Chemistry of Heterocyclic Compounds, Vol. 40, No. 9, 2004

STUDIES ON PYRAZINE DERIVATIVES. 38. SYNTHESIS, REACTIONS, AND TUBERCULOSTATIC ACTIVITY OF PYRAZINYL-SUBSTITUTED DERIVATIVES OF HYDRAZINOCARBODITHIOIC ACID

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The synthesis of N'-[amino(6-chloro- and 6-cycloaminopyrazin-2-yl)methylene]carbodithioic acid mono- and diesters and their reactions are described. Cyclization of monoesters with secondary amines in acidic media gave the 1,3,4-thiadiazole derivatives, while the cyclization of diesters with amines yielded 1,2,4-triazoles with the amine substituent in position 3. The in vitro tuberculostatic activity of the prepared compounds was tested.

Keywords: 6-chloro-2-cyanopyrazine, amidrazones, mono- and diesters of hydrazinocarbodithioic acids, imino esters, 1,3,4-thiadiazole-2-thiol, 1,2,4-triazoles, carbon disulfide, tuberculostatics.

Amidrazones can react easily with carbon disulfide. It is known that the reactions of phenyl- and pyridylamidrazones with carbon disulfide in neutral medium give exclusively 5-substituted 1,3,4-triazolo-2-thiones [1]. We have reported [2, 3] that reactions of carbon disulfide with pyrazine derivatives of amidrazone give various products, depending on the reaction condition. It was found that carbon disulfide and amidrazone addition product can be alkylated to give mono- and diesters of pyrazinecarbiminodithiocarbazoic acid. The latter reacts with amines, yielding heterocyclic compounds difficultly obtainable by other methods. Some of these products showed high tuberculostatic activity.

This paper presents reactions of 6-chloropyrazine-2-carbamidrazone with carbon disulfide, as well as application of the products formed to the syntheses of other organic compounds.

The presence of chlorine in position 6 of the pyrazine ring opens new possibilities for the synthesis of pyrazine derivatives compared to those reported for unsubstituted pyrazinecarbamidrazone.

CHEMISTRY

In a first step of this study the possibility of formation of thiadiazoles bearing the thiol or S-alkyl group in position 2 of the ring was tested. As expected, carbon disulfide reacted easily with 6-chloropyrazinecarbamidrazone in ethanolic medium to give 5-(6-chloropyrazin-2-yl)-1,3,4-thiadiazole-2-thiol (**1**). Thus, the reaction proceeded analogously as reported earlier [1]. It was also found that addition of alkyl halide (MeI, $ClCH_2Ph$) to the reaction mixture led to the corresponding S-alkylthiadiazole derivatives **2a-b**.

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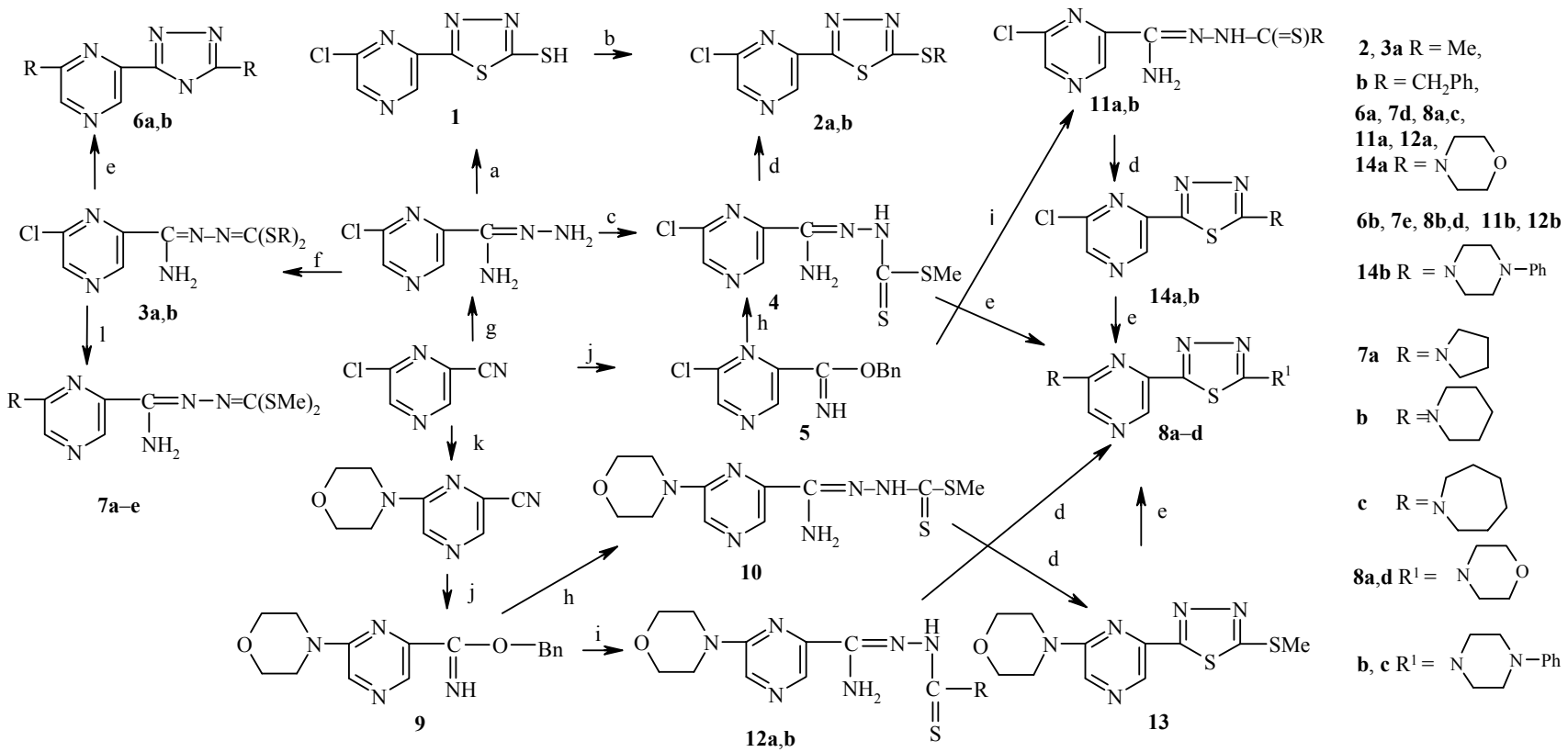

a) CS_2, EtOH; b) KOH, RX, EtOH; c) CS_2, KOH, MeI, EtOH; d) EtOH, H^+; e) amines, boiling; f) CS_2, KOH, EtOH, 2RX; g) H_2NNH_2, EtOH; h) $H_2NNHCSSMe$, MeOH; i) $H_2NNH–C(=S)–NR$; j) BnOH, benzene; k) morpholine, benzene; l) amines, DMF, boiling 0.25 h

TABLE 1. Characteristics of the Newly Synthesized Pyrazinyl Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (solvent for crystalization)	Yield, % (method)
		C	H	N		
1	$C_6H_3ClN_4S_2$	31.41 / 31.24	1.53 / 1.31	24.43 / 24.28	205-206 (EtOH)	64
2a	$C_7H_5ClH_4S_2$	34.43 / 34.36	2.12 / 2.06	23.02 / 22.89	102-103 (EtOH–H_2O)	40 (A) 65 (B) 95 (C)
2b	$C_{13}H_9ClN_4S_2$	48.90 / 48.67	3.11 / 2.83	17.52 / 17.46	100-102 (MeOH)	30
3a	$C_8H_{10}ClN_5S_2$	34.73 / 34.84	3.82 / 3.65	25.56 / 25.39	152-153 (EtOH)	82
3b	$C_{20}H_{18}ClN_5S_2$	56.02 / 56.13	4.33 / 4.24	16.42 / 16.36	133-134 (EtOH)	63
4	$C_7H_8ClN_5S_2$	32.27 / 32.12	3.19 / 3.08	26.70 / 26.75	174→360 (MeOH)	45 (A) 60 (B)
6a	$C_{14}H_{19}N_7O_2$	52.85 / 52.99	6.14 / 6.03	31.13 / 30.90	273-275 (dioxane–MeOH)	40
6b	$C_{26}H_{29}N_9$	66.81 / 66.79	6.50 / 6.25	27.13 / 26.96	267-269 (dioxane–MeOH)	40
7a	$C_{12}H_{18}N_6S_2$	46.26 / 46.43	5.97 / 5.84	27.18 / 27.07	171-173 (EtOH)	80
7b	$C_{13}H_{20}N_6S_2$	48.34 / 48.12	6.36 / 6.21	25.86 / 25.90	153-154 (MeOH)	95
7c	$C_{14}H_{22}N_6S_2$	49.74 / 49.68	6.83 / 6.55	24.96 / 24.83	128-130 (MeOH)	95
7d	$C_{12}H_{18}N_6OS_2$	44.26 / 44.15	5.71 / 5.56	25.62 / 25.74	158-159 (MeOH)	90
7e	$C_{18}H_{23}N_7S_2$	53.76 / 53.84	5.93 / 5.77	24.56 / 24.42	126-127 (MeOH)	95
8a	$C_{14}H_{18}N_6O_2S$	45.94 / 45.88	5.16 / 4.95	23.20 / 22.93	273-275 (dioxane–EtOH)	35 (A) 75 (B) 55 (C) 45 (D)
8b	$C_{26}H_{28}N_8S$	64.61 / 64.43	5.96 / 5.82	23.37 / 23.12	244-247 (dioxane)	30
8c	$C_{20}H_{23}N_7O_3$	58.77 / 58.67	5.82 / 5.66	24.18 / 23.94	216-217 (dioxane)	85 (A) 75 (B)
8d	$C_{20}H_{23}N_7O_3$	58.81 / 58.67	5.62 / 5.66	23.98 / 23.94	249-250 (dioxane)	85
9	$C_{16}H_{18}N_4O_2$	64.58 / 64.41	6.17 / 6.08	18.92 / 18.78	152-154 (benzene)	50
10	$C_{11}H_{16}N_6OS_2$	42.51 / 42.29	5.32 / 5.16	27.03 / 26.90	155→280 (EtOH)	80
11a	$C_{10}H_{13}ClN_6OS$	40.14 / 39.93	4.51 / 4.36	28.12 / 27.94	152-154 (EtOH–dioxane)	65
11b	$C_{16}H_{18}ClN_7S$	51.24 / 51.13	4.97 / 4.83	26.18 / 26.08	124-126 (EtOH)	55
12a	$C_{14}H_{21}N_7O_2S$	47.96 / 47.85	6.18 / 6.02	28.12 / 27.90	170-280 (EtOH)	70
12b	$C_{20}H_{26}N_8OS$	56.47 / 56.32	6.26 / 6.14	26.38 / 26.27	180-182 (EtOH)	50
13	$C_{11}H_{13}N_5OS_2$	14.91 / 14.73	4.62 / 4.44	23.93 / 23.71	189-190 (dioxane)	90
14a	$C_{10}H_{10}ClN_5OS$	42.42 / 42.33	3.78 / 3.55	24.84 / 24.68	181-182 (MeOH)	90
14b	$C_{16}H_{15}ClN_6S$	53.50 / 53.55	4.26 / 4.21	23.57 / 23.42	198-200 (EtOH)	70

TABLE 2. IR and ^{1}H NMR data for compounds **1-14**

Com-pound	IR, cm^{-1}	^{1}H NMR, δ, ppm, solvent
1	2	3
1	3109, 2965, 2864, 1433, 1398, 1231, 1166, 1143, 1070,1005, 743, 455	DMSO-d_6: 8.95 and 9.20 (2s, 2H pyrazine)
2a	3051, 2930, 1511, 1346, 1311, 1164, 1150, 1008, 812, 453	$CDCl_3$: 2.90 (3H, s, CH_3); 8.68 and 9.45 (2s, 2H pyrazine)
2b	3040, 1511, 1338, 1165, 1144, 1025, 1006, 715, 454	$CDCl_3$: 4.65 (2H, s, CH_2); 7.35-7.50 (m, 5H phenyl); 8.65 and 9.45 (2s, 2H pyrazine)
3a	3469, 3355, 1615, 1486, 1435, 1401, 1174, 1039, 1010, 945, 876, 449	$CDCl_3$: 2.55 and 2.60 (6H, 2s, $2CH_3$); 6.00 (2H, br. s, NH_2); 8.63 and 9.45 (2s, 2H pyrazine)
3b	3494, 3387, 1614, 1494, 1434, 1170, 1017, 703	$CDCl_3$: 4.35 and 4.45 (4H, 2s, $2CH_2$); 5.80 (2H, br. s, NH_2); 7.30-7.50 (10H, m, 2 phenyl); 8.60 and 9.40 (2s, 2H pyrazine)
4	3433, 3283, 3061, 2916, 1625, 1502, 1368, 1318, 1170, 1006	$(CD_5)_2CO$: 2.57 (3H, s, CH_3); 6.98 (2H, br. s, NH_2); 8.78 and 9.32 (2s, 2H pyrazine); 11.10 (1H, br. s, NH)
6a	3164, 3080, 2958, 2863, 1535, 1520, 1442, 1261, 1114, 923, 761	DMSO-d_6: 3.30-3.70 (2m, 16H morpholine); 8.33 and 8.36 (2s, 2H pyrazine)
6b	3175, 3061, 2829, 1599, 1538, 1518, 150, 1446, 1232, 1158, 940, 757, 692	DMSO-d_6: 3.37; 3.60 and 3.88 (16H, 3m, 2 pyrazine); 6.80-7.32 (3m, 10H phenyl); 8.42 and 8.45 (2s, 2H pyrazine)
7a	3440, 3283, 2963, 2920, 2848, 1619, 1578, 1526, 1499, 1429, 1217, 1172, 1026, 848, 469	$CDCl_3$: 1.95 and 3.40 (2m, 8H pyrolidine); 2.45 and 2.50 (6H, 2s, $2CH_3$); 5.90 (2H, br. s, NH_2); 7.70 and 8.65 (2s, 2H pyrazine)
7b	3459, 3288, 2921, 2851, 1621, 1571, 1524, 1498, 1427, 1258, 1215, 1181, 1125, 1024, 998, 934, 469	$CDCl_3$: 1.60:3.50 (2m, 10H piperidine); 2.42 and 2.50 (6H, 2s, $2CH_3$); 5.85 (2H, br. s, NH_2); 8.05 and 8.65 (2s, 2H pyrazine)
7c	3446, 3300, 2923, 2848, 1614, 1569, 1524, 1438, 1154, 1024, 997	$CDCl_3$: 1.40 and 1.90 (8H, 2m, $4CH_2$); 2.45 and 2.50 (6H, 2s, $2CH_3$); 3.60 (4H, t, $2CH_2N$); 5.90 (2H, br. s, NH_2); 8.95 and 9.60 (2s, 2H pyrazine)
7d	3449, 3307, 2952, 2851, 1613, 1571, 1525, 1440, 1260, 1205, 1117, 1022, 1003, 935	$CDCl_3$: 2.45 and 2.50 (6H, 2s, $2CH_3$); 3.40 and 3.90 (2m, 8H morpholine); 5.85 (2H, br. s, NH_2); 8.10:8.75 (2s, 2H pyrazine)
7e	3482, 3368, 1615, 1573, 1523, 1494, 1446, 1232, 1002, 938, 756, 692	$CDCl_3$: 2.52 and 2.58 (6H, 2s, $2CH_3$); 3.34 and 3.79 (2m, 8H piperazine); 6.97 (2H, br. s, NH_2); 6.89:7.36 (2m, 5H phenyl); 8.23 and 8.86 (2s, 2H pyrazine)
8a	2960, 2902, 1510, 1446, 1253, 1198, 1115, 910	$CDCl_3$: 3.60-3.90 (2m, 16H morpholine); 8.13 and 8.77 (2s, 2H pyrazine)
8b	2822, 1599, 1493, 1452, 1264, 1229, 761, 695	$CDCl_3$: 3.40 and 3.85 (2m, 16H piperazine); 7.20-7.35 (10H, 2m, 2 phenyl); 8.20 and 8.77 (2s, 2H pyrazine)
8c	2959, 2854, 1503, 1447, 1259, 1229, 1119, 936, 764	DMSO-d_6: 3.40-3.90 (16H, 4m, $8CH_2$); 7.00-7.40 (2m, 5H phenyl); 8.37 and 8.50 (2s, 2H pyrazine)
8d	3058, 2959, 2851, 2827, 1599, 1567, 1497, 1446, 1267, 1234, 1116, 904, 758, 690	$CDCl_3$: 3.35-3.90 (16H, 3m, $8CH_2$); 6.95-7.40 (2m, 5H phenyl); 8.20 and 8.76 (2s, 2H pyrazine)
9	3275, 3062, 2965, 2843, 1648, 1574, 1530, 1476, 1448, 1348, 1267, 1238, 1118, 1002, 865, 733, 445	DMSO-d_6: 3.60-3.75 (m, 8H morpholine); 5.37 (2H, s, CH_2); 7.32-7.50 (m, 5H phenyl); 8.27 and 8.49 (2s, 2H pyrazine); 9.28 (s, 1H, NH)
10	3394, 3279, 3123, 2858, 1668, 1601, 1533, 1414, 1297, 1262, 1117, 991, 877	$(CD_3)_2CO$: 2.44 (3H, s, SCH_3); 2.55 (3H, s, SCH_3); 3.65-3.85 (16H, 2m, 2 × morpholine); 6.60 (2H, br. s, NH_2); 8.33 (s, 1H pyrazine); 8.62 (d, 2H pyrazine); 8.69 (s, 1H pyrazine). Two isomers 1:1 [9]

TABLE 2 (continued)

1	2	3
11a	3401, 3306, 3262, 2919, 2855, 1637, 1528, 1434, 1360, 1279, 1173, 1112, 1008, 848	DMSO-d_6: 3.50-3.90 (2m, 8H morpholine); 8.90 and 9.20 (2s, 2H pyrazine)
11b	3288, 3147, 1664, 1634, 1599, 1495, 1429, 1367, 1340, 1303, 1266, 1228, 1169, 1016, 927, 757, 692, 453	$CDCl_3$: 3.35 and 4.20 (2m, 8H piperazine); 6.95 and 7.30 (2m, 5H phenyl); 8.66 and 9.20 (2s, 2H pyrazine)
12a	3476, 3359, 3276, 2972, 2857, 1677, 1560, 1527, 1429, 1303, 1260, 1116, 1024, 891	DMSO-d_6: 3.35-3.90 (16H, m, 2 morpholine); 8.57 and 8.60 (2s, 2H pyrazine); 12.67 (1H, s, NH)
12b	3383, 3033, 2853, 1664, 1598, 1532, 1427, 1347, 1301, 1260, 1233, 1118	$CDCl_3$: 3.28; 3.73; 3.87 and 4.20 (4m, 16H morpholine and piperazine); 6.30 (2H, br. s, NH_2); 6.90-7.35 (2m, 5H phenyl); 8.31 and 8.40 (2s, 2H pyrazine); 13.36 (1H, s, NH)
13	3067, 2963, 2859, 1577, 1525, 1469, 1360, 1260, 1209, 1118, 1082, 993, 948, 859	$CDCl_3$: 2.84 (3H, s, CH_3); 3.64 and 3.86 (2m, 8H morpholine); 8.18 and 8.79 (2s, 2H pyrazine)
14a	2921, 2864, 1512, 1264, 1164, 1118, 1006, 906	$CDCl_3$: 3.51 and 3.90 (2m, 8H morpholine); 8.58 and 9.36 (2s, 2H pyrazine)
14b	1600, 1513, 1450, 1399, 1310, 1298, 1273, 1230, 1162, 1026, 1008, 933, 764, 696, 456	$CDCl_3$: 3.37 and 3.84 (2m, 8H morpholine); 7.00 and 7.32 (2m, 5H phenyl); 8.56 and 9.35 (2s, 2H pyrazine)

The alkylation reaction proceeded differently in alkaline medium, and the reaction products depended on the molar ratios of the reagents. The use of at least double molar excess of the base and the alkyl halide produced pure dithiocarbazoic acid diesters **3a,b** in very good yields, while the use of stoichiometric amounts of the reagents gave dithiocarbazoic acid monoester **4** as the main product, and only small amounts of the diester. The mixtures of mono and diesters were difficult to separate, and for this reason another way of monoester **4** synthesis was designed. Namely, benzyl-6-chloropyrazine-2-carbimide (**5**), synthesized according to the known method [4], was reacted with dithiocarbazoic acid methyl ester to give the desired compound.

In the next step of the study, the reactivity of the synthesized dithiocarbazoic acid mono- and diesters towards secondary amines was tested. Because of the two potential reaction centers in the substrate molecules, namely, the halide and methylthio groups, the reaction products depended strongly on the solvent, molar ratios of the reagents, and the way the reactions were carried out. Prolonged heating of the diester **3a** with morpholine and 4-phenylpiperazine led to the formation of 1,2,4-triazole derivatives **6a,b**, with amine substituents in position 6 of the pyrazine ring and in position 3 of the triazole ring. Low-boiling amines, pyrrolidine, piperidine, and homopiperidine, in spite of long reflux, gave only the products of chlorine atom substitution. In addition, yields of the products **7a-e** were poor, and the compounds were strongly contaminated. Good yields of pure compounds **7a-e** were obtained in the reactions with all the amines upon heating for 15-30 min in dimethylformamide.

The reactions of dithiocarbazoic acid monoester **4** with morpholine and 4-phenylpiperazine gave different products. In this case, attempts at selective substitution of the chlorine atom in the piperazine ring or the methylthio group failed. Short heating in the neat amines and in various solvents led to difficultly separable mixtures, while prolonged heating in neat amines produced compounds **8a** and **8b** formed by replacement of both chlorine atom and the methylthio group by the amine residue, and simultaneous cyclization to the 1,3,4-thiadiazole system.

The structures of compounds **8a** and **8b** were confirmed by independent synthesis. Thus, imino esters **5** and **9** were reacted with hydrazinocarbodithioic acid methyl ester, as well as with hydrazino-, morpholino- and 1-phenylpiperazine-4-carbothioic acid hydrazide, to give compounds **11a,b** and **10**, **12a,b**, respectively.

Compounds **10** and **11a,b** in acidic media underwent cyclization to the corresponding 1,3,4-triazole derivatives **13** and **14a,b**, similarly as compound **2a** obtained from methyl N'-[amino(6-chloropyrazin-2-yl)methylene]hydrazinocarbodithioate (**4**). Heated in an excess of morpholine or 1-phenylpiperazine, compounds **2a**, **13**, and **14a,b** yielded the pyrazinylthiadiazole derivatives **8a,b**. The same compounds were formed by cyclization of compounds **12a,b** in acidic media.

Variation of the secondary amine in the above reactions would, presumably, make possible synthesis of analogues of compounds **8a,b** with any desired amine substituent. The reactions of compounds **13** and 1**4a** with 1-phenylpiperazine seem to confirm this presumption, as the phenylpiperazine substituent was found in position 2 of the 1,2,4-thiadiazole system of compound **8c** and in the pyrazine ring of compound **8d**.

MICROBIOLOGY

The tuberculostatic activity of the new compounds was tested towards *Myc. tbc* $H_{37}Rv$ strain and two "wild" strains isolated from tuberculosis patients: one resistant to *p*-aminosalicylic acid (PAS), isonicotinic acid hydrazide (INH), ethambutol (EMB), and ryfampycine (RFP), and the other fully sensitive to the drugs administered.

In vitro investigations were carried on by a classical test tube method [5] of successive dilutions with Youman's fluid medium containing 10% of bovine serum.

The determined minimum concentrations inhibiting the growth of tuberculous strains (MIC) showed the tested group of compounds to be of low activity. MIC values for most of the compounds were within the limits 125-500 μg/ml.

The highest activity was shown by compound **8**, with MIC value for $H_{37}Rv$ strain 32 μg/ml, and 63 μg/ml for both "wild" strains, and by compound **4**, with MIC value 32 μg/ml for all the strains used.

EXPERIMENTAL

Melting points were determined with a Boetius apparatus and are uncorrected. The IR spectra were taken with a Satellite spectrophotometer. The ^1H NMR spectra were taken with a Varian Gemini 200 spectrometer BS-487c. Reaction yields and the physical constants of the compounds obtained are given in Table 1.

5-(6-Chloropyrazin-2-yl)[1,3,4]thiadiazole-2-thiol (1). To a solution of 6-chloropyrazine-carbamidrazone [5] (0.85 g, 5 mmol) in ethanol (25 ml), carbon disulfide (0.6 ml, 10 mmol) was added and the mixture was refluxed for 1 h. After cooling, the resulting precipitate was filtered off and recrystallized.

5-(6-Chloropyrazin-2-yl)-2-methylthio[1,3,4]thiadiazole (2a). A. To a solution of 6-chloro-pyrazinecarbamidrazone (0.85 g, 5 mmol) in ethanol (25 ml), carbon disulfide (0.5 ml, 8 mmol) was added and after 5 min MeI (0.35 ml, 5 mmol) was introduced to the reaction mixture, which was refluxed for 1 h. After cooling, the resulting precipitate was filtered off and recrystallized.

B. Compound **1** (0.22 g, 10 mmol) was added to a solution of KOH (0.56 g, 10 mmol) in ethanol (5 ml), then MeI (0.6 g, 10 mmol) was introduced and the mixture was refluxed for 0.5 h. The product precipitated after cooling.

C. To a solution of compound **4** (0.26 g, 1 mmol) in ethanol (5 ml) concentrated HCl (0.5 ml) was added and the mixture was heated to boiling. On cooling, 20 g of ice was added and the precipitated compound **2a** filtered off.

3-Benzylthio-5-(6-chloropyrazin-2-yl)[1,3,4]thiadiazole (2b). This compound was obtained as described for **2a** (see Method A) taking benzyl chloride (0.8 ml, 5 mmol) instead of MeI.

N'-[Amino-(6-chloropyrazin-2-yl)methylene]hydrazinocarbodithioic Acid Dimethyl Ester (3a). A mixture of 6-chloropyrazinecarbamidrazone (10.3 g, 0.06 mmol), methanol (200 ml), triethylamine (20 ml, 0.15 mmol), CS_2 (8 ml, 0.13 mmol), and MeI (10 ml, 0.16 mmol) was refluxed until homogenization and allowed to cool. After additional ice-cooling the precipitated compound **3a** was filtered off and recrystallized.

N'-[Amino-(6-chloropyrazin-2-yl)methylene]hydrazinocarbodithioic Acid Dibenzyl Ester (3b). Obtained as described for **3a**, starting from chloroamidrazone (3.4 g, 20 mmol), methanol (20 ml), triethylamine (6 ml, 40 mmol), CS_2 (2 ml, 33 mmol), and benzyl chloride (5.5 ml, 50 mmol).

N'-[Amino-(6-chloropyrazin-2-yl)methylene]hydrazinocarbodithioic acid methyl ester (4). A. To 6-chloropyrazinecarbamidrazone (8.5 g, 50 mmol) dissolved in ethanol (100 ml) a solution of KOH (2.8 g, 50 mmol) in ethanol (50 ml) was added, and then, through a reflux condenser, CS_2 (3 ml, 5 mmol) was introduced. Water was added to the suspension until the solution clarified (ca 50 ml) and then MeI (3.2 ml, 50 mmol) was added dropwise. The mixture was allowed to stand for 0.5 h, then evaporated to half of its initial volume and cooled. The precipitate was collected and recrystallized. TLC analysis showed a small admixture of compound **3a**.

B. A warm solution of compound **5** [4] (2.5 g, 10 mmol) in methanol (10 ml) was treated with hydrazinocarbodithioic acid methyl ester [6] (1.2 g, 10 mmol) dissolved in methanol (20 ml) and stirred for 0.5 h. A few seconds after combining both solutions, a yellow crystalline precipitate appeared. After another hour of standing and cooling the mixture, the compound was filtered off.

3-Morpholino-5-(6-morpholinopyrazin-2-yl)[1,2,4]triazole (6a). Compound **3a** (0.45 g, 2 mmol) and morpholine (2 ml, 25 mmol) were refluxed for 10 h. After cooling, methanol was added (5 ml) and the precipitated product was collected and recrystallized.

3-(4-Phenylpiperazin-1-yl)-5-[6-(4-phenylpiperazin-1-yl)pyrazin-2-yl][1,2,4]triazole (6b). Compound **3a** (1.38 g, 5 mmol), 1-phenylpiperazine (3.5 ml, 20 mmol), and DMF (2 ml) were refluxed for 3 h. Methanethiol was evolved vigorously throughout the procedure. After cooling to ambient temperature, the mixture was treated with methanol (5 ml), ice-cooled, and a precipitate of compound **6b** was collected.

N'-[Amino(6-cycloaminopyrazin-2-yl)methylene]hydrazinocarbodithioic Acid Dimethyl Esters (7a-e). Compound **3a** (1.38 g, 5 mmol), the corresponding amine (3 ml), and DMF (3 ml) were refluxed for 15 min. The mixture was then poured on ice (30 g) and the precipitate was collected and recrystallized.

3-Morpholino-5-(6-morpholinopyrazin-2-yl)[1,3,4]thiadiazole (8a). A. Compound **4** (1.3 g, 5 mmol) and morpholine (5 ml, 50 mmol) were refluxed for 3 h. On cooling, a precipitate was formed. The solid was filtered off, washed with methanol, and crystallized.

B. Compound **12a** (0.9 g, 2.5 mmol) dissolved in warm methanol (10 ml) was treated with concentrated HCl (0.5 ml) and allowed to stand until cooled. The precipitate was collected and recrystallized.

C. Compound **2a** or 13 (2 mmol), morpholine (3 ml, 50 mmol), and DMF (2 ml) were refluxed till the methanethiol evolution ceased (about 20 h). On cooling, water (10 ml) was added, the mixture was allowed to cool, and the precipitate was filtered off.

D. The compound was obtained as described above (see Method C) from **14c** by heating in neat morpholine for 3 h.

2-(4-Phenylpiperazin-1-yl)-5-[6-(4-phenylpiperazin-1-yl)pyrazin-2-yl][1,3,4]thiadiazole (8b). Compound **4** (0.65 g, 2.5 mmol) and 1-phenylpiperazine (1.5 ml, 10 mmol) in anhydrous dioxane (5 ml) were refluxed for 20 h. Then water (20 ml) was added and the mixture was cooled in ice. The crystalline residue was, after decantation of the liquid, purified by recrystallization.

2-(4-Phenylpiperazin-1-yl)-5-(6-morpholinopyrazin-2-yl)[1,3,4]thiadiazole (8c). A. Compound **13** (0.26 g, 1 mmol), 1-phenylpiperazine (2 ml, 13 mmol), and DMF (1 ml) were refluxed for 4 h and allowed to stand for crystallization. Then MeOH (5 ml) was added and the product collected and recrystallized.

B. A solution of compound **10** (0.3 g, 1 mmol) in chloroform (2 ml) was added to a solution of 4-phenylpiperazinecarbodithioic acid hydrazide (0.24 g, 1 mmol) in DMSO (2 ml) and the mixture was stirred for 48 h. Then methanol (10 ml) and concentrated HCl (1 ml) were added. The oily deposit crystallized while

stirred. The whole was neutralized with saturated $NaHCO_3$ solution. On cooling, the precipitate was filtered off, washed with water, and crystallized from MeOH–water mixture.

2-Morpholino-5-[6-(4-phenylpiperazin-1-yl)pyrazin-2-yl][1,3,4]thiadiazole (8d). Compound **14a** (0.46 g, 2.5 mmol), 1-phenylpiperazine (1.5 ml, 10 mmol), and dioxane (3 ml) were refluxed for 2 h. On boiling, the amine hydrochloride deposited. After cooling to ambient temperature the mixture was additionally ice-cooled. The precipitate was collected and recrystallized from dioxane.

6-Morpholinopyrazine-2-carboimidic Acid Benzyl Ester (9). Obtained as described for compound **5**; 2-cyano-6-morpholinopyrazine [8] (3.8 g, 20 mmol) and benzyl alcohol (3 ml, 30 mmol) were taken for the reaction.

N'-[Amino(6-morpholinopyrazin-2-yl)-methylene]hydrazinocarbodithioic Acid Methyl Ester (10). Compound **9** (1.5 g, 5 mmol) was dissolved in hot MeOH (25 ml), and a solution of hydrazinecarbodithioic acid methyl ester [7] (1.22 g, 10 mmol) in MeOH (10 ml) was added. The mixture was stirred for 2 h. After strong cooling, the product was filtered off and recrystallized from ethanol.

Morpholine-4-carbothioic Acid N'-[Amino(6-chloropyrazin-2-yl)methylene]hydrazide (11a). To compound **5** (1.28 g, 5 mmol) dissolved in hot MeOH (10 ml) a hot solution of morpholine-4-carbothioic acid hydrazide [7] (0.8 g, 5 mmol) in MeOH (15 ml) and water (5 ml) was added. The mixture was stirred for 2 h, then ice-cooled and the product filtered off. From the filtrate an additional portion of product was precipitated by water.

4-Phenylpiperazine-1-carbothioic Acid N'-[Amino(6-chloropyrazin-2-yl)methylene]hydrazide (11b). To a solution of 4-phenylpiperazinecarbothioic acid hydrazide (0.24 g, 1 mmol) in DMSO (2 ml), compound 4 (0.25 g, 1 mmol) was added and the mixture was stirred for 48 h. Then the reaction mixture was diluted with water (10 ml) and extracted twice with CHCl3 (3 × 30 ml). The combined extracts were dried with anhydrous MgSO4, chloroform was evaporated, and the residue was crystallized from ethanol.

Morpholine-4-carbothioic Acid N'-[Amino(6-morpholinopyrazin-2-yl)methylene]hydrazide (12a). Obtained by analogy to compound **10**; morpholine-4-carbothioic acid hydrazide (5 mmol) was taken for the reaction instead of $H_2NNHCSSMe$.

4-Phenylpiperazine-1-carbothioic Acid N'-[Amino(6-morpholinopyrazin-2-yl)methylene]hydrazide (12b). Obtained as described for compound **11b**; compound **9** was taken for the reaction instead of **4**.

2-(5-Methylthio)-5-(6-morpholinopyrazin-2-yl)[1,3,4]thiadiazole (13). Compound **10** (1.1 g, 3.3 mmol) dissolved in hot MeOH (40 ml) was treated with concentrated HCl (1 ml) and allowed to cool down. After additional ice-cooling the product was filtered off.

5-(6-Chloropyrazin-2-yl)-2-morpholino[1,3,4]thiadiazole (14a). Obtained by analogy to compound **13** from compound **11a** (1.5 g, 5 mmol).

5-(6-Chloropyrazin-2-yl)-2-(4-phenylpiperazino)[1,3,4]thiadiazole (14b). To a solution of 4-phenyl-piperazine-1-carbodithioic acid hydrazide (0.24 g, 1 mmol) in DMSO (2 ml), compound **4** (0.25 g, 1 mmol) was added and the mixture was stirred for 48 h. Then the reaction mixture was diluted with water (10 ml) and treated with concentrated HCl (1 ml). On cooling, the deposited product was filtered off and crystallized from ethanol.

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