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THIAZOLE AND BENZOTHIAZOLE DERIVATIVES OF CYTISINE

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Several new derivatives were prepared by reacting N-*1(5*-R-*thiazol-2-yl)-2-chloroacetamides and* N-*1(6*-R-*benzothiazol-2-yl)chloroacetamides with cytisine.*

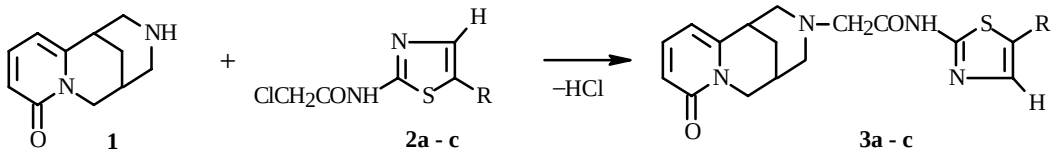
Key words: cytisine, alkylation, thiazole, benzothiazole.

The thiazole ring is known to be a part of vitamin B_1, cocarboxylase, and the cyclic system of penicillin [1]. Compounds containing the benzothiazole moiety are also of special interest because they have an even broader spectrum of biological activity. Thus, they possess antibacterial [2], antiulcer [3], antitumor [4, 5], anti-inflammatory [6], antiallergic [7], and antiarrhythmic [8] activities.

Thus, adding the aforementioned moieties to the natural alkaloid cytisine (**1**) gives hope that new biologically active compounds can be prepared.

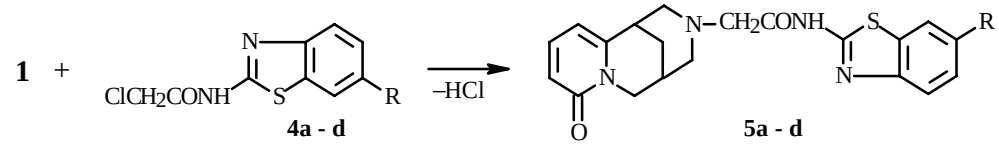
In continuation of research on the chemical modification of **1** [9], we prepared its new synthetic derivatives containing thiazole and benzothiazole moieties.

For this, cytisine was amidoalkylated with *N*-1(5-*R*-thiazol-2-yl)-2-chloroacetamides (**2a-c**) to give *N*-1[5-*R*-thiazol-2-yl]aminocarbonylmethyl cytisine derivatives (**3a-c**) in yields of 63-87%.



R = H, CH_3, C_2H_5

Reaction of **1** with *N*-1(6-*R*-benzothiazol-2-yl)chloroacetamides (**4a-d**) proceeded analogously to **2a-c**. The yields of products (**5a-d**) were slightly higher (79-95%).



R = H, CH_3, OCH_3, Cl

The results showed that the presence of electron-donating substituents in the 5-position of the thiazole ring and the 6-position of benzothiazole compounds increased the yields of **3b**, **3c**, and **5b-d**.

The structures of **3a-c** and **5a-d** were confirmed by IR and PMR spectra.

The IR spectra of **3a-c** and **5a-d** contained characteristic absorption bands for the α-pyridone ring at 1645-1662, 1520-1555, and 796-808 cm^{-1}. The amide carbonyl (N–CH_2–CO–NH) absorption appeared at 1556-1583 cm^{-1}. The NH group was characterized by absorption at 3247-3289 cm^{-1}.

According to preliminary data, some of the synthesized compounds exhibit bactericidal activity.

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EXPERIMENTAL

IR spectra were obtained on a Perkin—Elmer Model 2000 Fourier—IR spectrometer. PMR spectra were recorded on a Tesla BS-567A instrument at working frequency 100 MHz in C_5D_5N with HMDS internal standard. The purity of products was monitored by TLC on Silufol UV-254 plates (Czech Rep.) using $CHCl_3$:CH_3OH (10:1) and development by Dragendorff's reagent.

Compounds **2a-c** [10] and **4a-d** [11, 12] were synthesized by reaction of chloroacetylchloride with the appropriate heterocyclic amines in benzene.

Synthesis of 3a-c and 5a-d (general method). Alkaloid **1** and chloroacetamides **2a-c** and **4a-d** were condensed by boiling in absolute benzene for 4 h at a 2:1 ratio of reagents, respectively.

Products **3a-c** and **5a-d** were white crystalline compounds that crystallized well from appropriate organic solvents.

Elemental analyses of the prepared compounds agreed with those calculated.

***N*-1(Thiazol-2-yl)aminocarbonylmethylenecytisine (3a).** Yield 63%, R_f 0.63, mp 190-191°C (hexane), $C_{16}H_{18}N_4O_2S$.

IR spectrum (KBr, ν cm^{-1}): 3149, 3094, 2930, 1695, 1645, 1556, 1434, 1422, 1275, 800.

PMR spectrum (100 MHz, Py-d_5, δ, ppm, J/Hz): 1.43 (2H, br.s, H-8), 2.05 (1H, m, H-9), 2.55-2.93 (5H, m, H-7, H-11, H-13), 3.28 (2H, s, N–CH_2–CO), 3.80 (1H, dd, J = 15.7, 6.4, H_{ax}-10), 4.16 (1H, d, J = 15.7, H_{eq}-10), 5.78 (1H, br.d, J = 7, H-5), 6.45 (1H, br.d, J = 9, H-3), 6.93 (1H, d, J = 6, H-4′), 7.05 (1H, dd, J = 9, 7, H-4), 7.43 (1H, d, J = 6, H-5′).

***N*-1(5′-Methylthiazol-2-yl)aminocarbonylmethylenecytisine (3b).** Yield 87%, R_f 0.68, mp 208-209°C (benzene:petroleum ether, 2:1, $C_{17}H_{20}N_4O_2S$.

IR spectrum (KBr, ν cm^{-1}): 3276, 3094, 2936, 1694, 1662, 1583, 1551, 1520, 1440, 1424, 1296, 802.

PMR spectrum (100 MHz, Py-d_5, δ, ppm, J/Hz): 1.45 (2H, m, H-8), 2.10 (1H, m, H-9), 2.50-2.77 (5H, m, H-7, H-11, H-13), 3.85 (1H, dd, J = 15.7, 6.4, H_{ax}-10), 4.01 (1H, d, J = 15.7, H_{eq}-10), 5.76 (1H, dd, J = 1.2, 7, H-5), 6.40 (1H, dd, J = 1.2, 9, H-3), 7.10 (1H, s, H-4′), 7.09 (1H, dd, J = 7, 9, H-4).

***N*-1(5′-Ethylthiazol-2-yl)aminocarbonylmethylenecytisine (3c).** Yield 81%, R_f 0.66, mp 111-112°C (EtOH:H_2O, 1:1), $C_{18}H_{22}N_4O_2S$.

IR spectrum (KBr, ν cm^{-1}): 3153, 2932, 1675, 1651, 1568, 1553, 1455, 1344, 1258, 801.

PMR spectrum (100 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.15 (3H, t, CH_3), 1.43 (2H, m, H-8), 2.45-2.95 (5H, m, H-7, H-11, H-13), 3.17 (2H, CH_2), 3.30 (2H, s, N–CH_2–CO), 3.73 (2H, H-10), 6.02 (1H, d, J = 7, H-5), 6.15 (1H, d, J = 9, H-3), 7.05 (1H, s, H-4′), 7.27 (1H, dd, J = 7, 9, H-4).

***N*-1(Benzothiazol-2-yl)aminocarbonylmethylenecytisine (5a).** Yield 79%, R_f 0.81, mp 125-127°C (benzene:ether, 1:1), $C_{20}H_{20}N_4O_2S$.

IR spectrum (KBr, ν cm^{-1}): 3122, 3034, 2938, 1703, 1651, 1601, 1568, 1548, 1536, 1442, 1265, 796.

PMR spectrum (100 MHz, Py-d_5, δ, ppm, J/Hz): 1.45 (2H, m, H-8), 2.08 (1H, m, H-9), 2.63-2.80 (5H, m, H-7, H-11, H-13), 3.30 (2H, s, N–CH_2–CO), 3.83 (1H, dd, J = 15.7, 6.4, H_{ax}-10), 4.18 (1H, d, J = 15.7, H_{eq}-10), 5.77 (1H, dd, J = 1.8, 7, H-5), 6.48 (1H, dd, J = 1.8, 9, H-3), 7.07-7.45 (5H, Ar, H-4).

***N*-1(6′-Methylbenzothiazol-2-yl)aminocarbonylmethylenecytisine (5b).** Yield 93%, R_f 0.77, mp 122-123°C (benzene:hexane, 1:1), $C_{21}H_{22}N_4O_2S$.

IR spectrum (KBr, ν cm^{-1}): 3289, 3034, 2937, 1703, 1652, 1607, 1568, 1542, 1462, 1262, 796.

PMR spectrum (100 MHz, Py-d_5, δ, ppm, J/Hz): 1.45 (2H, m, H-8), 2.05 (1H, m, H-9), 2.18 (3H, CH_3), 2.63-2.88 (5H, m, H-7, H-11, H-13), 3.31 (2H, s, N–CH_2–CO), 3.82 (1H, dd, J = 15.7, 6.4, H_{ax}-10), 4.18 (1H, d, J = 15.7, H_{eq}-10), 5.75 (1H, br.d, J = 7, H-5), 6.44 (1H, br.d, J = 9, H-3), 7.00* (1H, d, J = 8, H-4′), 7.12 (1H, m, H-4), 7.20 (1H, s, H-7′), 7.75* (1H, d, J = 8, H-5′).

***N*-1(6′-Methoxybenzothiazol-2-yl)aminocarbonylmethylenecytisine (5c).** Yield 95%, R_f 0.84, mp 109-110°C (benzene:hexane, 1:1), $C_{21}H_{22}N_4O_3S$.

IR spectrum (KBr, ν cm^{-1}): 2939, 1698, 1651, 1606, 1568, 1548, 1471, 1437, 1260, 798.

PMR spectrum (100 MHz, Py-d_5, δ, ppm, J/Hz): 1.45 (2H, m, H-8), 2.05 (1H, m, H-9), 2.50-2.88 (5H, m, H-7, H-11, H-13), 3.33 (2H, s, N–CH_2–CO), 3.58 (3H, s, OCH_3), 3.90 (1H, dd, J = 15.7, 6.4, H_{ax}-10), 4.10 (1H, d, J = 15.7, H_{eq}-10), 5.78 (1H, dd, J = 1.8, 6.8, H-5), 6.46 (1H, dd, J = 1.8, 9, H-3), 7.03 (1H, dd, J = 6.8, 9, H-4), 7.22 (1H, s, H-7′), 6.95-7.18* (1H, H-5′), 7.75* (1H, d, J = 7.5, H-4′).

***N*-1(6′-Chlorobenzothiazol-2-yl)aminocarbonylmethylenecytisine (5d).** Yield 89%, R_f 0.76, mp 244-245°C (benzene), $C_{20}H_{19}N_4O_2SCl$.

IR spectrum (KBr, ν cm^{-1}): 3311, 2943, 1651, 1598, 1568, 1549, 1538, 1444, 1421, 1262, 808.

PMR spectrum (100 MHz, Py-d_5, δ, ppm, J/Hz): 1.48 (2H, m, H-8), 2.08 (1H, m, H-9), 2.48-2.90 (5H, m, H-7, H-11, H-13), 3.33 (2H, s, N–CH_2–CO), 3.91 (1H, dd, J = 15.7, 6.4, H_{ax}-10), 4.10 (1H, d, J = 15.7, H_{eq}-10), 5.77 (1H, br.d, J = 6.8, H-5), 6.43 (1H, br.d, J = 8.8, H-3), 7.00-7.15 (1H, H-4), 7.27 (1H, dd, J = 8, 1.6, H-5′), 7.65 (d, J = 8, H-4′), 7.86 (1H, d, J = 1.2, H-7′).

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