4-[(Alkylamino)methyl]furo[3,2-c]pyridines: A New Series of Selective κ-Receptor Agonists

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

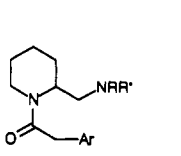
Departments of Medicinal Chemistry and Neuropharmacology, Glaxo Group Research Ltd., Ware, Hertfordshire SG12 0DP, England

Received January 13, 1994®

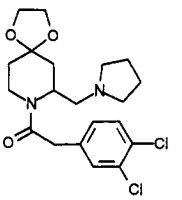
The synthesis of 5-(arylacetyl)-4-[(alkylamino)methyl]furo[3,2-c]pyridines (**16–23, 26, 27**) and their activities as κ-opioid receptor agonists are described. κ-Agonist potency was particularly sensitive to the nature of the basic moiety. In particular, in the rabbit vas deferens (κ-specific tissue), the 3-pyrrolidinol analogue **17** (IC_{50} = 2.7 nM) was found to be approximately 5-fold more potent than the corresponding pyrrolidine analogue **16** (IC_{50} = 15 nM). In the rat and hamster vasa deferentia (μ-specific and δ-specific tissues, respectively), **17** showed only weak antagonist activity ($pK_B > 5.5$), underlining its selectivity for the κ-opioid receptor. The major activity for **17** is resident in the 4*S*,3′*S*-isomer **26** (rabbit vas deferens IC_{50} = 1.1 nM). Compound **26** displays excellent antinociceptive activity, as determined in the mouse acetylcholine-induced abdominal constriction test (ED_{50} = 0.001 mg/kg, sc).

The high level of interest in the medicinal chemistry of opioids during the past decade has stemmed, in large part, from the identification of three distinct opioid receptor subtypes: μ, κ, and δ.[1] It is well established that activation of each of these receptors can produce antinociceptive effects in a variety of animal models.[2] In particular, considerable effort has been expended in obtaining selective κ-agonists with the expectation that such compounds should be strong analgesics[3] devoid of many of the undesirable side effects associated with morphine-like μ-agonists (e.g., respiratory depression, constipation, physical dependence).[4] In addition to playing a role in antinociception, activation of the κ-opioid receptor can produce neuroprotective effects in certain animal models of cerebral ischaemia,[5] i.e., clincal use of κ-agonists may provide a novel approach for the treatment of stroke.

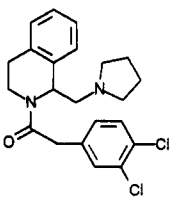
As part of a program of research aimed at identifying selective κ-receptor agonists as potential analgesic[6] and neuroprotective[7] agents, our interest in this area has centered on the 2-[(alkylamino)methyl]piperidine class of κ-agonist **1**. It has previously been shown that certain compounds within this group [e.g., **2** (GR45809)] are both potent and selective agonists at the κ-opioid receptor.[8,9] As an extension of these discoveries, we and others[6,10] have studied the effect of fusion of benzenoid (e.g., **3**) and heteroaromatic ring systems onto the piperidine nucleus of **1**. The finding that these modifications furnished potent and selective κ-agonists encouraged us to evaluate the profiles of structures incorporating an electron-rich furan nucleus. We now report on the synthesis and κ-agonist activity of a novel series of 4-[(alkylamino)methyl]furo-[3,2-c]pyridines (**16–23, 26, 27**). Structure–activity studies[9] have shown that within the 2-[(alkylamino)methyl]-piperidine series (**1**), (3,4-dichlorophenyl)acetyl[11] is one of the optimum *N*-acyl groups for κ-agonist activity. Accordingly, in the present work, this feature has been retained and we have focused on selected modifications of the basic moiety which, based upon our previous studies,[8] can result in high κ-agonist potency.



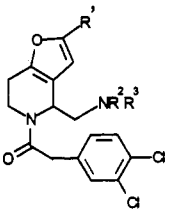
(1)



GR45809



(3)



(16-23, 26, 27)

Chemistry

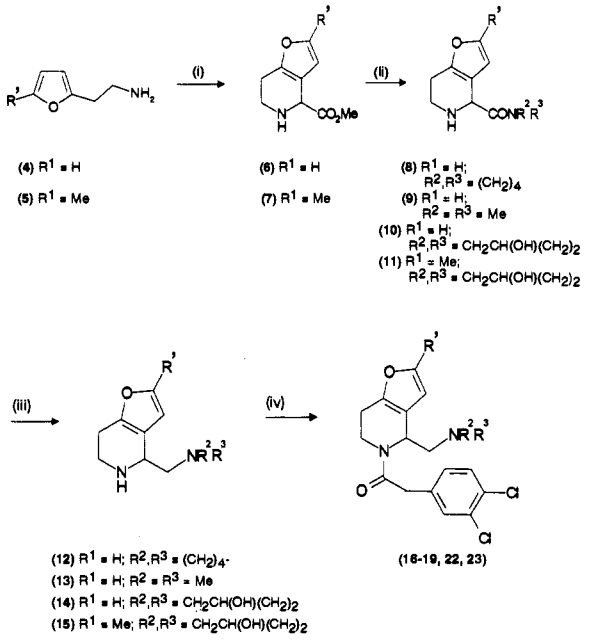
The general route shown in Scheme 1 was used to synthesize the majority of the compounds described in this paper. The novel methyl 4,5,6,7-tetrahydrofuro[3,2-c]pyridine-4-carboxylate intermediates **6** and **7** were prepared from the known furanethylamines **4**[12] and **5**,[13] respectively, and converted into the amides **8–11** by heating with the appropriate neat amine. Subsequent reduction with lithium aluminum hydride followed by acylation of the resulting diamines **12–15** with 3,4-dichlorophenylacetic acid, using 1,1′-carbonyldiimidazole activation, provided the desired analogues **16–19, 22,** and **23**. In the case of analogues possessing the 3-pyrrolidinol group, some *O,N*-diacylation was observed at this latter stage. However, selective *O*-deacylation could be readily effected upon hydrolysis with lithium hydroxide.

The 3-pyrrolidinone **20** was obtained *via* Swern oxidation of the alcohols **17** (Scheme 2). Preparation of the 1,2,3,6-tetrahydropyridinyl derivative **21** necessitated an alternative approach *via* the alcohol **28** which was obtained by reduction of the ester **6** (Scheme 3). *O,N*-Diacylation of the alcohol **28** with 3,4-dichlorophenylacetic acid followed by *O*-deacylation gave the amido alcohol **29**. Swern oxidation of **29** and immediate reductive amination of the resulting crude aldehyde with 1,2,3,6-tetrahydropyridine

§ Department of Medicinal Chemistry.
† Department of Neuropharmacology.
® Abstract published in *Advance ACS Abstracts*, June 1, 1994.

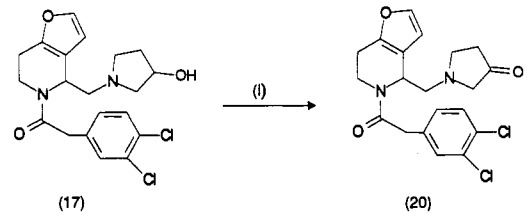
0022-2623/94/1837-2138$04.50/0

Scheme 1[a]



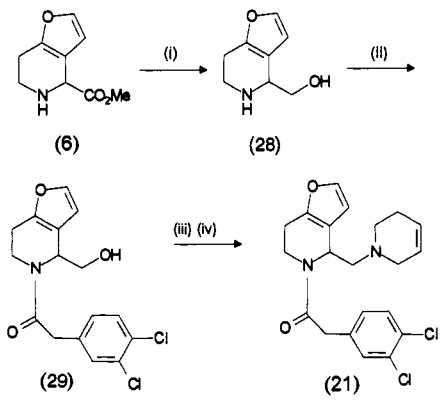
[a] (i) $CHO{\cdot}CO_2Me$, HCl; (ii) HNR^2R^3; (iii) $LiAlH_4$; (iv) (a) 3,4-Cl_2-$C_6H_3CH_2CO_2H$, 1,1'-carbonyldiimidazole, (b) LiOH.

Scheme 2[a]



[a] (i) $(COCl)_2$, DMSO, Et_3N.

Scheme 3[a]

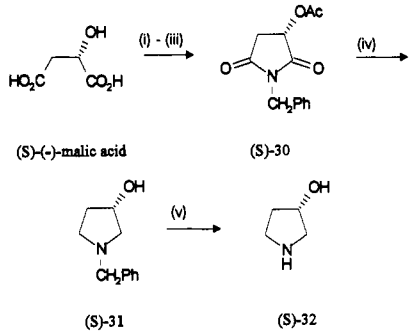


[a] (i) $LiAlH_4$; (ii) (a) 3,4-Cl_2-$C_6H_3CH_2CO_2H$, 1,1'-carbonyldiimidazole, (b) LiOH; (iii) $(COCl)_2$, DMSO, Et_3N; (iv) 1,3,5,6-tetrahydropyridine, $NaCNBH_3$.

and sodium cyanoborohydride afforded the required analogue **21**.

The component diastereoisomers of **17** (i.e., **22** and **23**) were synthesized by employing 3(*R*)- and 3(*S*)-pyrrolidinol in the general route illustrated in Scheme 1. The preparation of 3(*R*)- and 3(*S*)-pyrrolidinol was based upon the method described by Joullé et al.[14] (Scheme 4). However, this method, which involves direct reaction of (*S*)-(−)-malic acid with benzylamine followed by lithium aluminium hydride reduction of the resulting hydroxysuccinimide, was reported to afford *N*-benzyl-3(*S*)-pyrrolidinol [(*S*)-**31**] in only 84% enantiomeric purity.

Scheme 4[a,b]



[a] (i) MeCOCl; (ii) $PhCH_2NH_2$; (iii) MeCOCl; (iv) $LiAlH_4$; (v) H_2, Pd–C.[b] Structures depict absolute configuration for the synthesis of (*S*)-**32**; an identical set of conditions was used to obtain the corresponding optical antipode.

Having confirmed that this is indeed the case, we elected to modify the procedure by using much milder conditions. Following initial activation using acetyl chloride, reaction with benzylamine was conducted at 20–25 °C, and then, further treatment with acetyl chloride gave (*S*)-**30**. Using this method, epimerization of the 3-hydroxyl group could be avoided; subsequent reduction with lithium aluminium hydride gave the enantiomer (*S*)-**31** in >98% ee (as determined by ^1H NMR using (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol as the chiral solvating agent), which upon hydrogenolysis provided (*S*)-**32**. A similar sequence starting from (*R*)-(+)-malic acid gave (*R*)-**32** in 95% ee.

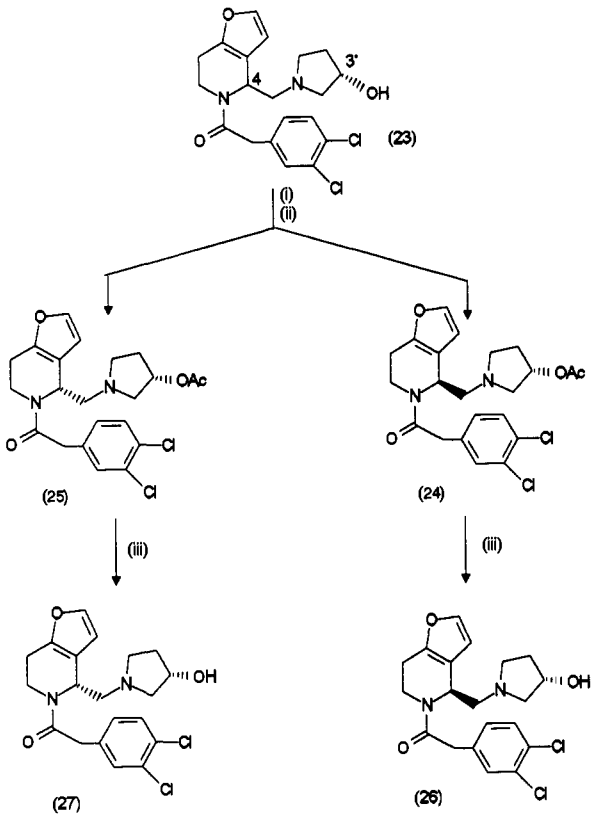
Since the κ-receptor agonist activity was found to predominate in **23** (mixture of *R*- and *S*-isomers at C-4), derived from (S)-3-pyrrolidinol, the diastereomeric acetate derivatives **24** and **25** were prepared, separated by HPLC, and converted to the 4*S*,3'*S*- and 4*R*,3'*S*-isomers **26** and **27**, respectively (Scheme 5). The absolute stereochemistry at C-4 of the piperidine nucleus was determined by X-ray analysis of compound **27** (Figure 1).

Biological Results and Discussion

The κ-agonist activity of the 4-[(alkylamino)methyl]-furo[3,2-*c*]pyridines was determined *in vitro* using the isolated rabbit vas deferens (LVD) preparation, which is rich in κ-opioid receptors.[15] The receptor selectivities for **16** and **17** were assessed by comparing the activity determined in the LVD preparation with that in the rat vas deferens (RVD)[16] and hamster vas deferens (HVD)[17] tissues which are rich in μ- and δ-opioid receptors, respectively. Antinociceptive activity was determined using the mouse acetylcholine-induced abdominal constriction test[18] following subcutaneous administration of the agonist, ED_{50} values being determined in each case.

All the compounds in this series were found to behave as high efficacy agonists in the LVD. Modification of the basic moiety was found to produce a pronounced effect on κ-agonist potency (Table 1). In particular, the 3-pyrrolidinol analogue **17** (GR91272) was found to be approximately 5-fold more potent than the corresponding pyrrolidine analogue **16**. Interestingly, this potency-enhancing effect of the 3-pyrrolidinol moiety is not necessarily observed in other aromatic-fused systems (cf., the 5-hydroxytetrahydroisoquinoline series **33** and **34**, Table 1). In the rat and hamster vasa deferentia, **16** showed no agonist nor antagonist activity up to 10^{-5} M and **17** showed only weak antagonist activity ($pK_B < 5.5$), thereby underlining their selectivity for the κ-opioid receptor. We

Scheme 5[a]



[a] (i) CH_3COCl, Et_3N; (ii) HPLC; (iii) LiOH, THF–H_2O.

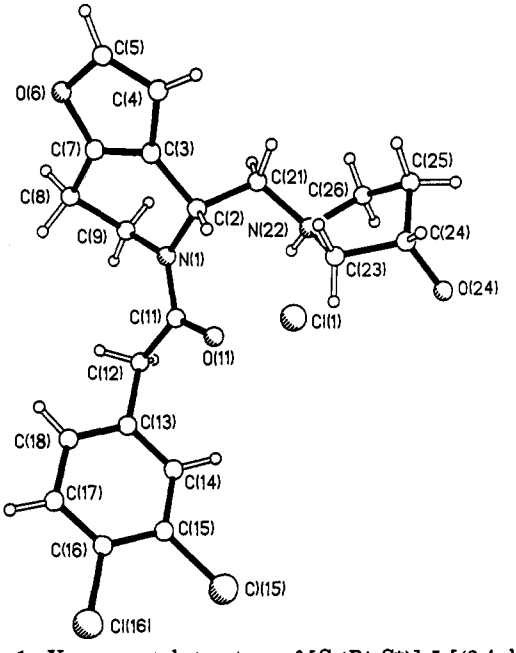


Figure 1. X-ray crystal structure of [*S*-(*R**,*S**)]-5-[(3,4-dichlorophenyl)acetyl]-4,5,6,7-tetrahydro-4-[(3-hydroxy-1-pyrrolidinyl)-methyl]furo[3,2-*c*]pyridine (**27**).

have reported elsewhere that **17** displays neuroprotective properties in a Mongolian gerbil model of global ischaemia.[7]

Since **17** contains two asymmetric centers, it was of importance to determine whether the κ-opioid receptor activity predominated in a single diastereoisomer. Initially, the diastereomeric pairs **22** and **23**, possessing 3′*R*- and 3′*S*-stereochemistry on the pyrrolidinol moiety, respectively, were evaluated. κ-Agonist activity was found to predominate in the 4*S*,3′*S*:4*R*,3′*S*-pair of isomers **23**, and subsequent isolation of the individual diastereomers revealed that activity was resident in the 4*S*,3′*S*-isomer **26** (Table 2). Compound **26** (GR107537) displays excellent antinociceptive activity and is among the most potent κ-agonists reported to date.

Replacement of the pyrrolidine group by a tetrahydropyridine moiety (compound **21**), a modification found to enhance potency in a previously described series of piperidine analogues,[8] had a similar effect in the furo-[3,2-*c*]pyridine series. Introduction of a 2-methyl group (to give **18**) resulted in a 7-fold increase in potency *in vitro* (LVD), although this was not reflected in the antinociceptive test. The reason for the reduced *in vivo* activity of **18** (relative to **17**) has not been investigated, but a more rapid metabolism to a less active species may be responsible.

Conclusion

We have demonstrated that the 4-[(alkylamino)methyl]-furo[3,2-*c*]pyridines represent a novel, potent series of κ-receptor agonists. Activity in this series is particularly sensitive to modification of the basic moiety. In particular, incorporation of a 3-pyrrolidinol group confers high *in vitro* activity which predominates in the 4*S*,3′*S*-isomer **26** (GR107537). This phenomenon is not observed in the analogous tetrahydroisoquinoline **34** and suggests subtle differences in agonist–receptor interactions. *In vivo*, **26** is a potent antinociceptive agent.

Experimental Section

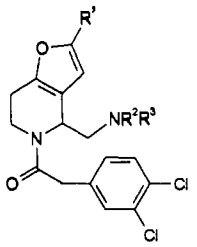
^1H NMR spectra were measured ($SiMe_4$ internal standard) on a Bruker WM250 (250-MHz) spectrometer. Signals for minor rotamers are indicated by an asterisk; in some cases, spectra were recorded at elevated temperature to remove this complication. Only the critical assignments and coupling constants are given. Mass spectra data were obtained using a VG 7070E instrument interfaced to an 11–250 data system. Optical rotations were obtained on a 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 either Merck Kieselgel 60 (Art. 9385, flash chromatography) or alumina UG1 (Phase Separations Ltd.). Solvents were dried according to standard procedures.

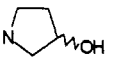
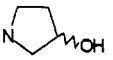
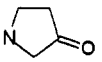
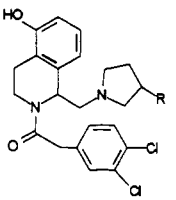
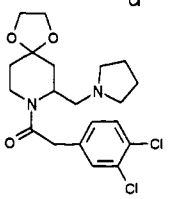
Methyl 4,5,6,7-Tetrahydrofuro[3,2-*c*]pyridine-4-carboxylate (6). A solution of 2-furanethanamine (**4**) (0.2 g, 1.8 mmol) in dry diethyl ether (5 mL) was treated with ethereal hydrogen chloride. The resulting solid was collected, dried (*in vacuo* at 23 °C), and dissolved in acetonitrile (10 mL). Freshly distilled methyl glyoxylate (0.2 g, 2.3 mmol) was added, and the mixture was stirred at 23 °C for 3 h. The resulting precipitate was filtered off to give **6** (0.14 g, 36%) as a white solid: mp 144–5 °C; NMR (D_2O, 298 K) δ 3.02 (2H, dt, CH_2), 3.58–3.82 (2H, m, CH_2), 3.90 (3H, s, Me), 5.38 (1H, t, CH), 6.63 (1H, d, furan CH), 7.52 (1H, d, furan CH). Anal. ($C_9H_{12}ClNO_3$) C, H, N.

Methyl 4,5,6,7-Tetrahydro-2-methylfuro[3,2-*c*]pyridine-4-carboxylate (7). This was similarly prepared from 5-methyl-2-furanethanamine (**5**) and was characterized as the hydrochloride salt (47%): mp 152–4 °C.

1-[(4,5,6,7-Tetrahydro-2-methylfuro[3,2-*c*]pyridin-4-yl)-carbonyl]-3-pyrrolidinol (11). The ester hydrochloride **7** (0.6 g, 2.6 mmol) was basified with potassium carbonate solution (1 g, in 10 mL of H_2O), and the free based was extracted into dichloromethane (3 × 10 mL). The combined extracts were dried and evaporated to give an oil (495 mg). A mixture of this oil (0.43 g, 2.2 mmol) and 3-pyrrolidinol (0.9 g, 10.3 mmol) was heated at 120 °C for 1 h. Excess 3-pyrrolidinol was removed by distillation (bp 125 °C, ~8 mmHg), and the residue was purified by flash column chromatography on silica gel, eluting with dichloromethane–methanol–ammonia (75:10:2), to give **11** (287 mg, 52%) as a pale brown foam: NMR (DMSO-d_6, 413 K) (diastereomeric mixture) δ 1.8–2.1 (2H, m, CH_2), 2.25 (3H, s, Me), 2.4–3.0

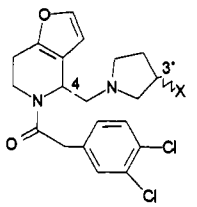
Table 1. Modification of Basic Moiety: Rabbit Vas Deferens (LVD) and Antinociception Test Results



no.	R^1	NR^2R^3	LVD IC_{50}, nM[a]	mouse Ach-induced abdominal constriction ED_{50}, mg/kg, sc
16	H		15	0.03 (0.02–0.07)
17	H		2.7	0.002 (0.001–0.004)
18	Me		0.39	0.012 (0.007–0.02)
19	H	NMe_2	22	NT
20	H		6.0	0.019 (0.012–0.03)
21	H		1.4	0.004 (0.002–0.006)
33	R = H		0.11	0.003 (0.001–0.004)
34	R = OH		3.8	0.084 (0.04–0.17)
GR45809			0.1	0.001

[a] Figures quoted are the mean of two independent determinations typically with the individual values within ±10% of the mean.

Table 2. Diastereoisomers of 17: Rabbit Vas Deferens (LVD) and Antinociception Test Results



no.	configuration at C-4	X	LVD IC_{50}, nM[a]	mouse Ach-induced abdominal constriction ED_{50}, mg/kg, sc
22	*R,S*	—— OH(*R*)	3.4	0.03 (0.008–0.065)
23	*R,S*	····· OH(*S*)	1.1	0.0015 (0.0011–0.002)
26	*S*	····· OH(*S*)	0.47	0.001 (0.0005–0.0021)
27	*R*	····· OH(*S*)	>1000	NT

[a] See footnote to Table 1.

(3H, m, CH_2 + OH), 3.3–3.7 (5H, m, CH, 2 × CH_2), 4.35–4.6 (3H, m, CH + CH_2), 5.80, 5.85 (1H, 2 × s, 2 × furan CH). Anal. ($C_{13}H_{18}N_2O_3$) C, H, N.

The following compounds were similarly prepared from **6** and the corresponding amines: **1-[(4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-4-yl)carbonyl]pyrrolidine** (**8**) (49%), **4,5,6,7-tetrahydro-*N,N*-dimethylfuro[3,2-*c*]pyridine-4-carboxamide** (**9**) (52%), and **1-[(4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-4-yl)carbonyl]-3-pyrrolidinol** (**10**) (67%). All of these intermediates were used directly in the next reactions.

1-[(4,5,6,7-Tetrahydro-2-methylfuro[3,2-*c*]pyridin-4-yl)methyl]-3-pyrrolidinol (**15**). A suspension of lithium aluminium hydride (110 mg, 2.9 mmol) in dry tetrahydrofuran (20 mL) was treated with a solution of **11** (277 mg, 1.1 mmol) in dry tetrahydrofuran (15 mL). The mixture was heated at 45 °C for 4 h. Water (0.11 mL) was cautiously added to the cooled (to 23 °C) mixture followed by aqueous sodium hydroxide (2 M, 0.33 mL) and water (0.11 mL). The mixture was filtered, and the filtrate was evaporated to give a pale yellow gum (233 mg, 89%) which was used directly in the next stage.

The following compounds were similarly prepared from the corresponding amides: **4,5,6,7-tetrahydro-4-(1-pyrrolidinylmethyl)furo[3,2-c]pyridine (12)** (100%), **4,5,6,7-tetrahydro-N,N-dimethylfuro[3,2-c]pyridine-4-methanamine (13)** (80%), and **1-[(4,5,6,7-tetrahydrofuro[3,2-c]pyridin-4-yl)methyl]-3-pyrrolidinol (14)** (97%). All of these intermediates were used directly in the next reactions.

5-[(3,4-Dichlorophenyl)acetyl]-4,5,6,7-tetrahydro-4-[(3-hydroxy-1-pyrrolidinyl)methyl]-2-methylfuro[3,2-c]pyridine (18). To a solution of 1,1'-carbonyldiimidazole (197 mg, 1.2 mmol) in dry dichloromethane (8 mL) was added 3,4-dichlorophenylacetic acid (249 mg, 1.2 mmol) in dry dichloromethane (2 mL), and the resulting solution was stirred under nitrogen for 1 h at 23 °C. A solution of **15** (115 mg, 0.49 mmol) in dry dichloromethane (8 mL) was added, and the mixture was stirred for 3 days. The reaction mixture was washed with sodium carbonate solution (2 N, 2 × 5 mL), dried, and evaporated to give a gum. A solution of this material in a mixture of tetrahydrofuran (8 mL) and water (2 mL) was treated with lithium hydroxide monohydrate (42 mg, 1.0 mmol), and the mixture was stirred at 23 °C for 0.5 h. The organic solvent was evaporated, and the aqueous residue was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried and evaporated to give a gum (233 mg) which was purified by flash column chromatography on silica gel, eluting with dichloromethane–methanol–ammonia (150:8:1), to give **18** (146 mg, 71%) as a colorless foam. Anal. ($C_{21}H_{24}Cl_2N_2O_3 \cdot 0.2H_2O$) C, H, N.

The following compounds were similarly prepared: **5-[(3,4-dichlorophenyl)acetyl]-4,5,6,7-tetrahydro-4-(1-pyrrolidinylmethyl)furo[3,2-c]pyridine fumarate (1:1.5) (16)** [mp 220–221 °C. Anal. ($C_{20}H_{22}Cl_2N_2O_2 \cdot 1.5C_4H_4O_4$) C, H, N], **5-[(3,4-dichlorophenyl)acetyl]-4,5,6,7-tetrahydro-4-[(3-hydroxy-1-pyrrolidinyl)methyl]furo[3,2-c]pyridine hydrochloride (17)** [mp 189–190 °C. Anal. ($C_{20}H_{23}Cl_3N_2O_3 \cdot 0.5H_2O$) C, H, N], **and 5-[(3,4-dichlorophenyl)acetyl]-4,5,6,7-tetrahydro-N,N-dimethylfuro[3,2-c]pyridine-4-methanamine fumarate (1:1) (19)** [mp 199–200 °C. Anal. ($C_{22}H_{24}Cl_2N_2O_6$) C, H, N].

5-[(3,4-Dichlorophenyl)acetyl]-4,5,6,7-tetrahydro-4-[(3-oxo-1-pyrrolidinyl)methyl]furo[3,2-c]pyridine (20). A solution of oxalyl chloride (0.085 mL, 124 mg, 0.97 mmol) in dry dichloromethane (2 mL) at −50 °C was treated with a solution of dry dimethyl sulfoxide (0.165 mL, 2.3 mmol) in dry dichloromethane (2 mL) over a 15-min period. Stirring was continued at −60 °C for 20 min, and the mixture was treated with **17** (220 mg, 0.54 mmol) in dry dichloromethane (10 mL) over a 20-min period. The mixture was stirred at −60 °C for 30 min and treated with triethylamine (0.4 mL). Water (10 mL) was added, and the product was extracted with dichloromethane (2 × 20 mL). The combined extracts were dried and evaporated to give an oil. This material was purified by flash column chromatography on silica gel, using dichloromethane–methanol–ammonia (200:8:1) as eluent, to give the free base of **20** as a gum. This was characterized as its fumarate salt (50 mg, 18%): mp 183–184 °C; NMR (DMSO-d_6, 413 K) δ 2.30 (2H, t, CH_2), 2.64–2.75 (2H, m, CH_2), 2.87 (2H, d, CH_2), 2.9–3.1 (4H, m, 2 × CH_2), 3.37 (1H, m, CH), 3.85 (2H, AB, CH_2), 4.38 (1H, br d, CH), 5.32 (1H, br t, CH), 6.45 (1H, d, furan CH), 7.25 (1H, dd, ArH), 7.4–7.6 (3H, m, ArH + furan CH). Anal. ($C_{24}H_{24}Cl_2N_2O_7$) C, H, N.

4,5,6,7-Tetrahydrofuro[3,2-c]pyridine-4-methanol (28). A suspension of lithium aluminium hydride (0.6 g, 16.0 mmol) in dry tetrahydrofuran (25 mL) was treated with a solution of **6** (1.8 g, 9.95 mmol) in dry tetrahydrofuran (10 mL) over a 10-min period. The mixture was stirred at 23 °C for 3 h. The reaction was quenched by sequential addition of water (0.6 mL), aqueous sodium hydroxide solution (2 M, 1.8 mL), and water (0.6 mL). The mixture was filtered, and the filtrate was evaporated to give **28** (1.15 g, 76%): mp 66–69 °C; NMR ($CDCl_3$, 298 K) δ 2.23 (2H, br s, OH + NH), 2.55–2.74 (2H, m, CH_2), 3.0–3.25 (2H, m, CH_2), 3.55–3.80 (2H, ABX, CH_2), 3.92 (1H, m, CH), 6.23 (1H, d, furan CH), 7.29 (1H, d, furan CH). Anal. ($C_6H_{11}NO_2$) C, H, N.

5-[(3,4-Dichlorophenyl)acetyl]-4,5,6,7-tetrahydrofuro[3,2-c]pyridine-4-methanol (29). A solution of 3,4-dichlorophenylacetic acid (4.6 g, 22 mmol) in dry dichloromethane (100 mL) was treated with 1,1'-carbonyldiimidazole (3.6 g, 22 mmol). The reaction mixture was stirred at 23 °C for 30 min. A solution of **28** (1.13 g, 7.4 mmol) in dry dichloromethane (20 mL) was added, and the mixture was stirred at 23 °C for 20 h. The reaction mixture was washed with aqueous sodium carbonate solution (1 M, 2 × 100 mL), dried, and evaporated to dryness. The residue was dissolved in tetrahydrofuran (ca. 50 mL), and a solution of lithium hydroxide monohydrate (0.375 g, 8.93 mmol) in water (40 mL) was added. The mixture was vigorously stirred at 23 °C for 1 h. Further lithium hydroxide monohydrate (0.2 g, 4.7 mmol) was added, and the mixture was stirred for 20 min. The organic solvent was evaporated, and the aqueous residue was extracted with dichloromethane (50 mL). The organic extract was dried and evaporated to give a solid which was crystallized from methyl acetate–hexane to give **29** (1.81 g, 72%): mp 155–156 °C; NMR (DMSO-d_6, 413 K) δ 2.55–2.80 (2H, m, CH_2), 3.30 (1H, m, CH), 3.70 (2H, d, CH_2), 3.90 (2H, AB, CH_2), 4.3–4.6 (2H, br d + br s, CH + OH), 5.19 (1H, br t, CH), 6.40 (1H, d, furan CH), 7.25 (1H, dd, ArH), 7.40–7.55 (3H, m, ArH + furan CH). Anal. ($C_{16}H_{15}Cl_2NO_3$) C, H, N.

5-[(3,4-Dichlorophenyl)acetyl]-4,5,6,7-tetrahydro-4-[(1,2,3,6-tetrahydro-1-pyridinyl)methyl]furo[3,2-c]pyridine (21). A solution of oxalyl chloride (0.16 mL, 0.23 g, 1.8 mmol) in dry dichloromethane (12 mL) at −65 °C was treated with a solution of dry dimethyl sulfoxide (0.21 mL, 0.23 g, 2.9 mmol) in dry dichloromethane (3 mL) at −65 °C, and the resulting solution was stirred for 20 min. A solution of **29** (0.40 g, 1.18 mmol) in dry dichloromethane (10 mL) was added over 5 min, and the mixture was stirred at −65 °C for 3 h. The mixture was allowed to warm to −20 °C, and triethylamine (1.0 mL, 0.7 g, 7 mmol) was added. Water (10 mL) was then added, and the product was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried and evaporated to dryness. A solution of the resultant crude aldehyde in methanol (12 mL), at −65 °C, was treated with tetrahydropyridine (0.2 mL, 2.2 mmol) and 3-Å molecular sieves (0.5 g). The pH of the reaction was adjusted to 6 using methanolic hydrogen chloride solution. Sodium cyanoborohydride (0.183 g, 2.9 mmol) was added, and the reaction mixture was stirred at 23 °C for 3 days. The mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in 2 N sodium carbonate solution (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined extracts were dried and evaporated to give an oil which was purified by flash column chromatography on silica gel, initially eluting with ether and then later with ether–methanol–ammonia (1000:8:1), to give **21** (89 mg, 19%). This compound was characterized as its fumarate salt: mp 199–200 °C. Anal. ($C_{25}H_{26}Cl_2N_2O_6$) C, H, N.

(R)-(+)-3-(Acetyloxy)-1-(phenylmethyl)-2,5-pyrrolidinedione [(R)-30]. A mixture of (*R*)-(+)-malic acid (6.7 g, 0.05 mol) and acetyl chloride (20 mL, 0.28 mol) was heated at reflux for 2 h. The solvent was removed, and the residue was dissolved in dichloromethane (100 mL) and treated with benzylamine (20 mL, 0.18 mol). The reaction mixture was stirred at 23 °C for 18 h, acetyl chloride (20 mL, 0.28 mol) was added, and the mixture was heated at reflux for 5 h. The reaction mixture was evaporated to dryness, and the residue was purified by dry flash column chromatography on silica gel, using ethyl acetate–hexane (3:1) as eluant, to give (*R*)-**30** (10.2 g, 83%): mp 49–51 °C; $[\alpha]^{20}_D$ +39° (1.0%, w/v MeOH); NMR ($CDCl_3$, 298 K) δ 2.15 (3H, s, CH_3), 2.60–3.21 (2H, *ABX*, CH_2), 4.69 (2H, AB, CH_2), 5.45 (1H, *ABX*, CH), 7.28–7.42 (5H, m, ArH). Anal. ($C_{13}H_{13}NO_4$) C, H, N.

Similarly prepared from (*S*)-(−)-malic acid was **(S)-(−)-3-(acetyloxy)-1-(phenylmethyl)-2,5-pyrrolidinedione [(S)-30]**: mp 58–60 °C; $[\alpha]^{20}_D$ −40.6° (1.0%, w/v MeOH). Anal. ($C_{13}H_{13}NO_4$) C, H, N.

(R)-(+)-1-(Phenylmethyl)-3-pyrrolidinol [(R)-31]. A suspension of lithium aluminum hydride (2.45 g, 0.064 mol) in dry tetrahydrofuran (50 mL) was treated with a solution of (*R*)-**30** (5.1 g, 0.0205 mol) in dry tetrahydrofuran (50 mL), and the reaction mixture was heated under reflux for 2 h. Water (2.5 mL) was cautiously added to the cooled (to 23 °C) reaction mixture followed by aqueous sodium hydroxide solution (2 M, 7.5 mL) and water (2.5 mL). The reaction mixture was filtered, the filtrate was evaporated, and the residue was purified by flash column chromatography on silica gel, with dichloromethane–methanol–ammonia (150:8:1) as eluant, to give (*R*)-**31** (2.33 g, 64%) as an oil: $[\alpha]^{20}_D$ +3.7° (0.9%, w/v MeOH). Anal. ($C_{11}H_{15}NO \cdot 0.2H_2O$) C, H, N.

Similarly prepared from (S)-30 was **(S)-(−)-1(phenylmethyl)-3-pyrrolidinol [(S)-31]**:[14] $[\alpha]^{20}_D$ −1.02° (0.7%, w/v MeOH).

(R)-(+)-Pyrrolidinol [(R)-32]. A solution of (R)-31 (2.2 g, 0.0124 mol) in a mixture of ethanol (30 mL) and acetic acid (1 mL) was hydrogenated at 70 psi over 10% palladium oxide on carbon (50% wet paste, 0.9 g) for 6 h. The reaction mixture was filtered through Hyflo, and the filtrate was evaporated to dryness. The residue was dissolved in a solution of potassium hydroxide (1.0 g, 0.023 mol) in ethanol (20 mL), and then, the solvent was evaporated and the residue triturated with dichloromethane (2 × 50 mL). The combined organic extracts were evaporated, and the resultant residue was purified by distillation (Kugelrohr; bp 100 °C at 1.5 mmHg) to give (R)-32 as a colorless oil (0.95 g, 88%): $[\alpha]^{20}_D$ +5.7° (0.7%, w/v MeOH). Anal. ($C_4H_9NO \cdot 0.2H_2O$) C, H, N.

Similarly prepared from (S)-31 was **(S)-(−)-3-pyrrolidinol [(S)-32]**:[14] $[\alpha]^{20}_D$ −5.2° (1.0%, w/v MeOH).

[R-(R*,R*)]- and [R-(R*,S*)]-1-[(4,5,6,7-Tetrahydrofuro-[3,2-c]pyridin-4-yl)carbonyl]-3-pyrrolidinol [[R-(R*,R*)]-10] and [[R-(R*,S*)]-10]. These were prepared from 6 and (R)-32 (58%), as an off-white foam, by the method described for 10: NMR (DMSO-d_6, 413 K) (diastereomeric mixture) δ 1.8–2.1 (2H, m, CH_2), 2.5–2.7 (2H, m + br s, CH + OH), 2.88–3.01 (1H, m, CH), 3.30–3.72 (5H, m, 2 × CH_2 + CH), 4.30–4.68 (3H, 2 × m, CH + CH_2), 6.22, 6.28 (1H, 2 × d, furan CH), 7.38 (1H, br s, furan CH). Anal. ($C_{12}H_{16}N_2O_3 \cdot 0.3H_2O$) C, H, N.

Similarly prepared from 6 and (S)-32 was [S-(R*,S*)]-10 and [S-(R*,R*)]-10 (68%).

[R-(R*,R*)]- and [R-(R*,S*)]-1-[(4,5,6,7-Tetrahydrofuro-[3,2-c]pyridin-4-yl)methyl]-3-pyrrolidinol [[R-(R*,R*)]-14] and [[R-(R*,S*)]-14]. These were prepared from [R-(R*,R*)]-10 and [R-(R*,S*)]-10 (93%) as described for 14.

Similarly prepared from [S-(R*,S*)]-10 and [S-(R*,R*)]-10 were **[S-(R*,R*)]- and [S-(R*,S*)]-1-[(4,5,6,7-tetrahydrofuro-[3,2-c]pyridin-4-yl)methyl]-3-pyrrolidinol [[S-(R*,R*)]-14] and [[S-(R*,S*)]-14].**

Both these diamines were used directly in subsequent reactions without purification.

[R-(R*,R*)]- and [R-(R*,S*)]-(−)-5-[(3,4-Dichlorophenyl)-acetyl]-4,5,6,7-tetrahydro-4-[(3-hydroxy-1-pyrrolidinyl)methyl]furo[3,2-c]pyridine (22). A solution of 3,4-dichlorophenylacetic acid (0.31 g, 1.51 mmol) and 1,1′-carbonyldiimidazole (0.25 g, 1.54 mmol) in dry dichloromethane (10 mL) was added to a solution of [R-(R*,R*)]-14 and [R-(R*,S*)]-14 (0.280 g, 1.25 mmol) in dry dichloromethane (20 mL). The mixture was stirred at 23 °C for 18 h. The reaction mixture was washed with aqueous sodium carbonate solution (1 M, 2 × 20 mL), dried, and evaporated to give an oily residue. This residue was purified by flash column chromatography on silica gel, with dichloromethane–methanol–ammonia (150:8:1) as eluant, to give 22 as a gum. This material was characterized as its hydrochloride salt (0.31 g, 55%): mp 185–189 °C. Anal. ($C_{20}H_{22}Cl_2N_2O_3 \cdot HCl$) C, H, N.

Similarly prepared from [S-(R*,R*)]-14 and [S-(R*,S*)]-14 were **[S-(R*,R*)]- and [S-(R*,S*)]-(−)-5-[(3,4-dichlorophenyl)acetyl]-4,5,6,7-tetrahydro-4-[(3-hydroxy-1-pyrrolidinyl-)methyl]furo[3,2-c]pyridine (23)** which were characterized as the hydrochloride salt: mp 184–187 °C. Anal. ($C_{20}H_{22}Cl_2N_2O_3 \cdot HCl \cdot 0.3H_2O$) C, H, N.

[S-(R*,R*)]- and [S-(R*,S*)]-1-[[5-[(3,4-Dichlorophenyl)-acetyl]-4,5,6,7-tetrahydrofuro[3,2-c]pyridin-4-yl]methyl]-3-pyrrolidinol Acetate (24 and 25). A solution of acetyl chloride (0.025 mL, 0.027 g, 0.35 mmol) in dichloromethane (1 mL) was added to a stirred solution of triethylamine (0.044 mL, 0.32 mmol) and [S-(R*,S*)]-23 and [S-(R*,R*)]-23 (0.118 g, 0.29 mmol) in dichloromethane (10 mL), and the mixture was stirred under nitrogen for 0.5 h. The mixture was washed with sodium carbonate solution (2 N, 10 mL), dried, and evaporated to give a gum (179 mg) which was purified by flash chromatography on silica gel, eluting with dichloromethane–methanol–ammonia (450:8:1), to give 24 and 25 (101 mg, 78%) as a gum: 1:1 ratio of diastereoisomers by HPLC. This material was used directly in the next stage.

[S-(R*,R*)]-5-[(3,4-Dichlorophenyl)acetyl]-4,5,6,7-tetrahydro-4-[(3-hydroxy-1-pyrrolidinyl)methyl]furo[3,2-c]pyridine (26) and [S-(R*,S*)]-Isomer 27. The acetates 24 and 25 (520 mg) were separated by preparative HPLC on Spherisorb, eluting with hexane–chloroform–methanol–ammonia (1800:200:50:1). A solution of 24 (138 mg, 0.31 mmol) in tetrahydrofuran (10 mL) was treated with a solution of lithium hydroxide monohydrate (22 mg, 0.52 mmol) in water (2 mL), and the mixture was stirred for 18 h. The organic solvent was evaporated, and the aqueous residue was extracted with dichloromethane (2 × 10 mL). The combined extracts were dried and evaporated to give 26 (90 mg, 72%) as a foam: NMR ($CDCl_3$, 298 K) δ 1.65–1.90 (2H, m, CH_2), 2.05–3.1 (6H, m), 3.45 (1H, m, CH), 3.7–4.0 (4H, m, CH_2, 2 × CH), 4.26–4.43 (1H, 2 × m, CH), 4.85*, 4.95* (2 × 1H, dd + br t, 2 × CH), 5.62 (1H, br t, CH), 6.25, 6.32 (1H, 2 × d, furan CH), 7.07*, 7.16 (1H, 2 × dd, ArH), 7.20–7.43 (3H, m, 2 × ArH + furan CH). Anal. ($C_{20}H_{22}Cl_2N_2O_3 \cdot 0.3H_2O$) C, H, N.

Similarly prepared, from 25, was **[S-(R*,S*)]-5-[(3,4-dichlorophenyl)acetyl]-4,5,6,7-tetrahydro-4-[(3-hydroxy-1-pyrrolidinyl)methyl]furo[3,2-c]pyridine (27)**, characterized as its hydrochloride salt: mp 216–218 °C. Anal. ($C_{20}H_{22}Cl_2N_2O_3 \cdot HCl$) 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.[18] **In Vitro.** Activities in the rabbit,[15] rat,[16] and hamster[17] vasa deferentia were determined as previously described. Potencies are quoted as IC_{50} (or pK_B) values.

Acknowledgment. The X-ray crystallographic structural data for compound 27 was kindly provided by Mr. R. B. Lamont (Computational Chemistry, Glaxo Group Research Ltd.). We thank Mr. S. A. Richards for the NMR spectral interpretations, Mr. R. J. Boughtflower for HPLC separations, and Mrs. M. Earl for the preparation of compound 18.

Supplementary Material Available: Crystal data for 27 and tables listing atomic coordinates, bond lengths, bond angles, and anisotropic displacement coefficients (7 pages); observed and calculated structure factors (10 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) Hayes, A. G.; Sheehan, M. J.; Tyers, M. B. Differential Sensitivity of Models of Antinociception in rat, mouse and guinea-pig to μ- and κ-opioid receptor agonists. *Br. J. Pharmacol.* **1987**, *91*, 823–832. Dickenson, A. H.; Sullivan, A. F.; Roques, B. P. Evidence that endogenous enkephalins and a δ-opioid receptor agonist have a common site of action in spinal antinociception. *Eur. J. Pharmacol.* **1988**, *148*, 437–439. Rodriguez, R. E.; Leighton, G. E.; Hill, R. G.; Hughes, J. *In vivo* evidence of spinal delta opiate receptor-operated antinociception. *Neuropeptides* **1986**, *8*, 221–242.

(3) For review, see: Millan, M. J. κ-Opioid receptors and analgesia. *Trends Pharmacol. Sci.* **1990**, *11*, 70–76.

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

(5) Tang, A. H. Protection from cerebral ischaemia by U-50488H, a specific kappa opioid analgesic agent. *Life Sci.* **1985**, *37*, 1475–1482. *Life Sci.* **1985**, *37*, 1475–1482. Hall, E. D.; Pazara, K. E. Quantitative analysis of effects of kappa-opioid agonists on post-ischaemic hippocampal CA1 neuronal necrosis in gerbils. *Stroke* **1988**, *19*, 1008–1012. Tang, A. H.; Silvia, R. C. Protection from cerebral ischaemia by U-50488 in cats subjected to occlusion of the middle cerebral artery. *Soc. Neurosci. Abstr.* **1986**, *12*, 64.

(6) 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.

(7) Birch, P. J.; Roger, 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.
(8) 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 Kappa-receptor agonists based upon a 2-[(alkylamino)methyl]-piperidine nucleus. *J. Med. Chem.* **1992**, *35*, 490–501.
(9) 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.
(10) Vecchietti, V.; Clarke, G. D.; Colle, R.; Giardina, G.; Petrone, G.; Soacchi, M. (1S)-1-(Aminomethyl)-2-(arylacetyl)-1,2,3,4-tetrahydroisoquinoline and Heterocycle Condensed Tetrahydropyridine Derivatives: Members of a Novel Class of Very Potent κ-Opioid Analgesics. *J. Med. Chem.* **1991**, *34*, 2624–2633.
(11) Szmuszkovicz, J.; Von Voightlander, P. F. Benzeneacetamide Amines: Structurally Novel Non-μ Opioids. *J. Med. Chem.* **1982**, *25*, 1125–1126.
(12) Herz, W.; Tocker, S. Furano(3,2-*c*)pyridines. *J. Am. Chem. Soc.* **1955**, *77*, 3554–3556.
(13) Eur. Pat. Appl. EP 99139A; *Chem. Abstr.* **1984**, *101*, 23473z.
(14) Bhat, K. L.; Flanagan, D. M.; Joullié, M. M. Synthetic Routes to Chiral 3-Pyrrolidinols. *Synth. Commun.* **1985**, *15*, 587–598.
(15) 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.
(16) Smith, C. F. C.; Rance, M. J. Opiate Receptors in the Rat Vas Deferens. *Life Sci.* **1983**, *33* (Suppl. 1), 327–330.
(17) 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.
(18) 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.