

Reaction of 4-Hydrazinoquinolines with β -Diketones.
 Synthesis and Spectroscopy (^1H , ^{13}C NMR, MS)
 of Some Pyrazolylquinolines

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 Received November 17, 1988

A series of 4-pyrazolylquinolines have been prepared from 4-hydrazinoquinolines and β -dicarbonyl compounds and the previously proposed diazepine structure for the reaction products has been ruled out. A ^{13}C nmr study established the 3-position of the methyl group when two isomers were possible. Finally, a careful ^1H nmr study of 2- and 4-pyrazolylquinolines led to the conclusion that intramolecular hydrogen bonds between aromatic (or heteroaromatic) C-H and pyridine like nitrogens is the factor that determines the conformation of these compounds.

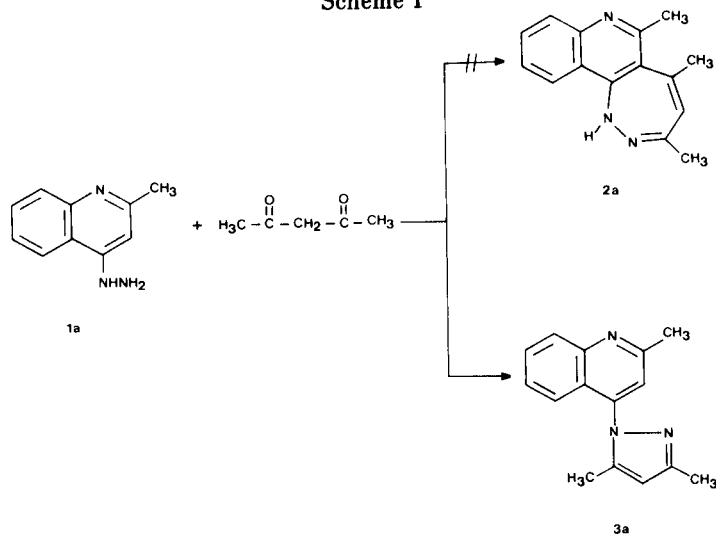
J. Heterocyclic Chem., **26**, 733 (1989).

As a part of a program aimed at investigating the structure of the products obtained by reaction of heterocyclic hydrazines with β -dicarbonyl compounds, a pyrazole structure was established [1-3] for several molecules to which a triazepine structure had been previously assigned [4,5]. Products obtained by reaction of 2- and 4-hydrazinoquinolines with pentane-2,4-dione have also been formulated either as diazepines [6,7] or as pyrazole derivatives [8,9]. Whilst the pyrazole structure in the case of 2-hydrazinoquinolines was firmly established [10], the structure of the product obtained by treating 4-hydrazinoquinolines with pentane-2,4-dione remains to be worked out. We present in this paper evidence that the diazepine structure proposed is not correct and the compound has indeed a pyrazole structure. Further, an inspection of the ^1H nmr spectra of 4-(pyrazol-1-yl)quinolines thus synthesized reveals large differences from the spectral characteristics of 2-(pyrazol-1-yl)quinolines.

Singhal and Joshi [7] treated 4-hydrazino-2-methylquinoline **1a** with pentane-2,4-dione in refluxing glycerol in the presence of sodium acetate and obtained a product, mp 72° , to which they assigned a diazepine **2a** rather than a pyrazole structure **3a** on the basis of ir and ^1H nmr arguments.

Following the same procedure, a product (mp 70°) was isolated which can be obtained in better yield by performing the reaction in refluxing ethanol containing a few drops of acetic acid. Both ^{13}C and ^1H nmr (see later) leave no doubt about the pyrazole structure. Further support was gained from the mass spectrum of compound **3a** (Chart 1). There are ions characteristic of the pyrazole fragmentation and, very significantly, presence of ions at m/z 95 and 142 was noted. A linked scan study reveals their formation directly from the molecular ion, and accurate mass measurement disclosed the elemental composition of the fragment ion at m/z 142 as $\text{C}_{10}\text{H}_8\text{N}$. The for-

Scheme I



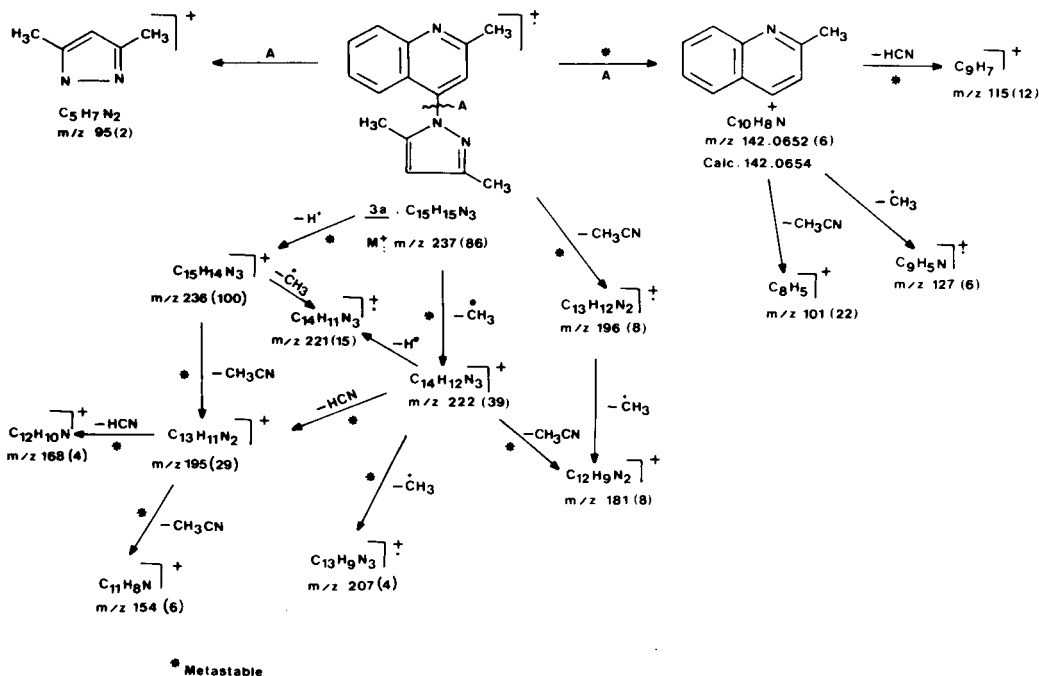
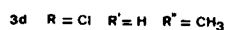
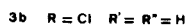
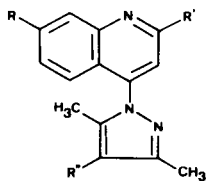
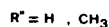
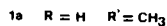
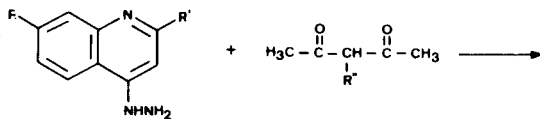


Chart 1

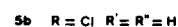
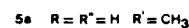
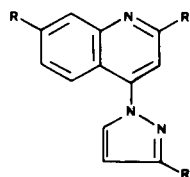
mation of ions at m/z 95 and 142 can be envisaged by the fission of the molecular ion through the C-N bond linking the two heterocyclic moieties in agreement with earlier observations [2].

The reaction has been extended in two directions; using another quinoline, 7-chloro-4-hydrazinoquinoline **1b**, and using another β -diketone, 3-methylpentane-2,4-dione (Scheme II).

Scheme II

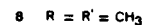
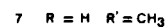
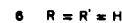
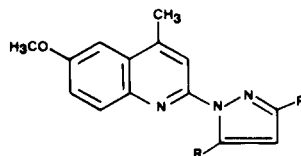


To further generalize this reaction the β -diketones were replaced by acetylacetaldehyde dimethyl acetal and by malonaldehyde bis(dimethyl acetal). In this way, compounds **4a**, **4b**, **5a** and **5b** were obtained.



In the case of compound **4a** and **4b**, the nmr study established that both are 3-methyl derivatives. Probably, the reaction proceeds in two steps; first the hydrazone is formed and it is subsequently transformed into a pure isomeric pyrazole by acid-catalyzed reaction.

In order to carry out a discussion of the proton chemical shifts of 4-pyrazolylquinolines, two new representatives, **6** and **7**, of 2-pyrazolylquinolines were prepared by analogous procedures (compound **8** has already been described [10]).



The carbon-13 nmr spectrum of compound **7** ($3'$ -CH₃ at 13.87 ppm, see Experimental) corresponds to a 3-methyl derivative. Thus, in our hands, the reaction between hydrazinoquinolines (both 2- and 4-) and acetylacetaldehyde dimethylacetal yielded only 3-methylpyrazoles when carried out in two steps.

Carbon-13 NMR Spectroscopy.

Carbon-13 chemical shifts are collected in Table I. They have been assigned using SFORD and APT techniques and they are consistent with the chemical shifts of quinolines and pyrazoles [10-15]. Three main consequences can be drawn from these values:

- i) All these compounds are undoubtedly pyrazoles.
- ii) Compound **4b** ($3'$ -CH₃ at 13.72 ppm) is a 3-methyl isomer.
- iii) When the 5-methyl group is removed (compare **3a** and **4b**), the 'ortho' carbons (C₃ and C₄) are shifted upfield, indicating a more planar structure [12,14].

Proton NMR Spectroscopy.

The proton nmr parameters of all the compounds here described are gathered in Table II. Some interesting conclusions concerning the preferred conformation of pyrazolylquinolines can be deduced from the chemical shifts of the groups, protons or methyl, near the C-N bond connecting both rings.

In the 4-pyrazolylquinoline series, the quinoline H₅ proton is very sensitive to the presence in **3b**, **3d** or the absence in **4b**, **5b** of a methyl group in the pyrazole 5'-po-

sition. In the first case, H₅ resonates at about 7.7 ppm, whereas in the second, the signal shifts to about 8.3 ppm. This can be assigned to a conformation where the N₂ atom is near H₅ when R₅ = H; the 5'-methyl group, due to a steric hindrance with H₃, produces a rotation of both rings about the C-N bond, resulting in an almost perpendicular conformation.

The 2-pyrazolylquinoline series shows a remarkable feature when compared with the preceding one: the signals of H₅ and 5'-Me are strongly deshielded (8.65 instead of 7.8 and 2.72 instead of 2.15 ppm). This can be attributed to the proximity of the quinoline N₁ atom in a planar conformation both for R₅ = H and CH₃. A similar observation has been made for 2-(pyrazol-1-yl)benzothiazoles [11]. Probably, the H₃ proton (7.85-7.92 ppm) is also deshielded by the proximity of the pyrazole N₂ atom.

In summary, the conformation in these systems is governed by the possibility of having a hydrogen bond between an acidic hydrogen and the lone pair of a pyridine type nitrogen. Three main situations can be found (Figure I).

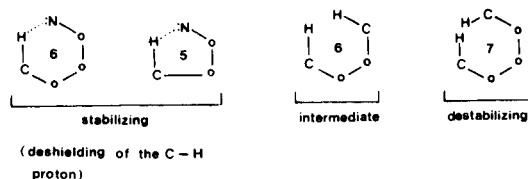


Figure I

Table I

¹³C-NMR Chemical Shifts (ppm) of Compounds **3a-3d** and **4b**

Compound	3a [a]	3c [a]	3b [a]	3d [b]	4b [a]
C ₂	159.15	159.23	151.35	152.11	151.25
C ₃	119.75	119.66	118.63	118.56	114.60
C ₄	144.22	144.50	144.00	143.37	144.35
C ₅	123.47	123.69	123.80	126.55	125.95
C ₆	126.66	126.54	125.64	127.80	128.49
C ₇	128.92	128.80	136.20	134.70	136.14
C ₈	130.01	130.04	128.55	127.96	131.65
C _{4a}	123.47	123.51	123.70	122.87	120.79
C _{8a}	149.07	149.30	150.02	149.54	150.18
C _{3'}	150.04	149.32	150.50	148.85	152.32
C _{4'}	106.65	113.31	107.27	113.39	108.49
C _{5'}	141.11	137.76	141.00	137.67	128.29
2-CH ₃	25.34	25.32	—	—	—
3'-CH ₃	13.57	12.01	13.55	11.78	13.72
4'-CH ₃	—	8.17	—	7.86	—
5'-CH ₃	11.64	10.44	11.68	10.14	—

[a] Solvent: deuteriochloroform. [b] Solvent: perdeuteriomethanol.

Table II

¹H-NMR Parameters: Chemical Shifts (ppm) and Coupling Constants (Hz) (Solvent: deuteriochloroform)

Compound	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-5'	H-3'	H-4'
5a [a]	2.78 (s)	←	→	→	→	→	→	→	→	→
4a [b]	2.78 (s)	<	→	→	→	→	→	→	→	→
3a	2.78 (s)	←	→	→	→	→	→	→	→	→
3c	2.77 (s)	←	→	→	→	→	→	→	→	→
5b [c]	8.96 (d)	7.43 (d)	—	8.31 (d)	7.54 (dd)	—	8.19 (d)	—	7.92 (m)	6.62 (dd) [a]
4b [c]	8.85 (d)	7.31 (d)	—	8.28 (d)	7.45 (dd)	—	8.08 (d)	—	7.73 (d)	6.31 (d) [b]
3b [c]	8.97 (d)	7.31 (d)	—	7.67 (d)	7.48 (dd)	—	8.17 (d)	—	2.35 (s)	6.12 (s)
3d [c]	8.97 (d)	7.28 (d)	—	7.73 (d)	7.48 (dd)	—	8.17 (d)	—	2.32 (s)	6.12 (s)
6 [d]	—	7.91 (s)	2.63 (s)	7.08 (d)	3.88 (s)	7.31 (dd)	7.88 (d)	8.69 (d)	7.74 (s)	2.10 (s)
7 [d]	—	7.92 (s)	2.68 (s)	7.18 (d)	3.92 (s)	7.31 (dd)	7.90 (d)	8.60 (d)	7.74 (s)	6.45 (dd) [a]
8 [d]	—	7.85 (s)	2.63 (s)	7.12 (d)	3.87 (s)	7.28 (dd)	7.82 (d)	2.72 (s)	2.38 (s)	6.25 (d) [b]
									2.29 (s)	5.96 (s)

[a] $J_{4,3'} = 1.5$, $J_{4,5'} = 2.5$, [b] $J_{4,5'} = 2.5$, [c] $J_{2,3} = 4.2$, $J_{5,6} = 8.2$, $J_{6,8} = 1.8$, [d] 300 MHz: $J_{5,7} = 2.7$, $J_{7,8} = 9.1$.

These situations correspond to the observed conformation of both series (Figure II).

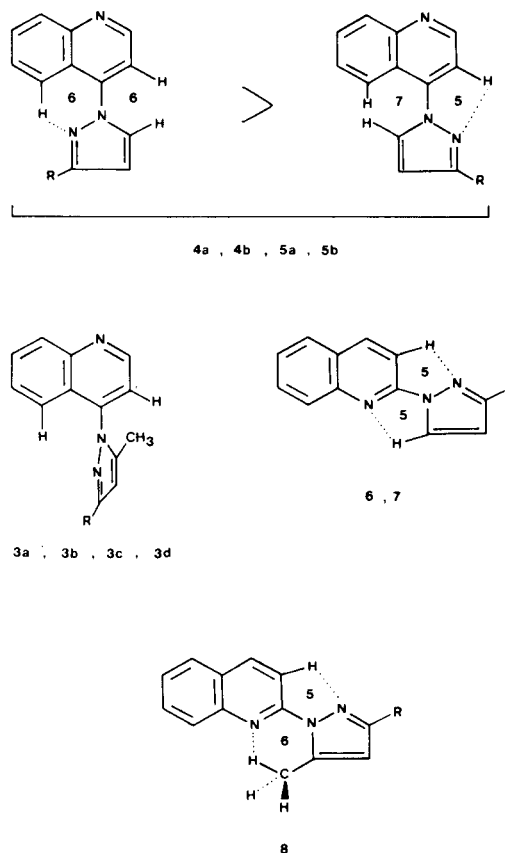


Figure II

EXPERIMENTAL

Melting points were recorded in open capillaries and are uncorrected. The ir spectra (in nujol) were recorded on a Beckman IR-20 spectrophotometer, ¹H nmr spectra on an R-32 Perkin Elmer (90 MHz) instrument and on a Varian XL-300 instrument operating at 300 MHz. Mass spectra were recorded on a Varian MAT-212 mass spectrometer. High resolution measurements and linked scan data were recorded on a JEOL JMS-DX 300 mass spectrometer linked to a JEOL, JMA-3100 data system at 70 eV, ionizing current 300 μ A, accelerating voltage 3.0 kV and ion source temperature 150°. The ¹³C nmr spectra were recorded on a Nicolet NT-360 spectrometer.

7-Chloro-4-hydrazinoquinoline, acetylacetaldehyde dimethyl acetal and malonaldehyde bis(dimethyl acetal) were commercially available. 4-Hydrazino-2-methylquinoline [16], 2-hydrazino-6-methoxy-4-methylquinoline [17] and 3-methylpentane-2,4-dione [18] were prepared according to the procedures described in literature.

4-(3',5'-Dimethylpyrazol-1'-yl)-2-methylquinoline (3a).

Method a).

A mixture of 4-hydrazino-2-methylquinoline **1a** (1.73 g, 0.01

mole) and pentane-2,4-dione (1.0 g, 0.01 mole) was refluxed for 4-5 hours in 30-40 ml of ethanol containing a few drops of acetic acid. The reaction mixture was cooled and extracted with chloroform. Column chromatography of the residue gave **3a**, mp 70° (Lit [7] 72°), yield 55%; ms: m/z 237.1227 (M^+) (Calcd. for $C_{15}H_{15}N_3$: M^+ 237.1260) (Found: N, 17.3. $C_{15}H_{15}N_3$ requires N, 17.7).

Method b).

Hydrochloride of **1a** (4.19 g, 0.02 mole) and anhydrous sodium acetate (2.0 g) were taken in glycerol (30 ml). To the well-stirred mixture, pentane-2,4-dione (2.0 g, 0.02 mole) was added with continuous stirring. The reaction mixture was refluxed for 1 hour, cooled and poured onto crushed ice. The crude product was crystallized from aqueous ethanol as pale yellow crystals, mp 70°, yield 50%. There was no depression in mp when mixed with the sample obtained by method a), both samples displayed the same ir and 1H nmr spectral characteristics.

7-Chloro-4-(3',5'-dimethylpyrazol-1'-yl)quinoline (**3b**).

Following method a) 7-chloro-4-hydrazinoquinoline **1b** (1.93 g, 0.01 mole) and pentane-2,4-dione (1.0 g, 0.01 mole) were allowed to react. On cooling, a white solid appeared which was crystallized from ethanol/water, mp 92°, yield 54%; ms: m/z 257/259 (M^+); major fragments at m/z 256/258 (M-H), 222 (M-Cl), 242/244 (M-CH), 162/164 ($M-C_5H_5N_2$), 95 ($M-C_5H_5ClN$) (Found: N, 16.19. $C_{14}H_{12}ClN_3$ requires N, 16.31).

Compounds **3c** and **3d** were prepared similarly by treating **1a** and **1b** with 3-methylpentane-2,4-dione, respectively. Their characterization data are as follows:

Compound **3c**.

This compound had mp 85°, yield 58%; ms: m/z 251 (M^+)/Major fragments at m/z 250 (M-H), 236 (M-CH₃), 210 (M-CH₃CN), 142 ($M-C_5H_5N_2$), 109 ($M-C_{10}H_8N$) (Found: N, 16.28. $C_{16}H_{17}N_3$ requires N, 16.73).

Compound **3d**.

This compound had mp 115°, yield 55%; ms: m/z 271/273 (M^+); major fragments at m/z 270/272 (M-H), 256/258 (M-CH₃), 230/232 (M-CH₃CN), 162/164 ($M-C_6H_5N_2$), 109 ($M-C_5H_5ClN$) (Found: N, 14.87. $C_{15}H_{14}ClN_3$ requires N, 15.46).

6-Methoxy-4-methyl-2(3'-methylpyrazol-1'-yl)quinoline (**7**).

A mixture of 2-hydrazino-6-methoxy-4-methylquinoline **1c** (2.03 g, 0.01 mole) and acetylacetaldehyde dimethyl acetal (1.3 g, 0.01 mole) in ethanol (70 ml) was refluxed for 5-6 hours. A few drops of hydrochloric acid were then added to the reaction mixture which was further refluxed for 3 hours and the volume reduced. On cooling, a yellowish crystalline solid separated out which was filtered, washed with 10% sodium bicarbonate solution, then with aqueous ethanol and crystallized from ethanol, mp 140°; ms: m/z 253 (M^+); major fragments at m/z 238 (M-CH₃), 212 (M-CH₃CN), 172 ($M-C_6H_5N_2$), 81 ($M-C_{11}H_{10}NO$) (Found: N, 16.45. $C_{15}H_{15}N_3O$ requires N, 16.60).

4-(3'-Methylpyrazol-1'-yl)-2-methylquinoline (**4a**).

According to the above procedure reacted **1a** (1.73 g, 0.01 mole) to give the salt mp 115° (Found: C, 65.10; H, 5.12. $C_{14}H_{13}N_3 \cdot HCl$ requires C, 64.73; H, 5.39). The free base was obtained by treating the hydrochloride with 10% solution of sodium bicarbonate, mp 70°; ms: m/z 223 (M^+); major fragments at m/z 222

(M-H), 208 (M-CH₃), 182 (M-CH₃CN), 142 ($M-C_6H_5N_2$), 81 ($M-C_{10}H_8N$).

Similarly, compound **4b** was prepared by treating **1b** with acetylacetaldehyde dimethyl acetal and crystallized from ethanol, mp 115°, yield 52%; ms: m/z 243/245 (M^+); major fragments at m/z 242/244 (M-H), 228/230 (M-CH₃), 202/204 (M-CH₃CN), 162/164 ($M-C_6H_5N_2$), 81 ($M-C_5H_5ClN$), 135/137 (162-HCN) (Found: C, 63.86; H, 4.5. $C_{13}H_{10}ClN_3$ requires C, 64.0; H, 4.1).

2-Methyl-4-(pyrazol-1'-yl)quinoline (**5a**).

A mixture of **1a** (1.73 g, 0.01 mole) and malonaldehyde bis(dimethyl acetal) (1.6 g, 0.01 mole) in ethanol containing a few drops of hydrochloric acid was refluxed for 4-5 hours and the volume was reduced. On cooling, hydrochloride salt of **5a** was obtained, mp 108° (Found: C, 63.86; H, 5.25. $C_{13}H_{11}N_3 \cdot HCl$ requires C, 63.54; H, 4.8). It was then treated with 10% solution of sodium bicarbonate; ms: m/z 209 (M^+); major fragments at m/z 208 (M-H), 194 (M-CH₃), 182 (M-HCN), 142 ($M-C_5H_5N_2$), 67 ($M-C_{10}H_8N$).

Compound **5b** was similarly prepared by treating **1b** and malonaldehyde bis(dimethyl acetal), mp 110°; yield 50%; ms: m/z 229/231 (M^+); major fragments at m/z 228/230 (M-H), 194 (M-Cl), 202/204 (M-HCN), 162-164 ($M-C_5H_5N_2$), 67 ($M-C_5H_5ClN$) (Found: C, 62.3; H, 3.7. $C_{12}H_8ClN_3$ requires C, 62.7; H, 3.4).

6-Methoxy-4-methyl-2-(pyrazol-1'-yl)quinoline (**6**).

Following the procedure described for **5a** reacted **1c** (2.03 g, 0.01 mole) and malonaldehyde bis(dimethyl acetal) (1.6 g, 0.01 mole) to give the salt of **7** mp 210°. It was then treated with a 10% solution of sodium bicarbonate, filtered and crystallized from ethanol, mp 112° (yield 55%); ^{13}C nmr (deuteriochloroform) 145.82 (C-2), 121.63 (C-3), 148.31 (C-4), 112.53 (C-5), 157.05 (C-6), 102.42 (C-7), 130.24 (C-8), 130.65 (C-4a), 142.08 (C-8a), 151.36 (C-3'), 107.96 (C-4'), 127.67 (C-5'), 19.04 (CH₃-4), 55.45 (OCH₃-6), 13.87 (CH₃-3'); ms: m/z 239 (M^+); major fragments at m/z 224 (M-CH₃), 172 ($M-C_5H_5N_2$), 67 ($M-C_{11}H_{10}NO$) (Found: C, 70.30; H, 5.90. $C_{14}H_{13}N_3O$ requires, C, 70.29; H, 5.43).

Acknowledgements.

We are grateful to Dr. I. O. O. Korhonen, University of Jyväskylä, Finland for mass spectral data, Dr. S. K. Arora, University of Illinois, Chicago, USA for ^{13}C nmr spectral data and Dr. T. Marunaka, Taiho Pharmaceutical Co. Ltd., Japan for providing high-resolution and linked-scan data. We also thank CSIR, New Delhi, India, for providing financial assistance and the Chairman, Chemistry Department, Kurukshetra University, for providing laboratory facilities.

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