Synthesis and Antitubercular Evaluation of *N*-Arylpyrazine and *N,N′*-Alkyl-diylpyrazine-2-carboxamide Derivatives

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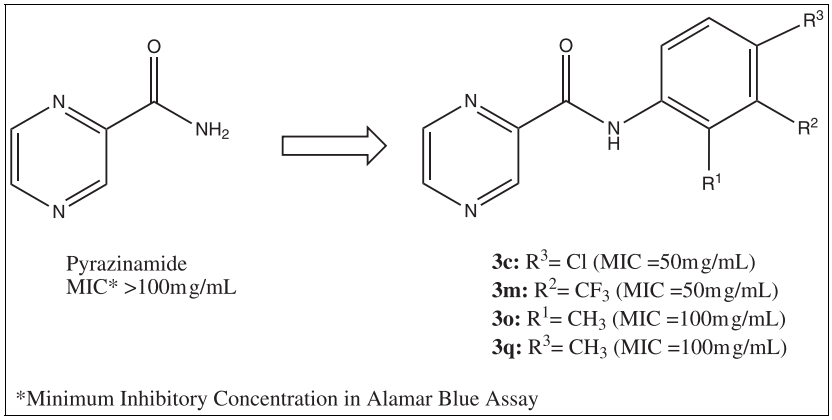

Two series of pyrazinamide (PZA) derivatives have been synthesized and evaluated for their *in vitro* antibacterial activity against *Mycobacterium tuberculosis* H37Rv. Some compounds exhibited minimum inhibitory concentration activity of 50–100 μg/mL, greater than the first line antituberculosis drug PZA in Alamar Blue assay (>100 μg/mL). The obtained activities can be considered promising results, which characterizes these compounds as good start points to development of new antitubercular agents.

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INTRODUCTION

Tuberculosis (TB) is a serious infectious disease caused by the *Mycobacterium tuberculosis.* According to the World Health Organization (WHO), one-third of population is infected with TB and nearly 2.0 million people die yearly [1]. The standard treatment against this disease is an association of four drugs, isoniazid, rifampicin, ethambutol, and pyrazinamide (PZA), which are called the first-line drugs [2]. In spite this regiment cure about 95% of TB cases, the rates of nonadherence is higher because of the occurrence of several side effects, such as hepatotoxicity, which can be serious and fatal [3], [4].

Among the first-line drugs, PZA has an important sterilizing activity, which is essential to a successful treatment [5]. PZA is considered to be a paradox drug because when used against *M. tuberculosis,* it shows activity *in vivo,* but not *in vitro* due to the pH of the usual culture medium used to *M. tuberculosis* growth be almost neutral [6], [7]. As a consequence of this, PZA is considered a prodrug that only acts in acid medium, where it is hydrolyzed by the mycobacterial enzyme pyrazinemidase to pyrazinoic acid, which is considered the active metabolite [8], [9].

In previous studies of our research program for the development of new antiTB agents, we indentified a series of thiophen-2-acetamide derivatives with moderated antimycobacterial activity (Fig. 1) [10–14]. Considering these results exhibited by this series, and the importance of PZA in TB treatment, the aim of the present work is the design, synthesis, and antimycobacterial evaluation of new derivatives, based on the molecular hybridization of our previous analogs with PZA (Fig. 1). The design concept of these compounds explores the maintenance of the scaffold aryl-amide (A) and alkyl-diamide (B) of our thiophen-2-acetamide derivatives and the replacement of the tiophene by the pyrazine nucleus (C). This modification aims to investigate the influence of the heterocyclic nucleus bounded to the amide function in the biological activity of these series.

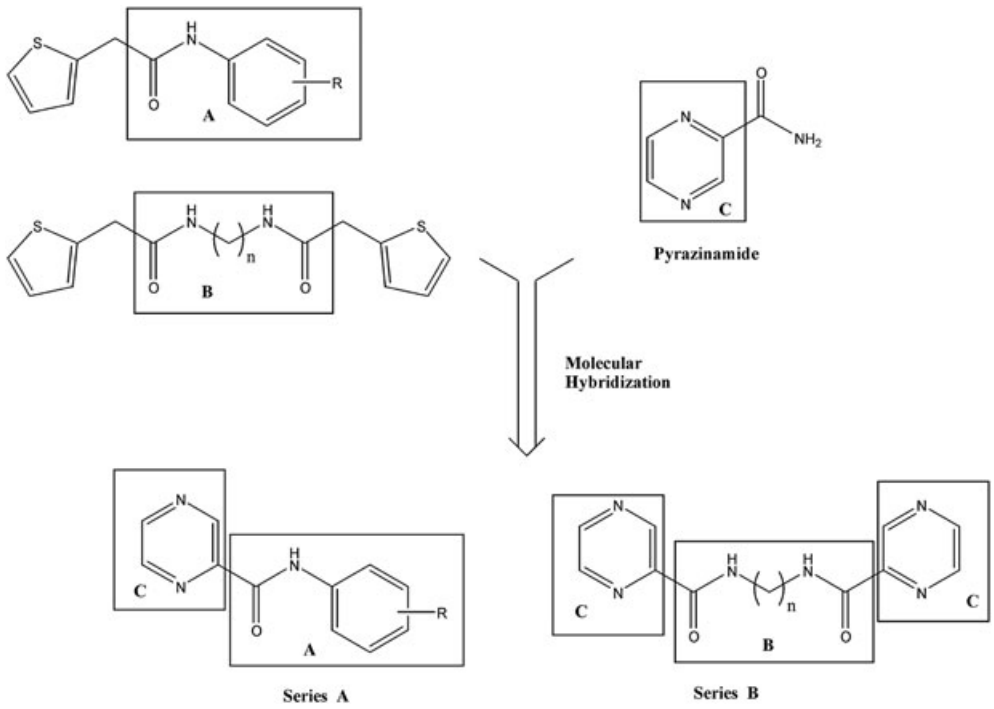


Figure 1. Molecular planning of the two series of 2-pyrazinecarboxamide derivatives.

RESULTS AND DISCUSSION

Chemistry. The synthesis of *N*-arylpyrazine-2-carboxamide derivatives **3a–q** is summarized in Scheme 1 and Table 1. First, 2-pyrazinecarbonyl chloride **2** was prepared by reacting pyrazinecarboxylic acid **1** with an excess of thionyl chloride in dichloromethane with catalytic amounts of *N,N*-dimethylformamide, under nitrogen atmosphere. After that, the crude compound **2** reacted with different substituted anilines in tetrahydrofuran (THF), leading to the desired products in 47–70% yields. The products were characterized by ^{1}H-NMR spectra showing a characteristic large singlet at 9.25–10.78 ppm, relative to CONH. In addition, the ^{13}C-NMR spectra showed the C O signals at 170.0–161.0 ppm.

The synthesis of the *N,N′*-alkyl-diylpyrazine-2-carboxamide derivatives **5** and **6a–f** is summarized in Scheme 2 and Table 2. Methylic ester **4** was obtained from the reaction of 2-pyrazinecarboxylic acid **1** with $SOCl_2$ in MeOH. Besides, compounds **5** and **6a–f** were prepared by the reaction of methylic ester **4** with different diamines, in THF, under reflux (Scheme 1 and Table 2). In general, ^{1}H-NMR spectra of the compounds **5** and **6a–f** showed two characteristic signals corresponding to CONH protons at 9.06–11.6 ppm and the ^{13}C-NMR spectra showed the C O signals at 178.0–162.0 ppm.

Antimycobacterial activity. The antimycobacterial activities of the derivatives **3a–q**, **5** and **6a–f** were assessed against *M. tuberculosis* ATCC 27294 [21] using the micro plate Alamar Blue assay [22] (Table 3). This methodology is nontoxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric methods [23], [24].

These results showed that the activities of compounds **5** and **6a–f** could not be determined, as these compounds were insoluble in the medium culture during the assay. However, compounds **3c, 3m, 3o**, and **3q** exhibited antimycobacterial activities between 50 and 100 μg/mL. Considering that the activity of PZA in Alamar Blue assay is >100 μg/mL, the obtained activities can be considered

Scheme 1. Reagents and conditions: (a) $SOCl_2$, DMF, CH_2Cl_2, r.t., 1 h and (b) THF, 0°–r.t., 1–3 h, 47–70%.

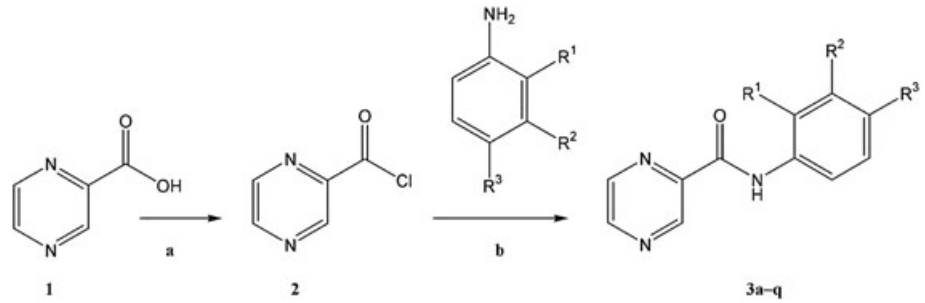
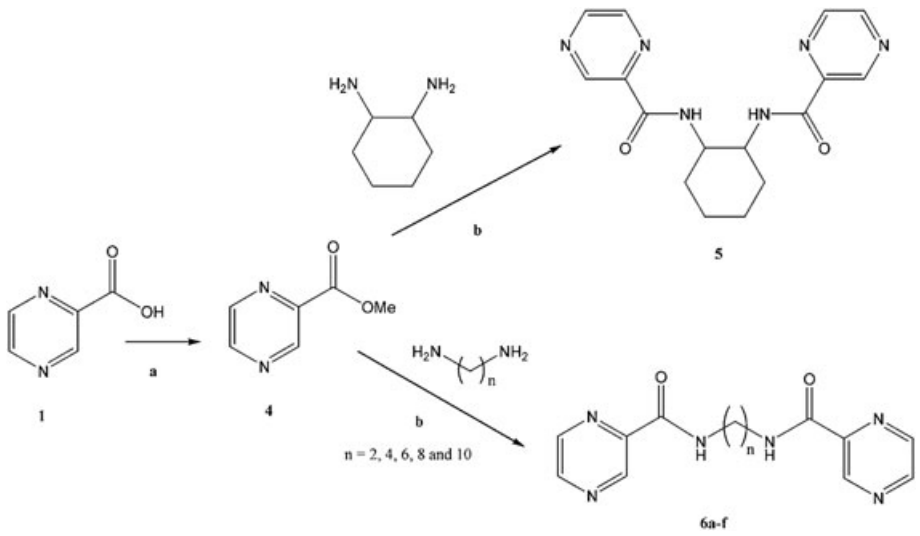


Table 1

Melting points and yields of *N*-arylpyrazine-2-carboxamide derivatives **3a–q.**

Compound	Substituted			Yield (%)	m.p (°C)
	R^1	R^2	R^3		
3a	H	H	H	52%	125 [15]
3b	H	Cl	H	60%	143–145 [15]
3c	H	H	Cl	54%	183 [15]
3d	H	H	F	50%	154–155 [16]
3e	H	H	Br	48%	200 [17]
3f	OCH_3	H	H	50%	117 [18]
3g	H	OCH_3	H	58%	115 [18]
3h	H	H	OCH_3	62%	146 [19]
3i	NO_2	H	H	64%	150 [19]
3j	H	NO_2	H	50%	160 [19]
3k	H	H	NO_2	70%	222 [19]
3l	CF_3	H	H	47%	120 [16]
3m	H	CF_3	H	52%	100–102 [16]
3n	H	H	CF_3	55%	150 [16]
3o	CH_3	H	H	50%	115 [20]
3p	H	CH_3	H	55%	147 [19]
3q	H	H	CH_3	56%	147 [19]

Scheme 2. Reagents and conditions: (a) $SOCl_2$, MeOH, 0°C–r.t., 1 h and (b) THF, 80°C, 12–18 h.



promising results, which characterizes these compounds as good start points to development of new antitubercular agents.

The comparison of the active compounds **3c, 3m, 3o**, and **3q** with the analogous thiophene series (Fig. 2) [10–14] shows that in derivative **3m**, the introduction of the pyrazine nucleus leads to an improvement of the antimycobacterial activity. While the derivatives **3c, 3o**, and **3q** displayed the same activities (100 μg/mL) (Fig. 2).

CONCLUSION

In the present work, we described the synthesis of two different series of 2-pyrazinecarboxamides. The compounds were obtained in good yields (47–97%) and their antimycobacterial activities were assayed against *M. tuberculosis*. It was found that the compounds **3c, 3m, 3o**, and **3q** exhibited better activities than PZA in Alamar Blue assay, displaying a minimum inhibitory concentration range of 50–100 μg/mL. These results suggest that they may be selectively targeted to *M. tuberculosis* growth, also considering that they were not cytotoxic to host cells at the same concentration. The comparison between thiophen-2-acetamide and 2-pyrazinecarboxamide series suggests that the introduction of the pyrazine nucleus could be an important feature to the improvement of the biological activity of the earliest series. More information about structure–activity relationship and their *in vivo* antibacterial activity test are in progress in our laboratory.

Table 2

Yields and melting points of the diamino-pyrazinecarboxamide derivatives (**5** and **6a–f**).

Entry	N	Yield (%)	m.p. (°C)
5	–	96	120–121
6a	2	88	145–147
6b	3	80	223–225
6c	4	83	169–173
6d	6	82	140–142
6e	8	97	136–138
6f	10	83	137–138

EXPERIMENTAL

General procedures. Melting points were determined on a Buchi apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet Nexus 670 spectrometer as potassium bromide pellets and frequencies are expressed in cm^{-1}. Mass spectra (ESI assay in solution of ammonium chloride) were recorded on Micromass ZQ Waters mass spectrometer. NMR spectra were recorded on a Bruker Avance 400 operating at 400.00 MHz (H^1) and 100.0 MHz (^{13}C) and Bruker Avance 500 spectrometer operating at 500.00 MHz (^1H) and 125.0 MHz (^{13}C), in deuterated dimethylsulfoxide or acetic acid. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane and *J*-coupling in Hertz (Hz). Proton and carbon spectra were typically obtained at room temperature. For TLC plates coated with silica gel were run in chloroform/methanol mixture and spots were developed in ultraviolet and solution of ninhidrine (0.2% p/v in ethanol).

Synthesis of 2-Pyrazinecarbonyl chloride (2). 2-Pyrazinecarbonyl chloride was prepared by reacting pyrazinecarboxylic acid (1.6 mmol) with a three-fold molar excess of thionyl chloride in dichloromethane solution at ambient temperature with continuous stirring under a dinitrogen atmosphere in the presence of 0.1 equivalents of *N,N*-dimethylformamide. After 1 h, the excess thionyl chloride and the other volatiles were removed under reduced pressure to leave the acyl chloride, which was used without purification in the next stage.

General procedure for the synthesis of N-arylpyrazine-2-carboxamide derivatives (3a–q). A solution of **2** (1.21 mmol), as prepared above, and the appropriate substituted aniline (1.45 mmol) in tetrahydrofuran (10 mL) was stirred at ambient temperature, for periods between 1 and 4 h depending on the rate of reaction as monitored by thin-layer chromatography. The reaction mixtures were then cooled and the solvent was removed under reduced pressure. Saturated aqueous sodium hydrogen carbonate solution was added to the residue, and the resulting mixture was exhaustively extracted with ethyl acetate. The combined organic fractions were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting solids were purified by successive washings with cold ethanol and diethyl ether, and finally recrystallized from ethanol, to give the products **3a–q** as a solid in 47–70% yields.

Synthesis of methyl 2-pyrazinecarboxylate (4). The methyl 2-pyrazinecarboxylate **4** was prepared by slow addition (during 15 min) of $SOCl_2$ (0.48 mole) in MeOH (300 mL) under stirring at 0°C, followed by the introduction of the compound **1** (15 g, 0.12 mole). The temperature of the reaction mixture was then, increased from 0°C to the room temperature and after 1 h, the excess of $SOCl_2$ was removed under reduced pressure. The crude product was neutralized with saturated aqueous solution of $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over $NaSO_4$ and concentrated under reduced pressure to afford only the desired product **2** as a white solid. This compound was used as such in the synthesis of 2-pyrazinehidrazide without further purification. Yield: 80%; mp: 59–60°C (62°C) [23–29].

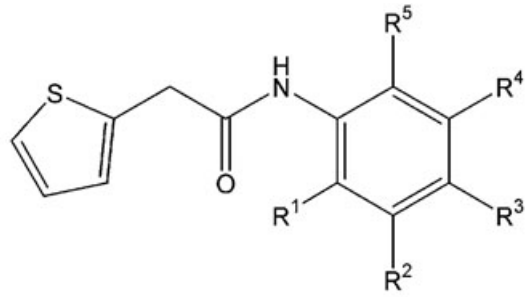
General procedures for the synthesis of N,N′-bis-pyrazinecarboxamide derivatives (5 and 6a–f). The synthesis of *N,N′*-bis-2-pyrazinecarboxamide derivatives **5** and **6a–f** were prepared by reaction between the appropriate diamines (1.44 mmol) and methyl 2-pyrazinecarboxylate (2.88 mmol) in tetrahydrofuran (30 mL). After 12–18 h of stirring, at 80°C, the resulting mixture was concentrated under reduced pressure and the residue was purified by washing with cold ethyl ether (3 × 20 mL), leading the pure derivatives **5** and **6a–f** as a solid in 80–97% yields.

Table 3

Antimycobacterial activities of PZA, *N*-arylpyrazine-2-carboxamide (**3a–q**) and *N,N′*-alkyl-diylpyrazine-2-carboxamide (**5** and **6a–f**) derivatives.

Entry	MIC (μg/mL)[a]	Entry	MIC (μg/mL)[a]
3a	>100	**3m**	50
3b	>100	**3n**	>100
3c	50	**3o**	100
3d	>100	**3p**	>100
3e	>100	**3q**	100
3f	>100	**5**	N.D.[b]
3g	>100	**6a**	N.D.
3h	>100	**6b**	N.D.
3i	>100	**6c**	N.D.
3j	>100	**6d**	N.D.
3k	>100	**6e**	N.D.
3l	>100	**6f**	N.D.
Pyrazinamide	>100	Pyrazinamide	>100

[a]Minimum inhibitory concentration.
[b]N.D. = not determined.



7a: R_3= Cl; R_1= R_2 =R_4 = R_5 = H (MIC= 100 μg/mL)
7b: R_2= CF_3; R_1= R_3 =R_4 = R_5 = H (MIC= >100 μg/mL)
7c: R_1= CH_3; R_2= R_3 =R_4 = R_5 = H (MIC= 100 μg/mL)
7d: R_3= CH_3; R_1= R_2 =R_4 = R_5 = H (MIC= 100 μg/mL)

Figure 2. Thiophen-2-acetamide derivatives previously synthesized by our group and its respective antimycobacterial activities.

N,N′-1,2-cyclohexanediyl-bis-2-pyrazinecarboxamide (5). This compound was obtained as pallet yellow, IR (cm^{-1}; KBr): 3299 (NH); 1659 (C O). ^{1}H-NMR [500.00 MHz (FIDRES ±0.15 Hz), Acetic acid-d_6] δ: 11.41 (2H; s; NH); 9.15 (2H; ls; H_3); 8.77 (2H; d; J = 2.0 Hz; H_6); 8.66 (2H; ls; H_5); 4.26 (2H; t; J = 9.2 Hz; $H_{1'}$ and $H_{6'}$); 2.13 (2H; d; J = 12.4 Hz; $H_{2'}$ or $H_{5'}$); 1.86–1.49 (6H; m; $H_{2'}$ or $H_{5'}$; $H_{3'}$ and $H_{4'}$) ppm; ^{13}C-NMR (125.0 MHz, Acetic acid-d_6) δ: 178.3; 164.9; 147.6; 145.9; 144.9; 143.9; 54.5; 32.6; 25.6 ppm. LC/MS: *m/z* [M-H]: 325. Anal. Calcd. for $C_{16}H_{18}N_6O_2{\cdot}H_2O$: C, 55.80; H, 5.85; N, 24.40. Found: C, 55.72; H, 5.83; N, 24.47.

N,N′-1,2-ethanediyl-bis-2-pyrazinecarboxamide (6a). This compound was obtained as pallet yellow, IR (cm^{-1}; KBr): 3340 (NH); 1661 (C O). ^{1}H-NMR [500.00 MHz (FIDRES ±0.15 Hz), Acetic acid-d_6] δ: 9.34 (2H; d; J = 1.5 Hz; H_3); 8.88 (2H; d; J = 2.5 Hz; H_6); 8.75 (2H; dd; J = 1.5 and 2.5 Hz; H_5); 3.87 (2H; t; J = 5.5 Hz; CH_2); 3.41 (2H; t; J = 5.5 Hz; CH_2) ppm; ^{13}C-NMR (125.0 MHz, Acetic acid-d_6) δ: 165.9; 147.7; 145.9; 144.9; 144.0; 40.7; 38.1 ppm. LC/MS: *m/z* [M-H]: 271. Anal. Calcd. for C12H12N6O2: C, 52.94; H, 4.44; N, 30.87. Found: C, 53.02; H, 4.47; N, 30.92

N,N′-1,3-propanediyl-bis-2-pyrazinecarboxamide (6b). This compound was obtained as pallet yellow, IR (cm^{-1}; KBr): 3512 (NH); 1658 (C O). ^{1}H-NMR [500.00 MHz (FIDRES ±0.15 Hz), Acetic acid-d_6] δ: 9.19 (2H; ls; H_3); 9.09 (2H; ls; NH); 8.87 (2H; ls; H_6); 8.73 (2H, ls, H_5) 3.39 (4H; m; NCH_2); 1.66–1.63 (2H; m; $NCH_2CH_2CH_2N$) ppm; ^{13}C-NMR (125.0 MHz, Acetic acid-d_6) δ: 162.8; 147.4; 144.8; 143.2; 39.1; 36.7; 29.0 ppm. LC/MS: *m/z* [M-H]: 285. Anal. Calcd. for $C_{13}H_{14}N_6O_2{\cdot}2H_2O$: C, 48.44; H, 5.63; N, 26.07. Found: C, 53.02; H, 4.47; N, 30.92.

N,N′-1,4-butanediyl-bis-2-pyrazinecarboxamide (6c). This compound was obtained as pallet yellow, IR (cm^{-1}; KBr): 3325 (NH); 1667 (C O). ^{1}H-NMR [400.00 MHz (FIDRES ±0.12 Hz), Acetic acid-d_6] δ: 11.49 (1H; s; NH); 9.34 (1H; s; H_3); 8.70 (1H; s; H_5); 8.66 (1H; s; H_6); 3.54 (2H; t; J = 4.0 Hz; $NCH_2(CH_2)_2CH_2N$); 2.05 (2H; ls; $NCH_2(CH_2)_2CH_2N$) ppm. ^{13}C-NMR (100.0 MHz Acetic acid-d_6) δ: 164.9; 147.6; 146.2; 144.8; 144.1; 40.2; 27.5 ppm. LC/MS: *m/z* [M-H]: 299. Anal. Calcd. for $C_{14}H_{16}N_6O_2$: C, 55.99; H, 5.37; N, 27.98. Found: C, 55.73; H, 5.32; N, 27.90.

N,N′-1,6-hexanediyl-bis-2-pyrazinecarboxamide (6d). This compound was obtained as pallet yellow, IR (cm^{-1}; KBr): 3341 (NH); 1653 (C O). ^{1}H-NMR [500.00 MHz (FIDRES ±0.12 Hz), DMSO-d_6] δ: 9.16 (2H; d; J = 1.5 Hz; H_3); 8.94 (2H; t; J = 6.0 Hz; NH); 8.86 (2H; d; J = 2.5 Hz; H_6); 8.72 (2H; dd; J = 2.5 e 1.5 Hz; H_5); 6.59 (4H; q; J = 7.0 Hz; $NCH_2(CH_2)_4CH_2N$); 1.54 (4H; t; J = 7.0 Hz; $NCH_2CH_2(CH_2)_2CH_2CH_2N$); 1.33–1.30 (4H; m; $NCH_2CH_2(CH_2)_2CH_2CH_2N$) ppm. ^{13}C-NMR (125.0 MHz DMSO-d_6) δ: 162.6; 147.2; 144.8; 143.3; 143.2; 38.6; 28.9; 26.0 ppm. LC/MS: *m/z* [M-H]: 327. Anal. Calcd. for $C_{16}H_{20}N_6O_2$: C, 58.52; H, 6.14; N, 25.59. Found: C, 58.49; H, 6.18; N, 25.65.

N,N′-1,8-octanediyl-bis-2-pyrazinecarboxamide (6e). This compound was obtained as pallet yellow, IR (cm^{-1}; KBr): 3337 (NH); 1657 (C O). ^{1}H-NMR [500.00 MHz (FIDRES ± 0.15 Hz), Acetic acid-d_6] δ: 11.57 (1H; s; NH); 9.35 (2H; ls; H2); 8.86 (2H; d; J = 2 Hz; H6); 8.70 (2H; ls; H5); 3.50 (4H; t; J = 5.6 Hz; $NCH_2(CH_2)_6CH_2N$); 1.66 (4H; t; J = 5.6Hz; $NCH_2CH_2(CH_2)_4CH_2CH_2N$); 1.38 (8H; ls; $NCH_2CH_2(CH_2)_4CH_2CH_2N$) ppm. ^{13}C-NMR (125.0 MHz, Acetic acid-d_6) δ: 164.7; 147.5; 146.2; 144.8; 144.1; 40.6; 30.1; 30.0 ppm. LC/MS: *m/z* [M-H]: 355. Anal. Calcd. for $C_{18}H_{24}N_6O_2$: C, 60.66; H, 6.79; N, 23.58. Found: C, 60.80; H, 6.83; N, 23.62.

N,N′-1,10-decanediyl-bis-2-pyrazinecarboxamide (6f). This compound was obtained as pallet yellow, IR (cm^{-1}; KBr): 3340 (NH); 1656 (C O). ^{1}H-NMR [500.00 MHz (FIDRES ±0.15 Hz), Acetic acid-d_6] δ: 11.59 (2H; s; NH); 9.35 (2H; s; H_3); 8.87 (2H; s; H_6); 8.70 (2H; s; H_5); 3.50 (4H; s; $NCH_2(CH_2)_8CH_2N$); 2.04 (4H; s; $NCH_2CH_2(CH_2)_6CH_2CH_2N$); 1.37 (12H; s; $NCH_2CH_2(CH_2)_6CH_2CH_2N$) ppm. ^{13}C-NMR (125.0 MHz, Acetic acid-d_6) δ: 164.7; 147.5; 146.2; 144.8; 144.1; 40.6; 30.4; 30.1; 27.7 ppm. LC/MS: *m/z* [M-H]: 383. Anal. Calcd. for $C_{20}H_{28}N_6O_2.H_2O$: C, 59.68; H, 7.51; N, 20.88. Found: C, 59.71; H, 7.48; N, 20.85.

General procedures for biological tests. Briefly, 200 µL of sterile deionized water was added to all outer-perimeter wells of sterile 96 well plates (falcon, 3072: Becton Dickinson, Lincoln Park, NJ) to minimize evaporation of the medium in the test wells during incubation. The 96 plates received 100 µL of the Middlebrook 7H9 broth (Difco laboratories, Detroit, MI) and a serial dilution of the compounds **3a–q**, **5**, and **6a–f** was made directly on the plate. The final drug concentrations tests were 0.01–100 µg/mL. Plates were covered and sealed with parafilm and incubated at 37°C for five days. After this time, 25 µL of a freshly prepared 1:1 mixture of Alamar Blue (Accumed International, Westlake, OH) reagent and 10% tween 80 was added to plate and incubated for 24 h. A blue color in the well was interpreted as no bacterial growth, and a pink color was scored as growth. The MIC was defined as the lowest drug concentration, which prevented a color change from blue to pink.

REFERENCES AND NOTES

[1] Available at: http://www.who.int/tb/publications/global_report/2009/pdf/chapter1.pdf (date of access: 10-24-2010).

[2] De Souza, M. V. N. Curr Opin Pulm Med 2006, 12, 167.

[3] Saukkonen, J. J.; Cohn, D. L.; Jasmer, R. M. Am J Respir Crit Care Med 2006, 174, 935.

[4] De Souza, M. V. N. Recent Pat Antiinfect Drug Discov 2006, 1, 33.

[5] Zhang, Y.; Mitchison, D. Int J Tuberc Lung Dis 2003, 7, 6.

[6] Zhang, Y.; Wade, M. M.; Scorpio, A.; Zhang, H.; Sun, Z. J Antimicrob Chemother 2003, 52, 790.

[7] Konno, K.; Feldmann, F. M.; McDermott, W. Am Rev Respir Dis 1967, 95, 461.

[8] De Ferreira, M. L.; Candéa, A. L. P.; Henriques, M. G. M. O.; Kaiser, C. R.; Lima, C. H. S.; De Souza, M. V. N. Lett Drug Des Discov 2010, 7, 275.

[9] Vergara, F. M. F.; Lima, C. H. S.; Henriques, M. G. M. O.; Candéa, A. L. P.; Lourenço, M. C. S.; Ferreira, M. L.; Kaiser, C. R.; De Souza, M. V. N. Eur J Med Chem 2009, 44, 4954.

[10] Lourenço, M. C. S.; Vicente, F. R.; Henriques, M. G. M. O.; Candéa, A. L. P.; Borges Gonçalves, R. S.; Nogueira, T. C. M.; de Lima Ferreira, M.; Nora de Souza, M. V. Bioorg Med Chem Lett 2007, 17, 6895.

[11] De Souza, M. V. N.; Ferreira, M. L.; Nogueira, T. C. M.; Gonçalves, R. S. B.; Peralta, M. A.; Lourenço, M. C. S.; Vicente, F. R. Lett Drug Des Discov 2008, 5, 221.

[12] De Souza, M. V. N.; Lourenço, M. C. S.; Peralta, M. A.; Gonçalves, R. S. B.; Nogueira, T. C. M.; Da Silva Lima, C. H.; Ferreira, M. L.; Da Silva, E. T. Phosphorus Sulfur Silicon Relat Elem 2008, 183, 2990.

[13] Nogueira, T. C. M.; De Souza, M. V. N.; Wardell, J. L.; Wardell, S. M. S. V.; Tiekink, E. R. T. Acta Crystallogr E 2010, 66, 177.

[14] De Lima, M. F.; De Souza, M. V. N.; Tiekink, E. R. T.; Wardell, J. L.; Wardell, S. M. S. V. Acta Crystallogr E 2009, 65, 3203.

[15] Kushner, S.; Dalalian, H.; Sanjurjo, J. L.; Bach, F. L. Jr; Safir, S. R.; Smith, V. K. Jr; Williams, J. H. J Am Chem Soc 1952, 74, 3617.

[16] Dolezal, M.; Cmedlova, P.; Palek, L.; Vinsova, J.; Kunes, J.; Buchta, V.; Jampilek, J.; Kralova, K. Eur J Med Chem 2008, 43, 1105.

[17] Vontor, T.; Palat, K.; Danek, J.; Lycka, A. Cesk Farm 1989, 38, 393.

[18] Robba, M. Ann Chim 1960, 5, 351.

[19] Wardell, S. M. S. V.; De Souza, M. V. N.; Vasconcelos, T. R. A.; De Lima Ferreira, M.; Wardell, J. L.; Low, J. N. Acta Crystallogr B 2008, 64, 84.

[20] McKenzie, W. L.; Foye, W. O. J Med Chem 1972, 15, 570.

[21] Canetti, G.; Rist, N.; Grosset, J Rev Tuberc Pneumol 1963, 27, 217.

[22] Franzblau, S. G.; Witzig, R. S.; Mclaughlin, J. C.; Torres, P.; Madico, G.; Hernandez, A.; Degnan, M. T.; Cook, M. B.; Quenzer, V. K.; Ferguson, R. M.; Gilman, R. H. J Clin Microbiol 1998, 36, 362.

[23] Reis, R.S.; Neves, I. Jr.; Lourenço, S. L. S.; Fonseca, L. S.; Lourenço, M. C. S. J Clin Microbiol 2004, 42, 2247.

[24] Vanitha, J. D.; Paramasivan, C. N. Diagn Microbiol Infect Dis 2004, 49, 179.

[25] Howie, R. A.; Lima, C. H. S.; Kaiser, C. R.; De Souza, M. V. N.; Wardell, J. L.; Wardell, S. M. S. V. Z Kristallogr 2010, 225, 19.

[26] Howie, R. A.; De Souza, M. V. N.; Wardell, S. M. S. V.; Wardell, J. L.; Tiekink, E. R. T. Acta Crystallogr E 2010, 66, 178.

[27] Howie, R. A.; Lima, C. H. S.; Kaiser, C. R.; De Souza, M. V. N.; Wardell, J. L.; Wardell, S. M. S. V. Z Kristallogr 2010, 225, 158.

[28] Baddeley, T. C.; Howie, R. A.; Lima, C. H.S.; Kaiser, C. R.; De Souza, M. V. N.; Wardell, J. L.; Wardell, S. M. S. V. Z Kristallogr 2009, 224, 506.

[29] Wardell, S. M. S. V.; De Souza, M. V. N.; Wardell, J. L.; Low, J. N.; Glidewell, C. Acta Crystallogr E 2006, 62, 3765.