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Synthesis, ^{1}H and ^{13}C NMR assignment of novel 2-pyridone derivatives

Karam Chand,[a,b] Atul K. Sharma[a] and Sunil K. Sharma[a]*

Introduction

The synthesis of the 2-pyridone core structure is an attractive target for the synthetic organic chemist owing to its significance in medicinal chemistry.[1,2] In addition, 2-pyridone constitutes a structural component of several naturally occurring lead compounds, such as Huperzine A,[3] Fredericamycin A,[4] Camptothecin (CTP),[5] Ilicicolin H, and Pyridoxatin.[6] Many drugs containing pyridone skeleton have been released into the clinical world and a few more are under clinical trials, e.g. Amrinone,[7] Milrinone or Primacor[8] are used as cardiotonic agents for the treatment of heart failure, Perampanel[9] is used for the treatment of Parkinson's disease, Pirfenidone is used for the treatment of idiopathic pulmonary fibrosis, and Ciclopiroxolamine is used for the topical treatment of dermal infections.[10] The potential clinical applicability and comparatively low toxicity of 2-pyridones have led the interest of many researchers to explore the utility of this moiety for better and varied pharmacological activities. Apart from the medicinal properties, 2-pyridone derivatives serve as viable synthons to pyridine, piperidine, quinolizidine, and indolizidine alkaloids and pyridone-tethered systems for dyes and pigments.[11,12] Because the substitution of various functional groups on pyridin-2(1*H*)-one nucleus greatly affects the chemical shift values in the magnetic resonance of the proton and carbon nucleus, herein, we have synthesized a series of *N*-substituted derivatives of benzoylpyridin-2-(1*H*)-ones and studied the impact of the different substituents on the chemical shifts of the protons and carbons of pyridone ring using one-dimensional (1D) and two-dimensional (2D) NMR spectroscopic techniques. This study may be helpful for the data exploration and structural elucidation of newer naturally occurring and synthetic 2-pyridone derivatives.

Synthesis

A series of 32 pyridone derivatives described in this study were prepared by following Schemes 1 and 2. The required key intermediates (**12–16**) were synthesized starting from corresponding hydroxyacetophenone (**1–3**) by following the literature method.[13,14] In the case of dihydroxyacetophenone (**2–3**), first mono-acetylation was carried out using acetic-anhydride in basic condition to give substrate **4–5** so as to avoid the formylation of the benzene ring in the next step. 4-Oxo-4*H*-1-chromen-3-yl-carbaldehydes (**6–8**) were then synthesized using Vilsmeir–Haack formylation reaction. The formylation reaction was followed by the Knoevenagel condensation with malonic acid to yield the respective 4-oxo-4*H*-chromen-3-yl acrylic acid (**9–11**).The desired pyridone precursors, i.e. compounds **12–14,** were obtained by esterification of acrylyl acid derivatives of 4-oxo-4*H*-1-benzopyran (**9–11**) with ethanol under acidic condition (Scheme 2). The methylation of the phenolic group for compounds **13** and **14** with methyl iodide under basic conditions gave (*E*)-ethyl 3-(7/6-methoxy-4-oxo-4*H*-chromen-3-yl) acrylates (**15**/**16**). All of the compounds were well characterized from their physical and spectral data and by comparing the data with literature value for the known compounds.

The desired 2-pyridone derivatives (**17–34**) were synthesized by reacting (*E*)-ethyl-3-(4-oxo-4*H*-chromen-3-yl) acrylates (**12–16**) with various alkylamines, or diaminoalkanes in the presence of triethylamine. The reaction followed a two-step addition-elimination sequence in one pot. First, the opening of chromone ring occurs by the nucleophilic attack of the amine group followed by a rearrangement leading to the formation of 2-pyridone ring (Scheme 2).

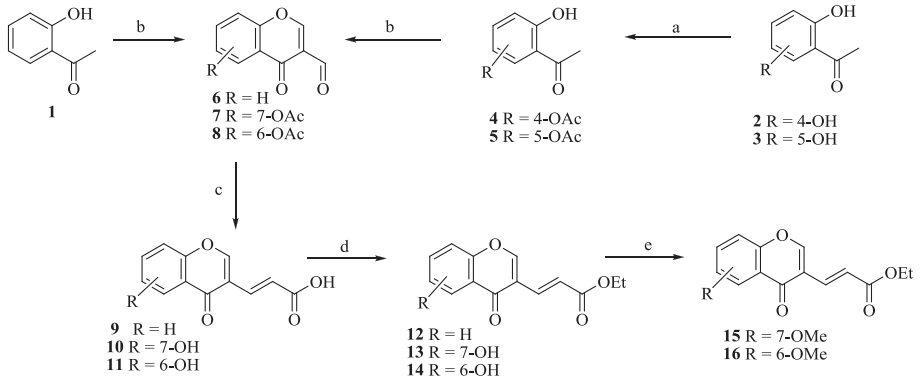
Experimental

The ^{1}H and ^{13}C NMR spectra were recorded either on Jeol-400 (400 MHz, 100.5 MHz) NMR spectrometer (JEOL USA, Inc.) or Bruker Avance-300 (300 MHz, 75.5 MHz) and Bruker Avance-400 (400 MHz, 100.5 MHz) spectrometers (Bruker Corporation, USA) using $CDCl_3$ as solvent as well as an internal standard. The concentration of all samples was approximately 10–15 mg/0.5 ml of $CDCl_3$ in 2.5-mm NMR tube for spectral analysis, and the chemical shifts were referenced to either the residual solvent peak (for ^{1}H NMR) or the peak for dutereated solvent (for ^{13}C NMR). The NMR data were recorded at 296–299 K, with chemical shifts (δ) reported in parts per million and coupling constants (*J*) in hertz. Signals are expressed as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad singlet (br s), and broad multiplet (br m). The instrumental settings for the Jeol-400 spectrometer were as follows: for the ^{1}H spectrum, relaxation delay (RD) = 4.0 s, acquisition time (AQ) = 1.36 s, pulse width = 11.57 μs, flip angle = 45°, digital resolution (DR) = 0.73 Hz, and spectral width = 30 ppm. For the ^{13}C spectrum, RD = 2 s, AQ = 1.0 s, pulse width = 11.75 μs, flip angle = 30°, DR = 0.95 Hz, and spectral width = 314 ppm. The instrumental settings for Bruker Avance-300 and Bruker Avance-400 spectrometers in proton NMR were as follows: RD = 1.0 s, AQ = 1.0 or 5.3 s; pulse width = 11.0 μs; DR = 0.30 Hz; spectral width = 19 or 20 ppm, and for ^{13}C were as follows: RD = 2.0 s, AQ = 1.8 s, pulse width = 8 μs, DR = 1.0 or 2.0 Hz,

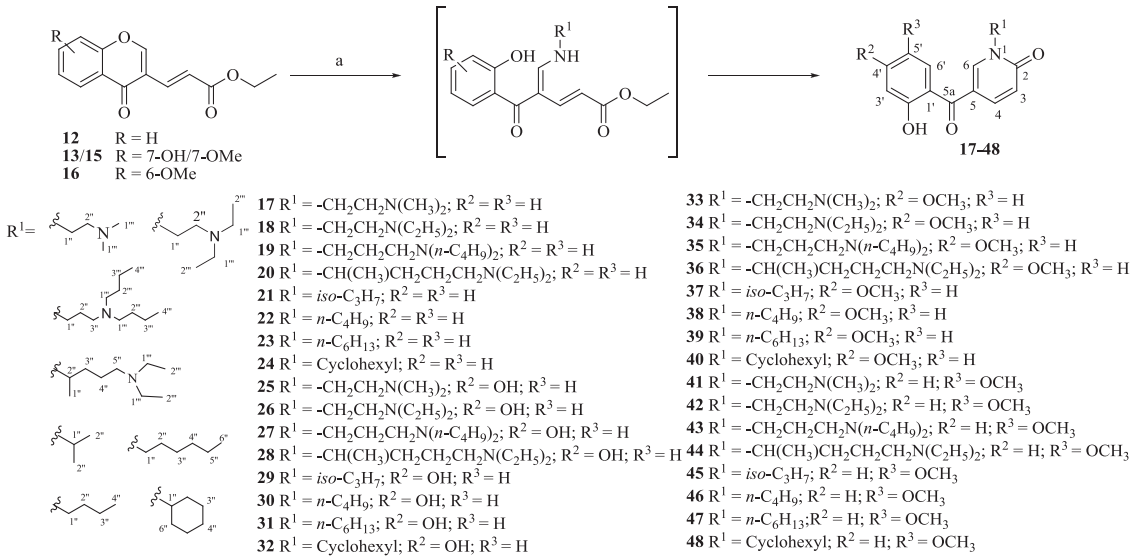
* *Correspondence to: Sunil K. Sharma, Department of Chemistry, University of Delhi, Delhi 110 007, India. E-mail: sksharma90@chemistry.du.ac.in*

a *Department of Chemistry, University of Delhi, Delhi 110007, India*

b *Centro de Quimica Estrutural, Instituto Superior Técnico, Universidade Técnica de Lisboa, Av. RoviscoPais 1, 1049-001, Lisboa, Portugal*



Scheme 1. Synthesis of (*E*)-alkyl 3-(4-oxo-4*H*-chromen-3-yl)acrylate; reagents and conditions: (a) Ac_2O, pyridine, 6 h; (b) $POCl_3$, *N*,*N*-Dimethylformamide, 50 °C, 13 h; (c) $CH_2(COOH)_2$, pyridine, 1.5 h; (d) EtOH, conc. H_2SO_4 (2–3 drops), 12 h; (e) CH_3I, K_2CO_3, anhyd. acetone, reflux, 12 h.



Scheme 2. Synthesis of pyridin-2(1*H*)-one derivatives; reagents and conditions: (a) R^1NH_2, NEt_3, C_2H_5OH, reflux, 4–5 h.

and spectral width = 239 or 250 ppm. For 2D experiments, such as COSY and HMQC, all data points ($t_2 \times t_1$) were acquired with 2 K × 256 as per literature method.[15,16] In all 2D experiments, the solvent resonance was suppressed by presaturation during the relaxation delay. The high-resolution mass spectroscopy (HRMS) was recorded on Agilent-6210 ES-TOF, JEOL JMX-SX-102A, and Waters LCT Micromass-KC455. The organic solvents were dried and distilled prior to their use. Reactions were monitored by performing thin-layer chromatography (TLC) on silica coated aluminium plates (Merck silica gel 60 F_{254}); the spots were visualized either by UV light or by spraying with 5% alcoholic $FeCl_3$ solution. Silica gel (100–200 mesh) was used for column chromatography. All of the chemicals and reagents were procured from Spectrochem Pvt. Ltd., India and Sigma-Aldrich Chemicals Pvt. Ltd., USA. Melting points were measured with a Buchi M-560 apparatus (BÜCHI Labortechnik AG, Flawil, Switzerland) and are uncorrected.

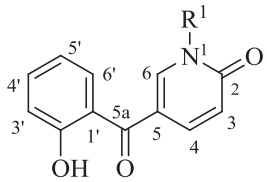
General procedure for the synthesis of *N*-substituted pyridone derivatives (17–48)

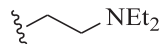
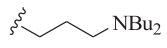
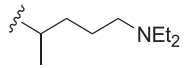
To a solution of (4-oxo-4*H*-chromen-3-yl) acrylate (**12–13** & **15–16**) (4 mmol) and aminoalkane/diaminoalkane (4.2 mmol) in ethanol (70 ml) was added triethylamine (2 drops), and the reaction mixture was refluxed for 4–5 h. The progress of the reaction was monitored on TLC. On completion of the reaction, the mixture was cooled to room temperature, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel (100–200 mesh) in 20–40% ethyl acetate/petroleum ether to give 2-pyridone derivatives (**17–48**) in 74–85% yield.

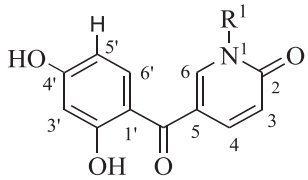
Results and discussion

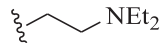
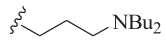
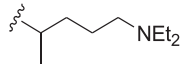
All the compounds described in Scheme 2 were characterized from their spectral data. The peak assignments in ^1H and ^{13}C NMR spectra were carried by comparing the data with theoretical values obtained from ChemDraw 10.0 (PerkinElmer, USA) as well the literature reports. Also, additional experiments, e.g. COSY, HMQC, and DEPT analysis were used for the peak assignment, the spectroscopic data are compiled in Tables 1–4. The constitution of compounds was further confirmed by the HRMS data as summarized in Table 5 along with their melting points. Analysis of the proton NMR data (Tables 1 and 2) reveals that in all the *N*-substituted benzoylpyridin-2-(1*H*)-one derivatives, H-6 of pyridone ring

Table 1. ^{1}H NMR chemical shifts (δ in ppm) of aromatic region of all compounds with multiplicities and coupling constants (*J* in Hz)



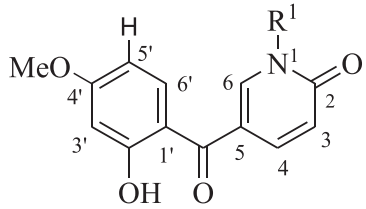
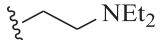
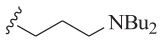
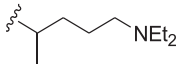
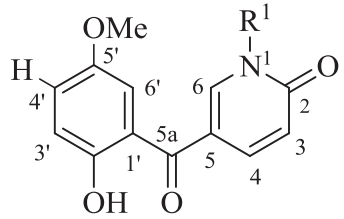
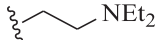
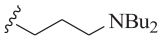
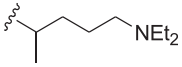
Compd.	R^1	H-3	H-4	H-6	H-3′	H-4′	H-5′	H-6′	OH
17		6.61 (d, 9.6)	7.82 (dd, 2.1, 9.6)	7.99 (d, 2.1)	7.07 (d, 7.5)	7.51 (t, 7.5)	6.91 (t, 7.5)	7.70 (d, 7.5)	11.54 (br s)
18		6.61 (d, 9.3)	7.82 (dd, 2.4, 9.3)	8.01 (br s)	7.07 (d, 7.5)	7.51 (t, 7.5)	6.91 (t, 7.5)	7.69 (d, 7.5)	11.55 (br s)
19		6.61 (d, 9.6)	7.77 (dd, 2.7, 9.6)	8.06 (br s)	7.08 (d, 8.4)	7.49–7.59 (m, H-4′, H-6′)	6.93 (t, 7.6)	7.49–7.59 (m, H-4′, H-6′)	absent
20		6.62 (d, 9.6)	7.82 (dd, 2.1, 9.6)	7.92 (d, 2.1)	7.06 (d, 7.5)	7.50 (t, 7.5)	6.95 (t, 7.5)	7.70 (d, 7.5)	11.06
21	-CH(Me)$_2$	6.58 (d, 9.5)	7.70 (d, 9.5)	7.97 (s)	7.05 (d, 8.4)	7.47–7.53 (m, H-4′, H-6′)	6.91 (t, 7.6)	7.47–7.53 (m, H-4′, H-6′)	11.44 (br s)
22	*n*-C$_4$H$_9$	6.54 (d, 9.6)	7.70 (dd, 2.7, 9.6)	7.87 (d, 2.7)	7.01 (d, 7.3)	7.45–7.51 (m, H-4′, H-6′)	6.87 (t, 6.9)	7.45–7.51 (m, H-4′, H-6′)	11.38 (br s)
23	*n*-C$_6$H$_{13}$	6.61 (d, 9.6)	7.76 (dd, 2.4, 9.6)	7.93 (d, 2.4)	7.07 (d, 8.1)	7.50–7.58 (m, H-4′, H-6′)	6.94 (t, 7.5 H-5′)	7.50–7.58 (m, H-4′, H-6′)	11.43 (br s)
24		6.61 (d, 9.3)	7.72 (d, 9.3)	7.99 (s)	7.08 (d, 8.1)	7.50–7.55 (m, H-4′, H-6′)	6.94 (t, 7.3)	7.50–7.55 (m, H-4′, H-6′)	11.48 (br s)



25		6.48 (d, 9.6)	7.74 (dd, 2.3, 9.6)	8.18 (d, 2.3)	6.37 (d, 2.3)	—	6.40 (dd, 2.3, 8.8)	7.53 (d, 8.8)	11.21 (br s)
26		6.64 (d, 9.3)	7.78 (d, 9.3)	7.95 (s)	6.45 (br s)	—	6.36 (d, 8.1)	7.53 (d, 8.4)	absent
27		6.61 (d, 9.6)	7.72 (d, 9.6)	7.89 (s)	6.26	----------	6.29 (m, H-3′, H-5′)	7.35 (d, 8.7)	10.62 (br s)
28		6.50 (d, 9.5)	7.58 (dd, 2.2, 9.5)	7.77 (d, 2.2)	6.18	----------	6.20 (m, H-3′, H-5′)	7.20 (d, 9.2)	10.04
29	-CH(Me)$_2$	6.42 (d, 9.6)	7.65 (dd, 2.4, 9.6)	8.07 (d, 2.4)	6.32	----------	6.36 (m, H-3′, H-5′)	7.36 (d, 8.8)	11.42 (br s)
30	*n*-C$_4$H$_9$	6.41 (d, 9.6)	7.67 (dd, 2.4, 9.6)	8.18 (d, 2.4)	6.31	----------	6.36 (m, H-5′, H-3′)	7.38 (d, 8.8)	11.34 (br s)
31	*n*-C$_6$H$_{13}$	6.41 (d, 9.6)	7.67 (dd, 2.4, 9.6)	8.18 (d, 2.4)	6.32	----------	6.36 (m, H-5′, H-3′)	7.38 (d, 8.4)	11.36 (br s)

(Continues)

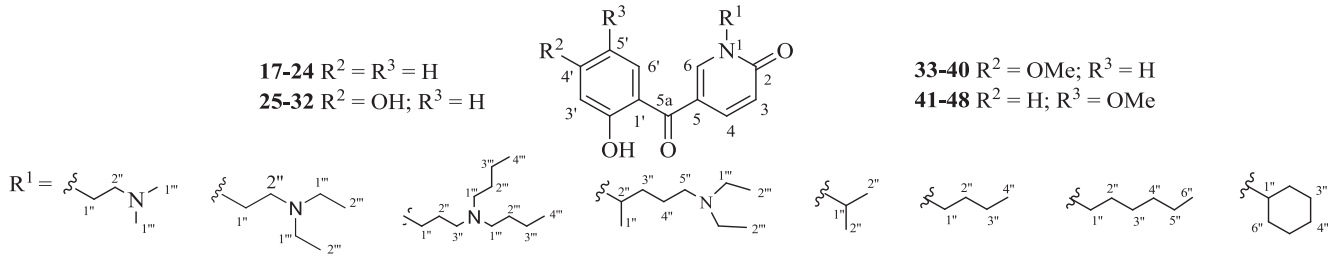
Table 1. (Continued)

Compd.	R^1	H-3	H-4	H-6	H-3′	H-4′	H-5′	H-6′	OH
32		6.66 (d, 9.3)	7.72 (dd, 2.4, 9.3)	7.96 (d, 2.4)	6.54 (d, 2.4)	—	7.47 (dd, 2.4, 8.8)	7.43 (d, 8.8)	12.19 (br s)
									
33		6.58 (d, 9.5)	7.73 (dd, 3.0, 9.5)	7.88 (d, 3.0)	6.48 (d, 2.9)	—	6.41 (dd, 2.9, 8.8)	7.61 (d, 8.8)	12.30 (br s)
34		6.56 (d, 9.5)	7.72 (dd, 2.9, 9.5)	7.89 (d, 2.9)	6.47 (d, 2.2)	—	6.41 (dd, 2.2, 8.8)	7.59 (d, 8.8)	12.33 (br s)
35		6.49 (d, 9.5)	7.63 (dd, 2.9, 9.5)	7.91 (d, 2.9)	6.42 (d, 2.2)	—	6.37 (dd, 2.2, 8.8)	7.42 (d, 8.8)	12.10 (br s)
36		6.49 (d, 9.5)	7.58 (dd, 2.2, 9.5)	7.77 (d, 2.2)	6.41 (d, 2.2)	—	6.36 (dd, 2.2, 8.8)	7.37 (d, 8.8)	absent
37	-$CH(Me)_2$	6.55 (d, 9.5)	7.64 (dd, 2.9, 9.5)	7.89 (d, 2.9)	6.48 (d, 2.2)	—	6.42–6.45 (m)	7.43 (d, 8.8)	11.57 (br s)
38	*n*-C_4H_9	6.53 (dd, 2.2, 9.5)	7.64 (dd, 2.9, 9.5)	7.82 (d, 2.9)	6.45 (d, 2.2)	—	6.41 (dd, 2.2, 8.8)	7.43 (d, 8.8)	12.17 (br s)
39	*n*-C_6H_{13}	6.55 (d, 9.5)	7.66 (dd, 2.9, 9.5)	7.83 (d, 2.9)	6.47 (d, 2.2)	—	6.43 (dd, 2.2, 8.8)	7.45 (d, 8.8)	12.19 (br s)
40		6.56 (d, 9.5)	7.63 (dd, 2.9, 9.5)	7.89 (d, 2.9)	6.48 (d, 2.2)	—	6.44 (dd, 2.2, 8.8)	7.43 (d, 8.8)	12.22 (br s)
									
41		6.67 (d, 9.5)	7.88 (dd, 2.9, 9.5)	8.06 (d, 2.9)	7.07 (d, 8.8)	7.19 (dd, 2.9, 8.8)	—	7.24 (d, 2.9)	11.00 (br s)
42		6.56 (d, 9.7)	7.77 (dd, 2.4, 9.7)	8.01 (d, 2.4)	7.08–7.12 (m, H-3′, H-6′)	7.0 (d, 1.2, 7.9)	—	7.08–7.12 (m, H-3′, H-6′)	absent
43		6.57 (d, 9.7)	7.75 (dd, 2.4, 9.7)	8.05 (d, 2.4)	6.98–7.01 (m, H-3′, H-6′)	7.11 (dd, 3.4, 9.2)	—	6.98–7.01 (m, H-3′, H-6′)	10.91
44		6.58 (d, 9.7)	7.74 (dd, 2.4, 9.7)	7.92 (d, 2.4)	6.99 (d, 8.5)	7.11 (dd, 3.0, 8.5)	—	6.96 (d, 3.0)	absent

45	-$CH(Me)_2$	6.52 (d, 9.5)	7.68 (dd, 2.2, 9.5)	7.96 (d, 2.2)	6.91–6.93 (m, H-4′, H-6′)	7.06 (dd, 2.9, 9.5)	—	6.91–6.93 (m, H-4′, H-6′)	10.86 (br s)
46	*n*-C_4H_9	6.48 (d, 9.5)	7.67 (dd, 2.9, 9.5)	7.90 (d, 2.9)	6.88–6.92 (m, H-3′, H-6′)	7.03 (dd, 2.2, 9.5)	—	6.88–6.92 (m, H-3′, H-6′)	10.77
47	*n*-C_6H_{13}	6.57 (d, 9.5)	7.73 (dd, 2.9, 9.5)	7.93 (d, 2.9)	6.97–7.00 (m, H-3′, H-6′)	7.12 (dd, 2.8, 8.7)	—	6.97–7.00 (m, H-3′, H-6′)	10.88 (br s)
48		6.56 (d, 9.5)	7.70 (d, 2.2, 9.5)	7.98 (d, 2.2)	6.95–6.98 (m)	7.09 (d, 2.2, 8.8)	—	6.94 (d, 2.9)	10.93 (br s)

appeared most deshielded either as a singlet or *meta* coupled doublet in the range of 7.77–8.18 ppm due to the proximity of the associated carbon with the electronegative nitrogen. While the chemical shift value of H-4, which appeared as *ortho* coupled doublet or *ortho-meta* coupled doublet of doublet, was found to be in the lower frequency region (7.58–7.77 ppm) as compared with H-6. The chemical shift value for this proton was further confirmed by the COSY spectra (see Supporting Information). Furthermore, it has been observed that H-3 exhibit a significant change in the chemical shift value with the introduction/positional shift of the functional group in the benzoyl ring. For 5-(2′-hydroxy-benzoyl)/(2′-hydroxy-5′-methoxy-benzoyl)-1*H*-pyridin-2-one derivatives, H-3 appears in lower frequency region with respect to the aromatic protons of benzoyl ring, however, in the case of 5-(2′,5′-dihydroxy-benzoyl)/(2′-hydroxy-5′-methoxy-benzoyl)-1*H*-pyridin-2-ones, H-3 appeared at the higher frequency region in comparison to the H-3′ and H-4′ of the benzoyl ring. Interestingly, the coupling constant of the *ortho* coupled protons (H-3 and H-4) of 2-pyridone ring was observed in the range of 9.3–9.5 Hz, whereas lower coupling constant in the range of 7.5–8.8 Hz was observed for the *ortho* coupled protons of benzoyl ring; this information may be used to distinguish the 2-pyridone ring's protons from the benzoyl ring's protons, apart from the 2D (COSY) NMR analysis. The hydroxyl group at the C-2′ of the benzoyl ring was observed to appear significantly deshielded (10.04–12.33 ppm) due to the chelation with the neighboring carbonyl group(C-1′). The chemical shifts of all protons of the alkyl chain are summarized in Table 2. The methylene group linked to heterocyclic nitrogen (H-1″ and H-2″) appeared as a triplet or multiplet in the high frequency region (3.91–5.28 ppm) and the corresponding carbon (C-1″) was observed in the range 47–55 ppm. The chemical shift values of the carbons of the 2-pyridone derivatives (**17–48**) are also summarized in Tables 3, , 4. The presence of a characteristic peak in the range of 192–195 ppm in the proton noise decoupled ^{13}C NMR spectra of all the synthesized 2-pyridone derivatives confirms the linkage of benzoyl ring to pyridone ring. The ^{1}H–^{13}C correlation spectra reveals that C-6 appears slightly deshielded than that of C-4, i.e. the C-6 and C-4 of 2-pyridone ring lies in the range of 139–145 and 137–139 ppm, respectively. The quaternary carbons, C-5 and C-1′ appeared in the range 115–118 and 110–119 ppm, respectively. The impact of the additional hydroxy/methoxy group or change in the position of the functional group is clearly observed on the chemical shift values of C-1′-C-6′ carbons of benzoyl ring (Table 3). The chemical shift values of C-1′ of 5-(2-hydroxy-benzoyl)-2-pyridones were observed in the range 118–120 ppm; however, the introduction of the additional OH or OMe group at C-4′ or C-5′ position of benzoyl ring led to a shift of C-1′ by 5–7 ppm towards the low frequency region. It has been observed that the presence of a hydroxyl group at C-4′ results shielding of C-3 of the 2-pyridone ring by 10–11 ppm, whereas introduction of the methoxy group at C-4′ or C-5′ did not show any significant change in the chemical shift in any of the 2-pyridone ring carbons. Further, the *N* alkylation of 2-pyridone derivatives showed no significant impact on the δ value of 2-pyridone or benzoyl ring. The ^{1}H-^{13}C correlation spectra of the *N*,*N*-dialkyl amino alkyl substituted pyridone derivatives showed that the C-1″ carbon attached to the nitrogen of 2-pyridone ring appears shielded in comparison to the carbon attached to the nitrogen of alkyl amine. The ^{1}H and ^{13}C NMR chemical shift values of all the remaining protons and carbons of 2-pyridone derivatives were also assigned as shown in Tables 1–5 and confirmed by ^{1}H–^{1}H and ^{1}H–^{13}C correlation spectroscopy.

Table 2. ^{1}H NMR chemical shifts (δ in ppm) of the aliphatic region of all synthesized compounds with multiplicities and coupling constants (*J* in Hz)



Compd	R1	H-1″	H-2″	H-3″	H-4″	H-5″	H-6″	H-1‴	H-2‴	H-3‴	H-4‴	OMe
17	NMe_2	4.05 (t, 5.4)	2.66 (t, 5.4)	—	—	—	—	2.30 (s)	—	—	—	—
18	NEt_2	3.99–4.00 (m)	2.77–2.79 (m)	—	—	—	—	2.56 (q, 6.9)	0.93 (t, 6.9)	—	—	—
19	NBu_2	4.07 (t, 7.05)	1.88–1.97 (m)	2.43 (t, 6.6)	—	—	—	2.35 (t, 7.2)	1.18------1.38 (1, H-2‴-H-3‴)		0.87 (t, 7.05)	
20	NEt_2	1.39–1.42 (m, 6.9)	5.23–5.26 (m)	1.80–1.82 (m)	1.62 (br s)		2.61----------2.78 (m, H-5″, H-1‴)		1.09 (t, 6.9)	—	—	—
21	$-CH(Me)_2$	5.25–5.28 (m)	1.38 (d, 6.8)	—	—	—	—	—	—	—	—	—
22	*n*-C_4H_9	3.94 (t, 7.3)	1.69–1.73 (m)	1.18–1.37 (m)	0.90 (t, 7.3)	—	—	—	—	—	—	—
23	*n*-C_6H_{13}	3.99 (t, 7.3)	1.76–1.81 (m)	1.34 (br m, H-5″, H-4″, H-3″)	0.89 (t, 6.6)	—	—	—	—	—		
24		4.89 (br s)	1.90–2.00 (m, H-2″, H-6″)	1.18–1.78 (m, H-3″, H-4″, H-5″)	1.90–2.00 (m, H-2″, H-6″)	—	—	—	—	—		
25	NMe_2	4.07 (t, 5.5)	2.54 (t, 5.5)	—	—	—	—	2.23 (s)	—	—	—	—
26	NEt_2	4.08 (br s)	2.86 (br s)	—	—	—	—	2.63 (q, 6.9)	0.99 (t, 6.9)	—	—	—
27	NBu_2	4.07 (t, 6.6)	2.02–2.05 (m)	2.53–2.65 (m) (H-1‴, H-3″)	—	—	—	2.53–2.65 (m) (H-1‴, H-3″)	1.26---------1.45 (m, H-2‴ H-3‴)		0.89 (t, 7.2),	
28	NEt_2	1.34 (d, 6.9)	5.13–5.14 (m)	1.68–1.72 (m)	1.46–1.50 (m)		2.53----------2.69 (m, H-5″, H-1‴)		1.04 (t, 6.6)	—	—	—
29	$-CH(Me)_2$	4.95–5.02 (m)	1.28 (d, 6.8)	—	—	—	—	—	—	—	—	—
30	*n*-C_4H_9	3.92 (t, 7.2)	1.57–1.61 (m)	1.22–1.28 (m)	0.85 (t, 7.2)	—	—	—	—	—	—	—
31	*n*-C_6H_{13}	3.91 (t, 7.2)	1.58–1.61 (m)	1.22 (br m, H-3″, H-4″, H-5″)			0.81 (t, 6.8)	—	—	—	—	—
32		4.89–4.93 (m)	1.92–2.05 (m, H-2″, H-6″)	1.43–1.80 (m, H-3″, H-4″, H-5″)			1.92–2.05 (m, H-2″, H-6″)	—	—	—	—	—
33	NMe_2	4.02 (t, 5.5)	2.63 (t, 5.5)	—	—	—	—	2.27 (s)	—	—	—	3.84 (s)

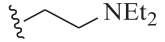
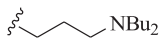
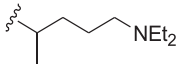
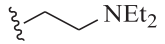
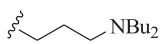
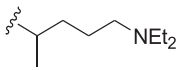
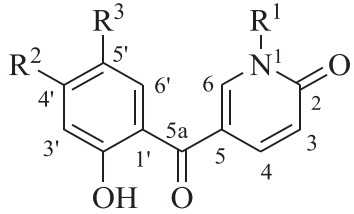
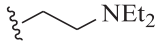
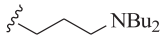
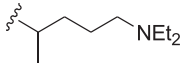
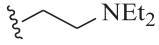
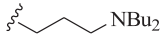
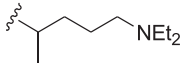
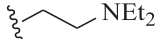
34		3.94 (t, 5.1)	2.73 (t, 5.1)	—	—	—	—	2.52 (q, 6.6)	0.89 (t, 6.6)	—	—	3.83 (s)
35		3.98 (t, 6.6)	1.82–1.86 (m)	2.35 (t, 6.6)	—	—	—	2.28 (t, 6.6 Hz)	1.38--------1.28 (m, H-2‴- H-3‴)	0.78 (t, 7.7)		3.78 (s)
36		1.30 (d, 6.6)	5.07–5.12 (m)	1.61–1.67 (m)	1.32–1.43 (m)		2.35----------2.46 (m, H-5″, H-1‴)		0.91 (t, 7.6)	—	—	3.77 (s)
37	-$CH(Me)_2$	5.21–5.28 (m)	1.37 (d, 6.6)	—	—	—	—	—	—	—	—	3.83 (s)
38	*n*-C_4H_9	3.94 (t, 8.0)	1.68–1.73 (m)	1.32–1.37 (m)	0.91 (t, 7.3)	—	—	—	—	—	—	3.81 (s)
39	*n*-C_6H_{13}	3.95 (t, 7.7)	1.72–1.76 (m)	1.28----------1.33 (m, H-3″, H-4″, H-5″)			0.85 (t, 7.3)	—	—	—	—	3.83 (s)
40		4.83–4.89 (m)	1.86–1.96 (m, H-2″- H-4″)	1.15–1.74 (m, H-3″, H-4″, H-5″)			1.86–1.96 (m, H-2″- H-4″)	—	—	—	—	3.69 (s)
41		4.11 (t, 5.5)	2.72 (t, 5.5)	—	—	—	—	2.36 (s)	—	—	—	3.84 (s)
42		3.98 (t, 5.5)	2.75 (t, 5.5)	—	—	—	—	2.53 (q, 6.7)	0.89 (t, 6.7)			3.74 (s)
43		4.04 (t, 6.6)	1.85–1.92 (m)	2.41 (t, 6.6)	—	—	—	2.32 (t, 7.4)	1.18-------1.33 (m, H-2‴-H-3‴)	0.84 (t, 7.0)		3.74 (s)
44		1.35–1.46 (m, H-1″, H-4″)	5.14–5.18 (m)	2.42–2.46 (m)	1.35–1.46 (m, H-1″, H-4″)		2.49----------2.54 (m, H-5″, H-1‴)		0.99 (t, 6.7)	—	—	3.74 (s)
45	-$CH(Me)_2$	5.22 (q, 6.2)	1.35 (d, 6.2)	—	—	—	—	—	—	—	—	3.68 (s)
46	*n*-C_4H_9	3.91 (t, 6.6)	1.66–1.70 (m)	1.28–1.35 (m)	0.88 (t, 7.3)	—	—	—	—	—	—	3.67 (s)
47	*n*-C_6H_{13}	3.96 (t, 7.3)	1.72–1.79 (m)	1.28–1.36 (br m, H-3″, H-4″, H-5″)			0.86 (t, 6.8)	—	—	—	—	3.74 (s)
48		4.82–4.88 (m)	1.86–1.96 (m, H-2″- H-4″)	1.18–1.74 (m, H-3″, H-5″)			1.86–1.96 (m, H-2″- H-4″)	—	—	—	—	3.72 (s)

Table 3. ^{13}C NMR chemical shift (δ in ppm) of the aromatic region of all the synthesized 2-pyridone derivatives

17-24 $R^2 = R^3 = H$
25-32 $R^2 = OH$; $R^3 = H$



33-40 $R^2 = OMe$; $R^3 = H$
41-48 $R^2 = H$; $R^3 = OMe$

Compd.	R^1	C-5a	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
17		195.2	161.9	118.6	138.9	116.1	145.0	118.9	162.5	118.7	135.9	119.8	131.8
18		195.2	162.1	118.7	139.1	115.8	145.4	118.9	162.5	118.8	135.9	119.5	131.7
19		195.2	162.1	118.7	138.9	116.8	144.4	118.9	162.4	118.8	136.0	119.8	131.5
20		195.1	162.2	118.5	138.3	117.7	139.7	119.5	162.5	119.0	135.8	119.6	131.3
21	-$CH(Me)_2$	195.3	161.8	118.8	138.3	117.5	139.5	118.9	162.5	118.9	136.2	119.7	131.6
22	n-C_4H_9	195.2	162.0	118.7	138.9	117.1	143.4	118.8	162.4	118.9	136.2	119.9	131.5
23	n-C_6H_{13}	195.2	161.9	118.7	138.8	117.0	143.4	118.8	162.3	118.7	136.1	119.9	131.5
24		195.3	161.4	118.8	138.1	117.1	139.9	119.6	162.5	118.9	136.1	119.6	131.5
25		192.7	161.1	107.9	139.0	115.6	145.3	112.7	163.0	102.8	164.2	118.5	133.9
26		193.2	161.7	108.3	139.6	115.9	146.2	113.6	163.3	103.3	164.4	118.7	134.2
27		193.1	162.4	109.6	139.7	118.4	142.2	111.2	165.9	103.8	166.9	119.6	134.1
28		192.9	162.1	109.6	137.8	118.6	138.7	110.8	165.8	103.7	167.5	119.0	133.9
29	-$CH(Me)_2$	192.9	161.4	108.5	138.9	117.6	140.6	114.3	162.5	103.3	164.2	118.9	134.2
30	*n*-C_4H_9	192.9	161.8	108.4	139.6	117.3	144.9	114.3	162.5	103.3	164.2	119.0	134.2
31	*n*-C_6H_{13}	192.9	161.8	108.4	139.6	117.3	144.9	114.2	162.6	103.3	164.2	119.1	134.2
32		192.0	160.5	107.6	137.9	116.6	140.0	113.4	161.6	102.4	163.4	118.0	133.3
33		193.9	161.9	119.7	138.9	116.2	144.0	112.6	165.8	101.1	165.9	107.4	133.5
34		193.9	162.0	119.4	139.1	116.0	144.4	112.6	165.8	101.2	165.9	107.5	133.4

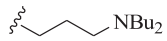
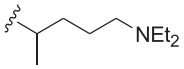
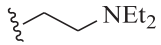
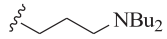
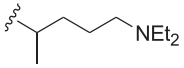
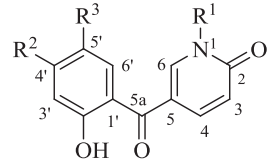
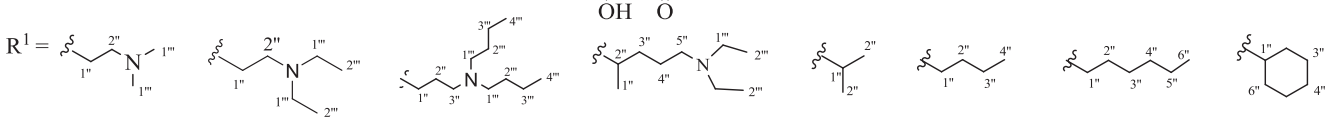
35		193.7	161.9	119.5	138.8	116.9	143.4	112.4	165.5	101.2	165.9	107.3	133.2
36		193.8	161.9	119.5	138.1	117.7	138.6	112.5	165.5	101.3	165.9	107.4	133.1
37	-$CH(Me)_2$	194.0	161.6	119.5	138.2	117.6	138.4	112.5	165.7	101.4	166.0	107.4	133.2
38	*n*-C_4H_9	193.8	161.9	119.7	138.8	117.3	142.5	112.4	165.6	101.3	166.0	107.4	133.2
39	*n*-C_6H_{13}	193.8	161.9	119.9	138.8	117.3	142.5	112.5	165.7	101.3	166.0	107.5	133.2
40		194.0	161.6	119.4	138.1	117.4	138.9	112.5	165.7	101.4	166.0	107.4	133.2
41		194.8	161.9	116.4	138.9	116.2	144.9	118.9	151.6	119.7	122.1	156.2	119.1
42		194.8	162.0	115.9	138.9	116.0	145.2	118.9	151.6	119.2	122.32	156.1	119.2
43		194.7	162.00	114.7	138.7	116.8	144.3	118.6	151.6	119.7	123.2	156.3	119.4
44		194.2	162.1	114.4	138.1	117.6	139.8	119.3	151.8	121.1	122.9	155.4	119.6
45	-$CH(Me)_2$	194.5	161.5	113.9	137.9	117.2	139.2	118.4	151.5	119.4	123.4	156.1	119.3
46	*n*-C_4H_9	194.5	161.8	114.5	138.6	116.9	143.3	118.6	151.5	119.6	123.1	155.9	119.2
47	*n*-C_6H_{13}	194.5	161.8	114.5	138.6	116.9	143.3	118.5	151.5	119.7	123.1	156.8	119.3
48		194.8	161.6	114.1	137.9	117.0	139.8	118.4	151.6	119.5	123.7	156.4	119.5

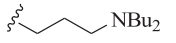
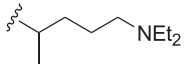
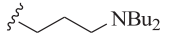
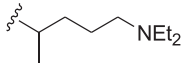
Table 4. ^{13}C NMR chemical shift (δ in ppm) of the aliphatic region of all the synthesized 2-pyridone derivatives



17-24 $R^2 = R^3 = H$
25-32 $R^2 = OH$; $R^3 = H$
33-40 $R^2 = OMe$; $R^3 = H$
41-48 $R^2 = H$; $R^3 = OMe$

$R^1 =$



Compd.	R^1	C-1″	C-2″	C-3″	C-4″	C-5″	C-6″	C-1‴	C-2‴	C-3‴	C-4‴	OMe
17		47.2	57.8	—	—	—	—	45.5	—	—	—	—
18		49.2	51.1	—	—	—	—	47.7	12.00	—	—	—
19		49.0	28.8	53.3	—	—	—	50.5	26.4	20.7	14.0	—
20		20.3	51.7	29.6	22.1	46.5	—	33.7	9.8	—	—	—
21	-$CH(Me)_2$	47.5	22.1	—	—	—	—	—	—	—	—	—
22	*n*-C_4H_9	50.5	31.3	19.8	13.6	—	—	—	—	—	—	—
23	*n*-C_6H_{13}	50.7	31.3	29.6	26.2	22.4	13.9	—	—	—	—	—
24		54.8	32.6	25.6	25.2	25.7	32.6	—	—	—	—	—
25		46.1	57.2	—	—	—	—	45.1	—	—	—	—
26		48.1	50.7	—	—	—	—	47.3	12.3	—	—	—
27		48.6	29.7	52.8	—	—	—	50.3	26.2	20.6	13.9	—
28		20.3	50.4	29.5	22.1	45.9	—	33.7	9.6	—	—	—
29	-$CH(Me)_2$	47.8	21.6	—	—	—	—	—	—	—	—	—
30	*n*-C_4H_9	49.4	31.2	19.7	14.1	—	—	—	—	—	—	—
31	*n*-C_6H_{13}	49.7	31.3	29.1	26.1	22.5	14.4	—	—	—	—	—
32		54.2	30.9	25.0	24.2	25.0	30.9	—	—	—	—	—
33		47.1	55.6	—	—	—	—	45.4	—	—	—	57.7

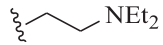
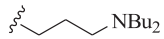
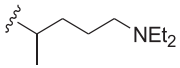
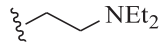
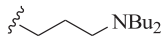
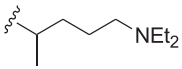
34		49.1	50.9	—	—	—	—	47.6	11.9	—	—	55.6
35		48.7	28.6	53.1	—	—	—	50.3	26.2	20.5	13.9	55.5
36		20.9	51.9	33.9	23.4	46.5	—	46.5	11.1	—	—	55.5
37	-$CH(Me)_2$	47.2	21.9	—	—	—	—	—	—	—	—	55.6
38	*n*-C_4H_9	50.3	31.6	19.7	13.5	—	—	—	—	—	—	55.6
39	*n*-C_6H_{13}	50.6	31.2	29.2	26.2	22.4	13.9	—	—	—	—	55.6
40		54.5	31.5	25.6	25.1	25.6	31.5	—	—	—	—	55.6
41		47.4	56.0	—	—	—	—	45.2	—	—	—	57.7
42		49.2	50.7	—	—	—	—	47.6	11.8	—	—	55.9
43		48.9	28.8	53.2	—	—	—	50.5	26.4	20.6	13.9	55.9
44		20.5	51.8	33.8	22.7	46.4	—	—	10.4	—	—	55.9
45	-$CH(Me)_2$	47.2	21.8	—	—	—	—	—	—	—	—	55.6
46	*n*-C_4H_9	50.2	31.2	19.7	13.5	—	—	—	—	—	—	55.7
47	*n*-C_6H_{13}	50.5	31.5	29.2	26.5	22.4	13.9	—	—	—	—	55.7
48		54.6	32.5	25.5	25.1	25.5	32.5	—	—	—	—	55.8

Table 5. High-resolution mass spectroscopy and melting point of all synthesized 2-pyridone derivatives

Compd.	Molecular formula	Mass (m/z) calcd/found	Melting point in °C	Compd.	Molecular formula	Mass (m/z) calcd/found	Melting point in °C
17	$C_{16}H_{18}N_2O_3$	287.1396 $[M+H]^+$ /287.1398	146–148	**33**	$C_{17}H_{20}N_2O_4$	317.1496 $[M+H]^+$ /317.1425	150–152
18	$C_{18}H_{22}N_2O_3$	315.1709 $[M+H]^+$ /315.1701	73–75	**34**	$C_{19}H_{24}N_2O_4$	367.1628 $[M+Na]^+$ /367.1772	83–85
19	$C_{23}H_{32}N_2O_3$	385.2491 $[M+H]^+$ /385.2518	semi solid at rt	**35**	$C_{24}H_{34}N_2O_4$	415.2591 $[M+H]^+$ /415.2588	40–42
20	$C_{21}H_{28}N_2O_3$	357.2178 $[M+H]^+$ / 357.2173	semi solid at rt	**36**	$C_{22}H_{30}N_2O_4$	387.2278 $[M+H]^+$ /387.2231	semi solid at rt
21	$C_{15}H_{15}NO_3$	280.0944 $[M+Na]^+$ /280.0949	107–109	**37**	$C_{16}H_{17}NO_4$	288.1236 $[M+H]^+$ /288.1259	141–143
22	$C_{16}H_{17}NO_3$	272.1287 $[M+H]^+$ / 272.1298	73–75	**38**	$C_{17}H_{19}NO_4$	302.1387 $[M+H]^+$ /302.1374	93–94
23	$C_{18}H_{21}NO_3$	322.1419 $[M+Na]^+$ /322.1418	72–74	**39**	$C_{19}H_{23}NO_4$	330.1700 $[M+H]^+$ /330.1708	72–74
24	$C_{18}H_{19}NO_3$	298.1443 $[M+H]^+$ / 298.1460	100–102	**40**	$C_{19}H_{21}NO_4$	328.1543 $[M+H]^+$ /328.1475	198–200
25	$C_{16}H_{18}N_2O_4$	303.1367 $[M+H]^+$ / 303.1372	189–191	**41**	$C_{17}H_{20}N_2O_4$	317.1496 $[M+H]^+$ /317.1435	147–148
26	$C_{18}H_{22}N_2O_4$	353.1472 $[M+Na]^+$ /353.1601	160–162	**42**	$C_{19}H_{24}N_2O_4$	345.1809 $[M+H]^+$ /345.1789	43–45
27	$C_{23}H_{32}N_2O_4$	401.2435 $[M+H]^+$ /401.2437	184–187	**43**	$C_{24}H_{34}N_2O_4$	437.2411$[M+Na]^+$/437.2571	74–76
28	$C_{21}H_{28}N_2O_4$	373.2127 $[M+H]^+$ /373.2147	semi solid at rt	**44**	$C_{22}H_{30}N_2O_4$	387.2278 $[M+H]^+$ /387.2278	33–35
29	$C_{15}H_{15}NO_4$	296.0893 $[M+Na]^+$ /296.0861	201–203	**45**	$C_{16}H_{17}NO_4$	288.1230 $[M+H]^+$ /288.1165	70–71
30	$C_{16}H_{17}NO_4$	288.1236 $[M+H]^+$ /288.1193	179–181	**46**	$C_{17}H_{19}NO_4$	324.1206 $[M+Na]^+$/324.1381	65–67
31	$C_{18}H_{21}NO_4$	338.1368 $[M+Na]^+$ /338.1378	166–168	**47**	$C_{19}H_{23}NO_4$	330.1705 $[M+H]^+$ /330.1709	78–80
32	$C_{18}H_{19}NO_4$	336.1212 $[M+Na]^+$ /336.1175	185–187	**48**	$C_{17}H_{21}NO_4$	328.1543 $[M+H]^+$ /328.1488	105–107

Conclusions

A series of 32 differently *N*-substituted benzoylpyridin-2-(1*H*)-ones were synthesized in moderate to high yields and were further characterized by 1D and 2D NMR and HRMS techniques that allowed full spectral assignments. Among the compounds synthesized, 22, i.e. the compounds **18–20**, **22**, **25–32**, **34–35**, **41–43**, and **45–48** are novel and reported for the first time. Although the compounds **17**, **21**, **23–24**, **33**, **37–40,** and **44** were previously reported by our group, however, for the sake of comparison, the data of known compounds are also reported. Analysis of the proton NMR data reveals that in all the *N*-substituted benzoylpyridin-2-(1*H*)-one derivatives, H-6 of 2-pyridone skeleton appears most deshielded, whereas in the ^{13}C NMR, ketonic carbonyl was most deshielded. The *ortho* coupled protons of the pyridone ring can be distinguished from that of *ortho*-aromatic protons of benzoyl moiety on the basis of higher coupling constant for the former. Interestingly, H-3 proton showed changes in the value of chemical shift with respect to the addition of functional group or change in the position of functional group in the benzoyl ring. The acquired data constitute a valuable database for the unambiguous identification of the 2-pyridones, and the information may be useful to researchers working in related area.

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References

[1] M. Ando, T. Wada, N. Sato. *Org. Lett.* **2006**, *8*, 3805–3808.
[2] I. W. Cheney, S. Yan, T. Appleby, H. Walker, T. Vo, N. Yao, R. Hamatake, Z. Hong, J. Z. Wu. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1679–1683.
[3] D. L. Bai, X. C. Tang, X. C. He. *Curr. Med. Chem.* **2000**, *7*, 355–374.
[4] J. A. Wendt, P. J. Gauvreau, R. D. Bach. *J. Am. Chem. Soc.* **1994**, *116*, 9921–9926.
[5] M. E. Wall. *Med. Res. Rev.* **1998**, *18*, 299–314.
[6] B. B. Snider, Q. Lu. *J. Org. Chem.* **1994**, *59*, 8065–8070.
[7] N. A. Klein, S. J. Siskind, W. H. Frishman, E. H. Sonnelblick, T. H. Le Jemtel. *Am. J. Cardiol.* **1981**, *48*, 170–175.
[8] A. A. Attois, J. M. Canter, M. J. Montanero, D. J. Fort, R. A. Hood. *J. Cardiovascular Pharmacology* **1983**, *303*, 535.
[9] M. D. Gottwald, M. J. Aminoff. *Drugs Today* **2008**, *44*, 531–545.
[10] M. Niewerth, D. Kunze, M. Seibold, M. Schaller, H. C. Korting, B. Hube. *Antimicrob. Agent and Chemother.* **2003**, *47*, 1805–1817.
[11] A. D. Elbein, R. J. Molyneux, in *Alkaloids: Chemical and Biological Perspectives*, vol. *5* (Ed: S. W. Pelletier)Ed:, Wiley, New York, **1981**, pp. 1.
[12] D. Z. Mijin, G. S. Uscumlic, N. U. Perisic-Janjic, N. V. Valentic. *Chem. Phys. Lett.* **2006**, *418*, 223–229.
[13] S. Kumar, B. K. Singh, A. K. Pandey, A. Kumar, S. K. Sharma, H. G. Raj, A. K. Prasad, E. V. Eycken, V. S. Parmar, B. Ghosh. *Bioorg. Med. Chem.* **2007**, *15*, 2952–2962.
[14] K. Chand, S. Prasad, R. K. Tiwari, A. N. Shirazi, S. Kumar, K. Parang, S. K. Sharma. *Bioorg. Chem.* **2014**, *53*, 75–82.
[15] H. Yoon, S. Ahn, D. Hwang, G. Jo, D. W. Kim, S. H. Kim, D. Koh, Y. Lim. *Magn. Reson. Chem.* **2012**, *50*, 759–764.
[16] A. Corazza, I. Harvey, P. J. Sadler. *Eur. J. Biochem.* **1996**, *236*, 697–705.

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