Characterization of Novel *N,N′*-Disubstituted Piperazines as σ Receptor Ligands

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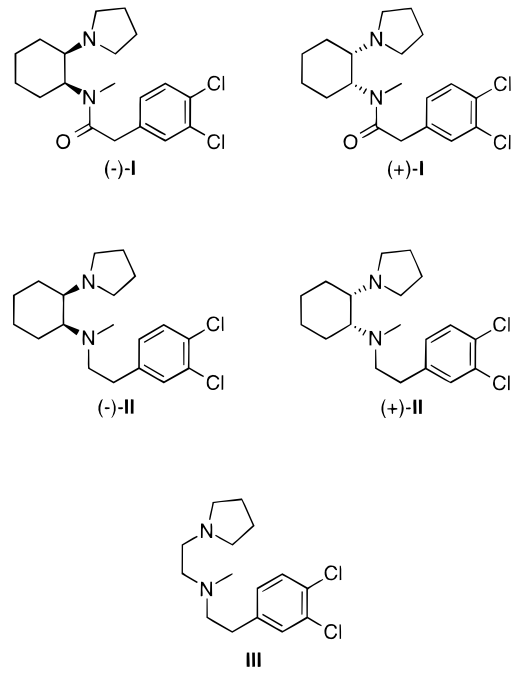
σ Receptors have been the focus of extensive studies because of their potential functional role in several important physiological and biochemical processes. To further evaluate the properties of σ receptors, especially σ-1 and σ-2 subtypes, we have synthesized a series of *N,N′*-disubstituted piperazine compounds (**1**−**32**). The design of these compounds was based upon the early structure−activity relationship (SAR) studies of the minimum structural requirements of a molecule necessary to elicit σ receptor binding activity. In the *N*-(3-phenylpropyl)piperazine series, compounds with the ethylenediamine moiety (**8**−**11**, **15**−**17**) showed 6−20-fold higher affinity for σ-1 and 2−40-fold higher affinity for σ-2 relative to their corresponding amides (**1**−**7**). The (*m*-nitrophenethyl)piperazine **10** exhibits a subnanomolar affinity for the σ-1 site, whereas the corresponding *o*-nitro compound **9** shows the highest affinity for the σ-2 site (K_i = 4.9 nM). Compounds with a free amino terminus were designed as precursors for use as bioconjugated affinity compounds. Some of these compounds displayed high affinity for σ-1 and moderate affinity for σ-2 sites and are currently used for the purification and characterization of the receptor subtypes.

Introduction

σ Receptors are involved in many important biological and physiological 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] neuroprotective[6,7] and neurodegenerative[8−10] effects, and modulation of glutamatergic and dopaminergic neurotransmission.[11,12] A wide array of structurally diverse compounds have been reported to bind to σ receptors. These include benzomorphans,[13] disubstituted guanidines,[14,15] substituted ethylenediamines,[16] substituted piperidines,[17] and substituted piperazines.[18,19] However, most of those compounds showed cross-reactivity with other receptors, such as dopamine D_2, PCP, or opioid receptors.[20] For example, the 6,7-benzomorphan (+)-pentazocine is one of the compounds that binds selectively to σ receptors with high affinity,[21] whereas the 6,7-benzomorphans as a class show cross-reactivity with PCP receptors.[13] Haloperidol, a neuroleptic agent, binds with comparable affinity to dopamine D_2 receptors and σ sites.[22] Thus, it has been a challenge to develop selective σ ligands that do not cross-react with the other receptor systems. Furthermore, the study of σ receptors has been complicated by the discovery of subtypes based partly on the differential binding properties of structurally diverse σ ligands.[23,24] The existence of at least two σ subtypes: σ-1 and σ-2 sites, has been proposed.[25] The σ-1 site has been implicated to regulate gastrointestinal effects,[26] mediate the inhibition by σ ligands of the muscarinic acetylcholine receptor phosphoinositide response,[5] modulate NMDA-stimulated neurotransmitter release,[11,12] and mediate neuroprotective and antiamnesic effects of σ ligands.[27] The σ-2 site has shown the ability to mediate the motor effects of σ ligands,[3,28] mediate the effects of certain σ drugs on K^+ channels,[29,30] modulate intracellular calcium levels,[31,32] and mediate σ ligand-induced morphological changes and cell death.[33] However the functional roles of σ-1 and σ-2 receptor sites are far from fully understood at the present time and have yet to be characterized using more selective and high-affinity σ ligands. Therefore, identifying novel classes of high-affinity, subtype-selective σ ligands has been an ongoing task.

Chart 1



It has been reported that the cis isomers (−)- and (+)-**I** (Chart 1) of the κ-selective agonist U50,488 displayed moderate affinity for the σ sites (labeled with [^{3}H]-(+)-PPP), showing K_i values of 81 and 211 nM,[34] whereas their reduction products cyclohexanediamines (−)- and (+)-**II** exhibited high affinity against displacement of

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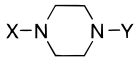
Chart 2



$X_1 = CH_2CH_2CH_2Ph$
$Y_1 = Substituted\ ArCH_2CH_2$

$X_2 = CH_2CH_2CH_2Ph$
$Y_2 = Substituted\ ArCH_2CO$

$X_3 = CH_2CH_2CH_2Ph$
$Y_3 = -CO(CH_2)_nNHBoc$

$X_4 = CH_2CH_2CH_2Ph$
$Y_4 = CO(CH_2)_nNH_2$

$X_5 = CH_2CH_2CH_2Ph$
$Y_5 = (CH_2)_mNH_2$

$X_6 = Y_6 = Substituted\ ArCH_2CO$

$X_7 = Y_7 = Substituted\ ArCH_2CH_2$

[^{3}H]-(+)-PPP (K_i values of 1.3 and 6.0 nM, respectively).[16] The higher-affinity isomer (−)-**II** shows higher selectivity for the σ sites and does not cross-react with κ, dopamine D_2, or PCP receptors. Further manipulation of the cyclohexyl moiety of **II** yielded a novel class of highly specific σ ligand **III**, *N*-[2-(3,4-dichlorophenyl)-ethyl]-*N*-methyl-2-(1-pyrrolidinyl)ethylamine, which binds to both σ-1 and σ-2 sites with nanomolar affinity (K_i-(σ_1) = 2.1 nM, $K_i(\sigma_2)$ = 8.1 nM).[16] Since then, much effort has been exerted in the studies of structure−activity relationships (SAR) and in seeking novel classes of σ ligands to further delineate the biological functions of the receptors. The earlier SAR studies on **III** yielded a series of analogues of **III** derived from incorporating **III** into more conformationally restricted structures such as piperazines, 2-aminotetralines, and rigid bicyclic bridgehead ring systems or from modifying the ethylene spacer and pyrrolidinyl moiety.[16,18] These studies indicated that an ethylenediamine moiety is the minimal structural requirement to achieve high affinity for σ receptor sites. To extend the SAR studies on the ethylenediamine series, we prepared a series of novel *N*, *N*′-disubstituted piperazines (Chart 2) and investigated their binding properties on both σ-1 and σ-2 sites. Portions of this work have been previously reported in abstract form.[35]

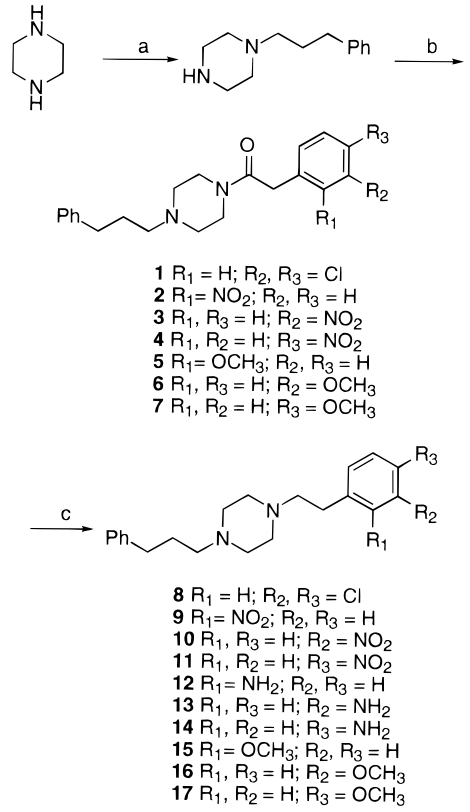
Chemistry

The preparation of compounds **1**−**17** and **24**−**32** proceeded from a monoalkylation of commercial piperazine with 1-chloro-3-phenylpropane (Scheme 1).[36] The resulting *N*-(3-phenylpropyl)piperazine was purified as the oxalate from methanol in 79% yield. The free base of *N*-(3-phenylpropyl)piperazine was then acylated with mono- or disubstituted phenylacetic acid in the presence of dicyclohexylcarbodiimide (DCC) in methylene chloride at room temperature to give compounds **1**−**7**, followed by AlH_3 reduction[16,37] to give compounds **8**−**17**. Compounds **1**−**17** were purified from methanol or acetone as their oxalates.

N-(3-Phenylpropyl)piperazine was acylated with *N*-Boc-protected amino acids, Boc-glycine, Boc-β-alanine, or Boc-GABA, to give **24**−**26** (Scheme 3), followed by the deprotection of amino group in 30% trifluoroacetic acid in chloroform to afford the amides **27**−**29**. Alane reduction of these compounds in THF provided the corresponding triamines **30**−**32**. Compounds **24**−**32** were purified as their oxalate salts from methanol or acetone.

The symmetrical disubstituted piperazine derivatives **18**−**23** was prepared from a coupling reaction between *o*-, *m*-, or *p*-methoxyphenylacetic acid and piperazine to give the diamides **18**−**20**, followed by amide reduction to afford **21**−**24** (Scheme 2). The purification of the diamines **21**−**24** was achieved by salt formation with maleic acid in ethanol or methanol. The structure and purity of these compounds were confirmed by CI-MS,

Scheme 1[a]

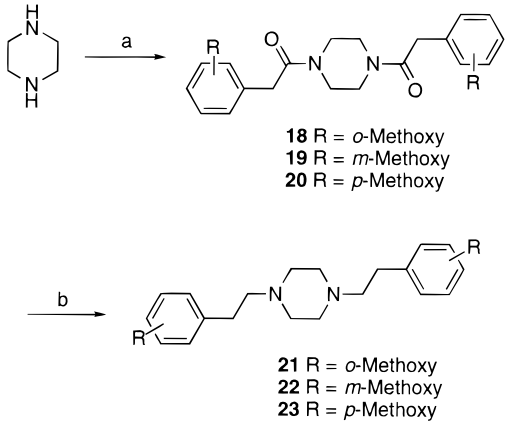


1 R_1 = H; R_2, R_3 = Cl
2 R_1= NO_2; R_2, R_3 = H
3 R_1, R_3 = H; R_2 = NO_2
4 R_1, R_2 = H; R_3 = NO_2
5 R_1= OCH_3; R_2, R_3 = H
6 R_1, R_3 = H; R_2 = OCH_3
7 R_1, R_2 = H; R_3 = OCH_3

8 R_1 = H; R_2, R_3 = Cl
9 R_1= NO_2; R_2, R_3 = H
10 R_1, R_3 = H; R_2 = NO_2
11 R_1, R_2 = H; R_3 = NO_2
12 R_1= NH_2; R_2, R_3 = H
13 R_1, R_3 = H; R_2 = NH_2
14 R_1, R_2 = H; R_3 = NH_2
15 R_1= OCH_3; R_2, R_3 = H
16 R_1, R_3 = H; R_2 = OCH_3
17 R_1, R_2 = H; R_3 = OCH_3

[a] (a) 3-Phenylpropyl chloride, K_2CO_3, DMF; (b) mono- or disubstituted phenylacetic acid, DCC, CH_2Cl_2, rt; (c) 1 or 0.5 M AlH_3, THF.

Scheme 2[a]

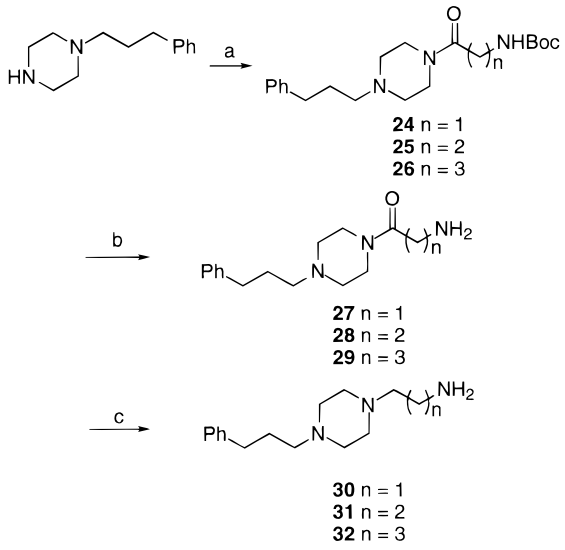


18 R = *o*-Methoxy
19 R = *m*-Methoxy
20 R = *p*-Methoxy

21 R = *o*-Methoxy
22 R = *m*-Methoxy
23 R = *p*-Methoxy

[a] (a) *o*-, *m*-, or *p*-Methoxyphenylacetic acid, DCC, CH_2Cl_2, rt; (b) 1 M AlH_3 in THF, rt.

Scheme 3[a]



[a] (a) Boc-protected amino acid, DCC, CH_2Cl_2, rt; (b) 30% TFA in $CHCl_3$, rt; (c) 1 M AlH_3 in THF, rt.

^{1}H NMR (300 MHz), and elemental analysis. The physical and chemical data of compounds **1**−**32** are reported in Tables 1−3.

Results and Discussion

As a continuation of the SAR study on the ethylenediamine σ ligands, we have synthesized a series of *N*,*N*′-disubstituted piperazine compounds and evaluated their binding properties for σ-1 and σ-2 receptors. In the *N*-(3-phenylpropyl)piperazine series (**1**−**17**), the compounds with the ethylenediamine moiety (**8**−**11**, **15**−**17**) showed 6−20-fold higher affinity for σ-1 and 2−40-fold higher affinity for σ-2 relative to their corresponding amides (**1**−**7**). This notion coincides with our observation in the *N*-(arylethyl)-*N*-methyl-2-(1-pyrrolidinyl)-ethylamine series[38] that compounds with the ethylenediamine moiety possess an overall higher affinity for both σ-1 and σ-2 subtypes than their corresponding arylacetamides.

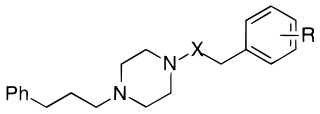
As demonstrated in our prior study,[38] the nitro compounds, once again, showed the highest affinity for both σ-1 and σ-2 among the compounds with other aromatic substitutions. Compound **9**, with a nitro substitution at the ortho position, showed an affinity of 4.9 nM at σ-2, the highest binding affinity for the σ-2 site among the known ethylenediamine compounds, whereas **10**, a *m*-nitro compound showed a subnanomolar affinity for the σ-1 site. However, unlike the *N*-(1-pyrrolidinyl)ethylamine series,[38] the presence of an electron-donating group, such as a methoxy or an amino function in the aromatic region, shows only minimal affects on the binding affinity for σ receptors. As shown in Table 4, compounds **12**−**17** containing electron-donating groups showed 1.3−4.8 nM affinity for σ-1 and 7.5−37 nM affinity for σ-2, while compounds with an electron-withdrawing group (**9**−**11**) showed affinities of 0.72−2.6 nM for σ-1 and 4.9−24.9 nM for σ-2.

Similar to observations in the *N*-(1-pyrrolidinyl)-ethylamine series,[38] no clear pattern was observed between the orientation of aromatic substituents and the σ binding activity in both diamine compounds (**8**−**17**) and amine amide compounds (**1**−**7**). However, both σ-1 and σ-2 receptors tolerate the amide functional group in the disubstituted piperazine series far better than the *N*-pyrrolidinylethylamine series. In the *N*-pyrrolidinylethylamine series, the σ-1 affinity decreased 75−350-fold simply by replacing the arylethylamine moiety with an arylacetamide, although affinity for the σ-2 subtype dropped only 4.8−22-fold.[38] In comparison, only 6−20-fold reduction for σ-1 affinity and 2−40-fold reduction for σ-2 affinity were observed in the piperazine series. De Costa et al. reported earlier that in the piperazine series containing the *N*′-3,4-dichlorophenethyl substituent,[18] increasing the size of the *N*-substituent from methyl to pentyl resulted in an increase in affinity with optimal binding occurring at butyl. In the current piperazine series, the σ-1 subtype well-tolerates further increase in size of the *N*-substituent to a phenylpropyl (**8**, $K_i(\sigma\text{-}1) = 2.2$ nM), showing an affinity comparable to the *N*-pentylpiperazine derivative ($K_i(\sigma\text{-}1) = 1.7$ nM). Considering the fact that the *N*-nor compound in the de Costa series showed a K_i (σ-1) value of 119 nM, a 70-fold decrease relative to the *N*-pentylpiperazine derivative in σ-1 binding, we conclude that a hydrophobic substituent is necessary on this nitrogen for strong binding interaction for the σ-1 site.

In the symmetrical piperazine series (**18**−**23**), the pattern is evident that the diamine compounds possess higher affinity for the σ receptors than their corresponding amide derivatives, showing as high as 1200-fold improvement in σ-1 binding. It can be concluded that at least one basic nitrogen is necessary to maintain the high-affinity binding for the σ receptors in the piperazine series. In this series, it also follows that the ethylenediamine compounds show higher affinity for the σ-1 subtype than the σ-2, with the only exception being that compound **21**, bis(*o*-methoxyphenethyl)piperazine, showed a K_i value of 16.7 nM for the σ-2 site, 8.7-fold selective for σ-2 relative to σ-1. This compound is by far the most selective compound for the σ-2 binding site among the ethylenediamine series. Considering the fact that ditoluylguanidine (DTG) possesses similar affinity for σ-1 and σ-2 sites, the structural similarity of this compound to DTG probably plays an important role.

Compounds **24**−**32** were designed as precursors for use as bioconjugated affinity compounds. By coupling the high-affinity disubstituted piperazine derivatives with a column matrix or affinity probe such as biotin, the macromolecules could be useful in the purification and identification of σ receptor subtypes. All the compounds of this series have a fixed alkyl group on one of the piperazine nitrogens, but with various lengths of the carbon chain on the other nitrogen. Compounds with a shorter chain seem to favor σ-1 binding as both the triamine and diamine amide compounds **30** and **27** showed high binding affinity (2.6 and 4.1 nM, respectively). These two compounds also showed relatively higher affinity for the σ-2 site compared to the rest of the triamines with a longer carbon chain. Of the nine compounds in this series, **26** showed an exceptionally high affinity for the σ-1 site, with $K_i(\sigma\text{-}1) = 0.32$ nM. This appears to be due to derivatization of the basic alkyl nitrogen when the σ-1 affinity of the free amine compound **29** is compared. The same pattern is observed in a comparison of compound **25** to **28**. However, at this point, more structurally related compounds are

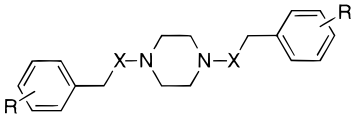
Table 1. Physical and Chemical Data of Compounds **1**−**17**



no.	method	X	R	salt	solvent	mp (°C)	analysis[a,c]
1[b]	A	C=O	3,4-di-Cl	oxalate	acetone	183−4	$C_{21}H_{24}N_2Cl_2O\cdot C_2H_2O_4$
2[b]	A	C=O	*o*-NO_2	oxalate	acetone	153−4	$C_{21}H_{25}N_3O_3\cdot C_2H_2O_4$
3[b]	A	C=O	*m*-NO_2	oxalate	acetone	180−1	$C_{21}H_{25}N_3O_3\cdot C_2H_2O_4$
4[b]	A	C=O	*p*-NO_2	oxalate	acetone	174−5	$C_{21}H_{25}N_3O_3\cdot C_2H_2O_4$
5[b]	A	C=O	*o*-OCH_3	oxalate	acetone	171−2	$C_{22}H_{28}N_2O_2\cdot C_2H_2O_4$
6[b]	A	C=O	*m*-OCH_3	oxalate	acetone	150−1	$C_{22}H_{28}N_2O_2\cdot C_2H_2O_4$
7[b]	A	C=O	*p*-OCH_3	oxalate	acetone	128−30	$C_{22}H_{28}N_2O_2\cdot C_2H_2O_4$
8[b]	D	CH_2	3,4-di-Cl	oxalate	methanol	219−21	$C_{21}H_{26}N_2Cl_2\cdot 2C_2H_2O_4$
9[b]	D	CH_2	*o*-NO_2	oxalate	methanol	221 dec	$C_{21}H_{27}N_3O_2\cdot 2C_2H_2O_4$
10[b]	D	CH_2	*m*-NO_2	oxalate	methanol	220 dec	$C_{21}H_{27}N_3O_2\cdot 2C_2H_2O_4$
11[b]	D	CH_2	*p*-NO_2	oxalate	methanol	220 dec	$C_{21}H_{27}N_3O_2\cdot 2C_2H_2O_4$
12[b]	C	CH_2	*o*-NH_2	oxalate	methanol	214 dec	$C_{21}H_{29}N_3\cdot 2C_2H_2O_4$
13[b]	C	CH_2	*m*-NH_2	oxalate	methanol	200 dec	$C_{21}H_{29}N_3\cdot 2C_2H_2O_4$
14[b]	C	CH_2	*p*-NH_2	oxalate	methanol	209 dec	$C_{21}H_{29}N_3\cdot 2C_2H_2O_4\cdot H_2O$
15[b]	C	CH_2	*o*-OCH_3	oxalate	methanol	227 dec	$C_{22}H_{30}N_2O\cdot 2C_2H_2O_4$
16[b]	C	CH_2	*m*-OCH_3	oxalate	methanol	226 dec	$C_{22}H_{30}N_2O\cdot 2C_2H_2O_4$
17[b]	C	CH_2	*p*-OCH_3	oxalate	methanol	223 dec	$C_{22}H_{30}N_2O\cdot 2C_2H_2O_4$

[a] Elemental compositions (%) were found to be within ±0.4% of the theoretical values of C, H and N. [b] The ^{1}H NMR data for the free base of this compound are shown in the Experimental Section. [c] All compounds gave CI-MS consistent with the expected structure.

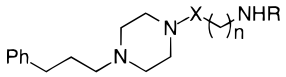
Table 2. Physical and Chemical Data of Compounds **18**−**23**



no.	method	X	R	salt	solvent	mp (°C)	analysis[a,c]
18[b]	B	C=O	*o*-OCH_3		ethanol/water	173−4	$C_{22}H_{26}N_2O_4$
19[b]	B	C=O	*m*-OCH_3		ethanol	132−3	$C_{22}H_{26}N_2O_4$
20[b]	B	C=O	*p*-OCH_3		ethanol	155−6	$C_{22}H_{26}N_2O_4$
21[b]	C	CH_2	*o*-OCH_3	maleate	ethanol	197−8	$C_{22}H_{30}N_2O_2\cdot 2C_4H_4O_4$
22[b]	C	CH_2	*m*-OCH_3	maleate	ethanol	193−5	$C_{22}H_{30}N_2O_2\cdot 2C_4H_4O_4$
23[b]	C	CH_2	*p*-OCH_3	maleate	methanol	202−3	$C_{22}H_{30}N_2O_2\cdot 2C_4H_4O_4$

[a] Elemental compositions (%) were found to be within ±0.4% of the theoretical values of C, H, and N. [b] The ^{1}H NMR data for the free base of this compound are shown in the Experimental Section. [c] All compounds gave CI-MS consistent with the expected structure.

Table 3. Physical and Chemical Data of Compounds **24**−**32**



no.	method	X	*n*	R	salt	solvent	mp (°C)	analysis[a,c]
24[b]	A	C=O	1	*t*-Boc	oxalate	acetone	145−6	$C_{20}H_{31}N_3O_3\cdot C_2H_2O_4$
25[b]	A	C=O	2	*t*-Boc	oxalate	acetone	64−6	$C_{21}H_{33}N_3O_3\cdot C_2H_2O_4$
26[b]	A	C=O	3	*t*-Boc	oxalate	acetone	143−4	$C_{22}H_{35}N_3O_3\cdot C_2H_2O_4\cdot 0.25H_2O$
27[b]	E	C=O	1	H	oxalate	acetone	180−1	$C_{15}H_{23}N_3O\cdot 2C_2H_2O_4\cdot$0.5 acetone
28[b]	E	C=O	2	H	oxalate	acetone	110−2	$C_{16}H_{25}N_3O\cdot 2C_2H_2O_4\cdot H_2O$
29[b]	E	C=O	3	H	oxalate	acetone/methanol	145−6	$C_{17}H_{27}N_3O\cdot 2C_2H_2O_4$
30[b]	C	CH_2	1	H	oxalate	methanol	215−6	$C_{15}H_{25}N_3\cdot 3C_2H_2O_4$
31[b]	C	CH_2	2	H	oxalate	acetone	209−10	$C_{16}H_{27}N_3\cdot 2C_2H_2O_4$
32[b]	C	CH_2	3	H	oxalate	methanol	202−3	$C_{17}H_{29}N_3\cdot 2C_4H_4O_4$

[a] Elemental compositions (%) were found to be within ±0.4% of the theoretical values of C, H, and N. [b] The ^{1}H NMR data for the free base of this compound are shown in the Experimental Section. [c] All compounds gave CI-MS consistent with the expected structure.

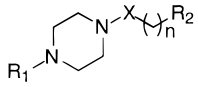
needed for the further SAR study to delineate the cause of the high binding affinity of this compound.

In conclusion, we have demonstrated a novel class of high-affinity ligands for σ-1 and σ-2 receptors. Some of these compounds may prove useful in functional studies and purification of the receptors.

Experimental Section

Chemical Materials and Methods. Melting points were determined on a Mel-Temp II capillary apparatus and are reported uncorrected. Elemental analyses were obtained from Atlantic Microlabs, Atlanta, GA, or Galbraith Laboratories, Inc., Knoxville, TN, and were determined to be within ±0.4% of the theoretical values for carbon, hydrogen, and nitrogen. CI-MS (chemical ionization mass spectra) were performed using a Finnigan 1015 mass spectrometer. ^{1}H NMR spectra were obtained on a Varian XL-300 spectrometer using $CDCl_3$ solutions of free bases. All the chemical shifts reported are relative to a tetramethylsilane internal reference in ppm on the δ scale. Thin-layer chromatography (TLC) was performed on Analtech GHLF silica gel plates (250 μm) with a solvent system of 90:9:1 $CHCl_3$/MeOH/concentrated NH_4OH.

Table 4. Biological Data for **1**−**32**[a]



no.	R_1	R_2	*n*	X	K_i([^{3}H]-(+)-pent) in guinea pig brain (σ_1) (nM)	K_i([^{3}H]-DTG + dextrallorphan) in rat liver (σ_2) (nM)	σ_1/σ_2
1	$Ph(CH_2)_3$	3,4-dichlorophenyl	1	C=O	28 ± 1	78 ± 3	0.4
2	$Ph(CH_2)_3$	*o*-nitrophenyl	1	C=O	7.9 ± 1.2	76 ± 11	0.1
3	$Ph(CH_2)_3$	*m*-nitrophenyl	1	C=O	7.6 ± 0.6	65 ± 0.2	0.1
4	$Ph(CH_2)_3$	*p*-nitrophenyl	1	C=O	14 ± 1	167 ± 4	0.08
5	$Ph(CH_2)_3$	*o*-methoxyphenyl	1	C=O	56 ± 8	294 ± 10	0.2
6	$Ph(CH_2)_3$	*m*-methoxyphenyl	1	C=O	26 ± 0.01	206 ± 2	0.1
7	$Ph(CH_2)_3$	*p*-methoxyphenyl	1	C=O	13 ± 2	464 ± 34	0.03
8	$Ph(CH_2)_3$	3,4-dichlorophenyl	1	CH_2	2.2 ± 0.2	39 ± 2	0.06
9	$Ph(CH_2)_3$	*o*-nitrophenyl	1	CH_2	1.2 ± 0.04	4.9 ± 0.01	0.2
10	$Ph(CH_2)_3$	*m*-nitrophenyl	1	CH_2	0.72 ± 0.14	9.4 ± 1.5	0.08
11	$Ph(CH_2)_3$	*p*-nitrophenyl	1	CH_2	2.6 ± 0.8	25 ± 2	0.1
12	$Ph(CH_2)_3$	*o*-aminophenyl	1	CH_2	4.8 ± 0.1	18 ± 0.2	0.3
13	$Ph(CH_2)_3$	*m*-aminophenyl	1	CH_2	2.0 ± 0.3	37 ± 1	0.05
14	$Ph(CH_2)_3$	*p*-aminophenyl	1	CH_2	4.1 ± 0.02	14 ± 1	0.3
15	$Ph(CH_2)_3$	*o*-methoxyphenyl	1	CH_2	3.9 ± 0.6	7.5 ± 0.2	0.5
16	$Ph(CH_2)_3$	*m*-methoxyphenyl	1	CH_2	1.4 ± 0.2	10 ± 1	0.1
17	$Ph(CH_2)_3$	*p*-methoxyphenyl	1	CH_2	1.3 ± 0.3	29 ± 2	0.05
18	*o*-methoxyphenethyl	*o*-methoxyphenyl	1	C=O	1465 ± 220	>10 μM	<0.15
19	*m*-methoxyphenethyl	*m*-methoxyphenyl	1	C=O	NA[b]	11.8 ± 1.5	NA[b]
20	*p*-methoxyphenethyl	*p*-methoxyphenyl	1	C=O	>10 μM	744 ± 35	>14
21	*o*-methoxyphenethyl	*o*-methoxyphenyl	1	CH_2	145 ± 8	17 ± 2	8.7
22	*m*-methoxyphenethyl	*m*-methoxyphenyl	1	CH_2	5.3 ± 0.7	29 ± 3	0.2
23	*p*-methoxyphenethyl	*p*-methoxyphenyl	1	CH_2	8.2 ± 0.9	99 ± 4	0.08
24	$Ph(CH_2)_3$	NHBoc	1	C=O	NA[b]	175 ± 38	NA[b]
25	$Ph(CH_2)_3$	NHBoc	2	C=O	86 ± 5	4561 ± 537	0.02
26	$Ph(CH_2)_3$	NHBoc	3	C=O	0.32 ± 0.07	126 ± 14	0.003
27	$Ph(CH_2)_3$	NH_2	1	C=O	4.1 ± 1.2	303 ± 62	0.01
28	$Ph(CH_2)_3$	NH_2	2	C=O	148 ± 6	1783 ± 103	0.08
29	$Ph(CH_2)_3$	NH_2	3	C=O	202 ± 41	3839 ± 72	0.05
30	$Ph(CH_2)_3$	NH_2	1	CH_2	2.6 ± 0.09	188 ± 13	0.01
31	$Ph(CH_2)_3$	NH_2	2	CH_2	181 ± 16	2000 ± 334	0.09
32	$Ph(CH_2)_3$	NH_2	3	CH_2	177 ± 16	999 ± 19	0.2

[a] Twelve concentrations of unlabeled test ligand ranging from 0.05 to 10 000 nM or from 0.5 to 100 000 nM were incubated with guinea pig brain membranes and [^{3}H]-(+)-pentazocine (σ-1 receptors) or with rat liver membranes and [^{3}H]DTG in the presence of 1 μM dextrallorphan (σ-2 receptors) as described in the Experimental Section. 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. Values are the averages of 2−3 experiments, ± SEM. Each experiment was carried out in duplicate. [b] Data not available.

***N*-(3-Phenylpropyl)piperazine.** This compound was prepared according to the reported method with modification.[36] To a suspension of 50 g (0.58 mol, 8 equiv) of piperazine in 100 mL of DMF was added 10.0 mL (70 mmol) of 1-chloro-3-phenylpropane dropwise. The mixture was stirred at room temperature for 2 days, and a yellow-colored solution with precipitate was obtained. The solvent was then evaporated on a rotavapor, and the obtained residue was dissolved in 150 mL of 10% aqueous NaOH solution. The aqueous layer was extracted with methylene chloride (50 mL) four times; then the combined organic layer was washed with water twice and saturated aqueous NaCl once, dried over Na_2SO_4, and evaporated to give 13.2 g (64.7 mmol) of crude product as a light-yellow-colored liquid (92%). This compound was purified through the oxalate from methanol to provide 21.1 g (78.5%) of salt as a white solid.

General Method A. To a stirred solution of DCC in CH_2Cl_2 (5 mmol of DCC in 20 mL of CH_2Cl_2) was added a solution of mono- or disubstituted phenylacetic acid or *N*-Boc-protected amino acid (5 mmol of carboxylic acid to 20 mL of CH_2Cl_2). The mixture was allowed to stir at room temperature for 10 min before a solution of *N*-(3-phenylpropyl)piperazine in CH_2Cl_2 (5 mmol of the free base in 10 mL of CH_2Cl_2) was added. The molar ratio of DCC/carboxylic acid:amine was 2:1.3−1.5:1. The reaction mixture was allowed to stir at room temperature until TLC indicated the completion of the reaction. The white precipitate of DCU was then filtered, and the filter cake was washed with CH_2Cl_2 twice. The combined organic layer was extracted with 15% aqueous citric acid solution three times or until TLC indicated that all product was extracted into the aqueous layer. The aqueous layer was back-washed with CH_2Cl_2 once, basified with concentrated NH_4OH to pH 9−11, and then extracted with CH_2Cl_2 three times. The obtained organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated to give the desired amides. The crude product was purified through salt formation (see Tables 1−3), or, if necessary, purified on a silica gel column with 150:10:1 CH_2Cl_2/MeOH/concentrated NH_4OH before salt formation. The yield range for this method was 85−95%.

Method B. To a stirred solution of DCC in CH_2Cl_2 (5 mmol of DCC to 20 mL of solvent) was added a solution of *o*-, *m*-, or *p*-methoxyphenylacetic acid in CH_2Cl_2 (5 mmol of carboxylic acid to 20 mL of solvent). The mixture was allowed to stir at room temperature for 10 min before piperazine was added slowly. The molar ratio of DCC/carboxylic acid:piperazine was 2.5:2.0−2.5:1, and the reaction was terminated when TLC indicated the disappearance of piperazine. The white precipitate of DCU was then filtered, and the filtrate was washed with water once, 3 N aqueous HCl twice, and brine once. The resulting organic layer was dried over Na_2SO_4 and evaporated to give the desired diamide. The crude product mixed with a small amount of DCU was recrystallized from ethanol to give the pure diamide as white crystalline solid. The yield range for this method was 80−95%.

Method C. A solution of amide in a minimum amount of THF was added dropwise to a stirred, freshly prepared solution of 1 M AlH_3 in THF.[16,37] The molar ratio of amide:AlH_3 was about 1:5. The reaction mixture was stirred at room temper-

ature for 10 min when TLC showed the disappearance of the amide. The mixture was then poured slowly into a 15% aqueous NaOH solution in an ice−water bath. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layer was then washed with water and brine, dried over Na_2SO_4, and evaporated to give the corresponding amine. The base was then purified through crystallization of the salt in the appropriate solvent (see Tables 1−3). The yield range for this method was 80−95%.

Method D. This method was the same as method C except that 0.5 M AlH_3 was utilized. The obtained mixture was worked up according to method C, and the crude product was purified on a silica gel column or on a preparative TLC plate with 200−400:10:1 CH_2Cl_2/MeOH/concentrated NH_4OH. The purified amine compounds were then crystallized as their salt from appropriate solvents (see Tables 1−3). The yield range for this method was 50−70%.

Method E. To a mixture of 40 mL of trifluoroacetic acid in 80 mL of chloroform was added 10 mmol of the *N*-Boc-protected compound **24**−**26**. The solution turned dark-brown and was allowed to stir at room temperature for 2 h when TLC showed the completion of the reaction. The solution was then evaporated to dryness on a rotavapor, and the residue was dissolved in 1:1 15% aqueous NaOH/CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layer was then washed with water and brine, dried over Na_2SO_4, and evaporated to give the deprotected compound with a terminal amino function (**27**−**29**) as a light-yellow oil. The crude product was purified through salt formation or purified on a silica gel column prior to the salt formation if necessary (see Table 3). The yield range for this method was 60−75%.

Biological Materials and Methods. [^{3}H]-(+)-Pentazocine (51.7 Ci/mmol) was synthesized as described previously.[21,39] [^{3}H]DTG (39.1 Ci/mmol) was purchased from DuPont/New England Nuclear (Boston, MA). Dextrallorphan was provided by Dr. F. I. Carroll (Research Trangle Institute, Research Triangle Park, NC). Haloperidol, Tris-HCl, and poly(ethylenimine) were purchased from Sigma Chemicals (St. Louis, MO).

***σ* Receptor Binding Method.** *σ*-1 Receptors were labeled as described previously, using the *σ*-1-selective probe [^{3}H]-(+)-pentazocine and guinea pig brain membranes.[39] Guinea pig brain membranes (300−350 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 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.[39]

σ-2 Receptors were labeled as previously described using rat liver membranes, a rich source of *σ*-2 sites, and [^{3}H]-1,3-di-*o*-tolylguanidine ([^{3}H]DTG) in the presence of 1 μM dextrallorphan to mask *σ*-1 receptors.[40] Assays were performed in 50 nM 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 prepared from the liver of male Sprague−Dawley rats as previously described.[40]

^{1}H NMR ($CDCl_3$) data for compounds **1**−**32** are as follows.

1: 7.16−7.41 (m, 7H, ArH), 7.09 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1H, ArH), 3.66 (s, 2H, $NCOCH_2$), 3.65 (t, J = 4.8 Hz, 2H, $CONCH_2$), 3.45 (t, J = 4.9 Hz, 2H, $CONCH_2$), 2.64 (t, J = 7.8 Hz, 2H, $ArCH_2$), 2.31−2.42 (m, 6H, NCH_2), 1.83 (tt, J = 7.8 Hz, 2H).

2: 8.10 (d, J = 7.5 Hz, 1H, ArH), 7.57 (t, J = 7.2 Hz, 1H, ArH), 7.44 (t, J = 7.8 Hz, 1H, ArH), 7.18−7.35 (m, 6H, ArH), 4.05 (s, 2H, $NCOCH_2$), 3.58−3.67 (m, 4H, $CONCH_2$), 2.66 (t, J = 7.7 Hz, 2H, $ArCH_2$), 2.35−2.52 (m, 6H, NCH_2), 1.84 (tt, J = 7.3 Hz, 2H).

3: 8.14 (d, J = 8.7 Hz, 1H, ArH), 8.11 (s, 1H, ArH), 7.61 (d, J = 7.8 Hz, 1H, ArH), 7.51 (t, J = 7.8 Hz, 1H, ArH), 7.16−7.31 (m, 5H, ArH), 3.81 (s, 2H, $NCOCH_2$), 3.67 (t, J = 5.1 Hz, 2H, $CONCH_2$), 3.51 (t, J = 5.1 Hz, 2H, $CONCH_2$), 2.64 (t, J = 7.6 Hz, 2H, $ArCH_2$), 2.37 (m, 6H, NCH_2), 1.81 (tt, J = 7.5 Hz, 2H).

4: 8.20 (d, J = 8.7 Hz, 2H, ArH), 7.42 (d, J = 8.7 Hz, 2H, ArH), 7.16−7.43 (m, 5H, ArH), 3.81 (s, 2H, $NCOCH_2$), 3.66 (t, J = 5.1 Hz, 2H, $CONCH_2$), 3.48 (t, J = 5.1 Hz, 2H, $CONCH_2$), 2.64 (t, J = 7.7 Hz, 2H, $ArCH_2$), 2.31−2.42 (m, 6H, NCH_2), 1.80 (tt, J = 7.8 Hz, 2H).

5: 7.15−7.30 (m, 7H, ArH), 6.85−6.94 (m, 2H, ArH), 3.82 (s, 3H, OCH_3), 3.69 (s, 2H, $NCOCH_2$), 3.66 (t, J = 5.1 Hz, 2H, $CONCH_2$), 3.46 (t, J = 5.0 Hz, 2H, $CONCH_2$), 2.63 (t, J = 7.7 Hz, 2H, $ArCH_2$), 2.39 (t, J = 5.1 Hz, 2H, NCH_2), 2.33 (t, J = 7.5 Hz, 2H, NCH_2), 2.27 (t, J = 5.0 Hz, 2H, NCH_2), 1.79 (tt, J = 8.0 Hz, 2H).

6: 7.15−7.25 (m, 7H, ArH), 6.78−6.83 (m, 2H, ArH), 3.79 (s, 3H, OCH_3), 3.70 (s, 2H, $NCOCH_2$), 3.65 (t, J = 5.1 Hz, 2H, $CONCH_2$), 3.44 (t, J = 5.1 Hz, 2H, $CONCH_2$), 2.62 (t, J = 7.7 Hz, 2H, $ArCH_2$), 2.38 (t, J = 5.1 Hz, 2H, NCH_2), 2.32 (t, J = 7.4 Hz, 2H, NCH_2), 2.24 (t, J = 4.9 Hz, 2H, NCH_2), 1.78 (tt, J = 7.6 Hz, 2H).

7: 7.13−7.25 (m, 7H, ArH), 6.85 (d, J = 8.7 Hz, 2H, ArH), 3.79 (s, 3H, OCH_3), 3.64 (m, 4H, $NCOCH_2$ + $CONCH_2$), 3.44 (t, J = 5.1 Hz, 2H, $CONCH_2$), 2.62 (t, J = 7.7 Hz, 2H, $ArCH_2$), 2.37 (t, J = 5.1 Hz, 2H, NCH_2), 2.32 (t, J = 7.6 Hz, 2H, NCH_2), 2.24 (t, J = 5.0 Hz, 2H, NCH_2), 1.78 (tt, J = 7.5 Hz, 2H).

8: 7.18 (m, 7H, ArH), 7.04 (dd, J_1 = 7.8 Hz, J_2 = 2.0 Hz, 1H, ArH), 2.75 (m, 2H, $ArCH_2$), 2.64 (t, J = 7.8 Hz, 2H, $ArCH_2$), 2.55−2.60 (m, 10H, NCH_2), 2.40 (t, J = 7.8 Hz, 2H, NCH_2), 1.86 (tt, J = 7.8 Hz, 2H).

9: 7.90 (d, J = 7.6 Hz, 1H, ArH), 7.51 (dd, J_1 = 8.1 Hz, J_2 = 1.9 Hz, 1H, ArH), 7.37 (d, J = 7.7 Hz, 2H, ArH), 7.18−7.32 (m, 5H, ArH), 3.09 (dd, J_1 = 9.0 Hz, J_2 = 2.5 Hz, 2H, CH_2ArNO_2), 2.53−2.69 (m, 12H, NCH_2), 2.41 (t, J = 7.7 Hz, 2H, $ArCH_2$), 1.84 (tt, J = 7.7 Hz, 2H).

10: 8.09 (m, 2H, ArH), 7.54 (d, J = 7.6 Hz, 1H, ArH), 7.44 (t, J = 7.8 Hz, 1H, ArH), 7.18−7.31 (m, 5H, ArH), 2.90 (dd, J_1 = 9.9 Hz, J_2 = 3.0 Hz, 2H, CH_2ArNO_2), 2.35−2.70 (m, 14H, $ArCH_2$ + NCH_2), 1.83 (m, 2H).

11: 8.13 (d, J = 8.5 Hz, 2H, ArH), 7.35 (d, J = 8.5 Hz, 2H, ArH), 7.17−7.37 (m, 5H, ArH), 2.90 (m, 2H, CH_2ArNO_2), 2.34−2.64 (m, 14H, $ArCH_2$ + NCH_2), 1.82 (m, 2H).

12: 7.18−7.30 (m, 5H, ArH), 7.02 (m, 2H, ArH), 6.68 (m, 2H, ArH), 4.50 (bs, 2H, NH_2), 2.35−2.73 (m, 16H, $ArCH_2$ + NCH_2), 1.82 (m, 2H).

13: 7.15−7.30 (m, 5H, ArH), 7.07 (t, J = 7.9 Hz, 1H, ArH), 6.61 (d, J = 7.6 Hz, 1H, ArH), 6.54 (s, 1H, ArH), 6.52 (d, J = 6.9 Hz, 1H, ArH), 2.36−2.74 (m, 16H, $ArCH_2$ + NCH_2), 1.83 (tt, J = 7.7 Hz, 2H).

14: 7.15−7.30 (m, 5H, ArH), 6.99 (d, J = 8.2 Hz, 2H, ArH), 6.62 (d, J = 8.5 Hz, 2H, ArH), 2.36−2.72 (m, 16H, $ArCH_2$ + NCH_2), 1.83 (tt, J = 7.8 Hz, 2H).

15: 7.13−7.30 (m, 7H, ArH), 6.85 (m, 2H, ArH), 3.80 (s, 3H, OCH_3), 2.83 (m, 2H, $ArCH_2$), 2.54−2.66 (m, 12H, NCH_2), 2.40 (m, 2H, $ArCH_2$), 1.83 (tt, J = 7.7 Hz, 2H).

16: 7.15−7.30 (m, 6H, ArH), 6.76 (m, 3H, ArH), 3.79 (s, 3H, OCH_3), 2.79 (m, 2H, $ArCH_2$), 2.53−2.66 (m, 12H, NCH_2), 2.38 (m, 2H, $ArCH_2$), 1.83 (tt, J = 7.7 Hz, 2H).

17: 7.15−7.30 (m, 5H, ArH), 7.12 (d, J = 8.6 Hz, 2H, ArH), 6.82 (d, J = 8.6 Hz, 2H, ArH), 3.77 (s, 3H, OCH_3), 2.75 (m, 2H, $ArCH_2$), 2.53−2.66 (m, 12H, NCH_2), 2.39 (m, 2H, $ArCH_2$), 1.83 (tt, J = 7.8 Hz, 2H).

18: 7.22 (d, J = 7.7 Hz, 4H, ArH), 6.92 (t, J = 7.6 Hz, 2H, ArH), 6.86 (d, J = 8.0 Hz, 2H, ArH), 3.82 (s, 6H, OCH_3), 3.70 (s, 4H, $CONCH_2$), 3.61 (s, 2H, $ArCH_2$), 3.45 (s, 4H, $CONCH_2$), 3.28 (s, 2H, $ArCH_2$).

19: 7.23 (t, J = 7.8 Hz, 2H, ArH), 6.79 (s + d, J = 7.8 Hz, 6H, ArH), 3.79 (s, 6H, OCH_3), 3.70 (s, 4H, $CONCH_2$), 3.60 (s, 2H, $ArCH_2$), 3.42 (d, J = 3.9 Hz, 4H, $CONCH_2$), 3.19 (s, 2H, $ArCH_2$).

20: 7.13 (d, J = 7.8 Hz, 4H, ArH), 6.85 (d, J = 8.7 Hz, 4H, ArH), 3.79 (s, 6H, OCH_3), 3.66 (s, 4H, $CONCH_2$), 3.59 (s, 2H, $ArCH_2$), 3.41 (s, 4H, $CONCH_2$), 3.19 (s, 2H, $ArCH_2$).

21: 7.15−7.19 (m, 4H, ArH), 6.89 (t, J = 6.8 Hz, 2H, ArH), 6.85 (d, J = 7.8 Hz, 2H, ArH), 3.82 (s, 6H, OCH_3), 2.57−2.87 (m, 16H, $ArCH_2$ + NCH_2).

22: 7.21 (m, 2H, ArH), 6.77 (m, 6H, ArH), 3.80 (s, 6H, OCH_3), 2.62−2.84 (m, 16H, $ArCH_2$ + NCH_2).

23: 7.13 (d, J = 8.5 Hz, 4H, ArH), 6.83 (d, J = 8.5 Hz, 4H, ArH), 3.79 (s, 6H, OCH_3), 2.76 (m, 4H, $ArCH_2$), 2.58 (m, 12H, NCH_2).

24: 7.17−7.29 (m, 5H, ArH), 3.96 (s, 50%, $COCH_2$), 3.94 (s, 50%, $COCH_2$), 3.64 (t, J = 4.9 Hz, 2H, $CONCH_2$), 3.39 (t, J = 4.9 Hz, 2H, $CONCH_2$), 2.65 (t, J = 7.8 Hz, 2H, $ArCH_2$), 2.35−2.44 (m, 6H, NCH_2), 1.82 (tt, J = 7.8 Hz, 2H), 1.45 (s, 9H, CH_3).

25: 7.17−7.28 (m, 5H, ArH), 3.62 (t, J = 5.4 Hz, 2H, $CONCH_2$), 3.42 (m, 4H, $COCH_2$ + $CONCH_2$), 2.65 (t, J = 7.8 Hz, 2H, $ArCH_2$), 2.50 (t, J = 4.9 Hz, 2H, CH_2NHBoc), 2.40 (m, 6H, NCH_2), 1.82 (tt, J = 7.6 Hz, 2H), 1.43 (s, 9H, CH_3).

26: 7.17−7.29 (m, 5H, ArH), 5.30 (bs, 1H, NHBoc), 3.62 (t, J = 4.9 Hz, 2H, $CONCH_2$), 3.46 (t, J = 4.9 Hz, 2H, $CONCH_2$), 3.18 (t, J = 5.9 Hz, 50%, $COCH_2$), 3.16 (t, J = 5.9 Hz, 50%, $COCH_2$), 2.65 (t, J = 7.3 Hz, 2H, $ArCH_2$), 2.33−2.43 (m, 8H, NCH_2 + CH_2NHBoc), 1.80−1.87 (m, 4H), 1.44 (s, 9H, CH_3).

27: 7.16−7.30 (m, 5H, ArH), 3.64 (t, J = 5.1 Hz, 2H, $CONCH_2$), 3.43 (s, 2H, $COCH_2$), 3.36 (t, J = 5.0 Hz, 2H, $CONCH_2$), 2.64 (t, J = 7.7 Hz, 2H, $ArCH_2$), 2.34−2.60 (m, 6H, NCH_2), 1.81 (tt, J = 7.6 Hz, 2H).

28: 7.17−7.31 (m, 5H, ArH), 3.63 (t, J = 5.1 Hz, 2H, $CONCH_2$), 3.47 (m, 2H, $CONCH_2$), 3.00 (t, J = 6.0 Hz, 2H, $COCH_2$), 2.65 (t, J = 7.7 Hz, 2H, $ArCH_2$), 2.46 (t, J = 6.1 Hz, 2H, CH_2NH_2), 2.40 (m, 6H, NCH_2), 1.82 (tt, J = 7.6 Hz, 2H).

29: 7.17−7.31 (m, 5H, ArH), 3.63 (t, J = 5.0 Hz, 2H, $CONCH_2$), 3.48 (t, J = 5.0 Hz, 2H, $CONCH_2$), 2.75 (t, J = 6.9 Hz, 2H, $COCH_2$), 2.65 (t, J = 7.7 Hz, 2H, $ArCH_2$), 2.35−2.43 (m, 8H, NCH_2), 1.73−1.87 (m, 4H).

30: 7.15−7.30 (m, 5H, ArH), 2.78 (t, J = 6.3 Hz, 2H, CH_2NH_2), 2.63 (t, J = 7.8 Hz, 2H, $ArCH_2$), 2.34−2.48 (m, 12H, NCH_2), 1.82 (tt, J = 7.7 Hz, 2H).

31: 7.17−7.30 (m, 5H, ArH), 2.74 (t, J = 6.9 Hz, 2H, CH_2NH_2), 2.63 (t, J = 7.8 Hz, 2H, $ArCH_2$), 2.34−2.48 (m, 12H, NCH_2), 1.82 (m, 2H), 1.66 (m, 2H).

32: 7.19−7.30 (m, 5H, ArH), 2.71 (t, J = 6.9 Hz, 2H, CH_2NH_2), 2.63 (t, J = 7.8 Hz, 2H, $ArCH_2$), 2.32−2.48 (m, 12H, NCH_2), 1.82 (tt, J = 7.6 Hz, 2H), 1.49 (m, 4H).

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