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Synthesis, stereochemical, structural and biological studies of some 2,6-diarylpiperidin-4-one *N*(4′)-cyclohexyl thiosemicarbazones

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HIGHLIGHTS

- Synthesis of 2,6-diarylpiperidin-4-one *N*(4′)-cyclohexyl thiosemicarbazones.
- Spectral and stereochemical analysis by means of ^{1}D NMR, ^{2}D NMR, and single crystal X-ray diffraction analysis.
- Screening of compounds for antibacterial and antifungal activities.

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ABSTRACT

A new series of 2,6-diarylpiperidin-4-one *N*(4′)-cyclohexyl thiosemicarbazones (**13–23**) were synthesized by corresponding 2,6-diarylpiperidin-4-ones (**1–11**) reaction with cyclohexyl thiosemicarbazide (**12**). The chemical structures were confirmed by means of IR, one and two dimensional NMR, Mass spectra and single crystal X-ray diffraction analysis. Compounds **13–23**, exist in chair conformation with equatorial orientation of all the substituents at piperidine ring except the methyl group at C-5 of compounds **21–23** oriented at axial disposition to stabilize the chair conformation. Single crystal X-ray structural analysis of compound **18**, evidences that the configuration about C=N double bond is *syn* to C-5 carbon (*E*-form). All the synthesized compounds were screened their biological activity.

1. Introduction

Heterocyclic ring systems having the piperidin-4-one nucleus have aroused great interest in the past and recent years due to their wide variety of biological properties, such as analgesic [1,2], anti-inflammatory [1], central nervous system (CNS) depressants [3–7], local anaesthetic [3,8], anticancer [9] and antimicrobial activity [10].

Thiosemicarbazones were reported to be associated with antimicrobial activity [11–13]. Several semicarbazones, as well as their sulfur analogues and its derivatives, have proved their efficiency and efficacy in combating various diseases [14]. It is of great interest because of their chemistry and potentially beneficial biological activities such as antitumour, antibacterial, antiviral, antimalarial and antiprotozoal activities [15–18]. Semicarbazones have documented consistent advances in the design of novel anticonvulsant agents, through the work of Dimmock and others [19–26]. When the thiosemicarbazone contained aliphatic amine moieties at 4th position, the effect was more obvious [27]. The in vitro cytotoxicities of the liquiritigenin thiosemicarbazone derivatives against K562 (human leukemia cell line), DU-145 (human prostate carcinoma cell line), SGC-7901 (human gastric cancer cell line), HCT-116 (human colon cancer cell line) and Hela (human cervical carcinoma cell line) cells were evaluated. The cytotoxicities of the resulting liquiritigenin thiosemicarbazone derivatives appeared to be related to the nature of the substituent group at thiocarbonyl. From the structure activity relationship results the introduction of thiosemicarbazone at 4th position in liquiritigenin is associated with enhanced cytotoxic activity. By considering the synthetic and biological significance of piperidin-4-one thiosemicarbazones, it was thought worthwhile to synthesize and screen their biological activity. A new series of 2,6-diarylpiperidin-4-one *N*(4′)-cyclohexyl thiosemicarbazones (**13–23**) were synthesized and characterized by IR, Mass, NMR (^{1}H, ^{13}C, ^{1}H–^{1}H COSY, ^{1}H–^{13}C COSY, HMBC and NOESY) spectra and single crystal X-ray diffraction techniques. The synthesized compounds were screened for their antibacterial and antifungal activity.

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2. Experimental

2.1. Materials and methods

All the chemicals were commercial and were obtained from Sigma–Aldrich and were used as received. The melting points were recorded in open capillaries and are uncorrected. IR spectra were recorded in AVATAR 330 FT-IR Thermo Nicholet spectrophotometer (range 4000–400 cm^{-1}) as KBr pellets. ^1H NMR spectra were recorded on Bruker AMX-400 spectrometer operating at 400.23 MHz and Bruker AVIII 500 MHz spectrometer operating at 500.3 MHz using TMS as internal reference. ^{13}C NMR spectra were recorded on Bruker AMX-400 spectrometer operating at 100.63 MHz and Bruker AVIII 500 MHz spectrometer operating at 125.75 MHz. ^1H–^1H COSY, HSQC, HMBC and phase-sensitive NOESY spectra of **18** were recorded on a Bruker DRX-500 NMR spectrometer using standard parameters. Mass spectra were measured on a JEOL GC MATE II spectrometer.

2.1.1. X-ray crystallography

Crystal was grown by slow evaporation technique using ethanol 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 0.30 × 0.20 × 0.20 mm. The structure was solved by direct methods and successive Fourier difference syntheses (SHELXS-97) [28] and refined by full matrix least square procedure on F^2 with anisotropic thermal parameters. All non-hydrogen atoms were refined (SHELXL-97) [29] and placed at chemically acceptable positions. A total of 696 parameters were refined with 8113 unique reflections which covered the residuals to R_1 = 0.0435. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 893461 for **18**. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033: or e-mail: deposit@ccdc.cam.ac.uk.

2.2. Synthesis of 2,6-diarylpiperidin-4-one N(4′)-cyclohexylthiosemicarbazones

2.2.1. 2,6-Diarylpiperidin-4-ones (**1–11**)

Piperidin-4-ones **1–11**, were prepared following the procedure of Noller and Baliah [30]. Dry ammonium acetate (100 mmol) was dissolved in ethanol and the solution was mixed with appropriated ketones (2-butanone, 3-methyl-2-butanone, 4-methyl-2-pentanone, 3-pentanone) (100 mmol) and appropriate substituted benzaldehyde (200 mmol). The mixture was just heated to boil and allowed to stand at room temperature overnight. The reaction mixture was diluted with ether (100 ml) and treated with Conc. HCl (20 ml). The precipitated hydrochloride was washed with ethanol–ether mixture. The hydrochloride was suspended in acetone and neutralized with aqueous ammonia. Dilution with water gave the free base which was recrystallized from ethanol.

2.2.2. 2,6-Diarylpiperidin-4-one N(4′)-cyclohexylthiosemicarbazones (**13–23**)

Thiosemicarbazones (**13–23**) were synthesized by refluxing a mixture of respective 2,6-diarylpiperidin-4-one (**1–11**) (25 mmol) and cyclohexylthiosemicarbazide **12** (25 mmol) in methanol (10 ml) containing few drops of acetic acid for 1 h. The separated solid was washed with ice-cold water and was recrystallized from methanol. The physical data for the synthesized compounds (**13–23**) are given in Table 1.

2.3. In vitro antibacterial and antifungal activity

The in vitro activities of the compounds were tested in sabourauds dextrose broth (SDB) (Hi-media, Mumbai) for fungi and nutrient broth (NB) (Hi-media, Mumbai) for bacteria by the two-fold serial dilution method [31]. The test compounds were dissolved in dimethylsulfoxide (DMSO) to obtain 1 mg ml^{-1} stock solutions. Seeded broth (broth containing microbial spores) was prepared in NB from 24 h old bacterial cultures on nutrient agar (Hi-media, Mumbai) at 37 ± 1 °C while fungal spores from 1 to 7 days old sabourauds agar (Hi-media, Mumbai) slant cultures were suspended in SDB. The colony forming units (cfu) of the seeded broth were determined by plating technique and adjusted in the range of 10^2–10^5 cfu ml^{-1}. The final inoculum size was 10^5 - cfu ml^{-1} for antibacterial assay and 1.1–1.5 × 10^2 cfu ml^{-1} for antifungal assay. Testing was performed at pH 7.4 ± 0.2. 0.2 ml of the solution of test compound was added to 1.8 ml of seeded broth to form the first dilution. One milliliter of this was diluted with a further 1 ml of the seeded broth to give the second dilution and so on till six such dilutions were obtained. A set of assay tubes containing only inoculated broth was kept as control and likewise solvent controls were also seen simultaneously. The tubes were incubated in BOD incubators at 37 ± 1 °C for bacteria and 28 ± 1 °C for fungi. The MICs were recorded by visual observations after 24 h (for bacteria) and 72–96 h (for fungi) of incubation. Ampicillin and amphotericin-B were used as standards.

3. Results and discussion

3.1. IR Spectral characterization of compounds **13–23**

IR spectra of the synthesized compounds (**13–23**) showed the absence of C=O stretching frequency around 1720–1700 cm^{-1} and the presence of C=N and C=S stretching frequencies around 1533–1516 cm^{-1} and 1247–1205 cm^{-1} confirms the condensation of 2,6-diarylpiperidin-4-one with cyclohexyl thiosemicarbazide. Besides, the target compounds were confirmed by the presence of cyclohexyl thiosemicarbazone N—H stretching frequency around 3357–3171 cm^{-1} and also the intense aliphatic stretching frequency around 2854–2848 cm^{-1} due to the presence of cyclohexyl ring. IR spectral data were presented in Table 2.

3.2. ^1H NMR spectral analysis of compound **18**

The spectroscopic numbering of carbon atoms in **13–23** is shown in Scheme 1. Protons are numbered accordingly. Thus, the proton at C-2 is denoted as H-2 and that at C-5′ is denoted as H-5′. Compound **18**, was taken as a representative and the signals were assigned based on the correlations in the 2D spectra. For the remaining compounds the signals were assigned based on their positions, multiplicity and integral values and by comparing with **18** and previous piperidone analogues using known effects [32,33] of the OMe and F substituent in the aryl rings. The observed ^1H and ^{13}C chemical shifts are given in Tables 3 and 5 respectively. The ^1H–^1H coupling constants and 2D spectral correlations are given in Tables 4 and 6 respectively. The 1D and 2D NMR spectra of compound **18** were shown in Figs. 1–6.

The ^1H NMR spectrum of compound **18** showed two broad signals in the downfield region. The singlet at 8.44 ppm with one proton integral, and a doublet at 7.54 ppm with one proton integral are due to NH proton of –NHCS and CSNH–Cy group respectively in the thiosemicarbazone moiety. The piperidin NH proton resonate in up field region of 1.93 ppm as singlet. Methyl group (a,e) protons at C-3, appear as two separate singlets due to γ-*gauche* ef-

Table 1
Physical data of compounds **13–23**.

Compound	R_1	R_2	R_3	X	Yield (%)	Melting point (°C)	Mass
13	CH_3	H	H	H	86	172–174	420.4
14	CH_3	H	H	F	80	198–200	457.1
15	CH_3	H	H	OCH_3	80	184–186	481.0
16	$CH(CH_3)_2$	H	H	H	85	202–204	448.4
17	$CH(CH_3)_2$	H	H	F	85	192–194	485.0
18	CH_3	CH_3	H	H	90	194–196	434.8
19	CH_3	CH_3	H	F	85	198–200	471.0
20	CH_3	CH_3	H	OCH_3	86	188–190	495.0
21	CH_3	H	CH_3	H	85	208–210	434.6
22	CH_3	H	CH_3	F	80	204–206	–
23	CH_3	H	CH_3	OCH_3	80	198–200	495.0

Table 2
IR spectral data of compounds **13–23**.

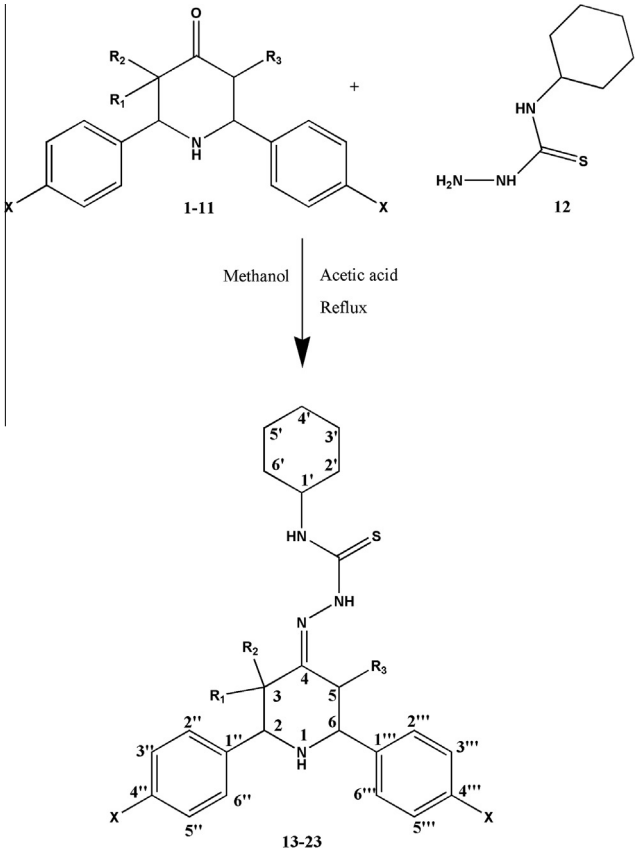
Compound	ν_{N-H}	ν_{C-H} (Aromatic)	ν_{C-H} (Alipahatic)	$\nu_{C=N}$	$\nu_{C=S}$
13	3357 3216	2967 2934	2854 2810	1517	1221
14	3357 3214	2969 2936	2854 2810	1516	1222
15	3324 3194	2928	2854	1533	1246
16	3330 3171	3030 2929	2848	1527	1205
17	3342 3183	3030 2926	2852	1528	1219
18	3319 3184	3030 2925	2852	1525	1207
19	3319 3181	3046 2975 2930	2854 2810	1525	1218
20	3347 3183	2975 2926	2850	1524	1245
21	3342 3194	3030 2969 2926	2852	1527	1205
22	3342	2926	2853	1516	1231
23	3342	2926	2853	1523	1247

fect at 1.06 and 1.22 ppm and among the two signals the shielded one is assigned to axial methyl protons.

A singlet at 3.76 ppm and a doublet of doublet at 3.86 ppm are assigned for benzylic protons H-2a and H-6a, respectively. Moreover, there are two double doublets one at 2.75 ppm with coupling constant values 14.00 Hz $J^2_{5a,5e}$)/3.00 Hz ($J^3_{6a,5e}$) and the other at 2.40 ppm with coupling constant values 14.00 Hz ($J^2_{5a,5e}$)/11.50 Hz ($J^3_{6a,5a}$). The large vicinal and germinal coupling constant values reveal that the double doublet at 2.40 ppm is due to the resonance of axial proton at C-5 (H-5a). The remaining proton signal at 2.75 ppm is unambiguously assigned for H-5e.

Cyclohexyl ring protons appear in the down field region as they are slightly deshielded. A multiplet at 4.31–4.35 ppm with one proton integral is assigned to H-1′a in C-1′. The observed deshielding is due to the presence of electronegative nitrogen atom at α position. H-2′e/H-6′e and H-2′a/H-6′a resonates at 2.09–2.14 and 1.35–1.38 ppm respectively as multiplets. In the up field region there are two multiplets at 1.72–1.77 and 1.47–1.51 ppm due to H-3′e/H-5′e and H-3′a/H-5′a protons. The H-4′e and H-4′a protons were observed at 1.64–1.67 and 1.31–1.33 ppm respectively.

The *ortho*, *meta* and *para* protons of phenyl group attached at C-2 and C-6 carbons of piperidin ring gives 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.



Scheme 1. Schematic diagram showing the synthesis of compounds **13–23**.

*3.2.1. Conformational analysis of **13–23***

Based on a previous study [34], 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 9.20–10.0 ($J^3_{2a,3a}$) and 11.20–11.60 Hz ($J^3_{6a,5a}$) and of small value of the vicinal coupling constants of 2.4–3.2 Hz ($J^3_{6a,5e}$) for the protons of C-6 and C-2 of the synthesized compounds **13–20** indicate that the six-membered heterocyclic ring of compounds **13–20** adopts normal chair conformation (Fig. 7) with equatorial orientation of phenyl groups at C-2 and C-6, and equatorial orientation of methyl group at C-3. However, compounds **18–20**, which have two methyl groups at C-3 carbon and in these compounds one of the methyl group should have the axial orientation and the remaining one is equatoraialy oriented [35,36]. Furthermore, equatorial disposition of phenyl

Table 3
^{1}H chemical shift (ppm) values of compounds **13–23**.

Proton	Compound										
	13	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**
–NHCS	8.54 (s)	8.58 (s)	8.50 (s)	8.54 (s)	8.44 (s)	8.44 (s)	8.59 (s)	8.43 (s)	8.53 (s)	8.57 (s)	8.52 (s)
CSNH–Cy	7.51 (d)	7.49 (d)	7.51 (d)	7.50 (d)	8.74 (d)	7.54 (d)	7.50 (d)	7.51 (d)	7.56 (d)	7.56 (d)	7.58 (d)
NH	1.79 (s)	1.99 (s)	1.96 (s)	–	1.80 (s)	1.93 (s)	1.93 (s)	1.81 (s)	1.83 (s)	1.80 (s)	1.79 (s)
H-2a	3.51 (d)	3.50 (d)	3.45 (d)	3.97 (d)	3.92 (d)	3.76 (s)	3.72 (s)	3.67 (s)	4.08 (d)	4.08 (d)	4.03 (d)
H-3a	2.54–2.63 (m)	2.48–2.55 (m)	2.48–2.56 (m)	2.64 (dd)	2.49 (dd)	–	–	–	2.69–2.77 (m)	2.67–2.71 (m)	2.68–2.71 (m)
H-5e	2.87 (dd)	2.86 (dd)	2.83 (dd)	2.83 (dd)	2.76 (dd)	2.75 (dd)	2.76 (dd)	2.68 (dd)	2.94–2.99 (m)	2.95–2.97 (m)	2.91–2.93 (m)
H-5a	2.20 (dd)	2.15 (dd)	2.17 (dd)	2.35 (dd)	2.22 (dd)	2.40 (dd)	2.32 (dd)	2.33 (dd)	–	–	–
H-6a	3.86 (dd)	3.84 (dd)	3.79 (dd)	3.99 (dd)	3.92 (dd)	3.86 (dd)	3.83 (d)	3.76 (d)	3.49 (d)	3.50 (d)	3.84 (d)
H-1′a	4.27–4.34 (m)	4.24–4.33 (m)	4.26–4.34 (m)	4.27–4.37 (m)	4.24–4.31 (m)	4.31–4.35 (m)	4.26–4.30 (m)	4.28–4.34 (m)	4.27–4.35 (m)	4.30–4.34 (m)	4.32–4.35 (m)
H-2′e, H-6′e	2.04–2.11 (m)	2.05–2.09 (m)	2.05–2.10 (m)	2.08–2.12 (m)	2.05–2.08 (m)	2.09–2.14 (m)	2.01–2.12 (m)	2.04–2.12 (m)	2.06–2.11 (m)	2.07–2.12 (m)	2.08–2.14 (m)
H-2′a, H-6′a	1.28–1.36 (m)	1.26–1.36 (m)	1.26–1.36 (m)	1.32–1.36 (m)	1.26–1.31 (m)	1.35–1.38 (m)	1.31–1.37 (m)	1.32–1.37 (m)	1.41–1.51 (m)	1.31–1.35 (m)	1.31–1.36 (m)
H-3′e, H-5′e	1.69–1.73 (m)	1.69–1.73 (m)	1.65–1.75 (m)	1.73–1.76 (m)	1.68–1.72 (m)	1.72–1.77 (m)	1.68–1.77 (m)	1.72–1.78 (m)	1.70–1.74 (m)	1.71–1.75 (m)	1.73–1.76 (m)
H-3′a, H-5′a	1.42–1.47 (m)	1.39–1.50 (m)	1.43–1.50 (m)	1.44–1.50 (m)	1.41–1.49 (m)	1.47–1.51 (m)	1.41–1.51 (m)	1.42–1.52 (m)	1.29–1.37 (m)	1.45–1.50 (m)	1.46–1.51 (m)
H-4′e	1.60–1.63 (m)	1.61–1.65 (m)	1.61–1.64 (m)	1.64–1.76 (m)	1.60–1.64 (m)	1.64–1.67 (m)	1.60–1.67 (m)	1.60–1.66 (m)	1.61–1.65 (m)	1.63–1.66 (m)	1.64–1.66 (m)
H-4′a	1.23–1.27 (m)	1.20–1.24 (m)	1.20–1.28 (m)	1.27–1.30 (m)	1.20–1.24 (m)	1.31–1.33 (m)	1.25–1.28 (m)	1.25–1.29 (m)	1.23–1.27 (m)	1.23–1.26 (m)	1.23–1.29 (m)
H-2″, H-6″	7.44–7.46 (m)	7.02–7.07 (m)	7.35 (d)	7.44–7.46 (m)	7.36–7.39 (m)	7.46–7.47 (m)	7.39–7.42 (m)	6.84–6.86 (m)	7.25–7.26 (m)	7.36–7.39 (m)	7.30 (d)
H-2‴, H-6‴	7.44–7.46 (m)	7.02–7.07 (m)	7.35 (d)	7.51–7.52 (m)	7.41–7.43 (m)	7.51–7.53 (m)	7.47–7.49 (m)	7.39–7.41 (m)	7.47–7.49 (m)	7.45–7.47 (m)	7.41 (d)
H-3″, H-5″	7.32–7.37 (m)	7.40–7.50 (m)	6.87 (d)	7.35–7.37 (m)	7.00–7.03 (m)	7.33–7.36 (m)	6.99–7.03 (m)	6.88–6.91 (m)	7.31–7.40 (m)	7.04–7.07 (m)	6.89 (d)
H-3‴, H-5‴	7.32–7.37 (m)	7.40–7.50 (m)	6.88 (d)	7.38–7.41 (m)	7.04–7.06 (m)	7.38–7.41 (m)	7.03–7.08 (m)	7.33–7.35 (m)	7.31–7.40 (m)	7.08–7.11 (m)	6.93 (d)
H-4″, H-4‴	7.26–7.29 (m)	–	–	7.29–7.34 (m)	–	7.31–7.33 (m)	–	–	7.31–7.40 (m)	–	–
3-Alkyl protons											
CH_3	0.88 (d)	0.87 (d)	0.87 (d)	0.94 (d)	0.88 (d)	1.06 (s)	1.01 (s)	1.00 (s)	1.00 (d)	1.01 (d)	1.02 (d)
CH_3	–	–	–	1.12 (d)	1.07 (d)	1.22 (s)	1.17 (s)	1.17 (s)	–	–	–
CH	–	–	–	1.88–1.92 (m)	1.81–1.88 (m)	–	–	–	–	–	–
5-Alkyl protons											
CH_3	–	–	–	–	–	–	–	–	0.87 (d)	0.88 (d)	0.88 (d)
p-OCH_3	–	–	3.80 (s), 3.81 (s)	–	–	–	–	3.80 (s), 3.81 (s)	–	–	3.83 (s), 3.85 (s)

Table 4
^{1}H–^{1}H coupling constant (Hz) values of compounds **13–23**.

Compound	$^3J_{6a,5a}$	$^3J_{2a,3a}$	$^2J_{5e,5a}$	$^3J_{6a,5e}$	$^3J_{3a,alkyl}$
13	11.6	10.0	14.0	2.4	6.8
14	11.6	10.0	14.0	2.4	6.4
15	11.6	10.0	14.0	2.4	6.4
16	11.2	9.2	14.8	3.2	3.6
17	11.2	9.6	14.8	3.2	3.6
18	11.5	–	14.0	3.0	–
19	11.6	–	14.0	[a]	–
20	11.6	–	14.0	[a]	–
21	–	10.4	–	3.2	6.4
22	–	8.4	–	2.4	5.2
23	–	8.4	–	2.8	4.8

[a] H-6 and H-5a were observed only as doublets due to poor resolution.

groups at C-2 and C-6 makes the chair conformation more rigid thereby preventing inter-conversion from one chair into another. In compounds **13–20** 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.

In the case compounds **21–23**, which have methyl substituent at C-3 and C-5 carbon, the methyl group at C-5 adopts axial orientation in order to avoid the 1,3 spatial interaction between the methyl and N–NH–CS–NHCy and to retain the chair conformation (Fig. 8). The equatorial orientation of the H-5e proton is substantiated from the vicinal coupling constant ($J^3_{6a,5e}$ = 2.4—3.2 Hz). The axial orientation of H-3a was confirmed from the diaxial coupling constant value ($J^3_{2a,3a}$ = 8.4—10.4 Hz). These observations suggest that the six-membered heterocyclic ring for compounds **21–23** may take a chair conformation with equatorial orientation of the aryl groups (C-2 and C-6), equatorial and axial orientations of methyl groups at C-3 and C-5 respectively [35,36]. The axial orientation of methyl group at C-5 carbon is in line with the previous studies [35].

Compared to **7–9**, in **18–20** H-5e is deshielded by ~0.5 ppm and H-5a is shielded by ~0.45 ppm. Similarly, C-5 is shielded to an extent of ~15.0 ppm whereas C-3 is shielded only to a small extent of ~6.0 ppm. These observations are similar to those made in 3*t*-alkyl-2r,6c-diarylpiperidin-4-one oximes [37] with *E* configuration about the C=N bond. Obviously, in **18–20** the configuration about C=N bond is *E* (Fig. 7). In the other thiosemicarbazones also H-5e has a higher chemical shift than H-5a and C-5 has a lower chemical shift than C-3. Hence, in all the thiosemicarbazones (**13–23**) the configuration about the C=N bond should be *E* and the six membered heterocyclic ring adopts chair conformation with the orientation of N–NH–CS–NHCy moiety syn to the C-5 carbon (Fig. 7).

2D NMR spectral analysis suggested that the cyclohexane fragment present in the compounds **13–23** also adopt a chair conformation. The axial proton H-1′a (at C-1′ carbon in cyclohexyl ring) orientated in anti to the N—H proton as shown in Fig. 7. It is evidenced that the N—H proton at 7.54 ppm has NOE with only axial H-2′a, H-6′a around 1.35–1.38 ppm and there is no NOE with H-1′a around 4.31–4.35 ppm. It is also supported by the single crystal XRD study of compound **18**.

3.3. ^{13}C NMR spectral analysis of compounds **13–23**

In the ^{13}C NMR spectrum of compound **18**, the aromatic carbons are distinguished from other carbons by their characteristic absorption in the region of 126.6–129.4 ppm. *Ipso* carbons of phenyl groups (C_1'' and C_1''') resonate at 140.0 and 143.0 ppm. Thiocarbonyl carbon (C=S) is absorbed at 177.0 ppm and the C-4 carbon (C=N) resonated at 157.0 ppm. The cyclohexyl ring carbons resonates in the lower frequency region and among the four carbons, C-1′ carbon is deshielded due to electronegative nitrogen atom at α position.

A set of signals in the upfield region of 43.3 and 32.4 ppm are assigned to C-3 and C-5 carbons respectively. Among these two carbons C-5 carbon is shielded due to γ-*syn* effect (the C—H bond is polarized and the carbon (C-5) acquired negative charge as shown in Fig. 7). Similarly, C-2 and C-6 carbon resonances were observed at 70.5 and 61.2 ppm respectively and the observed shielding of C-6 is due to extended γ-*syn* effect.

Table 5
^{13}C chemical shift (ppm) values of compounds **13–23**.

Carbon	Compound										
	13	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**
C=S	176.8	176.8	176.8	176.7	176.8	177.0	176.9	176.9	176.9	176.9	176.8
C-2	69.2	68.4	68.6	65.2	64.3	70.5	69.7	69.9	69.3	68.5	68.7
C-3	45.0	45.2	45.2	54.6	54.8	43.3	43.2	43.4	40.7	40.7	40.8
C-4	153.5	152.9	153.8	151.8	151.1	157.0	156.6	157.4	158.0	157.3	158.3
C-5	36.0	36.1	36.1	36.2	36.3	32.4	30.9	32.5	36.4	36.3	36.6
C-6	60.8	60.1	60.3	59.8	59.0	61.2	60.5	60.6	62.9	62.2	62.4
C-1′	52.6	52.6	52.6	52.5	52.6	52.6	52.5	52.6	52.6	52.6	52.6
C-2′	32.6	32.6	32.6	32.6	32.6	32.6	32.6	32.6	36.4	32.6	32.6
C-3′	24.6	24.6	24.6	24.8	24.5	24.5	24.6	24.6	24.6	24.5	24.5
C-4′	25.5	25.5	25.5	25.5	25.5	25.6	25.5	25.6	25.5	25.5	25.5
C-5′	24.6	24.6	24.5	24.8	24.5	24.5	24.6	24.6	24.6	24.5	24.5
C-6′	32.6	32.6	32.6	32.6	32.6	32.6	32.6	32.6	36.4	32.6	32.6
C-1″	142.3	138.0	134.6	142.8	138.6	140.0	135.6	132.2	140.6	136.3	132.8
C-1‴	142.7	138.5	135.0	142.8	138.7	143.0	138.7	135.3	142.7	138.3	134.9
C-2″, C-6″	128.7	129.4	114.0	128.7	129.4	129.1	115.6	114.1	128.6	129.3	128.8
C-2‴, C-6‴	126.6	128.3	113.8	126.6	115.4	126.6	114.6	113.1	126.9	115.3	113.7
C-3″, C-5″	127.9	115.4	127.7	127.9	115.6	128.1	130.4	130.0	127.9	115.4	113.8
C-3‴, C-5‴	128.5	115.7	128.8	128.6	128.2	128.8	128.3	127.7	128.5	128.4	127.9
C-4″	128.0	161.2	134.6	128.0	161.2	127.8	161.1	159.1	127.6	161.3	158.9
C-4‴	128.0	163.6	135.0	128.0	163.3	127.8	163.6	159.3	128.0	163.3	159.3
3-Alkyl carbons											
CH_3	12.0	11.9	12.0	18.6	18.7	21.0	20.9	20.9	12.0	11.9	11.9
CH_3	–	–	–	20.8	21.1	22.5	22.4	22.5	–	–	–
CH	–	–	–	32.6	32.6	–	–	–	–	–	–
5-Alkyl carbons											
CH_3	–		–	–	–	–	–	–	11.2	11.1	11.1
p-OCH_3	–	–	55.3	–	–	–	–	55.3	–	–	55.3

Table 6
Correlations in the ^1H–^1H COSY, NOESY, HSQC and HMBC spectra of compound **18**.

Signals in the ^1H spectrum	Correlations in the ^1H–^1H COSY spectrum	Correlations in the NOESY spectrum	Correlations in the HSQC spectrum	Correlations in the HMBC spectrum
1.06 (s, 3H, CH_3)	–	3.76, 7.46–7.47, 7.51–7.53,	22.5 (CH_3)	21.0 (CH_3, β), 43.3 (C-3, α), 70.5 (C-2, β), 157.0 (C-4, β)
1.22 (s, 3H, CH_3)	–	2.40, 7.46–7.47	21.0 (CH_3)	22.5 (CH_3, β), 43.3 (C-3, α), 70.5 (C-2, β), 157.0 (C-4, β)
1.31–1.33 (m, 1H, H-4′a)	1.64–1.67	1.64–1.67	25.6 (C-4′)	–
1.35–1.38 (m, 2H, H-2′a/H-6′a)	2.09–2.14, 4.31–4.35	1.72–1.77, 2.09–2.14	32.6 (C-2′)	24.5 (C-3′, α), 24.5 (C-5′, α)
1.47–1.51 (m, 2H, H-3′a/H-5′a)	1.72–1.77, 2.09–2.14	1.72–1.77, 1.64–1.67, 2.09–2.14, 4.31–4.35	24.5 (C-3′)	32.6 (C-2′, α), 32.6 (C-6′, α)
1.64–1.67 (m, 1H, H-4′e)	1.31–1.33	1.31–1.33	25.6 (C-4′)	–
1.72–1.77 (m, 2H, H-3′e/H-5′e)	1.47–1.51, 2.09–2.14	1.35–1.38, 1.47–1.51	24.5 (C-5′)	32.6 (C-2′, α), 32.6 (C-6′, α), 52.6 (C-1′, β)
1.93 (s, 1H, NH)	–	3.76, 3.86, 7.46–7.47, 7.51–7.53	–	–
2.09–2.14 (m, 2H, H-2′e/H-6′e)	1.35–1.38, 1.47–1.51, 1.72–1.77, 4.31–4.35	1.35–1.38, 1.47–1.51, 1.72–1.77, 4.31–4.35	32.6 (C-6′)	–
2.40 (dd, 1H, H-5a)	3.86, 2.75	1.22, 2.75, 3.76, 7.51–7.53	32.4 (C-5)	61.2 (C-6, α), 143.1 (C-1‴, β), 157.0 (C-4, α)
2.75 (dd, 1H, H-5e)	3.86, 2.40	2.40, 3.86, 8.44	32.4 (C-5)	43.3 (C-3, β), 61.2 (C-6, α), 157.0 (C-4, α)
3.76 (s, 1H, H-2a)	–	1.06, 1.93, 3.86, 7.46–7.47	70.5 (C-2)	21.0 (CH_3, β), 22.5 (CH_3, β), 43.3 (C-3, α), 61.2 (C-6, β), 140.0 (C-1″, α), 157.0 (C-4, β) 129.1 (C-2″/C-6″, β)
3.86 (dd, 1H, H-6a)	2.40, 2.75	1.93, 2.40, 2.75,3.76, 7.51–7.53	61.2 (C-6)	143.1 (C-1‴, β), 70.5 (C-2, β), 126.6 (C-2‴/C-6‴, β)
4.31–4.35 (m, 1H, H-1′a)	1.35–1.38, 2.09–2.14, 7.54	1.47–1.51, 2.09–2.14	52.6 (C-1′)	32.6 (C-2′, α), 32.6 (C-6′, α)
7.31–7.33 (m, 2H, H-4″/H-4‴)	7.33–7.3, 7.38–7.41	7.33–7.36, 7.38–7.41	127.8 (C-4″/C-4‴)	128.1 (C-3″/C-5″, α) 128.8 (C-3‴/C-5‴, α)
7.33–7.36 (m, H-3″/H-5″)	7.31–7.33, 7.46–7.47	7.31–7.33, 7.46–7.47	128.1 (C-3″/C-5″)	127.8 (C-4″/C-4‴, α), 129.1 (C-2″/C-6″, α), 140.0 (C-1″, β)
7.38–7.41 (m, H-3‴/H-5‴)	7.31–7.33, 7.51–7.53	7.31–7.33, 7.51–7.53	128.8 (C-3‴/C-5‴)	127.8 (C-4″/C-4‴, α), 126.6 (C-2″/C-6″, α), 143.1 (C-1‴, β)
7.46–7.47 (m, H-2″/H-6″)	7.33–7.36	1.06, 1.22, 1.93, 3.76, 7.33–7.36	129.1 (C-2″/C-6″)	70.5 (C-2,β), 128.1(C-3″/C-5″, α)
7.51–7.53 (m, H-2‴/H-6‴)	7.38–7.41	1.06, 2.40, 3.86, 7.38–7.41	126.6 (C-2‴/C-6‴)	61.2 (C-6, β) 128.8 (C-3‴/C-5‴, α)
7.54 (d, 1H, C═SNH)	4.31–4.35	1.06, 1.35–1.38	–	–
8.44 (s, 1H, C═N—NH)	–	2.75	–	157.0 (C-4, β), 177.0 (—C═S, α)

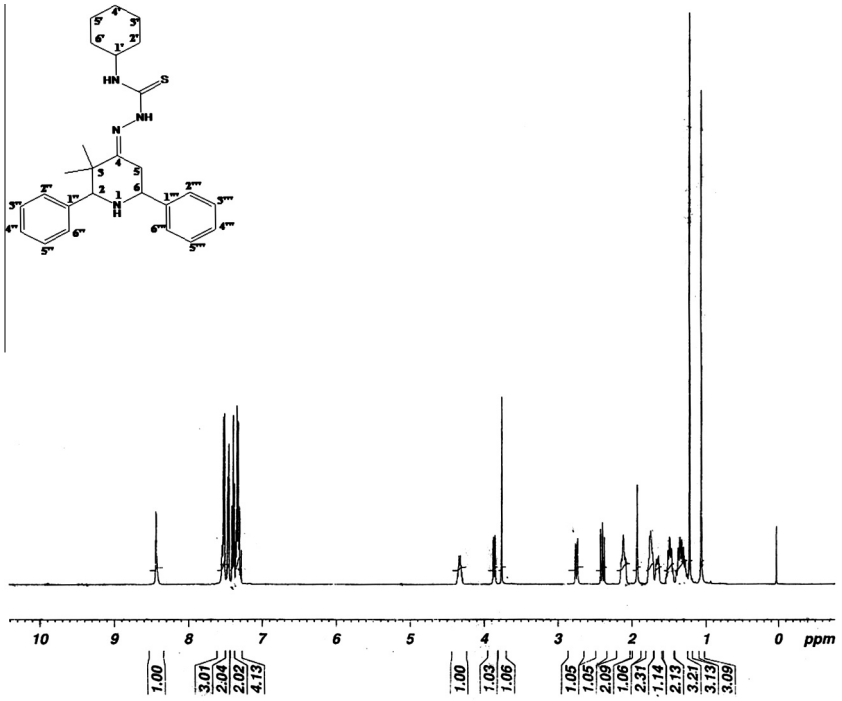


Fig. 1. ^1H NMR spectrum of compound **18**.

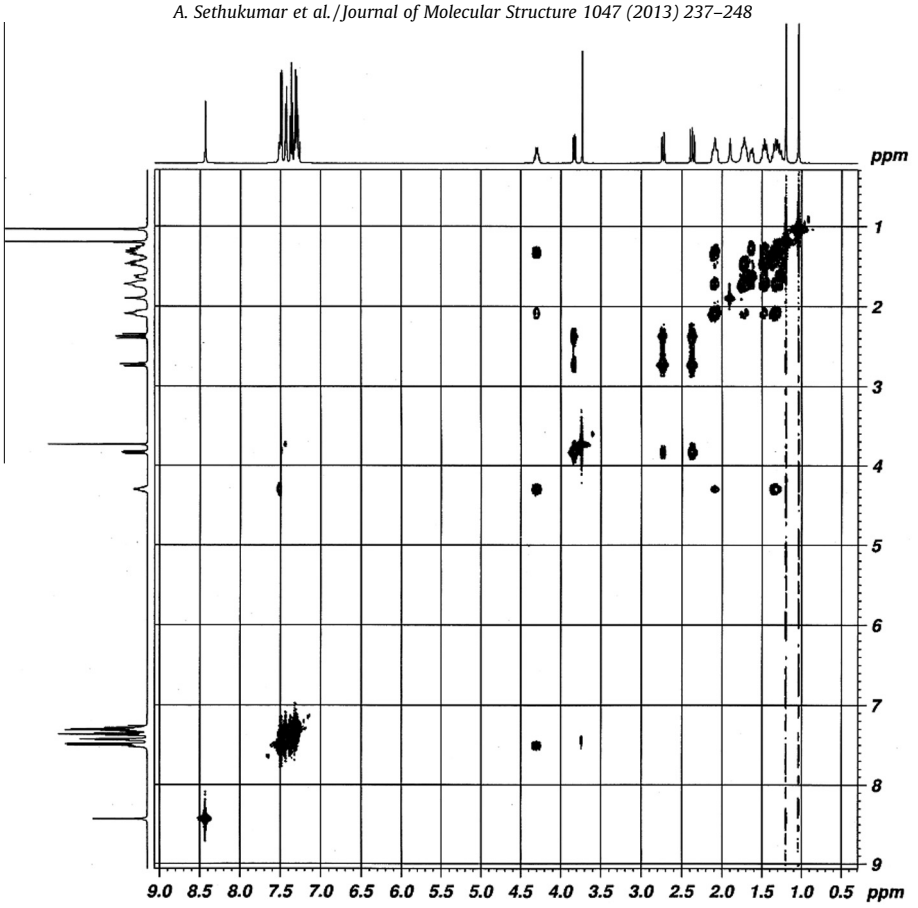


Fig. 2. ^{1}H–^{1}H COSY spectrum of compound **18**.

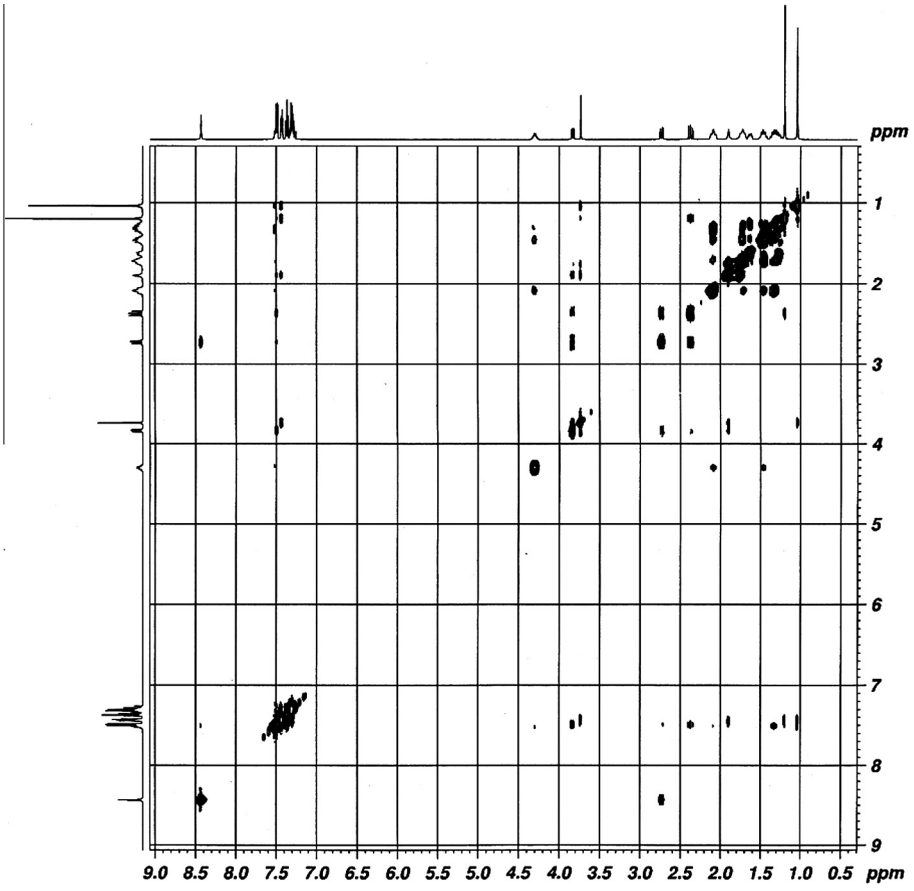


Fig. 3. NOESY spectrum of compound **18**.

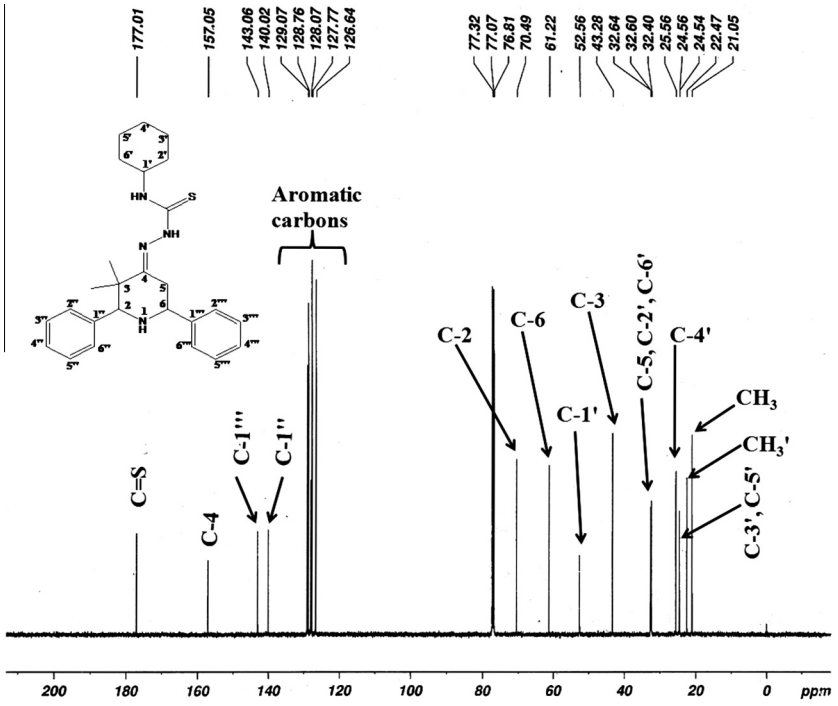


Fig. 4. ^{13}C NMR spectrum of compound **18**.

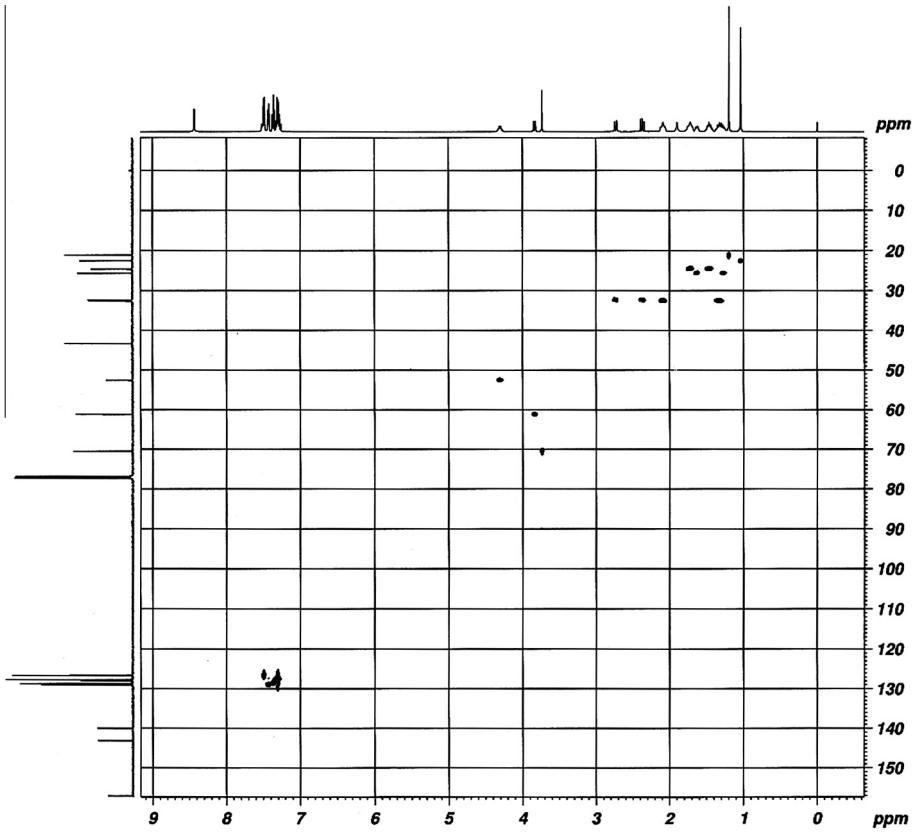


Fig. 5. HSQC (^{1}H–^{13}C one bond correlation) spectrum of compound **18**.

It has been found that in cyclohexanes, the substituent (equatorial or axial) shields the δ-carbon and this shielding has been attributed to linear electric field effect. In these cases the δ-carbons are not involved in a steric interaction with the substituents. In **13–23**, the *ortho* carbons of aryl moiety C-2″ and C-6″ are at δ-positions relative to the alkyl groups at C-3. In these cases there is steric

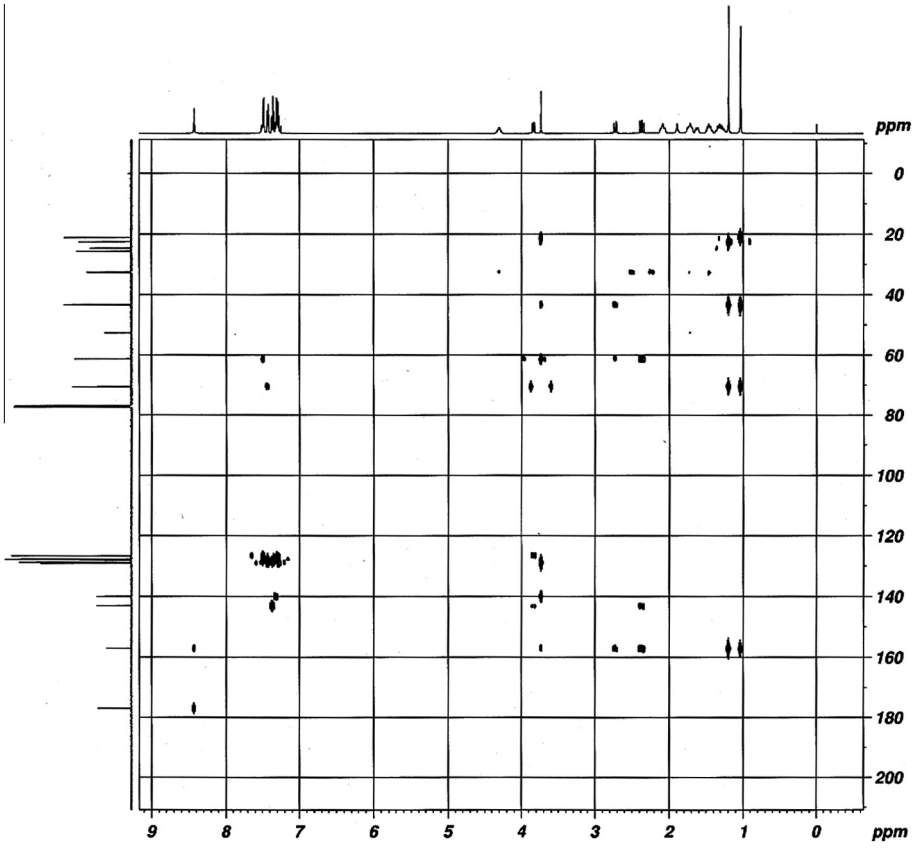


Fig. 6. HMBC (^{1}H–^{13}C multiple bond correlation) spectrum of compound **18**.

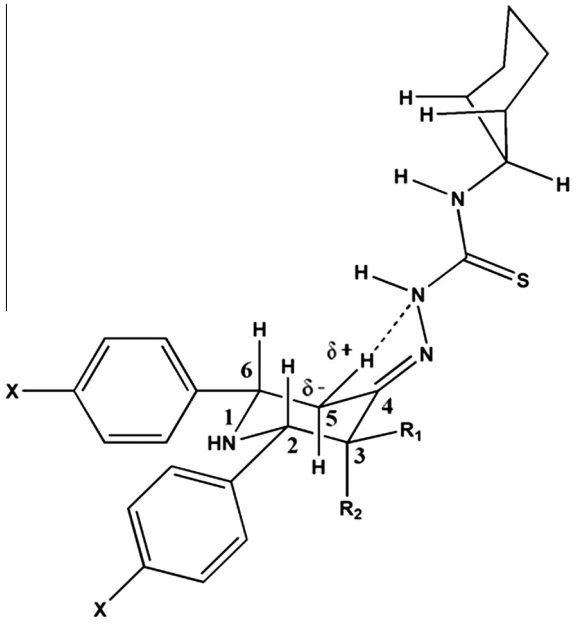


Fig. 7. Conformation of compounds **13–20**.

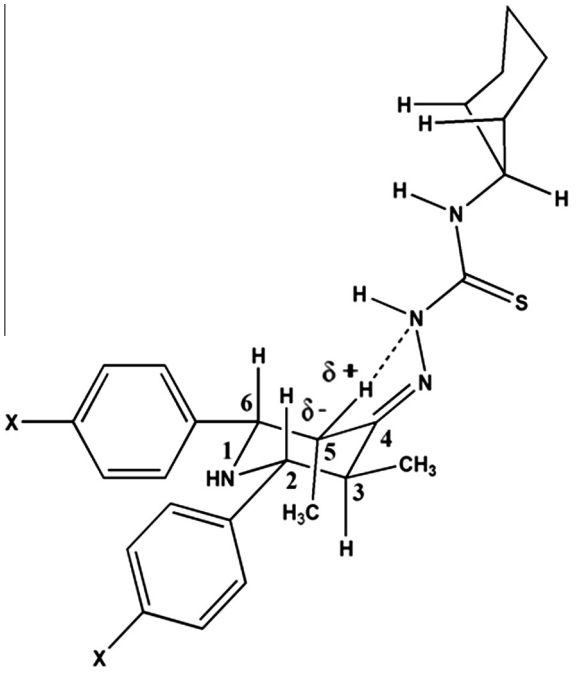


Fig. 8. Conformation of compounds **21–23**.

interaction between the δ-carbons and the substituents. From Table 5 it is seen that the ortho carbons C-2″ and C-6″ are deshielded by the alkyl groups at C-3 and the observed deshielding is around 1 ppm compared to C-2‴, C-6‴ carbon chemical shifts.

By comparing the chemical shifts of α-carbons (C-3 and C-5) of the thiosemicarbazones with the corresponding piperidones, the α-effect was analyzed. Due to the diminished electronegativity of C=N compared with C=O, the α-carbons are significantly shielded in thiosemicarbazones compared with their respective parent piperidones. Though the shielding of α-carbons to C=N is in accord with the expected electronegativity effect, the *syn* α-carbon is

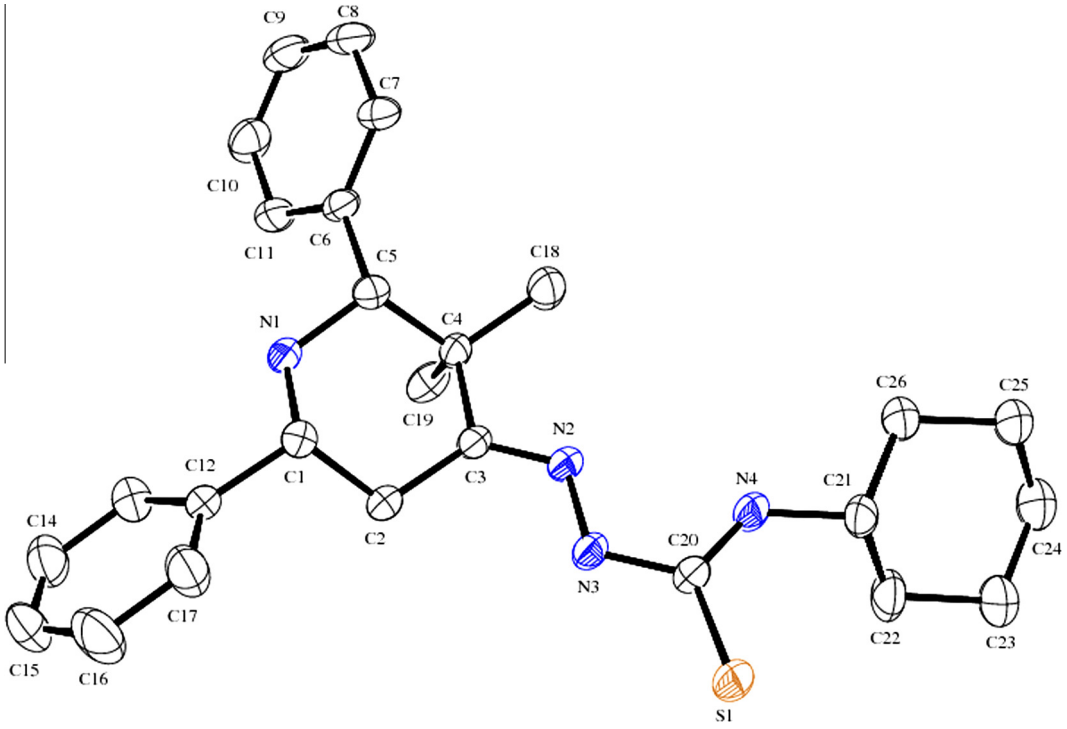


Fig. 9. ORTEP diagram of the compound **18**.

Table 7
Crystal data and structure refinement details for **18**.

Empirical formula	C_{26} H_{34} N_4 S
Formula weight	434.63
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, *Pca21*
Unit cell dimensions	a = 23.8428(11) Å
	α = 90°
	b = 8.8422(4) Å
	β = 90°
	c = 23.0770(10) Å
	γ = 90°
Volume	4865.2(4) Å^3
Z, calculated density	8, 1.187 Mg/m^3
Absorption coefficient	0.153 mm^{-1}
F(000)	1872
Crystal size (mm)	0.30 × 0.20 × 0.20
Theta range for data collection	1.92–25.00°
Limiting indices	$-28 \leqslant h \leqslant 28$, $-10 \leqslant k \leqslant 10$, $-26 \leqslant l \leqslant 26$
Reflections collected/unique	23,500/8113 [R(int) = 0.0305]
Completeness to theta = 25.00	97.7%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.965 and 0.932
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	8113/439/696
Goodness-of-fit on F^2	1.013
Final R indices [I > 2sigma(I)]	R_1 = 0.0435, wR_2 = 0.0996
R indices (all data)	R_1 = 0.0633, wR_2 = 0.1102
Extinction coefficient	0.0018(3)
Largest diff. peak and hole	0.246 and −0.188 eA^{-3}

more shielded than that of *anti* α-carbon. This is substantiated by the interaction of the CN—NH— bond with the *syn* α C—H(e) bond (Fig. 7). This interaction induces a polarity in the *syn* α C—H(e) bond, so that the *syn* α-equatorial proton (H-5e) acquires a slight positive charge and the C-5 carbon acquires a slight negative charge. And, as a consequence, the proton and carbon are respectively deshielded and shielded [38]. The sum of shielding experienced on *syn* α-carbon is about ~11–18 ppm for all compounds whereas the shielding experienced on *anti* α-carbon is only about ~4–10 ppm. Particularly in 3-substituted compounds, the shielding of *anti* α-carbon is about ~7.5 ppm while in the symmetric thiosemicarbazone the shielding magnitude increased to ~9–10 ppm. This variation is solely due to the effect of the alkyl substituents at the *anti* α-carbon (C-3). ^{13}C NMR spectral study supported the proposed chair conformation of the synthesized compounds with the equatorial orientation of the bulky aryl groups.

3.4. Single-crystal XRD study of 3,3-dimethyl-2,6-diarylpiperidin-4-one N(4′)-cyclohexyl thiosemicarbazone (**18**)

The structure and geometry of **18** in the solid state is established by single crystal X-ray structural analysis. Compound **18**, crystallizes in an orthorhombic system with *Pca21* space group and there are two asymmetric molecules with very little differences in bond parameters. Eight molecules are present in the unit cell. ORTEP of **18** is shown in Fig. 9. Crystal data, data collection and structure refinement parameters are given in Table 7. Selected bond distances and angles are given in Table 8.

The ketone condenses with thiosemicarbazide resulted a new C=N bond whose bond length is 1.283(4) Å [C3—N2]. The configuration about the C=N bond is *E*. Thiosemicarbazone moiety is planar and oriented to the best plane of piperidine ring at an angle of 24.45°. The observed dihedral angle between the S1 and N2 is 175.3(2)° [S1—C20—N3—N2]. The delocalization of π electron density over thiosemicarbazone moiety resulted in variations of C=N, N—N and C=S bond distances from the normal values [39]. From the geometrical parameters it is observed that the piperidine ring adopts chair conformation and the atoms N1 and C3 deviate from the plane defined by C1/C2/C4/C5 to an extent of 0.668 and −0.567 Å respectively [40] on either side of the plane. The phenyl groups attached to C1 and C5 carbons are equatorially oriented with the angle of 57.73 and 66.25° respectively from the mean

Table 8
Selected bond distances (Å) and angles (°) for **18**.

Bond length (Å)	
C(1) —N(1)	1.455(4)
C(1)—C(12)	1.509(4)
C(1)—C(2)	1.527(4)
C(2)—C(3)	1.498(4)
C(3)—N(2)	1.283(4)
C(3)—C(4)	1.519(4)
C(4)—C(19)	1.523(5)
C(4)—C(18)	1.529(4)
C(4)—C(5)	1.555(4)
C(5)—N(1)	1.461(4)
C(5)—C(6)	1.519(4)
C(6)—C(7)	1.379(4)
C(6)—C(11)	1.382(4)
C(20)—N(4)	1.322(4)
C(20)—N(3)	1.368(4)
C(20)—S(1)	1.681(3)
C(21)—N(4)	1.462(4)
N(7)—H(7A)···S(1)#1	2.82(3)
Bond angles (°)	
N(1)—C(1)—C(12)	111.1(2)
N(1)—C(1)—C(2)	108.6(2)
C(12)—C(1)—C(2)	109.6(2)
C(3)—C(2)—C(1)	112.0(2)
N(2)—C(3)—C(2)	126.2(2)
N(2)—C(3)—C(4)	117.4(2)
C(2)—C(3)—C(4)	116.4(2)
C(3)—C(4)—C(19)	108.3(2)
C(3)—C(4)—C(18)	111.0(2)
C(19)—C(4)—C(18)	108.5(3)
C(3)—C(4)—C(5)	107.2(2)
C(19)—C(4)—C(5)	111.6(2)
C(18)—C(4)—C(5)	110.1(2)
N(1)—C(5)—C(6)	108.4(2)
N(1)—C(5)—C(4)	110.3(2)
C(6)—C(5)—C(4)	113.4(2)
N(4)—C(20)—N(3)	115.6(3)
N(4)—C(20)—S(1)	124.6(2)
N(3)—C(20)—S(1)	119.8(2)
N(4)—C(21)—C(22)	109.6(5)
N(4)—C(21)—C(26)	110.7(3)
N(7)—H(7A)···S(1)#1	177(3)

plane of piperidine ring. The cyclohexyl ring in the thiosemicarbazone fragment also adopts chair conformation as expected and all other bond parameters are normal.

3.5. In vitro antimicrobial activity

3.5.1. Antibacterial activity of compounds *13–23*

All the synthesized compounds **13–23**, were tested for their antibacterial activity in vitro against *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pyogenes*. The antibacterial potency of the compounds were compared with standard drug ampicillin, a broad spectrum antibiotic and their minimum inhibitory concentration (MIC) values are summarized in Table 9. In general all the synthesized compounds (**13–23**) exerted a wide range of modest antibacterial activity in vitro against the tested organisms.

Compound **13**, without any substituent at *para* position of the aryl moieties at C-2 and C-6 positions of the six membered heterocyclic ring and with methyl group at C-3 position exhibited in vitro antibacterial activity at 50 μg ml^{-1} against *E. coli*, *S. pyogenes* but in the case of *P. aeruginosa* and *B. subtilis* increase in activity was observed. However, the introduction of electronegative fluorine atom in the *para* position (Compound **14)** resulted in the almost same effect against all the tested strains except *S. aureus.* It inhibited *S. aureus* at a MIC of 12.5 μg ml^{-1}. Replacement of fluorine group present at the *para* position of the aryl moieties at C-2 and C-6 by electron donating methoxy functionalities (Compound **15**) yielded no improvement in activity against *E. coli* but the activity decreased against *S. aureus*, *B. subtilis*, *P. aeruginosa*, and *S. pyogenes.*

Compound **16**, exhibits same activity against *B. subtilis* and *S. aureus* compared to **13** and there is no inhibitory effect against *E. coli*, *P. aeruginosa*, and *S. pyogenes* even at maximum tested concentration of 200 μg ml^{-1}. Introduction of fluoro functionalities at *para* position of the aryl group and C-3 isopropyl group (Compound **17**) enhances the activity against all the tested organisms except *B. subtilis.*

Compound **18**, with two methyl groups at C-3 and without substituents in the aryl groups showed excellent results against all the tested bacterial strains, which are comparable with the standard drug (ampicillin). It exhibits good activity than the other compounds in this series also. However, **19** and **20** are less potent against all the tested organisms.

Compound **21**, exerted appreciable antibacterial activity against all the tested microbes. Similarly, the introduction of fluro and methoxy functionalities in aryl group of **21** (Compounds **22** and **23**) shown one and twofold enhancement in the activity against bacterial strains except *S. aureus*. **23** exert excellent activity and it was the second best in this series.

3.5.2. Antifungal activity of compounds *13–23*

In vitro antifungal activity of the synthesized compounds **13–23**, were examined against five fungal strains viz. *Aspergillus flavus*, *Aspergillus niger*, *Penicillium chryogenum*, *Trioderma veride and Fusarium oxysporum*. Amphotericin-B was used as the standard drug. The MIC values of the test compounds and the standard are furnished in Table 10.

Table 9
Antibacterial activity of compounds **13–23**.

Compounds	MIC in μg/ml				
	Bacillus subtilis	*Escherichia coli*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Streptococcus pyogenes*
13	12.5	50	25	200	50
14	12.5	25	50	12.5	50
15	25	25	100	25	100
16	12.5	200	>200	50	>200
17	50	25	100	25	100
18	12.5	12.5	12.5	12.5	12.5
19	25	100	50	50	200
20	100	100	>200	25	100
21	50	25	50	50	50
22	25	50	25	100	12.5
23	12.5	12.5	12.5	200	12.5
Ampicillin	12.5	12.5	12.5	12.5	12.5

Table 10
Antifungal activity of compounds **13–23**.

Compounds	MIC in μg/ml				
	Aspergillus flavus	*Aspergillus niger*	*Penicillium chryogenum*	*Trioderma veride*	*Fusarium oxysporum*
13	25	50	25	25	25
14	50	100	50	25	>200
15	25	50	>200	50	50
16	100	50	50	50	100
17	25	25	50	>200	100
18	50	25	50	25	25
19	25	>200	25	100	50
20	100	25	100	50	50
21	100	50	50	100	50
22	50	25	>200	>200	100
23	50	25	100	50	25
Amphotericin-B	25	25	25	25	25

Compound **13**, with methyl group at C-3 in the heterocyclic ring showed equivalent potency to the standard drug amphotericin-B against all the fungal strains at MIC of 25 μg ml^{-1} level except against *A. niger* (MIC of 50 μg ml^{-1}). Introduction of fluorine and methoxy functionality at the *para* position of phenyl group (compounds **14** and **15**) resulted in minimum to moderate decrease in inhibition potency against all the tested fungal organisms with MIC ranging from 25 to 200 μg ml^{-1}. Replacement of methyl group by isopropyl group at C-3 position (compound **16**) demonstrates lesser activity against all the tested strains. Similarly, no improvement in activity was noticed for **17**.

Compound **18**, with two methyl groups at C-3 position excreted fine potency against *A. niger*, *T. veride* and *F. oxysporum* but one fold lower activity against *A. flavus*, and *P. chryogenum* compared to the reference. Compounds **19–23**, exhibit decreased activity against all the tested strains.

4. Conclusion

A series of *N*(4′)-cyclohexyl thiosemicarbazones have been synthesized successfully in appreciable yields and were characterized by IR, NMR and Mass spectra. Single crystal XRD analysis was also performed for compound **18**. The observed vicinal proton–proton coupling constants suggest that in thiosemicarbazones **13–23**, 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 **13–20**, the equatorial alkyl carbon attached to C-3 is shielded by the nitrogen atom of the C=N bond due to γ-*syn* effect. The cyclohexyl fragment present in thiosemicarbazone moiety also exist normal chair conformation. The single-crystal XRD study of compound **18**, also evidences *E* configuration about the C=N bond and the chair conformation of piperidin and cyclohexyl rings. Results of the biological studies suggested that the compounds **18** (against bacteria) and **13 (**against fungi)P display antimicrobial activity similar to that of standards ampicillin and amphotericin-B respectively against all the tested strains. The other compounds showed moderate to good inhibition against tested bacterial and fungal strains.

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