

Novel bis-crown ethers and their sodium complexes as antimicrobial agent: synthesis and spectroscopic characterizations

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Abstract A series of new compounds containing formyl and imine group were synthesized. New formyl-substituted compounds were prepared by the reaction of 1,2-bis(bromomethyl)benzene with benzaldehyde derivatives in the presence of NaOH. New bis-crown ether imine compounds were prepared by the condensation of corresponding aldehydes with 4'-aminobenzo-15-crown-5. Sodium complexes of the bis-crown ethers form crystalline 2:1 ($\text{Na}^+:\text{ligand}$) stoichiometries were also been synthesized. The prepared compounds were structurally confirmed by analytical and spectral data and evaluated for their antibacterial and antifungal activities. The results show that the antibacterial activity of compounds including *o*-methoxy group was significantly higher against *S. epidermis* compared to the other studied antimicrobial group.

Keywords bis-Crown ethers · Schiff bases · Aldehydes · Antibacterial activity · Sodium complexes

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Introduction

It is known that macrocyclic compounds show high affinity to alkali, alkaline earth, and transition metal cations forming stable complexes with them (Pedersen, 1967; Dmitrieva *et al.*, 2011; Gümüş *et al.*, 2010). Because macrocyclic ethers have a hydrophilic cavity structure, medium polarity and strong electronegative effect of heteroatoms on the macrocyclic ring. Many different modifications of the crown ethers, such as changing the ring size, the kinds of substituents, and the types of donor atoms, have made to enhance their complexation properties (Gromov *et al.*, 2011; Izatt *et al.*, 1991). The cation–polyether complexes are formed by ion–dipole interaction between the cation and the negatively charged oxygens symmetrically arranged in the polyether ring. From the earliest beginning of the development of crown compounds, benzo-crown ethers have been a very useful class of host molecules, forming the basis for more complex macrocyclic ligand frameworks such as the bis-crown ether compounds (Hayvalı *et al.*, 1999, 2000). Bis-crown ethers are composed of two crown ether moieties linked by different chains in the same molecule. The two effective binding sites, the bis-crown ethers can form intermolecular and intramolecular complexes depending on the relative size of the ion and the hole in the polyether ring, the coplanarity of the oxygen atoms, and even the chain lengths that bridge the two units. The linking of two crown ether units can lead to the formation of sandwich complex. If the diameter of the cation is too large to fit inside the available crown cavity, formation of the so-called “sandwich” complexes with metal:crown ether ratio at 1:1 can occur (Weber *et al.*, 1990; Kikukawa *et al.*, 1987). The stability of such complexes is higher with respect to the monocyclic crown ether analogs owing to the so-called “bis-crown effect” (Kikukawa *et al.*, 1987; Kimura *et al.* 1985).

Mono- and *bis-crown* ethers have been a topic of great interest in chemical and biological research for more than four decades (Supek *et al.*, 2011; Tusek-Bozic *et al.*, 2009; Uğraş *et al.*, 2006; Marjanovic *et al.*, 2007). They have recently demonstrated function as antimicrobial agents (Supek *et al.*, 2011). Crown ethers exhibit ionophoric properties in membranes, behaving very similarly to the biologically important ionophores (such as gramicidin, valinomycin, and nonactin) which makes crown ethers particularly interesting and useful in chemical and biological study and their pharmaceutical potential remains large (Gokel *et al.*, 2004; Kralj *et al.*, 2008). In addition, methoxy derivatives have continued to attract attention for their interesting biological activities. Their anticancer (Ziedan *et al.*, 2010), antifungal, anti-inflammatory (Sahoo *et al.*, 2011), and antimicrobial activities (Flipo *et al.*, 2011) including human immunodeficiency virus activities are well known. Methoxy derivatives form an important

class of compounds possessing wide range of biological activities (Bandgar *et al.*, 2012).

In this article, we describe the synthesis and characterization of a series of new *bis-crown* ethers and complexes. We report (i) the synthesis of new aldehyde compounds which have *bis-formyl* group (**1–4**) (Fig. 1a); (ii) the synthesis and characterization of Schiff bases containing *bis-benzo-15-crown-5* (**5–8**) (Fig. 1b); (iii) complexation of sodium within the crown ether cavity (**5a–8a**) (Fig. 2); (iv) analytical, physical, and spectral (IR, ^1H , ^{13}C NMR, and MS) data; and (v) all of these compounds were examined for antimicrobial activity against pathogenic strains *Staphylococcus aureus*, *Shigella dysenteriae* typ 7, *Listeria monocytogenes* 4b, *Escherichia coli*, *Salmonella typhi* H, *Staphylococcus epidermis*, *Brucella abortus*, *Micrococcus luteus*, *Bacillus cereus*, *Pseudomonas putida*, and antifungal activity against *Candida albicans*.

Fig. 1 Structures of the novel *bis*-aldehydes (**1–4**) (a) and Schiff bases (**5–8**) (b)

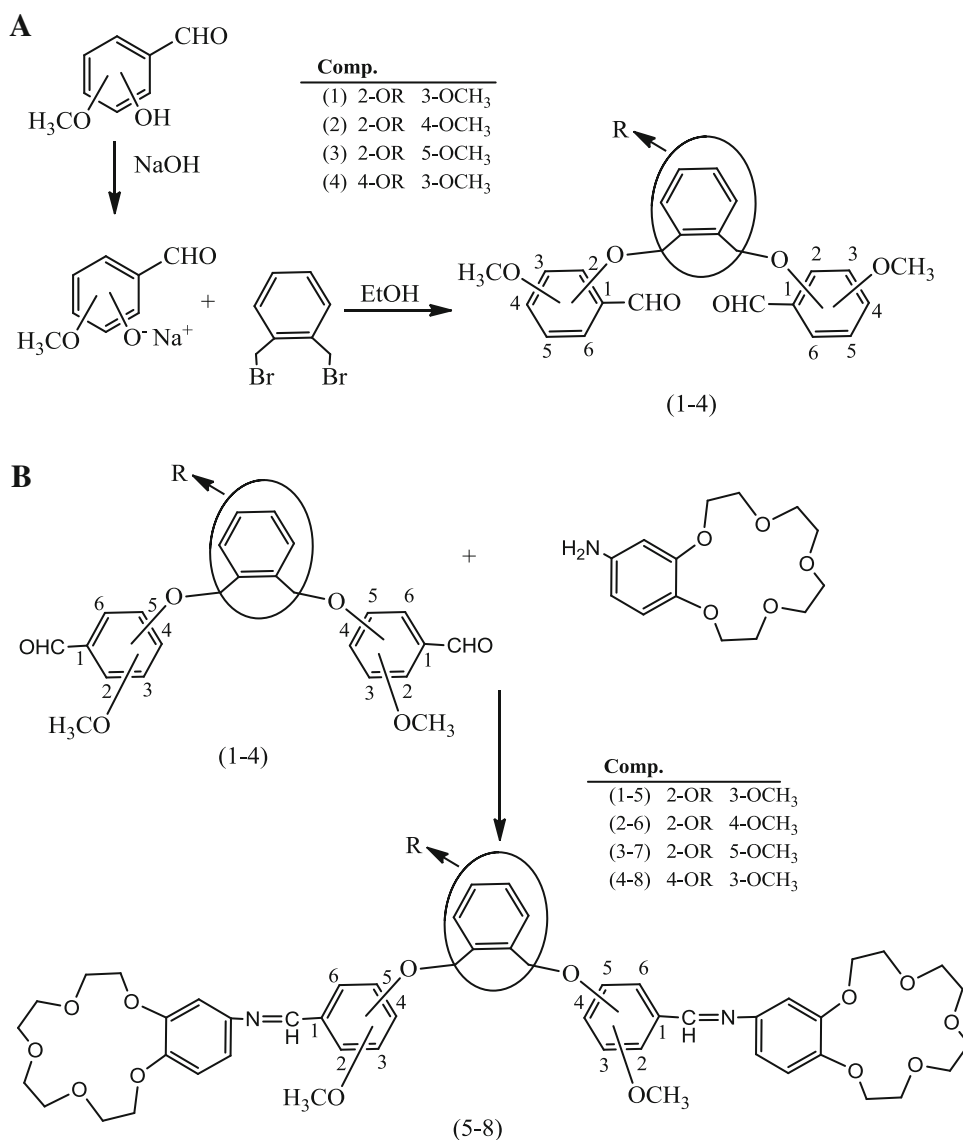
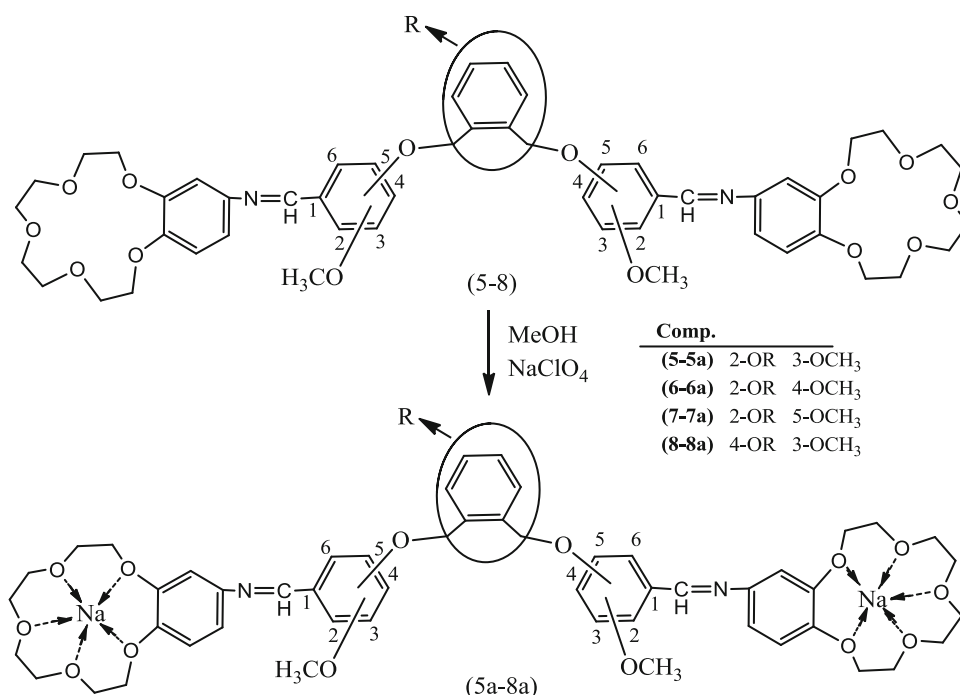


Fig. 2 Structures of the sodium complexes (**5a–8a**)



Materials and methods

Reagents and equipments

4-Hydroxy-3-methoxybenzaldehyde (vanillin), 2-Hydroxy-3-methoxybenzaldehyde (*o*-vanillin), 2-hydroxy-4-methoxybenzaldehyde, and 2-hydroxy-5-methoxybenzaldehyde were purchased from Aldrich and used without further purification. 1,2-bis(bromomethyl)benzene was prepared according to the literature (Zhu *et al.*, 2011). Solvents were dried and distilled before use according to the standard procedure. Melting points were measured on a Thomas–Hoover apparatus using a capillary tube. ¹H and ¹³C NMR spectra were recorded on a Varian Mercury, High Performance Digital FT-NMR (400 MHz) spectrometer (SiMe₄ as an internal standard). Chemical shifts for proton and carbon resonances were reported in ppm (δ). IR spectra were obtained from PEL-DATA spectrum 100 series spectrometer. Carbon, nitrogen, and hydrogen analyses were performed on LECO CHNS-932 elemental analyzer. Mass spectrometric analyses were performed on the Waters 2695 Allonze ZQ LC/MS spectrometer.

Detection of antimicrobial activity

The bacterial subcultures chosen were *S. aureus* RSKK-07035, *S. dys. typ* 7NCTC-9363, *L. monocytogenes* 4b ATCC 19115, *E. coli* ATCC 1280, *S. typhi* H NCTC 901.8394, *S. epidermis* sp., *B. abortus* RSKK-03026, *M. luteus* ATCC-9341, *B. cereus* sp., and *P. peptide* sp. An antifungal

susceptibility test was used by *C. albicans* Y-1200-NIH, Tokyo. The ligands and the complexes were tested for their antimicrobial activity by the well-diffusion method (Sari *et al.*, 2013). Each ligand and complex was kept dry at room temperature and dissolved (10³ μM) in DMF. DMF was used as solvent and also for control. It was found to have no antimicrobial activity against any of the tested organisms. 1 % (v/v) of a 24-h broth culture containing 10⁶ CFU/ml was placed in sterile Petri dishes. Mueller–Hinton Agar (15 ml) kept at 45 °C was then poured into the Petri dishes and allowed to solidity. Then 6-mm diameter wells were punched carefully by using a sterile cork borer and were entirely filled with the test solutions. The plates were incubated for 24 h at 37 °C. On completion of the incubation period, the mean value obtained for the two holes was used to calculate the zone of growth inhibition of each sample.

General method for prepare of novel bis-aldehydes (1–4)

The corresponding vanillin or methoxysalicylaldehyde derivatives (0.35 g, 2.30 mmol) were dissolved in EtOH (15 mL). NaOH (0.09 g, 2.30 mmol) was added in small amounts and the resulting reaction mixture was refluxed for 1 h. Subsequently, 1,2-bis(bromomethyl)benzene (0.30 g, 1.15 mmol) in EtOH (15 mL) was added dropwise to the reaction mixture. The resulting solution was refluxed for 24 h, and the complete consumption of the starting material was observed by TLC (silica; eluent; CHCl₃). The white precipitate was isolated and recrystallized from ethanol.

2,2'-[1,2-Phenylenebis(methyleneoxy)]
bis(3-methoxybenzaldehyde) (**1**)

White; m.p. 159–160 °C; IR (KBr) $\nu_{\max}$ 2,949–2,846 (w), 1,691 (s), 1,584 (s), 1,251, 1,183, 1,067 (s), 1,059 (s) cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ = 10.25 (2H, s), 7.54–7.13 (10H, m), 5.32 (s, 4H), 3.86 (s, 6H); ^{13}C NMR (CDCl_3 , 125 MHz): δ = 190.6 (C, CHO), 153.0 (C, C-4), 151.6 (C, C-5), 142.8 (C, C-3), 130.0 (C, C-1), 129.1 (C, C-2), 122.3 (C, C-8), 130.2 (C, C-9), 119.2 (C, C-7), 115.1 (C, C-6), 57.1 (C, OCH_2), 69.9 (C, OCH_3); Anal. Calcd. for $\text{C}_{24}\text{H}_{22}\text{O}_6$: C, 70.92; H, 5.46. Found: C, 71.21; H, 5.67.

2,2'-[1,2-Phenylenebis(methyleneoxy)]
bis(4-methoxybenzaldehyde) (**2**)

White; m.p. 129–130 °C; IR (KBr) $\nu_{\max}$ 2,928–2,866 (w), 1,676 (s), 1,595, 1,577 (s), 1,260, 1,164, 1,044 (s), 1,030 (s) cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ = 10.31 (2H, s), 7.87–7.23 (10H, m), 5.31 (s, 4H), 3.83 (s, 6H); ^{13}C NMR (CDCl_3 , 125 MHz): δ = 189.1 (C, CHO), 166.7 (C, C-4), 166.2 (C, C-5), 139.5 (C, C-3), 130.8 (C, C-2), 130.1 (C, C-8), 128.6 (C, C-1), 122.8 (C, C-9), 108.7 (C, C-7), 101.5 (C, C-5), 68.6 (C, OCH_2), 56.1 (C, OCH_3); Anal. Calcd. for $\text{C}_{24}\text{H}_{22}\text{O}_6$: C, 70.92; H, 5.46. Found: C, 70.99; H, 5.45.

2,2'-[1,2-Phenylenebis(methyleneoxy)]
bis(5-methoxybenzaldehyde) (**3**)

White; m.p. 143–144 °C; IR (KBr) $\nu_{\max}$ 2,963–2,842 (w), 1,677 (s), 1,586 (s), 1,256, 1,164 (s), 1,043 (s) cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ = 10.41 (2H, s), 7.53–6.97 (10H, m), 5.22 (s, 4H), 3.79 (s, 6H); ^{13}C NMR (CDCl_3 , 125 MHz): δ = 189.3 (C, CHO), 154.92 (C, C-8), 153.9 (C, C-4), 134.1 (C, C-3), 128.8 (C, C-2), 128.6 (C, C-1), 125.9 (C, C-9), 123.9 (C, C-6), 114.2 (C, C-5), 111.1 (C, C-8), 69.5 (C, OCH_2), 56.0 (C, OCH_3); Anal. Calcd. for $\text{C}_{24}\text{H}_{22}\text{O}_6$: C, 70.92; H, 5.46. Found: C, 70.69; H, 5.32.

4,4'-[1,2-Phenylenebis(methyleneoxy)]bis(3-methoxybenzaldehyde) (**4**)

White; m.p. 137–138 °C; IR (KBr) $\nu_{\max}$ 2,946–2,814 (w), 1,675 (s), 1,583, 1,513 (s), 1,267, 1,134 (s), 1,032 (s) cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ = 10.36 (2H, s), 7.54–6.96 (10H, m), 5.29 (s, 4H), 3.82 (s, 6H); ^{13}C NMR (CDCl_3 , 125 MHz): δ = 189.1 (C, CHO), 156.1 (C, C-4), 151.1 (C, C-5), 141.2 (C, C-3), 131.9 (C, C-2), 129.4 (C, C-1), 126.0 (C, C-7), 128.8 (C, C-6), 126.0 (C, C-7), 113.2 (C, C-9), 69.4 (C, OCH_2), 55.2 (C, OCH_3); Anal. Calcd. for $\text{C}_{24}\text{H}_{22}\text{O}_6$: C, 70.92; H, 5.46. Found: C, 71.02; H, 5.63.

General method for prepare of bis-crown ether Schiff bases (**5–8**)

10 mL of methanol was added to a solution of corresponding bis-aldehyde (**1–4**) (0.20 g, 0.49 mmol) with continuous stirring of 4'-aminobenzo-15-crown-5 (0.27 g, 0.98 mmol). The resulting solution was stirred under reflux for 5 h, and then the reaction mixture was allowed to stand for 2 h at room temperature. The yellow product was recrystallized from CH_3OH .

N,N'-[1,2-phenylbis[methyleneoxy(3-methoxy-2,1-phenyl)methylene]]bis(2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxocyclopentadien-15-amin) (**5**)

Yellow; m.p. 82–83 °C; IR (KBr) $\nu_{\max}$ 2,922–2,867 (w), 1,621 (s), 1,577, 1,511 (s), 1,260, 1,125–1,069 (s) cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ = 8.69 (2H, s), 7.68–6.61 (16H, m), 5.24 (4H, s), 4.12–3.75 (32H, m) 3.79 (6H, s); ^{13}C NMR (CDCl_3 , 125 MHz): δ = 155.7 (C, $\text{CH}=\text{N}$), 152.3 (C, C-1), 150.1 (C, C-2), 149.1 (C, C-3), 148.1 (C, C-4), 146.1 (C, C-5), 136.1 (C, C-6), 130.9 (C, C-7), 130.5 (C, C-8), 128.7 (C, C-9), 124.6 (C, C-10), 119.2 (C, C-11); 115.0 (C, C-12), 114.9 (C, C-13), 113.9 (C, C-14); 108.0 (C, C-15); 73.5 (C, OCH_2) 71.4–68.9 (C, $\text{OCH}_2\text{CH}_2\text{O}$), 56.9 (C, OCH_3); Anal. Calcd. for $\text{C}_{52}\text{H}_{60}\text{O}_{14}\text{N}_2$: C, 66.65; H, 6.45; N, 2.99. Found: C, 66.89; H, 6.46; N, 3.02.

N,N'-[1,2-phenylbis[methyleneoxy(4-methoxy-2,1-phenyl)methylene]]bis(2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxocyclopentadien-15-amin) (**6**)

Yellow; m.p. 129–128 °C; IR (KBr) $\nu_{\max}$ 2,917–2,865 (w), 1,610 (s), 1,585, 1,511 (s), 1,259, 1,118–1,036 (s) cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ = 8.75 (2H, s), 8.06–6.46 (16H, m), 5.22 (4H, s), 4.11–3.74 (32H, m) 3.75 (6H, s); ^{13}C NMR (CDCl_3 , 125 MHz): δ = 156.2 (C, $\text{CH}=\text{N}$), 153.2 (C, C-1), 149.4 (C, C-2), 149.1 (C, C-3), 147.6 (C, C-4), 146.2 (C, C-5), 137.3 (C, C-6), 129.1 (C, C-7), 129.9 (C, C-8), 126.4 (C, C-9), 124.7 (C, C-10), 118.5 (C, C-11); 115.6 (C, C-12), 114.1 (C, C-13); 112.8 (C, C-14); 107.7 (C, C-15); 72.3 (C, OCH_2) 70.9–68.3 (C, $\text{OCH}_2\text{CH}_2\text{O}$), 72.3 (C, OCH_3); 56.2 (C, OCH_2); Anal. Calcd. for $\text{C}_{52}\text{H}_{60}\text{O}_{14}\text{N}_2$: C, 66.65; H, 6.45; N, 2.99. Found: C, 66.63; H, 6.87; N, 2.89.

N,N'-[1,2-phenylbis[methyleneoxy(5-methoxy-2,1-phenyl)methylene]]bis(2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxocyclopentadien-15-amin) (**7**)

Green; m.p. 95–96 °C; IR (KBr) $\nu_{\max}$ 2,921–2,866 (w), 1,623 (s), 1,579, 1,508 (s), 1,262, 1,125–1,029 (s) cm^{-1} ; ^1H

Table 1 ^1H -NMR spectral data

Compound	$-\text{OCH}_3$	$-\text{OCH}_2$	$-\text{CHO}$	$\text{HC}=\text{N}$	$-\text{OCH}_2\text{CH}_2\text{O}-$	Ar-H
1	3.86 (s, 6H)	5.32 (s, 4H)	10.25 (s, 2H)	—	—	7.54–7.13 (m, 10H)
2	3.83 (s, 6H)	5.31 (s, 4H)	10.31 (s, 2H)	—	—	7.87–7.23 (m, 10H)
3	3.79 (s, 6H)	5.22 (s, 4H)	10.41 (s, 2H)	—	—	7.53–6.97 (m, 10H)
4	3.82 (s, 6H)	5.29 (s, 4H)	10.36 (s, 2H)	—	—	7.54–6.96 (m, 10H)
5	3.79 (s, 6H)	5.24 (s, 4H)	—	8.69 (s, 2H)	4.12–3.75 (m, 32H)	7.68–6.61 (m, 16H)
6	3.75 (s, 6H)	5.22 (s, 4H)	—	8.75 (s, 2H)	4.11–3.74 (m, 32H)	8.06–6.46 (m, 16H)
7	3.81 (s, 6H)	5.20 (s, 4H)	—	8.84 (s, 2H)	4.13–3.75 (m, 32H)	7.64–6.67 (m, 16H)
8	3.93 (s, 6H)	5.35 (s, 4H)	—	8.33 (s, 2H)	4.19–3.76 (m, 32H)	7.56–6.74 (m, 16H)
5a	3.82 (s, 6H)	5.21 (s, 2H)	—	8.57 (s, 2H)	4.19–3.70 (m, 32H)	7.67–6.24 (m, 16H)
6a	3.76 (s, 6H)	5.25 (s, 4H)	—	8.66 (s, 2H)	4.15–3.70 (m, 32H)	8.01–6.48 (m, 16H)
7a	3.86 (s, 6H)	5.21 (s, 4H)	—	8.74 (s, 2H)	4.17–3.69 (m, 32H)	7.61–6.79 (m, 16H)
8a	3.97 (s, 6H)	5.32 (s, 4H)	—	8.24 (s, 2H)	4.24–3.72 (m, 32H)	7.53–6.71 (m, 16H)

Chemical shifts (δ) are reported in ppm (in CDCl_3)

s singlet, *m* multiplet

NMR (CDCl_3 , 500 MHz): δ = 8.84 (2H, s), 7.64–6.67 (16H, m), 5.20 (4H, s), 4.13–3.75 (32H, m) 3.81 (6H, s); ^{13}C NMR (CDCl_3 , 125 MHz): δ = 155.9 (C, $\text{CH}=\text{N}$), 152.8 (C, C-1), 149.0 (C, C-2), 148.6 (C, C-3), 147.3 (C, C-4), 145.0 (C, C-5), 137.5 (C, C-6), 128.8 (C, C-7), 128.0 (C, C-8), 126.2 (C, C-9), 125.2 (C, C-10), 117.5 (C, C-11), 115.2 (C, C-12), 114.0 (C, C-13), 112.9 (C, C-14), 106.1 (C, C-15); 73.2 (C, OCH_2) 71.33–68.2 (C, $\text{OCH}_2\text{CH}_2\text{O}$), 56.5 (C, OCH_3); Anal. Calcd. for $\text{C}_{52}\text{H}_{60}\text{O}_{14}\text{N}_2$: C, 66.65; H, 6.45; N, 2.99. Found: C, 66.42; H, 6.49; N, 2.91.

N,N'-{1,2-phenylbis[methyleneoxy(3-methoxy-4,1-phenyl)methylene]}bis(2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxocyclopentadien-15-amin) (**8**)

Green; m.p. 95–96 °C; IR (KBr) ν_{max} 2,925–2,865 (w), 1,619 (s), 1,586, 1,506 (s), 1,261, 1,118–1,046 (s) cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ = 8.75 (2H, s), 7.56–6.74 (16H, m), 5.35 (4H, s), 4.19–3.76 (32H, m) 3.93 (6H, s); ^{13}C NMR (CDCl_3 , 125 MHz): δ = 156.05 (C, $\text{CH}=\text{N}$), 151.9 (C, C-1), 151.0 (C, C-2), 148.7 (C, C-3), 148.0 (C, C-4), 147.2 (C, C-5), 136.2 (C, C-6), 131.1 (C, C-7), 130.1 (C, C-8), 128.1 (C, C-9), 125.3 (C, C-10), 118.2 (C, C-11), 114.2 (C, C-12), 113.2 (C, C-13), 112.9 (C, C-14), 106.2 (C, C-15); 72.2 (C, OCH_2) 70.9–68.6 (C, $\text{OCH}_2\text{CH}_2\text{O}$), 55.6 (C, OCH_3); Anal. Calcd. for $\text{C}_{52}\text{H}_{60}\text{O}_{14}\text{N}_2$: C, 66.65; H, 6.45; N, 2.99. Found: C, 66.74; H, 6.67; N, 3.12.

General methods for prepare of NaClO_4 complexes (5a–8a)

To a solution of corresponding ligand (**5–8**) (0.10 g, 0.10 mmol) in methanol (10 mL), a solution of NaClO_4

(0.02 g, 0.21 mmol) was slowly added in methanol (5 mL) with stirring for 1 h. The crude complexes were filtered and then left to dry in open air. For characteristic peaks, see Table 1.

N,N'-{1,2-phenylbis[methyleneoxy(3-methoxy-2,1-phenyl)methylene]}bis(2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxocyclopentadien-15-amin) sodium complex (**5a**)

Compound (5a) White; m.p. 132–133 °C; IR (KBr) ν_{max} 2,919–2,876 (w), 1,620 (s), 1,577, 1,508 (s), 1,265 (s), 1,080, 622 (s) cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ = 8.57 (2H, s), 7.67–6.24 (16H, m), 5.21 (4H, s), 4.19–3.70 (32H, m) 3.82 (6H, s); ^{13}C NMR (CDCl_3 , 125 MHz): δ = 155.6 (C, $\text{CH}=\text{N}$); 153.9, 151.69, 148.7, 148.0, 145.9, 136.2, 130.5, 129.6, 129.2, 125.5, 118.1, 114.7, 113.2, 112.7, 106.2 (C, C1-15); 72.7 (C, OCH_2); 71.5–69.2 (C, $\text{OCH}_2\text{CH}_2\text{O}$); 52.9 (C, OCH_3); Anal. Calcd. for $\text{C}_{52}\text{H}_{60}\text{O}_{22}\text{N}_2\text{Na}_2\text{Cl}_2$: C, 52.84; H, 5.12; N, 2.37. Found: C, 52.58; H, 5.32; N, 2.38.

N,N'-{1,2-phenylbis[methyleneoxy(4-methoxy-2,1-phenyl)methylene]}bis(2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxocyclopentadien-15-amin) sodium complex (**6a**)

Compound (6a) White; m.p. 142–143 °C; IR (KBr) ν_{max} 2,927–2,878 (w), 1,606 (s), 1,591, 1,509 (s), 1,262 (m), 1,085, 623 (s) cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ = 8.66 (2H, s), 8.01–6.48 (16H, m), 5.25 (4H, s), 4.15–3.70 (32H, m) 3.76 (6H, s); ^{13}C NMR (CDCl_3 , 125 MHz): δ = 155.12 (C, $\text{CH}=\text{N}$); 152.8, 150.5, 149.1, 147.7, 144.9, 137.8, 131.6, 130.2, 129.6, 126.2, 119.5, 113.8, 112.2, 111.5,

105.9 (C, C1-15); 72.2 (C, OCH₂); 71.1–68.8 (C, OCH₂-CH₂O); 56.6 (C, OCH₃); Anal. Calcd. for C₅₂H₆₀O₂₂N₂-Na₂Cl₂: C, 52.84; H, 5.12; N, 2.37. Found: C, 52.66; H, 5.27; N, 2.58.

N,N'-{1,2-phenylbis[methyleneoxy(5-methoxy-2,1-phenyl)methylene]}bis(2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxocyclopentadien-15-amin) sodium complex (**7a**)

Compound (7a) Yellow; m.p. 138 °C; IR (KBr) $\nu_{\max}$ 2,925–2,882 (w), 1,625 (m), 1,588, 1,509 (m), 1,252 (m), 1,082, 623 (s) cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ = 8.74 (2H, s), 7.61–6.79 (16H, m), 5.21 (4H, s), 4.17–3.69 (32H, m) 3.86 (6H, s); ¹³C NMR (CDCl₃, 125 MHz): δ = 155.8 (C, CH=N); 153.6, 151.2, 148.2, 147.2, 145.34, 138.7, 130.9, 130.1, 128.7, 125.5, 118.2, 113.9, 113.0, 111.7, 105.6 (C, C1-15); 77.9 (C, OCH₂); 71.9–69.2 (C, OCH₂-CH₂O); 56.2 (C, OCH₃); Anal. Calcd. for C₅₂H₆₀O₂₂N₂-Na₂Cl₂: C, 52.84; H, 5.12; N, 2.37. Found: C, 53.08; H, 5.16; N, 2.61.

N,N'-{1,2-phenylbis[methyleneoxy(3-methoxy-4,1-phenyl)methylene]}bis(2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxocyclopentadien-15-amin) sodium complex (**8a**)

Compound (8a) Green; m.p. <200 °C (decompose); IR (KBr) $\nu_{\max}$ 2,920–2,879 (w), 1,606 (m), 1,591, 1,509 (m), 1,263 (m), 1,085, 623 (s) cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ = 8.24 (2H, s), 7.53–6.71 (16H, m), 5.32 (4H, s), 4.24–3.72 (32H, m) 3.97 (6H, s); ¹³C NMR (CDCl₃, 125 MHz): δ = 156.1 (C, CH=N); 152.1, 151.4, 147.9, 147.1, 146.9, 137.1, 128.2, 127.9, 127.22, 125.36, 119.22, 114.69, 112.19, 111.23, 107.78 (C, C1-15); 72.12 (C, OCH₂); 70.97–68.63 (C, OCH₂CH₂O); 56.11 (C, OCH₃); Anal. Calcd. for C₅₂H₆₀O₂₂N₂Na₂Cl₂: C, 52.84; H, 5.12; N, 2.37. Found: C, 52.79; H, 5.36; N, 2.19.

Results and discussion

Characterization of Schiff bases and their Na Complexes

The new aldehydes (**1–4**) were synthesized in 82–92 % yields from the reaction of 1,2-bis(bromomethyl)benzene with 2-hydroxy-3-methoxybenzaldehyde (*o*-vanillin), 2-hydroxy-4-methoxybenzaldehyde, 2-hydroxy-5-methoxybenzaldehyde, and 4-hydroxy-3-methoxybenzaldehyde in EtOH, in the presence of NaOH (Fig. 1). Crown ether Schiff bases (**5–8**) (Fig. 2) were prepared by the condensation of 4'-aminobenzo-15-crown-5 with corresponding

aldehydes in 2:1 molar ratio in methanol. The sodium complexes (**5a–8a**) were carried out by combining the respective bis-crown ethers with two molar NaClO₄ in methanol. In the proposed structures, the ligands have bis-benzo-15-crown-5 cores to form dinuclear metal complexes. Ligands have bis-benzo-15-crown-5 cores are form dinuclear metal complexes.

The spectroscopic data indicated that the stoichiometry of the complex formed between Na⁺ benzo-15-crown-5 (M:L) is 2:1 (Fig. 2). Analytical and physical data of aldehydes (**1–4**), crown ether Schiff bases (**5–8**), and sodium complexes (**5a–8a**) are presented in “Materials and methods” section. The structures of all compounds were fully characterized by using melting points, elemental analysis (C, H, N), FT-IR, ¹H-, and ¹³C NMR spectral data. There are selected spectra as supplementary data for studied compounds (Figs S1–S8).

FT-IR spectra, ¹H and ¹³C NMR spectra

Selected IR spectral data for the aldehydes (**1–4**), bis-crown ethers (**5–8**), and sodium complexes (**5a–8a**) are listed in “Materials and methods” section. For the aldehydes (**1–4**), characteristic aldehyde ν (C=O) vibrations for carbonyl groups were detected at 1,691, 1,676, 1,677, and 1,675 cm⁻¹, respectively. In the imine compounds (**5–8**), the relatively strong bands attributable to ν (C=N), were observed at 1,621, 1,610, 1,623, and 1,619 cm⁻¹, respectively. The $\nu_{\text{as}}(\text{C}-\text{O}-\text{C})_{\text{arom.}}$ and $\nu_{\text{s}}(\text{C}-\text{O}-\text{C})_{\text{aliph.}}$ vibrations appear between 1,262 and 1,029 cm⁻¹ in the spectra of the crown ethers (**5–8**). The aliphatic ν (C-H) vibrations exerted by -OCH₂ and -OCH₃ groups for compounds (**1–8**) were observed in the range of 2,963–2,814 cm⁻¹. For sodium complexes (**5a–8a**), the anion ClO₄⁻ gives rise to IR absorption bands at 1,080; 622, 1,085; 623, 1,082; 623; and 1,085; 623 cm⁻¹, respectively. These bands attributable to the asymmetric $\nu_{\text{as}}(\text{Cl}-\text{O})$ stretching modes ca. between 1,085 and 1,080 cm⁻¹ and the asymmetric $\nu_{\text{as}}(\text{O}-\text{Cl}-\text{O})$ bending modes ca. between 623 and 622 cm⁻¹, suggest that both bounded and uncoordinated free anions are present.

The ¹H-NMR spectral data for the aldehydes (**1–4**), bis-crown ethers (**5–8**), and sodium complexes (**5a–8a**) are summarized in Table 1. The ¹H-NMR spectra of the compounds indicated singlets between 3.75 and 3.97 ppm and between 5.20 and 5.35 ppm, corresponding to the -OCH₃ and -OCH₂ protons, respectively. The singlet at 10.25, 10.31, 10.41, and 10.36 ppm belong to aldehyde protons (-CHO) (for **1–4**). The aromatic protons of aldehydes, crown ether imine compounds, and sodium complexes appear as multiplets in the ranges of 8.06–6.46 ppm (for **1–4**), 8.06–6.46 ppm (for **5–8**), and 8.01–6.24 ppm (for **5a–8a**), respectively. For the bis-crown ether Schiff

bases (**5–8**), the characteristic imine protons ($\text{HC}=\text{N}$) were observed as singlets at 8.69, 8.75, 8.84, and 8.33 ppm, respectively. The absence of aldehyde proton signal and detecting azomethine ($\text{HC}=\text{N}$) signal indicate the presence of imine compounds. The ^1H NMR spectra indicated that substituted $-\text{OCH}_3$ group was effective for the imine proton shift, because imine proton was seen at 8.33 ppm for **8**, while this peak was detected at 0.36, 0.42, and 0.51 ppm upfield ($\delta = 8.69, 8.75$ and 8.84 ppm) for compounds **5–7**, respectively. The imine protons for sodium complexes were approximately the same for the ligands imine protons. Bis-crown ether protons ($-\text{OCH}_2-\text{CH}_2\text{O}-$) appeared as multiplets between 4.19 and 3.74 ppm for compounds (**5–8**). In the ^1H -NMR spectra of sodium complexes (**5a–8a**), the small downfield or upfield chemical shifts were detected for the crown ether protons ($-\text{OCH}_2-\text{CH}_2\text{O}-$). These small shifts may be attributed to the differences in the longer distances between Na^+ and the five oxygen atoms of the benzo-15-crown-5 (Hayvalı *et al.*, 2003; Atkinson *et al.*, 1907).

The ^{13}C NMR data for compounds (**1–4**), (**5–8**) and (**5a–8a**) were recorded in CDCl_3 solution (Table 2). In all of the ligands (**1–8**), the characteristic aliphatic $-\text{OCH}_3$ carbons were detected between at 55.18 and 57.14 ppm. The

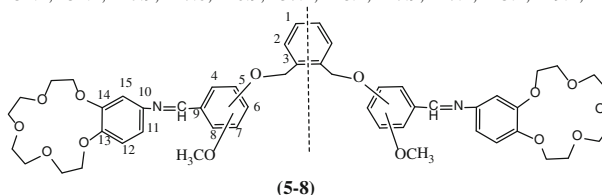
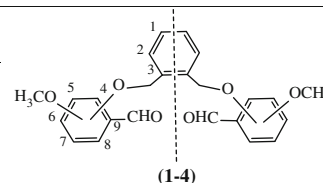
aldehyde carbons ($-\text{CHO}$) for compounds (**1–4**) were observed at 190.63, 189.13, 189.32, and 189.08 ppm, respectively. As expected, the imine carbons ($\text{HC}=\text{N}$) of the compounds **5–8** were detected at 155.72, 156.19, 155.97, and 156.05 ppm, respectively. The signals of the eight crown ether $-\text{OCH}_2\text{CH}_2\text{O}-$ carbons were observed between at 71.35 and 68.17 ppm, as expected. The signals of the aromatic carbons were detected in the expected region, and were equal to the number in the proposed structures of aldehydes and bis-crown ethers. In the ^{13}C NMR spectra of sodium complexes (**5a–8a**), the small up field chemical shifts were detected for the crown ether protons ($-\text{OCH}_2-\text{CH}_2\text{O}-$). In addition, the spectra indicated the characteristic signals for the $-\text{OCH}_3$, $-\text{OCH}_2$, $-\text{HC}=\text{N}$ and aromatic carbons.

Mass spectra

The API-ES and APCI mass spectra of compounds were recorded. Compounds examined provided nice quality mass spectra, and the molecular weight of the ligands and complexes have been confirmed. In the API-ES mass spectra of all aldehydes (**1–4**), the respective molecular ion peaks $[\text{M}+\text{H}]^+$ were detected at m/z 407.5 (100 %). The major

Table 2 ^{13}C NMR spectral data. Chemical shifts (δ) are reported in ppm (in CDCl_3)

Comp	$-\text{OCH}_3$ $-\text{OCH}_2$	$-\text{CHO}$ $\text{HC}=\text{N}$	$\text{OCH}_2\text{CH}_2\text{O}-$	Ar- C_{1-3}	Ar- C_{4-9}
1	57.1 69.8	190.6 -	-	130.0; 129.1; 142.8	153.0, 151.7, 115.1 119.2, 122.3, 130.2
2	56.1 68.6	189.1 -	-	128.6; 130.8; 139.5	166.7, 101.5, 166.2 108.7, 130.1, 122.8
3	56.0 69.5	189.3 -	-	128.6; 128.8; 134.1	153.9, 114.2, 123.9
4	55.2 69.4	189.1 -	-	129.4; 131.9; 141.2	154.9, 111.1, 125.9 156.1, 151.1, 110.3 128.8, 126.0, 113.1
Ar- C_{1-15}					
5	56.9 73.5	- 155.7	71.4-68.9	152.3; 150.1; 149.1; 148.1; 146.1; 136.1; 130.9; 130.5; 128.7; 124.6; 119.2; 115.0; 114.9; 113.9; 108.0	
6	56.2 72.3	- 156.2	70.9-68.3	153.2; 149.4; 149.1; 147.6; 146.2; 137.3; 129.1; 129.9; 126.4; 124.7; 118.5; 115.6; 114.1; 112.8; 107.7	
7	56.5 73.2	- 155.9	71.3-68.2	152.8; 149.0; 148.6; 147.3; 145.0; 137.5; 128.8; 128.0; 126.2; 125.2; 117.5; 115.2; 114.0; 112.9; 106.1	
8	55.6 72.2	- 156.1	70.9-68.6	151.9; 151.0; 148.7; 148.0; 147.2; 136.2; 130.1; 131.1; 128.1; 125.3; 118.2; 114.2; 113.1; 112.9; 106.2	
5a	56.9 72.7	- 155.6	71.5-69.2	153.9; 151.7; 148.7; 148.0; 145.7; 136.2; 130.5; 129.6; 129.2; 125.5; 118.1; 114.7; 113.2; 112.7; 106.2	
6a	56.6 72.2	- 155.1	71.1-68.8	152.8; 150.5; 149.1; 147.7; 144.9; 137.8; 131.6; 130.2; 129.6; 126.2; 119.5; 113.8; 112.2; 111.5; 105.9	
7a	56.2 71.9	- 155.8	71.9-69.2	153.6; 151.2; 148.2; 147.2; 145.3; 138.7; 130.9; 130.1; 128.7; 125.5; 118.2; 113.88; 113.0; 111.7; 105.6	
8a	56.1 72.1	- 156.1	70.9-68.6	152.1; 151.4; 147.9; 147.0; 146.9; 137.1; 128.2; 127.9; 127.2; 125.4; 119.2; 114.7; 112.2; 111.2; 107.8	



fragments for compounds (**1–4**) were obtained at m/z 104.1 (49.4, 51.1, 50.3, and 48.3 %) corresponding to the $[C_8H_8]$.

In the APCI mass spectra of the Schiff bases (**5–8**), the molecular ion peaks were recorded at m/z 938.2 (29.1, 32.1, 20.3, and 28.3 %, respectively). The major fragments were obtained at m/z 974.0 (58.1 %), 974.1 (54.1 %), 974.2 (51.1 %), and 974.2 (52.5 %) corresponding to the $[M+2H_2O]^+$, for the Schiff bases. The fragmentation pattern proceeding by the loss of ether chains is in accordance with previous papers (Coco *et al.*, 2008; Bush and Truter, 1972; Fenton *et al.*, 1981).

In the API-ES mass spectra of sodium complexes (**5a–8a**), the dominant peak at m/z 961.3 (55.1 %), 961.1 (52.1 %), 961.5 (53.1 %), and 961.2 (54.2 %) corresponds to the ligand plus sodium $[M+Na]^+$. The molecular ion peaks and fragments of the ligands and complexes support the proposed structures.

Antibacterial studies

The ligands and their sodium complexes were screened for antimicrobial activity in DMF solvent as a control substance. The compounds were tested with the same concentrations in DMF solution (10^3 μ M). All the synthesized compounds and antibiotic exhibited varying degree of inhibitory effects on the growth of different tested strains

(Table 3). All of the compounds were active against *Sh. dys. typ* and *B. cereus*.

Effective of methoxy substituent in the bis-aldehydes As shown in Fig. 1, three electron-donor derivatives were prepared, containing 3-methoxy, 4-methoxy, and 5-methoxy. The pharmacology test revealed that their activity order was 3-methoxy < 4-methoxy < 5-methoxy for *L. monocytogenes*, *Br. abortus*, and *C. albicans*. As shown in Table 3, the compound (**3**) that has 5-methoxy substituent showed a significant activity against *M. luteus*; however, *S. aureus* did not display any activity against.

Effective of methoxy substituent in Schiff bases Table 3 and Fig. 2 were analyzed together; the antibacterial activity order was 3-methoxy < 4-methoxy < 5-methoxy for *B. cereus*. The compound (**7**) (Schiff bases including 5-methoxy) was highly active against Gram-positive and Gram-negative bacteria with a 10^3 μ M.

Effective of methoxy substituent in sodium complexes: Regular order was not observed in none of studied bacteria species and fungal effective of methoxy substituent in sodium complexes.

In general, the sodium complexes are more potent bactericides than the ligand. This enhancement in activity may be explained on the basis of chelation theory (Sarı *et al.*, 2013). As shown in Table 3, complexes (**5a**), (**7a**), and (**8a**) showed a significant activity against *S. epidermis*, *S. aureus*

Table 3 Antimicrobial activity of studied compounds (10^3 μ M) and standard reagents (diameter of zone inhibition (mm))

	1	2	3	4	5	5a	6	6a	7	7a	8	8a	Control
<i>S. aureus</i>	–	–	–	–	13	–	–	–	15	–	15	–	–
<i>Sh.dys. typ 7</i>	16	15	16	17	11	15	15	17	13	20	19	15	–
<i>L. monocytogenes</i>	11	12	14	13	–	12	11	11	11	12	12	11	–
<i>E. coli</i>	14	15	13	15	–	16	–	18	14	17	20	–	–
<i>S. typhi H</i>	12	11	14	13	–	13	–	14	14	14	13	14	–
<i>S. epidermis</i>	20	16	18	18	–	33	–	16	20	25	21	25	–
<i>Br. abortus</i>	17	15	22	20	–	23	25	19	19	24	–	15	–
<i>M. luteus</i>	20	15	26	20	–	25	–	20	12	19	16	23	–
<i>B. cereus</i>	18	13	16	15	12	28	15	15	18	20	18	19	–
<i>P. putida</i>	19	–	15	14	–	19	–	20	–	24	13	20	–
<i>C. albicans</i>	24	20	27	26	12	24	–	20	21	23	21	22	–
Positive control	<i>S. aureus</i>		<i>L. monocytogenes</i>		<i>E. coli</i>		<i>S. typhi H</i>		<i>Br. abortus</i>		<i>C. albicans</i>		
K30	25		15		25		20		–		–		
SXT25	24		11		18		17		–		–		
AMP10	30		16		10		11		–		–		
AMC30	30		22		14		19		–		–		
NYS100	–		–		–		–		–		20		
SCF	–		–		–		–		12		–		

K30 kanamycin 30 μ g, SXT25 sulfamethoxazol 25 μ g, AMP10 ampicillin 10 μ g, CIP5 Ciprofloxacin 5 μ g, AMC30 amoxycillin 30 μ g, NYS100 nystatin 100 μ g, SCF sulbactam (30 μ g)

did not display any activity against them. The results of antifungal and antibacterial screening indicated that the complexes of (**3**) showed more activity than the other complexes for *B. cereus*.

Furthermore, the antibacterial activity of these compounds was also compared with seven commercial antibiotics, namely, kanamycin, sulfamethoxazol, ampicillin, ciprofloxacin, amoxycillin, sulbactam, and nystatin. It was seen that the synthesized compounds were effective as the antibiotics above mentioned.

Conclusion

In conclusion, new formyl-substituted compounds (**1–4**) were prepared by reacting with the appropriate hydroxy benzaldehydes with 1,2-bis(bromomethyl)benzene in EtOH in the presence of NaOH. These compounds reacted with 4'-aminobenzo-15-crown-5 to afford the corresponding bis-crown ethers (**5–8**). Dinuclear sodium complexes (**5a–8a**) of the bis-crown ethers were prepared with NaClO₄. Most of the compounds had potential antibacterial activities against studied bacteria. In particular, compound (**5a**) was found to have the most antibacterial effective. Previous papers on bioactive properties of methoxy derivatives highlight importance substituent in the 5-position (Fenton *et al.*, 1981; Husain *et al.*, 2011). This study shows that crown ether compounds that have 5-methoxy derivatives may have presented greater antimicrobial properties. These results suggested that further development of such compounds may be of interest.

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