N-Substituted Oxazolo[5,4-*b*]pyridin-2(1*H*)-ones: A New Class of Non-Opiate Antinociceptive Agents

Marie-Claude Viaud,*,† Patricia Jamoneau,† Christine Flouzat,† Jean-Guy Bizot-Espiard,‡ Bruno Pfeiffer,§ Pierre Renard,§ Daniel-Henri Caignard,§ Gérard Adam,§ and Gérald Guillaumet†

Laboratoire de Chimie Bioorganique et Analytique, associé au CNRS, Université d'Orléans, B.P. 6759, 45067 Orleans Cedex 2, France, IRI Servier, 6, place des Pléiades, 92415 Courbevoie Cedex, France, and ADIR, 1, rue Carle Hébert, 92415 Courbevoie Cedex, France

Received March 18, 1994®

A series of 1-(aminoalkyl)- and 1-[(4-aryl-1-piperazinyl)alkyl]oxazolo[5,4-*b*]pyridin-2(1*H*)-one derivatives of oxazolo[5,4-*b*]pyridin-2(1*H*)-one, incorporating modifications to the length of the alkyl side chain and to the amino or 4-aryl-1-piperazinyl substituents, were tested for safety and analgesic efficacy in mice and rats. Some compounds with 4-(substituted or nonsubstituted phenyl)-1-piperazinyl substituents and a 3–4-carbon alkyl side chain had significantly greater analgesic activity than that of the oxazolo[4,5-*b*]pyridin-2(3*H*)-one analogs. To reduce the metabolic N-dealkylation of the piperazine observed in our previous work on oxazolo[4,5-*b*]-pyridin-2(3*H*)-ones, analogs of the most active compounds with steric hindrance on the alkyl side chain were prepared and tested. The compound with the maximal combination of safety and analgesic efficacy was 1-[[4-(4-fluorophenyl)-1-piperazinyl]propyl]oxazolo[5,4-*b*]pyridin-2(1*H*)-one (compound **3b**), with ED_{50} values of 5.6 mg/kg po (mouse, phenylquinone writhing test) and 0.5 mg/kg po (rat, acetic acid writhing test). Compound **3b** is a potent, rapid-acting, non-opioid, nonantiinflammatory analgesic with low acute toxicity and sustained effect.

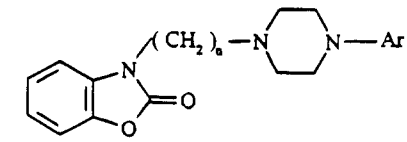
Introduction

Despite increasing understanding of the endogenous nociceptive and antinociceptive system,[1] two classes of compounds continue to dominate clinical analgesia: cyclooxygenase inhibitors (nonsteroidal antiinflammatory agents, e.g., aspirin, paracetamol, ibuprofen), which act mainly peripherally by inhibiting prostaglandin synthesis, and opiates (e.g., morphine, codeine), which act on specific central nervous system receptors. However, each class has its drawbacks: cyclooxygenase inhibitors induce gastrointestinal lesions,[2] while opiates induce tolerance, constipation, respiratory depression, physical dependency, and fear of addiction.[3] The main objective in current pain research is to develop improved non-opioid analgesics which are as effective as the opioids but without their side effects.

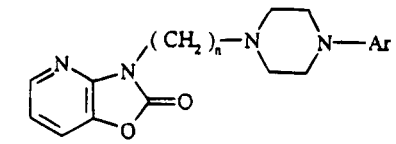
Previous work showed structure A, with a single (arylpiperazinyl)alkyl group, to have significant analgesic activity.[4] Replacing a carbon by a heteroatom in a drug template is a common strategy in medicinal chemistry. Accordingly, a pyridine ring was substituted for the benzene ring. 3-[(4-Aryl-1-piperazinyl)alkyl]-oxazolo[4,5-*b*]pyridin-2(3*H*)-ones (structure B) have been shown to possess potent analgesic activity[5] but low bioavailibility, due to rapid and comprehensive metabolism[6] involving the opening of the oxazolopyridone moiety in 3-hydroxy-2-aminopyridines and cleavage of the aminoalkyl side chain in carboxyalkyl derivatives.

Continuing earlier work on heteropolycyclic compounds with potential biological activity,[7–12] with the aim of obtaining metabolically more stable derivatives with a similar analgesic profile, a new series of oxazolo-[5,4-*b*]pyridin-2(1*H*)-one analogs with the general structure C was synthesized and tested in rodents.

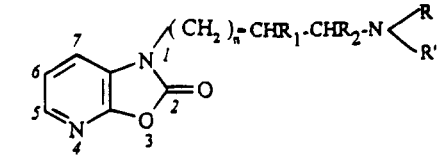
To determine the structural requirements necessary for high antinociceptive activity and low side effects,



A



B



C

modifications were made to the basic amino moiety and alkyl spacer. According to the structure–activity relationships previously established in our laboratory,[5] only compounds with cyclic amines (e.g., aryl or arylalkylpiperazines, morpholine, pyrrolidine) were synthesized. Variations in length of the alkyl spacer were also tested. The potentially most active compound, **3b**, was structurally modified as follows to enhance its resistance to metabolism: (1) addition of steric hindrance on the alkyl spacer *via* α or β substitution with a methyl group (compounds **3g,h**) and (2) replacement of the metabolically labile N–CH_2 bond by a theoretically less metabolically labile N–C=O bond (compound **10**).

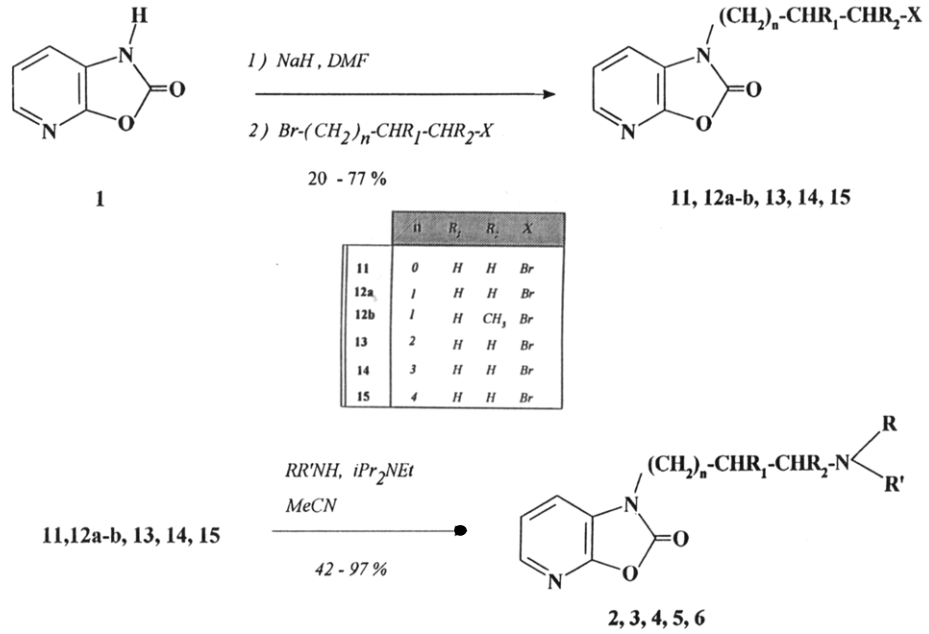
Chemistry

Two synthetic pathways were used. Pathway 1 (Scheme 1) was used to prepare the 1-(aminoalkyl)- and 1-[(4-aryl-1-piperazinyl)alkyl]oxazolo[5,4-*b*]pyridin-2(1*H*)-ones **2–6**. Oxazolo[5,4-*b*]pyridin-2(1*H*)-one[13] was con-

† Université d'Orléans.
‡ IRI Servier.
§ ADIR.
® Abstract published in *Advance ACS Abstracts,* March 1, 1995.

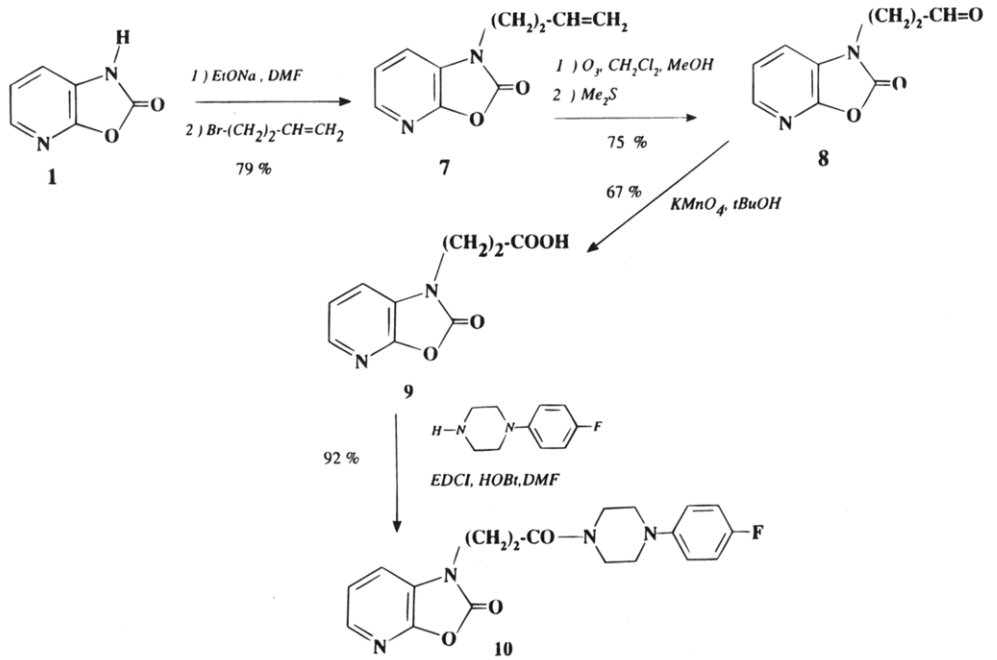
0022-2623/95/1838-1278$09.00/0

Scheme 1



	n	R_1	R_2	X
11	0	H	H	Br
12a	1	H	H	Br
12b	1	H	CH_3	Br
13	2	H	H	Br
14	3	H	H	Br
15	4	H	H	Br

Scheme 2



verted by reaction with sodium hydride in dry dimethylformamide (DMF) at room temperature into its anion which reacted with dihaloalkanes to provide good yields of **11, 12a,b,** and **13**–**15**. Compounds **2**–**6** were obtained in excellent yields by alkylation of **11, 12a,b,** and **13**–**15** with piperazine intermediates, in acetonitrile as solvent, in the presence of diisopropylethylamine. Compounds **2e,g** and **3e** were synthesized under the same conditions using morpholine and pyrrolidine as the starting material (Table 1).

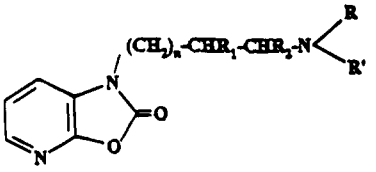
Pathway 2 (Scheme 2) was used to synthesize compound **10**. The anion of compound **1** was obtained by reaction with sodium ethoxide in dry ethanol. After evaporation of the solvent, it was alkylated in DMF with 4-bromo-1-butene, giving **7** in good yield. Ozonolysis of **7**, using the standard procedure, gave the aldehyde **8** which was oxidized to **9** with potassium permanganate in *tert*-butanol. Condensation of **9** in DMF with 4-(fluorophenyl)piperazine, in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole, gave **10** in good yield. Table 1 summarizes the experimental and physical data of synthesized compounds.

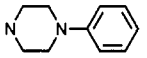
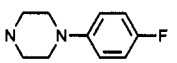
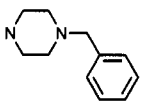
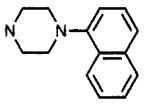
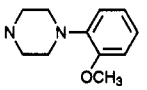
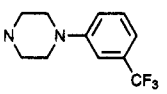
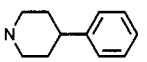
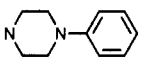
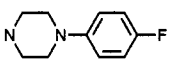
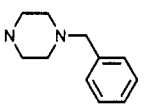
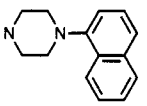
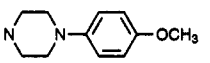
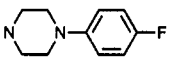
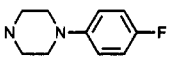
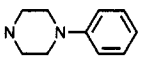
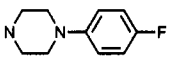
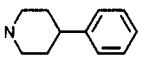
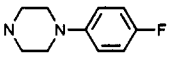
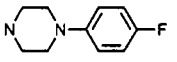
Biological Results and Discussion

Twenty-three oxazolo[5,4-*b*]pyridin-2(1*H*)-ones were synthesized and evaluated. All were prescreened for analgesic activity at a standard dose of 50 mg/kg po using the phenylquinone (PBQ) and acetic acid writhing tests. Results were also expressed as an activity ratio versus aspirin to correct for slight variations in response between the same evaluation procedures not performed simultaneously (Table 2).

Prescreening showed that, whatever the length (2–6 carbon atoms) of the alkyl spacer between the oxazolo-[5,4-*b*]pyridin-2(1*H*)-one and the basic amino moiety, the best results were always obtained with a 4-phenylpiperazine moiety, whether or not this was substituted with

Table 1. 1-(Aminoalkyl)- and 1-[(4-Aryl- or 4-benzyl-1-piperazinyl)alkyl]oxazolo[5,4-*b*]pyridin-2(1*H*)-ones



compd	*n*	R_1	R_2	R–N–R′	yield,[a] %	mp, °C	solvent[b]	formula	anal.
2a	0	H	H		90	182–183	iPrOH	$C_{18}H_{20}N_4O_2$	C, H, N
2b	0	H	H		89	136	EtOH	$C_{18}H_{19}N_4FO_2$	C, H, N
2c	0	H	H		79	142	EtOH	$C_{19}H_{22}N_4O_2$	C, H, N
2d	0	H	H		88	166	EtOH	$C_{22}H_{22}N_4O_2$	C, H, N
2e	0	H	H		79	102–103	EtOH	$C_{12}H_{15}N_3O_3$	C, H, N
2f	0	H	H		91	146	EtOH	$C_{19}H_{22}N_4O_3$	C, H, N
2g	0	H	H		64	90–91	iPrOH	$C_{12}H_{15}N_3O_2$	C, H, N
2h	0	H	H		85	99–100	iPrOH	$C_{19}H_{19}N_4O_2F_3$	C, H, N
2i	0	H	H		84	128	EtOH	$C_{19}H_{21}N_3O_2$	C, H, N
3a	1	H	H		96	120	EtOH	$C_{19}H_{22}N_4O_2$	C, H, N
3b	1	H	H		97	129	EtOH	$C_{19}H_{21}N_4O_2F$	C, H, N
3c	1	H	H		80	96	EtOH	$C_{20}H_{24}N_4O_2$	C, H, N
3d	1	H	H		83	142	EtOH	$C_{23}H_{24}N_4O_2$	C, H, N
3e	1	H	H		93	110	EtOH	$C_{13}H_{17}N_3O_3$	C, H, N
3f	1	H	H		84	152	EtOH	$C_{20}H_{24}N_4O_3$	C, H, N
3g	1	H	CH_3		42	113	EtOH	$C_{20}H_{23}N_4O_2F$	C, H, N
3h	1	CH_3	H		27	113	EtOH	$C_{20}H_{23}N_4O_2F$	C, H, N
4a	2	H	H		95	94	EtOH	$C_{20}H_{24}N_4O_2$	C, H, N
4b	2	H	H		81	130	EtOH	$C_{20}H_{23}N_4O_2F$	C, H, N
4c	2	H	H		84	107	iPrOH	$C_{21}H_{25}N_3O_2$	C, H, N
5	3	H	H		95	99	EtOH	$C_{21}H_{25}N_4O_2F$	C, H, N
6	4	H	H		83	88	EtOH	$C_{22}H_{27}N_4O_2F$	C, H, N

[a] Isolated yields of pure products following the general procedure. For compound **3h**, the yield is calculated from **1**. [b] Solvent of recrystallization.

Table 2. Analgesic Activity Screening of 1-(Aminoalkyl)- and 1-[(4-Aryl- or 4-benzyl-1-piperazinyl)alkyl]oxazolo[5,4-*b*]-pyridin-2(1*H*)-ones

	phenylquinone (PBQ)-induced writhing test (mice)		acetic acid-induced writhing test (rat)	
compd	% inhibtn at 50 mg/kg po[a]	activity ratio versus aspirin[b]	% inhibtn at 50 mg/kg po[a]	activity ratio versus aspirin[b]
2a	ND[c]	ND	74**[d]	ND
2b	83***	1.2	85**	1.2
2c	43**	0.9	48***	0.7
2d	33**	0.7	6	0.1
2e	ND	ND	35*	ND
2f	52*	0.8	53*	0.8
2g	55*	0.8	55*	0.8
2h	10	0.1	11	0.2
2i	9	0.1	50*	0.7
3a	98***	1.4	92**	1.3
3b	85***	1.6	79**	2.0
3c	14	0.3	12	0.2
3d	44***	0.9	0	0
3e	48***	0.9	0	0
3f	35***	0.7	14	0.2
3g	63***	1.3	51***	0.7
3h	99***	1.4	100***	1.6
4a	91***	1.3	96***	1.4
4b	100***	1.9	87***	2.2
4c	0	0	59*	1.5
5	100***	1.4	100***	1.6
6	100***	1.4	100***	1.6
10	25	0.4	43*	0.5

[a] Treated, $n = 5$; controls, $n = 7$. [b] Activity ratio = (% inhibition with the compound at 50 mg/kg po)/(% inhibition with aspirin at 50 mg/kg po). [c] Not determined. [d] $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

a fluorine in the para position. Every attempt to replace 1-phenylpiperazine by a morpholine (**2e, 3e**), pyrrolidine (**2g**), 4-phenylpiperidine (**2i, 4c**), 1-benzylpiperazine (**2c, 3c**), or 1-(1-naphthyl)piperazine (**2d, 3d**) led to a significant decrease of activity.

Substitutions on the phenyl ring of the phenylpiperazine moiety by a *m*-trifluoromethyl group (**2h**) or an *o*- or *p*-methoxy group (**2f, 3f**) markedly decreased activity versus nonsubstituted analogs (**2a, 3a**). On the other hand, analgesia was enhanced by substitution with *p*-fluorine (**2b, 3b**).

On the basis of the prescreening results, compound **3b** was selected as the starting point for structural modifications designed to decrease potential metabolic N-dealkylation. Compounds **3g,h** were synthesized with steric hindrance (methyl group) in the α or β position of the alkyl side chain, respectively, but both proved less active than the parent compound. Activity was also markedly decreased by replacing the $N-CH_2$ bond with an N−C=O bond (compound **10**).

Compounds more potent than aspirin in both screening tests (Table 2) were further investigated to isolate those with the highest analgesic activity and safety index, using the following parameters (Table 3): (1) determination of the ED_{50} po in the PBQ and acetic acid writhing tests, (2) evaluation of general acute toxicity and behavioral changes (the latter helps also to reduce false positives in the writhing test), and (3) determination of a safety index, defined as the ratio of the ED_{50} po over the dose causing the first behavioral changes in the Irwin test.

The ED_{50} data confirmed the prescreening results, i.e., whatever the length of the alkyl spacer, analgesic activity was significantly greater in 1-(4-fluorophenyl)-piperazine compounds **2b, 3b,** and **4b** than in their nonsubstituted analogs **2a, 3a,** and **4a**. Greatest potency was conferred by 3- and 4-carbon atom linear alkyl spacers (**3b** and **4b**, respectively). The compounds were arranged as follows by order of increasing activity: **4b** > **3b** > **2b** > **6** > **5**.

Sedation was the first behavioral change in almost all cases. **4b** and **3b** were equivalent in analgesic potency but had markedly different safety indices: in mice, sedation appeared at an 8-fold lower dose with **4b** (8 mg/kg po; safety index = 2.76) than with **3b** (64 mg/kg po; safety index = 11.43).

With a steric hindrance (methyl group) in the β position of the propyl side chain (compound **3h**), sedation appeared at a markedly higher dose (256 mg/kg po) versus the parent compound **3b** but the safety index remained unchanged (10.4) due to the lower analgesic activity. The mortality threshold doses in mice of the most active compounds, **3b,a** and **4b**, were approximately 1024, >1024, and <512 mg/kg po, respectively.

On the basis of analgesic potency and (in two cases) high safety index, **3b,a** and **4b** were selected for further pharmacological investigations (Table 4). The results of the hot-plate test in mice showed a significant increase in foot-licking latency: 30% (**3a,** 32 mg/kg ip), 87% (**3b,** 32 mg/kg ip), and 113% (**4b,** 8 mg/kg ip). Compound **4b** was also the most active as in the writhing tests but was not selected as the leader of the series because of its too low safety index. Compound

Table 3. Antinociceptive Potency, Acute Toxicity, and Safety Index of Preselected Compounds

	ED_{50}, mg/kg po[a]		orientative acute toxicity Irwin test (3 mice/dose)		
compd	phenylquinone (PBQ)-induced writhing test (8 mice/dose)	acetic acid-induced writhing test (8 rats/dose)	first adverse effect[b]	mortality threshold,[c] mg/kg po	safety index[d]
2a	25 (16.5−32.3)	13.6 (11−17)	sedation (128 mg/kg ip)		≥5.1[e]
2b	6.7 (3.0−14.3)	3.6 (1.6−6.4)	sedation (8 mg/kg ip)		≥1.2[e]
3a	12.7 (5.4−42.1)	3.3 (0.8−7.3)	sedation (64 mg/kg ip)	>1024	≥5.0[e]
3b	5.6 (4.4−7.2)	0.5 (0.2−0.8)	sedation (64 mg/kg po)	1024 (33%)	11.4
3h	24.6 (18.2−33.2)	20.5 (13.7−30.7)	sedation (256 mg/kg po)		10.4
4a	27 (9−76.1)	13.6 (11−17)	sedation (8 mg/kg po)		0.3
4b	2.9 (2.2−4.0)	0.5 (0.3−0.8)	sedation (8 mg/kg po)	512 (100%)	2.8
5	11.4 (8.9−14.5)	30.4 (28.4−32.5)	sedation (8 mg/kg po)		0.7
6	7.7 (6.3−9.6)	14.2 (9.7−20.6)	sedation (16 mg/kg po)		2.1
16	41.3 (15.5−162.6)[f]			>1000[f]	
17	15.5 (2.6−85.0)[f]			1000 (10%)[f]	
acetyl salicylic acid	63 (56−75)	32 (28−46)			

[a] Values in parentheses are confidence intervals determined at 95% ($p = 0.05$). [b] Values in parentheses represent the dose inducing the first adverse effect. [c] Values in parentheses represent the percent mortality. [d] Safety index = [dose inducing onset of the first behavioral effect in the Irwin test (mice po)]/[ED_{50} PBQ writhing test in the mice (po)]. [e] Safety index calculated with the ip dose inducing onset of sedation and therefore possibly underestimated. [f] See ref 5.

Table 4. Complementary Analgesic Studies and Antiinflammatory Evaluation

compd	hot-plate, % change in foot-licking latency (10 mice/dose)[a]	tail clip, no. of protected animals/total (10 mice/dose)[a]	carrageenan-induced rat paw edema (6 rats/dose)			
			dose, mg/kg po	variation of edema volume, %	inhibtn of PGE_2 synthesis, %	inhibtn of LTB_4 synthesis, %
3a	30 (32 mg/kg ip)* [b]		100	−20	5	35
3b	87 (32 mg/kg ip)*	3/10 (18 mg/kg po)* 8/10 (60 mg/kg po)***	50	−11	−5	16
4b	113 (8 mg/kg ip)***		50	−25	2	0
morphine sulfate	283 (16 mg/kg ip)***	5/10 (5 mg/kg po)***				
phenidone			200	−68	100	100
indomethacin			10	−57	100	18

[a] Doses are in parentheses. [b] $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

Table 5. Time Course of Analgesic Effects

compd	dose, mg/kg po	% inhibtn of acetic acid-induced writhing (rat) at time (min) postdose[a]					
		15 min	30 min	60 min	120 min	180 min	360 min
3b	1.5	47* [b]	65***	50**	63*	44*	4
acetylsalicyclic acid	30	53**	37**	60**	26	18	0

[a] Five rats per compound at each time. [b] $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

3b, which showed significant activity from 18 mg/kg po upwards in the tail clip test was therefore selected as being overall the most promising molecule in the series.

All the compounds **3a,b** and **4b** were shown to be lacking in antiinflammatory properties po in a carrageenan-induced rat paw edema test. No effect was observed on the edema volume or PGE_2 and LTB_4 production, reflecting an absence of activity on both cyclooxygenase and 5-lipoxygenase. In order to investigate possible mechanisms of action, binding studies were performed and showed an absence of affinity for the opioid and neurokin receptors (μ, δ, K, NK_1, NK_2, NK_3). Finally, the time course effect of **3b** was studied in the acetic acid writhing test in rats at a dose of 1.4 mg/kg po, and this compound proved to be analgesic 15 min after administration and at least 3 h afterwards (Table 5).

In conclusion, within the class of 1-(aminoalkyl)- and 1-[(4-aryl-1-piperazinyl)alkyl]oxazolo[5,4-*b*]pyridin-2(1*H*)-ones, we have shown that some compounds possess potent non-opioid antinociceptive activity without antiinflammatory properties. When compared, compounds having the oxazolo[5,4-*b*]pyridin-2(1*H*)-one moiety (i.e., **2b**, **3a**; structure C) proved to be more analgesic than their oxazolo[4,5-*b*]pyridin-2(3*H*)-ones analogs[5] (i.e., **16**, **17**; structure B), as shown in Table 3. We have finally selected compound **3b** as having a superior analgesic profile with a long time course effect, a rapid-onset action, and a low acute toxicity. Assuming it proves safe on chronic toxicity testing, **3b** could be a promising candidate for chemical development.

Experimental Section

Chemistry. Melting points were determined on a Köfler hot-stage apparatus and are uncorrected. Proton NMR were recorded on a Bruker 300 spectrometer. The coupling constants are recorded in hertz (Hz), and the chemical shifts are reported in parts per million (δ, ppm) downfield from tetramethylsilane (TMS), which was used as an internal standard. Infrared spectra were obtained with a Perkin-Elmer spectrophotometer 297. Mass spectra were recorded on a R 10-10 C Nermag (70 eV) apparatus. Organic solvents were purified when necessary by the methods described by D. D. Perin, W. L. F. Armarego, and D. R. Perrin (*Purification of Laboratory Chemicals*; Pergamon: Oxford, 1986) or purchased from Aldrich Chimie. All solutions were dried over anhydrous magnesium sulfate and evaporated on a Büchi rotatory evaporator. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel, 60 F-254), and spots were visualized with UV light or an alcohol solution of ammonium cerium(IV) nitrate. Column chromatography was performed with Kieselgel 60 (70−230 mesh) silica gel for gravity columns and Kieselgel 60 (230−400 mesh) silica gel (Merck) for flash columns. Where analyses in the tables are indicated by symbols of the elements, analytical results obtained for those elements were ±0.4% of the theoretical values. All anhydrous reactions were performed in over-dried glassware under an atmosphere of argon. The column chromatography solvents employed were distilled, and solvent mixtures were reported as volume to volume ratios. For the synthesis of compounds **2d** and **3d**, the 1-(1-naphthyl)piperazine used was prepared according to R. A. Glennon et al.[14]

1-(2-Bromoethyl)oxazolo[5,4-*b*]pyridin-2(1*H*)-one (11). To a stirred solution of oxazolo[5,4-*b*]pyridin-2(1*H*)-one (**1**)[13] (1.00 g, 7.35 mmol) in DMF (30 mL) was added sodium hydride (0.26 g, 11.02 mmol) (60% dispersion in oil) at room temperature, the reaction mixture was stirred at 60 °C over 40 min. After cooling, a solution of 1,2-dibromoethane (3.8 mL, 44.10 mmol) in DMF (5 mL) was added slowly to the reaction mixture. Then the mixture was stirred for 1.5 h at 110 °C. After cooling, the resulting residue was poured into water (50 mL), extracted with CH_2Cl_2 (2 × 50 mL), and dried over magnesium sulfate, and after evaporation the resulting product was purified by flash chromatography (eluent: MeCN/CH_2Cl_2, 5/95) to provide 1.36 g (77%) of **11**: mp 111 °C; IR (KBr) 3000−2900, 1760, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.48 (t, 2H, J = 6.6 Hz, **CH_2**), 4.26 (t, 2H, J = 6.6 Hz, **CH_2**), 7.15 (dd, 1H, J = 8.2, 5.6 Hz, C_6-H), 7.35 (d, 1H, J = 8.2 Hz, C_7-H), 8.08 (d, 1H, J = 5.6 Hz, C_5-H).

1-(3-Bromopropyl)oxazolo[5,4-*b*]pyridin-2(1*H*)-one (12a). Compound **12a** was prepared similarly to **11**, using 1,3-dibromopropane as starting reagent, and obtained with a yield of 55%: mp 64 °C; IR (KBr) 3000, 2900, 1760, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45 (m, 2H, **CH_2**), 3.48 (t, 2H, J = 6.6 Hz, **CH_2**), 4.10 (t, 2H, J = 6.6 Hz, **CH_2**), 7.18 (dd, 1H, J = 8.1, 5.2 Hz, C_6-H), 7.40 (dd, 1H, J = 8.1, 2.2 Hz, C_7-H), 8.15 (dd, 1*H*, J = 5.2, 2.2 Hz, C_5-H).

1-(3-Bromobutyl)oxazolo[5,4-*b*]pyridin-2(1*H*)-one (12b). Compound **12b** was prepared similarly to **11**, using 1,3-dibromobutane as starting reagent, and obtained with a yield of 68%: mp 70−72 °C; IR (KBr) 3000−2900, 1760, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75 (d, 3H, **CH_3**), 2.10−2.25 (m, 2H, **CH_2**), 2.40−2.50 (m, 2H, **CH_2**), 3.98−4.12 (m, 1H, **CH**), 7.18 (dd, 1H, J = 8.2, 5.2 Hz, C_6-H), 7.42 (d, 1H, J = 8.2, 2.2 Hz, C_7-H), 8.05 (d, 1H, J = 5.2, 2.2 Hz, C_5-H).

1-(4-Bromobutyl)oxazolo[5,4-*b*]pyridin-2(1*H*)-one (13). Compound **13** was prepared similarly to **11**, with 1,4-dibromobutane as starting reagent, and obtained with a yield of 64%: mp 50 °C; IR (KBr) 3100−2900, 1760, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92−2.03 (m, 4H, **$2CH_2$**), 3.46 (m, 2H, **CH_2**), 3.91 (m, 2H, **CH_2**), 7.16 (dd, 1H, J = 8.2, 5.2 Hz, C_6-H), 7.26 (dd, 1H, J = 8.1, 2.2 Hz, C_7-H), 8.05 (dd, 1H, J = 5.2, 2.2 Hz, C_5-H).

1-(5-Bromopentyl)oxazolo[5,4-*b*]pyridin-2(1*H*)-one (14). Compound **14** was prepared similarly to **11** with 1,5-dibromopentane as starting reagent. Before extractions, DMF and any excess of 1,5-dibromopentane were distilled using a Kugelröhr apparatus. Flash chromatography of the residue (eluent: Et_2O/petroleum ether, 3/1) gave pure **14** (20%): mp 74 °C; IR (KBr) 3100–2900, 1760, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16–1.56 (m, 2H, $\mathbf{CH_2}$), 1.73–1.82 (m, 2H, $\mathbf{CH_2}$), 1.83–1.93 (m, 2H, $\mathbf{CH_2}$), 3.36 (t, 2H, J = 6.6 Hz, $\mathbf{CH_2}$), 3.82 (t, 2H, J = 6.6 Hz, $\mathbf{CH_2}$), 7.11 (dd, 1H, J = 8.1, 5.2 Hz, C_6-H), 7.20 (dd, 1H, J = 8.1, 2.2 Hz, C_7-H), 8.00 (dd, 1H, J = 5.2, 2.2 Hz, C_5-H).

1-(6-Bromohexyl)oxazolo[5,4-*b*]pyridin-2(1*H*)-one (15). Compound **15** was prepared similarly to **14**, using 1,6-dibromohexane as starting reagent, and obtained with a yield of 26%: mp 50 °C; IR (KBr) 3100–2800, 1760, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37–1.59 (m, 4H, $\mathbf{2CH_2}$), 1.75–1.90 (m, 4H, $\mathbf{2CH_2}$), 3.38 (t, 2H, J = 6.6 Hz, $\mathbf{CH_2}$), 3.85 (t, 2H, J = 6.6 Hz, $\mathbf{CH_2}$), 7.13 (dd, 1H, J = 7.3, 5.2 Hz, C_6-H), 7.23 (dd, 1H, J = 7.3, 1.0 Hz, C_7-H), 8.03 (dd, 1H, J = 5.2, 1.0 Hz, C_5-H).

1-(Aminoalkyl)- and 1-[*n*-(4-Aryl- or 4-benzyl-1-piperazinyl)alkyl]oxazolo[5,4-*b*]pyridin-2(1*H*)-ones. General Procedure (Scheme 1). A mixture containing **11,12a,b**, and **13–15** (4.12 mmol), appropriate amine (6.17 mmol), diisopropylethylamine (0.80 g, 6.17 mmol), and MeCN (30 mL) was treated at 85 °C for 12 h. After cooling, the resulting residue was poured into water (100 mL), extracted with CH_2Cl_2 (2 × 100 mL), and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the desired product was purified by flash chromatography (eluents: Et_2O/CH_2Cl_2, 1/2, or MeOH/CH_2Cl_2, 5/95) and recrystallized from a suitable solvent.

1-[2-(4-Phenyl-1-piperazinyl)ethyl]oxazolo[5,4-*b*]pyridin-2(1*H*)-one (2a): IR (KBr) 3000–2600, 1750, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65–2.71 (m, 4H, $\mathbf{CH_{2piperaz}}$), 2.77 (t, 2H, J = 6.0 Hz, $\mathbf{CH_2}$), 3.12–3.17 (m, 4H, $\mathbf{CH_{2piperaz}}$), 3.99 (t, 2H, J = 6.0 Hz, $\mathbf{CH_2}$), 6.82–6.93 (m, 3H, **arom**), 7.13 (dd, 1H, J = 7.6, 5.1 Hz, C_6-H), 7.22–7.28 (m, 2H, **arom**), 7.31 (dd, 1H, J = 7.6, 1.0 Hz, C_7-H), 8.04 (dd, 1H, J = 5.1, 1.0 Hz, C_5-H); MS *m/z* 325 (M + 1).

1-[2-[4-(4-Fluorophenyl)-1-piperazinyl]ethyl]oxazolo-[5,4-*b*]pyridin-2(1*H*)-one (2b): IR (KBr) 3100–2800, 1760, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65–2.70 (m, 4H, $\mathbf{CH_{2piperaz}}$), 2.77 (t, 2H, J = 6.2 Hz, $\mathbf{CH_2}$), 3.03–3.08 (m, 4H, $\mathbf{CH_{2piperaz}}$), 4.00 (t, 2H, J = 6.2 Hz, $\mathbf{CH_2}$), 6.81–6.87 (m, 2H, **arom**), 6.92–6.98 (m, 2H, **arom**), 7.13 (dd, 1H, J = 7.7, 5.3 Hz, C_6-H), 7.30 (dd, 1H, J = 1.4 Hz, C_7-H), 8.04 (dd, 1H, J = 5.3, 1.4 Hz, C_5-H); MS *m/z* 343 (M + 1).

1-[2-(4-Benzyl-1-piperazinyl)ethyl]oxazolo[5,4-*b*]pyridin-2(1*H*)-one (2c): IR (KBr) 3100–2700, 1790, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30–2.45 (m, 4H, $\mathbf{CH_{2piperaz}}$), 2.47–2.50 (m, 4H, $\mathbf{CH_{2piperaz}}$), 2.67 (t, 2H, J = 6.2 Hz, $\mathbf{CH_2}$), 3.46 (s, 2H, $\mathbf{CH_{2benzyl}}$), 3.90 (t, 2H, J = 6.2 Hz, $\mathbf{CH_2}$), 7.09 (dd, 1H, J = 7.6, 5.1 Hz, C_6-H), 7.21–7.29 (m, 6H, C_7-H, **arom**), 7.99 (dd, 1H, J = 5.1, 1.3 Hz, C_5-H); MS *m/z* 339 (M + 1).

1-[2-(4-Naphthyl-1-piperazinyl)ethyl]oxazolo[5,4-*b*]pyridin-2(1*H*)-one (2d): IR (KBr) 3100–2700, 1800, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.73–2.89 (m, 6H, $\mathbf{CH_{2piperaz}}$, $\mathbf{CH_2}$), 3.10–3.12 (m, 4H, $\mathbf{CH_{2piperaz}}$), 4.02 (t, 2H, J = 6.0 Hz, $\mathbf{CH_2}$), 7.02 (d, 1H, **arom**), 7.12 (dd, 1H, J = 7.5, 5.3 Hz, C_6-H), 7.32–7.43 (m, 4H, C_7-H, **arom**), 7.51 (d, 1H, **arom**), 7.76–7.81 (m, 1H, **arom**), 8.01 (dd, 1H, J = 5.3, 1.3 Hz, C_5-H), 8.10–8.15 (m, 1H, **arom**); MS *m/z* 375 (M + 1).

1-(2-Morpholinoethyl)oxazolo[5,4-*b*]pyridin-2(1*H*)-one (2e): IR (KBr) 3000–2700, 1760, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.49–2.65 (m, 4H, $\mathbf{CH_{2morph}}$), 2.70 (t, 2H, J = 6.2 Hz, $\mathbf{CH_2}$), 3.62–3.66 (m, 4H, $\mathbf{CH_{2morph}}$), 3.93 (t, 2H, J = 6.2 Hz, $\mathbf{CH_2}$), 7.14 (dd, 1H, J = 8.1, 5.2 Hz, C_6-H), 7.27 (dd, 1H, J = 8.1, 1.4 Hz, C_7-H), 8.06 (dd, 1H, J = 5.2, 1.4 Hz, C_5-H); MS *m/z* 250 (M + 1).

1-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]oxazolo-[5,4-*b*]pyridin-2(1*H*)-one (2f): IR (KBr) 3000–2700, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.68–2.74 (m, 4H, $\mathbf{CH_{2piperaz}}$), 2.77 (t, 2H, J = 6.3 Hz, $\mathbf{CH_2}$), 2.99–3.06 (m, 4H, $\mathbf{CH_{2piperaz}}$), 3.84 (s, 3H, OCH_3), 3.97 (t, 2H, J = 6.3 Hz, $\mathbf{CH_2}$), 6.82–6.92 (m, 3H, **arom**), 6.95–7.02 (m, 1H, **arom**), 7.13 (dd, 1H, J = 7.9, 5.5 Hz, C_6-H), 7.31 (dd, 1H, J = 7.9, 1.2 Hz, C_7-H), 8.03 (dd, 1H, J = 5.5, 1.2 Hz, C_5-H); MS *m/z* 355 (M + 1).

1-[2-(1-Pyrrolidino)ethyl]oxazolo[5,4-*b*]pyridin-2(1*H*)-one (2g): IR (KBr) 3000–2800, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50–1.62 (m, 4H, $\mathbf{CH_{2pyrrol}}$), 1.71–1.81 (m, 2H, $\mathbf{CH_{2pyrrol}}$), 2.51–2.63 (m, 2H, $\mathbf{CH_{2pyrrol}}$), 2.85 (t, 2H, J = 6.3 Hz, $\mathbf{CH_2}$), 3.97 (t, 2H, J = 6.3 Hz, $\mathbf{CH_2}$), 7.13 (dd, 1H, J = 7.9, 5.5 Hz, C_6-H), 7.31 (dd, 1H, J = 7.9, 1.2 Hz, C_7-H), 8.03 (dd, 1H, J = 5.5, 1.2 Hz, C_5-H); MS *m/z* 234 (M + 1).

1-[2-[4-[3-(Trifluoromethyl)phenyl]-1-piperazinyl]ethyl]-oxazolo[5,4-*b*]pyridin-2(1*H*)-one (2h): IR (KBr) 3000–2700, 1760, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65–2.70 (m, 4H, $\mathbf{CH_{2piperaz}}$), 2.78 (t, 1H, J = 6.0 Hz, $\mathbf{CH_2}$), 3.14–3.19 (m, 4H, $\mathbf{CH_{2piperaz}}$), 3.98 (t, 2H, J = 6.0 Hz, $\mathbf{CH_2}$), 7.00–7.09 (m, 2H, **arom**), 7.14 (dd, 1H, J = 7.4, 5.4 Hz, C_6-H), 7.29–7.36 (m, 3H, C_7-H, **arom**), 8.02 (dd, 1H, J = 5.4, 1.0 Hz, C_5-H); MS *m/z* 393 (M + 1).

1-[2-(4-Phenyl-1-piperidinyl)ethyl]oxazolo[5,4-*b*]pyridin-2(1*H*)-one (2i): IR (KBr) 3100–2600, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58–173 (m, 2H, $\mathbf{CH_{2piperid}}$), 1.74–1.85 (m, 2H, $\mathbf{CH_{2piperid}}$), 2.12–2.20 (m, 2H, $\mathbf{CH_{2piperid}}$), 2.44–2.52 (m, 1H, $\mathbf{CH_{piperid}}$), 2.83 (t, 2H, J = 6.3 Hz, $\mathbf{CH_2}$), 3.06–3.15 (m, 2H, $\mathbf{CH_{2piperid}}$), 4.09 (t, 2H, J = 6.3 Hz, CH_2), 7.04 (dd, 1H, J = 7.09, 5.5 Hz, C_6-H), 7.14–7.31 (m, 5H, **arom**), 7.37 (d, 1H, J = 7.09, 1.2 Hz, C_7-H), 8.10 (d, 1H, J = 5.5, 1.2 Hz, C_5-H); MS *m/z* 324 (M + 1).

1-[3-(4-Phenyl-1-piperazinyl)propyl]oxazolo[5,4-*b*]pyridin-2(1*H*)-one (3a): IR (KBr) 3100–2700, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95–2.05 (m, 2H, $\mathbf{CH_2}$), 2.49 (t, 2H, J = 6.3 Hz, $\mathbf{CH_2}$), 2.50–2.55 (m, 4H, $\mathbf{CH_{2piperaz}}$), 3.10–3.15 (m, 4H, $\mathbf{CH_{2piperaz}}$), 3.92 (t, 2H, $\mathbf{CH_2}$), 6.82–6.93 (m, 3H, **arom**), 7.13 (dd, 1H, J = 7.5, 5.1 Hz, C_6-H), 7.23–7.29 (m, 2H, J = 6.3 Hz, $\mathbf{CH_{arom}}$), 7.34 (dd, 1H, J = 7.5, 1.2 Hz, C_7-H), 8.02 (dd, 1H, J = 5.1, 1.2 Hz, C_5-H); MS *m/z* 339 (M + 1).

1-[3-[4-(4-Fluorophenyl)-1-piperazinyl]propyl]oxazolo-[5,4-*b*]pyridin-2(1*H*)-one (3b): IR (KBr) 3100–2700, 1760, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95–2.05 (m, 2H, $\mathbf{CH_{2piperaz}}$), 2.46 (t, 2H, J = 6.1 Hz, $\mathbf{CH_2}$), 2.50–2.55 (m, 2H, $\mathbf{CH_{2piperaz}}$), 3.01–3.06 (m, 2H, $\mathbf{CH_{2piperaz}}$), 3.96 (t, 2H, J = 6.1 Hz, $\mathbf{CH_2}$), 6.82–6.88 (m, 2H, **arom**), 6.91–6.99 (m, 2H, **arom**), 7.13 (dd, 1H, J = 7.7, 5.1 Hz, C_6-H), 7.32 (dd, 1H, J = 7.7, 1.3 Hz, C_7-H), 8.03 (dd, 1H, J = 5.1, 1.3 Hz, C_5-H); MS *m/z* 356 (M).

1-[3-(4-Benzyl-1-piperazinyl)propyl]oxazolo[5,4-*b*]pyridin-2(1*H*)-one (3c): IR (KBr) 3100–2700, 1780, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.86–1.96 (m, 2H, $\mathbf{CH_2}$), 2.40–2.50 (m, 6H, $\mathbf{CH_2}$, $\mathbf{CH_{2piperaz}}$), 3.50 (s, 2H, $\mathbf{CH_{2benz}}$), 3.88 (t, 2H, J = 6.2 Hz, $\mathbf{CH_2}$), 7.08 (dd, 1H, J = 7.3, 5.4 Hz, C_6-H), 7.24–7.30 (m, 6H, C_7-H, **arom**), 7.98 (dd, 1H, J = 5.4, 1.0 Hz, C_5-H); MS *m/z* 353 (M + 1).

1-[3-(4-Naphthyl-1-piperazinyl)propyl]oxazolo[5,4-*b*]-pyridin-2(1*H*)-one (3d): IR (KBr) 3100–2700, 1800, 1700, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95–2.10 (m, 2H, $\mathbf{CH_2}$), 2.50 (t, 2H, J = 6.3 Hz, $\mathbf{CH_2}$), 2.60–2.80 (m, 2H, $\mathbf{CH_{2piperaz}}$), 2.95–3.15 (m, 2H, $\mathbf{CH_{2piperaz}}$), 3.96 (t, 2H, J = 6.3 Hz, $\mathbf{CH_2}$), 7.03 (d, 1H, **arom**), 7.10 (dd, 1H, J = 7.5, 5.2 Hz, C_6-H), 7.32–7.45 (m, 4H, C_7-H, **arom**), 7.52 (dd, 1H, **arom**), 7.75–7.81 (m, 1H, **arom**), 8.00 (dd, 1H, J = 5.2, 1.3 Hz, C_5-H), 8.08–8.15 (m, 1H, **arom**); MS *m/z* 389 (M + 1).

1-[3-(1-Morpholino)propyl]oxazolo[5,4-*b*]pyridin-2(1*H*)-one (3e): IR (KBr) 3100–2700, 1760, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.86–1.97 (m, 2H, $\mathbf{CH_2}$), 2.28–2.33 (m, 2H, $\mathbf{CH_{2morph}}$), 2.36 (t, 2H, J = 6.4 Hz, $\mathbf{CH_2}$), 3.55–3.61 (m, 2H, $\mathbf{CH_{2morph}}$), 3.91 (t, 2H, J = 6.4 Hz, $\mathbf{CH_2}$), 7.09 (dd, 1H, J = 7.6, 5.1 Hz, C_6-H), 7.26 (dd, 1H, J = 7.6, 1.3 Hz, C_7-H), 7.99 (dd, 1H, J = 5.1, 1.3 Hz, C_5-H); MS *m/z* 264 (M + 1).

1-[3-[4-(4-Methoxyphenyl)-1-piperazinyl]propyl]oxazolo[5,4-*b*]pyridin-2(1*H*)-one (3f): IR (KBr) 3000–2700, 1760, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90–2.03 (m, 2H, $\mathbf{CH_2}$), 2.42 (t, 2H, J = 6.2 Hz, $\mathbf{CH_2}$), 2.46–2.53 (m, 4H, $\mathbf{CH_{2piperaz}}$), 2.95–3.02 (m, 4H, $\mathbf{CH_{2piperaz}}$), 3.73 (s, 3H, OMe), 3.92 (t, 2H, J = 6.2 Hz, $\mathbf{CH_2}$), 6.77–6.87 (m, 4H, **arom**), 7.09 (dd, 1H, J = 7.6, 5.3 Hz, C_6-H), 7.30 (dd, 1H, J = 7.6, 1.2 Hz, C_7-H), 7.98 (dd, 1H, J = 5.3, 1.2 Hz, C_5-H); MS *m/z* 369 (M + 1).

1-[3-[4-(4-Fluorophenyl)-1-piperazinyl]butyl]oxazolo-[5,4-*b*]pyridin-2(1*H*)-one (3g): IR (KBr) 3100–2700, 1800, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (d, 3H, J = 6.5 Hz, $\mathbf{CH_3}$), 1.75–1.88 (m, 1H, $\mathbf{CH_2}$), 1.90–2.05 (m, 1H, $\mathbf{CH_2}$), 2.48–2.58 (m, 2H, $\mathbf{CH_{2piperaz}}$), 2.70–2.80 (m, 3H, $\mathbf{CH_{2piperaz}}$, CH), 2.98–3.16 (m, 4H, $\mathbf{CH_{2piperaz}}$), 3.97 (t, 2H, J = 6.9 Hz, $\mathbf{CH_2}$), 6.83–

6.90 (m, 2H, **arom**), 6.93–7.00 (m, 2H, **arom**), 7.13 (dd, 1H, J = 7.7, 5.0 Hz, C_6-H), 7.34 (dd, 1H, J = 7.7, 1.3 Hz, C_7-H), 8.02 (dd, 1H, J = 5.0, 1.3 Hz, C_5-H); MS m/z 371 (M + 1.

1-[2-Methyl-3-[4-(4-fluorophenyl)-1-piperazinyl]-propyl]oxazolo[5,4-*b*]pyridin-2(1*H*)-one (3h). Compound **3h** was prepared according to the following procedure. Compound **1** was treated similar to **11**, using 1-bromo-3-chloro-2-methylpropane as starting reagent. The resulting compound of this reaction was engaged without purification with 4-(fluorophenyl)piperazine, following the general procedure: IR (KBr) 3100–2700, 1760, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, 3H, J = 6.5 Hz, **CH_3**), 2.18–2.24 (m, 1H, **CH_2**), 2.30–2.42 (m, 4H, **CH_2**, **$CH_{2piperaz}$**, **CH**), 2.47–2.57 (m, 2H, **$CH_{2piperaz}$**), 2.77–2.88 (m, 2H, **$CH_{2piperaz}$**), 2.89–3.00 (m, 4H, **$CH_{2piperaz}$**), 3.65 (dd, 1H, J = 14.3, 5.9 Hz, **CH_2**), 3.95 (m, 1H, **CH_2**), 6.74–6.81 (m, 4H, **arom**), 6.88–6.94 (m, 2H, **arom**), 7.08 (dd, 1H, J = 7.5, 5.4 Hz, C_6-H), 7.24 (d, 1H, J = 7.5 Hz, C_7-H), 7.98 (d, 1H, J = 5.4 Hz, C_5-H); MS m/z 371 (M + 1).

1-[4-(4-Phenyl-1-piperazinyl)butyl]oxazolo[5,4-*b*]pyridin-2(1*H*)-one (4a): IR (KBr) 3100–2700, 1760, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56–1.62 (m, 2H, **CH_2**), 1.80–1.92 (m, 2H, **CH_2**), 2.44 (t, 2H, J = 7.1 Hz, **CH_2**), 2.55–2.60 (m, 4H, **$CH_{2piperaz}$**), 3.15–3.20 (m, 4H, **$CH_{2piperaz}$**), 3.89 (t, 2H, **CH_2**), 6.82–6.94 (m, 3H, **arom**), 7.14 (dd, 1H, J = 7.5, 5.2 Hz, C_6-H), 7.23–7.29 (m, 2H, **arom**), 7.26 (dd, 1H, J = 7.5, 1.3 Hz, C_7-H), 8.04 (dd, 1H, J = 5.2, 1.3 Hz, C_5-H); MS m/z 353 (M + 1).

1-[4-[4-(4-Fluorophenyl)-1-piperazinyl]butyl]oxazolo-[5,4-*b*]pyridin-2(1*H*)-one (4b): IR (KBr) 3100–2700, 1750, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55–1.70 (m, 2H, **CH_2**), 1.80–1.91 (m, 2H, **CH_2**), 2.44 (t, J = 6.6 Hz, **CH_2**), 2.54–2.59 (m, 4H, **$CH_{2piperaz}$**), 3.07–3.12 (m, 4H, **$CH_{2piperaz}$**), 3.89 (t, 2H, J = 6.6 Hz, **CH_2**), 6.82–6.98 (m, 4H, **arom**), 7.14 (dd, 1H, J = 6.4, 5.5 Hz, C_6-H), 725 (dd, 1H, J = 6.4, 1.3 Hz, C_7-H), 8.04 (dd, 1H, J = 5.5, 1.3 Hz, C_5-H); MS m/z 370 (M).

1-[4-(4-Phenyl-1-piperazinyl)butyl]oxazolo[5,4-*b*]pyridin-2(1*H*)-one (4c): IR (KBr) 3100, 2700, 1760, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55–1.65 (m, 2H, **CH_2**), 1.72–1.89 (m, 2H, **CH_2**), 1.99–2.10 (m, 5H, **$CH_{2piperid}$**), 2.41 (t, 2H, J = 7.1 Hz, **CH_2**), 2.95–3.04 (m, 4H, **$CH_{2piperid}$**), 3.85 (t, 2H, J = 7.1 Hz, **CH_2**), 7.12 (dd, 1H, J = 7.4, 5.2 Hz, C_6-H), 7.16–7.30 (m, 6H, C_7-H, **arom**), 8.12 (dd, 1H, J = 5.2, 1.3 Hz, C_5-H); MS m/z 352 (M + 1).

1-[5-[4-(4-Fluorophenyl)-1-piperazinyl]pentyl]oxazolo-[5,4-*b*]pyridin-2(1*H*)-one (5): IR (KBr) 3000–2700, 1760, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35–1.48 (m, 2H, **CH_2**), 1.52–1.64 (m, 2H, **CH_2**), 1.75–1.88 (m, 2H, **CH_2**), 2.38 (t, 2H, J = 7.4 Hz, **CH_2**), 2.55–2.60 (m, 4H, **$CH_{2piperaz}$**), 3.05–3.15 (m, 4H, **$CH_{2piperaz}$**), 3.85 (t, 2H, J = 7.4 Hz, **CH_2**), 6.80–6.99 (m, 4H, **arom**), 7.13 (dd, 1H, J = 7.4, 5.2 Hz, C_6-H), 7.22 (dd, 1H, J = 7.4, 1.5 Hz, C_7-H), 8.03 (dd, 1H, J = 5.2, 1.5 Hz, C_5-H); MS m/z 385 (M + 1).

1-[6-[4-(4-Fluorophenyl)-1-piperazinyl]hexyl]oxazolo-[5,4*b*]pyridin-2(1*H*)-one (6): IR (KBr) 3100–2700, 1760, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30–1.42 (m, 4H, **CH_2**), 1.45–1.56 (m, 2H, **CH_2**), 1.70–1.82 (m, 2H, **CH_2**), 2.36 (t, 2H, J = 7.4 Hz, **CH_2**), 2.53–2.61 (m, 4H, **$CH_{2piperaz}$**), 3.05–3.15 (m, 4H, **$CH_{2piperaz}$**), 3.81 (t, 2H, J = 7.4 Hz, **CH_2**), 6.80–6.95 (m, 4H, **arom**), 7.11 (dd, 1H, J = 7.4, 5.2 Hz, C_6-H), 7.19 (dd, 1H, J = 7.4, 1.3 Hz, C_7-H), 8.00 (dd, 1H, J = 5.2, 1.3 Hz, C_5-H); MS m/z 399 (M + 1).

1-(3-Butenyl)oxazolo[5,4-*b*]pyridin-2(1*H*)-one (7). To a solution of sodium ethoxide, prepared by addition of sodium (0.46 g, 20 mmol) to 200 mL of anhydrous EtOH, was added oxazolo[5,4-*b*]pyridin-2(1*H*)-one (**1**) (2.72 g, 20 mmol), and the resulting solution was stirred at room temperature for 1 h. The solvent was removed by rotatory evaporation yielding the sodium salt. The resulting solid was dissolved in 20 mL of DMF, and this solution was added dropwise to a solution of 4-bromo-1-butene (2.03 mL, 20 mmol) in 8 mL of DMF. The reaction mixture was heated at 110 °C for 1 h, at which time the reaction mixture was cooled to room temperature and concentrated. After addition of water (2 × 100 mL), the mixture was extracted with CH_2Cl_2 (2 × 100 mL). The extracts were dried with $MgSO_4$, and the solvent was removed under vacuum. Flash chromatography (eluent: CH_2Cl_2) of the residue gave 2.71 g of pure **7** (70%): IR (KBr) 3100–2900, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48 (m, 2H, J = 7.3 Hz, **CH_2**), 3.85 (m, 2H, **CH_2**), 5.02 (dd, J = 3.7, 12 Hz, 2H), 5.65–5.80 (m, 1H, **CH**), 7.07 (dd, 1H, J = 5.2, 8.1 Hz, C_6-H), 7.17 (dd, 1H, J = 1.5, 8.1 Hz, C_7-H), 7.97 (dd, 1H, J = 5.2, 1.5 Hz, C_5-H).

3-[1-(Oxazolo[5,4*b*]pyridin-2(1*H*)-one)]propanal (8). Compound **7** (0.9 g, 4.71 mmol) was dissolved in a solution of (CH_2Cl_2/MeOH, 4/1) at −78 °C and placed in an ozonolysis apparatus. After 10 min of reaction, the excess of ozone was removed by nitrogen stream and 10 equiv of methyl sulfide was added to the solution, which was then allowed to warm up to room temperature. The solvents were evaporated. Flash chromatography (eluent: MeOH/CH_2Cl_2, 5/95) of the residue gave 0.600 g of pure **8** (75%): IR (KBr) 3500–3000, 1760, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.07 (t, 2H, J = 6.1 Hz, **CH_2**), 4.10 (t, 2H, **CH_2**), 7.16 (dd, 1H, J = 5.2, 7.7 Hz, C_6-H), 7.47 (dd, 1H, J = 7.7, 1.1 Hz, C_7-H), 8.01 (dd, 1H, J = 5.2, 1.1 Hz, C_5-H), 9.80 (s, 1H, **CHO**); MS m/z 193 (M + 1).

3-[1-(Oxazolo[5,4-*b*]pyridin-2(1*H*)one)]propanoic Acid (9). Compound **8** (1.0 g, 5.2 mmol) was dissolved in tBuOH (25 mL). To this solution was added a solution 1 M $KMnO_4$ (25 mL) at room temperature. The mixture was stirred for 3 h at the same temperature. Addition of a solution of Na_2SO_3, followed by filtration and evaporation, gave a residue which was poured into water (50 mL) and extracted with methylene chloride (2 × 100 mL). The aqueous layer was adjusted to pH = 4. Filtration gave 0.725 g of pure **9** (67%): IR (KBr) 3000–2800, 1760, 1700 cm^{-1}; ^1H NMR (DMSO) δ 2.68 (t, 2H, J = 6.6 Hz, **CH_2**), 3.97 (t, 2H, J = 6.6 Hz, **CH_2**), 7.22 (dd, 1H, J = 5.9, 8.1 Hz, C_6-H), 7.67 (dd, 1H, J = 8.1, 1.3 Hz, C_7-H), 7.91 (dd, 1H, J = 5.9, 1.3 Hz, C_5-H), 12.4 (s, 1H, COOH); MS m/z 209 (M + 1).

1-[3-Oxo-3-[4-(4-fluorophenyl)-1-piperazinyl]propyl]-oxazolo[5,4-*b*]pyridin-2(1*H*)-one (10). To a stirred solution of compound **9** (800 mg, 3.84 mmol) in DMF (12 mL) was added at room temperature 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (810 mg, 4.22 mmol), hydroxybenzotriazole (590 mg, 3.84 mmol), and 4-(fluorophenyl)piperazine (762 mg, 4.22 mmol). The reaction mixture was stirred for 18 h at room temperature. After evaporation of the solvent, the residue was poured into water (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The extracts were dried over $MgSO_4$, and the solvent was removed under vacuum. Chromatography (eluent: AcOEt) of the residue gave 1.31 g of pure **10** (92%): mp 136 °C; ^1H NMR ($CDCl_3$) δ 2.88 (t, 2H, J = 6.1 Hz, **CH_2**), 2.96 (t, 2H, **$CH_{2piperaz}$**), 3.01 (t, 2H, **$CH_{2piperaz}$**), 3.95 (t, 2H, **$CH_{2piperaz}$**), 3.67 (t, 2H, **$CH_{2piperaz}$**), 4.15 (t, 2H, **CH_2**), 6.78–6.84 (m, 2H, **arom**), 6.90–6.97 (m, 2H, **arom**), 7.13 (dd, 1H, J = 5.0, 7.7 Hz, C_6-H), 7.53 (dd, 1H, J = 7.7, 1.3 Hz, C_7-H), 7.98 (dd, 1H, J = 5.0 Hz, C_5-H); MS m/z 371 (M + 1).

Pharmacological Methods. Phenylquinone (PBQ)-Induced Writhing in Mice. Male CD1 mice in the weight range of 20–25 g were used for the study after an overnight fast. The test compounds were suspended in 0.5% carboxymethyl cellulose at each of the required doses immediately prior to dosing. The mice were dosed orally with either test compound or vehicle using a constant dose volume of 10 mL/kg. For the screening evaluation at 50 mg/kg, there were seven animals in the control group and five animals in each of the treated groups. Thirty minutes after oral treatment, each mouse received an intraperitoneal injection of 0.25 mL or a solution containing 0.01% phenylquinone in 5% ethanol. The number of writhes elicited in each mouse during the period between the 5th and 25th minute after phenylquinone administration was recorded.[15,16] The ratio of the mean writhes of the control animals versus the mean writhes of the treated animals was calculated, and the results are expressed as a percentage of inhibition (Table 2). For the ED_{50} determination, eight animals were used per dose and the 95% confidence limits were estimated using the probit method of Finney.[17]

Acetic Acid-Induced Writhing in Rats. Male Wistar rats in the weight range of 140–160 g were used for the study after an overnight fast. The test compounds were suspended in 0.5% carbomethyl cellulose at each of the required doses immediately prior to dosing. The rats were dosed orally with either the test compound or the vehicle using a constant dose volume of 10 mL/kg. For the screening evaluation at 50 mg/kg, there were seven animals in the control group and five

animals in each of the treated groups. Thirty minutes after oral treatment, each rat received an intraperitoneal injection of 1.0 mL of a solution containing 1% acetic acid in distilled water. The number of writhes elicited in the following 25 min period was recorded.[18] The ratio of the mean writhes of the control animals versus the mean writhes of the treated animals was calculated, and the results are expressed as a percentage of inhibition (Table 2). For the ED_{50} determination, eight animals were used per dose and the 95% confidence limits were estimated using the probit method of Finney.[17]

Examination of the Time Course of Analgesic Effects in the Acetic Acid Writhing Test in Rats. Using the same methodology, a group of 60 rats (male, Wistar) were used. Subgroups of 10 rats were examined 15, 30, and 60 min and 2, 3, and 6 h after oral administration of the compound or vehicle. At the postdose times indicated, each rat received an intraperitoneal injection of 1.0 mL of a 1.0% solution of acetic acid. The number of writhes elicited in each rat in the following 25 min period was recorded.[18]

Hot-Plate Test in Mice. According to the method described by Eddy,[19] mice were placed on a heated plate (55 °C) inside a plexiglass cylinder. The latency before the animals started to lick their feet was measured. If no reaction was noted, the test was terminated after 120 s. Ten animals were studied per dose (dispersed in a 5% acacia gum suspension at a volume of 0.25 mg/20 g). The compound administration was performed 1 h (po) or 30 min (ip) before the test.

Evaluation of Toxic, Physiological, and Behavioral Effects in Mice (Irwin). Three animals per dose were administered po with the test compound (dispersed in a 5% acacia gum suspension at a volume of 0.25 mg/20 g) and observed according to a standardized observation grid at regular intervals for up to 24 h. The presence or absence and the intensity of various symptoms were noted.[20,21]

Tail Clip Test in Mice. Male CD1 mice were used in the study. The test was performed according to the method of Bianchi and Francheschini[22] with 10 animals per group. At 45 and 90 min and 3 and 6 h after administration, all animals were tested for a pain response induced by application of an artery clip to the base of the tail. Biting of the clip three or more times in a 30 s period was taken as the criteria for lack of analgesia.[23]

Receptor Binding Assay. Receptor binding assays were performed by incubating membranes prepared from the rat central nervous system with [^{3}H]DAMGO, [^{3}H]-*p*-Cl-Phe-DPDPE, [^{3}H][Sar^9,Met(O_2)^{11}]-SP, and [^{3}H]SENKTIDE, respectively, for receptors μ, δ, NK_1, and NK_3.[24-27] For receptor K, membrane was prepared from guinea pig cerebellum incubated with [^{3}H]U 69593.[28] For receptor NK_2, membrane was prepared from rat duodenum incubated with [^{125}I]His-NKA.[29] After the incubation period, bound and unbound radioligand were separated by filtration. Radioactivity bound to membranes in the absence and presence of compounds was counted in a liquid scintillation counter. Triplicates of each compound were studied at two concentrations (10^{-7} and 10^{-5} M).

Carrageenan Paw Edema in Rats. Wistar male rats (200 ± 20 g) were used for the study (six animals per group). One hour after oral administration of the compound (suspended in 2% gelatine), 0.1 mL of a 2% solution of carrageenan in saline was injected into the plantar area of the hind paw. Three hours later, the inflammation was characterized by the increased volume of the hind paw (measured with a plethysmometer, UGO BASILE) compared to the value obtained before carrageenan injection.[30] The potential antiinflammatory activity of the compounds was evaluated by the reduction of the increased volume compared to the control animals (results are expressed as the percentage of the increased volume of the control animals). Afterwards, animals were sacrified and antiinflammatory mediators were isolated. After prostaglandin and leukotriene extraction, the cyclooxygenase and 5-lipoxygenase activities were determined by a radioimmunoassay measuring the level of PGE_2 and LTB_4, respectively (results are expressed as the percentage of control animal activity).[31-33]

Acknowledgment. The phenylquinone- and acetic acid-induced writhing tests and tail clip tests were performed at the Hungtington Research Centre (Cambridgeshire, PE18 6ES, England). The receptor binding assays and carrageenan paw edema tests were performed at CEREP (86600 Celle l'Evescault, France). The hot-plate and general behavior tests were performed at ITEM Labo (53940 Le Genest Sainte Isle, France). The authors thank Miss N. Le Pors for typing the manuscript.

Supplementary Material Available: Further text and four tables corresponding to the information presented in this article (6 pages). Ordering information is given on any current masthead page.

References

(1) Vaught, J. L.; Carson, J. R.; Carmosin, R. J.; Blum, P. S.; Persico, F. J.; Hageman, W. E.; Hank, R. P.; Raffa, R. B. Antinociceptive Action of MCN-5195 in Rodents: a Structurally Novel (Indolizine) Analgesic with a Nonopioid Mechanism of Action. *J. Pharmacol. Exp. Ther.* **1990**, *255*, 1-10.
(2) Clinch, D.; Banerjee, A. K.; Ostick, G.; Levy, D. W. Non-Steroidal Anti-Inflammatory Drugs and Gastrointestinal Adverse Effects. *J. R. Coll. Physicians London* **1983**, *17*, 228-230.
(3) Jaffe, J. H.; Martin, W. R. Opioid Analgesics and Antagonists. In *Pharmacological Basis of Therapeutics*; Goodman, L. S., Gilman, A., Rall, T. W., Nics, A. S., Taylor, P., Eds.; Pergamon Press: New York, 1990; pp 485-521.
(4) Bermann, M. C.; Bonte, J. P.; Lesieur-Demarquilly, I.; Debaert, M.; Lesieur, D.; Leinot, M.; Benoit, J.; Labrid, C. Pharmacomodulation du Modèle Benzoxazolinone par la Structure Arylpipérazinique. *Eur. J. Med. Chem.* **1982**, *17*, 85-88.
(5) Flouzat, C.; Bresson, Y.; Mattio, A.; Bonnet, J.; Guillaumet, G. Novel Non Opioid Non Anti-inflammatory Analgesics: 3-aminoalkyl and 3-(4-aryl-1-piperazinylalkyl)oxazolo[4,5-*b*]pyridin-2(3*H*)-ones. *J. Med. Chem.* **1993**, *36*, 497.
(6) Adam, G. Unpublished results.
(7) Csik, G.; Besson, T.; Coudert, G.; Guillaumet, G.; Nocentini, S. Biophysical and Biological Properties of Newly Synthesized Dioxinocoumarin Derivatives. I. Dark Effects on T7 Phage and Hela Cells. *J. Photochem. Photobiol., Biol. Sect.* **1993**, *19*, 119-124.
(8) Benarab, A.; Guillaumet, G. Synthesis and Serotoninergic Activity of 8-[4-(2,3-Dihydro-1,4-dioxino[2,3-*b*]pyridine-2-yl-methylamino)butyl]-8-azaspiro[4,5]decane-7,9-dione. *Heterocycles* **1993**, *36*, 2327-2333.
(9) Besson, T.; Podona, T.; Baudin, M. L.; Coudert, G.; Guillaumet, G. Fluorescent Probes for 5-HT_{1A} Receptors: Synthesis and Characterization of 5-Methoxy-3-[n-propyl-(4-n-aminobutyl)]-amino-3,4-dihydro-2*H*-1-benzopyran Derivatives. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1935-1940.
(10) Guillaumet, G.; Hretani, M.; Coudert, G.; Averbeck, D.; Averbeck, S. Synthesis and Photoinduced Biological Properties of Linear Dioxinocoumarins. *Eur. J. Med Chem.* **1990**, *25*, 45-51.
(11) Al Neirabeyeh, M.; Reynaud, D.; Podona, T.; Ou, L.; Perdicakis, C.; Coudert, G.; Guillaumet, G.; Pichat, L.; Gharib, A.; Sarda, N. Methoxy and Hydroxy Derivatives of 3,4-dihydroxy-3-(di-n-propylamino)-2*H*-1-benzopyrans: New Synthesis and Dopaminergic Activity. *Eur. J. Med. Chem.* **1991**, *26*, 497-504.
(12) Bagley, J. R.; Thomas, S. A.; Rudo, F. G.; Kenneth Spencer, H.; Doorley, B. M.; Ossipov, M. H.; Jerussi, T. P.; Benvenga, M. J.; Spaulding, T. New 1-(heterocycloalkyl)-4-(propionanilido)-4-piperidinyl Methyl Ester and Methylene Methyl Ether Analgesics. *J. Med. Chem.* **1991**, *34*, 827-841.
(13) Flouzat, C.; Blanchet, M.; Guillaumet, G. Synthesis and N-Substitution of an Uncommon Heterocylic System: Oxazolo[5,4-*b*]pyridin-2(1*H*)-one. *Tetrahedron Lett.* **1992**, *33*, 4571-4574.
(14) Glennon, R. A.; Slusher, R. M.; Lyon, R. A.; Titeler, M.; McKenney, J. D. 5-HT_1 and 5-HT_2 Binding Characteristics of Some Quipazine Analogues. *J. Med. Chem.* **1986**, *29*, 2375-2380.
(15) Siegmund, E.; Cadmus, R.; Lu, G. A. Method for Evaluating Both Non-Narcotic and Narcotic Analgesia. *Proc. Sol. Exp. Biol. Med.* **1957**, *95*, 729-731.
(16) Pearl, J.; Stander, H.; McKean, D. B. Effects of Analgesic and other Drugs in Mice in Phenylquinone and Rotarod Tests. *J. Pharmacol. Exp. Ther.* **1968**, *167*, 9-13.
(17) Finney, D. J. *Probit Analysis*, 3rd ed.; Cambridge University Press: Cambridge, U.K., 1971.
(18) Koster, R.; Anderson, M.; Debeer, E. J. Acetic Acid for Analgesic Screening. *Fed. Proc.* **1959**, *18*, 412.
(19) Eddy, N. B.; Leimbach, D. Synthetic Analgesics-II-Dithienylbutenyl- and Dithienylbutylamines. *J. Pharmacol. Exp. Ther.* **1953**, *107*, 385-393.
(20) Irwin, S. Comprehensive Observational Assessment: Ia. A Systematic Quantitative Procedure for Assessing the Behav-

ioural and Physiologic State of the Mouse. *Psychopharmacologia* **1968**, *13*, 222–257.
(21) Boissier, J. M.; Simon, P. Action de la Caféine sur la Mobilité Spontanée de la Souris. *Arch. Int. Pharmacodyn.* **1965**, *158*, 212–221.
(22) Bianchi, C.; Francheschini, J. Experimental Observations on Haffner's Method for Testing Analgesic Drugs. *Br. J. Pharmacol.* **1954**, *9*, 280–284.
(23) Haffner, F. Experimentelle Prüfung Schmerzstillender Mittel. *Dtsch. Med. Wochenschr.* **1929**, *55*, 731–733.
(24) Yoburn, B. C.; Lutfy, K.; Candido, J. Species Differences in μ- and δ-Opioid Receptors. *Eur. J. Pharmacol.* **1991**, *193*, 105–108.
(25) Vaughn, L. K.; Knapp, R. J.; Toth, G.; Wan, Y. P.; Hruby, V. J.; Yamamura, H. J. A High Affinity, Highly Selective Ligand for the Delta Opioid Receptor: [^{3}H]-(D-Pen^2,pCl-Phe^4,D-Pen^5)-enkephalin. *Life Sci.* **1989**, *45*, 1001–1008.
(26) Beresford, I. J. M.; Birch, P. J.; Hagan, R. M.; Ireland, S. J. Investigation into Species Variants in Tachykinin NK_1 Receptors by Use of the Non-Peptide Antagonists, CP-96,345. *Br. J. Pharmacol.* **1991**, *104*, 292–293.
(27) Guard, S.; Watson, S. P.; Maggio, J. E.; Phon Too, H.; Watling, K. J. Pharmacological Analysis of [^{3}H]-Senktide Binding to NK_3 Tachykinin Receptors in Guinea-Pig Ileum Longitudinal Muscle-Myenteric Plexus and Cerebral Cortex Membranes. *Br. J. Pharmacol.* **1990**, *99*, 767–773.
(28) Kinouchi, K.; Pasternak, G. W. Evidence for κ_1 Opioid Receptor Multiplicity in the Guina Pig Cerebellum. *Mol. Pharmacol.* **1991**, *207*, 135–141.
(29) Patacchini, R.; Astolfi, M.; Brown, M. C. S.; Maggi, C. A. Actinomycin D is a Competitive and Selective Antagonist at NK_2 Tachykinin Receptors. *Neuropeptides* **1991**, *20*, 109–114.
(30) Winter, C. A.; Risley, E. A.; Nuss, G. W. Carrageenan-Induced Edema In Hind Paw of the Rat as an Assay for Anti-Inflammatory Drugs. *Proc. Soc. Exp. Med.* **1962**, *111*, 544–547.
(31) Dowling, E. J.; Symons, A. M.; Parke, D. V. Free Radical Production at the Site of an Acute Inflammatory as Measured by Chemiluminescence. *Agents Actions* **1986**, *19*, 203–207.
(32) French, C. E.; Allen, J. R.; David, K. J. Bioassay for Anti-Inflammatory Substances. *Proc. Soc. Exp. Biol. Med.* **1955**, *89*, 41–43.
(33) Palm, C. D.; Levin, B. A. A New Approach to the extraction for Prostaglandins 6-Keto, F1a, F2a, E2 and E1, from Gastric Mucosa with Quantitative Analysis by Reverse Phase Liquid Chromatography. *J. Liq. Chromatogr.* **1988**, *11*, 811–826.

JM9401826