Design, Synthesis, and Study of 9-Substituted Ellipticine and 2-Methylellipticinium Analogues as Potential CNS-Selective Antitumor Agents

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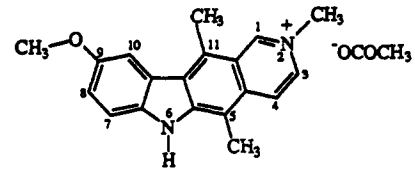
N,N-Dimethylformamide (DMF) dineopentyl acetal-mediated *O*-alkylations of 9-hydroxyellipticine gave 9-ethoxy-, 9-(1-methylethoxy)-, and 9-(1,1-dimethylethoxy)ellipticine (**3a**, **4a**, and **5a**, respectively). Methylation of the *O*-alkylellipticines gave the corresponding *N*-methylpyridinium iodides (**3b**, **4b**, and **5b**). The iodides were converted to the acetates (**3c**, **4c**, and **5c**) by ion-exchange resin. Attempts to prepare 9-(2,2,2-trifluoroethoxy)ellipticine (**6a**) using the DMF acetal gave 10-(2,2,2-trifluoroethoxy)-9-hydroxyellipticine (**8a**). 9-(2,2,2-Trifluoroethoxy)- and 9-phenoxyellipticine (**6a** and **7a**, respectively) were prepared by total synthesis. The ellipticines and *N*-methylellipticinium derivatives were evaluated for in vitro antitumor activity against a panel of human tumors. 2-Methyl-9-(1,1-dimethylethoxy)ellipticinium acetate (**5c**) was inactive, but all of the other compounds exhibited significant antitumor activity. The ellipticines showed no significant subpanel specificity; however, the *N*-methylellipticinium compounds tested did exhibit specificity for the CNS tumor subpanel.

Introduction

Interest in ellipticine and ellipticine analogues as potential cancer chemotherapeutic agents has promoted considerable activity in the search for newer analogues with superior antitumor activity.[1] 9-Hydroxy-2-methylellipticinium acetate (**2**; Elliptinium or Celiptium) is one of several ellipticine analogues shown to possess significant antitumor activity and, during phase II clinical trials, has been shown to elicit modest responses in patients with advanced breast cancer.[2] The drug is not myelotoxic but does produce renal toxicity which has been associated with oxidized metabolites of the drug.[3]

Recently, 9-methoxy-2-methylellipticinium acetate (**1**) has been shown to exhibit significant, selective cytotoxicity against a subpanel of human central nervous system (CNS) tumors when compared with a broader panel of human tumor cells (in vitro).[4] The closely related phenol, 9-hydroxy-2-methylellipticinium acetate (**2**), also showed CNS selectivity at lower drug concentrations, but the selectivity was absent at higher concentrations. Is 9-methoxy-2-methylellipticinium acetate (**1**) active or must it be transformed to 9-hydroxy-2-methylellipticinium acetate (**2**) in order to exert its effect (*i.e.*, is 9-methoxy-2-methylellipticinium acetate a prodrug)? The 9-hydroxy group is important for interactions with topoisomerase II and for DNA base-pair binding selectivity.[5] Metabolically, 9-hydroxy-2-methylellipticinium acetate (**2**) can be oxidized to an electrophilic quinonimine[6] that can undergo nucleophilic attack at C-10; furthermore, **2** can act as a precursor to oxy radicals which act as free-radical scavengers.[7] Oxidation of the C-5 and/or C-11 methyl group(s) also yield electrophilic products which have been implicated in the activity of **2**.[8]

One concern with the observed in vitro activity of **1** relates to the problem that simple intercalating agents often show in vitro cytotoxicity but fail to exhibit significant activity against experimental tumors in vivo. For example, the ellipticine derivatives known as oxazolopyridocarbazoles (OPC's) are potent intercalating agents which show cytotoxicity comparable to potent ellipticines. However, the OPC's have no significant in vivo antitumor activity.[9] This is consistent with structure–activity relationship studies with ellipticine analogues which show a high correlation between a free phenolic hydroxyl group at C-9 and in vivo antitumor activity. Analogues with a group that can be metabolized to a C-9 phenol also exhibit in vivo antitumor activity (*e.g.*, hydrolysis of an 9-*O*-acyl derivative, hydrolysis of a 9-*O*-glycoside, or oxidation of a C-9 unsubstituted analogue to a phenol).[10] Several postulates can be offered to rationalize the activity of **1** without prior conversion to **2**. For example, deprotonation of the methoxy compound **1** would yield an azaquinone methide (Scheme 1) similar to the azaquinone methide that could be derived from **2**, and if such species are responsible for the activity if these agents, demethylation of **1** would not be necessary. However, the significance (or existence) of such a species remains to be demonstrated.



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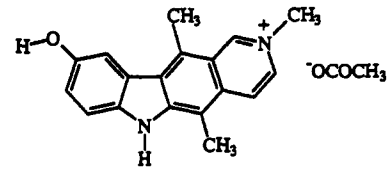

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It would seem unlikely that the human tumor cells in the in vitro assay could effect the transformation of **1** to **2**,[11] but if **1** is converted to **2** in the cell, the differences between the CNS antitumor activity of **1** and **2** could be due to differences in cell uptake (alternatively, it may be possible that some types of tumor cells have a greater capacity to "activate" **1** in this manner). Oxidative *O*-demethylation reactions catalyzed by cytochrome P450 are well-known in mammalian metabolism; therefore, it

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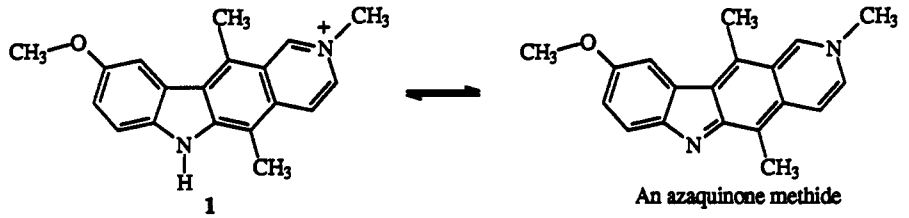
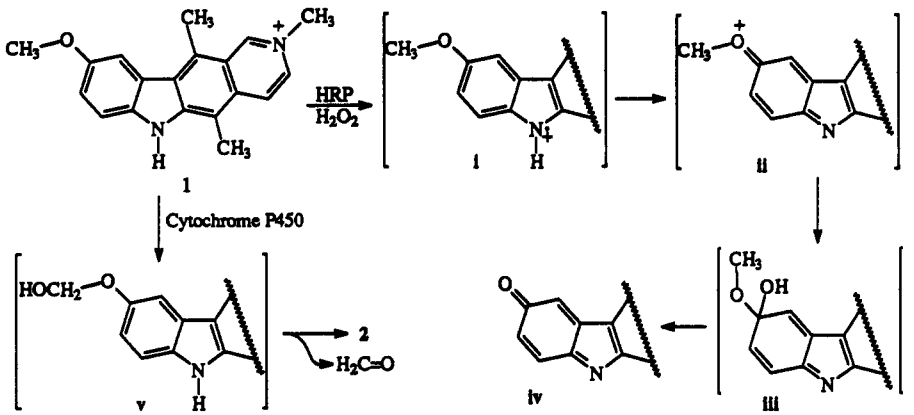
Scheme 1. Deprotonation of 2-Methyl-9-methoxyellipticinium To Generate an Azaquinone Methide



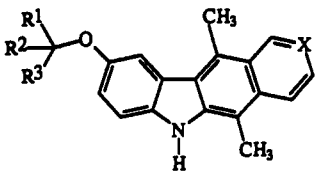
Scheme 2. Demethylation of 2-Methyl-9-methoxyellipticinium by Cytochrome P450 and by H_2O_2-Horse Radish Peroxidase (HRP)



is probable that the CNS selectivity shown by **1** in vitro will be lost in vivo due to facile metabolic *O*-demethylation to **2**.

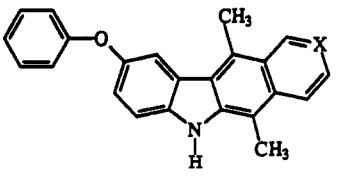
O-Dealkylations of **1** have been reported to proceed under cytochrome P450 catalysis and by hydrogen peroxide-horse radish peroxidase (HRP), although it is not clear whether or not a HRP-like route occurs in mammalian metabolism. The cytochrome P450 catalyzed *O*-dealkylation presumably involves the oxidation of the "α-carbon" of the ether to give a hemiacetal, but the mechanism of the oxidation is not known with certainty. The oxidation most likely proceeds through an "oxenoid" species in which the reactive moiety is singlet oxygen bound to the heme iron in cytochrome P450. Most evidence supports the notion that oxidation proceeds with a concerted insertion of the "oxenoid" species into the C–H bond (analogous to a carbene insertion reaction), although in some cases it is not possible to exclude a stepwise reaction involving hydrogen atom abstraction from the C–H bond to give a free radical intermediate. The HRP-catalyzed reaction is quite distinct from the monooxygenase transformation (cytochrome P450). The proposed mechanism (Scheme 2) involves an initial one-electron oxidation of the indole nitrogen followed by a second one-electron oxidation of the putative radical-cation intermediate, nucleophilic addition of hydroxide, and cleavage of the resultant hemiketal.[12]

We report the synthesis and evaluation of analogues of 2-methyl-9-methoxyellipticinium acetate (**1**) in which the cytochrome P450 mediated metabolic conversion to **2** might be impeded or completely inhibited. The compounds proposed for our preliminary studies include 9-ethoxy-, 9-(1-methylethoxy)-, and 9-(1,1-dimethylethoxy)ellipticine, **3a**, **4a**, and **5a**, respectively, and the 2-methylellipticinium derivatives (**3b/c**, **4b/c**, and **5b/c**). Steric effects are known to retard the rate of cytochrome P450 mediated oxidative *O*-dealkylation so the isopropyl ether **4** should be dealkylated at a slower rate than the ethoxy compound **3**. The 9-(1,1-dimethylethoxy) analogue **5** cannot undergo α-hydroxylation, so cleavage of **5** by this mechanism is not possible. Aryloxy analogues of **1** also lack an ether α-hydrogen for C–H insertion or hydrogen atom abstraction. The phenoxy derivative **7** chosen for synthesis and biological evaluation also has a planar phenyl ring in the biaryl ether **7** that may enhance binding of this analogue to the putative target (DNA, or topoisomerase II, or to the DNA–topoisomerase II complex).



3: $R^1 = R^2 = H$; $R^3 = CH_3$
4: $R^1 = H$; $R^2 = R^3 = CH_3$
5: $R^1 = R^2 = R^3 = CH_3$
6: $R^1 = R^2 = H$; $R^3 = CF_3$

(where: a, X = N; b, X = N^+CH_3 I^-; c, X = N^+CH_3 AcO^-)



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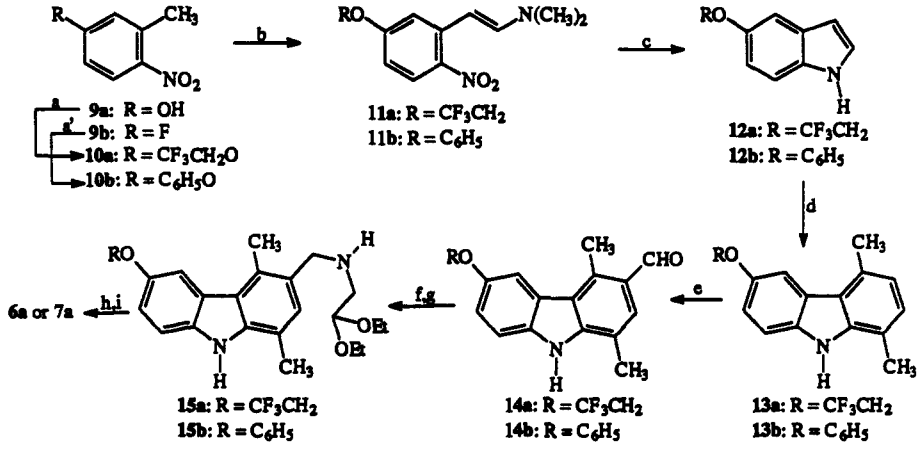
The trifluoroethyl ether, **6**, is an analogue of **4** that was designed to evaluate the influence of a small, electron-withdrawing group on the alkyl ether. A comparison of the in vitro antitumor activity of **3**, **4**, and **5** will afford information concerning the relationship between cytotoxicity, CNS selectivity, and steric bulk on the ether moiety. A comparison of **3** and **6** will provide information concerning possible electronic requirements of the ether moiety for antitumor activity, CNS selectivity, and the rate of ether *O*-dealkylation.

Scheme 3. Synthesis of 9-(2,2,2-Trifluoroethoxy)ellipticine (**6a**) and 9-Phenoxyellipticine (**7a**)[a]

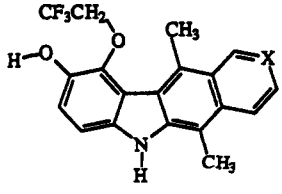


[a] (a) NaH, CF_3CH_2OTs, HMPA; (a') PhOK; (b) $(CH_3)_2NCH(OEt)_2$, DMF; (c) Pd–C, H_2; (d) 2,5-hexanedione, *p*-TsOH, EtOH; (e) *N*-methylformanilide, $POCl_3$; (f) aminoacetaldehyde diethyl acetal; (g) $NaBH_4$, MeOH; (h) Na_2CO_3, *p*-TsCl; (i) H_2O–HCl–dioxane.

Chemistry

Demethylation of 9-methoxyellipticine[13] with pyridine hydrochloride at 220 °C for 1 h furnished 9-hydroxyellipticine; *O*-alkylation (*N*,*N*-dimethylformamide dineopentyl acetal in ethanol at reflux) gave 9-ethoxyellipticine **3a**.[14] Compound **3a** was treated with iodomethane to give the quaternary iodide **3b**. The methiodide was passed through AG1-X8 anion-exchange resin (acetate form) to give **3c**. 9-(1-Methylethoxy)ellipticine (**4a**) and the 9-(1,1-dimethylethoxy) analogue **5a**, as well as the two sets of pyridinium salts **4b**/**4c** and **5b**/**5c**, were prepared in a similar manner.

9-(2,2,2-Trifluoroethoxy)ellipticine (**6a**) could not be prepared from 9-hydroxyellipticine by *O*-alkylation: treatment of 9-hydroxyellipticine with sodium hydride (1 equiv) and 2,2,2-trifluoroethyl *p*-toluenesulfonate in HMPA[15] led to the recovery of starting material. The reaction of 9-hydroxyellipticine with 2,2,2-trifluoroethanol and *N*,*N*-dimethylformamide dineopentyl acetal at reflux temperature resulted in the unexpected formation of the 10-*O*-alkyl-9-hydroxy derivative, **8a**, instead of the desired 9-*O*-alkyl derivative **6a**. The structure of **8a** was assigned on the basis of the known propensity of ellipticines to undergo nucleophilic attack at C-10, although the ^1H NMR data do not rigorously exclude the isomeric 8-trifluoroethoxy structure. This compound was not as stable as the other 9-alkoxyellipticine derivatives. Compound **8a** was treated with iodomethane to give the iodide **8b**. This iodide was sparingly soluble in water. Iodide **8b** was also unstable, and attempts to exchange the anion for acetate by anion-exchange chromatography led to decomposition.



8a: X = N
b: X = N$^+$CH$_3$ I$^-$

Our inability to *O*-trifluoroethylate 9-hydroxyellipticine led us to a total synthesis of **6a** as summarized in Scheme 3. Commercially available 3-methyl-4-nitrophenol (**9a**) was alkylated[15] (sodium hydride and 2,2,2-trifluoroethyl *p*-toluenesulfonate in HMPA) and the ether **10a** was condensed with *N*,*N*-dimethylformamide diethyl acetal in DMF[16] to give the enamine **11a**. Reductive cyclization (Pd/C in ethyl acetate)[17] afforded 5-(2,2,2-trifluoroethoxy)-indole (**12a**). Condensation of **12a** with hexane-2,5-dione gave the carbazole **13a** which was formylated[14b,18] regioselectivity (*N*-methylformanilide and phosphorus oxychloride) to afford aldehyde **14a**. Reductive amination[14b] of **14a** (aminoacetaldehyde diethyl acetal and then sodium borohydride) gave the amine **15a** that was tosylated and cyclized in 6 N HCl in dioxane[14b] to give 9-(2,2,2-trifluoroethoxy)ellipticine (**6a**). Methylation of **6a** with iodomethane in acetone afforded the iodide **6b**, which was passed through AG1-X8 anion-exchange resin (acetate form) to provide the acetate **6c**.

Several attempts were made to prepare 9-phenoxyellipticine (**7a**) by direct arylation of 9-hydroxyellipticine. Treatment of 9-hydroxyellipticine with triphenylbismuth diacetate[21] or triphenylphosphine–DEAD–DMF–phenol (Mitsunobu conditions)[20a] failed to give **7a**. Similarly, treatment of the phenoxide derived from 9-hydroxyellipticine with either diphenyliodonium iodide,[14b,20b] or *p*-fluoronitrobenzene[19] also failed to afford **7a**.

The synthesis of 9-phenoxyellipticine (**7a**) followed the procedure described for the 9-(2,2,2-trifluoroethoxy) derivative, **6a**.[22] Fusion of molten potassium phenoxide with 2-nitro-5-fluorotoluene (**9b**) at 130 °C for 30 min[19] gave the diphenyl ether **10b** precursor for 5-phenoxyindole, **12b** (Scheme 3). The indole **12b** was converted to the carbazole **13b**; regioselective formylation of the carbazole, condensation of the resulting aldehyde **14b** with aminoacetaldehyde diethylacetal, and reduction of the imine intermediate gave the amine **15b**. *N*-Tosylation of **15b** followed by acid-catalyzed cyclization afforded 9-phenoxyellipticine (**7a**). Methylation of N-2 in 9-phenoxyellipticine (**7a**) with iodomethane gave **7b**. The methiodide was converted (AG 1-X8 anion-exchange resin) to 2-methyl-9-phenoxyellipticinium acetate (**7c**) in quantitative yield.

Biological Results and Discussion

The compounds prepared in this study were evaluated (in vitro) in the NCI disease-oriented human tumor cell line panels. The data summarized in Table 1 show that analogues with bulkier C-9 substituents retain activity, although the potency of 9-phenoxyellipticine (**7a**) is slightly lower than 9-(2,2,2-trifluoroethoxy)ellipticine (**6a**), 9-

Table 1. Summary of in Vitro Screening Data Using Disease-Oriented Human Tumor Cell Line Panels: Drug Concentration (μM) *vs* Percent Growth (PG) at Three Levels [+50% (GI_{50}), 0% (TGI), and −50% (LC_{50})][a]

compd	GI_{50}, μM (range)	TGI, μM (range)	LC_{50}, μM (range)
1	1.86 (0.02–>100)	14.79 (0.30–>100)	48.98 (1.20–>100)
2	2.95 (0.02–>100)	41.69 (1.35–>100)	>100
3a	1.12 (0.38–>100)	3.24 (1.62–>100)	8.32 (4.68–>100)
3b	1.17 (0.060–>100)	12.02 (0.68–>100)	54.95 (3.02–>100)
3c	2.34 (0.19–>100)	19.50 (0.65–>100)	74.13 (5.6–>100)
4a	1.32 (0.32–2.00)	3.02 (1.91–>100)	6.61 (5.25–>100)
4b	1.62 (0.06–>100)	13.18 (0.06–>100)	58.88 (5.25–>100)
4c	3.80 (0.43–>100)	23.44 (3.47–>100)	66.07 (7.94–>100)
5a	2.57 (1.58–11.22)	7.24 (2.95–54.95)	32.36 (5.50–>100)
5c	>100	>100	>100
6a	1.58 (0.62–2.95)	3.24 (2.00–5.50)	8.13 (4.09–>100)
6b	1.58 (0.20–2.95)	22.39 (0.68–>100)	79.43 (12.30–>100)
6c	3.47 (0.22–52.48)	62.66 (0.83–>100)	>100
7a	2.63 (1.55–16.6)	6.03 (2.75–41.69)	19.50 (5.75–>100)
7b	1.91 (0.23–>100)	33.88 (0.89–>100)	93.33 (16.98–>100)
7c	1.82 (0.23–29.5)	30.90 (1.55–>100)	97.72 (67.61–>100)
8a	5.89 (1.38–15.14)	15.85 (3.24–37.15)	42.66 (8.13–>76)
8b	2.24 (0.51–12.88)	13.49 (1.10–>55)	50.12 (22.91–>55)

[a] Each cell line was incubated with drug at drug concentrations of 0.01, 0.1, 1, 10, and 100 μM. A dose–response curve was obtained [percent growth (PG) *vs* log drug concentration]: GI_{50}, TGI, and LC_{50} represent drug concentrations where PG was +50, 0, and −50%, respectively. The inhibitory concentrations given above are mean inhibitory concentrations for the entire tumor panel. The mean PG uses values at either limit (> or <) in the calculation. The drug concentrations necessary for growth inhibition (PG values of +50, 0, or −50%) varied in each tumor cell line and the drug concentrations required for the most and least sensitive cell lines are given in parentheses (*i.e.*, range).

Table 2. Summary of in Vitro Screening Data Using Disease-Oriented Human Tumor Cell Line Panels [Drug Concentration (μM) *vs* Percent Growth (PG) at Three Levels (+50, 0, and −50%)]: A Comparison of the CNS Tumor Subpanel with All NonCNS Tumors[a]

	nonCNS/CNS (ratio)		
compd	GI_{50}, μM	TGI, μM	LC_{50}, μM
1	2.51/0.15 (16.73)	21.38/0.63 (33.94)	68/3.24 (20.99)
2	4.07/0.25 (6.28)	55/5.89 (9.34)	>100/95 (1.05)
3a	1.12/1.26 (0.89)	3.39/2.57 (1.32)	9.12/5.37 (1.70)
3b	1.58/0.20 (7.90)	16.60/1.74 (9.54)	>69/13.80 (5)
3c	3.02/0.51 (5.92)	25.70/3.63 (7.08)	>86/>28 (3)
4a	1.29/1.66 (0.78)	2.97/3.31 (0.90)	5.88/38.91 (0.15)
4b	2.17/0.26 (8.35)	17.08/2.63 (6.49)	>74/>39 (1.9)
4c	4.52/1.51 (2.99)	25.88/12.37 (2.09)	>76/>51 (1.49)
5a	2.63/2.40 (1.10)	7.41/6.31 (1.17)	33.11/33.88 (0.98)
5c	>100/>100 (1)	>100/>100 (1)	>100/>100 (1)
6a	1.15/1.82 (0.63)	2.45/3.39 (0.73)	6.17/8.32 (0.74)
6b	2.19/0.35 (6.26)	29.51/3.24 (9.11)	>80/>74 (1.08)
6c	4.79/0.37 (12.95)	>72/5.25 (13.71)	>100/>100 (1)
7a	2.56/3.11 (0.82)	5.85/7.18 (0.81)	19.08/21.69 (0.88)
7b	2.23/0.73 (3.05)	37.58/18.20 (2.06)	>96/>80 (1.2)
7c	2.16/0.62 (3.48)	36.59/11.95 (3.06)	>99/>92 (1.03)
8a	5.89/5.50 (1.07)	15.85/16.22 (0.98)	41.69/46.77 (0.89)
8b	2.88/0.51 (5.65)	16.60/4.27 (3.89)	52.48/38.91 (1.35)

[a] The "ratio" is the ratio of the mean activity (μM) for all nonCNS tumor cell lines (ca. 40–50 cell lines) over the mean activity (μM) of the CNS tumor subpanel (eight cell lines); the larger the ratio, the greater the CNS selectivity.

Table 3. Pearson Correlations of Ellipticinium Analogues Using GI_{50} Values

compd	2	1	3c	6c	4c	7c	(a)	3a
2	–	0.57	0.57	0.56	0.48	0.35	0.52	0.21
1	0.57	–	0.88	0.87	0.83	0.52	0.95	0.18
3c	0.57	0.88	–	0.91	0.87	0.61	0.83	0.16
6c	0.56	0.87	0.91	–	0.89	0.66	0.81	0.20
4c	0.48	0.83	0.87	0.89	–	0.71	0.79	0.09
7c	0.35	0.52	0.61	0.66	0.71	–	0.51	0.27
*[a]	0.52	0.95	0.83	0.81	0.79	0.51	–	0.02
3a[b]	0.21	0.18	0.16	0.20	0.09	0.27	0.02	–

[a] * = 2-methylellipticinium iodide (test data for this compound were in the NCI database and were used for purposes of this COMPARE analysis but the data are not given in either Table 1 or Table 2). [b] Compound **3b**, a nonquaternized ellipticine analogue, is included in the table for comparison purposes.

ethoxyellipticine (**3a**), or 9-(1-methylethoxy)ellipticine (**4a**). The 9-(1,1-dimethylethoxy) analogue, **5c**, is the exception: the nonquaternary analogue **5a** exhibits activity comparable to the other nonquaternary analogues (**1**, **3a**, **4a**, and **7a**), but the ellipticinium acetate **5c** is inactive. There are small but relatively insignificant differences in the activities of the iodide *vs* the corresponding acetate salts.[23] The most significant feature of the data in Table 1 is the range of activity seen with different tumor cell lines. The tumor cell specificity exhibited by the 2-methylellipticinium analogues was most notable in the CNS cell lines. The analogues retain, to varying degrees, the CNS selectivity exhibited by the "lead" structure, 9-methoxy-2-methylellipticinium acetate! These data are further summarized in Table 2, where the lack of specificity of the free, unquaternized bases are contrasted with the CNS selectivity of the quaternary pyridinium analogues. Statistical analysis of the tumor panel data using the COMPARE algorithm[24] afforded a correlation of the antitumor profiles for selected compounds. The Pearson correlation coefficients are given in Table 3 (values > *ca.* 0.8 are considered to represent meaningful similarities).

The CNS selectivities (compare the ratios of nonCNS to CNS tumors in Table 2) of the pyridinium compounds are seen in the growth inhibitory response (GI_{50}) and the tumor growth inhibitory response (TGI). The pyridinium compounds show minimal cytotoxic activity (the LC_{50} response), so the CNS selectivity is less apparent at this response. The one exception, the ethoxy analogue (**3b**), shows some selectivity at the cytotoxic level. In general with this assay, differences in cell sensitivities are more common at the low drug concentration response (*i.e.*, the GI_{50} response) than at the intermediate drug concentration response (the TGI response). Selectivities at the cytotoxic dose level (LC_{50}) are least common.

The selectivity (although less pronounced compared to the other pyridinium compounds) is perhaps most interesting in the case of the 9-phenoxy analogues because the diaryl ether is not expected to be cleaved in vivo. Furthermore, substitutions on the phenyl ring and replacement of the phenyl ring with other aryl and heterocyclic moieties should give rise to a very interesting structure–activity relationship study. The 9-phenoxy-2-methylellipticinium salts in fact represent a significant new "lead" structure in the continued development of drugs in this class. The compound presents an opportunity to probe for new binding sites which could increase the potency and selectivity of these agents.

The 10-(2,2,2-trifluoroethoxy)-9-hydroxy compounds, **8a** and **8b**, both exhibited antitumor activity. This represents another potentially interesting lead, considering few active C-10 substituted ellipticines have been reported. Quaternization of **8a** also led to an increase in CNS selectivity.

The conclusions derived from these studies are: (a) quaternization of N-2 of ellipticine generates compounds with a very different tumor profile than the nonquaternized material (*cf.* **3a** *vs* all of the other compounds in Table 3); (b) the data in Table 3 show that the antitumor profile of 9-methoxy-2-methylellipticinium acetate (**1**) is signifi-

cantly different from that of 9-hydroxyellipticine (2) but that variation of the O-alkyl group does not change the antitumor profile (*cf.* 1, 3c, 4c, and 6c); (c) the profile for 2-methylellipticinium iodide is the same as that for the 9-alkoxy-substituted compounds; and (d) the 9-phenoxy compound 7c has an antitumor profile that is statistically different from the 9-alkoxy compounds. The steric properties of the C-9 alkoxy group appear to be important for CNS selectivity. Comparison of the nonCNS/CNS ratios (Table 2) for compounds 1, 3c, and 4c (5c was inactive) showed that CNS selectivity decreased (*e.g.*, at the GI_{50} level, 16.73, 5.92, and 2.99, respectively) as the size of the alkoxy substituent increased, whereas the overall cytotoxicity against the entire panel was not significantly changed. The 9-trifluoroethoxy analogue 6c showed comparable potency to the 9-ethoxy analogue 3c but greater CNS selectivity. The increased CNS selectivity of 6c *vs* 3c may be due to electronic differences between the CF_3CH_2O and CH_3CH_2O groups, but a wider series of compounds would have to be evaluated to provide greater support for such a conclusion. Finally, with regard to possible strategies to avoid oxidative O-dealkylation of 9-alkoxy derivatives, the 9-trifluoroethoxy analogue 6c may be more resistant to dealkylation than either 1 or 3c.

Experimental Section

All melting points (uncorrected) were determined in unsealed capillary tubes using a Hoover-Thomas Unimelt apparatus. NMR spectra were determined with a Varian Gemini 300 spectrometer, and solutions contained tetramethylsilane as an internal standard. Mass spectra were determined with a VG70-ES mass spectrometer. IR spectra were determined with a Matteson FT-IR. Microanalyses were performed by Atlantic Microlabs, Altanta, GA.

5,11-Dimethyl-9-hydroxy-6*H*-pyrido[4,3-*b*]carbazole (9-Hydroxyellipticine). A mixture of 5,11-dimethyl-9-methoxy-6*H*-pyrido[4,3-*b*]carbazole (9-methoxyellipticine, 400 mg, 1.45 mmol) and pyridine hydrochloride (6.7 g, 58 mmol) was stirred under argon at 200–210 °C (bath temp) for 40 min. The reaction mixture was cooled to room temperature and treated with brine (40 mL). The solid was collected by filtration, washed with brine, and dissolved in hot water (40 mL). The solution was cooled to room temperature, the resulting precipitate was removed by filtration, and the filtrate was treated with sodium bicarbonate (700 mg). The precipitate was collected by filtration, dried (1 mm for 12 h), and continuously extracted with THF for 24 h. The THF was evaporated to give 9-hydroxyellipticine as a light cream-colored solid (250 mg, 66%): mp 303–305 °C (lit.[14b] mp 306–309 °C); R_f = 0.36 (10% MeOH–CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 2.72 (s, 3 H), 3.21 (s, 3 H), 7.08 (dd, 1 H), 7.35 (d, 1 H), 7.67–7.89 (m, 2 H), 8.21–8.47 (d, 1 H), 9.0 (br, 1 H, -OH), 9.62 (s, 1 H), 11.12 (br s, 1 H, NH).

9-Ethoxy-5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole (9-Ethoxyellipticine, 3a). A stirred mixture of 9-hydroxyellipticine (262 mg, 1 mmol), dimethylformamide dineopentyl acetal (1 mL), and absolute ethanol (12 mL) was heated at reflux (bath temperature 100–105 °C) for 72 h. The reaction mixture was cooled to 22 °C, the volatiles were removed in vacuo, and the crude product was purified by flash column chromatography (4% MeOH–CH_2Cl_2) to afford 3a as a yellow solid (191 mg, 68%): mp 225–230 °C dec; R_f = 0.53 (10% MeOH–CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 1.42 (t, J = 7 Hz, 3 H), 2.75 (s, 3 H), 3.23 (s, 3 H), 4.13 (q, J = 7 Hz, 2 H), 7.15 (dd, J = 2.3 and 8.7 Hz, 1 H), 7.43 (d, J = 8.7 Hz, 1 H), 1 H), 7.81 (d, J = 2.3 Hz, 1 H), 7.82 (d, J = 6 Hz, 1 H), 8.36 (d, J = 6 Hz, 1 H), 9.62 (s, 1 H), 11.06 (s, 1 H); IR (KBr) 3427, 3182, 1599, 1482, 1402, 1282 cm^{-1}; mass (EI) 290 (M^+), 261 (M – CH_3CH_2), 233, 218. Anal. Calcd for $C_{19}H_{18}N_2O + 0.3C_2H_5OH$: C, 77.39; H, 6.55; N, 9.21. Found: C, 77.20; H, 6.38; N, 9.31.

9-Ethoxy-2,5,11-trimethyl-6*H*-pyrido[4,3-*b*]carbazolium Iodide (3b). Iodomethane (1 mL) was added to a stirred mixture of 3a (100 mg, 0.34 mmol) in acetone (150 mL) at 22 °C. The reaction mixture was stirred at 22 °C for 36 h in the dark under argon. The yellow solid was collected by filtration, washed with ether, and dried in vacuo to afford 3b (134 mg, 91%): mp 321–326 °C dec; R_f = 0.13 (10% MeOH–CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 1.44 (t, J = 7 Hz, 3 H), 2.75 (s, 3 H), 3.22 (s, 3 H), 4.14 (q, J = 7 Hz, 2 H), 4.40 (s, 3 H), 7.20 (br d, J = 8.8 Hz, 1 H), 7.50 (d, J = 8.8 Hz, 1 H), 7.74 (d, J = 2.1 Hz, 1 H), 8.24 (d, J = 7 Hz, 1 H), 8.30 (d, J = 7 Hz, 1 H), 9.96 (s, 1 H), 11.78 (s, 1 H); IR (KBr) 3443, 3144, 1600, 1480, 1416, 1285 cm^{-1}. Anal. Calcd for $C_{20}H_{21}N_2IO$: C, 55.56; H, 4.89; N, 6.48. Found: C, 55.48; H, 4.90; N, 6.39.

9-Ethoxy-2,5,11-trimethyl-6*H*-pyrido[4,3-*b*]carbazolium Acetate (3c). The iodide 3b (40 mg, 0.092 mmol) was dissolved in methanol (30 mL) with sonication and passed through AG1-X8 anion-exchange resin (acetate form) column. The column was eluted with water (HPLC grade). The methanol and water were removed in vacuo, the residue was azeotropically dried with benzene, and the residue was dried (1 mm at 22 °C for 24 h) to give 3c (33 mg, 100%) as a red solid: mp 133–138 °C dec; R_f = 0.12 (10% MeOH–CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 1.43 (t, J = 6.6 Hz, 3 H), 1.74 (s, 3H), 2.75 (s, 3 H), 3.11 (s, 3 H), 4.11 (q, J = 6.6 Hz, 2 H), 4.38 (s, 3 H), 7.17 (br d, J = 8.7 Hz, 1 H), 7.59 (d, J = 8.7 Hz, 1 H), 7.65 (br s, 1 H), 8.16 (d, J = 7.1 Hz, 1 H), 8.22 (d, J = 7.1 Hz, 1 H), 8.40 (s, 1 H), 9.87 (s, 1 H); IR (KBr) 3416, 3168, 1644, 1585, 1472, 1402 cm^{-1}.

9-(1-Methoxyethoxy)-5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole (4a). A mixture of 9-hydroxyellipticine (262 mg, 1 mmol), *N,N*-dimethylformamide dineopentyl acetal (1 mL), and 2-propanol (15 mL) was stirred at 115 °C for 60 h. The reaction mixture was cooled to 22 °C, and the volatiles were evaporated in vacuo to afford a dark residue that was purified by flash column chromatography (3% MeOH–CH_2Cl_2) to give a dark yellow solid 4a (197 mg, 65%): mp 203–208 °C softening, 230–240 °C dec; R_f = 0.48 (MeOH–CH_2Cl_2, 1:9); ^{1}H NMR (DMSO-d_6) δ 1.32 (d, J = 6 Hz, 6 H), 2.75 (s, 3 H), 3.33 (s, 3 H), 4.66 (m, 1 H), 7.16 (dd, J = 2 and 8 Hz, 1 H), 7.45 (d, J = 8 Hz, 1 H), 7.85 (d, J = 2 Hz, 1 H), 7.88 (d, J = 6 Hz, 1 H), 8.38 (d, J = 6 Hz, 1 H), 9.67 (s, 1 H), 11.20 (s, 1 H); IR (KBr) 3431, 3141, 1597, 1476, 1405 cm^{-1}; mass (EI) 304 (M^+), 262 [M – $CH(CH_3)_2$]. Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.91; H, 6.62; N, 9.21. Found: C, 79.09; H, 6.65; N, 9.12.

9-(1-Methylethoxy)-2,5,11-trimethyl-6*H*-pyrido[4,3-*b*]carbazolium Iodide (4b). Iodomethane (1 mL) was added to a stirred solution of 4a (115 mg, 0.44 mmol) in acetone (30 mL) at 22 °C and stirred at 22 °C under argon in the dark for 12 h. The yellow solid was collected by filtration, washed with ether, and dried at 1 mm for 12 h to afford 4b (176 mg, 90%): mp 263–270 °C dec; R_f = 0.17 (MeOH–CH_2Cl_2, 1:9); ^{1}H NMR (DMSO-d_6) δ 1.34 (d, J = 6 Hz, 6 H), 2.74 (s, 3 H), 3.20 (s, 3 H), 4.41 (s, 3 H), 4.60 (m, 1 H), 7.27 (dd, J = 2 and 8 Hz, 1 H), 7.52 (d, J = 8 Hz, 1 H), 7.82 (d, J = 2 Hz, 1 H), 8.34 (br s, 2 H), 9.94 (s, 1 H), 11.89 (s, 1 H); IR (KBr) 3410, 3140, 1597, 1476 cm^{-1}. Anal. Calcd for $C_{21}H_{23}N_2OI$: C, 56.51; H, 5.19; N, 6.28. Found: C, 56.59; H, 5.21; N, 6.19.

9-(1-Methylethoxy)-2,5,11-trimethyl-6*H*-pyrido[4,3-*b*]carbazolium Acetate (4c). The iodide 4b (50 mg, 0.11 mmol) was dissolved in methanol (10 mL) and passed through AG1-X8 anion-exchange resin (acetate form) column. The column was eluted with water, and the methanol–water was evaporated in vacuo. The residue was azeotropically dried with benzene, and the resulting dark reddish brown colored solid dried at 1 mm for 12 h to afford 4c (40 mg, 96%): mp 135–140 °C dec; R_f = 0.11 (10% MeOH–CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 1.33 (d, J = 6 Hz, 6 H), 1.67 (s, 3 H), 2.77 (s, 3 H), 3.18 (s, 3 H), 4.36 (s, 3 H), 4.63 (m, 1 H), 7.23 (br d, J = 8.8 Hz, 1 H), 7.64 (d, J = 8.8 Hz, 1 H), 7.8 (br s, 1 H), 8.24 (br s, 2 H), 9.88 (s, 1 H); IR (KBr) 3378, 2974, 1643, 1573, 1470 cm^{-1}.

9-(1,1-Dimethylethoxy)-5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole (5a). A mixture of 9-hydroxyellipticine (524 mg, 2 mmol), 2-methyl-2-propan-1-ol (15 mL), and *N,N*-dimethylformamide dineopentyl acetal (0.8 mL) was heated at reflux under argon for 72 h. The reaction mixture was cooled to room temperature, the solvent was removed at 35 °C in vacuo, and the crude residue was purified by flash column chromatography (3% MeOH, then 5% MeOH in CH_2Cl_2) to afford starting material (380 mg) and 5a (50 mg, 32%, based on unrecovered starting

material): mp 283–286 °C dec; R_f = 0.56 (MeOH–CH_2Cl_2, 1:9); ^{1}H NMR (5% CF_3COOD in DMSO-d_6) δ 1.31 (s, 9 H), 2.66 (s, 3 H), 3.14 (s, 3 H), 7.06–7.56 (m, 3 H), 7.73–7.98 (m, 1 H), 8.14–8.40 (m, 2 H), 9.79 (br s, 1 H); IR (KBr) 3130, 2921, 1602, 1555 cm^{-1}; Mass (DCI) 319 (M + 1), 262 (M – C_4H_9). Anal. Calcd for $C_{21}H_{22}N_2O$ + 0.5H_2O: C, 77.03; H, 7.08; N, 8.56. Found: C, 77.46; H, 6.92; N, 8.63.

9-(1,1-Dimethylethoxy)-2,5,11-trimethyl-6*H*-pyrido[4,3-*b*]carbazolium Iodide (5b). Iodomethane (1.0 mL) was added to a stirred solution of **5a** (100 mg, 0.31 mmol) in acetone (140 mL) at 22 °C. The mixture was stirred under argon in the dark for 70 h at 22 °C. The solid was filtered, washed with ether, and dried at 0.1 mm to afford **5b** (115 mg, 81%): mp 335–337 °C dec; R_f = 0.18 (MeOH–CH_2Cl_2, 1:9); ^{1}H NMR (DMSO-d_6) δ 1.30 (s, 9 H), 2.69 (s, 3 H), 3.12 (s, 3 H), 4.36 (s, 3 H), 7.10–7.59 (m, 2 H), 7.74–7.94 (m, 1 H), 8.2–8.4 (m, 2 H), 9.92 (s, 1 H), 11.78 (br s, 1 H); IR (KBr) 3125, 2935, 1603, 1575, 1423 cm^{-1}. Anal. Calcd for $C_{22}H_{25}N_2IO$ + 0.5H_2O: C, 56.30; H, 5.58; N, 5.97; I, 27.04. Found: C, 56.43; H, 5.56; N, 6.03; I, 27.14.

9-(1,1-Dimethylethoxy)-2,5,11-trimethyl-6*H*-pyrido[4,3-*b*]carbazolium Acetate (5c). Compound **5b** (100 mg, 0.22 mmol) was dissolved in 20% MeOH–H_2O (125 mL) and passed through AG1-X8 anion-exchange resin (acetate form). The resin was washed with water. The water was removed from the eluant (35 °C at 5 mm), and the residue was azeotropically dried with benzene to afford **5c** (65 mg, 76%): mp 35 °C; R_f = 0.13 (20% MeOH–CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 1.36 (s, 9 H), 1.76 (s, 3 H), 2.74 (s, 3 H), 3.22 (s, 3 H), 4.38 (s, 3 H), 7.27–7.38 (m, 1 H), 7.52–7.87 (m, 2 H), 8.05–8.29 (m, 2 H), 9.86 (s, 1 H), 11.86 (br s, 1 H); IR (KBr) 2971, 1647, 1602, 1560, 1467 cm^{-1}; mass (FAB) 333 (M – 59), 277 (M – 115), 261 (M – 131).

9-(2,2,2-Trifluoroethoxy)-5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole (9-(Trifluoroethoxy)ellipticine, 16a). A stirred mixture of amine **15a** (1.23 g, 2.8 mmol), Na_2CO_3 (0.368 g, 3.47 mmol), THF (11 mL), and water (5 mL) was treated with *p*-toluenesulfonyl chloride (0.7 g, 3.67 mmol) at 22 °C. The reaction mixture was stirred for 2 h, diluted with more water (120 mL), and extracted with ethyl acetate. The combined organic extract was washed with 0.1 N HCl, water, 2% $NaHCO_3$, water, and brine and dried (Na_2SO_4). The organic layer was evaporated to afford crude 3-[[*N*-tosyl(2,2-diethoxyethyl)amino]methyl]-6-(2,2,2-trifluoroethoxy)-1,4-dimethylcarbazole (1.58 g, 95%, which was taken to next step without further purification): R_f = 0.2 (25% EtOAc-hexane); ^{1}H NMR ($CDCl_3$) δ 1.08 (t, *J* = 7 Hz, 6 H), 2.41 (s, 6 H), 2.78 (s, 3 H), 3.19 (d, *J* = 5.4 Hz, 2 H), 3.32 (q, *J* = 7 Hz, 2 H), 3.53 (q, *J* = 7 Hz, 2 H), 4.46 (m, 3 H), 4.67 (s, 2 H), 6.98 (s, 1 H), 7.15 (dd, *J* = 2.6 and 8.7 Hz, 1 H), 7.28 (d, *J* = 8.7 Hz, 1 H), 7.40 (d, *J* = 8 Hz, 2 H), 7.75 (d, *J* = 8 Hz, 2 H), 7.91 (m, 2 H); IR (KBr) 3358, 2975, 1596, 1461 cm^{-1}.

A mixture of 3-[[*N*-tosyl(2,2-diethoxyethyl)amino]methyl]-6-(2,2,2-trifluoroethoxy)-1,4-dimethylcarbazole (0.593 g, 1 mmol) in dioxane (15 mL) was stirred at 22 °C, 6 N HCl (10 mL) was slowly added, and the mixture was stirred at 22 °C for 12 h. The separated solid was collected by filtration, washed with dioxane, and suspended in water (100 mL). The stirred suspension was cooled to 0 °C, basified to pH 10 with 1 N NaOH, and stirred at 22 °C for 15 min. The yellow solid was collected by filtration, dried, and crystallized from methanol to afford **6a** (258 mg, 75%) as a yellow solid: mp 273–278 °C dec; R_f = 0.31 (5% MeOH–CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 2.78 (s, 3 H), 3.28 (s, 3 H), 4.90 (q, *J* = 8.9 Hz, 2H), 7.30 (dd, *J* = 2.5 and 8.8 Hz, 1 H), 7.51 (d, *J* = 8.8 Hz, 1 H), 7.93 (d, *J* = 6 Hz, 1 H), 8.01 (d, *J* = 2.5 Hz, 1 H), 8.42 (d, *J* = 6 Hz, 1 H), 9.71 (s, 1 H), 11.34 (s, 1 H); IR (KBr) 3442, 3172, 1599, 1482 cm^{-1}; mass (CI) 345 (M + 1), 261 (M – CF_3CH_2). Anal. Calcd for $C_{19}H_{15}N_2OF_3$ + 0.25CH_3OH: C, 65.61; H, 4.57; N, 7.95. Found: C, 65.52; H, 4.46; N, 8.00.

9-(2,2,2-Trifluoroethoxy)-2,5,11-trimethyl-6*H*-pyrido[4,3-*b*]carbazolium Iodide (6b). Iodomethane (1 mL) was added to a stirred mixture of **6a** (90 mg, 0.26 mmol) in acetone (100 mL) at 22 °C. The reaction mixture was stirred in the dark at 22 °C for 36 h. The yellow solid was collected by filtration, washed with ether, and dried (22 °C at 1 mm for 12 h) to afford **6b** (116 mg, 92%): mp 335–340 °C dec; R_f = 0.13 (10% MeOH–CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 2.77 (s, 3 H), 3.26 (s, 3 H), 4.44 (s, 3 H), 4.85 (q, *J* = 8.8 Hz, 2 H), 7.35 (br d, *J* = 8.8 Hz, 1 H), 7.55 (d, *J* = 8.8 Hz, 1 H), 7.94 (d, *J* = 2 Hz, 1 H), 8.31 (d, *J* = 7.4 Hz, 1 H), 8.36 (d, *J* = 7.4 Hz, 1 H), 9.99 (s, 1 H), 11.93 (s, 1 H); IR (KBr) 3434, 1600, 1480, 1397 cm^{-1}. Anal. Calcd for $C_{20}H_{18}N_2IF_3O$: C, 49.39; H, 3.73; N, 5.76. Found: C, 49.29; H, 3.77; N, 5.70.

9-(2,2,2-Trifluoroethoxy)-2,5,11-trimethyl-6*H*-pyrido[4,3-*b*]carbazolium Acetate (6c). The iodide **6b** (40 mg, 0.082 mmol) was dissolved in methanol (70 mL) with sonication and passed through an AG1-X8 anion-exchange resin column. The column was eluted with water (HPLC grade). The methanol and water were removed from the eluant in vacuo, and the residue was evaporated azeotropically with benzene under argon and dried (1 mm at 22 °C for 24 h) to afford **6c** (34 mg, 100%) as a dark brown to light red colored solid: mp 224–230 °C dec; R_f = 0.12 (10% MeOH–CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 1.70 (s, 3 H), 2.83 (s, 3 H), 3.27 (s, 3 H), 4.41 (s, 3 H), 4.87 (q, *J* = 8.7 Hz, 2 H), 7.36 (br d, *J* = 8.7 Hz, 1 H), 7.68 (d, *J* = 8.7 Hz, 1 H), 7.97 (br s, 1 H), 8.27 (br s, 1 H), 8.31 (br s, 1 H), 9.98 (s, 1 H); IR (KBr) 3447, 3162, 1642, 1585, 1401 cm^{-1}.

5,11-Dimethyl-9-phenoxy-6*H*-pyrido[4,3-*b*]carbazole (9-Phenoxyellipticine, 7a). A stirred mixture of **15b** (3.23 g, 7.5 mmol), Na_2CO_3 (1.051 g, 9.9 mmol), THF (20 mL), and water (8 mL) was treated with *p*-toluenesulfonyl chloride (1.992 g, 10.48 mmol) at 22 °C. The reaction mixture was stirred for 2 h, diluted with more water (120 mL), and extracted with ethyl acetate. The combined organic extract was washed with 0.1 N HCl, water, 2% $NaHCO_3$, water, and brine and dried (Na_2SO_4). The organic layer was evaporated to afford crude tosylate, which was crystallized (ethyl acetate–hexane) to give pure 3-[[*N*-tosyl(2,2-diethoxyethyl)amino]methyl]-6-phenoxy-1,4-dimethylcarbazole (89%): mp 168–169 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (t, *J* = 7 Hz, 6 H), 2.4 (s, 3 H), 2.42 (s, 3 H), 2.77 (s, 3 H), 3.18 (d, *J* = 5.5 Hz, 2 H), 3.35 (m, 2 H), 3.5 (m, 2 H), 4.67 (t, *J* = 5.5 Hz, 1 H), 6.9 (d, *J* = 7.5 Hz, 1 H), 7.02 (t, *J* = 7.5 Hz, 1 H), 7.15 (dd, *J* = 8.7 Hz, *J* = 2.5 Hz, 1 H), 7.4–7.34 (m, 3 H), 7.44 (d, *J* = 8.7 Hz, 1 H), 7.74 (d, *J* = 8.7 Hz, 1 H), 7.9 (d, *J* = 1.5 Hz, 1 H), 8.02 (br s, 1 H); IR (KBr) 3361, 3276, 2972–2863, 1597, 1488, 1460, 1215, 1058 cm^{-1}. Anal. Calcd for $C_{34}H_{38}N_2O_5S$: C, 69.60; H, 6.53; N, 4.78; S, 5.47. Found: C, 69.66; H, 6.5; N, 4.78; S, 5.47.

A mixture of 3-[[*N*-tosyl(2,2-diethoxyethyl)amino]methyl]-6-phenoxy-1,4-dimethylcarbazole (3.5 g, 6 mmol) in dioxane (50 mL) was stirred at 22 °C, 6 N HCl (60 mL) was added slowly, and the reaction mixture was stirred for 12 h. The separated solid was collected by filtration and washed with dioxane. The solid was suspended in water (100 mL), and the stirred suspension was cooled to 0 °C, basified to pH 10 with 1 N NaOH, and stirred at 22 °C for 15 min. The yellow solid was collected by filtration, dried, and crystallized from methanol to afford **7a** (50%): mp 276–277 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.8 (s, 3 H), 3.2 (s, 3 H), 7.0 (d, *J* = 8.3 Hz, 1 H), 7.1 (t, *J* = 8.3 Hz, 2 H), 7.25 (dd, *J* = 8.3 Hz, *J* = 1.6 Hz, 1 H), 7.4 (t, *J* = 8.3 Hz, 2 H), 7.6 (d, *J* = 8.3 Hz, 1 H), 7.95 (d, *J* = 6.5 Hz, 1 H), 8.1 (d, *J* = 2 Hz, 1 H), 8.45 (d, *J* = 6.5 Hz, 1 H), 9.72 (s, 1 H), 11.45 (s, 1 H); IR (KBr) 3438, 3145, 2862, 1598, 1472, 1220 cm^{-1}. Anal. Calcd for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.28. Found: C, 81.51; H, 5.43; N, 8.24.

2,5,11-Trimethyl-9-phenoxy-6*H*-pyrido[4,3-*b*]carbazolium Iodide (7b). Iodomethane (1 mL) was added to a stirred mixture of **7a** (90 mg, 0.26 mmol) in acetone (100 mL) at 22 °C. The reaction mixture was stirred in the dark at 22 °C for 36 h. The yellow solid was collected by filtration, washed with ether, and dried at 1-mm vacuum for 12 h at 22 °C to afford **7b** (116 mg, 92%): mp 320 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.84 (s, 3 H), 3.24 (s, 3 H), 4.44 (s, 3 H), 7.00 (d, *J* = 8.3 Hz, 1 H), 7.38 (m, 3 H), 7.7 (d, *J* = 8.5 Hz, 1 H), 8.15 (s, 1 H), 8.45 (dd, *J* = 15 Hz, *J* = 6.7 Hz, 1 H), 10.05 (s, 1 H), 12.21 (s, 1 H); IR (KBr) 3430, 1598, 1480, 1397, 1220 cm^{-1}. Anal. Calcd for $C_{24}H_{21}N_2OI$: C, 60.05; H, 4.43; N, 5.81. Found: C, 60.00; H, 4.40; N, 5.83.

2,5,11-Trimethyl-9-phenoxy-6*H*-pyrido[4,3-*b*]carbazolium Acetate (7c). The iodide **7a** (40 mg, 0.082 mmol) was dissolved in methanol (200 mL) with sonication and passed through AG1-X8 anion-exchange resin column. The column was eluted with water (HPLC grade). The methanol and water were removed from the eluant under reduced pressure, and the residue was evaporated azeotropically with benzene under argon and dried at 1 mm at 22 °C for 24 h to afford **7c** (90%) as a yellow solid: mp 200 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.07 (s, 3 H), 2.83 (s, 3 H), 3.15 (s, 3 H), 4.34 (s, 3 H), 6.89 (d, *J* = 8 Hz, 2 H),

7.28–7.38 (m, 3 H), 7.79 (d, J = 8 Hz, 1 H), 8.04 (d, J = 3.5 Hz, 1 H), 8.2 (m, 2 H), 8.3 (s, 1 H), 9.82 (s, 1 H); IR (KBr) 3405, 3160, 1645, 1580, 1401, 1210 cm^{-1}.

9-Hydroxy-5,11-dimethyl-10-(2,2,2-trifluoroethoxy)-6*H*-pyrido[4,3-*b*]carbazole (8a). A mixture of 9-hydroxyellipticine (1.1 g, 4.2 mmol), 2,2,2-trifluoroethanol (25 mL), and *N,N*-dimethylformamide dineopentyl acetal (2 mL) was heated at reflux under argon for 72 h. The reaction mixture was cooled to room temperature, and the solvent was removed in vacuo. The crude residue was purified by flash column chromatography to afford **8a** (125 mg, 18%, based on the recovery of 550 mg of 9-hydroxyellipticine): mp 168–172 °C dec; R_f = 0.41 (10% MeOH–CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 2.77 (s, 3 H), 3.42 (s, 3 H), 4.78 (q, 2 H), 7.30 (m, 2 H), 7.87 (m, 1 H), 8.40 (m, 1 H), 9.29 (br s, 1 H), 9.65 (s, 1 H), 11.14 (br s, 1 H); IR (KBr) 3235, 1600, 1387, 1271, 1157 cm^{-1}; mass (DCI) 361 (M + 1), 292 [M – CF_3 (69)], 276 [M – 83 (CF_3CH_2)]. The phenol **8a** was used directly in the next step without further purification.

9-Hydroxy-10-(2,2,2-trifluoroethoxy)-2,5,11-trimethyl-6*H*-pyrido[4,3-*b*]carbazolium Iodide (8b). Iodomethane (434 mg, 3.1 mmol) was added to a stirred solution of **8a** (110 mg, 0.32 mmol) in acetone (85 mL). The reaction mixture was stirred under argon in the dark at room temperature for 72 h. The yellow-colored solid was filtered, washed with ether, and dried at 1 mm for 12 h to afford **8b** (110 mg; 73%): mp >260 °C; R_f = 0.19 (10% MeOH–CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 2.76 (s, 3 H), 3.43 (s, 3 H), 4.46 (s, 3 H), 4.85 (q, 2 H), 7.33 (m, 2 H), 8.38 (m, 2 H), 9.74 (br s, 1 H), 9.97 (s, 1 H), 11.90 (s, 1 H, NH); IR (KBr) 3220, 1644, 1596, 1501, 1461 cm^{-1}. Anal. Calcd for $C_{20}H_{18}F_3IN_2O_2$: C, 47.63; H, 3.61; N, 5.56; I, 25.16; F, 11.72. Found: C, 47.86; H, 3.74; N, 5.38.

3-Methyl-4-nitro-1-(2,2,2-trifluoroethoxy)benzene (10a). A solution of 3-methyl-4-nitrophenol (**9a**, 15.3 g, 100 mmol) in HMPA (50 mL) was added dropwise to a cold (5 °C) suspension of NaH (2.52 g, 105 mmol) in HMPA (10 mL) with efficient stirring. The reaction mixture was stirred at 24 °C for 1 h. 2,2,2-Trifluoroethyl *p*-toluenesulfonate (26.95 g, 106 mmol) in HMPA (15 mL) was added dropwise to the stirred reaction mixture at 24 °C over 15 min. The reaction mixture was stirred at 140 °C (bath temperature) for 20 h, cooled to 24 °C, poured in ice water (800 mL), and extracted with ether (4 × 400 mL). The combined extract was washed with water and brine and dried (Na_2SO_4). The ether was evaporated, and the crude residue was purified by flash column chromatography (6% and 10% ethyl acetate–hexane) to afford **10a** (21.8 g, 93%): mp 63–64 °C; R_f = 0.54 (25% EtOAc–hexane); ^{1}H NMR ($CDCl_3$) δ 2.6 (s, 3 H), 4.43 (q, J = 8 Hz, 2 H), 6.84–6.88 (m, 2 H), 8.05–8.12 (m, 1 H); IR (KBr) 1613, 1596, 1510, 1454, 1340, 1333, 1298 cm^{-1}. Anal. Calcd for $C_9H_8F_3NO_3$: C, 45.96; H, 3.43; N, 5.95. Found: C, 46.06; H, 3.46; N, 5.97.

Triphenylbismuth Diacetate. Anhydrous chlorine gas was passed through a solution of triphenylbismuth (8.8 g, 20 mmol) in chloroform (50 mL) at –10 °C until the solution was saturated (formation of yellow color) and a white precipitate formed. Methanol was added, and excess chlorine and the solvents were removed in vacuo. The solid was crystallized from chloroform and methanol to give triphenylbismuth dichloride (7.2 g, 76%): mp 157–158 °C (lit.[21a] mp 158–159 °C).

A solution of potassium carbonate (2.2 g) in water (15 mL) was added to a solution of triphenylbismuth dichloride (7.25 g, 14 mmol) in acetone (50 mL). After 5 min the precipitate was collected by filtration, washed with acetone, and dried to give triphenylbismuth carbonate (7.08 g, 98%): mp 168 °C dec (lit.[21b] mp 155 °C).

Glacial acetic acid (2 mL) was added to triphenylbismuth carbonate (3 g), and the stirred reaction mixture was warmed to 80 °C. More acid was added dropwise until all the solid had dissolved. The homogeneous solution was cooled to room temperature, water (1 mL) was added, and the white precipitate that formed was collected by filtration and washed with hexane. The solid was crystallized from acetic acid and water to give triphenylbismuth diacetate (2.5 g): mp 159 °C (lit.[21a] mp 162 °C); ^{1}H NMR ($CDCl_3$) δ 1.8 (s, 6 H), 7.3–8.2 (m, 15 H).

2-Nitro-5-phenoxytoluene (10b). Method A. Copper powder (20 mg, 0.3 mmol) and triphenylbismuth diacetate (2.008 g, 3.6 mmol) were added to a solution of 3-methyl-4-nitrophenol (**9a**, 459 mg, 3 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred under argon for 20 h (monitored by TLC), heated at reflux for 40 h, concentrated, and passed through a flash column of silica (CH_2Cl_2–hexane, 1:4) to **10b** as a colorless oil (386 mg, 56%): ^{1}H NMR ($CDCl_3$) δ 2.3 (s, 3 H), 6.6–7.4 (m, 7 H), 7.8 (d, J = 10 Hz, 1 H).

Method B. Potassium hydroxide (3 g) was added to molten phenol (15 g, 0.16 mol), and the mixture was heated at 110 °C until the potassium hydroxide has dissolved. The solution was cooled to room temperature, and 5-fluoro-2-nitrotoluene (**9b**, 7.75 g, 0.05 mol) was added in one aliquot. The reaction mixture was heated at 130 °C for 30 min (the mixture turned deep red) and then it was cooled to room temperature and poured into 10% sodium hydroxide solution (200 mL). The solution was extracted with ether (2 × 100 mL), washed with 10% sodium hydroxide solution (2 × 100 mL) and water (2 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by flash column chromatography to give **10b** as a colorless oil (9.7 g, 88%): ^{1}H NMR ($CDCl_3$) δ 2.3 (s, 3 H), 6.6–7.4 (m, 7 H), 7.8 (d, J = 10 Hz, 1 H).

***trans*-1-[2-(*N,N*-Dimethylamino)ethenyl]-2-nitro-5-(2,2,2-trifluoroethoxy)benzene (11a).** A mixture of **10a** (21 g, 89.3 mmol) and *N,N*-dimethylformamide diethyl acetal (15.8 g, 107.2 mmol) in DMF (30 mL) was stirred at 150 °C (bath temperature) for 23 h. The reaction mixture was cooled to 24 °C, and the volatiles were removed in vacuo. The excess DMF and acetal were removed at 60 °C under vacuum (1 mm) to yield a dark red residue. The residue was diluted with hexane and filtered. The solid was washed with hexane (3 × 15 mL) to remove the unreacted starting material and dried at 1 mm for 1 h to afford **11a** (18.9 g, 73%): mp 124–126 °C; R_f = 0.3 (25% EtOAc–hexane); ^{1}H NMR ($CDCl_3$) δ 2.93 (s, 6 H), 4.4 (q, J = 8 Hz, 2 H), 6.01 (d, J = 13 Hz, 1 H), 6.48–6.55 (m, 1 H), 6.89–6.97 (m, 2 H), 7.95 (d, J = 9 Hz, 1 H); IR (KBr) 1623, 1618, 1566, 1483, 1422 cm^{-1}. The enamine **11a** was used directly in the next step without further purification.

***trans*-1-[2-(*N,N*-Dimethylamino)ethenyl]-5-phenoxy-2-nitrobenzene (11b).** A solution of **10b** (9.16 g, 40 mmol) and *N,N*-dimethylformamide diethyl acetal (6.82 g, 46.4 mmol) in DMF (25 mL) was heated at 150 °C for 22 h. The reaction mixture was turned deep red. The excess acetal and the solvent were removed by distillation (120 °C at 30 mm). The deep red residue was stirred with hexane to remove the unreacted starting material. The red solid obtained was collected and crystallized from 2-propanol to afford **11b** as red, shiny plates (9 g, 79%): mp 66–67 °C; ^{1}H NMR ($CDCl_3$) δ 2.9 (s, 6 H), 6.0 (d, J = 13 Hz, 1 H), 6.55 (dd, J = 9 Hz, J = 2.5 Hz, 1 H), 6.85 (d, J = 13 Hz, 1 H), 7.0 (d, J = 2.5 Hz, 1 H), 7.5–7.65 (m, 6 H), 7.95 (d, J = 10 Hz, 1 H); IR (KBr) 3102, 2914–2809, 1620, 1491, 1282 cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.58; H, 5.67; N, 9.86. Found: C, 67.05; H, 5.72; N, 9.75.

5-(2,2,2-Trifluoroethoxy)indole (12a). The enamine **11a** (18.6 g, 64 mmol) was dissolved in EtOAc (150 mL) in a 500-mL Parr hydrogenation bottle, and 10% Pd–C (1 g) was added. The bottle was flushed with hydrogen, and hydrogenation continued at 50 psi for 1 h at 24 °C. The catalyst was removed by filtration through Celite and washed with ethyl acetate. The combined filtrate was washed with 4% aqueous HCl (2 × 15 mL), water, and brine and dried (Na_2SO_4). The EtOAc was evaporated, and the crude residue was purified by flash column chromatography (5% and 10% EtOAc–hexane) to afford **12a** (8.96 g, 65%): mp 43–44 °C; R_f = 0.39 (25% EtOAc–hexane); ^{1}H NMR ($CDCl_3$) δ 4.40 (q, J = 8 Hz, 2 H), 6.51 (br s, 1 H), 6.93 (dd, J = 2.4, 6.4 Hz, 1 H), 7.17 (d, J = 8.8 Hz, 1 H), 8.12 (br s, 1 H); IR (KBr) 3444, 1584, 1480, 1453, 1273 cm^{-1}. Anal. Calcd for $C_{10}H_8F_3NO$: C, 55.83; H, 3.74; N, 6.51. Found: C, 55.83; H, 3.73; N, 6.47.

5-Phenoxyindole (12b). A mixture of 10% Pd–C (1 g) and **11b** (9 g, 31.7 mmol) in EtOAc (100 mL) was placed in a Parr bottle. The bottle was attached to a low-pressure hydrogenation apparatus, flushed with hydrogen, and pressurized at 50 psi with hydrogen. Hydrogen uptake was rapid, and the reaction was complete in 1.5 h (as monitored by TLC). The catalyst was removed by filtration, and the filtrate was concentrated and passed through a column of flash silica (35% CH_2Cl_2 in hexane) to afford **12b** as white needles (4.2 g, 64%): mp 117 °C (lit.[25] mp 118–119 °C); ^{1}H NMR ($CDCl_3$) δ 6.5 (br s, 1 H), 6.9–7.1 (m, 4 H),

7.2–7.35 (m, 4 H), 7.4 (d, J = 9 Hz, 1 H), 8.2 (br s, 1 H); IR 3224, 3102–3052, 1579, 1485, 1454, 1218 cm^{-1}. Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.27; H, 5.31; N, 6.71.

1,4-Dimethyl-6-(2,2,2-trifluoroethoxy)carbazole (13a). A mixture of **12a** (8.6 g, 40 mmol), hexane-2,5-dione (4.56 g, 40 mmol), and *p*-toluenesulfonic acid (4.0 g, 21 mmol) in ethanol (80 mL) was heated at reflux for 1.5 h. The reaction mixture was cooled to 22 °C, the volume of ethanol was reduced to *ca.* 30 mL in vacuo, and water (100 mL) was added. The aqueous mixture was extracted with ether (3 × 50 mL), and the combined ether extract was washed with water and brine and then dried (Na_2SO_4). The organic layer was concentrated in vacuo, and the black residue was extracted with hot hexane. The combined hexane extracts were treated with charcoal, filtered, and concentrated in vacuo to afford a white solid that was crystallized from hexane to give **13a** (6.44 g, 55%) as a white fluffy solid: mp 131–133 °C; R_f = 0.45 (EtOAc–hexane, 1:4); ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3 H), 2.84 (s, 3 H), 4.48 (q, J = 8.3 Hz, 2 H), 6.93 (d, J = 7 Hz, 1 H), 7.12 (dd, J = 2.4 and 8.7 Hz, 1 H), 7.15 (d, J = 7 Hz, 1 H), 7.41 (d, J = 8.7 Hz, 1 H), 7.74 (d, J = 2.4 Hz, 1 H), 7.94 (s, 1 H); IR (KBr) 3417, 1619, 1481, 1285 cm^{-1}; mass (CI) 294 (M + 1), 210 (M – CF_3CH_2). Anal. Calcd for $C_{16}H_{14}NOF_3$: C, 65.52; H, 4.81; N, 4.77. Found: C, 65.39; H, 5.00; N, 4.61.

1,4-Dimethyl-6-phenoxycarbazole (13b). The indole **12b** was converted to the carbazole by the method described for **13a**. The black residue obtained from the workup was purified by flash column chromatography (CH_2Cl_2–hexane, 1:4) to give **13b** as a white crystalline solid in 68% yield: mp 130–131 °C; ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3 H), 2.84 (s, 3 H), 6.93 (d, J = 7 Hz, 1 H), 6.98–7.4 (m, 7 H), 7.5 (d, J = 7 Hz, 1 H), 7.9 (s, 1 H), 8.0 (br s, 1 H); IR (KBr) 3432, 3068–2859, 1594, 1470, 1222 cm^{-1}. Anal. Calcd for $C_{20}H_{17}NO$: C, 83.59; H, 5.96; N, 4.87. Found: C, 83.47; H, 6.03; N, 4.87.

3-Formyl-1,4-dimethyl-6-(2,2,2-trifluoroethoxy)carbazole (14a). A mixture of **13a** (4.68 g, 15.95 mmol), *N*-methylformanilide (3.71 g, 27.45 mmol), and phosphorus oxychloride (3.45 g, 22.5 mmol) in 1,2-dichlorobenzene (20 mL) was heated at 105 °C (bath temperature) for 4 h. The reaction mixture was cooled to 22 °C, diluted with sodium acetate (10 g) in water (140 mL), and steam distilled. The resulting black solid was collected by filtration and dried *in vacuo*. The solid was extracted with toluene (800 mL) in a Soxhlet extractor for 24 h. The hot extract was decolorized (charcoal), filtered through Celite, and concentrated to 80 mL in vacuo. The solid was collected by filtration and dried (1 mm for 2 h) to give **14a** (4.63 g, 83%): mp 218–220 °C; R_f = 0.49 (EtOAc–hexane, 1:1); ^{1}H NMR ($CDCl_3$) δ 2.57 (s, 3 H), 3.18 (s, 3 H), 4.5 (q, J = 8 Hz, 2 H), 7.16 (dd, J = 2.4 and 8.7 Hz, 1 H), 7.46 (d, J = 8.7 Hz, 1 H), 7.77 (s, 1 H), 7.84 (d, J = 2.4 Hz, 1 H), 8.30 (s, 1 H), 10.46 (s, 1 H); IR (KBr) 3443, 3248, 1648, 1584, 1499 cm^{-1}; MS, $C_{17}H_{14}F_3NO_2$ requires M + 1 322.1054, found 322.1008.

3-Formyl-1,4-dimethyl-6-phenoxycarbazole (14b). The carbazole **13b** was formylated as described for **14a**. The black solid from the steam distillation was collected by filtration, dried, and extracted with ethyl acetate (800 mL) in a Soxhlet extractor for 24 h. The hot extract was decolorized (charcoal), filtered through Celite, and concentrated to 80 mL in vacuo. The solid was collected by filtration and dried (1 mm for 2 h) to afford **14b** (83%): mp 228–230 °C; ^{1}H NMR ($CDCl_3$) δ 2.58 (s, 3 H), 3.11 (s, 3 H), 7.00 (d, J = 8 Hz, 1 H), 7.07 (t, J = 8.0 Hz, 1 H), 7.22 (dd, J = 8.5 Hz, J = 1.5 Hz, 1 H), 7.26 (s, 1 H), 7.35 (t, J = 8.5 Hz, 1 H), 7.52 (d, J = 8.5 Hz, 1 H), 7.79 (s, 1 H), 7.98 (s, 1 H), 8.36 (s, 1 H), 10.46 (s, 1 H); IR (KBr) 3243, 3067–2854, 1646, 1582, 1489, 1218 cm^{-1}. Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.97; H, 5.43; N, 4.44. Found: C, 79.78; H, 5.64; N, 4.40.

3-[[(2,2-Diethoxyethyl)amino]methyl]-1,4-dimethyl-6-(2,2,2-trifluoroethoxy)carbazole (15a). A mixture of aldehyde **14a** (1.21 g, 3.75 mmol) and aminoacetaldehyde diethyl acetal (1.7 g, 12.75 mmol) was stirred at 110–115 °C (bath temperature) under argon for 3 h. The reaction mixture was cooled to 22 °C, and the water formed in the reaction was removed by azeotropic distillation with benzene (30 mL). The resulting solid was dried (1 mm for 6 h) and crystallized from benzene to afford 3-[[(2,2-diethoxyethyl)imino]methyl]-1,4-dimethyl-6-(2,2,2-trifluoroethoxy)carbazole (1.42 g, 85%): mp 153–155 °C; R_f = 0.5 (EtOAc–hexane, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 6 H), 2.5 (s, 3 H), 2.93 (s, 3 H), 3.62 (q, J = 7 Hz, 2 H), 3.75 (q, J = 7 Hz, 2 H), 3.85 (d, J = 5 Hz, 2 H), 4.47 (q, J = 8.2 Hz, 2 H), 4.87 (t, J = 5.0 Hz, 2 H), 7.12 (dd, J = 2.4 and 8.7 Hz, 1 H), 7.43 (d, J = 8.7 Hz, 1 H), 7.8 (d, J = 2.4 Hz, 1 H), 7.88 (s, 1 H), 8.16 (s, 1 H), 8.82 (s, 1 H); IR (KBr) 3324, 1639, 1586, 1501, 1285 cm^{-1}.

Sodium borohydride (461 mg, 12.2 mmol) was added in portions to a stirred mixture of 3-[[(2,2-diethoxyethyl)imino]methyl]-1,4-dimethyl-6-(2,2,2-trifluoroethoxy)carbazole (1.3 g, 2.97 mmol) in methanol (50 mL) at 22 °C. The mixture was stirred for 1 h and concentrated to dryness in vacuo, the residue was dissolved in ethyl ether (60 mL), and the ether solution was washed with water. The ether solution was cooled to 0 °C and acidified with 0.5 N HCl to pH 4. The separated solid was collected by filtration, combined with the acidic aqueous layer, and diluted with water. This mixture was cooled to 0 °C and basified with 10 N NaOH to pH 10 and extracted with chloroform. The organic layer was washed with water then brine, dried (Na_2SO_4), and evaporated to give **15a** (1.28 g, 98%): mp 98–101 °C; R_f = 0.3 (5% CH_3OH–CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 6 H), 2.5 (s, 3 H), 2.84 (s, 3 H), 2.86 (d, J = 5.5 Hz, 2 H), 3.5 (q, J = 7 Hz, 2 H), 3.7 (q, J = 7 Hz, 2 H), 3.96 (s, 2 H), 4.47 (q, J = 8.1 Hz, 2 H), 4.67 (t, J = 5.5 Hz, 1 H), 7.10 (dd, J = 2.2 and 8.7 Hz, 1 H), 7.19 (s, 1 H), 7.37 (s, 1 H), 7.39 (d, J = 8.7 Hz, 1 H), 7.8 (d, J = 2.2 Hz, 1 H), 7.95 (s, 1 H); IR (KBr) 3357, 1607, 1502, 1458, 1283 cm^{-1}; MS, $C_{23}H_{29}F_3N_2O_3$ requires M + 1 439.2208, found 439.2134.

3-[[(2,2-Diethoxyethyl)amino]methyl]-1,4-dimethyl-6-phenoxycarbazole (15b). The aldehyde **14b** was converted to 3-[[(2,2-diethoxyethyl)imino]methyl]-1,4-dimethyl-6-phenoxycarbazole as described for **15a**. The imine was reduced with sodium borohydride; the mixture was stirred for 1 h and concentrated to dryness in vacuo, and the residue was dissolved in ethyl acetate, washed with water, dried, and concentrated to give a brown viscous gum that was purified by flash column chromatography (EtOAc) to give **15b** as a gum (90%): ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 6 H), 2.5 (s, 3 H), 2.78 (s, 3 H), 2.92 (d, J = 5.5 Hz, 2 H), 3.5 (m, 2 H), 3.70 (m, 2 H), 3.95 (s, 2 H), 4.67 (t, J = 5.5 Hz, 1 H), 6.98 (d, J = 7.5 Hz, 1 H), 7.2 (t, J = 7.5 Hz, 1 H), 7.15–7.35 (m, 4 H), 7.5 (d, J = 7 Hz, 1 H), 7.9 (d, J = 1.5 Hz, 1 H), 8.02 (br s, 1 H); IR (KBr) 3326, 3065–2872, 1589, 1462, 1058 cm^{-1}. Anal. Calcd for $C_{27}H_{32}N_2O_3$: C, 74.96; H, 7.46; N, 6.48. Found: C, 75.09; H, 7.57; N, 6.41.

Screening Data Summary. The in vitro antitumor evaluations were performed under the auspices of the National Cancer Institute. The log GI_{50}, TGI, and LC_{50} data were taken from the NCI "mean graph" reports.[24a] The following cell lines were used in the following panels: leukemia [CCRF-CEM; HL-60(TB); K-562; MOLT-4; RPMI-8226; SR], non-small cell lung cancer (A549/ATCC; EKVX; HOP-18; HOP-62; HOP-92; NCI-H226; NCI-H23; NCI-H322M; NCI-H460; NCI-H522; LXFL 529), small cell lung cancer (DMS 114; DMS 273), colon cancer (COLO 205; DLD-1; HCC-2998; HCT-116; HCT-15; HT29; KM12; KM20L2; SW-620), CNS cancer (SF-268; SF-295; SF-539; SNB-19; SNB-75; SNB-78; U251; XF 498), melanoma (LOX IMVI; MALME-3M; M14; M19-MEL; SK-MEL-2; SM-MEL-28; SK-MEL-5; UACC-257; UACC-62), ovarian cancer (IGROVI; OVCAR-3; OVCAR-4; OVCAR-5; OVCAR-8; SK-OV-3), renal cancer (786-0; A498; ACHN; CAKI-1; RXF-393; RXF-631; SN12C; TK-10; UO-31).

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(22) Another approach to the synthesis of 9-phenoxyellipticine (**7a**) involved the acylation of 1-(phenylsulfonyl)-2-lithio-5-phenoxyindole with *freshly purified* pyridine-3,4-dicarboxylic acid anhydride at −100 °C; however, the attack on the anhydride was not regioselective, and both the ellipticine and isoellipticine precursors were obtained.

(23) The unquaternized ellipticines were insoluble in water, and the 2-methylellipticinium analogues were water soluble; the acetates were *ca.* 10–100 times more soluble than the corresponding iodides (*e.g.*, 0.01 mmol of the iodide **4b** dissolved in 13 mL of water at 22 °C, whereas 0.01 mmol of the acetate **4c** dissolved in 0.2 mL of water). Aqueous solutions of the quaternary iodides and acetates showed no signs of decomposition on standing at 22 °C for 10 days.

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