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Reference Data

^{13}C NMR Spectral Characterization of Some Antimalarial Tricyclic Quinolone Derivatives

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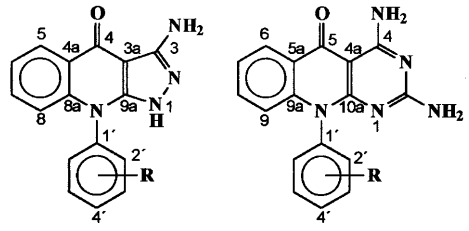
ABSTRACT: We report the ^{13}C NMR chemical shifts of some active quinolones against *Plasmodium falciparum*, namely 3-amino-9-phenyl-1*H*-pyrazolo[3,4-*b*]quinolones and 2,4-diamino-10-phenylpyrimido[4,5-*b*]quinolones. They were characterized and assigned on the basis of ^{13}C–^{1}H (short and long-range) correlated spectra. © 1998 John Wiley & Sons, Ltd.

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

INTRODUCTION

Malaria remains one of the most important infectious disease problems in the world. Hundreds of millions of cases of malaria occur each year, of which nearly two million are fatal, mostly children.[1] Efforts to control this endemia have been unsuccessful and the development of new agents active against resistant strains of malaria has become an urgent need.[2] In recent years, there have been a number of reports concerned with the synthesis and biological activity of some new and potent antimalarial agents against *Plasmodium falciparum*.[3] Our synthetic efforts have been centered around a series of steps which were used to synthesize some new quinolone analogues with promising antimalarial activity, **1**–**18** (Fig. 1).[4] This paper presents ^{13}C NMR data for these quinolones.



1-9 10-18

Figure 1. Structures of quinolones **1**–**18**.

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EXPERIMENTAL

Compounds

The quinolones **1**–**18** were synthesized according to the literature.[4] The structures and purities of the compounds were confirmed by their melting points, elemental analyses, mass spectra (LSIMS) and ^{1}H NMR spectra.

NMR spectroscopy

All NMR spectra were recorded on a Jeol JNM EX 270 Fourier transform NMR spectrometer in DMSO-d_6 solutions; tetramethylsilane (TMS) was used as an internal standard. The instrument was equipped with a 5 mm broadband probe head. The processing was performed using the program DELTA V1.6, running on a Silicon Graphics workstation.

In 1D ^{13}C 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, 2000–3000. All 2D NMR spectra were obtained using standard JEOL software.

Homonuclear ^{1}H-^{1}H COSY experiments were typically performed with a spectral width of 4000 Hz, relaxation delay 1.5 s, mixing pulse 90°, number of increments 64 and a number of scans of 16. The spectra were collected as 256 × 64 blocks of data and were processed by sinusoidal multiplication in each dimension, followed by symmetrization of the final data matrix. The heteronuclear ^{1}H–^{13}C 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 1028 × 64 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.

RESULTS AND DISCUSSION

^{13}C NMR chemical shift assignments are given in Tables 1 and 2. The resonances were assigned with the data provided by ^{13}C–^{1}H (short- and long-range) HETCOR experiments. The long-range correlations were particularly useful in making many of the carbon assignments. The ^{1}H NMR for **10**–**18** included two doublets around 7.6 and 9.5 ppm which were assigned to the amine group linked to C-4 and having a ^{2}J (4.7 Hz) (see Fig. 2). Earlier investigation on related compounds had shown in x-ray crystallography good correlations in their distance for the formation of hydrogen bonding.[5] This provides clear evidence of the presence of hydrogen bonding between one of the NH_2 protons and the carbonyl group attached to the carbon at C-5. Hence the availability of these techniques provides an important tool which has stimulated much interest, because of the biological properties of these quinolones. In this work we found that structures with hydrogen bonding, **10**–**18**, do not have antimalarial activity. However, compounds **1**–**9**, without hydrogen bonding, were active as antimalarials. These results might be taken into consideration in further studies.

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Table 1. ^{13}C NMR chemical shifts (ppm relative to internal TMS) for 3-amino-9-phenylpyrazolo[3,4-*b*]quinolones **1–9**[a]

Carbon	**1** (R = H)	**2** (R = 4′-OMe)	**3** (R = 3′-OMe)	**4** R = 2′-Me)	**5** (R = 4′-Br)	**6** (R = 4′-Cl)	**7** (R = 4′-F)	**8** (R = 2′,4′-Cl)	**9** (R = 3′-CF_3)
C-3	152.13	152.07	151.88	151.64	151.76	151.63	152.57	151.30	151.96
C-3a	95.15	95.30	95.19	95.38	95.21	95.25	95.17	94.88	95.21
C-4	174.78	174.63	174.68	174.82	174.60	174.59	174.80	174.75	174.67
C-4a	122.77	122.90	122.78	122.69	122.90	122.90	122.87	122.83	122.96
C-5	126.36	126.29	126.28	126.48	126.40	126.41	126.38	126.56	126.32
C-6	120.44	120.30	120.45	120.44	120.73	120.71	120.61	120.95	120.79
C-7	132.78	132.72	132.77	132.46	132.88	132.87	132.84	133.16	132.97
C-8	115.35	115.42	115.49	114.76	115.28	115.27	115.29	114.69	115.12
C-8a	143.74	143.71	143.67	143.15	143.31	143.36	143.67	142.67	143.34
C-9a	148.63	148.75	148.63	148.67	149.11	149.00	148.60	148.69	148.67
1′	138.18	139.95	139.16	137.35	137.81	136.93	134.25a	135.13	138.95
2′	129.29	131.08	115.16	133.01	132.42	130.82	132.13b	134.48	126.36e
3′	130.75	115.89	161.20	129.71	133.78	132.10	117.64c	133.16	133.23f
4′	130.04	159.65	115.28	130.31	122.37	133.82	162.27d	135.04	127.30g
5′	130.75	131.08	121.92	129.76	133.42	132.10	117.64	134.19	131.53
6′	129.29	115.89	120.73	128.41	132.46	130.82	132.13	129.93	131.73
CH_3		56.02	55.8	17.46					
CF_3									123.16h

[a] $J_a = 3.4$; $J_b = 9.5$; $J_c = 22.4$; $J_d = 243$; $J_e = 3.82$; $J_f = 33.27$; $J_g = 3.27$; $J_h = 272.9$ Hz.

Table 2. ^{13}C NMR chemical shifts (ppm relative to internal TMS) for 2,4-diamino-10-phenylpyrimido[4,5-*b*]quinolones **10–18**[a]

Carbon	**10** (R = H)	**11** (R = 4′-OMe)	**12** (R = 3′-OMe)	**13** (R = 2′-Me)	**14** (R = 4′-Br)	**15** (R = 4′-Cl)	**16** (R = 4′-F)	**17** (R = 2′,4′-Cl_2)	**18** (R = 3′-CF_3)
C-2	165.25	165.29	165.24	165.30	165.19	165.20	165.24	165.14	165.18
C-4	159.43	159.51	159.35	158.92	159.35	159.40	159.54	159.00	159.48
C-4a	93.52	93.62	93.51	93.48	93.51	93.51	93.55	93.37	95.54
C-5	176.32	176.32	176.32	176.31	176.31	176.32	176.33	176.31	176.36
C-5a	122.69	122.60	122.67	122.85	122.80	122.79	122.74	123.21	122.84
C-6	126.23	126.18	126.14	126.41	123.41	123.42	122.43	126.52	126.36
C-7	130.63	131.45	131.30	131.89	126.29	126.29	126.26	130.82	131.84
C-8	133.29	133.25	133.30	133.61	133.41	133.41	133.36	133.93	133.47
C-9	117.23	117.37	117.35	116.48	117.14	117.14	117.18	116.28	116.92
C-9a	142.41	142.79	142.31	141.50	142.08	142.14	142.42	140.94	142.14
C-10a	163.43	163.48	163.48	137.86	163.37	163.68	163.40	163.52	163.34
1′	139.00	137.73	140.13	137.86	138.35	137.90	135.17a	135.36	139.86
2′	130.31	131.25	114.89	136.87	132.72	130.69	132.49b	134.61	126.18e
3′	130.63	115.69	161.08	123.40	133.63	132.38	117.46c	133.92	131.35f
4′	129.19	159.54	115.24	129.51	122.41	133.77	162.30d	123.45	127.47g
5′	130.63	131.25	122.66	130.11	133.63	132.38	117.46	129.80	135.04
6′	130.31	115.69	122.28	128.32	132.72	130.69	132.49	129.93	131.11
CH_3		55.92	55.94	17.57					
CF_3									124.40h

[a] $J_a = 1.72$; $J_b = 8.7$; $J_c = 22.5$; $J_d = 242.2$; $J_e = 3.84$; $J_f = 32.38$; $J_g = 3.83$; $J_h = 271.7$ Hz.

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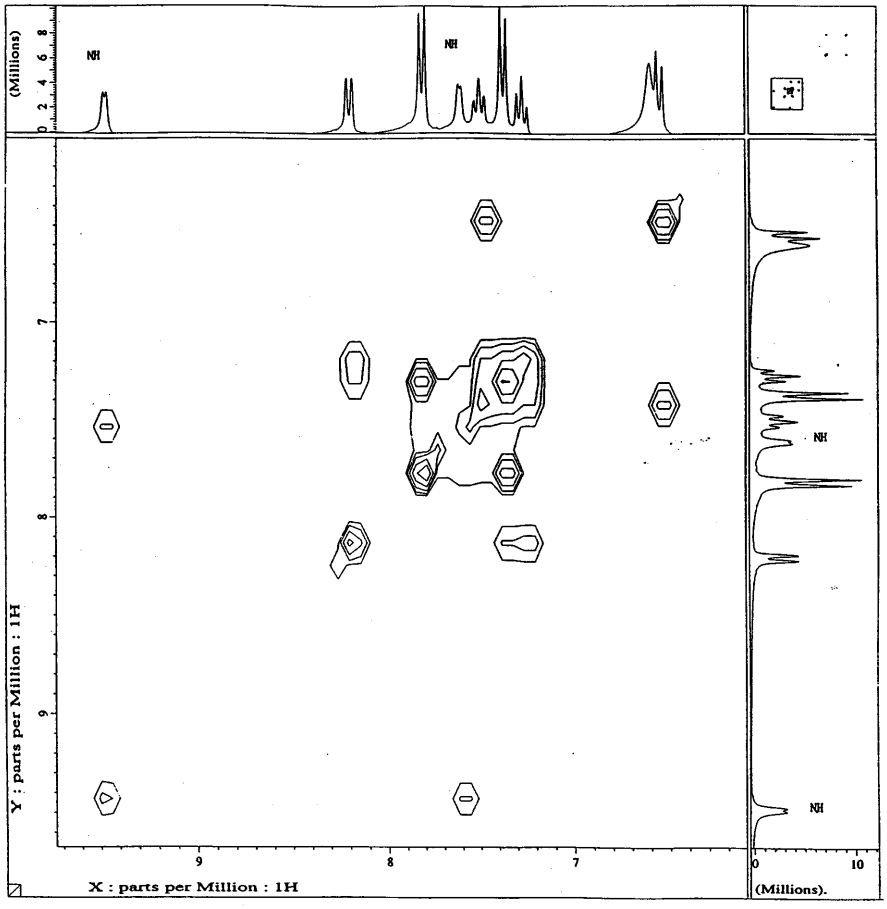

Figure 2. COSY spectrum of **14**.

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