Synthesis and Characterization of Some New Polymeric Macrocycle (Thia-Crown Ether) and Study Biological Activity

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Abstract
This study investigates the synthesis, characterization, and biological activity of novel polymeric thia-crown ethers. On of the best solutions to save time and costs by mobilizing the chiral macrocycles on polymers which allows the recyclability and green conditions, The selecting of glucose as a model for the synthesis of macrocyclic thia crown ether The synthesis of thia-crown ether is started with protection of 4,6-positions on methyl D-glucopyranoside 1 by benzylidene protecting group, the reaction of compound 2 with bis(2-chloroethyl)ether under basic conditions to get compound 3 to obtain the structure which is ready to build up the macrocycle, the chloride can be enhanced by replacing it by iodide applying Flenksteien reaction to get compound 4. The macrocycle5 was treated in different reagent to get two derivatives in which 6 has only one free hydroxyl group, and 7 with two functional groups The compound 6 was crafted the PVC in order to obtain the target linear polymer 8. In the same context, the cross-linked polymer 9. All the compounds and polymers have been characterized by the instrumental techniques, include FT-IR, ^{1}HNMR, ^{13}CNMR and FESEM. The macrocycles 6, 7 and its polymeric materials was examined against two strains of bacteria, Gram + and Gram.

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Keywords: Macrocycles, Thia-crown ethe, bacteria, Gram +

Introduction

Chemists have paid significant attention to Thia-crown ethers as part of the crown ether group because these compounds display impressive behavior when interacting with metal ions [1, 2] while showing broad applications through catalysis and ion detection and drug transport techniques [3]. The sulfur atom substitution for oxygen in system crowns enables these compounds to attain better attributes when used in the binding of metal ions and host-guest chemistry applications [4]. Thia-crown ethers have experienced substantial development in both synthesis and application methods through studies about structural modifications and biological function assessments [5]. involved synthesis of thia-crown ether sugar derivatives which they tested for anticancer properties [6]. Research results demonstrated that thia-crown ethers showed substantial biological properties which establish new possibilities for upcoming anticancer drug research [8]. The need to improve therapeutic properties of thia-crown ethers stands proven by this research. [9] The need to improve therapeutic properties of thia-crown ethers stands proven by this research [10]. The recovery of metal ions represents a key environmental function that thia-crown ethers achieve alongside their biomedical applications. [11]. Research shows that thia-crown ethers achieve two beneficial effects by serving as therapeutic agents and environment-friendly solutions. The development of several methods for altering the structural composition of thia-crown ethers pushed forward the synthesis process toward specialized applications [12]. The synthesis of thia-crown ethers began when Reeder (1975) introduced new methods which became fundamental for their preparation and selection of specific ion binding possibilities [13]. This research project focuses on polymeric thia-crown ether synthesis while investigating their structure-property associations and their antibiological activity evaluation [14].

Experimental

A solution of methyl-α-D-glucopyranoside 1 (10 gm, 51.54 mmol) in dry DMF (50 ml) was treated with benzaldehyde dimethyl acetal (10 ml, 65.78 mmol) and sulphonic acid monohydrate (100 mg) (. compound 2 (15 g, 53.19 mmol) and tetra-butyl ammonium hydrogen sulfate (12.5 g, 36.9 mmol) in bis(2-chloroethyl) ether (200 mL) which acted as reactant and solvent, was vigorously stirred with 50% NaOH solution (85 mL) at room temperature for 72 hours. A solution of compound 4 (10 g, 14.7mmol) and sodium sulfide (6 g, 76,9 mmol) in dry ethanol (200 ml). The stirred reaction mixture was refluxed for 24–48 hour and monitored by TLC. solution of methyl 4,6-benzylidene-2,3-[15-thiacrown-5]-β-glucopyranoside 5 (2.78 g, 6.1 mmol) in (50:50) dichloromethane/diethyl ether (50 mL), $LiAlH_4$ (1.1 g ,28.9 mmol) was added in two portions with stirring. The combined organic phases were washed with water (4 x 20 mL), dried and concentrated under rotary evaporator to give the desired compound 6 (2.46 g, 88 %).

^{1}HNMR (400 MHz, Chloroform-*d*) δ 7.47 – 406 7.22 (m, 5H), 5.26-5.16, $PhCH_2$, *J* = 10.4 Hz, 1.4 Hz), 4.42 (d, 1H, *J* = 4.7 Hz, H-1), 4.36 – 4.21 (m, 2H, , H-6eq, , H-6ax), 4.13 – 4.04 (m, 1H, CH_2O,), 4.04 – 3.77 (m, 4H, CH_2O,),3.74 – 3.64 (m, 3H, CH_2O,), 3.64 – 3.51 (m, 8H; H-2, H-4, CH_2O), 3.51 – 3.41 (m,4H; 4-OH, OCH_3), 3.37 – 3.25 (m, 1H; H-3), 3.25 – 3.14 (m, 1H; H-5). 2.95-2.68 (m,4H; CH_2S).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 137.28, 133.74, 129.02, 128.25 (Ph), 102.78(C-1), 82.82 (C-2), 81.67, 80.84 (C-3/C-4) , 72.42 (Ph-CH_2), 72.39, 71.13, 71.08,70.82, 70.80, 70.63 (6 CH_2O), 68.74, 66.04 (C-6), 60.40 (C-5), 31.59, 30.28 (CH_2S).

Compound 5 (4.6 g, 10 mmol) was dissolved in chloroform: methanol 1 : 1 (150 ml), p-toluene sulfonic acid (200 mg) was added. The mixture was stirred for 12 hours at room temperature. Distilled water (150 ml) was added and the organic phase washed with saturated sodium bicarbonate solution (2 × 50 ml). The organic phase was dried over magnesium sulfate, and the solvents were evaporated. The product was sufficient clean for the next step.

^{1}H NMR (600MHz, $CDCl_3$) d (ppm) 4.86 (d, 1H; H-1, 3J1,2 3.8 Hz), 4.47 (dd,1H; H-1, H-6eq, 3J6eq,6ax 12, 3J5,6 4.5 Hz), 4.40–4.03 (m, 5H;CH_2O, H-6eq), 3.87–3.46 (m, 13H; H-2, H-3, H-4, H-5, CH_2O),3.43 (s, 3H; OCH_3), 2.95–2.68 (m, 4H; CH_2S);

Compound 6 (2.46g, 5.3mmol) was dissolved in (200 mL) of dry acetonitrile, sodium carbonate (6 g, 56.6mmol) and (5 g) of polyvinyl chloride (PVC) was added. The mixture was refluxed for 72 h and monitored by TLC. After cooling, the precipitate was filtered off and washed with acetonitrile and water extensively, dried in vacuum to furnish polymeric macrocycle 8 light brown powder (6.2 g, 83 %).

Route, I compound 7 (0.6 g) was dissolved in (100 mL) of dry DMF, and the solution was cooled down to 0^{o}C using ice-bath. Sodium hydride (2 g, 83.33 mmol) was added portion-wise to the solution with keeping the temperature less than 5oC. After one hour the polyvinyl chloride (PVC) (3 g) was added in small portions of intervals of 5 min. The mixture was stirred for 72 hour and monitored by TLC. The excess of sodium hydride was destroyed by adding water carefully, and filtered in vacuum and washed with ethanol and water extensively, dried in vacuum to furnish polymeric macrocycle 9 as brown powder (3.34 g, 78 %).

Route II compound 7 (0.6 g) was dissolved in (100 mL) of toluene, sodium hydroxide (50%) 40 ml, and tetra-butyl ammonium bromide (8 g, 24.81 mmol) was stirred at room temperature for 15 min. After that the polyvinyl chloride **(PVC)** (3 g) was added in small portions. The mixture was stirred for 72 h and monitored by TLC. The solid was filtered in vacuum and washed with toluene and water extensively, dried in vacuum to furnish polymeric macrocycle 9 as brown powder (5.1 g, 66 %).

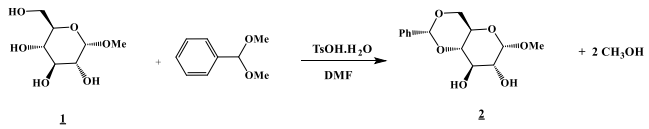
Antibacterial assay:

The compounds were used for their antibacterial activity against the Staphylococcus aureous(Gram-positive) and Escherichia coli (Gram-negative) by Well diffusion method. Each bacteria isolate was inoculated on to the Muller-Hinton Agar (MHA) [sterilize in autoclave] by dipping a cotton swab in to the suspension and streaking over the surface of the agar plates. Then, in the solidified medium, four holes were made (6 mm). These holes were filled with (0.5 ml) of the prepared compounds (10 mg of the compound dissolved in 1ml of DMSO solvent). These plates were incubated at 37 0C and measured of zone inhibition after 24 hours.

Results and Discussion

Synthesis of methyl 4,6-ben-α-D-glucopyranoside 2

The first step is protecting the hydroxyls on positions 4- and 6- positions using acetals as a suitable option for this purpose. Two options are available for that are isopropylidene and benzylidene protecting groups which represent the most popular acetal reagents. The selective protecting of 4,6-hydroxyls due to the fact that stable dioxane (six-membered ring) would be formed more likely over the corresponding five-member ring dioxane. The benzaldehyde dimethyl acetal was choosing instead of benzaldehyde depends on the kinetic control of the reaction over thermodynamic control. The entropy will increase due to the releasing of three molecules from two reactants.



1 2

(Scheme 1) The synthesis of compound 2

The FT-IR spectrum of compound 2 showed the following characteristic peaks which is may be attributed to the aromatic protons of benzylidene in the region (3100- 3034) cm^{-1} due to the stretching vibrations of (H-aromatic). Furthermore, the stretching vibrations of (C=C aromatic) would be appear at the region (1600-1500 cm^{-1}) (Figure 2)

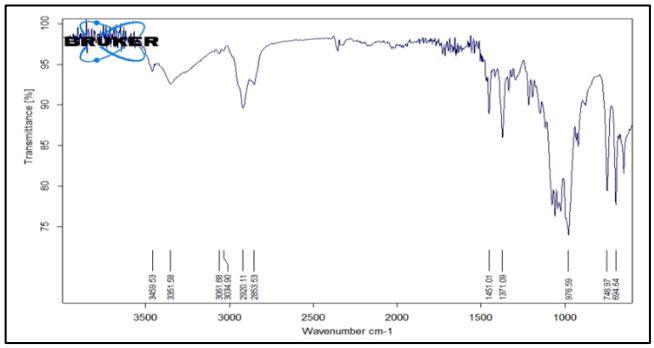


Fig 1: FT-IR spectrum of compound 2

Synthesis of methyl-4,6-O-benzylidene-2,3-bis[(2-chloroethoxy) ethyl]-α -D-glucopyranoside 3

The benzylidene acetal leave the free hydroxyls on the 2- and 3- positions ready to be a good precursor for construction the macrocycle with specific chiral centers on the glucose moiety. To construct the macrocycle, the free hydroxyl groups on 2,3- positions of glucoside 2 were react with bis(chloroethyl)ether under phase transfer conditions. the most common reactions, is Williamson etherification that use widely to prepare an etheric bond from alcohols and alkyl halides. The Williamson reaction could be following the SN2 mechanism, in which the primary alkyl halide is attacked from the back side by an alkoxide as illustrated.The FT-IR spectrum, (Figure 3) of compound 3 shows the disappearing of the stretching vibration bands in the range of (3459-3351 cm^{-1}) due to the absorption of stretching vibration of (OH-group). In addition, the new signal in the region (747 cm^{-1}) which can be attributed to the stretching vibrations of (CH_2-Cl) bond.

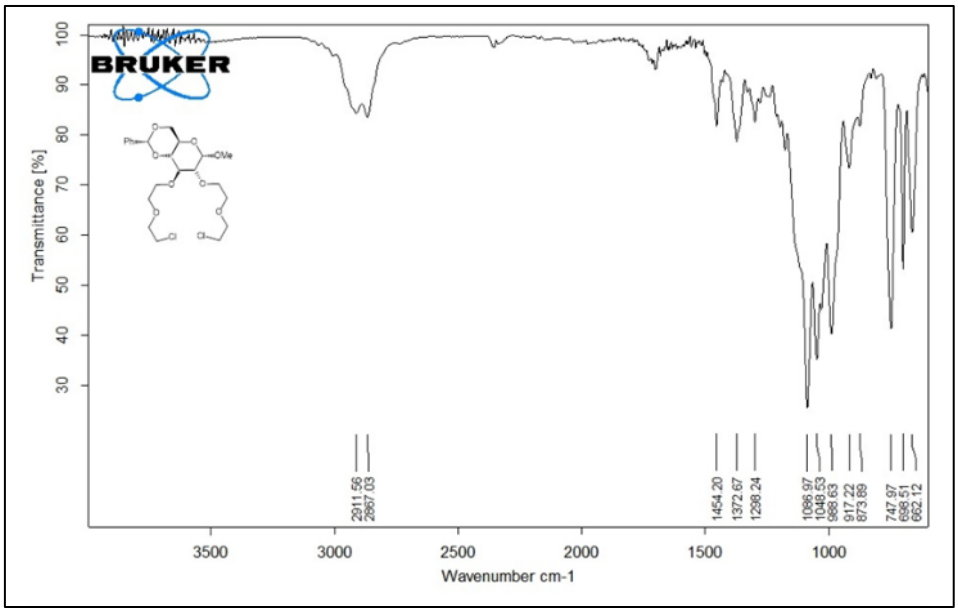


Fig 2: FTIR spectrum of compound 3

The ^{1}HNMR spectrum of compound 3 shows there was new signals in the range of 3-4 ppm arising from the groups (O-$CH_2CH_2)_2Cl$) with increasing to integration value of hydrogens compare to compound 2. (Figure 3).

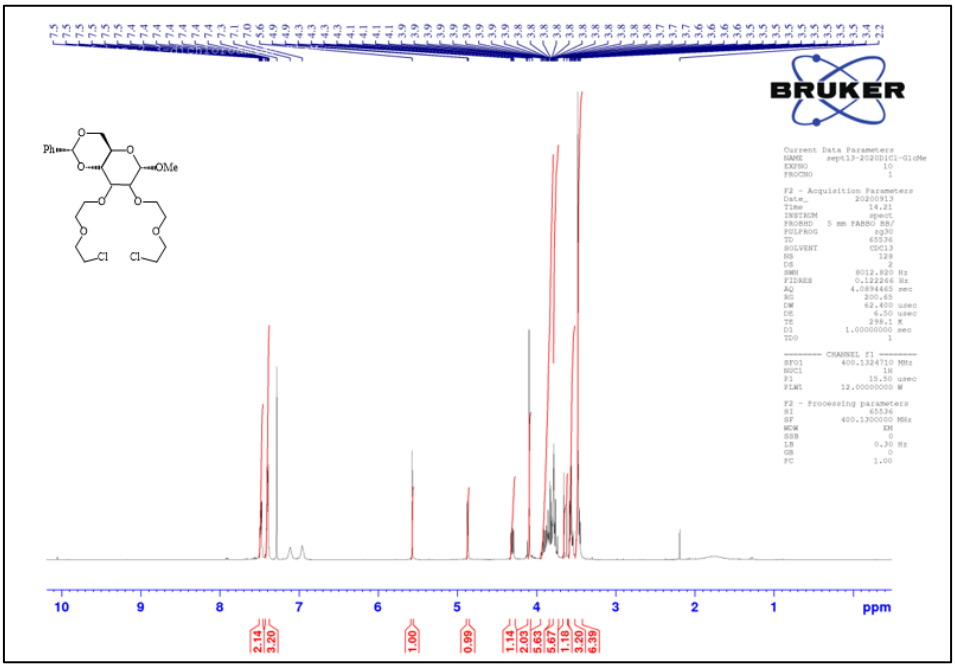


Fig 3: ^{1}HNMR spectrum of compound 3

The ^{13}CNMR spectrum of compound 3 showed a new signal at the range of (72- 67) ppm which could be assigned to the carbons attached directly to the oxygens, while the two signals at 42.81 and 42.78 ppm is refer to the carbons attached directly to chlorine atoms (R-CH_2Cl). The HSQC experiment is assisted to assign all carbons and protons as it correlation

with attachment of each proton to its corresponding carbons Figure (5).

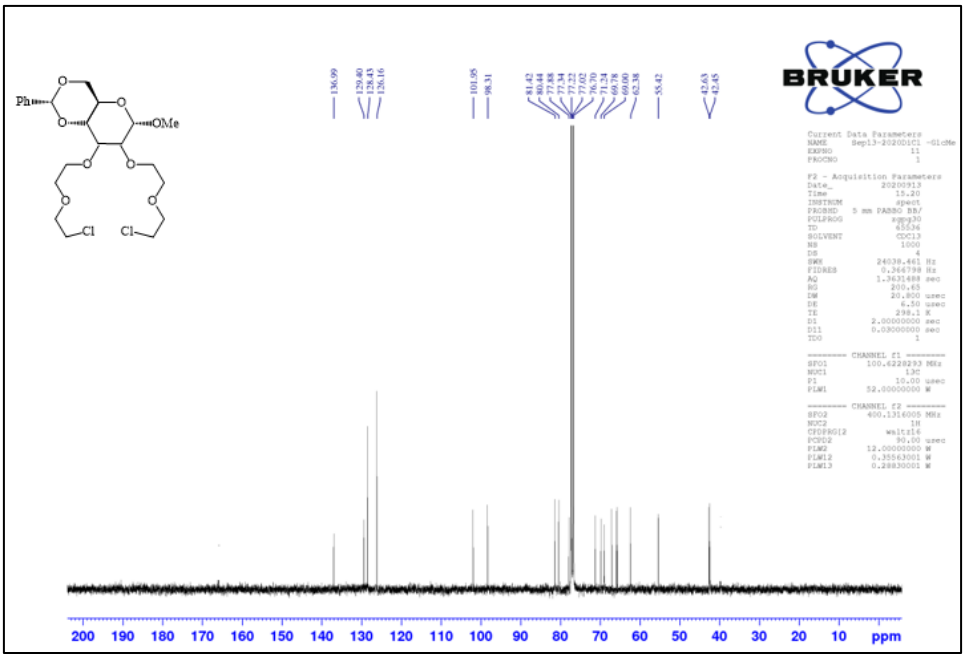


Fig 4: ^{13}CNMR spectrum of compound 3

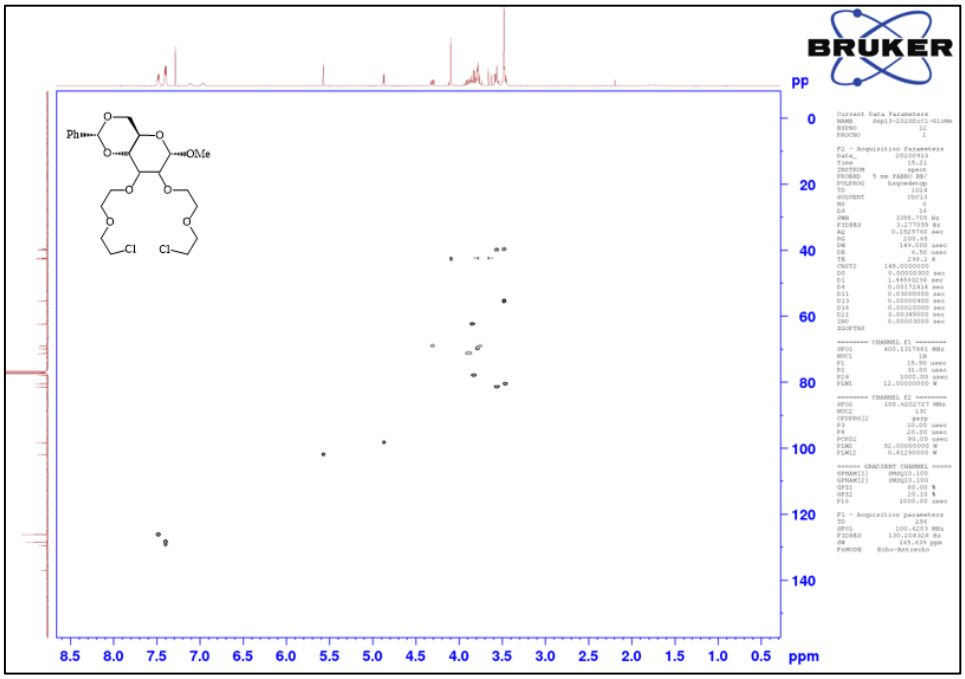


Fig 5: HSQC spectrum of compound 3

Synthesis of methyl-4,6-O-benzylidene-2,3-bis[(2-iodoethoxy) ethyl] -α-D-glucopyranoside 4

The chloro derivative 3 is converted to the corresponding iodide analogue 4 in order to increase the electrophilicity of carbon atoms attached directly to the halide. The such reaction can be replaced the chlorine atom with more reactive iodide in simple reaction condition using acetone and sodium iodide. The FT-IR spectrum, Figure [6] of compound 4 shows the absorption bands that characterize the product.

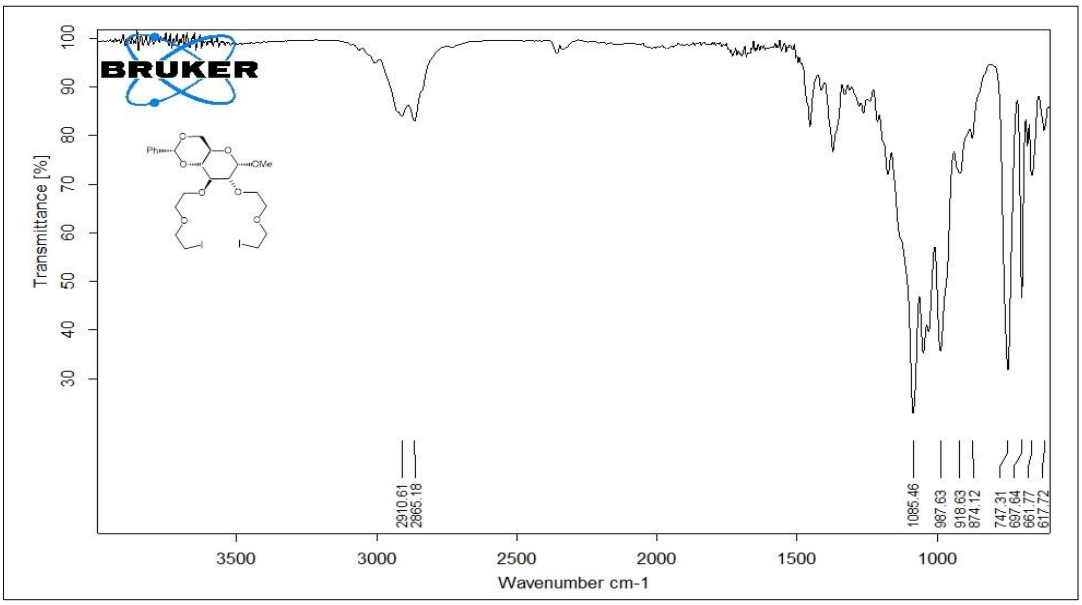
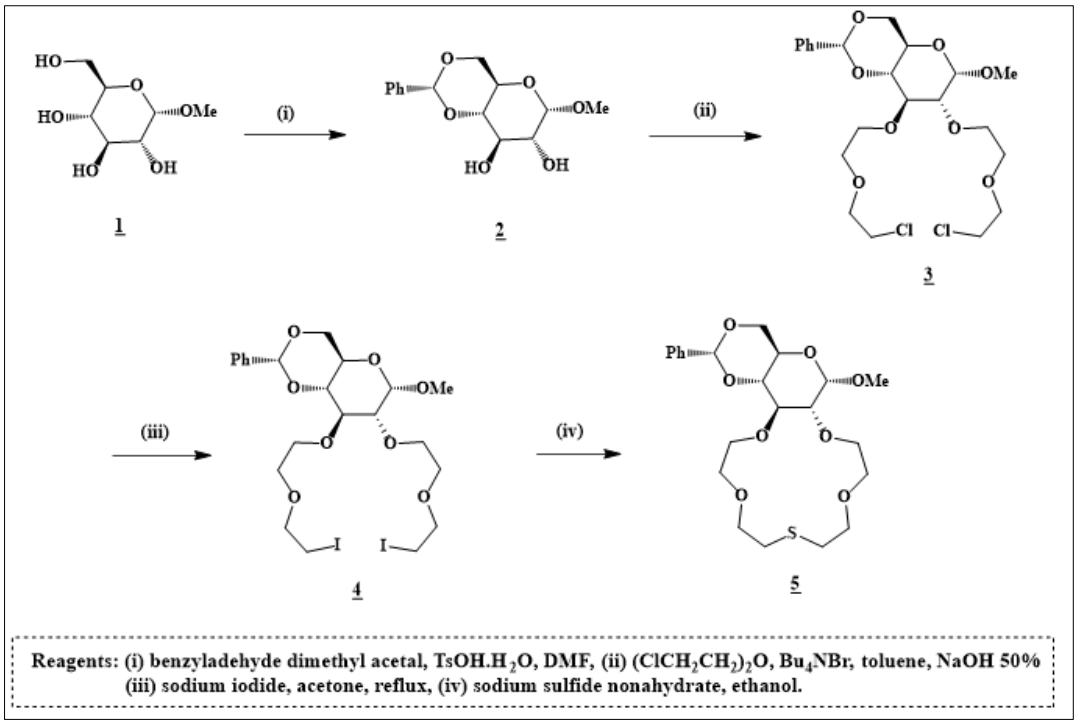


Fig 6: FTIR spectrum of compound 4

Synthesis of 4,6-O-ben-2,3-benzylidene thia-[15cr5]-GlcMe 5.

The compound 4 now is ready to build up the macrocycle 5 by the treatment with sodium sulfide nonahydrates in aqueous ethanol.



(Scheme 2) Overall synthesis of thia-crown ethers 5

The FT-IR spectrum, Figure [7] of the compound 5 is showed the disappearance one of absorption bands for (CH_2-I) at (661 cm^{-1}) of compound 4 and some other peaks are appeared in the spectrum to confirm the desired structure

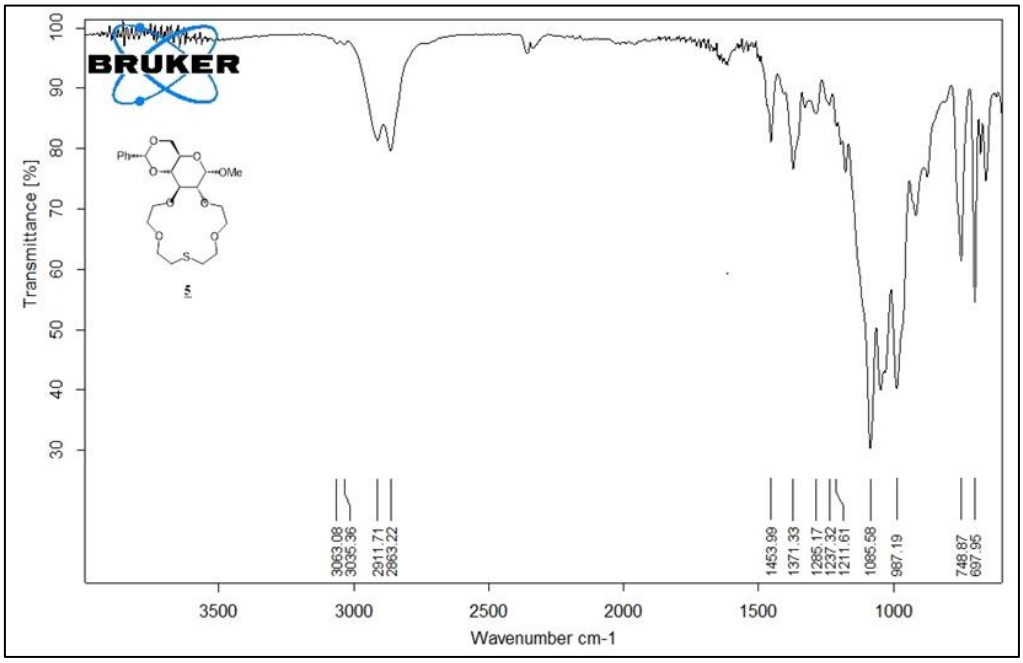


Fig 7: FTIR spectrum of compound 5

The 1H-NMR spectrum of compound 5 figure [8] showed the characteristic peak of the compound. The spectrum is indicating the disappearance of four protons in the region of (3.50-3.0) ppm which is corresponding to the (CH_2I) groups. In addition, there are four protons in the region between 2.95–2.68 ppm which is assigned to the four protons of two (CH_2) groups attached directly to the S atom.

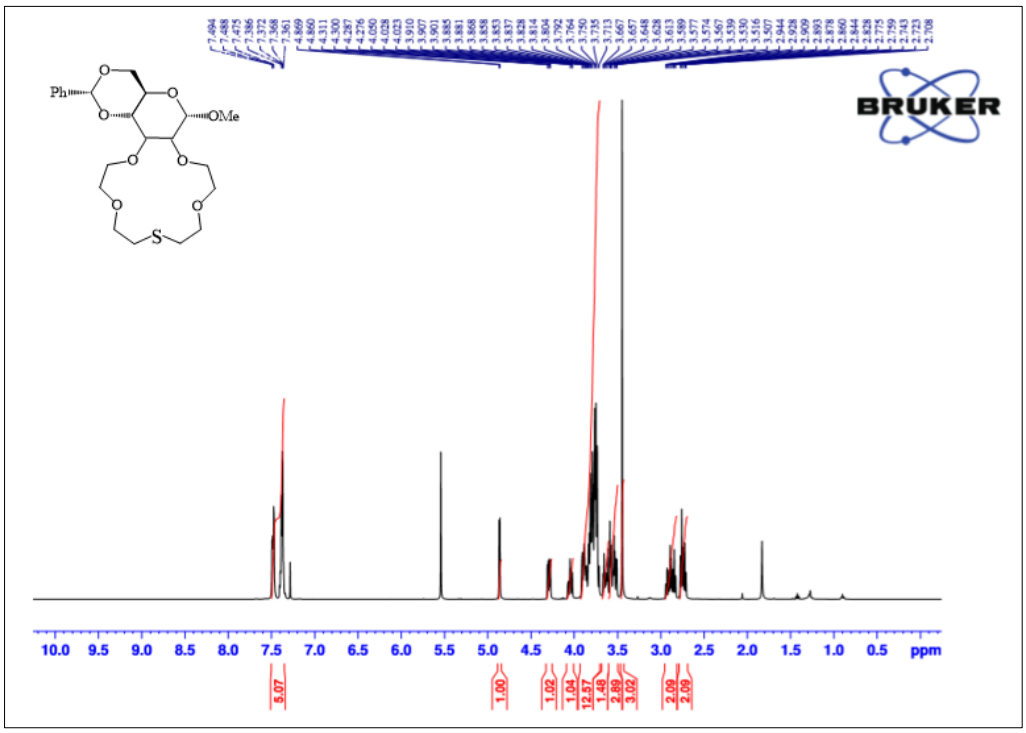


Fig 8: [1]HNMR spectrum of compound 5

the [13]CNMR spectrum of macrocycle 5 (figure 9) showed new characteristic peaks in different parts. There were disappear of the peaks at 42.3 and 42.0 ppm in compound 3 and was appear two peaks instead in the 31.58 and 31.37 ppm which are assigned to the carbons attached directly to the sulfur after the macrocycle formation.

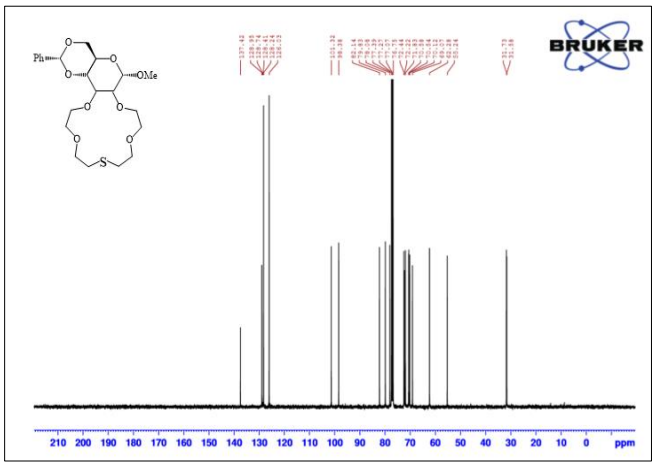


Fig 9: ^{13}CNMR spectrum of compound 5

The HMBC and HSQC is assisted the confirm of the structure through the relationship of each experiment to show the connectivity of the atoms according to their J-coupling. The HSQC look for the J-coupling between the carbon and its related hydrogens which is attached directly to the carbon. While the HMBC looking for the *J*-coupling of carbon and proton of three to four bonds. In other words, the J-coupling 3 or 4 among the proton and carbons.

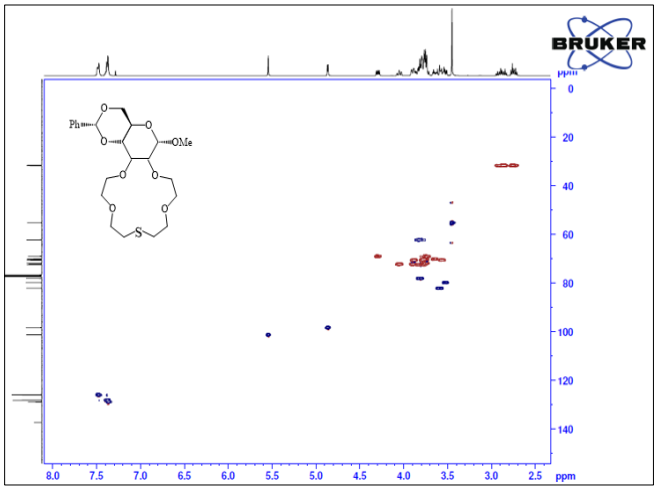


Fig 10: HSQC spectrum of compound 5

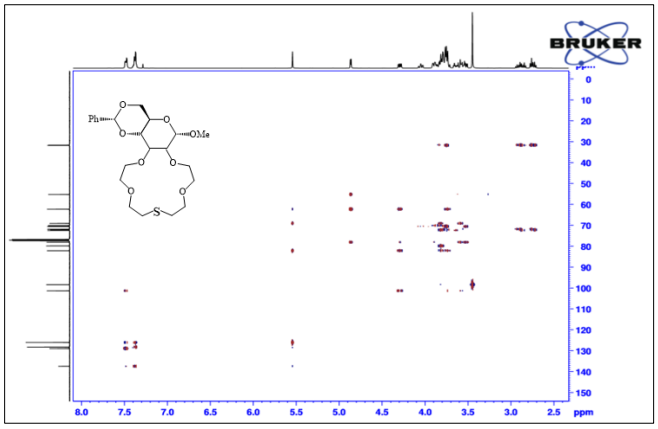


Fig 11: HMBC spectrum of compound 5

Synthesis of 4-benzyl-2,3-thia-[15cr5]-GlcMe 6**.**
The ^{1}HNMR spectrum showed of compound 6 the absence for the benzylidene proton at 5.5 ppm and shaved that there is a new double doublet (dd) signal 4.7 ppm for the protons of benzylic (CH_2) (Figure 11).

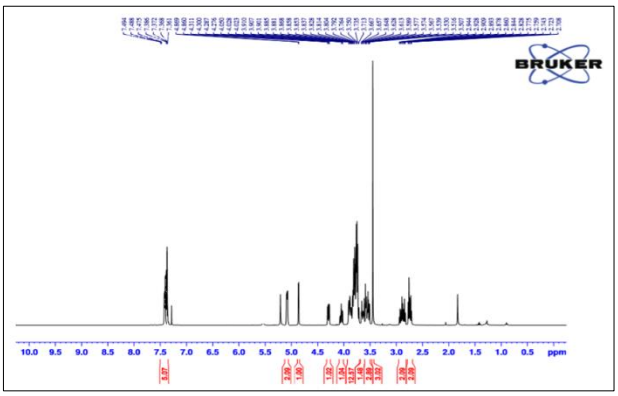


Fig 12: ^{1}HNMR spectrum of compound 6

Besides that, the ^{13}CNMR spectrum of compound 4 showed that there is a disappearance of the carbon signal at 101 ppm of benzylidene carbon and the appearance of a new carbon signal at 73.22 ppm for the benzylic carbon (Figure 12).

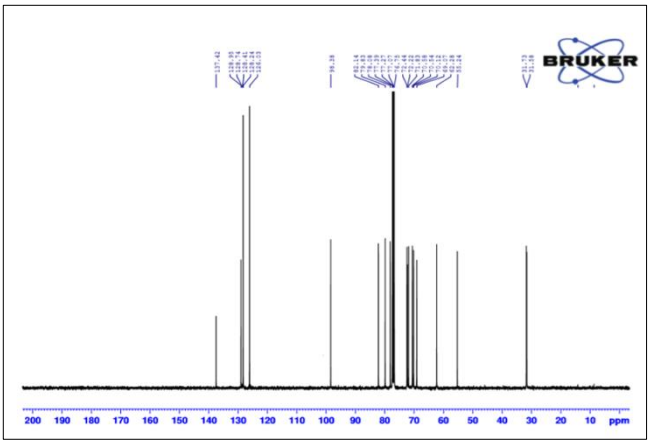


Fig 13: ^{13}CNMR spectrum of compound 6

Synthesis of free 2,3-thia-[15cr5]-GlcMe 7.
The ^{1}HNMR spectrum of compound 7 is showed the disappearance of aromatic protons at the range of 7.6-7.0 ppm, as well as the benzylidene proton at the 5.5 ppm (Figure 13).

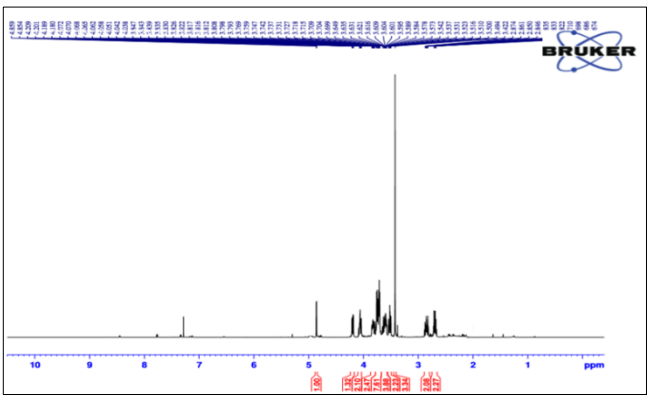


Fig 14: ^{1}HNMR spectrum of compound 7

In the same manner the ^{13}CNMR spectrum is showed the disappearance of aromatic carbon at the range of 150-120

ppm. The benzylidene carbon at 101 ppm is also disappear as good evidence to remove the benzylidene protecting group (Figure14).

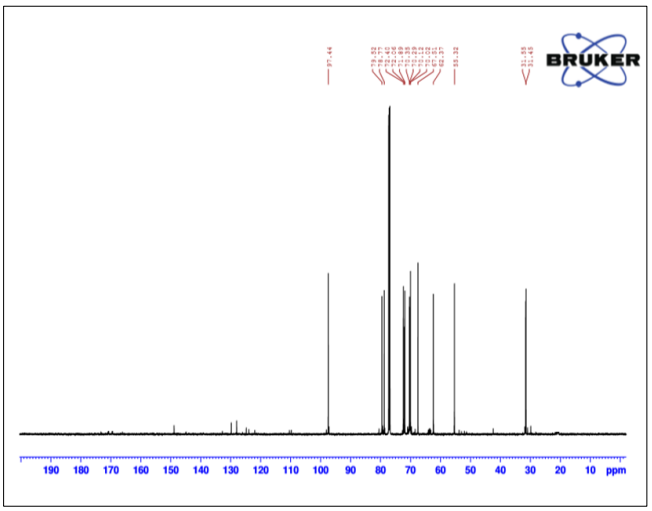
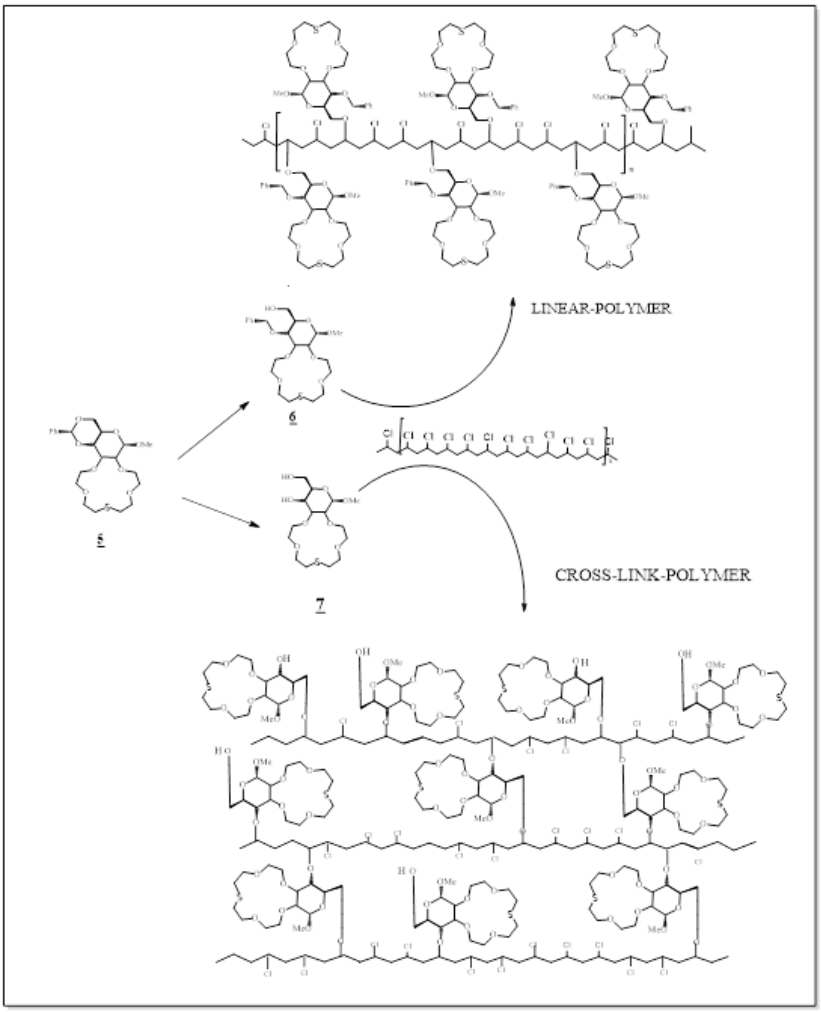


Fig 15: ^{13}CNMR spectrum of compound 7

Synthesis of grafting polymers with macrocycles

The polymerization process typically needs certain requirements. Sugar, however, contains macrocycles that are involved as a defensive group strategy that increases the synthesis cost. Thus, the polymerization of such materials will increase the cost, as a result, the procedure will move to the resulting structure's further proof. Instead, the crafting of this costly material on a commercially available polymer was our point of view in the synthesis of such polymeric catalysis. Among them, Polyvinyl chloride (PVC) was suitable for the development of thia-crown ether as a starting polymer.

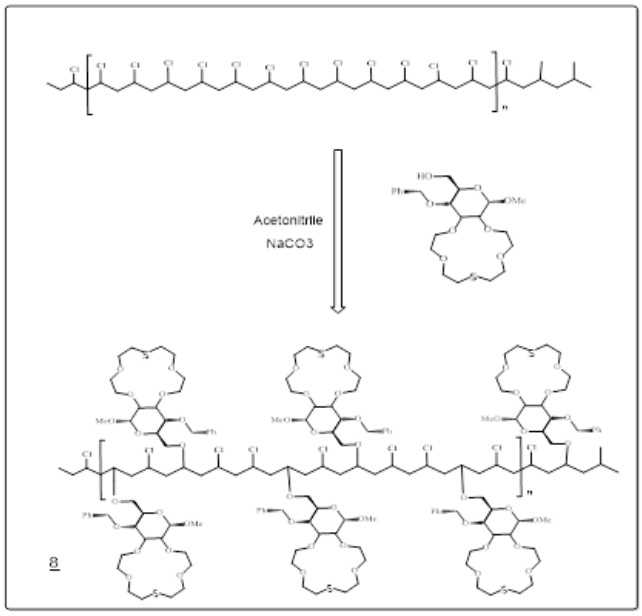


(Scheme 3) Overall synthesis of polymers 9 and 10

Synthesis of linear polymeric thia-crown ether 8

The selective cleavage of benzylidene protecting group offer a good precursor with single functional group, i.e. hydroxy group on 6-position. This functional group could be reacted with polymers which have a good leaving group for grafting. The polyvinyl chloride offers a simple and fast route for synthesis a new crafted polymer via Williamson reaction. The reaction basically is followed S_N2 mechanism in which the alkoxide ion attack the carbon which bear the halogen atom from back side.

It is clear that, according to the design of the attachment of the original linear structure with only one functional group, the reaction will make linear form of the polymer. The scale of the thia-crown ether will result in homogeneity of distribution along the polymeric chain of PVC compound 8.



(Scheme 4) Synthesis of linear polymer 8

The FT-IR spectrum of compound 8 was showed additional peaks in comparison to the PVC spectrum. The macrocycle characteristic peaks is appeared beside the PVC peaks, the carbon-oxygen stretching vibrations in the range of 1200-1050 cm^{-1} would appear due to several C-O bonds.

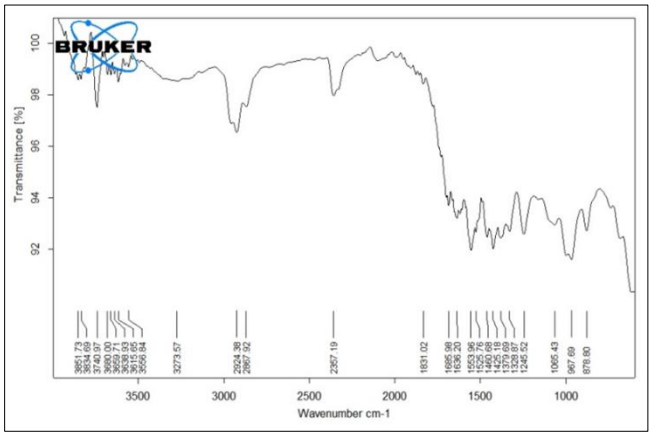
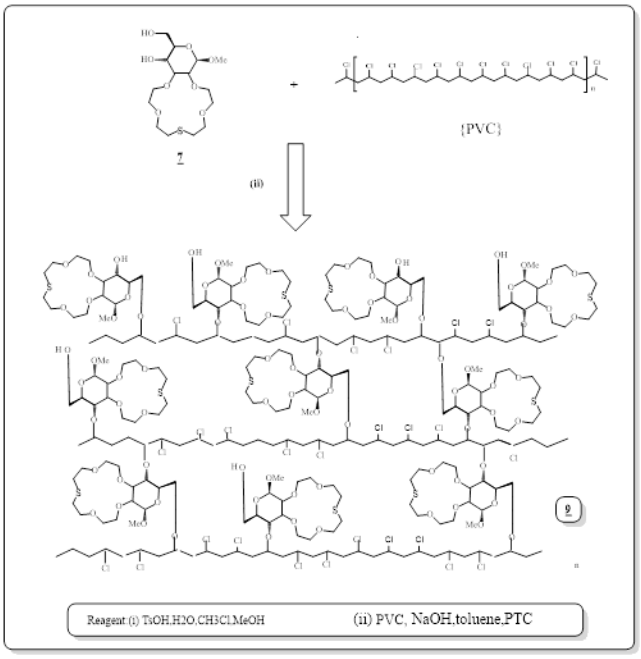


Fig 16: FTIR spectrum of polymer 8

Synthesis of cross-link polymer 9

The cross-linked grafted polymer required two functional groups to be ready for the attachment between two mono-functional polymer PVC. When the benzylidene group is removed completely form the structure of macrocycle 5 to furnish two hydroxyl groups 7. These hydroxyls can be easily undergone a Williamson etherification reaction with standard conditions to obtain the desired polymer 9 (scheme 5).



(Scheme 5) Synthesis of cross-link polymer 9

The FT-IR spectrum of compound **9** was showed additional peaks in comparison to the PVC spectrum. The macrocycle characteristic peaks are appeared beside the PVC peaks, the carbon-oxygen stretching vibrations in the range of 1200-1050 cm^{-1} would appear due to several C-O bonds (Figure 16).

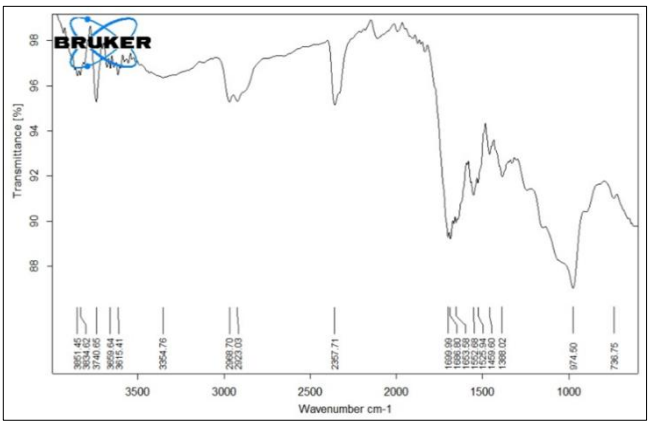


Fig 17: FTIR spectrum of compound 9

Field Emission Scanning electron microscopy (FESEM).

The FESEM technique is used for the study of materials morphology in order to understand some properties arise from the surfaces which is likely can give good recommendation for applying these materials in different applications. The morphological examination of FESEM image of the linear polymer 8 (figure 17) is showed that the surface of 8 was slightly rougher and some of the agrégations of polymeric chain have been assumed.

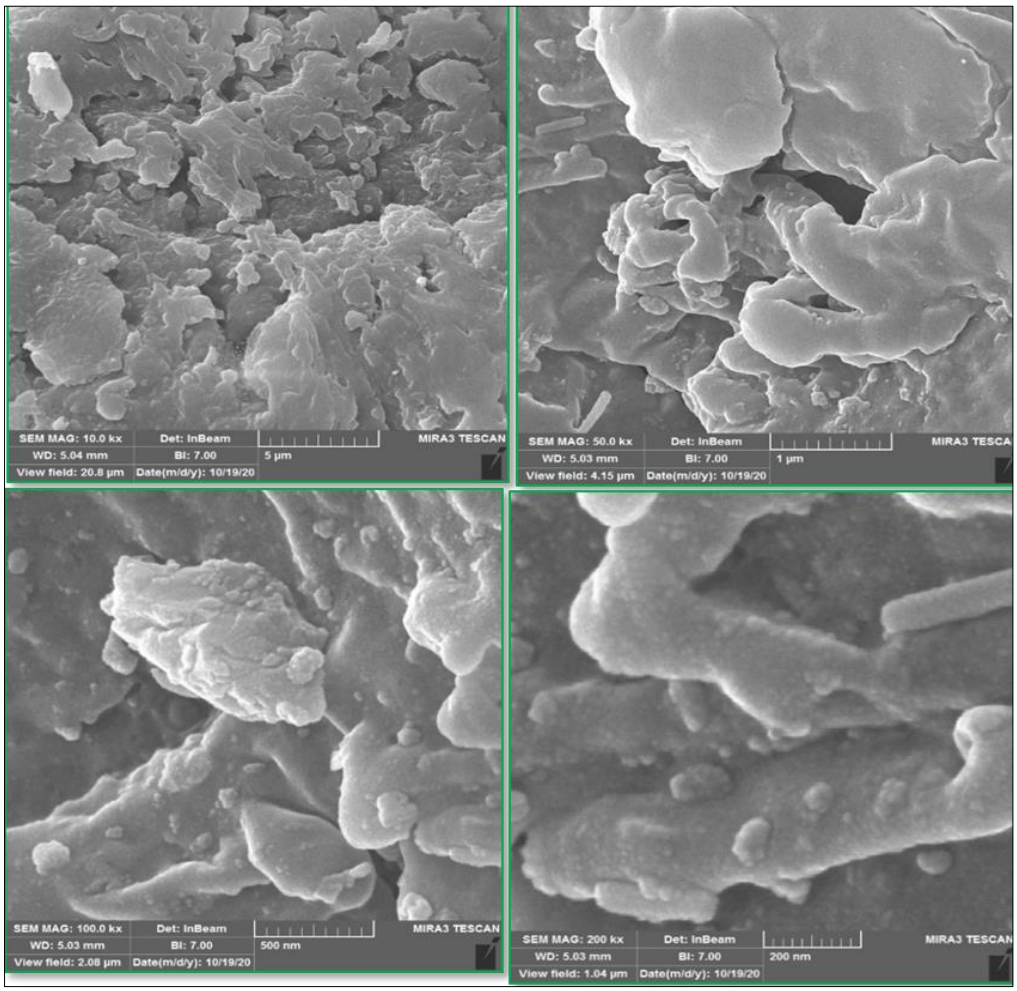
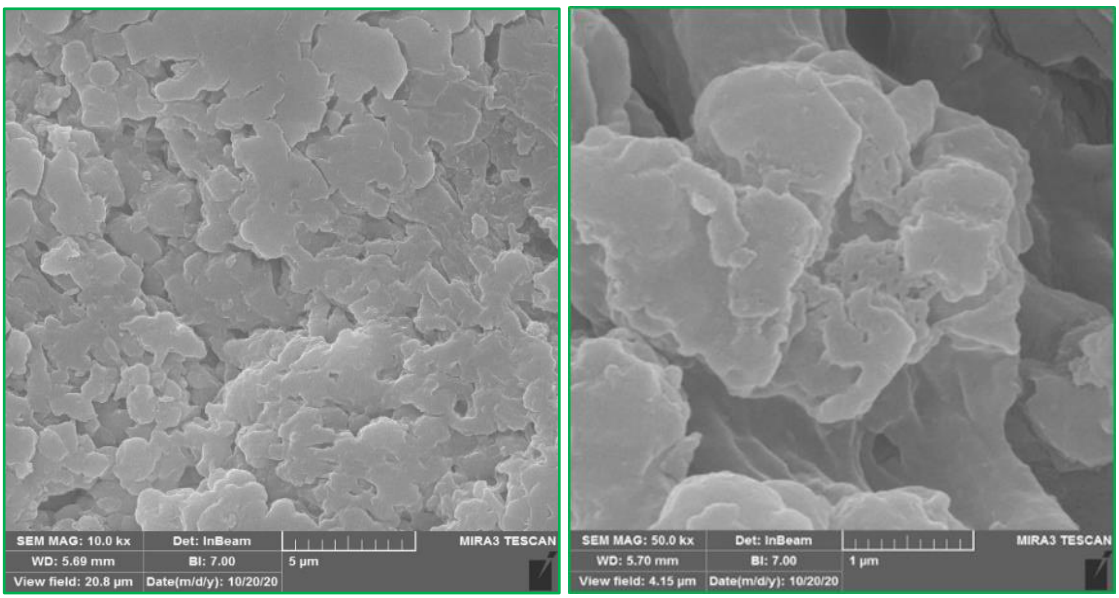


Fig 18: Show the morphology of the linear polymer 8 in different magnifications

In the same way the cross-linked polymer 9, figure [18] was showed in its FESEM image stiffer morphology and accumulation of particles together, which is can be resulted from the big number of cross linking through the polymeric series of original polyvinyl chloride.



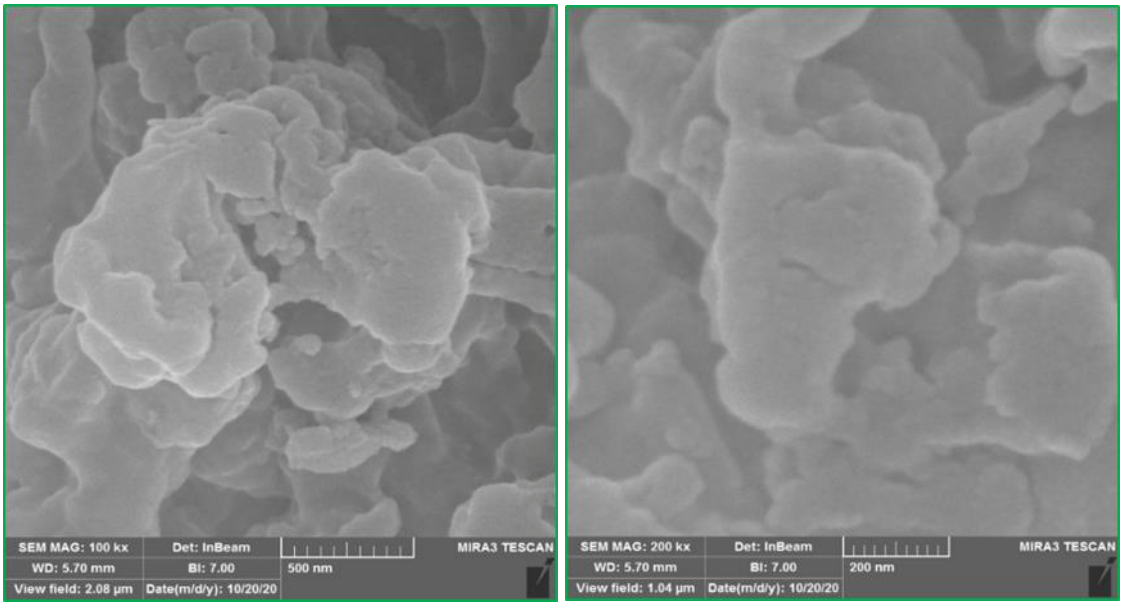


Fig 19: Show the morphology of the cross-link polymer 9 in different magnifications

Table 1: Tested compounds in inhibition zone

Comp.		6	7	8	9
Inhibition zone (mm)	*E. coli*	5	11	26	24
	S. aureus	32	40	15	18

Biological Activity

Most of the biological processes involve recognition, membrane transport, signal transduction, biocatalysts, information storage, these functions can be done by supramolecules like crown ethers and involvement in the toxicity analysis of bacteria and cancer cell lines, and the position of carriers and ion channels is also played by crown ethers via membranes. The complex and fascinating biological activities associated with the macrocyclic compound class have been connected to characteristic structural features. Their complexing properties make crown ethers in biological research and in chemistry particularly important and useful compounds. The ion complex-carrying capacity of crown ethers results in natural ionophores (such as gramicidin) resembling them. In this context, their ability to channel ions through lipid membranes, similar to natural ionophores, has enabled the use of crown ethers in various biological applications. Furthermore, crown ether derivatives have been shown to exhibit antibacterial activity against gram- positive (*Staphylococcus aureous, Staphylococcus saprophyticus*) and gram-negative (*Kelebsiella pneumonia, Escherichia. Coli*) bacteria

The polymers 8 and 9 were subjected to the antibacterial study against two types of bacteria *Escherichia coli* as Gram-negative and *Staphylococcus aureus* as Gram-positive, the original polymer (PVC *10* as well as the macrocycles 6, 7

The macrocycles 6, 7 and its polymeric materials was examined and the result shows that the polymers were moderate in their effects in comparison with corresponding macrocycles monomers.by well diffusion method in Mueller-Hinton agar medium. In the table [3-2] the inhibition zones were assessed after 24 hours of incubation and the results were summarized.

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