Novel 1-Phenylcycloalkanecarboxylic Acid Derivatives Are Potent and Selective σ_1 Ligands†

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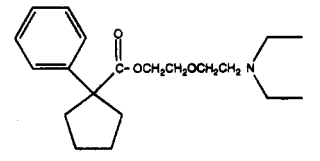
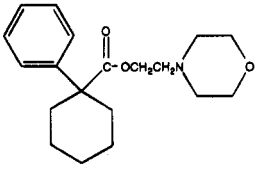
Carbetapentane (**1**, 2-[2-(diethylamino)ethoxy]ethyl 1-phenyl-1-cyclopentanecarboxylate) binds with high affinity to σ sites and is a potent antitussive, anticonvulsant, and spasmolytic agent. However, carbetapentane interacts at muscarinic binding sites as well, and it is not clear whether either of these receptor systems is involved in the mechanism(s) of action(s) of this drug. In an attempt to determine whether these psychoactivities can be attributed to interaction at σ sites, a series of carbetapentane analogs were prepared. Phenyl ring substitution; contraction, expansion, and replacement with a methyl group of the cyclopentyl ring; replacement of the carboxylate function with an amide, methyl ether, and methylamine; and replacement of the *N*,*N*-diethyl substituent with a morpholino or piperidino moiety were investigated. All of these novel analogs were evaluated for binding to σ_1 and σ_2 sites, and comparison of binding at muscarinic m_1 and m_2 and PCP (1-(1-phenylcyclohexyl)piperidine) receptors was performed. All of the compounds were selective for σ_1 over σ_2 sites, with the three most selective analogs being compounds **34** (65-fold), **35** (78-fold), and **39** (51-fold). None of the compounds were active at PCP sites, and chemical modification including (1) replacing the ester function, (2) replacing the cyclopentyl ring with a smaller ring system (cyclopropyl) or a methyl group, and (3) replacing the diethylamino moiety with a morpholino group resulted in >220-fold selectivity over muscarinic receptor binding. Therefore, several of these novel compounds are potent, σ_1-selective ligands which can now be investigated as potential antitussive, anticonvulsant, and antiischemic agents. These studies may reveal whether σ_1 sites play a role in the pharmacological actions of these drugs.

Carbetapentane (**1**, 2-[2-(diethylamino)ethoxy]ethyl 1-phenyl-1-cyclopentanecarboxylate) binds with high affinity to σ sites ([^{3}H]-(+)-3-PPP ((+)-3-(3-hydroxyphenyl)-*N*-propylpiperidine; K_i = 11 nM), [^{3}H]dextromethorphan (K_i = 11 nM), [^{3}H]-(+)-pentazocine (K_i = 32 nM))[1,2] and demonstrates anticonvulsant,[3] antitussive,[4] and spasmolytic[5] actions. Although the mechanisms for these actions have not been determined, some of them are characteristic of other compounds that interact at σ binding sites (i.e., dextromethorphan).[6] We have prepared a number of analogs of both carbetapentane[7] and dextromethorphan[8] and evaluated them as potential anticonvulsant agents in the rat maximal electroshock model. Structure–activity relationships have been derived for these series of compounds, reflecting optimal structural requirements for anticonvulsant action.

The characterization of σ binding sites through the evaluation of numerous structurally diverse compounds has lead to the identification of drugs with important therapeutic utility as atypical antipsychotics, anticonvulsants, neuroprotectants, and antitussives, which all



1



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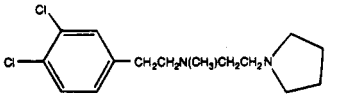

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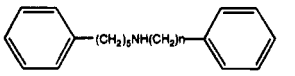

4

bind to these sites (for review, see refs 9 and 10). However, it remains unclear whether the psychoactivities of these drugs can be attributed to their interaction at σ binding sites since most of these agents bind at other receptor systems including dopamine-D_2, PCP (1-(1-phenylcyclohexyl)piperidine), and muscarinic receptors. Another complicating factor is the as of yet undetermined agonist–antagonist profile at these sites. In addition, there is generally a disparity in comparing potencies of these ligands in functional and behavioral assays and their binding affinities to σ sites.[9,10] Subtypes of the σ binding sites exist, and to date, σ_1 ([^{3}H]-(+)-SKF 10047 ((+)-*N*-allylnormetazocine) in the presence of cold MK 801 ((+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine; dizocilpine), PCP, or [^{3}H]-(+)-pentazocine) and σ_2 ([^{3}H]DTG (1,3-di(2-tolyl)-guanidine) in the presence of cold pentazocine or (+)-

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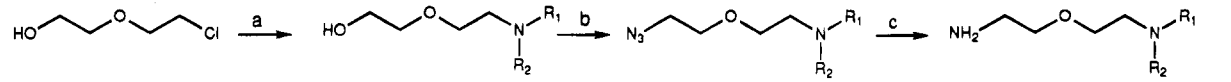
Scheme 1[a]



5

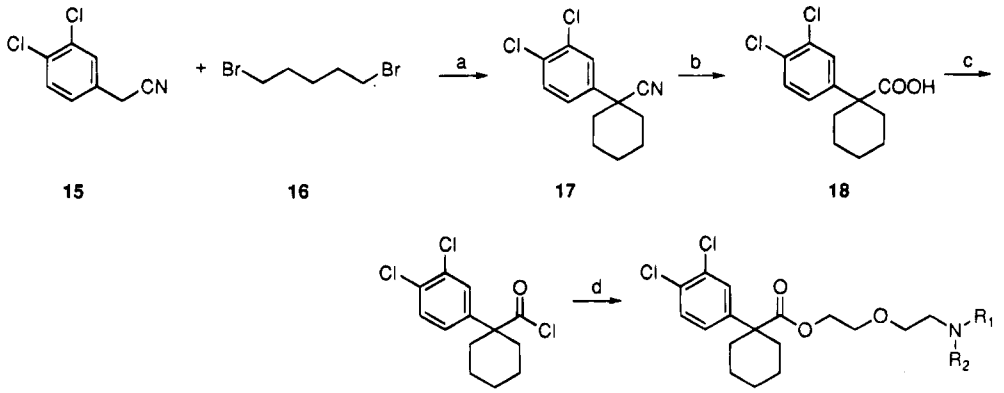
6; R_1=R_2= -CH_2-CH_3
7; R_1-R_2 = -$(CH_2)_4$-
8; R_1-R_2 = -$(CH_2)_2$-O-$(CH_2)_2$-

9; R_1=R_2= -CH_2-CH_3
10; R_1-R_2= -$(CH_2)_4$-
11; R_1-R_2=-$(CH_2)_2$-O-$(CH_2)_2$-

12; R_1=R_2= -CH_2-CH_3
13; R_1-R_2 = -$(CH_2)_4$-
14; R_1-R_2 = -$(CH_2)_2$-O-$(CH_2)_2$-

[a] (a) Amine (morpholine or pyrrolidine)/K_2CO_3/toluene; (b) ZnN_6·2Pyr/DIAD/Ph_3P; (c) H_2/10% Pd/C.

Scheme 2[a]



15 16 17 18

19

20; R_1=R_2= -CH_2-CH_3
21; R_1, R_2= -$(CH_2)_4$-
22; R_1, R_2= -$(CH_2)_2$-O-$(CH_2)_2$-

[a] (a) NaH/DMSO; (b) 40% KOH/diethylene glycol; (c) $SOCl_2$/benzene; (d) **6**, **7**, or **8**/Et_3N/toluene.

SKF 10047) sites have been characterized.[11-13] Perhaps with increased knowledge regarding neuroanatomical location and structural requirements of drugs that bind selectively to these subtypes, functional roles will ultimately be revealed.[13]

In the past three years, the development of very potent and selective σ ligands has led to proposed binding site models. In general, limited stereochemical and topographical requirements have been determined,[14,15] although more specific structural requirements, within a series of structurally similar molecules, have been proposed.[16-26] Recently, a series of compounds derived from PCP but structurally similar to carbetapentane were described.[16] Several potent σ ligands were identified in this series of compounds, and one derivative, PRE-084 (**2**, 2-(4-morpholino)ethyl 1-phenylcyclohexane-1-carboxylate) (K_i = 44 nM, [^{3}H]-(+)-SKF 10047), was very selective over the following receptors: PCP, dopamine-D_2, muscarinic, α- and β-adrenergic, and serotonin$_2$ (5-HT_2).[16] Structure-activity relationships revealed the following structural moieties for optimal σ binding affinity and selectivity: 3-Cl substitution in the phenyl ring, cyclohexane ring, ethyl carboxylate function, *N*-morpholino, piperidino, or pyrrolidino, with the morpholino providing highest selectivity.

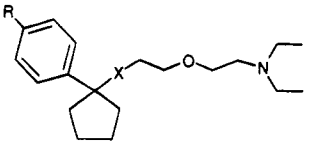
Another series of compounds that share several of these structural features have been described by deCosta et al.[19,27] *N*-[2-(3,4-Dichlorophenyl)ethyl]-*N*-methyl-2-(1-pyrrolinyl)ethylamine (**3**) and structurally related analogs have been shown to bind to σ sites with subnanomolar affinities (K_i = 0.34 nM, [^{3}H]-(+)-3-PPP).[19] In this series, optimal σ binding was achieved with a 3,4-dichlorophenyl ring and a diamino system, one of which was substituted with a small alkyl group and the other tied into a pyrrolidino ring (increasing this ring size resulted in slightly more potent analogs).[19] Some flexibility in distance between the nitrogens and the phenyl ring was allowed, but in a structurally related series of compounds, i.e., **4**, this distance was found to be more flexible (n = 1-4, $K_i \cong$ 2 nM, [^{3}H]-DTG).[22,28]

Carbetapentane (**1**) most closely resembles PRE-084 (**2**) and its analogs but also shares structural features of other potent σ ligands.[16,19,22] Therefore, in an effort to further characterize structure-activity relationships within this series of compounds, we incorporated many of the above described moieties into the carbetapentane structure to optimize binding to σ sites. Phenyl ring substitution and contraction, expansion, and replacement with a methyl group of the cyclopentyl ring were explored as well as replacement of the carboxylate function with an amide, methyl ether, and methylamine. Finally, tying the *N*,*N*-diethyl substituent into a morpholino or piperidino function was investigated. All of these novel analogs were evaluated in binding assays specifically designed for labeling σ_1 and σ_2 sites.[13,29] Comparison of binding at muscarinic m_1 and m_2 and PCP receptors was performed to demonstrate σ_1 selectivity.

Chemistry

The compounds were prepared according to the reactions outlined in Schemes 1-4. The side chains were synthesized by N-alkylation of the alkyl chloride **5** with the appropriate amine. The azides were obtained by treatment of the primary alcohols **6**-**8** with zinc azide, in the form of the bis(pyridine) complex under Mitsunobu conditions.[30] Catalytic reduction of the azides **9**-**11** gave the diamino side chains **12**-**14**. In Scheme 2, the synthesis of 1-(3,4-dichlorophenyl)-1-cyclohexanecarbonitrile (**17**) was accomplished by treating 3,4-dichlorophenylacetonitrile (**15**) with 1,5-dibromopentane (**16**) in DMSO using NaH as a base.[31] Basic hydrolysis of the nitrile gave the carboxylic acid deriva-

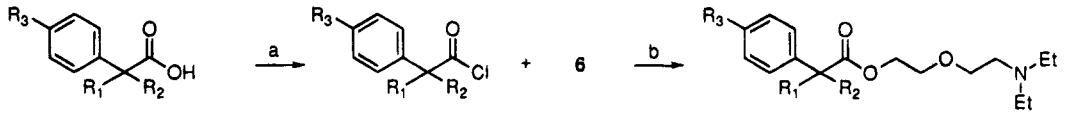
Table 1. Binding Data for Carbetapentane Analogs[a]



compd	X	R	σ_1[c]	σ_2[c]	σ_2/σ_1	PCP[d]	m_1[d]	m_2[d]	m_1/σ_1
SKF			67 (29)	NT		IA	NT	NT	
DTG			NT	42 (27)		IA	NT	NT	
atropine			NT	NT		NT	2 (13)	1 (11)	
1	CO_2	H	41 (16)	894 (18)	22	IA	76 (9)	167 (19)	1.9
36	CO_2	Cl	24 (13)	648 (23)	27	IA	75 (8)	97 (12)	3.1
37	CO_2	OCH_3	59 (19)	1500 (15)	25	IA	1058 (29)	692 (29)	18
40[b]	CONH	H	215 (12)	2840 (18)	13	IA	>10000	4900 (39)	>46
41[b]	CH_2O	H	27 (19)	463 (24)	17	IA	910 (14)	844 (26)	34
42[b]	CH_2NH	H	884 (10)	1100 (38)	1.2	IA	1697 (24)	2271 (25)	1.9
43[b]	$CH_2N(CH_3)$	H	34 (14)	1100 (29)	32	IA	843 (24)	1569 (24)	25

[a] K_i values in nM (% error) are means of N determinations, each performed in triplicate. [b] Synthesis is described in ref 7. [c] $N = 3$. [d] $N = 2-3$. NT = not tested. IA = inactive at concentrations up to 100 μM.

Scheme 3[a]



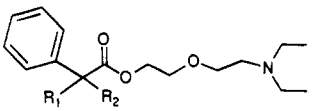
23; R_1-R_2= -$(CH_2)_5$-, R_3= H
24; R_1-R_2= -$(CH_2)_2$-, R_3= H
25; R_1= CH_3, R_2= H, R_3= H
26; R_1-R_2= -$(CH_2)_4$-, R_3=Cl
27; R_1-R_2= -$(CH_2)_4$-, R_3= -OCH_3

28; R_1-R_2= -$(CH_2)_5$-, R_3= H
29; R_1-R_2= -$(CH_2)_2$-, R_3= H
30; R_1= CH_3, R_2= H, R_3= H
31; R_1-R_2= -$(CH_2)_4$-, R_3=Cl
32; R_1-R_2= -$(CH_2)_4$-, R_3= -OCH_3

33; R_1-R_2= -$(CH_2)_5$-, R_3= H
34; R_1-R_2= -$(CH_2)_2$-, R_3= H
35; R_1= CH_3, R_2= H, R_3= H
36; R_1-R_2= -$(CH_2)_4$-, R_3=Cl
37; R_1-R_2= -$(CH_2)_4$-, R_3= -OCH_3

[a] (a) $SOCl_2$/benzene; (b) Et_3N/toluene.

Table 2. Binding Data for Carbetapentane Analogs[a]



compd	R_1/R_2	σ_1[b]	σ_2[b]	σ_2/σ_1	PCP[c]	m_1[c]	m_2[c]	m_1/σ_1
33	$-(CH_2)_5-$	34 (17)	780 (21)	23	IA	135 (12)	145 (15)	4.0
34	$-(CH_2)_2-$	45 (15)	2910 (19)	65	IA	>10000	>10000	>220
35	CH_3/H	40 (14)	3110 (11)	78	IA	>10000	>10000	>250

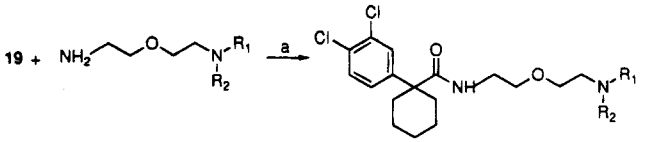
[a] K_i values in nM (% error) are means of N determinations, each performed in triplicate. [b] $N = 3$. [c] $N = 2-3$. IA = inactive at concentrations up to 100 μM.

tive **18** which was converted to the acid chloride **19** with thionyl chloride. The ester derivatives **20**–**22** were synthesized by reaction of the acid chloride **19** and the corresponding alcohol **6**–**8**. In Scheme 3, conversion of the carboxylic acids **23**–**27** to the acid chlorides **28**–**32** and then reaction with the corresponding alcohol **6** followed the same sequence as described in Scheme 2, to obtain the esters **33**–**37**. In Scheme 4, the acid chloride **19** was prepared and reacted with the diamino side chains **12** or **14** under biphasic reaction conditions to obtain the desired amides **38** or **39**, respectively.

Results of Binding Experiments

Carbetapentane (**1**) and all of the analogs dose-dependently displaced both [^{3}H]-(+)-SKF 10047 and [^{3}H]-DTG from the σ_1 and σ_2 binding sites, respectively, in rat brain. All but two of the carbetapentane analogs bound to these sites with high affinity (22–59 nM), with the notable exceptions of compounds **40** and **42**, which showed 8–26-fold less binding affinity to these sites compared to, for example, **41** and **43**, respectively. All

Scheme 4[a]



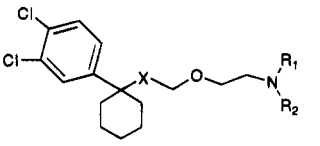
12; R_1=R_2= -CH_2-CH_3
14; R_1, R_2= -$(CH_2)_2$-O-$(CH_2)_2$-

38; R_1=R_2= -CH_2-CH_3
39; R_1, R_2= -$(CH_2)_2$-O-$(CH_2)_2$-

[a] (a) Pentene-stabilized $CHCl_3/H_2O$–$NaHCO_3$.

of the compounds were selective for σ_1 over σ_2 sites, with the three most selective analogs being compounds **34** (65-fold), **35** (78-fold), and **39** (51-fold). The least selective compound was **42** (1.2-fold), largely due to its relatively low affinity for σ_1 sites. Carbetapentane (**1**) and compounds **20**, **21**, **33**, and **36** bound to muscarinic receptor subtypes (m_1 and m_2) with K_i values in the 20–167 nM range. All of the other compounds were inactive or weakly active at these receptors. None of these compounds displaced [^{3}H]TCP (1-[1-(2-thienyl)cyclohexyl]piperidine) from PCP sites at concentrations up to 100 μM. See Tables 1–3 for tabulation of results.

Table 3. Binding Data for Carbetapentane Analogs[a]



compd	X	R_1/R_2	σ_1[b]	σ_2[b]	σ_2/σ_1	PCP[c]	m_1[c]	m_2[c]	m_1/σ_1
20	CO_2	Et/Et	22 (26)	667 (15)	30	IA	20 (12)	22 (10)	0.9
21	CO_2	$-(CH_2)_4-$	32 (38)	688 (15)	22	IA	63 (9)	74 (12)	2.0
22	CO_2	$-[(CH_2)_2]_2O-$	39 (36)	981 (10)	25	IA	3110 (29)	1189 (31)	80
38	CONH	Et/Et	27 (20)	527 (13)	20	IA	581 (14)	500 (26)	22
39	CONH	$-[(CH_2)_2]_2O-$	32 (20)	1640 (20)	51	IA	>10000	>10000	>310

[a] K_i values in nM (% error) are means of N determinations, each performed in triplicate. [b] $N = 3$. [c] $N = 2-3$. IA = inactive at concentrations up to 100 μM.

Structure–Activity Relationships

It appears that at σ_1 binding sites there is significant flexibility, since all of the compounds, except **40** and **42**, bind with high affinity (K_i = 22–59 nM) despite significant structural variation. This observation has been recorded for several other series of σ ligands.[19–22,27,28] None of the carbetapentane analogs bind with high affinity to the σ_2 sites, although structural variation does significantly affect binding affinity for these sites. Specifically, the most potent σ_2 ligand is the only ether compound (**41**). In contrast, the compounds that have no cycloalkyl ring are the least potent at this site, i.e., **34** and **35**. Furthermore, phenyl ring substitution modestly effects binding affinity at the σ_2 site, wherein the 4-methoxy-substituted analog (**37**) is less potent than the unsubstituted parent compound (**1**) which is less potent than the 4-chloro-substituted analog (**36**). An additional chloro group in the 3-position (**21**) does not appear to further enhance binding affinity at either σ_1 or σ_2 sites. The parent compound has intermediate affinity at the σ_2 site.

The most selective σ_1 ligands are compounds **34**, **35**, and **39**, respectively. This selectivity is largely due to the lack of binding affinity at σ_2 sites, and thus, herein, may be a clue to separability between these two binding sites. Compounds **34** and **35** have a small cyclopropyl group or a methyl group, respectively, instead of the cyclopentyl ring of the parent compound (**1**). Compound **39** has been modified at the ester function (amide) and has a morpholino group instead of the *N*,*N*-diethylamine which confers selectivity over both σ_2 and muscarinic sites. In general, selectivity over muscarinic receptor binding was achieved by (1) replacing the ester function (**38**–**43**), (2) replacing the cyclopentyl function with a smaller ring system (cyclopropyl; **34**) or a methyl group (**35**), and (3) replacing the diethylamino moiety with a morpholino group (**22** and **39**). The most selective σ_1 (over σ_2) ligands also displayed the highest σ_1 selectivity over m_1 receptors, i.e., **34** (>222-fold), **35** (>250-fold), and **39** (>312-fold).

In conclusion, these analogs represent a novel class of σ_1-selective ligands which can now be investigated as potential antitussive, anticonvulsant, and antiischemic agents. These studies may reveal whether σ_1 sites play a role in the pharmacological actions of these drugs. Furthermore, future studies on the actions of these compounds may shed light on the physiological function of σ_1 binding sites.

Experimental Section

Synthesis. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Thin-layer chromatography (silica gel GF; Analtech, DE) was used to detect product homogeneity. Flash column chromatography (silica gel, grade 60, 230–400 mesh; Aldrich Chemical Co., Milwaukee, WI) was used for purification. The solvent system used for all chromatography was $CHCl_3$/MeOH/NH_4-OH (90:10:1) unless otherwise specified. Drying refers to the use of Na_2SO_4. ^1H NMR spectra were obtained on a Varian Gemini 300 MHz NMR spectrometer using tetramethylsilane as an internal standard. Infrared spectra were determined on a Perkin-Elmer 1600 series FTIR (KBr pellets). CIMS (NH_3) were obtained on a Finnigan 1015 mass spectrometer. All compounds exhibited NMR, IR, and mass spectral data consistent with those of the structures assigned. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA) and were within 0.4% of the theoretical values.

2-[2-(1-Pyrrolidino)ethoxy]ethanol (7). In a modification of the procedure described by Sorba et al.,[32] a mixture of 2-(2-chloroethoxy)ethanol (**5**; Aldrich; 25.3 mL, 239.6 mmol), pyrrolidine (20 mL, 239.6 mmol), and anhydrous potassium carbonate (66.25 g, 479.3 mmol) in 200 mL of anhydrous toluene was stirred at reflux overnight. The reaction mixture was filtered, and the volatiles were evaporated under reduced pressure. Distillation of the crude mixture under reduced pressure (2 mmHg) resulted in collection of the main fraction (**7**; yield 55%) at 88–90 °C: ^1H NMR ($CDCl_3$) δ 1.77–1.82 (m, 4 H), 2.56–2.6 (m, 6 H), 2.7 (t, J = 5.5 Hz, 2 H), 3.6–3.7 (m, 6 H); CIMS m/z 159 (M + 1), 176 (M + 18).

2-[2-(4-Morpholino)ethoxy]ethanol (8). Compound **8** was prepared according to the procedure described for the synthesis of **7**. A mixture of **5** (25.0 mL, 236.81 mmol), morpholine (20.65 mL, 236.81 mmol), and anhydrous potassium carbonate (65.46 g, 473.62 mmol) in 200 mL of anhydrous toluene was stirred at reflux overnight. The reaction mixture was filtered, and the volatiles were evaporated under reduced pressure. Distillation of the crude mixture under reduced pressure (2 mmHg) resulted in collection of the main fraction (**8**; yield 66%) at 85–87 °C: ^1H NMR ($CDCl_3$) δ 2.43 (t, J = 4.5 Hz, 4 H), 2.5 (t, J = 5.4 Hz, 2 H), 3.5–3.65 (m, 10 H); CIMS m/z 176 (M + 1).

2-[2-(1-Pyrrolidino)ethoxy]ethylamine (13). In a modification of the procedure described for the synthesis of compound **12**,[7] a zinc azide–bis(pyridine) complex (7.40 g, 24.08 mmol) was prepared according to the procedure described by Claude and Rollin[30] and suspended in a solution of **7** (3.83 g, 24.08 mmol) in 100 mL of anhydrous toluene. To this stirred solution was added dropwise diisopropyl azodicarboxylate (9.48 mL, 48.16 mmol). The reaction mixture was stirred overnight at room temperature. The solution was filtered and the solvent evaporated down under reduced pressure. The crude mixture was taken up into 400 mL of a 1 N HCl solution, and several extractions were performed with ether until all the triphenylphosphine oxide was extracted from the mixture. The solution was brought to pH 9 with NH_4OH, and the desired compound was extracted in $CHCl_3$ (5 × 50 mL). The organic

layer was dried and the solvent evaporated under reduced pressure. Distillation of the residue under reduced pressure (8 mmHg) resulted in collection of the main fraction (**10**; yield 30%) at 98–100 °C: IR 2100 cm^{-1}; CIMS m/z 185 (M + 1). A solution of the clear distillate (0.5 g) in 20 mL of anhydrous EtOH was catalytically reduced by hydrogenation in a Parr hydrogenator (40 psi) with 10% Pd/C (0.150 g) at room temperature for 18 h. Evaporation of the solvent gave a residue that was homogeneous by TLC ($CHCl_3$/MeOH/NH_4OH, 70:30:1): CIMS m/z 159 (M + 1). The dioxalate salt was prepared by dissolving the free base (0.46 g, 2.91 mmol) in 2-PrOH and adding it to a solution of 0.53 g of oxalic acid (5.82 mmol) in hot MeOH. The salt was recrystallized from MeOH/2-PrOH: mp 141–142 °C. Anal. ($C_{12}H_{22}N_2O_9$) C, H, N.

2-[2-(4-Morpholino)ethoxy]ethylamine (14). Compound **11** was prepared (2.2 g, 11 mmol, 46%) from **8** (4.21 g, 24.08 mmol) according to the procedure described for the synthesis of **10** (bp (8 mmHg) 65–70 °C): IR 2104 cm^{-1}; CIMS m/z 201 (M + 1). Compound **14** was prepared by catalytic hydrogenation of **11** according to the procedure described for the synthesis of **13**: CIMS m/z 174 (M + 1). The dioxalate salt was prepared by dissolving the free base (0.476 g, 2.73 mmol) in 2-PrOH and adding it to a solution of 0.49 g of oxalic acid (5.46 mmol) in hot MeOH. The salt was recrystallized from MeOH/2-PrOH: mp 112–115 °C. Anal. ($C_{12}H_{22}N_2O_{10}$) C, H, N.

1-(3,4-Dichlorophenyl)-1-cyclohexanecarbonitrile (17). In a modification of the procedure described by Bridges et al.,[31] a solution of 3,4-dichlorophenylacetonitrile (**15**, Aldrich; 10.0 g, 53.8 mmol) in anhydrous DMSO (30 mL) was added dropwise over a 20 min period to a suspension of previously washed 60% NaH dispersion in mineral oil (5.38 g, 134.5 mmol) in anhydrous DMSO (100 mL) at 0 °C. After the addition was completed, the reaction mixture was allowed to stir at room temperature for 30 min and a solution of 1,5-dibromopentane (**16**; 11 mL, 80.7 mmol) in anhydrous DMSO (30 mL) was added over a 30 min period. The reaction mixture was allowed to stir at room temperature for 1 h, and the reaction was quenched by pouring it over 1.2 L of ice–H_2O. Compound **17** was extracted with $CHCl_3$ (5 × 50 mL). The organic layer was washed with H_2O (2 × 25 mL) and dried, and the volatiles were removed under reduced pressure. Purification by flash chromatography, elution with hexane/ethyl acetate (4:1), and evaporation of the solvent gave 12.81 g (94%) of **17**: ^1H NMR δ 1.3–1.8 (m, 8 H), 2.1 (d, J = 11.8 Hz, 2 H), 7.33 (dd, J = 2.1 Hz, J = 8.4 Hz, 1 H), 7.45 (d, J = 8.4 Hz, 1 H), 7.55 (d, J = 2.1 Hz, 1 H); CIMS m/z 271 (M + 17), 273 (M + 17 + 2), 275 (M + 17 + 4).

1-(3,4-Dichlorophenyl)-1-cyclohexanecarboxylic Acid (18). A modification of the procedure for hydrolysis of nitriles by Shirai et al.[33] was used to obtain compound **18**. A mixture of **17** (24.24 g, 95.43 mmol), 40% aqueous KOH (300 mL), and diethylene glycol (250 mL) was stirred at reflux overnight. The solution was diluted with H_2O (700 mL) and extracted with ether (2 × 100 mL). The aqueous layer was acidified with concentrated HCl, and compound **18** was extracted in ethyl acetate. The solution was dried, and the volatiles were removed under reduced pressure to give 20.14 g of **18** (77%), mp 155–157 °C, from ethyl acetate/ethanol: ^1H NMR ($CDCl_3$) δ 1.25–1.3 (m, 2 H), 1.49–1.75 (m, 6 H), 2.39–2.43 (m, 2 H), 7.27 (dd, J = 2.2 Hz, J = 8.5 Hz, 1 H), 7.39 (d, J = 8.5 Hz, 1 H), 7.5 (d, J = 2.2 Hz, 1 H).

2-[2-(Diethylamino)ethoxy]ethyl 1-(3,4-Dichlorophenyl)-1-cyclohexanecarboxylate (20). A solution of **18** (0.682 g, 1.25 mmol) in toluene (13 mL) and $SOCl_2$ (1.25 mL) was stirred at reflux for 2 h under Ar. The solvent was evaporated under reduced pressure, and the acid chloride **19** was taken up into 10 mL of toluene. The volatiles were evaporated under reduced pressure, and the residue was dissolved in 20 mL of toluene. A solution of **6** (0.43 mL, 1.25 mmol) and triethylamine (0.48 mL) was added dropwise to the acid chloride solution. The reaction mixture was stirred at reflux for 2 h and then was left to stand at room temperature overnight. The triethylamine hydrochloride formed was separated by filtration, and the filtrate was washed with toluene (2 × 1 mL). The solvent was evaporated under reduced pressure, and the residue was dissolved in 25 mL of 2 N NaOH. The product was extracted with $CHCl_3$ (3 × 15 mL), and the combined organic fraction was washed with H_2O (1 × 15 mL) and dried. The solvent was evaporated, affording **20** as an oil. The citrate salt was prepared by dissolving the free base (0.418 g, 1 mmol) in a minimal volume of hot MeOH and adding it to a solution of 0.19 g of citric acid (1 mmol) in hot MeOH. Addition of anhydrous ether resulted in the crystalline salt, which was recrystallized from MeOH/ether: mp 95–96 °C; ^1H NMR (D_2O) δ 1.17 (t, J = 7.3 Hz, 6 H), 1.41–1.8 (m, 8 H), 2.4–2.5 (m, 2 H), 3.05–3.12 (m, 6 H), 3.54–3.67 (m, 4 H), 4.25–4.28 (m, 2 H), 7.37 (dd, J = 2.2 Hz, J = 8.5 Hz, 1 H), 7.54 (d, J = 8.5 Hz, 1 H), 7.63 (d, J = 2.2 Hz, 1 H); CIMS m/z 416 (M), 418 (M + 2), 420 (M + 4). Anal. ($C_{27}H_{39}NOCl_2$) C, H, N.

2-[2-(1-Pyrrolidino)ethoxy]ethyl 1-(3,4-Dichlorophenyl)-1-cyclohexanecarboxylate (21). Compound **21** was prepared (0.885 g, 2.14 mmol, 86%) from **18** (0.683 g, 2.5 mmol) according to the procedure described for the synthesis of **20**. The citrate salt was prepared by dissolving the free base (0.883 g, 2.13 mmol) in a minimal volume of hot MeOH and adding it to a solution of 0.41 g of citric acid (2.13 mmol) in hot MeOH. The solvent was evaporated, and the salt was recrystallized twice from 2-PrOH/ether: mp 98–100 °C; ^1H NMR (D_2O) δ 1.3–2.1 (m, 14 H), 2.3–2.5 (m, 2 H), 2.71–2.9 (m, 2 H), 3.4–3.72 (m, 6 H), 4.28–4.3 (m, 2 H), 7.38 (dd, J = 2.2 Hz, J = 8.5 Hz, 1 H), 7.55 (d, J = 8.5 Hz, 1 H), 7.62 (d, J = 2.2 Hz, 1 H); CIMS m/z 414 (M), 416 (M + 2), 418 (M + 4). Anal. ($C_{27}H_{37}NO_{10}Cl_2H_2O$) C, H, N.

2-[2-(4-Morpholino)ethoxy]ethyl 1-(3,4-Dichlorophenyl)-1-cyclohexanecarboxylate (22). Compound **22** was prepared (0.985 g, 2.29 mmol, 91%) from **18** (0.683 g, 2.5 mmol) according to the procedure described for the synthesis of **20**. The citrate salt was prepared by dissolving the free base (0.763 g, 1.77 mmol) in a minimal volume of hot MeOH and adding it to a solution of 0.341 g of citric acid (1.77 mmol) in hot MeOH. The solvent was evaporated, and the salt was recrystallized from 2-PrOH/ether: mp 75–78 °C; ^1H NMR (D_2O) δ 1.4 –1.8 (m, 8 H), 2.3–2.4 (m, 2 H), 3.1–3.4 (m, 6 H), 3.6 –3.8 (m, 6 H), 4.0–4.2 (b, 2 H), 4.3–4.32 (m, 2 H), 7.39 (dd, J = 2.1 Hz, J = 8.5 Hz, 1 H), 7.57 (d, J = 8.5 Hz, 1 H), 7.66 (d, J = 2.1 Hz, 1 H); CIMS m/z 430 (M), 432 (M + 2), 434 (M + 4). Anal. ($C_{27}H_{37}NO_{11}Cl_2$) C, H, N.

2-[2-(Diethylamino)ethoxy]ethyl 1-Phenyl-1-cyclopropanecarboxylate (34). A solution of **24** (5.0 g, 30.86 mmol) and 15.4 mL of $SOCl_2$ in 25 mL of toluene was refluxed for 4 h under Ar. The solvent was evaporated under reduced pressure, and the acid chloride **29** was dissolved in 20 mL of toluene. The volatiles were evaporated under reduced pressure, and the residue was dissolved in 60 mL of toluene. A solution of **6** (5.29 mL, 30.86 mmol) and triethylamine (6.02 mL, 43.20 mmol) was added dropwise to the acid chloride solution. The reaction mixture was stirred at reflux overnight and filtered. The solvent was evaporated under reduced pressure, and the residue was dissolved in 25 mL of 2 N NaOH. The product was extracted with $CHCl_3$ (3 × 15 mL), and the combined organic fraction was washed with H_2O (1 × 15 mL) and dried. The solvent was evaporated, affording **34** as an oil (8.75 g, 93%). The citrate salt was prepared by dissolving the free base (1.0 g, 3.27 mmol) in a minimal volume of hot MeOH and adding it to a solution of 0.63 g of citric acid (3.27 mmol) in hot MeOH. Addition of anhydrous ether resulted in the crystalline salt, which was recrystallized from 2-PrOH: mp 77–79 °C; ^1H NMR (D_2O) δ 1.26 (t, J = 7.3 Hz, 6 H), 1.35 (dd, J = 7.3 Hz, J = 4.2 Hz, 2 H), 1.65 (dd, J = 7.3 Hz, J = 4.2 Hz, 2 H), 3.1–3.3 (m, 6 H), 3.6–3.7 (m, 4 H), 4.2–4.3 (m, 2 H), 7.3–7.5 (m, 5 H); CIMS m/z 306 (M + 1). Anal. ($C_{24}H_{35}NO_{10}$) C, H, N.

2-[2-(Diethylamino)ethoxy]ethyl 2-Phenylpropionate (35). Compound **35** was prepared (8.8 g, 90%) from **25** (5.0 g, 33.29 mmol) according to the procedure described for the synthesis of **34**. The citrate salt was prepared by dissolving the free base (2.2 g, 7.50 mmol) in a minimal volume of hot MeOH and adding it to a solution of 1.44 g of citric acid (7.50 mmol) in hot MeOH. Addition of anhydrous ether resulted in a crystalline salt, which was recrystallized from 2-PrOH: mp 71-73 °C; ^1H NMR (D_2O) δ 1.21 (t, J = 7.3 Hz, 6 H), 1.48 (d, J = 7.2 Hz, 3 H), 3.0–3.2 (m, 6 H), 3.6–3.74 (m, 4 H), 3.86 (q, J

= 7.2 Hz, 1 H), 4.2–4.4 (m, 2 H), 7.3–7.5 (m, 5 H); CIMS m/z 294 (M + 1). Anal. ($C_{25}H_{35}NO_{10}$) C, H, N.

2-[2-(Diethylamino)ethoxy]ethyl 1-(4-Chlorophenyl)-1-cyclopentanecarboxylate (36). Compound **36** was prepared (7.43 g, 91%) from **26** (5.0 g, 22.25 mmol) according to the procedure described for the synthesis of **34**. The citrate salt was prepared by dissolving the free base (1.0 g, 2.72 mmol) in a minimal volume of hot MeOH and adding it to a solution of 0.523 g of citric acid (2.72 mmol) in hot MeOH. The volatiles were removed under reduced pressure, and the residue was recrystallized from MeOH/ethyl acetate: mp 79–80 °C; ^{1}H NMR (D_2O) δ 1.23 (t, J = 7.3 Hz, 6 H),1.7–1.8 (m, 4 H), 1.94–2.04 (m, 2 H), 2.4–2.5 (m, 2 H), 3.1–3.2 (m, 6 H), 3.5–3.6 (m, 2 H), 3.62–3.7 (m, 2 H), 4.2–4.3 (m, 2 H), 7.4 (s, 4 H); CIMS m/z 368 (M + 1). Anal. ($C_{26}H_{38}NO_{10}Cl$) C, H, N.

2-[2-(Diethylamino)ethoxy]ethyl 1-(4-Methoxyphenyl)-1-cyclopentanecarboxylate (37). Compound **37** was prepared (2.15 g, 52%) from **27** (2.5 g, 11.35 mmol) according to the procedure described for the synthesis of **34**. The citrate salt was prepared by dissolving the free base (1.0 g, 2.75 mmol) in a minimal volume of hot MeOH and adding it to a solution of 0.529 g of citric acid (2.75 mmol) in hot MeOH. The volatiles were removed under reduced pressure, and the residue was recrystallized from MeOH/ethyl acetate: mp 80–82 °C; ^{1}H NMR (D_2O) δ 1.21 (t, J = 7.4 Hz, 6 H), 1.6–1.7 (m, 4 H), 1.9–2.1 (m, 2 H), 2.5–2.6 (m, 2 H), 3.1–3.2 (m, 6 H), 3.5–3.6 (m, 2 H), 3.65–3.7 (m, 2 H), 3.8 (s, 3 H), 4.2–4.3 (m, 2 H), 7.01 (d, J = 8.7 Hz, 2 H), 7.42 (d, J = 8.7 Hz, 2 H); CIMS m/z 364 (M + 1). Anal. ($C_{27}H_{41}NO_{11}$) C, H, N.

***N*-[2-[2-(Diethylamino)ethoxy]ethyl]-1-(3,4-dichlorophenyl)-1-cyclohexanecarboxamide (38).** A solution of **18** (1.48 g, 5.42 mmol) in toluene (15 mL) and $SOCl_2$ (3 mL) was stirred at reflux for 4 h under Ar. The solvent was evaporated under reduced pressure, and the acid chloride **19** was taken up into 10 mL of toluene. The volatiles were evaporated under reduced pressure, and the residue was dissolved in 20 mL of toluene (this procedure was repeated twice). The acid chloride was dissolved in 10 mL of pentene-stabilized $CHCl_3$. The resulting solution was added dropwise to a mechanically stirred solution of the amine **12** (1.42 g of the dioxalate salt, 4.18 mmol) and $NaHCO_3$ (3.51 g, 10 mmol) in 85 mL of H_2O. The biphasic reaction mixture was allowed to stir at room temperature for 3 h. The $CHCl_3$ layer was separated and evaporated under reduced pressure. The residue was purified by flash column chromatography to give 1.2 g (60%) of **38** as an oil that was homogeneous by TLC. The citrate salt was prepared by dissolving the free base (200 mg, 0.48 mmol) in a minimal volume of hot MeOH and adding it to a solution of 0.093 g of citric acid (0.48 mmol) in hot MeOH. The solvent was evaporated, and the salt was recrystallized from 2-PrOH/ether: mp 80–82 °C; ^{1}H NMR ($CDCl_3$) δ 1.0 (t, J =7.1 Hz, 6 H), 1.2–1.4 (m, 2 H), 1.5–1.7 (m, 4 H), 1.8–2.0 (m, 2 H), 2.2–2.4 (m, 2 H), 2.5–2.7 (m, 6 H), 3.3–3.5 (m, 6 H), 5.9 (s, 1 H), 7.23 (dd, J = 8.5 Hz, J = 2.2 Hz, 1 H), 7.38 (d, J = 8.5 Hz, 1 H), 7.47 (d, J = 2.2 Hz, 1 H); CIMS m/z 415 (M), 417 (M + 2), 419 (M + 4). Anal. ($C_{27}H_{40}N_2O_9Cl_2$·0.5$H_2$0) C, H, N.

***N*-[2-[2-(4-Morpholino)ethoxy]ethyl]-1-(3,4-dichlorophenyl)-1-cyclohexanecarboxamide (39).** Compound **39** was prepared (0.876 g, 2.01 mmol, 90.4%) from **19** (0.803 g, 2.94 mmol) according to the procedure described for the synthesis of **38**. The oxalate salt was prepared by dissolving the free base (0.100 g, 0.23 mmol) in a minimal volume of MeOH and adding it to a solution of 0.021 g of oxalic acid (0.23 mmol) in hot MeOH. The solvent was evaporated, and the salt was recrystallized from 2-PrOH/ether: mp 75–78 °C; ^{1}H NMR ($CDCl_3$) δ 1.2–1.4 (m, 2 H), 1.5–1.6 (m, 4 H), 1.8–1.9 (m, 2 H), 2.2–2.3 (m, 2 H), 2.4–2.5 (m, 6 H), 3.3–3.45 (m, 8 H), 3.68 (t, J = 4.6 Hz, 2 H), 5.8 (s, 1 H), 7.22 (dd, J = 2.2 Hz, J = 8.5 Hz, 1 H), 7.37 (d, J = 8.5 Hz, 1 H), 7.45 (d, J = 2.2 Hz, 1 H); CIMS m/z 429 (M), 431 (M + 2), 433 (M + 4). Anal. ($C_{23}H_{32}N_2O_7Cl_2$·0.5$H_2$0) C, H, N.

Radiolabeled Ligand Displacement Assays—Materials and Methods. [^{3}H]-(+)-SKF 10047 and [^{3}H]DTG Binding Assay. Tissue preparation and binding assays were performed as previously described.[13] Frozen brains from male Sprague–Dawley rats (Bioproducts for Science, Inc., Indianapolis, IN) were thawed for 1 h in 25 volumes of ice-cold 5 mM Tris-HCl/10 mM K^+-EDTA (pH 8.0 at 25 °C) and then homogenized for 15 s with a Brinkmann polytron homogenizer (setting 6). Homogenates were centrifuged at 45000g for 15 min at 4 °C. The supernatant was discarded, and the pellets were resuspended in fresh ice-cold buffer and recentrifuged once. Final pellets were suspended in ice-cold 5 mM Tris-HCl (pH 8.0 at 25 °C).

In a final volume of 0.5 mL, membrane suspensions were incubated with radioligand in the presence of 5 mM Tris-HCl (pH 8.0) at 25 °C for 60 min. σ_1 binding assays were performed in the presence of 300 nM unlabeled MK 801 to block binding of [^{3}H]-(+)-SKF 10047 (final concentration 5 nM; New England Nuclear; specific activity 60.3 Ci/mmol) to PCP receptors. In all σ_2 binding assays, 3 μM unlabeled (+)-SKF 10047 was included to block binding of [^{3}H]DTG (final concentration 5 nM; New England Nuclear; specific activity 37.2 Ci/mmol) to σ_1 receptors. The reactions were terminated by the addition of 5 mL of ice-cold 5 mM Tris-HCl (pH 8.0) followed by rapid filtration through Whatman GF/B filter papers (presoaked in 0.5% poly(ethyleneimine) in H_2O to reduce nonspecific binding) using a Brandel cell harvester (Gaithersburg, MD). Filters were then rinsed twice with 5 mL aliquots of the same buffer. Absolute ethanol and Beckman ready value scintillation cocktail were added to the vials which were counted the next day at an efficiency of about 36%. K_i values were determined using LIGAND.[34]

[^{3}H]TCP Binding Assay. After decapitation of male Sprague–Dawley rats (Taconic Farms, Germantown, NY), whole brains minus the cerebellum were rapidly removed and disrupted with 45 volumes of ice-cold 5 mM Tris-HCl buffer (pH 7.4) using a Brinkmann polytron homogenizer (setting 6, 20 s). The homogenates were centrifuged at 20000g for 20 min at 5 °C. The pellet was washed in fresh buffer and recentrifuged for a total of three times. The final resuspension was done in 45 volumes of assay buffer and kept on ice until needed.

Binding to homogenates was determined in a 1 mL incubation volume consisting of 900 μL of tissue (containing approximately 0.8 mg of protein by Lowry analysis), 50 μL of [^{3}H]TCP (40.8 Ci/mmol; New England Nuclear, Boston, MA) for a final concentration of 2 nM, and 50 μL of buffer, test compound, or 10 μM TCP (for determination of nonspecific binding). After a 90 min incubation at 5 °C, the reaction was terminated by rapid filtration using a Brandel cell harvester (Gaithersburg, MD) through #32 Schleicher and Schuell glass fiber filters which had been presoaked in 0.03% poly(lysine) (Sigma Chemical Co., St. Louis, MO; molecular weight 150 000–300 000) for 2 h at 5 °C. The filters were washed with three 5 mL aliquots of ice-cold assay buffer, placed in counting vials with 4 mL of CytoScint ES scintillation cocktail (ICN Biomedicals, Inc., Irvine, CA), and allowed to stand overnight before counting. The inhibition constants (K_i) for the various compounds were calculated using GraphPAD software (ISI Software, Philadelphia, PA) using a K_d for [^{3}H]TCP of 16.5 nM as determined by nonlinear analysis of the saturation curves.

[^{3}H]NMS (*N*-Methylscopolamine) Binding Assay. NIH 3T3 cells stably expressing muscarinic receptors (mAChRs) upon transfection with an expression vector carrying genes for m_1 or m_2 human mAChRs have been previously described.[35] Cells expressed 600 and 500 fmol of [^{3}H]NMS binding sites/mg of protein for m_1 or m_2 NIH 3T3 transfected cells, respectively. Semiconfluent plates of cells were washed twice with phosphate-buffered saline and scraped in 1 mL per plate of ice-cold binding buffer (10 mM Tris-HCl buffer (pH 7.4), 100 mM NaCl, 5 mM $MgCl_2$). Cells were disrupted using a Brinkman polytron homogenizer (setting 6, 15 s). Cell membranes were recovered by centrifugation at 14000g for 20 min at 4 °C and then resuspended in ice-cold binding buffer.

Fifty micrograms of membrane protein was incubated with radioligand ([^{3}H]NMS (85.0 Ci/mmol; New England Nuclear, Boston, MA), 100 pM) in a final volume of 1.0 mL of binding buffer at 25 °C for 60 min. Nonspecific binding was determined in the presence of 10 μM atropine. Reactions were terminated by rapid filtration using a Brandel cell harvester

(Brandel, Inc., Gaithersburg, MD) through #32 Schleicher and Schuell glass fiber filters. The filters were washed with three 5 mL aliquots of ice-cold binding buffer, placed in counting vials with 10 mL of CytoScint ES scintillation cocktail (ICN Biomedicals, Inc., Irvine, CA), and counted. The inhibition constants (K_i) for the various compounds were calculated using GraphPAD software (ISI Software, Philadelphia, PA) using a K_d for [^{3}H]NMS of 144 and 270 pM for m_1 and m_2 receptors, respectively, as determined by nonlinear analysis of the saturation curves.

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