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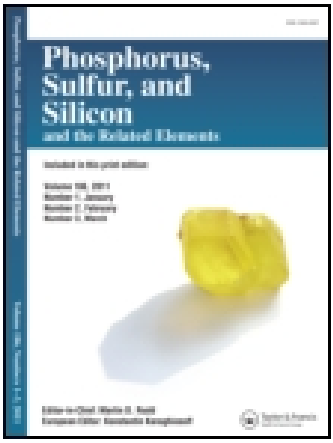


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# Studies on Pyrazine Derivatives, XLIV: Synthesis and Tuberculostatic Activity of 4-Substituted 3,4,5,6-Tetrahydro-2H-[1,2′]-Bis-Pyrazine Derivatives

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# Studies on Pyrazine Derivatives, XLIV: Synthesis and Tuberculostatic Activity of 4-Substituted 3,4,5,6-Tetrahydro-2H-[1,2′]-Bis-Pyrazine Derivatives

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*2-chloro-3-cyanopyrazine was a substrate in the syntheses of some potentially tuberculostatic pyrazine derivatives. This compound, upon action of secondary amines, pyrazine derivatives 1-phenyl-, 1-piperonyl-, 1-(4-fluorophenyl)-, 1-(2-pyridil)-, and 1-benzylpiperazine, gave the corresponding nitriles (**1a–e**). Compounds **1c**, **d**, **e** were changed into the amidoximes (**2c**, **d**, **e**) by hydroxylamine action. Derivatives **1a–e** were transformed into the corresponding thioamides (**3a–e**) when treated with ammonium polysulphide. Two of these, thioamides, **3a** and **3b**, in the cyclization reactions with ethylenediamine gave the imidazolines (**4a**, **b**) with phenacyl bromide—the thiazole derivatives (**5a**, **b**). The compounds obtained were tested in vitro for their tuberculostatic activity. The tuberculostatic activity of compound **5b** was the highest: MIC 3.1–7.8 μg/mL.*

**Keywords** 1,4-disubstituted piperazine; 2,3-disubstituted pyrazine; thioamides; tuberculostatic

## INTRODUCTION

The aim of this work was to obtain the new pyrazine derivatives and check their tuberculostatic activity. The amide of pyrazinecarboxylic acid (pyrazinamide) has been used as the antituberculytic drug since 1936, and its derivative, N-(4-morpholinomethyl)-amide,

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of the same acid (morinamide) appeared to be even stronger and a less toxic chemotherapeutic agent.[1,2,3] Ethylthioisonicotinic acid amide (ethionamide) has been used in consumption treatment as well.[4] Our earlier works showed that pharmacological activity used to be increased by introducing the phenylpiperazine system into the molecule. This system can be found in the molecules of some potent chemotherapeutics such as ophlexacine, ciprofloxacine, and sparfloxacine—the most powerful drug in the fight against Mycobacterium tuberculosis.[5,6,7]

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## INVESTIGATIONS AND RESULTS

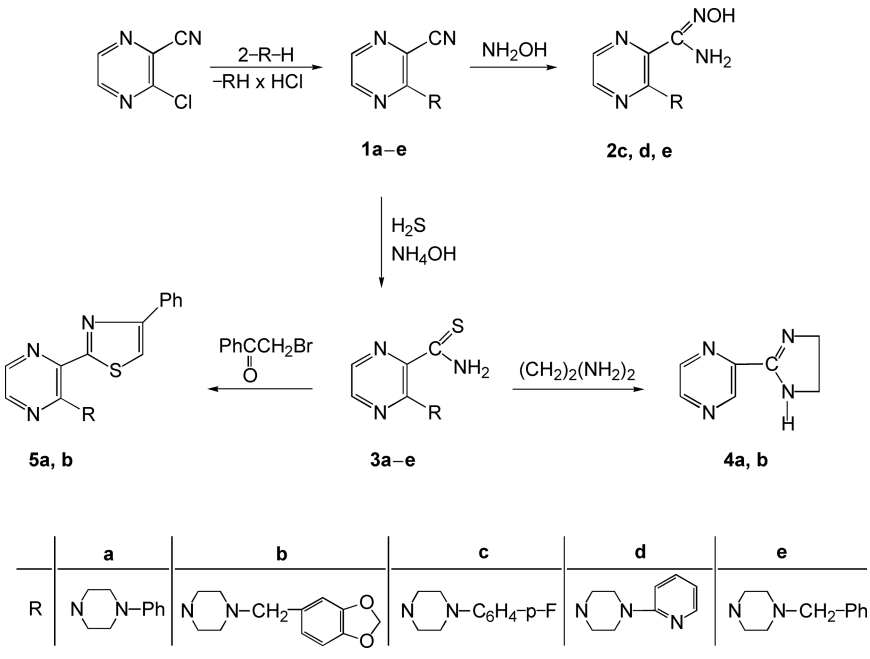
### Synthesis of the Derivatives

The substrate used in the syntheses was 2-chloro-3-cyanopyrazine, which was obtained by cyanopyrazine chlorination with sulphuryl chloride.[8] The compound was treated with the secondary amines 1-phenyl-, 1-piperonyl-, 1-(4-fluorophenyl)-, 1-(2-pyridil)-, and 1-benzylpiperazine, which resulted in the corresponding products of chlorine substitution by the piperazine system (**1a–e**). The nitriles obtained (**1c**, **d**, **e**) were changed into the amidoximes (**2c**, **d**, **e**) by hydroxylamine action. The treatment with ammonium polysulphide transformed compounds **1a–e** into thioamide derivatives (**3a–e**). The thioamides **3a**, **b** underwent cyclization reactions with ethylenediamine to the corresponding imidazolines (**4a**, **b**), and with phenacyl bromide to thiazole derivatives (**5a**, **b**; Scheme 1).

The structure of new compounds (**1–5**) that were obtained was established by the analysis of IR and $^1$H NMR spectra, and their characteristics are given in Table I.

### Pharmacological Tests

The compounds obtained (**1–5**) were tested for their tuberculostatic activity towards the Mycobacterium tuberculosis $H_{37}Rv$ strains and two strains that were isolated from the tuberculotic patients: (1) one resistant to isonicotinic acid hydrazide, ethambutol, and rifampicine, and (2) the other fully susceptible to the tuberculostatics administered. Tuberculostatic activity was tested with the test tube method on Youman's liquid medium containing 10% of a bovine serum.[9] Minimum growth inhibiting concentration (MIC) values were within the limits of 3.1–500 $\mu$g/mL (Table I). The most active compound—thiazole




**SCHEME 1**

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derivative (**5b**)—was tested on a broad basis with use of the following standard strains (MIC values are given in parentheses): Myc. $H_{37}Rv$—human strain (3.1), Myc. $An_5$—cattle strain (12.5), Myc. kansasii—photochromogenic strain (50), Myc. scrofulaceum—scotochromogenic strain (100), Myc. intracellulare—non chromogenic strain (50), Myc. fortuitum—quick-growing strain from IV group according to Runyn (100), Myc. kirchberg—bird strain (50), Myc. wells—rodent's strain (25), and from quick-growing saprophytic strains Myc. smegmatic (100) and Myc. phlei (50).

## EXPERIMENTAL

Melting points were determined with a Reichert apparatus and are uncorrected. The IR 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 I. The results of elemental analyses (C and H) for all of the compounds that were obtained are in good agreement with the data calculated.

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**TABLE I Characteristics of the Newly Synthesized Pyrazinyl Compounds**

| Compound | Formula | Yield [%] | M.p. [°C] Solvent | $^1$H NMR Solvent $\delta$ [ppm] | MIC $\mu$g/mL | | |
|---|---|---|---|---|---|---|---|
| | | | | | Myc. $H_{37}$Rv | Resistant Strain | Fully Susceptible Strain |
| **1a** | $C_{15}H_{15}N_5$ 265.31 | 47 | 56–58 cyclohexane | ($CDCl_3$): 3.2(m, 4H, $CH_2$); 3.0(m, 4H, $CH_2$); 6.9; 7.2(2m, 5H, Ph); 8.0; 8.2(2m, 2H, CH, pyrazine) | 125 | 250 | 62.5 |
| **1b** | $C_{17}H_{17}O_2N_5$ 323.35 | 63 | 94–97 cyclohexane | ($CDCl_3$): 2.5(m, 4H, $CH_2$); 3.4(s, 2H, $CH_2$); 3.7(m, 4H, $CH_2$); 5.9(s, 2H,$CH_2$); 6.7(m, 3H, Ph); 7.8; 8.1(2s, 2H, CH, pyrazine) | 125 | 62.5 | 125 |
| **1c** | $C_{15}H_{14}FN_5$ 283.30 | 50 | 105–110 MeOH | ($CDCl_3$): 3.3(m, 4H, $CH_2$); 3.9(m, 4H, $CH_2$); 6.9(m, 5H, Ph); 8.1; 8.3(2d, 2H, CH, pyrazine) | 100 | 100 | 100 |
| **1d** | $C_{14}H_{14}N_6$ 266.30 | 36 | 90–93 MeOH | ($CDCl_3$): 3.8(m, 4H, $CH_2$); 3.9(m, 4H, $CH_2$); 6.7(m, 5H, CH, pyrydine); 8.0; 8.3(2d, 2H, CH, pyrazine) | 100 | 100 | 100 |
| **1e** | $C_{16}H_{17}N_5$ 279.34 | 49 | 96–99 cyclohexane | ($CDCl_3$): 2.6(m, 4H, $CH_2$); 3.5(s, 1H, $CH_2$); 3.87(m, 4H, $CH_2$); 7.3(s, 5H, Ph); 8.8; 8.2(2d, 2H, CH, pyrazine) | 100 | 50 | 100 |
| **2c** | $C_{15}H_{17}FN_6O$ 316.33 | 79 | 186–190 EtOH | ($CDCl_3$): 3.2(m, 4H, $CH_2$); 3.6(m, 4H, $CH_2$); 6.9(m, 4H, Ph); 8.1 (m, 2H, CH, pyrazine) | 100 | 50 | 100 |
| **2d** | $C_{14}H_{17}N_7O$ 299.33 | 65 | 197–201 EtOH | ($CDCl_3$): 3.6(m, 8H, $CH_2$); 6.6(m, 4H, pyrydine); 8.1(m, 2H, CH, pyrazine) | 100 | 50 | 100 |
| **2e** | $C_{16}H_{20}N_6O$ 312.37 | 38 | 200–203 MeOH | ($CDCl_3$): 3.5(m, 4H, $CH_2$); 3.7(m, 4H, $CH_2$); 5.40(s, 2H, $CH_2$); 6.60 (m, 3H, Ph); 7.5(m, 2H, Ph); 8.1; 8.2(2d, 2H, CH, pyrazine) | 100 | 50 | 100 |
| **3a** | $C_{15}H_{17}N_5S$ 299.33 | 63 | 164–167 EtOH | ($CDCl_3$): 3.1(m, 4H, $CH_2$); 3.6(m, 4H, $CH_2$); 6.8–7.1(m, 5H, Ph); 7.8; 8.0(2d, 2H, CH, pyrazine) | 62.5 | 125 | 125 |
| **3b** | $C_{17}H_{19}N_5O_2S$ 357.36 | 62 | 74–75 MeOH | ($CDCl_3$): 2.3(m, 4H, $CH_2$); 3.3(m, 6H, $CH_2$); 5.8(s, 2H, $CH_2$); 6.6–6.7(m, 3H, Ph); 7.6; 7.9(2d,2H, CH, pyrazine) | 250 | 250 | 125 |
| **3c** | $C_{15}H_{16}FN_5S$ 317.38 | 79 | 185–189 MeOH | (DMSO-$d_6$): 3.2(m, 4H, $CH_2$); 3.6(m, 4H, $CH_2$); 7.0(m, 4H, Ph); 7.9; 8.2(2d, 2H, CH, pyrazine) | 100 | 50 | 100 |
| **3d** | $C_{14}H_{16}N_6S$ 300.38 | 35 | 160–162 EtOH | ($CDCl_3$): 3.7(m, 8H, $CH_2$); 6.7(m, 4H, CH, pyrydine); 7.9; 8.2(2d, 2H, CH, pyrazine) | 100 | 100 | 100 |
| **3e** | $C_{16}H_{19}N_5S$ 313.42 | 50 | 144–146 EtOH + $H_2O$ | ($CDCl_3$); 2.5(m, 4H, $CH_2$); 3.5(m, 4H, $CH_2$); 7.3(m, 5H, Ph); 7.8; 8.1(2d, 2H, CH, pyrazine) | 100 | 50 | 100 |
| **4a** | $C_{17}H_{20}N_6$ 308.38 | 82 | 146–148 cyclohexane | ($CDCl_3$): 3.2(m, 4H, $CH_2$); 3.6(m, 8H, $CH_2$); 6.8; 7.2(2m, 5H, Ph); 7.9; 8.1(2d, 2H, CH, pyrazine) | 250 | 250 | 250 |
| **4b** | $C_{19}H_{22}N_6O_2$ 366.41 | 79 | 121–123 cyclohexane | ($CDCl_3$): 2.4(m, 4H, $CH_2$); 3.2–3.8(m, 10H, $CH_2$); 5.8(s, 2H, $CH_2$); 6.7(m, 3H, Ph); 7.8; 8.1(2m, 2H, pyrazine) | 500 | 500 | 250 |
| **5a** | $C_{23}H_{21}N_5S$ 399.44 | 88 | 195–198 EtOH | ($CDCl_3$): 2.4–2.9(m, 8H, $CH_2$); 5.9–7.0(m, 10H, Ph, 1H, thiazole, 2H pyrazine) | 250 | 250 | 500 |
| **5b** | $C_{25}H_{23}N_5O_2S$ 457.47 | 80 | 240–245 MeOH | (DMSO-$d_6$): 3.6(m, 4H, $CH_2$); 4.0(m, 4H, $CH_2$); 4.7(m, 2H, $CH_2$); 6.3(s, 2H, $CH_2$); 7.1–8.6(m, 11H, arom.) | 3.1 | 7.8 | 7.8 |

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### 4-Phenyl-, 4-benzo[1,3]dioxol-5-ylmethyl-, 4-(4-fluorophenyl)-, 4-pyridin-2-yl-, 4-benzyl-3,4,5,6-tetrahydro-2H-[1,2′]bispyrazinyl-3′-carbonitrile (1a–e)

2-chloro-3-cyanopyrazine (5 mmole) was dissolved in benzene (10 mL), treated with corresponding amine: 1-phenyl-, 1-piperonyl-, 1-(4-fluorophenyl)-, 1-(2-pyridyl)-, or 1-benzylpiperazine, and refluxed for 1 h. On cooling, water (20 mL) was added, the benzene phase was separated, and the aqueous phase was extracted twice with benzene (10 mL). Combined benzene extracts were dried over anhydrous $Na_2SO_4$. Upon benzene evaporation, the liquids that were obtained were allowed to stand for crystallization (**1a–e**).

### 4-(4-Fluorophenyl)-, 4-pyridyn-2-yl-, 4-benzyl-N-hydroxy-3,4,5,6-tetrahydro-2H-[1,2′]-bis-pyrazinyl-3′-carboxamidine (2c, d, e)

Two solutions were prepared $NH_2OH \times HCl$ (1.2 g) dissolved in methanol (10 mL), and KOH (1.15 g) dissolved in methanol (10 mL) were joined, the precipitated KCl was filtered, and the filtrate was treated with the corresponding nitrile **1c**, **d**, **e** (2.5 mmole). The mixture was refluxed for 1 h. On cooling, the products were precipitated (**2c**, **d**, **e**).

### 4-Phenyl-, 4-benzo[1,3]dioxol-5-ylmethyl-, 4-(4-fluorophenyl)-, 4-pyridin-2-yl-, 4-benzyl-3,4,5,6-tetrahydro-2H-[1,2′]-bipyrazinyl-3′-carbothioic acid amide (3a–e)

Corresponding nitrile (2.5 mmole) was added to concentrated $NH_4OH$ (20 mL) that was saturated with $H_2S$ and stood for 2 days at ambient temperature. The precipitates were filtered, washed with water, and recrystallized (**3a–e**).

### 3′-(4,5-Dihydro-1H-imidazol-2-yl)-4-phenyl-3,4,5,6-tetrahydro-2H-[1,2′]-bipyrazinyl (4a), 4-benzo[1,3]dioxol-5-ylmethyl-3′-(4,5-dihydro-1H-imidazol-2-yl)-3,4,5,6-tetrahydro-2H-[1,2′]-bipyrazinyl (4b)

Compound **3a** or **3b** (5 mmole) was refluxed with ethylenediamine (2 mL) for 2 h. On cooling, water (10 mL) was added, and the precipitates were filtered and washed with water (**4a**, **b**).

### 4-Phenyl-, 4-benzo[1,3]dioxol-5-ylmethyl-3′-(4-phenyl-thiazol-2-yl)-3,4,5,6-tetrahydro-2H-[1,2′]-bipyrazinyl (5a, b)

Phenacyl bromide (5 mmole) was dissolved in hot absolute ethanol (20 mL). The solution was cooled a little and treated with compound **3a** or **3b**, then refluxed for 1 h. On cooling, the precipitated compounds **5a** or **5b** were filtered.

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