Synthesis and Evaluation of Aryl-Substituted *N*-(Arylethyl)-*N*-methyl-2-(1-pyrrolidinyl)ethylamines and Corresponding Arylacetamides for Sigma Receptor Affinity

Ying Zhang, Wanda Williams, Wayne D. Bowen, and Kenner C. Rice*

Laboratory of Medicinal Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 8 Center Drive, MSC 0815, Bethesda, Maryland 20892-0815

Received January 26, 1996[⊗]

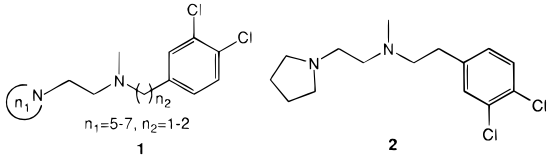
A series of aryl-monosubstituted arylacetamides (**4**−**9**) and arylethylenediamine (**10**−**18**) compounds were synthesized based on the structure of the high-affinity sigma ligand *N*-[2-(3,4-dichlorophenyl)ethyl]-*N*-methyl-2-(1-pyrrolidinyl)ethylamine (**2**). These compounds were prepared to evaluate the effect of aromatic substitution patterns on sigma-1 and sigma-2 receptor binding affinity and selectivity. The data indicate that **10**−**18** possessed higher affinity than **4**−**9** for both sigma sites, especially when substituted with an electron-withdrawing group. The diamine compounds **10**−**18** were selective for sigma-1 binding sites, whereas the arylacetamide compounds **4**−**9** generally exhibited an increased selectivity for sigma-2 sites compared to sigma-1. No clear pattern between the orientation of aromatic substituents and the sigma binding activity was observed.

Introduction

Sigma receptors have been the focus of extensive studies because of their potentially important roles in several biochemical, physiological, and behavioral processes. Some of these include regulation of motor behavior and postural tone,[1−3] negative modulation of the phosphoinositide response to muscarinic cholinergic agonists,[4,5] modulation of NMDA receptor responses,[6] regulation of smooth muscle contraction,[7,8] neuroprotective activity,[9,10] and neurodegenerative effects.[11−13] They also exhibit high affinity for several classes of psychotropic drugs.[14] Evidence has been presented for at least two sigma receptor subtypes, designated as sigma-1 and sigma-2, based upon the differential properties of structurally diverse ligands.[15,16] Early studies suggested that σ_1 sites regulate gastrointestinal effects,[17,18] inhibit both electrically and serotonin-induced guinea pig ileum contractions,[19] and mediate the inhibition by sigma ligands of the muscarinic acetylcholine receptor phosphoinositide response.[5] On the other hand, the σ_2 subtype has been shown to mediate the motor effects of σ ligands,[3,20] and σ_2 sites may also mediate the effects of certain sigma drugs on K^+ channels.[21] The ability of σ ligands to affect motor systems has suggested a role in the regulation of motor behavior and in mediation of motor side effects of neuroleptics. Thus, sigma compounds, especially σ_2-specific agents, may be useful therapeutic agents for treatment of drug-induced and idiotypic motor disorders such as dystonia.

It has been shown that compounds of the arylethylenediamine class (**1**) (Chart 1) have high affinity for σ receptors.[22] The ethylenediamine σ ligand **2** possesses high affinity for both σ_1 and σ_2 receptors [$K_i(\sigma_1) = 2.1$ nM; $K_i(\sigma_2) = 8.1$ nM], although it shows higher potency for the σ_1 binding site. Previous studies have shown that both σ_1 binding and σ_2 binding are greatly affected by aromatic halogen substitution, and that the binding affinity at the σ_2 site varies considerably more with the nature and orientation of the halogen.[23] This finding indicates that the substitution pattern on the aromatic ring has a significant impact on the sigma receptor subtype selectivity. However, aside from halogenation, the effects of other aromatic substitution have not yet been studied. Earlier work has shown that small changes in aromatic substitution can have a dramatic effect on biological activity as in the etonitazene series of opioids[24] and 1,4-benzodiazapines.[25] Thus, the aim of this research is to use the nonhalogenated **2** as a template to study the relationship between the aromatic substitution pattern of the ethylenediamine series of ligands and the sigma binding activity, with particular interest in finding compounds that selectively bind with high affinity to the σ_2 site.

Chart 1



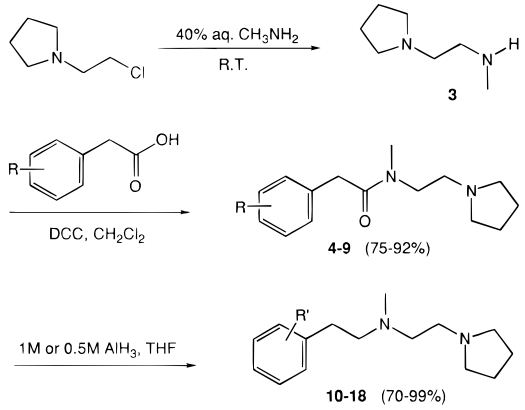
Chemistry

The precursor **3** was synthesized as described previously.[22] Coupling of this compound with *ortho*-, *meta*-, and *para*-substituted phenylacetic acids, using DCC (1,3-dicyclohexylcarbodiimide) as a coupling agent, afforded the corresponding amides **4**−**9** in a yield of 75−92% (Scheme 1). The methoxyphenylethylenediamine compounds **10**−**12** were obtained directly from a reduction of amides **4**−**6** using 1 M alane in THF.[22,30] Alane (1 M in THF) reduction of the nitroaromatic amine amides **7**−**9** for 10 min resulted in formation of the corresponding aminophenylethylenediamine **16**−**18**. The preparation of the nitro diamines **13**−**15** required a milder reducing medium, with 0.5 M alane in THF and shorter reaction time (2 min). All of the compounds were purified by appropriate salt formation followed by recrystallization, or a combination of column chromatography and appropriate salt formation. The structure

[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1996.

S0022-2623(96)00081-7

Scheme 1. Synthesis of Aryl-Substituted Acetamides and Ethylenediamines



and purity of these compounds were confirmed by CI-MS, ^{1}H-NMR (300 MHz), and elemental analysis.

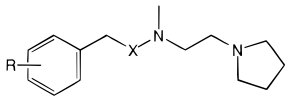
Results and Discussion

A series of aryl mono-substituted ethylenediamine compounds and their corresponding arylacetamides were synthesized based upon the structure of the high-affinity sigma ligand *N*-[2-(3,4-dichlorophenyl)ethyl]-*N*-methyl-2-(1-pyrrolidinyl)ethylamine **2**.[22] The study of the effects of aromatic substitution on sigma binding activities allows us to further delineate the structural requirements for sigma affinity and separation of sigma-1 and sigma-2 binding activities.

Inspection of Table 1 shows that, overall, the ethylenediamine compounds **10**−**18** had higher affinity than the arylacetamides **4**−**9** at both σ_1 and σ_2 binding sites. This observation is consistent with the previous view that a minimum of two amine functions with an ethylene spacer is required in the structure to achieve high sigma binding affinity. The nitro-substituted compounds among the series generally possessed higher potency than the corresponding methoxy or aromatic amino compounds, following the trend nitro > methoxy > amino. This result indicates that an electron-withdrawing group on the aromatic region may favor sigma binding affinity.

The ethylenediamines **10**−**18** all showed higher affinity at σ_1 sites compared to σ_2. Among the ethylenediamine series, the *o*-, *m*-, and *p*-nitro-substituted ethylenediamines showed the highest potency and selectivity at the σ_1 binding site [$K_i(\sigma_1) = 4.26-7.74$ nM]. Of the nitro derivatives, the *o*-nitro compound **13** showed the lowest affinity at σ_2 sites, making it 40-fold selective for σ_1 sites. The *p*-nitro compound **15** was the most potent for σ_1 binding among the series. It also exhibited the highest σ_2 affinity of all compounds shown in Table 2 [$K_i(\sigma_2) = 62.7$ nM]. For those compounds with an amine function on the aromatic ring **16**−**18**, both σ_1 and σ_2 binding affinities decreased dramatically,

Table 1. Physical and Chemical Data



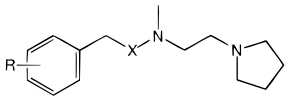
4-9 X= C=O

10-18 X= CH_2

compd no.	R	salt	method	yield (%)[a]	cryst solvent	mp (°C)	CI-MS *m/z* (MH^+)	analysis[b]
4[c]	*o*-OMe	oxalate	A	87	2-PrOH	151−315	277	$C_{16}H_{24}N_2O_2 \cdot C_2H_2O_4$
5[c]	*m*-OMe	oxalate	A	75	acetone	91−92	277	$C_{16}H_{24}N_2O_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$
6[c]	*p*-OMe	oxalate	A	84	2-PrOH	121−122	277	$C_{16}H_{24}N_2O_2 \cdot C_2H_2O_4$
7[c]	*o*-NO_2	oxalate	A	91	EtOH	123−124	292	$C_{15}H_{21}N_3O_3 \cdot C_2H_2O_4$
8[c]	*m*-NO_2	oxalate	A	92	acetone	111−112	292	$C_{15}H_{21}N_3O_3 \cdot C_2H_2O_4$
9[c]	*p*-NO_2	oxalate	A	83	acetone	162−163	292	$C_{15}H_{21}N_3O_3 \cdot C_2H_2O_4$
10[c]	*o*-OMe	diHBr	B	95	EtOH	221−222	263	$C_{16}H_{26}N_2O \cdot 2HBr$
11[c]	*m*-OMe	diHBr	B	94	MeOH	227−229	263	$C_{16}H_{26}N_2O \cdot 2HBr$
12[c]	*p*-OMe	diHBr	B	99	EtOH	239−240	263	$C_{16}H_{26}N_2O \cdot 2HBr$
13[c]	*o*-NO_2	difumarate	C	70	EtOH	189−190	278	$C_{15}H_{23}N_3O_2 \cdot 2C_4H_4O_4$
14[c]	*m*-NO_2	difumarate	C	74	EtOH	198−199	278	$C_{15}H_{23}N_3O_2 \cdot 2C_4H_4O_4$
15[c]	*p*-NO_2	difumarate	C	86	EtOH	177−178	278	$C_{15}H_{23}N_3O_2 \cdot 2C_4H_4O_4$
16[c]	*o*-NH_2	difumarate	B	80	EtOH	182−183	248	$C_{15}H_{25}N_3 \cdot 2C_4H_4O_4$
17[c]	*m*-NH_2	difumarate	B	86	EtOH	166−168	248	$C_{15}H_{25}N_3 \cdot 2C_4H_4O_4$
18[c]	*p*-NH_2	difumarate	B	80	acetone	184−185	248	$C_{15}H_{25}N_3 \cdot 2C_4H_4O_4$

[a] All reported yields are nonoptimized. [b] Elemental compositions (%) were found to be within ±0.4% of the theoretical values of C, H, and N. [c] The ^{1}H-NMR data for the free base of this compound are shown in ref 26.

Table 2. Sigma Binding of Aryl Mono-Substituted σ Ligands **4**−**18**[a]



compd no.	R	X	K_i'([^{3}H](+)-pent) in guinea pig (σ_1) (nM)	K_i([^{3}H]DTG + dextrallorphan) in rat liver (σ_2) (nM)	σ_1/σ_2
4	*o*-OMe	C=O	5460 ± 690	3170 ± 140	1.7
5	*m*-OMe	C=O	3100 ± 20	1110 ± 55	2.8
6	*p*-OMe	C=O	2220 ± 61	1220 ± 95	1.8
7	*o*-NO_2	C=O	736 ± 120	1490 ± 130	0.49
8	*m*-NO_2	C=O	1850 ± 180	539 ± 1	3.4
9	*p*-NO_2	C=O	869 ± 4	596 ± 37	1.5
10	*o*-OMe	CH_2	15.7 ± 2.0	144 ± 1	0.11
11	*m*-OMe	CH_2	23.8 ± 1.7	209 ± 22	0.11
12	*p*-OMe	CH_2	30.3 ± 1.4	256 ± 2	0.12
13	*o*-NO_2	CH_2	7.7 ± 0.9	311 ± 4	0.02
14	*m*-NO_2	CH_2	6.4 ± 1.6	95.2 ± 0.7	0.07
15	*p*-NO_2	CH_2	4.3 ± 0.9	62.7 ± 0.1	0.07
16	*o*-NH_2	CH_2	291 ± 38	640 ± 25	0.45
17	*m*-NH_2	CH_2	579 ± 35	2240 ± 260	0.26
18	*p*-NH_2	CH_2	276 ± 13	974 ± 77	0.28

[a] Assays were carried out under the conditions described under Experimental Section. Twelve concentrations of unlabeled test ligand ranging from 0.05 nM to 10 000 nM or from 0.5 nM to 100 000 nM were incubated with guinea pig brain membranes and 3 nM [^{3}H](+)-pentazocine (σ_1 receptors) or with rat liver membranes and 5 nM [^{3}H]DTG in the presence of 1 μM dextrallorphan (σ_2 receptors). IC_{50} values were determined using the iterative curve-fitting program GraphPAD InPlot (San Diego, CA). IC_{50} values were then converted to apparent K_i values using the Cheng−Prusoff equation and radioligand K_d values determined previously.[28,29] Values are the averages of 2−3 experiments, ±SEM. Each experiment was carried out in duplicate.

although they showed an improved trend toward selectivity for the σ_2 binding site among the ethylenediamine series.

Comparing the aniline derivatives (**16**−**18**) with the corresponding phenylmethoxy compounds (**10**−**12**) in the ethylenediamine series, we found that **16**−**18** showed a 10−25-fold decrease in sigma-1 affinity and a 4−10-fold decrease in sigma-2 affinity, although both amino and methoxy functions are considered as strong electron-donating groups. This observation indicates that the hydrophobicity at the aromatic region may also play an important role in the binding affinity at σ_1 and σ_2 sites. We are currently engaged in preparing compounds with a more hydrophobic aromatic region such as naphthalene or alkylphenyl derivatives, and compounds with a more hydrophilic aromatic region such as phenolic or phenylsulfonic acid derivatives.

Unlike the ethylenediamines, the arylacetamide compounds with one exception exhibited higher affinity for σ_2 sites compared to σ_1. Compound **8** had a σ_1/σ_2 ratio of 3.4, and showed the highest selectivity as well as the most potency for the σ_2-subtype binding among the compounds in the arylacetamide series **4**−**9**. These results suggest that introduction of structural rigidity from an amide function may increase σ_2 selectivity of the acetamide compounds. Alternatively, the carbonyl portion of the amide function may allow hydrogen bonding to a group present in the σ_2 receptor which does not occur in the σ_1 receptor.

No consistent relationship was observed between the orientation of aromatic substituents and the sigma binding activity in both arylacetamide **4**−**9** and arylethylenediamine **10**−**18** series. The same was observed in the series of halogenated sigma ligands reported by He *et al.*[23] Furthermore, as observed in the study by He *et al.*,[23] among arylethylenediamines there was generally a larger effect of substituent orientation on sigma-2 binding compared to sigma-1 binding. This was especially apparent in the nitro and amino series (**13**−**18**). This is consistent with more stringent structural requirements of the sigma-2 site, which is also indicated by the greater difficulty in finding compounds with high sigma-2 affinity. In the arylethylenediamine series, the binding affinity of **13**−**15** presented a trend of *p*-nitro higher than *m*-nitro and higher than *o*-nitro at both σ_1 and σ_2 sites. This seems to follow the same pattern as the similar compounds with an iodo group in the aromatic region.[23] However, more compounds and further studies will be needed in order to more precisely define the structure−activity relationship (SAR) of both σ_1 and σ_2 receptor subtypes.

Experimental Section

Chemical Materials and Methods. Melting points were taken on a Mel-Temp II capillary apparatus and are reported uncorrected. CI-MS (chemical ionization mass spectra) were obtained using a Finnigan 1015 mass spectrometer. ^{1}H-NMR spectra were performed using $CDCl_3$ solutions of free bases on a Varian XL-300 spectrometer. Chemical shifts are expressed relative to a tetramethylsilane internal reference in parts per million (ppm) on the δ scale. Elemental analyses were obtained from Atlantic Microlabs, Atlanta, GA. Thin-layer chromatography (TLC) was performed on Analtech GHLF silica gel plates (250 μm) eluted with 90:9:1 CH_2Cl_2/MeOH/concentrated aqueous NH_4OH.

[^{3}H](+)-Pentazocine (51.7 Ci/mmol) was synthesized as described previously.[27] [^{3}H]DTG (39.1 Ci/mmol) was purchased from DuPont/New England Nuclear (Boston, MA). Haloperidol, Tris-HCl, and poly(ethylenimine) were purchased from Sigma Chemicals (St. Louis, MO).

General Method A. To a stirred solution of DCC in CH_2Cl_2 (5 mmol of DCC to 20 mL of CH_2Cl_2) was added a solution of carboxylic acid in CH_2Cl_2 (5 mmol of acid to 20 mL of CH_2Cl_2). The mixture was stirred at room temperature for 10 min before a solution of *N*-methyl-2-(1-pyrrolidinyl)ethylamine **3** in CH_2Cl_2 (5 mmol of **3** to 10 mL of CH_2Cl_2) was added. The reaction mixture was stirred at room temperature until TLC indicated the completion of the reaction. The molar ratio of DCC/carboxylic acid/diamine **3** was 2:1.5:1. The white precipitate of DCU was filtered off, and the filter cake was washed with CH_2Cl_2. The filtrate was extracted 3 times with 15% aqueous citric acid solution. The combined aqueous layer was

washed with diethyl ether, and then basified with concentrated aqueous NH_4OH to pH 10−11. The obtained aqueous layer was then extracted with CH_2Cl_2 3 times, and the combined organic layer was washed with water and a saturated aqueous NaCl solution, dried over $MgSO_4$, and evaporated to give the corresponding amine amides, which were further purified through their appropriate salts (see Table 1).

Method B. A solution of amine amide in THF was added dropwise to a stirred, freshly prepared solution of 1 M AlH_3 in THF.[22,30] The molar ratio of amide to AlH_3 was about 1:5. The reaction mixture was stirred at room temperature until TLC showed the disappearance of the amine amide. The reaction was then quenched by slowly pouring it into an aqueous NaOH solution (10%) in the ice/water bath. The mixture was extracted with CH_2Cl_2 3 times, and the combined organic layer was washed with water once and with saturated aqueous NaCl once, dried over $MgSO_4$, and evaporated to give the corresponding free base diamine compounds. These crude diamines were purified through crystallization or recrystallization of the denoted salt (see Table 1).

Method C. To a stirred, freshly prepared 0.5 M solution of AlH_3 in THF[22,30] was added dropwise a solution of amine amide in THF at room temperature. The molar ratio of amide to AlH_3 was approximately 1:5. The reaction was found to be complete within 2 min, and was quenched by pouring into an aqueous NaOH (10%) solution in an ice/water bath. The reaction was worked up according to method B, and the crude product was purified on a silica gel column with a mixed solvent of 200:10:1 CH_2Cl_2/MeOH/concentrated aqueous NH_4OH. The obtained diamines were further purified by the appropriate salt formation (see Table 1).

Biological Materials and Methods. (A) Ligand Binding Assay (σ_1 Receptors). σ_1 receptors were labeled as described previously, using the σ_1-selective probe [^{3}H](+)-pentazocine and guinea pig brain membranes.[28] Guinea pig brain membranes (350−500 μg of membrane protein) were incubated with 3 nM [^{3}H](+)-pentazocine in a total volume of 0.5 mL of 50 mM Tris-HCl, pH 8.0. Incubations were carried out for 120 min at 25 °C. Nonspecific binding was determined in the presence of 10 μM unlabeled haloperidol. Assays were terminated by dilution with 5 mL of ice-cold 10 mM Tris-HCl, pH 8.0, and vacuum filtration through glass fiber filters using a Brandel cell harvester (Gaithersburg, MD). Filters were then washed twice with 5 mL of ice-cold 10 mM Tris-HCl, pH 8.0. Filters were soaked in 0.5% poly(ethylenimine) for at least 30 min at 25 °C prior to use. Filters were counted in CytoScint cocktail (ICN, Costa Mesa, CA) after an overnight extraction of counts. Membranes were prepared from frozen guinea pig brains (minus cerebella) as previously described.[28]

(B) Ligand Binding Assays (σ_2 Receptors). σ_2 receptors were labeled as previously described using rat liver membranes, a rich source of σ_2 sites, and [^{3}H]DTG in the presence of 1 μM dextrallorphan to mask σ_1 receptors.[29] Assays were performed in 50 mM Tris-HCl, pH 8.0, for 120 min at 25 °C in a volume of 0.5 mL with 160 μg of membrane protein and 5 nM radioligand. Assays included 1 μM dextrallorphan to mask σ_1 binding. Nonspecific binding was determined in the presence of 10 μM haloperidol. All other manipulations were as described above for the σ_1 receptor assay. Rat liver membranes were prepared from the livers of male Sprague-Dawley rats as previously described.[29]

Acknowledgment. The authors offer their sincere appreciation to Noel Whittaker and Wesley White, LAC, NIDDK, for performing mass spectral analysis of all compounds in this paper. Y. Zhang acknowledges the financial support from the NIDDK Intramural Research Training Award Program.

References

(1) Walker, J. M.; Matsumoto, R. R.; Bowen, W. D.; Gans, D. L.; Jones, K. D.; Walker, F. O. Evidence for a role of haloperidol-sensitive sigma opiate receptors in the motor effects of antipsychotic drugs. *Neurology* **1988**, *38*, 961−965.

(2) Goldstein, S. R.; Matsumoto, R. R.; Thompson, T. L.; Patrick, R. L.; Bowen, W. D.; Walker, J. M. Motor effects of two sigma ligands mediated by nigrostriatal dopamine neurons. *Synapse* **1989**, *4*, 254−258.

(3) Matsumoto, R. R.; Hemstreet, M. K.; Lai, N.; Thurkauf, A.; de Costa, B. R.; Rice, K. C.; Hellewell, S. B.; Bowen, W. D.; Walker, J. M. Drug specificity of pharmacological dystonia. *Pharmacol. Biochem. Behav.* **1990**, *36*, 151−155.

(4) Bowen, W. D.; Kirschner, B. N.; Newman, A. H.; Rice, K. C. Sigma receptors negatively modulate agonist-stimulated phosphoinositide metabolism in rat brain. *Eur. J. Pharmacol.* **1988**, *149*, 399−400.

(5) Bowen, W. D.; Tolentino, P. J.; Hsu, K. K.; Cutts, J. M.; Naidu, S. S. Inhibition of the cholinergic phosphoinositide response by sigma ligands: Distinguishing a sigma receptor-mediated mechanism from a mechanism involving direct cholinergic antagonism. *Multiple Sigma and PCP Receptor Ligands: Mechanisms for Neuromodulation and Neuroprotection*; Kamenka, J.-M., Domino, E. F., Eds.; NPP Books: Ann Arbor, MI, 1992, pp 155−167.

(6) (a) Monnet, F. P.; Debonnel, G.; de Montigny, C. *In vivo* electrophysiological evidence for a selective modulation of *N*-methyl-D-aspartate-induced neuronal activation in rat CA3 dorsal hippocampus by sigma ligands. *J. Pharmacol. Exp. Ther.* **1992**, *261*, 123−130. (b) Gonzalez-Alvear, G. M.; Werling, L. L. Regulation of [^{3}H]dopamine release from rat striatal slices by sigma receptor ligands. *J. Pharmacol. Ther.* **1994**, *271*, 212−219.

(7) Vaupel, D. B.; Su, T. P. Guinea pig vas deferens preparation may contain both sigma receptors and phencyclidine receptors. *Eur. J. Pharmacol.* **1987**, *139*, 125−128.

(8) Massamiri, T.; Duckles, S. P. Multiple vascular effects of Sigma and PCP ligands. Inhibition of amine uptake and contractile responses. *J. Pharmacol. Exp. Ther.* **1990**, *253*, 124−129.

(9) Long, J. B.; Tidwell, R. E.; Tortella, F. C.; Rice, K. C.; de Costa, B. R. Selective sigma ligands protect aginst dynorphin A-induced spinal cord injury in rats. *Soc. Neurosci. Abstr.* **1990**, *16*, 1122, abstr. 461.4.

(10) Contreras, P. C.; Ragan, D. M.; Bremer, M. E.; Lanthorn, T. H.; Gray, N. M.; Iyengar, S.; Jacobson, A. E.; Rice, K. C.; de Costa, B. R. Evaluation of U50,488H analogs for neuroprotective activity in the gerbil. *Brain Res.* **1991**, *546*, 79−82.

(11) Vilner, B. J.; Bowen, W. D. Sigma receptor-active neuroleptics are cytotoxic to C6 glioma cells in culture. *Eur. J. Pharmacol., Mol. Pharmacol. Sect.* **1993**, *244*, 199−201.

(12) Bowen, W. D.; Vilner, B. J. Sigma receptor-mediated morphological and cytotoxic effects on primary cultures of rat central and peripheral nervous system. *Soc. Neurosci. Abstr.* **1994**, *20*, 747, abstr. 314.10.

(13) Vilner, B. J.; de Costa, B. R.; Bowen, W. D. Cytotoxic effects of sigma ligands: Sigma receptor-mediated alterations in cellular morphology and viability. *J. Neurosci.* **1995**, *15*, 117−134.

(14) Walker, J. M.; Bowen, W. D.; Walker, F. O.; Matsumoto, R. R.; de Costa, B. R.; Rice, K. C. Sigma receptors: biology and function. *Pharmacol. Rev.* **1990**, *42*, 355−402.

(15) Hellewell, S. B.; Bowen, W. D. A sigma-like binding site in rat pheochromocytoma (PC12) cells: Decreased affinity for (+)-benzomorphans and lower molecular weight suggest a different sigma receptor form from that in guinea pig brain. *Brain Res.* **1990**, *527*, 244−253.

(16) Quirion, R.; Bowen, W. D.; Itzhak, Y.; Junien, J. L.; Musacchio, J. M.; Rothman, R. B.; Su, T. P.; Tam, S. W.; Taylor, D. P. A proposal for the classification of sigma binding sites. *Trends Pharmacol. Sci.* **1992**, *13*, 85−86.

(17) Riviere, P. J. M.; Pascaud, X.; Junien, J. L.; Porreca, F. Neuropeptide Y and JO1784, a selective σ ligand, alter intestinal ion transport through a common, haloperidol-sensitive site. *Eur. J. Pharmacol.* **1980**, *187*, 557−559.

(18) Pascaud, X.; Defaux, J. P.; Roze, C.; Junien, J. L. Effect of selective sigma ligands on duodenal alkaline secretion in the rat. *J. Pharmacol. Exp. Ther.* **1990**, *255*, 1354−1359.

(19) Campbell, B. G.; Scherz, M. W.; Keana, J. F. W.; Weber, E. Sigma receptors regulate contractions of the guinea-pig ileum longitudinal muscle/myenteric plexus preparation elicited by both electrical stimulation and exogenous serotonin. *J. Neurosci.* **1989**, *9*, 3380−3391.

(20) Walker, J. M.; Bowen, W. D.; Patrick, S. L.; Williams, W. E.; Mascarella, S. W.; Bai, X.; Carroll, F. I. A comparison of (−)-deoxybenzomorphans devoid of opiate activity with their dextrorotatory phenolic counterparts suggests role of σ_2 receptors in motor function. *Eur. J. Pharmacol.* **1993**, *231*, 61−68.

(21) (a) Wu, X. Z.; Bell, J. A.; Spivak, C. E.; London, E. D.; Su, T. P. Electrophysiological and binding studies on intact NCB-20 cells suggest presence of a low affinity sigma receptor. *J. Pharmacol. Exp. Ther.* **1991**, *257*, 351−359. (b) Jeanjean, A. P.; Mestre, M.; Maloteaux, J. M.; Laduron, P. M. Is the sigma-2 receptor in rat brain related to the K^+ channel of class III antiarrhythmic drugs? *Eur. J. Pharmacol.* **1993**, *241*, 111−116.

(22) de Costa, B. R.; Radesca, L.; Di Paolo, L.; Bowen, W. D. Synthesis, characterization, and biological evaluation of a novel class of *N*-(arylethyl)-*N*-alkyl-2-(1-pyrrolidinyl)ethylamines: structural requirements and binding affinity at the σ receptor. *J. Med. Chem.* **1992**, *35*, 38−47.

(23) He, X. S.; Bowen, W. D.; Lee, K. S.; Williams, W.; Weinberger, D. R.; de Costa, B. R. Synthesis and binding characteristics of potential SPECT imaging agents for σ-1 and σ-2 binding sites. *J. Med. Chem.* **1993**, *36*, 566−572.

(24) Hunger, von A.; Kebrle, J.; Rossi, A.; Hoffman, A. Benzimidazolderivate und verwandte heterocyclen III) Synthese von 1-aminoalkyl-2-benzyl-nitro-benzimidazolen. *Helv. Chim. Acta* **1960**, *43*, 1032−1046.

(25) Haefely, W.; Kyburz, E.; Gerecke, M.; Mohler, H. Recent advances in the molecular pharmacology of benzodiazepine receptors and in the structure−activity relationships of their agonist. *Adv. Drug Res.* **1985**, *14*, 165−322.

(26) The ^{1}H NMR ($CDCl_3$) δ of free base forms of compounds in Table 2: **4**: 7.22 (t, J = 6.9 Hz, 1H, ArH), 6.84−6.93 (m, 3H, ArH), 3.81 (s, 3H, OCH_3), 3.71 (45%), 3.67 (55%) (s, 2H, benzylic CH_2), 3.55 (55%), 3.45 (45%) (t, J = 7.5 Hz, 2H, NCH_2), 3.02 (55%), 2.97 (45%) (s, 3H, NCH_3), 2.50−2.64 (m, 6H), 1.76 (m, 4H, pyrrolidinyl CH_2). **5**: 7.23 (t, J = 7.9 Hz, 1H, Ar-H^5), 6.78−7.20 (m, 3H, ArH), 3.79 (s, 3H, OCH_3), 3.73 (45%), 3.69 (55%) (s, 2H, benzylic CH_2), 3.50 (55%), 3.48 (45%) (t, J = 7.5 Hz, 2H), 3.01 (55%), 2.97 (45%) (s, 3H, NCH_3), 2.47−2.66 (m, 6H), 1.77 (m, 4H, pyrrolidinyl CH_2). **6**: 7.16−7.20 (dd, J_{ortho} = 8.5 Hz, J_{meta} = 3.6 Hz, 2H, ArH^2, ArH^6), 6.85 (d, J = 8.7 Hz, 2H, ArH^3, ArH^5), 3.79 (s, 3H, OCH_3), 3.68 (44%), 3.64 (56%) (s, 2H, benzylic CH_2), 3.53 (56%), 3.43 (44%) (t, J = 7.5 Hz, 2H, NCH_2), 3.01 (56%), 2.96 (44%) (s, 3H, NCH_3), 2.55 (m, 6H), 1.76 (m, 4H, pyrrolidinyl CH_2). **7**: 8.09 (d, J = 8.0 Hz, 1H, ArH^3), 7.57 (t, J = 7.5 Hz, 1H, ArH^5), 7.43 (t, J = 7.4 Hz, 1H, ArH^6), 7.33 (d, J = 7.5 Hz, d, J = 7.6 Hz, 1H, ArH^4), 4.13 (40%), 4.04 (60%) (s, 2H, benzylic CH_2), 3.54 (m, 2H, NCH_2), 3.17 (60%), 2.98 (40%) (s, 3H, NCH_3), 2.77 (40%), 2.65 (60%) (t, J = 7.5 Hz, 2H), 2.56 (m, 4H), 1.76 (m, 4H, pyrrolidinyl CH_2). **8**: 7.47−8.13 (m, 4H, ArH), 3.86 (44%), 3.81 (56%) (s, 2H, benzylic CH_2), 3.56 (56%), 3.52 (44%) (t, J = 7.1 Hz, 2H, NCH_2), 3.50 (56%), 3.47 (44%) (s, 3H, NCH_3), 2.62−3.10 (m, 6H), 1.77 (m, 4H, pyrrolidinyl CH_2). **9**: 8.18 (d, J = 8.6 Hz, 2H, ArH^3, ArH^5), 7.44 (d, J = 8.5 Hz, 2H, ArH^2, ArH^6), 3.86 (42%), 3.81 (58%) (s, 2H, benzylic CH_2), 3.56 (58%), 3.46 (42%) (t, J = 7.2 Hz, 2H, NCH_2), 3.06 (58%), 2.99 (42%) (s, 3H, NCH_3), 2.54−2.66 (m, 6H), 1.79 (m, 4H, pyrrolidinyl CH_2). **10**: 6.82−7.20 (m, 4H, ArH), 3.81 (s, 3H, OCH_3), 2.54−2.83 (m, 10H, NCH_2), 2.35 (s, 3H, NCH_3), 1.77 (m, 4H, pyrrolidinyl CH_2). **11**: 6.73−7.23 (m, 4H, ArH), 3.80 (s, 3H, OCH_3), 2.55−2.79 (m, 12H, benzylic CH_2, NCH_2), 2.34 (s, 3H, NCH_3), 1.78 (m, 4H, pyrrolidinyl CH_2). **12**: 7.10 (d, J = 8.7 Hz, 2H, ArH^2, ArH^6), 6.82 (d, J = 8.7 Hz, 2H, ArH^3, ArH^5), 3.78 (s, 3H, OCH_3), 2.50−2.75 (m, 12H, benzylic CH_2, NCH_2), 2.33 (s, 3H, NCH_3), 1.76 (m, 4H, pyrrolidinyl CH_2). **13**: 7.90 (d, J = 7.5 Hz, 1H, ArH^3), 7.52 (t, J = 8.0 Hz, 1H, ArH^5), 7.36 (m, 2H, ArH^4, ArH^6), 3.07 (m, 2H, benzylic CH_2), 2.50−2.74 (m, 12H, benzylic CH_2, NCH_2), 2.36 (s, 3H, NCH_3), 1.77 (m, 4H, pyrrolidinyl CH_2). **14**: 8.07 (d, J = 8.4 Hz, 1H, ArH^4, 1H, ArH^2), 7.55 (d, J = 6.8 Hz, 1H, ArH^6), 7.45 (t, J = 7.7, 1H, ArH^5), 2.89 (m, 2H, benzylic CH_2), 2.69 (m, 2H, NCH_2), 2.60 (m, 4H, pyrrolidinyl NCH_2), 2.52 (m, 4H, NCH_2), 2.34 (s, 3H, NCH_3), 1.77 (m, 4H, pyrrolidinyl CH_2). **15**: 8.14 (d, J = 8.6 Hz, 2H, ArH^3, ArH^5), 7.36 (d, J = 8.5 Hz, 2H, ArH^2, ArH^6), 2.89 (m, 2H, benzylic CH_2), 2.68 (m, 2H, NCH_2), 2.60 (s, 4H, pyrrolidinyl NCH_2), 2.53 (m, 4H, NCH_2), 2.33 (s, 3H, NCH_3), 1.77 (m, 4H, pyrrolidinyl CH_2). **16**: 7.01 (d, J = 7.5 Hz, 2H, ArH^4, ArH^6), 6.65−6.72 (m, 2H, ArH^3, ArH^5), 2.63−2.72 (m, 4H, benzylic CH_2), NCH_2), 2.60 (s, 4H, pyrrolidinyl NCH_2), 2.51 (m, 4H, NCH_2), 2.34 (s, 3H, NCH_3) 1.76 (m, 4H, pyrrolidinyl CH_2). **17**: 7.07 (t, J = 8.3 Hz, 1H, ArH^5), 6.60 (d, J = 7.8 Hz, 1H, ArH^4), 6.53 (d, J = 6.9 Hz, 1H, s, 1H, ArH^2, ArH^6), 3.61 (s, 2H, NH_2), 2.51−2.73 (m, 12H, benzylic CH_2, NCH_2), 2.33 (s, 3H, NCH_3), 1.77 (m, 4H, pyrrolidinyl CH_2). **18**: 6.99 (d, J = 8.1 Hz, 2H, ArH^2, ArH^6), 6.62 (d, J = 8.0 Hz, 2H, ArH^3, ArH^5), 3.55 (s, 2H, NH_2), 2.53−2.70 (m, 12H, benzylic CH_2, NCH_2), 2.32 (s, 3H, NCH_3), 1.76 (m, 4H, pyrrolidinyl CH_2).

(27) de Costa, B. R.; Bowen, W. D.; Hellewell, S. B.; Walker, J. M.; Thurkauf, A.; Jacobson, A. E.; Rice, K. C. Synthesis and evaluation of optically pure [^{3}H](+)-pentazocine, a highly potent and selective radioligand for σ receptors. *Fed. Eur. Biochem. Soc.* **1989**, *251*, 53−58.

(28) Bowen, W. D.; de Costa, B. R.; Hellewell, S. B.; Walker, J. M.; Rice, K. C. [^{3}H](+)-Pentazocine: A potent and highly selective benzomorphan-based probe for sigma-1 receptors. *Mol. Neuropharmacol.* **1993**, *3*, 117−126.

(29) Hellewell, S. B.; Bruce, A.; Feinstein, G.; Orringer, J.; Williams, W.; Bowen, W. D. Rat liver and kidney contain high densities of sigma-1 and sigma-2 receptors. Characterization by ligand binding and photoaffinity labeling. *Eur. J. Pharmacol., Mol. Pharmacol. Sect.* **1994**, *268*, 9−18.

(30) Yoon, N. M.; Brown, H. C. Selective Reductions. XII. Explorations in some representative applications of aluminum hydride for selective reductions. *J. Am. Chem. Soc.* **1968**, *90*, 2927−2938.

JM9600813