Heterocyclic Quinones. XIV.[1] Pharmacomodulation in a Series of 11*H*-Indolo[3,2-*c*]quinolinediones: Synthesis and Cytotoxicity of 8-Substituted 11*H*-Indolo[3,2-*c*]quinoline-7,10-diones

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4-Chloro-8-methoxy-11*H*-indolo[3,2-*c*]quinoline could be obtained from 8-chloro-2,3-dihydro-1*H*-quinolin-4-one and 4-methoxyphenylhydrazine by applying Fischer's indole synthesis. Its nitration led to the 7-nitro derivative which was reduced to 7-amino-4-chloro-8-methoxy-11*H*-indolo[3,2-*c*]quinoline when Raney nickel was employed as a catalyst and to 7-amino-8-methoxy-11*H*-indolo[3,2-*c*]quinoline when palladium charcoal was used. Oxidation of the amines by potassium nitrosodisulfonate produced the corresponding 11*H*-indolo[3,2-*c*]quinoline-7,10-diones. Diplacement of the methoxy group by (*N*,*N*-diethylamino)ethylamine or by *N*-methylpiperazine afforded the 8-aminoquinones. The quinones unsubstituted at the 4-position were more cytotoxic than the previously described 2-methoxy-11*H*-indolo[3,2-*c*]-quinoline-1,4-diones.

Keywords cytotoxity; Fischer's indole synthesis; Fremy's salt; heterocyclic quinone; 11*H*-indolo[3,2-*c*]quinoline-7,10-dione

In a previous paper, we described the synthesis of 2-methoxy-11*H*-indolo[3,2-*c*]quinoline-1,4-diones **1** and their cytotoxicity to L 1210 leukemia cells.[2] In order to establish structure–activity relationships in the present study, we examined the synthesis and *in vitro* cytotoxicity to L 1210 leukemia cells of 8-methoxy-11*H*-indolo[3,2-*c*]quinoline-7,10-diones **7** ($R^8=OCH_3$) (Chart 2) and of some derivatives in which the quinonic function was introduced on the indole nucleus instead of the quinoline nucleus.

Some indoloquinones are antitumoral drugs. Kinamycin C (**2**), an indoloquinone annellated with two homocycles, has been claimed to exert antineoplastic effects.[3] Mitomycins such as mitomycin C (**3**), used in anticancer chemotherapy, are 2,3-dihydroindoloquinones condensed to a tetrahydropyrrole, itself annellated with an aziridine. Salts of 9-hydroxy-2-methylellipticinium (**4**) could be oxidized by a biomimetic system (H_2O_2 and peroxidase) into a powerfully electrophilic indoloquinonimine **5** which may be responsible for antitumoral activity.[4] On the other hand, methoxatine (**6**) could be considered as an *o*-indoloquinone annellated with a pyridine nucleus. The natural compound is a cofactor of bacterial dehydrogenases known as quino-

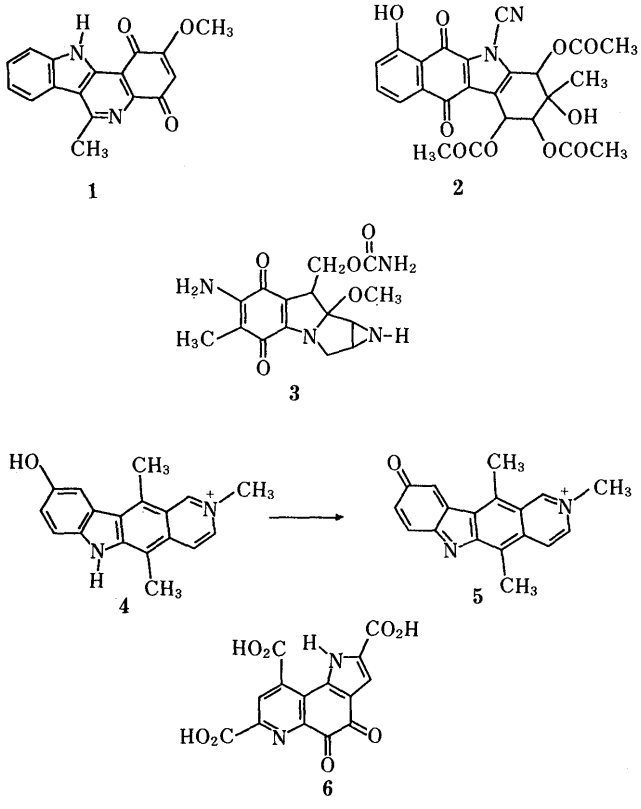


Chart 1

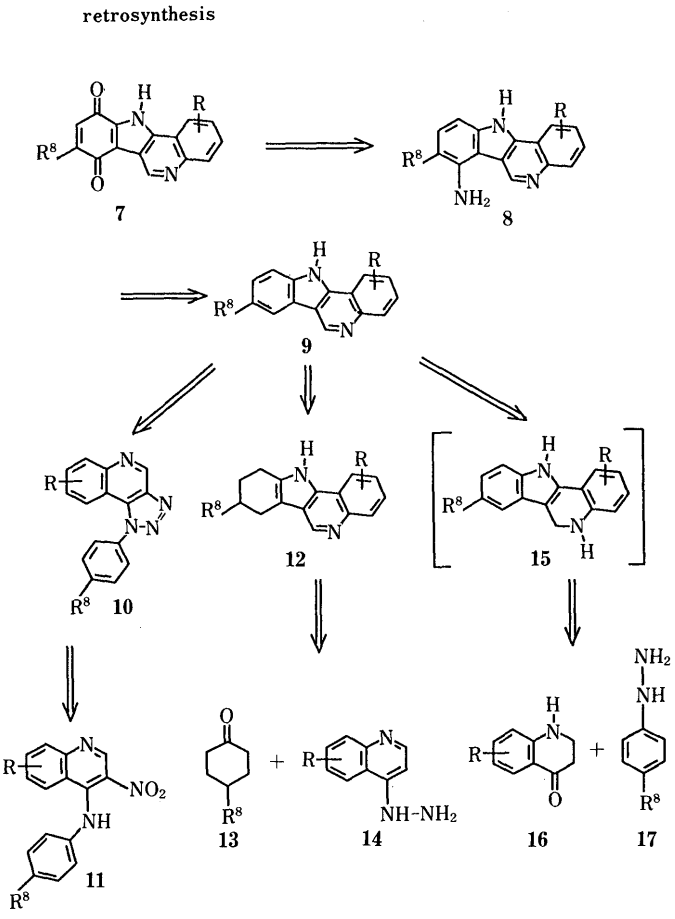


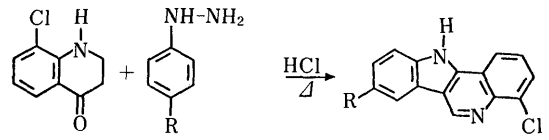
Chart 2

proteins[5] (Chart 1).

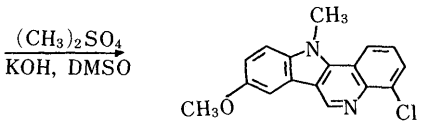
Synthesis Retrosynthesis of the quinone **7**, indicated in Chart 2, shows that it could be prepared by oxidation of 7-amino-11*H*-indolo[3,2-*c*]quinoline **8** which could itself be prepared from 11*H*-indolo[3,2-*c*]quinoline **9**.

Compound **9** could be obtained by several methods. We have rejected the Kermach and Storey method[6] which requires the two-step synthesis of the triazolo[4,5-*c*]-quinoline **10** from 4-arylamino-3-nitroquinoline **11**, itself obtained with difficulty by applying the method of Bachman *et al.*[7] We prefered to synthesize the indole nucleus according to Fischer's method. There were two possibilities. First, the hydrazone prepared from non-commercial cyclohexanone **13** and hydrazine **14** could be thermally cyclized according to Khan and da Rocha's method[8] to give 7,8,9,10-tetrahydro-11*H*-indolo[3,2-*c*]-quinoline **12** and then dehydrogenated with a catalyst. The second possibility involved Cross and Jones' method.[9] Phenylhydrazine **17** was condensed with 2,3-dihydro-1*H*-quinolin-4-one **16** into 5,6-dihydro-11*H*-indolo[3,2-*c*]quinoline **15** which was spontaneously oxidized by air. We chose the latter method, which is more straightforward and utilizes commercial grade phenylhydrazines.

In this reaction, we did not use the 2,3-dihydro-1*H*-quinolin-4-one **16**(R=H), obtained in a 47% yield,[10] but its 8-chloro derivative **18** obtained in an 80% yield.[11] The 4-methoxyphenylhydrazine (**19**) reacted with **18** to give the 4-chloro-8-methoxy-11*H*-indolo[3,2-*c*]quinoline (**21**) in 50% yield.



18 19 : R=OCH_3, 20 : R=CH_3 21 : R=OCH_3, 22 : R=CH_3

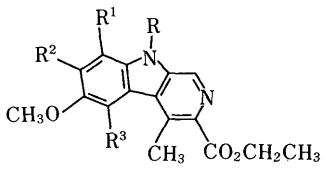


23

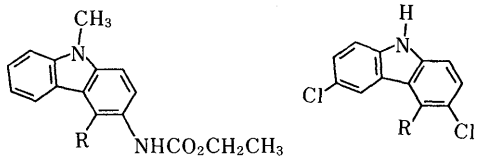
Chart 3

To examine the influence of the presence of an N-11 substituent on the biological activity, we prepared the methylated derivative **23** by reaction of dimethylsulfate with **21** in the presence of potassium hydroxide.

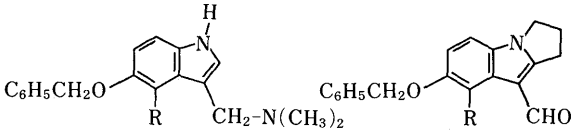
Synthesis of the 7-amino-4-chloro-8-methoxy-11*H*-indolo[3,2-*c*]quinolines **44** and **45** implied previous preparation of the nitro derivatives **37** and **38** (Chart 5). No electrophilic substitution has been described for compounds such as **21** or **23** except nitration of 3-methoxy-6-methyl-11*H*-indolo[3,2-*c*]quinoline.[12] For related heterocycles, nitration gives various results. With the 6-methoxy-9*H*-pyrido[3,4-*b*]indole **24**, nitration produces only the dinitro compound **25**.[13] On the other hand, when nitrogen is acetylated, compound **26** and two dinitro derivatives **25** and **27** are obtained with only a 10% yield of the mononitro derivative **28**.



24 : R=R^1=R^2=R^3=H
25 : R=R^1=H, R^2=R^3=NO_2
26 : R=$COCH_3$, R^1=R^2=R^3=H
27 : R=R^2=H, R^1=R^3=NO_2
28 : R=R^1=R^2=H, R^3=NO_2

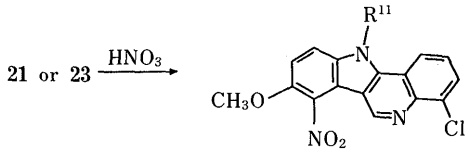


29 : R=H
30 : R=NO_2
31 : R=H
32 : R=NO_2



33 : R=H
34 : R=NO_2
35 : R=H
36 : R=NO_2

Chart 4



37 : R^{11}=H
38 : R^{11}=CH_3

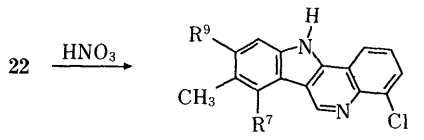
Chart 5

Nitration of the carbazole **29** takes place at the 4-position to give compound **30**,[14] just as that of the dichloro derivative **31** does to give **32**.[15] Nitration of indole has also been studied: 5-benzyloxygramine (**33**)[16] and 7-benzyloxy-2,3-dihydro-9-formylpyrrolo[1,2-*a*]indole (**35**)[17] gave the mononitro compounds **34** and **36**, respectively.

Reaction of 4-chloro-8-methoxy-11*H*-indolo[3,2-*c*]quinoline (**21**) or of its methylated derivative **23** with nitric acid in acetic medium afforded only the mononitro compounds **37** and **38**, respectively in 90% and 92% yields. The structures were established by proton nuclear magnetic resonance (^{1}H-NMR).

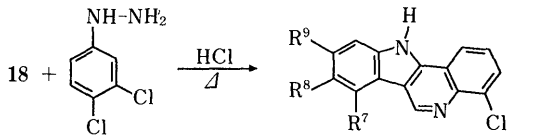
In order to prepare variously 8-substituted quinones, we needed to extend such nitration to indolo [3,2-*c*]quinolines substituted at the 8-position by groups other than a methoxy. Actually, the presence of substituents can modify the quinone redox potential and hence have an influence on the production of oxygen radicals which are responsible for the biological activity of our model,[2] streptonigrin, a natural quinolinedione.[18]

4-Chloro-8-methylindolo[3,2-*c*]quinoline (**22**) was obtained in a 40% yield from **18** and **20** (Chart 3). Nitration gave a 90% yield of a mixture of the two mononitro compounds **39** (67%) and **40** (25%) with 8% of an unidentified derivative (^{1}H-NMR titration). Recrystallization afforded a 92:8 mixture of **39** and **40** but in only a 27% yield. We therefore gave up preparing **39**.



39 : $R^7=NO_2$, $R^9=H$
40 : $R^7=H$, $R^9=NO_2$

Chart 6



42 : $R^7=R^8=Cl$, $R^9=H$
43 : $R^7=H$, $R^8=R^9=Cl$

Chart 7

We expected to solve the nitration problem by preparing 4,8,9-trichloro-11*H*-indolo[3,2-*c*]quinoline (**43**) which has an electron-withdrawing chlorine atom instead of an electron-donating methoxy group on the quinone moiety (Chart 7). We hoped that steric hindrance at the 2-position of **41** would lead to a regiospecific cyclization in the 6-position to afford **43**. Roussel *et al.*[19] and Marquez *et al.*[20] have shown such a specificity for the syntheses of 8,9-dimethyl-11*H*-indolo[3,2-*c*]quinoline and of 3-chloro-9-(*N*,*N*-dimethylamino)-8-methoxy-11*H*-indolo[3,2-*c*]-quinoline, respectively. Although a chlorine atom and a methyl group have identical steric hindrances,[21] in practice, a mixture of 4,7,8-trichloro and 4,8,9-trichloro-11*H*-indolo[3,2-*c*]quinolines (**42**) and (**43**) was obtained in a ratio of 41% to 59%. These could not be separated. Such a phenomenon has been pointed out in the case of Skraup's synthesis and could not be explained: the 3-methylaniline produced exclusively the 7-methylquinoline, whereas the 3-chloroaniline produced a mixture of the 5-chloro- and 7-chloroquinolines.[22]

When Raney nickel was employed as a catalyst, reduction of the nitro groups of **37** and **38** produced the 7-aminoindolo[3,2-*c*]quinolines **44** and **45** without breaking the C–Cl bond even in the presence of alkali. When palladium on charcoal was used, hydrogenolysis occurred to give the amines **46** and **47**.

The aminoindolo[3,2-*c*]quinolines **44**—**47** were stable when dry but unstable when in solution. Oxidation by potassium nitrosodisulfonate (Fremy's salt)[23] afforded the orange colored quinones **48**—**51** in approximately 30% yield.

In order to obtain quinones more hydrophilic than **44**—**47**, an amino function was introduced. The labile methoxy group of the vinylogous ester: $-C(-NH_2)=CH-C(=O)-OCH_3$ was replaced by amines to give the fine purple-colored aminoquinones **52**—**55**. The aminoquinones are more water-soluble than the methoxyquinones, when indolic nitrogen is not substituted. When it is methylated, they are less water-soluble.

TABLE I. Effect of 8-Substituted Indolo[3,2-*c*]quinoline-7,10-diones (**48**—**55**) and of Indolo[3,2-*c*]quinoline-7-amines (**44**, **46**, **47**) on the Growth of L1210 Cells

No.	IC_{50}[a]		Correlation coefficient
	ng/ml	μM	
1[2]	>10000	>33.2	—
48	4091	12.2	0.982
49	>2000	>5.8	—
50	723	2.44	0.99
51	486	1.66	0.969
52	818	2.26	9.993
53	525	1.40	0.990
54	487	1.41	0.996
55	586	1.63	0.977
44	6196	20.8	0.95
46	3313	11.1	0.99
47	834	2.87	0.99
Doxorubicin[b]	28	0.048	0.99

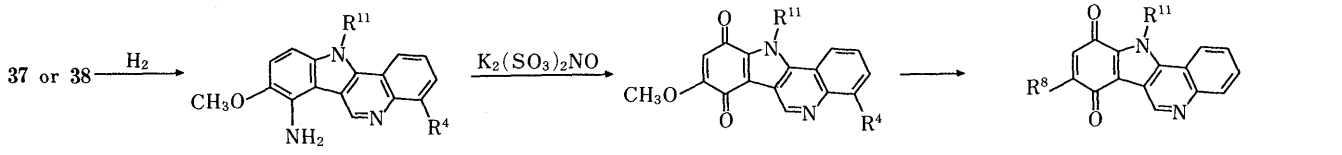
a) Drug concentration that decreased the growth rate of the cells by 50% after 48 h of culture. The rate was determined by least-squares plotting of the experimental data. *b*) Doxorubicin was used as a reference.

Pharmacology The *in vitro* cytotoxicity towards L 1210 leukemia cells was determined. The dose-effect relationships of the various compounds tested were evaluated from the regression line of the percent cell growth inhibition plotted as a function of the logarithm of the dose. From these curves, the dose of drug reducing the cell growth by 50% after 48 h as compared of the controls (IC_{50}) was estimated. Data for the cytotoxicity of the synthesized quinones are listed in Table I.

Discussion

A comparison between compounds **50** and **1** shows that the cytotoxicity was increased by the presence of the quinone group on the indole moiety. These quinones were therefore not very cytotoxic ($IC_{50}>1$ μM). The present results explain why no *in vitro* tests have been made. Indolic nitrogen methylation, affording compound **51**, did not improve the activity.

On the other hand, introduction of a chlorine atom at the 4-position was somewhat unfavorable, as seen in compounds **48** and **49**. Replacement of the methoxy group



44 : $R^4=Cl$, $R^{11}=H$
45 : $R^4=Cl$, $R^{11}=CH_3$
46 : $R^4=R^{11}=H$
47 : $R^4=H$, $R^{11}=CH_3$

48 : $R^4=Cl$, $R^{11}=H$
49 : $R^4=Cl$, $R^{11}=CH_3$
50 : $R^4=R^{11}=H$
51 : $R^4=H$, $R^{11}=CH_3$

52 : $R^8=NH(CH_2)_2N(CH_2CH_3)_2$, $R^{11}=H$
53 : $R^8=NH(CH_2)_2N(CH_2CH_3)_2$, $R^{11}=CH_3$
54 : $R^8=$ N-CH$_3$, $R^{11}=H$
55 : $R^8=$ N-CH$_3$, $R^{11}=CH_3$

Chart 8

either by an (*N*,*N*-diethylamino)ethylamino chain, to give compounds **52** and **53**, or by an *N*-methylpiperazinyl group, to give compounds **54**, or **55**, had no influence on the cytotoxicity.

In some cases, a comparison between the quinones and related aminoquinolines revealed the influence of the quinone function (compounds **48**, **44** and **50**, **46**). In another case, the quinone was no more active (compounds **51**, **47**).

Experimental

All melting points were determined on a Maquenne apparatus and are uncorrected Infrared (IR) spectra were obtained on a Perkin Elmer 157G spectrometer. ^{1}H-NMR spectra were measured with a Bruker 270 MHz spectrometer employing trimethylsilane $(Me_3Si)_2$ as an internal reference. Thin layer chromatography (TLC) was carried out on Merck GF 254 silica gel plates.

4-Chloro-8-methoxy-11*H*-indolo[3,2-*c*]quinoline (21) A suspension of 4-methoxy-phenylhydrazine hydrochloride (**19**) (2.01 g, 11.5 mmol) and 8-chloro-2,3-dihydro-1*H*-quinoline-4-one (**18**) (1.81 g, 10 mmol) in a mixture of EtOH (20 ml) and hydrochloric acid (5 ml, $d=1.18$) was boiled for 24 h. The solution was cooled to 5 °C, and the hydrochloride was filtered off, washed with ice-cooled EtOH, and then stirred for 12 h with H_2O (50 ml) and ammonia (6 ml, $d=0.89$). The precipitate was filtered off, washed with H_2O, and then purified by recrystallization from EtOH–H_2O to give **21** (1.42 g, 50%), mp 279 °C. IR (KBr): 3160 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.85 (3H, s, OCH_3), 7.10 (1H, dd, $J=9$, 2 Hz, 9-H), 7.60 (2H, m, 2-H and 10-H), 7.85 (2H, m, 3-H and 7-H), 8.50 (1H, dd, $J=8$, 2 Hz, 1-H), 9.60 (1H, s, 6-H), 12.65 (1H, NH). Protons were assigned by double irradiation.[12] *Anal.* Calcd for $C_{16}H_{11}ClN_2O$: C, 67.96; H, 3.89; N, 9.91. Found: C, 68.05; H, 3.92; N, 9.86.

4-Chloro-8-methyl-11*H*-indolo[3,2-*c*]quinoline (22) Compound **22** was prepared in the same manner as that used for **21** from tolylhydrazine hydrochloride (**20**) (1.82 g, 11.5 mmol) and recrystallized from EtOH–H_2O. Yield 1.07 g, 40%, mp 271 °C. IR (KBr): 3300 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.50 (3H, s, CH_3), 7.30 (1H, dd, $J=9$, 2 Hz, 9-H), 7.57 (1H, d, $J=9$ Hz, 10-H), 7.60 (1H, t, $J=8$ Hz, 2-H), 7.85 (1H, dd, $J=8$, 2 Hz, 3-H), 8.10 (1H, d, $J=2$ Hz, 7-H), 8.45 (1H, dd, $J=8$, 2 Hz, 1-H), 9.60 (1H, s, 6-H), 12.70 (1H, NH). *Anal.* Calcd for $C_{16}H_{11}ClN_2$: C, 70.05; H, 4.12; N, 10.5. Found: C, 69.88; H, 4.06; N, 9.82.

4,7,8-Trichloro-11*H*-indolo[3,2-*c*]quinoline (42) and 4,8,9-Trichloro-11*H*-indolo[3,2-*c*]quinoline (43) Reaction of **18** (1.81 g, 10 mmol) and 3,4-dichlorophenylhydrazine hydrochloride (2.45 g, 11.5 mmol) in the same manner as that used for **21** produced a mixture of **42** (41%) and **43** (59%). Titration was carrying out by ^{1}H-NMR by employing separated 7-H of **43** (s, 8.55), 6-H of **43** (s, 9.60) and 6-H of **42** (s, 9.75).

4-Chloro-8-methoxy-11-methylindolo[3,2-*c*]quinoline (23) A suspension of powdered potassium hydroxyde (1.68 g, 30 mmol) and indoloquinoline (**21**) (2.82 g, 10 mmol) in dry dimethyl sulfoxide (DMSO) (40 ml) was stirred at room temperature for 15 min. After cooling at 5 °C, dimethylsulfate (1.9 ml, 20 mmol) was added and the mixture was stirred for 5 h at 20 °C, and then pured onto ice. The precipitate was filtered off, washed with H_2O, and recrystallized from CH_3CN: Yield 2.29 g, 77%, mp 189—190 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.80 (3H, s, OCH_3), 4.45 (3H, s, NCH_3), 7.25 (1H, dd, $J=9$, 2 Hz, 9-H), 7.85 (1H, t, $J=8$ Hz, 2-H), 7.95 (1H, d, $J=9$ Hz, 10-H), 8.15 (1H, d, $J=2$ Hz, 7-H), 8.20 (1H, dd, $J=8$, 2 Hz, 3-H), 8.90 (1H, dd, $J=8$, 2 Hz, 1-H), 9.80 (1H, s, 6-H). *Anal.* Calcd for $C_{17}H_{13}ClN_2O$: C, 68.80; H, 4.39; N, 9.44. Found: C, 68.87; H, 4.32; N, 9.65.

4-Chloro-8-methoxy-7-nitro-11*H*-indolo[3,2-*c*]quinoline (37) Nitric acid (12 ml, $d=1.51$, 228 mmol) was slowly added at 30 °C to a stirred suspension of **21** (2.82 g, 10 mmol) in acetic acid (150 ml). The mixture was stirred for 3 h and then poured onto ice. Ammonia ($d=0.9$) was added until pH 7 was reached. The solid was separated by filtration, washed with H_2O, and recrystallized from dimethylformamide (DMF) to give **37** (2.95 g 90%), mp > 400 °C. IR (KBr): 1310, 1510 (NO_2), 3400 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.95 (3H, s, OCH_3), 7.40 (1H, d, $J=9$ Hz, 9-H), 7.65 (1H, t, $J=8$ Hz, 2-H), 7.90 (2H, m, 3-H and 10-H), 8.45 (1H, dd, $J=8$, 2 Hz, 1-H), 9.15 (1H, s, 6-H), 13.15 (1H, NH). *Anal.* Calcd for $C_{16}H_{10}ClN_3O_3$: C, 58.63; H, 3.05; N, 12.82. Found: C, 58.65; H, 3.23; N, 12.80.

4-Chloro-8-methoxyl-11-methyl-7-nitroindolo[3,2-*c*]quinoline (38) Compound **38** was prepared by a similar procedure to **37** with nitric acid (15 ml, $d=1.51$, 360 mmol), and acetic acid (100 ml), and then recrystallized from DMF. Yield 3.14 g, 92%, mp 297 °C. IR (KBr): 1360, 1520 (NO_2) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.95 (3H, s, OCH_3), 4.40 (3H, s, NCH_3), 7.60 (1H, d, $J=9$ Hz, 9-H), 7.75 (1H, t, $J=8$ Hz, 2-H), 7.95 (1H, dd, $J=8$, 2 Hz, 3-H), 8.20 (1H, d, $J=9$ Hz, 10-H), 8.75 (1H, dd, $J=8$, 2 Hz, 1-H), 9.10 (1H, s, 6-H). *Anal.* Calcd for $C_{17}H_{12}ClN_3O_3 \cdot 1/2\ H_2O$: C, 58.20; H, 3.71; N, 11.98. Found: C, 58.28; H, 3.67; N, 12.31.

4-Chloro-8-methyl-7-nitro-11*H*-indolo[3,2-*c*]quinoline (nitrate) (39·HNO_3) and 4-Chloro-8-methyl-9-nitro-11*H*-indolo[3,2-*c*]quinoline (nitrate) (40·HNO_3) Nitration of **22** under the same conditions as used for **37** but without ammoniacal treatment produced 67% of **39** and **25**% of **40** (^{1}H-NMR titration). Yield 90%. Recrystallization from MeOH gave a 92 : 8 mixture of **39** and **40** respectively.

39 (as nitrate): ^{1}H-NMR (DMSO-d_6) δ: 2.55 (3H, s, CH_3), 7.60 (1H, d, $J=9$ Hz, 9-H), 7.80 (1H, t, $J=8$ Hz, 2-H), 7.90 (1H, dd, $J=8$, 2 Hz, 3-H), 8.10 (1H, d, $J=9$ Hz, 10-H), 8.50 (1H, dd, $J=8$, 2 Hz, 1-H), 9.20 (1H, s, 6-H), 14.00 (1H, NH). $C_{16}H_{10}ClN_3O_2 \cdot HNO_3$.

40 (as nitrate): ^{1}H-NMR (DMSO-d_6) δ: 2.60 (3H, s, CH_3), 7.80 (1H, t, $J=8$ Hz, 2-H), 8.25 (1H, s, 7-H or 10-H), 8.40 (1H, s, 7-H or 10-H), 8.50 (1H, dd, $J=8$, 2 Hz, 1-H), 9.80 (1H, s, 6-H), 13.85 (1H, NH). $C_{16}H_{10}ClN_3O_2 \cdot HNO_3$.

7-Amino-8-methoxyindolo[3,2-*c*]quinoline (44—47). General Procedure Compounds **37** and **38** (2 mmol) in suspension in MeOH (100 ml) were hydrogenated with Raney nickel (2 g) (method A) or with 10% palladium on activated charcoal (0.8 g) in the presence of triethylamine (1.1 ml, 8 mmol) (method B) until the gas uptake ceased. After filtration to remove the catalyst, the mixture was treated with charcoal and evaporated under reduced pressure. The amines were recrystallized from MeOH–H_2O. They are stable in an N_2 atmosphere at 20 °C.

7-Amino-4-chloro-8-methoxy-11*H*-indolo[3,2-*c*]quinoline (**44**): Method A, yield 0.51 g, 85%, mp 288 °C. IR (KBr) 3360, 3420 (NH_2) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.80 (3H, s, OCH_3), 5.35 (2H, NH_2), 6.85 (1H, d, $J=9$ Hz, 9-H), 7.10 (1H, d, $J=9$ Hz, 10-H), 7.50 (1H, t, $J=8$ Hz, 2-H), 7.80 (1H, dd, $J=8$, 2 Hz, 3-H), 8.40 (1H, dd, $J=8$, 2 Hz, 1-H), 9.65 (1H, s, 6-H), 12.45 (1H, NH). *Anal.* Calcd for $C_{16}H_{12}ClN_3O \cdot 5/4H_2O$: C, 60.01; H, 4.53; N, 13.12. Found: C, 60.20; H, 4.18; N, 12.99.

7-Amino-4-chloro-8-methoxy-11-methylindolo[3,2-*c*]quinoline (**45**): Method A, yield 0.50 g 80%, mp 141 °C. IR (KBr): 3320, 3420 (NH_2) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.85 (3H, s, OCH_3), 4.30 (3H, s, NCH_3), 5.40 (2H, NH_2), 7.00 (1H, d, $J=9$ Hz, 9-H), 7.20 (1H, d, $J=9$ Hz, 10-H), 7.60 (1H, t, $J=8$ Hz, 2-H), 7.90 (1H, dd, $J=8$, 2 Hz, 3-H), 8.75 (1H, dd, $J=8$, 2 Hz, 1-H), 9.75 (1H, s, 6-H). *Anal.* Calcd for $C_{17}H_{14}ClN_3O \cdot 5/4H_2O$: C, 61.08; H, 4.94; N, 12.57. Found: C, 61.26; H, 4.82; N, 12.39.

7-Amino-8-methoxy-11*H*-indolo[3,2-*c*]quinoline (**46**): Method B, yield 0.375 g, 71%, mp 203—205 °C. IR (KBr): 3100—3400 (very broad) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.85 (3H, s, OCH_3), 5.55 (2H, NH_2), 7.00 (1H, d, $J=9$ Hz, 9-H), 7.20 (1H, d, $J=9$ Hz, 10-H), 7.75 (1H, m, 2-H), 7.85 (1H, m, 3-H), 8.20 (1H, dd, $J=8$, 2 Hz, 4-H), 8.60 (1H, dd, $J=8$, 2 Hz, 1-H), 9.80 (1H, s, 6-H), 13.30 (1H, NH). 2-H and 3-H were assigned by double irradiation. *Anal.* Calcd for $C_{16}H_{13}N_3O \cdot 2H_2O$: C, 64.21; H, 5.68; N, 14.05. Found: C, 64.31; H, 5.99; N, 14.25.

7-Amino-8-methoxy-11-methylindolo[3,2-*c*]quinoline (**47**): Method B, yield 0.28 g, 51%, mp 192 °C. IR (KBr): 3350, 3440 (NH_2) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.80 (3H, s, OCH_3), 4.25 (3H, s, NCH_3), 5.25 (2H, NH_2), 6.75 (1H, d, $J=9$ Hz, 9-H), 7.15 (1H, d, $J=9$ Hz, 10-H), 7.50 (1H, m, 2-H), 7.65 (1H, m, 3-H), 8.10 (1H, dd, $J=8$, 2 Hz, 4-H), 8.70 (1H, dd, $J=8$, 2 Hz, 1-H), 9.60 (1H, s, 6-H). 2-H and 3-H were assigned by double irradiation. *Anal.* Calcd for $C_{17}H_{15}N_3O \cdot 3/4\ H_2O$: C, 70.22; H, 5.68; N, 14.46. Found: C, 70.09; H, 5.50; N, 14.32.

8-Methoxyindolo[3,2-*c*]quinoline-7,10-diones (48—51). General Procedure A solution of monobasic potassium phosphate (680 mg, 5 mmol) in H_2O (20 ml) was added to a suspension of crude amine (**44—47**) (1 mmol) in a 1 : 1 mixture of MeOH–acetone (40 ml). Potassium nitrosodisulfonate (1.07 g, 4 mmol) was added over 15 min at room temperature. The mixture was stirred for 5 h. A 2 M HCl solution (6 ml) was added for hydrolysis of the intermediary quinonimine and the whole mixture was stirred for an additional 3 h. $NaHCO_3$ saturated solution was added to reach pH 7. The precipitate was filtered off and extracted with 1 : 1 MeOH–$CHCl_3$. The organic layer was dried on Na_2SO_4 and treated with charcoal, and the solvent was removed under reduced pressure. The residue was recrystallized from MeOH–$CHCl_3$ to give the orange-colored quinone.

4-Chloro-8-methoxy-11*H*-indolo[3,2-*c*]quinoline-7,10-dione (**48**): Yield 0.088 g, 28%, mp 369 °C. IR (KBr): 1650, 1680 (C=O), 3120 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.85 (3H, s, OCH_3), 6.05 (1H, s, 9-H), 7.60 (1H, t, $J=8$ Hz, 2-H), 7.85 (1H, dd, $J=8$, 2 Hz, 3-H), 8.60 (1H, dd, $J=8$, 2

Hz, 1-H), 9.45 (1H, s, 6-H), 13.10 (1H, NH). *Anal.* Calcd for $C_{16}H_9ClN_2O_3 \cdot 5/4H_2O$: C, 57.31; H, 3.43; N, 8.36. Found: C, 57.14; H, 3.17; N, 8.41.

4-Chloro-8-methoxy-11-methylindolo[3,2-*c*]quinoline-7,10-dione (**49**): Yield 0.11 g, 34%, mp 330 °C. IR (KBr): 1645, 1670 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.80 (3H, s, OCH_3), 4.60 (3H, s, NCH_3), 6.00 (1H, s, 9-H), 7.65 (1H, t, J=8 Hz, 2-H), 7.95 (1H, dd, J=8, 2 Hz, 3-H), 8.60 (1H, dd, J=8, 2 Hz, 1-H), 9.50 (1H, s, 6-H). *Anal.* Calcd for $C_{17}H_{11}ClN_2O_3 \cdot H_2O$: C, 59.22; H, 3.77; N, 8.13. Found: C, 59.41; H, 3.73; N, 8.18.

8-Methoxy-11*H*-indolo[3,2-*c*]quinoline-7,10-dione (**50**): Yield 0.095 g, 34%, mp 329 °C. IR (KBr): 1670 (C=O), 3060, 3540 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.80 (3H, s, OCH_3), 6.00 (1H, s, 9-H), 7.65 (1H, m, 2-H), 7.70 (1H, m, 3-H), 8.05 (1H, dd, J=8, 2 Hz, 4-H), 8.60 (1H, dd, J=8, 2 Hz, 1-H), 9.35 (1H, s, 6-H), 13.20 (1H, NH). 2-H and 3-H were assigned by double irradiation. *Anal.* Calcd for $C_{16}H_{10}N_2O_3 \cdot H_2O$: C, 64.86; H, 4.05; N, 9.46. Found: C, 64.99; H, 3.78; N, 9.79.

8-Methoxy-11-methylindolo[3,2-*c*]quinoline-7,10-dione (**51**): Yield 0.11 g, 38%, mp 321 °C. IR (KBr): 1640, 1665 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6, CF_3CO_2H) δ: 3.90 (3H, s, OCH_3), 4.75 (3H, s, NCH_3), 6.15 (1H, s, 9-H), 8.00 (2H, m, 2-H and 3-H), 8.40 (1H, dd, J=8, 2 Hz, 4-H), 8.90 (1H, dd, J=8, 2 Hz, 1-H), 9.90 (1H, s, 6-H). *Anal.* Calcd for $C_{17}H_{12}N_2O_3$: C, 69.85; H, 4.11; N, 9.60. Found: C, 69.69; H, 4.10; N, 9.61.

8-Aminoindolo[3,2-*c*]quinoline-7,10-diones (52—55). General Procedure A suspension of quinone (**50**, **51**) (0.5 mmol) in MeOH (5 ml) and *N*,*N*-diethylethylenediamine (2.5 mmol) or *N*-methylpiperazine (50 mmol) was stirred under an N_2 atmosphere for 72 h at 20 °C. The precipitate was filtered off and washed with ligroin.

8-[2-(*N*,*N*-Diethylamino)ethylamino]-11*H*-indolo[3,2-*c*]quinoline-7,10-dione (**52**): Violet crystals, yield 0.053 g, 29%, mp 303 °C (MeOH–$CHCl_3$). IR (KBr): 1680 (C=O), 3160 (11-NH), 3310 (8-NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.95 (6H, t, J=8 Hz, $N(CH_2\underline{CH_3})_2$), 2.50 (4H, m, $N(\underline{CH_2}CH_3)_2$), 2.60 (2H, t, J=8 Hz, $NCH_2\underline{CH_2}NEt_2$), 3.20 (2H, m, $NCH_2\underline{CH_2}NEt_2$), 5.30 (1H, s, 9-H), 7.40 (1H, t, J=8 Hz, 8-NH), 7.65 (2H, m, 2-H and 3-H), 8.05 (1H, dd, J=8, 2 Hz, 4-H), 8.65 (1H, dd, J=8, 2 Hz, 1-H), 9.35 (1H, s, 6-H), 13.20 (1H, 11-NH). *Anal.* Calcd for $C_{21}H_{22}N_4O_2 \cdot 1/2H_2O$: C, 67.92; H, 6.20; N, 15.09. Found: C, 68.09; H, 6.20; H, 14.84.

8-[(2-*N*,*N*-Diethylamino)ethylamino]-11-methylindolo[3,2-*c*]quinoline-7,10-dione (**53**): Violet crystals; yield 0.062 g, 33%, mp 202 °C (DMF). IR (KBr): 1665 (C=O), 3330 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6, CF_3CO_2H) δ: 1.20 (6H, t, J=8 Hz, $N(CH_2\underline{CH_3})_2$), 3.20 (4H, m, $N(\underline{CH_2}CH_3)_2$), 3.35 (2H, m, $NCH_2\underline{CH_2}NEt_2$), 3.60 (2H, m, $NCH_2\underline{CH_2}NEt_2$), 4.80 (3H, s, NCH_3), 5.70 (1H, s, 9-H), 8.00 (2H, m, 2-H and 3-H), 8.45 (1H, dd, J=8, 2 Hz, 4-H), 8.90 (1H, dd, J=8, 2 Hz, 1-H), 9.80 (1H, s, 6-H). *Anal.* Calcd for $C_{22}H_{24}N_4O_2 \cdot 1/2H_2O$: C, 68.57; H, 6.47; N, 14.54. Found: C, 68.78; H, 6.26; H, 14.16.

8-(4-Methyl-1-piperazinyl)-11*H*-indolo[3,2-*c*]quinoline-7,10-dione (**54**): Violet crystals, yield 0.059 g, 34%, mp 303 °C (MeOH–$CHCl_3$). IR (KBr): 1640, 1660 (C=O), 3100 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.20 (3H, s, NCH_3), 2.45 (4H, m, $N(CH_2\underline{CH_2})_2NMe$), 3.50 (4H, m, $N(\underline{CH_2}CH_2)_2NMe$), 5.65 (1H, s, 9-H), 7.65 (2H, m, 2-H and 3-H), 8.05 (1H, dd, J=8, 2 Hz, 4-H), 8.60 (1H, dd, J=8, 2 Hz, 1-H), 9.35 (1H, s, 6-H), 13.30 (1H, NH). *Anal.* Calcd for $C_{20}H_{18}N_4O_2$: C, 69.36; H, 5.20; N, 16.18. Found: C, 69.10; H, 5.21; N, 16.59.

11-Methyl-8-(4-methyl-1-piperazinyl)indolo[3,2-*c*]quinoline-7,10-dione (**55**): Violet crystals, yield 0.10 g, 61%, mp 263 °C (DMF). IR (KBr): 1655 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6, CF_3CO_2H) δ: 2.85 (3H, s, NCH_3), 3.30 (4H, m, $2CH_2$), 3.55 (2H, m, CH_2), 4.25 (2H, m, CH_2), 4.70 (3H, s, 11-NCH_3), 5.95 (1H, s, 9-H), 8.00 (2H, m, 2-H and 3-H), 8.35 (1H, dd, J=8, 2 Hz, 4-H), 8.85 (1H, dd, J=8, 2 Hz, 1-H), 9.75 (1H, s, 6-H). *Anal.* Calcd for $C_{21}H_{20}N_4O_2$: C, 70.01; H, 5.55; N, 15.56. Found: C, 69.72; H, 5.43; N, 15.19.

Pharmacology Growth inhibition of L 1210 cells in culture was examined according to the experimental protocol reported previously.[24]

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