Novel (4-Phenylpiperidinyl)- and (4-Phenylpiperazinyl)alkyl-Spaced Esters of 1-Phenylcyclopentanecarboxylic Acids as Potent σ-Selective Compounds

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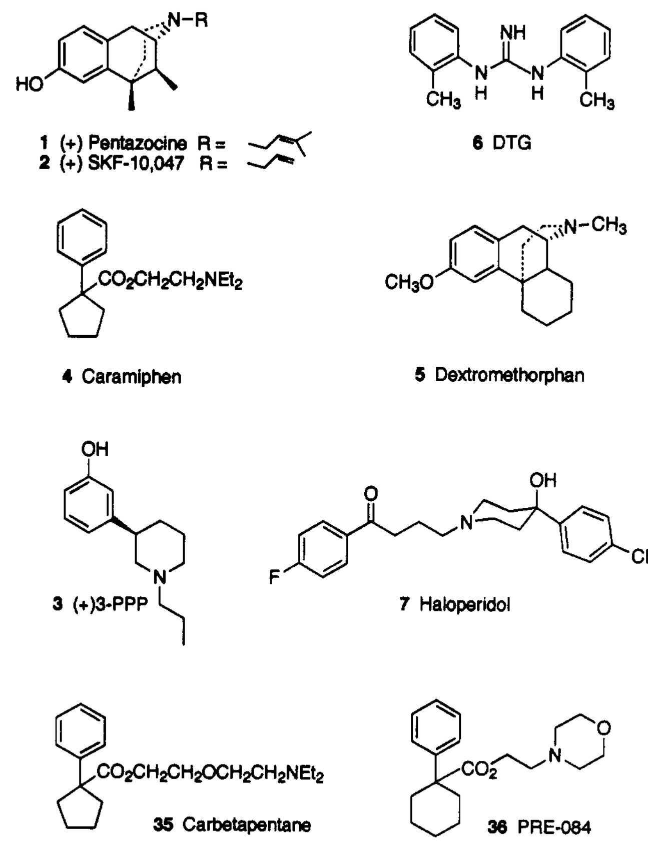
A series of novel 4-phenylpiperidinyl and (4-phenylpiperazinyl)alkyl 1-phenylcyclopentanecarboxylates was synthesized and evaluated for affinity at σ_1 and σ_2 sites by inhibition of [^{3}H]-(+)-pentazocine (PENT) and [^{3}H]-1,3-di(2-tolyl)guanidine (DTG) binding in guinea pig brain. The phenylpiperidines were more potent σ ligands than the corresponding piperazines. Structural modifications varying the optimal spatial distance between the piperidine nitrogen and ester functions led to the identification of the propyl compound **24** ([^{3}H]PENT K_i = 0.50 nM; [^{3}H]DTG K_i = 1.17 nM) and the butyl derivative **32** ([^{3}H]PENT K_i = 0.51 nM; [^{3}H]DTG K_i = 0.69 nM) as novel high-affinity σ-selective agents. An ethylene spacer was optimum with para-substituted analogs. A notable finding was the discovery of 2-(4-phenylpiperidinyl)ethyl 1-(4-nitrophenyl)-cyclopentanecarboxylate hydrochloride (**15**) (RLH-033), which demonstrated potent affinity for the [^{3}H]PENT-defined σ site with a K_i of 50 pM, selectivity for σ_1 over muscarinic M_1 (> 17 600-fold), M_2 (> 34 200-fold), dopamine D_1 (> 58 000-fold), and D_2 (> 7000-fold) receptors, and inactivity at phencyclidine, NMDA, and opioid receptors. RLH-033 is a valuable tool which will aid further in understanding the biology of the σ recognition site. Information from this research has further defined the topography of the σ recognition site, which may provide an explanation for the diverse structures which bind with relatively high affinity.

Introduction

The function of the sigma (σ) recognition site in brain remains the subject of interest and critical investigation. σ Sites are pharmacologically distinct from dopamine, opioid, and phencyclidine receptors.[1] Despite this, the σ binding site has been hypothesized to play a role in psychosis,[2] since benzomorphans, antipsychotics and antidepressants exhibit high affinity.[3] Compounds which demonstrate lower affinity for dopamine (DA) D_2 receptors may be exerting their antipsychotic effects through a nondopaminergic mechanism.[4] Therefore, σ receptor ligands have been proposed as potential antipsychotic agents that will not induce extrapyramidal side effects or tardive dyskinesia,[5–7] although this has yet to be proven in the clinic.[7] The exact mechanism for the interaction between the σ binding site and the dopamine system has not been clearly elucidated despite a number of studies demonstrating σ/DA interactions.[5,7–15] Recently, anti-ischemic and neuroprotective effects have been reported among structurally diverse classes of σ ligands,[16–20] and a link between σ and *N*-methyl-D-aspartate (NMDA) receptors has been proposed to account for at least some of the neuroprotective effects observed.[20–23] Thus, the identification of functional events linked to stimulation or inhibition at σ recognition sites may reveal insights into the role of this site in various neurological and neurodegenerative disorders.

While considerable research has focused on the study of σ sites, a true functional role for the σ recognition site remains unclear.[24] Subtypes of σ recognition sites have

Chart 1



been proposed, based on differences between the interactions of prototypical σ ligands with the sites labeled by various σ radioligands[25] (Chart 1). The σ_1 site exhibits high affinity for (+)-benzomorphans such as (+)-pentazocine (**1**) and (+)-*N*-allylnormetazocine (SKF-10,047, **2**), (*R*)-(+)-3-(3-hydroxyphenyl)-*N*-propylpiperidine (3-PPP,

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3), caramiphen (4), and dextromethorphan (5). Conversely, σ_2 sites are selective for (−)-benzomorphans, and caramiphen and dextromethorphan have low affinity at these sites.[25] DTG (6) and haloperidol (7) do not discriminate between σ_1 and σ_2 sites.[25] Recently, a potential novel σ site which recognizes 1-phenyl-3-aminotetralins has been reported, although studies of this site warrant further investigation.[26]

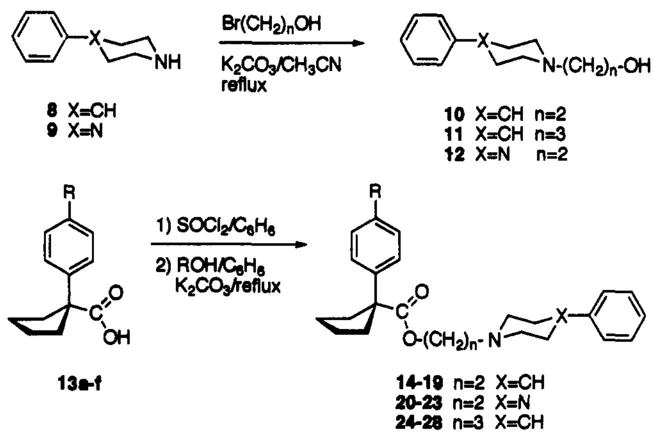
Our studies of σ/muscarinic interactions have shown that caramiphen (4) binds competitively to and has high affinity for the σ_1 site.[27,28] We have also demonstrated that caramiphen and certain analogs bind with high affinity and selectivity to the M_1 subtype of the muscarinic receptor.[29–31] Because caramiphen has high affinity for the muscarinic receptor, it has little utility for the study of σ function. On the basis of our observations of the competitive nature of the binding of caramiphen to the σ site,[27,28] and on previously proposed models of σ receptor topography, we made structural modifications of caramiphen with the goal of developing high-affinity σ-selective ligands that would also help elucidate the mode of binding of caramiphen to the σ site. Previously proposed σ models[1,32,33] have suggested that the 4-phenylpiperidine moiety may be a pharmacophore for the competitive σ site. These propose a lipophilic and an amine binding site, as well as an additional lipophilic site on the receptor. Certain structural types of σ ligands such as the (+)-benzomorphan SKF-10,047 or (+)-3-PPP may only partially overlap and interact with this latter site. Therefore, binding to all three points of attachment is not required for high-affinity σ binding.

We propose that the tertiary amine nitrogen of caramiphen binds to the competitive σ nitrogen binding site, while the 1-phenylcyclopentyl portion may bind more favorably to the second lipophilic site. The series described in this paper was designed to incorporate the 4-phenylpiperidine pharmacophore with the caramiphen skeleton in order to probe the mode of binding of caramiphen and to help describe the topography of the σ site. The distance between the nitrogen atom of the piperidine ring and the ester functionality in the caramiphen portion of the molecule was varied to determine optimum separation between these two key features. Also, preliminary studies of both para substitution on the phenyl ring of the 1-arylcyclopentyl portion and a comparison of arylpiperidine with piperazine derivatives were performed. The compounds were evaluated for binding to putative σ_1 and σ_2 sites in guinea pig brain using [^{3}H]-(+)-pentazocine (PENT) and [^{3}H]-1,3-di(2-tolyl)guanidine (DTG) as ligands. Important derivatives were also evaluated for selectivity at muscarinic M_1 and M_2, dopamine D_1 and D_2, phencyclidine (PCP), opioid, and NMDA receptors.

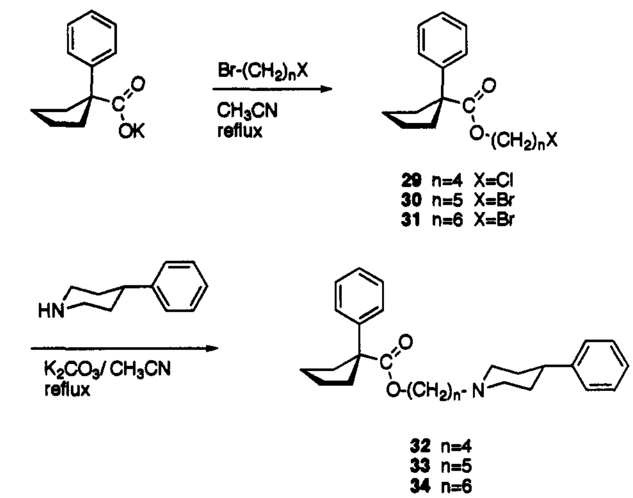
Chemistry

The 2-(4-phenylpiperidinyl)ethyl (14-19) (method A), 2-(4-phenylpiperazinyl)ethyl (20–23) (method B), and 3-(4-phenylpiperidinyl)propyl (24–28) (method A) derivatives were prepared by coupling the corresponding amino alcohol with the appropriate 1-phenylcyclopentanecarbonyl chloride (Scheme 1).[29] The known aryl amino alcohols were prepared by a general procedure by reaction of 4-phenylpiperidine (8) with 2-bromoethanol or 3-bromopropanol (CH_3CN/K_2CO_3) to give the corresponding 2-ethanol (10) and 3-propanol (12). Similarly, alkylation of 1-phenylpiperazine (9) with 2-bromoethanol gave 11 in 65% yield. This compound was previously prepared in low yield by cyclization of *N,N*-bis(2-bromoethyl)aniline with ethanolamine.[34] 2-(4-Phenylpiperidinyl)ethanol (10) was reported in good yield by reaction of 4-phenylpiperidine with ethylene oxide,[35] and the 3-propanol (12) was previously prepared in three steps in a 56% yield.[36] The general method we report gives the amino alcohols in 55–65% yield, in a convenient one-step procedure. The 4-substituted-1-phenylcyclopentanecarboxylic acids (13a–f) used were either commercially available or were prepared using standard literature procedures.[29] The synthesis of the 4-phenylpiperidinylbutyl, -pentyl, and -hexyl analogs (32–34) is outlined in Scheme 2 (method C). Potassium 1-phenylcyclopentanecarboxylate[37] was reacted with 1-bromo-4-chlorobutane, 1,5-dibromopentane, or 1,6-dibromohexane to give, after purification by column chromatography, the corresponding halo esters 29–31. Alkylation of 4-phenylpiperidine gave the 4-phenylpiperidinyl esters 32–34 in good yield.[38]

Scheme 1



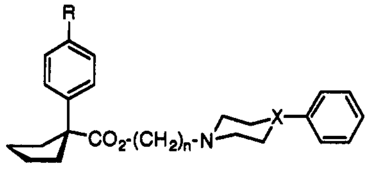
Scheme 2



Results and Discussion

This study evaluated a series of 4-phenylpiperidinyl- and (4-phenylpiperazinyl)alkyl-spaced esters of 1-phenylcyclopentanecarboxylic acid for binding to σ_1 and σ_2 sites by inhibition of [^{3}H]-(+)-pentazocine (PENT) and [^{3}H]-DTG binding to homogenates of guinea pig brain. The inhibition constants for reference and novel σ compounds at these sites are shown in Table 1. As expected, (+)-PENT exhibited an affinity of 2.1 nM for the [^{3}H]-(+)-PENT-defined site, with low affinity (562 nM) for the [^{3}H]DTG-defined σ site. The affinities of haloperidol for σ_1 and σ_2 sites were 0.6 and 6 nM, respectively. Carami-

Table 1. σ Binding Affinities and Physicochemical Properties of Novel σ Piperidine and Piperazine Analogs



compd	R	n	X	method[b] (%)	mp, °C	formula	σ binding K_i,[a] nM [³H]PENT	σ binding K_i,[a] nM [³H]DTG
14	H	2	CH	A (28)	180–182	$C_{25}H_{31}NO_2{\cdot}HCl$	3.95 ± 1.14	52.3 ± 10.8
15	NO_2	2	CH	A (29)	140–144	$C_{25}H_{30}N_2O_4{\cdot}HCl$	0.05 ± 0.02	3.93 ± 0.95
16	I	2	CH	A (36)	184–185	$C_{25}H_{30}INO_2{\cdot}HCl$	1.44 ± 0.31	52.0 ± 11.4
17	CN	2	CH	A (37)	126–128	$C_{26}H_{30}N_2O_2{\cdot}HCl{\cdot}0.5H_2O$	1.30 ± 0.13	26.8 ± 6.0
18	Cl	2	CH	A (43)	168–170	$C_{25}H_{30}ClNO_2{\cdot}HCl{\cdot}0.5H_2O$	1.34 ± 0.15	23.9 ± 6.5
19	OCH_3	2	CH	A (10)	86–89	$C_{26}H_{33}NO_3{\cdot}HCl$	1.02 ± 0.23	31.8 ± 1.23
20	H	2	N	B (19)	198–200	$C_{24}H_{30}N_2O_2{\cdot}HCl$	62.8 ± 9.77	696 ± 124
21	NO_2	2	N	B (32)	208–210	$C_{24}H_{29}N_3O_4{\cdot}2HCl$	2.78 ± 0.47	30.3 ± 1.67
22	I	2	N	B (15)	186–188	$C_{24}H_{29}INO_2{\cdot}HCl{\cdot}H_2O$	22.8 ± 4.99	293 ± 10.7
23	Cl	2	N	B (19)	199–202	$C_{24}H_{29}ClN_2O_2{\cdot}HCl$	76.9 ± 9.77	763 ± 21.7
24	H	3	CH	A (50)	187–188	$C_{26}H_{33}NO_2{\cdot}HCl$	0.50 ± 0.11	1.17 ± 0.29
25	NO_2	3	CH	A (67)	177–180	$C_{26}H_{32}N_2O_4{\cdot}HCl$	0.27 ± 0.08	0.88 ± 0.10
26	Cl	3	CH	A (62)	157–158	$C_{26}H_{32}ClNO_2{\cdot}HCl$	1.51 ± 0.12	4.41 ± 1.21
27	I	3	CH	A (25)	165–168	$C_{26}H_{32}INO_2{\cdot}HCl$	0.88 ± 0.22	6.49 ± 1.06
28	OCH_3	3	CH	A (33)	154–155	$C_{27}H_{35}NO_3{\cdot}HCl{\cdot}0.5H_2O$	0.65 ± 0.18	1.71 ± 0.39
32	H	4	CH	C (31)	128–130	$C_{27}H_{35}NO_2{\cdot}HCl{\cdot}0.25H_2O$	0.51 ± 0.12	0.69 ± 0.08
33	H	5	CH	C (81)	135–138	$C_{28}H_{37}NO_2{\cdot}HCl{\cdot}0.25H_2O$	0.61 ± 0.02	1.05 ± 0.12
34	H	6	CH	C (76)	150–158	$C_{29}H_{39}NO_2{\cdot}HCl$	1.21 ± 0.05	1.88 ± 0.18
4, caramiphen							26 ± 4	658 ± 129
1, (+)-pentazocine							2.1 ± 0.1	562 ± 165
7, haloperidol							0.6 ± 0.1	6 ± 0.6
6, DTG							107 ± 21	70 ± 11

[a] Data are the mean ± SEM of at least three separate determinations performed in triplicate. [b] For explanation of chemistry methods A, B, and C and details of binding methodology, see the Experimental Section.

phen, which we previously proposed as a σ_1-selective ligand,[28] had higher affinity for the [³H]-(+)-PENT site (26 nM) than the [³H]DTG site (658 nM).

An evaluation of the new ligands shows that substitution of the diethylamino with a 4-phenylpiperidinyl moiety into the caramiphen framework (compound **14**) increased affinity 7-fold for σ_1 (3.9 nM) and 13-fold for σ_2 sites (52.3 nM). To evaluate the effect on σ binding of the distance between the piperidine nitrogen and lipophilic 1-phenylcyclopentanecarboxylate moiety, the alkyl spacer was varied from two to six carbons. Increasing the distance to three methylenes (**24**) resulted in approximately an 8-fold increase in affinity for σ_1 sites (0.50 nM) and a 45-fold increase in affinity for the [³H]DTG-defined σ_2 site (1.17 nM). The affinity of the butyl analog **32** was equal at the [³H]-(+)-PENT site (0.51 nM), with a slight increase in affinity for σ_2 sites (0.69 nM) compared to the propyl spaced derivative **24**. Further increasing the distance between these two key features resulted in a modest decrease in affinity. For example, the pentyl analog **33** had affinities of 0.61 and 1.05 nM at σ_1 and σ_2 sites respectively, whereas these values were 1.21 and 1.88 nM for the hexyl analog **34**. A distance of either three or four carbons was equally potent at [³H]-(+)-PENT binding sites, while a spacer of four methylenes showed optimum affinity for [³H]DTG sites.

A preliminary evaluation of the effect of para substitition on the phenyl ring of the lipophilic ester moiety also was conducted. Substituents greatly affected σ binding affinity and selectivity when the alkyl linker was a two-carbon distance (**15–19**) but showed a lesser effect with the propyl-spaced derivatives (**25–28**). Substitution of **14** with a *p*-nitro group (**15**) enhanced affinity for the [³H]-(+)-PENT site 80-fold with a 13-fold increase in affinity for the [³H]DTG site. The I, CN, Cl, and OCH_3 derivatives showed only a 3–4-fold (**16–19**) increase in affinity at the [³H]-(+)-PENT site. The affinity of the iodo derivative (**16**) at the [³H]DTG site was unchanged compared to **14**, while the CN (**17**), Cl (**18**) and OCH_3 (**19**) analogs showed approximately a 2-fold increase in binding affinity. With the unsubstituted analogs, increasing the alkyl spacer length to three methylenes enhanced affinity for the [³H]-(+)-PENT site (**24**, K_i = 0.5 nM) 8-fold. Substitution of **24** with a nitro (**25**) caused a further 2-fold increase (K_i = 0.27 nM for the [³H]-(+)-PENT site). The Cl (**26**), iodo (**27**), and OCH_3 (**28**) derivatives all showed weaker affinity for the [³H]-(+)-PENT and [³H]DTG sites. It is important to note **25** had 5-fold less affinity than the ethylene-spaced nitro analog **15** for the [³H]-(+)-PENT σ site. The piperazine derivatives were considerably weaker than the corresponding piperidine analogs (compare **20** to **14**), although the nitropiperazine analog **21** did result in an increase in affinity for both the [³H]-(+)-PENT and [³H]-DTG sites of approximately 20-fold compared to the unsubstituted derivative **20**. The iodopiperazine (**22**) showed a 2-fold increase in affinity for both sites while the chloro derivative (**23**) exhibited binding equal to **20**. Since para substitution of the propyl-spaced derivative showed minimal effects on σ binding, the higher homologs were not evaluated. To summarize, while numerous derivatives have affinities of 0.3 to 1.5 nM for [³H]-(+)-PENT sites, they are at least 6-fold less potent than the nitro-substituted piperidine analog **15**, one of the most potent inhibitors (K_i = 50 pM) of binding to the [³H]-(+)-PENT-defined σ site yet reported.

The pharmacophore for optimal σ binding has been the focus of numerous studies, resulting in many proposed models of the σ binding site.[1,3,15,32,33,39–41] As noted earlier, the σ site is composed of a primary lipophilic site and a site capable of binding a nitrogen atom. In addition, a second lipophilic site exists on the receptor that can be utilized in ligand binding. Thus, it is known that (+)-

Table 2. Receptor Selectivity[a] for σ Compounds

	Dopamine		muscarinic				
compd	D_1	D_2	M_1	M_2	NMDA	PCP	opioid
14	4900	1100	170	20%	15%	8%	63%
15	2900	350	880	1710	12%	7%	42%
16	>1000	55	-	-	-	8%	25%
17	>1000	195	-	-	-	-	-
20	-	>500	1470	98%	7%	1%	43%
21	1000	500	-	-	19%	10%	25%
22	650	215	-	-	-	7%	25%
24	10000	1200	170	670	-	-	-
28	6000	1000	-	-	-	-	-
32	3100	470	-	-	-	-	-
caramiphen	>1000	>500	1.2	32	19%	11%	ND
dextromethorphan	ND	ND	5070	>10000	2%	2246	ND
DTG	>5000[b]	>5000[b]	744	2960	0%	6690	3950
haloperidol	47[b]	1.1[b]	2140	6120	25%	>10000	1210
(+)-pentazocine	>5000[b]	>5000[b]	225	525	ND	4190	651

[a] Data are expressed as K_i values in nanomolar or percent inhibition at a final concentration of 10 μM and are the mean of at least two separate determinations performed in triplicate. Binding methods are described in the Experimental Section. ND = Not determined. [b] Data taken from ref 26.

benzomorphans bind to the PCP as well as the σ binding site.[42] One proposed difference between the two sites is the presence of this second lipophilic site on the σ receptor; this presumably results in increased affinity and selectivity.[32,33] For example, *N*-phenylalkyl substitution of *N*-normetazocine significantly enhanced affinity for the σ site labeled with [^{3}H]-(+)-3-PPP while affinity for PCP sites was decreased.[33] (+)-Pentazocine (**1**) [(+)-*N*-(3,3-dimethylallyl)normetazocine] bound with higher affinity than (+)-*N*-allylnormetazocine (**2**) (SKF-10,047) to σ receptors.[27] The *N*-phenylpropyl-, -butyl-, and -pentyl-*N*-normetazocine derivatives also had higher affinity for σ sites than the (+)-benzomorphan (+)-SKF-10,047.[33] Presumably the increase in affinity is a result of the effect of substituents capable of interacting with the second lipophilic site.

Glennon and co-workers[40] have proposed the N-substituted phenylethylamine moiety to constitute the primary pharmacophore, while Largent and co-workers[3] have suggested that 3- and 4-phenylpiperidines constitute important pharmacophores for σ binding. Glennon et al.[43] later reported that 4-phenylpiperidines were more potent σ ligands than the more flexible phenylethylamine derivatives. While many studies have focused on evaluating optimum structure for binding to the primary pharmacophore, very little information is available that evaluates structural variations (other than simple arylalkyls) for binding to the second lipophilic site. It has been demonstrated that binding to the second lipophilic site is not mandatory for σ affinity,[32,33] and it may even be possible for a compound to bind to lipophilic site two and not interact with site one, while retaining potent σ binding affinity. This assumes the second site is a primary component of the σ receptor and that a proper lipophilic shape and volume for significant interaction must be present to effectively bind in this mode. Our original work demonstrated that caramiphen binds with high affinity (26 nM) to the [^{3}H]-(+)-PENT site (nH = 0.98).[27,28] The 1-phenylcyclopentyl portion of caramiphen may bind more appropriately to the second site, rather than the primary lipophilic site. Our modeling studies have shown the shape and volume of the 1-phenylcyclopentyl group, and the N–π distance geometry, are both too large to fit the (+)-benzomorphan or 4-phenylpiperidine template to bind lipophilic site one. This distance is even longer with carbetapentane (**35**), although it has a K_i of 32 nM at [^{3}H]-(+)-PENT sites.[27] Further, dextromethorphan contains a cyclohexyl group fused on the benzomorphan skeleton, suggesting that increasing bulk at the primary lipophilic site decreases σ binding affinity (K_i = 228 nM).[27] Also, the inability of caramiphen to inhibit PCP binding supports the notion that caramiphen may not overlap with the (+)-benzomorphan site, but rather the second lipophilic site. In support of this observation, if the models proposed by Manallack[32] and Carroll[33] are correct, caramiphen should also exhibit some, albeit weak, affinity for the PCP site. Caramiphen was, however, unable to inhibit PCP binding even at concentrations of 10 μM (see Table 2). Su et al.[44] attempted to fit PRE-084 (**36**, IC_{50} = 44 nM vs [^{3}H]-(+)-SKF-10,047 binding) onto the primary σ-pharmacophore. Their model suggests PRE-084 binds to lipophilic site one without noting the unfavorable interaction caused by the bulky cyclohexyl group being away from the plane of the template. In further support of our proposed model, we have found in evaluating the σ affinity of a series of caramiphen derivatives that increasing the alkyl distance from the nitrogen atom (diethylamine group) to the ester function to three or four carbons further enhances σ binding affinity, as was observed with the novel 4-phenylpiperidine derivatives reported in this series.[45] In addition, there was a parallel effect of aromatic substituents on the 1-arylcyclopentyl portion[27,45] on σ binding affinity of both the caramiphen and the novel 4-phenylpiperidine caramiphen analogs, inferring the aryl groups in both series share common modes of binding. The higher affinity of the 4-phenylpiperidine analogs compared to the caramiphen derivatives was not unexpected since they interact with the three primary components of the σ binding site. Based on the very high affinity of the 4-phenylpiperidine derivatives reported in this series, a more favorable mode of binding of the 1-phenylcyclopentyl portion would be one in which the lipophilic ester portion binds to the second site in a similar fashion as the butyrophenone moiety of haloperidol. Figure 1 shows a low-energy conformation of compound **32** interacting with the three recognition sites of the σ receptor. Lipophilic site 1 and the amine site taken together bind 4-arylpiperidines or (+)-benzomorphans. Molecular modeling studies of the σ model are the subject of a separate publication.

A goal of this study was to design ligands with increased σ receptor selectivity. Numerous σ ligands also have affinity for dopamine D_1 and D_2, PCP, opioid, and/or NMDA receptors; some ligands like caramiphen have

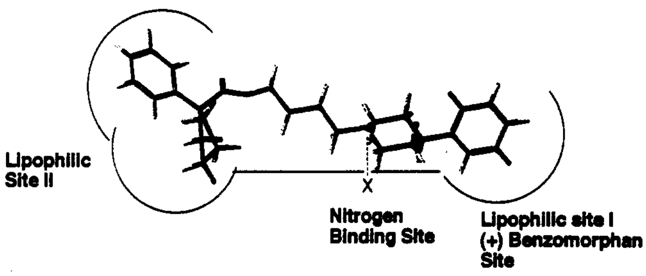


Figure 1. Schematic representation of a low-energy conformation of compound **32** binding to the σ site.

affinity for muscarinic M_1 and M_2 receptors. Thus, selected members of this series were evaluated for their ability to bind to these other receptors (Table 2). Incorporation of large bulky groups at the nitrogen atom of antimuscarinic agents has been reported to reduce muscarinic receptor affinity.[46,47] Compound **14**, which exhibits significantly greater affinity for σ sites, showed 140-fold lower binding affinity for muscarinic M_1 receptors (K_i = 170 nM) and was essentially inactive at M_2 sites compared to caramiphen. Compound **24** also showed weak binding affinity at M_1 and M_2 sites. All compounds tested showed weak affinity for D_1 sites, whereas a few had moderate D_2 binding affinity (**15**, **16**, **17**, **22**). Compounds **14** and **24** exhibited 5 and 10 μM affinity for D_1 receptors, respectively, and greater than 1 μM for D_2 receptors. The iodo derivative **16**, a potent σ binding ligand, had some affinity for D_2 sites (K_i = 55 nM). None of the compounds tested displaced greater than 50% of specific binding at PCP, opioid, or NMDA binding sites at a concentration of 10 μM.

The nitro derivative **15** (RLH-033) is one of the most potent σ ligands reported to date for the [^{3}H]-(+)-PENT-labeled σ site (K_i = 50 pM). RLH-033 displayed significant selectivity for the [^{3}H]-(+)-PENT site over M_1 (> 17 600-fold), M_2 (> 34 200-fold), D_1 (> 58 000-fold), or D_2 (> 7000-fold) receptors. It also was essentially inactive at PCP, NMDA, and opioid receptors. The derivative **24** also shows promise as a σ-selective agent, demonstrating subnanomolar σ binding affinity and a selectivity for [^{3}H]-(+)-PENT over M_1 (> 340-fold), M_2 (> 1340-fold), D_1 (>20 000-fold), and D_2 (>2400-fold) receptors.

It was predicted that the compounds in this series would show weak affinity for dopamine receptors. The dopamine receptor, similar to the σ site, has been described as consisting of an aromatic ring binding site, a nitrogen binding site, and a hydrogen bond donor site as primary binding sites.[48–50] Importantly, there is also a lipophilic accessory binding site located on the dopamine receptor surface that binds effectively groups such as the *tert*-butyl of butaclamol, the butyrophenone phenyl of haloperidol, or the azaspiro[4.5]decane-7,9-dione of buspirone. Proper occupancy of this accessory binding site is essential for high neuroleptic activity.[48,49] This site has been viewed as a uniquely shaped cavity, accepting a specific volume and having a surface diameter of 2.5 Å.[48] The molecular volume of the 1-phenylcyclopentyl group (molecular modeling shows the phenyl to cyclopentyl distance to be ca. 6 Å) makes this an unfavorable interaction for efficiently binding to the dopamine D_2 receptor.

In conclusion, a novel series of (4-phenylpiperidinyl)-alkyl 1-phenylcyclopentanecarboxylates was prepared that had high affinity and selectivity for the σ recognition site. The 4-phenylpiperidines were more potent than the corresponding 4-phenylpiperazines. For unsubstituted derivatives an optimum distance was obtained with a three (**24**) or four (**32**) methylene spacer between the ester and piperidinyl nitrogen, while with para substitution a two-carbon spacer was optimum. From this research, 2-(4-phenylpiperidinyl)ethyl 1-(4-nitrophenyl)cyclopentanecarboxylate (**15**) was designed and found to be one of the most potent ligands reported for inhibition of binding to the σ site labeled by [^{3}H]-(+)-PENT, with a K_i of 50 pM. This compound displayed significant selectivity for σ receptors over muscarinic M_1, M_2, dopamine D_1, D_2, PCP, opioid, and NMDA receptors. Compounds **15** (RLH-033), **24** (RLH-095), and **32** (RLH-102) are valuable tools that can be used to define further the biology of the σ recognition site.

Experimental Section

Chemistry. Proton magnetic resonance spectra were obtained with a Varian XL-200 spectrometer with tetramethylsilane as an internal standard. Infrared spectra were obtained with a Perkin-Elmer 1310 spectrophotometer. Spectral data were consistent with the assigned structure. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Quantitative Technologies, and values were within 0.4% of the calculated values. Column chromatography was performed on silica gel 60 (230–400 mesh). 1-(4-Chlorophenyl)cyclopentanecarboxylic acid and 1-(4-methoxyphenyl)cyclopentanecarboxylic acid were purchased from Aldrich Chemical Co. and used as received. 1-(4-Iodophenyl)cyclopentanecarboxylic acid, 1-(4-cyanophenyl)-cyclopentanecarboxylic acid, and 1-(4-nitrophenyl)cyclopentanecarboxylic acid were prepared by literature methods.[29]

2-(4-Phenylpiperidinyl)ethanol (10). A mixture of 4-phenylpiperidine (2.0 g, 12.4 mmol) and 2-bromoethanol (1.54 g, 12.4 mmol) in acetonitrile (25 mL) containing 2.0 g of anhydrous K_2CO_3 was stirred at reflux 4 h. After cooling to ambient temperature, the mixture was filtered and concentrated under reduced pressure. The residue was suspended in saturated NaCl solution (20 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined CH_2Cl_2 layers were dried ($MgSO_4$) and then concentrated at reduced pressure to give an oil. Purification by column chromatography (9:1:0.5 CH_2Cl_2:MeOH:NH_4OH) gave 1.6 g (63%) of **10** as a golden oil.[35] ^{1}H NMR ($CDCl_3$): δ 1.65–1.95 (m, 4H), 2.0–2.3 (m, 2H), 2.4–2.7 (m, 3H), 2.9 (bs, 1H), 3.1–3.3 (m, 2H), 3.7 (t, 2H), 7.2–7.4 (m, 5H).

1-(2-Hydroxyethyl)-4-phenylpiperazine (11). A mixture of 1-phenylpiperazine (4.0 g, 24.8 mmol) and 2-bromoethanol (3.1 g, 24.8 mmol) in acetonitrile containing 2.0 g of anhydrous K_2CO_3 was stirred at reflux for 4 h. The solution was cooled to ambient temperature, filtered, and then concentrated at reduced pressure to give a crude solid. Recrystallization from 2-propanol gave 3.3 g (65%) of **11** as a white solid, mp 83–84 °C (lit.[34] mp 82.5–83.0). ^{1}H NMR ($CDCl_3$): δ 2.6 (t, 2H), 2.7 (t, 4H), 2.8 (bs, 1H), 3.2 (t, 4H), 3.7 (t, 2H), 6.8–7.0 (m, 3H), 7.2–7.3 (m, 2H).

3-(4-Phenylpiperidinyl)propanol (12). A mixture of 4-phenylpiperidine (2.0 g, 12.4 mmol) and 3-bromopropanol (1.7 g, 12.4 mmol) in acetonitrile (25 mL) containing 2.0 g of anhydrous K_2CO_3 was stirred at reflux for 4 h. The solution was cooled to ambient temperature, filtered, and then concentrated at reduced pressure to give a crude solid. The solid was suspended in saturated NaCl solution (25 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined CH_2Cl_2 layers were dried ($MgSO_4$) and concentrated at reduced pressure. The product was recrystallized from 2-propanol to give 1.5 g (55%) as a white solid, mp 87–89 °C (lit.[36] mp 89–91 °C). ^{1}H NMR ($CDCl_3$): δ 1.7–1.95 (m, 6H), 2.05–2.2 (m, 2H), 2.45–2.65 (m, 1H), 2.7 (t, 2H), 3.2–3.3 (bd, 2H), 3.85 (t, 2H), 7.15–7.35 (m, 5H).

2-(4-Phenylpiperidinyl)ethyl 1-Phenylcyclopentanecarboxylate Hydrochloride (14) (Method A). To a solution of 1-phenylcyclopentanecarboxylic acid (500 mg, 2.63 mmol) in dry benzene (20 mL) were added dropwise thionyl chloride (2 mL, 27.4 mmol) and DMF (2 drops), and then the mixture was stirred at reflux for 2 h. After being cooled to ambient temperature, the mixture was concentrated at reduced pressure to an oil and then reconcentrated with benzene (2 × 15 mL) to remove traces of thionyl chloride. The acid chloride was dissolved in dry benzene (20 mL) and anhydrous K_2CO_3 (2.0 g) added. 2-(4-Phenylpiperidinyl)ethanol (**10**) (600 mg, 2.9 mmol) in benzene (3 mL) was added, and the mixture was stirred at reflux 6 h. The reaction mixture was cooled to ambient temperature, filtered, and concentrated at reduced pressure. The product was dissolved in $CHCl_3$ (20 mL), extracted with 2 N Na_2CO_3 (2 × 20 mL), 2 N HCl (2 × 20 mL), H_2O (2 × 20 mL), and saturated NaCl solution (3 × 20 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration, and 1 mL of a saturated ether–HCl(g) solution was added. The solvent was concentrated at reduced pressure to give a solid. Recrystallization from $CHCl_3$–Et_2O gave 300 mg (28%) of **14** as a white solid, mp 180–182 °C. ^1H NMR ($CDCl_3$): δ 1.6 (bs, 6H), 1.85–2.45 (m, 7H), 2.55–2.7 (m, 2H), 3.05–3.3 (m, 4H), 4.6 (m, 2H), 7.15–7.45 (m, 10H). Anal. ($C_{25}H_{31}NO_2$·HCl) C, H, N.

2-(4-Phenylpiperazinyl)ethyl 1-Phenylcyclopentanecarboxylate Hydrochloride (20) (Method B). To a solution of 1-phenylcyclopentanecarboxylic acid (500 mg, 2.63 mmol) in dry benzene (20 mL) were added dropwise thionyl chloride (2 mL, 27.4 mmol) and DMF (2 drops), and then the mixture was stirred at reflux for 2 h. The mixture was concentrated at reduced pressure to an oil and then reconcentrated with benzene (2 × 15 mL) to remove traces of thionyl chloride. The acid chloride was dissolved in dry benzene (20 mL) and anhydrous K_2CO_3 (2.0 g) added. 1-(2-Hydroxyethyl)-4-phenylpiperazine (**11**) (1.1 g, 5.3 mmol) in benzene (3 mL) was added, and the mixture was stirred at reflux for 4 h. The reaction mixture was cooled to ambient temperature, filtered, and concentrated at reduced pressure. The residue was dissolved in $CHCl_3$ (20 mL), extracted with 2 N Na_2CO_3 (2 × 20 mL) and saturated NaCl solution (2 × 20 mL), and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent concentrated. The product was purified by column chromatography (silica gel, CH_2Cl_2:MeOH:NH_4OH, 95:5:0.5). The hydrochloride salt was prepared by adding an Et_2O–HCl(g) solution to a cold solution of the base in $CHCl_3$. The solvent was concentrated and the product dried under vacuum (0.1 mm; 12 h). Recrystallization from MeOH–Et_2O gave 210 mg (19%) of **20** as a white solid, mp 198–200 °C. ^1H NMR ($CDCl_3$): δ 1.6 (bs, 4H), 1.8–2.0 (m, 2H), 2.45–2.6 (m, 2H), 2.9–3.25 (m, 6H), 3.3 (bs, 2H), 3.6 (bd, 2H), 4.4 (m, 2H), 6.8–7.0 (m, 3H), 7.2–7.45 (m, 7H). Anal. ($C_{24}H_{30}N_2O_2$·HCl) C, H, N.

4-Chlorobutyl 1-Phenylcyclopentanecarboxylate (29). A mixture of potassium 1-phenylcyclopentanecarboxylate (500 mg, 2.2 mmol) and 1-bromo-4-chlorobutane (1.5 g, 8.8 mmol) in acetonitrile (25 mL) was stirred at reflux 12 h. The solution was cooled on an ice bath, filtered, and then concentrated at reduced pressure to give an oil. The excess 1-bromo-4-chlorobutane was removed by distillation (110 °C, 0.25 mm) to leave an orange oil. Column chromatography (hexane-EtOAc, 2:1) gave **29** as a clear oil, 530 mg (91%). ^1H NMR ($CDCl_3$): δ 1.6–1.8 (bm, 8H), 1.8–2.0 (m, 2H), 2.55–2.75 (m, 2H), 3.3–3.5 (m, 2H), 4.1 (t, 2H), 7.2–7.5 (m, 5H).

5-Bromopentyl 1-Phenylcyclopentanecarboxylate (30). This compound was prepared by the same general procedure as **29** using potassium 1-phenylcyclopentanecarboxylate (1.0 g, 4.4 mmol) and 1,5-dibromohexane (4.03 g, 17.5 mmol) to give 1.3 g (82%) of **30** as a clear oil. ^1H NMR ($CDCl_3$): δ 1.2–1.4 (m, 2H), 1.45–1.6 (m, 2H), 1.7 (m, 6H), 1.75–2.0 (m, 2H), 2.6–2.75 (m, 2H), 3.3 (t, 2H), 4.0 (t, 2H), 7.2–7.45 (m, 5H).

6-Bromohexyl 1-Phenylcyclopentanecarboxylate (31). This compound was prepared by the same general procedure as **29** using potassium 1-phenylcyclopentanecarboxylate (1.2 g, 5.2 mmol) and 1,6-dibromohexane (5.1 g, 20.7 mmol) to give 1.45 g (78%) of **31** as a clear oil. ^1H NMR ($CDCl_3$): δ 1.2 (m, 2H), 1.35 (m, 2H), 1.5 (m, 2H), 1.7 (bs, 6H), 1.75–1.95 (m, 2H), 2.6–2.75 (m, 2H), 3.35 (t, 2H), 4.0 (t, 2H), 7.2–7.45 (m, 5H).

6-(4-Phenylpiperidinyl)hexyl 1-Phenylcyclopentanecarboxylate Hydrochloride (34) (Method C). A mixture of 6-bromohexyl 1-phenylcyclopentanecarboxylate (**31**) (600 mg, 1.7 mmol) and 4-phenylpiperidine (275 mg, 1.7 mmol) in acetonitrile (75 mL) containing anhydrous K_2CO_3 (2.0 g) was stirred at reflux 12 h. The solution was cooled to ambient temperature, filtered, and concentrated at reduced pressure. The residue was dissolved in $CHCl_3$ (25 mL), extracted with 2 N HCl (2 × 25 mL) and saturated NaCl solution (3 × 25 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration, the solvent concentrated at reduced pressure, and the product dried under vacuum at ambient temperature (0.2 mm, 14 h). Recrystallization ($CHCl_3$–Et_2O–hexane) gave 610 mg (76%) of **34** as a white solid, mp 150–158 °C. ^1H NMR ($CDCl_3$): δ 1.2 (m, 4H), 1.5 (t, 2H), 1.6–2.05 (m, 10H), 2.5–2.95 (m, 9H), 3.6 (bd, 2H), 4.0 (t, 2H), 7.15–7.45 (m, 10H). Anal. ($C_{29}H_{39}NO_2$·HCl) C, H, N.

Radioligand Binding Studies. The binding of [^3H]-(+)-PENT and [^3H]DTG to σ sites was performed as previously described.[24,27,28] Briefly, brains from male Hartley guinea pigs (Hazelton Labs, Denver, PA) were homogenized in 10 volumes (wt/vol) of 0.32 M sucrose with a Brinkmann Polytron at setting 5, 30 s. The homogenate was centrifuged at 900*g* for 10 min at 4 °C, and the resulting supernatant was collected and centrifuged at 22000*g* for 20 min at 4 °C. The pellet was resuspended in 10 volumes of Tris-HCl buffer (50 mM, pH 7.4), incubated at 37 °C for 30 min, and centrifuged at 22000*g* for 20 min at 4 °C. Following this, the pellet was resuspended in Tris buffer and frozen in 5–10-mL aliquots, corresponding to a tissue concentration of 100 mg/mL, at −70 °C. On the day of the assay, membrane aliquots were thawed, resuspended in fresh Tris-HCl buffer, and stored on ice until use. Each assay tube contained 100 μL of [^3H]ligand at a final concentration of approximately 0.5 nM for [^3H]-(+)-pentazocine or 4 nM for [^3H]di(2-tolyl)guanidine (DTG), 100 μL of various concentrations of the compounds of interest, 500 μL of the tissue suspension, and 300 μL of buffer to a final assay volume of 1 mL and a final tissue concentration of approximately 0.3 mg of protein/tube. Non-specific binding was defined by addition of a final concentration of 1 (for [^3H]-(+)-pentazocine) or 10 μM haloperidol (for [^3H]DTG) to blank tubes. Incubation conditions were 37 °C for 150 min in the [^3H]-(+)-pentazocine assay and 25 °C for 90 min in the [^3H]DTG assay. The reaction was terminated by rapid filtration over Whatman GF/B glass fiber filters that were presoaked in a solution of 0.5% poly(ethyleneimine) for at least 1 h prior to use. Filters were washed with three 4 mL volumes of cold Tris-HCl buffer. Following addition of scintillation cocktail, samples were allowed to equilibrate overnight. The amount of bound radioactivity was determined by liquid scintillation spectrometry using a Beckman LS 5000TA liquid scintillation counter with an efficiency for tritium of approximately 60%. K_i values for the binding of test compounds were calculated using the EBDA/LIGAND program, purchased from Elsevier/Biosoft, Inc.

Measurement of binding to muscarinic M_1 and M_2 receptor subtypes in rat cortex or heart was performed as previously described,[29] using the ligands [^3H]pirenzepine and [^3H]QNB at concentrations of 0.5 and 0.05 nM, respectively. Binding to dopamine receptors in rat striata was performed using the method of Mottola et al.,[51] with [^3H]SCH-23390 and [^3H]spiperone at concentrations of 0.25 and 0.07 nM to label D_1 and D_2 receptors. Compounds were screened at a final concentration of 10 μM for inhibition of [^3H]CGS-19755 binding[52] to NMDA receptors, [^3H]TCP binding[53] to PCP receptors, and [^3H]naloxone binding[54] to opioid receptors in rat forebrain using established methods.

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