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Article

Synthesis of a Novel Macrocyclic Derivatives Based on Gluco-pyranoside and Application as Anticancer Activity

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Abstract: Cyclic compounds have gained attention in a variety of fields for their unique properties. Crown ethers, cryptands, and calixarenes are cyclic compounds that have been used in a range of applications such as chemical sensors and drug delivery systems. Cyclic peptides have shown promise in treating various diseases due to their enhanced stability and bioavailability. This study focuses on the synthesis and characterization of a pyranoside compound, -methyl 4,6-benzylidene-2,3-di-O-benzyl-D-glucopyranoside, which was synthesized via a phase transfer catalysis method. The synthesized compound was analyzed using FT-IR, 1H NMR, and 13C NMR spectroscopy. Field-emission scanning electron microscopy and EDX analysis were also carried out to study the morphology and elemental composition of the compound. The results of this study contribute to the potential applications compounds -methyl 4,6-benzylidene-2,3-di-O-benzyl-D-glucopyranoside were evaluated for their anticancer potential against two cancer cell lines PC3 (prostate cancer cells) and WRL68 (normal liver cells) compound 12 appears to have a greater effect on prostate cancer cells (PC3) compared to compound 11. At the highest concentration tested (400 μM), compound 12 showed a mean percentage inhibition of 95.72% in PC3 cells, while compound 11 showed a mean percentage inhibition of 33.29% at the same concentration. Furthermore, the IC50 value for compound 12 in PC3 cells was 112.9 μM, while the IC50 value for compound 11 was 24.38 μM, indicating that compound 11 is less potent in inhibiting the growth of PC3 cells. These results suggest that compound 12 may have greater potential as a therapeutic agent for prostate cancer.

Keywords: methyl 4,6-benzylidene-2,3-di-O-benzyl-D-glucopyranoside; PC3; pyranoside; WRL68; cancer cell lines

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1. Introduction

Cyclic compounds, which are molecules with a closed loop or ring structure, have gained attention for their unique properties that differ from their linear counterparts. They have become a significant focus in a range of fields, including pharmaceuticals, environmental remediation, and materials science. The discovery of crown ethers by Pedersen in the 1960s marked an important milestone in the study of cyclic compounds. These molecules contain oxygen atoms arranged in a crown-like structure and can selectively bind certain ions or molecules, making them useful in a range of applications such as chemical sensors and catalysts [2]. The discovery of crown ethers has also led to the development of other cyclic compounds such as cryptands and calixarenes, which have similar properties and uses. The development of cyclic peptides as drug candidates has become a recent focus of research [3]. Cyclic peptides are composed of amino acids arranged in a ring structure, which gives them enhanced stability and bioavailability compared to linear peptides [4]. They have shown promise in treating a range of diseases, including cancer and infectious

diseases. Nature provides examples of cyclic compounds, with carbohydrates forming cyclodextrins, which are widely used in drug delivery and food additives. Cyclodextrins have the ability to selectively bind certain molecules and enhance their solubility and stability [5]. The chirality of cyclic compounds is also an essential factor to consider, with many-having chiral centers that can result in different biological activity between their two enantiomers. Selectively synthesizing one enantiomer of a cyclic compound can lead to drugs or other compounds with improved selectivity and efficacy [6]. While initial studies have shown that crown ether carbohydrates have cytotoxic effects on cancer cells, there is a need for further research to determine their efficacy and specificity for different types of cancer. Additionally, more research is needed to determine the optimal dosage and delivery methods of these compounds to maximize their anticancer potential while minimizing toxicity [7].

Furthermore, the mechanism of action of crown ether carbohydrates as anticancer agents is not yet fully understood. Understanding the molecular targets of these compounds will be essential for developing effective and targeted anticancer treatments. Addressing these research gaps is critical for the development of crown ether carbohydrates as effective and safe anticancer agents. By determining their efficacy, specificity, and mechanism of action, researchers can optimize their therapeutic potential and develop targeted treatments that minimize harm to healthy cells. This research may ultimately lead to the development of new and effective treatments for cancer patients. The aim of this research is to investigate the effect of D-glucopyranoside crown ether on two different cell types, PC3 (prostate cancer cells) and WRL68 (normal liver cells). The primary objective of this research is to investigate the potential of D-glucopyranoside crown ether as a novel therapeutic agent for prostate cancer. To achieve this, we aim to determine the cytotoxic effects of D-glucopyranoside crown ether on prostate cancer cells) PC3 (and WRL68 (normal liver cells) and assess its selectivity towards cancer cells compared to normal cells. Furthermore, we will investigate the mechanism of action of D-glucopyranoside crown ether on cancer cells to gain a better understanding of how it exerts its cytotoxic effects. Ultimately, our research aims to explore the potential of D-glucopyranoside crown ether as a viable treatment option for prostate cancer, which could lead to the development of a new generation of cancer therapeutics.

2. Materials and Methods

2.1. Instruments and materials

Across provided sodium azide (99%), cobalt(II) nitrate hexahydrate (98%), copper(I) chloride (97%), lead nitrate (99%), propargyl bromide (80% solution in toluene), and sodium ascorbate (96%). Methyl glucopyranoside (99%), benzaldehyde dimethyl acetal (98%), toluene sulfonic acid monohydrate (98%), bis(2-chloroethyl)ether (99%), aluminum chloride (98%), sodium iodide (99%), and cadmium(II) nitrate tetrahydrate (98%) were obtained from Sigma-Aldrich. All solvents used in the experiment were procured from Merck and were used without any further purification. Flash column chromatography was performed using silica gel 60 (230-400 mesh, E. Merck). FTIR measurements were conducted using the Shimadzu 8400 Series Japan. The FESEM and EDX BRUKER X FLASH6l 10 were recorded on FEI NOVA NANOSEM 450I. The Hanna, HI9811-5 pH–meter was used for microprocessor-based pH measurements. XRD spectra were recorded in Rigaku (Japan). 1H and 13C NMR spectra were recorded on Bruker Avance 400 MHz spectrometers. High-resolution mass spectra were recorded on an Agilent Technologies 6530 Accurate Q-TOF LC-MS system with MeOH–water eluents. A gas flow of 250 °C hot nitrogen at 5 mL/min and electrospray ionization at 125 eV were applied.

Synthesis of Methyl-4,6-di-O-benzylidine-α-D-glucopyranoside (2a) and Caprylic acid-4,6-di-O-benzylidine-α-D-glucopyranoside (2b)

(20g, 103 mmol) of Methyl α-D-glucopyronside **1** was dissolved in 100 mL of *N,N*-Dimethylformamid, then (20g, 131.6 mmol) of benzaldehyde dimethyl acetal was added to the reaction vessel and the medium was acidified by (0.10 g, 0.585mmol) toly-sulfonic acid. The mixture was stirred in a rotary evaporator until TLC showed there is no starting material left [8]. The solvent was evaporated under vacuum and the residue was extracted by chloroform: water mixture to obtain the crude which was co-evaporating by a mixture of toluene: water (50:50) twice to furnish a white soft powder **2**. The Yield (16.3g, 56%). m. p.= (161-163) ºC, and **2a** = Chemical Formula: $C_{14}H_{18}O_6$, Molecular Weight: 282.29, **2b** = Chemical Formula: $C_{23}H_{36}O_6$, Molecular Weight: 408.54.

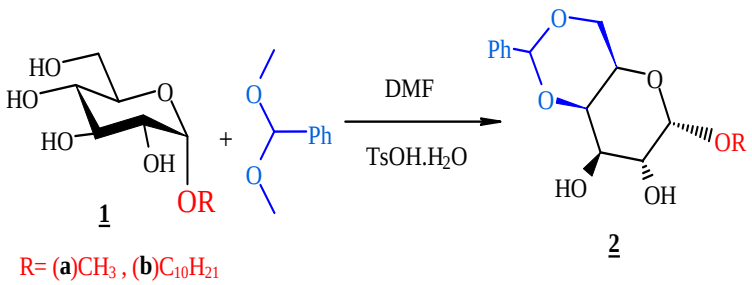
FT-IR peaks: (3332, 2972, 2885, 1473, 1387, 1242) cm^{-1}.

^{1}H NMR 2a ($CDCl_3$, 500 MHz):- δ (ppm) 7.43 – 7.33(m, **5H**; Ar-H), 5.8(s, **1H**; Ph-CH), 5.20 (d, *J*=3.5 Hz, **1H**; H-1), 4.05 (dd, *J*=10.9, 4.9 Hz ,**1H**; H_{ax}-6), 4.00-3.92 (m, **3H**; H-4, H-3, H-2), 3.78 (, **1H**; H_{eq}-6), 3.50(s, **3H**; OCH_3), 3.37 (dd, *J*=10.1, 9.1 Hz, **1H**; H-5).

^{1}H NMR 2b ($CDCl_3$, 500 MHz): δ (ppm) 7.40 – 7.30(m, **5H**; Ar-H), 5.8(s, **1H**; Ph-CH), 5.12 (d, *J*=3.5 Hz, **1H**; H-1), 4.05 (dd, *J*=10.9, 4.9 Hz, **1H**; H_{ax}-6), 4.00-3.92(m, **2H**; H-4, H-3), 3.88(dd, *J*=10.9, 4.9 Hz, **1H**; H_{eq}-6), 3.82(dd, *J*=9.7, 3.6 Hz, **1H**; H-2), 3.32-3.27(m, **2H**; OCH_2), 3.37 (dd, *J*=10.1, 9.1 Hz **1H**; H-5), 1.48-1.475(m, **4H**; $2CH_2$), , 1.37-1.25(m **12H**; $6CH_2$), 0.88-0.84(m,**3H**; $1CH_3$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8 (**Aromatic C**), 128.63,128.44 (**2Aromatic CH**), 127.8(**1 Aromatic CH**), 126.30,126.20 (**2Aromatic CH**), 108.85,109.2 (**C-1 , PhCHO**), 81.80 (**C-3**), 80.70 (**C-2**), 70.07 (**C-4**), 68.80 (**C-6**), 66.60 (**C-5**), 55.44 (**OCH_3**). [9][10]

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.55 (**Aromatic C**), 127.80,127.42 (**2Aromatic CH**), 126.45(**1 Aromatic CH**), 125.34,125.20 (**2Aromatic CH**), 106.20(**C-1**), 109.50**, (PhCHO**), 83.20 (**C-2**), 82.76 (**C-3**), 73.40(**C-4**) 72.34 (**C-6**), 69.86 (**C-5**), 67.54 (**OCH_2**). 31.32, 30.88, 30.40, 29.95, 29.78, 29.62, 29.60, 29.58 (**CH_2**) 14.58(**CH_3**) [9][10].



2.2. General procedure of the phase transfer catalysis

A solution of alcohol (20 mmol), alkyl halides (25 mmol), and tetra butyl ammonium bromide (10 mmol) in toluene (100 mL) was vigorously stirred with 50% NaOH solution (40 mL) in 25 ºC for 48h. The phases were separated and the organic layer was washed

vigorously with water, then dried over magnesium sulfate and the solvent was evaporated to furnish the crude product [11].

Synthesis of Methyl-4,6-di-O-benzylidine-2,3-di-O-benzyl-α-D-glucopyranoside 3a Caprylic acid-4,6-di-O-benzylidine-2,3-di-O-benzyl-α-D-glucopyranoside 3b

The compound **3** was synthesis according to the general procedure [2.3.2]. (16.3g, 57.7 mmol) of compound **2**, (11g, 120 mmol) of benzyl chloride, and (1.61g, 5 mmol) tetra butyl ammonium bromide [12], Product **3** the yield (20.2g, 43.63 mmol, 75.6%). m. p. = (183-185) ºC, **3a** Chemical Formula: $\mathbf{C_{28}H_{30}O_6}$, Molecular Weight: **462.54** and **3b** $\mathbf{C_{37}H_{48}O_6}$, Molecular Weight: **588.79**.

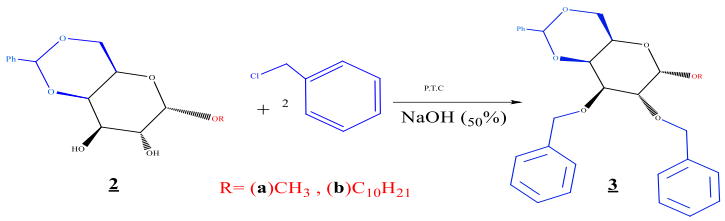
FT-IR peaks = (3029, 2917, 2865, 1487, 1363, 1277) cm^{-1}

^{1}H NMR($CDCl_3$, 500 MHz): δ (ppm) 7.68–7.45(m, **15H**; Ar-H), 5.91(dd, *J*=9.3 Hz, **1H**; H-4), 5.6(s, *J*=10.9 Hz, **1H**; Ph-CH), 5.55(d, *J*=3.5 Hz, **1H**; H-1) 4.66 (d, *J*=10.9 Hz, **1H**; PhCH_2), 4.64 (d, *J*=12.1 Hz, **1H**; PhCH_2), 4.62 (d, *J*=12.2 Hz, **1H**; PhCH_2), 4.6(d, Hz, **1H**; PhCH_2), 3.93(dd, *J*=10.9, 4.9 Hz ,**1H**; H_{ax}-6), 3.81(dd, *J*=10.9, 4.9 Hz, **1H**; H_{eq}-6), 3.79-3.76(m, **2H**; H-2, H-3), 3.44(s, **3H**; OCH_3), 3.38(dd, *J*=10.1, 9.1 Hz, **1H**; H-5).

^{1}H NMR($CDCl_3$, 500 MHz): δ (ppm) 7.70–7.62(m, **15H**; Ar-H), 5.43(dd, *J*=9.3 Hz, **1H**, H-4), 5.6(m, *J*=10.9 Hz, **1H**; Ph-CH), 5.50(d, *J*=3.5 Hz, **1H**; H-1), 4.62(d, *J*=10.9 Hz, **1H**; PhCH_2), 4.60 (d, *J*=12.1 Hz, **1H**; PhCH_2), 4.62 (d, *J*=12.2 Hz, **1H**; PhCH_2), 4.45 (d, Hz, **1H**; PhCH_2), 3.93(dd, *J*=10.9, 4.9 Hz ,**1H**; H H_{ax}-6), 3.81(dd, *J*=10.9, 4.9 Hz, **1H**; H_{eq}-6), 3.79-3.76(m, **2H**; H-2, H-3), 3.38(dd, *J*=10.1, 9.1 Hz, **1H**; H-5), 3.32-2.28(m, **2H**; OCH_2), 1.49-1.45(m **4H**; 2CH_2),1.38-1.25(m **12H**; 6CH_2), 0.88-0.84(m,**3H**; 1CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.52, 137.6 ,137.30 (**3Aromatic C**), 129.62-128.10 (**6 Aromatic CH**), 126.84(**3 Aromatic CH**), 126.4(**4 Aromatic CH**), 125.36(**2Aromatic CH**), 110.2-108.72 **(PhCHO)**,(**C-1**), 76.34(**PhCH_2O**), 75.14(**PhCH_2O**) 74.10(**C-2**), 73.32(**C-3**), 72.00(**C-4**), 69.77(**C-6**), 67.60(**C-5**), 55.8(**OCH_3**) [9], [10].

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.62, 136.34 ,136.30 (**3Aromatic C**), 128.84-127.20 (**6 Aromatic CH**), 126.55(**3 Aromatic CH**), 126.43-125.50(**4 Aromatic CH**), 125.76(**2Aromatic CH**), 109.80 **(PhCHO)**, 105.87(**C-1**), 76.65(**PhCH_2O**), 74.56(**PhCH_2O**) 74.26(**C-2**), 73.83(**C-3**), 71.72(**C-4**), 68.80(**C-6**) , 67.50(**C-5**), 67.24 (**OCH_2**). 31.60, 30.56, 30.30, 29.90, 29.66, 29.42, 29.34, 29.18 (**CH_2**) 14.60 (**CH_3**) [9], [10].



Synthesis of Methyl-2,3-di-O-benzyl-*α*-D-glucopyranoside 4a Caprylic acid-2,3-di-O-benzyl-*α*-D-glucopyranoside 4b

(20g, 43.63 mmol) of compound **3** was dissolved in 150 mL of 1:1 mixture methanol and chloroform, then (0.10 g, 0.6mmol) of toly- sulfonic acid monohydrate was added and the mixture was stirred for 12 hrs. The TLC showed there is no starting material was left. The mixture was washed twice with saturated aqueous sodium carbonate followed by water, dry over magnesium sulfate [13]. The evaporating of chloroform was furnished the crude product which is almost clean. yield reaction (13.2g, 35.3 mmol, 80.8%). m. p. = (157-160) ºC, Chemical Formula: $\mathbf{C_{21}H_{26}O_6}$, Molecular Weight: **374.43** and $\mathbf{C_{30}H_{44}O_6}$, Molecular Weight: **500.68**.

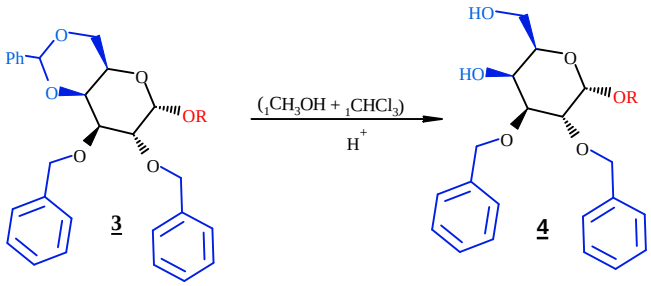
FT-IR peaks = (3318, 2972, 2885, 1482, 1363, 1179) cm^{-1}

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.38 – 7.26 (m, 10H; Ar-H), 5.48 (d, *J*=3.5 Hz, 1H, H-1), 4.80(d, *J*=10.9 Hz, 1H; $PhCH_2$), 4.75 (d, *J*=10.9 Hz, 1H; $PhCH_2$), 4.72(d, *J*=12.1 Hz, 1H; $PhCH_2$), 4.69 (d, *J*=12.2 Hz, 1H; $PhCH_2$) 3.98(dd, *J*=9.3 Hz, 1H, H-4), 3.80(dd, *J*=9.7, 3.6 Hz, 1H; H-2), 3.72-3.66(m, 3H; H-3, H-5, H_{ax}-6), 3.54(dd, *J*=10.9, 4.9 Hz, **1H**; H_{eq}-6), 3.4 (s, 3H; OCH_3).

^{1}H NMR($CDCl_3$, 500 MHz): δ (ppm) 7.30 – 7.18 (m, 10H; Ar-H), 5.45 (d, *J*=3.5 Hz, 1H, H-1), 4.82(d, *J*=10.9 Hz, 1H; $PhCH_2$), 4.76 (d, *J*=10.9 Hz, 1H; $PhCH_2$), 4.74(d, *J*=12.1 Hz, 1H; $PhCH_2$), 4.67 (d, *J*=12.2 Hz, 1H; $PhCH_2$), 4.10 (dd, *J*=9.3 Hz, **1H**, H-4), 3.80(dd, *J*=9.7, 3.6 Hz, 1H; H-2), 3.68-3.62(m, 3H; H-3, H-5, H_{ax}-6) , 3.50(dd, *J*=10.9, 4.9 Hz, **1H**; H_{eq}-6), 3.32(m, **2H**; OCH_2), 1.49-1.45(m **4H**; $2CH_2$),1.38-1.25(m **12H**; $6CH_2$), 0.88-0.84(m,**3H**; $1CH_3$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5 (**2 Aromatic C**), 128.6-127.2 (**10 Aromatic CH**), 107.20 (**C-1**), 83.10 (**C-4**), 81.70 (**C-6**), 76.0 (**C-5**), 73.40 (**PhCH$_2$O**), 72.9 (**PhCH$_2$O**), 69.60 (**C-2**), 68.20 (**C-3**), 55.8 (**OCH$_3$**). [9], [10]

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.80 (**2 Aromatic C**), 128.2-127.00 (**10 Aromatic CH**), 104.43 (**C-1**), 82.10 (**C-4**), 81.70 (**C-6**), 78.00 (**C-5**), 73.50 (**PhCH$_2$O**), 72.80 (**PhCH$_2$O**), 68.60(**C-2**), 67.50 (**OCH$_2$**). 66.20 (**C-3**), 31.60, 30.56, 30.30, 29.90, 29.66, 29.42, 29.34, 29.18 (**CH$_2$**) 14.60 (**CH$_3$**) [9], [10]



R= (**a**)CH_3 , (**b**)$C_{10}H_{21}$

Synthesis of Methyl-2,3-di-O-benzle-4,6-di-cyanomethoxy-α-D-glucopyranoside 5a Caprylic acid -2,3-di-O-benzle-4,6-di-cyanomethoxy-α-D-glucopyranoside 5b

According to the general phase transfer catalyst method, 20 mmol of each of the sugar-bound fatty acid and the methoxy derivatives were reacted with bromoacetonitrile and tetra butyl ammonium bromide (10 mmol) in toluene (100 mL) was vigorously stirred with 50% NaOH solution (40 mL) in 25 ºC for 48h The phases were separated and the organic layer was washed vigorously with water, then dried over magnesium sulfate, and the solvent was evaporated to furnish the crude product [14], [15].

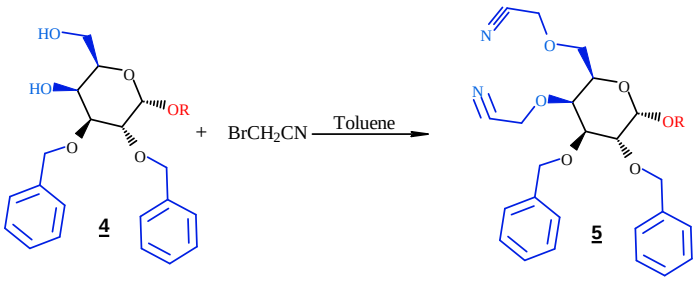
Chemical Formula: **$C_{25}H_{28}N_2O_6$**, Molecular Weight: **452.51** and **$C_{34}H_{46}N_2O_6$**, Molecular Weight: **578.75**.

^{1}H NMR($CDCl_3$, 600 MHz):- δ (ppm), 7.40 – 7.28(m, **10H**; **Ar-H**), 5.60 (d, *J*=3.5 Hz, **1H**, **H-1**), 4.85(d, *J*=10.9 Hz, **1H**; **Ph-CH_2**), 4.84 (d, *J*=10.9 Hz, **1H**; **Ph-CH_2**), 4.80 (d, *J*=12.1 Hz, **1H**; **Ph-CH_2**), 4.77 (d, *J*=12.2 Hz, **1H**; **Ph-CH_2**), 4.66-4.58(m,4H: 2CH_2CN), 3.95(dd, *J*=10.1, 9.1 Hz, **1H**; H-5), 3.9-3.86(m, 2H: **H-2, H-3)**, 3.77 (dd, *J*=10.9, 4.9 Hz ,**1H**; **H_{ax}-6**), 3.58 (dd, *J*=9.3 Hz, **1H**, **H-4**), 3.43 (dd, *J*=10.9, 4.9 Hz, **1H**; H_{eq}-6), 3.82 – 3.80 (m, **4H**; **H-5**, **OCH_2**), 3.38 (s, **3H**; **OCH_3**)

^{1}H NMR($CDCl_3$, 600 MHz):- δ (ppm), 7.40 – 7.28(m, **10H**; **Ar-H**), 5.60 (d, *J*=3.5 Hz, **1H**, **H-1**), 4.85(d, *J*=10.9 Hz, **1H**; **Ph-CH_2**), 4.84 (d, *J*=10.9 Hz, **1H**; **Ph-CH_2**), 4.80 (d, *J*=12.1 Hz, **1H**; **Ph-CH_2**), 4.77 (d, *J*=12.2 Hz, **1H**; **Ph-CH_2**), 4.66-4.58(m,4H: 2CH_2CN), 3.95(dd, *J*=10.1, 9.1 Hz, **1H**; H-5), 3.90-3.86(m, 2H: **H-2, H-3)**, 3.82 – 3.80(m, **4H**; **H-5**, **OCH_2**), 3.77 (dd, *J*=10.9, 4.9 Hz ,**1H**; **H_{ax}-6**), 3.58 (dd, *J*=9.3 Hz, **1H**, **H-4**), 3.43 (dd, *J*=10.9, 4.9 Hz, **1H**; H_{eq}-6), 3.32(m, **2H**; OCH_2), 1.49-1.45(m **4H**; 2CH_2),1.38-1.25(m **12H**; 6CH_2), 0.88-0.84(m,**3H**; 1CH_3). [9], [10]

^{13}C NMR (151 MHz, $CDCl_3$) δ 138.92, 138.20 (**2Aromatic C**), 129.30 , 129.26, 129.20 ,128.90,128.45, 128.37, 128.13, 128.00, 127.88, 127.56 (**10Aromatic CH**), 115.80 (**CN**), 114.46 (**CN**). 108. 2 (**C-1**), 81.22 (**C-4**), 80.87 (**C-6**), 75.60 (**C-5**), 73.64 (**PhCH_2O**) , 73.40 (**PhCH_2O**), 70.73 (**C-2**) , 69.60 (**C-3**), 55.8 (**OCH_3**) , 55.1 (**OCH_2**CN),, 53.6 (**OCH_2**CN)

^{13}C NMR (151 MHz, $CDCl_3$) δ 138.5, 137.80 (**2Aromatic C**), 129.40 , 129.00, 128.70 ,128.60,128.33, 128.00, 127.93, 127.87, 127.48, 127.26 (**10Aromatic CH**), 115.64 (**CN**), 114.42 (**CN**). 105. 00 (**C-1**), 81.30 (**C-4**), 79.70 (**C-6**), 75.20 (**C-5**), 73.60 (**PhCH$_2$O**) , 73.45 (**PhCH$_2$O**), 70.55 (**C-2**) , 69.77 (**C-3**), 55.1 (**OCH$_2$**CN), 53.6 (**OCH$_2$**CN), 67.50 (**OCH$_2$**), 31.60, 30.56, 30.30, 29.90, 29.66, 29.42, 29.34, 29.18 (**CH$_2$**) 14.60 (**CH$_3$**) [9][10]



Synthesis of Methyl-2,3-di-O-benzle-4,6-di-O-ethanamine-α-D-glucopyranoside (6a) Caprylic acid-2,3-di-O-benzle-4,6-di-O-ethanamine-α-D-glucopyranoside (6b)

Selective reduction of polar groups in the presence of other reducible functions can frequently be achieved by an inverse addition method: the reagent is added slowly to the substance to be reduced so that the reagent is never present in excess. Thus by inverse addition –C≡N can be reduced to –CH=NH (normal addition gives –CH_2NH_2). The nitrile (1 gram, 80.7 mmoles) in ether was added to $LiAlH_4$ (3 g, 79 mmoles) in ether (40 ml) and stirred at room temperature overnight. Sodium hydroxide (5 ml, 10% solution) was added at 0 C^0 and after 30 minutes, water (10 mL) was added to give a granular precipitate. The mixture was filtered and the precipitate was washed profusely with ether [16], [17]. The combined, washed and dried organic layers were evaporated "in vacuo" to give the product as an oil (580 mg, 58%).

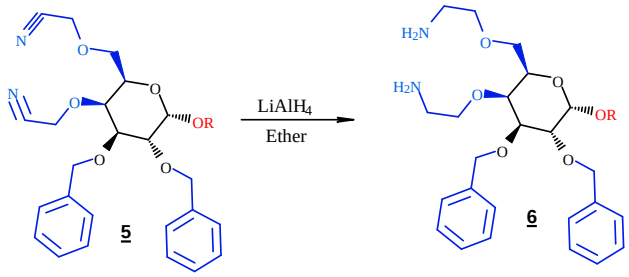
Chemical Formula: **$C_{25}H_{36}N_2O_6$**, Molecular Weight: **460.57** and **$C_{34}H_{54}N_2O_6$**, Molecular Weight: **586.81.**

^{1}H NMR($CDCl_3$, 600 MHz): δ (ppm) 7.43 – 7.30(m, 10H; Ar-H), 5.65(d, J=3.5 Hz, 1H, H-1), 4.88 (d, J=10.9 Hz, 1H; $PhCH_2$), 4.85 (d, J=10.9 Hz, 1H; $PhCH_2$), 4.83 (d, J=12.1 Hz, 1H; $PhCH_2$), 4.79 (d, J=12.2 Hz, 1H; $PhCH_2$), 3.90(dd, J=10.9, 4.9 Hz ,1H; H-5), 3.85-3.81(m, 2H: H-2, H-3), 3.65 – 3.57(m, 5H; H_{ax}-6, $2OCH_2$), 3.45(dd, J=9.3 Hz, 1H, H-4), 3.39 – 3.35(m, 4H; H_{eq}-6, OCH_3), 3.07–2.95(m, 4H;, 2 CH_2NH_2).

^{1}H NMR($CDCl_3$, 600 MHz): δ (ppm) 7.43 – 7.30 (m, 10H; Ar-H), 5.65 (d, J=3.5 Hz, 1H, H-1), 4.88 (d, J=10.9 Hz, 1H; $PhCH_2$), 4.85 (d, J=10.9 Hz, 1H; $PhCH_2$), 4.83 (d, J=12.1 Hz, 1H; $PhCH_2$), 4.79 (d, J=12.2 Hz, 1H; $PhCH_2$), 3.90(dd, J=10.9, 4.9 Hz ,1H; H-5), 3.85-3.81(m, 2H: H-2, H-3), 3.65 – 3.57(m, 5H; H_{ax}-6, $2OCH_2$), 3.45(dd, J=9.3 Hz, 1H, H-4), 3.39 – 3.35(m, 4H; H_{eq}-6,OCH_3), 3.32(m, **2H**; OCH_2R), 3.07–2.95(m, 4H;2 CH_2NH_2), 1.49-1.45(m **4H**; $2CH_2$),1.38-1.25(m **12H**; $6CH_2$), 0.88-0.84(m,**3H**; $1CH_3$).

^{13}C NMR (151 MHz, $CDCl_3$) δ 137.5 **(2 Aromatic C)**, 127.4 – 128.6 **(10 Aromatic CH)** , 107.22 **(C-1)**, 82.50 (**C-4**), 82.10**(C-6)**, 80.34 **(C-5)**, 75.82**(PhCH$_2$O)** , 72.92 **(PhCH$_2$O)** , 72.34 **(C-2)** 71.75 **(C-3)**, 70.3 **(CH$_2$O)** , 55.8 **(OCH$_3$)** , 41.9 **(CH$_2$NH$_2$)** 41.60**(CH$_2$NH$_2$)**. [9][10]

^{13}C NMR (151 MHz, $CDCl_3$) δ 138.5 **(2 Aromatic C)**, 126.64 – 125.80 **(10 Aromatic CH)** , 104.22 **(C-1)**, 82.33 (**C-4**), 81.00 **(C-6)**, 78.70 **(C-5)**, 75.60**(PhCH$_2$O)** , 73.00 **(PhCH$_2$O)** , 72.60 **(C-2)** 72.25 **(C-3)**, 71.3-70.6 **(3OCH$_2$)**, 41.9 **(CH$_2$NH$_2$)** 41.65**(CH$_2$NH$_2$)**. 31.65, 30.46, 30.10, 29.80, 29.66, 29.30, 29.14, 29.00 (**CH$_2$**) 14.80 (**CH$_3$**) [9][10]



Synthesis of Methyl-2,3-di-O-benzle[1,13] dioxa [7]thia[4,10]diaza-15-crownether-*α*-D-glucopyranoside (7a) and Caprylic acid-2,3-di-O-benzle[1,13]dioxa[7]thia[4,10]di-aza-15-crownether-*α*-D-glucopyranoside (7b)

Two reactions were supplied to synthesise macrocyclic derivatives the first included activated by mild acidic medium and the other used the template method to obtain a macrocyclic compound [18]**.**

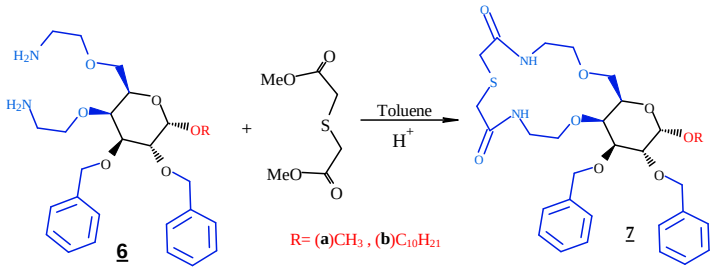
Chemical Formula: **$C_{29}H_{38}N_2O_8S$**, Molecular Weight: 574.69 and **$C_{38}H_{56}N_2O_8S$**, Molecular Weight: 700.93.

^{1}H NMR($CDCl_3$, 600 MHz): δ (ppm) 7.45 – 7.30 (m, 10H; Ar-H), 5.68(d, J=3.5 Hz, 1H, H-1) 4.90(d, *J*=10.9 Hz, 1H; $PhCH_2$), 4.87(d, *J*=10.9 Hz, 1H; $PhCH_2$), 4.85(d, *J*=12.1 Hz, 1H; $PhCH_2$), 4.81 (d, *J*=12.2 Hz, 1H; $PhCH_2$), 3.95(dd, J=10.9, 4.9 Hz ,1H; H-5), 3.88-3.84(m, 2H: H-2, H-3), 3.75-3.69(m, 3H; $2CH_2O$(ax), H_{ax}-6), 3.6 (dd, *J*=9.3 Hz, 1H, H-4), 3.58-3.41 (m, 6H; $2CH_2O$(eq), OCH_3, H_{eq}-6), 3.38 – 3.34 (m, 4H; $2CH_2NH$), 3.32-3.28(m, 4H; $2CH_2S$).

^{1}H NMR($CDCl_3$, 600 MHz): δ (ppm) 7.45 – 7.30 (m, 10H; Ar-H), 5.68(d, J=3.5 Hz, 1H, H-1) 4.90(d, *J*=10.9 Hz, 1H; $PhCH_2$), 4.87(d, *J*=10.9 Hz, 1H; $PhCH_2$), 4.85(d, *J*=12.1 Hz, 1H; $PhCH_2$), 4.81 (d, *J*=12.2 Hz, 1H; $PhCH_2$), 3.95(dd, J=10.9, 4.9 Hz ,1H; H-5), 3.88-3.84(m, 2H: H-2, H-3), 3.75-3.69(m, 3H; $2CH_2O$(ax), H_{ax}-6), 3.6 (dd, *J*=9.3 Hz, 1H, H-4), 3.58-3.46 (m, 6H; $2CH_2O$(eq), OCH_3, H_{eq}-6), 3.40 – 3.36 (m, 4H; $2CH_2NH$), 3.34(m, **2H**; OCH_2R), 3.30-3.26(m, 4H; $2CH_2S$), 1.49-1.45(m **4H**; $2CH_2$),1.38-1.25(m **12H**; $6CH_2$), 0.88-0.84(m,**3H**; $1CH_3$).

^{13}C NMR (151 MHz, $CDCl_3$) δ 171(C=O) , 170.5(C=O) 138.92, 138.20 (**2Aromatic C**), 129.30 , 129.26, 129.20 ,128.90,128.45, 128.37, 128.13, 128.00, 127.88, 127.56 (**10Aromatic CH**), 108.2 (**C-1**), 83.80 (**C-4**), 82.10 (**C-6**), , 77.20 (**C-5**), 73.64 (**Ph-CH_2-O**) ,73.40 (**Ph-CH_2-O**), 70.73 (**C-2**), 69.70 (**C-3**), 68.7 (**OCH_2**), 67.8 (**OCH_2**), , 55.84 (**OCH_3**), 43.4(CH_2NH) **,** 43.1(CH_2NH) **,** 36.2(CH_2S) **,** 36.1(CH_2S) [9], [10].

^{13}C NMR (151 MHz, $CDCl_3$) δ 171(C=O) , 170.5(C=O) 138.92, 138.20 (**2Aromatic C**), 129.30 , 129.26, 129.20 ,128.90,128.45, 128.37, 128.13, 128.00, 127.88, 127.56 (**10Aromatic CH**), 108.2 (**C-1**), 84.60 (**C-4**), 83.84 (**C-6**), 75.10 (**C-5**), 73.62 (**PhCH_2O**) ,73.28 (**PhCH_2O**), 70.60(**C-2**), 70.35(**C-3**) , 69.80-67.72(**3OCH_2**), 43.4(CH_2NH)**,** 43.1(CH_2NH)**,** 36.2(CH_2S)**,** 36.1(CH_2S) 31.65, 30.46, 30.10, 29.80, 29.66, 29.30, 29.14, 29.00 (**CH_2**), 14.80(**CH_3**) [9][10]



Synthesis of Methyl-2,3-di-O-benzle[1,13]dioxa [4,7,10] triaza-15-crownether-*α*-D-glucopyranoside (8a) and Caprylic acid -2,3-di-O-benzle [1,13] dioxa [4,7,10]triaza-15-crownether-*α*-D-glucopyranoside (8b)

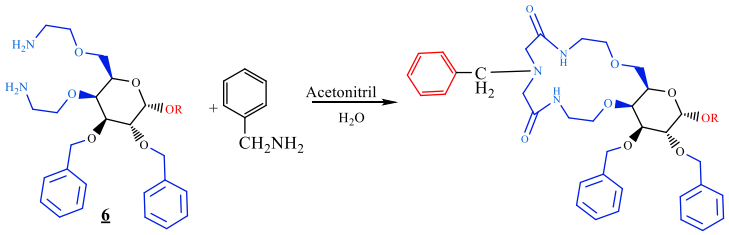
Chemical Formula: **$C_{29}H_{39}N_3O_8$**, Molecular Weight: 557.64 and **$C_{45}H_{63}N_3O_8$**, Molecular Weight: 683.89.

^{1}H NMR($CDCl_3$, 600 MHz): δ (ppm) 7.42 – 7.28(m, 10H; Ar-H), 5.68(d, J=3.5 Hz, 1H, H-1) 4.90(d, *J*=10.9 Hz, 1H; $PhCH_2$), 4.87(d, *J*=10.9 Hz, 1H; $PhCH_2$), 4.85(d, *J*=12.1 Hz, 1H; $PhCH_2$), 4.81(d, *J*=12.2 Hz, 1H; $PhCH_2$), 3.90(dd, J=10.9, 4.9 Hz ,1H; H-5), 3.88-3.84(m, 2H: H-2, H-3), 3.78-3.72(m, 3H; 2CH_2O(ax), H_{ax}-6), 3.60(dd, *J*=9.3 Hz, 1H, H-4), 3.58-3.40(m, 10H; 2$CH_2O_{(eq)}$,2CH_2NH, OCH_3, H_{eq}-6), 3.38 – 3.34(m, 4H; 2CH_2NH).

^{1}H NMR($CDCl_3$, 600 MHz): δ (ppm) 7.45 – 7.30(m, 10H; Ar-H), 5.68(d, J=3.5 Hz, 1H, H-1) 4.90(d, *J*=10.9 Hz, 1H; $PhCH_2$), 4.87(d, *J*=10.9 Hz, 1H; $PhCH_2$), 4.85(d, *J*=12.1 Hz, 1H; $PhCH_2$), 4.81 (d, *J*=12.2 Hz, 1H; $PhCH_2$), 3.95(dd, J=10.9, 4.9 Hz ,1H; H-5), 3.88-3.84(m, 2H: H-2, H-3), 3.75-3.69(m, 3H; 2CH_2O(ax), H_{ax}-6), 3.6 (dd, *J*=9.3 Hz, 1H, H-4), 3.58-3.41 (m, 6H; 2CH_2O(eq),2CH_2NH, OCH_3, H_{eq}-6), 3.34(m, 2H; OCH_2R), 3.29-3.25(m, 4H; 2CH_2NH), 1.55-1.49(m 4H; 2CH_2),1.41-1.28(m 12H; 6CH_2), 0.9-0.86(m,3H; 1CH_3).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.6(**C**=O) , 168.5(**C**=O) 138.2, 138 (**2Aromatic C**), 128.80 , 128.76, 128.20 ,128.00,127.85, 127. 7, 127.3, 127.05, 126.98, 126.88 (**10Aromatic CH**), 107.8 (**C-1**), 80.20 (**C-4**), 80.05 (**C-6**), 79.20 (**C-2**), 77.80 (**C-3**) 73.54 (**PhCH$_2$O**) ,73.35 (**PhCH$_2$O**), 72.05 (**PhCH$_2$N**), , 71.10 (**C-5**) 69.7[(**C-6**) , (**OCH$_2$**)], 67.7 (**OCH$_2$**), , 55.84 (**OCH$_3$**), 53.5(CH$_2$NH) **,** 53.4(CH$_2$NH) **,** 43.8(**C**H$_2$NHCO) **,** 43.5(**C**H$_2$NHCO) [9][10]**.**

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.6(**C**=O) , 168.5(**C**=O) 139.2 -138.18 (**3Aromatic C**), 128.34-126.88 (**15Aromatic CH**), 107.75 (**C-1**), 78.80 (**C-4**), 78.10 (**C-6**), 76.00 (**C-2**), 76.20 (**C-3**), 74.55 (**PhCH$_2$O**) ,74.45 (**PhCH$_2$O**), 71.45 (**PhCH$_2$N**), 70.32(**C-5**), 69.7[(**C-5**),(**CH$_2$O**)], 67.7(**OCH$_2$**), 53.50(**C**H$_2$NH) **,**53.41(**C**H$_2$NH)**,** 43.8(**C**H$_2$NHCO)**,** 43.5(**C**H$_2$NHCO) **,**31.65, 30.46, 30.10, 29.80, 29.66, 29.30, 29.14, 29.00 (**CH$_2$**) 14.80 (**CH$_3$**) [9], [10]



Synthesis of Methyl[1,13]dioxa[7]thia[4,10]diaza-15-crownether-α-D-glucopyranoside (9a) and Caprylic acid[1,13]dioxa[7]thia[4,10]diaza-15-crownether-α-D-glucopyranoside (9b)

Compound 8 (a,b) (5 g, 7.8 mmol) was dissolved in dry methanol (100 mL) in a three-necked round bottom flask (100 mL) and 5% palladium on charcoal (1 g, 9.4 mmol) and glacial acetic acid (5ml) was added. After flashing out the air with a stream of hydrogen gas in the fume hood. The reaction was stirred under hydrogen pressure(10 atm) using a hydrogen bump reactor for 24 hrs [19], [20]. The palladium catalyst was filtered off and evaporated the solvent to obtain compound 9 (a,b) as a light-yellow syrup (3.25.g,7.00 mmol, 88.2%).

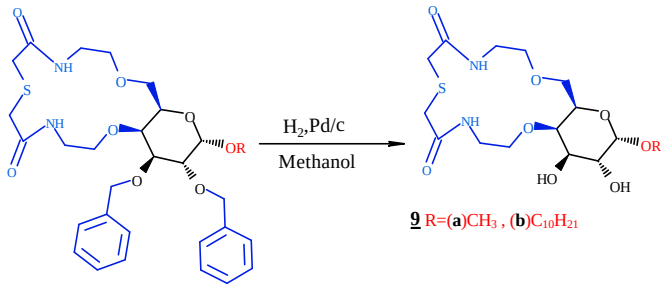
Chemical Formula: **C$_{15}$H$_{26}$N$_2$O$_8$S**, Molecular Weight: **394.44** and **C$_{24}$H$_{44}$N$_2$O$_8$S**, Molecular Weight: **520.68**.

^{1}H NMR($CDCl_3$, 600 MHz): δ (ppm) 5.72(d, J=3.5 Hz, 1H, H-1), 4.02(dd, J=10.9, 4.9 Hz ,1H; H-5), 3.94-3.89(m, 2H: H-2, H-3), 3.78-3.72(m, 3H; 2CH$_2$O(ax), H$_{ax}$-6), 3.65(dd, *J*=9.3 Hz, 1H, H-4), 3.62-3.45 (m, 10H; 2CH$_2$O$_{(eq)}$,2CH$_2$NH, OCH$_3$, H$_{eq}$-6), 3.39 – 3.32(m, 4H; 2CH$_2$NH).

^{1}H NMR($CDCl_3$, 600 MHz): δ (ppm) 5.68(d, J=3.5 Hz, 1H, H-1) 4.05(dd, J=10.9, 4.9 Hz ,1H; H-5), 3.95-3.90(m, 2H: H-2, H-3), 3.75-3.70(m, 3H; 2CH$_2$O(ax), H$_{ax}$-6), 3.64 (dd, *J*=9.3 Hz, 1H, H-4), 3.60-3.55(m, 4H; 2CH$_2$S), 3.50-3.33 (m, 6H; 2CH$_2$O(eq),2CH$_2$NH, OCH$_3$, H$_{eq}$-6), 3.34(m, 2H; OCH$_2$R), 1.50-1.44(m 4H; 2CH$_2$),1.41-1.28(m 12H; 6CH$_2$), 0.87-0.83(m,3H; 1CH$_3$).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172(C=O) , 171.5(C=O) 109.2 (**C-1**), 86.20 (**C-2**), 83.9 (**C-3**), 78.84 (**C-4**),78.70- (**C-6**), 69.7-68.8 [(**C-5**), (**OCH$_2$**)] , 67.7 (O**CH$_2$**) , 55.8 (**OCH$_3$**) ,43.4 (**CH$_2$**NH) 43.1 (**CH$_2$**NH) 36.2(**CH$_2$**S) , 36.1(**CH$_2$**S)**.** [9], [10]

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4(C=O) , 171.35(C=O) 108.2 (C-1), 85.66 (C-2), 83.80 (C-3), 78.80 (C-4),78.67(C-6), 69.5-69.0[(C-5),(OCH$_2$), 67.7(2CONH) , 43.4 (CH$_2$NH), 43.1 (CH$_2$NH) ,36.2(CH$_2$S) , 36.1(CH$_2$S). 31.65, 30.46, 30.10, 29.80, 29.66, 29.30, 29.14, 29.00 (CH$_2$) 14.80 (CH$_3$) [9][10]



9 R=(**a**)CH_3 , (**b**)$C_{10}H_{21}$

Synthesis of Methyl [1,13] dioxa[4,7,10]triaza-15-crownether-*α*-D-glucopyranoside 10a and Caprylic acid[1,13]dioxa[4,7,10]triaza-15-crownether-*α*-D-glucopyranoside 10b

Chemical Formula: 10a **$C_{15}H_{27}N_3O_8$**, Molecular Weight: **377.39** 10b **$C_{24}H_{45}N_3O_8$**, Molecular Weight: **503.64**.

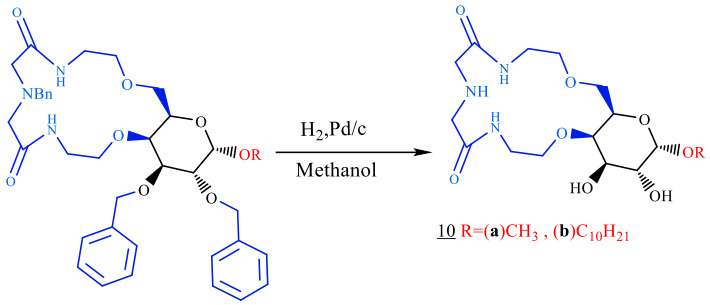
^{1}H NMR($CDCl_3$, 600 MHz): δ (ppm) 5.72(d, J=3.5 Hz, 1H, H-1), 4.02(dd, J=10.9, 4.9 Hz ,1H; H-5), 3.94-3.89(m, 2H: H-2, H-3), 3.78-3.72(m, 3H; 2CH$_2$O(ax), H$_{ax}$-6), 3.65(dd, *J*=9.3 Hz, 1H, H-4), 3.62-3.45 (m, 10H; 2CH$_2$O$_{(eq)}$,2CH$_2$NH, OCH$_3$, H$_{eq}$-6), 3.39 – 3.32(m, 4H; 2CH$_2$NH).

^{1}H NMR($CDCl_3$, 600 MHz): δ (ppm) 5.78(d, J=3.5 Hz, 1H, H-1) 3.98(dd, J=10.9, 4.9 Hz ,1H; H-5), 3.93-3.87(m, 2H: H-2, H-3), 3.74-3.70(m, 3H; 2CH$_2$O(ax), H$_{ax}$-6), 3.64(dd, *J*=9.3 Hz, 1H, H-4),3.58-3.45 (m, 6H; 2CH$_2$O(eq),2CH$_2$NH, OCH$_3$, H$_{eq}$-6), 3.40(m, 2H; OCH$_2$R), 3.33-3.28(m, 4H; 2CH$_2$NH)1.50-1.44(m 4H; 2CH$_2$),1.41-1.28(m 12H; 6CH$_2$), 0.87-0.83(m,3H; 1CH$_3$).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.8(C=O) , 168.5(C=O) 109.2 (**C-1**), 82.20 (**C-4**), 78.9 (**C-5**), 74.8 (**C-2**),74.7 (**C-3**), 69.7 (**C-6**), 68.20(**OCH$_2$**), 67.7 (**OCH$_2$**) , 55.8 (**OCH$_3$**) , 52.5 2(CO**C**H$_2$NH),43.8 (**CH$_2$**NH) 43.5 (**CH$_2$**NH) **[9][10].**

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.6(C=O) , 168.5(C=O) 108.2 (C-1), 82.20 (C-2), 79.2 (C-3), 77.8 (C-4), 74.77(C-6), 69.7(C-5), 68.20-67.7(3OCH$_2$), 52.5-52.2(2CONH), 43.8(CH$_2$NH)

43.5 (CH_2NH), 31.65, 30.46, 30.10, 29.80, 29.66, 29.30, 29.14, 29.00 (8$\underline{C}H_2$) 14.80 ($\underline{C}H_3$) [9], [10].



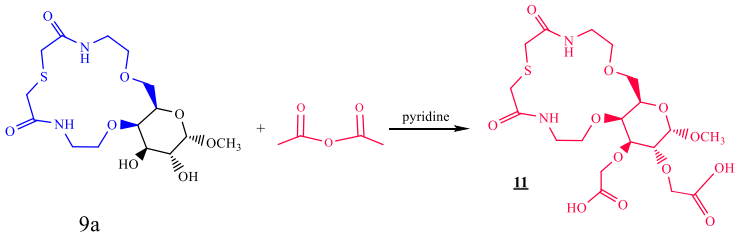
Methyl-2,3-di-O-acetic acid-[1,13]dioxa[7]thia[4,10]diaza-15-crownether-α-D-glucopyranoside (MODDCEGln) 11

The compound (**9a, 9b)** was reacted with acetic anhydride in pyridine to produce the compounds in good yield. The acetylated free hydroxyl on the sugar is not only to get new compounds but also a good method to reduce the polarity of the compounds [21], [22] before subjected them to column chromatography to get pure compound. The compound **11** and **12** was showed in the FT-IR technique that the disappearance of O-H stretching vibration at 3300 cm^{-1}, and appear the strong peak at the 1748 cm^{-1} for the carbonyl group of acetate.

Chemical Formula: 11 $C_{19}H_{30}N_2O_{12}S$, Molecular Weight: **510.51**.

^{1}H NMR($CDCl_3$, 600 MHz): δ (ppm) 5.82(d, J=3.5 Hz, 1H, H-1), 4.61-4.55(m, 4H;CH_2COOH), 3.96(dd, J=10.9, 4.9 Hz ,1H; H-5), 3.85-3.80(m, 2H: H-2, H-3), 3.75-3.71(m, 4H; 2$CH_2O_{(eq)}$,) 3.66-3.62(m, 3H;2CH_2O(ax), H_{ax}-6), 3.60(dd,*J*=9.3Hz,1H,H-4), 3.45-3.31(m,10H;2$CH_2O_{(eq)}$), 2CH_2NH, OCH_3, H_{eq}-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.73 (2$\underline{C}OOH$), 169.47(2$\underline{C}ONH$), 97.33 ($\underline{C}$-1), 79.58 ($\underline{C}$-4), 78.82 ($\underline{C}$-2), 72.40 ($\underline{C}$-3), 72.07($\underline{C}$-5), 71.89 ($\underline{C}$-6) , 70.35($\underline{C}H_2O$), 70.29,70.12 (2$\underline{C}H_2COOH$), 62.37($\underline{C}H_2O$), 55.32($O\underline{C}H_3$), 40.76,40.72(2$\underline{C}H_2NH$) ($\underline{C}H_2S$), 31.56, 31.45($\underline{C}H_2S$) [9], [10].



Caprylic acid-2,3-di-O-acetic acid[1,13]dioxa[4,7,10]triaza-15-crownether-α-D-glucopyranoside 12

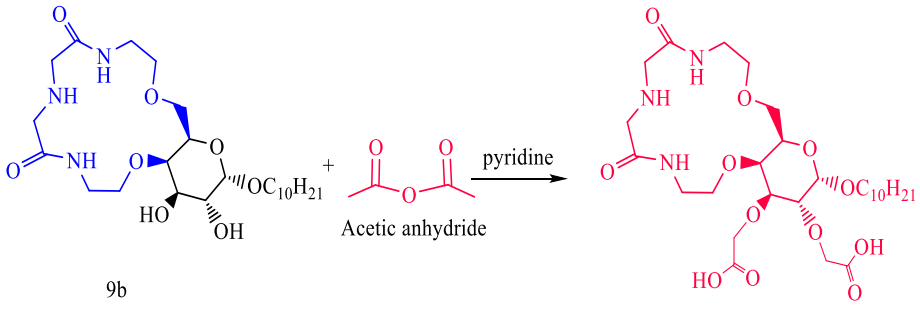
Chemical Formula: **12** $C_{28}H_{49}N_3O_{12}$, Molecular Weight: **619.71**.

^{1}H NMR($CDCl_3$, 600 MHz): δ (ppm) 5.77(d, J=3.5 Hz, 1H, H-1), 4.66-4.60(m, 4H;CH_2COOH), 4.02(dd, J=10.9, 4.9 Hz ,1H; H-5), 3.96-3. 92(m, 2H: H-2, H-3), 3.78-3.72(m, 3H; 2CH_2O(ax),

H_{ax}-6), 3.65(dd, *J*=9.3 Hz, 1H, H-4), 3.62-3.45 (m, 10H; 2C$H_2O_{(eq)}$,2CH_2NH, OCH_3, H_{eq}-6), 3.39 – 3.32(m, 4H; 2CH_2NH).

^{13}CNMR (151 MHz, $CDCl_3$) δ 172.24 172.15 (2COOH), 170.81, 170.57(2CONH), 104.08 (C-1), 82.84(C-2), 79.72(C-3), 77.18(C-4), 76.23(C-6), 72.90 (C-5), 71.02,70.26(2CH_2), 62.25 (2CH_2COOH), 52.83 (OCH_2), 39.54, 39.41, 38.40, 38.30 (4CH_2NH), 32.0,31.42, 31.30, 31.10, 30.99 , 29.82 , 28.95, 26.74 (8CH_2) ,14.24 (CH_3) [9][10].

Chemical Formula: $C_{28}H_{49}N_3O_{12}$
Molecular Weight: 619.71



9b

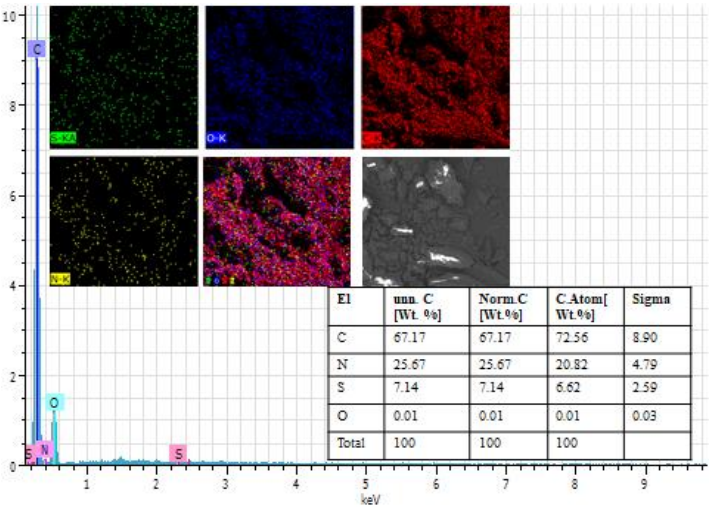
12

3. Results and Discussion

3.1. Study morphology Field-emission scanning electron microscopy (FESEM) and electron destructive x-ray (EDX)

A pyronside sulphar and pyronoside compound has been synthesized and characterized by EDX analysis. The compound was found to be composed of carbon, oxygen, and nitrogen, with trace amounts of sulphar. EDX was used for the elemental analysis of the (compound 11and 12) which were used for nitrogen, Carbone and sulphar in map structure. The spectral analyses shows the sulphar had a higher value (2.33 % weight) in comparison with compound 12 (0.01 %) Figure 1 [23].

(A)



El	unn. C [Wt. %]	Norm.C [Wt.%]	C.Atom[Wt.%]	Sigma
C	67.17	67.17	72.56	8.90
N	25.67	25.67	20.82	4.79
S	7.14	7.14	6.62	2.59
O	0.01	0.01	0.01	0.03
Total	100	100	100	

(B)

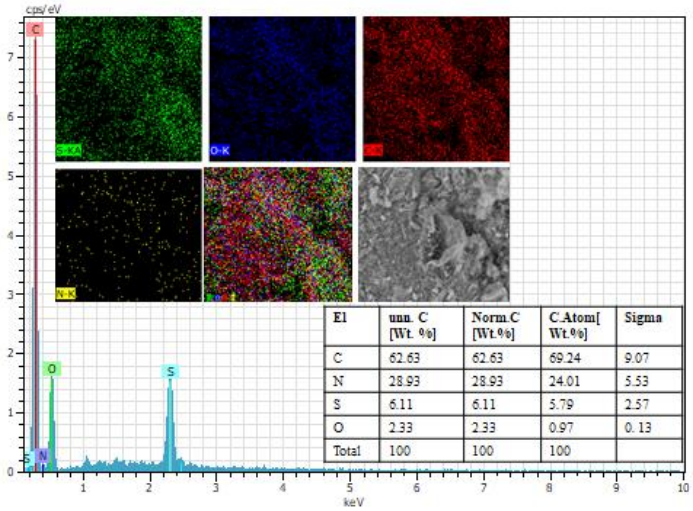


Figure 1. EDX analysis of (A) compound 11 and (B) compound 12

Field-emission scanning electron microscopy was used to analyze the morphology (FESEM). Figure 2 show FESEM images of the 11 and 12 compounds, respectively. The 11 displayed a smooth plated surface with a uniform shape, which may be related to the aggregation of structural crystal interactions in a uniform distribution. While Figure 12 showed rods that may be referred to as increasing the liner chain [24].

(A) (B)

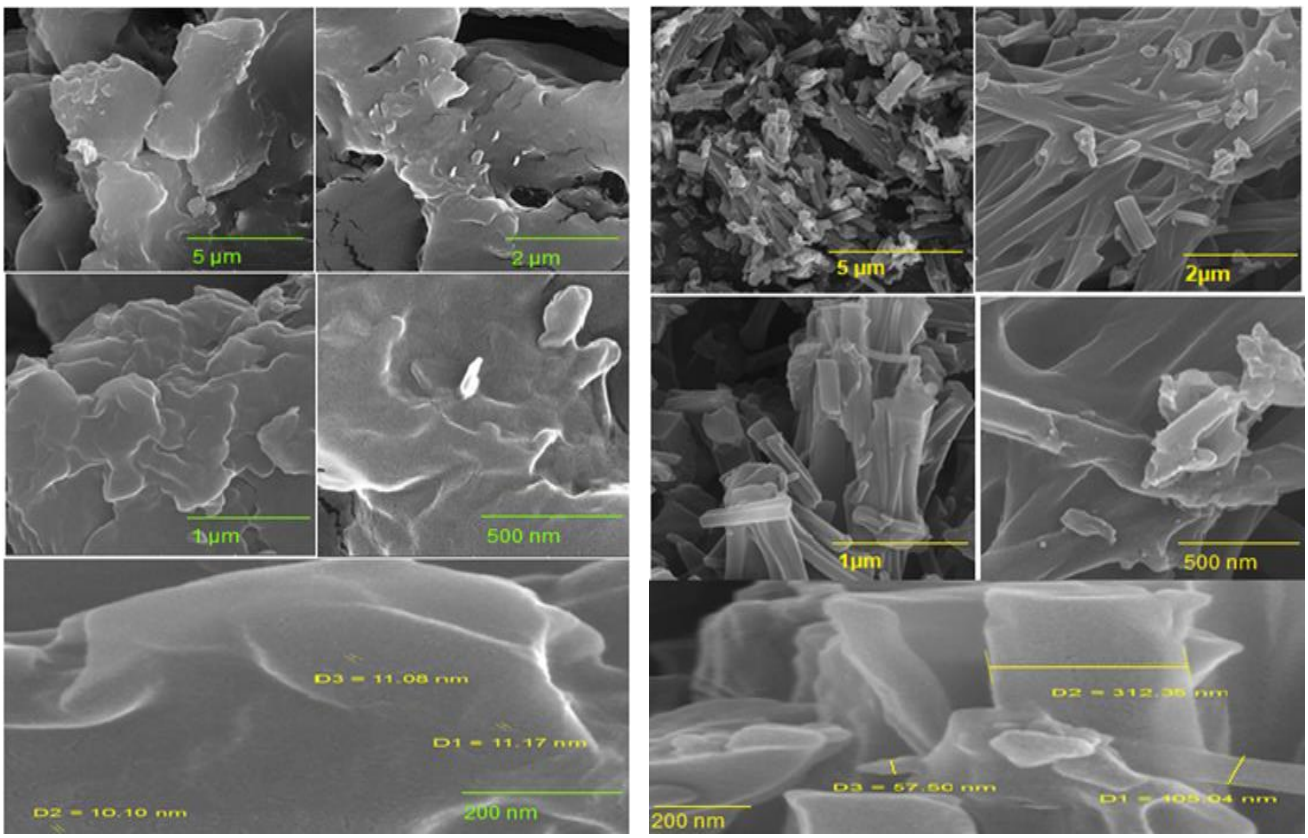


Figure 2. FESEM image of (A) 11 and (B) 12

3.2. X-ray diffraction (XRD)

In Figure 3, the XRD patterns of 12 and 11 compounds are shown by intensity versus diffraction peak angle (2 theta). At two angles, the diffracted intensities ranged from 0 to 80. The 510's XRD patterns revealed two primary distinctive peaks at 2 = 23.2 and 42.00. The observed widening and noise were most likely caused by structural modifications from pure 11. The presence of high peaks typical of sulfur, as well as a lack of clarity as in the crystalline form, supports the probability that the element sulfur is not distributed and generated in the form of a crystalline phase in compound 11 [25]. When it comes to compound 12, The curve between the angles (20–50) was found to be unique, as the nitrogen peaks between the angles (20,25,40) demonstrated the existence of the nitrogen element within the crystal lattice of the compound and not outside it. The x-ray curve shows the amorphous dispersion of the molecule, indicating the presence of carbon atoms bonded to each other inside the crystal lattice. The curve was examined in relation to the crystallinity index value. As shown in Table 1, the curve is separated into four sections with ranges of (5-20), (20-40), (40-60), and (60-80). They observe a congruence between the two produced compounds, with a difference in the angles contained between (20–60), indicating the influence of the sulfur element inside the crystal and its absence outside the crystal. The crystalline index 530 has a higher CI (13.41%) than the crystalline index 610 (13.03%). This means that the crystalline index 530 is more dominant in the sample. The FWHM (full width at half maximum) for both crystalline indices is relatively narrow, indicating that the peaks are well-defined. The CI% for both crystalline indices is relatively high, indicating that the peaks are significant. Based on these results, it is likely that the sample contains a higher proportion of crystalline index compound 11 than crystalline index compound 12. The narrow FWHMs for both crystalline indices also indicate that the peaks are well-defined and significant [26].

$$Crystalline\ Index\ (CI)\ \frac{Area\ of\ all\ crystalline\ peak}{Area\ of\ all\ crystalline\ and\ amorphouse\ peak}$$

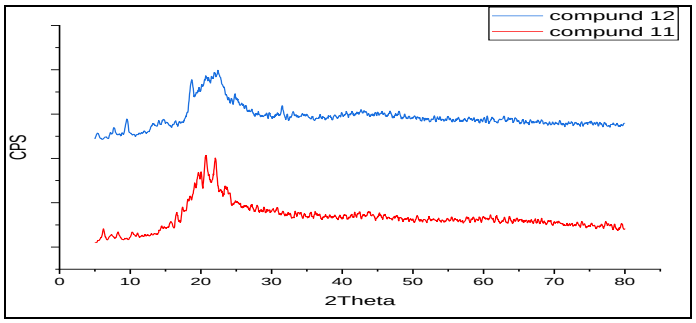


Figure 3. XRD compound 11 and 12

Table 1. Crystalline index (CI), (CI%) of the compound 11 and 12 calculated by area peak

Compound	Angle	Area of peak	All peak	CI	CI %	FWHM
11	**5-20**	566.61979	4223.1651	0.134169	13.41695	17.38629
	20- 40	1704.06145	4223.1651	0.403503	40.35034	4.35015
	40-60	1104.30978	4223.1651	0.261489	26.14887	37.17592
	60-80	899.75129	4223.1651	0.213051	21.30514	20.33804
12	**5-20**	483.38141	3709.1082	0.130323	13.03228	2.84914
	20- 40	1436.10923	3709.1082	0.387185	38.71845	5.98015
	40-60	1020.75291	3709.1082	0.275202	27.52017	26.15623
	60-80	764.74571	3709.1082	0.20618	20.61805	26.51066

3.3. Application

Using the (MTT) Thiazolyl Blue Tetrazolium Bromide method, various concentrations of the 11 and 12 compounds were determined for cytotoxicity towards their PC3 and WRL68cell cultures. PC3 and WRL68 cells were cultured overnight on a 96-well plate at 37°C, 5% CO_2, and 88% humidity. The total quantity of DEMEM supplemented medium and chemical supernatant used was 200 microL, with final concentrations of 0.5 to 3 mg/L.

The plate was incubated at 37°C with 5% CO_2 for three days [27]. Following incubation, debris and dead cells were washed away three times with new media. Each well received 20 L of MTT solution (5 mg/mL MTT in PBS buffer) and was shaken for 5 minutes at 150 rpm to properly mix the MTT into the medium. The cells were cultured for 3-5 hours at 37°C with 5% CO_2 to allow viable cells to metabolize MTT. At least 200 L of dimethylsulfoxide (DMSO) was added to each well and agitated in centrifuge for 5 minutes at 150 rpm before calculating cell viability by subtracting optical density at 630 nm from optical density at 570 nm [28]. The proportion of viable cells was measured by comparing them to control cells (without the addition of the produced chemicals to the cells) using the following equation: (A) test/(A) control 100.

Based on the Table 2, it can be observed that both compounds 11 and 12 exhibited concentration-dependent effects on the PC3 and WRL68 cell lines. In general, the IC50 values for both compounds were higher in the WRL68 cells compared to the PC3 cells, indicating a greater sensitivity of the PC3 cells to the compounds. For compound 11, the bottom and top values for the PC3 cells were 37.83 and 95.99, respectively, while those for the WRL68 cells were 66.63 and 95.71. The logIC50 values were 2.053 for the PC3 cells and 2.378 for the WRL68 cells, and the Hill slope values were -2.771 and -2.897, respectively. The IC50 values for the PC3 and WRL68 cells were 112.9 and 238.6, respectively, and the span values were 58.16 for the PC3 cells and 29.08 for the WRL68 cells. For compound 12, the bottom and top values for the PC3 cells were 11.54 and 133.6, respectively, while those for the WRL68 cells were 64.87 and 96.09. The logIC50 values were 1.387 for the PC3 cells and 2.212 for the WRL68 cells, and the Hill slope values were -0.5481 and -3.990, respectively.

The IC50 values for the PC3 and WRL68 cells were 24.38 and 163.0, respectively, and the span values were 122.1 for the PC3 cells and 31.23 for the WRL68 cells.

Overall, the data suggest that both compounds have selective cytotoxic effects on the PC3 cells compared to the WRL68 cells, and that the compounds may have potential as therapeutic agents for prostate cancer. However, further studies are needed to investigate the mechanism of action of the compounds on the cancer cells and to determine their efficacy in vivo [29].

Based on the results of the study, compound 11 appears to have a greater effect on prostate cancer cells (PC3) compared to compound 12. At the highest concentration tested (400 μM), compound 11 showed a mean percentage inhibition of 95.72% in PC3 cells, while compound 12 showed a mean percentage inhibition of 33.29% at the same concentration. Furthermore, the IC50 value for compound 11 in PC3 cells was 112.9 μM, while the IC50 value for compound 12 was 24.38 μM, indicating that compound 12 is less potent in inhibiting the growth of PC3 cells. These results suggest that compound 11 may have greater potential as a therapeutic agent for prostate cancer Figure 4 [30], [31].

Table 2. Mean and Standard Deviation of 11 and 12 Concentrations at Different Concentrations of Compound in PC3 and WRL68 Cell Lines

Conc.mg/l	Compound 11				Compound 12			
	PC3		WRL68		PC3		WRL68	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
400.0	39.35	4.78	71.95	0.81	33.29	6.75	65.70	3.65
200.0	48.03	2.55	84.80	1.20	40.55	2.12	74.46	0.85
100.0	71.49	3.40	93.60	2.10	50.62	8.99	92.13	1.56
50.00	90.70	3.18	95.33	1.18	59.72	5.32	96.18	1.25
25.00	95.72	0.81	95.22	0.82	73.40	4.48	96.95	1.14
12.50	95.18	1.28	95.95	1.03	82.79	1.82	94.91	2.20
6.25	95.95	0.53	95.95	0.20	94.57	1.05	96.10	0.48

Table 3. Best-Fit Parameters for Non-Linear Regression Models of PC3 and WRL68 Cell Lines

	Compound 11		Compound 12	
	PC3	WRL68	PC3	WRL68
Alternative hypothesis	Different curve for each data set		Different curve for each data set	
P value	<0.0001		<0.0001	
Conclusion (alpha = 0.05)	Reject null hypothesis		Reject null hypothesis	
Preferred model	Different curve for each data set		Different curve for each data set	
F (DFn, DFd)	175.9 (4, 34)		284.8 (4, 34)	
Different curve for each data set				
Best-fit values				
Bottom	11.54	64.87	37.83	66.63
Top	133.6	96.09	95.99	95.71
LogIC50	1.387	2.212	2.053	2.378

Hill Slope	-0.5481	-3.990	-2.771	-2.897
IC50	24.38	163.0	112.9	238.6
Span	122.1	31.23	58.16	29.08

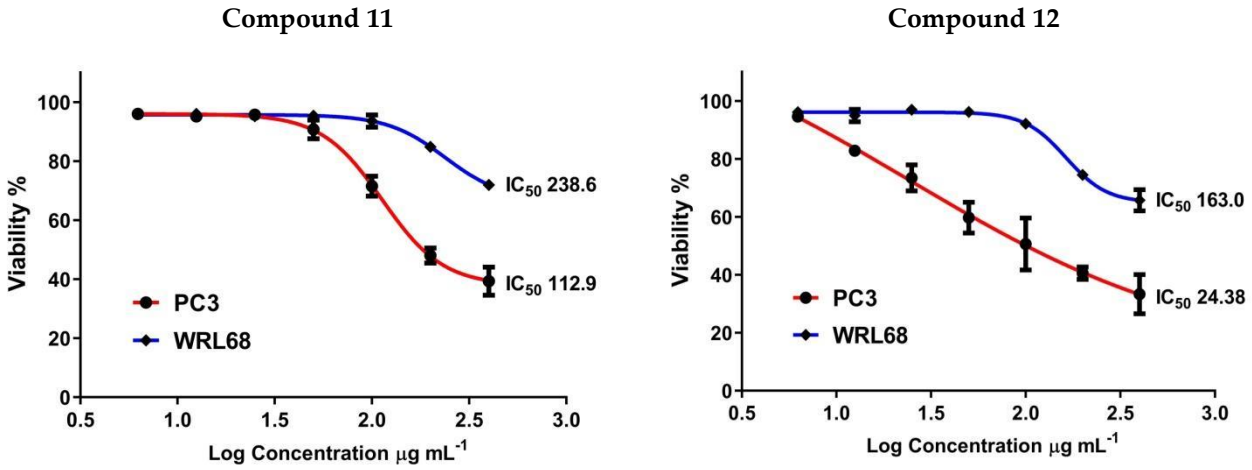


Figure 4. Results of an MTT assay to measure the anticancer activity of a compound in two cell lines, PC3 and WRL68

4. Conclusion

Because of their special qualities, cyclic compounds have drawn interest from a wide range of disciplines. Cyclic compounds, such as crown ethers, cryptands, and calixarenes, have found several uses in various fields, including medication delivery systems and chemical sensors. Cyclic peptides' improved stability and bioavailability have made them promising candidates for the treatment of a number of illnesses. The synthesis and characterisation of -methyl 4,6-benzylidene-2,3-di-O-benzyl-D-glucopyranoside, a pyranoside molecule, are the main topics of this work. Phase transfer catalysis was used to accomplish this. Three different NMR spectroscopies were used to evaluate the produced compound: 1H, 13C, and FT-IR. Additionally, EDX analysis and field-emission scanning electron microscopy were used to examine the compound's shape and elemental makeup. The study's findings add to the possible applications Compounds -methyl 4,6-benzylidene-2,3-di-O-benzyl-D-glucopyranoside were tested against two cancer cell lines to determine their anticancer potential. WRL68 (normal liver cells) and PC3 (prostate cancer cells) In comparison to compound 11, compound 12 seems to have a stronger effect on prostate cancer cells (PC3). Compound 12 had a mean percentage inhibition of 95.72% in PC3 cells at the highest dose tested (400 μM), whereas compound 11 demonstrated a mean percentage inhibition of 33.29% at the same concentration. Additionally, compound 12's IC50 value in PC3 cells was 112.9 μM, but compound 11's IC50 value was 24.38 μM, suggesting that compound 11's ability to block PC3 cell growth is less strong. Based on these findings, compound 12 could be a more promising treatment agent for prostate cancer.

REFERENCES

[1] F. Ullah *et al.*, "Fluorescent and Phosphorescent Nitrogen-Containing Heterocycles and Crown Ethers: Biological and Pharmaceutical Applications," *Molecules*, vol. 27, no. 19, p. 6631, 2022.

[2] O. Özbek, Ö. Isildak, M. B. Gürdere, and A. Cetin, "The use of crown ethers as sensor material in potentiometry technique.," *Organic Communications*, vol. 14, no. 3, 2021.

[3] A. Carvalho, P. M. Ferreira, and J. A. Martins, "New 2, 6-Bis (5-phenyloxazolyl) pyridine Ligands for Luminescent LnIII Complexes," *Chemistry Proceedings*, vol. 12, no. 1, p. 56, 2022.

[4] N. M. Helmy and K. Parang, "Cyclic Peptides with Antifungal Properties Derived from Bacteria, Fungi, Plants, and Synthetic Sources," *Pharmaceuticals*, vol. 16, no. 6, p. 892, 2023.

[5] H. Wei *et al.*, "Bioinspired porphyrin–peptide supramolecular assemblies and their applications," *Journal of Materials Chemistry B*, vol. 10, no. 45, pp. 9334–9348, 2022.

[6] T. A. Ramelot, J. Palmer, G. T. Montelione, and G. Bhardwaj, "Cell-permeable chameleonic peptides: Exploiting conformational dynamics in de novo cyclic peptide design," *Current Opinion in Structural Biology*, vol. 80, p. 102603, 2023.

[7] G. N. Maity *et al.*, "Structural studies of a water insoluble β-glucan from Pleurotus djamor and its cytotoxic effect against PA1, ovarian carcinoma cells," *Carbohydrate polymers*, vol. 222, p. 114990, 2019.

[8] J. Xie and N. Bogliotti, "Synthesis and Applications of Carbohydrate-Derived Macrocyclic Compounds," 2014, doi: 10.1021/cr400035j.

[9] P. S. Kalsi, *Spectroscopy of organic compounds*. New age international, 2007.

[10] R. M. Silverstein, F. X. Webster, D. J. Kiemle, and D. L. Bryce, "Spectrometric identification of organic compounds," in *Spectrometric identification of organic compounds*, 2015, p. 455.

[11] M. Zeng, C.-L. Liu, and K. R. Wilson, "Catalytic Coupling of Free Radical Oxidation and Electrophilic Chlorine Addition by Phase-Transfer Intermediates in Liquid Aerosols," *The Journal of Physical Chemistry A*, vol. 126, no. 19, pp. 2959–2965, 2022.

[12] E. V Dehmlow, "Advances in Phase-Transfer Catalysis [New synthetic methods (20)]," *Angewandte Chemie International Edition in English*, vol. 16, no. 8, pp. 493–505, 1977.

[13] N. É. Byramova, M. V Ovchinnikov, L. V Backinowsky, and N. K. Kochetkov, "Selective removal of O-acetyl groups in the presence of O-benzoyl groups by acid-catalysed methanolysis," *Carbohydrate research*, vol. 124, no. 1, pp. C8–C11, 1983.

[14] K. J. Sabah, N. I. Zahid, and R. Hashim, "Synthesis of new chiral macrocycles-based glycolipids and its application in asymmetric Michael addition," *Research on Chemical Intermediates*, vol. 47, pp. 2653–2667, 2021.

[15] Y. Zhan *et al.*, "One-step selective dehydrogenation of cyclic hemiacetal sugars toward to their chiral lactones," *Chinese Chemical Letters*, vol. 34, no. 4, p. 107677, 2023.

[16] D. Seebach, A. K. Beck, and D. J. Bierbaum, "The world of β-and γ-peptides comprised of homologated proteinogenic amino acids and other components," *Chemistry & biodiversity*, vol. 1, no. 8, pp. 1111–1239, 2004.

[17] V. K. Ahluwalia, "Different Types of Reducing Agents," in *Reduction in Organic Synthesis*, Springer, 2023, pp. 3–53.

[18] E. Marsault and M. L. Peterson, "Macrocycles are great cycles: applications, opportunities, and challenges of synthetic macrocycles in drug discovery," *Journal of medicinal chemistry*, vol. 54, no. 7, pp. 1961–2004, 2011.

[19] L. T. Nguyen, H. Le Tran, P. T. Mai, V. B. Duong, L.-T. T. Nguyen, and H. T. Nguyen, "Poly (L-glutamic acid) via catalytical hydrogenation for the fabrication of carbon nanotube nanocomposites," *Materials Research*, vol. 24, p. e20200321, 2021.

[20] B. Elamin, G. M. Anantharamaiah, G. P. Royer, and G. E. Means, "Removal of benzyl-type protecting groups from peptides by catalytic transfer hydrogenation with formic acid," *The Journal of Organic Chemistry*, vol. 44, no. 19, pp. 3442–3444, 1979.

[21] M. M. Matin and M. Z. Iqbal, "Methyl 4-O-(2-chlorobenzoyl)-α-L-rhamnopyranosides: Synthesis, characterization, and thermodynamic studies," *Orbital: The Electronic Journal of Chemistry*, pp. 19–27, 2021.

[22] A. Oberlintner, B. Likozar, and U. Novak, "Hydrophobic functionalization reactions of structured cellulose nanomaterials: Mechanisms, kinetics and in silico multi-scale models," *Carbohydrate Polymers*, vol. 259, p. 117742, 2021.

[23] J. Ali *et al.*, "A new biosource for synthesis of activated carbon and its potential use for removal of methylene blue and eriochrome black T from aqueous solutions," *Industrial Crops and Products*, vol. 179, p. 114676, 2022.

[24] H. M. Aliabadi and K. Zargoosh, "Synthesis of 3-amino-1, 2, 4-triazole-5-thiol functionalized p-phenylenediamine covalent organic polymer as a highly selective adsorbent for Hg2+ ions," *Reactive and Functional Polymers*, vol. 186, p. 105575, 2023.

[25] H. Montes-Andrés *et al.*, "Synthesis, Structural Features, and Hydrogen Adsorption Properties of Three New Flexible Sulfur-Containing Metal–Organic Frameworks," *Crystal Growth & Design*, vol. 20, no. 10, pp. 6707–6714, Oct. 2020, doi: 10.1021/acs.cgd.0c00857.

[26] Q. Cheng *et al.*, "Li+-ion bound crown ether functionalization enables dual promotion of dynamics and thermodynamics for ambient ammonia synthesis," *Journal of Energy Chemistry*, 2023.

[27] A. Rawat and A. V. B. Reddy, "Recent advances on anticancer activity of coumarin derivatives," *European Journal of Medicinal Chemistry Reports*, vol. 5, p. 100038, 2022.

[28] Z. M. Noufal, P. Sivaperumal, and P. Elumalai, "Extraction, characterization, and anticancer potential of extracellular polymeric substances from marine actinobacteria of Streptomyces species," *Journal of advanced pharmaceutical technology & research*, vol. 13, no. Suppl 1, p. S125, 2022.

[29] R. A. Ali, E. O. Al-Tamimi, and S. A. Wadood, "Synthesis and Characterization of New 1, 3, 4-Oxadiazole Ring on Creatinine Derivatives Using Iodine and Study Their Anticancer Effect," *Russian Journal of Bioorganic Chemistry*, pp. 1–3, 2023.

[30] A. T. Odularu, "Manganese Schiff base complexes, crystallographic studies, anticancer activities, and molecular docking," *Journal of Chemistry*, vol. 2022, 2022.