New κ-Receptor Agonists Based upon a 2-[(Alkylamino)methyl]piperidine Nucleus

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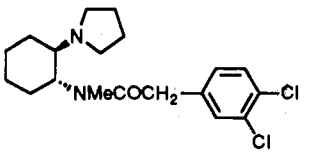
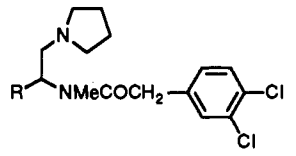
The syntheses of some 1-[(3,4-dichlorophenyl)acetyl]-2-[(alkylamino)methyl]piperidines and their activities as κ-opioid receptor agonists are described. Selected structural modifications are made to the basic moiety and at the 2-, 3-, 4-, 5-, and 6-positions on the piperidine nucleus to enable structure–activity relationships to be delineated. As a result, some highly potent and selective κ-receptor agonists have been identified. In particular, this has been achieved by introduction of oxygen-containing functionality into the 4-position of the piperidine nucleus or the 3-position of the pyrrolidinylmethyl side chain. Thus, 1-[(3,4-dichlorophenyl)acetyl]-2-[[1-(3-oxopyrrolidinyl)]methyl]piperidine (**10**) possesses high activity in the rabbit vas deferens (LVD, κ-specific tissue) (IC_{50} = 0.20 nM) and is a potent antinociceptive agent, as determined by the mouse acetylcholine-induced abdominal constriction test (MAC) (ED_{50} = 0.06 mg/kg, sc). The spirocyclic analogue 8-[(3,4-dichlorophenyl)acetyl]-7-(1-pyrrolidinylmethyl)-1,4-dioxa-8-azaspiro[4.5]decane (**39**) showed exceptionally potent activity: LVD, IC_{50} = 0.10 nM; MAC, ED_{50} = 0.001 mg/kg, sc. Both **10** and **39** displayed high selectivity for κ-opioid receptors over both μ- and δ-opioid receptor subtypes.

The quest for novel, strong analgesics free of the abuse potential and side effects of narcotics such as morphine has received fresh impetus during the past decade. A major driving force has been the considerable evidence that has accumulated in support of the existence of three distinct opioid receptor subtypes: μ, κ, and δ.[1] Of particular significance has been the demonstration of the involvement of κ-opioid receptors in the control of nociception.[2] This has led to the suggestion that compounds with a prominent κ-agonist component might provide safer analgesics than traditional morphine-like μ-agonists: such analgesics should not cause the respiratory depression or constipation normally associated with morphine and in addition may not cause physical dependence.[3]

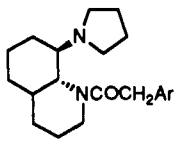
A key development in this area was the discovery by Upjohn researchers[4] of *N*-(2-aminocyclohexyl)arylacetamides, for which U-50488 is the prototype, as a class of selective κ-agonists. This has triggered an immense amount of research on κ-opioid receptors as medicinal chemists have sought to capitalize on this lead to obtain other series of structures and more potent/selective entities. Of these endeavors some structures represent aryl ring modifications[5] of U-50488 and others have incorporated alternative carbon frameworks. For example, ICI[6] has reported a series of acyclic κ-agonists (**1**), and Roussel[7] has reported a series of the conformationally constrained analogues (**2**). More recently a novel series of 2-[(alkylamino)methyl]piperidines (**3**) have been described which exhibit potent and selective κ-agonist activity.[8] This disclosure prompts us to describe in some detail our studies on this interesting class of compound, in particular structure–activity relationships with respect to the basic moiety and substitution of the piperidine nucleus. These studies have enabled us to identify GR 45809 (**39**), which incorporates a spirocyclic dioxolane moiety at the piperidine 4-position, as the most potent and selective κ-agonist in this series.



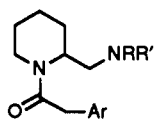
U-50488



1



2



3

Chemistry

Modification of the Basic Moiety. Our central intermediate for acquiring analogues incorporating changes in the basic nitrogen substituent was the carboxaldehyde **5** (Scheme I) which was obtainable in 69% overall yield from 2-piperidinemethanol. Reductive amination, although generally proceeding in modest (unoptimized) yields provided direct access to a variety of structures (**6–9**, **14–18**). The 3-hydroxypyrrolidinyl derivative **9** was selected as a suitable intermediate for exploring substitutions at the pyrrolidine ring 3-position. Thus, standard interconversions afforded the derivatives **10–13** (Scheme II).

† Department of Medicinal Chemistry.
‡ Department of Neuropharmacology.

(1) Martin, W. R.; Eades, C. G.; Thompson, J. A.; Huppler, R. E.; Gilbert, P. E. The Effects of Morphine- and Nalorphine-like Drugs in the Nondependent and Morphine-Dependent Chronic Spinal Dog. *J. Pharmacol. Exp. Ther.* **1976**, *197*, 517–532. Gilbert, P. E.; Martin, W. R. The Effects of Morphine- and Nalorphine-like Drugs in the Nondependent, Morphine-Dependent and Cyclazocine-Dependent Chronic Spinal Dog. *J. Pharmacol. Exp. Ther.* **1976**, *198*, 66–82. Lord, J. A. H.; Waterfield, A. A.; Hughes, J.; Kosterlitz, H. W. Endogenous Opioid Peptides: Multiple Agonists and Receptors. *Nature* **1977**, *267*, 495–499. For reviews, see Martin, W. R. Pharmacology of Opioids. *Pharmacol. Rev.* **1984**, *35*, 283–323. Paterson, S. J.; Robson, L. E.; Kosterlitz, H. W. Classification of Opioid Receptors. *Br. Med. Bull.* **1983**, *39*, 31–36. Zukin, R. S.; Zukin, S. R. The Case for Multiple Opiate Receptors. *Trends Neurosci.* **1984**, *7*, 160–164.

(2) For review, see Millan, M. J. κ-Opioid Receptors and Analgesia. *Trends Pharmacol. Sci.* **1990**, *11*, 70–76.

(3) Cowan, A.; Gmerek, D. E. In Vivo Studies on Kappa Opioid Receptors. *Trends Pharmacol. Sci.* **1986**, *7*, 69–72.

(4) Szmuszkovicz, J.; Von Voightlander, P. F. Benzeneacetamide Amines: Structurally Novel Non-μ Opioids. *J. Med. Chem.* **1982**, *25*, 1125–1126.

(5) Clark, C. R.; Halfpenny, P. R.; Hill, R. G.; Horwell, D. C.; Hughes, J.; Jarvis, T. C.; Rees, D. C.; Schofield, D. Highly Selective κ-Opioid Analgesics. Synthesis and Structure–Activity Relationships of Novel *N*-[(2-Aminocyclohexyl)aryl]-acetamide and *N*-[(2-Aminocyclohexyl)aryloxy]acetamide Derivatives. *J. Med. Chem.* **1988**, *31*, 831–836.

(6) Costello, G. F.; Main, B. G.; Barlow, J. J.; Carroll, J. A.; Shaw, J. S. A Novel Series of Potent and Selective Agonists at the Opioid κ-receptor. *Eur. J. Pharmacol.* **1988**, *151*, 475–478.

(7) Clemence, F. et al. *Fr. Demande* FR 2,592,879, Jan 13, 1986.

(8) Vecchietti, V.; Giordani, A.; Giardina, G.; Colle, R.; Clarke, G. D. (2*S*)-1-(Arylacetyl)-2-(aminomethyl)piperidine Derivatives: Novel, Highly Selective κ-Opioid Analgesics. *J. Med. Chem.* **1991**, *34*, 397–403.

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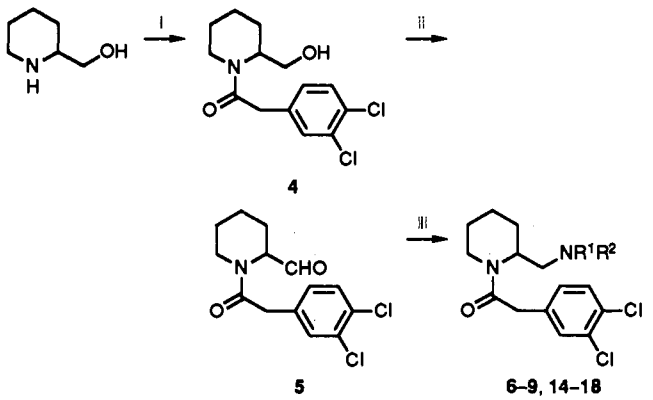
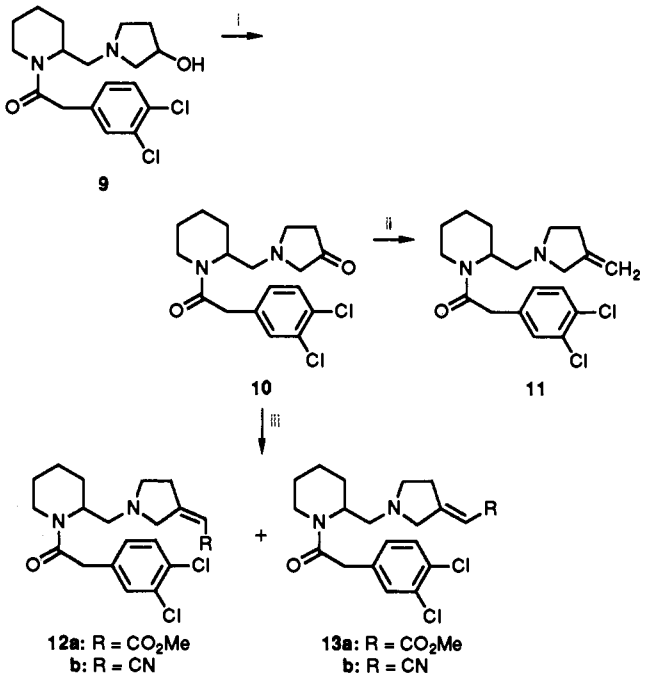
Scheme I[a]



[a] (i) 1,1′-Carbonyldiimidazole, 3,4-Cl_2-$C_6H_3CH_2CO_2H$; (ii) CrO_3, pyridine; (iii) HNR^1R^2, $NaBH_3CN$.

Scheme II[a]



[a] (i) DMSO, $(COCl)_2$, Et_3N; (ii) NaH, DMSO, $Ph_3P^+CH_3Br^-$; (iii) NaH, THF, $(MeO)_2P(=O)CH_2R$.

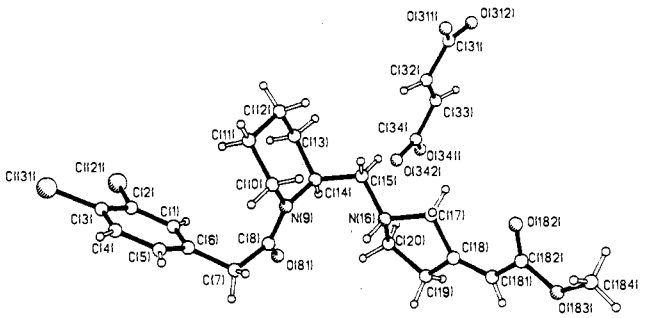
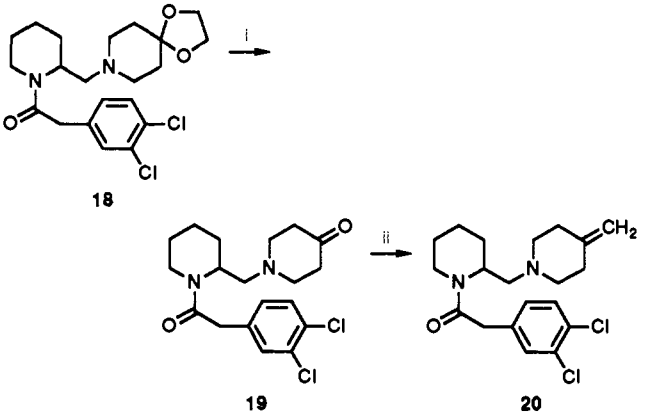


Figure 1. X-ray crystal structure of (±)-(*Z*)-methyl [1-[[1-[(3,4-dichlorophenyl)acetyl]-2-piperidinyl]methyl]-3-pyrrolidinylidene]acetate (**12a**).

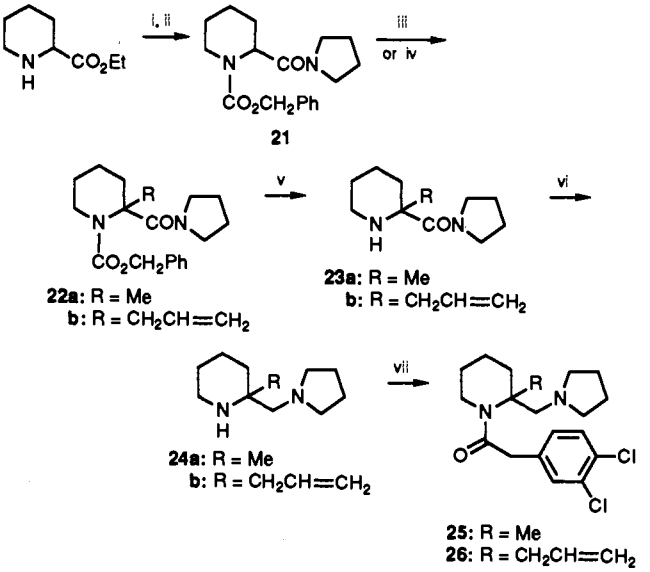
An X-ray crystal structure confirmed the structure of the *Z*-isomer **12a** (Figure 1), particularly noteworthy being the axial disposition of the pyrrolidinylmethyl side chain, a common feature within the *N*-acyl[(alkylamino)methyl]-piperidine class of κ-agonist (unpublished data and vide infra). The ketal **18** served as a suitable precursor to the piperidine derivatives **19** and **20** (Scheme III).

Scheme III[a]



[a] (i) 1 N H_2SO_4, CH_3COCH_3; (ii) NaH, DMSO, $Ph_3P^+CH_3Br^-$.

Scheme IV[a]



[a] (i) Pyrrolidine; (ii) $ClCO_2CH_2Ph$, Et_3N; (iii) LDA, MeI; (iv) LDA, CH_2=$CHCH_2Br$; (v) H_2, Pd–C (R = Me); CF_3SO_3H, anisole (R = CH_2CH=CH_2); (vi) $LiAlH_4$; (vii) 1,1′-carbonyldiimidazole, 3,4-Cl_2-$C_6H_3CH_2CO_2H$.

Table I. ^1H NMR Coupling Constant Data for *cis*- and *trans*-1-[(3,4-Dichlorophenyl)acetyl]-2-(1-pyrrolidinylmethyl)-3-piperidinols

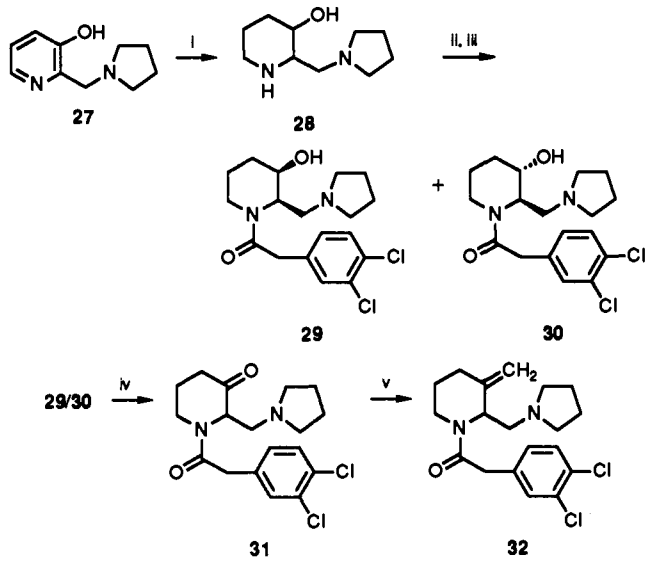
29	30
$J_{2eq,3ax}$ = 4.5 Hz	$J_{2eq,3eq}$ = 3 Hz
$J_{3ax,4ax}$ = 11 Hz	$J_{3eq,4ax}$ = 3 Hz
$J_{3ax,4eq}$ = 5 Hz	$J_{3eq,4eq}$ = 3 Hz

Substitution at the 2-Position of the Piperidine Nucleus. Compounds of this class were synthesized from ethyl pipecolinate (Scheme IV). The crucial quaternary center was constructed via alkylation (or allylation) of the stabilized anion generated from the carboxamide **21** using either LDA or *n*-butyllithium. Of particular note were the excellent yields (95–100%) obtained for the lithium aluminum hydride reduction of the hindered amide function in both **23a** and **23b**.

Substitution at the 3-Position of the Piperidine Nucleus. The Mannich product **27** of 3-hydroxypyridine[9] served as a convenient entry to this series (Scheme V). Thus, hydrogenation and acylation of **27** afforded an epimeric mixture of alcohols which were separated via frac-

(9) Stempel, A.; Buzzi, E. C. 3-Pyridols in the Mannich Reaction. *J. Am. Chem. Soc.* **1949**, *71*, 2969–2972.

Scheme V[a]

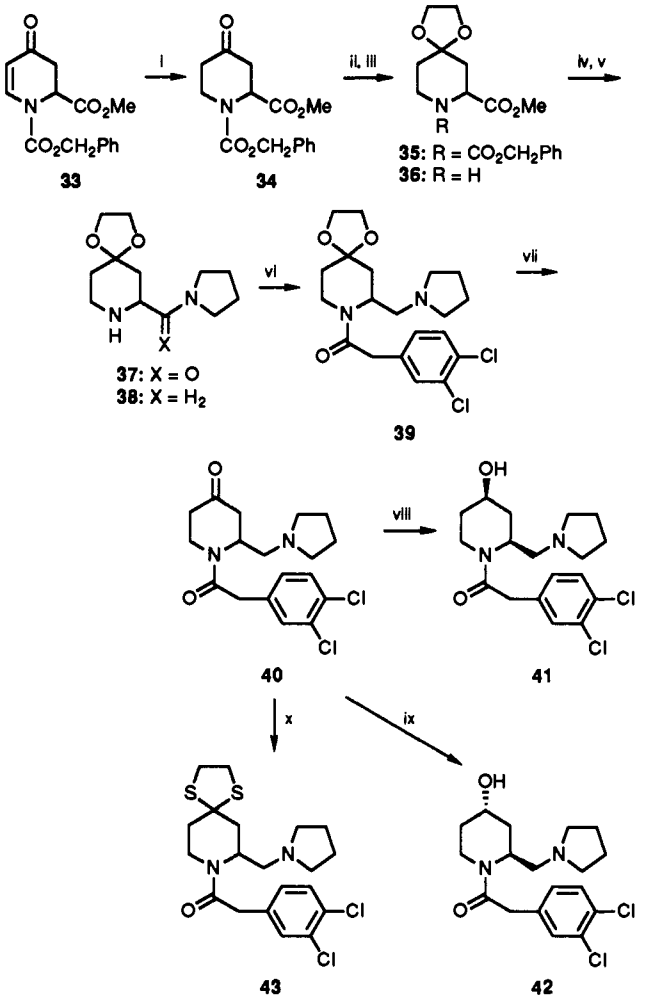


[a] (i) H_2, Pt, CH_3CO_2H; (ii) 1,1'-carbonyldiimidazole, 3,4-Cl_2-$C_6H_3CH_2CO_2H$; (iii) fractional crystallization of HCl salts; (iv) DMSO, $(COCl)_2$, Et_3N; (v) KOBu^t, THF, $Ph_3P^+CH_3Br^-$.

tional crystallization of their hydrochloride salts. Stereochemical assignment of the *cis*- and *trans*-3-hydroxy derivatives, **29** and **30**, respectively, was established by ^1H NMR spectroscopy (Table I): coupling constants ($J_{2,3}$) also indicate that for both isomers the pyrrolidinylmethyl substituent adopts an axial conformation. If **30** had adopted a conformation with the 2-pyrrolidinylmethyl side chain equatorial (and the 3-hydroxyl group axial), then two axial–axial couplings would have been expected. Swern oxidation and subsequent Wittig methylenation afforded the 3-keto **31** and 3-methylene **32** analogues.

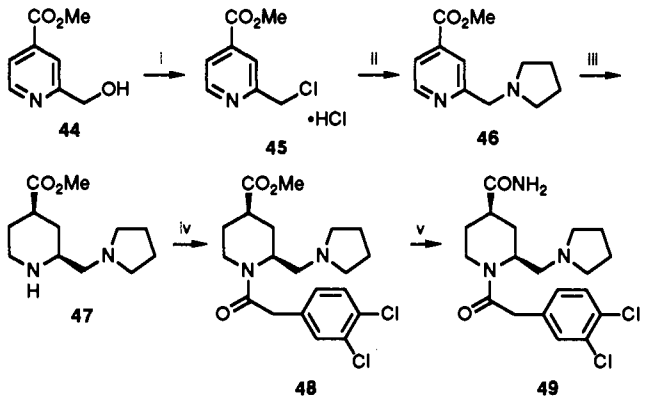
Substitution at the 4-Position of the Piperidine Nucleus. For introduction of oxygen functionality at the 4-position we selected the dihydropyridone **33** as starting material (Scheme VI). This intermediate is readily accessed via the aza Diels–Alder reaction developed by Jung et al.[10] Conventional catalytic hydrogenation of enone **33** gave variable results, but the use of methyldiphenylsilane in the presence of Wilkinson's catalyst[11] afforded good yields of the ketone **34**. Following ketalization and deblocking of the nitrogen, the intermediate amino ester **36** was converted via standard transformations to the spirocyclic dioxolane version **39** of the "parent" system (**6**). Compound **39** was deketalized to give the ketone **40** which in turn served as a precursor to the alcohols **41** and **42** and the spirocyclic dithiolane **43**. The *cis*-4-hydroxy derivative **41** was obtained stereospecifically from the corresponding ketone in good yield using diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide.[12] The relative stereochemistry of **41** was confirmed by ^1H NMR spectroscopy (at 404 K to remove complications of rotamers about the arylacetamide linkage): the signal for 4-H was a quintet, J = 4 Hz, i.e. equatorial, and that for 2-H displayed cou-

Scheme VI[a]



[a] (i) Me_2PhSiH, $(Ph_3P)_3RhCl$; (ii) $(HOCH_2)_2$, PTSA; (iii) H_2, Pd–C; (iv) pyrrolidine; (v) $LiAlH_4$; (vi) 1,1'-carbonyldiimidazole, 3,4-Cl_2-$C_6H_3CH_2CO_2H$; (vii) H_2SO_4, CH_3COCH_3; (viii) DIBAL, BHT; (ix) $NaBH_4$, Al_2O_3; (x) $(HSCH_2)_2$, BF_3·Et_2O.

Scheme VII[a]

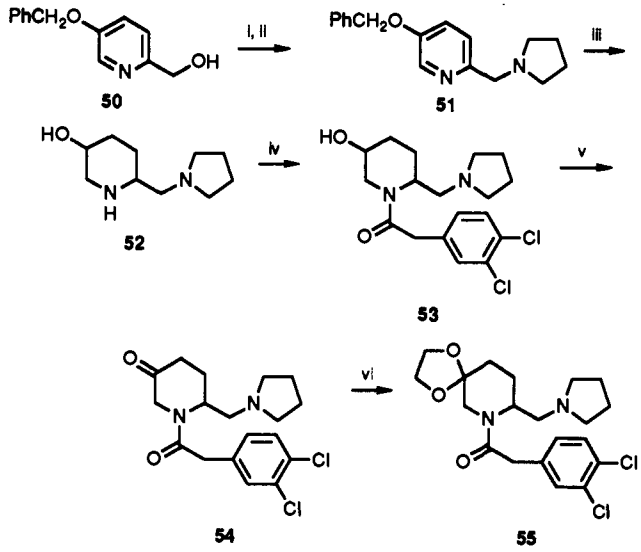


[a] (i) $SOCl_2$; (ii) Et_3N, then pyrrolidine; (iii) H_2, Rh–C; (iv) 1,1'-carbonyldiimidazole, 3,4-Cl_2-$C_6H_3CH_2CO_2H$; (v) NH_3, EtOH.

plings of 2.5, 6, 6.5, and 7.5 Hz to adjacent protons, confirming it also to be equatorial. Preparation of the trans isomer presented greater difficulty, and we resorted to sodium borohydride reduction which afforded a 70:30 mixture of trans–cis isomers which were separated after extensive chromatography. The 4-methoxycarbonyl and 4-carboxamide analogues, **48** and **49**, respectively, were obtained via the route outlined in Scheme VII. For the

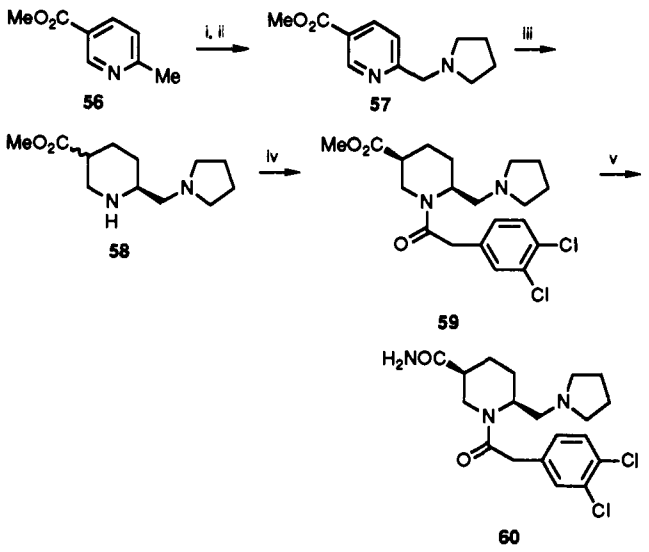
(10) Jung, M. E.; Shishido, K.; Light, L.; Davis, L. Preparation of Di- and Triacylimines and Their Use in the Synthesis of Nitrogen Heterocycles. *Tetrahedron Lett.* 1981, *22*, 4607–4610.
(11) Ojima, I.; Kogure, T.; Nagai, Y. Selective Reduction of α,β-Unsaturated Terpene Carbonyl Compounds Using Hydrosilane-Rhodium (I) Complex Combinations. *Tetrahedron Lett.* 1972, 5035–5038.
(12) Iguchi, S.; Nakai, H.; Hayashi, M.; Yamamoto, H.; Maruoka, K. Diisobutylaluminum 2,6-di-*t*-butyl-4-methylphenoxide. Novel Stereoselective Reducing Agent for Prostaglandin Synthesis. *Bull. Chem. Soc. Jpn.* 1981, *54*, 3033–3041.

Scheme VIII[a]



[a] (i) $SOCl_2$; (ii) pyrrolidine; (iii) H_2, $Rh-Al_2O_3$; (iv) 1,1′-carbonyldiimidazole, 3,4-Cl_2-$C_6H_3CH_2CO_2H$; (v) DMSO, $(COCl)_2$, Et_3N; (vi) $(HOCH_2)_2$, PTSA.

Scheme IX[a]



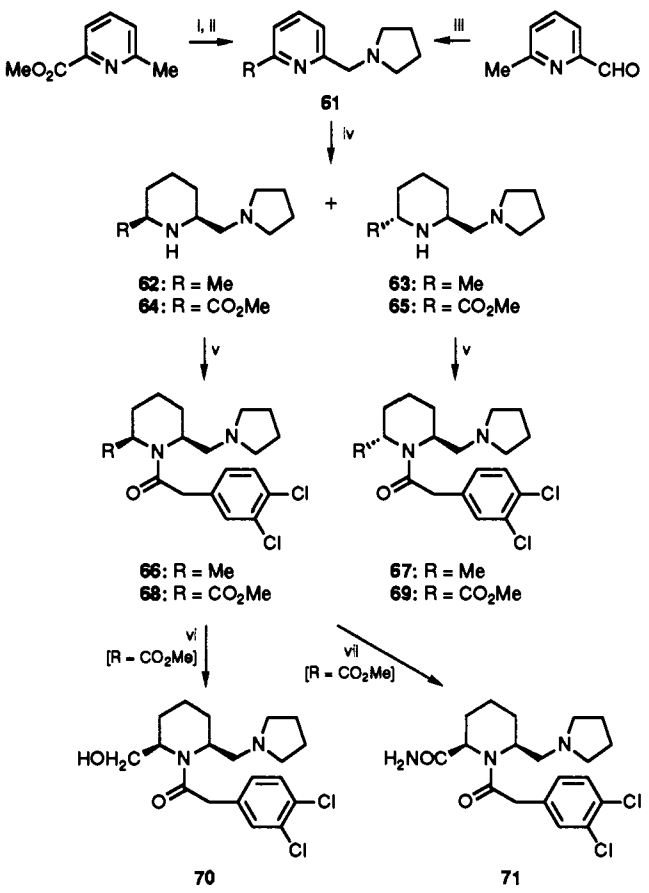
[a] (i) NBS, $(PhCO_2)_2$, $h\nu$; (ii) pyrrolidine; (iii) H_2, Pt, CH_3CO_2H; (iv) 3,4-Cl_2-$C_6H_3CH_2COCl$, Et_3N; (v) NH_3, MeOH.

conversion of the intermediate (chloromethyl)pyridine **45** to the pyrrolidinylmethyl derivative **46** it was crucial to run the displacement reaction at low temperature to avoid amidation of the 4-ester group.

Substitution at the 5-Position of the Piperidine Nucleus. As above, appropriately substituted pyridines served as precursors for this series (Schemes VIII and IX). Thus, to obtain the 5-oxo and 5-spirodioxolane derivatives, **54** and **55**, respectively, standard transformations starting from 5-(benzyloxy)-2-pyridinemethanol (**50**) were employed. No attempt was made to separate the epimeric mixture of piperidinols (**53**), and these were directly converted via Swern oxidation to provide ketone **54** and thence ketalization to afford **55**. The synthesis of the 5-methoxycarbonyl and 5-carboxamide analogues, **59** and **60**, respectively, are outlined in Scheme IX.

Substitution at the 6-Position of the Piperidine Nucleus. Hydrogenation of the pyridines **61** (R = Me, CO_2Me) gave predominantly the *cis*-diamines **62** and **64**, which were converted to the arylacetamides **66** and **68** in

Scheme X[a]



[a] (i) NBS, $(PhCO_2)_2$, $h\nu$; (ii) pyrrolidine; (iii) pyrrolidine, H_2, Pt; (iv) H_2, Pt, CH_3CO_2H; (v) 1,1′-carbonyldiimidazole, 3,4-Cl_2-$C_6H_3CH_2CO_2H$; (vi) $NaBH_4$; (vii) NH_3.

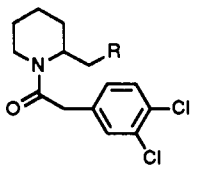
the usual way (Scheme X). However, it was possible to isolate a small amount of each of the corresponding trans isomers from the hydrogenation reaction, and these allowed access to systems **67** and **69**. The methoxycarbonyl group of **68** was further modified to afford the *cis*-hydroxymethyl and *cis*-carboxamide analogues, **70** and **71**, respectively.

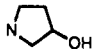
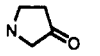
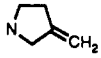
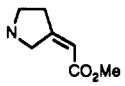
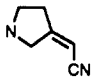
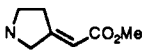
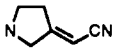
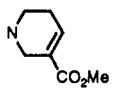
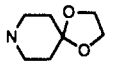
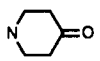
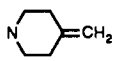
Biological Results and Discussion

The κ-agonist potency of the 2-[(alkylamino)methyl]-piperidine amides was determined in vitro using the rabbit vas deferens (LVD) preparation, which contains only κ-opioid receptors.[13] For selected compounds, receptor selectivity was assessed by comparing activity in the LVD with that in the rat vas deferens (RVD)[14] and hamster vas deferens (HVD),[15] which contain only μ- and δ-receptors, respectively. Antinociceptive activity was determined using the mouse acetylcholine-induced abdominal constriction test[16] following subcutaneous administration.

(13) Oka, T.; Negishi, K.; Suda, M.; Matsumiya, T.; Ueki, M. Rabbit Vas Deferens: A Specific Bioassay for Opioid κ-Receptor Agonists. *Eur. J. Pharmacol.* **1981**, *73*, 235–236.
(14) Smith, C. F. C.; Rance, M. J. Opiate Receptors in the Rat Vas Deferens. *Life Sci.* **1983**, *33* (Suppl. 1), 327–330.
(15) Corbett, A. D.; Kosterlitz, H. W.; McKnight, A. T.; Marcoli, M. Hamster Vas Deferens Contains δ-Opioid Receptors. *J. Physiol.* **1984**, *357*, 128P. Sheehan, M. J.; Hayes, A. G.; Tyers, M. B. Pharmacology of δ-Opioid Receptors in the Hamster Vas Deferens. *Eur. J. Pharmacol.* **1986**, *130*, 57–64.
(16) Hayes, A. G.; Sheehan, M. J.; Tyers, M. B. Differential Sensitivity of Models of Antinociception in the Rat, Mouse and Guinea-Pig to μ- and κ-Opioid Receptor Agonists. *Br. J. Pharmacol.* **1987**, *91*, 823–832.

Table II. Modification of Basic Moiety: Rabbit Vas Deferens (LVD) and Antinociception Test Results



no.[a]	R	LVD: IC_{50}, nM[b]	mouse Ach-induced abdominal constriction: ED_{50}, mg/kg, sc
6		11	0.03 (0.02–0.05)
7		3.5	0.04 (0.003–0.5)
8		69	0.38 (0.15–0.93)
9		0.88	0.01 (0.005–0.021)
10		0.20	0.06 (0.03–0.09)
11		29	0.05 (0.03–0.1)
12a		4.7	0.07 (0.02–0.16)
12b		0.12	0.19 (0.11–0.32)
13a		1020	6.6 (2.9–15.5)
13b		690	>10
14	NMe_2	102	0.064 (0.004–0.4)
15		260	0.24 (0.04–0.75)
16		6.3	0.009 (0.003–0.024)
17		15	0.41 (0.26–0.70)
18		NT[c]	>10
19		NT	>10
20		550	NT
U-50488		370	0.41 (0.23–0.70)

[a] All compounds tested as racemates. [b] Figures quoted are the mean of two independent determinations typically with the individual values within ±10% of the mean. [c] NT = not tested.

ED_{50} values were determined in each case.

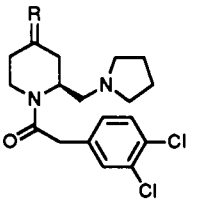
All of the compounds[17] which were active in the LVD behave as full agonists. One striking feature apparent from modifying the basic moiety (Table II) was the marked fall in in vitro κ-agonist potency (LVD data) and antinociceptive activity upon replacement of the pyrrolidinyl (6) group by a piperidinyl (15) group. Subtle effects are, however, in evidence since the tetrahydropyridine analogue 16 and its 3-carbomethoxy derivative 17 show appreciable activity. Substitution at the 4-position of the piperidine ring (basic side chain) is clearly detrimental (cf. 18–20), presumably reflecting steric constraints in this region.

(17) Although in the present work compounds were tested as their racemates, it has previously been demonstrated that the κ-agonist activity of 6 resides in its (S)-enantiomer.[8]

Table III. Measured pK_a Values of Selected κ-Agonists

compd	pK_a	compd	pK_a
6	9.0	10	5.3
9	8.1	11	7.7

Table IV. Substitution at the 4-Position of the Piperidine Nucleus: Rabbit Vas Deferens (LVD) and Antinociception Test Results



no.[a]	R	LVD: IC_{50}, nM[b]	mouse Ach-induced abdominal constriction: ED_{50}, mg/kg, sc
39	OCH_2CH_2O	0.1	0.001 (0.0003–0.002)
40	O	46	0.018 (0.012–0.027)
41	β-OH, α-H	120	0.27 (0.16–0.43)
42	α-OH, β-H	1400	1.4 (0.74–2.6)
43	SCH_2CH_2S	5	0.025 (0.02–0.04)
48	β-CO_2Me, α-H	250	>10
49	β-$CONH_2$, α-H	1200	>10

[a] All compounds tested as racemates. [b] Figures quoted are the mean of two independent determinations typically with the individual values within ±10% of the mean.

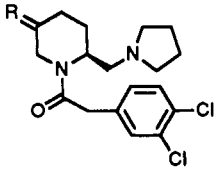
Considerable variation is possible in the nature of the substitution at the 3-position of the pyrrolidine ring,[18] and this can lead to some highly potent κ-agonists. For example, in the case of the 3-oxo derivative 10, its activity in vitro at κ-receptors is some 50 times that of the "parent" structure (6). However, there are clear steric constraints as demonstrated by the pairs of α,β-unsaturated esters/nitriles (12a and 13a) and (12b and 13b). The Z-isomers are some 2–3 orders of magnitude more potent than the E-isomers, and it could be argued that in the latter isomers the carboethoxy/nitrile group is held in the position occupied by the 4-substituent on a piperidine ring (cf. 18–20).

Compound 10 showed high selectivity for the κ-receptor as evidenced by the lack of agonist or antagonist activity in the RVD and HVD up to a concentration of 10^{-5} M. In the mouse, 10 produced only low maximum effects in causing respiratory depression and inhibition of gut propulsion over a dose range of 0.3–3 mg/kg, sc, and in the rat, a maximal diuretic effect[21] was observed over the dose range 0.125–2 mg/kg, sc.

A further interesting feature to emerge from this group of compounds is that κ-opioid activity is independent of the pK_a of the basic nitrogen (Table III). For example, compounds 9 and 10, which display similar activity as

(18) Halfpenny, P. R.; Hill, R. G.; Horwell, D. C.; Hughes, J.; Hunter, J. C.; Johnson, S.; Rees, D. C. Highly Selective κ-Opioid Analgesics. 2. Synthesis and Structure–Activity Relationships of Novel N-[(2-Aminocyclohexyl)aryl]acetamide Derivatives. J. Med. Chem. 1989, 32, 1620–1626.
(19) Hayes, A. G.; Birch, P. J.; Hayward, N. J.; Sheehan, M. J.; Rogers, H.; Tyers, M. B.; Judd, D. B.; Scopes, D. I. C.; Naylor, A. A Series of Novel, Highly Potent and Selective Agonists for the κ-Opioid Receptor. Br. J. Pharmacol. 1990, 101, 944–948.
(20) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. Purification of Laboratory Chemicals; Pergamon: Oxford, 1980.
(21) Hayes, A. G.; Skingle, M.; Tyers, M. B. Evaluation of the Receptor Selectivities of Opioid Drugs by Investigating the Block of Their Effect on Urine Output by β-Funaltrexamine. J. Pharmacol. Exp. Ther. 1987, 240, 984–988.

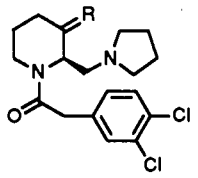
Table V. Substitution at the 5-Position of the Piperidine Nucleus: Rabbit Vas Deferens (LVD) and Antinociception Test Results



no.[a]	R	LVD: IC_{50}, nM[b]	mouse Ach-induced abdominal constriction: ED_{50}, mg/kg, sc
54	O	390	0.91 (0.59–1.4)
55	OCH_2CH_2O	160	1.1 (0.76–1.8)
59	β-CO_2Me, α-H	300	NT[c]
60	β-$CONH_2$, α-H	>10000	NT

[a] All compounds tested as racemates. [b] Figures quoted are the mean of two independent determinations typically with the individual values within ±10% of the mean. [c] NT = not tested.

Table VI. Substitution at the 3-Position of the Piperidine Nucleus: Rabbit Vas Deferens (LVD) and Antinociception Test Results



no.[a]	R	LVD: IC_{50}, nM[b]	mouse Ach-induced abdominal constriction: ED_{50}, mg/kg, sc
29	β-OH, α-H	590	1.7 (1.2–2.5)
30	α-OH, β-H	970	3.6 (2.3–5.7)
31	O	2000	3.4 (1.6–7.6)
32	CH_2	NT[c]	0.11 (0.07–0.16)

[a] All compounds tested as racemates. [b] Figures quoted are the mean of two independent determinations typically with the individual values within ±10% of the mean. [c] NT = not tested.

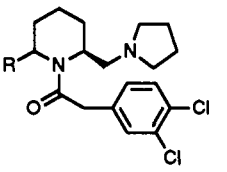
κ-agonists (LVD data), span almost 3 pK_a units in terms of their basicity.

The most dramatic increase in potency was achieved through introduction of a spirocyclic dioxolane ring at the 4-position of the piperidine nucleus (**39**, GR 45809), one of the most potent κ-agonists thus far reported[19] (Table IV). In contrast, a marked fall in activity was observed when this modification was incorporated at the 5-position (**55**) (Table V). The corresponding keto derivatives are less active with the 4-ketopiperidine **40** being of similar potency to the unsubstituted system (**6**). The selectivity of GR 45809 for κ-opioid receptors was established by the fact that in both the RVD and the HVD this compound showed only weak antagonist activity (pK_b 5.5). Clearly the position and nature of the dioxolanyl moiety is crucial: hydroxylation at the 3- or 4-position (Tables IV and VI) markedly attentuates activity (cf. **29**, **30**, **41**, and **42**). The activities in vitro are essentially paralleled by the antinociceptive potencies, GR 45809 being some 400 times more potent than U-50488.

Incorporation of ester and amide functionalities at the 4-, 5-, and 6-positions (Tables IV, V, and VII) was detrimental to κ-opioid activity, whereas introduction of 6-methyl is far better tolerated, and in the case of the cis diaxial isomer this results in a more potent compound than the "parent" system (**6**).

Although we have conducted only a limited investigation of 2-substitution in the piperidine nucleus (Table VIII),

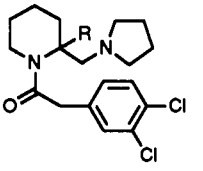
Table VII. Substitution at the 6-Position of the Piperidine Nucleus: Rabbit Vas Deferens (LVD) and Antinociception Test Results



no.[a]	R	LVD: IC_{50}, nM[b]	mouse Ach-induced abdominal constriction: ED_{50}, mg/kg, sc
66	β-Me	1.7	0.034 (0.02–0.07)
67	α-Me	57	0.4 (0.003–2.5)
68	β-CO_2Me	>10000	NT[c]
69	α-CO_2Me	110	0.43 (0.16–1.34)
70	β-CH_2OH	2200	NT
71	β-$CONH_2$	>10000	NT

[a] All compounds tested as racemates. [b] Figures quoted are the mean of two independent determinations typically with the individual values within ±10% of the mean. [c] NT = not tested.

Table VIII. Substitution at the 2-Position of the Piperidine Nucleus: Rabbit Vas Deferens (LVD) and Antinociception Test Results



no.[a]	R	LVD: IC_{50}, nM	mouse Ach-induced abdominal constriction: ED_{50}, mg/kg, sc
25	Me	>10000	0.66 (0.38–1.17)
26	$CH_2CH{=}CH_2$	>10000	2.4 (1.1–5.1)

[a] Compounds tested as racemates.

in both cases (**25** and **26**) there was no evidence for κ-opioid activity (agonist or antagonist). However, compound **25** had an IC_{50} of 5.3×10^{-8} M in the guinea pig ileum (a tissue which contains both μ- and κ-opioid receptors), suggesting that this structure has μ-agonist activity, and this may account for its activity in the antinociceptive test. A similar profile was observed for the 2-allyl analogue **26**.

In conclusion, this work demonstrates that highly potent and selective κ-receptor agonists can be obtained through modification of the 2-[(alkylamino)methyl]piperidine system (**3**). In particular, this has been achieved by the introduction of oxygen-containing functionality into either the piperidine nucleus (C-4 position) or the pyrrolidinylmethyl side chain (C-3 position).

Experimental Section

^1H NMR spectra were measured ($SiMe_4$ internal standard) on a Bruker WM250 (250 MHz) spectrometer. Signals for minor rotamers are indicated by an asterisk. IR spectra were recorded on Perkin-Elmer 357 or 377 spectrometers. Spectroscopic and microanalytical data were obtained by Glaxo Structural Chemistry Department. All melting points are uncorrected. Column chromatography was performed using either Merck Kieselgel 60 (Art 9385, flash chromatography) or alumina UG1 (Phase Separations Ltd.). Solvents were dried according to standard procedures.[20]

1-[(3,4-Dichlorophenyl)acetyl]-2-piperidinemethanol (4). A solution of 3,4-dichlorophenylacetic acid (10.1 g, 49 mmol) and 1,1′-carbonyldiimidazole (8.45 g, 52 mmol) in acetonitrile (200 mL) was stirred at room temperature for 20 min. A solution of 2-piperidinemethanol (5.6 g, 49 mmol) in acetonitrile (50 mL) was added, and the reaction mixture was stirred at room temperature

for 6 h. The acetonitrile was evaporated, and the residue was dissolved in dichloromethane (200 mL) and washed first with aqueous sodium carbonate (2 M, 80 mL) and then hydrochloric acid (0.5 N, 40 mL). The organic phase was dried and evaporated, and the residue was purified by column chromatography on silica gel, eluting with dichloromethane–methanol (9:1) to give 4 (7.65 g, 52%): mp 108–110 °C. Anal. ($C_{14}H_{17}Cl_2NO_2$) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-2-piperidinecarboxaldehyde (5). Chromium trioxide (5.40 g, 54 mmol) was added portionwise to a solution of pyridine (9.0 g, 8.6 mL, 110 mmol) in dichloromethane (120 mL) at room temperature under nitrogen, and the resulting solution was stirred for 30 min. A solution of 4 (3.0 g, 9.93 mmol) in dichloromethane (40 mL) was added, and the mixture was stirred for 1 h. The reaction mixture was poured into ether (2 L) and filtered. The filtrate was evaporated to dryness, and the residue was purified by flash column chromatography on silica gel. Elution with ethyl acetate–hexane (1:1) afforded 5 (2.05 g, 69%) as a colorless oil which crystallized upon standing: mp 64–68 °C; NMR ($CDCl_3$) δ 1.21–1.45 (2 H, m), 1.5–1.8 (3 H, m), 2.28 (1 H, br d), 2.58*, 3.14 (1 H, 2 × br t, H_{6aX}), 3.6–3.8, 4.67* (3 H, m, H_{6eq} + $COCH_2Ar$), 4.38*, 5.21 (1 H, 3 × br d, H_2), 7.12 (1 H, dd, ArH), 7.3–7.5 (2 H, m, ArH), 9.52, 9.56* (1 H, 2 × s, CHO). Anal. ($C_{14}H_{15}Cl_2NO_2$) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-2-[[1-(3-hydroxypyrrolidinyl)]methyl]piperidine (9). A solution of 5 (3.00 g, 10.0 mol) in methanol (75 mL) was added to a solution of 3-hydroxypyrrolidine (1.31 g, 15.0 mmol) in methanol (50 mL) containing 5 N hydrochloric acid in methanol (3.75 mL) and 3-Å molecular sieves (4 g). Sodium cyanoborohydride (945 mg, 15.0 mmol) was added portionwise, and the mixture was stirred at room temperature for 3 days. The reaction mixture was filtered, the filtrate was evaporated to dryness, and the residue was partitioned between dichloromethane (100 mL) and aqueous 2 M sodium carbonate solution (30 mL). The aqueous layer was separated and reextracted with dichloromethane (100 mL). The combined organic extracts were washed with water, dried, and evaporated to give a colorless gum. This material was purified by flash chromatography on silica gel, eluting with dichloromethane–methanol (9:1), to afford 9 (2.59 g, 70%). This material was characterized as its maleate salt: mp 141–144 °C; NMR (D_2O) δ 1.22–1.44 (1 H, m), 1.45–1.85 (5 H, m), 1.95–2.5 (2 H, m), 3.2–3.4 (3 H, m), 3.7–4.1 (7 H, m), 4.65 (1 H, br s), 5.11 (1 H, br d), 7.18 (1 H, br d), 7.42 (1 H, br s), 7.52 (1 H, d). Anal. ($C_{22}H_{28}Cl_2N_2O_6$) C, H, N, Cl.

The following compounds were similarly prepared:

1-[(3,4-Dichlorophenyl)acetyl]-2-(1-pyrrolidinylmethyl)piperidine (6) (76%), characterized as the fumarate salt: mp 186 °C. Anal. ($C_{22}H_{28}Cl_2N_2O_5$) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-2-[[1-(3-pyrrolinyl)]methyl]piperidine (7) (28%), characterized as the maleate salt: mp 162–164 °C. Anal. ($C_{22}H_{26}Cl_2N_2O_5$) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-2-(2-isoxazolidinylmethyl)piperidine (8) (47%), characterized as the hydrochloride salt: mp 170–172 °C. Anal. ($C_{17}H_{22}Cl_2N_2O_2$·HCl) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-*N*,*N*-dimethyl-2-piperidinemethanamine (14) (71%), characterized as the maleate salt: mp 116–119 °C. Anal. ($C_{20}H_{26}Cl_2N_2O_5$) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-2-(1-piperidinylmethyl)piperidine (15) (36%), characterized as the fumarate salt: mp 178–180 °C. Anal. ($C_{23}H_{30}Cl_2N_2O_5$) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-2-[[1-(1,2,3,6-tetrahydropyridinyl)]methyl]piperidine (16) (46%), characterized as the fumarate salt: mp 181–183 °C. Anal. ($C_{23}H_{28}Cl_2N_2O_5$) C, H, N.

Methyl 1-[[1-[(3,4-dichlorophenyl)acetyl]-2-piperidinyl]methyl]-1,2,5,6-tetrahydro-3-pyridinecarboxylate (17): 18%; characterized as the fumarate salt; mp 78–80 °C. Anal. ($C_{25}H_{30}Cl_2N_2O_7 \cdot {}^2/_3H_2O$) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-2-[(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)methyl]piperidine (18) (66%), characterized as the maleate salt: mp 172.5–174 °C. Anal. ($C_{25}H_{32}Cl_2N_2O_7$) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-2-[[1-(3-oxopyrrolidinyl)]methyl]piperidine (10). DMSO (0.93 g, 11.9 mmol) in dichloromethane (3 mL) was added to a stirred solution of oxalyl chloride (0.75 g, 5.9 mmol) in dichloromethane (12 mL) at −60 °C. The mixture was stirred for 3 min, and the alcohol 9 (2.00 g, 5.39 mmol) in dichloromethane (5 mL) was added over a 5-min period. Stirring was continued for an additional 15 min, and triethylamine (2.72 g, 26.9 mmol) was added. The reaction mixture was stirred for 5 min and then allowed to warm to room temperature. Water (30 mL) was added, the organic layer was separated, and the aqueous layer was further extracted with dichloromethane (30 mL). The combined organic phases were washed with saturated aqueous NaCl solution and dried, and the solvent was removed to give a yellow oil which crystallized upon standing at 4 °C. This material was recrystallized from ethyl acetate–diethyl ether to afford 10 (0.605 g, 30%). The mother liquors were purified by column chromatography on alumina, eluting with ethyl acetate, to afford a further quantity of product: 0.615 g. Total yield of 10: 1.22 g (61%). This compound was characterized as its maleate salt: mp 152–155 °C; NMR ($CDCl_3$) (free base) δ 1.20–1.84 (6 H, m, 3 × CH_2), 2.32–2.70 (3 H, m), 2.80–3.20 (6 H, m), 3.72 (2 H, AB system, J = 15 Hz, $COCH_AH_BAr$), 3.6, 4.6* (1 H, 2 × m, H_6), 4.0*, 5.0 (1 H, 2 × m, H_2), 7.1 (1 H, dd, J = 2, 8 Hz, ArH), 7.3–7.45 (2 H, m, ArH). Anal. ($C_{22}H_{26}Cl_2N_2O_6$) C, H, Cl, N.

1-[(3,4-Dichlorophenyl)acetyl]-2-[[1-(3-methylenepyrrolidinyl)]methyl]piperidine (11). To the Wittig reagent, prepared from sodium hydride (0.16 g, 3.3 mmol, 50% dispersion with oil) and methyltriphenylphosphonium bromide (1.18 g, 3.3 mmol) in dry DMSO (15 mL) was added the ketone 10 (0.61 g, 1.65 mmol) in dry DMSO (5 mL) over a 10-min period. The reaction mixture was stirred at 45 °C for 1 h, cooled, and poured into ice–water. The resultant aqueous mixture was extracted with ethyl acetate (2 × 100 mL). The combined ethyl acetate extracts were washed with saturated aqueous NaCl solution, dried, and evaporated to leave a pale yellow gum. This material was purified by column chromatography on alumina, eluting with diethyl ether–ethyl acetate (1:1), to afford 11 as a colorless gum (500 mg, 82%). This compound was characterized as its maleate salt: mp 129–131 °C. Anal. ($C_{23}H_{28}Cl_2N_2O_5$) C, H, N, Cl.

(*Z*)-Methyl [1-[[1-[(3,4-Dichlorophenyl)acetyl]-2-piperidinyl]methyl]-3-pyrrolidinylidene]acetate (12a) and *E*-Isomer (13a). A solution of trimethyl phosphonoacetate (543 mg, 2.98 mmol) in dry tetrahydrofuran (2 mL) was added dropwise to a stirred suspension of sodium hydride (50% dispersion in oil, 307 mg, 6.4 mmol) in dry tetrahydrofuran (60 mL) under nitrogen. The suspension was stirred for 5 min before a solution of 10 (1.0 g, 2.7 mmol) in dry tetrahydrofuran (5 mL) was added dropwise. The reaction mixture was refluxed under nitrogen for 2.5 h, cooled, quenched with water (60 mL), and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with saturated aqueous NaCl solution, dried, and evaporated to afford a brown oil. This crude product was purified by column chromatography, eluting with ethanol–ethyl acetate (1:49), to provide initially the *E*-isomer 13a (269 mg, 23%) and then the *Z*-isomer 12a (267 mg, 23%). Compound 13a was characterized as its fumarate salt: mp 161–163 °C. Anal. ($C_{25}H_{30}Cl_2N_2O_7$) C, H, N.

Compound 12a was characterized as its fumarate salt: mp 115–118 °C. Anal. ($C_{25}H_{30}Cl_2N_2O_7$) C, H, N.

***Z*-2-[[3-(Cyanomethylene)-1-pyrrolidinyl]methyl]-1-[(3,4-dichlorophenyl)acetyl]piperidine (12b) and *E*-Isomer (13b).** A solution of diethyl (cyanomethyl)phosphonate (1.06 g, 6.0 mmol) in dry tetrahydrofuran (10 mL) was added dropwise to a stirred suspension of sodium hydride (57% dispersion in oil, 0.28 g, 6.6 mmol) in dry tetrahydrofuran (80 mL) at 0–5 °C. Stirring was continued at 0–5 °C for 1 h, and a solution of the ketone 10 (2 g, 5.4 mmol) in dry tetrahydrofuran (25 mL) was added. The mixture was stirred at ambient temperature overnight and then heated at reflux for 1 h. The reaction mixture was cooled, poured into aqueous NaCl solution (12% w/v, 50 mL) and extracted with ethyl acetate (2 × 75 mL). The combined organic extracts were washed with saturated aqueous NaCl (20 mL), dried, and evaporated to dryness. The residue was purified by flash chromatography on silica gel, with ethyl acetate–ethanol (100:1) as eluant, to give initially the *E*-isomer 13b (0.97 g, 46%) [mp 88–90 °C. Anal. ($C_{20}H_{23}Cl_2N_3O$) C, H, N] and then the *Z*-isomer 12b (0.42 g, 20%). Compound 12b was characterized as its hydrochloride salt: mp 218–221 °C. Anal. ($C_{20}H_{23}Cl_2N_3O$·HCl) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-2-[(4-oxo-1-piperidinyl)methyl]piperidine (19). Sulfuric acid (1 N, 10 mL) was added

to a solution of 18 (630 mg, 1.5 mmol) in acetone (20 mL), and the mixture was heated under reflux for 3.5 days. After cooling to room temperature, the acetone was removed, and the residue was treated with aqueous sodium carbonate solution (2 N, 4 mL). The mixture was extracted with ethyl acetate (3 × 10 mL), and the combined organic extracts were dried and evaporated to give an oil (448 mg). This was purified by flash column chromatography on silica gel, with ether–methanol (9:1) as eluant, to afford **19** (380 mg, 67%): mp 106–108 °C. This material was characterized as its maleate salt: mp 179–181 °C (from 2-propanol). Anal. ($C_{23}H_{28}Cl_2N_2O_6 \cdot 0.2C_3H_7OH$) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-2-[(4-methylene-1-piperidinyl)methyl]piperidine (20). To the Wittig reagent prepared from sodium hydride (1.2 g, 25 mmol, 50% dispersion in oil) and methyltriphenylphosphonium bromide (8.93 g, 25 mmol) in dry DMSO (10 mL) was added the ketone **19** (960 mg, 2.5 mmol) in dry DMSO (20 mL). The reaction mixture was stirred at 60 °C under nitrogen for 20 h, cooled, and poured into saturated aqueous ammonium chloride solution (100 mL). The resultant aqueous mixture was extracted with diethyl ether (3 × 100 mL) and the combined ether extracts were extracted with hydrochloric acid (0.1 M, 3 × 20 mL). The combined acidic phases were basified by addition of sodium carbonate and extracted with diethyl ether (3 × 40 mL). The combined organic extracts were washed with saturated aqueous NaCl solution, dried, and evaporated to dryness. The residue was purified by flash chromatography on silica gel, eluting with diethyl ether–methanol (19:1), to give **20** (830 mg, 87%), which was characterized as its maleate salt: mp 136–138 °C. Anal. ($C_{24}H_{30}Cl_2N_2O_5$) C, H, N.

Phenylmethyl 2-(1-Pyrrolidinylcarbonyl)-1-piperidinecarboxylate (21). Benzyl chloroformate (11.4 mL, 13.6 g, 80 mmol) was added dropwise over a 10-min period to a stirred solution of triethylamine (13.9 mL, 10.1 g, 100 mmol) and 1-(2-piperidinylcarbonyl)pyrrolidine (7.29 g, 40 mmol) in dichloromethane (100 mL) at −50 °C under nitrogen. The reaction mixture was stirred for 30 min at −50 °C, allowed to warm slowly to room temperature, and stirred for a further 3 h under nitrogen. The mixture was quenched with 2 N hydrochloric acid (100 mL), and the layers were separated. The aqueous fraction was further extracted with dichloromethane (2 × 50 mL), and the combined organic fractions were concentrated and purified by flash chromatography on silica gel, with ethyl acetate as eluant, to give **21** as a colorless oil (12.5 g, 98%). Anal. ($C_{18}H_{24}N_2O_3$) C, H, N.

Phenylmethyl 2-Methyl-2-(1-pyrrolidinylcarbonyl)-1-piperidinecarboxylate (22a). *n*-Butyllithium (7.1 mL, 11 mmol, 1.55 M solution in hexane) was added dropwise over a 10-min period to a stirred solution of diisopropylamine (1.61 mL, 1.16 g, 11.5 mmol) in dry tetrahydrofuran (15 mL) at −30 °C under nitrogen. The resulting solution was cooled to −60 °C and transferred, via a cannula, to a stirred solution of **21** (3.16 g, 10 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (6.0 mL, 6.4 g, 50 mmol) in dry tetrahydrofuran (5 mL) at −60 °C under nitrogen. The resulting solution was stirred at −60 °C for 1.5 h, and then methyl iodide (0.72 mL, 1.63 g, 11.5 mmol) was added dropwise over a 2-min period. The reaction mixture was stirred at −60 °C for 1 h, allowed to warm to room temperature, and stirred for a further 1 h and quenched with water (10 mL). The reaction mixture was concentrated and extracted with diethyl ether (2 × 20 mL). The combined ether extracts were dried, evaporated to dryness, and purified by flash chromatography on silica gel, with ethyl acetate–hexane (1:1 to 4:1) as eluant, to give **22a** as a colorless gum (0.69 g, 21%). Anal. ($C_{19}H_{26}N_2O_3$) C, H, N.

The following compounds were similarly prepared:

Phenylmethyl 2-(2-Propenyl)-2-(1-pyrrolidinylcarbonyl)-1-piperidinecarboxylate (22b): 61%; obtained as a colorless gum and used directly in the next stage.

1-[(2-Methylpiperidin-2-yl)carbonyl]pyrrolidine (23a). A mixture of **22a** (1.45 g, 4.4 mmol) and 5% palladium on carbon (145 mg) in ethanol (22 mL) was hydrogenated at room temperature and atmospheric pressure for 24 h. The reaction mixture was filtered, and the residue was washed with ethanol. The filtrate was concentrated and dried to give **23a** (0.86 g, 100%) as a white solid: mp 67–69 °C; NMR ($CDCl_3$) δ 1.1–1.3 (1 H, m), 1.22 (3 H, s, Me), 1.3–1.6 (3 H, m), 1.6–2.0 (6 H, m), 2.40 (1 H, td, J = 4, 13 Hz, H_{3eq}), 2.55 (1 H, dt, J = 3, 13 Hz, H_{6ax}), 2.88 (1 H, br d, J = 13 Hz, H_{6eq}), 3.45–3.80 (4 H, m, 2 × CH_2N).

1-[[2-(2-Propenyl)piperidin-2-yl]carbonyl]pyrrolidine (23b). Trifluoromethanesulfonic acid (2.12 mL, 3.6 g, 24 mmol) was added dropwise over a 5-min period to a solution of anisole (0.78 mL, 0.78 g, 7.2 mmol) and **22b** (1.71 g, 4.8 mmol) in dichloromethane (24 mL) at 0–5 °C under nitrogen. The reaction mixture was stirred at 0–5 °C for 30 min, quenched with water (10 mL), and basified with 2 N sodium hydroxide solution (15 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 25 mL). The combined organic extracts were dried and concentrated to give a yellow oil. This was purified by flash chromatography on silica gel, eluting with dichloromethane–methanol–0.88 ammonia (120:8:1), to give **23b** (0.91 g, 85%) as a pale yellow gum, which was used directly in the next stage.

2-Methyl-2-(1-pyrrolidinylmethyl)piperidine (24a). A solution of **23a** (140 mg, 0.7 mmol) in diethyl ether (7 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (80 mg, 2.1 mmol) in diethyl ether (3.5 mL) at room temperature under nitrogen. The stirred reaction mixture was heated at reflux for 6 h, cooled, and quenched with water (0.1 mL). Sodium hydroxide solution (5 N, 0.25 mL) and water (0.1 mL) were added, and the reaction mixture was stirred for 30 min at ambient temperature. The mixture was filtered, and the residues were washed with diethyl ether. The filtrate was concentrated to give **24a** as a colorless gum (120 mg, 92%), which was used directly in the next stage.

2-(2-Propenyl)-2-(1-pyrrolidinylmethyl)piperidine (24b). A solution of **23b** (1.04 g, 4.7 mmol) in diethyl ether (30 mL) was added dropwise to a suspension of lithium aluminum hydride (0.54 g, 14.1 mmol) in diethyl ether (20 mL) at room temperature under nitrogen. The stirred reaction mixture was heated at reflux for 6 h, cooled, and quenched with water (1 mL). Sodium hydroxide solution (5 N, 2 mL) and water (1 mL) were added cautiously to the cooled reaction mixture, which was stirred for 1 h at ambient temperature. The reaction mixture was filtered, the residues were washed with diethyl ether, and the filtrate was concentrated to give **24b** (0.97 g, 100%) as a colorless oil. Anal. ($C_{13}H_{24}N_2$) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-2-methyl-2-(1-pyrrolidinylmethyl)piperidine (25). 1′,1-Carbonyldiimidazole (647 mg, 4 mmol) was added portionwise to a stirred suspension of 3,4-dichlorophenylacetic acid (820 mg, 4 mmol) in dichloromethane (8 mL) at room temperature under nitrogen, and the resulting solution was stirred at ambient temperature for 1.5 h. 2-Methyl-2-(1-pyrrolidinylmethyl)piperidine (**24a**) (364 mg, 2 mmol) was added, and the mixture was stirred for 22 h under nitrogen. The reaction mixture was washed with 2 M sodium carbonate solution (2 × 10 mL). The organic phase was dried, concentrated, and purified by flash chromatography on silica gel, with dichloromethane–methanol–ammonia (200:8:1) as eluant, to give **25** (510 mg, 69%) as a gum. The product was characterized as its maleate salt: mp 118–120 °C; NMR (DMSO-d_6) δ 1.43 (3 H, s, Me), 1.6, 1.9 (10 H, 2 × m, 5 × CH_2), 3.2–3.75 (8 H, m, 4 × CH_2N), 3.76 (1 H, d, J = 15 Hz, CH_AH_BAr), 3.84 (1 H, d, J = 15 Hz, CH_AH_BAr), 7.22 (1 H, dd, J = 2, 8 Hz, ArH), 7.50 (1 H, d, J = 2 Hz, ArH), 7.58 (1 H, d, J = 8 Hz, ArH). Anal. ($C_{23}H_{30}Cl_2N_2O_5$) C, H, N.

The following compounds were similarly prepared:

1-[(3,4-Dichlorophenyl)acetyl]-2-(2-propenyl)-2-(1-pyrrolidinylmethyl)piperidine (26) (57%) which was obtained as a colorless viscous oil. Anal. ($C_{21}H_{28}Cl_2N_2O$) C, H, N.

2-(1-Pyrrolidinylmethyl)-3-piperidinol (28). A mixture of 2-(1-pyrrolidinylmethyl)-3-pyridinol (21.0 g, 118 mmol) and platinum oxide (1.0 g) in glacial acetic acid (120 mL) was hydrogenated at 70 psi and room temperature for 20 h. Further platinum oxide (1.0 g) was then added, and hydrogenation was continued at 70 psi for a further 24 h. The reaction mixture was then filtered through Celite, and the Celite was washed with glacial acetic acid. The combined filtrates were evaporated to dryness, and the residue was dissolved in water (200 mL). This solution was acidified to pH 1 with 5 N hydrochloric acid before washing with dichloromethane (2 × 70 mL). The aqueous layer was then basified (pH 14) with 5 N aqueous sodium hydroxide and extracted with dichloromethane (3 × 70 mL). The combined extracts were dried and concentrated to give an oil which was distilled

(Kugelrohr, 140 °C, 0.8 mmHg) to give **28** (6.17 g, 28%), which solidified as a colorless waxy solid. Anal. ($C_{10}H_{20}N_2O$) C, H, N.

***cis*-1-[(3,4-Dichlorophenyl)acetyl]-3-hydroxy-2-(1-pyrrolidinylmethyl)piperidine (29) and Trans Isomer (30).** A solution of 3,4-dichlorophenylacetic acid (4.45 g, 21.8 mmol) and 1,1′-carbonyldiimidazole (4.16 g, 26.2 mmol) in tetrahydrofuran (60 mL) was stirred at room temperature for 20 min before addition of a solution of **28** (4.0 g, 60:40 mixture of trans–cis isomers, 21.7 mmol). The reaction mixture was stirred for 16 h under nitrogen and then evaporated to dryness. Column chromatography of the residue on alumina, with graded elution from dichloromethane to dichloromethane–methanol (9:1) removed polar impurities but failed to separate cis and trans isomers. The isomeric mixture was converted to the hydrochloride salts and recrystallized from ethyl acetate–methanol (1:2). Filtration of the crystals thus formed gave the cis isomer **29** as its hydrochloride salt: mp 255–260 °C (HPLC determined this to be 98:2 cis–trans); NMR ($CDCl_3$) (free base) δ 1.2–1.52 (1 H, m), 1.56–1.90 (6 H, m), 1.92–2.05 (1 H, m), 2.10* (<1 H, dd, J = 4, 12 Hz, CH_AH_BN), 2.25 (<1 H, dd, J = 4, 12 Hz, CH_AH_BN), 2.30–2.95 (5 H, m), 3.40 (<1 H, t, J = 12 Hz, CH_AH_BN), 3.62* (<1 H, t, J = 12 Hz, CH_AH_BN), 3.66 (<1 H, dd, H_{6eq}), 3.5–3.8 (2 H, m, $COCH_2Ar$), 3.76 (1 H, ddd, J = 4.5, 5, 11 Hz, H_{3ax}), 4.22* (<1 H, ddd, J = 4, 4.5, 12 Hz, H_{2eq}), 4.49* (<1 H, dd, H_{6eq}), 5.16 (<1 H, ddd, J = 4, 4.5, 12 Hz, H_{2eq}), 7.0–7.1 (1 H, m, ArH), 7.3–7.5 (1 H, m, ArH). Anal. ($C_{18}H_{24}Cl_2N_2O_2$·HCl), C, H, N.

The mother liquors afforded the corresponding trans isomer **30** as its hydrochloride salt: mp 115–120 °C (HPLC determined this to be 97:3 trans–cis); NMR (DMSO-d_6, 423 K) (free base) δ 1.2–2.0 (8 H, m, 4 × CH_2), 2.5–3.0 (7 H, m, 3 × CH_2N, H_{6ax}), 3.6–3.8 (2 H, AB system, $COCH_AH_BAr$), 4.02 (1 H, br d, H_{6eq}), 4.32 (1 H, br t, $J \approx 7$ Hz, H_{2eq}), 3.84 (1 H, q, J = 3 Hz, H_{3eq}), 7.10 (1 H, dd, J = 2, 8 Hz, ArH), 7.43 (1 H, d, J = 8 Hz, ArH), 7.46 (1 H, d, J = 2 Hz, ArH). Anal. ($C_{18}H_{24}Cl_2N_2O_2$·HCl·0.57H_2O) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-2-(pyrrolidinylmethyl)-3-piperidone (31). DMSO (0.925 g, 11.86 mmol) in dichloromethane (3 mL) was added dropwise to a stirred solution of oxalyl chloride (0.753 g, 5.93 mmol) in dichloromethane (12 mL) at −60 °C under nitrogen. The reaction mixture was stirred for 3 min before addition of a solution of a mixture of cis and trans alcohols **29/30** (2.0 g, 5.37 mmol) in dichloromethane (5 mL) over ca. 5 min. After 15 min at −60 °C, triethylamine (2.72 g, 26.95 mmol) was added, and stirring was continued for a further 5 min. The reaction mixture was allowed to warm to 20 °C before addition of water (30 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (30 mL). The combined organic phases were dried and concentrated to give a pale yellow solid. This material was triturated with dry diethyl ether to give **31** (1.54 g, 77%) as an off-white solid, mp 74–76 °C, which was characterized as its hydrochloride salt: mp 145–147 °C; NMR ($CDCl_3$) (free base) δ 1.6–2.1 (6 H, m, 3 × CH_2), 2.4–3.0 (8 H, m, 3 × CH_2N, CH_2CO), 3.08*, 3.48 (1 H, m, H_{6ax}), 3.6–3.8 (3 H, m, $COCH_2Ar$, H_{6eq}), 4.60* (1 H, m, H_{6eq}), 4.40*, 5.20 (1 H, 2 × br t, H_2), 7.0–7.2 (1 H, m, ArH), 7.3–7.5 (2 H, m, ArH). Anal. ($C_{18}H_{22}Cl_2N_2O_2$·HCl) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-3-methylene-2-(1-pyrrolidinylmethyl)piperidine (32). A mixture of potassium *tert*-butoxide (129 mg, 1.15 mmol) and methyltriphenylphosphonium bromide (428 mg, 1.20 mmol) in dry tetrahydrofuran (10 mL) was stirred at ambient temperature for 1 h under nitrogen. To the stirred mixture was added a solution of **31** (369 mg, 1 mmol) in dry tetrahydrofuran (5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 4 h, and quenched with water (10 mL). The mixture was concentrated to remove the tetrahydrofuran, acidified with 2 N hydrochloric acid (10 mL), and washed with ethyl acetate (2 × 20 mL). The aqueous phase was basified with 5 N sodium hydroxide solution (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried and evaporated to dryness. The residue was purified by flash chromatography on silica gel, eluting with dichloromethane–methanol–0.88 ammonia (250:8:1), to give **32** (180 mg, 49%) as a colorless gum. This product was characterized as its maleate salt: mp 124–125 °C; NMR (DMSO-d_6) δ 1.32 (1 H, m, H_{5ax}), 1.7–2.1 (5 H, m, H_{5eq}, 2 × CH_2), 2.32 (2 H, m, H_{4ax}, H_{4eq}), 3.0–3.7 (7 H, m, 3 × CH_2N, H_{6ax}), 3.74 (1 H, d, J = 15 Hz, $COCH_AH_BAr$), 3.87 (1 H, d, J = 15 Hz, $COCH_AH_BAr$), 3.90 (1 H, m, H_{6eq}), 4.95, 5.06 (2 H, 2 × s, C=CH_2), 5.39 (1 H, dd, J = 5, 10 Hz, H_2), 7.22 (1 H, dd, J = 2, 8 Hz, ArH), 7.52 (1 H, d, J = 2 Hz, ArH), 7.60 (1 H, d, J = 8 Hz, ArH). Anal. ($C_{23}H_{28}Cl_2N_2O_5$) C, H, N.

7-Methyl 8-(Phenylmethyl) 1,4-Dioxa-8-azaspiro[4.5]decane-7,8-dicarboxylate (35). A mixture of **33** (2.89 g, 10 mmol), tris(triphenylphosphine)rhodium(I) chloride (48 mg, 0.05 mmol, 0.5 mol %) and dimethylphenylsilane (1.7 mL, 11.1 mmol) was stirred under nitrogen at 50 °C for 3 h and then evaporated to give a brown oil. This material was dissolved in acetonitrile (65 mL) and 40% aqueous hydrogen fluoride (1 mL, 20 mmol) was added to the solution in a polypropylene vessel. The mixture was allowed to stand at room temperature for 18 h and was then poured into saturated aqueous sodium bicarbonate (80 mL). After stirring for 2 h, ether (50 mL) was added, and the layers were separated. The aqueous layer was further extracted with ether (2 × 50 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride, dried, and evaporated to give an oil. This material was purified by column chromatography on silica gel, with ether–hexane (9:1) as eluant, to afford **34** (1.62 g, 56%) as a yellow oil which was used directly in the next stage. A solution of **34** (5.06 g, 17.4 mmol) and 1,2-ethanediol (1.06 mL, 19.1 mmol) in benzene (100 mL) containing 4-toluenesulfonic acid (0.2 g) was heated at reflux under a Soxhlet cup filled with 4-Å molecular sieves. After 4 h the reaction was allowed to cool to room temperature, washed with aqueous sodium carbonate solution (2 M, 2 × 20 mL) and water (20 mL), and dried. The benzene was evaporated to leave the **35** as a yellow oil (5.75 g, 99%). Anal. ($C_{17}H_{21}NO_6$) C, H, N.

Methyl 1,4-Dioxa-8-azaspiro[4.5]decane-7-carboxylate (36). A solution of **35** (5.50 g, 16.4 mmol) in ethyl acetate (60 mL) was hydrogenated over 10% palladium on carbon (0.50 g). After 4 h the catalyst was filtered off, and the filtrate was evaporated to give **36** as an oil: 3.0 g (91%); NMR ($CDCl_3$) δ 1.55–1.8 (3 H, m, H_{5ax}, H_{5eq}, H_{3ax}), 2.05 (2 H, m, H_{3eq}, NH), 2.87 (1 H, m, H_{6ax}), 3.16 (1 H, dt, H_{6eq}), 3.62 (1 H, dd, J = 4, 11 Hz, H_2), 3.74 (3 H, s, CH_3), 4.00 (4 H, m, OCH_2CH_2O). Anal. ($C_9H_{15}NO_4$) C, H, N.

1-[(8-Aza-1,4-dioxaspiro[4.5]dec-7-yl)carbonyl]pyrrolidine (37). A mixture of **36** (0.887 g, 4.4 mmol) and pyrrolidine (2.2 mL, 26.3 mmol) was heated at 150 °C for 2 h. The cooled reaction mixture was evaporated to dryness to give an oil. This was purified by flash chromatography on silica gel, with chloroform–methanol (9:1) as eluant, yielding **37** (841 mg, 79%) as an oil which crystallized to a yellow solid on standing: mp 72.5–74.5 °C. Anal. ($C_{12}H_{20}N_2O_3$) C, H, N.

7-(1-Pyrrolidinylmethyl)-8-aza-1,4-dioxaspiro[4.5]decane (38). A solution of **37** (712 mg, 2.96 mmol) in tetrahydrofuran (7.5 mL) was added dropwise to a stirred solution/suspension of lithium aluminum hydride (363 mg, 9.6 mmol) in tetrahydrofuran (15 mL) under nitrogen. The mixture was heated under reflux for 19 h and allowed to cool, and water (15 mL) was added dropwise. Aqueous sodium hydroxide (2 N, 5 mL) was added followed by chloroform (25 mL). Insoluble material was removed by filtration and washed thoroughly with chloroform, and the filtrate layers were separated. The organic solution was dried and evaporated to give crude product as a yellow oil. This was purified by column chromatography on alumina, with ether–methanol (19:1) as eluant, to yield **38** (287 mg, 43%). This material was used directly in the next stage: NMR ($CDCl_3$) δ 1.35 (1 H, t), 1.6–1.85 (8 H, m), 2.18 (1 H, dd, J = 4, 12 Hz), 2.22–2.7 (5 H, m), 3.06 (1 H, m), 3.96 (4 H, s).

8-[(3,4-Dichlorophenyl)acetyl]-7-(1-pyrrolidinylmethyl)-1,4-dioxa-8-azaspiro[4.5]decane (39). A solution of 1,1′-carbonyldiimidazole (200 mg, 1.23 mmol) in warm acetonitrile (2.2 mL) was added to a solution of 3,4-dichlorophenylacetic acid (240 mg, 1.17 mmol) in acetonitrile (4.2 mL) under nitrogen, and the mixture was stirred at room temperature for 1 h. A solution of **38** (250 mg, 1.1 mmol) in acetonitrile (2 mL) was added. Stirring was continued for a further 4 h, and the reaction mixture was then evaporated to dryness. The residue was partitioned between chloroform (25 mL) and aqueous sodium carbonate (2 M, 12 mL). The chloroform layer was washed with aqueous sodium carbonate (2 M, 12 mL) and water (2 × 12 mL), dried, and evaporated to dryness. The residue was purified by flash chromatography on silica gel, with dichloromethane–methanol (9:1) as eluant, to give

39 (347 mg, 76%) as an oil. This product was characterized as its hydrochloride salt: mp 139–141 °C; NMR (D_2O) δ 1.60 (1 H, dt, J = 5, 13 Hz, H_{5ax}), 1.77–2.15 (7 H, m, 3 × CH_2, H_{5eq}), 3.23 (1 H, dd, J = 3, 14 Hz, CH_AH_BN), 3.45 (1 H, t, J = 14 Hz, CH_AH_BN), 3.1–3.6 (5 H, m, 2 × CH_2N, H_{6ax}), 3.83–4.13 (7 H, m, $COCH_2Ar$, OCH_2CH_2O, H_{6eq}), 5.27 (1 H, m, H_2), 7.18 (1 H, dd, J = 2, 8 Hz, ArH), 7.44 (1 H, d, J = 2 Hz, ArH), 7.55 (1 H, d, J = 8 Hz, ArH). Anal. ($C_{20}H_{27}Cl_3N_2O_3 \cdot 0.75H_2O$) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-4-oxo-2-(1-pyrrolidinylmethyl)piperidine (40). A solution of **39** (2 g, 4.8 mmol) in acetone (120 mL) and dilute sulfuric acid (0.25 M, 60 mL) was heated at reflux for 40 h. The acetone was evaporated, and the aqueous residue was washed with ether (3 × 50 mL), basified with aqueous sodium carbonate (1 M, 40 mL), and extracted with ethyl acetate (3 × 50 mL). The combined ethyl acetate extracts were washed with saturated aqueous NaCl, dried, and evaporated to afford a yellow oil. This material was purified by flash chromatography on silica gel, with dichloromethane–methanol (9:1) as eluant, to give **40** (1.19 g, 67%) as an oil. Compound **40** was characterized as it hydrochloride salt: mp 248–250 °C. Anal. ($C_{18}H_{22}Cl_2N_2O_2 \cdot HCl$) C, H, N.

***cis*-1-[(3,4-Dichlorophenyl)acetyl]-4-hydroxy-2-(1-pyrrolidinylmethyl)piperidine (41).** Diisobutylaluminum hydride (142 mL of a 1 M solution in hexane, 0.142 mol) was added dropwise to a stirred solution of 2,6-di-*tert*-butyl-4-methylphenol (BHT) (62.24 g, 0.28 mol) in dry toluene (600 mL) at 4 °C and under nitrogen. After stirring for 45 min, the mixture was cooled to −60 °C and a solution of **40** (5.2 g, 14.1 mmol) in dry toluene (95 mL) was added over 5 min. The reaction mixture was stirred at −60 °C for 2 h and then allowed to warm to room temperature over the next 3 h. Hydrochloric acid (1 N, 500 mL) was added, and the resulting mixture stirred vigorously for 1 h. The layers were separated, and the aqueous layer was washed with ether (500 mL), basified with aqueous sodium hydroxide (2 N, 500 mL), and extracted with dichloromethane (3 × 500 mL). The dichloromethane extracts were combined, dried, and evaporated to give crude product as a foam. A portion of this material was purified and characterized as its hydrochloride salt (669 mg, 61%): mp 202–203 °c (from ethanol–ethyl acetate); NMR (DMSO-d_6, 404 K) (free base) δ 1.36–1.80 (8 H, m, 4 × CH_2), 2.3–2.5 (4 H, 2 × CH_2N), 2.61 (1 H, dd, J = 6.5, 13 Hz, CH_AH_BN), 2.80 (1 H, dd, J = 7.5, 13 Hz, CH_AH_BN), 3.08 (1 H, m, H_{6ax}), 3.56 (1 H, d, J = 15.5 Hz, $COCH_AH_BAr$), 3.65 (1 H, d, J = 15.5 Hz, $COCH_AH_BAr$), 3.74 (1 H, m, H_{6eq}), 3.80 (1 H, quintet, J = 4 Hz, H_{4eq}), 4.24 (1 H, dddd, J = 2.5, 6, 6.5, 7.5, H_{2eq}), 7.1 (1 H, br d, ArH), 7.34 (1 H, s, ArH), 7.36 (1 H, d, ArH). Anal. ($C_{18}H_{25}Cl_3N_2O_2$) C, H, N.

***trans*-1-[(3,4-Dichlorophenyl)acetyl]-4-hydroxy-2-(1-pyrrolidinylmethyl)piperidine (42).** A solution of **40** (1.1 g, 3 mmol) in ethanol (6 mL) was added dropwise to a stirred suspension of sodium borohydride on alumina (1.7 g of 10% sodium borohydride, ca. 4.5 mmol) in ethanol (18 mL). Stirring at room temperature was continued for 1.5 h, and then hydrochloric acid (1 N, 25 mL) was added. Insoluble material was removed by filtration, and the filtrate was basified with aqueous sodium carbonate (2 N, 25 mL) and extracted with dichloromethane. The dichloromethane extract was dried and evaporated to give a foam. This material was purified by column chromatography on neutral alumina, with dichloromethane–methanol–ammonia (450:8:1) as eluant, to give, after foreruns comprising the cis isomer and starting material (262 mg, 24%) and mixed cis and trans isomers (510 mg, 46%), the trans isomer **42** (174 mg, 16%) as a colorless foam. The latter product was characterized as its maleate salt: mp 144–146 °C; NMR (DMSO-d_6, 400 K) δ 1.28 (1 H, dq, J = 5, 13 Hz, H_{5ax}), 1.46 (1 H, dt, J = 6, 12 Hz, H_{3ax}), 1.9–2.1 (6 H, m, 2 × CH_2, H_{3eq}, H_{5eq}), 3.1–3.5 (7 H, 2 × m, 3 × CH_2N, H_{6ax}), 3.8–4.0 (3 H, m, $COCH_2Ar$, H_{4ax}), 4.10 (1 H, m, H_{6eq}), 4.95 (1 H, m, H_{2eq}), 7.35 (1 H, dd, J = 2, 8 Hz, ArH), 7.60 (1 H, s, ArH), 7.63 (1 H, d, ArH). Anal. ($C_{22}H_{28}Cl_2N_2O_6$) C, H, N.

8-[(3,4-Dichlorophenyl)acetyl]-7-(1-pyrrolidinylmethyl)-1,4-dithia-8-azaspiro[4.5]decane (43). A solution of the ketone **40** (0.25 g, 0.678 mmol) and ethanedithiol (0.1 mL, 1.2 mmol) in dichloromethane (5 mL) at 0–5 °C was treated with boron trifluoride etherate (0.02 mL, 0.16 mmol). The mixture was stirred at ambient temperature for 18 h. Aqueous sodium hydroxide (2 N, 5 mL) was added, and the product was extracted with dichloromethane (2 × 15 mL). The combined organic extracts were dried and evaporated to dryness. The residue was purified by flash chromatography on silica gel, with dichloromethane–methanol–ammonia (200:8:1) as eluant, to give **43** (0.155 g, 51%): mp 119–120 °C. Anal. ($C_{20}H_{26}Cl_2N_2OS_2$) C, H, N, S.

Methyl 2-(Chloromethyl)-4-pyridinecarboxylate Hydrochloride (45). A solution of the alcohol **44** (1.42 g, 8.5 mmol) in ethyl acetate (5 mL) was treated with ethereal hydrogen chloride (ca. 5 mL). The resulting solid was collected by filtration and added to thionyl chloride (7.5 mL) at 0–5 °C. The mixture was stirred at 0–5 °C for 3 h and then at ambient temperature for 1 h. Diethyl ether (100 mL) was added, and the resulting solid was collected by filtration and washed with diethyl ether (2 × 50 mL), to give **45** as a white solid (1.7 g, 90%), which was used directly in the next stage.

Methyl 2-(1-Pyrrolidinylmethyl)-4-pyridinecarboxylate (46). A solution of the hydrochloride **45** (1.6 g, 7.2 mmol) in dichloromethane (50 mL) at −50 °C was treated with triethylamine (0.777 g, 7.69 mmol), and the mixture was stirred for 5 min. A precooled solution of pyrrolidine (1.09 g, 15.3 mmol) in dichloromethane (30 mL) was added at −60 °C, and the mixture was stirred at −60 °C for 1 h and at ambient temperature for 72 h. The reaction mixture was poured into aqueous sodium carbonate solution (1 M, 50 mL), and the product was extracted with dichloromethane (50 mL). The organic phase was dried and evaporated, leaving an oily residue which was purified by flash chromatography on silica gel, with dichloromethane–methanol–ammonia (200:10:1) as eluant, to give **46** as a colorless oil (1.01 g, 64%). Anal. ($C_{12}H_{16}N_2O_2$) C, H, N.

Methyl 2-(1-Pyrrolidinylmethyl)-4-piperidinecarboxylate (47). A solution of the amino ester **46** (50 mg) in ethanol (2 mL) was hydrogenated at 70 psi and 70 °C over 5% rhodium on carbon (35 mg) for 14 h. The mixture was filtered, and the filtrate was evaporated to dryness. The residue was purified by flash chromatography on silica gel, with dichloromethane–methanol–ammonia (200:10:2) as eluant, to give **47** as a colorless oil (0.018 g, 35%), which was used directly in the next stage.

***cis*-Methyl 1-[(3,4-Dichlorophenyl)acetyl]-2-(1-pyrrolidinylmethyl)-4-piperidinecarboxylate (48).** This compound was prepared by coupling **47** with 3,4-dichlorophenylacetic acid using the procedure described for the preparation of **25**. The crude product was purified by flash chromatography on silica gel, eluting with dichloromethane–methanol–ammonia (200:8:1), to give **48** as an oil (58%). It was characterized as its maleate salt: mp 106–108 °C.

***cis*-Methyl 1-[(3,4-Dichlorophenyl)acetyl]-2-(1-pyrrolidinylmethyl)-4-piperidinecarboxamide (49).** A solution of the ester **48** (0.25 g, 0.60 mmol) in a mixture of ethanol (5 mL) and liquid ammonia (50 mL) was heated at 100 °C for 3 days in an autoclave. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel, with dichloromethane–methanol–ammonia (100:10:2) as eluant, to afford **49** as an oil (0.14 g, 58%). This was characterized as its hydrochloride salt. Anal. ($C_{19}H_{25}Cl_2N_3O_2 \cdot HCl \cdot 1.5H_2O$).

5-(Phenylmethoxy)-2-(1-pyrrolidinylmethyl)pyridine (51). A solution of the pyridine **50** (3.45 g, 16.0 mmol) in methanol (20 mL) was treated with excess ethereal hydrogen chloride. The solvent was evaporated, and the residue was triturated with ether and filtered. The collected hydrochloride salt was added over 10 min, with ice-cooling and stirring, to thionyl chloride (14 mL). After 4 h at 0 °C, ether (200 mL) was added and the precipitated solid was collected by filtration. This solid was then added over 10 min, with ice-cooling and stirring, to pyrrolidine (6 mL) and water (12 mL). After stirring for 1 h, the reaction mixture was allowed to stand for 16 h, diluted with 2 M sodium carbonate solution (20 mL), and extracted with dichloromethane (2 × 20 mL). The combined organic extracts were dried and evaporated to dryness, and the residue was purified by flash chromatography on silica gel, with dichloromethane–ethanol–ammonia (200:8:1 to 25:8:1) as eluant, to give **51** as an oil (3.35 g, 78%). Anal. ($C_{17}H_{20}N_2O$) C, H, N.

6-(1-Pyrrolidinylmethyl)-3-piperidinol (52). A solution of the pyridine **51** (1.06 g, 3.95 mmol) in ethanol (100 mL) was hydrogenated over 5% rhodium on alumina (1.0 g) at 70 psi and 70 °C for 18 h. The reaction mixture was filtered, and the filtrate was evaporated to dryness. The residue was purified by flash

column chromatography on silica gel, with dichloromethane–methanol–ammonia (140:10:2) as eluant, to give the alcohols **52** as a colorless oil (0.24 g, 33%) which were used directly in the next stage. The ^{1}H NMR spectrum indicated this was a ca. 1:1 mixture of cis and trans alcohols.

1-[(3,4-Dichlorophenyl)acetyl]-6-(1-pyrrolidinylmethyl)-3-piperidinols (53). To a solution of 3,4-dichlorophenylacetic acid (0.64 g, 3.12 mmol) in dichloromethane (15 mL) was added portionwise 1,1'-carbonyldiimidazole (0.51 g, 3.14 mmol) over a 5-min period. The mixture was stirred at ambient temperature for 40 min and then added to a solution of the piperidinols **52** (0.55 g, 3.0 mmol) in dichloromethane (20 mL). The reaction mixture was stirred at ambient temperature for 18 h, diluted with dichloromethane (50 mL), and washed with aqueous sodium carbonate solution (2 M, 2 × 10 mL). The organic phase was dried and evaporated to give an oily residue. The latter was purified by flash column chromatography on silica gel, with dichloromethane–methanol–ammonia (200:8:1) as eluant, to give piperidinols **53** as an oil (0.32 g, 28%). This product was used directly in the next stage without further purification.

1-[(3,4-Dichlorophenyl)acetyl]-6-(1-pyrrolidinylmethyl)-3-piperidinone (54). A solution of oxalyl chloride (0.21 mL, 2.4 mmol) in dichloromethane (2 mL) at −50 °C was treated with a solution of DMSO (0.45 mL, 6.4 mmol) in dichloromethane (2 mL). The mixture was stirred at −55 °C for 20 min and then treated with a solution of the piperidinols **53** (0.49 g, 1.37 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at −60 °C for 2 h, and triethylamine (1.75 mL, 12.5 mmol) was added. Water (20 mL) was added, and the product was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried and evaporated to give an oily residue. The latter was purified by flash column chromatography on silica gel, with dichloromethane–methanol–ammonia (200:8:1) as eluant, to give the ketone **54** (0.26 g, 53%) as an oil. The material was characterized as its hydrochloride salt: mp 193–4 °C; NMR ($CDCl_3$) (free base) δ 1.7–1.95 (6 H, m, 3 × CH_2), 2.05–2.8 (8 H, m, 3 × CH_2N, H_{4ax}, H_{4eq}), 3.50 (1 H, d, J = 19 Hz, H_2), 3.55–3.90 (2 H, m, $COCH_2Ar$), 4.05 (1 H, d, J = 19 Hz, H_2), 4.15*, 4.88 (1 H, m, H_6), 7.09 (1 H, dd, J = 2, 8 Hz, ArH), 7.30–7.45 (2 H, m, ArH). Anal. ($C_{18}H_{22}Cl_2N_2O_2$·HCl·0.4H_2O) C, H, N.

7-[(3,4-Dichlorophenyl)acetyl]-8-(1-pyrrolidinylmethyl)-7-aza-1,4-dioxaspiro[4.5]decane (55). A mixture of the ketone **54** (0.16 g, 0.43 mmol), *p*-toluenesulfonic acid (0.14 g, 0.74 mmol) and ethanediol (1.0 g, 18 mmol) in dry toluene (10 mL) was heated in a Dean–Stark apparatus for 2 h. The cooled reaction mixture was diluted with dichloromethane (50 mL), and the organic solution was washed with aqueous sodium carbonate solution (1 M, 2 × 15 mL). The organic phase was dried and evaporated to dryness. The residue was purified by flash column chromatography on silica gel, with dichloromethane–methanol–ammonia as eluant, to give **55** (0.12 g, 67%) as a gum. The material was characterized as its hydrochloride salt: mp 255 °C dec; NMR (D_2O) δ 1.7–2.2 (8 H, m, 4 × CH_2), 3.18 (2 H, m), 3.23 (1 H, dd, J = 4, 14 Hz, CH_AH_BN), 3.36 (1 H, d, J = 14 Hz, CH_AH_BN), 3.45–4.2 (10 H, m), 5.15 (1 H, br d, H_8), 7.18 (1 H, dd, J = 2, 8 Hz, ArH), 7.44 (1 H, d, J = 2 Hz, ArH), 7.54 (1 H, d, J = 8 Hz, ArH). Anal. ($C_{20}H_{26}Cl_2N_2O_3$) C, H, N.

Methyl 2-(1-Pyrrolidinylmethyl)pyridine-5-carboxylate (57). A solution of methyl 2-methyl-5-pyridinecarboxylate (**56**) (0.43 g, 2.9 mmol), *N*-bromosuccinimide (0.59 g, 3.3 mmol), and dibenzoyl peroxide (50 mg) in dry carbon tetrachloride (10 mL) was stirred at 22 °C and irradiated with a 200-W light bulb for 2 days. Pyrrolidine (2.06 g, 29.0 mmol) was added, and after 15 min the solution was partitioned between dichloromethane (20 mL) and 2 M sodium carbonate solution (20 mL). The organic phase was washed with water and saturated aqueous NaCl solution, dried, and evaporated to give an oil. The oil was purified by flash column chromatography on silica gel, with dichloromethane–ethanol–ammonia (300:8:1) as eluant, to give **57** (0.22 g, 34%) as an oil. Anal. ($C_{12}H_{16}N_2O_2$) C, H, N.

Methyl 2-(1-Pyrrolidinylmethyl)piperidine-5-carboxylate (58). A solution of **57** (4.1 g, 18.6 mmol) in glacial acetic acid (80 mL) was hydrogenated at 22 °C and atmospheric pressure over Adams' catalyst (3 g). The reaction mixture was filtered, and the residue was washed with ethanol. The combined filtrate and washings were evaporated to give an oil which was partitioned between 2 M sodium carbonate solution (100 mL) and dichloromethane (100 mL). The aqueous phase was further extracted with dichloromethane (100 mL). The combined organic extracts were washed with saturated aqueous NaCl solution, dried, and evaporated to give an oil. This material was purified by flash chromatography on silica gel, with dichloromethane–ethanol–ammonia (200:8:1) as eluant, to give **58** (3:1 cis/trans mixture) as an oil (2.6 g, 62%). The product was used directly in the next stage without further purification.

***cis*-Methyl 1-[(3,4-Dichlorophenyl)acetyl]-6-(1-pyrrolidinylmethyl)-3-piperidinecarboxylate (59).** A solution of 3,4-dichlorophenylacetyl chloride (2.53 g, 11.3 mmol) in dichloromethane (20 mL) was added dropwise during a period of 15 min to an ice-cold, stirred solution of **58** (2.32 g, 10.3 mmol) and triethylamine (1.14 g, 11.3 mmol) in dichloromethane (50 mL), and the resulting mixture was stirred at 22 °C for 18 h. The reaction mixture was diluted with dichloromethane (20 mL), washed with 2 M sodium carbonate solution (50 mL) and saturated aqueous NaCl solution, dried, and concentrated to give an oil. This material was purified by flash chromatography on silica gel, with dichloromethane–ethanol–ammonia (500:8:1) as eluant, to give **59** (1.0 g, 23%). This material was characterized as its hydrochloride salt: mp 135–140 °C; NMR ($CDCl_3$) (free base) δ 1.25–1.5 (1 H, m), 1.55–2.0 (7 H, m), 2.23 (1 H, tt, J = 4, 13 Hz, $CHCO_2Me$), 2.35–2.85 (6 H, m), 3.14 (1 H, t, J = 13 Hz, H_{2ax}), 3.69 (3 H, s, OCH_3), 3.72 (2 H, AB system, J = 15 Hz, $COCH_AH_BAr$), 3.82* (<1 H, br d, H_{2eq}), 3.98* (<1 H, m, peak width 20 Hz, H_6), 4.81 (<1 H, dd, J = 3, 13 Hz, H_{2eq}), 4.96 (<1 H, m, peak width 20 Hz, H_6), 7.09* (<1 H, dd, J = 2, 8 Hz, ArH), 7.14 (<1 H, dd, J = 2, 8 Hz, ArH), 7.3–7.42 (2 H, m, ArH). Irradiation of signal at δ 2.23 caused simplification of the H_{2ax} signal (δ 3.14) to a doublet (J = 13 Hz). Anal. ($C_{20}H_{26}Cl_2N_2O_3$·HCl·0.5H_2O) C, H, N.

***cis*-1-[(3,4-Dichlorophenyl)acetyl]-6-(1-pyrrolidinylmethyl)-3-piperidinecarboxamide (60).** A solution of **59** (0.27 g, 0.65 mmol) in a mixture of methanol (3 mL) and liquid ammonia was heated at 90 °C for 18 h. The ammonia was vented, and the methanol was evaporated. The dark residue was purified by flash chromatography on silica gel, with dichloromethane–ethanol–ammonia (200:8:1) as eluant, to give **60** (0.17 g, 65%). This material was characterized as its maleate salt: mp 240–243 °C. Anal. ($C_{23}H_{29}Cl_2N_3O_6$) C, H, N.

2-Methyl-6-(1-pyrrolidinylmethyl)pyridine (61; R = Me). A mixture of 6-methylpyridine-2-carboxaldehyde (1.2 g, 0.01 mol), pyrrolidine (0.78 g, 0.011 mol), and platinum oxide (0.15 g) in ethanol (50 mL) was hydrogenated at room temperature and atmospheric pressure. The catalyst was filtered off, and the filtrate was evaporated to dryness. The residue was purified by chromatography on alumina, eluting with ether–hexane (1:1), to afford **61** (R = Me) as a colorless oil (1.15 g, 65%): NMR ($CDCl_3$) δ 1.80 (4 H, m, 2 × CH_2), 2.55 (3 H, s, Me), 2.57 (4 H, m, 2 × CH_2N), 3.76 (2 H, s, CH_2N), 7.01 (1 H, d, J = 7 Hz, pyridine-H), 7.22 (1 H, d, J = 7 Hz, pyridine-H), 7.53 (1 H, t, J = 7 Hz, pyridine-H).

Methyl 6-(1-Pyrrolidinylmethyl)-2-pyridinecarboxylate (61; R = CO_2Me). A solution of methyl 6-methyl-2-pyridinecarboxylate (0.43 g, 2.9 mmol) in carbon tetrachloride (10 mL) was treated with *N*-bromosuccinimide (0.59 g, 3.3 mmol) followed by dibenzoyl peroxide (50 mg). The stirred reaction mixture was irradiated with a 200-W light bulb for 24 h and then diluted with dichloromethane (10 mL) and cooled to −70 °C. A solution of pyrrolidine (0.43 g, 6.0 mmol) in dichloromethane (2 mL) was added, and the mixture was stirred at ambient temperature overnight. The reaction mixture was poured into aqueous sodium carbonate (2 M, 20 mL), and the product was extracted with dichloromethane (2 × 10 mL). The combined extracts were dried and evaporated to dryness. The residue was purified by flash chromatography on silica gel, with dichloromethane–methanol–ammonia (200:8:1) as eluant, to give **61** (R = CO_2Me) as an oil (0.28 g, 44%): NMR ($CDCl_3$) δ 1.82 (4 H, m, 2 × CH_2), 2.62 (4 H, m, 2 × CH_2N), 3.93 (2 H, s, CH_2N), 4.00 (3 H, s, OMe), 7.71 (1 H, d, J = 7 Hz, pyridine-H), 7.82 (1 H, t, J = 7 Hz, pyridine-H), 8.01 (1 H, d, J = 7 Hz, pyridine-H).

***cis*-2-Methyl-6-(1-pyrrolidinylmethyl)piperidine (62) and *trans*-2-Methyl-6-(1-pyrrolidinylmethyl)piperidine (63).** A solution of **61** (R = Me) (4.75 g, 27 mmol) in acetic acid (75 mL) was hydrogenated at atmospheric pressure and room temperature

over platinum oxide (0.5 g) for 19 h. The catalyst was filtered off, and the filtrate was evaporated to dryness. The residue was partitioned between dichloromethane (100 mL) and aqueous sodium hydroxide (2 N, 75 mL). The organic phase was dried and evaporated to give an oil which was purified by vacuum distillation to give a colorless oil (3.7 g, 69%) bp 120 °C (0.4 mmHg). An aliquot (2.5 g) was further purified by flash column chromatography on silica gel, with dichloromethane–methanol–ammonia (75:8:1) as eluant, to give initially the cis isomer **62** (1.98 g, 79%) and subsequently the trans isomer **63** (65 mg, 2.5%) as colorless oils, which were used directly in the next stage.

***cis*-Methyl 6-(1-Pyrrolidinylmethyl)-2-piperidinecarboxylate (64) and *trans*-Methyl 6-(1-Pyrrolidinylmethyl)-2-piperidinecarboxylate (65).** A solution of **61** (R = CO_2Me) (4.8 g, 0.02 mol) in acetic acid (50 mL) was hydrogenated over platinum oxide (2 g) at atmospheric pressure for 4 h. The mixture was filtered, and the filtrate was evaporated to dryness. The residue was partitioned between aqueous sodium carbonate (2 M, 150 mL) and dichloromethane (2 × 100 mL). The combined organic extracts were dried and evaporated to give an oily residue, which was purified by flash chromatography on silica gel, with dichloromethane–methanol–ammonia (125:8:1) as eluant, to give initially the cis isomer **64** (2.4 g, 49%) and subsequently the trans isomer **65** (0.3 g, 6%) as colorless oils, which were used directly in the next stage.

***trans*-1-[(3,4-Dichlorophenyl)acetyl]-2-methyl-6-(1-pyrrolidinylmethyl)piperidine (67).** 1,1'-Carbonyldiimidazole (188 mg, 1.16 mmol) was added to a solution of 3,4-dichlorophenylacetic acid (238 mg, 1.16 mmol) in dichloromethane (5 mL), and the resulting solution was stirred at room temperature under nitrogen for 1.5 h. A solution of **63** (141 mg, 0.77 mmol) in dichloromethane (6 mL) was added, and the mixture was stirred for 72 h. The reaction mixture was washed with 2 M sodium carbonate (2 × 5 mL). The organic phase was dried and evaporated to give an oil which was purified by flash column chromatography on silica gel, with dichloromethane–methanol–ammonia (200:8:1) as eluant, to afford **67** (163 mg, 57%). The product was characterized as the fumarate salt: mp 169–172 °C; NMR (D_2O) δ 1.38 (3 H, d, J = 7 Hz, CH_3), 1.6–1.9, 1.9–2.2 (10 H, 2 × m, 5 × CH_2), 3.14 (2 H, m, CH_2N), 3.36 (1 H, dd, J = 6, 13 Hz, CH_AH_BN), 3.5–3.8 (3 H, m, CH_2N, CH_AH_BN), 3.81, 3.92, (2 H, 2 × d, $COCH_AH_BAr$), 4.27 (2 H, m, H_2, H_6), 7.16 (1 H, dd, J = 2, 8 Hz, ArH), 7.43 (1 H, d, J = 2 Hz, ArH), 7.52 (1 H, d, J = 8 Hz, ArH). Anal. ($C_{23}H_{30}Cl_2N_2O_5$) C, H, N.

The following compounds were similarly prepared:

***cis*-1-[(3,4-Dichlorophenyl)acetyl]-2-methyl-6-(1-pyrrolidinylmethyl)piperidine (66):** 91%; characterized as the fumarate salt; mp 185–187 °C; NMR ($CDCl_3$) (free base) δ 1.17, 1.19 (3 H, 2 × d, J = 7 Hz, CH_3), 1.3–1.85 (9 H, m), 2.0 (1 H, br t), 2.4–2.7 (4 H, m, 2 × CH_2N), 2.24 (<1 H, dd, J = 4, 11 Hz, CH_AH_BN), 2.30* (<1 H, dd, J = 4.5, 12.5 Hz, CH_AH_BN), 2.88 (<1 H, t, J = 11 Hz, CH_AH_BN), 3.02* (<1 H, dd, J = 11, 12.5 Hz, CH_AH_BN), 3.56–3.84 (2 H, 2 × AB systems, $COCH_2Ar$), 3.92* (<1 H, m, peak width 19 Hz, H_6), 4.06 (<1 H, m, peak width 28 Hz, H_2), 4.78* (<1 H, m, H_2), 4.78 (<1 H, m, H_6), 7.10 (1 H, m, ArH), 7.38 (2 H, m, ArH). Irradiation of methyl signal (δ 1.17, 1.19) simplifies signal at δ 4.06 to a br t, $J \approx 3$ Hz. Anal. ($C_{23}H_{30}Cl_2N_2O_5$) C, H, N.

***trans*-Methyl 1-[(3,4-Dichlorophenyl)acetyl]-6-(1-pyrrolidinylmethyl)-2-piperidinecarboxylate (69):** 32%; characterized as the fumarate salt; mp 160–161 °C. Anal. ($C_{24}H_{30}Cl_2N_2O_7$) C, H, N.

***cis*-Methyl 1-[(3,4-Dichlorophenyl)acetyl]-6-(1-pyrrolidinylmethyl)-2-piperidinecarboxylate (68):** 68%; characterized as the fumarate salt; mp 109 °C. Anal. ($C_{20}H_{26}Cl_2N_2O_3$) C, H, N.

***cis*-1-[(3,4-Dichlorophenyl)acetyl]-6-(1-pyrrolidinylmethyl)-2-piperidinemethanol (70).** A solution of the ester **68** (0.5 g, 1.21 mmol) and sodium borohydride (0.12 g, 3.2 mmol) in *tert*-butyl alcohol (6 mL) and methanol (0.9 mL) was heated at reflux for 6 h. A further quantity of sodium borohydride (0.2 g, 5.3 mmol) and methanol (1 mL) was added, and the mixture was heated under reflux for 10 h. Acetic acid (0.2 mL) was added, and the reaction mixture was evaporated to dryness. The residue was partitioned between aqueous sodium carbonate (2 M, 20 mL) and dichloromethane (2 × 30 mL). The organic extracts were combined, dried, and evaporated to dryness, and the resultant residue was purified by flash chromatography on silica gel, with dichloromethane–methanol–ammonia (150:8:1) as eluant, to give **70** (0.15 g, 22%): mp 138–139 °C; NMR ($CDCl_3$) δ 1.40–1.83 (10 H, m, 5 × CH_2), 2.15 (1 H, dd, J = 6, 13 Hz, CH_AH_BN), 2.43, 2.77 (4 H, 2 × m, 2 × CH_2N), 3.26 (1 H, t, J = 13 Hz, CH_AH_BN), 3.52 (1 H, dd, J = 6, 12 Hz, CH_AH_BOH), 3.71 (1 H, t, J = 12 Hz, CH_AH_BOH), 3.78, 3.95 (2 H, AB system, J = 15 Hz, $COCH_AH_BAr$), 4.13 (1 H, m, peak width 24 Hz, $CHCH_2OH$), 5.23 (1 H, m, peak width 22 Hz, $CHCH_2N$), 6.65 (1 H, br, OH), 7.08 (1 H, dd, J = 2, 8 Hz, ArH), 7.35 (1 H, d, J = 2 Hz, ArH), 7.38 (1 H, d, J = 8 Hz, ArH). Anal. ($C_{19}H_{26}Cl_2N_2O_2$) C, H, N.

***cis*-1-[(3,4-Dichlorophenyl)acetyl]-6-(1-pyrrolidinylmethyl)-2-piperidinecarboxamide (71).** A mixture of the ester **68** (0.3 g, 0.73 mmol) and liquid ammonia (ca. 5 mL) was heated in an autoclave at 90 °C for 20 h. Excess ammonia was allowed to evaporate, and the residue was purified by flash chromatography on silica gel, with dichloromethane–methanol–ammonia (200:8:1 to 100:4:1) as eluant to give **71** (0.07 g, 26%). This material was characterized as its maleate salt: mp 151–152 °C; NMR (D_2O) δ 1.5–1.85, 1.85–2.2 (10 H, 2 × m), 3.05–3.35 (3 H, m), 3.55 (1 H, dd), 3.70 (2 H, m), 3.75, 3.93 (2 H, 2 × d, J = 15 Hz, $COCH_AH_BAr$), 4.9 (1 H, m, H_6), 5.12 (1 H, m, H_2), 7.17 (1 H, dd, J = 2, 8 Hz, ArH), 7.41 (1 H, d, J = 2 Hz, ArH), 7.54 (1 H, d, J = 8 Hz, ArH). Anal. ($C_{23}H_{29}Cl_2N_3O_6$) C, H, N.

pK_a Determination. The pK_a values for compounds **6** and **9–11** were determined by titration at a sample concentration of 0.002 M using as solvent a 10% methanol–water solution.

Pharmacological Methods. In Vivo. Compounds were evaluated for antinociceptive activity in the mouse acetylcholine-induced abdominal constriction test following subcutaneous administration. ED_{50} values were determined in each case.[16] Urine-output experiments, in the rat, were performed as previously described.[21]

In Vitro. Activities in the rabbit,[22] rat,[14] and hamster[15] vasa deferentia were determined as previously described. Potencies were quoted as IC_{50} (or pK_B) values.

Acknowledgment. The X-ray crystallographic structural data for compound **12a** was kindly provided by Dr. R. Highcock (Structural Chemistry Department, Glaxo Group Research Ltd.). We thank Mr. S. Richards and Dr. T. Cholerton for some of the NMR spectral interpretations and Mrs. Jane Lloyd for the preparation of compounds **12a**, **13a**, and **17**.

Supplementary Material Available: Crystal data for **12a** and tables listing atomic coordinates, bond lengths, bond angles, anisotropic displacement coefficients (8 pages); structure factors (9 pages). Ordering information is given on any current masthead page.

(22) Hayes, A. G.; Kelly, A. Profile of Activity of κ-Receptor Agonists in the Rabbit Vas Deferens. *Eur. J. Pharmacol.* **1985**, *110*, 317–322.