# Synthesis and Screening of 8-(4′-Thiazolyl)purines[1]

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8-(4′-Thiazolyl)purines and deazapurines were obtained by condensation of 4-carboxythiazole derivatives with 4,5-diaminopyrimidines or pyridines. Thus, the 8-(4′-thiazolyl) derivatives of purine (**2**), adenine (**4**), hypoxanthine (**6**), guanine (**12**), 6-mercapto- (**8**) and 6-methylmercaptopurine (**10**), and others were obtained. Chlorination of **10** led to the 6-methylsulfonyl compound **23**, which upon reaction with hydrazine gave 8-(4′-thiazolyl)-6-hydrazinopurine (**24**). Treatment of **24** with $FeCl_3$ in a Sandmeyer-type reaction resulted in the synthesis of 8-(4′-thiazolyl)-6-chloropurine (**25**). Interaction of **23** with ethanolic hydroxylamine afforded 8-(4′-thiazolyl)-$N^6$-hydroxyadenine. Several 8-(4′-thiazolyl)purines have been assayed against S180J mouse sarcoma; of these, 6-mercaptopurine (**8**) and thioguanine (**14**) were the only derivatives giving some tumor regression. In L1210 mouse leukemia, compound **26** exerted some growth inhibition. Screening of 8-(4′-thiazolyl)-6-mercaptopurine (**8**) against AKR mouse leukemia gave no increase in survival time. In in vitro antiviral screening (HSV-1), only compound **14** showed some inhibitory effect. Assays carried out with compounds **2**, **8**, **14**, and **25** to determine their possible immunopotentiating effect (lymphocyte proliferation technique) were negative.

Nonspecific immunostimulants such as *Corynebacterium parvum*[2] and *Bacillus Calmette-Guerin* or BCG[3,4] have been used in tumor therapy. Other immunotherapeutic approaches consist of the attachment (by loose or covalent binding) of antineoplastic drugs to a specific cancer antibody[5-9] with the aim of obtaining a directing and synergistic effect against tumor growth. Two thiazole derivatives, tetramisole and its 1-isomer levamisole[10-12] [(±)-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole monohydrochloride], are potent antihelmintic agents and also act as immunopotentiators by increasing the cellular and humoral immunity in animals.[13-17] Levamisole has been found active against mouse leukemia[18] and solid tumors,[19] although it failed to induce remission in other types of experimental tumors.[20,21] This drug has been found to increase the cellular immune response in cancer patients[22] and is used clinically.[23,24]

Other thiazole derivatives of current interest are thiabendazole[25] [(4′-thiazolyl)benzimidazole], a widely used antihelmintic,[26,27] which has an immunoenhancing effect[28] and *p*-chlorophenyl derivatives of levamisole which have been reported to exert antitumor and antimetastatic activity in animals.[29,30]

Thiazoles fused to certain purines, [3′,2′-*h*]thiazolinopurines, such as the xanthine[31] and theophylline[32] homologues, were synthesized by Todd and Ochiai, respectively, as potential purine antagonists. The 2,6-diamino and guanine homologues were later described by Gordon.[33,34] Other similar 2-methylhypoxanthine derivatives[35] include dihydrothiazolopurines reported by Montgomery[36] and others.[37]

We were interested in determining the effect of the 4′-thiazolyl group attached to the C-8 of purines and deazapurines on the biological properties of several purines. They were naturally occurring purines (adenine, hypoxanthine, and guanine) and purine analogues clinically or experimentally used as anticancer agents, such as 6-mercapto-[38] and 6-chloropurine,[39] $N^6$-hydroxyadenine,[40] and thioguanine.[41] These thiazolylpurine compounds can also be considered as analogues of thiabendazole.

**Synthetic Studies.** The synthesis of purines linked to heterocyclic compounds is carried out by ring closure of 4,5-diaminopyrimidines with the appropriate carboxy or cyano heterocyclic derivatives. This method is adapted from that originally described by Traube.[42-44] Condensation of 4-cyano-, 4-carboxamido-, or 4-thiocarboxamidothiazole with the appropriate pyrimidines in polyphosphoric acid at various temperatures and times yielded 8-(4′-thiazolyl)purines (Table I). A common feature to these compounds is their low solubility in water or in alkaline solutions and organic solvents, but most of them are freely soluble in dilute mineral acids.

The synthesis of 8-(4′-thiazolyl)-6-chloropurine (**25**), a key intermediate for the preparation of several amino derivatives by nucleophilic displacements, was attempted by the standard methods used in purine chemistry (phosphoryl chloride reaction with hydroxypurines or the chlorination of 6-mercaptopurines). Thus, 8-(4′-thiazolyl)hypoxanthine (**6**) after prolonged $POCl_3$ treatment gave the 6-chloropurine derivative **25** (Scheme I). The synthesis of **25** by condensation of 6-chloro-4,5-diaminopyrimidine and 4-acetamidothiazole was not feasible since the acidic conditions of the ring closure result in the hydrolysis of the chlorine atom to hydroxy, yielding 8-(4′-thiazolyl)hypoxanthine (**6**).

A procedure for the preparation of compound **25** was also found in the conversion previously described by us[45,46] of 6-hydrazinopurine[47] and ferric chloride, which in a Sandmeyer-type[48] reaction led to 6-chloropurine.[39] Thus, compound **25** was obtained by the sequence shown in Scheme I. 8-(4′-Thiazolyl)-6-methylmercaptopurine (**10**) upon chlorination gave 8-(4′-thiazolyl)-6-methylsulfonylpurine (**23**) in 70% yield. Similar treatment of the 2,6-dimethylmercapto derivative **20** in anhydrous or aqueous methanol led to the corresponding 2-methylsulfonyl-6-chloropurine (**27**) and 2,6-dimethysulfonylpurine (**28**) derivatives, respectively.[49] Compound **23** and ethanolic hydrazine at 80 °C afforded 8-(4′-thiazolyl)-6-hydrazinopurine (**24**), which upon reaction with ferric chloride gave 8-(4′-thiazolyl)-6-chloropurine (**25**). The latter was transformed with hydrazine back to the 6-hydrazinopurine derivative **24**. Attempts to obtain compound **25** from **8** with chlorine at low temperature[49-51] failed. Compound **25** was relatively resistant to the nucleophilic attack of 0.6 M ethanolic hydroxylamine, in contrast to the ease in which 6-chloropurine was smoothly converted into $N^6$-hydroxyadenine.[45] The electron-withdrawing effect of the thiazole group may result in a lack of reactivity of the chlorine atom at C-6. However, when compound **23** reacted with 0.6 M ethanolic hydroxylamine, 8-(4′-thiazolyl)-$N^6$-hydroxyadenine (**26**) was obtained. Refluxing of **28** with ethanolic hydrazine led to 8-(4′-thiazolyl)-2-methylsulfonyl-6-hydrazinopurine (**29**). The deazapurines, 8-(4′-thiazolyl)imidazopyridines **31** and **33**, were obtained by condensation of the corresponding diaminopyridines **30** and **32** with carboxamidothiazole.

## Experimental Section

**Synthesis.** Ultraviolet absorption spectra were determined with a Unicam recording spectrophotometer. Ascending paper

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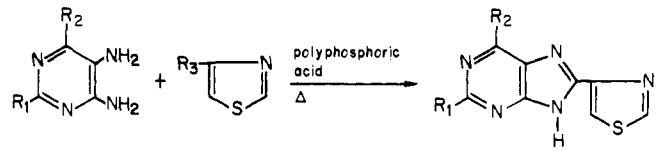
Table I. Synthesis of 8-(4'-Thiazolyl)purines




| $R_1$ | $R_2$ | $R_3$[a] | mmol used | Temp, °C | Rxn time, min | % yield[c] | Mp, °C | Formula[b] | Analyses |
|---|---|---|---|---|---|---|---|---|---|
| H | H (1) | C | 22 | 190 | 75 | 40 | 335 | $C_8H_5N_5S$ (2) | C, H, N, S |
| H | $NH_2$ (3) | C | 25 | 210 | 100 | 81 | 380 | $C_8H_6N_6S \cdot H_2O$ (4) | C, H, N, S |
| H | OH (5) | C | 5 | 180 | 45 | 16 | >350 | $C_8H_5N_5OS$ (6) | C, H, N, S |
| H | SH (7) | C | 20 | 210 | 45 | 72 | 286 | $C_8H_5N_5S_2$ (8) | C, H, N, S |
| H | $SCH_3$ (9) | A | 54 | 195 | 60 | 97 | 305 | $C_9H_7N_5S_2$ (10) | C, H, N, S |
| $NH_2$ | OH (11) | C | 14 | 190 | 120 | 13 | 335 | $C_8H_6N_6OS \cdot 1.5H_2O$ (12) | C, H, N, S |
| $NH_2$ | SH (13) | A | 32 | 190 | 60 | 28 | 312 | $C_8H_6N_6S_2$ (14) | C, H, N, S |
| $NH_2$ | $SCH_3$ (15) | A | 20 | 180 | 30 | 20 | 330 | $C_9H_8N_6S_2$ (16) | C, H, N, S |
| SH | SH (17) | A | 15 | 200 | 180 | 29 | 390 | $C_8H_4N_4OS_2$ (18)[d] | C, H, N, S |
| $SCH_3$ | $SCH_3$ (19) | C | 3 | 180 | 90 | 71 | 317 | $C_{10}H_9N_5S_3$ (20) | C, H, N, S |
| $NH_2$ | $CH_3$ (21) | C | 10 | 180 | 35 | 33 | 350 | $C_9H_8N_6S$ (22) | C, H, N, S |

[a] $R_3$ = A, amide; C, cyano. [b] Analyses were correct within 0.15%. [c] Yield of recrystallized product, except for 10 which was sufficiently pure for use in further reactions (recrystallized from 70% EtOH-$H_2O$). [d] 8-(4'-Thiazolyl)-2-mercaptohypoxanthine was obtained instead of the expected 2,6-dimercaptopurine derivative.

chromatography was run on Whatman No. 1 paper on the following solvent systems: concentrated aqueous ammonia–water–isopropyl alcohol (10:20:70); 1-butanol–water–acetic acid (50:25:25); and 1 M ammonium acetate–ethanol (30:70). The determination of melting points was carried out with a Mel-Temp and a Thomas-Hoover melting point apparatus, and the temperatures were corrected. Analytical samples were obtained by repeated crystallization with EtOH or MeOH. Analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Mich.

8-(4'-Thiazolyl)purines and deazapurines can be prepared by reaction of 4,5-diaminopyrimidines or pyridines, respectively, with 4-cyanothiazole,[52,53] 4-carboxamidothiazole, thioacetamidothiazole, or 4-ethylcarboxythiazole suspended in ten parts of polyphosphoric acid,[25,54] but best results were obtained with the carboxamido and the cyano derivatives (Table I). The mixture was heated with stirring at temperatures ranging from 180 to 210 °C, for variable amounts of time (30 min to 3 h), then cooled to about 120 °C, poured into crushed ice, and stirred, and 5 N NaOH was added (at a temperature not exceeding 10 °C) to bring the pH to 5. After cooling for 1 h, the resulting precipitate was collected by filtration, thoroughly washed with $H_2O$, and recrystallized from 90% EtOH. The UV spectra of some 8-(4'-thiazolyl)purines (Table II) show a shift in absorption patterns as compared with those of the corresponding purines.

**8-(4'-Thiazolyl)-6-methylsulfonylpurine (23).** 8-(4'-Thiazolyl)-6-methylmercaptopurine (**10**, 3.32 g, 14 mmol) was suspended in 70% aqueous MeOH (200 mL). Chlorine was bubbled at 5–10 °C for 30 min. The resulting precipitate was filtered and suspended in cold $H_2O$, and the pH was adjusted to 7 with NaAc. After washing with cold $H_2O$, the product was dried: colorless thin needles; mp 305 °C; yield 3.06 g (81%). Anal. ($C_9H_7N_5S_2O_2$) C, H, N, S.

**8-(4'-Thiazolyl)-6-hydrazinopurine (24).** A suspension of **23** (4 g, 14 mmol) in 30% ethanolic hydrazine (40 mL) was refluxed for 2 h. The resulting product after washing with EtOH was dried: colorless thin hairy needles; mp 273 °C dec; yield 3.1 g (95%). Anal. ($C_8H_7N_7S$) C, H, N, S.

**8-(4'-Thiazolyl)-6-chloropurine (25). Method A.** A suspension of **24** (3.1 g, 13.5 mmol) was added slowly with stirring to a 30% $FeCl_3$ aqueous solution (80 mL) at 25 °C. After the effervescence subsided, the green-colored mixture was stirred at 25 °C for 18 h. The precipitate was washed with cold $H_2O$ until the filtrate gave a negative Fe test (KSCN). The brown crystalline product upon recrystallization from 90% aqueous EtOH yielded pale yellow needles (0.90 g, 29%), mp 277 °C dec. Anal. ($C_8H_4N_5SCl$) C, H, N, S, Cl.

A sample (5 mg) of this compound when refluxed for 1 h with 30% ethanolic hydrazine (0.5 mL) gave a solution with UV spectrum identical with that of **24**.

Table II. Ultraviolet Spectral Data of Some 8-(4'-Thiazolyl)purines

| Compd | pH | λ max, nm (ε × $10^{-3}$) |
|---|---|---|
| 8-(4'-Thiazolyl)-purine (2) | 4.8 | 296 (29.1) |
| | 6.9 | 296 (28.5) |
| | 12.6 | 312 (21.5) |
| 8-(4'-Thiazolyl)-adenine (4) | 1.2 | 206 (25.0) |
| | 6.9 | 295 (20.7), 232 (19.3) |
| | 10.7 | 300 (21.7), 233 (21.7) |
| 8-(4'-Thiazolyl)-6-mercaptopurine (8) | 4.5 | 318 (14.0), 292 (9.93), 252 (17.9), 245 (16.5) |
| | 1.0 | 317 (16.7), 303 (16.7) |
| | 3.0 | 317 (16.4), 293 (13.1), 245 (16.5) |
| 8-(4'-Thiazolyl)-thioguanine (14) | 0.9 | 314 (25.4), 222 (21.8) |
| | 2.8 | 314 (24.5), 233 (16.4) |
| | 13.8 | 329 (21.4), 222 (18.6) |
| 8-(4'-Thiazolyl)-6-sulfonylpurine (23) | 0.9 | 314 (17.8) |
| | 4.8 | 314 (17.2) |
| | 13 | 326 (15.2) |
| 8-(4'-Thiazolyl)-6-chloropurine (25) | 2.2 | 298 (22.0) |
| | 6.4 | 299 (21.0) |
| | 12.8 | 302 (20.0) |
| 8-(4'-Thiazolyl)-$N^6$-hydroxyadenine (26)[a] | 2.8 | 303 (19.5), 237 (10.5) |
| | 6.9 | 300 (12.8), 234 (14.6) |

[a] Instability in alkali did not allow determination of ε.

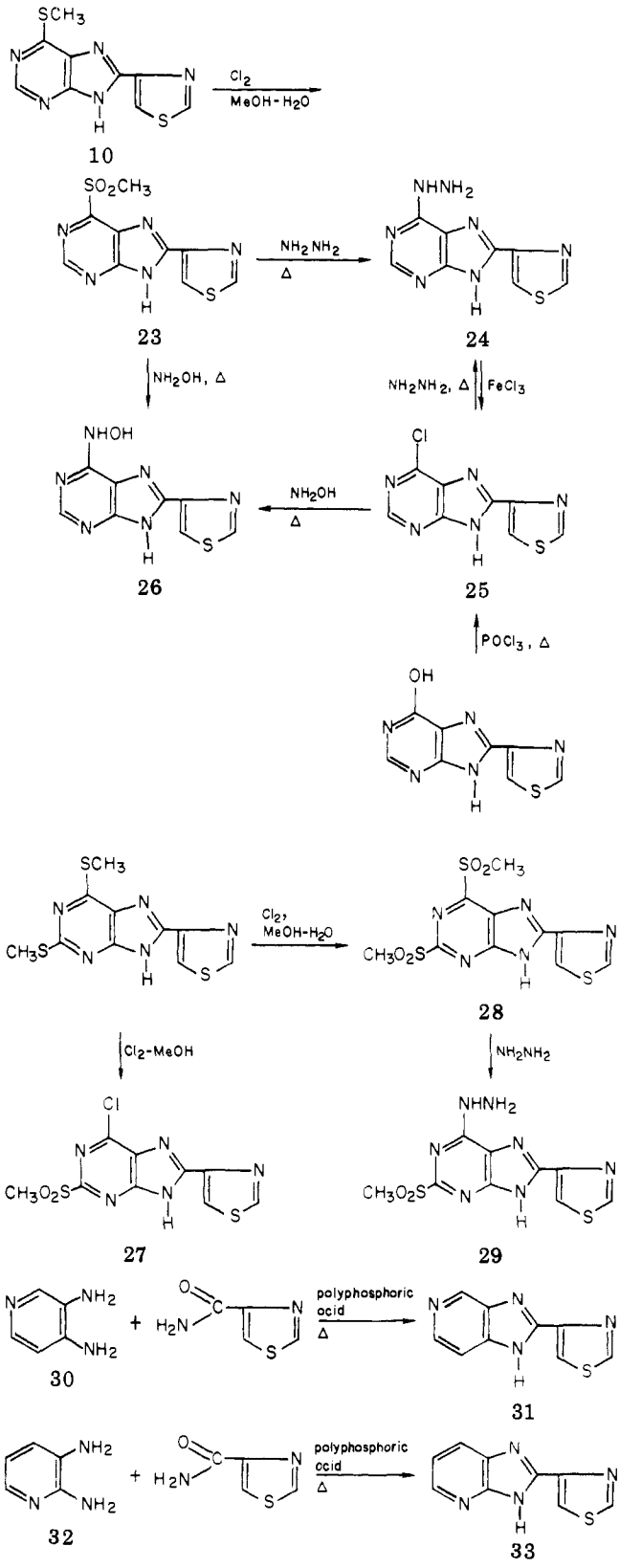
**Method B.** A suspension of 8-(4'-thiazolyl)hypoxanthine (**6**, 1.5 g, 7.9 mmol) in $POCl_3$ (17.5 mL) and *N*,*N*'-dimethylaniline (1.0 mL) was refluxed for 18 h. After standing at 22 °C overnight, the resulting mixture was filtered; the precipitate was suspended in ice and neutralized with anhydrous sodium acetate. The precipitate was thoroughly washed with cold water and dried to yield 1.3 g (80%) of product which was identical with **25**.

**8-(4'-Thiazolyl)-$N^6$-hydroxyadenine (26).** A suspension of **23** (200 mg, 0.7 mmol) in 0.6 M ethanolic hydroxylamine (200 mL) was kept at 25 °C for 3 days. The reaction mixture was evaporated in vacuo to ca. 20 mL and cooled, and the resulting precipitate was washed thoroughly with $H_2O$ and EtOH: short, colorless needles; mp >300 °C; 0.12 g (72%). A solution of this compound gave, with a solution of $FeCl_3$, a deep blue color (–NHOH function) and, with 2 N NaOH, a red color and precipitate (azoxy formation). Anal. ($C_8H_6N_6OS \cdot 0.75H_2O$) C, H, N, S.

Treatment of **25** with 0.6 M ethanolic $NH_2OH$ at 70 °C for 5 h afforded a lower yield of crude **26**.

**8-(4'-Thiazolyl)-6-chloro-2-methylsulfonylpurine (27).** A suspension of **20** (8.3 g, 28 mmol) in anhydrous MeOH (100 mL) was cooled to 5 °C. Chlorine was bubbled through the solution

Scheme I



for 60 min at below 5 °C. After bubbling air in for 15 min, the resulting precipitate was filtered, suspended in cold $H_2O$, and neutralized to pH 7 with NaAc. It was washed with $H_2O$ at 5 °C and recrystallized from 70% aqueous EtOH, giving colorless needles: mp 270 °C; yield 2.0 g (26%). Anal. ($C_9H_8N_5S_2ClO_2$) C, H, N, S, Cl.

**8-(4′-Thiazolyl)-2,6-dimethylsulfonylpurine (28).** The method is essentially the same as for **23**. 8-(4′-Thiazolyl)-2,6-dimethylmercaptopurine (**20**, 6 g, 20 mmol) in 70% aqueous MeOH gave 3.1 g (42%) of a pale yellow crystalline product, mp 280 °C. Anal. ($C_{10}H_9N_5S_3O_4$) C, H, N, S.

**8-(4′-Thiazolyl)-2-methylsulfonyl-6-hydrazinopurine (29).** A suspension of **28** (1.7 g, 4.7 mmol) in 25% ethanolic hydrazine was refluxed for 2 h. The resulting precipitate was collected by filtration and washed with $H_2O$ and EtOH to yield light brown needles: yield 0.63 g (43%); mp 291 °C dec. Anal. ($C_9H_9N_7O_2S_2$) C, H, N, S.

**8-(4′-Thiazolyl)-1-imidazo[4′,5′-*c*]pyridine (31)** was prepared by the general procedure described above for purines, by heating 3,4-diaminopyridine (**30**, 1 g, 9.2 mmol) and 4-carboxamidothiazole (1.4 g, 11 mmol) in polyphosphoric acid (20 g) at 180 °C for 1 h: yield 1.6 g (89%); colorless needles; mp 272 °C dec. Anal. ($C_9H_6N_4S$) C, H, N, S.

**8-(4′-Thiazolyl)-3*H*-imidazo[4′,5′-*b*]pyridine (33)** was prepared as indicated for compound **31** by condensation of 2,3-diaminopyridine (**32**) (0.3 g, 3 mmol) and 4-carboxamidothiazole (0.46 g, 3.6 mmol) in polyphosphoric acid (8.0 g). This mixture was heated at 180 °C for 80 min. After working as indicated above for purines, a yield of 0.15 g (56%) of colorless cubes, mp 298 °C dec, was obtained. Anal. ($C_9H_6N_4S$) C, H, N, S.

**Biological Studies. Antitumor Screening Data.** In S180J mouse sarcoma several of the new 8-(4′-thiazolyl)purines have been assayed. Treatment was made at different dosages and started the day after the inoculation of tumor cells ($7.5 \times 10^5$ cells). The agent was administered intraperitoneally to groups of six CD-1 female mice six times in consecutive days (CMC suspension in saline). The results are summarized on Table III. 8-(4′-Thiazolyl)-6-mercaptopurine (**8**) and 8-(4′-thiazolyl)thioguanine (**14**) were the only compounds with an inhibitory effect in this type of tumor. Less active or ineffective were the purine (**2**) and adenine (**4**) analogues.

Table III. Effect of Some 8-(4′-Thiazolyl)purines on S180 Tumor Growth

| Compd | Dose, mg/kg | Tumor regression[a] |
|---|---|---|
| 8-(4′-Thiazolyl)-purine (2) | 100 | 1/6 |
| | 30 | 2/6 |
| | 10 | 1/6 |
| | 0 | 1/6 |
| 8-(4′-Thiazolyl)-adenine (4) | 30 | 0/6 |
| | 10 | 1/6 |
| | 3 | 1/6 |
| 8-(4′-Thiazolyl)-thioguanine (14) | 100 | 0/6 |
| | 30 | 0/6 |
| | 10 | 2/6 |
| 8-(4′-Thiazolyl)-6-mercaptopurine (8) | 256 | 1/6 |
| | 64 | 3/6 |
| | 32 | 0/6 |
| | 16 | 0/6 |
| | 4 | 0/6 |
| | 1 | 0/6 |
| | 0 | 0/6 |

[a] Determined 42 days after start of treatment.

The 8-(4′-thiazolyl) derivatives of purine (**2**), adenine (**4**), 6-mercaptopurine (**8**), 6-methylmercaptopurine (**10**), thioguanine (**14**), 6-chloropurine (**25**), and $N^6$-hydroxyadenine (**26**) were evaluated on L1210 and P815 mouse leukemia at dosages ranging from 1 to 125 mg/kg qd × 5 by methods previously described.[55] Only compound **26** gave an increase in survival time (129%, T/C) in L1210 mouse leukemia at 125 mg/kg (qd × 6). The compounds were tolerated by mice at dosages up to 500 mg/kg (qd × 5).

8-(4′-Thiazolyl)-6-mercaptopurine (**8**) was tested against AKR mouse leukemia at dosages of 0.2, 2.0, and 20 mg/kg. The routes of administration were intraperitoneal, oral, and subcutaneous; no increase in survival time was observed. The techniques used in this assay have been reported.[56]

**Antiviral Screening Data.** In vitro assays of some of the 8-(4′-thiazolyl)purines were carried out by Dr. Carlos Lopez in our Institute. These in vitro assays consist of the addition of a suspension or solution of the compound to Herpes simplex virus type 1 (HSV-1) infected Vero cell monolayers at different concentrations.[57] In this manner the capacity of the compound to inhibit HSV-1 replication as compared with that of controls can

Table IV. Effect of Some 8-(4'-Thiazolyl)purines on the Growth of Herpesvirus HSV-1

| Compd | Dose, μg/mL | PFU,[a] mL |
|---|---|---|
| 8-(4'-Thiazolyl)adenine (4) | 100 | $9.2 \times 10^5$ |
| | 10 | $8.5 \times 10^5$ |
| | 1 | $3.2 \times 10^5$ |
| | 0[b] | $2.7 \times 10^5$ |
| 8-(4'-Thiazolyl)-6-chloropurine (25) | 100 | $2.2 \times 10^6$ |
| | 10 | $2.5 \times 10^6$ |
| | 1 | $4.0 \times 10^6$ |
| | 0[b] | $1.2 \times 10^6$ |
| 8-(4'-Thiazolyl)thioguanine (14) | 100 | $8.2 \times 10^5$ |
| | 10 | $5.3 \times 10^6$ |
| | 1 | $3.5 \times 10^6$ |
| | 0[b] | $1.2 \times 10^6$ |

[a] Plaque-forming units. [b] Control.

be determined. The results of the tested compounds, as indicated in Table IV were negative, with the exception of 8-(4'-thiazolyl)thioguanine (14), which gave a small growth inhibition at 100 μg/mL.

**Immunopotentiation Assays.** In order to determine the possible immunopotentiator ability of some of the thiazolyl purines, assays were made by Dr. J. W. Hadden and co-workers in our Institute using their recently published technique.[58] This assay is based on the ability of a given compound to increase lymphocyte proliferation both in the presence and in the absence of a suboptimal concentration of the lectin mitogen phytohemoagglutinin (PHA). 8-(4'-Thiazolyl) derivatives of purine (2), adenine (4), hypoxanthine (6), 6-mercaptopurine (8), thioguanine (14), and 6-chloropurine (25) were tested at concentrations of 1, 10, and 100 μg/mL. No significant increase was observed in the incorporation of the tritiated thymidine in the presence or in the absence of the mitogen. At 100 μg/mL a suppression of the mitogenic response was observed with these compounds.

Most of these 8-(4'-thiazolyl)purines have been tested for their potential antimalarial (by the Department of Medicinal Chemistry, Walter Reed Army Institute of Research, Washington, D.C.,) and antihelmintic activity (Dr. H. Mrozik, Merck, Sharp & Dohme Research Laboratory, Rahway, N.J.), and the results will be published elsewhere.

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## References and Notes

(1) Presented in part at the 173rd National Meeting of the American Chemical Society, New Orleans, La., March 1977, Abstracts, MEDI 67.
(2) M. T. Scott, *J. Natl. Cancer Inst.*, **55**, 65 (1975).
(3) L. J. Old, D. A. Clarke, and B. Benacerraf, *Nature (London)*, **184**, 291 (1959).
(4) G. Mathé, *Br. Med. J.*, **4**, 487 (1970).
(5) T. Ghose, M. Cerini, M. Carter, and R. C. Nairn, *Br. Med. J.*, 1, 90 (1967).
(6) T. Ghose, S. T. Norvell, A. Guclu, D. Cameron, A. Bodurtha, and A. S. MacDonald, *Br. Med. J.*, **3**, 495 (1972).
(7) T. Ghose, S. T. Norvell, A. Guclu, A. Bodurtha, J. Tai, and A. S. MacDonald, *J. Natl. Cancer Inst.*, **58**, 845 (1977).
(8) J. Vidal-Gomez, J. H. Greenbaum, and A. Giner-Sorolla, *J. Heterocycl. Chem.*, **12**, 273 (1975).
(9) J. Vidal-Gomez and A. Giner-Sorolla, *Cienc. Ind. Farm.*, **6**, 335 (1974).
(10) A. H. M. Raeymaekers, F. T. N. Allewijn, J. Vandenberk, P. J. A. Demoen, T. T. T. V. Ottenwert, and P. A. J. Janssen, *J. Med. Chem.*, **9**, 545 (1966).
(11) D. C. I. Thienpont, O. F. J. Vanparijs, A. H. M. Raeymaekers, J. Vandenberk, P. J. A. Demoen, F. T. N. Allewijn, R. P. H. Marsboom, C. J. E. Niemegueers, K. H. L. Schellekens, and P. A. J. Janssen, *Nature (London)*, **209**, 1084 (1966).
(12) M. W. Bullock, J. J. Hand, and E. Waletsky, *J. Med. Chem.*, 11, 169 (1968).
(13) J. L. Lichtenfeld, M. H. Desner, P. H. Wiernik, and M. R. Mardiney, Jr., *Cancer Chemother. Rep.*, **60**, 571 (1976).
(14) H. Verhaegen, J. DeCrêe, W. DeCock, and F. Verbruggen, *N. Engl. J. Med.*, **289**, 1148 (1973).
(15) G. Renoux and M. Renoux, *C. R. Hebd. Seances Acad. Sci.*, **278**, 1139 (1974).
(16) J. W. Hadden, R. G. Coffey, E. M. Hadden, E. Lopez-Corrales, and G. H. Sunshine, *Cell. Immunol.*, **20**, 98 (1975).
(17) G. Renoux and M. Renoux, *Immunity*, **8**, 544 (1972).
(18) M. A. Chirigos, J. W. Pearson, and J. Pryor, *Cancer Res.*, **33**, 2615 (1973).
(19) G. Renoux and M. Renoux, *Nature (London), New Biol.*, **240**, 217 (1974).
(20) R. K. Johnson, D. P. Houchens, M. R. Gaston, and A. Goldin, *Cancer Chemother. Rep.*, **59**, 697 (1975).
(21) I. J. Fidler and L. E. Spitler, *J. Natl. Cancer Inst.*, **55**, 1107 (1975).
(22) D. Tripodi, L. C. Parks, and J. Brugmans, *N. Engl. J. Med.*, **289**, 354 (1973).
(23) Study group for bronchongenic carcinoma, *Br. Med. J.*, **3**, 461 (1975).
(24) A. F. Rojas, J. N. Feierstein, E. Mickiewicz, H. Glait, and A. J. Olivari, *Lancet*, 1, 211 (1976).
(25) H. D. Brown, A. R. Matzuk, I. R. Ilves, L. H. Peterson, S. A. Harris, L. H. Sarett, J. R. Egerton, J. J. Yakstis, W. C. Campbell, and A. C. Cuckler, *J. Am. Chem. Soc.*, **83**, 1765 (1961).
(26) J. R. Douglas and N. F. Baker, *Annu. Rev. Pharmacol.*, **8**, 213 (1968).
(27) J. Polonsky, *Fortschr. Chem. Org. Naturst.*, **30**, 101 (1973).
(28) G. Renoux, personal communication.
(29) S. C. Bell and P. H. L. Wei, *J. Med. Chem.*, **19**, 524 (1976).
(30) R. L. Fenichel, F. J. Gregory, and H. E. Alburn, *Br. J. Cancer*, **33**, 329 (1976).
(31) A. R. Todd and F. Bergel, *J. Chem. Soc.*, 1559 (1936).
(32) E. Ochiai, *Ber.*, **69B**, 1650 (1936).
(33) M. Gordon, *J. Am. Chem. Soc.*, **73**, 984 (1951).
(34) M. Gordon, J. B. Siri, and J. G. Campbell, *Science*, **113**, 61 (1951).
(35) R. C. Elderfield and R. N. Prasad, *J. Org. Chem.*, **24**, 1410 (1959).
(36) R. W. Balsiger, A. L. Fikes, T. P. Johnston, and J. A. Montgomery, *J. Org. Chem.*, **26**, 3446 (1961).
(37) R. Marumoto, Y. Yoshioka, and M. Honjo, *Chem. Pharm. Bull.*, **22**, 342 (1974).
(38) G. B. Elion, E. Burgi, and G. H. Hitchings, *J. Am. Chem. Soc.*, **74**, 411 (1952).
(39) A. Bendich, P. J. Russell, Jr., and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954).
(40) A. Giner-Sorolla, J. H. Burchenal, and A. Bendich in "The Purines, Theory and Experiment", E. D. Bergmann and B. Pullman, Ed., The Israel Academy of Sciences, Jerusalem, 1972, p 478.
(41) G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **77**, 1676 (1955).
(42) W. Traube, *Ber.*, **33**, 1371, 3035 (1900).

(43) A. Bendich in "The Nucleic Acids", E. Chargaff and J. N. Davidson, Ed., Academic Press, New York, N.Y., 1955, p 81.
(44) L. H. Lister in "The Purines", Wiley, New York, N.Y., 1971, p 38.
(45) A. Giner-Sorolla and A. Bendich, *J. Am. Chem. Soc.*, **81**, 2515 (1959).
(46) A. Giner-Sorolla and J. T. Segarra in "Improved Procedures in Nucleic Acid Chemistry", L. Townsend, Ed., Wiley-Interscience, New York, N.Y., 1977, in press.
(47) J. A. Montgomery and L. B. Holum, *J. Am. Chem. Soc.*, **79**, 2185 (1957).
(48) Cf. H. Priewe and A. Poljack, *Chem. Ber.*, **88**, 1932 (1955).
(49) Cf. C. W. Noell and R. K. Robins, *J. Am. Chem. Soc.*, **81**, 5997 (1959).
(50) Wellcome Foundation Ltd., British Patent 767 216 (1957); *Chem. Abstr.*, **51**, 14796 (1957).
(51) A. G. Beaman and R. K. Robins, *J. Appl. Chem.*, **12**, 432 (1962).
(52) G. D. Hartman, M. Sletzinger, and L. M. Weinstock, *J. Heterocycl. Chem.*, **12**, 1081 (1975).
(53) Kindly supplied by Merck, Sharp & Dohme, Inc., Rahway, N.J.
(54) Supplied by courtesy of Stauffer Co., Westport, Conn.
(55) J. H. Burchenal, J. R. Burchenal, M. N. Kushida, S. F. Johnston, and B. S. Williams, *Cancer*, **2**, 113 (1949).
(56) R. L. Kassel, L. J. Old, E. A. Carswell, N. C. Fiore, and W. D. Hardy, Jr., *J. Exp. Med.*, **138**, 925 (1973).
(57) C. Lopez and A. Giner-Sorolla, *Ann. N.Y. Acad. Sci.*, **284**, 351 (1977).
(58) J. W. Hadden, E. Hadden, J. R. Sadlik, and R. G. Coffey, *Proc. Natl. Acad. Sci. U.S.A.*, **73**, 1717 (1976).

# 5-Chloro-2-phenyl-1-benzo[*b*]thiophene-3-alkanamines, Potential Antipsychotic Agents

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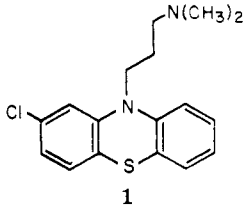
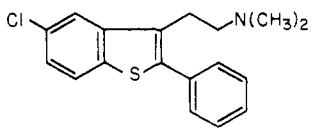
The title compounds (most notably **2a**) were synthesized on the basis of the N-methylation hypothesis of schizophrenia. They were evaluated in dopamine and haloperidol receptor assays. The binding characteristics were comparable in some cases to known neuroleptics.

The N-methylation hypothesis of psychosis is based on the premise that endogenous neurotransmitters are methylated by an *N*-methyltransferase to yield aberrant chemicals which are causative in abnormal behavior.[1] Isolation of the aforementioned enzyme[2] and demonstration of the hallucinogenic properties of *N,N*-dimethyltryptamine[3] have lent credence to these assertions.

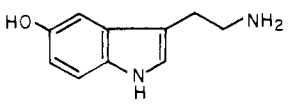
Smythies has reported[4] that chlorpromazine is an effective inhibitor of the transmethylation of tryptamine and implied that this property is related to the effectiveness of chlorpromazine as an antipsychotic agent. Consequently, the title benzothiophenes (most notably **2a**) were synthesized on the basis of their obvious structural similarity to both chlorpromazine (**1**) and serotonin (**3**), a tryptamine derivative which serves as a neurotransmitter. The expectation was that a molecule closer in structure to the natural substrate could be a more effective inhibitor of the methyltransferase and thus exhibit neuroleptic properties. The logic of this rationale was bolstered by Kier's study of the conformational similarities of **1** and **3** and the possible correlation of this conformation with biological activity of the former.[5]



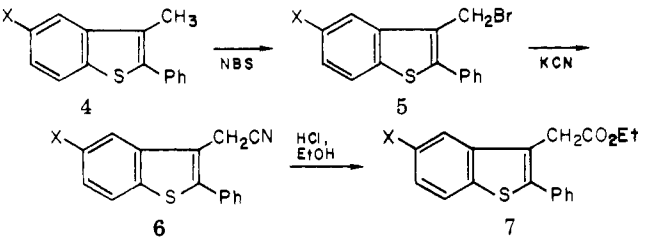

1




2a




Scheme I




4 5 6 7

a, X = Cl
b, X = H
c, X = F

More recently, Snyder[6] has pointed out that chlorpromazine can attain a conformation that mimics the extended form of dopamine (3,4-dihydroxyphenethylamine) in the distance relationship between a phenyl ring and terminal amine. This was the basis for the contention that chlorpromazine acts as a dopamine antagonist. It seems entirely likely that **2a** might also assume a conformation common to these molecules and function in a similar manner.

The initial goal was to obtain **2a**. Subsequently, the desired variations were to assess (a) the effect of different amine functions; (b) whether slight changes to the aromatic substituent would alter biological activity; and (c) the alteration of chain lengths of **2** to one fewer and one more methylene.

**Chemistry.** Our synthetic efforts centered around a series of steps which have been used to synthesize ester **7a**[7] (Scheme I) and from which target structure **2a** and amine analogues **9–13** were accessible. Reduction of **7a** with lithium aluminum hydride ($LiAlH_4$), followed by derivatization with *p*-toluenesulfonyl chloride as shown in Scheme II, yielded the requisite tosylate **8** for amine nucleophilic displacements.

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