SYNTHESIZING N(4)-SUBSTITUTED THIOSEMICARBAZONES AND THEIR STRUCTURAL CHARACTERISTICS

DUONG BA VU[*], TRAN BUU DANG[**]

ABSTRACT

Some thiosemicarbazones such as 4-nitrobenzaldehyde-[N(4)-methyl, N(4)-phenyl thiosemicarbazone] (L1), Fluoren-9-one-[N(4)-(4-methylpiperidyl) thiosemicarbazone] (L2) and 4'-hydroxyacetophenone-[N(4)-(4-methylpiperidyl) thiosemicarbazone] (L3) were prepared by the classical method. Their components and structures were determined by the spectra of IR, UV-Vis, ^{1}H-NMR,^{13}C-NMR, COSY, HSQC, HRMS. According to the results of SciFinder at KU Leuven (Belgium) on December 19th 2014, the structures of L2 and L3 have not been reported in any scientific studies.

Keywords: thiosemicarbazide, thiosemicarbazone, piperidyl thiosemicarbazone.

TÓM TẮT

Tổng hợp và đặc điểm cấu trúc của một số dẫn xuất thế N(4)-thiosemicacbazon

Một số thiosemicacbazon gồm 4-nitrobenzandehit-[N(4)-metyl, N(4)-phenyl thiosemicacbazon] (L1), Fluoren-9-on-[N(4)-(4-metylpiperidin) thiosemicacbazon] (L2) và 4'-hydroxyaxetophenon-[N(4)-(4-metylpiperidin) thiosemicacbazon] (L3) đã được tổng hợp bằng phương pháp truyền thống. Thành phần và cấu trúc của chúng đã được xác nhận bởi các phương pháp đặc trưng: phổ IR, UV-Vis, ^{1}H-NMR,^{13}C-NMR, COSY, HSQC, HRMS. Đối chiếu danh mục chất trong SciFinder của đại học Leuven, Vương quốc Bỉ thì cho thấy hai chất L2 và L3 chưa từng được các nhà khoa học công bố.

***Từ khóa*:** thiosemicacbazit, thiosemicacbazon, piperidin thiosemicacbazon.

1. Introduction

Many studies have illustrated that N(4)-substituted thiosemicarbazones are the important class of organic compounds due to their structural chemistry and biological activities such as antivirus, anticancer and so on [1,3,4,5]. This great potential increased significantly when these compounds coordinate transition metals, especially platinum. In this paper, 4-nitrobenzaldehyde-[N(4)-methyl, N(4)-phenyl thiosemicarbazone], Fluoren-9-one-[N(4)-(4-methylpiperidyl) thiosemicarbazone] and 4'-hydroxyacetophenone-[N(4)-(4-methylpiperidyl) thiosemicarbazone] were

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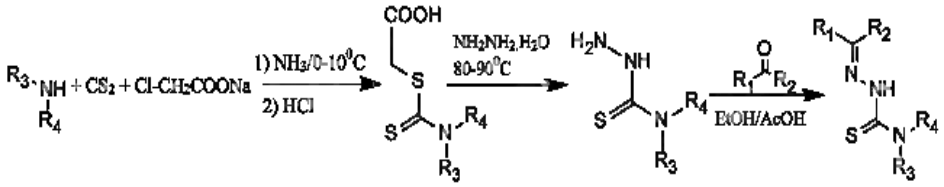
synthesized. Their structural were investigated by some kinds of spectra.

2. Experimental

2.1. Synthesis

The equivalent mixture consisting of N-methylaniline (or 4-methylpiperidine) and CS_2 was treated in NH_3 25% in the range of 0-10^{0}C for nearly 2 hours. The filtered yellow precipitate was dissolved entirely in water, followed by treatment with the saturated solution of $ClCH_2COONa$ at the room temperature for around 5-6 hours. After standing overnight, the yellowish solution was acidified by concentrated HCl. The obtained white solid carboxyl N-alkyl dithiocarbamate (CAT) was filtered and recrystallized from ethanol (or ethanol: water = 1:1). In the next step, the solution of CAT and $N_2H_4.H_2O$ in 10ml water was heated in the rings of a steam bath in the range of 80-90^{0}C. When the white N-alkyl thiosemicarbazide (ATZ) separated, heating was continued for 20 minutes. ATZ re-crystallized from ethanol (or hot water) was experienced the condensable stage with 4-nitrobenzaldehyde (or 4'-hydroxybenzaldehyde; fluoren-9-one) respectively in ethanol/glacial acetic acid as a catalyst prior to filtration and re-crystallization [3,4].

The general process of these ligands was represented in scheme 1 below:



Scheme 1. *The synthetic process of N(4)-substituted thiosemicarbazones (TSCs) from amine, CS_2 and $ClCH_2COONa$*

2.2. Structural analysis

FTIR analysis (FTIR-8400S SHIMADZU) was operated in the range of 4000–450 cm^{-1} in compressed KBr pellets. UV measurement was done by using PERKIN-ELMER LAMBDA 25 UV-VIS SPECTRUM in the range of 200-700nm in absolute ethanol.

The melting point was determined by Gallenkamp MPD-350 equipment.

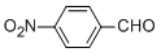
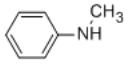
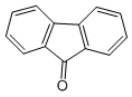
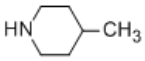
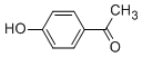
The NMR were investigated by using the equipments such as NMR, Brucker 500 MHz (in d_6-DMSO) and MS spectra was resulted from FT-ICR-MS, Varian 910 MS.

3. Results and discussion

The physicochemical properties, molecular weight, as well as UV absorption

bands of TSCs were reported statistically in table 1. The π→π* transition of aromatic moiety were observed in the range of 245-264 nm

Table 1. *The features of TSCs synthesized*

TSC	R_1-CO-R_2	R_3-NH-R_4	Yield (%)	Melting point (^{0}C)	Shape and colour	$(M+H)^+$ (MS)	UV, λ_{max} (nm) **sh:shoulder*
L1			48.87	232-234	Needle, orange-red	315	255, 300/sh* 381, 420/ sh*
L2			35.44	187-189	Needle, orange	336	245, 280/sh* 430
L3			42.32	251-253	Needle, pale yellow	292	264 329

Obviously the relation between colour and absorptions was considerable in UV spectrum. In case of L3, no bands observed in the visible radiation leads to its pale yellow. Meanwhile, the colour of either L1 or L2 was deeper because of their absorption in the range of 420 - 430 nm. The peaks of molecular ion in HRMS indicated that the molecular weights were completely accurate as the predictions.

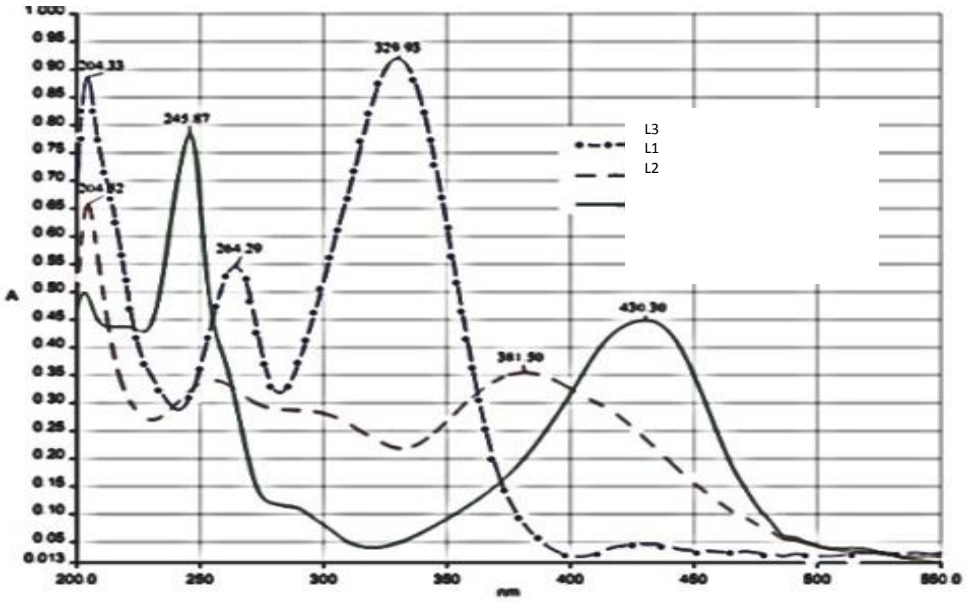


Fig1. *UV spectra of TSCs*

On the other hand, comparing with the IR spectrums of initial materials, v(C=O) near 1720 cm^{-1} was not present in almost spectrums of tested substances. It proved the high purity of products after the condensation reaction taking place completely. The stretching vibration of S-H at 2570 cm^{-1}-was absent in both of IR spectrums. That of N-H was observed in those of them, which was a single broad band at 3196-3190 cm^{-1}. Therefore, it was indicated that TSCs existed predominantly in thione form when they were in solid state. Besides, the observation of v(Csp^3-H) of 4-methylpiperidine was recorded significantly. The azomethine C=N vibration was in the range of 1653 – 1572 cm^{-1} as some assignments of N(4)-substituted thiosemicarbazones according to the previous researches [3,4]. The stretching vibration of N-N was investigated by the sharp band in the range of 1030 – 1014 cm^{-1}. In case of L3, the highest frequency at 3396 cm^{-1} with a broad band was assigned to the vibration of –OH groups as the expectation

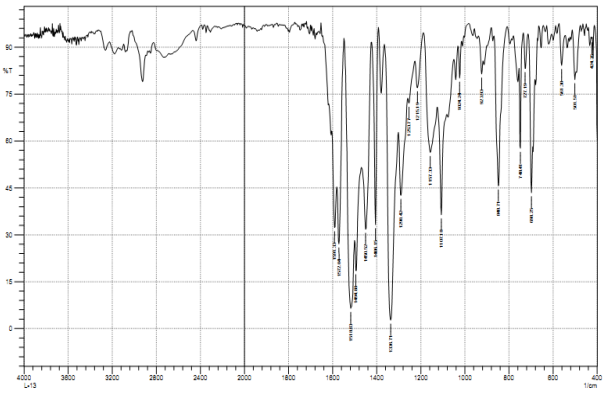


Fig 2. *IR spectrum of L1*

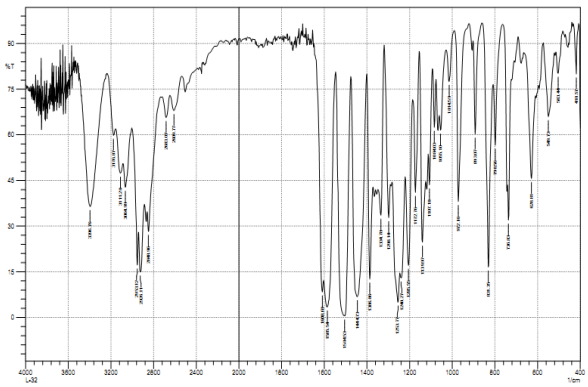


Fig 3. *IR spectrum of L2*

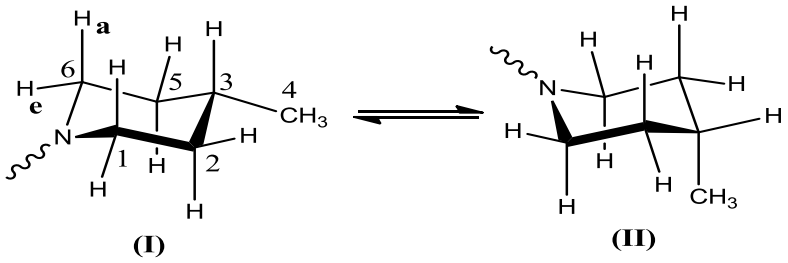
Table 2. *IR spectral data (cm^{-1}) of TSCs*

No.	ν_{O-H}	ν_{N-H}	ν_{Csp2-H}	ν_{Csp3-H}	$\nu_{C=C(Ar)}$ δ_{N-H} ν_{-CSNH-}	$\nu_{C=N}$	$\nu_{C=S}$	ν_{N-N}	δ_{Csp3-H} $\nu_{N=O}$	δ_{CH2}	$\delta_{C-H(Ar)}$ out-of-plane
L1	-	3190	3100	2900	1591 1494 1450 1406	1572	1336 923	1024	1518 1290	-	848 748 727 698
L2	-	3196	3100 3060	2950 2924 2862	1604 1417	1653 1577	1321 889	1030	1521	1446	779 731 698
L3	3396	3176	3111 3064	2953 2926 2848	1608	1585	1334 893	1014	1504	1444	831 798

All compounds were dissolved in d_6-DMSO to investigate the spectrums of ^1H NMR, COSY, ^{13}C-NMR, HSQC. The COSY information promoted accurate assigment

of protons in ^{1}H NMR ones thanks to their spin-coupling shown in 2D diagrams. Similarly, the interaction between protons and their own carbons was presented in HSQC, which provided reliable evidences for carbon determination in ^{13}C-NMR. The integration of these imformative data determined approximate models of coumpound structures. All figures were tabulated in table 3. Generally, there were 7 signals of protons in the ^{1}H-NMR spectrum of L1 with the ratio of 1:2:1:2:4:1:3 (from the downfield to the upfield in priority). This proportion represented the quantity of each kinds of proton. The singlet signal at 8.06ppm (1H) was assigned to H9. According to [2], this figure revealed that L1 existed *E* configuration.

4-methylpiperidine has two common conformations (scheme 2).

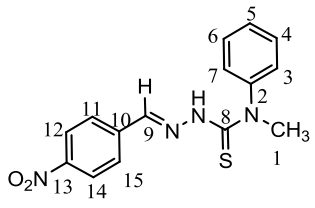


Scheme 2. *Equilibrium of two conformations of 4-methylpiperidine*

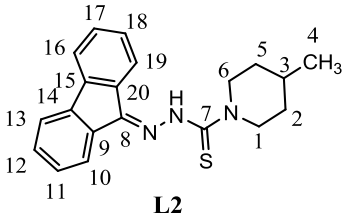
The signals of 4-methylpiperidine part were analyzed similarly in the spectrum of either L2 or L3. Due to optimized reduction of the intramolecular interactions, (I) was the major conformation in a mixture. There were 6 carbon atoms obviously in molecule of this moiety, whereas only 4 signals appeared in ^{13}C-NMR spectrum at the upfield. The observation of HSQC spectrums of L2 and L3 illustrated that the signals of (H_2^e, H_5^e); (H_2^a, H_5^a) crossed to the only signal of carbon. That of (H_1^e, H_6^e); (H_1^a, H_6^a) was entirely a similar picture. There upon, C2 and C5; C1 and C6 were chemically equivalent couples of carbon whose signals were at 32.6; 48.4 ppm respectively. This delighted feature proved the fixed conformation of 4-methylpiperidine part and interpreted the chemically distinguishable shifts of H^a and H^e in ^{1}H-NMR spectrum. The signals of C3 and C4 were assigned at 29.8 ppm; 21.6 ppm respectively. Besides the analysed figures, at the upfield of L3 spectrum there was a signal at 14.0 ppm, which was assigned to C15. This evidence identified the *Z* configuration of L3 [2]. The relaxation of 4-ordered carbon atom (C=S) required more time than others, which led to its absent signal after previous scannings during the investigation.

In general, the characteristic of signals was observed adequately as the prediction due to some instrumental analysis. Furthermore, this examination demonstrated the fixed conformation of 4-methylpiperidine part, the *E* configuration of L1, the *Z* configuration of L3 as well.

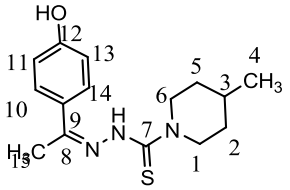
Table 3. ^{1}H, ^{13}C-NMR spectral data (ppm) of TSCs



L1



L2



L3

	The shift of proton (ppm)							The shift of carbon (ppm)		
	L1	**L2**		**L3**				**L1**	**L2**	**L3**
1	3.42 (3H.s)	H_a	3.00 (2H,t-d); $^{3}J_{aa}$=12.5Hz $^{3}J_{ae}$=2,5Hz; $^{2}J_{gem}$=12.5Hz	Ha	2.94 (2H, t-d); $^{3}J_{aa}$=12.5Hz; $^{3}J_{ae}$=2.5Hz; $^{2}J_{gem}$=12.5Hz	**1**		39.5	48.4	49.3
		H_e	3.69 (2H,d); $^{2}J_{gem}$=12.5Hz	H_e	3.68 (2H, d); $^{2}J_{gem}$=12.5Hz					
2	-	H_a	1.20 (2H,q-d); $^{3}J_{aa}$=12.5Hz $^{3}J_{ae}$=4.0Hz; $^{2}J_{gem}$=12.5Hz	H_a	1.20 (2H, q-d); $^{3}J_{aa}$=12.5Hz $^{3}J_{ae}$=4.0Hz; $^{2}J_{gem}$=12.5Hz	**2**		129.6	32.6	32.8
		H_e	1.67 (2H,d); $^{2}J_{gem}$=11Hz	H_e	1,66(2H, d); $^{2}J_{gem}$=11Hz					
3	7.44 (4H, m)	1.58 (1H, m)		1.56 (1H, m)		**3**		123.9	29.8	30.0
4	7.44 (4H, m)	0.93 (3H, d); J=7.0Hz		0.92 (3H, d); J=6.5 Hz		**4**		129.8	21.6	21.7
5	7.29 (1H,t) J = 7Hz	H_a	1.20 (2H,q-d); $^{3}J_{aa}$=12.5Hz $^{3}J_{ae}$=4.0Hz; $^{2}J_{gem}$=12.5Hz	H_a	1,20 (2H, q-d); $^{3}J_{aa}$=12.5Hz $^{3}J_{ae}$=4.0Hz; $^{2}J_{gem}$=12.5Hz	**5**		126.1	32.6	32.8
		H_e	1.67 (2H,d); $^{2}J_{gem}$=11Hz	H_e	1,66 (2H, d); $^{2}J_{gem}$=11Hz					
6	7.44 (4H ,m)	H_a	3.00 (2H,t-d); $^{3}J_{aa}$=12.5Hz $^{3}J_{ae}$=2.5Hz; $^{2}J_{gem}$=12.5Hz	H_a	2.94 (2H, t-d); $^{3}J_{aa}$=12.5Hz $^{3}J_{ae}$=2,5Hz; $^{2}J_{gem}$=12.5Hz	**6**		129.8	48.4	49.3
		H_e	3.69 (2H,d); $^{2}J_{gem}$=12.5Hz	H_e	3.68 (2H, d); $^{2}J_{gem}$=12.5Hz					
7	7.44 (4H, m)-	-		-		**7**		123.9	-	-
8	-	-		-		**8**		-	139.8	-
9	8.06 (1H, s)	-		-		**9**		147.0	131.1	129.1
10	-	7.71 (1H,d); J=7.5Hz		7.56 (2H,d); J = 9.0Hz		**10**		124.1	120.5	127.1
11	7.77 (2H, d) J = 9 Hz	7.31 (1H,t-d); J_{ortho}=7.5Hz; J_{meta}=1.0Hz		6.76 (2H,d); J = 9.0Hz		**11**		126.9	127.5	115.2
12	8.19 (2H, d) J = 9Hz	7.36 (2H,t-d) J_{ortho}=7.5Hz; J_{meta}=1.0Hz		-		**12**		124.1	128.6	158.1

	The shift of proton (ppm)				The shift of carbon (ppm)		
	L1	**L2**	**L3**		**L1**	**L2**	**L3**
13	-	7.81 (1H,d); *J*=7,0Hz	6.76 (2H,d); *J* = 9.0Hz	**13**	140.9	120.1	115.2
14	8.19 (2H, d) *J* = 9Hz	-	7.56 (2H,d); *J* = 9.0Hz	**14**	124.1	138.6	127.1
15	7.77 (2H, d) *J* = 9Hz	-	2.20 (1H,s)	**15**	126.9	136.9	14.0
16	-	7.85 (1H,d); *J*=7.5Hz	-	**16**	-	120.0	-
17	-	7.42 (1H,t-d); J_{ortho}=7.5Hz; J_{meta}=1.0Hz	-	**17**	-	129.4	-
18	-	7.36 (2H,t-d) J_{ortho}=7.5Hz; J_{meta}=1.0Hz	-	**18**	-	128.0	-
19	-	8.64 (1H,d); *J*=7.5Hz	-	**19**	-	127.6	-
20	-	-	-	**20**	-	131.1	-
NH	12.3,br	12.3, br	9.6, br	**-**	-	-	-

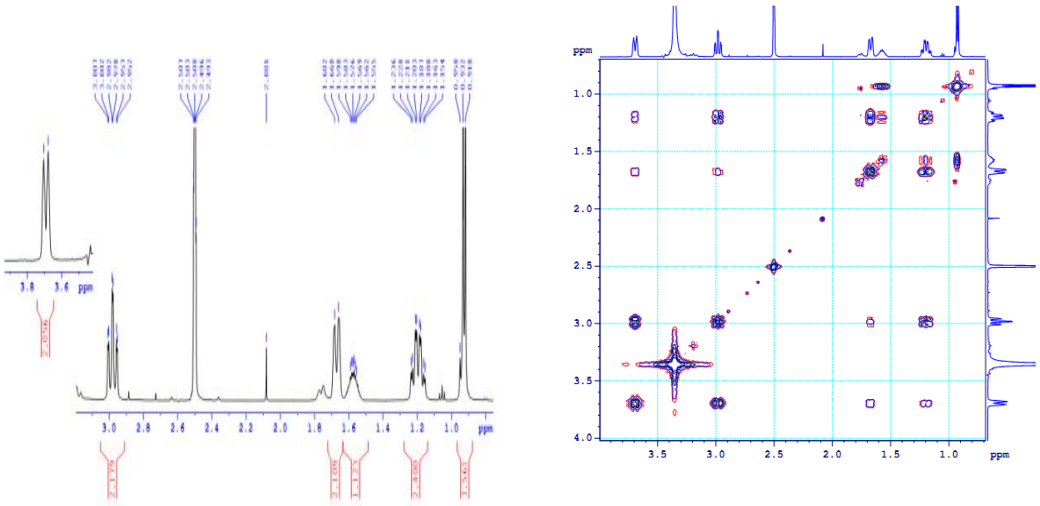


Fig 4. *^{1}H-NMR and COSY spectrums of L2*

4. Conclusion

Three substances such as 4-nitrobenzaldehyde-[N(4)-methyl, N(4)-phenyl thiosemicarbazone], Fluoren-9-one-[N(4)-(4-methylpiperidyl) thiosemicarbazone] and 4'-hydroxyacetophenone-[N(4)-(4-methylpiperidyl) thiosemicarbazone] were synthesized. Their colours, components and structures were determined due to the spectrums of UV, IR, MS, ^{1}H-NMR, COSY, ^{13}C-NMR, HSQC. In addition, the fixed conformation of 4-methylpiperidine was identified during the investigation of ^{1}H-NMR, COSY, HSQC. The structures of L2, L3 have not been reported by any scientific studies according to the results of SciFinder on December 19th 2014.

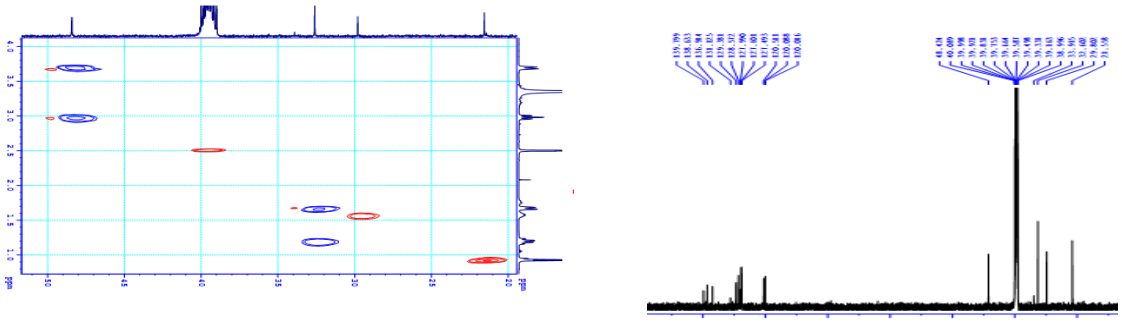


Fig 5. *^{13}C-NMR and HSQC spectrums of L2*

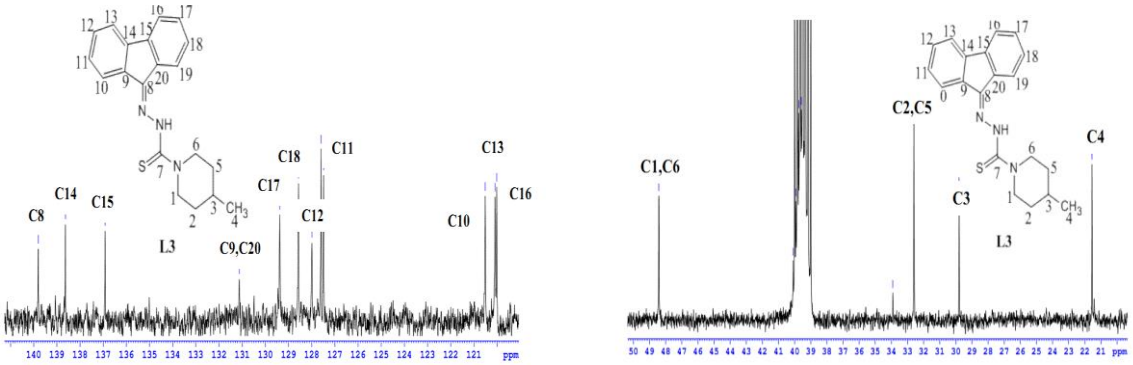


Fig 6. *Assigned signals in ^{13}C-NMR spectrums of L2*

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