A Potent New Class of κ-Receptor Agonist: 4-Substituted 1-(Arylacetyl)-2-[(dialkylamino)methyl]piperazines

Alan Naylor,*,† Duncan B. Judd,† Jane E. Lloyd,† David I. C. Scopes,† Ann G. Hayes,‡ and Philip J. Birch‡

Departments of Medicinal Chemistry and Neuropharmacology, Glaxo Group Research Ltd., Ware, Hertfordshire SG12 ODP, England

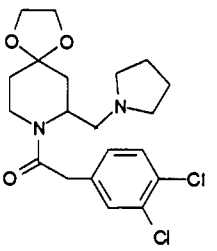
Received December 28, 1992

The synthesis of 4-substituted 1-(arylacetyl)-2-[(alkylamino)methyl]piperazines (**10–22, 26, 27,** and **30–33**) and their activities as κ-opioid receptor agonists are described. This includes a range of 4-acyl and 4-carboalkoxy derivatives with the latter series showing the greatest κ-agonist activity. In particular, methyl 4-[(3,4-dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate (**18**) displays exceptional potency and selectivity. It showed the following activities in functional *in vitro* assays: rabbit vas deferens (κ-specific tissue) IC_{50} = 0.041 nM, rat vas deferens (μ-specific tissue) IC_{50} > 10 000 nM, and hamster vas deferens (δ-specific tissue) IC_{50} > 10 000 nM. Compound **18** is also a highly potent antinociceptive agent, as determined in the mouse acetylcholine-induced abdominal constriction test: ED_{50} = 0.000 52 mg/kg, sc. The activity of **18** resides solely in its 3(*R*)-enantiomer. The κ-agonist activity in both the 4-acyl and the 4-carbamate series is sensitive to the size of the 4-substituent. In addition, it would appear that an appreciable negative electrostatic potential in this region of the molecule is an important requirement for optimal potency.

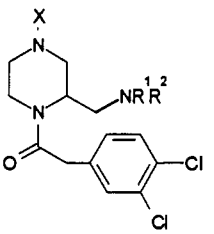
The identification of three distinct opioid receptor subtypes, μ, κ, and δ, has resulted in a surge in interest in the medicinal chemistry of opioids during the past decade.[1] It is well established that activation of each of these receptors can produce antinociceptive effects in a variety of animal models. More specifically, it has been recognised that a selective κ-agonist should be a strong analgesic devoid of many of the side effects associated with μ-agonists (e.g. respiratory depression, constipation, physical dependence), although there is some concern that their effectiveness as analgesics may be limited by unwanted properties linked to activation of κ-receptors (e.g. sedation, diuresis, and dysphoria).[2,3] Ultimately these issues will only be resolved when selective κ-agonists are fully evaluated in the clinic.

An early structural lead in this area was the *N*-(2-aminocyclohexyl)arylacetamide U-50488.[4] This compound spawned much subsequent research which resulted in the discovery of a range of structural classes that demonstrated selective κ-receptor agonist activity.[5] We[6] and others[7] have previously reported on a series of 2-[(alkylamino)methyl]piperidine κ-agonists. Notably, the spirocyclic dioxolane GR45809 (**1**) was shown to be a highly potent and selective κ-agonist.[6] The success of this 4-substitution on the piperidine nucleus encouraged us to investigate further modification at this locus. However, to overcome the relative inaccessibility of the requisite 2,4-disubstituted piperidine intermediates we elected to evaluate the piperazine nucleus as a template onto which a range of N-4-substituents could easily be introduced.

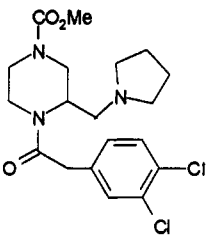
We now describe the synthesis, antinociceptive activity, and κ-opioid receptor selectivity of a series of 4-substituted 1-(arylacetyl)-2-[(alkylamino)methyl]piperazines (**2**), a new class of potent κ-agonist, and show how we have been able to rapidly probe key structural features which result in high κ-agonist activity. In particular, we have identified GR89696 (**18**) as the most potent and selective κ-agonist hitherto reported.



(1) GR 45809



(2) X = COR, CO_2R



(18) GR 89696

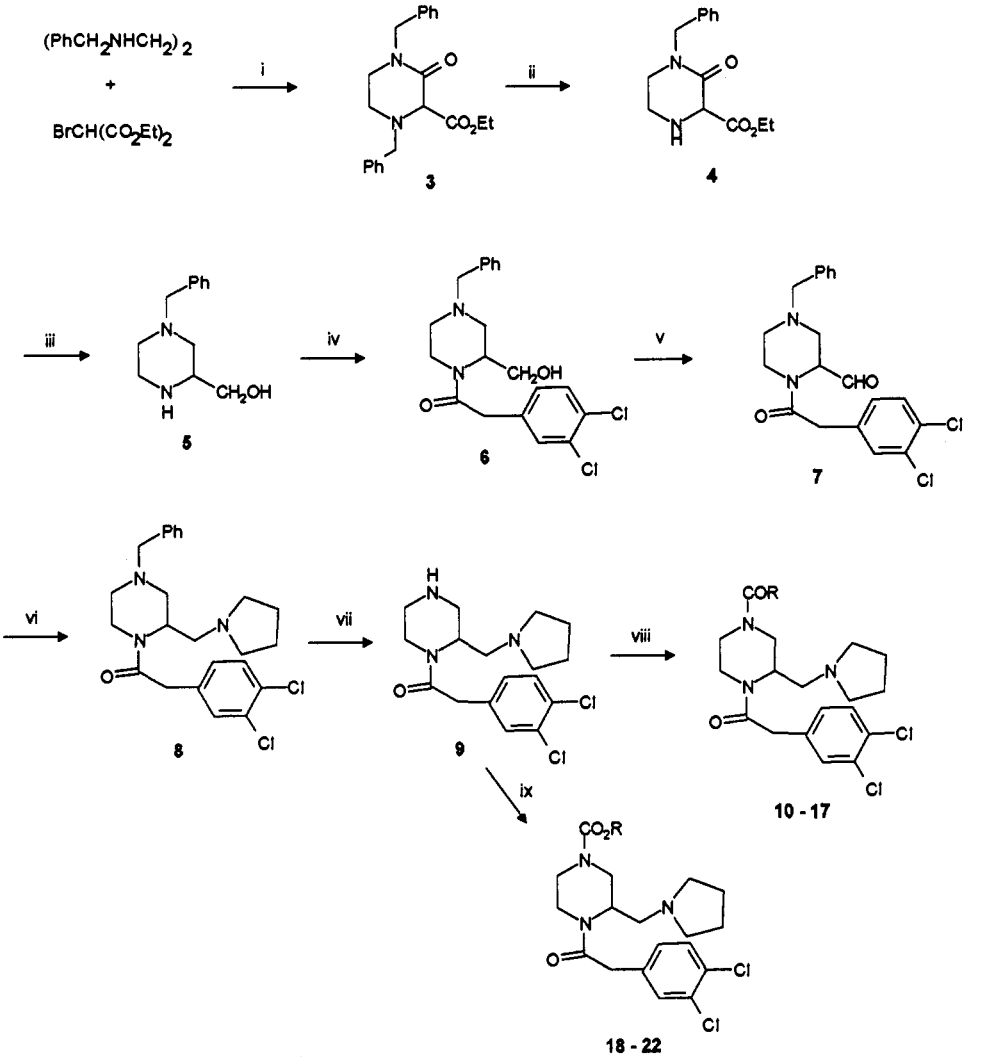
Chemistry

Racemic 4-acyl- and 4-(alkoxycarbonyl)-1-(arylacetyl)-2-[(alkylamino)methyl]piperazines were synthesized *via* the route outlined in Scheme I which utilizes the condensation of diethyl bromomalonate and *N,N'*-dibenzylethylenediamine to provide the 2-substituted piperazine nucleus. Selective *N*-debenzylation of the basic nitrogen followed by reduction using lithium aluminum hydride provided the 2-piperazinemethanol **5** and thereafter the synthesis is modeled on the chemistry used in the

† Department of Medicinal Chemistry.
‡ Department of Neuropharmacology.

0022-2623/93/1836-2075$04.00/0

Scheme I [a]



[a] (i) MeCN, Δ; (ii) H_2, Pd–C; (iii) $LiAlH_4$, THF; (iv) 1,1′-carbonyldiimidazole, 3,4-$Cl_2C_6H_3CH_2CO_2H$; (v) $(COCl)_2$, DMSO, Et_3N; (vi) pyrrolidine, $NaBH_3CN$; (vii) H_2, Pd–C, HCl; (viii) HCO_2Me (R = H); RCOCl, pyridine, DMAP or RCO_2H, 1,1′-carbonyldiimidazole; (ix) $ClCO_2R$, Et_3N.

2-[(alkylamino)methyl]piperidine series.[6] Catalytic debenzylation of **8** afforded the key secondary amine **9** which was acylated to provide the target compounds (**10–22**). An X-ray crystal structure of **18** (Figure 1) indicated that the pyrrolidinylmethyl side chain adopts an axial configuration, analogous to the piperidine κ-agonists.[6]

Within the 4-carbomethoxy series, two variants of this route were used to introduce alternative basic moieties. In the first, the key intermediate was the 2-piperazinemethanol **25**,[8] and subsequent Swern oxidation followed by reductive amination of the resultant carboxaldehyde afforded the amines **26** and **27** (Scheme II). Alternatively, further modifications to the basic residue (Scheme III) were made *via* the 3-hydroxypyrrolidine **30**. Thus, oxidation afforded the 3-oxopyrrolidine **31**, reaction of which with trimethyl phosphonoacetate provided the *E*- and *Z*-acrylates **32** and **33**, respectively. Assignment of the double bond geometry was made by analogy with the piperidine series[6] wherein much greater κ-agonist activity resides in the *Z*-isomer.

The exceptional potency and selectivity associated with **18** (GR89696) directed us to evaluating the biological profiles of its component enantiomers. A number of attempts to achieve this *via* diastereomeric salt formation and fractional crystallization were unsuccessful, and ultimately we resorted to dedicated chiral syntheses of (*R*)- and (*S*)-**18** (Scheme IV). In the case of the (*R*)-isomer this started from BOC protected *N*-benzylglycyl-D-serine methyl ester [(*R*)-**34**] which could readily be cyclized to the piperazinedione (*R*)-**35**, the function of the benzyl group being to aid the isolation of this and the subsequent intermediate (*S*)-**5** from aqueous media as well as to improve solubility in THF for the lithium aluminum hydride reduction step. This function having been served, the benzyl group was removed by catalytic hydrogenolysis, and subsequent carbomethoxylation took place at the least hindered, more basic nitrogen to afford (*S*)-**24**. The latter was *N*,*O*-bis-acylated, using excess 3,4-dichlorophenylacetic acid, and then selectively *O*-deacylated using lithium hydroxide to give (*S*)-**25**. Swern oxidation of the alcohol (*S*)-**25** required the use of *N*-methylmorpholine, in place of the commonly used triethylamine, to minimize racemization of the chiral center at C-2 on the piperazine nucleus (i.e. α to the newly generated carboxaldehyde residue). These conditions worked very effectively, and following reductive amination with pyrrolidine, using sodium cyanoborohydride, (*R*)-**18** was obtained in >99% ee (HPLC). Carrying through the synthesis starting from BOC protected *N*-benzylglycyl-L-serine methyl ester [(*S*)-**34**] provided (*S*)-**18**, also in >99% ee.

Biological Results and Discussion

The κ-agonist potency of the 4-substituted 1-(arylacetyl)-2-[(alkylamino)methyl]piperazines was determined *in*

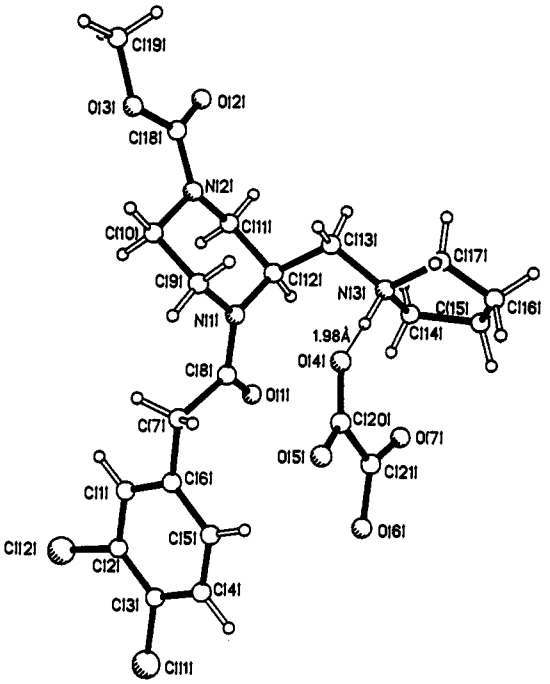
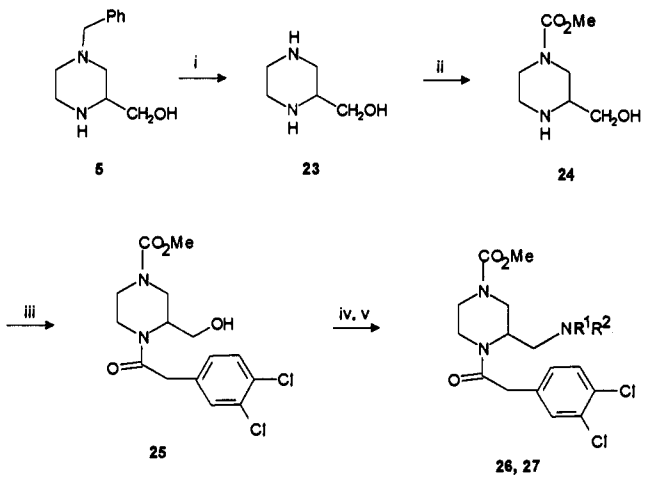


Figure 1. X-ray crystal structure of (±)-methyl 4-[(3,4-dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate, oxalate salt (18).

Scheme II [a]

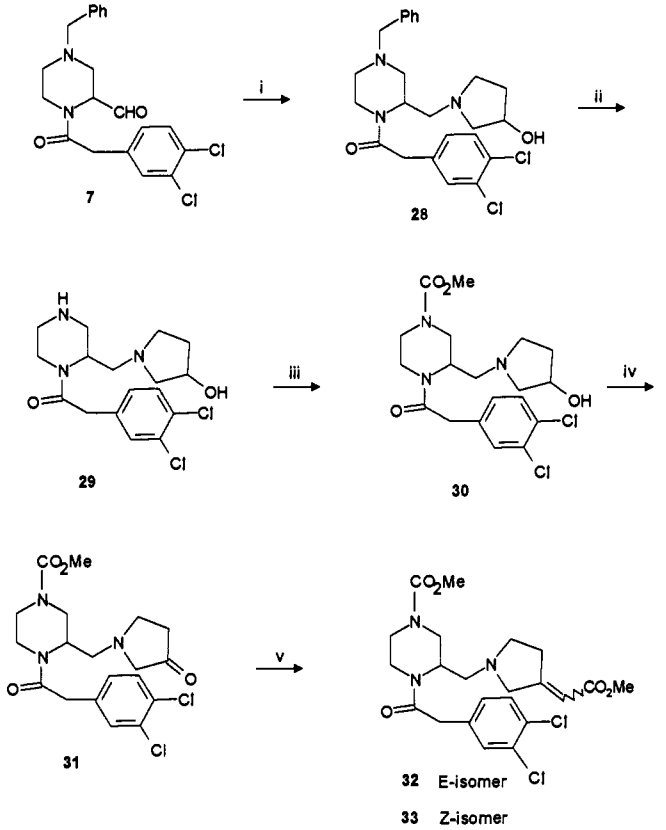


[a] (i) H_2, Pd–C; (ii) $ClCO_2Me$; (iii) 1,1′-carbonyldiimidazole, 3,4-$Cl_2C_6H_3CH_2CO_2H$; (iv) $(COCl)_2$, DMSO, Et_3N; (v) $NaBH_3CN$, NHR^1R^2.

vitro using the rabbit vas deferens (LVD) preparation, which is rich in κ-opioid receptors.[9] For selected compounds, receptor selectivity was assessed by comparing activity in the LVD with that in the rat vas deferens (RVD)[10] and hamster vas deferens (HVD),[11] which are rich in μ- and δ-opioid receptors, respectively. Antinociceptive activity was determined using the mouse acetylcholine-induced abdominal constriction (MAC) test[12] following subcutaneous administration, ED_{50} values being determined in each case.

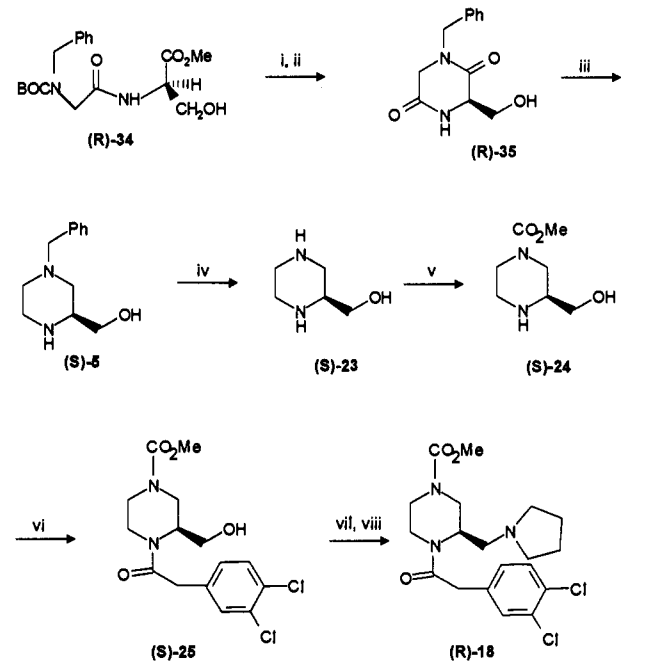
All of the compounds which were active in the LVD behaved as full agonists. In the 4-acyl series (Table I) it is apparent that steric factors are important in determining κ-agonist potency. Both *in vitro* and *in vivo* the acryloyl derivative (15) was the most potent; relatively little difference was exhibited between the formyl (10), acetyl (11), and propanoyl (12) analogues, but a reduction in potency was evident with larger groups, the benzoyl and phenylacetyl being inactive in the LVD. At 10^{-5} M (11)

Scheme III [a]



[a] (i) $NaBH_3CN$, 3-hydroxypyrrolidine; (ii) H_2, Pd–C; (iii) $ClCO_2Me$; (iv) $(COCl)_2$, DMSO, Et_3N; (v) $(EtO)_2P(=O)CH_2CO_2Me$, NaH.

Scheme IV [a,b]

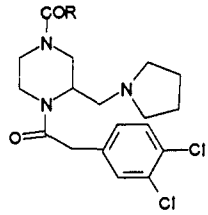


[a] (i) MeOH, $SOCl_2$; (ii) NH_3; (iii) $LiAlH_4$; (iv) H_2, Pd–C; (v) $ClCO_2Me$; (vi) 1,1′-carbonyldiimidazole, 3,4-$Cl_2C_6H_3CH_2CO_2H$; then LiOH; (vii) $(COCl)_2$, DMSO, *N*-methylmorpholine; (viii) $NaBH_3CN$, pyrrolidine. [b] Structures depict absolute configuration for the synthesis of (*R*)-18; an identical set of conditions was used to obtain the corresponding antipodes (see the Experimental Section).

showed no agonist or antagonist activity in the rat vas deferens preparation, underlining its high κ/μ-receptor selectivity.

This knowledge of the influence of steric factors and the fact that the propanoyl derivative (12) showed good

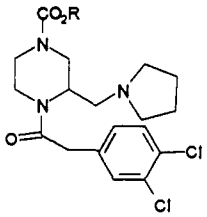
Table I. *N*-Acyl Derivatives: Rabbit Vas Deferens (LVD) and Antinociception Test Results



no.[a]	R	LVD IC_{50}, nM[b]	mouse Ach-induced abdominal constriction ED_{50}, mg/kg, sc
10	H	15	0.23 (0.12–0.48)
11	Me	10	0.08 (0.04–0.15)
12	Et	6.9	0.05 (0.03–0.08)
13	Pr^n	60	0.41 (0.20–1.09)
14	CH_2OMe	2900	NT
15	$CH{=}CH_2$	0.42	0.02 (0.012–0.032)
16	Ph	>10000	NT
17	CH_2Ph	>10000	NT
GR45809 (1)		0.1	0.001 (0.0003–0.002)
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.

Table II. Carbamate Derivatives: Rabbit Vas Deferens (LVD) and Antinociception Test Results

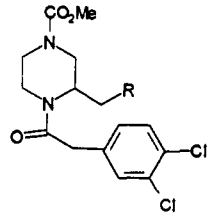


no.[a]	R	LVD IC_{50}, nM[b]	mouse Ach-induced abdominal constriction ED_{50}, mg/kg sc
18	Me	0.041	0.00052 (0.00027–0.00086)
19	Et	3.5	0.01 (0.007–0.018)
20	Pr^n	300	0.68
21	Ph	>10000	NT
22	CH_2Ph	450	NT
(*R*)-18	Me	0.018	0.00025 (0.00012–0.00045)[c]
(*S*)-18	Me	6.0[d]	NT
GR 45809 (1)		0.1	0.001 (0.0003–0.002)

[a] Except where indicated, all compounds were tested as racemates. [b] Figures quoted are the mean of two independent determinations typically with the individual values within ±10% of the mean. [c] ED_{50} following oral administration: 0.012 (0.005–0.035) mg/kg. ED_{50} in the rat paw pressure test: 0.00093 (0.00058–0.0014) mg/kg, sc. [d] This level of activity may be a reflection of ca. 0.3% contamination by (*R*)-18 (see the Experimental Section).

activity encouraged us to synthesize the isosteric methoxycarbonyl derivative (18). The result was striking. Structure 18 (GR89696) (Table II) is the most potent and selective κ-agonist reported to date: some 10 000 times more potent at κ-receptors (LVD) than the prototype κ-agonist U-50488 and 1000 times more potent than morphine (ED_{50} = 0.47 mg/kg, sc) in the antinociceptive (MAC) test. The effect of GR89696 in the LVD was antagonized by naloxone with a mean pK_B value of 7.70 ± 0.04, consistent with a κ-opioid receptor-mediated effect. GR89696 shows excellent selectivity for the κ-receptor since it did not display agonist or antagonist activity in the HVD and RVD at concentrations up to 10^{-5} M. The κ-agonist activity of 18 resides exclusively[13] in the *R*-enantiomer (Table II), which was predicted on the basis of earlier observations in the piperidine series.[7]

Table III. Modification of Basic Moiety of *N*-Methoxycarbonyl Derivatives: 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
18		0.041	0.00052 (0.00027–0.00086)
30		0.34	0.044 (0.024–0.066)
31		0.34	0.023 (0.015–0.037)
32		0.28	0.004 (0.002–0.007)
33		4.0	0.10 (0.059–0.173)
26	NMe_2	1.2	0.016 (0.01–0.02)
27		0.04	0.000096 (0.000033–0.000241)

[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.

As in the case of the 4-acyl series the 4-alkoxycarbonyl derivatives exhibit a clear relationship between κ-agonist potency and the steric bulk of the R group, the ethyl and *n*-propyl analogues, 19 and 20, respectively, being some 85 and 7300 times less potent than 18 (Table II).

We also examined modification of the basic moiety by incorporating some of those groups we had found to have a potency enhancing effect in the piperidine series[6] (Table III). With the exception of the tetrahydropyridine (27), which was also a very potent κ-agonist, there was little parallel between the two series; notably the 3-hydroxy- and 3-oxopyrrolidines, 30 and 31, respectively, were considerably less active (LVD data).

The striking effect upon changing the 4-substituent from propanoyl to carbomethoxyl suggested a possible difference in electronic properties might account for the dramatic enhancement in activity. A comparison of the electrostatic potential surface of compounds 12, 18, and GR45809 (1) suggests that the potency of these analogues correlates with the magnitude of the negative electrostatic potential associated with the 4-N-substituent (in the case of the piperazines) and the spirodioxolane system (Figure 2). It is perhaps noteworthy that the acryloyl derivative 15, somewhat intermediate in this property, shows κ-agonist potency (LVD data) midway between that of 12 and 18. The deleterious effect of introducing the larger alkyl/aryl groups may be due to sterically hindered access of the area of negative potential to the receptor.

In conclusion, we have identified a series of novel 4-substituted 1-(arylacetyl)-2-[(alkylamino)methyl]piperazine κ-agonists, of which GR89696 (18) exhibits exceptional potency and selectivity. This high level of activity appears to be the result of an optimal combination of the steric and electronic properties of the methoxycarbonyl group. GR89696 should prove to be a useful probe for

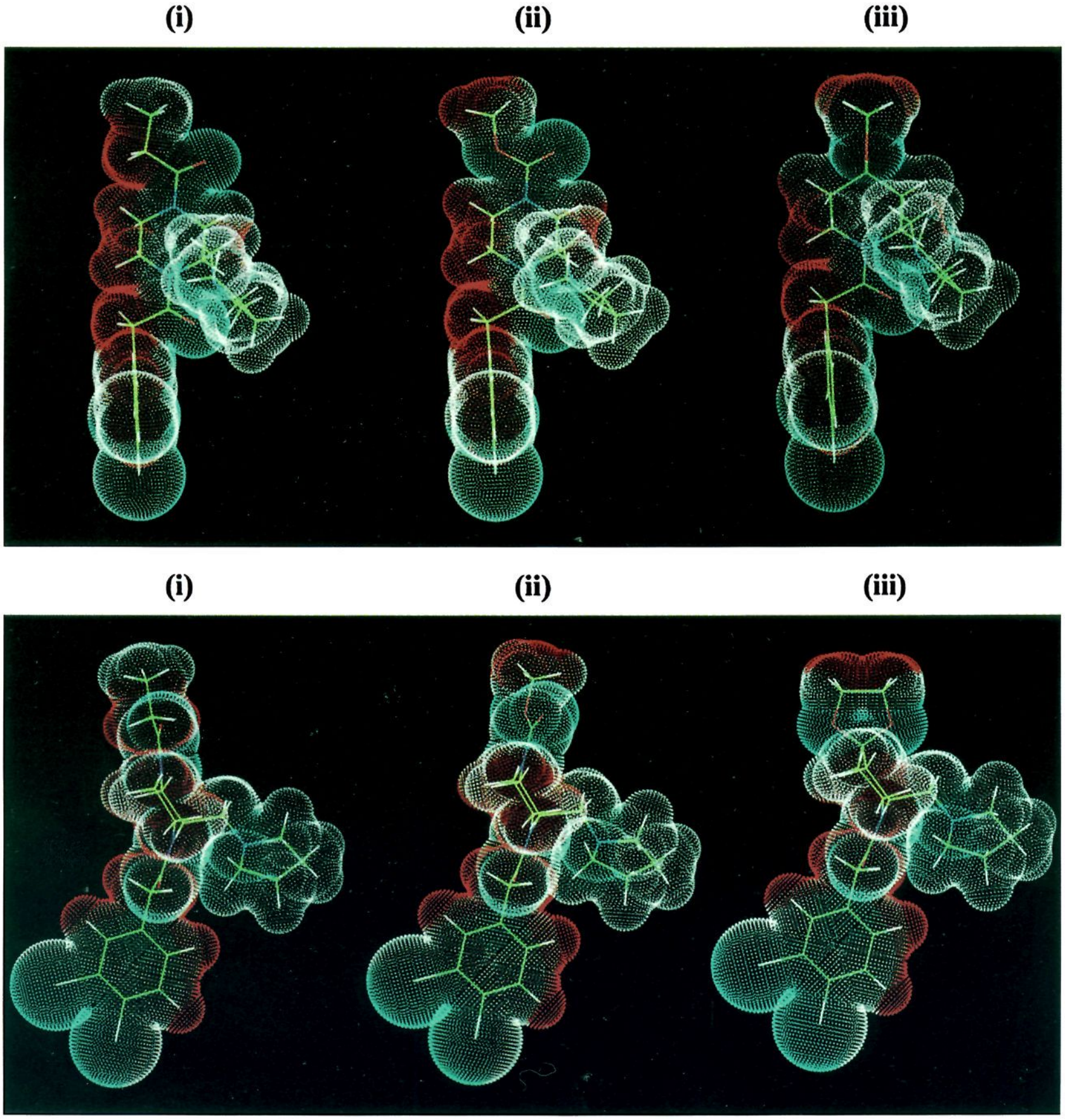


Figure 2. (a, Top) Molecular electrostatic potential maps of compounds **12** (i), **18** (ii), and **1** (iii). (b, Bottom) As for part a except that molecules have been rotated through 90°.

ascertaining further the functional significance of the κ-opioid receptor. Data have been presented elsewhere which demonstrates its excellent neuroprotective properties.[14]

Experimental Section

^{1}H NMR spectra were measured ($SiMe_4$ internal standard) on a Bruker WM250 (250 MHz) or a Varian Unity 400-MHz spectrometer. Signals for minor rotamers are indicated by an asterisk. IR spectra were recorded on Perkin-Elmer 357 or 377 spectrometers. Optical rotations were obtained on an Perkin-Elmer 241 polarimeter. Spectroscopic and microanalytical data were obtained by Glaxo Structural Chemistry Department. All melting points are uncorrected. Column chromatography was performed using Merck Kieselgel 60 (Art 9385; flash chromatograph). Solvents were dried according to standard procedures.[15]

Ethyl 3-Oxo-1,4-bis(phenylmethyl)-2-piperazinecarboxylate (3). Diethyl bromomalonate (7.20 g, 30 mmol) was added to a stirred solution of *N,N'*-dibenzylethylenediamine (14.40 g, 60 mmol) in acetonitrile (90 mL) at room temperature under nitrogen, and the resulting solution was heated at reflux for 6 h. After cooling, the solvent was removed and the residue was diluted with sodium hydroxide (1 N, 90 mL). The aqueous mixture was extracted with diethyl ether (3 × 60 mL). The combined organic extracts were dried and evaporated to give an oil. This material was purified by flash column chromatography on silica gel, eluting with hexane–ethyl acetate (2:1), to give **3** (7.96 g, 75%) as a yellow oil: NMR ($CDCl_3$) δ 1.36 (3H, t, CH_3CH_2), 2.55 (1H, m, H_6), 3.2 (3H, m, 2 × H_5, H_6), 3.60, 3.74 (2H, AB system, J = 13 Hz, 1-CH_AH_BPh), 4.08 (1H, s, $CHCO_2Et$), 4.30 (2H, q, CH_3CH_2), 4.5, 4.73 (2H, AB system, J = 14 Hz, 4-CH_AH_BPh), 7.29 (10H, m, ArH). Anal. ($C_{21}H_{24}N_2O_3$) C, H, N.

Ethyl 3-Oxo-4-(phenylmethyl)-2-piperazinecarboxylate (4). A solution of **3** (98 g, 0.28 mol) in absolute ethanol (1 L) was hydrogenated over 5% palladium on carbon (11 g) for 24 h at room temperature. The catalyst was filtered off and the filtrate evaporated to give **4** (64.3 g, 88%) as an oil, which was of sufficient purity to use in the next stage. A small sample was purified by flash column chromatography on silica gel, eluting with dichloromethane–methanol (98:2): NMR ($CDCl_3$) δ 1.35 (3H, t, CH_3-

CH_2), 2.17 (1H, br, NH), 3.0 (1H, m, H_6), 3.1–3.3 (3H, 2 m, 2 × H_5, H_6), 4.30 (2H, m, $CHCO_2Et$ + CH_3CH_2), 4.54, 4.72 (2H, AB system, J = 14 Hz, CH_AH_BPh), 7.30 (5H, m, ArH). Anal. ($C_{14}H_{18}N_2O_3$) C, H, N.

4-(Phenylmethyl)-2-piperazinemethanol (5). A solution of **4** (34 g, 0.13 mol) in dry THF (500 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (13.6 g, 0.36 mol) in dry THF (250 mL) under nitrogen over a 50-min period. The reaction mixture was stirred at room temperature for 1.5 h. The mixture was quenched, sequentially, with water (14 mL), sodium hydroxide solution (2 N, 40 mL), and then water (14 mL). The resulting suspension was stirred for 30 min and then filtered. The filtrate was evaporated to dryness to give an oil. This material was purified by flash column chromatography on silica gel, eluting with dichloromethane–methanol–0.88 ammonia (100:8:1.6), to give **5** (17.8 g, 67%) as a pale brown solid. This material was used directly in the next stage.

1-[(3,4-Dichlorophenyl)acetyl]-4-(phenylmethyl)-2-piperazinemethanol (6). 1,1′-Carbonyldiimidazole (4.95 g, 30.5 mmol) was added to a stirred solution of 3,4-dichlorophenylacetic acid (6.57 g, 32.1 mmol) in dry dichloromethane (125 mL) at room temperature under nitrogen. The resulting solution was stirred at room temperature for 1 h and added dropwise to a cooled (0–5 °C) solution of 4-(phenylmethyl)-2-piperazinemethanol (**5**) (6.29 g, 30.5 mmol) in dry dichloromethane (60 mL). The reaction mixture was stirred at room temperature for 18 h. It was then diluted with dichloromethane (100 mL) and washed with sodium carbonate solution (2 M, 3 × 200 mL). The organic layer was dried and evaporated to give a pale brown solid. This material was recrystallized from ethyl acetate–methanol to give **6** (4.40 g, 37%) as a cream-colored solid. The mother liquors were purified by flash column chromatography on silica gel, eluting with dichloromethane–methanol (97:3), to afford a further quantity of **6** (0.55 g, 5%): mp 148–150 °C. Anal. ($C_{20}H_{22}Cl_2N_2O_2$) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-4-(phenylmethyl)-2-piperazinecarboxaldehyde (7). A solution of dimethyl sulfoxide (369 mg, 4.73 mmol) in dichloromethane (3 mL) was added to a stirred solution of oxalyl chloride (300 mg, 2.36 mmol) in dichloromethane (7 mL) at −60 °C under nitrogen, and the resulting solution was stirred at −60 °C for 30 min. A solution of **6** (774 mg, 1.97 mmol) in dichloromethane (5 mL) was added dropwise, and the reaction mixture was stirred at −60 °C for 2.5 h. Triethylamine (995 mg, 9.85 mmol) was added, and the mixture was allowed to warm to −20 °C and then quenched with water (15 mL). The layers were separated, and the aqueous phase was further extracted with dichloromethane (2 × 15 mL). The combined organic extracts were dried and evaporated to give **7** (830 mg), as an oil, which was used directly in the next stage.

1-[(3,4-Dichlorophenyl)acetyl]-4-(phenylmethyl)-2-[(1-pyrrolidinyl)methyl]piperazine (8). A solution of **7** (2.05 g, 5.24 mmol) in methanol (35 mL) was added to a stirred solution of pyrrolidine (0.46 g, 6.47 mmol) in methanol (20 mL) containing 3-Å molecular sieves (2.5 g), the mixture being adjusted to ca. pH 6 using methanolic hydrogen chloride solution. The reaction mixture was stirred under nitrogen for 15 min, and sodium cyanoborohydride (0.75 g, 11.86 mmol) was added portionwise. The resulting suspension was stirred under nitrogen for 18 h and filtered, and the filtrate was evaporated to dryness. The residue was partitioned between aqueous sodium carbonate solution (2 M, 100 mL) and dichloromethane (40 mL). The aqueous layer was further extracted with dichloromethane (2 × 40 mL). The combined organic extracts were dried and evaporated to give a viscous oil which was purified by flash column chromatography on silica gel, eluting with dichloromethane–methanol–0.88 ammonia (175:8:1), to give **8** (1.07 g, 46%) as a colorless oil. This was characterized as the maleate salt: mp 117–120 °C (EtOAc); NMR (MeOH-d_4) δ 1.94 (1H, dt, J = 3, 12 Hz, H_{5ax}), 2.25 (4H, br s, CH_2CH_2), 2.18 (1H, dd, J = 4, 12.5 Hz, H_{3ax}), 2.85 (2H, br d, H_{3eq}, H_{5eq}), 3.20 (1H, dd, J = 3.5, 13.5 Hz, CH_AH_BN), 3.42, 3.52 (2H, AB system, J = 13 Hz, CH_AH_BPh), 3.3–3.55 (5H, m, pyrrolidine $N(CH_2)_2$ + H_{6ax}), 3.70, 3.91 (2H, AB system, J = 16 Hz, $COCH_AH_BAr$), 3.92 (1H, br d, H_{6eq}), 4.05 (1H, dd, J = 10.5, 13.5 Hz, CH_AH_BN), 4.98 (1H, m, H_2), 7.19 (1H, dd, J = 2, 8 Hz, ArH), 7.22–7.34 (5H, m, C_6H_5), 7.44 (1H, d, J = 2 Hz, ArH), 7.47 (1H, d, J = 8 Hz, ArH). Anal. ($C_{24}H_{29}Cl_2N_3O \cdot 1.35C_4H_4O_4$) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]piperazine (9). A solution of **8** (697 mg, 1.56 mmol) in tetrahydrofuran–water (1:1, 14 mL) and concentrated hydrochloric acid (1.4 mL) was hydrogenated over 10% palladium on carbon (280 mg) at atmospheric pressure for 5.5 h. The catalyst was filtered off, and the filtrate was evaporated. The residue was diluted with water (15 mL) and basified with 2 M sodium carbonate solution, and then the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were dried and evaporated to give an oil. This material was purified by flash column chromatography on silica gel, eluting with dichloromethane–methanol–0.88 ammonia (100:8:1), to give **9** (479 mg, 86%) as an oil. This material was characterized as the maleate salt: mp 160–162 °C (EtOAc); NMR (free base in D_2O + DCl) δ 1.88–2.22 (4H, m), 3.2 (3H, m), 3.35–3.58 (4H, m), 3.66–3.81 (3H, m), 3.95 (2H, br s, $COCH_2Ar$), 3.98 (1H, br t, H_{6ax}), 4.2 (1H, br d, H_{6eq}), 5.39 (1H, m, H_2), 7.19 (1H, br d), 7.46 (1H, br s), 7.53 (1H, d). Anal. ($C_{17}H_{23}Cl_2N_3O \cdot 1.5\ C_4H_4O_4$), C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-4-formyl-2-[(1-pyrrolidinyl)methyl]piperazine (10). A mixture of **9** (200 mg, 0.56 mmol) and methyl formate (3 mL) was allowed to stand at room temperature for 18 h. The excess methyl formate was removed, and the residue was purified by flash column chromatography on silica gel, eluting with dichloromethane–methanol–0.88 ammonia (100:8:1) to give **10** (164 mg, 76%) as a colorless oil. This material was characterized as the fumarate salt: mp 179–182 °C (EtOH–MeOH); NMR (D_2O) δ 5.2 (1H, m, H_2), 8.04*, 8.15 (1H, 2 s, CHO). Anal. ($C_{22}H_{27}Cl_2N_3O_6$) C, H, N.

4-Acetyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]piperazine (11). Acetyl chloride (49 mg, 0.62 mmol) was added dropwise to a stirred solution of **9** (200 mg, 0.56 mmol), pyridine (53 mg, 0.67 mmol), and 4-(dimethylamino)pyridine (5 mg) in dry dichloromethane (5 mL) under nitrogen at 0 °C. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 2 h. The resulting mixture was washed with aqueous sodium carbonate solution (2 M, 2 × 5 mL), dried, and evaporated to give a colorless oil. This oil was purified by flash column chromatography on silica gel, eluting with dichloromethane–methanol–0.88 ammonia (200:8:1), to give **11** (190 mg, 85%) as a colorless gum. This material was characterized as its maleate salt: mp 137–140 °C (EtOAc–MeOH). Anal. ($C_{23}H_{29}Cl_2N_3O_6$) C, H, N.

The following compounds were similarly prepared:

1-[(3,4-Dichlorophenyl)acetyl]-4-(1-oxobutyl)-2-[(1-pyrrolidinyl)methyl]piperazine (13) (87%), characterized as the maleate salt: mp 172–174 °C (EtOAc–MeOH). Anal. ($C_{25}H_{33}Cl_2N_3O_6$) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-4-(1-oxo-2-propenyl)-2-[(1-pyrrolidinyl)methyl]piperazine (15) (68%), characterized as the fumarate salt: mp 163–166 °C (EtOAc–MeOH). Anal. ($C_{24}H_{29}Cl_2N_3O_6$) C, H, N.

4-Benzoyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]piperazine (16) (73%), characterized as the maleate salt: mp 62–66 °C (EtOAc–Et_2O). Anal. ($C_{28}H_{31}Cl_2N_3O_6 \cdot 0.5H_2O$) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-4-(1-oxopropyl)-2-[(1-pyrrolidinyl)methyl]piperazine (12). 1,1′-Carbonyldiimidazole (100 mg, 0.62 mmol) was added to a stirred solution of propionic acid (47 mg, 0.63 mmol) in dry dichloromethane (3 mL) at room temperature under nitrogen, and the resulting solution was stirred at room temperature for 1 h. A solution of **9** (200 mg, 0.56 mmol) in dry dichloromethane (3 mL) was added, and stirring was continued for a further 20 h. The reaction mixture was diluted with dichloromethane (5 mL) was washed with aqueous sodium carbonate solution (2 M, 2 × 5 mL). The organic layer was dried and evaporated to give a colorless oil, which solidified on standing. The solid was triturated under dry diethyl ether, and the resulting material was crystallized from *tert*-butyl methyl ether to give **12** (90 mg, 39%) as a colorless solid: mp 110–112 °C. Anal. ($C_{20}H_{27}Cl_2N_3O_2$) C, H, N.

The following compounds were similarly prepared:

1-[(3,4-Dichlorophenyl)acetyl]-4-(methoxyacetyl)-2-[(1-pyrrolidinyl)methyl]piperazine (14) (90%), characterized as the maleate salt: mp 162–165 °C (EtOAc–MeOH). Anal. ($C_{24}H_{31}Cl_2N_3O_7$) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-4-(phenylacetyl)-2-[(1-pyrrolidinyl)methyl]piperazine (17) (91%), characterized as

the hydrochloride salt: mp 200–201 °C (EtOAc–MeOH). Anal. ($C_{25}H_{30}Cl_8N_3O_2$) C, H, N.

Methyl 4-[(3,4-Dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazinecarboxylate (18). A solution of **9** (1.5 g, 4.21 mmol) and triethylamine (0.60 mL, 4.30 mmol) in dry dichloromethane (50 mL) at −25 °C was treated with a solution of methyl chloroformate (0.33 mL, 4.2 mmol) in dry dichloromethane (10 mL) over a 5-min period. The mixture was stirred at −20 °C for 20 min, and then an aqueous solution of sodium carbonate (2 M, 25 mL) was added. The product was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were dried and evaporated to give an oil. This material was purified by flash column chromatography on silica gel, eluting with dichloromethane–methanol–0.88 ammonia (200:8:1), to give **18** (1.51 g, 87%) as a colorless viscous oil. This material was characterized as the fumarate salt: mp 178–179 °C (EtOAc–MeOH); NMR (MeOH-d_4) δ 2.12 (4H, m, CH_2CH_2), 2.98 (1H, m, H_{6ax}), 3.23 (3H, m + dd, J = 4, 13 Hz, H_{2ax} + CH_AH_BN) 3.42 (4H, m, pyrrolidine $N(CH_2)_2$), 3.55 (1H, m, H_{5ax}), 3.74 (1H, dd, J = 10, 13 Hz, CH_AH_BN), 3.81 (3H, s, OMe), 3.84, 3.99 (2H, AB system, J = 16 Hz, $COCH_AH_BAr$), 4.1 (1H, m, H_{6eq}), 4.12 (2H, m, H_{2eq}, H_{5eq}), 5.10 (1H, m, H_{3eq}), 7.30 (1H, dd, J = 2.8 Hz, ArH), 7.5 (1H, d, J = 2 Hz), 7.57 (1H, d, J = 8 Hz). Anal. ($C_{23}H_{29}Cl_2N_3O_7$) C, H, N.

The following compounds were similarly prepared:

Ethyl 4-[(3,4-dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazinecarboxylate (19) (33%), characterized as the fumarate salt: mp 190–192 °C (EtOAc). Anal. ($C_{24}H_{31}Cl_2N_3O_7$) C, H, N.

Propyl 4-[(3,4-dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazinecarboxylate (20) (89%), characterized as the fumarate salt: mp 187 °C (EtOAc). Anal. ($C_{25}H_{33}Cl_2N_3O_7$) C, H, N.

Phenyl 4-[(3,4-dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate (21) (82%), characterized as the fumarate salt: mp 186 °C (EtOAc–MeOH). Anal. ($C_{28}H_{31}Cl_2N_3O_7$) C, H, N.

Phenylmethyl 4-[(3,4-dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate (22) (66%), characterized as the fumarate salt: mp 186–187 °C (EtOAc–MeOH). Anal. ($C_{29}H_{33}Cl_2N_3O_7$) C, H, N.

2-Piperazinemethanol (23). A solution of the piperazine **5** (5.15 g, 0.025 mol) in a mixture of tetrahydrofuran (100 mL), water (100 mL), and concentrated hydrochloric acid (20 mL) was hydrogenated over 10% palladium on carbon (1.75 g) for 2.5 h. The reaction mixture was filtered and the filtrate evaporated to dryness. The solid residue was triturated with hot ethanol (50 mL), and the resulting material was collected by filtration to afford **23** (4.3 g, 91%) as its dihydrochloride salt, an off-white solid; mp 169–172 °C dec. Anal. ($C_5H_{14}Cl_2N_2O$) C, H, N.

Methyl 3-(Hydroxymethyl)-1-piperazinecarboxylate (24). A solution of **23** (432 mg, 3.72 mmol) and triethylamine (0.7 mL, 5.1 mmol) in acetonitrile (40 mL) at 5 °C was treated with a solution of methyl chloroformate (0.29 mL, 3.72 mmol) in acetonitrile (5 mL) dropwise over 0.5 min. The reaction mixture was stirred for 10 min, and then an aqueous solution of sodium carbonate (2 N, 20 mL) was added. The mixture was evaporated, sodium carbonate solution (10 mL) was added, and the mixture was extracted with dichloromethane (3 × 10 mL). The aqueous phase was saturated with sodium chloride and further extracted with dichloromethane (3 × 10 mL). The combined organic solutions were dried, filtered, and evaporated to give an oil which was purified by flash column chromatography on silica gel, eluting with dichloromethane–methanol–0.88 ammonia (100:10:2) to give **24** (147 mg, 23%) as an oil which was used directly in the next stage.

Methyl 4-[(3,4-Dichlorophenyl)acetyl]-3-(hydroxymethyl)-1-piperazinecarboxylate (25). To a solution of 1,1′-carbonyldiimiazole (3.26 g, 20.1 mmol) in dichloromethane (120 mL) was added portionwise 3,4-dichlorophenylacetic acid (4.12 g, 20.1 mmol) and the resulting solution stirred under nitrogen for 1 h, at room temperature. A solution of **24** (1.4 g, 8.0 mmol) in dichloromethane (120 mL) was added and the mixture stirred at room temperature for 18 h. The reaction mixture was washed with sodium carbonate solution (2 N, 2 × 100 mL), dried, and evaporated to give a viscous oil. This material was dissolved in a mixture of tetrahydrofuran (80 mL) and water (25 mL) and treated with lithium hydroxide (671 mg, 16.0 mmol). The reaction mixture was stirred at room temperature for 0.5 h. The organic solvent was removed, and the aqueous residue was extracted with dichloromethane (3 × 50 mL). The combined organic extracts were dried and evaporated to give a colorless gum which was purified by flash column chromatography on silica gel, eluting with ethyl acetate–methanol (40:1), to give **25** (2.2 g, 76%) as a colorless foam: NMR (DMSO-d_6, 413 K) δ 2.9–3.16 (3H, 3 m, H_{2ax}, H_{5ax}, H_{6ax}), 3.55 (2H, d, CH_2OH), 3.68 (3H, s, OMe), 3.80 (2H, AB system, $COCH_2Ar$), 3.8–4.1 (3H, m, H_{2eq}, H_{5eq}, H_{6eq}), 4.28 (1H, m, H_3), 4.2–4.4 (1H, br, OH), 7.25 (1H, dd, J = 2, 8 Hz, ArH), 7.49 (1H, d, J = 2 Hz, ArH), 7.52 (1H, d, J = 8 Hz, ArH).

Methyl 4-[(3,4-Dichlorophenyl)acetyl]-3-[(1,2,3,6-tetrahydro-1-pyridinyl)methyl]-1-piperazinecarboxylate (27). A solution of dimethyl sulfoxide (0.52 mL, 0.57 g, 7.3 mmol) in dry dichloromethane (6 mL) was added to a stirred solution of oxalyl chloride (0.40 mL, 0.59 g, 4.62 mmol) in dry dichloromethane (30 mL) at −65 °C under nitrogen. The resulting solution was stirred at −65 °C for 20 min, and a solution of the alcohol **25** (1.08 g, 3.0 mmol) in dry dichloromethane (25 mL) was then added dropwise at −65 °C. The reaction mixture was stirred at −65 °C for 3 h. Triethylamine (2.5 mL, 1.82 g, 17.9 mmol) was added, followed by water (25 mL) at −20 °C. The organic layer was dried and evaporated to give the intermediate carboxaldehyde.

A solution of this aldehyde (539 mg, 1.5 mmol) in dry methanol (15 mL) was added to a stirred solution of 1,2,3,6-tetrahydropyridine (0.2 mL, 180 mg, 2.2 mmol) in dry methanol (10 mL) containing 3-Å molecular sieves (1 g). The pH of the reaction mixture was adjusted to 6 using methanolic hydrogen chloride solution. Sodium cyanoborohydride (225 mg, 3.6 mmol) was added and the resulting mixture stirred for 3 days. The mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in aqueous sodium carbonate solution (2 M, 10 mL) and extracted with dichloromethane (3 × 10 mL). The combined dichloromethane extracts were dried and evaporated to dryness. The residue was dissolved in hydrochloric acid (0.1 M, 45 mL, 4.5 mmol) and washed with diethyl ether (3 × 10 mL). The aqueous solution was basified with sodium carbonate solution (2 N, 10 mL), and the product was extracted into dichloromethane (3 × 10 mL). The combined extracts were dried and evaporated to give a yellow oil (532 mg) which was purified by flash column chromatography on silica gel, eluting with dichloromethane–methanol–0.88 ammonia (300:8:1), to give **27** (253 mg, 40%) as a colorless oil. This material was characterized as the fumarate salt: mp 158–160 °C. Anal. ($C_{24}H_{29}N_3Cl_2O_7$) C, H, N.

The following compound was similarly prepared:

Methyl 4-[(3,4-dichlorophenyl)acetyl]-3-[(dimethylamino)methyl]-1-piperazinecarboxylate (26) (40%), characterized as the hydrochloride salt: mp 229–231 °C (EtOAc). Anal. ($C_{17}H_{24}N_3Cl_3O_3$) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-4-(phenylmethyl)-2-[(3-hydroxy-1-pyrrolidinyl)methyl]piperazine (28). This compound was prepared from **7** and 3-pyrrolidinol using the method described for the preparation of **8**. **28** (2.38 g, 55%) was obtained as a foam: NMR (DMSO-d_6, 413 K) δ 1.57 (1H, m, $CHCHOH$), 1.82–2.1 (4H, m, $CHCHOH$, 2 × H_5, 1 × H_3), 2.4–2.98 (7H, m, 3 × CH_2N, 1 × H_3), 3.07 (1H, dt, J = 3.5, 12 Hz, H_{6ax}), 3.43, 3.52 (2H, AB system, J = 13 Hz, $COCH_2Ar$), 3.72, 3.74 (2H, AB system, J = 13.5 Hz, CH_2Ph), 3.96 (1H, br d, H_{6eq}), 4.18 (1H, m, $CHOH$), 4.28 (1H, m, H_2), 7.22 (1H, dd, J = 2, 8 Hz, ArH), 7.30 (5H, m, CH_2Ph), 7.45 (2H, m, ArH). Anal. ($C_{24}H_{29}Cl_2N_3O_2 \cdot CH_3OH$) C, H, N.

1-[(3,4-Dichlorophenyl)acetyl]-2-[(3-hydroxy-1-pyrrolidinyl)methyl]piperazine (29). A solution of **28** (2.34 g, 5.06 mmol) in a mixture of tetrahydrofuran (30 mL), water (30 mL), and concentrated hydrochloric acid (4.5 mL) was hydrogenated over 10% palladium on carbon (1.0 g) at atmospheric pressure for 15 min. The catalyst was filtered off and washed thoroughly with a mixture of tetrahydrofuran and water. The filtrate was evaporated to dryness, and the residue was triturated under dry diethyl ether. The resulting solid was dried to give **29** (1.99 g, 88%) as a cream-colored solid. Anal. ($C_{17}H_{23}Cl_2N_3O_2 \cdot 2HCl \cdot H_2O$) C, H, N.

Methyl 4-[(3,4-Dichlorophenyl)acetyl]-3-[(3-hydroxy-1-pyrrolidinyl)methyl]-1-piperazinecarboxylate (30). A solution of methyl chloroformate (243 mg, 0.20 mL, 2.57 mmol) in dry dichloromethane (3 mL) was added dropwise to a stirred

solution of **29** (1.0 g, 2.45 mmol) and triethylamine (495 mg, 4.90 mmol) in dry dichloromethane (25 mL) at −25 °C under nitrogen. The resulting solution was stirred at −25 °C for 30 min, quenched with aqueous sodium carbonate solution (2 M, 30 mL), and extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried and evaporated to give a foam. This residue was purified by flash column chromatography on silica gel, eluting with dichloromethane–methanol–0.88 ammonia (150:8:1), to give **30** (800 mg, 76%) as a colorless foam. Anal. ($C_{19}H_{25}Cl_2N_3O_4 \cdot {}^1/_2H_2O$) C, H, N.

Methyl 4-[(3,4-Dichlorophenyl)acetyl]-3-[(3-oxo-1-pyrrolidinyl)methyl]-1-piperazinecarboxylate (31). This compound was prepared from **30** using the method described for the preparation of **7**. **31** (520 mg, 76%) was characterized as the maleate salt: mp 180–183 °C (EtOAc–MeOH). Anal. ($C_{23}H_{27}Cl_2N_3O_8$) C, H, N.

(*E*)-Methyl 4-[(3,4-Dichlorophenyl)acetyl]-3-[[3-(2-methoxy-2-oxoethylidene)-1-pyrrolidinyl]methyl]-1-piperazinecarboxylate (32) and *Z*-Isomer 33. A solution of trimethyl phosphonoacetate (181 mg, 0.99 mmol) in dry tetrahydrofuran (5 mL) was added to a stirred suspension of sodium hydride (58% dispersion with oil, 45 mg, 1.06 mmol) in tetrahydrofuran (10 mL) at 0 °C under nitrogen. The resulting mixture was stirred at 0 °C for 15 min and treated with a solution of **31** (386 mg, 0.90 mmol) in dry tetrahydrofuran (5 mL). The reaction mixture was heated at reflux for 2 h, diluted with ethyl acetate (20 mL), and washed with saturated sodium chloride solution (2 × 10 mL). The aqueous layer was extracted with ethyl acetate (2 × 10 mL), and the combined organic extracts were washed with saturated sodium chloride solution (20 mL), dried, and evaporated to give an oil. This material was purified by flash column chromatography on silica gel, eluting with ethyl acetate–ethanol (60:1) to give a pale yellow oil (200 mg). This material was further purified by flash column chromatography on silica gel, eluting with dichloromethane–methanol–0.88 ammonia (200:8:1) to provide initially the *E*-isomer **32** (31 mg, 7%) as a viscous colorless oil [NMR ($CDCl_3$) δ 5.79 (1H, s, $=CHCO_2Me$); HRMS (FAB) *m/e* 484.140594 $(M + H)^+$ calcd for $C_{22}H_{28}N_3O_5Cl_2$ 484.140602] and then the *Z*-isomer **33** (30 mg, 7%) as a viscous colorless oil: NMR ($CDCl_3$) δ 5.75 (1H, s, $=CHCO_2Me$); HRMS (FAB) *m/e* 484.139038 $(M + H)^+$ calcd for $C_{22}H_{28}Cl_2N_3O_5$ 484.140602.

***N*-[(1,1-Dimethylethoxy)carbonyl]-*N*-(phenylmethyl)-glycyl-D-serine Methyl Ester [(*R*)-34].** A solution of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.15 g, 6.0 mmol) in dry dichloromethane (25 mL) was treated with a solution of pentafluorophenol (1.5 g, 8.1 mmol) in dry dichloromethane (10 mL), and the mixture was stirred at ambient temperature for 1 h. A solution of *N*-(phenylmethyl)-*N*-[(1,1-dimethylethoxy)carbonyl]glycine (1.32 g, 5.0 mmol) in dry dichloromethane (20 mL) was added, and the mixture was stirred for 3 h. A solution of D-serine methyl ester hydrochloride (0.63 g, 6.0 mmol) in a mixture of triethylamine (2.5 mL, 18 mmol) and dichloromethane (20 mL) was added. The reaction mixture was stirred at ambient temperature for 20 h and then washed with aqueous sodium carbonate solution (1 M, 100 mL), aqueous citric acid solution (1 M, 100 mL), and water (50 mL). The organic phase was dried and evaporated to give an oil which was purified by flash column chromatography on silica gel, eluting with ethyl acetate–hexane (3:2), to give (*R*)-**34** (1.1 g, 60%) as a colorless viscous oil: $[\alpha]_D = -32.2°$ (*c* = 0.4, $CHCl_3$). Anal. ($C_{18}H_{26}N_2O_6$) C, H, N.

The following compound was similarly prepared:

***N*-[(1,1-Dimethylethoxy)carbonyl]-*N*-(phenylmethyl)-glycyl-L-serine methyl ester [(*S*)-34]** (65%): $[\alpha]_D = +33.7°$ (*c* = 0.4, $CHCl_3$). Anal. ($C_{18}H_{26}N_2O_6$) C, H, N.

(*R*)-3-(Hydroxymethyl)-1-(phenylmethyl)-2,5-piperazinedione [(*R*)-35]. A solution of (*R*)-**34** (0.82 g, 2.10 mmol) in methanol (5 mL) was treated with thionyl chloride (0.8 mL, 11 mmol) dropwise at such a rate that the temperature was maintained below 40 °C. The mixture was stirred at ambient temperature for 2 h, and the solvent was then removed. The residue was triturated under ether (20 mL). The resultant solid was dissolved in methanol (10 mL) and was treated with ammonia (0.88, 10 mL). The solvent was evaporated to give a solid which was purified by flash column chromatography on silica gel, eluting with dichloromethane–methanol–0.88 ammonia (75:10:2), to give (*R*)-**35** (0.32 g, 66%) as a colorless solid: mp 186–187 °C; $[\alpha]_D = -37.1$ (*c* = 0.4, MeOH); NMR (400 MHz) (DMSO-d_6) δ 3.58 (1H, ddd, *J* = 11, 5, 2.5 Hz, CH_AH_BOH), 3.64, 3.86 (2H, AB system, *J* = 16.5 Hz, 2 × H_5), 3.85 (1H, ddd, *J* = 11, 5, 3 Hz, CH_AH_BOH), 4.47, 4.65 (2H, AB system, *J* = 15 Hz, CH_2Ph), 5.26 (1H, t, *J* = 5 Hz, H_2), 7.26–7.38 (5H, m, ArH), 8.17 (1H, br s, NH). Anal. ($C_{12}H_{14}N_2O_3$) C, H, N.

The following compound was similarly prepared:

(*S*)-3-(Hydroxymethyl)-1-(phenylmethyl)-2,5-piperazinedione [(*S*)-35] (69%): $[\alpha]_D = +36.3°$ (*c* = 0.4, MeOH).

(*R*)-4-(Phenylmethyl)-2-piperazinemethanol [(*R*)-5]. A suspension of lithium aluminum hydride (1.45 g, 0.038 mol) in dry tetrahydrofuran (20 mL) was treated with a solution of the piperazinedione (*S*)-**35** (2.3 g, 0.01 mol) in dry tetrahydrofuran (500 mL). The reaction mixture was heated at reflux for 1.5 h and then cooled. Water (1.4 mL) was added followed by aqueous sodium hydroxide (2 M, 4.5 mL) and water (1.4 mL). The mixture was filtered, and the filtrate was evaporated to give (*R*)-**5** (1.85 g, 91%) as a viscous oil. Anal. ($C_{12}H_{18}N_2O \cdot 0.25H_2O$) C, H, N.

The following compound was similarly prepared:

(*S*)-4-(Phenylmethyl)-2-piperazinemethanol [(*S*)-5] (92%), which was used directly in the next stage.

(*R*)-2-Piperazinemethanol [(*R*)-23]. A solution of (*R*)-**5** (1.8 g, 8.73 mmol) in ethanol (100 mL) was hydrogenated over 5% palladium on carbon (0.7 g) at atmospheric pressure. The catalyst was filtered off, and the filtrate was evaporated to dryness. The residue was crystallized from acetonitrile to give (*R*)-**23** (0.57 g, 56%) as a pale yellow solid: $[\alpha]_D = -4.9°$ (*c* = 0.4, MeOH).

(*S*)-2-Piperazinemethanol [(*S*)-23]. A solution of (*S*)-**5** (4.1 g, 0.02 mol) in a mixture of tetrahydrofuran (80 mL), water (80 mL), and concentrated hydrochloric acid (16 mL) was hydrogenated over 10% palladium on carbon (1.4 g) at atmospheric pressure. The catalyst was filtered off, and the filtrate was evaporated to dryness. The residue was triturated with hot ethanol to give (*S*)-**23** as a pale brown solid (2.56 g, 68%): mp 128–131 °C; $[\alpha]_D = 3.2°$ (*c* = 0.3, MeOH). Anal. ($C_5H_{14}Cl_2N_2O$) C, H, N.

(*S*)-Methyl 3-(Hydroxymethyl)-1-piperazinecarboxylate [(*S*)-24]. A solution of the diamine (*S*)-**23** (800 mg, 0.69 mmol) in acetonitrile (10 mL) was treated with a solution of methyl chloroformate (71 mg, 0.75 mmol) in acetonitrile (3 mL) over a 5-min period. The mixture was stirred at ambient temperature for 30 min, and then aqueous sodium carbonate solution (1 mL) was added. The organic solvent was removed, and the aqueous residue was extracted with chloroform (3 × 5 mL). The combined organic extracts were washed with aqueous sodium carbonate solution (1 M, 5 mL), dried, and evaporated to give (*S*)-**24** (100 mg, 83%) as an oil, which was used directly in the next stage.

The following compound was similarly prepared:

(*R*)-Methyl 3-(hydroxymethyl)-1-piperazinecarboxylate [(*R*)-24] (96%), which was used directly in the next stage.

(*S*)-Methyl 4-[(3,4-Dichlorophenyl)acetyl]-3-(hydroxymethyl)-1-piperazinecarboxylate [(*S*)-25]. 3,4-Dichlorophenylacetic acid (0.35 g, 1.7 mmol) and 1,1′-carbonyldiimidazole (0.28 g, 1.7 mmol) in dichloromethane (5 mL) was stirred at ambient temperature for 1 h. A solution of (*S*)-**24** (0.1 g, 0.375 mmol) in dichloromethane (2 mL) was added, and the mixture was stirred at ambient temperature for 20 h. The mixture was diluted with dichloromethane (30 mL) and washed with aqueous sodium carbonate solution (1 M, 3 × 50 mL). The organic solution was dried and evaporated to give an oil. A solution of this oil in a mixture of tetrahydrofuran and water (6 mL, 1:1) was treated with lithium hydroxide (50 mg, 1.2 mmol). The reaction mixture was stirred at ambient temperature for 1 h, and then the organic solvent was evaporated. The aqueous residue was extracted with dichloromethane (3 × 50 mL), dried, and evaporated to give an oil. This material was purified by flash column chromatography on silica gel, eluting with ethyl acetate–methanol (40:1), to give (*S*)-**25** (0.185 g, 89%) as a colorless foam. Anal. ($C_{15}H_{18}Cl_2N_2O_4$) C, H, N.

The following compound was similarly prepared:

(*R*)-Methyl 4-[(3,4-dichlorophenyl)acetyl]-3-(hydroxymethyl)-1-piperazinecarboxylate [(*R*)-25] (43%) was obtained as a colorless foam and used directly in the next stage.

(*S*)-Methyl 4-[(3,4-Dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate [(*S*)-18]. A solution of oxalyl chloride (0.36 mL, 4.12 mmol) in dichloromethane (7 mL) at −65 °C was treated with a solution of dimethyl sulfoxide

(0.75 mL, 10.6 mmol) in dichloromethane (4 mL) maintaining the reaction temperature below −65 °C. The mixture was stirred at −70 °C for 10 min, and then a solution of the piperazinemethanol (*S*)-**25** (0.62 g, 1.71 mmol) in dichloromethane (5 mL) was added at such a rate that the reaction temperature was maintained below −68 °C. The reaction mixture was stirred at −68 °C for 2.5 h, and a solution of *N*-methylmorpholine (0.9 mL, 8.2 mmol) in dichloromethane (3 mL) was added. The mixture was stirred at −20 °C for 45 min and then washed with ice-cold hydrochloric acid (0.01 M, 150 mL and 50 mL), dried, and evaporated. The residue was dissolved in methanol (4 mL) and was added to a solution of pyrrolidine (0.3 mL, 3.6 mmol) in methanol (5 mL) at −10 °C, which had been adjusted to pH 6 by the addition of methanolic hydrogen chloride. Sodium cyanoborohydride (0.22 g, 3.5 mmol) and 3-Å molecular sieves (0.2 g) were added, and the mixture was stirred at ambient temperature for 18 h. The mixture was filtered, and the filtrate was evaporated to dryness. The residue was dissolved in aqueous sodium carbonate (1 M, 25 mL) and extracted with dichloromethane (2 × 50 mL). The organic layer was dried and evaporated to give an oil which was purified by flash column chromatography on silica gel, eluting with dichloromethane–methanol–0.88 ammonia (250:8:1), followed by column chromatography on alumina, eluting with ethyl acetate to give (*S*)-**18** (0.26 g, 37%). This material was characterized as the fumarate salt: mp 186–188 °C (EtOAc–MeOH); $[\alpha]_D$ = +25.3° (*c* = 0.5, H_2O). Analytical HPLC conditions as for (*R*)-**18**. (*S*)-**18**: >99.5% ee. Anal. ($C_{23}H_{29}Cl_2N_3O_7$) C, H, N.

The following compound was similarly prepared:

(*R*)-Methyl 4-[(3,4-dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate [(*R*)-18], characterized as the fumarate salt: mp 184–185 °C (EtOAc–MeOH); $[\alpha]_D$ = −25.6° (*c* = 0.5, H_2O). Analytical HPLC conditions were as follows: 15-cm × 4.6-mm-i.d. column packed with spherisorb 3μ cyano-bonded; mobile phase: 25% CH_3CN/75% TFA (0.12% v/v TFA). (*R*)-**18**: 99.4% ee. Anal. ($C_{23}H_{29}Cl_2N_3O_7$) C, H, N.

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.[12]

In Vitro. Activities in the rabbit,[16] rat,[10] and hamster[11] vasa deferentia were determined as previously described. Potencies are quoted as IC_{50} (or pK_B) values.

Computational Methods. The electrostatic potentials on the van der Waal's surfaces of the molecules are computed based on point charges derived from the MNDO method.[17] Program MOPAC was used for geometry optimizations and CHEMX for plotting electrostatic potential surfaces. The potential surfaces are colored according to the following scheme: < −10 kcal/mol, blue; > −10 and < 10 kcal/mol, yellow; > 10 kcal/mol, red.

Acknowledgment. The X-ray crystallographic structural data for compound **18** was kindly provided by Mr. R. B. Lamont (Structural Chemistry Department, Glaxo Group Research Ltd.) Electrostatic potential maps were provided by Mrs. X. Q. Lewell. We thank Mr. S. A. Richards and Dr. I. M. Ismail for the NMR spectral interpretations, Mr. R. J. Boughtflower for HPLC data, and Mrs. M. Earl for the preparation of compounds **26** and **27**.

Supplementary Material Available: Crystal data for **18** and tables listing atomic coordinates, bond lengths, bond angles, and anisotropic displacement coefficients (9 pages); observed and calculated structure factors (7 pages). Ordering information is given on any current masthead page.

References

(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) 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. 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. Clemence, F.; et al. Fr. Demande FR 2,592,879, Jan 13, 1986. For a recent review, see: Rees, D. C. Chemical Structures and Biological Activities of Non-Peptide Selective Kappa Opioid Ligands. *Prog. Med. Chem.* **1992**, *29*, 109.

(6) Scopes, D. I. C.; Hayes, N. F.; Bays, D. E.; Belton, D.; Brain, J.; Brown, D. S.; Judd, D. B.; McElroy, A. B.; Meerholz, C. A.; Naylor, A.; Hayes, A. G.; Sheehan, M. J.; Birch, P. J.; Tyers, M. B. New κ-Receptor Agonists Based upon a 2-[(Alkylamino)methyl]piperidine Nucleus. *J. Med. Chem.* **1992**, *35*, 490–501.

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

(8) In the conversion of **24** into **25** it proved more convenient to effect *N,O*-bis-acylation and then to selectively cleave the *O*-acyl substituent.

(9) 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.

(10) Smith, C. F. C.; Rance, M. J. Opiate Receptors in the Rat Vas Deferens. *Life Sci.* **1983**, *33* (Suppl. 1), 327–330.

(11) 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.

(12) 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.

(13) The small amount of activity exhibited by the *S*-enantiomer is almost certainly due to contamination (ca. 0.3%) by the *R*-enantiomer.

(14) Birch, P. J.; Rogers, H.; Hayes, A. G.; Hayward, N. J.; Tyers, M. B.; Scopes, D. I. C.; Naylor, A.; Judd, D. B. Neuroprotective Actions of GR 89696, a Highly Potent and Selective κ-Opioid Receptor Agonist. *Br. J. Pharmacol.* **1991**, *103*, 1819–1823.

(15) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon, Oxford, 1980.

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

(17) Dewar, M. J. S.; Thiel, W. Ground State of Molecules. 38. The MNDO Method. Approximations and Parameters. *J. Am. Chem. Soc.* **1977**, *99*, 4899–4907.