Syntheses of Potassium 1,1-Dioxopyrido[4,3-*e*]-1,4,2-dithiazine-3-thiolate and Its Application to the Synthesis of Novel Sulfonamides with Potential Biological Activity

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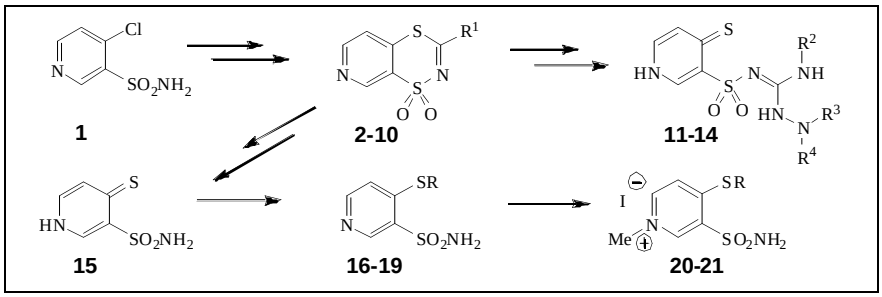

Potassium 1,1-dioxopyrido[4,3-*e*]-1,4,2-dithiazine-3-thiolate **2** has been synthesized and applied to the syntheses of 7*H*-1,1-dioxopyrido[4,3-*e*]-1,4,2-dithiazolium-3-thiolate **3** and 3-methylthiopyrido[4,3-*e*]-1,4,2-dithiazine 1,1-dioxide **4** which provided easy access to a variety of its 3-amino derivatives **5-10**. Hydrazinolysis of **7**, **8** and **10** afforded the corresponding 3-amino-2-(1,4-dihydro-4-thioxopyrid-3-ylsulfonyl)guanidines **11-13**. Subsequent reaction of **12** with 4-chlorobenzaldehyde gave condensation product **14**. 1,4-Dihydro-2-thioxopyridine-3-sulfonamide **15** was also prepared from the potassium salt **2** upon alkaline hydrolysis, whereas alkylation of **15** gave the appropriate *S*-substituted derivatives **16-19** or *S*,*N*-disubstituted compounds **20-21**.

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INTRODUCTION

Arylsulfonamides constitute an important class of compounds with several types of biological activities and well-established safety profile [1]. Currently, there is significant interest in the discovery and development of novel arylsulfonamides for the treatment of cancer and HIV infections [2-5]. Previously, as part of a broad investigation of structures containing 2-thiobenzene-sulfonamide scaffold, we have synthesized several series of novel sulfonamides with remarkable antitumor activity (**A** [6-17], **B** [18-21], **C** [22-24] and **D** [25], Figure 1) or anti-HIV activity (**A** [6-9,17,26-30], **B** [31], **C** [24] **E** and **F** [32], Figure 1). All the sulfonamides of types **A-F** have been obtained starting from 1,4,2-benzodithiazine 1,1-dioxides (**B**, R^3 = SK, SH, SMe or NHR^4, Figure 1).

The above results prompted us to investigate the chemistry of the related 1,1-dioxopyrido[4,3-*e*]-1,4,2-dithiazine heterocyclic ring system (**G**, Figure 1). In this study we describe the facile syntheses of potassium 1,1-

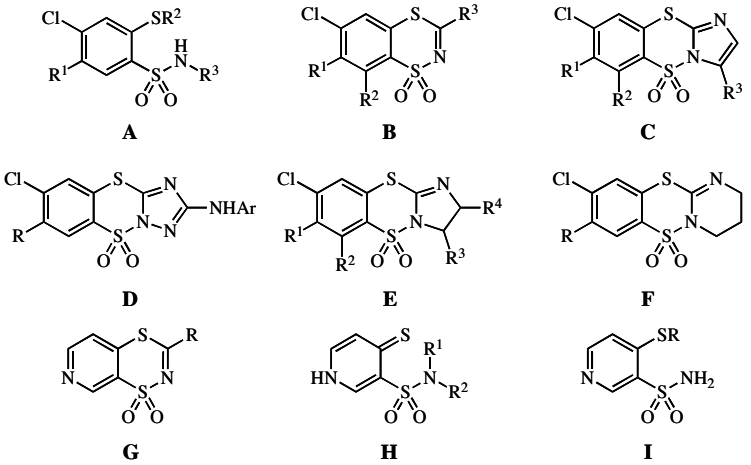


Figure 1

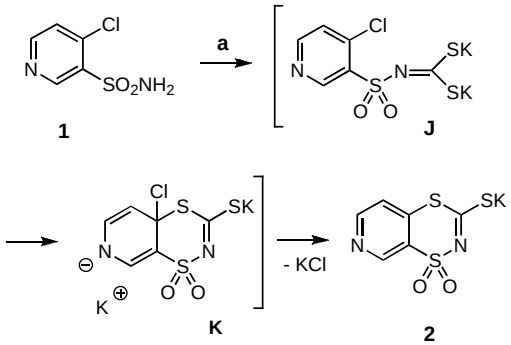
dioxopyrido[4,3-*e*]-1,4,2-dithiazine-3-thiolate which provides access to 3-substituted pyrido[4,3-*e*]-1,4,2-dithiazines, 1,4-dihydro-4-thioxopyridine-3-sulfonamide as well as *S*-substituted 4-mercaptopyridine-3-sulfonamides (**G**, **H** and **I**, Figure 1).

RESULTS AND DISCUSSION

As shown in Schemes 1 and 2, the syntheses of the target pyrido[4,3-*e*]-1,4,2-dithiazine 1,1-dioxides **2-10** were achieved by convenient procedures starting from commercially available 4-chloropyridine-3-sulfonamide **1**. First, the reaction of **1** with carbon disulfide and KOH carried out in ethanol at temperatures gradually increasing (from –1 ºC to reflux) led to the formation of potassium 1,1-dioxopyrido[4,3-*e*]-1,4,2-dithiazine-3-thiolate **2** in 90% yield. The reaction sequence involved the initial formation of dipotassium salt of dithiocarbamic acid **J**, followed by intermolecular ring closure *via* two-step addition-elimination (S_NAr) process which gave rise to the formation of **2** *via* the potassium salt **K** (Scheme 1). Then, upon acidification of the salt **2** with hydrochloric acid the corresponding internal salt **3** was produced in 91% yield. The later compound upon treatment with methyl iodide under mild reaction conditions was converted to the *S*-methyl derivative **4** which subsequently reacted with primary and secondary aliphatic amines in boiling methanol to afford the expected 3-aminopyrido[4,3-*e*]-1,4,2-dithiazine derivatives **5-10** (Scheme 2).

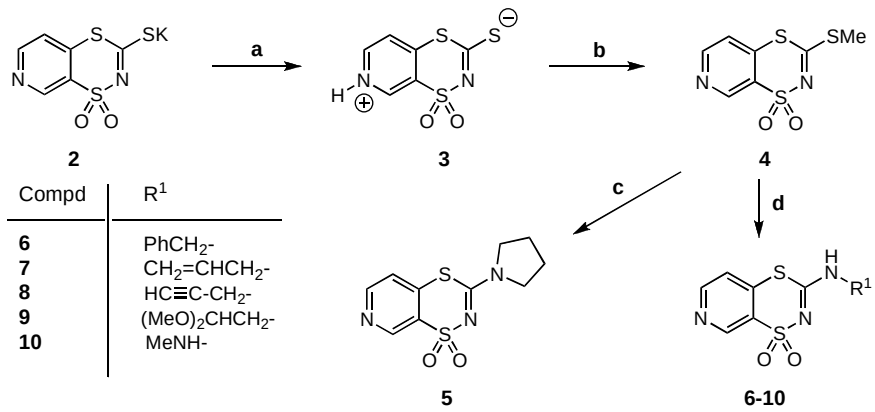
The desired 3-amino-2-(1,4-dihydro-4-thioxopyrid-3-ylsulfonyl)guanidine derivatives **11-13** were obtained by reacting the pyrido[4,3-*e*]-1,4,2-dithiazines **7**, **8** or **10** with hydrazine hydrate in methanol at room temperature (Scheme 3). The intermediary formed nucleophilic ring opening products of type **L** were not isolated and were converted to the corresponding thiols **M** by acidification of the reaction mixtures to pH = 6 with hydrochloric acid.

Scheme 1



Synthesis of potassium 1,1-dioxopyrido[4,3-*e*]-1,4,2-dithiazine-3-thiolate **2**. Reagents, conditions and yield: (a) KOH (2.5 molar equiv.), carbon disulfide (1.5 molar equiv.), ethanol, -1 to 2 ºC 1 h, room temperature 2 h, reflux 32 h, 90%.

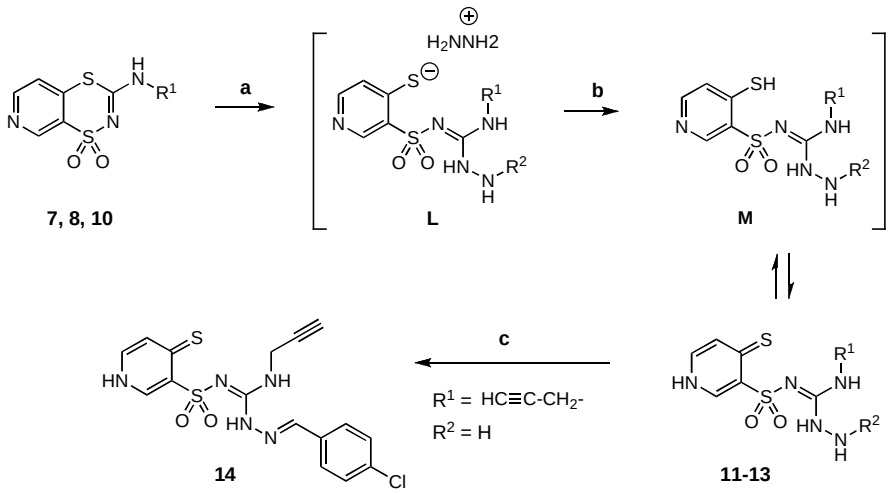
Scheme 2



Compd	R^1
6	$PhCH_2$-
7	CH_2=$CHCH_2$-
8	HC≡C-CH_2-
9	$(MeO)_2CHCH_2$-
10	MeNH-

Application of thiolate **2** to the synthesis of 3-substituted pyrido[4,3-*e*]-1,4,2-benzodithiazine 1,1-dioxides **3-10.** Reagents, conditions and yields: (a) 36% hydrochloric acid (1.1 – 1.2 molar equiv.), water, room temperature, 3 h, 91%; (b) Et_3N (1.05 molar equiv.), MeI (1.05 molar equiv.), CH_2Cl_2, 0 ºC, 1-2 h, room temperature, 16 h, 88%; (c) pyrrolidine (1.1 molar equiv.), methanol, reflux, 28 h, 90%; (d) RNH_2 (1.03 molar equiv.), methanol, room temperature, 48 h, reflux, 26-40 h, 84-98%.

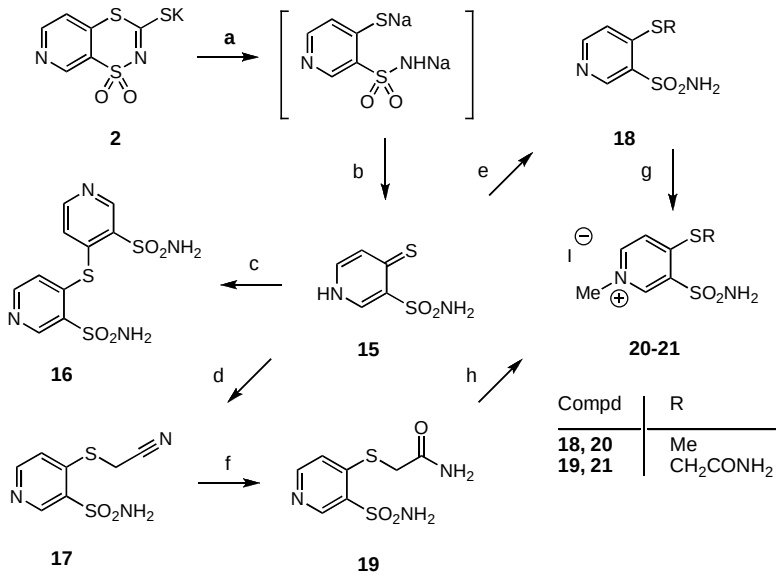
Scheme 3



Compd	R^1	R^2
7, 11	H_2C=CH-CH_2-	H
8, 12	HC≡C-CH_2-	H
10, 13	MeNH-	Me

Usage of 3-aminopyrido[4,3-*e*]-1,4,2-dithiazines **7, 8** and **10** to the synthesis of 2-(1,4-dihydro-4-thioxopyrid-3-ylsulfonyl)guanidine derivatives **11**-**14**. Reagents, conditions and yields: (a) hydrazine hydrate or methylhydrazine (2.0 molar equiv.), methanol, room temperature, 28-30 h; (b) 1% hydrochloric acid to pH 6, 82-91%; (c) 4-chlorobenzaldehyde (1.08 molar equiv.), ethanol, reflux, 10 h, 85%).

Scheme 4



Compd	R
18, 20	Me
19, 21	CH_2CONH_2

Practical application of thiolate **2** to the synthesis of 2-mercaptopyridine-3-sulfonamide derivatives **15-22**. Reagents, conditions and yields: (a) NaOH (3.0 molar equiv.), water, reflux, 6 h; (b) 1.5% hydrochloric acid to pH 3, room temperature, 8 h, 78%; (c) 4-chloropyridine-3-sulfonamide (1.0 molar equiv.), acetonitrile, reflux, 60 h, room temperature, water, NaOH to pH 7.8, 65%; (d) Et_3N (1.06 molar equiv.), bromoacetonitrile (1.06 molar equiv.), acetonitrile, 10-18 ºC, 1 h, room temperature, 2 h, reflux, 2 h, 94%; (e) Et_3N (1.13 molar equiv.), methyl iodide (1.0 molar equiv.), 0-20 ºC, 1.5 h, reflux, 1.5 h, 96%; (f) aqueous solution of H_2O_2 (3.0 molar equiv.), NaOH (3.0 molar equiv.), DMSO, EtOH, 0 ºC, 0.5 h, 74%; (g) methyl iodide (1.1 molar equiv.), acetonitrile, 0-8 ºC, 1 h, room temperature, 8 h, reflux 15 h, 95%; (h) methyl iodide (2.5 molar equiv.), acetonitrile, reflux, 20 h, 96%.

As evidenced by the IR and NMR spectroscopic data (see Experimental), the products **M**, both in solid state and in DMSO solution, exist in pyridine-4-thione tautomeric form **11**-**13**. Finally, the aminoguanidine **12** was subjected to the reaction with 4-chlorobenzaldehyde in boiling ethanol to give the condensation product **14** in 85% yield.

We have also applied potassium pyrido[4,3-*e*]-1,4,2-dithiazine-3-thiolate (**2**) to the synthesis of various *N*- and *S*-substituted 4-mercaptopyridine-3-sulfonamide derivatives **15-21**, as shown in Scheme 4. Thus, the selective alkaline hydrolysis of the thiolate **2** led to the formation of the readily water soluble 4-mercapto-pyridine-3-sulfonamide salt **N**, which upon acidification afforded 1,4-dihydro-4-thioxopyridine-3-sulfonamide **15** in 78% yield. Then, the reactions of **15** with alkyl or aryl halides in acetonitrile followed by neutralization of the reaction mixtures with aqueous NaOH led to the formation of *S*-substituted products **16**-**18** in high yields (Scheme 4).

The alkaline hydrolysis of cyanomethyl sulfide **17** furnished carbamoylmethyl sulfide **19** in 74% yield. Subsequent *N*-alkylation of *S*-substituted 4-mercapto-pyridine-3-sulfonamides **18** and **19** with methyl iodide in acetonitrile led to the formation of the desired 3-sulfamoyl-1-methylpyridinium iodide derivatives **20** and **21** in excellent yields.

The structures of the compounds **2-21** were confirmed by elemental analyses (C, H, N) and spectroscopic data presented in the experimental section. For example, the ^{1}H nmr spectra of compounds **2-19** revealed characteristic two doublet signals of H-5 and H-6 of the 3,4-disubstituted pyridine protons in the region δ 7.23 – 7.83 ppm and δ 7.52 – 8.77 ppm (J = 4.4 – 6.8 Hz), respectively, while the singlet of H-2 proton appeared in the downfield region δ 8.29 – 9.26 ppm. The presence of the sulfonamide moiety in compounds **15**, **16** and **17-21** was indicated by singlet (2H) of NH_2 protons at δ 7.21 – 8.21 ppm. Furthermore, the inspection of ^{13}C nmr spectra of **11**, **12**, **14** and **15** revealed the signal in the downfield region δ 186.1 – 188.1 ppm attributable to the carbon atom of thione group C=S

CONCLUSION

We have developed a method for the preparation of potassium 1,1-dioxopyrido[4,3-*e*]-1,4,2-dithiazine-3-thiolate (**3**) representing a new heterocyclic ring system, which in turn, provides access to a variety of substituted pyrido[4,3-*e*]-1,4,2-dithiazine 1,1-dioxides **3-10**, and novel series of pyridine-3-sulfonamide derivatives **11-21**.

Further structural modifications and biological evaluation of these compounds are in progress and will be described elsewhere.

EXPERIMENTAL

The following instruments and parameters were used: melting points Bűchi 535 apparatus; ir spectra: KBr pellets, 400-4000 cm^{-1} Perkin Elmer 1600 FTIR spectrometer; ^{1}H and ^{13}C nmr: Varian Gemini 200 apparatus at 200 and 50 MHz, respectively; chemical shifts are expressed at δ values relative to Me_4Si as standard.

Potassium 1,1-dioxopyrido[4,3-*e*]-1,4,2-dithiazine-3-thiolate (2). To an ice-cold solution of KOH (42.07 g, 0.75 mol) in 96% ethanol (370 mL), 4-chloro-3-pyridinesulfonamide (57.8 g, 0.3 mol) and carbon disulfide (34.2 g, 0.45 mol) were added with stirring (CAUTION: due to a high toxicity of CS_2 reaction should be performed under the hood). The reaction mixture was stirred at –1 to 2 ºC for 1 h, followed at room temperature for 2 h, and then at reflux for 32 h. After cooling to room temperature the suspension was left overnight. The precipitate was collected by filtration, washed with ethanol (20 mL) and water (6 x 15 mL), and dried at temperatures gradually increasing to 105 ºC. Yield 73.1 g (90%), mp 232-234 ºC; ir (KBr): 1570, 1535 (C=N, C=C), 1380, 1155 (SO_2) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.35 (d, J = 5.5 Hz, 1H, H-5), 8.56 (d, J = 5.5 Hz, 1H, H-6), 8.90 (s, 1H, H-8) ppm; ^{13}C nmr (dimethyl sulfoxide-d_6): δ 118.99, 126.22, 144.77, 147.03, 150.82, 188.72 ppm. *Anal*. Calcd. for $C_6H_3KN_2O_2S_3$ (270.39): C, 26.65; H, 1.12; N, 10.36. Found: C, 26.60, H, 1.25, N, 10.46.

7*H*-1,1-Dioxopyrido[4,3-*e*]-1,4,2-dithiazolium-3-thiolate (3). To a suspension of potassium thiolate **2** (76.6 g, 0.25 mol) in water (360 mL), 36% hydrochloric acid (28 mL) was added with stirring. The reaction mixture was stirred at room temperature for 3 h, and the resulting yellow precipitate was collected by filtration, washed with water (4 x 3 mL) and dried under reduced pressure to give pure thiolate **3**. Yield 52.6 g (91%), mp 169-170 ºC dec.; ir (KBr): 2720, 2700, 2650, 2550, 2060 (NH^+), 1620, 1590 (C=N and C=C), 1375, 1350, 1165, 1155 (SO_2) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.71 (d, J = 5.8 Hz, 1H, H-5), 8.38 (br.s, 1H, NH^+), 8.67 (d, J = 5.8 Hz, 1H, H-6), 9.11 (s, 1H, H-8) ppm. *Anal*. Calcd. for $C_6H_4N_2O_2S_3$ (230.30): C, 30.42; H, 1.74; N, 12.16. Found: C, 30.11, H, 1.88, N, 12.27.

3-Methylthiopyrido[4,3-*e*]-1,4,2-dithiazine 1,1-dioxide (4). To an ice-cold suspension of dithiazolium thiolate **3** (46.06 g, 0.2 mol) in CH_2Cl_2 (250 mL) was added drop by drop with stirring triethylamine (21.2 g, 0.21 mol) and solution of methyl iodide (29.8 g, 0,21 mol) in CH_2Cl_2 (100 mL). After 1 h ice-bath was removed and the resulting solution was stirred at room temperature for 16 h. A small amount of insoluble by-products was filtered out, and the solvent was evaporated *in vacuo*. Resulting residue was triturated with water (200 mL), and precipitate was filtered off, washed successively with water (5 x 30 mL), 50% methanol (3 x 15 mL) and finally with dry methanol (3 x 10 mL), then dried at temperatures gradually increasing to 80 ºC. Yield 43.5 g (88%), mp 153-154 ºC; ir (KBr): 1565, 1540 (C=N and C=C), 1330, 1170 (SO_2) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.70 (s, 3H, CH_3S), 7.33 (d, J = 5.1 Hz, 1H, H-5), 7.75 (d, J = 5.1 Hz, 1H, H-6), 9.26 (s, 1H, H-8) ppm; ^{13}C nmr (deuterio-chloroform): δ 16.83, 120.91, 126.80, 141.43, 147.40, 152.39, 179.34 ppm. *Anal*. Calcd. for $C_7H_6N_2O_2S_3$ (246.63): C, 34.13; H, 2.45; N, 11.37. Found: C, 34.17, H, 2.54, N, 11.53.

3-(Pyrrolidino)pyrido[4,3-*e*]-1,4,2-dithiazine 1,1-dioxide (5). A mixture of **4** (1.73 g, 7 mmol) and pyrrolidine (0.57 g, 8 mmol) in anhydrous methanol (15 mL) was refluxed for 28 h, then allowed to cool to room temperature. The precipitate that obtained was filtered off, washed with methanol (3 x 1 mL) and dried to give **5**. Yield 1.7 (90%), mp 206-207 ºC; ir (KBr): 1565, 1530 (C=N and C=C), 1310, 1165 (SO_2) cm^{-1}; ^{1}H nmr (dimethyl

sulfoxide-d_6): δ 1.89-2.07 (m, 4H, pyrrolidine), 3.58-3.65 (m, 4H, pyrrolidine), 7.83 (d, J = 5.3 Hz, 1H, H-5), 8.75 (d, J = 5.3 Hz, 1H, H-6), 9.05 (s, 1H, H-8) ppm; *Anal*. Calcd. for $C_{10}H_{11}N_3O_2S_2$ (269.35): C, 44.59; H, 4.12; N, 15.60. Found: C, 44.66, H, 4.17, N, 15.64.

General Procedure for the Preparation of 3-(R-Amino)pyrido[4,3-*e*]-1,4,2-dithiazine 1,1-dioxides (6-10). A mixture of **4** (1.73 g, 7 mmol) and the appropriate amine RNH_2 (7.2 mmol) in anhydrous methanol (10 mL) was stirred at room temperature for 48 h, followed at reflux until the evolution of MeSH had ceased (26-40 h) (Caution: because of high toxicity, MeSH should be trapped in aqueous NaOH solution). After cooling to room temperature the precipitate was collected by filtration, washed with methanol (3 x 2 mL) and dried. In this manner the following products were obtained.

3-Benzylaminopyrido[4,3-*e*]-1,4,2-dithiazine 1,1-dioxide (6). Starting from benzylamine (0.77 g), the title compound **6** was obtained (1.9 g, 89%): mp 194-195 ºC; ir (KBr): 3180 (NH), 1590, 1575 (C=N and C=C), 1325, 1160 (SO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.61 (s, 2H, CH_2), 7.30-7.38 (m, 5H, Ph), 7.81 (d, J = 5.5 Hz, 1H, H-5), 8.75 (d, J = 5.5 Hz, 1H, H-6), 9.04 (s, 1H, H-8), 10.33 (s, 1H, NH) ppm. *Anal*. Calcd. for $C_{13}H_{11}N_3O_2S_2$ (305.38): C, 51.13; H, 3.63; N, 13.76. Found: C, 51.11, H, 3.74, N, 13.82.

3-Allylaminopyrido[4,3-*e*]-1,4,2-dithiazine 1,1-dioxide (7). Starting from allylamine (0.41 g), the title compound **7** was obtained (1.5 g, 84%): mp 136-137 ºC; ir (KBr): 3160 (NH), 1645, 1575 (C=N and C=C), 1320, 1170 (SO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.02 (d, J = 5.4 Hz, 2H, CH_2), 5.20 (dd, J_{cis} = 10.2 Hz, J_{gem} = 1.0 Hz, 1H, $NCH_2CH_C{=}CH_A$), 5.25 (dd, J_{trans} = 16.1 Hz, J_{gem} = 1.0 Hz, 1H, $NCH_2CH_C{=}CH_B$), 5.83-5.90 (m, 1H, $NCH_2CH_C{=}CH_2$), 7.81 (d, J = 5.3 Hz, 1H, H-5), 8.75 (d, J = 5.3 Hz, 1H, H-6), 9.03 (s, 1H, H-8), 10.05 (s, 1H, NH) ppm. *Anal*. Calcd. for $C_9H_9N_3O_2S_2$ (255,32): C, 42.33; H, 3.55; N, 16.46. Found: C, 42.30, H, 3.63, N, 16.41.

3-(2-Propynylamino)pyrido[4,3-*e*]-1,4,2-dithiazine 1,1-dioxide (8). Starting from 2-propynylamine (0.4 g), the title compound **8** was obtained (1.6 g, 90%): mp 192-194 ºC; ir (KBr): 3280 (NH), 2110 (C≡CH), 1620, 1575 (C=N and C=C), 1325, 1170 (SO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.33 (s, 1H, C≡CH), 4.21 (s, 2H, CH_2), 7.81 (d, J = 5.3 Hz, 1H, H-5), 8.74 (d, J = 5.3 Hz, 1H, H-6), 9.04 (s, 1H, H-8), 10.37 (br s, 1H, NH) ppm; ^{13}C nmr (dimethyl sulfoxide-d_6): δ 32.28, 75.19, 78.38, 122.58, 127.89, 139.67, 144.39, 151.68, 160.90 ppm. *Anal*. Calcd. for $C_9H_7N_3O_2S_2$ (253.31): C, 42.67; H, 2.78; N, 16.59. Found: C, 42.60, H, 2.87, N, 16.67.

***N*-(1,1-Dioxopyrido[4,3-*e*]-1,4,2-dithiazin-3-yl)aminoacetaldehyde dimethyl acetal (9).** Starting from aminoacetaldehyde dimethyl acetal (0.79 g), the title compound **9** was obtained (1.9 g, 89%): mp 172-173 ºC; ir (KBr): 3200 (NH), 1570, 1550 (C=N and C=C), 1330, 1170 (SO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.37 (s, 6H, 2 x CH_3O), 3.53 (d, J = 5.1 Hz, 2H, CH_2), 4.55 (t, J = 5.1 Hz, C*H*CH_2), 7.84 (d, J = 5.4 Hz, 1H, H-5), 8.78 (d, J = 5.4 Hz, 1H, H-6), 9.07 (s, 1H, H-8), 10.03 (s, 1H, NH) ppm. *Anal*. Calcd. for $C_{10}H_{13}N_3O_4S_2$ (303.36): C, 39.59; H, 4.32; N, 13.85. Found: C, 39.65, H, 4.41, N, 13.97.

3-(2-Methylhydrazino)pyrido[4,3-*e*]-1,4,2-dithiazine 1,1-dioxide (10). Starting from methylhydrazine (0.33 g), the title compound **10** was obtained (1.5 g, 87%): mp 231-232 ºC dec.; ir (KBr): 3325, 3235 (NH-NH), 1645, 1575, 1550 (C=N and C=C), 1315, 1160 (SO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.37 (s, 3H, CH_3), 5.82 (s, 2H, NH-NH), 7.80 (d, J = 5.3 Hz, 1H, H-5), 8.73 (d, J = 5.3 Hz, 1H, H-6), 9.03 (s, 1H, H-8) ppm. *Anal*. Calcd. for $C_7H_8N_4O_2S_2$ (244.30): C, 34.41; H, 3.29; N, 22.93. Found: C, 34.40, H, 3.36, N, 23.11.

Procedures for the Preparation of 2-(1,4-Dihydro-4-thioxopyrid-3-ylsulfonyl) guanidine derivatives (11-13). A mixture of the corresponding pyridodithiazine **7**, **8** or **10** (4 mmol) and 99-100% hydrazine hydrate (0.4 g, 8 mmol) or methylhydrazine (0.37 g, 8 mmol) in anhydrous methanol (4 mL) was stirred at room temperature for 28-30 h. The suspension obtained (pH ~8.5) was acidified with 1% hydrochloric acid to pH 6. The resulting precipitate was collected by filtration, washed successively with methanol (4 x 1 mL) water (6 x 1 mL) and methanol (3 x 1 mL), and dried at temperatures gradually increasing to 90 ºC. In this manner the following guanidines were obtained.

1-Allyl-3-amino-2-(1,4-dihydro-4-thioxopyrid-3-ylsulfon-yl)-guanidine (11). Starting from pyridodithiazine **7** (1.02 g) and hydrazine hydrate, the title compound **11** was obtained (0.95 g, 82%): mp 185-186 ºC dec.; ir (KBr): 3445, 3265, 3170, 3130 (NH_2, NH), 1650, 1615, 1560 (C=N and C=C), 1340, 1190 (SO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.65 (t, J = 5.0 Hz, 2H, CH_2), 4.50 (br s, 2H, NH_2), 4.93-5.09 (m, 3H, N*H*-$CH_2CH{=}CH_2$), 5.66-5.85 (m, 1H, CH_2-C*H*=CH_2), 7.23 (d, J = 6.7 Hz, 1H, H-5, pyrid), 7.30 (t, J = 6.0 Hz, 1H, N*H*-NH_2), 7.52 (d, J = 6.7 Hz, 1H, H-6, pyrid.), 8.23 (s, 1H, H-2, pyrid.), 8.29 (s, 1H, H-1, pyrid.) ppm; ^{13}C nmr (dimethyl sulfoxide-d_6): δ 42.41, 115.05, 131.50, 134.03, 135.48, 135.85, 141.68, 158.61, 187.15 ppm. *Anal*. Calcd. for $C_9H_{13}N_5O_2S_2$ (287.36): C, 37.61; H, 4.56; N, 24.37. Found: C, 37.60, H, 4.71, N, 24.50.

3-Amino-1-(2-propynyl)-2-(1,4-dihydro-4-thioxopyrid-3-yl-sulfonyl)guanidine (12). Starting from pyridodithiazine **8** (1.01 g) and hydrazine hydrate, the title compound **12** was obtained (1.04 g, 91%): mp 199-201 ºC dec.; ir (KBr): 3440, 3280, 3170, 3150 (NH_2, NH), 1620, 1575, 1550 (C=N and C=C), 1350, 1190 (SO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.04 (s, 1H, C≡CH), 3.81 (s, 2H, CH_2), 3.94 (s, 1H, $NHCH_2$), 4.54 (s, 2H, NH_2), 7.24 (d, J = 5.8 Hz, 1H, H-5, pyrid.), 7.48 (s, 1H, HN-N), 7.55 (d, J = 5.8 Hz, 1H, H-6, pyrid.), 8.31 (s, 1H, H-2, pyrid.), 8.33 (s, 1H, H-1, pyrid.) ppm; ^{13}C nmr (dimethyl sulfoxide-d_6): δ 30.48, 73.67, 82.06, 132.74, 134.72, 137.11, 142.06, 158.79, 187.33 ppm. *Anal*. Calcd. for $C_9H_{11}N_5O_2S_2$ (285.35): C, 37.88; H, 3.88; N, 24.54. Found: C, 37.86, H, 3.95, N, 24.45.

1,3-Di(methylamino)-2-(1,4-dihydro-4-thioxopyrid-3-ylsulfonyl)guanidine (13). Starting from pyridodithiazine **10** (0.98 g) and methylhydrazine, the title compound **13** was obtained (1.04 g, 89%): mp 188-189 ºC dec.; ir (KBr): 3310, 3280, 3210 (NH), 1630, 1610 (C=N and C=C), 1380, 1165 (SO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.42 (s, 4H, 2 x HN-NH), 3.36 (s, 6H, 2 x NCH_3), 7.27 (d, J = 6.8 Hz, 1H, H-5, pyrid.), 7.58 (d, J = 6.8 Hz, 1H, H-6, pyrid.), 8.30 (br s, 1H, H-1, pyrid.), 8.38 (s, 1H, H-2, pryid.) ppm. *Anal*. Calcd. for $C_8H_{14}N_6O_2S_2$ (290.37): C, 33.09; H, 4.86; N, 28.94. Found: C, 33.16, H, 4.19, N, 28.89.

3-(4-Chlorobenzylideneamnio)-2-(1,4-dihydro-4-thioxopyrid-3-ylsulfonyl)-1-(2-propynyl)guanidine (14). A mixture of aminoguanidine **12** (1.14 g, 4 mmol) and 4-chlorobenzalehyde (0.6 g, 4.3 mmol) in ethanol (40 mL) was stirred at reflux for 10 h. After cooling to room temperature the resulting suspension was left overnight. The precipitate was collected by filtration, washed successively with ethanol (2 x 2 mL) and methanol (3 x 1 mL), and dried initially at room temperature and then at 90 ºC to give **14** (1.4 g, 85%): mp 190-191 ºC dec.; ir (KBr): 3290, 3255, 3220 (NH), 2110 (C≡CH), 1620, 1600, 1560 (C=N and

C=C), 1365, 1345, 1185 (SO_2), 1260 (C=S) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.11 (s, 1H, C≡CH), 3.93 (d, J = 3.4 Hz, 2H, CH_2), 7.27 (d, J = 6.6 Hz, 1H, H-5, pyrid.), 7.52 (d, J = 8.1 Hz, 2H, 4-ClPh), 7.59 (d, J = 6.6 Hz, 1H, H-6, pyrid.), 7.92 (d, J = 8.1 Hz, 2H, 4-ClPh), 8.27 (s, 2H, 2 x NH, guanidine), 8.40 (s, 1H, H-2, pyrid.), 10.17 (s, 1H, N=C*H*Ph), 12.80 (s, 1H, H-1, pyrid.) ppm; ^{13}C nmr (dimethyl sulfoxide-d_6): δ 30.77, 73.93, 81.61, 129.44, 129.87, 132.43, 133.54, 134.85, 135.33, 136.94, 141.58, 144.97, 154.11, 188.01 ppm. *Anal*. Calcd. for $C_{16}H_{14}ClN_5O_2S_2$ (407.90): C, 47.11; H, 3.46; N, 17.16. Found: C, 47.21, H, 3.50, N, 17.15.

1,4-Dihydro-4-thioxopyridine-3-sulfonamide (15). To a solution of NaOH (6 g, 0.15 mol) in water (60 mL) the thiolate **2** (11.52 g, 0.05 mol) was added. The reaction mixture was refluxed with stirring for 6 h. The resulting solution was acidified with 15% hydrochloric acid to pH 3. After stirring at room temperature for 8 h, the crude product was collected by filtration, washed with water (2 x 5 mL) and purified by crystallization from water. Yield 7.5 g (78%), mp 225-226 ºC dec.; ir (KBr): 3220, 3180, 3105 (NH_2), 1620, 1575 (C=N and C=C), 1365, 1340, 1170, 1160 (SO_2), 1230 (C=S) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 7.21 (s, 2H, NH_2), 7.38 (d, J = 6.7 Hz, 1H, H-5), 7.70 (d, J = 6.7 Hz, 1H, H-6), 8.37 (s, 1H, H-2), 13.04 (s, 1H, H-1) ppm; ^{13}C nmr (dimethyl sulfoxide-d_6): δ 133.25, 133.92, 135.65, 140,44, 186.10 ppm. *Anal*. Calcd. for $C_5H_6N_2O_2S_2$ (190.24): C, 31.56; H, 3.18; N, 14.12. Found: C, 31.58, H, 3.21, N, 14.22.

4,4'-Thiodipyridine-3-sulfonamide (16). A mixture of **15** (0.95 g, 5 mmol) and 4-chloropyridine-3-sulfonamide (0.96 g, 5 mmol) in acetonitrile (50 mL) was stirred at reflux for 60 h. After cooling to room temperature the suspension was left overnight. The mixture of crude product and its hydrochloride was collected by filtration, washed with acetonitrile (3 x 1.5 mL) and then treated with water (15 mL). The resulting suspension (pH ~1.5) was adjusted to pH 7.8 with 1% aqueous solution of NaOH. After 1 h of stirring the title product was collected by filtration, washed successively with water (5 x 3 mL) and hot acetonitrile (5 x 3 mL), and dried. Yield 1.13 g (65%), mp 216-218 ºC dec.; ir (KBr): 3300, 3205 (SO_2NH_2), 1635, 1560 (C=N and C=C), 1335, 1160 (SO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 7.25 (d, J = 5.5 Hz, 2H, H-5 and H-5'), 7.88 (s, 4H, 2 x SO_2NH_2), 8.65 (d, J = 5.5 Hz, 2H, H-6 and H-6'), 9.16 (s, 2H, H-2 and H-2') ppm; ^{13}C nmr (dimethyl sulfoxide-d_6): δ 128.27, 139.74, 143.76, 148.79, 153.58 ppm. *Anal*. Calcd. for $C_{10}H_{10}N_4O_4S_3$ (346.41): C, 34.67; H, 2.91; N, 16.17. Found: C, 34.61, H, 3.06, N, 16.13.

4-(Cyanomethylthio)pyridine-3-sulfonamide (**17**). To a solution of the sulfonamide **15** (1.52 g, 8 mmol) and triethylamine (0.85 g, 8,5 mmol) in acetonitrile (15 mL) a solution of bromoacetonitrile (1.02 g, 8.5 mmol) in acetonitrile (10 mL) was added with stirring while the temperature was maintained below 18 ºC with external cooling. Stirring was continued at room temperature for 2 h, and at reflux for additional 2 h. After cooling to room temperature, the precipitate was collected by filtration, washed with water (5 x 4 mL) and dried at temperatures gradually increasing to 100 ºC. Yield 1.73 g (94%), mp 205-206 ºC dec.; ir (KBr): 3340, 3170 (SO_2NH_2), 2250 (C≡N), 1570_{vs} (C=N and C=C), 1340, 1170 (SO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.54 (s, 2H, CH_2), 7.62 (d, J = 5.4 Hz, 1H, H-5), 7.85 (s, 2H, NH_2), 8.72 (d, J = 5.4 Hz, 1H, H-6), 8.92 (s, 1H, H-2) ppm; ^{13}C nmr (dimethyl sulfoxide-d_6): δ 16.23, 117.26, 120.39, 136.33, 144.99, 148.02, 152.18 ppm. *Anal*. Calcd. for $C_7H_7N_3O_2S_2$ (229.29): C, 36.67; H, 3.08; N, 18.32. Found: C, 36.63, H, 3.17, N, 18.34.

4-Methylthiopyridine-3-sulfonamide (18). Ta an ice-cold solution of **15** (2.85 g, 15 mmol) and triethylamine (1.72 g, 17 mmol) in acetonitrile (20 mL) a solution of methyl iodide (2.13 g, 15 mmol) in acetonitrile (12 mL) was added drop by drop with stirring. After 1 h, the ice bath was removed and the reaction mixture was refluxed for 1.5 h. The solvent was partially evaporated under normal pressure and the resulting suspension was stirred at room temperature for 4 h. The precipitate was collected by filtration, washed with acetonitrile (2 x 1 mL) and water (5 x 3 mL), and dried. Yield 2.95 g (96%), mp 222-223 ºC.; ir (KBr): 3295, 3160 (SO_2NH_2), 1570_{vs} (C=N and C=C), 1345, 1165 (SO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.55 (s, 3H, CH_3S), 7.44 (d, J = 5.5 Hz, 1H, H-5), 7.60 (s, 2H, SO_2NH_2), 8.53 (d, J = 5.5 Hz, 1H, H-6), 8.79 (s, 1H, H-2) ppm; ^{13}C nmr (dimethyl sulfoxide-d_6): δ 14.37, 119.92, 135.80, 147.31, 149.69, 151.71 ppm. *Anal*. Calcd. for $C_6H_8N_2O_2S_2$ (204.27): C, 35.28; H, 3.94; N, 13.71. Found: C, 35.30, H, 4.11, N, 13.83.

4-(Carbamoylmethythio)pyridine-3-sulfonamide (19). To an ice-cold solution of thioacetonitrile **17** (1.38 g, 6 mmol) in DMSO (5 mL) and ethanol (10 mL) aqueous solutions of H_2O_2 (0.6 g, 17.6 mmol) in 2 mL of water and aqueous solution of NaOH (0.7 g) in 3 mL of water were added successively with stirring. After 0.5 h the ice bath was removed and the reaction mixture obtained was poured into water (40 mL). The precipitate thus obtained was immediately collected by filtration and washed thoroughly with water, and dried. Yield 1.1 g (74%), mp 199-200 ºC dec.; ir (KBr): 3405, 3315, 3170 (NH_2), 1690, 1665 (C=O) 1635 (C=N), 1330, 1160 (SO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.85 (s, 2H, CH_2), 7.33 (s, 1H, $CONH_A$), 7.50 (d, J = 4.4 Hz, 1H, H-5), 7.64 (s, 2H, SO_2NH_2), 7.70 (s, 1H, $CONH_B$), 8.56 (d, J = 4.4 Hz, 1H, H-6), 8.82 (2, 1H, H-2) ppm. *Anal*. Calcd. for $C_7H_9N_3O_3S_2$ (247.30): C, 33.99; H, 3.67; N, 16.99. Found: C, 34.06, H, 3.73, N, 17.10.

4-Methylthio-3-sulfamoyl-1-methylpyridinium iodide (20). To an ice-cold suspension of **18** (2.04 g, 10 mmol) in acetonitrile (20 mL) a solution of methyl iodide (1.56 g, 11 mmol) in acetonitrile (15 mL) was added dropwise with stirring while the temperature was maintained below 8 ºC. Stirring was continued at room temperature for 8 h, and at reflux for 15 h. After cooling to room temperature, the precipitate was collected by filtration, washed with acetonitrile (3 x 2 mL), and dried. Yield 3.3 g (95%), mp 218-219 ºC.; ir (KBr): 3210, 3125 (NH_2), 1630_{vs} (C=N and C=C), 1350, 1165 (SO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.81 (s, 3H CH_3S), 4.26 (s, 3H, CH_3N^+), 8.05 (d, J = 6.9 Hz, 1H, H-5), 8.17 (s, 2H, SO_2NH_2), 8.82 (dd, J_{ortho} = 6.9 Hz, J_{meta} = 1.3 Hz, 1H, H-6), 9.07 (d, J = 1.3 Hz, 1H, H-2) ppm. *Anal*. Calcd. for $C_7H_{11}IN_2O_2S_2$ (346.21): C, 24.28; H, 3.20; N, 8.08. Found: C, 24.33, H, 3.24, N, 8.12.

4-(Carbamoylmethylthio)-3-sulfamoyl-1-methylpyridinium iodide (21). A mixture of **19** (0.99 g, 4 mmol) and methyl iodide (1.42 g, 10 mmol) in acetonitrile (20 mL) was refluxed with stirring for 20 h, then allowed to cool to room temperature. The precipitate was collected by filtration, washed with acetonitrile (4 x 2 mL), and dried. Yield 1.5 g (96%), mp 220-221 ºC dec.; ir (KBr): 3385, 3285, 3240, 3180, 3120 (SO_2NH_2, $CONH_2$), 1680 (C=O), 1630, 1605 (C=N and C=C), 1340, 1155 (SO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.19 (s, 2H, SCH_2), 4.25 (s, 3H, CH_3N^+), 7.49 (s, 1H, $CONH_A$), 7.82 (s, 1H, $CONH_B$), 8.04 (d, J = 5.6 Hz, 1H, H-5),

8.21 (s, 2H, SO_2NH_2), 8.84 (d, J = 5.6 Hz, 1H, H-6), 9.09 (s, 1H, H-2) ppm; ^{13}C nmr (dimethyl sulfoxide-d_6): δ 35.73, 47.22, 123.75, 137.21, 142.80, 145.08, 160.02, 167.80 ppm. *Anal*. Calcd. for $C_8H_{12}IN_3O_3S_2$ (389.24): C, 24.68; H, 3.10; N, 10.79. Found: C, 24.70, H, 3.15, N, 10.84.

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