manner except for the addition of 3. Following this incubation, the homogenates were washed three times by centrifugation at 30000g for 10 min followed by resuspension in 10 mL of 50 mM phosphate buffer. For measurement of radioligand binding, the final pellets were resuspended to a concentration of 1.0 mg of tissue (original wet weight) per mL of 50 mM phosphate buffer.

Additional radioligand binding assays were carried out on homogenates of the brains of mice which had been treated in vivo with 3. For these experiments, mice were injected intravenously (tail vein) with the parent mustard 3 at a dose of 50 μmol/kg. The mice were killed 4.3 h later, and the forebrain and hindbrain were separated by a midcollicular transection. The forebrain and hindbrain were homogenized in approximately 30 and 100 volumes, respectively, of 50 mM phosphate buffer. These homogenates were washed three times by centrifugation at 30000g for 10 min followed by resuspension in fresh 50 mM phosphate buffer. For measurement of radioligand binding, the final pellets from the forebrain and hindbrain were resuspended to concentrations of 1.0 and 4.0 mg of tissue (original wet weight) per mL of 50 mM phosphate buffer, respectively.

The binding of the specific muscarinic antagonists (-)-[^{3}H]QNB (33.4 Ci/mmol, New England Nuclear) and (-)-[^{3}H]NMS (84.8 Ci/mmol, New England Nuclear) was measured essentially as described previously.[20] An aliquot (1.0 mL) of brain homogenate was incubated in a final volume of 2.0 mL containing 50 mM phosphate buffer. The incubation with (-)-[^{3}H]QNB was 60 min at 37 °C whereas that with (-)-[^{3}H]NMS was 30 min at 30 °C. Nonspecific binding was defined as the residual binding in the presence of 10 μM atropine. Protein was measured by the method of Lowry et al.[21] using bovine serum albumin as the standard.

Acknowledgment. This work was supported by USPHS Grants GM-37816 and MH-17691. Additional support (to C.M.) was provided by IF's Stiftelse and Sederholms Stipendiefond. The excellent secretarial assistance of Holly Batal is gratefully acknowledged.

Registry No. 2, 123567-32-8; 2·oxalate, 123567-33-9; 3, 123567-34-0; 3·oxalate, 123567-35-1; 4 (X = Cl), 123567-36-2; 4 (X = Br), 123567-37-3; 5, 123567-38-4; 5·oxalate, 123567-39-5; 2-propynyl *N*-(3-chlorophenyl)carbamate, 3004-45-3; *N*-methyl-*N*-(2-hydroxyethyl)amine, 109-83-1.

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Highly Selective κ-Opioid Analgesics. 3. Synthesis and Structure–Activity Relationships of Novel *N*-[2-(1-Pyrrolidinyl)-4- or -5-substituted-cyclohexyl]arylacetamide Derivatives

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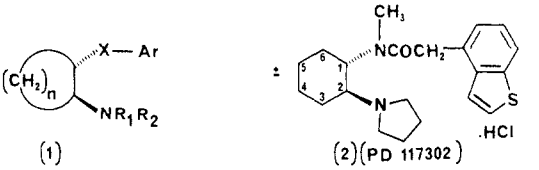
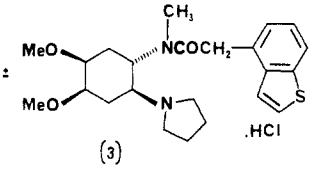
This paper describes the chemical synthesis, μ/κ opioid receptor selectivity and analgesic activity of 14 novel *N*-[2-(1-pyrrolidinyl)-4- or -5-substituted-cyclohexyl]arylacetamide derivatives. The prototype κ-selective agonist, PD117302 (*trans*-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzo[*b*]thiophene-4-acetamide, 2) has been regio- and stereoselectively substituted in the C-4 and C-5 positions of the cyclohexyl ring with the methyl ether and spiro tetrahydrofuran groups. It is observed that optimal μ/κ-receptor selectivity is obtained when the oxygen atom of the methyl ether or the tetrahydrofuran ring is joined to the equatorial C-4 position. Hence, (-)-(5β,7β,8α)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]benzo[*b*]furan-4-acetamide monohydrochloride (21) has exceptionally high κ opioid receptor affinity and selectivity in vitro (κ K_i = 0.83 nM, μ/κ ratio = 1520) is the most potent κ-selective analgesic ever reported. Compound 21 is 25 times more potent than morphine and 17 times more potent than U-62066 (spiradoline, 19) when assayed by the rat paw pressure test by intravenous administration (MPE_{50} = 0.024, 0.6, and 0.4 mg/kg, respectively).

Previous studies[1-9] have established that certain *N*-(2-aminocyclohexyl)arylacetamides with general structure 1 exhibit high in vitro selectivity and affinity for the κ-opioid receptor. These compounds elicit potent analgesia in rodent tests without the undesired μ-opioid effects (respiratory depression, dependence-inducing liability, and inhibition of gastrointestinal motility), which characterize morphine and its congeners.[3]





We have previously shown[1,2] that derivatives of the general structure 1 possess high κ opioid receptor binding affinity and high μ/κ selectivity when the aromatic group

(1) Part 2: Halfpenny, P. R.; Hill, R. G.; Horwell, D. C.; Hughes, J.; Hunter, J. C.; Johnson, S.; Rees, D. C. *J. Med. Chem.* **1989**, *32*, 1620.
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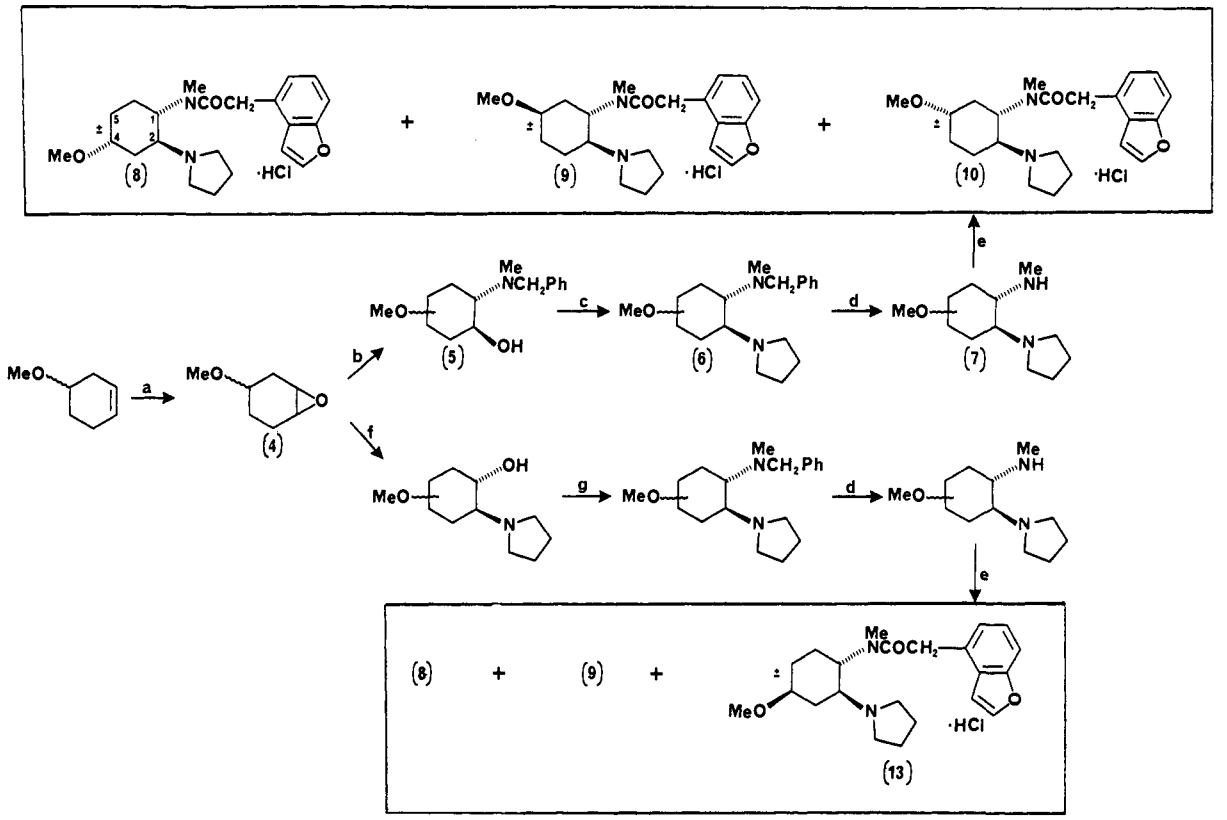
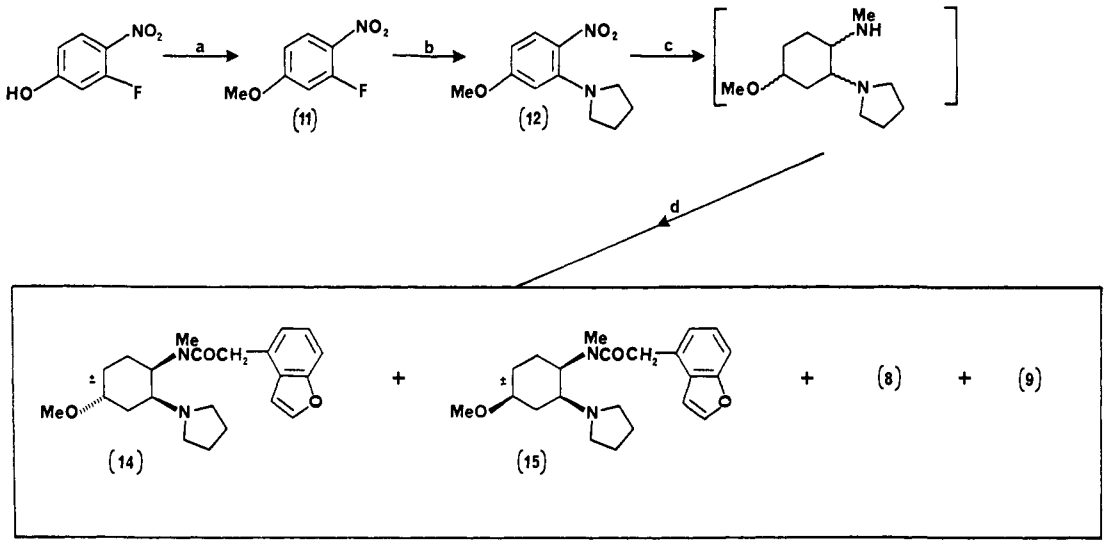
Scheme I[a]



[a] Reagents: a = MCPBA; b = *N*-benzylmethylamine; c = (i) mesyl chloride, (ii) pyrrolidine; d = H_2; e = 4-benzofuranacetyl chloride; f = pyrrolidine; g = (i) mesyl chloride, (ii) *N*-benzylmethylamine.

Scheme II[a]



[a] Reagents: a = MeI; b = pyrrolidine; c = (i) H_2, (ii) ethyl formate, (iii) lithium aluminum hydride; d = 4-benzofuranacetyl chloride.

is a benzo[*b*]thiophene or benzo[*b*]furan attached via the 4-position to the carbocyclic ring by an *N*-methylacetamide (X = $-NMeCOCH_2-$). The optimal carbocyclic ring size has been found to be cyclohexyl (n = 4) and the basic amine group a pyrrolidine (R_1,R_2 = cyclo-C_4H_8). For example, compound **2** (PD 117302) has been shown to have nanomolar affinity for the κ-opioid receptor (K_i = 3.7 nM) and a μ/κ ratio = 110[1] [$K_i(\mu)/K_i(\kappa)$]. The compound is approximately $^1/_2$ as potent as morphine in the rat paw pressure test for analgesia after oral administration.

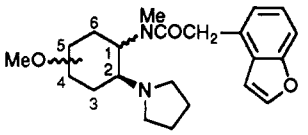
Furthermore, compound **3**, which has two cis-fused geminally substituted methoxy groups attached to the cyclohexane ring, has high κ-opioid affinity and selectivity (κ K_i = 16 nM, μ/κ ratio = 51) and is equipotent with morphine as an analgesic in the rat paw pressure test for analgesia after intravenous administration (MPE_{50} = 0.8 and 0.6 mg/kg, respectively).[2] MPE_{50} is defined as the dose required to produce 50% of the maximum possible analgesic effect.

The objective of this study is to explore further the SAR of these ether substituents. This objective has been achieved by (i) devising a new synthetic strategy to provide derivatives of **3** with a single methoxy substituent at either the C-4 or C-5 position and (ii) by preparing compounds in which the ether oxygen is incorporated into a spiro tetrahydrofuran ring fused to position C-4 or C-5.

Table I. Physical Data

no.	molecular formula	anal.	mp/bp, °C	cryst solv
4	$C_7H_{12}O_2$	C, H	70–77 (20 mmHg)	
5	$C_{15}H_{23}NO_2$	C, H, N	133–134 (0.04 mmHg)	
6	$C_{19}H_{30}N_2O{\cdot}0.33H_2O$	C, H, N	151–155 (0.15 mmHg)	
7	$C_{12}H_{24}N_2OC_7H_8SO_3$	C, H, N, S	120–136	$(CH_3)_2CHOH$–Et_2O
8	$C_{22}H_{30}N_2O_3{\cdot}HCl{\cdot}0.65H_2O$	C, H, N, Cl	200–208	CH_2Cl_2–Et_2O
9	$C_{22}H_{30}N_2O_3{\cdot}HCl{\cdot}0.77H_2O$	C, H, N, Cl	102–106	CH_2Cl_2–Et_2O
10	$C_{22}H_{30}N_2O_3{\cdot}HCl{\cdot}0.5H_2O$	C, H, N	197–209	CH_2Cl_2–Et_2O
11	$C_7H_6FNO_3$	C, H, N, F	47–49	Et_2O–H_2O
12	$C_{11}H_{14}N_2O_3$	C, H, N	46–48.5	PhMe
13	$C_{22}H_{30}N_2O_3{\cdot}HCl{\cdot}0.89H_2O$	C, H, N	150–165	CH_2Cl_2–Et_2O
14	$C_{22}H_{30}N_2O_3{\cdot}HCl{\cdot}0.5H_2O$	C, H, N	120–134	CH_2Cl_2–Et_2O
15	$C_{22}H_{30}N_2O_3{\cdot}HCl$	C, H, N	131–156	CH_2Cl_2–Et_2O
17	$C_{24}H_{32}N_2O_3{\cdot}HCl{\cdot}0.65H_2O$	C, H, N	187–190	CH_2Cl_2–Et_2O
18	$C_{24}H_{32}N_2O_2S{\cdot}HCl{\cdot}0.25H_2O$	C, H, N	231–234	$(CH_3)_2CHOH$
20	$C_{14}H_{26}N_2O{\cdot}C_{20}H_{18}O_8{\cdot}0.2H_2O$	C, H, N	151–152	$(CH_3)_2CHOH$
21	$C_{24}H_{32}N_2O_3{\cdot}HCl{\cdot}H_2O$	C, H, N, Cl	117–124	CH_2Cl_2–Et_2O
22	$C_{24}H_{32}N_2O_3{\cdot}HCl{\cdot}H_2O$	C, N, H, Cl	123–125	CH_2Cl_2–Et_2O
23	$C_{24}H_{32}N_2O_2S{\cdot}HCl{\cdot}0.6H_2O{\cdot}0.05Et_2O$	C, H, N	135–140	CH_2Cl_2–Et_2O
25	$C_{24}H_{32}N_2O_3{\cdot}HCl{\cdot}0.4H_2O$	C, H, N	125–130	CH_2Cl_2–Et_2O
26	$C_{24}H_{32}N_2O_2S{\cdot}HCl{\cdot}0.8H_2O$	C, H, N	140–145	CH_2Cl_2–Et_2O

Table II. κ- and μ-Opioid Binding and Rat Paw Pressure Analgesia Assay for Monomethoxy Derivatives



no.	position of OMe	C_1–C_2 stereochemistry	opioid receptor binding affinity, K_i,[a] nM κ	opioid receptor binding affinity, K_i,[a] nM μ	μ/κ ratio[d]	rat paw pressure[b] assay (iv): MPE_{50}, mg/kg
8	4-α	trans	22.0 ± 6.0	2200 ± 200	100	0.07
9	5-β	trans	135 ± 30	8780 ± 3700	65	5.6
10	5-α	trans	24 ± 4	4300 ± 400	179	1.5
13	4-β	trans	7.1 ± 4.2	3300 ± 1900	465	0.07
14	4-α	cis	69 ± 10	4610 ± 283	67	>3
15	4-β	cis	85 ± 9.6	3180 ± 570	37	c

[a] Each K_i value represents the mean from concentration–response curves performed in triplicate. [b] MPE_{50} is defined as 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] Not tested. [d] μ/κ ratio = $K_i(\mu)/K_i(\kappa)$.

Synthesis

The methoxy substituted derivatives (**8–10** and **13–15**) were prepared according to the routes described in Schemes I and II. 4-Methoxycyclohexene[10] was converted into diamine **7**, which was shown by ^1H NMR spectroscopy to consist of a mixture of three (racemic) isomers. This mixture was treated with 4-benzo[*b*]furanacetyl chloride to give, after silica gel chromatography, **8–10** (Scheme I). Compound **13** was prepared from 4-methoxycyclohexene by an analogous procedure to that described in Scheme I except that pyrrolidine was used instead of *N*-benzylmethylamine and vice versa.

Scheme II describes a shorter route to **8** and **13** in which the key step is a catalytic hydrogenation of the aromatic precursor **12** to give a mixture of substituted cyclohexyl diamines. In this route, acylation followed by silica gel chromatography produced trans isomers **8** and **13** together with cis substituted amino amides **14** and **15**. Physical data of new compounds are shown in Table I.

Diamines **16**, **20**, and **24** were prepared according to the method of Kaplan[11] and coupled with 4-benzo[*b*]-thiopheneacetic acid (Aldrich Chemical Co.) or 4-benzo-[*b*]furanacetic acid[2] via the corresponding acyl chlorides to give the corresponding amides (**17–19**, **21–23**, **25**, and **26**) (Scheme III).

Results and Discussion

1. Monomethoxy Derivatives. It has been previously reported[1] that bismethoxy compound **3** represents a chemically novel κ-selective opioid analgesic (vide supra). To investigate, in more detail, the effect of the methoxy groups on the κ-receptor affinity, the four monomethoxy derivatives (**8–10**, **13**) were synthesized. From these four isomers the highest κ opioid binding affinity and selectivity is obtained when the methoxy group is in the C-4 equatorial position (**13**, κ K_i = 7.1 nM, μ K_i = 3300 nM, μ/κ ratio = 465) and the lowest binding affinity and selectivity is recorded for the C-5 axial isomer (**9**, κ K_i = 135 nM, μ/κ ratio = 65) (Table II). Furthermore, **13** is 20 times more potent than cyclohexane compound **2**, 9 times more potent than morphine, and 11 times more potent than bismethoxy derivative **3** in the rat paw pressure test for analgesic activity after iv administration (MPE_{50} = 0.07, 1.4, 0.6, 0.8 mg/kg, respectively). When the 1,2-nitrogen atom moieties are fused cis instead of trans, the κ-receptor affinity and selectivity are reduced (compounds **14** and **15** have κ K_i = 69, 85 nM, μ/κ ratio = 67, 37, respectively).

It is concluded that a single methoxy group substituted on the cyclohexane ring can increase the κ opioid analgesic potency compared to those of the corresponding disubstituted or unsubstituted analogues in these cyclohexylarylacetamides. This is also a stereoselective effect and

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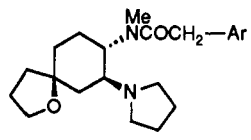
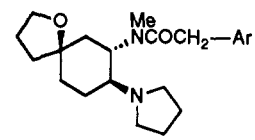
(11) Kaplan, L. J. U.S. Patent 4,438,130, March 20, 1984; *Chem. Abstr.* **1984**, *101*, 54912*w*.

Table III. κ- and μ-Opioid Binding and Rat Paw Pressure Analgesia Assay for Spiroether Derivatives



isomer 1

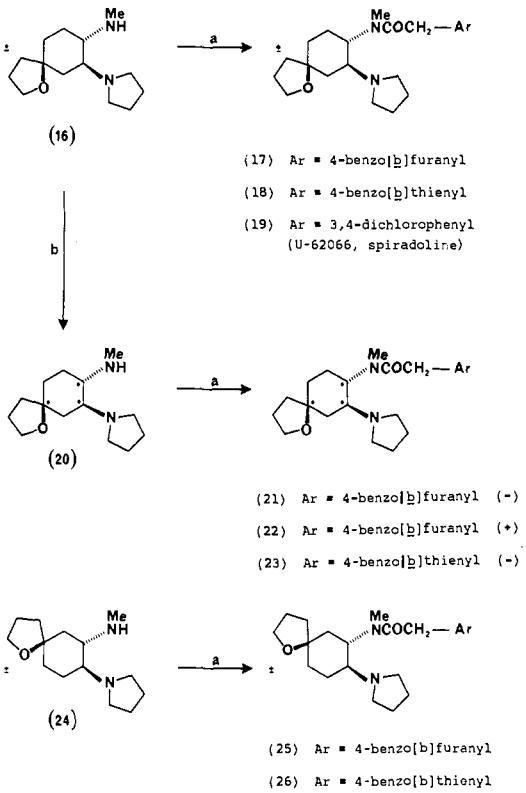


isomer 2

no.	isomer	Ar	opioid receptor binding affinity: K_i[a] nM κ	opioid receptor binding affinity: K_i[a] nM μ	μ/κ ratio[d]	rat paw pressure[b] assay (iv): MPE_{50}, mg/kg
17	1 (±)	4-benzo[*b*]furanyl	2.57 ± 0.47	539 ± 106	210	0.027
18	1 (±)	4-benzo[*b*]thienyl	1.75 ± 0.67	112 ± 30	64	0.04
19	1 (±)	3,4-dichlorophenyl (U-62066)	7.6 ± 0.9	82.7 ± 12	11	0.4
21[e]	1 (−)	4-benzo[*b*]furanyl	0.83 ± 0.06	1260 ± 170	1520	0.024
22	1 (+)	4-benzo[*b*]furanyl	1630 ± 260	623 ± 60	0.38	2.5
23	1 (−)	4-benzo[*b*]thienyl	2.48 ± 0.75	418 ± 13	169	0.05
25	2 (±)	4-benzo[*b*]furanyl	81.3 ± 1.5	21700 ± 900	267	*c*
26	2 (±)	4-benzo[*b*]thienyl	58.9 ± 6.4	9300 ± 2620	158	>3.3

[a-d] See Table II. [e] δ opioid receptor binding affinity of compound 21 was determined: K_i = 1036 ± 77 nM.

Scheme III[a]



[a] Reagents: a = $ArCH_2COCl$; b = di-*p*-toluoyltartaric acid.[11]

the optimal orientation for the methoxy group is the C-4 equatorial position (compound **13**).

2. Spiro Ether Derivatives (17, 18, 21–23, 25, 26). Von Voigtlander et al. have reported that U-62066 (spiradoline, **19**) and other derivatives which have a spirocyclic tetrahydrofuran ring fused to the C-4 carbon of the cyclohexane moiety are κ-opioid analgesics.[4] This spiro ether modification in this series gives **17** and **18**, which have high κ affinity (κ K_i = 2.57, 1.75 nM, μ/κ ratio = 210, 64, respectively) and high analgesic potency in the rat paw pressure test via iv administration (MPE_{50} = 0.027 and 0.04 mg/kg, respectively).

Since the analgesic activity of morphine and the racemic κ agonist **2** is known to be a property of only one enantiomer,[2] both enantiomers of **17** were prepared for comparison. (−)-Enantiomer **21** has exceptionally high κ selectivity in vitro (κ K_i = 0.83 nM, μ/κ ratio = 1520) and is the most potent κ analgesic to date as assayed by the rat paw pressure test via iv administration. This exceptionally potent compound is 25 times more potent than morphine and 17 times more potent than U-62066 (spiradoline, **19**) (MPE_{50} = 0.024, 0.6, 0.4 mg/kg, respectively). (+)-Enantiomer **22** is neither κ selective (μ/κ ratio = 0.38) nor a potent analgesic (Table III). (−)-Enantiomer **23** of racemate **18** was also found to be a potent κ-selective opioid analgesic (MPE_{50} = 0.05 mg/kg).

Regioisomerically substituted spiro ethers **25** and **26** (Table III) have significantly weaker affinity for the κ receptor (K_i = 81.3, 58.9 nM, respectively), showing that there is a high degree of selectivity required for interaction between the κ receptor and this spiro ether moiety.

Conclusion

It is concluded that the analgesic activity of these selective κ opioid *N*-[2-(1-pyrrolidinyl)cyclohexyl]arylacetamides is enhanced significantly when the oxygen atom of a methyl ether or a tetrahydrofuran ring is joined to the equatorial C-4 position.

Similar substitutions at the axial C-4 position or at the C-5 position do not produce such potent analgesics, indicating that stereoselective binding to the κ receptor by the ether oxygen atom may be an important factor. Compound **21** [(−)-(5β,7β,8α)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl]benzo[*b*]furan-4-acetamide monohydrochloride] is the most potent κ-selective opioid analgesic yet reported, being 25 times more potent than morphine (rat paw pressure test, iv administration).

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 using the compound (neat) on a sodium chloride disk with a Perkin-Elmer 1750 spectrophotometer. Optical rotations were determined in dichloromethane solution using a Perkin-Elmer 241 polarimeter. Silica gel used for chromatography was Kiesel gel-60 (230–400 mesh, E. Merck A.G., Darmstadt, Germany). Mass spectra were recorded with a Finnegan 4500 spectrometer.

3-Methoxy-7-oxabicyclo[4.1.0]heptane (4). *m*-Chloroperoxybenzoic acid (3.5 g, 20 mmol) in 1:1 dichloromethane–carbon tetrachloride (70 mL) was added over 25 min to a stirred solution of 4-methoxycyclohexene[10] (2.0 g, 18 mmol) in carbon tetrachloride (10 mL) at −5 °C. After 5 h the mixture was allowed to warm to room temperature and after a further 2 h the slurry was filtered. The filtrate was washed with 5% aqueous sodium bisulfite (40

mL) and then saturated aqueous sodium carbonate (2 × 40 mL). The organic phase was dried (K_2CO_3) and distilled with a vigreaux column at atmospheric pressure to give epoxide 4 as a mixture of two diastereoisomers (1.0 g, 7.8 mmol, 43%): bp 175–176 °C (760 mmHg); IR (neat) 2938, 1104 cm^{-1}; NMR δ ($CDCl_3$) 3.22 (1 H, m), 3.24 (s) and 3.22 (s) (total 3 H), 3.05 (2 H, m), 2.3–1.2 (6 H, m); MS *m/e* (EI^+) 129 (11), 111 (35), 97 (65), 58 (100).

***trans*-(±)-4- or -5-Methoxy-2-[methyl(phenylmethyl)amino]cyclohexanol (5).** Epoxide 4 (2.0 g, 15.6 mmol) and *N*-benzylmethylamine (3.0 g, 25 mmol) were dissolved in propan-2-ol (10 mL) and heated to reflux for 20 h. The resulting solution was distilled to give amino alcohols 5 as a mixture of three isomers (3.2 g, 13 mmol, 83%): bp 133–134 °C (0.04 mmHg); IR (neat) 3460, 2939, 2866 cm^{-1}; NMR δ ($CDCl_3$, D_2O) 7.3 (5 H, m), 4.0–2.7 (7 H, m, st s at 3.36, 3.30, 3.29), 2.4–1.2 (10 H, m st s at 2.19, 2.18, 2.15); MS *m/e* (EI^+) 249 (10), 218 (8), 190 (100); ^1H NMR spectra of the individual isomers were obtained after separation by silica gel chromatography using 20:1 dichloromethane–methanol. Isomer A: NMR δ ($CDCl_3$, D_2O) 7.24 (5 H, m), 3.61 (1 H, d, *J* = 14), 3.45 (1 H, d, *J* = 14), 3.43 (1 H, m), 3.36 (3 H, s), 3.18 (1 H, m), 2.36 (1 H, m), 2.19 (3 H, s), 2.27–1.99 (3 H, m), 1.22 (3 H, m). Isomer B: NMR δ ($CDCl_3$, D_2O) 7.28 (5 H, m), 3.70 (1 H, d, *J* = 15 Hz), 3.65 (1 H, m), 3.45 (1 H, m), 3.44 (1 H, d, *J* = 15 Hz), 3.30 (3 H, s), 2.83 (1 H, m), 2.15 (3 H, s), 2.20–1.85 (3 H, m), 1.60 (1 H, m), 1.30 (2 H, m). Isomer C: NMR δ ($CDCl_3$, D_2O) 7.28 (5 H, m), 3.79 (1 H, m), 3.74 (1 H, d, *J* = 15 Hz), 3.55 (1 H, m), 3.45 (1 H, d, *J* = 15 Hz), 3.29 (3 H, s), 2.42 (2 H, m), 2.18 (3 H, s), 2.05 (1 H, m), 1.55 (2 H, m), 1.30 (2 H, m).

***trans*-(±)-4- or -5-Methoxy-*N*-methyl-*N*-(phenylmethyl)-2-(1-pyrrolidinyl)cyclohexanamine (6).** The diastereoisomeric mixture of amino alcohols 5 (8.0 g, 32 mmol) was dissolved in dichloromethane (105 mL), and triethylamine (7.1 mL) was added and the mixture was cooled to −10 °C and treated with methanesulfonyl chloride (2.7 mL, 35 mmol) dropwise such that the temperature remained below −5 °C. After 1.5 h the mixture was concentrated in vacuo to a volume of 20 mL and treated with pyrrolidine (22 mL, 260 mmol) under reflux for 1.5 h. The resulting mixture was poured into aqueous sodium carbonate (700 mL) and extracted with dichloromethane (3 × 100 mL) to give, after concentration, an orange oil (15 g), which was distilled to give *N*-benzyl diamines 6 as a mixture of three (racemic) isomers (9.3 g, 31 mmol, 97%): bp 151–155 °C (0.15 mmHg); IR (neat) 2936, 2791 cm^{-1}; MS *m/e* (EI^+) 303 (5); 287 (10); 270 (10); 84 (100); NMR δ ($CDCl_3$, D_2O) 7.30 (5 H, m), 3.65 (2 H, s), 3.75–3.50 (1 H, m), 3.36 (s) and 3.32 (s) and 3.29 (s) (total 3 H) 2.19 (s) and 2.17 (s) and 2.15 (s) (total 3 H), 3.10–1.00 (16 H, m).

***trans*-(±)-4- or -5-Methoxy-*N*-methyl-2-(1-pyrrolidinyl)cyclohexanamine (7).** *N*-benzyl diamines 6 (3.5 g, 12 mmol) were dissolved in ethanol (50 mL) and treated with 20% palladium hydroxide on carbon (0.94 g) and hydrogen at 50 psi and 60 °C for 2 h. The mixture was filtered through kieselguhr and distilled to give diamines 7 as a mixture of three (racemic) isomers (1.4 g, 6.6 mmol, 55%): bp 84–85 °C (0.3 mbar); IR (neat) 3402, 2942 cm^{-1}; MS *m/e* (EI^+) 197 (5), 180 (10), 84 (100); NMR δ ($CDCl_3$, D_2O) 3.36 (s) and 3.31 (s) and 3.28 (s) (total 3 H), 2.38 (s) and 2.37 (s) (total 3 H), 3.7 (1 H, m), 2.8–0.9 (17 H, m). An analytically pure sample was obtained by treating 7 (212 mg, 1.0 mmol) with *p*-toluenesulfonic acid (190 mg, 1.0 mmol) in propan-2-ol (1 mL) to give a white solid, which was recrystallized from propan-2-ol–diethyl ether, yielding the mono-*p*-toluenesulfonate salt (200 mg, 0.50 mmol, 50%), mp 120–136 °C.

(±)-(1α,2β,4α)-*N*-Methyl-*N*-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-4-benzo[*b*]furanacetamide (8), (±)-(1α,2β,5β)-*N*-Methyl-*N*-[5-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-4-benzo[*b*]furanacetamide (9), and (±)-(1α,2β,5α)-*N*-Methyl-*N*-[5-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-4-benzo[*b*]furanacetamide (10). 4-Benzo[*b*]furanacetic acid (0.76 g, 4.3 mmol) was dissolved in thionyl chloride (3 mL) and heated under reflux for 70 min. The resulting solution was concentrated in vacuo to furnish an oil, which was dissolved in dichloromethane (10 mL), cooled to 0 °C, and treated with a solution of diamines 7 (0.80 g, 3.8 mmol) in dichloromethane (5 mL). The mixture was stirred at room temperature for 10 min and chromatographed on silica gel using 10:1 dichloromethane–methanol to give 8–10. (±)-(1α,2β,5β)-*N*-Methyl-*N*-[5-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-4-benzo[*b*]furanacetamide (9, 150 mg, 0.41 mmol, 11%): IR (neat) 1642 cm^{-1}; MS *m/e* (CI^+) 371 (3), 275 (100); NMR δ ($CDCl_3$) 7.6–6.9 (5 H, m), 4.78 (1 H, m, C_1-H), 3.95 (2 H, m, CH_2), 3.56 (m) and 3.46 (m) (together are 1 H, C_5-H), 3.33 (s) and 3.13 (s) (total 3 H), 2.83 (s) and 2.82 (s) (total 3 H), 2.80–1.20 (15 H, m). (±)-(1α,2β,4α)-*N*-Methyl-*N*-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-4-benzo[*b*]furanacetamide (8, 100 mg, 0.27 mmol, 7%): IR (neat) 1635 cm^{-1}; MS *m/e* (CI^+) 371 (100); NMR δ ($CDCl_3$) 7.55–6.90 (5 H, m), 4.60 (1 H, dt, *J* = 12, 5 Hz, C_1-H), 3.95 (2 H, m, CH_2), 3.7–3.4 (1 H, m, C_4-H), 3.29 (s) and 3.24 (s) (total 3 H), 3.09 (1 H, dt, *J* = 12, 5 Hz, C_2-H), 2.83 (s) and 2.82 (s) (total 3 H), 2.65–1.25 (14 H, m). (±)-(1α,2β,5α)-*N*-Methyl-*N*-[5-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-4-benzo[*b*]furanacetamide (10, 92 mg, 0.25 mmol, 7%): IR (neat) 1640 cm^{-1}; MS *m/e* (CI^+) 371 (100), 339 (38); NMR δ ($CDCl_3$) 7.65–6.85 (5 H, m), 4.65 (1 H, m, C_1-H), 3.95 (2 H, m, CH_2), 3.33 (3 H, s), 3.70–3.20 (2 H, m, C_5-H and C_2-H), 2.83 (s) and 2.80 (s) total 3 H), 2.80–0.80 (14 H, m).

Analytically pure samples were obtained by treating the above compounds (100 mg) in diethyl ether (10 mL) with hydrogen chloride. The resulting precipitates were filtered to give the monohydrochloride salts (100 mg) (see the tables).

(±)-(1β,2β,4β)-*N*-Methyl-*N*-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-4-benzo[*b*]furanacetamide (13). Compound 13 was prepared from epoxides 4 by an analogous procedure to that described above for 8–10 except that pyrrolidine was used instead of *N*-benzylmethylamine and vice versa.

Epoxides 4 (2.0 g, 16 mmol) and pyrrolidine (2.0 g, 28 mmol) were heated to 65 °C for 19 h and then concentrated in vacuo to give an oil (3.0 g), which was dissolved in dichloromethane (30 mL) and treated with triethylamine (2.5 mL, 18 mmol) and then methanesulfonyl chloride (1.28 mL, 16.5 mmol) at 0 °C for 1.5 h. The mixture was diluted with dichloromethane (70 mL) and then washed with water (3 × 70 mL), dried ($MgSO_4$), and evaporated in vacuo to give an oil (3.2 g). This was dissolved in *N*-benzylmethylamine (7 mL), heated to 85–90 °C for 1.5 h, poured into aqueous potassium carbonate, and extracted with dichloromethane (50 mL). Bulb to bulb distillation (oven temperature 170–225 °C/0.05 mbar) gave a mixture of diamines 6 (1.1 g, 3.6 mmol, 22%).

The mixture of diamines 6 (1.1 g, 3.6 mmol) was dissolved in ethanol (30 mL) and treated with 20% palladium hydroxide on carbon (0.21 g) and hydrogen at 53 psi and 40 °C for 5 h to give, as described above, a mixture of diamines 7 (0.60 g, 2.8 mmol, 78%). This mixture of diamines (0.60 g, 2.8 mmol) was treated with 4-benzo[*b*]furanacetyl chloride [generated from 4-benzo[*b*]furanacetic acid (0.6 g, 3.5 mmol) as described above] to give 9 (130 mg, 0.35 mmol, 10%), 8 (25 mg, 0.068 nmol, 2%), and 13 (25 mg, 0.068 mmol, 2%): IR (neat) 1635 cm^{-1}; MS *m/e* (CI^+) 371 (67), 275 (65), 159 (100); NMR δ ($CDCl_3$, NaOD) 7.65–6.85 (5 H, m), 4.55 (1 H, br, C_1-H), 3.95 (2 H, m, CH_2), 3.34 (s) and 3.31 (s) (total 3 H), 2.79 (s) and 2.77 (s) (total 3 H), 3.60–0.80 (16 H, m).

2-Fluoro-4-methoxy-1-nitrobenzene (11). 3-Fluoro-4-nitrophenol (Fluorochem, 10 g, 64 mmol) was dissolved in butan-2-one (60 mL) and treated with potassium carbonate (16.6 g, 120 mmol) at 40 °C for 10 min. The resulting suspension was cooled to 0 °C, treated with methyl iodide (7.5 mL, 120 mmol), heated to 40 °C, for 3 h, and concentrated in vacuo to 20 mL. The mixture was poured into dichloromethane (35 mL) and filtered, and the filtrate was evaporated to give 2-fluoro-4-methoxy-1-nitrobenzene (11) as a white solid (8.0 g, 73%). An analytically pure sample was obtained by recrystallization from aqueous ethanol (4:1): mp 47–49 °C; IR (neat) 1608 cm^{-1}.

4-Methoxy-1-nitro-2-(1-pyrrolidinyl)benzene (12). 2-Fluoro-4-methoxy-1-nitrobenzene (11, 8.0 g, 47 mmol) was added over 10 min to pyrrolidine (25 mL) at room temperature. The resulting mixture was poured into dilute aqueous sodium hydroxide (100 mL) and extracted with dichloromethane (4 × 50 mL) to give an orange solid (7.5 g), which was purified by silica gel chromatography (CH_2Cl_2 as eluant) to give 12 as an orange solid (5.2 g, 50%): mp 46–48.5 °C; IR (neat) 1613, 1569 cm^{-1}.

Hydrogenation of 12, Formation of 8, 13–15. 4-Methoxy-1-nitro-2-(1-pyrrolidinyl)benzene (12, 0.50 g, 2.2 mmol), 5% rhodium on alumina (0.40 g), isopropyl alcohol (75 mL), and 48

wt % aqueous fluoroboric acid (80 mg) were treated with hydrogen at 1000 psi and 80 °C for 8 h. The resulting mixture was filtered, concentrated in vacuo, dissolved in ethyl formate (5 mL) and triethylamine (1 mL), and heated to reflux for 50 min. The mixture was concentrated in vacuo and the residue was dissolved in tetrahydrofuran (5 mL) and then treated with a 1.0 M solution of lithium aluminum hydride in diethyl ether (4 mL) at 30–40 °C for 12 h. Aqueous sodium hydroxide (0.2 mL) was added and the resulting precipitate was removed by filtration. The filtrate was evaporated to give an oil (0.9 g), which, without further purification, was treated with 4-benzo[*b*]furanacetyl chloride [from 4-benzo[*b*]furanacetic acid (430 mg) according to the general method below] to give **14**, **15**, **13**, and **8**. (±)-(1β,2β,4α)-*N*-Methyl-*N*-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-4-benzo[*b*]-furanacetamide (**14**): 54 mg; 0.15 mmol; 7% from **12**; IR (neat) 1636 cm^{-1}; MS *m/e* (CI) 371 (5); NMR δ ($CDCl_3$) 7.61 (1 H, d, *J* = 2.3), 7.40 (1 H, d, *J* = 8), 7.22 (1 H, t, *J* = 8), 7.09 (1 H, d, *J* = 8), 6.90 (1 H, m), 4.40 (1 H, m, C_1-H), 3.95 (2 H, s), 3.34 (1 H, m, C_4-H), 3.31 (3 H, s), 3.00 (3 H, s), 2.40 (3 H, m), 2.20–1.85 (3 H, m), 1.7–1.1 (9 H, m). (±)-(1β,2β,4β)-*N*-Methyl-*N*-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-4-benzo[*b*]furanacetamide (**15**): 112 mg; 0.30 mmol; 14% from **12**; IR (neat) 1536 cm^{-1}; MS *m/e* (EI) 355 (3), 339 (5); NMR δ ($CDCl_3$) 7.60 (1 H, d, *J* = 2.2), 7.40 (1 H, d, *J* = 8), 7.22 (1 H, t, *J* = 8), 7.10 (1 H, d, *J* = 8), 6.89 (1 H, m), 4.70 (1 H, m, C_1-H), 3.98 (2 H, s), 3.36 (3 H, s), 3.26 (3 H, s), 3.26 (1 H, m, C_4-H), 2.5–2.2 (5 H, m), 2.1–1.8 (2 H, m), 1.7–1.4 (8 H, m). **13**: 38 mg; 1.0 mmol; 5% from **12**. **8**: 32 mg; 0.86 mmol; 4% from **12**.

(−)-(5α,7α,8β)-*N*-Methyl-7-(1-pyrrolidinyl)-1-oxaspiro[4.5]decan-8-amine [(−)-20]. (±)-(5α,7α,8β)-*N*-Methyl-7-(1-pyrrolidinyl)-1-oxaspiro[4.5]decan-8-amine (racemic **20**,[11] 4.6 g, 19 mmol) and L-(−)-di-*p*-toluoyltartaric acid (Aldrich Chemical Co., 7.8 g, 19 mmol) were dissolved in propan-2-ol (28 mL). The solution was cooled and left to stand at room temperature for 18 h and then filtered to give the mono L-(−)-di-*p*-toluoyltartaric acid salt of diamine **20** as white crystals (3.8 g, 6 mmol, 63%): $[\alpha]^{20}_D$ = −41.8° (*c* = 1, EtOH); mp = 151–152 °C. Anal. C, H, N. The parent diamine **20** was obtained by placing the above salt in 1 M aqueous sodium hydroxide solution (100 mL) and extracting with dichloromethane (4 × 25 mL). The combined dichloromethane extracts were dried over magnesium sulphate and concentrated in vacuo.

General Method for Formation of Amides 17, 18, 21–23, 25, and 26. A solution of the aromatic acetyl chloride (1.0 mmol) [prepared by the action of thionyl chloride on either 4-benzo[*b*]furanacetic acid[2] or 4-benzo[*b*]thiopheneacetic acid[2]] in dichloromethane (5 mL) was added dropwise to a stirred solution of diamine **16**,[11] **20**, or **24**[11] (1.0 mmol) in dichloromethane at 0 °C. After stirring for 10 min, diethyl ether was added until no further precipitation occurred. The product was collected by filtration, washed with diethyl ether, and dried in vacuo to yield the amine hydrochloride. Products were purified by recrystallization (recrystallization solvents in Table I) or by medium-pressure chromatography on silica gel using dichloromethane–methanol as eluant.

The enantiomeric purity of the separated enantiomers of amine **20** and of amides **21–23** was assayed by ^1H NMR spectroscopy using the chiral solvating agent method of Pirkle and Hoover[12] as described in part 1[2] of this series.

(+)-(5α,7α,8β)-*N*-Methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl]benzo[*b*]furan-4-acetamide monohydrochloride (**22**) has $[\alpha]^{20}_D$ = +28° (*c* = 0.9, CH_2Cl_2). (−)-(5β,7β,8α)-*N*-Methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl]benzo[*b*]furan-4-acetamide monohydrochloride (**21**) has $[\alpha]^{20}_D$ = −28° (*c* = 0.9, CH_2Cl_2). (−)-(5β,7β,8α)-*N*-Methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl]benzo[*b*]thiophene-4-acetamide monohydrochloride (**23**) has $[\alpha]^{20}_D$ = −23° (*c* = 0.56, CH_2Cl_2).

Biological Assays. μ and κ opioid receptor binding assays and analgesia assay were performed as previously described.[2] δ opioid receptor binding assay was performed by the method of Paterson.[13]

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Supplementary Material Available: 2D-absorption-mode double-quantum filtered COSY NMR Spectra of compound **13** and a discussion thereof (4 pages). Ordering information is given on any masthead page.

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Cephalosporins to Carbapenems: 1-Oxygenated Carbapenems and Carbapenams

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The photo "Wolff" rearrangement of readily available 2-diazoceph-3-em oxides (**1**) directly affords carbapen-2-ems, allowing a facile entry into a ring system previously accessible only by total synthesis, lengthly semisynthesis or fermentation. The chirality of the cephalosporin is accurately translated into the corresponding carbapenem. The resulting 1-oxocarbapenems (**2**) were selectively transformed through reduction into 1-oxygenated carbapenems and carbapenams (**3** and **4**, respectively). On microbiological screening, a carbapenem (**3c**) was found to possess a broad spectrum of activity. An interesting antibacterial profile was discovered for a carbapenam (**26**).

A prior communication[1] from our laboratory described chemistry leading to the synthesis of 1-substituted carbapenems. Since that time the 1-substituted carbapenem structural type has become a very productive area of research.[2] Our synthesis (Scheme I) transforms cephalosporins **1** directly into the corresponding 1-oxocarbapenems **2** with retention of chirality, thus leading to the synthesis of agents having the natural configuration at the crucial C-5; carbapenems **2** in turn can be reduced selectively to either 1-hydroxycarbapenems **3**, or to carbapenams **4** possessing the natural configuration at C-3.

We would now like to detail our studies utilizing this chemistry to synthesize substances with antibacterial activity. To this end, previously described carbapenem **3a** and carbapenam **4b** must be modified at C-6 to maximize antibacterial effectiveness. Accordingly, thienamycin-like **3c** and penicillin V-like **4d** were chosen as target structures,

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