Novel Piperidine σ Receptor Ligands as Potential Antipsychotic Drugs

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σ receptor ligands represent a new class of potential antipsychotic drugs. This paper presents the structure–activity relationships leading to novel disubstituted piperidine σ ligands, which have little or no affinity for dopamine D_2 receptors. Selectivity for σ sites over dopamine D_2 or serotonin 5-HT_2 receptors appears to be governed by the chemical nature of the piperidine nitrogen substituent, its distance from the basic nitrogen, and its orientation relative to the other piperidine substituent. Several of these compounds have good oral potency in some animal models used to evaluate potential antipsychotic drugs. The *N*-cyclopropylmethyl ketones and ethers (e.g. **6i** (DuP 734), **6q**, **18a**, and **18n**) have the best in vivo potency. Compounds **6i** (DuP 734) and **6q** did not cause catalepsy in the rat, even at very high doses. On the basis of the pharmacology profiles of these σ ligands, we propose these compounds may be effective antipsychotic drugs, which do not induce extrapyramidal side effects or tardive dyskinesia.

Schizophrenia is a complex, severe mental illness characterized by bizarre thought patterns, hostility, and social impairment.[1-5] The symptoms of the disease may be divided into two broad categories: the positive or florid symptoms, which add to the normal psyche (e.g. aggression, hallucinations) and the negative ones, which detract from the normal psyche (e.g. flat affect, poverty of speech). Schizophrenic patients often require intensive hospital or home maintenance care. The emotionally and physically debilitating symptoms, as well as the economic burdens, imposed by this disease have created an urgent demand for effective therapy.

Unfortunately, the antipsychotic drugs, which are currently used in therapy, suffer from limitations in efficacy or side effect profiles.[6-9] Therapy utilizing dopamine D_2 antagonists, which constitute the largest group of antipsychotic drugs, ameliorates mainly the positive symptoms of schizophrenia and often causes several adverse motor side effects, e.g. tardive dyskinesia, akathisia, dystonia, and Parkinsonian syndrome, as well as some endocrine side effects caused by increased prolactin levels. There are some atypical agents with partially defined mechanisms of action. Clozapine[10,11] is the most noteworthy of these drugs due to its efficacy against both the positive and negative symptoms of schizophrenia and its low extrapyramidal symptom liability. The use of clozapine is limited, however, by some serious side effects, such as agranulocytosis and seizures. Since the currently available agents have serious limitations on their use, there is a major medical need for a new antipsychotic drug which has a novel mechanism of action, good oral efficacy and a superior side effect profile.[12]

The discovery of the psychotomimetic effects of *N*-allylnormetazocine (SKF 10047) and related benzomorphans opened a new avenue for antipsychotic drug research.[13-15] SKF 10047 caused some psychotic symptoms (delusions, dysphoria) in a limited Phase I clinical trial as a potential analgesic.[16-18] SKF 10047 was discovered to cause psychotomimetic effects in dogs using the chronic spinal model.[19-21] The (+)-isomer was shown to be more potent that its (−)-counterpart in inducing psychotomimetic effects in squirrel monkeys.[22,23] (+)-SKF 10047 does not bind to dopamine D_2 or opioid receptors, but rather

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it binds to a novel site, denoted the σ receptor.[24,25] Furthermore, this binding site has been distinguished from the phencyclidine (PCP) receptor.[26-28] A σ ligand, BMY14802, was reported to alter the firing rates of dopamine neurons in a manner similar to dopamine D_2 antagonists, suggesting that σ sites may indirectly modulate dopamine D_2 receptors.[29-33] Many classical antipsychotic drugs have high binding affinity for the σ receptor, in addition to many other receptor affinities, suggesting that σ sites may mediate some of their antipsychotic activity.[34] The connection between σ receptors and schizophrenia was further strengthened by the fact that [^{3}H]haloperidol binding in guinea pig brain was strongly inhibited by σ receptor ligands and that the majority of these [^{3}H]haloperidol binding sites represented σ binding sites.[35] σ receptors have been identified in the human brain and the selective loss of σ receptors in the cerebral cortex regions of schizophrenics has been demonstrated.[36-38] Furthermore, the density of σ sites in regions of the human brain involved in mental function, mood, and emotionality (e.g. cortex, nucleus accumbens) is higher than the density in regions involved in motor function (e.g. striatum).[36] Rimcazole,[39-46] a weak but selective σ ligand, partially reduced schizophrenic symptomatology in a majority of patients in open-label trials at 400 mg/day. However, further studies were discontinued since rimcazole could not match the efficacy of the classical neuroleptics and it caused seizures at slightly higher doses. The above data suggest that σ-selective ligands may be effective antipsychotic drugs, which do not induce the extrapyramidal symptoms and tardive dyskinesia caused by therapy with classical neuroleptic drugs.

The pharmacophore for optimal binding to the σ receptor has been the focus of intense study in recent years. Several classes of compounds have been reported to bind with high affinity to the σ receptor;[47-50] these classes include benzomorphans, N,N′-disubstituted guanidines, phenylpiperidine derivatives, and cyclohexyldiamine analogs. Many laboratories have sought a unified pharmacophoric model to explain the affinity of these divergent structures to the same receptor. The most notable studies, made by Manallack,[51,52] Largent,[53] and their co-workers, propose the σ receptor is comprised of two lipophilic regions, a locus capable of hydrogen bonding to a basic nitrogen lone

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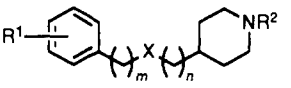
Table I. Substituted Phenyl Piperidines: Physical Data



no.	X	*m*	*n*	R^1	R^2	salt	method[a]	mp (°C)	analysis[b]
1	CO	0	1	4-F	CH_2Ph	mal[n]	A, B	106–108	$C_{20}H_{22}FNO·C_4H_4O_4·0.25H_2O$
6a	CO	0	1	4-F_3C	CH_2Ph		D, F, E	64–65	$C_{21}H_{22}F_3NO·0.25H_2O$
6b	CO	0	1	4-MeO	CH_2Ph		D, F, E	59–60	$C_{21}H_{25}NO_2$
6c	CO	0	1	4-MeS	CH_2Ph		D, F, E	98–99	$C_{21}H_{25}NOS$
6d	CO	0	1	4-HO	CH_2Ph		X	197–198	$C_{20}H_{23}NO_2·0.25H_2O$
6e	CO	0	1	4-Ph	CH_2Ph		A, B	121–122	$C_{26}H_{27}NO$
6f	CO	0	1	4-$HOCH_2$	CH_2Ph		X	154–155	$C_{21}H_{25}NO_2·0.5H_2O$
6g	CO	0	1	4-MeO_2S	CH_2Ph		X	135–137	$C_{21}H_{25}NO_3S$
6h	CO	0	1	4-Me(O)S	CH_2Ph		X	135–136	$C_{21}H_{25}NO_2S·0.25H_2O$
6i	CO	0	1	4-F	CH_2-c-C_3H_5	HBr	A, B	141–143	$C_{17}H_{22}FNO·HBr$
6j	CO	0	1	4-Cl	CH_2-c-C_3H_5	HBr	A, B	154–155	$C_{17}H_{22}ClNO·HBr$
6k	CO	0	1	4-OMe	CH_2-c-C_3H_5	HBr	A, B	167–168	$C_{18}H_{25}NO_2·HBr$
6l	CO	0	1	4-*t*-Bu	CH_2-c-C_3H_5	HBr	A, B	142–144	$C_{21}H_{31}NO·HBr·0.5H_2O$
6m	CO	0	1	Ph	CH_2-c-C_3H_5	HBr	A, B	233–234	$C_{23}H_{25}NO·HBr$
6n	CO	0	1	4-CF_3	CH_2-c-C_3H_5	HCl	A, B	140–142	$C_{18}H_{22}F_3NO·HCl·0.5H_2O$
6o	CO	0	1	4-NMe_2	CH_2-c-C_3H_5	2HBr	A, B	113–115	$C_{19}H_{28}N_2O·2HBr·0.5H_2O$
6p	CO	0	1	4-NH_2	CH-c-C_3H_4		X	140–146 dec	$C_{17}H_{22}N_2O·0.75H_2O$
6q	CO	0	1	4-CN	CH_2-c-C_3H_5	fum[n]	X	149	$C_{18}H_{22}N_2O·C_4H_4O_4$
6r	CO	0	1	4-F	$CH_2C_6H_4CF_3$-*p*		A, B	57–58	$C_{21}H_{21}F_4NO$
6s	CO	0	1	4-F	$CH_2C_6H_4F$-*p*		A, B	67–68	$C_{20}H_{21}F_2NO$
6t	CO	0	1	4-F	$(CH_2)_2$-3-indolyl		X	135–140	$C_{23}H_{25}FN_2O·H_2O$[c]
6u	CO	0	1	4-F	$(CH_2)_2C_6H_4F$-*p*		A, B	96–98	$C_{21}H_{23}F_2NO$
6v	CO	0	1	4-F	$(CH_2)_2Ph$		A, B	73–74	$C_{21}H_{24}FNO$
6w	CO	0	1	4-F	$(CH_2)_2C_6H_4Cl$-*p*		A, B	88–90	$C_{21}H_{23}ClFNO$
6x	CO	0	1	4-F	$(CH_2)_2C_6H_4CF_3$-*p*		A, B	44–45	$C_{22}H_{23}F_4NO$
6y	CO	0	1	4-F	$(CH_2)_2$-c-C_3H_5	HBr	A, B	108–109	$C_{18}H_{24}FNO·HBr$
7a	CHOH	0	1	4-F	$(CH_2)_2$-c-C_3H_5		C	114–116	$C_{17}H_{24}FNO$
7b	CHOH	0	1	4-F	CH_2Ph	HCl	C or H, I	189–191	$C_{20}H_{24}FNO·HCl$
7c	CHOH	0	1	4-MeS	CH_2Ph		H, I	113–114	$C_{21}H_{27}NOS$
7d	CHOH	0	1	4-MeO	CH_2Ph	HCl	H, I	170–171	$C_{21}H_{27}FNO_2·HCl$
7e	CHOH	0	1	4-F_3C	CH_2Ph	HCl	H, I	249–250	$C_{21}H_{24}F_3NO·HCl$
7f	CHOH	0	1	4-F	$(CH_2)_2Ph$		C	190	$C_{21}H_{26}FN·0.4H_2O$
10a	CHOH	1	0	4-F	CH_2Ph	HCl	D, F, E	64–66	$C_{20}H_{24}FNO·HCl·0.25H_2O$
10b	CHOH	1	0	H	CH_2Ph	HCl	D, F, E		$C_{20}H_{25}NO·HCl·0.5HCl$
10c	CHOH	1	0	4-F	$(CH_2)_3Ph$		D, F, E	91–92	$C_{22}H_{28}FNO·0.1H_2O$
10d	CHOH	1	0	4-F	$(CH_2)_4Ph$		D, F, E	90–91	$C_{23}H_{30}FNO$
11a	CO	1	0	4-F	CH_2Ph	mal[n]	D, F, E	132–134	$C_{20}H_{22}FNO·C_4H_4O_4·0.75H_2O$
11b	CO	1	0	4-F	CH_2-4-pyridyl	2 mal[n]	X	108–109	$C_{19}H_{21}FNO·2C_4H_4O_4·0.75H_2O$
11c	CO	1	1	4-F	CH_2Ph	mal[n]	D, F, E	109–111	$C_{21}H_{24}FNO·C_4H_4O_4$
11d	CO	1	0	4-F	$(CH_2)_3COC_6H_4F$-*p*		X	99–100	*d*
18a	O	0	1	4-F	CH_2-c-C_3H_5		M-O	67–68	$C_{16}H_{22}FNO$
18b	O	0	1	4-Cl	CH_2-c-C_3H_5	HCl	M-O	145–146	$C_{16}H_{22}ClNO·HCl$
18c	O	0	1	4-MeO	CH_2-c-C_3H_4	HCl	M-O	125–127	$C_{17}H_{25}NO_2·HCl·0.25H_2O$
18d	O	0	1	4-Ph	CH_2-c-C_3H_5		M-P	81–83	$C_{22}H_{27}NO·0.1H_2O$
18e	O	0	1	4-$HOCH_2$	CH_2-c-C_3H_5		M-O[e]	120–121	$C_{17}H_{25}NO_2·0.3H_2O$
18f	O	0	1	4-*t*-Bu	CH_2-c-C_3H_5		M-O	84–86	$C_{20}H_{31}NO$
18g	O	0	1	4-MeCH(OH)	CH_2-c-C_3H_4		M-O[f]	125–127	$C_{18}H_{27}NO_2$
18h	O	0	1	3,4-F_2	CH_2-c-C_3H_5	HCl	M-O	151–152	$C_{16}H_{21}F_2NO·HCl$
18i	O	0	1	F_5	CH_2-c-C_3H_5	HCl	M-O	173–174	$C_{16}H_{18}F_5NO·HCl$
18j	O	0	1	3,4,5-$(MeO)_3$	CH_2-c-C_3H_5	HCl	M-O	113–114	$C_{19}H_{29}NO_4·HCl$
18k	O	0	1	4-MeS	CH_2-c-C_3H_5	HCl	M-O	157–158	$C_{17}H_{25}NO_2·HCl$
18l	O	0	1	4-$MeSO_2$	CH_2-c-C_3H_5		X	134–135	$C_{17}H_{25}NO_3S$
18m	O	0	1	4-NO_2	CH_2-c-C_3H_5		P	68–70	$C_{16}H_{22}N_2O_3·0.75H_2O$
18n	O	0	1	4-NC	CH_2-c-C_3H_5		M-O	109–111	$C_{17}H_{22}N_2O$
18o	O	0	1	4-H_3CCO	CH_2-c-C_3H_5		P	41–43	$C_{18}H_{25}NO_2$
18p	O	0	1	4-Me_2NSO_2	CH_2-c-C_3H_5		R-T	118–119	$C_{18}H_{22}N_2O_3S$
18q	O	0	1	4-PhO	CH_2-c-C_3H_5		M-O	62–63	$C_{22}H_{27}NO_2$
18r	O	0	1	4-(4′-FC_6H_4)	CH_2-c-C_3H_5		M-O	81–83	$C_{22}H_{26}FNO$
18s	O	0	1	4-(4′-$MeOC_6H_4$)	CH_2-c-C_3H_5		M-O	122–123	$C_{23}H_{29}NO_2·0.5H_2O$
18t	O	0	1	H	CH_2-c-C_3H_5		M-O	54–56	$C_{16}H_{23}NO$
18u	O	0	1	3-Me_2N	CH_2-c-C_3H_5		M-O	52–53	$C_{18}H_{28}N_2O·0.1H_2O$
18v	O	0	1	3,4-Cl_2	CH_2-c-C_3H_5	HCl	M-O	190–195 dec	$C_{16}H_{21}Cl_2NO·HCl$
18w	O	0	1	2,4-Cl_2	CH_2-c-C_3H_5	HCl	M-O	169–171	$C_{16}H_{21}Cl_2NO·HCl$
18x	O	0	1	4-EtNH	CH_2-c-C_3H_5	HCl	M-O[g]	130–133	$C_{18}H_{28}N_2O·2HCl·0.5H_2O$
18y	O	0	1	4-F	CH_2-(2′-Me-cp)[h]	mal[n]	M-O	156–157	$C_{17}H_{24}FNO·C_4H_4O_4$
18z	O	0	1	4-F	CH_2-(Me-Cl_2-cp)[i]	fum[n]	M-O	115–117	$C_{17}H_{22}Cl_2FNO·C_4H_4O_4$
18aa	O	0	1	4-F	CH_2Ph	HCl	Q	209–211	$C_{19}H_{22}FNO·HCl·0.1H_2O$
18ab	O	0	1	4-Cl	CH_2Ph	HCl	Q	210–212	$C_{19}H_{22}ClNO·HCl$
18ac	O	0	1	4-NO_2	CH_2Ph	HCl	Q	>250	$C_{19}H_{22}N_2O_3·HCl$
18ad	O	0	1	4-MeO	CH_2Ph		Q	65–66	$C_{20}H_{25}NO_2$
18ae	O	0	1	4-F_3C	CH_2Ph		R-T	225–228	$C_{20}H_{22}F_3NO·HCl$
18af	O	0	1	4-F	$CH_2C_6H_5F$-*p*		R-T	50–53	$C_{19}H_{21}F_2NO$
18ag	O	0	1	4-F	$CH_2C_6H_4OMe$-*p*	mal[n]	R-T	80–85	$C_{20}H_{24}FNO_2·C_4H_4O_4·0.5H_2O$

Table I. (Continued)

no.	X	m	n	R¹	R²	salt	method[a]	mp (°C)	analysis[b]
18ah	O	0	1	4-F	CH_2-2-naphthyl		R-T	85-87	$C_{23}H_{24}FNO$
18ai	O	0	1	4-F	CH_2-4-pyridyl		R-T	30-32	$C_{18}H_{21}FN_2O \cdot 0.25H_2O$
18aj	O	0	1	4-F	$(CH_2)_2C_6H_4Cl$-p	HCl	R-T	186	$C_{18}H_{22}ClFNO \cdot HCl$
18ak	O	0	1	4-F	$(CH_2)_2$-c-C_3H_5	fum[n]	M-O	124-126	$C_{17}H_{24}FNO \cdot C_4H_4O_4$
18al	O	1	1	4-F	CH_2Ph	mal[n]	P	115-116	$C_{20}H_{24}FNO \cdot C_4H_4O_4$
18am	O	1	1	4-MeO	CH_2Ph	mal[n]	P	93-95	$C_{21}H_{27}NO_2 \cdot C_4H_4O_4$
18an	O	1	1	4-Ph	CH_2Ph	mal[n]	P	113-119	$C_{26}H_{29}NO \cdot C_4H_4O_4 \cdot 0.5H_2O$
18ao	O	1	1	H	CH_2Ph	HCl	P	158-160	$C_{20}H_{25}NO \cdot HCl$
18ap	O	1	1	4-H_3CO_2C	CH_2Ph	HCl	P	169-170	$C_{22}H_{27}NO_3 \cdot HCl \cdot 0.3H_2O$
18aq	O	1	1	4-F	$(CH_2)_2Ph$	mal[n]	P	90-92	$C_{21}H_{26}FNO \cdot C_4H_4O_4$
18ar	O	1	1	4-F	$(CH_2)_3Ph$	HCl	P	146-149	$C_{22}H_{28}FNO \cdot HCl$
18as	O	1	1	4-F	$CH_2C_6H_4CO_2Me$-p	HCl	R-T	188-189	$C_{22}H_{26}FNO_3 \cdot HCl$
18at	O	1	1	4-F	$CH_2C_6H_4Cl$-p	HCl	R-T	181-183	$C_{20}H_{23}ClNO \cdot HCl$
18au	O	1	1	4-F	$Ch_2C_6H_4 \cdot Ph$-p	HCl	P	195-196	*k*
18av	O	1	1	4-F	$CH_2C_6H_4 \cdot OH$-p	HCl	P[j]	134-136	$C_{20}H_{24}FNO_2 \cdot HCl$
18aw	O	1	1	4-F	$CH_2C_6H_4 \cdot OCH_2Ph$-p	HCl	R-T	182-184	$C_{27}H_{30}FNO_2 \cdot HCl$
18ax	O	1	1	4-F	CH_2-4-pyridyl	fum[n]	P	96-102	$C_{18}H_{23}FN_2O \cdot C_4H_4O_4$
18ay	O	1	1	4-F	CH_2-cyclohexyl	HCl	R-T	>250	$C_{20}H_{30}FNO \cdot HCl$
18az	O	1	1	4-F	CH_2-2-naphthyl	HCl	P	172-173	$C_{24}H_{27}ClFNO \cdot HCl$
18ba	O	1	1	4-F	CH_2-1-naphthyl	HCl	P	175-176	$C_{24}H_{26}FNO \cdot HCl$
18bb	O	1	1	4-F	$(CH_2)_4CH_3$	HCl	R-T	158-160	$C_{18}H_{30}ClFNO \cdot HCl$
18bc	O	0	2	4-F	CH_2Ph	HCl	M-O	107-109	$C_{20}H_{23}FNO \cdot HCl \cdot 0.2H_2O$
18bd	O	3	0	H	CH_2Ph	mal[n]	P	96-96	$C_{21}H_{27}NO \cdot C_4H_4O_4$
18be	O	3	1	H	CH_2Ph	mal[n]	P	85-87	$C_{22}H_{29}NO \cdot C_4H_4O_4$
18bf	O	4	1	H	CH_2Ph	HCl	P	125-127	$C_{23}H_{31}NO \cdot HCl$
18bg	O	5	1	H	CH_2Ph	HCl	P	>250	$C_{24}H_{33}NO \cdot HCl$
18bh	O	1	2	4-*t*-Bu	CH_2Ph	HCl	P	129-133	$C_{25}H_{25}NO \cdot HCl$
18bt	S	0	1	4-F	$(CH_2)_2$-c-C_3H_5		M-O	34-35	*l*
22	S(O)	0	1	4-F	$(CH_2)_2$-c-C_3H_5		X	49-50	*m*
23	SO_2	0	1	4-F	$(CH_2)_2$-C_3H_5		X	73	$C_{18}H_{22}FNO_2S$

[a] Methods A-T are described in the text; for method X, see Experimental Section. [b] Combustion analyses were performed for all elements except oxygen; experimental values are within 0.4% of theoretical values unless otherwise stated below. [c] F: calcd, 4.96; found, 4.08. [d] HRMS: calcd for $C_{23}H_{22}F_2NO_2$ 385.1853, found 385.1851. [e] Synthesized via the corresponding *tert*-butyldimethylsilyl ether. [f] Synthesized starting with 4-fluoro-1-acetylbenzene. The ketone is reduced during method O. [g] Synthesized starting with 4-acetamidophenol. The acetyl group is reduced in method O. [h] CH_2-(2-methylcyclopropyl). [i] CH_2-(1-methyl-2,2-dichlorocyclopropyl). [j] Synthesized starting witn 4-(bromomethyl)(methoxycarboxy)benzene. The carbonate is hydrolyzed under the workup conditions of the last step of method P. [k] HRMS: calcd for $C_{26}H_{26}FNO$ 389.2155, found 389.2158. [l] HRMS: calcd for $C_{18}H_{22}FNS$ 279.1457, found 279.1460. [m] HRMS: calcd for $C_{18}H_{22}FNOS$ 295.1406, found 295.1406. [n] mal = maleate, fum = fumarate.

pair vector and, possibly, an "electrostatic" site, which can accommodate hydroxyl or halogen substituents on certain σ ligands. These studies have major limitations. Many of the ligands employed for the molecular modeling computations have multiple receptor affinities. Furthermore, these studies were unable to distinguish the criteria for agonist vs antagonist binding to the σ receptor. The paucity of σ-selective ligands and functional tests for distinguishing agonists from antagonists caused these deficiencies. These models may be revised to account for the new evidence for σ receptor subtypes.[54-56] Recent work has revealed there are two subtypes in the central nervous system, which are distinguished on the basis of the relative binding affinities for two ligands: [^{3}H]-(+)-SKF 10047 and [^{3}H]ditolylguanidine (DTG). (+)-SKF 10047 has high affinity for σ-1 sites and low affinity for σ-2 receptors, while DTG has high affinity for both subtypes. We have chosen to study σ-1 ligands as potential antipsychotic drugs since there is some connection between the behavioral pharmacology of (+)-SKF 10047 in animals and psychotomimetic symptomatology in man. The link between the behavioral pharmacology of the other main class of σ-selective ligands, diarylguanidines which also bind σ-2 sites, and psychotomimetic symptoms in man needs to be established.[57-59]

We report herein the structure-activity relationships (SAR) for novel piperidine ligands for σ receptors characterized with [^{3}H]-(+)-SKF 10047. Some of the compounds described below are very active in some animal models for evaluating antipsychotic drugs. Moreover, some antagonize the behavioral effects of (+)-SKF 10047 in rats at low doses. Empirical screening and exploratory SAR studies led to the discovery of lead compound 1, which had selective affinity for σ receptors over dopamine D_2 sites (σ K_i = 6 nM, dopamine D_2 IC_{50} > 1000 nM) and phencyclidine receptors (K_i > 10000 nM). This compound antagonized the behavioral effects of a hallucinogen, mescaline, in mice (ED_{50} = 4.8 mg/kg, po) and it blocked the aggressive response of mice to intruders after prolonged isolation (ED_{50} = 8.6 mg/kg, po). The structure of 1 may conceptually be divided into four regions: the nitrogen heterocycle (region C), the substituent on the piperidine nitrogen (region D), the distal aromatic group (region A),

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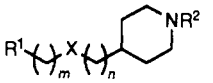
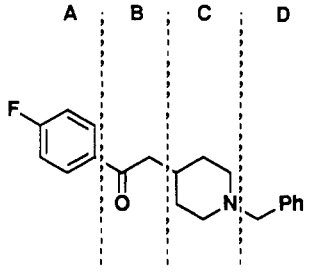
Table II. Miscellaneous Piperidines: Physical Data



no.	X	m	n	R¹	R²	salt	method[a]	mp (°C)	analysis[b]
7g	CHOH	0	1	2-naphthyl	CH_2Ph		H-I	33–35	$C_{24}H_{27}NO·0.25H_2O$
7h	CHOH	0	1	2-thienyl	CH_2Ph		H-I	118–120	$C_{18}H_{23}NO·0.25H_2O$
7i	CHOH	0	1	2-furyl	CH_2Ph		H-I	118–119	$C_{18}H_{23}NO_2·0.25H_2O$
18bi	O	0	1	2-naphthyl	CH_2-c-C_3H_5		M-O	69–71	$C_{20}H_{25}NO·0.2H_2O$
18bj	O	0	1	4-pyridyl	CH_2-c-C_3H_5		M-O	53–54	$C_{15}H_{22}N_2O·0.25H_2O$
18bk	O	0	1	4-quinolinyl	CH_2-c-C_3H_5		M-O	85–86	$C_{19}H_{24}N_2O·0.75H_2O$
18bl	O	0	1	2-pyrimidyl	CH_2-c-C_3H_5	HCl	P	151–152	$C_{14}H_{21}N_3O·1.5HCl$
18bm	O	0	1	2-pyridyl	CH_2-c-C_3H_5	HCl	P	176–178	$C_{15}H_{22}N_2O·1.5HCl$
18bn	O	0	1	5-indolyl	CH_2-c-C_3H_5		M-O	104–106	$C_{18}H_{24}N_2O$
18bo	O	0	1	2-naphthyl	CH_2Ph		Q	79–82	$C_{23}H_{25}NO·0.75H_2O$
18bp	O	0	1	cyclohexyl	CH_2Ph	HCl	R-T	>250	$C_{20}H_{31}NO·HCl$
18bq	O	0	1	2-quinolinyl	CH_2Ph	HCl	P	169–171	$C_{23}H_{26}N_2O·HCl$
18br	O	0	1	3-pyridyl	CH_2Ph	mal[c]	M-O	68–73	$C_{19}H_{24}N_2O·C_4H_4O_4·0.5H_2O$
18bs	O	0	1	cyclopropyl	CH_2Ph	mal[c]	M-O	93–96	$C_{21}H_{29}NO_5$

[a] Methods A–T are described in the text; for method X, see Experimental Section. [b] Combustion analyses were performed for all elements except oxygen; experimental values were within 0.4% of theoretical values. [c] Mal = maleate.

and the space between the heterocycle and the distal aromatic group (region B). We describe the effects of structural modification in these regions on σ binding affinity and selectivity as well as potency in some animal models for detecting antipsychotic drugs. The structure–activity relationships emerging from this study suggest some modifications in the models proposed for the σ receptor.



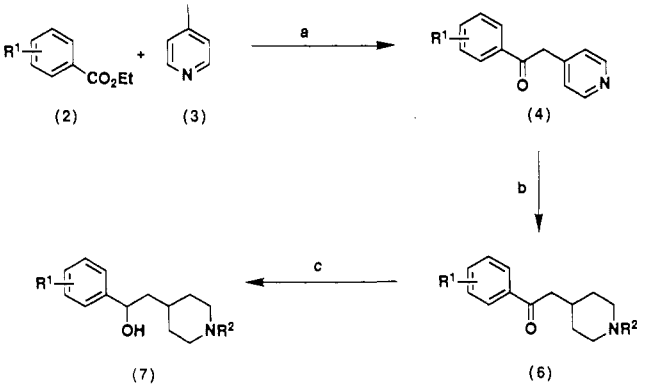
(1) (maleate salt)

Chemistry

Several synthetic routes were employed to prepare various analogs of 1 (cf. Tables I and II), by which selected parts of the parent structure could be systematically modified. These routes are depicted in generic Schemes I–VII.

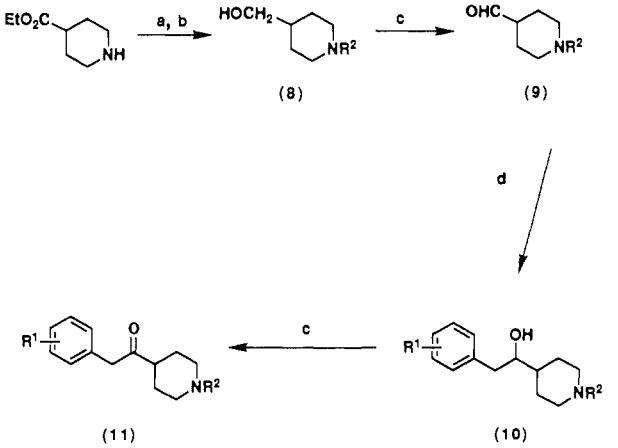
Various ketone and alcohol analogs of 1 were prepared via the corresponding pyridines (Scheme I). Aryl esters 2 were condensed with the anion of 4-picoline 3 in tetrahydrofuran (THF) to afford pyridyl ketones 4 (method A).[60] Ketones 4 were converted to the corresponding pyridinium salts by treatment with an alkyl or aralkyl halide, with or without solvent (e.g. acetonitrile or *N,N*-dimethylformamide (DMF)), at reflux temperature. Many of the pyridinium salts were hygroscopic and were immediately reduced to the cognate piperidines (method B). Hydrogenation[61] of these intermediates over a platinum catalyst (obtained by prereduction of PtO_2) in ethanol generated ketones 6. Ketones 6 were also reduced, as their free bases, with sodium borohydride ($NaBH_4$) in ethanol to give the corresponding alcohols 7 (method C, Scheme I).

Scheme I[a]



[a] (a) $NaN(TMS)_2$, THF, −78 to 0 °C (Method A); (b) R^2X, heat; H_2, PtO_2, EtOH (Method B); (c) $NaBH_4$, EtOH (Method C).

Scheme II[a]



[a] (a) K_2CO_3, R^2X, EtOH, heat (Method D); (b) LAH or B_2H_6, THF, heat (Method E); (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt (Method F); (d) $R^1C_6H_4CH_2MgX$ or $R^1C_6H_4CH_2TMS$, THF (Method G).

Various ketone and alcohol analogs of 1 were also prepared from N-substituted derivatives of ethyl piperidine-4-carboxylate (Scheme II). N-Alkylation of the parent ester (method D), followed by reduction with lithium aluminum hydride (LAH) or diborane in THF

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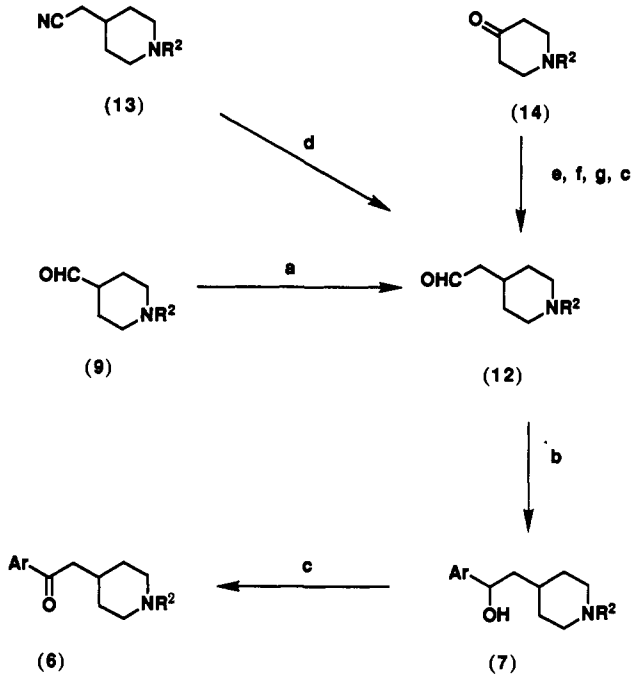
Scheme III[a]



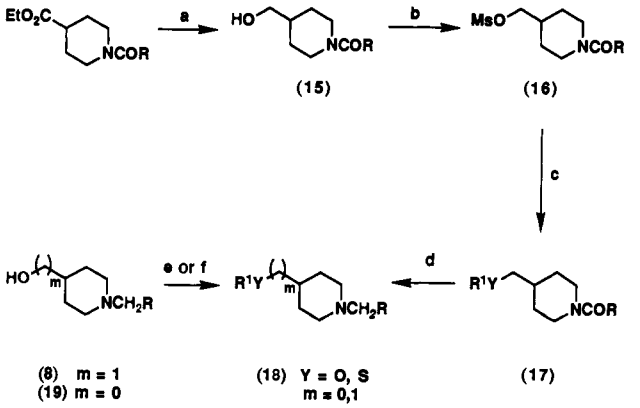
Ar = substituted phenyl, thienyl, furyl, naphthyl

[a] (a) $MeOCH_2PPh_3Cl$, LDA, THF, −40 °C; then HCl, H_2O (Method H); (b) ArMgX or ArLi, THF (Method I); (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (Method F); (d) DIBAL-H, toluene (Method J); (e) $(EtO)_2P(O)CH_2CO_2Et$, NaH, DME (Method K, references 63 and 64); (f) H_2, PtO_2, EtOH (Method L, reference 64); (g) LAH, THF, heat (Method E).

(method E), produced several 1-substituted-4-(hydroxymethyl)piperidines 8. Swern oxidation[62] afforded a series of 1-substituted-4-formylpiperidines 9 (method F). Treatment of these aldehydes with either substituted benzylmagnesium halides or benzyltrimethylsilanes[63] and tetrabutylammonium fluoride afforded alcohols 10 (method G). Swern oxidation gave the corresponding ketones 11 (method F).

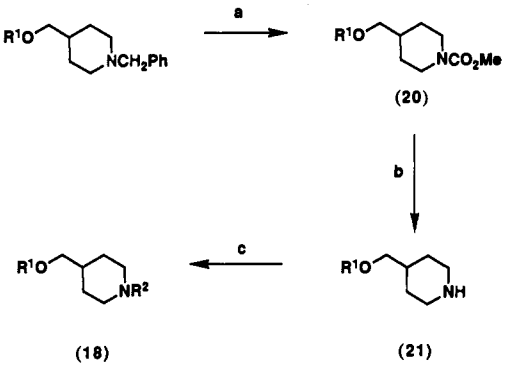
Scheme III depicts alternate routes to ketones 6 and alcohols 7. Aldehydes 9 were also homologated by (1) reaction with (methoxymethyl)triphenylphosphonium chloride and LDA in THF at −40 °C and (2) hydrolysis of the resultant enol ether with aqueous hydrochloric acid (method H, Scheme III).[64] The 4-(formylmethyl)piperidines 12 were then treated with Grignard or organolithium reagents to give alcohols 7 (method I, Scheme III). Swern oxidation then afforded ketones 6 (method F, Scheme III). Intermediates 12 were also accessible from nitriles 13 by reduction with diisobutylaluminum hydride (DIBAL-H) in refluxing toluene (method J, Scheme III).[65] Alternatively, these targets could be prepared from piperidones 14 by a four-step sequence (Scheme III): (1) Emmons–Wadsworth condensation with triethyl phosphonoacetate (method K),[66,67] (2) hydrogenation[67] over palladium on carbon (Pd/C) (method L), (3) reduction with LAH (method E), and (4) Swern oxidation (method F).

Scheme IV[a]



[a] (a) $LiBH_4$, $B(OMe)_3$, THF (Method M); (b) MsCl, Et_3N, CH_2Cl_2, 0 °C (Method N); (c) NaH, R^1YH, THF or DMF (Method O); (d) LAH or B_2H_6, THF, heat (Method E); (e) NaH, R^1X, THF or DMF, heat (Method P); (f) R^1OH, PPh_3, $EtO_2CN{=}NCO_2Et$, THF or C_6H_6, RT or heat (Method Q).

Scheme V[a]



[a] (a) $ClCO_2Me$ (Method R); (b) KOH, MeOH (Method S); (c) R^2X, K_2CO_3, EtOH (Method T).

Ether or thioether analogs of 1 were synthesized via *N*-acyl derivatives 15 of 4-(hydroxymethyl)piperidine (methods M, N, O and E, Scheme IV). Conversion to the mesylates,[68] followed by nucleophilic displacement with alkoxides, phenoxides, or thiophenoxides gave *N*-acyl intermediates 17. Reduction with LAH or diborane in THF at reflux temperatures generated the desired ethers or thioethers 18. An alternate route to ether analogs 18 consisted of reacting N-alkylated derivatives of 4-(hydroxymethyl)piperidine or 4-hydroxypiperidine, 8 or 19, with alkyl or aralkyl halides, R^1X, using the Williamson ether synthesis[69] (method P, Scheme IV). Nucleophilic displacement on electron-deficient aryl fluorides or heteroaryl halides with 1-substituted-4-(hydroxymethyl)-piperidines also produced ether analogs 18 in good yields (method P, Scheme IV).[70] Finally, intermediates 8 or 19

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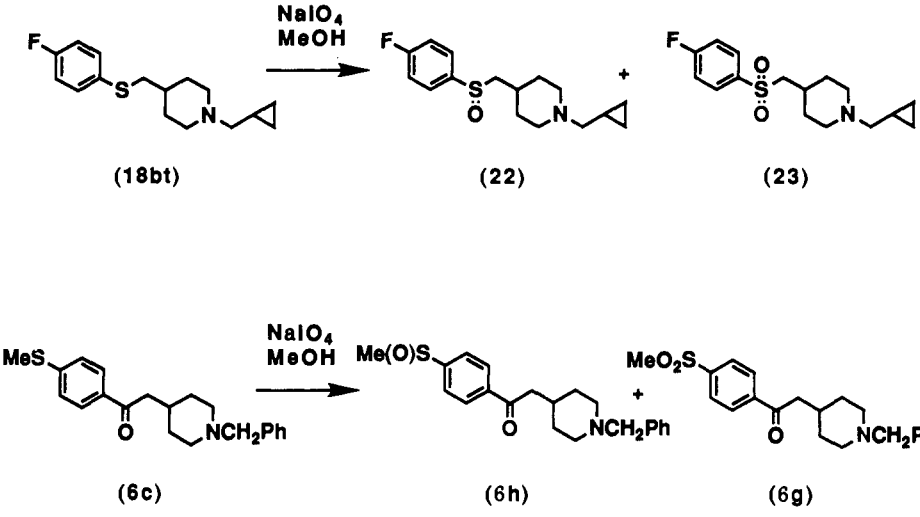
Scheme VI



could also be coupled with substituted phenols or alcohols using the Mitsunobu protocol[71] (method Q, Scheme IV).

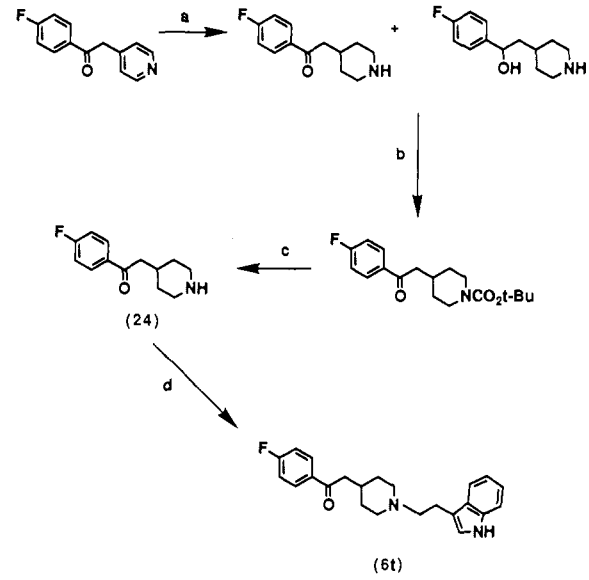
The use of carbamates[72] provided a versatile method for varying substitution on the piperidine nitrogen in the ether series (Scheme V, methods R, S, T). Reaction of several *N*-benzylpiperidines with methyl chloroformate gave carbamates **20**. Treatment with methanolic KOH generated intermediates **21**. Simple alkylation afforded a varity of N-substituted ethers **18**.

Some miscellaneous compounds required specific methods for their preparation. Sulfoxide **22** and sulfone **23** were prepared by oxidation of thioether **18bt** with sodium periodate in methanol, followed by chromatographic separation (Scheme VI). Similarly, ketones **6g** and **6h** were prepared from compound **6c**. Indolylethyl ketone **6t** was prepared by alkylation of fluoro ketone **24** with tryptophyl bromide[73] (Scheme VII). Hydroxyphenyl ketones **6d** and **6f** were prepared by cleavage of the corresponding *tert*-butyldimethylsilyl ethers[74] with tetra-*n*-butylammonium fluoride in THF. The use of the silyl protecting group was mandated by the reaction conditions described above for Scheme III. Butyrophenone **11d** was prepared from the free base of **11a** by a three-step sequence (Scheme VIII): (1) transfer hydrogenolysis, (2) alkylation with the ethylene ketal of 1-chloro-4-(4-fluorophenyl)-butan-4-one, and (3) acidic hydrolysis of the ketal.[75]

Results and Discussion

This study seeks to define the structural requirements for selective binding to σ receptors, characterized with [^{3}H]-(+)-SKF 10047 (i.e. σ-1 sites),[55] to discover potential antipsychotic drugs. Two issues confronted us at the outset of our investigations: the binding selectivity of (+)-SKF 10047 for σ sites vs phencyclidine (PCP) receptors and the choice of in vivo tests. (+)-SKF 10047 has moderate affinity for PCP receptors.[76] We therefore routinely tested our novel structures for binding affinity for PCP sites, using [^{3}H]-MK801 as a PCP receptor radioligand.[77] In this study, none of the compounds described below have affinity for phencyclidine sites (K_i > 10 000 nM). All known animal models for evaluating antipsychotic drugs were developed retrospectively. The clinical efficacies of the first drugs were established long before their behavioral pharmacology in animals and their mechanism of action were fully defined. These models have been "validated" with dopamine D_2 antagonists, simply because these constituted the first class of antipsychotic drugs to be discovered. At the outset of our study, it was not clear whether these models would detect agents, acting by nondopaminergic mechanisms of action.

Scheme VII[a]



[a] (a) H_2, PtO_2, HOAc; (b) (t-BOC)$_2$O, NaOH, THF; chromatography; (c) TFA, heat; (d) 3-(2-bromoethyl)indole, Et_3N, THF, heat.

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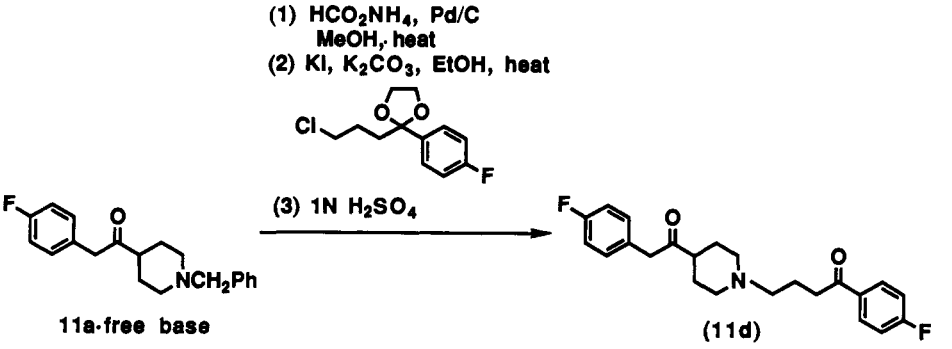
Scheme VIII



Initially, our testing strategy employed two mouse behavioral models, the antimescaline[78] and the antiaggression[79,80] tests, in which the activities of known antipsychotic drugs correlate well with their clinical efficacies in man.

A variety of spacer groups could be inserted in region B of parent structure 1 with minimal effect on σ binding affinity or selectivity (cf. Table III). If the terminal substituents are held constant, oxoethylene, oxymethylene, and thiomethylene spacers appear to have comparable effects on σ binding affinity (e.g. **6i**, **18a**, and **18bt**). In one subseries of compounds, oxidation of the thiomethylene chain to the corresponding sulfone reduced σ binding affinity slightly, but conversion to the sulfoxide drastically reduced this affinity (e.g. **18bt**, **22**, and **23**). Lengthening the spacer chain did not appear to alter σ binding affinity or selectivity appreciably in the ether series (e.g. **18bc**–**18bg**).

The effects of varying substituents on the distal phenyl group (region A) were examined next (cf. Table III). Addition of either electron-donating or electron-withdrawing groups on this phenyl ring contributed to good σ binding affinity. Compounds bearing halogens on this ring, especially fluorine, generally had lower binding selectivity for σ sites over serotonin $5HT_2$ receptors. Compound 1 and other fluoro analogs (e.g. **6i**, **6v**, **18a**, **18h**, and **18aa**) had the lowest selectivity for σ receptors over $5HT_2$ sites. Electron-withdrawing groups (defined by the Hansch resonance factor R,[81] e.g. CN or $MeSO_2$) greatly enhanced binding selectivity for σ sites over D_2 and $5HT_2$ receptors (e.g. **6q**, **18l**). Bulky substituents on the distal phenyl moiety appeared to be tolerated up to a certain limit (e.g. **18r** vs **18s**) and seemed to enhance σ binding selectivity (e.g. **18d**, **18f**). Para-substituted phenyl analogs are primarily reported here; additional substituents at the meta and ortho positions did not appear to adversely effect σ binding affinity (e.g. **18j**, **18v**, and **18w**). Substitution on the distal phenyl ring had minimal effect on binding selectivity of compounds for σ over dopamine D_2 receptors, when the substituent on the piperidine nitrogen was held constant. The σ/D_2 selectivity of analogs was highly dependent on the nature of the piperidine nitrogen substituent (vide infra).

Replacement of the distal phenyl group with other aryl or heteroaryl nuclei did not appreciably effect σ binding affinity or selectivity (cf. Table IV). Two exceptions were found: the 2-pyrimidyl analog **18bl** and the 4-pyridyl compound **18bj** had poor affinity for the σ receptor. In contrast, the 2-pyridyl counterpart **18bm** has excellent σ binding affinity. Cycloalkyl groups may replace the distal aromatic group with no loss in σ binding affinity (e.g. **18bp** and **18bs**).

Variations in the piperidine nitrogen terminus (region D) produced the most dramatic changes in the binding selectivity of compounds. Increases in the distance between the piperidine nitrogen and a phenyl group tethered to it reduced the selectivity of compounds for σ sites over $5HT_2$ receptors. Furthermore, affinity for D_2 receptors increased with the introduction of a butyrophenone side chain (i.e. **11d**); this substitution effect has ample precedent in the literature.[75]

Changes in the points of attachment on the piperidine ring of the distal hydrophobic group and its tether relative to the nitrogen substituent altered selectivity for σ receptors over dopamine D_2 sites in the ketone series. Compound 1 had far superior selectivity (1550-fold) for σ sites over D_2 receptors than its 3-piperidyl isomer,[82] **25** (2.4-fold), and its 2-piperidyl counterpart, **26** (90-fold) (cf. Table V). Similarly, compound **6i** had greater selectivity (163-fold) for σ sites than its 3-piperidyl counterpart,[82] **27** (11-fold) (cf. Table V).

The focus of our study then shifted to the determinants of in vivo activity in some animal antipsychotic models. Many of the compounds in this study, which had good affinity for σ-1 sites ($K_i \leq 100$ nM), antagonized the behavioral effects of a hallucinogen, mescaline, in mice[78] as well as the aggressive behavior of mice toward intruders after prolonged isolation.[79,80] Most of the classical antipsychotic drugs are quite potent in these tests; moreover, the potencies of these compounds in these models correlate well with their clinical efficacies. While the structural requirements for σ binding affinity and selectivity were relatively loose, the requirements for good in vivo activity were more stringent.

Aromatic substituents in region A greatly improved oral potency in the antimescaline test. Some analogs bearing phenyl groups substituted by halogens or small electron-withdrawing groups (e.g. **6i**, **6q**, **18m**, or **18ae** (Table III)), had very good oral activity in the antimescaline model. Heteroaryl and cycloalkyl substitution in region A generally reduced oral potency in this test (Table IV).

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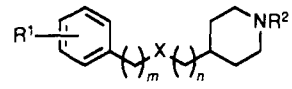
Table III. Substituted Phenyl Piperidines: In Vitro and Antimescaline Data



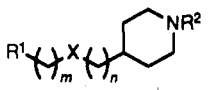
no.	X	*m*	*n*	R^1	R^2	salt[b]	σK_i (nM)	D_2 IC_{50} (nM)[c]	$5HT_2$ K_i (nM)[c]	antimescaline ED_{50} (mg/kg)[d]
1	CO	0	1	4-F	CH_2Ph	mal	1	1550	20	4.8[e]
6a	CO	0	1	4-F_3C	CH_2Ph		10	4667	>1000	>10
6b	CO	0	1	4MeO	CH_2Ph		4	6070	313	>30
6c	CO	0	1	4-MeS	CH_2Ph		8	715	208	>30
6d	CO	0	1	4-HO	CH_2Ph		18	1345	>1000	>30
6e	CO	0	1	4-Ph	CH_2Ph		33	3009	>100	30
6f	CO	0	1	4-$HOCH_2$	CH_2Ph		31	>10000	438	>30
6g	CO	0	1	4-MeO_2S	CH_2Ph		18	>10000	116	>30
6h	CO	0	1	4-Me(O)S	CH_2Ph		53	>10000	204	>30
6i	CO	0	1	4-F	CH_2-c-C_3H_5	HBr	10[e]	1630[e]	15[e]	0.35[e]
6j	CO	0	1	4-Cl	CH_2-c-C_3H_5	HBr	8	2004	495	0.46
6k	CO	0	1	4-OMe	CH_2-c-C_3H_5	HBr	55	1802	1883	>10 (ip)
6l	CO	0	1	4-*t*-Bu	CH_2-c-C_3H_5	HBr	8	1573	>1000	>30
6m	CO	0	1	Ph	CH_2-c-C_3H_5	HBr	51	1718	547	4.7
6n	CO	0	1	4-CF_3	CH_2-c-C_3H_5	HCl	45	>10000	278	6.6
6o	CO	0	1	4-NMe_2	CH_2-c-C_3H_5	2HBr	33	>10000	559	30
6p	CO	0	1	4-NH_2	CH_2-c-C_3H_5		146	>10000	NT	10
6q	CO	0	1	4-CN	CH_2-c-C_3H_5	fum	11	>10000	>10000	0.8
6r	CO	0	1	4-F	$CH_2C_6H_4CF_3$-*p*		3	195	6	1.8
6s	CO	0	1	4-F	$CH_2C_6H_4F$-*p*		3	608	26	4.5
6t	CO	0	1	4-F	$(CH_2)_2$-3-indolyl		26	7	3.6	<10
6u	CO	0	1	4-F	$(CH_2)_2C_6H_4F$-*p*		7	57	10	0.13
6v	CO	0	1	4-F	$(CH_2)_2Ph$		8	42	8	4.1
6w	CO	0	1	4-F	$(CH_2)_2C_6H_4Cl$-*p*		5	14	8.4	1.8
6x	CO	0	1	4-F	$(CH_2)_2C_6H_4CF_3$-*p*		9	10	3.3	<10
6y	CO	0	1	4-F	$(CH_2)_2$-c-C_3H_5	HBr	11	220	12	<10
7a	CHOH	0	1	4-F	$(CH_2)_2$-c-C_3H_5		155	>10000	NT	NT
7b	CHOH	0	1	4-F	CH_2Ph	HCl	8	5658	323	5[e]
7c	CHOH	0	1	4-MeS	CH_2Ph		10	7634	>100	>30
7d	CHOH	0	1	4-MeO	CH_2Ph	HCl	20	>10000	187	>30
7e	CHOH	0	1	4-F_3C	CH_2Ph	HCl	6	>10000	>100	>30
7f	CHOH	0	1	4-F	$(CH_2)_2Ph$		7	806	101	<10
10a	CHOH	1	0	4-F	CH_2Ph	HCl	3	789	360	5
10b	CHOH	1	0	H	CH_2Ph	HCl	18	8300	1603	<10
10c	CHOH	1	0	4-F	$(CH_2)_3Ph$		7	1700	41	NT
10d	CHOH	1	0	4-F	$(CH_2)_4Ph$		11	900	65	18
11a	CO	1	0	4-F	CH_2Ph	mal	3	4561	290	18
11b	CO	1	0	4-F	CH_2-4-pyridyl	2mal	7	>10000	1705	17
11c	CO	1	1	4-F	CH_2Ph	mal	3	1100	316	>30
11d	CO	1	0	4-F	$(CH_2)_3COC_6H_4F$-*p*		40	55	17	1.9
18a	O	0	1	4-F	CH_2-c-C_3H_5		2	381	9	2.9
18b	O	0	1	4-Cl	CH_2-c-C_3H_5	HCl	4	>10000	40	4.4
18c	O	0	1	4-MeO	CH_2-c-C_3H_5	HCl	18	>10000	>100	>30
18d	O	0	1	4-Ph	CH_2-c-C_3H_5		12	>10000	>10000	7.5
18e	O	0	1	4-$HOCH_2$	CH_2-c-C_3H_5		35	>10000	>100	>30
18f	O	0	1	4-t-Bu	CH_2-c-C_3H_5		14	3154	>1000	<30
18g	O	0	1	4-MeCH(OH)	CH_2-c-C_3H_5		98	>10000	NT	NT
18h	O	0	1	3,4-F_2	CH_2-c-C_3H_5	HCl	2	2836	41	4.5
18i	O	0	1	F_5	CH_2-c-C_3H_5	HCl	10	5684	3356	26.2
18j	O	0	1	3,4,5-$(MeO)_3$	CH_2-c-C_3H_5	HCl	50	>10000	8706	>30
18k	O	0	1	4-MeS	CH_2-c-C_3H_5	HCl	7	1979	114	>30
18l	O	0	1	4-$MeSO_2$	CH_2-c-C_3H_5		53	>10000	1135	>30
18m	O	0	1	4-NO_2	CH_2-c-C_3H_5		13	>10000	215	0.85
18n	O	0	1	4-NC	CH_2-c-C_3H_5		10	>10000	2818	1.7
18o	O	0	1	4-H_3CCO	CH_2-c-C_3H_5		9	539	>1000	>30
18p	O	0	1	4-Me_2NSO_2	CH_2-c-C_3H_5		>10000	NT	NT	NT
18q	O	0	1	4-PhO	CH_2-c-C_3H_5		24	>10000	584	>30
18r	O	0	1	4-(4′-FC_6H_4)	CH_2-c-C_3H_5		83	>10000	396	<30
18s	O	0	1	4-(4′-$MeOC_6H_4$)	CH_2-c-C_3H_5		218	7217	NT	NT
18t	O	0	1	H	CH_2-c-C_3H_5		7	3169	53	30
18u	O	0	1	3-Me_2N	CH_2-c-C_3H_5		5	7326	1158	<10 (ip)
18v	O	0	1	3,4-Cl_2	CH_2-c-C_3H_5	HCl	8	1652	87	3.3[e]
18w	O	0	1	2,4-Cl_2	CH_2-c-C_3H_5	HCl	4	111	32	2.9
18x	O	0	1	4-EtNH	CH_2-c-C_3H_4	HCl	33	>10000	>10000	>30
18y	O	0	1	4-F	CH_2-(2′-Me-cp)[f]	mal	5	945	24	>10
18z	O	0	1	4-F	CH_2-($MeCl_2$cp)[g]	fum	2	179	15	<10
18aa	O	0	1	4-F	CH_2Ph	HCl	2	870	28	4[e]
18ab	O	0	1	4-Cl	CH_2Ph	HCl	8.3[e]	4212[e]	137[e]	8
18ac	O	0	1	4-NO_2	CH_2Ph	HCl	5	4386	272	14
18ad	O	0	1	4-MeO	CH_2Ph		3	>10000	55	>30
18ae	O	0	1	4-F_3C	CH_2Ph		2	1930	350	6
18af	O	0	1	4-F	$CH_2C_6H_4F$-*p*		8	1070	38	5.9

Table III. (Continued)

no.	X	*m*	*n*	R^1	R^2	salt[b]	σ K_i (nM)	D_2 IC_{50} (nM)[c]	5HT_2 K_i (nM)[c]	antimescaline ED_{50} (mg/kg)[d]
18ag	O	0	1	4-F	$CH_2C_6H_5OMe$-*p*	mal	30	1340	NT	6.5
18ah	O	0	1	4-F	CH_2-2-naphthyl		51	4336	118	1.7
18ai	O	0	1	4-F	CH_2-4-pyridyl		7	2753[e]	31	1.1
18aj	O	0	1	4-F	$(CH_2)_2C_6H_4Cl$-*p*	HCl	5	368[e]	26	1.7
18ak	O	0	1	4-F	$(CH_2)_2$-c-C_3H_5	fum	3	428		3.1
18al	O	1	1	4-F	CH_2Ph	mal	2	3900	272	14
18am	O	1	1	4-MeO	CH_2Ph	mal	3.5[e]	26000	287	>30
18an	O	1	1	4-Ph	CH_2Ph	mal	20	1850	47	10 (ip)
18ao	O	1	1	H	CH_2Ph	HCl	4	>10000	>1000	>10 (ip)
18ap	O	1	1	4-H_3CO_2C	CH_2Ph	HCl	15	970	>10000	>30
18aq	O	1	1	4-F	$(CH_2)_2Ph$	mal	4	560	24	15
18ar	O	1	1	4-F	$(CH_2)_3Ph$	HCl	304	>10000	NT	NT
18as	O	1	1	4-F	$CH_2C_6H_4CO_2Me$-*p*	HCl	7	1980	313	>10 (ip)
18at	O	1	1	4-F	$CH_2C_6H_4Cl$-*p*	HCl	2	488	281	<10 (ip)
18au	O	1	1	4-F	$CH_2C_6H_4$-Ph-*p*	HCl	14	818	>1000	>10 (ip)
18av	O	1	1	4-F	$CH_2C_6H_4$-OH-*p*	HCl	7	3135	500	>10 (ip)
18aw	O	1	1	4-F	$CH_2C_6H_4$-OCH_2Ph-*p*	HCl	27	773	<100	>30
18ax	O	1	1	4-F	CH_2-4-pyridyl	fum	2	>10000	NT	<10 (ip)
18ay	O	1	1	4-F	CH_2-cyclohexyl	HCl	3	3350	127	>10 (ip)
18az	O	1	1	4-F	CH_2-2-naphthyl	HCl	4	305	251	>10 (ip)
18ba	O	1	1	4-F	CH_2-1-naphthyl	HCl	22	219	25	12
18bb	O	1	1	4-F	$(CH_2)_4CH_3$	HCl	9	1321	NT	<10 (ip)
18bc	O	0	2	4-F	CH_2Ph	HCl	4	114	<100	16
18bd	O	3	0	H	CH_2Ph	mal	2	8100	NT	<10 (ip)
18be	O	3	1	H	CH_2Ph	mal	3.2	839	260	<10 (ip)
18bf	O	4	1	H	CH_2Ph	HCl	2	4340	224	>10 (ip)
18bg	O	5	1	H	CH_2Ph	HCl	26	1850	186	>10 (ip)
18bh	O	1	2	4-*t*-Bu	CH_2Ph	HCl	4.5	6753	939	>10 (ip)
18bt	S	0	1	4-F	$(CH_2)_2$-c-C_3H_5		5	1702	53	>10
22	S(O)	0	1	4-F	$(CH_2)_2$-c-C_3H_5		310	>10000	NT	NT
23	SO_2	0	1	4-F	$(CH_2)_2$-c-C_3H_5		28	>10000	745	6.4
rimcazole							820	>10000	2482	22
BMY 14802							174	2431	410	6

[a] All test values are single measurements unless otherwise indicated. [b] Mal = maleate, fum = fumurate. [c] D_2 = dopamine D_2, 5HT_2 = serotonin 5HT_2. [d] The oral route of administration was used unless otherwise indicated; those compounds, for which ip data are reported, are inactive (ED_{50} > 30 mg/kg) by the oral route of administration. [e] Average of three measurements. [f] 2-Me-cp = 2-methylcyclopropyl. [g] $MeCl_2cp$ = 1-methyl-2,2-dichlorocyclopropyl.

Table IV. Miscellaneous Piperidines: In Vitro and Antimescaline Data



no.	X	*m*	*n*	R^1	R^2	salt[b]	σ K_i (nM)	D_2 IC_{50} (nM)[c]	5HT_2 K_i (nM)[c]	antimescaline ED_{50} (mg/kg)[d]
7g	CHOH	0	1	2-naphthyl	CH_2Ph		31	3329	>100	>10
7h	CHOH	0	1	2-thienyl	CH_2Ph		5	3717	446	>30
7i	CHOH	0	1	2-furyl	CH_2Ph		11	>10000	1323	>30
18bi	O	0	1	2-naphthyl	CH_2-c-C_3H_5		5	2964	>100	>10 (ip)
18bj	O	0	1	4-pyridyl	CH_2-c-C_3H_5		175	>10000	NT	NT
18bk	O	0	1	4-quinolinyl	CH_2-c-C_3H_5		50	4847	>100	19.2
18bl	O	0	1	2-pyrimidyl	CH_2-c-C_3H_5	HCl	347	4445	NT	NT
18bm	O	0	1	2-pyridyl	CH_2-c-C_3H_4	HCl	44	4667	1378	>30
18bn	O	0	1	5-indolyl	CH_2-c-C_3H_5		34	2349	112	<30
18bo	O	0	1	2-naphthyl	CH_2Ph		6	1022	173	>30
18bp	O	0	1	cyclohexyl	CH_2Ph	HCl	2	>10000	1363	<10 (ip)
18bq	O	0	1	2-quinolinyl	CH_2Ph	HCl	5.6	6300	311	<10 (ip)
18br	O	0	1	3-pyridyl	CH_2Ph	mal	5	>10000	>10000	>30
18bs	O	0	1	cyclopropyl	CH_2Ph	mal	2	>10000	>10000	>30
rimcazole							820	>10000	2482	22
BMY 14802							174	2431	410	6

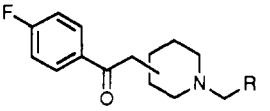
[a] All test values are single measurements. [b] Mal = maleate. [c] D_2 = dopamine D_2, 5HT_2 = serotonin 5HT_2. [d] The oral route of administration was used unless otherwise indicated; those compounds, for which ip data are reported, are inactive (ED_{50} > 30 mg/kg) by the oral route of administration.

However, the cyclohexyl and 2-quinolinyl derivatives, **18bp** and **18bq**, did have good activity when given by intraperitoneal (ip) administration.

The choice of a spacer group in region B caused modest changes in oral potency, provided the terminal groups were held constant. Compounds with oxoethylene or oxymethylene spacers (i.e. **6a–y** or **18a–k**) generally had superior oral activity in the antimescaline and the antiaggression tests (Tables III and VI). Analogs with other spacers generally had low oral potency in the antimescaline model; however, a few of these had good ip activity (Table III).

The substituent on the piperidine nitrogen (region D) had a great impact on oral potency in the antimescaline and antiaggression models (Tables III and VI). Analogs with the *N*-cyclopropylmethyl substituent generally had

Table V. Piperidine Positional Isomers: Biological Data[a]



1: 4-piperidyl, R = Ph, maleate salt
25: 3-piperidyl, R = Ph
26: 2-piperidyl, R = Ph, maleate salt
6i: 4-piperidyl, R = c-C_3H_5, HBr salt
27: 3-piperidyl, R = c-C_3H_5

compound no.	1	25	26	6i	27
binding affinity					
σ K_i (nM)	1	14	37	10	17
D_2 IC_{50} (nM)	1550	34	3344	1630	185
in vivo data					
antimescaline					
ED_{50} (mg/kg po)	4.8	1.1	4.3	0.35	1.3
antiaggression					
ED_{50} (mg/kg po)	8.6	20	>30	1.9	21

[a] All test values are single measurements, except as indicated in Table III.

Table VI. In Vivo Data

example	antiaggression ED_{50}[a]	5-HTP head twitch ED_{50}[a]	apomorphine climbing ED_{50}[a]
1	8.6	2.8	18
6i	1.9	1.8	15
6j	14	30	>30
6m	8.4	10	>30
6n	>30	NT	>30
6q	0.44	22.3	>90
6s	4.5	<10	<10
11b	38	28	NT
7b	32	6.8	>30
10a	>30	NT	>30
18a	12	10	>30
18b	26	27	>30
18d	30	>30	>30
18f	>30	NT	>30
18m	1.4	>10	>30
18n	2.6	29	NT
18aa	8.2	NT	>30
18ab	10	>10	NT
18aj	10	>10	NT
18ak	4.5	<10	NT
rimcazole	48	NT	>90
BMY 14802	45	2.3	>90

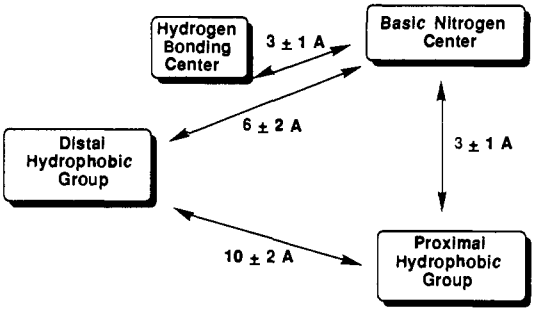
[a] mg/kg, po; all test values are single measurements. [b] NT = not tested.

the best oral potency, provided substitution had been optimized elsewhere as described above. Phenylalkyl substituents in region D contributed to good oral efficacy in the antimescaline test, but reduced activity in the antiaggression model (Tables III and VI).

Changes in the points of attachment on the piperidine ring of the distal hydrophobic group and its tether relative to the nitrogen substituent in the ketone series had minor effects on antimescaline activity, but significantly reduced potency in the mouse antiaggression model (Table V). Compound 1 was roughly equipotent to its 3- and 2-piperidyl isomers, 25 and 26, in the antimescaline test, but more potent than these isomers in the antiaggression model. A similar trend was observed for 6i and its 3-piperidyl isomer, 27. Alterations in piperidine isomerism appear to adversely affect the spectrum of in vivo activity, based on this limited data.

Analogs, which had selective receptor binding affinity profiles, also had corresponding selective activity in animal models (Table VI). σ-selective compounds had poor oral activity in the rat 5-hydroxy-L-tryptophan (5HTP) induced

Scheme IX



head twitch test,[83,84] a measure of $5HT_2$ antagonist in vivo activity, and in the mouse apomorphine-induced climbing test,[85,86] a measure of D_2 antagonist potency. Derivatives with mixed binding profiles showed moderate to good activity in these two models.

The results from testing structural variants of compound 1, suggest a model for ligands of σ receptors, characterized by [^{3}H]-(+)-SKF 10047 (i.e. σ-1 sites) (Scheme IX), which agrees with the general precepts of the Manallack and Largent models for the σ receptor (vide supra) but diverges from these models on a few points. Fifteen σ-selective analogs, which were orally active in the antimescaline or antiaggression tests (6j, 6m, 6n, 6q, 7b, 10a, 10b, 11b, 18d, 18i, 18m, 18n, 18ac, 18ae, and 18al), were evaluated using the CHEM-X[87] and CONCORD[88] programs, employing the standard geometry-optimization and energy-minimization calculations. Analysis of the optimized structures suggests the following structural components contribute to optimal σ binding affinity *and* oral activity in our two primary in vivo models: (1) a basic nitrogen, (2) two hydrophobic groups, which have different distances from the basic nitrogen, and (3) a hydrogen-bonding center midway between the basic nitrogen and the distal hydrophobic locus. The average distances between the basic nitrogen and the other groups are given in Scheme IX, along with standard deviations. Aromatic groups are preferred for the distal hydrophobic moiety to optimize in vivo potency. The hydrogen bonding center replaces the "electrostatic" group in the Manallack model. Hydroxyl, ketone, and ether groups contribute to good in vitro binding and in vivo activity. In three cases (18bt, 22, 23), sulfur-containing spacers appeared to be less effective. The distance between the basic nitrogen and the proximal hydrophobic group as well as the chemical nature of this latter group appear to be critical to receptor binding selectivity for σ sites over D_2 and $5HT_2$ receptors (vide supra). These effects are not obvious from an examination of the Manallack and Largent models.

Our simplified model for σ ligand structures has limitations. The computations for this model were based

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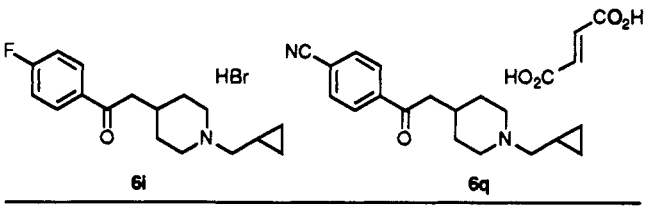
(85) Costall, B.; Naylor, R. J.; Nohria, V. Climbing Behavior Induced by Apomorphine in Mice: a Potential Model for the Detection of Neuroleptic Activity. *Eur. J. Pharmacol.* 1978, *50*, 39–50.
(86) Protais, P.; Costentin, S.; Schartz, J. C. Climbing Behavior Induced by Apomorphine in Mice; a Simple Test for the Study of Dopamine Receptors in Striatum. *Psychopharmacology* 1976, *50*, 1–6.
(87) CHEM-X, Chemical Design Ltd, Oxford, UK, 1986.
(88) Rusinko, A.; Sheridan, R. P.; Nilakantan, R.; Haraki, K. S.; Bauman, N.; Venkataraghaven, R. Using CONCORD To Construct Large Database of Three Dimensional Coordinates from Connection Tables. *J. Chem. Inf. Comput. Sci.* 1989, *29*, 251–255.

mainly on structures containing flexible chains between the piperidine nucleus and the hydrophobic centers. The resulting free rotation in these structures makes it difficult to assign rigorously the three-dimensional steric requirements for optimal in vitro and in vivo activity. The synthesis and evaluation of conformationally restricted analogs would better define these requirements. The effects of the basicity of the nitrogen heterocycle are not defined here; the preparation and evaluation of piperidine surrogate structures would address this point. Finally, our model may not represent the minimal pharmacophore. The testing of structures lacking one or more of the foci in our model would define the minimal requirements for in vitro and in vivo activity.

The next objective of our study was to explore the pharmacology of selected analogs further and to support the hypothesis that σ receptor ligands may be potential antipsychotic drugs. Compound **6i** (hereafter designed DuP 734) is a combined ligand for σ-1 and serotonin $5HT_2$ receptors,[89] while analog **6q** is a σ-selective agent.[91] Here, a subtle change in substitution on the distal aromatic moiety led to a profound change in σ binding selectivity and in vivo pharmacological profile (vide supra). Both compounds had very low affinity (K_i > 1000 nM) for muscarinic-1, muscarinic-2, dopamine D_1, serotonin $5HT_1$, NMDA, quisqualate, kainate, phencyclidine, glycine (strychnine-sensitive and insensitive sites), adrenergic (α-1, β-1, β-2), and benzodiazepine receptors. The affinities of these compounds for σ-2 sites cannot be determined readily in the absence of a selective σ-2 ligand. Both compounds had excellent oral activity in the antimescaline and antiaggression tests (Table VII). Both compounds strongly blocked the rotation in brain-lesioned rats, induced by (+)-SKF 10047.[90,91,94] Furthermore, DuP 734 (**6i**) blocked the effects of the σ ligand, (+)-3-(3-hydroxyphenyl)-1-propylpiperidine (3-PPP), on dopamine neuronal firing rates.[89] We propose, therefore, that DuP 734 (**6i**) and **6q** are σ-1 antagonists. DuP 734 (**6i**) strongly antagonized the behavior induced in the rat by the serotonin precursor, 5HTP, which is consistent with its high affinity for $5HT_2$ sites (Table VI). DuP 734 (**6i**) and **6q** had weak activities in the mouse apomorphine climbing test, which is consistent with their low affinities for dopamine D_2 sites.[91,94] Both compounds also had weak activity in the rat conditioned avoidance response (CAR) test after oral administration.[91,94] DuP 734 (**6i**), however, has been found to potentiate the therapeutic effect of haloperidol in this model during combination studies with this neuroleptic.[92,94] Thus, the ED_{50} for haloperidol in blocking avoidance responses declines when haloperidol is coadministered with increasing doses of DuP 734 (**6i**). In contrast, the ED_{50} of haloperidol for blocking escape responses is essentially unchanged. Neither DuP 734 (**6i**) nor **6q** caused catalepsy in the rat at very high doses.[91,94] DuP 734 (**6i**) did not increase the catalepsy induced by haloperidol in the rat.[94] Thus, DuP 734 (**6i**) and **6q** are active in some animal models used to evaluate antipsychotic drugs, but not in those which may rely on dopamine D_2 antagonist effects; furthermore, these compounds do not evoke adverse motor side effects in the rodent, which are induced by conventional neuroleptics.

Table VII. **6i** (DuP 734) and **6q**: Comparative Data



6i **6q**

	6i	6q
binding affinity data		
σ K_i (nM)	10	11
dopamine D_2 IC_{50} (nM)	1630	>10000
dopamine D_1 K_i (nM)	>1000	>10000
serotonin $5HT_2$ K_i (nM)	15	>10000
in vivo data		
mouse antimescaline ED_{50} (mg/kg, po)	0.35	0.7
mouse antiaggression ED_{50} (mg/kg, po)	1.9	0.44
rat (+)-SKF 10047 rotation ED_{50} (mg/kg, po)	2.4	5.3[b]

[a] All values are averages of three measurements, except as indicated below. [b] Single measurement.

Conclusion

The pharmacology and chemical syntheses of novel σ receptor ligands, which are analogs of 1, have been described. Selectivity for σ-1 sites over dopamine D_2 or serotonin $5HT_2$ receptors appears to be governed by the chemical nature of the nitrogen substituent, its distance from the basic nitrogen and its orientation relative to the distal hydrophobic group for these series of compounds. σ receptor affinity and selectivity is less dramatically affected by structural diversity in other regions of the parent structure. None of the compounds described above have affinity for phencyclidine receptors. The requirements for potency and spectrum of in vivo activity are more stringent than those for binding affinity and selectivity. The cyclopropylmethyl ketones and ethers (e.g. DuP 734 (**6i**) and 18a) have the best in vivo potency in the most animal models. On the basis of the pharmacology profiles of antagonists of (+)-SKF 10047, such as DuP 734 (**6i**) and **6q**, we propose these compounds may be effective antipsychotic drugs, which do not induce extrapyramidal side effects or tardive dyskinesia.

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 IBM-Bruker FT-NMR spectrometer (200 MHz or 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. Mass spectra (MS), high-

(89) Tam, S. W.; Steinfels, G. F.; Gilligan, P. J.; Schmidt, W. K.; Cook, L. DuP 734 [1-(Cyclopropylmethyl)-4-(2′-(4″-fluorophenyl)-2-oxoethyl)-piperidine HBr], a *Sigma* and $5HT_2$ Receptor Antagonist: Receptor Binding, Electrophysiological, and Neuropharmacological Profiles. *J. Pharmacol. Exp. Ther.*, in press.

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resolution mass spectra (HRMS), or chemical-ionization high-resolution mass spectra (CI-HRMS) were recorded on a Finnegan MAT 8230 spectrometer or a Hewlett Packard Model 5988A spectrometer. Melting points were recorded on a Büchi Model 510 melting point apparatus and are uncorrected. Boiling points are uncorrected. Combustion analyses were performed by Quantitative Technologies, Whitehouse, NJ, Spang Microanalyses, Eagle Harbor, MI, or Robertson Labs, Edison, NJ.

Reagents were purchased from commercial sources and, where necessary, purified prior to use according to the literature procedures.[95] For hydrogenations, the reaction solvent was purged by bubbling anhydrous nitrogen through it before addition of the substrate(s) or the catalyst. 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 consists of drying the combined organic layers over magnesium sulfate, filtration, and removal of solvent in vacuo.

Common abbreviations include THF (tetrahydrofuran), DMF (*N,N*-dimethylformamide), and LAH (lithium aluminum hydride).

1-(4-Fluorophenyl)-2-(4-pyridyl)ethanone (28)[96] (Method A). A solution of sodium bis(trimethylsilylamide) in anhydrous THF (1 M, 400 mL, 0.4 mol) was cooled to 0–5 °C with stirring under a nitrogen atmosphere. A solution of 4-picoline (37.25 g, 38.9 mL, 0.4 mol) in anhydrous THF (560 mL) was added dropwise over 30 min. The reaction mixture was stirred at 0–10 °C for 30 min.

A solution of ethyl 4-fluorobenzoate (33.6 g, 29.3 mL, 0.2 mol) in anhydrous THF (400 mL) was cooled to 0–5 °C with stirring under a nitrogen atmosphere. The above solution of (4-pyridinylmethyl)sodium was added dropwise via an insulated additional funnel such that the internal temperature did not exceed 15 °C. The reaction mixture was then stirred at ambient temperature for 3 h. The reaction mixture was poured onto water (1 L) and extracted three times with EtOAc. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Vacuum distillation (bp 140 °C, 0.1 mmHg) gave the product (25.3 g), which solidified on standing: mp 90–93 °C; IR (KBr) 1684 (s), 1596 (s), 1505 (m), 1417 (m); NMR ($CDCl_3$, 200 MHz) δ 8.65–8.5 (m, 2 H), 8.05 (dd, 2 H, J = 8, 6), 7.25–7.1 (m, 4 H), 4.3 (s, 2 H); MS *m/e* 215.

1-[2-(4-Fluorophenyl)ethyl]-4-[2-(4-fluorophenyl)-2-oxoethyl]piperidine (6u) (Method B). A mixture of 1-(4-fluorophenyl)-2-(4-pyridyl)ethanone (1.5 g, 7 mmol) and 1-(2′-bromoethyl)-4-fluorobenzene (2.8 g, 14 mmol) in acetonitrile (7 mL) was stirred at reflux temperature under a nitrogen atmosphere for 3.5 h. The reaction mixture was cooled to ambient temperature and diluted with ether (100 mL). Filtration and trituration with copious amounts of ether afforded the crude pyridinium salt, a pale yellow solid, which was carried on to the next step.

Platinum dioxide (1 g) was suspended in purged EtOH (100 mL), and this suspension was stirred under a hydrogen atmosphere until hydrogen uptake ceased. A solution of the crude pyridinium salt in purged EtOH (200 mL) was added, and the mixture was stirred under a hydrogen atmosphere (20 psi). After the theoretical amount of hydrogen had been taken up, the suspension was filtered through Celite. Solvent was removed in vacuo to give the product as its hydrobromide salt, a white solid.

This solid was dissolved in water; the solution was basified with a 2 N sodium hydroxide solution and then extracted with chloroform three times. Standard workup gave an oil. Column chromatography ($CHCl_3$/MeOH 95:5) gave the product, a pale yellow solid (R_f = 0.2, 1.49 g, 62% yield): mp 96–98 °C; IR (KBr) 3072 (w), 3006 (w), 1690 (s), 1510 (s); NMR ($CDCl_3$, 300 MHz) δ 8.1–7.9 (m, 2 H), 7.2–6.9 (m, 8 H), 3.0 (br d, 2 H, J = 10), 2.9 (d, 2 H, J = 7), 2.9–2.7 (m, 2 H), 2.6–2.4 (m, 2 H), 2.1–1.2 (m, 5 H); MS *m/e* 343. Anal. ($C_{21}H_{23}F_2NO$) C, H, N, F.

1-Benzyl-4-[2-(4-fluorophenyl)-2-hydroxyethyl]piperidine Hydrochloride Salt (7b) (Method C). A solution of 1-benzyl-4-[2-(4-fluorophenyl)-2-oxoethyl]piperidine (2.06 g, 6.4 mmol) and sodium borohydride (0.97 g, 26 mmol) in EtOH (50 mL) was stirred at ambient temperature under a nitrogen atmosphere for 18 h. Solvent was removed in vacuo to give a yellow-white slurry, which was taken up in a 1 N NaOH solution (200 mL). Extraction with EtOAc three times, drying over magnesium sulfate, treatment with Darco, filtration through Celite, and removal of solvent in vacuo afforded a pale yellow solid (1.8 g): mp 84–86 °C; NMR ($CDCl_3$, 200 MHz) δ 7.4–7.25 (m, 7 H), 7.0 (t, 2 H, J = 8), 4.7 (dd, 1 H, J = 8, 6), 3.45 (s, 2 H), 2.9–2.75 (m, 2 H), 2.1–1.2 (m, 10 H), HRMS calcd for $C_{20}H_{24}FNO$ 313.1842, found 313.1862.

The free base was dissolved in ether and the resulting solution was mixed with a 1 N HCl solution in ether (10 mL). Filtration, washing with ether, and drying in vacuo at 60 °C generated the product, a white powder (1.8 g, 80% yield): mp 189–191 °C; NMR (DMSO-d_6, 300 MHz) δ 11.0–10.8 (m, 1 H), 7.7–7.6 (m, 2 H), 7.5–7.35 (m, 5 H), 7.1 (t, 2 H, J = 8), 5.35–5.25 (m, 1 H), 4.65–4.55 (m, 1 H), 4.3–4.15 (m, 2 H), 3.35–3.2 (m, 2 H), 2.95–2.75 (m, 2 H), 2.0–1.3 (m, 7 H). Anal. ($C_{20}H_{24}FNO$·HCl) C, H, N, F, Cl.

1-Benzyl-4-carbethoxypiperidine (29) (Method D). A mixture of ethyl isonipecotate (212 g, 1.35 mol), benzyl chloride (170 g, 1.35 mol), and potassium carbonate (322 g, 2.33 mol) in absolute EtOH (1.8 L) was stirred mechanically at room temperature for 72 h. Solvent was removed in vacuo, and the residue was dissolved in water and then extracted with ether three times. Standard workup gave a pale yellow oil. Vacuum distillation (bp 134–136 °C, 1.0 Torr) gave a colorless liquid (252 g, 76% yield): NMR ($CDCl_3$, 200 MHz) δ 7.30–7.22 (m, 5 H), 4.12 (q, 2 H, J = 7), 3.48 (s, 2 H), 2.88–2.82 (m, 2 H), 2.33–2.19 (m, 1 H), 2.08–1.67 (m, 6 H), 1.24 (t, 3 H, J = 7). Anal. ($C_{15}H_{21}NO_2$) C, H, N.

1-Benzyl-4-(hydroxymethyl)piperidine (30) (Method E, Scheme II). A suspension of LAH (22.8 g, 0.6 mol) in anhydrous THF (400 mL) was stirred mechanically at 0 °C under a nitrogen atmosphere. A solution of 1-benzyl-4-carbethoxypiperidine (26.5 g, 0.1 mol) in anhydrous THF (400 mL) was added dropwise. After the addition was completed, the reaction mixture was heated to reflux temperature and stirred for 18 h. The reaction mixture was cooled to 0 °C and ethyl acetate (900 mL) was added dropwise. Water (23 mL), 2 N sodium hydroxide solution (23 mL), and then water (69 mL) were added with vigorous stirring. The inorganic salts were filtered, and the filtrate was concentrated in vacuo. Vacuum distillation (bp 140 °C, 0.4 Torr) gave a clear, colorless liquid (12.5 g, 61% yield): NMR ($CDCl_3$, 300 MHz) δ 7.36–7.22 (m, 5 H), 3.50 (s, 2 H), 3.49 (dd, 2 H, J = 7, 7), 2.94–2.86 (m, 2 H), 2.02–1.17 (m, 8 H). Anal. ($C_{13}H_{19}NO$) C, H, N.

1-(Cyclopropylmethyl)-4-[(3,4-dichlorophenoxy)methyl]piperidine Hydrochloride Salt (18v) (Method E, Scheme IV). A solution of 1-(cyclopropylcarbonyl)-4-[(3,4-dichlorophenoxy)methyl]piperidine (2.9 g, 8.84 mmol) in anhydrous THF (50 mL) was stirred at ambient temperature under a nitrogen atmosphere. A solution of diborane in THF (1 M, 20 mL, 20 mmol) was added dropwise via syringe. The reaction mixture was then stirred at reflux temperature for 24 h, and then it was cooled to room temperature. Glacial acetic acid (20 mL) was added dropwise; mild gas evolution ensued. The resulting solution was refluxed for 30 min. Solvent was removed in vacuo; the residue was treated with a 1 N NaOH solution and extracted with EtOAc three times. Standard workup afforded an oil (2.21 g): NMR ($CDCl_3$, 300 MHz) δ 7.3 (d, 1 H, J = 8), 6.95 (d, 1 H, J = 2), 6.75 (dd, 1 H, J = 8, 2), 3.75 (d, 2 H, J = 7), 3.15 (br d, 2 H, J = 10), 2.25 (d, 2 H, J = 7), 2.1–1.7 (m, 5 H), 1.5–1.35 (m,

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(98) We propose that the azide intermediate may decompose thermally to a nitrene, which may abstract hydrogen from wet solvent to give the amine product. Cf. Abramovitch, R. A.; Kyba, E. P. Decomposition of Organic Azides. In *The Chemistry of the Azido Group*; Patai, S., Ed.; Interscience Publishers: New York, 1971; pp 256–278.

2 H), 0.95–0.8 (m, 1 H), 0.6–0.45 (m, 2 H), 0.15–0.05 (m, 2 H); HRMS calcd for $C_{16}H_{21}Cl_2NO$ 313.1000, found 313.0999.

The oil was dissolved in ether (30 mL); a solution of HCl in ether (1 M, 10 mL, 10 mmol) was then added with stirring. Filtration, washing with copious amounts of ether, and drying in vacuo at 60 °C afforded a white powder (2.34 g, 76% yield): mp 190–195 °C dec; NMR (DMSO-d_6, 300 MHz) δ 10.6–10.3 (m, 1 H), 7.45 (d, 1 H, J = 8), 7.3 (d, 1 H, J = 1), 7.0 (dd, 1 H, J = 8, 1), 3.9 (d, 2 H, J = 6), 3.55 (br d, 2 H, J = 10), 3.35 (br s, 2 H), 3.1–2.85 (m, 3 H), 2.1–1.9 (m, 2 H), 1.85–1.6 (m, 2 H), 1.2–1.0 (m, 1 H), 0.7–0.6 (m, 1 H), 0.7–0.6 (m, 2 H), 0.5–0.35 (m, 2 H). Anal. ($C_{16}H_{21}Cl_2NO$·HCl) C, H, N, Cl.

1-Benzyl-4-formylpiperidine (31) (Method F, Scheme II). A solution of oxalyl chloride (3 g, 2.1 mL, 23.6 mmol) in dichloromethane (100 mL) was cooled to −78 °C with stirring under a nitrogen atmosphere. A solution of dimethyl sulfoxide (3.7 g, 3.36 mL, 47.3 mmol) in dichloromethane (100 mL) was added dropwise. The reaction mixture was stirred for 15 min. A solution of 1-benzyl-4-(hydroxymethyl)piperidine (3.6 g, 17.6 mmol) in dichloromethane (100 mL) was added dropwise, and then the reaction mixture was stirred at −65 °C to −60 °C for 15 min. The reaction mixture was cooled to −78 °C and triethylamine (6.83 g, 9.41 mL, 67.5 mmol) was added in one portion. The reaction mixture was warmed to ambient temperature over 6 h, and then it was poured onto water, mixed, and extracted three times with ether. Standard workup gave an oil. Column chromatography (EtOAc) gave the product, a clear pale yellow liquid (2.6 g, 72% yield), which was routinely carried on to subsequent reactions, since it decomposes during storage: NMR ($CDCl_3$, 300 MHz) δ 9.65 (s, 1 H), 7.4–7.3 (m, 5 H), 3.5 (s, 2 H), 2.9–2.75 (m, 2 H), 2.4–1.6 (m, 7 H); MS m/e 203.

1-Benzyl-4-[2-(4-fluorophenyl)-2-oxoethyl]piperidine Maleate Salt (1) (Method F, Scheme III). A solution of oxalyl chloride (0.21 g, 0.14 mL, 2.2 mmol) in dichloromethane (5 mL) was cooled to −78 °C with stirring under a nitrogen atmosphere. A solution of dimethyl sulfoxide (0.33 g, 0.3 mL, 4.4 mmol) in dichloromethane (5 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 15 min. A solution of **7b** (0.5 g, 1.6 mmol) in dichloromethane (5 mL) was added dropwise. The reaction mixture was then stirred for 15 min, and then triethylamine (0.59 g, 0.8 mL, 5.78 mmol) was added in one portion. The reaction mixture was warmed gradually to ambient temperature with stirring over 25 h, and then it was poured onto water (50 mL), mixed, and extracted three times with ether. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. Column chromatography (EtOAc) gave the product, a pale yellow solid (R_f = 0.25, 186 mg): NMR ($CDCl_3$, 200 MHz) δ 7.95 (dd, 2 H, J = 8, 6), 7.35–7.25 (m, 5 H), 7.15 (t, 2 H, J = 6), 3.5 (s, 2 H), 2.95–2.8 (m, 4 H), 2.1–1.9 (m, 3 H), 1.8–1.7 (m, 2 H), 1.5–1.25 (m, 2 H); HRMS calcd for $C_{20}H_{22}FNO$ 311.1685, found 311.1687.

A saturated solution of maleic acid in ether (20 mL) was added to a solution of the above solid in ether (10 mL) with stirring. The white precipitate was filtered and washed with copious amounts of ether. Drying in vacuo afforded a white powder (254 mg, 37% yield): mp 106–108 °C; NMR δ 12.2–12.0 (m, 1 H), 8.0 (dd, 2 H, J = 8, 6), 7.5–7.35 (m, 5 H), 7.15 (t, 2 H, J = 8), 6.4 (s, 2 H), 4.2 (s, 2 H), 3.65–3.4 (m, 2 H), 2.95 (d, 2 H, J = 6), 2.9–2.7 (m, 2 H), 2.4–1.6 (m, 5 H). Anal. ($C_{20}H_{22}FNO$·$C_4H_4O_4$·0.25H_2O) C, H, N.

1-Benzyl-4-[2-(4-fluorophenyl)-1-hydroxyethyl]piperidine Hydrochloride Salt (10a) (Method G). Magnesium mesh (1.21 g, 50 mmol) was suspended in anhydrous THF (100 mL) with stirring under a nitrogen atmosphere. A solution of 4-fluorobenzyl chloride (7.23 g, 6.0 mL, 50 mmol) in dry THF (50 mL) was added dropwise over 5 min. The reaction mixture was stirred at reflux temperature for 30 min. A solution of 1-benzyl-4-formylpiperidine (5.0 g, 24.6 mmol) in dry THF (50 mL) was added dropwise. The resulting mixture was stirred at reflux temperature for 14.5 h. After being cooled to ambient temperature, the mixture was poured onto water, mixed, and extracted three times with EtOAc. Standard workup gave a yellow oil. Column chromatography (EtOAc) gave the product, a clear yellow oil (R_f = 0.12, 5.74 g): IR (neat) 3412 (s, br), 3063 (m), 3029 (m), 2938 (s), 2803 (m), 1601 (s), 1510 (s), 1467 (s), 1453 (s); NMR ($CDCl_3$, 200 MHz) δ 7.35–6.85 (m, 9 H), 4.60–4.45 (m, 1 H), 4.50 (s, 2 H), 3.0–2.45 (m, 4 H), 2.00–1.6 (m, 7 H); MS m/e 313.

The free base was dissolved in diethyl ether (200 mL) with stirring. Anhydrous hydrogen chloride was bubbled through the solution; the precipitate was collected by filtration, triturated with fresh ether, and filtered again. Drying in vacuo afforded a white powder (3.9 g, 45% yield): mp 64–66 °C; NMR (DMSO-d_6, 200 MHz) δ 11.1–10.8 (m, 1 H), 7.75–7.0 (m, 9 H), 5.9–5.75 (m, 1 H), 4.4–4.25 (m, 2 H), 3.5–2.5 (m, 8 H), 2.0–1.3 (m, 3 H). Anal. ($C_{20}H_{24}FNO$·HCl·0.25H_2O) C, H, N.

1-Benzyl-4-(formylmethyl)piperidine (32) (Method H). A solution of diisopropylamine (4.38 g, 6.1 mL, 43.3 mmol) in anhydrous THF (50 mL) was cooled to 0 °C was stirring. A solution of n-butyllithium in hexanes (2.4 M, 17.3 mL, 43.3 mmol) was added dropwise; the resulting solution was stirred for 15 min. The reaction mixture was transferred via cannula to a suspension of (methoxymethyl)triphenylphosphonium chloride (14.9 g, 43.3 mmol) in anhydrous THF (100 mL), stirred at −20 °C. The reaction mixture was stirred at −20 °C for 35 min, and then it was cooled to −40 °C. A solution of 1-benzyl-4-formylpiperidine (8 g, 39.4 mmol) in anhydrous THF (50 mL) was added dropwise. The reaction mixture was warmed gradually to ambient temperature over 21 h, and then it was poured onto water (500 mL) mixed and extracted three times with EtOAc (500 mL). The combined organic layers were dried over magnesium sulfate, treated with decolorizing charcoal, and filtered through Celite. Solvent was removed in vacuo to give an orange oil. Column chromatography (EtOAc) gave 1-benzyl-4-(methoxyethenyl)piperidine as a mixture of E- and Z-isomers (R_f = 0.41, 5.06 g, 56% yield): NMR ($CDCl_3$, 200 MHz) δ 7.4–7.2 (m, 5 H), 6.3 (d, 0.6 H, J = 13), 5.8 (d, 0.4 H, J = 6), 4.65 (dd, 0.6 H, J = 13, 6), 4.2 (dd, 0.4 H, J = 6, 5), 3.5 (s, 1.2 H), 3.45 (s, 1.8 H), 2.9–2.7 (m, 2 H), 2.5–2.3 (m, 2 H), 2.1–1.3 (m, 7 H); HRMS calcd for $C_{15}H_{21}NO$ 231.1623, found 231.1633.

A mixture of the enol ether, a 4 N hydrochloric acid solution (50 mL), and THF (10 mL) was stirred at room temperature for 17 h. The solution was carefully neutralized with solid potassium carbonate. The layers were separated. The aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. Column chromatography (EtOAc/hexanes 1:1) gave a clear pale yellow liquid (R_f = 0.1, 3.65 g, 78% yield): IR (neat) 3085 (m), 3062 (m), 3057 (m), 2920 (s), 2803 (s), 2757 (s), 2723 (s), 1724 (s), 1603 (w), 1495 (m), 1467 (m), 1454 (m); NMR ($CDCl_3$, 200 MHz) δ 9.7 (t, 1 H, J = 1), 7.45–7.2 (m, 5 H), 3.5 (s, 2 H), 2.95–2.75 (m, 2 H), 2.35 (dd, 2 H, J = 7, 1), 2.1–1.6 (m, 4 H), 1.45–1.2 (m, 2 H); HRMS calcd for $C_{14}H_{19}NO$ 217.1466, found 217.1460.

1-Benzyl-4-[2-(4-fluorophenyl)-2-hydroxyethyl]piperidine Hydrochloride Salt (7b) (Method I). A mixture of a solution of (4-fluorophenyl)magnesium bromide in ether (2 M, 12.5 mL, 25 mmol) and anhydrous THF (25 mL) was stirred at ambient temperature under a nitrogen atmosphere. A solution of 1-benzyl-4-(formylmethyl)piperidine (3.6 g, 16.6 mmol) in anhydrous THF (25 mL) was added dropwise. The reaction mixture was stirred for 19 h, and then it was poured onto a saturated ammonium chloride solution, mixed, extracted three times with EtOAc (50 mL), and worked up by the standard procedure. Column chromatography (EtOAc/hexanes 1:1) gave a pale yellow solid (R_f = 0.08, 2.7 g), which was identical in every respect to the free base obtained in method C.

A solution of hydrogen chloride in ether (1 M, 30 mL) was added dropwise to a solution of the free base in ether (100 mL) with vigorous stirring. The white precipitate was filtered and washed with copious amounts of ether. Drying in vacuo afforded a white powder (2.3 g, 40% yield), which was identical in every respect to the salt obtained in method C.

1-Benzyl-4-(formylmethyl)piperidine (32) (Method J). A solution of 1-benzylpiperidine-4-acetonitrile[34] (45 g, 210 mmol) in toluene (500 mL) was stirred under a nitrogen atmosphere at ambient temperature. A solution of diisobutylaluminum hydride in toluene (1.5 M, 166 mL, 250 mmol) was added dropwise. The reaction mixture was heated to reflux temperature and stirred for 24 h. After cooling to room temperature, a saturated ammonium chloride solution (400 mL) was added gradually. The mixture was poured onto 500 mL of 1 N sodium hydroxide solution and mixed. The layers were separated. The aqueous layer was extracted twice with toluene and worked up by the standard

procedure. Column chromatography (EtOAc) gave the starting nitrile (R_f = 0.33, 14.7 g) and the product (R_f = 0.25, 10.1 g, 22% yield), which was identical in every respect to the product from method H above.

1-(Cyclopropylcarbonyl)-4-(hydroxymethyl)piperidine (33) (Method M). A solution of 1-(cyclopropylcarbonyl)-4-carbethoxypiperidine[99] (35 g, 156 mmol) in anhydrous THF (350 mL) was stirred at ambient temperature under a nitrogen atmosphere. A solution of lithium borohydride in THF (2 M, 78 mL, 156 mmol) was added dropwise. Trimethyl borate (1.77 mL, 15.7 mmol) was added, and then the reduction mixture was stirred for about 48 h. Water was added dropwise with vigorous stirring until the vigorous gas evolution ceased. The mixture was diluted 2-fold with water, extracted three times with EtOAc, and worked up by the standard procedure. Vacuum distillation (bp 165 °C, 0.5 Torr) gave a clear, colorless liquid (18.2 g, 64% yield): IR (neat) 3410 (br, s), 3094 (w), 3008 (s), 2918 (s), 2858 (s), 1738 (m), 1613 (s), 1448 (s), 1375 (s), 1316 (s); NMR ($CDCl_3$, 300 MHz) δ 4.7–4.5 (m, 1 H), 4.4–4.1 (m, 1 H), 3.6–3.4 (m, 2 H), 3.2–2.5 (m, 3 H), 2.0–1.7 (m, 5 H), 1.4–1.1 (m, 1 H), 1.0–0.8 (m, 2 H), 0.8–0.65 (m, 2 H); HRMS calcd for $C_{10}H_{17}NO_2$ 183.1259, found 183.1250. Anal. ($C_{10}H_{17}NO_2$) C, H, N.

1-(Cyclopropylcarbonyl)-4-[(methylsulfonyl)oxy]piperidine (34) (Method N). A solution of 1-(cyclopropylcarbonyl)-4-(hydroxymethyl)piperidine (6.0 g, 33 mmol) and triethylamine (11.9 g, 16.4 mL, 118 mmol) in dichloromethane (150 mL) was stirred at about 0 °C under a nitrogen atmosphere. A solution of methanesulfonyl chloride (4.5 g, 3.0 mL, 39 mmol) in dichloromethane (20 mL) was added dropwise. The reaction mixture was then stirred at about 0–5 °C for 35 min. The pale yellow turbid mixture was poured into a separatory funnel and washed once with an ice-cold 1 N hydrochloric acid solution (100 mL), twice with a saturated sodium bicarbonate solution (100 mL) and once with brine (100 mL). Standard workup gave a pale yellow oil (8.5 g), which was routinely carried on to subsequent steps: NMR ($CDCl_3$, 300 MHz) δ 4.8–4.5 (m, 1 H), 4.4–4.2 (m, 1 H), 4.2–3.95 (m, 2 H), 3.2–2.8 (m, 4 H), 2.7–2.5 (m, 1 H), 2.2–1.6 (m, 4 H), 1.5–1.1 (m, 2 H), 1.05–0.9 (m, 2 H), 0.85–0.7 (m, 2 H); MS *m/e* 261.

1-(Cyclopropylcarbonyl)-4-[(4-fluorophenoxy)methyl]piperidine (35) (Method O). Sodium hydride (50% in oil, 1.0 g, 20 mmol) was washed with hexanes twice and then suspended in anhydrous THF (20 mL) with stirring under a nitrogen atmosphere. A solution of 4-fluorophenol (2.13 g, 19 mmol) in THF (10 mL) was added dropwise with vigorous gas evolution. The reaction mixture was stirred at room temperature for 15 min, and then a solution of 1-(cyclopropylcarbonyl)-4-[[(methylsulfonyl)oxy]methyl]piperidine (983 mg, 3.77 mmol) in THF (10 mL) was added dropwise. The reaction mixture was then stirred at reflux temperature for about 22 h, cooled to ambient temperature, poured onto a 2 N sodium hydroxide solution, and mixed. The aqueous mixture was extracted three times with ether; the combined organic layers were washed with a 2 N sodium hydroxide solution. Standard workup gave a yellow liquid.

Column chromatography (EtOAc) gave, after removal of solvent in vacuo, the product, a clear, colorless liquid (617 mg, 57% yield): NMR ($CDCl_3$, 300 MHz) δ 7.05–6.75 (m, 4 H), 4.8–4.55 (br m, 1 H), 4.45–4.2 (m, 1 H), 3.9–3.6 (br s, 2 H), 3.25–3.0 (br t, 1 H, J = 6), 2.8–2.5 (br t, 1 H, J = 6), 2.2–1.7 (m, 4 H), 1.5–1.2 (m, 2 H), 1.05–0.9 (m, 2 H), 0.8–0.7 (m, 2 H); HRMS calcd for $C_{16}H_{20}FNO_2$ 277.1478, found 277.1466. Anal. ($C_{16}H_{20}FNO_2$) C, H, N.

1-Benzyl-4-[[(4-fluorobenzyl)oxy]methyl]piperidine Maleate Salt (18al) (Method P). A suspension of sodium hydride (60% dispersion in oil, 0.76 g, 19 mmol) in anhydrous THF (38 mL) was stirred at room temperature under a nitrogen atmosphere. A solution of 1-benzyl-4-(hydroxymethyl)piperidine (3.82 g, 18.6 mmol) in anhydrous THF (38 mL) was added dropwise. After the addition was completed, the reaction mixture was stirred for 2 h. 4-Fluorobenzyl bromide (2.4 mL, 19 mmol) was added dropwise, and then the reaction mixture was stirred for 72 h. Water (50 mL) was added and the resulting mixture was extracted three times with EtOAc. Standard workup gave an oil. Vacuum distillation (170 °C (Kugelrohr oven), 1.0 Torr) gave a colorless oil (3.45 g, 59% yield): NMR ($CDCl_3$, 200 MHz) δ 7.34–6.98 (m, 9 H), 4.46 (s, 2 H), 3.50 (s, 2 H), 2.93–2.87 (m, 2 H), 2.02–1.59 (m, 5 H), 1.39–1.25; HRMS calcd 313.1479, found 313.1479. Anal. ($C_{20}H_{24}FNO$) C, H, N.

The above free base was dissolved in ether and treated with an excess volume of a saturated solution of maleic acid in ether. The precipitate was filtered and washed with copious amounts of ether. Drying in vacuo at 60 °C afforded a white solid (4.5 g, 95% yield): mp 127–129 °C. Anal. ($C_{20}H_{24}FNO \cdot C_4H_4O_4$) C, H, N.

1-(Cyclopropylmethyl)-4-[(4-cyanophenoxy)methyl]piperidine (18n) (Method P). Sodium hydride (50% in oil, 0.48 g, 10 mmol) was washed with hexanes twice (decanting the solvent each time) and suspended in DMF (20 mL) with stirring under a nitrogen atmosphere. A solution of 1-(cyclopropylmethyl)-4-(hydroxymethyl)piperidine (1.6 g, 9.5 mmol) in DMF (10 mL) was added dropwise. Gas evolution occurred. 4-Fluorobenzonitrile (1.21 g, 10 mmol) was added, and then the reaction mixture was stirred at 100 °C for 17 h. Water was added. The solvent was distilled in vacuo. The residue was taken up in water, basified with a 1 N sodium hydroxide solution, and extracted three times with EtOAc. Standard workup gave a brown oil.

Column chromatography ($CHCl_3$/MeOH 9:1) gave a brown oil, after removal of solvent in vacuo. The oil was crystallized from ether/hexanes and filtered. Drying in vacuo afforded the product, a white powder (1.23 g, 48% yield): mp 109–111 °C; IR (KBr) 3074 (w), 2997 (m), 2962 (w), 2939 (s), 2918 (s), 2883 (s), 2826 (s), 2779 (m), 2232 (s), 1607 (s), 1574 (m), 1511 (s); NMR ($CDCl_3$, 300 MHz) 7.75 (d, 2 H, J = 8), 6.9 (d, 2 H, J = 8), 3.85 (d, 2 H, J = 7), 3.1 (br d, 2 H, J = 10), 2.25 (d, 2 H, J = 7), 2.0 (td, 2 H, J = 8), 1.9–1.75 (m, 3 H), 1.5–1.35 (m, 2 H), 0.9–0.8 (m, 1 H), 0.55–0.45 (m, 2 H), 0.15–0.05 (m, 2 H); HRMS calcd for $C_{17}H_{22}N_2O$ 270.1732, found 270.1727. Anal. ($C_{17}H_{22}N_2O$) C, H, N.

1-Benzyl-4-[(4-fluorophenoxy)methyl]piperidine Hydrochloride Salt (18aa) (Method Q). A mixture of 4-fluorophenol (6.01 g, 54 mmol), triphenylphosphine (6.87 g, 64 mmol), and 1-benzyl-4-(hydroxymethyl)piperidine (11.0 g, 54 mmol) in benzene (300 mL) was stirred at 10–15 °C. Diethyl azodicarboxylate (11.2 g, 10.1 mL, 64 mmol) was added dropwise. The reaction mixture was heated to reflux temperature and stirred for 24 h. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. The residue was dissolved in EtOAc; the organic solution was washed with water three times and then with a 2 N sodium hydroxide solution three times. Standard workup gave the crude product. Column chromatography (EtOAc/hexanes 1:1) gave, after removal of solvent, a pale yellow oil (3.88 g, 24% yield): IR (neat) 3084 (m), 3062 (m), 2921 (s), 2802 (s), 2758 (s), 1601 (m), 1505 (s), 1467 (s), 1454 (s), 1394 (s); NMR ($CDCl_3$, 200 MHz) 7.40–7.25 (m, 5 H), 7.0–6.7 (m, 4 H), 3.75 (d, 2 H, J = 4), 3.50 (s, 2 H), 2.9 (br d, 2 H, J = 4), 2.1–1.25 (m, 7 H); HRMS calcd for $C_{19}H_{22}FNO$ 299.1684, found 299.1685.

The free base was dissolved in ether (100 mL) and mixed with a solution of HCl in ether (1 M, 30 mL, 30 mmol). The precipitate was filtered and washed with ether. Drying in vacuo afforded a white solid (3.7 g, 85% yield): mp 209–211 °C; NMR (DMSO-d_6, 200 MHz) δ 7.70–7.35 (m, 5 H), 7.2–6.8 (m, 4 H), 4.25 (d, 2 H, J = 3), 3.75 (d, 2 H, J = 3), 3.45–3.35 (m, 4 H), 3.1–2.75 (m, 1 H), 2.1–1.5 (m, 5 H). Anal. ($C_{19}H_{22}FNO \cdot HCl \cdot 0.1H_2O$) C, H, N.

1-Carbomethoxy-4-[[(4-fluorobenzyl)oxy]methyl]piperidine (36) (Method R). 1-Benzyl-4-[(4-fluorobenzyl)oxy]piperidine (15.2 g, 48.6 mmol) and methyl chloroformate (4.5 mL, 58 mmol) were dissolved in benzene (150 mL), and the resulting solution was stirred at reflux temperature for 16.5 h. The reaction mixture was cooled to ambient temperature and solvent was removed on a rotary evaporator. Vacuum distillation (bp 163–174 °C, 0.9 Torr) gave the title compound, a colorless oil (13.3 g, 97% yield). Anal. ($C_{15}H_{20}FNO_3$) C, H, N.

4-[(4-Fluorobenzyl)oxy]piperidine (37) (Method S). The above carbamate (13.3 g, 47.3 mmol) and potassium hydroxide (35 g, 625 mmol) were dissolved in a mixture of water (30 mL) and MeOH (120 mL). The mixture was stirred at reflux temperature for 20 h. The reaction mixture was concentrated in vacuo after being cooled to room temperature. The residue was dissolved in EtOAc; the organic solution was washed with

(99) Cain, G. A.; Gilligan, P. J.; Tam, S. W. Antipsychotic Cycloalkylpiperidines. *US5109002*, 1992, 27.

water three times and then with brine. Standard workup gave an oil. Vacuum distillation (bp 116–127 °C, 0.4 Torr) afforded the product, a colorless oil (10.2 g, 87% yield). Anal. ($C_{13}H_{18}$·FNO) C, H, N.

1-(4-Carbomethoxybenzyl)-4-[[(4-fluorobenzyl)oxy]methyl]piperidine Hydrochloride Salt (18as) (Method T). A mixture of 4-[[(4-fluorobenzyl)oxy]methyl]piperidine (3.0 g, 13 mmol), methyl 4-(bromomethyl)benzoate (3.1 g, 13 mmol), and potassium carbonate (2.0 g, 15 mmol) in MeOH (30 mL) was stirred at reflux temperature for 24 h. The reaction mixture was cooled to room temperature for 24 h. The reaction mixture was cooled to room temperature and poured onto water. Three extractions with EtOAc, followed by the standard workup, gave an oil. Recrystallization from chlorobutane, filtration, and drying in vacuo gave a solid (2.8 g, 56% yield): NMR ($CDCl_3$, 200 MHz) δ 8.0 (d, 2 H, J = 8), 7.4 (d, 2 H, J = 8), 7.33–7.26 (m, 2 H), 7.1–7.0 (m, 2 H), 4.45 (s, 2 H), 3.91 (s, 3 H), 3.52 (s, 2 H), 3.31 (d, 2 H, J = 6), 2.9–2.8 (m, 2 H), 2.0–1.2 (m, 7 H); HRMS calcd for $C_{22}H_{26}$·FNO_3 371.1897, found 371.1894.

The free base was dissolved in ether (100 mL) and mixed with a 1 N HCl in ether solution (15 mL). The precipitate was filtered and washed with ether. Drying in vacuo afforded a white solid (2.9 g, 94% yield): mp 188–189 °C. Anal. ($C_{22}H_{26}FNO_3$·HCl) C, H, N.

1-(Cyclopropylmethyl)-4-[2-(4-cyanophenyl)-2-oxoethyl]piperidine Fumarate Salt (6q). A mixture of sodium cyanide (27.5 g, 562 mmol) and **6i** (31 g, 112 mmol) in DMF (250 mL) was stirred at 120 °C for 26 h. The excess solvent was distilled in vacuo; the residue was dissolved in a 1 N sodium hydroxide solution and extracted three times with EtOAc. Standard workup gave an oil.

Column chromatography ($CHCl_3$/MeOH 9:1) afforded an oily solid. The crude product was dissolved in hot ether and filtered. The filtrate was concentrated 3-fold and cooled to ambient temperature. The precipitate was filtered and dried in vacuo. The solid and fumaric acid (23 g, 200 mmol) were dissolved in EtOH (200 mL) with warming. Solvent was removed in vacuo. The residue was recrystallized from acetone. Filtration and drying in vacuo afforded a solid (35 g, 78% yield): mp 149 °C; NMR (DMSO-d_6, 300 MHz) δ 8.15 (d, 2 H, J = 7), 8.05 (d, 2 H, J = 7), 6.5 (s, 2 H), 3.25 (d, 2 H, J = 8), 3.1–3.0 (m, 2 H), 2.6–2.4 (m, 4 H), 2.1–1.9 (m, 1 H), 1.85–1.7 (m, 2 H), 1.5–1.3 (m, 2 H), 1.0–0.9 (m, 1 H), 0.6–0.5 (m, 2 H), 0.3–0.15 (m, 2 H). Anal. ($C_{16}H_{22}N_2O$·$C_4H_4O_4$) C, H, N.

1-(Cyclopropylmethyl)-4-[2-(4-aminophenyl)-2-oxoethyl]piperidine (6p). According to the procedure for **6q**, sodium azide (6.5 g, 100 mmol) was reacted with **6i** (1.0 g, 3.6 mmol). Column chromatography ($CHCl_3$/MeOH 9:1) afforded the title product[98] (0.35 g, 36% yield): mp 140–146 °C dec; NMR ($CDCl_3$, 300 MHz) δ 7.8 (d, 2 H, J = 8), 6.65 (d, 2 H, J = 8), 4.15 (br s, 2 H), 3.10 (br d, 2 H, J = 10), 2.8 (d, 2 H, J = 7), 2.2 (d, 2 H, J = 7), 2.1–1.9 (m, 2 H), 1.75 (br d, 2 H, J = 10), 1.5–1.3 (m, 2 H), 0.95–0.8 (m, 1 H), 0.55–0.45 (m, 2 H), 0.15–0.05 (m, 2 H); MS m/e 272. Anal. ($C_{17}H_{22}N_2O$·0.75H_2O) C, H, N.

1-(Cyclopropylmethyl)-4-[[4-(methylsulfonyl)phenoxy]methyl]piperidine (18l). A mixture of a 1 N NaOH solution (10 mL) and **18k** (0.5 g, 1.5 mmol) was stirred for 15 min and then extracted three times with EtOAc. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. Solvent was removed in vacuo. The residue was taken up in a mixture of MeOH (10 mL) and water (10 mL). Sodium periodate (2.13 g, 10 mmol) was added; the resulting suspension was stirred for 22 h. The reaction mixture was diluted with 250 mL of water, basified with 1 N NaOH solution, extracted three times with EtOAc, and worked up by the standard procedure.

Column chromatography ($CHCl_3$/MeOH 9:1) afforded a solid (0.29 g, 60% yield): mp 134–135 °C; NMR ($CDCl_3$, 300 MHz) 7.85 (d, 2 H, J = 8), 7.0 (d, 2 H, J = 8), 3.9 (d, 2 H, J = 7), 3.15 (br d, 2 H, J = 10), 3.05 (s, 3 H), 2.3 (d, 2 H, J = 7), 2.1 (br t, 2 H, J = 7), 1.95–1.8 (m, 3 H), 1.6–1.4 (m, 2 H), 0.95–0.85 (m, 1 H), 0.6–0.5 (m, 2 H), 0.2–0.1 (m, 2 H); HRMS calcd for $C_{17}H_{25}$·NO_3S 323.1555, found 323.1554.

1-(Cyclopropylmethyl)-4-[[(4-fluorophenyl)sulfonyl]methyl]piperidine (23) and 1-(Cyclopropylmethyl)-4-[[(4-fluorophenyl)sulfinyl]methyl]piperidine (22). Compound **18bt** (1.0 g, 3.6 mmol) was reacted with sodium periodate (7.7 g, 36 mmol) in MeOH (30 mL) and water (30 mL for 21.5 h) with stirring. The reaction mixture was diluted with water (500 mL), basified with a 1 N NaOH solution, extracted three times with EtOAc, and worked up by the standard procedure.

Column chromatography ($CHCl_3$/MeOH 9:1) gave two products. (1) **23** (R_f = 0.3, 367 mg, 33% yield): mp 73 °C; NMR ($CDCl_3$, 200 MHz) δ 7.95 (dd, 2 H, J = 7, 2), 7.25 (dd, 2 H, J = 8, 2), 3.1–2.95 (m, 2 H), 3.05 (d, 2 H, J = 7), 2.25 (d, 2 H, J = 7), 2.1–1.85 (m, 5 H), 1.55–1.4 (m, 2 H), 0.9–0.8 (m, 1 H), 0.55–0.45 (m, 2 H), 0.15–0.05 (m, 2 H). Anal. ($C_{16}H_{22}FNO_2S$) C, H, N, F, S,; (2) **22** (R_f = 0.17, 90 mg, 8% yield): NMR ($CDCl_3$, 200 MHz) δ 7.65 (dd, 2 H, J = 7, 2), 7.25 (dd, 2 H, J = 8, 2), 3.1 (br t, 2 H, J = 9), 2.85 (dd, 1 H, J = 10, 2), 2.5 (dd, 1 H, J = 10, 8), 2.4–2.2 (m, 2 H), 2.15–1.9 (m, 4 H), 1.8–1.7 (m, 1 H), 1.55–1.4 (m, 2 H), 0.9–0.8 (m, 1 H), 0.6–0.45 (m, 2 H), 0.15–0.05 (m, 2 H); HRMS calcd for $C_{16}H_{22}FNOS$ 295.1406, found 295.1409.

1-Benzyl-4-[2-(4-hydroxyphenyl)-2-oxoethyl]piperidine (6d). According to the procedure of method G, 1-benzyl-4-(formylmethyl)piperidine (2.0 g, 9.2 mmol), magnesium mesh (0.14 g, 13.8 mmol), and 1-bromo-4-[(*tert*-butyldimethylsilyl)oxy]benzene[95] (3.96 g, 13.8 mmol) were reacted in dry THF. After workup, column chromatography (EtOAc) afforded 1-benzyl-4-[2-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-2-hydroxyethyl]piperidine (R_f = 0.2, 1.74 g, 40% yield): NMR ($CDCl_3$, 300 MHz) δ 7.5–7.3 (m, 7 H), 6.8 (d, 2 H, J = 8), 4.8–4.7 (m, 1 H), 3.5 (s, 2 H), 2.8 (br d, 2 H, J = 10), 2.0–1.2 (m, 10 H), 1.0 (s, 9 H), 0.2 (s, 6 H); MS m/e 425.

According to the procedure of method F, the above alcohol, oxalyl chloride (0.74 g, 0.51 mL, 5.9 mmol), dimethyl sulfoxide (0.92 g, 0.83 mL, 11.7 mmol), and triethylamine (1.48 g, 2.0 mL, 14.7 mmol) were reacted. After workup, column chromatography (EtOAc) gave 1-benzyl-4-[2-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-2-oxoethyl]piperidine (R_f = 0.36, 1.2 g, 69% yield): NMR ($CDCl_3$, 300 MHz) δ 7.85 (d, 2 H, J = 7), 7.4–7.2 (m, 5 H), 6.8 (d, 2 H, J = 8), 3.5 (s, 2 H), 2.85 (br d, 2 H, J = 9), 2.85 (d, 2 H, J = 7), 2.0–1.1 (m, 7 H), 1.0 (s, 9 H), 0.2 (s, 6 H); MS m/e 423.

The above ketone was dissolved in dry THF (10 mL); a solution of tetra-*n*-butylammonium fluoride in THF (1 M, 5.7 mL, 5.7 mmol) was added with stirring. The mixture was stirred for 16 h, and then quenched with water (50 mL). Extraction with ether three times and the standard workup gave a brown oily solid. Trituration with EtOAc, filtration, and drying in vacuo afforded a pale yellow solid (238 mg, 27% yield): mp 197–198 °C; NMR ($CDCl_3$, 300 MHz) δ 7.8 (d, 2 H, J = 8), 7.4–6.8 (m, 7 H), 3.5 (s, 2 H), 3.2–3.0 (m, 4 H), 2.9 (dd, 4 H, J = 10, 7), 2.5 (s, 1 H), 2.1–1.2 (m, 9 H); MS m/e 309. Anal. ($C_{20}H_{23}NO_2$·0.25H_2O) C, H, N.

1-Benzyl-4-[2-[4-(hydroxymethyl)phenyl]-2-oxoethyl]piperidine (6f). According to the procedure used for **6d** above, using 1-bromo-4-[[(*tert*-butyldimethylsilyl)oxy]methyl]benzene, a white solid was obtained in 10% overall yield: mp 154–155 °C; NMR ($CDCl_3$, 300 MHz) 7.9 (d, 2 H, J = 8), 7.5–7.2 (m, 7 H), 4.8 (s, 2 H), 3.5 (s, 2 H), 2.8 (br d, 4 H, J = 8), 2.0–1.2 (m, 9 H); MS m/e 323. Anal. ($C_{21}H_{26}NO_2$·0.5H_2O) C, H, N.

1-Benzyl-4-[2-[4-(methylsulfonyl)phenyl]-2-oxoethyl]piperidine (6g) and 1-Benzyl-4-[2-[4-(methylsulfinyl)phenyl]-2-oxoethyl]piperidine (6h). According to the procedure for **22** and **23** above, **6c** (2.18 g, 6.4 mmol) and sodium periodate (13.7 g, 64.2 mmol) were reacted in methanol/water (1:1, 65 mL). After workup, column chromatography ($CHCl_3$/MeOH 9:1) gave **6g** and **6h**. (1) **6g** (R_f = 0.63, 165 mg, 7% yield): mp 135–137 °C; NMR ($CDCl_3$, 300 MHz) δ 8.1 (q, 4 H, J = 7), 7.4–7.2 (m, 5 H), 3.5 (s, 2 H), 3.1 (s, 3 H), 2.9 (d, 2 H, J = 7), 2.0–1.2 (m, 9 H); MS m/e 371. Anal. ($C_{21}H_{25}NO_3S$) C, H, N, S. (2) **6h** (R_f = 0.48, 690 mg, 30% yield): mp 135–136 °C; NMR ($CDCl_3$, 300 MHz) δ 8.1 (d, 2 H, J = 7), 7.75 (d, 2 H, J = 7), 7.4–7.2 (m, 5 H), 3.5 (s, 2 H), 2.9 (d, 4 H, J = 7), 2.8 (s, 3 H), 2.0–1.2 (m, 7 H); MS m/e 355. Anal. ($C_{21}H_{25}NO_2S$) C, H, N, S.

4-[2-(4-Fluorophenyl)-2-oxoethyl]piperidine (24). 4-[2-(4-Fluorophenyl)-2-oxoethyl]pyridine (10.0 g, 46.5 mmol), platinum dioxide (1.0 g), and glacial acetic acid (200 mL) were shaken in a Parr apparatus at atmospheric pressure for 8 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was taken up in a 3 N NaOH solution (300 mL) and extracted three times with EtOAc. Standard workup gave a crude mixture of the product and its corresponding alcohol.

The crude material was reacted with di-*tert*-butyl dicarbonate (10.9 g, 50 mmol) and NaOH pellets (2 g, 50 mmol) in dry THF (100 mL) (mild exotherm initially). The reaction mixture was stirred for 24 h, and then it was poured on to a 1 N NaOH solution (200 mL) and extracted three times with EtOAc (100 mL). Standard workup gave an oil. Column chromatography (EtOAc/hexanes 1:4) afforded 1-[(*tert*-butyloxy)carbonyl]-4-(2-(4-fluorophenyl)-2-oxoethyl)piperidine (R_f = 0.2, 4.4 g): NMR ($CDCl_3$, 300 MHz) δ 7.95 (dd, 2 H, J = 8, 6), 7.15 (t, 2 H, J = 8), 4.2–4.0 (m, 2 H), 2.9 (d, 2 H, J = 7), 2.85–2.7 (m, 2 H), 2.25–2.1 (m, 1 H), 1.75 (br d, 2 H, J = 8), 1.5 (s, 9 H), 1.4–1.1 (m, 2 H); MS m/e 321.

The above carbamate was reacted with trifluoroacetic acid (45 mL) at reflux temperature for 20 h. The excess solvent was distilled and the residue was treated with a 2 N NaOH solution. Three extractions with EtOAc (75 mL) and the standard workup gave a yellow wax (3.2 g, 31% yield): mp 39–40 °C; NMR ($CDCl_3$, 300 MHz) δ 8.0 (dd, 2 H, J = 8, 6), 7.15 (t, 2 H, J = 8), 3.1 (br d, 2 H, J = 10), 2.9 (d, 2 H, J = 7), 2.7 (t, 2 H, J = 7), 2.75–2.5 (m, 2 H), 2.25–2.05 (m, 1 H), 1.8 (d, 2 H, J = 10), 1.4–1.2 (m, 2 H), 1.0–0.8 (m, 1 H); CI-HRMS calcd for $C_{13}H_{16}FNO$ 222.1294 (M + 1), found 222.1289.

1-[2-(3-Indolyl)ethyl]-4-[2-(4-fluorophenyl)-2-oxoethyl]-piperidine (6t). A solution of **24** (1.0 g, 4.5 mmol), 3-(2-bromoethyl)indole (1.1 g, 5 mmol), and triethylamine (5.0 g, 7.0 mL, 50 mmol) in dry THF (50 mL) was stirred at reflux temperature for 22 h. The reaction mixture was cooled to ambient temperature and poured onto a 1 N NaOH solution (100 mL) and mixed. Three extractions with EtOAc (100 mL) and the standard workup gave an oil. Column chromatography (EtOAc/MeOH 9:1) afforded a pale yellow solid (R_f = 0.1, 663 mg, 40% yield): mp 135–140 °C dec; NMR (DMSO-d_6, 300 MHz) δ 10.8 (s, 1 H), 8.05 (dd, 2 H, J = 8, 6), 7.55 (d, 1 H, J = 8), 7.4–7.25 (m, 3 H), 7.15 (s, 1 H), 7.05 (t, 1 H, J = 8), 6.95 (t, 1 H, J = 8), 3.2–2.8 (m, 4 H), 2.75–2.6 (m, 2 H), 2.25–2.0 (m, 2 H), 2.0–1.8 (m, 2 H), 1.7 (br d, 2 H, J = 8), 1.45–1.2 (m, 2 H), 0.95–0.75 (m, 2 H); MS m/e 364. Anal. ($C_{23}H_{25}FN_2O\cdot H_2O$) C, H, N.

1-(4-Pyridylmethyl)-4-[2-(4-fluorophenyl)oxoethyl]-piperidine Bismaleate Salt (11b). A mixture of 11a (3.5 g, 11.3 mmol), 10% palladium-on-carbon (3.5 g), and ammonium formate (7 g, 113 mmol) in purged methanol (100 mL) was stirred at reflux temperature for 45 min. The reaction mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated in vacuo. The residue was treated with a 1 N NaOH solution (100 mL) and extracted three times with EtOAc. Standard workup gave a clear yellow liquid.

The crude debenzylated material was reacted with picolyl chloride hydrochloride (0.33 g, 2.0 mmol) and triethylamine (1.0 g, 1.4 mL, 10 mmol) in dry THF (10 mL) at reflux temperature for 20 h. The mixture was cooled to room temperature, poured onto a 1 N NaOH solution (50 mL), and extracted with EtOAc (50 mL) three times. Standard workup gave an oil. Chromatography ($CHCl_3$/MeOH 9:1) afforded an oil (R_f 0.4, 216 mg): NMR ($CDCl_3$, 200 MHz) δ 8.5 (d, 2 H, J = 6), 7.4–6.95 (m, 6 H), 3.75 (s, 2 H), 2.95–2.80 (m, 2 H), 2.55–2.4 (m, 1 H), 2.15–1.6 (m, 8 H); HRMS calcd for $C_{19}H_{21}FN_2O$ 312.1638, found 312.1642.

The oil was dissolved in ether and treated with an excess of a saturated solution of maleic acid in ether. The precipitate was filtered, washed with ether, and dried in vacuo to give a white powder (206 mg, 3% yield): mp 108–109 °C; NMR ($CDCl_3$, 200 MHz) δ 8.65 (d, 2 H, J = 6), 7.5 (d, 2 H, J = 6), 7.3–6.95 (m, 4 H), 6.25 (s, 4 H), 4.25 (s, 2 H), 3.4–3.2 (m, 2 H), 3.05–2.65 (m, 3 H), 2.2–1.7 (m, 4 H). Anal. ($C_{19}H_{21}FN_2O\cdot 2(C_4H_4O_4)\cdot 0.75H_2O$) C, H, N.

1-[4-(4-Fluorophenyl)-4-oxobutyl]-4-[2-(4-fluorophenyl)-1-oxoethyl]piperidine (11d). According to the procedure for **11b** above, 11a (1.0 g, 3.2 mmol) was debenzylated and the crude material was reacted with 4-chloro-4′-fluorobutyrophenone, ethylene glycol ketal[97] (1.1 g, 4.4 mmol), potassium carbonate (2.76 g, 20 mmol), and potassium iodide (1.66 g, 10 mmol) in acetonitrile (25 mL) at reflux temperature for 24 h. The reaction mixture was cooled to ambient temperature, poured onto water (100 mL), extracted three times with EtOAc (75 mL), and worked up by the standard method. Column chromatography (EtOAc/MeOH 9:1) afforded a yellow oil (R_f 0.3, 195 mg): NMR ($CDCl_3$, 200 MHz) δ 7.5–6.9 (m, 8 H), 4.1–3.9 (m, 4 H), 2.7–2.55 (m, 3 H), 3.0–2.9 (m, 2 H), 2.1–1.5 (m, 10 H); MS m/e 429.

The ketal was taken up in a mixture of ethanol (2 mL) and a 3 N HCl solution (0.5 mL). The reaction mixture was stirred for 24 h. Solvent was removed in vacuo; the residue was treated with a 1 N NaOH solution (10 mL) and extracted three times with EtOAc (10 mL). Standard workup gave an oil. Recrystallization from dichloromethane–hexanes and drying in vacuo afforded a pale yellow solid (54 mg, 6% yield): mp 99–100 °C; NMR ($CDCl_3$, 200 MHz) δ 8.05–7.9 (m, 2 H), 7.2–6.95 (m, 6 H), 3.7 (s, 2 H), 3.05–2.8 (m, 4 H), 2.5–2.3 (m, 3 H), 2.05–1.5 (m, 8 H); HRMS calcd for $C_{23}H_{25}F_2NO_2$ 385.1853, found 385.1851.

1-Benzyl-3-[2-(4-fluorophenyl)-2-oxoethyl]piperidine (25). A solution of benzoyl chloride (28.1 g, 200 mmol) in THF (250 mL) was added dropwise to a stirred solution of 3-piperidinemethanol (17.9 g, 155 mmol) and triethylamine (60.7 g, 600 mmol) in THF (250 mL) over 1 h. The resulting suspension was stirred for 48 h. Solvent was removed in vacuo; the residue was treated with a 2 N NaOH solution (500 mL) and extracted three times with dichloromethane (200 mL). Standard workup gave an oil. Vacuum distillation (bp 185–190 °C, 0.3 Torr) afforded 1-benzoyl-3-piperidinemethanol (26.2 g), which was contaminated with its dibenzoyl derivative.

The crude product from above was reacted with lithium aluminum hydride (11.4 g, 300 mmol) in dry THF (300 mL) at reflux temperature for 17 h using mechanical stirring. After being cooled to ambient temperature, the reaction mixture was quenched carefully with ethyl acetate (1 L), followed by water (12 mL), a 2 N NaOH solution (12 mL), and water (36 mL) with vigorous stirring. The inorganic salts were filtered; the filtrate was dried over magnesium sulfate and filtered. Solvent was removed in vacuo. Column chromatography (EtOAc) afforded 1-benzyl-3-piperidinemethanol (7.6 g, 24% overall yield from 3-piperidinemethanol): NMR ($CDCl_3$, 200 MHz) δ 7.4–7.2 (m, 5 H), 3.7–3.4 (m, 2 H), 3.5 (s, 2 H), 3.2–3.0 (br s, 1 H), 2.85 (br d, 1 H, J = 7), 2.7–2.5 (m, 1 H), 2.25–1.95 (m, 2 H), 1.85–1.5 (m, 4 H), 1.2–1.0 (m, 1 H); HRMS calcd for $C_{13}H_{19}NO$ 205.1467, found 205.1454.

The above alcohol was reacted with oxalyl chloride (6.33 g, 4.35 mL, 50 mmol), dimethyl sulfoxide (7.8 g, 7.1 mL, 100 mmol), and triethylamine (14.3 g, 19.7 mL, 141 mmol) in dichloromethane (500 mL) using the procedure described in method F above. Column chromatography (EtOAc/hexanes 1:1) gave 1-benzyl-3-formylpiperidine (6.1 g, 81% yield): NMR ($CDCl_3$, 200 MHz) δ 9.65 (d, 1 H, J = 1), 7.4–7.2 (m, 5 H), 3.6–3.4 (m, 2 H), 2.8–2.65 (m, 1 H), 2.55–2.25 (m, 5 H), 1.8–1.5 (m, 5 H); MS m/e 203.

The above aldehyde was reacted with (methoxymethyl)-triphenylphosphonium chloride (12 g, 35 mmol), diisopropylamine (3.54 g, 4.9 mL, 35 mmol) and butyllithium (2.5 M in hexanes, 14 mL, 35 mmol) in dry THF (150 mL), followed by treatment with a 4 N HCl solution (38 mL) in THF (15 mL), using the procedure described in method H above to give 1-benzyl-3-(formylmethyl)piperidine (3.1 g, 48% yield): NMR ($CDCl_3$, 300 MHz) δ 9.7 (t, 1 H, J = 0.5), 7.4–7.2 (m, 5 H), 3.5 (s, 2 H), 2.8–2.6 (m, 2 H), 2.4–1.5 (m, 8 H), 1.15–0.9 (m, 1 H); MS m/e 217.

The above aldehyde was reacted with a solution of (4-fluorophenyl)magnesium bromide in ether (2 M, 14 mL, 28 mmol) in dry THF (100 mL) using the procedure described in method G above to produce 1-benzyl-3-[2-(4-fluorophenyl)-2-hydroxyethyl]piperidine (3.88 g, 87% yield) after chromatography (EtOAc/hexanes 1:1): NMR ($CDCl_3$, 200 MHz) δ 7.4–7.2 (m, 7 H), 7.0 (t, 2 H, J = 7), 4.7–4.6 (m, 1 H), 3.45 (s, 2 H), 2.8–2.5 (m, 2 H), 2.225–0.85 (m, 10 H); HRMS calcd for $C_{20}H_{24}FNO$ 313.1842, found 313.1846.

The above alcohol was reacted with oxalyl chloride (1.88 g, 14.8 mmol), dimethyl sulfoxide (2.3 g, 2.1 mL, 14.8 mmol), and triethylamine (3.92 g, 5.4 mL, 38.8 mmol) in dichloromethane (110 mL), using method F, to generate 1-benzyl-3-[2-(4-fluorophenyl)-2-oxoethyl]piperidine (2 g, 59% yield): mp 112–113 °C; NMR ($CDCl_3$, 200 MHz) δ 7.9 (dd, 2 H, J = 8, 6), 7.35–7.25 (m, 5 H), 7.1 (t, 2 H, J = 8), 4.55 (d, 1 H, J = 14), 4.45 (d, 1 H, J = 14), 3.0–2.65 (m, 5 H), 2.45–2.25 (m, 1 H), 2.1–0.9 (m, 6 H); HRMS calcd for $C_{20}H_{22}FNO$ 311.1685, found 311.1675.

1-Benzyl-2-[2-(4-fluorophenyl)-2-oxoethyl]piperidine Maleate Salt (26). This product was prepared by following the procedure described for compound **25** above.

Piperidine-2-ethanol (20 g, 155 mmol) was reacted with benzoyl chloride (28.1 g, 200 mmol) and triethylamine (60.7 g, 600 mmol)

in THF (1 L) to afford 1-benzoyl-2-piperidineethanol, contaminated with its dibenzoyl derivative (23.2 g): bp 175–180 °C (0.5 Torr).

The above material (13 g) was then reacted with LAH (7.6 g, 200 mmol) in dry THF (200 mL) to give 1-benzyl-2-piperidineethanol (4.4 g, 34% yield) after chromatography (EtOAc): NMR ($CDCl_3$, 200 MHz) δ 7.4–7.2 (m, 5 H), 5.2–4.7 (m, 1 H), 4.2 (d, 1 H, J = 14), 4.0–3.8 (m, 1 H), 3.7–3.6 (m, 1 H), 3.5 (d, 1 H, J = 14), 3.1–2.7 (m, 2 H), 2.25–1.2 (m, 8 H); MS 219.

The above alcohol was reacted with oxalyl chloride (3.43 g, 27 mmol), dimethyl sulfoxide (4.23 g, 54.1 mmol), and triethylamine (7.73 g, 76.4 mmol) in dichloromethane (350 mL) to generate 1-benzyl-2-(formylmethyl)piperidine (3.0 g, 68% yield) after chromatography (EtOAc): NMR ($CDCl_3$, 200 MHz) δ 9.8 (t, 1 H, J = 1), 7.4–7.2 (m, 5 H), 3.85 (d, 1 H, J = 13), 3.25 (d, 1 H, J = 13), 3.05–2.85 (m, 1 H), 2.75–2.5 (m, 3 H), 2.25–1.3 (m, 7 H); HRMS calcd for $C_{14}H_{19}NO$ 217.1467, found 217.1463.

The above aldehyde was reacted with a solution of (4-fluorophenyl)magnesium bromide in ether (2 M, 15 mL, 30 mmol) in dry THF (100 mL) to produce 1-benzyl-2-[2-(4-fluorophenyl)-2-hydroxyethyl]piperidine (3.88 g, 87% yield) after chromatography ($CHCl_3$/MeOH 9:1): NMR ($CDCl_3$, 200 MHz) δ 7.4–7.2 (m, 5 H), 7.1–6.9 (m, 4 H), 5.25–5.1 (m, 1 H), 4.8 (br d, 1 H, J = 13), 3.95 (br s, 2 H), 3.35–2.9 (m, 4 H), 2.7–2.6 (m, 2 H), 2.4–1.2 (m, 7 H); HRMS calcd for $C_{20}H_{24}FNO$ 313.1842, found 313.1850.

The above alcohol was reacted with oxalyl chloride (1.88 g, 14.8 mmol), dimethyl sulfoxide (2.3 g, 29.5 mmol), and triethylamine (3.92 g, 38.8 mmol) in dichloromethane (110 mL) to generate the title product as its free base (1.94 g) after chromatography (EtOAc/hexanes 1:1). The oil was dissolved in ether and treated with a saturated solution of maleic acid in ether (50 mL). The solution was decanted and the crude past was triturated with copious amounts of ether. Drying in vacuo at 60 °C afforded a white powder (1.7 g, 37% yield): mp 122–124 °C; NMR (DMSO-d_6, 200 MHz) δ 8.25–8.05 (m, 2 H), 7.65–7.35 (m, 7 H), 6.0 (s, 2 H), 4.75–2.9 (m, 6 H), 2.1–1.5 (m, 6 H). Anal. ($C_{20}H_{22}FNO \cdot C_4H_4O_4$) C, H, N.

Pharmacology. The in vitro assays and animal models are described in full detail in the literature.[78-80,83-86,89-94]

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