

ANALYSIS OF NMR SPECTRA OF BENZALDEHYDE HEPTA-O-ACETYL- β -LACTOSYL

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TÓM TẮT

PHÂN TÍCH PHỎ NMR CỦA CÁC BENZALDEHYD HEPTA -O-ACETYL- β -LACTOSYL THIOSEMICARBAZON

Phỏ 1H và ^{13}C NMR của các benzaldehyd (peracetyl- β -lactosyl)thiosemicarbazone đã được thảo luận. Các tín hiệu cộng hưởng từ trong phỏ NMR của chúng chỉ ra mối quan hệ giữa cấu trúc và vị trí của nhóm thé theo tương quan Hammett. Cấu hình β của các thiosemicarbazone này được xác nhận dựa vào hằng số ghép cặp $J = 9.0\text{--}8.5$ Hz giữa proton NH-4 của liên kết thiosemicarbazone và proton H-1' trong hợp phần lactosyl.

INTRODUCTION

The synthetic method of hepta- O -acetyl- β -lactosyl-thiosemicarbazones has been reported previously using microwave-assisted method [1]. In previous articles we announced the synthesis and properties of another aldehyde/ketone glycosyl per- O -acetylated thiosemicarbazones [2]. There are several discussions herein about the influence of structural factors to the positions of resonance signals in their 1H and ^{13}C NMR spectra of hepta- O -acetyl- β -lactosyl)-thiosemicarbazones of

benzaldehydes and acetophenones.

EXPERIMENTAL PART

Substituted acetophenone hepta- O -acetyl- β -lactosyl thiosemicarbazones **1** (Scheme 1) were synthesized in bellow procedure [1]. Their 1H and ^{13}C NMR spectra was recorded on FT-NMR Avance AV500 Spectrometer (Bruker, Germany) at 500.13 MHz and 125.76 MHz, respectively, using DMSO- d_6 as solvent and TMS as an internal standard. Spectral data of 1H and ^{13}C NMR were summarized in Tables 1 and 2.

*General procedure for substituted benzaldehyde (hepta-O-acetyl- β -lactosyl)-thiosemicarbazones (**3LB a-v**).*

A mixture of hepta-O-acetyl- β -maltosyl thiosemicarbazide **1L** (1 mmol), benzaldehyde **2a-v** (1 mmol), glacial acetic acid (0.5 ml) in absolute ethanol (in the presence of glacial acetic acid as catalyst) or glacial acetic acid (20 ml) was heated at reflux using domestic microwave oven TIFANY 750W in 5-7 min. The solvent was evaporated to one half the original volumes. The resulting colorless crystals were filtered by suction. The crude product when recrystallized from 96% ethanol to afford the title compounds **3 LB a-v**.

RESULTS AND DISCUSSION

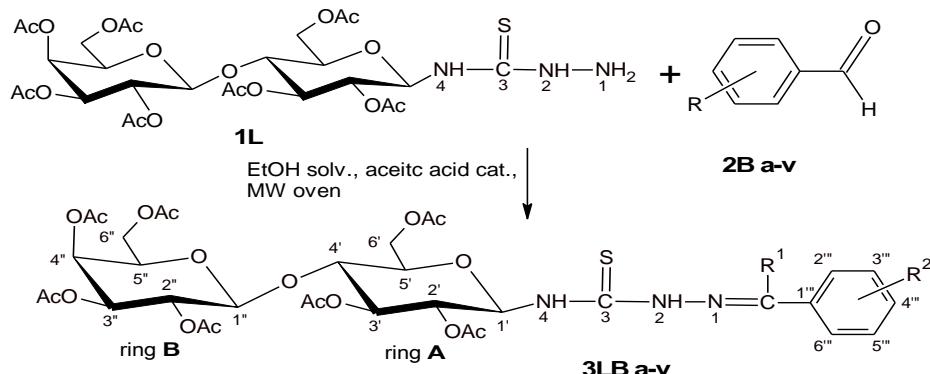
The selected ^1H and ^{13}C NMR spectral data of benzaldehyde hepta-O-acetyl- β -lactosyl thiosemicarbazones **3LB a-v** were listed in Table 1 and 2. From Tables 1 and 2 it's shown that protons and carbon-13 atoms in these molecules have proper resonance signals in corresponding spectral regions which are characteristic for each atom type.

Protons in NH-2 and NH-4 groups have signal at $\delta=12.18-11.67$ ppm (singlet) and $\delta=8.88-8.06$ ppm (doublet, $J=9.5-9.0$ Hz), respectively. Proton of azomethin group ($\text{CH}=\text{N}$) shows chemical shift at $\delta=8.53-8.00$ ppm (singlet). Aromatic protons have resonance signals in region at $\delta=8.33-$

6.27 ppm, and the multicity of these signals depend on substituted patterns in benzene rings. Protons in CH_3 group in acetate functions have signals in region at $\delta=2.06-1.92$ ppm. Protons of disaccharide component have signals including in range from 5.90 ppm to 3.93 ppm. Protons on C-1" and C-2" carbon in pyranose ring **A** magnetically interact each to other with coupling constant, in this case, $^3J=8.0-7.0$ Hz that indicated that these both protons on C-1" and C-2" positions have *trans*-type interaction. This one comfirm that linkage between two pyranose rings, glucopyranose and galactopyranose, in this disaccharide is β -(1 \rightarrow 4)-glycoside bond that completely agree with the structure of β -lactose. The distinct stucture pattern of galactopyranose ring, compared with the one of glucopyranose ring, is confirmed by coupling constant between H-4" and H-3" protons with $^3J=3.75-2.5$ Hz in galactopyranose ring, compared with the coupling constant $^3J=9.75-9.25$ Hz in glucopyranose ring. Protons on C-1' and C-2' carbon atoms in ring **B** have similar interaction with coupling constant $^3J=9.0-8.5$ Hz, in relation to H-H interaction of *trans* type, therefore, thiosemicarbazide linkage group is *equatorial* direction, i.e. all benzaldehyde hepta-O-acetyl- β -lactosyl thiosemicarbazones **3LB a-v** have β -anomeric configuration [4]. Other subrituents (hydroxy, methyl or methoxy)

also have specific signals. The ^{13}C -NMR spectra of compound **3LB a-v** showed the regions at δ 179.1–177.3 ppm ($\text{C}=\text{S}$), 170.2–169.0 ppm ($\text{C}=\text{O}$ ester), 144.1–138.9 ppm (azomethine $\text{CH}=\text{N}$), 146.4–

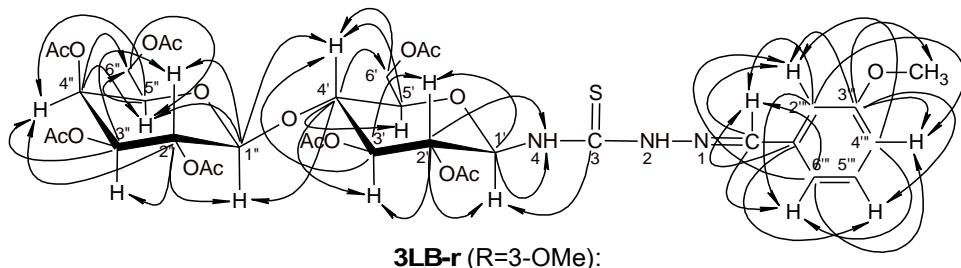
122.9 ppm (aromatic carbon atoms), 100.1–60.9 ppm (carbon atoms in lactose component), and 21.2–20.1 ppm (methyl carbon atoms in acetate groups). (Table 3).



where, $\text{R} = 4\text{-NO}_2$ (**3B-a**), 3-NO_2 (**3B-b**), 2-NO_2 (**3B-c**), 4-F (**3B-d**), $2,4\text{-diCl}$ (**3B-e**), 4-Cl (**3B-f**), 3-Cl (**3B-g**), 2-Cl (**3B-h**), 4-Br (**3B-i**), 2-OH-5-Br (**3B-j**), H (**3B-k**), 4-Me (**3B-l**), 4-iPr (**3B-m**), 4-OMe (**3B-n**), 3-OMe (**3B-o**), 2-OMe (**3B-p**), 4-OH (**3B-q**), 3-OH (**3B-r**), 2-OH (**3B-s**), 3-OMe-4-OH (**3B-t**), 3-OEt-4-OH (**3B-u**), 4-NMe_2 (**3B-v**).

Scheme 1. Synthesis of benzaldehyde (hepta-O-acetyl- β -lactosyl)thiosemicarbazones.

The $^1\text{H}-^{13}\text{C}$ long-ranged interaction in HMBC spectrum of thiosemicarbazone molecule **3LB-r** is shown in scheme below:



Homonuclear $^1\text{H}-^1\text{H}$ interactions in COSY spectrum in compound **3LB-r** are as follows: $\text{NH-2}(11.95)\leftrightarrow\text{H-1}'(5.79)\leftrightarrow\text{H-2}'(5.19)\leftrightarrow\text{H-3}'(5.31)\leftrightarrow\text{H-4}'(3.81)\leftrightarrow\text{H-5}'(3.88)\leftrightarrow\text{H-6}'\text{b}(4.07)\leftrightarrow\text{H-6}'\text{a}(4.30)$; $\text{H-1}''(4.79)\leftrightarrow\text{H-2}''(4.88)\leftrightarrow\text{H-3}''(5.15)\leftrightarrow\text{H-4}''(5.24)$; $\text{H-5}''(4.24)\leftrightarrow\text{H-6}''\text{a}(4.03)$ và $\text{H-6}''\text{b}(4.03)$; $\text{H-2}'''(7.44)\leftrightarrow\text{H-5}'''(7.34)$ và $\text{H-6}'''(7.31)$;

$\text{H-4}'''(7.00)\leftrightarrow\text{H-5}'''(7.34)$. The positions of resonance signals of protons NH-2 , NH-4 and $\text{CH}=\text{N}$ in compounds **3LB a-v** (Fig. 2 A, B and C) had linear regression expressions as follows, respectively:
 $\delta_{\text{NH-2}} = 0.298\sigma + 11.903 \quad (\text{R}^2 = 0.96)$
 $\delta_{\text{NH-4}} = 0.308\sigma + 8.621 \quad (\text{R}^2 = 0.93)$
 $\delta_{\text{CH=N}} = 0.145\sigma + 8.065 \quad (\text{R}^2 = 0.77)$

*Table 1. Selected 1H NMR spectra of substituted benzaldehyde (hepta-O-acetyl- β -lactosyl)thiosemicarbazones
[δ (ppm), multiplicity, J (Hz)]*

R	4-NO ₂	3-NO ₂	4-F	4-Cl	3-Cl	4-Br	H
Proton	3LB-a	3LB-b	3LB-d	3LB-f	3LB-g	3LB-i	3LB-k
NH-2	12.16,s	12.10,s	11.90,s	11.95,s	11.99,s	12.00,s	11.95,s
NH-4	8.88,d,9.0	8.83,d,9.0	8.66,d,9.0	8.70,d,9.0	8.75,d,9.0	8.70,d,9.0	8.67,d,9.5
CH=N	8.18,s	8.21,s	8.09,s	8.08,s	8.08,s	8.08,s	8.10,s
H-2”	8.10,d,9.0	8.58,s	7.88,d,5.5,8.5	7.85,d,8.5	7.98,s	7.82,d,8.5	7.82–7.80,m
H-3”	8.25,d,9.0	–	8.10,d,8.5	7.49,d,8.5	–	7.66,d,8.5	7.45–7.43,m
H-4”	–	8.30,d,7.5	–	–	7.48–7.44,m	–	7.45–7.43,m
H-5”	8.25,d,9.0	7.72,t,8.0	8.10,d,8.5	7.49,d,8.5	7.48–7.44,m	7.66,d,8.5	7.45–7.43,m
H-6”	8.10,d,9.0	8.24,dd,1.5,8.0	7.88,d,5.5,8.5	7.85,d,8.5	7.70,dd,7.0,1.5	7.82,d,8.5	7.82–7.80,m
H-1'	5.88,t,9.0	5.86,t,9.0	5.85,t,9.25	5.85,t,9.0	5.85,t,9.0	5.90,t,9.0	5.86,t,9.25
H-2'	5.24–5.21,m	5.20,t,9.5	5.19, ¹ H,9.25	5.20,t,9.25	5.21,t,9.25	5.24,t,9.25	5.19,t,9.5
H-3'	5.31,t,9.25	5.31,t,9.0	5.30,d,9.25	5.30,t,9.25	5.30,t,9.0	5.33,t,9.25	5.31,t,9.25
H-4'	3.81,t,9.25	3.82,t,9.25	3.81,t,9.5	3.80,t,9.5	3.81,t,9.5	3.84,t,9.75	3.80,t,9.5
H-5'	3.90–3.87,m	3.91–3.84,m	3.90–3.87,m	3.90–3.88,m	3.89,ddd, 1.5,5.5,10.0	3.84,t,9.75	3.89,ddd, 1.75,5.75,9.75
H-6'a	4.31,d,11.5	4.31,d,11.0	4.31,d,11.5	4.30,d,11.5	4.31,d,11.0	4.33,d,11.0	4.30,d,11.0
H-6'b	4.07,dd,5.5,12.5	4.08,dd,5.5,12.0	4.07,dd,5.5,11.0	4.08–4.05,m	4.07,5.75,12.25	4.09,dd,5.5,12.0	4.07,dd,5.5,12.0
H-1”	4.80,d,8.0	4.80,d,8.0	4.80,d,8.0	4.80,d,7.5	4.80,d,8.0	4.83,d,8.0	4.80,d,8.0
H-2”	4.88,t,8.75	4.88,dd,8.25,10.25	4.88,dd,3.25,10.5	4.88,t,9.0	4.88,dd,2.0,8.0	4.91,dd,3.0,11.5	4.87,dd,3.0,10.0
H-3”	5.15,dd,3.5,10.0	5.15,dd,3.5,10.0	5.17,dd,3.75,9.75	5.16,dd,3.5,10.0	5.16,dd,3.5,10.0	5.16,dd,3.75,10.25	5.15,dd,3.5,10.5
H-4”	5.24–5.21,m	5.24,d,3.5	5.24,d,3.5	5.24,d,3.5	5.24,d,3.5	5.28,d,3.5	5.24,d,3.5
H-5”	4.25,t,6.5	4.25,t,6.75	4.25,t,6.5	4.25,t,6.0	4.25,t,6.75	4.29,t,6.5	4.26,t,6.75
H-6”a	4.03,d,6.0	4.03,dd,2.25,6.75	4.04–4.02,m	4.04–4.03,m	4.04–4.00,m	4.07–4.05,m	4.04,dd,2.25,6.25
H-6”b	4.03,d,6.0	4.03,dd,2.25,6.75	4.04–4.02,m	4.04–4.03,m	4.04–4.00,m	3.94–3.91,m	4.04,dd,2.25,6.25
COCH₃	2.11–2.01	2.11–1.91	2.11–2.01	2.11–1.91	2.11–1.90	2.15–1.94	2.11–1.90

*Table 1(continuing). Selected ^1H NMR spectra of substituted benzaldehyde (hepta-O-acetyl- β -lactosyl)thiosemicarbazones
[δ (ppm), multiplicity, J (Hz)]*

R	4-Me	4-iPr	4-OMe	3-OMe	4-OH	4-NMe ₂
Proton	3LB-l	3LB-m	3LB-n	3LB-o	3LB-q	3LB-v
NH-2	11.86,s	11.87,s	11.81,s	11.95,s	11.76,s	11.67,s
NH-4	8.59,d,9.5	8.57,d,9.0	8.55,d,9.0	8.62,d,9.0	8.51,d,9.5	8.41,d,9.5
CH=N	8.06,s	8.09,s	8.05,s	8.07,s	8.00,s	7.97,s
H-2”	7.69,d,8.5	7.72,d,8.0	7.75,d,8.5	7.44,s	6.81,d,8.5	7.59,d,8.5
H-3”	7.25,d,8.5	7.30,d,8.0	6.99,d,8.5	—	7.64,d,8.5	6.72,d,8.5
H-4”	—	—	—	7.00,dd,1.5,8.0	—	—
H-5”	7.25,d,8.5	7.30,d,8.5	6.99,d,8.5	7.34,t,8.0	7.64,d,8.5	6.72,d,8.5
H-6”	7.69,d,8.5	7.72,d,8.0	7.75,d,8.5	7.31,t,8.0	6.81,d,8.5	7.59,d,8.5
H-1'	5.84,t,9.0	5.83,t,9.25	5.83,t,9.25	5.79,t,9.0	5.83,t,9.25	5.82,t,9.0
H-2'	5.21,t,9.25	5.18,t,9.5	5.18,t,9.25	5.18,t,9.25	5.18,t,9.25	5.17–5.14,m
H-3'	5.30,t,9.25	5.30,t,9.25	5.30,t,9.0	5.31,t,9.25	5.30,t,9.25	5.30,t,9.0
H-4'	3.81,t,9.5	3.81,t,9.25	3.82–3.79,m	3.81,t,9.0	3.89–3.86,m	3.81,t,9.25
H-5'	3.90–3.87,m	3.88–3.87,m	3.89–3.87,m	3.88,ddd,3.5,5.5, 10.0	3.80,t,9.75	3.88–3.85,m
H-6'a	4.30,d,11.0	4.30,d,11.5	4.30,d,11.5	4.30,d,11.0	4.30,d,11.0	4.30,d,11.0
H-6'b	4.07,dd,5.75,12.25	4.09–4.03,m	4.09–4.05,m	4.07,dd,12.5,6.75	4.06,dd,5.5,9.5	4.09–4.05,m
H-1”	4.80,d,8.0	4.80,d,8.0	4.80,d,7.5	4.79,d,7.5	4.80,d,8.0	4.79,d,7.5
H-2”	4.88,t,9.0	4.88,t,9.75	4.88,t,9.25	4.88,dd,10.0,3.0	4.87,dd,10.0,3.0	4.88,t,9.0
H-3”	5.15,dd,3.75,10.25	5.15,dd,10.5,3.75	5.15,dd,10.0,3.0	5.15,dd,10.5,3.5	5.16,dd,10.0,4.0	5.17–5.14,m,
H-4”	5.24,d,3.5	5.24,d,3.5	5.24,d,3.0	5.24,d,3.5	5.24,d,3.5	5.25,d,2.5
H-5”	4.25,t,6.5	4.25,t,5.75	4.24,t,6.75	4.24,t,6.75	4.25,t,6.75	4.25,t,6.0
H-6”a	4.04–4.03,m	4.09–4.03,m	4.04–4.03,m	4.03,d,6.5	4.03–4.02,m	4.04–4.03,m
H-6”b	4.04–4.03,m	4.09–4.03,m	4.04–4.03,m	4.03,d,6.5	4.03–4.02,m	4.04–4.03,m
COCH₃	2.11–1.90	2.11–1.90	2.11–1.91	2.11–2.01	2.11–1.90	2.11–1.91
Other protons	2.34,s,4”-Me	2.92,q,7.0,4”-CH(CH ₃) ₂ ; 1.21,d,7.0,4”-CH(CH ₃) ₂	3.81,s,4”-OMe	3.83,s,3”-OMe	9.97,s,4”-OH	2.97,s,6H,4”-N(Me) ₂

Table 2. Selected ^{13}C NMR spectra of substituted benzaldehyde (hepta-O-acetyl- β -lactosyl)thiosemicarbazones, δ (ppm)

R	4-NO ₂	3-NO ₂	4-F	4-Cl	3-Cl	4-Br	H	4-Me	4-iPr	4-OMe	3-OMe	4-OH	4-NMe ₂
Cacbon	3LB-a	3LB-b	3LB-d	3LB-f	3LB-g	3LB-i	3LB-k	3LB-l	3LB-m	3LB-n	3LB-o	3LB-q	3LB-v
C=S	178.8	178.7	178.4	178.3	178.6	178.4	178.3	178.2	178.2	177.8	178.4	177.7	177.3
COCH ₃	170.2–	170.2–	170.2–	170.5–	170.1–	170.2–	170.3–	170.2–	170.2–	170.5–	170.2–	170.2–	170.2–
	169.0	69.1	169.1	169.4	169.0	169.0	169.1	169.0	169.0	169.4	169.0	169.0	169.0
CH=N	141.1	141.6	142.6	142.7	142.2	142.5	143.7	143.9	143.8	144.1	143.5	144.1	144.8
C-1”	140.2	135.7	130.4	132.5	135.9	133.0	133.7	131.0	131.4	126.0	135.1	124.6	120.8
C-2”	128.4	121.9	129.7	129.8	126.3	129.4	128.7	127.5	127.6	129.2	111.4	129.4	128.9
C-3”	123.8	148.4	115.7	128.8	133.7	131.7	127.6	129.3	126.6	114.2	159.6	115.6	111.6
C-4”	147.8	124.4	163.3	134.9	130.5	123.5	130.3	140.2	150.9	161.1	116.5	159.6	151.7
C-5”	123.8	130.2	115.7	128.8	129.8	131.7	127.6	129.3	126.6	114.2	129.6	115.6	111.6
C-6”	128.4	133.4	129.7	129.8	126.7	129.4	128.7	127.5	127.6	129.2	120.7	129.4	128.9
C-1'	81.3	81.3	81.3	81.2	81.3	81.2	81.2	81.2	81.1	81.1	81.2	81.1	81.1
C-2'	71.2	71.1	71.1	70.9	71.1	71.1	71.1	71.1	71.0	70.9	70.9	71.1	71.0
C-3'	72.8	72.7	72.7	72.6	72.7	72.7	72.7	72.7	72.7	72.6	72.5	72.7	72.7
C-4'	76.0	76.0	76.0	75.9	76.0	76.0	76.1	76.0	76.0	75.9	76.1	76.1	76.1
C-5'	73.4	73.5	73.4	73.5	73.4	73.4	73.3	73.4	73.4	73.5	73.4	73.3	73.4
C-6'	62.4	62.4	62.4	62.2	62.3	62.4	62.4	62.3	62.3	62.2	62.3	62.3	62.3
C-1”	99.6	99.6	99.6	99.6	99.6	99.6	99.6	99.6	99.6	99.6	99.6	99.6	99.6
C-2”	68.9	68.9	68.9	68.8	68.9	68.8	68.8	68.9	68.8	68.8	68.8	68.8	68.9
C-3”	70.4	70.4	70.4	70.3	70.4	70.4	70.4	70.4	70.3	70.3	70.4	70.3	70.4
C-4”	67.1	67.1	67.1	67.0	67.1	67.1	67.1	67.1	67.1	67.1	67.1	67.1	67.1
C-5”	69.7	69.8	69.8	69.7	69.7	69.7	69.7	69.7	69.7	69.7	69.7	69.7	69.7
C-6”	61.0	61.0	61.0	60.9	61.0	60.9	61.0	60.9	60.9	60.9	60.9	60.9	60.9
COCH ₃	20.7–	20.7–	20.7–	20.5–	20.8–	20.7–	20.7–	20.6–	20.6–	20.5–	20.6–	20.7–	20.6–
	20.3	20.3	20.2	20.1	20.2	20.4	20.3	20.2	20.2	20.1	20.2	20.3	20.2

Note: Other $\delta(^{13}\text{C})$: 21.0, 4”-Me (**3LB-l**); 33.4, 5, 4”-CH(Me)₂; 23.5, 4”-CH(Me)₂ (**3LB-m**);

55.2, 4”-OCH₃ (**3LB-n**); 55.2, 3”-OCH₃ (**3LB-o**); 40.0, 4”-N(Me)₂ (**3LB-v**).

Conversely, carbon atom in imine group were affected clearly by these substituents with opposite trend: the donating ones (with $\sigma < 0$, such as 4-OH, 4-OMe, 4-Me on benzene ring of benzaldehyde) caused signal to be shifted to upfield region, and the withdrawing ones (with $\sigma < 0$, such as 3-NO₂-4-Cl, 4-

NO₂, 3-NO₂-4-Me, 3-NO₂-4-OMe, 4-Cl, 4-Br in benzaldehyde series) caused the resonance of this carbon atom to be in downfield region (Table 3). These tendencies could be shown in equations as follows (Fig. 2D).

$$\delta_{CH=N} = -2.458\sigma + 143.31 \quad (R^2 = 0.91)$$

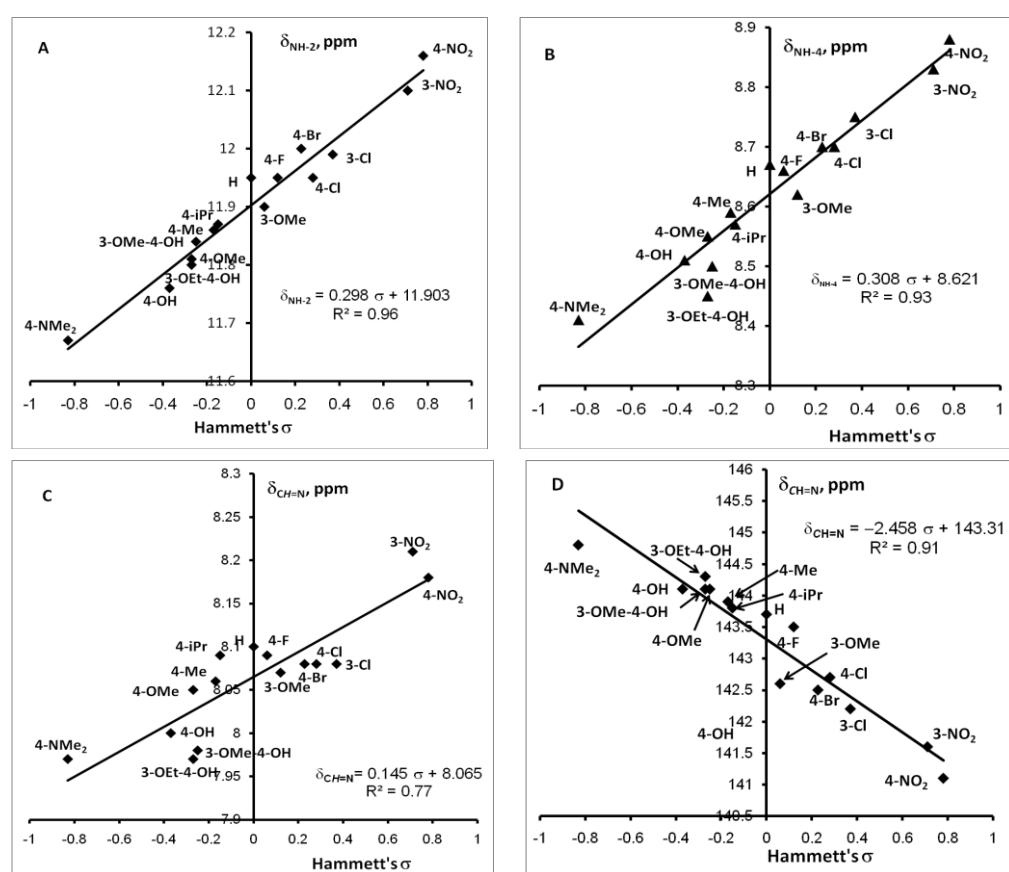


Figure 2. Linear relationships between δ_{NH-2} (A), δ_{NH-4} (B), $\delta_{CH=N}$ (C) v& $\delta_{C=N}$ (D) and Hammett's σ in compounds 3LBa-v

CONCLUSIONS

The ¹H and ¹³C NMR spectra of substituted benzaldehyde peracetylated β -lactosyl)thiosemicarbazones have been studied and discussed. The magnetic

signals in their NMR spectra show the relationships between the structural features and positions of the substituted groups in benzene ring.

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