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Bis-naphthylureas and related compounds: synthesis, chemical properties, DNA affinity and antineoplastic activity

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A series of bis-naphthalene derivatives in which these moieties are linked by a symmetric bis-urea functionalized chain or by an asymmetric amide and urea or amino and urea functionalized chain, were synthesized. The tentative synthesis of other types of related compounds did not give the products expected. The compounds were assayed as antineoplastics on human tumor cell lines at the National Cancer Institute (USA). Bis-urea derivatives were active on lung, colon, renal and CNS tumor cell lines. The degree of affinity of these compounds to DNA was also studied, showing low affinity.

1. Introduction

Echynomicin, a natural product, is a potent antineoplastic agent which cannot be therapeutically used due to its cytotoxicity [1, 2]. We carried out an extensive laboratory work introducing simplifications on this molecule which offered a series of active bis-aminoquinoxalines and bis-aminomethylnaphthalenes with potent cytostatic activity. The latter show a strong interaction with DNA [3–6]. That is why, the National Cancer Institute (NCI, USA) selected some of them for assays in a xenographic model. In order to determine whether the activity was due to a non-specific siamese structure or it was influenced by the functional characteristic of the bridge between the two naphthalenes, a new series of this type of molecules was developed. These conserved the naphthalene nuclei but were linked to the chain by different functional groups; urea-urea, urea-amide and urea-amine.

Furthermore, the synthesis of other types related to the above compounds was unsuccessfully attempted. These molecules have naphthylcarboxamide and aminomethylnaphthalene moieties; others have aminomethyl moieties linked to position 1- and 2- of naphthalene.

The compounds were sent to the NCI for evaluation as antineoplastics on human tumor cell lines [7]. DNA affinity was tested by a procedure based on the interference of their UV spectra by addition of calf thymus DNA [8]. The test was validated by repeating assays with recognized intercalating agents like mitoxantrone, m-AMSA, ethydiumbromide and bis-benzimide, the last closely binding to DNA along the minor groove [9].

2. Investigations, results and discussion

2.1. Synthesis of the compounds

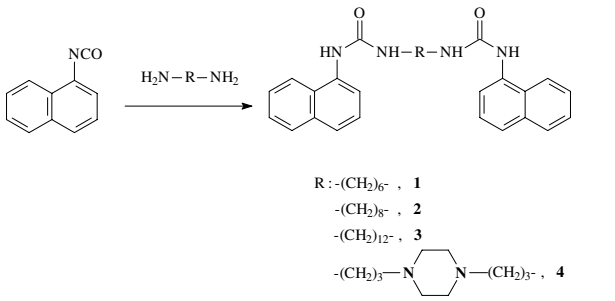
2.1.1. Bis-naphthylureas

Yields of this series – obtained by reaction of an excess of 1-naphthylisocyanate with the corresponding diamine in anh. ethanol (Scheme 1), were very good. Yields, melting points, recrystallization solvents and elemental analysis data are shown in Table 1.

Table 1: Physical properties of bis-naphthylureas

Compd.	Yield (%)	mp (°C)	Recryst. solv.	Formula
1	80	238–42	DMF	$C_{28}H_{30}N_4O_2$
2	88	235–37 d	DMF	$C_{30}H_{34}N_4O_2$
3	82	219–20 d	DMF	$C_{34}H_{42}N_4O_2$
4	84	202–6 d	DMF	$C_{32}H_{38}N_6O_2$

Scheme 1



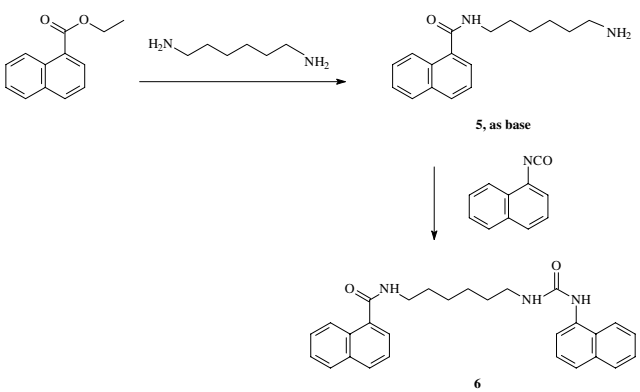
2.1.2. N-(1-Naphthyl)-N′-[6-aminohexyl-N-(1-naphthoyl)]urea

1-Ethyl-naphthoate dissolved in an excess of 1,6-diaminohexane reacted slowly at room temperature. A careful fractional distillation in vacuo yielded *N*-mononaphthoyl-1,6-hexanodiamine (**5**), crystallized as hydrochloride with a good yield and purity. The corresponding base of this compound reacted at room temperature with 1-naphthylisocyanate giving compound **6** (Scheme 2).

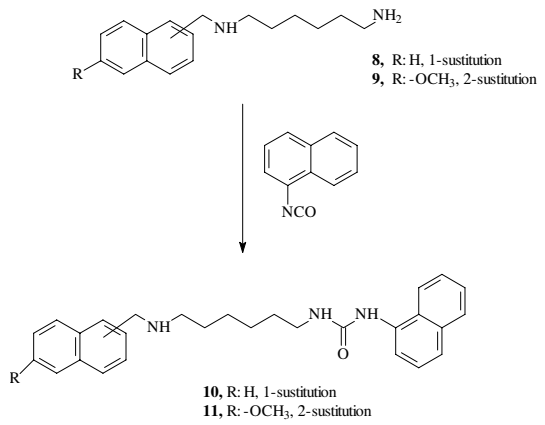
2.1.3. Aminomethylnaphthyl-naphthylureas

Methylnaphthyldiamines **8** and **9** also reacted readily with 1-naphthylisocyanate, specifically with the primary amino group, and gave good yields of **10** and **11** [10] (Scheme 3).

Scheme 2



Scheme 3



2.1.4. N-(1-Naphthoyl)-N′-(1-methylnaphthyl)-1,6-diaminohexane and N-(1-naphthoyl)-N′-(6-methoxy-2-methylnaphthyl)-1,6-diamino-hexane. Unsuccessful synthesis by reductive amination

A mixture of amine-amide **5** as a base and 6-methoxy-2-naphthaldehyde in ethanol was subjected to hydrogenation with palladium-charcoal. Instead of the expected amino-amide, two compounds were received. One of them was a basic substance that was then extracted with an aqueous acid. Elemental analysis and spectroscopic studies of both compounds determined the corresponding structure of *N,N′*-bis-(1-methylnaphthyl)-1,6-diaminohexane (**13**) and *N,N′*-bis-(1-naphthoyl)-1,6-diaminohexane (**14**, Scheme 4). The structures were identical as proven by melting points, mixed melting point and spectra, with samples obtained previously [6]. Probably, an instantaneous shift of the naphtoyl group takes place in the primary hydrogenation product through bimolecular interaction. The naphthoyl group was a particularly decisive factor in this transformation while the similar acetamide-amine compound **7** was perfectly stable [10].

2.1.5. N-(1-Methylnaphthoyl)-N′-(6-methoxy-2-methylnaphthyl)-1,6-diaminohexane. Unsuccessful synthesis

When condensation of *N*-(1-methylnaphthyl)-1,6-diaminohexane (**8**) with 6-methoxy-2-naphthaldehyde was attempted, only a reaction product of unknown structure was obtained. It was submitted to a number of acid extractions which only allowed recovery of the initial material. Mixing the starting materials under catalytic hydrogenation did also yield the same product and not the desired compound. A possible explanation for this behavior could be the reversible formation of an aminol with the secondary amine rather than the primary one. Obviously, this intermediary **15** could not dehydrate into an imine. A TLC in silica gel showed a typical "in tailing" development, where only the two reactants could be identified. The literature on this topic defines numerous cases of chain-ring tautomerism as a result of the interaction of aliphatic primary diamines with aldehydes, but none was described for diamines where one of the amine groups is primary and the other is secondary [11].

Scheme 4

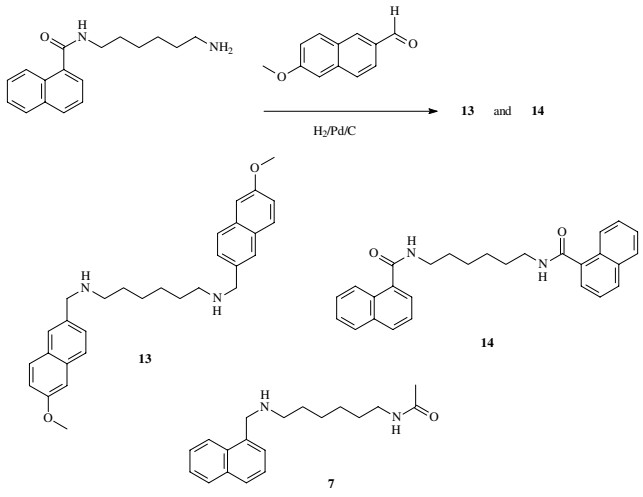


Table 2: DNA affinity assay

Compd. N⁰ (NSC Code)	DNA Affinity (a_{24}/a_0)
2 (682237)	0.9
3 (682238)	0.85
4 (682234)	0.69
6 (682235)	0.87
10 (682236)	0.83
11 (695802)	0.45
m-AMSA	0.54
Mitoxantrone	0.00
Bis-benzimide	0.57

Scheme 5

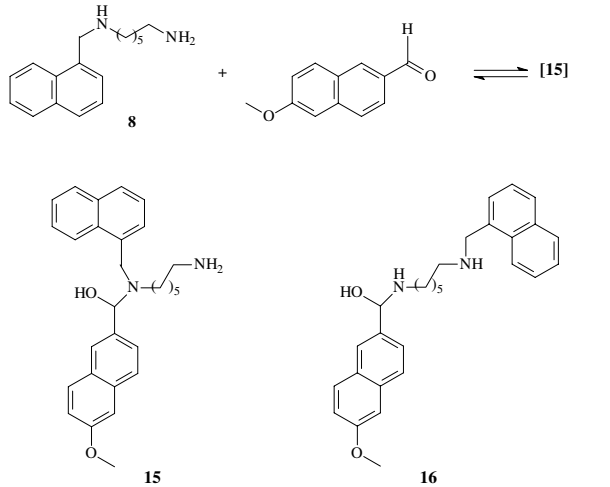


Table 3: *In vitro* antitumor activity on 60 human tumor cell lines

Compd.	Log_{10} GI_{50}[a]		$Log_{10}TGI_{50}$[b]		Log_{10} LC_{50}[c]	
	MG-MID[d]	Range	MG-MID	Range	MG-MID	Range
2	−4.57	1.84	−4.15	1.38	−4.04	0.80
3	−4.78	0.61	−4.46	0.60	−4.17	0.35
4	−4.86	1.58	−4.51	1.34	−4.20	1.04
6	−4.01	0.34	−4.00	0.00	−4.00	0.00
10	−4.02	0.47	−4.00	0.00	−4.00	0.00
11	−4.00	0.00	−4.00	0.00	−4.00	0.00

a: GI_{50}: log_{10} of molar concentration for 50% growth inhibition of tumor cells; b:TGI_{50}: log_{10} of molar concentration that produces a total growth inhibition; c: LC_{50}: log_{10} of molar concentration that produces cytotoxic effect in 50% of tumor cell; d: Meangraph-Midpoint: Parameter giving averaged activity on all cell lines.

Table 4: Antitumor activity in most sensitive tumor cell lines

Tumor	Cell Lines	GI_{50}
Compd. 2 NSC 682237		
LEU	CCRF-CEM	−4.89
	K-562	−4.84
NSLC[a]	HOP-62	−4.89
	HOP-92	−5.16
	NCI-H460	−5.46
	NCI-H522	−4.79
COLON	HCT-116	−5.02
	SW-620	−5.02
OVARIAN	OVCAR-4	−5.84
	OVCAR-8	−4.74
CNS	SF-268	−4.85
	SF-539	−4.97
	U251	−5.56
RENAL	786-O	−5.00
	A498	−4.96
	RXF393	−4.65
	SN12C	−4.74
	UO-31	−4.67
BREAST	MCF7	−4.86
	MDA-MB-231/ATCC	−5.11
	HS578T	−4.85
	MDA-MB-435	−4.76
Compd. 3 NSC 682238		
COLON	HCC-2998	−4.85
	SW-620	−4.76
NSLC[a]	HOP-62	−5.21
	HOP-92	−4.92
	NCI-H460	−4.81
	NCI-H522	−4.86
OVARIAN	OVCAR−4	−4.95
MELANOMA	MALME-3M	−4.82
	SK-MEL-2	−4.82
	UACC-62	−4.90
CNS	SF-268	−4.84
	SF-539	−4.88
	U251	−4.85
	SNB-75	−4.89
RENAL	786-O	−4.87
	ACHN	−4.85
	RXF393	−4.82
	SN12C	−4.75
	TK-10	−4.75
BREAST	BT-549	−4.84
	HS578T	−4.83
	MDA-MB-435	−4.75
	SF-268	−4.85
Compd. 4 NSC 682234		
NSLC[a]	HOP-62	−4.93
	HOP-92	−4.86
	EKVX	−5.01
	NCI-H522	−4.80
COLON	HCC-2998	−5.64
	SW-620	−5.08
OVARIAN	OVCAR-5	−4.82
	OVCAR-3	−4.87
RENAL	A498	−4.82
	RXF393	−4.95
	SN12C	−4.79
	UO-31	−4.78
	TK-10	−4.85
CNS	SF-268	−4.85
	SF-295	−4.86
	U251	−5.26
BREAST	MDA-MB-435	−4.79
	MDA-MB-231/ATCC	−5.65
	MDA-N	−4.81
	BT-549-435	−4.88
	T-47D	−4.88
MELANOMA	LOX IMVI	−5.07
	MALME-3M	−5.50
	SK-MEL-28	−4.84
	UACC-257	−4.88
	UACC-62	−5.48
PROSTATE	PC-3	−5.00
	DC-145	−4.77
Compd. 6 NSC 682235		
RENAL	UO-31	−4.34
Compd. 10 NSC 682236		
MELANOMA	M14	−4.47
OVARIAN	OVCAR-5	−4.20
RENAL	UO-31	−4.29
COLON	HCC-2998	−4.07

a: Non-small cell lung cancer

2.2. DNA affinity

As the bis-aminomethylnaphthalenes displayed close affinity to calf thymus DNA, we expected the synthesized compounds to conserve this property [5]. The binding capacity of these compounds was tested by measuring the hypochromic and bathochromic effects of their absorbance in the UV spectra. The typical procedure was enhanced by means of a slow rotation of DNA-drug mixture stirring, in a 5 : 1 ratio, during 24 h, and it was validated by repeating assays with well-known intercalating agents (m-AMSA and mitoxantrone) and a compound which binds closely in the minor groove (bis-benzimide, Hoechst no. 33258) [12].

The degree of interaction was expressed by means of the ratio between the final absorbance area after 24 h (a_{24}) and that of the compound at the same concentration (a_0). Values of 1 or greater indicate a total lack of affinity and value 0 shows that the whole compound was bound to DNA. Under such experimental conditions, values ranged from 0.7 to 0.9 thus indicating low affinity (Table 2), except for compound **11** that scored 0.45. This value was similar to those shown by m-AMSA, and bis-benzimide.

2.3. Antineoplastic activity

All the compounds were evaluated for antiproliferative properties according to NCI *in vitro* protocols.

They were assayed *in vitro* against a panel consisting of 60 human tumor cell lines, derived from nine cancer types (melanoma and leukemia, lung, colon, brain, ovarian, renal, prostate and breast cancers). Compounds were tested at five, 10-fold dilutions from a maximum concentration of 10^{-4} M. The results are displayed in Table 3. The

Table 5: AIDS-related lymphoma values

Cell Name	**2** GI_{50}	**3** GI_{50}	**4** GI_{50}	**6** GI_{50}	**10** GI_{50}
CCRF-CEM	1.70×10^{-5}	3.08×10^{-5}	2.20×10^{-5}	$> 1.00\ 10^{-4}$	$> 1.00\ 10^{-4}$
RL	2.46×10^{-5}	4.01×10^{-6}	2.03×10^{-5}	$> 1.00\ 10^{-4}$	$> 1.00\ 10^{-4}$
KD488	1.63×10^{-5}	1.89×10^{-5}	1.4×10^{-5}	$> 1.00\ 10^{-4}$	$> 1.00\ 10^{-4}$
AS283	$> 1.00\ 10^{-4}$	2.66×10^{-5}	2.52×10^{-5}	$> 1.00\ 10^{-4}$	$> 1.00\ 10^{-4}$
PA682	9.38×10^{-5}	8.10×10^{-6}	2.96×10^{-5}	$> 1.00\ 10^{-4}$	$> 1.00\ 10^{-4}$
SV-DHL-7	1.26×10^{-5}	1.71×10^{-5}	1.65×10^{-5}	$> 1.00\ 10^{-4}$	ND

mean graph-midpoint (MG-MID) values, which indicate the average sensitivity of all cell lines to each tested compound, are also given in each case.

Table 4 shows that compound **4** (NCS 682234) is particularly active against a number of solid hard-to-treat tumors such as lung, colon and CNS cancers. Compounds **2**, **3**, and **4** (NSC 682237, 682238 and 682234) are those which display significant broad spectrum bioactivity. Only symmetrical bis-ureas were of an active structural type [13]. Melanoma and lung, colon, renal cancers proved to be the subpanels most sensitive to these compounds.

All compounds were further evaluated in an investigational AIDS-related lymphoma (ARL) screen *in vitro* at NCI. The ARL screen uses parameters similar to those in the antitumor drug screen.

The ARL screen utilizes five human lymphoma cell lines (two established from AIDS patients), which grow in suspension and CCRF-CEM, a leukemia cell line is also included in the antitumor screen. As in the antitumor screen, agents are tested at five, 10-fold dilutions from a maximum concentration of 10^{-4} M, for a continuous exposure during 48 h. The cells are assayed for viability and their toxicity is determined with fluorescent dye propidium iodide by an assay optimized for single cell and clustered cell suspension. Results are shown in Table 5. The bis-urea derivatives showed moderate activity which was, however, insufficient for further *in vivo* studies.

3. Experimental

All the melting points were determined on a Büchi apparatus in open capillaries and are uncorrected. IR spectra were recorded on a Jasco A-200 spectrometer using KBr disks. ^{1}H NMR spectra were obtained with Brucker A80 and AC 200 spectrometers with tetramethylsilane as internal standard. Chemical shifts are reported in parts per million (ppm, δ units). UV spectra were measured with a Jasco 7850 UV-VIS recording spectrophotometer. All the elemental analysis results were in an acceptable range.

3.1. Chemistry

3.1.1. Bis-(1-naphthyl) ureas, general procedure

To an ice-cooled solution of 1.75 mmol of the corresponding diamine in 20 ml of anh. ethanol 0.5 ml (3.50 mmol) of 1-naphthylisocyanate was added dropwise with stirring. The solid products **1**–**4** collected by filtration and was crystallized from DMF in all the cases. Physical properties and elemental analysis data of the compounds obtained are summarized in Table 1. Spectroscopic data for these compounds are as follows:

1: ^{1}H NMR (DMSO-d_6): 1.48 (m, 8 H); 3.25 (c, 4 H); 6.65 (t, 2 H); 7.25–8.25 (m, 14 H); 8.5 (s, 2 H).

4: ^{1}H NMR (DMSO-d_6): 1.70 (m, 4 H); 2.20–2.40 (m, 12 H); 3.10–3.30 (m, 4 H); 6.6 (t, 2 H); 7.30–8.20 (m, 14 H); 8.5 (s, 2 H).

3.1.2. N-(1-Naphtoyl)-1,6-diaminohexane hydrochloride (**5**)

A mixture of 8.0 g (0.04 mol) of 1-ethylnaphthoate and 14.0 g (0.12 mol) of 1,6-diaminohexane was heated at 60–75 °C for 5 days. The excess of diamine was removed by distillation *in vacuo* (b.p.: 65–70 °C, 10 mmHg). The residue was dissolved in anh. ethanol and the hydrochloride crystallized after adding anh. ethanol-HCl. Yield: 6.38 g (52%), m.p. 150–153 °C. IR (as base) cm^{-1}: 3300, 2900, 1650, 1550, 795, 695.

$C_{17}H_{23}ClN_2O$

3.1.3. N-(1-Naphthyl)-N′-[6-aminohexyl-N-(1-naphthoyl)] urea (**6**)

The hydrochloride **5** was converted into the corresponding base by alkalinization with NaOH 40% and was extracted with CH_2Cl_2. To an ice-cooled solution of 1.0 g (3.7 mmol) of this base in 10 ml of anh. ethanol, 0.625 g (3.7 mmol) of 1-naphthylisocyanate was added dropwise, with stirring in 30 min. A yellow solid was obtained and crystallized from ethanol-ethylacetate. Yield: 0.70 g, 44%; m.p.: 157–159 °C. IR (KBr) cm^{-1}: 3300; 2920; 1620; 1550; 780, 670. ^{1}H NMR ($CDCl_3$) δ: 1.4–1.8 (m, 8 H); 3.3 (t, 2 H); 3.5 (t, 2 H); 6.6 (t, 1 H) ; 7.4–8.1 (m, 14 H); 8.2 (m, 1 H); 8.5 (s, 1 H).

$C_{28}H_{29}N_3O_2$

3.1.4. N-(1-Naphthyl)-N′-[6-aminohexyl-N-(1-methylnaphthyl)]-urea (**10**)

To a suspension of 0.350 g (1.4 mmol) of *N*-(1-methylnaphthyl)-1,6-diaminohexane (**8**) in 10 ml of anh. ethanol 0.230 g (1.4 mmol) of 1-naphthylisocyanate were added dropwise, with stirring at 0 °C. The solid was collected by filtration and washed with acetone to give **10** (0.320 g, 62%) as a white powder, m.p.: 168–170 °C. IR (KBr) cm^{-1}: 3320; 3050; 2900; 1650; 1550; 800, 780. ^{1}H NMR (CD_3OD) δ: 1.2–1.6 (m, 8 H); 1.7–1.8 (br s, 1H); 3.2 (t, 4 H); 3.5 (t, 2 H); 7.4–8.0 (m, 14 H); 8.2 (m, 2 H).

$C_{28}H_{31}N_3O$

3.1.5. N-(6-Methoxy-2-methylnaphthyl)-1,6-diaminohexane (**9**)

A solution of 0.50 g (2.6 mmol) of 6-methoxy-2-naphthaldehyde and 0.42 g (2.6 mmol) of *N*-acetyl-1,6-diaminohexane in a mixture of 20 ml of benzene and 20 ml of methanol was hydrogenated over 10% Pd-C (0.5 g) at 35 p.s.i. for 6 h. The catalyst was filtered off and the solvent was evaporated under reduced pressure. The residue was dissolved in 20 ml of HCl 3N and heated at 100 °C during 4 h. The solution was then treated with charcoal and filtered. The water was removed under reduced pressure to give a white solid, m.p.: 248–250 °C. Alkalinization of an aqueous solution of this hydrochloride gave the base as a solid which was crystallized from isopropanol yielding 0.49 g, (64%) of **9**, m.p.: 195–202 °C. IR (KBr) cm^{-1}: 3320, 2920, 2850, 1620, 1260, 790. ^{1}H NMR (CD_3OD) δ: 1.4–1.6 (m, 8 H); 2.5 (t, 4 H); 3.8 (s, 2 H); 3.9 (s, 3 H); 7.0 (m, 2 H); 7.4 (dd, 1 H), 7.5 (s, 2 H); 7.6 (s, 1 H).

$C_{18}H_{26}N_2O$

3.1.6. N-(1-Naphthyl)-N′-[6-aminohexyl-N-(6-methoxy-2-methyl-naphthyl)]urea (**11**)

To a suspension of 0.40 g (1.4 mmol) of **9** in 10 ml of anh. ethanol at 0 °C, 0.23 g (1.4 mmol) of 1-naphthylisocyanate were added dropwise. The solid was collected by filtration, washed with EtOH and cristallyzed from DMF-benzene to give 0.55 g, (90%) of **11**, m.p.: 158–162 °C. IR (KBr) cm^{-1}: 3320, 2920, 2850, 1640, 1530, 1260, 790. ^{1}H NMR (CD_3OD) δ: 1.2–1.6 (m, 8 H); 1.6–1.8 (br s, 1 H); 3.2 (t, 4 H); 3.5 (t, 2 H); 3.9 (s, 3 H); 7.4–8 (m, 13 H arom); 8.2 (m, 2 H).

$C_{29}H_{33}N_3O$

3.1.7. N-(1-Naphthoyl)-N′-(6-methoxy-2-methylnaphthyl)-1,6-diaminohexane

A mixture of 0.50 g (2.7 mmol) of 6-methoxy-2-naphthaldehyde and 0.73 g (2.7 mmol) of **5** in 25 ml of CH_2Cl_2 was heated under reflux for 12 h, then cooled, and the resulting solution was hydrogenated over 10% Pd-C (0.5 g) at 35 p.s.i. until constant pressure was reached. The catalyst was filtered off and the solution extracted three times with the same volume of HCl 15%. The organic layer was washed with water, dried and evaporated under reduced pressure. The white solid was crystallized from DMF-ethanol to give 0.14 g (25%) of a product of m.p.: 184–186 °C whose mixed m.p., IR and ^{1}H NMR spectra were identical to *N,N′*-bis-(1-naphthoyl)-1,6-diaminohexane.

The aqueous solution was neutralized with NaOH 5% and 0.12 g (21%) of a solid was obtained, whose mp, IR and ^{1}H NMR were coincident with *N,N′*-bis-(6-methoxy-2-methylnaphthyl)-1,6-diaminohexane.

3.1.8. N-(1-Methylnaphthyl)-N′-(6-methoxy-2-methylnaphthyl)-1,6-diaminohexane

A suspension of 0.23 g (0.90 mmol) of **8** and 0.162 mg (0.9 mmol) of 6-methoxy-2-naphthaldehyde in 20 ml of Cl_2CH_2 was hydrogenated over 10% Pd-C (0.5 g) at 35 psi for 3h. The catalyst was filtered off and the solution was concentrated under reduced pressure. The residue was treated with EtOH-HCl. The solvent was removed under reduced pressure and the residue was analyzed by TLC on silica gel and MeOH, producing development in tailing where only the starting material could be identified.

3.2. DNA affinity assay

DNA solution: Calf thymus DNA (12.5 mg) was slowly magnetically stirred in 5 ml Tris-HCl buffer (10 mM, pH 7.4) for 24 h at 4 °C. 0.6 ml were taken from this solution and diluted to 25 ml with the same buffer.

The test compound solution was prepared at a 10^{-4} M concentration using a minimal volume of ethanol and then diluted adding water to a concentration of 2×10^{-5}. A 3.0 ml sample of this solution was mixed with 3.0 ml of the DNA solution. The mixture was slowly rotated during 24 h and, then, its UV spectra were recorded at 20 °C using a 1 cm cell.

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