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CONDENSED SULFUR-CONTAINING PYRIDINE SYSTEMS 3.* CONSTRUCTION OF PENTA- AND HEXACYCLIC HETEROCYCLIC SYSTEMS BY THE CASCADE REACTION OF 3-CYANOPYRIDINE-2(1*H*)-THIONES AND 3-CYANO-PYRIDINE-2(1*H*)-THIOLATES WITH 8-CHLOROMETHYL-3-METHYL-7-(2-OXO-2-PHENYLETHYL)XANTHENE

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The alkylation of 3-cyanopyridine-2(1H)-thiones with 8-chloromethyl-3-methyl-7-(2-oxo-2-phenylethyl)-xanthene in a KOH–H_2O–DMF system upon heating leads to the formation of pyrido-[3",2":4',5']thieno[3',2':5,6][1,4]diazepino[7,1-f]purine-2,4(3H,6H)-dione derivatives in good yields. Under milder conditions, the intermediates of the cascade reactions, namely, 2-({[3-methyl-2,6-dioxo-7-(2-oxo-2-phenylethyl)-2,3,6,7-tetrahydro-1H-purin-8-yl]methyl}thio)pyridine-3-carbonitriles, can be isolated and characterized.

Keywords: 8-chloromethyl-3-methyl-7-(2-oxo-2-phenylethyl)xanthene, 3-cyanopyridine-2(1*H*)-thiones, thieno[2,3-*b*]pyridines, alkylation, cascade reaction, Thorpe-Ziegler reaction.

Cascade reactions, which are also termed tandem or domino reactions, are a current approach to the synthesis of polycyclic structures. In comparison with multistep syntheses, cascade reactions are more efficient and atom-economical, permitting the construction of complex molecules from simple low-molecular substrates in a single step in much less time. Many such heterocyclization reactions have already been described (see reviews of domino reactions [2-9]).

Some of the most rapidly developing areas in the chemistry of cascade reactions are heterocyclizations using readily available 3-cyanopyridine-2(1*H*)-thiones (see reviews by Litvinov et al. [10-14]), leading to the formation of condensed thieno[2,3-*b*]pyridine derivatives [15-18]. Thus, there have been many recent reports concerning the reactions of substituted 3-cyanopyridine-2(1*H*)-thiones with various multifunctional alkylating

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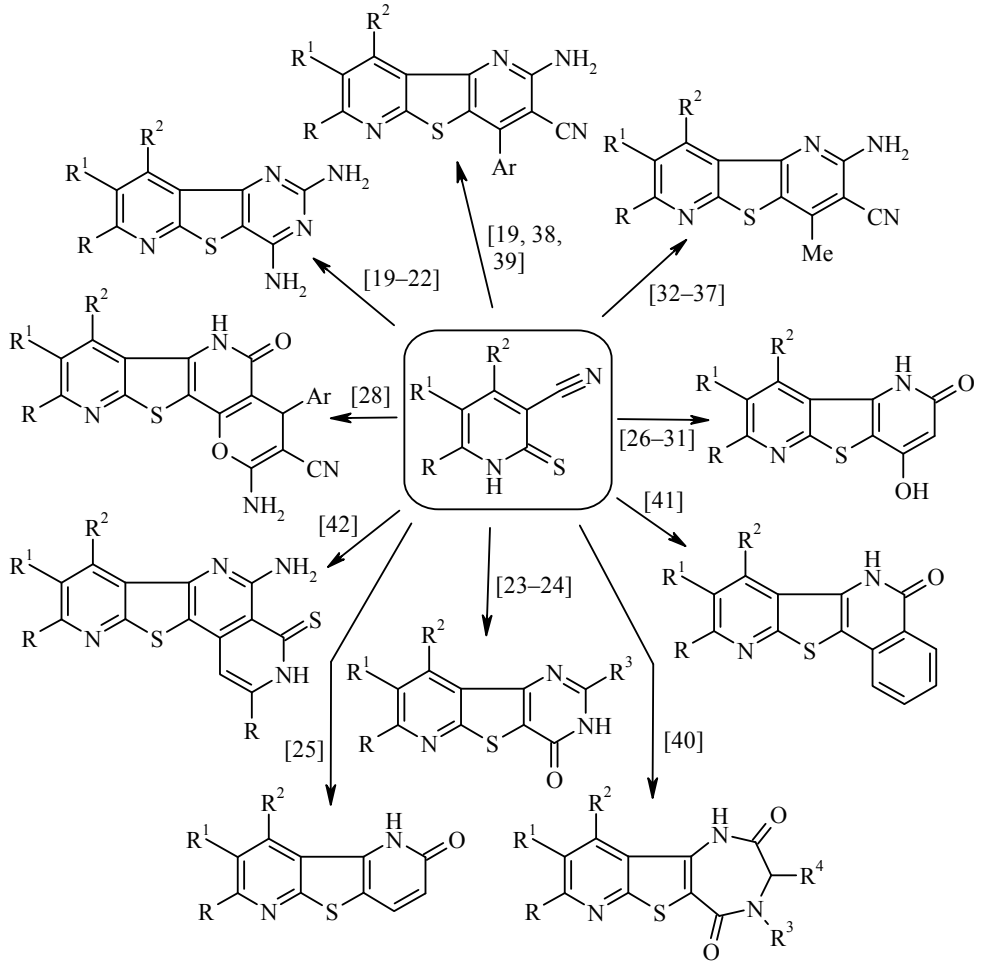
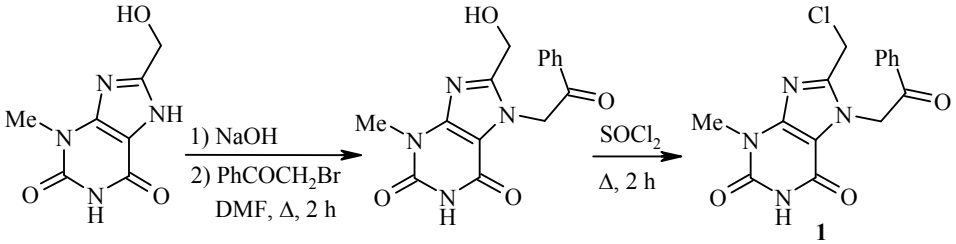
agents, leading to the formation of heterocyclic pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine [19-24], pyrido-[2',3':4,5]thieno[2,3-*b*]pyridine [19, 25-39], pyrano[2,3-*d*]pyrido[3',2':4,5]thieno[3,2-*b*]pyridine [28], pyrido-[3',2':4,5]thieno[3,2-*e*][1,4]diazepine [40], pyrido[3',2':4,5]thieno[3,2-*c*]isoquinoline [41], and pyrido[3',2':4,5]-thieno[3,2-*c*][2,7]naphthyridine derivatives [42].

In a continuation of work on cascade reactions in the synthesis of condensed analogs of thieno[2,3-*b*]-pyridine, we turned our attention to 8-chloromethyl-3-methyl-7-(2-oxo-2-phenylethyl)xanthene (**1**) as a starting compound for the construction of polycyclic systems based on 3-cyanopyridine-2(1*H*)-thione derivatives.



Chloromethylxanthene **1** may be readily obtained from 8-hydroxymethyl-3-methylxanthene [43] by consecutive treatment with phenacyl bromide and $SOCl_2$.



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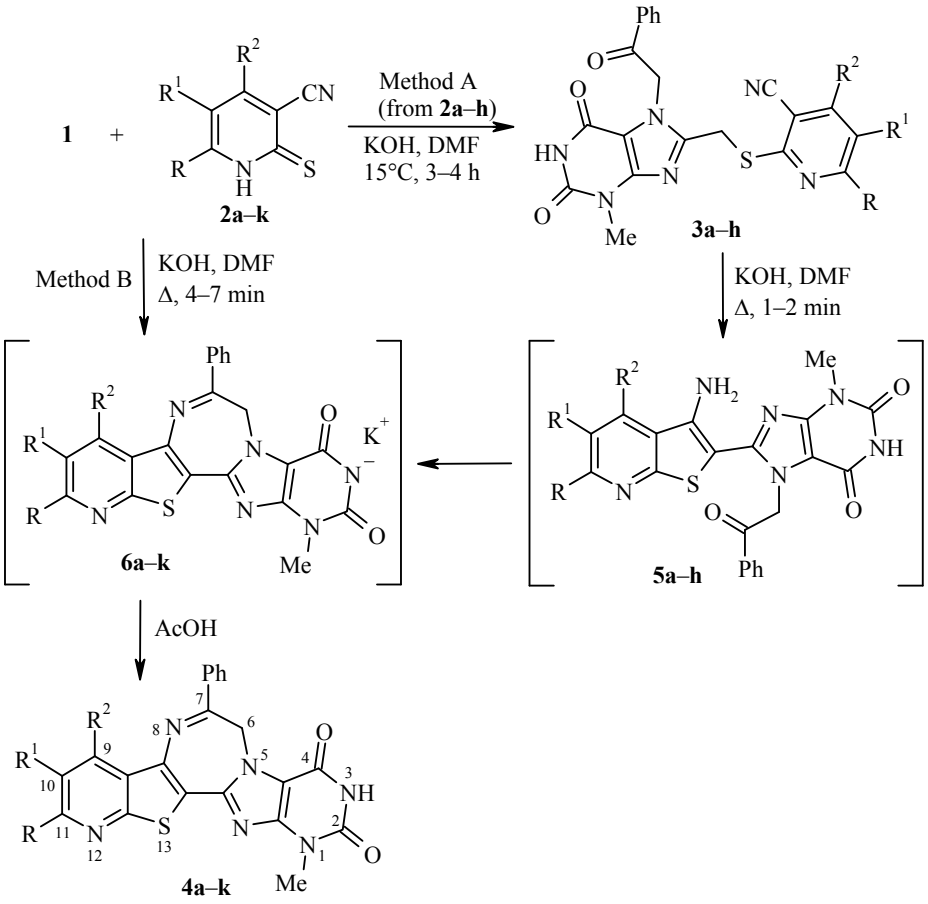
It was found that the chloromethylxanthene **1** reacts under mild conditions (15°C, DMF) with pyridinethiones **2a-h** in the presence of one equivalent of 10% aqueous KOH to give sulfides **3a-h** in 53-74%

yield. Upon treatment with excess KOH, these sulfides are readily cyclized to give pyrido[3",2":4',5']-thieno[3',2':5,6][1,4]diazepino[7,1-*f*]purine-2,4(3*H*,6*H*)-diones **4a-h** in 72-90% yields (method A). We should note that the Thorpe-Ziegler cyclization products formed in the first step of the cascade reaction, namely, thieno[2,3-*b*]pyridines **5a-h**, could not be isolated. An alternative method for the synthesis of diones **4** is based on the direct reaction of chloromethylxanthene **1** and pyridinethione **2** in the presence of excess KOH in DMF at reflux, without isolation of the *S*-alkylation products **3** (method B). This reaction gives polycyclic diones **4a-k** in 45-88% yield. Comparison of the results obtained using methods A and B indicates that the preferred procedure is the one-pot method B, which eliminates the need to isolate the *S*-alkylation product and gives higher yields of the desired polycyclic diones **4**.

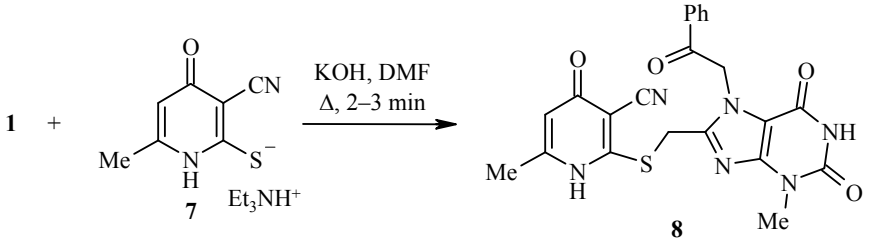


2–6 a R+R^1 = $(CH_2)_6$, R^2 = H; **b** R+R^1 = $(CH_2)_4$, R^2 = 2-ClC_6H_4; **c** R = Me, R^1+R^2 = $(CH_2)_4$;
d R = Me, R^1+R^2 = $(CH_2)_3$; **e** R+R^1 = $CH_2CH_2CH(t\text{-Bu})CH_2$, R^2 = H; **f** R = R^2 = Me, R^1 = H;
g R+R^1 = $(CH_2)_4$, R^2 = 4-ClC_6H_4; **h** R = R^2 = Ph, R^1 = H; **i** R+R^1 = $(CH_2)_3CO$, R^2 = H;
j R+R^1 = $(CH_2)_5$, R^2 = 2-ClC_6H_4; **k** R+R^1 = $(CH_2)_4$, R^2 = 2-thienyl

The products of the cascade cyclization are formed as potassium salts **6a-k**, which convert to diones **4a-k** upon mild acidification of the reaction mixture by adding a slight excess of acetic or hydrochloric acid. In the case of 4,6-dimethyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**2f**), we isolated and characterized the corresponding potassium salt **6f** (R = R^2 = Me, R^1 = H).

Sulfides **3a-h** are white or light-yellow fine crystalline powders, which are insoluble in ethanol, have slight solubility in acetone, but are moderately soluble in DMSO and DMF. Polycyclic diones **4a-k** are high-melting, bright-yellow or brown fine crystalline powders, which are insoluble in ethanol and acetone but moderately soluble in hot DMSO and DMF.

It is interesting to note that triethylammonium 3-cyano-6-methyl-4-oxo-1,4-dihydropyridine-2-thiolate (**7**) [44] upon reaction with chloromethylxanthene **1** under analogous conditions (DMF and then heating with 1.5 equivalents of KOH at reflux) gives only the *S*-alkylation product **8** in 76% yield. This behavior may be attributed to the enhanced NH-acidity of both the purine and pyridine fragments of carbonitrile **8**, which leads to binding of the base required for the Thorpe-Ziegler reaction and initiation of the cascade reaction.



As we have recently shown [45], the starting 1-methyl-3-thioxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (**2c**) and 1-methyl-3-thioxo-3,5,6,7-tetrahydro-2*H*-cyclopenta[*c*]pyridine-4-carbonitrile (**2d**), obtained by the procedure described in our previous work [46] and used for the synthesis of compounds **3c**, **4c** and **3d**, **4d**, respectively, are actually mixtures with the regioisomeric quinoline-2-thione **2'c** and cyclopenta[*b*]pyridine-2-thione **2'd** (Fig. 1). Thus, derivatives **3c**, **4c** and **3d**, **4d** are also regioisomer mixtures. The ratio of isoquinoline derivative **3c** to quinoline derivative **3'c** in the mixture obtained in the reaction of thione **2c** with chloromethylxanthene **1**, according to ^{1}H NMR spectral data (500 MHz), is ~9:2. However, it proved impossible to unequivocally establish the regioisomer ratio in the mixture of products of the Thorpe-Ziegler cascade cyclization **4c + 4'c** due to complete signal overlap in the spectrum.

^{1}H NMR spectral data showed a ~5:3 ratio for the mixture of cyclopenta[*c*]- (**3d**) and cyclopenta[*b*]pyridine (**3'd**) regioisomers in the product of thione **2d** reaction with chloromethylxanthene **1** and a ~9:4 **4d:4'd** ratio for the cascade reaction product **4d**. The ^{1}H NMR spectra of compounds **3a-h** and **8** show signals for the SCH_2 methylene group as broad pseudo singlets or two doublets (4.97-4.74 ppm) and for the NCH_2CO methylene group as a pseudo singlet at 6.09-5.93 ppm. The signals for the NH protons appear as a broad singlet at 11.35-10.95 ppm, while signals for the NCH_3 protons appear as a sharp singlet at 3.42-3.21 ppm. The ^{1}H NMR spectra of polycyclic diones **4a-k** lack signals for SCH_2 and NCH_2CO groups, but display signals for $NC(6)H_2$ as a broad pseudo singlet or two doublets at 5.54-5.23 ppm. The signals for the NH and NCH_3 protons are shifted somewhat downfield in comparison with the analogous signals in the spectra of nitriles **3a-h** and appear at 11.46-11.04 and 3.45-3.38 ppm, respectively. The ^{1}H NMR spectrum of salt **6f** shows only a slight shift in the signals relative to the spectrum of polycyclic dione **4f** and also lacks the NH proton signal at 11.37 ppm. The IR spectra of nitriles **3a-h** have absorption bands for a conjugated nitrile group at 2213-2230 cm^{-1} and carbonyl groups at 1665-1720 cm^{-1}, while the IR spectra of polycyclic diones **4** lack CN group absorption bands. The absorption band for the C(8)=N(7) fragment is most often observed at 1630-1660 cm^{-1} as a shoulder on the strong C=O band. The spectral data for products **3** and **4** are given in Table 1.

Thus, the reaction of 3-cyanopyridine-2(1*H*)-thiones with 8-chloromethyl-3-methyl-7-(2-oxo-2-phenylethyl)xanthene in the presence of KOH proceeds as a cascade process to give polycyclic products, namely, pyrido[3",2":4',5']thieno[3',2':5,6][1,4]diazepino[7,1-*f*]purine-2,4(3*H*,6*H*)-dione derivatives. The intermediates of this cascade reaction have been isolated and characterized.

EXPERIMENTAL

The IR spectra were recorded on an IKS-29 spectrophotometer for vaseline mulls. The ^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer (500 MHz) for compounds **3a-c**,**e**,**f** and **4a-d** and a Varian

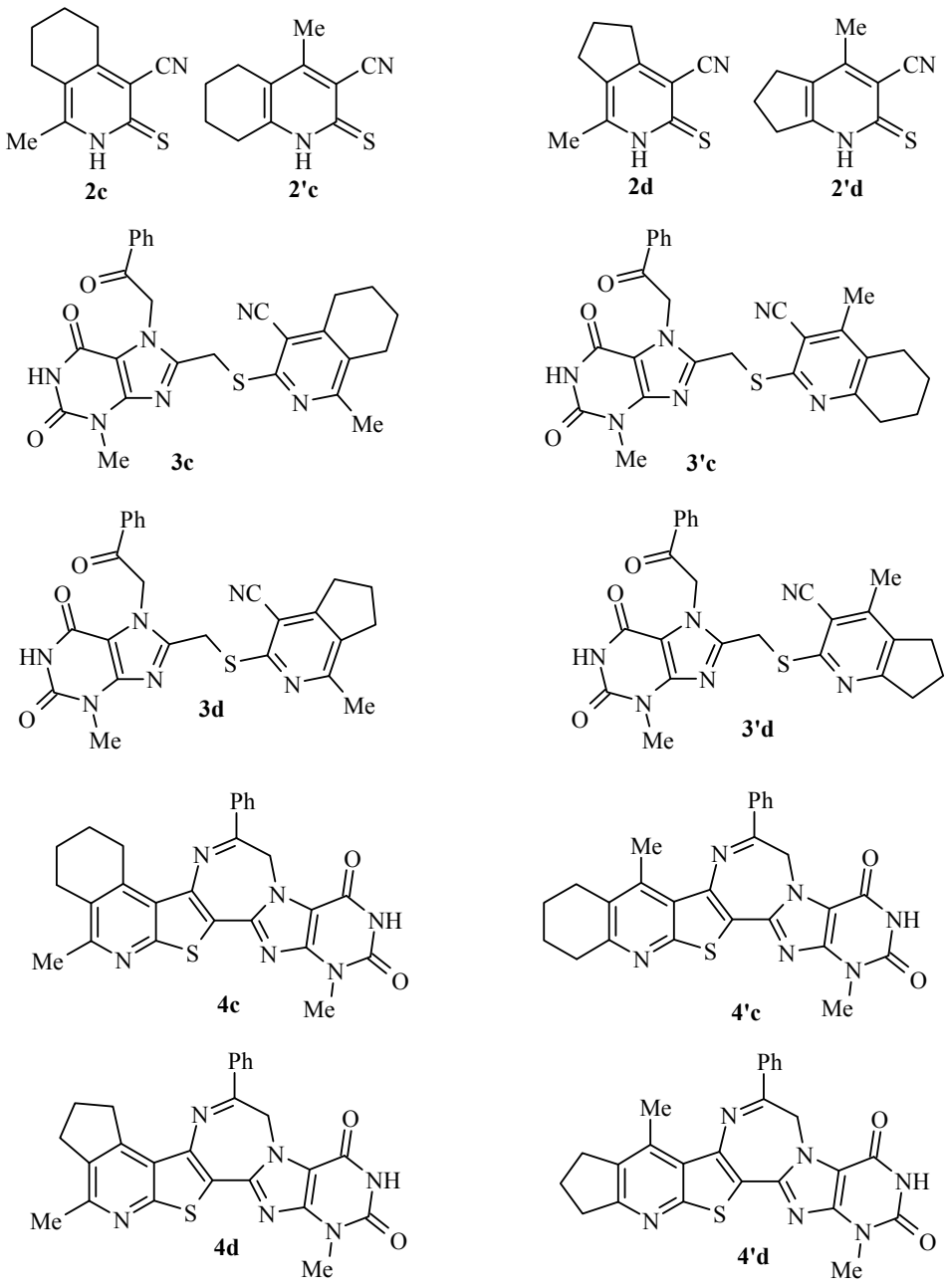


Fig. 1. Structure of regioisomeric compounds **2c-4c**, **2'c-4'c**, **2d-4d**, and **2'd-4'd**.

Unity Plus spectrometer (400 MHz) for the other compounds. The solvent was DMSO-d_6 with TMS as internal standard. The IR spectra of starting 8-chloromethyl-3-methyl-7-(2-oxo-2-phenylethyl)xanthene (**1**) and its hydroxymethyl precursor were recorded on a Specord M-80 spectrometer for KBr pellets. The ^{1}H NMR spectra for these compounds were recorded on a Varian Gemini 200 spectrometer (200 MHz) in DMSO-d_6 with TMS as internal standard. The elemental analyses were carried out on a Perkin Elmer CHN Analyzer. The melting points were determined on a Koefler hot stage and not corrected. The purity of the products was checked by thin-layer chromatography on Silufol UV-254 plates using 1:1 acetone–hexane as the eluent and visualization by UV light and iodine vapor.

TABLE 1. Spectral Characteristics for Compounds **3a-h** and **4a-k**

Compound	IR spectrum, ν, cm^{-1}			^{1}H NMR spectrum, δ, ppm (*J*, Hz)							
	NH	C≡N	C=O	R	R^1	R^2	SCH_2 (2H)	NCH_2 (2H)	COPh	NCH_3 (1H, s)	NH (1H, br. s)
1	2	3	4	5	6	7	8	9	10	11	12
3a	3145	2230	1693, 1720	2.84-2.76 (2H, m, CH_2); 2.70-2.61 (2H, m, CH_2); 1.66-1.54 (4H, m) and 1.32-1.20 (4H, m, $(CH_2)_4$)		7.90 (1H, s, CH)	4.76 (br. pseudo s)	6.01 (br. pseudo s)	8.00-7.94 (2H, m, H-2,6); 7.76-7.69 (1H, m, H-4); 7.62-7.55 (2H, m, H-3,5)	3.21	11.00
3b	3165	2224	1665, 1695, 1705	2.83-2.78 (2H, m, CH_2); 2.16-2.09 (2H, m, CH_2); 1.64-1.55 (4H, m, $(CH_2)_2$)		7.69-7.34 (4H, m, 2-ClC_6H_4)	4.83 (d, ^2J = 14.9); 4.77 (d, ^2J = 14.9)	6.09 (br. pseudo s)	8.02 (2H, br. d, ^3J = 7.8, H-2,6); 7.77-7.54 (3H, m, H-3,4,5)	3.39	11.14
3c+3'c*	3150	2218	1680, 1703	2.70-2.65 (2H, m, CH_2); 2.36-2.30 (2H, m, CH_2); 2.25-2.22 (3H, s, CH_3); 1.70-1.62 (4H, m, $(CH_2)_2$)			Major isomer **3c**: 4.81 (br. pseudo s). Minor isomer **3'c**: 4.76 (br. pseudo s)	5.93 (br. pseudo s)	7.86 (2H, br. d, ^3J = 7.8, H-2,6); 7.73-7.71 (1H, m, H-4); 7.56 (2H, dd, ^3J = 7.8, ^3J = 7.4, H-3,5)	3.38	11.15
3d+3'd*	3180	2213	1670, 1698, 1710	Major isomer **3d**: 2.82-2.78 (2H, m, CH_2); 2.72-2.69 (2H, m, CH_2); 2.29 (3H, s, CH_3); 1.96-1.92 (2H, m, CH_2). Minor isomer **3'd**: 2.93-2.90 (2H, m, CH_2); 2.74-2.72 (2H, m, CH_2); 2.26 (3H, s, CH_3); 2.06-2.02 (2H, m, CH_2)			**3d**: 4.74 (br. pseudo s). **3'd**: 4.80 (br. pseudo s)	**3d**: 5.98 (br. pseudo s). **3'd**: 5.95 (br. pseudo s)	7.93 (2H, br. d, ^3J = 7.6, H-2,6, major isomer); 7.90 (2H, br. d, ^3J = 7.2, H-2,6, minor isomer); 7.75-7.71 (1H, m, H-4); 7.61-7.55 (2H, m, H-3,5)	**3d**: 3.39 **3'd**: 3.42	**3d**: 11.05 **3'd**: 11.35
3e	3160	2225	1700, 1709	2.81-2.77 (1H, m, CH); 2.64-2.60 (2H, m, CH_2); 2.27-2.21 (1H, m, CH); 1.86-1.81 (1H, m, CH); 1.19-1.09 (2H, m, CH_2); 0.89 (9H, s, $C(CH_3)_3$)		7.85 (1H, s, CH)	4.79 (d, ^2J = 15.2); 4.75 (d, ^2J = 15.2)	5.95 (br. pseudo s)	7.86 (2H, br. d, ^3J = 7.4, H-2,6); 7.74-7.71 (1H, m, H-4); 7.57 (2H, dd, ^3J = 7.8, ^3J = 7.4, H-3,5)	3.38	11.14
3f	3160	2220	1680, 1700	6.99 (1H, s, CH); 2.35 (3H, s, CH_3); 2.33 (3H, s, CH_3)			4.77 (br. pseudo s)	6.02 (br. pseudo s)	7.97 (2H, br. d, ^3J = 8.0, H-2,6); 7.75-7.72 (1H, m, H-4); 7.59 (2H, dd, ^3J = 7.5, ^3J = 8.0, H-3,5)	3.38	11.15
3g	3150	2222	1685, 1710	2.82-2.76 (2H, m, CH_2); 2.27-2.21 (2H, m, CH_2); 1.71-1.62 (2H, m, CH_2); 1.59-1.52 (2H, m, CH_2)		7.62-7.60 (2H, m, H-3,5); 7.33 (2H, br. d, ^3J = 8.0, H-2,6)	4.79 (br. pseudo s)	6.02 (br. pseudo s)	8.03 (2H, br. d, ^3J = 7.2, H-2,6); 7.76-7.73 (1H, m, H-4); 7.62-7.60 (2H, m, H-3,5)	3.40	10.95
3h	3150	2217	1681, 1712	8.37 (2H, br. d, ^3J = 6.0, H Ph); 7.89 (1H, s, CH); 7.61-7.51 (8H, m, H Ph)			4.97 (br. pseudo s)	6.05 (br. pseudo s)	7.95 (2H, br. d, ^3J = 7.6, H-2,6); 7.73-7.68 (3H, m, H-3,4,5)	3.37	11.16
4a	3160	—	1695	3.16-3.12 (2H, m, CH_2); 3.05-2.98 (2H, m, CH_2); 1.85-1.74 (4H, m, $(CH_2)_2$); 1.43-1.36 (4H, m, $(CH_2)_2$)		8.25 (1H, s, CH)	—	5.54 (br. pseudo s)	8.46-8.40 (2H, m, H-2,6); 7.64-7.57 (3H, m, H-3,4,5)	3.44	11.25

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11
4b	3200	—	1665, 1700	3.14-3.08 (2H, m, CH_2); 2.49-2.45 (1H, m, CH); 2.34-2.27 (1H, m, CH); 1.93-1.83 (2H, m, CH_2); 1.82-1.67 (2H, m, CH_2)	7.64-7.44 (4H, m, H Ar)	—	5.23 (d, ^2J = 14.5); 5.39 (d, ^2J = 14.5)	7.52-7.33 (5H, m)	3.40	11.44
4c+4'c*	3165	—	1678, 1702	2.55 (3H, s, CH_3)	3.04-2.98 (2H, m, CH_2); 2.80-2.75 (2H, m, CH_2); 1.94-1.82 (4H, m, $(CH_2)_2$)	—	Major isomer **4c**: 5.43 (br. pseudo s). Minor isomer **4'c**: 5.46 (br. pseudo s)	8.33-8.28 (2H, m, H-2,6); 7.60-7.55 (3H, m, H-3,4,5)	3.41	11.04
4d+4'd*	3170	—	1678, 1710	2.58 (3H, s, CH_3)	Major isomer **4d** 3.50-3.43 (2H, m, CH_2); 3.03-2.96 (2H, m, CH_2); 2.26-2.14 (2H, m, CH_2). Minor isomer **4'd**: 3.62-3.58 (2H, m, CH_2); 3.11-3.04 (2H, m, CH_2); 2.40-2.34 (2H, m, CH_2)	—	5.44 (br. pseudo s)	8.36-8.29 (2H, m, H-2,6); 7.61-7.56 (3H, m, H-3,4,5)	3.38	11.36
4e	3160	—	1681	2.91-2.68 (3H, m, 3CH); 2.37-2.30 (1H, m, CH); 2.16-2.07 (1H, m, CH); 1.63-1.49 (2H, m, CH_2); 1.01 (9H, s, $C(CH_3)_3$)	8.23 (1H, s, CH)	—	5.53 (br. pseudo s)	8.45-8.40 (2H, m, H-2,6); 7.63-7.57 (3H, m, H-3,4,5)	3.44	11.16
4f	3160	—	1688, 1720	2.62 (3H, s, CH_3); 7.29 (1H, s, CH)	2.86 (3H, s, CH_3)	—	5.46 (br. pseudo s)	8.37-8.30 (2H, m, H-2,6); 7.63-7.57 (3H, m, H-3,4,5)	3.41	11.37
4g	3185	—	1685, 1698	2.68-2.62 (2H, m, CH_2); 2.39-2.35 (2H, m, CH_2); 2.02-1.98 (4H, m, $(CH_2)_2$)	7.61-7.19 (4H, m, H Ar) overlap with Ph	—	5.34 (br. pseudo s)	7.61-7.19 (5H, m) overlap with 4-ClC_6H_4)	3.40	11.43
4h	3185	—	1674, 1710	8.02 (1H, s, CH); 7.88-7.32 (10H, m, H Ph)		—	5.54 (br. pseudo s)	8.31 (2H, d, ^3J = 7.5, H-2,6); 7.61-7.55 (3H, m, H-3,4,5)	3.45	11.37
4i	3150	—	1670, 1720	3.56-3.43 (2H, m, CH_2); 2.82-2.76 (2H, m, CH_2); 2.25-2.18 (2H, m, CH_2)	8.73 (1H, s, CH)	—	5.54 (br. pseudo s)	8.42-8.40 (2H, m, H-2,6); 7.64-7.59 (3H, m, H-3,4,5)	3.40	11.39
4j	3165	—	1685, 1705	3.32-3.23 (2H, m, CH_2); 2.70-2.65 (2H, m, CH_2); 2.63-2.59 (2H, m, CH_2); 1.82-1.54 (4H, m, $(CH_2)_2$)	7.61-7.35 (4H, m, H Ar) overlap with Ph	—	5.40 (d, ^2J = 13.7); 5.23 (d, ^2J = 13.7)	7.61-7.35 (5H, m) overlap with 2-ClC_6H_4	3.40	11.44
4k	3165	—	1683	3.12-3.06 (2H, m, CH_2); 2.67-2.60 (2H, m, CH_2); 1.93-1.86 (2H, m, CH_2); 1.80-1.71 (2H, m, CH_2)	7.79-7.76, 7.26-7.22, 7.20-7.16 (all 1H, m, thien-2-yl)	—	5.37 (br. pseudo s)	7.63 (2H, br. d, ^3J = 7.2, H-2,6); 7.50-7.47 (1H, m, H-4); 7.39 (2H, dd, ^3J = 7.2, ^3J = 7.2, H-3,5)	3.41	11.46

*The signals of individual protons of the regioisomeric products were not found in the ^{1}H NMR spectra due to complete coincidence of their chemical shifts.

8-Chloromethyl-3-methyl-7-(2-oxo-2-phenylethyl)xanthene (1). A solution of NaOH (8.0 g, 0.2 mol) in water (50 ml) was added to 8-hydroxymethyl-3-methylxanthene [43] (39.2 g, 0.2 mol) in warm water (150 ml) and heated until the solid dissolved. The solvent was removed in vacuum to give a solid residue, which was washed on the filter with acetone and dried at 70-75°C to give the 8-hydroxymethyl-3-methyl-xanthene sodium salt. Yield 43.0 g (98%); mp >360°C. This product was used without further purification.

A mixture of 8-hydroxymethyl-3-methylxanthene sodium salt (2.18 g, 10 mmol) and phenacyl bromide (2.39 g, 12 mmol) in DMF (15 ml) was heated at reflux for 2 h. The reaction mixture was cooled and poured into water (50 ml). The precipitate formed was filtered off and recrystallized from ethyl cellosolve to give 8-hydroxymethyl-3-methyl-7-(2-oxo-2-phenylethyl)xanthene. Yield 2.14 g (68%). Mp 269-270°C. IR spectrum, ν, cm^{-1}: 1615-1550 (C=N), 1715-1696 (3C=O), 3120 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.09 (1H, s, NH); 8.06-7.51 (5H, m, H Ph); 5.95 (2H, s, NCH_2); 5.62 (1H, t, *J* = 6.0, $CH_2O\underline{H}$); 4.54 (2H, br. pseudo d, *J* = 6.0, $C\underline{H_2}OH$); 3.42 (3H, s, NCH_3). Found, %: C 57.32; H 4.53; N 17.80. $C_{15}H_{14}N_4O_4$. Calculated, %: C 57.32; H 4.49; N 17.83.

A mixture of 8-hydroxymethyl-3-methyl-7-(2-oxo-2-phenylethyl)xanthene (3.14 g, 0.01 mol) and $SOCl_2$ (35 ml) was heated for 6 h at reflux on an oil bath. Excess $SOCl_2$ was removed in vacuum to give 8-chloromethyl-3-methyl-7-(2-oxo-2-phenylethyl)xanthene (**1**). Yield 3.23 g (97%); mp 255-257°C (dioxane). IR spectrum, ν, cm^{-1}: 1610-1555 (C=N), 1705-1690 (3C=O), 3100 (N–H). ^{1}H NMR spectrum, δ, ppm: 11.21 (1H, s, NH); 8.12-7.56 (5H, m, H Ph); 5.99 (2H, s, NCH_2); 4.97 (2H, s, CH_2Cl); 3.36 (3H, s, NCH_3). Found, %: C 54.10; H 4.01; N 16.82. $C_{15}H_{13}ClN_4O_3$. Calculated, %: C 54.15; H 3.94; N 16.84.

2-Thioxo-1,2,5,6,7,8,9,10-octahydrocycloocta[*b*]pyridine-3-carbonitrile (2a) was obtained according to a published procedure [47, 48]. **4-(2-Chlorophenyl)-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (2b), 4-(4-chlorophenyl)-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (2g), 4-(2-chlorophenyl)-2-thioxo-2,5,6,7,8,9-hexahydro-1*H*-cyclopenta[*b*]pyridine-3-carbonitrile (2j),** and **4-(2-thienyl)-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (2k)** were synthesized by the reaction of *N*-(cyclohexen-1-yl)morpholine or *N*-(cyclohepten-1-yl)morpholine with 3-aryl- or 3-hetaryl-2-cyanoprop-2-enethioamides according Sharanin et al. [49-51]. **4,6-Dimethyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (2f)** was obtained quantitatively by the reaction of cyanothioacetamide with acetylacetone [52], **4,6-diphenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (2h)** was synthesized according to Krauze et al. [53]. **5-Oxo-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (2i)** was synthesized by the reaction of 2-(*N*-phenylaminomethylene)-1,3-cyclohexanedione with cyanothioacetamide [54]. **1-Methyl-3-thioxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (2c)** and **1-methyl-3-thioxo-3,5,6,7-tetrahydro-2*H*-cyclopenta[*c*]pyridine-4-carbonitrile (2d)** were synthesized by the reaction of the 2-acetylcycloalkanones with cyanothioacetamide [46]. Refined data on the structure of these products were given in our previous work [45].

6-*tert*-Butyl-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (2e). A solution of 4-*tert*-butylcyclohexanone (10.0 g, 64.8 mmol) and ethyl formate (dried over potassium carbonate) (7.0 ml, 87 mmol) in absolute ether (50 ml) was added dropwise with vigorous stirring and cooling with ice and salt bath to a suspension of potassium *tert*-butoxide (7.3 g, 65 mmol) in absolute ether (100 ml). An exothermic reaction was observed, the mixture turned yellow and viscous. The reaction mixture was stirred for 6 h and then maintained for 24 h at 4°C. The precipitate was filtered off, washed with ether and acetone, and dried at 20°C to give 12.3 g (86%) of 4-*tert*-butyl-2-formylcyclohexanone potassium salt, which was used immediately in the following reaction.

A mixture of 4-*tert*-butyl-2-formylcyclohexanone potassium salt (12.3 g, 55.8 mmol), cyanothioacetamide (5.6 g, 55.9 mmol), and acetic acid (4.0 ml, 70.0 mmol) in 96% ethanol (25 ml) was heated slowly to reflux with stirring. The suspension formed was stirred for 6 h at 20°C. The precipitate was filtered off to give carbonitrile **2e**. Yield 8.4 g (61%). Bright-yellow powder, decomp. temp. 305-310°C. IR spectrum, ν, cm^{-1}: 3195 (NH), 2227 (C≡N), 1605 (C=C). ^{1}H NMR spectrum (500 MHz), δ, ppm: 13.91 (1H, br. s, NH); 7.89 (1H, s, H-4); 2.91-2.83 (1H, m, CH); 2.70-2.57 (2H, m, CH_2); 2.26-2.21 (1H, m,CH); 1.96-1.93 (1H, m, CH);

1.39-1.23 (2H, m, 7-CH_2); 0.90 (9H, s, $C(CH_3)_3$). Found, %: C 68.26; H 7.35; N 11.44. $C_{14}H_{18}N_2S$. Calculated, %: C 68.25; H 7.36; N 11.37.

2-({[3-Methyl-2,6-dioxo-7-(2-oxo-2-phenylethyl)-2,3,6,7-tetrahydro-1H-purin-8-yl]methyl}thio)pyridine-3-carbonitriles 3a-h (General Method A). A suspension of 3-cyanopyridine-2(1*H*)-thione **2a-h** (1.50 mmol) in warm DMF (3.0 ml) was treated with 10% aqueous KOH solution (0.8 ml, 1.56 mmol). A solution of 8-(chloromethyl)-3-methyl-7-(2-oxo-2-phenylethyl)xanthene (**1**) (0.5 g, 1.50 mmol) in DMF (1.0 ml) was added to the obtained solution of the corresponding potassium pyridine-2-thiolate. A precipitate formed after a few seconds. The reaction mixture was stirred for 3-4 h at 15°C and diluted by adding an equal volume of ethanol. After 2 h, the precipitate formed was filtered off, washed consecutively with ethanol, water, ethanol, and petroleum ether, and dried at 60°C to give carbonitriles **3a-h** as analytically pure compounds.

2-({[3-Methyl-2,6-dioxo-7-(2-oxo-2-phenylethyl)-2,3,6,7-tetrahydro-1*H*-purin-8-yl]methyl}thio)-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyridine-3-carbonitrile (3a). Yield 0.53 g (69%). Pale-yellow powder, mp 280-282°C. Found, %: C 62.77; H 5.09; N 16.40. $C_{27}H_{26}N_6O_3S$. Calculated, %: C 63.02; H 5.09; N 16.33.

4-(2-Chlorophenyl)-2-({[3-methyl-2,6-dioxo-7-(2-oxo-2-phenylethyl)-2,3,6,7-tetrahydro-1*H*-purin-8-yl]methyl}thio)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (3b). Yield 0.63 g (70%). Beige powder, mp 285-287°C. Found, %: C 62.38; H 4.20; N 14.26. $C_{31}H_{25}ClN_6O_3S$. Calculated, %: C 62.36; H 4.22; N 14.07.

1-Methyl-3-({[3-methyl-2,6-dioxo-7-(2-oxo-2-phenylethyl)-2,3,6,7-tetrahydro-1*H*-purin-8-yl]methyl}-thio)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (3c) and 4-Methyl-2-({[3-methyl-2,6-dioxo-7-(2-oxo-2-phenylethyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl]methyl}thio)-5,6,7,8-tetrahydroisoquinoline-3-carbonitrile (3'c) (~9:2 ratio). Yield 0.40 g (53%). Sand-colored powder, mp 249-260°C (decomp.). Found, %: C 62.13; H 4.88; N 16.85. $C_{26}H_{24}N_6O_3S$. Calculated, %: C 62.39; H 4.83; N 16.79.

1-Methyl-3-({[3-methyl-2,6-dioxo-7-(2-oxo-2-phenylethyl)-2,3,6,7-tetrahydro-1*H*-purin-8-yl]methyl}-thio)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-4-carbonitrile (3d) and 4-Methyl-2-({[3-methyl-2,6-dioxo-7-(2-oxo-2-phenylethyl)-2,3,6,7-tetrahydro-1*H*-purin-8-yl]methyl}thio)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carbonitrile (3'd) (~5:3 ratio). Yield 0.47 g (64%). Pale-brown powder, mp 263-268°C (decomp.). Found, %: C 62.02; H 4.58; N 17.25. $C_{25}H_{22}N_6O_3S$. Calculated, %: C 61.72; H 4.56; N 17.27.

6-*tert*-Butyl-2-({[3-methyl-2,6-dioxo-7-(2-oxo-2-phenylethyl)-2,3,6,7-tetrahydro-1*H*-purin-8-yl]methyl}-thio)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (3e). Yield 0.51 g (63%). Fine, white crystalline powder, mp 263-265°C. Found, %: C 64.12; H 5.58; N 15.65. $C_{29}H_{30}N_6O_3S$. Calculated, %: C 64.19; H 5.57; N 15.49.

4,6-Dimethyl-2-({[3-methyl-2,6-dioxo-7-(2-oxo-2-phenylethyl)-2,3,6,7-tetrahydro-1*H*-purin-8-yl]methyl}-thio)nicotinonitrile (3f). Yield 0.46 g (66%). Yellow powder, mp 260-265°C (decomp., AcOH). Found, %: C 60.22; H 4.40; N 18.33. $C_{23}H_{20}N_6O_3S$. Calculated, %: C 59.99; H 4.38; N 18.25.

4-(4-Chlorophenyl)-2-({[3-methyl-2,6-dioxo-7-(2-oxo-2-phenylethyl)-2,3,6,7-tetrahydro-1*H*-purin-8-yl]methyl}thio)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (3g). Yield 0.49 g (55%). Flesh-colored powder, mp 260-261°C. Found, %: C 62.20; H 4.25; N 14.30. $C_{31}H_{25}ClN_6O_3S$. Calculated, %: C 62.36; H 4.22; N 14.07.

2-({[3-Methyl-2,6-dioxo-7-(2-oxo-2-phenylethyl)-2,3,6,7-tetrahydro-1*H*-purin-8-yl]methyl}thio)-4,6-diphenylnicotinonitrile (3h). Yield 0.65 g (74%). White powder, mp 286-288°C (decomp.). Found, %: C 67.67; H 4.17; N 14.50. $C_{33}H_{24}N_6O_3S$. Calculated, %: C 67.79; H 4.14; N 14.37.

Pyrido[3",2":4',5']thieno[3',2':5,6][1,4]diazepino[7,1-*f*]purine-2,4(3*H*,6*H*)-diones 4a-h (General Method A). Carbonitrile **3a-h** (1.00 mmol) was dissolved in DMF (3-4 ml) at reflux and 10% aqueous potassium hydroxide solution (0.8 ml, 1.56 mmol) was added dropwise with stirring. The mixture darkened, and a potassium salt **6a-h** precipitated. The suspension was stirred and heated at reflux for 1-2 min and cooled. Acetic acid (1-2 ml) was added, and the reaction mixture turned a lighter color. After 2 h, the precipitate was filtered off, washed consecutively with ethanol, water, hot ethanol, and petroleum ether, and dried at 60°C to give diones **4a-h** as analytically pure samples.

Pyrido[3",2":4',5']thieno[3',2':5,6][1,4]diazepino[7,1-*f*]purine-2,4(3*H*,6*H*)-diones 4a-k (General Method B). A suspension of 3-cyanopyridine-2-(1*H*)-thione **2a-k** (0.80 mmol) in warm DMF (3-4 ml) was

treated with 10% aqueous potassium hydroxide solution (0.5 ml, 0.97 mmol) and stirred until full dissolution. Then, 8-chloromethyl-3-methyl-7-(2-oxo-2-phenylethyl)xanthene (**1**) (0.27 g, 0.81 mmol) was added to the obtained solution. A precipitate of alkylation product **3a-k** formed after several seconds. The reaction mixture was carefully heated at reflux for 3-5 min with continuous stirring. Then, an excess of 10% aqueous potassium hydroxide solution (1.0 ml, 1.95 mmol) was added dropwise. The precipitate of **3a-k** dissolved, and a precipitate of potassium salt **6a-k** formed immediately. The mixture was heated carefully at reflux with stirring for 1-2 min, stirred for 1 h at 25-30°C, treated with acetic acid (1.0-1.5 ml) or several drops of hydrochloric acid to achieve pH 4-5. An equal volume of ethanol was added. After 2 h the precipitate was filtered off, washed consecutively with ethanol, water, hot ethanol, acetone, and petroleum ether, and dried at 60°C to give products **4a-k** as analytically pure samples.

1-Methyl-7-phenyl-10,11,12,13,14,15-hexahydro-1*H*-cycloocta[5",6"]pyrido[3",2":4',5']thieno-[3',2':5,6][1,4]diazepino[7,1-*f*]purine-2,4(3*H*,6*H*)-dione (4a). Yield 0.38 g (77%, method A), 0.27 g (69%, method B). Bright-yellow powder, mp > 300°C. Found, %: C 65.22; H 4.89; N 16.90. $C_{27}H_{24}N_6O_2S$. Calculated, %: C 65.30; H 4.87; N 16.92.

9-(2-Chlorophenyl)-1-methyl-7-phenyl-10,11,12,13-tetrahydro-1*H*-purino[7",8":1',7'][1,4]diazepino-[5',6':4,5]thieno[2,3-*b*]quinoline-2,4(3*H*,6*H*)-dione (4b). Yield 0.42 g (72%, method A), 0.25 g (54%, method B). Bright-yellow powder, mp > 300°C. Found, %: C 64.12; H 3.98; N 14.66. $C_{31}H_{23}ClN_6O_2S$. Calculated, %: C 64.30; H 4.00; N 14.51.

2,14-Dimethyl-8-phenyl-3,4,5,6-tetrahydro-9*H*-purino[7",8":1',7'][1,4]diazepino[5',6':4,5]thieno-[2,3-*c*]isoquinoline-11,13(12*H*,14*H*)-dione (4c) and 1,9-Dimethyl-7-phenyl-10,11,12,13-tetrahydro-1*H*-purino[7",8":1',7'][1,4]diazepino[5',6':4,5]thieno[2,3-*b*]quinoline-2,4(3*H*,6*H*)-dione (4'c) (the regioisomer ratio was not determined). Yield 0.36 g (75%, method A), 0.26 g (61%, method B). Yellow powder, mp > 300°C. Found, %: C 64.42; H 4.65; N 17.36. $C_{26}H_{22}N_6O_2S$. Calculated, %: C 64.71; H 4.60; N 17.42.

2,13-Dimethyl-7-phenyl-4,5-dihydro-3*H*,8*H*-cyclopenta[4",5"]pyrido[3",2":4',5']thieno[3',2':5,6]-[1,4]diazepino[7,1-*f*]purine-10,12(11*H*,13*H*)-dione (4d) and 1,9-Dimethyl-7-phenyl-11,12-dihydro-1*H*,6*H*-cyclopenta[5",6"]pyrido[3",2":4',5']thieno[3',2':5,6][1,4]diazepino[7,1-*f*]purine-2,4(3*H*,10*H*)-dione (4'd) (regioisomer ratio ~9:4). Yield 0.38 g (80%, method A), 0.24 g (65%, method B). Bright-yellow powder, mp > 300°C. Found, %: C 64.01; H 4.32; N 18.06. $C_{25}H_{20}N_6O_2S$. Calculated, %: C 64.09; H 4.30; N 17.94.

11-*tert*-Butyl-1-methyl-7-phenyl-10,11,12,13-tetrahydro-1*H*-purino[7",8":1',7'][1,4]diazepino[5',6':4,5]-thieno[2,3-*b*]quinoline-2,4(3*H*,6*H*)-dione (4e). Yield 0.42 g (79%, method A), 0.26 g (63%, method B). Bright-yellow powder, mp > 300°C. Found, %: C 66.25; H 5.42; N 16.16. $C_{29}H_{28}N_6O_2S$. Calculated, %: C 66.39; H 5.38; N 16.02.

1,9,11-Trimethyl-7-phenyl-1*H*-pyrido[3",2":4',5']thieno[3',2':5,6][1,4]diazepino[7,1-*f*]purine-2,4(3*H*,6*H*)-dione (4f). Yield 0.40 g (90%, method A), 0.26 g (72%, method B). Bright-yellow powder, mp > 300°C. Found, %: C 62.20; H 4.13; N 19.01. $C_{23}H_{18}N_6O_2S$. Calculated, %: C 62.43; H 4.10; N 18.99.

9-(4-Chlorophenyl)-1-methyl-7-phenyl-10,11,12,13-tetrahydro-1*H*-purino[7",8":1',7'][1,4]diazepino-[5',6':4,5]thieno[2,3-*b*]quinoline-2,4(3*H*,6*H*)-dione (4g). Yield 0.42 g (73%, method A), 0.24 g (52%, method B). Bright-yellow powder, mp > 300°C. Found, %: C 64.16; H 4.03; N 14.74. $C_{31}H_{23}ClN_6O_2S$. Calculated, %: C 64.30; H 4.00; N 14.51.

1-Methyl-7,9,11-triphenyl-1*H*-pyrido[3",2":4',5']thieno[3',2':5,6][1,4]diazepino[7,1-*f*]purine-2,4(3*H*,6*H*)-dione (4h). Yield 0.42 g (74%, method A), 0.27 g (59%, method B). Bright-yellow powder, mp > 300°C. Found, %: C 69.76; H 3.95; N 14.99. $C_{33}H_{22}N_6O_2S$. Calculated, %: C 69.95; H 3.91; N 14.83.

1-Methyl-7-phenyl-12,13-dihydro-1*H*-purino[7",8":1',7'][1,4]diazepino[5',6':4,5]thieno[2,3-*b*]quinoline-2,4,10(3*H*,6*H*,11*H*)-trione (4i). Yield 0.23 g (59%, method B). Red-brown powder, mp > 300°C. Found, %: C 62.05; H 3.78; N 17.59. $C_{25}H_{18}N_6O_3S$. Calculated, %: C 62.23; H 3.76; N 17.42.

9-(2-Chlorophenyl)-1-methyl-7-phenyl-11,12,13,14-tetrahydro-1*H*,6*H*-cyclohepta[5",6"]pyrido-[3",2":4',5']thieno[3',2':5,6][1,4]diazepino[7,1-*f*]purine-2,4(3*H*,10*H*)-dione (4j). Yield 0.42 g (88%, method B).

Bright-yellow powder, mp > 300°C. Found, %: C 64.45; H 4.29; N 14.39. $C_{32}H_{25}ClN_6O_2S$. Calculated, %: C 64.80; H 4.25; N 14.17.

1-Methyl-7-phenyl-9-(2-thienyl)-10,11,12,13-tetrahydro-1*H*-purino[7",8":1',7']\[1,4]diazepino[5',6':4,5]-thieno[2,3-*b*]quinoline-2,4(3*H*,6*H*)-dione (4k). Yield 0.20 g (45%, method B). Bright-yellow powder, mp > 300°C. Found, %: C 62.95; H 4.09; N 15.47. $C_{29}H_{22}N_6O_2S_2$. Calculated, %: C 63.25; H 4.03; N 15.26.

1,9,11-Trimethyl-7-phenyl-1*H*-pyrido[3",2":4',5']thieno[3',2':5,6]\[1,4]diazepino[7,1-*f*]purine-2,4(3*H*,6*H*)-dione Potassium Salt (6f). A suspension of 3-cyanopyridine-4,6-dimethyl-2(1*H*)thione (**2f**) [52] (0.115 g, 0.70 mmol) in warm DMF (1.8 ml) was treated with 10% aqueous potassium hydroxide solution (0.4 ml, 0.78 mmol) and stirred until full dissolution. 8-(Chloromethyl)-3-methyl-7-(2-oxo-2-phenylethyl)-xanthene (**1**) (0.232 g, 0.70 mmol) was added to the solution formed. A precipitate of the alkylation product **3f** formed immediately. The reaction mixture was carefully heated at reflux for 3-5 min with continuous stirring, and 10% aqueous potassium hydroxide solution (0.6 ml, 1.17 mmol) was added dropwise. The precipitate of compound **3f** dissolved, and a new precipitate of potassium salt **6f** formed immediately. The mixture was heated carefully at reflux with stirring for 1-2 min and stirred for 1 h at 15°C. An equal volume of ethanol was added. After 2 h, the precipitate was filtered off, washed consecutively with ethanol, water, acetone, and petroleum ether, and dried at 60°C to give salt **6f** as an analytically pure sample. Yield 0.252 g (75%). Yellow powder, mp > 300°C. IR spectrum, ν, cm^{-1}: 1710, 1680, 1635, 1605. ^{1}H NMR spectrum, δ, ppm: 8.41-8.38 (2H, m, H-2,6 Ph); 7.60-7.58 (3H, m, H-3,5 Ph); 7.28 (1H, s, H-10); 5.52 (2H, br. pseudo s, NCH_2); 3.40 (3H, s, NCH_3); 2.88 (3H, s, CH_3); 2.62 (3H, s, CH_3). Found, %: C 57.31; H 3.60; N 17.62. $C_{23}H_{17}KN_6O_2S$. Calculated, %: C 57.48; H 3.57; N 17.49.

6-Methyl-2-({\[3-methyl-2,6-dioxo-7-(2-oxo-2-phenylethyl)-2,3,6,7-tetrahydro-1*H*-purin-8-yl]methyl}-thio)-4-oxo-1,4-dihydropyridine-3-carbonitrile (8). 8-Chloromethyl-3-methyl-7-(2-oxo-2-phenylethyl)xanthene (**1**) (0.196 g, 0.59 mmol) was added to a solution of triethylammonium 3-cyano-6-methyl-4-oxo-1,4-dihydro-pyridine-2-thiolate (**7**) [44] (0.150 g, 0.56 mmol) in warm DMF (2.0 ml), and the mixture was heated to reflux with stirring. Then, 10% aqueous potassium hydroxide solution (0.4 ml, 0.78 mmol) was added dropwise to the dark solution formed, heated at reflux carefully for 2-3 min, and left for 24 h at 15°C. Several drops of concentrated hydrochloric acid were added to the reaction mixture to achieve pH 3-4, and the mixture was diluted by adding water (6 ml). After five days the precipitate was filtered off, washed consecutively with ethanol, water, acetone, and petroleum ether, and dried at 60°C to give carbonitrile **8** as an analytically pure sample. Yield 0.197 g (76%). Brown powder, mp 232-235°C (decomp.). IR spectrum, ν, cm^{-1}: 3165 (NH); 2221 (C≡N); 1715-1680 (4C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.03 (1H, br. s, NH xanthene); 7.98 (2H, br. d, *J* = 7.6, H-2,6 Ph); 7.75-7.71 (1H, m, H-4 Ph); 7.58 (2H, dd *J* = 7.6, *J* = 7.6, H-3,5 Ph); 6.53 (1H, s, H-5 Py); 6.01 (2H, br. pseudo s, NCH_2CO); 4.72 (2H, br. pseudo s, SCH_2); 3.38 (3H, s, NCH_3); 2.22 (3H, s, CH_3).

The pyridone fragment NH signal does not appear, presumably due to a tendency towards rapid deuterium exchange with water contained in the sample of DMSO-d_6 [44]. Found, %: C 57.29; H 3.96; N 18.27. $C_{22}H_{18}N_6O_4S$. Calculated, %: C 57.14; H 3.92; N 18.17.

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