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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

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

Zeliha Hayvalı · Hüseyin Güler · Hatice Öğütcü · Nurşen Sarı

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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 (Na^+: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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Z. Hayvalı · H. Güler
Department of Chemistry, Faculty of Science, Ankara University, 06100 Tandoğan, Ankara, Turkey

H. Öğütcü
Department of Biology, Faculty of Arts and Science, Ahi Evran University, 40100 Kırşehir, Turkey

N. Sarı (✉)
Department of Chemistry, Gazi University, Faculty of Science, 06500 Teknikokullar, Ankara, Turkey
e-mail: nursens@gazi.edu.tr

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 (Hayvali *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 coplanirity 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, ^{1}H, ^{13}C NMR, and MS) data; and (v) all of these compounds were examined for antimicrobial activity against pathogenic strains *Staphylococcus aureus, Shigella dysenteria 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*.

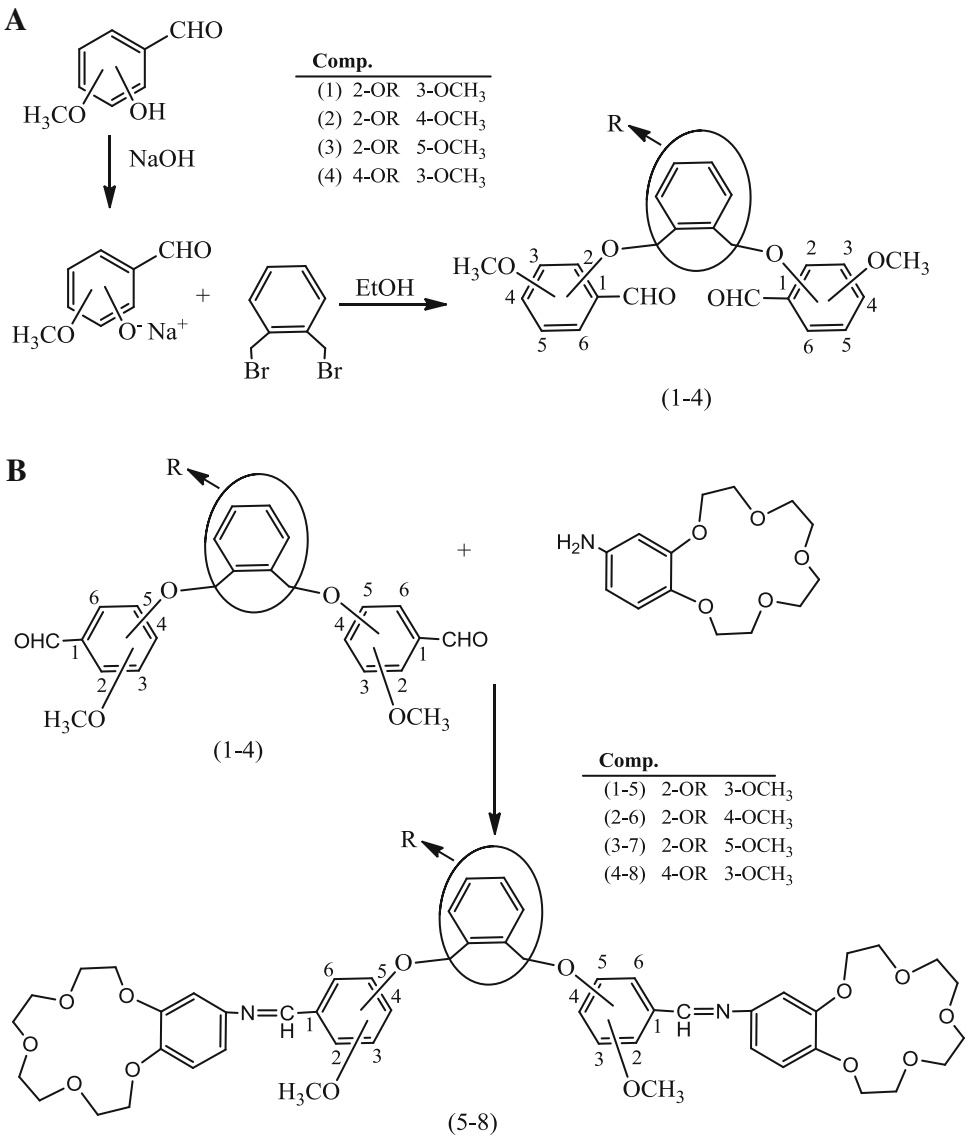


Fig. 1 Structures of the novel bis-aldehydes (**1**–**4**) (**a**) and Schiff bases (**5**–**8**) (**b**)

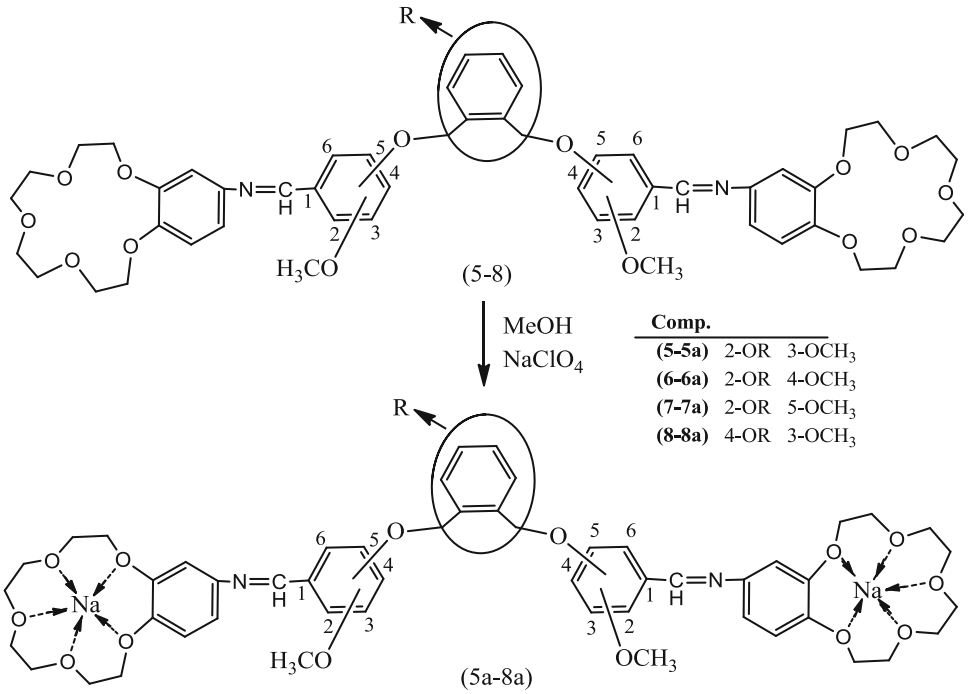


Fig. 2 Structures of the sodium complexes (**5a**–**8a**)

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. ^{1}H and ^{13}C NMR spectra were recorded on a *Varian Mercury, High Performance Digital FT-NMR* (400 MHz) spectrometer ($SiMe_4$ 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 Allonce ZQ LC/MS* spectrometer.

Detection of antimicrobial activity

The bacterial subcultures chosen were *S. aureus RSKK-07035, S. dys. typ 7 NCTC-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 (10^3 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 10^6 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; $CHCl_3$). 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) ν_{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,): $\delta = 10.25$ (2H, s), 7.54–7.13 (10H, m), 5.32 (s, 4H), 3.86 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz,): $\delta = 190.6$ (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 $C_{24}H_{22}O_6$: 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) ν_{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,): $\delta = 10.31$ (2H, s), 7.87–7.23 (10H, m), 5.31 (s, 4H), 3.83 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz,): $\delta = 189.1$ (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 $C_{24}H_{22}O_6$: 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) ν_{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,): $\delta = 10.41$ (2H, s), 7.53–6.97 (10H, m), 5.22 (s, 4H), 3.79 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz,): $\delta = 189.3$ (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 $C_{24}H_{22}O_6$: 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) ν_{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,): $\delta = 10.36$ (2H, s), 7.54–6.96 (10H, m), 5.29 (s, 4H), 3.82 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz,): $\delta = 189.1$ (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 $C_{24}H_{22}O_6$: 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) ν_{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,): $\delta = 8.69$ (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,): $\delta = 155.7$ (C, CH=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, OCH_2CH_2O), 56.9 (C, OCH_3); Anal. Calcd. for $C_{52}H_{60}O_{14}N_2$: 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) ν_{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,): $\delta = 8.75$ (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,): $\delta = 156.2$ (C, CH=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, OCH_2CH_2O), 72.3 (C, OCH_3); 56.2 (C, OCH_2); Anal. Calcd. for $C_{52}H_{60}O_{14}N_2$: 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) ν_{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 ^{1}H-NMR spectral data

Compound	–OCH_3	–OCH_2	–CHO	HC=N	–OCH_2CH_2O–	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,): $\delta = 8.84$ (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,): $\delta = 155.9$ (C, CH=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, OCH_2CH_2O), 56.5 (C, OCH_3); Anal. Calcd. for $C_{52}H_{60}O_{14}N_2$: 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}; ^{1}H NMR ($CDCl_3$, 500 MHz,): $\delta = 8.75$ (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,): $\delta = 156.05$ (C, CH=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, OCH_2CH_2O), 55.6 (C, OCH_3); Anal. Calcd. for $C_{52}H_{60}O_{14}N_2$: 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}; ^{1}H NMR ($CDCl_3$, 500 MHz,): $\delta = 8.57$ (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,): $\delta =$ 155.6 (C, CH=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, OCH_2-CH_2O); 52.9 (C, OCH_3); Anal. Calcd. for $C_{52}H_{60}O_{22}N_2$-Na_2Cl_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}; ^{1}H NMR ($CDCl_3$, 500 MHz,): $\delta = 8.66$ (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,): $\delta =$ 155.12 (C, CH=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, OCH_2); 71.1–68.8 (C, OCH_2-CH_2O); 56.6 (C, OCH_3); Anal. Calcd. for $C_{52}H_{60}O_{22}N_2$-Na_2Cl_2: 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) ν_{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 ($CDCl_3$, 500 MHz,): $\delta = 8.74$ (2H, s), 7.61–6.79 (16H, m), 5.21 (4H, s), 4.17–3.69 (32H, m) 3.86 (6H, s); ^{13}C NMR ($CDCl_3$, 125 MHz,): $\delta =$ 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, OCH_2); 71.9–69.2 (C, OCH_2-CH_2O); 56.2 (C, OCH_3); Anal. Calcd. for $C_{52}H_{60}O_{22}N_2$-Na_2Cl_2: 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) ν_{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 ($CDCl_3$, 500 MHz,): $\delta = 8.24$ (2H, s), 7.53–6.71 (16H, m), 5.32 (4H, s), 4.24–3.72 (32H, m) 3.97 (6H, s); ^{13}C NMR ($CDCl_3$, 125 MHz,): $\delta = 156.1$ (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, OCH_2); 70.97–68.63 (C, OCH_2CH_2O); 56.11 (C, OCH_3); Anal. Calcd. for $C_{52}H_{60}O_{22}N_2Na_2Cl_2$: 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 $NaClO_4$ 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 ^{13}C NMR spectral data. There are selected spectra as supplementary data for studied compounds (Figs S1–S8).

FT-IR spectra, ^1H and ^{13}C 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 υ(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 υ(C=N), were observed at 1,621, 1,610, 1,623, and 1,619 cm^{-1}, respectively. The $\upsilon_{as}(C–O–C)_{arom.}$ and $\upsilon_s(C–O–C)_{aliph.}$ vibrations appear between 1,262 and 1,029 cm^{-1} in the spectra of the crown ethers (**5–8**). The aliphatic υ(C–H) vibrations exerted by $–OCH_2$ and $–OCH_3$ groups for compounds (**1–8**) were observed in the range of 2,963–2,814 cm^{-1}. For sodium complexes (**5a–8a**), the anion ClO_4^- 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 υ_{as}(Cl–O) stretching modes ca. between 1,085 and 1,080 cm^{-1} and the asymmetric υ_{as}(O–Cl–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 $–OCH_3$ and $–OCH_2$ 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 (HC=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 (HC=N) signal indicate the presence of imine compounds. The ^{1}H NMR spectra indicated that substituted –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 (δ = 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 (–OCH_2–CH_2O–) appeared as multiplets between 4.19 and 3.74 ppm for compounds (**5–8**). In the ^{1}H-NMR spectra of sodium complexes (**5a–8a**), the small downfield or upfield chemical shifts were detected for the crown ether protons (–OCH_2–CH_2O–). 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).

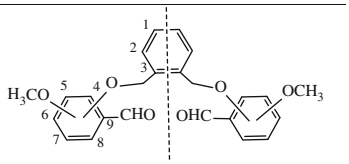
The ^{13}C NMR data for compounds (**1–4**), (**5–8**) and (**5a–8a**) were recorded in $CDCl_3$ solution (Table 2). In all of the ligands (**1–8**), the characteristic aliphatic –OCH_3 carbons were detected between at 55.18 and 57.14 ppm. The aldehyde carbons (–CHO) for compounds (**1–4**) were observed at 190.63, 189.13, 189.32, and 189.08 ppm, respectively. As expected, the imine carbons (HC=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 –OCH_2CH_2O– 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 (–OCH_2–CH_2O–). In addition, the spectra indicated the characteristic signals for the –OCH_3, –OCH_2, –HC=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 $[M+H]^+$ were detected at *m/z* 407.5 (100 %). The major

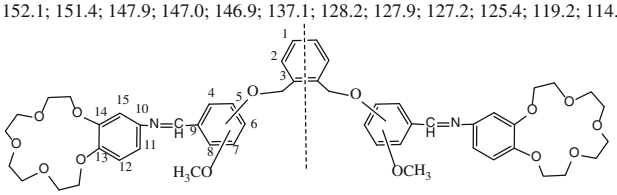
Table 2 ^{13}C NMR spectral data. Chemical shifts (δ) are reported in ppm (in $CDCl_3$)

Comp	-O<u>C</u>H$_3$ -O<u>C</u>H$_2$	-<u>C</u>HO HC=N	O<u>C</u>H$_2$<u>C</u>H$_2$O-	Ar-<u>C</u>$_{1\text{-}3}$	Ar-<u>C</u>$_{4\text{-}9}$
1	57.1	190.6	-	130.0; 129.1; 142.8	153.0, 151.7, 115.1 119.2, 122.3,
	69.8	-			130.2
2	56.1	189.1	-	128.6; 130.8; 139.5	166.7, 101.5, 166.2 108.7, 130.1,
	68.6	-			122.8
3	56.0	189.3	-	128.6; 128.8; 134.1	153.9, 114.2, 123.9
	69.5	-			154.9, 111.1, 125.9
4	55.2	189.1	-	129.4; 131.9; 141.2	156.1, 151.1, 110.3
	69.4	-			128.8, 126.0, 113.1



(1-4)

Comp	-O<u>C</u>H$_3$ -O<u>C</u>H$_2$	-<u>C</u>HO HC=N	O<u>C</u>H$_2$<u>C</u>H$_2$O-	Ar-<u>C</u>$_{1}$-<u>C</u>$_{15}$
5	56.9	-	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
	73.5	155.7		
6	56.2	-	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
	72.3	156.2		
7	56.5	-	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
	73.2	155.9		
8	55.6	-	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
	72.2	156.1		
5a	56.9	-	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
	72.7	155.6		
6a	56.6	-	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
	72.2	155.1		
7a	56.2	-	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
	71.9	155.8		
8a	56.1	-	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
	72.1	156.1		



(5-8)

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 μM). 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 μM.

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 μM) and standard reagents (diameter of zone inhibition (mm))

	1	**2**	**3**	**4**	**5**	**5a**	**6**	**6a**	**7**	**7a**	**8**	**8a**	Control
S. aureus	–	–	–	–	13	–	–	–	15	–	15	–	–
Sh.dys. typ 7	16	15	16	17	11	15	15	17	13	20	19	15	–
L. monocytogenes	11	12	14	13	–	12	11	11	11	12	12	11	–
E. coli	14	15	13	15	–	16	–	18	14	17	20	–	–
S. typhi H	12	11	14	13	–	13	–	14	14	14	13	14	–
S. epidermis	20	16	18	18	–	33	–	16	20	25	21	25	–
Br. abortus	17	15	22	20	–	23	25	19	19	24	–	15	–
M. luteus	20	15	26	20	–	25	–	20	12	19	16	23	–
B. cereus	18	13	16	15	12	28	15	15	18	20	18	19	–
P. putida	19	–	15	14	–	19	–	20	–	24	13	20	–
C. albicans	24	20	27	26	12	24	–	20	21	23	21	22	–

Positive control	*S. aureus*	*L. monocytogenes*	*E. coli*	*S. typhi H*	*Br. abortus*	*C. albicans*
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 μg, *SXT25* sulfamethoxazol 25 μg, *AMP10* ampicillin 10 μg, *CIP5* Ciprofloxacin 5 μg, *AMC30* amoxycillin 30 μg, *NYS100* nystatin 100 μg, *SCF* sulbactam (30 μg)

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 $NaClO_4$. 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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