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SYNTHESIS OF CONDENSED HETEROCYCLES CONTAINING A PYRIMIDO[5,4-*e*][1,3]-THIAZINE FRAGMENT

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The cyclocondensation of 4,6-dichloro-2-methylthiopyridine-5-carbaldehyde and heterocyclic thiones such as 1,2,4-triazole-5-thione, imidazolidine-2-thione, imidazole-2-thione, and 4,5-diphenylimidazole-2-thione in dimethylformamide gave tricyclic heterocycles containing a pyrimido[5,4-e][1,3]thiazine fragment. The reaction of 6-chloro-8-methylthio-5H-pyrimido[5,4-e][1,2,4]triazolo[5,1-b][1,3]thiazin-5-ol with diethylamine, pyrrolidine, and morpholine gave the corresponding 6-dialkylamino-pyrimidotriazolothiazines.

Keywords: azole-2-thiones, 4,6-dichloropyrimidine-5-carbaldehyde, tricyclic pyrimido[5,4-*e*][1,3]-thiazines, cyclocondensation, antitumor activity.

DNA intercalators form one of the best known class of compounds with antitumor activity. These drugs usually contain an aromatic or heteroaromatic polycyclic system with one or two cationic substituents [1]. Linearly fused polycyclic heterosystems containing a pyrimido[5,4-*e*][1,3]thiazine fragment hold interest in this regard. However, the synthesis of such compounds has not been studied sufficiently. We are aware of only two studies featuring the synthesis of pyrimido[5,4-*e*][1,3]thiazinones by the cyclocondensation of ethyl esters of 4-chloropyrimidine-5-carboxylic acids with imidazole-2-thiones and benzimidazole-2-thiones [2] or with N-substituted thioureas [3]. In recent work [4], we have shown that the reaction of 4,6-dichloro-2-methylthiopyrimidine-5-carbaldehyde (**1**) with benzimidazole-2-thione involves cyclocondensation leading to the benzimidazo[2,1-*b*]pyrimido[5,4-*e*][1,3]thiazine heterocyclic system. In order to expand the scope of this reaction for the synthesis of pyrimidines fused with heterocycles and search for new antitumor compounds, we studied the reaction of carbaldehyde **1** with other thiones. We selected 1,2,4-triazole-5-thione (**2**), imidazolidine-2-thione (**3**), imidazole-2-thione (**4a**), and 4,5-diphenylimidazole-2-thione (**4b**).

The cyclocondensation of aldehyde **1** and heterocyclic thiones proceeds upon heating equimolar amounts of these compounds in dimethylformamide solution at 50-70°C. Product **6** was isolated as a water-soluble hydrochloride salt. The structures of the products were supported by ^{1}H NMR and IR spectroscopy and elemental analysis. The ^{1}H NMR spectra of compounds **5-7** have a characteristic singlet at 2.28-2.6 ppm for the SCH_3 group protons. The 5-H proton in the heterocyclic systems gives a signal at 6.22-7.2 ppm. The IR spectra of all these compounds feature a broad OH group band at 3048-3421 cm^{-1} and lack a carbonyl group band, which is characteristic for starting carbaldehyde **1**.

The reaction of compound **5** with several secondary amines was carried out to obtain 6-aminopyrimido[5,4-*e*][1,2,4]triazolo[5,1-*b*][1,3]thiazinols. 6-Dialkylamino derivatives **8a-c** were obtained in 77-88% yield upon heating the reaction mixture at 40°C for 4 h.

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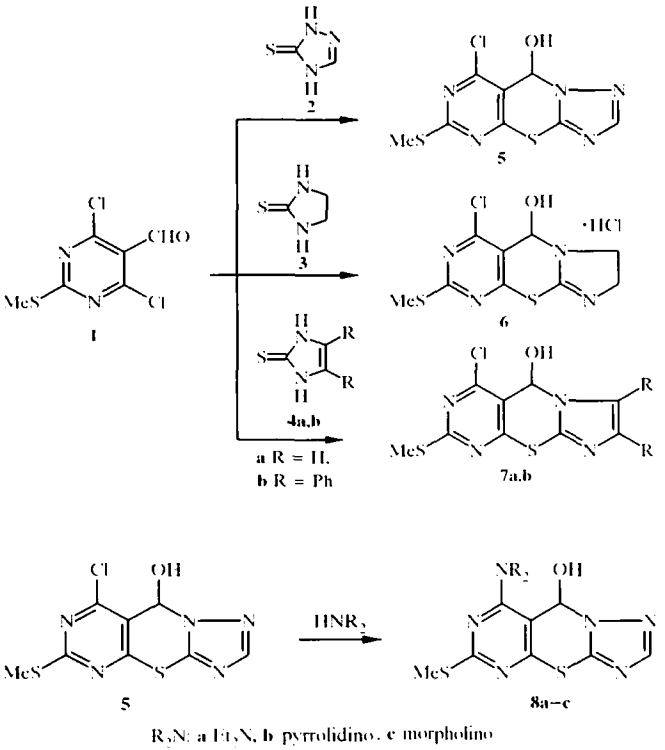

Products **5** and **8a** were screened *in vitro* for antitumor activity at the United States National Cancer Institute on 60 types of malignant neoplastic cells. Product **5** has a broad range of antitumor activity with $\log GI_{50} = -5.14$. Furthermore, compound **5** selectively inhibits the growth of HL-60(TB) leukemia cells ($GI_{50} = 0.05$ μM) and SF-539 CNS cancer cells ($GI_{50} = 0.319$ μM). Diethylamino derivative **8a** has only weak antitumor activity. According to preliminary data, at 100 μM concentration, this compound inhibits the growth of NCI-H460, MCF7, and SF-268 cells by 48, 64, and 54%, respectively.

EXPERIMENTAL

The IR spectra were taken on a Perkin-Elmer FT Spectrum BX II spectrometer for KBr pellets. The ^{1}H NMR spectra were obtained on a Tesla BS-567A spectrometer at 80 MHz using TMS as the internal standard. The reaction course and purity of the products were determined by thin-layer chromatography on Silufol UV-254 plates.

1,2,4-Triazole-5-thione (**2**) was obtained according to a standard procedure [5], imidazolidine-2-thione (**3**) – according to [6], imidazole-2-thione (**4a**) – according to [7], 4,5-diphenylimidazole-2-thione (**4b**) – according to [8], and 4,6-dichloro-2-methylthiopyridine-5-carbaldehyde – according to [9].

6-Chloro-8-methylthio-5H-pyrimido[5,4-*e*][1,2,4]triazolo[5,1-*b*][1,3]thiazin-5-ol (5). A mixture of compound **1** (0.5 g, 2.34 mmol) and triazole-5-thione **2** (0.236 g, 2.34 mmol) in DMF (10 ml) was heated for 3 h at 50°C. The reaction mixture was poured into water. The precipitate was filtered off, washed with water, and recrystallized to give 0.56 g (88%) of compound **5**; mp 223-225°C (2-propanol). IR spectrum: 3048 cm^{-1} (OH). ^{1}H NMR spectrum (DMSO-d_6): 2.28 (3H, s, SCH_3); 7.12 (1H, s, 5-CH); 8.39 ppm (1H, s, 2-CH). Found, %: C 33.03; H 2.49; N 24.44. $C_8H_6ClN_5OS_2$. Calculated, %: C 33.39; H 2.10; N 24.34.

Hydrochloride Salt of 4-Chloro-2-methylthio-7,8-dihydro-5H-imidazo[2,1-*b*]pyrimido[5,4-*e*][1,3]-thiazin-5-ol (6). A mixture of compound **1** (0.25 g, 1.12 mmol), imidazolidine-2-thione **3a** (0.144 g, 1.12 mmol), and DMF (5 ml) was heated at 70°C for 8 h. After cooling, the precipitate was filtered off, washed with

2-propanol, and recrystallized to give 0.157 g (43%) of compound **6**; mp 295°C (dec.) (ethanol). IR spectrum: 3397 cm^{-1} (OH). ^1H NMR spectrum (DMSO-d_6): 2.59 (3H, s, SCH_3); 3.85-4.27 (4H, m, CH_2); 6.22 ppm (1H, s, 5-CH). Found, %: C 33.63; H 3.08; N 17.34. $C_9H_{10}Cl_2N_4OS_2$. Calculated, %: C 33.24; H 3.1; N 17.23.

4-Chloro-2-methylthio-5H-imidazolo[2,1-*b*]pyrimido[5,4-*e*][1,3]thiazin-5-ol (7a) was obtained in 33% yield analogously to **5**. The reaction time was 2 h; mp 178-180°C (DMSO–methanol). IR spectrum: 3396 cm^{-1} (OH). ^1H NMR spectrum (DMSO-d_6) 2.56 (3H, s, SCH_3); 6.98 (1H, s, 5-CH); 7.20 (1H, s, 8-CH); 7.70 ppm (1H, s, 7-CH). Found, %: C 37.45; H 2.65; N 19.5. $C_9H_7ClN_4OS_2$. Calculated, %: C 37.7; H 2.46; N 19.54.

4-Chloro-2-methylthio-7,8-diphenyl-5H-imidazo[2,1-*b*]pyrimido[5,4-*e*][1,3]thiazin-5-ol (7b) was obtained in 75% yield analogously to **5**. The reaction time was 2 h; mp 228-230°C (DMF–ethanol). IR spectrum: 3330 cm^{-1} (OH). ^1H NMR spectrum (DMSO-d_6): 2.60 (3H, s, SCH_3); 6.48 (1H, s, 5-CH); 7.09-7.19 (3H, m, arom. protons); 7.32-7.42 (3H, m, OH, arom. protons); 7.50-7.57 ppm (5H, m, arom. protons). Found, %: C 57.77; H 3.44; N 12.9. $C_{21}H_{15}ClN_4OS_2$. Calculated, %: C 57.46; H 3.44; N 12.76.

6-Dialkylamino-8-methylthio-5H-pyrimido[5,4-*e*][1,2,4]triazolo[5,1-*b*][1,3]thiazin-5-ol (8a-c). General Method. A mixture of compound **5** (0.2 g, 0.69 mmol), ethanol (5 ml), and corresponding dialkylamine (3.4 mmol) was heated for 4 h at 40°C and poured into water. The precipitate was filtered off and recrystallized.

6-Diethylamino-8-methylthio-5H-pyrimido[5,4-*e*][1,2,4]triazolo[5,1-*b*][1,3]thiazin-5-ol (8a) was obtained in 88% yield; mp 172-174°C (2-propanol). IR spectrum: 3379 cm^{-1} (OH). ^1H NMR spectrum (DMSO-d_6): 1.30 (6H, t, CH_3); 2.51 (3H, s, SCH_3); 3.70 (4H, q, NCH_2); 6.90 (1H, s, 5-CH); 8.28 ppm (1H, s, 2-CH). Found, %: C 44.28; H 4.91; N 25.81. $C_{12}H_{16}N_6OS_2$. Calculated, %: C 44.43; H 4.97; N 25.9.

8-Methylthio-6-pyrrolidino-5H-pyrimido[5,4-*e*][1,2,4]triazolo[5,1-*b*][1,3]thiazin-5-ol (8b) was obtained in 86% yield; mp 195-196°C (2-propanol). IR spectrum: 3220 cm^{-1} (OH). ^1H NMR spectrum (DMSO-d_6): 1.94 (4H, m, CH_2); 2.46 (3H, s, SCH_3); 3.82 (4H, m, CH_2); 7.19 (1H, d, 5-CH); 7.59 (1H, d, OH); 8.21 ppm (1H, s, 2-CH). Found, %: C 44.93; H 4.02; N 25.92. $C_{12}H_{14}N_6OS_2$. Calculated, %: C 44.71; H 4.38; N 26.07.

8-Methylthio-6-morpholino-5H-pyrimido[5,4-*e*][1,2,4]triazolo[5,1-*b*][1,3]thiazin-5-ol (8c) was obtained in 77% yield; mp 177-178°C (2-propanol). IR spectrum: 3390 cm^{-1} (OH). ^1H NMR spectrum (DMSO-d_6): 2.5 (3H, s, SCH_3); 3.73 (8H, m, CH_2); 6.87 (1H, d, 5-CH); 7.90 (1H, d, OH); 8.28 ppm (1H, s, 2-CH). Found, %: C 42.23; H 3.92; N 24.44. $C_{12}H_{14}N_6O_2S_2$. Calculated, %: C 42.59; H 4.17; N 24.83.

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