Synthesis and Cytotoxic Activity of Pyranophenanthridine Analogues of Fagaronine and Acronycine

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Condensation of 5-amino, 6-amino, 7-amino and 8-amino-2,2-dimethyl-2*H*-chromenes with either 6-bromoveratraldehyde or 6-chloropiperonal afforded the corresponding Schiff bases, which were subsequently reduced to the corresponding benzylchromenylamines 30—33 and 36—39. Lithium diisopropylamide-mediated cyclization of those amines, followed by spontaneous air oxidation, afforded pyranophenanthridines 3—14. The cytotoxicity of compounds 3—14 was evaluated against L1210 and HT29 cell lines. 9,9-Dimethyl-9*H*-pyrano[3,2-*b*]phenanthridines appear to be the most promising compounds of the series, since both the dimethoxy derivative 11 and the methylenedioxy derivative 12 exhibit significant cytotoxic activity. Compound 12 was the most active and induced a massive accumulation of cells in G_2+M phases, suggesting that the cytotoxicity is due to a perturbation of the integrity or function of DNA.

Key words pyranophenanthridines; cytotoxicity; fagaronine; acronycine

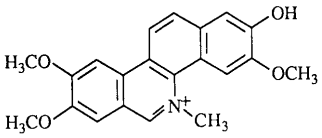
The benzophenanthridine alkaloid fagaronine (**1**), isolated from the roots of *Fagara zanthoxyloides* LAM. (Rutaceae)[1,2] has antitumor activity against P388 and L1210 murine leukemias.[1-4] In contrast, it exhibits no significant activity against solid tumors, such as B16 melanocarcinoma,[4] so new structural analogues with an enlarged spectrum of activity would be highly desirable. Fagaronine induces cell accumulation in G2 and late-S phases,[5] but its mechanism of action at the molecular level has not yet been unambiguously ascertained. It would seem that it acts by intercalation within the DNA double-strand[6-9] and, from an enzymatic point of view, by inhibition of DNA polymerase[8,9] and DNA topoisomerases I and II.[10] The structurally related pyrano[3,2-*c*]acridone alkaloid acronycine (**2**) exhibits a broad spectrum of antitumor activity.[11-14] It has recently been postulated that it should act by alkylation of nucleophilic targets, such as cellular proteins, after bioactivation of the dimethylpyran ring to the corresponding epoxide.[15,16]

This paper describes the synthesis and cytotoxic properties of various dimethoxy and methylenedioxy pyrano [*a*], [*b*], and [*c*] phenanthridines (**3—14**). Such compounds combine the dioxygenated phenanthridine tricyclic system most probably involved in the DNA-intercalating properties of fagaronine (**1**) and the dimethylpyran pharmacophore of acronycine (**2**).

Chemistry

Our synthesis is outlined in Chart 1. The key step of our approach was a benzyne-mediated cyclization of a conveniently substituted *N*-(2-halobenzyl)aminochromene.[3,17-20] Lithium diisopropylamide was used for this purpose, since this reagent had previously given satisfactory results for the cyclization of various anils to benzo[*c*]phenanthridines[21] and phenanthridines[22] bearing methoxy and methylenedioxy groups.

The starting 5-amino, 6-amino and 7-amino-2,2-dimethyl-2*H*-chromenes (**15—17**) were essentially prepared as previously described.[23-29] Copper (I) iodide-catalyzed[29] alkylation of 2-nitrophenol (**18**) by 3-chloro-3-methyl butyne (**19**)[30-31] led to 3-(2-nitrophenoxy)-3-methylbutyne (**20**) in high yield. Claisen rearrangement of



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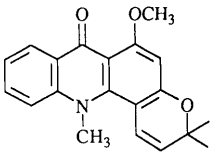

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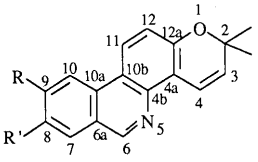
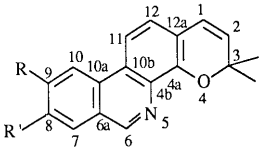


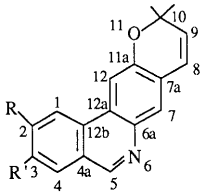
3 R=R'=OCH$_3$

4 R=R'=OCH$_2$O



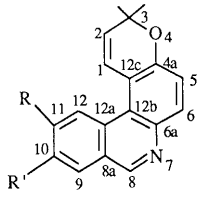
5 R=R'=OCH$_3$

6 R=R'=OCH$_2$O



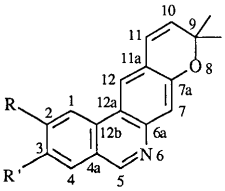
7 R=R'=OCH$_3$

8 R=R'=OCH$_2$O



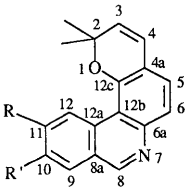
9 R=R'=OCH$_3$

10 R=R'=OCH$_2$O



11 R = R' = OCH$_3$

12 R = R' = OCH$_2$O



13 R = R'= OCH$_3$

14 R = R' = OCH$_2$O

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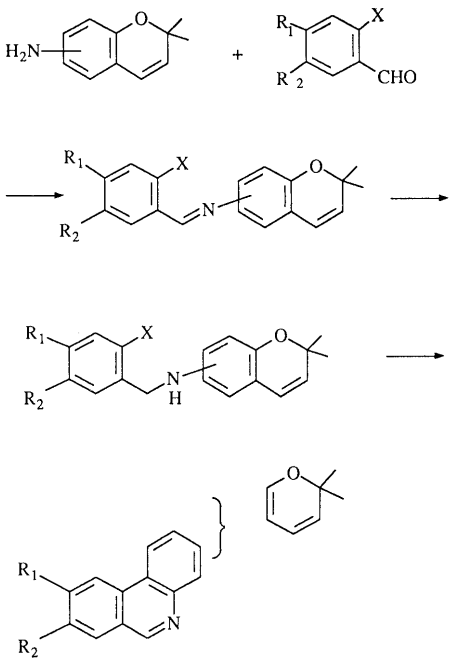
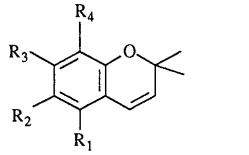


Chart 1. Synthesis of Pyranophenanthridines

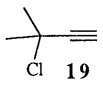
20 afforded 8-nitro-2,2-dimethyl-2*H*-chromene (**21**). Reduction of **21** with stannous chloride[32] afforded smoothly the required 8-amino-2,2-dimethyl-2*H*-chromene (**22**). Alternatively, reduction of **20** with stannous chloride gave 3-(2-aminophenoxy)-3-methylbutyne (**23**), which was cyclized to **22** by heating at 160 °C in 1,2-dichlorobenzene.

Condensation of aminochromenes **15** and **16** either with 6-bromoveratraldehyde (**24**) or with 6-chloropiperonal (**25**) afforded the Schiff bases **26**—**29** in 66—99% yield. Those imines were subsequently reduced with sodium borohydride to give the corresponding benzylchromenylamines **30**—**33** in almost quantitative yield. In contrast, when the aminochromenes **17** and **22** were condensed with aldehydes **24** or **25**, the corresponding Schiff bases were found to be unstable and almost impossible to purify on a preparative scale. Only the imines **34** and **35**, resulting from the reaction of **17** with **24** and **25**, respectively, could be isolated by preparative TLC for analytical purposes. Nevertheless, one-pot borohydride reduction of the reaction mixtures permitted access to the required benzylchromenylamines **36**—**39**. ^{1}H- and ^{13}C-NMR data of imines **26**—**29**, **34** and **35**, and of benzylchromenylamines **30**—**33** and **36**—**39** are summarized in Tables 1—4.

Cyclization of benzylchromenylamines **30**—**31** and **38**—**39** using lithium diisopropylamide in tetrahydrofuran at −78 °C[21] was followed by spontaneous air-oxidation of the unstable dihydrophenanthridine intermediates during the work-up,[22] affording 2,2-dimethyl-2*H*-pyrano[2,3-*c*]phenanthridines, **3** and **4**, and 3,3-dimethyl-3*H*-pyrano[3,2-*c*]phenanthridines **5** and **6**, respectively. In a similar way, cyclization of **32** and **33** led to approximatively equal amounts of 10,10-dimethyl-10*H*-pyrano[2,3-*b*]phenanthridines **7** and **8**, and 3,3-dimethyl-3*H*-pyrano[3,2-*a*]phenanthridines **9** and **10**, whereas 9,9-dimethyl-9*H*-pyrano[3,2-*b*]phenanthridines **11** and **12**, and 2,2-dimethyl-2*H*-pyrano[2,3-*a*]phenanthridines **13** and **14** were only obtained in moderate yield upon cyclization of



15 $R_1 = NH_2$ $R_2 = R_3 = R_4 = H$
16 $R_2 = NH_2$ $R_1 = R_3 = R_4 = H$
17 $R_3 = NH_2$ $R_1 = R_2 = R_4 = H$
21 $R_4 = NO_2$ $R_1 = R_2 = R_3 = H$
22 $R_4 = NH_2$ $R_1 = R_2 = R_3 = H$



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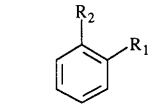
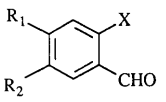
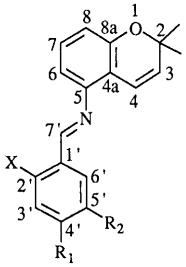


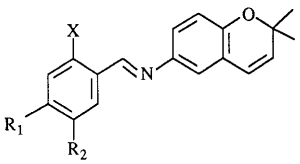
18 $R_1 = OH$ $R_2 = NO_2$
20 $R_1 = O\text{-}C(CH_3)_2\text{-}C \equiv CH$ $R_2 = NO_2$
23 $R1 = O\text{-}C(CH_3)_2\text{-}C \equiv CH$ $R_2 = NH_2$



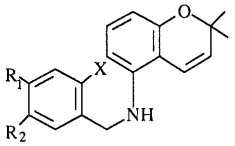
24 $R_1 = R_2 = OCH_3$ X = Br
25 $R_1 = R_2 = OCH_2O$ X = Cl



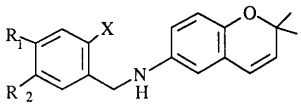
26 $R_1 = R_2 = OCH_3$ X = Br
27 $R_1 = R_2 = OCH_2O$ X = Cl



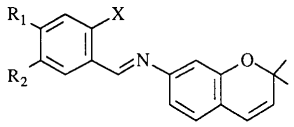
28 $R_1 = R_2 = OCH_3$ X = Br
29 $R_1 = R_2 = OCH_2O$ X = Cl



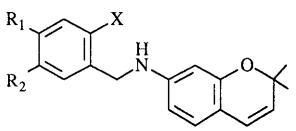
30 R_1=R_2=OCH_3 X=Br
31 R_1=R_2=OCH_2O X=Cl



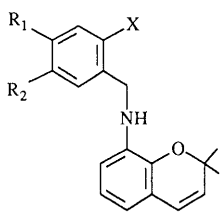
32 R_1=R_2=OCH_3 X=Br
33 R_1=R_2=OCH_2O X=Cl



34 R_1=R_2=OCH_3 X=Br
35 R_1=R_2=OCH_2O X=Cl



36 R_1=R_2=OCH_3 X=Br
37 R_1=R_2=OCH_2O X=Cl



38 R_1=R_2=OCH_3 X=Br
39 R_1=R_2=OCH_2O X=Cl

36 and **37**. In each case, the two isomers resulting from cyclization could be easily separated by column chromatography on silica gel. ^{1}H- and ^{13}C-NMR data for the pyranophenanthridines **3**—**14** are summarized in Tables 5 and 6.

Table 1. ^{1}H-NMR Data for the Imines **26**—**29**, **34** and **35** ($CDCl_3$, TMS) δ (ppm), J (Hz)

H	26	27	28	29	34	35
3	5.65, 1H, d, J=10	5.66, 1H, d, J=10	5.64, 1H, d, J=10	5.66, 1H, d, J=10	5.60, 1H, d, J=10	5.62, 1H, d, J=10
4	6.83, 1H, d, J=10	6.86, 1H, d, J=10	6.35, 1H, d, J=10	6.35, 1H, d, J=10	6.34, 1H, d, J=10	6.35, 1H, d, J=10
5			6.94, 1H, d, J=2.5	6.94, 1H, d, J=2.5	6.98, 1H, d, J=8	7.00, 1H, d, J=8
6	6.58, 1H, dd, J=8, 1	6.61, 1H, dd, J=8, 1			6.76, 1H, dd, J=8.2	6.77, 1H, dd, J=8.2
7	7.12, 1H, t, J=8	7.12, 1H, t, J=8	7.07, 1H, dd, J=8, 2.5	7.08, 1H, dd, J=8, 2.5		
8	6.70, 1H, dd, J=8, 1	6.72, 1H, dd, J=8, 1	6.80, 1H d, J=8	6.80, 1H, d, J=8	6.70, 1H, d, J=2	6.71, 1H d, J=8
3′	7.05, 1H, s	6.87, 1H, s	7.00, 1H, s	6.82, 1H, s	7.03, 1H, s	6.87, 1H, s
6′	7.78, 1H, s	7.72, 1H, s	7.71, 1H, s	7.66, 1H, s	7.73, 1H, s	7.70, 1H, s
7′	8.69, 1H, s	8.78, 1H, s	8.71, 1H, s	8.79, 1H, s	8.72, 1H, s	8.82, 1H, s
2×($C\underline{H}_3$)	1.48, 6H, s	1.49, 6H, s	1.46, 6H, s	1.47, 6H, s	1.46, 6H, s	1.49, 6H, s
2×($OC\underline{H}_3$)	3.94, 3H, s, 3.98, 3H, s	—	3.90, 3H, s, 3.95, 3H, s	—	3.90, 3H, s, 3.97, 3H, s	—
O–$C\underline{H}_2$–O	—	6.04, 2H, s	—	6.00, 2H, s		6.05, 2H, s

Table 2. ^{13}C-NMR Data for the Imines **26**—**29**, **34** and **35** ($CDCl_3$, TMS) δ (ppm)

C	26	27	28	29	34	35
2	75.7	75.8	76.3	76.3	76.3	76.5
3	130.0	130.0	131.3	131.2	130.1	130.2
4	118.5	118.5	122.1	122.1	121.9	122.0
4a	118.0	115.9	121.5	121.5	119.5	119.7
5	147.8	147.5	118.9	118.9	126.7	126.8
6	110.5	110.1	144.6	144.5	114.5	114.6
7	129.0	128.9	121.9	121.9	152.4	152.5
8	114.1	114.2	116.7	116.7	108.4	108.5
8a	153.3	153.2	151.6	151.7	153.6	153.7
1′	127.1	127.3	127.3	129.4	127.1	127.4
2′	115.6	127.3	117.6	127.4	118.0	127.4
3′	115.0	109.7	114.9	109.5	115.0	109.8
4′	152.2	150.7	151.7	150.3	152.1	150.8
5′	148.7	147.2	148.6	147.1	148.6	147.3
6′	110.4	106.9	109.8	106.7	110.0	107.1
7′	158.7	155.9	156.4	153.6	158.1	155.7
2×($C\underline{H}_3$)	27.8	27.8	27.8	27.8	27.9	28.0
2×($OC\underline{H}_3$)	56.1, 56.2	—	56.0, 56.1		56.1	
O–$C\underline{H}_2$–O	—	102.2	—	102.1	—	102.3

Pharmacology

The study of the biological properties of the new pyranophenanthridines **3**—**14** was carried out *in vitro* on L1210 murine leukemia and HT29 human colon carcinoma cell line. The results (IC_{50}) are reported in Table 7. The two cell lines were equally sensitive to the compounds, except for **4** and **8**, which were less cytotoxic to HT29 cell line. The most active compound on both cell lines was **12**. The effect of compounds **4**, **5**, **7**, **9**, **11**—**13** on the cell cycle was studied on L1210 cells. Compounds **4**, **5**, **9** inhibited the proliferation of L1210 cells without modifying their distribution in the different phases of the cell cycle (not shown). Compounds **7**, **11**, **13** significantly increased the number of cells in the G_2+M phases, while **12** induced a massive accumulation of cells in G_2+M (Table 8). This result suggests that the cytotoxicity of **12** is due to an interaction with DNA, directly or indirectly.

Conclusion

Considering the structure–cytotoxicity relationships, 9,9-dimethyl-9*H*-pyrano[3,2-*b*]phenanthridines appear to be a promising series of compounds. Indeed, both the dimethoxy derivative **11** and the methylenedioxy derivative **12** exhibit significant cytotoxic activity in this series. These two compounds exhibit a G_2+M cell-cycle specificity, which suggests similar mechanisms of action.

Experimental

Chemistry Mass spectra were recorded with a Nermag R-10-10C spectrometer using electron impact (EI-MS) and/or chemical ionization (CI-MS; reagent gas: NH_3) techniques. UV spectra (λ_{max} in nm, $\log\varepsilon$) were determined in spectroscopic grade MeOH or EtOH on a Beckman Model 34 spectrophotometer. IR spectra (ν_{max} in cm^{-1}) were obtained in potassium bromide pellets or chloroform solutions on a Perkin-Elmer 257 instrument. ^{1}H-NMR (δ [ppm], J [Hz]) and ^{13}C-NMR spectra were recorded at 300 and 75 MHz, respectively, using a Bruker AC-300 spectrometer. When necessary, assignments were confirmed by two dimensional correlation spectroscopy, heteronuclear correlation spectroscopy, and correlation spectroscopy *via* long-range coupling experiments using standard Bruker microprograms. Column chromatography was conducted using silica gel 60 SDS® (20—45 μm) with an overpressure of 300 mbars. Analytical samples were prepared by crystallization when stated, or by repeated column chromatographies. Elemental analyses were performed by the 'Service de Microanalyse du CNRS' at Gif-sur-Yvette (France).

3-(2-Nitrophenoxy)-3-methylbutyne (20) 3-Chloro-3-methylbutyne (**19**) (10.25 g, 100 mmol) and a catalytic amount of CuI (137 mg, 0.72 mmol) were added to a mixture of 2-nitrophenol (**18**) (5 g, 36 mmol), anhydrous K_2CO_3 (10 g, 72 mmol) and KI (10 g, 60 mmol) in anhydrous dimethylformamide (50 ml). The reaction mixture was heated at 65 °C with stirring for 2 h. Then, CH_2Cl_2 (100 ml) and 1 N aqueous NaOH (300 ml) were added. The organic layer was washed with H_2O (2 × 150 ml), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to afford **20** (6.5 g, 86%) as a reddish oil. UV λ_{max} (MeOH) nm ($\log\varepsilon$): 214 (4.04), 249 (3.89); IR (neat) cm^{-1}: 3280, 2980, 2120, 1600, 1520, 1480, 1355, 1145, 950, 900, 850, 775, 745; ^{1}H-NMR ($CDCl_3$) δ: 1.71 (6H, s, C3(CH_3)$_2$), 2.65 (1H, s, C1-H), 7.12 (1H, td, J=8, 1 Hz, C4′-H), 7.48 (1H, td, J=8, 2 Hz, C5′-H) 7.72 (1H, dd, J=8, 1 Hz, C6′-H), 7.75 (1H, dd, J=8, 2 Hz, C3′-H); ^{13}C-NMR ($CDCl_3$) δ: 29.3 (q, C($C\underline{H}_3$)$_2$), 75.0 (d, C-1, s, C-3), 85.0 (s, C-2), 122.2 (d, C-6′), 122.5 (d, C-4′), 124.9 (d, C-3′), 132.8 (d, C-5′), 143.7 (s, C-2′), 148.9 (s, C-1′); CI-MS m/z: 223 $(M+NH_4)^+$, 206 $(M+H)^+$. *Anal.* Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.27; H, 5.38; N, 6.89.

8-Nitro-2,2-dimethyl-2*H*-chromene (21) A solution of 3-(2-nitrophenoxy)-3-methylbutyne (**20**) (410 mg, 2 mmol) in 1,2-dichlorobenzene (2.5 ml) was heated under reflux for 8 h. The reaction mixture was diluted with Et_2O (50 ml), washed with H_2O (2 × 100 ml), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to give **21** (205 mg, 50%) as a reddish oil. UV λ_{max} (MeOH) nm ($\log\varepsilon$): 215 (4.27), 253 (4.01), 276 (sh.) (3.85), 286 (sh.) (3.85), 330 (3.73); IR (neat) cm^{-1}: 2970, 1515, 1440, 1340, 1270, 1205, 1160, 1105, 940, 910, 830, 800, 735; ^{1}H-NMR ($CDCl_3$) δ 1.50 (6H, s, C2(CH_3)$_2$), 5.77 (1H, d, J=10 Hz, C3-H), 6.37 (1H, d, J=10 Hz, C4-H), 6.88 (1H, t, J=8 Hz, C6-H), 7.17 (1H, dd, J=8, 2 Hz, C5-H), 7.68 (1H, dd, J=8, 2 Hz, C7-H); ^{13}C-NMR ($CDCl_3$) δ: 27.9 (q, C($C\underline{H}_3$)$_2$), 78.5 (s, C-2), 119.7 (d, C-6), 121.1 (d, C-4), 123.8 (s, C-4a), 124. (d, C-7), 130.4 (d,C-5), 132.2 (d, C-3), 138.7

Table 3. ^{1}H-NMR Data for the Benzylchromenylamines **30**—**33** and **36**—**39** ($CDCl_3$, TMS) δ (ppm), J (Hz)

H	30	31	32	33
3	5.60, 1H, d, J=10	5.62, 1H, d, J=10	5.61, 1H, d, J=10	5.62, 1H, d, J=10
4	6.42, 1H, d, J=10	6.42, 1H, d, J=10	6.23, 1H, d, J=10	6.25, 1H, d, J=10
5			6.32, 1H, d, J=2.5	6.29, 1H, d, J=2.5
6	6.28, 1H, d, J=8	6.29, 1H, d, J=8		
7	6.97, 1H, t, J=8	6.98, 1H, t, J=8	6.44, 1H, dd, J=8, 2.5	6.42, 1H, dd, J=8, 2.5
8	6.18, 1H, d, J=8	6.18, 1H, d, J=8	6.65, 1H, d, J=8	6.65, 1H, d, J=8
3′	6.92, 1H, s	6.87, 1H, s	6.95, 1H, s	6.86, 1H, s
6′	7.03, 1H, s	6.88, 1H, s	7.03, 1H, s	6.91, 1H, s
7′	4.33, 2H, d, J=6	4.35, 2H, d, J=6	4.25, 2H, d, J=6	4.26, 2H, d, J=6
2×($C\underline{H}_3$)	1.42, 6H, s	1.43, 6H, s	1.40, 6H, s	1.41, 6H, s
2×($OC\underline{H}_3$)	3.78, 3H, s, 3.88, 3H, s	—	3.79, 3H, s, 3.87, 3H, s	—
O–$C\underline{H}_2$–O	—	5.95, 2H, s	—	5.95, 2H, s
O–$C\underline{H}_2$–O	4.12, 1H, t, J=6	4.17, 1H, t, J=6	3.80, 1H, m	3.82, 1H, t, J=6

H	36	37	38	39
3	5.39, 1H, d, J=10	5.38, 1H, d, J=10	5.60, 1H, d, J=10	5.62, 1H, d, J=10
4	6.25, 1H, d, J=10	6.24, 1H, d, J=10	6.32, 1H, d, J=10	6.34, 1H, d, J=10
5	6.79, 1H, d, J=8	6.79, 1H, d, J=8	6.43, 1H, d, J=8	6.45, 1H, d, J=8
6	6.14, 1H, dd, J=8, 2	6.12, 1H, dd, J=8, 2	6.72, 1H, t, J=8	6.75, 1H, t, J=8
7			6.46, 1H, d, J=8	6.45, 1H, d, J=8
8	6.11, 1H, d, J=2	6.07, 1H, d, J=2		
3′	6.93, 1H, s	6.86, 1H, s	6.95, 1H, s	6.88, 1H, s
6′	7.04, 1H, s	6.88, 1H, s	7.05, 1H, s	6.92, 1H, s
7′	4.29, 2H, s	4.30, 2H, s	4.36, 2H, s	4.39, 2H, s
2×($C\underline{H}_3$)	1.41, 6H, s	1.42, 6H, s	1.47, 6H, s	1.50, 6H, s
2×($OC\underline{H}_3$)	3.53, 3H, s, 3.59, 3H, s	—	3.77, 3H, s, 3.87, 3H, s	—
O–$C\underline{H}_2$–O	—	5.95, 2H, s	—	5.95, 2H, s
O–$C\underline{H}_2$–O	4.12, 1H, sl	4.13, 1H, br s	4.66, 1H, t, J=6	4.71, 1H, br s

Table 4. ^{13}C-NMR Data for the Benzylchromenylamines **30**—**33**, **36** and **39** ($CDCl_3$, TMS) δ (ppm)

C	30	31	32	33	36	37	38	39
2	74.8	74.7	75.4	75.5	76.2	76.2	76.3	76.3
3	129.5	129.5	131.6	131.6	126.2	126.2	130.1	130.0
4	116.4	116.3	122.5	122.6	122.1	122.1	120.8	120.8
4a	107.8	107.7	121.9	121.9	113.0	112.2	120.1	120.0
5	143.5	143.2	111.2	108.9	127.1	129.8	115.2	110.8
6	107.0	106.9	142.0	141.8	105.7	105.5	122.8	122.6
7	129.0	129.0	114.0	111.0	149.1	148.9	111.3	108.5
8	104.4	104.1	116.7	116.8	100.6	100.4	136.9	136.6
8a	153.4	153.4	145.2	145.2	154.2	154.2	139.4	139.3
1′	130.0	129.7	130.5	130.3	130.1	129.8	130.6	130.3
2′	113.1	124.6	112.9	124.6	112.2	124.6	112.9	124.4
3′	112.2	109.8	116.7	109.8	112.2	109.9	112.0	109.7
4′	148.6	147.2	148.5	147.1	148.6	146.9	148.5	147.6
5′	148.4	146.8	148.5	146.8	148.5	146.9	148.5	146.8
6′	115.5	108.7	115.4	113.9	115.6	108.7	115.6	115.0
7′	48.5	45.9	49.2	46.7	48.2	45.6	48.0	45.4
2×($\underline{C}H_3$)	27.7	27.3	27.5	27.6	28.0	28.1	27.9	27.9
2×($O\underline{C}H_3$)	56.0, 56.1	—	55.9, 56.1		56.0, 56.2	—	56.0, 56.2	—
O–$\underline{C}H_2$–O	—	101.6	—	101.6	—	101.6	—	101.5

(s, C-8), 147.2 (s, C-8a); CI-MS m/z: 223 $(M+NH_4)^+$, 206 $(M+H)^+$, 190. *Anal.* Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.42; H, 5.38; N, 6.91.

3-(2-Aminophenoxy)-3-methylbutyne (23) A solution of **20** (17.1 g, 83 mmol) and $SnCl_2 \cdot 2H_2O$ (95 g, 420 mmol) in EtOH (70 ml) was heated at 70 °C for 45 min. The reaction mixture was poured on ice (200 ml), alkalinized with 5% aqueous $NaHCO_3$ and then extracted with EtOAc (3 × 300 ml). The organic layer was washed with brine. Activated charcoal (1 g) was added and the mixture was filtered over celite (50 g). The filtrate was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to afford **23** (14.2 g, 97%) as a yellow oil. UV λ_{max} (MeOH) nm (log ε): 243 (3.93), 283 (3.52); IR (neat) cm^{-1}: 3440, 3290, 2990, 2940, 2100, 1600, 1490, 1200, 1120, 940, 880, 730; ^{1}H-NMR ($CDCl_3$) δ: 1.71 (6H, s, C3(CH_3)$_2$), 2.60 (1H, s, C1-H), 3.83 (2H, br s, D_2O exch., NH_2), 6.71 (1H, td, J=8, 2 Hz, C5′-H), 6.76 (1H, dd, J=8, 2 Hz, C3′-H), 6.90 (1H, td, J=8, 1 Hz, C4′-H), 7.42 (1H, dd, J=8, 1 Hz, C6′-H); ^{13}C-NMR ($CDCl_3$) δ: 29.4 (q, C($\underline{C}H_3$)$_2$), 72.8 (s, C-3), 73.3 (d, C-1), 86.3 (s, C-2), 115.7 (d, C-3′), 117.9 (d, C-5′), 120.4 (d, C-6′), 123.4 (d, C-4′), 139.6 (s, C-2′), 142.8 (s, C-1′); CI-MS m/z: 176 $(M+H)^+$. *Anal.* Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.31; H, 7.39; N, 8.05.

8-Amino-2,2-dimethyl-2*H*-chromene (22) Method a: A solution of **21** (2.05 g, 10 mmol) and $SnCl_2 \cdot 2H_2O$ (11.3 g, 50 mmol) in EtOH (20 ml) was heated under reflux for 1 h. A work-up similar to that described for the preparation of **23** afforded **22** (1.23 g, 70%) as a pale yellow oil. UV λ_{max} (EtOH) nm (log ε): 225 (4.92), 272 (4.31), 279 (sh.) (4.24); IR (neat) cm^{-1}: 3475, 3040, 2980, 2930, 1600, 1480, 1260, 1210, 1160, 960, 790, 760; ^{1}H-NMR ($CDCl_3$) δ: 1.47 (6H, s, C2(CH_3)$_2$), 3.73 (2H, br s, D_2O exch., NH_2), 5.60 (1H, d, J=10 Hz, C3-H), 6.31 (1H, d, J=10 Hz, C4-H), 6.46 (1H, dd, J=8, 2 Hz, C7-H), 6.61 (1H, dd, J=8, 2 Hz, C5-H) 6.70 (1H, t, J=8 Hz, C6-H); ^{13}C-NMR ($CDCl_3$) δ: 28.0 (q, C($\underline{C}H_3$)$_2$), 76.1 (s, C-2), 115.5 (d, C-5), 116.3 (d, C-7), 120.6 (d, C-6), 120.9 (s, C-4a), 122.6 (d, C-4) 130.3 (d, C-3), 135.0 (s, C-8), 139.9 (s, C-8a); CI-MS m/z: 193 $(M+NH_4)^+$, 176 $(M+H)^+$, 160. *Anal.* Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.47; H, 7.51; N, 8.09.

Method b: A solution of 3-(2-aminophenoxy)-3-methylbutyne (**23**) (14.2 g, 81 mmol) in 1,2-dichlorobenzene (75 ml) was heated under reflux for 2 h. The reaction mixture was diluted with Et_2O (750 ml), and extracted with 1 N aqueous HCl (3 × 400 ml). The acidic solution was basified with 10% KOH and then extracted with CH_2Cl_2 (3 × 300 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure, to give **22** (10.8 g, 76%) as an oily free base.

***N*-(2,2-Dimethylchromen-5-yl)-2-bromo-4,5-dimethoxyphenylmethanimine (26)** A solution of 5-amino-2,2-dimethylchromene (**15**) (134 mg, 0.76 mmol) and 6-bromoveratraldehyde (**24**) (186 mg, 0.76 mmol) in toluene (30 ml) was refluxed in a Dean-Stark apparatus for 12 h. The solvent was evaporated under reduced pressure. Column chromatog-

Table 5. ^{1}H-NMR Data for the Pyranophenanthridines **3**—**14** ($CDCl_3$, TMS), δ (ppm), J (Hz)

3	1.53 (6H, s, $C(CH_3)_2$), 4.05 (3H, s, OCH_3), 4.12 (3H, s, OCH_3), 5.80 (1H, d, J=10 Hz, C3-H), 7.17 (1H, d, J=9 Hz, C12-H), 7.29 (1H, s, C7-H), 7.59 (1H, d, J=10 Hz, C4-H), 7.73 (1H, s, C10-H), 8.20 (1H, d, J=9 Hz, C11-H), 9.08 (1H, s, C6-H).
4	1.52 (6H, s, $C(CH_3)_2$), 5.79 (1H, d, J=10 Hz, C3-H), 6.12 (2H, s, OCH_2O), 7.15 (1H, d, J=9 Hz, C12-H), 7.23 (1H, s, C7-H), 7.57 (1H, d, J=10 Hz, C4-H), 7.72 (1H, s, C10-H), 8.10 (1H, d, J=9 Hz, C11-H), 9.00 (1H, s, C6-H).
5	1.60 (6H, s, $C(CH_3)_2$), 4.00 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 5.67 (1H, d, J=10 Hz, C2-H), 6.43 (1H, d, J=10 Hz, C1-H), 7.20 (1H, d, J=8 Hz, C12-H), 7.23 (1H, s,C7-H), 7.67 (1H, s, C10-H), 7.79 (1H, d, J=8 Hz, C11-H), 9.13 (1H, s, C6-H).
6	1.42 (6H, s, $C(CH_3)_2$), 5.57 (1H, J=10 Hz, C2-H), 5.97 (2H, s, OCH_2O), 6.31 (1H, d, J=10 Hz, C2-H), 7.10 (1H, d, J=8 Hz, C12-H), 7.12 (1H, s, C7-H), 7.63 (1H, s, C10-H), 7.64 (1H, d, J=8 Hz, C11-H), 8.78 (1H, s, C6-H).
7	1.50 (6H, s, $C(CH_3)_2$), 3.97 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 5.78 (1H, d, J=10 Hz, C9-H), 6.54 (1H, d, J=10 Hz, C8-H), 7.16 (1H, s, C4-H), 7.58 (1H, s, C1-H), 7.62 (1H, s, C12-H), 7.67 (1H, s, C7-H), 8.88 (1H, s, C5-H).
8	1.52 (6H, s, $C(CH_3)_2$), 5.83 (1H, d, J=10 Hz, C9-H), 6.08 (2H, s, OCH_2O), 6.56 (1H, d, J=10 Hz, C8-H), 7.18 (1H, s, C4-H), 7.59 (1H, s, C1-H), 7.64 ((1H, s, C12-H), 7.69 (1H, s, C7-H), 8.84 (1H, s, C5-H).
9	1.59 (6H, s, $C(CH_3)_2$), 4.08 (6H, s, $2OCH_3$), 5.78 (1H, d, J=10 Hz, C2-H), 7.23 (1H, d, J=10 Hz, C1-H), 7.27 (1H, d, J=9 Hz, C5-H), 7.33 (1H, s, C9-H), 7.88 (1H, s, C12-H), 7.96 (1H, d, J=9 Hz, C6-H), 8.90 (1H, s, C8-H).
10	1.58 (6H, s, $C(CH_3)_2$), 5.74 (1H, d, J=10 Hz, C2-H), 6.14 (2H, s, OCH_2O), 7.12 (1H, d, J=10 Hz, C1-H), 7.26 (1H, d, J=9 Hz, C5-H), 7.31 (1H, s, C9-H), 7.87 (1H, s, C12-H), 7.95 (1H, d, J=9 Hz, C6-H), 8.90 (1H, s, C8-H).
11	1.52 (6H, s, $C(CH_3)_2$), 4.06 (3H, s, OCH_3), 4.12 (3H, s, OCH_3), 5.88 (1H, d, J=10 Hz, C10-H), 6.62 (1H, d, J=10 Hz, C11-H) 7.28 (1H, s, C7-H), 7.48 (1H, s, C4-H), 7.72 (1H, s, C1-H), 7.97 (1H, s, C12-H), 9.02 (1H, s, C5-H).
12	1.53 (6H, s, $C(CH_3)_2$), 5.88 (1H, d, J=10 Hz, C10-H), 6.06 (2H, s, OCH_2O), 6.60 (1H, d, J=10 Hz, C11-H), 7.27 (1H, s, C7-H), 7.50 (1H, s, C4-H), 7.78 (1H, s, C1-H), 7.92 (1H, s, C12-H), 9.00 (1H, s, C5-H).
13	1.62 (6H, s, $C(CH_3)_2$), 4.08 (3H, s, OCH_3), 4.12 (3H, s, OCH_3), 5.74 (1H, d, J=10 Hz, C3-H), 6.53 (1H, d, J=10 Hz, C4-H), 7.33 (1H, s, C9-H), 7.34 (1H, d, J=8 Hz, C5-H), 7.71 (1H, d, J=8 Hz, C6-H), 9.04 (1H, s, C8-H), 9.22 (1H, s, C12-H).
14	1.53 (6H, s, $C(CH_3)_2$), 5.72 (1H, d, J=10 Hz, C3-H), 6.15 (2H, s, OCH_2O), 6.50 (1H, d, J=10 Hz, C4-H), 7.29 (1H, s, C9-H), 7.32 (1H, d, J=8 Hz, C5-H), 7.69 (1H, d, J=8 Hz, C6-H), 8.96 (1H, s, C12-H), 9.07 (1H, s, C8-H).

Table 6. ^{13}C-NMR Data for the Pyranophenanthridines **3**—**14** ($CDCl_3$, TMS), δ (ppm)

3	27.9 (2C, q, $C(CH_3)_2$), 56.0 (2C, q, $2OCH_3$), 76.6 (s, C-2), 101.2 (d, C-10), 107.6 (d, C-7), 117.4 (d, C-12), 117.4 (s, C-4a), 117.9 (s, C-10b), 118.7 (d, C-4), 120.7 (s, C-6a), 121.9 (d, C-11), 128.6 (s, C-10a), 129.8 (d, C-3), 140.1 (s, C-4b), 149.1 (s, C-8), 151.4 (d, C-6), 152.6 (s, C-12a), 152.9 (s, C-9).
4	27.9 (2C, q, $C(CH_3)_2$), 76.6 (s, C-2), 99.3 (d, C-10), 101.7 (t, OCH_2O), 105.2 (d, C-7), 117.1 (s, C-4a), 117.5 (d, C-12), 118.5 (s, C-10b), 118.9 (d, C-4), 121.9 (s, C-6a), 122.2 (d, C-11), 129.7 (d, C-3), 130.7 (s, C-10a), 140.3 (s, C-4b), 147.2 (s, C-8), 151.4 (d, C-6), 151.4 (s, C-12a), 152.7 (s, C-9).
5	28.0 (2C, q, $C(CH_3)_2$), 55.9 (2C, q, $2OCH_3$), 76.6 (s, C-3), 101.7 (d, C-10), 107.5 (d, C-7), 113.0 (d, C-11), 118.6 (s, C-12a), 122.2 (d, C-1), 124.6 (d, C-12), 125.0 (s, C-10b), 127.9 (s, C-10a), 130.3 (d, C-2), 134.6 (s, C-4b), 149.0 (s, C-4a), 149.7 (s, C-8), 150.8 (d, C-6), 152.5 (s, C-9).
6	27.3 (2C, q, $C(CH_3)_2$), 76.6 (s, C-3), 99.7 (d, C-10), 101.7 (t, OCH_2O), 105.0 (d, C-7), 113.2 (d, C-11), 118.6 (s, C-12a), 121.6 (s, C-6a), 121.8 (d, C-1), 122.6 (s, C-6a), 124.7 (d, C-12), 125.1 (s, C-10b), 130.1 (s, C-10a), 130.5 (d, C-2), 133.8 (s, C-4b), 148.1 (s, C-4a), 150.1 (s, C-8), 150.1 (d, C-6), 151.5 (s, C-9).
7	28.1 (2C, q, $C(CH_3)_2$), 55.8 (2C, q, $2OCH_3$), 76.7 (s, C-10), 101.6 (d, C-1), 106.4 (d, C-12), 107.3 (d, C-4), 121.5 (s, C-4a), 122.1 (d, C-8), 122.7 (s, C-12a), 124.7 (s, C-7a), 126.9 (d, C-7), 127.1 (s, C-12b), 132.8 (d, C-9), 139.4 (s, C6a), 149.3 (d, C-5), 149.6 (s, C-3), 151.5 (s, C-11a), 152.2 (s, C-2).
8	28.2 (2C, q, $C(CH_3)_2$), 76.7 (s, C-10), 99.8 (d, C-1), 101.7 (t, OCH_2O) 105.1 (d, C-12), 106.7 (d, C-4), 122.1 (d, C-8), 123.0 (s, C-4a), 123.0 (s, C-12a), 125.3 (s, C-7a), 129.2 (s, C-12b), 129.3 (d, C-7), 133.2 (d, C9), 139.6 (s, C-6a), 148.0 (s, C-3), 149.4 (d, C-5), 150.8 (s, C-2), 151.7 (s, C-11a).
9	26.7 (2C, q, $C(CH_3)_2$), 56.0 (2C, q, $2OCH_3$), 74.8 (s, C-3), 107.2 (d, C-12), 107.6 (d, C-9), 115.6 (s, C-12c), 118.5 (d, C-5), 121.8 (s, C-12b), 122.8 (d, C-1), 123.2 (s, C-8a), 127.7 (d, C-2), 127.7 (s, C-12a), 131.4 (d, C-6), 140.2 (s, C-6a), 149.3 (s, C-10), 149.3 (d, C-8), 151.5 (s, C-11), 153.0 (s, C-4a).
10	26.6 (2C, q, $C(CH_3)_2$), 75.0 (s, C-3), 101.8 (t, OCH_2O), 104.7 (d, C-12), 105.4 (d, C-9), 115.8 (s, C-4), 118.8 (d, C-5), 122.3 (s, C-12b), 123.1 (d, C-1), 124.4 (s, C-8a), 127.6 (d, C-2), 129.3 (s, C-12a), 131.3 (d, C-6), 140.3 (d, C-6a), 147.5 (s, C-10), 149.4 (d, C-8), 150.2 (s, C-11), 152.8 (s, C-4a).
11	28.1 (2C, q, $C(CH_3)_2$), 56.0 (2C, q, $20CH_3$), 77.0 (s, C-9), 101.2 (d, C-4), 107.8 (d, C-7), 114.7 (d, C-4c), 118.5 (s, C-11a), 118.9 (d, C-12), 120.9 (s, C-4a), 122.2 (d, C-11), 127.4 (s, C-12a), 129.4 (s, C-12b), 133.6 (d, C-10), 145.3 (s, C-6a), 149.2 (s, C-3), 151.7 (d, C-5), 152.9 (s, C-7a), 153.0 (s, C-2).
12	28.2 (2C, q, $C(CH_3)_2$), 78.0 (s, C-9), 99.4 (d, C-1), 101.8 (t, OCH_2O), 105.6 (d, C-7), 114.0 (d, C-4), 119.2 (s, C-11a), 119.2 (d, C-12), 122.1 (d, C-11), 122.3 (s, C-4a), 130.5 (s, C-12a), 130.7 (s, C-12b), 133.9 (d, C-10), 144.9 (s, C-6a), 147.5 (s, C-3) 151.3 (d, C-5), 151.8 (s, C-2), 153.3 (s, C-7a).
13	28.1 (2C, q, $C(CH_3)_2$), 55.9 (2C, q, $2OCH_3$), 77.0 (s, C-2), 107.6 (d, C-9), 108.3 (d, C-12), 114.7 (s, C-12b), 118.4 (s, C-4a), 122.4 (d, C-6), 122.5 (s, C-8a), 123.3 (d, C-4), 125.8 (d, C-5), 127.9 (s, C-12a), 129.3 (d, C-3), 145.9 (s, C-6a), 148.8 (s, C-10), 150.2 (s, C-12C), 151.7 (s, C-11), 152.0 (d, C-8).
14	28.0 (2C, q, $C(CH_3)_2$), 77.4 (s, C-2), 101.7 (t, OCH_2O), 105.4 (d, C-9), 105.9 (d, C-12), 115.2 (s, C-12b), 118.5 (s, C-4a), 122.2 (d, C-6), 123.2 (d, C-4), 123.7 (s, C-8a), 126.0 (d, C-5), 129.7 (d, C-3), 129.8 (s, C-12a), 145.8 (s, C-6a), 147.1 (s, C-10), 150.3 (s, C-12c), 150.7 (s, C-11), 152.0 (d, C-8).

raphy of the residue on silica gel (eluent: cyclohexane/EtOAc 90/10) afforded **26** (200 mg, 66%) as an amorphous solid. UV λ_{max} (EtOH) nm ($\log\varepsilon$): 224 (4.40), 278 (4.22), 282 (sh.) (4.21), 336 (4.13); IR (KBr) cm^{-1}: 2950, 2930, 1610, 1590, 1560, 1500, 1450, 1390, 1270, 1200, 1160, 1100, 1020, 870, 760; ^{1}H- and ^{13}C-NMR: Tables 1, 2; CI-MS m/z: 404 $(M+H)^+$, 402 $(M+H)^+$, 388, 386. *Anal.* Calcd for $C_{20}H_{20}BrNO_3$: C, 59.71; H, 5.01, Br, 19.86; N, 3.48. Found: C, 59.82; H, 4.96; Br, 19.94; N, 3.54.

Table 7. Cytotoxicity of the Pyranophenanthridines **3**—**14**

Compound	IC_{50} (μM) L 1210	IC_{50} (μM) HT29
3	51.7	42.9
4	14.1	35.4
5	23.9	22.0
6	35.2	42.5
7	4.7	7.2
8	13.9	31.4
9	9.7	6.6
10	72.8	130.1
11	14.7	12.2
12	1.2	1.4
13	7.6	5.4
14	32.5	36.9

Table 8. Effect of Compounds **7**, **11**, **12** and **13** on the Cell Cycle of L1210 Cell Line

Compound (concentration)	% of cells accumulated in the indicated phases		
	G1	S	G_2+M
Control	42.9	32.1	24.3
7 (25 μM)	36.7	22.3	40.4
11 (100 μM)	16.0	40.7	43.4
12 (2.5 μM)	7.3	19.3	72.9
13 (25 μM)	32.5	25.6	41.3

***N*-(2,2-Dimethylchromen-5-yl)-2-chloro-4,5-methylenedioxyphenylmethanimine (27)** Condensation of 5-amino-2,2-dimethylchromene (**15**) (293 mg, 1.67 mmol) with 6-chloropiperonal (**25**) (298 mg, 1.67 mmol) under conditions similar to those described for the preparation of **26**, afforded **27** (489 mg, 86%) as crystals, mp 113—115 °C (EtOH). UV λ_{max} (EtOH) nm (log ε): 226 (4.45), 277 (4.23), 283 (sh.) (4.21) 342 (4.20); IR (KBr) cm^{-1}: 2960, 2900, 1610, 1570, 1560, 1500, 1470, 1450, 1420, 1350, 1270, 1250, 1100, 1030, 910, 880, 840, 760; ^{1}H- and ^{13}C-NMR: Tables 1, 2; CI-MS *m/z*: 344 $(M+H)^+$, 342 $(M+H)^+$. *Anal.* Calcd for $C_{19}H_{16}ClNO_3$: C, 66.77; H, 4.72; Cl, 10.37; N, 4.10. Found: C, 66.86; H, 4.71, Cl, 10.49; N, 4.01.

***N*-(2,2-Dimethylchromen-6-yl)-2-bromo-4,5-dimethoxyphenylmethanimine (28)** Condensation of 6-amino-2,2-dimethylchromene (**16**) (175 mg, 1 mmol) with 6-bromoveratraldehyde (**24**) (245 mg, 1 mmol) under conditions similar to those described for the preparation of **26**, afforded **28** (400 mg, 99%) as an amorphous solid. UV λ_{max} (EtOH) nm (log ε): 234 (4.68), 282 (4.47), 340 (sh.) (4.38) 355 (4.39); IR (KBr) cm^{-1}: 2960, 2840, 1570, 1430, 1380, 1360, 1250, 1200, 1150, 1110, 1020, 860, 790, 750; ^{1}H- and ^{13}C-NMR: Tables 1, 2; CI-MS *m/z*: 404 $(M+H)^+$, 402 $(M+H)^+$ 388, 386. *Anal.* Calcd for $C_{20}H_{20}BrNO_3$: C, 59.71; H, 5.01; Br, 19.86; N, 3.48. Found: C, 59.60; H, 5.07, Br 19.96; N, 3.42.

***N*-(2,2-Dimethylchromen-6-yl)-2-chloro-4,5-methylenedioxyphenylmethanimine (29)** Condensation of 6-amino-2,2-dimethylchromene (**16**) (175 mg, 1 mmol) with 6-chloropiperonal (**25**) (184.5 mg, 1 mmol) under conditions similar to those described for the preparation of **26**, afforded **29** (311 mg, 91%) as an amorphous solid. UV λ_{max} (EtOH) nm (log ε): 234 (4.71), 282 (4.41), 341 (sh.) (4.31) 356 (4.39); IR (KBr) cm^{-1}: 2960, 2890, 1580, 1460, 1410, 1240, 1200, 1110, 1020, 990, 920, 870, 760, 710; ^{1}H- and ^{13}C-NMR: Tables 1, 2; CI-MS *m/z*: 344 $(M+H)^+$, 342 $(M+H)^+$. *Anal.* Calcd for $C_{19}H_{16}ClNO_3$: C, 66.77; H, 4.72, Cl 10.37; N, 4.10. Found: C, 66.83; H, 4.76; Cl, 10.45, N, 4.02.

***N*-(2-Bromo-4,5-dimethoxybenzyl)-2,2-dimethyl-5-chromenylamine (30)** Sodium borohydride (11 g, 290 mmol) was added over 30 min to a solution of imine **26** (5.2 g, 12.9 mmol) in MeOH (200 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The solvent was evaporated under reduced pressure. Water (300 ml) and CH_2Cl_2 (300 ml) were added to the residue. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure, to afford **30** (5.0 g, 95%) as an amorphous solid. UV λ_{max} (MeOH) nm (log ε): 234 (4.28), 286 (3.94), 334 (3.63); IR (KBr) cm^{-1}: 3380, 2940, 2920, 1610, 1570, 1550, 1480, 1450, 1410, 1240, 1200, 1140, 1100, 1010, 840, 790, 730; ^{1}H- and ^{13}C-NMR: Tables 3, 4; CI-MS *m/z*: 406 $(M+H)^+$, 404 $(M+H)^+$. *Anal.* Calcd for $C_{20}H_{22}BrNO_3$: C, 59.42; H, 5.48; Br 19.76; N, 3.47. Found: C, 59.53; H, 5.39; Br, 19.84; N, 3.42.

***N*-(2-Chloro-4,5-methylenedioxybenzyl)-2,2-dimethyl-5-chromenylamine (31)** Reduction of **27** (4.1 g, 12 mmol) with sodium borohydride (8 g, 211 mmol) under conditions similar to those described for the preparation of **30**, afforded **31** (4.0 g, 97%) as an amorphous solid. UV λ_{max} (MeOH) nm (log ε): 226 (4.64), 260 (sh.) (4.20), 266 (4.12), 281 (4.18), 334 (3.70); IR (KBr) cm^{-1}: 3400, 2960, 2880, 1610, 1560, 1460, 1400, 1230, 1110, 1020, 920, 850, 820, 735; ^{1}H- and ^{13}C-NMR: Tables 3, 4; CI-MS *m/z*: 346 $(M+H)^+$, 344 $(M+H)^+$. *Anal.* Calcd for $C_{19}H_{18}ClNO_3$: C, 66.38; H, 5.28; Cl 10.31; N, 4.07. Found: C, 66.24; H, 5.35; Cl, 10.24; N, 3.99.

***N*-(2-Bromo-4,5-dimethoxybenzyl)-2,2-dimethyl-6-chromenylamine (32)** Reduction of **28** (5.8 g, 14.4 mmol) with sodium borohydride (11 g, 290 mmol), under conditions similar to those described for the preparation of **30**, gave **32** (5.5 g, 95%) as an amorphous solid. UV λ_{max} (MeOH) nm (log ε): 253 (4.36), 260 (sh.) (4.33), 350 (3.58); IR (KBr) cm^{-1}: 3390, 2960, 2920, 1560, 1490, 1460, 1245, 1190, 1145, 950, 850, 790, 750; ^{1}H- and ^{13}C-NMR: Tables 3, 4; CI-MS *m/z*: 406 $(M+H)^+$, 404 $(M+H)^+$. *Anal.* Calcd for $C_{20}H_{22}BrNO_3$: C, 59.42; H, 5.48; Br 19.76; N, 3.47. Found: C, 59.37; H, 5.48; Br, 19.90; N, 3.32.

***N*-(2-Chloro-4,5-methylenedioxybenzyl)-2,2-dimethyl-6-chromenylamine (33)** Reduction of **29** (3.4 g, 10 mmol) with sodium borohydride (6 g, 158 mmol) under conditions similar to those described for the preparation of **30**, afforded **33** (3.25 g, 95%) as an amorphous solid. UV λ_{max} (MeOH) nm (log ε): 236 (4.45), 270 (sh.) (3.78), 289 (3.72), 350 (2.87); IR (KBr) cm^{-1}: 3380, 2960, 2870, 1600, 1550, 1470, 1350, 1230, 1200, 1150, 1100, 1025, 920, 850, 825, 800, 750; ^{1}H- and ^{13}C-NMR: Tables 3, 4; CI-MS *m/z*: 346 $(M+H)^+$, 344 $(M+H)^+$. *Anal.* Calcd for $C_{19}H_{18}ClNO_3$: C, 66.38; H, 5.28; Cl 10.31; N, 4.07. Found: C, 66.43; H, 5.35; Cl, 10.42; N, 3.98.

***N*-(2-Bromo-4,5-dimethoxybenzyl)-2,2-dimethyl-7-chromenylamine (36)** A solution of 7-amino-2,2-dimethylchromene (**17**) (1.53 g, 8.75 mol) and 6-bromoveratraldehyde (2.14 g, 8.75 mmol) in toluene (250 ml) was refluxed in a Dean-Stark apparatus for 24 h. The solvent was evaporated under reduced pressure to afford 3.2 g of crude imine **34**. Purification of an aliquot (100 mg) by preparative TLC on silica gel (solvent: cyclohexane/EtOAc 97/3) gave an analytical sample of **34**, ^{1}H- and ^{13}C-NMR: Tables 1, 2. The crude imine **34** was dissolved in MeOH (100 ml) and sodium borohydride (5 g, 132 mmol) was added at 0 °C over 30 min. The reaction mixture was stirred for 2 h at 0 °C and the solvent was evaporated under reduced pressure. Water (150 ml) and CH_2Cl_2 (150 ml) were added. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. Column chromatography of the residue on silica gel (eluent: cyclohexane/EtOAc 70/30) afforded **36** (1.88 g, 34%) as an amorphous solid. UV λ_{max} (MeOH) nm (log ε): 230 (4.81), 250 (4.43), 256 (4.39), 262 (4.31), 267 (4.23), 281 (4.16), 324 (3.78); IR (KBr) cm^{-1}: 3400, 2960, 2920, 2840, 1610, 1580, 1500, 1460, 1430, 1280, 1260, 1210, 1160, 1120, 1020, 980, 860, 790, 740; ^{1}H- and ^{13}C-NMR: Tables 3, 4; CI-MS *m/z*: 406 $(M+H)^+$, 404 $(M+H)^+$. *Anal.* Calcd for $C_{20}H_{22}BrNO_3$: C, 59.42; H, 5.48; Br 19.76; N, 3.47. Found: C, 59.34; H, 5.39; Br, 19.91; N, 3.35.

***N*-(2-Chloro-4,5-methylenedioxybenzyl)-2,2-dimethyl-7-chromenylamine (37)** Condensation of 7-amino-2,2-dimethylchromene (**17**) (1.84 g, 10.5 mmol) and 6-chloropiperonal (1.11 g, 10.5 mmol) under conditions similar to those described for the preparation of **36** afforded the crude imine **35**, which was subsequently reduced by sodium borohydride (5 g, 132 mmol) to give **37** (1.2 g, 33%) as an amorphous solid. UV λ_{max} (MeOH) nm (log ε): 237 (4.13), 296 (4.09), 312 (sh.) (4.01), 324 (sh.) (3.97); IR (KBr) cm^{-1}: 3380, 2960, 2880, 1600, 1490, 1440, 1400, 1230, 1110, 1025, 960, 920, 820, 745; ^{1}H- and ^{13}C-NMR: Tables 3, 4; CI-MS *m/z*: 346 $(M+H)^+$, 344 $(M+H)^+$. *Anal.* Calcd for $C_{19}H_{18}ClNO_3$: C, 66.38; H, 5.28; Cl 10.31; N, 4.07. Found: C, 66.49; H, 5.17; Cl, 10.19; N, 3.96.

***N*-(2-Bromo-4,5-dimethoxybenzyl)-2,2-dimethyl-8-chromenylamine (38)** A solution of 8-amino-2,2-dimethylchromene (**22**) (5.40 g, 30 mmol) and 6-bromoveratraldehyde (7.50 g, 30.6 mmol) in toluene (150 ml) was refluxed in a Dean-Stark apparatus for 24 h. The solvent was removed under reduced pressure. The residue was taken up in MeOH (200 ml) and sodium borohydride (20 g, 528 mmol) was added at 0 °C within 1 h. The mixture was stirred for 2 h at 0 °C and the solvent was evaporated under reduced pressure. Water (200 ml) and CH_2Cl_2 (200 ml) were added.

The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to afford **38** (12.3 g, 92%) as an amorphous solid. UV λ_{max} (MeOH) nm (log ε): 235 (4.44), 274 (4.05), 282 (4.02), 332 (3.40); IR (KBr) cm^{-1}: 3380, 2960, 2840, 1600, 1570, 1500, 1460, 1430, 1260, 1210, 1165, 1110, 1030, 950, 860, 790, 730; ^1H- and ^{13}C-NMR: Tables 3, 4; CI-MS *m/z*: 406 $(M+H)^+$, 404 $(M+H)^+$. *Anal.* Calcd for $C_{20}H_{22}BrNO_3$: C, 59.42; H, 5.48; Br 19.76; N, 3.47. Found: C, 59.37; H, 5.37; Br, 19.87; N, 3.49.

***N*-(2-Chloro-4,5-methylenedioxybenzyl)-2,2-dimethyl-8-chromenylamine (39)** Condensation of 8-amino-2,2-dimethylchromene (**22**) (3.41 g, 19.5 mmol) and 6-chloropiperonal (3.60 g, 19.5 mmol) followed by sodium borohydride reduction, under conditions essentially similar with those described for the preparation of **38**, afforded **39** (5.40 g, 80%) as an amorphous solid. UV λ_{max} (MeOH) nm (log ε): 227 (4.42), 264 (4.06), 274 (4.05), 330 (3.39); IR (KBr) cm^{-1}: 3400, 2960, 2880, 1590, 1560, 1470, 1400, 1360, 1230, 1190, 1100, 1025, 920, 850, 820, 780, 750; ^1H- and ^{13}C-NMR: Tables 3, 4; CI-MS *m/z*: 346 $(M+H)^+$, 344 $(M+H)^+$. *Anal.* Calcd for $C_{19}H_{18}ClNO_3$: C, 66.38; H, 5.28; Cl, 10.31; N, 4.07. Found: C, 66.49; H, 5.34; Cl, 10.27; N, 4.15.

General Procedure for Cyclization into Pyranophenanthridines. 8,9-Dimethoxy-2,2-dimethyl-2*H*-pyrano[2,3-*c*]phenanthridine (3) A 2 M lithium diisopropylamide solution in heptane–tetrahydrofuran–ethylbenzene (36.2 ml, 72.4 mmol) was added at −78 °C under argon to a solution of *N*-(2-bromo-4,5-dimethoxybenzyl)-2,2-dimethyl-5-chromenylamine (**30**) (7.3 g, 18.1 mmol). The reaction mixture was stirred at −78 °C for 4 h and allowed to warm to room temperature within 16 h. The resulting suspension was diluted with CH_2Cl_2 (300 ml) and washed with H_2O (200 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. Column chromatography of the residue (eluent: CH_2Cl_2/MeOH 99/1) afforded **3** (3.2 g, 44%) as crystals, mp 188—190 °C (CH_2Cl_2). UV λ_{max} (EtOH) nm (log ε): 232 (4.10), 259 (sh.) (4.42), 265 (4.46), 290 (sh.) (3.93), 298 (sh.) (3.81), 314 (3.69), 329 (3.64), 370 (3.23), 385 (3.23); IR (KBr) cm^{-1}: 2960, 2800, 1600, 1580, 1490, 1460, 1420, 1350, 1280, 1260, 1250, 1140, 1100, 1030, 840, 810, 785, 740; ^1H- and ^{13}C-NMR: Tables 5, 6; MS *m/z*: 321 (M^+) 306, 290. *Anal.* Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.54; H, 5.97; N, 4.21.

The following pyrano[*c*]phenanthridines were prepared in a manner similar to that used for **3**, from the appropriate benzylchromenylamines.

8,9-Methylenedioxy-2,2-dimethyl-2*H*-pyrano[2,3-*c*]phenanthridine (**4**): Yield 25% from **31**. Amorphous solid. UV λ_{max} (EtOH) nm (log ε): 235 (4.29), 262 (sh.) (4.68), 267 (4.69), 290 (sh.) (4.08), 301 (4.04), 315 (3.89), 329 (3.77), 370 (3.43), 385 (3.43); IR (KBr) cm^{-1}: 2960, 2900, 1615, 1590, 1490, 1450, 1430, 1350, 1260, 1250, 1155, 1100, 1040, 1010, 940, 900, 850, 815, 740; ^1H- and ^{13}C-NMR: Tables 5, 6; MS *m/z*: 305 (M^+), 290. *Anal.* Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.64; H, 5.03; N, 4.53.

8,9-Dimethoxy-3,3-dimethyl-3*H*-pyrano[3,2-*c*]phenanthridine (**5**): Yield 50% from **38**. Crystals, mp 206—208 °C (CH_2Cl_2). UV λ_{max} (EtOH) nm (log ε): 220 (4.48), 242 (4.58), 257 (4.72), 278 (4.77), 284 (4.80), 288 (4.79), 295 (4.75) 318 (sh.) (4.29), 340 (sh.) (3.98), 361 (sh.) (3.68), 378 (3.53); IR (KBr) cm^{-1}: 3000, 2960, 1600, 1520, 1500, 1450, 1250, 1190, 1140, 900, 850, 790; ^1H- and ^{13}C-NMR: Tables 5, 6; MS *m/z*: 321 (M^+), 306, 290, 262. *Anal.* Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.74; H, 5.89; N, 4.32.

8,9-Methylenedioxy-3,3-dimethyl-3*H*-pyrano[3,2-*c*]phenanthridine (**6**): Yield 40% from **39**. Crystals, mp 166 °C (CH_2Cl_2). UV λ_{max} (EtOH) nm (log ε): 247 (4.60), 252 (sh.) (4.46), 262 (4.53), 274 (4.39), 286 (4.53), 324 (sh.) (3.83), 342 (sh.) (3.52), 362 (sh.) (3.21), 379 (sh.) (2.87); IR (KBr) cm^{-1}: 2960, 2880, 1600, 1520, 1490, 1460, 1440, 1280, 1240, 1200, 1115, 1025, 930, 860, 780; ^1H- and ^{13}C-NMR: Tables 5, 6; MS *m/z*: 305 (M^+), 290. *Anal.* Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.52; H, 4.99; N, 4.52.

The following pyrano [*a*] and [*b*] phenanthridines were prepared from the appropriate benzylchromenylamines in a manner similar to that used for **3**. In each case, the two [*a*] and [*b*] isomers obtained were easily separated by column chromatography (eluent: CH_2Cl_2/MeOH 99/1).

2,3-Dimethoxy-10,10-dimethyl-10*H*-pyrano[2,3-*b*]phenanthridine (**7**): Yield 19% from **32**. Amorphous solid. UV λ_{max} (EtOH) nm (log ε): 221 (4.59), 237 (4.53), 263 (sh.) (4.78), 274 (4.95), 285 (4.97), 300 (sh.) (4.60), 315 (sh.) (4.53) 337 (sh.) (3.85), 357 (3.98) 375 (4.06); IR (KBr) cm^{-1}: 2940, 2900, 1600, 1500, 1470, 1250, 1240, 1140, 1100, 1000, 910, 820, 790, 740; ^1H- and ^{13}C-NMR: Tables 5, 6; MS *m/z*: 321 (M^+), 306, 290, 262, 248. *Anal.* Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.58; H, 5.92; N, 4.29.

10,11-Dimethoxy-3,3-dimethyl-3*H*-pyrano[3,2-*a*]phenanthridine (**9**): Yield 21% from **32**. Crystals, mp 173 °C (CH_2Cl_2). UV λ_{max} (EtOH) nm (log ε): 225 (4.80), 234 (sh.) (4.77), 265 (sh.) (4.77), 274 (4.80), 285 (4.81), 298 (sh.) (4.69), 330 (sh.) (4.29), 338 (sh.) (3.88), 355 (sh.) (3.69) 371 (sh.) (3.36); IR (KBr) cm^{-1}: 2980, 2920, 1610, 1590, 1520, 1500, 1460, 1400, 1380, 1360, 1320, 1260, 1140, 1110, 1080, 1030, 1010, 950, 910, 840, 820, 790, 750; ^1H- and ^{13}C-NMR: Tables 5, 6; MS *m/z*: 321 (M^+), 306, 290. *Anal.* Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.87; H, 6.02; N, 4.39.

2,3-Methylenedioxy-10,10-dimethyl-10*H*-pyrano[2,3-*b*]phenanthridine (**8**): Yield 15% from **33**. Amorphous solid. UV λ_{max} (EtOH) nm (log ε): 257 (4.55), 266 (sh.) (4.60), 274 (4.66), 287 (4.66), 303 (sh.) (4.41), 314 (sh.) (4.35), 338 (sh.) (3.65), 357 (3.67), 376 (3.74); IR (KBr) cm^{-1}: 2980, 2920, 1610, 1500, 1470, 1450, 1250, 1210, 1110, 1040, 940, 850, 750; ^1H- and ^{13}C-NMR: Tables 5, 6; MS *m/z*: 305 (M^+), 290. *Anal.* Calcd for $C_{19}H_{15}NO_3$: C, 74.74 ; H, 4.95; N, 4.59. Found: C, 74.59; H, 4.87; N, 4.61.

10,11-Methylenedioxy-3,3-dimethyl-3*H*-pyrano[3,2-*a*]phenanthridine (**10**): Yield 14% from **33**. Amorphous solid. UV λ_{max} (EtOH) nm (log ε): 234 (4.46), 244 (sh.) (4.33), 261 (4.41), 277 (sh.) (4.40), 287 (4.47), 299 (4.38), 326 (sh.) (3.85), 340 (sh.) (3.81), 356 (sh.) (3.60), 375 (sh.) (3.20); IR (KBr) cm^{-1}: 2940, 2880, 1610, 1570, 1500, 1470, 1440, 1340, 1310, 1240, 1200, 1140, 1100, 1050, 1020, 930, 850, 810, 800, 730; ^1H- and ^{13}C-NMR: Tables 5, 6; MS *m/z*: 305 (M^+), 290. *Anal.* Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.61; H, 5.01; N, 4.47.

2,3-Dimethoxy-9,9-dimethyl-9*H*-pyrano[3,2-*b*]phenanthridine (**11**): Yield 10% from **36**. Amorphous solid. UV λ_{max} (EtOH) nm (log ε): 266 (sh.) (4.54), 270 (4.58), 298 (sh.) (4.06), 318 (3.97), 330 (3.95), 362 (3.46), 382 (3.39); IR (KBr) cm^{-1}: 2960, 2920, 1610, 1510, 1460, 1440, 1260, 1160, 1120, 1040, 850, 760; ^1H- and ^{13}C-NMR: Tables 5, 6; MS *m/z*: 321 (M^+), 306, 290. *Anal.* Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.72; H, 5.87; N, 4.29.

10,11-Dimethoxy-2,2-dimethyl-2*H*-pyrano[2,3-*a*]phenanthridine (**13**): Yield 10% from **36**. Amorphous solid. UV λ_{max} (EtOH) nm (log ε): 250 (4.15), 266 (3.91), 296 (sh.) (3.85), 327 (sh.) (3.56), 342 (sh.) (3.45), 358 (sh.) (3.34), 379 (3.23); IR (KBr) cm^{-1}: 2940, 2900, 1595, 1570, 1490, 1440, 1360, 1240, 1190, 1140, 1030, 840, 810, 730; ^1H- and ^{13}C-NMR: Tables 5, 6; MS *m/z*: 321 (M^+), 306, 290. *Anal.* Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.87; H, 5.85; N, 4.44.

2,3-Methylenedioxy-9,9-dimethyl-9*H*-pyrano[3,2-*b*]phenanthridine (**12**): Yield 5% from **37**. Amorphous solid. UV λ_{max} (EtOH) nm (log ε): 262 (4.40), 268 (sh.) (4.47), 304 (sh.) (4.27), 330 (3.57), 366 (sh.) (3.49); IR (KBr) cm^{-1}: 2960, 2890, 1600, 1560, 1230, 920, 850, 750; ^1H- and ^{13}C-NMR: Tables 5, 6; MS *m/z*: 305 (M^+), 290. *Anal.* Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.59; H, 4.84; N, 4.66.

10,11-Methylenedioxy-2,2-dimethyl-2*H*-pyrano[2,3-*a*]phenanthridine (**14**): Yield 5% from **37**. Amorphous solid. UV λ_{max} (EtOH) nm (log ε): 250 (4.40), 271 (4.28), 299 (4.13), 330 (3.66), 344 (sh.) (3.62), 362 (3.52), 381 (3.46); IR (KBr) cm^{-1}: 2960, 2880, 1600, 1550, 1480, 1460, 1430, 1350, 1230, 1110, 1020, 920, 850, 810, 740; ^1H- and ^{13}C-NMR: Tables 5, 6; MS *m/z*: 305 (M^+), 290. *Anal.* Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.85; H, 5.02; N, 4.67.

Pharmacology. Compounds The compounds were solubilized at 10^{-2} M in dimethylsulfoxide and diluted in complete culture medium.

Cell Culture and Cytotoxicity L1210 cells were provided by the NCI, Frederick, U.S.A. and HT29 cells by the American Type Culture Collection, Rockville, U.S.A. They were cultivated in Roosevelt Park Memorial Institute 1640 medium (Gibco) supplemented with 10% fetal calf serum, 2 mM L-glutamine, 100 units/ml penicillin, 100 μg/ml streptomycin, and 10 mM HEPES buffer (pH 7.4). Cytotoxicity was measured by the microculture tetrazolium assay as described.[33] Cells were exposed to graded concentrations of the compounds (nine serial dilutions in triplicate) for 48 h (L1210) or 96 h (HT29). Results were expressed as IC_{50}, the concentration which reduced by 50% the optical density of treated cells with respect to untreated controls.

Cell Cycle Analysis For the cell cycle analysis, L1210 cells (2.5×10^5 cells/ml) were incubated for 21 h with various concentrations of the compounds. Cells were then fixed with 70% ethanol (v/v), washed and incubated in phosphate buffered saline containing 100 μg/ml RNAse and 25 μg/ml propidium iodide for 30 min at 20 °C. For each sample, 10^4 cells were analyzed on an ATC3000 flow cytometer (Bruker, France)

using an argon laser (Spectra-Physics) emitting 400 mW at 488 nm. The fluorescence of propidium iodide was collected through a 615 nm long-pass filter. Data are displayed as linear histograms (not shown) and results are expressed as the percentage of cells found in the different phases of the cell cycle.

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