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NEW HYBRID CYTISINE DERIVATIVES CONTAINING A THIENOPYRIMIDINE FRAGMENT

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*New cytisine–thienopyrimidine hybrid molecules were synthesized by reacting cytisine with 4-chlorothieno [2,3-*d*]pyrimidines in the presence of Et_3N. The solvent effect on the course of the reaction was studied. The structures of the obtained compounds were elucidated using IR, ^1H and ^{13}C NMR spectroscopy and TLC-MS spectrometry. X-ray crystal structure analyses of the synthesized compounds were performed.*

Keywords: cytisine, 4-chlorothieno[2,3-*d*]pyrimidines, Et_3N, condensation, XSA.

Functionalization of natural compounds by synthesizing hybrid molecules with various properties that contain biologically active natural moieties is known to be an effective method for constructing biologically active compounds.

The spectrum of natural substrates is rather broad and comprises alkaloids, flavonoids, steroids, terpenoids, etc. [1].

The quinolizidine alkaloid (–)-cytisine and chloro-substituted thieno[2,3-*d*]pyrimidines (TPs) were selected for research to expand the repertoire of new hybrid molecules. The use of cytisine as one of the pharmacophores could lead to effective results because cytisine possesses a broad spectrum of pharmacological properties [2–4], particularly antitobacco and antiviral [5].

Although substituted TPs do not exist in nature, most of them are potential biologically active compounds that exhibit activity against microbes [6, 7], viruses [8], inflammation [9], and diabetes [10]. Several TP derivatives are antidepressants, antihypertensive agents [11], and antioxidants [12]. Those with an NH bridge in the 4-position have therapeutic activity against malignant tumors [6, 13, 14] and are especially interesting for synthesizing hybrid cytisine–thienopyrimidine molecules.

For this, substituted TP-4-ones (**2a**–**e**) were synthesized in two steps via formation of 2-aminothiophene esters **1a**–**e** according to the published method [15]. Compounds **2a**–**e** reacted with $POCl_3$ in CCl_4 solution to form 4-Cl-TPs (**3a**–**e**) with a 4-Cl atom in high yields. These compounds were intermediates for the synthesis of antitumor agents and played important roles as necessary synthons in targeted organic syntheses. The imidoyl Cl atom on the pyrimidine ring was highly reactive although the molecules (**3a**–**e**) were stable, so they could be used in reactions with various nucleophilic reagents.

Compounds **3a**–**e** were reacted with cytisine as a secondary heterocyclic amine to synthesize new hybrid molecules containing cytisine and synthetic TP-4-ones. The reactions occurred in 6 h between **3a**–**e** and cytisine in a 1:1.5 ratio in refluxing solvents (EtOH, C_6H_6, CCl_4) in the presence of 1.5 equivalents of Et_3N (TEA). As a result, compounds **4a**–**e** were synthesized in high yields.

The reactions in CCl_4 were found to occur with comparatively higher yields than in other solvents because of the good solubility of 4-Cl-TPs (**3a**–**e**) in this solvent.

The structures of the synthesized compounds were proven using IR, ^1H and ^{13}C NMR spectroscopic and TLC-MS mass spectrometric methods. In particular, their IR spectra exhibited absorption bands specific for the cytisine carbonyl (C=O) at 1660–1650 cm^{-1} and for C–N at 1430–1420 cm^{-1}. The aliphatic C–H bonds absorbed at 2935–2915 cm^{-1}. Bands for two (2 C=N and 4 C=N) azomethine bonds appeared in the ranges 1560–1490 and 1480–1440 cm^{-1}.

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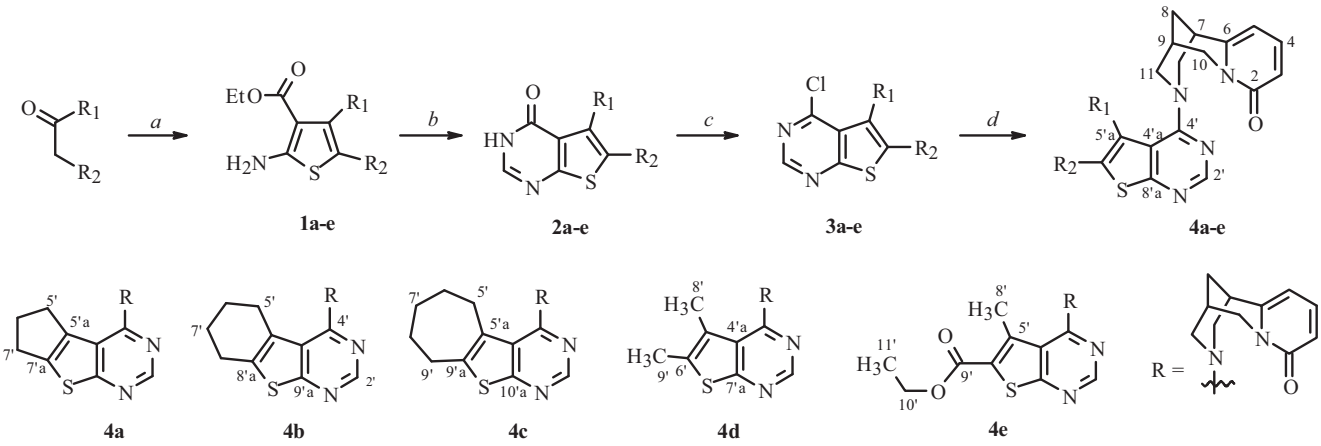
TABLE 1. Chemical Shifts in ^1H and ^{13}C NMR Spectra of **4b** and **4d** (Py-d_5, δ, ppm, J/Hz)

C atom	4b		4d	
	δ_H	δ_C	δ_H	δ_C
2	–	168.9 (C)	–	167.8 (C)
3	6.55 (d, J = 9.1)	117.0 (CH)	6.52 (dd, J = 9.1, 1.4)	117.1 (CH)
4	7.17 (dd, J = 9.1, 6.7)	138.5 (CH)	7.13 (t, J = 7.9)	138.5 (CH)
5	5.93 (dd, J = 6.8, 1.5)	104.8 (CH)	5.89 (dd, J = 6.8, 1.5)	104.8 (CH)
6	–	151.6 (C)	–	151.3 (C)
7	2.87 (m)	35.2 (CH)	2.85 (m)	35.2 (CH)
8	1.69 (t, J = 3.2)	27.9 (CH_2)	1.69 (t, J = 3.2)	28.0 (CH_2)
9	2.34 (m)	26.1 (CH)	2.27 (m)	26.1 (CH)
10α	3.81(dd, J = 15.5, 6.5)	58.4 (CH_2)	3.81(dd, J = 15.5, 6.5)	58.1 (CH_2)
10β	4.53 (d, J = 15.5)		4.57 (d, J = 15.4)	
11α	3.19(d, J = 12.4)	55.7 (CH_2)	3.14 (d, J = 11.3)	55.3 (CH_2)
11β	3.75 (d, J = 12.6)		3.78 (d, J = 6.3)	
13α	3.60 (d, J = 12.0)	49.1 (CH_2)	3.61 (d, J = 12.2)	49.0 (CH_2)
13β	3.07 (dd, J = 12.0, 2.3)		3.12 (dd, J = 10.0, 2.3)	
2′	8.76 (s)	162.9 (CH)	8.71 (s)	162.6 (CH)
4′	–	163.1 (C)	–	163.0 (C)
4a′	–	122.1 (C)	–	121.9 (C)
5′	2.31 (t, J = 6.0)	25.5 (CH_2)	–	124.9 (C)
5a′	–	127.5 (C)		
6′	1.42 (m)	22.6 (CH_2)	–	131.6 (C)
7′	1.55 (m)	22.7 (CH_2)		
7a′			–	150.1 (C)
8′	2.55 (td, J = 6.2, 1.7)	25.8 (CH_2)	1.89 (s)	13.3 (CH_3)
8a′	–	134.6 (C)		
9′			2.12 (s)	13.4 (CH_3)
9a′	–	150.3 (C)		



a. Ethyl cyanoacetate, S_8, morpholine, anhydr. EtOH, 40–45°C, 24 h; *b*. formamide, 150°C, 8 h; *c*. $POCl_3$, CCl_4, TEA, 77°C, 5 h; *d*. (–)-cytisine, TEA, anhydr. EtOH (or C_6H_6, CCl_4), 80°C, 6 h.

Absorption bands in the range 815–790 cm^{-1} were indicative of C–S–C bonds. ^1H NMR spectra of **4a**–**e** showed singlets at δ 8.7 ppm for aromatic C–H protons of the pyrimidine ring in all products and characteristic resonances for aliphatic (1.69–3.82 ppm) and aromatic cytisine protons (5.93–7.20 ppm). Table 1 presents detailed data for the ^1H and ^{13}C NMR spectra of **4b** and **4d**. Also, the appearance of molecular ions (*m*/*z* $[M + H]^+$) for **4a**, 365.7896; **4b**, 379.2539; **4c**, 393.2397; **4d**, 353.2268; and **4e**, 411.3690 in the mass spectra confirmed the structures of the synthesized compounds.

TABLE 2. Main Parameters of X-ray Crystal Structure Analyses and Calculations

Parameters	**4a**	**4b**	**4d**	**4e**
Molecular formula	$C_{20}H_{20}N_4OS$	$2(C_{21}H_{22}N_4OS)\cdot H_2O$	$2(C_{19}H_{20}N_4OS)\cdot H_2O$	$C_{21}H_{22}N_4O_3S$
MM	364.46	774.99	722.91	410.48
Space group	$P2_1$, Z = 4	$C222_1$, Z = 4	$C2$, Z = 2	$P2_12_12_1$, Z = 8
a, Å	10.5895 (9)	8.3300 (4)	21.3816 (5)	7.3150 (1)
b, Å	7.3683 (6)	19.2371 (5)	7.2472 (1)	17.9096 (6)
c, Å	22.6528 (16)	23.1687 (6)	11.1278 (3)	29.2636 (6)
α, deg	90	90	90	90
β, deg	97.004 (8)	90	93.013 (2)	90
γ, deg	90	90	90	90
V, Å^3	1754.3 (2)	3712.7 (2)	1721.95 (6)	3833.79 (16)
ρ, g/cm^3	1.380	1.386	1.394	1.422
Crystal size, mm	0.45 × 0.40 × 0.25	0.55 × 0.12 × 0.06	0.40 × 0.20 × 0.12	0.40 × 0.08 × 0.04
Scan range θ	3.8 ≥ 71.2	3.8 ≥ 71.4	3.9 ≥ 70.9	2.9 ≥ 71.3
Number of independent reflections	4903	3595	2174	6739
Number of reflections with I > 2σ(I)	3912	3334	2110	6035
R_1 (I > 2σ(I) and total)	0.097 (0.108)	0.049 (0.051)	0.036 (0.037)	0.047 (0.052)
WR_2	0.251 (0.267)	0.158 (0.163)	0.113 (0.115)	0.114 (0.119)
GOOF	1.06	1.32	0.97	1.00
ED difference peaks (e Å^{-3})	0.85 and –0.64	0.20 and –0.51	0.18 and –0.44	0.25 and –0.42
CCDC	2279685	2279686	2279687	2279688

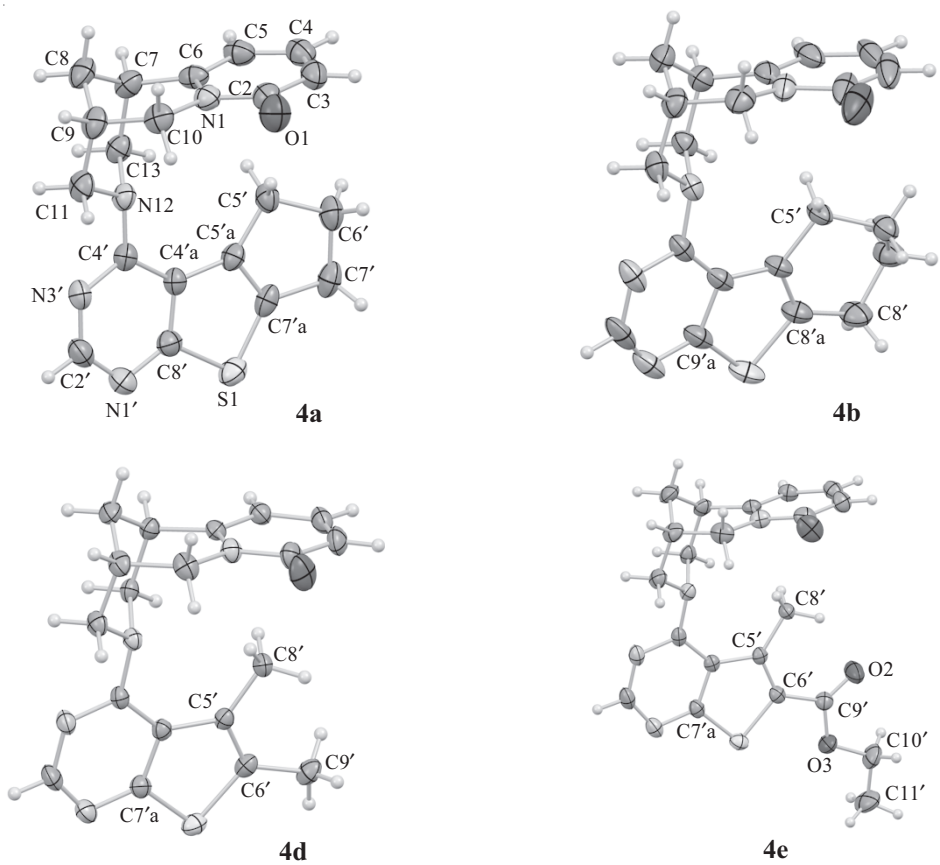


Fig. 1. Molecular structures of derivatives **4a**–**e** (one of two asymmetric molecules is shown for **4a** and **4e**).

Figure 1 shows the structures of synthesized **4a**, **4b**, **4d**, and **4e** from X-ray crystal structure analyses (XSAs) in approximately the same projection of the cytisine core. All derivatives were obtained with the α-equatorial orientation of tetrahedral N12. The rigid cytisine core with conformationally identical stereochemistry was retained in all studied derivatives. The pseudo-aromatic ring (A) in the cytisine core was planar. The next six-membered ring (B) adopted a half-boat conformation with C8 deviating from the plane of the other five atoms. The third six-membered ring (C) had an ideal chair conformation. These data agreed with the literature found for cytisine itself [16–18] and various derivatives of it at N12 [19–22].

Crystals of **4a** and **4e** had two molecules in the asymmetric (independent) part of the unit cell. Crystals of **4b** and **4d** contained one water molecule near a special position (2-fold axis), i.e., they were monohydrates.

The substituted TP rings in these derivatives (**4a**, **4b**, **4d**, and **4e**) were planar because the TP core itself was a heteroaromatic bicycle. The saturated six-membered ring in both of the two independent molecules of **4b** had the same half-chair conformation with the terminal atoms deviating to different sides of the plane of the substituted TP core. However, the carboxyethylene moiety in one molecule of **4e** deviated from the plane of the TP core because of the influence of intermolecular interactions (packing factor).

Torsion angle C11–N12–C4′–N3′ characterized the mutual positioning of the TP core and starting cytisine. The values for the two molecules of **4a** were 14.2° and 15.1°; for **4b**, 14.9°; for **4d**, 21.9°; for **4e**, 21.4° and 22.7°. This meant that the torsion angles for the tricyclic derivatives (**4a** and **4b**) were ~15°; for bicyclic derivatives (**4d** and **4e**), ~22°.

The crystal structures of monohydrates **4b** and **4d** had intermolecular H-bonds O–H…O involving the water molecules. The water H atoms in the crystal of **4b** were H-bonded to the cytisine carbonyl O atom and were fundamental in nature. The H-bond parameters were distances H…O1 2.21 and O_w…O1 2.838 Å and angle O_w–H…O1 135°. However, the water H atoms in the crystal of **4d** approached the N4 unshared pair (2.44 and 3.12 Å and 105°, respectively).

Thus, a method for preparing new hybrid cytosine–TP molecules via the reaction of the alkaloid cytisine with Cl-substituted thieno[2,3-*d*]pyrimidines in the presence of an acid acceptor (TEA) was developed. The structures of the synthesized compounds were unambiguously proven by modern physical methods, including XSAs.

EXPERIMENTAL

IR spectra were taken from KBr pellets on a System 2000 FTIR spectrometer (PerkinElmer, USA). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, DMSO-d_6, and Py-D_5 solutions with TMS internal standard (0 ppm) on a JNM-ECZ400R instrument (JEOL, Japan) at 400 MHz for ^{1}H. Mass spectra were measured in a CAMAG TLC-MS equipped with an Acquity QDa detector. TLC used Silufol UV-254 L/W (20 × 20 cm) and Whatman® UV-254 plates (Sigma–Aldrich, Germany) with elution by C_6H_6–MeOH (5:1, I) and C_6H_6–Me_2CO (3:1, II). Melting points of synthesized compounds were determined on Biobase BMP-M70 (China) and Mel-Temp apparatuses (USA).

2-Amino-5,6-disubstituted thiophene-3-ethylcarboxylates (1a–e) were prepared by the literature method [15]. Cyclopentanone (3.55 mL, 3.36 g, ρ = 0.95 g/mL, 0.04 mol), cyanoacetic ester (4.52 g, ρ = 1.06 g/mL, 0.04 mol), S_8 (1.408 g, 0.044 mol), anhydrous EtOH (12 mL), and morpholine (4.0 mL, 4.05 g, 0.046 mol) gave **1a** (7.10 g, 85%), mp 88–90°C (cyclohexane), R_f 0.70 (system I).

5,6-Disubstituted thieno[2,3-*d*]pyrimidin-4-ones (2a–e) were prepared by the literature method [15]. 2-Amino-4,5,6-trihydrocyclopenta[*b*]thiophene-3-ethylcarboxylate (**1a**, 4.22 g, 0.002 mol) and formamide (10 mL, 11.3 g, ρ = 1.13 g/mL, 0.24 mol) gave **2a** [3.27 g, 85%, mp 216–218°C (EtOH), R_f 0.36 (system I)].

4-Chloro-5,6-disubstituted Thieno[2,3-*d*]pyrimidines (3a–e) (General Method). A mixture of 3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-one (**2a**, 0.96 g, 0.005 mol), $POCl_3$ (2.0 mL), CCl_4 (5.0 mL), and Et_3N (1.0 mL) was refluxed at 77°C for 4 h and cooled to room temperature. The mixture was diluted with $CHCl_3$ (15 mL), neutralized with $NaHCO_3$ solution (15%, 50 mL), and washed several times with distilled H_2O. The $CHCl_3$ part was dried over anhydrous Na_2SO_4 (4 h). The Na_2SO_4 was filtered off. The $CHCl_3$ was distilled in a rotary evaporator. The solid was recrystallized from EtOH to afford **3a** (1.0 g, 96%) as a white crystalline product, mp 103–104°C, R_f 0.89 (system II). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.53 (2H, m, H-6), 3.06 (2H, m, H-5), 3.16 (2H, m, H-7), 8.70 (1H, s, H-2).

3-(5,6,7-Trihydrocyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-yl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (4a). Compound **3a** (0.44 g, 0.002 mol) and cytisine (0.6 g, 0.0031 mol) were treated with Et_3N (1.0 mL) and CCl_4 (10 mL). The mixture was refluxed on a water bath for 6 h and left overnight at room temperature. The resulting precipitate was filtered off, rinsed with NaOH solution (5%) and H_2O (3×), and dried at room temperature

to afford **4a** (0.625 g, 86%), mp 183–185°C (C_2H_5OH). $C_{20}H_{20}N_4OS$, R_f 0.26 (system I). IR (KBr, ν, cm^{-1}): 3466, 2979–2947 (CH_2), 1644 (C=O), 1533 (C=C), 1480 (4-C=N), 1443 (2-C=N), 1311 (C–N), 791 (C–S–C). ^{1}H NMR (400 MHz, Py-d_5, δ, ppm, J/Hz): 1.74 (2H, t, J = 3.3, H-8), 2.05 (2H, m, H-6′), 2.30 (1H, m, H-9), 2.64 (4H, m, H-5′, 7′), 2.91 (1H, m, H-7), 3.13 (1H, ddd, J = 12.8, 2.6, 1.3, H_α-11), 3.22 (1H, dd, J = 12.4, 2.3, H_β-13), 3.79 (1H, ddd, J = 15.5, 6.4, 1.4, H_α-10), 4.03 (1H, d, J = 12.5, H_α-13), 4.21 (1H, d, J = 13.0, H_β-11), 4.60 (1H, d, J = 15.5, H_β-10), 5.93 (1H, dd, J = 6.9, 1.5, H-5), 6.45 (1H, dd, J = 9.0, 1.3, H-3), 7.08 (1H, dd, J = 9.0, 6.8, H-4), 8.61 (1H, s, H-2′). ^{13}C NMR (100 MHz, Py-d_5, δ, ppm): 160.9 (C-2′), 163.0 (C-4′), 27.8 (C-5′), 135.9 (C-5a′), 26.1 (C-6′), 28.0 (C-7′), 138.5 (C-7a′), 173.8 (C-2), 117.0 (C-3), 139.2 (C-4), 104.8 (C-5), 151.3 (C-6), 35.2 (C-7), 31.6 (C-8), 29.5 (C-9), 56.7 (C-10), 54.3 (C-11), 48.8 (C-13). Mass spectrum *m/z* 365.7896 $[M + H]^+$ (calcd for $C_{20}H_{21}N_4OS$, 365.4597).

3-(5,6,7,8-Tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-yl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (4b) was prepared analogously to **4a** from **3b** (0.45 g, 0.002 mol), cytisine (0.60 g, 0.0031 mol), and Et_3N (1.0 mL) in CCl_4 (10 mL) to afford **4b** (0.70 g, 93%), mp 155–157°C (EtOH). $C_{21}H_{22}N_4OS$, R_f 0.25 (system I). IR (KBr, ν, cm^{-1}): 3471, 2932, 2865, 2839, 1645,1543, 1528, 1428, 1249, 976, 799. Table 1 presents the ^{1}H and ^{13}C NMR spectral data. Mass spectum *m/z* 379.2539 $[M + H]^+$ (calcd for $C_{21}H_{23}N_4OS$, 379.4855).

3-(6,7,8,9-Tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (4c) was prepared by the above method from **3c** (0.478 g, 0.002 mol), cytisine (0.60 g, 0.0031 mol), Et_3N (1.0 mL), and anhydrous EtOH (10 mL) to afford **4c** (0.675 g, 86%), mp 143–144°C (EtOH). $C_{22}H_{24}N_4OS$, R_f 0.27 (system I). IR (KBr, ν, cm^{-1}): 3510, 3382, 2923, 2905, 2850, 1646, 1566, 1549, 1525, 1429, 1374, 977, 794. Mass spectrum *m/z* 393.2397 $[M + H]^+$ (calcd for $C_{22}H_{25}N_4OS$, 393.5113).

3-(5,6-Dimethylthieno[2,3-*d*]pyrimidin-4-yl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (4d) was prepared analogously as above from **3d** (0.40 g, 0.002 mol), cytisine (0.60 g, 0.0031 mol), Et_3N (1.0 mL), and CCl_4 (10 mL) to afford **4d** (0.62 g, 88%), mp165–167°C (EtOH). $C_{19}H_{20}N_4OS$, R_f 0.30 (system I). IR (KBr, ν, cm^{-1}): 2915, 2837, 1651, 1543, 1527, 1423, 1358, 1335, 1190, 1159, 1017, 975, 811. Table 1 presents the PMR and ^{13}C NMR spectral data. Mass spectrum *m/z* 353.2268 $[M + H]^+$ (calcd for $C_{19}H_{21}N_4OS$, 353.4689).

5-Methyl-4-{8-oxo-1,5,6,8-tetrahydro-2*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-3(4*H*)-yl}thieno[2,3-*d*]pyrimidine-6-ethylcarboxylate (4e) was prepared by the above method from **3e** (0.52 g, 0.002 mol), cytisine (0.60 g, 0.0031 mol), Et_3N (1.0 mL), and CCl_4 (10 mL) to afford **4e** (0.75 g, 90%), mp 191–192°C (EtOH). $C_{21}H_{22}N_4O_3S$, R_f 0.28 (system I). IR (KBr, ν, cm^{-1}): 2940, 2844, 2814, 1702, 1651, 1536, 1496, 1429, 1275, 1232, 1020, 973, 808. ^{1}H NMR (400 MHz, Py-d_5, δ, ppm, J/Hz): 1.38 (3H, t, J = 7.0, H-11′), 2.13 (2H, d, J = 13.0, H-8), 2.58 (3H, s, H-8′), 3.14 (1H, m, H-9), 3.28 (1H, m, H-7), 3.49 (1H, d, J = 13.2, H_α-13), 3.65 (1H, d, J = 5.8, H_β-13), 3.70 (1H, m, H_α-11), 3.96 (1H, d, J = 12.8, H_β-10), 4.33 (2H, q, J = 7.0, H-10′), 4.48 (1H, d, J = 15.0, H_α-10), 4.59 (1H, d, J = 13.6, H_b-10), 6.04 (1H, d, J = 7.0, H-5), 6.21 (1H, dd, J = 9.0, 1.4, H-3), 7.17 (1H, dd, J = 9.0, 6.9, H-4), 8.19 (1H, s, H-2′). ^{13}C NMR (100 MHz, Py-d_5, δ, ppm): 162.7 (C-2′), 163.8 (C-4′), 118.6 (C-4a′), 123.1 (C-5′), 138.9 (C-6′), 149.0 (C-7a′), 16.2 (C-8′), 162.3 (C-9′), 61.2 (C-10′), 13.9 (C-11′), 168.5 (C-2), 116.5 (C-3), 139.3 (C-4), 107.0 (C-5), 152.7 (C-6), 35.8 (C-7), 28.3 (C-8), 26.0 (C-9), 58.4 (C-10), 53.1 (C-11), 49.0 (C-13). Mass spectrum *m/z* 411.3690 $[M + H]^+$ (calcd for $C_{21}H_{23}N_4O_3S$, 411.5043).

X-ray Crystal Structure Analyses (XSAs). Unit-cell constants of single crystals were determined and refined on an HPC XtaLAB Synergy diffractometer (Rigaku, Japan) using Cu Kα-radiation (T = 293 K). Table 2 presents the main parameters of the XSAs and the calculations. Absorption corrections were applied using the SADABS program [23].

The structures were solved by direct methods using the SHELXS-97 program suite [24] and were refined using the SHELXL-2014/8 program [25]. All nonhydrogen atoms were refined by anisotropic full-matrix least-squares methods (over F^2). H atoms on C atoms were fixed geometrically and refined by a rider model with fixed isotropic shift parameters $U_{iso} = nU_{eq}$, where n = 1.5 for methyls and 1.2 for others (U_{eq} is the equivalent isotropic shift parameter of the corresponding C atoms).

Data for the XSAs were deposited as CIF files in the Cambridge Crystallographic Data Centre (CCDC).

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