Synthesis of Purinobenzothiazine and Pyridothiazinopurine Derivatives. Two New Heterocyclic Ring Systems

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The synthesis of derivatives of two new heterocyclic systems, purino[8,7-*b*][1,3]benzothiazine and pyrido[3',2':5,6][1,3]thiazino[3,2-*f*]purine, was effected by the Ullmann reaction between 8-mercaptotheophylline or 8-bromotheophylline with the appriopriately substituted benzoic or nicotinic acid, respectively. The 8,8'-dithiobistheophylline is also reported.

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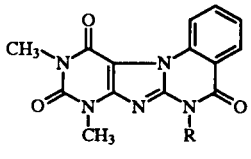
DNA intercalating agents are very important classes of antitumor drugs and usually possess planar or almost planar aromatic or heteroaromatic polycyclic systems.

As part of a general study based on the above observations, our attention was focused on the development of new planar heteropolycyclic compounds. In the last few years we have reported the synthesis of molecules which contain new heteropolycyclic ring systems, such as a number of 8,10-dimethylpurino[7,8-*a*]quinazoline-5,9,11(6*H*,8*H*,10*H*)-triones **1** and 1,3-dimethylpurino-[8,7-*b*]quinazoline-2,4,6(1*H*,3*H*,11*H*)-triones **2** [1].



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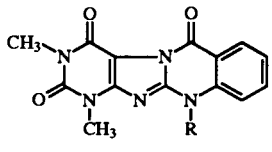

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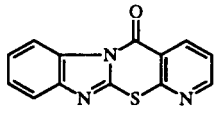
Variations of chromophore size or electronics, such as the inclusion of various heteroatoms, usually cause variations in antitumor properties. On this basis, Wentland *et al.* have recently described the outstanding *in vivo* antitumor activity of some benzothiopyranoindazoles [2].

In continuation of our study on new heteropolycyclic compounds as potential antitumor agents, in this paper we report the synthesis of purino[8,7-*b*][1,3]benzothiazine-1,3,11(2*H*,4*H*)-trione derivatives **10a-b** and of 2,4-dimethylpyrido[3',2':5,6]thiazino[3,2-*f*]purine-1,3,11(2*H*,4*H*)-trione **14**, which represent two new heterocyclic ring systems.

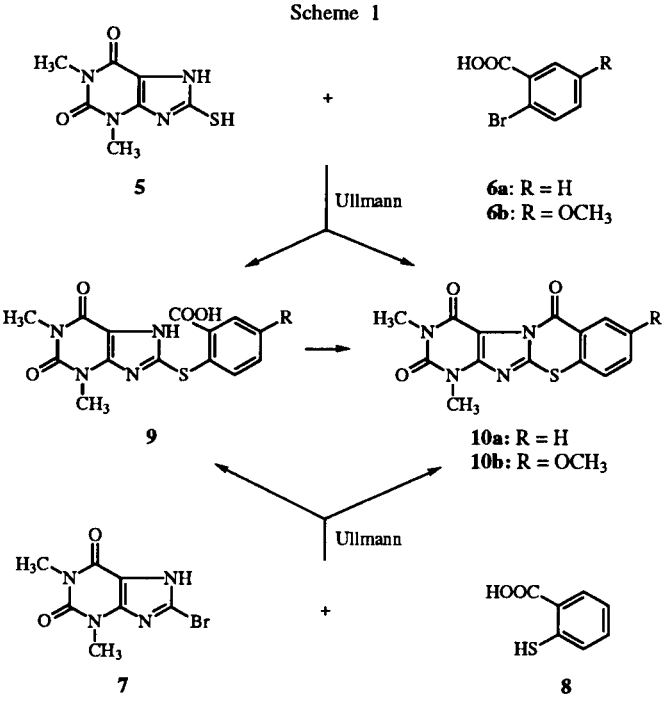
To the best of our knowledge, only one report on an analogous ring system, the 5*H*-5-oxobenzimidazo[2,1-*b*]-pyrido[3,2-*e*][1,3]thiazine **3**, is found in the literature [3].



3

The preparation of the starting 8-mercaptotheophylline **5** has already been described [4]. The target compound **10a** was synthesized *via* an Ullmann reaction between **5** and 2-bromobenzoic acid **6a** in dimethylformamide at 120° under a nitrogen atmosphere, in the presence of anhydrous potassium carbonate and a catalytic amount of cuprous bromide (Scheme 1). In this

Scheme 1



5 **9** **7** **8**

reaction the intermediate acid **9** was also isolated in low yield (6.4%). Compound **9** was easily cyclized to **10a** (43% yield) by reflux in dimethylformamide. The structure proposed for **10a** is very logical, because the cyclization of the acid **9** on the N(9) of theophylline is not possible, due to the steric hindrance of the 3-methyl group [5].

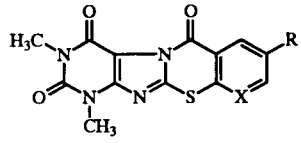
In a similar manner, compound **10b** (37% yield) was directly obtained from **5** and 2-bromo-5-methoxybenzoic acid **6b**, *via* an Ullmann reaction.

The structures of **10a-b** were unequivocally confirmed by analytical, ir, ^{1}H-nmr and mass spectral data (Table I) and by chemical evidence. In fact, a mixture of the acid **9** (7.8% yield) and **10a** (32% yield) was also obtained *via* Ullmann reaction between 8-bromotheophylline **7** and 2-thiosalicylic acid **8** (Scheme 1).

spectral data (Table I) and by chemical evidence. In fact when 8-bromotheophylline **7** and 2-mercaptopyridine-3-carboxylic acid **12** were directly heated in polyphosphoric acid at 150°, the compound **14** (13% yield) was obtained (Scheme 2). Numerous attempts to obtain **13** and **14** from **7** and **12** *via* an Ullmann reaction were unsuccessful.

Table I

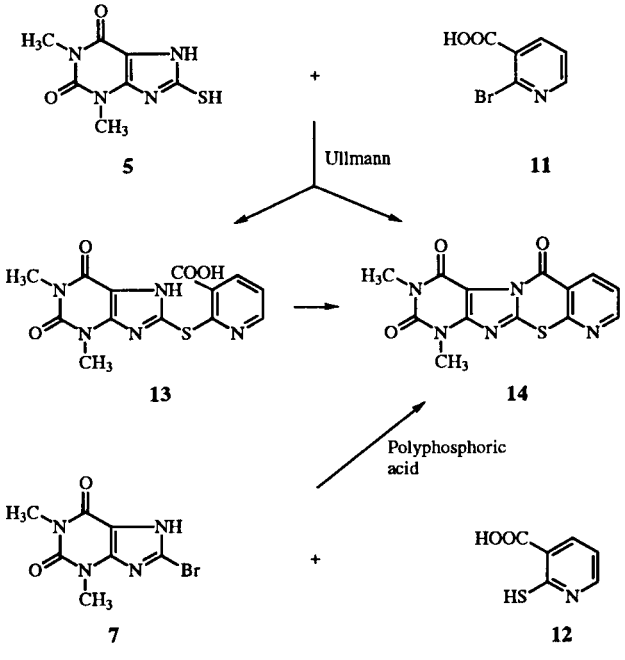
Physical and Spectral Data of Compounds **10a-b** and **14**



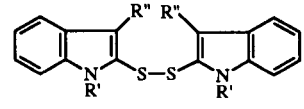
No.	R	X	Yield (%)	Mp (°C) (recrystallization solvent)	^{1}H-NMR (δ ppm)	MS m/z (R.I. %)	Molecular Formula	Analysis(%) Calcd./Found C	H	N
10a	H	CH	*a*: 34	>300	3.27 (s, 3H, N_3-CH_3), 3.50 (s, 3H, N_1-	M^+314	$C_{14}H_{10}N_4O_3S$	53.50	3.21	17.82
			b: 32	(DMF)	CH_3), 7.65-8.48 (m, 4H, Ar-H)	(100)		53.16	3.39	17.62
10b	OCH_3	CH	37	290-292	3.29 (s, 3H, N_3-CH_3), 3.52 (s, 3H, N_1-	M^+344	$C_{15}H_{12}N_4O_4S$	52.32	3.51	16.27
				(DMF)	CH_3), 3.92 (s, 3H, OCH_3), 7.70-8.23 (m, 3H, Ar-H)	(77)		51.96	3.65	16.21
14	H	N	*a*: 39	>300(dec.)	3.30 (s, 3H, N_3-CH_3), 3.50 (s, 3H, N_1-	M^+315	$C_{13}H_9N_5O_3S$	49.52	2.88	22.21
			b: 13	(DMF)	CH_3), 7.70-8.90 (m, 3H, Ar-H)	(100)		49.46	2.82	22.37

When 8-mercaptotheophylline **5** and 2-bromopyridine-3-carboxylic acid **11** were submitted to the Ullmann reaction, a mixture of the intermediate acid **13** (7.9% yield) and of the 2,4-dimethylpyrido[3',2':5,6][1,3]thiazino[3,2-*f*]purine-1,3,11(2*H*,4*H*)-trione **14** was obtained (Scheme 2). By heating compound **13** with dimethylformamide at 120°, the cyclized product **14** (30% yield) was obtained. The structure of **14** was confirmed by analytical, ir, ^{1}H-nmr and mass

Scheme 2



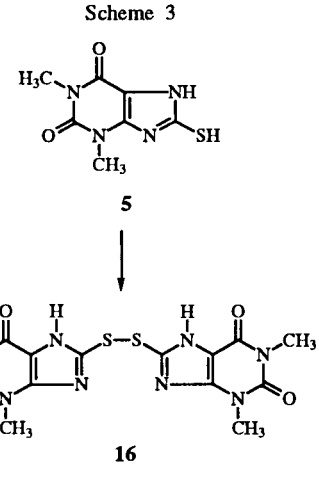
Recently a series of 3-substituted 2,2'-dithiobis-1*H*-indoles **15** were synthesized and evaluated *in vitro* for inhibition of receptor and nonreceptor protein tyrosine kinases [6].



15

In this light, with the aim to obtain new molecules with potential antitumor activity, we have synthesized in good yield (58%) the 8,8'-dithiobistheophylline **16** from **5** by reflux in dimethylformamide solution (Scheme 3).

Scheme 3



The structure of **16** was confirmed by analytical, ir, ^{1}H-nmr and mass (M^+, m/z = 422) spectral data. This new compound will be functionalized in a similar manner as described for compound **15** [6].

EXPERIMENTAL

Melting points were determined using a Reichert Köfler hot-stage apparatus and are uncorrected. Infrared spectra were obtained on a Pye/Unicam Model PU 9561 spectrophotometer in Nujol mulls. Nuclear magnetic resonance spectra were recorded on a Varian CFT-20 spectrometer, in dimethyl sulfoxide solution, using tetramethylsilane as the internal standard. Mass spectra were obtained on a Hewlett-Packard 5988 A spectrometer using a direct injection probe and an electron beam energy of 70eV. Magnesium sulfate was always used as the drying agent. Evaporations were made *in vacuo* (rotating evaporator). Analytical tlc was carried out on Merck 0.2 mm precoated silica gel aluminium sheets (60 F-254). Elemental analyses were performed by our Analytical Laboratory.

2,4-Dimethylpurino[8,7-*b*][1,3]benzothiazine-1,3,11(2*H*,4*H*)-trione (**10a**).

Procedure a.

A suspension of 8-mercaptotheophylline **5** (0.30 g, 1.41 mmoles), 2-bromobenzoic acid **6a** (0.29 g, 1.44 mmoles), anhydrous potassium carbonate (0.21 g, 1.52 mmoles) and a catalytic amount of cuprous bromide in 7 ml of freshly distilled dimethylformamide was heated with stirring at 120° for 24 hours under a nitrogen atmosphere.

After cooling, the reaction mixture was diluted with water and acidified with concentrated hydrochloric acid. The solid was collected and then treated with an aqueous solution of sodium bicarbonate yielding 0.137 g (31%) of compound **10a** as the insoluble material (Table I). The sodium bicarbonate solution was acidified with diluted hydrochloric acid giving 0.030 g (6.4%) of the intermediate 8-[2-(carboxyphenyl)thio]-theophylline **9**, which was characterized without any purification because of its easy cyclization to **10a** in the recrystallization process, mp 200-205° dec; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 3.24 (s, 3H, 1-N-CH_3), 3.44 (s, 3H, 3-N-CH_3), 6.71-8.01 (m, 4H, Ar-H), 13.92 (s, 1H, 2'-COOH); ms: m/z 332 (M^+).

Anal. Calcd. for $C_{14}H_{12}N_4O_4S$: C, 50.60; H, 3.61; N, 16.86. Found: C, 50.42; H, 3.27; N, 16.94.

Compound **9** was refluxed for a few minutes in dimethylformamide (4-5 ml) to give an additional amount of pure **10a** (total yield 34%).

Procedure b.

A suspension of 8-bromotheophylline **7** (0.72 g, 2.78 mmoles), 2-thiosalicylic acid **8** (0.43 g, 2.79 mmoles), anhydrous potassium carbonate (0.41 g, 2.97 mmoles) and a catalytic amount of cuprous bromide in 14 ml of freshly distilled dimethylformamide was heated with stirring at 120° for 24 hours under a nitrogen atmosphere. Further work-up was similar to that previously described in procedure a, obtaining the heterocyclic compound **10a** (0.281 g, 32% yield) and the intermediate **9** (0.072 g, 7.8% yield).

2,4-Dimethyl-9-methoxypurino[8,7-*b*][1,3]benzothiazine-1,3,11(2*H*,4*H*)-trione (**10b**).

A suspension of 8-mercaptotheophylline **5** (0.20 g, 0.94 mmoles), 2-bromo-5-methoxybenzoic acid **6b** (0.22 g, 0.95 mmoles), anhydrous potassium carbonate (0.14 g, 1.01 mmoles) and a catalytic amount of cuprous bromide in 5 ml of freshly distilled dimethylformamide was heated with stirring at 120° for 24 hours under a nitrogen atmosphere. After cooling, the reaction mixture was diluted with water and acidified with concentrated hydrochloric acid. The solid was collected and then recrystallized from dimethylformamide, to yield 0.120 g of pure **10b** (Table I).

2,4-Dimethylpyrido[3',2':5,6][1,3]thiazino[3,2-*f*]purine-1,3,11(2*H*,4*H*)-trione (**14**).

Procedure a.

A suspension of 8-mercaptotheophylline **5** (0.30 g, 1.41 mmoles), 2-bromopyridine-3-carboxylic acid **11** (0.29 g, 1.44 mmoles), anhydrous potassium carbonate (0.21 g, 1.52 mmoles) and a catalytic amount of cuprous bromide in 7 ml of freshly distilled dimethylformamide was heated with stirring at 120° for 24 hours under a nitrogen atmosphere. After cooling, the reaction mixture was diluted with water and acidified with concentrated hydrochloric acid. The solid was collected and then treated with an aqueous solution of sodium bicarbonate, yielding 0.161 g (37%) of compound **14** as the insoluble material (Table I). The sodium bicarbonate solution was acidified with diluted hydrochloric acid giving 0.0368 g (7.9%) of the intermediate 8-[2-(carboxypyridyl)-thio]theophylline **13**, which was characterized without any purification because of its easy cyclization to **14** in the recrystallization process, mp 240° dec; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 3.21 (s, 3H, 1-N-CH_3), 3.42 (s, 3H, 3-N-CH_3), 6.71-8.01 (m, 3H, Ar-H), 13.89 (s, 1H, 2'-COOH); ms: m/z 333 (M^+).

Anal. Calcd. for $C_{13}H_{11}N_5O_4S$: C, 46.84; H, 3.30; N, 21.02. Found: C, 46.74; H, 3.21; N, 20.85.

Compound **13** was refluxed for a few minutes in dimethylformamide (4-5 ml) to give an additional amount of pure **14** (total yield 39%).

Procedure b.

A mixture of 8-bromotheophylline **7** (2.4 g, 9.26 mmoles), 2-thionicotinic acid **12** (1.44 g, 9.3 mmoles) and 24 g of polyphosphoric acid was heated at 150° for 4 hours. After cooling, the reaction mixture was diluted with ice-water. The solid was collected and washed with water to give crude cyclized compound **14**, which was purified by recrystallization from dimethylformamide (0.380 g), Table I.

8,8'-Dithiobistheophylline (**16**).

A suspension of 8-mercaptotheophylline **5** (0.30 g, 1.41 mmoles) in 7 ml of freshly distilled dimethylformamide was heated at 100° for 24 hours. After cooling, the precipitated product was collected, washed with a small amount of ethanol and purified by recrystallization from dimethylformamide to yield 0.342 g (58%) of pure **16**, mp>300°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 3.24 (s, 6H, 1-N-CH_3 +1'-N-CH_3), 3.40 (s, 6H, 3-N-CH_3 + 3'-N-CH_3); ms: m/z 422 (M^+).

Anal. Calcd. for $C_{14}H_{14}N_8O_4S_2$: C, 39.81; H, 3.32; N, 26.54; S, 15.17. Found: C, 39.93; H, 3.35; N, 26.30; S, 15.50.

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REFERENCES AND NOTES

* Author to whom all correspondence should be addressed.

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