Probes for Narcotic Receptor Mediated Phenomena. 26.[1−3] Synthesis and Biological Evaluation of Diarylmethylpiperazines and Diarylmethylpiperidines as Novel, Nonpeptidic δ Opioid Receptor Ligands

Xiaoyan Zhang,[†,||] Kenner C. Rice,*[,†] Silvia N. Calderon,[†,⊥] Hiroshi Kayakiri,[†,▽] Larren Smith,[†] Andrew Coop,[†,#] Arthur E. Jacobson,[†] Richard B. Rothman,[‡] Peg Davis,[§] Christina M. Dersch,[‡] and Frank Porreca[§]

Laboratory of Medicinal Chemistry, Building 8, Room B1-23, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892, and Clinical Psychopharmacology Section, National Institute on Drug Abuse, Addiction Research Center, Baltimore, Maryland 21224, and Department of Pharmacology, College of Medicine, The University of Arizona, Tucson, Arizona 85724

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We recently reported (+)-4-[(α*R*)-α-{(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl}-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (**1b**, SNC80) as a novel nonpeptidic δ receptor agonist and explored the structure−activity relationships (SAR) of a series of related derivatives. We have found that δ binding activities and selectivity showed little change when the 3-methoxy group in **1b** was removed or replaced by the other substituents, whereas the *N*,*N*-diethylbenzamide group is important for interaction with the δ receptor. Extensive modification of the piperazine nucleus led to the synthesis of a new series of *N*,*N*-diethyl(α-piperazinylbenzyl)benzamides (**2**, **3a**−**e**), *N*,*N*-diethyl(α-piperidinyl or piperidinylidenebenzyl)benzamides (**4a**, **5a**−**c**, **6a**−**b**), and related derivatives (**4b**, **7a**−**c**). Several compounds (**2**, **3a**, **3e**, **6a**) strongly bound to the δ receptor with K_i values in the low nanomolar range. On the other hand, the binding affinities of these compounds for the μ and κ receptors were negligible, indicating excellent δ opioid receptor subtype selectivity. The two nitrogen atoms on the piperazine nucleus showed different SAR in the interaction of this series of compounds at the δ receptor. Nitrogen N^4 appears to be an important structural element and is essential for electrostatic interaction, while N^1 seems to be unnecessary for recognition at the δ receptor.

Classification of opioid receptors into mu (μ), delta (δ), and kappa (κ) is widely accepted, and they have been identified by molecular cloning and pharmacological means.[4−6] Recent advances in the understanding of the physiological functions of the δ opioid receptors have highlighted the important role of this receptor in the regulation of pain,[7−10] and the search for δ receptor agonists has been pursued in numerous laboratories. A number of selective δ agonists, such as DPDPE and [D-Ala^2]deltorphin II, have been developed for probing the function of the δ receptor.[10] Despite their δ agonist activity, their therapeutic use is limited due to their peptidic structure. The discovery and identification of (±)-4-[(α*R*)-α-(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]-*N*,*N*-diethylbenzamide ((±)-BW373U86, (±)-**1a**) as a selective and nonpeptidic δ receptor agonist was a major advance in this area.[11−13] This compound has been described as the first systemically active, nonpeptide δ agonist and has proven useful in the characterization of the behavioral effects mediated by central δ receptors in primates.[14,15]

Recently, we reported the synthesis and absolute configuration of the optically pure enantiomers of the nonpeptide δ opioid agonist, (±)-**1a**, its benzylic epimers, and their methyl ethers.[1,2] Among this series, we have found that replacement of the phenolic hydroxyl group in **1a** with either a methoxyl group ((+)-4-[(α*R*)-α-(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide, **1b**, SNC80) or a hydrogen atom (**1c**) gave ligands which retained the potent δ activities and significantly increased the μ/δ selectivity in both opioid receptor binding and in vitro functional assays (Chart 1). Subsequent studies included an investigation of the role of the amide functional group of **1b**−**c** at the opioid receptors.[3] We found that the *N*,*N*-*p*-disubstituted amide functional group is important for the interaction of this series of compounds at the δ receptor. Furthermore, from the above studies we also learned that the spatial orientation of the α-benzylic position dramatically influenced the activity and selectivity of these molecules at δ opioid receptors. The pharmacological profile of compound **1b** is similar to (±)-**1a** in mice, both producing antinociception and mild transient convulsions at the same dose range.[16] However, compound **1b** produces greater antinociceptive activity in assays of thermal nociception without convulsant activity in the rhesus monkey, suggesting that

† National Institute of Diabetes and Digestive and Kidney Diseases.
‡ National Institute on Drug Abuse.
§ The University of Arizona.
|| Present address: Neurogen Inc., 35 NE Industrial Road, Branford, CT.
⊥ Present address: Division of Anesthetic, Critical Care and Abuse Drug Products, HFD 170, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.
▽ Present address: Fujisawa Pharmaceutical Co., Ltd., Medicinal Chemistry Research Laboratories, 2-1-6, Kashima, Yodogawa-ku, Osaka 532-8514, Japan.
Present address: Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, 20 North Pine St., Baltimore, MD 21201.

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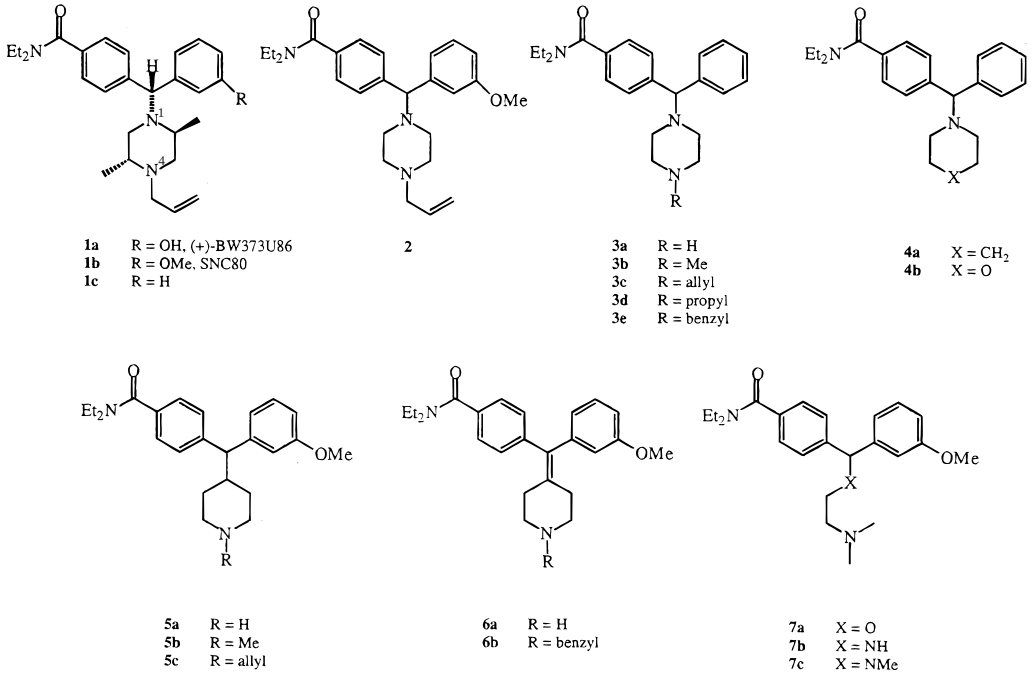
Chart 1. Structures of δ Opioid Receptor Selective Ligands



1b and related nonpeptidic δ agonists may be promising candidates for development as safe and effective clinical analgesics.[17] Extensive chemical modifications of this compound enabled us to further refine the basic framework for the interaction of this series of compounds at the δ receptor.

Most of the nonpeptidic δ opioid ligands (such as naltrindole and 17-(cyclopropylmethyl)-4,5-α-epoxy-7(*E*)-(1-naphthylidene)-3,14-dihydroxymorphinan (BNTX)) contain only one basic nitrogen atom. Site-directed mutagenesis experiments and molecular modeling studies have suggested that a basic nitrogen in δ opioid ligands is an essential structural element for receptor recognition, although there is conflicting evidence as to which receptor residue is important for that recognition.[18−21] Compound **1b** has a carbon−nitrogen skeleton that is very different from the well-known fused-ring opioids, such as naltrindole and BNTX, and thus any structure−activity relationships dependent upon the better-known fused-ring opioids may not pertain to this new structure. Herein, we report our continuing structure−activity relationship studies of **1b** focused on the investigation of the role of the two basic nitrogen atoms (N^1 and N^4) and the influence of substituents on N^4. We initially examined the effects of the *trans*-dimethyl groups on the piperazine ring of **1b** and found that piperazine derivative **2**, lacking the ring methyl groups of **1b**, retained reasonable δ binding affinity and μ/δ selectivity. Furthermore, we found that the desmethoxy analogue **3c** shows a similar δ opioid receptor binding profile as the methoxy analogue **1b**. We then prepared a series of piperazine derivatives with various substituents on N^4 (**3a**−**e**). The influence of the two nitrogens was studied by replacement of one of the nitrogen atoms (N^1 or N^4) with carbon (**4a**, **5a**−**c**, **6a**−**b**) or oxygen (**4b**, **7a**). Diarylmethyldiamines (**7b**−**c**) were also prepared to compare the δ activity of **7a**. The synthesis and the structure−activity relationships of these new compounds on the opioid receptors are reported herein. The newly synthesized analogues were tested as racemates in order to evaluate the broad effect of the modification. During this work, similar modifications were published with comparable results.[22−28]

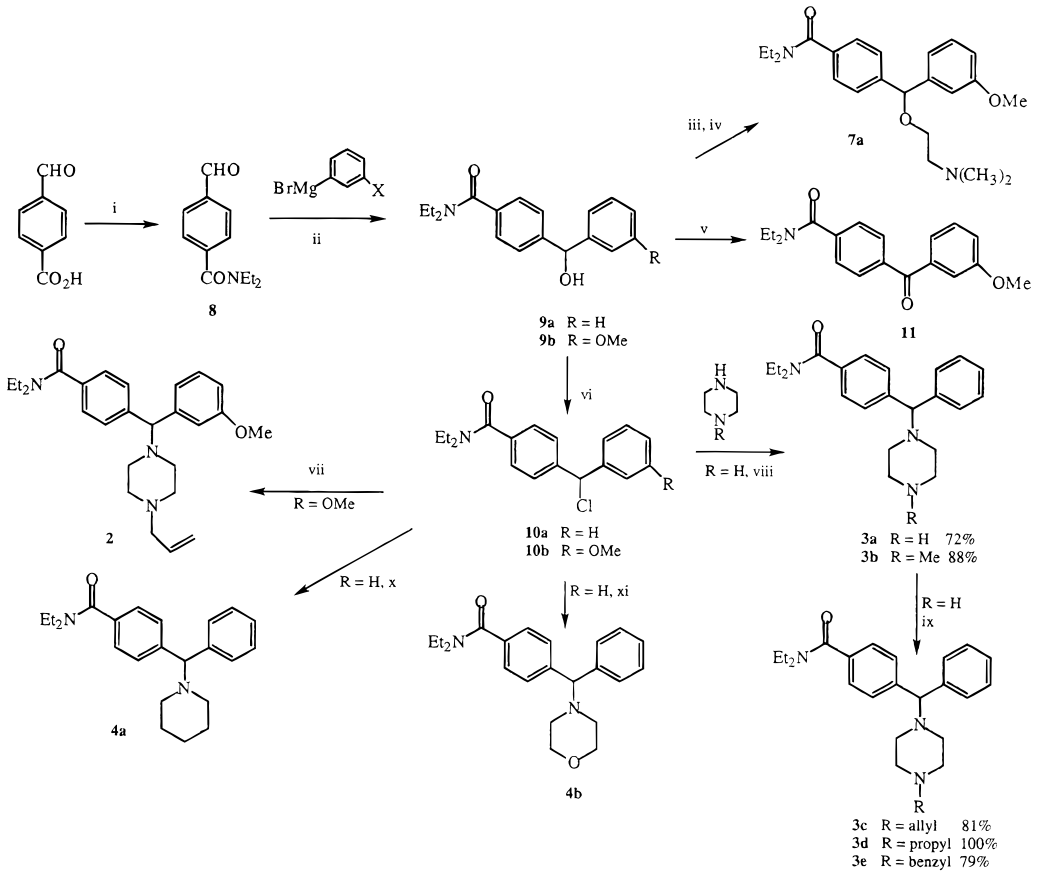
Chemistry

The synthetic intermediates **9**−**11** were prepared according to the previously reported method[2] or an alternative pathway[26,27] (Scheme 1) more applicable to the synthesis of these intermediates on a large scale. Condensation of 4-formylbenzoic acid with diethylamine in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) gave 4-formyl-*N*,*N*-diethylbenzamide (**8**).[25] The Grignard reaction of aldehyde **8** with (3-methoxyphenyl)magnesium bromide provided benzhydryl alcohol **9b**.[2,26] Oxidation of the alcohol **9b** with MnO_2 gave the corresponding benzoylbenzamide **11**,[2,28] while treatment of **9b** with concentrated hydrochloric acid generated the corresponding chloride **8b**[2] in quantitative yield. This newer approach[26,27] of preparing intermediates **9a** and **9b** offered significant advantages over the previous one[2] in terms of fewer steps, higher yields, and the easier isolation of the products.

Treatment of the benzhydryl chloride **10a**[2] or **10b**[2] with the appropriate amine yielded the corresponding analogues **2**,[23,27] **3a**−**b**,[27] and **4a**−**b**, as shown in Scheme 1. N-Alkylation of **3a** afforded analogues **3c**−**e**.[22,25] Compound **7a** was synthesized in two steps from benzhydryl alcohol **9b**[2,26] with chloroethanol, followed by the displacement of the chloride atom with dimethylamine.

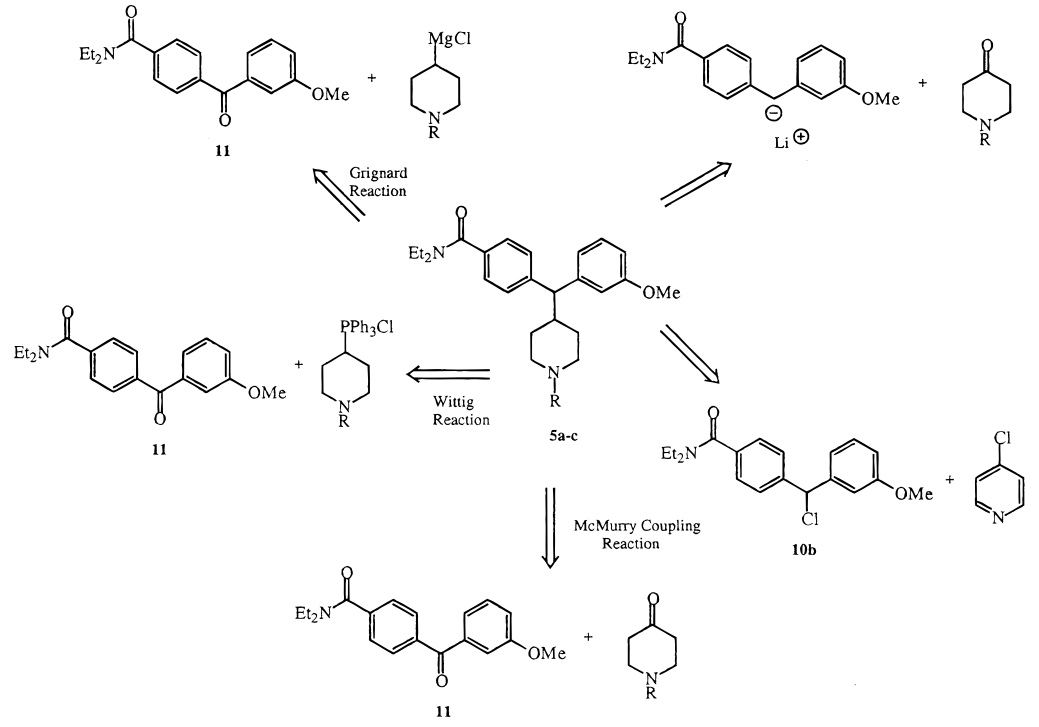
Several approaches different from that of Delorme et al.[24] were examined to construct the diarylmethylpiperidines **5**[29,30] (Scheme 2), and only the McMurry coupling reaction[31] of **11**[2,28] with *N*-benzyl-1-piperidone gave the desired intermediate **6b**[24] in reasonable yield (Scheme 3). Hydrogenation of **6b** with a catalytic

Scheme 1[a]



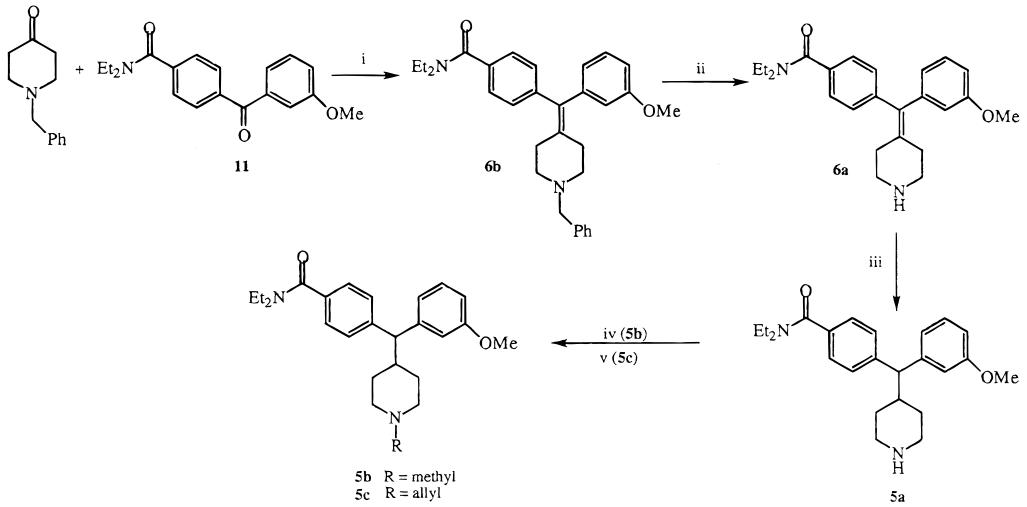
[a] Conditions: (i) EDCI, Et_2NH, CH_2Cl_2, rt, 97%; (ii) THF, rt, 91%; (iii) H^+, 2-chloroethanol, $PhCH_3$, reflux; (iv) $HNMe_2$, K_2CO_3, KI, THF, 60−65 °C, sealed, 72%; (v) MnO_2, CH_2Cl_2, 100%; (vi) HCl (conc), $CHCl_3$, 100%; (vii) *N*-allylpiperazine, K_2CO_3, CH_3CN, 66%; (viii) K_2CO_3, CH_3CN; (ix) alkyl halide, K_2CO_3, CH_3CN; (x) piperidine, K_2CO_3, CH_3CN, 38%; (xi) morpholine, K_2CO_3, CH_3CN, 78%.

Scheme 2



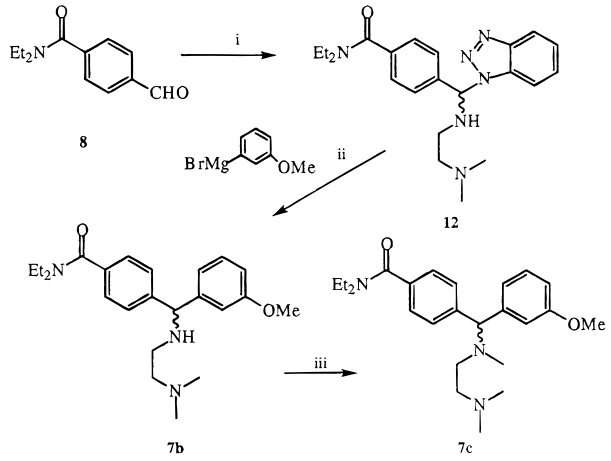
amount of Pd/C (10%) in acetic acid yielded a partially reduced intermediate **6a**,[24] which was further reduced with an equal amount of Pd/C (30%) to give diarylmethylpiperidines **5a**. Eschweiler−Clarke reaction of **5a** afforded *N*-methyl analogue **5b**, while alkylation of **5a** with allyl bromide provided *N*-allyl derivative **5c**.

Scheme 3[a]



[a] Conditions: (i) Zn, $TiCl_4$, DME, reflux; (ii) H_2 (60 psi), AcOH, Pd/C (10%); (iii) H_2 (60 psi), AcOH, Pd/C (30%); (iv) H_2CO, HCO_2H; (v) allyl bromide, K_2CO_3, THF.

Scheme 4[a]



[a] Conditions: (i) 2-(diaminomethyl)ethylamine, benzotriazole, PhH, reflux; (ii) THF, rt; (iii) H_2CO, HCO_2H.

The modified Katritzky tertiary amine method[32,33] yielded diarylmethyldiamine derivative **7b** in a yield of 59%, as illustrated in Scheme 4. Eschweiler−Clarke reaction of **7b** afforded analogue **7c**.

Results and Discussion

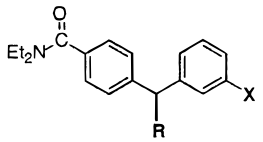
All compounds were tested for inhibition of specific binding of [^{3}H]DAMGO (Tyr-D-Ala-Gly-(Me)-Phe-Gly-ol)[34] to μ receptors and [^{3}H]DADLE (Tyr-D-Ala-Gly-Phe-D-Leu)[35] to δ receptors at rat brain membranes as previously reported.[1−3] The affinity of these derivatives for κ receptors was determined by inhibition of binding of [^{3}H]U69,593[36] at guinea pig brain membranes. The values for the μ, δ, and κ receptors are listed in Table 1.

All compounds displayed low affinity at μ and κ receptors, thus the most δ selective compounds are the ligands with the greatest δ affinity. The simple didemethylpiperazine derivative **2** had about one-seventh of the δ receptor affinity (δ K_i = 27 nM) of its *trans*-dimethyl relative **1b**. The affinity of **2** indicates that *trans*-dimethyl groups on the piperazine ring are not critical for recognition at the δ receptor, a finding consistent with that of Morphy.[22,23] Furthermore, in accord with our findings that the aromatic methoxyl group of **1b** is not essential (its demethoxylated relative **1c** had very high affinity for the δ receptor), replacement of the aromatic methoxyl of **2** with a proton in **3c** increased δ affinity (K_i = 10.5 nM). Thus, the influence of the N^4 substitution was investigated using this simplified carbon−nitrogen skeleton. It was shown that replacement of the *N*-allyl group with an alkyl moiety (**3b**,**d**) somewhat reduced affinity at the δ receptor. However, the *N*-benzyl derivative **3e** had very high affinity for the δ receptor (K_i = 1.5 nM), more than twice the affinity of **1b**, in accord with the binding data of Delorme et al. (1.2 nM).[25] It would appear that an electron rich substituent on N^4 leads to increased δ receptor affinity.

The high affinity of **3e** for the δ receptor in this series is in marked contrast to the observed decrease in affinity that is obtained when an *N*-benzyl group is introduced in naltrindole-like molecules. Thus, **3e**, a highly δ-selective ligand (μ/δ = >4500, Table 1), was found to have >70 times higher affinity at the δ receptor than *N*-benzyl-substituted oxymorphindole, 17-benzylnoroxymorphindole.[37] The differences in the δ receptor affinity between *N*-substituted naltrindole-like molecules and compounds similar to **1b** could be ascribed to the distinctively different three-dimensional spatial orientation of the lone-pair electrons on the nitrogen atom which have been found in these compounds.[38]

Piperidine analogue **4a** and morpholine analogue **4b** showed little or no affinity for the three opioid receptor subtypes. In contrast, piperidine analogues **5a** and **5c** exhibited moderate binding affinity at the δ receptor. This observed structure−activity relationship suggests that the basic nitrogen N^4 is an important structural element in the interaction of this series of compounds at the δ receptor whereas the N^1 nitrogen could be modified while retaining reasonable interaction with the δ receptor. It should noted that ligands **5a** and **5c** possess a methoxy-substituted aromatic ring, whereas **4a** and **4b** do not, however the SAR above suggest that this aromatic substituent would not affect affinity to the extent observed. The poor affinity of **5b** is consistent

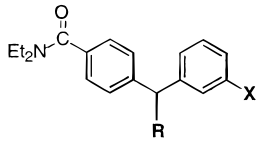
Table 1. Binding Affinities of Diarylmethylpiperazines and Diarylmethylpiperidines for μ, δ, and κ Receptors



compd	R	X	mp (°C)	formula[b]	K_i (nM ± SEM) μ binding[c]	K_i (nM ± SEM) δ binding[d]	K_i (nM ± SEM) κ binding[e]	K_i ratio μ/δ
1b[f]	*trans*-2*S*,5*R*-dimethyl-*N*-allyl-1-piperazinyl	OCH_3			3970 ± 170	4 ± 0.18	11700 ± 630	990
1c[g]	*trans*-2*S*,5*R*-dimethyl-*N*-allyl-1-piperazinyl	H			3000 (1840)[h]	0.5 ± 0.05	3000 (1900)[h]	>3600
2	*N*-allyl-1-piperazinyl	OCH_3	125−127	$C_{26}H_{35}N_3O_2 \cdot C_2H_2O_4$	10000 (6300)[h]	27 ± 2	10000 (8000)[h]	>230
3a	*N*-piperazinyl	H	168−169	$C_{22}H_{29}N_3O$	10000 (6800)[h]	4.85 ± 0.51	ND	>1400
3b	*N*-methyl-1-piperazinyl	H	182[a]	$C_{23}H_{31}N_3O \cdot HCl \cdot 2H_2O$	10000 (5600)[h]	43.2 ± 3	10000 (7000)[h]	>130
3c	*N*-allyl-1-piperazinyl	H	150[a]	$C_{25}H_{33}N_3O \cdot HCl \cdot 2.5H_2O$	10000 (6600)[h]	10.5 ± 0.9	ND	>600
3d	*N*-propyl-1-piperazinyl	H	170−172	$C_{25}H_{35}N_3O \cdot C_2H_2O_4$	10000 (6800)[h]	44.2 ± 3.9	10000 (7000)[h]	>150
3e	*N*-benzyl-1-piperazinyl	H	153−155	$C_{29}H_{35}N_3O \cdot C_2H_2O_4 \cdot 0.25H_2O$	10000 (6800)[h]	1.48 ± 0.8	2000 (1400)[h]	>4500
4a	*N*−1-piperidinyl	H	125−127	$C_{23}H_{30}N_2O \cdot 0.5H_2O$	10000 (6800)[h]	3000 (1700)[h]	10000 (7000)[h]	>4
4b	*N*-morpholinyl	H	98−100	$C_{22}H_{28}N_2O_2$	10000 (6800)[h]	3000 (1700)[h]	10000 (7000)[h]	>4
5a	4-piperidinyl	OCH_3	98[a]	$C_{24}H_{32}N_2O_2 \cdot HCl \cdot H_2O$	10000 (6300)[h]	20 ± 2	10000 (8000)[h]	>300
5b	*N*-methyl-4-piperidinyl	OCH_3	59[a]	$C_{25}H_{34}N_2O_2 \cdot HCl \cdot 1.75H_2O$	10000 (6300)[h]	328 ± 21	10000 (8000)[h]	>15
5c	*N*-allyl-4-piperidinyl	OCH_3	75[a]	$C_{27}H_{36}NO_2 \cdot HCl \cdot 0.5H_2O$	10000 (6300)[h]	27 ± 2	10000 (8000)[h]	>200
6a	4-piperidinylidene	OCH_3	83−85	$C_{24}H_{30}N_2O_2 \cdot HCl \cdot 0.5H_2O$	10000 (6300)[h]	5 ± 0.3	10000 (8000)[h]	>1200
6b	*N*-benzyl-4-piperidinylidene	OCH_3	92−95	$C_{31}H_{36}N_2O_2 \cdot HCl \cdot 0.5H_2O$	10000 (6300)[h]	12 ± 1	7650 ± 429	>500
7a	2-(*N*,*N*-dimethylamino)ethoxy	OCH_3	51[a]	$C_{23}H_{32}N_2O_3 \cdot C_2H_2O_4$	10000 (6300)[h]	258 ± 30	10000 (8000)[h]	>20
7b	2-(*N*,*N*-dimethylamino)ethamino	OCH_3	92−94	$C_{31}H_{41}N_3O_{10}$	10000 (6300)[h]	622 ± 42	10000 (8000)[h]	>10
7c	2-(*N*,*N*-dimethylamino)-*N*-methylethylamino	OCH_3	95−97	$C_{24}H_{35}N_3O_2 \cdot 2HCl \cdot 1.5H_2O$	10000 (6300)[h]	248 ± 26	10000 (8000)[h]	>20

[a] Amorphous powder. [b] Analyses for C, H, and N were within ±0.4% of the theoretical values. [c] Inhibitory effect to [^{3}H]DAMGO in rat brain membranes. [d] Inhibitory effect to [^{3}H]DADAL in rat brain membranes. [e] Inhibitory effect to [^{3}H]U69,593 in guinea pig brain membrane. [f] See refs 1 and 2. [g] See ref 2. [h] No exact number could be given. The highest concentration tested (nM) is given with the maximum binding affinity (nM) in parentheses.

Table 2. Agonist Activity of Selected Compounds in the Mouse Vas Deferens (MVD) and Guinea Pig Ileum (GPI) Bioassay



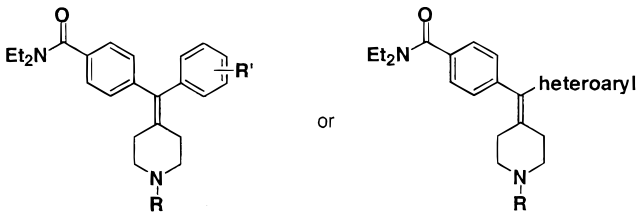
compd	R	X	IC_{50} (nM ± SEM) GPI (μ)	IC_{50} (nM ± SEM) MVD (δ)	μ/δ ratio
1b[a]	*trans*-2*S*,5*R*-dimethyl-*N*-allyl-1-piperazinyl	OCH_3	5450 ± 2050	2.73 ± 0.48	2000
1c[a]	*trans*-2*S*,5*R*-dimethyl-*N*-allyl-1-piperazinyl	H	8580 ± 1300	10.5 ± 0.4	813
2	*N*-allyl-1-piperazinyl	OCH_3	20300 ± 1300	33.1 ± 3.0	610
3e	*N*-benzyl-1-piperazinyl	H	9850 ± 1050	25.7 ± 6.5	382
6a	4-piperidinylidene	OCH_3	27700 ± 900	125 ± 28	220

[a] Data from ref 2.

with the findings above that an N^4-substituent should be an electron rich system. When the relative orientation of the three rings were partially restricted by a double bond, piperidine **6a** exhibited 4-fold higher affinity at the δ receptor (K_i = 5 nM) than the unrestricted piperidine **5a**. Replacement of N^1 and N^4 with oxygen led to an ether linked ring-opened analogue **7a**, which showed decreased affinity at the δ receptor. As comparison, diarylmethyldiamines **7b** and **7c** also showed a considerable loss of affinity at the δ receptor, indicating that a cyclic amine is required for recognition at the receptor.

Compounds **2**, **3e**, and **6a**, which possessed good δ affinity and therefore the greatest δ selectivity in this series, were evaluated for opioid agonist activity in the mouse vas deferens (MVD) and guinea pig ileum (GPI) preparations (Table 2).[39] The agonism displayed by these ligands in the MVD was inhibited by the δ antagonist, ICI 174,864. Though the current ligands were less potent δ agonists than the parent compound

Chart 2. Structures of δ Opioid Receptor Selective Piperidines



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1b, all three ligands showed high δ selectivity (GPI/MVD), which is consistent with the studies in the binding assays.

Conclusions

We have investigated a series of *N*,*N*-diethyl(α-piperazinylaryl)benzamides, *N*,*N*-diethyl(α-piperidinyl or piperidinylidenearyl)benzamides, and related derivatives as novel δ opioid receptor ligands. All of these compounds showed low binding affinity at μ and κ receptors, and several displayed high binding affinity at the δ receptor. Two important structure−activity relationships were observed from this present data: (1) the alkyl substituent pattern on the nitrogen N^4 decreased δ binding, and an electron rich substituent aids interaction with the δ receptor; (2) the nitrogen N^4 of the piperazine is sufficient to provide an essential electrostatic interaction with the δ receptor; N^1 is relatively unnecessary for binding to the δ receptor.

Recently, it has been reported that a series of *N*,*N*-diethyl(α-piperidinylidenearyl)benzamides **13** (Chart 2), structurally related analogues of **6a**−**b**, display δ selective agonism, though the biological activities of these new compounds were not disclosed.[24] Thus, the *N*,*N*-diethyl(α-piperidinylidene-3-methoxybenzyl)benzamides **6a**−**b** could be used as a valuable template for the development of new nonpeptidic ligands for the δ receptor.

Experimental Section.

Chemistry. Melting points were determined on a MEL-TEMP II capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) were recorded in $CDCl_3$ (unless otherwise noted) with tetramethylsilane (TMS) as the internal standard on a Varian Gemini-300 spectrometer. Mass spectra (MS) were recorded on a VG 7070E spectrometer or a Finnigan 4600 spectrometer in the chemical ionization mode (MS, CI−NH_3). Thin-layer chromatography (TLC) was performed on Analtech silica gel GHLF 0.25 mm plates. Flash column chromatography was performed with Fluka silica gel 60 (mesh 220−240). Elemental analyses were performed by Atlantic Microlabs. Inc., Norcross, GA, and the results were within ±0.4% of the theoretical values unless otherwise indicated. Unless specifically indicated otherwise, amine salts were obtained and purified by the following standard procedures: (a) hydrochlorides: by the dropwise addition of 1.0 M HCl/Et_2O solution to a solution of the amine in acetone, until the resulting mixture was acidic to moist pH paper; (b) maleates and oxalates: by the dropwise addition of a molar equivalent solution of maleic acid or oxalic acid in anhydrous Et_2O to a solution of the amine in absolute methanol.

4-Formyl-*N*,*N*-diethylbenzamide (8).[25] 1-(3-Dimethylaminopropyl)-3-ethylcarbodimide hydrochloride (30.0 g, 157 mmol) was added portionwise to a cold solution (0 °C) of 4-formylbenzoic acid (21.36 g, 142 mmol), diethylamine (10.41 g, 142 mmol), and triethylamine (20 mL) in 350 mL of anhydrous CH_2Cl_2. The mixture was stirred at 0 °C for 30 min and warmed to the room temperature under Ar. After 4 h, the reaction was quenched by the addition of 200 mL of saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organics were washed successively with water, aqueous hydrochloric acid (5%), water, and brine, then dried over Na_2SO_4, and concentrated. The product **8** (27.2 g, 93%) was purified by high vacuum distillation: bp 113−116 °C/0.1 mmHg; ^{1}H NMR δ 1.12 (bs, 3H, CH_3), 1.27 (bs, 3H, CH_3), 3.22 (bd, J = 6.84 Hz, 2H, NCH_2), 3.57 (bd, J = 6.84 Hz, 2H, NCH_2), 7.53 (d, J = 8.14 Hz, 2H), 7.93 (d, J = 8.03 Hz, 2H), 10.05 (s, 1H, CHO); ^{13}C NMR δ 192 (CHO); MS (CI−NH_3) *m*/*z* 206 (MH^+).

4-[Hydroxy(3-methoxyphenyl)methyl]-*N*,*N*-diethylbenzamide (9b).[2,26] A solution of 3-(methoxyphenyl)magnesium bromide was prepared by stirring 3-bromoanisole (11.22 g, 60 mmol) in 120 mL of anhydrous THF with 1.8 g of magnesium turnings and refluxing for 1 h. The Grignard solution was cooled, and the clear supernate was transferred into a 500 mL round-bottom flask equipped with a mechanical stirrer and reflux condenser via a double-end needle under an atmosphere of Ar. A solution of **8** (6.15 g, 30 mmol) in 25 mL of anhydrous THF was added to the Grignard solution via syringe. The resulting mixture was stirred vigorously for 1 h, and the reaction was quenched by the addition of 100 mL of saturated aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organics were dried over $MgSO_4$ and concentrated. The crude product was crystallized from EtOAc/hexane to yield 8.55 g (91%) of **9b** as white crystals: mp 90−91.5 °C (lit.[2] mp 89−90 °C); ^{1}H NMR δ 1.10−1.25 (m, 6H, $2CH_3$), 2.37 (d, J = 3.8 Hz, 1H, OH), 3.24 (bs, 2H, NCH_2), 3.51 (bs, 2H, NCH_2), 3.79 (s, 3H, OCH_3), 5.82 (d, J = 3.26 Hz, 1H, CH), 6.80−6.84 (m, 1H), 6.93−6.95 (m, 2H), 7.23−7.42 (m, 5H).

4-(3-Methoxybenzoyl)-*N*,*N*-diethylbenzamide (11).[2,28] To a solution of **9b** (10.6 g, 34 mmol) in 200 mL of anhydrous CH_2Cl_2 was added activated manganese (IV) oxide (14.8 g, 5 equiv). The resulting mixture was heated at reflux for 3 h under Ar and then filtered through Celite. The filtrate was concentrated to give 10.5 g (100%) of **11** as a white solid: mp 88−89.5 °C (lit.[2] mp 88−89 °C); ^{1}H NMR δ 1.13−1.28 (bd, 6H), 3.26 (bs, 2H, NCH_2), 3.58 (bs, 2H, NCH_2), 3.87 (s, 3H, OCH_3), 7.15 (dd, J = 1.96, 6.46 Hz, 1H), 7.27−7.50 (m, 5H), 7.84 (d, J = 7.92 Hz, 2H).

4-[(4-Allyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (2).[23,27] A mixture of **10b**[2] (1.36 g, 4.13 mmol), *N*-allyl-piperazine (0.65 g, 5.15 mmol) and K_2CO_3 (1.70 g, 12.39 mmol) in 20 mL of anhydrous acetonitrile was heated to reflux overnight under Ar. The reaction mixture was poured into a mixture of EtOAc and water. The organic layer was washed with water, saturated aqueous solution of sodium carbonate twice and brine, dried over Na_2SO_4 and evaporated in a vacuum to give **2** as a colorless oil (1.13 g, 66%): ^{1}H NMR δ 1.12−1.21 (m, 6H), 2.30−2.55 (bs, 8H), 2.99 (d, J = 6.51 Hz, 2H), 3.21 (bs, 2H), 3.50 (bs, 2H), 3.78 (s, 3H, OCH_3), 4.20 (s, 1H, CHN), 5.11−5.20 (m, 2H, C=CH_2), 5.75−5.90 (m, 1H, C=CH), 6.74−6.75 (m, 1H), 6.97−7.00 (m, 2H), 7.19 (t, J = 8.1 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H); MS (CI−NH_3) *m*/*e* 422 (MH^+). Compound **2**·oxalate: mp 125−127 °C; Anal. ($C_{26}H_{35}N_3O_2 \cdot C_2H_2O_4$) C, H, N.

4-(1-Piperazinylbenzyl)-*N*,*N*-diethylbenzamide (3a).[27] A mixture of **10a**[2] (1.85 g, 6.13 mmol), piperazine (1.58 g, 18.3 mmol), K_2CO_3 (4.24 g, 30.7 mmol), and anhydrous acetonitrile (100 mL) was treated in a manner similar to that described above for the preparation of **2**. This gave 1.55 g (72%) of **3a** as colorless crystals: mp 168−169 °C (lit.[27] 157−169 °C); ^{1}H NMR δ 1.10 (bs, 3H), 1.20 (bs, 3H), 2.33 (bs, 4H), 2.88 (t, J = 5 Hz, 4H), 3.25 (bs, 2H), 3.51 (bs, 2H), 4.23 (s, 1H, CHN), 7.16−7.32 (m, 5H), 7.40 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H); MS (CI−NH_3) *m*/*e* 352 (MH^+). Anal. ($C_{22}H_{29}N_3O$) C, H, N.

4-[(4-Methyl-1-piperazinyl)benzyl]-*N*,*N*-diethylbenzamide (3b). A mixture of **10a**[2] (0.51 g, 1.68 mmol), *N*-methylpiperazine (0.19 g, 1.85 mmol), K_2CO_3 (0.70 g, 5.04 mmol), and anhydrous acetonitrile (5 mL) was treated in a manner similar to that described above for the preparation of **2**. This gave 0.54 g (88%) of **3b** as a colorless oil: ^{1}H NMR δ 1.10 (bs, 3H), 1.20 (bs, 3H), 2.28 (s, 3H, NCH_3), 2.43 (bs, 8H), 3.24 (bs, 2H), 3.51 (bs, 2H), 4.22 (s, 1H, CHN), 7.17−7.32 (m, 5H), 7.40 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H); MS (CI−NH_3) *m*/*e* 366 (MH^+). Compound **3b**·HCl: mp 182 °C (soften). Anal. ($C_{23}H_{31}N_3O$·HCl·$2H_2O$) C, H, N.

4-[(4-Allyl-1-piperazinyl)benzyl]-*N*,*N*-diethylbenzamide (3c).[22,27] A mixture of **3a** (0.21 g, 0.60 mmol), allyl bromide (0.09 g, 0.72 mmol), K_2CO_3 (0.17 g, 1.20 mmol), and anhydrous acetonitrile (6 mL) was treated in a manner similar to that described above for the preparation of **2**. This gave 0.19 g (81%) of **3c** as a colorless oil: ^{1}H NMR δ 1.10 (bs, 3H), 1.20 (bs, 3H), 2.46 (bs, 8H), 3.00 (d, J = 7.0 Hz, 2H), 3.23 (bs, 2H), 3.51 (bs, 2H), 4.23 (s, 1H), 5.10−5.22 (m, 3H), 5.85−5.87 (m, 1H), 7.19 (dd, J = 10.0, 7.0 Hz, 1H), 7.24−7.31 (m, 4H), 7.40 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H); MS *m*/*e* calcd for $C_{25}H_{33}N_3O$: 391.2624, found 391.2611. Compound **3c**·HCl: mp 150 °C (soften). Anal. ($C_{25}H_{33}N_3O$·HCl·$2.5H_2O$) C, H, N.

4-[(4-Propyl-1-piperazinyl)benzyl]-*N*,*N*-diethylbenzamide (3d).[22] A mixture of **3a** (0.35 g, 1 mmol), propyl iodide (0.2 mL, 2 mmol), K_2CO_3 (0.28 g, 2 mmol), and anhydrous acetonitrile (20 mL) was treated in a manner similar to that described above for the preparation of **2**. This gave 0.39 g (100%) of **3d** as a colorless oil: ^{1}H NMR δ 0.89 (t, J = 7.8 Hz, 3H), 1.10−1.20 (m, 6H), 1.46−1.60 (m, 4H), 2.28−2.45 (m, 8H), 3.24 (bs, 2H), 3.51 (bs, 2H), 4.24 (s, 1H, CHN), 7.19−7.29 (m, 5H), 7.38−7.45 (m, 4H); MS (CI−NH_3) *m*/*e* 394 (MH^+). Compound **3d**·oxalate: mp 170−172 °C. Anal. ($C_{25}H_{35}N_3O$·$C_2H_2O_4$) C, H, N.

4-[(4-Benzyl-1-piperazinyl)benzyl]-*N*,*N*-diethylbenzamide (3e).[25] A mixture of **3a** (0.20 g, 0.57 mmol), benzyl chloride (0.13 mL, 1.14 mmol), K_2CO_3 (0.16 g, 1.14 mmol), and anhydrous acetonitrile (6 mL) was treated in a manner similar to that described above for the preparation of **2**. This gave 0.20 g (79%) of **3e** as a colorless oil: ^{1}H NMR δ 1.00−1.25 (bd, 6H), 2.43−2.48 (m, 8H), 3.24 (bs, 2H), 3.51 (bs, 4H), 4.24 (s, 1H, CHN), 7.18−7.29 (m, 10H), 7.37−7.44 (m, 4H); MS (CI−NH_3) *m*/*e* 442 (MH^+). Compound **3e**·oxalate: mp 153−155 °C. Anal. ($C_{29}H_{35}N_3O$·$C_2H_2O_4$·$0.25H_2O$) C, H, N.

4-[(1-Piperidinyl)benzyl]-*N*,*N*-diethylbenzamide (4a). A mixture of **10a** (0.50 g, 1.66 mmol), morpholine (0.4 mL, 4.15 mmol), K_2CO_3 (0.70 g, 5.04 mmol), and anhydrous acetonitrile (10 mL) was treated in a manner similar to that described above for the preparation of **2**. This gave 0.22 g (38%) of **4a** as colorless crystals: mp 125−127 °C; ^{1}H NMR δ 1.12−1.25 (m, 6H), 1.42−1.58 (m, 6H, $3CH_2$), 2.31 (bs, 4H, $2NCH_2$), 3.26 (bs, 2H, $CONCH_2$), 3.49 (bs, 2H, $CONCH_2$), 4.24 (s, 1H, CHN), 7.19−7.30 (m, 5H), 7−7.44 (m, 4H); MS (CI−NH_3) *m*/*e* 351 (MH^+). Anal. ($C_{23}H_{30}N_2O$·$0.5H_2O$) C, H, N.

4-[(4-Morpholinyl)benzyl]-*N*,*N*-diethylbenzamide (4b). A mixture of **10a** (0.50 g, 1.66 mmol), morpholine (0.4 mL, 4.15 mmol), K_2CO_3 (0.70 g, 5.04 mmol), and anhydrous acetonitrile (10 mL) was treated in a manner similar to that described above for the preparation of **2**. This gave 0.45 g (78%) of **4b** as colorless crystals: mp 98−100 °C; ^{1}H NMR δ 1.10−1.25 (m, 6H), 2.36−2.39 (m, 4H, $2NH_2$), 3.21 (bs, 2H, $CONCH_2$), 3.52 (bs, 2H, $CONCH_2$), 3.69−3.72 (m, 4H, $2OCH_2$), 4.22 (s, CHN), 7.22−7.31 (m, 5H), 7.40−7.47 (m, 4H); MS (CI−NH_3) *m*/*e* 353 (MH^+). Anal. ($C_{22}H_{28}N_2O_2$) C, H, N.

4-[(1-Benzyl-4-piperidinylidene)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (6b).[24] Titanium (IV) chloride (2.85 g, 15 mmol) was added to a mechanically stirred suspension of zinc powder (1.96 g) in dry dimethoxyethane (75 mL) at −10 °C under Ar. When the addition was complete, the mixture was warmed to room temperature and then refluxed for 2 h. A mixture of **11** (1.56 g, 5 mmol) and *N*-benzylpiperidone (0.95 g, 5 mmol) in 25 mL of dimethoxyethane was added to the cooled suspension of the titanium reagent. The mixture was refluxed for 4 h, cooled, and poured into 10% aqueous K_2CO_3 (300 mL). After the mixture was stirred overnight, the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined ether extracts were dried over Na_2SO_4 and concentrated. The crude product was purified by acid−base extraction, followed by chromatography, to yield 1.53 g (65%) of **6b** as a light yellow powder: ^{1}H NMR δ 1.12−1.25 (m, 6H, $2CH_3$), 2.48 (m, 4H), 2.49 (m, 4H), 3.27 (bs, $CONCH_2$), 3.49−3.54 (m, 4H, $CONCH_2$, NCH_2Ph), 3.76 (s, 3H, OCH_3), 6.65−6.78 (m, 3H), 7.13−7.33 (m, 5H); MS *m*/*e* calcd for $C_{31}H_{36}N_2O_2$: 468.2777, found 468.2763. Compound **6b**·HCl, lyophilizate, mp 92−95 °C (lit.[24] 100−110 °C. Anal. ($C_{31}H_{36}N_2O_2$·HCl·$0.5H_2O$) C, H, N.

4-[(4-Piperidinylidene)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (6a).[24] To a solution of **6b** (0.70 g, 1.5 mmol) in acetic acid (15 mL) was added 70 mg of 10% Pd/C under Ar. The mixture was subjected to 60 psi of H_2 for 24 h. The mixture was filtered through Celite, and the solvent was evaporated. The residue was partitioned between 40 mL of saturated $NaHCO_3$ and 25 mL of CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organics were dried over Na_2SO_4 and concentrated. The crude product was filtered through a short silica column, eluting with $CHCl_3$:CH_3OH:NH_4OH (100:8:1) to give 0.40 g (70%) of **6a** as a glass: ^{1}H NMR δ 1.21−1.33 (m, 6H, $2CH_3$), 2.37−2.41 (m, 4H), 2.96−3.00 (m, 4H), 3.36 (bs, 2H, $CONCH_2$), 3.61 (bs, 2H, $CONCH_2$), 3.85 (s, 3H, OCH_3), 6.74−6.87 (m, 3H), 7.22−7.39 (m, 5H); ^{13}C NMR δ 12.77 (CH_3), 14.08 (CH_3), 33.32, 33.47, 39.12 ($CONCH_2$), 43.28 ($CONCH_2$), 48.44, 55.12 (OCH_3), 111.63, 115.76, 122.44, 126.26, 129.09, 129.79, 135.04, 135.16, 137.07, 143.32, 143.63, 159.44, 171.43 (CON); MS (CI−NH_3) *m*/*z* 379 (MH^+). Compound **6a**·HCl, lyophilizate, mp 83−85 °C (lit.[24] mp >90 °C (dec)). Anal. ($C_{24}H_{30}N_2O_2$·HCl·$0.5H_2O$) C, H, N.

4-[(4-Piperidinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (5a). To a solution of **6a**[24] (1.87 g, 4.0 mmol) in acetic acid (30 mL) was added 1.87 g of 30% Pd/C under Ar. The mixture was subjected to 60 psi of H_2 for 10 h. The mixture was filtered through Celite, and the solvent was evaporated. The residue was partitioned between 40 mL of saturated $NaHCO_3$ and 40 mL of CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (40 mL × 3) and the combined organics were dried over Na_2SO_4 and concentrated. The crude product was filtered through a short silica column, eluting with $CHCl_3$:CH_3OH:NH_4OH (100:15:1) to give 1.25 g (82%) of **5a** as a glass: ^{1}H NMR δ 1.10−1.34 (m, 9H), 1.63 (t, J = 15.6 Hz, 2H), 2.20−2.27 (m, 2H), 2.61−2.71 (m, 2H), 3.17−3.21 (m, 2H), 3.50−3.54 (m, 3H), 3.79 (s, 3H, OCH_3), 6.72−6.75 (m, 1H), 6.82−6.89 (m, 2H), 7.19−7.30 (m, 5H); MS *m*/*e* calcd for $C_{24}H_{32}N_2O_2$: 380.2464, found 380.2467. Compound **5a**·HCl, mp 98 °C (soften). Anal. ($C_{24}H_{32}N_2O_2$·HCl·H_2O) C, H, N.

4-[(1-Methyl-4-piperidinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (5b). A solution of **5a** (0.38 g, 1 mmol) in 1 mL of formic acid (98%) was treated with 1.5 mL of formaldehyde aqueous solution (37%) and stirred at 70−80 °C overnight. The reaction mixture was cooled and basified with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (3 × 10 mL), and the combined organics were dried over Na_2SO_4 and concentrated. The crude product was filtered through a short silica column, eluting with $CHCl_3$:CH_3OH:NH_4OH (100:10:1) to give 0.34 g (86%) of **5b** as a colorless oil: ^{1}H NMR δ 1.11−1.29 (m, 9H), 1.56 (t, J = 13.7 Hz, 2H), 1.84−1.89 (m, 1H), 1.90−2.06 (m, 1H), 2.24 (s, 3H, NCH_3), 2.79 (d, J = 10.7 Hz, 2H), 3.25 (bs, 2H), 3.45−3.60 (m, 3H), 3.79 (s, 3H, OCH_3), 6.70−6.74 (m, 1H), 6.83−6.90 (m, 2H), 7.18−7.32 (m, 5H); MS *m*/*e* calcd for $C_{25}H_{34}N_2O_2$: 394.2620, found 394.2637. Compound **5b**·HCl: lyophilizate, mp 59 °C (soften). Anal. ($C_{25}H_{34}N_2O_2$·HCl·$1.75H_2O$) C, H, N.

4-[(1-Allyl-4-piperidinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (5c). To a solution of **5a** (0.40 g, 1.1 mmol) in 10 mL of anhydrous THF were added allyl bromide (0.1 mL, 1.15 mmol) and K_2CO_3 (0.18 g, 1.3 mmol). The resulting mixture was stirred at room temperature under Ar. After 4 h, TLC analysis ($CHCl_3$:CH_3OH:NH_4OH 90:9:1) showed that no **5a** remained. The reaction suspension was filtered, and the filter cake was washed with CH_2Cl_2. The filtrate was evaporated and filtered through a short silica column, eluting with $CHCl_3$:CH_3OH:NH_4OH (100:3:0.5). The appropriate fractions were collected and dried under high vacuum to give 0.40 g (91%) of **5c** as a colorless oil: ^{1}H NMR δ 1.12−1.29 (m, 9H),

1.56 (t, $J = 14.6$ Hz, 2H), 1.88−2.09 (m, 2H), 2.88 (d, $J = 11.7$ Hz, 2H), 2.97 (d, $J = 6.9$ Hz, 2H), 3.25 (bs, 2H, $CONCH_2$), 3.46−3.60 (m, 3H), 3.79 (s, 3H, OCH_3), 5.10−5.18 (m, 2H, C=CH_2), 5.81−5.91 (m, 1H, C=CH), 6.70−6.74 (m, 1H), 6.82−6.89 (m, 2H), 7.18−7.29 (m, 5H); MS *m/e* calcd for $C_{27}H_{36}NO_2$: 420.2777, found 420.2772. Compound **5c**·HCl: mp 75 °C (soften). Anal. ($C_{27}H_{36}NO_2$·HCl·0.5H_2O) C, H, N.

4-[(2,2-Dimethylaminoethoxy)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (7a). The benzhydrol **9b** was placed in 20 mL of toluene and heated to solution. The solution was transferred into acidic chloroethanol in 10 mL of toluene and brought to reflux for 4 h. The reaction was cooled and treated with 20 mL of saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic were dried over $MgSO_4$ and concentrated to yield 2.11 g (99%) of 4-[(2-chloroethoxy)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide as a colorless oil: ^{1}H NMR δ 1.13−1.26 (bd, 6H, $2CH_3$), 3.27 (bs, 3H, NCH_2), 3.54 (bs, 3H, NCH_2), 3.67−3.77 (m, 4H), 3.80 (s, 3H, OCH_3), 5.41 (s, 1H, OCH), 6.81−6.84 (m, 1H), 6.91−6.94 (m, 2H), 7.23−7.29 (m, 1H), 7.32−7.41 (m, 4H); MS (CI−NH_3) *m/z* 376 (MH^+). This material was used in the next step.

To a 2.0 M solution of dimethylamine (6 mL, 12 mmol) in THF were added the chloride from above (0.75 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol), and KI (0.332 g, 2 mmol). The resulting mixture was stirred in a sealed tube at 60−65 °C overnight. The reaction mixture was then cooled and poured into 20 mL of saturated aqueous $NaHCO_3$ and Et_2O (20 mL). The aqueous layer was extracted with Et_2O (2 × 20 mL), and the combined organics were dried over Na_2SO_4 and concentrated. The crude product was filtered through a short silica column, eluting with $CHCl_3$:CH_3OH:NH_4OH (100:3:1) to yield 0.554 g (72%) of **7a** as colorless oil: ^{1}H NMR δ 1.11−1.22 (bd, 6H), 2.27 (s, 6H), 2.60 (t, $J = 5.8$ Hz, 2H), 3.25−3.59 (m, 4H), 3.79 (s, 3H, OCH_3), 5.35 (s, 1H, OCH), 6.78−6.82 (m, 1H), 6.91−6.93 (m, 2H), 7.21−7.39 (m, 5H); MS (CI−NH_3) *m/z* 385 (MH^+). The free base was converted to the oxalate salt (**7a**·oxalate): mp 51 °C (soften). Anal. ($C_{23}H_{32}N_2O_3$·$C_2H_2O_4$) C, H, N.

4-[(2,2-Dimethylaminoethylamino)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (7b). This material was prepared by the modified Katritzky tertiary amine method.[32,33] A solution of 3-(methoxyphenyl)magnesium bromide was prepared by stirring 3-bromoanisole (5 mL, 40 mmol) in 40 mL of anhydrous THF with 1 g of magnesium turnings and refluxing for 4 h. The imine adduct **12** was prepared by refluxing *N*,*N*-dimethylethylamine (0.93 g, 10 mmol) and **8** (2.28 g, 10 mmol) in 30 mL of benzene with a Dean−Stark trap attached to remove water. After being refluxed for 3 h, the cold solution of **12** was added dropwise to the Grignard solution, and the resulting mixture was stirred vigorously under Ar. The reaction mixture was quenched with HCl (10%, 100 mL) at 0 °C. The acidic aqueous layer was washed (Et_2O, 100 mL) and then carefully basified with aqueous NaOH to pH ∼ 12 at 0 °C. The basic aqueous layer was extracted with $CHCl_3$ (3 × 100 mL), and the combined $CHCl_3$ layers were dried over Na_2SO_4 and concentrated. The crude product was purified by chromatography (silica; $CHCl_3$:CH_3OH:NH_4OH (100:3:1)) to yield 2.28 g (59%) of **7b** as a glass: ^{1}H NMR δ 1.17−1.22 (bd, 6H), 1.67 (bs, 1H, NH), 1.74 (s, 6H), 2.44 (t, $J = 5.97$ Hz, 2H, NCH_2), 2.64 (t, $J = 6.30$ Hz, 2H, NCH_2), 3.25 (bs, 2H, $CONCH_2$), 3.52 (bs, 2H, $CONCH_2$), 3.79 (s, 3H, OCH_3), 4.78 (s, 1H, CH), 6.75 (dd, $J = 2.71$, 8.04 Hz, 1H), 6.97 (d, $J = 6.51$ Hz, 2H), 7.19−7.31 (m, 3H), 7.42 (d, $J = 8.03$ Hz, 2H); MS (CIMS) *m/e* 384 (MH^+). The free base was converted to the maleate salt (**7b**·maleate): mp 92−94 °C. Anal. ($C_{31}H_{41}N_3O_{10}$) C, H, N.

4-[(2,2-Dimethylamino-1-methylethylamino)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (7c). A solution of **7b** (0.4 g, 1 mmol) in 1 mL of formic acid (96%) was treated with 1.5 mL of formaldehyde aqueous solution (37%) and stirred at 70−80 °C overnight. The reaction mixture was cooled and basified with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (3 × 10 mL), and the combined organics were dried over Na_2SO_4 and concentrated. The crude product was filtered through a short silica column, eluting with $CHCl_3$:CH_3OH:NH_4OH (100:6:1) to give 0.25 g (61%) of **7c** as a glass: ^{1}H NMR δ 1.11−1.25 (bd, 6H), 2.16 (s, 6H, $2NCH_3$), 2.17 (s, 3H, NCH_3), 2.44−2.46 (m, 4H, $2NCH_2$), 3.25 (bs, 2H, $CONCH_2$), 3.51 (bs, 2H, $CONCH_2$), 3.78 (s, 3H, OCH_3), 4.35 (s, 1H, NCH), 6.73−6.75 (m, 1H), 6.97−6.99 (m, 2H), 7.19 (t, $J = 7.8$ Hz, 1H), 7.28 (d, $J = 10.8$ Hz, 2H), 7.44 (d, $J = 7.8$ Hz, 2H); MS (CI−NH_3) *m/e* 398 (MH^+). Compound **7c**·HCl, lyophilizate, mp 95−97 °C. Anal. ($C_{24}H_{35}N_3O_2$·2HCl·1.5H_2O) C, H, N.

Biological Assays. Radioligand Binding Assays for μ, δ, and κ Receptors. μ-Binding sites were labeled using [^{3}H]-DAMGO (2 nM) and rat brain membranes as previously described[34] with several modifications. Rat membranes were prepared daily, 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, each at 30000*g* for 10 min. After the second centrifugation, the membranes were resuspended in 50 mM Tris-HCl, pH 7.4 (50 mL/brain), at 25 °C. Incubations proceeded for 2 h at 25 °C in 50 mM Tris-HCl, pH 7.4, along with a protease inhibitor cocktail (PIC). The nonspecific binding was determined using 20 μM levallorphan. δ-Binding sites were labeled using [^{3}H]-DADLE (2 nM) and rat brain membranes as previously described[34] with several modifications. Rat membranes were prepared daily as with the μ-binding sites, above, except that incubations proceeded for 2 h at 25 °C in 50 mM Tris-HCl, pH 7.4, containing 100 mM choline chloride, 3 mM $MnCl_2$, and 100 mM DAMGO to block binding to μ sites, and PIC. Nonspecific binding was determined using 20 μM levallorphan. κ_1−Binding sites were labeled using [^{3}H]U69,593 (2 nM) as previously described[36] with several modifications. Guinea pig brain membranes were prepared daily, using partially thawed guinea pig brain which was polytroned in 10 mL/brain of ice cold 10 mM Tris-HCl, pH 7.0. Membranes were then centrifuged twice, each at 30000*g* for 10 min. After the second centrifugation, the membranes were resuspended in 50 mM Tris-HCl, pH 7.4 (75 mL/brain), at 25 °C. Incubations proceeded for 2 h at 25 °C in 50 mM Tris-HCl, pH 7.4, containing PIC and 1 μg/mL of captopril. Nonspecific binding was determined using 1 μM U69,593. Each [^{3}H] ligand was displaced by 10 concentrations of test drug, two times. All drug dilutions were done in 10 mM Tris-HCl, pH 7.4, containing 1 mg/mL bovine serum albumin. All washes were done with ice-cold 10 mM Tris-HCl, pH 7.4. The IC_{50} and slope factor (*N*) were obtained by using the program MLAB-PC (Civilized Software, Bethesda, MD). K_i values were calculated according to the equation $K_i = IC_{50}/(1 + [L]/K_d)$.

GPI and MVD Bioassays.[39] Electrically induced smooth muscle contraction of mouse vas deferens and strips of guinea pig ileum longitudinal muscle myenteric plexus were used. Tissues came from male ICR mice weighing 25−40 g and male Hartley guinea pigs weighing 250−500 g. The tissues were tied to gold chain with suture silk, suspended in 20 mL baths containing 37 °C oxygenated (95% O_2, 5% CO_2) Krebs bicarbonate solution (magnesium free for the MVD), and allowed to equilibrate for 15 min. The tissues were then stretched to an optimal length previously determined to be 1 g tension (0.5 g for MVD) and allowed to equilibrate for 15 min. The tissues were stimulated transmurally between platinum wire electrodes at 0.1 Hz, 0.4 ms pulses (2 ms pulses for MVD), and supramaximal voltage. Drugs were added to the baths in 14−60 mM volumes. The agonists remained in contact with the tissue until maximum inhibition was reached before the addition of the next cumulative dose. Percent inhibition was calculated by using the average contraction height for 1 min preceding the addition of the agonist divided by the contraction height at maximal inhibition after exposure to the dose of agonist. IC_{50} estimates and their associated standard errors were determined by using a computerized nonlinear least-squares method.[40] Sensitivity to the antagonist ICI-174,864 was tested by adding a 1 μM concentration of the antagonist to the tissue bath at the completion of the agonist dose−response curve. Partial or complete restoration of contraction height on addition of the antagonist was used as an indicator of the agonistic action at the δ receptor in the case of ICI-174,864.

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