New Diarylmethylpiperazines as Potent and Selective Nonpeptidic δ Opioid Receptor Agonists with Increased In Vitro Metabolic Stability

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Nonpeptide δ opioid agonists are analgesics with a potentially improved side-effect and abuse liability profile, compared to classical opioids. Andrews analysis of the NIH nonpeptide lead SNC-80 suggested the removal of substituents not predicted to contribute to binding. This approach led to a simplified lead, *N*,*N*-diethyl-4-[phenyl(1-piperazinyl)methyl]benzamide **(1)**, which retained potent binding affinity and selectivity to the human δ receptor (IC_{50} = 11 nM, μ/δ = 740, κ/δ > 900) and potency as a full agonist (EC_{50} = 36 nM) but had a markedly reduced molecular weight, only one chiral center, and increased in vitro metabolic stability. From this lead, the key pharmacophore groups for δ receptor affinity and activation were more clearly defined by SAR and mutagenesis studies. Further structural modifications on the basis of **1** confirmed the importance of the *N*,*N*-diethylbenzamide group and the piperazine lower basic nitrogen for δ binding, in agreement with mutagenesis data. A number of piperazine *N*-alkyl substituents were tolerated. In contrast, modifications of the phenyl group led to the discovery of a series of diarylmethylpiperazines exemplified by *N*,*N*-diethyl-4-[1-piperazinyl(8-quinolinyl)-methyl]benzamide (**56**) which had an improved in vitro binding profile (IC_{50} = 0.5 nM, μ/δ = 1239, EC_{50} = 3.6 nM) and increased in vitro metabolic stability compared to SNC-80.

Introduction

It is now well-established that three different types of opioid receptors exist in the central nervous system and that agonists of all receptor subtypes are known to produce antinociception. Morphine and morphine-like compounds are widely used clinically as analgesics. However, it is also known that they induce unwanted side effects such as respiratory depression, dependence, constipation, and euphoria. All of these side effects are primarily due to the fact that they are agonists at the μ receptor. Consequently the discovery of an opioid analgesic that acts at different opioid receptor subtypes may have the advantage of analgesia but without unwanted side effects. Studies based on δ-selective opioid peptide ligands have suggested potential advantages over other opioid receptors.[1] However the inherent inability for systemically administered peptides to be well-absorbed from the gastrointestinal tract and to cross the blood−brain barrier has encouraged various approaches to develop nonpeptide δ ligands.[2]

The discoveries of the nonpeptidic δ opioid agonist (±)-BW373U86[3] ((+)-isomer, SNC-86) and the more δ-selective methyl ether analogue SNC-80[4] were important developments, and SAR data around SNC-80 has continued to be published,[5] but these compounds and their close analogues have also been associated with side effects such as seizures[6] and poor distribution, metabolism, and pharmacokinetics (DMPK) attributes[7] which make them unsuitable as therapeutic agents.

The purpose of this study was to explore further the SAR around SNC-80 with the aim of finding new structures with improved pharmacological properties by eliminating sites of metabolism, removing centers of chirality, and lowering molecular weight while retaining high affinity and selectivity for the δ opioid receptor.[8] Here we discuss how structural simplification of SNC-80 first led to the lead compound **1** and was further optimized to a number of new potent δ agonists by modifications of the different parts of the molecule (Figure 1).[9] We present binding data for the racemic compounds against the cloned human δ, μ, and κ receptors and agonist potency as measured by the GTP-[γ-^{35}S] binding assay.

Chemistry

The synthetic pathways to the target compounds are outlined in Schemes 1−13. Synthesis of substituted piperazines **3** and **4** is described in Scheme 1. *N*-Boc-2-aminoisobutyric acid was coupled with D,L-alanine methyl ester using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC). *N*-Boc deprotection with trifluoroacetic acid (TFA) followed by heating in 2-butanol gave the diketopiperazine **2**. Reduction with lithium aluminum hydride (LAH) in THF gave the racemic piperazine **3**, which was selectively *N*-Boc-protected at the least sterically hindered nitrogen with Boc_2O in THF to give **4**. Compounds **1** and **10**−**16** where

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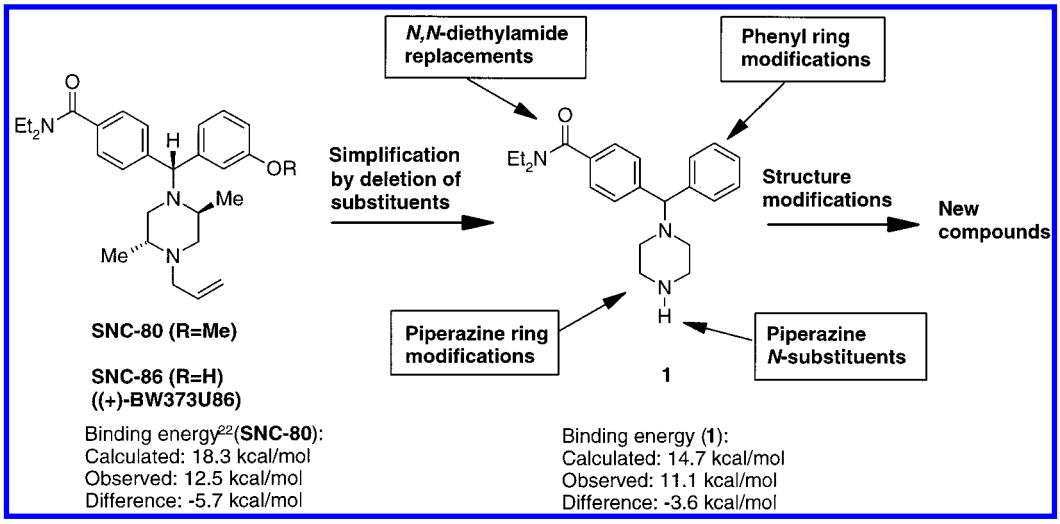
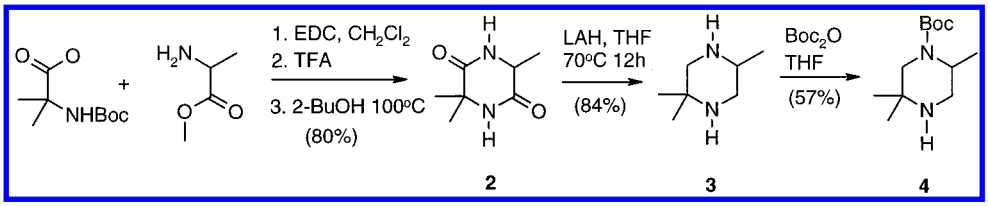
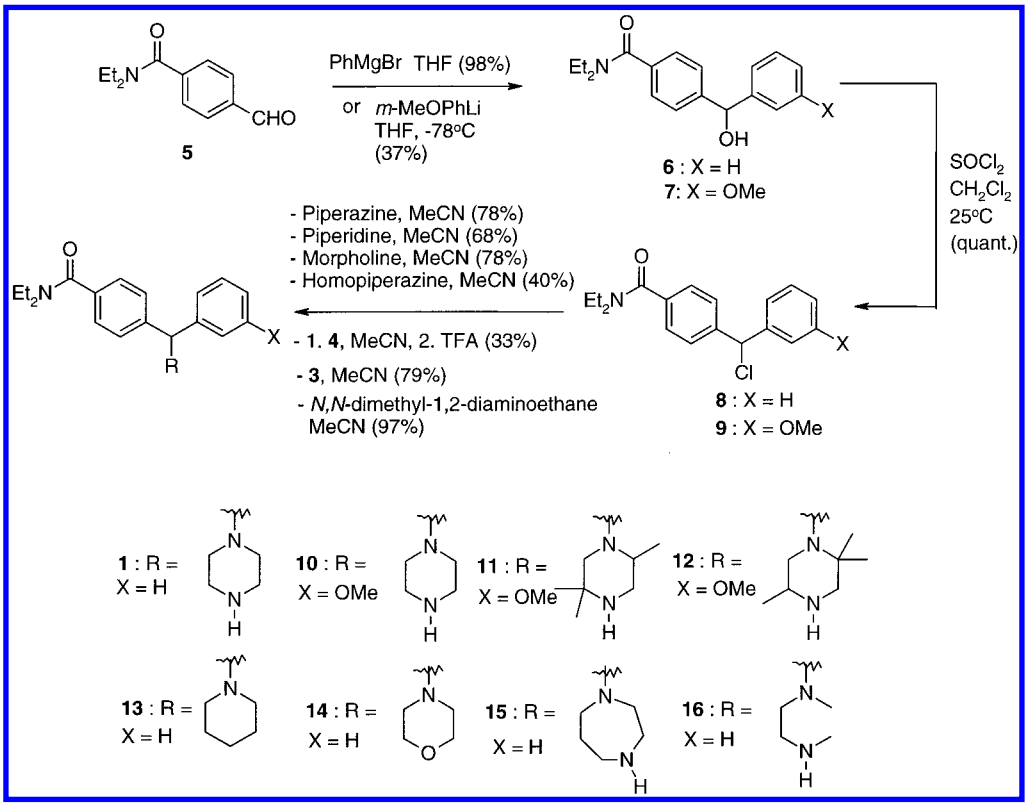


Figure 1. SAR strategy from SNC-80 and compound **1**.

Scheme 1. Synthesis of Piperazines **3** and **4**



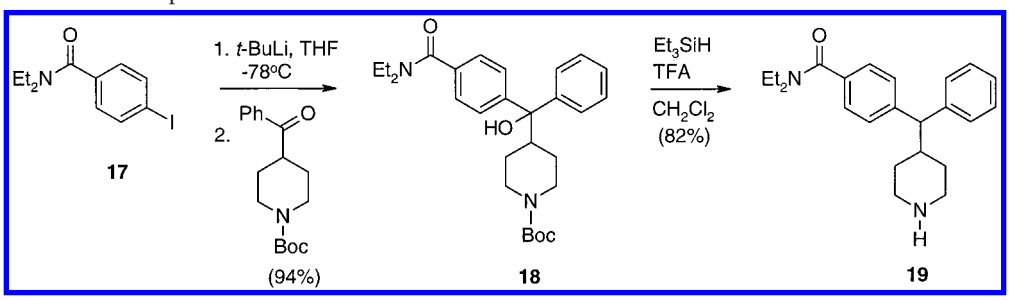
Scheme 2. Synthesis of Compounds **1** and **10**−**16**



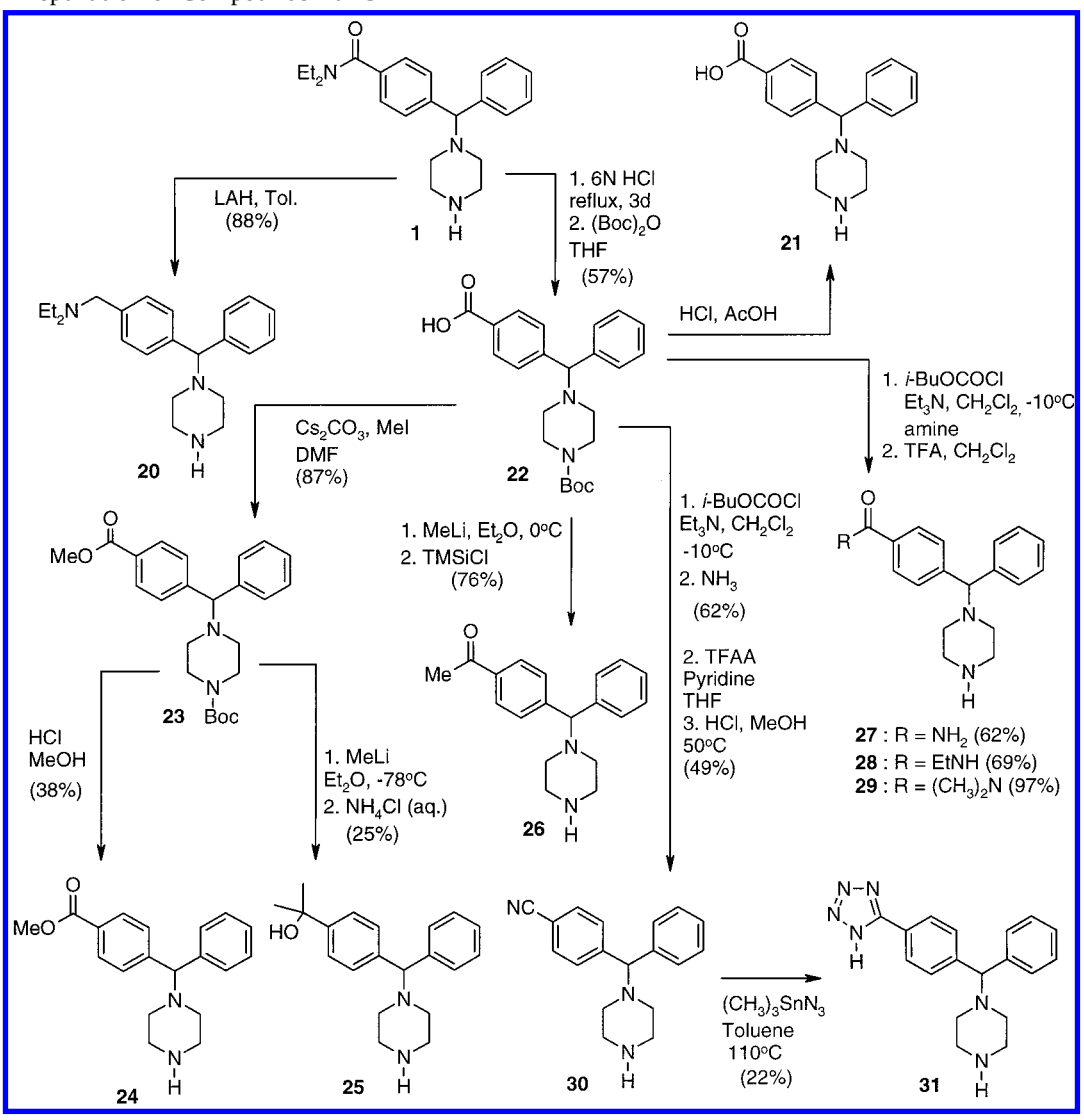
the piperazine ring has been replaced or altered were prepared as described in Scheme 2. Reaction between *N*,*N*-diethyl-4-formylbenzamide (**5**)[10] and phenylmagnesium bromide or reaction with *m*-methoxyphenyllithium gave compounds **6** and **7**, respectively. Compounds **6** and **7** were subsequently treated with thionyl chloride to give compounds **8** and **9**, respectively, which were directly treated with the corresponding amine in acetonitrile to give compounds **1**, **10**−**11**, and **13**−**16**. Reaction with piperazine **4** followed by *N*-Boc deprotection with TFA gave the compound **12**.

The carbon analogue **19** was obtained using the synthetic pathway described in Scheme 3. *N*,*N*-Diethyl-4-iodobenzamide (**17**)[11] was subjected to lithium−halogen exchange with *t*-BuLi in THF at low temperature followed by the addition of *N*-Boc-4-benzoylpiperidine

Scheme 3. Synthesis of Compound **19**



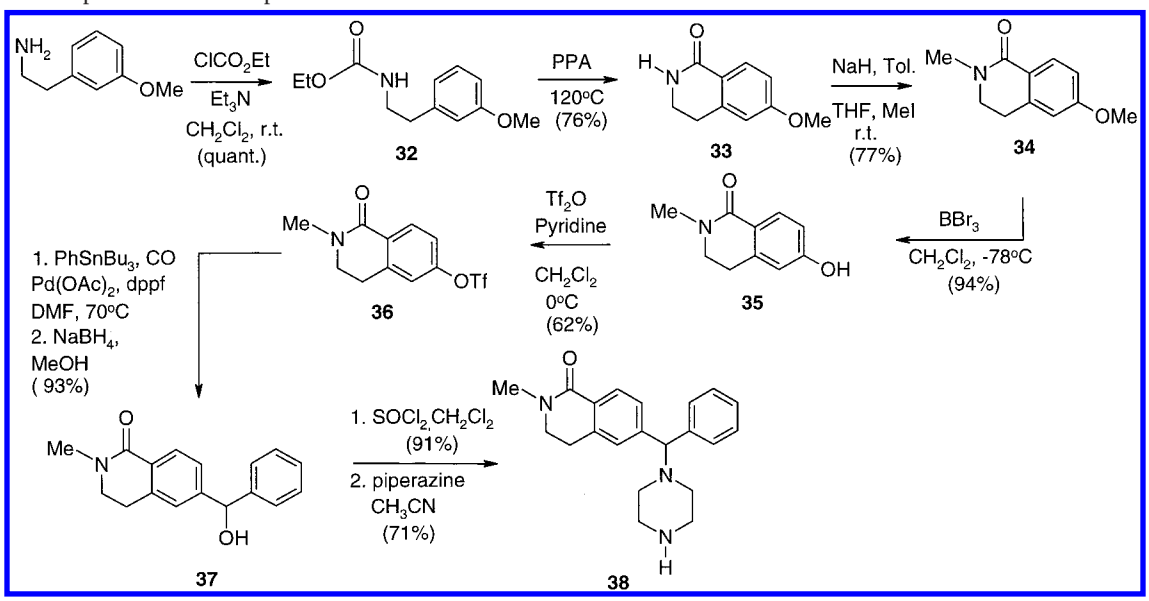
Scheme 4. Preparation of Compounds **20**−**31**



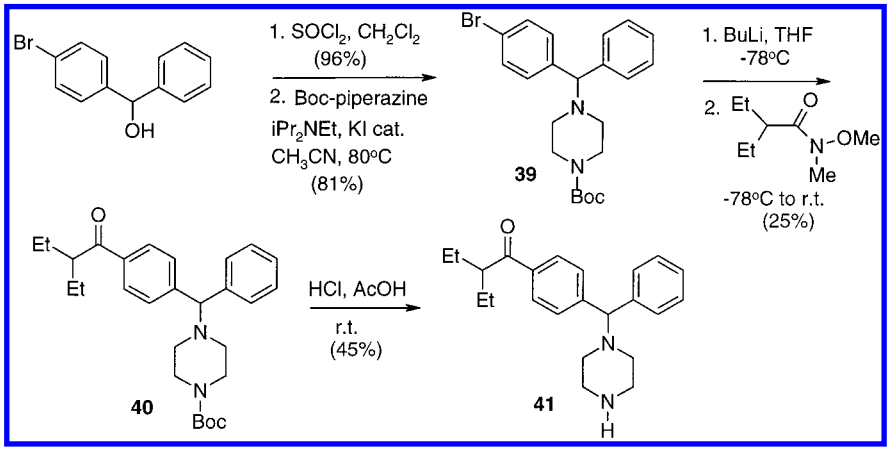
to furnish compound **18** in 94% yield. Reduction of the benzylic alcohol was effected using triethylsilane in methylene chloride in the presence of TFA[12] giving compound **19** in 82% yield.

Compounds where the *N*,*N*-diethylamide group had been replaced were prepared using the synthetic pathway described in Scheme 4. Reduction of the amide with lithium aluminum hydride in toluene gave the *N*,*N*-diethylaminomethyl compound **20**. The *N*-Boc-protected acid **22** was prepared from the *N*,*N*-diethylamide **1** by hydrolysis in refluxing 6 N hydrochloric acid followed by treatment with Boc_2O in THF and used as a general starting material for the preparation of different derivatives. The acid **21** was prepared by *N*-Boc cleavage with HCl in AcOH. Esterification of **22** with iodomethane in DMF in the presence of cesium carbonate gave the ester **23** and after *N*-Boc cleavage the methyl ester **24**. The tertiary alcohol **25** was prepared by addition of methyllithium to the methyl ester **23** which at the same time cleaved the *N*-Boc group. The methyl ketone **26** was obtained from **22** by treatment with excess methyllithium followed by trimethylsilyl chloride.[13] Different amides were prepared by the mixed anhydride method[14] by treatment with isobutyl chloroformate followed by the addition of the corresponding amine. *N*-Boc deprotection gave amides **27**−**29**. Conversion of **22** to the primary amide as for **27** followed by treatment with trifluoroacetic anhydride in THF in the presence of

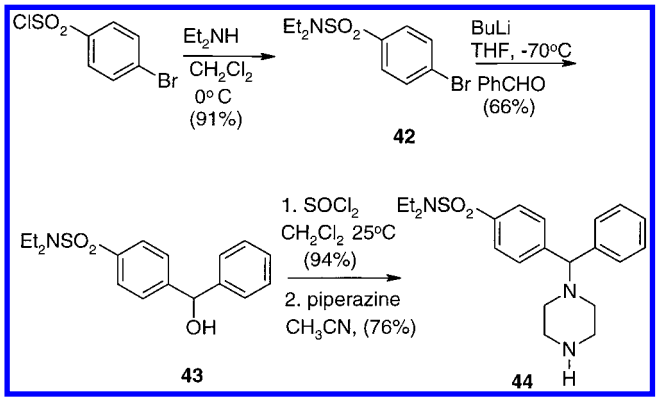
Scheme 5. Preparation of Compound **38**



Scheme 6. Preparation of Compound **41**



Scheme 7. Preparation of Compound **44**



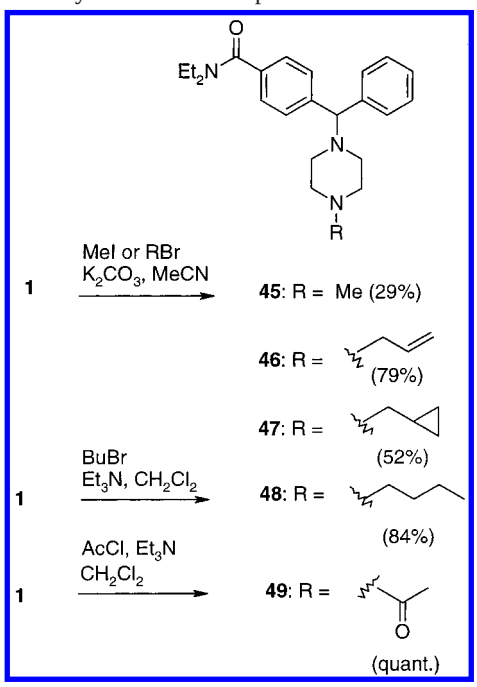
pyridine gave quantitatively the nitrile **30** where the Boc protecting group has also been cleaved. The tetrazole **31** was prepared by treating **30** with trimethyltin azide in refluxing toluene.[15]

The *N*-methyl-3,4-dihydroisoquinolone (**38**) was prepared using the synthetic pathway described in Scheme 5. 3-Methoxyphenethylamine was treated with ethyl chloroformate giving the corresponding carbamate **32** which was subsequently cyclized with polyphosphoric acid at 120 °C to give 6-methoxy-3,4-dihydroisoquinolone (**33**) in 76% yield. *N*-Methylation of **33** to give **34**, followed by *O*-demethylation with boron tribromide, gave in 72% yield the phenol **35**. The phenyl ring was introduced using arylcarbonylation[16] on the triflate **36**. Thus, treatment of **36** with phenyltributyltin in the presence of carbon monoxide and palladium acetate, bis-diphenylphosphinoferrocene as catalyst, in warm DMF gave after sodium borohydride reduction 93% yield of the benzylic alcohol **37**. Finally chlorination and reaction with piperazine gave **38** in 64% yield over two steps.

Ketone **41** was prepared following the synthetic route described in Scheme 6. (4-Bromophenyl)(phenyl)methanol was used as the starting material. Chlorination and substitution with *N*-Boc-piperazine in acetonitrile gave compound **39** in 78% yield for two steps. The ketone functionality was introduced by lithium−halogen exchange on **39** using *n*-BuLi in THF followed by addition of 2-ethyl-*N*-methoxy-*N*-methylbutanamide[17] to give the protected ketone **40** in 25% yield. *N*-Boc deprotection using HCl in acetic acid gave compound **41** in 45% yield.

The sulfonamide **44** was prepared using 4-bromobenzenesulfonyl chloride which upon treatment with diethylamine in methylene chloride gave compound **42** in 91% yield (Scheme 7). Lithium−halogen exchange with *n*-BuLi followed by addition of benzaldehyde furnished

Scheme 8. Synthesis of Compounds **45**−**49**



the benzylic alcohol **43** in 66% yield. Chlorination and reaction with piperazine gave the sulfonamide **44** in 76% yield.

Compounds **45**−**49** representing different *N*-alkyl groups of compound **1** have been prepared as depicted in Scheme 8. Compound **1** was treated with iodomethane or with different alkyl bromides in the presence of potassium carbonate or triethylamine in methylene chloride or acetonitrile at room temperature to produce compounds **45**−**48**. Finally, the *N*-acetyl compound **49** was obtained quantitatively by reaction with acetyl chloride in methylene chloride.

Variations of the phenyl ring were made following reaction sequences described in Scheme 9. Addition of **5** to either Grignard reagents or aryllithium compounds from metal−halogen exchange between the aryl bromide and BuLi at low temperature in THF furnished the corresponding benzylic alcohols in 14−72% yield. The standard transformations of chlorination and reaction with piperazine then gave compounds **50**−**57**.

Quinolyl analogues **58**−**60** were prepared by a similar synthetic approach utilizing the addition of the lithium compound derived from lithium−halogen exchange between **17** and *n*-BuLi in THF at −78 °C to different quinolinecarboxaldehydes (Scheme 10). The 4-quinolinecarboxaldehyde was commercially available, and the 6- and 7-quinolinecarboxaldehydes were obtained from the corresponding methylquinolines by oxidation with selenium dioxide. Chlorination and reaction with piperazine gave quinoline analogues **58**−**60** in good yields.

The 5-isoquinoline analogue **63** was obtained using the protocol described in Scheme 11. DIBAL reduction of 5-carbomethoxyisoquinoline in toluene at low temperature gave the aldehyde **61** in 51% yield. The aldehyde **61** was converted into the piperazine **63** via the alcohol **62** by the standard procedures.

The synthesis of the indole analogue **67** was effected using the protocol described in Scheme 12. 6-Formylindole (**64**) was made from 6-bromoindole[18] by deprotonation of indole with potassium hydride followed by lithium−halogen exchange with *t*-BuLi and quenching with DMF to give **64**.[19] Protection of the indole nitrogen by sulfonylation with phase-transfer catalysis[20] gave compound **65** in 54% yield. The standard transformations via the alcohol **66** gave the 6-indolyl analogue **67** in 51% overall yield. The *N*-phenylsulfonyl group was simultaneously cleaved during the reaction with piperazine.

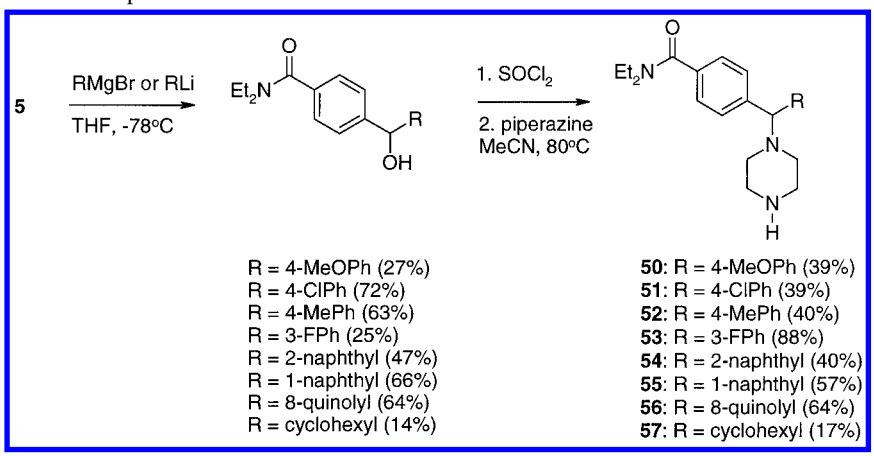
The 2,3-dihydro-2,2-dimethyl-7-benzofuranyl analogue **72** was synthesized starting from 2,3-dihydro-2,2-dimethyl-7-benzofuranol (Scheme 13). Preparation of the triflate **68** followed by palladium-catalyzed carbonylation[21] gave the methyl ester **69**. The ester was transformed to the aldehyde **70** by DIBAL reduction to the alcohol followed by pyridinium dichromate (PDC) oxidation. The standard transformations via the alcohol **71** led to **72** in 22% overall yield.

Results and Discussion

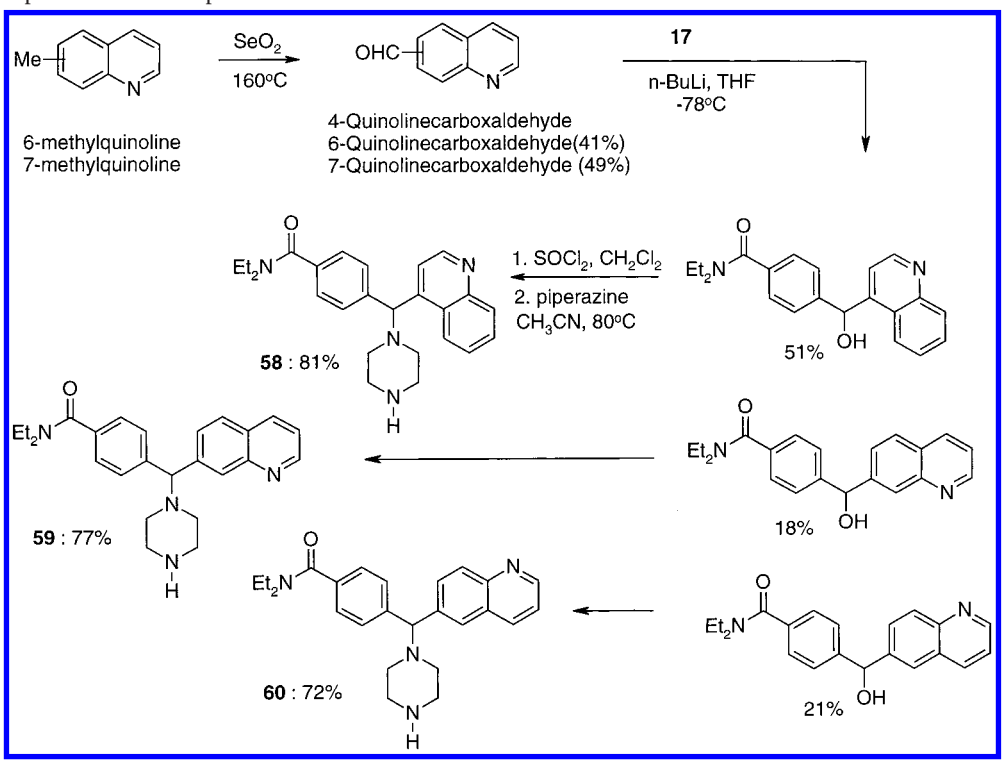
The pharmacological profile of the compounds was determined in radioligand binding studies. The binding affinities (IC_{50}) of the compounds against cloned human δ, μ, and κ receptors were determined. Agonist potency (EC_{50}) was measured using the GTP[γ-^{35}S] binding assay.

A calculation of the binding energy of SNC-80 by Andrews analysis[22] gave a significantly higher binding energy (ΔG_{calc}= 18.3 kcal/mol) compared to the experimental value (ΔG_{obs}= 12.5 kcal/mol). The large difference suggested that not all parts of SNC-80 were

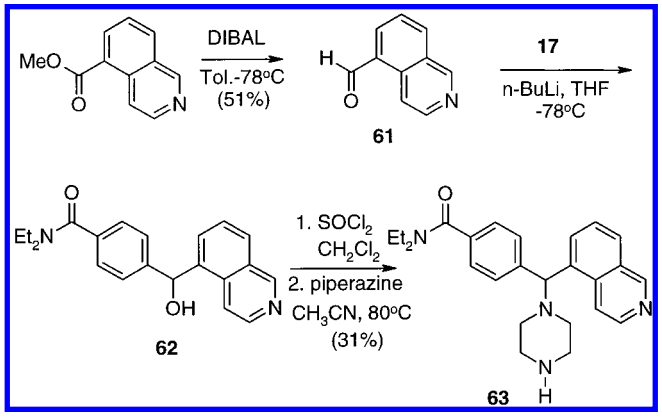
Scheme 9. Preparation of Compounds **50**−**57**



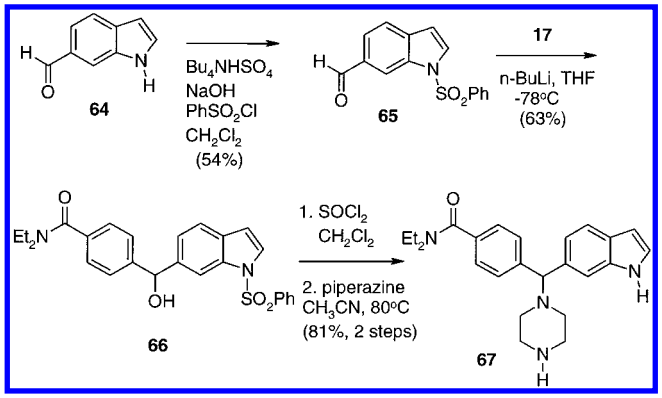
Scheme 10. Preparation of Compounds **58**–**60**



Scheme 11. Preparation of Compound **63**



Scheme 12. Preparation of Compound **67**



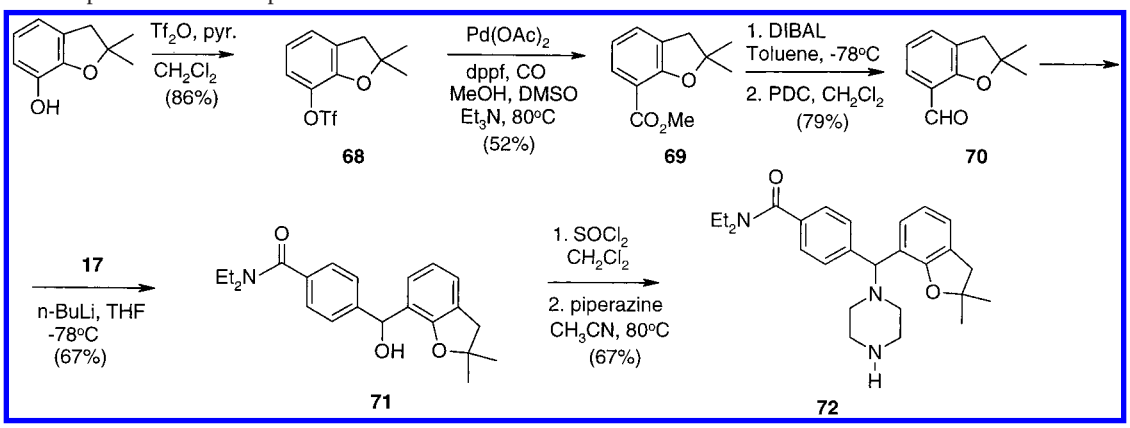
optimally involved in binding to the receptor (Figure 1). This indicated the possibility for deletions and alterations to the structure without a decrease in binding affinity.

Variations to the piperazine ring are shown in Table 1. Initially, the structure of SNC-80 was altered by changing the number of substituents in order to reduce the number of chiral centers and investigate the effects of steric bulkiness of the piperazine ring. It was found that the simple analogue **10** in which the *N*-allyl group and the piperazine methyl groups had been removed had the same selectivity as SNC-80 and retained significant binding affinity and agonist potency. On the other hand, an additional methyl group was found to be tolerated away from the benzylic carbon (**11**) with decreased selectivity for δ receptors over μ and κ receptors, but near the benzylic carbon (**12**) it led to much decreased selectivity and also to decreased affinity and lower δ agonist potency, indicating a less good fit into the receptor or that inappropriate conformational effects hinder proper alignment in the receptor.

Next, the structure was further simplified by replacing the aryl methoxy group by hydrogen to give the simplified piperazine **1** which retained strong δ binding affinity (IC_{50} = 11 nM), had improved selectivity (μ/δ = 700, κ/δ > 900), and was a full agonist (ED_{50} = 36 nM) at the human δ receptor. The approach of simplification of the structure of SNC-80 was independently taken also by others[5c,e] leading to **1**[5c] and closely related structures.

Compared with SNC-80, **1** had a reduced molecular weight from 450 to 350, two of the three chiral centers were removed, and several possible metabolic sites were eliminated. Indeed, **1** was found to be considerably more stable in rat liver microsomes. 60% of **1** remained after 1-h incubation at 10 μM compared to 1% for SNC-80. The same trend was observed at 100 μM concentration (Table 2). A radioactive analogue of SNC-80 has been shown to undergo rapid metabolism in vivo, and the main metabolite was identified as the *O*-demethylation product.[7] In vitro metabolic profiling of SNC-80 and SNC-86 (see separate section) showed that *O*-demethylation and *N*-deallylation were the major metabolic reactions. The increased stability of **1** could be explained by the absence of these two metabolic sites.

Scheme 13. Preparation of Compound **72**



Using Andrews analysis,[22] the difference between calculated binding energy and observed binding energy was found to be smaller for **1** (ΔG_{calc}= 14.7 kcal/mol, ΔG_{obs}= 11.1 kcal/mol, $\Delta\Delta G = -3.6$ kcal/mol) than for SNC-80 (ΔG_{calc}= 18.3 kcal/mol, ΔG_{obs}= 12.5 kcal/mol, $\Delta\Delta G = -5.7$ kcal/mol), indicating that the binding of **1** to the receptor was more optimized, compared to that for SNC-80 (Scheme 1). Compound **1**, containing only the most essential structural features for binding, was therefore taken as a new lead compound for further modifications to improve the pharmacological and DMPK profile.

The pharmacophore groups of **1** could be more clearly identified in comparison with SNC-80, and a binding model evolved with support from mutagenesis experiments[23] showing that amino acid residues of the third extracellular loop of the δ receptor were important for recognition and selectivity. The *N*,*N*-diethylamide carbonyl could interact by hydrogen bonding with a tryptophan side chain (W284) at one side of the extracellular loop, while at the other end the phenyl group could form a hydrophobic interaction with a leucine (L300) or valine (V296) side chain. Subsequently, the lower basic piperazine nitrogen could form an ionic bond with an aspartic acid (D128) within the transmembrane domain.

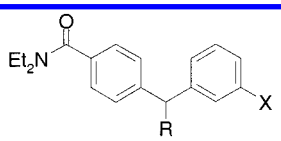
The effect of further changes to the piperazine moiety in **1** on biological activity was then investigated (Table 1). Similarly to the results by others in this and a closely related series,[5c,e] replacement of the lower piperazine ring nitrogen in **1** with carbon or oxygen (**13** and **14**)[5c] sharply reduced δ binding indicating the loss of an ionic interaction, as would be expected from the receptor model. The upper piperazine nitrogen could be replaced with carbon (**19**) with marginal effect on binding affinity compared to **1**, which showed that the upper basic piperazine nitrogen was not directly involved in ionic bonding to the receptor. However, **19** had 3 times lower potency as an agonist. The larger seven-membered ring analogue homopiperazine **15** had comparable binding affinity but was 10 times less potent as an agonist. The ring-opened analogue **16** showed a 5-fold decrease in binding affinity as would be predicted by the increase in conformational freedom.

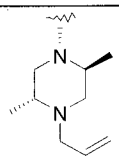
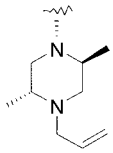
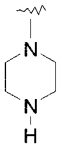
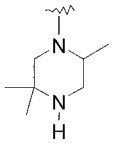
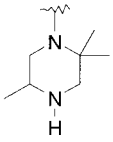
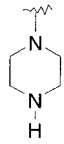
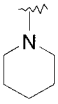
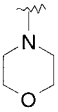
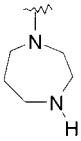
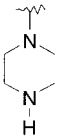
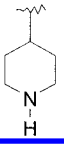
The importance of the *N*,*N*-diethylamide for binding, selectivity, and agonist activity in this series of compounds was confirmed by our attempts to find a replacement group. A number of *N*,*N*-diethylamide replacements and isosteres were made (Table 3) that complement binding data reported by others for a large number of substituted amides and amide replacements in related series.[3,5b,5d] Removal of the carbonyl (**20**) or replacement of the nitrogen (**41**) or one or two of the ethyl groups (**27**, **28**) all led to much decreased δ receptor affinity compared with **1**. The *N*,*N*-dimethylamide (**29**) had 6 times lower δ binding. Replacement of the amide with other functional groups such as the carboxylic acid (**21**), tetrazole (**31**), methyl ester (**24**), methyl ketone (**26**), tertiary alcohol (**25**), or nitrile (**30**) all led to a significant drop in affinity (>30-fold). Of the *N*,*N*-diethylamide replacements made, only the *N*,*N*-diethylsulfonamide (**44**) had comparable binding affinity and selectivity but was 20 times less potent as an agonist (Table 3). Torsional constraint to rotation of the amide bond as in **38** led to a large drop in affinity (>100-fold), indicating that the alignment of the amide bond out of the plane of the aromatic ring is necessary for efficient binding. The X-ray crystal structures published on two related compounds[5a,9] both show the *N*,*N*-diethylamide carbonyl group to be out of plane with the aromatic ring.

A series of lower alkyl substituents on the lower piperazine nitrogen were made (Table 4), and our results paralleled and complemented the results reported earlier for this series.[5c,e,f] The methyl derivative (**45**) had decreased agonist potency and was only a partial δ agonist. The allyl derivative (**46**) was comparable to **1** but showed slightly reduced selectivity, whereas the cyclopropyl (**47**) and butyl (**48**) congeners had much reduced selectivity (μ/δ = 68 and 17, respectively). On the other hand, the *N*-acetyl substituent (**49**) led to almost complete loss of binding affinity, again emphasizing the importance of the basicity of the lower piperazine nitrogen.

Significant improvements were made when modifications were done to the phenyl ring of **1**. The phenyl ring was replaced with a variety of substituted aryl and heteroaryl groups (Table 5). First, substitutions on the phenyl ring were explored. As discussed previously, the replacement of the 3-methoxy group (**10**) with hydrogen (**1**) was found to increase selectivity for δ over μ and to retain strong δ binding. Both electron-withdrawing and -donating groups were tolerated on the phenyl ring (**10**, **50**−**53**), but substitution in the 4-position tended to produce less potent agonists (**51, 52**). Replacement of the phenyl ring with a cyclohexyl ring (**57**) gave a sharp decrease in affinity and selectivity. Increasing the size

Table 1. Binding Affinity and Agonist Activity for Derivatives with Piperazine Ring Substitutions and Piperazine Ring Replacements[a]



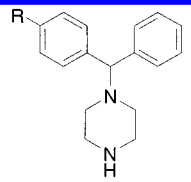
Compound	R	X	δ IC_{50} (nM)	μ IC_{50} (nM)	κ IC_{50} (nM)	μ/δ	δ EC_{50} (nM)	E_{max} (%)
SNC-80		OMe	1.31±0.17	320±58	2480±378	245	3.67±0.70	100±(ref)
SNC-86		OH	0.23±0.02	2.10±0.19	20.0±2.5	9	0.12±0.037	98±2
10		OMe	24.8±6.8	5290±469	>10000	213	42±4	109±7
11		OMe	8.44±0.98	620±105	>10000	73	10.4±1.1	100±4
12		OMe	53.3±9.3	284±29	>10000	5	273±50	94±1
1		H	11.3±2.3	8150±370	>10000	740	36.5±5.9	104±5
13		H	2230±100					
14		H	>10000					
15		H	19.6±1.7	2290±200	4530±310	116	303±9	96±3
16		H	91.6±15	6970±340	>10000	76		
19		H	8.76±0.89	>10000	>10000	>1000	121±15	97±3

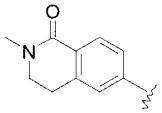
[a] Average of $n \geq 3$ determinations; > signifies $n = 2$ determinations.

Table 2. Metabolic Stability of Selected δ Agonists following a 1-h Incubation in Rat Liver Microsomes

	% compound remaining at	
agonist	10 μM	100 μM
SNC-80	1 ± 1 (n = 5)	24 ± 6 (n = 5)
SNC-86	4 (n = 2)	59 (n = 2)
1	60 ± 4 (n = 4)	89 ± 4 (n = 4)
56	52 ± 2 (n = 3)	83 ± 5 (n = 3)
72	43 ± 4 (n = 4)	93 ± 2 (n = 3)

Table 3. Binding Affinity and Agonist Activity for Derivatives with *N*,*N*-Diethylamide Replacements



Compound	R	δ	δ	
		IC_{50} (nM)	EC_{50} (nM)	E_{max} (%)
1	Et_2NOC-	11.3±2.3	36.5±5.9	104±5
20	Et_2NCH_2-	555±130		
21	HO_2C-	410±54		
24	MeO_2C-	307±43		
25	$HOC(Me)_2$-	406±80		
26	MeOC-	1045±63		
27	H_2NOC-	509±22		
28	EtNHOC-	175±4		
29	Me_2NOC-	60.4±1.5		
30	NC-	1294±138		
31		250±13		
38		1653±117		
41	Et_2CHOC-	100±20		
44	Et_2NSO_2-	37.8±4.2	635±63	110±2

of the aromatic group with the aim of increasing the hydrophobic interactions led to the 1-naphthyl (**54**) and 2-naphthyl (**55**) derivatives. Compound **55** had both improved binding affinity and agonist potency. Addition of a heteroatom to allow for a hydrogen bond acceptor atom as in SNC-80 led to the 8-quinolyl derivative (**56**) which had significantly higher binding affinity, improved selectivity, and 10-fold increased agonist potency (IC_{50} = 0.5 nM, μ/δ = 1239, ED_{50} = 3.6 nM). The 7-quinolyl isomer (**59**) was almost as potent, but the presence of a heteroatom in other positions as in the 4-quinolyl (**58**) and 6-quinolyl (**60**) had a strong negative effect on binding affinity. Other nitrogen heterocycle derivatives made were the isoquinoline (**63**) and indole (**67**) which also had higher binding affinity and were comparable in agonist potency to **1**. A heterocyclic derivative with an oxygen hydrogen bond acceptor was found to be the 2,2-dimethyl-2,3-dihydro-1-benzofuran-7-yl derivative (**72**) which gave a 10-fold increase in binding affinity and 5 times higher agonist potency compared to **1**. Compounds **56** and **72** showed in vitro metabolic stability in rat liver microsomes comparable to **1** and markedly superior to SNC-80 (Table 2 and Metabolic Profiling section).

Metabolic Profiling of SNC-80, SNC-86, and 56. The main metabolic pathways of SNC-80 in vitro, in rat liver microsomes, appeared to be *N*-deallylation (M − 40) and *O*-demethylation (M − 14) into SNC-86. Both routes of metabolism accounted for approximately 80% of SNC-80's microsomal metabolism in vitro. Under the same experimental conditions, SNC-86 was slightly more stable than SNC-80 (Table 2), being essentially metabolized by *N*-deallylation (M − 40), which accounted for approximately 85% of its in vitro metabolism. In vitro, **56** was significantly more stable than either SNC-80 or SNC-86. **56** was mostly metabolized by *N*-deethylation (M − 28), which represented 70% of its in vitro metabolism. Other metabolites included hydroxylated derivatives (M + 16).

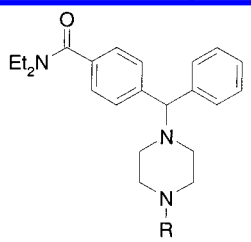
Conclusions

The results presented here complement and extend the scope of SAR studies around diarylmethylpiperazines of the SNC-80 type. The initial simplification of the structure of SNC-80 (Figure 1) by deletions of substituents led to the lead compound **1** with only the most essential pharmacophore groups remaining. In **1**, the number of chiral centers was decreased from three to one, and it had substantially reduced molecular weight. In addition, **1** had increased in vitro metabolic stability as predicted by the removal of metabolically labile sites such as the methyl ether. Further SAR studies were made on the basis of the lead compound **1** by modifications of the piperazine ring, replacements of the *N*,*N*-diethylamide group, introduction of piperazine *N*-alkyl substituents, and replacements of the phenyl ring. The result was the discovery of several new, more potent and selective δ receptor agonists. In particular, variations of the phenyl ring led to the more potent 1-naphthyl (**55**), 8-quinolyl (**56**), and 2,2-dimethyl-2,3-dihydro-1-benzofuran-7-yl (**72**) derivatives. The new compounds presented here are potentially useful as drugs and therefore represent a significant advance with respect to SNC-80. They have an improved in vitro profile, a simplified structure, and greater metabolic stability which, in the case of **56**, is manifest in good oral bioavailability (F = 33% in the rat) in contrast to SNC-80.[24]

Experimental Section

Materials and Methods. Purification by flash chromatography was done on silica gel 60 (70−230 mesh), eluting with gradients of EtOAc in heptane or MeOH (with 1% NH_4OH) in CH_2Cl_2. Revers-phase chromatography was done on LiChroprep RP-18 (40−63 μm) from EM Separations, eluting with

Table 4. Binding Affinity and Agonist Activity for Derivatives with *N*-Alkyl Substituents



Compound	R	δ IC$_{50}$ (nM)	μ IC$_{50}$ (nM)	κ IC$_{50}$ (nM)	μ/δ	δ EC$_{50}$ (nM)	E$_{max}$ (%)
1	H	11.3±2.3	8150±370	>10000	740	36.5±5.9	104±5
45	Me	40.4±5.7	>10000	6970±960	>247	211±42	58±7
46		15.9±3.6	5064±511	7574±648	318	33±8	109±3
47		35.3±6.0	2398±569	>5000	68		
48		28.6±6.1	486±77	>10000	17		
49	COMe	>2000					

gradient of acetonitrile in water each containing 0.1% TFA, followed by lyophilization. Melting points were recorded of the corresponding salt if not noted otherwise, on a Büchi 535 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus 400 MHz spectrometer. Spectra in $CDCl_3$ are of the free base and chemical shifts are given in ppm relative to TMS. In D_2O, chemical shifts are given relative to DSS. IR spectra were recorded of the corresponding salt if not noted otherwise, on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. MS spectra were obtained on a Hewlett-Packard G1800A GCD system. Dry solvents with molecular sieves were obtained from Fluka. Elemental analyses were made by Canadian Microanalytical Service Ltd., Delta, British Columbia, and were within ±0.4% of calculated values unless noted otherwise.

2,2,5-Trimethylpiperazine (3). *N*-(*tert*-Butoxycarbonyl)-2-methylalanine (5.0 g, 25 mmol) and d,L-alanine methyl ester hydrochloride (3.5 g, 25 mmol) were dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C. Et_3N (3.5 mL, 25 mmol) and then 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (4.8 g, 25 mmol) were added and the mixture was stirred at 0 °C until dissolved. The reaction mixture was then left in the freezer 4 days at −20 °C. The organic solution was washed with water, 1 M citric acid (aq), water, dried (Na_2SO_4) and evaporated in vacuo to give 6.0 g (83%) of coupling product. Most of the coupling product (5 g) was dissolved in formic acid (50 mL) and stirred 12 h at 25 °C. The acid was removed in vacuo and the residue dissolved in 2-butanol and heated at reflux for 4 h. The solution was cooled to 0 °C and the crystals filtered off and dried in vacuo at 100 °C. Yield 2.6 g of pure 3,3,6-trimethyl-2,5-piperazinedione **(2)** (82%). The product (2.2 g, 14 mmol) was dissolved in dry THF (120 mL). $LiAlH_4$ (42 mL, 1 M in THF) was added in portions. When addition complete, the solution was heated at reflux overnight. The solution was allowed to cool, then excess hydride was destroyed by dropwise addition of water (1.6 mL), NaOH (1.6 mL, 15% solution) and water (4.8 mL). The granular precipitate was filtered off and solvent evaporated in vacuo. The residue was dissolved in CH_2Cl_2, dried (K_2CO_3) and evaporation of solvent in vacuo gave 1.5 g of **3** (84%). Treatment with excess HCl in ether gave the dihydrochloride: mp >300 °C (MeOH/ether); IR (KBr, ν_{max}) 2760, 1570 cm^{-1}; MS 128, 113; ^{1}H NMR (2xHCl, D_2O+DSS) δ 0.94−1.00 (s+d, 6H), 1.14 (s, 3H), 2.50−2.70 (m, 5H). Anal. ($C_7H_{17}ClN_2$) C, H, N.

Procedure A: Grignard Reagent Addition to Aldehyde. *N,N*-Diethyl-4-[hydroxy(phenyl)methyl]benzamide (6). *N,N*-Diethyl-4-formylbenzamide (**5**)[10] (19.5 g, 95 mmol) was dissolved in dry THF, cooled to −78 °C under nitrogen. Phenylmagnesium bromide (104 mL, 1.0 M in THF) was added dropwise at −78 °C. After 1 h, NH_4Cl (aq) was added. The solvent was removed in vacuo, the residue dissolved in EtOAc/heptane, 1:1, washed with brine and dried ($MgSO_4$). Evaporation of solvent in vacuo gave 26.5 g of **6** (98%). Spectral data were identical with those reported.[5a]

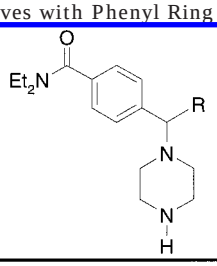
Procedure B: Organolithium Reagent Addition to Aldehyde. *N,N*-Diethyl-4-[hydroxy(3-methoxyphenyl)-methyl]benzamide (7). 3-Bromophenyl methyl ether (1.1 mL, 8.5 mmol) was dissolved in THF (25 mL) and cooled to −78 °C. *n*-BuLi (6.1 mL, 1.4 M in hexanes, 8.5 mmol) was added dropwise. After 30 min *N,N*-diethyl-4-formylbenzamide (1.7 g, 8.5 mmol) was added dissolved in THF (5 mL). The solution was stirred 1 h, then NH_4Cl (aq) was added. After aqueous workup and chromatography on silica (50−70% EtOAc in heptane) 1.0 g (37%) of **7** was obtained. Spectral data were identical with those reported.[5a]

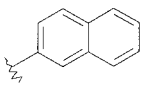
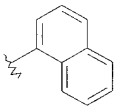
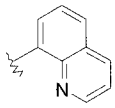
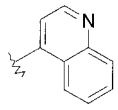
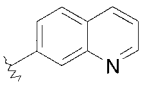
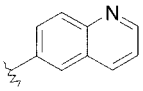
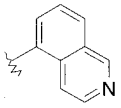
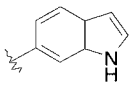
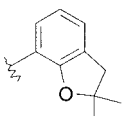
Procedure C: Chlorination of Benzylic Alcohols. 4-[Chloro(phenyl)methyl]-*N,N*-diethylbenzamide (8). Compound **6** (24.5 g, 93 mmol) was dissolved in dry CH_2Cl_2 (300 mL) and $SOCl_2$ (7.5 mL, 103 mmol) was added. The solution was stirred at 25 °C for 1 h and the solvent was evaporated in vacuo. Compound **8** was obtained as an oil (~100%) and used in the next reaction without further purification. Spectral data were identical with those reported.[5a]

4-[Chloro(3-methoxyphenyl)methyl]-*N,N*-diethylbenzamide (9) was prepared analogously to **8** and spectral data were identical with those reported.[5a]

Procedure D: Reaction of Benzylic Chlorides with Piperazines. *N,N*-Diethyl-4-[phenyl(1-piperazinyl)methyl]benzamide (1). Compound **8** (28 g, 93 mmol) and piperazine (40 g, 0.46 mol) were dissolved in dry MeCN (200 mL) and heated at reflux 12 h. The solvent was removed in vacuo, the residue dissolved in CH_2Cl_2 and washed with 1 M NaOH

Table 5. Binding Affinity and Agonist Activity for Derivatives with Phenyl Ring Replacements



Compound	R	δ	μ	κ	μ/δ	δ	
		IC_{50} (nM)	IC_{50} (nM)	IC_{50} (nM)		EC_{50} (nM)	E_{max}(%)
1	Ph-	11.3±2.3	8150±370	>10000	740	36.5±5.9	104±5
10	3-MeO-Ph-	24.8±6.9	5290±469	>10000	213	42±4	109±7
50	4-MeO-Ph-	8.13±1.63	4538±1192	>10000	558	187±17	90±2
51	4-Cl-Ph-	19.3±4.1	5330±476	>10000	276	113±37	107±3
52	4-Me-Ph-	8.42±1.53	7092±314	>10000	842	78.1±10.5	84±4
53	3-F-Ph-	4.50±0.75	5647±580	>10000	1254	53.3±5.0	97±4
54		7.63±1.89	2677±157	>10000	350	50±12	110±3
55		2.36±0.26	777±66	4906±1489	329	18±2	99±2
56		0.51±0.05	632±142	7017±802	1239	3.60±0.24	104±2
57		98.4±11.0	185±14	724±131	1.9		
58		132±17					
59		1.10±0.28	1016±131	3160±379	923	6.86±2.19	100±1
60		61.6±7.9					
63		4.11±0.44	1477±80	>10000	359	54.6±11.6	106±4
67		6.81±0.57	2222±186	3967±220	326	44.9±12.2	105±2
72		1.15±0.12	785±82	>7600	682	7.10±1.05	101±4

and the organic phase dried (K_2CO_3) and evaporated in vacuo. The crude product was recrystallized from MeCN to give 26 g of **1** (78%). The dihydrochloride salt was prepared with HCl in ether or with HCl (aq) followed by lyophilization: mp 157−69 °C; IR (KBr, ν_{max}) (free amine) 3690, 3630, 1613, 1435, 1265 cm^{-1}; MS 351, 306, 295, 266, 194, 165; ^1H NMR ($CDCl_3$) δ 1.1, 1.2 (2 brs, 6H), 1.94 (brs, 1H), 2.36 (brs, 4H), 2.89 (m, 4H), 3.2, 3.5 (2 brs, 4H), 4.24 (s, 1H), 7.16−7.46 (m, 9H). Anal. ($C_{22}H_{31}Cl_2N_3O$) C, H, N.

***N,N*-Diethyl-4-[(3-methoxyphenyl)(1-piperazinyl)-methyl]benzamide (10).** Procedure D. Compound **9** was reacted with piperazine to give **10**. Dihydrochloride made with HCl in ether: mp 165−82 °C; IR (KBr, ν_{max}) (free amine) 3688, 1611, 1458, 1436, 1285 cm^{-1}; MS 381, 336, 296, 224, 196, 165, 152, 112; ^1H NMR ($CDCl_3$) δ 1.05, 1.15 (2 brs, 6H), 2.51, 3.02 (2 brs, 8H), 3.2, 3.45 (2 brs, 4H), 3.72, 3.73 (2s, 3H), 4.21 (s, 1H), 4.5 (brs, 1H), 6.60−7.40 (m, 8H). Anal. ($C_{23}H_{33}Cl_2N_3O$) C, H, N.

***N,N*-Diethyl-4-[(3-methoxyphenyl)(2,5,5-trimethyl-1-piperazinyl)methyl]benzamide (11).** Compound **9** (0.61 g, 2.0 mmol) and **3** (0.50 g, 3.9 mmol) were dissolved in dry MeCN (5 mL). K_2CO_3 (0.26 g, 2.0 mmol) was added and the mixture heated at reflux for 48 h. The solvent was removed in vacuo and the residue purified by chromatography on silica (CH_2Cl_2/MeOH/NH_3 (aq), 98:1:1 to 95:5:1) to yield 0.65 g of **11** (79%). Treatment with excess of HCl in ether, filtering and drying crystals in vacuo over KOH gave the dihydrochloride: mp 134−6 °C; IR (KBr, ν_{max}) 3400, 2900, 1600, 1283, 1038 cm^{-1}; MS 423, 353, 325, 296, 127; ^1H NMR ($CDCl_3$) δ 0.9−1.3 (m, 15H), 2.0−3.1 (m, 5H), 3.2, 3.4 (2 brs, 4H), 3.70 (s, 3H), 4.61, 5.25, 5.26 (3s, 1H), 6.60−7.40 (m, 8H). Anal. ($C_{26}H_{39}Cl_2N_3O_2$) C, H, N.

***N,N*-Diethyl-4-[(3-methoxyphenyl)(2,2,5-trimethyl-1-piperazinyl)methyl]benzamide (12).** Compound **3** (42 mg, 0.33 mmol) and K_2CO_3 (46 mg, 0.33 mmol) were dissolved in water (2 mL) and di-*tert*-butyl dicarbonate (79 mg, 0.36 mmol) was added. After stirring 1 h the solvent was evaporated in vacuo and the residue purified by chromatography on silica (CH_2Cl_2/MeOH, 90:10) to give 43 mg of *tert*-butyl 2,5,5-trimethyl-1-piperazinecarboxylate (**4**) which was dissolved in dry MeCN together with K_2CO_3 (26 mg, 0.19 mmol) and **9** (63 mg, 0.19 mmol). After heating 4 days at reflux, the solvent was removed in vacuo and residue purified by chromatography on silica (0−5% MeOH in CH_2Cl_2). Treatment with TFA (5 mL) for 3 h, evaporation of solvent in vacuo and extraction of the residue with CH_2Cl_2/1 M NaOH, drying of the organic phase (K_2CO_3) and evaporation of solvent in vacuo gave 27 mg (33%) of **12**. Treatment with excess HCl in ether gave the dihydrochloride which was dissolved in water and lyophilized: mp 145−50 °C; IR (KBr, ν_{max}) 3500−3400, 1601, 1442, 1285 cm^{-1}; MS 423, 296, 325, 127; ^1H NMR ($CDCl_3$) δ 0.85 (s, 3H), 0.90 (d, 3H), 1.15 (s, 3H), 1.0−1.25 (brm, 6 H), 1.5 (brs, 1H), 2.05, 2.50, 2.80 (3m, 5H), 3.25, 3.5 (2 brs, 4H), 3.75 (s, 3H), 5.36, 5.39 (2s, 1H), 6.6−7.4 (m, 8H). Accurate mass determination of **12** with the calculated monoisotopic mass of 424.2964 Da was detected as 424.2973 Da (error 2.12 ppm).

***N,N*-Diethyl-4-[phenyl(1-piperidinyl)methyl]benzamide (13).** Procedure D. Compound **8** was reacted with piperidine. Compound **13** was obtained in 68% yield (0.18 g). The hydrochloride was made with HCl in ether: mp (free base) 124−5 °C (EtOAc−petroleum ether); IR (KBr, ν_{max}) 2925, 2793, 1620, 1447, 1281, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (brs, 3H), 1.17 (brs, 3H), 1.39 (d, 2H), 1.52 (m, 4H), 2,29 (brs, 4H), 3.21 (brs, 2H), 3.48 (brs, 2H), 4.20 (s, 1H), 7.16−7.42 (m, 9H). Anal. ($C_{23}H_{30}N_2O$) C, H, N.

***N,N*-Diethyl-4-[4-morpholinyl(phenyl)methyl]benzamide (14).** Procedure D. Compound **8** was reacted with morpholine. Compound **14** was obtained in 78% yield (0.15 g). The hydrochloride was made with HCl in ether: mp (free base) 143.5−6 °C (EtOAc−ether); IR (KBr, ν_{max}) 3488, 2973, 2362, 1622, 1438, 1288, 1128, 1076 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (brs, 3H), 1.20 (brs, 3H), 1.67 (brs, 2H), 2.27 (brs, 2H), 3.23 (brs, 2H), 3.58 (brs, 4H), 3.88 (brs, 2H), 4.62 (brs, 1H), 4.82 (s, 1H), 7.45 (m, 5H), 7.96 (m, 4H). Anal. ($C_{22}H_{29}ClN_2O_2$) C, H, N.

4-[1,4-Diazepan-1-yl(phenyl)methyl]-*N,N*-diethylbenzamide (15). Procedure D. Compound **8** was reacted with homopiperazine. The product **15** was obtained as an oil (354 mg, 40%). The dihydrochloride salt made with HCl: mp 155−65 °C (AcOEt−ether); IR (KBr, ν_{max}) 3418, 1628, 1591, 1074 cm^{-1}; MS 365, 322, 295, 281, 267, 236, 194, 165; ^1H NMR ($CDCl_3$) δ 1.08 (brs, 3H), 1.18 (brs, 3H), 1.69 (m, 2H), 2.56 (s, 1H), 2.62 (m, 4H), 2.85 (m, 2H), 2.97 (m, 2H), 3.23 (brs, 2H), 3.50 (brs, 2H), 4.63 (s, 1H), 7.16 (m, 1H), 7.26 (m, 4H), 7.40 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.6, 14.0, 30.7, 39.0, 43.1, 46.9, 49.6, 52.9, 56.1, 74.9, 126.4, 126.7, 127.6, 127.7, 128.3, 135.5, 142.9, 144.8, 171.0. Anal. ($C_{23}H_{33}Cl_2N_3O$) C, H, N.

***N,N*-Diethyl-4-[{methyl[2-(methylamino)ethyl]amino}-(phenyl)methyl]benzamide (16).** Procedure D. Compound **8** (0.11 g, 0.36 mmol) was reacted with N^1,N^2-dimethyl-1,2-ethanediamine (0.32 mL, 3.0 mmol). Purification with reverse phase chromatography (TFA in mobile phase) gave **16** (0.20 g, 97%) as the ditrifluoroacetate: mp 40−50 °C (H_2O); IR (KBr, ν_{max}) 3029, 2487, 2788, 2282, 1705, 1667, 1596 cm^{-1}; ^1H NMR (CD_3OD) δ 1.04−1.16 (br, 3 H), 1.16−1.28 (br, 3 H), 2.52 (s, 3 H), 2.68 (s,3 H), 2.96−3.06 (br, 2 H), 3.20−3.35 (br, 4 H), 3.48−3.58 (br, 2 H), 4.89 (s, 2 H), 4.97 (s, 1 H), 7.32−7.41 (m, 5 H), 7.57 (d, J = 7.6 Hz, 2 H), 7.68 (d, J = 7.6 Hz, 2 H). Anal. ($C_{26}H_{33}F_6N_3O_5$) C, H, N.

Procedure E: Lithium−Halogen Exchange and Reaction with Electrophile. *N,N*-Diethyl-4-iodobenzamide (**17**) (0.60 g, 2.0 mmol) was dissolved in THF (10 mL) and cooled to −78 °C under nitrogen atmosphere. *n*-BuLi (1.2 mL, 1.6 M solution in hexane, 2.0 mmol) was added dropwise. Stirring was continued for 30 min at −78 °C. The electrophile (2.0 mmol) was added dropwise dissolved in THF (2 mL). The temperature was allowed to reach room temperature and after NH_4Cl (aq) addition, extraction with EtOAc, drying ($MgSO_4$) and evaporation of the organic phase, the residue was purified by chromatography on silica.

Procedure F. Alternatively the lithium−halogen exchange was done as for procedure E but with *t*-BuLi (2 equiv) instead of *n*-BuLi (1 equiv).

***tert*-Butyl 4-[{4-[(Diethylamino)carbonyl]phenyl}-(hydroxyphenyl)methyl]-1-piperidinecarboxylate (18).** A mixture of 4-benzoylpiperidine hydrochloride (6.77 g, 30.0 mmol), di-*tert*-butyl dicarbonate (7.2 g, 33.0 mmol) and $KHCO_3$ (6.0 g, 60 mmol) in H_2O−THF (50/20 mL) was refluxed for 1 h. The reaction mixture was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). Removal of solvents gave *tert*-butyl 4-benzoyl-1-piperidinecarboxylate (8.54 g, 98%): ^1H 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). Following procedure F, **17** (6.67 g, 22.0 mmol) in dry THF (70 mL) and *t*-BuLi (18.0 mL, 2.5 M, 45.0 mmol) and *tert*-butyl 4-benzoyl-1-piperidinecarboxylate (4.34 g, 15.0 mmol) gave a crude product, which was purified by silica gel column (0−5% MeOH in CH_2Cl_2) to provide **18** (6.56 g, 94%): mp 100−3 °C (CH_2Cl_2); IR (KBr, ν_{max}) 3426, 2973, 1687, 1618, 1428, 1289, 1168 cm^{-1}; ^1H 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, 1H), 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.

***N,N*-Diethyl-4-[phenyl(4-piperidinyl)methyl]benzamide (19).** To a solution of **18** (3.26 g, 7.0 mmol) and triethylsilane (2.44 g, 21.0 mmol) in dry CH_2Cl_2 (20 mL) was added trifluoroacetic acid (30.0 mL) at 25 °C. The reaction mixture was stirred for 3 days at 25 °C and then concentrated in vacuo. The residue was dissolved in AcOEt (100 mL). The resulting solution was washed with 1 M NaOH solution, aqueous NH_4Cl solution and brine, dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by silica

gel column eluting with NH_4OH (1 N)−MeOH−CH_2Cl_2 (2.5:15:82.5) to provide **19** (2.0 g, 82%): mp 160−2 °C (CH_2Cl_2); IR (KBr, ν_{max}) 3325, 2937, 1613, 1461, 1283, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (brs, 3H), 1.07 (m, 2H), 1.19 (brs, 3H), 1.53 (m, 2H), 2.04 (brs, 1H), 2.20 (m, 1H), 2.55 (t, J = 11.6 Hz, 2H), 3.01 (m, 2H), 3.23 (brs, 2H), 3.51 (d, J = 10.4 Hz, 1H), 3.52 (brs, 2H), 7.15 (m, 1H), 7.27 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 12.8, 14.1, 32.2, 39.0, 39.9, 43.1, 46.5, 59.0, 126.1, 126.5, 127.9, 128.0, 128.3, 134.8, 143.0, 144.7, 171.0. Anal. ($C_{23}H_{31}ClN_2O$) C, H, N.

***N*-Ethyl-*N*-{4-[phenyl(1-piperazinyl)methyl]benzyl}-1-ethanamine (20).** Compound **1** (0.10 g, 0.28 mmol) was dissolved in toluene (2 mL) and treated with $LiAlH_4$ (0.56 mL, 1 M in THF, 0.56 mmol) at 25 °C for 12 h. After adding silica gel, concentration in vacuo and chromatography on silica (0−20% MeOH in CH_2Cl_2 (1% NH_4OH), 83 mg (88%) of **20** was obtained. Treatment with HCl in ether gave trihydrochloride salt: mp 185−95 °C (ether); IR (KBr, ν_{max}) 3661, 2650, 1590, 1437, 1325 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (m, 6H), 2.45 (m, 4H), 2.33, 2.85 (2 brs, 8H), 3.0 (s, 1H), 3.45, 3.50 (2s, 2H), 4.17 (s, 1H), 7.40−7.09 (m, 9H). Anal. ($C_{22}H_{34}Cl_3N_3$) C, H, N.

4-[Phenyl(1-piperazinyl)methyl]benzoic Acid Dihydrochloride (21) and 4-[[4-(*tert*-Butoxycarbonyl)-1-piperazinyl](phenyl)methyl]benzoic Acid (22). Compound **1** (6.0 g, 17 mmol) was heated at reflux in 6 N HCl (50 mL) for 72 h. The solution was made basic with NaOH, then di-*tert*-butyl dicarbonate (3.7 g, 17 mmol) was added in THF (100 mL). After 1 h the solution was acidified with 1 M citric acid and extracted with EtOAc. The organic phase was dried ($MgSO_4$) and evaporated in vacuo and the residue purified by chromatography on silica (EtOAc/heptane/AcOH, 10:90:0 to 66: 33:1) which gave **22 (**3.85 g, 57%). Treatment with HCl in AcOH (4 equiv, 1 M solution) for 1 h, then evaporation of solvent in vacuo, dissolving in water and freeze-drying gave **21** as a white powder: mp 172−80 °C; IR (KBr, ν_{max}) 3000, 1700, 1606, 1454 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.85 (s, 1H), 8.95 (s, 2H), 7.92−7.20 (m, 9H), 4.56 (s, 1H), 3.33 (s, 8H). Anal. ($C_{18}H_{21}ClN_2O_2$) C, H, N.

Methyl 4-[Phenyl(1-piperazinyl)methyl]benzoate (24). Compound **22** (0.87 g, 2.2 mmol) was dissolved in dry DMF (5 mL) and potassium carbonate (0.33 g, 2.4 mmol) and methyl iodide (0.22 mL, 3.5 mmol) were added. After stirring 12 h the methyl ester was isolated by extraction with EtOAc and washing with water and brine followed by evaporation in vacuo. The methyl ester **23** (0.13 g, 0.31 mmol) was treated with excess HCl in MeOH for 30 min, the solvent was evaporated and the residue purified by chromatography on silica, 0 to 10% methanol in CH_2Cl_2 (with 10% NH_4OH), to give **24** (35 mg, 38%). Treatment with HCl in ether gave the dihydrochloride: mp 185−95 °C (ether); IR (KBr, ν_{max}) 3400, 2700, 1720, 1612, 1430, 1285, 1190, 1112 cm^{-1}; ^1H NMR (D_2O/CD_3OD +DSS) δ 3.08 (m, 4H), 3.42 (m, 4H), 3.89 (s, 3H), 5.03 (s, 1H), 7.34−8.20 (m, 9H). Anal. ($C_{19}H_{24}Cl_2N_2O_2$) C, H, N.

2-{4-[Phenyl(1-piperazinyl)methyl]phenyl}-2-propanol (25). Compound **23** (0.13 g, 0.31 mmol) was dissolved in dry THF (5 mL) under nitrogen atmosphere and cooled to −78 °C. Methyllithium (3.8 mL, 0.9 M in ether, 3.4 mmol) was added and the temperature was allowed to reach 0 °C before NH_4Cl (aq) was added and the reaction was worked up by extraction with CH_2Cl_2. The organic phase was evaporated in vacuo and chromatography on silica, 0 to 10% methanol (with 10% NH_4OH), in CH_2Cl_2 gave 26 mg (25%) of **25**. Dihydrochloride salt made with HCl (ether): mp 180−90 °C (ether); IR (KBr, ν_{max}) (free amine) 3308, 2650, 1588, 1431, 1379 cm^{-1}; MS 310, 265, 254, 225, 206, 165; ^1H NMR ($CDCl_3$) δ 1.52 (s, 6H), 2.34 (s, 4H), 2.47 (s, 2H), 2.85 (m, 4H), 4.19 (s, 1H), 7.14−7.42 (m, 9H). Anal. ($C_{20}H_{28}Cl_2N_2O$) C, H, N.

1-{4-[Phenyl(1-piperazinyl)methyl]phenyl}-1-ethanone (26). Compound **22** (0.20 g, 0.50 mmol) was dissolved in dry THF (5 mL) under nitrogen atmosphere and cooled to 0 °C. MeLi (3.1 mL, 0.8 M in ether, 2.5 mmol) was added over 1 min. The reaction was stirred for 2 h, then trimethylsilyl chloride (0.63 mL, 5.0 mmol) was added in one portion and the temperature allowed to reach 25 °C. A solution of NH_4Cl (aq) was added and the organic phase decanted off and evaporated in vacuo. Chromatography on silica, (0 to 5% methanol in CH_2Cl_2 with 1% NH_4OH) gave 0.11 g (76%) of **26**. Dihydrochloride salt made with HCl (ether): mp 175−85 °C (ether); IR (KBr, ν_{max}) 3400, 2700, 1680, 1607, 1424, 1269 cm^{-1}; MS 294, 249, 209, 165; ^1H NMR ($CDCl_3$) δ 2.40 (m, 4H), 2.43 (s, 3H), 2.92 (m, 4H), 4.22 (s, 1H), 7.04−7.77 (m, 9H). Anal. ($C_{19}H_{24}Cl_2N_2O$) C, H, N.

4-[Phenyl(1-piperazinyl)methyl]benzamide (27). Prepared analogously to **28**. Reaction with excess NH_3 (1 M solution in CH_2Cl_2). Compound **27** obtained in 62% yield (70 mg). Dihydrochloride made with HCl in ether: mp 192−200 °C (ether); IR (KBr, ν_{max}) 3939, 3184, 2700, 1665, 1610, 1565, 1426 cm^{-1}; ^1H NMR (amine, CD_3OD) δ 2.46, 2.94 (2m, 8H), 4.40 (s, 1H), 4.93 (s, 2H), 7.22−7.96 (m, 9H). Anal. ($C_{18}H_{23}Cl_2N_3O$) C, H, N.

4-((1-Piperazinyl)benzyl)-*N*-ethylbenzamide (28). Compound **22** (0.12 g, 0.31 mmol) was dissolved in dry THF (5 mL) under nitrogen atmosphere and cooled to −20 °C. Et_3N (87 μL, 0.62 mmol) and isobutyl chloroformate (40 μL, 0.31 mmol) were added. Stirring was continued for 10 min, then ethylamine (0.31 mL, 0.62 mmol) was added and temperature was allowed to rise to 25 °C. After 3 h, the solvent was evaporated and the residue treated with excess TFA for 30 min. Evaporation of solvent in vacuo and chromatography on silica, 0 to 20% methanol (with 10% NH_4OH), in CH_2Cl_2 gave 69 mg (69%) of **28**.The dihydrochloride salt was made by treatment with excess HCl in ether, filtering and drying in vacuo over NaOH: mp 180−5 °C; IR (KBr, ν_{max}) 3331, 2700, 1640, 1545, 1440, 1308 cm^{-1}; MS 323, 278, 267, 238, 195, 165; ^1H NMR (CD_3OD) δ 1.20 (m, 3H), 2.65, 3.25 (2m, 8H), 3.40 (m, 2H), 4.45 (s, 1H), 4.9 (brs, 1H), 7.14−7.84 (m, 9H). Anal. ($C_{20}H_{27}Cl_2N_3O$) C, H, N.

***N*,*N*-Dimethyl-4-[phenyl(1-piperazinyl)methyl]benzamide (29).** Prepared analogously to **28**. Reaction with excess dimethylamine (2 M solution in THF). Compound **29** obtained in 97% yield (0.40 g). Dihydrochloride made with HCl in ether: mp 182−90 °C; IR (KBr, ν_{max}) 3372, 2953, 2698, 2480, 1620, 1492, 1448, 1405, 1266, 1084 cm^{-1}; MS 323, 278, 267, 238, 194, 165; ^1H NMR ($CDCl_3$) δ 1.8 (s, 1H), 2.32, 2.85 (2m, 8H), 2.9, 3.0 (2 brs, 6H), 4.20 (s, 1H), 7.10−7.44 (m, 9H). Anal. ($C_{20}H_{27}Cl_2N_3O$) C, H, N.

4-[Phenyl(1-piperazinyl)methyl]benzonitrile (30). Compound **22** (0.11 g, 0.28 mmol) was converted to the amide as for **27** but without TFA treatment. The amide (45 mg, 0.11 mol) was dissolved in dry THF (2 mL) and cooled to 0 °C. Pyridine (36 μL, 0.44 mmol) and trifluoroacetic anhydride (31 μL, 0.22 mmol) were added and stirring was continued for 1 h at 25 °C. Water was added and the solution was extracted with EtOAc. The organic phase was washed with dilute $NaHCO_3$ (aq), dried (K_2CO_3) and evaporated in vacuo. The residue was treated with HCl in MeOH 3 h at 50 °C. Removal of solvent in vacuo and chromatograpy on silica (CH_2Cl_2/MeOH/NH_3, 90:10:1) of residue gave 15 mg (49%) of **30**. Treatment with excess HCl in ether/MeOH gave the dihydrochloride: mp 141−5 °C; IR (KBr, ν_{max}) 3400, 2700, 2230, 1434 cm^{-1}; MS 277, 232, 192, 165; ^1H NMR ($CDCl_3$) δ 1.70 (s, 1H), 2.35, 2.89 (2m, 8H), 4.27 (s, 1H), 7.18−7.58 (m, 9H). Anal. ($C_{18}H_{21}Cl_2N_3$) C, H, N.

1-{Phenyl[4-(1*H*-1,2,3,4-tetraazol-5-yl)phenyl]methyl}-piperazine (31). Trimethylsilyltin azide (0.21 g, 1.0 mmol) was added to **30** (0.25 g, 0.9 mmol) in toluene (10 mL) and heated at 110 °C under inert atmosphere. After 24 h, another portion of azide was added and heating continued for 48 h. The solution was cooled to 0 °C and filtered. The beige solid was dissolved in MeOH (5 mL) and stirred with concentrated HCl (1 mL) at 60 °C for 15 min. Solvent was removed in vacuo and chromatography on silica, 0 to 50% methanol (with 10% NH_4OH) in CH_2Cl_2 gave 65 mg **31** (22%). Dihydrochloride salt with HCl (ether): mp >240 °C dec; IR (KBr, ν_{max}) 3405, 2912, 2663, 1567, 1496, 1442, 1302, 1067 cm^{-1}; ^1H NMR (amine, CD_3OD) δ 2.74, 3.34 (2s, 8H), 4.55 (s, 1H), 7.28−8.08 (m, 9H). Anal. ($C_{18}H_{22}Cl_2N_6$) C, H, N.

Ethyl 3-Methoxyphenethylcarbamate (32), 6-Methoxy-3,4-dihydro-1(2*H*)-isoquinolinone (33), 6-Methoxy-2-meth-

yl-3,4-dihydro-1(2*H*)-isoquinolinone (34), 6-Hydroxy-2-methyl-3,4-dihydro-1(2*H*)-isoquinolinone (35), 2-Methyl-1-oxo-1,2,3,4-tetrahydro-6-isoquinolinyl Trifluoromethanesulfonate (36), 6-[Hydroxy(phenyl)methyl]-2-methyl-3,4-dihydro-1(2*H*)-isoquinolinone (37), and 2-Methyl-6-[phenyl(1-piperazinyl)methyl]-3,4-dihydro-1(2*H*)-isoquinolinone (38). 2-(3-Methoxyphenyl)-1-ethanamine (5 g, 33 mmol) was dissolved in CH_2Cl_2 (100 mL) with Et_3N (5.1 mL, 36 mmol) at 0 °C. Ethyl chloroformate (3.5 mL, 36 mmol) was added and stirring was continued 1.5 h. After aqueous workup, 7.6 g (100%) of ethyl 3-methoxyphenethylcarbamate (**32**) was obtained. Compound **32** was treated with polyphosphoric acid (PPA) (30 g) at 120 °C under nitrogen atmosphere for 1.5 h. After addition of water and repeated extraction with EtOAc, a total of 6.4 g (76%) of 6-methoxy-3,4-dihydro-1(2*H*)-isoquinolinone (**33**) was obtained. Compound **33** (3.1 g, 17 mmol) was dissolved in THF/toluene 1:1 (80 mL) and NaH (60% in oil, 7.0 g, 175 mmol) was added in portions. Methyl iodide (5.5 mL, 87 mmol) was added and stirring was continued for 2 h. The reaction mixture was slowly added to 1 N HCl (aq). After extractive workup with EtOAc, crude **34** (1.6 g, 8.8 mmol, 77%) was obtained. Compound **34** was dissolved in CH_2Cl_2 (45 mL) and BBr_3 (18 mL, 1 M in CH_2Cl_2, 18 mmol) was added at −78 °C and solution was stirred at 25 °C overnight. MeOH was added at 0 °C until all was dissolved and the solvent was removed in vacuo. Extractive workup with EtOAc and 1 N HCl (aq) gave **35** (0.80 g, 4.5 mmol, 94%). Compound **35** (0.40 g, 2.2 mmol) and pyridine (0.36 mL, 4.5 mmol) were dissolved in CH_2Cl_2 (10 mL), then trifluoromethanesulfonic anhydride (0.45 mL, 2.7 mmol) was added dropwise at 0 °C and the reaction mixture was allowed to reach 25 °C. Aqueous workup with EtOAc and 1 N HCl followed by chromatography on silica (20% EtOAc in hexane) gave **36** (0.30 g, 0.97 mmol) and recovered **35** (0.12 g). Compound **36** (0.20 g, 0.65 mmol) was dissolved in DMF (4 mL) and tributyl(phenyl)stannane (0.26 g, 0.71 mmol) was added. Carbon monoxide was passed through the solution 2−3 min, then palladium acetate (15 mg, 67 μmol) and diphenylphosphinoferrocene (dppf) (72 mg, 0.13 mmol) were added and the mixture heated at 70 °C under a CO atmosphere. After 12 h, Aqueous workup with EtOAc and 1 N HCl followed by chromatography on silica (EtOAc) gave the crude coupling product (0.12 g, 0.45 mmol). Reduction with $NaBH_4$ (25 mg, 0.66 mmol) in MeOH (3 mL) gave **37** (72 mg, 0.27 mmol, 93%). Treatment of **37** following procedures C and D gave **38** (58 mg, 65%): IR (KBr, ν_{max}) (free amine) 2943, 2818, 1643, 1491, 1446, 1335, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (bs, 4H), 2.94 (m, 6H), 3.08 (s, 3H,), 3.48 (t, J = 6.8 Hz, 2H), 4.21 (s, 1H), 7.15−7.39 (m, 7H), 7.94 (d, J = 8 Hz, 1H). Anal. ($C_{21}H_{27}Cl_2N_3O$) C, H, N.

***tert*-Butyl 4-[(4-Bromophenyl)(phenyl)methyl]-1-piperazinecarboxylate (39).** (4-Bromophenyl)(phenyl)methanol was treated according to procedure C and then according to procedure D with *tert*-butyl 1-piperazinecarboxylate, diisopropylethylamine, and a catalytic amount of potassium iodide to give **39** in 80% yield: mp 136−9 °C (EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 1.43 (s, 9H), 2.27−2.37 (m, 4H), 3.37−3.46 (m, 4 H), 4.19 (s, 1H), 7.16−7.22 (m, 1H), 7.24−7.32 (m, 4H), 7.33−7.42 (m, 4 H).

***tert*-Butyl 4-[[4-(2-Ethylbutanoyl)phenyl](phenyl)methyl]-1-piperazinecarboxylate (40) and 2-Ethyl-1-{4-[phenyl(1-piperazinyl)methyl]phenyl}-1-butanone (41).** Compound **39** (0.62 g, 1.4 mmol) was converted following procedure E to the aryllithium and then quenched with 2-ethyl-*N*-methoxy-*N*-methylbutanamide[16] (0.23 g, 1.4 mmol). Aqueous workup and chromatography on silica (10% EtOAc in heptane) gave **40** (0.15 g, 25%). Treatment with 1 M HCl in AcOH and extraction with K_2CO_3(aq)/CH_2Cl_2 gave **41** (52 mg, 45%). Further purification with reverse-phase chromatography (mobile phase with TFA) and lyophilization gave the ditrifluoroacetate salt: mp 37−45 °C (H_2O); IR (NaCl, ν_{max}) 3777−3004, 2962, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78−1.00 (t, J = 7.2 Hz, 6H), 1.46−1.63 (m, 2H), 1.63−1.86 (m, 3H), 2.24−2.49 (m, 4H), 2.81−3.02 (t, J = 4.8 Hz, 4H), 3.19−3.30 (m, 1H), 4.28 (s,1H), 7.19 (m, 1H), 7.29 (m, 2H), 7.40 (m, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2 H). Anal. ($C_{27}H_{32}F_6N_2O_4$) C, H, N.

4-Bromo-*N*,*N*-diethylbenzenesulfonamide (42), *N*,*N*-Diethyl-4-[hydroxy(phenyl)methyl]benzenesulfonamide (43), and *N*,*N*-Diethyl-4-[phenyl(1-piperazinyl)-methyl]benzenesulfonamide (44). 4-Bromobenzenesulfonyl chloride (0.50 g, 2.0 mmol) was treated with diethylamine (0.61 mL, 5.9 mmol) in CH_2Cl_2 (20 mL) at 0 °C and stirred 12 h at 25 °C. After aqueous workup with 1 N HCl (aq) and chromatography on silica (EtOAc in hexane), **42** (0.52 g, 1.8 mmol) was obtained. Compound **42** was treated with *n*-BuLi and benzaldehyde following procedure B to give **43** (0.18 g, 0.57 mmol). Treatment of **43** following procedures C and D gave **44** (0.15 g, 71%): mp >220 °C; IR (NaCl, ν_{max}) 3055, 2986, 1423, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (t, J = 7.2 Hz, 6H), 2.64 (m, 4H), 3.18 (m, 8H), 4.37 (s, 1H), 7.27 (m, 5H), 7.51 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H). Anal. ($C_{21}H_{29}N_3O_2S$) C, H, N.

Procedure G: *N*-Alkylation of Piperazine Compounds. 4-[(4-Allyl-1-piperazinyl)(phenyl)methyl]-*N*,*N*-diethylbenzamide (46). Compound **1** (0.30 g, 0.85 mmol) was dissolved in MeCN (5 mL). K_2CO_3 (0.17 g, 1.3 mmol) and allyl bromide (110 μL, 1.3 mmol) were added. After 3 h at 25 °C the solvent was evaporated and the residue purified by chromatography on silica (0−5% MeOH in CH_2Cl_2), to give a total of 0.26 g **46** (79%). Treatment with HCl in ether gave the dihydrochloride salt: mp 175−205 °C; IR (KBr, ν_{max}) (free amine) 3689, 1613, 1455, 1434, 1290, 1143 cm^{-1}; MS 391, 165, 125; ^1H NMR ($CDCl_3$) δ 1.1 (2 brs, 6H), 2.4−2.6 (brs, 8H), 3.00 (m, 2H), 3.2, 3.5 (2 brs, 4H), 4.23 (s, 1H), 5.10 (m, 2H), 5.81 (m, 1H), 7.12−7.42 (m, 9H). Anal. ($C_{25}H_{37}Cl_2N_3O$) C, H, N.

***N*,*N*-Diethyl-4-[(4-methyl-1-piperazinyl)(phenyl)methyl]benzamide (45).** Procedure G. Alkylation with methyl iodide gave 60 mg (29%) of **45**: mp 180−5 °C (ether); IR (KBr, ν_{max}) 3328, 2978, 2485, 1603, 1449, 1361, 1292, 1180, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1, 1.2 (2 m, 6H), 2.27 (s, 3H), 2.3−2.6 (m, 8H), 3.2, 3.5 (2 m, 4H), 3.50 (s, 2H), 4.24 (s, 1H), 7.10−7.50 (m, 14H). Anal. ($C_{23}H_{33}Cl_2N_3O$) C, H, N.

4-[[4-(Cyclopropylmethyl)-1-piperazinyl](phenyl)-methyl]-*N*,*N*-diethylbenzamide (47). Procedure G. Alkylation with cyclopropyl chloride (0.18 g, 2 mmol), KI (0.30 g, 2 mmol) and K_2CO_3 (0.28 g, 2 mmol) gave 0.21 g of **47** (52%). Dihydrochloride made with HCl in ether: IR (KBr, ν_{max}) 3679, 3431, 3050, 2977, 2389, 1624, 1433, 1275 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (m, 2H), 0.48 (m, 2H), 0.85 (m, 1H), 1.10 (brs., 6H), 2.25 (d, J = 6.8 Hz, 2H), 2.50 (m, 8H), 3.24 (br d, 2H), 3.50 (brs, 2H), 4.26 (s, 1H), 7.18 (m, 1 H), 7.28 (m, 4H), 7.41 (m, 4H). Anal. ($C_{26}H_{37}Cl_2N_3O$) C, H, N.

4-[(4-Butyl-1-piperazinyl)(phenyl)methyl]-*N*,*N*-diethylbenzamide (48). Procedure G. Compound **1** (0.20 g, 0.57 mmol) and Et_3N (0.80 mmol) were dissolved in dry CH_2Cl_2 (15 mL), followed by the addition of the 1-iodobutane (0.52 g, 2.8 mmol); the reaction mixture was stirred at room temperature for 48 h. Compound **48** (0.20 g, 84%) was obtained. The dihydrochloride salt was made with HCl in ether: mp 212−4 °C dec; IR (amine, NaCl, ν_{max}) 3439, 2967, 2414, 1621, 1439, 1288 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 3H), 1.10−1.26 (br, 6H), 1.32 (m, 2H), 1.53 (m, 2H), 2.42 (m, 2H), 2.46−2.70 (br, 8H), 3.16−3.60 (br, 4H), 4.27 (s, 1H), 7.19−7.45 (m, 9H). Anal. ($C_{26}H_{39}Cl_2N_3O$) C, H, N.

4-[(4-Acetyl-1-piperazinyl)(phenyl)methyl]-*N*,*N*-diethylbenzamide (49). 1 (0.10 g, 0.28 mmol) and Et_3N (43 μL, 0.31 mmol) were dissolved in CH_2Cl_2 (5 mL) and acetyl chloride (22 μL, 0.31 mmol) was added at 0 °C. After aqueous workup and chromatography on silica (0−5% MeOH in CH_2Cl_2), **49** (0.11 g, quant.) was obtained. Treatment with HCl gave the hydrochloride salt: mp 140−50 °C (ether); IR (KBr, ν_{max}) 3480, 2987, 2500, 1623, 1429, 1285,1245 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (brm, 6H), 2.05 (s, 3H), 2.36 (m, 4H), 3.15−3.70 (m, 8H), 4.25 (s, 1H), 7.18−7.46 (m, 9H). Anal. ($C_{24}H_{32}ClN_3O_2$) C, H, N.

Compounds 50−57 were made following procedure A using the corresponding grignard reagent or procedure B using the corresponding bromide. Treatment by procedures C and D gave

the target compounds. Intermediate alcohols were purified by chromatography on silica (EtOAc in heptane) and final compounds purified as bases by chromatography on silica (0−10% MeOH in CH_2Cl_2 (1% NH_4OH)). Dihydrochlorides were made with HCl in ether.

***N,N*-Diethyl-4-[(4-methoxyphenyl)(1-piperazinyl)-methyl]benzamide (50).** Procedure B (0.12 g of **50** obtained, 39%): mp (free base) 142−4 °C (MeCN); IR (KBr, ν_{max}) 3318, 2965, 2813, 1611, 1511, 1465, 1286, 1250, 1100, 1032, 833 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1, 1.2 (2 brs, 6H), 1.63 (brs, 1H), 2.33 (brs, 4H), 2.46 (brs, 2H), 2.85−2.89 (m, 4H), 3.25 (brs, 2H), 3.51 (brs, 2H), 3.76 (s, 3H), 4.19 (s, 1H), 6.78−6.84 (m, 2H), 7.25−7.32 (m, 4H), 7.40−7.44 (m, 2H). Anal. ($C_{23}H_{31}N_3O_2$) C, H, N.

4-[(4-Chlorophenyl)(1-piperazinyl)methyl]-*N,N*-diethylbenzamide (51). Procedure A (0.45 g of **51** obtained, 39%): mp (free base) 112−3 °C (MeCN); IR (KBr, ν_{max}) 3347, 2947, 2809, 1615, 1451, 1318, 1284, 1094, 836 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (brs, 3H), 1.21 (brs, 3H), 1.69 (brs, 1H), 2.33 (brs, 4H), 2.86−2.89 (m, 4H), 3.24 (brs, 2H), 3.51 (brs, 2H), 4.22 (s, 1H), 7.23−7.41 (m, 8H). Anal. ($C_{22}H_{28}ClN_3O$) C, H, N.

***N,N*-Diethyl-4-[(4-methylphenyl)(1-piperazinyl)methyl]benzamide (52).** Procedure A (0.50 g of **52** obtained, 40%): mp (free base) 129−32 °C (MeCN); IR (KBr, ν_{max}) 3320, 2957, 2811, 1610, 1437, 1285, 1128, 1010, 838 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (brs, 3H), 1.20 (brs, 3H), 1.83 (brs, 1H), 2.30 (s, 3H), 2.34 (brs, 4H), 2.86−2.89 (m, 4H), 3.24 (brs, 2H), 3.51 (brs, 2H), 4.20 (s, 1H), 7.06−7.46 (3m, 8H). Anal. ($C_{23}H_{31}N_3O$) C, H, N.

***N,N*-Diethyl-4-[(3-fluorophenyl)(1-piperazinyl)methyl]-benzamide (53).** Procedure B (85 mg of **53** obtained, 88%): mp 155−65 °C (ether); IR (KBr, ν_{max}) 3408, 2926, 2461, 1612, 1437, 1290, 1097 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1 (m, 6H), 1.6 (s, 1H), 2.38, 2.85 (2m, 8H), 3.4 (m, 4H), 4.23 (s, 1H), 6.85−7.45 (m, 8H). Anal. ($C_{22}H_{30}Cl_2FN_3O$) C, H, N.

***N,N*-Diethyl-4-[2-naphthyl(1-piperazinyl)methyl]benzamide (54).** Procedure B (0.50 g, of **54** obtained, 40%): mp (free base) 106−8 °C (MeCN); IR (KBr, ν_{max}) 3324, 3052, 2964, 2810, 2774, 1613, 1465, 1287, 1130, 1098 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (brs, 3H), 1.19 (brs, 3H), 1.89 (brs, 1H), 2.40 (brs, 4H), 2.89−2.92 (m, 4H), 3.21 (brs, 2H), 3.50 (brs, 2H), 4.41 (s,1H), 7.24−7.84 (3m, 11H). Anal. ($C_{26}H_{31}N_3O$) C, H, N.

***N,N*-Diethyl-4-[1-naphthyl(1-piperazinyl)methyl]benzamide (55).** Procedure B (0.30 g of **55** obtained, 57%): IR (KBr, ν_{max}) 3307, 3050, 2966, 2814, 1625, 1431, 1287, 1098, 843, 797 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (brs, 3H), 1.17 (brs, 3H), 2.14 (brs, 1H), 2.40 (brs, 2H), 2.46 (brs, 2H), 2.83−2.95 (m, 4H), 3.17 (brs, 2H), 3.48 (brs, 2H), 5.05 (s, 1H), 7.22−7.28 (m, 2H), 7.40−7.54 (m, 5H), 7.70−7.94 (m, 3H), 8.40−8.43 (m, 1H). Anal. ($C_{26}H_{31}N_3O$) C, H, N.

***N,N*-Diethyl-4-[1-piperazinyl(8-quinolinyl)methyl]benzamide (56).** Procedure B. 8-Quinolyllithium made from 8-Bromoquinoline with *s*-BuLi[25] (0.22 g of **56** obtained, 64%): mp 180−90 °C (ether); IR (KBr, ν_{max}) 3297, 2982, 2716, 2474, 1611, 1434, 1380, 1288, 1098 cm^{-1}; MS 402, 318, 246, 217, 109; ^1H NMR ($CDCl_3$) δ 1.2, 1.1 (2s, 6H), 2.94, 2.51 (2m, 8H), 3.5−3.1 (m, 5H), 6.05 (s, 1H), 8.94−7.20 (m, 10H). Anal. ($C_{25}H_{32}Cl_2N_4O$) C, H, N.

4-[Cyclohexyl(1-piperazinyl)methyl]-*N,N*-diethylbenzamide (57). Procedure A (60 mg of **57** obtained, 17%): mp (free base) 113−6 °C (MeCN); IR (KBr, ν_{max}) 3330, 2936, 2845, 1623, 1431, 1286, 1096, 823 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.64−2.02 (m, 18H), 2.18−2.40 (m, 4H), 2.75−2.87 (m, 4H), 3.06 (d, J = 9 Hz, 1H), 3.27 (brs, 2H), 3.52 (brs, 2H), 7.11 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H). Anal. ($C_{22}H_{35}N_3O$) C, H, N.

***N,N*-Diethyl-4-[1-piperazinyl(4-quinolinyl)methyl]benzamide (58).** Preparation as for **60**, starting from 4-quinolinecarboxaldehyde, gave 0.21 g of **58** (41%): mp 180−5 °C; IR (KBr, ν_{max}) 3345, 2698, 1600, 1434, 1382, 1289 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03, 1.18 (2s, 6H), 2.45 (m, 4H), 2.94 (m, 5H), 3.15, 3.47 (2s, 4H), 5.06 (s, 1H), 7.26−8.94 (m, 10H). Anal. ($C_{25}H_{30}N_4O$) C, H, N.

***N,N*-Diethyl-4-[1-piperazinyl(7-quinolinyl)methyl]benzamide (59).** Preparation as for **60** gave 0.11 g of **59** (7%) from 7-methylquinoline: mp 180−3 °C; IR (KBr, ν_{max}) 3406, 2660, 1614, 1439, 1372, 1287, 1175, 1124 cm^{-1}; MS 383, 363, 335, 266, 165; ^1H NMR ($CDCl_3$) δ 1.1, 1.2 (2s, 6H), 1.8 (s, 1H), 2.3, 2.9 (2m, 8H), 3.24, 3.52 (2s, 4H), 4.35 (s, 1H), 8.09−6.56 (m, 10H). Accurate mass determination of **59** with the calculated monoisotopic mass of 403.2498 Da was detected as 403.2486 Da (error 2.98 ppm).

***N,N*-Diethyl-4-[1-piperazinyl(6-quinolinyl)methyl]benzamide (60).** 6-Methylquinoline (1.0 g, 6.9 mmol) was heated to 160 °C and selenium dioxide (0.5 g, 4.6 mmol) was added. After 12 h the mixture was cooled and diluted with heptane and the solution was decanted off and evaporated onto silica gel. Chromatography on silica, 0 to 30% ethyl acetate in heptane, gave 0.45 g 6-formylquinoline (41%). Procedure E gave 0.15 g (0.43 mmol) of the benzylic alcohol. Following procedures C and D, the alcohol was converted into **60** (0.12 g, 0.31 mmol, 72%). The dihydrochloride salt was prepared by treatment with excess HCl in ether, filtering and drying the crystals in a vacuum over NaOH: mp 185−95 °C; IR (KBr, ν_{max}) (free amine) 3358, 2648, 1615, 1439, 1310 cm^{-1}; MS 350, 196, 173, 146, 91; ^1H NMR ($CDCl_3$) δ 1.07, 1.20 (2s, 6H), 2.60, 3.09 (2s, 8H), 3.20, 3.50 (2s, 4H), 4.5 (s, 1H), 5.7 (s, 1H), 7.26−8.86 (m, 10H). Anal. ($C_{25}H_{30}N_4O$) C, H, N.

5-Isoquinolinecarbaldehyde (61). A solution of DIBAL (1.5 M, 7.3 mL, 10.95 mmol) in 15 mL of toluene which was precooled to −78 °C and added dropwise to a solution of methyl 5-isoquinolinecarboxylate (1.7 g, 9.09 mmol) in 90 mL of toluene at −78 °C, under a nitrogen atmosphere. After addition, the resulting mixture was stirred at −78 °C for 4 h. 1 mL of methanol was added to quench the reaction at −78 °C and gradually warmed to 25 °C. The mixture was filtered through Celite and the filtrate extracted with ethyl acetate several times. The combined organic phases were washed with water and brine, and dried over sodium sulfate. Concentration and chromatography on silica (ethyl acetate) afforded **61** (725 mg, 51% yield): IR (NaCl, ν_{max}) 3031, 2859, 2753, 1683, 1619, 1569 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75 (m, 1H), 8.2 (m, 2H), 8.65 (d, J = 6.1 Hz,1H), 8.95 (d, J = 6.1 Hz, 1H), 9.3 (s, 1H), 10.4 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 116.6, 122.8, 125.4, 129.6, 132.2, 133.6, 138.7, 145.3, 151.8, 191.4.

N,*N*-Diethyl-4-[hydroxy(5-isoquinolinyl)methyl]benzamide (62) and *N*,*N*-Diethyl-4-[5-isoquinolinyl(1-piperazinyl)methyl]-benzamide (63). Following procedure E, 61 (400 mg, 2.545 mmol) was converted to 62 (110 mg, 12% yield). Following procedures C and D, 62 was converted into 63 (40 mg, 31% yield) after chromatography on silica (0−10% MeOH in CH_2Cl_2 with 1% NH_4OH). Trihydrochloride salt made with HCl: IR (NaCl, ν_{max}) 3383, 1669, 1617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90−1.25 (m, 6H), 2.40 (m, 4H), 2.90 (m, 4H), 3.15 (m, 2H), 3.50 (m, 2H), 4.95 (s, 1H), 7.25 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 7.60 (t, J = 7.3 Hz, 1H), 7.85 (d, J = 8.5 Hz, 1H), 8.05 (d, J = 7.3 Hz, 1H), 8.15 (d, J = 6 Hz, 1H), 8.50 (d, J = 6 Hz, 1H), 9.20 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.7, 14.1, 39.1, 43.1, 46.1, 53.3, 71.3, 116.3, 126.6, 127.0, 127.2, 128.3, 129.1, 129.5, 131.1, 134.0, 136.0, 137.2, 142.9, 153.3, 170.7. Anal. ($C_{25}H_{33}Cl_3N_4O$) C, H, N.

1-(Phenylsulfonyl)-1*H*-indole-6-carbaldehyde (65). 1*H*-Indole-6-carbaldehyde **(64)**[17] (0.14 g, 1.0 mmol) was dissolved in CH_2Cl_2 (5 mL). Ground NaOH (0.8 g) and phenylsulfonyl chloride (1.3 mL, 1.0 mmol) were added, then tetrabutylammonium hydrogen sulfate (50 mg) was added, and the reaction stirred at 25 °C for 1 h. The organic solution was filtered in a glass filter, washed with water and brine, dried ($MgSO_4$) and evaporated. Chromatography on silica (0−50% EtOAc in heptane) gave **65** (0.15 g, 0.54 mmol): ^1H NMR ($CDCl_3$) δ 6.74 (m, 1H), 7.42−7.94 (m, 10H), 8.50 (m, 1H), 10.08 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 109.1, 116.1, 122.0, 123.9, 126.7 (2), 129.5 (2), 130.0, 133.2, 134.2, 134.5, 135.6, 137.8, 191.7.

***N,N*-Diethyl-4-{hydroxy[1-(phenylsulfonyl)-1*H*-indol-6-yl]methyl}benzamide (66) and *N,N*-Diethyl-4-[1*H*-indol-6-yl(1-piperazinyl)methyl]benzamide (67).** Compound **65** was converted to **66** in 66% yield according to procedure E. Compound **66** was converted to **67** by treatment first with $SOCl_2$ and then with piperazine with concomitant loss of the

phenylsulfonyl protecting group, according to procedures C and D. The desired product **67** (0.1 g, 81%) was obtained after chromatography on silica. Treatment with HCl in ether gave the dihydrochloride salt: mp 180−5 °C; IR (KBr, ν_{max}) 3439, 2694, 1607, 1400, 1385, 1293 cm^{-1}; MS 266, 207, 195, 165; ^1H NMR ($CDCl_3$) δ 1.1, 1.2 (2s, 6H), 1.8 (s, 1H), 2.42, 2.91 (2m, 8H), 3.2, 3.5 (2s, 4H), 4.48 (s, 1H), 7.26−8.90 (m, 10H). Anal. ($C_{24}H_{30}N_4O$) C, H, N.

2,2-Dimethyl-2,3-dihydro-1-benzofuran-7-yl Trifluoromethanesulfonate (68). 2,2-Dimethyl-2,3-dihydro-1-benzofuran-7-ol (19 g, 0.11 mol) and pyridine (18 mL, 0.23 mol) were dissolved in CH_2Cl_2 at 0 °C. Triflic anhydride (23 mL, 0.14 mol) was added dropwise. After strirring 1 h at 25 °C the mixture was diluted with CH_2Cl_2 and washed with HCl (aq), dried ($MgSO_4$) and evaporated in vacuo. Compound **68** (32 g, 96%) was obtained, which did not need purification and was used directly in the following step: ^1H NMR ($CDCl_3$) δ 1.50 (s, 6H), 3.09 (s, 2H), 6.81 (m, 1H), 7.03 (m, 1H), 7.11 (m, 1H); MS (EI) *m*/*e* 296, 163, 135, 107.

Methyl 2,2-Dimethyl-2,3-dihydro-1-benzofuran-7-carboxylate (69). Compound **68** (32 g, 0.11 mol) was dissolved in DMSO (200 mL), MeOH (100 mL) and Et_3N (34 mL, 0.25 mol). Carbon monoxide was passed through the solution 2−3 min, then palladium acetate (0.24 g) and dppf (1.1 g) were added and the mixture heated at 70 °C under a CO atmosphere. After 4 h, more palladium acetate (0.10 g) and dppf (0.50 g) were added. After 12 h, EtOAc and water were added and the organic phase was washed with HCl (aq), brine, dried ($MgSO_4$) and evaporated. Chromatography on silica (0−20% EtOAc in heptane) gave 12 g (52%) of **69**: ^1H NMR ($CDCl_3$) δ 1.52 (s, 6H), 3.00 (s, 2H), 3.88 (s, 3H), 6.82 (m, 1H), 7.27 (m, 1H), 7.70 (m, 1H); MS (EI) *m*/*e* 206, 174, 159, 146, 131.

2,2-Dimethyl-2,3-dihydro-1-benzofuran-7-carbaldehyde (70). Compound **69** (5.0 g, 24 mmol) was dissolved in toluene (100 mL) and DIBAL in toluene (33 mL, 1.5 M, 50 mmol) was added at −78 °C under a nitrogen atmosphere. After 30 min, the reaction was worked up by addition of HCl (aq), the organic phase was dried ($MgSO_4$) and evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and finely ground pyridinium dichromate (PDC) (11 g, 29 mmol) was added in portions. The mixture was heated to 40 °C and portions of PDC (1 g) were added until reaction was complete. Dilution with heptane, filtering through silica and evaporation gave a crude product which was purified by chromatography on silica (0−20% EtOAc in heptane) to give **70** (3.3 g, 19 mmol, 79% from **69**): ^1H NMR ($CDCl_3$) δ 1.54 (s, 6H), 3.03 (s, 2H), 6.88 (m, 1H), 7.34 (m, 1H), 7.58 (m, 1H), 10.22 (s, 1H); MS (EI) *m*/*e* 176, 161, 147, 130.

4-[(2,2-Dimethyl-2,3-dihydro-1-benzofuran-7-yl)(hydroxy)methyl]-*N*,*N*-diethylbenzamide (71) and 4-[(2,2-Dimethyl-2,3-dihydro-1-benzofuran-7-yl)(1-piperazinyl)-methyl]-*N*,*N*-diethylbenzamide (72). Compound **70** (3.0 g, 17 mmol) was reacted with **17** (10 g, 34 mmol) according to procedure E to give alcohol **71** (4.0 g, 67%) followed by procedures C and D to give **72** (3.2 g, 67%). Dihydrochloride made with HCl: mp 130−40 °C (water); IR (KBr, ν_{max}) 2982, 2722, 2481, 1628, 1450, 1371, 1292, 1140 cm^{-1}; ^1H NMR (CD_3OD) δ 1.1,1.2 (2m, 6H), 1.36, 1.43 (2s, 6H), 2.72 (m, 4H), 2.95 (m, 2H), 3.25 (m, 6H), 3.5 (m, 2H), 4.8 (s, 1H), 6.74−7.60 (m, 7H). Anal. ($C_{26}H_{35}N_3O_2$) C, H, N.

Accurate Mass Determination by Time-of-Flight Mass Spectrometry. Time-of-flight mass spectrometer (LCT, Micromass Inc. England) and HPLC (HP1100, Hewlett-Packard) were used for the accurate mass determination with instrument parameters of: ion mode, electrospray; desolvation temp, 350 °C; source temp, 130 °C; sample cone voltage, 30 V. Acquisition was carried out in the mass range 100−1000 Da, 1 spectrum/s at 5000 resolution. The sample was introduced into LCT mass spectrometer in loop injection mode with a HPLC flow of 0.4 mL/min. The mobile phase consists of 50% water and 50% acetonitrile. Leucine−enkephalin (lock mass 556.2771 Da) was used as the reference standard (Sigma Ref.L-9133; 1 mg/mL in water). The sample was prepared with the analyte compound and the reference standard in methanol each at 0.5 μg/μL. One microliter of the sample solution was injected into the LCT. The mass calibration was performed with poly(ethylene glycol) (PEG) according to the LCT operator's manual.

Pharmacology. 1. Test Compounds. The compounds were tested as their corresponding hydrochloride or trifluoroacetate salts.

2. Cell Culture and Membrane Preparations. 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.

3. 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 = 1.1 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.

4. GTP[γ-^{35}S] Binding Assays. Membranes expressing human δ receptors (9.7 pmol/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}.

5. In Vitro Metabolism. Incubation conditions: All incubations [rat liver microsomes (0.4 mg/mL proteins; Xenotech LLC, Kansas City, KS), substrate at 10 or 100 μmol/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% of 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. Precipitated proteins were removed following a 10-min centrifugation at 8500*g* and supernatants were directly injected into the LC−MS system (Hewlett-Packard, Kirkland, Quebec, Canada) using a micro plate sampler (HP220, Hewlett-Packard).

HPLC conditions (metabolic stability): Aliquots (5 μL) of the supernatants were directly injected onto a Zorbax Eclipse XDB C18 column (4.6 × 30 mm, 3.5-μm particles). 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.

HPLC conditions (metabolic profiling): Supernatants (30-μL aliquots) were directly injected onto a Phenomenex Luna column (4.6 × 75 mm, 3-μm particles). Metabolites and parent compounds were separated using a linear gradient of acetonitrile (from 0% to 95% over 15 min) in 0.04% formic acid in water. The flow rate was kept at 1.0 mL/min.

MS conditions: The LC system (HP1100, Hewlett-Packard) was interfaced with a MS detector (MSD) equipped with an electrospray source. The MSD was operated in selected ion monitoring mode for the metabolic stability studies (m/z = MH^+, M being the mass of the parent compound) and in scan mode for the metabolic profiling studies (m/z from 85 to 650). 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.

6. Data Analysis. For metabolic stability determinations, chromatograms were analyzed for 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. For metabolic profiling studies, chromatograms were analyzed for both the disappearance of parent drug and the appearance of metabolites. For each metabolite, the metabolite peak area in the 60-min incubation sample was compared to the sum of all peak areas corresponding to metabolites and expressed as percent (%) contribution to total microsomal metabolism.

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