SYNTHESIS OF 11-AMINOSUBSTITUTED 6, 8-DIMETHYL-12H-[1]-BENZO[5,6]THIOPYRANO-[2,3-c]QUINOLIN-12-ONES AS BENZO ANALOGUES OF LUCANTHONE

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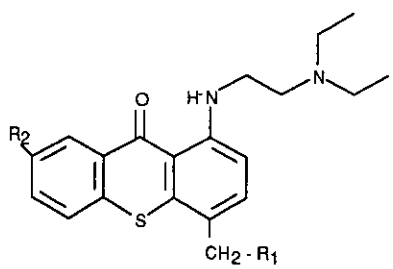
Abstract - Condensation of acetonyl 2-methyl-5-chlorophenyl sulfide with potassium isatates led to 2-methyl-3-(2-methyl-5-chlorophenylthio)-4-quinolinecarboxylic acids. Polyphosphoric acid cyclodehydration then afforded 6,8-dimethyl-11-chloro-*12H*-[1]benzo[5,6]-thiopyrano[2,3-c]quinolin-12-ones whose substitution by dialkylaminoalkylamines gave the title compounds. Whereas 2- and 3-methoxy - substituted products were transformed into their phenolic derivatives by hydrobromic acid. Regioselective oxidation of the 6-methyl group successively led to 6-formyl, 6-carboxy and 6-H- series.
Evaluation of cytotoxic and antitumor properties showed that these new benzolucanthone analogues are devoid of biological activity.

It has been known for a long time that thioxanthen-9-one derivatives containing dialkylaminoalkylamino side chains display marked antileukemia activity.[1,2] 1-[(2-Diethylamino)ethyl]amino-4-methylthioxanthen-9-one (lucanthone) (**1**) has been found active on a number of mouse tumors[1] and has been studied clinically. A significant increase of activity against lymphocytic leukemia P388 has been obtained by Archer and all through the introduction of a hydroxyl group on the 4-methyl substituent[2] (**2**) and on the 7-position of the thioxanthone (**3**) heterocyclic system.[3]

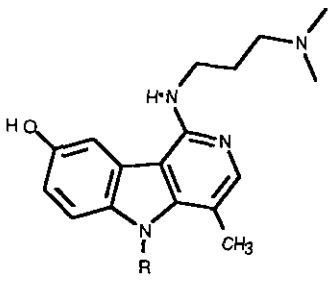


1 : $R_1 = R_2 = H$; (Lucanthone)

2: R_1 = OH ; R_2 = H; (Hycanthone)

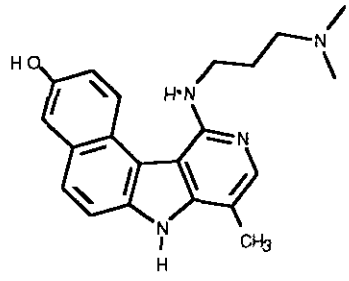
3 : R_1 = H ; R_2 = OH

In our laboratory, it has been shown that related compounds such as conveniently substituted *5H*-pyrido-[4,3-b]indoles (**4a,b**) display potent antitumor properties[4] and their benzo analogue *5H*-pyrido-[4,3-b]benzo[c]indole (**5**) is a higher active antitumor drug which is now selected for clinical trials.[5,6]



4a : R=H

4b : R= CH_3



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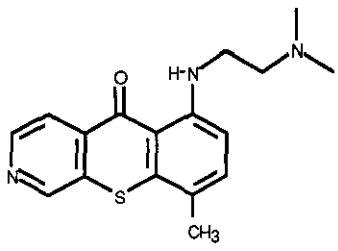
As it was demonstrated that *5H*-[1]benzothiopyrano [2,3-c]pyridin-5-one derivative (**6**) is a weakly active aza-analogue of lucanthone (**1**),[7] we decided to investigate on the yet unknown series of 11-aminosubstituted 6,8-dimethyl - (and 8-methyl-) *12H*-[1]benzo[5,6]thiopyrano[2,3-c]quinolin-12-ones of general formula (**7**).



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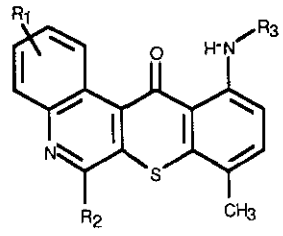

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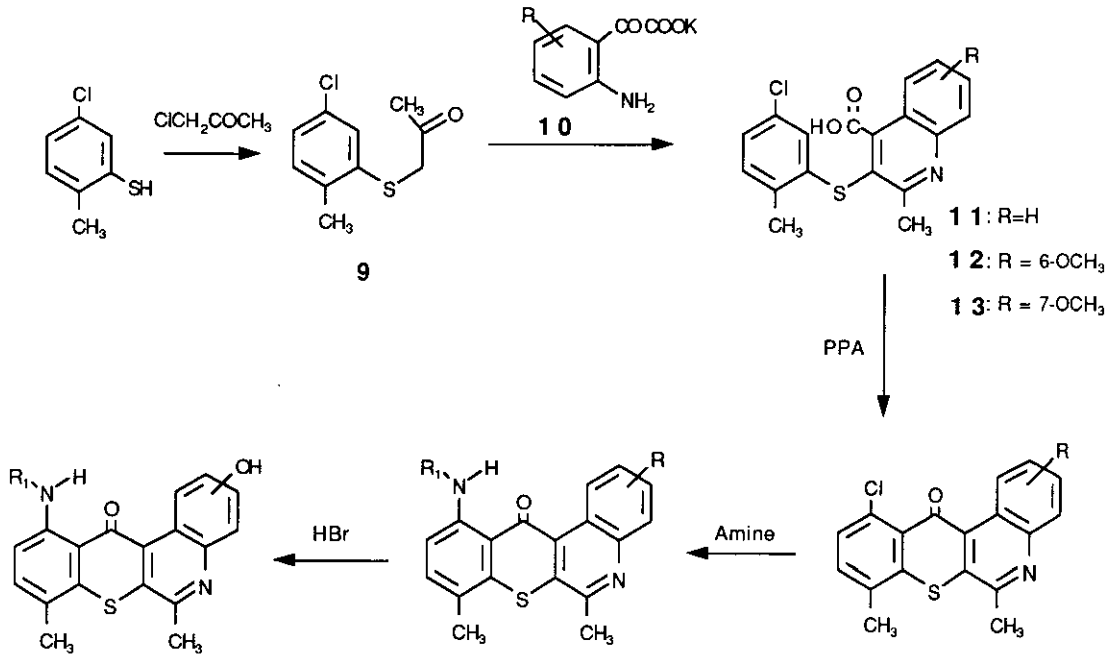
This paper describes the chemical and biological results which have been obtained.

Chemistry. The sodium salt of 3-chloro-6-methylthiophenol (**8**) was reacted with chloroacetone at room temperature, giving acetonyl 5-chloro-2-methylphenyl sulfide (**9**). Condensation of this compound with potassium isatates (**10**) (R = H, 4-OCH_3, 5-OCH_3) easily led to 2-methyl-3-(5-chloro-2-methylphenyltio)-4-quinolinecarboxylic acids (**11-13**), according to the conditions of Pfitzinger reaction.[8] Cyclodehydration by means of polyphosphoric acid then afforded 11-chloro-6,8-dimethyl-12H-[1]benzo[5,6]thiopyrano-

[2,3-c]quinolin-12-ones (**14-16**) (with respectively 60, 65 and 40% overall yield from **9**). Substitution of compound (**14**) took place in an excess of refluxing diamines (120-140°C) affording the expected derivatives (**17a-d**) in 50 to 70 % yields. However, for substitution of methoxylated products (**15**) and (**16**), the reaction was performed in steel vessel, at 170°C for 4 days. The resulting 11-[(dialkylamino)alkyl]amino-*12H*-[1]benzo[5,6]-thiopyrano[2,3-c]quinolin-12-ones (**18a-c**) and (**19a-c**) were then transformed into their phenolic derivatives (**20a-c**) and (**21a-c**) (50-70 % yields) in boiling hydrobromic acid (Scheme I).



20a : 2-OH ; $R_1 = (CH_2)_2N(CH_3)_2$
20b : 2-OH ; $R_1 = (CH_2)_2N(C_2H_5)_2$
20c : 2-OH ; $R_1 = (CH_2)_3N(CH_3)_2$

21a : 3-OH ; $R_1 = (CH_2)_2N(CH_3)_2$
21b : 3-OH ; $R_1 = (CH_2)_2N(C_2H_5)_2$
21c : 3-OH ; $R_1 = (CH_2)_3N(CH_3)_2$

17a : R = H ; $R_1 = (CH_2)_2N(CH_3)_2$
17b : R = H ; $R_1 = (CH_2)_2N(C_2H_5)_2$
17c : R = H ; $R_1 = (CH_2)_3N(CH_3)_2$
17d : R = H ; $R_1 = (CH_2)_3N(C_2H_5)_2$

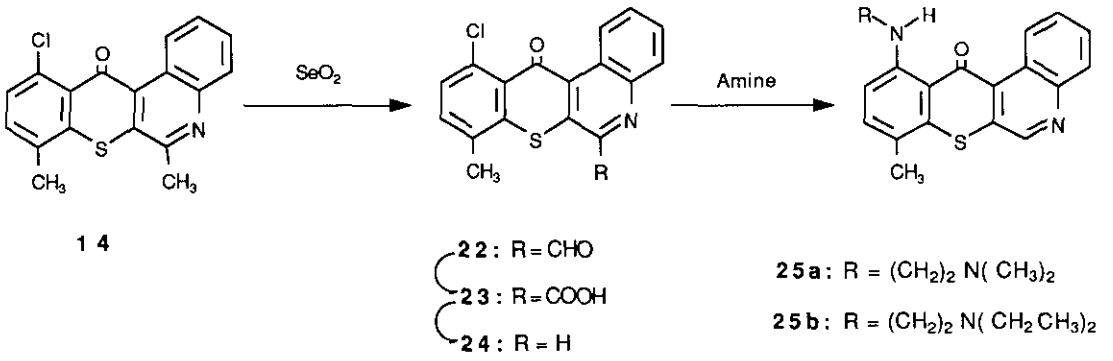
18a : R = 2-OCH_3 ; $R_1 = (CH_2)_2N(CH_3)_2$
18b : R = 2-OCH_3 ; $R_1 = (CH_2)_2N(C_2H_5)_2$
18c : R = 2-OCH_3 ; $R_1 = (CH_2)_3N(CH_3)_2$

19a : R = 3-OCH_3 ; $R_1 = (CH_2)_2N(CH_3)_2$
19b : R = 3-OCH_3 ; $R_1 = (CH_2)_2N(C_2H_5)_2$
19c : R = 3-OCH_3 ; $R_1 = (CH_2)_3N(CH_3)_2$

14 : R = H
15 : R = 2-OCH_3
16 : R = 3-OCH_3

Scheme I

For preparation of 6-unsubstituted derivatives, we first tried to use the same pathway, by starting from chloroacetaldehyde or chloroacetaldehyde diethyl acetal. Unfortunately, we failed to obtain the expected aryl substituted thioacetaldehyde. We then studied selective oxidation of the 6-methyl group of **14**. Indeed, selenium dioxide gave the aldehyde (**22**), which was transformed into the corresponding carboxylic acid (**23**) by silver (I) oxide.[9] However, treating the resulting mixture in boiling acetic acid for purification, we observed a partial decarboxylation, giving a 1/2 mixture of **23** and **24** (66 % overall yield). This decarboxylation **23** → **24** was completed in boiling quinoline. Finally, substitution of 11-chloro-8-methyl-*12H*-[1]benzo[5,6]thiopyrano-[2,3-c]quinolin-12-one (**24**) easily afforded diamino derivatives (**25a,b**) (Scheme II).



Scheme II

Biological evaluation. All the compounds were tested *in vitro* on the growth of L1210 leukaemia cells in culture. Most of them were found toxic at 5 x 10^{-5}M and completely inactive at 10^{-6}M. Under these conditions, the dose inhibiting the growth of L1210 cells by 50 % (IC 50) was estimated for only four compounds.

Compound	IC 50 (μM)
17a	3
17b	4
17c	2.8
21a	2.4

In spite of these disappointing results, compounds (**21a**), (**21b**)and (**25a**) were tentatively tested *in vivo* in P388 system at 15 and 30 mg/kg but were found highly toxic after a single i.p. injection. The lack of cytostatic properties among this series is rather surprising since introduction of a nitrogen atom in the ring system of lucanthone as in compound (**6**)[7] or hydroxylation of the aromatic nucleus, *e.g.* molecule (**3**),[3] do not suppress and even increase antitumor activity.

On the other hand we have shown that "benzologation" of tricyclic compound such as **4a** potentiate substantially the biological potency as demonstated by the high activity of **5**. Using simple Hückel molecular orbital calculation, various electronic properties like charge and LUMO/HOMO indexes at the methyl group as well as at various other sites of the molecules were determined but neither significant difference nor clear correlation were found between active (*e.g.* **3-6**) and inactive (*e.g.* **17-21**) compounds. These observations might suggest some geometrical parameters to be considered as in the receptor/effector mediated biological response, possibly at the DNA/Topoisomerase site of interaction or at some kinase activation level.

EXPERIMENTAL SECTION

All melting points were determined with a Reichert hot stage microscope and are uncorrected. ^{1}H Nmr spectra were recorded either on a Varian XL100 (100 MHz) or on a Bruker WB400 (400 MHz). Chemical shifts are given in ppm related to tetramethylsilane ($\delta_{tms} = 0$). Abbreviations are : s = singlet ; d = doublet ; dd = double doublet ; t = triplet ; q = quartet ; qt = quintet ; m = multiplet ; br s = broad singlet. All elemental analyses were performed at the "Institut des substances naturelles", C.N.R.S., Gif sur Yvette).

Acetonyl 5-chloro-2-methylphenyl sulfide (9). 5-Chloro-2-methylthiophenol (**8**) (10g, 63 mmol) and NaOH (2.8 g, 70 mmol) were disolved in water (100 ml). Then chloroacetone (5.8 g, 63 mmol) was added dropwise under continuous stirring at room temperature. The mixture was allowed to stand for 2 h at room temperature. The precipitate that resulted was filtered off, washed with a small amount of cold water and dried. Recrystallization from n-hexane gave **9** as colorless needles (13 g, 96 %), mp 55°C. *Anal.* Calcd for $C_{10}H_{11}OClS$: C, 55.94 ; H, 517 ; S, 14.93. Found : C, 55.73 ; H, 5.13 ; S, 14.63.^{1}H-Nmr ($CDCl_3$, 100 MHz) δ : 2.30 (3H, s, CH_3, Ar), 2.36 (3H, s, $CO.CH_3$), 3.70 (2H, s, CH_2), 7.09 (2H, m, 4-H + 5-H) 7.21 (1H, br s, H_2).

Preparation of cinchoninic acids (11, 12 and 13). General procedure : A mixture of isatine (4.1 g, 28 mmol) or methoxyisatine (4.95 g, 28 mmol) and KOH (3.5 g, 61.5 mmol) in a few drops of water and compound (**9**) (6 g, 28 mmol) dissolved in ethanol (100 ml) was refluxed for 24 h (48 h for compound (**13**)).

Ethanol was removed by evaporation and the residue was dissolved in water. After filtration the solution was acidified with acetic acid and the solid was collected by filtration, washed with water and ethanol and dried to provide a colorless powder, mp > 300°C, which was used without purification for the next step.

2-Methyl-3-(5-chloro-2-methylphenylthio)-4-quinolinecarboxylic acid (**11**) was obtained in 77 % yield from isatine.

6-Methoxy-2-methyl-3-(5-chloro-2-methylphenylthio)- 4-quinolinecarboxylic acid (**12**) was obtained using 5 - methoxyisatine [11] in 77 % yield.

7-Methoxy-2-methyl-3-(5-chloro-2-methylphenylthio)-4-quinolinecarboxylic acid (**13**) was obtained using 6-methoxyisatine [12] in 56 % yield.

Cyclization of acids into *12H*-[1]benzo[5,6]thiopyrano[2,3-c]quinolin-12-ones (14, 15 and 16). General procedure. The above acids (**11**), (**12**), (**13**) (15 mmol) was added in one portion to polyphosphoric acid (50 g) heated at 80°C. The mixture was stirred at 130°C for 3 h. After cooling, it was poured into ice-water, basified by 32 % ammonium hydroxide and extrated with dichloromethane. The combined extracts were washed with 1N NaOH and evaporated to afford a solid, which was purified by crystallization from toluene.

11-Chloro-6,8-diméthyl-*12H*-[1]benzothiopyrano[2,3-c] quinolin-12-one (**14**) was obtained in 77 % yield (from **11**) as yellow needles, mp 209°C. *Anal* . Calcd for $C_{18}H_{12}NOClS$: C, 66.35 ; H, 3.71 ; N, 4.30. Found: C, 66.08 ; H, 3.95 ; N, 4.31. ^{1}H-Nmr [$(CD_3)_2SO$, 100 MHz] δ : 2.60 (3H, s, 8-CH_3), 2.93 (3H, s, 6-CH_3), 7.68 (2H, s, 9-H + 10-H), 7.82 (2H, m, 2-H + 3-H), 8.09 (1H, m, 4-H), 8.84 (1H, m, 1-H).

11-Chloro-6,8-dimethyl-2-methoxy-*12H*-[1]benzothiopyrano[2,3-c]quinolin-12-one (**15**) was obtained in 84 % yield (from **12**) as yellow cristals, mp 241°C. *Anal* . Calcd for $C_{19}H_{14}NO_2ClS$: C, 64.13 ; H, 3.96 ; N, 3.95. Found : C, 64.07 ; H, 4.15 ; N, 3.76. ^{1}H-Nmr ($CDCl_3$, 100 MHz) δ : 2.58 (3H, s, 8-CH_3), 2.91 (3H, s, 6-CH_3), 4,02 (3H, s, OCH_3), 7.39 (3H, m, 4-H + 9-H + 10-H), 7.98 (1H, d, J_{H3-H4} = 9 Hz, 3-H), 8.43 (1H, d, J_{H1-H4} = 2.7 Hz, 1-H).

11-Chloro-6,8-dimethyl-3-methoxy-*12H*-[1]benzothiopyrano[2,3-c]quinolin-12-one (**16**) was obtained in 70 % yield (from **13**) as yellow needles, mp 229°C. *Anal* . Calcd for $C_{19}H_{14}NO_2ClS$: C, 64.13 ; H, 3.97 ; N, 3.93. Found: C, 64.07 ; H, 4.29 ; N, 3.76. ^{1}H-Nmr ($CDCl_3$, 100 MHz) δ : 2.57 (3H, s, 8-CH_3), 2.93 (3H, s, 6-CH_3), 3.98 (3H, s, OCH_3), 7.39 (4H, m, 2-H + 4-H + 9-H + 10-H), 8.88 (14, d, J_{H1-H2} = 9.3 Hz,1-*H*).

General procedure for obtaining amino derivatives (17a-d, 18a-c, 19a-c and 25a-b). A mixture of the required chloro derivative (1.5 mmol) and the appropriate amine (15 ml, large excess) was refluxed for the

time indicated in Table I, under N_2. Excess of diamine was removed under reduced pressure, the residue was dissolved in 10 % aqueous hydrochloric acid and washed with methylene chloride. The aqueous layer was basified with 32 % aqueous ammonium hydroxide and extracted with methylene chloride. The organic layer was dried ($MgSO_4$), filtered and evaporated, giving a red solid, which was chromatographed on an alumina column with methylene chloride as eluent. The resulting pure compound was taken up in hexane or cyclohexane, giving red crystals. The physical data are reported in Table I.

Preparation of hydroxy derivatives (20a-c and 21a-c). A mixture of methoxylated compound (100 mg) and concentrated hydrobromic acid (d = 1.47 ; 10 ml) was stirred under argon and heated at reflux for 5 h. The mixture was evaporated under reduced pressure and the residue was taken up in water, filtered and the filtrate was basified with 32 % ammonium hydroxide. The resulting precipitate was extracted with ethyl acetate and the organic layer was dried ($MgSO_4$). Evaporation of the solvent provided a red residue, which was recrystalized from methanol or ethanol to give orange or red crystals. The physical data were reported in Table II.

11-Chloro-6-formyl-8-methyl-*12H*-[1]benzo[5,6]thiopyrano[2,3-c]quinolin-12-one (22). A mixture of compound (**14**) (3.2 g, 9.89 mmol) and selenium (IV) oxide (2.2g, 19.8 mmol) suspended in diethylene glycol diethyl ether (50ml) was refluxed with stirring for 4 h. After this time, the mixture was cooled to room temperature and filtered. Evaporation of the filtrate gave a solid which was dissolved in toluene, filtered and purified by chromatography on silica gel eluting with toluene. Recrystallization from toluene yielded **22** as yellow needles (1.9 g, 57 %), mp 260°C. *Anal.* Calcd for $C_{18}H_{10}NO_2ClS$: C, 63.62 ; H, 2.96 ; N, 4.18. Found : C, 63.48 ; H, 2.81 ; N, 4.17. ^{1}H-Nmr ($(CD_3)_2SO$, 100 MHz) δ : 7.81 (2H, s, 9-H + 10-H), 8.01 (2H, m, 2-H + 3-H), 8.50 (1H, m, 4-H), 8.97 (1H, m, 1-H), 10.40 (1H, s, CHO).

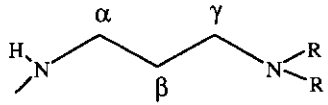
11-Chloro-8-methyl-*12H*-[1]benzo[5,6]thiopyrano[2,3-c]quinolin-12-one-6-carboxylic acid (23). To the above aldehyde (**22**) (1.9 g, 5.6 mmol) dissolved in a mixture of THF (250 ml) and water (40 ml) was added Ag_2O (1.2 g, 5.2 mmol). The resulting mixture was stirred at room temperature for 24 h, refluxed for 4 h and then allowed to cool to room temperature. Subsequently, water (20 ml) and 30 % NaOH (30 ml) were added successively with stirring for 1 h. Water (100 ml) was added and the mixture was filtered off. The solid product was extracted with hot acetic acid (3 x 50 ml). The resulting yellow solution obtained by filtration was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with aqueous 1N NaOH (3 x 250 ml). The aqueous phase was acidified with 37 % aqueous HCl and the resulting precipitate was collected by filtration, dried and crystallized from ethanol to afford the expected acid (**23**) as pale yellow crystals (400 mg, 20 %). *Anal.* Calcd for $C_{18}H_{10}NO_3ClS$: C, 60.76 ; H, 2.83 ; N, 3.93. Found : C, 60.51 ; H, 2.79 ;

N, 3.86. ^{1}H-Nmr ($(CD_3)_2SO$, 100 MHz) δ : 7.67 (2H, s, 9-H + 10-H), 7.95 (2H, m, 2-H +3-H), 8.27 (1H, m, 4-H), 8.84 (1H, m, 1-H).

The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure. Purification of the resulting residue by chromatography on silica gel eluting with toluene gave first the recovered starting material (200 mg) then the 11-chloro-8-methyl-*12H*-[1]benzo[5,6]thiopyrano[2,3-c]quinolin-12-one (**24**) (700 mg, 44 %) as yellow microcrystals, mp 195 °C from ethanol. *Anal.* Calcd for $C_{17}H_{10}NOClS$: C, 65.48 ; H, 3.23 ; N, 4.50. Found : C, 65.63 ; H, 3.29 ; N, 4.55. ^{1}H-Nmr ($CDCl_3$, 400 MHz) δ : 2.56 (3H, s, CH_3), 7.38 (1H, d, J_{H10-H9} = 8.4 Hz, 10-H), 7.49 (1H, d, 9-H), 7.76 (2H, m, 2-H + 3-H), 8.18 (1H, dd, J_{H4-H3} = 8.2 Hz, J_{H4-H2} = 1.6 Hz, 4-H), 9.02 (1H, s, 6-H), 9.08 (1H, m, 1-H).

11-Chloro-8-methyl-*12H*-[1]benzo[5,6]thiopyrano[2,3-c]quinolin-12-one (24). A mixture of acid (**23**) (0.4 g, 1.125 mmol) in quinoline (5 ml) and a catalytic amount of copper powder was refluxed for 1 h. After cooling the mixture was poured into 37 % aqueous HCl and extracted with methylene chloride. The dried ($MgSO_4$) organic layer was evaporated to afford a yellow solid ,which was purified by chromatography on silica gel eluting with toluene. This compound (200 mg, 57 %) is identical to that obtained above.

Biological testing. L1210 (ATCC-CCL 219) cells were cultivated in Dulbecco's MEM supplemented with 10 % fetal calf serum at 37°C in a water-jacketed CO_2 incubator (5 % CO_2). Cells were seeded at 10^5 cells/ml in 1 ml microwell plates. After 24 h (usually 3 to 4 x 10^5 cells/ml), tested compounds were added in duplicate at various concentrations and incubated for 24 h. Cells were counted with a Coulter-Counter ZM (Coultronics Inc.). The dose inhibiting the growth by 50 % (IC 50) was extrapolated from regression curves obtained with experimental points without significant toxicity. For *in vivo* assays BDF1 mice were injected intraperitonealy 0.2 ml of a solution of tested compound at an appropriate concentration in neutral olive oil, 24 h after i.p. inoculation of 10^6 P 388 leukemia cells. Unfortunately, after the first injection, all mice became cachectic and had to be sacrified.

Compd No	Method [a]	Yield (%)	mp °C	 ^{1}H nmr δ (ppm)	
17a	A	69	161	400 MHz $CDCl_3$	2.39 (6H, s, $N(CH_3)_2$), 2.42 (3H, s, 8-CH_3), 2.72 (2H, t, J = 7 Hz, βCH_2,), 2.94 (3H, s, 6-CH3), 3.39 (2H, dd, J = 7, 5 Hz, αCH_2), 6.64 (1H, d, J = 8.6 Hz, 10-H), 7.03 (1H, d, J = 8.6 Hz, 9-H), 7.65 (2H, m, 2-H + 3-H), 8.06 (1H, dd, J = 8.4, 1.5 Hz, 4-H), 9.50 (1H, dd, J = 8.5, 1.45 Hz, 1-H,), 9.66 (1H, t, J = 5 Hz, NH).
17b	A	55	94	100 MHz $CDCl_3$	1.15 (6H, t, J = 7 Hz, $N(CH_2 CH_3)_2$) , 2.43 (3H, s, 8-CH_3), 2.68 (6H, q, J = 7 Hz, βCH_2 + $N(CH_2$-$CH_3)_2$), 2.94 (3H, s, 6-CH_3), 3.36 (2H, q, J = 7 Hz, αCH_2), 6.64 (1H, d, J = 8.5 Hz, 10H), 7.30 (1H, d, J = 8.5 Hz, 9-H), 7.68 (2H, m, 2-H + 3-H), 8.07 (1H, m, 4-H), 9.48 (1H, m, 1-H), 9.65 (1H, br s, NH).
17c	A	70	138	400 MHz ($CDCL_3$)	2.04 (2H, qt, J = 7 Hz, βCH_2), 2.39 (6H, s, $N(CH_3)_2$), 2.42 (3H, s, 8-CH_3), 2.61 (2H, t, J = 7 Hz, γ CH_2), 2.94 (3H, s, 6-CH_3), 3.37 (2H, dd, J = 7, 5 Hz, αCH_2), 6.66 (1H, d, J = 8.6 Hz, 10-H), 7.30 (1H, d, J = 8.6 Hz, 9-H), 7.70 (2H, m, 2-H + 3-H), 8.75 (1H, m, 4-H), 9.48 (1H, m, 1-H), 9.88 (1H, t, J = 5 Hz, NH).
17d	A	60	83	100 MHz $CDCl_3$	1.09 (6H, s, N(CH2 $CH_3)_2$), 1.98 (2H, m, βCH_2), 2.43 (3H, s, 8-CH_3), 2.61 (6H, m, γ CH_2 + $N(CH_2CH_3)_2$), 2.95 (3H, s, 6-CH_3), 3.35 (2H, q, J = 7 Hz, αCH_2), 6.66 (1H, d, J = 8.5 Hz, 10-H), 7.30 (1H, d, J = 8.5 Hz, 9H), 7.66 (2H, m, 2-H + 3-H), 8.08 (1H, m, 4-H), 9.52 (1H, m, 1-H), 9.68 (1H, br s, NH).
18a	B	77	152	100 MHz $CDCl_3$	2.40 (6H, s, $N(CH_3)_2$), 2.42 (3H, s, 8-CH_3), 2.73 (2H, t, J = 7 Hz, βCH_2), 2.90 (3H, s, 6-CH_3), 3.40 (2H, dd, J = 5, 7 Hz, αCH_2), 4 .02 (3H, s, OCH_3), 6.62 (1H, d, J = 8.4 Hz, 10-H), 7.34 (2H, m, 9-H + 3-H), 7.96 (1H, d, J = 9Hz, 4-H), 9.09 (1H, d, J = 2.7 Hz, 1-H), 9.77 (1H, br s, NH).
18b	B	70	119	100 MHz $CDCl_3$	1.15 (6H, t, J = 7.3 Hz, $N(CH_2$-$CH_3)_2$), 2.42 (3H, s, 8-CH_3), 2.66 (4H, q, J = 7.3 Hz, $N(CH_2$-$CH_3)_2$), 2.88 (2H, t, J = 7 Hz, βCH_2), 2.90 (3H, s, 6-CH_3), 3.34 (2H, dd, J = 7, 5 Hz, αCH_2), 4.01 (3H, s, OCH_3), 6.63 (1H, d, J = 8.5 Hz, 10-H), 7.35 (2H, m, 9-H + 3-H), 2.97 (1H, d, J = 9.1 Hz, 4-H), 9.12 (1H, d, J = 2.9 Hz, 1-H), 9.78 (1H, br s, NH).

Amino compounds

Table I

18c	B	82	108	100 MHz $CDCl_3$	1.99 (2H, m, βCH_2), 2.33 (6H, s, N-$(CH_3)_2$), 2.42 (3H, s, 8-CH_3), 2.50 (2H, t, J = 7 Hz, γ CH_2), 2.90 (3H, s, 6-CH_3), 3.38 (2H, q, J = 7 Hz, αCH_2), 4.02 (3H, s, OCH_3), 6.66 (1H, d, J = 8.7 Hz, 10-H), 7.32 (2H, m, 9-H + 3-H), 7.98 (1H, d, J = 9 Hz, 4-H), 9.11 (1H, d, J = 2.7 Hz, 1-H), 9.78 (1H, br s, NH).
19a	B	64	149	100 MHz $CDCl_3$	2.38 (6H, s, $N(CH_3)_2$), 2.41 (3H, s, 8-CH_3), 2.71 (2H, t, J = 7 Hz, βCH_2), 2.91 (3H, s, 6-CH_3), 3.39 (2H, q, J = 7 Hz, αCH_2), 3.97 (3H, s, OCH_3), 6.61 (1H, d, J = 8.5 Hz, 10-H), 7.30 (1H, d, J = 8.5 Hz, 9-H), 7.29 (1H, d, J = 9.5 Hz, 2-H), 7.43 (1H, d, J = 2.7 Hz, 4-H), 9.44 (1H, d, J = 9.5 Hz, 1-H), 9.67 (1H, br s, NH).
19b	B	67	139	100 MHz $CDCl_3$	1.15 (6H, t, J = 7 Hz, $N(CH_2\text{-}C\underline{H}_3)_2$), 2.41 (3H, s, 8-$CH_3$), 2.67 (4H, q, J = 7 Hz, $N(C\underline{H}_2\text{-}CH_3)_2$), 2.84 (3H, t, J = 7 Hz, βCH_2), 2.92 (3H, s, 6-CH_3), 3.36 (2H, q, J = 7 Hz, αCH_2), 3.97 (3H, s, OCH_3), 6.63 (1H, d, J = 8.6 Hz, 10-H), 7.28 (2H, m, 9-H + 2-H), 7.43 (1H, d, J = 2.6 Hz, 4-H), 9.42 (1H, d, J = 9.5 Hz, 1-H), 9.65 (1H, br s, NH).
19c	B	70	96	100 MHz $CDCl_3$	1.98 (2H, m, βCH_2), 2.30 (6H, s, $N(CH_3)_2$), 2.42 (3H, s, 8-CH_3), 2.46 (2H, t, J = 7 Hz, γ CH_2), 2.93 (3H, s, 6-CH_3), 3.35 (2H, q, J = 7 Hz, αCH_2), 3.98 (3H, s, OCH_3), 6.65 (1H, d, J = 8.5 Hz, 10-H), 7.28 (2H, m, 9-H + 2-H), 7.45 (1H, d, J = 2.8 Hz, 4-H), 9.44 (1H, d, J = 9.3 Hz, 1-H), 9.67 (1H, br s, NH).
25a	A	45	167	100 MHz $CDCl_3$	2.41 (3H, s, CH_3), 2.44 (6H, s, $N(CH_3)_2$), 2.58 (2H, t, J = 7 Hz, βCH_2), 2.92 (2H, q, J = 7 Hz, αCH_2), 6.67 (1H, d, J = 8.6 Hz, 10-H), 7.33 (1H, d, J = 8.6 Hz, 9-H), 7.73 (2H, m, 2-H + 3-H), 8.17 (1H, m, 4-H), 9.02 (1H, s, 6-H), 9.67 (1H, m, 1-H), 9.83 (1H, m, NH).
25b	A	70	108	100 MHz $CDCl_3$	1.18 (6H, t, J = 7 Hz, $N(CH_2\text{-}C\underline{H}_3)_2$), 2.40 (3H, s, CH_3), 2.89 (2H, t, J = 7 Hz, βCH_2), 2.74 (4H, q, J = 7 Hz, $N(C\underline{H}_2\text{-}CH_3)_2$), 3.43 (2H, q, J = 7 Hz, αCH_2), 6.68 (1H, d, J = 8.7 Hz, 10-H), 7.31 (1H, d, J = 8.7 Hz,9-H), 7.71 (2H, m, 2-H + 3-H), 8.16 (1H, m, 4-H), 9.02 (1H, s, 6-H), 9.64 (1H, m, 1-H), 9.81 (1H, m, NH).

A : at reflux of the diamine for a 24 h period.

B : steel vessel at 180°C for 4 days.

Table I (continued)

No	Yield %	mp °C		^{1}H nmr δ (ppm)
20a	52	266	400 MHz [$CDCl_3$]	2.38 (3H, s, 8-CH3), 2.57 (6H, s, $N(CH_3)_2$), 2.86 (3H, s, 6-CH3), 2.99 (2H, t, J = 7 Hz, β CH_2), 3.47 (2H, q, J = 7 Hz, α-CH_2), 6.48 (1H, d, J = 8.6 Hz, 10-H), 7.19 (1H, d, J = 8.6 Hz, 9-H), 7.25 (1H, dd, J = 9.1, 2.8 Hz, 3-H), 7.87 (1H, d, J = 9.1 Hz, 4-H), 8.94 (1H, d, J= 2.8 Hz, 1-H), 9.67 (1H, br s, NH).
20b	67	216	100 MHz [$(CD_3)_2SO$]	1.06 (6H, t, J = 7.3 Hz, $N(CH_2-CH_3)_2$), 2.34 (3H, s, 8-CH_3), 2.76 (3H, s, 6-CH_3), 2.88 (6H, m, $N(CH_2-CH_3)_2$)+β CH_2), 3.39 (2H, m, α CH_2), 6.74 (1H, d, J = 8.4 Hz, 10-H), 7.21 (1H, dd, J = 9.1, 2.8 Hz, 3-H), 7.42 (1H, d, J = 8.4 Hz, 9-H), 7.84 (1H, d, J = 9.1 Hz, 4-H), 8.76 (1H, d, J = 2.8 Hz, 1-H), 9.72 (1H, br s, NH), 10.17 (1H, br s, OH).
20c	62	241	400 MHz $CDCl_3$	2.04 (3H, s, 8-CH_3), 2.14 (2H, m, β CH_2), 2.60 (6H, s, N-$(CH_3)_2$), 2.85 (3H, s, 6-CH_3), 3.11 (2H, t, J = 7 Hz, γ CH_2), 3.33 (2H, q, J = 7 Hz, α CH_2), 5.93 (1H, d, J = 8.5 Hz, 10-H), 6.53 (1H, d, J = 8.5 Hz, 9-H), 7.11 (1H, dd, J = 8.8, 2.5 Hz, 3-H), 7.71 (1H, d, J = 8.8 Hz, 4-H), 8.73 (1H, d, J = 2.5 Hz, 1-H), 9.85 (1H, br s, NH), 11.60 (1H, br s, OH).
21a	69	252	100 MHz [$(CD_3)_2SO$]	2.33 (9H, s, 8-CH_3 + $N(CH_3)_2$), 2.67 (2H ,t, J = 7 Hz, β CH_2), 2.82 (3H, s, 6-CH_3), 3.34 (2H, q, J = 7 Hz, α CH_2), 6.73 (1H, d, J = 8.5 Hz, 10-H), 7.27 (1H, dd, J = 9, 2.8 Hz, 2-H), 7.32 (1H, app s, 4-H), 7.42 (1H, d, J = 8.5 Hz, 9-H), 9.31 (1H, d, J = 9 Hz, 1-H), 9.57 (1H, br s, NH), 10.20 (1H, br s, OH).
21b	62	247	* 100 MHz [$(CD_3)_2SO$]	1.09 (6H, t, J = 7.1 Hz, $N(CH_2-CH_3)_2$), 2.39 (3H, s, 8-CH_3), 2.84 (3H, s, 6-CH_3), 6.74 (1H, d, J = 8.3 Hz, 10-H), 7.21 (1H, dd, J = 9.4, 2.7 Hz, 2-H), 7.32 (1H, d, J= 2.7 Hz, 4-H), 7.36 (1H, d, J = 8.3 Hz, 9-H), 9.28 (1H, d, J = 9.4 Hz, 1-H), 9.56 (1H, m, NH), 10.08 (1H, br s, OH).
21c	52	214	* 100MHz [$(CD_3)_2SO$]	1.84 (2H, m, β CH_2), 2.22 (6H, s, $N(CH_3)_2$), 2.37 (3H, s, 8-CH_3), 2.83 (3H, s, 6-CH_3), 6.74 (1H, d, J = 8.6 Hz, 10-H), 7.25 (1H, dd, J = 8.8, 2.8 Hz, 2-H), 7.31 (1H, app s, 4-H), 7.43 (1H, d, J = 8.6 Hz, 9-H), 9.32 (1H, d, J = 8.8 Hz, 1-H), 9.57 (1H, br s, NH), 10.18 (1H, br s, OH).

* CH_2 signals were hidden by $[(CD_3)_2SO]$.

Hydroxy compounds

Table II

Table III. Analytical data for amino compounds.
Analysis %

No	Formula	Calcd			Found		
		C	H	N	C	H	N
17a	$C_{22}H_{23}N_3OS$	69.99	6.14	11.13	69.92	6.10	11.09
17b	$C_{24}H_{27}N_3OS$	71.07	6.71	10.36	71.20	6.65	10.47
17c	$C_{23}H_{25}N_3OS$	70.55	6.43	10.73	70.47	6.25	10.93
17d	$C_{25}H_{29}N_3OS$	71.56	6.96	10.01	71.48	6.63	9.83
18a	$C_{23}H_{25}N_3O_2S$	67.78	6.18	10.31	67.99	6.22	10.47
18b	$C_{25}H_{29}N_3O_2S$	68.93	6.71	9.64	69.22	6.98	9.48
18c	$C_{24}H_{27}N_3O_2S$	68.57	6.45	9.98	68.65	6.21	9.69
19a	$C_{23}H_{25}N_3O_2S$	67.78	6.18	10.31	67.77	6.14	10.30
19b	$C_{25}H_{29}N_3O_2S$	68.93	6.71	9.64	68.93	6.69	9.48
19c	$C_{24}H_{27}N_3O_2S$	68.38	6.45	9.97	68.27	6.54	10.02
20a	$C_{21}H_{21}N_3OS$	69.39	5.82	11.56	69.26	5.73	11.69
20b	$C_{23}H_{25}N_3OS$	70.55	6.43	10.73	70.47	6.38	10.81
20c	$C_{22}H_{23}N_3O_2S$	67.15	5.89	10.67	66.91	6.02	10.39
21a	$C_{24}H_{27}N_3O_2S$	68.38	6.45	9.97	68.49	6.62	10.16
21b	$C_{23}H_{25}N_3O_2S$	67.78	6.18	10.31	67.80	6.35	10.46
21c	$C_{22}H_{23}N_3O_2S$	67.15	5.89	10.67	67.02	5.80	10.46
25a	$C_{21}H_{21}N_3OS$	69.39	5.82	11.56	69.26	5.73	11.69
25b	$C_{23}H_{25}N_3OS$	70.55	6.43	10.73	70.47	6.38	10.81

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