NMR analysis of a series of substituted pyrazolo[3,4-*d*]pyrimidines-4-amines

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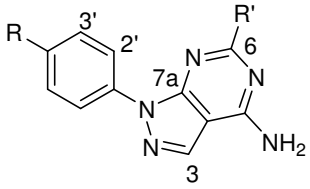
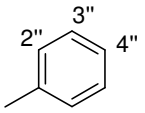
A series of twenty one substituted pyrazolo[3,4-*d*]pyrimidines-4-amines were studied by ^{1}H and ^{13}C NMR. The application of two-dimensional techniques, HMQC and HMBC, allowed the complete assignment of the spectra for all the compounds.

KEYWORDS: NMR; 2D NMR; ^{1}H NMR; ^{13}C NMR; pyrazolo[3,4-*d*]pyrimidines-4-amines

Structure	Compound	R	R´
	**1a**	H	
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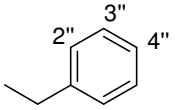
	1b	H	
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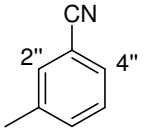
	1c	H	
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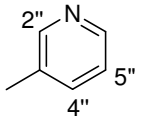
	1d	H	
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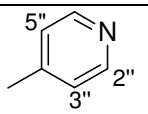
	1e	H	
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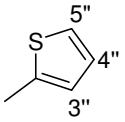
	1f	H	
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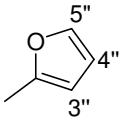
	1g	H	
	2g	Cl	
	3g	Br	

Figure 1. Structures and numbering for compounds

INTRODUCTION

As part of our ongoing research program on heterocyclic compounds which may serve as leads for designing novel chemotherapeutic agents, we have been involved on the preparation of pyrazolopyrimidines [1, 2]. These compounds and other related fused heterocycles are known to exhibit biological activity of several types such as CNS depressant [3], neuroleptic [4], tuberculostatic [5], antibacterial and antifungal [2, 6]. It was also reported that pyrazolo[3,4-*d*]pyrimidines inhibit xanthine oxidase [7, 1].

RESULTS AND DISCUSSION

The compounds described (Figure 1) constitute a series of pyrazolo[3,4-*d*]pyrimidines containing in position 1 a *p*-substituted phenyl group and in position 6 a heterocyclic or aryl ring.

The ^{1}H NMR signals of the aryl substituent on position 1, the proton 3 and NH_2 were readily attributed.

The assignment of the remaining protons and the ^{13}C signals was achieved by concerted application of proton-detected (C,H) 1-bond (HMQC) and long range (HMBC) heteronuclear two-dimensional chemical shift correlation experiments.

The proton and carbon chemical shifts assignments are presented in tables 1 and 2.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75.4 MHz both on a Varian Unity Plus Spectrometer. The spectra were obtained at 298 K, in 5 mm tubes, using DMSO-d_6 or acetone- d_6, with the solvent (residual) peak as internal reference: DMSO-d_6: δ 2.49 (^{1}H) and δ 39.5 (^{13}C); acetone- d_6: δ 2.05 (^{1}H) and δ 29.9 (^{13}C).

^{1}H NMR parameters were as follows: spectral width, 4000 Hz; data points, 32 K; pulse width 45º, acquisition time 2.8 s. ^{13}C NMR parameters were as follows: spectral width, 18850; data points, 64K; pulse width 45º, acquisition time 1.8 s; delay 1 s.

Heteronuclear ^{1}H-^{13}C HMQC and HMBC experiments were carried out using standard procedures. The spectra widths were F_1 = 18100 Hz and F_2 = 5000 Hz. The spectra were collected as 2048 x 256 block data and processed using a sinusoidal multiplication in each dimension. HMQC was optimized for ^{1}J (^{13}C, ^{1}H = 140 Hz) and HMBC for long-range ^{13}C, ^{1}H coupling constants of 8 Hz.

Materials

The pyrazolo[3,4-d]pyrimidine derivatives used in this study were prepared in our laboratory [2].

Acknowledgments

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Table 1. [1]H chemical shifts[a] (multiplicities, coupling constants in Hertz) of pyrazolopyrimidines

	H3	NH_2	H-2' H6'	H3' H5'	H4'	H2"	H6"	H3"	H5"	H4"
1a	8.36 (s)	7.92(vbrs)	8.32(d, 9.0)	7.59(t, 8.2)	7.35(t, 7.2)	8.47-8.40 (m)			7.51-7.47(m)	7.51-7.47 8m)
2a	8.30 (s)	7.97(vbrs)	8.38(d, 8.7)	7.65(d, 9.0)	-	8.46-8.41(m)			7.54-7.47 (m)	7.54-7.47 (m)
3a	8.38 (s)	7.98(vbrs)	8.31(d, 9.0)	7.78(d, 9.0)	-	8.47-8.39 (m)			7.54-7.47 (m)	7.54-7.47 (m)
1b*	8.28 (s)	7.80(vbrs)	8.20(dt, 7.5, 1.5)	7.51(t, 7.5)	7.17(tt, 7.2, 1.2)	7.35-7.22 (m)			7.35-7.22 (m)	7.35-7.22 (m)
2b*	8.29 (s)	7.85(brs)	8.27(d, 7.0)	7.58(d, 7.0)	-	7.38-7.14 (m)			7.28(t, 7.5)	7.18(t, 7.2)
3b*	8.33 (s)	7.84(vbrs)	8.22(d, 8.7)	7.71(d, 8.7)	-	7.36-7.23 (m)			7.36-7.23 (m)	7.18(tt, 6.9, 1.2)
1c	8.38 (s)	8.14(vbrs)	8.26(dd, 8.7, 1.2)	7.59(t, 8.0)	7.36(tt, 7.5,1.2)	8.66-8.73 (m)	7.96(dt, 7.5, 1.5)	-	7.73(t, 8.8)	8.66-8.73 (m)
2c	8.39 (s)	8.20;8.00(2 brs)	8.32(dd, 7.2, 2.1)	7.65(dd, 6.9, 2.1)	-	8.66-8.64 (m)	7.95(dt, 7.8, 1.5)	-	7.73(t, 7.8)	8.66-8.64 (m)
3c	8.38 (s)	8.18(vbrs)	8.26(d, 8.7)	7.76(d, 8.7)	-	8.72-8.66 (m)	7.95(dt, 7.5, 1.2)	-	7.71(t, 8.1)	8.72-8.66 (m)
1d	8.39 (s)	8.16;7.96(2 brs)	8.30(dd, 8.7, 1.2)	7.52-7.64(m)	7.52-7.64(m)	9.54(d, 2.1)	8.67-8.64 (m)	-	7.36(t, 7.5)	8.67-8.64 (m)
2d	8.39 (s)	8.16;8.00(2 brs)	8.36(d, 9.0)	7.65(d, 9.0)	-	9.50(brs)	8.73-8.65 (m)	-	7.58-7.50 (m)	8.73-8.65 (m)
3d	8.41 (s)	8.17 (brs)	8.31(d, 9.0)	7.79(d, 9.0)	-	9.56(d, 2.1)	8.68(d, 7.0)	-	7.58-7.52 (m)	8.68(d, 7.0)
1e	8.41 (s)	8.18;8.01(2 brs)	8.32-8.21(m)	7.60(tt, 7.5, 2.0)	7.36(tt, 7.2, 1.2)	8.74(brd, 6.0)			8.32-8.21(m)	-
2e	8.42 (s)	8.20;8.00(2 (brs)	8.34(d, 9.0)	7.66(d, 6.5)	-	8.74(d, 6.3)			8.28(d, 6.3)	-
3e	8.41 (s)	8.22;8.04(2 brs)	8.29(d, 8.7)	7.77(d, 8.7)	-	8.74(d, 4.7)			8.26(d, 4.8)	-
1f	8.33 (s)	7.93(vbrs)	8.30(dd, 7.5, 1.5)	7.57(t, 7.5)	7.34(t, 7.5)	-	-	7.93 (dd, 3.6, 1.2)	7.69(dd, 5.3, 1.5)	7.18(dd, 5.0, 3.9)

2f	8.34 (s)	7.97(vbrs)	8.33(d, 9.0)	7.62(d, 9.3)	-	-	-	7.94(dd, 3.9, 1.2)	7.70(dd, 5.1, 1.2)	7.18(dd, 5.1, 3.9)
3f**	8.34 (s)	7.37(brs)	8.47(d, 9.0)	7.78(d, 9.0)	-	-	-	8.06(dd, 3.9, 1.2)	7.65(dd, 5.1, 1.2)	7.20(dd, 5.1, 3.9)
1g	8.78 (s)	7.87(brs)	8.92(d, 7.8)	8.03(t, 8.0)	8.40-7.76(m)	-	-	8.40-7.76 (m)	8.25-8.20 (m)	7.10(dd, 3.6, 1.5)
2g	8.35 (s)	8.00(brs)	8.53(d, 9.3)	7.62(d, 9.3)	-	-	-	7.34(dd, 3.3, 0.9)	7.90-7.70 (m)	6.66(dd, 3.3, 1.8)
3g	8.35 (s)	8.00(vbrs)	8.28(d, 9.3)	7.75(d, 9.0)	-	-	-	7.26(dd, 3.3, 0.9)	7.90-7.87 (m)	6.67(dd, 3.3, 1.5)

[a] In ppm from the solvent peak *CH_2 4.01; 4.01; 4.02 (for compounds 1b, 2b, 3b, respectively); **Acetone-d_6. Vbrs-very broad singlet

Table 2. ^{13}C chemical shifts of pyrazolopyrimidines

Compound	C-2' C6'	C3' C5'	C4'	C1'	C3	C3a	C4	C6	C7a	C1"	C2"	C6"	C3"	C5"	C4"
1a	120.5	129.3	126.0	139.3	134.3	100.4	158.3	162.0	154.6	138.0	128.2	128.2	128.4	128.4	130.5
2a	121.8	129.2	130.5	137.8	134.6	100.3	158.2	162.0	154.7	138.0	128.1	128.1	128.3	128.3	129.9
3a	122.2	132.2	118.3	137.9	134.7	100.4	158.3	162.1	154.8	138.5	128.4	128.4	128.2	128.2	130.6
1b*	120.4	129.2	126.2 or 4"	139.2	134.1	99.8	158.4	167.7	154.4	139.0	129.1	129.1	128.3	128.3	126.0 or 4')
2b*	121.6	129.1	129.8	138.0	134.4	99.8	158.3	167.8	154.4	138.8	129.0	129.0	128.2	128.2	126.2
3b*	121.9	132.0	118.0	138.5	134.5	99.8	158.3	167.8	154.5	138.8	129.0	129.0	128.2	128.2	126.2
1c**	120.7	129.4	126.2	139.0	134.3	100.7	158.4	159.8	154.2	111.6	131.5	133.8	139.2	129.9	132.6
2c**	122.0	129.3	130.1	137.8	134.6	100.7	158.3	159.9	154.3	111.6	131.4	133.8	139.0	129.8	132.6
3c**	122.4	132.2	118.8	138.3	134.7	100.7	158.3	159.9	154.3	111.6	131.5	133.9	139.0	129.9	132.6
1d	120.6	129.3	126.2	139.1	134.3	100.6	158.4	160.2	154.2	--	151.1	135.4	133.4	123.6	149.4
2d	122.0	129.3	130.1	137.9	134.7	100.6	158.4	160.4	154.4	--	149.4	135.5	133.3	123.6	151.1
3d	122.2	132.2	118.3	138.3	135.4	100.6	158.3	160.3	154.3	--	151.1	134.7	133.2	123.6	149.4
1e	120.6	129.3	126.2	139.0	134.3	100.9	158.4	159.9	154.1	--	150.2	150.2	122.0	122.0	145.2
2e	122.0	129.3	130.2	137.8	134.7	101.0	158.4	160.0	157.4	--	150.2	150.2	122.0	122.0	145.1
3e	122.3	132.2	118.4	138.2	134.7	101.0	158.4	160.0	154.3	--	150.2	150.2	122.0	122.0	145.1
1f	120.2	129.2	125.9	139.2	134.3	100.1	158.1	158.6	154.0	--	144.0	--	128.5	130.1	128.2

2f	121.8	129.4	128.4	138.1	134.8	100.3	158.3	158.9	154.3	--	143.9	--	130.4	128.8	130.1
3f* **	122.9	132.8	119.1	139.9	134.8	101.3	159.3	160.1	155.6	--	145.2	--	130.5	128.7	129.6
1g	121.3	129.7	126.6	140.7	134.2	101.3	156.4	159.4	155.5	--	154.1	--	113.8	145.5	112.7
2g	122.6	129.8	131.3	139.5	134.7	101.3	156.6	159.4	154.0	--	145.6	--	114.0	141.8	112.7
3g	122.0	132.1	118.2	138.4	134.7	100.2	155.3	158.2	154.2	--	152.4	--	113.2	145.2	112.2

[a] In ppm from the solvent peak *CH_2 45.5; 45.4; 45.4 (for compounds 1b, 2b, 3b, respectively); ** CN 118.8; 118.7; 118.4 (for compounds **1c**, **2c**, **3c**, respectively) ***Acetone-d_6