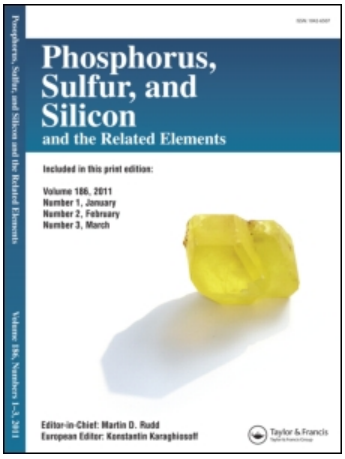

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Synthesis and Antibacterial Activity of New 1,4-Disubstituted Piperazine Derivatives

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Synthesis and Antibacterial Activity of New 1,4-Disubstituted Piperazine Derivatives

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In search of antibacterial agents new 4-phenylpiperazine derivatives were obtained. Their structures include some heterocyclic (thiazole, oxadiazole, piperazine, and benzimidazole) systems, as well as functional (thioamide and amidoxime) groups, frequently present in biologically active compounds. Thioamides ***2b****,* **e** *and amidoximes* ***3b–e*** *were examined towards 25 strains of aerobic and 25 strains of anaerobic bacteria. The derivatives* ***2e*** *and* ***3b*** *showed the highest antimicrobial activity towards anaerobes, both Gram-negative and Gram-positive. The compounds studied were inactive towards the aerobes, however. Their tuberculostatic activity towards the standard $H_{37}Rv$ strain and two strains isolated from tuberculotic patients was studied in vitro. The obtained MIC values were within the limits 12.5–100 $\mu g/mL$.*

Keywords 1,2,4-oxadiazole; 4-Phenylpiperazine derivatives; Antibacterial activity; Benzimidazoles; Thioamides; Thiazole

INTRODUCTION

Piperazine derivatives appear to be widely applicable in therapeutics.[1] The piperazine ring is present in molecules of antibiotics such as ciprofloxacine, pefloxacine, and rifampycine,[2] of antimycotic drugs like ketokonazole,[1,2–4] of circulatory system drugs,[5,6] and of antiparasitical agents.[1] Novel piperazine containing cephalosporines, active towards both Gram-positive and Gram-negative bacteria, were obtained

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by Heyningen and Brown.[7] To the new phenylpiperazine derivatives reported here, thiazole and benzimidazole heterocyclic systems, as well as thioamide and amidoxime functional groups[8,9] were introduced. These can be found in such well-known medicines, as thiabendazole, ethionamide, and prothionamide.[10]

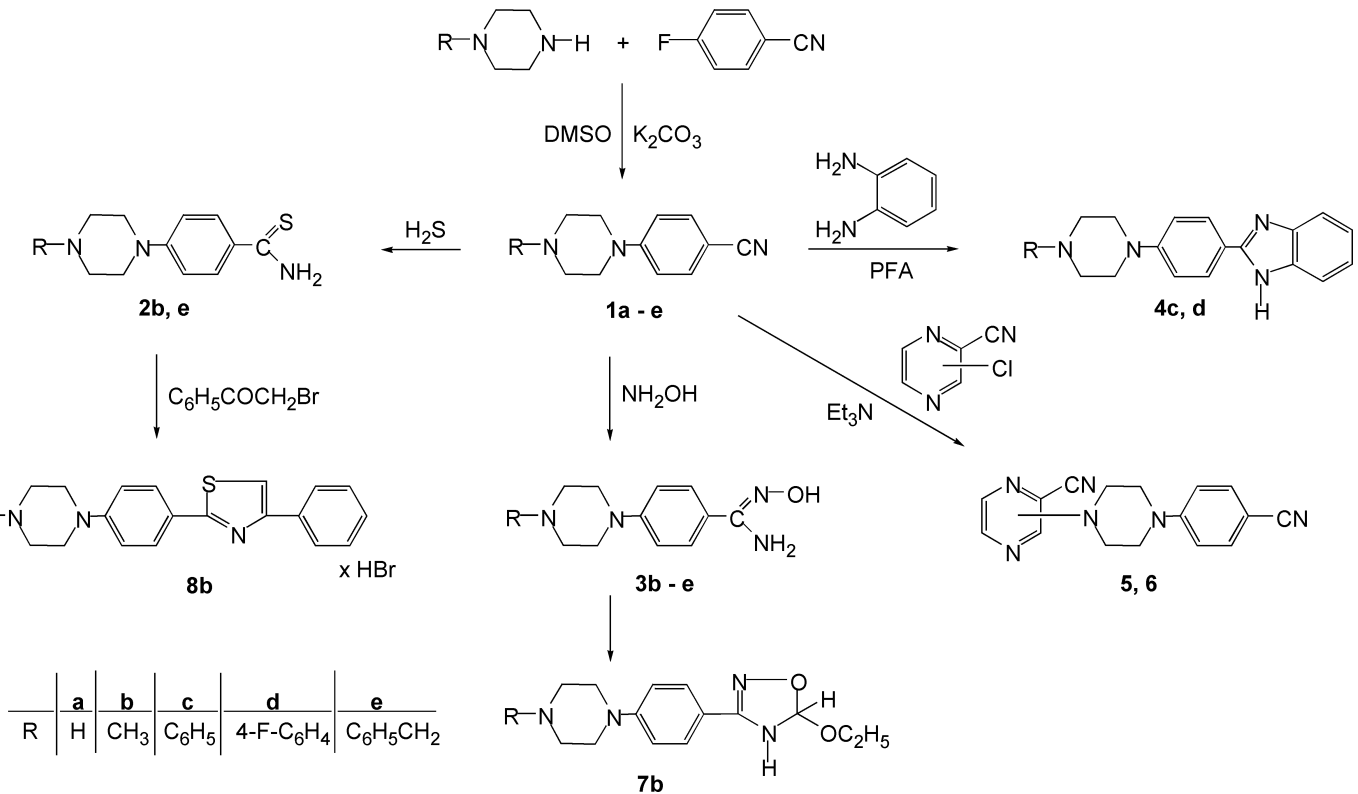
RESULTS AND DISCUSSION

The preparation of the benzonitriles **1a–e** with a phenylpiperazine group in *para* position was the initial step of the syntheses. These compounds were formed upon action of *p*-fluoro-benzonitrile on the corresponding piperazines in dimethylsulphoxide-potassium carbonate medium. The thioamides **2b–e** were then obtained by the reaction of alcoholic solutions of the nitriles **1b–e** with hydrogen sulphide. The amidoximes **3b–e** were prepared starting from the nitriles **1b–e** by reaction with hydroxylamine. The 2-substituted benzimidazoles **4c**,**d** were obtained from the phenyl- and *p*-fluorophenylpiperazyl substituted nitriles by reaction with *o*-phenylenediamine in polyphosphoric acid (PPA). The pyrazine derivatives **5** and **6** were produced in the reaction of 3- and 6-chloropyrazine-2-carbonitriles[11,12] with benzonitrile **1a**. The reaction was conducted in anhydrous benzene in the presence of triethylamine as hydrogen chloride acceptor. Attempts to transform the nitrile group in these compounds (**5** and **6**) into a thioamide or amidoxime function failed. Heating of the amidoxime **3b** in ethyl orthoformate resulted in the formation of the 4,5-dihydro-1,2,4-oxadiazole derivative **7b.**

1-Methyl-4-[4-(5-phenyl-thiazol-2-yl)]-phenylpiperazine hydrobromide **8b** was obtained from the reaction of the thioamide **2b** with phenacyl bromide. The reactions are shown in Scheme 1. Characteristics of the compounds obtained are given in Table I.

MICROBIOLOGY

The investigations included 25 strains of obligate anaerobic bacteria isolated from the oral cavity, respiratory tract and abdominal cavity as well as 6 standard strains. The anaerobes belonged to the following genera: Peptococcus (1 strain), Peptostreptococcus (4), Actinomyces (2), Propionibacterium (2), Prevotella (6), Porphyromonas (2), Fusobacterium (3), Bacteroides (5), and standard strains: Bacteroides fragilis ATCC 25285, Bacteroides vulgatus ATCC 8482, Bacteroides ovatus ATCC 8483, Fusobacterium nucleatum ATCC 25586, Peptostreptococcus anaerobius ATCC 27337 and Propionibacterium acnes ATCC 11827.



SCHEME 1

TABLE I Characteristics of the New Compounds Synthesized

	Formula	Yield (%)	Mp (°C) cryst. solvent	IR (KBr) ν_{max} (cm^{-1})	^1H NMR 200 MHz (solvent) δ [ppm]
1a	$C_{11}H_{13}N_3$ 187.2	35	65–66 (cyclohexane)	3968, 3616, 3328, 3056, 2840, 2208, 1600, 1508, 1448, 1376, 1248	($CDCl_3$): 3.02, 3.25 (m, 8H, CH_2 piperazine); 6.83, 7.50 (m, 4H, CH, Ph)
1b	$C_{12}H_{15}N_3$ 201.3	88	104–105 (cyclohexane)	3936, 3584, 3392, 3040, 2944, 2896, 2848, 2816, 2800, 2208, 1600, 1512	($CDCl_3$): 2.39 (s, 3H, CH_3); 2.61, 3.29 (m, 8H, CH_2 piperazine); 6.86, 7.53 (m, 4H, CH, Ph)
1c	$C_{17}H_{17}N_3$ 263.3	61	169–170 (cyclohexane)	3984, 3723, 2232, 2208, 1744, 1600, 1568, 1552, 1536, 1504, 1460, 1440	($CDCl_3$): 3.35 (m, 4H, CH_2 piperazine); 3.50 (m, 4H, CH_2 piperazine); 6.88, 7.51, 7.50 (m, 9H, CH, Ph)
1d	$C_{17}H_{16}FN_3$ 281.3	83	158–160 (EtOH)	2832, 2216, 1600, 1504, 1440, 1392, 1232, 1152	($CDCl_3$): 3.25, 3.52 (m, 8H, CH_2 piperazine); 6.95, 7.53 (m, 8H, CH, Ph)
1e	$C_{18}H_{19}N_3$ 277.4	70	110–111 (cyclohexane)	2816, 2763, 2208, 1600, 1508, 1392, 1344, 1248	($CDCl_3$): 2.58, 3.33 (m, 8H, CH_2 pyrazine); 3.56 (s, 2H, CH_2); 6.83, 7.26, 7.47 (m, 9H, CH, Ph)
2b	$C_{12}H_{17}N_3S$ 235.3	52	186–188 (EtOH)	3296, 3144, 1648, 1600, 1392, 1248, 1200	(DMSO-d_6): 2.21 (s, 3H, CH_3); 2.49, 3.27 (m, 8H, CH_2 piperazine); 6.87, 7.91 (d, $J = 9$ Hz, 4H, CH, Ph); 9.12, 9.40 (s, 2H, NH)
2e	$C_{18}H_{21}N_3S$ 311.4	87	206–208 (EtOH)	3344, 3216, 2960, 2832, 1648, 1600, 1552, 1520, 1392, 1328	(DMSO-d_6): 2.49, 3.82 (m, 8H, CH_2 piperazine); 3.51 (s, 2H, CH_2); 6.91, 7.32, 7.92 (m, 9H, CH, Ph); 9.12, 9.40 (s, 2H, NH)
3b	$C_{12}H_{18}N_4O$ 234.3	88	165–172 (H_2O)	3304, 2824, 1648, 1616, 1600, 1520, 1392, 1296, 1248	($CDCl_3$): 2.39 (s, 3H, CH_3); 2.60, 3.30 (m, 8H, CH_2 pipe-razine); 4.82 (s, 2H, NH_2); 6.91, 7.52 (m, 4H, CH, Ph)
3c	$C_{17}H_{20}N_4O$ 296.4	78	170 R (MeOH)	3488, 3360, 2832, 1660, 1600, 1520, 1488, 1440, 1392, 1328, 1232	(DMSO-d_6): 3.30 (m, 8H, CH_2 piperazine); 5.58 (s, 2H, NH_2); 6.90, 7.22, 7.58 (m, 9H, CH, Ph); 9.39 (s, 1H, OH)

(Continued on next page)

TABLE I Characteristics of the New Compounds Synthesized *(Continued)*

	Formula	Yield (%)	Mp (°C) cryst. solvent	IR (KBr) ν_{max} (cm^{-1})	^1H NMR 200 MHz (solvent) δ [ppm]
3d	$C_{17}H_{19}FN_4O$ 314.4	83	198–202 (MeOH)	3472, 3344, 2832, 1640, 1600, 1516, 1456, 1388, 1308, 1232	(DMSO-d_6): 3.20, 3.32 (m, 8H, CH_2 piperazine); 5.63 (s, 2H, NH_2); 7.00, 7.53 (m, 8H, CH, Ph); 9.39 (s, 1H, OH)
3e	$C_{18}H_{22}N_4O$ 310.4	63	188 R (EtOH)	3360, 2832, 1664, 1600, 1520, 1392, 1328, 1232	(DMSO-d_6): 2.50, 3.92 (m, 10H, CH_2); 5.68 (s, 2H, NH_2); 6.89, 7.21, 5.58 (m, 9H, CH, Ph); 9.39 (s, 1H, OH)
4c	$C_{23}H_{22}N_4$ 354.3	49	235–236 (DMF)	2841, 2756, 1608, 1514, 1464, 1395, 1229	(DMSO-d_6): 3.28, 3.41 (m, 8H, CH_2 piperazine); 6.81 (t, $J = 7$ Hz, 1H, Ar-H); 6.98 (d, $J = 8$ Hz, 2H, Ar-H); 7.08–7.30 (m, 6H, Ar-H); 7.54 (m, 2H, Ar-H); 8.02 (d, $J = 9$ Hz, 2H, Ar-H)
4d	$C_{23}H_{21}FN_4$ 372.3	46	247–250 (DMF)	2966, 2841, 2779, 2289, 1611, 1513, 1465, 1399, 1232	(DMSO-d_6): 3.25, 3.45 (m, 8H, CH_2 piperazine); 6.90–8.10 (m, 12H, Ar-H)
5	$C_{16}H_{14}N_6$ 290.3	68	150–155 (EtOH)	2848, 2208, 1552, 1520, 1440, 1424, 1376, 1280, 1232, 1184	($CDCl_3$): 3.53, 4.02 (m, 8H, CH_2 piperazine); 6.90, 7.59 (m, 4H, CH, Ph); 8.10, 8.32 (d, $J = 3$ Hz, 2H, CH pyrazine)
6	$C_{16}H_{14}N_6$ 290.3	81	235–236 (EtOH)	2848, 2208, 1600, 1568, 1520, 1472, 1436, 1392, 1248	($CDCl_3$): 3.52, 3.90 (m, 8H, CH_2 piperazine); 6.90, 7.59 (d, $J = 4$ Hz, 4H, CH, Ph); 8.20, 8.39 (m, 2H, CH pyrazine)
7b	$C_{15}H_{22}N_4O$ 274.4	42	110–112 (cyclohexane)	3424, 2928, 2800, 1632, 1524, 1504, 1408, 1376, 1296, 1236	($CDCl_3$): 1.30 (t, $J = 7$ Hz, 3H, CH_3); 2.33 (s, 3H, CH_3); 2.60, 3.28 (m, 8H, CH_2 piperazine); 3.80 (m, 2H, CH_2); 4.88 (s, 1H, NH); 5.80 (s, 1H, CH); 6.90, 7.53 (m, 4H, CH, Ph)
8b	$C_{20}H_{22}N_3SBr$ 416.4	83	255 R (EtOH)	3440, 2584, 1600, 1520, 1472, 1408, 1392, 1232, 1056	(DMSO-d_6): 2.82 (s, 3H, CH_3); 3.32 (m, 8H, CH_2 pipera-zine); 7.10, 7.41, 7.90, 8.02 (m, 10H, CH)

The susceptibility of the anaerobic bacteria was determined by means of the plate dilution technique in Brucella agar, supplemented with 5% sheep's blood.[13,14] The derivatives were dissolved in 1 mL of DMSO immediately before the experiment. Sterile distilled water was used for ultimate dilutions. The following concentrations of the piperazine derivatives were used: 200, 100, 50, 25, 12,5, and 6,2 μg/mL. The inoculum containing 10^6 CFU/spot was applied to the agar plates with Steers replicator. The inoculated agar plates and compound-free ones were incubated in anaerobic jars for 48 h at 37°C in 10% CO_2, 10% H_2, and 80% N_2 atmosphere with palladium catalyst and indicator of anaerobiosis. The minimal inhibitory concentration (MIC) was defined as the lowest concentration of the derivative that inhibited growth of the anaerobes.

Aerobic Bacteria

The investigations included 25 strains of aerobes isolated from the oral cavity, respiratory tract and abdominal cavity, as well as 6 standards strains. The aerobes were as follows: Staphylococcus aureus (4 strains), Corynebacterium spp. (2), Klebsiella pneumoniae (3), Acinetobacter baumannii (2), Escherichia coli (6), Pseudomonas aeruginosa (6), Pseudomonas stutzeri (2) and 6 standard strains: Staphylococcus aureus ATCC 25923, Enterococcus faecalis ATCC 29212, Klebsiella pneumoniae ATCC 13883, Acinetobacter baumannii ATCC19606, Escherichia coli ATCC 25922 and Pseudomonas aeruginosa ATCC 27853. The susceptibility of the aerobic bacteria was determined by means of agar dilution technique with Mueller–Hinton agar.[13,14] Sterile distilled water was used for ultimate dilutions. The inoculum containing 10^6 CFU/spot was applied to the agar plates with Steers replicator. The inoculated agar plates and the derivative-free ones were incubated for 24 h at 37°C. The minimal inhibitory concentration (MIC) was defined as the lowest derivative concentration, that inhibited growth of aerobic bacteria.

Mycobacterium Tuberculosis

The compounds were examined for their tuberculostatic activity towards *Mycobacterium tuberculosis* H_{37}Rv strain and two "wild" strains isolated from tuberculotic patients: one (Spec. 210) resistant to *p*-aminosalicylic acid (PAS), isonicotinic acid hydrazide (INH), etambutol (ETB) and rifampicine (RFP), and the other (Spec. 192) fully susceptible to the drugs administered. In vitro investigations were performed by a classical test tube method of successive dilutions with Youman's liquid medium containing 10% of bovine serum.[11]

TABLE II The Minimal Inhibitory Concentration (MIC) for the Compounds 2b–3e

	MIC *[μg/mL]*						
Anaerobic bacteria	Metronidazole	**2b**	**2e**	**3b**	**3c**	**3d**	**3e**
Gram-positive:							
Peptococcus niger	≤ 6.2	≥ 200	≥ 200	≥ 200	≥ 200	25	≥ 200
Peptostreptococcus magnus	≤ 6.2	≥ 200	12.5	12.5	100	≥ 200	25
Peptostreptococcus micros	≤ 6.2	≥ 200	12.5	12.5	12.5	50	25
Actinomyces israelii	≤ 6.2	≥ 200	12.5	≤ 6.2	12.5	≥ 200	25
Actinomyces neaslundii	≤ 6.2	≥ 200	≥ 200	≤ 6.2	50	100	≥ 200
Propionibacterium granulosum	≥ 200	≥ 200	25	≤ 6.2	50	100	≤ 6.2
Gram-negative:							
Prevotella bivia	≤ 6.2	≥ 200	≥ 200	≥ 200	100	≥ 200	≥ 200
Prevotella buccalis	≤ 6.2	≥ 200	≥ 200	≥ 200	≥ 200	≥ 200	≥ 200
Prevotella intermedia	≤ 6.2	≥ 200	25	≥ 200	100	100	≥ 200
Prevotella loescheii	≤ 6.2	≥ 200	≥ 200	≥ 200	≥ 200	25	≥ 200
Porhyromonas asaccharolytica	≤ 6.2	≥ 200	25	50	≥ 200	100	50
Fusobacterium nucleatum	≤ 6.2	≥ 200	≥ 200	12.5	100	100	25
Fusobacterium necrophorum	≤ 6.2	25	12.5	≤ 6.2	100	50	25
Bacteroides forsythus	≤ 6.2	≥ 200	100	100	≥ 200	100	12.5
Bacteroides fragilis	≤ 6.2	≥ 200	25	100	≥ 200	≥ 200	≥ 200

The susceptibility of anaerobic bacteria towards metronidazole and piperazine derivatives **2b**, **e** and **3b–e** is shown in Table II. Metronidazole, the medicine of preference in treatment of the infections breeded or accompanied by anaerobes, showed the activity at low concentrations 6.2–12.5 μg/mL towards 22 (88%) strains tested. These results were consistent with those reported elsewhere.[16–20] The strains of bacillus Propionibacterium granulosum (MIC > 200 μg/mL) showed the highest refractoriness towards metronidazole. The high susceptibility of the Gram-positive rod-bacteria towards this medicament was confirmed by many authors.[15,17–20] Among the amidoxime derivatives, compound **3a** showed the highest activity towards anaerobes. Almost 1/3 of the strains tested (28%) was susceptible to low concentrations ranging from 12.5 to

6.2 μg/mL, and the next five (25%) strains—to 25 μg/mL. For 11 (44%) strains the growth-inhibiting concentrations were $\geq$200 μg/mL. More susceptible to this amidoxime derivatives were the strains of Gram-positive anaerobes. MIC within the limits of 50 $\leq$ 6.2 μg/mL inhibited the growth of 77% of these bacteria, and of only 31% of Gram-negative strains. Compound **3a** inhibited the growth of Propionibacterium granulosum strains in lower concentrations (25 $<$ MIC $\leq$ 6.2 μg/mL) than metronidazole (MIC $\geq$ 200 μg/mL). Similar activity towards the anaerobic bacteria was shown by the derivative **2e**. Its growth inhibiting concentrations towards 4 (16%) strains were within 12.5 $\leq$ 6.2 μg/mL, towards 7 (28%) strains—25 μg/mL, towards the next 11 (44%), however, at least 200 μg/mL. The activity towards the anaerobes, shown by the compounds **3c** and **2b**, was even lower. Low concentrations—12.5 μg/mL inhibited the growth of 3 (13%) and 2 (8%) strains respectively, while concentrations within 25–50 μg/mL the growth of 1 (4%) and 3 (12%), respectively. The growth of the majority of the strains tested (60% and 76%, respectively) was inhibited by concentrations $\geq$200 μg/mL. The least activity, particularly in the range of low concentrations, was shown by the derivative **3d**. The lowest growth-inhibiting concentrations were within 25–50 μg/mL towards only 4 (16%) strains. In the case of about 1/3 (28%) of the strains these concentrations were 100 μg/mL, and at least 200 μg/mL—toward the remaining strains (56%). The compounds were, however, more active towards Gram-positive rod-bacteria of Propionibacterium genus (MIC 100–200 μg/mL), as compared to metronidazole (MIC $>$ 200 μg/mL). The highest activity towards Gram-positive anaerobes from all the amidoximes tested was demonstrated by the compounds **2e** and **3b**. Within the range of concentrations 6.2 $\geq$ 25 μg/mL the growth of 7 (77%) strains was inhibited by metronidazole, and that of 6 (66%) strains by both the derivatives **2e** and **3b**. However, the strains of Gram-negative bacteria—most of them (93%) highly susceptible (MIC $\leq$ 6.2 μg/mL) towards metronidazole—appeared to be much less susceptible towards the amidoxime derivatives tested. The highest activity towards these bacteria was shown by the derivatives **2e** and **3b**. Within the range of concentrations 6.2–25 μg/mL the growth-inhibiting effect of **2e** was 31% and that of **3b** was 25%. The compounds tested were inactive towards aerobic bacteria within the range of concentrations 6.2–200 μg/mL.

CONCLUSIONS

The derivatives tested showed differentiated activity towards the anaerobic bacteria. The maximum activity was exhibited by the compounds **3b**, **2e**, **3e** and the lowest by compound **3d**. The maximum

TABLE III Tuberculostatic Activity of the 1,4-Disubstituted Piperazines

	Bacterial strain MIC [μg/mL]		
	$H_{37}Rv$	192	210
1a	100	>100	100
1b	100	100	100
1c	50	100	50
1d	50	100	50
1e	50	100	50
2b	50	25	100
2e	100	50	50
3b	100	100	100
3c	50	100	50
3d	100	100	100
3e	50	50	50
4c	100	100	100
4d	100	100	>100
5	100	>100	100
6	100	>100	100
7b	25	50	50
8b	12.5	25	12.5

susceptibility towards derivatives **2e** and **3b** was shown by both Gram-positive and Gram-negative bacteria. The amidoxime derivatives tested appeared to be inactive towards the aerobic bacteria used for the investigation. The determined minimum concentrations inhibiting (Table III) the growth of tuberculous strains (MIC) for most of the compounds examined were within the limits 12–100 μg/mL. MIC of the most active compound **8b** was 12.5 μg/mL for $H_{37}Rv$ strain and 25 μg/mL for other strains.

EXPERIMENTAL

Melting points were determined with the Reichert apparatus and are uncorrected. The IR spectra were recorded with a Satellite spectrophotometer. The ^1H NMR spectra were obtained with a Varian Gemini 200 spectrometer. Reaction yields and the physical constants of the compounds obtained are given in Table I. The results of elemental analyses for C and H for all the compounds obtained were in good agreement ($\pm$ 0.4%) with the data calculated.

4-Piperazin-1-yl-benzonitrile (1a)

4-Fluorobenzonitrile (1 mmol, 0.121 g), piperazine (2 mmol, 0.172 g) and anhydrous K_2CO_3 (0.5 g) were refluxed in DMSO (15 mL) for 1.5 h. On cooling down to ambient temperature, water (25 mL) was added. The mixture was extracted with diethyl ether (3 × 15 mL), the extracts dried over anhydrous $MgSO_4$, and the ether was evaporated. The oily residue crystallized gradually.

4-(4-Methyl-, 4-phenyl-, 4-p-fluorophenyl, and 4-benzyl-piperazin-1-yl)-benzonitriles (1b–e)

4-Fluorobenzonitrile (1 mmol, 0.121 g) dissolved in DMSO (20 mL) was treated with the corresponding piperazine (4-methyl-, 4-phenyl-, 4-*p*-fluorophenyl-, and benzylpiperazine) (5 mmol) and anhydrous K_2CO_3 (1 g). The resulting reaction mixture was refluxed for 1.5 h. On cooling down to ambient temperature water was added and the resulting precipitate was separated by filtration.

4-(4-Methyl- and 4-benzyl-piperazin-1-yl)thioamides (2b, e)

4-(4-Methyl-, or 4-benzyl-piperazin-1-yl)-benzonitrile **1b**, **e** (1 mmol) was dissolved in warm ethanol (20 mL), concentrated NH_4OH (20 mL) saturated with H_2S was added and the reaction mixture was allowed to stand at ambient temperature for a few days. The resulting precipitate was filtered off and purified by crystallization from ethanol.

4-(4-Methyl-, 4-phenyl-, 4-p-fluorophenyl- and 4-benzyl-piperazin-1-yl)-N-hydroxybenz-amidines (3b–e)

Two solutions were prepared: 1) hydroxylamine hydrochloride (1.2 g) in methanol (10 mL); 2) KOH (1.15 g) in methanol (10 mL). The solutions were mixed, the KCl precipitate was filtered off, the filtrate was treated with the corresponding nitrile (1 mmol) (**1b**–**e**), and the reaction mixture was refluxed for 8 h. On ice cooling the product precipitated and was separated by filtration.

3-[4-(4-Phenyl- and 4-*p*-fluorophenyl-piperazin-1-yl)-phenyl]-1*H*-benzimidazoles (4c, d)

Compound **1c** or **1d** (1 mmol) and *o*-phenylenediamine (4 mmol) were heated with polyphosphoric acid (15 g) for 2.5 h at a temperature of 180–200°C. On cooling to ambient temperature ice was added until

the product precipitated completely. The precipitate was filtered and washed with water.

4-(4-Cyanophenyl)-3,4,5,6-tetrahydro-2*H*-[1,2′]-bipyrazinyl-3′- and 6′-carbonitriles (5, 6)

Compound **1a** (2 mmol) and 3-chloro- or 6-chloro-pyrazino-2-carbonitrile (2 mmol) were dissolved in benzene (15 mL) and treated with triethylamine (0.5 mL). The reaction mixture was refluxed for 0.5 h and then evaporated to dryness. On addition of water (10 mL) and cooling to 0°C the product precipitated and was separated by filtration.

1-Methyl-4-[4-(5-ethyl-4,5-dihydro[1,2,4]-oxadiazol-3-yl)phenyl]-piperazine (7b)

Compound **3b** (0.5 mmol, 0.117 g) and ethyl orthoformate (10 mL) were refluxed for 1 h. The orthoformate was then evaporated and the residue recrystallized from cyclohexane.

1-Methyl-4-[4-(phenyl-thiazol-2-yl)-phenyl]-piperazine hydridobromide (8b)

To compound **2b** (1 mmol, 0.235 g) dissolved in absolute ethanol (10 mL) ω-bromo-acetophenone (1 mmol, 0.199 g) was added and the reaction mixture was refluxed for 1 h. On cooling to ambient temperature the product **8b** precipitated and was separated by filtration.

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