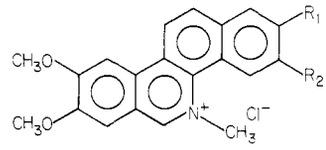
Synthesis and Biological Activity of Benzothiazolo- and Benzoxazolo[3,2-*a*]quinolinium Salts[1]

Osvaldo Cox,*[†] Henry Jackson,[†] Vanessa A. Vargas,[†] Adriana Báez,*[‡] Julio I. Colón,[‡] Blanca C. González,[‡] and Marino de León[‡]

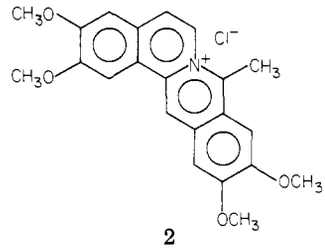
Department of Chemistry, University of Puerto Rico, Río Piedras Campus, Rio Piedras, Puerto Rico 00931, and Department of Pharmacology, Department of Pathology, and Puerto Rico Cancer Center, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico 00936. *Received August 26, 1981*

The hitherto unknown 3-nitrobenzothiazolo- and 3-nitrobenzoxazolo[3,2-*a*]quinolinium salts were synthesized via the photochemically induced cyclization of the corresponding 2-(2-chloro-5-nitrostyryl)benzothiazole and 2-(2-chloro-5-nitrostyryl)benzoxazole. Results on their cytotoxic and antitumor activity are presented.

The benzo[*c*]phenanthridine alkaloids fagaronine (**1a**)[2]



1a, R_1 = OH; R_2 = OCH_3
b, R_1 = R_2 = OCH_2O



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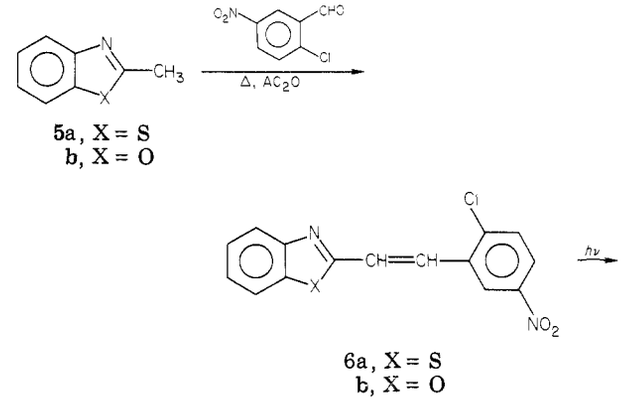
and nitidine (**1b**)[3] represent a class of compounds isolated from the Rutaceae family that show potent antitumor activity against L1210 and P-388 murine leukemias. Coralyne (**2**),[4] a berbenium alkaloid structurally related to the benzo[*c*]phenantridines, exhibits antitumor activity against both tumor screens. Studies on the mechanism of action of fagaronine and nitidine indicate that both alkaloids inhibit DNA synthesis probably by interacting with A-T base pairs.[5] Derivatives of these compounds have been synthesized in order to study the structure–activity relationships and showed that the positively charged nitrogen atom is necessary for their reported antitumor activity.[6–10]

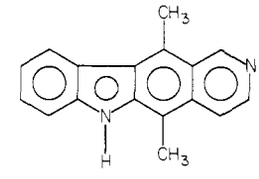
Scheme I



5a, X = S
b, X = O

6a, X = S
b, X = O

In addition, studies on the mode of action of ellipticine (**3**) and analogues have suggested that the presence of a



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positive charge on the nitrogen atom helps to stabilize the complexes formed with DNA.[11,12] Furthermore, it is well established that a variety of thiazole[13] and fused thiazole[14] derivatives also display biological activity.

The synthesis of new compounds incorporating the structural features present in compounds of known biological activity is an attractive and reasonable route to seek new and effective therapeutic agents. Thus, we have synthesized compounds **4b** and **4d** as part of a program aimed at synthesizing compounds combining both structural features described above, namely, a quaternized ring nitrogen atom and a fused thiazole ring. We report in the present article the synthesis and the cytotoxic and antitumor activities of these compounds.

Chemistry. A number of synthetic schemes have been employed to introduce a quaternized ring nitrogen atom at a bridgehead as in **4** (Scheme I).[15–18] However, the

[†] University of Puerto Rico, Rio Piedras Campus.
[‡] University of Puerto Rico, Medical Sciences Campus.

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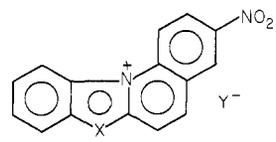
Table I. Cytotoxic Activity[a]

compd	ED_{50}, μg/mL KB	HeLa
1a	0.7	
4b	0.6	0.9
4d	12	15

[a] Results are the average of at least three experiments ($p < 0.05$).

method of Fozard and Bradsher[15] was considered the most appropriate in order to develop a general synthesis of ions of type 4 (X = O, S, Se, NH). The general synthetic route is outlined in Scheme I.



4a, X = S; Y = Cl
b, X = S; Y = ClO_4
c, X = O; Y = Cl
d, X = O; Y = ClO_4

According to Bradsher[15] the nitro group located para to the leaving group in **6** is necessary to promote the cyclization step. Compound **4a** was obtained in 10% yield by the synthetic sequence outlined in Scheme I. The synthetic sequence commences with the condensation of 2-chloro-5-nitrobenzaldehyde with 2-methylbenzothiazole (**5a**) in boiling acetic anhydride to give 2-(2-chloro-5-nitrostyryl)benzothiazole (**6a**). This procedure is an extension of the well-known condensation reaction described by Horwitz[19] for the synthesis of stilbazoles and is known to produce the *E* isomer as the major product. Exposure of dilute solutions of **6a** in a benzene–dioxane (3:1) solution to a Hanovia 400-W mercury arc lamp for 24 h, with an internally cooled Vycor vessel, resulted in the formation of 3-nitrobenzothiazolo[3,2-*a*]quinolinium chloride (**4a**).

Compound **4a** (Y = Cl^-) is very soluble in water; however, the perchlorate salt **4b** precipitates upon addition of 70% perchloric acid to the aqueous solution. Confirmation of the structure of **4b** rests on satisfactory elemental composition for $C_{15}H_9ClN_2O_6S$ by combustion analysis, ^1H NMR, ^{13}C NMR, and UV spectral data (see Experimental Section).

Irradiation of **6b**, obtained from the condensation of 2-chloro-5-nitrobenzaldehyde with 2-methylbenzoxazole (**5b**), under similar conditions led in 1% yield to **4c**. Addition of 70% perchloric acid to the aqueous solution of **4c** gave the perchlorate salt **4d**. The structure of **4d** was likewise secured by elemental analysis and spectral data.

Biological and Biochemical Results and Conclusions

The biological activity data for the two compounds are summarized in Tables I and II. Cytotoxic activities of compounds **4b** and **4d** were tested on both KB and HeLa cells following the standard techniques.[21] The results in Table I show that compound **4b** is highly cytotoxic to both KB (0.6 μg/mL) and HeLa (0.9 μg/mL) cells. The ED_{50} for KB cells of compound **4b** is comparable to that of **1a**

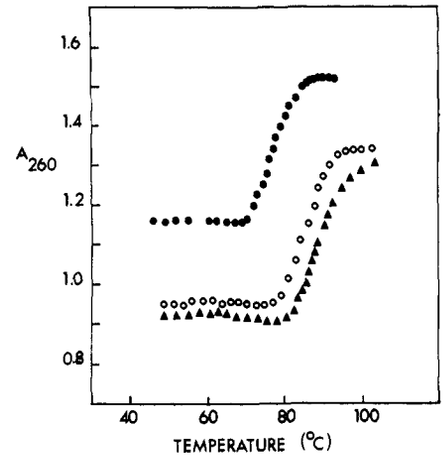


Figure 1. Thermal denaturation profile of calf thymus DNA in the presence of **1a** and **4b**. DNA, 180 μM (●); DNA·**4b** at a 0.1 drug/phosphate ratio (○); DNA·**1b** at a 0.2 drug/phosphate ratio (▲).

(0.7 g/mL) obtained in this work. In contrast, compound **4d** displayed moderate activity against both types of cultured cells. These results are surprising in view of the minor structural differences between analogues **4b** and **4d**. It appears that the substitution of the sulfur atom by the oxygen atom at position 7 is a critical factor in eliciting the inhibitory activity. This substitution probably induces a change in the electronic environment around the nitrogen atom, thus decreasing the inhibitory activity in **4d**.

It has been pointed out that a correlation exists between compounds that are active in the KB cells assay and that also display antimicrobial activity.[20] Thus, the antibacterial activity of both compounds was studied, and no antimicrobial activity was observed against bacterial strains of *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* (results not presented).

The antitumor activity of compound **4b** was assessed in mice bearing Ehrlich ascites tumor and the P-388 ascitic leukemia (Table II). Swiss female mice inoculated with 10^6 cells of Ehrlich ascites were given single ip injections in the 90–400 mg/kg dose range, 24 h after tumor implantation. The most effective dose was 200 mg/kg, which gave T/C value of −6.2%. Mice that were given a dose of 400 mg/kg died within 24 h of injections, presumably from drug toxicity. The lowest dose tested (90 mg/kg) was moderately effective, leaving three survivors out of five with no evidence of tumor development 60 days after beginning of treatment.

Against P-388 leukemia in BDG_1 mice, compound **4b** also showed greater efficacy (T/C = 218) at the 200 mg/kg dose administered on day 1. The effective dose level in this test is comparable to that obtained in the Ehrlich ascites tumor system. Although data are not directly comparable, since they were obtained by different dosages and schedules, compound **4b** showed activity comparable to that reported for fagaronine (**1a**; T/C = 290 at 320 mg/kg)[8] and nitidine (**1b**; T/C = 129 at 100 mg/kg),[7] both on a qd 1–9 dose schedule.

In order to assess any possible effects of the perchlorate ion present in **4b**, mice were injected a potassium perchlorate solution at the highest dose used for **4b** (400 mg/kg). No host toxicity nor antitumor activity was observed, thus indicating that the biological activity of **4b**

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Table II. Antitumor Activity of **4b** against Ehrlich Ascites Tumor and P-388 Leukemia in Mice[a]

Ehrlich ascites[b]					P-388 leukemia[c]			
dose,[d] mg/kg	T/C,[e] %	survival	toxicity[f]	LTS[g]	dose,[d] mg/kg	T/C,[h] %	survival	toxicity
400		0/6	6/6		400		0/6	6/6
250	−2.5	6/6		15/18				
200	−6.9	6/6		18/18	200	218	6/6	
150	−0.4	6/6		15/18				
100[i]	35.8	6/6		12/12	100	153	6/6	
90[i]	57.3	3/5		5/10				

[a] Average of three tests, except when noted. [b] Assay performed according to the method described under Experimental Section. [c] Assay performed according to protocols of the NCI (see ref 21). 5-Fluorouracil (200 mg/kg injn) was used positive control. [d] Treatment given ip on day 1. [e] Significant response shows a T/C ≤ 42% at day 12. [f] Toxicity = number of toxic deaths/number of treated mice. [g] LTS = long-term survivors (>60 days)/number of treated mice. [h] Median survival time of treated mice/median survival of control mice × 100. Values of T/C > 120 denote activity. [i] Average of two test results.

can be ascribed to the cation solely (results not presented).

The interaction of certain drugs with native DNA leads to the stabilization of the double-helical structure of the macromolecule toward thermal denaturation. Since the rationale behind the synthesis of compounds **4b** and **4d** was their potentiality to interact with DNA, we determined the effect of **4b** and fagaronine (**1a**) on the T_M of DNA. The effect of both drugs on the thermal denaturation of calf thymus DNA is presented in Figure 1. It is evident that both compounds are capable of inducing an increase in the denaturing temperature of DNA. Thus, in the presence of 3.3 μM **4a**, the melting point of calf thymus DNA (77.8 °C) is increased to 84.8 °C (ΔT_M = 7 °C). Similarly, 5 μM fagaronine (**1a**) increases the melting temperature of DNA to 88.6 °C (ΔT_M = 10.8 °C). Our unpublished observations[22] indicate that these results correlate well with the DNA intercalating model for compound **4b**.

Experimental Section

Melting points were determined in a Thomas-Hoover or a Melt-Temp apparatus and are uncorrected. The ^1H and ^{13}C nuclear magnetic resonance spectra were recorded in a JEOL-FX-90Q NMR spectrometer. Chemical shifts are referenced to internal tetramethylsilane. Ultraviolet spectra were recorded in a Hitachi Perkin-Elmer 200 UV–visible spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Analysis indicated only by symbols of the elements means that analytical results obtained for those elements were within ±0.4% of the theoretical values. Irradiations were conducted under an Argon atmosphere in 450-W Hanovia mercury vapor lamp in a standard immersion well fitted with a Vycor filter. Thermal denaturation studies were carried out with a Beckman DU-8 spectrophotometer. Calf thymus DNA type 1 was purchased from Sigma Chemical Co., St. Louis, MO. Fagaronine (NCS-157995) was a kind gift of Dr. J. Douros, Natural Products Branch, National Cancer Institute, Silver Spring, MD.

General Procedure for the Synthesis of 2-(2-Chloro-5-nitrostyryl)benzothiazole (6a) and 2-(2-Chloro-5-nitrostyryl)benzoxazole (6b). This procedure is illustrated for the synthesis of **6a**. A solution of 12.4 g (0.067 mol) of 2-chloro-5-nitrobenzaldehyde and 10.0 g (0.067 mol) of freshly distilled 2-methylbenzothiazole (**5a**) in 60 mL of acetic anhydride was refluxed for 5 h. The precipitated yellow solid was collected by filtration and recrystallized from toluene to afford 14.9 g (70.2%) of **6a**: mp 188–189 °C; UV (EtOH) λ_{max} 214 nm (ε 16 808), 332.5 (28 445); ^1H NMR (Me_2SO-d_6) δ 8.58 (d, J = 2.7 Hz, 1 H), 8.16–7.26 (complex pattern, 8 H); ^{13}C NMR (Me_2SO-d_6) δ 121.6, 121.9, 123.6, 124.0, 126.0, 126.7, 127.3, 130.7, 131.1, 134.9, 135.3, 140.2, 147.1, 154.0, 165.0. Anal. ($C_{15}H_9ClN_2O_2S$) C, H, Cl, N, S.

Compound **6b** was obtained in a similar manner in 6% yield, from the condensation of 2-chloro-5-nitrobenzaldehyde and **5b**: mp 177–178 °C (recrystallized from dioxane); UV (EtOH) λ_{max} 202 nm (ε 11 156), 324.5 (18 945); ^1H NMR (Me_2SO-d_6) 8.58 (d, J = 2.7 Hz, 1 H), 8.22–7.12 (complex pattern, 8 H); ^{13}C NMR (Me_2SO-d_6) 110.6, 119.5, 120.5, 122.1, 124.4, 124.9, 126.1, 132.2, 132.7, 135.1, 140.5, 142.3, 147.1, 150.7, 161.5. Anal. ($C_{15}H_9ClN_2O_3$) C, H, N.

General Method for the Synthesis of 3-Nitrobenzothiazolo- and 3-Nitrobenzoxolo[3,2-*a*]quinolinium Perchlorate (4b and 4d). This procedure is illustrated for the synthesis of **4b**. A solution of 2.0 g (6.3 mmol) of **6a** in 400 mL of a 3:1 benzene–dioxane solution was exposed to a 450-W Hanovia mercury vapor lamp with a standard immersion well fitted with a Vycor filter. The solution was kept under an argon atmosphere throughout the irradiation period of 24 h. The irradiation was stopped at 2-h intervals in order to remove the water-soluble substance adhered to the insert. The aqueous solution was filtered and there was added 0.25 mL of 70% perchloric acid. The precipitated solid was collected by filtration, washed several times with cold water, and dried to afford 187 mg (9% yield) of **4b**: mp 309 °C dec; UV (EtOH) λ_{max} 206 nm (ε 23 340), 272.5 (15 426), 364 (15 212); ^1H NMR (Me_2SO-d_6) complex pattern between δ 7.47 and 9.59; ^{13}C NMR (Me_2SO-d_6) δ 120.1, 121.1, 121.3, 125.5, 126.3, 126.6, 127.3, 129.4, 129.6, 129.7, 138.7, 139.0, 140.0, 145.7, 162.0. Anal. ($C_{15}H_9ClN_2O_6S$) C, H, Cl, N, S.

Compound **4b** was prepared in a similar manner in 1% yield: mp 200 °C dec; UV (EtOH) λ_{max} 223 nm (ε 29 927), very broad peak centered at 250 (29 197), ^{13}C NMR (Me_2SO-d_6) δ 115.9, 117.0, 119.4, 119.8, 120.9, 123.5, 124.3, 124.8, 129.7, 130.3, 139.6, 141.5, 144.5, 153.0, 160.6. Anal. ($C_{15}H_9ClN_2O_7$) C, H, N.

Cells and Growth Conditions. HeLa 229 and KB cells were used for in vitro tissue culture cytotoxicity experiments. Cells were grown in monolayer culture in Difco TC Eagles's minimum essential medium and supplemented with 10% fetal calf serum (Flow). Subculturing was performed every 6–7 days. Ehrlich ascites tumor was maintained in serial passages at 2-week intervals in Albino Swiss mice by intraperitoneal implant.

Cytotoxicity Studies. The method used was essentially as previously described.[21] Drugs were always suspended in sterile 0.5% carboxymethylcellulose. As a positive control, 1 μM 6-mercaptopurine was always included.

Preparation of Test Compound. Test compounds were suspended in 0.9% (w/v) NaCl solution containing 0.10% (v/v) Tween 80 at the higher concentration. Lower doses were obtained by serial dilutions with 0.9% NaCl.

Animal Maintenance and Antitumor Experiments. The mice used throughout these experiments were female Albino Swiss mice and female BDF_1 mice. All the animals were maintained ad libitum on normal purina chow and water.

Ehrlich Ascites Tumor Assay. Each group consisted of five to six weight-matched animals. To begin the antitumor experiment, 1 × 10^6 viable cells (Trypan blue exclusion test) were injected intraperitoneally (ip). When necessary, animal body weights were recorded daily during the next 30 days, and the survival was followed for the next 60 days. Data of the assay were evaluated according to protocols 1100 and 1200 from the NCI.[21]

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The P-388 leukemia assay was performed according to standard protocol.[21]

Toxicity Tests. Toxicity tests of the perchlorate ion in mice were carried out by the procedure described above. Mice were also checked visually daily for any change in their appearance.

Melting Curve. Thermal denaturation studies were carried out with a Beckman DU-8 spectrophotometer. The temperatures of the thermal denaturations were obtained with a programmed temperature of 0.7 °C per minute. Calf thymus DNA, 3-nitrobenzothiazolo[3,2-*a*]quinolinium salt (**4b**), and fagaronine (**1a**) were dissolved in SHE buffer (2 μM Hepes, 10 μM EDTA, 0.4 μM NaCl adjusted to pH 7.0 with NaOH). For determination of thermal denaturation profiles, the final concentration of DNA was identical in the presence or absence of the test drug in all experiments.

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Structure–Activity Relationships for Hallucinogenic *N,N*-Dialkyltryptamines: Photoelectron Spectra and Serotonin Receptor Affinities of Methylthio and Methylenedioxy Derivatives

Toni B. Kline,[†,‡] Frederick Benington,*[,†] Richard D. Morin,[†] John M. Beaton,[†] Richard A. Glennon,[§] L. N. Domelsmith,[∥,⊥] K. N. Houk,[∥,#] and Melvin D. Rozeboom[∥]

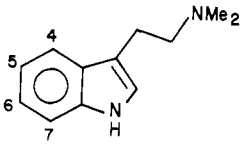
Neurosciences Program, University of Alabama in Birmingham, Birmingham, Alabama 35294, Department of Pharmaceutical Chemistry, Medical College of Virginia, Virginia Commonwealth University, MCV Station, Richmond, Virginia 23298, and Departments of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803, and University of Pittsburgh, Pittsburgh, Pennsylvania 15260. *Received April 19, 1982*

Serotonin receptor affinity and photelectron spectral data were obtained on a number of substituted *N,N*-dimethyltryptamines. Evidence is presented that electron-donating substituents in the 5-position lead to enhanced behavioral disruption activity and serotonin receptor affinity as compared to unsubstituted *N,N*-dimethyltryptamine and analogues substituted in the 4- or 6-position. Some correlation was found between ionization potentials and behavioral activity, which may have implications concerning the mechanism of receptor binding.

In a recent communication,[1a] we described the relative behavioral activities of a series of ring-substituted *N,N*-dialkyltryptamines, as well as the effectiveness of these compounds in displacing tritiated serotonin (5-HT) and lysergic acid diethylamide (LSD) from 5-HT binding sites. Because photoelectron sepctral (PES) properties and rat fundus 5-HT receptor affinities (pA_2 values) have been previously used to study various hallucinogenic agents,[1b] we have undertaken an examination of those properties for five novel substituted *N,N*-dimethyltryptamines (**1–5**).

Photoelectron Spectroscopy. Figure 1 shows the PES of compounds **1** through **5**. The vertical ionization potentials[2] (IP, in eV) taken from these spectra appear in Table I. Each distinct IP_i can be assigned to an ionization event from a particular molecular orbital, ϕ_i. The changes in IP_is, which, by sign convention, are lowered as ϕ_i is raised, indicate the influence of the substitutents upon the corresponding molecular orbital of *N,N*-dimethyltryptamine, DMT (**7**). Assignments were made in accordance with the methodology of Domelsmith et al.[2,4,5] in these experiments.

Ionization Potentials. From the relative coefficient magnitudes and symmetry properties of the wave function of indole,[2] it is possible to make some predictions regarding substituent effects in this series of compounds. Generally,



R

1	4,5-<O,O
2	5,6-<O,O
3	4-CH_3S-
4	5-CH_3S-
5	6-CH_3S-
6	5-CH_3O-
7	H

electron-donating substituents lower aromatic IPs most when attached at a site where the electron density in ϕ at the substitution site is large. The high-lying filled orbitals of the indole nucleus, shown in Figure 2, are useful in interpreting the spectra obtained here.[6] Thus, substitu-

[†] University of Alabama in Birmingham.
[‡] Present address: Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY 11794.
[§] Medical College of Virginia.
[∥] Louisiana State University and University of Pittsburgh.
[⊥] Present address: Department of Chemistry, University of Nebraska at Omaha, Omaha, NE 68182.
[#] Present address: Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260.

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(6) These were obtained by ab initio STO-3G calculations on indole.

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