nM)	4.4	56	10	820	174	2.4	174	13
dopamine D_2 K_i (nM)	>10000	2189	1630	>10000	2431	640	>10000	>10000
serotonin $5HT_2$ K_i (nM)	4.2	16	15	2482	410	1934	1378	183
				In Vivo Data				
mouse antimescaline ED_{50} (mg/kg, po)	0.064	10	0.35	22	6	>30	>30	>30
mouse antiaggression ED_{50} (mg/kg, po)	10	30	1.9	48	45	>30	NT	NT
rat 5HTP head twitch ED_{50} (mg/kg, po)	0.07	10	1.8	NT	2.3	>30	NT	NT

[a] All values are averages of three measurements, except for compound 2i where the values are single measurements. NT = not tested. All ED_{50}'s are expressed as free base weights. See the notes for Tables 3 and 4 for information on the radioligands used for the binding studies.

THF (100 mL) was stirred at 0 °C under an inert atmosphere. A solution of NaHMDS in THF (1 M, 100 mL, 100 mmol) was added dropwise via an addition funnel over 30 min. The reaction mixture was stirred at 0 °C for 30 min; then 2-(bromoethyl)-benzene (22.2 g, 16.4 mL, 120 mmol) was added dropwise over 15 min. The reaction mixture was warmed gradually to ambient temperature over 18 h and poured onto water. Three extractions with ethyl acetate, followed by the standard workup, afforded a red liquid. Vacuum distillation provided the product, a pale yellow oil (13.2g, 49% yield): bp 172 °C (2 Torr); NMR ($CDCl_3$,

300 MHz) 8.55 (d, 2H, J = 5), 7.3–7.1 (m, 7H), 4.2–4.0 (m, 2H), 3.55 (t, 1H, J = 6) 2.6 (t, 2H, J = 6), 2.45 (sextet, 1H, J = 6), 2.1 (sextet, 1H, J = 6), 1.25 (t, 3H, J = 6); CI-HRMS calcd 270.1416, found 270.1420.

2-(4-Pyridinyl)tetralone (8a). A mixture of ester **6a** (2.7 g, 10 mmol), a 20% NaOH solution (5 mL), and THF (5 mL) were stirred at room temperature for 24 h. A concentrated HCl solution was added dropwise until pH = 5 (test paper), and the resulting precipitate was collected by filtration. The white solid was washed with ice water, air-dried, and triturated with ether. Drying *in vacuo* afforded 4-(3-phenyl-1-carboxypropyl)pyridine as a crude white powder (2.15 g): NMR (DMSO-d_6): 8.45 (d, 1H, J = 7), 8.35 (d, 1H, J = 7), 7.3–7.1 (m, 7H), 3.15 (t, 1H, J = 7), 2.65-2.55 (m, 2H), 1.95–1.7 (m, 2H); CI-MS: 197 (M + H − CO_2).

PPA (40 g) was warmed with mechanical stirring to 80–85 °C. The crude acid was added portionwise over 30 min. The reaction mixture was then heated to 120–125 °C and stirred for 5 h. The mixture was poured onto water (200 mL) with vigorous stirring and basified with a concentrated NaOH solution. After being cooled to ambient temperature, the aqueous mixture was extracted three times with EtOAc (100 mL); standard workup gave an orange yellow oil. Column chromatography (EtOAc) afforded tetralone **8a**, a yellow liquid (1.5 g, 67% overall yield, R_f 0.44): NMR ($CDCl_3$) 8.6 (d, 2H, J = 7), 8.1 (d, 1H, J = 8), 7.55 (t, 1H, J = 7), 7.4–7.2 (m, 2H), 7.15 (d, 2H, J = 7), 3.8 (dd, 1H, J = 8), 3.25–3.0 (m, 2H), 2.5–2.4 (m, 2H); CI-HRMS calcd 224.0997 (M + H), found 224.0999.

2-(1-((4-Fluorophenyl)methyl)piperidin-4-yl)tetralone Hydrochloride (1c). A solution of tetralone **8a** (1.0 g, 4.5 mmol) and 4-fluorobenzyl bromide (1.89 g, 10 mmol) in acetonitrile was stirred at reflux temperature for 2 h. After being cooled to ambient temperature, the reaction mixture was poured onto ether, mixed, and filtered. The crude solid was thoroughly triturated with ether, filtered, and air-dried. The solid was dissolved in degassed EtOH (40 mL), and PtO_2 (0.2 g) was added. The mixture was shaken in a Parr apparatus under a hydrogen atmosphere (≤20 psi) until hydrogen uptake ceased. The mixture was filtered through Celite, and solvent was removed *in vacuo* from the filtrate. The residue was treated with a 1 N NaOH solution and extracted three times with EtOAc. The standard workup gave an oil. Column chromatography ($CHCl_3$/MeOH, 9:1) gave the product as its free base (R_f 0.55). The free base was dissolved in ether (10 mL), and a solution of HCl in ether (10 mL) was added slowly with stirring. The resulting precipitate was collected, triturated with copious amounts of ether, and collected again. Drying *in vacuo* afforded a white powder (532 mg, 31% yield): mp >250 °C; NMR (DMSO-d_6): 10.2–10.0 (m, 1H), 7.85 (d, 1H, J = 7), 7.7–7.5 (m, 3H), 7.4–7.2 (m, 4H), 4.25 (d, 2H, J = 1), 3.5–3.3 (m, 2H), 3.1–2.9 (m, 4H), 2.7–2.5 (m, 2H), 2.4–2.2 (m, 1H), 2.15–2.05 (m, 1H), 1.95–1.6 (m, 4H). Anal. ($C_{22}H_{24}FNO$·HCl): C, H, N, F, Cl.

4-(3-(4-Methoxyphenyl)-1-carbethoxypropyl)-1-(phenylmethyl)piperidine (7e). A solution of 4-(3-(4-methoxyphenyl)-1-carbethoxypropyl)pyridine (**6e**) (2.0 g, 6.7 mmol, prepared according to the procedure described for **6a** above) and benzyl bromide (2.57 g, 15 mmol) in acetonitrile (20 mL) was stirred at reflux temperature for 2 h. After being cooled to room temperature, the reaction mixture was poured into ether, and the resulting solid was collected, triturated with fresh ether, and collected again. The crude pyridinium salt was dissolved in degassed EtOH (50 mL); PtO_2 (0.4 g) was added, and the mixture was shaken in a Parr apparatus under a hydrogen atmosphere (≤20 psi) until hydrogen uptake ceased. The mixture was then filtered through Celite and concentrated *in vacuo*. The residue was treated with a 1 N NaOH solution and extracted three times with EtOAc. The standard workup afforded an oil. Column chromatography (EtOAc/hexanes, 1:1) provided the product as a pale yellow oil (1.2 g, 45% yield, R_f 0.4): NMR ($CDCl_3$) 7.3–7.15 (m, 6H), 6.8–6.6 (m, 3H), 4.15 (q, 2H, J = 7), 3.8 (s, 3H), 3.45 (s, 2H), 2.9–2.8 (m, 2H), 2.7–2.4 (m, 2H), 2.3–2.2 (m, 1H), 2.0–1.8 (m, 3H), 1.75–1.65 (m, 1H), 1.6–1.45 (m, 1H), 1.3 (t, 3H, J = 7); CI-HRMS calcd 396.2461 (M + H), found 396.2463.

2-(1-(Phenylmethyl)piperidin-4-yl)-6-methoxy tetralone (1n). A mixture of ester **7e** (550 mg, 1.4 mmol), a 1 N NaOH solution (6 mL) and THF (6 mL) was stirred at reflux temperature for 4 h. The reaction mixture was then concentrated 2-fold *in vacuo* and extracted three times with EtOAc. The standard workup afforded a tan solid, which was added to PPA (10 g) at 80 °C with mechanical stirring. After the addition was complete, the reaction mixture was heated to 120–125 °C and stirred for 3 h. The reaction mixture was poured onto water with vigorous stirring, basified with a concentrated NaOH solution, and extracted three times with EtOAc. The standard workup afforded an oil. Column chromatography ($CHCl_3$/ MeOH, 9:1) gave the product, a pale yellow oil (160 mg, 33% yield, R_f 0.3): NMR ($CDCl_3$) 8.0 (d, 1H, J = 7), 7.35–7.2 (m, 5H), 6.8 (d, 1H, J = 7), 6.65 (s, 1H), 3.85 (s, 3H), 3.5 (s, 2H), 3.05–2.85 (m, 4H), 2.35–2.3 (m, 1H), 2.25–1.9 (m, 5H), 1.7–1.2 (m, 5H); CI-HRMS calcd 349.4678, found 349.4670.

Piperidine-1,4-dicarboxylic Acid, 4-Ethyl 1-*tert*-Butyl Diester (9). A suspension of ethyl piperidine-4-carboxylate (60 g, 381 mmol) and NaOH (18.3 g, 458 mmol) in THF (400 mL) was stirred mechanically at ambient temperature in a flask equipped with a reflux condenser. A solution of di-*tert*-butyl dicarbonate (100 g, 105 mL, 458 mmol) in THF (170 mL) was added dropwise over 1 h, during which time there was a gentle reflux. After the addition was complete, the reaction mixture was stirred for 22 h, poured onto water (2 L), and extracted three times with EtOAc (500 mL). The combined organic extracts underwent the standard workup to give a clear yellow oil. Vacuum distillation afforded the product as a clear colorless oil (88.5 g, 90% yield): bp 103–105 °C (0.75 Torr); NMR ($CDCl_3$) 4.15 (q, 2H, J = 7), 4.1–3.95 (m, 2H), 2.85 (br t, 2H, J = 8), 2.5–2.4 (m, 1H), 1.95–1.8 (m, 2H), 1.7–1.55 (m, 2H), 1.5 (s, 9H), 1.3 (t, 3H, J = 7); CI-MS 258 (M + H).

These physical data correspond with those reported in the literature for this compound.[29]

4-(2-Phenylethyl)piperidine-1,4-dicarboxylic Acid, 4-Ethyl 1-*tert*-Butyl Diester (10a). A solution of diisopropylamine (13 g, 18 mL, 128 mmol) in anhydrous THF (500 mL) was cooled to 0 °C with mechanical stirring under an inert atmosphere. A solution of *n*-butyllithium in hexanes (2.5 M, 51 mL, 128 mmol) was added dropwise via syringe. The reaction was stirred at 0 °C for 15 min; then it was cooled to −70 °C (internal temperature). A solution of compound **9** (30 g, 117 mmol) in anhydrous THF (250 mL) was added dropwise via an addition funnel over 30 min. The reaction mixture was then stirred at −70 °C for 1 h. A solution of (2-bromoethyl)benzene (22.8 g, 17.1 mL, 122 mmol) in anhydrous THF (250 mL) was added dropwise via an addition funnel over 30 min. The reaction mixture was then warmed to ambient temperature over 22 h, after which time it was poured onto water (1 L) and extracted three times with EtOAc (500 mL). The standard workup gave a liquid. The residual (2-bromoethyl)-benzene was removed *in vacuo* at 50 °C (0.6 Torr); the remainder of the crude product was chromatographed (EtOAc/hexanes, 1:3) to afford the product, a liquid (40.6 g, 96% yield): NMR ($CDCl_3$) 7.35–7.1 (m, 5H), 4.2 (q, 2H, J = 7), 4.05–3.8 (m, 2H), 3.05–2.75 (m, 2H), 2.55–2.45 (m, 2H), 2.2 (br d, 2H, J = 14), 1.9–1.75 (m, 2H), 1.7–1.5 (m, 1H), 1.5–1.2 (m, 10H), 1.3 (t, 3H, J = 7); CI-MS 362 (M + H).

The compound is thermally unstable; therefore, the compound could not be distilled *in vacuo* without considerable decomposition, and a satisfactory combustion analysis could not be obtained.

Ethyl 1-(2-Naphthylmethyl)-4-(2-phenylethyl)piperidine-4-carboxylate (12h). A solution of **10a** (1.7 g, 4.7 mmol) in TFA (15 mL) was stirred at reflux temperature under an inert atmosphere for 17 h. The solvent was removed by distillation; the residue was taken up in a 1 N NaOH solution and extracted three times with EtOAc. The combined organic layers were washed with a 1 N NaOH solution and worked up in the standard manner to give ethyl 4-(2-phenylethyl)piperidine-4-carboxylate as a crude oil (1.3 g): NMR ($CDCl_3$) 7.3–7.1 (m, 5H), 4.2 (q, 2H, J = 7), 3.1–3.0 (m, m, 2H), 2.8–2.6 (m, 2H), 2.6–2.5 (m, 2H), 2.3–2.15 (m, 2H), 2.0 (s, 1H, concentration-dependent), 1.9–1.8 (m, 2H), 1.5–1.4 (m, 2H), 1.3 (t, 3H, J = 7); CI-MS 262 (M + H).

A mixture of the crude oil, 2-(bromomethyl)naphthalene (1.68 g, 7.6 mmol), triethylamine (5.5 mL, 38 mmol), and anhydrous THF (31 mL) was stirred at reflux temperature under an inert atmosphere for 22 h. The reaction mixture was cooled to ambient temperature, poured onto a 1 N NaOH solution, and extracted three times with ethyl acetate. The standard workup gave a

yellow oil. Column chromatography (EtOAc/hexanes, 1:5) afforded the product, a yellow oil (1.36 g, 72% overall yield): NMR ($CDCl_3$) 7.9–7.8 (m, 3H), 7.75 (s, 1H), 7.5–7.4 (m, 3H), 7.3–7.2 (m, 2H), 7.2–7.1 (m, 3H), 4.2 (q, 2H, J = 7), 3.6 (s, 2H), 2.8–2.7 (m, 2H), 2.6–2.4 (m, 2H), 2.3–2.1 (m, 4H), 1.9–1.8 (m, 2H), 1.7–1.6 (m, 3H), 1.3 (t, 3H, J = 7); CI-HRMS calcd: 402.2433 (M + H), found 402.2434.

3,4-Dihydro-1-oxonaphthalene-2(1*H*)-spiro-4′-[1′-(naphthylmethyl)piperidine], Maleate Salt (2h). A mixture of **12h** (1.3 g, 3.2 mmol), a 20% NaOH solution (17 mL), and EtOH (17 mL) was stirred at reflux temperature for 17 h. The reaction mixture was concentrated 2-fold *in vacuo*. A 1 N HCl solution was added dropwise until pH = 3 (test paper); the resulting solid was collected and washed with ice water. Drying *in vacuo* provided crude 1-(naphthylmethyl)-4-(2-phenylethyl)piperidine-4-carboxylic acid (**13h**) as a white powder (1.22 g): NMR (DMSO-d_6): 7.9–7.8 (m, 3H), 7.75 (m, 1H), 7.5–7.4 (m, 3H), 7.3–7.2 (m, 2H), 7.2–7.1 (m, 3H), 3.55 (m, 2H), 2.6–2.4 (m, 7H), 2.2–2.0 (m, 4H), 1.6–1.5 (m, 2H), 1.3–1.2 (m, 2H); CI-MS 374 (M + H).

Phosphorus pentoxide (1.4 g, 9.9 mmol) was dissolved in methanesulfonic acid (20 mL) with stirring at 80–85 °C. The crude acid **13h** was added portionwise over 15 min. The reaction mixture was heated to 110–120 °C for 1.5 h, cooled to ambient temperature, and then poured slowly onto ice water. The aqueous mixture was basified with a concentrated NaOH solution and extracted with EtOAc three times. The standard workup afforded an orange oil. Column chromatography (EtOAc/hexanes, 1:2) provided the product, a yellow-orange oil (0.56 g, 48% yield, R_f 0.3): NMR ($CDCl_3$) 8.0 (d, 1H, J = 7), 7.85–7.75 (m, 4H), 7.5–7.4 (m, 5H), 7.3–7.2 (m, 2H), 3.75 (s, 2H), 2.95 (t, 2H, J = 7), 2.7–2.6 (m, 2H), 2.6–2.5 (m, 2H), 2.05 (t, 4H, J = 7), 1.7–1.5 (m, 3H); CI-HRMS calcd 356.2014 (M + H), found 356.2012.

The oil was dissolved in MeOH, and maleic acid (0.18 g, 1.6 mmol) was added. The mixture was stirred with gentle warming until a precipitate formed. Solvent was removed *in vacuo*, and the residue was triturated with excess ether. Collection and drying *in vacuo* afforded the title compound as a white powder (0.6 g): mp 204 °C; NMR (DMSO-d_6) 8.1–7.95 (m, 3H), 7.9 (d, 1H, J = 7), 7.7–7.5 (m, 5H), 7.4–7.35 (m, 2H), 6.1 (s, 2H), 4.5 (br s, 2H), 3.6–3.2 (m, 18H), 3.15–3.05 (m, 2H), 2.55 (br s, 2H), 2.3–2.0 (m, 4H), 1.9–1.7 (m, 2H). Anal. ($C_{25}H_{25}NO{\cdot}C_4H_4O_4$) C, H, N.

3,4-Dihydro-1-hydroxynaphthalene-2(1*H*)-spiro-4′-[1′-(2-phenylethyl)piperidine], Hydrochloride Salt (14). A mixture of the free base of **2i** (9.84 g, 30.9 mmol, prepared by treatment of **2i** with a 1 N NaOH solution, extraction with EtOAc, and the standard workup), sodium borohydride (7.0 g, 185 mmol,) and EtOH (220 mL) was stirred at reflux temperature for 14 h. The reaction mixture was cooled to ambient temperature; solvent was removed *in vacuo*. The residue was treated with a 1 N NaOH solution (100 mL) and extracted three times with ether. The standard workup afforded a yellow oil, which solidified on standing. Recrystallization from ether–hexanes provided the free base of the title compound as a white powder (8.2 g, 83% yield): mp 98–100 °C; NMR ($CDCl_3$) 7.4–7.1 (m, 9H), 4.35 (s, 1H), 2.9–2.7 (m, 5H), 2.7–2.6 (m, 3H), 2.5–2.35 (m, 2H), 2.0–1.8 (m, 2H), 1.8–1.4 (m, 6H); CI-HRMS calcd 322.2171 (M + H), found: 322.2170.

The free base was dissolved in ether (100 mL) and treated with a 1 N solution of HCl in ether (30 mL). The precipitate was collected and triturated with copious amounts of ether. Recrystallization from 2-propanol and drying *in vacuo* afforded the title product as a white solid (9.0 g): mp 202 °C; NMR (DMSO-d_6) 10.5–10.2 (m, 1H), 7.4–7.05 (m, 9H), 5.45 (d, 0.8H, J = 6), 5.25 (d, 0.2 H, J = 6), 4.65 (d, 0.2H, J = 6), 4.1 (d, 0.8H, J = 6), 3.5–3.0 (m, 8H), 2.75–2.65 (m, 2H), 2.2–1.2 (m, 6H). Anal. ($C_{22}H_{27}NO$·HCl). C, H, N, Cl.

Pharmacology. The *in vitro* assays and animal models are described in full detail in the literature.[7,8]

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