Synthesis and Antitumor Evaluation of New Thiazolo[5,4-*b*]quinoline Derivatives

Carlos Alvarez-Ibarra,* Rocío Fernández-Granda, María L. Quiroga, Angélica Carbonell, Francisco Cárdenas,† and Ernest Giralt†

Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, Ciudad Universitaria, s/n. 28040 Madrid, Spain, and Departamento de Química Orgánica, Facultad de Química, Universidad de Barcelona, c/Martí i Franqués, 1. 08028 Barcelona, Spain

Received July 29, 1996[⊗]

A new synthesis of 9-hydroxy- and 9-(alkylamino)thiazolo[5,4-*b*]quinolines by cyclization of 4-(ethoxycarbonyl)-5-(arylamino)thiazoles and 5-(arylamino)-4-carbamoylthiazoles, respectively, is described. *In vitro* cytotoxicity of a large number of derivatives of these compounds has been tested against several cell lines. The highest activities observed are associated with the presence of a 2-[[(*N*,*N*-diethylamino)ethyl]amino] substituent at C-2 and a fluorine atom at the C-7 position of the tricyclic planar heteroaromatic framework. Three structural features seem to be essential for antitumor activities: a positive charge density at carbon C-7, a side chain at position C-2 or C-9 of the thiazoloquinoline skeleton with two basic nitrogens and a pK_a value of 7.5−10 in the most basic center, and a conformational flexibility of this basic side chain. These structural requirements must be simultaneously satisfied in order to ensure a significant antitumor activity.

Introduction

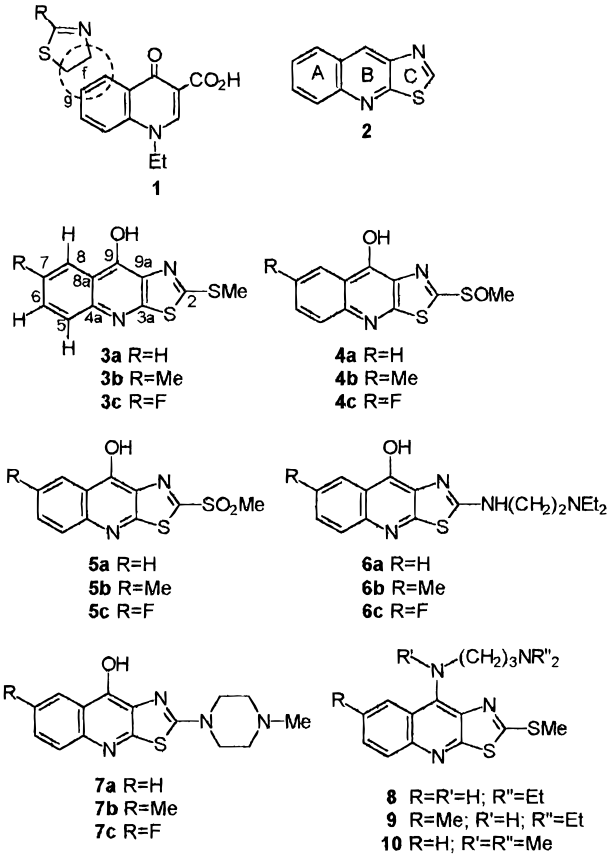
Acridine and quinoline derivatives[1] have been extensively studied as potential antitumor agents, since they are capable of binding to DNA.[1a] Additionally, quinacrine and related derivatives have also been tested as antimalarial[1a] and antineoplastic[1d,e,2] agents. The chemistry of quinoline derivatives has received particular attention over the last few years,[3] and a large variety of quinolines has been synthesized and assessed as antimalarial,[4] antiallergic,[5] antiinflammatory,[6] fungicidal,[7] and antiviral[8] agents. Among all these derivatives, thiazolo[4,5-*g*]-, -[5,4-*g*]-, -[4,5-*h*]-, -[5,4-*h*]-, -[4,5-*f*]-, and [5,4-*f*]quinolines[9] **1** (Chart 1) have shown high activity as antibacterial agents. On the other hand, the synthesis of thiazolo[5,4-*b*]quinoline derivatives **2** has rarely been reported in the literature.[10−12] These compounds have been described as potential antispasmodics,[13] precursors of symmetrical cyanines,[14] antiinflammatories,[15] and fluorescent probes[16] (Chart 1).

The purpose of the present study was the synthesis of the previously unknown thiazolo[5,4-*b*]quinoline derivatives **3**−**10** (Chart 1) and the study of the *in vitro* evaluation of these derivatives as potential antitumor agents. Derivatives **3**−**10** can be structurally related to quinolones and acridines by isosteric substitution of a benzene moiety for a thiazole ring.

Results and Discussion

Chemistry. The synthesis of thiazolo[5,4-*b*]quinolin-9-one skeleton **11** can be rationalized by the retrosynthetic pathways outlined in Scheme 1. Thiazolo[5,4-*b*]quinoline derivatives were previously obtained by different methods which can be related to synthetic pathways I−III (Scheme 1). Tanasescu *et al.*[10,16] have reported the synthesis of 2-(arylamino)- and 2-(alkylamino)thiazolo[5,4-*b*]quinolines in low yields (50−60%) by condensation of primary or secondary amines with 2-chloro-3-isothiocyanatoquinolines which were used as precursors of **12** (Scheme 1, pathway I). Quinolines **13** have been obtained from 2-mercapto-3-aminoquinolines and transformed into thiazoloquinolones **11** with low yields (35−60%) (Scheme 1, pathway II). Finally, pathway III has been previously applied to obtain 2-(arylamino)- or 2-(alkylamino)thiazolo[5,4-*b*]quinolines from 2-aryl- or 2-(alkylamino)-4-thiazolidone[13] and thiazolo[5,4-*b*]quinolin-2-one from 2,4-thiazolinedione.[11]

Chart 1

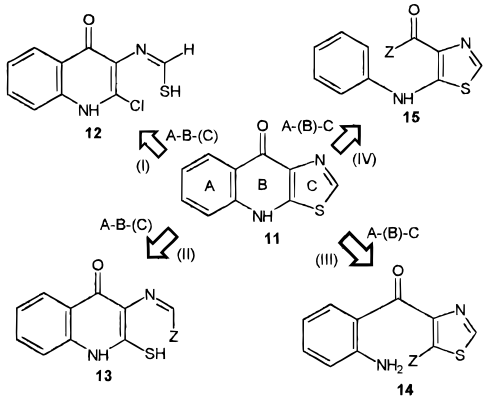


† Universidad de Barcelona.

[⊗] Abstract published in *Advance ACS Abstracts,* January 15, 1997.

S0022-2623(96)00556-0 CCC: $14.00

Scheme 1



As far as we know, the synthetic pathway IV using 2-(methylthio)-4-(ethoxycarbonyl)-5-(arylamino)thiazoles **15a**−**c** as precursors of hydroxythiazolo[5,4-*b*]quinolines is reported here for the first time (Scheme 2). Thiazoles **15a**−**c** were obtained in high yields (94−98%) from ethyl *N*-[bis(methylthio)methylene]glycinate[17,18] and aryl isothiocyanates.[19]

The synthesis of 9-hydroxythiazolo[5,4-*b*]quinolines **3a**−**c** was achieved in good yields (63−90%) by reacting aminothiazoles **15a**−**c** in PPA in the presence of $POCl_3$[20] (Scheme 2). Among all the dehydration reagents described in the literature ($POCl_3$, PPA, H_2SO_4,[21] $SOCl_2$,[22] $(CF_3CO)_2O$[23]), the $POCl_3$/PPA system offers several advantages. It is a nonoxidative system which can be used at high temperature, and it consequently affords higher yields than other dehydrating reagents. After several attempts to optimize the reaction conditions, we found that sulfoxides **4a**−**c** were selectively obtained in good yields by oxidation of derivatives **3a**−**c** with MCPBA in dichloromethane[24] for 1 h at −15 °C. On the other hand, sulfones **5a**−**c** were achieved in good yields by reacting sulfides **3a**−**c** with potassium permanganate in an acetic acid−water mixture for 40 min at 50−70 °C.[25]

Earlier studies of the structure−antileukemic relationships, for congeners of the DNA-intercalating 4′-(9-acridinylamino)alkanesulfonanilides, demonstrated that examples bearing a second strongly basic function could provide exemplary activity in usual screening tests.[26] Bearing in mind this possibility, a linking of a [(dialkylamino)alkyl]amino function at C-2 and C-9 positions for studying the effects of these substituents on cytotoxicities was considered. Amino substituents at position C-2 of the planar tricyclic chromophore of 9-hydroxythiazolo[5,4-*b*]quinolines **6a**−**c** and **7a**−**c** were introduced in quantitative yields by nucleophilic substitution of the methanesulfonyl group of derivatives **5a**−**c** with *N*,*N*-(diethylamino)ethylenediamine or *N*-methylpiperazine, respectively, for 20 min at 140 °C.[27]

9-(Alkylamino)thiazolo[5,4-*b*]quinoline derivatives **8**−**10** were obtained from thiazoles **15a,b** (Scheme 2). Esters were first hydrolyzed to carboxylic acids **16a,b** by treatment with KOH/H_2O−EtOH which were then successively reacted with thionyl chloride and the amine to give amides **17a**−**c**. Cyclization to thiazolo[5,4-*b*]quinoline derivatives was rather difficult: under various conditions, reaction of amides with $POCl_3$,[28] $POCl_3$/$SnCl_4$/nitrobenzene,[29] or $POCl_3$/$SnCl_4$/nitromethane[29] led to the formation of a mixture of starting materials and/or decomposition products. However, we found that cyclization of amides to tricyclic derivatives **8**−**10** could be easily afforded with moderate yields by following the known procedure[20] with $POCl_3$/PPA at 130 °C for 15 min.

Table 1. ^{1}H NMR Chemical Shifts (ppm) of Thiazolo[5,4-*b*]quinolines **3**−**10**

compd[a]	H-5	H-6	H-7	H-8	compd[a]	H-5	H-6	H-7	H-8
3a	8.09	7.78	7.67	8.38	**6a**	7.93	7.66	7.62	8.22
3b	7.96	7.59		8.12	**6b**	7.68	7.37		7.83
3c	8.04	7.50		7.92	**6c**	7.91	7.37		7.70
4a	8.21	7.91	7.77	8.47	**7a**	8.00	7.63	7.59	8.25
4b	8.03	7.69		8.13	**7b**	7.89	7.45		8.01
4c	8.21	7.68		8.05	**7c**	7.95	7.35		7.81
5a	8.21	7.95	7.79	8.50	**8**	7.86	7.59	7.35	7.97
5b	8.09	7.76		8.23	**9**	7.74	7.42		8.17
5c	8.23	7.72		8.09	**10**	7.83	7.63	7.47	8.21

[a] For numbering of hydrogens, see Chart 1.

Free bases **3**−**10** were transformed to their hydrochloride salts[30] in order to test their stabilities and to perform the biological assays. These hydrochlorides were also used to measure pK_a values,[31] and their structural parameters have been previously described.[31] 2-Methylsulfinyl derivatives **4a**−**c** yielded the 2-chloro-9-hydroxythiazolo[5,4-*b*]quinolines **18a**−**c** (Scheme 3). This competitive reaction pathway may be explained by intramolecular catalysis of the nucleophilic substitution of the *O*-protonated 2-methylsulfinyl derivatives by a chloride anion in a preformed ion pair.

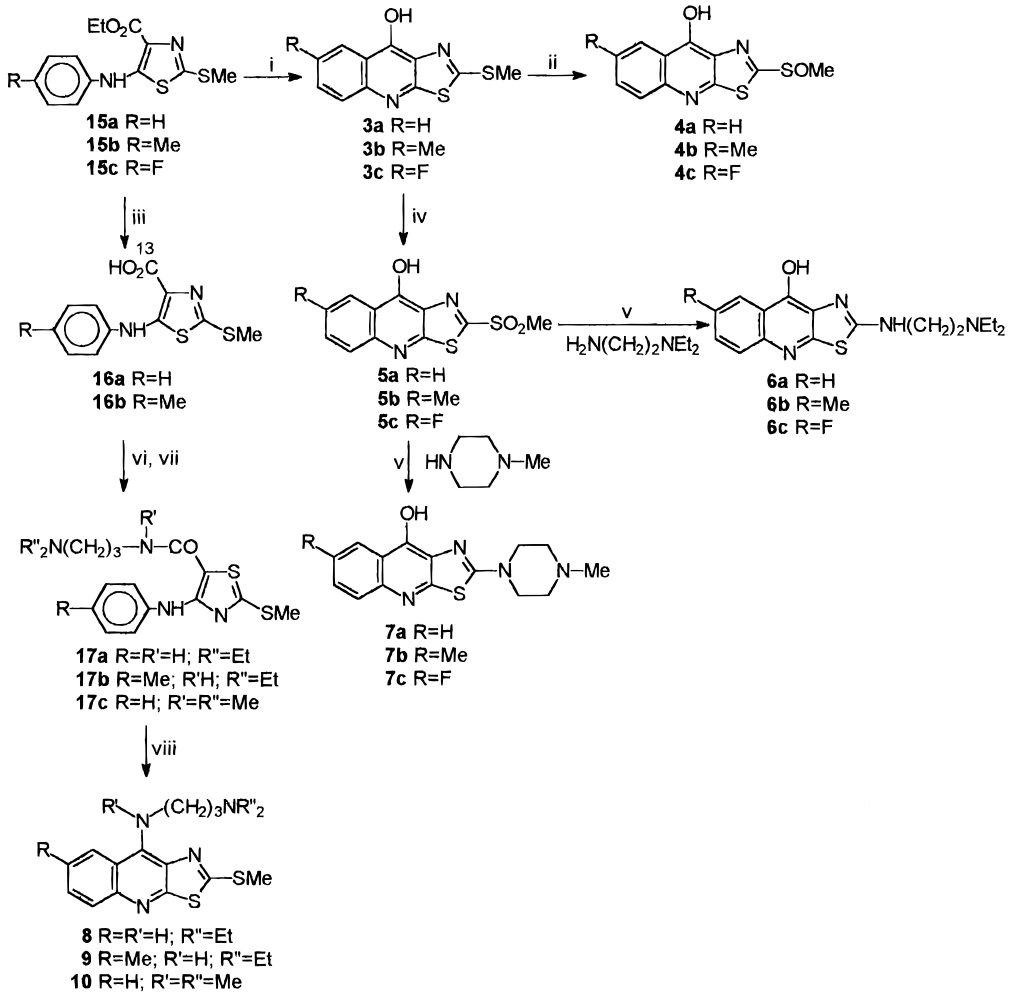
Structural Assignment. All thiazolo[5,4-*b*]quinolines **3**−**10** gave correct elemental analyses, and their structures were confirmed by IR, ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra. IR spectra of compounds **4a**−**c** show a strong absorption band at 1060 cm^{-1} which can be assigned to the stretching vibration of a sulfoxide group.[32] On the other hand, IR spectra of compounds **5a**−**c** have a strong band at 1170 cm^{-1} corresponding to the stretching vibration of a sulfone group.[32]

The unequivocal assignment of observed signals in the ^{1}H NMR spectra of thiazolo[5,4-*b*]quinolines **3**−**10** to hydrogens H-5/H-8 of the benzene ring was carried out from the observed chemical shifts (Table 1) and couplings. The ^{1}H−^{19}F observed couplings in the spectra of fluorinated derivatives **3c**−**7c** (see the Experimental Section) allowed to carry out the assignment proposed for these compounds (Table 1). Theoretical chemical shifts of hydrogens H-5, H-6, and H-8 for compounds **3a,b**/**7a,b** were calculated from induced chemicals shifts related in the literature[33] for a methyl group and a fluorine atom. The comparison between observed and calculated chemical shifts was very satisfactory.[34]

The assignment proposed in Table 1 for aromatic hydrogens of compounds **8**−**10** was supported in the observed chemical shifts and the splitting of signals.[35] The assignment of ^{13}C NMR observed signals (Table 2) was carried out as follows.

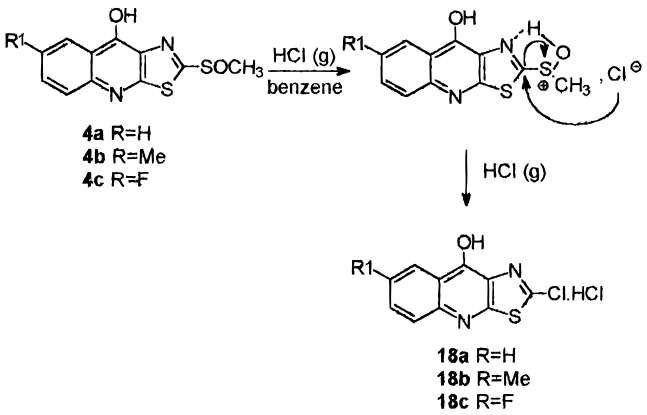
(a) Assignment of Signals to Carbons C-4a, C-5, C-6, C-7, C-8, and C-8a. The signals of methine carbons should be stronger than signals for carbons C-4a and C-8a.[36] The ^{13}C−^{19}F couplings observed in the spectra of fluorinated derivatives **3c**−**7c** (see the Experimental Section) allowed the assignment of all benzene carbons proposed in Table 2. Theoretical chemical shifts of these carbons on related unfluorinated derivatives were calculated from the induced chemical shifts published[38] for a methyl group and a fluorine

Scheme 2[a]



[a] (i) $POCl_3$/PPA/130 °C/4 h; (ii) MCPBA/CH_2Cl_2/−15 °C/1 h; (iii) KOH/EtOH−H_2O/65 °C/20 min; (iv) $KMnO_4$/AcOH−H_2O/55-70 °C/40 min; (v) 140 °C/20 min; (vi) $SOCl_2$/pyr/0 °C/1.5 h; (vii) amine/20 °C/1 h; (viii) $POCl_3$/PPA/130 °C/15 min.

Scheme 3



atom in a benzene ring. The comparison between observed and calculated chemical shifts was very satisfactory.[39] 2D-Heteronuclear $^1H-^{13}C$ (HETCOR) spectra strengthened the assignments of methine carbons proposed in Table 2.

(b) Assignment of Signals to Carbons C-2, C-3a, C-9, and C-9a. These assignments were carried out as follows. (i) The most deshielded carbons of this group should be C-2 and C-9. Carbon C-2 is bonded to three heteroatoms,[40] and carbon C-9 is a γ-type atom of a 4-hydroxyquinoline.[41] (ii) Chemical shifts of carbons C-2 should vary over a larger range than the chemical shifts of carbons C-9 due to the electronic effects of substituents bonded to carbon C-2. (iii) The assignment of signals to carbons C-3a and C-9a could be reasonably established considering that the carbon C-3a has to be more deshielded than the carbon C-9a. The first one is bound to two heteroatoms, and the carbon C-9 is attached to one heteroatom. Furthermore, chemical shifts of carbons C-3a and C-9a could be reasonably estimated as follows. The induced chemical shifts as a consequence of cyclization of thiazoles **15a−c** and **17a−c** to thiazolequinolines **3a−c** and **8−10**, respectively, could be reasonably calculated as 15 ppm for carbon C-9a and −3 ppm for carbon C-3a. These induced chemical shifts have been calculated from chemical shifts described[42] for compounds **19** and **20** (Chart 2).

Thus, the chemical shifts of carbons C-3a and C-9a could be estimated as the algebraic addition of calculated induced chemical shifts and the observed averaged values for carbons C-4 and C-5 on thiazoles **15a−c** and **17a−c**. These calculations were supported by the charge densities on carbons C-3a and C-9a calculated by MNDO[43] for tricyclic derivatives **3−10** (Table 3). In all compounds, except for derivatives **7b**,**c**, the charge density on carbon C-9a was greater than on carbon C-3a.

The oxidation of methylsulfenyl derivatives **3a−c** to sulfoxides **4a−c** or sulfones **5a−c** was very selective,

Table 2. ^{13}C NMR Chemical Shifts (ppm) Observed for Compounds **3**−**10**[a]

compd[b]	C-2	C-3a	C-4a	C-5	C-6	C-7	C-8	C-8a	C-9	C-9a
3a	171.8	145.9	130.6	128.2	129.4	126.7	124.4	124.6	160.3	141.8
3b	171.5	144.6	131.3	128.0	131.7	136.9	123.0	124.5	159.2	141.8
3c	172.8	142.9[c]	129.8	130.9	119.9	160.7	108.0	125.7	159.6	142.2[c]
4a	183.3	147.0	135.9	128.7	131.1	127.4	124.6	124.6	159.0	144.9
4b	182.8	146.0	134.9	128.3	133.6	137.7	123.4	124.6	157.9	142.3
4c	184.5	144.5	135.0	131.6	122.0	160.9	108.1	125.8	158.5	142.9
5a	169.3	148.5	138.5	128.8	131.8	127.8	124.9	125.0	158.8	140.9
5b	168.9	147.4	138.2	128.4	134.4	137.4	123.3	124.9	157.7	140.9
5c	171.5	145.8[d]	131.3	131.7	122.8	161.0	108.2	126.1	164.7	144.9[d]
6a	167.0	145.4	126.6	128.5[e]	128.8[e]	127.7	124.6	126.0	160.2	144.3
6b	167.0	144.2[f]	126.5	128.2	130.9	138.0	123.4	125.5	164.2	144.0[f]
6c	167.3	144.7	124.7	131.3	118.4	162.0	108.1	127.6	159.6	142.2
7a	166.4	144.4	125.4[g]	127.9	127.4	126.3	123.6	125.3[g]	158.6	143.0
7b	166.5	144.9	125.3	127.6	129.8	136.3	122.5	124.7	157.9	143.0
7c	171.4	143.5	124.1	130.3	117.4	160.5	107.4	126.5	157.8	141.2
8	163.6	146.6	142.4	128.3[h]	128.6[h]	122.9	121.8	117.3	158.5	145.0
9	162.4	146.0	142.5	130.2	125.1	127.9	121.4	124.4	157.6	145.0
10	164.0	147.1[i]	137.7	128.2[j]	128.5[j]	125.2	124.2	123.5	162.9	147.2[i]

[a] For signals of aromatic tricyclic backbone substituents, see the Experimental Section. [b] For numbering of carbons, see Chart 1. [c] Interchangeable assignments.

Chart 2

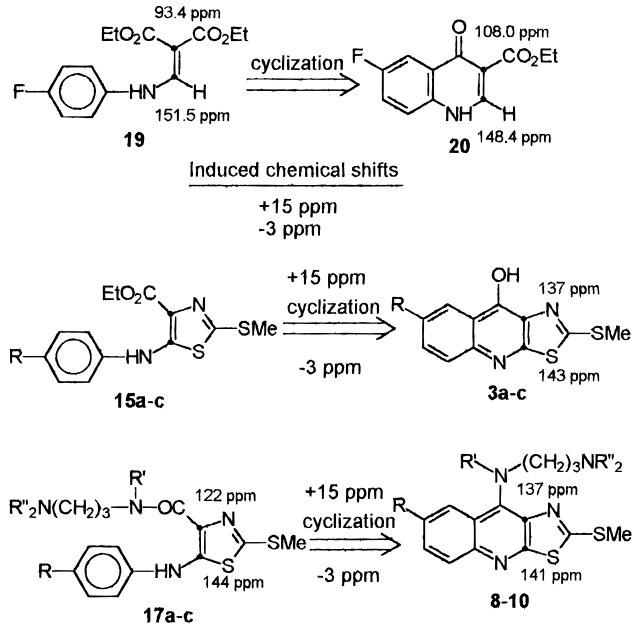


Table 3. Charge Densities Calculated by MNDO on Carbons C-3a and C-9a of Compounds **3**−**10**

compd	Q_{C-3a}	Q_{C-9a}	compd	Q_{C-3a}	Q_{C-9a}
3a	−0.089	−0.186	**6a**	−0.096	−0.176
3b	−0.089	−0.224	**6b**	−0.096	−0.179
3c	−0.093	−0.178	**6c**	−0.098	−0.141
4a	−0.096	−0.157	**7a**	−0.181	−0.192
4b	−0.100	−0.154	**7b**	−0.183	−0.172
4c	−0.074	−0.215	**7c**	−0.186	−0.166
5a	−0.095	−0.154	**8**	−0.102	−0.128
5b	−0.081	−0.229	**9**	−0.093	−0.152
5c	−0.090	−0.214	**10**	−0.111	−0.117

and the N-oxidation was not observed as demonstrated by the ^{13}C NMR spectroscopic data. Induced chemical shifts on carbons C-2 and C-3a and the methyl group by the oxidation of the methylsulfenyl group to SOMe and SO_2Me can be estimated from the ^{13}C NMR data reported[27c] for thiazoles **21** and **22** (Figure 1). The induced chemical shifts of carbons C-2 and C-3a and the methyl group for derivatives **4a**−**c** and **5a**−**c** have been gathered in Table 4. Calculated values for these parameters are practically identical with estimated values from literature data[27c] (Figure 1).

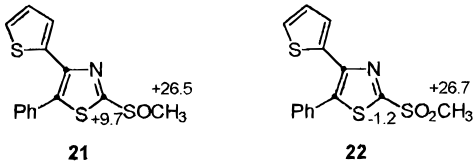


Figure 1. ^{13}C NMR induced chemical shifts on thiazole carbons and the methyl group by oxidation of the SMe group to SOMe and SO_2Me.

Table 4. ^{13}C NMR Induced Chemical Shifts[a] on Carbons C-2, C-3a, C-4a, and C-9 and Methyl Groups for Derivatives **4a**−**c** and **5a**−**c**

compd	*n*	ΔSO_nCH_3	ΔC-2	ΔC-3a	ΔC-4a	ΔC-9
4a	1	27.5	11.5	1.1	5.3	−1.3
4b	1	27.6	11.3	1.4	3.6	−1.3
4c	1	27.6	11.7	1.6	5.2	−1.1
5a	2	26.2	−2.5	2.6	7.9	−1.5
5b	2	26.2	−2.6	2.8	6.9	−1.5
5c	2	26.1	−1.3	2.9	1.5	5.1

[a] Calculated as the difference between chemical shifts observed for the oxidized derivative and the unoxidized precursor.

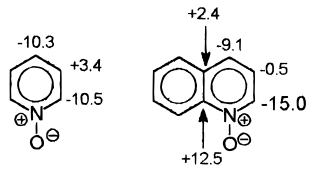


Figure 2. ^{13}C NMR induced chemical shifts by N-oxidation.

^{13}C NMR chemical shifts induced by an N-oxidation of a pyridine nitrogen can be calculated from data reported for pyridine,[42] quinoline,[44] and their *N*-oxides (Figure 2). The N-oxidation causes a clear shielding of α- and γ-carbons (≈ −10 ppm). However, the observed chemical shifts for these carbons in compounds **4** and **5** do not support the N-oxidation hypothesis (Table 4): carbons C-3a and C-4a of derivatives **4** and **5** and the carbon C-9 of compound **5c** show a clear deshielding of these signals, whereas the observed shieldings for carbon C-9 on derivatives **4a**−**c** and **5a**,**b** were much lower than −10 ppm.

Cytotoxicity Results and Discussion. The results of the evaluation of thiazolo[5,4-*b*]quinolines **3a**−**c**, **5**−**10**, and **18a**−**c** against the proliferation of mouse lymphoid neoplasm (P-388), human lung carcinoma (A-

Table 5. Physicochemical Properties and Biological Data for Thiazolo[5,4-*b*]quinolines **3**, **5**−**10**, and **18a**−**c**

			IC_{50} (μM) (*in vitro*)[d]		
compd[a]	Q_{C-7}[b]	pK_a[c]	P-388 (±SE)	A-549 (±SE)	HT-29 (±SE)
3a	−0.076	5.9[e]	>70.2	>70.2	>70.2
3b	−0.116	4.6[e]	>66.9	>66.9	>66.9
3c	0.131	5.7[e]	>66.1	>66.1	>66.1
5a	−0.056	5.2[e]	32.4 (0.9)	32.4 (0.9)	32.4 (0.9)
5b	−0.113	4.0[e]	>60.4	>60.4	>60.4
5c	0.134	5.5[e]	6.0 (0.8)	6.0 (0.8)	6.0 (0.8)
6a	−0.076	9.3[f]	5.76 (0.07)	7.22 (0.02)	7.22 (0.02)
6b	−0.115	8.4[f]	3.3 (0.3)	5.6 (0.2)	3.3 (0.2)
6c	0.132	8.3[f]	1.65 (0.05)	2.9 (0.3)	5.0 (0.5)
7a	−0.143	8.6[g]	18.8 (0.3)	18.8 (0.3)	18.8 (0.3)
7b	−0.080	10.0[g]	16.9 (0.6)	29.6 (1.0)	17.0 (0.3)
7c	0.079	8.0[g]	>56.4	>56.4	>56.4
8	−0.065	7.5[h]	6.0 (0.7)	6.0 (0.7)	6.0 (0.7)
9	−0.110	7.9[h]	5.4 (0.5)	5.4 (0.5)	5.4 (0.5)
10	−0.069	6.5[h]	12.1 (0.9)	12.1 (0.9)	12.1 (0.9)
18a	−0.079	5.9[e]	5.3 (0.4)	11.6 (0.9)	11.6 (0.9)
18b	−0.114	5.0[e]	34.6 (0.7)	34.6 (0.7)	34.6 (0.7)
18c	0.134	4.9[e]	7.4 (1.1)	7.4 (1.1)	7.4 (1.1)

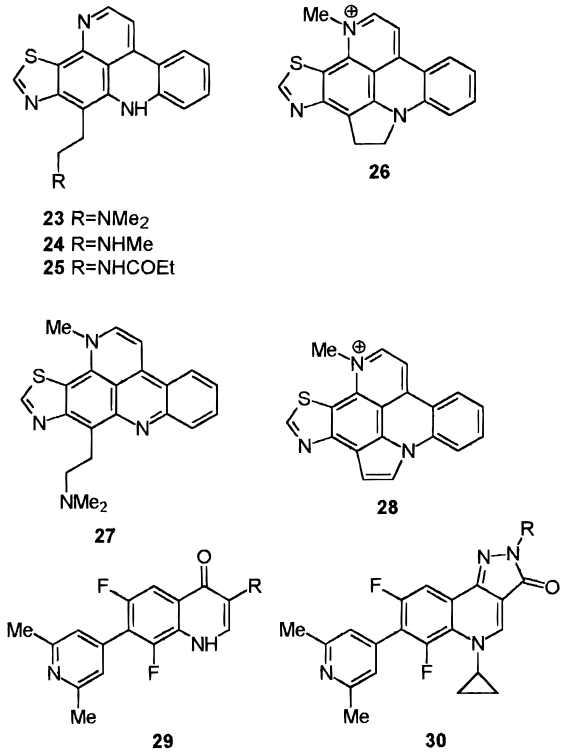
[a] Tested as hydrochloride salts. [b] Charge density at carbon C-7 calculated by MNDO.[43] [c] pK_a values were determined by differential pulse polarography as detailed in ref 31. [d] SE: standard error. Analytical data were fitted to a sigmoid function with the Fig. P software[46] with excellent regression correlation coefficients (0.994−0.999). [e] Protonation of the quinoline nitrogen. [f] Protonation of the nitrogen of the *N*,*N*-diethylamino group. [g] Protonation of nitrogen N-4 of the 4-methyl-1-piperazinyl group. [h] Protonation of the nitrogen of the *N*,*N*-diethylamino group (compounds **8** and **9**) or the *N*,*N*-dimethylamino group (compound **10**).

549), and human colon tumor (HT-29) cell lines *in vitro* are shown in Table 5.[45]

Some information on structure−activity relationships can be identified as follows. (a) It is clear from these data that the compound **6c** has the highest levels of cytotoxicity against P-388 and A-549 cell lines. (b) Both the fluorine atom at the C-7 position and the [(*N*,*N*-diethylamino)ethyl]amino group at the C-2 carbon seem to be important for the induction of significant antitumor activities. Comparing the thiazolo[5,4-*b*]quinolines with an identical group at C-2, the change of the fluorine atom at C-7 to a methyl group or hydrogen atom was shown to be very important for antitumor activity against all three tested tumor types (compare IC_{50} values of fluorinated derivatives **3c**, **5c**, **6c**, and **18c** with IC_{50} data from methyl-substituted compounds **3b**, **5b**, **6b**, and **18b** and unsubstituted derivatives **3a**, **5a**, **6a**, and **18a**.[47] Compounds **3a**−**c**, **5a**−**c**, and **18a**−**c** lacking one NCH_2CH_2N side chain at C-2 were not effective against all three tumor types (**3a**−**c**) or were less active than derivatives **6a**−**c**. (c) The difference of the substitution at C-2 between the [(*N*,*N*-diethylamino)ethyl]amino and 1-(4-methylpiperazinyl) groups was shown to be critical for antitumor activity (compare IC_{50} values of **6a**−**c** to IC_{50} data of **7a**−**c**, respectively). (d) The change of the [(*N*,*N*-dialkylamino)alkyl]amino group at C-2 to the C-9 position resulted in a slight decrease of IC_{50} values for compounds **8** and **9** and in a large decrease of activities for compound **10**, as seen from a comparison in IC_{50} data of **6a** to **8** or **10** and also **6b** to **9**.

In the light of the activities displayed in Table 5, three structural features seem essential for antitumor activities *in vitro*: the charge density induced by the substituent at C-7 position, the pK_a value, and the conformational flexibility on the basic side chain at the C-2 position. These three structural requirements must be simultaneously satisfied in order to ensure a significant antitumor activity.

Chart 3



The charge density at the C-7 carbon must be positive. Substitution with a fluorine atom resulted in a significant decrease of charge density on this carbon, as seen from a comparison of fluorinated derivatives **3c**, **5c**, **6c**, **7c**, and **18c** with their methyl-substituted analogs **3b**, **5b**, **6b**, **7b**, and **18b** or unsubstituted congeners **3a**, **5a**, **6a**, **7a**, and **18a**. These results suggest that an electron-withdrawing group at the C-7 position seems to be significant for the antitumor activity.

Substitution of a flexible [(*N*,*N*-diethylamino)ethyl]-amino side chain at the C-2 position by a 1-(4-methylpiperazinyl) group was shown to be critical for antitumor activity (compare IC_{50} values for compounds **6a**−**c** to IC_{50} data for compounds **7a**−**c**, respectively). The pK_a of the side chain had a significant influence on the cytotoxicity of thiazolo[5,4-*b*]quinoline derivatives: a pK_a value less than 7.5, which is associated with the presence of a side chain with two basic amine nitrogens, could be related to a significant decrease of activity.

Some interesting comparisons of cytotoxic activities described in this paper for thiazolo[5,4-*b*]quinolines with data previously published for acridine and quinoline derivatives can be made.[48] Cytotoxic activities of a new class of acridine alkaloids which possesses a thiazolo-[5,4-*b*]acridine nucleus (**23**−**28**) (Chart 3) have been recently reported.[49,50] It was found that compounds **23**−**26** and **28** displayed an antitumor activity comparable to that of thiazolo[5,4-*b*]quinolines **5c**, **6a**−**c**, **7a,b**, **8**−**10**, and **18a**,**c**, whereas the compound **27** has an activity slightly higher than derivative **6c**.

Wetland *et al*. have recently reported some antitumor activities of 3-benzylquinolones **29**[51] and pyrazoloquinolines **30**[52] against the proliferation of mice lymphoid neoplasm P-388 (*in vitro*) (Chart 3). Thirteen quinolones **29** proved to be as equally active as some of our thiazoloquinolines, and six derivatives were shown to

be slightly more active (IC_{50}: 0.3−0.9 μM) than derivative **6c**. Thirteen quinolines **30** (Chart 3) showed an antitumor activity comparable to that of thiazoloquinoline **6c**, seven derivatives were slightly better than compound **6c** (IC_{50}: 0.2−0.4 μM), and only two derivatives **29** ((*R*)-4-(1-methylpiperidinyl)-, 4-[(1-*N*,*N*-dimethylamino)cyclohexyl]) showed to be more active (IC_{50}: 0.07−0.10 μM) than compound **6c**.

Conclusions

Two new series of thiazolo[5,4-*b*]quinoline derivatives, namely, 9-hydroxy- and 9-[[(*N*,*N*-dialkylamino)propyl]-amino]thiazolo[5,4-*b*]quinolines, were synthesized in high yields. The preliminary antitumor studies of these thiazolo[5,4-*b*]quinoline derivatives showed that 7-fluoro-2-[[(*N*,*N*-diethylamino)ethyl]amino]thiazolo[5,4-*b*]quinolines exhibited significant cytotoxicity against mouse leukemic P-388, human lung carcinoma A-549, and human colon tumor HT-29 cell growth *in vitro*. Three structural features seem to be essential for antitumor activities: a positive charge density, induced by the substituent, at carbon C-7, a side chain at position C-2 or C-9 of the tricyclic system with two basic nitrogens and a pK_a value of 7.5−10, and conformational flexibility of this basic side chain. All these structural requirements must be simultaneously satisfied to ensure significant antitumor activity.

Experimental Section

All starting materials were commercially available research-grade chemicals and used without further purification. 2-(Methylthio)-4-(ethoxycarbonyl)-5-(arylamino)thiazoles **15a**−**c** were prepared according to the previously described procedure.[19] Analytical TLC was performed using silica gel 60 F_{254} with UV light detection. Flash column chromatography was carried out on silica gel 60. IR spectra were recorded as KBr solid pellets or as $CHCl_3$ solutions in 0.1 mm NaCl cells with compensation. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, in $CDCl_3$ or CD_3OD solutions with TMS as internal reference.

The Eagle's minimum essential medium with Earle's balanced salts, with nonessential amino acids with 2.0 mM L-glutamine, and without sodium bicarbonate (EMEM) was purchased from JRH Biosciences. Fetal calf serum (FCS) and the trypsin were obtained from Seromed.

Cyclization of 5-(Arylamino)-4-(ethoxycarbonyl)-2-(methylthio)thiazoles 15a−c to 9-Hydroxy-2-(methylthio)thiazolo[5,4-*b*]quinolines 3a−c. General Procedure. To **15a**−**c** (1 mmol) at 20 °C were successively added $POCl_3$ (470 mg) and PPA (71 mg). The mixture was vigorously stirred for 4 h at 130−5 °C. The mixture was then cooled to room temperature, 1 mL of ethanol was added, and the reaction mixture was concentrated at reduced pressure. The reaction was hydrolyzed with H_2O (10 mL) and neutralized with a 20% aqueous solution of $NaHCO_3$. The solution was then extracted with $CHCl_3$ (3 × 5 mL), and the combined organic layers were washed with brine (3 × 5 mL) and dried over Na_2SO_4. After concentration of the solution, the pale yellow crude product was purified by flash chromatography (hexane/ethyl acetate: 80/20).

9-Hydroxy-2-(methylthio)thiazolo[5,4-*b*]quinoline, 3a: white solid (90%); mp 162−4 °C (ethyl acetate); IR ($CHCl_3$) ν 3660, 3380, 1590, 1550 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.89 (3H, s), 7.67 (1H, ddd, ^3J = 8.4, 6.9 Hz, ^4J = 1.2 Hz), 7.78 (1H, ddd, ^3J = 8.4, 6.9 Hz, ^4J = 1.5 Hz), 8.09 (1H, ddd, ^3J = 8.4 Hz, ^4J = 1.2 Hz, ^5J = 0.6 Hz), 8.38 (1H, ddd, ^3J = 8.4 Hz, ^4J = 1.5 Hz, ^5J = 0.6 Hz); ^{13}C NMR ($CDCl_3$) δ 15.3, 124.4, 124.6, 126.7, 128.2, 129.4, 130.6, 141.8, 145.9, 160.3, 171.8. Anal. ($C_{11}H_8N_2S_2O$) C, H, N.

9-Hydroxy-7-methyl-2-(methylthio)thiazolo[5,4-*b*]quinoline, 3b: white solid (63%); mp 172−3 °C (ethyl acetate); IR ($CHCl_3$) ν 3660, 3390, 1590, 1550, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.61 (3H, s), 2.88 (3H, s), 7.59 (1H, dd, ^3J = 8.7 Hz, ^4J = 2.1 Hz), 7.96 (1H, dd, ^3J = 8.7 Hz, ^5J = 0.6 Hz), 8.12 (1H, dd, ^4J = 2.1 Hz, ^5J = 0.6 Hz); ^{13}C NMR ($CDCl_3$) δ 15.2, 21.7, 123.0, 124.5, 128.0, 131.3, 131.7, 136.9, 141.8, 144.6, 159.2, 171.5. Anal. ($C_{12}H_{10}N_2S_2O$) C, H, N.

7-Fluoro-9-hydroxy-2-(methylthio)thiazolo[5,4-*b*]quinoline, 3c: white solid (74%); mp 182−4 °C (ethyl acetate); IR ($CHCl_3$) ν 3660, 3390, 1590, 1550, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.88 (3H, s), 7.50 (1H, ddd, ^3J = 9.3, 7.8 Hz, ^4J = 2.9 Hz), 7.92 (1H, dd, ^3J = 9.8 Hz, ^4J = 2.9 Hz), 8.04 (1H, dd, ^3J = 9.3 Hz, ^4J = 5.1 Hz); ^{13}C NMR ($CDCl_3$) δ 15.3, 108.0 (d, $^2J_{C,F}$ = 25.2 Hz), 119.9 (d, $^2J_{C,F}$ = 26.2 Hz), 125.7 (d, $^3J_{C,F}$ = 10.0 Hz), 129.8 (d, $^4J_{C,F}$ = 6.0 Hz), 130.9 (d, $^3J_{C,F}$ = 9.0 Hz), 142.2, 142.9, 159.6, 160.7 (d, $^1J_{C,F}$ = 248.8 Hz), 172.8. Anal. ($C_{11}H_7N_2S_2OF$) C, H, N.

Oxidation of 3a−c with *m*-Chloroperbenzoic Acid. General Procedure. To a solution of **3a**−**c** (0.8 mmol) in CH_2Cl_2 (5 mL) at −15 °C was added *m*-chloroperbenzoic acid (0.8 mmol), and the mixture was stirred for 1 h at −15 °C. The reaction mixture was then allowed to reach room temperature, washed successively with a 5% aqueous solution of $Na_2S_2O_3$ (3 × 5 mL), a 50% aqueous solution of $NaHCO_3$ (3 × 5 mL), and brine (3 × 10 mL), and dried over $MgSO_4$. After concentration of the solution, the pale yellow crude solid was recrystallized from methanol.

9-Hydroxy-2-(methylsulfinyl)thiazolo[5,4-*b*]quinoline, 4a: white solid (85%); mp 151−3 °C (CH_3OH); IR ($CHCl_3$) ν 3680, 3400, 1590, 1550, 1490, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.20 (3H, s), 7.77 (1H, ddd, ^3J = 8.7, 6.9 Hz, ^4J = 1.2 Hz), 7.91 (1H, ddd, ^3J = 8.4, 6.9 Hz, ^4J = 1.5 Hz), 8.21 (1H, ddd, ^3J = 8.4 Hz, ^4J = 1.2 Hz, ^5J = 0.6 Hz), 8.47 (1H, ddd, ^3J = 8.7 Hz, ^4J = 1.5 Hz, ^5J = 0.6 Hz).; ^{13}C NMR ($CDCl_3$) δ 42.8, 124.6, 124.6, 127.4, 128.7, 131.1, 135.9, 144.9, 147.0, 159.0, 183.3. Anal. ($C_{11}H_8N_2S_2O_2$) C, H, N.

9-Hydroxy-7-methyl-2-(methylsulfinyl)thiazolo[5,4-*b*]-quinoline, 4b: white solid (95%); mp 172−3 °C (CH_3OH); IR ($CHCl_3$) ν 3680, 3400, 1590, 1550, 1500, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.64 (3H, s), 3.19 (3H, s), 7.69 (1H, dd, ^3J = 8.7 Hz, ^4J = 1.8 Hz), 8.03 (1H, d, ^3J = 8.7 Hz), 8.13 (1H, d, ^4J = 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 21.8, 42.8, 123.4, 124.6, 128.3, 133.6, 134.9, 137.7, 142.3, 146.0, 157.9, 182.8. Anal. ($C_{12}H_{10}N_2S_2O_2$) C, H, N.

7-Fluoro-9-hydroxy-2-(methylsulfinyl)thiazolo[5,4-*b*]-quinoline, 4c: white solid (88%); mp 126−7 °C (CH_3OH); IR ($CHCl_3$) ν 3680, 3400, 1590, 1550, 1490, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.20 (3H, s), 7.68 (1H, ddd, ^3J = 9.4, 7.7 Hz, ^4J = 2.8 Hz), 8.05 (1H, dd, ^3J = 9.4 Hz, ^4J = 2.8 Hz), 8.21 (1H, dd, ^3J = 9.5 Hz, ^4J = 5.1 Hz); ^{13}C NMR ($CDCl_3$) δ 42.9, 108.1 (d, $^2J_{C,F}$ = 25.2 Hz), 122.0 (d, $^2J_{C,F}$ = 26.3 Hz), 125.8 (d, $^3J_{C,F}$ = 9.9 Hz), 131.6 (d, $^3J_{C,F}$ = 9.9 Hz), 135.0 (d, $^4J_{C,F}$ = 6.6 Hz), 142.9, 144.5, 158.5, 160.9 (d, $^1J_{C,F}$ = 250.8 Hz), 184.5. Anal. ($C_{11}H_7N_2S_2O_2F$) C, H, N.

Oxidation of 3a−c with $KMnO_4$. General Procedure. To a solution of **3a**−**c** (0.8 mmol) in glacial AcOH (10 mL) at 55−70 °C was slowly added (40 min) 6 mL of an aqueous solution of $KMnO_4$ (1.6 mmol). After addition, the reaction mixture was cooled to room temperature, and 0.13 mL of a saturated aqueous solution of sodium bisulfite and 4.5 mL of an 80% aqueous solution of NH_4OH were added. The mixture was then extracted with $CHCl_3$ (3 × 25 mL), and the combined organic layers were successively washed with a 5% aqueous solution of $NaHCO_3$ (3 × 25 mL) and brine (3 × 25 mL) and dried over Na_2SO_4. After concentration of the solution at reduced pressure, the pale yellow crude solid was purified by recrystallization on ethyl acetate.

9-Hydroxy-2-(methylsulfonyl)thiazolo[5,4-*b*]quinoline, 5a: white solid (84%); mp 205−7 °C (ethyl acetate); IR ($CHCl_3$) ν 3680, 3400, 1590, 1550, 1500, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.53 (3H, s), 7.79 (1H, ddd, ^3J = 8.7, 6.9 Hz, ^4J = 1.2 Hz), 7.95 (1H, ddd, ^3J = 8.4, 6.9 Hz, ^4J = 1.5 Hz), 8.21 (1H, ddd, ^3J = 8.4 Hz, ^4J = 1.2 Hz, ^5J = 0.6 Hz), 8.50 (1H, ddd, ^3J = 8.7 Hz, ^4J = 1.5 Hz, ^5J = 0.6 Hz) ^{13}C NMR ($CDCl_3$) δ 41.5, 124.9, 125.0, 127.8, 128.8, 131.8, 138.5, 140.9, 148.5, 158.8, 169.3. Anal. ($C_{11}H_8N_2S_2O_3$) C, H, N.

9-Hydroxy-7-methyl-2-(methylsulfonyl)thiazolo[5,4-*b*]quinoline, 5b: white solid (90%); mp 204−5 °C (ethyl acetate); IR ($CHCl_3$) ν 3680, 3400, 1590, 1550, 1500, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.67 (3H, s), 3.52 (3H, s), 7.76 (1H, dd, ^3J = 8.7 Hz, ^4J = 1.8 Hz), 8.09 (1H, d, ^3J = 8.7 Hz), 8.23 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 21.9, 41.5, 123.3, 124.9, 128.4, 134.4, 137.4, 138.2, 140.9, 147.4, 157.7, 168.9. Anal. ($C_{12}H_{10}N_2S_2O_3$) C, H, N.

7-Fluoro-9-hydroxy-2-(methylsulfonyl)thiazolo[5,4-*b*]quinoline, 5c: white solid (82%); mp 230−1 °C (ethyl acetate); IR ($CHCl_3$) ν 3400, 1590, 1550, 1500, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.53 (3H, s), 7.72 (1H, ddd, ^3J = 9.5, 7.6 Hz, ^4J = 2.8 Hz), 8.09 (1H, dd, ^3J = 9.4 Hz, ^4J = 2.8 Hz), 8.23 (1H, dd, ^3J = 9.5 Hz, ^4J = 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 41.4, 108.2 (d, $^2J_{C,F}$ = 25.2 Hz), 122.8 (d, $^2J_{C,F}$ = 27.1 Hz), 126.1 (d, $^3J_{C,F}$ = 7.0 Hz), 131.3 (d, $^4J_{C,F}$ = 7.0 Hz), 131.7 (d, $^3J_{C,F}$ = 10.1 Hz), 144.9, 145.8, 161.0 (d, $^1J_{C,F}$ = 252.8 Hz), 164.7, 171.5. Anal. ($C_{11}H_7N_2S_2O_3F$) C, H, N.

Synthesis of 2-(Alkylamino)-9-hydroxythiazolo[5,4-*b*]quinolines 6a−c and 7a−c. General Procedure. A solution of **5a−c** (1 mmol) in *N*,*N*-diethylethylenediamine (3 mmol) or *N*-methylpiperazine (3 mmol) was stirred for 20 min at 140 °C. The reaction mixture was then cooled to room temperature. Chloroform (20 mL) was then added, and the resulting solution was successively extracted with a 1 N NaOH solution (3 × 10 mL), a saturated aqueous solution of NH_4Cl (3 × 10 mL), and brine (3 × 10 mL) and dried over Na_2SO_4. After concentration of the solution under reduced pressure, the pale yellow crude product was purified by preparative TLC (twice) (**6a−c**) (methanol) or by flash chromatography (ethyl acetate/methanol: 90/10) and preparative TLC (ethyl acetate/methanol: 95/5) (**7a−c**).

2-[[2-(*N*,*N*-Diethylamino)ethyl]amino]-9-hydroxythiazolo[5,4-*b*]quinoline, 6a: white solid (91%); mp 128−30 °C; IR ($CHCl_3$) ν 3360, 3320, 1605, 1550, 1460 cm^{-1}; ^1H NMR (CD_3OD) δ 1.23 (6H, t, ^3J = 7.2 Hz), 2.95 (4H, q, ^3J = 7.2 Hz), 3.10 (2H, t, ^3J = 6.6 Hz), 3.81 (2H, t, ^3J = 6.6 Hz), 7.62 (1H, ddd, ^3J = 8.4, 6.9 Hz, ^4J = 1.5 Hz), 7.66 (1H, ddd, ^3J = 8.4, 6.9 Hz, ^4J = 1.8 Hz), 7.93 (1H, ddd, ^3J = 8.4 Hz, ^4J = 1.5 Hz, ^5J = 0.6 Hz), 8.22 (1H, ddd, ^3J = 8.7 Hz, ^4J = 1.8 Hz, ^5J = 0.6 Hz); ^{13}C NMR (CD_3OD) δ 11.6, 42.3, 48.5, 52.2, 124.6, 126.0, 126.6, 127.7, 128.5, 128.8, 144.3, 145.4, 160.2, 167.0. Anal. ($C_{16}H_{20}N_4SO$) C, H, N.

2-[[2-(*N*,*N*-Diethylamino)ethyl]amino]-9-hydroxy-7-methylthiazolo[5,4-*b*]quinoline, 6b: white solid (95%); mp 107−8 °C; IR ($CHCl_3$) ν 3360, 3320, 1605, 1550, 1460 cm^{-1}; ^1H NMR (CD_3OD) δ 1.13 (6H, t, ^3J = 7.2 Hz), 2.50 (3H, s), 2.70 (4H, q, ^3J = 7.2 Hz), 2.85 (2H, t, ^3J = 6.9 Hz), 3.66 (2H, t, ^3J = 7.8 Hz), 7.37 (1H, dd, ^3J = 8.7 Hz, ^4J = 1.5 Hz), 7.68 (1H, d, ^3J = 8.7 Hz), 7.83 (1H, br s); ^{13}C NMR (CD_3OD) δ 11.7, 21.9, 42.4, 48.3, 52.2, 123.4, 125.5, 126.5, 128.2, 130.9, 138.0, 144.0, 144.2, 164.2, 167.0. Anal. ($C_{17}H_{22}N_4SO$) C, H, N.

2-[[2-(*N*,*N*-Diethylamino)ethyl]amino]-7-fluoro-9-hydroxythiazolo[5,4-*b*]quinoline, 6c: white solid (97%); mp 120−5 °C; IR ($CHCl_3$) ν 3360, 3320, 1630, 1550, 1460 cm^{-1}; ^1H NMR (CD_3OD) δ 1.11 (6H, t, ^3J = 7.2 Hz), 2.74 (4H, q, ^3J = 7.2 Hz), 2.88 (2H, t, ^3J = 7.0 Hz), 3.69 (2H, t, ^3J = 6.9 Hz), 7.37 (1H, ddd, ^3J = 9.3, 8.7 Hz, ^4J = 2.8 Hz), 7.70 (1H, dd, ^3J = 10.2 Hz, ^4J = 2.8 Hz), 7.91 (1H, ddd, ^3J = 8.7 Hz, ^4J = 5.4 Hz, ^5J = 0.6 Hz); ^{13}C NMR (CD_3OD) δ 11.4, 42.1, 48.3, 52.0, 108.1 (d, $^2J_{C,F}$ = 25.2 Hz), 118.4 (d, $^2J_{C,F}$ = 26.2 Hz), 124.7 (d, $^4J_{C,F}$ = 5.0 Hz), 127.6 (d, $^3J_{C,F}$ = 10.1 Hz), 131.3 (d, $^3J_{C,F}$ = 9.0 Hz), 142.2, 144.7, 159.6, 162.0 (d, $^1J_{C,F}$ = 246.8 Hz), 167.3. Anal. ($C_{16}H_{19}N_4SOF$) C, H, N.

9-Hydroxy-2-(4-methylpiperazin-1-yl)thiazolo[5,4-*b*]quinoline, 7a: white solid (95%); mp 167−8 °C; IR ($CHCl_3$) ν 3660, 3400, 1600, 1550, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.39 (3H, s), 2.59 (4H, t, ^3J = 5.4 Hz), 3.82 (4H, t, ^3J = 5.4 Hz), 7.59 (1H, ddd, ^3J = 8.4, 6.9 Hz, ^4J = 1.5 Hz), 7.63 (1H, ddd, ^3J = 8.7, 6.9 Hz, ^4J = 1.8 Hz), 8.00 (1H, ddd, ^3J = 8.7 Hz, ^4J = 1.5 Hz, ^5J = 0.9 Hz), 8.25 (1H, ddd, ^3J = 8.4 Hz, ^4J = 1.8 Hz, ^5J = 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 45.9, 47.9, 54.1, 123.6, 125.3, 125.4, 126.3, 127.4, 127.9, 143.0, 144.4, 158.6, 166.4. Anal. ($C_{15}H_{16}N_4SO$) C, H, N.

9-Hydroxy-7-methyl-2-(4-methylpiperazin-1-yl)thiazolo[5,4-*b*]quinoline, 7b: white solid (82%); mp 180−1 °C; IR ($CHCl_3$) ν 3660, 3400, 1600, 1550, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (3H, s), 2.58 (3H, s), 2.58 (4H, t, ^3J = 5.2 Hz), 3.81 (4H, t, ^3J = 5.2 Hz), 7.45 (1H, dd, ^3J = 8.7 Hz, ^4J = 1.8 Hz), 7.89 (1H, d, ^3J = 8.7 Hz), 8.01 (1H, d, ^4J = 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 21.7, 46.0, 47.8, 54.1, 122.5, 124.7, 125.3, 127.6, 129.8, 136.3, 143.0, 144.9, 157.9, 166.5. Anal. ($C_{16}H_{18}N_4SO$) C, H, N.

7-Fluoro-9-hydroxy-2-(4-methylpiperazin-1-yl)thiazolo[5,4-*b*]quinoline, 7c: white solid (94%); mp 187−8 °C; IR ($CHCl_3$) ν 3660, 3400, 1605, 1545, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (3H, s), 2.58 (4H, t, ^3J = 5.6 Hz), 3.80 (4H, t, ^3J = 5.6 Hz), 7.35 (1H, ddd, ^3J = 9.1, 7.9 Hz, ^4J = 2.7 Hz), 7.81 (1H, dd, ^3J =10.2 Hz, ^4J = 2.7 Hz), 7.95 (1H, dd, ^3J = 9.1 Hz, ^4J = 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 45.9, 47.9, 54.1, 107.4 (d, $^2J_{C,F}$ = 25.2 Hz), 117.4 (d, $^2J_{C,F}$ = 25.2 Hz), 124.1 (d, $^4J_{C,F}$ = 6.0 Hz), 126.5 (d, $^3J_{C,F}$ = 10.1 Hz), 130.3 (d, $^3J_{C,F}$ = 10.1 Hz), 141.2, 143.5, 157.8, 160.5 (d, $^1J_{C,F}$ = 246.8 Hz), 171.4. Anal. ($C_{15}H_{15}N_4SOF$) C, H, N.

Synthesis of 5-(Arylamino)-4-[[3-(*N*,*N*-diethyl(or dimethyl)amino)propyl]carbamoyl]-2-(methylthio)thiazoles. General Procedure. The carboxylic acids used as precursors of the amides **17a−c** were obtained with good yields (75%) by saponification of esters **15a,b** following a standard procedure.[53] To a suspension of the carboxylic acid (11.4 mmol) in dry benzene (35 mL) and dry pyridine (11.3 mmol) at 0 °C was slowly added thionyl chloride (33.9 mmol). The mixture was then vigorously stirred at 0 °C for 1.5 h, and the benzene and excess thionyl chloride were eliminated at reduced pressure. After consecutive addition of dry benzene (25 mL) and *N*,*N*,*N*′-trimethyl-1,3-propylidenediamine (22.6 mmol), the reaction mixture was stirred at room temperature for 1 h, and H_2O (50 mL) and $CHCl_3$ (50 mL) were added. The aqueous layer was extracted with $CHCl_3$ (3 × 30 mL), and the combined organic layers were successively washed with a 5% aqueous solution of $NaHCO_3$ (3 × 25 mL), a saturated solution of NH_4Cl (3 × 25 mL) and brine (3 × 25 mL), and dried over Na_2SO_4. The organic phase was evaporated to dryness under reduced pressure, and the pale yellow oil was purified by flash chromatography (CH_2Cl_2/CH_3OH: 90/10).

4-[[3-(*N*,*N*-Diethylamino)propyl]carbamoyl]-2-(methylthio)-5-(phenylamino)thiazole, 17a: colorless oil (74%); IR (KBr) ν 3680, 3400, 1670, 1610, 1590, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (6H, t, ^3J = 7.0 Hz), 1.79 (2H, quint, ^3J = 6.6 Hz), 2.63 (3H, s), 2.77 (2H, t, ^3J = 7.2 Hz), 2.78 (4H, q, ^3J = 7.0 Hz), 3.49 (2H, q, ^3J = 6.3 Hz), 7.02 (2H, t, ^3J = 7.0 Hz), 7.16 (2H, d, ^3J = 7.0 Hz), 7.33 (2H, t, ^3J = 7.0 Hz), 7.91 (1H, br t, ^3J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 11.3, 17.3, 26.1, 38.2, 46.7, 51.3, 116.8, 122.4, 125.4, 129.4, 140.9, 145.9, 150.2, 164.4.

4-[[3-(*N*,*N*-Diethylamino)propyl]carbamoyl]-2-(methylthio)-5-(*p*-tolylamino)thiazole, 17b: colorless oil (70%); IR (KBr) ν 3680, 3400, 1670, 1610, 1590, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (6H, t, ^3J = 7.0 Hz), 2.04 (2H, quint, ^3J = 7.0 Hz), 2.25 (3H, s), 2.67 (3H, s), 2.77 (4H, q, ^3J = 7.0 Hz), 2.95 (2H, t, ^3J = 7.2 Hz), 3.43 (2H, q, ^3J = 6.3 Hz), 7.00 (2H, t, ^3J = 7.0 Hz), 7.15 (2H, d, ^3J = 7.0 Hz), 7.75 (1H, br t, ^3J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 11.4, 17.3, 20.5, 26.4, 38.3, 48.8, 51.3, 116.6, 124.9, 127.3, 129.9, 138.7, 145.3, 151.0, 164.4.

4-[*N*-Methyl[3-(*N*′,*N*′-dimethylamino)propyl]carbamoyl]-2-(methylthio)-5-(phenylamino)thiazole, 17c: colorless oil (89%); IR (KBr) ν 1635, 1600, 1550 cm^{-1}; two rotamers A (52%) and B (48%) observed by NMR, ^1H NMR ($CDCl_3$) rotamer A δ 1.91 (2H, br q, ^3J = 7.2 Hz), 2.28 (6H, s), 2.38 (2H, br t, ^3J = 7.2 Hz), 2.62 (3H, s), 3.09 (3H, br s), 3.94 (2H, br t, ^3J = 7.2 Hz), 7.02 (1H, t, ^3J = 7.2 Hz), 7.18 (2H, d, ^3J = 7.2 Hz), 7.32 (2H, t, ^3J = 7.2 Hz), rotamer B δ 1.93 (2H, br q, ^3J = 7.2 Hz), 2.22 (6H, s), 2.39 (2H, br t, ^3J = 7.2 Hz), 2.62 (3H, s), 3.48 (3H, br s), 3.54 (2H, br t, ^3J = 7.2 Hz), 7.02 (1H, t, ^3J = 7.2 Hz), 7.18 (2H, ^3J = 7.2 Hz), 7.32 (2H, t, ^3J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) rotamer A δ 17.0, 26.8, 34.9, 45.2, 49.3, 56.7, 117.3, 118.2, 122.5, 129.3, 141.2, 143.4, 153.5, 165.2, rotamer B δ 17.1, 24.8, 37.9, 45.2, 47.0, 56.7, 117.3, 118.2, 122.5, 129.3, 141.0, 142.4, 152.0, 164.8.

Cyclization of 5-(Arylamino)-4-[[3-(*N*,*N*-dialkylamino)propyl]carbamoyl]-2-(methylthio)thiazoles to 2-(Methylthio)-9-[[3-(*N*,*N*-dialkylamino)propyl]amino]thiazolo[5,4-*b*]quinolines 8−10. General Procedure. 2-(Methylthio)-9-[[3-(*N*,*N*-dialkylamino)propyl]amino]thiazolo[5,4-*b*]quin-

olines **8**−**10** were obtained following the general procedure described previously for 9-hydroxythiazolo[5,4-*b*]quinolines **3a**−**c**. The crude products were purified by flash chromatography ($CH_2Cl_2/CH_3OH/NH_4OH$: 98/2/traces).

9-[[3-(*N*,*N*-Diethylamino)propyl]amino]-2-(methylthio)thiazolo[5,4-*b*]quinoline, 8: colorless oil (49%); IR ($CHCl_3$) ν 3450, 3200, 1605, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (6H, t, ^3J = 6.9 Hz), 1.93 (2H, quint, ^3J = 5.7 Hz), 2.70 (4H, t, ^3J = 6.9 Hz), 2.71 (2H, t, ^3J = 6.9 Hz), 2.75 (3H, s), 4.33 (1H, t, ^3J = 5.1 Hz), 4.35 (1H, t, ^3J = 5.4 Hz), 7.35 (1H, ddd, ^3J = 8.4, 6.6 Hz, ^4J = 1.2 Hz), 7.59 (1H, ddd, ^3J = 8.4, 6.6 Hz, ^4J = 1.2 Hz), 7.86 (1H, dd, ^3J = 8.4 Hz, ^4J = 1.2 Hz), 7.97 (1H, d, ^3J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 10.9, 15.1, 25.7, 44.7, 46.9, 52.7, 117.3, 121.8, 122.9, 128.3, 128.6, 142.4, 145.0, 146.6, 158.5, 163.6. Anal. ($C_{18}H_{24}N_4S_2$) C, H, N.

9-[[3-(*N*,*N*-Diethylamino)propyl]amino]-7-methyl-2-(methylthio)thiazolo[5,4-*b*]quinoline, 9: colorless oil (37%); IR ($CHCl_3$) ν 3450, 3200, 1605, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (6H, t, ^3J = 7.2 Hz), 2.25 (2H, quint, ^3J = 5.7 Hz), 2.67 (3H, s), 2.80 (3H, s), 3.05 (4H, q, ^3J = 7.2 Hz), 3.06 (4H, q, ^3J = 7.2 Hz), 4.54 (1H, t, ^3J = 7.2 Hz), 7.42 (1H, d, ^3J = 8.7 Hz), 7.74 (1H, d, ^3J = 8.7 Hz), 8.17 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 10.9, 15.2, 21.7, 25.7, 44.7, 47.1, 51.2, 121.4, 124.4, 125.1, 127.9, 130.2, 142.5, 145.0, 146.0, 157.6, 162.4. Anal. ($C_{19}H_{26}N_4S_2$) C, H, N.

9-[*N*-Methyl[3-(*N*′,*N*′-dimethylamino)propyl]amino]-2-(methylthio)thiazolo[5,4-*b*]quinoline, 10: colorless oil (39%); IR ($CHCl_3$) ν 1605, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.82 (2H, quint, ^3J = 7.5 Hz), 2.15 (6H, s), 2.33 (2H, t, ^3J = 7.5 Hz), 2.78 (3H, s), 3.27 (3H, s), 3.73 (2H, t, ^3J = 7.5 Hz), 7.47 (1H, ddd, ^3J = 8.1, 6.9 Hz, ^4J = 1.2 Hz), 7.63 (1H, ddd, ^3J = 8.1, 6.9 Hz, ^4J = 1.2 Hz), 7.83 (1H, dd, ^3J = 8.1 Hz, ^4J = 1.2 Hz), 8.21 (1H, dd, ^3J = 8.1 Hz, ^4J = 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 15.1, 26.2, 43.1, 45.3, 54.5, 57.1, 123.5, 124.2, 125.2, 128.2, 128.5, 137.7, 147.1, 147.2, 162.9, 164.0. Anal. ($C_{17}H_{22}N_4S_2$) C, H, N.

Antineoplastic Bioassays. Four solutions of each sample at different concentrations (20, 10, 5, and 2.5 μg/mL) were used to perform the cytotoxicity bioassays for compounds **3a**−**c**, **5a**,**b**, **7a**−**c**, and **18b**. Four 10-fold diluted additional solutions were used for compounds **5c**, **6a**−**c**, **8**−**10**, **18a**−**c**. The first solution was prepared by dilution of 1 mg of sample in a mixture of dimethyl sulfoxide (100 μL), methanol (450 μL), and acetone (450 μL). Additional solutions were obtained by successive dilutions up to the required final concentrations. Aliquots of 20 μL of each of the four solutions were added to cultures, and the methanol and acetone were evaporated in a sterile cabin of laminar flow at room temperature. The *in vitro* antitumor activity was screened using an adapted procedure of the method described by Bergeron *et al*.[54] against three cell lines: a suspension culture of a lymphoid neoplasm from DBA/2 mouse (P-388), a monolayer culture of the human lung carcinoma (A-549), and a monolayer culture of the human colon carcinoma (HT-29). Cells were maintained in exponential phase of growth in Eagle's minimum essential medium (EMEM) which was supplemented with 5% fetal calf serum (FCS), a 10^{-2} M solution of sodium bicarbonate, a mixture of 0.1 g/L penicillin G and 0.1 g/L streptomycin sulfate, Earle's balanced salts, and 2.0 mM L-glutamine.

Cells were seeded into 16 mm wells at 1×10^4 (P-388) or 2×10^4 (A-549 and HT-29) cells/well in 1 mL aliquots of EMEM 5% FCS containing the samples at different concentrations (*vide supra*). In each case, a separate set of cultures without drugs was seeded as control of growth to ensure that cells remained in the exponential phase of growth. All determinations were carried out in duplicate. After 3 days of incubation at 37 °C, 10% CO_2 in a 98% humid atmosphere, cells were fixed with 0.4% formalin and stained with 0.1% crystal violet. The results of these assays were used to obtain the dose-response curves from which IC_{50} (μM) values were determined. An IC_{50} value represents the concentration (μM) of the sample which produces a 50% cell growth inhibition.

Acknowledgment. Financial support from the Comisión Interministerial para la Ciencia y la Tecnología (CICYT Grant No. PB90-0043) is gratefully acknowledged as well as Universidad Complutense de Madrid and Universidad de Barcelona for their NMR Service support. R.F.-G. gratefully acknowledges the Fundación Uriach for a grant. We thank Dr. Dolores G. Gávalos of Pharma Mar I + D Laboratory for performing the cytostatic results and Pilar Navarro for technical support.

References

(1) (a) Peacocke, A. R. In *Heterocyclic Compounds: The Acridines*; Acheson, R. M., Ed.; Wiley Interscience: New York, **1973**. (b) Ledochowski, A. Ledakin-Anticancerous Medicine 1-Nitro-9-(3-dimethylaminopropylamino)acridine dihydrochloride monohydrate. *Mater. Med. Polon.* **1976**, *8*, 237−251. (c) Gniazdowski, M.; Filipsky, J.; Chorazy, M. In *Antibiotics*; Hahn, F. E., Ed.; Springer Verlag: Berlin, **1979**; Vol. 2, pp 275−297. (d) Denny, W. A.; Baguley, B. C.; Cain, B. F.; Waring, M. J. In *Molecular Aspects of Anticancer Drug Action*; Neidle, S., Waring, M. J., Eds.; MacMillan Publishing Co.: London, 1983; pp 1−34. (e) Denny, W. A. In *The Chemistry of Antitumor Agents*; Wilman, D. E. V., Ed.; Blackie: Glasgow, 1990; pp 1−29.

(2) Cain, B. F.; Atwell, G. J.; Denny, W. A. Potential Antitumor Agents. 17. 9-Anilino-10-methylacridinium Salts. *J. Med. Chem.* **1976**, *19*, 772−777.

(3) (a) Albrecht, R. Development of Antibacterial Agents of the Nalidixic Acid Type. *Prog. Drug Res.* **1977**, *21*, 9−104. (b) Bouzard, D. In *Recent Progress in the Chemical Synthesis of Antibiotics: Recent Advances in the Chemistry of Quinolones*; Lukacz, G., Ohno, M., Eds.; Springer Verlag: Berlin, 1990; p 249.

(4) (a) Lednicer, D.; Mitscher, L. A. *Organic Chemistry of Drug Synthesis*; John Wiley: New York, 1977; Vol. 1, p 340. (b) Smith, J. T.; Lewin, C. S. Quinolones. In Chemistry and Mechanism of Action of the Quinolone Antibacterials; Andriole, V. T., Ed.; Academic Press: London, 1988. (c) Mekheimer, R.; Ahmed, E. Kh.; Khattab, A. F. A Novel Nucleophilic Substitution with Quinoline Derivatives. Synthesis of Quinolones and Pyrazolo-[4,3-*c*]quinoline Derivatives. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2936−2940 and references cited herein.

(5) (a) Ridgway, M. H.; Waters, M. D.; Peel, E. M.; Ellis, P. G. Tetrazolyloxodihydroquinoline Carboxamides. Ger. Offen. 2,407,-744, 1974. (b) Buckle, D. R.; Cantello, B. C. C.; Smith, H. H.; Spicer, B. A. 4-Hydroxy-3-nitro-2-quinolones and Related Compounds as Inhibitors of Allergic Reactions. *J. Med. Chem.* **1975**, *18*, 726−732.

(6) Stotnichi, S. J.; Gilman, C. S.; Steinbaugh, A. B.; Musser, H. J. Preparation of Pyrazolo[4,3-*c*]quinolines as Antiinflammatories. U.S. Patent 4,748,246, 1988.

(7) Schubert, J.; Wild, J.; Roeser, K.; Sauter, H.; Pommer, E. H. Preparation of 2-Anilinoquinolines as Agrochemical Fungicides. Ger. Offen. DE 3,716,512, 1988.

(8) Bell, R. M.; Ackerman, H. Preparation of Pyrazolo[3,4-*b*]quinolines as Antiviral Agents. U.S. Patent 4,920,128, 1990.

(9) (a) Suzuki, N.; Tamaka, Y.; Domori, R. Synthesis of Antimicrobial Agents. Y. Synthesis and Antimicrobial Activities of Thiazoloquinoline Derivatives. *Chem. Pharm. Bull.* **1979**, *27*, 1−11. (b) Domori, R.; Kadoya, S.; Takamura, Y.; Suzuki, N. Synthetic Chemotherapeutic Agents. Y. Synthesis of 2-Substituted Thiazolo[5,4-*f*]quinoline Derivatives. *Chem. Pharm. Bull.* **1976**, *24*, 130−135. (c) Suzuki, N.; Nagata, Y.; Tanaka, Y.; Domori, R. Thiazoloquinolinecarboxylic Acids. Japan Kokai 77,125,196, 1978. (d) Suzuki, N.; Nagata, Y.; Tanaka, Y.; Domori, R. Thiazoloquinolinecarboxylic Acids. Japan Kokai 77,83,596, 1978. (e) Kadoya, S.; Nagasaki, S. Synthetic Chemotherapeutic Agents. V. Antibacterial Activities of Thiazolo[5,4-*f*]-quinolinecarboxylic Acid Derivatives. *Yakugaku Zasshi* **1979**, *99*, 483−920.

(10) (a) Tanasescu, Y.; Denes, Y.; Rusus, G. Thiazoloquinolines. II. Thiazolo[5,4-*b*]quinoline Substituted in the thiazole Ring. *Chem. Ber.* **1957**, *90*, 1295−1299. (b) Tanasescu, Y.; Denes, Y.; Rusus, G. Thiazoloquinolines. IV. The Chlorination of the 2-Mercapto Derivatives of Thiazolo[4,5-*b*]- and [5,4-*b*]quinoline. *Chem. Ber.* **1959**, *92*, 869−871. (c) Tanasescu, Y.; Denes, Y.; Makkay, K. Thiazoloquinolines. V. Some Alkylation Reactions of 2-Hydroxythiazolo[4,5-*b*]- and [5,4-*b*]quinolines. *Chem. Ber.* **1959**, *92*, 2779−2783.

(11) Sabata, B. K.; Tripathy, P. B.; Rout, M. K. Antispasmodic Compounds. *J. Proc. Inst. Chem.* **1960**, *32*, 147−150.

(12) Kiprianova, L. A.; Yarovi, D. K.; Schetsinskaya, E.; Babiechev, F. S. Benzothiazolylalkanoic Acids and Their derivatives. VI. Condensation of 2-amino-1-thionaphtol and 3-amino-2-mercaptoquinoline with the Anhydrides of Dibasic Carboxylic Acids. *Ukr. Khim. Zh.* **1964**, *30*, 859−862.

(13) Das, B.; Rout, M. K. Potential Antispasmodics. Quinolinothiazoles. *J. Sci. Ind. Res.* **1957**, *16C*, 125−126.

(14) Modica, G. di; Barni, E. Cyanine Dyes Derived from Thiazoloquinolines. *Gazz. Chim. Ital.* **1963**, *93*, 679−686.

(15) Moersdorf, P.; Schickaneder, H.; Engler, H.; Ahrens, K. H. Preparation of Hydrazinothiazolopyridines as Antiinflammatories. Ger. Offen. DE 3,533,331, 1987.
(16) Bernstein, S. C.; Abrams, S. K.; Leckrone, K. J.; Paul, L. A. Chloroisotiocyanatoquinolines as Fluoregenic Derivatizing Agents for Primary and Secondary Amines. *J. Pharm. Biomed. Anal.* **1993**, *11*, 61−69.
(17) Ethyl *N*-[bis(methylthio)methylene]glycinate is easily obtained in a single step from ethyl glycinate, carbon disulfide, and methyl idodide; see: Alvarez-Ibarra, C.; Quiroga, M. L.; Toledano, E. A One-pot Preparation of dimethyl N-alkyliminodithiocarbonates. *Org. Prep. Proc. Int.* **1991**, *23*, 611−616.
(18) Representative articles on the first usages of *N*-[bis(methylthio)-methylene]glycine ester enolates for glycine anion reagents are as follows: (a) Hoppe, D. Chain-Extended and α-Branched α-Amino Acids by Alkylation of Metalated α-[Bis(methylthio)-methylene]amino Acid Esters. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 426−427. (b) Hoppe, D.; Beckmann, L. Metalated Nitrogen Derivatives of Carbonic Acid in Organic Synthesis. XIII. Selective Mono- and Dialkylation of *N*-[Bis(methylthio)-methylene]glycine Ester for Synthesis of Higher and α-Branched α-Amino Acids. *Liebigs Ann. Chem.* **1979**, 2066−2075.
(19) Alvarez-Ibarra, C.; Gil, M.; Ortiz, P.; Quiroga, M. L. An Efficient Synthesis of 5-Aryl- (or alkyl)amino-4-ethoxycarbonyl-2-methylthio-1,3-thiazoles from Dimethyl *N*-(Ethoxycarbonylmethyl)-iminodithiocarbonate and Isothiocyanates. *Heterocycles* **1988**, *27*, 2177−2183.
(20) Hermecz, Y.; Mèszáros, Z.; Vasvari-Debreczy, L.; Horváth, G.; Ponger-Csákvar, M. Nitrogen Bridgedhead Compounds. Part 4. 1-3-N-C-Acyl Migration. *J. Chem. Soc., Perkin Trans. 1* **1977**, 789−795.
(21) Taporewala, Y. B. Thiazolo[5,4-*b*]acridines and thiazolo[4,5-*b*]acridines: Probable Pharmacophores of Antiviral and Anti-tumor Marine Alkaloids. *Tetrahedron Lett.* **1991**, *32*, 39−42.
(22) Kaufman, J. M.; Taporewala, Y. B. Synthesis of *p*-Nitrophenyl Ester of Acridine-2-acetic Acid. *J. Heterocycl. Chem.* **1982**, *19*, 1557−1559.
(23) Laughead, D. G. Synthesis of Des-*N*-methylacronycine and Acronycine. *J. Org. Chem.* **1990**, *55*, 2245−2246.
(24) Leysen, D. C.; Haemers, A.; Bollaert, W. Thiazolopyridine Analogs of Nalidixic Acid. 2. Thiazolo[4,5-*b*]pyridines. *J. Heterocycl. Chem.* **1984**, *21*, 1361−1366.
(25) (a) Madesclaire, M. Synthesis of sulfoxides by oxidation of thioethers. *Tetrahedron* **1986**, *42*, 5459−5495. (b) Bourdais, J.; Abenhain, D.; Saborault, B.; Lorre, A. Polycyclic Thiazoles. I. Anionic Nucleophilic Substitution on 2-methylsulfonyl derivatives of thiazolo[5,4-*b*]pyridine and Benzothiazoles. *J. Heterocycl. Chem.* **1976**, *13*, 491−496.
(26) Cain, B. F.; Baguley, B. C.; Denny, W. A. Potential Antitumor Agents. 28. Deoxyribonucleic Acid Polyintercalating Agents. *J. Med. Chem.* **1978**, *21*, 658−668.
(27) (a) Barlin, G. B.; Brown, W. V. Useful Reactions of Nucleophiles with Some Methylsulphonyl Derivatives of Nitrogen Heterocycles. *J. Chem. Soc. C* **1967**, 2473−2476. (b) Brown, D. J.; Ford, P. W. Simple Pyrimidines. Part X. The Formation and Reactivity of 2-, 4-, and 5-Pyrimidinyl Sulphones and Sulphoxides. *J. Chem. Soc. C* **1967**, 568−572. (c) Alvarez-Ibarra, C.; Asperilla, R.; Dios-Corredor, C. de; Martínez-Santos, E.; Quiroga, M. L. A New Synthetic Approximation to Thiazoles with a Versatile Persubstitution and/or Perfunctionalization. *Heterocycles* **1991**, *32*, 2127−2137.
(28) (a) Price, C. C.; Boekelheide, V. A Synthesis of Substituted 4-Aminoquinolines. *J. Am. Chem. Soc.* **1946**, *68*, 1246−1250. (b) Goodall, R.; Kermack, W. O. Attempts to Find New Antimalarials. Part XV. The Synthesis of Acridine Compounds Related to Atebrin. *J. Chem. Soc.* **1936**, 1546−1550. (c) Noguchi, I.; MacLean, D. B. Synthesis of (±)-Cularicine. *Can. J. Chem.* **1975**, *53*, 125−130.
(29) Olah, G. A. *Friedel-Crafts Chemistry*; John Wiley: New York, 1973; Vol. 1, pp 216−217, 272−273, 312−316 and references cited herein.
(30) Vogel, A. I. *Practical Organic Chemsitry*, 3rd ed.; Longmans: London, 1962, pp 179−180.
(31) Alvarez-Ibarra, C.; Fernández-Granda, R.; Quiroga, M. L.; Pingarrón, J. M.; Pedrero, M. Determination of the pK_a Values for Polycationic Species Derived from 9-Hydroxy- and 9-Aminothiazolo[5,4-*b*]quinolines. A Problem Related to the Tautomerism of these Systems. *Tetrahedron* **1996**, *52*, 11929−11946.
(32) Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. *Tables of Spectral Data for Structural Determination of Organic Compounds*, 2nd ed.; Springer Verlag: Berlin, 1989.
(33) For induced chemical shifts for a methyl group and a fluorine atom in a benzene ring, see ref 32.
(34) The correlation coefficient for the linear regression between observed and calculated chemical shifts was 0.959 (30 data points).
(35) Hydrogens H-7 and H-6 for compounds **8** and **10** appeared as a doublet of doublet of doublets (ddd), hydrogens H-5 (compound **10**) and H-8 (compounds **8** and **10**) appeared as a doublet of doublets (dd), hydrogens H-6 and H-5 for compound **9** appeared as a doublet, and the signal of H-8 for compound **9** was a broad singlet.
(36) The protonic decoupling causes an increase of signals for hydrogenated carbons as a consequence of the NOE effect.[37]
(37) Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*, 3rd ed.; Verlag Chemie: Weinheim, 1987; p 46.
(38) See ref 32, p 74.
(39) The correlation coefficient for the linear regression between observed and calculated chemical shifts was 0.989 (60 data points).
(40) (a) Garnier, R.; Faure, R.; Babadjamian, A.; Vicent, E. J. Carbon-13 Chemical Shifts and J_{C-H} coupling constants of Alkylthiazoles. *Bull. Soc. Chim. Fr.* **1972**, 1040−1041. (b) Faure, R.; Llinas, J. R.; Vicent, E. J.; Rajzmann, M. Experimental and Theoretical Studies of the Carbon-13 Chemical Shifts in a Series of Isothiazoles. *Can. J. Chem.* **1975**, *53*, 1677−1681.
(41) Bergental, D.; Mester, Y.; Rosza, Z. S.; Reisch, J. Studies in the Field of natural Product Chemistry. Part 63. Carbon-13 NMR Spectra of Acridone Alkaloids. *Phytochemistry* **1979**, *18*, 161−163.
(42) Anet, F. L.; Yavari, I. Carbon-13 Nuclear Magnetic Resonance of Pyridine N-Oxide. *J. Org. Chem.* **1976**, *41*, 3589−3591.
(43) (a) Dewar, M. J. S.; Thiel, W. Ground States of Molecules. 38. Method Approximations and Parameters. *J. Am. Chem. Soc.* **1977**, *99*, 4899−4907. (b) Dewar, M. J. S.; Thiel, W. Ground States of Molecules. 39. MNDO Results for Molecules Containing Hydrogen, Carbon, Nitrogen, and Oxygen. *J. Am. Chem. Soc.* **1977**, *99*, 4907−4917. (c) Dewar, M. J. S.; McKee, M. L. Ground States of Molecules. 56. MNDO Calculations for Molecules Containing Sulfur. *J. Comput. Chem.* **1983**, *4*, 84−103.
(44) (a) van der Plas, H. C.; Wozniak, M.; van der Haak, H. J. W. Reactivity of Naphthyridines toward Nitrogen Nucleophiles. *Adv. Heterocycl. Chem.* **1983**, *33*, 95. (b) Paudler, W. W.; Sheets, R. M. Recent Developments in Naphthyridine Chemistry. *Adv. Heterocycl. Chem.* **1983**, *33*, 147. (c) Levy, G. C.; Lichter, R. L.; Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance Spectroscopy*; John Wiley: New York, 1981; p 125.
(45) Results have been quoted as IC_{50} values in μM units. IC_{50} values stand for the concentration of sample which inhibits 50% of normal cell culture growth in the exponential phase.
(46) Fig. P and P.Fit. Fig. P Software Corp., Cambridge, U.K., version 6.0a, 1991.
(47) Two exceptions to this relationship can be considered as follows: compare $IC_{50} = 3.2$ μM of **6b** to $IC_{50} = 5.0$ μM of **6c** (for HT-29 cell line) and $IC_{50} = 5.3$ μM of **18a** to $IC_{50} = 7.4$ μM of **18c** (for P-388 cell line).
(48) IC_{50} data (μM) against lymphoid neoplasm P-388 cell line in culture have been used as comparative results.
(49) (a) Gunawardana, G. P.; Kohmoto, S.; Gunasekera, S. P.; McConnell, O. J.; Koehn, F. E. Dercitin, a New Biologically Active Acridine Alkaloid from a Deep Water Marine Sponge, *Dercitus sp. J. Am. Chem. Soc.* **1988**, *110*, 4856−4858. (b) Gunawardana, G. P.; Kohmoto, S.; Burres, N. S. New Cytotoxic Acridine Alkaloids from Two Deep Water Marine Sponges of the *Family Pachas trellidae. Tetrahedron Lett.* **1989**, *30*, 4359−4362.
(50) Gunawardana *et al.* have reported two different IC_{50} values for dercitin (**26**): 0.08 μM (ref 49b) and 0.14 μM (ref 49a).
(51) Eisenstat, M. A.; Kuo, G.-H.; Weaver, J. D., III; Wentland, M. P.; Robinson, R. G.; Klingbeil, K. M.; Danz, D. W.; Corbett, T. H.; Couglin, S. A. 3-Benzylquinolones: Novel, Potent Inhibitors of Mammalian Topoisomerase II. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1021−1026.
(52) Wentland, M. P.; Aldous, S. C.; Gruett, M. D.; Perni, R. B.; Powles, R. G.; Danz, D. W.; Klingbeil, K. M.; Peverly, A. D.; Robinson, R. G.; Corbett, T. H.; Rake, J. B.; Coughlin, S. A. The Antitumor Activity of Novel Pyrazoloquinoline Derivatives. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 405−410.
(53) (a) Meyer, R. Thiazole and Its Derivatives. In *The Chemistry of Heterocyclic Compounds*; Metzger, J. V., Ed.; Wiley: New York, 1979; Part 1, Vol. *34*, pp 519−531. (b) Erlenmeyer, H.; Junod, J.; Guex, W.; Erne, M. Thiazole Carboxylic Acids. *Helv. Chim. Acta* **1948**, *31*, 1342−1349.
(54) Bergeron, R. J.; Cavanaugh, P. F., Jr.; Kline, S. J.; Hughes, R. G., Jr.; Elliot, G. T.; Porter, C. W. Antineoplastic and Antiherpetic Activity of Spermidine Cathecholamide Iron Chelators. *Biochem. Biophys. Res. Commun.* **1984**, *21*, 848−854.

JM960556Q