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STUDY OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES. 54.* PROPERTIES AND CONVERSIONS OF PYRIMIDO[4,5-*b*]-1,4-BENZOTHIAZEPINES. SYNTHESIS OF A NOVEL HETEROCYCLIC SYSTEM: PYRIMIDO[5,4-*c*]ISOQUINOLINE

T. S. Safonova[1], M. P. Nemeryuk[1], N. A. Grineva[1], A. F. Keremov[2], O. S. Anisimova[1], and N. P. Solov'eva[1]

We have studied some properties and conversions of pyrimido[4,5-b]-1,4-benzothiazepines: reduction, oxidation, reactions with nucleophilic reagents (methanol, hydrazine, hydroxylamine, o-methylhydroxylamine, and thiosemicarbazide). We have synthesized derivatives of a novel heterocyclic system: pyrimido[5,4-c]isoquinoline.

Keywords: pyrimidyl aryl sulfides, pyrimido[4,5-*b*]-1,4-benzothiazepine, pyrimido[5,4-*c*]isoquinoline.

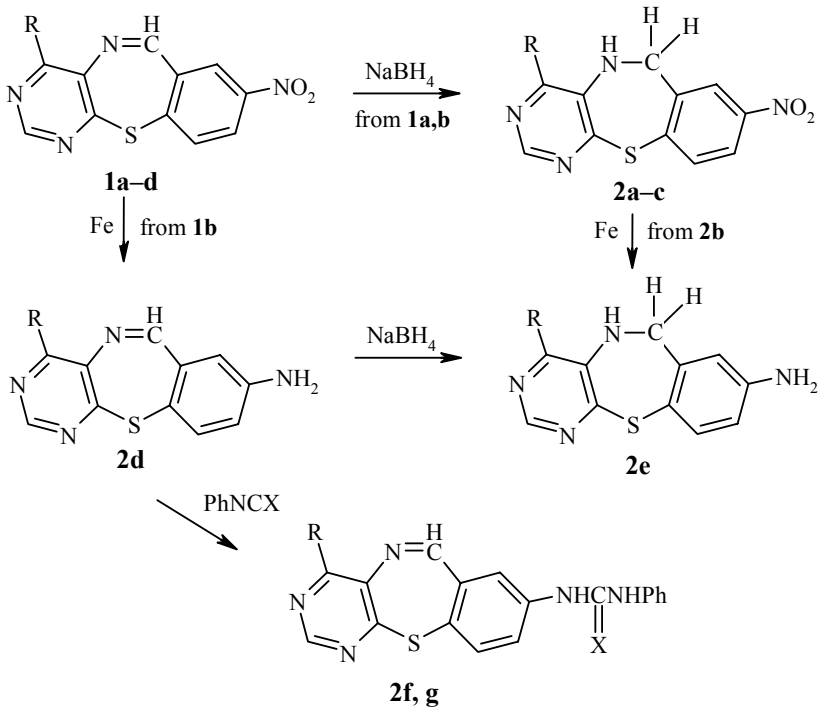
In previous work [2, 3], we described synthesis of derivatives of 1,4-thiazine tricyclic systems, which include substances with antitumor and psychotropic activity. In continuing these studies, we have developed a method for obtaining 4-alkoxy(amino)-8-nitro derivatives of pyrimido[4,5-*b*]-1,4-benzothiazepines **1a-d** [1]. This work is devoted to study of the properties of compounds **1a-d** and synthesis of novel derivatives of this heterocyclic system which are of interest for biological tests.

In the first step of this work, we studied reduction of pyrimidobenzothiazepines **1a-c**. We established that when these substances are treated with sodium borohydride in ethanol medium at 18-20°C, the dihydropyrimidobenzothiazepines **2a-c** are smoothly formed. Their structure has been confirmed by the presence of absorption bands in the IR spectra of compounds **2a,b** for the NH group in the 3280 cm^{-1} and 3380 cm^{-1} region respectively.

For the example of compounds **1b** and **2b**, we established that their reduction by iron filings in acetic acid leads to 8-amino derivatives **2d** and **2e**. The compound **2e** is also formed when pyrimidobenzothiazepine **2d** is treated with sodium borohydride under the conditions for synthesis of derivatives **2a-c**. Reactions of compound **2d** with phenyl isocyanate and phenyl isothiocyanate yield derivatives **2f,g**.

* For Communication 53, see [1].

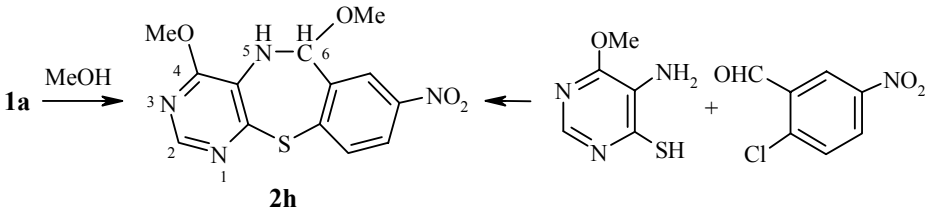
[1] Center for Drug Chemistry/All-Russian Scientific Research Pharmaceutical Chemistry Institute, Moscow 119815; e-mail: sedov@drug.org.ru. [2] Dagestan State University, Makhachkala 367010, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1863-1872, December, 2004. Original article submitted March 25, 2002.



1a, **2a** R = OMe, **1b**, **2b**,**d–g** R = NMe_2, **1c**, **2c** R = NHMe, **1d** R = NH_2; **2f** X = O; **2g** X = S

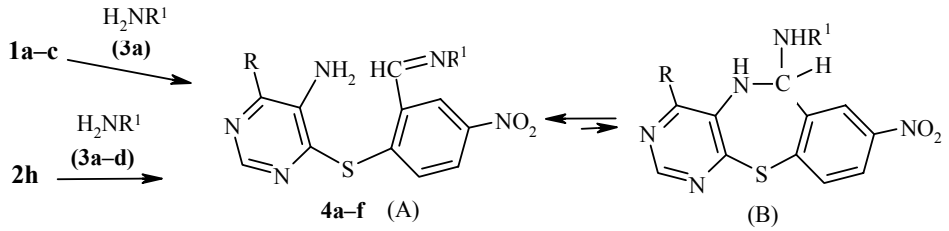
In this work, we also studied the reactivity of the azomethine group in pyrimidobenzothiazepines **1a-c** with respect to nucleophilic reagents. We observed that when compound **1a** is heated in methanol in the presence of KOH, a molecule of this alcohol is added to the azomethine group –N=CH– with formation of an –NH–CH(OMe)– bond. As a result, compound **1a** is smoothly converted to compound **2h** (89% yield).

Compound **2h** (90% yield) was also obtained by an alternate synthesis from 5-amino-6-mercapto-4-methoxypyrimidine and 6-chloro-3-nitrobenzaldehyde in methanol in the presence of 2 moles of KOH.



The structure of compound **2h** has been confirmed by the presence of an absorption band in the IR spectrum for the NH group at 3350 cm^{-1}. In the ^1H NMR spectrum in pyridine-d_5, besides signals from the two OMe groups at 3.75 ppm and 3.37 ppm we observe two doublet signals at 5.70 ppm and 6.54 ppm, each with an intensity of one proton unit. These signals are due to coupling of the H-5,6 protons, which is confirmed when we record the spectrum in the presence of deuteromethanol. In this case, as a result of substitution of the H-5 proton by deuterium, in the spectrum we observe only a singlet signal from the H-6 proton at 5.74 ppm.

The reactions of thiazepines **1a-c** with hydrazine hydrate **3a** occur with opening of the thiazepine ring, as a result of which pyrimidyl aryl sulfides **4a-c** are formed. We obtained compound **4a** and also substances **4d-f** with a similar structure by reaction of dihydrothiazepine **2h** with hydrazine hydrate, hydroxylamine (**3b**), O-methylhydroxylamine (**3c**), and thiosemicarbazide (**3d**) respectively.



3 a $R^1 = NH_2$, **b** $R^1 = OH$, **c** $R^1 = OMe$, **d** $R^1 = NHCSNH_2$; **4 a**,**d–f** R = OMe; **b** R = NMe_2, **c** R = NHMe, **a–c** $R^1 = NH_2$, **d** $R^1 = OH$, **e** $R^1 = OMe$, **f** $R^1 = NHCSNH_2$

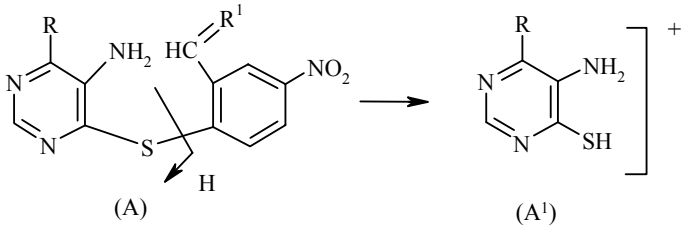
When alkaloids of the dihydroisoquinoline series, which contain an azomethine group, react with phenylhydrazine, hydroxylamine, and a number of other similar compounds, they form cyclic derivatives that are in equilibrium with the corresponding open form [4].

In analogy with these data, we might hypothesize that compounds **4a-f** exist both in open form A and in the isomeric cyclic form B or as an equilibrium mixture of these forms. When choosing between the open and cyclic structures A and B, we decided in favor of A based on the IR, ^{1}H NMR, and mass spectra of compounds **4a-e.** Thus in the IR spectrum of *o*-methyloxime **4e**, we see absorption bands for the NH_2 group at 3400-3500 cm^{-1}. The IR spectral data for oxime **3d** in the region of the stretching vibrations of the NH_2 group are difficult to interpret because of the presence of the hydroxyl group. However, the presence of a free amino group in compound **4d** is supported by the significant decrease in the intensity of the absorption band for the bending vibrations of this group at 1610 cm^{-1} that we observe upon deuteration. Furthermore, when the IR spectra of compounds **4d,e** were recorded in CCl_4, we did not observe absorption bands for the NH group characteristic of the cyclic form B.

The existence of compounds **4a-d** preferentially in the open form A is supported by the presence in the ^{1}H NMR spectra of a signal from the methine proton at the double bond with δ 8.24-8.44 ppm, characteristic of form A. If compounds **4a-d** had a cyclic structure B or existed as a mixture of forms A and B, then in their ^{1}H NMR spectra we should have observed a doublet signal from the H-6 proton, split as a result of coupling with the H-5 proton, as was observed in the case of compound **2h**.

According to the mass spectral data for compounds **4a-d**, they are found in the gas phase as a mixture of cyclic B and open A forms, with a significant predominance of the latter. Thus in the mass spectra* of compounds **4a-d**, besides the molecular ion peaks 320, 333, 319, and 321 respectively, we observed ions characteristic for the open form. The most intense peak in the spectra of hydrazones **4a-c** is the ion peak $[M–NH_2]^+$, respectively 304, 317, and 303. Analogous decomposition is also observed for oxime **4d**, as a result of which the ions $[M–OH]^+$ 304 and $[M–H_2O]^+$ 303 are formed. A common feature of fragmentation of compounds **4a-d** is elimination of the NR^1 group (present in the A structure) from the molecular ion to form ions with *m*/*z* 320 (for substances **4a,d**), 303 (for **4b**), and 289 (for **4c**). The correctness of the assignment is proven by the corresponding shift of the mass number for the peak of this fragment when the substituents R and R' are varied. In the mass spectra of compounds **4a-d**, the most intense peaks are those for ions with *m*/*z* 157 (for substances **4a,d**), 170 (for **4b**), and 156 (for **4c**). The structure A^1 is assigned to these ions, which is supported by the change in the mass number of these ions depending on the substituent R on the $C_{(4)}$ atom. The A^1 fragment is missing in the mass spectra of pyrimidobenzothiazepines **1a-c**, which are the model compounds in this case. Consequently, the presence of the A^1 fragment in the mass spectra of compounds **4a-d** may be due to decomposition of the open form A.

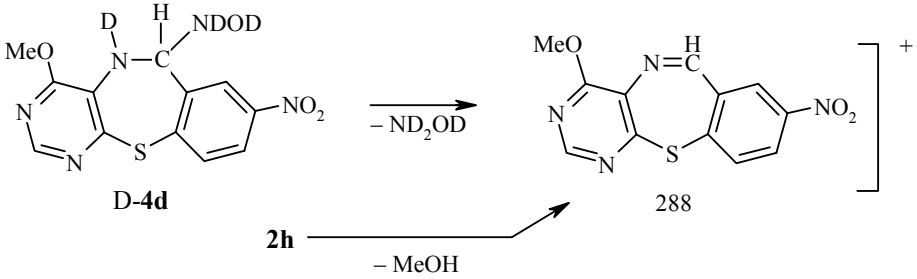
* Here and in the following, we give the *m*/*z* values for the ion peaks.



(A) (A[1])

Furthermore, in the mass spectra of compounds **4a-d** there are ion peaks corresponding to decomposition of the cyclic form B. Thus, for example, we observe low-intensity ion peaks with *m*/*z* 288 (for substances **4a,d**), 301 (for **4b**), and 287 (for **4c**). These ions correspond to detachment of an NH_2R^1 group (characteristic of cyclic form B) from the molecular ion. In the case of the oxime **4d**, we obtained the mass spectrum of its deutero analog derivative D-**4d**. We noted that the mass number for the 288 fragment was retained just as in the mass spectrum of the undeuterated compound **4d**. These data suggest that the eliminated ND_2OD group contains all three mobile hydrogen atoms present in the cyclic form of compound **4d**.

Analogous decomposition is also observed for 2,6-dimethoxypyrimidobenzothiazepine **2h**, which is the model compound for the cyclic structure.



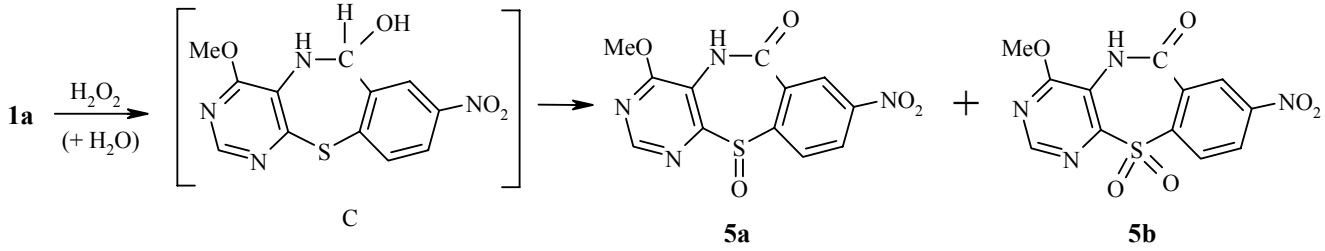
D-**4d** 288

Fragmentation of compound **2h** to form the ion $[M–MeOH]^+$ with *m*/*z* 288 is predominant. Further decomposition of the $[M–MeOH]^+$ ion and also compound **4d** exactly matches the decomposition of 4-methoxypyrimidobenzothiazepine **1a**, which has an azomethine group.

The data presented support the idea that the $[M–NH_2R^1]^+$ ion peaks observed in the mass spectra of hydrazones **4a-c** and oxime **4d** are the consequence of fragmentation of cyclic form B for these substances.

Thus using spectral data we have established that compounds **4a-d** in crystals and in solutions exist predominantly in the open form A, while in the gas phase they exist as a mixture of the cyclic B and open A forms, with predominance of the latter.

Then we studied oxidation of pyrimidobenzothiazepines **1a-c** by hydrogen peroxide. We observed that treatment of the 4-methoxy derivative **1a** with hydrogen peroxide in acetic acid at 60-65°C leads to formation of a mixture of compounds, from which we could isolate sulfoxide **5a** and sulfone **5b** in pure form. The initial step of this reaction is probably addition of a water molecule to the azomethine group to form the unstable intermediate compound C. Oxidation of the latter occurs both at the carbon atom in the 6 position and at the sulfur atom, and leads to formation of a mixture of compounds **5a** and **5b**.



C **5a** **5b**

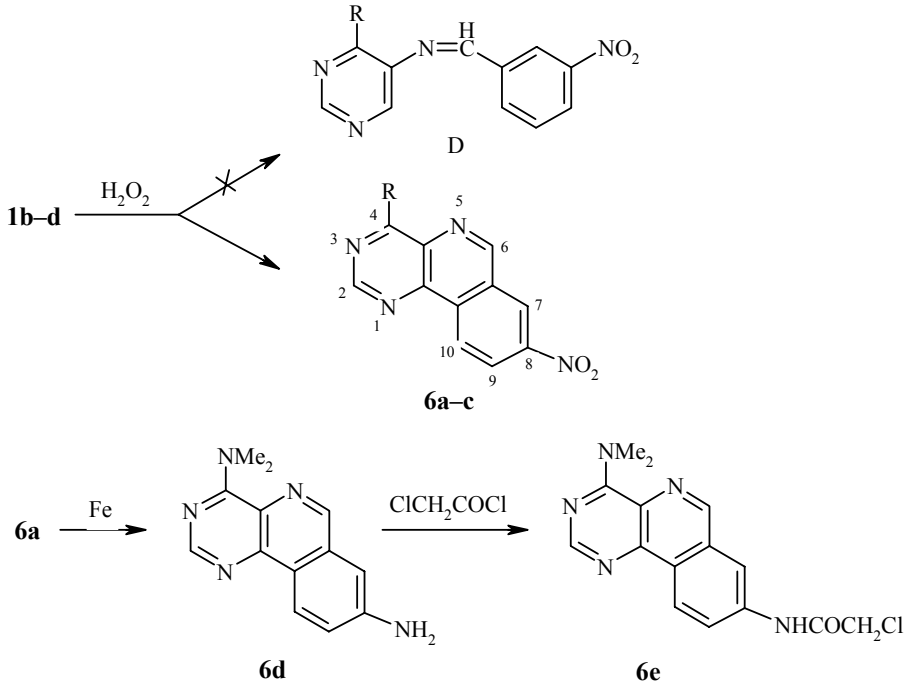
Unexpected results were obtained upon oxidation of 4-amino-substituted 8-nitropyrimidobenzothiazepines **1b-d** under the conditions indicated above (H_2O_2 + AcOH, 60-65°C). In this case, we obtained derivatives of a novel heteroaromatic system pyrimido[5,4-*c*]isoquinolines **6a-c** in satisfactory yields.

Derivatives of the isomeric system pyrimido[4,5-*c*]isoquinoline, obtained by heating 4-amino-5-arylpyrimidines with excess formic acid in the presence of phosphorus trichloride, have been described earlier in [5].

Compounds **6a-c** do not contain a sulfur atom; in their mass spectra, there are intense molecular ion peaks with *m*/*z* 269, 255, and 241 corresponding to their structures. In the ^{1}H NMR spectra, we observe a set of signals from aromatic protons in the 8.58-9.53 ppm region with integrated intensity corresponding to five proton units. This suggests a tricyclic structure for compounds **6a-c** and rules out the alternative Schiff's base structure D, in the ^{1}H NMR spectra of which there should be signals from six aromatic protons.

Formation of pyrimidoisoquinolines **6a-c** upon oxidation of compounds **1b-d** is obviously a consequence of elimination of a sulfur atom in the thiazepine ring with formation of a C–C bond between the pyrimidine and benzene rings, with simultaneous contraction of the seven-membered ring down to a six-membered ring.

For the example of 8-nitropyrimidoisoquinoline **6a**, we studied its reduction by iron filings in acetic acid to form the corresponding amine **6d**, from which we obtained the chloroacetyl derivative **6e** by acylation with chloroacetyl chloride.



6 a R = NMe_2, **b** R = NHMe, **c** R = NH_2

Biological studies of the synthesized compounds showed that pyrimidobenzothiazepines **1a,b** and **2d** exhibit neuroleptic activity. The pyrimidobenzaldehyde thiosemicarbazone **4f** and pyrimidoisoquinoline **6b** suppress the growth of the tuberculosis bacillus in *in vitro* experiments, while compound **4f** additionally inhibits growth of lactic acid bacteria.

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				mp, °C*	Yield, %
		C	H	N	S		
2a	$C_{12}H_{10}N_4O_3S$	49.86 / 49.66	3.39 / 3.45	19.73 / 19.31	11.04 / 11.03	216-218	89
2b	$C_{13}H_{13}N_5O_2S$	51.52 / 51.48	4.33 / 4.29	23.20 / 23.10	10.64 / 10.56	190-192	93
2c	$C_{12}H_{11}N_5O_2S$	49.93 / 49.90	3.65 / 3.81	24.17 / 24.20	11.20 / 11.10	262-264	92
2d	$C_{13}H_{13}N_5S$	57.29 / 57.56	4.79 / 4.79	25.67 / 25.83	11.72 / 11.80	179-181	43
2e	$C_{13}H_{15}N_5S$	57.20 / 57.14	5.51 / 5.49	25.68 / 25.64	—	169-171	66-83
2f	$C_{20}H_{18}N_6OS$	61.46 / 61.54	4.39 / 4.82	21.64 / 51.54	8.44 / 8.20	215-216	54
2g	$C_{20}H_{18}N_6S_2$	58.96 / 59.11	4.62 / 4.43	20.45 / 20.68	15.37 / 15.76	167-170	52
2h	$C_{13}H_{12}N_4O_4S$	49.01 / 48.70	3.87 / 3.76	17.56 / 17.50	10.14 / 10.00	195-200	89-90
4a	$C_{12}H_{12}N_6O_3S$	44.85 / 45.00	3.60 / 3.75	26.42 / 26.25	—	199-201	76-90
4b	$C_{13}H_{15}N_7O_2S$	47.01 / 46.84	4.46 / 4.50	29.79 / 29.42	—	190-192	76
4c	$C_{12}H_{13}N_7O_2S$	44.96 / 45.14	4.02 / 4.07	31.01 / 30.72	—	213-214	87
4d	$C_{12}H_{11}N_5O_4S$	44.89 / 44.86	3.44 / 3.43	22.00 / 21.81	—	177-179	80
4e	$C_{13}H_{13}N_5O_4S$	46.86 / 46.57	3.96 / 3.88	21.00 / 20.89	—	170-172	96
4f	$C_{13}H_{13}N_7O_3S_2$	41.73 / 41.16	3.12 / 3.43	—	16.80 / 16.88	329-331 (dec.)	91
5a	$C_{12}H_8N_4O_5S$	44.72 / 45.00	2.57 / 2.50	17.57 / 17.50	10.19 / 10.00	140-142	36
5b	$C_{12}H_8N_4O_6S$	43.09 / 42.85	2.55 / 2.37	16.61 / 16.67	9.84 / 9.52	250-252	52
6a	$C_{13}H_{11}N_5O_2$	58.00 / 58.00	4.01 / 4.08	26.36 / 26.10	—	246-248	63
6b	$C_{12}H_9N_5O_2$	56.30 / 56.47	3.48 / 3.52	27.42 / 27.45	—	251-253	67
6c	$C_{11}H_7N_5O_2$	54.60 / 54.77	2.74 / 2.90	28.89 / 29.00	—	>300	66
6d	$C_{13}H_{13}N_5$	65.18 / 65.40	5.78 / 5.45	29.70 / 29.40	—	219-221	25
6e	$C_{15}H_{14}ClN_5O$	57.61 / 57.05	4.00 / 4.43	22.21 / 22.18	—*[2]	199-201	58

* Solvents for crystallization: methanol (compounds **2a,d-f,h, 4b,e**), ethanol (compounds **2b,c,g, 4a,d, 5a,b, 6a,b,d**), DMF–water, 1:1 (compounds **4c,f**), and DMF (compounds **6c,e**).

*[2] Found, %: Cl 11.19. Calculated, %: Cl 11.30.

EXPERIMENTAL

The IR spectra were obtained on a Perkin–Elmer 457 spectrometer in vaseline oil and in CCl_4 solution. The ^1H NMR spectra were recorded on a Varian XL-200 (200 MHz), internal standard TMS. The mass spectra were obtained on an MX-1303 mass spectrometer with injection of the substance directly into the ion source with ionizing electron energy 30 eV and temperature 125°C.

The course of the reactions and the purity of the compounds were monitored by TLC on Silufol UV-254 plates in a 5:5:1.5 benzene–ethyl acetate–ethanol system. Visualization in UV light.

TABLE 2. Spectral Characteristics of Synthesized Compounds

Compound	IR spectrum, ν, cm^{-1}	^1H NMR, δ, ppm*	Mass spectrum, M^+, *m/z*
2a	3380	7.48 (1H, d, NH), 7.61 (2H, d, CH_2)	
2b	3280		
2c	3340		
2h	3350	5.76 (1H, d, NH), 6.55 (2H, d, CH_2-6), 3.75 (3H, s, OCH_3-4), 3.37 (3H, s, OCH_3-6)	320, 288, 157
4a	3400, 3300, 1630	8.24 (1H, s, CH=NR^1), 8.12 (1H, s, H-2), 8.74-7.74 (benzene ring protons)	320, 304, 288, 157
4b		8.24 (1H, s, CH=NR^1), 7.24 (1H, s, H-2), 8.82-7.74 (benzene ring protons)	333, 317, 303, 301, 170
4c		8.42 (1H, s, CH=NR^1), 8.29 (1H, s, H-2), 8.72-7.74 (benzene ring protons)	319, 303, 289, 287, 156
4d	3310, 3230, 1610	8.34 (1H, s, CH=NR^1), 7.92 (1H, s, H-2), 8.50-8.00 (benzene ring protons)	379, 320, 304, 303, 288, 157
4e	3500, 400, 1600	8.44 (1H, s, CH=NR^1), 7.90 (1H, s, H-2), 8.08-8.05 (benzene ring protons)	
5a	3200, 1650, 1065		
5b	3170, 1660, 1160		
6a		8.58-9.36 (aromatic protons)	
6b	3360	8.60-9.42 (aromatic protons)	
6c	3470, 3400	8.70-9.53 (aromatic protons)	

* The ^1H NMR spectra were taken in pyridine-d_5 (compounds **2a,h** and **4a-d**) and in DMSO-d_6 (compounds **6a-c**).

The physicochemical and spectral characteristics of the compounds obtained are presented in Tables 1 and 2.

4-Methoxy(dimethylamino, methylamino, amino)-8-nitropyrimido[4,5-*b*]-1,4-benzothiazepines 1a-d were obtained by the method in [1].

4-Methoxy-8-nitro-5,6-dihydropyrimido[4,5-*b*]-1,4-benzothiazepine (2a). $NaBH_4$ (0.19 g, 5 mmol) was added with vigorous stirring to a suspension of 4-methoxy-8-nitropyrimido[4,5-*b*]-1,4-benzothiazepine (**1a**) (0.57 g, 2 mmol) in anhydrous ethanol (10 ml). The mixture was stirred for 3 h at 20°C and evaporated under vacuum to dryness. Water (5 ml) was added to the residue and then it was acidified with 10% HCl down to pH 5-6; the precipitate was filtered out, washed with water, and dried. Compound **2a** (0.52 g) was obtained.

Compounds 2b,c were obtained similarly.

8-Amino-4-dimethylaminopyrimido[4,5-*b*]-1,4-benzothiazepine (2d). Iron filings (1.6 g) and glacial acetic acid (2 ml) were added to a suspension of 4-dimethylamino-8-nitropyrimido[4,5-*b*]-1,4-benzothiazepine (**1b**) (0.8 g, 2.7 mmol) in methanol (65 ml). The mixture was boiled for 8 h and filtered. The solution was evaporated under vacuum to dryness. Water (20 ml) was added to the residue and it was alkalinized with aqueous NaOH up to pH 6-7 and then extracted with ethyl acetate. The solution was dried with Na_2SO_4, filtered, and evaporated under vacuum to dryness. Obtained 0.31 g of compound **2d.**

8-Amino-4-dimethylamino-5,6-dihydropyrimido[4,5-*b*]-1,4-benzothiazepine (2e). A. Iron filings (2 g) and glacial acetic acid (2 ml) were added to a suspension of 4-dimethylamino-8-nitro-5,6-dihydropyrimido[4,5-*b*]-1,4-benzothiazepine (**2b**) (1.0 g, 3.3 mmol). The mixture was boiled for 12 h and then was treated as indicated in the synthesis of compound **2d**. Obtained 0.6 g (66%) of compound **2e**.

B. $NaBH_4$ (0.19 g, 5 mmol) was added with vigorous stirring to a suspension of compound **2d** (0.6 g, 2.2 mmol) in anhydrous ethanol (10 ml). The mixture was stirred for 4 h at 20°C and then treated as described in

synthesis of compound **2a**. Obtained 0.5 g (83%) of compound **2e**, identical to the compound synthesized by method A with respect to melting point and spectral characteristics.

4-Dimethylamino-8-(3-phenylureido)pyrimido[4,5-*b*]-1,4-benzothiazepine (2f). Phenylisocyanate (0.22 g, 1.8 mmol) was added to a suspension of compound **2d** (0.5 g, 1.8 mmol) in ethyl acetate (20 ml). The mixture was boiled for 3 h and then cooled; the precipitate formed was filtered out and then dried. Obtained 0.39 g of compound **2f**.

4-Dimethylamino-8-(3-phenylthioureido)pyrimido[4,5-*b*]-1,4-benzothiazepine (2g). Phenylisothiocyanate (0.22 g, 1.6 mmol) was added to a suspension of compound **2d** (0.22 g, 0.81 mmol) in ethanol (10 ml). The mixture was boiled for 20 min and cooled; the precipitate formed was filtered out and dried. Obtained 0.17 g of compound **2g**.

4,6-Dimethoxy-8-nitro-5,6-dihydropyrimido[4,5-*b*]-1,4-benzothiazepine (2h). A. A suspension of compound **1a** (0.5 g, 1.73 mmol) in MeOH (23 ml), containing KOH (0.12 g, 2.14 mmol), was heated for 2 h at 65°C and then cooled down; the precipitate formed was filtered out and dried. Obtained 0.5 g (89%) of compound **2h**.

B. A solution of 6-chloro-3-nitrobenzaldehyde (0.59 g, 3.18 mmol) in MeOH (20 ml) was added to a solution of 5-amino-6-mercapto-4-methoxypyrimidine (0.5 g, 3.18 mmol) in MeOH (25 ml) containing KOH (0.3 g, 5.37 mmol). The mixture was heated for 2 h at 65°C and then cooled; the precipitate formed was filtered out and dried. Obtained 0.9 g (90%) of compound **2h**, identical to the compound synthesized by method A with respect to melting point and spectral characteristics.

6-(5-Amino-4-methoxy-6-pyrimidyl)-3-nitromercaptobenzaldehyde Hydrazone (4a). A. A mixture of compound **1a** (0.5 g, 1.73 mmol), MeOH (40 ml), and hydrazine hydrate (1 ml) was heated for 4 h at 60-63°C and then cooled down; the precipitate was filtered out and dried. Obtained 0.42 g (76%) of compound **4a**.

Hydrazones 4b,c were obtained similarly from compounds **1b,c**.

B. A mixture of compound **2h** (0.5 g, 1.57 mmol), MeOH (60 ml), and hydrazine hydrate (1 ml) was heated and treated as described above. Obtained 0.42 g of compound **4a**. An additional 0.1 g of this substance was isolated by evaporation of the mother liquor. Total yield 0.45 g (90%). Compound **4a** was identical to the substance synthesized by method A with respect to melting point and spectral characteristics.

6-(5-Amino-4-methoxy-6-pyrimidyl)-3-nitromercaptobenzaldehyde oxime (4d). Compound **2h** (0.5 g, 1.57 mmol) was added to a mixture of hydroxylamine hydrochloride (0.2 g, 2.88 mmol), ethanol (10 ml), and pyridine (1 ml). The solution was boiled for 4 h, evaporated down under vacuum to dryness, and the residue was triturated with water (5 ml). The insoluble precipitate was filtered out, washed with water, and dried. Obtained 0.4 g of compound **4d**.

Compounds 4e,f were synthesized similarly.

4-Methoxy-8-nitro-6-oxo-5,6-dihydropyrimido[4,5-*b*]-1,4-benzothiazepine sulfoxide (5a) and **4-methoxy-8-nitro-6-oxo-5,6-dihydropyrimido[4,5-*b*]-1,4-benzothiazepine sulfone (5b)**. A 30% aqueous solution of H_2O_2 (1 ml) was added to a suspension of **1a** (0.2 g, 0.695 mmol) in glacial acetic acid (20 ml). The mixture was heated with stirring for 4 h at 63-65°C and then cooled down, and the precipitate formed was filtered out. Obtained 0.12 g of sulfone **5b**. The filtrate was evaporated down under vacuum to dryness; the solid residue was triturated with ethanol (5 ml) and then the precipitate was filtered out, washed with ethanol (3 ml), and dried. Obtained 0.08 g of sulfoxide **5a**.

4-Dimethylamino-8-nitropyrimido[5,4-*c*]isoquinoline (6a). A 30% aqueous solution of H_2O_2 (2 ml) was added to a suspension of compound **1b** (0.52 g, 1.8 mmol) in glacial acetic acid (40 ml). The mixture was heated for 3 h at 60-63°C and then evaporated down under vacuum to dryness; the residue was triturated with water and the insoluble precipitate was filtered out, washed with water, and dried. Obtained 0.30 g of compound **6a**.

Compounds 6b,c were obtained similarly.

8-Amino-4-dimethylaminopyrimido[5,4-*c*]isoquinoline (6d). Iron filings (0.9 g) and glacial acetic acid (2 ml) were added to a suspension of the nitro compound **6a** (0.9 g, 3.35 mmol) in MeOH (50 ml). The mixture was boiled for 12 h and then filtered to remove solids. The filtrate was then evaporated down under vacuum to dryness. The residue was dissolved in water (10 ml) and then the solution was alkalinized with an aqueous solution of NaOH up to pH 6-7 and extracted with ethyl acetate. The extract was dried with Na_2SO_4 and filtered out; then the filtrate was evaporated down under vacuum to dryness. Obtained 0.2 g of compound **6d**.

8-Chloroacetylamino-4-dimethylaminopyrimido[5,4-*c*]isoquinoline (6e). A solution of chloroacetyl chloride (0.12 g, 1.23 mmol) was added dropwise to a suspension of compound **6d** (0.2 g, 0.83 mmol) in acetone (20 ml). The mixture was stirred for 6 h at 18-20°C and then evaporated under vacuum to dryness. The residue was triturated with water (5 ml) and then the precipitate was filtered out, washed with water, and dried. Obtained 0.15 g of compound **6e**.

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