Synthesis of glycosyl diethylamino and piperidyl-carbodithiolates

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Abstract:

Reaction of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl chloride (5) and 4-O-(2,3,4,6-tetra-O-acetyl-β –D-galactopyranosyl)-D-2,3,4,6-tetra-O-acetyl-α-1-bromo-D-glucopyranoside (8) with sodium diethylaminocarbodithiolate (3) or sodium piperidylcarbodithiolate (4) gave the corresponding glycosylcarbodithiolates, 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl 1-diethylaminocarbodithiolate (6), 2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl 1-piperidylcarbodithiolate, (7), 4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2,3,6-tri-O-acetyl-β-D-glucopyranosyl 1-diethylaminocarbodithiolate (9) and 4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl) 2,3,6-tri-O-acetyl-β-D-glucopyranosyl 1- piperridylcarbodithiolate (10) in good yield. The structures were confirmed by using elemental analysis, IR, ^{1}H, ^{13}C, and 2D NMR spectra.

Keywords: glycosylcarbodithiolates; thioglycosides; carbodithiolates; NMR spectra.

INTRODUCTION

Carbodithiolates have been studied extensively over last decades in a response to their growing applications in much new area of chemistry, industry or biology [1–4]. The most challenging property of carbodithiolates is their strong metal-binding ability and the ease with which these complexes undergo sequential one-electron transfer reactions. Consequently, a number of chemical, electrochemical, physical, and spectroscopic characteristics of carbodithiolate ligands themselves as well as the metal complexes have been examined. Carbodithiolate complexes containing variously substituted carbodithiolate groups have been investigated extensively from several aspects and to explain the role of these compounds in vulcanization, high pressure lubricant agents, fungicides and pesticides [5-6]. Carbodithiolate are considerable group of chemotherapeutic agent development field [7]. Increasing number of studies has been published on carbodithiolate and their anticancer activity since the brassinin, first isolated from cabbage and reported as antineoplastic compound, and its structural analog sulforamate was discovered [8].

The glycosyl carbodithiolates have been considered as valuable glycosyl donors [9]. Continuing our work on thioglycosides and glycosyl donors[10], we have synthesized new carbodithiolates possessing of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl and 4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2,3,6-tri-O-acetyl-β-D-glucopyranosyl, which can be used as a glycosyl donors.

EXPERIMENTAL

General

Melting points were measured on a Mel-Temp apparatus and are uncorrected. IR spectra were recorded for the compounds in a KBr matrix with a Unicam SP 1025 spectrophotometer. NMR spectra were measured with

Bruker Advance spectrometer (300 MHz) using TMS (0.00 ppm) or the signal of the deuterated solvent as internal standard. Chemical shifts (δ) are given in ppm relative to the signal for TMS as internal standard, and coupling constants in Hz. The assignments of ^{1}H NMR spectra were based on chemical-shift correlation DQFCOSY spectra, while the assignment of ^{13}C NMR spectra were based on heteronuclear multiple quantum coherence HMQC experiments. Elemental analyses were performed in the Microanalysis Unit at the Faculty of Science, University of Cairo, Egypt.

Synthesis of glycosyl diethylamino carbodithiolate derivatives 6 and 9 (General procedure).

Sodium diethylamino carbodithiolate (1 mmol) was dissolved in DMF (2 ml) at 0 °C, then carbon disulfide (0.12 mmole) was added dropwise, and was stirred 30 min. A solution of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl chloride or 4-O-(2,3,4,6-tetra-O-acetyl-β–D-galactopyranosyl)-D-2,3,4,6-tetra-O-acetyl-α-1-bromo-D-glucopyranoside (1 mmole) in DMF (1 ml) was then added drop wise during 10 min. The mixture was allowed to warm up to room temperature, and stirring was continued for 4-12 h. The mixture was poured onto ice, and the solid was collected.

2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl 1-diethylaminocarbodithiolate (6)

It was obtained in 80 % yield; mp 134-136 °C, IR (KBr), ν cm^{-1}: 3375 (NH), 1740 (OAc), 1660 (NCO), ^{1}H NMR (300 MHz, $CDCl_3$): 1.28 (t, 6 H, CH_3), 1.92 (s, 3H, NAc), 2.04, 2.05, 2.15 (3 s, 9 H, 3×AcO), 3.36 (m, 1 H, H-5'), 3.68, 3.81 (2 dd, 4 H, CH_2), 4.18 (dd, 1 H, $J_{6',6''}$ = 12.2 Hz, $J_{6',5'}$ = 2.1 Hz, H-6'), 4.30 (m, 1 H, H-6''), 4.61 (m, 1 H, H-2'), 5.32 (m, 2 H, H-3', H-4'), 5.91 (d, 1 H, $J_{1',2'}$ = 10.1 Hz, H-1'), 6.21 (d, 1 H, NH). ^{13}C NMR (75 MHz, $CDCL_3$) 11.78, 13.07 (CH_3), 20.95, 21.04 (CH_3CO), 22.11 (NHCO), 47.43, 50.34 (CH_2), 65.32 (C-2'), 61.59 (C-6'), 74.66 (C-4'), 72.67 (C-3'), 75.33 (C-5'), 88.19 (C-1'), 167.83, 167.90, 168.27, 168.71 (3×CH_3CO, NHCO), 188.93 (C=S).

Anal. Calc. ($C_{19}H_{30}N_2O_8S_2$) for CHN: C, 47.68; H, 6.32, N, 5.85. Found: C, 47.12; H, 6.09; N, 5.54.

4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2,3,6-tri-O-acetyl-β-D-glucopyranosyl 1- diethylaminocarbodithiolate (9)

white crystal in 72% yield; m.p 124-126 °C, IR (KBr), ע Cm^{-1}: 3376 (NH), 1752 (OAc), 1664 (NCO), ^{1}H NMR (300 MHz, $CDCl_3$) 1.25 (t, 6 H, CH_3), 1.95 (s, 3 H, NAc), 2.01, 2.03, 2.05, 2.06, 2.09, 2.14 (7 s, 21 H, 7×AcO), 3.58, 3.74 (2 dd, 4 H, CH_2), 3.91 (m, 3 H, H-4'a, H-5'a, H-5'b), 4.16 (m, 3 H, H-6'b, H-6',6''a), 4.44 (d, 1 H, $J_{1'b,2'b}$ = 10.2 Hz, H-1'b), 4.46 (m, 1 H, H-6''b), 4.96 (dd, 1 H, $J_{3'b,4'b}$ = 3.4 Hz, $J_{3'b,2'b}$ = 9.9 Hz, H-3'b), 5.16 (dd, 1 H, $J_{2'b,3'b}$ = 9.9 Hz, $J_{2'b,1'b}$ = 10.2 Hz, H-2'b), 5.20 (dd, 1 H, $J_{2'a,1'a}$ = 10.1 Hz, $J_{2'a,3'a}$ = 9.3 Hz, H-2'a), 5.30 (dd, 1 H, $J_{3'a,2'a}$ = 9.3 Hz, $J_{3'a,4'a}$ = 9 Hz, H-3'a), 5.34 (dd, 1 H, $J_{4'b,5'b}$ = 7.9 Hz, $J_{4'b,3'b}$ = 3.4 Hz, H-4'b), 5.79 (d, 1 H, $J_{1'a,2'a}$ = 10.1 Hz, H-1'a). ^{13}C NMR ($CDCl_3$, 75 MHz) 12.21, 12.90 (CH_3), 20.9, 21.0, 21.16, 21.35 (7× CH_3CO), 45.91, 49.42 (CH_2), 61.33 (C-6'b), 62.54 (C-6'a), 67.05 (C-3'a), 69.26 (C-2'a), 69.34 (C-2'b), 71.15 (C-4'b), 71.42 (C-4'a), 74.49 (C-3'b), 76.39 (C-5'b), 87.24 (C-1'b), 101.2 (C-1'a), 169.45, 169.98, 170.4, 170.56 (CH_3*CO*), 190.9 (C=S).

Anal. Calc. ($C_{31}H_{45}NO_{17}S_2$) for CHN: C, 48.49; H, 5.91, N, 1.82. Found: C, 48.54; H, 5.54; N, 1.96.

Synthesis of piperidyl carbodithiolate derivatives 7 and 10 (General procedure).

Piperidine (1mmole) was added to a stirred suspension of NaH (0.024 g, 1 mmol) in DMF (2 ml) at 0°C. After 10 minutes carbon disulfide (0.12 mmol) was added dropwise, and stirring was continued for 30 min. A solution of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl chloride or 4-O-(2,3,4,6-tetra-O-acetyl-β–D-galactopyranosyl)-D-2,3,4,6-tetra-O-acetyl-α-1-bromo-D-glucopyranoside (1 mmole) in 1 ml DMF was then added drop wise during 10 min, the mixture was allowed to warm up to room temperature, stirring was continued for 4-12 h, and the mixture was poured onto ice, the solid was collected.

2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl 1-piperidylcarbodithiolate (7)

The product was recystalized from ethanol/water to give **5** in 83% yield; mp 164-166 °C. IR (KBr), ע Cm^{-1}: 3370 (NH), 1745 (OAc), 1665 (NAc), ^{1}H NMR (300 MHz, $CDCl_3$) 1.69 (m, 6 H, CH_{2pip}), 1.91 (s, 3H, NAc), 2.03, 2.04, 2.06 (3 s, 9 H, 3×AcO), 3.85 (m, 3 H, NCH_{2pip}, H-5'), 4.13 (dd, 1 H, $J_{6',6''}$ = 12.4 Hz, $J_{6',5'}$ = 2.1 Hz, H-6'), 4.27 (m, 3 H, CH_{2pip}, H-6''), 4.56 (m, 1 H, H-2'), 5.21 (m, 2 H, H-3', H-4'), 5.88 (d, 1 H, $J_{1',2'}$ = 10.0 Hz, H-1'), 6.10 (d, 1 H, NH). 13C NMR (75 MHz, $CDCL_3$) 21.03, 21.09, 21.2 (CH_3CO), 23.6 (NHCO), 24.49, 25.78, 26.48 (CH_{2pip}), 52.36 (C-2'), 52.57, 53.88 (NCH_{2pip}), 62.29 (C-6'), 67.50 (C-4'), 74.02 (C-3'), 76.90 (C-5'), 89.12 (C-1'), 169.61, 170.5, 171.10, 171.5 (3×CH_3CO, NHCO), 191.24 (C=S).

Anal. Calc. ($C_{20}H_{30}N_2O_8S_2$) for CHN: C, 48.96; H, 6.16, N, 5.71. Found: C, 49.26; H, 6.41; N, 5.97.

4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl) 2,3,6-tri-O-acetyl-β-D-glucopyranosyl 1- piperidylcarbodithiolate (10)

The product recrystalized from ethanol gave **10** white crystal in 67% yield; mp 146-148 °C, IR (KBr), ע Cm^{-1}: 3373 (NH), 1756 (OAc), 1666 (NAc), ^{1}H NMR (300 MHz, $CDCl_3$) 1.70 (m, 6 H, CH_{2pip}), 1.96, 199, 2.04, 2.06, 2.07, 2.11, 2.18 (7 s, 21 H, 7×AcO), 3.87 (m, 5 H, CH_{2pip}, H-5'b, H-5'a, H-4'a), 4.14 (m, 3 H, H-6'b, H-6',6''a), 4.47 (d, 1 H, $J_{1'b,2'b}$ = 10.0 Hz, H-1'b), 4.96 (dd, 1 H, $J_{3'b,4'b}$ = 3.6 Hz, $J_{3'b,2'b}$ = 9.95 Hz, H-3'b), 5.12 (dd, 1 H, $J_{2'b,3'b}$ = 9.95 Hz, $J_{2'b,1'b}$ = 10.0 Hz, H-2'b), 5.24 (dd, 1 H, $J_{2'a,1'a}$ = 10.3 Hz, $J_{2'a,3'a}$ = 9.23 Hz, H-2'a), 5.33 (dd, 1 H,

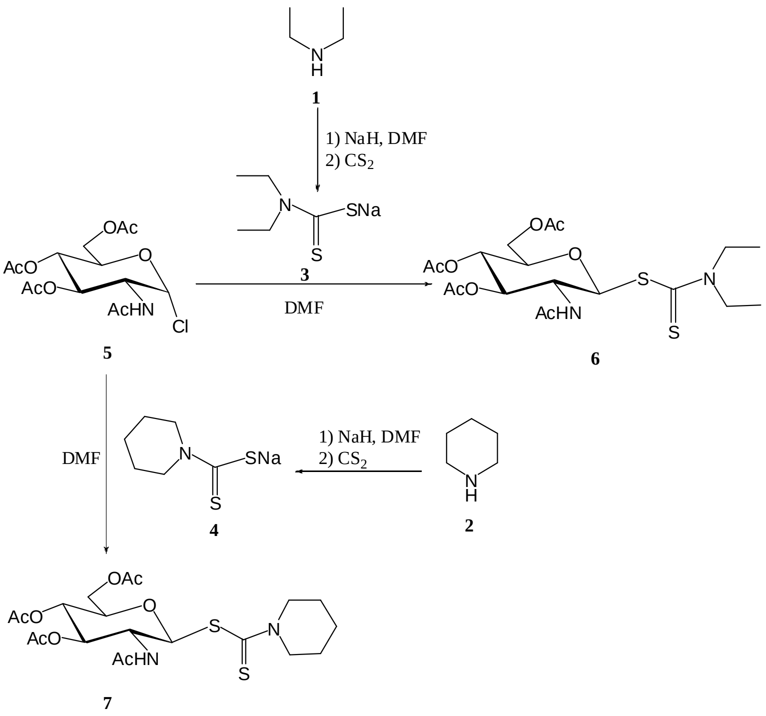
$J_{3'a,2'a}$ = 9.23 Hz, $J_{3'a,4'a}$ = 9 Hz, H-3'a), 5.36 (dd, 1 H, $J_{4'b,5'b}$ = 8.7 Hz, $J_{4'b,3'b}$ = 3.4 Hz, H-4'b), 5.86 (d, 1 H, $J_{1'a,2'a}$ = 10.3 Hz, H-1'a). ^{13}C NMR ($CDCl_3$, 75 MHz) 20.9, 21.0, 21.16, 21.35 (7× CH_3CO), 24.52, 25.65, 26.42 (CH_2pip), 52.14, 53.63, (NCH_2pip), 61.33 (C-6'b), 62.54 (C-6'a), 67.05 (C-3'a), 69.26 (C-2'a), 69.34 (C-2'b), 71.15 (C-4'b), 71.42 (C-4'a), 74.49 (C-3'b), 76.39 (C-5'b), 87.26 (C-1'b), 101.2 (C-1'a), 169.45, 169.98, 170.4, 170.56 (CH_3*CO*), 190.9 (C=S).

Anal. Calc. ($C_{32}H_{45}NO_{17}S_2$) for CHN: C, 49.29; H, 5.82, N, 1.80. Found: C, 49.34; H, 5.56; N, 1.71.

RESULTS AND DISCUSSION

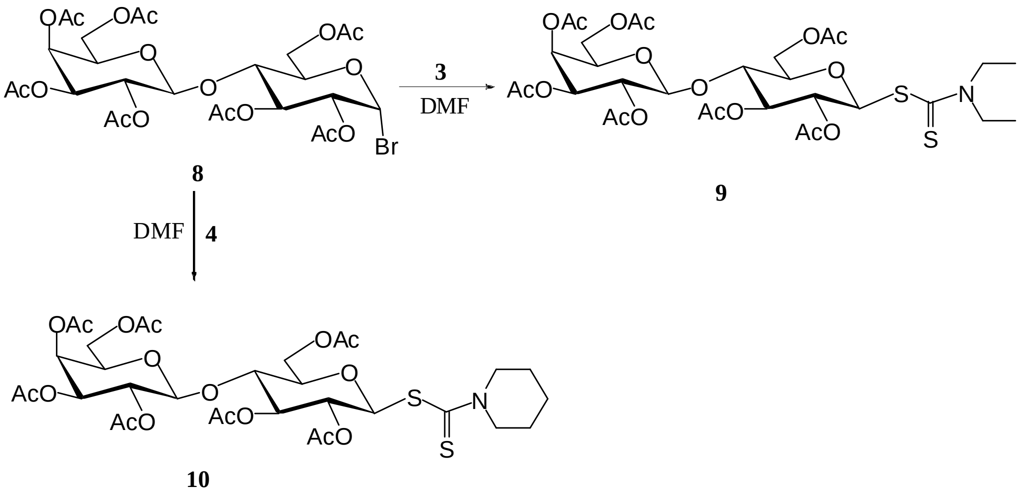
The β-S-glycosyl 1-piperdylcarbodithiolates have been prepared from the reaction of piperdylcarbodithiolate salt with 2,3,4,6-tetra-O-acetyl-α-D-glycopyranosyl bromide[9].

In the present work, the acetamido-glucopyranosyl carbodithiolate and lactose carbodithiolates have been synthesized. Thus, carbodithiolate of N-acetylglucosamine **6** and **7** were prepared when the diethyl amine **1** or piperdine **2** were treated with sodium hydride in dry DMF, then treated with carbon disulfide, the resulting salts **3** or **4** were treated with 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl chloride (**5**) in situ in DMF under stirring for 6 hr in 78-80% yield, Scheme1.



Scheme1

Similarly, the reaction extended to the disaccharide, whereby the carbodithiolate derivatives **9** and **10** were synthesized from the acylated lactose bromide **8** by reaction with carbodithiolate salts **3** and **4**, under stirring for 12 hr in 67-72% yield, Scheme 2.



Scheme2

The structures of the products were confirmed by their spectral data. The ^{1}H NMR spectra of **7** and **10** showed characteristic signals corresponding to piperidyl moieties, assigned as multiblet at δH 1.69 and 3.84.

The β- anomeric configuration in the products has been readily deduced from their ^{1}H NMR spectra, H-1` appeared as a doublet with $J_{1`,2`}$ 10.0 Hz at δH 5.88 and C-1' appeared at δC 87.26 in compound **7** as example.

Moreover, the 2 D NMR spectra (^{1}H-^{1}H DQFCosy and ^{1}H-^{13}C HMQC); facilitated the spectra assignment of the sugar moieties of compound **10**. Thus, the anomeric proton H-1'a was resonated as doublet at δH 5.86 which correlated with the multiblet of H-2'at δH 5.25 whereas their respective the carbon were assigned at δC 89.12 and 69.80. Both of H-3'a and H-4'a were assigned as multiblet at δH 4.95 and 5.11 which were correlated with their carbons at δC 74.02 and 67.50, respectively.

At the lower frequency region H-5'a and $CH_{2(pip)}$ resonated at δH 3.84 as multiblet, H-5'a correlated with H-6'a and H-6''a at δH 4.13 and 4.27 respectively, assigned as doublet of doublet. Their respective carbons resonated at δC 76.9 and 62.3. The 2D ^{1}H-^{1}H DQFCosy spectrum of **7** is shown in Fig. 1.

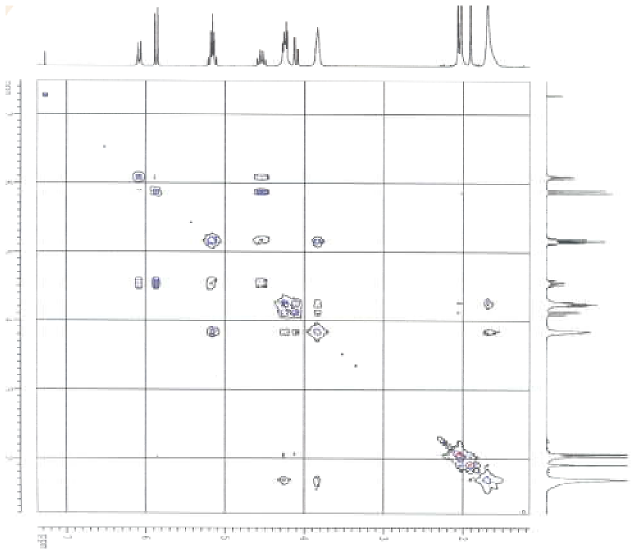


Fig. 1. 300 MHZ 2D ^{1}H-^{1}H DQFCosy spectra of 7

The lactose moiety have two anomeric protons, H-1'b and H-1'a appeared as a doublet with $J_{1b',2b'}$ = 10.0 Hz and $J_{1a',2a'}$ = 10.3 Hz respectively, and the S-glycosidic anomeric carbon C-1'b appeared at δC 87.2 compared to the O-glycosidic anomeric carbon that resonated at higher frequency at δC 101.2 as a result of the deshielding effect of oxygen. Moreover, the DEPT-135° experiment showed the presence of six negative signal corresponding to five (CH_2) group of piperidyl moiety and (CH_2) of C-6' of glucosamine, whereas for lactose derivatives showed the presence of seven negative signals corresponding to five (CH_2) for piperidyl molecule, C-6'a and C-6'b. The DEPT-135 spectrum of **10** is shown in Fig. 2.

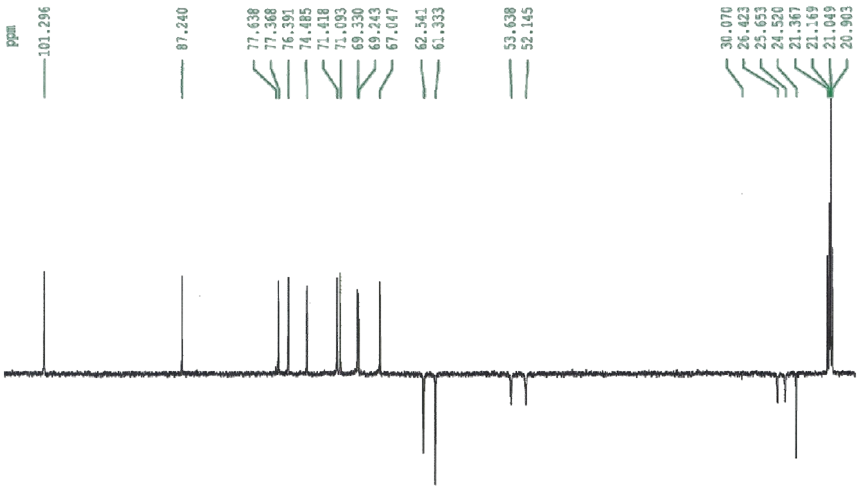


Fig. 2. 300 MHZ DEPT-135 spectra of 10

REFERENCES

[1] Thorn, G. D.; Ludwig, R. A., "The Dithiocarbamates and Related Compounds", Elsevier, Amsterdam, **1962**.

[2] Bond, A. M.; Martin, R.L., *Coord. Chem. Rev.* 1984, 54, 23-98.

[3] Sevilla, M. T.; Procopio, J. R.; Pinilla, J. M.; Hernandez, L., *Electroanalysis,*
1990, 2, 475-479.

[4] Lieder, M., *Electrochimica Acta*, **2004**, 49, 1813-1822.

[5] Deyanira, F. A.; Rubén-Alfredo, T.; Miguel, M. H.; Marcela, L. C.; Patricia, G. G.; Raymundo, C. O., J Organomet. Chem. **2008**, 693, 3166–3170; **Bulman, R. A., Struct. Bond. Berl.** 1987**, 67, 130-.**

[6] Ali, B. F.; Al-Akramawi, W. S.; Al-Obaidi, K. H.; Al-Karboli, A. H., Thermochim. Acta **2004**, 419, 39–43; Lippard, S. J., *Pure Appl. Chem.* **1987**, 59, 739-.; Barone, G.; Chaplin, T.; Hibbert,T. G.; Kana,A. T.; Mahon,M. F.; Molloy, K. C.; Worsley, I. D.; Parkin, I. P.; Price, L. S., *J. Chem. Soc., Dalton Trans.* **2002**, 1085-1093; Komulanien, H.; Saroleine, K., *Arch.*

Toxicol. **1985**, 8, 77-.; Deyanira F.; Toscano, R.; Hernández, M. M.; Cardoso, M. L.; Olivares, R. C., . *J. Organomet Chem.* **2008**, 693, 3166-3170.

[7] Cao, S. L.; Feng, Y. P.; Jiang, Y.Y.; Liu, S. Y.; Ding, G. Y.; Li, R. T., *Bioorg. Med. Chem. Lett.* **2005**, 15, 1915-1917 ; Cao, S. L.; Feng, Y. P.; Zhang, X. L., *Arch Pharm Chem Life Sci,* **2006**, 33, 250-254.

[8] Liu, S. Y.; Liu, F.; Yu, X. Q., *Bioorgan Medic Chem,* **2006**, 14, 1425-1430; Malaguarnera, L.; Pilastro, M. R.; Vicari, L.; Dimarco, R.; Manzella, L.; Palumbo, G.; Messina, A., *Cancer Invest.* **2005**, 23, 404-412.

[9] Fugedi, P.; Garegg, P. J.; Oscarson, S.; Rosen, G.; Silwanis, B. A., *Carbohydr. Res.* **1991**, 211, 157-162.

[10] El Ashry, E. S. H.; Awad, L. F.; Atta, A. I., *Tetrahedron*, **2006**, 62, 2943-2998; El Ashry, E. S. H.; Awad, L. F.; Abdel Hamid, H. M.; Atta, A. I., *J. Carbohydr. Chem.* **2005**, 24, 745-753-; El Ashry, E. S. H.; Awad, L. F.; Abdel Hamid, H. M.; Atta, A. I., *Synthetic Comm.*, **2006**, 36, 2769-2785; Ali, I. A. I.; El Ashry, E. S. H.; Schmidt, R. R., *Eur. J. Org. Chem.,* **2003**, 4121-4131; Ali, A. I. A.; El Ashry, E. S. H.; Schmidt, R. R., *Tetrahedron*, **2004**, 60, 4773-4780; El Ashry, E. S. H.; Awad, L. F.; Rashed, N.; Abdel Rahman, A.; Rasheed, N. A. *Nucleosides, Nucleotides Nucleic Acids.*, **2008**, 27 309-317.