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Facile synthesis of N-benzylated 3-alkyl-2,6-diarylpiperidin-4-ones: Stereochemical investigation by 1D/2D NMR and single-crystal XRD

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ABSTRACT

A series of thirteen 1-benzyl-3-alkyl-2,6-diarylpiperidin-4-ones **14**–**26** were conveniently synthesized in high yields 87–92%. In order to find the impact on piperidone stereochemistry, beside the N-benzylation, methyl/ethyl/isopropyl groups at C-3 and halo/alkyl/alkoxy/benzyloxy groups on the phenyl rings at C-2/C-6 were introduced. All the synthesized compounds were characterized by mass, ^{1}H and ^{13}C NMR spectral studies. Of them, the 1-benzyl-3-ethyl-2,6-diphenylpiperidin-4-one **22** was completely characterized by 2D NMR techniques such as $^{1}H—^{1}H$ COSY, $^{1}H—^{13}C$ COSY and NOESY to assign the signals, unambiguously. The proton coupling constants and NOE correlations provided the complete stereochemistry of **22**, which is further witnessed by its single-crystal XRD analysis. The NMR and XRD studies revealed that the compound **22** exists in a chair conformation with equatorial orientation of all the substituents in both solution and solid states. On the basis of their vicinal coupling constants, the chair conformation with equatorial orientation of the substituents at C-2, C-3, C-6 and N is proposed for all compounds **14**–**26**; moreover, a considerable population of boat conformation also suggested for the compound **26** along with the predominant chair conformation, in solution.

1. Introduction

Piperidone nucleus are interested because of their broad-spectrum of biological activities such as antibacterial, antifungal, antituberculostic, antioxidant, antiinflammatory, neuronal nicotinic antagonistic activity, CNS stimulant as well as depressant and anticancer activity [1–8]. Albeit their presence in a countless of alkaloids, synthesis of new molecules with piperidone nucleus is of continuous interest in the field of organic/medicinal chemistry [9–11]. Since the stereochemistry of the synthesized molecules is a major criterion for their biological activities, it is of immense help to establish the stereochemistry of the newly synthesized molecules [12,13].

According to the literature [5–8], substitution on the secondary amino group and its adjacent positions as well as on active methylene centers will enhance the biological activity. Moreover, the introduction of certain hetero-conjugate groups such as NO, CHO, $COCH_3$, COC_6H_5, CH_3, and $COCH_2Cl$ at the ring nitrogen of 2,6-disubstituted piperidone system have been reported to cause a major change in ring conformation [14–24]. Hence, for the present study, we have synthesized and N-benzylated a series of 3-alkyl-2,6-diarylpiperidin-4-ones **1–13** to investigate their stereochemical and conformational changes.

Since the NMR spectroscopy is a versatile tool for the structural elucidation of organic compounds, we subjected a range of 1D and 2D NMR studies for the synthesized compounds. Particularly, the vicinal coupling constants derived from the proton NMR and NOE correlations from the NOESY are very useful for the conformational and stereochemical assignments [25,26]. Although NMR spectroscopy is playing a vital role in solution and solid states, the single-crystal XRD analysis is an ultimate tool to unambiguously establish the stereochemistry of the synthesized compounds in the solid state.

2. Experimental

2.1. Materials and methods

All reagents were obtained from Aldrich and Alfaaesar, which were used directly without further purification. Solvents used were of commercial grade and purified according to the literature [27]. The progress of the reactions was monitored by thin layer chromatography (TLC) on 250 μm silica plates using 9:1 *n*-hexane and ethyl acetate as an eluent. Melting points are taken in open capillaries and are uncorrected; Electrothermal-9100 (Japan) instrument was used to determine the melting point of the

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compounds. Mass spectra were recorded by the Jeol JMS-700 mass spectrometer.

2.1.1. Recording of 1D NMR spectra

All the 1D NMR spectra of the synthesized compounds were recorded on Jeol JNM ECP 400 NMR spectrometer at 294 K. The ^{1}H and ^{13}C NMR spectra were measured respectively 0.03 M and 0.05 M solutions in $CDCl_3$ with TMS as internal reference in 5 mm NMR tubes. The pulse conditions were as follows: ^{1}H NMR spectra: SF 399.78 MHz, AQ 2.73 s, NS 32, DS 0, SW 5998.8 Hz, pulse 4.65 μs, angle 45°, width 9.3 μs, DR 0.366 Hz, RD 5 s, RG 13, data points 16,384, pre scan delay 1 s; ^{13}C NMR spectra: SF 100.52 MHz, AQ 1.25 s, NS 250, DS 4, SW 26178.01 Hz, Pulse 3.13 μs, angle 30°, width 9.4 μs, DR 0.798 Hz, RD 1 s, RG 25, data points 32,768, pre scan delay 1 s.

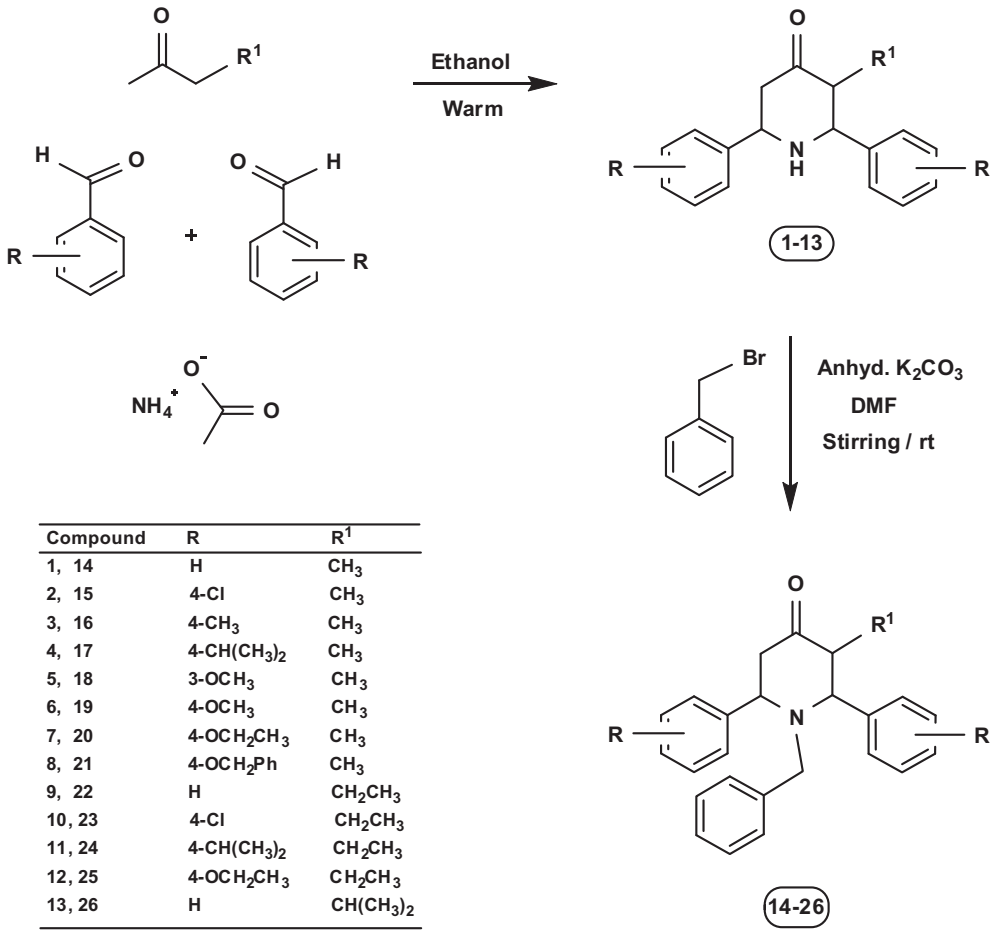
2.1.2. Recording of 2D NMR spectra

All the 2D NMR spectra were recorded on Jeol JNM ECP 400 NMR spectrometer at 294 K using 0.05 M solution in $CDCl_3$ with TMS in a 5 mm NMR tube. The pulse conditions were as follows: SF of protons and carbons are 399.78 and 100.52 MHz for all experiments; $^{1}H—^{1}H$ COSY: Spectral width of 3815.3 Hz was used in both dimensions and the acquisition data points are 1024 × 256, NS 60, AQ 0.26 s (X), 67.09 ms (Y), P1, P2 90°, RD 1 s, RG 14, G. selection 1:1, G. shape sine, G. type 2, DR 3.72 (X), 14.90 Hz (Y), DS 4 (X), 0 (Y), pre scan delay 0.1 s. NOESY: Spectral width of 3815.3 Hz was used in both dimensions and the number of data points are 1024 × 73, mixing time 700 ms, NS 16, AQ 0.26 s (X), 33.54 ms (Y), RD 7 s, RG 11, G. shape sine, G. type 2, DR 3.72 (X), 52.26 Hz (Y), DS 4 (X), 0 (Y), pre scan delay 1 s; $^{1}H—^{13}C$ COSY (HSQC): Spectral width of 3815.3 Hz in X and 18181.8 Hz in Y was used. The experiment was optimized for C—H coupling of 140.0 Hz. Acquisition data size was 1024 points, and the number of increments for evolution was 512. The number of scans per increment was 4, with a 2.0 s delay between transients, AQ 0.26 (X), 28.16 (Y), DS 4 (X), 0 (Y), RG 31, G. recover 0.1 ms, pre scan delay 0.1 ms.

The ^{1}H and ^{13}C chemical shift values are given in δ scale (ppm) and referred to TMS, (^{13}C, via the solvent signal of $CHCl_3$ at 77.16 ppm). Coupling constants *J* are reported in Hz. The expansions for the abbreviations used are s: singlet, br s: broad singlet, d: doublet, dd: doublet of doublet, ddd: doublet of doublet of doublet, dt: doublet of triplet, t: triplet, td: triplet of doublet, q: quartet, qn: quintet, m: multiplet, unr m: unresolved multiplet, SF: spectrometer frequency, AQ: acquisition time, NS: number of transients, DS: dummy scans, SW: spectral width, DR: digital resolution, RD: relaxation delay, RG: receiver gain.

2.1.3. Recording of single-crystal XRD

The X-ray diffraction quality crystals of 1-benzyl-3-ethyl-2,6-diarylpiperidin-4-one **22** were obtained by slow evaporation from ethanol and the crystal structure was determined by the X-ray diffraction data of the compound, which collected on a Bruker SMART APEX CCD diffractometer [28] using Mo Kα radiation with fine focus tube with 50KV and 30 mA. Crystal to detector distance 6.05 cm, 512 × 512 pixels/frame, oscillation/frame −0.3°, maximum detector swing angle = −30.0°, beam center = 260.2 and 252.5, in plane spot width = 1.24, SAINT integration, *T* = 273(2) K,



Compound	R	R^1
1, 14	H	CH_3
2, 15	4-Cl	CH_3
3, 16	4-CH_3	CH_3
4, 17	4-$CH(CH_3)_2$	CH_3
5, 18	3-OCH_3	CH_3
6, 19	4-OCH_3	CH_3
7, 20	4-OCH_2CH_3	CH_3
8, 21	4-OCH_2Ph	CH_3
9, 22	H	CH_2CH_3
10, 23	4-Cl	CH_2CH_3
11, 24	4-$CH(CH_3)_2$	CH_2CH_3
12, 25	4-OCH_2CH_3	CH_2CH_3
13, 26	H	$CH(CH_3)_2$

Scheme 1. Synthesis of 1-benzyl-3-alkyl-2,6-diarylpiperidin-4-ones.

Table 1
The ^{1}H NMR chemical shift values of compounds **14**–**26** (δ, ppm).

Compound	H-2a	H-3a	H-5e	H-5a	H-6a	N—CH_2-Ph	Substituent at C-3	Aromatic protons	Substituent at phenyl rings
14	3.48 (d, 1H)[10.2][a]	2.81–2.74 (m, 1H)	2.53 (dd, 1H) [13.2, 3.6]	2.86 (t, 1H) [12.4]	3.95 (dd, 1H) [11.3, 3.5]	3.63 (d, 1H) [15.0], 3.53 (d, 1H) [15.0]	0.72 (d, 3H) [6.6]	7.50 (d, 4H) [7.7], 7.38–7.33 (m, 4H), 7.29–7.24 (m, 2H), 7.11–7.09 (m, 3H)	–
15	3.45 (d, 1H) [10.2]	2.75–2.67 (m, 1H)	2.50 (dd, 1H) [13.3, 3.5]	2.80 (t, 1H) [12.4]	3.91 (dd, 1H) [11.5, 3.5]	3.56 (d, 1H) [15.0], 3.47 (d, 1H) [15.0]	0.71 (d, 3H) [6.5]	7.40 (dd, 4H) [8.4, 3.3], 7.33–7.29 (m, 4H), 7.13–7.07 (m, 3H), 6.77–6.75 (m, 2H)	–
16	3.41 (d, 1H) [10.2]	2.78–2.71 (m, 1H)	2.50 (dd, 1H) [13.1, 3.6]	2.84 (t, 1H) [12.2]	3.88 (dd, 1H) [11.5, 3.5]	3.61 (d, 1H) [15.0], 3.51 (d, 1H) [15.0]	0.71 (d, 3H) [6.6]	7.36 (d, 4H) [7.6], 7.15 (q, 4H), 7.09–7.08 (m, 3H), 6.82–6.80 (m, 2H)	2.34 (s, 3H), 2.33 (s, 3H)
17	3.40 (d, 1H) [10.2]	2.82–2.75 (m, 1H)	2.52 (dd, 1H) [13.3, 3.5]	2.91–2.84 (m, 1H) overlapped with $CH(CH_3)_2$	3.87 (dd, 1H) [11.7, 3.3]	3.59 (d, 1H) [14.6], 3.50, (d, 1H) [15.0]	0.71 (d, 3H) [6.6]	7.36 (q, 4H) 7.16 (q, 4H, 7.05 (t, 3H) [3.1], 6.80–6.78 (m, 2H)	1.25 (d, 6H) [2.5], 1.23 (d, 6H) [2.5], 2.91–2.84 (m, 2H) overlapped with H-5a
18	3.43 (d, 1H) [10.6]	2.80–2.73 (m, 1H)	2.53 (dd, 1H) [13.1, 3.3]	2.86 (t, 1H) [12.4]	3.91 (dd, 1H) [11.3, 3.3]	3.65 (d, 1H) [15.0], 3.55 (d, 1H) [15.0]	0.73 (d, 3H) [6.6]	7.29–7.21 (m, 2H), 7.09–7.05 (m, 7H), 6.87–6.86 (m, 2H), 6.80, 6.76 (m, 2H)	3.79 (s, 1H), 3.78 (s, 1H)
19	3.39 (d, 2H) [10.2]	2.78–2.73 (m, 1H)	2.50 (dd, 1H) [13.2, 3.3]	2.84 (t, 1H) [12.8]	3.86 (dd, 1H) [11.7, 3.3]	3.59 (d, 1H) [14.6], 3.50 (d, 1H) [15.0]	0.71 (d, 3H) [6.6]	7.37 (dd, 4H) [8.6, 2], 7.08 (t3, H) [3.1], 6.88–6.86 (m, 4H), 6.81–6.79 (m, 2H)	3.81 (s, 3H), 3.79 (s, 3H)
20	3.38 (d, 1H) [10.6]	2.80–2.70 (m, 1H)	2.49 (dd, 1H) [13.2, 3.3]	2.83 (t, 1H) [12.2]	3.85 (dd, 1H) [11.7, 3.3]	3.60 (d, 1H) [15.0], 3.51 (d, 1H) [15.0]	0.71 (d, 3H) [6.6]	8.42(q, 4H), 7.07 (t, 3H) [3.1], 6.87–6.84 (m, 4H), 6.82–6.79 (m, 2H)	4.04–3.97 (m, 4H), 1.41–1.39 (m, 6H)
21	3.39 (d, 1H) [10.2]	2.78–2.70 (m, 1H)	2.50 (dd, 1H) [13.0, 3.5]	2.84 (t, 1H) [12.4]	3.86 (dd, 1H) [11.3, 3.3]	3.59 (d, 1H) [15.0], 3.51 (d, 1H) [15.0]	0.75 (d, 2H) [6.6]	7.45–7.32 (m, 14H), 7.07 (t, 3H) [2.94], 6.95–6.92 (m, 4H), 6.81–6.78 (m, 2H)	5.05 (s, 2H), 5.04 (s, 2H)
22	3.62[b]	2.68 (unresolved dt, 1H)	2.54 (dd, 1H) [12.8, 4.0]	2.88 (t, 1H) [12.1]	3.97 (dd,1H) [11.7, 3.7]	3.61[c], 3.50 (d, 1H) [15.0]	1.56–1.45 (m, 1H), 1.05–0.98 (m,1H), 0.68 (t, 3H) [7.3]	7.51 (dd, 4H) [11.1, 7.4], 7.36 (dd, 4H, seems to be a quartet) [15.0, 7.3], 7.30–7.24 (m, 2H), 7.10 (t, 3H) [3.3], 6.82 (dd, 2H) [6.2, 2.9]	–
23	3.58 (d, 1H) [10.2]	2.60 (unresolved dt, 1H)	2.5 (dd, 1H) [12.8, 3.7]	2.8 (t, 1H) [12.2]	3.92 (dd, 1H) [11.3, 3.7]	3.53 (d, 1H) [15.0], 3.44 (d, 1H) [15.0]	1.52–1.41 (m, 1H), 1.02–0.96 (m, 1H), 0.68 (t, 3H) [7.3]	7.42–7.37 (m, 4H), 7.31 (t, 3H) [8.4], 7.1–7.07 (m, 3H), 6.76–6.74 (m, 2H)	–
24	3.53[b]	2.68 (unresolved dt, 1H)	2.50 (dd, 1H) [12.8, 3.7]	2.91–2.83 (m, 1H) overlapped with $CH(CH_3)_2$	3.87 (dd, 1H) [11.3, 3.3]	3.55[c], 3.46 (d, 1H) [15.0]	1.51–1.38 (m, 1H), 1.09–0.95 (m, 1H), 0.68 (t, 3H) [7.3]	7.36 (dd, 4H) [8.0, 2.9], 7.15 (d, 4H) [6.9], 7.04 (t, 3H) [3.1], 6.79–6.77 (m, 2H)	2.91–2.83 (m, 1H) overlapped with H-5e, 1.24 (d, 6H) [3.3], 1.23 (d, 6H) [3.3]
25	3.53[b]	2.62 (unresolved dt, 1H)	2.48 (dd, 1H) [12.8, 3.3]	2.8 (t, 1H) [12]	3.85 (dd, 1H) [11.3, 3.3]	3.57[c], 3.47 (d, 1H) [14.6]	1.53–1.43 (m, 1H overlapped with CH_3—CH_2—O), 1.05–0.96 (m, 1H), 0.67 (t, 3H) [7.3]	7.37–7.33 (m, 4H), 7.07–7.06 (m, 3H), 6.86–6.83 (m, 4H), 6.80–6.79 (m, 2H)	4.05–3.98 (m, 4H), 1.44–1.35 (m, 6H, overlapped with CH_2 at C-3)
26	3.99 (d,1H) [9.9]	2.67 (dd, 1H) [9.5, 3.2]	2.55 (dd, 1H) [13.5, 4.2]	2.77 (q, 1H)	4.05 (dd, 1H) [10.2, 4.4]	3.60 (d, 1H) [15.0], 3.49 (d, 1H) [15.0]	1.44 (m, 1H), 0.95 (d, 3H) [6.9], 0.92 (d, 3H) [6.9]	7.49 (d, 2H) [7.6], 7.43 (d, 2H) [7.3], 7.33 (dd, 4H, seems to be a quartet) 7.26–7.20 (m, 2H), 7.07 (t, 3H) [2.74], 6.85–6.83 (m, 2H)	–

[a] Values in the square brackets are coupling constants in Hz.
[b] Overlapped with N—CH_2-Ph.
[c] Overlapped with H-2a.

Table 2
The ^{13}C chemical shift values of compounds **14–26** (δ, ppm).

Compound	C-2	C-3	C-4	C-5	C-6	N—CH_2-Ph	R	R^1 at C-3	Aromatic carbons
14	72.65	51.64	208.93	51.16	65.67	53.37	–	11.30 (CH_3)	143.28 (C-6′), 142.01 (C-2′), 136.54 (N—Bn *ipso* carbon), 129.84, 128.88, 128.57, 127.79, 127.65, 127.62, 126.74
15	72.28	51.36	207.82	50.64	65.25	53.90	–	11.19 (CH_3)	141.50 (C-6′), 140.28 (C-2′), 136.4 (N—Bn *ipso* carbon), 133.45 (C-6‴), 133.28 (C-2‴), 130.09, 129.48, 129.05, 128.94, 128.80, 127.81, 126.89
16	72.44	51.64	209.07	51.24	65.45	53.24	21.22 (CH_3 at C-6‴), 21.18 (CH_3 at C-2‴)	11.29 (CH_3)	140.35 (C-6‴), 139.02 (C-2‴), 137.24 (C-6′), 137.12 (C-2′), 136.76 (N—Bn *ipso* carbon), 129.80, 129.16, 127.53, 127.50
17	73.26	51.66	209.35	51.17	66.27	54.02	33.90 [$CH(CH_3)_2$] at C-6‴, C-2‴), 24.16, 24.11 [$CH(CH_3)_2$]	11.38 (CH_3)	148.31 (C-6‴), 148.17 (C-2‴), 140.54 (C-6′), 139.25 (C-2′), 137.59 (N—Bn *ipso* carbon), 129.62, 128.84, 127.69, 127.53, 126.75, 126.47, 126.37
18	72.74	50.54	208.42	51.22	65.66	53.77	55.11 (OCH_3 at C-6‴, C-2‴)	11.18 (CH_3)	159.89 (C-6‴), 159.73 (C-2‴), 144.75 (C-6′), 143.41 (C-2′), 136.81 (N—Bn *ipso* carbon), 129.69, 129.61, 129.30, 127.44, 126.49, 121.36, 119.85, 114.41, 113.32, 112.73, 112.69
19	72.35	51.49	208.78	50.98	65.32	53.39	55.05 (OCH_3 at C-6‴, C-2‴)	11.11 (CH_3)	158.84 (C-6‴), 158.76 (C-2‴), 137.20 (C-6′), 135.08 (C-2′), 133.79 (N—Bn *ipso* carbon), 129.62, 129.34, 128.53, 127.35, 126.25, 114.10, 113.93, 113.66
20	72.41	51.73	209.08	51.27	65.39	53.38	63.43 (O—CH_2—CH_3), 14.93 (CH_3CH_2—O)	11.25 (CH_3)	158.37 (C-6‴), 158.27 (C-2‴), 137.23 (C-6′), 135.15 (C-2′), 133.87 (N—Bn *ipso* carbon), 129.77, 129.57, 128.66, 127.48, 126.43, 114.62, 114.34
21	72.51	51.75	209.09	51.25	65.50	53.57	70.18 (O—CH_2-Ph)	11.31 (CH_3)	158.34 (C-6‴), 158.23 (C-2‴), 137.31 (N—Bn *ipso* carbon), 137.09 (O—Bn *ipso* carbon), 135.62 (C-6′), 134.36 (C-2′), 129.87, 129.59, 128.68, 128.08, 127.62, 126.50, 115.06, 114.79
22	71.06	58.53	208.47	51.67	65.97	53.39	–	12.24 (CH_3), 18.82 (CH_2)	143.23 (C-6′), 141.90 (C-2′), 136.70 (N—Bn *ipso* carbon, 129.69, 128.96, 128.77, 128.49, 127.72, 127.58, 127.53, 126.62,
23	70.61	58.21	207.59	51.16	65.54	53.96	–	12.16 (CH_3), 18.76 (CH_2)	141.49 (C-6′), 140.22 (C-2′), 136.59 (N—Bn *ipso* carbon), 133.40 (C-6‴), 133.21 (C-2‴), 130.21, 129.36, 128.98, 128.89, 128.73, 127.77, 126.79
24	71.67	58.53	208.97	51.72	66.64	54.12	33.86 $CH(CH_3)_2$ at (C-6‴, C-2‴), 24.16 $CH(CH_3)_2$ at C-6‴), 24.07 $CH(CH_3)_2$ at C-2‴	12.24 (CH_3), 18.91 (CH_2)	148.24 (C-6‴), 148.10 (C-2‴), 140.55 (C-6′), 139.14 (C-2′), 137.82 (N—Bn *ipso* carbon), 129.49, 126.70, 126.41
25	70.88	58.69	208.76	51.81	65.74	53.46	63.40 (O—CH_2—CH_3), 14.91 (O—CH_2—CH_3)	12.25 (CH_3), 18.81 (CH_2)	158.35 (C-6‴), 158.26 (C-2‴), 137.46 (C-6′), 135.15 (C-2′), 133.76 (N—Bn *ipso* carbon), 129.90, 129.46, 128.63, 127.46, 126.35, 114.58, 114.29
26	68.33	61.60	208.98	51.36	64.92	54.52	–	27.15 (CH), 21.62 (CH_3), 17.17 (CH_3')	143.45 (C-6′), 142.39 (C-2′), 137.61 (N—Bn *ipso* carbon), 129.36, 128.75, 128.54, 127.69, 126.66

Quadrant data acquisition, total scans = 4, total frames = 2424. All the data were corrected for Lorentzian, polarisation and absorption effects. SADABS correction applied, SHELX-97 (ShelxTL) [29] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model.

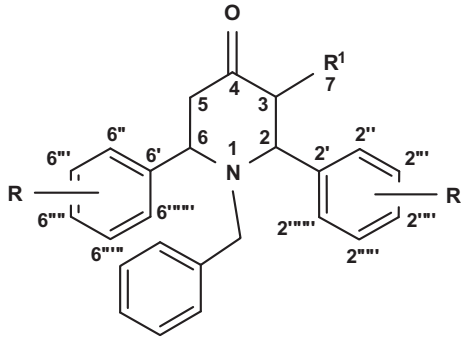


Fig. 1. Numbering of the atoms in the target compounds.

2.2. Synthesis of 1-benzyl-2,6-diarylpiperidin-4-ones

2.2.1. Synthesis of 3-alkyl-2,6-diarylpiperidin-4-ones (**1–13**)

All the parent 2,6-diarylpiperidin-4-ones were synthesized by adopting the literature precedent Noller and Baliah [30] with the condensation of respective ketones, aldehydes and ammonium acetate in warm ethanol in 1:2:1 ratio.

2.2.2. Synthesis of 1-benzyl-3-alkyl-2,6-diarylpiperidin-4-ones (**14–26**)

A mixture of respective 3-alkyl-2,6-diarylpiperidin-4-ones (**1–13**) (0.01 mol), anhydrous potassium carbonate (0.02 mol, 2.76 g) and benzyl bromide (0.015 mol, 1.78 ml) in DMF (20 ml) was stirred at room temperature for 36–48 h. Progress and completion of the reactions were monitored by the TLC. After the completion, an excess of ice-cold water was added and extracted with dichloromethane. The organic layer, thus separated was thrice washed with brine solution (3×10 ml) and dried over anhydrous Na_2SO_4. Then the organic layer was concentrated in *rota* to obtain the crude product, followed by purification on silica-gel (Merck, 230–400

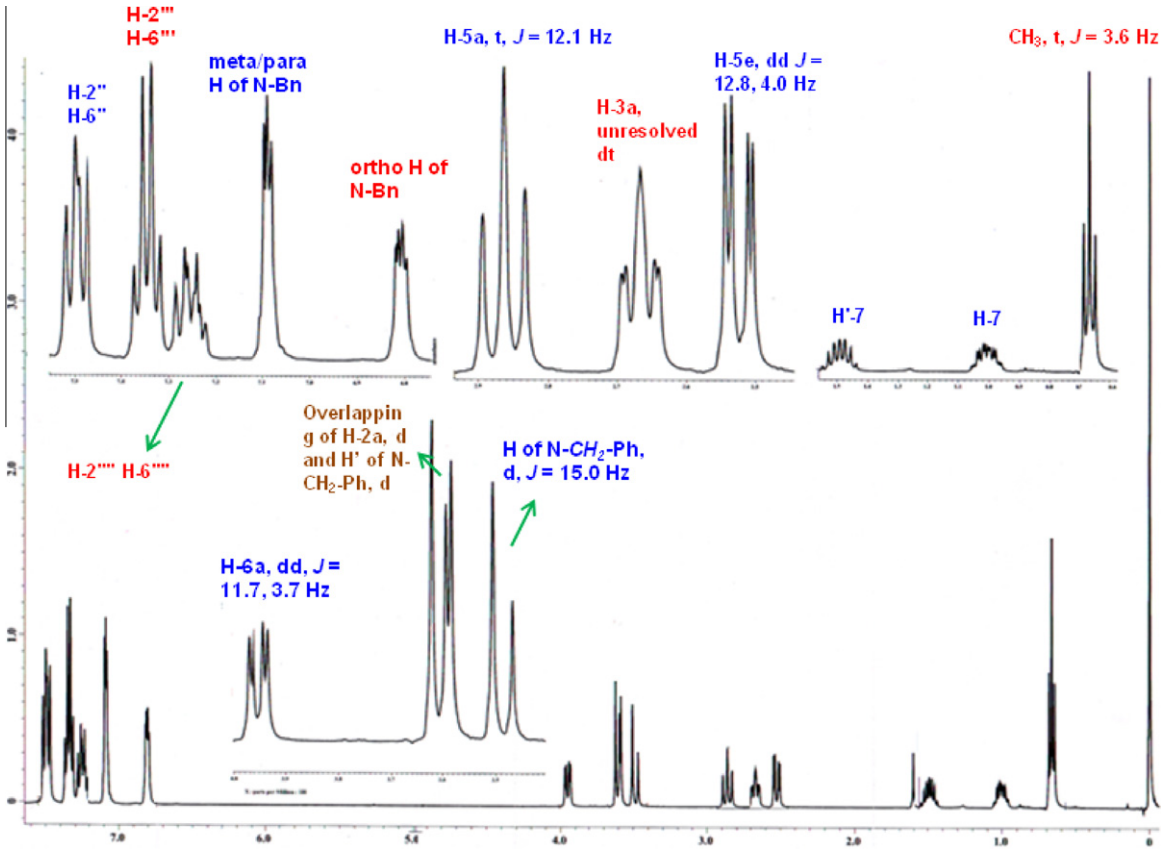


Fig. 2. ^{1}H NMR spectrum of compound **22**.

mesh), using *n*-hexane and ethyl acetate mixture, afforded the pure 1-benzyl-3-alkyl-2,6-diarylpiperidin-4-ones **14**–**26** in good yields 87–92%.

3. Result and discussion

3.1. Synthesis of compounds

According to Scheme 1, all compounds were synthesized and characterized by use of their analytical and spectral data. For the compound **22**, in addition to the 1D NMR (^{1}H and ^{13}C NMR), 2D NMR (^{1}H—^{1}H COSY, ^{1}H—^{13}C COSY and NOESY) and single-crystal XRD studies were performed to make an unambiguous configurational and conformational characterizations. The ^{1}H and ^{13}C NMR chemical shift values of all the synthesized N-benzyl piperidones are provided in Tables 1 and 2. For better understanding, the numbering of atoms in the target molecules is shown in Fig. 1.

3.2. ^{1}H NMR spectral study of 1-benzyl-3-alkyl-2,6-diarylpiperidin-4-ones **22**–**25**

In the proton NMR spectrum (Fig. 2) of 1-benzyl-3-ethyl-2,6-diphenylpiperidin-4-one **22**, five-sets of signals with a total of 15 protons integral appear in the range 6.82–7.51 ppm ($CDCl_3$ peak is overlapped with the multiplet at 7.30–7.24 ppm), which correspond to the phenyl groups at C-2, C-4 and N—Bn. A six-set of signals with a total of seven protons integral appears between 2.5 and 4.0 ppm, which corresponds to the protons in the piperidone ring and methylenic protons of the N—Bn group. Besides, two multiplets between 1.0 and 1.5 ppm, each corresponds to one proton, and a triplet with three protons integral appears because of the ethyl substituent. The proton assignment of **22** is executed by their positions, multiplicity and integral values; further, to carry out the individual assignments in an unambiguous way, ^{1}H—^{1}H COSY and NOESY spectra have been recorded. For better understanding, the

Table 3
Correlations in the ^{1}H—^{1}H COSY and NOESY spectra of compound **22**.

Signal (δ in ppm)	Correlations in the ^{1}H—^{1}H COSY	Correlations in the NOESY
7.51 (dd, 4H, *ortho* protons of the Ph at C-2/C-6. *i.e.*, H-2″/H-6″)	7.36	3.97, 3.62, 2.88, 2.68, 3.50, 6.82 (w), 7.36 (s)
7.36 (dd, 4H, *meta* protons of the Ph at C-2/C-6. *i.e.*, H-2‴/H-6‴)	7.51	7.51 (s)
7.27 (m, 2H, *para* protons of the Ph at C-2/C-6. *i.e.*, H-2⁗/H-6⁗)	7.36 (w)	–
7.10 (t, 3H, *meta* and *para* protons of the N—Bn)	6.82	6.82
6.82 (dd, 2H, *ortho* protons of the N—Bn)	7.10	3.61 (s), 3.50 (s), 3.97 (w), 7.10, 7.51 (w)
3.97 (dd, 1H, H-6a)	2.54, 2.88	3.62, 2.54 (s), 2.88 (w), 7.51, 6.82 (w)
3.62 (1H, H-2a)	2.68	3.97 (s), 2.68 (w), 7.51 (s)
3.61 (1H, H of N—CH_2-Ph)	3.50	3.50, 6.82 (s)
3.50 (1H, H′ of N—CH_2-Ph)	3.61	3.61, 7.51 (w), 6.82 (s)
2.88 (t, 1H, H-5a)	3.97, 2.54	7.51 (s)
2.68 (unresolved dt, 1H, H-3a)	1.02, 1.51, 3.62	3.62 (w), 0.68 (w), 7.51
2.54 (dd, 1H, H-5e)	2.88, 3.97	3.97 (s)
1.51 (m, 1H, H′-7)	2.68, 1.02, 0.68	0.68 (s), 1.02 (w)
1.02 (m, 1H, H-7)	2.68, 1.51, 0.68	0.68 (w), 1.51 (w)
0.68 (t, 3H, CH_3)	1.51, 1.02	1.02, 1.51, 2.68 (w)

w = Weak correlation; s = strong correlation.

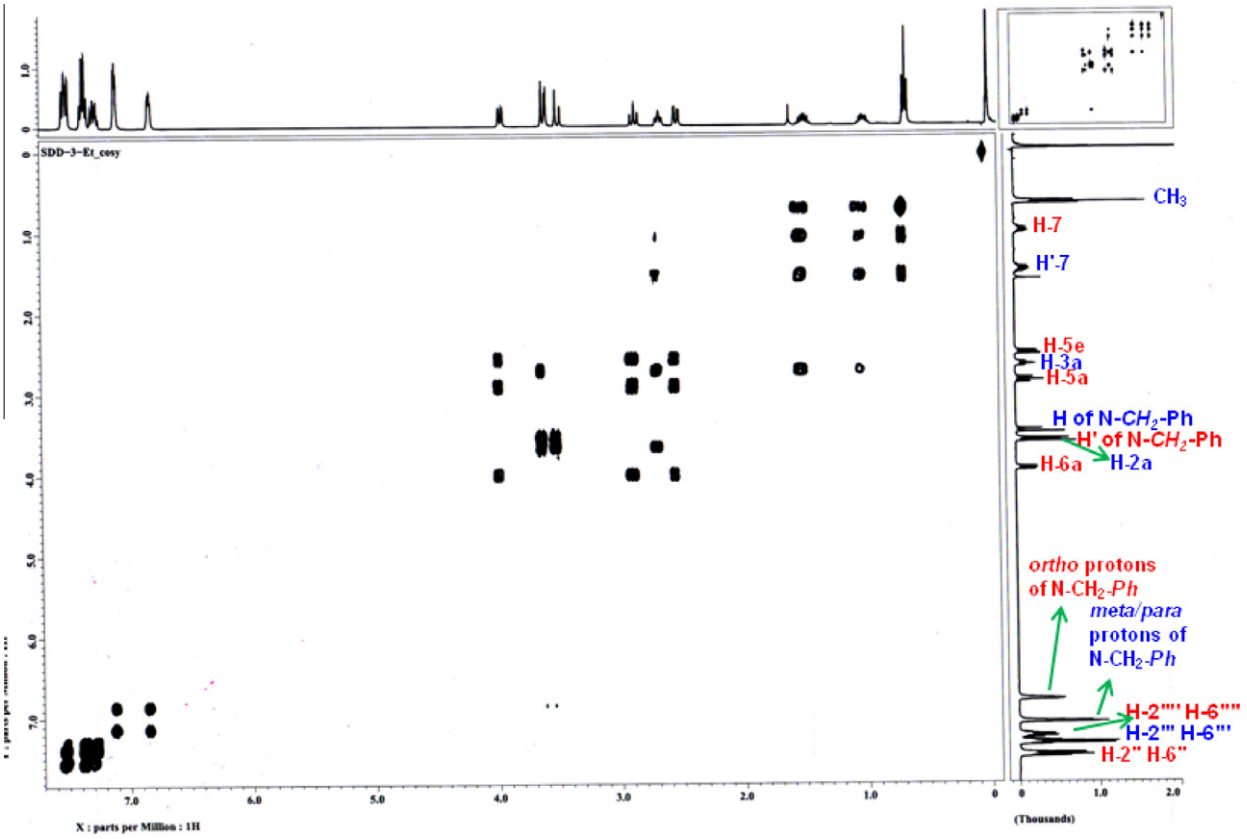


Fig. 3. ^{1}H—^{1}H COSY spectrum of compound **22**.

^{1}H—^{1}H COSY and NOESY correlations are presented in Table 3 and the spectra are reproduced in Figs. 3 and 4, respectively.

The triplet at 0.68 ppm (3H, J = 3.6 Hz) shows a ^{1}H—^{1}H correlation with the multiplets at 1.51 (1H) and 1.02 (1H) ppm, and which shows the NOEs with the same multiplets; also a weak NOE with the signal at 2.68 ppm (unresolved dt, 1H). These correlations clearly designate the triplet and multiplets, respectively to the methyl and methylene protons of the ethyl substituent at C-3 of the piperidone ring. Because of its diastereotopic nature, the methylene protons of the ethyl substituent appear as two separate signals, due to their stereochemical orientations, each methylene proton appear as multiplets with different splitting pattern. They are denoted as H-7 (1.02 ppm) and H′-7 (1.51 ppm); of the two multiplets, H′-7 has strong NOE with the methyl protons rather than H-7.

The weak NOE between 0.68 and 2.68 ppm (Fig. 5) suggest that the signal at 2.68 ppm is due to H-3a. The ^{1}H—^{1}H correlation between 2.68 and 3.62 ppm and a strong NOE between 3.62 and 3.97 ppm (dd, 1H, J = 11.7, 3.7 Hz) clearly indicate that the signals at 3.62 and 3.97 ppm are respectively due to H-2a and H-6a. The H-6a proton has correlation with the signals at 2.54 (dd, 1H, J = 12.8, 4.0 Hz) and 2.88 ppm (t, 1H, J = 12.1 Hz). Moreover, the 2.54 and 2.88 ppm signals having a correlation between them, which clearly indicates that, the signals are due to the protons from the same carbon C-5. Of the two signals, the doublet of doublet at 2.54 ppm has NOE with the benzylic proton H-6a, whereas, the triplet at 2.88 ppm shows NOE with the aryl signal doublet of doublet at 7.51 ppm, which gives an unambiguous idea to designate the signals at 2.54 and 2.88 ppm to H-5e and H-5a, respectively.

As H-5a, the H-3a, H-2a and H-6a are also showing NOE with the signal at 7.51 ppm (dd, 4H), which clearly indicate that the doublet of doublet at 7.51 ppm corresponds to the *ortho* protons of the phenyl groups at C-2 and C-6 (*i.e.*, H-2″ and H-6″). According to ^{1}H—^{1}H and NOE correlations between 7.51 and 7.36 ppm (dd, 4H), the latter is assigned to the *meta* protons of the phenyl groups at C-2 and C-6 (*i.e.*, H-2‴ and H-6‴). The correlation between 7.36 and 7.27 ppm (m, 2H) supports to assign the multiplet to the *para* protons of the phenyl groups at C-2 and C-6 (*i.e.*, H-2⁗ and H-6⁗). The NOEs of 6.82 ppm (dd, 2H) with the doublets at 3.50 and 3.61 ppm, as well as by the ^{1}H—^{1}H correlation between 7.10 (t, 3H) and 6.82 ppm, the phenyl protons of the N—Bn are assigned. According to these correlations, the signals at 6.82 and 7.10 ppm are designated to the *ortho* and *meta*/*para* protons of the N—Bn group.

An interesting observation is, the N—Bn methylenic protons are raised to give two separate signals at 3.50 (d, J = 15.0 Hz) and 3.61 ppm because of their diastereotopic nature. Of them, the doublet at 3.61 ppm is overlapped with the doublet of the H-2a appeared at 3.62 ppm, thus appearing as like as a triplet.

Overall, the chemical shifts and coupling constants as well as COSY and NOE correlations clearly suggest that the compound exists in a chair conformation with equatorial orientation of all the substituents; *i.e.*, phenyl groups at C-2/C-6, benzyl and ethyl group at nitrogen and C-3 of the piperidone ring, respectively. A decrease of $^3J_{5a,6a}$ and a counter-wise increase of $^3J_{5e,6a}$ is observed compare to its non-N-benzylated parent piperidone **9**, which suggest that there is a puckering about the C-5 and C-6 bond, due to the incorporation of the benzyl moiety at the secondary amino group. Conformation of the ethyl group is schematically represented in Fig. 6. The proton chemical shifts of analogous C-3 ethyl substituted compounds **23**–**25** are assigned according to **22** and provided in Table 1. Akin to **22**, compounds **23**–**25** are also adopted the same stereochemistry as in Fig. 5.

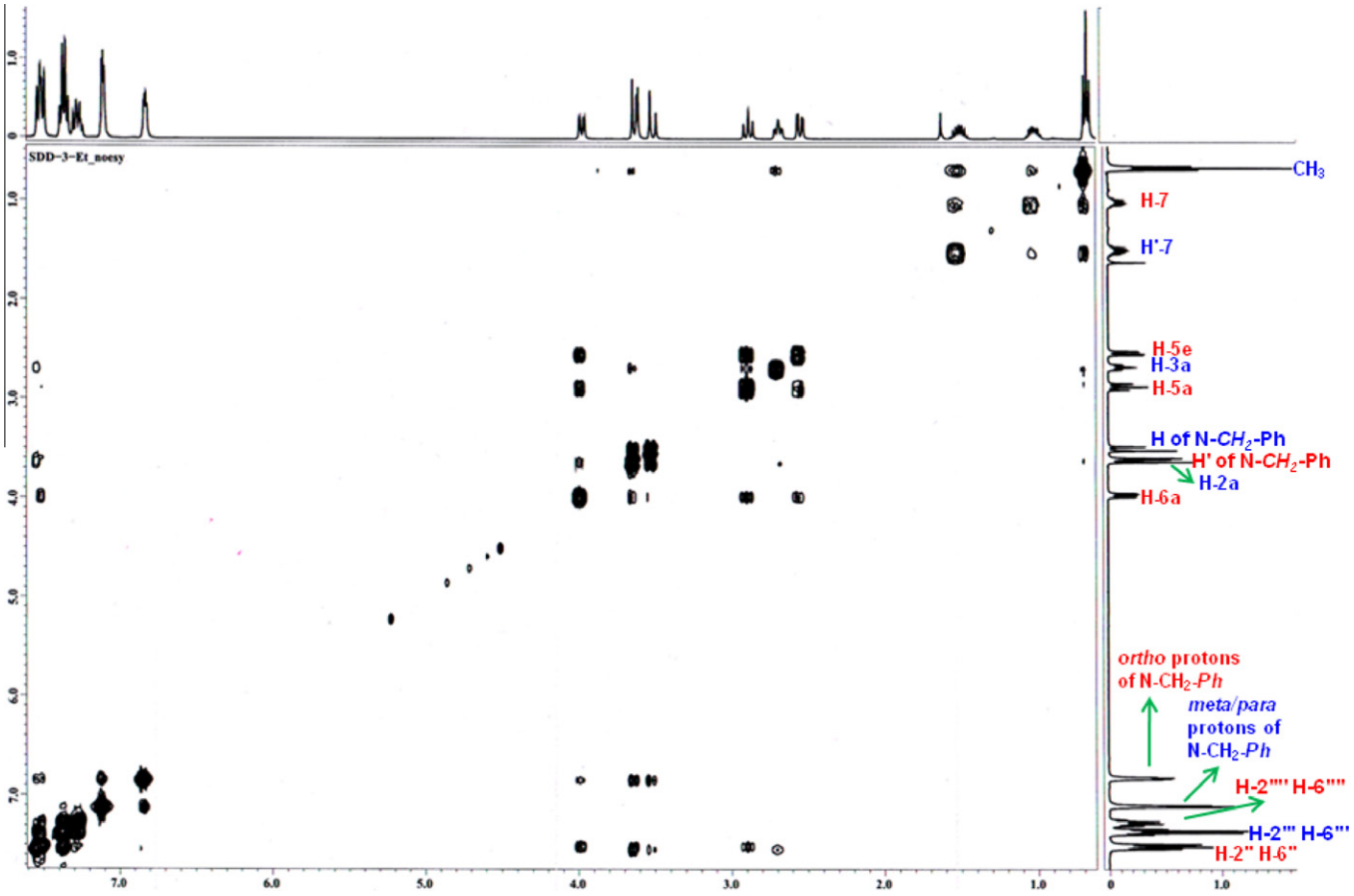


Fig. 4. NOESY spectrum of compound **22**.

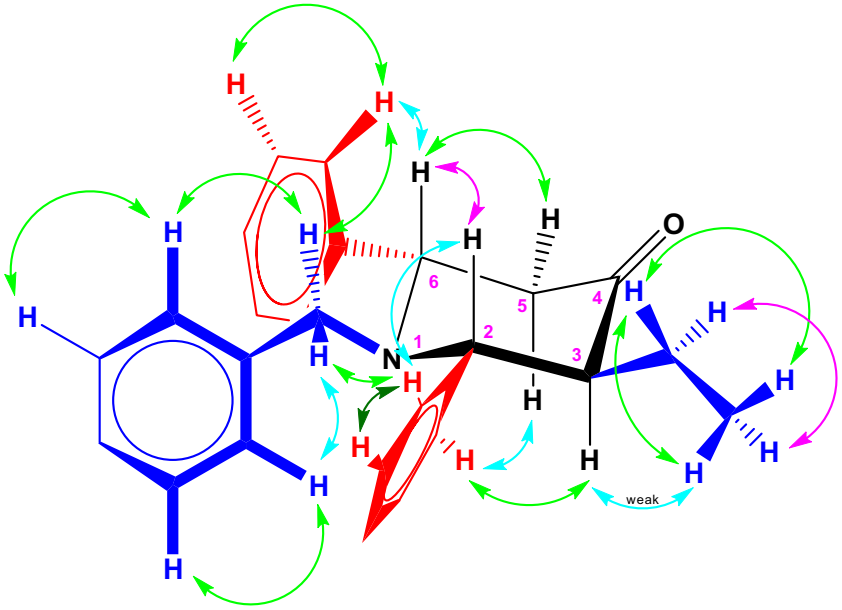


Fig. 5. The important NOE correlations observed in the NOESY spectrum of compound **22**.

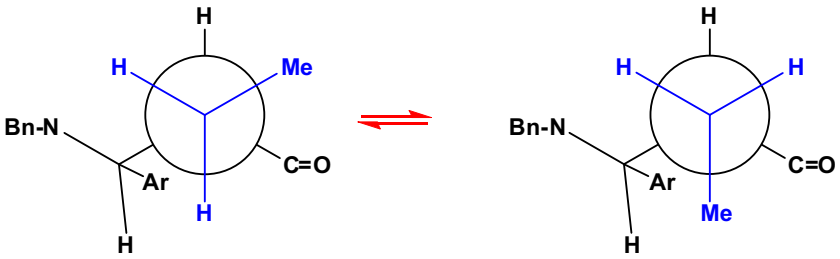


Fig. 6. Conformation of the ethyl group of compounds **22**–**25**.

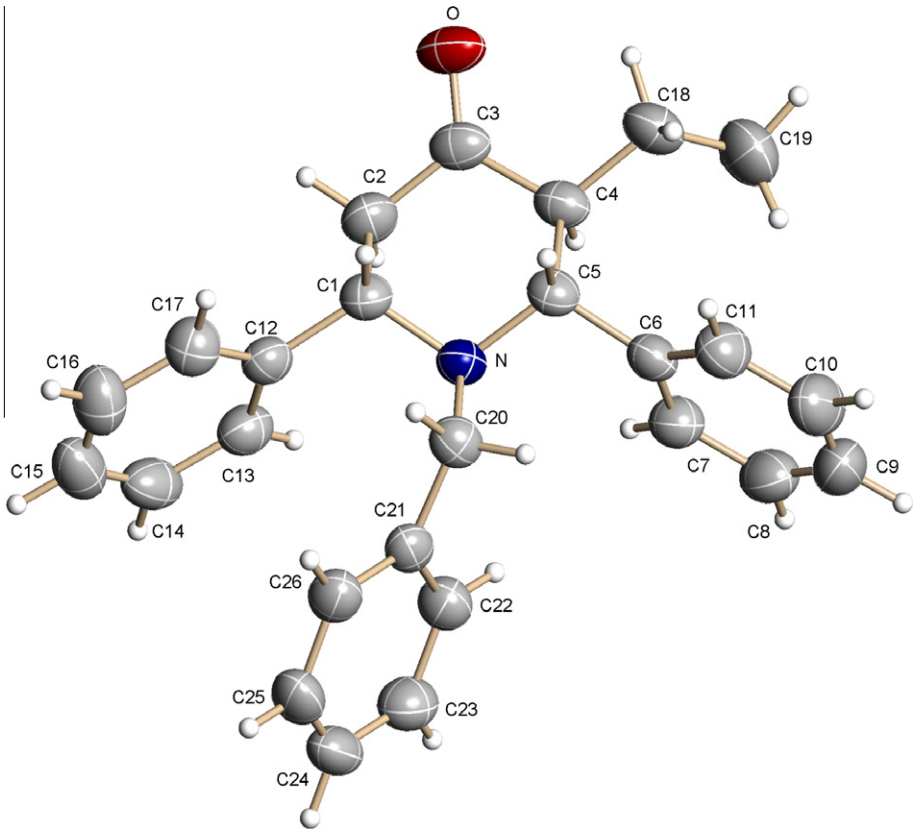


Fig. 7. ORTEP of the compound **22**. Displacement ellipsoids are drawn at 50% probability.

*3.3. Single-crystal XRD study of 1-benzyl-3-ethyl-2,6-diarylpiperidin-4-one **22***

To confirm the above ascertained stereochemistry of **22** by 1D and 2D NMR studies, a single-crystal X-ray diffraction analysis has been performed, and as a result, the following information about the puckering in the piperidone ring C1—C2—C3—C4—C5—N has been acquired. According to Nardelli [31], the smallest displacement asymmetry parameters q_2 and q_3 are 0.0908 and −0.5634 Å, respectively. In accordance with Cremer and Pople [32], the ring puckering parameters such as total puckering amplitude 'Q_T' and the phase angle 'θ' are 0.5707 Å and 170.85°. Thus, all puckering parameters strongly support a slightly distorted chair conformation for the piperidone ring; for the ideal chair, 'Q_T' and 'θ' should be 0.63 Å and 0° or 180°. ORTEP of the compound **22** is shown in Fig. 7.

An equatorial orientation of the ethyl group is witnessed by its torsion angles −176.42(12)° [C2—C3—C4—C-18] and 177.34(11)° [N—C5—C—4—C18]. The torsion angles of the phenyl groups on both sides of the amino group are 172.91(11) [C3—C2—C1—C12] and 172.64(10)° [C3—C4—C5—C6], which support the equatorial orientation of the phenyl groups on both sides of the amino group. The N atom of the piperidone molecule shows the sp^3 hybridization, which can be noticed from the angles around that nitrogen. The N—Bn group also adopts an equatorial disposition to the best plane of the piperidone ring, which is evidenced from the torsion angles C20—N—C1—C2 = −176.95(10)° and C20—N—C5—C4 = −177.81(10)°. The orientations of the phenyl groups at various positions of the molecule **22** are schematically represented in Fig. 8.

Overall, the detailed crystallographic studies such as asymmetry parameters, ring puckering parameters and torsion angles calculated for **22** proved that the piperidone ring exists in a slightly distorted chair conformation with equatorial orientation of the phenyl rings on both sides of the tertiary amino group along with an equatorial orientation of all other substituents.

Even though there is no classical hydrogen bond, the molecule is stabilized by inter and intramolecular interactions as follows. The crystal packing is stabilized by an intermolecular C1—H1——O interaction as shown in Fig. 9 (C1—H1——O = 2.52 Å) and, there is

an intramolecular interaction exists between C18—H18A and O (C18—H18—O = 2.53 Å). Further, the crystal packing is stabilized by two weak N—H···π interactions *viz.*, C19–H19A——*Cg* (*Cg* = C6 to C11) and C9–H9——*Cg* (*Cg* = C12 to C17) with 2.81 and 2.82 Å, respectively.

3.4. ^{13}C NMR spectral study of 1-benzyl-3-ethyl-2,6-diarylpiperidin-4-one **22**

The ^{13}C NMR spectrum of compound **22** is reproduced in Fig. 10 and the assignments are summarized in Table 2. To make an unambiguous assignment one-bond ^{1}H—^{13}C correlation spectrum (HSQC) has been recorded and reproduced in Fig. 11; for the better understanding, the correlations are provided in Table 4. The overlapped two doublets at 3.62 (H-2a) and 3.61 ppm (H of NCH_2-Ph) show the correlations with 71.06 and 53.39 ppm, respectively. The H′ of NCH_2-Ph at 3.50 also shows correlation with 53.39 ppm. Hence, without ambiguity 53.39 ppm is assigned to the methylene carbon of the N—Bn, vice-versa, it confirms the methylene protons assignments. The signal at 71.06 ppm is designated to the C-2 and the signal at 65.97 ppm is allocated to the C-6 by their respective correlation with the doublet of doublets at 3.62 and 3.97 ppm. Similarly, the ascertained protons such as H-7 and H′-7 as well as H-5a and H-5e by ^{1}H—^{1}H COSY and NOESY also further confirmed by the HSQC correlations and as a consequence the signals at 18.82 and 51.67 ppm are assigned to C-7 and C-5, respectively.

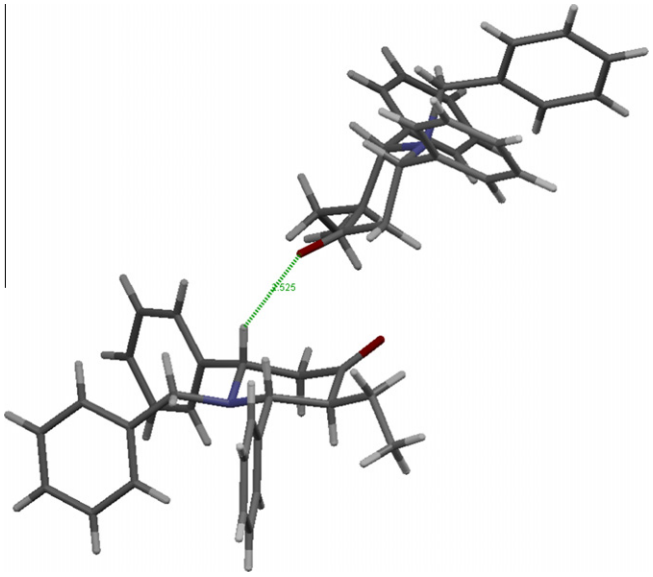


Fig. 9. The crystal structure is stabilized by the weak intermolecular C—H—O interaction. The C1—H1——O1 = 2.525 Å.

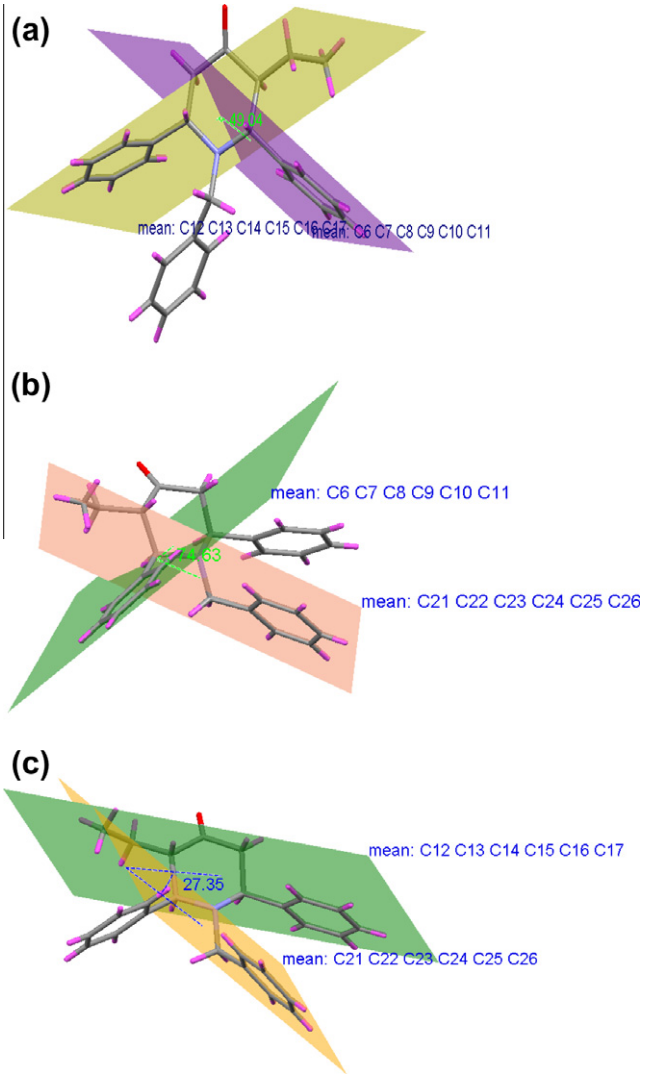


Fig. 8. Angles between the various phenyl groups of compound **22**: (a) between C1 and C-5 is 49.04°; (b) between C5 and C20 is 74.63°; (c) between C1 and C20 is 27.35°.

The aryl carbons are also assigned based on their correlation with corresponding protons; however, the signals at 136.70, 141.90, 143.23 and 208.47 have no correlation with any of the proton signals, they are due to the *ipso* carbons. Of them, the resonances at 208.47 and 136.70 ppm are designated to the carbonyl carbon C-4 and N—Bn *ipso* carbon whereas 141.90 and 143.23 are assigned to the *ipso* carbons C-2′ and C-6′, respectively [26]. With reference to **22**, the carbon signals of **22**–**25** are assigned and reproduced in Table 2.

The effects on the carbon chemical shifts of **9** by the N-benzylation (*i.e.*, in **22**) are accounted and summarized in Table 5. Because of N-benzylation, α, β and γ carbons to the ring nitrogen experienced deshielding. Of them, very particularly, the α-carbons C-2 and C-6 are deshielded to the maximum of 4.45 and 4.35 ppm, respectively.

3.5. ^{1}H and ^{13}C NMR spectral studies of 1-benzyl-3-methyl-2,6-diarylpiperidin-4-ones **14**–**21**

The proton NMR spectrum of 1-benzyl-3-methyl-2,6-diphenylpiperidin-4-one **14** is reproduced in Fig. 12. In this, one of the doublets of N-CH_2-Ph and the doublet of H-2a are slightly merged, not overlapped as in **22**. The H and H′ of N—CH_2-Ph appear at 3.63 (d, 1H, J = 15.0 Hz) and 3.53 ppm (d, 1H, J = 15.0 Hz) whereas the H-2a appears at 3.48 (d, 1H, J = 10.2 Hz). All other piperidone ring and aryl protons signals are almost similar to that **22** whereas the methyl at C-3 appears as a doublet at 0.72 ppm (J = 6.6 Hz). Similarly, the proton chemical shifts of **15**–**21** are assigned and summarized in Table 1.

In the compounds **14**–**21**, the coupling constants as well as the chemical shifts and multiplicity are similar to that of **22**. Hence, suggest that these compounds also exist in a chair conformation with equatorial orientation of all the substituents as in Fig. 5. As in **22** and its analogs, a decrease of $^{3}J_{5a,6a}$ and a counter-wise increase of $^{3}J_{5e,6a}$ are observed for **14** and its analogs **15**–**21**, compare to corresponding non-N-benzylated compounds. In **14**,

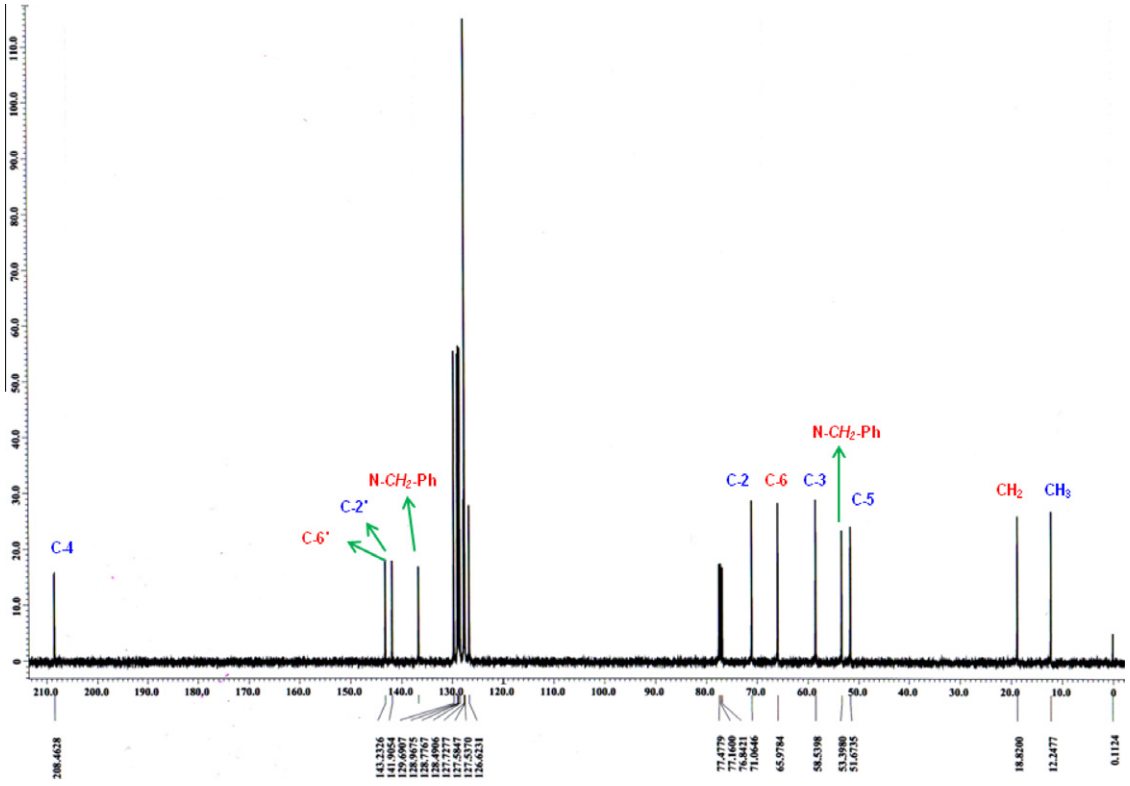


Fig. 10. The ^{13}C NMR spectrum of compound **22**.

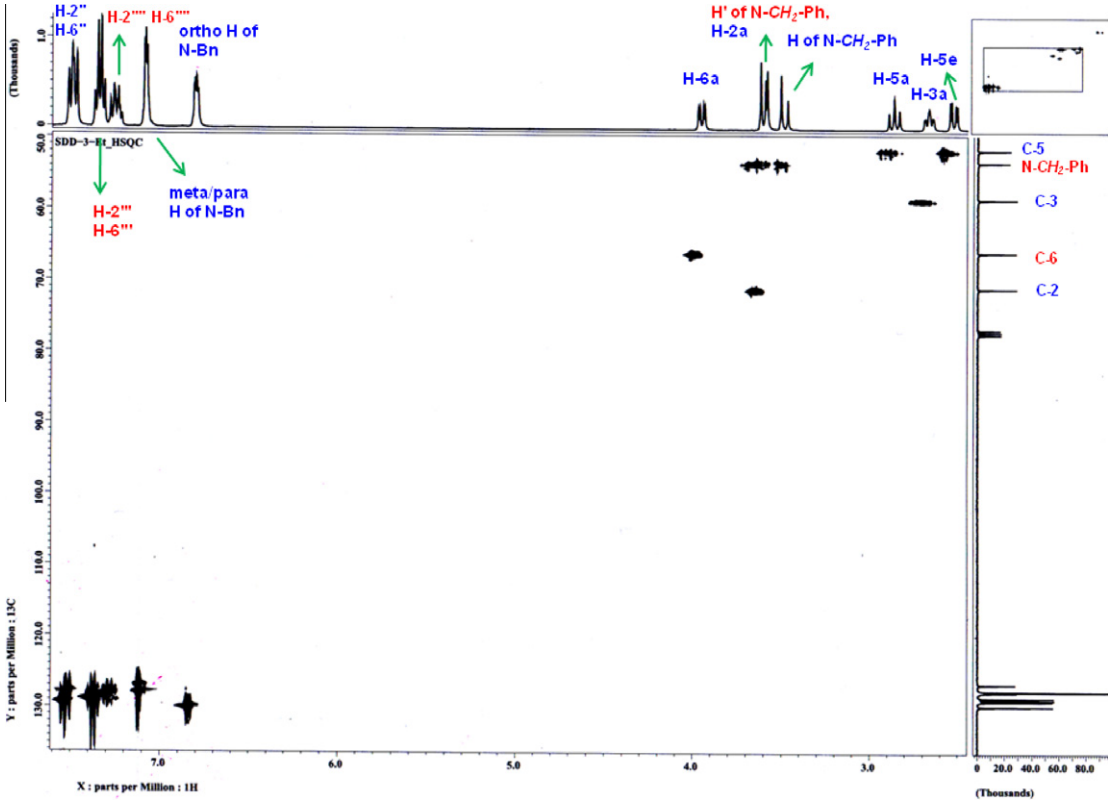


Fig. 11. HSQC ($^{1}H—^{13}C$ one bond correlation) spectrum of compound **22**.

the $^{3}J_{5a,6a}$ and $^{3}J_{5e,6a}$ are 0.5 and 0.63 Hz decreased and increased, respectively, compare to its parent piperidone **1**, which leads to conclude the puckering about the C-5 and C-6 bond, due to the incorporation of the benzyl group at ring nitrogen.

Table 4
Correlations in the HSQC spectrum of compound **22**.

Signal (δ in ppm)	Correlations
7.51 (dd, 4H, *ortho* protons of the Ph at C-2/ C-6. *i.e.*, H-2″/H-6″)	128.96, 127.58
7.36 (dd, 4H, *meta* protons of the Ph at C-2/ C-6. *i.e.*, H-2‴/H-6‴)	128.49
7.27 (m, 2H, *para* protons of the Ph at C-2/ C-6. *i.e.*, H-2⁗/H-6⁗)	127.53
7.10 (t, 3H, *meta* and *para protons* of the N—Bn)	127.72, 126.62
6.82 (dd, 2H, *ortho* protons of the N—Bn)	129.69
3.97 (dd, 1H, H-6a)	65.97
3.62 (1H, H-2a)	71.06
3.61 (1H, H of N—CH_2-Ph)	53.39
3.50 (1H, H′ of N—CH_2-Ph)	53.39
2.88 (t, 1H, H-5a)	51.67
2.68 (unresolved dt, 1H, H-3a)	58.53
2.54 (dd, 1H, H-5e)	51.67
1.51 (m, 1H, H′-7)	18.82
1.02 (m, 1H, H-7)	18.82
0.68 (t, 3H, CH_3)	12.24

The carbon signals are assigned (Table 2) with the comparison of **22** as well as corresponding parent compound with the effect of N-benzylation.

*3.6. ^1H and ^{13}C NMR spectral studies of 1-benzyl-3-isopropyl-2,6-diphenylpiperidin-4-one **26***

The ^1H NMR spectrum of **26** is reproduced in Fig. 13. In this spectrum, due to the diastereotopic nature of the methyl groups of isopropyl at C-3, they raised to give two doublets, though with very close variations in their resonances respectively at 0.95 (d, 3H, J = 6.9 Hz) and 0.92 (d, 3H, J = 6.9 Hz). Similarly, the N—Bn methylene protons appear as two doublets at 3.60 (d, 1H, J = 15.0 Hz) and 3.49 (d, 1H, J = 15.0 Hz) with characteristic diastereotopic couplings. The phenyl protons resonances are assigned according to **22** and there is no significant deviation; however, there is some significant variations noticed in the piperidone ring protons and their coupling constants due to the replacement of the ethyl by isopropyl at C-3 of **22**.

Table 5
The effect of N-benzylation on ^{13}C chemical shifts of parent piperidones (δ, ppm).

Compound	C-2	C-3	C-4	C-5	C-6	C-2′	C-6′	C-7
14	−4.45	−0.26	−0.61	−0.53	−4.36	−0.32	−0.73	−1.21
15	−4.73	0.15	0.65	0.05	−4.49	−0.08	−0.43	−1.22
16	−4.27	0.00	0.73	−0.29	−4.18	1.88	2.66	−1.19
19	−4.63	0.23	1.01	0.97	−4.47	−0.96	−2.19	−1.02
22	−4.45	−0.24	−0.33	−0.32	−4.35	−0.21	−0.66	−0.98
26	−3.43	−0.30	0.02	0.74	−3.62	0.01	−0.35	−1.05

A negative sign denotes deshielding.

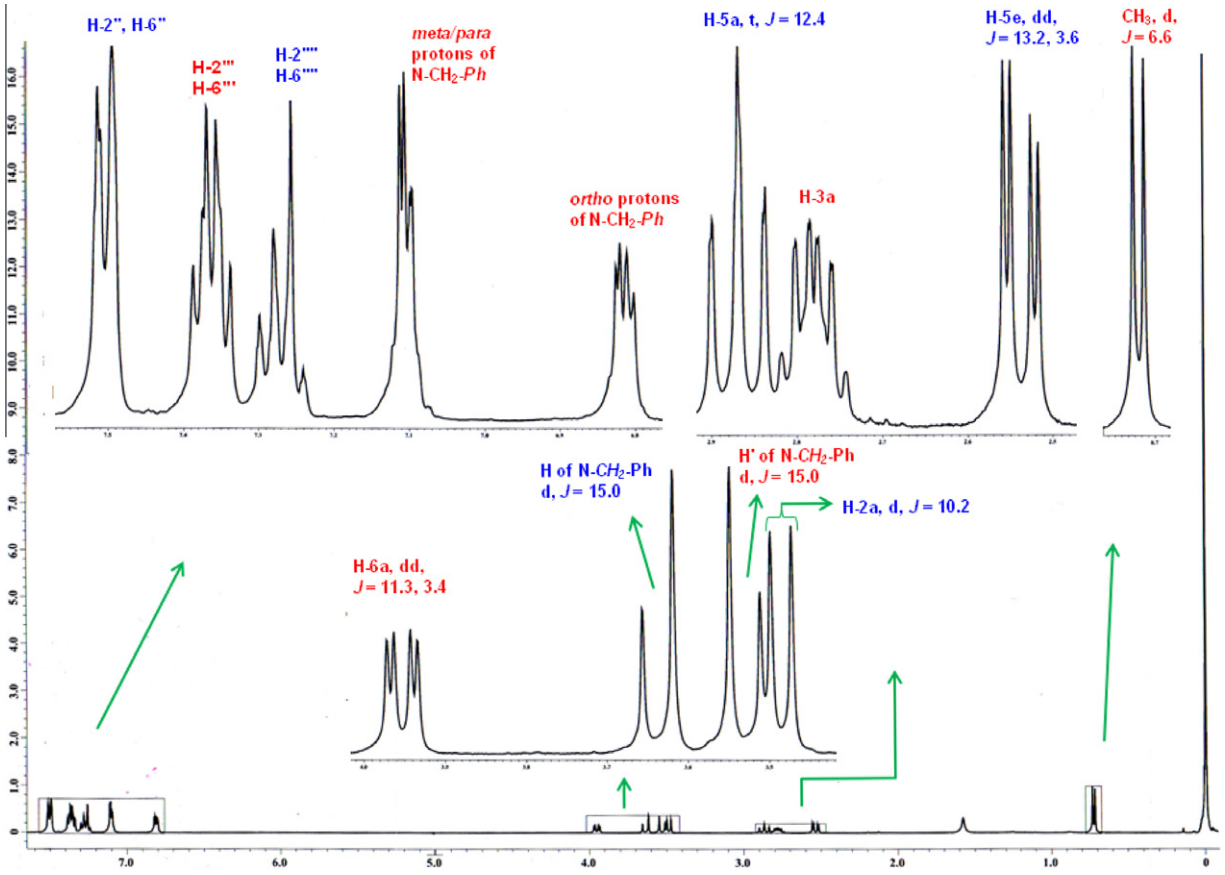


Fig. 12. ^1H NMR spectrum of compound **14**.

The benzylic protons H-2a and H-6a are deshielded by 0.37 and 0.08 ppm respectively whereas the H-5a is shielded by 0.11 ppm; however, there is no variation in H-3a and H-5e, but the multiplicity of H-3a is varied from **22**. In **22**, H-3a appears as an unresolved doublet of triplet at 2.54 ppm while in **26**, which appears as a doublet of doublet at 2.55 ppm (1H, J = 9.5, 3.2 Hz). The coupling constants 9.5 and 3.2 Hz are due to the vicinal couplings $^3J_{2a,3a}$ and $^3J_{2a,H\text{-}7}$, respectively. On the basis of this coupling constant, conformation of the isopropyl group at C-3 is deduced and depicted in Fig. 14a.

Although the vicinal coupling constants support the chair conformation with equatorial orientations of all the substituents, a decrease of 0.7 Hz in $^3J_{2a,3a}$ and 1.1 Hz in $^3J_{5a,6a}$ and an increase of 1 Hz in $^3J_{5e,6a}$ are observed compare to **14**. These variations suggest that there is a possibility for the existence of this molecule in boat conformation to a considerable population in solution state as in Fig. 14b. Further, the possibility of boat conformation is supported by the decrease of H-5a; in the boat form of **26**, H-5a would not be perfectly in axial position and seems to occupy an equatorial position and, as a consequence, which involved in the interaction with C=O and hence, the H-5a in boat form is more deshielded than H-5e.

The ^{13}C NMR spectral assignments are made by the comparison of **14** and **22** with the impact of isopropyl group at C-3. Moreover, compound **13** used to assign the signals with the impact of N-benzylation. The ^{13}C NMR chemical shifts of **26** and the impact of N-benzylation on its chemical shifts are summarized in Tables 2 and 5, respectively.

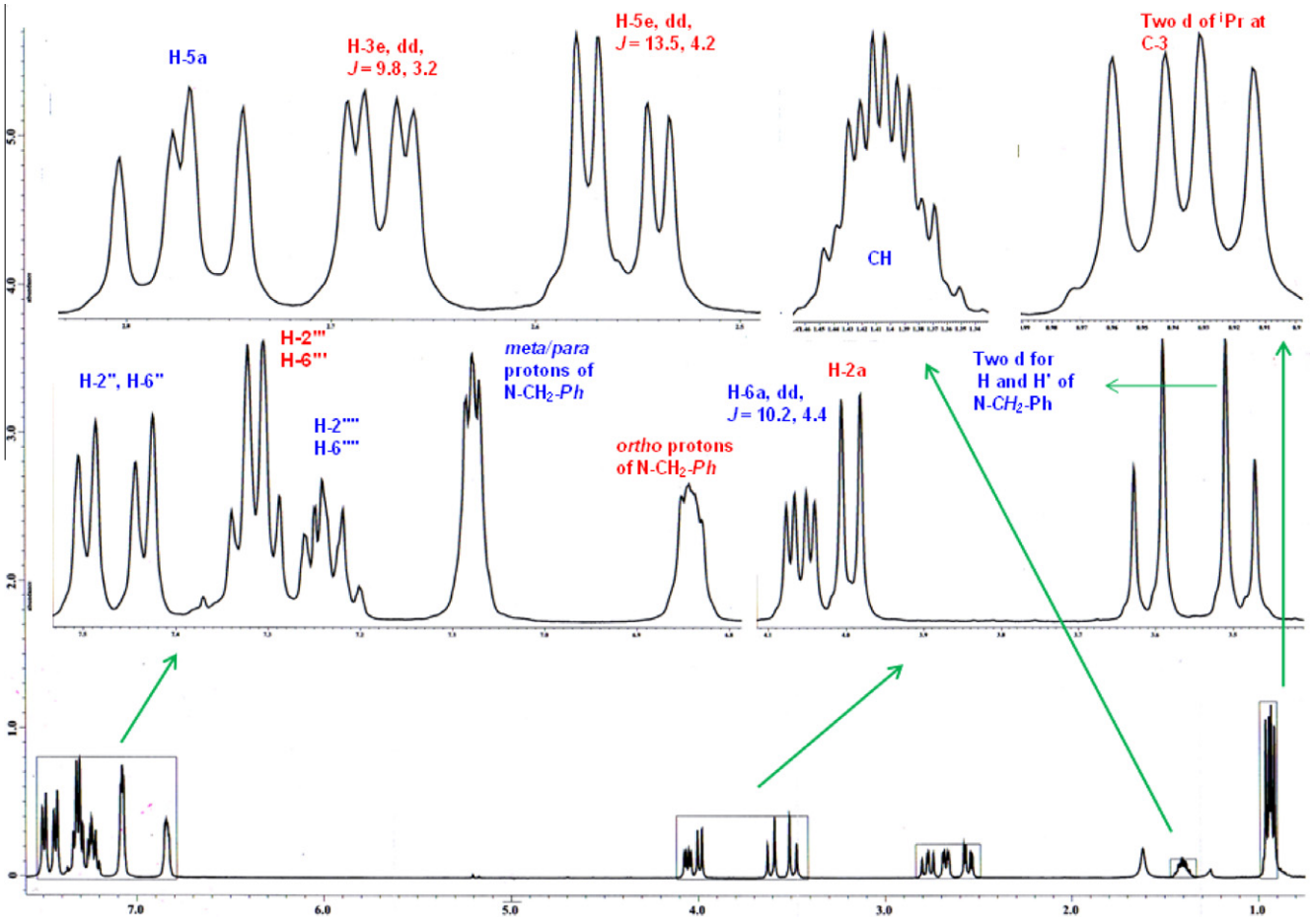


Fig. 13. ^{1}H NMR spectrum of compound **26**.

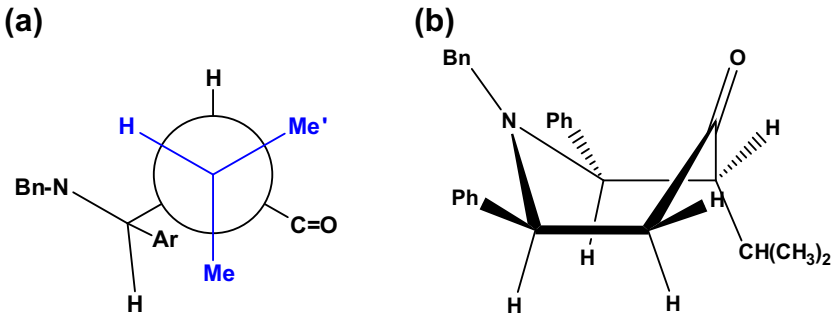


Fig. 14. (a) Conformation of the isopropyl group of compound **26**; (b) possible boat conformation of **26**.

4. Conclusions

Thirteen novel N-benzylated 3-alkyl-2,6-diarylpiperidin-4-ones **14**–**26** were conveniently synthesized in high yields 87–92% and characterized by their analytical and spectral data. The $^{1}H/^{13}C$ NMR spectral/stereochemical assignments have been unambiguously carried out by use of $^{1}H—^{1}H$ COSY, $^{1}H—^{13}C$ COSY and NOESY correlations. According to NMR studies, there is a marked effect of N-benzylation is observed on the piperidone carbons and their associated protons. On the other hand, irrespective of the nature and position of the substituents at C-3 as well as phenyl groups at C-2/C-6, all compounds **14**–**26** exist in a chair conformation with equatorial orientation of the substituents at C-2, C-3, C-6 and N. Beside the impact on chemical shifts of **26** by the introduction of $CH(CH_3)_2$ at C-3 of **14**, a notable deviation in the coupling constants (a decrease of 0.7 Hz in $^{3}J_{2a,3a}$ and 1.1 Hz in $^{3}J_{5a,6a}$ and an increase of 1 Hz in $^{3}J_{5e,6a}$) suggest the possibility of significant population of boat conformation in solution, along with the predominant chair conformation. Moreover in all compounds, a decrease ($\approx$0.5–1.5 Hz) of $^{3}J_{5a,6a}$ and counter-wise increase of $^{3}J_{5e,6a}$ are observed compare to their corresponding non-N-benzylated analogs, which suggest that there is a puckering about C-5 and C-6 due to the incorporation of benzyl group at ring nitrogen, and it perhaps due to the proximity of the benzyl toward the phenyl at C-6 rather than the phenyl at C-2. This is supported by the single-crystal XRD data of **22**, the phenyl groups at C-6 and N—Bn is oriented at an angle of 27.35° with respect to one another, whereas C-2 and N—Bn is 74.63°. Moreover, as evidenced by the ring puckering parameters (Q_T = 0.5707 Å and θ = 170.85°), the compound **22** is deviated from the ideal chair conformation. The stereochemistry of C-2, C-3 and C-6 are identified as R, S and S, respectively.

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Appendix A. Supplementary material

All crystallographic parameters and data of **22** are provided. The complete set of structural parameters for **22** (CCDC No. 796481) in CIF format is available as an Electronic Supplementary Publication from the Cambridge Crystallographic Data Centre www.ccdc.cam.ac.uk/conts/retrieving.html. Mass spectra of all the N-benzylated compounds **14**–**26** are provided. Yields and melting points are provided in Table 5. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2010.12.054.

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