g, 18.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise over a 5-min period. A solution of **22** (2.38 g, 17.9 mmol) in CH_2Cl_2 (9 mL) was then added dropwise to the reaction mixture. The reaction was stirred at 0 °C for 1 h followed by stirring at 25 °C for 2 h. The reaction was worked up as for (*SS*)-**9**. Flash chromatography (silica gel, 60/40 hexanes/ethyl acetate elution) to yielded 2.27 g (78%) of **23** as an off-white solid: mp 170–173 °C; ^{1}H NMR (DMSO-d_6) δ 9.95 (s, 2 H), 8.44 (s, 1 H), 8.41 (s, 2 H), 4.02 (s, 4 H), 1.24 (s, 18 H); ^{13}C NMR (DMSO-d_6) δ 169.73, 147.95, 139.42, 116.81, 109.49, 74.26, 62.54, 27.05; mass spectrum (FAB, thioglycerol/DMSO matrix), *m/e* $(M + H)^+$ 382 ($C_{18}H_{27}N_3O_6$), 365, 326, 270 (base), 254.

3,5-Bis(2-hydroxyacetamido)nitrobenzene (24). A solution of **23** (0.75 g, 1.97 mmol) and anisole (0.46 g, 4.30 mmol) in 1:1 $CF_3CO_2H/CHCl_3$ (10 mL) was heated at reflux for 17 h. The reaction mixture was cooled to 25 °C and H_2O (3 mL) was added to precipitate the product, which was collected by vacuum filtration to yield 0.40 g (75%) of **24** as a yellow solid: mp >255 °C; ^{1}H NMR (DMSO-d_6) δ 10.22 (s, 2 H), 8.48 (s, 1 H), 8.41 (s, 2 H), 4.05 (s, 4 H), 3.40 (br, 2 H); ^{13}C NMR (DMSO-d_6) δ 171.95, 147.51, 139.91, 115.11, 108.21, 62.0; mass spectrum (FAB, thioglycerol/DMSO matrix), *m/e* $(M + H)^+$ 270 ($C_{10}H_{11}N_3O_6$), 254, 214, 181, 149, 109, 91 (base).

(*Z*)-*N*,*N*'-[5-[[1-(5-Acetyl-4-hydroxy-2,6-dioxo-2*H*-pyran-3(6*H*)-ylidene)ethyl]amino]-1,3-phenylene]bis(2-hydroxyacetamide) (26). Nitro diamide **24** (0.33 g, 1.2 mmol) was hydrogenated at 30 psi in the presence of 10% Pd/C (0.033 g). After 20 h the reaction mixture was filtered through Celite and concentrated in vacuo to yield 0.22 g (77%) of **25** as an off-white solid: mp 135–137 °C dec; ^{1}H NMR (DMSO-d_6) δ 9.23 (s, 2 H), 7.01 (s, 1 H), 6.72 (s, 2 H), 5.57 (s, 2 H), 5.13 (s, 2 H), 3.94 (s, 4 H); ^{13}C NMR (DMSO-d_6) δ 170.22, 149.05, 138.81, 100.95, 61.71. Compounds **25** (0.16 g, 0.67 mmol) and **11** (0.14 g, 0.67 mmol) were dissolved in methanol (12 mL) and heated at reflux for 1.5 h. The reaction mixture was cooled to 25 °C and pyranenamine **26** was collected by vacuum filtration to yield 0.20 g (69%) of **26** as a tan solid: mp 227–229 °C; FTIR (KBr) 2856–3500, 1736, 1691, 1674, 1553 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 18.89 (br, 1 H), 13.20 (br, 1 H), 9.92 (s, 2 H), 8.12 (s, 1 H), 7.48 (s, 2 H), 4.02 (s, 4 H), 3.48 (br, 2 H), 2.58 (s, 6 H); ^{13}C NMR (DMSO-d_6) δ 201.10, 184.26, 173.88, 171.26, 162.91, 159.65, 139.63, 135.63, 111.86, 110.52, 96.41, 90.78, 61.87, 27.33, 20.86; mass spectrum (FAB, thioglycerol/DMSO matrix), *m/e* $(M + H)^+$ 434 ($C_{19}H_{19}N_3O_9$), 416, 390, 332, 297, 91 (base). Anal. C, H, N.

log *P* Calculations. The method of Cramer[7] was used along with the CLOGP3, CONVERT, and STARLIST Databases.[11]

Rat POA Assay. The method of Iso[7] was used with modification. Rats weighing between 150 and 200 g were sensitized with three injections per eye of rat IgE polyclonal antibody to ovalbumin. Fifty microliters of a 1:4 dilution of antisera was injected into the bulbar conjunctiva, palpebral, and lower conjunctiva. After a period of 24 h, the animals were challenged intravenously with ovalbumin (25 mg/kg) and Evans blue (12.5 mg/kg in saline). For topical drug instillation, 10 μL of drug was given 15 min before, just prior to, and 15 min after ovalbumin challenge. For intravenous drug administration, the drug was injected just before the ovalbumin challenge. The animals were sacrificed 30 min after the antigen injection and the eye tissues (eyelids and eyeballs) were removed. These tissues were placed into a solution of acetone and 0.5% sodium sulfate to extract the Evans blue dye. Extract supernatant fractions were read with a spectrophotometer at 620 nm. The amount of dye extracted was used to measure the degree of the anaphylactic reaction. The Evans blue values were determined from a standard curve and expressed as percent inhibition of control dye leakage.

Acknowledgment. We thank Dr. John Gleason of SmithKline Beecham for useful discussions.

(2*S*)-1-(Arylacetyl)-2-(aminomethyl)piperidine Derivatives: Novel, Highly Selective κ Opioid Analgesics

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This paper describes the synthesis and structure–activity relationships as κ opioid analgesics of a novel class of 1-(arylacetyl)-2-(aminomethyl)piperidine derivatives (**8**). The active conformation of the pharmacophore, with a torsional angle ($N_1C_2C_7N_8$) of 60°, was defined with computational studies and ^{1}H NMR. A quantitative structure–activity relationship study of the arylacetic moiety substitution indicated that the presence of an electron-withdrawing and lipophilic substituent in para and/or meta positions is required for good analgesic activity and κ affinity. The lead compounds (2*S*)-1-[(3,4-dichlorophenyl)acetyl]-2-(pyrrolidin-1-ylmethyl)piperidine hydrochloride (**14**) and (2*S*)-1-[[4-(trifluoromethyl)phenyl]acetyl]-2-(pyrrolidin-1-ylmethyl)piperidine hydrochloride (**21**) are the most κ/μ selective (respectively 6500:1 and 4100:1) and among the most potent (K_i κ 0.24 and 0.57 nM, respectively) κ ligands identified so far. In the mouse tail flick model of antinociception, compound **14** (ED_{50} = 0.05 mg/kg sc) was 25 times more potent than morphine and 16 times more potent than the standard κ ligand U-50488.

There is now considerable pharmacological and biochemical evidence to support the existence of multiple types of opioid receptors.[1-3] Although activation of three of these receptor types, μ, δ, κ, is known to be associated with analgesia,[4] most of the opioid analgesics used at present are thought to act via the μ receptor at which morphine is the exogenous prototypic ligand. However, interaction with the μ receptor is also believed to induce the spectrum of unwanted side effects such as physical dependence, constipation and respiratory depression which are associated with current opioid analgesics.[5a,b]

In recent years considerable attention has been focused on the development of κ agonists as potent and efficacious analgesics devoid of the undesirable side effects of the μ analgesics. Initially, κ agonists based on the benzomorphan skeleton[6] were synthesized because ketazocine was the κ agonist identified in the pioneering work by Martin[2]. However, these analogues have generally shown only marginal selectivity for the κ receptor and showed evidence of psychotomimetic effects.[7]

Recently, several classes of more selective κ agonists (Figure 1), unrelated to the benzomorphans, have been

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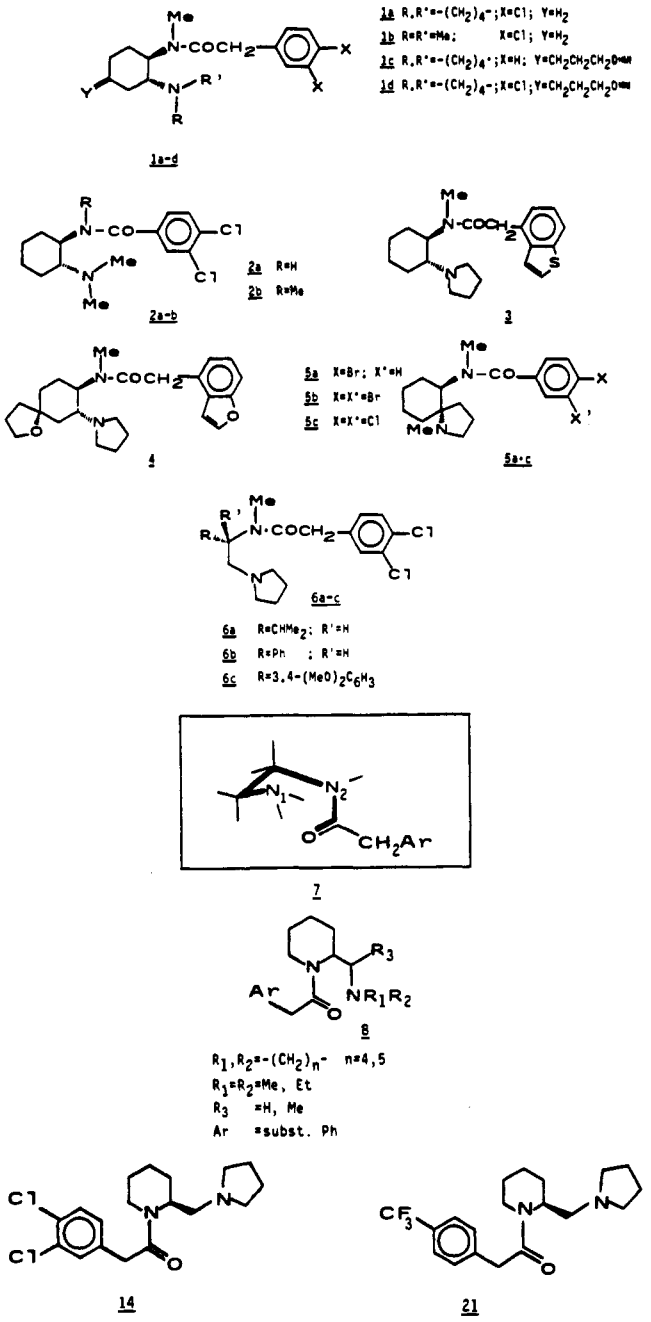
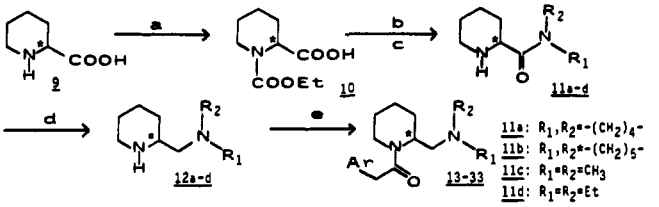


Figure 1.

identified. The benzeneacetamides **1a** (U-50488) and **1b**, derived from *trans*-cyclohexane-1,2-diamines, are highly selective κ agonists lacking the behavioral properties associated with morphine but with a similar analgesic potency.[8]

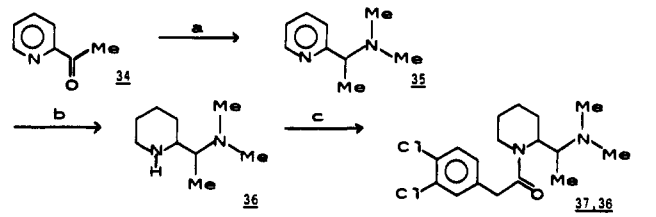
Interestingly, related benzamides **2a** and **2b** also exhibited antinociceptive activity, but this was associated with morphine-like behavioral responses.[8,9] In comparison with U-50488, cyclohexylbenzeneacetamide derivative **1c** (U-69593) is even more κ selective while its chlorinated analogue **1d** (U-62066) is less selective but more potent as an analgesic.[10,11] Appropriate modification of the aryl-

Scheme I[a]



[a] Reagents: (a) EtOCOCl, $NaOH/H_2O$, 0 °C; (b) $SOCl_2$, $CHCl_3$; (c) R_1R_2NH, 0 °C; (d) LAH, THF, 30 °C; (e) $ArCH_2COCl$, $CHCl_3$, K_2CO_3, room temperature.

Scheme II[a]



[a] Reagents: (a) $(Me)_2NH$, $NaCNBH_3$, MeOH/NaOH, room temperature; (b) H_2/PtO_2, $AcOH/CF_3COOH$, 50 psi, 60 °C; (c) 3,4-$Cl_2C_6H_3CH_2COCl$, $CHCl_3$, K_2CO_3, room temperature.

acetyl moiety of U-50488 [e.g. **3** (PD117302)] and of U-69593 [e.g. **4** (CI-977)] increases κ affinity and κ/μ selectivity.[12a,b,13]

A series of constrained 1-azaspiro[4,5]decan-10-ylamides, e.g. **5a**, **5b** or **5c**, related to cyclohexylbenzeneacetamide U-50488, has been recently synthesized to clarify how the orientation of the aromatic ring relative to the basic nitrogen influences the binding profile of the molecules.[14] An alternative approach[15a,b] has the cyclohexane ring replaced by a substituted ethylene chain, e.g. **6a**, **6b**, or **6c**. These compounds display greater κ affinity and selectivity, and have a greater antinociceptive potency, than U-50488.

A completely different chemical structure from those indicated above is represented by the benzodiazepine tifluadom, which has high affinity for κ receptors and seems to act selectively on these receptors in vivo.[16,17]

All the opioid analgesics **1**–**6** described above exhibit a common pharmacophore, **7**. This is characterized by a basic tertiary nitrogen atom and an aromatic amide separated by two carbon atoms bearing lipophilic substituents. Generally, the torsional angle between N_1 and N_2 is approximately 60°.

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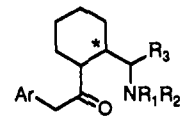
Table I. Physical Properties of Compounds 13–33, 37, 38, 41, 42



no.	formula	*	Ar	R_1 R_2	R_3	mp, °C	analyses	cryst solvent	$[\alpha]^{20}_D$, deg (c = 1, MeOH)
13	$C_{18}H_{24}Cl_2N_2O\cdot HCl$	*RS*	3,4-$Cl_2C_6H_3$	$-(CH_2)_4-$	H	246–248	C,H,N,Cl	MeOH	
14	$C_{18}H_{24}Cl_2N_2O\cdot HCl\cdot H_2O$	*S*	3,4-$Cl_2C_6H_3$	$-(CH_2)_4-$	H	160–161	C,H,N,Cl	MeOH	−49.0
15	$C_{18}H_{24}Cl_2N_2O\cdot HCl\cdot H_2O$	*R*	3,4-$Cl_2C_6H_3$	$-(CH_2)_4-$	H	159–160	C,H,N,Cl	MeOH	+47.6
16	$C_{16}H_{22}Cl_2N_2O\cdot HCl$	*RS*	3,4-$Cl_2C_6H_3$	Me Me	H	207–208	C,H,N,Cl	EtOH–Me_2CO	
17	$C_{16}H_{22}Cl_2N_2O\cdot HCl\cdot {}^3/_2H_2O$	*S*	3,4-$Cl_2C_6H_3$	Me Me	H	196–197	C,H,N,Cl	EtOH–Me_2CO	−52.0
18	$C_{18}H_{26}Cl_2N_2O$	*S*	3,4-$Cl_2C_6H_3$	Et Et	H	oil	H;C,N,Cl[a]		
19	$C_{19}H_{26}Cl_2N_2O\cdot HCl$	*S*	3,4-$Cl_2C_6H_3$	$-(CH_2)_5-$	H	156–158	C,H,N,Cl	EtOAc	−50.2
20	$C_{19}H_{25}F_3N_2O\cdot HCl$	*RS*	4-$CF_3C_6H_4$	$-(CH_2)_4-$	H	180–184	C,H,N,Cl,F	Me_2CO	
21	$C_{19}H_{25}F_3N_2O\cdot HCl$	*S*	4-$CF_3C_6H_4$	$-(CH_2)_4-$	H	180–181	C,H,N,Cl,F	Me_2CO	−45.7
22	$C_{18}H_{25}ClN_2O\cdot HCl$	*RS*	4-ClC_6H_4	$-(CH_2)_4-$	H	200–202	C,H,N,Cl	EtOH	
23	$C_{18}H_{25}FN_2O\cdot HCl$	*RS*	4-FC_6H_4	$-(CH_2)_4-$	H	198–200	C,H,N,Cl,F	EtOAc	
24	$C_{18}H_{25}BrN_2O\cdot HCl$	*RS*	4-BrC_6H_4	$-(CH_2)_4-$	H	197–199	C,H,N,Br,Cl	Me_2CO	
25	$C_{18}H_{25}N_3O_3\cdot HCl$	*RS*	4-$NO_2C_6H_4$	$-(CH_2)_4-$	H	195–197	C,H,N,Cl	Me_2CO	
26	$C_{18}H_{25}N_3O_3\cdot HCl\cdot {}^1/_2H_2O$	*RS*	3-$NO_2C_6H_4$	$-(CH_2)_4-$	H	223–225	C,H,N,Cl	EtOH	
27	$C_{19}H_{25}F_3N_2O\cdot HCl\cdot {}^1/_2H_2O$	*RS*	3-$CF_3C_6H_4$	$-(CH_2)_4-$	H	214–216	H,N,Cl;C[b]	Me_2CO	
28	$C_{19}H_{25}F_3N_2O\cdot HCl$	*RS*	2-$CF_3C_6H_4$	$-(CH_2)_4-$	H	247–249	C,H,N,Cl	Me_2CO	
29	$C_{19}H_{28}N_2O\cdot HCl$	*RS*	4-MeC_6H_4	$-(CH_2)_4-$	H	177–180	C,H,N,Cl	Me_2CO	
30	$C_{20}H_{30}N_2O\cdot HCl$	*RS*	3,4-$Me_2C_6H_3$	$-(CH_2)_4-$	H	165–166	C,H,N,Cl	Me_2CO	
31	$C_{22}H_{34}N_2O\cdot HCl$	*S*	4-$Me_3CC_6H_4$	$-(CH_2)_4-$	H	229–231	C,H,N	EtOAc	−51.4
32	$C_{24}H_{36}N_2O\cdot HCl$	*RS*	4-c-$C_6H_{11}C_6H_4$	$-(CH_2)_4-$	H	228–230	C,H,N,Cl	Me_2CO	
33	$C_{18}H_{26}N_2O_2\cdot HCl$	*RS*	4-OHC_6H_4	$-(CH_2)_4-$	H	230–232	C,H,N,Cl	MeOH–Me_2CO	
37 (threo)	$C_{17}H_{24}Cl_2N_2O\cdot HCl$	*RS*	3,4-$Cl_2C_6H_3$	Me Me	Me	135–141	H;C,N,Cl[c]	Me_2CO	
38 (erythro)	$C_{17}H_{24}Cl_2N_2O\cdot HCl$	*RS*	3,4-$Cl_2C_6H_3$	Me Me	Me	201–205	H,N;C,Cl[d]	Me_2CO	
41 (threo)	$C_{18}H_{24}Cl_2N_2O\cdot HCl$	*RS*	3,4-$Cl_2C_6H_3$	Me $-(CH_2)_3-$		175–177	C,H,N,Cl	EtOAc	
42 (erythro)	$C_{18}H_{24}Cl_2N_2O\cdot HCl$	*RS*	3,4-$Cl_2C_6H_3$	Me $-(CH_2)_3-$		210–213	C,H,N,Cl	Me_2CO	

[a] Calcd: C, 60.50; N, 7.84; Cl, 19.85. Found: C, 60.04; N, 7.07; Cl, 18.72. [b] Calcd: C, 57.06. Found: C, 57.55. [c] Calcd: C, 53.76; N, 7.38; Cl, 28.01. Found: C, 51.78; N, 6.14; Cl, 29.81. [d] Calcd: C, 53.76; Cl, 28.01. Found: C, 52.10; Cl, 26.85.

With the aim of producing a novel, highly selective κ agonist and potent antinociceptive agent bearing some of the structural features seen with the above compounds, we have incorporated the pharmacophore in an original type of cyclization, including the arylacetyl amidic nitrogen into a ring. This flexible system allows the pharmacophore to assume a 60° torsional angle between the amidic and basic nitrogen, as in the rigid U-50488 and U-62066.

In this paper we describe the synthesis and structure–activity relationship (SAR) of a series of 1-(arylacetyl)-2-(aminomethyl)piperidines (8).[18]

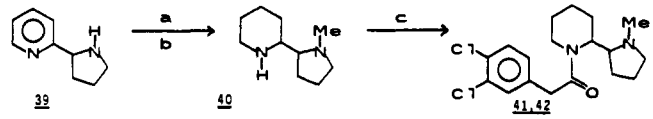
The amide moiety ($ArCH_2CO$), the tertiary amino group (NR_1R_2) and the side chain (R_3) have been variously modified to demonstrate the influence of each modification on the analgesic potency and κ affinity. Since both of these activities have been shown to be extremely enantiospecific, when racemic compounds of particular interest were identified, the active enantiomers were synthesized. Biological activity has been determined in terms of κ receptor binding affinity, κ/μ selectivity, and analgesic potency by subcutaneous and, for some compounds, oral routes of administration.

Chemistry

Compounds in Table I were synthesized according to Schemes I–III.

Racemic pipecolic acid (see Scheme I) was *N*-carbethoxy protected under Schotten–Baumann conditions and treated with thionyl chloride and then with an excess of amine below 0 °C. Removal of the *N*-carbethoxy group spontaneously occurred under the reaction conditions by the action of thionyl chloride. Possibly the reaction involved the formation of *N*-carboxy anhydride as reactive intermediate. A similar reaction was described for N-carbobenzyloxy amino acids.[19] The resulting 2-carboxy amides **11a–d** were reduced with lithium aluminum hydride, providing diamines **12a–d**.

Scheme III[a]



[a] Reagents: (a) 40% HCHO, $NaCNBH_3$, CH_3CN, AcOH, 35 °C, 1 h; (b) H_2/PtO_2, 99% AcOH, HCl, 50 psi; (c) 3,4-$Cl_2C_6H_3CH_2COCl$, CH_2Cl_2, K_2CO_3, room temperature.

Acylation with suitable arylacetyl chlorides in dry chloroform in the presence of anhydrous potassium carbonate gave the desired racemic compounds **13**, **16**, **20**, **22–30**, **32**, and **33**. The pure enantiomers shown in Table I were obtained, with excellent optical purity (>99%), starting from (*S*)-(−)- and (*R*)-(+)-pipecolic acids.[20]

2-[1-(Dimethylamino)ethyl]pyridine (**35**; see Scheme II) was obtained by reductive amination of 2-acetylpyridine (**34**) using sodium cyanoborohydride[21] in dry MeOH in the presence of an excess of dimethylamine hydrochloride and NaOH.

The reductive step to compound **36** was accomplished with catalytic hydrogenation over Adams Pt in glacial AcOH containing 4–7% CF_3COOH (1–2 equiv). The mixture of the diastereoisomeric diamines was acylated with (3,4-dichlorophenyl)acetyl chloride. The threo and

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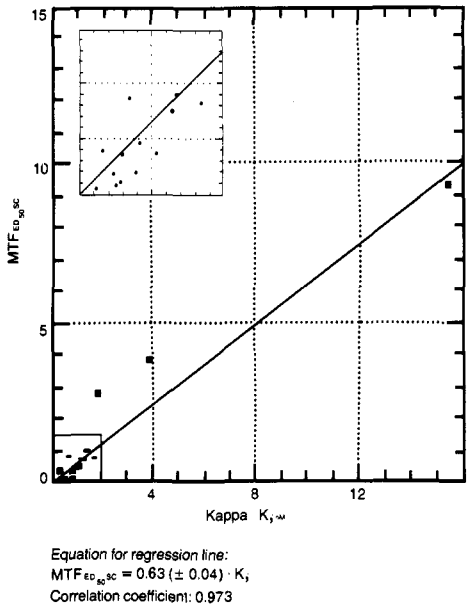

Figure 2. Regression analysis of analgesia (MTF ED_{50} sc) against κ binding (k_i, nM).

erythro isomers where separated by silica gel column chromatography, to yield compounds **37** and **38**.

α-Nicotine was obtained by treating α-nornicotine (**39**; see Scheme III)[22] with 40% formaldehyde and sodium cyanoborohydride in the presence of a small amount of AcOH in MeCN.

The reductive step to compound **40** was achieved by catalytic hydrogenation of α-nicotine hydrochloride over Adams Pt in glacial AcOH at 50 psi. The diastereoisomeric mixture of diamines was then acylated with (3,4-dichlorophenyl)acetyl chloride and diastereoisomeric compounds **41** and **42** were separated by silica gel column chromatography.

Results and Discussion

Pharmacology. The antinociceptive activities of compounds **13–33**, **37**, **38**, **41**, **42**, U-50488, and morphine in the mouse tail flick (MTF) test following subcutaneous administration are recorded in Table II. Also shown are the binding affinities to the κ and μ opioid receptors of guinea pig brain (minus cerebellum).

The regression analysis of MTF ED_{50} values versus κ binding affinities is shown in Figure 2. A linear correlation was found, suggesting that binding affinity and antinociceptive activity are, indeed, related. However, it is recognized that other factors such as agonist efficacy, distribution, metabolism, and excretion are also very important determinants of the in vivo activity. For example the presence of aromatic methyl groups in **29** and **30** may provide a further potential for metabolism and explain the reduced in vivo activity seen with these compounds. With a multiple linear regression analysis for both κ and μ affinity, a lack of significance was found for the correlation between antinociceptive activity and μ affinity.

The antinociceptive potency of compounds **14** and **21** have also been evaluated after oral administration (see footnotes c and d of Table II).

Conformation, Configuration, and SAR of Pharmacophore

Computational Studies. Computational studies using MM2 and AMPAC methods of geometric optimization were performed, using 1-acetylpiperidine as theoretical probe, to assess the degree of planarity of the nitrogen in the piperidine ring.

Irrespective of whether the N-substituent was designed to have tetrahedral equatorial, tetrahedral axial, or planar conformation, the resultant minimized structures indicated that the amide nitrogen geometry was completely planar.

The same methods of geometric minimization were performed with (2*R*)-1-acetyl-2-methylpiperidine as theoretical probe. Each of the four possible conformations [chair (eq), chair (ax.), boat (eq), boat (ax.)] of the probe were optimized under the assumption that the amide N was planar.

The chair conformation of the piperidine ring was preferred by ca. 2.0–3.0 kcal/mol over the boat conformation, while the axial conformation of the 2-substituent was preferred by 1.5–2.0 kcal/mol over the equatorial conformation.

A series of constrained piperidines branched in the basic chain (**37**, **38**, **41**, **42**) for comparison with the nonconstrained analogue **13** were constructed by using the MM2 method, adopting the optimum piperidine geometry described above.

As the calculated energy difference between the equatorial and axial conformers of the 2-substituted probe was found to be sufficiently low to be easily overcome in vivo, both conformers were considered in this study.

Determination of the minimum-energy conformer of the theoretical *S* enantiomers of **13**, **37**, and **41** showed that they were capable of adopting a minimum-energy conformation with an $N_1C_2C_7N_8$ torsional angle of 60°, while the theoretical *S* enantiomers of **38** and **42** were unable of adopting such a conformation with a low energy (Table III).

Table II. Antinociceptive Activity and Binding Affinity to κ, μ, and δ Opioid Receptors

no.	mouse tail flick ED_{50} mg/kg sc (95% CL) or % protection at 10 mg/kg sc	binding affinity; K_i,[a,b] nM κ	μ
13	0.09 (0.03–0.15)	0.53 ± 0.09	1860 ± 220
14	0.05[c] (0.03–0.08)	0.24 ± 0.06	1560 ± 250
15	17.53[e]	15.4 ± 2.90	7110 ± 400
16	0.92 (0.58–1.40)	1.36 ± 0.28	3050 ± 480
17	0.87 (0.16–1.65)	0.70 ± 0.13	2160 ± 220
18	0.77 (0.65–0.92)	1.28 ± 0.07	ca. 5000 (2)
19	0.19 (0.03–0.36)	0.48 ± 0.06	4810 ± 240
20	0.20 (0.05–0.46)	0.78 ± 0.06	3520 ± 230
21	0.11[d] (0.07–0.17)	0.57 ± 0.12	2340 ± 110
22	0.84 (0.37–1.30)	1.68 ± 0.28	5910 ± 250
23	9.22 (4.64–15.67)	15.4 ± 0.14	>10000 (2)
24	0.46 (0.29–0.71)	0.84 ± 0.06	2980 ± 180
25	0.49 (0.32–0.78)	not determined	
26	0.86 (0.31–1.48)	not determined	
27	0.38 (0.23–0.56)	1.07 ± 0.14	>10000 (2)
28	60%	8.54 ± 0.95	≥10000 (2)
29	3.88 (1.72–6.02)	3.84 ± 0.37	≥10000 (2)
30	2.89 (0.75–6.50)	1.83 ± 0.19	5310 ± 280
31	1.00[e]	not determined	
32	0%	827 ± 35	974 ± 90
33	0%	194 ± 9.8	>10000 (2)
37	0.38 (0.18–0.62)	0.60 ± 0.05	762 ± 58
38	0%	1000 ± 140	≥10000 (2)
41	0.40 (0.24–0.58)	0.33 ± 0.03	464 ± 25
42	40%	11.7 ± 0.59	864 ± 136
U-50488	1.90 (1.35-2.77)	0.97 ± 0.05	616 ± 50
morphine	2.80 (1.68-3.67)	151 ± 10	3.30 ± 0.30

[a] Each K_i value represents the mean from concentration–response curves performed in triplicate (n = 3 experiments) unless otherwise indicated in parentheses. [b] δ binding affinity for compounds **13–33**, **37**, **38**, **41**, **42**, and U-50488 is ≥10000 (n2) nM. The value for morphine is 460 ± 60 nM. [c] Mouse tailflick ED_{50} po = 0.89 mg/kg (0.15–1.80). [d] Mouse tail flick ED_{50} po = 1.17 mg/kg (0.75–2.63). [e] Not calculable.

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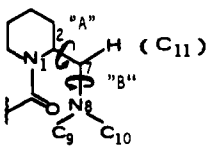
Table III[a]



compound	conformer 1		conformer 2		conformer 3		conformer 4		conformer 5		conformer 6	
	"A"	"B"	"A"	"B"	"A"	"B"	"A"	"B"	"A"	"B"	"A"	"B"
13 ax. *S*	180	180	60	180								
13 eq *S*	180	300	300	150	60	180	330	300	150	180	60	300
37 ax. *SS*	60	210	180	300	60	60	150	60	300	210		
37 eq *SS*	330	180	300	90	60	90	60	300	180	150	60	180
38 ax. *SR*	180	300										
38 eq *SR*	180	300	90	180	150	60	300	180				
41 ax. *SS*	60		180									
41 eq *SS*	60		180		320							
42 ax. *SR*	150											
42 eq *SR*	320		180									

[a] Each compound was subjected to computational analysis by allowing the $N_1C_2C_7N_8$ ("A") and the $C_2C_7N_8C_{10}$ ("B") torsional angles to vary from 0° to 360° in 30° increments. At each point the atoms defining the torsional variable were held fixed relative to each other, while the rest of the molecule was allowed to relax in accordance with the minimization procedure. A contour map was drawn for each structure and the minimum-energy conformers (within 4 kcals/mol of overall minimum) were determined. The associated angles are tabulated.

NMR Studies. ^1H NMR (300 MHz) studies were in good agreement with the computational results. A high $J_{H_2H_7}$ (CD_3OD) for compounds **37** and **38** (11.5 and 9.0 Hz, respectively) was observed, indicating a $H_2C_2C_7H_7$ torsional angle of nearly 180° and a severely restricted rotation about the C_2–C_7 bond (see Newman projection, Figure 3). Moreover, the stereochemistry was demonstrated by the NOE difference experiments: irradiation of methyl 11 of compound **38** produced NOE at H_{14} and H_{18}, which showed that methyl 11 is close to the aromatic ring.

Nonselective irradiation of the two methyl groups 9 and 10 produced NOE at H_{3eq}, confirming the erythro configuration for compound **38**, indicating a $N_1C_2C_7N_8$ torsional angle of nearly 180°. Irradiation of methyl groups 9–11 of compound **37** produced no definitive NOE's and therefore the stereochemistry cannot be determined directly.

However the spectrum is consistent with the opposite diastereoisomer of **38** and the threo configuration was assigned to compound **37**, indicating a $N_1C_2C_7N_8$ torsional angle of nearly 60°. Similar NOE experiments assigned the threo configuration to **41** and erythro to **42**. It is important to note that compounds **37** and **41** demonstrate high analgesic activity and κ affinity while **38** and **42** do not (see Table II). This would seem to indicate that a pharmacophore dihedral angle of ca. 60° (similar to that assumed by the conformationally restricted U-50488) is necessary to confer activity.

Further investigations were carried out to establish the conformation of the 2-substituent. A low value of the coupling constants between H_2–H_{3eq} (2.5 Hz) and H_2–H_{3ax} (5.0 Hz) for compound **37** indicated the axial conformation of the 2-substituent.

Moreover a clear NOE effect (6.2%) was observed on H_7 by irradiation of H_{6ax}, indicating that the two protons are very close each other as shown by the Dreiding model of the 2(ax.)-substituted compound. This achievement was confirmed for the corresponding nonbranched **16**.

Conformation of Amide Moiety

Further NMR studies on **16** and **37** showed that planar conformation of amide moiety could exist in two isomeric forms with the carbonyl oxygen oriented toward the same (syn conformation) or the opposite (anti conformation) side of the molecule as the basic chain. While the free bases

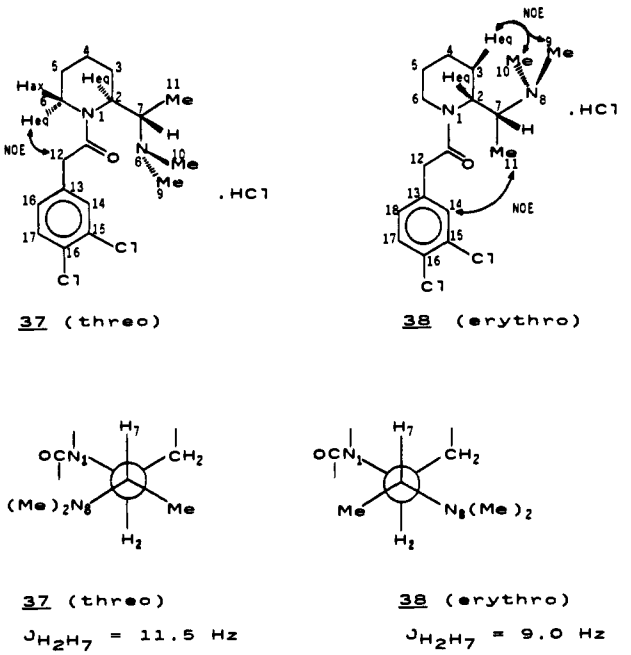


Figure 3. Structures and Newman projections of threo and erythro branched piperidines **37** and **38**.

exist in different ratios of syn and anti conformers, depending on the nature of the solvent, analyses of the positive NOE between the lower field benzylic proton and H_{6eq} (2.9% for **16** and 3.2% for **37**), observed for the hydrochlorides (Figure 3), revealed that the planar amide was oriented exclusively in the syn conformation independent of solvent. This could be due to an electrostatic interaction between the carbonyl group and the charged nitrogen which would stabilize the syn over the anti conformation.

This result suggests that, under physiological conditions of pH, the compounds described would approach the receptors in the syn conformation of the pharmacophore.

SAR of the Acylating Group and the Tertiary Amino Moiety

Examination of the three possible positions for ring substitution revealed that para- and meta-substituted compounds **20** and **27** were both highly active, while ortho substitution (cf. compound **28**) was not well-tolerated.

This lack of activity probably reflects steric hinderance effects associated with the ortho-substituted compounds. The antinociceptive potency sc of the para-substituted arylacetamides was slightly greater than that for the corresponding meta compounds (cf. compounds **20** and **25** with **27** and **26**), and the 3,4-dihalo substitution gave rise to an increase of activity in comparison with the corresponding 4-substituted compound (cf. **13** with **22**).

A quantitative structure–activity relationship (QSAR) examination of a homogeneous series of these (*RS*)-1-(arylacetyl)-2-(pyrrolidin-1-ylmethyl)piperidines revealed a good correlation (r = 0.97) between log (MTF ED_{50} sc)$^{-1}$ and the π and σ values calculated according to Hansch et al.[23] Thus, with stepwise regression analysis the following equation was produced:

$$\log (\text{MTF } ED_{50} \text{ sc})^{-1} = a\pi^2 + b\pi + c\sigma + d$$

$$a = -0.16,\ b = 0.97,\ c = 1.73,\ d = -0.89$$

where n = 11 and the standard error of the estimate = 0.184.

Figure 4 is a graphic representation of the actual antinociceptive potencies of the 11 compounds studied plotted against their potencies predicted by the above equation.

The amino moiety was modified in the (2*S*)-1-[3,4-(dichlorophenyl)acetyl] series. Pyrrolidino derivative **14** was extremely potent as an analgesic (ED_{50} ca. 0.05 mg/kg sc) and exhibited very high κ binding affinity (K_i = 0.24 nM), while an increase in the number of carbon atoms (e.g. **19**) caused a reduction in potency and binding affinity (ED_{50} = 0.19 mg/kg sc, K_i = 0.48 nM). The introduction of noncyclic tertiary amines, as in **17** and **18**, generated compounds with slightly less κ affinity (K_i ca. 1.0 nM) and antinociceptive potency (ED_{50} ca. 0.8 mg/kg), in relation with the corresponding cyclic compounds. Antinociceptive activity and κ affinity were found to be extremely enantiospecific since only compounds with the *S* configuration (at *) displayed significant activity (cf. **14** with its inactive *R* enantiomer **15**).

Conclusions

In the series of 2-(aminomethyl)piperidines (**8**), the most important chemical features required for optimization of κ affinity and antinociceptive potency may be summarized as follows: (i) The capability to adopt a torsional $N_1C_2C_7N_8$ angle of 60° in a low-energy conformation, (ii) The presence of an electron-withdrawing and lipophilic substituent in para and/or meta position(s) of the arylacetyl moiety, and (iii) The chiral center in the *S*-(−) configuration.

These 2-(aminomethyl)piperidines represent a novel class of very potent antinociceptive agents. In radioligand binding assays, compounds with extremely high affinity for the κ opioid receptor have been identified (i.e. **14** and **21**) and these compounds are among the most potent and the most selective κ ligands described. Indeed, compound **14**, because of its exceptionally high κ affinity and selectivity, has been tritiated for use in subsequent radioligand studies.

In the mouse tail flick model of antinociception, compounds **14** and **21** had ED_{50} values of 50 and 110 μg/kg sc, respectively.

The most active compound, **14**, was thus 25 times more potent than morphine and 16 times more potent than the standard κ ligand U-50488. These compounds also showed good antinociceptive activity following administration by the oral route: in this regard, **14** was 10 times more potent than morphine.

Taken together, the preclinical data for this class of substituted piperidines indicate that they represent a novel group of potent analgesics, for potential therapeutic use, which may lack the adverse side effects associated with current opioid analgesic therapies.

Compound **21** has entered clinical trials to explore whether the therapeutic approach of utilizing a κ-selective analgesic is valid.

Experimental Section

Biological Assays. κ, μ, and δ receptor binding assays. Determination of the opioid receptor site binding affinity of compounds was performed on fresh guinea pig brain homogenates (minus cerebellum).[24]

Binding to κ Sites. The highly selective κ opioid ligand [^{3}H]U-69593 was used to label κ binding sites. The radioligand was incubated with brain homogenates and cold ligand for 50 min at 25 °C, filtered through Whatman GF/C filters, and washed. The radioactivity bound to the filters was counted by liquid-scintillation spectrophotometry.

Binding to μ Sites.[25] [^{3}H]DAGO, an enkephalin analogue that binds selectively to μ receptors, was added to the homogenate, incubated at 25 °C for 40 min, filtered through Whatman GF/C filters, and washed with ice-cold Tris buffer. The filters were then dried and solubilized in Filtercount, and the radioactivity was monitored.

Binding to δ Sites.[25] The affinity to δ sites was determined by displacement of [^{3}H]DADLE binding under the condition of μ suppression (50 nM of cold DAGO).

Nonspecific binding was determined in the presence of 10^{-6} M naloxone for κ and μ sites and MR 2266[26] (500 nM) for δ sites.

For the calculation of the kinetic parameters of the binding of labeled and unlabeled ligands, the equilibrium dissociation constant (K_D), the inhibition constant (K_i), calculated from the Cheng and Prusoff equation,[27] and the maximum number of binding sites (B_{max}) were determined from saturation curves and competition experiments.

In Vivo Antinociceptive Studies. The mouse tail flick test was performed by following the procedure of D'Amour and Smith,[28] modified according to Ling et al.[29] ED_{50} values and their 95% confidence intervals were determined by using the probit analysis method of Finney.[30]

Chemistry. Melting points were determined with a Büchi 512 hot-stage apparatus and are uncorrected. Proton NMR spectra were either recorded on a Bruker AC80 or on a Bruker CXP 300 spectrometer. Chemical shifts were recorded in parts per million downfield from tetramethylsilane. IR spectra were recorded as a liquid film on sodium chloride disks or in KBr with a Perkin-Elmer 1420 spectrophotometer. Optical rotations were determined in MeOH solution with a Perkin-Elmer 241 polarimeter. The ee of compounds **14**, **15**, and **21** were found to be greater than 99% from 300-MHz ^{1}H NMR studies using Eu(hfc)$_3$ as chiral shift reagent. The ^{1}H NOE effects were determined by using the monodimensional difference spectroscopic technique. Typically four to six experiments were performed with a selective irradiation (2–3 s) of different protons and then subtracted from the control spectrum (off-resonance irradiation). Catalytic hydrogenations were performed with a Parr 3911 hydrogenation apparatus. Silica gel used for chromatography was Kiesegel-60 (230–400 mesh) (E. Merck A.G., Darmstadt, Germany). Computer modeling calculations were run with the CHEM-X molecular modeling package

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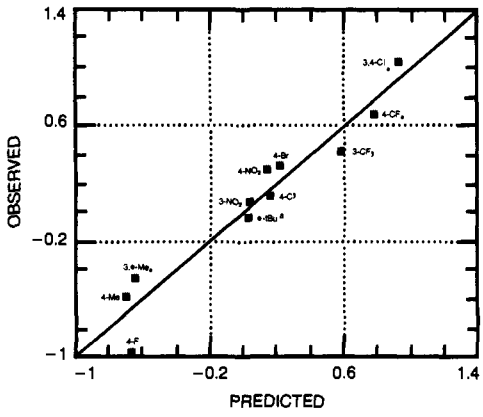

Figure 4. Plot of log (MTF ED_{50} sc)$^{-1}$. [a]Extrapolated value from (S)-31.

supplied by Chemical Design Ltd., Oxford, UK.

Synthesis of Known Intermediates. (S)-(-)- and (R)-(+)-pipecolic acids were prepared by selective crystallization of a diastereomeric mixture of (-)- and (+)-tartrates.[20] N-Carbethoxypipecolic acid was prepared by using Schotten-Baumann conditions. α-Nornicotine (compound **39**, Scheme III) was obtained by a multistep synthetic pathway from 2-cyanopyridine according to the method of L. C. Craig.[22]

Arylacetyl chlorides were prepared from the corresponding acid by treatment with an excess of oxalyl chloride in dry $CHCl_3$ at room temperature.

Arylacetic acids, racemic pipecolic acid, 2-acetylpyridine, and 2-cyanopyridine were obtained from Aldrich Chemical Co. and were used without further purification.

General Procedure for the Preparation of Amino Amides 11a-d. Redistilled thionyl chloride (62.0 mmol) was added dropwise to a solution of 1-(ethoxycarbonyl)pipecolic acid (22.0 mmol) in dry CH_2Cl_2 (60 mL) at -5 °C. After stirring of the mixture for 24 h at room temperature, the solvent was evaporated in vacuo; the residue was dissolved in CH_2Cl_2 (30 mL) and added dropwise to a solution of an excess of a secondary amine (48.0 mmol) in CH_2Cl_2 (40 mL) at -5 °C. The reaction mixture was washed with 5% $NaHCO_3$ solution, dried, and evaporated in vacuo to yield amino amides **11a-d**, which were used without further purification in the subsequent reaction.

As an example, the analytical data of **11a**·HCl are reported: yield 95%; mp 261-263 °C; IR (KBr) 3500, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.2 (m, 1 H), 4.0-2.9 (m, 6 H), 2.3-1.5 (m, 10 H).

General Procedure for the Preparation of Diamines 12a-d. A solution of amino amides **11a-d** (20 mmol) in dry THF was added dropwise at room temperature to a slurry of LAH (15 mmol) in dry THF (20 mL) under a nitrogen atmosphere. After stirring of the mixture for 3 h at 30 °C, an alkaline workup afforded the crude diamines.

As an example, the analytical data of **12a** are reported: yield 71%; bp (22 mmHg) 118-120 °C; IR (neat) 3340, 2940 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.1 (m, 1 H), 2.8-2.2 (m, 9 H), 1.9-1.3 (m, 10 H).

(±)-2-[1-(Dimethylamino)ethyl]pyridine (35). A mixture of 2-acetylpyridine (10.0 mmol), dimethylamine hydrochloride (20.0 mmol), NaOH (10.0 mmol), and sodium cyanoborohydride[21] (10.0 mmol) in dry MeOH (80 mL) was stirred for 3 days at room temperature. The solvent was evaporated in vacuo and the residue, saturated with NaOH pallets, was exhaustively extracted with Et_2O. The ethereal solution, dried and evaporated to dryness, afforded the crude product which was purified by silica gel column chromatography, eluting with CH_2Cl_2 containing increasing amounts of MeOH (from 2 to 10%), to yield **35** (80%) as a red oil: bp (15 mmHg) 106-108 °C; IR (neat) 2980, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.5 (m, 1 H), 7.8-7.0 (m, 3 H), 3.6-3.3 (m, 1 H), 2.2 (s, 6 H), 1.4 (d, 3 H).

(±)-2-[1-(Dimethylamino)ethyl]piperidine (Diastereoisomeric Mixture) (36). Compound **35** (8.0 mmol), dissolved in glacial AcOH (50 mL) containing CF_3COOH (16.0 mmol), was hydrogenated in a Parr apparatus in the presence of PtO_2 (200 mg) at 45 psi for 4 h. The Pt was filtered off; the filtrate was concentrated in vacuo and treated with 40% NaOH solution at 0 °C. Extraction with Et_2O afforded **36** (95%) as a yellow oil which was used without further purification in the subsequent acylation: IR (neat) 3320, 2930 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.8-3.2 (m, 1 H), 3.2-2.9 (m, 1 H), 2.9-1.9 (m, 3 H), 2.1 (ds, 6 H), 1.9-0.6 (m, 9 H).

(±)-2-(1'-Methyl-2'-pyrrolidinyl)piperidine (Diastereoisomeric Mixture) (40). Formaldehyde (40%, 0.670 mol) was added dropwise to a solution of **39** (0.017 mol) in MeCN (25 mL). After 30 min, sodium cyanoborohydride (0.05 mol) was added at 0 °C and stirring continued for 30 min at 35 °C. Glacial AcOH (2.5 mL) was added dropwise and the solution was stirred an additional hour. The reaction mixture was treated with 40% NaOH solution and exhaustively extracted with Et_2O. Concentration of the ethereal solution and treatment with a saturated solution of HCl in Et_2O afforded α-nicotine hydrochloride (85%), which was dissolved in glacial AcOH (70 mL) and hydrogenated in a Parr apparatus in the presence of PtO_2 (200 mg) at 45 psi for 4 h. The work-up of the reaction mixture was carried out in the same manner as that described for compound **36** (yield 68% from α-nornicotine): IR (neat) 3320, 2920 cm^{-1}.

Compound **40** was directly acylated without further purification.

General Method of Acylation of Diamines 12a-d, 36, and 40 To Obtain Compounds of General Formula 8. A solution of the aromatic acetyl chloride (1.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of the diamine (0.9 mmol) in the same solvent (15 mL) in the presence of anhydrous potassium carbonate (1.0 mmol) at 0 °C. After stirring for 3 h, the reaction mixture was washed with 5% $NaHCO_3$ solution, dried, and evaporated in vacuo to yield the free bases, which were purified by silica gel flash column chromatography using CH_2Cl_2-MeOH as eluent. Diastereoisomers **37** and **38**, and **41** and **42** were separated by silica gel column chromatography eluting with CH_2Cl_2 containing increasing amounts of MeOH from 0.1 to 2%. The purified, dissolved compounds were treated with a solution of HCl in Et_2O to give the HCl salts as white solids. The analytically pure samples were obtained by recrystallization (see Tables I and II).

As examples, the 300-MHz ^{1}H NMR of compounds **16**, **37**, and **38** are reported. Each proton is indicated with the same numbering used in Figure 3.

Compound **16**: ($CDCl_3$) δ 11.92 (s, br, H^+), 7.40 (d, H_{14}), 7.37 (d, H_{17}), 7.20 (dd, H_{18}), 5.28 (m, H_2, $J_{2,7}$ = 12.0 Hz, $J_{2,7'}$ = 4.0 Hz), 4.13 (d, H_{12}, $J_{12,12'}$ = 16.0 Hz), 3.84 (m, H_{6eq}, $J_{6eq,6ax}$ = 15.0 Hz, $J_{6eq,5eq} \cong$ 5 Hz, $J_{6eq,5ax} \cong$ 5 Hz), 3.71 (d, $H_{12'}$), 3.68 (m, H_7, $J_{7,7'}$ = 13.0 Hz), 3.44 (m, H_{6ax}, $J_{6ax,5ax}$ = 13.0 Hz, $J_{6ax,5eq}$ = 2.5 Hz), 2.93 (d, Me_9), 2.87 (d, Me_{10}), 2.70 (m, $H_{7'}$), 1.85-1.68 (m, H_{3ax}, H_{3eq}, H_{4ax}, H_{4eq}, H_{5ax}, H_{5eq}).

Compound **37**: (CD_3OD) δ 12.20 (s, br, H^+), 7.48 (d, H_{14}), 7.47 (d, H_{17}), 7.22 (dd, H_{18}), 4.92* (m, H_2, $J_{2,3eq}$ = 2.5 Hz, $J_{2,3ax}$ = 5.0 Hz), 4.06 (dq, H_7, $J_{2,7}$ = 11.5 Hz, $J_{7,11}$ = 6.7 Hz), 3.91 (m, H_{6eq}), 3.89 (s, H_{12}, $H_{12'}$) 3.25 (m, H_{6ax}), 2.95 (s, Me_9), 2.74 (s, Me_{10}), 1.83 (m, H_{3eq}), 1.66 (m, H_{4eq}), 1.55-1.67 (m, H_{3ax}, H_{5ax}, H_{5eq}), 1.34 (d, Me_{11}), 1.25 (m, H_{4ax}) (*, seen in $CDCl_3$).

Compound **38**: (CD_3OD) δ 12.00 (s, br, H^+), 7.48 (d, H_{17}), 7.46 (d, H_{14}), 7.20 (dd, H_{18}), 4.84 (m, H_2), 3.89 (m, H_{6eq}), 3.84 (dq, H_7, $J_{2,7}$ = 9.0 Hz, $J_{7,11}$ = 6.9 Hz), 3.84 (s, H_{12}, $H_{12'}$), 3.06 (m, H_{6ax}), 2.96 (s, Me_9), 2.80 (s, Me_{10}), 1.92 (m, H_{3eq}), 1.75-1.60 (m, H_{3ax}, H_{5eq}, H_{4ax}, H_{4eq}), 1.42 (m, H_{5ax}), 1.16 (d, Me_{11}).

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Supplementary Material Available: Output of the multiple linear regression analysis correlating antinociceptive activity with κ and μ binding affinities, molecular modeling contour maps for compounds **13**, **37**, **38**, **41**, and **42**, a table of π and σ values of the compounds examined in the QSAR (Hansch-type) analysis, other equations examined in the above QSAR analysis (13 pages). Ordering information is given on any current masthead page.