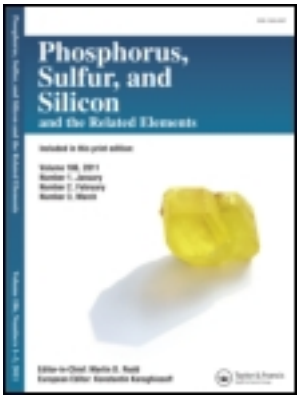

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Studies on Pyrazine Derivatives, XLII: Synthesis and Tuberculostatic Activity of 6-(1,4-Dioxa-8-azaspiro-[4, 5]-decano)- and 6-(1-Ethoxycarbonylpiperazino)-pyrazinocarboxylic Acid Derivatives

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Studies on Pyrazine Derivatives, XLII: Synthesis and Tuberculostatic Activity of 6-(1,4-Dioxa-8-azaspiro-[4,5]-decano)- and 6-(1-Ethoxycarbonylpiperazino)-pyrazinocarboxylic Acid Derivatives

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*The 2-cyano-6-chloropyrazine's chlorine atom reactivity was substituted with amines 1,4-dioxo-8-azaspiro-[4,5]-decane and 1-ethoxycarbonylpiperazine. The substrates thus obtained were used in the syntheses of the new derivatives, which were tested for their tuberculostatic activity. Minimum inhibitory concentration (MIC) value of the most active ones (**5b**, **12a**, **14b**, **16b**, **21b**) was 25 μg/mL.*

Keywords 2-Cyano-6-chloropyrazine; 6-aminosubstituted-2-cyanopyrazine; N^1-substituted thioamidopyrazincarboxyamidrazones; thioamides

INTRODUCTION

The tuberculostatic activity of pyrazine and its derivatives has been, among other properties, a subject of intensive studies. Most of the active compounds made the pyrazino-carboxylic acid derivatives.[1–5] An introduction of the 1,3,4-oxathiazolino-2-one system into the pyrazine molecule increased the tuberculostatic activity 16 times in comparison with that of pyrazinamide.[6]

The earlier reports of Foks and colleagues[7,8] on some new 2-cyano-6-substituted pyrazine derivatives showed the considerable tuberculostatic activity of these compounds as well.

Received September 7, 2004; accepted September 16, 2004.
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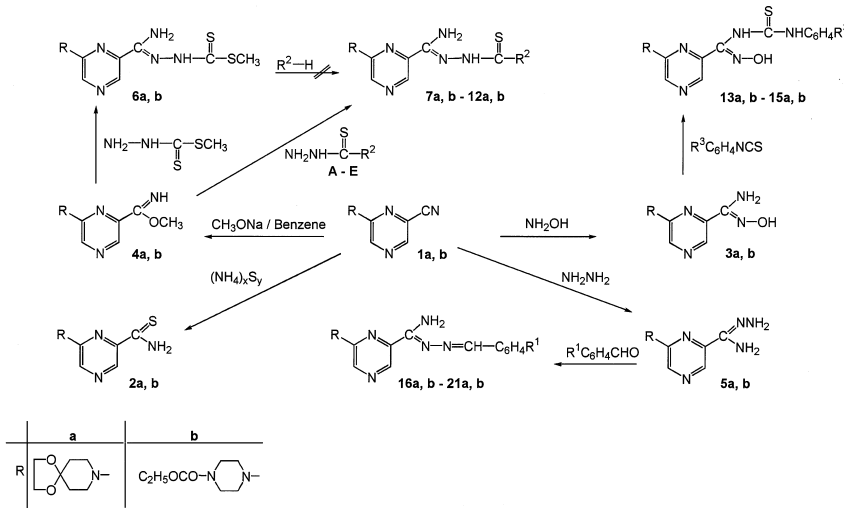
RESULTS AND DISCUSSION

In continuation of our studies on the reactivity and applications of pyrazine derivatives, the new 2,6-disubstituted pyrazines have been synthesized (Scheme).[1]



SCHEME 1

The reaction of 2-cyano-6-chloropyrazine with amines 1,4-dioxa-8-azaspiro-[4,5]-decane and 1-ethoxycarbonylpiperazine produced the initial pyrazinonitriles **1a** and **1b**, which were converted into thioamides (**2**), amidoximes (**3**), imidoesters (**4**), and amidrazones (**5**). The amidoximes obtained thus were allowed to react with aromatic isothiocyanates (*p*-chloro-, *p*-bromo-, and *p*-methyloisothiocyanate) the derivatives (**13–15**). The reaction course and time were controlled by means of thin layer chromatography.

In the reactions of imidoesters (**4**) with the substituted thiosemicarbazides **A**–**E** the N^1-substituted thioamidopyrazincarboxyamidrazones (**7**–**12**) were formed (see Table I). The attempts at obtaining the same compounds by the earlier preparation of 3-carbonimidoyldithiocarbazoic acid S-methyl esters, followed by their reactions with the corresponding secondary amines, failed.

The condensation of amidrazones (**5a**, **b**) with aromatic aldehydes *p*-bromo-; *o*-, *m*-, and *p*-chloro-; *p*-nitro-; *o*-methoxy-; and 2,5-dimethoxybenzoic) produced the corresponding Schiff bases (**16**–**21**) (see Table II). The addition of piperidine increased the reaction yields.

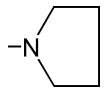
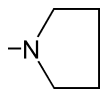
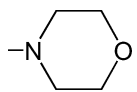
TABLE I Characteristics of the Synthesized Compounds 1a, b–15a, b

Compound no.	R^2	R^3	Formula molecular weight	M.p [°C] solvent for crystallization	Reaction yield [%]	IR (KBr) cm^{-1}	^1H NMR (500 MHz) δ [ppm] solvent: **A**—$CDCl_3$; **B**—DMSO-d_6
1a	—	—	$C_{12}H_{14}N_4O_2$ 246.2	85–86 Methanol	42	3078 (=CH), 2062, 2232 (CN), 1579, 1514, 1100 (C—O—C)	**A**: 1.7(m, CH_2CCH_2); 3.65(m, 4H CH_2NCH_2); 3.9(s, 4H OCH_2CH_2O); 8.2, 8.4(s, 2H Py)
1b	—	—	$C_{12}H_{15}N_5O_2$ 261.0	104–106 Methanol	40	3075 (=CH), 2987, 2907, 2238 (CN), 1688 (C=O), 1588, 1520, 1251 (C—O)	**B**: 1.2(q, 3H CH_3); 3.55, 3.7(m, 8H piperazine); 4.05(q, 2H CH_2); 8.3, 8.7(s, 2H Py)
2a	—	—	$C_{12}H_{16}N_4O_2S$ 280.0	182–183 Methanol	80	3347, 3147 (NH_2), 2998 (=CH), 2953, 2880, 1615, 1584, 1330, 1288, 1109 (C—O—C)	**A**: 1.8(m, 4H CH_2CCH_2); 3.8(m, 4H CH_2NCH_2); 4.02(s, 4H OCH_2CH_2O); 7.8(s, NH); 8.4, 9.1(s, 2H Py); 9.0(s, NH)
2b	—	—	$C_{12}H_{17}N_5O_2S$ 295.0	161–168 Methanol	93	3380, 3258, 3178 (NH_2), 3060 (=CH), 2981, 2908, 1701 (C=O), 1611, 1584, 1279 (C=S), 1225 (C—O)	**A**: 1.3(t, 3H CH_3); 3.67(m, 8H piperazine); 4.2(q, 2H CH_2); 8.4, 9.1(s, 2H Py); 7.9, 8.9 (s, 2H NH)
3a	—	—	$C_{12}H_{17}N_5O_3$ 279.0	194–200 Methanol	49	3493 (NOH), 3382, 3107 (NH_2), 2964, 2847, 1655, 1579, 1464, 1099 (C—O—C)	**B**: 1.65(m, 4H CH_2CCH_2); 3.7(m, 4H CH_2NCH_2); 3.9(m, 4H OCH_2CH_2O); 5.8 (2H NH_2)+ D_2O decay; 8.21, 8.27(s, 2H Py); 9.95(s, 1H NOH) + D_2O decay
3b	—	—	$C_{12}H_{18}N_6O_3$ 294.0	183–191 Methanol	73	3495, 3374, 3179 (NH_2, NOH), 3060(=CH), 2980, 2868, 1694 (C=O), 1648, 1578, 1250 (C—O)	**B**: 1.19(t, 3H CH_3); 3.47, 3.64(m, 8H piperazine); 4.07(q, 2H CH_2); 5.85(s, 2H NH); 8.25(d, 2H Py); 9.97(s, 1H NOH)

(Continued on next page)

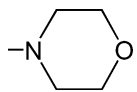
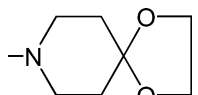
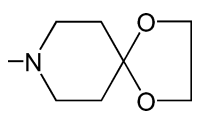
TABLE I Characteristics of the Synthesized Compounds 1a, b–15a, b *(Continued)*

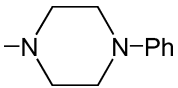
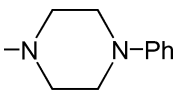
Compound no.	R^2	R^3	Formula molecular weight	M.p [°C] solvent for crystallization	Reaction yield [%]	IR (KBr) cm^{-1}	^1H NMR (500 MHz) δ [ppm] solvent: **A**—$CDCl_3$; **B**—DMSO-d_6
4a	—	—	$C_{13}H_{18}N_4O_3$ 278.0	99–105 Benzene	86	3232 (NH), 3059 (=CH), 3000, 2954, 1653, 1568, 1525, 1256, 1122 (C—O)	**B**: 1.8(m, 4H CH_2CCH_2); 3.8(m, 4H CH_2NCH_2); 4.0-4.03(m, 4H OCH_2CH_2O + 3H CH_3); 8.28, 8.3(s, 2H Py; 8.8–9.1(NH)
4b	—	—	$C_{13}H_{19}N_5O_3$ 293.0	106–110 Benzene	59	3271 (NH), 2962, 2905, 1719 (C=O), 1648, 1577, 1250, 1111 (C—O)	**B**: 1.15(t, 3H CH_3); 3.25(s, 3H CH_3O); 3.3, 3.7(m, 8H piperazine); 4.05(q, 2H CH_2); 8.2, 8.5(s, 2H Py); 9.2(s, 1H NH)
5a	—	—	$C_{12}H_{18}N_6O_2$ 278.0	84–87 Methanol/ H_2O	64	3404, 3355, 3300, 3200 (NH_2), 3050 (=CH), 2955, 2915, 1639, 1573, 1106 (C—O—C)	**A**: 1.78(m, 4H CH_2CCH_2); 3.78(m, 4H CH_2NCH_2); 4.0(s, 4H OCH_2CH_2O); 8.07, 8.3(s, 2H Py)
5b	—	—	$C_{12}H_{19}N_7O_2$ 293.0	121–122 Methanol/ H_2O	92	3419, 3321, 3199 (NH_2), 2986, 2917, 1698 (C=O), 1645, 1575, 1248 (C—O)	**A**: 1.3(t, 3H CH_3); 3.65(m, 8H piperazine); 4.17(q, 2H CH_2); 5.0(s, 2H NH_2); 8.1, 8.6(s, 2H Py)
6a	—	—	$C_{14}H_{20}N_6O_2S_2$ 368.0	153–158 Benzene	33	3392, 3145 (NH), 2954, 2918, 1670 (HN—C=S), 1617, 1580, 1107	**B**: 1.67(m, 4H CH_2CCH_2); 2.44(d, 3H CH_3); 3.75, 3.8(t, 4H CH_2NCH_2); 3.92(s, 4H OCH_2CH_2O); 7.14, 9.2, 12.0(s, NH); 8.4, 8.6(s, 2H Py)
6b	—	—	$C_{14}H_{21}N_7O_2S_2$ 383.0	130–131 Methanol/ H_2O	34	3373, 3202 (NH), 3060 (=CH), 2983, 2920, 1669 (C=O), 1628, 1583, 1286, 1247	**A**: 1.3(t, 3H CH_3); 1.65(s, 3H CH_3); 3.65 (m, 8H piperazine); 4.2(q, 2H CH_2); 5.95, 8.8(s, NH); 8.2, 8.4(s, 2H Py)

7a		—	$C_{17}H_{25}N_7O_2S$ 391.0	170–172 Methanol	83	3408, 3324, 3170 (NH), 3060 (=CH), 2955, 2875, 1647, 1562, 1506, 1356, 1105	**A**: 1.68(m, 4H CH_2CCH_2); 1.91(m, 4H pyrrolidine); 3.62(m, 4H pyrrolidine); 3.82 (m, 4H CH_2NCH_2); 3.92(m, 4H OCH_2CH_2O); 8.49, 8.67(s, 2H Py); 9.8–10.0(NH)
7b		—	$C_{17}H_{26}N_8O_2S$ 406.0	166–170 Methanol/ H_2O	54	3434, 3299, 3156 (NH), 3070 (=CH), 2960, 2860, 1697 (C=O), 1666, 1600, 1573, 1286, 1249	**A**: 1.29(t, 3H CH_3); 1.99(m 4H pyrrolidine); 3.67(m, 8H pyrrolidine + piperazine); 3.82(m, 4H CH_2NCH_2); 4.19(q, 2H CH_2); 6.3(NH); 8.2, 8.5(s, 2H Py)
8a		—	$C_{17}H_{25}N_7O_3S$ 407.0	160–166 Acetone	34	3418, 3257, 3150 (NH), 3088 (=CH), 2950, 2892, 1668, 1601, 1575, 1368, 1343, 1247, 1101	**A**: 1.8(m, 4H CH_2CCH_2); 3.84(m, 4H CH_2NCH_2); 3.74, 4.0(m, 8H morpholine + 4H OCH_2CH_2O); 6.9–7.0(NH); 8.3, 8.42(s, 2H Py)

(Continued on next page)

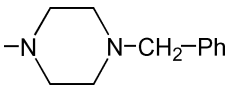
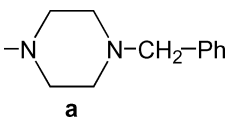
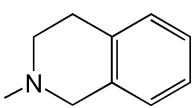
TABLE I Characteristics of the Synthesized Compounds 1a, b–15a, b *(Continued)*

Compound no.	R^2	R^3	Formula molecular weight	M.p [°C] solvent for crystallization	Reaction yield [%]	IR (KBr) cm^{-1}	^1H NMR (500 MHz) δ [ppm] solvent: **A**—$CDCl_3$; **B**—DMSO-d_6
8b		—	$C_{17}H_{26}N_8O_3S$ 422.0	170–175 Methanol/ Acetone	69	3461, 3348 (NH), 3050 (=CH), 2958, 2897, 1696 (C=O), 1666, 1568, 1526, 1248, 1116	**B**: 1.19(t, 3H CH_3); 3.48(t, 4H CH_2NCH_2); 3.56, 3.81(t, 8H morpholine); 3.75(t, 4H CH_2NCH_2); 4.06(q, 2H CH_2); 8.51, 8.57(s, 2H Py); 12.66(NHC=S)
9a	 **a**	—	$C_{20}H_{29}N_7O_4S$ 463.0	175–178 Ethyl acetate/ Acetone	59	3362, 3291 (NH), 2951, 2884, 1677, 1570, 1526, 1312, 1260, 1131	**B**: 1.54(m, 4H CH_2CCH_2-**a**); 1.67(m, 4H CH_2CCH_2); 3.8(m, 4H CH_2NCH_2-**a**); 3.9 (m, 4H CH_2NCH_2); 3.95(m, 8H OCH_2CH_2O); 8.47, 8.6(s, 2H Py); 12.6(1H NHC=S)
9b		—	$C_{20}H_{30}N_8O_4S$ 478.0	180–182 Acetone	77	3379, 3300, 3129 (NH), 3040 (=CH), 2956, 2892, 1698 (C=O), 1585, 1531, 1360, 1232, 1131	**B**: 1.19(t, 3H CH_3); 1.55(m, 4H CH_2CCH_2); 3.48(m, 4H CH_2NCH_2); 3.75, 3.93(m, 8H piperazine); 3.9(s, 4H OCH_2CH_2O); 4.05(q, 2H CH_2); 8.51, 8.56(s, 2H Py); 12.7 (NHC=S)

10a		—	$C_{23}H_{30}N_9O_2S$ 482.0	165–168 Methanol	31	3427, 3284, 3143 (NH), 3059 (=CH), 2952, 2885, 1670, 1598, 1224	**B**: 1.67(m, 4H CH_2CCH_2); 3.1(m, 4H piperazine); 3.82(m, 4H piperazine); 3.82(m, 4H piperidine); 3.92(s, 4H OCH_2CH_2O); 3.98(m, 4H piperazine); 6.78, 6.97, 7.2(m, 5H Ph); 7.7(s, NH_2+ D_2O-decay); 8.49, 8.6(s, 2H Py); 12.67(s, NH–C=S + D_2O-decay)
10b	 **a**	—	$C_{23}H_{31}N_9O_2S$ 497.0	173–175 Methanol	29	3448, 3345, 3166 (NH), 3065 (=CH), 2976, 2921, 1673 (C=O), 1599, 1577, 1529, 1347, 1227	**B**: 1.1(t, 3H CH_3); 3.1(m, 8H piperazine-**a**); 3.49(m, 8H piperazine); 4.06(q, 2H CH_2); 6.78, 6.98, 7.2(m, 5H Ph); 8.52, 8.57(s, 2H Py); 12.7(NH–C=S)

(Continued on next page)

TABLE I Characteristics of the Synthesized Compounds 1a, b–15a, b *(Continued)*

Compound no.	R^2	R^3	Formula molecular weight	M.p [°C] solvent for crystallization	Reaction yield [%]	IR (KBr) cm^{-1}	^1H NMR (500 MHz) δ [ppm] solvent: **A**—$CDCl_3$; **B**—DMSO-d_6
11a		—	$C_{24}H_{32}N_8O_2S$ 496.0	157–159 Benzene	55	3290, 3143 (NH), 3030 (=CH), 2928, 2887, 1683, 1578, 1421, 1303, 1243, 1108	**B**: 1.67(t, 4H CH_2CCH_2); 2.33(m, 4H piperazine); 3.47(s, 2H CH_2); 3.8-3.83(m, 8H CH_2NCH_2 piperidine and piperazine); 3.92 (s, 4H OCH_2CH_2O); 7.3–7.35(m, 5H Ph); 8.47, 8.6(s, 2H Py); 12.7(NH–C=S + D_2O-decay)
11b	 **a**	—	$C_{24}H_{33}N_9O_2S$ 511.0	132–138 Benzene	43	3419, 3290 (NH), 3062 (=CH), 2923, 1700 (C=O), 1635, 1600, 1578, 1233, 1115	**A**: 1.19(t, 3H CH_3); 2.33(s, 2H CH_2); 3.47 (m, 8H piperazine-**a**); 3.74, 3.84(m, 8H piperazine); 4.07(q, 2H CH_2); 7.25, 7.31(m, 5H Ph); 8.5, 8.56(s, 2H Py); 12.7(NH–C=S)
12a		—	$C_{22}H_{27}N_7O_2S$ 453.0	154–158 Benzene	55	3302, 3155 (NH), 2955, 2884, 1685, 1579, 1530, 1350, 1239, 1108, 750	**B**: 1.67(m, 4H CH_2CCH_2); 2.79 and 4.11(t, 4H CH_2CH_2); 3.81(s, 4H CH_2NCH_2); 3.92 (s, 4H OCH_2CH_2O); 5.0(s, 2H CH_2); 7.14 (m, 4H Ar); 8.48, 8.60(s, 2H Py); 12.7(s, 1H NH–C=S)

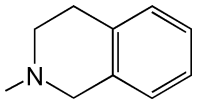
12b		—	$C_{22}H_{28}N_8O_2S$ 468.0	140–146 Benzene	40	3350, 3084 (NH), 2926, 2859, 1692 (C═O), 1601, 1573, 1353, 1280, 1231 (C-O)	**B**: 1.19(t, 3H CH_3); 2.79 and 4.11(t, 4H CH_2CH_2); 3.48 and 3.75(s, 8H piperazine); 4.07(q, 2H CH_2); 7.15(m, 4H Ar); 8.5, 8.57 (s, 2H Py); 12.7(s, 1H NH─C═S)
13a	—	p-Cl	$C_{19}H_{21}N_6O_3SCl$ 448.45	204–207.5 Acetone/ Methanol	74	3377, 3257 (NH), 3050 (═CH), 2952, 2920, 1641, 1614, 1526, 1307, 1105	**A**: 1.82(m, 4H CH_2CCH_2); 3.8(m, 4H CH_2NCH_2); 4.02(s, 4H OCH_2CH_2O); 7.3, 7.6(m, 4H Ar); 8.55, 8.9(s, 2H Py); 9.6(s, 1H NOH)
13b	—	p-Cl	$C_{19}H_{22}N_7O_3SCl$ 463.45	207–210 Methanol/ Acetone	70	3390, 3250 (NH), 3050 (═CH), 2985, 2920, 1689 (C═O), 1650, 1575, 1305, 1250	**A**: 1.3(t, 3H CH_3); 3.67(m, 8H piperazine); 4.2(q, 2H CH_2); 7.3, 7.55(m, 4H Ar); 8.5 (m, 2H Py); 8.8(s, NOH)
14a	—	p-Br	$C_{19}H_{21}N_6O_3SBr$ 492.9	207–211 Acetone	52	3375, 3251 (NH), 3050 (═CH), 2952, 2919, 1640, 1613, 1574, 1307, 1250, 1102	**B**: 1.68(m, 4H CH_2CCH_2); 3.79(m, 4H CH_2NCH_2); 3.81(s, 4H OCH_2CH_2O); 7.4, 7.6(m, 4H Ar); 8.5, 8.6(s, 2H Py); 8.58, 9.3 (s, 2H NH); 9.7(s, 1H NOH)
14b	—	p-Br	$C_{19}H_{22}N_7O_3SBr$ 508.0	193–194 Methanol/ acetone	16	3389, 3267 (NH), 3055 (═CH), 2980, 2924, 1674 (C═O), 1654, 1577, 1515, 1437, 1248, 1133	**A**: 1.2(t, 3H CH_3); 3.49, 3.72(m, 8H piperazine); 4.07(q, 2H CH_2); 7.44, 7.64(m, 4H Ar); 8.5, 8.7(s, 2H Py); 8.6, 9.3(s, 2H NH); 9.69(s, NOH)

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TABLE I Characteristics of the Synthesized Compounds 1a, b–15a, b *(Continued)*

Compound no.	R^2	R^3	Formula molecular weight	M.p [°C] solvent for crystallization	Reaction yield [%]	IR (KBr) cm^{-1}	^1H NMR (500 MHz) δ [ppm] solvent: **A**—$CDCl_3$; **B**—DMSO-d_6
15a	—	p-CH_3	$C_{20}H_{24}N_6O_3S$ 428.0	202–205 Acetone/ Methanol	59	3367, 3251 (NH), 3050 (=CH), 2952, 2920, 1640, 1614, 1574, 1525, 1340, 1257, 1107	**B**: 1.68(m, 4H CH_2CCH_2); 2.2(s, 3H CH_3); 3.8(m, 4H CH_2NCH_2); 3.92(s, 4H OCH_2CH_2O); 7.05, 7.5(m, 4H Ar); 8.45, 9.3(s, 2H NH); 8.5, 8.65(s, 2H Py); 9.45(s, NOH)
15b	—	p-CH_3	$C_{20}H_{25}N_7O_3S$ 443.0	198–200 Methanol/ Acetone	55	3295, 2984, 2918, 1697 (C=O), 1635, 1576, 1434, 1402, 1249	**B**: 1.19(t, 3H CH_3); 2.2(s, 3H CH_3); 3.5(m, 4H piperazine); 3.7(m, 4H piperazine); 4.06(q, 2H CH_2); 7.05, 7.55(m, 4H Ar); 8.5, 8.7(m, 2H Py); 9.45(s, 1H NOH + D_2O-decay)

Ar—aromatic, Ph—phenyl, Py—pyrazine.

TABLE II Physicochemical Data of Condensation Products of Amidrazones with Aromatic Aldehydes

Compound no.	R^1	Formula molecular weight	M.p [°C] solvent for crystallization	Yield [%]	IR (KBr) cm^{-1}	^1H NMR δ [ppm] 500 MHz solvent: **A**—$CDCl_3$; **B**—DMSO-d_6
16a	p-Cl	$C_{19}H_{21}N_6O_2Cl$ 400.4	175–177 Methanol	65	3454, 3334 (NH_2), 3050 (=CH), 2984, 2941, 2880, 1621, 1602, 1560, 1520, 1108 (C—O—C)	**B**: 1.68(t, 4H CH_2CCH_2); 3.78(t, 4H CH_2NCH_2); 3.9 (4H CH_2CH_2); 7.0–7.2(s, 2H NH); 7.5–7.9(m, 4H Ar); 8.4, 8.46(s, 2H Py); 8.54(s, 1H CH)
16b	p-Cl	$C_{19}H_{22}N_7O_2Cl$ 415.4	209–210 Methanol	26	3493, 3378 (NH_2), 3061 (=CH), 2983, 2960, 2853, 1697 (C=O), 1626, 1603, 1560, 1437, 1250 (C—O)	**A**: 1.3(t, 3H CH_3); 3.5–3.75(m, 8H piperazine); 4.2 (q, 2H CH_2); 6.4(s, NH); 7.4, 7.75(d, 4H Ar); 8.3, 8.6 (s, 2H Py); 8.9(s, 1H CH)
17a	o-Cl	$C_{19}H_{21}N_6O_2Cl$ 400.4	160–163 Acetone/ H_2O	96	3480, 3290 (NH_2), 3067 (=CH), 2954, 2887, 1616, 1568, 1105 (C—O—C)	**B**: 1.68(t, 4H CH_2CCH_2); 3.78(t, 4H CH_2NCH_2); 3.93(4H CH_2CH_2); 7.0–7.2(s, 2H NH); 7.5–7.9(m, 4H Ar); 8.4, 8.46(s, 2H Py); 8.54(s, 1H CH)
17b	o-Cl	$C_{19}H_{22}N_7O_2Cl$ 415.4	173–176 Benzene	19	3489, 3373 (NH_2), 3062 (=CH), 2983, 2961, 2855, 1696 (C=O), 1625, 1603, 1560, 1437, 1250 (C—O)	**A**: 1.3(t, 3H CH_3); 3.65(m, 8H piperazine); 4.19(q, 2H CH_2); 6.4(s, NH); 7.4-7.8(m, 4H Ar); 8.2, 8.5(s, 2H Py)
18a	p-Br	$C_{19}H_{21}N_6O_2Br$ 445.0	188–189 Dioxane	80	3454, 3336 (NH_2), 3050 (=CH), 2942, 1620, 1559, 1525, 1465, 1107 (C—O—C)	**A**: 1.8(m, 4H CH_2CCH_2); 3.8(m, 4H CH_2NCH_2); 4.03(s, 4H CH_2CH_2); 6.3(s, NH); 7.5–7.7(m, 4H Ar); 8.3(s, 1H CH); 8.5, 8.8(s, 2H Py)
18b	p-Br	$C_{19}H_{22}N_7O_2Br$ 460.0	256–258 Dioxane	59	3493, 3372 (NH_2), 3061 (=CH), 2975, 2961 (CH_2), 1697 (C=O), 1625, 1605, 1560, 1439, 1251 (C—O)	**A**: 1.3(t, 3H CH_3); 3.67(m, 8H piperazine); 4.19(q, 2H CH_2); 6.4(s, 2H NH); 7.96, 8.27(d, 4H Ar); 8.3, 8.6(s, 2H Py); 8.9(s, 1H CH)

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TABLE II Physicochemical Data of Condensation Products of Amidrazones with Aromatic Aldehydes *(Continued)*

Compound no.	R^1	Formula molecular weight	M.p [°C] solvent for crystallization	Yield [%]	IR (KBr) cm^{-1}	^1H NMR δ [ppm] 500 MHz solvent: **A**—$CDCl_3$; **B**—DMSO-d_6
19a	p-NO_2	$C_{19}H_{21}N_7O_4$ 411.0	222–226 Acetone/ Methanol	92	3458, 3335 (NH_2), 3050 (=CH), 2961, 2933, 2878, 1630, 1608, 1594, 1473, 1366 (NO_2), 1107 (C—O—C)	**B**: 1.7(t, 4H CH_2CCH_2); 3.8(t, 4H CH_2NCH_2); 3.92 (s, 4H CH_2CH_2); 7.2–7.4(s, NH_2); 8.2, 8.26(m, 4H Ar); 8.45(s, 1H CH); 8.55, 8.58(s, 2H Py)
19b	p-NO_2	$C_{19}H_{22}N_8O_4$ 426.0	245–251 Dioxane	70	3505, 3391 (NH_2), 2890, 2913, 2857, 1696 (C=O), 1625, 1608, 1592, 1527, 1433, 1335 (NO_2); 1250 (C—O)	**A**: 1.28(t, 3H CH_3); 3.65(m, 8H piperazine); 4.18(q, 2H CH_2); 6.4(s, 2H NH); 7.9, 8.25(s, 4H Ar); 8.26, 8.6(s, 2H Py); 8.9(s, 1H CH)
20a	o-CH_3O	$C_{20}H_{24}N_6O_3$ 396.0	187–192 Acetone/ H_2O	52	3501, 3386 (NH_2), 3067 (=CH), 2957, 2889, 1622, 1563, 1254, 1112	**B**: 1.68(t, 4H CH_2CCH_2); 3.77(m, 4H CH_2NCH_2); 3.85(s, 3H CH_3O); 3.93(s, 4H CH_2CH_2); 6.98(s, NH_2); 7–7.1, 7.4–8.1(m, 4H Ar); 8.4(s, 1H CH); 8.55, 8.7(s, 2H Py)
20b	o-CH_3O	$C_{20}H_{25}N_7O_3$ 411.0	185–187 Methanol	73	3451, 3249 (NH_2), 3051 (=CH), 2984, 2908, 1695 (C=O), 1607, 1566, 1279 (C—O)	**B**: 1.2(t, 3H CH_3); 3.5–3.7(m, 8H piperazine); 3.9(s, 3H CH_3O); 4.07(q, 2H CH_2); 7.0(s, NH); 7.0–7.1, 7.4–8.2(m, 4H Ar); 8.38(s, 1H CH); 8.6, 8.7(s, 2H Py)
21a	2,5-$(CH_3O)_2$	$C_{21}H_{27}N_6O_4$ 427.0	180–181 Acetone	74	3469, 3268 (NH_2), 3072 (=CH), 2955, 2870, 1611, 1565, 1521, 1258, 1193, 1101	**B**: 1.68(m, 4H CH_2CCH_2); 3.77(s, 6H $(CH_3O)_2$); 3.8(m, 4H CH_2NCH_2); 3.93(s, 4H CH_2CH_2); 7.0, 7.7(m, 3H Ar); 6.9–7.1(s, NH_2); 8.4(s, 1H CH); 8.55, 8.67(s, 2H Py)
21b	2,5-$(CH_3O)_2$	$C_{21}H_{27}N_7O_4$ 441.0	112–117 Benzene	43	3469, 3261 (NH_2), 3052 (=CH), 2990, 2937, 1697 (C=O), 1667, 1613, 1587, 1245 (C—O)	**A**: 1.3(t, 3H CH_3); 3.66, 3.85(m, 8H piperazine + 6H CH_3O); 4.2(q, 2H CH_2); 6.2(1H NH); 7.0–7.4(m, 3H Ar); 8.25, 8.45(s, 2H Py); 9.0(s, 1H CH)

Ar—aromatic, Py—pyrazine.

The structure of the newly obtained compounds was established by the analyses of IR and ^{1}H NMR spectra. The spectral data are given in the Tables I and II.

MICROBIOLOGY

The newly obtained derivatives were tested for their tuberculostatic activity towards the standard Mycobacterium tuberculosis $H_{37}Rv$ strain, as well as two strains isolated from tuberculotic patients (Table III). One strain, Myc. species 210, was resistant to *P*-Aminosalicylic Acid (PAS), Isonicotinic Acid Hydrazide (INH), Ethambutol (EMB) and Rifampycine (RFP); the other strain, Myc. species 192, was fully susceptible to the drugs administered.

Tuberculostatic activity was tested in vitro with the classical test tube method on Youman's liquid medium containing 10% of a bovine serum.[9] The Minimum Growth Inhibiting Concentration (MIC) values obtained showed that some compounds were noteworthy. MIC values of the compounds **5b**, **12a**, **14b**, **16b**, and **21b** were within the limits of 25–50 μg/mL. The MIC values obtained for pyrazinamide were within 30–60 μg/mL using the same method.

TABLE III Tuberculostatic Activity [μg/mL]

Compound no.	Myc. tbc. $H_{37}Rv$	Myc. spec. 192 susceptible	Myc. spec. 210 resistant	Compound no	Myc. tbc. $H_{37}Rv$	Myc. spec. 192 susceptible	Myc. spec. 210 resistant
1a	50	100	50	**12a**	25	50	25
1b	50	100	50	**12b**	50	50	50
2a	100	50	50	**13a**	50	100	100
2b	50	50	50	**13b**	50	50	50
3a	50	100	50	**14a**	100	100	100
3b	50	50	50	**14b**	50	25	25
5a	50	100	50	**15a**	100	50	50
5b	50	50	25	**15b**	50	50	50
6a	50	50	50	**16a**	50	50	50
6b	50	50	50	**16b**	50	50	25
7a	50	50	50	**18a**	100	100	100
7b	50	50	50	**18b**	50	50	50
8a	50	100	50	**19a**	50	100	50
8b	50	50	50	**19b**	50	50	50
9b	50	50	50	**20a**	50	50	50
10a	50	50	100	**20b**	50	50	50
10b	50	50	50	**21a**	50	50	50
11a	50	50	50	**21b**	50	50	25
11b	50	50	50				

EXPERIMENTAL

All melting points were obtained with a Boëtius apparatus and are uncorrected. The elemental analysis results for C and H of all the compounds obtained were in good agreement with the data calculated.

The IR spectra were taken with a Satellite spectrophotometer, and the ^{1}H NMR spectra were taken with a Varian Unity 500 MHz apparatus. The reaction yields and physical constants of the new compounds are given in the Tables I and II.

Syntheses of Substituted 2-Cyanopyrazine Derivatives (1a, 1b)

To a solution of 2-cyano-6-chloropyrazine (0.1 mol) in benzene (150 cm^3), triethylamine (0.15 mol) and corresponding amine (0.1 mol), i.e., 1,4-dioxa-8-azaspiro-[4,5]-decane or 1-ethoxycarbonylpiperazine, was added. The mixture was refluxed for 2 h. On cooling down, water (60 cm^3) was added and the mixture was extracted with benzene. The benzene extracts were dried over anhydrous $MgSO_4$. The solution obtained was thickened by evaporation under vacuum and allowed to stand for crystallization. The precipitate was filtered off and recrystallized.

Syntheses of Thioamides (2a, 2b)

The corresponding nitrile (2 mmol) was dissolved in ethanol (8 cm^3) and ammonium polysulfide was added until turbidity appeared. After 12 h, the precipitate was filtered off and crystallized.

Syntheses of Amidoximes (3a, 3b)

To a solution of hydroxylamine hydrochloride (17.0 mmol) in absolute methanol (10 cm^3) the solution of KOH (22 mmol) in absolute methanol (10 cm^3) was added. The precipitated KCl was filtered off and the filtrate was treated with the corresponding nitrile **1a** or **1b** (2.5 mmol). The whole was refluxed for 2 h. The solvent was then evaporated under reduced pressure and the residue treated with acetic acid (0.8 cm^3) in water (10 cm^3). The precipitate was filtered off and recrystallized.

Syntheses of Imidoesters (4a, 4b)

To the solution of nitrile **1a** or **1b** (4 mmol) in benzene (60 cm^3) the solution of NaOH (10 g) in water (10 cm^3) was added, followed by methanol (10 cm^3) and a small amount of triethylbenzylamine (TEBA). The whole

was stirred for 2 h at ambient temperature. The water (70 cm^3) was then added and the aqueous layer after separation was extracted with benzene. The combined benzene extracts were dried over anhydrous $MgSO_4$. The benzene solution was thickened under reduced pressure and the oily residue was treated with petroleum ether. The precipitates were filtered off and recrystallized.

Syntheses of Amidrazones (5a, 5b)

To the solution of nitrile **1a** or **1b** (2.5 mmol) in methanol (8 cm^3), 80%—hydrazine (1.3 cm^3) was added. The solution was heated to 50°C for 1 h. The solvent and an excess of hydrazine were evaporated under reduced pressure. The residue was cooled and treated with a small amount of water. The precipitate obtained was filtered off and crystallized.

The Reactions of Amidoximes with Aryloisothiocyanates (13a, b–15a, b)

Amidoxime **3a** or **3b** (0.5 mmol) and corresponding isothiocyanate (0.5 mmol) were suspended in DMF (5 cm^3) and stirred at ambient temperature for 3–5 days. The mixture was ice-cooled and treated with water. The precipitate was filtered off and crystallized.

Condensation of Amidrazones with Aromatic Aldehydes (16a, b–21a, b)

To the solution of the corresponding amidrazone (0.64 mmol) in absolute methanol (8 cm^3) aromatic aldehyde (0.64 mmol) and a few drops of piperidine were added. The whole was refluxed for 4 h. On cooling down, the precipitates obtained were filtered off and crystallized.

Syntheses of 3-Carbonimidoyldithiocarbazonic Acid S-Methyl Esters (6a, 6b)

Imidoester **4a** or **4b** (1 mmol) in absolute methanol (8 cm^3) was treated with methyl dithiocarbazones (1 mmol) dissolved in methanol (3 cm^3). The whole was stirred at ambient temperature for 24 h. The precipitate was filtered off and crystallized.

Syntheses of Thiosemicarbazides A–E

A suspension of methyl dithiocarbazone (2 mmol) in water (5 cm^3) was treated with the corresponding amine (6 mmol), i.e., pyrrolidine

(**A**), morpholine (**B**), phenylpiperazine (**C**), 1,4-dioxa-8-azaspiro-[4,5]-decane (**D**), or 1-benzylpiperazine (**E**), dissolved in water (3 cm^3). The whole was heated with a water bath for 6 h. On cooling down, the precipitate was filtered off and washed with water.

Thiosemicarbazide: **A** M.p. 165–9°C (45% yield); **B** M.p. 186–6°C (23%); **C** M.p. 170–3°C (42%); **D** M.p. 130–6°C (15%); **E** M.p. 161–5°C (34%).

Syntheses of N^1-Substituted Thioamidopyrazincarboxyamidrazones (7a, b–12a, b)

A solution of imidoester **4a** or **4b** (1 mmol) and the corresponding thiosemicarbazide **A**–**E** (1 mmol) in methanol (20 mcm^3) was stirred at ambient temperature for 4 days. The solvent excess was distilled off. On cooling down, the oily residue was treated with benzene and petroleum ether. The precipitate obtained was filtered off and crystallized.

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