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Conformational analysis of 2,6-diarylpiperidin-4-one hydrazones by X-ray diffraction and NMR spectroscopy

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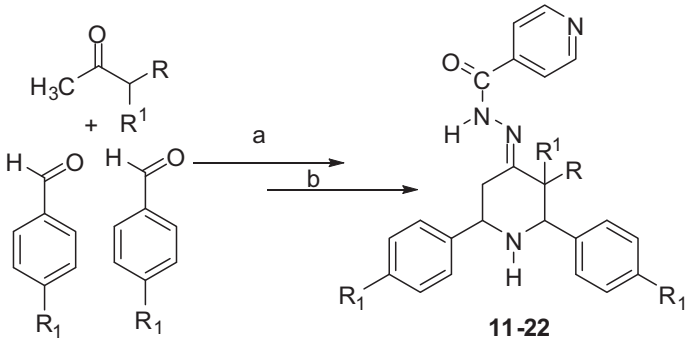
HIGHLIGHTS

- Conformational analysis study of 3*t*-alkyl-2*r*,6*c*-diarylpiperidin-4-one N-isonicotinoyl hydrazone.
- In solution compounds exist in two forms, there are the ***E*** and ***Z*** forms.
- Single crystal X-ray diffraction analysis.
- In solid state the compound have ***E*** configuration about the C=N bond.

GRAPHICAL ABSTRACT

A series of 3*t*-alkyl-2*r*,6*c*-diarylpiperidin-4-one N-isonicotinoylhydrazone (**11–22**) derivatives have been synthesized.



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ABSTRACT

A new series of 3*t*-alkyl-2*r*,6*c*-diarylpiperidin-4-one N-isonicotinoylhydrazones (**12–22**) derived from the condensation of 3*t*-alkyl-2*r*,6*c*-diarylpiperidin-4-ones with isoniazid (INH) is reported. Newly synthesized compounds have been characterized by using elemental analysis, IR, ^{1}H, ^{13}C and 2D NMR spectral analysis. Moreover, representative crystal structure of 3,3-dimethyl-2*r*,6*c*-diarylpiperidin-4-one N-isonicotinoylhydrazone has been determined by X-ray diffraction analysis.

NMR data revealed that two geometrical isomers (***E*** and ***Z***) are formed in all cases, and the piperidine ring adopts chair conformation. Whereas in solid state the compounds have ***E*** configuration about the C=N bond. These conclusions have also been confirmed by X-ray data of compound **16**.

Introduction

The NMR techniques are useful for the conformational analysis too. ^{1}H and ^{13}C NMR techniques have been extensively applied in deriving stereodynamical information about a wide variety of systems. These techniques gives information about the influence of

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electronic and conformational effects on chemical shifts [1,2]. Coupling constants can be used for conformational analysis since they depend on the torsional angle between two protons in adjacent carbons [3].

Continuing our studies on the synthesis of heterocyclic compounds with potential therapeutic activity, we report in this paper the synthesis and the structural study of a series of isoniazide hydrazones (**12–22**) derived from 3*t*-alkyl-2*r*,6*c*-diarylpiperidin-4-ones (**1–11**) characterized by IR and NMR spectroscopy. The unambiguous assignment of all proton and carbon resonances was achieved by double resonance experiments. The structure of 3,3-dimethyl-2*r*,6*c*-diarylpiperidin-4-one N-isonicotinoylhydrazone (**16**) in the solid state was determined by X-ray diffraction.

Experimental

Purchasing materials and recording spectra

All the solvents and chemicals (INH) were purchased from Sigma–Aldrich and were used as received and the purity of the compounds was checked by TLC. The melting points were recorded in open capillaries and are uncorrected. IR spectra were recorded in KBr (pellet forms) on AVATAR-330 FT-IR spectrophotometer (Thermo Nicolet) and noteworthy absorption levels (reciprocal centimeters) alone are listed. ^{1}H and ^{13}C NMR spectra of **12–22** have been recorded on a BRUKER DRX 500 NMR spectrometer operating at 500.03 MHz for ^{1}H and 125.75 MHz for ^{13}C, in DMSO-d_6. The following spectral parameters were used ^{1}H; acquisition time = around 3.0 s, number of scans = around 100 s, number of data points = 32 K and special with = 5000 Hz. ^{13}C; acquisition time = around 0.5 s, number of scans = around 1000, number of data points = 32 K and special with = 30,000 Hz. ^{1}H–^{1}H COSY, HSQC, HMBC spectra were recorded on a BRUKER DRX 500 MHz NMR spectrometer using standard parameters. All NMR measurements were made on 5 mm NMR tubes. The solutions were prepared by dissolving about 10 mg of the compound in 0.5 mL of DMSO-d_6.

Material synthesis

*Synthesis of 2r,6c-diarylpiperidin-4-ones (**1–11**)*

The parent 2*r*,6*c*-diarylpiperidin-4-one (**1–11**) were synthesized through Mannich reaction by adopting literature methods [4]. A mixture of ketone (0.1 mol), dried ammonium acetate (0.1 mol), appropriate benzaldehyde (0.2 mol) in ethanol (30 ml) and heated to simmering carefully. It was kept at room temperature for 12 h. Dry ether (50 ml) was added followed by concentrated hydrochloric acid (30 ml) and cooled in ice water. The precipitated hydrochloride was filtered and washed repeatedly with ethanol–ether (1:5) mixture. The hydrochloride was suspended in acetone, and made alkaline using strong ammonia solution. On dilution with excess of water, the base was precipitated which was filtered, vacuum dried and recrystallized from absolute alcohol.

*Synthesis of 2r,6c-diarylpiperidin-4-one N-isonicotinoylhydrazones (**12–22**)*

A mixture of 3*t*-alkyl-2*r*,6*c*-diarylpiperidin-4-ones (**1–11**) (1.0 mmol), isoniazid (1.5 mmol) in methanol and few drops of acetic acid was added and refluxed for 1–2 h. On the completion of reaction a solid mass was formed. After cooling to room temperature the precipitate was filtered and washed with cold mixture of ethanol and water. The crude product was recrystallized from ethanol. The results of elemental analysis and IR data are given in Tables 1 and 2. Elemental analysis shows excellent agreement between calculated and experimental values. Spectroscopic data for compounds **12–22** are presented below.

*2r,6c-Diphenylpiperidin-4-one isonicotinylhydrazone (**12**).* Pale yellow powder, yield 95%, mp: 172–173 °C; **^{1}H NMR**: δ = 3.93 (d, $J_{2a,3a}$ = 11.0 Hz; 1H, H-2a), 3.85 (d, $J_{5a,6a}$ = 12.3 Hz; 1H, H-6a), 2.42 (t, 1H, H-3a), 2.58 (d, $J_{3a,3e}$ = 12.8 Hz, 1H, H-3e), 2.04 (t, 1H, H-5a), 3.14 (d, 1H, H-5e), 2.88 (bs, 1H, NH), 11.04 (s, 1H, —CO—*NH*—), 8.71 (d, 2H, pyridine α), 7.72 (d, 2H, pyridine β), 7.73 (d, 4H, H-o, H-*o*′), 7.35-7.48 (dd, 4H, H-*m*, H-*m*′), 7.27 (m, 2H, H-*p*, H-*p*′) ppm; **^{13}C NMR**: δ = 60.84 (C-2), 59.62 (C-6), 43.25 (C-3), 36.80 (C-5), 163.33 (C=O), 161.98 (C=N), 149.94 (pyridine α), 121.59 (pyridine β), 141.02 (pyridine *ipso* carbon), 143.89 (C-2′, C-6′), 126.71, 126.51 (C-*o*, C-*o*′), 128.12 (C-*m*, C-*m*′), 127.03 (C-*p*, C-*p*′) ppm.

*3t-Methyl-2r,6c-diphenylpiperidin-4-one isonicotinylhydrazone (**13**).* White powder, yield 94%, mp: 209–210 °C; **^{1}H NMR**: δ = 3.53 (d, $J_{2a,3a}$ = 9.8 Hz, 1H, H-2a), 3.87 (d, $J_{5a,6a}$ = 11.5,Hz, 1H, H-6a), 2.62 (sextet, 1H, H-3a), 2.16 (t, 1H, H-5a), 3.16 (d, $J_{5a,5e}$ = 12.8 Hz, 1H, H-5e), 2.71 (s, 1H, NH), 11.06 (s,

Table 2
Characteristic IR stretching frequencies (cm^{-1}) of compounds **12–22**.

Compound	C=O	C=N	N—H (ring)	NH (amide)
12	1661	1511	3303	3167
13	1651	1546	3311	3183
14	1644	1524	3239	3189
15	1649	1510	3309	3173
16	1650	1545	3311	3183
17	1649	1546	3292	3189
18	1652	1548	3287	3186
19	1650	1545	3287	3178
20	1652	1544	3309	3204
21	1650	1547	3326	3181
22	1651	1549	3258	3188

Table 1
Physical data and analytical data of compounds **12-22**.

Compounds	Yield (%)	mp (°C)	Calculated			Experimental		
			% C	% H	% N	% C	% H	% N
12	90	172–173	75.50	5.94	15.12	74.55	5.88	15.07
13	91	209–210	74.91	6.24	14.57	73.86	6.20	14.54
14	90	210–212	63.52	4.85	12.35	63.53	4.80	12.30
15	85	184–185	68.49	5.23	13.32	67.40	5.21	13.36
16	89	216–217	75.28	6.52	14.05	75.24	6.55	13.09
17	75	206–207	75.95	7.03	13.13	77.90	7.01	13.15
18	72	180–182	70.66	6.54	12.21	70.62	6.57	12.26
19	94	210–211	64.19	5.13	11.98	64.21	5.09	11.96
20	85	196–197	69.05	5.52	12.89	69.08	5.47	12.76
21	65	165–166	–	–	–	–	–	–
22	62	185–187	–	–	–	–	–	–

1H, CO—NH—), 0.84 (d, $J_{3a,Me}$ = 6.4 Hz, 3H, —CH_3 at C-3), 8.71 (d, 2H, pyridine α), 7.72 (d, 2H, pyridine β), 7.49 (d, 4H, H-*o*, H-*o*′), 7.23-7.37 (m, 6H, H-*m*, H-*m*′, H-*p*, H-*p*′); **^{13}C NMR**: δ = 69.39 (C-2), 60.92 (C-6), 45.54 (C-3), 37.61 (C-5), 12.18 (CH_3 at C-3), 168.80 (C═O), 156.84 (C═N), 149.49 (pyridine α), 123.82 (pyridine β), 140.88 (pyridine *ipso* carbon), 142.35, 143.00 (C-2′, C-6′), 127.59, 127.84 (C-*o*, C-*o*′), 128.68, 128.489 (C-*m*, C-*m*′), 126.68 (C-*p*, C-*p*′) ppm.

*3t-Methyl-2r,6c-bis(p-chlorophenyl)piperidin-4-one isonicotinylhydrazone (**14**).* White powder, yield 90%, mp: 210–212 °C; **^{1}H NMR**: δ = 3.54 (d, $J_{2a,3a}$ = 9.53 Hz, 1H, H-2a), 3.89 (d, $J_{6a,5a}$ = 10.9 Hz; 1H, H-6a), 2.58 (sextet, 1H, H-3a), 2.10 (1H, H-5a), 3.15 (d, $J_{5a,5e}$ = 12.87 Hz; 1H, H-5e), 2.93 (bs, 1H, NH), 11.06 (s, 1H, —CO—*NH*—), 0.84 (d, *J* = 6.3 Hz, 3H, —CH_3 at C-3), 8.72 (d, 2H, pyridine α), 7.73 (d, 2H, pyridine β), 7.51 (t, 4H, H-*o*, H-*o*′), 7.41 (dd, 4H, H-*m*, H-*m*′); **^{13}C NMR**: δ = 67.52 (C-2), 58.95 (C-6), 44.66 (C-3), 37.19 (C-5), 12.22 (—CH_3 at C-3), 165.90 (C═O), 161.82 (C═N), 149.98 (pyridine α), 121.60 (pyridine β), 141.15 (pyridine *ipso* carbon), 142.76 (C-6′), 141.91 (C-2′), 129.7 (C-*o*, C-*o*′), 128.57 (C-*m*, C-*m*′), 131.49, 131.72 (C-*p*, C-*p*′) ppm.

*3t-Methyl-2r,6c-bis(p-flurophenyl)piperidin-4-one isonicotinylhydrazone (**15**).* White powder, yield 85%, mp: 184–185 °C; **^{1}H NMR**: δ = 3.55 (d, $J_{2a,3a}$ = 9.59 Hz, 1H, H-2a), 3.88 (d, $J_{6a,5a}$ = 11.5 Hz; 1H, H-6a), 2.57 (sextet, 1H, H-3a), 2.12 (t, 1H, H-5a), 3.15 (d, $J_{5a,5e}$ = 13.0 Hz; 1H, H-5e), 2.81 (bs, 1H, NH), 11.06 (s, 1H, —CO—*NH*—), 0.84 (d, 3H, —CH_3 at C-3), 8.72 (d, 2H, pyridine α), 7.73 (d, 2H, pyridine β), 7.51 (t, 4H, H-*o*, H-*o*′), 7.41 (dd, 4H, H-*m*, H-*m*′); **^{13}C NMR**: δ = 67.46 (C-2), 58.85 (C-6), 44.65 (C-3), 37.15 (C-5), 165.90 (C═O), 161.82 (C═N), 12.04 (—CH_3 at C-3), 166.23 (C═O), 160.05 (C═N), 149.84 (pyridine α), 121.45 (pyridine β), 139.05 (pyridine *ipso* carbon), 141.15 (C-6′), 139.87 (C-2′), 129.47 (C- C-*o*, C-*o*′), 114.69 (C-*m*, C-*m*′), 162.35 (J_{C-F} = C-*p*, C-*p*′) ppm.

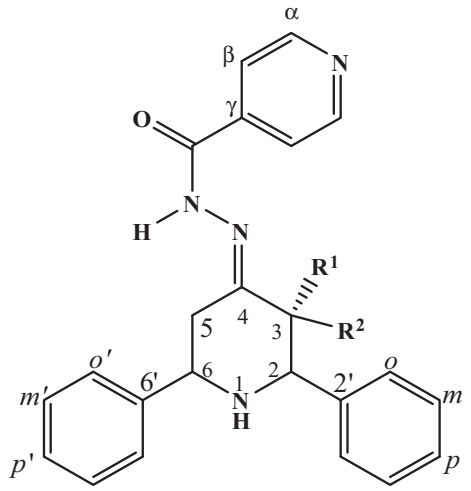
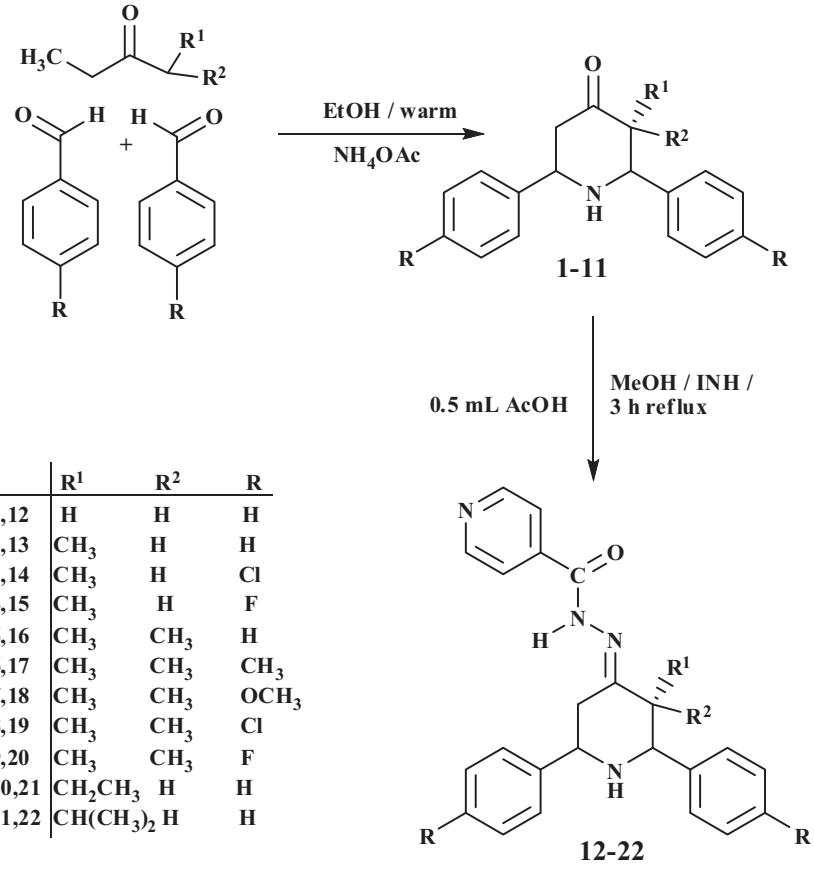


Fig. 1. Numbering and designation of carbon atoms in **12–22**.

*3,3-Dimethyl-2r,6c-diphenylpiperidin-4-one isonicotinylhydrazone (**16**).* White powder, yield 89%, mp: 216–217 °C; **^{1}H NMR**: δ = 3.76 (s, 1H, H-2a), 3.85 (d, $J_{6a,5a}$ = 11.6 Hz, 1H, H-6a), 2.28 (t, 1H, H-5a), 3.01 (d, $J_{5e,5a}$ = 13.11 Hz, 1H, H-5e), 2.67 (bs, 1H, NH), 11.03 (s, 1H, —CO—*NH*—), 1.03, 1.14 (s, 6H, —$CH_{3(a)}$, $CH_{3(e)}$ at C-3), 8.71 (d, 2H, pyridine α), 7.73 (d, 2H, pyridine β), 7.55 (d, 2H, H-2″), 7.46 (d, 2H, H-6″), 7.28–7.39 (m, 6H, H-*m*, H-*m*′, H-*p*,



	R^1	R^2	R
1,12	H	H	H
2,13	CH_3	H	H
3,14	CH_3	H	Cl
4,15	CH_3	H	F
5,16	CH_3	CH_3	H
6,17	CH_3	CH_3	CH_3
7,18	CH_3	CH_3	OCH_3
8,19	CH_3	CH_3	Cl
9,20	CH_3	CH_3	F
10,21	CH_2CH_3	H	H
11,22	$CH(CH_3)_2$	H	H

Scheme 1. Schematic diagram showing the synthesis of title compounds **12–22**.

H-*p*′); **^{13}C NMR**: δ = 69.61 (C-2), 60.04 (C-6), 42.97 (C-3), 33.79 (C-5), 22.77, 21.22 (—$CH_{3(e,a)}$ at C-3), 170.37 (C=O), 161.69 (C=N), 149.98 (pyridine α), 121.58 (pyridine β), 140.36 (pyridine *ipso* carbon), 144.10, 141.12 (C-6′, C-2′), 128.95, 128.16 (C-*o*, C-*o*′), 126.76 (C-2‴, C-6‴, 127.31, 127.16 (C-*p*, C-*p*′) ppm.

*3,3-Dimethyl-2r,6c-bis(p-methylphenyl)piperidin-4-one isonicotinylhydrazone (**17**).* White powder, yield 75%, mp: 206–207 °C; **^{1}H NMR**: δ = 3.72 (s, 1H, H-2a), 3.80 (d, $J_{6a,5a}$ = 11.64 Hz, 1H, 6a), 2.28 (t, 1H, H-5a), 2.95 (d, $J_{5a,5e}$ = 13.50 Hz, 1H, H-5e), 11.03 (s, 1H, —CO—*NH*—), 1.02, 1.13 (s, 6H, —$CH_{3(a)}$, $CH_{3(e)}$ at C-3), 8.72 (d, 2H, pyridine α), 7.73 (d, 2H, pyridine β), 7.42 (d, 2H, H-*m*), 7.34 (d, 2H, H-*m*′); **^{13}C NMR**: δ = 69.35 (C-2), 59.78 (C-6), 42.99 (C-3), 33.85 (C-5), 21.18, 20.58 ($CH_{3(a,e)}$ at C-3), 22.69 (CH_3 at C-2‴ and C-6‴), 170.81 (C=O), 161.55 (C=N), 149.95 (pyridine α), 121.51 (pyridine β), 136.14 (pyridine *ipso* carbon), 141.11, 137.35 (C-6′, C-2′), 126.58 (C-*o*, C-*o*′), 127.89 (C-*m*, C-*m*′), 128.68 (C-*p*, C-*p*′) ppm.

*3,3-Dimethyl-2r,6c-bis(p-methoxyphenyl)piperidin-4-one isonicotinylhydrazone (**18**).* White powder, yield 72%, mp: 180–182 °C; **^{1}H NMR**: δ = 3.72 (s, 1H, H-2a), 3.80 (1H, 6a), 2.28 (t, 1H, H-5a), 2.95 (d, $J_{5e,5a}$ = 14.5, $J_{5e,6a}$ = 3.0 Hz, 1H, H-5e), 11.03 (s, 1H, —CO—*NH*—), 1.02, 1.13 (s, 6H, —$CH_{3(a)}$, $CH_{3(e)}$ at C-3), 8.72 (d, 2H, pyridine α), 7.73 (d, 2H, pyridine β), 7.42 (d, 2H, H-*o*), 7.34 (d, 2H H-*o*′), 7.16 (m, 6H, H-*m*, H-*m*′); **^{13}C NMR**: δ = 69.02 (C-2), 59.49 (C-6), 43.10 (C-3), 33.92 (C-5), 22.73, 21.17 ($CH_{3(a,e)}$ at C-3), 55.01 (OCH_3 at C-2‴, C-6‴)ppm, 170.83 (C=O), 161.62 (C=N), 149.99 (pyridine α), 121.56 (pyridine β), 136.21 (pyridine *ipso* carbon), 141.13, 136.19 (C-6′, C-2′), 129.84, 127.80 (C-*o*, C-*o*′), 113.56, 112.75 (C C-*m*, C-*m*′), 158.41(C-*p*, C-*p*′).

*3,3-Dimethyl-2r,6c-bis(p-chlorophenyl)piperidin-4-one isonicotinylhydrazone (**19**).* White powder, yield 94%, mp: 210–211 °C; **^{1}H NMR**: δ = 3.76 (s, 1H, H-2a), 3.85 (d, $J_{6a,5a}$ = 11.4 Hz, 1H, H-6a), 2.28 (t, 1H, H-5a), 3.01 (d, $J_{5e,5a}$ = 13.4 Hz, 1H, H-5e), 2.67 (bs, 1H, NH), 11.03 (s, 1H, —CO—*NH*—), 1.03, 1.14 (s, 6H, —$CH_{3(a)}$, $CH_{3(e)}$ at C-3), 8.71 (d, 2H, pyridine α), 7.73 (d, 2H, pyridine β), 7.55 (d, 2H, H-*o*), 7.46 (d, 2H, H-*o*′), 7.28-7.39 (m, 4H, H-*m*, H-*m*′); **^{13}C NMR**: δ = 69.61 (C-2), 60.04 (C-6), 42.97 (C-3), 33.79 (C-5), 22.77, 21.22 (—$CH_{3(e,a)}$ at C-3), 169.65 (C=O), 161.67 (C=N), 149.95 (pyridine α), 121.53 (pyridine β), 139.21 (pyridine *ipso* carbon), 142.97, 141.07 (C-6′, C-2′), 128.95, 128.16 (C-*o*, C-*o*′), 126.76 (C-*m*, C-*m*′), 127.31, 127.16 (C-*p*, C-*p*′) ppm.

*3,3-Dimethyl-2r,6c-bis(p-fluorophenyl)piperidin-4-one isonicotinylhydrazone (**20**).* White powder, yield 85%, mp: 196–197 °C; **^{1}H NMR**: δ = 3.75 (s, 1H, H-2a), 3.84 (d, $J_{6a,5e}$ = 11.68 Hz, 1H, H-6a) 2.23 (t, 1H, H-5a), 2.99 (d, $J_{5a,5e}$ = 12.96 Hz, 1H, H-5e), 2.77 (bs, 1H, NH),

Table 3
Crystal data and structure refinement of compound **16**.

Empirical formula	$C_{25}H_{26}N_4O$
Formula weight	398.5
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, *P*–*1*
Unit cell dimension	*a* = 6.21280(10) Å, α = 65.29(10)° *b* = 12.8346(3), Å, β = 78.82(10)° *c* = 15.0022(3), Å, γ = 86.94(10)°
Volume	1065.62(4) Å^3
Z, density	2, 1.242 Mg/m^3
Absorption coefficient	0.078 mm^{-1}
F(000)	424
Crystal size	0.22 × 0.18 × 0.16 mm
Theta range for data collection	1.78–28.61°
Limiting indices	$-8 \leqslant h \leqslant 8$, $-17 \leqslant k \leqslant 17$, $-20 \leqslant l \leqslant 20$
Reflections collected	25,613/5420 [*R*(int) = 0.0232]
Completeness to theta	25 99.8%
Absorption correction	Semi-empirical from equivalents
Refinement method on	Full-materix least square on F^2
Data/restraints/parameter s	5420/0/271
Goodness-of-fit on F^2	1.041
Final R Indices [$I > 2$sigma(I)]	[$I > 2$sigma(I)] R_1 = 0.0505, wR_2 = 0.1406
CCDC No	653067

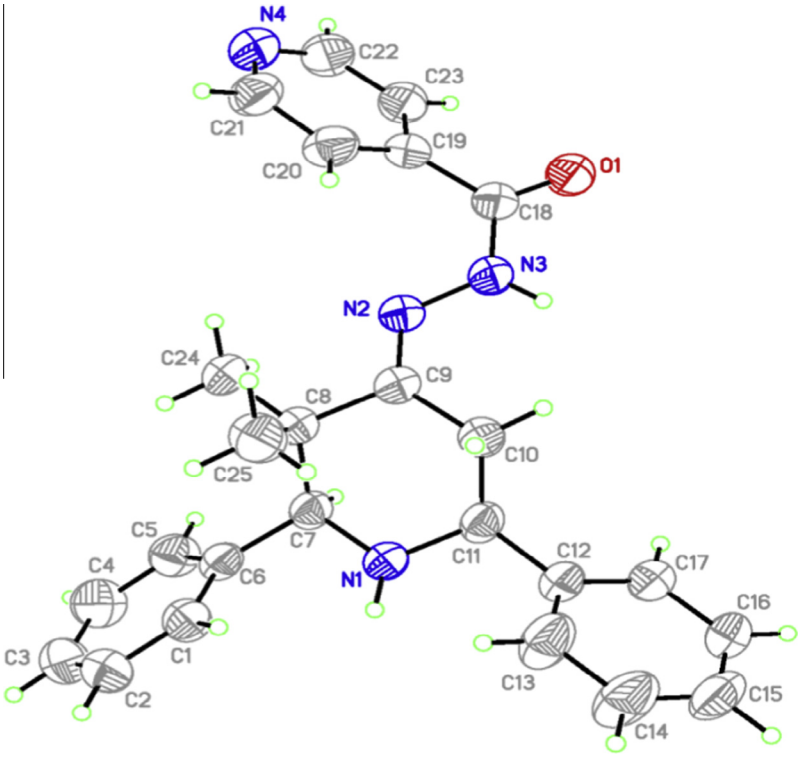


Fig. 2. ORTEP diagram of compound **16**.

Table 4
Selected Bond lengths, Bond angles and Torsional angles for **16**.

Bond lengths [A]		Torsional angles [°]	
C(7)—N(1)	1.4600(17)	C(4)—C(5)—C(6)—C(7)	176.04(16)
C(7)—C(8)	1.555(2)	C(2)—C(1)—C(6)—C(7)	−175.73(15)
C(7)—H(7A)	0.98	C(5)—C(6)—C(7)—N(1)	−138.40(15)
C(8)—C(9)	1.524(2)	C(1)—C(6)—C(7)—N(1)	37.83(19)
C(8)—C(25)	1.530(2)	C(5)—C(6)—C(7)—C(8)	97.18(17)
C(8)—C(24)	1.530(2)	C(1)—C(6)—C(7)—C(8)	−86.59(17)
C(9)—N(2)	1.2752(19)	N(1)—C(7)—C(8)—C(9)	56.96(15)
C(9)—C(10)	1.506(2)	C(6)—C(7)—C(8)—C(9)	−178.86(11)
C(10)—C(11)	1.531(2)	N(1)—C(7)—C(8)—C(25)	−62.36(16)
C(11)—N(1)	1.4564(19)	C(6)—C(7)—C(8)—C(25)	61.82(17)
C(18)—O(1)	1.2266(19)	N(1)—C(7)—C(8)—C(24)	176.34(12)
C(18)—N(3)	1.3429(19)	C(6)—C(7)—C(8)—C(24)	−59.48(17)
C(18)—C(19)	1.498(2)	C(25)—C(8)—C(9)—N(2)	−115.11(16)
N(1)—H(1B)	0.86	C(7)—C(8)—C(9)—N(2)	124.08(15)
N(2)—N(3)	1.3886(17)	C(25)—C(8)—C(9)—C(10)	66.94(18)
N(3)—H(3B)	0.86	C(24)—C(8)—C(9)—C(10)	−171.70(14)
Bond angles [°]		C(7)—C(8)—C(9)—C(10)	−53.86(17)
		N(2)—C(9)—C(10)—C(11)	−124.05(17)
C(5)—C(6)—C(7)	120.10(14)	C(8)—C(9)—C(10)—C(11)	53.63(18)
N(1)—C(7)—C(6)	109.42(11)	C(9)—C(10)—C(11)—N(1)	−53.48(16)
N(1)—C(7)—C(8)	109.88(12)	C(9)—C(10)—C(11)—C(12)	−175.89(12)
C(6)—C(7)—C(8)	115.27(12)	N(1)—C(11)—C(12)—C(17)	146.91(15)
C(9)—C(8)—C(25)	109.77(13)	C(10)—C(11)—C(12)—C(17)	−91.77(18)
C(9)—C(8)—C(24)	111.20(12)	N(1)—C(11)—C(12)—C(13)	−33.1(2)
N(2)—C(9)—C(10)	127.76(14)	C(10)—C(11)—C(12)—C(13)	88.2(2)
N(2)—C(9)—C(8)	116.54(13)	C(11)—C(12)—C(13)—C(14)	179.40(19)
C(10)—C(9)—C(8)	115.66(12)	O(1)—C(18)—C(19)—C(23)	32.7(2)
C(9)—C(10)—C(11)	109.85(13)	N(3)—C(18)—C(19)—C(23)	−148.77(16)
N(1)—C(11)—C(12)	110.57(12)	O(1)—C(18)—C(19)—C(20)	−143.86(18)
N(1)—C(11)—C(10)	108.68(12)	N(3)—C(18)—C(19)—C(20)	34.6(2)
O(1)—C(18)—N(3)	120.36(14)	C(18)—C(19)—C(20)—C(21)	177.20(16)
O(1)—C(18)—C(19)	119.62(13)	C(12)—C(11)—N(1)—C(7)	−174.80(12)
N(3)—C(18)—C(19)	120.01(13)	C(10)—C(11)—N(1)—C(7)	61.97(15)
C(11)—N(1)—C(7)	112.80(11)	C(6)—C(7)—N(1)—C(11)	167.08(12)
C(9)—N(2)—N(3)	119.05(13)	C(8)—C(7)—N(1)—C(11)	−65.41(16)
C(18)—N(3)—N(2)	119.97(13)	C(10)—C(9)—N(2)—N(3)	0.3(2)
C(18)—N(3)—H(3B)	120	C(8)—C(9)—N(2)—N(3)	−177.35(13)
N(2)—N(3)—H(3B)	120	O(1)—C(18)—N(3)—N(2)	−166.94(16)
		C(19)—C(18)—N(3)—N(2)	14.6(2)
		C(9)—N(2)—N(3)—C(18)	−175.73(16)

Table 5
C—N Bond lengths in **16**.

Bond	Bond lengths [Å]
C(7)—N(1)	1.460(17)
C(11)—N(1)	1.4564(19)
C(9)=N(2)	1.2752(19)
C(18)—N(3)[a]	1.3429(19)

[a] C(18)—N(3) bond is C(O)—N bond.

11.02 (s, 1H, —CO—*NH*—), 1.10, 1.00 (s, 6H, —$CH_{3(a)}$, $CH_{3(e)}$ at C-3), 8.70 (d, 2H, pyridine α), 7.72 (d, 2H, pyridine β), 7.48 (m, 2H, H-*o*), 7.58 (m, 2H, H-*o*′), 7.28–7.39 (m, 4H, H-*m*, H-*m*′); **^{13}C NMR**: δ = 68.71 (C-2), 59.22 (C-6), 42.89 (C-3), 33.78 (C-5), 21.08, 22.69 ($CH_{3(a,e)}$ at C-3), 169.87 (C=O), 161.76 (C=N), 150.00 (pyridine α), 121.61 (pyridine β), 136.47 (pyridine *ipso* carbon), 141.13, 140.26 (C-6′, C-2′), 130.66, 128.72 (C-*o*, C-*o*′), 114.4 (C-*m*, C-*m*′), 162.51 (C-*p*, C-*p*′) ppm.

*3t-Ethyl-2r,6c-diphenylpiperidin-4-one isonicotinylhydrazone (**21**).* White solid, yield 65%, mp: 165–166 °C; ^{1}H NMR: δ = 3.66 (d, $J_{2a,3a}$ = 8.08 Hz, 1H, H-2a), 3.89 (d, $J_{6a,5a}$ = 11.2 Hz, 1H, H-6a), 2.14 (t, 1H, H-5a), 3.16 (d, $J_{5a,5e}$ = 12.7 Hz, 1H, H-5e), 1.62 (heptet, 1H, H of —C*H*H′ of C-7), 1.19 (m, H, H′ of C-7), 0.81 (t, 3H, —CH_3 at C-7), 2.62 (bs, 1H, NH), 11.07 (s, 1H, —CO—*NH*—), 8.71 (d, 2H, pyridine α), 7.73 (d, 2H, pyridine β), 7.49 (m, 4H, H-*o*, H-*o*′), 7.23–7.37 (m, 6H, H-*m*, H-*m*′, H-*p*, H-*p*′) ppm; **^{13}C NMR**: δ = 67.22 (C-2), 60.42 (C-6), 51.89 (C-3), 38.17 (C-5), 19.38 (—*C*H_2—CH_3) 12.47 (—CH_2—*C*H_3), 165.92 (C=O), 162.34 (C=N), 150.60 (pyridine α), 122.23 (pyridine β), 141.73 (pyridine *ipso* carbon), 144.36, 143.47 (C-2′, C-6′), 127.14, 127.33 (C-*o*, C-*o*′), 128.52, 128.70 (C-*m*, C-*m*′), 127.68 (C-*p*, C-*p*′″) ppm.

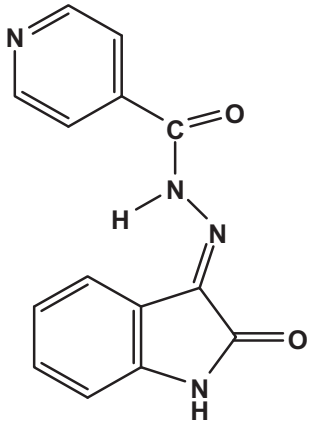


Fig. 3. Conformation of isatin-3-isonicotinoylhydrazone.

*3t-Isopropyl-2r,6c-diphenylpiperidin-4-one isonicotinylhydrazone (**22**).* Faint yellow solid, yield 62%, mp: 185–187 °C; ^{1}H NMR: δ = 3.99 (d, 2H, H-2a, H-6a), 2.54 (1H, H-3a), 2.27 (d, $J_{5a,6a}$ = 11.3 Hz, 1H, H-5a), 3.07 (dd, $J_{5a,5e}$ = 14.4 Hz, 1H, H-5e), 11.98 (s, 1H, —CO—*NH*—), 8.71 (d, 2H, pyridine α), 7.72 (d, 2H, pyridine β), 1.81 (m, 2H, —*C*H(CH_3)$_2$), 1.09 (d, *J* = 6.7 Hz, 3H, —CH_3 at C-7); 0.93 (d, *J* = 6.7 Hz, 3H, -CH_3' at C-7), 7.48 (m, 4H, H-*o*, H-*o*′), 7.23–7.37 (m, 6H, H-*m*, H-*m*′, H-*p*, H-*p*′) ppm; **^{13}C NMR**: δ = 64.03 (C-2), 58.5074 (C-6), 54.96 (C-3), 37.31 (C-5), 27.89 [—*C*H(CH_3—CH_3)], 20.88 [—*C*H(*C*H_3—CH_3)], 18.44[—*C*H(CH_3—*C*H_3)], 165.07 (C=O), 161.65 (C=N), 149.96 (pyridine α), 121.61 (pyridine β), 141.09 (pyridine *ipso* carbon), 144.16, 144.06 (C-2′, C-6′), 127.01, 126.62 (C-*o*, C-*o*′), 127.71, 128.09 (C-*m*, C-*m*′), 127.11 (C-*p*, C-*p*′) ppm.

X-ray crystallographic analysis

Crystals were grown by slow evaporation technique using a mixture of ethanol and ethyl acetate as solvent. Diffraction data were collected on a Bruker, 2004 APEX 2 diffractometer using graphite-monochromated Mo Kα radiation (*K* = 0.71073 Å) at 293 K with crystal size of 0.22 × 0.18 × 0.16 mm. The structure was solved by direct methods and successive Fourier difference syntheses (SHELXS-97) [5] and refined by full matrix least square procedure on F^2 with anisotropic thermal parameters. All non-hydrogen atoms were refined (SHELXL-97) [6] and placed at chemically acceptable positions. A total of 696 parameters were refined with 25613 unique reflections which covered the residuals to R_1 = 0.0232. Crystallographic data for **16** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 653067 for **16**.

Results and discussion

Numbering and designation of atoms

The reported new hydrazones **12–22** were synthesized as shown in Scheme 1 and their analytical data (Table 1) are fit well with their proposed molecular formula.

The numbering of the carbons of the piperidine ring is shown in Fig. 1. The *ipso* carbons of the aryl groups at C-2 and C-6 are designated as C-2′ and C-6′. The other carbons of the aryl group at C-2 are denoted as *o, m* and *p*-carbons and those of the aryl group at

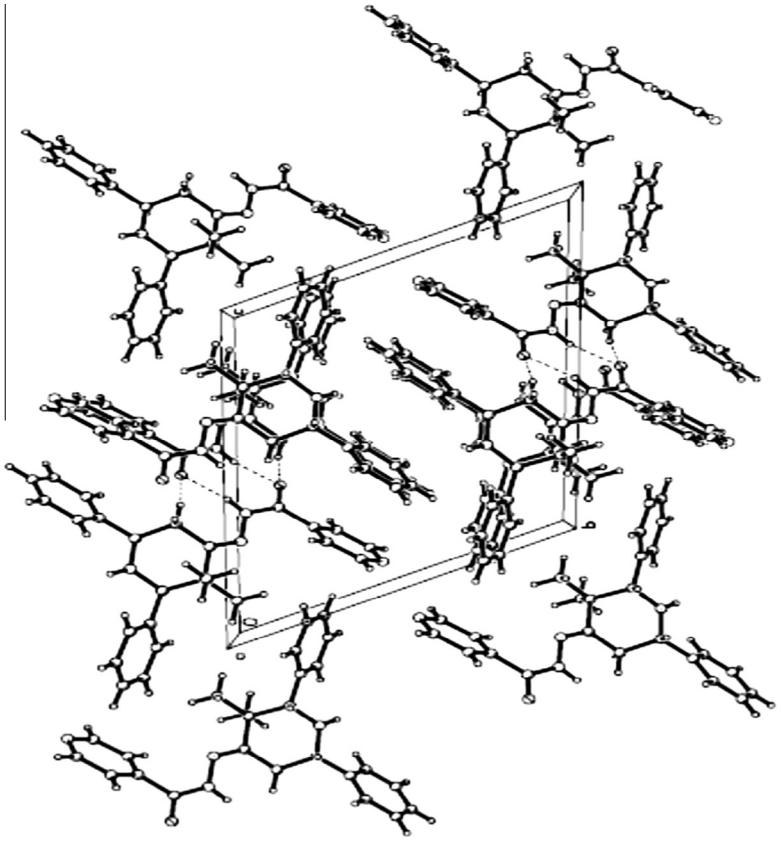


Fig. 4. Packing diagram of compound **16**.

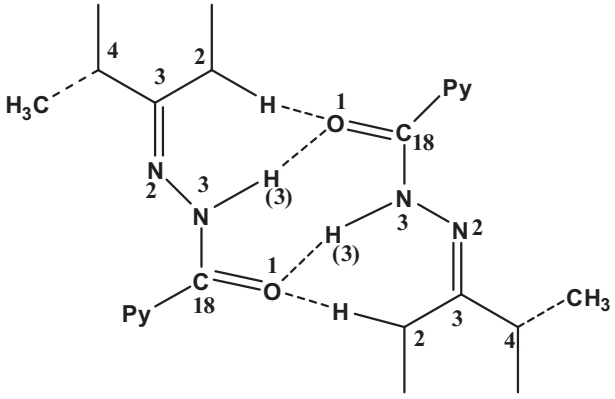


Fig. 5. Hydrogen bonding interactions of **16**.

C-4 are denoted as *o*′, *m*′ and *p*′-carbons. The carbons of the pyridine ring are designated using Greek letters α, β and γ. The protons are denoted accordingly. For example, the benzylic proton at C-2 is denoted as H-2, that at C-α is denoted as H-α and so on. The methylene protons at C-5 are denoted as H-5a and H-5e assuming chair conformation for the piperidine ring.

IR spectral studies

The important IR stretching frequencies of **12–22** are given in Table 2. In IR spectra, the presence of C═N stretching frequency around 1540 cm^{-1} confirm the hydrazone formation. The bands observed in the region of 3160–3220 cm^{-1} are due to N—H stretching frequency of hydrazone analogues and the piperidine NH stretching frequency are in the range 3230–3310 cm^{-1}. The absorption band in the region 3070–2800 cm^{-1} are ascribed to aromatic and aliphatic C—H stretching frequencies. The band observed in the region 1645–1660 cm^{-1} are due to C═O stretching frequency of amide carbonyl group.

*Crystal structure determination of 3,3-dimethyl-2r,6c-diphenylpiperidine-4-one N-isonicotinoylhydrazone **(16)***

X-ray crystallographic study has been made for 3,3-dimethyl-2*r*,6*c*-diphenylpiperidin-4-one N-isonicotinoylhydrazone (**16**). The crystal is a triclinic system with *P–1* symmetry. The molecular structure of **16** is shown in Fig. 2 as the ORTEP diagram. The numbering of carbon atoms in the ORTEP diagram differs from that in Fig. 1. Crystal data and structure refinement of compound **16** is given in Table 3. The selected bond lengths, bond angles and torsional angles, obtained from XRD-study, are given in Table 4.

From the geometrical parameters it is observed that the piperidine ring adopts chair conformation. The phenyl groups and one

Table 6
Hydrogen bond geometry (Å, °).

Compounds	D—H···A	d(D—H)	d(H···A)	d(D···A)	<(D—H···A)
16	N(3)—H(3B)...O(1)#1	0.86	2.22	2.9654(18)	144.6

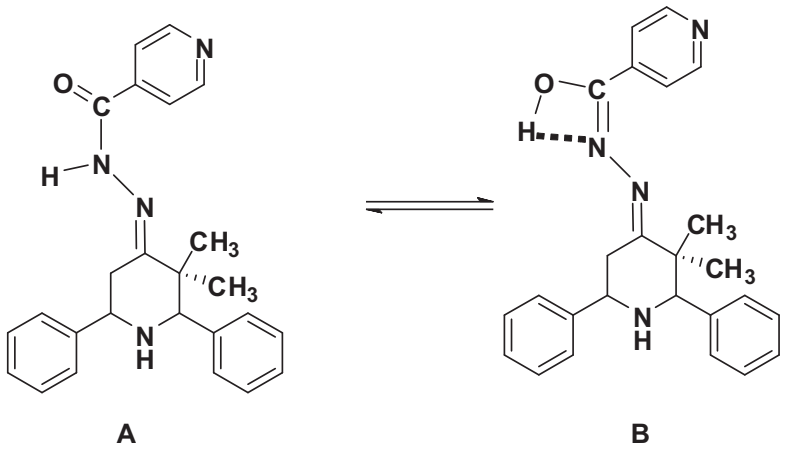


Fig. 6. Possible Tautomeric forms of hydrazone **16**.

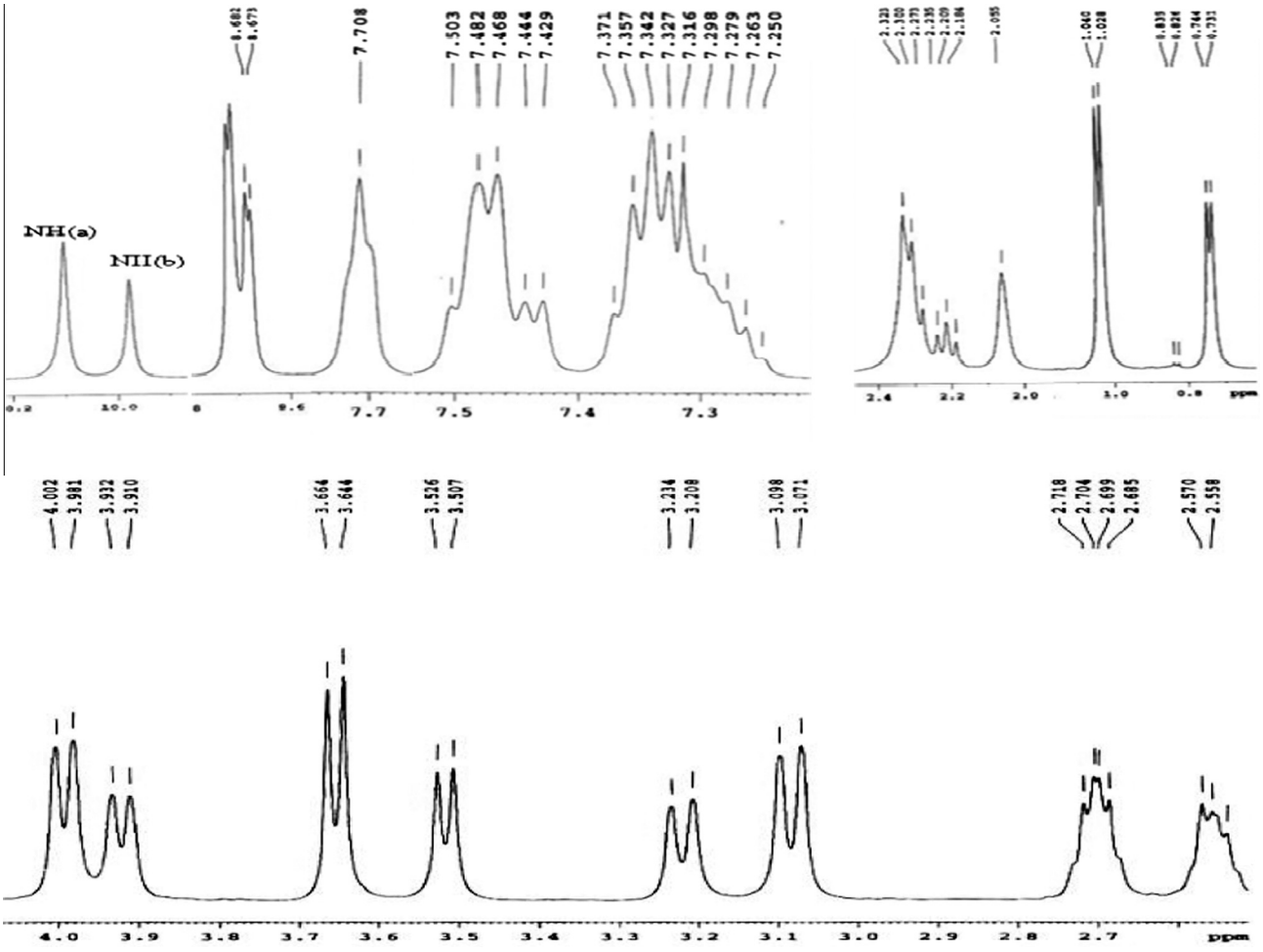


Fig. 7. ^{1}H NMR spectrum of compound **16**.

methyl group adopt equatorial orientations. The other methyl group adopts axial orientation. The pyridine ring is tilted about the C(γ)=O plane by 32.7°. Also the molecule **16** has ***E*** configuration about the C=N bond. The observed C—N bond distances in **16** are given in Table 5.

It is seen that (O)C—N bond length lies between those of typical C—N and C=N bonds, suggesting that (O)C—N bond has partial double bond character. In the solid state the configuration exists in one tatutomeric form **A** with ***E*** orientation about the (O)C—NH bond Fig. 2. This contrasts with the observation that isatin-3-isonicotinoylhydrazone adopts ***Z*** configuration (Fig. 3) about the (O)C—NH bond in the solid state [7].

Compound **16** exist as dimers, which are stabilized by NH···O intermolecular hydrogen bonds. The type of hydrogen bonding is

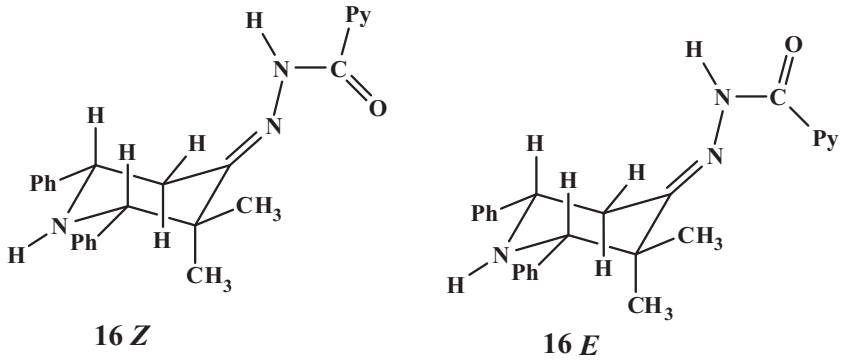


Fig. 8. *E* and *Z* forms (**16** ***E***) and **16** ***Z***).

Table 7
Proton chemical shifts of compound **16**.

Protons	Chemical shifts (δ, ppm)	
	Major	Minor
amide NH	11.03	11.12
H-α	8.71	8.71
H-β	7.73	7.73
o-H	7.46	7.46
o′-H	7.55	7.55
m-H, *m*′-H	7.34	7.34
p-H, *p*′-H	7.24	7.24
H-2a	3.76	3.66
H-5a	2.28	2.16
H-5e	3.01	3.30[a]
H-6a	3.85	3.85
CH_3 (a)	1.14	1.03
CH_3 (e)	1.03	0.69
piperidine NH	2.67	2.67

[a] Merged with solvent signals and approximately taken.

shown in Fig. 4. These dimers are linked by CH···O hydrogen bonds as shown in Fig. 5. The details about the geometries of the intermolecular hydrogen bonds are given in Table 6.

^{1}H NMR spectral analysis

It is very likely that the tautomeric form **A** (Fig. 6) observed in crystal is stabilized due to the formation of intermolecular H-bonds. However, the behavior of carbohydrazide in solution is much more complex. Thus, two sets of signals were observed in the ^{1}H NMR spectrum of all compounds in DMSO-d_6. This result indicates that several interconverting forms of compounds exist in solution.

In order to analyze the spectral assignments of synthesized novel compounds **12–22**, we have chosen compounds **16** as the representative compound. The ^{1}H and ^{13}C signals for the remaining compounds were assigned by comparison with **16** considering known effects [8,9] of the Cl, CH_3 and OCH_3 substituents in the aryl rings.

In the ^{1}H NMR spectrum of **16** two signals are attributed to the NH proton of the amide group at 11.03 and 11.12 ppm Fig. 7. Three signals are observed for the benzylic protons at 3.66, 3.77 and 3.85 ppm. Four signals are observed for the methyl protons at 1.03, 0.69 and 1.14 ppm. Two signals are observed for the methane proton at 2.28 and 2.16 ppm.

These observations suggest that the compound exists in two forms in solution. These are ***E*** and ***Z*** forms (**16*E***) and **16*Z***) Shown in Fig. 8. For the amide NH-proton, H-2a, H-5a and H-5e separate signals are observed for the two isomers. For the minor isomer the signal for H-5e has merged with the solvent signal. Three signals are observed at 1.14, 1.03 and 0.69 ppm for the methyl protons at C-3. The signal at 0.69 ppm corresponds to the ***E*** minor isomer. This should be due to the signal for the equatorial methyl protons to the minor ***E***-isomer. Since the axial methyl protons should have a higher chemical shift than the equatorial methyl protons the signal at 1.14 ppm is assigned to the axial methyl protons of the major isomer. The integral value of the signal at 1.03 ppm is almost equal to the sum of the integral values for the signals at 1.14 and 0.69 ppm. The signal at 1.03 ppm is due to the equatorial methyl protons of the major isomer and axial

Table 8
Correlations for the Major isomer in the COSY and NOESY spectra **16**.

Protons	Correlations in the **COSY** spectrum	Correlations in the **NOESY** spectrum
11.03 (amide NH)	–	7.73 (H-β), 3.01 (H-5e)
8.71 (H-α)	7.73 (H-β)	11.03 (amide NH)
7.73 (H-β)	8.71 (H-α)	11.03 (amide NH), 8.71 (H-α)
7.46 (*o*-H)	7.34 (*m*-H, *m*′-H)	1.03 (CH_3a), 1.14 (CH_3a), 3.76 (H-2a), 2.67 (NH)
7.55 (*o*′-H)	7.34 (*m*-H, *m*′-H)	2.28 (H-5a), 3.85 (H-6a)
		2.67 NH
7.34 (*m*-H, *m*′-H)	7.55 (*o*′-H), 7.46 (*o*-H), 7.24 (*p*-H, *p*′-H)	7.55 (*o*′-H), 7.46 (*o*-H), 7.24 (*p*-H, *p*′-H)
7.24 (*p*-H, *p*′-H)	7.34 (*m*-H, *m*′-H)	7.34 (*m*-H, *m*′-H)
3.76 (H-2a)	–	7.46 (*o*-H), 2.67 (NH), 1.03 (CH_3e)
2.28 (H-5a)	3.85 (H-6a), 3.01 (H-5e)	7.55 (*o*′-H), 3.01 (H-5e)
		1.14 (CH_3a)
3.01 (H-5e)	2.28 (H-5a)	11.03 (amide NH), 2.28 (H-5a)
3.85 (H-6a)	2.28 (H-5a)	7.55 (*o*′-H), 3.01 (H-5e)
1.03 (CH_3e)	–	7.46 (*o*-H), 3.76 (H-2a)
1.14 (CH_3a)	–	7.46 (*o*-H), 2.28 (H-5a)
2.67 piperidine NH	–	7.46 (*o*-H), 7.55 (*o*′-H), 3.76 (H-2a)

Table 9
Correlations for the major isomer in the HSQC and HMBC spectra **16**.

^{13}C Chemical shifts (δ, ppm)	Correlations in the **HSQC** spectrum	Correlations in the **HMBC** spectrum
170.4	–	11.03 (amide NH), 2.28 (H-5a) 1.14 (CH_3a), 1.03 (CH_3e)
161.7	–	11.03 (amide NH), 7.73 (H-β)
150.0	8.71 (H-α)	–
121.6	7.73 (H-β)	8.71 (H-α)
141.1	–	8.71 (H-α)
140.4	–	7.34 (*m*-H, *m*′-H), 3.76 (H-2a)
144.1	–	7.34 (*m*-H, *m*′-H)
129.0	7.46 (*o*-H)	7.24 (*p*-H, *p*′-H)
126.8	7.55 (*o*′-H)	7.24 (*p*-H, *p*′-H)
128.2	7.34 (*m*-H, *m*′-H)	7.55 (*o*′-H)
127.3, 127.2	7.24 (*p*-H, *p*′-H)	7.46 (*o*-H), 7.55 (*o*′-H)
69.6	3.76 (H-2a)	7.46 (*o*-H), 1.14 (CH_3a) 1.03 (CH_3e)
43.0	–	3.76 (H-2a), 1.14 (CH_3a) 1.03 (CH_3e)
33.8	2.28 (H-5a), 3.01 (H-5e)	–
60.0	3.85 (H-6a)	7.55 (*o*′-H), 2.28 (H-5a), 3.76 (H-2a)
21.2 (a)	1.14 (CH_3a)	3.76 (H-2a), 1.03 (CH_3e)
22.8 (e)	1.03 (CH_3e)	1.14 (CH_3a)

Table 10
Carbon chemical shifts of compound **16**.

Carbons	Chemical shifts (δ, ppm)	
	Major	Minor
C=O	161.7	160.0
C=N	170.4	170.04
α-C	150.0	149.2
β-C	121.6	123.1
γ-C	141.1	141.1
C-2′	140.4	140.4
C-6′	144.1	144.1
o-C	129.0	129.0
o′-C	126.8	126.8
m-C, *m*′-C	128.2	128.2
p-C, *p*′-C	127.3; 127.2	127.3, 127.2
C-2	69.6	69.6
C-3	43.0	42.5
C-5	33.8	32.0
C-6	60.0	60.0
Alkyl	21.2 (a), 22.8 (e)	20.7 (a), 22.8 (e)

Table 11
Relative population of *Z* and *E* isomers for compounds **13–22**.[a]

Compounds	% *Z* isomer	% *E* isomer
13	78.23	21.77
14	71.49	28.51
15	75.09	24.91
16	80.63	19.37
17	80.57	19.43
18	81.23	18.77
19	80.67	19.33
20	77.30	22.70
21	77.89	22.11
22	80.27	19.63

[a] Relative population could not calculated for **12.**

methyl protons of the minor isomer. The ^{1}H chemical shifts of the both the isomers of **16** are given in Table 7.

In order to confirm the above assignments ^{1}H–^{1}H COSY and NOESY spectra have been recorded. The observed correlations for the major isomer in the ^{1}H–^{1}H COSY and NOESY spectra of **16** are given in Table 8. The observed ^{1}H–^{1}H COSY correlations confirm the assignments made.

In the NOESY spectrum the signal for amide NH proton at 11.03 ppm has nOe with the pyridine H-β signal at 7.73 ppm. Such a nOe is possible only in the ***Z*** form. Obviously, the signal due to 11.03 ppm is due to ***Z*** form. In other words the major form is ***Z*** form (**16*Z***) and the minor form is ***E*** form (**16*E***).

In the NOESY spectrum the signal for H-2a of the major isomer has nOe with the methyl protons at 1.03 ppm. Obviously, this signal should be due to the equatorial methyl protons, because only the equatorial methyl protons can have nOe with the adjacent axial proton H-2a.

If there is slow interconversion between the two isomers correlations will be observed between the two exchanging nuclei in the NOESY spectrum. Indeed correlation between the methyl signals at 1.03 ppm and 0.0.69 ppm is observed. Thus, it is obvious that there is interconversion between the two isomers at room temperature. However, the interconversion is slow on NMR time scale, so that different signals are observed for the two isomers.

In **12–15** and **17–22,** individual assignments of the protons were made based on their positions, multiplicities, integral values of the signals and by comparison with **16**. Normally, the *ortho*, *meta* and *para* protons of phenyl group attached at C-2 and C-6 carbons of piperidine ring give separate signals. *Ortho* protons are deshielded by the lone pair of electrons on the nitrogen while the *meta* and *para* protons are shielded and resonate in the upfield region. The ^{1}H chemical shifts of major isomer of **12–15** and **7–22** are given in Tables 12 and 13.

^{13}C NMR spectral analysis

In order to assign the signals unambiguously HSQC and HMBC spectra have been recorded for **16**. The observed correlations in the HSQC and HMBC spectra are given in Table 9. The signals for carbons linked to hydrogen are assigned based on the observed correlations in the HSQC spectrum. Signals which do not show any correlation in the HSQC spectrum are those that are not linked to protons due to carbons containing no proton.

The ^{13}C NMR spectrum shows weak signal at 170.4 ppm with no correlation in the HSQC spectrum. In the HMBC spectrum, this signal shows correlation with the amide NH proton, H-5a and the methyl protons. Hence, this signal must be due to C-4. There are four weak signals at 161.7, 141.1, 144.1 and 140.4 ppm. These signals have no correlation in the HSQC spectrum. The signal at 161.7 ppm shows correlation with H-β and amide NH proton at 11.03 ppm. Hence, this signal should be due to the carbonyl carbon

Table 12
Proton chemical shifts in major isomer of compounds.[a]

Protons	**12**[b] (H)	**14** [(3-CH_3)/*p*-Cl]	**15** [(3-CH_3)/*p*-F]	**17**[d] [(3,3-CH_3)/*p*-CH_3]	**18** [(3,3-CH_3)/*p*-OCH_3][g]
Amide NH	11.04	11.06 (11.23)	11.06 (11.23)	11.03 (11.10)	11.03 (11.08)
H-α	8.71	8.72 (8.65)	8.72 (8.64)	8.71	8.71 (8.67)
H-β	7.72	7.73 (7.60)	7.73	7.72	7.72 (7.60)
o-H,	7.51	7.51	7.52	7.40	7.36
o′-H	7.51	7.51	7.52	7.33	7.43
m-H, *m*′-H	7.35	7.41	7.16	7.14	6.90
p-H, *p*′-H	7.26	–	–	–	–
H-2a	3.93	3.54 (3.43)	3.55 (3.42)	3.71 (3.61)	3.70 (3.62)
H-3a	2.42 (2.27)	2.58	2.57 (2.41)	–	2.26 (2.13)
H-5a	2.04 (1.96)	2.10[c] (1.96)	2.12 (1.98)	2.29[e] (2.12)	2.95 (3.2)
H-5e	3.16	3.15	3.15	2.97	3.78
H-6a	3.85	3.89 (3.84)	3.88 (3.83)	3.80	1.12 (1.05)
Alkyl proton at C-3 (ax)	–	–	–	1.13 (1.00)	1.00 (0.66) (e)
Alkyl proton at C-3 (eq)	–	0.84 (0.51)	0.84 (0.51)	1.00 (0.67)	2.44
NH in piperidine ring	2.88	2.93	2.81	[f]	11.03 (11.08)

[a] Wherever separate signals are observed for the two isomers the chemical shifts for the minor isomer are given in parenthesis. Otherwise both isomers have the chemical shift.
[b] The chemical shift same of H-3e is 2.58 ppm.
[c] The signal for H-5a is merged with moisture peak and the chemical shift was approximately taken as 2.10 ppm.
[d] The chemical shift of *p*-CH_3 is 2.29 ppm.
[e] The signal for H-5a is merged with *p*-CH_3 and chemical shift was approximately taken as 2.29 ppm.
[f] NH proton signal is merged with DMSO signal.
[g] The chemical shift of *p*-OCH_3 is 3.74 ppm.

Table 13
Proton chemical shifts in major isomer for compounds.[a]

Protons	**19h** [(3,3-CH_3)/*p*-Cl]	**20i** [(3,3-CH_3)/*p*-F]	**21j**[h] (3-CH_2CH_3)	**22k**[h] [3-$CH(CH_3)_2$]
amide NH	11.02 (11.14)	11.02 (11.12)	11.07 (11.22)	10.98 (11.08)
H-α	8.72 (8.78)	8.68 (8.66)	8.71 (8.60)	8.71 (8.62)
H-β	7.72 (7.65)	7.71	7.73 (7.54)	7.72
o-H	7.48	7.48	7.48	7.48
o′-H	7.57	7.52		
m-H, *m*′-H	7.41	7.16	7.30	7.36
p-H, *p*′-H	–	–	7.23	7.25
H-2a	3.76 (3.65)	3.75 (3.64)	3.67 (3.53)	3.99[i]
H-5a	2.23 (2.11)	2.23 (2.14)	2.16 (2.01)	2.27
H-5e	3.00 (3.11)	2.99 (3.29)	3.17 (3.42)	3.07
H-6a	3.85	3.84 (3.79)	3.90 (3.82)	3.99[i]
Alkyl proton at C-3 (ax)	1.10 (0.81)	1.10	–	–
Alkyl proton at C-3 (eq)	1.01 (0.66) (e)	1.00 (0.66) (e)	1.19, 1.62 (CH_2); 0.81 (CH_3)	1.08 (CH_3); 0.92 (CH_3); 1.81 (CH)
NH in piperidine ring	2.90	2.77	2.62	[f]

[a] Wherever separate signals are observed for the two isomers the chemical shifts for the minor isomer are given in parenthesis. Otherwise both isomers have the chemical shift.
[f] NH proton signal is merged with DMSO signal.
[h] The signal for H-3a is merged with DMSO signal and the chemical shift was approximately taken as 2.50 ppm.
[i] The signals for H-2a and H-6a have merged and the chemical shift was approximately taken as 3.99 ppm.

(C═O). In the HMBC spectrum the signal at 141.1 ppm has correlation with H-α. Hence, this signal should be due to C-γ. The signal at 140.4 ppm has correlation with the benzylic proton H-2a. Therefore, this signal can be assigned to *ipso*-carbon C-2′. Obviously, the signal at 144.1 ppm can be assigned to C-6′. The ^{13}C signals for the major isomer **16*Z*** are assigned based on the observed HSQC and HMBC correlations. The ^{13}C chemical shifts of the minor isomer **16*E*** are assigned by comparison. The ^{13}C chemical shifts are given in Table 10. The equatorial methyl protons in the ***E***-isomers are shielded by 0.34 ppm relative to the ***Z***-isomer. This shielding is comparable to that (0.32 ppm) observed in **16**. The axial methyl protons in the ***E***-isomer are shielded only by 0.11 ppm relative to the ***Z***-isomer. Thus, the shielding by the magnetic anisotropic effects of the pyridine ring is considerably less on the axial methyl protons than on the equatorial methyl protons. In both isomers the equatorial methyl carbons have the same chemical shift. However, the axial methyl carbon in the ***E***-isomer has a slightly lower chemical shift than that in the ***Z***-isomer. The relative populations of the ***Z*** and ***E*** isomers have been calculated from the observed integral values and are given in Table 11.

The ^{13}C signals for **12–15** and **17–22** were assigned based on their positions, intensities and by comparison with those of **16**. The observed ^{13}C chemical shifts of major isomer of **12–15** and **17–22** are given in Tables 14 and 15.

Analysis of coupling constants

In order to understand the conformation of piperidine ring, vicinal coupling constants are an important parameter. The observed coupling constant for the major isomer (**16*Z***) of the piperidine ring could be determined for **16**. These values are $J_{5a,6a}$ = 11.68 Hz and $J_{5a,5e}$ = 13.12 Hz. The observed vicinal coupling constants suggest

Table 14
Carbon chemical shifts in major isomer for compounds.[a]

Carbons	**12a** (H)	**14c** [(3-CH_3)/*p*-Cl]	**15d** [(3-CH_3)/*p*-F]	**17e** [(3,3-CH_3)/*p*-CH_3][b]	**18f** [3,3-CH_3)/*p*-OCH_3][c]
C═O	162.0	161.8	166.2	161.6	161.6
C═N	163.3	165.9	171.3	170.8	170.8
α-C	150.0	150.0 (149.1)	149.8	150.0 (149.5)	150.0 (149.2)
β-C	121.6	121.6 (123.0)	121.5	121.6 (123.0)	121.6 (123.0)
γ-C	141.0	141.9	139.9	137.4	136.2
C-2′,C-6′	143.9	141.2	139.0	136.1	132.4
		142.8	141.2	141.1	141.1
o-C	127.0	129.6	129.5	126.6	129.8
o′-C	127.0	128.6	128.5	126.6	127.8
m-C, *m*′-C	128.1	128.0	114.5	127.9	113.6, 112.8
p-C, *p*′-C	126.7, 126.5	131.7, 131.5	162.0, 160.0	128.7	158.4
C-2	60.8	67.5	67.5	69.4	69.0
C-3	43.3	44.7	44.7	43.0	43.1
C-5	36.8	37.2 (35.8)	37.2	33.9	33.9 (32.1)
C-6	59.6	59.0	58.9	59.8	59.5
CH_3(ax) at C-3	–	–	–	20.6	21.2 (20.6)
CH_3(eq) at C-3	–	12.2	12.0	21.8	22.7

[a] Wherever separate signals are observed for the two isomers the chemical shifts for the minor isomers are given in parenthesis. Otherwise both isomers have the same chemical shift.
[b] The chemical shift of *p*-CH_3 is 22.7 ppm.
[c] The chemical shift of *p*-OCH_3 is 54.9 ppm.

Table 15
Carbon chemical shifts in major isomer in compounds.

Carbons	**19g** [(3,3-CH_3)/*p*-Cl]	**20h** [(3,3-CH_3)/*p*-F]	**21i** (3-CH_2CH_3)	**22j** [3-$CH(CH_3)_2$]
C═O	161.7	162.5	161.8	161.7
C═N	169.7	169.9	165.4	165.0
α-C	150.0 (149.1)	150.0 (149.2)	150.0	150.0 (149.2)
β-C	121.5 (123.0)	121.6 (122.5)	121.6	121.6 (122.1)
γ-C	141.1	140.3	142.9	141.1
C-2′,C-6′	139.2, 143.0	136.5, 141.1,	141.2, 143.8,	144.0, 144.1
o-C	130.7	130.7	128.0	128.1
o′-C	128.1	128.7	127.8	127.1
m-C, *m*′-C	128.6, 127.3	114.8, 114.1	126.7	127.7, 127.0
p-C, *p*′-C	131.7, 131.6	162.5, 160.1	127.2, 127.0	126.6
C-2	68.7	68.7	66.7	64.0
C-3	42.8	42.9	51.4 (51.1)	55.0 (54.3)
C-5	33.6	33.8 (31.5)	37.5 (36.2)	37.3 (36.3)
C-6	59.1	59.2	59.8	58.1
Alkyl (ax) at C-3	21.0	21.1 (19.6)	–	–
Alkyl (eq) at C-3	22.6	22.7	18.8 (CH_2); 11.8 (11.4) (CH_3)	27.9 (26.9) (CH); 20.9 (20.2)(CH_3); 18.4 (17.8) (CH_3)

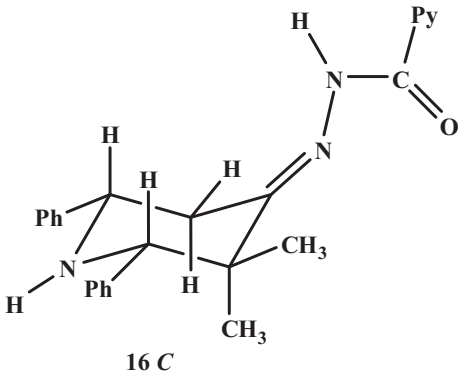
that piperidine ring adopts chair conformation **16C** on which equatorial orientations of the aryl groups and of one methyl group should be equatorial and the other methyl group should be axial.

The parent piperidin-4-ones (**1–11**) should exist in chair conformation. In these conformations the aryl groups are equatorial and the alkyl group at C-3 is equatorial in the 3t-alkyl compounds. The coupling constant values and position of the chemical shifts were used to predict the conformation of the compounds. The observations of large vicinal coupling constant values between 9.53–11.0 ($J^3_{2a,3a}$) and 10.90–11.60 Hz ($J^3_{5a,6a}$) and of small value of the vicinal coupling constants of 2.5– 3.2 Hz ($J^3_{6a,5e}$) for the protons of C-6 and C-2 of the synthesized compounds **12–22** indicate that the six-membered heterocyclic ring of compounds **12–22** adopts normal chair conformation (Fig. 9) with equatorial orientation of phenyl groups at C-2 and C-6, and equatorial orientation of methyl group at C-3. However, compounds **17–22**, which have two methyl groups at C-3 carbon and in these compounds one methyl group should have the axial orientation and the remaining one is equatorially oriented [10,11]. Furthermore, equatorial disposition of phenyl groups at C-2 and C-6 makes the chair conformation more rigid thereby preventing inter-conversion from one chair into another. In the other compounds **12–22** the heterocyclic ring may be flattened or distorted about the C2—C3 bond to decrease gauche interaction between the equatorial phenyl group and the equatorial methyl groups at C-2 and C-3 respectively.

The vicinal coupling constant between the isopropyl methine proton and H-3 is 2.3 Hz in **22** suggesting that in **22** also the isopropyl group adopts a similar conformation. Hence, the CH bond of the isopropyl group cannot interact with the nitrogen of the C═N group in **22**. In this compound there may be a shielding due to the eclipsing of C═N bond with the C(3)-$CHMe_2$ bond.

Configuration about C(4)═N bond

In all cases the chemical shift of H-5e is greater than that of H-5a by about 0.73 ppm. Also, C-5 has a much lower chemical shift than C-3. Those observations suggest that the configuration about C(4)═N bond is ***E***. In such a configuration the C(5)—H(5e) bond will be polarized by gamma-syn effect, so that H-5e gets a partial positive charge and C-5 gets a partial negative charge. The partial positive charge on H-5e deshields it. The partial negative charge on C-5 shields it and H-5a. Indeed in this reaction two isomers should be



16 *C*

Fig. 9. Chair conformation of **16C**.

formed. However, only in this study we report the formation of two isomers.

Analysis of chemical shifts

In compounds **13–22** H-2a has a lower chemical shift than H-6a. However, H-2a has a higher chemical shift in **16–22** than in **13–15**. These observations suggest that an equatorial methyl group shields an adjacent axial proton but an axial methyl group deshields an adjacent axial proton. These observations are consistent with those made earlier [1,12]. Also C-2 has a higher chemical shift than in 9-12. Moreover, C-2 in **17-22** has a higher chemical shift than in **13-15**. It has been observed that an equatorial for methyl group deshields adjacent carbon [2].

Comparison of **16** and **19** suggest that the methyl group shields the *meta* protons significantly. Also the *ipso* carbons and *meta* carbons are shielded. The methoxy group places significant negative charges on the *meta* and *ipso* carbons due to mesomeric effect. This results in a shielding of *ortho* protons, *ortho* and *ipso* carbons. The shielding on *ortho* carbons is greater than those on the *ipso* carbon, because *meta* carbons are subjected to additional shielding by steric interaction.

Conclusion

A series of piperidin-4-one hydrazones have been synthesized successfully in appreciable yields and were characterized by IR and NMR. Single crystal XRD analysis was also performed for compound **16**. The observations suggest that the compound exists in two forms in solution, the ***E*** and ***Z*** forms **16(*E*)** and **16(*Z*).** The observed vicinal proton–proton coupling constants suggest that in hydrazones **12–22**, the piperidine ring adopts chair conformation with equatorial orientations of the aryl groups. The observed chemical shifts of H-5e, H-5a and C-5 are in accord with *E* configuration about the C═N bond. In **12–22**, the equatorial alkyl carbon attached to C-3 is shielded by the nitrogen atom of the C═N bond due to *δ-syn* effect. However in the solid state the configuration exist in tatutomeric form **A** with ***E*** orientation about the (O)C—NH bond.

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