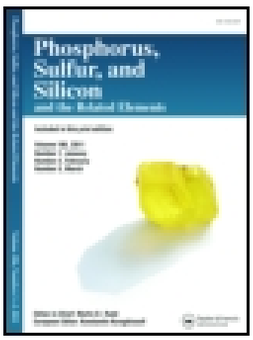

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CHEMOSELECTIVE SYNTHESIS AND SPECTRAL STUDIES OF *N*--THIOCYANATOACETYL DERIVATIVES OF 3--ALKYL--2,6--DIARYLPIPERIDIN--4--ONES

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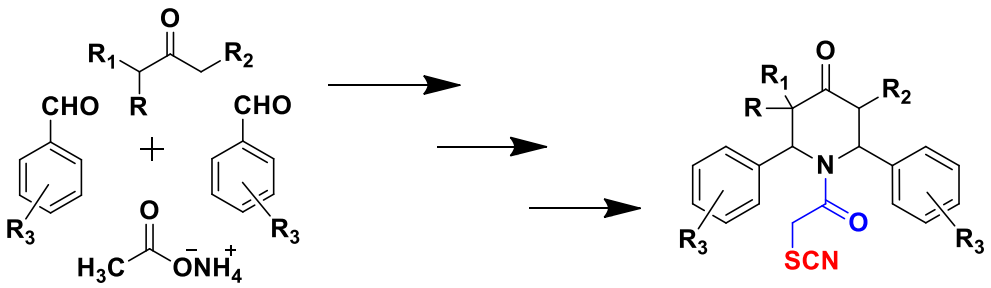
Abstract

A series of *N*--thiocyanatoacetyl derivatives of 3--alkyl--2,6--diarylpiperidin--4--ones has been synthesized by the reaction between the *N*--chloroacetyl derivatives of the respective piperidin--4--ones and the ambident thiocyanate nucleophile. The synthesized compounds have been characterized through FT--IR, ^{1}H, ^{13}C, ^{1}H--^{1}H COSY, ^{1}H--^{13}C COSY and NOESY spectra. The spectral data reveal the conformational priority of the six membered heterocyclic ring.



Key words

Chemoselective, piperidin--4--ones, thiocyanatoacetyl, NMR spectra, stereochemistry

Introduction

The thiocyanate group is present in various anticancer natural products formed by the deglycosylation of glucosinolates derived from cruciferous vegetables [1]. Further, this functional group could be used as a masked mercapto group and as a precursor for sulphur containing heterocycles whose role as pesticides [2,3] in agriculture is also significant industrially. Other important applications of alkyl thiocyanates are biocidal [4], antiasthmatic [5], vulcanization accelerators [6]. The synthetic applications of organic thiocyanates are exemplified by their use in the synthesis of sulphur--containing compounds such as sulfides [7], cyano--thiolated compounds [8], and nitriles (through desulphuration) [9]. Despite the above facts, it is pertinent to note that thiocyanate moiety is present in some biologically active natural products [10].

2--Chloroacetamides derived from a primary amine are widely used intermediates in organic synthesis because they could be transformed to thiazoles by cyclization reaction with ammonium or potassium thiocyanate. In the case of chloroacetamides derived from secondary amines, no cyclization is possible upon reaction with thiocyanate salts; instead alkyl thiocyanates are formed which are also functionally significant molecules with biological value.

Results and Discussion

Chemistry

N--chloroacetyl piperidin--4--ones subjected to thiocyanation using potassium thiocyanate in acetonitrile as the solvent, in reflux conditions, yielded the title compounds. Here,

there are two possibilities of attack by the triatomic fragment --SCN upon the substrate. The first one is the displacement of chlorine atom by thiocyanate to give thiocyanato acetyl derivatives and the second possibility is the reaction between enolizable ketone part of the substrate with the thiocyanogen [$(SCN)_2$] that could be formed from the thiocyanate salt to yield α--ketothiocyantes. In this case, the second possibility is ruled out and chemoselectivity is achieved due to the reactivity of the chloroacetyl moiety.

Among the solvents reported in the literature for thiocyanation *viz.* acetone, *N*,*N*'--dimethylformamide and acetonitrile, the reaction was found to be smooth and better with acetonitrile when heated under reflux for 3--6 h. The solid formed upon cooling to room temperature was separated by filtration and recrystallization in ethanol--ethyl acetate mixture (2:1 ratio) gave pure compound. The Scheme 1 illustrates the procedure for the synthesis of *N*--thiocyanato acetyl piperidin--4--ones, 23--33.

Spectral Characterization and Analysis

Analysis of IR and Mass spectra

Infrared spectra of the synthesized compounds exhibited significant absorptions pertaining to the functional groups present such as thiocyanate (SCN), ketone carbonyl (C = O), amido carbonyl (CONH) and the absorption frequencies (cm^{-1}) are presented in the experimental section along with mass spectral data. FT--IR and GC--Mass spectra of the synthesized compounds are available in the Supplemental **materials (Figures S 1 -- S 12).**

Analysis of ^{1}H NMR spectra

Among the different *N*--thiocyanatoacetyl derivatives of 3--alkyl--2,6--diarylpiperidin--4--one (23--33) synthesized, compound 23 is taken as a representative to discuss the spectral features of the compounds. The numbering scheme followed for discussion is shown through Figure 1. The ^{1}H NMR and the 2--D correlation spectra of the synthesized compounds are given in the supplemental materials (Figures S 13 -- S23 and Figure S35 -- S37) and the ^{1}H chemical shift values, splitting pattern and coupling constant values are listed in the experimental section.

In the ^{1}H NMR spectrum of compound 23 (Figure 2), all the aromatic protons resonate in between 7.03 ppm and 7.38 ppm. The protons of the C3--Me group are observable as a singlet at 0.98 ppm. The ^{1}H--^{1}H COSY spectrum reveals the correlation (Table 1) between the C3--Me protons and H3 proton resonating at 3.02 ppm as a singlet. The methylene protons attached to C--5 carbon atom resonate separately at 3.76 (bs) and 3.96 ppm (d, ^{2}J = 13.2 Hz) respectively. This identification is based on the observation of cross peaks between these two protons in the ^{1}H--^{1}H COSY spectrum. Further, it is known from the literatures [11] that in cyclohexane and related saturated six membered cyclic systems, the equatorial protons are deshielded than axial protons due to ring current effect. Therefore, the former signal is assigned for H5e proton and the latter for H5a proton.

A doublet of doublets encompassing H3 proton observed around 3 ppm is identified as the signal due to the diastereotopic protons $H8_A$ and $H8_B$ from the correlations between these two in the ^{1}H--^{1}H COSY spectrum as well as their large coupling constant values (J >15 Hz) typical for geminal coupling pattern. The remaining two broad singlets at 5.10 and 5.98 ppm corresponding to one proton each are assigned to H2 and H6 protons based on the literature

reports [12] available for similar compounds as there are no correlations exhibited by these protons with their neighbours. The broadening of these signals is accounted by the ring flattening caused due to the involvement of lone pair of electrons available on the nitrogen atom [13]. The change in hybridization state of nitrogen atom from sp^3 to sp^2 is pronounced in the extent of deshielding, broadening and weakening of the signals of the adjacent protons [14].

Analysis of ^{13}C NMR spectra

The ^{13}C NMR spectra of the synthesized compounds are given in the Supplemental Materials (Figured S 24 -- S 34) and the spectral data of the same are shown in the experimental section.

In the ^{13}C NMR spectrum of compound 23 (Figure 3), the resonance due to C4, C7, and C10 carbons are observed at 207.8, 167.9 and 112.2 ppm respectively. The *ipso* carbons of the phenyl ring attached at C2 and C6 carbons showed their signals at 140.2 and 139.8 ppm while the signals of remaining aromatic carbons are observed between 126.7 and 129.3 ppm.

From the observed correlations in the ^{1}H--^{13}C COSY spectrum (Figure 5 and Table 1) between proton signals of C3--Me group and the ^{13}C signal at 13.1 ppm, the latter is assigned to that of methyl carbon at C3 carbon. The cross peaks correlating ^{13}C signal at 40.1 ppm with ^{1}H signals at 3.76 and 3.96 ppm (due to H5a and H5e protons) provide sufficient support to assign the signal to the former. Likewise, the ^{13}C signal at 42.6 ppm correlating with the signals of diastereotopic hydrogens of C8 (at 2.86 and 3.23 ppm) is assigned to C8 carbon. The resonance of C3 carbon is ascertained as that one present at 46.3 ppm by the correlation observed in the ^{1}H--^{13}C COSY spectrum.

The signals of C2 and C6 carbons of the piperidine ring are observed as broad and less intense at 63.2 and 54.7 ppm respectively. These carbons didn't shown correlations with respective protons in the ^{1}H--^{13}C COSY spectrum and the assignment is carried out with the help of previous literature reports available for similar compounds [12, 13].

Stereochemistry

The compounds 23--33 contain a piperidine ring system with vicinal protons at C2--C3 and C5--C6 part of the ring. It is generally possible to deduce the relative stereochemistry of the vicinally coupled protons in conformationally rigid molecules like piperidines substituted with relatively bulky groups. However, in this case the expected signal patterns of the H2 and H6 protons are lost due to the puckering of piperidine ring due to amide formation. The signals of H2 and H6 protons are found as broad singlets against the expected doublet and doublet of doublet pattern. In ^{1}H--^{1}H COSY and ^{1}H--^{13}C COSY spectra, no correlations were observed between H2 and H6 with their neighbours and attached carbons. So, deciding stereochemistry is only partial using these spectral results and NOESY correlations observed helped in this regard for compound **23**.

The NOESY correlations observed in compound 23 are shown in Figure 6 and Table 1. There are significant correlations among C3--Me protons H3, H2, H6, H5e and also with one of the diastereotopic protons at C8 carbon. Similarly correlation between H6 and H5a proton and correlation between the latter one with H5e proton are observed. The correlation between the $H8_A/H8_B$ proton(s) and H6, H5a and H5e protons reveals the fact that the *N*--acyl moiety is oriented in such a way that both C3--Me and N--C = O groups are lying in the same side of the piperidine ring. The conformational preference of the molecule from the NOESY correlations

could be deduced as twist boat as the flattening of the ring about the plane containing C2, C6 and N atoms doesn't allow the molecule to take a chair or boat form. The puckering caused due to flattening prevents the coupling between H2 & H3 and H6 & H5 protons. The preferential conformation of compounds 23--33 is as shown in Figure 6.

Experimental

Materials and methods

Procedure for recording FT--IR, ^{1}H, ^{13}C NMR and 2D--NMR spectra

All the solvents used for recrystallization and thin layer chromatography were of analytical grade and used without further purification. All reactions were monitored by thin layer chromatography on silica gel precoated aluminum sheets (Type 60 GF254, Merck). FT--IR spectra were recorded on an AVATAR--330 FT--IR spectrometer (Thermo Nicolet) using KBr (pellet form). The melting points were recorded in open capillaries and are uncorrected. Elemental analysis of compounds have been carried out on a C, H, N analyzer type 1180 (Carlo--Erba) and the report is shown in the experimental section. Mass spectrum was recorded on a Varian Saturn 2000 GC--MS/MS spectrometer using electron impact technique. Sample was prepared by dissolving about 1 mg of compound in 5 mL of spectral grade methanol. ^{1}H and ^{13}C NMR spectra for all the compounds were recorded at 400 MHz and 100 MHz, in a Bruker ULTRASHIELD 400 PLUS instrument, using deuterated chloroform as the solvent by taking about 10 mg and 50 mg of compound respectively for recording ^{1}H NMR and ^{13}C NMR spectra. Tetramethylsilane (TMS) was used as an internal reference for all NMR spectra, with chemical shifts reported in δ units (parts per million) relative to the standard. ^{1}H NMR splitting patterns

are designated as singlet (s), broad singlet (bs), doublet (d), doublet of doublet (dd), triplet (t) and multiplet (m). Coupling constants are expressed in Hertz (Hz).

Synthesis of N--thiocyanatoacetyl derivatives of 3--alkyl--2,6--diarylpiperidin--4--ones (23--33)

The parent compounds 3--alkyl--2,6--diarylpiperidin--4--ones, **(1--11)** were synthesized by the Mannich condensation of aromatic aldehydes, ketones and ammonium acetate in ethanol. The typical procedure involves the steps as given below: An ethanolic solution of ketone (0.1 mole), aromatic aldehyde (0.2 mole) and ammonium acetate (0.1 mole) was heated to boiling and kept aside for cooling. After cooling to the room temperature, an equal quantity of diethyl ether was added followed by the addition of concentrated hydrochloric acid in drop wise to precipitate the hydrochloride salt of the piperidin--4--ones. The solid thus formed was filtered and washed with ethanol:ether mixture (2:1) to remove any impurities present. Hydrochloride salt of the piperidin--4--ones was made into a paste with acetone and aqueous ammonia added in drops to get the free base in pure form as solid after diluting the solution with water.

The piperidin--4--ones **(1--11)** were further chloroacetylated with chloroacetyl chloride in benzene medium using Et_3N as the base following the literature report [15] to get *N*--chloroacetyl derivatives of 3--alkyl--2,6--diarylpiperidin--4--ones, **12--22**. The title compounds 3--alkyl--2,6--diaryl--1--(2--thiocyanatoacetyl)piperidin--4--ones, (**23--33**) were prepared as follows: An equimolar mixture of *N*--chloroacetyl piperidin--4--one and potassium thiocyanate in acetonitrile was heated to reflux for 3--6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, a solid formed after cooling of the reaction mixture to the

room temperature was collected. This solid was washed with water and recrystallized from ethanol--chloroform mixture to get the pure product.

The spectral and other physical data of the newly synthesized compounds are given below.

3--Methyl--2,6--diphenyl--1--(2--thiocyanatoacetyl)piperidin--4--one (23): Yellow solid; Yield 79%; m. p.: 166°C; (KBr, cm^{-1}): 2154 (SCN), 1718 (C = O, Ketone), 1611 (C = O, Amide); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.10 (bs, **H2**), 3.02 (s, **H3**), 3.76 (bs, **H5a**), 3.96 (d, J = 13.2 Hz, **H5e**), 5.98 (bs, **H6**), 3.23 (d, J = 17.2 Hz, $\mathbf{H8_A}$), 2.86 (d, J = 16 Hz, $\mathbf{H8_B}$), 0.98 (s, C3--**Me**), (7.03 (s), 7.30 (s), 7.37 (d, J = 7.2 Hz), (**Aromatic**)); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 63.2 (**C2**), 46.3 (**C3**), 207.8 (**C4**), 42.6 (**C5**), 54.7 (**C6**), 167.9 (**C7**), 40.1 (**C8**), 112.2 (**C9/C10**), 139.8 & 140.2 (***ipso***), 126.7--129.3 (**Aromatic**), 13.1 (C3--**Me**); **C, H, N Analysis: C** = 69.20, **H** = 5.53, **N** = 7.69; **Found: C** = 69.19, **H** = 5.54, **N** = 7.67.

3--Ethyl--2,6--diphenyl--1--(2--thiocyanatoacetyl)piperidin--4--one, 24: Pale yellow solid; Yield 81%; m. p.: 159°C; (KBr, cm^{-1}): 2156 (SCN), 1713 (C = O, Ketone), 1608 (C = O, Amide); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.06 (bs, **H2**), 2.94 (s, **H3**), 3.76 (d, J = 8.8 Hz, **H5a**), 4.01 (d, J = 13.2 Hz, **H5e**), 5.35 (bs, **H6**), 3.03 (s, $\mathbf{H8_A}$), 2.70 (d, J = 14.8 Hz, $\mathbf{H8_B}$), 1.03 (s, C3--**Me**), 1.64 (m, C3--**C**H_2), (7.04 (s), 7.27 (s), 7.31 (s) (**Aromatic**)); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 57.3 (**C2**), 51.9 (**C3**), 207.9 (**C4**), 44.7 (**C5**), 168.0 (**C7**), 39.8 (**C8**), 112.1 (**C9/C10**), 140.0 & 140.4 (***ipso***), 126.2--129.5 (**Aromatic**), 22.8 (C3--$\mathbf{CH_2}$), 11.6 (C3--**Me**); **C, H, N Analysis: C** = 69.81, **H** = 5.86, **N** = 7.40; **Found: C** = 69.79, **H** = 5.87, **N** = 7.41.

3,5--Dimethyl--2,6--diphenyl--1--(2--thiocyanatoacetyl)piperidin--4--one, 25: Pale yellow solid; Yield 73%; m. p.: 157°C; (KBr, cm^{-1}): 2153 (SCN), 1714 (C = O, Ketone), 1613 (C = O,

Amide); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.33 (bs, **H2**, Merged with **H3** signal), 3.88 (s, **H3**, Merged with **H2** signal), 3.88 (s, **H5e,** Merged with **H3** signal), 5.33 (bs, **H6**, Merged with **H2** signal), 3.17 (s, $\mathbf{H8_A}$), 3.17 (s, $\mathbf{H8_B}$), 1.08 (s, C3--**Me**), 1.09 (s, C5--**Me**) (7.12 (s), 7.34 (s), (**Aromatic**)); ^{13}C NMR (100 MHz, $CDCl_3$) δ*:* 61.8 (**C2**), 45.3 (**C3**), 210.1 (**C4**), 40.1 (**C5**), 45.3 (**C6**), 168.1 (**C7**), 40.1 (**C8**), 112.2 (**C9/C10**), 140.0 & 140.6 (***ipso***), 127.0--129.3 (**Aromatic**), 14.3 (C3--**Me &** C5--**Me**); **C, H, N Analysis: C** = 69.81, **H** = 5.86, **N** = 7.40; **Found: C** = 69.82, **H** = 5.84, **N** = 7.39.

3--Isopropyl--5--methyl--2,6--diphenyl--1--(2--thiocyanatoacetyl)piperidin--4--one, 26: Yellow solid; Yield 77%; m. p.: 155°C; (KBr, cm^{-1}): 2152 (SCN), 1722 (C = O, Ketone), 1617 (C = O, Amide); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.48 (bs, **H2**), 2.89 (dd, *J* = 8.4 Hz & 1.6 Hz **H3**), 3.64 (bs, **H5a**), 4.09 (d, *J* = 14.4 Hz, **H5e**), 6.48 (bs, **H6**), 2.87 (dd, *J* = 17.2 Hz & 10.4 Hz $\mathbf{H8_A}$), 2.68 (dd, *J* = 17.2 Hz & 4.8 Hz $\mathbf{H8_B}$), 2.07 (CH, m, C3--***i* Pr**) 1.10 (s, CH_3), (6.93 (s), 7.21 (s), 7.31 (m) (**Aromatic**)); ^{13}C NMR (100 MHz, $CDCl_3$) δ*:* 58.2 (**C2**), 54.6 (**C3**), 207.8 (**C4**), 45.5 (**C5**), 57.0 (**C6**), 167.8 (**C7**), 39.8 (**C8**), 112.1 (**C9/C10**), 140.3 (***ipso***), 125.9--129.5 (**Aromatic**), 28.9 (**CH**, **C3--*i* Pr**) 20.5 C3--*i* Pr--**Me**) 21.1 (C3 *i* Pr--**Me'**); **C, H, N Analysis: C** = 70.38, **H** = 6.16, **N** = 7.14; **Found: C** = 70.37, **H** = 6.17, **N** = 7.13.

3,3--Dimethyl--2,6--diphenyl--1--(2--thiocyanatoacetyl)piperidin--4--one, 27: Beige solid; Yield 78%; m. p.: 160°C; (KBr, cm^{-1}): 2157 (SCN), 1715 (C = O, Ketone), 1636 (C = O, Amide); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.11 (s, **H2**), 3.50 (s, **H5a**), 4.06 (d, *J* = 14.4 Hz, **H5e**), 5.18 (s, **H6**), 3.05 (dd, *J* = 18 Hz & 11.2 Hz, $\mathbf{H8_A}$), 2.94 (dd, *J* = 18 Hz & 5.2 Hz, $\mathbf{H8_B}$), 1.35 (s, C3--**Me**), 1.36 (s, C3--**Me'**), (6.64 (d, *J* = 4.8 Hz), 7.18 (s), 7.33 (s) (**Aromatic**)); ^{13}C NMR (100 MHz, $CDCl_3$) δ*:* 69.5 (**C2**), 47.3 (**C3**), 209.8 (**C4**), 47.2 (**C5**), 58.2 (**C6**), 167.4 (**C7**), 39.5 (**C8**),

112.1 (**C9/C10**), 138.2 & 141.3 (***ipso***), 125.2--129.7 (**Aromatic**), 21.4 (C3--**Me**), 26.0 (C3--**Me'**); **C, H, N Analysis: C** = 69.81, **H** = 5.86, **N** = 7.40; **Found: C** = 69.80, **H** = 5.85, **N** = 7.41.

3--Methyl--1--(2--thiocyanatoacetyl)--2,6--di--p--tolylpiperidin--4--one, 28: Beige solid; Yield 73%; m. p.: 154°C; (KBr, cm^{-1}): 2156 (SCN), 1718 (C = O, Ketone), 1619 (C = O, Amide); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 5.98 (bs, **H2**), 3.00 (s, **H3**), 3.76 (bs, **H5a**), 3.94 (d, *J* = 13.6 Hz, **H5e**), 5.03 (bs, **H6**), 3.21 (d, *J* = 16.4 Hz, $\mathbf{H8_A}$), 2.82 (d, *J* = 16.8 Hz, $\mathbf{H8_B}$), 0.96 (s, C3--**Me**), (6.91 (s), 7.10 (d, *J* = 6.8 Hz), 7.17 (s), (**Aromatic**)), 2.32 (s, Ar--$\mathbf{CH_3}$), 2.36 (s, Ar--$\mathbf{CH_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 63.1 (**C2**), 46.5 (**C3**), 208.1 (**C4**), 42.7 (**C5**), 53.9 (**C6**), 167.9 (**C7**), 40.3 (**C8**), 112.4 (**C9/C10**), 138.2 & 138.3 ***(ipso***), 125.1--129.9 (**Aromatic**), 12.6 (C3--**Me**), 21.0 (Ar--$\mathbf{CH_3}$), 21.1 (Ar--$\mathbf{CH_3'}$); **C, H, N Analysis: C** = 70.38, **H** = 6.16, **N** = 7.14; **Found: C** = 70.38, **H** = 6.17, **N** = 6.17.

2,6--Bis(4--methoxyphenyl)--3--methyl--1--(2--thiocyanatoacetyl)piperidin--4--one, 29: Brown solid; Yield 70%; m. p.: 170°C; (KBr, cm^{-1}): 2155 (SCN), 1713 (C = O, Ketone), 1610 (C = O, Amide), 1181 (C--O); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 6.03 (bs, **H2**), 2.99 (s, **H3**), 3.80 (d, *J* = 13.2 Hz, **H5a**), 3.98 (d, *J* = 12 Hz, **H5e**), 4.96 (bs, **H6**), 3.20 (d, *J* = 16.4 Hz, $\mathbf{H8_A}$), 2.84 (d, *J* = 14.4 Hz, $\mathbf{H8_B}$), 0.96 (s, C3--**Me**), (6.81 (d) *J* = 7.2 Hz), 6.89 d) *J* = 8 Hz), 7.16 (s), (**Aromatic**)), 3.79 (Ar--O$\mathbf{C}H_3$), 3.82 (Ar--O$\mathbf{C}H_3'$); ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 62.8 (**C2**), 46.6 (**C3**), 208.2 (**C4**), 42.6 (**C5**), 53.6 (**C6**), 167.8 (**C7**), 40.3 (**C8**), 112.5 (**C9/C10**), 131.9, 132.2, 159.3 & 159.4 ***(ipso***), 113.9--129.9 (**Aromatic**), 12.9 (C3--**Me**), 55.3 (Ar--O$\mathbf{C}H_3$), 55.6 (Ar--O$\mathbf{C}H_3'$); **C, H, N Analysis: C** = 65.07, **H** = 5.70, **N** = 6.60; **Found: C** = 65.08, **H** = 5.69, **N** = 6.61.

2,6--Bis(4--fluorophenyl)--3--methyl--1--(2--thiocyanatoacetyl)piperidin--4--one, 30: Yellow solid; Yield 76%; m. p.: 172°C; (KBr, cm^{-1}): 2157 (SCN), 1713 (C = O, Ketone), 1611 (C = O, Amide), 1227 (C--F); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.96 (bs, **H2**), 2.96 (s, **H3**), 3.82 (bs, **H5a**), 3.99 (d, J = 12.4 Hz, **H5e**), 5.12 (bs, **H6**), 3.18 (d, J = 16.8 Hz, $\mathbf{H8_A}$), 2.90 (d, J = 18.4 Hz, $\mathbf{H8_B}$), 1.01 (s, C3--**Me**), (7.00 (s), 7.07 (s), 7.21 (s), (**Aromatic**)); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 62.5 (**C2**), 46.5 (**C3**), 207.2 (**C4**), 42.5 (**C5**), 53.6 (**C6**), 167.7 (**C7**), 39.9 (**C8**), 112.0 (**C9/C10**), 135.6, 135.9, 161.1 & 163.6 (***ipso***), 116.2--129.2 (**Aromatic**), 13.2 (C3--**Me**); **C, H, N Analysis: C** = 62.99, **H** = 4.53, **N** = 7.00; **Found: C** = 63.01, **H** = 4.54, **N** = 7.01.

2,6--Bis(4--bromophenyl)--3--methyl--1--(2--thiocyanatoacetyl)piperidin--4--one, 31: Brown solid; Yield 80%; m. p.: 168°C; (KBr, cm^{-1}): 2156 (SCN), 1720 (C = O, Ketone), 1638 (C = O, Amide); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.92 (bs, **H2**), 2.89 (d) Merged with **H8** signal, **H3**), 3.83 (bs, **H5a**), 3.99 (d, J = 13.2 Hz, **H5e**), 5.08 (bs, **H6**), 3.16 (d, J = 18 Hz, $\mathbf{H8_A}$), 2.89 (d, J = 16.4 Hz, $\mathbf{H8_B}$), 0.99 (s, C3--**Me**), (6.90 (bs), 7.11 (bs), 7.44 (d, J = 7.2 Hz), 7.51 (d, J = 7.2 Hz), (**Aromatic**)); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 62.7 (**C2**), 46.3 (**C3**), 206.9 (**C4**), 42.0 (**C5**), 54.3 (**C6**), 167.8 (**C7**), 39.7 (**C8**), 112.1 (**C9/C10**), 138.7 & 138.9 (***ipso***), 122.6--132.5 (**Aromatic**), 13.1 (C3--**Me**); **C, H, N Analysis: C** = 48.30, **H** = 3.47, **N** = 5.36; **Found: C** = 48.28, **H** = 3.46, **N** = 5.38.

2,6--Bis(2--chlorophenyl)--3--methyl--1--(2--thiocyanatoacetyl)piperidin--4--one, 32: Brown solid; Yield 78%; m. p.: 171°C; (KBr, cm^{-1}): 2151 (SCN), 1720 (C = O, Ketone), 1643 (C = O, Amide), 755 (C--Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.03 (bs, **H2**), 3.06 (s, **H3**), 3.93 (d, J = 15.2 Hz, **H5a**), 4.09 (d, J = 15.2 Hz, **H5e**), 5.72 (s, **H6**), 3.12 (s, $\mathbf{H8_A}$), 3.01 (s, $\mathbf{H8_B}$), 1.17 (d, J = 4.8 Hz, C3--**Me**), (6.93 (d, J = 6.8 Hz), 7.18 (s), 7.28 (t, J = 7.2 Hz, 8.4 Hz), 7.46 (s),

(**Aromatic**)); ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 59.0 (**C2**), 47.7 (**C3**), 207.6 (**C4**), 42.5 (**C5**), 53.1 (**C6**), 167.6 (**C7**), 39.0 (**C8**), 112.0 (**C9/C10**), 137.2 & 137.3 (***ipso***), 127.5--134.1 (**Aromatic**), 13.5 (C3--**Me**); **C, H, N Analysis: C** = 58.20, **H** = 4.19, **N** = 6.46; **Found: C** = 58.22, **H** = 4.18, **N** = 6.44; **Mass (M+H$^+$)** 433.07.

2,6--Bis(4--chlorophenyl)--3--methyl--1--(2--thiocyanatoacetyl)piperidin--4--one, 33: Brown solid; Yield 78%; m. p.: 167°C; (KBr, cm^{-1}): 2155 (SCN), 1720 (C = O, Ketone), 1641 (C = O, Amide); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 5.93 (bs, **H2**), 2.89 (d, Merged with **H8** signal **H3**), 3.81 (s, **H5a**), 3.98 (d, *J* = 14 Hz, **H5e**), 5.07 (bs, **H6**), 3.17 (d, *J* = 16.8 Hz, **H8$_A$**), 2.89 (d, *J* = 18 Hz, **H8$_B$**), 1.00 (s, C3**--Me**), (6.97 (s), 7.17 (s), 7.29 (d, *J* = 6.8 Hz) 7.36 (d, *J* = 6.8 Hz) (**Aromatic**)); ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 62.6 (**C2**), 46.3 (**C3**), 206.8 (**C4**), 42.1 (**C5**), 53.9 (**C6**), 167.7 (**C7**), 39.7 (**C8**), 111.9 (**C9/C10**), 138.1 & 138.4 (***ipso***), 128.1--134.7 (**Aromatic**), 13.1 (C3--**Me**); **C, H, N Analysis: C** = 58.20, **H** = 4.19, **N** = 6.46; **Found: C** = 58.21, **H** = 4.20, **N** = 6.48.

Conclusion

A series of *N*--thiocyanatoacetyl derivatives of 3--alkyl--2,6--diarylpiperidin--4--ones were synthesized by the reaction between *N*--chloroacetyl piperidones and potassium thiocyanate. Replacement of the chlorine atom of the chloroacetyl moiety by the thiocyanate nucleophile took place in a facile manner while using acetonitrile as the solvent. The synthesized compounds were characterized by FT--IR, 1D and 2D NMR techniques and all the signals in the ^{1}H and ^{13}C NMR spectra were unambiguously assigned. The stereochemistry of the substituents present in the piperidone ring was found out and the conformational preference of the molecules in the solution state is twist boat as evidenced from the ^{1}H NMR and NOESY spectral analyses.

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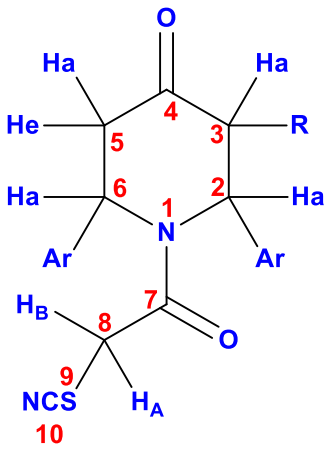
Table 1 ^{1}H--^{1}H COSY, ^{1}H--^{13}C COSY and NOESY spectral correlations of compound **23**

^{1}H chemical shifts (ppm)	**Correlations in the ^{1}H--^{1}H COSY (^{1}H chemical shifts in ppm)**	**Correlations in the ^{1}H--^{13}C COSY (^{13}C chemical shifts in ppm)**	**Correlations in the NOESY (^{1}H chemical shifts in ppm)**
7.03, 7.30--7.38 (Aromatic Hydrogens)	7.30--7.38, 7.03	126.7--129.3	0.98, 3.02, 3.23, 3.96, 5.10, 5.96
5.98 (H6)	----	----	2.86. 7.30--7.38
5.10 (H2)	----	----	0.93, 3.96, 7.03
3.96 (H5e)	3.76	40.1	3.02, 3.76,5.10, 5.98,7.03, 7.30--7.38
3.76 (H5a)	3.96	40.1	3.02, 3.96, 7.03
3.23 & 2.86 ($H8_A$ & $H8_B$)	2.86, 3.23	42.6	2.86, 3.23, 3.76,7.03--7.38,5.98
3.02 (H3)	0.98	46.3	0.98, 7.03, 7.30--7.38
0.98 (C3--Me)	3.02	13.1	3.02, 3.96, 5.10, 5.98,7.03, 7.30--7.38



Ha- Axial hydrogens;
He -Equatorial hydrogens;
H_A, H_B - Diastereotopic hydrogens

Figure 1 Numbering pattern followed for compounds **23--33** to explain NMR spectra

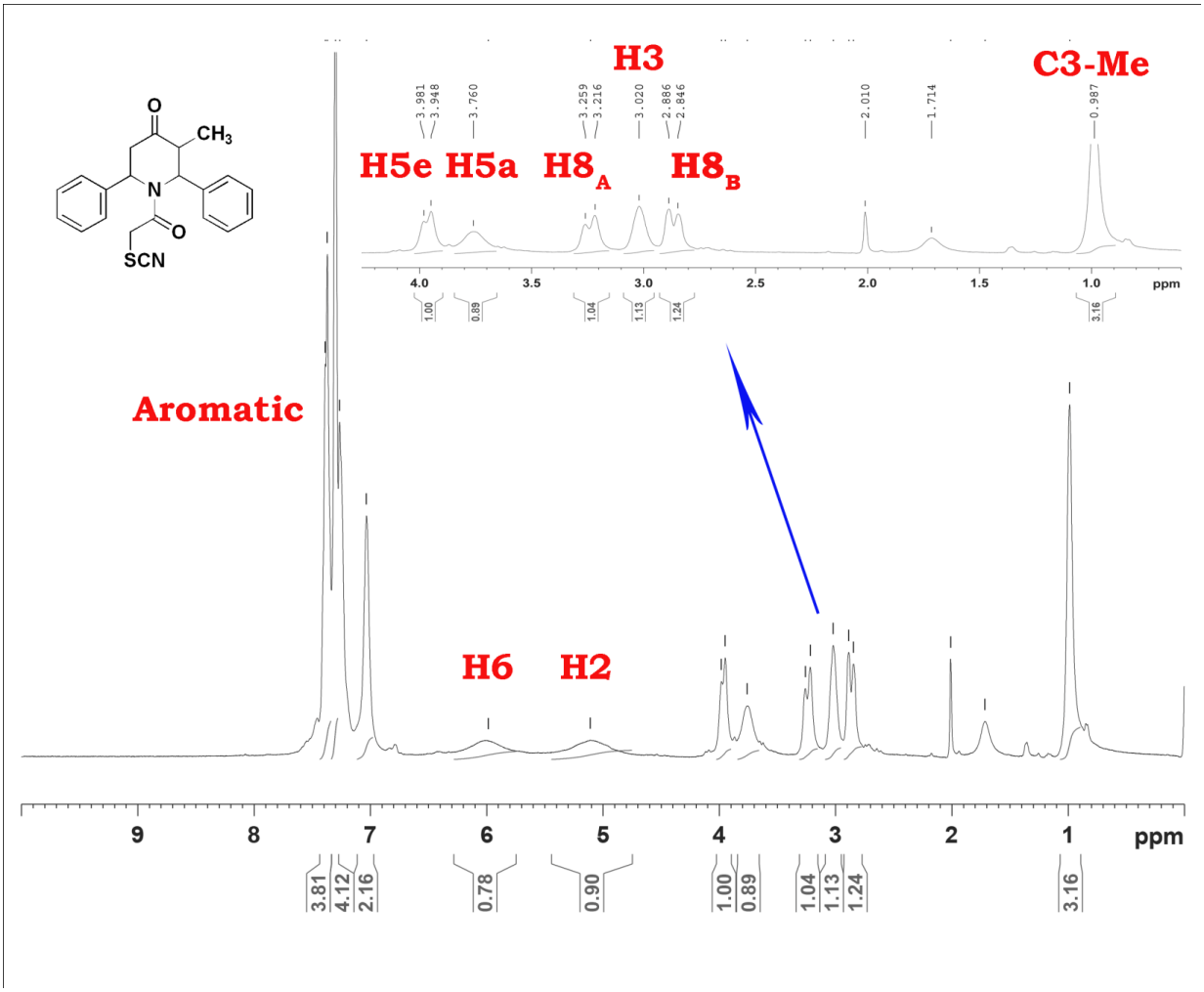


Figure 2 ^{1}H NMR spectrum of compound **23**

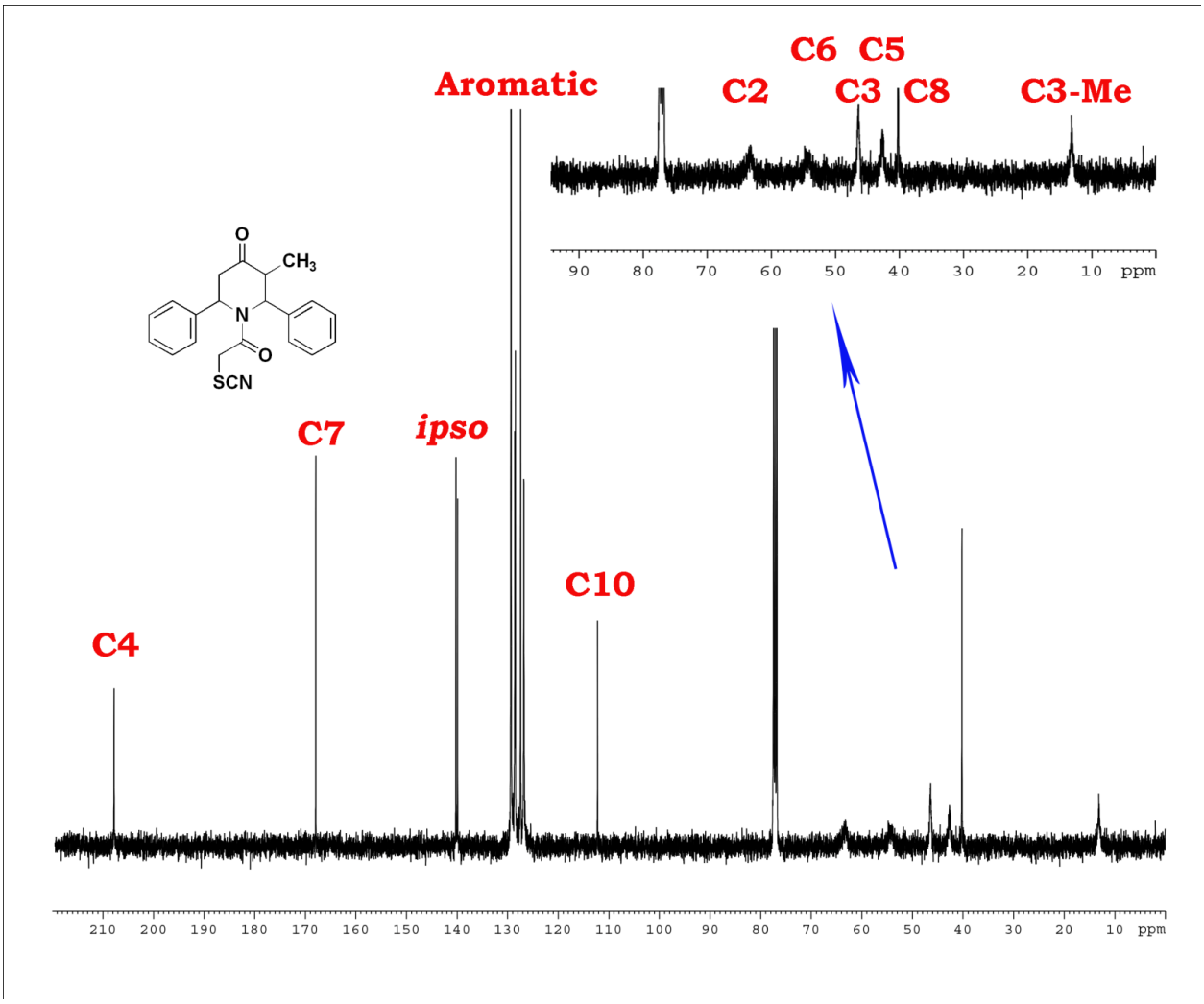


Figure 3 ^{13}C NMR spectrum of compound **23**

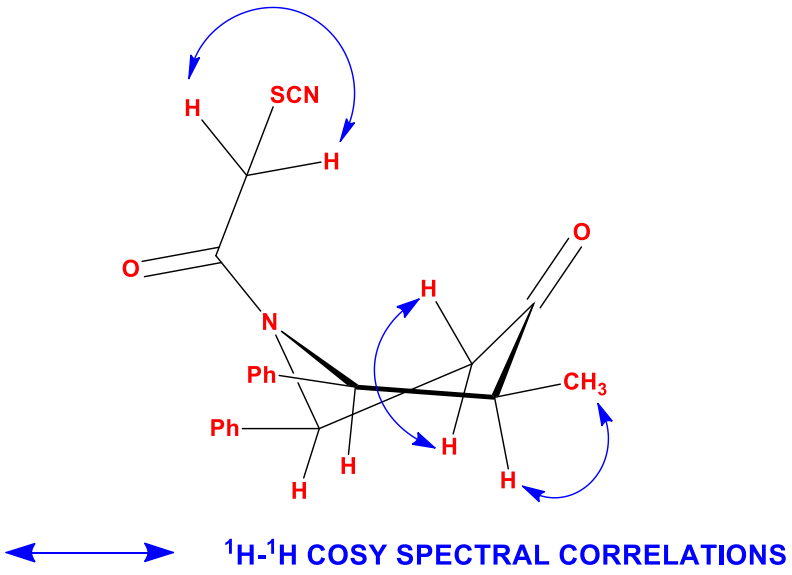


Figure 4 Selected ^{1}H--^{1}H COSY correlations of compound **23**

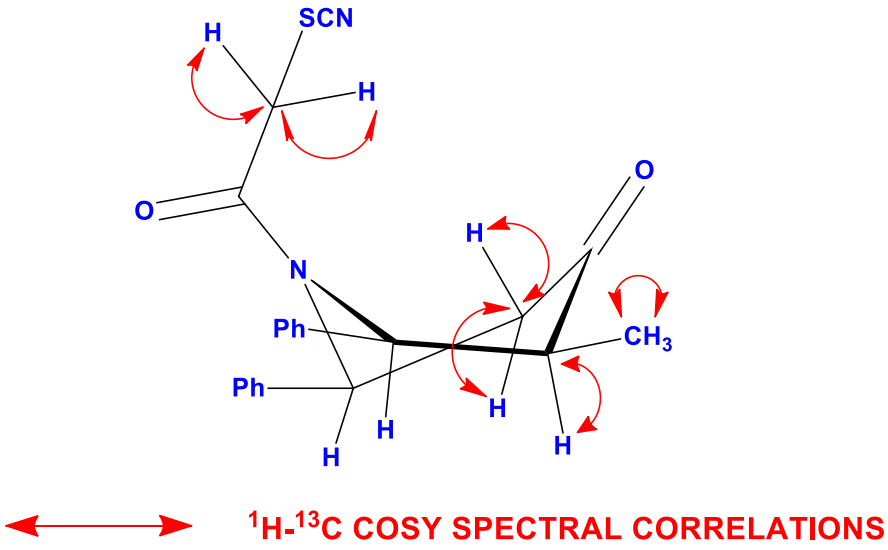


Figure 5 Selected ^{1}H--^{13}C COSY correlations of compound **23**

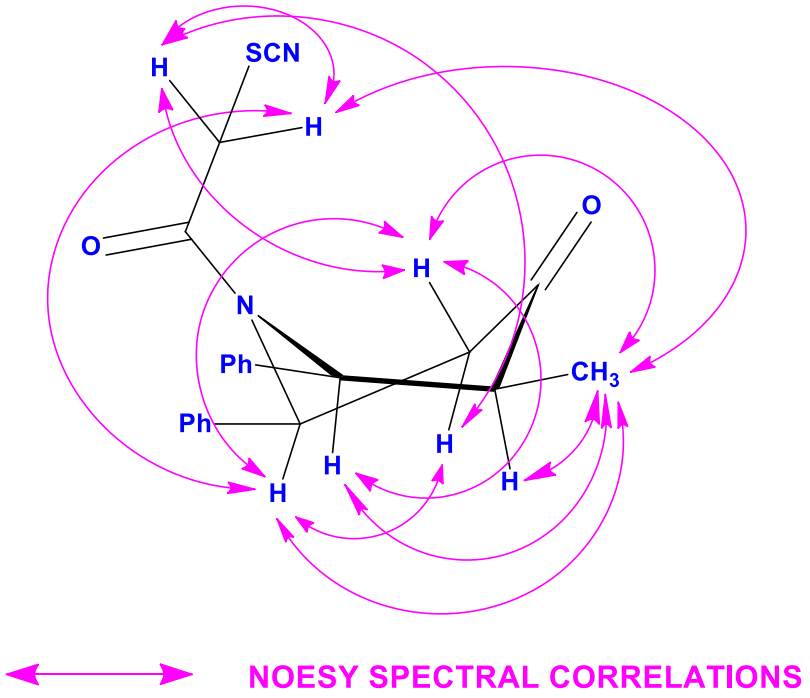


Figure 6 Selected NOESY spectral correlations and the preferred conformation of compound **23**