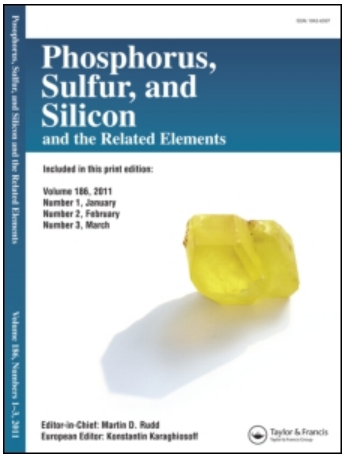

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Studies on Pyrazine Derivatives, XLIII: Synthesis and Antituberculosis Activity of 6-(1,2,3,4-Tetrahydroisoquinolino) and 6-(1,3,3-Trimethyl-6-azabicyclo-[3, 2, 1]-octano)-pyrazinocarboxylic Acid Derivatives

Barbara Milczarska[a]; Henryk Foks[b]; Zofia Zwolska[b]
[a] Department of Organic Chemistry, Medical University of Gdańsk, Poland, Gdańsk, Poland [b] Department of Microbiology, Institute of Tuberculosis and Pulmonary Diseases, Warsaw, Poland

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Studies on Pyrazine Derivatives, XLIII: Synthesis and Antituberculosis Activity of 6-(1,2,3,4-Tetrahydroisoquinolino) and 6-(1,3,3-Trimethyl-6-azabicyclo-[3,2,1]-octano)-pyrazinocarboxylic Acid Derivatives

Barbara Milczarska
Henryk Foks
Department of Organic Chemistry, Medical University of Gdańsk Poland, Gdańsk, Poland

Zofia Zwolska
Department of Microbiology, Institute of Tuberculosis and Pulmonary Diseases, Warsaw, Poland

*The reactivity of the chloride atom of 2-cyano-6-chloropyrazine was used in the reactions with amines, 1,2,3,4-tetrahydroisoquinoline and 1,3,3-trimethyl-6-azabicyclo-[3,2,1]-octane, which yielded the substrates for the syntheses of a series of new derivatives. The bulk of them were tested for their tuberculostatic activity. MIC values of the most active ones (**2a**, **b**, **5b**, **7a**, **9b**, and **11b**) were within 3.1–50 μg/mL.*

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

INTRODUCTION

The syntheses of pyrazine derivatives of varied biological (incl. tuberculostatic) activity are, in the major part, patented.[1]

The compounds of tuberculostatic activity are, in the greater part, the pyrazinocarboxylic acid derivatives,[2–5] the reported earlier amidrazone derivatives of nicotinic and isonicotinic acid,[6,7] as well as the derivatives of isonicotino-hydrazones.[8]

The tuberculosis treatment grows more and more difficult, which results from bacteria-growing refractoriness towards the administered

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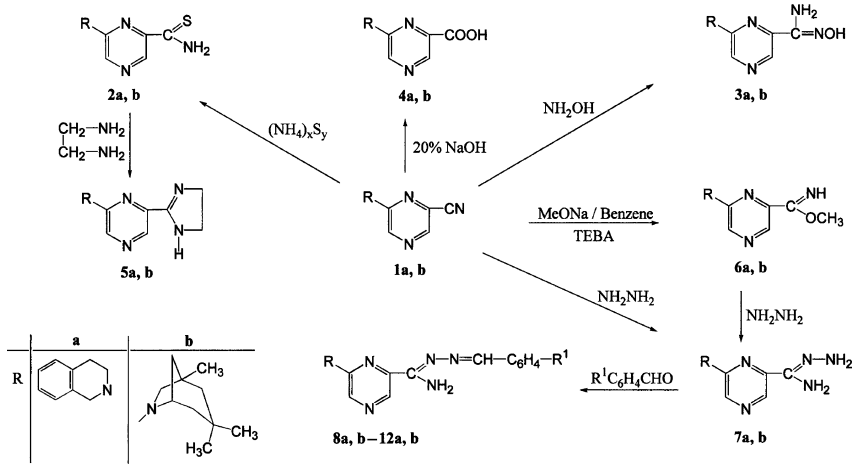
Address correspondence to Henryk Foks, Medical University of Poland, Department of Organic Chemistry, Al Gen J Hallera 107, Gdańsk, PL 80-416, Poland. E-mail: hfoks@amg.gda.pl

tuberculostatic. The structures of these compounds must be continuously modified.

RESULTS AND DISCUSSION

In this work, many 2,6-disubstituted pyrazine derivatives were obtained (Scheme 1). The substrate used was 2-cyano-6-chloropyrazine. As the halogen atom was in α-position towards the pyrazine ring nitrogen atom, its exchange for an amine group was quite easy.



SCHEME 1

The 2-cyano-6-substituted pyrazines obtained this way were changed into the corresponding acids, thioamides, imidoesters, imidazolines, amidoximes, and amidrazones (Table I). The syntheses of amidrazones from nitriles and hydrazine were conducted in methanolic solutions at 50°C to avoid the byproducts—dihydrotetrazines formation. These byproducts were not formed, however, when imidoesters were used for the syntheses of amidrazones.

The amidrazones were transformed into the Schiff's bases in the reactions with substituted benzoic aldehydes: *p*- and *m*-chloro, *p*-bromo-, *p*-hydroxy-, and *o*- and *p*-nitro- (Table II).

Some of the newly obtained aldehydes were tested for their tuberculostatic activity towards the standard Mycobacterium tuberculosis $H_{37}Rv$ strain and two "wild" strains were isolated from the tuberculotic patients (Table III): one, Myc. species 210, resistant to *p*-aminosalicylic acid (PAS), isonicotinic acid hydrazide (INH), ethambutol (EMB) and

TABLE I Characteristics of the Synthesized Compounds 1a, b–7a, b. Ar, Aromatic; Py, Pyrazine

Compound no.	M.p.[°C] solvent for crystallization	Reaction yield [%]	Formula molecular weight	^{1}H NMR (500 MHz) δ[ppm], solvent (**A**—$CDCl_3$; **B**—DMSO-d_6)	IR (KBr) (cm^{-1})
1a	92–4 Methanol	78	$C_{14}H_{12}N_4$ 236,3	**A**: 3.05(t, 2H CH_2); 3.9(t, 2H CH_2); 4.77(s, 2H CH_2); 7.3(m, 4H Ar); 8.1, 8.3(2H Py)	3075, 2980–2863, 2238, 1610, 1580, 1520, 1490, 1230, 1000, 920, 870
1b	67–71 Methanol	25	$C_{15}H_{20}N_4$ 256,38	**A**: 0.8(s, 3H CH_3); 0.97(s, 3H CH_3); 1.18(s, 3H CH_3); 1.4–2.0, 3.2–3.4(m, 9H azabicycl.); 7.3, 8.0(s, 2H Py)	3071, 2960–2857, 2232, 1600, 1585, 1530, 1470, 1250, 1020, 910
2a	161–5 Dioxane	96	$C_{14}H_{14}N_4S$ 270,38	**B**: 2.96(t, 2H CH_2); 3.9(t, 2H CH_2); 4.8(s, 2H CH_2); 7.27(m, 4H Ar); 8.4, 8.7(2H Py)	3385, 3250, 3100–2860, 1640, 1620, 1580, 1385, 1300, 1285, 1226, 1180, 1000, 912, 860, 745
2b	204–8 Dioxane	89	$C_{15}H_{22}N_4S$ 290,43	**A**: 0.79(s, 3H CH_3); 0.97(s, 3H CH_3); 1.19(s, 3H CH_3); 1.25–3.5(m, 9H azabicycl.); 7.3, 8.0(s, 2H Py); 9.0($CSNH_2$)	3450, 3300, 3050, 2970–2860, 1620, 1584, 1523, 1279, 1220, 1170, 910, 850
3a	183–5 Methanol	92	$C_{14}H_{15}N_5O$ 269,34	**B**: 2.95(t, 2H CH_2); 3.3(2H NH_2); 3.9(t, 2H CH_2); 4.8 (s, 2H CH_2); 7.3(m, 4H Ar); 8.2, 8.3(2H Py); 9.5(s, 1H NOH)	3490, 3371, 3180, 2980–2870, 1640, 1600, 1580, 1250, 1100, 1000, 870
3b	215–7 Methanol + Dioxane	92	$C_{15}H_{23}N_5O$ 289,38	**A**: 0.81(s, 3H CH_3); 0.97(s, 3H CH_3); 1.19(s, 3H CH_3); 1.36–2.0, 3.1–3.4(m, 9H azabicycl.); 5.5(NH); 7.5(OH); 7.8, 8.4(s, 2H Py)	3470, 3365, 3115, 2950–2880, 1670, 1585, 1565, 1254, 1220, 1100, 1030, 995, 885
4a	160–3 Methanol	84	$C_{14}H_{13}N_3O_2$ 255,30	**A**: 3.05(t, 2H CH_2); 3.9(t, 2H CH_2); 4.8(s, 2H CH_2); 7.3(m, 4H Ar); 8.5, 8.7(2H Py)	3100–2850, 2800–2500, 1730, 1650, 1600, 1550, 1280, 1250, 1180, 1150, 1000, 800, 750
4b	189–192 Acetone	74	$C_{15}H_{21}N_3O_2$ 275,35	**A**: 0.8(s, 3H CH_3); 0.97(s, 3H CH_3); 1.2(s, 3H CH_3); 1.4–1.8, 1.9–3.5(m, 9H azabicycl.); 8.1, 8.6(s, 2H Py)	3000–2900, 2700–2470, 1723, 1600, 1550, 1500, 1280, 1223, 1195, 1000, 900

(Continued on next page)

TABLE I Characteristics of the Synthesized Compounds 1a, b–7a, b. Ar, Aromatic; Py, Pyrazine *(Continued)*

Compound no.	M.p.[°C] solvent for crystallization	Reaction yield [%]	Formula molecular weight	^{1}H NMR (500 MHz) δ[ppm], solvent (**A**—$CDCl_3$; **B**—DMSO-d_6)	IR (KBr) (cm^{-1})
5a	142–4 Methanol	96	$C_{16}H_{17}N_5$ 279,38	**A**: 3.04(t, 2H CH_2); 3.6–3.8(m, 4H CH_2CH_2); 3.9(t, 2H CH_2); 4.76(s, 2H CH_2); 7.2–7.3(m, 4H Ar); 8.2, 8.6(2H Py)	3210, 2930–2880, 1625, 1600, 1577, 1530, 1288, 1194, 1047, 980, 750
5b	153–5 Methanol + Dioxane	71	$C_{17}H_{25}N_5$ 299,42	**A**: 0.79(s, 3H CH_3); 0.95(s, 3H CH_3); 1.19(s, 3H CH_3); 1.35–3.45(m, 9H azabicycl.); 3.8(m, 4H CH_2-CH_2); 7.8, 8.5(s, 2H Py)	3250, 2970–2830, 1620, 1595, 1550, 1510, 1280, 1220, 1180, 1000
6a	104–8 Methanol	88	$C_{15}H_{16}N_4O$ 268,35	**A**: 3.06(t, 2H CH_2); 3.5(s, 3H CH_3); 3.9(t, 2H CH_2); 4.8(s, 2H CH_2); 7.3(m, 4H Ar); 8.3, 8.4(s, 2H Py); 9.0(1H NH)	3320, 3000–2850, 1645, 1571, 1528, 1480, 1220, 1150, 900, 850
6b	127–131 Methanol	58	$C_{16}H_{24}N_4O$ 288,4	**A**: 0.79(s, 3H CH_3); 0.96(s, 3H CH_3); 1.19(s, 3H CH_3); 1.35–3.2(m, 9H azabicycl.); 4.0(s, 3H OCH_3); 7.9, 8.2(s, 2H Py); 9.0(1H NH)	3400–3100, 3000–2880, 1665, 1580, 1530, 1470, 1220, 1180, 1010
7a	157–160 Dioxane	57	$C_{14}H_{16}N_6$ 268,36	**A**: 3.07(t, 2H CH_2); 3.96(t, 2H CH_2); 4.85(s, 2H CH_2); 7.25(m, 4H Ar); 7.3(2H NH_2); 8.3, 8.5(2H Py); 8.6(2H NH_2)	3400, 3340, 3190, 2900, 2960, 1650, 1600, 1530, 1500, 1270, 1240, 1200, 1000, 900, 870, 770
7b	152–7 Methanol + H_2O	62	$C_{15}H_{24}N_6$ 288,4	**A**: 0.8(s, 3H CH_3); 0.96(s, 3H CH_3); 1.19(s, 3H CH_3); 1.36–1.9, 2.0–3.4(m, 9H azabicycl.); 7.8(s, NH); 8.3, 8.4(s, 2H Py); 8.7(2H NH_2)	3400–3180, 3000–2880, 1650, 1600, 1500, 1240, 1200, 1100, 1000, 850

TABLE II Physicochemical Data of Condensation Products of Amidrazones With Aromatic Aldehydes. Ar, Aromatic, Py, Pyrazine

Compound no.	R^1	M.p.[°C] solvent for crystallization	Yield [%]	Formula molecular weight	^{1}H NMR δ[ppm] (200 MHz) Solvent: (**A**—$CDCl_3$; **B**—DMSO-d_6)	IR (KBr) (cm^{-1})
8a	p-Cl	219–220 Methanol/ Dioxane	65	$C_{21}H_{19}N_6Cl$ 390,9	**B**: 2.95(t, 2H CH_2); 3.95(t, 2H CH_2N); 4.85(s, 2H CH_2); 7.2 (m, 4H Ar); 7.5, 8.0(d, 4H C_6H_4); 8.4(s, 1H CH); 8.5, 8.6(s, 2H Py)	3493, 3261, 3060, 2975–2908, 1695, 1245, 1170, 1085, 1015, 860
8b	p-Cl	178–180 Methanol	73	$C_{22}H_{27}N_6Cl$ 410,9	**A**: 0.8(s, 3H CH_3); 0.96(s, 3H CH_3); 1.2(s, 3H CH_3); 1.4–1.9, 2.0–3.4(m, 9H azabicycl.); 6.5(s, NH); 7.4–7.7(m, 4H C_6H_4); 7.9 (s, 1H CH); 8.5, 8.7(s, 2H Py)	3450, 3295, 2950–2850, 1674, 1624, 1578, 1530, 1460, 1215, 1180, 1090, 1015, 847
9a	m-Cl	146–148 Methamol/ Dioxane	65	$C_{21}H_{19}N_6Cl$ 390,9	**A**: 3.03(t, 2H CH_2); 3.9(t, 2H CH_2N); 4.8(s, 2H CH_2); 6.5(s,NH) + D_2O decay; 7.3, 7.65(m, 4H Ar); 7.9(s, 4H C_6H_4); 8.27 (s, 1H CH); 8.5, 8.8(s, 2H Py)	3451, 3391, 3070, 2990–2800, 1665, 1630, 1570, 1470, 1220, 1160, 1100, 1020, 850
9b	m-Cl	181–185 Dioxane/H_2O	34	$C_{22}H_{27}N_6Cl$ 410,9	**A**: 0.8(s, 3H CH_3); 0.97(s, 3H CH_3); 1.2(s, 3H CH_3); 1.4–1.9, 2.0–3.5(m, 9H azabicycl.); 6.5(s, NH); 7.4, 7.87(m, 4H C_6H_4); 7.92(s, 1H CH); 8.6, 8.76(s, 2H Py)	3480, 3290, 3067, 2954–2880, 1616, 1568, 1524
10a	p-Br	218–220 Methanole/ Dioxane	56	$C_{21}H_{19}N_6Br$ 435,4	**A**: 3.04(t, 2H CH_2); 3.9(t, 2H CH_2N); 4.8(s, 2H CH_2); 6.5(s, NH); 7.3, 7.6–7.7(m, 8H Ar); 8.28(s, 1H CH); 8.6, 8.84(s, 2H Py)	3490, 3372, 3061, 2975, 2900, 1665, 1625, 1605, 1560, 1440

(Continued on next page)

TABLE II Physicochemical Data of Condensation Products of Amidrazones With Aromatic Aldehydes. Ar, Aromatic, Py, Pyrazine *(Continued)*

Compound no.	R^1	M.p.[°C] solvent for crystallization	Yield [%]	Formula molecular weight	^{1}H NMR δ[ppm] (200 MHz) Solvent: (**A**—$CDCl_3$; **B**—DMSO-d_6)	IR (KBr) (cm^{-1})
10b	p-Br	184–187 Acetone/H_2O	74	$C_{22}H_{27}N_6Br$ 454,4	**A**: 0.8(s, 3H CH_3); 0.96(s, 3H CH_3); 1.2(s, 3H CH_3); 1.4–1.9, 1.96–3.5(m, 9H azabicycl.); 7.5–7.7(m, 4H C_6H_4); 7.9(s, 1H CH); 8.6, 8.7(s, 2H Py)	3454, 3336, 3050, 2940–2850, 1620, 1575, 1525, 1465
11a	o-NO_2	225–227 Dioxane	70	$C_{21}H_{19}N_7O_2$ 401,4	**A**: 3.04(t, 2H CH_2); 3.9(t, 2H CH_2N); 4.8(s, 2H CH_2); 6.4(s, 2H NH); 7.2, 7.6–7.9(m, 8H Ar); 8.3(s, 1H CH); 8.85, 8.95(s, 2H Py)	3410, 3350, 3072, 2990–2825, 1625, 1580, 1530, 1480, 1370
11b	o-NO_2	179–182 Methanol	67	$C_{22}H_{27}N_7O_2$ 421,5	**A**: 0.8(s, 3H CH_3); 0.97(s, 3H CH_3); 1.2(s, 3H CH_3); 1.4–1.9, 2.0–3.45(m, 9H azabicycl.); 6.7(s, NH); 7.5–8.1(m, 4H C_6H_4+ 1H CH); 8.7, 8.9(s, 2H Py)	3430, 3340, 3060, 2990–2830, 1647, 1630, 1590, 1565, 1475, 1365
12a	p-OH	206–210 Methanol	53	$C_{21}H_{20}N_6O$ 372,4	**B**: 2.95(t, 2H CH_2); 3.95(t, 2H CH_2N); 4.8(s, 2H CH_2); 7.0–7.2 (m, 4H Ar); 7.4–7.75(m, 4H C_6H_4); 8.15, 8.35(s, 2H Py)	3452–3250, 3052, 2980–2865, 1660, 1625, 1600, 1590, 1565, 1520, 1465, 1310, 1280
12b	p-NO_2	242–248 Dioxane	72	$C_{22}H_{27}N_7O_2$ 421,5	**B**: 0.79(s, 3H CH_3); 0.87(s, 3H CH_3); 0.99(s, 3H CH_3); 1.3–3.5 (m, 9H azabicycl.); 7.0–7.3(m, 4H C_6H_4); 8.0, 8.2(s, 2H Py); 9.0 (s, 2H NH_2)	3458, 3335, 3050, 2961–2878, 1630, 1608, 1594, 1567, 1473, 1366

TABLE III Tuberculostatic Activity [μg/mL]

Compound no.	Myc.tbc $H_{37}Rv$	Myc.spec. 192	Myc.spec. 210
2a	25	100	50
2b	25	100	50
3a	50	100	100
3b	50	50	50
4a	50	50	100
5a	50	50	50
5b	25	50	50
7a	25	100	50
7b	50	50	50
8a	50	100	100
8b	100	100	50
9a	100	100	100
9b	50	25	3,1
10a	100	100	100
10b	50	100	50
11a	50	100	100
11b	50	50	25

rifampycine (RFP), and the other, Myc. species 192, which were fully susceptible to the drugs administered.

The tuberculostatic activity was determined *in vitro* by classical test tube method with Youman's liquid medium containing 10% of bovine serum.[9] Based of the Minimum Inhibiting Concentration (MIC) values, we concluded that some compounds were worthy of notice, e.g., **2a**, **2b**, **5b**, **7a**, **9b**, and **11b** because their MIC values were within the limits 3.1–50 μg/mL.

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 and a Varian Gem 200 MHz apparatus. The reaction yields and physical constants of the new compounds were given in Tables I and II.

Syntheses of 6-Substituted 2-Cyanopyrazine Derivatives (1a, 1b)

To a solution of 2-cyano-6-chloropyrazine (0.1 mol) in benzene (150 mL), triethylamine (0.15 mol) and the corresponding amine (0.1 mol), i.e.,

1,2,3,4-tetrahydroisoquinoline or 1,3,3-trimethyl-6-azabicyclo-[3,2,1]-octane, was added. The mixture was refluxed for 3 h. On cooling, water (60 mL) was added and the mixture 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 and recrystallized.

Syntheses of Thioamides (2a, 2b)

The corresponding nitrile (2 mmol) was dissolved in ethanol (10 mL) and ammonium polysulphide was added until turbidity appeared. After 12 h, the precipitate was filtered and crystallized.

Syntheses of Amidoximes (3a, 3b)

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

Syntheses of Pyrazinocarboxylic Acids (4a, 4b)

To nitrile **1a** or **1b** (2.7 mmol) in methanol (4 mL) a 20% solution of NaOH (10 mL) was added. The mixture was refluxed for 6 h. The solution was cooled with ice and acidified with diluted HCl—to pH 3. The precipitated product was filtered and recrystallized.

Syntheses of Pyrazine-2-imidazolines (5a, 5b)

To thioamide **2a** or **2b** (1.0 mmol), ethylenediamine (0.22 mol) was added and allowed to stand at room temperature for 1 h. On cooling with ice, the precipitate was filtered and crystallized.

Syntheses of Imidoesters (6a, 6b)

To the solution of nitrile **1a** or **1b** (4 mmol) in benzene (60 mL), the solution of NaOH (10 g) in water (10 mL) was added. Methanol (10 mL) and a small amount of Triethylbenzyl-amine (TEBA) was added. The

mixture was stirred for 2 h at ambient temperature. Water (70 mL) was 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 and recrystallized.

Syntheses of Amidrazones (7a, 7b)

(a)

To the solution of nitrile **1a** or **1b** (2.5 mmol) in methanol (10 mL), a 80% solution of hydrazine (1.3 mL) was added. The solution was heated under reflux at 50°C for 1 h. The excess solvent was evaporated under reduced pressure. The residue was cooled and treated with a small amount of water. The precipitate obtained was filtered and crystallized.

(b)

To the solution of imidoester **6a** or **6b** (1 mmol) in absolute methanol (40 mL), anhydrous hydrazine (0.1 mL) was added. The mixture was refluxed for 1 h, the solvent was evaporated under vacuum, and the residue treated with benzene and petroleum ether. The precipitate was filtered and crystallized.

Condensation of Amidrazones with Aromatic Aldehydes (8a, b–12a, b)

To the solution of the corresponding amidrazone (1.25 mmol) in absolute methanol (10 mL) aromatic aldehyde (1.25 mmol) and few drops of piperidine were added. The mixture was refluxed for 3 h. On cooling, the precipitates obtained were filtered and crystallized.

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