P_2O_5) to obtain a yellow powder (0.452 g, 46%): IR (KBr) 3340 (NH_2), 1740 (ester C=O), 1670, 1660, 1645 (amide C=O) cm^{-1}.

Hydrolysis of 2-[*N*-(4-Amino-4-deoxy-N^{10}-methylpteroyl)amino]alkanedioic Acid Diesters. Procedure 6. 2-[*N*-(4-Amino-4-deoxy-N^{10}-methylpteroyl)amino]tridecanedioic Acid (6). A solution of diester **19** (1.18 g, 1.9 mmol) in a mixture of MeOH (25 mL) and 1 N NaOH (6 mL) was kept at room temperature for 24 h. After rotary evaporation of most of the MeOH and dilution with H_2O, the pH was adjusted to 4.5 with 10% AcOH. The solid was filtered and dried, first with the aid of a lyophilizer and then under vacuum at 100 °C over P_2O_5, to obtain a yellow powder (1.06 g, 97%): IR (KBr) 3395 (NH_2), 1710 (acid C=O), 1640, 1610 (amide C=O) cm^{-1}.

Hydrolysis of 2-[*N*-(4-Amino-4-deoxy-N^{10}-formylpteroyl)alkanedioic Acid Diesters. Procedures 7. 2-[*N*-(4-Amino-4-deoxypteroyl)amino]decanedioic Acid (8). A solution of **23** (0.427 g, 0.656 mmol) in a mixture of MeOH (13 mL) and 0.5 N NaOH (12 mL) was stirred at 25 °C for 48 h. The progress of the reaction was monitored by TLC (cellulose, pH 7.4 phosphate buffer), which showed a blue UV-fluorescent spot at R_f 0.78 for the N^{10}-formyl monoacid and diacid and a dark UV-absorbing spot at R_f 0.35 for the fully deblocked product. The solution was acidified to pH 4 with 10% AcOH, and the precipitated solid was filtered, redissolved in 3% NH_4HCO_3 (10 mL), and applied onto a DEAE-cellulose column (17 × 2.0 cm), which was eluted first with H_2O and then successively with 1% and 3% NH_4CO_3. Fractions whose TLC (silica gel, 5:4:1 $CHCl_3$–MeOH–NH_4OH) showed a UV-absorbing spot with R_f 0.44 were pooled and freeze-dried to give a yellow powder (0.13 g). This material was redissolved in a 1:3 mixture of EtOH and 0.05 M NH_4HCO_3 and subjected to gradient LPLC on C_{18}-bonded silica gel with 0.05 M NH_4HCO_3, pH 8.8, in reservoir A and a 1:3 mixture of EtOH and 0.05 M NH_4HCO_3 in reservoir B. Fractions containing pure product (elution time 175 min) were evaporated, and the residue was dried, first in a lyophilizer and then in vacuo over P_2O_5 at 100 °C, to obtain a yellow powder (0.079 g, 21%): IR (KBr) 3390 (NH_2), 1640 (acid C=O), 1610 (amide C=O) cm^{-1}.

Procedure 8. 2-[*N*-(4-Amino-4-deoxypteroyl)amino]tridecanedioic Acid (9). A solution of **24** (0.488 g, 0.682 mmol) in a nitrogen-purged mixture of MeOH (45 mL) and 0.25 N NaOH (25 mL) was sonicated at 36 °C (bath temperature) for 20.5 h and kept at 36 °C for an additional 5.5 h. The progress of the reaction was monitored by TLC as in the preceding experiment. The crude product obtained after acidification to pH 4 with 10% AcOH was redissolved in 3% NH_4HCO_3 (10 mL) and chromatographed on a DEAE-cellulose (22 × 2.0 cm) column, which was successively eluted with H_2O, 1% NH_4HCO_3, and 3% NH_4HCO_3. The partly purified product (0.35 g) was redissolved in 35:65 EtOH-0.05 M NH_4HCO_3 and subjected to gradient LPLC on C18-bonded silica gel with 0.05 M NH_4HCO_3, pH 8.8, in reservoir A and 35:65 EtOH–0.05 M NH_4HCO_3 in reservoir B. The pure product (elution time 137 min) weighed 0.255 g (66%): IR (KBr) 3340 (NH_2), 1640–1620 (broad, acid C=O), 1610 (amide C=O).

Acknowledgment. This work was supported in part by Grants CA25394 (A.R.), CA19589 (A.R.), CA41461 (J.H.F.), and CA39867 (R.G.M.) from the National Cancer Institute. R.G.M. is a Scholar of the Leukemia Society of America.

Registry No. **2**, 113976-23-1; **3**, 113976-24-2; **4**, 113976-25-3; **5**, 113976-26-4; **6**, 113976-27-5; **7**, 113976-28-6; **8**, 113976-29-7; **9**, 113976-30-0; **11a**, 108208-10-2; **11b**, 113976-39-9; **11c**, 113976-40-2; **11u**, 113976-41-3; **11e**, 113976-42-4; **12**, 113976-43-5; **13a**·HCl, 5722-16-7; **13b**·HCl, 5686-32-8; **13c**·HCl, 5686-31-7; **13d**·HCl, 5686-30-6; **13e**·HCl, 113976-44-6; **14**, 19741-14-1; **15**, 113976-31-1; **16**, 113976-32-2; **17**, 113976-33-3; **18**, 113976-34-4; **19**, 113976-35-5; **20**, 89043-75-4; **21**, 11976-36-6; **22**, 113976-37-7; **23**, 113976-38-8; **24**, 95485-01-1; DHFR, 9002-03-3; FPGS, 63363-84-8; H-Glu-OH, 56-86-0; $HOOC(CH_2)_{11}COOMe$, 3927-59-1.

Only One Pharmacophore Is Required for the κ Opioid Antagonist Selectivity of Norbinaltorphimine[1]

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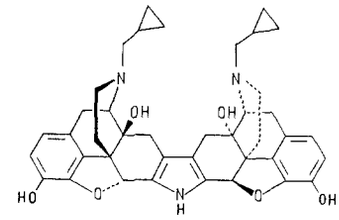
We have investigated whether one or two pharmacophores are required for the κ opioid receptor selectivity of the bivalent opioid antagonist norbinaltorphimine, (−)-1 (nor-BNI), by the synthesis and testing of its meso isomer **2**. In smooth muscle preparations **2** was more potent than **1** and about half as selective as a κ antagonist. Since **2** contains only one antagonist pharmacophore but yet retains substantial κ selectivity, it is concluded that κ selectivity is not dependent on the presence of two (−)-naltrexone-derived pharmacophores of **1**. It is suggested that the κ selectivity of (−)-**1** and **2** is derived from the portions of the second halves of these molecules in that they mimic key "address" components of dynorphin at κ opioid receptors.

We recently have reported on the structure–activity relationship of a series of bimorphinans with potent and selective κ opioid antagonist activity.[2,3] Since these ligands have the highest κ selectivity reported, they are of interest as pharmacologic tools in opioid research. One of the compounds in this series, norbinaltorphimine, (−)-**1** (nor-BNI), is presently employed for this purpose.

A key question in the structure–activity studies[3] of nor-BNI and its congeners pertained to whether or not two pharmacophores are required for κ antagonist selectivity. One possibility was that selectivity is due to the simultaneous interaction of both pharmacophores of nor-BNI with two proximal opioid receptors. A second possibility was that a unique recognition site proximal to the binding site of one of the pharmacophores is responsible for the κ selectivity. While prior structure–activity relationship studies[2] tended to implicate the latter, the former could



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† Department of Medicinal Chemistry.
‡ Department of Pharmacology.

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Table I. Opioid Antagonist Activities of Nor-BNI and Its Stereoisomers

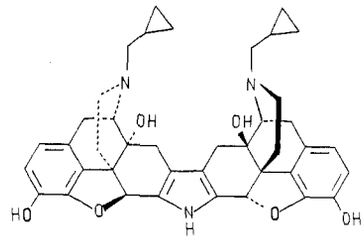
		EK[a] (κ)		M[a] (μ)		DADLE[b] (δ)		K_e ratio	
compd no.	concn, nM	K_e[c]	IC_{50} ratio	K_e[c]	IC_{50} ratio	K_e[c]	IC_{50} ratio	μ/κ	δ/κ
(−)-1	20	0.41	49.8 ± 7.8	12.5	2.6 ± 0.6	10	2.0 ± 0.1	30	24
(+)-1	100	*d*	1.9 ± 0.8	77	3.6 ± 0.7	*d*	1.0 ± 0.2		
2	20	0.08	252 ± 6	1.1	18.8 ± 1.3	1.3	16.8 ± 2.8	14	16
3	100	5.5	19.3 ± 5.9	1.0	98 ± 24	24	5.1 ± 1.3	0.2	4.4

[a] Ethylketazocine (EK) and morphine (M) in the GPI. The IC_{50} ratio is the IC_{50} of the agonist in the presence of antagonist divided by the control IC_{50} in the same preparation ($n \geq 3$). [b] [D-Ala^2,D-Leu^5]enkephalin (DADLE) in the MVD. [c] K_e expressed in nanomolars. [d] The K_e value cannot be determined because the IC_{50} ratio is not significantly different from 1.

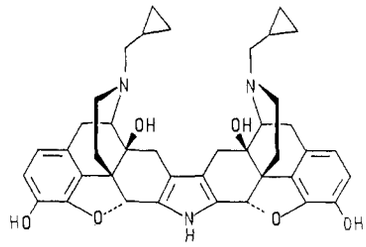
not be excluded as a possibility. Here we present evidence that only one pharmacophore is required for the κ antagonist selectivity of nor-BNI.

Design Rationale and Chemistry

The approach employed to investigate whether interaction with a single receptor or two proximal opioid receptor sites is associated with κ antagonist selectivity involved the synthesis of the nor-BNI diastereomer **2**. This compound contains a combination of the antagonist pharmacophore derived from (−)-naltrexone (**3**) and its inactive (+)-enantiomer.[4] These enantiomeric elements were linked through a conformationally rigid pyrrole spacer in a manner identical with nor-BNI, (−)-1. This diastereomer **2** is classified as the meso isomer of (−)-1. The enantiomer (+)-nor-BNI, (+)-1, also was of interest in this study.



(+)-1



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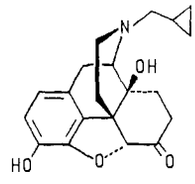

3

The meso isomer **2** was obtained in 26% yield by heating equivalent amounts of (−)- and (+)-naltrexone hydrochloride with *N*-aminosuccinimide hydrochloride in DMF.[5] In conformity with the meso stereochemistry, **2** was for all practical purposes optically inactive, $[\alpha]_D$ −2.1°, when compared to the reported[2] value, $[\alpha]_D$ −377° for (−)-**1**. The expected second product, racemic nor-BNI, (±)-**1**, was obtained in 47% yield, which is close to the expected amount that could arise by combination of (+)- and (−)-naltrexone. Conducting the same reaction with (+)-naltrexone afforded (+)-**1**.

Pharmacology

Opioid antagonist activities (Table I) were determined on the electrically stimulated guinea pig ileum[6] (GPI) and mouse vas deferens[7] (MVD) preparations. Morphine (M), ethylketazocine (EK), and [D-Ala^2,D-Leu^5]enkephalin (DADLE) were employed as μ, κ, and δ agonists, respectively. K_e values were determined from the equation K_e = [antagonist]/(IC_{50} ratio − 1), where the IC_{50} ratio is the IC_{50} of agonist in presence of antagonist divided by agonist control IC_{50}.

The meso isomer **2** was about 15 times more effective in antagonizing EK relative to morphine or to DADLE. This is about half that of the selectivity observed for nor-BNI, (−)-1. Compound **2** was approximately five times more potent than nor-BNI as a κ opioiod receptor antagonist. At μ and δ receptors, **2** was 10 times more potent. The enantiomer (+)-1 did not significantly antagonize any of the agonist ligands. The antagonist potencies of (−)-naltrexone are listed to illustrate the substantial change in selectivity upon doubling the size of the molecule.

Discussion

The finding that the meso diastereomer **2** is a κ-selective ligand in the smooth muscle preparations argues against the interaction of nor-BNI, (−)-1, with two proximal opioid receptors. This is based on the knowledge that the nor-BNI enantiomer (+)-1 and (+)-naltrexone[4] are inactive as opioid antagonists. Also, the greater potency of **2** relative to nor-BNI, (−)-1, lends additional support to the idea that the proximal site that binds the (+)-naltrexone-derived moiety is not a neighboring opioid receptor.

The perspective formulas **4** and **5** corresponding to nor-BNI, (−)-1 (threo isomer), and its meso isomer **2**, illustrate the difference between the geometries of these molecules. It can be seen that **4** has its phenolic groups in an anti orientation whereas in **5** they are syn. This suggests that one of the aromatic rings of nor-BNI does not contribute to the κ selectivity. In view of our finding[8] that the pyrrole-containing monovalent ligand **6** is not κ-selective, it seems unlikely that the pyrrole spacer is directly involved in the selection process. It is probable that a portion of the octahydroisoquinoline ring in the (+)-naltrexone-derived portion of **2** or substitution arising from this ring system may confer κ selectivity. Of possible

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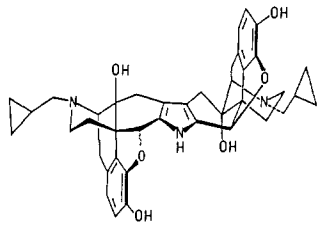

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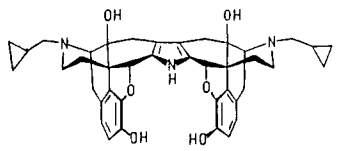

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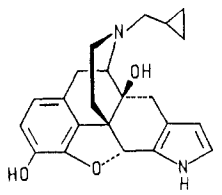
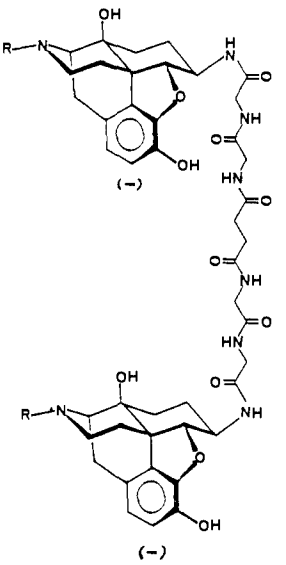


6

significance is the common position of the basic nitrogen in the right halves of (−)-1 and 2 (compare 4 and 5). Could it be that this basic nitrogen mimics the Arg[6] or Arg[7] residues of the endogenous κ-selective opioid peptide dynorphin?[9]

The results of the present study are in contrast with those reported[10] for the μ-selective bivalent antagonist 7 (threo isomer). It was found that the meso isomer 8 and its monovalent analogue had nearly equal μ antagonist potencies, but they were considerably less than that of the threo isomer 7. This indicated that the recognition between the neighboring site and the second pharmacophore in 7 has an enantiopreference characteristic of an opioid receptor. In this regard, the relatively longer spacer length of 7 makes the idea of bridging neighboring μ receptors a more plausible possibility than in the case of nor-BNI, (−)-1, where the short pyrrole spacer may hold the pharmacophores too close to one another to permit bridging.

If the second half of the nor-BNI molecule and its meso isomer do not interact with a neighboring opioid receptor, then what is the role of the subsite that confers κ selectivity? An obvious answer to this question is that the (−)-naltrexone-derived pharmacophore component of both nor-BNI, (−)-1, and of meso isomer 2 bind to a morphinan recognition locus while a portion of the second half of these molecules interacts with a unique subsite that is part of the remainder of the κ receptor. This view is reminiscent of the "message–address" concept[11] that was employed to rationalize the selectivity of peptide hormones. Accordingly, the "message" segment (Tyr-Gly-Gly-Phe) of the opioid peptide confers opioid activity; the "address" sequence is comprised of amino acid residues that confer selectivity.[12]



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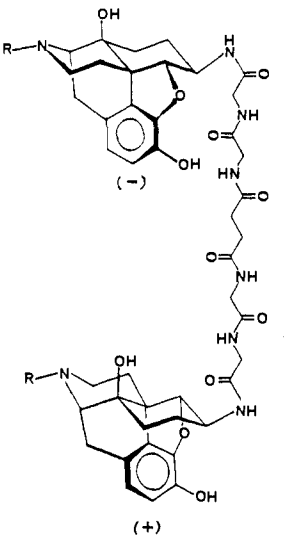

8

Recently we have employed the message–address concept in modifying the opioid selectivity of morphinan structures in a predictable way by linking to them specific address opioid peptide segments.[13] In this context, the (−)-naltrexone-derived pharmacophore of (−)-1 or 2 can be viewed as the "message", with moieties in the second half serving as the "address". We therefore view the selectivity of (−)-1 and 2 to be due to the projection of the second half of these molecules into the "address" recognition locus of the κ receptor. We believe that the conformational restriction of the "address" segment of nor-BNI is an important aspect of this selectivity, in that it permits binding to an "address" subsite that is unique to the κ opioid receptor system. Indeed, this concept recently has been employed in the successful design of highly selective nonpeptide δ opioid receptor antagonists.[8]

Conclusions

The present study has indicated that only one of the two antagonist pharmacophores of nor-BNI, (−)-1, is required for κ opioid antagonist selectivity. The proposed mechanism by which selectivity is achieved is based on the "message–address" concept that has been employed to explain the selectivity of families of endogenous peptides. Accordingly, one of the naltrexone pharmacophores of nor-BNI, (−)-1, is postulated to serve as the "message", and a portion of the second naltrexone pharmacophore functions as the "address". *The results of the present study suggest that it may be possible to alter opioid antagonist selectivity in a predictable way by simulating a portion of the address peptide component with a rigid nonpeptide moiety.*

Experimental Section

Melting points were determined in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ, and are within ±0.4% of the theoretical values. IR spectra were obtained on a Perkin-Elmer 281 infrared spectrometer. NMR spectra were recorded at ambient temperature on an IBM-Bruker AC-300 spectrometer with Me_2SO-d_6 and $CDCl_3$ as solvents and Me_4Si as internal standard. Mass spectra were obtained on a VG70,70EF instrument. Optical rotations were determined with a Perkin-Elmer 141 polarimeter. All TLC data were determined with Analtech, Inc., silica gel GHF 21521, and the eluents $CHCl_3$–MeOH–NH_4OH or *n*-BuOH–AcOH–H_2O are

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denoted by CMA and BAW, respectively. Unless otherwise stated, all reagents and solvents were reagent grade and used without subsequent purification.

Reaction of (+)- and (−)-Naltrexone Hydrochloride with *N*-Aminosuccinimide. To a stirred solution of (+)-naltrexone hydrochloride (110 mg, 0.29 mmol) and (−)-naltrexone hydrochloride (110 mg, 0.29 mmol) in DMF (2.5 mL) was added *N*-aminosuccinimide hydrochloride[5] (200 mg, 1.33 mmol). The mixture was stirred at 100 °C for 18 h, and the solvent was removed in vacuo. Methanol, saturated sodium bicarbonate solution, and chloroform were added to the residue. The mixture was filtered (Celite), and the filtrate was extracted with chloroform (three times). The combined organic phases were washed with brine, dried, and concentrated to give a crude product that was purified on a Sephadex column (LH-20, MeOH) to afford pure meso isomer **2** (50 mg, 26%) and (±)-**1** (90 mg, 46.9%). Data for **2**: R_f 0.25 (CMA 18:2:0.1); IR (KBr, cm^{-1}) 3400, 3000, 2830, 1640, 750; ^1H NMR ($CDCl_3$) δ 0.12 (4 H, m), 0.52 (4 H, m), 0.82 (2 H, m), 1.63 (2 H, d, J = 8.2 Hz), 2.00–2.50 (12 H, m), 2.65 (4 H, m), 3.06 (2 H, d, J = 18.4 Hz), 3.20 (2 H, d, J = 5.8 Hz), 5.56 (2 H, S), 6.45 (2 H, d, J = 7.8 Hz), 6.60 (2 H, d, J = 7.8 Hz); FABMS 662.2 ($M^+ + 1$), 660.1 ($M^+ - 1$). Data for **2**·2HCl: mp >265 °C dec; R_f 0.37 (BAW, 2:1:1); $[\alpha]^{25}_D$ −2.1° (*c* 0.1, MeOH). Anal. ($C_{40}H_{43}O_6N_3$·2HCl·4H_2O) C, H, N, Cl. Data for (±)-**1**: R_f 0.36 (CMA, 18:2:0.1); IR (KBr, cm^{-1}) 3400, 2920, 2830, 1630, 1500, 1458; ^1H NMR ($CDCl_3$) δ 0.13 (4 H, m), 0.52 (4 H, m), 0.84 (2 H, m), 1.67 (2 H, d, J = 9.5 Hz), 2.15–2.50 (12 H, m), 2.65 (4 H, m), 3.05 (2 H, d, J = 18.4 Hz), 3.16 (2 H, d, J = 6.0 Hz), 5.50 (2 H, S), 6.46 (2 H, d, J = 8.0 Hz), 6.63 (2 H, d, J = 8.0 Hz); FABMS 662.2 ($M^+ + 1$), 660.1 ($M^+ - 1$). Data for (±)**1**·2HCl: mp >265 °C dec; $[\alpha]^{25}_D$ −5.2° (*c* 0.1, MeOH); R_f 0.46 (BAW, 2:1:1). Anal. ($C_{40}H_{43}O_6N_3$·2HCl·4H_2O) C, H, N, Cl.

(5*S*,5′*S*,9*S*,9′*S*,13*R*,13′*R*,14*R*,14′*R*)-17,17′-Bis(cyclopropylmethyl)-6,6′,7,7′-tetrahydro-4,5:4′,5′-diepoxy-6,6′-(imino)[7,7′-bimorphinan]-3,3′,14,14′-tetrol, (+)-1. The procedure was identical with that employed for the preparation[2] of (−)-**1** except that (+)-naltrexone hydrochloride (50 mg, 0.13 mmol) was employed in place of (−)-naltrexone hydrochloride. Column chromatography (Sephadex L-20, MeOH) afforded pure (+)-**1** (20 mg, 40%): R_f 0.36 for free base (CMA, 18:2:0.1) and 0.46 for hydrochloride (BAW, 2:1:1); IR of (+)-**1** was identical with that of nor-BNI, (−)-**1**.

Acknowledgment. We thank Michael Powers and Barbara Taylor for in vitro testing, and Dr. K. C. Rice for the (+)-naltrexone hydrochloride employed in this study. This work was supported by the National Institute on Drug Abuse.

Registry No. (−)-**1**, 105618-26-6; (+)-**1**, 114375-46-1; (±)-**1**, 114375-45-0; **2**, 114375-44-9; (+)-naltrexone·HCl, 114274-32-7; (−)-naltrexone·HCl, 16676-29-2; *N*-aminosuccinimide, 19283-13-7.

7-Aminoquinolines. A Novel Class of Agents Active against Herpesviruses

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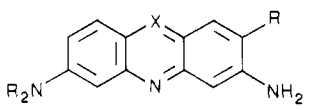
A series of 7-aminoquinoline derivatives was synthesized and evaluated for their capacity to produce cytotoxicity in KB cells and to inhibit the replication of herpes simplex virus (HSV) type 1. All compounds tested inhibited the replication of HSV-1 with 50% inhibitory concentrations in the range of 2–50 μg/mL. The antiviral activity of many compounds, however, was separated from cytotoxicity to replicating uninfected cells by only two- to fivefold higher than those required for antiviral activity. Nonetheless, six compounds (**10**, **28**, **29**, **32**, **34**, and **36**) were identified in which the separation was greater than fivefold. All compounds examined were more potent inhibitors of viral DNA synthesis than the cellular DNA synthesis.

In recent years considerable research efforts have been conducted in order to find drugs useful for the treatment of herpes virus infections.[1-5] Also, herpes viruses have been implicated as the cause of a number of carcinomas.[6-9] Heterocyclic dyes, such as neutral red (**1a**) and proflavine (**1b**), are among the wide variety of compounds that exhibit



1a: R = Me; X = N
b: R = H; X = CH

activity against herpesviruses.[1,10,11] These drugs act by intercalation and photodynamic disruption of DNA. Although these dyes are not appropriate for human therapy,[11] another group of planar heterocyclic compounds—the 4-aminoquinolines such as chloroquine—act through intercalation[12] and have extensive therapeutic usefulness.[13] Because 7-aminoquinolines may be considered analogues of proflavine and because they are relatives of chloroquine, we have prepared and tested a series of such compounds. This article describes the synthesis and evaluation of novel

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