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SYNTHESIS AND ANTITUBERCULOTIC ACTIVITY OF SOME NEW IMIDAZO[4,5-*b*]PYRIDINE DERIVATIVES

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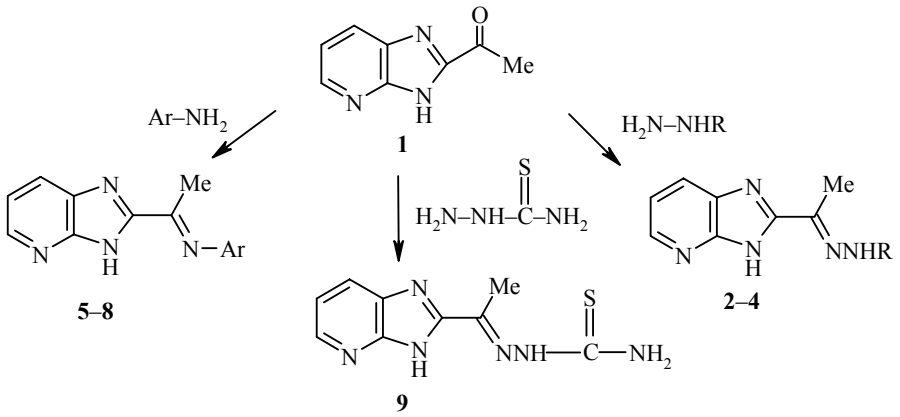
The reactions of 2-acetylimidazo[4,5-b]pyridine hydrazone with some alkyl- and arylisothiocyanates and some orthoesters were carried out. Various new derivatives of the titled compound such as thiosemicarbazones, ethoxymethylenehydrazones, and derivatives of the new pyrido-[3',2':4,5]imidazo[1,2-d][1,2,4]triazine ring system were obtained. Biological data for selected compounds are presented.

Keywords: hydrazones, imidazo[4,5-*b*]pyridine, pyrido[3',2':4,5]imidazo[1,2-*d*][1,2,4]triazine, thiosemicarbazones, antituberculotic activity.

It is known that thiosemicarbazones show various biological activites. To date many of them have been applied in pharmacotherapy [1, 2]. Imidazo[4,5-*b*]pyridine derivatives have also revealed a broad spectrum of biological activity and have been applied in pharmacotherapy [2]. These biological data prompted us to synthesize a series of thiosemicarbazones fused with the imidazo[4,5-*b*]pyridine ring and to investigate their biological activity.

First, the starting 2-acetylimidazo[4,5-*b*]pyridine (**1**) [3] was transformed to hydrazones **2**-**4** and imines **5**-**8**.

Scheme 1



2 R = H; **3** R = Ph; **4** R = 6-chloropyridazin-3-yl; **5** Ar = thiazol-2-yl; **6** Ar = pyridin-3-yl; **7** Ar = 4-methylpiperazin-1-yl; **8** Ar = [1,2,4]triazol-4-yl

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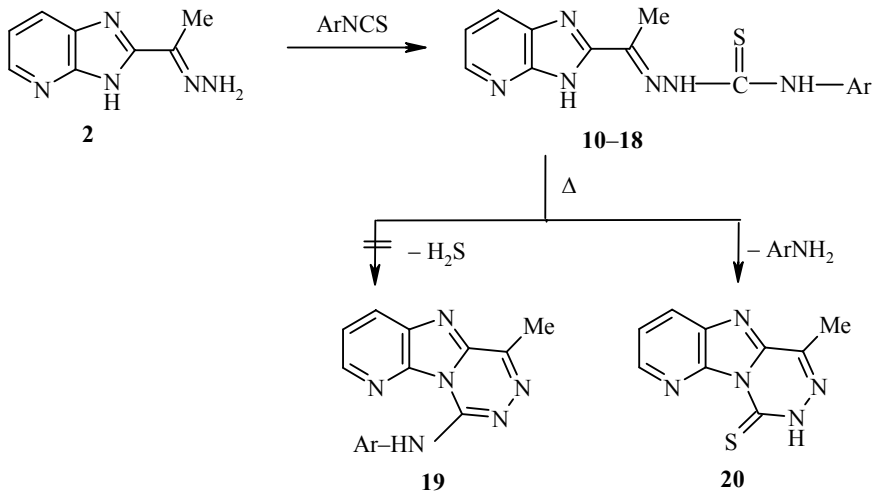
The desirable thiosemicarbazones were synthesized either by reaction of ketone **1** with thiosemicarbazide (compound **9**) or reaction of 2-acetylimidazo[4,5-*b*]pyridine hydrazone **2** with appropriate isothiocyanates (compounds **10**-**18**).

While the melting point of compounds **9**-**18** had being determined, it was observed that after meltdown they recrystallized and melted again at about 280°C. This observation allowed us to suppose the possibility of their cyclization. This fact was confirmed experimentally. All compounds **9**-**18** upon heating in boiling N,N-dimethylaniline underwent intramolecular cyclization to the new heterocyclic system, the pyridoimidazo[1,2,4]triazine reported by us previously [4].

As shown in Scheme 2 there are two possibilities of this cyclization: elimination of hydrogen sulfide to give compound **19** containing at position 9 a substituted amino group, or elimination of the appropriate amine to give product **20** containing at this position the thioxo group.

Since from all thiosemicarbazones **9**-**18** the same compound was obtained and it contained sulfur, one can conclude that the result of cyclization was compound **20**.

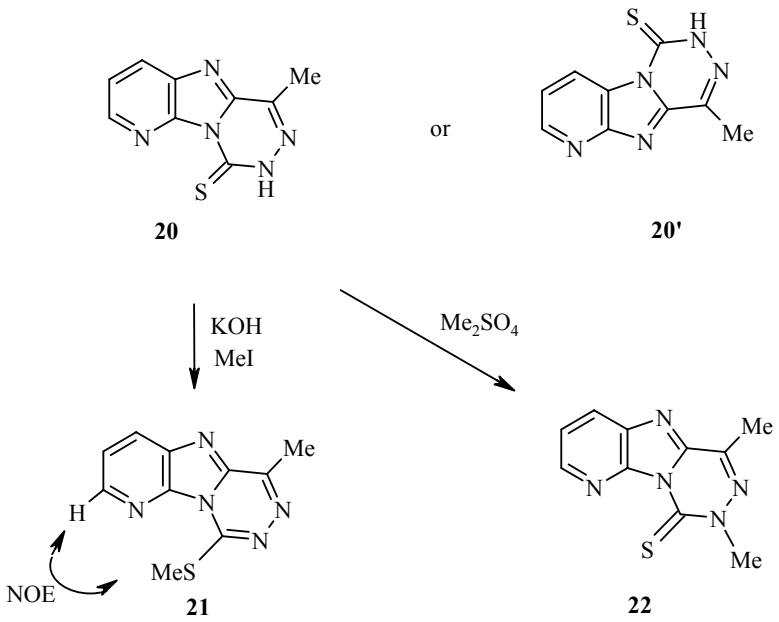
Scheme 2



10 Ar = Me; **11** Ar = CH_2–CH=CH_2; **12** Ar = C_6H_{11}; **13** Ar = Ph; **14** Ar = C_6H_4Cl-*p*; **15** Ar = C_6H_4CN-*p*; **16** Ar = C_6H_4OMe-*p*; **17** Ar = C_6H_4SMe-*p*; **18** Ar = $C_6H_4CF_3$-*p*

Due to the tautomeric properties of the imidazo[4,5-*b*]pyridine system the cyclization may lead either to compound **20** or to alternative product **20'** (ring closure with participation of N(1) or N(3) atoms, Scheme 3). In order to find its correct structure, synthesis of its S-methyl derivative (**21**) was carried out with MeI as an alkylating agent. Compound **21** was then examined by NOE experiment. Since in this investigation a positive effect between the S-methyl group protons of the 1,2,4-triazine ring and the α-proton of the pyridine ring was observed, the structure of the tricyclic system **20** was supported (cyclization to N(3)). Looking for optimum conditions for the synthesis of compound **21**, methylation of thione **20** was carried out with MeI in ethanol or DMF (in the presence of KOH) as well as with dimethyl sulfate in nitrobenzene. In the latter case the N-methyl derivative **22** was obtained instead of the expected **21** (Scheme 3).

Scheme 3



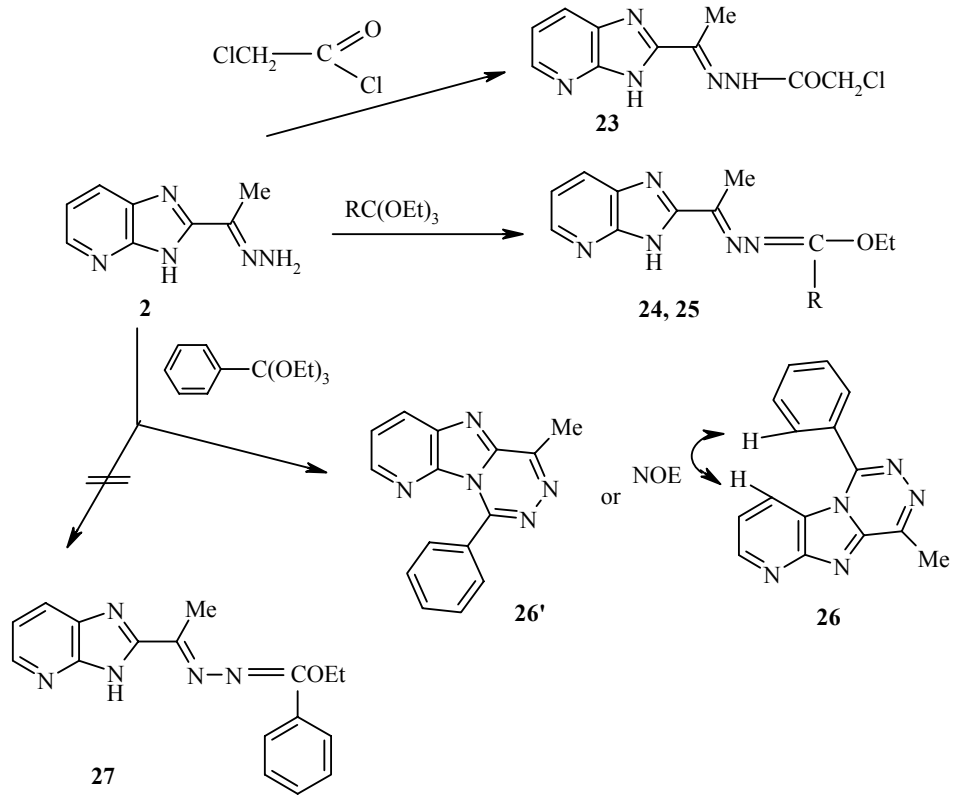
In the next set of experiments the reactions of hydrazone **2** with chloroacetyl chloride and with some ortho esters (triethyl orthoformate, triethyl orthoacetate, triethyl orthobenzoate) were investigated. As the result of the first three reactions, products **23-25** were prepared (Scheme 4). Unexpectedly from the reaction of hydrazone **2** with triethyl orthobenzoate a tricyclic compound **26** was obtained. Due to the already mentioned tautomeric properties of the imidazo[4,5-*b*]pyridine system, the cyclization may lead to two isomeric forms **26** and **26'** (or to their mixture). As in the NOE investigation of compound **26**, a correlation between the γ-proton of the pyridine ring and orthoprotons of the benzene ring was observed, and the structure of **26** was confirmed.

Compounds **2**, **4**, **5**, **9**, **10**, **13**, **14**, **23**, **24** chosen as examples were tested *in vitro* for their antituberculotic activity against *Mycobacterium tuberculosis* $H_{37}Rv$ and two "wild" strains isolated from tuberculotic patients: the 210 strain, resistant to isoniazid (INH), *p*-aminosalicylic acid (PAS), ethambutol (ETB), and rifampicin (RFP), as well as the 192 strain, fully susceptible to the drugs administered.

TABLE 1. Antituberculotic Activity, MIC Values (μg/ml)

Compound	Mycobacterium		
	$H_{37}Rv$	192	210
2	100	100	50
4	6.2	6.2	6.2
5	50	> 100	50
9	12.5	50	50
10	50	50	50
13	12.5	12.5	12.5
14	6.25	< 6.2	< 6.2
23	50	50	50
24	50	100	50

Scheme 4



24 R = H; **25** R = Me

The antibacterial activity of the compounds was determined in liquid Youmans medium containing 10% bovine serum using the method previously described [3]. The lowest concentration of the investigated compound, when no growth of strains could be observed, was taken as the MIC. The results obtained are given in Table 1.

TABLE 2. Physical and Analytical Data of Compounds **2-26**

Com-pound	Empirical formula	Found, % / Calculated, %			mp, °C (solvent)	Yield, %
		C	H	N		
1	2	3	4	5	6	7
2	$C_8H_9N_5$	54.61 / 54.84	5.03 / 5.18	40.12 / 39.98	293-294 (DMF–H_2O)	90
3	$C_{14}H_{13}N_5$	66.82 / 66.91	5.16 / 5.21	28.11 / 27.87	240-242 (EtOH–H_2O)	80
4	$C_{12}H_{10}ClN_7$	49.95 / 50.09	3.48 / 3.50	34.32 / 34.07	245-247 (DMF–H_2O)	71
5	$C_{11}H_9N_5S$	54.27 / 54.32	3.78 / 3.73	29.06 / 28.80	242-244 (H_2O)	65
6	$C_{13}H_{11}N_5$	65.72 / 65.81	4.56 / 4.67	29.78 / 29.52	228-230 (EtOH)	70
7	$C_{13}H_{18}N_6$	60.31 / 60.44	6.93 / 7.02	32.76 / 32.54	224-225 (toluene)	72

TABLE 2 (continued)

1	2	3	4	5	6	7
8	$C_{10}H_9N_7$	52.69 52.85	3.90 3.99	43.27 43.15	284-286 (dioxane)	30
9	$C_9H_{10}N_6S$	45.98 46.15	4.16 4.30	36.24 35.88	235-237 (DMF–H_2O)	87
10	$C_{10}H_{12}N_6S$	48.26 48.38	4.80 4.87	34.05 33.86	266-268 (DMF–H_2O)	63
11	$C_{12}H_{14}N_6S$	52.47 52.54	5.11 5.15	30.80 30.64	221-223 (EtOH)	71
12	$C_{15}H_{20}N_6S$	56.89 56.95	6.32 6.37	26.62 26.57	239-242 (DMF–H_2O)	73
13	$C_{15}H_{14}N_6S$	58.13 58.05	4.46 4.55	27.18 27.09	214-216 (DMF–H_2O)	68
14	$C_{15}H_{13}ClN_6S$	52.16 52.25	3.64 3.80	24.53 24.37	230-232 (DMF–H_2O)	72
15	$C_{16}H_{13}N_7S$	57.23 57.31	3.78 3.91	29.52 29.24	230-231 (DMF–H_2O)	70
16	$C_{16}H_{16}N_6OS$	56.41 56.46	4.62 4.74	24.96 24.70	190-194 (DMF–H_2O)	84
17	$C_{16}H_{16}N_6S_2$	53.86 53.93	4.48 4.53	23.65 23.59	203-205 (DMF–H_2O)	82
18	$C_{16}H_{13}F_3N_6S$	50.69 50.78	3.42 3.46	22.38 22.21	235-237 (DMF–H_2O)	71
20	$C_9H_7N_5S$	49.62 49.77	3.18 3.25	32.46 32.25	291-293 (EtOH)	62
21	$C_{10}H_9N_5S$	51.72 51.94	3.81 3.92	30.53 30.29	248-250 (EtOH)	69
22	$C_{10}H_9N_5S$	51.80 51.94	3.76 3.92	30.64 30.29	236-238 (DMF–H_2O)	54
23	$C_{10}H_{10}ClN_5O$	47.53 47.72	3.84 4.00	28.07 27.83	308-310 (DMF–H_2O)	45
24	$C_{11}H_{13}N_5O$	57.02 57.13	5.46 5.67	20.72 20.68	185-188 (acetone)	72
25	$C_{12}H_{15}N_5O$	58.64 58.76	6.03 6.16	28.68 28.56	202-204 (acetone)	63
26	$C_{15}H_{11}N_5$	68.76 68.95	4.18 4.24	26.93 26.81	276-278 (acetone)	22

TABLE 3. IR and MS Data for Compounds **2-26**

Com-pound	IR spectrum, ν, cm^{-1}	*m/z* (*I*, %)
1	2	3
2	3375, 3305 (NH_2), 3158, 2898, 1648 (C=N)	175 $[M]^+$ (100), 146 (83), 145 (63), 144 (58), 120 (12), 119 (13), 93 (32), 92 (11), 66 (19), 64 (11), 57 (13), 44 (12)
3	3500-2700 (NH), 1604 (C=N)	251 $[M]^+$ (100), 252 (20), 250 (11), 235 (12), 234 (10), 146 (38), 145 (22), 144 (21), 119 (12), 93 (21), 92 (23), 91 (23), 77 (96), 65 (46), 39 (36)
4	3467 (NH), 3081, 1677 (C=N)	287 $[M]^+$ (13), 289 (4), 274 (20), 272 (75), 225 (10), 224 (100), 169 (20), 146 (36), 145 (29), 144 (25), 119 (48), 92 (20), 73 (20), 64 (23), 39 (17)
5	3362, 3059, 2969, 1693	243 $[M]^+$ (6), 161 (93), 146 (19), 133 (46), 119 (88), 92 (48), 65 (12), 64 (24), 43 (100), 42 (10), 39 (13), 38 (17)
6	3425, 3053, 2976, 1631	237 $[M]^+$ (20), 236 (100), 222 (9), 196 (17), 169 (8), 119 (8), 92 (6), 78 (38), 64 (7), 52 (6), 51 (24), 39 (13)
7	3450, 3051, 2969, 2937, 2821, 1609	258 $[M]^+$ (4), 188 (9), 174 (5), 160 (11), 119 (28), 99 (92), 98 (52), 97 (15), 83 (12), 71 (20), 70 (30), 69 (13), 58 (12), 57 (31), 56 (100), 55 (19), 44 (15)

TABLE 3 (continued)

1	2	3
8	3420, 3049, 2970, 1590	227 $[M]^+$ (22), 172 (100), 171 (42), 161 (49), 146 (17), 145 (48), 144 (56), 130 (27), 119 (88), 118 (17), 104 (27), 92 (57), 84 (25), 65 (31), 64 (49), 52 (25), 43 (71), 42 (28), 41 (25), 40 (36), 39 (40)
9	3481, 3402, 3174, 1693, 1614, 1278, 1120	234 $[M]^+$ (58), 217 (10), 178 (9), 174 (29), 146 (100), 145 (22), 144 (15), 119 (18), 93 (20), 92 (11), 66 (15), 64 (10), 60 (17), 43 (9), 39 (14)
10	3460-2600, 1685, 1558, 1279, 1230	248 $[M]^+$ (81), 179 (93), 175 (12), 174 (36), 161 (18), 147 (17), 146 (100), 145 (42), 144 (28), 120 (22), 119 (43), 93 (36), 92 (20), 91 (13), 74 (82), 66 (26), 64 (19), 42 (21)
11	3500-2650 (NH), 1642 (C=C), 1590 (C=N), 1275 (C=S)	274 $[M]^+$ (4), 162 (10), 161 (100), 160 (10), 146 (28), 145 (20), 144 (16), 120 (17), 119 (43), 92 (8), 56 (8), 41 (14)
12	3276, 2931, 2852, 1589, 1491, 1271	316 $[M]^+$ (16), 162 (17), 161 (100), 146 (26), 145 (11), 120 (14), 119 (18), 98 (12), 35 (9)
13	3600-2500, 1652, 1513, 1278, 1189	310 $[M]^+$ (10), 217 (73), 179 (21), 175 (11), 146 (39), 145 (14), 144 (11), 136 (10), 135 (17), 119 (20), 93 (100), 91 (18), 77 (16), 66 (30), 65 (21), 64 (13), 39 (19)
14	3600-2500, 1680, 1550, 1280, 1200	344 $[M]^+$ (4), 217 (64), 188 (10), 175 (9), 146 (14), 145 (11), 144 (10), 135 (11), 129 (26), 127 (100), 119 (19), 92 (23), 91 (13), 64 (15), 44 (13), 39 (15)
15	3432, 3267, 3073, 2227, 1665, 1538, 1271	217 [M–118] (100), 188 (15), 160 (10), 144 (9), 135 (14), 119 (13), 118 (84), 91 (21), 64 (11)
16	3460, 3184, 2960, 1655, 1590, 1514, 1247, 1032	217 [M–108] (12), 288 (21), 254 (40), 239 (47), 165 (38), 150 (34), 123 (64), 122 (38), 108 (100), 92 (15), 80 (34), 77 (18), 64 (15), 52 (10), 43 (10), 39 (10)
17	3450, 3183, 2917, 1655, 1508, 1271, 1192	356 $[M]^+$ (4), 218 (16), 217 (100), 188 (31), 175 (9), 145 (13), 144 (15), 139 (69), 135 (21), 124 (91), 119 (12), 108 (14)
18	3254, 3059, 2933, 1656, 1531, 1275	378 $[M]^+$ (84), 218 (28), 217 (100), 190 (15), 188 (26), 179 (49), 174 (26), 161 (51), 146 (90), 145 (54), 135 (15), 120 (17), 119 (33), 111 (18), 93 (20), 91 (17)
20	3448, 3055, 2922, 1546, 1393, 1358, 1303, 1267	217 $[M]^+$ (100), 219 (12), 188 (64), 145 (28), 144 (26), 136 (36), 135 (85), 118 (15), 117 (13), 108 (40), 103 (20), 92 (22), 59 (25), 56 (19), 52 (16), 39 (34)
21	2997, 2919, 1554, 1436, 1403	231 $[M]^+$ (100), 233 (6), 230 (13), 204 (11), 186 (10), 145 (17), 144 (28), 135 (10), 117 (12)
22	3474, 3375, 3075, 2985, 1630, 1545, 1256, 1070	231 $[M]^+$ (100), 233 (7), 217 (22), 203 (13), 198 (17), 172 (10), 171 (18), 162 (14), 146 (12), 144 (21), 135 (28), 108 (18), 103 (17)
23	3600-2600, 1685, 1608	251 $[M]^+$ (48), 253 (15), 202 (24), 175 (28), 174 (97), 147 (41), 146 (100), 144 (46), 119 (27), 93 (89), 78 (26), 77 (18), 66 (58), 44 (20), 43 (21), 39 (51)
24	3436, 3064, 2984, 2924, 1629, 1247, 1054	231 $[M]^+$ (11), 203 (42), 185 (15), 174 (31), 161 (12), 160 (15), 147 (18), 146 (100), 145 (16), 144 (15), 119 (51), 93 (21), 39 (15)
25	3449, 3064, 2978, 1642, 1052	245 $[M]^+$ (18), 188 (39), 187 (46), 174 (10), 161 (58), 160 (28), 147 (17), 146 (100), 145 (27), 144 (18), 120 (22), 119 (78), 93 (21), 92 (13), 66 (15), 57 (12), 43 (77), 42 (20), 41 (15), 39 (16)
26	3058, 2924, 1618	261 $[M]^+$ (100), 260 (45), 246 (44), 220 (30), 219 (17), 193 (29), 117 (16), 103 (11), 77 (12), 76 (11)

EXPERIMENTAL

Melting points are uncorrected. IR spectra – Specord 75 spectrophotometer (pellets in KBr); ^{1}H NMR – Varian Gemini 200 (200 MHz) or Varian Unity 500 (500 MHz) Plus spectrometers with TMS as an internal

TABLE 4. ^{1}H NMR Data for Compounds **20-26**

Compound	Solvent	Chemical shifts, δ, ppm (*J*, Hz)
20	DMSO-d_6	2.68 (3H, s, CH_3); 7.63 (1H, dd, *J* = 5, C(3) H); 8.83 (1H, d, *J* = 6, C(4) H); 9.55 (1H, d, *J* = 5, C(2) H); 14.32 (1H, s, NH)
21	$CDCl_3$	2.99 (3H, s, CH_3); 3.02 (3H, s, SCH_3); 7.55 (1H, dd, *J* = 5, C(3) H); 8.69 (1H, d, *J* = 8, C(4) H); 8.96 (1H, d, *J* = 5, C(2) H)
22	DMSO-d_6	2.76 (3H, s, CH_3); 4.47 (3H, s, NCH_3); 7.85 (1H, t, *J* = 6, C(3) H); 9.04 (1H, d, *J* = 7, C(4) H); 10.55 (1H, d, *J* = 8, C(2) H)
23	DMSO-d_6	2.38 (3H, s, CH_3); 4.97 (2H, s, CH_2); 7.26 (1H, dd, *J* = 5, C(6) H); 7.94-8.02 (1H, br.s, C(7) H); 8.38 (1H, d, *J* = 3.5, C(5) H)
24	CD_3OD	1.40 (3H, t, *J* = 7, $CH_2\underline{CH_3}$); 2.53 (3H, s, CH_3); 4.39 (2H, q, *J* = 7, $\underline{CH_2}CH_3$); 7.33 (1H, dd, *J* = 5, *J* = 7, C(6) H); 8.02 (1H, br. s); 8.41 (2H, d, *J* = 5, C(5) H); 8.46 (1H, s, CHO)
25	$CDCl_3$	1.38 (3H, t, *J* = 7, $CH_2\underline{CH_3}$); 2.18 (3H, s, CH_3); 2.55 (3H, s, CH_3); 4.33 (2H, q, *J* = 7, $\underline{CH_2}CH_3$); 7.26 (1H, dd, *J* = 5, *J* = 8, C(6) H); 8.11 (1H, d, *J* = 8, C(7) H); 8.43 (1H, d, *J* = 7, C(5) H)
26	DMSO-d_6	2.94 (3H, s, CH_3); 7.08 (1H, d, *J* = 8, C(4) H); 7.38 (1H, dd, *J* = 5, C(3) H); 7.69-7.86 (5H, m, ArH); 8.80 (1H, d, *J* = 4, C(2) H)

standard; MS spectra – Varian MAT-711 apparatus with direct inlet, ionization energy 70 eV. The characteristics of the synthesized compounds are given in Tables 2-4.

1-(3H-Imidazo[4,5-*b*]pyridin-2-yl)ethan-1-one hydrazones 2-4. Compound **1** [3] (0.64 g, 4 mmol) and an appropriate hydrazine (6 mmol) in anhydrous ethanol (30 ml) were refluxed with stirring for 1 h. The solid precipitate after cooling or after evaporation of the solvent was filtered off and recrystallized.

2-(1-Aryliminoethyl)imidazo[4,5-*b*]pyridines 5-8. Compound **1** [3] (2 mmol) and an appropriate amine (3 mmol) were heated at 155-165°C with stirring for 15 min. After cooling the solid obtained was washed with ether and recrystallized.

2-Acetylimidazo[4,5-*b*]pyridine Thiosemicarbazone (9). A suspension of compound **1** [3] (0.32 g, 2 mmol) and thiosemicarbazide (0.23 g, 2.5 mmol) in anhydrous ethanol (10 ml) was refluxed with stirring for 5 h. The precipitate obtained after cooling was filtered off and recrystallized.

2-Acetylimidazo[4,5-*b*]pyridine Arylthiosemicarbazones 10-18. Compound **2** (0.52 g, 3 mmol) and an appropriate isothiocyanate (4 mmol) in anhydrous pyridine (15 ml) were heated at 100-105°C with stirring for 5 h. The solvent was then removed *in vacuo*, and the residue was treated with a small amount of methanol, filtered off, and recrystallized from the proper solvent.

6-Methyl-9(8H)-thioxopyrido[3',2':4,5]imidazo[1,2-*d*][1,2,4]triazine (20). The proper thiosemicarbazone (**2** or **10-18**, 2 mmol) in N,N-dimethylaniline (10 ml) was refluxed for 4-5 h. Then, the solvent was removed *in vacuo*, a small amount of benzene was added to the residue, and the solid was filtered off and recrystallized.

6-Methyl-9-(methylthio)pyrido[3',2':4,5]imidazo[1,2-*d*][1,2,4]triazine (21). A suspension of powdered KOH (3 mmol) and compound **20** (2 mmol) in anhydrous ethanol (12 ml) was stirred at room temperature until a solution was obtained. It was then cooled to 0-2°C, and a cooled solution of methyl iodide (3.2 mmol) in anhydrous ethanol (3 ml) was added dropwise during 10 min. Next, the reaction mixture was heated at 40-50°C for 6 h and, after cooling, the solid was filtered off and recrystallized.

6,8-Dimethyl-9-thioxopyrido[3',2':4,5]imidazo[1,2-*d*][1,2,4]triazine (22). To a stirred solution of compound **20** (2 mmol) in nitrobenzene (10 ml) (heated at 130-135°C) a solution of dimethyl sulfate (3 mmol) in nitrobenzene (2 ml) was added dropwise during 10 min. The stirring was then continued at the same

temperature for 4 h. After cooling, the formed solid was filtered off, washed with ether, dissolved in a small amount of H_2O, and alkalized with NH_3. The resultant precipitate was filtered off and recrystallized.

2-Chloro-N'-[1-(3H-imidazo[4,5-*b*]pyridin-2-yl)ethylidene]acetohydrazide (23). Compound **2** (0.52 g, 3 mmol) and triethylamine (4 mmol) in anhydrous THF (10 ml) were stirred at room temperature for 20 min. Next, chloroacetyl chloride (3.5 mmol) was added dropwise during 10 min and the stirring was continued for an additional 20 min. The reaction mixture was then refluxed for 1 h, and the formed solid was filtered off, dissolved in a small amount of water, and alkalized with NH_3. The resultant precipitate was filtered off and recrystallized.

Ethyl-N-[1-(3H-imidazo[4,5-*b*]pyridin-2-yl)ethylidene]hydrazonoformate (24), Ethyl N-[1-(3H-Imidazo[4,5-*b*]pyridin-2-yl)ethylidene]hydrazonoacetate (25). Compound **2** (0.52 g, 3 mmol), dry DMF (8 ml), and triethyl orthoformate or triethyl orthoacetate (3 ml) were refluxed for 5 h. The reaction mixture was then concentrated under vacuum, and the residue was washed with a small amount of acetone, filtered off, and recrystallized.

9-Methyl-6-phenylpyrido[2',3':4,5]imidazo[1,2-*d*][1,2,4]triazine (26). Compound **2** (0.52 g, 3 mmol), dry DMF (8 ml), and triethyl orthobenzoate (4 ml) were refluxed for 5 h. The reaction mixture was then concentrated under vacuum, and the residue was washed with a small amount of acetone, filtered off, and recrystallized.

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