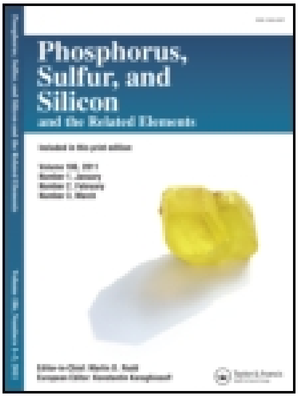

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Synthesis of 2-Aminoaryl-5-Substituted-1,3,4- Thiadiazoles in a Thermal 1,3-Dipolar Cycloaddition Reaction

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Synthesis of 2-Aminoaryl-5-Substituted-1,3,4-Thiadiazoles in a Thermal 1,3-Dipolar Cycloaddition Reaction

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The preparation of a series of new 2-aminoaryl-1,3,4-thiadiazoles substituted with methylsulfanyl, methansulfinyl, or amine in the 5-position is described in this article. The compounds were obtained from N-hydroxyimidoyl chlorides and methyl dithiocarbazinate or 4-substituted thiosemicarbazides in a thermal 1,3-dipolar cycloaddition reaction. The new derivatives were tested for their activity against Mycobacterium tuberculosis.

Keywords 1,3-Dipolar cycloaddition; 1,3,4-thiadiazoles; 4-substituted thiosemicarbazides; antituberculosis activity; hydroxamoyl chlorides; methyl dithiocarbazinate

INTRODUCTION

Many 1,3,4-thiadiazole derivatives show various pharmacological activities, including antibacterial,[1] antifungal,[2] and antituberculosis activity.[3] It is also well documented that some agents possessing a pyrazine or pyridine ring, such as pyrazinamide and isoniazide, are very effective antituberculosis drugs.

These facts prompted us to synthesize 1,3,4-thiadiazoles substituted with pyrazine or a pyridine moiety in the 2-position. The 2-amino-5-aryl-1,3,4-thiadiazoles already have been obtained from

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arylthiosemicarbazones[4] or by direct cyclization of carboxylic acid and thiosemicarbazide in phosphorus oxychloride.[5] Reaction of the aromatic hydroxamoyl chlorides with methyl dithiocarbazinate also was described as a method of 2-aminoaryl-1,3,4-thiadiazole obtainment.[6,7] However, the cyclization reactions of hydroxamoyl chlorides with 4-amino-substituted thiosemicarbazides have not been reported yet.

In this work, a series of 2-aminopyrazinyl-, 2-pyridin-2-, 3- or 4-yl- and 1-oxy-isonicotin-1,3,4-thiadiazole-5-sulfides, sulfoxides, and amines were synthesized and evaluated for in vitro antituberculosis activity.

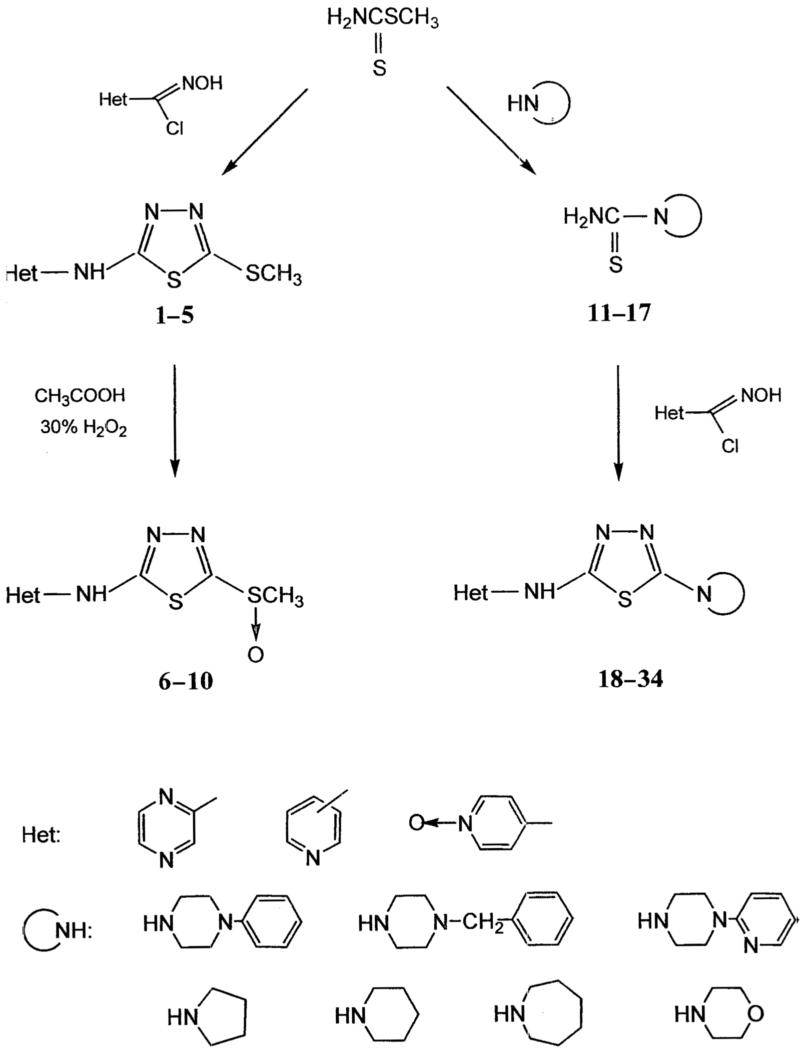
RESULTS AND DISCUSSION

The required compounds were obtained according to the reaction sequences outlined in Scheme 1. Hydroxamoyl chlorides were used as starting material. *N*-hydroxypyrazinecarboximidoyl, *N*-hydroxypyridinecarboximidoyl, and 1-oxy-isonicotincarboximidoyl chlorides were prepared from the corresponding amidoximes on treatment with sodium nitrite in hydrochloric acid solution at 0°C. That method has been published by Kočevar and colleagues as a simple procedure for the synthesis of pyridinecarbohydroximoyl chlorides.[8]

Hydroxamoyl chlorides were refluxed in ethanol with two equivalent amounts of methyl dithiocarbazinate, giving 2-aminoaryl-5-methylsulfanyl-1,3,4-thiadiazoles **1–5**. Methyl dithiocarbazinate was obtained by the method of Kleyman and colleagues[9] from hydrazine, potassium hydroxide, carbon disulfide, and methyl iodide in water-isopropanol solution. The products of condensation reactions formed with moderated yields. Similar syntheses were described by Dornow and Fischer.[6] The products that were obtained suggest that this kind of reaction is a thermal 1,3-cycloaddition (Scheme 2(a)). That mechanism is typical for all hydroxamoyl chlorides. However, Sasaki and Yoshioka[7] reported that some of these compounds can give 2-aryl-5-methylsulfanyl-1,3,4-thiadiazole as a second product, which is a result of a simple substitution reaction followed by hydroxylamine elimination (Scheme 2(b)). We did not obtain the second kind of products.

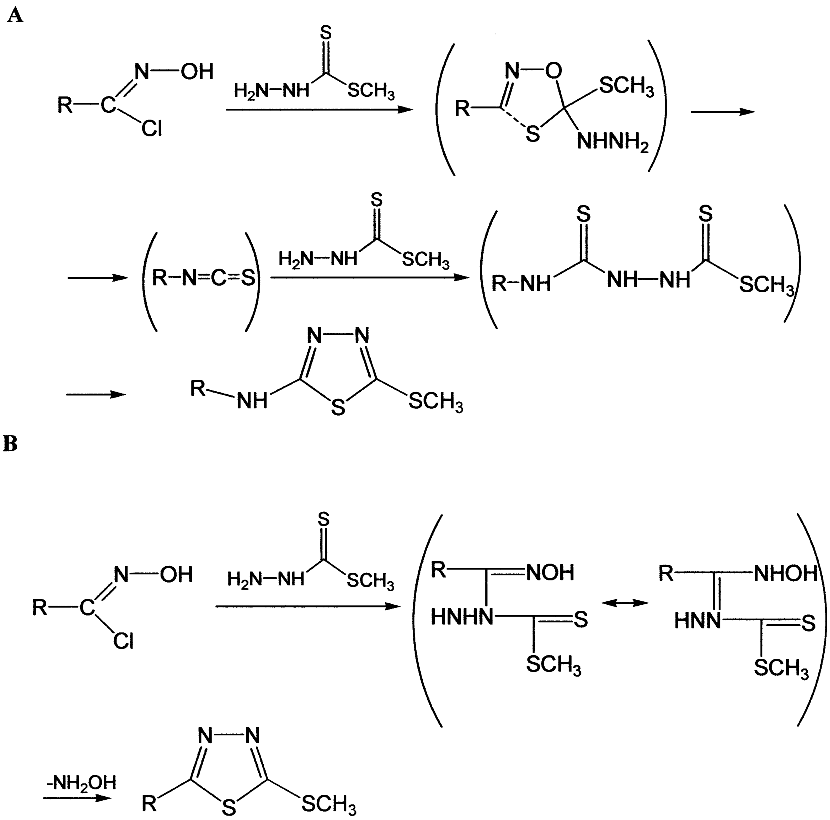
Subsequent oxidation of sulfides **1–5** using an excess of 30% hydrogen peroxide and glacial acetic acid gave sulfoxides **6–10**. The yields of these reactions were rather good, and sulfoxides isolation was very easy. Further oxidation resulted in sulfones, which were formed next to other products, and finally their synthesis was given up.

4-substituted thiosemicarbazides **11–17**, the intermediates employed for the syntheses of corresponding 2-amino-5-aminoaryl-1,3,



SCHEME 1

4-thiadiazoles **18–34**, were prepared by the procedure of Agrawal and colleagues.[10] The various amines, such as pyrrolidine, piperidine, hexamethyleneimine, morpholine, 1-phenylpiperazine, 1-benzylpiperazine, and 1-(2-pyridyl)piperazine, that were used for the nucleophilic substitution of methyl dithiocarbazinate were commercially obtained. For more basic amines, water was a suitable solvent, but for 1-phenylpiperazine and its derivatives, reactions were carried



SCHEME 2

out in ethanol. The yields of the reactions were not very high, although amines were used in large excess to methyl dithiocarbazinate (3:1). This fact prompted us to work out another method for these syntheses, which will be a subject of a future article.

The reactions of *N*-hydroxyimidoyl chlorides with two equivalent amounts of 4-(1-phenylpiperazino)thiosemicarbazide **15** gave the desired 2-aminoaryl-5-phenylpiperazino-1,3,4-thiadiazoles **22**, **29**, and **32–34**. The syntheses were performed in refluxing DMF and the reaction yields presented similar tendency as obtained for the appropriate sulfides **1–5**. The structures of the products led us to conclude that these reactions also follow the thermal 1,3-dipolar cycloaddition mechanism, as maintained for the sulfides **1–5** obtainment.

Treatment of *N*-hydroxypyrazine and *N*-hydroxy-2-pyridinecarboximidoyl chlorides with 6 other 4-substituted thiosemicarbazides

11–14, **16**, and **17** under similar reaction conditions resulted in the formation of 2-amino-5-aminopyrazin-2-yl- or 5-aminopyridin-2-yl-1,3,4-thiadiazoles **18–21**, **23–28**, **30**, and **31**.

The synthesized 1,3,4-thiadiazoles were examined for their tuberculostatic activity towards the *Mycobacterium tuberculosis* $H_{37}Rv$ strain and two "wild" strains isolated from tuberculotic patients: one (Spec. 210) was resistant to p-aminosalicic acid, isonicotinic acid hydrazide, etambutol and rifampicine, another (Spec. 192) was fully sensitive to the administrated drugs. The determined minimum concentrations inhibiting the growth of tuberculous strains for all of the tested compounds were within the limits 50–100 μg/mL, which indicates low antituberculosis activity.

EXPERIMENTAL

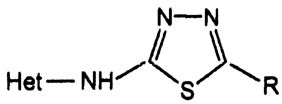
All materials and solvents were of an analytical reagent grade. Thin-layer chromatography was performed on Merck Kieselgel $60F_{254}$ plates and visualized with UV. The results of elemental analyses (%C, H, N, S) for all the compounds obtained were in good agreement with the data that was calculated. Reaction yields and the physical constants of the compounds are given in Tables I and II. ^{1}H NMR spectra in DMSO-d_6 were recorded on Varian Unity Plus (500 MHz) and Varian Gemini (200 MHz) instruments. IR Spectra (KBr) were determined as KBr pellets of the solids on a Satellite FT-IR spectrophotometer (Table III). Mass spectra for compounds **1**, **6**, and **22** were taken on Finnigan MAT 95 by a chemical ionization method with isobutane. Melting points were determined on a BOETIUS apparatus and were uncorrected.

2-Aminoaryl-5-Methylsulfanyl-1,3,4-Thiadiazoles (1–5)

A solution of 5 mmol of appropriate hydroxamoyl chloride and 11 mmol of methyl dithiocarbazinate in 30 mL of ethanol was refluxed for 12 h. After cooling, the precipitate was filtered, washed with cold ethanol, and recrystallized. For compound **1**, a mass spectrum was taken. MS: (m/z) = 226 (100 MH^+), 227 (11), and 268 (4).

2-Aminoaryl-5-Methansulfinyl-1,3,4-Thiadiazoles (6–10)

A quantity of 1 mmol of appropriate 5-methylsulfanylthiadiazole (**1–5**) was suspended in 3 mL of glacial acetic acid. Next, 3 mL of 30% of $H_2O_2$was added dropwise. The reaction mixture was heated for 2.5–7 h at 50°C with stirring. The reaction progress was controlled by TLC method. Then the mixture was neutralized with a saturated $NaHCO_3$

TABLE I Physical Constants of 

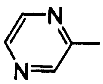
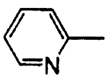
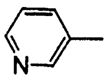
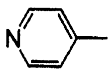
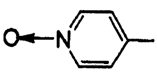
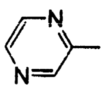
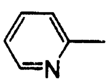
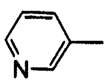
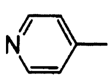
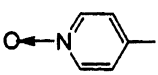
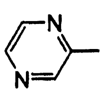
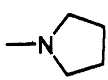
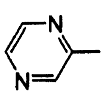
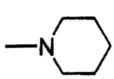
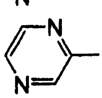
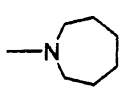
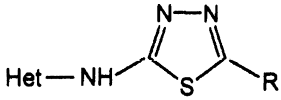
Compound no.	Het	R	Yield [%]	M.p.[°C] solvent for crystallization	Formula MW
1		SCH_3	47	250–251 Pyridine-ethanol	$C_7H_7N_5S_2$ 225.29
2		SCH_3	38	236–237 Pyridine-ethanol	$C_8H_8N_4S_2$ 224.29
3		SCH_3	34	215–216 Ethanol	$C_8H_8N_4S_2$ 224.29
4		SCH_3	20	213–214 Ethanol	$C_8H_8N_4S_2$ 224.29
5		SCH_3	54	236–237 DMF	$C_8H_8N_4OS_2$ 240.29
6		$SOCH_3$	91	249–250 Pyridine-ethanol	$C_7H_7N_5OS_2$ 241.29
7		$SOCH_3$	88	235–236 Pyridine-ethanol	$C_8H_8N_4OS_2$ 240.29
8		$SOCH_3$	63	210–211 Ethanol	$C_8H_8N_4OS_2$ 240.29
9		$SOCH_3$	35	218–219 Ethanol-water	$C_8H_8N_4OS_2$ 240.29
10		$SOCH_3$	61	150–151 DMF	$C_8H_8N_4O_2S_2$ 256.29
18			28	225–226 DMF	$C_{10}H_{12}N_6S$ 248.31
19			44	216–217 DMF	$C_{11}H_{14}N_6S$ 262.33
20			37	230–231 DMF-water	$C_{12}H_{16}N_6S$ 276.36

TABLE I Physical Constants of  ***(Continued)***

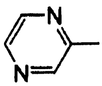
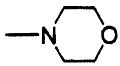
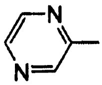
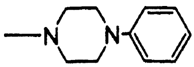
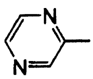
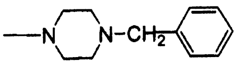
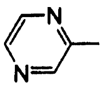
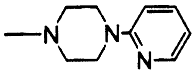
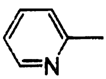
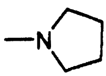
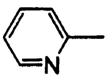
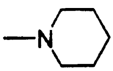
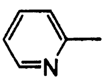
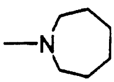
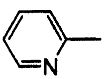
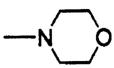
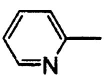
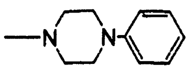
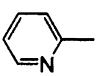
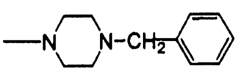
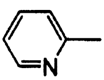
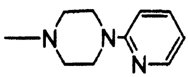
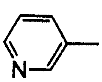
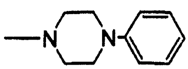
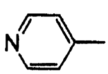
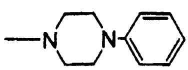
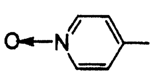
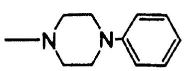
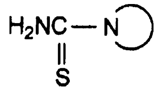
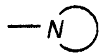
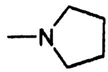
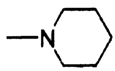
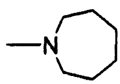
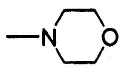
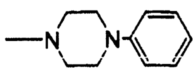
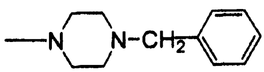
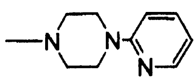
Compound no.	Het	R	Yield [%]	M.p.[°C] solvent for crystallization	Formula MW
21			40	230–231 Pyridine-ethanol	$C_{10}H_{12}N_6OS$ 264.31
22			47	302–303 Pyridine-ethanol	$C_{16}H_{17}N_7S$ 339.41
23			23	226–228 Pyridine-ethanol	$C_{17}H_{19}N_7S$ 353.43
24			36	223–224 Pyridine-ethanol	$C_{15}H_{16}N_8S$ 340.40
25			30	240–241 DMF/water	$C_{11}H_{13}N_5S$ 247.31
26			26	252–253 Ethanol	$C_{12}H_{15}N_5S$ 261.34
27			20	201–202 DMF	$C_{13}H_{17}N_5S$ 275.37
28			29	208–209 DMF-water	$C_{11}H_{13}N_5OS$ 263.31
29			14	230–231 Pyridine-ethanol	$C_{17}H_{18}N_6S$ 338.42
30			25	205–206 DMF	$C_{18}H_{20}N_6S$ 352.45
31			26	214–215 DMF-water	$C_{16}H_{17}N_7S$ 339.41
32			19	215–216 Ethyl acetate	$C_{17}H_{18}N_6S$ 338.42
33			18	235–236 DMF-water	$C_{17}H_{18}N_6S$ 338.42
34			28	285–286 DMF	$C_{17}H_{18}N_6OS$ 354.42

TABLE II Physical Constants of 

Compound no.		Yield [%]	M.p.[°C] solvent for crystallization	Formula MW
11		63	168–169 Ethanol	$C_5H_{11}N_3S$ 145.22
12		24	86–87 Ethanol-water	$C_6H_{13}N_3S$ 159.24
13		28	115–116 Ethanol-water	$C_7H_{15}N_3S$ 173.27
14		49	170–171 Ethanol	$C_5H_{11}N_3OS$ 161.22
15		55	178–179 Ethanol	$C_{11}H_{16}N_4S$ 236.33
16		55	167–168 Ethanol	$C_{12}H_{18}N_4S$ 250.35
17		57	179–180 Ethanol	$C_{10}H_{15}N_5S$ 237.32

solution. The precipitate was filtered, washed with cold water, and recrystallized. For compound **6**, a mass spectrum was taken. MS: (m/z) = 226 (30), 242 (100 MH^+), 243 (10), 466 (25), 482 (66), 483 (13), and 484 (12).

4-Substituted Thiosemicarbazides (11–17)

Methyl dithiocarbazinate (2.44 g, 20 mmol), made according to Kleyman and colleagues,[9] was dissolved in 20 mL of water. The solution was treated with appropriate amine (60 mmol). The mixture was heated under reflux for about 6 h until the evolution of methyl mercaptan almost completely ceased. Methyl mercaptan was detected by the yellow color it imparted to moisten the $Pb(OAc)_2$ paper, which was placed at the mouth of the reflux condenser. In the case of 1-phenylpiperazine and its derivatives, the reactions were carried out in ethanol. Then the solution was cooled and neutralized with AcOH. Further cooling yielded the desired thiosemicarbazides, which were filtered and recrystallized.

TABLE III IR and ^{1}H NMR Spectral Data of Newly Synthesized Compounds

Compound no.	IR [cm^{-1}]	^{1}H NMR DMSO-d_6 δ[ppm]
1	3257, 3052, 2925, 2745, 1626, 1529, 1451, 1399, 1063, 830, 663	500 MHz: 2.69 (s; 3H, SCH_3), 8.17 (d; 1H, pyrazine, *J* 2.2 Hz), 8.28 (s; 1H, pyrazine), 8.44 (s; 1H, pyrazine), 12.14 (s; 1H, NH)
2	3262, 3186, 2919, 2769, 1630, 1552, 1486, 1441, 1425, 772, 664	200 MHz: 2.71 (s; 3H, SCH_3), 7.00–7.10 (m; 2H 2-pyridyl), 7.73–7.82 (m; 1H, 2-pyridyl), 8.26–8.31 (m; 1H, 2-pyridyl), 11.72 (s; 1H, NH)
3	3207, 3165, 2925, 2606, 1580, 1550, 1509, 1463, 1403, 1383, 803, 675	200 MHz: 2.73 (s; 3H, SCH_3), 7.96–8.04 (m; 1H, 3-pyridyl), 8.53–8.60 (m; 2H, 3-pyridyl), 9.28 (d; 1H, 3-pyridyl, *J* 2.3 Hz), 12.32 (s; 1H, NH)
4	3201, 3077, 2893, 2808, 1640, 1586, 1510, 1339, 808, 743	200 MHz: 2.76 (s; 3H, SCH_3), 8.08 (d; 2H, 4-pyridyl, *J*7 Hz), 8.65 (d; 2H, 4-pyridyl, *J* 7 Hz), 11.01 (s; 1H, NH)
5	3246, 3106, 3031, 2948, 2549, 1636, 1620, 1567, 1518, 1396, 1344, 1194, 1178, 856	200 MHz: 2.75 (s; 3H, SCH_3), 8.03 (d; 2H, 4-pyridine-N-oxide, *J* 7.7 Hz), 8.74 (s; 2H, 4-pyridine-N-oxide, *J* 7.7 Hz), 12.92 (brs; 1H, NH)
6	3254, 3153, 2909, 2755, 1624, 1525, 1439, 1405, 1054	200 MHz: 3.13 (s; 3H, $SOCH_3$), 8.30 (m; 1H pyrazine), 8.43 (m; 1H, pyrazine), 8.56 (d; 1H, pyrazine, *J* 1.5Hz), 12.63 (s; 1H, NH)
7	3258, 3184, 1552, 1068, 1051, 1627, 1485, 1445, 1432, 785, 667	200 MHz: 3.11 (s; 3H, $SOCH_3$), 7.06–7.19 (m; 2H, 2-pyridyl), 7.80–7.89 (m; 1H, 2-pyridyl), 8.39–8.41 (m; 1H, 2-pyridyl), 12.21 (s; 1H, NH)
8	3027, 2680, 1633, 1591, 1498, 1471, 1430, 1056	200 MHz: 3.12 (s; 3H, $SOCH_3$), 7.41–7.50 (m; 1H, 3-pyridyl), 8.18–8.34 (m; 2H, 3-pyridyl), 8.79 (t; 1H, 3-pyridyl, *J* 2.4 Hz), 12.81 (s; 1H, NH)
9	2921, 1635, 1607, 1552, 1491, 1425, 1074, 764	200 MHz: 3.55 (s; 3H, $SOCH_3$), 7.60 (m; 2H, 4-pyridyl), 8,46 (m; 2H, 4-pyridyl), 11,50 (brs; 1H, NH)
10	3241, 3109, 2995, 2906, 1630, 1494, 1447, 1332, 1207, 1179, 1156, 1062, 846	200 MHz: 3.37 (s; 3H, $SOCH_3$), 7.69 (s, 2H, 4-pyridine-N-oxide), 8.20 (s; 2H, 4-pyridine-N-oxide), 11.44 (brs; 1H, NH)

(Continued on next page)

TABLE III IR and ^{1}H NMR Spectral Data of Newly Synthesized Compounds *(Continued)*

Compound no.	IR [cm^{-1}]	^{1}H NMR DMSO-d_6 δ[ppm]
11	3200, 3136, 2946, 2872, 1556, 1426, 1368, 1287, 1253, 1029	500 MHz: 1.84 (s; 4H, CH_2), 3.43 (s; 4H, NCH_2), 4.55 (s; 2H, NH_2), 8.57 (s; 1H, NH)
12	3207, 3141, 2964, 1501, 1458, 1443, 1282, 1005, 634	200 MHz: 1.45–1.59 (m; 6H, CH_2), 3.69 (t; 4H, NCH_2), 4.65 (s; 2H, NH_2), 8.91 (brs; 1H, NH)
13	3224, 3036, 2926, 2850, 1522, 1359, 1274, 1209	200 MHz: 1.44 (m; 4H, $NCH_2CH_2C\underline{H_2}$), 1.65 (m; 4H, $NCH_2C\underline{H_2}$), 3.68 (t; 4H, NCH_2, *J* 8.7 Hz), 4.69 (s; 2H, NH_2), 8.69 (s; 1H, NH)
14	3263, 3216, 3035, 2990, 2968, 2925, 2863, 1546, 1422, 1277, 1228, 1204, 1040, 1028, 1012, 1123	200 MHz: 3.53–3.70 (m; double triplet, 8H, NCH_2, OCH_2), 4.70 (brs; 2H, NH_2), 9.13 (brs; 1H, NH)
15	3264, 3218, 3037, 2921, 2835, 1600, 1550, 1502, 1424, 1392, 1367, 1341, 1225, 1165, 751, 685	500 MHz: 3.13 (t; 4H, NCH_2, *J* 4.9 Hz), 3.85 (t; 4H, NCH_2, *J*4.9 Hz), 4.85 (brs; 2H, NH_2), 6.78 (t; 1H, ArH, *J* 7 Hz), 6.92–6.97 (m; 2H, ArH), 7.19–7.25 (m; 2H, ArH), 9.18 (brs; 1H, NH)
16	3239, 3024, 2952, 2815, 1637, 1532, 1413, 1372, 1337, 1295, 1235, 1139, 736, 695	500 MHz: 2.32 (t; 4H, NCH_2, *J* 4.6 Hz), 3.46 (s; 2H, NCH_2Ar), 3.69 (t; 4H, NCH_2, *J* 4.4 Hz), 4.80 (brs; 2H, NH_2), 7.22–7.33 (m; 5H, ArH), 8.55 (brs; 1H, NH)
17	3294, 3204, 3021, 2850, 1598, 1483, 1439, 1420, 1392, 1365, 1232, 767, 725	200 MHz: 3.50–3.55 (m; 4H, NCH_2), 3.82–3.87 (m; 4H, NCH_2), 4.75 (s; 2H, NH_2), 6.62–6.68 (m; 1H, 2-pyridyl), 6,81 (d; 1H, 2-pyridyl, *J* 8.7 Hz), 7.50–7.59 (m; 1H, 2-pyridyl), 8.12 (m; 1H, 2-pyridyl), 9.15 (s; 1H, NH)
18	3056, 2971, 2850, 2707, 1630, 1548, 1514, 1450, 1401, 1364, 1143, 828	500 MHz: 1.96 (s; 4H, CH_2), 3.38 (s; 4H, NCH_2), 8.05 (s; 1H, pyrazine), 8.21 (s; 1H, pyrazine), 8.36 (s; 1H, pyrazine), 11.44 (s; 1H, NH)
19	3266, 2934, 2852, 1630, 1538, 1507, 1445, 1399, 1353, 1255, 1131, 1006, 827	200 MHz: 1.61 (s; 6H, CH_2), 3.40 (s; 4H, NCH_2), 8.08 (d; 1H, pyrazine, *J* 2.8 Hz), 8.21–8.23 (m; 1H, pyrazine), 8.39 (d; 1H, pyrazine, *J* 1.4 Hz), 11.53 (s; 1H, NH)
20	3048, 2935, 2858, 1627, 1544, 1513, 1574, 1445, 1400, 1346, 1141, 1109, 823	200 MHz: 1.51 (m;4H, $NCH_2CH_2C\underline{H_2}$), 1,73 (m; 4H, $NCH_2C\underline{H_2}$), 3.51 (t; 4H, NCH_2, *J* 5.8 Hz), 8.03 (d; 1H, pyrazine, *J* 2.8 Hz), 8.2 (m; 1H, pyrazine), 8.35 (d; 1H, pyrazine, *J* 1.5 Hz), 11.42 (s; 1H, NH)

21	3266, 3150, 2923, 2862, 1632 1512, 1450, 1401, 1269, 1235, 1114	200 MHz: 3.36 (t; 4H, NCH_2, *J*4.8 Hz), 3.72 (t; 4H, OCH_2, *J*4.8 Hz), 8.08 (d; 1H, pyrazine, *J* 2.8 Hz), 8.20–8.22 (m; 1H, pyrazine), 8.38 (d; 1H, pyrazine, *J* 1.49 Hz), 11.48 (s; 1H, NH)
22	3058, 2920, 2842, 1631, 1497, 1444, 1404, 1233	500 MHz: 3.25 (s; 4H, NCH_2), 3.51 (s; 4H, NCH_2), 6.80 (s; 1H, ArH), 6.97 (s; 2H, ArH), 7.22 (s; 2H, ArH), 8.06 (s; 1H, pyrazine), 8.20 (s; 1H, pyrazine), 8.37 (s; 1H, pyrazine), 11.58 (s; 1H, NH)
23	3254, 3029, 2937, 2809, 1622, 1510, 1540, 1448, 1400, 1139	200 MHz: 2.53 (t; 4H, NCH_2, *J*4.8 Hz), 3.41 (t; 4H, NCH_2, *J* 4.8 Hz), 3.55 (s; 2H, NCH_2Ar), 7.25–7.41 (m; 5H, ArH), 8.09 (d; 1H, pyrazine, *J* 2.8 Hz), 8.22–8.24 (dd; 1H, pyrazine,J_1 2.79 Hz, J_2 1.47 Hz), 8.39 (d; 1H, pyrazine, *J* 1.46 Hz), 10.52 (brs; 1H, NH)
24	3053, 2850, 1633, 1596, 1541, 1514, 1484, 1437, 1404, 1238, 1144	200 MHz: 3.49 (m; 4H, NCH_2), 3.64 (m; 4H, NCH_2), 6.65–6.71 (m; 1H, pyridyl), 6.90 (d; 1H, pyridyl, *J* 8.6 Hz), 7.56 (m; 1H, pyridyl), 8.08–8.38 (m; 3H, 2H pyrazine and 1H 2-pyridyl), 8.39 (d; 1H, pyrazine, *J* 1.32), 10.35 (brs; 1H, NH)
25	3224, 2956, 2851, 1627, 1595, 1564, 1527, 1479, 1450, 1415, 1338, 1225, 772	200 MHz: 1.87–2.01 (m; 4H, CH_2), 3.39 (t; 4H, NCH_2, *J* 6.7 Hz), 6.84–7.25 (m; 2H, 2-pyridyl), 7.63–7.88 (m; 1H, 2-pyridyl), 8.21–8.28 (m; 1H, 2-pyridyl), 10.96 (s; 1H, NH)
26	3043, 2935, 2850, 1628, 1595, 1557, 1520, 1483, 1446, 1419, 1349, 1256, 770	500 MHz: 1.59 (s; 6H, CH_2), 3.36 (s; 4H, NCH_2), 6.86 (t; 1H, 2-pyridyl, *J* 5.8 Hz), 6.96 (d; 1H, 2-pyridyl, *J* 8.3 Hz), 7.66 (t; 1H, 2-pyridyl, *J* 8.6 Hz), 8.19 (d; 1H, 2-pyridyl, *J* 4.9 Hz), 10.99 (s; 1H, NH)
27	3262, 3042, 2926, 2853, 1625, 1597, 1560, 1519, 1482, 1455, 1415, 1340, 770	200 MHz: 1.53 (d; 4H, $NCH_2CH_2C\underline{H}_2$, *J* 3.1 Hz), 1.75 (d; 4H, $NCH_2C\underline{H}_2$, *J* 1.75 Hz), 3.54 (t; 4H, NCH_2, *J* 5.5 Hz), 6.85–7.00 (m; 2H, 2-pyridyl), 7.63–7.72 (m; 1H, 2-pyridyl), 8.19–8.22 (m; 1H, 2-pyridyl), 11.13 (brs; 1H, NH)
28	3266, 3188, 2950, 2852, 1633, 1560, 1514, 1484, 1446, 1419, 1240, 1115	200 MHz: 3.33 (t; 4H, NCH_2, *J* 4.27 Hz), 3.72 (t; 4H, OCH_2, *J*4.27 Hz), 6.90 (m; 2H, 2-pyridyl), 7.68 (m; 1H, 2-pyridyl), 8.20 (d; 1H, 2-pyridyl, *J* 4 Hz), 11.10 (s; 1H, NH)

(Continued on next page)

TABLE III IR and ^{1}H NMR Spectral Data of Newly Synthesized Compounds *(Continued)*

Compound no.	IR [cm^{-1}]	^{1}H NMR DMSO-d_6 δ[ppm]
29	3255, 3044, 2830, 1626, 1597, 1557, 1480, 1445, 1416, 1234, 939, 757	200 MHz: 3.30 (t; 4H, NCH_2, J 4.9 Hz), 3.53 (t; 4H, N CH_2, J4.9 Hz), 6.85–7.04 (m; 3H, ArH), 7.23–7.44 (m; 2H, ArH), 7.66–7.81 (m; 2H, 2-pyridyl), 8.23 (m; 1H, 2-pyridyl), 8.58–8.62 (m; 1H, 2-pyridyl), 10,95 (brs; 1H, NH)
30	3263, 3154, 2944, 2912, 2817, 1629, 1559, 1513, 1481, 1448, 1417, 1242, 1147, 1004, 769, 743	200 MHz: 2.51 (t; 4H, NCH_2, J 4.7 Hz), 3.39 (t; 4H, NCH_2, J 4.9 Hz), 6.86–6.96 (m; 3H, ArH), 7.00–7.36 (m; 4H, 2H ArH and 2H 2-pyridyl), 7.64–7.73 (m; 1H, 2-pyridyl), 8.20–8.22 (m; 1H, 2-pyridyl), 11.85 (brs; 1H, NH)
31	3260, 3042, 2892, 2846, 1623, 1595, 1510, 1479, 1436, 1415, 1239, 773	200 MHz: 3.41–3.68 (m; 8H, NCH_2), 6.67 (q; 1H, 2-pyridyl, J_1 5.05 Hz, J_2 1.98 Hz), 6.92 (m; 3H, 2-pyridyl), 7.53–7.72 (m; 2H, 2-pyridyl), 8.13–8.23 (m; 2H, 2-pyridyl), 11.11 (s; 1H, NH)
32	3161, 3045, 2863, 2654, 1632, 1578, 1557, 1546, 1491, 1453, 1232, 761	200 MHz: 3.29 (m; double triplet, 8H, NCH_2, J5 Hz), 6.85 (t; 1H, ArH, J 7.25 Hz), 7.02 (d; 2H, ArH, J7.96 Hz), 7.25 (t; 2H, ArH, J 8.4 Hz), 7.90 (q; 1H, 3-pirydyl, $J_1$5.44 Hz, J_2 3.12 Hz), 8.45 (m; 2H, 3-pyridyl), 9.19 (d; 1H, 3-pyridyl, J 2.2 Hz), 11.86 (brs; 1H, NH)
33	3204, 2891, 2760, 1642, 1588, 1525, 1500, 1447, 1231, 756	200 MHz: 3.28 (s; 4H, NCH_2), 3.56 (s; 4H, NCH_2), 6.83 (t; 1H, ArH,J 7.2 Hz), 7.02 (d; 2H, ArH, J 8 Hz), 7.25 (t; 2H, ArH, J7.6 Hz), 7.89 (d; 2H, 4-pyridyl, J 6.5 Hz), 8.51 (d; 2H, 4-pyridyl, J 6.6 Hz), 12,50 (brs; 1H, NH)
34	3410, 3220, 2848, 1642, 1601, 1529, 1493, 1444, 1384, 1349, 1233, 1199, 934	200 MHz: 3.31 (s; 4H, NCH_2), 3.58 (s; 4H, NCH_2), 6.85 (t; 1H, ArH, J 7 Hz), 7.02 (d; 2H, ArH, J 7.9 Hz), 7.27 (t; 2H, ArH, J 7.5 Hz), 7.82 (d; 4-pyridine N-oxide, J 6.1 Hz), 8.51 (d; 2H, 4-pyridine-N-oxide, J 6.1 Hz), 12.78 (brs; 1H, NH)

2-Amino-5-Aminopyrazinyl-1,3,4-Thiadiazoles (18–24)

N-hydroxy-pyrazinecarboximidoyl chloride (0.39 g, 5 mmol) was dissolved in 20 mL of DMF and treated with 10 mol of appropriate thiosemicarbazide **11–17**. The reaction mixture was refluxed for 10 h, cooled and the precipitate was filtered and recrystallized. For compound **22**, a mass spectrum was taken. MS: (m/z) = 340 (100 MH^+), 341 (19), and 342 (7).

2-Amino-5-(Aminopyridin-2-yl)-1,3,4-Thiadiazoles (25–31)

N-hydroxy-pyrazincarboxyimidoyl chloride (0.39 g, 5 mmol) was dissolved in 20 mL of DMF and treated with 10 mmol of appropriate thiosemicarbazide **11–17**. The reaction mixture was refluxed for 10 h and was concentrated to about 5 mL and cooled. The precipitate was filtered and recrystallized.

2-(Aminopyridin-3-Yl)-5-(4-Phenylpiperazin-1-yl)-1,3,4-Thiadiazole (32)

The synthesis was carried out as described for **25–31**. The concentrated mixture was treated with a small amount of ethyl acetate. After cooling, the precipitate was filtered and recrystallized.

2-(Aminopyridin-4-yl)-5-(4-Phenylpiperazin-1-yl)-1,3,4-Thiadiazole (33) and 2-(Amino-1-Oxy-Isonicotin)-5-(4-Phenylpiperazin-1-yl)-1,3,4-Thiadiazole (34)

The synthesis was carried out as described for **25–31** but the solvent was evaporated to dryness and the residue was treated with 15 mL of ethanol. After cooling, the precipitate was filtered and recrystallized.

Antituberculotic Activity

In vitro investigations were performed by a classical test-tube method of successive dilution with Youman's liquid medium containing 10% of a bovine serum.[11]

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