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Contribution of NMR Spectroscopy, Mass Spectrometry and X-Ray Diffractometry Techniques to the Characterization of 2-Chloro-8-methyl-3-formylquinoline

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ABSTRACT
Quinoline and its analogues have been known to possess diverse pharmacological activities. In the last three decades 2-chloro-8-methyl-3-formylquinoline has been utilized as building blocks for the development of various quinolines fused heteroaryl rings. In this article we report the complete spectral details of 2-chloro-8-methyl-3-formylquinoline. The techniques involved in the characterization of title compounds are various NMR experiments such as HSQC, COSY and HMBC. Molecular weight was determined by FAB-mass spectrometry. The powder XRD study revealed crystal behavior of the title compound.

Keywords: HSQC, COSY, HMBC, XRD and 2-chloro-8-methyl-3-formylquinoline.

INTRODUCTION

Quinoline ring containing compounds exhibit potent biological activities which have been proven by number of recent reports. [1-3] Among various available intermediates of quinoline, 2-chloro-3-formyl-quinoline **1** and its related aldehyde analogues occupy a prominent space due to its ability to undergo further multiple [a], [b] or/and [c]-annelations leading to formation of wide variety of rings. The applications of these methodologies have yielded a large number of new heteroaryl fused quinoline derivatives such as pyrrolo[3,4-*c*]quinoline, 2*H*-pyrano[2,3-*b*]quinoline, tetrazolo[1,5-a]quinoline, isothiazolo[5,4-b]quinoline, [4-11] and various new approaches for alkaloids synthesis such as camptothecin [12] (Fig. 1). These intermediates have also been exploited immensely for various functional groups interconversions. [13-14] So far the single crystal analysis of 2-chloro-8-methyl-3-formylquinoline is reported by F. Nawaz Khan *et al.* [15], no one yet made any attempt to present spectral details of the compound. As single crystal analysis and spectral applications are complimentary for the determination of structure, we have aimed in this article to present 2D-NMR (HSQC, COSY, HMBC) details, of 2-chloro-8-methyl-3-formylquinoline (Fig. 2) along with powder XRD and softer ionization mass analyses to confirm the basic structure.

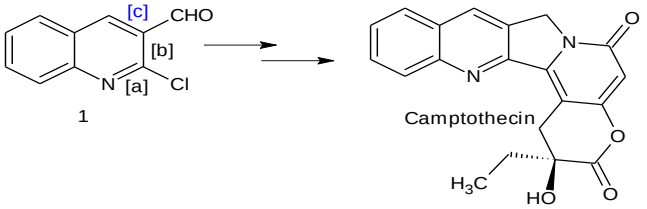

Fig. 1: Synthesis of anticancer natural product Campotothecin starting from 2-chloro-3-formyl-quinoline 1

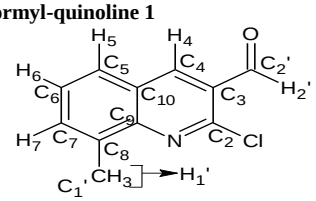

Fig. 2: Structural formula of 2-chloro-8-methyl-3-formylquinoline and position of H and C designated in HMBC

MATERIAL AND METHODS

All the chemicals required for the synthesis of 2-chloro-8-methyl-3-formylquinoline were procured from E. Merck (Germany). Melting points was determined by the open tube capillary method and is uncorrected. IR spectra were recorded as KBr (pellet) on Bio Rad FT-IR spectrophotometer. C, H, N elemental analysis was carried out on Vario EL III CHNOS-Elemantar analyzer and was found to be within the range of ±0.4%. The title compound 2-chloro-8-methyl-3-formylquinoline needed in the study was prepared as the per the method reported by O. Meth-Cohn *et al.* [16]

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NMR Analysis

^{1}H, ^{13}C NMR, COSY, HSQC, and HMBC spectrum of 2-chloro-8-methyl-3-formylquinoline was recorded on a Bruker at 300 MHz Bruker (DPX) spectrospin spectrophotometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C equipped with a 5-mm probe, in deutarated DMSO. Tetramethylsilane (TMS) was used as internal standard and the values of chemical shifts δ are expressed in part per million. Splitting patterns are designated as follows: s, singlet; bs, broad singlet; d, doublet; t, triplet.

Mass Analysis

The mass spectra of title compounds was recorded using Fast Atom Bombardment (FAB) technique on JEOL SX 102/DA-6000 Mass Spectrometer/ Data System using Xenon (6kV, 10mA) as the FAB gas. The accelerating voltage was 10kV and the spectra were recorded at room temperature. m-Nitrobenzyl alcohol (NBA) was used as the matrix. The matrix peaks appeared at m/z 136, 137, 154, 289, 307.

X-ray diffractometry (XRD)

In x-ray studies, an automatic x-ray diffractometer (Philips PW 3710; Eindhoven, The Netherlands) equipped with a PW R30 x-ray generator was used. Nickel-filtered Cu kα1 radiation having a wavelength of 1.5106 Å, operating at 35 kW and 20 mA in the range (2θ) of 5 to 70 degrees, was used. X-ray diffractograms were obtained at a scanning rate of 1 degree (2θ) per minute.

Table 1: HSQC details of 2-chloro-8-methyl-3-formylquinoline

^{1}H (δ) ppm	^{13}C (δ) ppm	Carbon No.
2.69 (s)	17.37	C_1'
8.52 (s)	136.91	C_4
7.69-7.66 (d)	133.30	C_5
7.46-7.40 (t)	127.26	C_6
7.63-7.60 (d)	127.56	C_7
10.45 (s)	188.83	C_2'

Table 2: ^{1}H--H COSY (DQF-COSY) spectrum of 2-chloro-8-methyl-3-formylquinoline

Position of (H)	1H-NMR (δ)	COSY
1'	2.69	--
4	8.52	--
5	7.69-7.66	H-6
6	7.46-7.40	H-5, H-7
7	7.63-7.60	H-6
2'	10.45	---

RESULTS AND DISCUSSION

HSQC

The sequential assignment of protons and carbon atoms of 2-chloro-8-methyl-3-formylquinoline was made with the help of HSQC experiment (Table 1 and Figure 3). Starting with the easily distinguishable methyl protons δ_H =2.69 (s) showed correlation with δ_C = 17.37 attributed at position 1'. The next singlet proton δ_H = 8.52 showed correlation with the carbon δ_C = 136.91 attributable at position 4'. Similarly, the proton δ_H = 7.69-7.66 (d, *J* = 8.1 Hz) exhibited correlation with carbon δ_C = 133.30 assignable at position 5. Another doublet was observed at δ_H = 7.63-7.60 (d, *J* = 8.1) which showed correlation with carbon δ_C = 127.56 attributable at position 7. A triplet was observed at chemical shift value δ_H = 7.46-7.40 (t, *J* = 7.65) assignable at position 6 and correlated with the carbon δ_C = 127.26. The highly distinguishable aldehydic protons δ_H = 10.45 (s) showed correlation with carbon at δ_C = 188.83 assignable at position 2'.

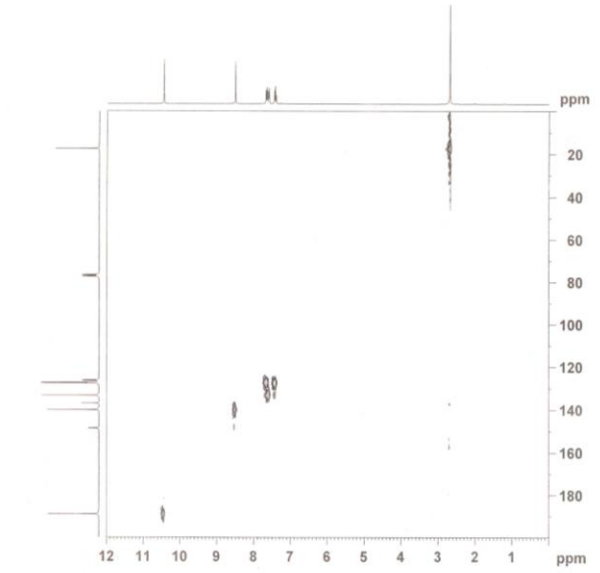

Fig. 3: HSQC- Contour plot of 2-chloro-8-methyl-3-formylquinoline

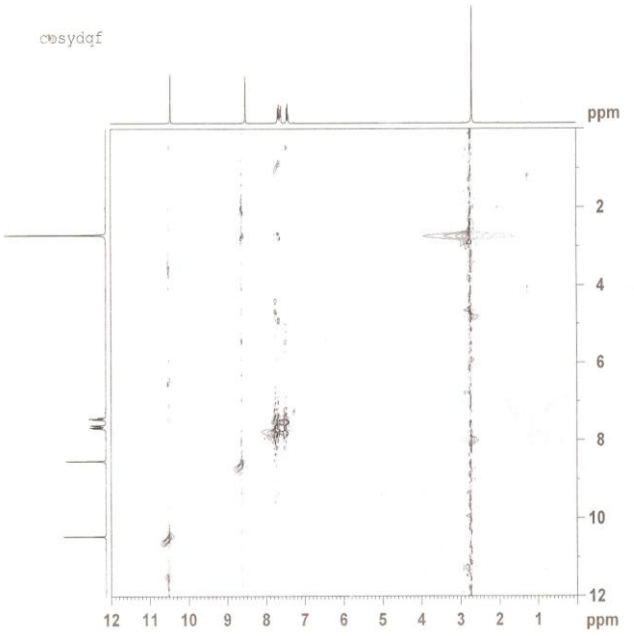

Fig. 4: COSY-DQF-Contour plot of 2-chloro-8-methyl-3-formylquinoline

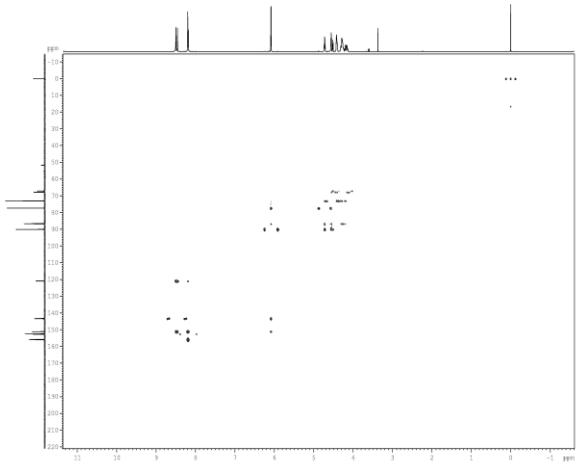

Fig. 5: HMBC-Contour plot of 2-chloro-8-methyl-3-formylquinoline

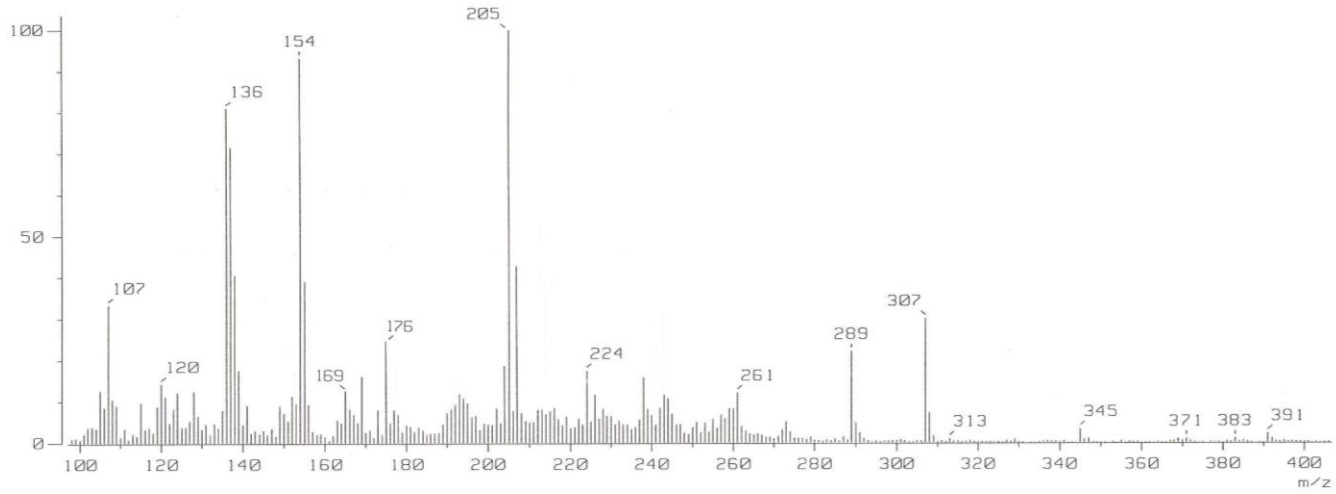

Fig. 6: FAB-MS spectrum of 2-chloro-8-methyl-3-formylquinoline

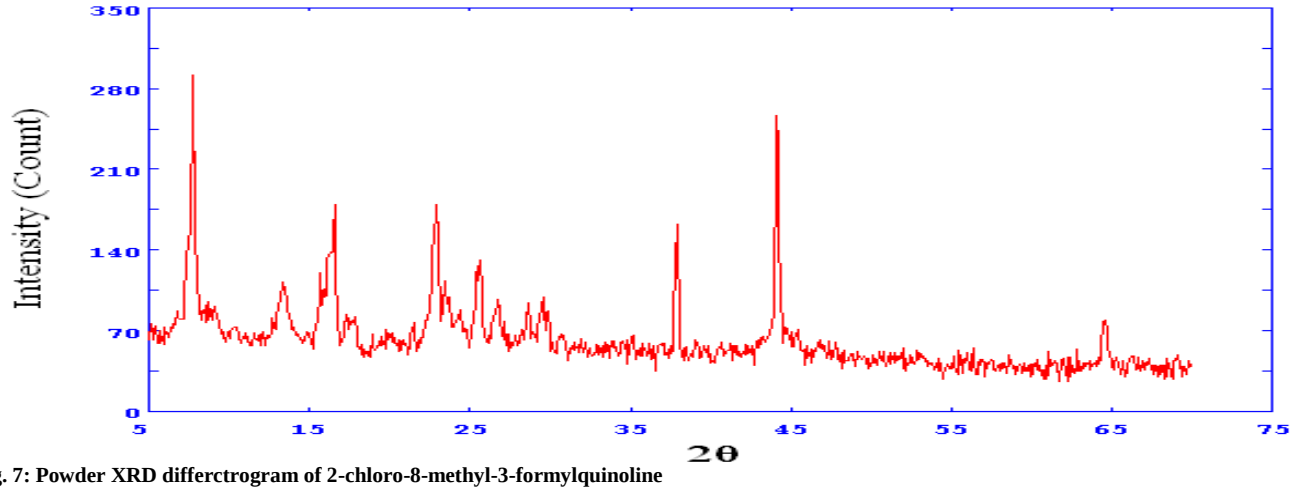

Fig. 7: Powder XRD differctrogram of 2-chloro-8-methyl-3-formylquinoline

Table 3: HMBC correlation data of compound 2-chloro-8-methyl-3-formylquinoline

Protons	Carbon	C1'	C2	C3	C4	C5	C6	C7	C8	C9	C10	C2'
	(ppm)	17.37	148.51	126.13	136.91	133.30	127.26	127.56	140.00	148.69	126.41	188.83
H-1'	2.69	--	--	--	---	---	--	3JCH	2JCH	3JCH	--	--
H-4	8.52	--	3JCH	2JCH	--	3JCH	--	---	--	3JCH	2JCH	3JCH
H-5	7.69-7.66	--	---	--	3JCH	--	2JCH	3JCH	--	3JCH	2JCH	---
H-6	7.46-7.40	--	--	--	---	2JCH	--	2JCH	3JCH	--	3JCH	--
H-7	7.63-7.60	3JCH	--	--	---	3JCH	2JCH	--	2JCH	3JCH	---	--
H-2'	10.45	--	3JCH	2JCH	3JCH	--	--	--	--	--	3JCH	--

^{1}H-^{1}H COSY (DQF-COSY)

In ^{1}H-H COSY (DQF-COSY) experiment (Figure 4), the proton exhibited chemical shift values δ_H = 2.69 did not correlate with any other proton. At position 4, the proton having chemical shift value δ_H = 8.52 did not show any correlation. The proton positioned at 5, owing chemical shift value δ_H = 7.69-7.66 showed correlation with H-6. Similarly, the number six proton displayed correlation with two different protons positioned at 5 and 6. The H-7 chemical shift value δ_H = 7.63-7.60 exhibited correlation with H-6 only. The 2' did not show any correlation (Table 2).

HMBC

In HMBC two bond correlations (2JCH) are almost always found, the three bond correlation (3JCH) are occasionally absent (Figure 5). As proceeding parallel to the carbon column we got the following results (Table 3).

1. The H-1' protons (δ_H = 2.69) showed correlation with C7 (3JCH), C8 (2JCH) and C9 (3JCH) carbon atom.

2 The H-4 proton (δ_H = 8.52) displayed multiple correlation such as C2 (3JCH), C3 (2JCH), C5 (3JCH), C9 (3JCH), C10 (2JCH) and C2'(3JCH) respectively.

3 Similarly H-5 proton exhibited correlation with carbon atoms C4 (3JCH), C6 (2JCH), C7 (3JCH), C9 (3JCH) and C10 (2JCH).

4 The H-6 proton correlated with carbon atoms C5 (2JCH), C7 (2JCH), C8 (3JCH) and C10 (3JCH) respectively.

5 The multiple correlation was observed between H-7 proton (δ_H = 7.63-7.60) and carbon atoms C1' (3JCH), C5 (3JCH), C6 (2JCH), C8 (2JCH), and C9 (3JCH) respectively.

6 The aldehydic proton also displayed multiple correlation with the carbon atoms C2 (3JCH), C3 (2JCH), C4 (3JCH) and C10 (3JCH) respectively. As proceeding parallel to the proton column we got the similar results e.g. C1' carbon atom showed only one correlation with proton H-7 (3JCH). Similarly C2 exhibited two correlation with protons H-4 (2JCH) and H-2' (3JCH).

FAB-MS

The mass spectrum of 2-chloro-8-methyl-3-formylquinoline using FAB-MS registered M^+ peak at *m/z* 205 (100 %) and M+2 peak at *m/z* 207 (30 %) due presence of chlorine atom (Figure 6), the spectrum also shows M+H peak at *m/z* 206 (10 %). A small peak due loss of H^+ ion, was appeared at 204 (20 %) and peak at *m/z* 176 may be attributed due to loss of -CHO from the molecular ion. A fragment peak at *m/z* 169 was also observed in the spectrum which expected to appear due to loss of HCl from the molecular ion.

Powder XRD

Figure 7 shows the powder XRD patterns of powder 2-chloro-8-methyl-3-formylquinoline. The XRD differctrogram of 2-chloro-8-methyl-3-formylquinoline contained sharp peaks indicating good crystallinity. The height of peaks varies with different 2θ values. This differctrogram may serve as a finger print for the characterization of this compound.

In the article we have presented correlation spectroscopic details of 2-chloro-8-methyl-3-formylquinoline. The HMBC studies indicate that all H-5, H-6 H-7 proton shows multiple correlation with carbon atoms.

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