Factors Influencing Agonist Potency and Selectivity for the Opioid δ Receptor Are Revealed in Structure−Activity Relationship Studies of the 4-[(*N*-Substituted-4-piperidinyl)arylamino]-*N*,*N*-diethylbenzamides

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A study of the effect of transposition of the internal nitrogen atom for the adjacent benzylic carbon atom in δ-selective agonists such as BW373U86 (**1**) and SNC-80 (**2**) has been undertaken. It was shown that high-affinity, fully efficacious, and δ opioid receptor-selective compounds can be obtained from this transposition. In addition to the *N*,*N*-diethylamido group needed as the δ address, the structural features identified to promote δ receptor affinity in the set of compounds studied included a *cis* relative stereochemistry between the 3- and 4-substituents in the piperidine ring, a *trans*-crotyl or allyl substituent on the basic nitrogen, the lack of a 2-methyl group in the piperidine ring, and either no substitution or hydroxyl substitution in the aryl ring not substituted with the *N*,*N*-diethylamido group. Structural features found to be important for μ affinity include hydroxyl substitution in the aryl ring, the presence of a 2-methyl group in a *cis* relative relationship to the 4-amino group as well as *N*-substituents such as cyclopropylmethyl. It was also determined that μ receptor affinity could be increased while maintaining δ receptor affinity, especially when hydroxyl-substituted compounds are considered. Additionally, it was discovered that the somewhat lower μ/δ selectivities observed for the piperidine compounds relative to the piperazine-based ligands appear to arise as a consequence of the carbon−nitrogen transposition which imparts an overall lower δ and higher μ affinity to the piperidine-based ligands. This higher affinity for the μ receptor, apparently intrinsic to the piperidine-based compounds, suggests that ligands of this class will more easily be converted to μ/δ combination agonists compared to the piperazine ligands such as **1**. This is particularly important since analogues of **1**, which show both μ- and δ-type activity, are now recognized as important for their strong analgesia and cross-canceling of many of the side effects found in agonists operating exclusively from either the δ or μ opioid receptor.

Introduction

The discovery of opioid analgesics that operate via δ or κ opioid receptors as opposed to the μ opioid receptor, which meditates the actions of morphine and its congeners, has been a goal of medicinal chemists for many years.[1] While morphine remains the painkiller of choice for severe pain, the accompanying respiratory depression and addiction liability associated with its use continue to drive the search for safer medications.[2] Much as the discovery of the non-peptide κ opioid receptor-selective ligand U50,488[3] opened the door to an explosion of research in this area during the 1980s, the discovery of the *N*,*N*-diethylbenzamide agonists BW373U86 (**1**)[4] and SNC-80 (**2**)[5] and the δ receptor-selective antagonist naltrindole (NTI, **3**)[6] (Chart 1) paved the way to the development of a variety of non-peptide δ ligands over the past decade. Of these two groups of compounds, naltrindole may be considered a classical ligand for the opioid receptor since it contains a tyramine-like substructure found in the tyrosine residue of the endogenous ligands (enkephalins). The former compounds have been referred to as nonclassical[7] since their piperazine substructure represents a motif not commonly associated with opioid binding compounds.

These two sets of compounds influenced the area of δ receptor research in different ways. The principal impact of the diethylbenzamide compounds such as **1** and **2** was their introduction of novel structural concepts by which δ selectivity could be realized. The impact of the discovery of NTI (**3**) related not only to its δ selectivity but also to the rationale behind its design.[8] Portoghese successfully applied the message-address concept of Schwyzer[9] to opioid small-molecule ligands by demonstrating that addition of a phenylalanine mimic (the address unit of the enkephalins) to the nonselective antagonist naltrexone resulted in a ligand with δ selectivity. Research by other groups led to the

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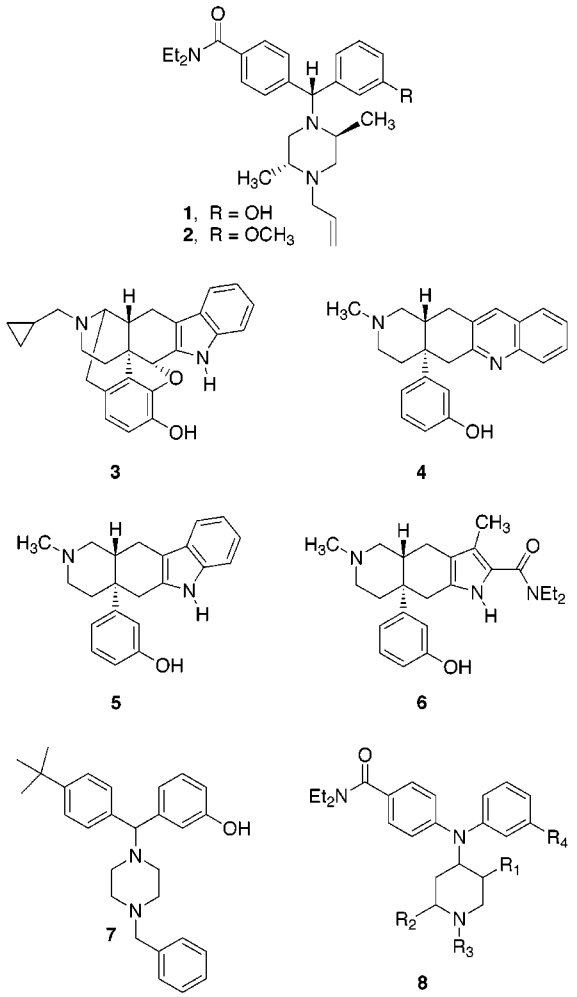
Chart 1



introduction of the δ-selective agonist TAN-67 (**4**) and the antagonist SB205588 (**5**).[7,10] These two compounds display simplified molecular structures relative to **3**, but both utilize Portoghese's enkephalin Phe[4] mimic concept to promote δ receptor subtype selectivity.

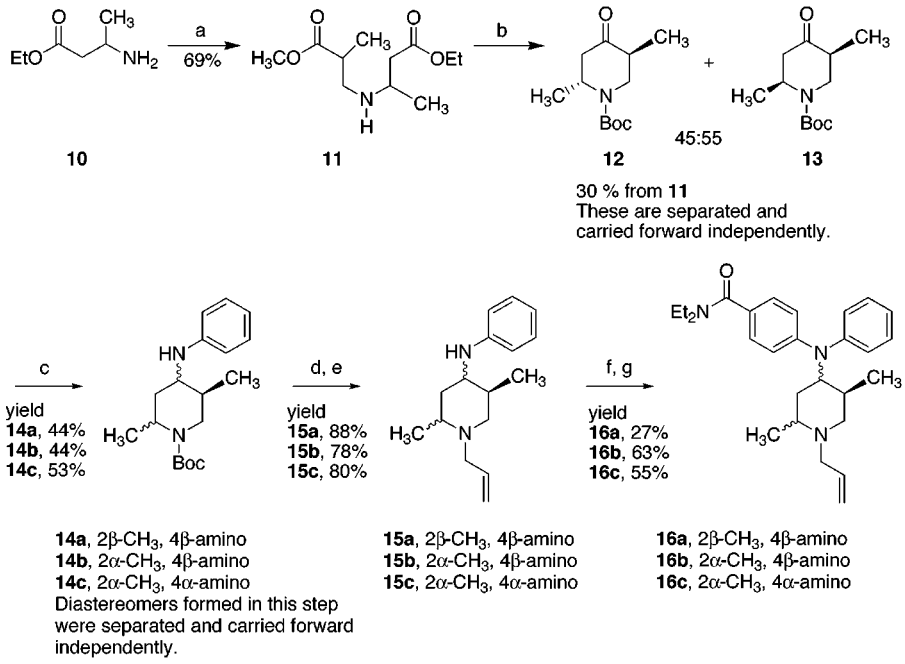
Additional discoveries important to this discussion include two compounds that do not fall neatly into either of the above categories. These are SB219825 (**6**), introduced by Dondio and co-workers, and the peptidomimetic SL-3111 (**7**), discovered by Liao et al.[11] The former compound is particularly interesting because it possesses structural elements of both the nonclassical *N*,*N*-diethylbenzamide agonists as well as the classical morphinan-based compounds and, therefore, represents a unique molecular hybrid. The latter compound **7**, designed as a small-molecule peptidomimetic from cyclic [penacillamine[2],penacillamine[5]]enkephalin (DPDPE), is an intriguing δ opioid ligand since it is so strikingly similar to **1** and **2** and yet possesses a structure−activity (SAR) profile completely different from that of the diethylbenzamides such as SNC-80 (**2**).

Recently, others, including our laboratory,[12,13] have disclosed findings relating to the SAR of structures closely related to the *N*,*N*-diethylbenzamides **1** and **2**.[14−27] In our discovery efforts in this field of δ opioid receptor ligands, we have carried out SAR studies on compounds of general structure **8**, derived from transposition of the internal nitrogen atom in compounds **2** with the adjacent benzylic carbon. This line of investigation produced not only high-affinity δ receptor-selective full agonists but also information essential to better our understanding of the fundamental elements governing ligand δ receptor selectivity at the molecular level. In the present article we relate our most recent findings derived from this series of compounds. Preliminary results from some of these studies have already been reported.[12,13]

Chemistry

Access to the required diarylanilinopiperidine system found in the subject compounds **8** (Chart 1) utilized an anionic aromatic nucleophillic substitution reaction between a given *N*-substituted 4-anilinopiperidine and the butylated hydroxyanisole (BHA) ester of 4-fluorobenzoic acid as the key step. This strategy, demonstrated by Hattori and co-workers[28] in the production of triarylamines, proved to be robust and allowed for multiple degrees of synthetic flexibility in the introduction of molecular diversity from readily available starting materials, piperidones and aniline derivatives. This strategy is illustrated in the synthesis of the 2,5-dimethylpiperidine derivatives **16a**−**c** as shown in Scheme 1. The requisite dimethylpiperidones **12** and **13** were prepared from ethyl 3-aminobutyrate (**10**) by treatment with excess methyl methacrylate to give the isolable intermediate **11** in 69% yield. This material was subsequently converted to the piperidones in a one-pot procedure involving cyclization of **11** by treatment with sodium in refluxing xylenes, decarboxylation with 20% HCl, and finally carbamate formation with di-*tert*-butyl dicarbonate. From this reaction mixture **12** and **13** were obtained in approximately equal proportions after flash chromatography in 30% overall yield from **11**. These two 4-piperidones then underwent reductive amination with aniline using titanium(IV) isopropoxide[29,30] and sodium borohydride to give intermediates **14a**−**c**. The diastereomers formed in this reaction were separated at this point and carried forward independently. While four diastereomers could arise in this reaction, only **14a**−**c** were isolated in synthetically useful quantities. The allyl derivatives **15a**−**c** were next prepared by treating **14a**−**c** with trifluoroacetic acid (TFA) to remove the *tert*-butyloxycarbonyl group followed by alkylation with allyl bromide in ethanol. Assembly of the diarylamine core, in 27−63% yields, was accomplished by treating **15a**−**c** with *n*-butyllithium in tetrahydrofuran (THF) followed by combining with the BHA ester of 4-fluorobenzoic acid. Removal of the BHA group was accomplished by transesterification with refluxing sodium methoxide in toluene/*N*-methylpyrrolidinone followed by saponification of the methyl ester in ethanol and water. The zwitterionic intermediates thus formed were not isolated but instead converted directly into *N*,*N*-diethylamides using benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP, a.k.a. Castro's reagent) and diethyl- and triethylamines in a THF slurry to give **16a**−**c**, respectively. Assignment of the relative stereochemistry in compounds **16a**−**c** was accomplished by single-crystal X-ray analysis of final products or of configurationally stable intermediates. The relative stereochemistry of the *cis*-piperidone **13** was established by single-crystal X-ray analysis and shown to be 2*SR*,5*RS* (Figure 1). The relative stereochemistry of the other stereoisomer obtained (**12**) was

Scheme 1[a]



[a] (a) Methyl methacrylate, EtOH, HOAc; (b) sodium, xylenes, reflux then 20% HCl, reflux then di-*tert*-butyl dicarbonate, MeOH, 10% triethylamine, reflux; (c) Ti(O*i*-Pr)$_4$, aniline then NaBH$_4$, EtOH; (d) TFA, CH_2Cl_2; (e) allyl bromide, EtOH, K_2CO_3; (f) *n*-BuLi, THF, HMPA then 2,6-di-*tert*-butyl-4-methoxyphenyl 4-fluorobenzoate; (g) *N*-methylpyrrolidinone, $NaOCH_3$, toluene then EtOH, H_2O then Et_2NH, BOP, Et_3N.

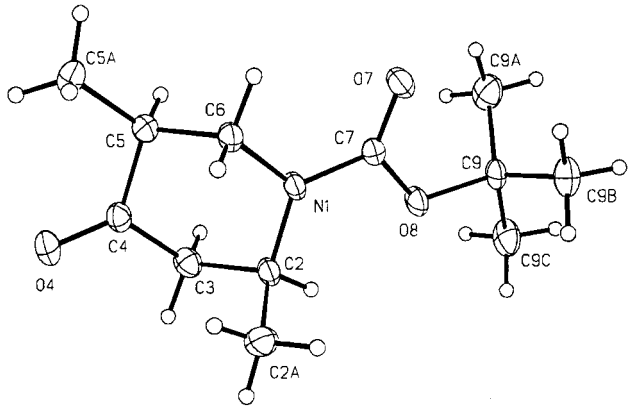


Figure 1. Results of the X-ray study on **13** drawn from the experimentally determined coordinates with anisotropic thermal parameters at the 20% probability level.

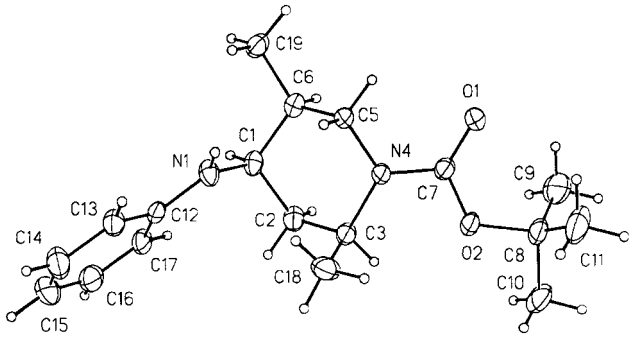


Figure 2. Results of the X-ray study on **14a** drawn from the experimentally determined coordinates with anisotropic thermal parameters at the 20% probability level.

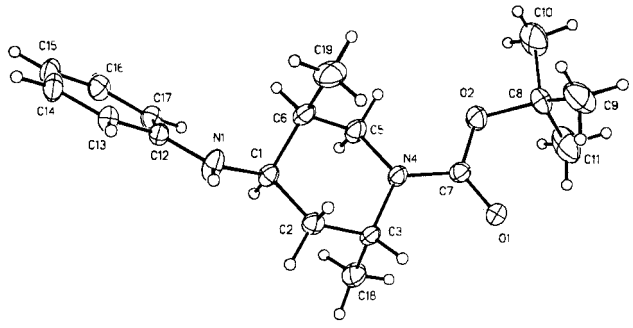
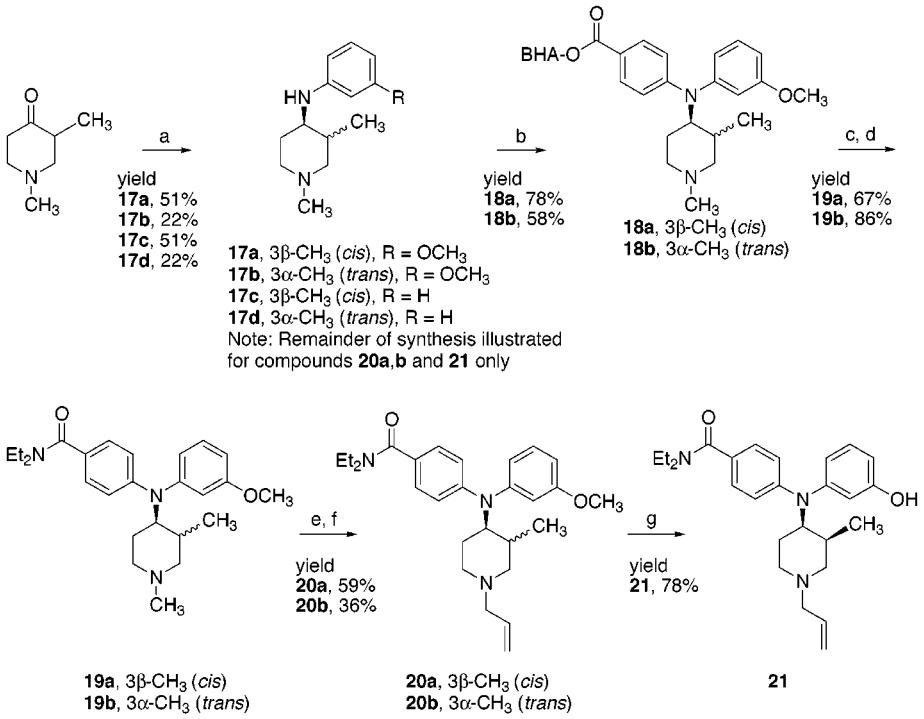


Figure 3. Results of the X-ray study on **14b** drawn from the experimentally determined coordinates with anisotropic thermal parameters at the 20% probability level.

assumed to be *trans*. This assumption was verified in the next step by single-crystal X-ray analysis of the products obtained in the reductive alkylation reaction. Thus, the *cis*-piperidone **13** provided predominantly **14a** (Figure 2), whereas the *trans*-piperidone provided predominantly **14b** (Figure 3). Given that the stereocenters in compounds **14a**,**b** are not disturbed during the transformation of **14a**,**b** to **16a**,**b**, the relative stereochemistry of 2*SR*,4*RS*,5*SR* and 2*RS*,4*RS*,5*SR* found for **14a**,**b** in Figures 2 and 3, respectively, will also be found in products **16a**,**b**. The stereochemistry of compound **16c** was shown to be the 2*RS*,4*SR*,5*SR* isomer by single-crystal X-ray analysis of its HCl salt (Figure 4).

Preparation of the monomethyl-substituted piperidine derivatives used in this study proceeded in a manner similar to that used for **16a**−**c**. The representative synthesis for all other compounds prepared for this study is illustrated for compounds **20a**,**b** and **21** in Scheme 2 starting from commercially available 1,3-dimethyl-4-piperidone. Following reductive amination with *m*-anisidine and titanium(IV) isopropoxide, the diastereomers **17a**,**b** were separated and independently coupled to the BHA ester of 4-fluorobenzoic acid to give **18a**,**b**. The yield for this reaction was observed to

Scheme 2[a]



[a] (a) Ti(O*i*-Pr)$_4$, aniline derivative then NaBH$_4$, EtOH; (b) *n*-BuLi, THF, HMPA then 2,6-di-*tert*-butyl-4-methoxyphenyl 4-fluorobenzoate; (c) *N*-methylpyrrolidinone, NaOCH$_3$, toluene then EtOH, H$_2$O; (d) Et$_2$NH, BOP, Et$_3$N; (e) PhOCOCl then KOH, *i*-PrOH, H$_2$O; (f) allyl bromide, EtOH, K$_2$CO$_3$; (g) BBr$_3$, CHCl$_3$.

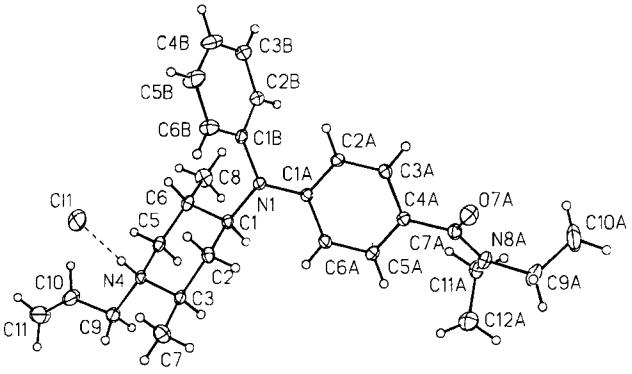


Figure 4. Results of the X-ray study on **16c** drawn from the experimentally determined coordinates with anisotropic thermal parameters at the 20% probability level.

depend on both the *N*-substituent as well as the relative stereochemistry (*cis* or *trans*) in the piperidine 3,4-position. *Trans* derivatives typically gave yields approximately one-third lower than *cis* derivatives. Also, as might be expected, the *N*-methyl derivatives faired better in this reaction than either *N*-allyl analogues or Boc-protected derivatives presumably due to interaction of *n*-BuLi with the latter *N*-substituents. Conversion of the BHA ester to the *N*,*N*-diethylamide to give **19a**,**b** was accomplished as described for the synthesis of **16a**−**c**. Preparation of a variety of *N*-substituent derivatives (illustrated for allyl) was accomplished in a two-pot procedure, whereby **19a**,**b** were first treated with phenyl chloroformate to form the carbamate which was not isolated but directly hydrolyzed to the secondary amine with potassium hydroxide in isopropyl alcohol. Following purification of this material, *N*-substituent derivatization proceeded under simple alkylation conditions to give **20a**,**b** in 35−60% yields from **19a**,**b**. Analogues with free phenolic groups (**21**) were prepared from the corresponding methyl ethers by treatment with boron tribromide in chloroform. A preliminary account of the synthesis of the optically pure compounds described herein has been published.[13]

Compound structures were based on elemental analysis and proton and carbon NMR spectral analyses including COSY and HMQC. The *cis* relative stereochemistry of **19**−**34** was based on a large vicinal coupling constant (J = 13.0 Hz) between the H5 axial and H4 protons that established the equatorial position for the 4-diarylamine group and a correlation in the NOESY spectrum between the H5 axial proton and the 3-methyl group which places this group *cis* to the 4-diarylamine group. Corroborating evidence for both the relative (*cis*) and absolute (3*S*,4*R*) stereochemistries of the most active enantiomer (−)-**23a** was obtained through single-crystal X-ray analysis of the HCl salt of (−)-**23a** (Figure 5).

Results and Discussion

The radioligand binding data for the test compounds **16**−**34** illustrated in Chart 2 along with comparative data for the prototypical *N*,*N*-diethylbenzamide δ receptor-selective agonists BW373U86 (**1**) and SNC-80 (**2**) are shown in Table 1. From the *N*-allyl compound set of **20a**,**b** and **23a**,**b** it was clearly established that with K_is of 22 and 11.9 nM, respectively, the 3,4-*cis*-monomethyl compounds **20a** and **23a** possess superior δ affinity relative to their similarly substituted *trans* counterparts **20b** and **23b** with K_is of 379 and 126 nM. The importance of the 3,4-*cis* stereochemical arrangement to binding affinity is further elaborated in the

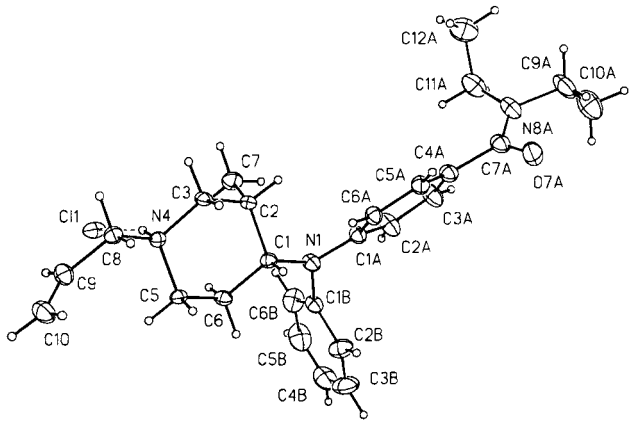
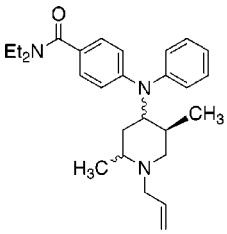


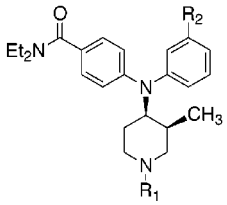
Figure 5. Results of the X-ray study on (−)-**23a** drawn from the experimentally determined coordinates with anisotropic thermal parameters at the 20% probability level.

Chart 2



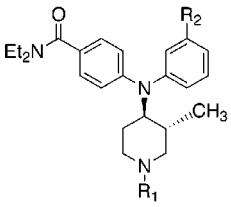
16a, 2β, 4β, 5β
16b, 2α, 4β, 5β
16c, 2α, 4α, 5β

16a–c



3,4-*cis* Series

19a, *cis*, R_1 = methyl, R_2 = OCH_3
20a, *cis*, R_1 = allyl, R_2 = OCH_3
21, *cis*, R_1 = allyl, R_2 = OH
22a, *cis*, R_1 = methyl, R_2 = H
23a, *cis*, R_1 = allyl, R_2 = H
(+)-23a, *cis*, R_1 = allyl, R_2 = H
(-)-23a, *cis*, R_1 = allyl, R_2 = H
24, *cis*, R_1 = trans-crotyl, R_2 = H
(−)-24, *cis*, R_1 = trans-crotyl, R_2 = H
25, *cis*, R_1 = trans-crotyl, R_2 = OCH_3
26, *cis*, R_1 = trans-crotyl, R_2 = OH
27a, *cis*, R_1 = cyclopropylmethyl, R_2 = H
28a, *cis*, R_1 = cyclopropylmethyl, R_2 = OCH_3
29, *cis*, R_1 = methallyl, R_2 = H
30, *cis*, R_1 = methallyl, R_2 = OCH_3
31, *cis*, R_1 = prenyl, R_2 = H
32, *cis*, R_1 = prenyl, R_2 = OCH_3
33, *cis*, R_1 = cinnamyl, R_2 = H
34, *cis*, R_1 = cinnamyl, R_2 = OCH_3



3,4-*trans* Series

19b, *trans*, R_1 = methyl, R_2 = OCH_3
20b, *trans*, R_1 = allyl, R_2 = OCH_3
22b, *trans*, R_1 = methyl, R_2 = H
23b, *trans*, R_1 = allyl, R_2 = H
27b, *trans*, R_1 = cyclopropylmethyl, R_2 = H
28b, *trans*, R_1 = cyclopropylmethyl, R_2 = OCH_3

monomethylpiperidine compounds **19a**, **22a**, **27a**, and **28a** wherein a 3,4-*cis* arrangement provides compounds of higher affinity for the δ receptor relative to corresponding 3,4-*trans* compounds tested, **19b**, **22b**, **27b**, and **28b**. Thus, the relative stereochemical position of the 3-methyl group is critical to overall δ receptor affinity.

Comparison of the data for 3-substituted monomethyl compound **23a** to that of the 2,5-dimethyl-substituted compounds **16a**,**b** (all have the 3,4-*cis* relative stereochemistry) provides an opportunity to assess the influence of an additional piperidine ring methyl group on receptor binding affinity and ultimately on ligand selectivity. Considering δ receptor affinity first, it is found that methyl group substitution in the piperidine ring α to the nitrogen and in a *cis* configuration relative to the other two substituents (**16a**) decreases δ receptor affinity nearly 5-fold compared with compound **23a** not substituted in this manner. In compound **16b**, with the methyl group in a *trans* configuration, the affinity for the δ receptor is decreased only 1.5-fold. Thus the relative stereochemistry of a methyl substituent in the 2-position on the piperidine ring can significantly impact δ receptor affinity.

Compared to the selectivity found in compound **23a**, methyl substitution in the piperidine 2-position is observed to decrease δ selectivity overall. In compound **16a**, this results predominately from the nearly 5-fold loss of δ receptor affinity for **16a** noted above since the μ affinity decreases only 3-fold relative to **23a**. This is not the case for **16b** with the additional methyl in the *trans* relative configuration. In **16b** the μ receptor affinity is dramatically improved compared to either **16a** or **23a**. Thus even though **16b** shows relatively good affinity for the δ receptor (K_i = 19 nM), this does not compete favorably with the 23-fold improvement in μ receptor affinity relative to **16a** and the compound is not selective for the δ receptor. Such a dramatic impact on μ receptor affinity is worthy of note since few other single structural modifications in this study produced this magnitude of change in binding affinity at any opioid receptor. Overall, it is evident that a methyl group in the 2-position of the piperidine ring of the subject compounds, regardless of the configuration, leads to compounds of lower δ affinity and selectivity. However, since compounds with the highest affinity (**16a**,**b**) for the δ receptor are also the ones possessing a *cis* arrangement between the substituents in positions 3 and 4 of the piperidine ring, the 3,4-*cis* series, this trend is apparently preserved in the presence of a 2-methyl substituent. The observed effects of this methyl group on δ affinity and μ/δ selectivity are in general agreement with the findings of Knapp et al.[31] in the SNC-80 series although the related piperidine compounds are observed to display comparatively lower δ affinity.

The general effect of aryl substitution on binding affinity in the 3,4-*cis* series of compounds is available from comparison of aryl methoxy, hydroxy, and unsubstituted compounds. Comparison of the 22 nM K_i value of compound **20a** (methoxy) with the 11.9 value for **23a** (unsubstituted) illustrates that methoxy substitution in the aryl ring decreases binding affinity 2-fold for the δ receptor. A comparison of the binding data for **20a** and **23a** at the κ and μ receptor shows 2- and 4-fold decreases, respectively. However, this same structural feature also imparts about a 2-fold improvement in δ receptor subtype selectivity. Overall, the methoxy substitution appears to decrease δ affinity but promote selectivity. The hydroxy-substituted compounds **21** and **26** with K_i values of 1.85 and 2 nM, respectively, display a 12- and 9-fold improvement in binding affinity at the δ receptor relative to their methyl ethers (**20a** and **25**). However, in terms of selectivity, the significant increase

Table 1. Radioligand Binding Results at the μ, δ, and κ Opioid Receptors for 4-[(*N*-Substituted-4-piperidinyl)arylamino]-*N*,*N*-diethylbenzamides

	K_i (nM ± SD)				
compd	μ [^{3}H]DAMGO[a]	δ [^{3}H]DADLE[b]	κ [^{3}H]U69,593[c]	μ/δ	κ/δ
1, BW373U86	36 ± 3.4	0.91 ± 0.05	NA	40	
2, SNC-80	1614 ± 131	1.57 ± 0.19	3535 ± 1841	1030	2250
16a	3895 ± 260	53 ± 4	2903 ± 310	74	55
16b	171 ± 15	18.8 ± 0.69	1164 ± 76	9	62
16c	9905 ± 448	93 ± 6	6324 ± 369	110	68
19a	>5917	141 ± 8.8	>6061	>42	>43
19b	3322 ± 269	178 ± 9	6302 ± 1092	19	35
20a	5330 ± 605	22 ± 1	>7463	240	>339
20b	4872 ± 541	379 ± 23	>7463	13	20
21	126 ± 9	1.85 ± 0.24	76.7 ± 4.6	68	41
22a	388 ± 13	45.6 ± 2.5	>6061	9	>132
22b	1511 ± 40	257 ± 7	>6061	6	24
23a	1212 ± 132	11.9 ± 0.9	3284 ± 299	102	275
23b	1589 ± 86	126 ± 5	8695 ± 978	13	69
(+)-**23a**	>4854	139 ± 11.4	3722 ± 556	>35	26
(−)-**23a**	2623 ± 307	5.58 ± 0.31	1448 ± 196	470	260
24	3590 ± 285	7.0 ± 0.6	>7463	510	>1100
(−)-**24**	938 ± 71	2.72 ± 0.62	1638 ± 166	344	602
25	3252 ± 236	18 ± 3	>7463	180	>414
26	40.8 ± 7.8	2.00 ± 0.12	164 ± 12	20	82
27a	160 ± 29	20 ± 3	2383 ± 225	8	120
27b	5341 ± 181	193 ± 5	>6061	28	>31
28a	>6536	36 ± 2	>7463	>180	>210
28b	>6536	230 ± 11	>7463	>28	>33
29	1260 ± 770	36 ± 3	>7463	35	>210
30	5685 ± 443	72 ± 6	>7463	80	>100
31	3785 ± 312	15.0 ± 0.6	>7463	252	>497
32	3387 ± 366	36 ± 4	6020 ± 695	94	170
33	6425 ± 471	68 ± 4	13459 ± 1715	95	200
34	>6536	93 ± 4	>7463	>70	>80

[a] [^{3}H]DAMGO [(D-Ala^2,MePhe^4,Gly-ol^5)enkephalin], tritiated ligand selective for the μ opioid receptor. [b] [^{3}H]DADLE [(D-Ala^2,D-Leu^5)enkephalin], tritiated ligand selective for the δ opioid receptor. [c] [^{3}H]U69,593 {[^{3}H]-(5α,7α,8β)-(−)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]benzeneacetamide}, tritiated ligand selective for the κ opioid receptor.

in binding affinity for the δ receptor is insufficient to offset the binding affinity increases found for μ and κ receptors, and thus, the δ selectivity of **21** and **26** relative to the methoxy-substituted ligands **20a** and **25** or the unsubstituted compounds **20a** and **23a** is diminished. These trends in receptor affinity modulation are in agreement with those observed within the piperazine series as related in several different studies[5,23,27] and in other closely related studies of piperidine analogues.[24]

To identify the effect on binding affinity associated with changes to the *N*-substituent group of the more selective compounds **20a** and **23a**, a series of "allyl-like" compounds were tested along with the *N*-methyl intermediates (**19a**, **22a**). With methyl as the *N*-substituent (**19a**, **22a**) a significant loss of binding affinity relative to the *N*-allyl compounds **20a** and **23a** was observed. Thus, with K_i values of 141 and 45 nM, respectively, in binding to the δ receptor, the *N*-methyl analogues **19a** and **22a** showed a 6- and 4-fold loss, respectively, in affinity compared to the *N*-allyl compounds **20a** and **23a**. The *N*-*trans*-crotyl derivative **24** with a K_i value of 7 shows higher affinity and selectivity at the δ receptor than similarly substituted allyl derivative **20a**, showing that the addition of a distal methyl to the *N*-allyl substituent can result in an increase in δ receptor affinity and selectivity. The K_i values of 7 and 18 nM found for **24** and **25**, respectively, represent a 2-fold improvement for the aryl unsubstituted compound **24** relative to **23a** but only a 1.2-fold improvement for the methoxy-substituted compound. In line with the allyl derivatives seen earlier, the *trans*-crotyl compound **24**, not substituted in the aryl ring, showed a binding affinity about 2.5-fold greater than the methoxy-substituted compound **25**. Indeed, this phenomenon was observed for every *N*-substituent tested and is discussed in more detail below.

Addition of a single methyl to the central carbon of the allyl group provided the *N*-methallyl derivatives **29** and **30**, which bind the δ receptor less effectively than their allyl (**20a** and **23a**) counterparts. The prenyl derivatives **31** and **32** possess two methyl groups at the distal carbon of the allyl group and showed somewhat lower affinity than the *N*-allyl compounds with K_is of 15 and 36 nM. However, this loss of affinity was only one-half that observed for the *N*-methallyl derivatives **29** and **30**. Compared with the more closely related *trans*-crotyl derivatives, however, the prenyl compounds display a 2-fold loss of affinity by the addition of a second methyl group. Incorporation of a phenyl group into the *N*-allyl substituent, in a *trans* geometric relationship, provided the *N*-*trans*-cinnamyl derivatives **33** and **34** that also lacked good affinity for the δ receptor. Indeed, of all the *N*-substituents tested, the cinnamyl derivatives gave the lowest affinity observed for the δ receptor. Assuming that high electron density is a requirement in the *N*-substituent, then the relative loss in affinity of about 6- and 4-fold, respectively, found in **33** and **34** is likely to result from the increased size since this was the most electron-rich substituent tested.

Relative to the allyl group the *N*-cyclopropylmethyl substituent retains a degree of high electron density but possesses an additional methylene group in what would

be the π cloud of the allyl substituent. In binding, the *N*-cyclopropylmethyl compounds **27a** and **28a** displayed a slight loss of binding affinity relative to the allyl analogues **20a** and **23a** with K_is of 20 and 36 nM, respectively, suggesting that *N*-substituents should be sp^2 hybridized between carbons 2 and 3 since the width of the substituent appears to affect binding. Overall, the data available from the *N*-substituent changes to **20a** and **23a** indicate that the binding site associated with this region of the receptor prefers electron-rich structures which is in accord with the findings of Zhang[27] and Furness[21] in the SNC-80 series. Additionally, the *trans*-crotyl group was found to provide compounds of higher affinity and selectivity compared with similarly substituted compounds possessing allyl as the *N*-substituent. Overall, these data fall in line with observations made in other piperazine[23] and piperidine[24,26] related studies.

The optical isomers of **23a** and **24** provided compounds of higher affinity and δ receptor selectivity as well as demonstrating a separation of activity between the optical antipodes. As illustrated in Table 1, comparison of racemic **23a** and its optical isomers reveals that the high δ opioid binding affinity as well as the δ receptor selectivity of the racemic mixture is due to (−)-**23a**. With a K_i value of 5.5 nM, the (−)-isomer (−)-**23a** is twice as potent as the racemic mixture (±)-**23a**, whereas (+)-**23a** with a K_i value of 139 nM is 12-fold less potent than (±)-**23a** resulting in a 25-fold separation of binding affinity between the (−)- and (+)-enantiomers. In terms of opioid receptor selectivity, (−)-**23a** demonstrates a nearly 5-fold increase in δ versus μ selectivity compared with the racemic material. This increased δ selectivity is due in part to the increase in δ receptor affinity and partly to a 2-fold decrease in affinity for the μ receptor. Relative to the racemic mixture or the (+)-**23a** isomer, (−)-**23a** shows a significantly improved δ opioid binding affinity and δ selectivity. Since racemic **24** had greater affinity and selectivity than did **23a**, (−)-**24** was prepared and evaluated. Compound (−)-**24** with a K_i of 2.7 nM had the highest affinity for the δ receptor of all of the aryl unsubstituted compounds tested. Compared with the racemic material, (−)-**24** like (−)-**23a** displayed an improvement in δ receptor binding affinity; however, unlike (−)-**23a** its δ selectivity was somewhat diminished. Inspection of the data for **24** and (−)-**24** indicates that this change in selectivity can be attributed to a much improved affinity of (−)-**24** for the μ receptor relative to the racemic material. Thus, the 2.5-fold improvement in affinity for the δ receptor shown by (−)-**24** relative to the racemic mixture is offset by an almost 4-fold increase affinity for the μ receptor. Worthy of note is the observed impact on δ selectivity resulting from the incorporation of this single methyl group in the *N*-substituent.

The overall affect of aryl substitution and *N*-substitution on δ affinity and selectivity as well as an interesting trend was revealed by graphical analysis of the receptor binding data obtained from the 3,4-*cis* series (Figure 6). As discussed previously, the most potent and selective compounds identified in this study were the 3,4-*cis* compounds as represented by **23a**. When the binding affinities of the compounds of this series are plotted as a function of aryl and *N*-substituent, two distinct levels

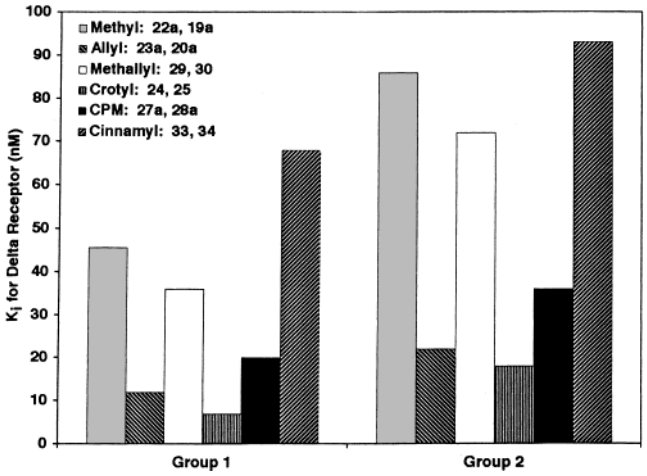


Figure 6. K_is for 3,4-*cis* compounds at the δ receptor as a function of aryl substitution and *N*-substituent (group 1 = unsubstituted aryl, group 2 = methoxy-substituted aryl).

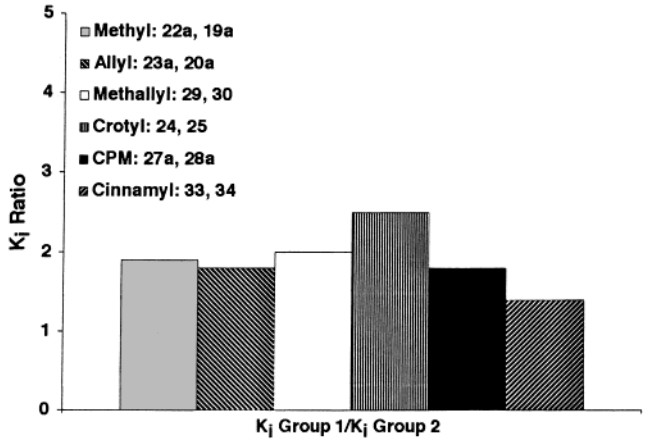


Figure 7. Ratio of K_i for group 2 (methoxy-substituted aryl ring) to group 1 (unsubstituted aryl ring) as a function of *N*-substituent in the δ binding assay.

of ligand affinity modulation are revealed. The aryl substituent (methoxy) is found to define broadly the fundamental level of binding affinity achievable by a given ligand while the *N*-substituent more narrowly defines the ultimate binding affinity displayed by the ligand. Stated another way, for any choice of *N*-substituent, the compound unsubstituted in the aryl ring (group 1) will bind with about twice the affinity as the compound possessing a methoxy substituent in the aryl ring (group 2), and this phenomenon is independent of the *N*-substituent. Though this trend is visible by inspection of Figure 6, it is more clearly revealed in Figure 7 wherein the K_i ratios for the two groups are compared as a function of the *N*-substituent. Remarkably, in this depiction, the ratio of K_i for the two groups for any given *N*-substituent large (cinnamyl) or small (methyl) is observed to remain nearly constant. Since only the allyl and crotyl analogues with hydroxy-substituted aryl rings were tested, a direct comparison point-by-point for this series is not possible, but the data available suggest that this trend appears to exist within this series of compounds as well. Taken together, these results indicate that the aryl substituent takes precedence over the *N*-substituent for establishing the gross δ receptor binding affinity available to a ligand of this

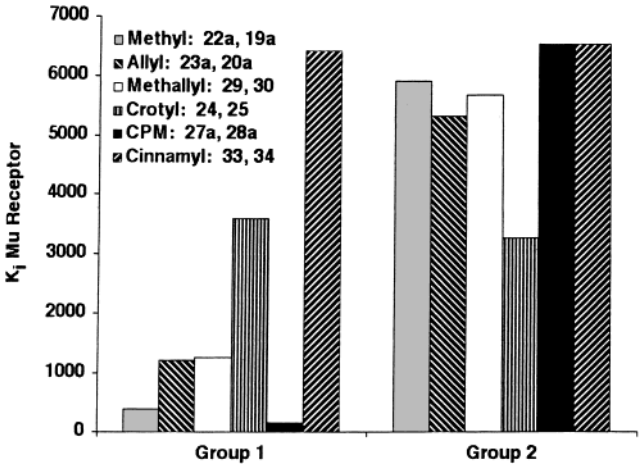


Figure 8. K_is for 3,4-*cis* compounds at the μ receptor as a function of aryl substitution and *N*-substituent (group 1 = unsubstituted aryl, group 2 = methoxy-substituted aryl).

series, while the *N*-substituent fine-tunes the K_i within the parameters set by the aryl substituent. Considered from a different perspective, as molecular probes of the δ receptor binding domain, the highly organized data obtained from the compounds of groups 1 and 2, as depicted in Figure 6, reflect the presence of a well-ordered region of highly specific requirements for binding. This is not the case for the μ receptor.

Graphical analysis of the μ binding data obtained for the same compounds reveals that in contrast to the δ assay analysis of Figure 6, no regular affinity profile, based on either the nitrogen or aryl substituent, is observed (Figure 8). This phenomenon arises because for some of the *N*-substituents studied like the *N*-methyl (**19a** and **22a**) or the *N*-cyclopropylmethyl (**27a** and **28a**) derivatives, very large differences in affinity between the aryl methoxy-substituted and aryl-unsubstituted compounds are observed. Thus, while the methoxy-substituted derivatives (group 2) as a group do not bind the μ receptor, some compounds unsubstituted in their aryl ring (group 1), like **27a**, are recognized by the μ receptor and exhibit moderate binding affinity (K_i for **27a** = 160 nM). This fact has significant consequences to the overall selectivity observed for a given ligand. Comparison of the selectivity for compounds, **19a** versus **22a** and **27a** versus **28a** in Table 1, illustrates this point. The δ versus μ selectivities for the cyclopropylmethyl-substituted compounds **27** and **28a**, for example, is 8 and >182, respectively; a striking difference considering the similarity of the two molecules. Inspection of their δ receptor affinities of 20 and 36 nM, respectively, which represents only a 1.8-fold difference demonstrates that this is not the source of the large difference in selectivities. However, comparison of the μ affinities of 160 and >6536 nM for the same two compounds, a difference of at least 40-fold, not only illustrates the source of the divergence in selectivities between groups 1 and 2 but also highlights the fact that compounds of group 1 when appropriately substituted on the nitrogen can effectively bind to the μ receptor.

The analyses of δ and μ affinity above provide a rationale for the empirical observation addressed earlier that compounds of group 1 (unsubstituted), on the whole, possessed greater δ receptor affinity but were less selective than compounds of group 2 (methoxy-substituted). Indeed compounds of group 1 have greater affinity for both μ and δ receptors than their methoxy-substituted counterparts. The importance of this observation is made clear when one considers that piperazine-based compounds such as **2** do not share such a behavior between aryl methoxy-substituted and unsubstituted compounds which strongly suggests that the transposition of the internal carbon and nitrogen atom fundamentally alters the overall conformation of the resulting ligands and provides compounds that have an intrinsically higher affinity for the μ opioid receptor compared with similarly substituted piperazine-based ligands.

To determine their effectiveness as δ receptor agonists, a selected set of high-affinity compounds from the binding assay were evaluated for their ability to stimulate binding of the nonhydrolyzable GTP analogue, [^{35}S]GTP-γ-S, in guinea pig caudate membranes and compared to the readily available, widely recognized full agonist SNC-80 (**2**) (Table 2). Since the data was obtained in a tissue preparation as opposed to receptors expressed from cloned cell lines, parallel experiments were performed utilizing combinations of the test ligand and opioid receptor subtype-selective antagonists in order to identify the receptor responsible for any observed stimulation. These experiments were then compared directly to the test ligand in the tissue preparation alone, the "unblocked" condition. Under these conditions, (+)-**23a**, which showed low radioligand binding affinity at the δ receptor, displays no stimulation in the unblocked case, whereas (−)-**23a**, which showed high affinity at the δ receptor, exhibits an ED_{50} of 2508 nM and an E_{max} value virtually identical to the full agonist SNC-80 (**2**). In the combination experiments with opioid receptor subtype-selective antagonists, (−)-**23a** was observed to stimulate GTP binding only in the absence of the δ-selective antagonist NTI indicating a δ receptor site of action.[8] When combined with the μ-selective antagonist CTAP[32] or the κ-selective antagonist *nor*-binaltorphimine (*nor*-BNI)[33] the ED_{50} for (−)-**23a** was found to double. This doubling does not appear to be related to the test ligand since the phenomenon was also observed for the standard δ agonist SNC-80 (**2**). Compound (−)-**24** with its *N*-*trans*-crotyl group displayed greater potency in this assay (ED_{50} = 1129 nM) than did the allyl-substituted (−)-**23a**. This is not surprising as (−)-**24** had a higher affinity for the δ receptor compared with (−)-**23a**. Compound (−)-**24** was also observed to retain full agonist activity and to operate via the δ receptor as its stimulation occurred in the presence of μ- and κ- but not δ-selective antagonists.

The racemic phenolic derivatives **21** and **26** were by far the most potent compounds seen in this assay with ED_{50} values of 90.6 and 28.6 nM, respectively. This is in line with the observation that they possessed the highest affinity for the δ receptor of all of the compounds tested. However, the ED_{50} values observed appear to be lower than one would have suspected based on their receptor affinity. The observed E_{max} of 98 obtained for the allyl derivative **21** indicates partial agonist character relative to SNC-80, while racemic **26** appears to be a full agonist with an ED_{50} value of 28.6 nM and an E_{max} of 121. In the functional assay, compounds **21** and **26** are observed to be δ-selective as evidenced by the

Table 2. Apparent Functional ED_{50} and E_{max} Values of DAMGO, SNC-80, U69,593, and the Selected 4-[(*N*-Alkyl-3-methyl-4-piperidinyl)phenylamino]-*N*,*N*-diethylbenzamides Using GTP-γ-S Binding Assays in Guinea Pig Caudate Membranes

compd	unblocked condition (nM ± SD)	blocked with 20 nM NTI[d]	blocked with 6 nM *nor*-BNI[e]	blocked with 6000 nM CTAP[f]
DAMGO[a] ED_{50}	592 ± 105	1850 ± 287	509 ± 111	
DAMGO[a] E_{max}	123 ± 6	124 ± 6	135 ± 7	no stimulation
SNC-80[b] ED_{50}	317 ± 54		629 ± 71	673 ± 108
SNC-80[b] E_{max}	142 ± 6	no stimulation	143 ± 4	131 ± 5
U69,593[c] ED_{50}	684 ± 74	1980 ± 269	no stimulation	2142 ± 223
U69,593[c] E_{max}	177 ± 5	178 ± 8		167 ± 6
23a ED_{50}	3500 ± 500	no stimulation	3722 ± 1094	4667 ± 1937
23a E_{max}	63 ± 5		60 ± 7	55 ± 9
(−)-**23a**, 3*S*,4*R* ED_{50}	2508 ± 248	no stimulation	2952 ± 440	3604 ± 837
(−)-**23a**, 3*S*,4*R* E_{max}	126 ± 5		91 ± 5	85 ± 8
(+)-**23a**, 3*R*,4*S* ED_{50}	no stimulation			
(−)-**24**, 3*S*,4*R* ED_{50}	1129 ± 230	no stimulation	1523 ± 605	4709 ± 1364
(−)-**24**, 3*S*,4*R* E_{max}	121 ± 7		116 ± 15	116 ± 15
21 ED_{50}	90.6 ± 32.4	3591 ± 202.4	54.0 ± 14.5	130 ± 23
21 E_{max}	98 ± 7	85 ± 14	79 ± 4	87 ± 3
26 ED_{50}	28.6 ± 12.5	1820 ± 361	43.3 ± 12.1	71.0 ± 16.5
26 E_{max}	121 ± 9	195 ± 11	120 ± 3	129 ± 6

[a] DAMGO [(D-Ala[2],MePhe[4],Gly-ol[5])enkephalin], agonist selective for the μ opioid receptor. [b] SNC-80 ([(+)-4-[(α*R*)-α-(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide), agonist selective for the δ opioid receptor. [c] U69,593 [(5α,7α,8β)-(−)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]benzeneacetamide], agonist selective for the κ opioid receptor. [d] Naltrindole (NTI), antagonist selective for the δ opioid receptor. [e] *nor*-Binaltorphimine (*nor*-BNI), antagonist selective for the κ opioid receptor. [f] CTAP, antagonist selective for the μ opioid receptor.

39- and 63-fold decreases in ED_{50} in the presence of NTI but only minor changes in ED_{50} when tested in combination with μ- and κ-selective antagonists. In direct comparison to **23a** the ED_{50} values of 90.6 and 28.6 nM found for **21** and **26** represent 38- and 122-fold increases in potency, respectively. These findings are important when viewed in the light of the recent findings by O'Neill et al.[34] who demonstrated that the δ/μ combination agonists provide strong analgesia with simultaneous cross-canceling of some of the side effects possessed by highly specific μ or δ agonists. Taken together with their high potency for both the μ and δ receptors, the data from O'Neill et al. suggests that **21** and **26** could prove valuable as analgesics with reduced side effects relative to compounds operating purely though either the μ or δ opioid receptors.

Conclusions

The importance of the contribution made to the area of δ receptor research by the discovery of the *N*,*N*-diethylbenzamides **1** and **2** should not be understated since such events occur infrequently. Their appearance in the literature spawned the development of a multitude of structurally related δ-selective ligands. A feature held in common with other important breakthroughs is that the *N*,*N*-diethylbenzamides **1** and **2** possessed a unique structure relative to contemporaneous δ receptor-selective ligands and thereby established a new direction of discovery utilizing novel δ address moieties. However, due to their novelty, it was not immediately apparent which of the structural features present in these ligands elicited δ selectivity since no other compounds with similar structural features existed. Studies performed over the past decade have provided evidence for the mechanism by which the *N*,*N*-diethylbenzamido substructure influences δ selectivity. For example, Bishop et al.[35] and Katsura et al.[36] have clearly shown that the *N*,*N*-diethylamido group serves as the δ address moiety in **1** by demonstrating that δ selectivity is lost upon moving this group from the *para* to the *meta* position. The demonstration by Katsura et al.[36] that changes to the amide alkyl substituents dramatically affects ligand affinity implies a direct interaction of the *N*,*N*-diethylamido group with the receptor and supports the previous findings. Other important findings include the demonstration by Knapp et al.[37] that the stereochemistry of the benzyl carbon in **2** is the single most important determinant of receptor selectivity and those of Zhang[27] and Barn[15] who showed that the piperidine methyl groups in **2** are not necessary for δ receptor recognition. The studies of the piperidine compounds presented herein and elsewhere[24] illustrate additional features influencing the behavior of the *N*,*N*-diethylbenzamide δ agonists.

For example, this study has shown that high-affinity, fully efficacious, and δ opioid receptor-selective compounds can be obtained from the transposition of the internal nitrogen atom in BW373U86 (**1**) or SNC-80 (**2**) with its adjacent benzylic carbon. In addition to the *N*-(4-diethylcarboxamidophenyl) group needed for the δ address and within the context of the examples studied, the structural features found to promote δ receptor affinity in this transposed class of δ agonist were a *cis* relative stereochemistry between the 3- and 4-substituents in the piperidine ring, a *trans*-crotyl or allyl substituent on the basic nitrogen, the lack of a 2-methyl group in the piperidine ring, and either no substitution or hydroxyl substitution in the aryl ring not substituted with the *N*,*N*-diethylcarboxamido group. In contrast, hydroxyl substitution in the aryl ring, the presence of a 2-methyl group in a *cis* relative relationship to the 4-amino group as well as *N*-substituents such as cyclopropylmethyl all appear to promote binding to the μ opioid receptor while preserving affinity at the δ receptor. Additionally it was found that the somewhat lower selectivities observed for the piperidine compounds relative to the piperazine-based ligands appear to arise directly from the carbon−nitrogen transposition which imparts an overall lower δ affinity and higher μ affinity to the piperidine-based ligands. The fundamentally higher affinity for the μ receptor intrinsic to the piperidine-based compounds suggests that ligands of

this class will more easily be converted to μ/δ combination agonists relative to the piperazine ligands such as **1** which are now recognized as important for their strong analgesia with diminished side effects relative to agonists operating exclusively from either the δ or μ opioid receptor.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary tube apparatus and are not corrected. Elemental analyses were obtained by Atlantic Microlabs, Inc. and are within ±0.4% of the calculated values. All optical rotations were determined at the sodium D-line using a Rudolph Research Autopol III polarimeter (1-dm cell). ^{1}H NMR were determined on a Bruker Avance DPX-300 or Bruker AMX-500 spectrometer using tetramethylsilane as an internal standard. Silica gel 60 (230−400 mesh) was used for all column chromatography. All reactions were followed by thin-layer chromatography using Whatman silica gel 60 TLC plates and were visualized by UV or by charring using 5% phosphomolybdic acid in ethanol. All solvents were reagent grade. THF and diethyl ether were dried over sodium benzophenone ketyl and distilled prior to use.

[^{3}H]DAMGO, DAMGO, and [^{3}H][D-Ala^2,D-Leu^5]enkephalin were obtained via the Research Technology Branch, NIDA, and were prepared by Multiple Peptide Systems (San Diego, CA). [^{3}H]U69,593 and [^{35}S]GTP-γ-S (s.a. = 1250 Ci/mmol) were obtained from DuPont New England Nuclear (Boston, MA). U69,593 was obtained from Research Biochemicals International (Natick, MA). Levallorphan was a generous gift from Kenner Rice, Ph.D., NIDDK, NIH (Bethesda, MD). GTP-γ-S and GDP were obtained from Sigma Chemical Co. (St. Louis, MO). The sources of other reagents are published.

General Procedures. 1. Reductive Alkylation. The appropriate piperidone (92.68 mmol), aniline (or derivative) (93.4 mmol) and titanium isopropoxide (35 mL, 117.7 mmol) were heated at 55 °C for 20 h under a nitrogen atmosphere. The reaction mixture was allowed to cool and diluted with ethanol (100 mL). Sodium borohydride (5.0 g, 131.6 mmol) was then added, and the reduction was allowed to proceed at room temperature for 4 h. The reaction was quenched by addition of water and filtered over Celite, and the cake was washed with ethanol. After evaporation of the filtrate under reduced pressure, the white residue was taken up in ethyl acetate and again filtered over Celite. This provided the 4-anilinopiperidines as an oil after evaporation of the solvent under reduced pressure. Chromatography on silica gel using ethyl acetate in hexanes provided separation of all diastereomers produced in this step. These compounds were then carried forward independently throughout the subsequent reaction steps.

2. Aromatic Substitution between 4-Anilinopiperidines and 2,6-Di-*tert*-butyl-4-methoxyphenyl 4-Fluorobenzoate. The appropriate 4-anilinopiperidine (16.72 mmol) was dissolved in dry THF (13 mL) and dry hexamethylphosphoramide (HMPA; 5 mL) and cooled to −42 °C. A 2.5 M solution of *n*-butyllithium in hexanes (19.25 mol) was slowly added, and the reaction mixture was kept at 0 °C for 1 h. The reaction mixture was cannulated into a solution of 2,6-di-*tert*-butyl-4-methoxyphenyl 4-fluorobenzoate (16.76 mmol) in dry THF (13 mL) and dry HMPA (5 mL) at room temperature then heated to 45−50 °C for 5 h. The reaction mixture was cooled then quenched with a solution of NH_4Cl and diluted with ether. The aqueous layer was made basic (pH = 14) with 25% NaOH and extracted with ether (200 mL), and the ethereal layer was washed with water three times. Drying with $MgSO_4$ and evaporation of the solvents under reduced pressure afforded a crude brown oil. Chromatography on silica gel using ethyl acetate in hexanes gave separation of all analogues prepared.

3. Hydrolysis of BHA Esters and Conversion to *N,N*-Diethylbenzamide Derivatives. 2,6-Di-*tert*-butyl-4-methoxyphenyl 4-[(*N*-substituted-4-piperidinyl)phenylamino]benzoate (11.99 mmol) in toluene (150 mL) and *N*-methylpyrrolidinone (NMP; 40 mL) was added to freshly prepared sodium methoxide (120 mmol) and heated at reflux for 4 h. After evaporation of the toluene under reduced pressure, the residue was dissolved in a mixture of ethanol and H_2O (12:1, 150 mL) and heated at reflux for 1 h. After evaporation of the alcohol, the residue was taken up in water (400 mL) and extracted with hexanes (2 × 100 mL). The aqueous layer was made acidic (pH = 1) with 10% HCl, saturated with NaCl and extracted with a mixture of CH_2Cl_2 and THF (3:1, 5 × 200 mL). After drying over Na_2SO_4, the solvents were evaporated under reduced pressure. This material was then treated with diethylamine (1.2 mL), BOP (a.k.a. Castro's reagent) (5.0 g, 11.31 mmol) and triethylamine (4.2 mL) in THF (100 mL) for 30 min. The reaction mixture was next diluted with ether (300 mL), washed with water (2 × 75 mL), saturated $NaHCO_3$ (75 mL) and dried over Na_2SO_4 providing a black oil following evaporation of the solvents under reduced pressure. Chromatography on silica gel using hexanes/ethyl acetate/ethanol/triethylamine (47:47:3:3) provided separation of all analogues prepared.

4. Conversion from *N*-Methylpiperidine to Various *N*-Alkylpiperidine Derivatives. The appropriate 4-[(*N*-methyl-4-piperidinyl)arylamino]-*N*,*N*-diethylbenzamide (10.82 mmol) was treated with phenyl chloroformate (1.25 mL, 11.13 mmol) in 1,2-dichloroethane (35 mL) at room temperature for 24 h. The reaction was quenched with water and 30% NaOH then extracted with $CHCl_3$. After drying over Na_2SO_4 and evaporation of the solvents under reduced pressure, the crude product was treated with methanol (100 mL), water (60 mL), 2-propanol (50 mL) and 50% NaOH (30 mL) at reflux for 5 h. The alcohols were evaporated under reduced pressure, and the aqueous layer was extracted with $CHCl_3$/THF (3:1). After drying with Na_2SO_4, the solvents were evaporated under reduced pressure. Chromatography of the crude residue on silica gel using hexanes/ethyl acetate/ethanol/triethylamine (47:47:3) gave the *N*-demethylated material. This was dissolved in absolute ethanol (40 mL) and treated with the appropriate alkyl bromide (2.54 mmol) and K_2CO_3 (1.0 g, 7.24 mmol) at room temperature for 24 h. After evaporation of the ethanol under reduced pressure, the residue was chromatographed on silica gel using hexanes/ethyl acetate/ethanol/triethylamine (47:47:3) to provide the desired products.

5. Cleavage of Methyl Ethers. To a solution of compound **25** (0.500 g, 1.11 mmol) in dry CH_2Cl_2 (25 mL) at −78 °C was added BBr_3 (0.524 mL, 5.55 mmol) dropwise over 5 min. The reaction mixture was allowed to warm to room temperature and then quenched with H_2O (25 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL), the organic layers were collected and dried (Na_2SO_4), and the solvent was removed under reduced pressure to yield crude product. This material was purified by flash chromatography (50% ($CHCl_3$/MeOH/NH_4OH, 80:18:2) in $CHCl_3$) to afford **21** (375 mg, 78%) as an off-white foam. Anal. ($C_{26}H_{35}N_3O_2$) C, H, N.

6. Removal of *tert*-Butoxycarbonyl Protecting Groups. The appropriate Boc-protected piperidine (2.21 g, 7.27 mmol) was dissolved in CH_2Cl_2 (20 mL), and TFA (20 mL) was slowly added. The reaction mixture was stirred for 1 h at room temperature, and then the solvents were evaporated under reduced pressure. The yellow oil was taken up in water (50 mL), and the aqueous phase was made basic (pH = 14) with 25% NaOH then extracted with CH_2Cl_2/THF (3:1, 6 × 150 mL). This residue was used directly in the alkylation step without further purification.

Ethyl 3-[*N*-(Methyl 2-methylpropionate)amino]butyrate (11). Ethyl 3-aminobutyrate (**10**; 50 g, 344 mmol), methyl methacrylate (100 mL, 936 mmol), acetic acid (3.0 mL, 54.3 mmol), and ethanol (80 mL, 1.26 mol) were heated at reflux for 16 h. The reaction mixture was allowed to cool and was poured into a beaker containing ether (700 mL). A white polymer of polymethyl methacrylate, formed in the reaction, was washed with ether (2 × 100 mL). The organic phase was washed with a saturated solution of $NaHCO_3$ (2 × 75 mL) and with a saturated solution of NaCl (50 mL). After drying the organic phase with $MgSO_4$ and evaporation of the solvents and excess methyl methacrylate under reduced pressure, a 75:25

mixture of the diester and the starting amine (55.0 g, 69%) was obtained as a yellow liquid. The mixture can be used as such in the next reaction or can be further purified to give the pure diester **11**: ^{1}H NMR ($CDCl_3$) δ 1.13 (d, 3H, J = 6.4 Hz), 1.17 (d, 3H, J = 6.9 Hz), 1.26 (t, 3H, J = 7.1 Hz), 2.26−2.49 (m, 2H), 2.58−2.70 (m, 2H), 2.29−2.91 (m, 1H), 3.08 (q, 1H, J = 6.4 Hz), 3.67 (s, 3H), 4.13 (q, 2H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 15.0, 20.0, 40.1, 41.5, 49.7, 49.9, 51.9, 60.1, 172.1, 176.0.

(2*RS*,5*RS*)-1-(*tert*-Butoxycarbonyl)-2,5-dimethyl-4-piperidone (12) and (2*RS*,5*SR*)-1-(*tert*-Butoxycarbonyl)-2,5-dimethyl-4-piperidone (13). Sodium (5.8 g, 252.2 mmol) in xylenes (100 mL) was heated to 100 °C. The 75:25 mixture of ethyl 3-[*N*-(methyl 2-methylpropionate)amino]butyrate (**11**) and ethyl 3-aminobutyrate (55.0 g, 238.1 mmol) in xylenes (100 mL) was slowly added, and the heating was continued at reflux for 2 h. The reaction mixture was allowed to cool, and the xylenes were removed under reduced pressure to afford the crude β-keto ester 3-(ethoxycarbonyl)-2,5-dimethyl-4-piperidone as a brown solid. The crude β-keto ester was dissolved in 20% HCl (200 mL) and heated at reflux for 16 h. The reaction mixture was allowed to cool, and water and HCl were evaporated under reduced pressure to afford the crude 2,5-dimethyl-4-piperidone hydrochloride as a brown solid. Methanol/triethylamine 10% v/v (750 mL) was slowly added to the crude piperidone hydrochloride. Di-*tert*-butyl dicarbonate (50.0 g, 229.0 mmol) was added to the reaction mixture, and the solution was heated to reflux for 2 h. The reaction mixture was allowed to cool, and the solvents were evaporated under reduced pressure. The crude product was dissolved in ether (750 mL), washed with water (2 × 50 mL), and with a saturated solution of NaCl (2 × 50 mL). After drying the organic phase with $MgSO_4$, evaporation of the solvents under reduced pressure and chromatography on silica gel using hexanes/ethyl acetate (80:20) as eluents, a 55:45 mixture of *cis* (**13**) and *trans* (**12**) piperidones was obtained (16.37 g, 30%) as a yellow liquid. Further chromatography afforded first the *cis*-piperidone then the *trans*-piperidone. The spectral data for the *cis*-piperidone, obtained as a white solid, were the following: ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 3H, J = 7.0 Hz), 1.04 (d, 3H, J = 6.6 Hz), 1.42 (s, 9H), 2.25 (dd, 1H, J = 2.2 Hz, J = 13.7 Hz), 2.53 (m, 1H, J = 6.2 Hz), 2.68 (dd, 1H, J = 6.8 Hz, J = 13.6 Hz), 2.82 (t, 1H, J = 12.6 Hz), 4.15−4.38 (m, 1H), 4.52−4.87 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 10.9, 17.9, 28.0, 44.1, 45.3, 46.3, 48.8, 80.0, 154.0, 209.6; mp 57−59 °C. The spectral data for the *trans*-piperidone, obtained as a yellow liquid, were the following: ^{1}H NMR ($CDCl_3$) δ 1.06 (d, 3H, J = 7.1 Hz), 1.00 (d, 3H, J = 6.7 Hz), 1.47 (s, 9H), 2.09 (dd, 1H, J = 3.6 Hz, J = 15.3 Hz), 2.29−2.40 (m, 1H), 2.64 (dd, 1H, J = 6.7 Hz, J = 15.3 Hz), 3.46 (dd, 1H, J = 5.2 Hz, J = 13.8 Hz), 3.60 (dd, 1H, J = 4.6 Hz, J = 13.8 Hz), 4.38 (m, 1H, J = 3.4 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3, 19.9, 28.1, 43.3, 44.3, 46.2, 47.3, 79.9, 154.6, 211.2.

4-[*N*-{(2*SR*,4*RS*,5*SR*)-*N*-Allyl-2,5-dimethyl-4-piperidinyl}phenylamino]-*N*,*N*-diethylbenzamide (16a). Compound **16a** was prepared according to the general procedures in 11% yield starting from compound **14a**. The product was characterized as its hydrochloride salt obtained as a white powder by addition of equimolar amounts of HCl, 1 M in ether, to an ethereal solution of the benzamide: ^{1}H NMR (CD_3OD) δ 1.16−1.20 (m, 6H), 1.19 (d, 3H, J = 7.3 Hz), 1.31 (d, 3H, J = 6.3 Hz), 1.58−1.62 (m, 2H), 2.89−2.94 (m, 1H), 3.44−3.51 (m, 5H), 3.73−3.79 (m, 1H), 3.97 (dd, 1H, J = 6.1 Hz, J = 13.6 Hz), 4.39−4.43 (m, 1H), 5.64 (m, 1H), 5.67 (d, 1H, J = 6.7 Hz), 5.95−6.70 (m, 1H), 6.78 (d, 2H, J = 6.8 Hz), 7.15 (dd, 2H, J = 1 Hz, J = 8.4 Hz), 7.23 (d, 2H, J = 8.8 Hz), 7.27 (t, 1H, J = 6.3 Hz), 7.41 (t, 2H, J = 7.8 Hz); ^{13}C NMR (CD_3OD) δ 14.7, 15.9, 17.2, 20.1, 32.8, 36.5, 43.4, 47.5, 58.6, 59.0, 60.1, 62.9, 121.8, 129.2, 129.9, 131.2, 133.2, 148.4, 153.2, 176.2. Anal. ($C_{27}H_{38}ClN_3O\cdot H_2O$) C, H, N.

4-[*N*-{(2*RS*,4*RS*,5*SR*)-*N*-Allyl-2,5-dimethyl-4-piperidinyl}phenylamino]-*N*,*N*-diethylbenzamide (16b). Compound **16b** was prepared according to the general procedures in 22% yield starting from compound **14b**. The product was characterized as its hydrochloride monohydrate salt obtained as previously described: ^{1}H NMR (CD_3OD) δ 1.16 (d, 3H, J = 6.5 Hz), 1.17 (t, 3H, J = 7.0 Hz), 1.17−1.25 (m, 3H), 1.39 (d, 3H, J = 5.6 Hz), 1.67−1.76 (m, 1H), 2.05−2.15 (m, 1H), 2.27 (d, 1H, J = 13.7 Hz), 3.03 (t, 1H, J = 12.5 Hz), 3.48 (q, 2H, J = 7.1 Hz), 3.47−3.55 (m, 2H), 3.71 (dd, 1H, J = 8.2 Hz, J = 13.6 Hz), 3.94 (dd, 1H, J = 6.2 Hz, J = 13.6 Hz), 4.29 (dt, 1H, J = 3.3 Hz, J = 11.4 Hz), 5.60 (s, 1H), 5.64 (d, 1H, J = 15.9 Hz), 5.94−6.03 (m, 1H), 6.81 (d, 2H, J = 8.7 Hz), 7.20 (d, 2H, J = 7.5 Hz), 7.26 (d, 2H, J = 8.7 Hz), 7.36 (t, 1H, J = 7.4 Hz), 7.50 (d, 2H, J = 7.7 Hz); ^{13}C NMR (CD_3OD) δ 13.9, 16.0, 17.9, 35.2, 37.5, 41.2, 44.9, 56.0, 57.8, 59.3, 59.9, 119.4, 127.1, 127.6, 128.8, 129.0, 129.6, 130.5, 131.2, 144.3, 151.7, 173.8. Anal. ($C_{27}H_{38}ClN_3O\cdot H_2O$) C, H, N.

4-[*N*-{(2*RS*,4*SR*,5*SR*)-*N*-Allyl-2,5-dimethyl-4-piperidinyl}-phenylamino]-*N*,*N*-diethylbenzamide (16c). Compound **16c** was prepared according to the general procedures in 23% yield starting from compound **14c**. The product was characterized as its hydrochloride monohydrate salt obtained as a white powder as previously described: ^{1}H NMR (CD_3OD) δ 1.16 (d, 3H, J = 6.5 Hz), 1.17 (t, 3H, J = 7.0 Hz), 1.17−1.25 (m, 3H), 1.39 (d, 3H, J = 5.6 Hz), 1.67−1.76 (m, 1H), 2.05−2.15 (m, 1H), 2.27 (d, 1H, J = 13.7 Hz), 3.03 (t, 1H, J = 12.5 Hz), 3.48 (q, 2H, J = 7.1 Hz), 3.47−3.55 (m, 2H), 3.71 (dd, 1H, J = 8.2 Hz, J = 13.6 Hz), 3.94 (dd, 1H, J = 6.2 Hz, J = 13.6 Hz), 4.29 (dt, 1H, J = 3.3 Hz, J = 11.4 Hz), 5.60 (s, 1H), 5.64 (d, 1H, J = 15.9 Hz), 5.94−6.03 (m, 1H), 6.81 (d, 2H, J = 8.7 Hz), 7.20 (d, 2H, J = 7.5 Hz), 7.26 (d, 2H, J = 8.7 Hz), 7.36 (t, 1H, J = 7.4 Hz), 7.50 (d, 2H, J = 7.7 Hz); ^{13}C NMR (CD_3OD) δ 13.9, 15.1, 16.9, 18.8, 36.2, 38.5, 42.9, 46.7, 56.9, 58.6, 59.9, 60.8, 117.4, 125.6, 127.8, 128.0, 129.1, 130.4, 132.0, 132.2, 144.4, 153.6, 175.1. Anal. ($C_{27}H_{38}ClN_3O\cdot 1.5H_2O$) C, H, N.

4-[*N*-{(3*SR*,4*RS*)-*N*,3-Dimethyl-4-piperidinyl}-3-methoxyphenylamino]-*N*,*N*-diethylbenzamide (19a). Compound **19a** was prepared according to the general procedures in 53% yield starting from compound **17a**. The product was characterized as its hydrochloride salt as a white powder obtained as previously described: ^{1}H NMR (CD_3OD) δ 1.09−1.36 (m, 12H), 1.49−1.64 (m, 1H), 1.75−1.96 (m, 1H), 2.61−2.70 (m, 3H), 3.06−3.13 (m, 1H), 3.30−3.60 (m, 4H), 3.76 (s, 3H), 4.30−4.45 (m, 1H), 6.65 (s, 3H), 6.69−6.78 (m, 1H), 6.79−6.93 (m, 2H), 7.20−7.37 (m, 3H). Anal. ($C_{25}H_{36}ClN_3O_2\cdot 1.25H_2O$) C, H, N.

4-[*N*-{(3*RS*,4*RS*)-*N*,3-Dimethyl-4-piperidinyl}-3-methoxyphenylamino]-*N*,*N*-diethylbenzamide (19b). Compound **19b** was prepared according to the general procedures in 50% yield starting from compound **17b**. The product was characterized as its hydrochloride salt as a white powder obtained as previously described: ^{1}H NMR (CD_3OD) δ 1.10−1.26 (m, 9H), 1.75−2.40 (m, 3H), 2.84 (s, 3H), 2.88−3.04 (m, 1H), 3.12−3.28 (m, 1H), 3.34−3.58 (m, 6H), 3.80 (s, 3H), 4.10−4.22 (m, 1H), 6.66 (s, 1H), 6.73 (d, 1H, J = 7.8 Hz), 6.82 (d, 2H, J = 8.6 Hz), 6.88 (d, 1H, J = 7.9 Hz), 7.24 (d, 2H, J = 8.6 Hz), 7.36 (t, 1H, J = 8.1 Hz); ^{13}C NMR (CD_3OD) δ 12.1, 16.2, 29.1, 35.3, 44.0, 55.4, 56.0, 58.9, 60.8, 115.9, 117.9, 127.8, 129.1, 131.6, 145.4, 151.5, 162.5, 173.9. Anal. ($C_{25}H_{36}ClN_3O_2\cdot 1.25H_2O$) C, H, N.

4-[*N*-{(3*SR*,4*RS*)-*N*-Allyl-3-methyl-4-piperidinyl}-3-methoxyphenylamino]-*N*,*N*-diethylbenzamide (20a). Compound **20a** was prepared according to the general procedures in 32% yield starting from compound **17a**. The product was characterized as its hydrochloride salt as a white powder obtained as previously described: ^{1}H NMR ($CDCl_3$) δ 1.12 (d, 3H, J = 6.0 Hz), 1.14−1.22 (m, 7H), 1.65 (q, 1H, J = 10.9 Hz), 1.96 (t, 1H, J = 10.9 Hz), 2.17 (d, 1H, J = 10.7 Hz), 2.54 (s, 1H), 2.79−2.89 (m, 3H), 2.93−3.02 (m, 1H), 3.41 (s, 4H), 3.74 (s, 3H), 3.91 (d, 1H, J = 12.1 Hz), 5.08 (d, 1H, J = 9.8 Hz), 5.14 (d, 1H, J = 17.1 Hz), 5.64−5.75 (m, 1H), 6.56 (s, 1H), 6.59 (d, 1H, J = 7.5 Hz), 6.66 (d, 1H, J = 7.5 Hz), 6.72 (d, 2H, J = 7.8 Hz), 7.18 (t, 1H, J = 7.8 Hz), 7.22 (d, 2H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 13.4, 27.0, 30.2, 41.1, 54.2, 55.1, 58.6, 58.7, 61.5, 109.4, 113.2, 117.0, 119.7, 119.8, 127.5, 128.2, 129.4, 135.5, 147.1, 148.9, 160.3, 171.4. Anal. ($C_{27}H_{38}ClN_3O_2\cdot 0.25H_2O$) C, H, N.

4-[*N*-{(3*RS*,4*RS*)-*N*-Allyl-3-methyl-4-piperidinyl}-3-methoxyphenylamino]-*N*,*N*-diethylbenzamide (20b). Compound **20b** was prepared according to the general procedures in 18% yield starting from compound **17b**. The product was characterized as its hydrochloride salt as a white powder obtained as previously described: ^{1}H NMR (CD_3OD) δ 1.12−1.25 (m, 9H), 1.78−2.00 (m, 1H), 2.03−2.30 (m, 2H), 2.84−3.02 (m, 1H), 3.10−3.27 (m, 1H), 3.38−3.55 (m, 7H), 3.73 (dd, 2H, J = 7.0 Hz), 3.70 (s, 3H), 4.11−4.28 (m, 1H), 5.56 (s, 1H), 5.61 (d, 1H, J = 5.6 Hz), 5.82−6.02 (m, 1H), 6.66 (s, 1H), 6.73 (d, 1H, J = 7.9 Hz), 6.82 (d, 2H, J = 8.6 Hz), 6.85−6.90 (m, 1H), 7.23 (d, 2H, J = 8.5 Hz), 7.36 (t, 1H, J = 8.1 Hz); ^{13}C NMR (CD_3OD) δ 12.1, 16.2, 28.9, 35.2, 53.0, 55.9, 58.4, 59.1, 60.2, 112.5, 115.9, 117.9, 121.9,126.9, 127.5, 128.2, 129.0, 131.7, 145.6, 151.4, 162.6, 173.8. Anal. ($C_{27}H_{38}ClN_3O_2\cdot H_2O$) C, H, N.

4-[*N*-{(3*SR*,4*RS*)-*N*-Allyl-3-methyl-4-piperidinyl}-3-hydroxyphenylamino]-*N*,*N*-diethylbenzamide (21). Compound **21** was prepared according to the general procedures in 18% yield starting from compound **17a**. The product was characterized as its hydrochloride salt as a white powder obtained as previously described: ^{1}H NMR ($CDCl_3$) δ 7.19 (d, 2H, J = 8.5 Hz), 7.09 (m, 1H), 6.65−6.50 (m, 5H), 5.82 (m, 1H), 3.78 (m, 2H), 3.88 (d, 1H, J = 8.7 Hz), 3.42 (br. 4H), 3.03−2.81 (m, 4H), 2.54 (br., 1H), 2.22 (d, 1H, J = 9.6 Hz), 1.99 (t, 1H, J = 11.5 Hz), 1.66 (q, 1H, J = 12.1 Hz), 1.25−1.15 (m, 7 Hz), 1.08 (d, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 172.3, 158.1, 149.8, 146.5, 135.0 (br.), 129.9, 129.2, 128.0, 126.8, 120.2, 118.3, 116.3, 113.0, 61.9, 58.9, 58.5, 54.3, 43.0 (br.), 30.5, 30.0, 22.0, 13.9 (br.). Anal. ($C_{26}H_{35}N_3O_2\cdot HCl\cdot EtOH$) C, H, N.

4-[*N*-{(3*SR*,4*RS*)-*N*,3-Dimethyl-4-piperidinyl}phenylamino]-*N*,*N*-diethylbenzamide (22a). Compound **22a** was prepared according to the general procedures in 61% yield starting from compound **17c**. The product was characterized as its hydrochloride salt as a white powder obtained as previously described: ^{1}H NMR (CD_3OD) δ 1.07−1.38, 6.80 (d, 2H, J = 8.3 Hz), 7.14 (d, 2H, J = 7.7 Hz), 7.26 (t, 3H, J = 7.5 Hz), 7.40 (t, 2H, J = 7.4 Hz); ^{13}C NMR (CD_3OD) δ 12.2, 25.6, 30.4, 44.5, 55.7, 56.0, 60.2, 119.4, 127.4, 128.8, 130.7, 130.8, 146.1, 150.8, 173.8. Anal. ($C_{24}H_{34}ClN_3O\cdot H_2O$) C, H, N.

4-[*N*-{(3*RS*,4*RS*)-*N*,3-Dimethyl-4-piperidinyl}phenylamino]-*N*,*N*-diethylbenzamide (22b). Compound **22b** was prepared according to the general procedures in 59% yield starting from compound **17d**. The product was characterized as its hydrochloride salt as a white powder obtained as previously described: ^{1}H NMR (CD_3OD) δ 1.10−1.25 (m, 12H), 1.76−2.28 (s, 3H), 2.99 (t, 1H, J = 12.5 Hz), 3.12−3.29 (m, 1H), 3.31−3.58 (m, 7H), 4.12−4.29 (m, 1H), 6.78 (d, 2H, J = 8.8 Hz), 7.18 (d, 2H, J = 7.3 Hz), 7.22 (d, 2H, J = 8.8 Hz), 7.33 (t, 1H, J = 7.4 Hz), 7.48 (t, 2H, J = 7.5 Hz); ^{13}C NMR (CD_3OD) δ 16.1, 29.0, 35.3, 43.8, 55.3, 58.7, 60.7, 116.9, 127.3, 127.8, 129.1, 130.7, 131.2, 144.0, 152.0, 173.9. Anal. ($C_{24}H_{34}ClN_3O\cdot 1.25H_2O$) C, H, N.

4-[*N*-{(3*SR*,4*RS*)-*N*-Allyl-3-methyl-4-piperidinyl}phenylamino]-*N*,*N*-diethylbenzamide (23a). Compound **23a** was prepared according to the general procedures in 43% yield starting from compound **17c**. The product was characterized as its hydrochloride salt as a white powder obtained as previously described: ^{1}H NMR ($CDCl_3$) 1.08−1.24 (m, 9H), 1.54 (d, 1H, J = 13.9 Hz), 1.82 (q, 1H, J = 12.1 Hz), 2.90 (s, 1H), 3.09 (t, 1H, J = 12.0 Hz), 3.33−3.52 (m, 7H), 3.75 (d, 2H, J = 6.6 Hz), 4.39 (d, 1H, J = 11.9 Hz), 5.59 (d, 1H, J = 4.9 Hz), 5.62 (s, 1H), 5.96−6.04 (m, 1H), 6.81 (d, 2H, J = 8.1 Hz), 7.23 (d, 2H, J = 7.8 Hz), 7.26 (d, 1H, J = 7.5 Hz), 7.40 (t, 2H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.7, 15.5, 16.6, 27.9, 32.7, 55.8, 58.6, 60.1, 63.0, 121.8, 129.3, 129.7, 129.9, 131.1, 131.2, 133.0, 133.1, 148.5, 153.1, 176.1. Anal. ($C_{26}H_{36}ClN_3O\cdot 0.25H_2O$) C, H, N.

(−)-4-[*N*-{(3*S*,4*R*)-*N*-Allyl-3-methyl-4-piperidinyl}phenylamino]-*N*,*N*-diethylbenzamide [(−)-23a]. This compound was prepared from (−)-*cis*-3-methyl-4-*N*-phenyl-4-piperidinamine[13,38] according to the general procedures in 31% yield. The product was characterized as its HCl salt which was recrystallized from an ethyl acetate/methanol mixture: $[\alpha]^{20}_D$ −204° (*c* 1.01, MeOH). Anal. ($C_{26}H_{35}N_3O_2\cdot HCl$) C, H, N.

(+)-4-[*N*-{(3*R*,4*S*)-*N*-Allyl-3-methyl-4-piperidinyl}phenylamino]-*N*,*N*-diethylbenzamide [(+)-23a]. This compound was prepared from (+)-*cis*-3-methyl-4-*N*-phenyl-4-piperidinamine[13,38] according to the general procedures in 28% yield. The product was characterized as its hydrochloride salt as a white powder obtained as previously described: $[\alpha]^{20}_D$ +203° (*c* 1.07, MeOH). Anal. ($C_{26}H_{35}N_3O_2\cdot HCl$) C, H, N.

4-[*N*-{(3*RS*,4*RS*)-*N*-Allyl-3-methyl-4-piperidinyl}phenylamino]-*N*,*N*-diethylbenzamide (23b). Compound **23b** was prepared according to the general procedures in 38% yield starting from compound **17d**. The product was characterized as its hydrochloride salt as a white powder obtained as previously described: ^{1}H NMR (CD_3OD) δ 1.10−1.26 (m, 9H), 1.74−1.96 (m, 1H), 1.98−2.29 (m, 2H), 2.88−01 (m, 1H), 3.10−3.22 (m, 1H), 3.35−3.61 (m, 7H), 3.73 (d, 2H, J = 7.3 Hz), 4.20 (dt, 1H, J = 3.4 Hz, J = 11.5 Hz), 5.55 (s, 1H), 5.61 (d, 1H, J = 5.4 Hz), 5.85−6.03 (m, 1H), 6.78 (d, 2H, J = 8.8 Hz), 7.19 (d, 2H, J = 7.8 Hz), 7.23 (d, 2H, J = 8.8 Hz), 7.34 (t, 1H, J = 7.4 Hz), 7.51 (t, 2H, J = 7.6 Hz); ^{13}C NMR (CD_3OD) δ 11.9, 13.9, 16.2, 28.9, 35.2, 52.9, 58.3, 59.1, 60.1, 117.0, 126.8, 127.6, 127.8, 129.0, 130.7, 131.2, 144.1, 151.8, 173.9. Anal. ($C_{26}H_{36}ClN_3O\cdot 0.25H_2O$) C, H, N.

4-[*N*-{(3*SR*,4*RS*)-*N*-Crotyl-3-methyl-4-piperidinyl}phenylamino]-*N*,*N*-diethylbenzamide (24). Compound **24** was prepared according to the general procedures in 22% yield starting from compound **17c**. The product was characterized as its hydrochloride salt as a white solid obtained as previously described: ^{1}H NMR (CD_3OD) δ 1.09−1.30 (m, 9H), 1.49−1.60 (m, 1H), 1.72−1.89 (m, 4H), 2.85−3.20 (m, 2H), 3.35−3.57 (m, 7H), 3.60−3.88 (m, 2H), 4.35−4.47 (m, 1H), 5.58−5.70 (m, 1H), 6.00−6.15 (m, 1H), 6.74−6.86 (m, 2H), 7.09−7.48 (m, 7H); ^{13}C NMR (CD_3OD) δ 12.4, 13.7, 18.3, 25.6, 30.3, 53.2, 53.3, 54.5, 56.3, 57.5, 57.6, 60.2, 119.1, 119.4, 120.1, 127.4, 128.4, 128.8, 130.7, 136.9, 140.0, 146.1, 150.9, 173.8 Anal. ($C_{27}H_{38}ClN_3O\cdot 1.5H_2O$) C, H, N.

(−)-4-[*N*-{(3*S*,4*R*)-*N*-Crotyl-3-methyl-4-piperidinyl}phenylamino]-*N*,*N*-diethylbenzamide [(−)-24]. This compound was prepared from (−)-*cis*-3-methyl-4-*N*-phenyl-4-piperidinamine[13,38] according to the general procedures in 33% yield. The product was characterized as its hydrochloride salt as an off-white foam obtained as previously described: $[\alpha]^{20}_D$ −204° (*c* 1.04, MeOH). Anal. ($C_{27}H_{37}N_3O\cdot HCl\cdot 0.5H_2O$) C, H, N.

4-[*N*-{(3*SR*,4*RS*)-*N*-Crotyl-3-methyl-4-piperidinyl}-3-methoxyphenylamino]-*N*,*N*-diethylbenzamide (25). Compound **25** was prepared according to the general procedures in 22% yield starting from compound **17a**. The product was characterized as its hydrochloride salt as a white powder obtained as previously described: ^{1}H NMR ($CDCl_3$) δ 1.11 (d, 3H, J = 6.6 Hz), 1.12 (d, 3H, J = 6.9 Hz), 1.13−1.20 (m, 7H), 1.58−1.71 (m, 4H), 1.92 (t, 1H, J = 11.7 Hz), 2.14 (d, 1H, J = 11.6 Hz), 2.54 (s, 1H), 2.75−2.94 (m, 4H), 3.41 (s, 4H), 3.73 (s, 3H), 3.86−3.93 (m, 1H), 5.41−5.47 (m, 1H), 5.52−5.59 (m, 1H), 6.55 (t, 1H, J = 2.1 Hz), 6.59 (d, 1H, J = 7.3 Hz), 6.63−6.68 (m, 1H), 6.72 (d, 2H, J = 8.7 Hz), 7.17 (dt, 1H, J = 3.6 Hz, J = 8.0 Hz), 7.22 (d, 2H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 13.5, 17.6, 27.0, 30.2, 41.1, 54.0, 54.6, 55.1, 58.7, 60.7, 109.4, 113.2, 119.7, 127.5, 127.9, 128.2, 129.4, 147.2, 148.9, 160.3, 171.4. Anal. ($C_{28}H_{40}ClN_3O_2\cdot 0.25H_2O$) C, H, N.

4-[*N*-{(3*SR*,4*RS*)-*N*-Crotyl-3-methyl-4-piperidinyl}-3-hydroxyphenylamino]-*N*,*N*-diethylbenzamide (26). Compound **26** was prepared according to the general procedures in 78% yield starting from compound **25**. The product was characterized as its hydrochloride salt as an off-white foam obtained as previously described: ^{1}H NMR ($CDCl_3$) δ 7.19 (d, 2H, J = 8.6 Hz), 7.09 (t, 1H, J = 7.8 Hz), 6.62 (m, 3H), 6.50 (m, 2H), 5.54 (m, 2H), 3.88 (m, 1H), 3.42 (br., 4H), 2.85 (m, 4H), 2.53 (br., 1H), 2.20 (m, 1H), 1.92 (t, 1H, J = 11.3 Hz), 1.65 (m, 4H), 1.18 (m, 8H), 1.07 (d, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 171.9, 157.9, 149.5, 145.8, 129.4, 129.0, 127.5, 127.0, 125.7, 119.7, 117.3, 116.2, 112.7, 60.7, 58.5, 58.1, 53.6, 41.5 (br.), 29.9, 26.4, 17.6, 13.4 (br.), 12.9. Anal. ($C_{27}H_{35}N_3O_2\cdot 1.5HCl\cdot 0.75H_2O$) C, H, N.

4-[*N*-{(3*SR*,4*RS*)-*N*-Cyclopropylmethyl-3-methyl-4-piperidinyl}phenylamino]-*N*,*N*-diethylbenzamide (27a). Compound **27a** was prepared according to the general procedures in 21% yield starting from compound **17c**. The product was characterized as its free base: ^{1}H NMR ($CDCl_3$) δ 0.08−0.09 (m, 2H), 0.31−0.50 (m, 2H), 0.66−0.82 (m, 1H), 1.07−1.18 (m, 9H), 1.58 (dq, 1H, J = 3.7 Hz, J = 12.4 Hz), 1.86−2.04 (m, 2H), 2.14−2.23 (m, 2H), 2.50 (s, 2H), 2.91 (d, 2H, J = 11.1 Hz), 3.27−3.48 (m, 4H), 3.84 (dt, 1H, J = 4.0 Hz, J = 8.0 Hz), 6.60 (d, 2H, J = 8.7 Hz), 6.99 (d, 2H, J = 7.3 Hz), 7.07 (t, 1H, J = 7.3 Hz), 7.16 (d, 2H, J = 8.7 Hz), 7.24 (t, 2H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 3.4, 4.1, 8.3, 13.5, 27.0, 29.9, 39.1, 54.1, 58.5, 58.8, 63.4, 118.0, 124.6, 127.0, 127.5, 129.0, 129.8, 145.3, 149.3, 171.4. Anal. ($C_{27}H_{37}N_3O$) C, H, N.

4-[*N*-{(3*RS*,4*RS*)-*N*-Cyclopropylmethyl-3-methyl-4-piperidinyl}phenylamino]-*N*,*N*-diethylbenzamide (27b). Compound **27b** was prepared according to the general procedures in 7% yield starting from compound **17d**. The product was characterized as its free base: ^{1}H NMR ($CDCl_3$) 0.10−0.15 (m, 2H), 0.49−0.58 (m, 2H), 0.81−0.89 (m, 1H), 1.06 (d, 3H, J = 6.1 Hz), 1.18 (t, 6H, J = 6.7 Hz), 1.72 (dq, 1H, J = 4.0 Hz, J = 12.6 Hz), 1.89−1.99 (m, 3H), 2.15−2.21 (m, 3H), 3.11 (d, 1H, J = 10.3 Hz), 3.16 (d, 1H, J = 10.3 Hz), 3.39−3.53 (m, 4H), 3.76−3.83 (m, 1H), 6.72 (d, 2H, J = 7.0 Hz), 7.15−7.22 (m, 4H), 7.26−7.31 (m, 1H), 7.41−7.47 (m, 2H); ^{13}C NMR ($CDCl_3$) 4.5, 4.6, 8.7, 13.8, 17.3, 30.7, 36.0, 54.3, 62.0, 62.6, 64.2, 116.7, 126.8, 127.2, 128.9, 130.6, 130.8, 145.0, 152.3, 174.0. Anal. ($C_{27}H_{37}N_3O\cdot0.25H_2O$) C, H, N.

4-[*N*-{(3*SR*,4*RS*)-*N*-Cyclopropylmethyl-3-methyl-4-piperidinyl}-3-methoxyphenylamino]-*N*,*N*-diethylbenzamide (28a). Compound **28a** was prepared according to the general procedures in 13% yield starting from compound **17a**. The product was characterized as its hydrochloride salt as a white solid obtained as previously described: ^{1}H NMR ($CDCl_3$) δ −0.02−0.01 (m, 2H), 0.36−0.46 (m, 2H), 0.69−0.82 (m, 1H), 1.02−1.19 (m, 10H), 1.55−1.73 (m, 1H), 1.87−2.11 (m, 2H), 2.13−2.30 (m, 2H), 2.51 (s, 1H), 2.94 (d, 2H, J = 10.6 Hz), 3.29−3.45 (m, 4H), 3.69 (s, 3H), 3.82−3.91 (m, 1H), 6.50−6.70 (m, 5H), 7.10−7.22 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 3.5, 4.1, 8.3, 13.5, 26.8, 30.1, 54.1, 55.1, 58.6, 58.8, 63.4, 109.4, 113.3, 119.6, 119.9, 127.6, 128.2, 129.5, 147.1, 148.9, 160.3, 171.4. Anal. ($C_{28}H_{40}ClN_3O_2\cdot0.25H_2O$) C, H, N.

4-[*N*-{(3*RS*,4*RS*)-*N*-Cyclopropylmethyl-3-methyl-4-piperidinyl}-3-methoxyphenylamino]-*N*,*N*-diethylbenzamide (28b). Compound **28b** was prepared according to the general procedures in 8% yield starting from compound **17b**. The product was characterized as its hydrochloride salt as a white powder obtained as previously described: ^{1}H NMR (CD_3OD) δ 0.35−0.49 (m, 2H), 0.74 (d, 2H, J = 7.6 Hz), 1.02−1.31 (m, 10H), 1.81−2.01 (m, 1H), 2.08−2.29 (m, 2H), 3.00 (d, 3H, J = 7.0 Hz), 3.11−3.30 (m, 1H), 3.34−3.52 (m, 4H), 3.57−3.74 (m, 2H), 3.77 (s, 3H), 4.09−4.28 (m, 1H), 6.67 (s, 1H), 6.74 (d, 1H, J = 8.0 Hz), 6.84 (d, 2H, J = 8.5 Hz), 6.85−6.89 (m, 1H), 7.23 (d, 2H, J = 8.3 Hz), 7.36 (t, 1H, J = 8.0 Hz); ^{13}C NMR (CD_3OD) δ 5.1, 6.6, 12.1, 16.3, 28.8, 35.1, 53.2, 55.9, 58.7, 59.3, 62.8, 112.5, 115.9, 117.9, 122.0, 128.1, 129.0, 131.8, 145.7, 151.4, 162.6, 173.8. Anal. ($C_{28}H_{40}ClN_3O_2\cdot0.75H_2O$) C, H, N.

4-[*N*-{(3*SR*,4*RS*)-*N*-Methallyl-3-methyl-4-piperidinyl}-phenylamino]-*N*,*N*-diethylbenzamide (29). Compound **29** was prepared according to the general procedures in 20% yield starting from compound **17c**. The product was characterized as its hydrochloride salt as a white solid obtained as previously described: ^{1}H NMR (CD_3OD) 1.10−1.19 (m, 6H), 1.22 (d, 3H, J = 7.3 Hz), 1.58 (d, 1H, J = 14.0 Hz), 1.81−1.88 (m, 1H), 1.89 (s, 3H), 2.92 (s, 1H), 3.09−3.18 (m, 1H), 3.35−3.55 (m, 6H), 3.65 (d, 1H, J = 12.5 Hz), 3.79 (d, 1H, J = 13.6 Hz), 4.38 (d, 1H, J = 12.2 Hz), 5.26 (s, 1H), 5.35 (s, 1H), 6.81 (d, 2H, J = 8.7 Hz), 7.16 (d, 2H, J = 7.4 Hz), 7.22−7.44 (m, 3H), 7.49−7.53 (m, 2H); ^{13}C NMR (CD_3OD) δ 12.2, 13.5, 21.5, 25.6, 30.3, 54.9, 56.3, 57.4, 63.8, 119.8, 122.8, 127.2, 128.7, 128.9, 130.5, 130.7, 136.0, 146.2, 150.7, 173.7. Anal. ($C_{27}H_{38}ClN_3O\cdot H_2O$) C, H, N.

4-[*N*-{(3*SR*,4*RS*)-*N*-Methallyl-3-methyl-4-piperidinyl}-3-methoxyphenylamino]-*N*,*N*-diethylbenzamide (30). Compound **30** was prepared according to the general procedures in 19% yield starting from compound **17a**. The product was characterized as its hydrochloride salt as a white solid obtained as previously described: ^{1}H NMR ($CDCl_3$) δ 1.13 (d, 3H, J = 6.9 Hz), 1.15−1.20 (m, 7H), 1.60−1.68 (m, 1H), 1.69 (s, 3H), 1.92 (t, 1H, J = 11.7 Hz), 2.10 (d, 1H, J = 10.9 Hz), 2.52 (s, 1H), 2.66−2.75 (m, 2H), 2.79 (d, 1H, J = 10.4 Hz), 2.84 (d, 1H, J = 13.0 Hz), 3.41 (s, 4H), 3.74 (s, 3H), 3.91 (dt, 1H, J = 3.9 Hz, J = 10.9 Hz), 4.78 (s, 1H), 4.83 (s, 1H), 6.57 (s, 1H), 6.60 (d, 1H, J = 7.9 Hz), 6.66 (dd, 1H, J = 2.3 Hz, J = 8.2 Hz), 6.72 (d, 2H, J = 8.5 Hz), 7.19 (t, 1H, J = 8.1 Hz), 7.23 (d, 2H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 13.2, 13.3, 20.5, 27.1, 30.3, 41.3, 54.3, 55.1, 58.5, 58.9, 65.1, 109.4, 112.1, 113.4, 119.6, 119.9, 127.5, 128.2, 129.4, 143.3, 147.2, 149.0, 160.3, 171.4. Anal. ($C_{28}H_{40}ClN_3O_2\cdot0.25H_2O$) C, H, N.

4-[*N*-{(3*SR*,4*SR*)-*N*-Prenyl-3-methyl-4-piperidinyl}phenylamino]-*N*,*N*-diethylbenzamide (31). Compound **31** was prepared according to the general procedures in 24% yield starting from compound **17c**. The product was characterized as its hydrochloride salt as a white solid obtained as previously described: ^{1}H NMR (CD_3OD) δ 1.11−1.30 (m, 9H), 1.52−1.60 (m, 1H), 1.70−1.80 (m, 1H), 1.80 (s, 3H), 1.87 (s, 3H), 2.90 (s, 1H), 3.06 (dt, 1H, J = 2.5 Hz, J = 12.8 Hz), 3.32−3.52 (m, 7H), 3.73 (d, 2H, J = 7.8 Hz), 4.23−4.30 (m, 1H), 5.32 (t, 1H, J = 7.9 Hz), 6.80 (d, 2H, J = 8.7 Hz), 7.15 (d, 2H, J = 7.3 Hz), 7.23−7.38 (m, 3H), 7.42 (t, 2H, J = 7.6 Hz); ^{13}C NMR (CD_3OD) δ 12.3, 13.5, 18.6, 25.6, 26.2, 30.3, 53.1, 56.0, 56.4, 57.3, 119.6, 128.6, 128.7, 130.6, 130.7, 146.1, 146.6, 150.8, 173.7. Anal. ($C_{28}H_{40}ClN_3O\cdot1.25H_2O$) C, H, N.

4-[*N*-{(3*SR*,4*RS*)-*N*-Prenyl-3-methyl-4-piperidinyl}-3-methoxyphenylamino]-*N*,*N*-diethylbenzamide (32). Compound **32** was prepared according to the general procedures in 20% yield starting from compound **17a**. The product was characterized as its hydrochloride salt as a white solid obtained as previously described: ^{1}H NMR ($CDCl_3$) δ 1.12 (d, 3H, J = 7.0 Hz), 1.14−1.22 (t, 7H), 1.61 (s, 3H), 1.67 (dd, 1H, J = 3.8 Hz, J = 12.3 Hz), 1.70 (s, 3H), 1.95 (t, 1H, J = 11.0 Hz), 2.17 (dd, 1H, J = 2.1 Hz, J = 11.4 Hz), 2.54 (s, 1h), 2.81 (d, 1H, J = 11.2 Hz), 2.82−2.86 (m, 3H), 3.42 (s, 4H), 3.74 (s, 3H), 3.92 (dt, 1H, J = 4.0 Hz, J = 8.1 Hz), 5.18 (t, 1H, J = 6.7 Hz), 6.56 (t, 1H, J = 2.0 Hz), 6.60 (dd, 1H, J = 1.6 Hz, J = 7.9 Hz), 6.66 (dd, 1H, J = 2.3 Hz, J = 8.2 Hz), 6.73 (d, 2H, J = 8.5 Hz), 7.18 (t, 1H, J = 8.1 Hz), 7.23 (d, 2H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 13.5, 17.9, 25.7, 27.0, 30.2, 42.3, 54.1, 55.1, 56.0, 58.7, 58.9, 109.4, 113.2, 119.7, 121.4, 127.5, 128.2, 129.4, 134.7, 147.2, 148.9, 160.3, 171.4. Anal. ($C_{29}H_{42}ClN_3O_2\cdot1.5H_2O$) C, H, N.

4-[*N*-{(3*SR*,4*RS*)-*N*-Cinnamyl-3-methyl-4-piperidinyl}-phenylamino]-*N*,*N*-diethylbenzamide (33). Compound **33** was prepared according to the general procedures in 15% yield starting from compound **17c**. The product was characterized as its hydrochloride salt as a white solid obtained as previously described: ^{1}H NMR (CD_3OD) δ 1.10−1.22 (m, 6H), 1.24 (d, 3H, J = 7.3 Hz), 1.58 (d, 1H, J = 14.0 Hz), 1.82 (q, 1H, J = 12.5 Hz), 2.88−2.98 (s, 1H), 3.13 (t, 1H, J = 12.3 Hz), 3.35−3.57 (m, 7H), 3.91 (d, 2H, J = 7.2 Hz), 4.39 (d, 1H, J = 12.3 Hz), 6.30−6.39 (m, 1H), 6.81 (d, 2H, J = 8.5 Hz), 6.92 (d, 1H, J = 15.7 Hz), 7.24 (d, 3H, J = 8.3 Hz), 7.32−7.43 (m, 7H), 7.51 (d, 2H, J = 7.2 Hz); ^{13}C NMR (CD_3OD) δ 11.0, 14.0, 24.2, 29.0, 51.9, 54.9, 56.4, 59.1, 116.1, 118.1, 125.9, 126.8, 127.3, 128.4, 128.7, 129.2, 129.3, 135.3, 140.7, 144.7, 149.7, 172.3. Anal. ($C_{32}H_{40}ClN_3O\cdot1.5H_2O$) C, H, N.

4-[*N*-{(3*SR*,4*RS*)-*N*-Cinnamyl-3-methyl-4-piperidinyl}-3-methoxyphenylam*ino*]-*N*,*N*-diethylbenzamide (34). Compound **34** was prepared according to the general procedures in 14% yield starting from compound **17a**. The product was characterized as its hydrochloride salt as a white solid obtained as previously described: ^{1}H NMR ($CDCl_3$) δ 1.14−1.24 (m, 10H), 1.71 (dq, 1H, J = 3.6 Hz, J = 12.4 Hz), 2.03 (t, 1H, J = 10.9 Hz), 2.26 (d, 1H, J = 9.6 Hz), 2.57 (s, 1H), 2.89 (d, 1H, J = 11.5 Hz), 2.93 (d, 1H, J = 9.7 Hz), 3.03 (dd, 1H, J = 6.8 Hz, J = 13.5 Hz), 3.14 (dd, 1H, J = 6.0 Hz, J = 13.6 Hz), 3.42 (s, 4H), 3.75 (s, 3H), 3.95 (dt, 1H, J = 4.0 Hz, J = 8.4 Hz), 6.22 (dt, 1H, J = 6.6 Hz, J = 15.8 Hz), 6.50 (d, 1H, J = 15.8

Hz), 6.59 (s, 1H), 6.62 (d, 1H, J = 7.9 Hz), 6.68 (dd, 1H, J = 1.9 Hz, J = 8.0 Hz), 6.74 (d, 2H, J = 8.6 Hz), 7.20 (t, 2H, J = 8.0 Hz), 7.25 (d, 2H, J = 8.6 Hz), 7.30 (t, 2H, J = 7.6 Hz), 7.36 (t, 2H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 13.5, 17.6, 27.0, 30.2, 41.1, 54.0, 54.6, 55.1, 58.7, 60.7, 109.4, 113.2, 119.7, 127.5, 127.9, 128.2, 129.4, 147.2, 148.9, 160.3, 171.4. Anal. ($C_{33}H_{42}ClN_3O_2 \cdot H_2O$) C, H, N.

Single-Crystal X-ray Diffraction Analysis of 13, 14a,b, 16c, and 23a. 13: $C_{12}H_{21}NO_3$ (0.36 × 0.18 × 0.13 mm), triclinic space group $P\bar{1}$; a = 5.912(1), b = 9.499(1), c = 12.353(1) Å; α = 70.63(1), β = 86.66(1), γ = 89.35(1)°; V = 653.3(1) Å^3, Z = 2, ρ_{calc} = 1.16 mg mm^{-3}, μ = 0.08 mm^{-1}; F(000) = 248, 1694 unique data, R_1 = 0.046 for 1398 observed data.

14a: $C_{18}H_{28}N_2O_2$ (0.722 × 0.08 × 0.06 mm), monoclinic space group $C2/c$; a = 30.164(4), b = 6.944(1), c = 22.976(4) Å; β = 128.96(1)°; V = 3742.6(9) Å^3, Z = 8, ρ_{calc} = 1.08 mg mm^{-3}, μ = 0.55 mm^{-1}; F(000) = 1328, 1680 unique data, R_1 = 0.077 for 1478 observed data.

14b: $C_{18}H_{28}N_2O_2$ (0.74 × 0.72 × 0.08 mm), orthorhombic space group $Pbca$; a = 12.328(2), b = 12.298(3), c = 24.583(4) Å; V = 3727.2(13) Å^3, Z = 8, ρ_{calc} = 1.08 mg mm^{-3}, μ = 0.56 mm^{-1}; F(000) = 1328, 2609 unique data, R_1 = 0.070 for 1797 observed data.

16c: $C_{27}H_{38}N_3O^+ \cdot Cl^-$ (0.64 × 0.38 × 0.07 mm), monoclinic space group $P2_1/n$; a = 7.150(1), b = 21.455(2), c = 16.616(2) Å; β = 99.11(1)°; V = 2516.7(5) Å^3, Z = 4; F(000) = 984, 3290 unique data, R_1 = 0.071 for 2187 observed data.

23a: $C_{26}H_{36}N_3O_5^+ \cdot Cl^-$ (0.09 × 0.21 × 0.68 mm), monoclinic space group $P2_1$; a = 6.901(1), b = 8.799(1), c = 20.990(2) Å; β = 96.94(1)°; V = 1265.3(2) Å^3, Z = 2, ρ_{calc} = 1.16 mg mm^{-3}, μ = 1.49 mm^{-1}; F(000) = 476, 2077 unique data, R_1 = 0.040 for 1737 observed data.

Data were collected using Cu Kα radiation (Mo Kα for **13**) on an automated Bruker P4 diffractometer equipped with an incident beam monochromator (Bruker SMART 1K CCD with Gobel mirrors in the incident beam for **14a**). All crystals remained stable throughout data collection. Corrections were applied for Lorentz, polarization, and absorption effects (face corrected absorption was applied to the data for **23a**). The structures were solved by direct methods and refined with the aid of the SHELXTL*plus* system of programs (Sheldrick, 1997, #442). The full-matrix least-squares refinement on F^2 values included atomic coordinates and anisotropic thermal parameters for all non-H atoms. H atoms were included using a riding model [coordinate shifts of C applied to attached H atoms, C−H distances set to 0.96, and N−H distances set to 0.90 Å, H angles idealized, U_{iso}(H) set to 1.2−1.5U_{eq}(C)]. Final difference maps were featureless. The X-ray results provided relative stereochemistry for the racemates of **13**, **14a**,**b**, and **16c** and absolute configuration for **23a**. Coordinates for all compounds have been deposited with the Crystallographic Data Centre, Cambridge CB2 1EW, England.

Opioid Binding Assays. μ Binding sites were labeled using [^{3}H][D-Ala^2-MePhe^4,Gly-ol^5]enkephalin ([^{3}H]DAMGO) (2.0 nM, s.a. = 45.5 Ci/mmol), and δ binding sites were labeled using [^{3}H][D-Ala^2,D-Leu^5]enkephalin (2.0 nM, s.a. = 47.5 Ci/mmol) using rat brain membranes prepared as follows. Rat membranes were prepared each assay day using a partially thawed, frozen rat brain which was polytroned in 10 mL/brain of ice-cold 10 mM Tris-HCl, pH 7.0. Membranes were then centrifuged twice at 30000*g* for 10 min each centrifugation. After the second centrifugation, the membranes were prepared each assay day using a partially thawed, frozen guinea pig brain which was polytroned in 20 mL/brain of ice-cold 10 mM Tris-HCl, pH 7.0. The membranes were then centrifuged twice at 30000*g* for 10 min each centrifugation. After the second centrifugation, the membranes were resuspended in 85 mL/brain of 25 °C 50 mM Tris-HCl, pH 7.4.

[^{3}H]DAMGO binding proceeded as follows: 12- × 75-mm polystyrene test tubes were prefilled with 100 μL of the test drug which was diluted in binding buffer (BB: 10 mM Tris-HCl, pH 7.4, containing 1 mg/mL BSA), followed by 50 μL of BB, and 100 μL of [^{3}H]DAMGO in a protease inhibitor cocktail (10 mM Tris-HCl, pH 7.4, which contained bacitracin (1 mg/mL), bestatin (100 μg/mL), leupeptin (40 μg/mL), and chymostatin (20 μg/mL). Incubations were initiated by the addition of 750 μL of the prepared membrane preparation containing 0.2 mg/mL of protein and proceeded for 2 h at 25 °C. The ligand was displaced by 10 concentrations of test drug, in triplicate, 2×. Nonspecific binding was determined using 20 μM levallorphan. Under these conditions, the ED_{50} of [^{3}H]DAMGO binding was 2.65 nM. Brandel cell harvesters were used to filter the samples over Whatman GF/B filters, which were presoaked in wash-buffer (ice-cold 10 mM Tris-HCl, pH 7.4).

[^{3}H][D-Ala^2,D-Leu^5]enkephalin binding proceeded as follows: 12- × 75-mm polystyrene test tubes were prefilled with 100 μL of the test drug which was diluted in BB, followed by 50 μL of a salt solution containing choline chloride (2 M, final concentration of 100 mM), $MnCl_2$ (1 M, final concentration of 3.0 mM), and, to block μ sites, DAMGO (2000 nM, final concentration of 100 nM), followed by 100 μL of [^{3}H][D-Ala^2,D-Leu^5]enkephalin in the protease inhibitor cocktail. Incubations were initiated by the addition of 750 μL of the prepared membrane preparation containing 0.41 mg/mL of protein and proceeded for 2 h at 25 °C. The ligand was displaced by 10 concentrations of test drug, in triplicate, 2×. Nonspecific binding was determined using 20 μM levallorphan. Under these conditions the ED_{50} of [^{3}H][D-Ala^2,D-Leu^5]enkephalin binding was 1.7 nM. Brandel cell harvesters were used to filter the samples over Whatman GF/B filters, which were presoaked in wash buffer (ice-cold 10 mM Tris-HCl, pH 7.4).

[^{3}H]U69,593 binding proceeded as follows: 12- × 75-mm polystyrene test tubes were prefilled with 100 μL of the test drug which was diluted in BB, followed by 50 μL of BB, followed by 100 μL of [^{3}H]U69,593 in the standard protease inhibitor cocktail with the addition of captopril (1 mg/mL in 0.1 N acetic acid containing 10 mM 2-mercaptoethanol to give a final concentration of 1 μg/mL). Incubations were initiated by the addition of 750 μL of the prepared membrane preparation containing 0.4 mg/mL of protein and proceeded for 2 h at 25 °C. The ligand was displaced by 10 concentrations of test drug, in triplicate, 2×. Nonspecific binding was determined using 1 μM U69,593. Under these conditions the ED_{50} of [^{3}H]-U69,593 binding was 4.48 nM. Brandel cell harvesters were used to filter the samples over Whatman GF/B filters, which were presoaked in wash buffer (ice-cold 10 mM Tris-HCl, pH 7.4) containing 1% PEI.

For all three assays, the filtration step proceeded as follows: 4 mL of the wash buffer was added to the tubes, rapidly filtered, and was followed by two additional wash cycles. The tritium retained on the filters was counted, after an overnight extraction into ICN Cytoscint cocktail, in a Taurus beta counter at 44% efficiency.

[^{35}S]GTP-γ-S Functional Assays. [^{35}S]GTP-γ-S binding was determined as described previously.[39] Guinea pig caudate membranes (10 μg) were suspended in 500 μL of buffer containing 50 mM Tris-HCl, pH 7.4, 100 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA, 1 mM DTT, 100 μM GDP, 0.1% BSA, 0.05 nM [^{35}S]GTP-γ-S, and 10 μM test drugs. The reaction was initiated by the addition of membranes and terminated after 3 h by the addition of 3 mL of cold (4 °C) 10 mM Tris-HCl, pH 7.4, followed by rapid vacuum filtration through Whatman GF/B filters. The filters were then washed twice with 5 mL of cold 10 mM Tris-HCl, pH 7.4. Bound radioactivity was counted using a Taurus (Micromedic) liquid scintillation counter at 98% efficiency. Nonspecific binding was determined in the presence of 40 μM GTP-γ-S. Assays were performed in triplicate, and each experiment was performed three times. The percent stimulation in the [^{35}S]GTP-γ-S binding was calculated according to the following formula: $[(S - B)/B] \times 100$, where B is the basal level of [^{35}S]GTP-γ-S binding and S is the stimulated level of [^{35}S]GTP-γ-S binding. The results are mean ± SD from three experiments with triplicate determinations.

Data Analysis. The data of two ligand binding experiments were pooled and fit, using MLAB-PC, to the two-parameter logistic equation for the best-fit estimates of the IC_{50} and slope factor. The K_i values were then determined using the equation

$K_i = IC_{50}/(1 + [L]/K_d)$. The data of three [^{35}S]GTP-γ-S assays were pooled and fit to a one-site binding model for the best-fit estimates of ED_{50} and E_{max}.[39]

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Supporting Information Available: Crystal data, structural refinement analysis, atomic coordinates, bond lengths, bond angles, anisotropic displacement parameters, hydrogen coordinates, and isotropic displacement parameters of **13**, **14a**,**b**, **16c**, and (−)-**23a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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