Synthesis and *in vitro* Antiproliferative Activity of New Substituted Benzo[3',2':5,6]thiopyrano[4,3-*d*]pyrimidines

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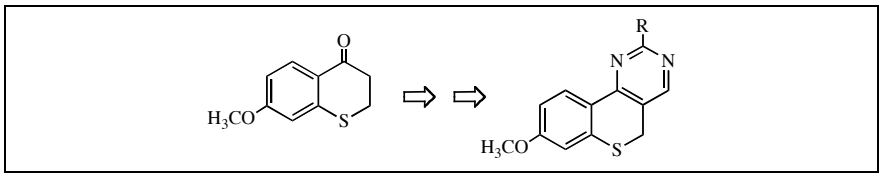

The synthesis of new planar benzo[3',2':5,6]thiopyrano[4,3-*d*]pyrimidine derivatives, carrying different side groups in the 2 position, is described. The novel substituted pyrimidines were obtained by reaction of the key intermediate 3-dimethylamino methylen-7-methoxy-2,3-dihydrobenzo[3',2':5,6]thiopyran-4(4*H*)-one, characterized by a reactive group adjacent to the C=O function, with the suitable binucleophile amidines in a basic medium. All the new compounds were evaluated for the antiproliferative ability by an *in vitro* assay on two human tumour cell lines (HL-60 and HeLa), and the 2-phenyl substituted derivative showed the capacity to inhibit cell growth on HL-60. Linear flow dichroism measurements indicated the inability to form a molecular complex with DNA.

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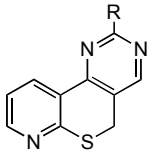
INTRODUCTION

DNA is recognized as the primary target for several clinically effective anti-tumour agents since drug-induced DNA damage can inhibit cell proliferation and induce cell death [1-4]. Despite their relative non selectivity, DNA-damaging agents are still of interest and, among them, DNA intercalating compounds are an important class of clinically useful anti-tumour agents, due to their high therapeutic potential [5].

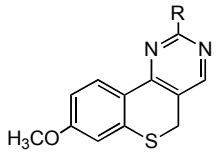
The antineoplastic activity of these drugs is the result of the interaction of their planar system between the DNA base pairs of the target cells, which causes changes of the nucleic acid structure and compromises its biological function [6,7].

In this field we have carried out extensive studies on several heterocyclic systems endowed with a detectable cytotoxic activity, characterized by a DNA intercalative binding mode [8-10]. More recently we described two new pyridothiopyranopyrimidine derivatives **1a** (R=NH_2) and **1b** (R=$NHSO_2C_6H_4$-*p*CH_3) [11], which, although endowed with antiproliferative activity, showed the inability to interact with the macromolecule. Nevertheless, these compounds were able to alter the mitochondrial functionality through a mechanism related to the induction of permeability transition [12], thus appearing to offer an interesting chromophore system.



1a-b

These results prompted us to synthesize the series of the new tricyclic derivatives **2a-h**, characterized by the isosteric benzothiopyranopyrimidine system.



2a-h

2a: R = H
2b: R = CH_3
2c: R = Ph
2d: R = NH_2
2e: R = $NHCH_2COOH$
2f: R = $N(CH_3)CH_2COOH$
2g: R = $NH(CH_2)_3CH(NH_2)COOH$
2h: R = $NHCH(CH_3)_2$

In the last years, the research on the benzothiopyrano-pyrimidine system gave rise to the synthesis of a large number of compounds endowed with interesting pharmacological properties [13] but, to date, the benzo-thiopyrano[4,3-*d*]pyrimidine nucleus **2a**, bearing a methoxy group in the 7-position, was never investigated. In the 2-position of the fused system, both lipophilic (compounds **2b,c**) and protonable groups (compounds **2d-h**) were introduced with the aim of enhancing the DNA-binding properties of the scaffold and/or its antiproliferative activity. Indeed it seemed reasonable that the presence of a pendant substituent might result in the possibility of supporting the formation of a reinforced complex with DNA, ascribable to electrostatic and/or to hydrogen bonding interactions.

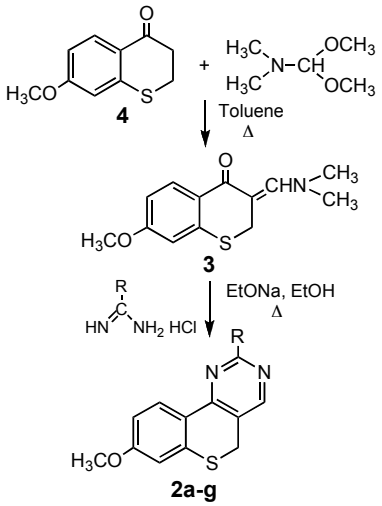
The ability of the new derivatives to exert an antiproliferative activity was evaluated by means of an inhibition growth assay on two human tumour cell lines, human promy-

elocitic leukemic cells (HL-60) and human cervix adenocarcinoma cells (HeLa). Linear flow dichroism experiments were performed to assess the occurrence of a molecular complex with DNA [14].

RESULTS AND DISCUSSION

The synthetic procedure leading to the target 8-methoxy-5*H*-benzo[3',2':5,6]thiopyrano[4,3-*d*]pyrimidine system **2a** takes advantage of the 1,3-bielectrophile reactivity of the intermediate 3-dimethylaminomethylen-7-methoxy-2,3-dihydrobenzo[3',2':5,6]thiopyran-4(4*H*)-one **3** in the reaction with a binucleophile amidine in a basic medium [9]. The preparation of compound **3** was accomplished, with good yields, using as starting compound the already described 7-methoxy-2,3-dihydrobenzo[3',2':5,6]thiopyrano-4(4*H*)-one **4** [15], by reaction with an excess of dimethylformamide dimethylacetal (DMF DMA) in refluxing toluene (Scheme 1). The 2-substituted analogues bearing the methyl (**2b**), phenyl (**2c**), amino (**2d**) groups or the aminoacidic side chains glycine (**2e**), N-methylglycine (**2f**) and ornithine (**2g**), respectively, were also synthesized. Compounds **2b-g** were thus obtained by reacting 3-dimethylaminomethylen-7-methoxy-2,3-dihydrobenzo[3',2':5,6]thiopyran-4(4*H*)-one **3** with the required amidine or aminoacidic derivative in an ethanolic refluxing solution, in the presence of sodium ethoxide (Scheme 1).

Scheme 1

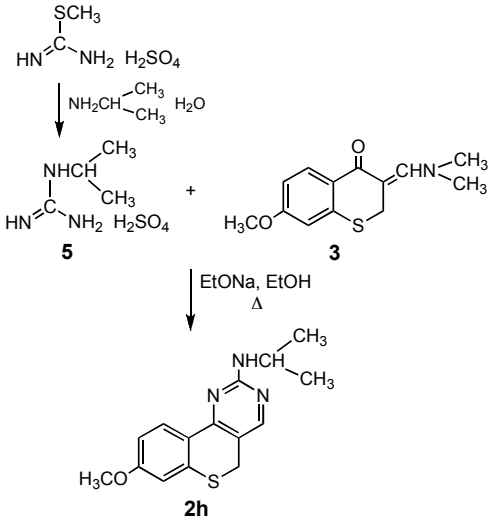


4 **3** **2a-g**

a: R = H
b: R = CH_3
c: R = C_6H_5
d: R = NH_2
e: R = $NHCH_2COOH$
f: R = $N(CH_3)CH_2COOH$
g: R = $NH(CH_2)_3CH(NH_2)COOH$

The synthetic pathway utilized in the preparation of compound **2h** involved, as a first step, the preparation of the isopropyl substituted amidine **5**, by condensation of methylthiopseudourea sulfate with isopropylamine in aqueous solution, as described in literature [16]. The subsequent condensation of **5** with the starting intermediate **3** afforded the desired 2-isopropylamino-pyrimidine derivative **2h** (Scheme 2).

Scheme 2



5 **3** **2h**

The crude target compounds were obtained as unique products (tlc analysis) in modest (**2e**,**g**,**h**) to high (**2a-d**,**f**) overall yields. This significant difference was ascribable to the lower cyclization capability of the amidino reactives bearing three instead of two amino groups [17].

All the derivatives were purified by crystallization and the proposed structures were assigned on the basis of analytical and spectral data (Tables I, II), which relied on those of earlier studies performed by our group [9].

The antiproliferative activity of compounds **2a-h** was evaluated by means of a cell growth inhibition assay on two human tumour cell lines, HL-60 and HeLa using Ellipticine as reference compound, in accordance with the experimental procedures previously described [8]. The results are expressed as IC_{50} values, *i.e.* the concentration (μM) of a compound able to cause 50% of cell death with respect to the control culture, and are reported in Table III. The obtained values indicated that neither the scaffold itself (**2a**) nor the derivatives (**2b**, **2d**-**h**) substituted in the 2-position exert any cytotoxic activity, while the 2-phenyl substituted compound, (**2c**), showed a significant anti-proliferative effect on HL-60 cells.

Linear flow dichroism (LD) experiments were performed, as reported in ref. [8], to assess the occurrence of a molecular complex with DNA. Figure 1 showed the LD spectra of DNA alone (continuous line) and in the presence of **2c** (dotted line) at [drug]/[DNA]=0.08. The dichroic spectra revealed the absence of any detectable signal in the region at wavelength higher than 300 nm, where only the benzothiopyranopyrimidine chromophore

Table I

Physical and Analytical Data of Compounds **2a-h**

Compound	R	Yield (%)	M. p. °C	Molecular Formula	Analysis (%) Calcd./Found		
					C	H	N
2a	H	83	139-142	$C_{12}H_{10}N_2OS$	62.59	4.35	12.17
					62.25	4.18	11.99
2b	CH_3	88	116-118	$C_{13}H_{12}N_2OS$	63.91	4.95	11.47
					63.84	4.73	11.56
2c	C_6H_5	94	82-85	$C_{18}H_{14}N_2OS$	70.56	4.61	9.14
					70.22	4.57	8.76
2d	NH_2	85	172-175	$C_{12}H_{11}N_3OS$	58.77	4.49	17.14
					58.69	4.23	16.95
2e	$NHCH_2COOH$	28	170-175 dec.	$C_{14}H_{13}N_3O_3S$	55.44	4.29	13.86
					55.15	4.46	13.77
2f	CH_3NCH_2COOH	60	175-177	$C_{15}H_{15}N_3O_3S$	56.77	4.73	13.25
					56.43	4.68	13.19
2g	$NH(CH_2)_3CH(NH_2)COOH$	38	180-185 dec.	$C_{17}H_{20}N_4O_3S$	56.66	5.55	15.55
					56.19	5.23	15.35
2h	$NHCH(CH_3)_2$	42	115-117	$C_{15}H_{17}N_3OS$	62.72	5.92	14.63
					62.34	5.79	14.47

Table II

Spectral Data of Compounds **2a-h**

Compound	R	ir (cm^{-1})	^1H nmr (δ ppm)	Ms m/z
2a	H	1595, 1570, 1400, 1245, 1220, 1035, 790	3.83 (s, 3H, OCH_3); 4.12 (s, 2H, CH_2S); 6.95 (dd, 1H, 9-H $J_{9\text{-}10}$ = 8.5 Hz $J_{9\text{-}7}$ = 2.4 Hz); 7.01 (d, 1H, 7-H $J_{7\text{-}9}$ = 2.4 Hz); 8.28 (d, 1H, 10-H $J_{10\text{-}9}$ = 8.5 Hz); 8.69 (s, 1H, 4-H); 9.07 (s, 1H, 2-H)	230
2b	CH_3	1605, 1575, 1530, 1425, 1250, 1225, 1060, 790	2.63 (s, 3H, 2-CH_3); 3.82 (s, 3H, OCH_3); 4.07 (s, 2H, CH_2S); 6.93 (dd, 1H, 9-H $J_{9\text{-}10}$ = 8.6 Hz $J_{9\text{-}7}$ = 2.1 Hz); 6.99 (d, 1H, 7-H $J_{7\text{-}9}$ = 2.1 Hz); 8.25 (d, 1H, 10-H); 8.57 (s, 1H, 4-H)	244
2c	C_6H_5	1595, 1570, 1420, 1250, 1215, 1045, 765, 730	3.84 (s, 3H, OCH_3); 4.16 (s, 2H, CH_2S); 6.96-7.03 (m, 2H, 9-H 7-H); 7.52-7.56 (m, 4H, ArH); 8.46-8.50 (m, 2H, ArH); 8.78 (s, 1H, 4-H)	306
2d	NH_2	3315, 3195, 1650, 1585, 1415, 1250, 1220, 1045, 790	3.80 (s, 3H, OCH_3); 3.90 (s, 2H, CH_2S); 6.57 (s, 2H, NH_2, exch.); 6.89 (dd, 1H, 9-H $J_{9\text{-}10}$ = 8.8 Hz $J_{9\text{-}7}$ = 2.4 Hz); 6.93 (d, 1H, 7-H $J_{7\text{-}9}$ = 2.4 Hz); 8.13 (d, 1H, 10-H $J_{10\text{-}9}$ = 8.8 Hz); 8.15 (s, 1H, 4-H)	245
2e	$NHCH_2COOH$	3360, 3270, 3160, 1660, 1580, 1250, 1045, 1025, 790	3.50 (m, 2H, $NHCH_2$); 3.80 (s, 3H, OCH_3); 3.90 (s, 2H, CH_2S); 6.21 (t, 1H, NH exch. J = 2.2 Hz); 6.86 (d, 1H, 7-H $J_{7\text{-}9}$ = 2.2 Hz); 6.90 (dd, 1H, 9-H $J_{9\text{-}10}$ = 8.4 Hz $J_{9\text{-}7}$ = 2.2 Hz); 8.17 (s, 1H, 4-H); 8.19 (d, 1H, 10-H $J_{10\text{-}9}$ = 8.4 Hz)	303
2f	CH_3NCH_2COOH	3390, 1720, 1595, 1505, 1220, 1050, 795	3.20 (s, 3H, NCH_3); 3.81 (s, 3H, OCH_3); 3.95 (s, 2H, CH_2S); 4.31 (s, 2H, NCH_2); 6.87-6.95 (m, 2H, 7-H 9-H); 8.16-8.28 (m, 2H, 10-H 4-H); 12.57 (s, 1H, COOH, exch.)	317
2g	$NH(CH_2)_3CH(NH_2)COOH$	3365, 3215, 1635, 1585, 1405, 1240, 1045, 790	1.61 (m, 4H, NCH_2-CH_2CH_2); 3.12 (t, 1H, CH_2CH J = 1.8 Hz); 3.32 (m, 2H, $NHCH_2$); 3.80 (s, 3H, OCH_3); 3.90 (s, 2H, CH_2S); 6.86-6.94 (m, 2H, 7-H 9-H); 7.18 (t, 1H, NH exch. J = 2.1 Hz); 7.56 (bs, 2H, NH exch.); 8.16-8.19 (m, 2H, 4-H 10-H)	360
2h	$NHCH(CH_3)_2$	3250, 1585, 1550, 1410, 1300, 1245, 1170, 850, 790	1.16 (d, 6H, $CH(CH_3)_2$ J = 6.4 Hz); 3.81 (s, 3H, OCH_3); 3.90 (s, 2H, CH_2S); 4.04-4.14 (m, 1H, $CH(CH_3)_2$); 6.86-6.95 (m, 2H, 7-H 9-H); 8.16 (d, 1H, 10-H J = 8.4 Hz); 8.18 (s, 1H, 4-H)	287

absorbs, thus indicating its inability to give rise to a molecular complex with the macromolecule.

Table III

Antiproliferative activity of compounds **2a-h**

compound	Cellular lines IC_{50} (μM)	
	HL-60	HeLa
2a	>20	>20
2b	>20	>20
2c	7,15 ± 0,01	>20

Table III (continued)

compound	Cellular lines IC_{50} (μM)	
	HL-60	HeLa
2d	>20	>20
2e	>20	>20
2f	>20	>20
2g	>20	>20
2h	>20	>20
ellipticine	0,64± 0,02	0,31± 0,01

Thus, it is reasonable to assume that the observed antiproliferative capacity (Table III) might ensue from the

effect on a different cellular target, which will be further investigated.

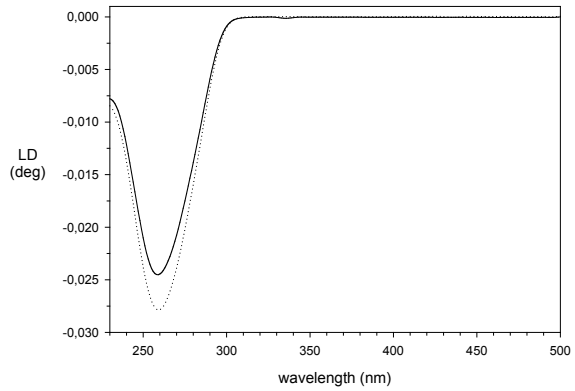


Figure 1. Linear flow dichroism spectra for compound **2c** at [drug]/[DNA]=0 (continuous line) and [drug]/[DNA]=0.08 (dotted line). [DNA]=1.9x10^{-3} M in ETN buffer (10 mM TRIS, 10 mM NaCl, 1 mM EDTA, pH=7)

EXPERIMENTAL

Melting points were determined using a Reichert Köfler hot-stage apparatus and are uncorrected. Infrared spectra (ir) were obtained on a NICOLET/AVATAR, 360 FT spectrophotometer as Nujol mulls. Nuclear magnetic resonance spectra (nmr) were recorded on a Varian Gemini 200 spectrometer, in dimethyl-d_6 sulfoxide solution using TMS as the internal standard. Mass spectra (ms) were obtained on a Finningan Polaris/GCQ Plus spectrometer using an electron beam energy of 70 eV. Magnesium sulfate was always used as the drying agent. Evaporations were made *in vacuo* (rotating evaporator). Analytical tlc were carried out on Merck 0.2 mm precoated silica gel aluminium sheets (60 F-254). Elemental analyses were performed by our Analytical Laboratory.

3-Dimethylaminomethylen-7-methoxy-2,3-dihydrobenzo-[3',2':5,6]thiopyran-4(4*H*)-one (**3**). An excess of dimethylformamide dimethylacetal (2.60 mL, 19.3 mmoles) was added to a stirred solution of 7-methoxy-2,3-dihydrobenzo[3',2':5,6]thiopyran-4(4*H*)-one **4** (1.500 g, 7.73 mmoles) in anhydrous toluene (10 mL) and the mixture was refluxed for 12 hours. After cooling, the solution obtained was evaporated under reduced pressure, giving a residue which was treated with ethyl ether, collected and purified by crystallization from toluene-petroleum ether 60-80°C (quantitative yield). m. p. 115-120°C; ir (nujol, cm^{-1}): 1635, 1590, 1325, 1230, 1065, 975, 770; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 3.11 (s, 6H, $N(CH_3)_2$); 3.77 (s, 3H, CH_3O); 4.07 (s, 2H, CH_2S); 6.75 (dd, 1H, 6-H J_{6-5} = 8.5 Hz J_{6-8} = 2.4 Hz); 6.80 (d, 1H, 8-H J_{8-6} = 2.4 Hz); 7.40 (s, 1H, *CH*$N(CH_3)_2$); 7.83 (d, 1H, 5-H J_{5-6} = 8.5 Hz); ms: m/z = 249 (M^+). Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.65; H, 6.02; N, 5.62; Found: C, 62.50; H, 6.33; N, 5.14.

8-Methoxy-5*H*-benzo[3',2':5,6]thiopyrano[4,3-*d*]pyrimidine (**2a**). Formamidine hydrochloride (0.219 g, 1.60 mmoles) was added, at room temperature, under nitrogen atmosphere, to a stirred solution of sodium ethoxide (0.055 g, 2.4 mmoles of sodium in 8 mL of anhydrous ethanol). The resulting suspension was stirred at room temperature for 15 minutes, then 3-dimethylaminomethylen-7-methoxy-2,3-dihydrobenzo[3',2':5,6]-thiopyran-4(4*H*)-one **3** (0.200 g, 0.8 mmole) was added and the reaction mixture was refluxed for 16 hours (tlc analysis). After cooling, the solid was collected and the solution was evaporated under reduced pressure. The solid and the residue were washed with water and collected to give crude pyrimidine **2a**, which was purified by crystallization from ethanol (Table I).

General procedure for the synthesis of 2-Methyl- (2b), 2-Phenyl- (2c) and 2-Amino-8-methoxy-5*H*-benzo[3',2':5,6]-thiopyrano[4,3-*d*]pyrimidine (2d). Acetamidine hydrochloride, benzamidine hydrochloride or guanidine hydrochloride (1.60 mmoles) was added, at room temperature, under nitrogen atmosphere, to a stirred solution of sodium ethoxide (0.055 g, 2.4 mmoles of sodium in 8 mL of anhydrous ethanol). The resulting suspension was stirred at room temperature for 15 minutes, then 3-dimethylaminomethylen-7-methoxy-2,3-dihydrobenzo[3',2':5,6]thiopyran-4(4*H*)-one **3** (0.200 g, 0.8 mmole) was added and the reaction mixture was refluxed for 8-24 hours (tlc analysis). After cooling, the solid, if present, was collected and the solution was evaporated under reduced pressure. The solid and the residue were washed with water and collected to give crude pyrimidines **2b-d**, which were purified by crystallization from ethanol (Tables I, II).

General procedure for the synthesis of 2-Glycinyl- (2e), 2-(*N*-methyl)glycinyl- (2f) and 2-(5*N*-ornithinyl)-8-methoxy-5*H*-benzo[3',2':5,6]thiopyrano[4,3-*d*]pyrimidine (2g). The required guanidineacetic acid, creatine monohydrate or arginine hydrochloride (1.60 mmoles) was added, at room temperature, under nitrogen atmosphere, to a stirred solution of sodium ethoxide (0.092 g, 4.0 mmoles of sodium in 8 mL of anhydrous ethanol). The resulting suspension was stirred at room temperature for 15 minutes, then 3-dimethylaminomethylen-7-methoxy-2,3-dihydrobenzo[3',2':5,6]thiopyran-4(4*H*)-one **3** (0.200 g, 0.8 mmole) was added and the reaction mixture was refluxed for 8-24 hours (tlc analysis). After cooling, the solution was acidified with concentrated hydrochloric acid (pH=6). The precipitate was collected to give crude pyrimidines **2e-g**, which were purified by crystallization from ethanol (Tables I, II).

Isopropylguanidine sulphate (**4**). [16] Isopropylamine (1.70 mL, 20 mmoles) was added to a stirred suspension of 2-methyl-2-thiopseudourea sulphate (2.780 g, 14.8 mmoles) in 2 mL of ice-cooled water. The resulting suspension was stirred at room temperature for 16 hours and then refluxed for 4 hours. After cooling the solution obtained was evaporated to dryness and the residue was purified by crystallization from ethanol, yield 35.0 %, m. p. 268-269°C, lit. m. p. 270-271°C. Anal. Calcd. for $C_4H_{13}N_3O_4S$: C, 24.12; H, 6.53; N, 21.10; Found: C, 24.50; H, 6.33; N, 21.14.

2-Isopropylamino-8-methoxy-5*H*-benzo[3',2':5,6]thiopyrano[4,3-*d*]pyrimidine (**2h**). Isopropylguanidine sulphate **4** (0.318 g, 1.6 mmoles) was added, at room temperature, under nitrogen atmosphere, to a stirred solution of sodium ethoxide (0.092 g, 4.0 mmoles of sodium in 8 mL of anhydrous ethanol). The resulting suspension was stirred at room temperature for 15 minutes, then 3-dimethylaminomethylen-7-methoxy-2,3-dihydrobenzo[3',2':5,6]thiopyran-4(4*H*)-one **3** (0.200 g, 0.8 mmole) was added and the reaction mixture was refluxed for 16 hours (tlc analysis). After cooling the obtained solution was evaporated to dryness and the residue was purified by crystallization from ethanol (Table I, II).

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