DMSO). The aortic strip was treated with the agents for 10 min before the addition of U-44069.

Guinea Pig Lung Contraction. Strips of the guinea pig lungs were prepared. Each strip (3 × 3 × 20 mm) was mounted in an organ bath containing Krebs solution at 37 °C. The reaction medium was continuously aerated with 5% CO_2–95% O_2 gas. An initial tension of the strips was loaded at 2 g, and U-46619-induced contraction was isometrically recorded on a polygraph via a force-displacement transducer. Following priming, U-46619 dose–response curve was obtained with a cumulative dose schedule (six doses). The preparations were then washed at regular intervals until the resting base line had returned. After an appropriate rest period (about 1 h), the U-46619 dose–response curve was repeated in the presence of drugs. pA_2 values were obtained by the method of Tallarida and Murray.[14]

Guinea Pig Platelet Aggregation. Platelet-aggregation studies were done as described.[15] Blood was collected in 3.15% sodium citrate (1 mL for 9 mL of blood) by cardiac puncture from conscious male guinea pigs. Platelet-rich plasma (PRP) was obtained by centrifuging the blood at 3000 rpm for 5 s at room temperature. The platelet concentration was adjusted to 450000/μL with a photometer (Rikadenki, Platelet Aggregometer, Japan). The PRP (250 μL) was preincubated at 37 °C for 2 min and then incubated for 2 min with U-44069. The concentrations of the aggregating agent were used to obtain submaximal aggregation.

[^{3}H]U-46619 Binding to Guinea Pig Platelets. The experiments were done according to the methods described by Kattelman et al.[16] with slight modifications. A syringe containing 0.315% citrate anticoagulant and 1 mM aspirin as final concentrations was used to collect the blood by cardiac puncture from conscious guinea pigs. The PRP fraction was collected by centrifuging the blood at 3000 rpm for 5 s at room temperature and the obtained PRP was treated with 1 μM PGE_1 after which the platelet pellet was obtained by centrifuging the PRP at 3000 rpm for 5 min. The platelet concentration was adjusted to 660000/μL with a modified 25 mM Tris-HCl buffer (pH 7.4) containing 138 mM NaCl, 5 mM KCl, 5 mM $MgCl_2$, and 5.5 mM glucose. Platelets in 460 μL of the buffer were preincubated with drugs (20 μL) for 6 min at 25 °C and [^{3}H]U-46619 (20 μL, 0.037 μCi for guinea pig) were then added to the mixtures, and the preparations were incubated for 6 min. The binding reaction was stopped by adding 3 mL of ice-cold 25 mM Tris-HCl buffer. Platelets were isolated by vacuum filtration on glass filters (Whatman, GF/C filter). Each tube and filter were washed twice with 3 mL of ice-cold 25 mM Tris-HCl buffer. The radioactivity on the glass filter was measured using a liquid-scintillation counter [(Aloka, LSC-900, Japan, scintillator containing toluene (12 L), bis-MSB (12 g), DPO (180 g), and nonion (5.16 L)]. Nonspecific binding of [^{3}H]U-46619 to the platelet was estimated in the presence of 10^{-5} M unlabeled U-46619.

In Vivo Experiments. Experimental Allergic Asthma. IgG_1-mediated bronchoconstriction was examined in guinea pigs sensitized intraperitoneally with an emulsion of egg albumin (EA) (1 mg/kg) and Freund's complete adjuvant (FCA), according to the method of Orange and Moore.[17] Three weeks later, the animals from which the sera at 1:1000 dilution showed a positive 3-h passive cutaneous anaphylaxis (PCA) in guinea pigs were used. The bronchoconstriction in the animals which were anesthetized with urethane (1.5 g/kg, ip) and treated with gallamine triethiodide (1 mg/kg, iv) was measured by the overflow technique of Konzentt–Rössler.[18] The increase in respiratory overflow volume provoked by antigen challenge (EA, 1 mg/kg, iv) was expressed as percent of the maximal overflow volume (100%) obtained by obstruction of the trachea. Drugs suspended in a 5% gum arabic solution were given orally 1 h before antigen challenge.

Spasmogen-Induced Bronchoconstriction. The bronchoconstriction induced by U-46619 (10 μg/kg, iv), LTD_4 (10 μg/kg, iv), and/or PAF (10 μg/kg, iv) was examined by the Konzentt–Rössler method as described above. Drugs suspended in a 5% gum arabic solution were given orally 1 h before the spasmogen challenge.

Acknowledgment. We thank Drs. Y. Nagawa, Y. Maki, K. Nishikawa, H. Kuriki, Y. Kawamatsu, and M. Fujino for their encouragement and valuable advice, and M. Takamoto and Y. Wada for X-ray crystallographic analyses.

Supplementary Material Available: Tables listing crystal data and atomic coordinates of the bonded atoms of the (7*R*)-(+)-anilide **9** (5 pages); structure factor amplitudes of **9** (8 pages). Ordering information is given on any current masthead page.

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(15) Terashita, Z.; Tsushima, S.; Yoshioka, Y.; Nomura, H.; Inada, Y.; Nishikawa, K. *Life Sci.* **1983**, *41*, 1975.
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Benzofuro[2,3-*c*]pyridin-6-ols: Synthesis, Affinity for Opioid-Receptor Subtypes, and Antinociceptive Activity

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A general synthetic approach to a novel series of *cis*-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ols is described together with their receptor-binding profile on opioid-receptor subtypes (μ, κ, δ). In addition, their in vivo antinociceptive activity was assessed. A number of the analogues synthesized showed potent affinity for opioid receptors and have potent antinociceptive activity in a mouse phenylquinone abdominal stretching model. In addition, the SAR for nitrogen substitution in the above series is explored with respect to the overall opioid receptor subtype binding profile. In general it was found that substituents which enhanced μ and κ binding affinity in the benzomorphan series had a similar effect in the benzofuropyridine series described in this manuscript. An overlap hypothesis topologically connecting the benzomorphan nucleus to the *cis*-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridine nucleus is also presented.

During the course of investigations directed toward the discovery of novel centrally acting analgetics, a series of *cis*-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ols (**1**) was synthesized and evaluated both for affinity at

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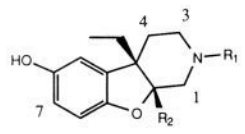
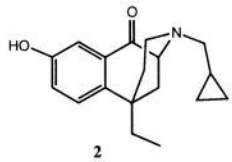


1



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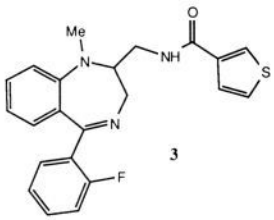

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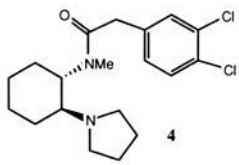


4

opioid-receptor subtypes[1] as well as for their antinociceptive activity. The principal focus of these studies was directed toward the discovery of structurally novel selective κ opioid receptor agonists which may produce central analgesia predominantly mediated by a spinal mechanism.[2] At the initiation of these studies, three types of molecules had been described which showed potent affinity for the κ-opioid-receptor subtype, the benzomorphans exemplified by ethylketocyclazocine (EKC, **2**),[3] benzodiazepines such as tifluadom (**3**),[4] and amides of *trans*-cyclohexanediamine such as U-50488 (**4**).[5] However, only in the benzomorphan series were the factors which enhanced κ-receptor affinity described. Accordingly, the basic strategy employed in the present studies was to select a basic template with high affinity for opioid receptors and make systematic modifications at the basic nitrogen group as had been previously examined in the benzomophan nucleus.[3] In order to successfully implement this strategy, it was necessary to chose a template in which one could postulate an overlap with the benzomorphan EKC (**2**). The benzomorphan nucleus is quite rigid and is considered to have predominantly two bioactive conformations, the chair and twist-boat conformers, which are illustrated for EKC in Figure 1. The twist-boat conformer is energetically less favorable for small nitrogen substituents such as methyl but becomes progressively more accessible as one increases the steric bulk of the substituent on nitrogen.[6] Also shown in Figure 1 are the chair and twist-boat conformers of the *cis*-benzofuropyridin-6-ol template **1**. Examination of Dreiding models shows an extraordinary degree of overlap between the chair benzofuropyridine conformer and the twist-boat benzomorphan conformer and vice versa. This homology includes the directional orientation of the lone pair of the nitrogen atom, considered to be important in determining agonist versus antagonist activity.[6] Accordingly, we chose to add a hydroxyl to position 6 of the benzofuropyridine template, to coincide with the phenolic hydroxyl found in EKC (**2**), and an ethyl group in position 4a since this group was also present in the potent κ-agonist EKC **2**. Further support for the notion that this benzofuropyridine nucleus might be a mimic for the benzomorphan ring system comes from the patent literature,[7] which revealed that the benzofuropyridines **5a,b** had antinociceptive activity presumably mediated by opioid-receptor activation. The patent cited above does not report the stereochemistry of the ring junction in **5a,b**. However, on the basis of the synthesis employed, it probably has the same cis stereochemistry as the compounds described in this manuscript.

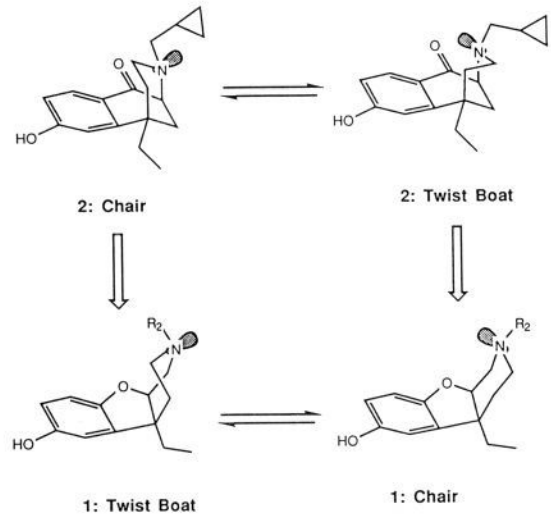
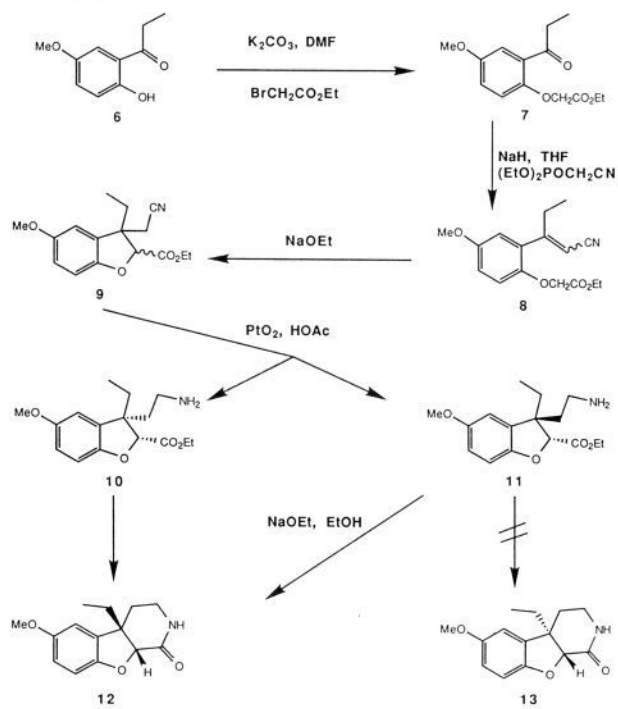


Figure 1.

Scheme I



5a: R=Me
5b: R=Ph

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(6) Kolb, V. M. *J. Pharm. Sci.* **1978**, *67*, 999. Loew, G. H.; Berkowitz, D. S. *J. Med. Chem.* **1975**, *18*, 656.
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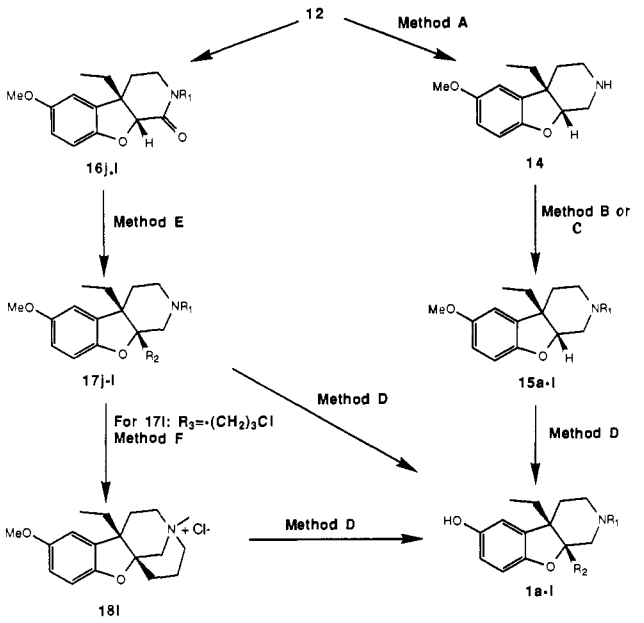
Scheme II[a]



[a] Method A: BH_3, THF. Method B: R_2X, $NaHCO_3$, DMF. Method C: (1) RCOCl, TEA, CH_2Cl_2, (2) LAH, THF. Method D: $LiPh_2P$, THF. Method E: (1) NaH, R_2X, toluene, (2) LiTMP, THF, R_3I, HMPT, (3) LAH, $AlCl_3$, THF. Method F: toluene, reflux.

Chemistry

The basic route for construction of the *cis*-benzofuropyridine system is outlined in Scheme I. The hydroxypropiophenone 6[8] was alkylated with ethyl bromoacetate in DMF with K_2CO_3 as the base to afford the ester 7 in 65% yield. This material was reacted with diethyl(cyanomethyl)phosphonate and NaH in THF to give the cyano ester 8 in 90% yield as an approximately equal mixture of double bond regioiosomers. This mixture was treated with sodium ethoxide to effect an intramolecular Michael addition to the benzofuranitrile 9 as a 1:1 mixture of diastereomers in 95% yield. This mixture was hydrogenated with platinum oxide in acetic acid to afford a mixture of *cis*-lactam 12 in 41% yield and *trans*-amine 11 in 29% yield, which could be separated by flash chromatography. Apparently, *cis*-amine 10 spontaneously cyclizes under the reaction conditions to *cis*-lactam 12 whereas *trans*-amine 11 does not form the more strained *trans*-lactam 13 under the same conditions. If *trans*-amine 11 was subjected to epimerizing conditions (sodium ethoxide in refluxing ethanol), *cis*-lactam 12 could be isolated in 54% yield, but in no case was *trans*-lactam 13 observed. Lactam 12 represents the central intermediate from which all of the compounds described in this paper are derived.

The conversion of lactam 12 to *cis*-benzofuropyridin-6-ols **1a–l** is shown in Scheme II. Analogues **1a–i** were prepared by reduction of lactam 12 with borane in THF in 96% yield to the secondary amine 14 (method A). The stereochemistry of the ring junction for lactam 12 as well as for all subsequent intermediates was assigned on the basis of the ^1H NMR spectra of 14 in which the proton at position 9a showed $J_{AX} = J_{BX} = 4.5$ Hz, a result consistent with a cis ring junction. This direct spectral evidence is also supported by the thermodynamic considerations outlined in the previous paragraph. The amine 14 was then alkylated, either directly, with an alkyl halide/$NaHCO_3$ in DMF system (method B), or indirectly via acylation of 14 with an acid chloride and triethylamine followed by reduction with $LiAlH_4$ in THF (method C). In this manner the tertiary amines **15a–i** were prepared in moderate to good yields. These compounds were deprotected to the corresponding phenols **1a–i** with lithium diphenylphosphide in THF[9] (method D). In the preparation of **1a**, direct alkylation of 14 with methyl iodide afforded the corresponding quaternary salt instead of the usual tertiary amine; however, deprotection with lithium diphenylphosphide also cleaved the quaternary methyl group to afford **1a** in good overall yield.

The analogues **1j,k** and the tetracyclic analogue **1l** were prepared in the following manner. Lactam 12 was alkylated with either (cyclopropyl)methyl chloride or methyl iodide in toluene with NaH to afford the tertiary lactams **16j** and **16i** in near quantitative yields. These compounds were alkylated at position 9a with LDA in THF and an alkyl iodide to afford the corresponding alkylated tertiary lactams in excellent yields. In all cases, these tertiary lactams appeared to be a single diastereomer on the basis of TLC and ^1H NMR analysis. They were tentatively assigned the cis ring fused stereochemistry shown in Scheme II on the basis of the assumption that the transition state for alkylation is at least somewhat productlike and there is a strong thermodynamic bias for the cis ring fusion in this system. Reduction of these lactams was effected with $LiAlH_4/AlCl_3$ in THF to afford the corresponding tertiary amines **17j–l** (method E) in overall yields of 70–90%, which were deprotected as described above. The tetracyclic analogue **1l** was prepared from **17l** via quaternization in refluxing toluene (method F) to afford the salt 18 followed by deprotection of the methyl ether with cleavage of the quaternary methyl group as described for **1a** to afford the tetracyclic analogue **18l**. The facile cyclization of **17l** to **18l** together with the thermodynamic considerations presented above suggest that the ring junction for the analogues **17j–l** is cis as was previously assigned. The substitution patterns, melting points, method of preparation, and overall yields for the method(s) listed for the analogues **1a–l** and **15a** are shown in Table I and analysis and spectral data for some of the compounds are available as supplementary material.

Biological Results and Discussion

cis-Benzofuropyridin-6-ols **1a–m** and the methyl ether **15a** were tested in standard binding assays for μ, κ, and δ receptors as described in the Experimental Section. Table II lists the K_i values for these compounds. Compounds which showed in vitro activity were subsequently tested for in vivo analgesia in a mouse phenylquinone abdominal stretching assay. The analgesic activities listed in Table II were measured 30 min after subcutaneous administration of the compound as described in the Experimental Section.

The basic N-methylated benzofuro[2,3-*c*]pyrindin-6-ol template **1a** is a reasonably active (K_i = 19 nM) μ agonist possessing virtually no κ affinity (K_i > 5 μM). However, when the *N*-methyl group was lengthened to a three-carbon chain as in **1b**, an increase in κ affinity was observed (K_i = 335 nM) with little change in μ activity. The weak κ affinity of **1b** could be further enhanced by using the nitrogen substituent found in EKC, namely the cyclopropylmethyl moiety resulting in analogue **1d**. This modification generated a relatively high κ affinity (K_i = 34 nM). Increasing the cycloalkyl ring size in **1d** led to a progressive decline in κ affinity, i.e. cyclobutylmethyl (**1e**, k_i = 270 nM) and cyclopentylmethyl (**1f**, K_i = 550 nM). In addition, an analogue employing another nitrogen

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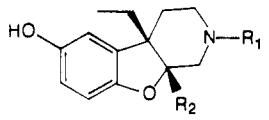
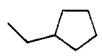
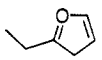
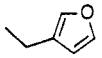
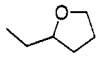
(9) Mann, F. G.; Pragnell, M. J. *J. Chem. Soc.* **1965**, 4120.

Table I. Physical and Analytical Data for the Analogues **15b** and **1a–l**



1a–l

compd no.	R_1, R_2[e]	% yield[a]	method[b]	mp, °C	formula	anal.[c]
15b	R_1 = *n*-Pr; Me ether of **1b**	85	B	135–137[d]	$C_{17}H_{26}ClNO_2$	C, H, N
1a	R_1 = Me	45	B, D	238–240[d]	$C_{14}H_{20}ClNO_2$	C, H, N
1b	R_1 = *n*-Pr	56	D	230–231[d]	$C_{16}H_{24}ClNO_2$	C, H, N
1c	R_1 = $(CH_2)_2Ph$	47	C, D	154–159	$C_{21}H_{25}NO_2$	C, H, N
1d	R_1 = 	45	B, D	185–189[d]	$C_{17}H_{24}ClNO_2$	C, H, N
1e	R_1 = 	43	C, D	157–159[d]	$C_{18}H_{26}ClNO_2$	C, H, N
1f	R_1 = 	73	C, D	125–128	$C_{19}H_{27}NO_2$	C, H, N
1g	R_1 = 	73	C, D	232–235[d]	$C_{18}H_{22}ClNO_3$	C, H, N
1h	R_1 = 	52	C, D	185–188[d]	$C_{18}H_{22}ClNO_3$	C, H, N
1i	R_1 = 	30	B, D	181–185[d,f]	$C_{18}H_{26}ClNO_3$	C, H, N
1j	R_1 = 	25	E, D	195–198[d]	$C_{18}H_{26}ClNO_2$	C, H, N
1k	R_2 = 	36	E, D	185–189[d]	$C_{20}H_{30}ClNO_2$	C, H, N
1l	R_1, R_2 = $(CH_2)_3$	46	E, F, D	196–199	$C_{16}H_{21}NO_2$	C, H, N

[a] Overall yields for the methods listed on this table. [b] Described in the Experimental Section and in Scheme II. [c] Combustion analysis were within ±0.4% of the theoretical value. [d] As the HCl salt. [e] R_2 = H unless otherwise noted. [f] Compound **1i** is a 1:1 mixture of diastereomers with respect to the α hydrogen on the tetrahydrofuryl moiety.

Table II. Opiate-Receptor Affinities and in Vivo Antinociceptive Activity for the Analogues **15b** and **1a–l**

	K_i, nM ± SEM			PQW ED_{50},
compd no.	binding[a,b]	μ binding[a,c]	δ binding[a,d]	μmol/kg sc (95%) CL)[e]
levorphanol	10 ± 2	0.3 ± 0.02	1.9 ± 0.06	NT[f]
EKC	6 ± 0.5	1.3 ± 0.3	2.3 ± 0.4	NT
15b	>5 μM	2880 ± 73	>6.4 μM	NT
1a	>5 μM	19 ± 0.5	212 ± 13	5.00 (2.41–8.19)
1b	335 ± 14	30 ± 0.5	231 ± 15	5.10 (2.22–13.0)
1c	2000 ± 48	0.9 ± 0.02	8 ± 0.3	0.37 (0.21–0.62)
1d	34 ± 3	4 ± 0.1	53 ± 3	1.19 (0.55–2.90)
1e	270 ± 10	17 ± 0.5	410 ± 45	1.45 (0.68–3.00)
1f	550 ± 24	50 ± 2	340 ± 17	52.1 (24.8–257)
1g	1500 ± 48	99 ± 0.8	571 ± 31	90.8 (49.7–166)
1h	190 ± 5	31 ± 1	115 ± 9	51.2 (26.2–88.7)
1i	3500 ± 240	73 ± 2	474 ± 51	5.00 (2.12–10.0)
1j	35 ± 1	8 ± 0.3	37 ± 1.3	22.5 (12.4–40.1)
1k	90 ± 13	21 ± 0.5	37 ± 0.6	>284
1l	2600 ± 165	126 ± 4	481 ± 35	>116

[a] Compounds were run at 5–10 concentrations in triplicate. IC_{50}s were determined ± standard deviations and converted to K_is with the Cheng–Prusoff equation, assuming all inhibition of binding was competitive. [b] [^{3}H]Ethylketocyclazocine binding.[13] [c] [^{3}H]-DAMCO binding.[11] [d] [^{3}H]DADLE binding.[12] Since no μ-blocking agent was employed, this number may reflect some μ activity. [e] Phenylquinone abdominal stretching model: compounds were given 30 min prior to testing as described in Experimental Section.[14] ED_{50}s were determined with 95% confidence limits (in parentheses). [f] Not tested.

substituent previously shown to produce good κ affinity in the benzomorphan series, namely the 2-tetrahydrofurylmethyl moiety found in MR 2034,[10] was prepared. This, however, produced another μ-selective agonist (**1i**, K_i = 73 nM). Several permutations of this substituent were also prepared, **1g** and **1h**, of which only **1h** showed significant κ affinity (K_i = 190 nM). Finally addition of a methyl group at position 9a (**1j**, K_i = 35 nM) resulted in retention of κ affinity to the extent seen with **1d**; however, addition of the larger *n*-propyl substituent to this position resulted in a partial loss in κ activity (**1k**, K_i = 90 nM). None of the benzofuropyridine analogues tested showed any real selectivity for κ-opioid receptors, always possessing greater affinity for the μ receptor. A similar lack of κ selectivity was also observed in the corresponding benzomorphan analogues.[3] In the cases studied, these benzofuropyridine analogues showed varying degrees of μ versus δ-receptor selectivity from 1.8-fold (**1k**) to 24-fold (**1e**). In contrast, the separation of μ from κ activity was much more apparent with compound **1c**, being greater than 2000-fold selective for a μ receptor as opposed to a κ receptor. The rigid tetracyclic analogue **1l** also showed weak μ- and δ-receptor affinity. The methyl ether of **1b**, **15b**, was also tested and shown to be inactive in vitro at opioid receptors, a result which indicates the importance of a free hydroxyl at position 6 for opioid-receptor affinity in this series. Substitution at nitrogen with phenethyl results in the very potent μ-selective agonist **1c** (K_i = 0.9 nM) as expected.

A number of the analogues **1a-l** possessed potent antinociceptive activity in vivo with analogue **1c** being the most potent (ED_{50} = 0.37 μmol/kg sc). Examination of the correlation between receptor-binding activity and antinociceptive activity, assuming bioavailability to be equivalent for all analogues tested, showed no correlation (r_s = 0.16, Spearman rank correlation) between κ-receptor affinity and activity in the PQW test procedure. However, for μ- and δ-receptor activity, r_s values of 1.2 and 0.70 were obtained, indicating some causal relationship between receptor binding and the observed in vivo activity. Exceptions to this relationship exist however, such as compound **1i**, which is more active in vivo than would be predicted by

(10) Johnson, N.; Pasternak, G. *Life Sci.* **1983**, *33*, 985.

its receptor-binding profile, and compounds **1d** and **1j**, which have similar binding profiles but differ markedly in their in vivo activity.

The possibility that the binding activity observed may also be reflective of intrinsic antagonist or partial agonist cannot be excluded. Furthermore, the combined activities at μ and δ receptors will probably contribute to the in vivo antinociceptive profile for many of the analogues **1**.

In conclusion, it has been shown that approximately substituted *cis*-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]-pyridines may show potent affinity for opioid-receptor subtypes and possess potent antinociceptive activity. In addition, the SAR presented indicates that a similar preference for receptor-subtype specificity exists for nitrogen substituents in the analogues **1a–11** as for the corresponding benzomorphan analogues. However, none of the analogues tested showed high selectivity for the κ-receptor subtype although several analogues possessed good μ-receptor specificity.

Experimental Section

μ and δ Opiate Receptor Binding. Membrane suspensions were prepared from male Hartley (Elm Hill, Chelmsford, MA, animal code Elm:(DH)) guinea pig (350–400 g) whole brains as previously described.[11,12] Whole brains minus cerebellum were dissected and homogenized with a Brinkman Polytron (setting 6, 20 s) in 10 volumes (w/v) of ice-cold 50 nM Tris-HCl buffer (pH 7.4 at 4 °C). The homogenate was centrifuged twice at 48,000g for 10 min at 4 °C with rehomogenization of the pellet in fresh Tris-HCl buffer between centrifugations. The pellet was homogenized in 10 volumes of Tris-HCl buffer, incubated at 37 °C for 45 min to remove endogenous opiate-like substances, and centrifuged. The final pellet was homogenized in 150 volumes (based on original tissue weight) of 50 mM Tris-HCl buffer. In the binding assay, 1.0-mL aliquots of the final tissue suspension (equivalent to about 15 mg of original tissue) were added to triplicate tubes containing [^{3}H]DAMGO (1.0 nM, specific activity 30–60 Ci/mmol, Du Pont NEN, μ-receptor binding) or [^{3}H]-D-Ala^2-D-Leu^5-enkephalin (DADLE) (1.0 nM, specific activity 30–50 Ci/mmol, Du Pont NEN, δ-receptor binding) plus or minus the test compound to a final volume of 1.3 mL. Nonspecific binding was determined in the presence of 10 mM levallorphan. Tubes were incubated at 25 °C for 1 h and the contents were filtered under vacuum through Whatman GF/B glass-fiber filters. Unbound radioactivity was removed with 3 × 4 mL washes with ice-cold Tris-HCl buffer and the filters were placed in scintillation vials with 3.5 mL of scintillation cocktail. After equilibration, radioactivity determinations were made and data calculations were performed as described below.

κ-Receptor Binding. [^{3}H]Ethylketocyclazocine (EKC) was measured as previously described.[13] The tissue pellet used in this assay was prepared as described for the μ- and δ-receptor binding assays. In the binding assay, 1.0-mL aliquots of the final tissue suspension (equivalent to about 15 mg of original tissue) were added to triplicate tubes containing [^{3}H]EKC (final concentration 2.0 nM, specific activity 15–30 Ci/mmol, Du Pont NEN) plus or minus the test compound and 100 mM NaCl, 20 mM cold DADLE, and 20 mM morphiceptin (Peninsula Labs) in a final volume of 1.3 mL. Nonspecific binding was determined in the presence of 10 mM unlabeled EKC. Tubes were incubated at 25 °C for 45 min and the contents were filtered under vacuum through Whatman GF/B glass-fiber filters. The filters were washed three times with 4.0-mL aliquots of ice-cold Tris-HCl buffer and placed in scintillation vials with 3.5 mL of scintillation cocktail. After equilibration, radioactivity determinations were made and the data calculations were performed as described below.

Phenylquinone Abdominal Stretching.[14] Male CF-1 (Charles River, animal code Crl:CF1BR) mice (18–23 g) were housed under standard laboratory conditions prior to testing. Ten mice were used per dose of test compound, which was administered subcutaneously. After 30 min, the mice received 3.75 mg/kg of phenylquinone in 5% aqueous ethanol injected intraperitoneally. The animals were immediately placed in observation cages, where they were allowed to move freely. If a stretching response was observed over a 10-min period, the compound is not considered to be inactive.

Data Analysis. The binding data from three separate experiments were analyzed simultaneously by nonlinear regression using RS/1 (RS/1 Release 2 Features; Bolt, Beranek and Newman Software Products Corp.: Cambridge, MA; 1985). The IC_{50} values generated by this analysis are expressed as the mean SEM. The IC_{50s} were converted to K_i values with the Cheng–Prusoff equation,[15] assuming all inhibition of binding was competitive, which is a reasonable approximation since all calculated Hill slopes were close to unity. The respective K_D values for the ligands used were taken from the literature.[11–13]

Chemistry. All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All 60-MHz NMR spectra were recorded on a Perkin-Elmer R-12 spectrometer, all 90-MHz NMR spectra were recorded on a Varian EM-390 spectrometer, and all 400-MHz NMR spectra were recorded on a Varian XL-400 spectrometer. All chemical shifts are expressed in ppm relative to a TMS internal standard. All reactions were carried out under a nitrogen atmosphere. All compounds synthesized were racemic mixtures and all stereochemistry depicted in this manuscript relates to relative sterochemistry only.

2-(Carbethoxymethoxy)-5-methoxypropiophenone (7). A mixture of 2-hydroxy-5-methoxypropiophenone (**6**)[8] (75.4 g, 0.419 mol), ethyl bromoacetate (73.5 g, 0.44 mol), powdered K_2CO_3 (121 g, 0.88 mol) in dry DMF (750 mL) was vigorously stirred at 90 °C for 6 h. The reaction mixture was poured onto ice water and the product was extracted with ether. After drying over $MgSO_4$, the solvent was removed in vacuo and the residue was triturated with methanol to afford 72.3 g (65%) of the title compound **7** as a buff solid melting at 58–60 °C. Anal. (CHO) C, H.

(*E*,*Z*)-2-(Carbethoxymethoxy)-5-methoxy-β-ethylcinnamonitrile (8). To a suspension of 50% NaH (13.7 g, 0.285 mol), which had been washed free of oil with hexane in THF (600 mL), was added diethyl (cyanomethyl)phosphonate (50.48 g, 0.285 mol) in a dropwise fashion. After 10 min at room temperature, a solution of **7** (72.25 g, 0.272 mol) in THF (350 mL) was added in a dropwise manner at 0 °C. After 2 h at 0 °C, the reaction mixture was poured onto ice water and the product was extracted with ether. After drying over $MgSO_4$, the solvent was removed in vacuo to afford 70.5 g (90%) of the title compound **8** as a yellow oil.

2-Carbethoxy-3-(cyanomethyl)-3-ethyl-5-methoxy-2,3-dihydrobenzofuran (9). A mixture of **8** (70.5 g, 0.244 mol), ethanol (10 mL), and 50% NaH (400 mg, 8.3 mmol) was heated at 80 °C for 90 min. After cooling to room temperature, the reaction mixture was poured onto ice water, and the product was extracted with ether, and the ethereal extracts were washed with a saturated $NaHCO_3$ solution. After drying over $MgSO_4$, the solvent was removed in vacuo to afford 67 g (95%) of the title compound **9** as a colorless oil.

***cis*-4a-Ethyl-6-methoxy-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]-pyridin-1-one (12) and *trans*-2-Carbethoxy-3-(aminomethyl)-3-ethyl-5-methoxy-2,3-dihydrobenzofuran (11).** A mixture of the nitrile **9** (67 g, 0.232 mol) and PtO_2 (5.0 g) in acetic acid (700 mL) was hydrogenated at 50 psi at room temperature for 6 h. After filtration, the solvent was removed in vacuo and the reaction mixture was poured onto ice water and the product was extracted with ethyl acetate and washed with a saturated $NaHCO_3$ solution. After drying over $MgSO_4$, the solvent was removed in vacuo and the residue was subjected to

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(13) Traynor, J. R.; Kelley, P. D.; Rance, M. J. *Life Sci.* **1982**, *31*, 1377.
(14) Hendershot, L. C.; Forsaith, J. *J. Pharmacol. Exp. Ther.* **1959**, *125*, 237.
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flash chromatography on silica gel with ethyl acetate as the eluent to afford 23.4 g (41%) of the title compound **12** as a colorless solid melting at 122–123 °C after trituration with ether. Eluting the above column with 10% methanol/CH_2Cl_2 also afforded 19 g (29%) of the title compound **11** as a colorless oil. NMR for **12** (CDCl3, 60 MHz): δ 0.74 (3 H, t, J = 7 Hz), 1.40–2.00 (4 H, m), 3.06 (2 H, m), 3.70 (3 H, s), 4.52 (1 H, s), 6.60 (3 H, m), 7.35 (1 H, brs). Anal. (CHNO) C, H, N.

Conversion of *trans*-Amine 11 to *cis*-Lactam 12. A mixture of the *trans*-amine **11** (3.8 g, 13.1 mmol) and NaOEt (132 mg, 2 mmol) in ethanol (5 mL) was refluxed for 2 h. After removal of the solvent, the residue was worked up as described above to afford 1.75 g (54%) of the *cis*-lactam **12**.

Method A. *cis*-4a-Ethyl-6-methoxy-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridine (14). To the *cis*-lactam **12** (5.0 g, 20.2 mmol) in THF (20 mL) was added 1 M borane in THF (50 mL, 50 mmol) and the mixture was refluxed for 2 h. The reaction was quenched after cooling to room temperature with 6 N HCl and washed with ether. After neutralization of the aqueous layer with 50% NaOH, the product was extracted with ethyl acetate, the organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo to afford 4.3 g (96%) of the title compound **14** as a colorless oil. NMR ($CDCl_3$, 60 MHz): δ 0.85 (3 H, t, J = 7 Hz), 1.35–1.90 (4 H, m), 2.20 (1 H, s), 2.55–3.05 (4 H, m), 3.75 (3 H, s), 4.25 (1 H, t, J = 4.5 Hz), 6.60 (3 H, s).

Method B. *cis*-2-(2-Tetrahydrofurylmethyl)-4a-ethyl-6-methoxy-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridine (15i). A mixture of the amine **14** (1.5 g, 6.44 mmol), tetrahydrofurfuryl bromide (1.28 g, 7.73 mmol), and $NaHCO_3$ (2.16 g, 25.75 mmol) in DMF (20 mL) was heated at 100 °C for 3 h. After cooling to room temperature, the reaction mixture was poured onto ice water, and the product was extracted with ether, and the ethereal extracts were washed with a saturated $NaHCO_3$ solution. After drying over $MgSO_4$, the solvent was removed in vacuo to afford an oil, which was subjected to flash chromatography on silica gel with 5% methanol in CH_2Cl_2 as the eluent to give 1.13 g (55%) of the title compound **15i** as a colorless oil.

Method C. *cis*-2-(2-Phenylethyl)-4a-ethyl-6-methoxy-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridine (15c). To a mixture of the amine **14** (1.0 g, 4.29 mmol) and Et_3N (867 mg, 8.58 mmol) in CH_2Cl_2 (10 mL) was added phenylacetyl chloride (0.62 mL, 4.72 mmol) at 0 °C in a dropwise fashion. After 1 h at room temperature, the reaction mixture was washed with water, the organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo. This material was dissolved in THF (10 mL) and added to a solution of $LiAlH_4$ (380 mg, 10 mmol) in THF (20 mL) in a dropwise manner. After refluxing for 2 h, the reaction was quenched with water and filtered, and the filter cake was washed with THF. The solvent was removed in vacuo and the residue was subjected to flash chromatography on silica gel with ether/CH_2Cl_2 as the eluent to afford 800 mg (55%) of the title compound **15c** as a colorless oil.

Method D. *cis*-2-Methyl-4a-ethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ol Hydrochloride (1a). To a solution of diphenylphosphine (777 mg, 4.18 mmol) in THF (10 mL) was added 1.6 M *n*-butyllithium in hexane[9] (1.6 mL, 3.55 mmol), after which was added the *N*-methyl iodide salt of the amine **15a** (388 mg, 1.00 mmol) suspended in THF (2 mL). The reaction mixture was refluxed for 7 h. After cooling to room temperature, the reaction mixture was poured onto ice water and the product was extracted with ether. After drying over $MgSO_4$, the solvent was removed in vacuo and the residue was subjected to flash chromatography on silica gel with 5% methanol in CH_2Cl_2 as the eluent. The resulting pure free base was converted to its hydrochloride with ethanolic HCl to afford 175 mg (65%) of the title compound **1a** mp 185–189 °C. Anal. (CHNOCl) C, H, N.

Method E. *cis*-2-(Cyclopropylmethyl)-4a-ethyl-6-methoxy-9a-methyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]-pyridine (17j). A mixture of lactam **12** (2.0 g, 8.1 mmol) and 50% NaH (480 mg/10 mmol), which had been previously washed with hexane in toluene (50 mL), was refluxed with stirring for 2 h. (Chloromethyl)cyclopropane (2.0 mL, 21.6 mmol) was added and refluxing was continued for 16 h. The reaction mixture was poured onto ice water and the product was extracted with ethyl acetate. After drying over $MgSO_4$, the solvent was removed in vacuo. This material was dissolved in THF (20 mL) and added slowly at -78 °C to a solution of LiTMP in THF prepared from 2,2,6,6-tetramethylpiperidine (1.24 g, 8.74 mmol), 2.6 M *n*-butyllithium in hexane (3.4 mL, 8.74 mmol), and THF (30 mL). After 30 min at −78 °C, methyl iodide (0.54 mL, 8.8 mmol) and HMPT (1.54 mL, 8.8 mmol) were added and stirring was continued for 1 h at −78 °C. After allowing the reaction to slowly warm to 0 °C, the mixture was poured onto ice water and worked up as before. The resulting residue dissolved in a small volume of THF was added to a mixture of $LiAlH_4$ (323 mg, 8.5 mmol) and anhydrous $AlCl_3$ (1.13 g, 8.5 mmol) in THF (50 mL). After 30 min at room temperature, the reaction was quenched with 10% NaOH and filtered, and the filter cake washed with CH_2Cl_2. The solvent was removed in vacuo and the residue was subjected to flash chromatography on silica gel with ether/CH_2Cl_2 (1:4) as the eluent to afford 1.66 g (65% overall) of the title compound **17j** as a colorless oil. This compound was a single diastereomer tentatively assigned the cis ring fused stereochemistry. NMR ($CDCl_3$, 60 MHz): δ 0.10 (2 H, m), 0.50 (3 H, m), 0.75 (3 H, t, J = 7 Hz), 1.15–2.25 (8 H, m), 1.55 (3 H, s), 2.75 (2 H, m), 3.70 (3 H, s), 6.60 (3 H, s).

Method F. Cyclization of 17l to 18l. A mixture of freshly prepared crude **7l** (1.7 g, 5.23 mmol) and toluene (20 mL) was refluxed with stirring for 6 h. The solvent was removed in vacuo to afford a quantitative yield of the cyclized quaternary salt **18i** as a hygroscopic solid, which was not further characterized.

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Supplementary Material Available: A listing of analytical data, melting points (for **7**, **12**, **15b**, **1a–l**), and ^1H NMR data (for **7–9**, **11**, **15c,i**, **1a**) (4 pages). Ordering information is given on any current masthead page.