NMR δ 5.67 (s, 1 H, H-3), 5.44 and 5.26 (AB q, 2 H, J = 12.0 Hz, CH_2O), 4.8-4.4 (m, 1 H, CHOH), 4.15-3.8 (m, 2 H, NCH_2), 3.81 (s, 3 H, OCH_3), 2.05 (s, 3 H, CH_3); MS, m/z (M^+) calcd 319.106, found 319.105. Anal. ($C_{16}H_{17}NO_6$) C, H, N.

1-(Acetyloxy)-9-[(acetyloxy)methyl]-7-(1-aziridinyl)-2,3-dihydro-6-methyl-1*H*-pyrrolo[1,2-*a*]indole-5,8-dione (16). A solution of **10b** (60.0 mg, 0.2 mmol) in dry methanol (80 mL) was treated with aziridine (2 mL), and after stirring for 3 h at room temperature, the reaction mixture was left at -20 °C overnight. The precipitate was collected by filtration to afford **16** in a yield of 50%: mp 210.5-211.5 °C (EtOH);[35] ^1H NMR δ 6.15 (dd, 1 H, J = 1.9 and 6.6 Hz, CHOAc), 5.29 (s, 1 H, CH_2O), 2.31 (s, 3 H, CH_3), 2.06 [s, 6 H, $C(O)CH_3$]; MS, m/z (M^+) calcd 372.132, found 372.129. Anal. ($C_{19}H_{20}N_2O_6$) H, N; C: calcd, 61.28; found, 60.48.

General Procedure for the Reactions of the Mitosenes 10a and 17 with Potassium Ethyl Xanthate and Potassium Thiobenzoate under Reductive Conditions. A solution of **10a** and **17** (0.17 mmol) in a mixture of CH_2Cl_2/MeOH/H_2O = 1:1:1 (50 mL) was purged with N_2 (10 min) at room temperature. Subsequently, potassium ethyl xanthate or thiobenzoate (0.85 mmol) was added followed by a solution of $Na_2S_2O_4$ (60.0 mg, 0.34 mmol) in water (1 mL). After the mixture was stirred for about 10 min, the reaction was complete and reoxidation by air had taken place. The reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL), the organic phase was dried over $MgSO_4$, and the solvent was removed in vacuo to give the crude compounds **20** and **21a,b**, which were purified by chromatography using $CHCl_3$/EtOAc = 1:1 as eluent. The yields, melting points, ^1H NMR data, and molecular ion values (M^+) are given in Table VI.

2,3,5,8-Tetrahydro-7-methoxy-6,9-dimethyl-1*H*-pyrrolo[1,2-*a*]indole-5,8-dione (22). A solution of **17** and **19** (21.0 mg, 0.04 mmol) in EtOH (5 mL) was treated with $NaBH_4$ (7.6 mg, 0.20 mmol). After the mixture was stirred for 15 min, reoxidation had taken place and water (10 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL); the combined extracts were dried with $MgSO_4$. After evaporation of the solvent and purification by chromatography ($CHCl_3$), **22** was obtained in a yield of 50%: mp 165-167 °C (EtOH) (lit.[20b] mp 164.5-167 °C).

Acknowledgment. We are grateful for financial support of this work by the Netherlands Cancer Foundation. The studies concerning the biological activities of the (modified) mitosenes were performed under the auspices of the Screening and Pharmacology Group of the European Organization for Research and Treatment of Cancer (EORTC). We express our gratitude to J. M. Visser and J. L. M. Vrielink for recording the NMR and T. W. Stevens for recording the mass spectra.

Registry No. **3a**, 96631-74-2; **3b**, 3188-31-6; **3c**, 109049-95-8; **3d**, 109049-96-9; (±)-**4a**, 120386-14-3; (±)-**4a** (alcohol), 120386-18-7; (±)-**4b**, 120386-15-4; (±)-**4b** (alcohol), 120386-19-8; (±)-**4c**, 120386-16-5; (±)-**4c** (alcohol), 120386-20-1; (±)-**4d**, 120386-17-6; (±)-**4d** (alcohol), 120386-21-2; (±)-**5a**, 120386-22-3; (±)-**5b**, 120386-23-4; (±)-**5c**, 120386-24-5; (±)-**5d**, 120386-25-6; (±)-**6a**, 120386-30-3; (±)-**6a** (nitro analogue), 120386-26-7; (±)-**6b**, 120386-31-4; (±)-**6b** (nitro analogue), 120386-27-8; (±)-**6c**, 120386-32-5; (±)-**6c** (nitro analogue), 120386-28-9; (±)-**6d**, 120386-33-6; (±)-**6d** (nitro analogue), 120386-29-0; (±)-**7a**, 120386-34-7; (±)-**7b**, 120386-35-8; (±)-**7c**, 120386-36-9; (±)-**7d**, 120386-37-0; (±)-**8a**, 120386-38-1; (±)-**8b**, 120386-39-2; (±)-**8c**, 120386-40-5; (±)-**8d**, 120386-41-6; **9**, 3188-26-9; (±)-**10a**, 120386-43-8; (±)-**10b**, 120386-44-9; (±)-**10c**, 120386-45-0; (±)-**10d**, 120386-46-1; (±)-**11**, 120386-47-2; (±)-**12**, 120386-48-3; (±)-**13a**, 120386-49-4; (±)-**13b**, 120386-50-7; (±)-**13c**, 120386-51-8; (±)-**13d**, 120386-52-9; (±)-**14**, 120386-53-0; (±)-**15**, 120386-58-5; (±)-**16**, 120386-59-6; **17**, 3188-27-0; (±)-**18**, 120386-42-7; (±)-**19**, 120386-54-1; **20**, 120386-55-2; (±)-**21a**, 120386-56-3; (±)-**21b**, 120386-57-4; (±)-**22**, 66865-11-0; KSC(S)OEt, 140-89-6; KSC(O)Ph, 28170-13-0; aziridine, 151-56-4.

Highly Selective κ-Opioid Analgesics. 2. Synthesis and Structure-Activity Relationships of Novel *N*-[(2-Aminocyclohexyl)aryl]acetamide Derivatives

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This paper describes the chemical synthesis and the development of structure-activity relationships (SAR) for the κ opioid receptor affinity and μ/κ opioid receptor selectivity of novel *N*-[(2-aminocyclohexyl)aryl]acetamide derivatives. The SAR of this series are investigated by consideration of structural modifications made to the aromatic moiety, the amide linkage, and cyclohexane and the pyrrolidine ring substituents of the prototype κ selective agonist, PD117302 (*trans*-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzo[*b*]thiophene-4-acetamide) (**1**). The κ and μ opioid receptor binding affinities of 23 novel compounds are reported. It is observed that optimal μ/κ receptor selectivity is obtained with a benzo[*b*]thiophene aromatic system attached via the C-4 position, which is discussed in terms of steric and electronic parameters. The amide linkage has been replaced with the reversed amide, an ester, an aminomethylene, a thioamide, and a secondary amide. The best of these isosteres is the *N*-methyl amide. Substitution of the pyrrolidine ring of PD117302 in the 3-position with a hydroxymethylene group increases the μ/κ selectivity compared to the unsubstituted compound, e.g. compound **14**, *trans*-(±)-*N*-methyl-*N*-[2-[3-(hydroxymethyl)-1-pyrrolidinyl]cyclohexyl]-4-benzo[*b*]furanacetamide monohydrochloride, μ/κ receptor selectivity = 244. The cis fused, 4,5 dimethyl ether substituted cyclohexane analogue *trans*-(±)-*N*-methyl-*N*-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]-benzo[*b*]thiophene-4-acetamide monohydrochloride (**32**) has high in vitro κ opioid receptor affinity (K_i = 16 nM) and equipotent analgesic activity to morphine after iv administration in rats.

Previous studies[1-7] have established that certain *N*-[(2-aminocyclohexyl)aryl]acetamides exhibit high in vitro selectivity and affinity for the κ opioid receptor and also elicit potent analgesia in rodent tests. For example, in part 1 of this work,[1] compound **1** (PD 117302) has been shown to have nanomolar affinity for the κ opioid receptor and a μ/κ ratio [$K_i(\mu)/K_i(\kappa)$] = 110. The compound after oral

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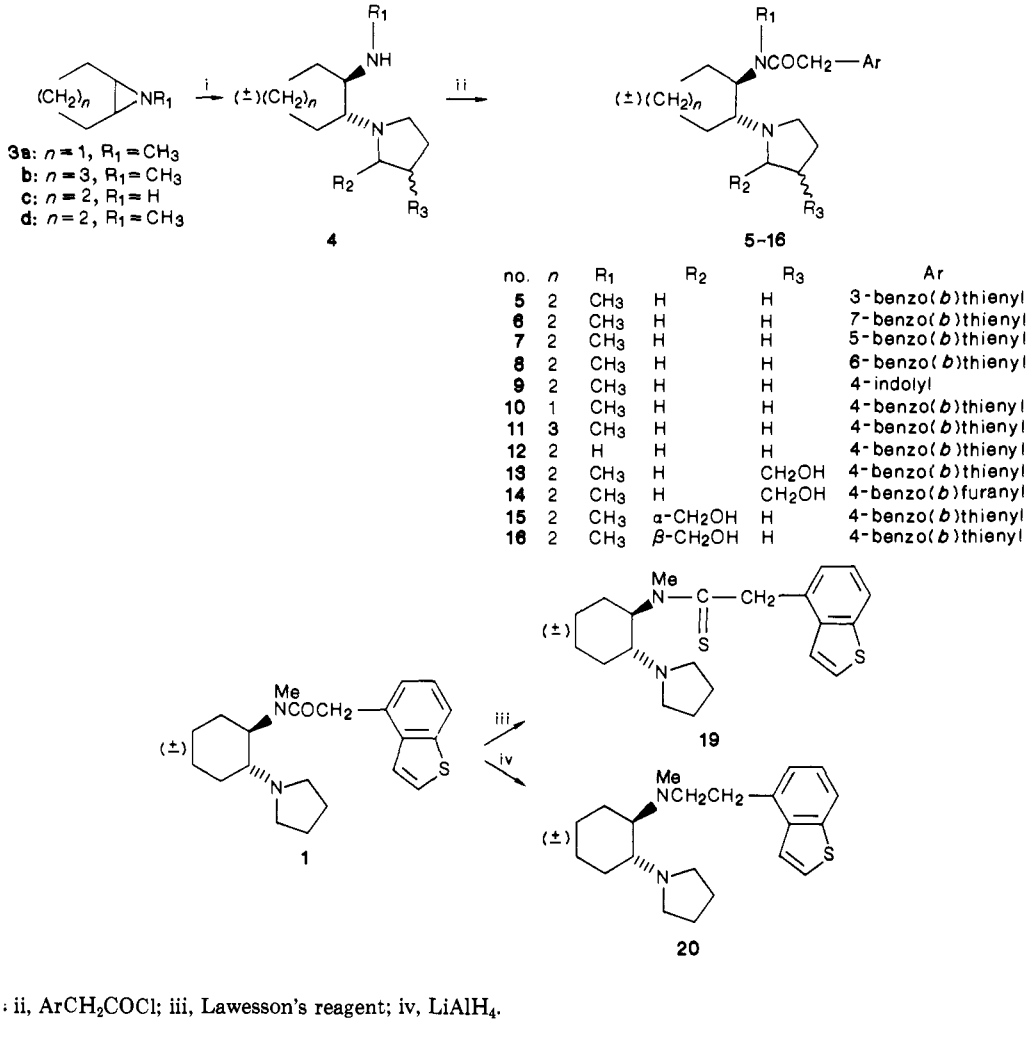
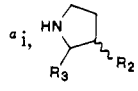
0022-2623/89/1832-1620$01.50/0

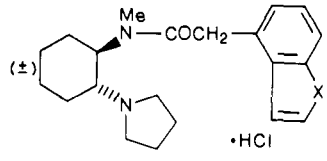
Scheme I[a]



no.	n	R_1	R_2	R_3	Ar
5	2	CH_3	H	H	3-benzo(*b*)thienyl
6	2	CH_3	H	H	7-benzo(*b*)thienyl
7	2	CH_3	H	H	5-benzo(*b*)thienyl
8	2	CH_3	H	H	6-benzo(*b*)thienyl
9	2	CH_3	H	H	4-indolyl
10	1	CH_3	H	H	4-benzo(*b*)thienyl
11	3	CH_3	H	H	4-benzo(*b*)thienyl
12	2	H	H	H	4-benzo(*b*)thienyl
13	2	CH_3	H	CH_2OH	4-benzo(*b*)thienyl
14	2	CH_3	H	CH_2OH	4-benzo(*b*)furanyl
15	2	CH_3	α-CH_2OH	H	4-benzo(*b*)thienyl
16	2	CH_3	β-CH_2OH	H	4-benzo(*b*)thienyl

[a] i,  ; ii, $ArCH_2COCl$; iii, Lawesson's reagent; iv, $LiAlH_4$.

administration is approximately half as potent as morphine in a rat paw pressure test for analgesia.



1: X = S (PD 117302)
2: X = O

The objective of this study is to further explore the structure–activity relationships (SAR) of this chemical series and to identify new opioid analgesics with high μ/κ binding ratios. Modifications have been made to the position of attachment of the aromatic group, the linkage between the cyclohexane ring and the aromatic group, the cyclohexane ring including rigid and flexible analogues, and the pyrrolidine ring. The effects of these changes upon the in vitro μ/κ opioid receptor binding and in vivo rat paw pressure analgesia assay are discussed.

Chemistry

The *trans*-1,2-diamino moiety is prepared by treating an aziridine (**3a–d**) with pyrrolidine.[1] Compounds **5**, **6**, **7**, and **8**, which are the 3, 7, 5, and 6 regioisomerically substituted benzo[*b*]thiophene derivatives, and the 4-indole analogue **9** were prepared by the general procedure (Scheme I) by coupling of diamine **4d** with benzo[*b*]-thiophene-3-acetic acid, benzo[*b*]thiophene-7-acetic acid,[8] benzo[*b*]thiophene-5-acetic acid,[9] benzo[*b*]thiophene-6-acetic[9] acid, or indole-4-acetic acid,[10] respectively, via the corresponding acid chlorides. The cyclopentane and cycloheptane analogues **10** and **11** were prepared by using similar methodology (Scheme I) from the corresponding aziridines **3a** and **3b**. Similarly, aziridine **3c**[11] was converted into the secondary amide, **12**.

The compounds with substituents on the pyrrolidine ring, **13–16**, were prepared by treating aziridine **3d** with 2-(hydroxymethyl)pyrrolidine[12] or 3-(hydroxymethyl)-pyrrolidine[13] (R_2 or R_3 = CH_2OH, Scheme I). Compound

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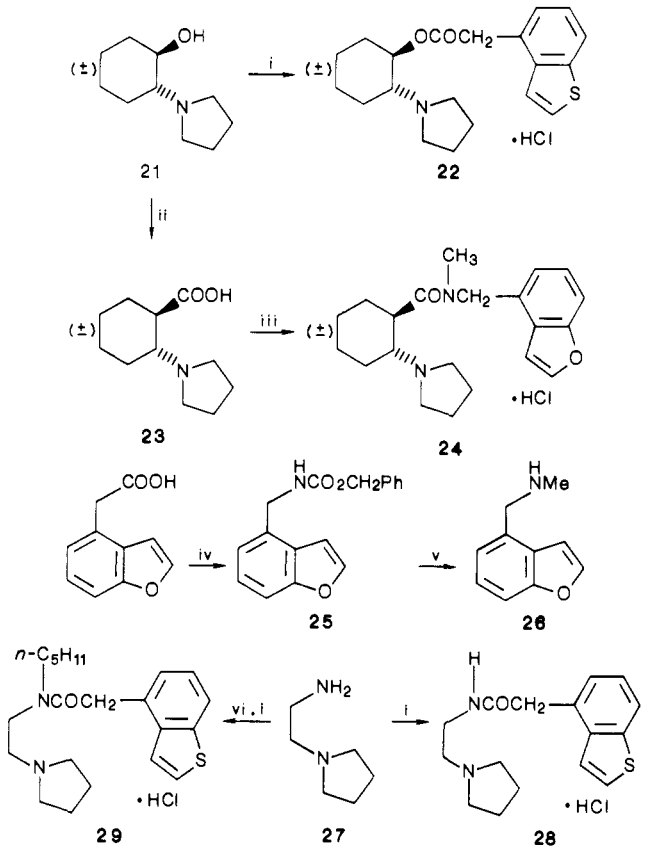
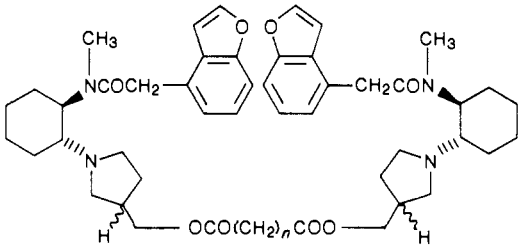
Scheme II[a]



[a] i, $ArCH_2COCl$; ii, (a) MsCl, (b) KCN, (c) KOH; iii, compound **26**; iv, Et_3N, $(PhO)_2P(O)N_3$, $PhCH_2OH$; v, (a) HBr, HOAc, (b) HCO_2Et, (c) $LiAlH_4$; vi, (a) C_4H_9COCl, (b) BH_3.

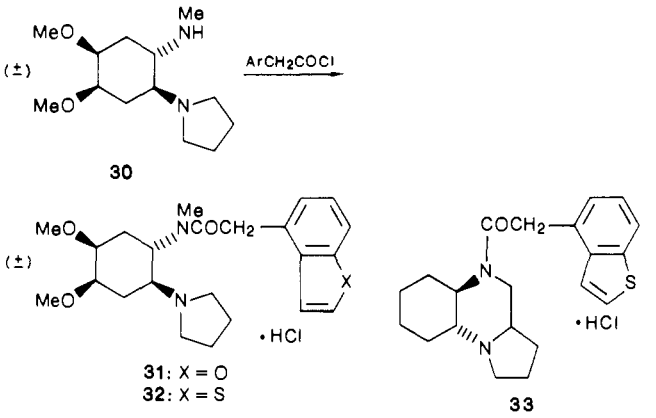
14 was treated with succinyl chloride or glutaryl dichloride to give dimeric esters **17** and **18**, respectively.



N-Methyl amide **1** was converted into the corresponding thioamide **19** by treatment with Lawesson's reagent, and **1** was converted into the aminomethylene analogue **20** by treatment with lithium aluminum hydride (Scheme I). Other modifications to this amide moiety were made as outlined in Scheme II. Trans amino alcohol **21**[14] (Scheme II) was converted into the ester isostere **22** by acylation with 4-benzo[*b*]thiopheneacetyl chloride and into the trans amino acid **23** by formation of the mesylate followed by treatment with potassium cyanide and hydrolysis of the resulting nitrile. The acid chloride of **23** was treated with *N*-methyl-4-benzo[*b*]furanmethanamine (**26**) (prepared as outlined in Scheme II) to give **24**, the reverse amide isostere of **1**.

N-(2-Aminoethyl)pyrrolidine **27** was converted into **28** by acylation with 4-benzo[*b*]thiopheneacetyl chloride and into **29** by a three-step procedure involving acylation with valeryl chloride and reduction of the resulting amide with borane in tetrahydrofuran followed by acylation of the resulting secondary amine with 4-benzo[*b*]thiopheneacetyl chloride.

The *cis*-4,5-dimethoxy-substituted cyclohexyl derivatives **31** and **32** were prepared from diamine **30**.[15] Dodecahydropyrrolo[1,2-*a*]quinoxaline (**33**) was prepared by the method of Rees.[16]



Results and Discussion

1. SAR of the Aromatic Group. In part 1,[1] it was reported that for high μ/κ opioid receptor selectivity the aromatic moiety of these arylacetamides should possess an electron-rich 4-benzo[*b*]thiophene moiety separated from the amide carbonyl by a single methylene group. An objective of this study was to investigate the effect on μ/κ selectivity of changing the position of attachment of the 4-benzo[*b*]thiophene group to this methylene group. Accordingly the 3-, 5-, 6-, and 7-substituted benzo[*b*]-thiophene regioisomers **5**–**8** were synthesized and compared with the previously reported 4-substituted compound **1**. The differences between the steric orientations that the benzo[*b*]thiophene group can adopt when substituted in the 4-position (**1**) versus the 5-position (**7**) are shown in Figure 1, which is the computer-generated representation of the molecule when the CH_2–Ar bond is rotated in 30° increments. The conformations for the 7-isomer, **6** ($K_i(\kappa)$ = 17 nM, μ/κ ratio = 39), are very similar to those for **1** ($K_i(\kappa)$ = 3.7 nM, μ/κ ratio = 110), the 6-isomer **8** ($K_i(\kappa)$ = 146 nM, μ/κ ratio = 3) is similar to **7** ($K_i(\kappa)$ = 94 nM, μ/κ ratio = 5), and the 3-isomer **5** ($K_i(\kappa)$ = 69 nM, μ/κ ratio = 21) is different from both of the above pairs. The two best compounds (Table I), **1** and **6**, both correspond to the set of conformations in Figure 1a, and these conformations may well be optimal for binding to the κ receptor.

Although the aromatic groups of **1** and **6** have similar conformational properties, the orientation of their dipole moments are different. 7-Methylbenzo[*b*]thiophene has a calculated dipole of 3.31 Db with a $(+X, -Y)$ orientation while in 4-methylbenzo[*b*]thiophene it is 3.57 Db but with a $(-X, -Y)$ orientation. The importance of dipole interactions of drugs in receptor binding has been studied widely,[17,18] and we propose that the improved κ affinity of **1** versus **6** is due to a favorable dipole interaction between

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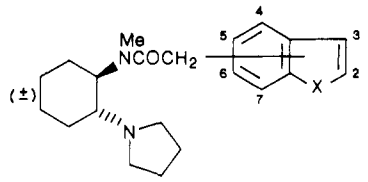
Table I. κ and μ Opioid Binding and Rat Paw Pressure Analgesia Assays: Substitution Position of Aromatic Group



no.	X	substit position	opioid receptor binding: affinity K_i,[a] nM κ	μ	μ/κ[e]	rat paw pressure[b] assay: MPE_{50}, mg/kg iv
5	S	3	69 ± 3	1400 ± 200	21	*3.3
6	S	7	17 ± 1	650 ± 170	39	>3.3
7	S	5	94 ± 7	475 ± 85	5	6.1
8	S	6	146 ± 4	425 ± 25	3	4.6
9	NH	4	816 ± 71	833 ± 120	1	*d*
1[c]	S	4	3.7 ± 0.4	410 ± 59	110	1.4

[a] Where standard errors are given, the K_i value represents the mean from concentration-response curves performed in triplicate (n = 3). Where no standard errors are given, the K_i value is from a single experiment (n = 1). [b] MPE_{50} values represent the dose required to produce 50% of the maximum possible analgesic effect. They are derived from a single experiment with six animals at each of five dose levels. [c] Previously reported compound, PD 117302.[1] [d] Not tested. [e] μ/κ ratio = $[K_i(\mu)/K_i(\kappa)]$.

Table II. κ and μ Opioid Binding and Rat Paw Pressure Analgesia Assay: Modification of Cyclohexane Ring

no.	opioid receptor binding: affinity K_i,[a] nM κ	μ	μ/κ[e]	rat paw pressure assay: MPE_{50},[b] mg/kg iv
28	25000 ± 3900	10000 ± 3700	0.4	*d*
29	2000 ± 200	5200 ± 940	2.7	*d*
10	154 ± 13	3600 ± 720	23	*d*
11	12 ± 1	1000 ± 50	83	*d*
33	28000 ± 2400	17500 ± 1200	0.63	*d*
31	16	820	51	0.8
32	18	2800	155	1.5
morphine	86	1.8	0.021	0.61

[a,b,d,e] See footnotes to Table I.

the 4-substituted aryl group and the κ receptor. In support of this hypothesis the 4-substituted indole derivative **9** ($K_i(\kappa)$ = 816 nM, μ/κ ratio = 1) has similar steric properties to those identified as being optimal in the benzo[*b*]-thiophene series, but the calculated dipole moment for the aromatic moiety is only 2.33 Db and is orientated in the opposite direction (+*X*, +*Y*) to that of **1**. In contrast, the dipole of the aromatic moiety in the active 4-benzo[*b*]furan derivative **2**[1] ($K_i(\kappa)$ = 12 nM, μ/κ ratio = 130) is orientated (−*X*, +*Y*) similarly to **1**. Hence we conclude the dipole orientation (−*X*) is optimal for high κ receptor affinity.

2. Modification to the Cyclohexane Ring. Compound **28** was synthesized as a flexible analogue of **1** and found to be inactive (μ and κ K_i > 10 000 nM) (Table II) although there is a slight improvement in compound **29**, in which the amide *N*-pentyl group was introduced to maintain comparable global lipophilicity with PD 117302 (**1**). Hence it appears that the rigid cyclohexane ring is needed to orientate the amino and acetamidoaryl moieties for binding to the κ receptor. The critical role of the cyclohexane ring in this regard has been established by preparing the cyclopentane **10** ($K_i(\kappa)$ = 154 nM, μ/κ ratio = 23) and cycloheptane **11** ($K_i(\kappa)$ = 12 nM, μ/κ ratio = 83) analogues. The six-membered ring is preferred over either of the 5- or 7-membered analogues. Having established this, the rigidity was further increased by fusing the pyrrolidine ring of **1** to the amide methyl group as in compound **33**. The low κ affinity (K_i > 1000 nM) indicates that this rigid structure may not adopt a conformation adopted by **1** at the receptor.

Martin has proposed a model of the opioid receptors in which the κ receptor is distinguished from the μ receptor by having an oxygen binding site capable of interacting with the ketonic oxygen of ethylketazocine.[19] To investigate this hypothesis and to increase the μ/κ selectivity of **1** we decided to incorporate an oxygen atom into our series of κ agonists. Two positions were chosen for the attachment of this accessory binding group: the cyclohexane ring, which has also been studied elsewhere,[20] and the pyrrolidine ring, which has not previously been substituted (see section 4). The diamine **30**[15] has two cis-fused, geminally substituted ether oxygen atoms attached to the cyclohexane ring and both the benzo[*b*]thiophene (**32**) and benzo[*b*]furan (**31**) derivatives have high κ affinity and selectivity (Table II) ($K_i(\kappa)$ = 16 and 18 nM, μ/κ ratio = 51 and 155, respectively). Furthermore, compound **32** is equipotent with morphine as an analgesic in a rat paw pressure test for analgesia after iv administration (MPE_{50} = 0.8 and 0.6 mg/kg, respectively).

3. Amide Isosteric Replacements. The NH amide **12**, the ester **22**, the aminomethylene **20**, and the reverse amide **24** were prepared and found to reduce κ affinity by 90-, 98-, 2190-, and 10000-fold, respectively, when compared to **1**. These compounds all change the amide bond in terms of conformational properties,[21] lipophilicity,[22] and potential for hydrogen-bonding interactions. The parameter that is most changed in each of **12**, **22**, **20**, and **24** is hydrogen bonding. In an attempt to mimic **1** in this respect the thioamide **19** ($K_i(\kappa)$ = 53 nM, μ/κ ratio = 13) was prepared. This has higher affinity than the other isosteres in Table III.

4. Substitution on the Pyrrolidine Ring. The pyrrolidine ring was the second site chosen for the attachment of an oxygen atom in an attempt to locate an accessory binding group on the κ receptor (vide supra). In compounds **15** and **16** a hydroxymethylene is joined at the 2-position and κ selectivity is lost completely ($K_i(\kappa)$ > 10 000 nM) (Table IV). However, compound **14**, which has the hydroxymethylene attached to the 3-position, has a higher selectivity than the unsubstituted derivative **2** (μ/κ ratio = 244 and 110,[1] respectively). This hydroxymethylene

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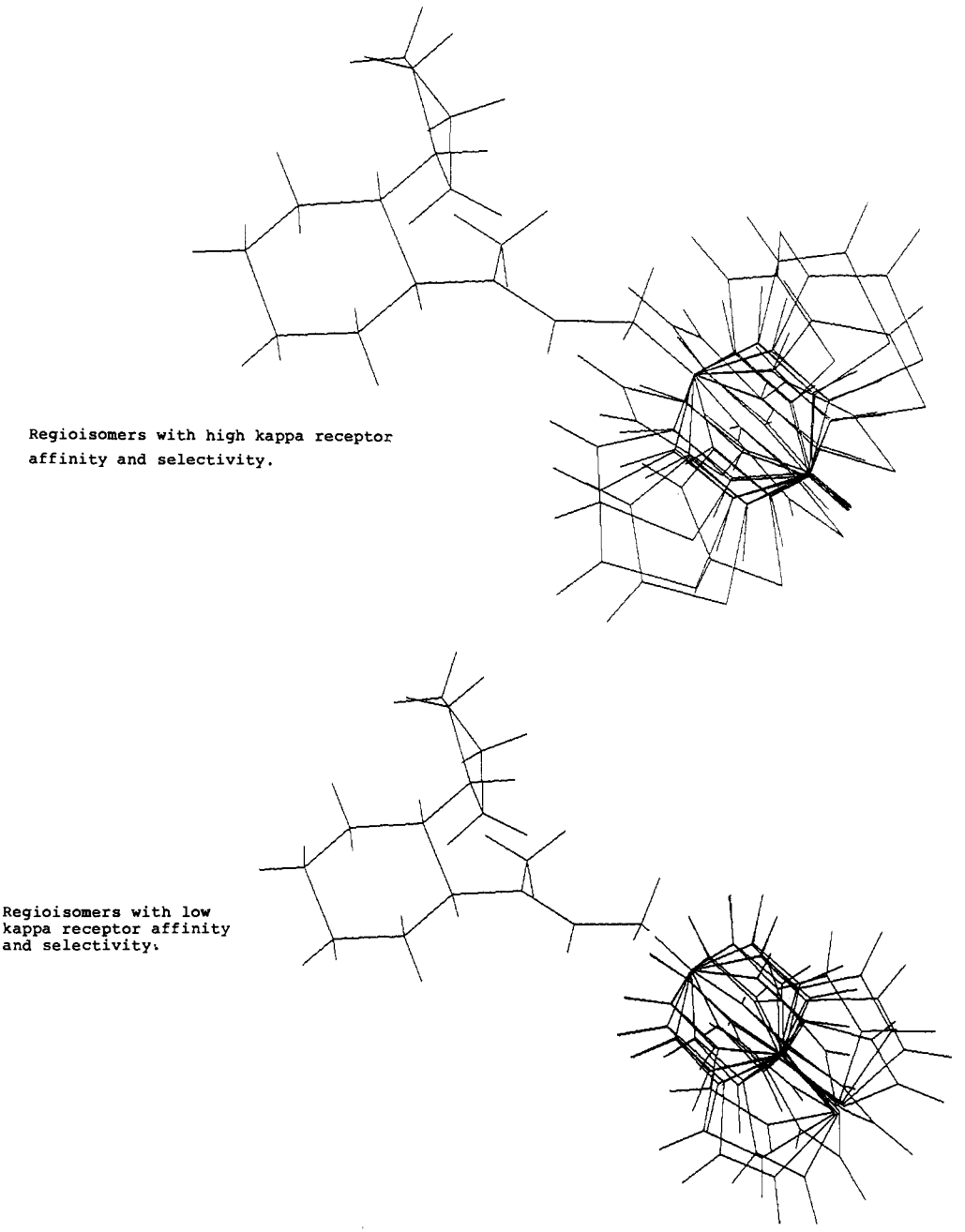
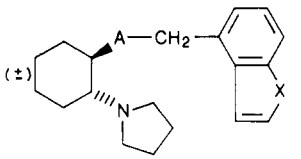


Figure 1. Computer representation of the conformations generated by rotation of the CH_2–Ar bond in 30° increments for (a, top) C-4 and C-7 regioisomers and (b, bottom) C-5 and C-6 regioisomers.

Table III. κ and μ Opioid Binding and Rat Paw Pressure Analgesia Assay: Amide Replacements

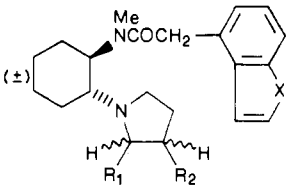


no.	X	A	opioid receptor binding: affinity K_i,[a] nM κ	μ	μ/κ[e]	rat paw pressure assay: MPE_{50},[b] mg/kg iv
1[e]	S	NMeCO	3.7 ± 0.4	410 ± 59	110	1.4
12	S	NHCO	333 ± 24	4800 ± 900	14	*d*
24	O	CONMe	37000 ± 3000	20300 ± 700	0.55	*d*
22	S	OCO	261 ± 39	3340 ± 800	13	>3.3
19	S	NMeCS	53 ± 11	700 ± 100	13	*d*
20	S	$NMeCH_2$	8100 ± 1000	14300 ± 900	20	*d*

[a,b,d,e] See footnotes to Table I.

moiety provides a functional group for the synthesis of dimeric analogues that are of interest because dimers of enkephalins[23] and morphine derivatives[24] have been shown to have enhanced selectivity for opioid receptor types

Table IV. κ and μ Opioid Binding and Rat Paw Pressure Analgesia Assay: Substitutions on the Pyrrolidine Ring



no.	X	R_1	R_2	opioid receptor binding: affinity K_i,[a] nM κ	μ	μ/κ[e]	rat paw pressure assay: MPE_{50},[b] mg/kg iv
13	S	H	CH_2OH	7	560	80	>3.3
14	O	H	CH_2OH	17 ± 4	4100 ± 400	244	4.0
15	S	CH_2OH (isomer 1)	H	>10000	>10000		*d*
16	S	CH_2OH (isomer 2)	H	>1000	>100		*d*
17	O	dimer *n* = 3		180	760	4.2	*d*
18	O	dimer *n* = 2		180	800	4.4	*d*

[a,b,d,e] See footnotes to Table I.

which depends upon the length of the bridging unit. The dimeric compounds **17** and **18** ($K_i(\kappa)$ = 180 nM, 180 nM μ/κ ratio = 4.2, 4.4, respectively) do indeed retain affinity for the κ receptor but do not have enhanced selectivity.

Conclusion

N-[(2-Aminocyclohexyl)aryl]acetamides have emerged as the most κ selective opioid analgesics yet described. This study probes further the SAR requirements of the prototype *trans*-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-benzo[*b*]thiopheneacetamides, Chemical modifications to the regiochemical fusion of the aromatic benzo[*b*]-thiophene, amide linkage, cyclohexyl, and pyrrolidine ring substituents have defined more closely the very precise requirements for receptor recognition. The preparation and examination of the κ opioid affinity and selectivity of the 3–7 fused regioisomers of the benzo[*b*]thiophene show that the 4- and 7-positions are preferred over the 3, 5, and 6 regioisomers. Computer graphics modeling show that the 4 and 7 isomers have similar space-filling requirements that are different from the 3, 5, and 6 isomer requirements. The *N*-methyl amide linkage between the cyclohexane ring and the methylenearyl moiety has been replaced by the reversed amide, ester, aminomethylene, thioamide, and the secondary amide analogues. The best of these isosteres is the *N*-methyl amide. Substitution of the pyrrolidine ring of PD117302 in the 3-position with a hydroxymethyl group increases the μ/κ selectivity compared to the unsubstituted compound, with a μ/κ selectivity of 244. The cis-fused 4,5-dimethyl ether substituted cyclohexane analogue *trans*-(±)-*N*-methyl-*N*-[4,5-dimethoxy-2-(1-pyrrolidinyl)-cyclohexyl]benzo[*b*]thiophene-4-acetamide (**32**) has high in vitro κ opioid receptor affinity (K_i = 18 nM) and has exceptionally potent analgesic activity comparable with that of morphine itself on iv administration to rats.

Experimental Section

Melting points were determined with a Reichart Thermovar hot-stage apparatus and are uncorrected. Proton NMR spectra were recorded on a Bruker AM 300 spectrometer; chemical shifts were recorded in parts per million downfield from tetramethylsilane. IR spectra were recorded as a liquid film on a sodium chloride disk with a Perkin-Elmer 1750 spectrophotometer. Optical rotations were determined in dichloromethane solution with a Perkin-Elmer 241 polarimeter. Silica gel used for chromatography was Kieselgel-60 (230–400 mesh) (E. Merck A.G., Darmstadt, Germany). Mass spectra were recorded with electron impact on a Finnegan 4500 spectrometer.

Benzo[*b*]thiophene-3-acetic acid was obtained from the Maybridge Chemical Co. *N*-(2-Aminoethyl)pyrrolidine was obtained from the Aldrich Chemical Co.

Computer modeling calculations were run with the CHEM-X molecular modeling package supplied by Chemical Design Ltd., Oxford, U.K.

The dipole moment calculations were done with the CNDO molecular orbital method with the heterocyclic moieties aligned in a similar way. Further studies on the dipole moments of κ ligands are in progress and will be published in full elsewhere.

General Method for Formation of Amides 5–16 and Ester 22. A solution of the aromatic acetyl chloride (1.0 mmol) (prepared by the action of thionyl chloride on the aromatic acetic acid) in dichloromethane (5 mL) was added dropwise to a stirred solution of the diamine (1.0 mmol) in dichloromethane at 0 °C. After stirring of the mixture for 10 min, diethyl ether was added until no further precipitate resulted. The product was collected by filtration, washed with diethyl ether, and dried in vacuo to yield the amide hydrochloride. Ester **22** was prepared by using the same procedure with *trans*-2-(1-pyrrolidinyl)cyclohexanol (**21**) instead of the diamine.

Products were purified by recrystallization (recrystallization solvents are listed in Table V) or by medium-pressure chromatography on silica gel using dichloromethane–methanol as eluant.

Compounds **13** and **14** are each a mixture of two diastereoisomers.

(±)-*trans*-*N*-Methyl-[2-(1-pyrrolidinyl)cyclohexyl]-benzo[*b*]thiophene-4-ethanethioamide Monohydrochloride (19). Amino amide **1**[1] (3.8 g, 10 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent) (3.8 g, 9.3 mmol) and toluene (100 mL) were mixed and heated to reflux for 14 h. The resulting mixture was dissolved in dichloromethane (200 mL), washed with aqueous potassium carbonate (2 × 200 mL), and purified by medium-pressure chromatography (silica gel) with dichloromethane–methanol (25:1) as eluant to give an oil which was dissolved in diethyl ether–dichloromethane (4:1) (10 mL) and treated with a solution of hydrogen chloride in diethyl ether to give **19** (300 mg, 7%): IR (neat) 2931, 1595, 1570, 1493 cm^{-1}; MS (EI) *m/e* 372 (M^+).

***trans*-(±)-*N*-Methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-benzo[*b*]thiophene-4-ethanamine Dihydrochloride (20).** The parent amino amide **1**[1] (1.0 g, 2.7 mmol) in tetrahydrofuran (50 mL) was added over 8 min to a stirred slurry of lithium aluminum hydride (234 mg, 6.2 mmol) in tetrahydrofuran (50 mL) at 0 °C. The mixture was heated to reflux for 6 h, quenched with water (1 mL), filtered, evaporated, and purified by medium-pressure chromatography using dichloromethane–methanol (10:1) as eluant. The resulting oil was converted to the dihydrochloride salt as described for **19** above to give **20** (0.71 g, 60%): IR (neat) 3380, 2950, 2600, 1450 cm^{-1}; MS (EI) *m/e* 342 (M^+).

(±)-Bis(*trans*,*trans*)-[1-[2-[(4-benzofuranylacetyl)-methylamino]cyclohexyl]-3-pyrrolidinyl]methyl Pentanedioic Acid Ester Dihydrochloride (17) and (±)-Bis(*trans*,-

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Table V. Physical Data for Previously Unreported Compounds

no.	molecular formula	analysis	mp, °C	recryst solvent
5	$C_{21}H_{28}N_2OS\cdot HCl\cdot 0.5H_2O$	C,H,N,S	221–223.5	CH_2Cl_2–Et_2O
6	$C_{21}H_{28}N_2OS\cdot HCl\cdot 0.45CH_2Cl_2$	C,H,N	270–272	CH_2Cl_2–Et_2O
7	$C_{21}H_{28}N_2OS\cdot 1.5HCl$	C,H,N	159–165	CH_2Cl_2–Et_2O
8	$C_{21}H_{28}N_2OS\cdot 1.25HCl$	C,H,N	182–185	CH_2Cl_2–Et_2O
9	$C_{21}H_{29}N_3O$	*a*	238–244	$(CH_3)_2CHOH$–EtOAc
10	$C_{20}H_{26}N_2OS\cdot HCl\cdot 0.4H_2O$	C,H,N	186–189	CH_2Cl_2–Et_2O
11	$C_{22}H_{30}N_2OS\cdot HCl$	*b*	170–178	CH_2Cl_2–Et_2O
12	$C_{20}H_{26}N_2O_2\cdot HCl\cdot 0.2H_2O$	C,H,N	174–177	CH_2Cl–Et_2O
13	$C_{22}H_{30}N_2O_2S\cdot HCl\cdot 0.5H_2O$	C,H,N	190–195	CH_2Cl_2–Et_2O
14	$C_{22}H_{30}N_2O_3\cdot HCl\cdot 0.5H_2O$	C,H,N,Cl	117–148	$(CH_3)_2CHOH$
15	$C_{22}H_{30}N_2O_2S\cdot HCl\cdot 0.6H_2O$	C,H,N	121–129	CH_2Cl_2–Et_2O
16	$C_{22}H_{30}N_2O_2S\cdot HCl\cdot H_2O$	C,H,N	117–124	CH_2Cl_2–Et_2O
17	$C_{49}H_{64}N_4O_8\cdot 2HCl\cdot 2.2H_2O$	C,H,N,Cl	132–137	CH_2Cl_2–Et_2O
18	$C_{48}H_{62}N_4O_8\cdot 2HCl\cdot 1.7H_2O$	C,H,N	138–144	CH_2Cl_2–Et_2O
19	$C_{21}H_{28}N_2S_2\cdot HCl\cdot 0.4H_2O$	C,H,N	138–144	CH_2Cl_2–Et_2O
20	$C_{21}H_{30}N_2S\cdot 2HCl\cdot 0.4H_2O$	C,H,N	*d*	CH_2Cl_2–Et_2O
22	$C_{20}H_{25}NO_2S\cdot HCl\cdot 0.4H_2O$	C,H,N,Cl	146–166	EtOAc
24	$C_{21}H_{28}N_2O_2$	HRMS[c]	*d*	
25	$C_{17}H_{15}NO_3$	C,H,N	71–73.5	Et_2O
26	$C_{10}H_{11}NO\cdot 0.5C_7H_8SO_3$	C,H,N,S	128–130	$(CH_3)_2CHOH$–Et_2O
28	$C_{16}H_{20}N_2OS$	C,H,N	119–121.5	CH_2Cl_2–Et_2O
29	$C_{21}H_{30}N_2OS\cdot HCl\cdot 0.3H_2O$	C,H,N	73–79	CH_2Cl_2–Et_2O
31	$C_{23}H_{32}N_2O_4\cdot HCl\cdot 0.5H_2O$	C,H,N	201–205	CH_2Cl_2–Et_2O
32	$C_{23}H_{32}N_2O_3S\cdot HCl\cdot 1.25H_2O$	C,H,N,S	219–220	CH_2Cl_2–Et_2O
33	$C_{21}H_{26}N_2OS\cdot HCl\cdot H_2O$	C,H,N	42–45	CH_2Cl_2–Et_2O

[a] Insufficient compound obtained for elemental analysis. MS (EI): $C_{21}H_{29}N_3O$ requires 339, found 339 (10%). NMR ($CDCl_3$): δ 8.35 (1 H, 1 Ar-H), 7.30–6.75 (5 H, 4 Ar-H and 1 NH), 4.20 (2 H, s, CH_2Ar), 4.0–2.7 (6 H, br m, 6 NCH), 3.35 (3 H, s, NCH_3), 2.25–1.20 (12 H, m, 12 CH). IR (liquid film on NaCl disk): 1640 cm^{-1}. [b] Insufficient compound obtained for elemental analysis. MS (EI): $C_{22}H_{30}N_2OS$ requires 370; found 370 (23%). NMR (DMSO-d_6): δ 7.9–7.15 (5 H, m, Ar-H), 4.70 (1 H, br m, 1 NCH), 4.28 (1 H, d, J = 16 Hz, 1 C*H*$_2$Ar), 4.03 (1 H, d, J = 16 Hz, 1 C*H*$_2$Ar), 3.60 (2 H, br m, 2 NC*H*), 3.28 (2 H, m, 2 NC*H*), 3.10–2.90 (1 H, m, 1 NCH), 3.02 (3 H, s, CH_3), 2.05–1.35 (14 H, m, 14 CCH). IR (Numol mull): 1641 cm^{-1}. [c] High-resolution MS (EI^+): $C_{21}H_{28}N_2O_2$ requires 340.2178, found 340.2175. NMR ($CDCl_3$): δ 7.65–6.85 (5 H, m, Ar-H), 5.00 (1 H, d, J = 15 Hz, 1 C*H*$_2$Ar), 4.62 (1 H, d, J = 15 Hz, 1 C*H*$_2$Ar), 3.85–2.60 (4 H, m), 3.25 (3 H, s, CH_3), 2.30–1.10 (14 H, m). IR (neat): 1634 cm^{-1}. [d] Hygroscopic, melting point determination not possible.

***trans*)-[1-[2-[(4-benzofuranylacetyl)methylamino]cyclohexyl]-3-pyrrolidinyl]methyl Butanedioic Acid Ester Dihydrochloride (18).** Amino alcohol **14** (140 mg, 0.34 mmol) was dissolved in dichloromethane (2 mL) with pyridine (0.16 mL, 2 mmol), 4-(dimethylamino)pyridine (5 mg, 0.04 mmol), and glutaryl dichloride (0.037 mL, 0.29 mmol) and heated to reflux for 2 h.

The resulting mixture was purified by medium-pressure chromatography (silica gel) using dichloromethane–methanol (15:1) as eluant to give an oil which was converted into the dihydrochloride salt as described for **19** above to give **17** (60 mg, 38%) as a mixture of diastereoisomers: IR (neat) 1734, 1645 cm^{-1}; MS (EI) m/e 837 (M^+).

Compound **18** (75 mg, 49%) was prepared by the same procedure using succinyl chloride instead of glutaryl dichloride: IR (neat) 1733, 1633 cm^{-1}.

***N*-Methyl-4-benzo[*b*]furanmethanamine (26).** Benzo[*b*]furan-4-acetic acid[1] (12 g, 68 mmol) was dissolved in toluene (40 mL) and triethylamine (14 mL), treated with diphenyl phosphorazidate (15 mL, 70 mmol), heated slowly to 70–80 °C for 40 min, and then cooled to 0 °C and treated with benzyl alcohol (20 mL, 190 mmol). The mixture was heated to 80 °C for 3 min and then poured into dichloromethane (200 mL) and washed with 1 N hydrochloric acid (200 mL) and then with 1 N potassium hydroxide (200 mL) to give a brown oil (28 g) which was recrystallized twice (diethyl ether–hexane and then diethyl ether) before chromatography on silica gel (dichloromethane) which gave (4-benzofuranylmethyl)carbamic acid, phenylmethyl ester (**25**) as a pale yellow solid (4.0 g, 14 mmol, 21%): mp 71–73.5 °C; IR (neat) 3312, 1682 cm^{-1}; ^1H NMR δ ($CDCl_3$) 7.6–7.05 (10 H, m), 6.85 (1 H, s, NH), 5.15 (2 H, s, CH_2Ph), 4.65 (2 H, d, J = 7 Hz, CH_2Ar). Anal. ($C_{17}H_{15}NO_3$) C, H, N. The above solid (3.5 g, 12 mmol) and anisole (3 mL, 28 mmol) were dissolved in hydrogen bromide in acetic acid [20 mL of a solution containing hydrogen bromide (40 g) and acetic acid (100 g)] at room temperature. After 50 min the mixture was made basic with 10 N potassium hydroxide solution and extracted with diethyl ether to give benzofuranmethanamine as an oil (0.75 g). This was unstable and was immediately dissolved in ethanol (1 mL) and treated with ethyl formate (10 mL, 124 mmol) and triethylamine (1.2 mL, 8.6 mmol) and heated to reflux for 50 min. The mixture was concentrated in vacuo to give an oil (IR (neat) 1667 cm^{-1}) which was dissolved in diethyl ether (5 mL), treated with a suspension of lithium aluminum hydride (0.50 g, 13 mmol), and heated to reflux for 12 h. The resulting mixture was quenched with water (1.0 mL), filtered, and concentrated to give *N*-methyl-4-benzofuranmethanamine (**26**) as an oil (0.50 g, 3.1 mmol, 22%): IR 2792, 1613, 1137 cm^{-1}; NMR δ ($CDCl_3$, 300 MHz) 7.62 (1 H, d, J = 2 Hz, C_2-H), 7.40 (1 H, d, J = 10, C_7-H), 7.20 (2 H, m, C_6-H and C_5-H), 6.88 (1 H, d, J = 2 Hz, C_3-H), 4.00 (2 H, br s, CH_2), 2.49 (4 H, br s, $NHCH_3$). An analytically pure sample was obtained by treating **26** (75 mg, 0.47 mmol) in isopropyl alcohol (1 mL) with toluenesulfonic acid monohydrate (94 mg, 0.49 mmol). Recrystallization (isopropyl alcohol–diethyl ether) gave the hemitosylate salt (68 mg, 0.27 mmol): mp 128–130 °C. Anal. ($C_{10}H_{11}NO\cdot 0.5C_7H_8SO_3$) C, H, N, S.

***trans*-*N*-(4-Benzofuranylmethyl)-*N*-methyl-2-(1-pyrrolidinyl)cyclohexanecarboxamide Monohydrochloride (24).** Amino alcohol **21** (0.96 g, 5.7 mmol) was dissolved in tetrahydrofuran (30 mL), treated with sodium hydride (0.15 g, of 80% dispersion in oil, 5.2 mmol), heated to reflux for 100 min, and then cooled to 5 °C and treated with methanesulfonyl chloride (0.45 mL, 5.8 mmol) over 3 min. The mixture was stirred for 90 min at 12–15 °C and then treated with *N*,*N*-dimethylformamide (15 mL), triethylamine (0.8 mL, 5.7 mmol), and a solution of potassium cyanide (0.37 g, 5.7 mmol) in water (20 mL) and heated at 65–80 °C for 2 h. The resulting mixture was poured into aqueous potassium carbonate (50 mL) and extracted with diethyl ether (4 × 60 mL) to give an oil (0.5 g) which showed IR (neat) 2240 cm^{-1}. This oil was dissolved in water (1 mL) and 98% sulfuric acid (1 mL) and heated to 110 °C for 80 min and after neutralization the mixture was chromatographed on silica gel with dichloromethane–methanol (4:1) as eluant to give *trans*-2-(1-pyrrolidinyl)cyclohexanecarboxylic acid (**23**) (197 mg, 1 mmol, 17%): IR (neat) 1593 cm^{-1}; NMR (DMSO-d_6) δ 3.3 (1 H, m, obscured, COOH), 2.75 (5 H, m, 2 CH_2N, CHN), 2.10 (2 H, m, C*H*COOH, one of CH_2), 1.9–1.7 (6 H, m, 3 CH_2), 1.6 (1 H, m, one of CH_2), 1.4–1.1 (4 H, m, 2 CH_2).

Amino acid **23** (197 mg, 1.0 mmol) was treated with thionyl chloride followed by the above amine (**26**), according to the general method for forming amides described above, to give **24** (30 mg, 8%): IR (neat) 1634 cm^{-1}; MS (EI) m/e 340.2176 ($C_{21}H_{28}N_2O_2$ requires m/e 340.2175).

Biological Assays. μ and κ receptor binding assays and analgesic assay were performed as previously described.[1]

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