MAGNETIC RESONANCE IN CHEMISTRY
Magn. Reson. Chem. 2000; **38**: 1039–1040

Reference Data

^{1}H and ^{13}C NMR spectral characterization of some antimalarial *in vitro* 3-amino-9-methyl-1*H*-pyrazolo[3,4-*b*]-4-quinolones

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Received 19 May 2000; accepted 5 July 2000

ABSTRACT: We report the ^{1}H NMR and ^{13}C NMR chemical shifts and J(H,H), J(H,F) and J(C,F) coupling constants of nine 3-amino-9-methyl-1*H*-pyrazolo[3,4-*b*]-4-quinolone derivatives, all of them active against *Plasmodium falciparum in vitro*. They were characterized and assigned on the basis of ^{1}H, ^{13}C and ^{13}C–^{1}H (short- and long-range) correlated spectra. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; quinolones; antimalarial

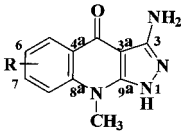
INTRODUCTION

Malaria remains one of the most important infectious disease problems in the world.[1] A significant and increasing problem in malaria control is the resistance of malaria parasites to available chemotherapeutic agents.[2] There is, therefore, a pressing need to identify new antimalarial drugs. We have recently reported the synthesis and spectral characterization of some 3-amino-9-phenylpyrazolo[3,4-*b*]-4-quinolones and 2,4-diamino-10-phenylpyrimido[4,5-*b*]-5-quinolones.[3,4] These compounds proved to be an interesting family of antimalarial agents *in vitro*. In view of those findings, there has been a renewed interest in our laboratories in the synthesis, identification and spectral characterization of new analogues bearing MeO, Cl and F substituents and a methyl group at position 9. In this paper we present the ^{1}H NMR and ^{13}C NMR data for 3-amino-9-methyl-1*H*-pyrazolo[3,4-*b*]-4-quinolone derivatives (Fig. 1). They have demonstrated high antimalarial activity against a chloroquine-resistant strain of *Plasmodium falciparum in vitro*.

EXPERIMENTAL

Compounds

The quinolones **1–4** were synthesized according to the literature[5] and compounds **5–9** were prepared by the synthetic route shown in Scheme 1. The respective phenyl isothiocyanate was condensed with ethyl cyanoacetate using potassium hydroxide, and MeI in dry 1,4-dioxane, the resulting *N*,*S*-acetal **I** was cyclized thermally and finally the quinolone **II** was *N*-alkylated regiospecifically by heating with potassium carbonate, DMF and MeI. The final products **III** were obtained when **II**, reacted with hydrazine hydrate. The structures and purities of the compounds were confirmed by their melting-points, elemental analysis (Atlantic Microlab, Norcross, GA, USA) and IR and NMR spectra.



1-9

Compound	R
1	H
2	6-OMe
3	7-OMe
4	8-OMe
5	6-Cl
6	7-Cl
7	5,6-Cl
8	6-F
9	6,7-F

Figure 1. Structures of 3-amino-9-methyl-1*H*-pyrazolo[3,4-*b*] 4-quinolone derivatives **1–9**.

NMR spectroscopy

NMR spectra were recorded on a JEOL EX 270 Fourier transform NMR spectrometer and a Bruker AMX 500 FT (500 MHz) instrument using DMSO-d_6; tetramethylsilane was used as an internal standard. The instruments were equipped with a 5 mm broadband probe head. Processing was performed using the program DELTA V1.8 and XWIN NMR V2.5, respectively, running on a Silicon Graphics Workstation.

In ^{1}H NMR experiments, the parameters were as follows: spectral window, 15 ppm; width of 30° pulse, 2 μs; relaxation delay, 4 s; and number of scans, 8. In the ^{13}C NMR experiments, the parameters were as follows: spectral window, 250 ppm; width of 30° pulse, 2.8 μs; relaxation delay, 2 s; and number of scans, 9000–10 000. ^{1}H, ^{13}C, COSY, HETCOR and FLOCK spectra were obtained using standard JEOL software.

Heteronuclear ^{13}C–^{1}H HETCOR experiments were carried out with a spectral width of 17 000 Hz for ^{13}C (F_2) and 4000 Hz for ^{1}H (F_1). The spectra were acquired with 1024 × 128 data points. The data were processed by exponential multiplication (LB: 3 Hz) in F_2 and sinusoidal multiplication in F_1 and zero filling was applied in F_1. The mixing delay for single-bond correlation was 3.4 ms and for long-range bond correlation it was 70 ms and the relaxation delay was 1.5 s.

Two-dimensional inverse hydrogen detected heteronuclear shift correlation HMQC spectra and long-range correlation HMBC were obtained with the standard Bruker pulse program [^1J(C,H): 140 Hz, F_2 27.930 Hz and F_1 5040 Hz, relaxation delay 1.5 s, 2K × 128 data points. ^nJ(C,H): 7 Hz, F_2 27.930 Hz and F_1 6666 Hz, relaxation delay 2.0 s, 2K × 128 data points].

RESULTS AND DISCUSSION

^{1}H and ^{13}C NMR chemical shift assignments are given in Tables 1 and 2, respectively. The resonances were obtained by the data provided by ^{13}C–^{1}H (short- and long-range) HETCOR, HMQC, FLOCK[6] and HMBC experiments. Short-range correlations provided an unambiguous assignment of all the methine carbons. The long-range correlations determined by FLOCK and HMBC were useful in the assignment of quaternary carbons, particularly C-4a, -8a, -9a and -4, which showed similar chemical shifts for almost all of the compounds. In all the structures a three-bond connectivity was observed between the proton located at position 5 and that of the carbon at positions 4, 7 and 8a. Also, all those structures showed a three-bond connectivity between the proton of the methyl group at position 9 and that of the carbon at positions 8a and 9a. The ^{1}H–^{19}F and ^{13}C–^{19}F coupling constants of the compounds are in agreement with the published data.[7] In this work we found that structures **1–9** have very promising antimalarial activity against *Plasmodium falciparum in vitro*,[8] compared with the activity of phenyl-substituted compounds reported previously.[3,4]

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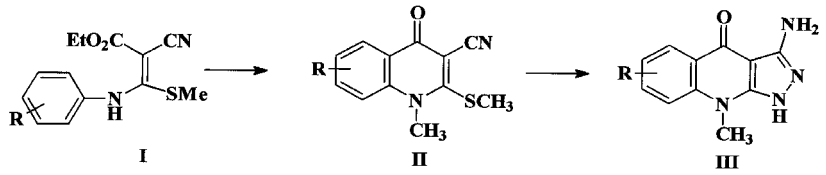
Contract/grant sponsor: IIF.
Contract/grant sponsor: CDCH-UCV; *Contract/grant number*: 060344095.
Contract/grant sponsor: CYTED.
Contract/grant sponsor: CONICIT; *Contract/grant numbers*: LAB-97000665; S1 95000496.

Reference Data



Scheme 1. Preparation of compounds **5–9**.

Table 1. ^{1}H NMR chemical shifts (ppm) and *J*(H,H) and *J*(F,H) coupling constants (Hz) for compounds **1–9**

Compound	NH[a]	NH_2[a]	OCH_3[b]	NCH_3[b]	5-H	6-H	7-H	8-H
1	11.72	6.41		3.62	8.13d, *J* 7.7	7.13dd, *J* 7.7, 6.9	7.65dd *J* 7.2, 6.9	7.42d, *J* 7.2
2	11.73	6.33	3.81	3.61	7.61d, *J* 2.9		7.27dd, *J* 9.2, 2.9	7.41d, *J* 9.2
3	11.67	6.32	3.89	3.60	8.05d, *J* 8.9	6.72dd, *J* 8.9, 3.2		6.79d, *J* 3.2
4	11.79	6.30	3.88	3.90	7.79d, *J* 7.8	7.08dd, *J* 7.4, 7.7	7.26d, *J* 7.4	
5	11.49	6.11		3.61	8.07d, *J* 2.5		7.46dd, *J* 8.9, 2.5	7.24d, *J* 8.9
6	11.77	6.44		3.61	8.09d, *J* 8.4	7.14d, *J* 8.7		7.48s
7	11.76	6.53		3.61			7.78d, *J* 8.9	7.42d, *J* 8.9
8	11.89	6.46		3.63	7.78d, *J* 8.8		7.50d, *J* 7.4	7.47d, *J* 4.3
9	11.82	6.50		3.61	7.95dd, *J* 10			7.51dd, *J* 11

[a] Broad singlet.
[b] Singlet.

Table 2. ^{13}C NMR chemical shifts (ppm) for compounds **1–9**[a]

Carbon	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
C-3	149.07	148.91	148.80	149.16	149.35	149.23	149.93	149.22	149.46
C-3a	95.81	95.55	97.83	95.60	95.73	95.58	96.09	95.37	94.95
C-4	174.66	173.56	174.39	174.06	174.53	173.68	173.60	173.73	172.88
C-4a	123.17	123.74	116.73	125.56	124.16	121.74	120.16	123.67	119.49
C-5	126.38	106.73	128.23	118.82	125.81	128.32	131.53	110.90a	113.95e
C-6	120.08	153.18	107.88	120.79	125.06	119.95	125.04	156.79b	151.53f
C-7	133.04	121.98	163.46	116.69	132.50	137.90	132.98	120.62c	120.24g
C-8	114.32	115.32	97.83	150.02	115.54	113.96	115.11	116.49d	103.72
C-8a	143.21	137.64	144.71	134.45	141.64	143.94	144.36	139.97	140.37
C-9a	151.73	152.07	151.88	152.96	151.72	151.96	150.68	151.64	152.37
NCH_3	30.92	31.97	31.20	29.19	30.80	30.84	32.08	30.73	31.70
OCH_3		55.93	56.02	57.37					

[a] J_a 22.32; J_b 243.60; J_c 23.88; J_d 5.19; J_e 24.9; J_f 242; J_g 225.30 Hz.

Acknowledgments

We thank the IIF, CDCH-UCV (grant No. 060344095 PG.06-30-4590-2000), CYTED and CONICIT (grant Nos LAB-97000665 and S1 95000496) for financial support.

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