Novel Nonopioid Non-Antiinflammatory Analgesics: 3-(Aminoalkyl)- and 3-[(4-Aryl-1-piperazinyl)alkyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-ones

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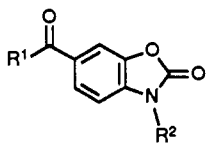
A series of 3-(aminoalkyl)- and 3-[(4-aryl-1-piperazinyl)alkyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-ones were prepared from their respective oxazolo[4,5-*b*]pyridin-2(3*H*)-ones. Several members of this group were found to possess potent analgesic activity in the mouse during a *p*-phenylquinone writhing induced test. Among them, phenylpiperazine compounds with two-carbon length alkyl chains, **2a** and **2b**, appeared by high analgesic with little toxicity having neither an antiinflammatory effect nor opioid receptor affinity. The synthesis and structure–affinity relationships for this series are detailed.

Introduction

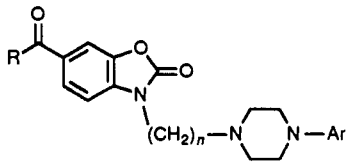
Today, many pain syndromes are still unsatisfactorily treated including those whose cause remains unknown such as low-back and female pelvic pains, as well as those stemming from known causes like rheumatoid arthritis and certain advanced cancers. Despite the numerous drugs available, as well as sensory and psychological techniques, these pains remain uncontrollable.[1]

Two main groups of analgesics on the market are the opioids such as morphine and codeine and the nonsteroidal antiinflammatory agents including aspirin, paracetamol, and ibuprofen. The opioids act on the central nervous system which can result in dependence, hence limiting their clinical use.[2] The nonsteroidal antiinflammatory drugs unfortunately act mainly peripherally by inhibiting the prostaglandin synthesis but induce gastrointestinal lesions.[3]

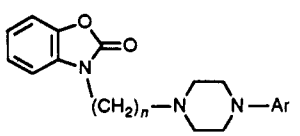
In the literature it is shown that the acylation of the benzoxazolinone moiety seems to bring an element of hope concerning these problems.[4] While compound A, having a hydrogen or methyl group on the nitrogen atom of the oxazolinone ring, shows favorable analgesic activity, compound B, having in addition to an acylic substituent fixed on the aromatic nucleus a (4-aryl-1-piperazinyl)alkyl moiety, displays much less analgesic activity. Moreover, nonacylated C derivatives, carrying a single (arylpiperazinyl)alkyl group, manifested significant analgesic activity.[5]



A

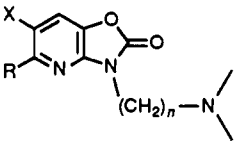


B



C

Replacing the carbon by a heteroatom in a drug template is a common strategy in medicinal chemistry. In connection with our studies on heteropolycyclic compounds with potential biological activity,[6-9] we report here the synthesis and biology of a series of general formula compounds D, 4-aza analogs of benzoxazolinones C.



D

Substitution of a pyridine ring for a benzene ring is often compatible with retention of biological activity even in the presence of the unshared basic pair of electrons in pyridine. There are, however, cases where the heterocyclic forms are an indispensable part of the pharmacophore. For example, a dihydropyridine is, an absolute requirement for calcium channel blocking activity.[10] In a similar manner, substituted 1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-ones have been shown to possess oral antiinflammatory activity. Moreover, when the pyridine nitrogen atom is removed, as in the benzene analog, antiinflammatory activity is completely lost.[11]

Chemistry

Three different synthetic approaches (Schemes II, III and IV, methods A–C) were employed for the preparation of the desired derivatives. As shown in Scheme I, key intermediates **13** and **14** can be prepared by ring closure of 2-amino-3-hydroxypyridine and 6-methyl-2-hydroxypyridine, respectively, with 1,1'-carbonyldiimidazole in tetrahydrofuran. In this way, the yields do not reach those obtained by Rüfenacht et al.[12] but the very toxic phosgen can be avoided. The bromo compound **18** was conveniently obtained by a method found in the literature.[12] Starting material such as the substituted arylpiperazine derivatives, if not commercially available, may be synthezised by known methods.[13]

The preparation of the target compounds **1** involved Mannich condensation of oxazolo[4,5-*b*]pyridin-2(3*H*)-one **13** with formaldehyde and the appropriate 1-arylpiperazines. Yields of all compounds **1** were generally very good and no attempts were made to optimize them. Because of their relative instability in an acidic medium, the

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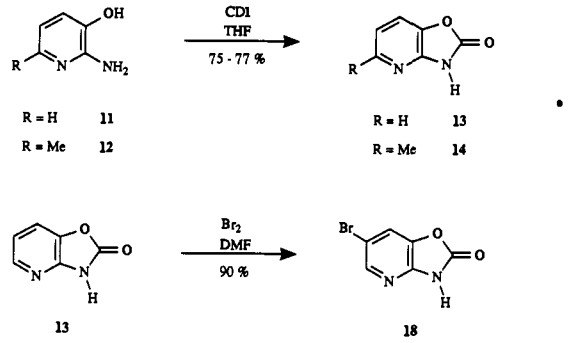
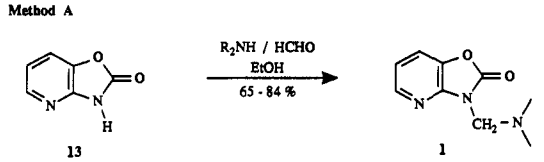
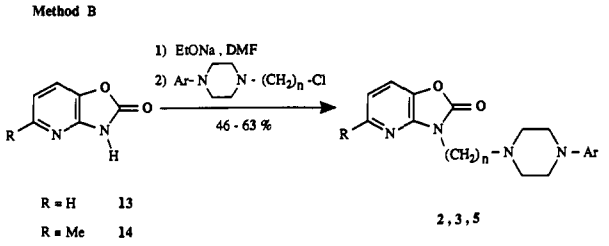
Scheme I



Scheme II



Scheme III

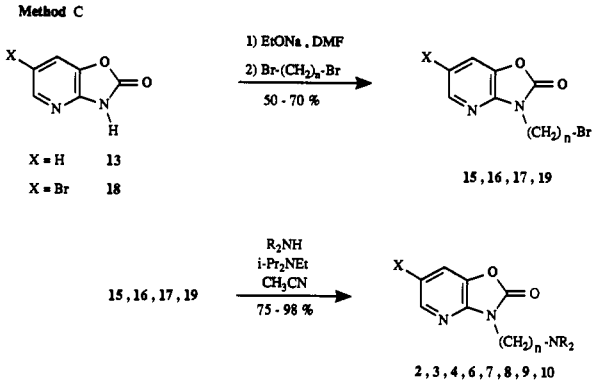


purification of compounds **1** was carried out without degradation using short silica gel column chromatography.

Two general synthetic procedures were used in preparing the desired 3-[(4-aryl-1-piperazinyl)alkyl]oxazolo[4,5-*b*]-pyridin-2(3*H*)-ones **2**, **3**, and **5**. In the first route (method B, Scheme III) oxazolo[4,5-*b*]pyridin-2(3*H*)-one **13** was converted into its anion by reaction with sodium ethoxide in dry ethanol and, after evaporation of organic solvent, alkylated in anhydrous DMF by reaction with 4-(2-chloroethyl)-1-arylpiperazines or 4-(3-chloropropyl)-1-arylpiperazines, giving compounds **2** and **3** in satisfactory yields. The (chloroalkyl)arylpiperazines were obtained by treatment of the appropriate arylpiperazines with 1-bromo-2-chloroethane or 1-bromo-3-chloropropane in the presence of potassium carbonate in anhydrous DMF according to the literature.[14] The congener of **13** with a methyl substituent on the pyridine ring was also prepared according to the above procedure with **14** as the starting material. This experimental procedure for the synthesis of **4** was not successful due to the intramolecular cyclization of 4-(4-chlorobutyl)-1-arylpiperazine into a spiro-fused quaternary salt.[15]

The second protocol (method C) outlined in Scheme IV conveniently circumvented this obstacle. The anions of compounds **13** and **18** reacted with dibromoalkanes in DMF to provide **15**, **16**, **17**, and **19** in satisfactory yields. A small excess of dibromoalkane essentially eliminated the formation of bis-substituted compounds as side products. Compounds **2**, **3**, **4**, **6**, and **9** were prepared in excellent yields by alkylation of the piperazine intermediates with the appropriate bromo compounds **15**, **16**, **17**, and **19** in an aprotic solvent such as DMF in the presence of potassium carbonate. However, alkylation was best carried out in acetonitrile as solvent in the presence of

Scheme IV



diisopropylethylamine. Compounds **7**, **8**, and **10** were synthesized under the same conditions using piperidine, morpholine, and diethylamine as starting material.

Table I summarizes the experimental and physical data for the desired compounds. General procedures detailing the synthesis of target structures are reported in the Experimental Section.

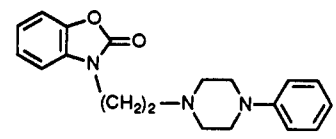
Biological Results and Discussion

The compounds were first evaluated for their analgesic activity by the *p*-phenylquinone test and for their acute toxicity in mice. The results, shown in Table II, include those obtained for codeine and glafenine which served as controls in the assays.

The compounds of the first series, with $n = 1$, exhibited a potent anaglesic effect. The phenyl-, [3-(trifluoromethyl)phenyl]-, and (4-fluorophenyl)piperazinyl compounds, **1a**, **1b**, and **1d**, respectively, were the most active, whereas the (chlorophenyl)piperazinyl compounds **1e**, **1f**, and **1g** were less potent, and (2-methoxyphenyl)piperazinyl compound **1c** was quite inactive. For this series the anaglesic activity observed was accompanied by convulsions and high toxicity with an oral dose of 500 mg/kg.

In contrast, the compounds of the second series, with $n = 2$, were much less toxic (no mortality at 1000 mg/kg). They showed a high analgesic activity with the same influence of the N substituent as for the $n = 1$ series. Compounds **2a**, **2b**, and **2d** were analgesic, whereas **2c** and **2e** were inactive. (4-Phenoxyphenyl)piperazinyl compound **2h** was also inactive.

Benzoxazolinone analogs **11** and **12** corresponding to **2a** and **2b** oxazolopyridinone compounds exerted a weak antinociceptive effect ($ED_{50} > 50$ mg/kg and $ED_{50} = 30$ mg/kg for compounds **11** and **12**, respectively), with low acute toxicity (no mortality at 1000 mg/kg).



11

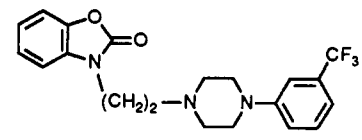


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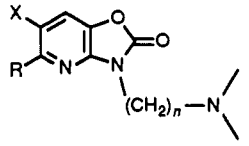
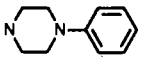
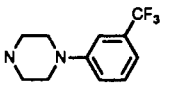
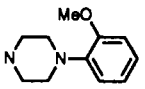
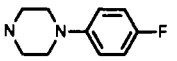
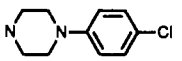
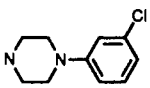
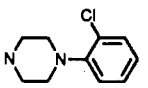
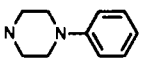
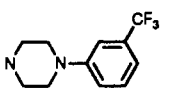
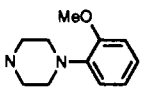
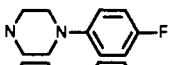
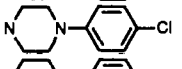
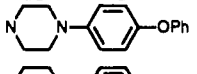
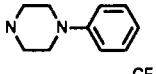
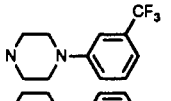
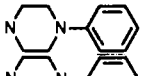
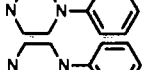
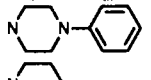
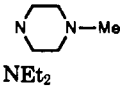
Table I. 3-(Aminoalkyl)- and 3-[(4-Aryl-1-piperazinyl)alkyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-ones



compd	R	X	N	*n*	method[a]	yield,[b] %	mp, °C	solvent	formula	anal.[c]
1a	H	H		1	A	81	151–152	EtOH	$C_{17}H_{18}N_4O_2$	C, H, N
1b	H	H		1	A	71	112–113	EtOH	$C_{18}H_{17}F_3N_4O_2$	C, H, N
1c	H	H		1	A	82	118–119	EtOH	$C_{18}H_{20}N_4O_3$	C, H, N
1d	H	H		1	A	70	125–126	EtOH	$C_{17}H_{17}FN_4O_2$	C, H, N
1e	H	H		1	A	65	153–154	EtOH	$C_{17}H_{17}ClN_4O_2$	C, H, N, Cl
1f	H	H		1	A	83	149–150	EtOH	$C_{17}H_{17}ClN_4O_2$	C, H, N, Cl
1g	H	H		1	A	84	111–112	i-PrOH	$C_{17}H_{17}ClN_4O_2$	C, H, N, Cl
2a	H	H		2	B C	50 97	110–112	EtOH	$C_{18}H_{20}N_4O_2$	C, H, N
2b	H	H		2	B C	46 86	94–96	EtOH	$C_{19}H_{19}F_3N_4O_2$	C, H, N
2c	H	H		2	B C	53 96	95–96	EtOH	$C_{19}H_{22}N_4O_3$	C, H, N
2d	H	H		2	C	98	94–95	EtOH	$C_{18}H_{19}FN_4O_2$	C, H, N
2e	H	H		2	C	97	110–111	EtOH	$C_{18}H_{19}ClN_4O_2$	C, H, N, Cl
2h	H	H		2	C	92	147–148	EtOAc	$C_{24}H_{24}N_4O_3$	C, H, N
3a	H	H		3	B C	50 92	140–141	EtOH	$C_{19}H_{22}N_4O_2$	C, H, N
3b	H	H		3	B C	63 85	62–63	EtOH	$C_{20}H_{21}F_3N_4O_2$	C, H, N
4a	H	H		4	C	84	78		$C_{20}H_{24}N_4O_2$	C, H, N
5	CH_3	H		2	B	50	101–102	EtOH	$C_{19}H_{22}N_4O_2$	C, H, N
6	H	Br		2	C	85	110	EtOH	$C_{18}H_{19}BrN_4O_2$	C, H, N
7	H	H		2	C	97	84–85	EtOH	$C_{13}H_{17}N_3O_2$	C, H, N
8	H	H		2	C	99	82–84	EtOH	$C_{12}H_{15}N_3O_3$	C, H, N
9	H	H		2	C	90	85–86	EtOH	$C_{13}H_{18}N_4O_2$	C, H, N
10	H	H	NEt_2	2	C	72	150–151[d]	EtOH	$C_{12}H_{17}N_3O_2 \cdot C_2H_2O_4$	C, H, N

[a] Method A is shown in Scheme II; method B is shown in Scheme III; method C is shown in Scheme IV; see the Experimental Section. [b] Isolated yields of pure products; no efforts were made to optimize yields. [c] Analytical results were within ±0.4% of the theoretical value. [d] Oxalate.

The congeners of the third series, **3a** and **3b**, showed about the same analgesic activity as **2a** and **2b**, but with toxic effects at 1000 mg/kg. Increasing the size of the alkyl chain to $n = 4$ (**4a**) led to decreased analgesic potency and high toxicity. The 6-bromo (**6**) and the 5-methyl (**5**) substitutions on the pyridine ring were associated with decreased activity and inactivity, respectively. Replacement of the phenylpiperazine moiety with a piperidino,

Table II. Pharmacological Activity of 3-(Aminoalkyl)- and 3-[(4-Aryl-1-piperazinyl)alkyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-ones

compd	analgesic effect: ED_{50}, mg/kg[a]	anti-inflammatory effect: % inhibn at 50 mg/kg	orientative acute toxicity: dose, mg/kg:% mortality, behavior
1a	5.9 (1.1–29.0)	11	500:70, convulsions
1b	3.6 (0–8.5)	25	500:50, increased muscular tonus
1c	>25	15	500:100, convulsions
1d	3.5 (1.0–11.7)	NT[c]	500:100, convulsions
1e	10.6	23	500:90, convulsions
1f	10.5 (0.9–83.5)	27	500:100, convulsions
1g	22.2	N[d]	500:100, convulsions
2a	19.4 (8.2–45.8)	13	1000:0, normal
2b	11.4 (3.0–38.0)	N	1000:0, increased locomotor activity, convulsive tendancy
2c	>50	N[b]	1000:0, normal
2d	41.3 (15.5–162.6)	16	1000:0, decreased muscular tonus
2e	>50	NT	1000:0, decreased locomotor activity, increased muscular tonus
2h	>50	NT	1000:0, normal
3a	15.5 (2.6–85.0)	16	1000:10, decreased locomotor activity, decreased muscular tonus
3b	22.0 (4.7–103.1)	N	1000:50, convulsions
4a	>25	NT	1000:100, convulsions
5	>50	2[b]	1000:0, normal
6	34.1 (10.6–59.5)	NT	1000:0, normal
7	>25	21[b]	1000:66, convulsions
8	>25	7[b]	1000:50, increased muscular tonus
9	>25	N[b]	1000:83, convulsions
10	>25	NT	1000:66, convulsions
11	>50	1	1000:0, sedation, decreased muscular tonus
12	30.2 (6.8–177.5)	N	1000:0, normal
codeine	9.7 (4.0–22.5)	20	750:40, convulsions
glafenine	29.3 (8.7–91.8)	36	1000:30, normal

[a] Values in parentheses are confidence intervals determined at 95% (p = 0.05). [b] 100 mg/kg. [c] NT: not tested. [d] N: no inhibition.

morpholino, or methylpiperazino group (**7**, **8**, or **9**, respectively) led to inactivity. And finally diethylamino compound **10** was also devoid of analgesic effect.

All the compounds showed very little or no antiinflammatory effect in the acute carrageenan paw edema test in rats.

To detect false positives in the *p*-phenylquinone-induced writhing in mice, according to Pearl,[16] general behavior was carefully observed during the test and in the acute toxicity assay, and the effects of the compounds were assessed in the rotarod test. Moreover antinociceptive activity was also evaluated in the hot-plate test. The compounds prevented phenylquinone-induced reaction at doses that did not produce behavioral effect and that did not affect rotarod performance. For example, compound **2a** was inactive in the rotarod test (doses tested from 50 to 200 mg/kg) and it did not modify mouse behavior at doses as high as 1000 mg/kg (acute toxicity assay). In the hot-plate test compound **2a** was as active as codeine (ED_{50} = 30 mg/kg SC), whereas glafenine, as well as other peripheral analgesic agents, was inactive.

Due to their analgesic potency, between that of codeine and glafenine, and their little toxicity, less than that of the two control substances, compounds **2a** and **2b** were selected for further pharmacological evaluation with particular attention to affinities of the opiod receptor subtypes. Displacement studies were performed and relative affinities calculated. The compounds proved inactive on all three receptors, while the enkephalin analogues used as the reference compounds ([D-Pen^2, D-Pen^5]enkephalin as a selective δ agonist, U50488H as a selective κ agonist, and Tyr-D-Ala-Gly-(Me)Phe-Gly-ol as a selective μ agonist) displayed nanomolar affinity.

In conclusion, within the class of 3-(aminoalkyl)- and 3-[(4-aryl-1-piperazinyl)alkyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-ones, we have shown that some compounds possess potent nonopioid antinociceptive activity without antiinflammatory properties. In particular, compounds **2a** and **2b** were found to have a superior analgesic profile with low acute toxicity, making them appealing for their development as clinically useful analgesics.

Experimental Section

Chemistry. Melting points were determined on a Köfler hot-stage apparatus and were 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. 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. Perrin, W. L. F. Armarego, and D. R. Perrin (*Purification of Laboratory Chemicals*; Pergamon: Oxford, 1986) or were purchased from the Aldrich Chimie Strasbourg. 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 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 nonaqueous reactions were performed in oven-dried glassware under an atmosphere of argon. The column chromatography solvents employed were glass distilled and solvent mixtures were reported as volume to volume ratios. The benzoxazolinones **11** and **12** were synthesized by the method of Lesieur et al.[5]

Oxazolo[4,5-*b*]pyridin-2(3*H*)-one (13). 2-Amino-3-hydroxypyridine (**11**) (5.5 g, 50 mmol) was dissolved in THF (100 mL), 1,1′-carbonyldiimidazole (12.15 g, 75 mmol) was added, and the solution was warmed to reflux with stirring for 6 h. The reaction mixture was cooled (20 °C) and the THF removed by rotatory evaporation, leaving a residue which was dissolved in CH_2Cl_2. The organic layer was washed with 1.5 N NaOH (5 × 100 mL). The combined aqueous layers were cooled with an ice bath and acidified to pH 5–6 with 2 N HCl. The resulting precipitate was collected by filtration, washed with water, and dried over P_2O_5 under vacuum to yield **13** (5.24 g, 77%) as a white crystalline product: mp 212–214 °C (lit.[17] mp 211–212 °C); IR (KBr) 3000–2900, 1750, 1610 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 7.13 (dd, 1 H, C_6-H,

J = 8.2, 5.1 Hz), 7.63 (dd, 1 H, C_7-H, J = 8.2, 1.0 Hz), 8.05 (dd, 1 H, C_5-H, J = 5.1, 1.0 Hz), 11.9 (br s, 1 H, NH).

5-Methyloxazolo[4,5-*b*]pyridin-2(3*H*)-one (14). This compound was prepared in an analogous manner to that for **13** from 2-amino-3-hydroxy-6-methylpyridine[18] (**12**) (1.24 g, 10 mmol) and 1,1'-carbonyldiimidazole (2.43 g, 15 mmol) in THF (20 mL). The resultant light yellow solid was filtered off and washed with water. This solid was dissolved in a minimum amount of hot methanol and the warm solution was filtered. The methanol was evaporated, yielding **14** (1.13 g, 75%) as a colorless crystalline product: mp 243 °C; IR (KBr) 3000–2900, 1750, 1610 cm^{-1} ^{1}H NMR (Me_2SO-d_6) δ 2.43 (s, 3 H, CH_3), 6.93 (d, 1 H, C_6-H, J = 8.0 Hz), 7.50 (d, 1 H, C_7-H, J = 8.0 Hz), 12.3 (br s, 1 H, NH). Anal. ($C_7H_6N_2O_2$) C, H, N.

6-Bromooxazolo[4,5-*b*]pyridin-2(3*H*)-one (18). Oxazolo[4,5-*b*]pyridin-2(3*H*)-one (**13**) (6.0 g, 44.11 mmol) was dissolved in 45 mL of DMF and then bromine (2.5 mL, 48.53 mmol) was added dropwise. The solution was stirred at room temperature for 1.5 h. The reaction mixture was poured onto crushed ice, and the solid was filtered off, washed with water, and dried over P_2O_5 under vacuum to afford **18** (8.54 g, 90%) as a white crystalline product: mp 234 °C (lit.[12] mp 232–233 °C); IR (KBr) 3050–2900, 1750, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.54 (d, 1 H, C_7-H, J = 2.4 Hz), 8.17 (d, 1 H, C_5-H, J = 2.4 Hz), 12.30 (br s, 1 H, NH_2).

Method A (Scheme II). 3-[(4-Aryl-1-piperazinyl)methyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-ones (1). General Procedure. To a solution of oxazolo[4,5*b*]pyridin-2(3*H*)-one (**13**) (4.08 g, 30 mmol) in 100 mL of EtOH was added to appropriate arylpiperazine (33 mmol) and then 30 mL of 30% aqueous formaldehyde was added. This mixture was stirred at 80 °C for 1.5 h, cooled to room temperature, and then stirred at this temperature for 1 h. The resulting solid was filtered off and purified on a short (10 × 3 cm) silica gel column (70–230 mesh) using CH_2Cl_2 as eluent to give **1** which was recrystallized from the appropriate solvent.

3-[(4-Phenyl-1-piperazinyl)methyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-one (1a): IR (KBr) 3100–2785, 1750, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.91–2.96 (m, 4 H, $CH_{2piperaz}$), 3.18–3.22 (m, 4 H, $CH_{2piperaz}$), 5.00 (s, 2 H, NCH_2), 6.80–6.92 (m, 3 H, H_{arom}), 7.03 (dd, 1 H, C_6-H, J = 8.3, 5.4 Hz), 7.20–7.30 (m, 2 H, H_{arom}), 7.37 (dd, 1 H, C_7-H, J = 8.3, 1.0 Hz), 8.10 (dd, 1 H, C_5-H, J = 5.4, 1.0 Hz); MS m/z 311 (M + 1), 175.

3-[[4-[3-(Trifluoromethyl)phenyl]-1-piperazinyl]methyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-one (1b): IR (KBr) 3100–2785, 1750, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.85–3.05 (m, 4 H, $CH_{2piperaz}$), 3.15–3.35 (m, 4 H, $CH_{2piperaz}$), 5.00 (s, 2 H, NCH_2), 6.90–7.15 (m, 4 H, C_6-H and 3 H_{arom}), 7.20–7.45 (m, 2 H, C_7-H and 1 H_{arom}), 8.10 (dd, 1 H, C_5-H, J = 4.8, 1.0 Hz); MS m/z 379 (M + 1), 243.

3-[[4-(2-Methoxyphenyl)-1-piperazinyl]methyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-one (1c): IR (KBr) 3100–2785, 1750, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.96–3.02 (m, 4 H, $CH_{2piperaz}$), 3.05–3.11 (m, 4 H, $CH_{2piperaz}$), 3.81 (s, 3 H, OCH_3), 5.00 (s, 2 H, NCH_2), 6.80–7.00 (m, 4 H, H_{arom}), 7.06 (dd, 1 H, C_6-H, J = 8.7, 5.6 Hz), 7.41 (dd, 1 H, C_7-H, J = 8.7, 1.2 Hz), 8.11 (dd, 1 H, C_5-H, J = 5.6, 1.2 Hz); MS m/z 341 (M + 1), 205.

3-[[4-(4-Fluorophenyl)-1-piperazinyl]methyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-one (1d): IR (KBr) 3100–2750, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.91–2.97 (m, 4 H, $CH_{2piperaz}$), 3.03–3.13 (m, 4 H, $CH_{2piperaz}$), 4.97 (s, 2 H, NCH_2), 6.82–6.97 (m, 4 H, H_{arom}), 7.07 (dd, 1 H, C_6-H, J = 7.9, 5.1 Hz), 7.41 (dd, 1 H, C_7-H, J = 7.9, 1.2 Hz), 8.11 (dd, 1 H, C_5-H, J = 5.1, 1.2 Hz); MS m/z 329 (M + 1), 193.

3-[[4-(4-Chlorophenyl)-1-piperazinyl]methyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-one (1e): IR (KBr) 3100–2785, 1750, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.92–2.97 (m, 4 H, $CH_{2piperaz}$), 3.14–3.19 (m, 4 H, $CH_{2piperaz}$), 5.00 (s, 2 H, NCH_2), 6.80 (d, 2 H, H_{arom}, J = 9.0 Hz), 7.08 (dd, 1 H, C_6-H, J = 8.0, 5.6 Hz), 7.18 (d, 2 H, H_{arom}, J = 9.0 Hz), 7.41 (dd, 1 H, C_7-H, J = 8.0, 1.2 Hz), 8.12 (dd, C_5-H, J = 5.6, 1.2 Hz); MS m/z 345 (M + 1), 209.

3-[[4-(3-Chlorophenyl)-1-piperazinyl]methyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-one (1f): IR (KBr) 3100–2785, 1750, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.97–3.03 (m, 4 H, $CH_{2piperaz}$), 3.20–3.27 (m, 4 H, $CH_{2piperaz}$), 5.00 (s, 2 H, NCH_2), 6.82–6.94 (m, 2 H, H_{arom}), 7.08 (dd, 1 H, C_6-H, J = 7.0, 4.7 Hz), 7.25 (m, 2 H, H_{arom}), 7.40 (dd, 1 H, C_7-H, J = 7.0, 1.0 Hz), 8.11 (dd, 1 H, C_5-H, J = 4.7, 1.0 Hz); MS m/z 345 (M + 1), 209.

3-[[4-(2-Chlorophenyl)-1-piperazinyl]methyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-one (1g): IR (KBr) 3100–2785, 1750, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.90–2.95 (m, 4 H, $CH_{2piperaz}$), 3.07–3.12 (m, 4 H, $CH_{2piperaz}$), 5.00 (s, 2 H, NCH_2), 6.71–6.84 (m, 3 H, H_{arom}), 7.05–7.16 (m, 3*H*, and 2 H_{arom}), 7.44 (dd, 1 H, C_7-H, J = 8.0, 1.2 Hz), 8.12 (dd, 1 H, C_5-H, J = 4.9, 1.2 Hz); MS m/z 345 (M + 1), 209.

Method B (Scheme III). 3-[(4-Aryl-1-piperazinyl)alkyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-ones 2, 3, and 5. General Procedure. To a solution of sodium ethoxide prepared by addition of sodium (0.92 g, 40 mmol) to 400 mL of anhydrous EtOH was added oxazolo[4,5-*b*]pyridin-2(3*H*)-one (**13**) (5.44 g, 40 mmol) or 5-methyloxazolo[4,5-*b*]pyridin-2(3*H*)-one (**14**) (7.5 g, 40 mmol), and the resulting solution was stirred at room temperature for 1 h. The mixture was evaporated to dryness and the residue was dissolved in 20 mL of DMF. To this solution was carefully added 40 mmol of 4-(2-chloroethyl)- or 4-(3-chloropropyl)-1-arylpiperazines (prepared by alkylation of arylpiperazines with 1-bromo-2-chloroethane or 1-bromo-3-chloropropane[14]) dissolved in 20 mL of DMF. The mixture was stirred at reflux for 1.5 h. The reaction was cooled and filtered to remove the mineral precipitate and the filtrate was evaporated to dryness.

The resulting residue was poured into water and extracted with CH_2Cl_2 and the organic extract was then separated. The extract was washed with H_2O, dried over anhydrous $MgSO_4$, and then evaporated. The resulting crude solid was purified by gravity column chromatography using CH_2Cl_2/MeOH 95/5 as eluent to give **2**, **3**, or **5** which were recrystallized from the appropriate solvent.

Method C (Scheme IV). 3-(2-Bromoethyl)oxazolo[4,5-*b*]pyridin-2(3*H*)-one (15). To a stirred solution of sodium ethoxide prepared by addition of sodium (0.92 g, 40 mmol) to 400 mL of dry ethanol, was added oxazolo[4,5-*b*]pyridin-2(3*H*)-one (**13**) (5.44 g, 40 mmol) at room temperature. The mixture was stirred for 1 h at the same temperature, and the solvent was removed by a rotary evaporator, yielding the sodium salt. The powder was dissolved in 40 mL of DMF and added dropwise to a solution of 1,2-dibromoethane (6.88 mL, 80 mmol) in 16 mL of DMF. The reaction mixture was heated at 110 °C for 1 h, at which time the reaction was cooled to room temperature, and concentrated in vacuo. After addition of water (100 mL), the mixture was extracted with CH_2Cl_2 (4 × 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 pure **15** (73%): mp 84 °C; IR (KBr) 3100–2900, 1760, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.78 (t, 2 H, CH_2, J = 6.3 Hz), 4.36 (t, 2 H, CH_2, J = 6.3 Hz), 7.10 (dd, 1 H, C_6-H, J = 8.2, 5.6 Hz), 7.43 (dd, 1 H, C_7-H, J = 8.2, 0.5 Hz), 8.13 (dd, 1 H, C_5-H, J = 5.6, 0.5 Hz); MS m/z 243 (M^+), 245 (M + 2). Anal. ($C_8H_7BrN_2O_2$) C, H, N.

3-(3-Bromopropyl)oxazolo[4,5-*b*]pyridin-2(3*H*)-one (16). Compound **16** was prepared similarly to **15**, using 1,3-dibromopropane as starting product (60%); mp 73–74 °C. IR (KBr) 3200–2900, 1760, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.44 (m, 2 H, CH_2), 3.47 (t, 2 H, CH_2, J = 7.5 Hz), 4.10 (t, 2 H, CH_2, J = 7.5 Hz), 7.07 (dd, 1 H, C_6-H, J = 8.3, 5.0 Hz), 7.41 (dd, 1 H, C_7-H, J = 8.3, 0.5 Hz), 8.12 (dd, 1 H, C_5-H, J = 5.0, 0.5 Hz); M/S m/z 257 (M^+), 259 (M + 2). Anal. ($C_9H_9BrN_2O_2$) C, H, N.

3-(4-Bromobutyl)oxazolo[4,5-*b*]pyridin-2(3*H*)-one (17). Compound **17** was prepared similarly to **16**, using 1,4-dibromobutane as starting product (50%): mp 46 °C; IR (KBr) 3100–2900, 1760, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.92–2.09 (m, 4 H, 2 × CH_2), 3.47 (t, 2 H, CH_2, J = 5.7 Hz), 3.99 (t, 2 H, CH_2, J = 5.7 Hz), 7.06 (dd, 1 H, C_6-H, J = 8.3, 5.3 Hz), 7.40 (dd, 1 H, C_7-H, J = 8.3, 1.0 Hz), 8.11 (dd, 1 H, C_5-H, J = 5.3, 1.0 Hz); MS m/z 271 (M^+), 273 (M + 2). Anal. ($C_{10}H_{11}BrO_2$) C, H, N.

6-Bromo-3-(2-bromoethyl)oxazolo[4,5-*b*]pyridin-2(3*H*)-one (19). Compound **19** was prepared similarly to **15**, using 6-bromooxazolo[4,5-*b*]pyridin-2(3*H*)-one (**18**) as starting material (61%): mp 108 °C; IR (KBr) 3100–2900, 1750, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.76 (t, 2 H, CH_2, J = 6.6 Hz), 4.34 (t, 2 H, CH_2, J = 6.6 Hz), 7.59 (d, 1 H, C_7-H, J = 2.4 Hz), 8.20 (d, 1 H, C_5-H, J = 2.4 Hz). Anal. ($C_8H_6Br_2N_2O_2$) C, H, N.

3-(Aminoalkyl)- and 3-[(4-Aryl-1-piperazinyl)alkyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-ones. General Procedure. A mixture containing the bromo compounds **15**, **16**, **17**, or **19** (2.52 mmol), appropriate amine (3.78 mmol), diisopropylethylamine

(0.490 g, 3.78 mmol), and MeCN (5 mL) was heated at 60 °C for 12 h. After cooling, the mixture was evaporated to dryness. The resulting residue was poured onto water, extracted with CH_2Cl_2, and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the desired product was purified by flash chromatography (eluent: CH_2Cl_2/MeOH 95/5) and recrystallized from the appropriate solvent.

3-[2-(4-Phenyl-1-piperazinyl)ethyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-one (2a): IR (KBr) 3100–2700, 1745, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.66–2.72 (m, 4 H, $CH_{2piperaz}$), 2.85 (t, 2 H, CH_2, J = 6.6 Hz), 3.07–3.13 (m, 4 H, $CH_{2piperaz}$), 4.10 (t, 2 H, CH_2, J = 6.6 Hz), 6.79–6.91 (m, 3 H, H_{arom}), 7.03 (dd, 1 H, C_6-H, J = 7.8, 5.4 Hz), 7.19–7.27 (m, 2 H, H_{arom}), 7.34 (dd, 1 H, C_7-H, J = 7.8, 1.1 Hz), 8.10 (dd, 1 H, C_5-H, J = 5.4, 1.1 Hz); MS m/z 325 (M + 1).

3-[2-[4-[3-(Trifluoromethyl)phenyl]-1-piperazinyl]ethyl]-oxazolo[4,5-*b*]pyridin-2(3*H*)-one (2b): IR (KBr) 3100–2700, 1765, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65–2.75 (m, 4 H, $CH_{2piperaz}$), 2.85 (t, 2 H, CH_2, J = 6.6 Hz), 3.00–3.20 (m, 4 H, $CH_{2piperaz}$), 4.10 (t, 2 H, CH_2, J = 6.6 Hz), 6.90–7.15 (m, 3 H, C_6-H, and 2 H_{arom}), 7.25–7.35 (m, 2 H, H_{arom}), 7.45 (dd, 1 H, C_7-H, J = 7.8, 1.1 Hz), 8.10 (dd, 1 H, C_5-H, J = 5.4, 1.1 Hz); MS m/z 393 (M + 1).

3-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]oxazolo-[4,5-*b*]pyridin-2(3*H*)-one (2c): IR (KBr) 3100–2630, 1775, 1590 cm^{-1}, ^1H NMR ($CDCl_3$) δ 2.69–2.78 (m, 4 H, $CH_{2piperaz}$), 2.86 (t, 2 H, CH_2, J = 6.7 Hz), 2.92–3.03 (m, 4 H, $CH_{2piperaz}$), 3.84 (s, 3 H, OCH_3), 4.10 (t, 2 H, CH_2, J = 6.7 Hz), 6.82–7.02 (m, 4 H, H_{arom}), 7.03 (dd, 1 H, C_6-H, J = 7.6, 5.0 Hz), 7.38 (dd, 1 H, C_7-H, J = 7.6, 1.0 Hz), 8.09 (dd, 1 H, C_5-H, J = 5.0, 1.0 Hz); MS m/z 355 (M + 1).

3-[2-[4-(4-Fluorophenyl)-1-piperazinyl]ethyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-one (2d): IR (KBr) 3100–2600, 1760, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.69–2.78 (m, 4 H, $CH_{2piperaz}$), 2.88 (t, 2 H, CH_2, J = 6.3 Hz), 3.00–3.10 (m, 4 H, $CH_{2piperaz}$), 4.12 (t, 2 H, CH_2, J = 6.3 Hz), 6.87–6.97 (m, 4 H, H_{arom}), 7.04 (dd, 1 H, C_6-H, J = 7.7, 5.3 Hz), 7.38 (dd, 1 H, C_7-H, J = 7.7, 1.0 Hz), 8.10 (dd, 1 H, C_5-H, J = 5.3, 1.0 Hz); MS m/z 343 (M + 1).

3-[2-[4-(4-Chlorophenyl)-1-piperazinyl]ethyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-one (2e): IR (KBr) 3100–2600, 1760, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65–2.74 (m, 4 H, $CH_{2piperaz}$), 2.86 (t, 2 H, CH_2, J = 6.6 Hz), 3.05–3.12 (m, 4 H, $CH_{2piperaz}$), 4.10 (t, 2 H, CH_2, J = 6.6 Hz), 6.80 (d, 2 H, H_{arom}, J = 8.0 Hz), 7.03 (dd, 1 H, C_6-H, J = 7.7, 5.0 Hz), 7.17 (d, 2 H, H_{arom}, J = 8.0 Hz), 7.40 (dd, 1 H, C_7-H, J = 7.7, 1.0 Hz), 8.10 (dd, 1 H, C_5-H, J = 5.0, 1.0 Hz); MS m/z 359 (M + 1), 361 (M + 3).

3-[2-[4-(4-Phenoxyphenyl)-1-piperazinyl]ethyl]oxazolo-[4,5-*b*]pyridin-2(3*H*)-one (2h): IR (KBr) 3100–2600, 1760, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.67–2.73 (m, 4 H, $CH_{2piperaz}$), 2.85 (t, 2 H, CH_2, J = 6.0 Hz), 3.02–3.08 (m, 4 H, $CH_{2piperaz}$), 4.10 (t, 2 H, CH_2, J = 6.0 Hz), 6.84–6.96 (m, 7 H, H_{arom}), 7.24–7.31 (m, 2 H, H_{arom}), 7.04 (dd, 1 H, C_6-H, J = 7.1, 4.7 Hz), 7.38 (dd, 1 H, C_7-H, J = 7.1, 1.0 Hz), 8.10 (dd, 1 H, C_5-H, J = 4.7, 1.0 Hz); MS m/z 417 (M + 1).

3-[3-(4-Phenyl-1-piperazinyl)propyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-one (3a): IR (KBr) 3100–2785, 1750, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00–2.10 (m, 2 H, CH_2), 2.46–2.56 (m, 6 H, CH_2 and $CH_{2piperaz}$), 3.00–3.10 (m, 4 H, $CH_{2piperaz}$), 4.07 (t, 2 H, CH_2, J = 5.4 Hz), 6.80–6.92 (m, 3 H, H_{arom}), 7.03 (dd, 1 H, C_6-H, J = 8.0, 5.4 Hz), 7.19–7.28 (m, 2 H, H_{arom}), 7.37 (dd, 1 H, C_7-H, J = 8.0, 0.3 Hz), 8.10 (dd, 1 H, C_5-H, J = 5.4, 0.3 Hz); MS m/z 339 (M + 1).

3-[3-[4-[3-(Trifluoromethyl)phenyl]-1-piperazinyl]propyl]-oxazolo[4,5-*b*]pyridin-2(3*H*)-one (3b): IR (KBr) 3100–2785, 1750, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00–2.10 (m, 2 H, CH_2), 2.45–2.60 (m, 6 H, CH_2 and $CH_{2piperaz}$), 3.00–3.10 (m, 4 H, $CH_{2piperaz}$), 4.07 (t, 2 H, CH_2, J = 6.6 Hz), 6.90–7.15 (m, 4 H, C_6-H and 3 H_{arom}), 7.25–7.45 (m, 2 H, C_7-H and 1 H_{arom}), 8.10 (dd, 1 H, C_5-H, J = 4.8, 0.3 Hz); MS m/z 407 (M + 1).

5-Methyl-3-[2-(4-phenyl-1-piperazinyl)ethyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-one (5): IR (KBr) 3100–2910, 1770, 1590 cm^{-1}; ^1HNMR ($CDCl_3$) δ 2.51 (s, 3 H, CH_3), 2.66–2.74 (m, 4 H, $CH_{2piperaz}$), 2.82 (t, 2 H, CH_2, J = 6.4 Hz), 3.05–3.14 (m, 4 H, $CH_{2piperaz}$), 4.08 (t, 2 H, CH_2, J = 6.4 Hz), 6.80–6.90 (m, 4 H, C_6-H and 3 H_{arom}), 7.20–7.30 (m, 3 H, C_7-H and 2 H_{arom}); MS m/z 339 (M + 1).

3-[4-(4-Phenyl-1-piperazinyl)butyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-one (4a): IR (KBr) 3100–2900, 1760, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56–1.68 (m, 2 H, CH_2), 1.86–1.97 (m, 2 H, CH_2), 2.46 (t, 2 H, CH_2, J = 6.6 Hz), 2.55–2.62 (m, 4 H, $CH_{2piperaz}$), 3.16–3.32 (m, 4 H, $CH_{2piperaz}$), 3.99 (t, 2 H, CH_2, J = 6.6 Hz), 6.84 (t, 1 H, H_{arom}, J = 8 Hz), 6.91 (d, 2 H, H_{arom}, J = 8.0 Hz), 7.05 (dd, 1 H, C_6-H, J = 8.0, 4.7 Hz), 7.25 (t, 2 H, H_{arom}, J = 8.0 Hz), 7.40 (dd, 1 H, C_7-H, J = 8.0, 0.1 Hz), 8.11 (dd, 1 H, C_5-H, J = 4.7, 0.1 Hz); MS m/z 353 (M + 1).

6-Bromo-3-[2-(4-phenyl-1-piperazinyl)ethyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-one (6): IR (KBr) 3100–2900, 1760, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65–2.72 (m, 4 H, H_2, $CH_{2piperaz}$), 2.83 (t, 2 H, CH_2, J = 6.6 Hz), 3.05–3.12 (m, 4 H, $CH_{2piperaz}$), 4.10 (t, 2 H, CH_2, J = 6.6 Hz), 6.80–6.92 (m, 3 H, H_{arom}), 7.19–7.27 (m, 2 H, H_{arom}), 7.54 (d, 1 H, C_7-H, J = 2.4 Hz), 8.17 (d, 1 H, C_5-H, J = 2.4 Hz); MS m/z 403 (M^+), 405 (M + 2).

3-(2-Piperidinoethyl)oxazolo[4,5-*b*]pyridin-2(3*H*)-one (7): IR (KBr) 3100–2700, 1760, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34–1.56 (m, 6 H, $CH_{2piperid}$), 2.42–2.55 (m, 4 H, $CH_{2piperid}$), 2.76 (t, 2 H, CH_2, J = 6.1 Hz), 4.07 (t, 2 H, CH_2, J = 6.1 Hz), 7.03 (dd, 1 H, C_6-H, J = 8.2, 5.2 Hz), 7.38 (dd, 1 H, C_7-H, J = 8.2, 1.0 Hz), 8.09 (dd, 1 H, C_5-H, J = 5.2, 1.0 Hz); MS m/z 248 (M + 1).

3-(2-Morpholinoethyl)oxazolo[4,5-*b*]pyridin-2(3*H*)-one (8): IR (KBr) 3100–2700, 1760, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.49–2.53 (m, 4 H, CH_{2morph}), 2.68 (t, 2 H, CH_2, J = 6.3 Hz), 3.54–3.58 (m, 4 H, CH_{2morph}), 4.04 (t, 2 H, CH_2, J = 6.3 Hz), 7.03 (dd, 1 H, C_6-H, J = 8.2, 5.6 Hz), 7.38 (dd, 1 H, C_7-H, J = 8.2, 1.0 Hz), 8.09 (dd, 1 H, C_5-H, J = 5.6, 1.0 Hz); MS m/z 250 (M + 1).

3-[2-(4-Methyl-1-piperazinyl)ethyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-one (9): IR (KBr) 3100–2700, 1760, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.23 (s, 3 H, CH_3), 2.25–2.45 (m, 4 H, $CH_{2piperaz}$), 2.48–2.70 (m, 4 H, $CH_{2piperaz}$), 2.79 (t, 2 H, CH_2, J = 6.0 Hz), 4.05 (t, 2 H, CH_2, J = 6.0 Hz), 7.04 (dd, 1 H, C_6-H, J = 7.7, 5.5 Hz), 7.39 (dd, 1 H, C_7-H, J = 7.7, 1.0 Hz), 8.09 (dd, 1 H, C_5-H, J = 5.5, 1.0 Hz); MS m/z 263 (M + 1).

3-[2-(Diethylamino)ethyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-one (10): IR (KBr) 3100–2700, 1760, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (t, 6 H, 2 × CH_3, J = 7.0 Hz), 2.53 (q, 4 H, 2 × CH_2, J = 7.0 Hz), 2.66 (t, 2 H, CH_2, J = 6.6 Hz), 4.01 (t, 2 H, CH_2, J = 6.6 Hz), 7.03 (dd, 1 H, C_6-H, J = 8.3, 5.3 Hz), 7.38 (dd, 1 H, C_7-H, J = 8.3, 1.0 Hz), 8.10 (dd, 1 H, C_5-H, J = 5.3, 1.0 Hz); MS m/z 236 (M + 1). The oxalate salt was prepared for pharmacological testing.

Pharmacology. The compounds were dissolved in water if available as soluble salts or suspended in 0.2% hydroxypropylcellulose when available as free bases. They were administered orally in a volume of 10 mL/kg for mice and 2 mL/kg for rats. Statistical evaluations were made using the Dunnett's t-test; a probability value of $p < 0.05$ was considered significant.

***p*-Phenylquinone-Induced Writhing in Mice.** A procedure modified from that described by Siegmund[19] was used. Swiss male CD1 mice (20–25 g) were injected intraperitoneally with *p*-phenylquinone (0.02% in a 5% ethanol–95% distilled water solution; 0.25 mL/mouse) 1 h after oral administration of the compounds. Groups of 12 animals were used for each dose tested, and a group of 24 was used as control. Codeine and glafenine served as reference analgesics. The number of writhes for each mouse was counted for a period of 5 min beginning 5 min after the *p*-phenylquinone. The mean of the writhes was compared for each treatment group with the mean of the vehicle treated control group. The inhibition percent was then calculated for each compound treated group. The ED_{50} was calculated by a linear regression analysis using the least squares method[20] or estimated from the dose–response curve.

Hot-Plate Test in Mice. The method described by Eddy[21] was used to determine the reaction time (licking the forepaws) of mice dropped on a hot-plate maintained at 55 ± 0.1 °C. Compounds were administered subcutaneously to groups of 12 mice 1 h before the test.

Rotarod Test. The method used has been previously described by Pearl.[16] Mice were orally dosed with test compounds, and 30 and 90 min later they were given trials of testing on the rotarod.

Carrageenan Paw Edema in Rats. The technique of Winter et al.[22] was used. Sprague-Dawley male CD rats (100–125 g) were used. They were housed in rooms with a temperature of 20 ± 2 °C and 45–65% relative humidity; lighting was set on the 12 h/12 h light/dark cycle. Animals were provided food (ref A04, UAR, Epinay-sur-Orge, France) and water ad libitum. One hour

after oral administration of the compounds at the dose of 50 mg/kg, 0.1 mL of 1.5% solution of carrageenan in saline was injected into the plantar area of the right hind paw. Groups of 10 animals were used for each dose. Three hours later, the volumes of the two hind paws were measured (Plethysmometer UGO BASILE, APELEX, France). For each rat, the result was expressed as increase of volume (mL), the left paw measure being taken as control. The mean of each compound treated group was compared with the vehicle-treated control group, and the inhibition percent was calculated.

Orientative Acute Toxicity. Each compound was tested in 10 mice at the initial oral dose of 1000 mg/kg and, if 100% mortality was observed, at 750 or 500 mg/kg. The animals were carefully observed for 3 h after treatment and then every day for 14 days.

Opiate Receptor Binding Assay. Receptor binding assays were performed by incubating membranes prepared from the rat central nervous system with ^{3}H-pCl-DPDP-enkephaline according to Vaughn[23] or with ^{3}H-DAGO according to Borea[24] for δ and μ receptors. For κ receptors, guinea-pig cerebellum homogenate was incubated with ^{3}H-U 69593 according to Nock.[25] After the incubation period, bound and unbound radioligands were separated by rapid filtration, and radioactivity bound to membranes in the absence and presence of unlabeled compounds was counted in a beta-scintillation counter. Specific binding was greater than 70%. Displacement curves were established, and IC_{50} values (molar concentration of unlabeled compound at which half-maximal displacement of radioligand occurred) were calculated by a Lundon program. Each experiment was performed in duplicate.

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