Synthesis of *N*-(9*H*-Xanthen-9-yl)aminoalkanamide and *N*-(9*H*-Thioxanthen-9-yl)aminoalkanamide Derivatives and their *in vitro* Evaluation as Potential Intercalators and Antitumor Drugs

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Received February 2, 1993

A series of new *N*-(9*H*-xanthen-9-yl)aminoalkanamide and *N*-(9*H*-thioxanthen-9-yl)aminoalkanamide derivatives was synthesized and evaluated as potential intercalators by measuring their DNA binding affinity. They were also tested for cytotoxic activity against L1210. The results suggest that the cytotoxicity of these molecules was not due to an intercalating mechanism.

Synthese, Zytotoxizität und DNA-Interaktion von neuen *N*-(9*H*-Xanthen-9-yl)aminoalkanamiden und *N*-(9*H*-Thioxanthen-9-yl)aminoalkanamiden

Eine Reihe von neuen *N*-(9*H*-Xanthen-9-yl)aminoalkanamiden und *N*-(9*H*-Thioxanthen-9-yl)aminoalkanamiden wurde dargestellt; DNA-Bindungsaffinität bzw. zytostatische Wirkung der neuen Verbindungen an der L1210-Zellinie wurden geprüft. Aus den Ergebnissen kann man schließen, daß die zytostatische Wirkung nicht auf eine Interkalation mit der DNA zurückzuführen ist.

The majority of the DNA intercalating antitumor drugs has a common general structure comprising a planar tricyclic or tetracyclic chromophore to which one or two flexible side chains bearing cationic charges are attached[1,2].

The aminoalkylamino side chains are very common in intercalating antitumor drugs (*e.g.* mitoxantrone and ametantrone)[1]. Recently *Martelli et al.*[2] studied the effect of the replacement of the aminoalkylamino group by an amidoalkylamino group and found that such a modification generally does not abolish the cytotoxic activity and can even cause its increase.

Lucanthon, hycanthon, miracil A and its 6-chloro analogue are intercalators[3] of the xanthene and thioxanthene series. It is noteworthy that most of the work reported on xanthene and thioxanthene derivatives refers to substituents located at positions 1 and 4.

Following the above structural requirements we decided to synthesise some new basic amides, *N*-(9*H*-xanthen-9-yl)aminoalkanamides and *N*-(9*H*-thioxanthen-9-yl)aminoalkanamides. As substituents of the basic N the methyl and ethyl[3] as well as a variety of heterocyclic[4] groups were selected.

Chemistry

The aminoalkanamide target compounds **7a-q**, Tables 2 and 3) were prepared according to Scheme 1.

The xanthones and thioxanthones **2a-d** were synthesized by a routine *Ullmann* ether synthesis either from the appropriate *o*-chlorobenzoic acid and a phenol (**2a**, **2b**, and **2d**)[5], or from the *o*-thiosalicylic acid and *o*-bromobenzene (**2c**)[6] followed by cyclization. This intramolecular cyclization of the aromatic acids **1a-d** was carried out either with conc. H_2SO_4 (**1a-c**)[7], or with polyphosphoric acid (**1d**)[8].

Reduction of xanthones and thioxanthones with sodium amagalm[9] led to the corresponding alcohols **3a-d**. The chloroalkanamides **6a-i** were obtained from xanthydrols and thioxanthydrols either through the intermediacy of the appropriate amine **5a**, **5b** in three steps (compounds **6g-i**) or in one step by condensation of the requisite xanthydrols **3a-c** with chloroacetamide or 2-chloropropanamide in glacial acetic acid (**6a-f**)[10]. In the former case the requisite 9*H*-xanthene-9-amines and 9*H*-thioxanthene-9-amines (prepared according to *Ollmann* and *Witiak*[11]) reacted with the appropriate chloroacyl chloride/K_2CO_3 in $CHCl_3$[12].

These ω-chloroalkanamides **6a-i** were coupled to *sec.* amines in absol. ethanol[4] to give the aminoalkanamido derivatives **7a-q**.

In the ^{1}H-NMR spectra of **7a-q**, 9-H of 9*H*-xanthene and 9*H*-thioxanthene couples with the NH proton. The NH signal disappeared and the 9-H signal became a singlet upon addition of D_2O.

Pharmacological results and discussion

The data shown in Table 1 compare the DNA affinities and the growth inhibitory effects of the different drugs at a concentration of 10 μg/ml. Although the compounds tested show a low DNA affinity which may be related to the presence of a planar ring and a bulky, positively charges side chain in the molecule, the results suggest that these molecules do not intercalate into the DNA.

Regarding the cytotoxic activity the most active compounds are **7n** and **7q** which provoke approximately a 80% cell growth reduction at 10 μg/ml in 24 h. Although none of the tested compounds displayed very potent cytotoxic activity some conclusions concerning their structure-activity relationship could be drawn: Thioxanthene derivatives were more potent than their oxo-analogs. Also the dialkylami-

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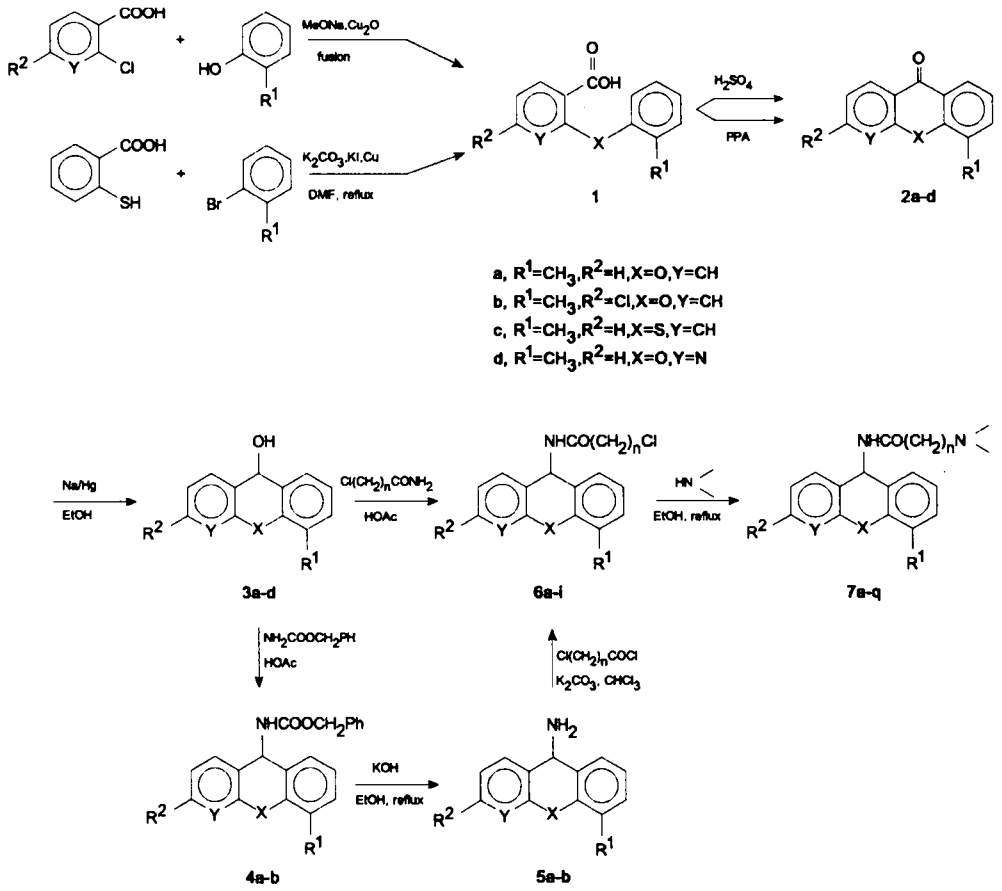


Scheme 1

Table 1: Biological results.

No	Binding Const.(M^{-1})	Toxicity[a]
7a	2.70×10^3	86
7c	6.00×10^3	85
7e	6.30×10^3	66
7g	1.26×10^3	73
7h	4.23×10^3	62
7i	3.60×10^3	35
7j	3.78×10^3	45
7k	1.62×10^3	81
7l	4.68×10^3	62
7n	1.58×10^3	21
7o	5.66×10^3	48
7p	$< 1.0 \times 10^3$	68
7q	1.30×10^3	20

[a] Residual growth after 24 h exposure to the tested compound at 10 µg/ml expressed as % of the growth of the untreated cells.

nopropanamides were more active than their corresponding dialkylaminoethanamides. Finally the addition of the chloro substituent at C-6 of the xanthene ring resulted in compounds with better activity.

Experimental Part

Chemistry

Melting points: Büchi apparatus, uncorrected.- ^{1}H-NMR spectra: $CDCl_3$, Bruker AC-200 (200 MHz) spectrometer, δ (ppm), internal Me_4Si. J-values in Hz.- IR-spectra: Perkin Elmer 388 spectrometer.- Elemental analyses: Service Central d'Analyse (CNRS France). Analyses indicated by the symbols of the elements were within ±0.4% of theoretical values.- Xanthydrol: Fluka AG.

4-Chloro-2-(2-methylphenoxy)benzoic acid (**1b**)

Sodium (2.10 g, 0.09 mol) was dissolved in anhydrous MeOH (35 mL) and 2,4-dichlorobenzoic acid (8.60 g, 0.045 mol) was added followed by *o*-cresol (9.72 g, 0.090 mol) and a catalytical amount of Cu_2O. The MeOH was removed by distillation and the residue was heated at 180°C for 1 h, cooled to 100°C, and poured into ice. The solution was extracted several times with Et_2O and the aqueous layer was acidified with 10% HCl, cooled and filtered. The solid was washed with H_2O, dried, and recrystallized from benzene-petroleum ether. Yield 6.74 g (57%); mp. 155-157°C.- ^{1}H-NMR ($CDCl_3$): δ = 2.22 (s, 3H, CH_3), 6.62 (m, 1H aromat.), 6.98-7.41 (m,

5H aromat.), 8.15 (d, 1H aromat., J = 8.6).- IR (KBr): OH 2780-2500, CO 1675 cm^{-1}.- Anal.: $C_{14}H_{11}ClO_3$ (C, H).

2-(2-Methylphenoxy)benzoic acid (**1a**)

mp. 131-133°C (lit.[13]): mp. 133.5°C).

2-(2-Methylphenylthio)benzoic acid (**1c**)

mp. 171-174°C (lit.[14]): mp. 171-174°C).

2-(2-Methylphenoxy)nicotinic acid (**1d**)

mp. 178-180°C (lit.[15]): mp. 179-181°C).

6-Chloro-4-methylxanthone (**2b**)

A mixture of **1b** and 10 times its weight of conc. H_2SO_4 was heated with stirring in a boiling bath for 1 h and poured into ice-water. The precipitate was collected, treated with N-Na_2CO_3, washed, and recrystallized from ethanol. Yield 65%; mp. 144-146°C.- ^{1}H-NMR ($CDCl_3$): δ = 2.88 (s, 3H, CH_3), 7.37-8.10 (m, 4H aromat.), 8.40-8.90 (m, 2H aromat.).- IR (nujol): CO 1650, COC (ether bridge) 1240 cm^{-1}.- Anal.: $C_{14}H_9ClO_2$ (C, H).

4-Methylxanthone (**2a**)

mp. 122-124°C (lit.[13]): mp. 126°C).

4-Methylthioxanthone (**2c**)

mp. 145-147°C (lit.[14]): mp. 145-147°C).

9-Methyl-5H-[1]benzopyrano[2,3-b]pyridin-5-one (**2d**)

mp. 178-180°C (lit.[15]): mp. 180-182°C).

6-Chloro-4-methylxanthydrol (**3b**)

A mixture of Hg (375 g, 1.86 mol), **2b** (15.9 g, 0.065 mol), and 80 mL of 95% EtOH was placed in a pressure bottle. Small pieces of Na (4.6 g, 0.2 mol) were added during 15 min while the mixture was being shaken. After shaking for an additional 30 min the alcohol layer was decanted. The sodium amalgam was washed with two 15 mL portions of hot EtOH and the combined alcoholic solutions were filtered and poured into ice-water. The precipitate was collected, dried, and recrystallized from EtOH. Yield 14.40 g (90%); mp. 128-130°C.- ^{1}H-NMR ($CDCl_3$): δ = 2.17 (d, 1H, OH, J = 9), 2.42 (s, 3H, CH_3), 5.78 (d, 1H, 9-H, J = 9), 6.90-7.28 (m, 4H aromat.), 7.42 (m, 1H aromat.), 7.52 (d, 1H aromat., J = 8).- IR (nujol): OH 3480-3260 cm^{-1}.- Anal.: $C_{14}H_{11}ClO_2$ (C, H).

4-Methylxanthydrol (**3a**)

mp. 89-92°C (lit.[14]): mp. 89-92°C).

4-Methylthioxanthydrol (**3c**)

mp. 102-104°C (lit.[14]): mp. 102-104°C).

5H-[1]benzopyrano-[2,3-b]pyridin-5-ol (**3d**)

Yield 89%, mp. 158-159°C.- ^{1}H-NMR ($CDCl_3$): δ = 2.42 (s, 3H, CH_3), 3.08 (d, 1H, OH, J = 9), 5.85 (d, 1H, 9-H, J = 9), 7.05-7.48 (m, 4H aromat.), 7.99-8.05 (m, 1H aromat.), 8.20-8.26 (m, 1H aromat.).- IR (nujol): OH 3290-3200 cm^{-1}.- Anal. $C_{13}H_{11}NO_2$ (C, H).

9-Methyl-5H-[1]benzoyprano[2,3-b]pyridin-5-amine (**5a**)

A solution of 2.34 g (0.011 mol) **3d** and 2.0 g (0.013 mol) of benzyl carbamate in 25 mL of glacial AcOH was stirred overnight at room temp. and poured into ice-water (150 ml). The precipitated carbamate **4a** was collected, dried, and recrystallized from ethanol. Yield 2.55 g (67%); mp. 152-153°C.- IR (nujol): NH 3293, CO 1681 cm^{-1}.- ^{1}H-NMR (200 MHz) ($CDCl_3$): δ = 2.46 (s, 3H, CH_3), 5.22 (s, 2H, CH_2Ph), 5.40 (d, 1H, NH, J = 9), 6.23 (d, 1H, 9-H, J = 9), 7.00-7.40 (m, 9H aromat.), 7.80-8.00 (m, 1H aromat.), 8.20-8.35 (m, 1H aromat.).- Anal.: $C_{21}H_{18}N_2O_3$ (C, H).

To a solution of KOH (5.0 g, 0.09 mol) in EtOH (50 mL) 1.73 g (0.005 mols) of **4a** were added. The mixture was heated for 12 h, cooled and concentrated *i.vac.* to ca. 15 mL. The concentrate was shaken with 25 mL of H_2O and extracted with Et_2O. The org. layer was washed with H_2O, dried (Na_2SO_4) and concentrated *i.vac.* The residual oil was used in the following step without further purification.

N-(4-Methylthioxanthen-9-yl)benzyl carbamate (**4b**)

mp. 118-120°C (lit.[14]): mp. 118-120°C).

4-Methyl-9H-thioxanthen-9-amine (**5b**, *as CH_3COOH salt*)

mp. 152-155°C (lit.[14]): mp. 152-155°C).

N-(9H-xanthen-9-yl)-1-chloropropanamide (**6b**)

A mixture of xanthydrol (1.98 g, 0.01 mol) and 3-chloropropionamide (1.20 g, 0.011 mol) in glacial AcOH (25 mL) was heated with stirring in a boiling water bath for 90 min. After standing at room temp. overnight the mixture was poured into ice water. The precipitate was washed with water, dried, and recrystallized from benzene-petrol ether. Yield 1.87 g (65%); mp. 177-179°C.- IR (nujol): NH 3270, CO 1640 cm^{-1}.- ^{1}H-NMR (200 MHz) ($CDCl_3$): δ = 2.75 (t, 2H, $COCH_2CH_2$, J = 6), 4.00 (t, 2H, $COCH_2CH_2$, J = 6), 6.70 (d, 1H, 9-H, J = 9), 7.10-8.20 (m, 8H aromat.).- Anal.: $C_{16}H_{14}ClNO_2$ (C, H).

N-(9H-Xanthen-9-yl)-1-chloroethanamide (**6a**)

mp. 208-9°C, (lit.[10]): mp. 208-209°C).

N-(4-Methyl-9H-xanthen-9-yl)-1-chloroethanamide (**6c**)

Yield 63%; mp. 213-215°C.- IR (nujol): NH 3265, CO 1650 cm^{-1}.- ^{1}H-NMR (200 MHz) ($CDCl_3$): δ = 2.50 (s, 3H, CH_3), 4.25 (s, 2H, CH_2Cl), 6.64 (d, 1H, 9-H, J = 9), 6.95-7.90 (m, 7H aromat.).- Anal.: $C_{16}H_{14}ClNO_2$ (C, H).

N-(4-Methyl-9H-xanthen-9-yl)-3-chloropropanamide (**6d**)

Yield 65%; mp. 158-161°C.- IR (nujol): NH 3270, CO 1640 cm^{-1}.- ^{1}H-NMR (200 MHz) ($CDCl_3$): δ = 2.49 (s, 3H, CH_3), 2.69 (t, 2H, $COCH_2CH_2$, J = 6), 3.99 (t, 2H, $COCH_2CH_2$, J = 6), 6.80 (d, 1H, 9-H, J = 9), 7.05-7.90 (m, 7H aromat.).- Anal.: $C_{17}H_{16}ClNO_2$ (C, H).

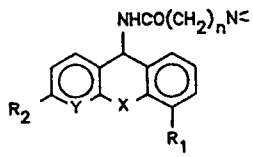
N-(6-chloro-4-methyl-9H-xanthen-9-yl)-1-chloroethanamide (**6e**)

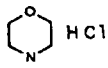
Yield 65%; mp. 184-185°C.- IR (nujol): NH 3260, CO 1645 cm^{-1}.- ^{1}H-NMR (200 MHz) ($CDCl_3$): δ = 2.49 (s, 3H, CH_3), 4.23 (s, 2H, CH_2Cl), 6.70 (d, 1H, 9-H, J = 9), 6.90-7.80 (m, 6H aromat.).- Anal.: $C_{16}H_{13}Cl_2NO_2$ (C, H).

N-(6-chloro-4-methyl-9H-xanthen-9-yl)-3-chloropropanamide (**6f**)

Yield 60%; mp. 197-199°C.- IR (nujol): NH 3275, CO 1640 cm^{-1}.- ^{1}H-NMR (200 MHz) ($CDCl_3$): δ = 2.49 (s, 3H, CH_3), 2.78 (t, 2H,

Table 2: Basic amides **7a-q**



No	R_1	R_2	N=	X	Y	n	mp[a] (°C)	Yield (%)	Formula[b]
7a	H	H	$N(C_2H_5)_2$	O	CH	1	98-100	75	$C_{19}H_{22}N_2O_2$
7b	H	H	$N(C_2H_5)_2$	O	CH	2	111-113	72	$C_{20}H_{24}N_2O_2$
7c	CH_3	H	$N(CH_3)_2$	O	CH	1	115-117	72	$C_{18}H_{20}N_2O_2$
7d	CH_3	H	$N(C_2H_5)_2$	O	CH	1	68-69	78	$C_{20}H_{24}N_2O_2$
7e	CH_3	H	$N(CH_3)_2$	O	CH	2	143-145	78	$C_{19}H_{22}N_2O_2$
7f	CH_3	H	$N(C_2H_5)_2$	O	CH	2	108-110	81	$C_{21}H_{25}ClN_2O_2$
7g	CH_3	Cl	$N(CH_3)_2$	O	CH	1	127-130	76	$C_{18}H_{19}ClN_2O_2$
7h	CH_3	Cl	$N(C_2H_5)_2$	O	CH	1	75-77	82	$C_{20}H_{23}ClN_2O_2$
7i	CH_3	H	$N(CH_3)_2$	S	CH	1	117-118	79	$C_{18}H_{20}N_2OS$
7j	CH_3	H	$N(C_2H_5)_2$	S	CH	1	84-85	79	$C_{20}H_{24}N_2OS$
7k	CH_3	H	$N(CH_3)_2$	S	CH	2	99-101	82	$C_{19}H_{22}N_2OS$
7l	CH_3	H	$N(C_2H_5)_2$	S	CH	2	59-61	77	$C_{21}H_{26}N_2OS$
7m	CH_3	H	$N(CH_3)_2$	O	N	1	148-149	83	$C_{17}H_{19}N_3O_2$
7n	CH_3	Cl	$N(C_2H_5)_2$	O	CH	2	123-125	70	$C_{21}H_{25}ClN_2O_2$
7o	CH_3	Cl		O	CH	2	161-162	80	$C_{23}H_{28}Cl_2N_3O_3$
7p	CH_3	Cl		O	CH	2	221-222	75	$C_{21}H_{24}Cl_2N_2O_2$
7q	CH_3	Cl		O	CH	2	168-169	78	$C_{22}H_{25}Cl_2N_2O_2$

[a] From ether-petroleum ether; [b] Anal (C, H, N).

$COCH_2CH_2$, J = 6), 4.05 (t, 2H, $COCH_2CH_2$, J = 6), 6.65 (d, 1H, 9-H, J = 9), 6.90-7.80 (m, 6H aromat.).- Anal.: $C_{17}H_{15}Cl_2NO_2$ (C, H).

N-(4-methyl-9H-thioxanthen-9-yl)-1-chloroethanamide (**6g**)

Chloroacetyl chloride (2.83 g, 0.025 mol) is added to a mixture of anhydrous K_2CO_3 (4.37 g, 0.042 mol) and 4-methyl-9H-thioxanthen-9-amine (4.77 g, 0.021 mol) in $CHCl_3$ (40 mL) at 0°C during 30 min. The mixture is stirred at 25°C for 1 h and filtered. The org. layer was washed with H_2O, dried (Na_2SO_4) and concentrated *i.vac.* The residue was crystallized from benzene-petrol ether. Yield 79%; mp. 141-143°C.- IR (nujol): NH 3240, CO 1665 cm^{-1}.- ^{1}H-NMR (200 MHz) ($CDCl_3$): δ = 2.51 (s, 3H, CH_3), 3.99 (s, 2H, CH_2Cl), 6.30 (d, 1H, 9-H, J = 9), 7.15-7.66 (m, 7H aromat.).- Anal.: $C_{16}H_{14}ClNOS$ (C, H).

N-(4-methyl-9H-thioxanthen-9-yl)-3-chloropropanamide (**6h**)

Yield 81%; mp. 156-158°C.- IR (nujol): NH 3300, CO 1645 cm^{-1}.- ^{1}H-NMR (200 MHz) ($CDCl_3$): δ = 2.48 (s, 3H, CH_3), 2.51 (t, 2H, $COCH_2CH_2$, J = 6), 3.73 (t, 2H, $COCH_2CH_2$, J = 6), 6.31 (d, 1H, 9-H, J = 9), 7.12-7.68 (m, 6H aromat.).- Anal.: $C_{17}H_{15}ClNOS$ (C, H).

N-(9-methyl-5H-[1]benzopyran[2,3-b]pyridin-5-yl)-1-chloroethanamide (**6i**)

Yield 70%; mp. 167-169°C.- IR (nujol): NH 3240, CO 1688 cm^{-1}.- ^{1}H-NMR (200 MHz) ($CDCl_3$): δ = 2.48 (s, 3H, CH_3), 4.15 (s, 2H, CH_2Cl), 6.55 (d, 1H, 9-H, J = 9), 7.00-7.35 (m, 4H aromat.), 7.90-8.00 (m, 1H aromat.), 8.30-8.40 (m, 1H aromat.).- Anal.: $C_{15}H_{13}ClN_2O_2$ (C, H).

Table 3: IR- and ^{1}H-NMR spectral data of compounds **7a-q**

No	IR[a] (cm^{-1}) νNH, νCO, νOH	^{1}H NMR[b]
7a	3310, 1655	0.88 (t, 6H, $N(CH_2\underline{CH_3})_2$, J=6.3), 2.40 (s, 3H, CH_3), 2.48 (q, 4H, $N(\underline{CH_2}CH_3)_2$, J=6.3), 3.12 (s, 2H, $COCH_2N$), 6.50 (d, 1H, H-9, J=9), 7.02-7.18 (m, 4H, ArH), 7.21-7.38 (m, 2H, ArH), 7.38-7.49 (m, 2H, ArH), 7.92 (d, 1H, NH, J=9).
7b	3300, 1635	0.70 (t, 6H, $N(CH_2\underline{CH_3})_2$, J=6.3), 2.35 (q, 4H, $N(\underline{CH_2}CH_3)_2$, J=6.3), 2.41 (t, 2H, $COCH_2\underline{CH_2}N$, J=5.7), 2.60 (t, 2H, $COCH_2\underline{CH_2}N$, J=5.7), 6.45 (d, 1H, H-9, J=8.6), 7.00-7.16 (m, 4H, ArH), 7.20-7.38 (m, 2H, ArH), 7.45-7.53 (m, 2H, ArH), 9.50 (d, 1H, NH, J=8.6).
7c	3265, 1650	2.17 (s, 6H, $N(CH_3)_2$), 2.40 (s, 3H, CH_3), 3.02 (s, 2H, $COCH_2N$), 6.53 (d, 1H, H-9, J=9.8), 6.92-7.22 (m, 4H, ArH), 7.22-7.40 (m, 2H, ArH), 7.40-7.50 (m, 1H, ArH), 7.62 (d, 1H, NH, J=9.8).
7d	3350, 1675	0.86 (t, 6H, $N(CH_2\underline{CH_3})_2$, J=7.2), 2.48 (q, 4H, $N(\underline{CH_2}CH_3)_2$, J=7.2), 3.12 (s, 2H, $COCH_2N$), 6.49 (d, 1H, H-9, J=9.6), 6.95-7.20 (m, 4H, ArH), 7.20-7.35 (m, 2H, ArH), 7.35-7.48 (m, 1H, ArH), 7.90 (d, 1H, NH, J=9.6).
7e	3278, 1637	2.08 (s, 6H, $N(CH_3)_2$), 2.32-2.58 (m, 7H, $COCH_2CH_2N$ & CH_3), 6.45 (d, 1H, H-9, J=9.7), 6.95-7.20 (m, 4H, ArH), 7.20-7.35 (m, 2H, ArH), 7.40-7.51 (m, 1H, ArH), 8.71 (d, 1H, NH, J=9.7).
7f	3276, 1638	0.70 (t, 6H, $N(CH_2\underline{CH_3})_2$, J=6.3), 2.31 (q, 4H, $N(\underline{CH_2}CH_3)_2$, J=6.3), 2.34-2.42 (m, 5H, $COCH_2\underline{CH_2}N$ & CH_3), 2.60 (t, 2H, $COCH_2\underline{CH_2}N$, J=5.7), 6.41 (d, 1H, H-9, J=8.6), 6.95-7.55 (m, 7H, ArH), 9.40 (d, 1H, NH, J=8.6).
7g	3260, 1650	2.18 (s, 6H, $(NCH_3)_2$), 2.40 (s, 3H, CH_3), 3.02 (s, 2H, $COCH_2N$), 6.50 (d, 1H, H-9, J=9), 6.98-7.30 (m, 5H, ArH), 7.42 (d, 1H, Ar, J=7), 7.62 (d, 1H, NH, J=9).
7h	3280 1650	0.89 (t, 6H, $N(CH_2\underline{CH_3})_2$, J=6.8), 2.39 (s, 3H, CH_3), 2.49 (q, 4H, $N(\underline{CH_2}CH_3)_2$, J=6.8), 3.12 (s, 2H, $COCH_2N$), 6.45 (d, 1H, H-9, J=9.6), 6.93-7.30 (m, 5H, ArH), 7.44 (d, 1H, ArH, J=7), 7.90 (d, 1H, NH, J=9.6).
7i	3340, 1670	2.11 (s, 6H, $N(CH_3)_2$), 2.48 (s, 3H, CH_3), 2.90 (s, 2H, $COCH_2N$), 6.25 (d, 1H, J=9.8, H-9), 7.10-7.35 (m, 4H, ArH), 7.37-7.62 (m, 3H, ArH), 7.83 (d, 1H, J=9.8).
7j	3320, 1665	0.85 (t, 6H, $N(CH_2\underline{CH_3})_2$, J=7), 2.40 (q, 4H, $N(\underline{CH_2}CH_3)_2$, J=7), 2.48 (s, 3H, CH_3), 2.98 (s, 2H, $COCH_2N$), 6.25 (d, 1H, H-9, J=9.6), 7.10-7.32 (m, 4H, ArH), 7.32-7.60 (m, 3H, ArH), 8.15 (d, 1H, NH, J=9.6).
7k	3265, 1645	2.15 (s, 6H, $N(CH_3)_2$), 2.27-2.52 (m, 7H, $COCH_2CH_2N$ & CH_3), 6.18 (d, 1H, H-9, J=9.7), 7.08-7.31 (m, 4H, ArH), 7.31-7.58 (m, 3H, ArH), 9.39 (d, 1H, NH, J=9.7)
7l	3270, 1650	0.76 (t, 6H, $N(CH_2\underline{CH_3})_2$, J=6.3), 2.22-2.58 (m, 11H, $N(\underline{CH_2}CH_3)_2$) & $COCH_2\underline{CH_2}N$ & CH_3), 6.25 (d, 1H, H-9, J=8.6), 7.08-7.61 (m, 7H, ArH), 9.61 (d, 1H, NH, J= 8.6).
7m	3277, 1657	2.28 (s, 6H, $(NCH_3)_2$), 2.50 (s, 3H, CH_3), 3.07 (s, 2H, $COCH_2N$), 6.55 (d, 1H, H-9, J=9), 7.00-7.30 (m, 4H, ArH), 7.70 (d, 1H, NH, J=9), 7.90-8.00 (m, 1H, ArH), 8.30-8.38 (m, 1H, ArH).
7n	3270, 1655	0.75 (t, 6H, $N(CH_2\underline{CH_3})_2$, J=6.3), 2.25-2.48 (m, 9H, $N(\underline{CH_2}CH_3)_2$) & $COCH_2CH_2N$ & CH_3), 2.60-2.70 (m, 2H, $COCH_2\underline{CH_2}N$), 6.35 (d, 1H, H-9, J=9.6), 6.90-7.27 (m, 5H, ArH), 7.40 (d, 1H, ArH, J=7), 9.38 (d, 1H, NH, J=9.6).

Table 3: Continued

7o	3297, 1633, 3385	2.20-2.70 (m, 17H, piperazine's H & NCH_2CH_2OH & CH_3 & $COCH_2CH_2N$), 3.55 (t, 2H, NCH_2CH_2OH, J=6), 6.28 (d, 1H, H-9, J=9), 6.90-7.35 (m, 5H, ArH), 7.45 (d, 1H, ArH, J=7), 9.10 (d, 1H, NH, J=9).
7p[c]	3266, 1650	2.35 (s, 3H, CH_3), 2.70-2.90 (m, 4H, $COCH_2CH_2N$), 3.10-3.40 (m, 4H, morpholine's H), 3.75-4.15 (m, 4H, morpholine's H), 6.25 (d, 1H, H-9, J=9), 6.85-7.25 (m, 5H, ArH), 7.35 (d, 1H, ArH, J=7).
7q	3285, 1650	1.05-1.35 (m, 6H, piperidine's H), 2.22-2.50 (m, 11H, piperidine's H & CH_3 & $COCH_2CH_2N$), 6.38 (d, 1H, H-9, J=8.5), 6.95-7.30 (m, 5H, ArH), 7.45 (d, 1H, ArH, J=7), 9.48 (d, 1H, NH, J=8.5).

[a] KBr tablets; [b] In $CDCl_3$; [c] In DMSO-D^6 as hydrochloride.

Compounds **7a-q**, *general method*

The appropriate ω-chloroalkanamide (0.01 mol) was suspended in 200 mL of ethanol and warmed to 70°C. The appropriate *sec.* amine (0.03 mol) was added dropwise over a 1 h period and the solution was refluxed for 5 h. When dimethylamine was used the reaction mixture was allowed to stand for several days at room temp. Finally, the solvent was removed *i.vac.* and the residue was crystallized from benzene-petroleum ether (Tables 2 and 3). Results of elem. analyses are within ±0.4% of the theoretical values.

Biological Methods

DNA Binding Affinity

The products were dissolved in dimethylsulfoxide and stored at 4°C. DNA binding affinities were determined in 0.05 M Tris-HCl, 2% DMSO, at pH 7.4, by competition with ethidium bromide[16].

Cytotoxicity

L1210 cells (1.7 x 10^5/ml) were grown in RPMI medium containing 10% calf thymus serum, 200 mM glutamine, 100 IU/ml penicillin, 100 μg/ml streptomycin, 60 μM mercaptoethanol at 37°C in a 5% CO_2 atmosphere, and in the presence of increasing drug concentrations. After 24 h, the cells were counted. Growth inhibition was determined as % of residual growth as compared to the untreated control.

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