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Heterocyclic Quinones. XVI.[1] Pharmacomodulation in the Series of 11*H*-Indolo[3,2-*c*]quinolinediones: Synthesis, Cytotoxicity and Antitumor Activity of 3-Substituted 11*H*-Pyrido[3′,4′:4,5]pyrrolo[3,2-*c*]quinoline-1,4-diones

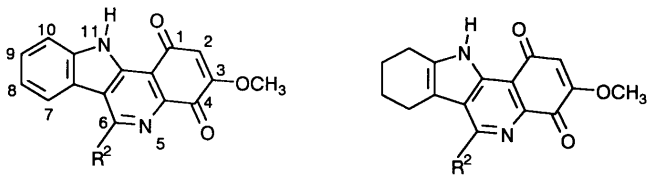
Phillippe HELISSEY,[a] Sylviane GIORGI-RENAULT,[a] Jean RENAULT,*[,a] and Suzanne CROS[b]

Laboratoire de Recherche sur les Hétérocycles azotés, Département de Chimie Organique, Faculté des Sciences Pharmaceutiques et Biologiques de l'Université René Descartes,[a] 4, avenue de l'Observatoire 75270 Paris Cédex 06, France and Laboratoire de Pharmacologie et de Toxicologie Fondamentales du CNRS,[b] 31400 Toulouse, France. *Received February 20, 1989*

With the aim of obtaining new antitumor drugs more active than previously described 11*H*-indolo[3,2-*c*]quinoline-1,4-diones and 7,8,9,10-tetrahydro-11*H*-indolo[3,2-*c*]quinoline-1,4-diones, the synthesis and activities of a series of 3-substituted 11*H*-pyrido[3′,4′:4,5]pyrrolo[3,2-*c*]quinoline-1,4-diones and of 7,8,9,10-tetrahydro-11*H*-pyrido-[3′,4′:4,5]pyrrolo[3,2-*c*]quinoline-1,4-diones were studied. Some quinones were more cytotoxic *in vitro* towards L1210 leukemia cells but were not active *in vivo* towards murine P388 leukemia.

Keywords antitumor activity; cytotoxicity; Fremy's salt; L1210 leukemia cell; 11*H*-pyrido[3′,4′:4,5]pyrrolo[3,2-*c*]quinoline-1,4-dione; heterocyclic quinone; 7,8,9,10-tetrahydro-11*H*-pyrido[3′,4′:4,5]pyrrolo[3,2-*c*]quinoline-1,4-dione

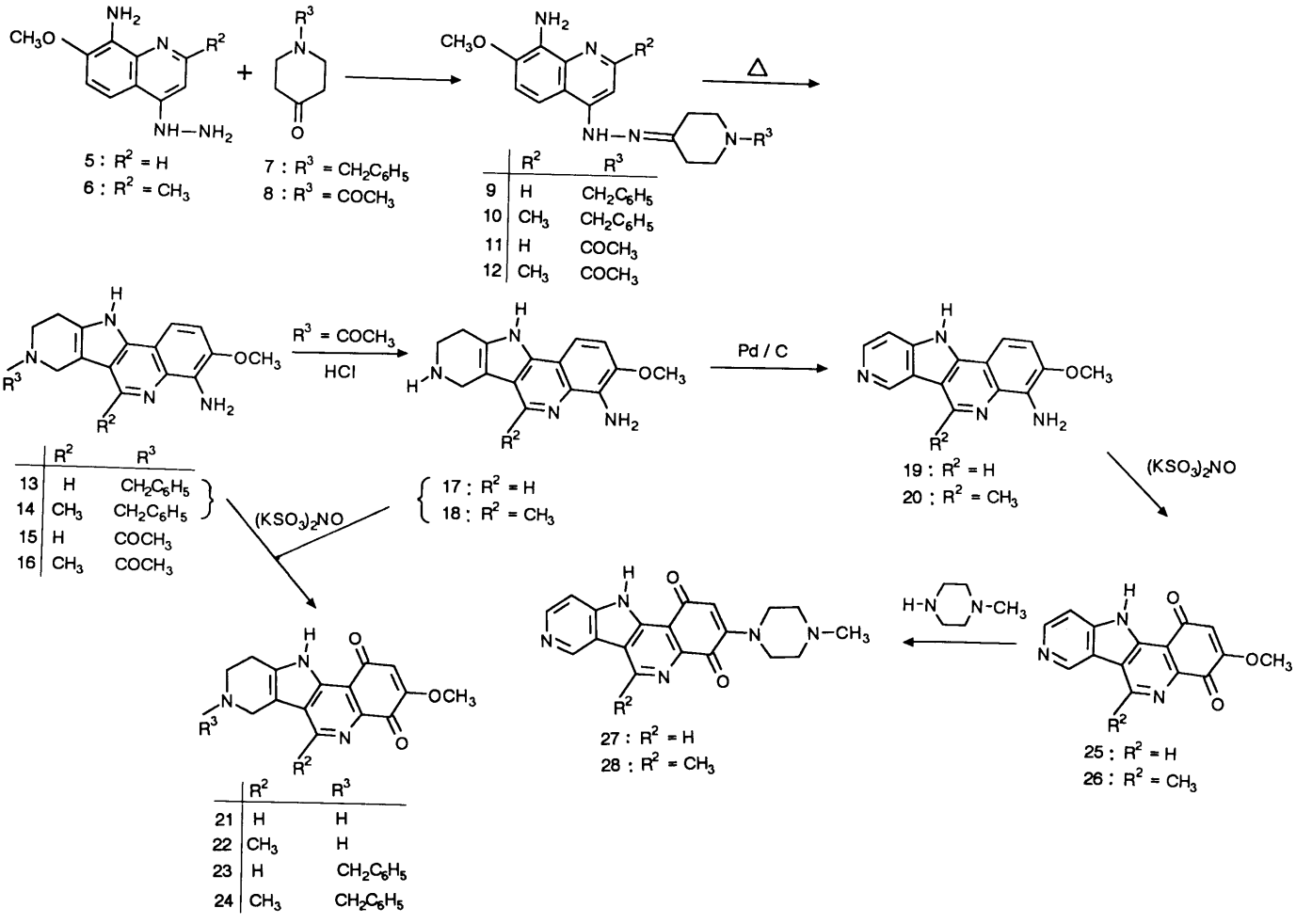
In our previous papers, we have described the synthesis of 3-methoxy-11*H*-indolo[3,2-*c*]quinoline-1,4-diones (**1** and **2**), and of their 7,8,9,10-tetrahydro derivatives (**3** and **4**), which were found to be cytotoxic towards L1210 leukemia cells.[2,3] Replacement of an aromatic CH by an intracyclic nitrogen atom has been used in pharmacomodulation by Rivalle *et al.* to obtain very active antitumor drugs.[4-9] Thus, with the aim of enhancing the biological



1: $R^2 = H$
2: $R^2 = CH_3$

3: $R^2 = H$
4: $R^2 = CH_3$

Chart 1



	R^2	R^3
9	H	$CH_2C_6H_5$
10	CH_3	$CH_2C_6H_5$
11	H	$COCH_3$
12	CH_3	$COCH_3$

	R^2	R^3
13	H	$CH_2C_6H_5$
14	CH_3	$CH_2C_6H_5$
15	H	$COCH_3$
16	CH_3	$COCH_3$

	R^2	R^3
21	H	H
22	CH_3	H
23	H	$CH_2C_6H_5$
24	CH_3	$CH_2C_6H_5$

Chart 2

activity, we synthesized the 11*H*-pyrido[3′,4′:4,5]pyrrolo-[3,2-*c*]quinoline-1,4-diones (**25**) and (**26**) and their 7,8,9,10-tetrahydro derivatives (**21**—**24**) (Chart 2).

Synthesis The quinones **21**—**26** were synthesized according to the method previously described for preparing the quinones **1**—**4**.[2,3] Because of the instability of the methoxy *p*-quinone group, the quinonic function was introduced in the last step of the synthesis by specific oxidation of the *o*-methoxyarylamine **13**, **14**, **17**—**20** using potassium nitrosodisulfonate (Fremy's salt).[10] The indolic nucleus was introduced according to Fisher's method *via* the tetrahydroindolic derivative which was catalytically dehydrogenated.

In the first attempt, the 1-benzyl-4-piperidone (**7**) was condensed with the 4-hydrazinoquinoline (**5** or **6**) to give the hydrazones **9** and **10**. Their cyclization by refluxing in diethylene glycol produced the benzylated compounds **13** and **14** in poor yield (35—38%). In the ellipticine series, it is well known that the annelated *N*-benzylpiperidines are readily aromatized on heating in decalin in the presence of palladium on charcoal.[11] Under these conditions, compounds **13** and **14** gave only tars.

Consequently, in the second attempt, we tried to aromatize the unbenzylated compounds **17** and **18**. Unfortunately, the debenzylation of the compounds **13** and **14** could not be achieved by hydrogenolysis using palladium on charcoal as a catalyst. Similar difficulties were found by Gouyette *et al.* in the debenzylation of the 2-benzyl-1,2,3,4-tetrahydro-6*H*-pyrido[4,3-*b*]carbazole.[11]

Finally, the amines **17** and **18** were obtained from the 1-acetyl-4-piperidone (**8**) according to the above reactions. The 1-acetylaminopyridopyrrolo[3,2-*c*]quinolines (**15** and **16**) were obtained in good yields (68—80%) on heating of **11** and **12** with diethylene glycol for only 10 min. A longer warming afforded tars. By heating in an acid medium, **15** and **16** gave the deacetylated derivatives **17** and **18**, which were aromatized to give the amines **19** and **20** in 59 and 51% yields, respectively, by refluxing in decalin in the presence of palladium on charcoal.

The amines **19** and **20** were oxidized into the quinones **25** and **26**, respectively, using Fremy's salt. Because of the presence of the tetrahydropyridinic nucleus which is more hydrophilic and more basic than the pyridinic nucleus and could facilitate binding to deoxyribonucleic acid (DNA)-phosphate groups, we were interested in the preparation of the quinones **21**—**24** from the amines **13**,**14**,**17** and **18**. Unfortunately, the quinones **21**—**24** were not water-soluble even as the hydrochlorides.

Because of the vinylogous ester-like properties, the methoxy group in the quinonic nucleus could be replaced by nucleophilic agents such as *N*-methylpiperazine to give **27** and **28** from the methoxyquinones **25** and **26**, respectively. These quinones were also water-insoluble.

Pharmacology The *in vitro* cytotoxicity on L1210 leukemia cells was determined. L1210 leukemia cells adapted to stationary suspension culture were grown in nutrient RPMI 1640 medium supplemented with 20% heat-inactivated serum (Gibco), 2 mM L-glutamine, penicillin (200 U/ml) and streptomycin (50 μg/ml). In the experiments, the cells in log-phase growth were exposed continuously to increasing quantities of drugs. All the products were dissolved in water with dimethyl sulfoxide (DMSO) (1% final). After 48 h, the concentration needed to produce a 50% inhibition of growth relative to the control (IC_{50}) was determined by linear regression analysis. Probits of the percent cell growth inhibition were plotted as a function of the logarithm of doses. The data are shown in Table I. The cytotoxicity of the two amines, **19** and **20** as precursors of the quinones **25** and **26**, was also determined.

The *in vivo* antitumor activity was also determined. Among the most cytotoxic drugs ($IC_{50} < 1$ μM), **21**, **25**, **26** and **28** were tested on P388 leukemia. CDF1 female mice received by the i.p. route 10^6 cells on day 0, and treatment was given by the same route on day 1 only. Drugs were dissolved in water (**21**) or were suspended in 0.4% Klucel JF (Hercules Inc.) water solution (**25**, **26**, **28**). The animals were observed for body weight and survival on days 1 and 5 after tumor implantation. The deaths of mice were recorded

Table I. Cytotoxic Effects of the Quinones **1**—**4**, **21**—**28** and the Amines **19** and **20** on the Growth of L1210 Cells

Compound	IC_{50}[a]		Correlation coefficient[b]
	ng/ml	mM	
1[3]	244	0.863	0.98
2[2]	501	1.62	0.99
3[3]	567	2.01	0.98
4[2]	867	2.57	0.98
21	217	0.595	0.98
22	345	0.890	0.97
23	406	1.09	0.98
24	913	2.36	0.98
25	86	0.308	0.93
26	137	0.410	0.90
27	86	0.227	0.99
28	173	0.479	0.97
19	604	2.14	0.99
20	1831	6.09	0.96

a) IC_{50}: drug concentration that decreased the growth rate of the cells by 50% after 48 h of culture. *b*) Correlation coefficient of the linear regression (log-probit) from which IC_{50} was calculated.

Table II. Effect of Heterocyclic Quinones on P388 Lymphocytic Leukemia (i.p. Graft, i.p. Treatment on Day 1)

Compound	Dose per inject. (mg/kg)	Toxicity (survivors)[a]	Body weight change (g)[b]	Median survival time (d)	T/C[c] (%)
21	30	7/10	−3.7	14.5	127
	20	9/10	−1.1	12.0	105
	10	8/8	−0.3	11.7	103
25	200	10/10	−2.7	11.4	100
	150	9/9	−2.5	12.2	107
	100	10/10	−1.2	11.2	98
26	200	10/10	−3.0	9.9	87
	150	10/10	−2.7	11.0	96
	100	10/10	−2.0	11.0	96
28	200	8/8	−3.7	12.7	111
	150	10/10	−1.7	12.1	106
	100	10/10	−1.0	12.7	111
Untreated controls	—	0/20	+0.5	11.4	—

a) Toxicity was evaluated in terms of the number of mice alive on day 5. *b*) Average weight change of animals between day 1 and day 5 after tumor implantation. *c*) T/C%: T is the median survival time of treated mice and C the median survival time of the controls (significant when ≥ 125).

daily during 30 d. Antitumor activity was evaluated from the survival time of treated mice over that of control mice. Results were confirmed by a second experiment (Table II).

Results and Discussion

Cytotoxicity Replacing the 8-CH of the indoloquinoline-1,4-diones (**1**—**4**) by a nitrogen atom increased the cytotoxicity towards L1210 leukemia cells from three- to four-fold either when the nucleus is aromatic (compounds **1**, **25** and **2**, **26**) or when it is saturated (compounds **3**, **21** and **4**, **22**). On the contrary, when the 8-CH of the tetrahydroindoloquinolinediones was replaced by a benzylated nitrogen, the cytotoxicity was not improved: compounds **3**, **23** and **4**, **24**. Substitution of the methoxy group of pyridopyrrolo[3,2-*c*]quinoline-1,4 diones (**25** and **26**) by an *N*-methylpiperazinyl group to give the quinones **27** and **28** had no influence on the cytotoxicity. Except in the case of the quinone **25** which is as cytotoxic as the quinone **21**, aromatization of the 7,8,9,10-tetrahydro-11*H*-pyrido[3′,4′:4,5]pyrrolo[3,2-*c*]quinoline-1,4-diones afforded an increase in cytotoxicity. This increament was greater when the 8-N was substituted: compare **23** to **25**, **22** and **24** to **26**. In some cases (compounds **25**, **26** and **21**, **22**), the presence of a methyl group at the 6-position did not improve the cytotoxicity and in other cases, it was unfavorable (compounds **23**, **24** and **27**, **28**).

In conclusion, the quinones **21**, **22**, **25**—**28** ($IC_{50} < 1\ \mu M$) have high cytotoxic activity, while the amino compounds **19**, **20**, precursors of the quinones **25**, **26**, were inactive.

***In Vivo* Antitumor Activity** As a preliminary step, the maximum tolerated dose (MTD)—used to determine the antitumor assay concentrations—was measured for each drug, after a single i.p. injection into CDF1 female mice. Compound **21** is most toxic, MTD being approximately 20 mg/kg against 150 mg/kg for **28** and 200 mg/kg for **25** and **26**. None of the compounds showed significant antitumor activity on the P388 leukemia model. At 30 mg/kg, compound **21** gave a *T/C* of 127%, but at this dose 30% of mice died of toxicity between day 1 and day 5.

Considering the encouraging results obtained in the cytotoxicity assays, the *in vivo* results were inexplicable.

Experimental

All melting points were determined on a Maquenne apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin-Elmer 157 G spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured with a Bruker 270 MHz spectrometer with hexamethyldisilane $(Me_3Si)_2$ as an internal reference. DCI/NH_3 mass spectra (MS) were recorded on a Nermag R10-10C instrument. Thin layer chromatography (TLC) was carried out on Merck GF 254 silica gel plates.

4-Amino-8-substituted-3-methoxy-7,8,9,10-tetrahydro-11*H*-pyrido-[3′,4′:4,5]pyrrolo[3,2-*c*]quinoline (13—16). General Procedure A solution of **5** or **6** (10 mmol) and 1-benzyl-4-piperidone (**7**) or 1-acetyl-4-piperidone (**8**) (12.5 mmol) in EtOH (50 ml) was refluxed under N_2 for 2 h. EtOH was evaporated under reduced pressure. The oily hydrazones **9** and **10** were decanted. The solid hydrazones **11** and **12** were separated by filtration and washed with ligroin. The crude hydrazones were dissolved in diethylene glycol (50 ml) and refluxed for *n* min (TLC monitoring). After cooling, H_2O (200 ml) was added. The *N*-benzyl derivatives **13** and **14** were filtered off and washed with H_2O. The *N*-acetyl derivatives **15** and **16** were extracted with $CHCl_3$.

4-Amino-8-benzyl-3-methoxy-7,8,9,10-tetrahydro-11*H*-pyrido-[3′,4′:4,5]pyrrolo[3,2-*c*]quinoline (**13**), $n=30$: Compound **13** was recrystallized from benzene–ligroin: yield 1.26 g, 35%; mp 242 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.80 (4H, m, 9-CH_2 and 10-CH_2), 3.65, 3.70 (each 2H, 2s, 7-CH_2 and $C\underline{H}_2$-C_6H_5), 3.80 (3H, s, OCH_3), 5.20 (2H, NH_2), 7.30 (7H, m, C_6H_5, 1-H and 2-H), 8.65 (1H, s, 6-H), 11.80 (1H, s, NH). Accurate elemental analysis could not be obtained because **13** solvated variable quantities of solvents. $C_{22}H_{22}N_4O$. MS *m/z*: 359 [$(M+H)^+$].

4-Amino-8-benzyl-3-methoxy-6-methyl-7,8,9,10-tetrahydro-11*H*-pyrido[3′,4′:4,5]pyrrolo[3,2-*c*]quinoline (**14**), $n=30$: Compound **14** was recrystallized from benzene–ligroin: yield 1.42 g, 38%; mp 182 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.60 (3H, s, CH_3), 2.75 (4H, m, 9-CH_2 and 10-CH_2), 3.70 (2H, s, 7-CH_2 or $C\underline{H}_2$-C_6H_5), 3.80 (3H, s, OCH_3), 3.85 (2H, s, 7-CH_2 or $C\underline{H}_2$-C_6H_5), 5.05 (2H, NH_2), 7.3 (7H, m, C_6H_5, 1-H and 2-H), 11.70 (1H, s, NH). Accurate elemental analysis could not be obtained for the same reason as in the case of **13**. $C_{23}H_{24}N_4O$. MS *m/z*: 373 [$(M+H)^+$].

8-Acetyl-4-amino-3-methoxy-7,8,9,10-tetrahydro-11*H*-pyrido[3′,4′:4,5]-pyrrolo[3,2-*c*]quinoline (**15**) $n=10$: Compound **15** was recrystallized from EtOH–H_2O: yield 2.11 g 68%; mp 290 °C. IR (KBr): 1650 (ν C=O), 3220 (br), 3380 and 3500 (ν NH and ν NH_2) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.10 (3H, s, CH_3CO), 2.8, 2.9 (each 1H, m), 3.75, 4.75 (each 2H, m, 7-CH_2 or 9-CH_2 or 10-CH_2), 5.25 (2H, NH_2), 7.25 (1H, d, $J=9$ Hz, 2-H), 7.45 (1H, d, $J=9$ Hz, 1-H), 8.85 (1H, s, 6-H), 11.95 (1H, s, NH). *Anal.* Calcd for $C_{17}H_{18}N_4O_2$: C, 65.81; H, 5.81; N, 18.06. Found: C, 65.70; H, 5.79; N, 17.80.

8-Acetyl-4-amino-3-methoxy-6-methyl-7,8,9,10-tetrahydro-11*H*-pyrido-[3′,4′:4,5]pyrrolo[3,2-*c*]quinoline (**16**), $n=10$: Compound **16** was recrystallized from EtOH–H_2O: yield; 2.60 g, 80%, mp 297 °C. IR (KBr): 1630 (νC=O), 3260 (br), 3330 and 3420 (ν NH and ν NH_2) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.10 (3H, s, CH_3CO), 2.70 (3H, s, CH_3), 2.75, 2.90 (each 1H, m, 7-CH or 9-CH or 10-CH), 3.75, 4.90 (each 2H, m, 7-CH_2or 9-CH_2 or 10-CH_2), 3.85 (3H, s, OCH_3), 5.15 (2H, NH_2), 7.20 (1H, d, $J=9$ Hz, 2-H), 7.40 (1H, d, $J=9$ Hz, 1-H), 11.95 (1H, s, NH). *Anal.* Calcd for $C_{18}H_{20}N_4O_2$: C, 66.67; H. 6.17; N, 17.28. Found: C, 66.36; H, 6.17; N, 17.03.

4-Amino-3-methoxy-7,8,9,10-tetrahydro-11*H*-pyrido[3′,4′:4,5]pyrrolo-[3,2-*c*]quinoline (17) A solution of 15 (2.17 g, 7 mmol) in a mixture of HCl solution (6 ml, $d=1.19$) and H_2O (6 ml) was refluxed under N_2 for 10 h. After cooling to 5°C, the hydrochloride of **17** was filtered off, and stirred for 10 h in H_2O (50 ml) and NH_4OH (5 ml, $d=0.89$) to give the crude **17**, which was filtered off, washed with H_2O and recrystallized from EtOH–H_2O: yield 1.22 g, 65%; mp 174 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.80, 3.15 (each 2H, each m, 9-CH_2 and 10- CH_2), 3.85 (3H, s, OCH_3), 4.05 (2H, s, 7-CH_2), 5.20 (1H, NH), 7.25 (1H, d, $J=9$ Hz, 2-H), 7.45 (1H, d, $J=9$ Hz, 1-H), 8.75 (1H, s, 6-H), 11.95 (1H, s, NH). *Anal.* Calcd for $C_{15}H_{16}N_4O \cdot 11/4H_2O$: C, 61.96; H, 6.37; N, 19.27. Found: C, 61.98; H, 6.32; N, 18.93.

4-Amino-3-methoxy-6-methyl-7,8,9,10-tetrahydro-11*H*-pyrido[3′,4′:4,5]-pyrrolo[3,2-*c*]quinoline (18) Compound **18** was prepared from **16** (2.27 g, 7 mmol) in the same manner as used for **17** and then recrystallized from EtOH–H_2O: yield 1.40 g, 71%; mp 177 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.70 (5H, m, CH_3 and 9-CH_2 or 10-CH_2), 3.00 (2H, m, 9-CH_2 or 10-CH_2), 3.80 (3H, s, OCH_3), 4.05 (2H, s, 7-CH_2), 5.05 (2H, NH_2), 7.10 (1H, d, $J=9$ Hz, 2-H), 7.35 (1H, d, $J=9$ Hz, 1-H), 11.65 (1H, s, NH). *Anal.* Calcd for $C_{16}H_{18}N_4O \cdot 11/4H_2O$: C, 63.50; H, 6.73; N, 18.39. Found: C, 63.09; H, 6.50; N, 18.35.

4-Amino-3-methoxy-11*H*-pyrido[3′,4′:4,5]pyrrolo[3,2-*c*]quinoline (19) A suspension of **17** (1.07 g, 4 mmol) and 1 g of 10% palladium on actived charcoal (Engelhard) in decalin (30 ml) was refluxed under N_2 for 4 h, then allowed to cool. The solid was filtered off, and extracted with $CHCl_3$–MeOH (1 : 1). The extract was dried, treated with charcoal and evaporated under reduced pressure. The oily residue was triturated with ligroin and the solid was filtered off. It was recrystallized from EtOH–H_2O to give **19** (0.62 g, 59%), mp 186 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.90 (3H, s, OCH_3), 5.40 (2H, NH_2), 7.40 (1H, d, $J=9$ Hz, 2-H), 7.60 (1H, d, $J=5$ Hz, 10-H), 7.70 (1H, d, $J=9$ Hz, 1-H), 8.45 (1H, d, $J=5$ Hz, 9-H), 9.45 (2H, s, 6-H and 7-H), 12.80 (1H, s, NH). *Anal.* Calcd for $C_{15}H_{12}N_4O \cdot H_2O$: C, 63.83; H, 4.96; N, 19.86. Found: C, 63.46; H, 4.91; N, 19.96.

4-Amino-3-methoxy-6-methyl-11*H*-pyrido[3′,4′:4,5]pyrrolo[3,2-*c*]-quinoline (20) Compound **20** was prepared from **18** (1.13 g, 4 mmol) in the same manner as used for **19** and then recrystallized from EtOH–H_2O: yield, 0.57 g, 51%; mp 198—200 °C. ^{1}H-NMR (DMSO-d_6): δ: 3.05 (3H, s, CH_3), 3.90 (3H, s, OCH_3), 5.30 (2H, NH_2), 7.35 (2H, d, $J=$ 9 Hz, 2-H), 7.55 (1H, d, $J=5$ Hz, 10-H), 7.60 (1H, d, $J=9$ Hz, 1-H), 8.40 (1H, d, $J=5$ Hz, 9-H), 9.30 (1H, s, 7-H), 12.80 (1H, s, NH). *Anal.* Calcd for $C_{16}H_{14}N_4O \cdot 11/4\,H_2O$: C, 63.89; H, 5.49; N, 18.64. Found: C, 63.98; H, 5.33; N, 18.33.

3-Methoxy-7,8,9,10-tetrahydro-11*H*-pyrido[3′,4′:4,5]pyrrolo[3,2-*c*]-quinoline-1,4-diones (21—24) and 3-Methoxy-11*H*-pyrido[3′,4′:4,5]pyrro-lo[3,2-*c*]quinoline-1,4-diones (25—26). General Procedure A solution

of monobasic potassium phosphate (1.36 g, 10 mmol) in H_2O (40 ml) was added to a solution of amines **13**, **14**, **17**—**20** (2 mmol) in acetone–MeOH (1 : 1) (80 ml). Potassium nitrosodisulfonate (2.15 g, 8 mmol) was added over 10 min. The mixture was stirred for 5 h, then 2 M HCl solution (6 ml) was added and the resulting mixture was stirred for an additional 4h. Saturated $NaHCO_3$ solution was added until pH 7 was reached. The organic solvent was removed under reduced pressure, (for the quinones **23** and **24** the residue was extracted with CH_2Cl_2 then the organic layer was washed with H_2O and evaporated to dryness). The quinones **23** and **24** were purified by preparative TLC on 150F 254 Merck aluminium oxide plates with $CHCl_3$ as an eluant. The crude quinones **21**, **22**, **25**, **26** were filtered off and extracted with $CHCl_3$–MeOH (1 : 1). The organic layer was dried, treated with charcoal and evaporated under reduced pressure. The quinones **21** and **22** were isolated as hydrochlorides.

3-Methoxy-7,8,9,10-tetrahydro-11*H*-pyrido[3′,4′ : 4,5]pyrrolo[3,2-*c*]-quinoline-1,4-dione Hydrochloride (**21**·HCl): The product was recrystallized from MeOH to give orange crystals of **21**·HCl (0.134 g, 21%), mp 276°C. IR (KBr): 1645 and 1685 (ν C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.90, 3.15 (each 2H, each m, 9-CH_2 and 10-CH_2), 3.85 (3H, s, OCH_3), 4.10 (2H, s, 7-CH_2), 6.20 (1H, s, 2-H), 8.90 (1H, s, 6-H), 12.05 (1H, s, NH). *Anal.* Calcd for $C_{15}H_{13}N_3O_3 \cdot HCl \cdot 2\ 1/4H_2O$: C, 49.38; H, 5.21; N, 11.52. Found: C, 49.15; H, 5.02; N, 11.18.

3-Methoxy-6-methyl-7,8,9,10-tetrahydro-11*H*-pyrido[3′,4′ : 4,5]pyrrolo-[3,2-*c*]quinoline-1,4-dione Hydrochloride (**22**·HCl): The product was recrystallized from MeOH to give orange crystals of **22**·HCl (0.153 g, 23%), mp 253°C. IR (KBr): 1640 and 1690 (ν C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.65 (3H, s, CH_3), 2.75, 2.95 (each 2H, each m, 9-CH_2 and 10-CH_2), 3.80 (3H, s, OCH_3), 4.10 (2H, s, 7-CH_2), 6.15 (1H, s, 2-H), 11.80 (1H, s, NH). *Anal.* Calcd for $C_{16}H_{15}N_3O_3 \cdot HCl \cdot 3H_2O$: C, 49.55; H, 5.68; N, 10.84. Found: C, 49.59; H, 5.39; N, 10.65.

8-Benzyl-3-methoxy-7,8,9,10-tetrahydro-11*H*-pyrido[3′,4′ : 4,5]-pyrrolo[3,2-*c*]quinoline-1,4-dione (**23**): The product was recrystallized from MeOH: yield, 0.157 g, 21%; mp 297°C. IR (KBr): 1645 and 1685 (ν C=O), 3170 (ν NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6)δ: 2.75, 2.85 (each 2H, each m, 9-CH_2 and 10- CH_2), 3.60, 3.70 (each 2H, each m, 7-CH_2 and $C\underline{H}_2$-C_6H_5), 3.80 (3H, s, OCH_3), 6.20 (1H, s, 2-H), 7.30 (5H, m, C_6H_5), 8.80 (1H, s, 6-H), 11.95 (1H, s, NH). *Anal.* Calcd for $C_{22}H_{19}N_3O_3 \cdot 1/4\ H_2O$: C, 69.93; H, 5.17; N, 11.13. Found: C, 69.86; H, 5.07; N, 10.95.

8-Benzyl-3-methoxy-6-methyl-7,8,9,10-tetrahydro-11*H*-pyrido-[3′,4′ : 4,5]pyrrolo[3,2-*c*]quinoline-1,4-dione (**24**): The product was recrystallized from MeOH: yield, 0.194 g, 25%; mp 290°C. IR (KBr): 1690 (ν C=O), 3320 (ν NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.60 (3H, s, CH_3), 2.70, 2.80 (each 2H, each m, 9-CH_2 and 10-CH_2), 3.70 (2H, s, 7-CH_2 or $C\underline{H}_2$-C_6H_5), 3.80 (5H, s, OCH_3 and 7-CH_2 or $C\underline{H}_2$-C_6H_5), 6.15 (1H, s, 2-H), 7.30 (5H, m, C_6H_5), 11.85 (1H, s, NH). *Anal.* Calcd for $C_{23}H_{21}N_3O_3$: C, 71.32; H, 5.43; N, 10.85. Found: C, 71.17; H, 5.22; N, 10.81.

3-Methoxy-11*H*-pyrido[3′,4′ : 4,5]pyrrolo[3,2-*c*]quinoline-1,4-dione (**25**): Compound **25** was recrystallized from MeOH: yield, 0.173 g, 31%; mp 220—222°C. IR (KBr): 1645 and 1690 (ν C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6 and CF_3CO_2H) δ: 3.95 (3H, s, OCH_3), 6.45 (1H, s, 2-H), 8.25 (1H, d, J=5 Hz, 10-H), 8.90 (1H, d, J=5 Hz, 9-H), 9.95, 10.0 (each 1H, each s, 6-H and 7-H). *Anal.* Calcd for $C_{15}H_9N_3O_3 \cdot MeOH$: C, 61.73; H, 4.18; N, 13.50. Found: C, 61.72; H, 4.19; N, 13.16.

3-Methoxy-6-methyl-11*H*-pyrido[3′,4′ : 4,5]pyrrolo[3,2-*c*]quinoline-1,4-dione (**26**): Compound **26** was recrystallized from MeOH: yield, 0.164 g, 28%; mp 346°C. IR (KBr): 1690 (ν C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6 and CF_3CO_2H) δ: 2.65 (3H, s, CH_3), 3.95 (3H, s, OCH_3), 6.45 (1H, s, 2-H), 8.45 (1H, d, J=5 Hz, 10-H), 8.80 (1H, d, J=5 Hz, 9-H), 9.75 (1H, s, 6-H). *Anal.* Calcd for $C_{16}H_{11}N_3O_3 \cdot MeOH \cdot 1/2H_2O$: C, 61.08; H, 4.79; N, 12.57. Found: C, 61.10; H, 4.41; N, 12.58.

3-(4-Methyl-1-piperazino)-11*H*-pyrido[3′,4′ : 4,5]pyrrolo[3,2-*c*]-quinoline-1,4-dione (27) A suspension of **25** (0.098 g, 0.35 mmol) and of *N*-methylpiperazine (3 ml, 27 mmol) in anhydrous MeOH (3 ml) was stirred under N_2 for 90 h. The solid was filtered off and washed with ligroin. The quinone was purified by flash chromatography on silica gel (SiO_2 Lichroprep Si 60, Merck) using $CHCl_3$–MeOH (9 : 1) as an eluent: yield, 0.048 g, 39%; mp 281°C. IR (KBr): 1685 (ν C=O), 3300 (νNH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.20 (3H, s, CH_3N), 2.40 (4H, m, $N(CH_2\text{–}C\underline{H}_2)_2NCH_3$), 3.45 (4H, m, $N(C\underline{H}_2\text{–}CH_2)_2NCH_3$), 6.00 (1H, s, 2-H), 7.65 (1H, d, J=5 Hz, 10-H), 8.50 (1H, d, J=5 Hz, 9-H), 9.50, 9.60 (each 1H, each s, 6-H and 7-H), 12.55 (1H, s, NH). *Anal.* Calcd for $C_{19}H_{17}N_5O_2 \cdot MeOH$: C, 63.32; H. 5.54; N, 18.47. Found: C, 63.27; H, 5.24; N, 18.62.

6-Methyl-3-(4-methyl-1-piperazino)-11*H*-pyrido[3′,4′ : 4,5]pyrrolo[3,2-*c*]quinoline-1,4-dione (28) This quinone was prepared from **26** (0.103 g, 0.35 mmol) in the same manner as used for **27**: yield, 0.046 g, 36%; mp 267°C. IR (KBr): 1700 (ν C=O), 3330 (br) (ν NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.15 (3H, s, CH_3N), 2.40 (4H, m, $N(CH_2\text{-}C\underline{H}_2)_2NCH_3$), 3.00 (3H, s, 6-$CH_3$), 3.45 (4H, m, $N(C\underline{H}_2\text{-}CH_2)_2NCH_3$), 5.95 (1H, s, 2-H), 7.65 (1H, d, J=5 Hz, 10-H), 8.50 (1H, d, J=5 Hz, 9-H), 9.35 (1H, s, 7-H), 12.5 (1H, NH). *Anal.* Calcd for $C_{20}H_{19}N_5O_2 \cdot MeOH$: C, 64.13; H, 5.85; N, 17.81. Found: C, 64.52; H, 5.51; N, 17.53.

Pharmacology Growth inhibition of L1210 cells in culture and anti-tumor activity were examined according to the experimental protocol reported previously.[13]

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References

1) Part XV: S. Giorgi-Renault, P. Gebel-Servolles, P. Helissey, J. Renault, J. L. Bernier, J. P. Hénichart, and S. Cros, *J. Pharm, Sci.*, **78**, 267 (1989).
2) P. Helissey, H. Parrot-Lopez, J. Renault, and S. Cros, *Eur. J. Med. Chem.*, **22**, 277 (1987).
3) P. Helissey, H. Parrot-Lopez, J. Renault, and S. Cros, *Eur. J. Med. Chem.*, **22**, 366 (1987).
4) C. Rivalle, C. Ducrocq, and E. Bisagni, *J. Chem. Soc., Perkin Trans. 1*, **1979**, 138.
5) C. Ducrocq, E. Bisagni, C. Rivalle, and J. M. Lhoste, *J. Chem. Soc. Perkin Trans. 1*, **1979**, 142.
6) C. Rivalle, C. Ducrocq, J. M. Lhoste, and E. Rivalle, *J. Org. Chem.*, **45**, 2176 (1980).
7) R. Lidereau, J. C. Chermann, J. Gruest, L. Montagnier, C. Ducrocq, C. Rivalle, and E. Bisagni, *Bull. Cancer*, **67**, 1 (1980).
8) J. C. Chermann, J. Gruest, L. Montagnier, F. Wendling, P. Tambourin, M. Perrin, F. Pochon, C. Ducrocq, C. Rivalle, and E. Bisagni, *C. R. Acad. Sci., Ser. D*, **285**, 945 (1977).
9) M. Tourbez-Perrin, F. Rochon, C. Ducrocq, C. Rivalle, and E. Bisagni, *Bull. Cancer*, **67**, 9 (1980).
10) H. Zimmer, D. C. Lankin, and S. W. Horgan, *Chem. Rev.*, **71**, 229 (1971).
11) A. Gouyette, R. Reynaud, J. Sadet, M. Baillarge, C. Gansser, S. Cros, F. LeGoffic, J. LePecq, C. Paoletti, and C. Viel, *Eur. J. Med. Chem.*, **15**, 503 (1980).
12) J. Renault, S. Giorgi-Renault, M. Baron, P. Maillet, C. Paoletti, S. Cros, and E. Voisin, *J. Med. Chem.*, **26**, 1715 (1983).
13) S. Giorgi-Renault, J. Renault, M. Baron, P. Gebel-Servolles, J. Delic, S. Cros, and C. Paoletti, *Chem. Pharm. Bull.*, **36**, 3933 (1988).