N,*N*-Diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide: A Novel, Exceptionally Selective, Potent δ Opioid Receptor Agonist with Oral Bioavailability and Its Analogues

Zhong-Yong Wei,* William Brown, Bryan Takasaki, Niklas Plobeck, Daniel Delorme,[§] Fei Zhou, Hua Yang, Paul Jones, Lars Gawell, Helene Gagnon, Ralf Schmidt, Shi-Yi Yue, Chris Walpole, Kemal Payza,[#] Stephane St-Onge,[#] Maryse Labarre,[#] Claude Godbout,[#] Andrea Jakob,[#] Joanne Butterworth,[#] Augustus Kamassah,[#] Pierre-Emmanuel Morin,[#] Denis Projean,[#] Julie Ducharme,[#] and Edward Roberts[†]

Departments of Chemistry and Pharmacology, AstraZeneca R&D Montreal, 7171 Frederick-Banting, Saint-Laurent, Quebec, Canada H4S 1Z9

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The design, synthesis, and pharmacological evaluation of a novel class of δ opioid receptor agonists, *N*,*N*-diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide (**6a**) and its analogues, are described. These compounds, formally derived from SNC-80 (**2**) by replacing the piperazine ring with a piperidine ring containing an exocyclic carbon carbon double bond, were found to bind with high affinity and exhibit excellent selectivity for the δ opioid receptor as full agonists. **6a**, the simplest structure in the class, exhibited an $IC_{50} = 0.87$ nM for the δ opioid receptors and extremely high selectivity over the μ receptors ($\mu/\delta = 4370$) and the κ receptors ($\kappa/\delta = 8590$). Rat liver microsome studies on a selected number of compounds show these olefinic piperidine compounds (**6**) to be considerably more stable than SNC-80. This novel series of compounds appear to interact with δ opioid receptors in a similar way to SNC-80 since they demonstrate similar SAR. Two general approaches have been established for the synthesis of these compounds, based on dehydration of benzhydryl alcohols (**7**) and Suzuki coupling reactions of vinyl bromide (**8**), and are herewith reported.

Introduction

Studies have indicated the existence of three main opioid receptor subtypes, μ, δ, and κ, that all appear to be present in both the central and peripheral nervous systems of many species including humans.[1−3] Agonists of all three receptor subtypes have been shown to produce analgesia.[4] Recently, increasing evidence[5−10] has accumulated to support the hypothesis that a selective δ opioid agonist will be an effective analgesic devoid of the side-effect liability associated with μ opioid agonists such as morphine (e.g., respiratory depression, dependence liability, and inhibition of gastrointestinal motility) or the clinically limiting side effects from κ opioid agonists such as CI977 (e.g., dysphoria, diuresis, and locomotor impairment). This has provided the impetus for the development of selective nonpeptide δ opioid agonists. Two major advances in the area of δ-selective agonists were the discoveries of diarylpiperazine derivative (±)-BW373U86 (**1**)[11] and morphinan derivative (−)-TAN-67 (**3**) (Figure 1).[12] Both compounds exhibit a high affinity for the δ opioid receptor with moderate selectivity with respect to the μ opioid receptor. An analogue of (+)-BW373U86, SNC-80 (**2**),[13] demonstrated an improved selectivity while retaining potent δ receptor agonist activity.

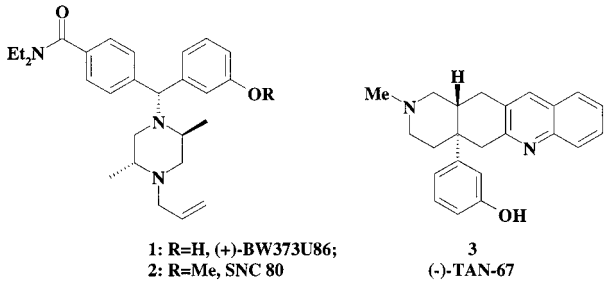

Figure 1. Structures of compounds **1**−**3**.

Due to the presence of three asymmetric carbon atoms, (+)-4-[(α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (SNC-80, **2**) has seven possible stereoisomers, which should exhibit different pharmacological profiles. As described in the first paper in the series,[14] we aimed to find a simple substructure of SNC-80 that retains δ receptor agonist activity and improves the selectivity of δ against μ or κ. Initial SAR studies[15] around SNC-80 indicated that the 4-*N*,*N*-diethylaminocarbonyl group is a key structural feature, but neither the methoxy group, the allyl group, nor the two methyl groups on the piperazine were essential for high affinity at the δ opioid receptor or for selectivity over the μ or κ opioid receptors. Compared to SNC-80, compound **4** displayed a limited decrease in δ binding affinity but improved selectivity. These observations are consistent with recent reports by Calderon et al.[16−18] and Cottney et al.[19] Further studies also indicated that nitrogen N^1 of the piperazine was not involved in binding to the δ opioid receptor. For

* To whom correspondence should be addressed. Tel: 514-832-3200, ext 2402. Fax: 514-832-3232. E-mail: john.wei@astrazeneca.com.
[#] Department of Pharmacology.
[§] Present address: Methylgene Inc., 7220 Frederick-Banting, Saint-Laurent, Quebec, Canada H4S 2A1.
[†] Present address: F. Hoffmann-La Roche Ltd., Pharmaceuticals Division, PRBC, Bldg 015/203, CH-4070 Basel, Switzerland.

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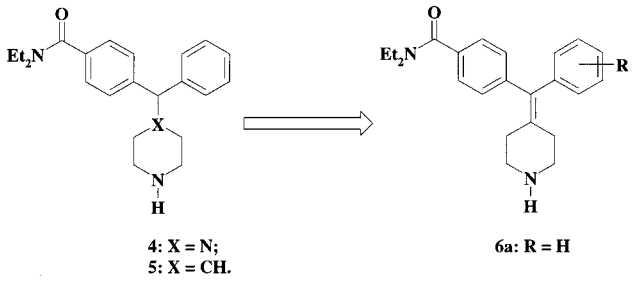


Figure 2. Structures of compounds **4**, **5**, and **6a**.

example, piperidine derivative **5** (IC_{50} = 8.8 nM) exhibited an almost identical δ binding affinity to compound **4** (IC_{50} = 11.3 nM) (Figure 2).

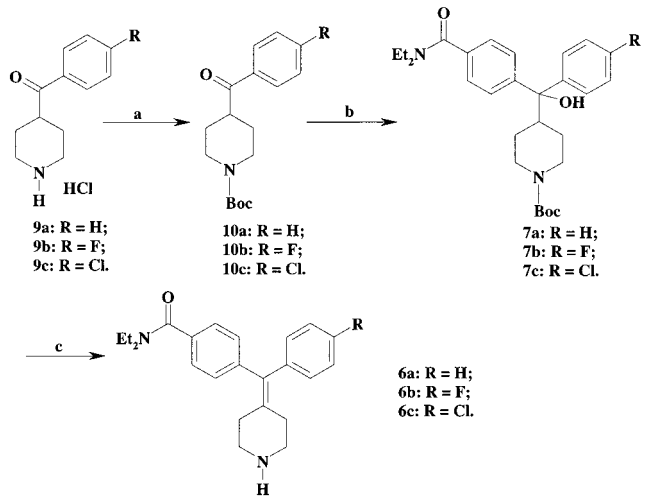
Introduction of conformational constraints in biologically active compounds is a well-established approach for enhancing receptor binding affinity and selectivity. On the basis of the above assumption, incorporation of an exocyclic carbon−carbon double bond into the piperidine ring of **5** became the most logical modification[20] on SNC-80. The resulting compound, **6a**, has displayed a 9-fold increase in binding affinity for the δ receptor (IC_{50} = 0.87 nM) and extremely high selectivity over the μ receptor (μ/δ = 4370) and the κ receptor (κ/δ = 8590). In this paper, we investigate the δ receptor binding effects of the substitution pattern on the aromatic ring of **6a** and the effect of *N*-substitution of the piperidine. All compounds were examined for their affinity for all three human opioid receptor subtypes, and their δ agonist activity was determined using the GTP[γ-^{35}S] binding assay.

Chemistry

Diarylmethylenepiperidines have been well-known as antihistamine drugs in the treatment of allergic diseases. The synthesis of these compounds has been achieved by several approaches such as Wittig−Horner reaction[21] and McMurry coupling reaction.[22] In our opinion, however, more efficient procedures were required to prepare compounds **6** with modified aromatic groups (Figure 3). Thus, novel approaches have been explored, including the methodology based on the Suzuki coupling reaction of compound **8** with different arylboronic acids and the procedure based on dehydration of compounds **7**, which were easily prepared by reacting a 4-benzoylpiperidine with an aryllithium or an arylmagnesium halide.

Synthesis of compounds **6a**−**6c** is described in Scheme 1. Thus 4-benzoylpiperidine hydrochloride **(9a)** was transformed to its N-Boc derivative **10a** in 98% yield under basic conditions. 4-Iodo-*N*,*N*-diethylbenzamide[23] was subjected to metal−halogen exchange with *t*-BuLi

Scheme 1[a]



[a] Reagents: (a) Boc_2O; (b) 4-iodo-*N*,*N*-diethylbenzamide/BuLi, −78 °C; (c) TFA.

in THF at −78 °C followed by the addition of **10a**, to furnish compound **7a** in 94% yield. Subsequent dehydration of the benzhydryl alcohol **7a** was performed in methylene chloride in the presence of trifluoroacetic acid to provide compound **6a** in 91% yield. Similarly compounds **6b** and **6c** were prepared from commercially available 4-benzoylpiperidines **9b** and **9c**.

A more efficient strategy based on the dehydration approach would react **10d** with a number of different arylmagnesium halides or aryllithiums. Thus as shown in Scheme 2, 4-(4′-*N*,*N*-diethylaminocarbonyl)benzoylpiperidine was prepared from ethyl isonipecotate **(11)** in 28% yield by a three-step procedure. Benzhydryl alcohols **7d**−**7g** were then obtained from reacting **10d** with a variety of aryllithium reagents. Dehydration under the same conditions as for **6a** provided the desired compounds **6d**−**6g**.

The synthetic approach based on Suzuki coupling reaction is shown in Scheme 3. The key intermediate **8** was prepared in five steps from compound **13**. Thus, methyl 4-(bromomethyl)benzoate was refluxed for 5 h in trimethyl phosphite to provide compound **14** in quantitative yield. Wittig−Horner olefination of *N*-*tert*-butoxycarbonyl-4-piperidone with compound **14** was performed in the presence of LDA. Addition of bromine to a solution of **15** in dichloromethane afforded compound **16** in 78% yield, which was then treated with aqueous NaOH in methanol at 40 °C to provide compound **17**. *N*,*N*-Diethylbenzamide **(8)** was then prepared in 73% yield from **17** by the mixed anhydride approach. The Suzuki coupling reaction of vinyl bromide **8** with a variety of arylboronic acids was performed in the

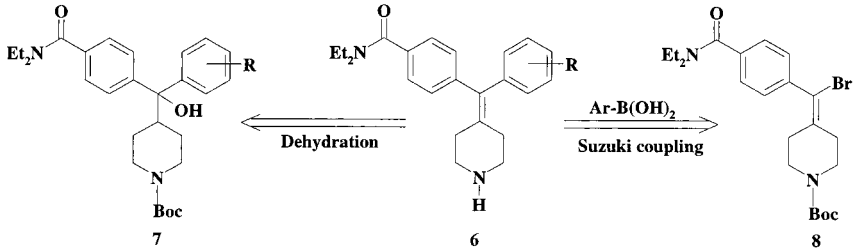
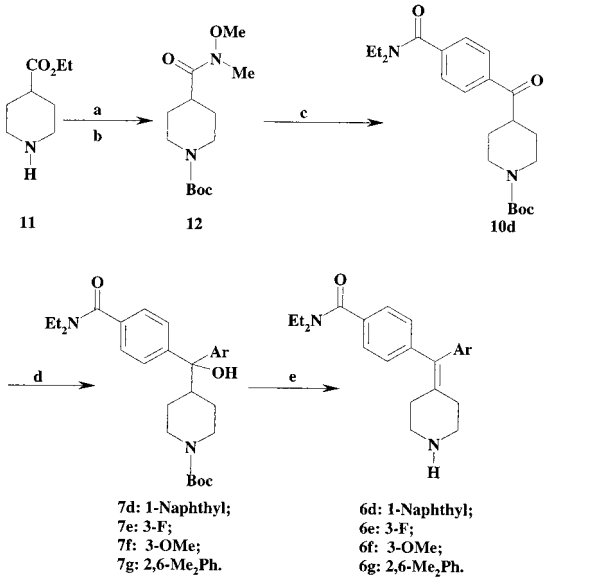


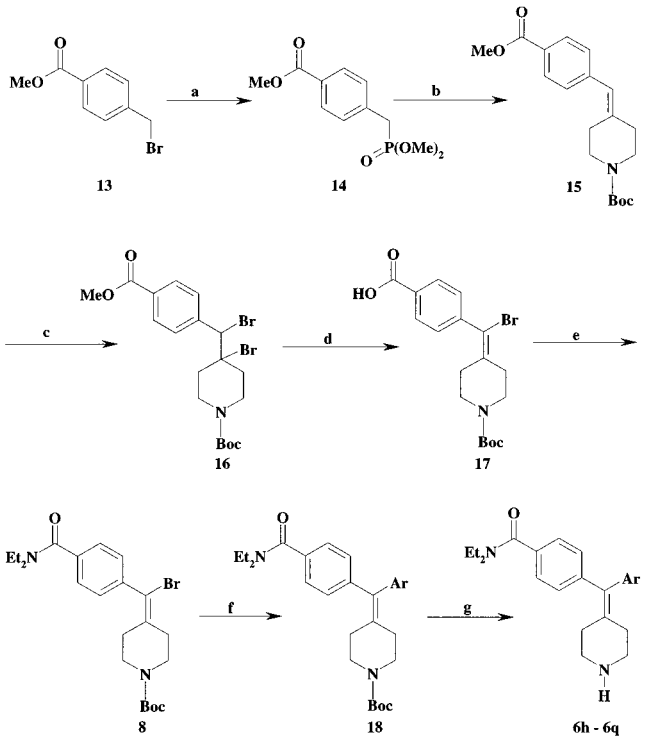
Figure 3. Reactions to prepare compound **6**.

Scheme 2[a]



[a] Reagents: (a) Boc_2O; (b) Me(MeO)NH, *i*-PrMgCl; (c) 4-iodo-*N*,*N*-diethylbenzamide/BuLi, −78 °C; (d) Ar-Li; (e) TFA.

Scheme 3[a]

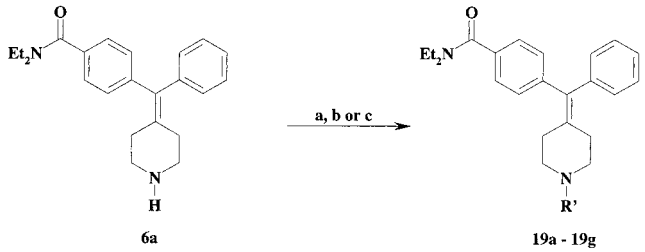


[a] Reagents: (a) $P(OMe)_3$; (b) LDA, *N*-*tert*-butoxycarbonyl-4-piperidone; (c) Br_2; (d) NaOH; (e) $(COCl)_2/Et_3N$, Et_2NH; (f) Ar-$B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3; (g) 4 N HCl.

presence of tetrakis(triphenylphosphine)palladium (0) using 2 M Na_2CO_3 as base. Subsequent cleavage of the Boc group was achieved with 4 N HCl in dioxane providing the final compounds **6h**−**6q**.

Compounds **19a**−**19g** representing different *N*-substituted analogues of **6a** were prepared as described in Scheme 4. Compounds **19a**−**19e** were obtained by treatment of **6a** with the corresponding alkyl halides in the presence of potassium carbonate in acetonitrile at room temperature. The *N*-cyclohexyl derivative **19f** was provided by reductive amination from **6a** and

Scheme 4[a]



[a] Reagents: (a) R′-X, K_2CO_3; (b) $R^1R^2C{=}O$, $NaBH_4$; or (c) Ph-Br, $Pd(dba)_2$, BINAP, NaO-*t*-Bu.

cyclohexanone. Finally the *N*-phenyl analogue **19g** was obtained by palladium catalyzed *N*-arylation[24] of **6a**.

Results and Discussion

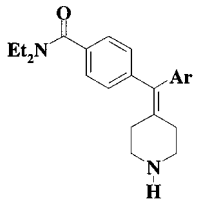
In Vitro Pharmacology. The binding affinities (IC_{50}) of all compounds were determined using cloned human δ, μ, and κ opioid receptors, and the δ agonist potency (EC_{50}) was measured with the GTP[γ-^{35}S] binding assay.

The opioid receptor binding affinity, selectivity, and agonist potency of the target compounds **6** are listed in Table 1, and those of SNC-80, diarylmethylpiperazine **4**, and diarylmethylpiperidine **5** are also included for comparison. As compared to SNC-80 [δ IC_{50} = 1.31 nM; μ/δ = 245; κ/δ = 1890 (K_i = 4 nM; μ/δ = 990 on rat brain membranes)[18]], compound **6f** displayed similar binding affinity [IC_{50} = 1.56 nM (K_i = 5 nM; μ/δ > 1200 on rat brain membranes)[18]] on δ receptors but an improved selectivity over μ and κ receptors (μ/δ = 3370; κ/δ > 6410). **6a**, a derivative of **6f** without the 3-MeO group on the phenyl ring, even further increased selectivity as a result of improved δ-affinity (IC_{50} = 0.87 nM; μ/δ = 4370; κ/δ = 8590). Considerable variation is possible in the nature of the substitution on the phenyl ring, and this can lead to some highly potent δ agonists. For example, compounds **6e** (EC_{50} = 4.6 nM) and **6h** (EC_{50} = 3.18 nM) exhibited improved agonist activities at δ receptors compared to the "parent" structure (**6a**, EC_{50} = 7.2 nM). The position of a substituent on the phenyl ring is important for both binding affinity and agonist activity. Substitution at the *para*-position of the phenyl ring appeared to be detrimental (**6b** vs **6e**, **6l**; **6p** vs **6f**, **6q**), presumably reflecting steric constraints in this region. The 2,6-dimethylphenyl analogue **6g** exhibited a dramatically reduced δ binding affinity as compared to the parent compound **6a**, suggesting that the steric constraints imposed by the two methyl groups may alter the conformation of the dimethylphenyl ring in a manner which is deleterious to activity. On the other hand, the phenyl group can be replaced by heteroaryl or other aryl groups. For example, 1-naphthyl (**6d**) and 2-thiophenyl (**6m**) analogues still retain potent δ affinity and high selectivity over μ and κ receptors.

In general, this entire series of compounds displayed extremely high affinity to δ opioid receptors (low nanomolar to subnanomolar range) and very high selectivity over μ or κ opioid receptors (>1000 in most cases). All compounds exhibited full δ agonism at the cloned human δ receptor as determined in GTP[γ-^{35}S] binding assay.

To examine the effect on biological activity of *N*-alkyl substitution on the piperidine nitrogen of **6a**, *N*-Me,

Table 1. Binding Affinities and Agonist Activities of Compounds **6**



(6)

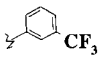
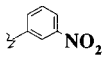
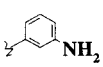
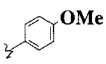
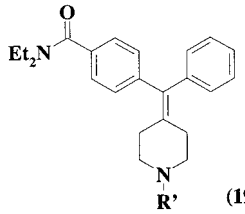
		IC$_{50}$ (nM)			selectivity ratio		δ	
compd	**Ar**	δ	μ	κ	μ / δ	κ / δ	**EC$_{50}$(nM)**	**E$_{max}$ (%)**
SNC-80		1.31 ± 0.17	320 ± 58	2480 ± 378	245	1890	3.67 ± 0.70	100± (REF)
4		11.3 ± 2.3	8150±373	>10000	741	>909	36.5 ± 5.9	105 ± 5
5		8.77 ± 0.89	n/a	n/a	n/a	n/a	121 ± 15	97 ± 3
6a		0.87 ± 0.23	3800 ± 172	7470 ± 606	4370	8590	7.2 ± 0.9	110 ± 3
6b		15.0 ± 2.4	>10000	>10000	>667	>667	98.1 ± 11.4	96 ± 7
6c		4.17 ± 1.20	5050 ± 272	8340 ±1710	1210	2000	25.5 ± 4.1	111 ± 2
6d		1.23 ± 0.07	817 ± 77	1660 ± 268	664	1350	5.9 ± 1.8	107 ± 4
6e		0.74 ± 0.14	3570 ± 444	>10000	4820	>13500	4.6 ± 0.5	112 ± 6
6f		1.56 ± 0.26	5250 ± 445	>10000	3370	>6410	13.7 ± 3.2	109 ± 7
6g		187 ± 15.4	1020 ± 66	2610 ±515	5.5	14	n/a	n/a
6h		0.63 ± 0.11	1510 ± 161	5350 ± 648	2400	8490	3.18 ± 0.56	110 ± 1
6i		2.31 ± 0.24	2590 ± 749	3870 ± 162	1120	1680	8.96 ± 2.19	104 ± 2
6j		0.86 ± 0.15	3290 ± 535	>10000	3820	>10000	10.6 ± 2.4	110 ± 1
6k		1.10 ± 0.32	2740 ± 304	>10000	2490	>9090	8.6 ± 2.5	98 ± 2
6l		1.04 ± 0.11	2980 ± 647	>10000	2860	>9620	15.9 ± 4.5	112 ± 5
6m		2.85 ± 0.21	5440 ± 656	>10000	1910	>3510	30.6 ± 6.3	99 ± 6
6n		2.09 ± 0.36	6760 ± 926	>10000	3240	>4790	23.4 ± 5.7	98 ± 5
6o		2.57 ± 0.23	5980 ±1060	>10000	2330	>3890	20.5 ± 2.9	96 ± 4
6p		2.04 ± 0.22	5440 ±1270	>10000	2670	>4900	12.1 ± 3.8	109 ± 2
6q		0.97 ± 0.08	3480 ± 579	>10000	3590	>10300	5.9 ± 0.4	104 ± 1

Table 2. Binding Affinities and Agonist Activities of **6a** Analogues (**19**)



(19)

compd	R'	IC50 (nM) δ	IC50 (nM) μ	IC50 (nM) κ	selectivity ratio μ / δ	selectivity ratio κ / δ	δ EC50(nM)	δ Emax (%)
6a	**H**	0.87 ± 0.23	3800 ± 172	7470 ± 606	4370	8590	7.2 ± 0.9	110 ± 3
19a	**Me**	27.0 ± 2.2	>10000	>8900	>370	>330	161 ± 12	85 ± 6
19b		3.00 ± 0.69	3330 ± 275	2290 ± 369	1110	763	28.3 ± 2.1	98 ± 3
19c		2.09 ± 0.11	1030 ± 100	982 ± 90	493	470	14.1 ± 1.8	106 ± 3
19e		9.35 ± 1.93	3390 ± 748	6140 ±1060	362	657	42.3 ± 8.2	108 ± 4
19d		6.53 ± 1.25	4130 ± 884	4270 ±1120	632	654	46 ± 3.9	111 ± 2
19f		35.5 ± 5.9	597 ± 164	1330 ± 135	16.8	37.4	n/a	n/a
19g		736 ± 145	>10000	3160 ± 602	>13.6	4.3	n/a	n/a

N-allyl, *N*-3,3-dimethylallyl, *N*-cyclopropylmethyl, *N*-butyl, *N*-cyclohexyl, and *N*-phenyl substituents were introduced (Table 2). None of these compounds bind to δ opioid receptors with as high affinity as the "parent" compound **6a**: compounds **19b** and **19c** with allyl substituents, which are known to be tolerated in piperazine series such as SNC-80, exhibited slightly decreased affinities relative to **6a**, while **19a** and **19f** showed more than 30-fold decreased δ receptor affinities. The *N*-phenyl derivative **19g** almost completely lost its ability to bind to the δ receptors, presumably because of the decreased basicity of the nitrogen (calculated pK_a values are 5.32 for compound **19g** and 9.68 for compound **6a** by ACD pK_a from Advanced Chemistry Development Inc., Toronto, Canada), which is an essential pharmacophore point to have an electrostatic interaction at an anionic receptor site. The butyl and cyclopropylmethyl derivatives (**19d**, **19e**) showed similar binding affinity and identical agonist activity in the δ receptor assay probably due to their similarity in size. In general, the *N*-alkyl compounds are also comparably weak ligands for μ and κ opioid receptors with respect to the parent compound **6a**, while **19f** exhibited somewhat increased μ receptor affinity.

In Vitro Metabolism. Selected compounds were examined in rat liver microsomes (Table 3). While SNC-80 is unstable in rat liver microsomes, most of the compound being degraded in 1 h at both concentrations, most olefinic analogues **6** were found to be significantly more stable. Major metabolites were *N*-deethylated analogues (M − 28), while minor metabolites included hydroxylated derivatives (M + 16).

Table 3. Microsomal Incubation Analysis[a]

compd	% parent remaining at 10 μM	% parent remaining at 100 μM
SNC-80	1 ± 1 (*n* = 5)	24 ± 6 (*n* = 5)
6a	77 ± 7 (*n* = 7)	95 ± 6 (*n* = 7)
6e	55 ± 14 (*n* = 3)	94 ± 6 (*n* = 3)
6f	1 (*n* = 2)	58 ± 3 (*n* = 2)
6h	75 ± 2 (*n* = 3)	95 ± 3 (*n* = 3)
6i	63 ± 17 (*n* = 2)	91 ± 9 (*n* = 3)
6k	80 ± 1 (*n* = 2)	100 (*n* = 2)
6q	55 (*n* = 2)	90 ± 1 (*n* = 2)

[a] After 1-h incubations in rat liver microsomes.

In agreement with the metabolic profiling data obtained for SNC-80 in rat liver microsomes,[14] the methoxy analogue **6f** was less stable than other compounds, being extensively metabolized into an *O*-demethylated derivative. The olefin **6a** is markedly more stable, being virtually undegraded at 100 μM, in sharp contrast to SNC-80. As could be predicted by the improved metabolic stability of **6a**, together with the low molecular weight and conformity with Lipinski's rules,[25] **6a** has exceptional oral bioavailability, approaching 100%.

Proposed Common Binding Mode of 2 (SNC-80) and 6a. The essential elements of the δ agonist pharmacophore (described in more detail in the previous paper in this series[14]) are the basic nitrogen, the 'right-

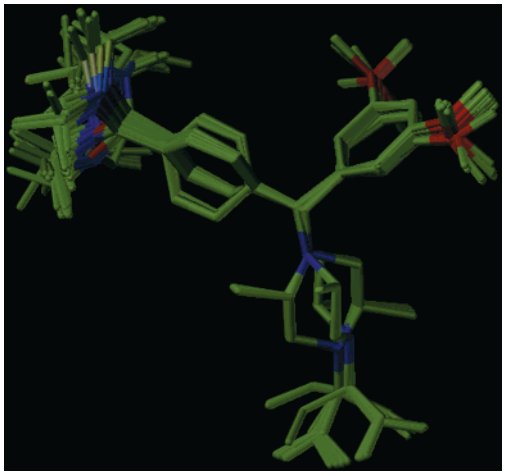


Figure 4. Superpositions of 64 conformers of SNC-80, generated from conformational search. Carbon atoms are in light green, nitrogen atoms in blue, and oxygen atoms in red.

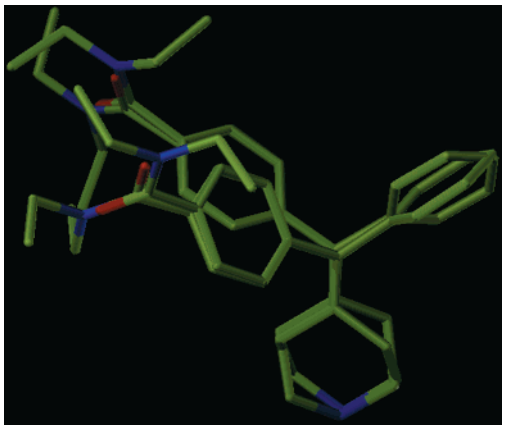


Figure 5. Superpositions of 4 conformers of **6a**, generated from conformational search with the same color coding as in Figure 4.

hand' (oxygenated in the case of SNC-80, unsubstituted in the case of **6a**) phenyl ring, and the diethylamide carbonyl group. To compare the pharmacophore groups in the two molecules, SNC-80 and **6a**, an extensive conformational search was performed and the correspondence of these key groups (the carbonyl carbon atom was taken to represent the amide pharmacophore to reduce the complexity of the conformational search) in low-energy conformers was examined (Figures 4 and 5). This comparison of the two compounds showed that compound **6a** only partially covers the conformational space available to SNC-80, while key pharmacophores are closely superimposed in **6a** and a population of SNC-80 conformers. The first interpretation of this conformational comparison is that compound **6a** can efficiently bind to and activate the δ opioid receptor but has improved selectivity compared to SNC-80, since it does not intrude into conformational space which might be attributed to recognition of the other opioid receptor subtypes.

Figure 6 shows a superposition of the crystallographic structures of SNC-80 and compound **6a**. The three-dimensional coordinates of SNC-80 were built according to its absolute stereochemistry.[13] The basic nitrogen, the two centroid phenyl rings, and the carbon atom of the carbonyl group were used for the superposition (rms = 0.36). It is interesting to notice that, while the C atoms

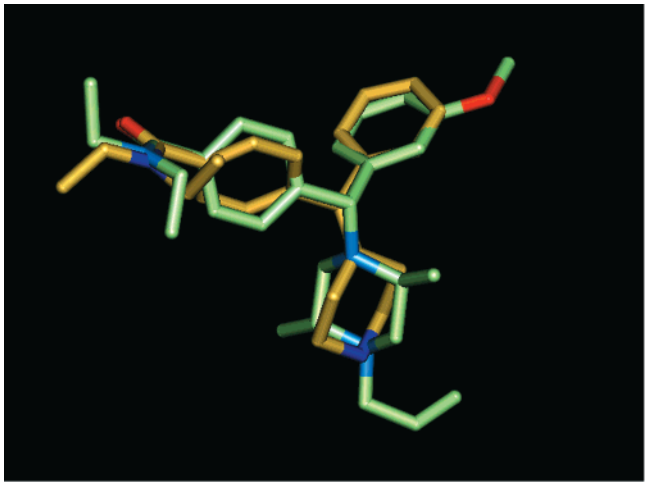


Figure 6. Superposition of the crystal structures between SNC-80 (carbon atoms in light green) and compound **6a** (carbon atoms in gold).

of the piperidine ring in **6a** and the piperazine ring of SNC-80 do not overlay well in the superposition, the basic N atoms are disposed very closely in space. The same phenomenon was also observed in the conformational search, suggesting that this part of the ring structure only serves as a spacer to connect the basic nitrogen and the two aromatic rings containing the other two pharmacophore groups. A recent publication[26] also experimentally proved this observation. The superposition of the amide carbonyl groups in the two molecules is excellent, despite the different orientations of the intervening phenyl rings. The 'right-hand' phenyl ring is well-overlaid in the two structures.

Conclusion

A novel class of exceptionally selective, potent δ opioid receptor ligands was identified as a result of replacing the piperazine N atom in the progenitor series of agonists with an olefinic C atom, resulting in **6a**, the simplest structure in the series which exhibited an $IC_{50} = 0.87$ nM for δ opioid receptors and exceptional selectivity over μ receptors ($\mu/\delta = 4370$) and κ receptors ($\kappa/\delta = 8590$). This compound and its analogues presented here have the highest selectivity in the human opioid receptors assay of any comparator compounds we have tested: 14 out of the 17 compounds showed δ affinity less than 3 nM, while 5 of these compounds had subnanomolar affinity. The majority of these compounds displayed a ratio of >1000 with respect to μ or κ opioid receptors. Furthermore evaluation of a number of compounds in rat liver microsomes showed these compounds (including **6a**) to be much more stable than the parent compound SNC-80. **6a** was subsequently found to have excellent oral availability[27] ($F = 90-100\%$ in the rat).

These *N*,*N*-diethyl-4-(piperidin-4-ylidenemethyl)benzamides are the most selective δ opioid receptor agonists described so far. They do not contain any chiral centers and can easily be prepared by established synthetic approaches. These important chemical features coupled with their excellent pharmacological profile and oral bioavailability make these compounds ideal for further investigation and development.

Experimental Section

Synthesis. Melting points were taken in a capillary tube by using a Thomas-Hoover melting point apparatus and are uncorrected. For the HCl salts of many final compounds, melting points were not measured because they were not crystalline due to the fractional amounts of HCl present from combustion analyses. IR spectra were determined with a Perkin-Elmer Pragon 100 FT-IR spectrometer. NMR spectra were recorded on a Varian Unity Plus 400 MHz spectrometer; chemical shifts were recorded in parts per million downfield from Me_4Si. Elemental analyses were performed by Canadian Microanalytical Service Ltd., Delta, British Columbia. Flash column chromatography was performed with silica gel 60 (70−230 mesh). Dry THF was distilled from sodium benzophenone prior to use. Other anhydrous solvents over molecular sieves were obtained from Fluka.

4-Benzoyl-*N*-*tert*-butoxycarbonylpiperidine (10a). A mixture of **9a** (6.77 g, 30.0 mmol), di-*tert*-butyl dicarbonate (7.2 g, 33.0 mmol) and Na_2CO_3 (6.36 g, 60 mmol) was refluxed in H_2O−THF (50/20 mL) for 1 h. The reaction mixture was then cooled and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to give **10a** (8.54 g, 98%): mp 95−96 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 1.70 (m, 2H), 1.83 (m, 2H), 2.91 (m, 2H), 3.42 (m, 1H), 4.18 (brs, 2H), 7.46 (m, 2H), 7.56 (m, 1H), 7.93 (m, 2H).

4-(4-Fluorobenzoyl)-*N*-*tert*-butoxycarbonylpiperidine (10b). Following the same method as used to prepare **10a** but starting with **9b** (2.44 g, 10 mmol) led to **10b** as a solid (2.27 g, 74%): mp 80−83 °C (CH_2Cl_2); IR (KBr) 1680, 1587 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.69 (m, 2H), 1.79 (m, 2H), 2.87 (m, 2H), 3.34 (m, 1H), 4.13 (brs, 2H), 7.12 (m, 2H), 7.95 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.4, 28.4, 43.2, 43.4, 79.6, 115.8, 115.9, 130.8, 130.9, 132.2, 154.6, 164.4, 166.9, 200.4.

4-(4-Chlorobenzoyl)-*N*-*tert*-butoxycarbonylpiperidine (10c). Following the same method as used to prepare **10a** but starting with **9c** (2.60 g, 10 mmol) led to **10c** as a solid (2.75 g, 85%): mp 122−125 °C (CH_2Cl_2); IR (KBr) 1680, 1582 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.47(s, 9H), 1.69 (m, 2H), 1.81 (m, 2H), 2.90 (m, 2H), 3.36 (m, 1H), 4.18 (brs, 2H), 7.44 (m, 2H), 7.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.3, 28.4, 43.2, 43.4, 79.6, 129.0, 129.6, 134.1, 139.4, 154.6, 200.7.

4-(α-Hydroxy-α-(4-*N*-*tert*-butoxycarbonylpiperidinyl)-benzyl)-*N*,*N*-diethylbenzamide (7a). To a solution of 4-iodo-*N*,*N*-diethylbenzamide (6.67 g, 22.0 mmol) in dry THF (70 mL) was added *tert*-butyllithium (18.0 mL, 2.5 M, 45.0 mmol) at −78 °C. After 10 min, **10a** (4.34 g, 15.0 mmol) in THF (5 mL) was dropwise added. The reaction mixture was warmed to room temperature and then quenched with aqueous NH_4Cl solution and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by flash chromatography eluting with MeOH−CH_2Cl_2 (0:100 → 5:95) to provide **7a** (6.56 g, 94%): mp 100−103 °C (CH_2Cl_2); IR (KBr) 3426, 1687, 1618 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 (brs, 3H), 1.20 (brs, 3H), 1.30 (m, 4H), 1.41 (s, 9H), 2.50 (t, J = 11.2 Hz, 1H), 2.66 (m, 2H), 2.86 (s, OH), 3.22 (brs, 2H), 3.50 (brs, 2H), 4.09 (brs, 2H), 7.18 (m, 1H), 7.26 (m, 4H), 7.45 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 12.8, 14.1, 26.2, 28.3, 39.1, 43.2, 44.3, 53.3, 79.2, 79.4, 125.75, 125.79, 126.2, 126.6, 128.1, 135.1, 145.3, 146.8, 154.6, 171.0.

4-(α-Hydroxy-α-(4-*N*-*tert*-butoxycarbonylpiperidinyl)-4-fluorobenzyl)-*N*,*N*-diethylbenzamide (7b). Method as described for **7a**, but starting with **10b** (1.54 g, 5.0 mmol) led to **7b** as a solid (1.14 g, 47%): mp 84−86 °C (CH_2Cl_2); IR (KBr) 3421, 1685, 1612 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.13 (brs, 3H), 1.23 (brs, 3H), 1.32 (m, 4H), 1.44 (s, 9H), 2.48 (m, 1H), 2.68 (brs, 2H), 3.26 (brs, 2H), 3.54 (brs, 2H), 3.57 (s, 1H), 4.11 (brs, 2H), 6.96 (m, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.44 (m, 2H), 7.47 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.9, 14.0, 26.2, 28.2, 39.1, 43.2, 43.6, 44.3, 78.9, 79.1, 114.5, 114.7, 125.7, 126.1, 127.5, 127.6, 135.0, 141.2, 146.9, 154.5, 160.0, 162.5, 170.9.

4-(α-Hydroxy-α-(4-*N*-*tert*-butoxycarbonylpiperidinyl)-4-chlorobenzyl)-*N*,*N*-diethylbenzamide (7c). Method as described for **7a**, but starting with **10c** (1.62 g, 5.0 mmol) led to **7c** as a solid (1.58 g, 63%): mp 100−105 °C (CH_2Cl_2); IR (KBr) 3411, 1685, 1617 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 (brs, 3H), 1.20 (brs, 3H), 1.33 (m, 4H), 1.41 (s, 9H), 2.44 (m, 1H), 2.63 (brs, 2H), 3.22 (brs, 2H), 3.49 (brs, 2H), 3.99 (s, 1H), 4.05 (m, 2H), 7.20 (m, 4H), 7.39 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.5, 13.9, 25.9, 28.1, 39.0, 43.0, 44.1, 78.7, 79.0, 125.6, 126.0, 127.2, 127.8, 131.9, 134.8, 144.1, 146.6, 154.3, 170.7.

***N*,*N*-Diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide (6a).** To a solution of **7a** (932 mg, 2.0 mmol) in dry dichloromethane (10 mL) was added trifluoroacetic acid (10.0 mL) at room temperature. The reaction mixture was stirred overnight and then concentrated. The residue was then dissolved in CH_2Cl_2 (100 mL), washed with 1 N NaOH, brine, and dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by flash chromatography eluting with MeOH−CH_2Cl_2 (20:80) to provide **6a** (632 mg, 91%): ^{1}H NMR ($CDCl_3$) δ 1.08 (brs, 3H), 1.17 (brs, 3H), 2.29 (m, 4H), 2.86 (m, 4H), 2.94 (brs, 1H), 3.24 (brs, 2H), 3.47 (brs, 2H), 7.09 (m, 4H), 7.15 (m, 1H), 7.24 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 12.6, 14.1, 32.7, 32.8, 39.1, 43.2, 47.9, 126.0, 126.4, 127.9, 129.6, 134.9, 135.4, 135.9, 141.7, 143.2, 171.1. HCl salt: mp 110−120 °C (CH_2Cl_2); IR (KBr) 3440, 1617. Anal. ($C_{23}H_{28}N_2O$·2.1HCl) C, H, N.

***N*,*N*-Diethyl-4-(4-fluorophenylpiperidin-4-ylidenemethyl)benzamide (6b).** Method as described for **6a**, but starting with **7b** led to **6b** in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.12 (brm, 3 H, C*H*$_3$CH$_2$-), 1.24 (brm, 3 H, C*H*$_3$CH$_2$-), 2.32 (m, 4 H, piperidine C*H*-), 2.54 (brm, 1 H, N*H*), 2.91 (m, 4 H, piperidine C*H*-), 3.27 (brm, 2 H, C*H*$_2$N-), 3.52 (brm, 2 H, C*H*$_2$N-), 7.00 (m, 2 H, Ar*H*), 7.09 (m, 2 H, Ar*H*), 7.11 (d, J = 8.0 Hz, 2H, Ar*H*), 7.29 (d, J = 8.0 Hz, 2 H, Ar*H*). Anal. ($C_{23}H_{27}FN_2O$·1.5HCl) C, H, N.

***N*,*N*-Diethyl-4-(4-chlorophenylpiperidin-4-ylidenemethyl)benzamide (6c).** Method as described for **6a**, but starting with **7c** led to **6c** in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.13 (brm, 3 H, C*H*$_3$CH$_2$-), 1.22 (brm, 3 H, C*H*$_3$CH$_2$-), 2.02 (brm, 1 H, N*H*), 2.30 (m, 4 H, piperidine C*H*-), 2.90 (m, 4 H, piperidine C*H*-), 3.28 (brm, 2 H, C*H*$_2$N-), 3.53 (brm, 2 H, C*H*$_2$N-), 7.04 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.11 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.25 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.30 (d, J = 8.0 Hz, 2 H, Ar*H*). HCl salt: mp 115−120 °C (CH_2Cl_2); IR (KBr) 3337, 1618 cm^{-1}. Anal. ($C_{23}H_{27}ClN_2O$·1.6HCl) C, H, N.

***N*-*tert*-Butoxycarbonyl-*N*′-methyl-*N*′-methoxyisonipecotamide (12).** Method as described for **10a**, but starting with ethyl isonipecotate (**11**; 4.71 g, 30.0 mmol) led to *N*-*tert*-butoxylcarbonyl ethyl isonipecotate (7.67 g): ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3H), 1.45 (s, 9H), 1.62 (m, 2H), 1.87 (m, 2H), 2.43 (m, 1H), 2.84 (m, 2H), 4.02 (m, 2H), 4.13 (q, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 27.8, 28.2, 40.9, 42.9, 60.2, 79.2, 154.4, 174.2.

To a mixture of the above product and NHMe(OMe) HCl (4.39 g, 45.0 mmol) in dry THF was added *i*-PrMgCl (2.0 M in THF, 45 mL, 90 mmol) at −20 °C. The resulting solution was stirred for 1 h at −5 °C, then quenched with aqueous NH_4Cl solution and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of solvents gave **12** (8.0 g, 98%): ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.54 (m, 4H), 2.65 (m, 3H), 3.02 (s, 3H), 3.56 (s, 3H), 3.99 (brs, 2H); ^{13}C NMR ($CDCl_3$) δ 27.7, 28.1, 32.0, 37.8, 43.1, 61.3, 79.1, 154.4, 176.0.

4-(4′-*N*′,*N*′-Diethylaminocarbonylbenzoyl)-*N*-*tert*-butoxycarbonylpiperidine (10d). To a solution of 4-iodo-*N*,*N*-diethylbenzamide (9.09 g, 30.0 mmol) and TMEDA (6.96 g, 60.0 mmol) in dry THF (60 mL) was added *tert*-butyllithium (35.0 mL, 1.7 M, 60.0 mmol) at −78 °C. After 30 min, **12** (8.0 g, 29.4 mmol) in THF (10 mL) was dropwise added. The reaction mixture was warmed to room temperature, then quenched with aqueous NH_4Cl solution, acidified with hydrochloric acid (concentrated, 20 mL) at 0 °C, and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with

brine and dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by flash chromatography eluting with MeOH−CH_2Cl_2 (2:98) to provide **10d** (3.15 g, 28%): ^{1}H NMR ($CDCl_3$) δ 1.08 (brs, 3H), 1.23 (brs, 3H), 1.43 (s, 9H), 1.61 (m, 2H), 1.80 (m, 2H), 2.89 (m, 2H), 3.20 (brs, 2H), 3.40 (m, 1H), 3.53 (brs, 2H), 4.11 (brs, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.94 (d, J = 8.0 Hz, 2H).

4-(α-Hydroxy-α-(4-*N*-*tert*-butoxycarbonylpiperidinyl)-α-(1-naphthyl)methyl)-*N*,*N*-diethylbenzamide (7d). To a solution of 1-bromonaphthalene (0.52 g, 2.5 mmol) in dry THF (10 mL) was added *n*-butyllithium (1.1 mL, 2.5 M, 2.75 mmol) at −78 °C. After 30 min, **10d** (776 mg, 2.0 mmol) in THF (2 mL) was dropwise added. The reaction mixture was warmed to room temperature, quenched with aqueous NH_4Cl solution, and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by flash chromatography eluting with MeOH−CH_2Cl_2 (0.5:99.5 → 5:95) to provide **7d** (760 mg, 74%): mp 121−124 °C (CH_2Cl_2); IR (KBr) 3402, 1685, 1626 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03 (brs, 3H), 1.16 (brs, 3H), 1.18−1.35 (m, 3H), 1.95 (m, 1H), 2.60 (m, 2H), 2.75 (brs, 2H), 3.15 (brs, 2H), 3.42 (brs, 2H), 4.10 (brs, 2H), 7.10−7.50 (m, 7H), 7.75 (m, 3H), 8.27 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 12.8, 14.1, 27.1, 27.2, 28.4, 39.2, 43.3, 45.4, 79.3, 80.4, 124.1, 124.9, 125.2, 125.3, 126.0, 127.3, 128.8, 129.2, 131.4, 135.0, 135.2, 139.4, 146.5, 154.6, 171.0. Anal. ($C_{32}H_{40}N_2O_4$·0.5H_2O) C, H, N.

***N*,*N*-Diethyl-4-[(*N*-*tert*-butoxycarbonylpiperidin-4-yl)-3-fluorophenylhydroxymethyl]benzamide (7e).** Method as for **7d** using 3-bromofluorobenzene provided **7e** (262 mg, 27%): ^{1}H NMR ($CDCl_3$) δ 1.03 (br, 3 H, C*H*$_3$CH$_2$N-), 1.15 (br, 3 H, C*H*$_3$CH$_2$N-), 1.19−1.29 (m, 4 H, piperidine C*H*-), 1.35 (s, 9 H, C*H*$_3$C), 2.39 (m, 1 H, piperidine C*H*-), 2.59 (br, 2 H, piperidine C*H*-), 3.17 (br, 2 H, CH$_3$C*H*$_2$N-), 3.28 (s, 1 H, O*H*), 3.45 (br, 2 H, CH$_3$C*H*$_2$N-), 4.02 (br, 2 H, piperidine C*H*-), 6.80 (m, 1 H, Ar*H*), 7.15 (m, 3 H, Ar*H*), 7.18 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.39 (d, J = 8.0 Hz, 2 H, Ar*H*).

***N*,*N*-Diethyl-4-[(*N*-*tert*-butoxycarbonylpiperidin-4-yl)-3-methoxyphenylhydroxymethyl]benzamide (7f).** Method as for **7d** using 3-bromoanisole provided **7f** (228 mg, 23%): mp 95−103 °C (CH_2Cl_2); IR (NaCl) 3422, 1684, 1614 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.07 (br, 3 H, C*H*$_3$CH$_2$N-), 1.19 (br, 3 H, C*H*$_3$CH$_2$N-), 1.31 (m, 4 H, piperidine C*H*-), 1.41 (s, 9 H, C*H*$_3$C), 2.46 (m, 1 H, piperidine C*H*-), 2.64 (br, 2 H, piperidine C*H*-), 3.22 (br, 2 H, CH$_3$C*H*$_2$N-), 3.49 (br, 2 H, CH$_3$C*H*$_2$N-), 3.65 (s, 1 H, O*H*), 3.72 (s, 3 H, OC*H*$_3$), 4.06 (br, 2 H, piperidine C*H*-), 6.69 (m, 1 H, Ar*H*), 7.01 (d, J = 7.6 Hz, 1 H, Ar*H*), 7.08 (s, 1 H, Ar*H*), 7.17 (d, J = 8.0 Hz, 1 H, Ar*H*), 7.21 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.48 (d, J = 8.0 Hz, 2 H, Ar*H*). Anal. ($C_{29}H_{40}N_2O_5$·0.6H_2O) C, H, N.

4-(α-Hydroxy-α-(4-*N*-*tert*-butoxycarbonylpiperidinyl)-2,6-dimethylbenzyl)-*N*,*N*-diethylbenzamide (7g). Method as described for **7d**, but using 2-bromo-*m*-xylene led to **7g** (752 mg, 76%): mp 92−96 °C (CH_2Cl_2); IR (KBr) 3451, 1690, 1631 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (brs, 3H), 1.21 (brs, 3H), 1.32 (m, 2H), 1.43 (s, 9H), 1.69 (m, 1H), 1.77 (m, 1H), 2.32 (s, 6H), 2.47 (s, 1H), 2.75 (m, 3H), 3.25 (brs, 2H), 3.51 (brs, 2H), 4.13 (brs, 2H), 6.91 (m, 2H), 7.00 (m, 1H), 7.26 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.6, 14.0, 25.0, 27.7, 28.2, 39.1, 42.9, 43.1, 44.4, 53.3, 79.1, 83.0, 125.8, 126.3, 127.2, 131.2, 135.3, 136.7, 142.9, 147.8, 154.5, 170.7. Anal. ($C_{30}H_{42}N_2O_4$·0.5H_2O) C, H, N.

***N*,*N*-Diethyl-4-(1-naphthylpiperidin-4-ylidenemethyl)-benzamide (6d).** Method as described for **6a**, but starting with **7d** (517 mg, 1.0 mmol) led to **6d** (283 mg, 71%): mp 80−85 °C (CH_2Cl_2); IR (KBr) 1628 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.06 (brs, 3H), 1.16 (brs, 3H), 2.00 (m, 2H), 2.53 (m, 2H), 2.64 (brs, NH), 2.77 (m, 2H), 2.97 (m, 2H), 3.20 (brs, 2H), 3.47 (brs, 2H), 7.26 (m, 5H), 7.43 (m, 3H), 7.74 (m, 2H), 8.0 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 12.8, 14.1, 32.6, 33.5, 39.1, 43.2, 47.9, 48.2, 125.5, 125.7, 125.8, 126.1, 127.1, 127.2, 129.1, 131.9, 132.5, 133.8, 135.1, 138.3, 139.8, 142.6, 171.1. Anal. ($C_{27}H_{30}N_2O$·0.4HCl) C, H, N.

***N*,*N*-Diethyl-4-(3-fluorophenylpiperidin-4-ylidenemethyl)benzamide (6e).** Method as described for **6a**, but starting with **7e** (242 mg, 0.5 mmol) led to **6e** (159 mg, 87%): ^{1}H NMR ($CDCl_3$) δ 1.08 (br, 3 H, C*H*$_3$CH$_2$N-), 1.19 (br, 3 H, C*H*$_3$CH$_2$N-), 2.09 (s, 1 H, N*H*), 2.25 (m, 4 H, piperidine C*H*-), 2.84 (br, 4 H, piperidine C*H*-), 3.23 (br, 2 H, CH$_3$C*H*$_2$N-), 3.47 (br, 2 H, CH$_3$C*H*$_2$N-), 6.74 (m, 1 H, Ar*H*), 6.86 (m, 2 H, Ar*H*), 7.06 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.18 (m, 1 H, Ar*H*), 7.24 (d, J = 8.0 Hz, 2 H, Ar*H*). HCl salt: mp ≥ 70 °C dec; IR (NaCl) 1605 cm^{-1}. Anal. ($C_{23}H_{27}FN_2O$·2.2HCl) C, H, N.

***N*,*N*-Diethyl-4-(3-methoxyphenylpiperidin-4-ylidenemethyl)benzamide (6f).** Method as described for **6a**, but starting with **7f** (199 mg, 0.4 mmol) led to **6f**[18] (148 mg, 98%). Anal. ($C_{24}H_{30}N_2O_2$·1.8HCl) C, H, N.

***N*,*N*-Diethyl-4-(2,6-dimethylphenylpiperidin-4-ylidenemethyl)benzamide (6 g).** Method as described for **6a**, but starting with **7g** (495 mg, 1.0 mmol) led to **6g** (301 mg, 80%): ^{1}H NMR ($CDCl_3$) δ 1.10 (brs, 3H), 1.21 (brs, 3H), 2.08 (m, 4H), 2.21 (s, 6H), 2.84 (m, 2H), 3.00 (m, 2H), 3.20 (brs, 1H), 3.25 (brs, 2H), 3.46 (brs, 2H), 6.94 (m, 1H), 7.00 (m, 2H), 7.04 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H). HCl salt: dec ≥ 115 °C (CH_2Cl_2); IR (KBr) 1590 cm^{-1}. Anal. ($C_{25}H_{32}N_2O$·2.2HCl) C, H, N.

4-(4-Methoxycarbonylbenzylidene)piperidine-1-carboxylic Acid *tert*-Butyl Ester (15). A mixture of **13** (11.2 g, 49 mmol) and trimethyl phosphite (25 mL) was refluxed under N_2 for 5 h. Excess trimethyl phosphite was removed by codistillation with toluene to give **14** in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 3.20 (d, 2H, J = 22 Hz), 3.68 (d, 3H, 10.8 Hz), 3.78 (d, 3H, 11.2 Hz), 3.91 (s, 3H), 7.38 (m, 2H), 8.00 (d, 2H, J = 8 Hz).

To a solution of the above product (**14**) in dry THF (200 mL) was added dropwise lithium diisopropylamide (32.7 mL 1.5 M in hexanes, 49 mmol) at −78 °C. The reaction mixture was then allowed to warm to room temperature prior to addition of *N*-*tert*-butoxycarbonyl-4-piperidone (9.76 g, 49 mmol in 100 mL dry THF). After 12 h, the reaction mixture was quenched with water (300 mL) and extracted with ethyl acetate (3 × 300 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to give a crude product, which was purified by flash chromatography (0−33% ethyl acetate in hexanes) to provide **15** as a white solid (5.64 g, 35%): IR (NaC1) 1718, 1688, 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 1H), 2.31 (t, J = 5.5 Hz, 2H), 2.42 (t, J = 5.5 Hz, 2H), 3.37 (t, J = 5.5 Hz, 2H), 3.48 (t, J = 5.5 Hz, 2H), 3.87 (s, 3H), 6.33 (s, 1H), 7.20 (d J = 6.7 Hz, 2H), 7.94 (d, J = 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.3, 29.2, 36.19, 51.9, 123.7, 127.8, 128.7, 129.4, 140.5, 142.1, 154.6, 166.8. Anal. ($C_{19}H_{25}NO_4$) C, H, N.

4-Bromo-4-[bromo(4-methoxycarbonylphenyl)methyl]-piperidine-1-carboxylic Acid *tert*-Butyl Ester (16). To a mixture of **15** (5.2 g, 16 mmol) and K_2CO_3 (1.0 g) in dry dichloromethane (200 mL) was added a solution of bromine (2.9 g, 18 mmol) in 30 mL CH_2Cl_2 at 0 °C. after 1.5 h at room temperature, the solution after filtration of K_2CO_3 was concentrated. The residue was then dissolved in ethyl acetate (200 mL), washed with water (200 mL), 0.5 M HC1 (200 mL) and brine (200 mL), and dried over $MgSO_4$. Removal of solvents provided a crude product, which was recrystallized from methanol to give **16** as a white solid (6.07 g, 78%): IR (NaC1) 1725, 1669 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9H), 1.75 (m, 2H), 1.90 (m, 2H), 2.1 (m, 4H), 3.08 (br, 4H), 3.90 (s, 3H), 4.08 (br, 4H), 5.14 (s, 1H), 7.57 (d, J = 8.4 Hz, 2H) 7.98 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.3, 36.6, 38.3, 40.3, 52.1, 63.2, 72.9, 129.0, 130.3, 130.4, 141.9, 154.4, 166.3. Anal. ($C_{19}H_{25}Br_2NO_4$) C, H, N.

4-[Bromo(4-carboxyphenyl)methylene]piperidine-1-carboxylic Acid *tert*-Butyl Ester (17). A solution of **16** (5.4 g 11 mmol) in methanol (300 mL) and 2.0 M NaOH (100 mL) was heated at 40 °C for 3 h. The solid was collected by filtration and dried overnight under vacuum. The dry salt was dissolved in 40% acetonitrile/water and was adjusted to pH 2 using concentrated HCl. The desired product (**17**; 3.8 g, 87%) was isolated as a white powder by filtration: ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 2.22 (dd, J = 5.5 Hz, 6.1 Hz, 2H), 2.64 (dd, J =

5.5 Hz, 6.1 Hz, 2H), 3.34 (dd, J = 5.5 Hz, 6.1 Hz, 2H), 3.54 (dd, J = 5.5 Hz, 6.1 Hz, 2H), 7.35 (d, J = 6.7 Hz, 2H), 8.08 (d, J = 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.3, 31.5, 34.2, 44.0, 115.3, 128.7, 129.4, 130.2, 137.7, 145.2, 154.6, 170.3. Anal. ($C_{18}H_{22}BrNO_4$) C, H, N.

4-[Bromo(4-diethylcarbamoylphenyl)methylene]piperidine-1-carboxylic Acid *tert*-Butyl Ester (8). To a solution of **17** (1.0 g, 2.5 mmol) in dry dichloromethane (10 mL) at −20 °C was added isobutyl chloroformate (450 mg, 3.3 mmol). After 20 min at −20 °C diethylamine (4 mL) was added and the reaction was allowed to warm to room temperature. After 1.5 h the solvents were evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with brine and dried over $MgSO_4$. Removal of solvents provided a crude product, which was purified by flash chromatography (0−60% ethyl acetate in heptanes) to give **8** as white needles (800 mg, 73%): ^{1}H NMR ($CDCl_3$) δ 1.13 (br, 3H), 1.22 (br, 3H), 1.44 (s, 9H), 2.22 (t, J = 5.5 Hz, 2H), 2.62 (t, J = 5.5 Hz, 2H), 3.31 (t, J = 5.5 Hz, 2H), 3.52 (t, J = 5.5 Hz, 2H), 7.27 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.71, 14.13, 28.3, 31.5, 34.2, 39.1, 43.2, 79.7, 115.9, 126.3, 129.3, 136.8, 137.1, 140.6, 154.6, 170.5. Anal. ($C_{22}H_{31}BrN_2O_3$) C, H, N.

***N,N*-Diethyl-4-[piperidin-4-ylidene(3-trifluoromethylphenyl)methyl]benzamide (6h).** A mixture of **8** (500 mg, 1.1 mmol), 3-trifluoromethylphenylboronic acid (500 mg, 2.6 mmol), 2 M Na_2CO_3 (3 mL), and tetrakis(triphenylphosphine)-palladium(0) (20 mg) in toluene (degassed, 5 mL) and ethanol (degassed, 5 mL) was refluxed at 85 °C for 5 h under N_2. The reaction mixture was then cooled to room temperature and extracted with ethyl acetate (2 × 100 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to give a crude product (**18a**).

The above product (**18a**) was treated with 4.0 M HC1 in dioxane at room temperature for 2 h. After evaporation, the residue was dissolved in 1 M HCl (100 mL) and impurities were extracted with diethyl ether (3 × 100 mL). The aqueous phase was basified with NH_4OH and extracted with dichloromethane (3 × 100 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and evaporated to give **6h** (291 mg, 64%): ^{1}H NMR ($CDCl_3$) δ 1.13 (brm, 3 H, C*H*$_3$-CH_2-), 1.22 (brm, 3 H, C*H*$_3$CH$_2$-), 1.96 (s, 1 H, NH), 2.28 (m, 2 H, piperidine C*H*-), 2.33 (m, 2 H, piperidine C*H*-), 2.92 (m, 4 H, piperidine C*H*-), 3.29 (brm, 2 H, CH_3CH_2N-), 3.54 (brm, 2 H, CH_3CH_2N-), 7.13 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.28−7.48 (m, 6 H, Ar*H*). HCl salt: mp > 85 °C dec; IR (NaCl) 3409, 1620 cm^{-1}. Anal. ($C_{24}H_{27}F_3N_2O$·1.3HCl) C, H, N.

***N,N*-Diethyl-4-(3,4-dichlorophenylpiperidin-4-ylidenemethyl)benzamide (6i).** Method as for **6h** using **8** (600 mg, 1.3 mmol) and 3,4-dichlorophenylboronic acid (500 mg, 2.6 mmol) provided **6i** (437 mg, 79%): ^{1}H NMR ($CDCl_3$) δ 1.12 (br, 3H), 1.20 (br, 3H), 2.28 (t, J = 5.6 Hz, 4H), 2.89 (m, 4H), 3.27 (br, 2H), 3.52 (br, 2H), 6.8−7.4 (m, 7H). Anal. ($C_{23}H_{26}$-Cl_2N_2O·1.5HCl) C, H, N.

***N,N*-Diethyl-4-(3-acetylphenylpiperidin-4-ylidenemethyl)benzamide (6j).** Method as for **6h** using **8** (500 mg, 1.1 mmol) and 3-acetylphenylboronic acid (500 mg, 3.0 mmol) provided **6j** (401 mg, 93%): ^{1}H NMR ($CDCl_3$) δ 1.11 (br, 3H), 1.20 (br, 3H), 2.06 (brs, 1H), 2.28 (m, 2H), 2.34 (m, 2H), 2.55 (s, 3H), 2.92 (m, 4H), 3.26 (br, 2H), 3.51 (br, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 7.2 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.74 (s, 1H), 7.81 (d, J = 7.2 Hz, 1H). Anal. ($C_{25}H_{30}N_2O_2$·1.8HCl) C, H, N.

***N,N*-Diethyl-4-(3-nitrophenylpiperidin-4-ylidenemethyl)benzamide (6k).** Method as for **6h** but using 3-nitrophenylboronic acid provided **6k** in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.11 (br, 3H), 1.21 (br, 3H), 2.27−2.34 (m, 4H), 2.92 (t, J = 6.0 Hz, 4H), 3.26 (br, 2H), 3.52 (br, 2H), 7.10 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.40−7.50 (m, 2H), 7.95−8.08 (m, 2H). Anal. ($C_{23}H_{27}N_3O_3$·1.4HCl) C, H, N.

***N,N*-Diethyl-4-(2-fluorophenylpiperidin-4-ylidenemethyl)benzamide (6l).** Method as for **6h** but using 2-fluorophenylboronic acid provided **6l** in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.11 (br, 3H), 1.15 (br, 3H), 2.10 (t, J = 5.2 Hz, 2H), 2.27 (t, J = 5.2 Hz, 2H), 2.83(m, 4H), 3.20 (br, 2H), 3.45 (br, 2H), 6.94−7.03 (m, 3H), 7.10−7.23 (m, 5H). Anal. ($C_{23}H_{27}FN_2O$·1.5HCl) C, H, N.

***N,N*-Diethyl-4-(2-thiophenylpiperidin-4-ylidenemethyl)benzamide (6m).** Method as for **6h** but using 2-thiophenylboronic acid provided **6m** in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.12 (br, 3H), 1.20 (br, 3H), 2.24 (t, J = 5.2 Hz, 2H), 2.50 (t, J = 5.2 Hz, 2H), 2.85 (t, J = 5.6 Hz, 2H), 2.92 (t, J = 5.6 Hz, 2H), 3.27 (br, 2H), 3.51 (br, 2H), 6.75 (d, J = 3.6 Hz, 1H), 6.93 (t, J = 3.6 Hz, 1H), 7.16 (d, J = 7.2 Hz, 2H), 7.21 (d, J = 3.6 Hz, 1H), 7.30 (d, J = 7.2 Hz, 2H). Anal. ($C_{21}H_{26}N_2OS$·1.5HCl) C, H, N.

***N,N*-Diethyl-4-(4-methylthiophenylpiperidin-4-ylidenemethyl)benzamide (6n).** Method as for **6h** but using 4-methylthiophenylboronic acid provided **6n** in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.11 (br, 3H), 1.20 (br, 3H), 2.32−2.75 (m, 4H), 2.45 (s, 3H), 2.90−2.87 (m, 4H), 3.26 (br, 2H), 3.51 (br, 2H), 7.01 (d, J = 6.0 Hz, 2H), 7,10 (d, J = 6.0 Hz, 2H), 7.15 (d, J = 6.8 Hz, 2H), 7.27 (d, J = 6.8 Hz, 2H). Anal. ($C_{24}H_{30}N_2OS$·2.5HCl) C, H, N.

***N,N*-Diethyl-4-(3-aminophenylpiperidin-4-ylidenemethyl)benzamide (6o).** Method as for **6h** but using 3-aminophenylboronic acid provided **6o** in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.11 (br, 3H), 1.20 (br, 3H), 2.27−2.33 (m, 4H), 2.86−2.90 (m, 4H), 3.27 (br, 2H), 3.51 (br, 2H), 3.57 (br, 2H), 3.68 (s, 1H), 6.39 (s, 1H), 6.52 (dd, J = 1.6 Hz, J = 7.6 Hz, 2H), 7.06 (t, J = 8.0 Hz, 1H), 7.12 (d, J = 6.4 Hz, 2H), 7.26 (d, J = 6.4 Hz, 2H). Anal. ($C_{23}H_{29}N_3O$·1.2HCl) C, H, N.

***N,N*-Diethyl-4-(4-methoxyphenylpiperidin-4-ylidenemethyl)benzamide (6p).** Method as for **6h** but using 4-methoxyphenylboronic acid provided **6p** in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.12 (br, 3H), 1.19 (br, 3H), 2.29 (m, 4H), 2.87 (m, 4H), 3.27 (br, 2H), 3.51 (br, 2H), 3.77 (s, 3H), 6.80 (m, 2H), 7.00 (m, 2H), 7.10 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz). Anal. ($C_{24}H_{30}N_2O_2$·1.95HCl) C, H, N.

***N,N*-Diethyl-4-(2-methoxyphenylpiperidin-4-ylidenemethyl)benzamide (6q).** Method as for **6h** but using 2-methoxyphenylboronic acid provided **6q** in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.09 (br, 3H), 1.18 (br, 3H), 2.10 (q, J = 4.8 Hz, 2H), 2.31 (q, J = 4.8 Hz, 2H), 2.8−2.9 (m, 4H), 3.25 (br, 2H), 3.50 (br, 2H), 3.68 (s, 3H), 6.83−6.90 (m, 2H), 7.0 (d, 1H), 7.15−7.25 (m, 5H). Anal. ($C_{24}H_{30}N_2O_2$·1.5HCl) C, H, N.

***N,N*-Diethyl-4-[(1-methylpiperidin-4-ylidene)phenylmethyl]benzamide (19a).** *N,N*-Diethyl-4-[(piperidin-4-ylidene)phenylmethyl]benzamide (**6a**; 0.35 g, 1.0 mmol) was dissolved in acetonitrile (5 mL). Potassium carbonate (0.14 g, 1.0 mmol) and methyl iodide (63 μL, 1.0 mmol) were added with stirring at 25 °C. After 30 min, the reaction mixture was evaporated and put onto silica gel for purification by chromatography using 0 to 10% MeOH (10% NH_4OH) in CH_2Cl_2 to give 48 mg of the final product (28% of converted starting material), which was converted to the hydrochloride salt by treatment with HCl in ether: ^{1}H NMR ($CDCl_3$) δ 1.1 (m, 6H, amide-Me), 2.40 (s, 3H, MeN), 2.49, 2.60 (2m, 8H, piperazine-H), 3.40 (m, 4H, amide-CH_2) 7.08−7.34 (m, 9H, Ar−H). HCl salt: mp ≥ 110 °C dec; IR (KBr) 1695 cm^{-1}. Anal. ($C_{24}H_{30}N_2O$·3.2HCl) C, H, N.

***N,N*-Diethyl-4-(phenyl-*N*-allylpiperidin-4-ylidenemethyl)benzamide (19b).** Method as described for compound **19a**, using allyl bromide as the alkylating reagent provided **19b** (86%): ^{1}H NMR ($CDCl_3$) δ 1.12 (brs, 3H), 1.21 (brs, 3H), 2.43 (m, 4H), 2.55 (m, 4H), 3.08 (d, J = 6.8 Hz, 2H), 3.25 (brs, 2H), 3.53 (brs, 2H), 5.18 (m, 2H), 5.86 (m, 1H), 7.12 (m, 4H), 7.20 (m, 1H), 7.27 (m, 4H). HCl salt: mp 85−95 °C (CH_2Cl_2); IR (KBr) 1624 cm^{-1}. Anal. ($C_{26}H_{32}N_2O$·1.6HCl) C, H, N.

***N,N*-Diethyl-4-[*N*-(3-methyl-2-butenyl)phenylpiperidin-4-ylidenemethyl]benzamide (19c).** Method as described for compound **19a**, using 1-bromo-3-methyl-2-butene as the alkylating reagent provided **19c** (71%): ^{1}H NMR ($CDCl_3$) δ 1.10−1.30 (br, 6 H, OCNCH$_2$C*H*$_3$), 1.64 (s, 3 H, =CC*H*$_3$), 1.73 (s, 3 H, =CC*H*$_3$), 2.40 (m, 4 H, NC*H*$_2$CH$_2$), 2.52 (m, 4 H, =CC*H*$_2$), 3.0 (d, J = 7.6 Hz, 2 H, NC*H*$_2$CH=C), 3.20−3.60 (br, 4 H,

OCNCH_2CH$_3$), 5.28 (m, 1 H, NCH$_2$CH=C), 7.16−7.45(m, 9 H, Ar). HCl salt: IR (NaCl) 1623 cm^{-1}. Anal. ($C_{28}H_{36}N_2O$·1.8HCl) C, H, N.

***N,N*-Diethyl-4-(*N*-butylphenylpiperidin-4-ylidenemethyl)benzamide (19d).** Method as described for compound **19a**, using 1-iodobutane as the alkylating reagent provided **19d** (85%): ^{1}H NMR (CDCl$_3$) δ 0.92 (t, J = 7.2 Hz, 3 H, CH$_2$CH_3), 1.10−1.26 (br, 6 H, OCNCH$_2$CH_3), 1.32 (m, 2 H, CH_2CH$_3$), 1.53 (m, 2 H, CH$_2$CH_2CH$_2$), 2.42 (m, 6 H, NCH_2), 2.55 (m, 4 H, =CCH$_2$), 3.20−3.60 (br, 4 H, OCNCH_2CH$_3$), 7.10−7.31 (m, 9 H, Ar). HCl salt: IR (NaCl) 1622 cm^{-1}. Anal. ($C_{27}H_{36}N_2O$·1.9HCl) C, H, N.

***N,N*-Diethyl-4-(1-cyclopropylmethylphenylpiperidin-4-ylidenemethyl)benzamide (19e).** Method as described for compound **19a**, using compound **6** and cyclopropylmethyl chloride provided **19e** (86%): ^{1}H NMR (CDCl$_3$) δ 0.20 (m, 2H), 0.59 (m, 2H), 1.04 (m, 1H), 1.14 (brs, 3H), 1.24 (brs, 3H), 2.48 (d, J = 6.4 Hz, 2H), 2.56 (brs, 4H), 2.80 (brs, 4H), 3.29 (brs, 2H), 3.53 (brs, 2H), 7.14 (m, 4H), 7.22 (m, 1H), 7.27 (m, 4H); ^{13}C NMR (CDCl$_3$) δ 4.18, 7.3, 12.8, 14.1, 30.3, 39.2, 43.2, 54.3, 62.7, 126.2, 126.6, 128.0, 129.5, 129.6, 134.1, 135.3, 136.3, 141.5, 142.9, 171.0. HCl salt: dec ≥ 100 °C (CH$_2$Cl$_2$); IR (KBr) 1620 cm^{-1}. Anal. ($C_{27}H_{34}N_2O$·2.3HCl) C, H, N.

4-[(1-Cyclohexylpiperidin-4-ylidene)phenylmethyl]-*N,N*-diethylbenzamide (19f). A mixture of **6a** (100 mg, 0.29 mmol), cyclohexanone (36 ul, 0.35 mmol) and Ti(OPr-*i*)$_4$ (0.17 mL, 0.58 mmol) was ultrasonicated for 1 h and then stirred at room temperature overnight under a nitrogen atmosphere. The mixture was diluted with ethanol (5 mL) followed by addition of NaBH$_4$ (33 mg, 0.87 mmol). The resulting mixture was stirred for 12 h at room temperature. 2 N NH$_3$·H$_2$O was added to quench the reaction and the mixture filtered through Celite. The filtrate was extracted with ethyl acetate several times and the combined organic phases were washed with water and brine and dried over Na$_2$SO$_4$. Concentration in vacuo and MPLC purification (0:100 to 100:0 EtOAc:heptane eluting on silca gel 60) gave the title compound **11f** (24 mg, 20%): ^{1}H NMR (CDCl$_3$) δ 1.00−1.25 (m, 19H), 1.60 (m, 1H), 1.75 (1H, m), 1.80 (m, 1H), 2.30 (m, 3H), 2.60 (m, 2H), 3.20 (bs, 2H), 3.50 (bs, 2H), 7.00−7.30 (m, 9H); ^{13}C NMR (CDCl$_3$) δ 12.7, 14.1, 25.9, 28.7, 32.0, 39.1, 43.2, 50.7, 50.8, 63.6, 126.0, 126.3, 127.9, 129.7, 129.8, 134.7, 134.9, 136.9, 142.0, 143.4, 171.2; mp (HCl salt) 105−109 °C. Anal. ($C_{29}H_{38}N_2O$·2.0HCl) C, H, N.

4-[(1-Phenylpiperidin-4-ylidene)phenylmethyl]-*N,N*-diethylbenzamide (19g). A mixture of **6a** (44 mg, 0.13 mmol), phenyl bromide (20 uL, 0.19 mmol), Pd(dba)$_2$ (1 mg, 0.0017 mmol), BINAP (2.5 mg, 0.004 mmol) and sodium *tert*-butoxide (20 mg, 0.20 mmol) in 2 mL toluene was heated at 80−90 °C for 12 h, under a nitrogen atmosphere. The solvent was removed in vacuo and the residue purified by MPLC (0 to 100% of EtOAc in heptane on silica gel) to give the desired title compound **19g** (30 mg, 56%): ^{1}H NMR (CDCl$_3$) δ 1.0−1.4 (m, 6H), 2.45 (m, 4H), 3.1−3.7 (m, 8H), 6.8−7.5 (m, 14H); ^{13}C NMR (CDCl$_3$) δ 12.77, 13.97, 31.29, 39.10, 43.21, 51.03, 116.23, 119.21, 126.12, 126.49, 127.98, 128.98, 129.66, 129.72, 135.13, 135.63, 135.73, 141.81, 143.15, 151.00, 171.09; IR (HCl salt) 1616 cm^{-1}. Anal. ($C_{29}H_{32}N_2O$·1.7HCl) C, H, N.

Biological Assays. 1. Cell Culture and Membrane Preparation. Human HEK-293S cells were subject to stable transfection with cDNA encoding the human μ, δ, and κ receptors. Clones were chosen for high receptor expression and grown in suspension culture. Cells were harvested and P2 membrane preparations were produced.

2. Receptor Binding Assays. Membranes were combined with test compounds and approximately 0.07 nM of the appropriate radioligand [^{125}I][D-Ala^2]deltorphin II (K_d = 0.93 nM at δ), [^{125}I]FK33824 (K_d = 1.14 nM at μ), and [^{125}I]-D-Pro^{10}-dynorphin A[1−11] (K_d = 0.16 nM at κ) in 50 mM Tris, 3 mM MgCl$_2$, 1 mg/mL BSA, pH 7.4. The amounts of bound radioactivity were determined at equilibrium by filtration. The nonspecific (NS) binding was defined in the presence of 10 μM naloxone. The IC$_{50}$ values of test compounds were determined from 2-parameter logistic curve fits of percent specific binding vs log(molar ligand), solving for IC$_{50}$ and Hill slope.

3. GTP[γ-^{35}S] Binding Assays. Membranes expressing 10 pmol of hDOR/mg protein were combined with test compounds and approximately 0.2 nM GTP[γ-^{35}S] in 50 mM Hepes, 20 mM NaOH, pH 7.4, 5 mM MgCl$_2$, 100 mM NaCl, 1 mM EDTA, 1 mM DTT, 0.1% BSA, 15 μM GDP. The bound radioactivity was determined after 1 h by filtration. Control and stimulated binding were determined in the absence and presence of 3 μM SNC-80, respectively. Values of EC$_{50}$ and E_{max} for ligands were obtained from 3-parameter logistic curve fits of percent stimulated GTP[γ-^{35}S] binding vs log(molar ligand), solving for EC$_{50}$, Hill slope, and %E_{max}.

4. In Vitro Metabolic Studies. Incubation conditions: All incubations [rat liver microsomes (0.4 mg/mL proteins; Xenotech LLC, Kansas City, KS), substrate at 10 or 100 nmol/L, 1 mM NADPH, 100 mM phosphate buffer at pH 7.4] were performed in duplicate in disposable 96-well plates on a gently shaking platform maintained at 37 °C. Control incubations were carried out by incubating the same substrate concentrations in phosphate buffer without rat liver microsomes or NADPH. The final assay volume was 500 μL, containing 1% DMSO (test article stock solutions were prepared at 10 mM in DMSO).

Incubations were started by the addition of NADPH (or buffer for NADPH-free controls) and were stopped after 0 and 60 min by the addition of 500 μL of ice-cold acetonitrile. The precipitated proteins were removed following a 10-min centrifugation at 8500*g* and the supernatants were analyzed for parent drug by a benchtop LC−MSD system.

Analytical conditions: Aliquots (5 μL) of the supernatants were directly injected onto a Zorbax Eclipse XDB C18 column (4.6 × 30 mm, 3.5-μm particles) using a micro plate sampler (HP220, Hewlett-Packard, Kirkland, Quebec, Canada). The mobile phase consisted of a mixture of acetonitrile, methanol and 0.04% formic acid in water (60−80:0−15:15−30, v/v). The flow rate was 1.0 mL/min. The LC system (HP1100, Hewlett-Packard) was equipped with a quaternary pump (Hewlett-Packard) and linked to a mass selective detector (MSD) with an electrospray interface (Hewlett-Packard). The MSD was operated in selected ion monitoring mode (the selected m/z being that of the parent compound). Nebulizer pressure was 60 psi, while the drying gas (nitrogen) was delivered at 13 L/min. The capillary voltage was 3500 V, and the fragmentor (collision-induced dissociation cell) was set at 70 eV.

5. Results (parent drug disappearance from the incubation medium). The parent drug peak area in the 0-min incubation sample was considered to be the 100% value, and parent drug levels were expressed as percent (%) parent remaining.

6. Molecular Modeling Studies. Models of compound **6a** and SNC-80 were constructed with standard parameters in Sybyl 6.2 (Tripos Inc., 1699 South Hanley Rd., St. Louis, MO 63144) using a SGI workstation (Indigo 2). The random conformational search and energy minimization were performed using the Tripos force field. An energy window of 5 kcal/mol ($E_i - E_{min}$) was used to collect low-energy conformers. The rotatable bonds with an interval of 30° were further used to classify the low-energy conformers. There were 12 different conformers for **6a** and 159 for SNC-80. The representative conformers were then compared between the two compounds. The superposition of the conformers was carried out with the piperazine ring (for SNC-80) or piperidine ring (for **6a**) and the right-hand phenyl rings. The superposition of X-ray structures of **6a** and SNC-80 was carried out between five points: the two nitrogen atoms of the piperazine ring, the centroid points of the two phenyl rings, and the carbon atom of the carbonyl group.

References

(1) Hughes, J.; Smith, T. W.; Kosterlitz, H. W.; Fothergill, L. A.; Morgan, B. A.; Morris, H. R. Identification of two Related Peptides From The Brain With Potent Opitae Agonistic Activity. *Nature* **1975**, *258*, 577−579.

(2) Hollt, V. Multiple Endogenous Opioid Peptides. *Trends Neurosci.* **1983**, *16*, 24−26.
(3) Maurer, R.; Cortes, R.; Probst, A.; Palacios, J. Mutiple Opiate Receptors in Human Brain: An Autoradiographic Investigation. *Life Sci.* **1983**, *33*, 231−234.
(4) Millan, M. Multiple Opioid Systems and Pain. *Pain* **1986**, *27*, 303−347.
(5) Porreca, F.; Mosberg, H. I.; Hurst, R.; Hruby, V. J.; Burks, T. F. A comparison of the analgesic and gastrointestinal transit effects of [D-Pen2,L-Cys5]enkephalin after intracerebroventricular and intrathecal administration to mice. *Life Sci.* **1983**, *33*, 457−460.
(6) Galligan, J. J.; Mosberg, H. I.; Hurst, R.; Hruby, V. J.; Burks, T. F. Cerebral delta opioid receptors mediate analgesia but not the intestinal motility effects of intracerebroventricularly administered opioids. *J. Pharmacol. Exp. Ther.* **1984**, *229*, 641−648.
(7) Cowan, A.; Zhu, X. Z.; Mosberg, H. I.; Omnaas, J. R.; Porreca, F. Direct dependence studies in rats with agents selective for different types of opioid receptor. *J. Pharmacol. Exp. Ther.* **1988**, *246*, 950−955.
(8) Sheldon, R. J.; Riviere, P. J. M.; Malarchik, M. E.; Mosberg, H. I.; Burks, T. F.; Porreca, F. Opioid regulation of mucosal ion transport in the mouse isolated jejunum. *J. Pharmacol. Exp. Ther.* **1990**, *253*, 144−151.
(9) Rapaka, R. S.; Porreca, F. Development of delta opioid peptides as nonaddicting analgesics. *Pharm. Res.* **1991**, *8*, 1−8.
(10) Cheng, P. Y.; Wu, D.; Decena, J.; Soong, Y.; McCabe, S.; Szeto, H. H. Opioid-induced stimulation of fetal respiratory activity by [D-Ala2]deltorphin I. *Eur. J. Pharmacol.* **1993**, *230*, 85−88.
(11) Chang, K. J.; Rigdon, G. C.; Howard, J. L.; McNutt, R. W. A Novel, Potent and Selective Non-peptide Delta-receptor Agonist BW373U86. *J. Pharmacol. Exp. Ther.* **1993**, *267*, 852−857.
(12) Nagase, H.; Wakita, H.; Kawai, K.; Endoh, H.; Matsura, H.; Tanaka, C.; Takezawa, Y. Synthesis of Nonpeptidic Delta Opioid Agonists and their Structure Activity Relationships. *Jpn. J. Pharmacol.* **1994**, *64* (Suppl. I), 35.
(13) Calderon, S. N.; Rothman, R. B.; Porreca, F.; Flippen-Anderson, J. L.; McNutt, R. W.; Xu, H.; Smith, L. E.; Bilsky, E. J.; Davis, P.; Rice, K. C. Probes for Narcotic Receptor Mediated Phenomena. 19. Synthesis of (+)-4-[(αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide (SNC-80): A Highly Selective, Nonpeptide δ Opioid receptor Agonist. *J. Med. Chem.* **1994**, *37*, 2125−2128.
(14) Plobeck, N.; Delorme, D.; Wei, Z. Y.; Yang, H.; Zhou, F.; Schwarz, P.; Gawell, L.; Gagnon, H.; Pelcman, B.; Schmidt, R.; Yue, S. Y.; Walpole, C.; Brown, W.; Zhou, E.; Labarre, M.; Payza, K.; St-Onge, S.; Kamassah, A.; Morin, P.-E.; Projean, D.; Ducharme, J.; Roberts, E. New Diarylmethylpiperazines as Potent and Selective Nonpeptidic δ Opioid Receptor Agonists with Increased in Vitro Metabolic Stability. *J. Med. Chem.* **2000**, *43*, 3878−3894.
(15) Roberts, E.; Plobeck, N.; Wahlestedt, C. Preparation of N-diarylmethylpiperazines as Analgesics. International Patent Application WO 97/23466, 1997.
(16) Calderon, S. N.; Rice, K. C.; Rothman, R. B.; Porreca, F.; Flippen-Anderson, J. L.; kayakiri, H..; Xu, H.; Becketts, K.; Smith, L. E.; Bilsky, E. J.; Davis, P.; Horwath, R. Probes for Narcotic Receptor Mediated Phenomena. 23. Synthesis, Opioid Receptor Binding, and Bioassay of the Highly Selective δ Agonist of (+)-4-[(αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide (SNC-80) and Related Novel Nonpeptide δ Opioid Receptor Ligands. *J. Med. Chem.* **1997**, *40*, 695−704.
(17) Katsura, Y.; Zhang, X.; Homma, K.; Rice, K. C.; Calderon, S. N.; Rothman, R. B.; Yamamura, H. I.; Davis, P.; Flippen-Anderson, J. L.; Xu, H.; Becketts, K.; Foltz, E. J.; Porreca, F. Probes for Narcotic Receptor Mediated Phenomena. 25. Synthesis and Evaluation of N-Alkyl-Substituted (α-Piperazinylbenzyl)-benzamides) as Novel, Highly Selective δ Opioid Receptor Agonists. *J. Med. Chem.* **1997**, *40*, 2936−2947.
(18) Zhang, X.; Rice, K. C.; Calderon, S. N.; Kayakiri, H.; Smith, L.; Coop, A.; Jacobson, A. E.; Rothman, R. B.; Davis, P.; Dersch, C. M.; and Porreca, F. Probes for Narcotic Receptor Mediated Phenomena. 26. Synthesis and Biological Evaluation of Diarylmethylpiperazines and Diarylmethylpiperidines as Novel, Nonpeptidic δ Opioid Receptor Ligands. *J. Med. Chem.* **1999**, *42*, 5455−5463.
(19) Cottney, J.; Rankovic, Z.; Morphy, J. R. Synthesis of Novel Analogues of the Delta Opioid Ligand SNC-80 Using Rem Resin. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1323−1328.
(20) Delorme, D.; Roberts, E.; Wei, Z. Y. Preparation of 4-[diaryl or Arylheteroaryl)methylene]piperidine Derivatives with Analgesic Effect. International Patent Application WO 98/28275, 1998.
(21) Christie, M. A.; Webb, R. L.; Tickner, A. M. Synthesis of Cyclohexylidenexanthenes via the Wittig−Horner Reaction. *J. Org. Chem.* **1982**, *47*, 2802−2804.
(22) Cid, M. M.; Seijas, J. A.; Villaverde, M. C.; Castedo, L. New Synthesis of Cyproheptadine and Related Compounds Using Low Valent Titanium. *Tetrahedron* **1988**, *44*, 6197−6200.
(23) 4-Iodo-*N*,*N*-diethylbenzamide was prepared in 92% yield by treatment of 4-iodobenzoyl chloride with 3 equiv of diethylamine in dichloromethane at 0 °C.
(24) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. An Improved Catalyst System for Aromatic Carbon−Nitrogen Bond Formation: The Possible Involvement of Bis(phosphine) Palladium Complexes as key Intermediates. *J. Am. Chem. Soc.* **1996**, *118*, 7215−7216.
(25) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and Computational Approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Delivery Rev.* **1997**, *23*, 3−25
(26) Dondio, G.; Ronzoni, S. Diaryldiamine derivatives and their use as delta opioid (ant)-agonists. International Patent Application WO 96/36620, 1996.
(27) Details to be published elsewhere.

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